Scientific paper

Synthesis of Novel 2-Alkyl-5-{4-[(3-alkylisoxazol -5-yl)methoxy]phenyl}-2*H*-tetrazoles

Yousef Rastgar Mirzaei,[1,*] Samad Bavili Tabrizi[2] and Laden Edjlali[2]

[1] *Organic Synthesis Laboratory, Faculty of Chemistry, University of Tabriz, Tabriz 51664, Iran*

[2] *Department of Applied Chemistry, Faculty of Science, Islamic Azad University-Tabriz, P. O. Box 1655 Tabriz, Iran*

* *Corresponding author: E-mail: mirzaeyr@uwec.edu; mirzaeiyousef@yahoo.com*
Fax: +(715) 836-4979

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Dedicated to Prof. Dr. Nicholas R. Natale on the occasion of his 57th birthday.

Abstract

Several alkyl(isoxazolylmethoxyphenyl)tetrazoles were synthesized and characterized. 3-Alkyl-5-(chloromethyl)isoxazoles **9** were prepared by the reaction of corresponding (3-alkylisoxazol-5-yl)methanols with thionyl chloride. 4-(2-Alkyl-2*H*-tetrazol-5-yl)phenols **8** were synthesized from the corresponding aldehyde **3** in five steps, which then reacted with 3-alkyl-5-(chloromethyl)isoxazoles **9** to produce the corresponding 2-alkyl-5-{4-[(3-alkylisoxazol-5-yl)methoxy]phenyl}-2*H*-tetrazoles **10a**–**h** in high yields.

Keywords: Cycloaddition, Isoxazole, Nitro compounds, Tetrazole.

1. Introduction

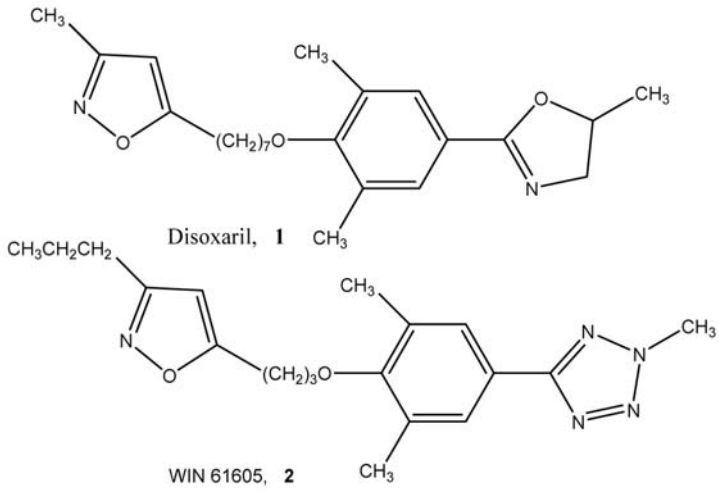
Tetrazoles are an important functionality[1] with wide-ranging applications in photography and information recording systems,[2] pharmaceutical[3a–f] and material sciences and appealing ligands in coordination chemistry.[4a–e] All aspects of the chemistry of tetrazoles as well as medicinal application of tetrazoles were covered in the literature.[1] The most direct method to form tetrazoles is via the formal [3 + 2] cycloaddition[5a–d] of azides and nitriles.[6a–c] Biological activity in tetrazoles is encountered due to the special metabolism of the disubstituted tetrazole system and also because in 5-substituted tetrazole compounds the tetrazole ring is isosteric with a carboxylic acid group and of comparable acidity.[1b,7] Hence for all biologically active molecules possessing a carboxylic group (CO_2H), there is a theoretical nitrogen analogue possessing a tetrazolic group (CN_4H) and since tetrazole moiety appears to be the metabolically more stable of the two a considerable exploration of these molecules is ongoing.[7]

Isoxazoles may show interesting medicinal or crop protection properties or have some other industrial utility.[8a] Various pharmacologically important isoxazoles with antibacterial, antiviral, anti-inflammatory, antidiabetic, antifungal, antiparkinson, antihypertensive and antitumor activity have already been reported.[8b] Isoxazoles are unique in their chemical behavior, not only among heterocyclic compounds in general, but also among related azoles. Isoxazoles functionalized with an additional nitrogen-containing group have seen application.[8,9]

The antipicornaviral activity of compounds related to disoxaril (**1**) (Figure 1) has been well documented.[10] However, disoxaril and related compounds suffer from the fact they have a very short half-life, particularly due to the acid lability of the oxazoline ring. The preparation of several isoxazoles with antipicornavirus activity has also been achieved[11] and the structure and reactivity of these compounds against human picornavirus have been investigated using various physical and statistical methods.[10,11] Recently, extensive studies have been focused on the antiviral activities of these types of compounds, mainly by determination of their minimum inhibitory concentration (MIC).[11]

