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Synthesis and Characterization of 2-Alkyl -5-{4-[(3-nitrophenyl-5-isoxazolyl)methoxy]phenyl}-2*H*-tetrazoles

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Dedicated to Prof. Dr. J. M. Shreeve for her great contribution to chemistry

Heteroaryl substituted analogs of antirhnoviral (**A**), was prepared by a convergent approach. 3-Nitrophenyl-5-bromooromethylisoxazoles **5a-b** were synthesized by [3+2] cycloaddition of 3-(benzoyloxy)-propyne **2** to *in situ* generated arylnitrile oxides followed by deprotection of cycloadducts **3a-b** and bromination of the resulting alcohols **4a-b**. Coupling of 3-nitrophenyl-5-bromooromethylisoxazoles (**5a-b**) with 4-[5-(2-alkyl-2*H*-tetrazolyl)]phenols (**6a-d**) in *N*-methylpyrrolidinone under mild conditions afforded a new series of 2-alkyl-5-{4-[1-(3-nitrophenyl-5-isoxazolyl)methyloxy]phenyl}-2*H*-tetrazoles (**7a-h**) in high yields. The structures of the synthesized compounds were confirmed by their ^{1}H NMR, Mass spectral, and Elemental Analysis data.

Keywords: Isoxazolyl-Tetrazolyl ethers, [3+2] Cycloaddition, Isoxazole, Nitro compounds, Tetrazole

INTRODUCTION

In this study we prepared analogs of antirhnoviral (**A**) where the oxazoline ring was replaced with 2-alkyltetrazoles, and alkylisoxazole with nitrophenylisoxazoles. Isoxazoles functionalized with an additional nitrogen-containing group have had applications in medicinal chemistry [1-7]. They possess interesting medicinal or crop protection properties as well as other industrial utility [1a]. Various pharmacologically important isoxazoles with antibacterial, antiviral, anti-inflammatory, antidiabetic, antifungal, antiparkinson, antihypertensive and antitumor activity have been reported [1b].

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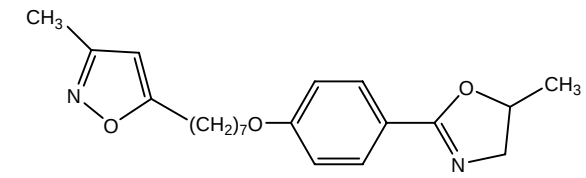
The chemistry of tetrazoles as well as their medicinal applications have been covered in the literature [8,9]. Tetrazoles have attracted considerable attention in recent years [8-16]; they have applications in photography and information recording systems [10], pharmaceutical [11-13] and material sciences and as ligands in coordination chemistry [14]. The most direct method to synthesize tetrazoles is *via* the formal [3+2] cycloaddition [15] of azides and nitriles [16]. Biological activity in tetrazoles is due to the special metabolism of the disubstituted tetrazole system and because tetrazole ring is isosteric with a carboxylic acid group and of comparable acidity [8b,17]. 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, an extensive study of these molecules is ongoing [17].

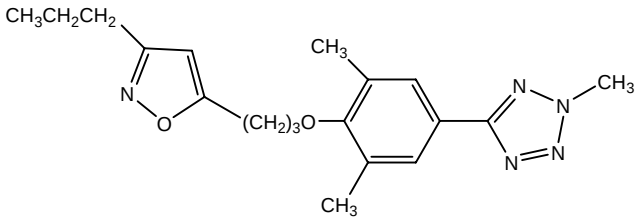
The antipicornaviral activity of compounds related to compound (**A**) (Fig. 1) is well-documented [18]. However, compound (**A**) and the related compounds suffer from having a very short half-life, particularly due to the acid liability of the oxazoline ring. The preparation of several isoxazoles with potential antipicornavirus activity has also been investigated [19,20].

In view of the chemical instability associated with the oxazoline ring of the compound (**A**), we examined the heterocyclic replacements with groups having comparable or enhanced antirhnovirus activity and which were considerably more stable to acid hydrolysis. It was found that one of the most promising replacements for the oxazoline ring is 2-methytetrazole [19].

In pursuit of our continuing interest in isoxazole chemistry [4-6,27] to improve antirhinovirus activity, and increase the possibility of the hydrophobic interactions in the binding site, we prepared a series of analogues of compound (**A**), where oxazoline ring was replaced with 2-alkyltetrazole, 3-methylisoxazole ring was replaced with 3-nitrophenylisoxazole, and the ether linkage between the isoxazole and the phenyl ring was modified. We chose 2-regioisomer of **6** because it was more potent than the corresponding 1-regioisomer [19f]. A second approach modified the electronic and steric environment about the tetrazole moiety, varying substituents in 2-position of the heterocycle, incorporating nitrophenyl-isoxazole moiety as well as decreasing the length of the ether linkage connecting the two heterocycles of WIN 61605 (**B**). Herein, we report the synthesis of tetrazole derivatives **7a-h** with possible antirhinovirus activity.



Disoxaril, (A)



WIN 61605, (B)

Fig. 1

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 70 eV. Elemental analyses were performed by Heareus CHN-O-RAPID analyzer. The solvents DMF, CH_3CN and N-methyl pyrrolidine (NMP) were dried over molecular sieves.

Synthesis of 1-[3-(3-nitrophenyl)isoxazole-5-yl]methyl benzoate (3a). To a suspension of 3-nitrobenzaldehyde (1.52 g, 10 mmol) in a 1:5 mixture of H_2O/EtOH (20 ml) was added hydroxylamine hydrochloride (1.41 g, 20.04 mmol). To this solution was added sodium acetate (4.09 g, 30 mmol), and the mixture was allowed to stir for 1 h at room temperature. The ethanol was then removed by rotary evaporation, and methylene chloride and water were added. The layers were separated, and the aqueous layer was extracted twice more with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Recrystallization of solid residue from EtOAc and petroleum ether afforded 3-nitrobenzaldoxime **1a** (1.58 g, 95%), m.p.: 122 °C, (116-118 °C [20f], 121-123 °C reported for *E-m*-nitrobenzaldoxime [20g]); IR (KBr, cm^{-1}) 3200-3500 (OH stretch), 1615 (C=C, C=N stretch), 1530 (NO_2 stretch), 1520, 1460, 1345 (NO_2 stretch), 1300, 1100, 960, 835 (oop bending stretch), 800, 730, 700; ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 1H), 8.06 (s, 1H), 8.16 (m, 2H), 8.52 (s, 1H), 8.70-9.12 (m, 1H). To a mixture of 3-butyn-1-ol (1.3 ml, 16.9 mmol), Et_3N (3.0 ml,