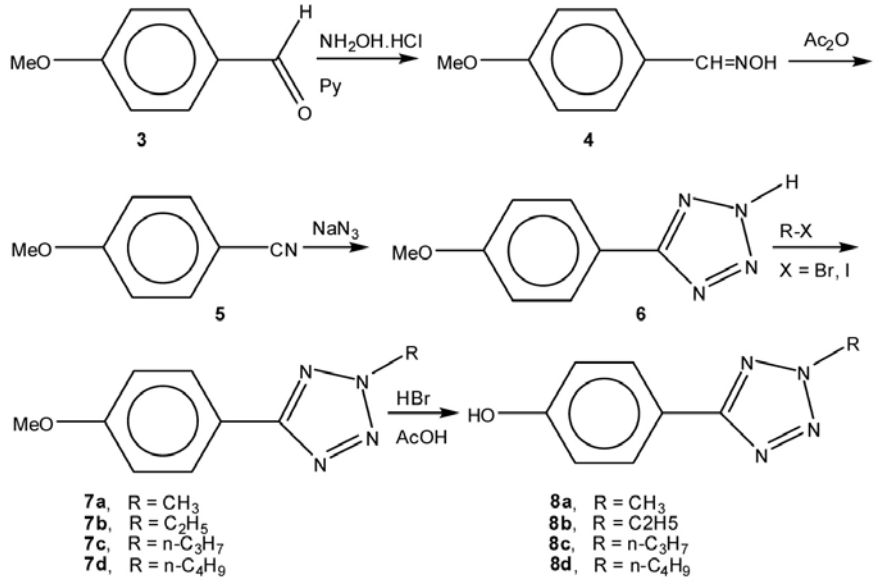
Encouraged by the intense recent research activity in the tetrazole field and in pursuit of our continuing interest in isoxazole chemistry[9] we envisioned the combination of these attractive functional groups by the synthesis of various 2-alkyl-5-{4-[(3-alkylisoxazol-5-yl)methoxy]

phenyl}-2*H*-tetrazoles **10**. Other variations of the isoxazoline ring were synthesized with the intent of discovering analogues being more stable towards hydrolysis but with comparable activity. To improve activity and decrease the side effects a series of new tetrazole-containing compounds with various functionality were synthesized via modification on the length of side chains of both heterocycles and also by decreasing the length of the ether link connecting the two heterocycles of WIN 61605 (**2**). The biological properties and structure-activity relationship (SAR) of the prepared compounds will be published upon completion.



2. Results and Discussion

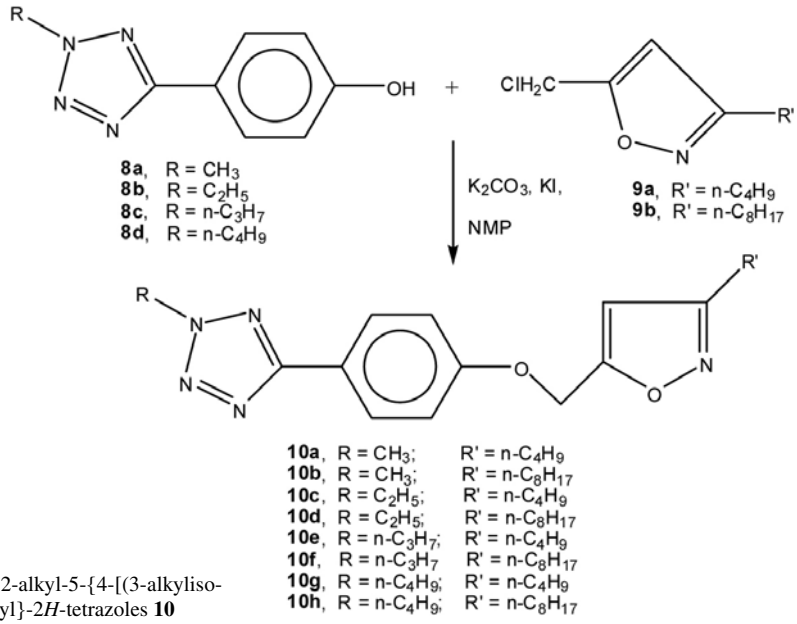
Tetrazoles **8** were synthesized using an efficient process in short reaction time and good yield as outlined in Scheme 1. The requisite nitrile **5** was prepared from aldehyde **3** via oxime formation, followed by dehydration with acetic anhydride. Treatment of nitrile **5** with sodium azide[3g] provided tetrazole **6** in 89% yield.[3i–j] Alkylation of **6** with alkyl halide and potassium carbonate in acetonitrile gave a mixture of 1- and 2-substituted tetrazoles **7** in a ratio of approximately 65 : 35 (R = Me), 82 : 18 (R = Et), 87 : 13 (R = *n*-Pr), 88 : 12 (R = *n*-Bu), which shows that C-5 aryl substituents tend to favor N(2)-alkylation.[15] The position of alkylation was also influenced by the steric requirement of the alkylating agent, as alkyl group gets bulkier, N(2) alkylation increases. When ethyl group is substituted at N(1) position of tetrazole it forces aromatic protons adjacent to the tetrazole ring to the diamagnetic region of the heterocyclic ring current and hence chemical shift becomes lower, this being a diagnostic criterion for characterization of the two isomers. Furthermore, besides the anisotropy, electron-donating resonance effect of the



Scheme 1. Synthesis of 4-(2-alkyl-2*H*-tetrazol-5-yl)phenols **8a–d**

tetrazole ring in N(2) alkyl isomer can contribute to the downfield shifts, which are not possible or at least greatly diminished in the N(1) alkyl isomer. The chemical shifts of the N(1) and N(2) isomers become δ 7.58 and δ 7.99 with J = 6.69 Hz and 7.10 Hz, respectively. Tetrazole **8** was prepared[16] from **7** by selective deprotection of the methoxy group by HBr-AcOH.[17] It must be mentioned that under the deprotection condition N(1) dealkylation also occurred while N(2) alkyl group resisted (Scheme 1).