21.6 mmol) and benzene (5.0 ml) at 0-5 °C was added PhCOCl (3.0 ml, 18 mmol) dropwise. The mixture stirred at room temperature for 2 h, filtration and evaporation gave a residue which was distillated at reduced pressure (12 mmHg, 37 °C) to yield 3-butynyl benzoate **2** as colorless oil (2.42 g, 94%) [20a-d]; IR (neat, cm^{-1}) 3295 (≡C-H), 3100, 2950, 2120, 1720 (C=O), 1600, 1450, 1260, 1100. To an ice-cooled solution of the 3-nitrobenzaldoxime **1a** (1.32 g, 8 mmol) and 3-butynyl benzoate **2** (0.74 g, 10 mmol) in CH_2Cl_2 (12 ml) was added 10% NaOCl (14.00 ml, 19 mmol) dropwise, and the solution was stirred at room temperature for 48 h [7,21a-c]. The mixture was poured into water (100 ml) and extracted with ether. The ethereal extracts were combined and dried over (Na_2SO_4), and concentrated to dryness. The crude product was purified on column chromatography (Silica Gel 100, CH_2Cl_2-petroleum ether 2:3, R_f = 0.30) to give 1-[3-(3-nitrophenyl)isoxazole-5-yl]methyl benzoate **3a** as a yellow solid (1.74 g, 67%), m.p.: 71 °C; IR (KBr, cm^{-1})ν_{max} 3100, 3055, 2950, 2850, 1720 (C=O stretch), 1605 (C=N ring stretch), 1525 (NO_2 stretch), 1445, 1420 (N-O stretch), 1340 (NO_2 stretch), 1265 (C-O stretch), 1170, 1100 (C-O stretch), 800, 700; ^{1}H NMR ($CDCl_3$) δ 5.23 (s, 2H), 6.61 (s, 1H, Isox C4-H), 7.35-7.52 (m, 3H); 7.59 (m, 1H, Ar-H), 7.99-8.02 (m, 2H, Ar-H), 8.18 (m, 2H, Ar-H), 8.57 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 61.9, 103.2, 124.2, 126.8, 128.4, 129.7, 129.8, 133.3, 137.1, 148.7, 161.3, 165.6, 171.6; Anal. Calcd. for ($C_{17}H_{12}N_2O_5$): C, 62.96; H, 3.73; N, 8.64. Found: C, 62.92; H, 3.70; N, 8.61.

1-[3-(4-Nitrophenyl)isoxazole-5-yl]methyl benzoate (3b). The same procedure as described for oxime **1a** from 4-nitrobenzaldehyde to give 4-nitrobenzaldoxime **1b** as yellow crystals (1.60, 96%), m.p.: 130 °C, (128.5-129 °C [20e], 129-130 °C reported for *E*-*p*-nitrobenzaldoxime [20g]); IR (neat, cm^{-1}) 3500-3200 (OH stretch), 1600 (C=C, C=N stretch), 1530 (NO_2 stretch), 1345 (NO_2 stretch), 1100, 840 (oop bending stretch), 745; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H), 8.02 (d, ^3J = 7.99 Hz, 2H, Ar-H), 8.28 (d, ^3J = 7.99 Hz, 2H, Ar-H), 8.54-8.85 (b, var., 1H). To an ice-cooled solution of the 4-nitrobenzaldoxime **1b** (0.99 g, 6 mmol) and 3-butynyl benzoate **2** (0.59 g, 7.5 mmol) in CH_2Cl_2 (10 ml) was added 10% NaOCl (10.0 ml, 14 mmol) dropwise, and the solution was stirred at room temperature for 48 h [7,21a-c]. The mixture was poured into water (100 ml) and extracted with ether. The ethereal extracts were combined and dried over (Na_2SO_4), and concentrated to dryness. The crude product was purified on column chromatography (Silica Gel 100, CH_2Cl_2-petroleum ether 2:3, R_f = 0.32) to give 1-[3-(4-nitrophenyl) isoxazole-5-yl]methyl benzoate **3b** as a yellow solid (1.37 g, 70%), m.p.: 136 °C; IR (KBr, cm^{-1})ν_{max} 3100, 3050, 2950, 2850, 1725 (C=O stretch), 1590 (C=N ring stretch), 1525 (NO_2 stretch), 1445, 1425 (N-O stretch), 1340 (NO_2 stretch), 1305, 1260 (C-O stretch), 1170, 1100 (C-O stretch), 845, 700; ^{1}H NMR ($CDCl_3$) δ 5.16 (s, 2H), 6.57 (s, 1H, Isox C4-H), 7.35-7.52 (m, 3H); 7.56 (m, 1H, Ar-H), 7.95-8.05 (m, 2H), 8.16 (m, 2H, Ar-H), 8.55 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.7, 102.2, 124.2, 127.05, 127.3, 128.6, 129.7, 129.9, 133.2, 137.3, 147.6, 161.3, 165.5, 171.6; Anal. Calcd. for ($C_{17}H_{12}N_2O_5$): C, 62.96; H, 3.73; N, 8.64. Found: C, 62.94; H, 3.72; N, 8.66.

3-(3-Nitrophenyl)-isoxazol-5-ylmethanol (4a). A mixture of compound **3a** (1.50 g, 4.39 mmol), ammonia (5.0 ml), and MeOH (15.00 ml) was refluxed for 80 h. The reaction mixture was concentrated and the residue was partitioned between H_2O and Et_2O. The combined ethereal extracts were dried and concentrated *in vacuo*, the crude product was purified on column chromatography (Silica Gel 100, EtOAc-$CHCl_3$; 4:1, R_f = 0.20) to give **4a** as a yellow solid (0.73 g, 75%), m.p.: 118 °C; IR (KBr, cm^{-1})ν_{max} 3500-3200 (OH stretch), 3150 (ArC-H stretch), 2954 (CH stretch), 2850 (CH stretch), 1605 (C=N ring stretch), 1570, 1525 (NO_2 stretch), 1495, 1470, 1420 (N-O stretch), 1340 (NO_2 stretch), 1030 (C-O stretch), 895, 760, 690; ^{1}H NMR ($CDCl_3$) δ 2.08 (br, s, 1H), 4.83 (s, 2H), 6.60 (s, 1H, Isox C4-H), 7.58 (m, 1H, Ar-H), 8.18 (m, 2H, Ar-H), 8.58 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.8, 100.1, 124.2, 126.9, 135.2, 148.7, 161.4, 171.7; MS *m/z* (rel. int.) 220.04 (M^+, 100), 202 (8), 177 (26), 191 (56), 174 (42), 123 (44), 78 (14), 93 (8), 77 (81), 69 (12), 68 (14), 67 (27), 65 (7), 59 (65), 43 (64), 41 (23), 26; Anal. Calcd. for ($C_{10}H_8N_2O_4$): C, 54.55; H, 3.66; N, 12.72. Found: C, 55.44; H, 3.61; N, 12.65.

3-(4-Nitrophenyl)-isoxazol-5-ylmethanol (4b). The same procedure as described for compound **4a** from 3-(4-nitrophenyl)-5-[5-(phenyl carboxylate)]isoxazole **3b** to give **4b** after column chromatography (Silica Gel 100, EtOAc-$CHCl_3$; 4:1, R_f = 0.22) as yellow solid (0.74 g, 68%), m.p.: 120 °C; IR (KBr, cm^{-1})ν_{max} 3600-3300 (OH stretch), 3100 (ArC-H stretch), 2950 (CH_2 stretch), 2850 (CH_2 stretch), 1610 (C=N

ring stretch), 1510 (NO_2 stretch), 1465, 1340 (NO_2 stretch), 1107, 830, 758; ^{1}H NMR ($CDCl_3$) δ 2.30 (bs, 1H), 5.07 (s, 2H), 6.85 (s, 1H, Isox-C4H), 8.18 (d, ^3J = 7.99 Hz, 2H, Ar-H), 8.53 (d, ^3J = 7.99 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.7, 101.03, 124.4, 127.07, 135.41, 148.9, 161.35, 171.64; MS *m/z* (rel. int.) 220.05 (M^+, 100), 202 (27), 191 (44), 190 (8), 177 (38), 174 (33), 123 (42), 96 (23), 93 (10), 78 (12), 77 (75), 69 (18), 68 (16), 67 (37), 65 (4), 59 (55), 43 (74), 41 (22), 26; Anal. Calcd. for ($C_{10}H_8N_2O_4$): C, 54.55; H, 3.66; N, 12.72. Found: C, 55.64; H, 3.56; N, 12.60.

5-Bromomethyl-3-(3-nitrophenyl)-isoxazole (5a). To a stirred solution of 4a (1.50 g, 6.8 mmol) in $CHCl_3$ (35.0 ml) was added dropwise PBr_3 (11.0 ml, 11.46 mmol) at -10 °C. Stirring was continued for 16 h at room temperature. The reaction mixture was concentrated and partitioned between 5% $NaHCO_3$ (100 ml) and CH_2Cl_2 (3 × 20 ml). The combined CH_2Cl_2 extracts were washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified on column chromatography (Silica Gel 100, EtOAc-$CHCl_3$ 1:5, R_f = 0.7) to give **5a** as a yellow solid (1.20 g, 80%), m.p.: 88 °C (83-85 °C [29]); IR (KBr, cm^{-1})ν_{max} 3150 (ArC-H stretch), 3050 (ArC-H stretch), 2920 (CH_2 stretch), 2820 (CH_2 stretch), 1605 (C=N ring stretch), 1575, 1530 (NO_2 stretch), 1490, 1460 (CH_2 bending), 1420 (N-O stretch), 1345 (NO_2 stretch), 1270 (CH_2Br bending), 1070, 900, 790, 685; ^{1}H NMR ($CDCl_3$) δ 4.60 (s, 2H, -C*H*$_2$Br), 6.67 (s, 1H, Isox-C4H), 7.58 (m, 1H, Ar-H), 8.18 (m, 2H, Ar-H), 8.53 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 100.4, 124.2, 130.2, 136.8, 148.7, 161.4, 171.7; MS *m/z* (rel. int.) 283.88 (M^+, 88), 281.92 (96), 253 (18), 237 (33), 204 (100), 203 (14), 202 (31), 159 (34), 123 (42), 94 (16), 93 (12), 77 (80), 69 (8), 68 (12), 67 (10), 65 (8), 43 (8), 41 (14); Anal. Calcd. for ($C_{10}H_7BrN_2O_3$): C, 42.43; H, 2.49; N, 9.90. Found: C, 42.36; H, 2.60; N, 9.71.

5-Bromomethyl-3-(4-nitrophenyl)-isoxazole (5b). The same procedure as described for compound **5a** to give **5b** after column chromatography (Silica Gel 100, EtOAc-$CHCl_3$ 1:5, R_f = 0.65) as yellow solid (0.84 g, 54.5%), m.p.: 136 °C; IR (KBr, cm^{-1})ν_{max} 3150 (ArC-H stretch), 3050 (ArC-H stretch), 2950 (CH_2 stretch), 2850 (CH_2 stretch), 1610 (C=N ring stretch), 1595, 1510 (NO_2 stretch), 1450 (CH_2 bending), 1421 (N-O stretch), 1340 (NO_2 stretch), 1230, 1100, 850; ^{1}H NMR ($CDCl_3$) δ 4.47 (s, 2H, -C*H*$_2$Br), 6.62 (s, 1H, Isox-C$_4$H), 7.93 (d, J = 6.91 Hz, 2H), 8.40 (d, J = 6.90 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.2, 100.1, 124.2, 131.3, 137.2, 147.7, 161.4, 171.7; MS *m/z* (rel. int.) 283.98 (M^+, 92), 281.92 (98), 253 (12), 237 (15), 204 (100), 203 (10), 202 (34), 159 (30), 123 (44), 94 (8), 93 (9), 77 (78), 69 (9), 65 (12), 43 (12), 41 (9), 28 (9). Anal. Calcd. for ($C_{10}H_7BrN_2O_3$): C, 42.43; H, 2.49; N, 9.90. Found: C, 42.34; H, 2.58; N, 9.82.