3-Alkyl-5-(chloromethyl)isoxazoles **9** were prepared[9f,9h] by the reaction of corresponding (3-alkylisoxazol-5-yl)methanols[9f,9h,12–14] with thionyl chloride.[18] Treatment of the 3-alkyl-5-(chloromethyl)isoxazoles **9a**,**b** with the 4-(2-alkyl-2-*H*-tetrazol-5-yl)phenols **8a**–**d** provided compounds **10a**–**h**, which we previously reported[9g] their electrochemical behavior in dimethylformamide (Scheme 2).



Scheme 2. Synthesis of 2-alkyl-5-{4-[(3-alkylisoxazol-5-yl)methoxy]phenyl}-2*H*-tetrazoles **10**

3. Experimental

Melting points were determined with an Electrothermal 9100 apparatus and are uncorrected. ^{1}H NMR, and ^{13}C NMR spectra were acquired on a Bruker AC-80, a General ElectricQE-300, or a Bruker FTNMR (400 MHz) spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm values relative to TMS as an internal standard. IR spectra were run on a Shimadzu IR-408 and Mattson FTIR spectrophotometer. Mass spectra were taken with a Finnigan-MAT 8400 at 70eV. Elemental analyses were performed by Heareus CHN-O-RAPID analyzer. The solvents DMF, CH_3CN and *N*-methylpyrrolidine (NMP) were dried over molecular sieves.

5-(4-Methoxyphenyl)-2-methyl-2*H*-tetrazole (7a).[15]

A solution of 4-methoxybenzaldehyde (9.1 mL, 0.082 mol), hydroxylamine hydrochloride (25.25 g, 0.365 mol), and pyridine (25 mL, 0.310 mol) was heated to reflux for 2 h, and then concentrated to dryness. The reaction mixture was dissoled in water and the aqueous layer was extracted with EtOAc. The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. Recrystallization of solid residue from EtOAc and petroleum ether afforded (8.93 g, 80%) oxime **4**, mp 60 °C. IR (KBr, cm^{-1}) ν_{max} 3200–3500 (OH), 1610, 1570, 1520, 960; ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H, OCH_3), 6.73 (d, ^3J = 8.82 Hz, 2H, Ar-*H*), 7.37 (d, ^3J = 8.87 Hz, 2H, Ar-*H*), 7.97 (s, 1H), 9.0 (s, 1H). A solution of oxime **4** (14.00 g, 0.987 mol) in acetic anhydride (300 mL) was refluxed for 20 h. The solution was concentrated to dryness and the resiue was partitioned between H_2O and EtOAc. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo*, leaving a dark solid. Recrystallization from ether and petroleum ether afforded nitrile **5** as a white solid (12 g, 86%), mp 59 °C; IR (KBr, cm^{-1}) ν_{max} 3025 (Ar-H), 2955, 2200 (CN), 1600, 1505, 1300, 1255, 1170, 1020, 825; ^{1}H NMR ($CDCl_3$) δ 4.02 (s, 3H, OCH_3), 7.10 (d, ^3J = 9.02 Hz, 2H, Ar-*H*), 7.74 (d, ^3J = 8.86 Hz, 2H, Ar-*H*). To a solution of nitrile **5** (6.00 g, 0.451 mol) in DMF (45 mL) under argon was added NaN_3 (3.00 g, 0.0463 mmol) and NH_4Cl (0.60 g, 0.113 mol). The mixture was shielded in a fume hood heated to ca. 110 °C for 48 h. The cooled solution was poured into H_2O (150 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The aqueous solution was chilled in ice and acidified carefully dropwise with 6 N HCl. The white solid residue was collected and dried. Recrystallization from CH_3CN afforded 5-(4-methoxyphenyl)tetrazole **6** (7.00 g, 88%), mp 229.7 °C (lit.[3d,g] mp 227–228 °C) (lit.[3h] mp 238–239 °C). IR (KBr, cm^{-1}) ν_{max} 3130 (N-H), 2700, 1612 (C=N), 1400, 1050, 750; ^{1}H NMR (DMSO-

d_6) δ 3.73 (s, 3H, OCH_3), 3.90 (s, 1H), 7.02 (d, ^3J = 8.93 Hz, 2H, Ar-*H*), 7.86 (d, ^3J = 9.03 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.43, 114.82, 116.25, 128.65, 154.58, 161.44. A suspension of tetrazole **6** (1.76 g, 10 mmol), milled K_2CO_3 (1.58 g, 11.5 mmol), and methyl iodide (0.7 mL, 1.14 mmol) in CH_3CN (28 mL) was refluxed for 1 h, then stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc and H_2O. The organic layer was washed with H_2O, dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the resulting yellow oil was subjected to column chromatography (Silica Gel 100, CH_2Cl_2, R_f = 0.2) to give **7a**[15] as a pale yellow solid (1.10 g, 58%), mp 86 °C (lit.[15a] mp 86.5–87.5 °C, lit.[15b] mp 85–86 °C); IR (KBr, cm^{-1}) ν_{max} 3009, 2950, 1605 (C=N ring stretch), 1580 (C=C), 1540, 1400, 1246, 1170, 1100, 1020, 835, 755, 715; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H, OCH_3), 4.27 (s, 3H, N-CH_3), 6.92 (d, ^3J = 8.92 Hz, 2H, *meta*-H with respect to tetrazole ring), 7.99 (d, $^3J_{o\text{-}m}$ = 8.89 Hz, 2H, *ortho*-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.33, 55.43, 114.78, 116.21, 128.64, 155.07, 161.41; MS (EI, 70 eV) *m/z* (rel. int.) 190.2 (M^+), 162 (100, $M^+ - N_2$), 161 (45), 152 (65), 147 (10), 139 (21), 134 (67), 43 (35). Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.69; H, 5.24; N, 29.38.