2-Methyl-5-{4-[(3-(3-nitrophenyl)-5-isoxazolyl) methoxy]phenyl}-2*H*-tetrazole (7a). A mixture of **6a** (0.20 g, 1.14 mmol) [6,27], milled K_2CO_3 (0.30 g, 2.17 mmol), KI (0.10 g, 0.6 mmol), **5a** (0.40 g, 1.41 mmol) and N-methylpyrrolidinone (10.0 ml) was magnetically stirred at 60 °C for 24 h. The cooled mixture was diluted with H_2O (20 ml) and extracted with EtOAc (3 × 20 ml). The combined EtOAc extracts were washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified on column chromatography (Silica Gel 100, $CHCl_3$-petroleum ether 2:1, R_f = 0.2) to give **7a** as a pure solid (0.37 g, 87%), m.p.: 175 °C; IR (KBr, cm^{-1})ν_{max} 3110 (ArC-H stretch) , 2950, 1610 (C=N ring stretch), 1580, 1530 (NO_2 stretch), 1495, 1455, 1345 (NO_2 stretch), 1290, 1230, 1100, 810; ^{1}H NMR ($CDCl_3$) δ 4.3 (s, 3H, N-C$\underline{H}_3$), 5.3 (s, 2H, C$\underline{H}_2$O), 6.71 (s, 1H, Isox-H), 7.04 (t, J = 6.70 Hz, 2H, Ar-H), 7.58 (m, 1H, Ar-H), 8.08 (m, 4H, Ar-H), 8.54 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 48.34, 81.38, 101.40, 115.11, 121.67, 121.88, 124.76, 128.55, 130.11, 132.52, 159.12, 160.76, 164.62, 169.24; MS *m/z* (rel. int.) 378.12 (M^+, 88), 351 (16), 350 (M^+-N_2, 100), 349 (65), 333 (34), 322 (M^+-2N_2, 35), 138 (22), 123 (45), 93 (9), 77 (82), 69 (20), 68 (24), 67 (12), 65 (8), 44 (19), 43 (55), 41 (23), 26 (17). Anal. Calcd. for ($C_{18}H_{14}N_6O_4$): C, 57.14; H, 3.73; N, 22.21. Found: C, 56.58; H, 3.71; N, 22.13.

2-Ethyl-5-{4-[(3-(3-nitrophenyl)-5-isoxazolyl)methoxy] phenyl}-2*H*-tetrazole (7b). The same procedure as described for compound **7a** to give **7b** after column chromatography (Silica Gel 100, $CHCl_3$-petroleum ether 2:1, R_f = 0.19) as pure yellow solid (0.35 g, 86%), m.p.: 134 °C; IR (KBr, cm^{-1})ν_{max} 3110 (ArC-H stretch), 2950, 1610 (C=N ring stretch), 1580, 1525 (NO_2 stretch), 1495, 1460, 1345 (NO_2 stretch), 1240. ^{1}H NMR ($CDCl_3$) δ 1.61 (t, J = 7.35 Hz, 3H), 4.63 (q, J = 7.35 Hz, 2H), 5.25 (s, 2H, C$\underline{H}_2$O), 6.71 (s, 1H, Isox-H), 7.10 (m, 2H, Ar-H), 7.58 (m, 1H, Ar-H), 8.07 (m, 4H, Ar-H), 8.56 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 39.42, 45.71, 61.38, 101.40, 115.14, 121.89, 124.77, 128.55, 130.11, 132.52, 159.12, 160.76, 164.61, 169.24; MS *m/z* (rel. int.)

392.12 (M^+, 89), 364 (M^+-N_2, 100), 363 (55), 346 (8), 336 (M^+-$2N_2$, 40), 335 (18), 138 (12), 123 (39), 93 (14), 77 (68), 69 (6), 68 (11), 67 (10), 57 (44), 44 (17), 43 (60), 41 (25), 26 (20). Anal. Calcd. for ($C_{19}H_{16}N_6O_4$) C, 58.16; H, 4.11; N, 21.42. Found: C, 58.01; H, 4.14; N, 21.33.

2-Propyl-5-{4-[(3-(3-nitrophenyl)-5-isoxazolyl)methoxy] phenyl}-2*H*-tetrazole (7c). The same procedure as described for compound **7a** to give **7c** after column chromatography (Silica Gel 100, $CHCl_3$-petroleum ether 2:1, R_f = 0.19) as pure yellow solid (0.35 g, 87%), m.p.: 120 °C; IR (KBr, cm^{-1})ν_{max} 3110 (ArC-H stretch), 2950, 1610 (C=N ring stretch), 1575, 1525 (NO_2 stretch), 1495, 1450, 1421 (N-O stretch), 1340 (NO_2 stretch), 1240, 800. ^{1}H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.20 Hz, 3H), 2.03 (sext, 2H), 4.49 (t, *J* = 7.0 Hz, 2H), 6.71 (s, 1H, Isox-H), 7.04 (m, 2H, Ar-H), 7.58 (t, 1H, Ar-H), 8.23 (m, 4H, Ar-H), 8.65 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 10.98, 22.88, 55.71, 61.48, 101.39, 115.11, 121.88, 124.71, 128.56, 130.11, 132.52, 159.11, 160.72, 164.58, 169.64; MS *m/z* (rel. int.) 406.14 (M^+, 94), 378 (M^+-N_2, 100), 377 (68), 360 (15), 350 (M^+-$2N_2$, 27), 338 (19), 337 (39), 138 (15) , 123 (45), 93 (17), 77 (76), 69 (12), 68 (14), 67 (27), 65 (4), 43 (74), 41 (12), 26 (12). Anal. Calcd. for ($C_{20}H_{18}N_6O_4$): C, 59.11; H, 4.46; N, 20.68. Found: C, 58.51; H, 4.42; N, 20.15.