2-Ethyl-5-(4-methoxyphenyl)-2*H*-tetrazole (7b).

The same procedure as described for compound **7a**, from tetrazole **6** and ethyl iodide to afford **7b** as a pale yellow solid (1.40 g, 68%), mp 63 °C; IR (KBr, cm^{-1}) ν_{max} 3010 (Ar-H), 2955, 1605 (C=N ring stretch), 1540, 1340, 1244, 1100, 1020, 835, 760, 675; ^{1}H NMR ($CDCl_3$) δ 1.60 (t, J = 7.31 Hz, 3H, N-CH_2CH_3), 3.75 (s, 3H, OCH_3), 4.55 (q, J = 7.4 Hz, 2H, N-CH_2CH$_3$), 6.98 (d, ^3J = 8.1 Hz, 2H, Ar-*H*), 7.99 (d, ^3J = 8.1 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.38, 48.12, 55.48, 114.85, 116.42, 128.68, 154.67, 161.43; MS (EI, 70 eV) *m/z* (rel. int.) 204.2 (M^+), 176 (100, $M^+ - N_2$), 152 (15), 148 (55), 139 (25), 57 (40). Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.67; H, 5.85; N, 27.36.

5-(4-Methoxyphenyl)-2-(*n*-propyl)-2*H*-tetrazole (7c).

The same procedure as described for compound **7a**, from tetrazole **6** and *n*-propyl iodide to afford **7c** as yellow viscose oil (1.25 g, 58%); IR (neat, cm^{-1}) ν_{max} 3007 (Ar-H), 2950, 2870, 1605 (C=N ring stretch), 1580 (C=C), 1540, 1450, 1380, 1300, 1245, 1100, 990, 840, 760; ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 7.13 Hz, 3H), 1.90 (m, 2H, N-CH_2CH_2CH$_3$), 3.60 (s, 3H, OCH_3), 4.40 (t, J = 6.99 Hz, 2H, N-CH_2CH$_2$CH$_3$), 6.85 (d, ^3J = 6.87 Hz, 2H, Ar-*H*), 7.95 (d, ^3J = 6.82 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.98, 22.88, 54.70, 55.49, 114.83, 116.44, 128.66, 154.62, 161.45; MS (EI, 70 eV) *m/z* (rel. int.) 218.2 (M^+), 190 (100, $M^+ - N_2$), 162 (55), 152 (30), 69 (22), 43 (18). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.48; H, 6.44; N, 25.71.

2-(*n*-Butyl)-5-(4-methoxyphenyl)-2*H*-tetrazole (7d).

The same procedure as described for compound **7a,** from tetrazole **6** and *n*-butyl iodide to afford **7d** as yellow viscose oil (1.23 g, 53%); IR (neat, cm^{-1}) ν_{max} 3008 (Ar-H), 2950, 2870, 1605 (C=N ring stretch), 1580 (C=C), 1460, 1300, 1250, 1100, 995, 835; ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 7.2 Hz, 3H), 1.15 (m, 2H), 1.88 (m, 2H), 3.62 (s, 3H, OCH_3), 4.45 (t, J = 7.22 Hz, 2H, N-CH_2CH$_2$CH$_2$CH$_3$), 6.85 (d, ^3J = 7.88 Hz, 2H, Ar-*H*), 7.95 (d, ^3J = 7.95 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.12, 19.64, 33.34, 52.89, 55.49, 114.85, 116.43, 128.67, 154.65, 161.45; MS (EI, 70 eV) *m/z* (rel. int.) 232.3 (M^+), 204 (100, $M^+ - N_2$), 176 (50), 139 (40), 99 (43), 71 (15). Anal. Calcd for $C_{12}H_{16}N_4O$: C, 62.05; H, 6.94; N, 24.13. Found: C, 62.08; H, 6.98; N, 24.11.

5-(4-Hydroxyphenyl)-2-methyltetrazole (8a).

A solution of **7a**, (1.00 g, 0.526 mol), HBr (5 mL), and AcOH (0.5 mL) was refluxed[17] for 5 h then the reaction mixture was cautiously poured into ice-water and the resulted white precipitate was collected and recrystallized from EtOH to afford **8a** as a white solid (0.85 g, 92%), mp 110 °C; IR (KBr, cm^{-1}) ν_{max} 3140 (OH), 3008 (Ar-H), 2950, 1605 (C=N ring stretch), 1540, 1460, 1370, 1270, 1230, 1165, 1050, 840, 720; ^{1}H NMR (DMSO-d_6) δ 4.40 (s, 3H, N-CH_3), 6.94 (d, ^3J = 8.0 Hz, 2H, Ar-*H*), 7.90 (d, ^3J = 8.0 Hz, 2H, Ar-*H*), 9.97 (s, 1H, Ar-O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.35, 114.65, 116.21, 128.84, 154.77, 160.21; MS (EI, 70 eV) *m/z* (rel. int.) 176.2 (M^+), 148 (100, $M^+ - N_2$), 147 (43), 138 (25), 119 (75.8), 118 (38). Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.69; H, 4.48; N, 31.57.

2-Ethyl-5-(4-hydroxyphenyl)tetrazole (8b).

The same procedure as described for compound **8a**, to give **8b** as pure white solid (0.79 g, 69%), mp 160 °C; IR (KBr, cm^{-1}) ν_{max} 3145 (OH), 3007 (Ar-H), 2950, 1605 (C=N ring stretch), 1590 (C=C), 1455, 1375, 1270, 1170, 835, 760; ^{1}H NMR (DMSO-d_6) δ 1.74 (t, J = 7.31 Hz, 3H, N-CH_2CH_3), 4.88 (q, J = 7.52 Hz, 2H, N-CH_2CH$_3$), 7.05 (d, ^3J = 6.84 Hz, 2H, Ar-*H*), 8.03 (d, ^3J = 6.76 Hz, 2H, Ar-*H*), 10.15 (s, 1H, Ar-O*H*);. ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.38, 48.12, 114.64, 116.25, 128.82, 154.66, 160.21; MS (EI, 70 eV) *m/z* (rel. int.) 190.2 (M^+), 162 (100, $M^+ - N_2$), 161 (46), 138 (25), 134 (72), 77 (52). Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.80; H, 5.26; N, 29.40.

5-(4-Hydroxyphenyl)-2-propyltetrazole (8c).

The same procedure as described for compound **8a**, to give **8c** as pure white solid (0.69 g, 53%), mp 142 °C; IR (KBr, cm^{-1}) ν_{max} 3150 (OH), 3010 (Ar-H), 2955, 1605 (C=N ring stretch), 1590 (C=C), 1540, 1450, 1378, 1270, 1230, 1160, 1100, 1040, 900, 835, 760; ^{1}H NMR (DMSO-d_6) δ 0.80 (t, J = 6.50 Hz, 3H, N-$CH_2CH_2CH_3$), 1.85 (m, 2H, N-CH_2CH_2CH$_3$), 4.55 (t, J = 6.91 Hz, 2H, N-

$CH_2CH_2CH_3$), 6.88 (d, ^3J = 8.05 Hz, 2H, Ar-*H*), 7.85 (d, ^3J = 8.05 Hz, 2H, Ar-*H*), 9.90 (s, 1H, Ar-O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.08, 23.15, 55.47, 114.64, 116.25, 128.82, 154.66, 160.21; MS (EI, 70 eV) *m/z* (rel. int.) 204.23 (M^+), 176 (100, $M^+ - N_2$), 175 (40), 148 (74), 138 (25), 43 (26). Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.97; H, 5.90; N, 27.39.

2-(*n*-Butyl-5-(4-hydroxyphenyl)tetrazole (8d).

The same procedure as described for compound **8a**, to give **8d** as pure white solid (0.72 g, 58%), mp 89 °C; IR (KBr, cm^{-1}) ν_{max} 3150 (OH), 3010 (Ar-H), 2954, 1605 (C=N), 1590 (C=C), 1450, 1380, 1280, 1230, 1170, 1045, 835, 760; ^{1}H NMR (DMSO-d_6) δ 0.90 (t, J = 6.51 Hz, 3H, N-$CH_2CH_2CH_2CH_3$), 1.30 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 1.95 (m, 2H, N-$CH_2CH_2CH_2CH_3$), 4.60 (t, J = 7.13 Hz, 2H, N-$CH_2CH_2CH_2CH_3$), 6.10 (s, 1H), 6.90 (d, ^3J = 7.89 Hz, 2H, Ar-*H*), 7.95 (d, ^3J = 7.76 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.12, 19.74, 31.34, 52.89, 114.65, 116.21, 128.81, 154.76, 160.22. MS (EI, 70 eV) *m/z* (rel. int.) 218.26 (M^+), 190 (100, $M^+ - N_2$), 189 (38), 162 (72), 125 (21). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.50; H, 6.41; N, 25.76.

3-(*n*-Butyl)-5-(chloromethyl)isoxazole (9a).[9f,9h]

A solution of 3-(1-butyl)-isoxazol-5-ylmethanol[9f,12–15] (1.0 g, 0.645 mol), cold thionyl chloride[16] (4.68 mL, 0.645 mmol) was stirred at 0 °C overnight, the reaction mixture was concentrated and partitioned between H_2O and Et_2O. The ethereal extracts were combined and washed with $NaHCO_3$ (5%), dried over Na_2SO_4 and concentrated to dryness. The crude product was purified on column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.56) to give **9a** as a yellow oil (0.8 g, 70%); IR (neat, cm^{-1}) ν_{max} 3150, 2950, 1717, 1600 (C=N ring stretch), 1469, 1420 (N-O ring stretch), 1375, 1275, 1000, 920, 870, 715; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.20 Hz, 3H), 1.22 (m, 2H), 1.45 (m, 2H), 2.60 (t, J = 7.21 Hz, 2H), 4.55 (s, 2H, CH_2Cl), 6.42 (s, 1H, Isox-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.32, 22.71, 26.89, 41.48, 44.95, 102.95, 163.68, 168.26; MS (EI, 70 eV) *m/z* (rel. int.) 173.64 (44, M^+), 138 (100), 137 (21), 124 (45), 68 (24), 56 (82), 43 (20), 41 (65), 28 (33). Anal. Calcd for $C_8H_{12}ClNO$: C, 55.34; H, 6.97; N, 8.07. Found: C, 55.50; H, 6.84; N, 8.10.