2-*n*-Butyl-5-{4-[(3-(3-nitrophenyl)-5-isoxazolyl) methoxy]phenyl}-2*H*-tetrazole (7d). The same procedure as described for compound **7a** to give **7d** after column chromatography (Silica Gel 100, $CHCl_3$-petroleum ether 2:1, R_f = 0.25) as pure yellow solid (0.30 g, 80%), m.p.: 128 °C; IR (KBr, cm^{-1}); IR (KBr, cm^{-1})ν_{max} 3080 (ArC-H stretch), 2950, 1610 (C=N ring stretch), 1575, 1530 (NO_2 stretch), 1495, 1450, 1420 (N-O stretch), 1345 (NO_2 stretch), 1240; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J* = 6.39 Hz, 3H), 1.27 (m, 2H), 1.94 (m, 2H), 4.57 (t, *J* = 7.05 Hz, 2H), 5.3 (s, 2H), 6.71 (s, 1H, Isox-H), 7.08 (m, 2H, Ar-H), 7.57 (m, 1H, Ar-H), 8.23 (m, *J* = 9.05 Hz, 4H, Ar-H), 8.60 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 10.97, 22.88, 37.00, 54.71, 61.38, 101.49, 115.11, 121.88, 124.76, 128.56, 130.53, 132.52, 159.11, 160.76, 164.58, 169.23; MS (EI, 70 ev) *m/z* (rel. int.) 420.15 (M^+, 92), 392 (M^+-N_2, 100), 391 (59), 364 (M^+-$2N_2$, 22), 337 (43), 138 (12), 123 (34), 93 (12), 83 (55), 77 (69), 69 (12), 68 (8), 67 (11), 43 (71), 26 (18). Anal. Calcd. for ($C_{21}H_{20}N_6O_4$): C, 59.99; H, 4.79; N, 19.99. Found: C, 59.50; H, 4.55; N, 20.10.

2-Methyl-5-{4-[(3-(4-nitrophenyl)-5-isoxazolyl) methoxy]phenyl}-2*H*-tetrazole (7e). The same procedure as described for compound **7a** to give **7e** after column chromatography (Silica Gel 100, $CHCl_3$-petroleum ether 2:1, R_f = 0.21) as pure pale yellow solid (0.35 g, 82%), m.p.: 192 °C; IR (KBr, cm^{-1}); IR (KBr, cm^{-1})ν_{max} 3089 (ArC-H stretch), 3047 (ArC-H stretch), 2998, 2919, 1613 (C=N ring stretch), 1517 (NO_2 stretch), 1468, 1419 (N-O stretch), 1339 (NO_2 stretch), 1307, 1248, 1044, 837; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.38 (s, 3H, N-C*H*$_3$), 5.31(s, 2H, C*H*$_2$O), 6.76 (s, 1H, Isox C4-H), 7.09 (d, *J* = 8.61 Hz, 2H, Ar-H), 7.99 (d, *J* = 8.48 Hz, 2H, Ar-H), 8.10 (d, *J* = 8.62 Hz, 2H, Ar-H), 8.31 (d, *J* = 8.42 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.32, 61.36, 101.59, 115.09, 121.75, 124.25, 127.75, 128.36, 132.40, 134.76, 148.84, 159.08, 160.80, 164.53, 169.28; MS (EI, 70 ev) *m/z* (rel. int.) 378.11 (M^+, 92), 350 (M^+-N_2, 100), 349 (66), 335 (23), 334 (20), 322 (M^+-$2N_2$, 22), 138, 123 (44), 93 (12), 77 (79), 69, 68, 67 (12), 65 (10), 43 (66), 41 (7), 26 (12). Anal. Calcd. for ($C_{18}H_{14}N_6O_4$): C, 57.14; H, 3.73; N, 22.21. Found: C, 57.40; H, 3.66; N, 21.67.

2-Ethyl-5-{4-[(3-(4-nitrophenyl)-5-isoxazolyl)methoxy] phenyl}-2*H*-tetrazole (7f). The same procedure as described for compound **7a** to give **7f** after column chromatography (Silica Gel 100, $CHCl_3$-petroleum ether 2:1, R_f = 0.19) as pure yellow solid (0.34 g, 83%), m.p.: 169 °C; IR (KBr, cm^{-1})ν_{max} 3107 (ArC-H stretch), 2997 (C-H stretch), 1616 (C=N ring stretch), 1583, 1532 (NO_2 stretch), 1465, 1421 (N-O stretch), 1338 (NO_2 stretch), 1042, 836; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.80 (t, *J* = 6.93 Hz, 3H, N-CH_2C*H*$_3$), 4.76 (q, *J* = 7.02 Hz, 2H, N-C*H*$_2$CH$_3$), 5.30 (s, 2H, C*H*$_2$O), 6.75 (s, 1H, Isox-H), 7.08 (d, *J* = 8.50 Hz, 2H, Ar-H), 8.03 (d, *J* = 8.51 Hz, 2H, Ar-H) 8.14 (d, *J* = 8.50 Hz, 2H, Ar-H), 8.25 (d, *J* = 8.52 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.58, 48.34, 61.33, 101.50, 101.56, 115.06, 121.66, 124.22, 127.72, 128.52, 132.49, 134.72, 148.8, 159.1, 160.76, 164.57, 169.24; MS (EI, 70 ev) *m/z* (rel. int.) 392.13 (M^+, 93), 364 (M^+-N_2, 100), 363 (67), 336 (M^+-$2N_2$, 21), 335 (43), 138 (11), 123 (46), 93 (12), 77 (80), 69 (11), 68 (8), 67 (10), 57 (60), 56 (34), 43 (67), 41 (12), 26 (10). Anal. Calcd. for ($C_{19}H_{16}N_6O_4$) C, 58.16; H, 4.11; N, 21.42; Found: C, 57.79; H, 4.12; N, 21.30.

2-Propyl-5-{4-[(3-(4-nitrophenyl)-5-isoxazolyl)methoxy] phenyl}-2*H*-tetrazole (7g). The same procedure as described for compound **7a** to give **7g** after column chromatography

(Silica Gel 100, $CHCl_3$-petroleum ether 2:1, R_f = 0.23) as pure yellow solid (0.33 g, 84%), m.p.: 150 °C; IR (KBr, cm^{-1}); IR (KBr, cm^{-1})ν_{max} 3119, 2939, 1614 (C=N ring stretch), 1519 (NO_2 stretch), 1422 (N-O stretch), 1339 (NO_2 stretch), 1054, 835; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, *J* = 7.01 Hz, 3H, N-$CH_2CH_2CH_3$), 2.09 (m, 2H, N-$CH_2CH_2CH_3$)), 4.54 (t, *J* = 6.90 Hz, 2H, N-$CH_2CH_2CH_3$), 5.30 (s, 2H, CH_2O), 6.75 (s, 1H, Isox-H), 7.1 (d, *J* = 8.50 Hz, 2H, Ar-H), 7.95 (d, *J* = 8.5 Hz, 2H, Ar-H), 8.14 (d, *J* = 8.49 Hz, 2H, Ar-H), 8.31 (d, *J* = 8.51 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.9, 22.8, 54.7, 61.3, 101.5, 115.1, 121.6, 124.2, 127.7, 128.5, 134.7, 148.8, 159.0, 160.7, 164.5, 169.2; MS (EI, 70 ev) *m/z* (rel. int.) 406.12 (M^+, 96), 378 (M^+-N_2, 100), 377 (59), 350 (M^+-$2N_2$, 22), 138 (24), 123 (43), 93 (12), 77 (74), 69 (12), 68 (22), 67 (8), 57 (11), 43 (75), 26 (32). Anal. Calcd. for ($C_{20}H_{18}N_6O_4$): C, 59.11; H, 4.46; N, 20.68. Found: C, 58.87; H, 4.42; N, 20.38.

2-*n*-Butyl-5-{4-[(3-(4-nitrophenyl)-5-isoxazolyl) methoxy]phenyl}-2*H*-tetrazole (7h). The same procedure as described for compound **7a** to give **7h** after column chromatography (Silica Gel 100, $CHCl_3$-petroleum ether 2:1, R_f = 0.25) as pure yellow solid (0.32 g, 82%), m.p.: 134 °C; IR (KBr, cm^{-1}) (KBr, cm^{-1})ν_{max} 3115 (ArC-H stretch), 2932 (C-H stretch), 1616 (C=N ring stretch), 1518 (NO_2 stretch), 1422 (N-O stretch), 1339 (NO_2 stretch), 1040, 832; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, *J* = 6.90 Hz, 3H), 1.40 (m, 2H), 2.04 (m, 2H), 4.14 (t, *J* = 7.02 Hz, 2H), 5.29 (s, 2H, CH_2O), 6.77 (s, 1H, Isox C4-H), 7.08 (d, *J* = 8.65 Hz, 2H, Ar-H), 8.01 (d, *J* = 8.55 Hz, 2H, Ar-H), 8.13 (d, *J* = 8.52 Hz, 2H, Ar-H), 8.30 (d, *J* = 8.54 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.37, 19.64, 31.33, 52.89, 61.30, 101.59, 115.09, 124.25, 127.76, 128.56, 134.76, 148.84, 159.08, 160.80, 164.53, 169.28; MS *m/z* (rel. int.) 420.14 (M^+, 90), 392 (100, M^+-N_2), 391 (45), 374 (20), 364 (M^+-$2N_2$, 17), 158 (25), 144 (12), 138 (8), 123 (37), 93 (12), 91 (14), 83 (56), 82 (30), 77 (81), 69 (12), 68 (8), 67 (7), 43 (66), 41 (8), 26 (9). Anal. Calcd. for ($C_{21}H_{20}N_6O_4$): C, 59.99; H, 4.79; N, 19.99. Found: C, 59.23; H, 4.68; N, 19.67.

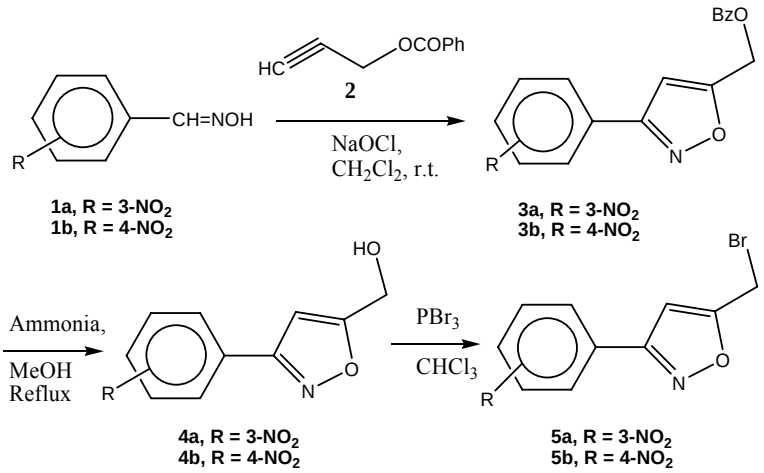
RESULTS AND DISCUSSION

A convergent method was used to synthesize the compounds described above. The isoxazole ring was synthesized with the intention of discovering analogues more stable towards hydrolysis but with comparable activity. Modifications on the isoxazole ring were made using the procedures outlined in Scheme 1. The heteroarylethers **7a-h**, with the homologation of the alkyl group on the tetrazole ring, and the modification of isoxazole moiety were carried out as outlined in Scheme 2.