5-Chloromethyl-3-(*n*-octyl)isoxazole (9b).

The same procedure as described for compound **9a**, from 3-(1-octyl)-isoxazol-5-ylmethanol[9f] to give yellow oil. The crude product was purified on column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.62) to give **9b** as a yellow oil (1.07g, 72%): IR (neat, cm^{-1}) ν_{max} 3100, 2926, 1716, 1608 (C=N ring stretch), 1422 (N-O ring stretch), 1273, 715; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.11 Hz, 3H), 1.50 (m, 12H), 2.80 (t, J = 7.11 Hz, 2H), 4.60 (s, 2H, CH_2Cl), 6.43 (s, 1H, Isox-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.66, 13.98, 22.50, 23.43, 27.64, 28.72, 31.67, 42.48, 44.45, 102.93, 163.78, 168.36; MS (EI, 70 eV) *m/z* (rel. int.) 229.75 (34, M^+), 194 (100), 193 (33), 137 (32), 124 (42), 111 (22), 68 (33), 56 (41), 43 (66), 41 (72), 28 (27). Anal. Calcd for $C_{12}H_{20}ClNO$: C, 62.73; H, 8.77; N, 6.10. Found: C, 63.01; H, 8.84; N, 6.06.

5-{4-[(3-Butyl-5-isoxazolyl)methoxy]phenyl}-2-methyl-2*H*-tetrazole (10a).

A mixture of **8a** (0.2 g, 114 mmol), milled K_2CO_3 (0.3 g, 2.17 mmol), KI (0.1 g, 0.6 mmol), **9a** (0.25g, 1.4 mmol) and *N*-methylpyrrolidinone (10 mL) was magnetically stirred at 60 °C for 24 h. The cooled reaction mixture was concentrated and partitioned between H_2O and Et_2O. The combined ethereal extracts were washed with $NaHCO_3$ (5%), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified on column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.1) to give pure **10a** as a white solid (0.3 g, 86%), mp 88 °C. IR (KBr, cm^{-1}) ν_{max} 3005 (Ar-H), 2950, 1605 (C=N ring stretch), 1580 (C=C), 1540, 1450, 1420 (N-O ring stretch), 1360, 1300, 1230, 1170, 1020; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 6.46 Hz, 3H), 1.75 (m, 4H), 2.89 (t, J = 6.45 Hz, 2H), 4.53 (s, 3H, N-CH_3), 5.35 (s, 2H, CH_2O), 6.37 (s, 1H, Isox-*H*), 7.22 (d, ^3J = 8.9 Hz, 2H, Ar-*H*), 8.25 (d, ^3J = 8.8 Hz, 2H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.48, 22.45, 26.89, 30.03, 40.33, 61.42, 102.65, 114.78, 122.12, 123.75, 128.72, 158.64, 164.78, 167.06; MS (EI, 70 eV) *m/z* (rel. int.) 313.6 (M^+), 285 (100), 258 (44), 147 (80), 146 (68), 91 (25), 65 (12), 43 (25). Anal. Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.50; H, 6.04; N, 22.10.

2-Methyl-5-{4-[(3-octyl-5-isoxazolyl)methoxy]phenyl}-2*H*-tetrazole (10b).

The same procedure as described for compound **10a** to give **10b** after column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.14) as pure white solid (0.35 g, 84%), mp 86 °C; IR (KBr, cm^{-1}) ν_{max} 3005 (Ar-H), 2950, 1605 (C=N ring stretch), 1580 (C=C), 1540, 1470, 1450, 1420 (N-O ring stretch), 1375, 1230, 1170, 1030; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.49 Hz, 3H), 1.20 (m, 10H), 1.57 (m, 2H), 2.55 (t, J = 7.51 Hz, 2H), 4.30 (s, 3H, N-CH_3), 5.11 (s, 2H, CH_2O), 6.12 (s, 1H, Isox-*H*), 6.98 (d, ^3J = 9.00 Hz, 2H, Ar-*H*), 8.01 (d, ^3J = 8.8 Hz, 2H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.66, 22.70, 25.23, 27.12, 27.64, 31.67, 40.48, 61.23, 102.95, 120.24, 124.88, 128.74, 158.57, 163.78, 168.35; MS (EI, 70 eV) *m/z* (rel. int.) 369.46 (M^+), 341 (100, $M^+ - N_2$), 340 (51), 313 (67), 195 (10), 180 (22), 137 (23), 147 (72), 57 (41). Anal. Calcd for $C_{20}H_{27}N_5O_2$: C, 65.02; H, 7.37; N, 18.96. Found: C, 65.21; H, 7.32; N, 19.28.

5-{4-[(3-Butyl-5-isoxazolyl)methoxy]phenyl}-2-ethyl-2*H*-tetrazole (10c).