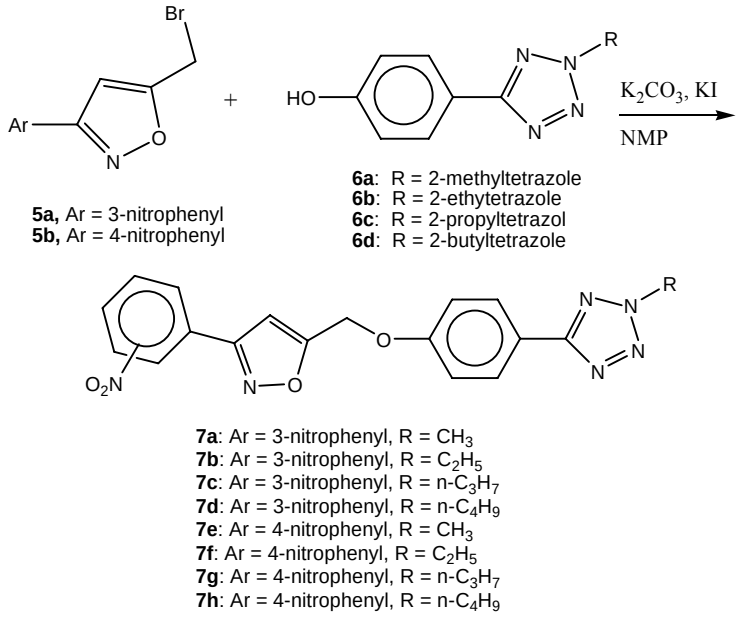
Isoxazoles **5a-b** were synthesized under mild conditions in a short reaction time with good overall yield as outlined in Scheme 1. Cycloaddition of 3-(benzoyloxy)-propyne **2** [20a-d] with *in situ* generated arylnitrile oxide [7,21] produced isoxazole **5** in good yield [22-24]. Removal of the protecting group [25] led to the primary alcohol **4**. The hydroxymethylisoxazole **4** was converted into the bromomethylisoxazole **5** by the reaction with phosphorous tribromide [26c] (Scheme 1). Coupling of the bromomethylisoxazoles **5a,b** with the 4-(2-alkyl-2*H*-tetrazol-5-yl)phenols **6a-d** provided the desired compounds **7a-h** in high yields (Scheme 2). A comparison of ^{1}H NMR spectra revealed that the introduction of nitro phenyl group on the isoxazole ring had a pronounced deshielding effect and shifted the isox-H signal of **7a-h** further downfield (*e.g.*, 6.75 ppm for 3-nitrophenylisoxazole; 6.00 ppm 3-alkylisoxazole). It is interesting to mention that, with the same alkyl group on the tetrazole ring of **7a-h**, *meta*-nitro group had more deshielding effect than did *para*-nitro group on aromatic protons and shifted them further downfield (-*M* effect, larger shifts). Biological and structural activity relationship (SAR) of the prepared compounds will be determined and reported upon completion.

CONCLUSIONS

In conclusion, we have presented a facile and an efficient route to nitrophenyl(isoxazolylmethoxyphenyl)alkyltetrazoles **7a-h** which were synthesized from 4-[5(2-alkyl-2*H*-tetrazolyl)]phenols **6** and 3-nitrophenyl-5-bromomethyl-isoxazoles **5a-b** in high yields. Isoxazoles **5a-b** were synthesized under mild conditions in a short reaction time with good overall yield. Cycloaddition of 3-(benzoyloxy)-propyne **2** with *in situ* generated arylnitrile oxide produced isoxazole **5** in good yield. Removal of the protecting group led to the primary alcohol **4a-b**. The hydroxymethylisoxazole **4** was



Scheme 1



Scheme 2

converted into the bromomethylisoxazole **5a-b** by the reaction with phosphorous tribromide. The structures of the synthesized compounds were confirmed by ^{1}H NMR, Mass spectral, and Elemental Analysis data.

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REFERENCES AND NOTES

[a]On leave from Organic Synthesis Laboratory, Faculty of Chemistry, University of Tabriz, Tabriz 51664, Iran.

[1] a) S.A. Lang, Y.-I. Lin, in: K.T. Potts (Ed.), Comprehensive Heterocyclic Chemistry, Pergamon Press, New York, 1984; b) N.K. Kochetkov, S.D. Sokolov, in: A.R. Katritzky (Ed.), Advances in Heterocyclic Chemistry, Academic Press, New York, 1963.

[2] a) B.J. Wakefield, D.J. Wright, Adv. Heterocycl. Chem. 25 (1979) 147; b) P. Krogsgaard-Larsen, G.A.R. Johnston, D.R. Curtis, C.J.S. Game, R.M. McGulloch, J. Neurochem. 25 (1975) 803; c) S.R. Naik, A. Guidotti, E. Costa, Neuropharmacol. 15 (1976) 479.

[3] a) P. Grünanger, P. Vita-Finzi, in: E.C. Taylor (Ed.), The Chemistry of the Heterocyclic Compounds, John Wiley & Sons, New York, 1991; b) R.E. Sammelson, R.B. Miller, M.J. Kurth, J. Org. Chem. 65 (2000) 2225 and references cited therein.

[4] a) Y.R. Mirzaei, B.M. Simpson, D.J. Triggle, N.R. Natale, J. Org. Chem. 57 (1992) 6271; b) Y.R. Mirzaei, T.N. Balasubramaniam, B.J. Lefler, N.R. Natale, J. Heterocycl. Chem. 27 (1990) 2001; c) T.N. Balasubramaniam, Y.R. Mirzaei, N.R. Natale, Synthesis 11 (1990) 1076; d) Y.R. Mirzaei, Diss. Abstr. Int. B 51 (1991) 4848. Chem. Abstr. 115 (1991) 29180; e) Y.R. Mirzaei, N.R. Natale, Org. Prep. Proced. Int. 25 (1993) 515.

[5] Y.R. Mirzaei, S.B. Tabrizi, M.H. Gohareh, H.Z. Neirizi, L. Edjlali, Org. Prep. Proced. Int. 35 (2003) 207.

[6] L. Edjlali, S.M. Golabi, Y.R. Mirzaei, Bull. Electrochem. 16 (2000) 354.

[7] H. Theobald, Ger. Offen: 2754832 (C1. C07C135100), 1979; Chem. Abstr. 91 (1979) P 140372b.

[8] a) J.A. Bladin, Ber. 18 (1885) 1544; b) F.R. Benson, Chem. Rev. 41 (1947) 1; c) R.N. Butler, in: A.R. Katritzky, A.J. Boulton (Eds.), Adv. Heterocyclic Chemistry, Academic Press, New York, 1977; d) R.N. Butler, in: A.R. Katritzky, C.W. Rees, E.F.V. Scriven (Eds.), Comprehensive Heterocyclic Chemistry II, Pergamon Press, New York, 1996; e) F.R. Benson, in: R.C. Elderfield (Ed.), Heterocyclic Compounds, Wiley, New York, 1967.