The same procedure as described for compound **10a** to give pure **10c** after column chromatography (Silica Gel

100, EtOAc-petroleum ether 1:10, R_f = 0.13) as a white solid (0.3 g, 87%), mp 73 °C. IR (KBr, cm^{-1}) ν_{max} 3005 (Ar-H), 2950, 1605 (C=N ring stretch), 1580 (C=C), 1460, 1423 (N-O ring stretch), 1360, 1230; ^{1}H NMR ($CDCl_3$) δ 0.8 (t, J = 6.99 Hz, 3H), 1.41 (m, 7H), 2.50 (t, J = 7.01 Hz, 2H), 4.54 (q, J = 7.00 Hz, 2H, N-CH_2CH$_3$), 5.04 (s, 2H, CH_2O), 6.06 (s, 1H, Isox-*H*), 6.92 (d, ^3J = 8.07 Hz, 2H, Ar-*H*), 7.90 (d, ^3J = 8.34 Hz, 2H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.48, 15.12, 22.45, 26.89, 48.14, 61.52, 102.55, 114.76, 122.18, 123.80, 128.71, 158.62, 164.79, 167.09; MS (EI, 70 eV) *m/z* (rel. int.) 327.38 (M$^+$), 299 (100, M$^+$ - N$_2$), 298 (55), 256 (30), 161 (77), 160 (55), 137 (18), 69 (10). Anal. Calcd for $C_{17}H_{21}N_5O_2$: C, 62.37; H, 6.47; N, 21.39. Found: C, 62.40; H, 6.19; N, 21.30.

2-Ethyl-5-{4-[(3-octyl-5-isoxazolyl)methoxy]phenyl}-2*H*-tetrazole (10d).

The same procedure as described for compound **10a** to give pure **10d** after column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.14) as a white solid (0.35 g, 88%), mp 59 °C; IR (KBr, cm^{-1}) ν_{max} 3005 (Ar-H), 2950, 1605 (C=N ring stretch), 1470, 1420 (N-O ring stretch), 1380, 1230, 1020; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.02 Hz, 3H), 1.14–1.23 (m, 10H), 1.48–1.67 (m, 4H), 2.57 (t, J = 6.98 Hz, 3H, N-CH$_2$CH_3), 4.59 (q, J = 7.02 Hz, 2H, N-CH_2CH$_3$), 5.11 (s, 2H, CH_2O), 6.08 (s, 1H, Isox-*H*), 7.96 (d, ^3J = 6.88 Hz, 2H, Ar-*H*), 7.98 (d, ^3J = 8.93 Hz, 2H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.66, 22.70, 25.23, 26.98, 27.64, 31.67, 39.42, 61.39, 102.95, 120.24, 124.88, 128.74, 158.57, 163.78, 168.35; MS (EI, 70 eV) *m/z* (rel. int.) 383.48 (M$^+$), 355 (100, M$^+$ – N$_2$), 354 (60), 161 (78), 137(12), 124 (21), 57 (32). Anal. Calcd for $C_{21}H_{29}N_5O_2$: C, 65.77; H, 7.62; N, 18.26. Found: C, 65.70; H, 7.60; N, 18.11.

5-{4-[(3-Butyl-5-isoxazolyl)methoxy]phenyl}-2-propyl-2*H*-tetrazole (10e).

The same procedure as described for compound **10a** to give pure **10e** after column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.12) as a white solid (0.3 g, 90%), mp 54 °C; IR (KBr, cm^{-1}) ν_{max} 3005 (Ar-H), 2950, 1605 (C=N ring stretch), 1570 (C=C), 1540, 1460, 1420 (N-O ring stretch), 1380, 1250, 1160, 1100, 1055; ^{1}H NMR ($CDCl_3$) δ 0.81 (m, 7H), 1.34 (m, 3H), 1.95 (q, J = 7.01 Hz, 2H), 2.53 (t, J = 6.99 Hz, 2H), 4.45 (t, J = 6.99 Hz, 2H, N-CH_2C), 5.04 (s, 2H, CH_2O), 6.05 (s, 1H, Isox-*H*), 6.91 (d, ^3J = 8.88 Hz, 2H, Ar-*H*), 7.96 (d, ^3J = 8.86 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.96, 12.48, 14.58, 21.61, 22.88, 29.51, 54.71, 61.55, 102.65, 114.36, 122.58, 128.51, 158.62, 164.49, 167.19; MS (EI, 70 eV) *m/z* (rel. int.) 342 (M + 1), 313 (100, M$^+$ – N$_2$), 285 (36), 176 (69), 175 (52), 137 (24), 68 (28). Anal. Calcd for $C_{18}H_{23}N_5O_2$: C, 63.31; H, 6.79; N, 20.52. Found: C, 63.60; H, 6.70; N, 20.59.

5-{4-[(3-Octyl-5-isoxazolyl)methoxy]phenyl}-2-propyl-2*H*-tetrazole (10f).

The same procedure as described for compound **10a** to give pure **10f** after column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.15) as a white solid (0.32 g, 82%), mp 64 °C; IR (KBr, cm^{-1}) ν_{max} 3005 (Ar-H), 2950, 1605 (C=N), 1580 (C=C), 1540, 1460, 1420 (N-O ring stretch), 1390, 1300, 1250. ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 6.95 Hz, 3H), 0.98 (t, J = 7.00 Hz, 3H), 1.07 (m, 12H), 1.89 (m, 2H), 2.46 (t, J = 7.06 Hz, 2H), 4.39 (t, J = 7.69 Hz, 2H, N-CH_2C), 4.96 (s, 2H, CH_2O), 6.00 (s, 1H, Isox-*H*), 6.86 (d, ^3J = 8.91 Hz, 2H, Ar-*H*), 7.90 (d, ^3J = 8.85 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.05, 10.96, 13.66, 19.70, 21.79, 22.82, 25.23, 27.52, 29.64, 39.27, 54.70, 61.33, 102.65, 122.24, 124.88, 128.64, 158.77, 163.98, 168.35; MS (EI, 70 eV) *m/z* (rel. int.) 397.52 (M$^+$), 370 (100, M$^+$ – N$_2$), 341 (34), 195 (12), 180 (17), 176 (75), 175 (44), 90 (10), 71 (24), 43 (52). Anal. Calcd for $C_{22}H_{31}N_5O_2$: C, 66.46; H, 7.86; N, 17.63. Found: C, 66.49; H, 7.80; N, 17.50.

2-Butyl-5-{4-[(3-butyl-5-isoxazolyl)methoxy]phenyl}-2*H*-tetrazole (10g).

The same procedure as described for compound **10a** to give pure **10g** after column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.14) as a white solid (0.3 g, 92%), mp 64 °C; IR (KBr, cm^{-1}) ν_{max} 3005 (Ar-H), 2950, 1605 (C=N ring stretch), 1580 (C=C), 1540, 1460, 1424 (N-O ring stretch), 1390, 1250; ^{1}H NMR ($CDCl_3$) δ 0.79 (m, 6H), 1.17 (m, 6H), 1.90 (m, 2H), 2.45 (t, J = 7.50 Hz, 2H), 4.45 (t, J = 6.97 Hz, 2H, N-CH_2C), 5.00 (s, 2H, CH_2O), 6.02 (s, 1H, Isox-*H*), 6.88 (d, ^3J = 8.93 Hz, 2H, Ar-*H*), 7.92 (d, ^3J = 8.89 Hz, 2H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.48, 13.30, 15.12, 19.61, 21.65, 29.39, 31.22, 52.84, 61.52, 102.56, 114.76, 122.38, 123.80, 128.71, 158.62, 163.79, 167.04; MS (EI, 70 eV) *m/z* (rel. int.) 355.43 (M$^+$), 327 (100, M$^+$ – N$_2$), 326 (43), 191 (73), 69 (11), 57 (25), 43 (42), 28 (34). Anal. Calcd for $C_{19}H_{25}N_5O_2$: C, 64.19; H, 7.09; N, 19.71. Found: C, 64.50; H, 7.11; N, 20.09.

2-Butyl-5-{4-[(3-octyl-5-isoxazolyl)methoxy]phenyl}-2*H*-tetrazole (10h).

The same procedure as described for compound **10a** to give pure **10h** after column chromatography (Silica Gel 100, EtOAc-petroleum ether 1:10, R_f = 0.16) as a white solid (0.33 g, 88%), mp 70 °C; IR (KBr, cm^{-1}) ν_{max} 3005 (Ar-H), 2950, 1605 (C=N ring stretch), 1580 (C=C), 1540, 1460, 1390, 1300, 1255; ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6H), 1.19 (m, 12H), 1.49 (m, 2H), 2.01 (m, 2H), 2.58 (t, J = 6.96 Hz, 2H), 4.54 (t, J = 6.99 Hz, 2H, N-CH_2C), 5.09 (s, 2H, CH_2O), 6.11 (s, 1H, Isox-*H*), 6.97 (d, ^3J = 8.34 Hz, 2H, Ar-*H*), 8.01 (d, ^3J = 8.69 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.15, 12.26, 13.46, 19.68, 21.79, 23.62, 25.23, 27.52, 29.64, 31.24, 39.27, 52.80, 61.33, 102.65, 122.24, 124.88, 128.64, 158.77, 163.88,

168.45; MS (EI, 70 eV) *m/z* (rel. int.) 411.44 (M^+), 383 (100, $M^+ - N_2$), 328 (29), 191 (70), 68 (11), 57 (22), 28 (32). Anal. Calcd for $C_{23}H_{33}N_5O_2$: C, 67.11; H, 8.09; N, 17.02. Found: C, 67.20; H, 7.89; N, 16.82.

4. Conclusion

In conclusion, we have presented a facile and an efficient route to 2-alkyl-5-[4-(3-alkyl-5-isoxazolyl)methoxyphenyl]-2*H*-tetrazoles **10a–h** which were synthesized from 4-[5(2-alkyl-2*H*-tetrazolyl)]phenols **8** and 3-alkyl-5-chloromethylisoxazole **9** in high yields. 3-Alkyl-5-chloromethylisoxazole **9** was prepared by the reaction of corresponding 3-(1-alkyl)isoxazol-5-ylmethanol with thionyl chloride. 4-[5-(2-Alkyl-2*H*-tetrazolyl)]phenols **8a–d** were synthesized from the corresponding aldehyde **3** in five steps.

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Povzetek

Pripravili in karakterizirali smo več alkil(izoksazolilmetoksifenil)tetrazolov. Alkil-5-(klorometil)izoksazole **9** smo pripravili z reakcijo med ustreznimi (3-alkilizoksazol-5-il)metanoli z uporabo tionil klorida. 4-(2-Alkyl-2*H*-tetrazol-5-il)]fenole **8** smo v petih stopnjah pripravili iz ustreznih aldehidov **3**. Dobljene produkte **8** smo nato reagirali z alkil-5-(klorometil)izoksazoli **9** pri čemer so z visokimi izkoristki nastali ustrezni 2-alkil-5-{4-[(3-alkilizoksazol-5-il)metoksi]fenil}-2*H*-tetrazoli **10a**–**h**.