[9] a) G.I. Koldobskii, V.A. Ostrovskii, V.S. Popavskii, Chem. Heterocycl. Comp. 17 (1981) 965; b) G.I. Koldobskii, R.B. Kharbash, Russ. J. Org. Chem. 39 (2003) 453; c) R.N. Butler, in: K.T. Potts (Ed.), Comprehensive Heterocyclic Chemistry, Pergamon Press, Oxford, 1984.

[10] a) G.I. Koldobskii, V.A. Ostrovskii, V.A. Usp. Khim. 63 (1994) 847; b) V.A. Ostrovskii, M.S. Pevzner, T.P. Kofmna, M.B. Sheherbinin, I.V. Tselinskii, Targets Heterocycl. Syst. 3 (1999) 467.

[11] a) H. Singh. A.S. Chawla, V.K. Kapoor, D. Paul, R.K. Malhotra, in: G.P. Ellis, G.B. West (Eds.), Progress in Medicinal Chemistry, Elsevier/North Holland. Biomedical Press, 1980; b) R.H. Bradbury, C.P. Allott, M. Dennis, J.A. Girwood, P.W. Kenny, J.S. Major, A.A. Oldham, A.H. Ratcliffe, J.E. Rivett, D.A. Roberts, P.J. Robins, J. Med. Chem. 36 (1993) 1245; c) D.J. Carini, J.V. Duncia, P.E. Aldrich, A.T. Chiu, A.L. Johnson, M.E. Pierce, W.A. Price, J.B. Santella III, G.J. Wells, R.R. Wexler, P.C. Wong, S.-E. Yoo, P.B.M.W.M. Timmermans, J. Med. Chem. 34 (1991) 2525; d) K. Raman, S.S. Parmar, S.P. Singh, J. Heterocycl. Chem. 17 (1980) 1137.

[12] a) R.S. Upadhayaya, S. Jain, N. Sinha, N. Kishore, R. Chandra, S.K. Arora, Eur. J. Med. Chem. 39 (2004) 579; b) D. Moderhack, J. Prakt. Chem. 340 (1998) 687; c) J.R. Maxwell, D.A. Wasdahl, A.C. Wolfson, V.I. Stenberg, J. Med. Chem. 27 (1984), 1565 and reference 17 cited therein; d) R.M. Herbst, K.R. Wilson, J. Org. Chem. 22 (1957) 1142.

[13] a) The earlier report of the synthesis of **9** using ammonium azide instead of sodium azide gives lower yield (43%), W.G. Finnegan, R.A. Henry, R. Lofquist, J. Am. Chem. Soc. 80 (1958) 3908; b) Synthesis of compound **9** is reported previously (decomp. 228 °C) W. Lossen, J. Colman, Ann. 298 (1887) 107.

[14] a) M. Hisky, D.E. Chavez, D.L. Naud, S.F. Son, H.L. Berghout, C. Bome, Proc. Int. Pyrotech. Semin. 27 (2000) 3; b) R.N. Butler, in: A.R. Katritzky, A.J. Boulton (Eds.), Adv. Heterocycl. Chem., Academic Press, New York, 1977; c) C. Matthias-Grunert, P. Weinberger, J. Schweifer, C. Hamper, A.F. Stassen, K. Mereiter, W. Linert, J. Molec. Struc. 733 (2005) 41; d) Y.S. Gyoung, J.-G. Shim, Y. Yamamoto, Tetrahedron Lett. 41 (2002) 4193; e) A.F. Stassen, E. Dova, J. Ensling, H. Schenk, P. Gütlich, J.G. Haasnoot, J.

Reedijk, Inorg. Chim. Acta 333 (2002) 61.

[15] a) R. Huisgen, J. Org. Chem. 33 (1968) 2291; b) R. Huisgen, Angew. Chem. Int. Ed. Engl. 2 (1963) 565; c) R. Huisgen, J. Org. Chem. 41 (1976) 403; d) F. Himo, Z.P. Demko, L. Noodleman, K.B. Sharpless, J. Am. Chem. Soc. 124 (2002) 12210 and references cited therein.

[16] a) R.N. Butler, in: K.T. Potts (Ed.), Comprehensive Heterocyclic Chemistry, Pergamon Press, Oxford, 1984; b) S.J. Wittenberger, Org. Prep. Proc. Int. 26 (1994) 499.

[17] a) R.M. Herbst, Essays in Biochemistry, John Wiley & Sons, New York, 1956; b) F. Lenda, F. Guenoun, J. Martinez, F. Lamaty, Tetrahedron Lett. 48 (2007) 805; c) K.L. Yu, R.L. Johnson, J. Org. Chem. 52 (1987) 2051; d) J. Zabrocki, D. Smith, J.B. Dunbar, H. Iijima, G.R. Marshal, J. Am. Chem. Soc. 110 (1988) 5875.

[18] a) G.D. Diana, M.A. Mckinlay, C.J. Brisson, E.S. Zaloy, J.V. Mirallco, U.J. Salvador, J. Med. Chem. 28 (1985) 748; b) G.D. Diana, M.A. Mckinlay, M.J. Otto, V. Akullian, C. Oglesby, J. Med. Chem. 28 (1985) 1906.

[19] a) G.D. Diana, P. Kowalczyk, A.M. Treasurywala, R.C. Oglesby, D.C. Pevear, F.J. Dutko, J. Med. Chem. 35 (1992) 1002; b) G.D. Diana, D. Cutcliffe, R.C. Oglesby, M.J. Otto, J.P. Mallamo, V. Akullian, M.A. Mckinlay, J. Med. Chem. 32 (1989) 450; c) G.D. Diana, D. Cutcliffe, D.L. Volkots, J.P. Mallanio, T.R. Bailey, N. Vescio, R.C. Oglesby, T.J. Nitz, J. Wetzel, V. Giranda, D.C. Pevear, F.J. Dutko, J. Med. Chem. 36 (1993) 3240; d) G.D. Diana, D.L. Volkots, T.J. Nitz, T.R. Bailey, M.A. Long, N. Vescio, S. Aldous, D.C. Pevear, F.J. Dutko, J. Med. Chem. 37 (1994) 2421; e) E.A. Hallinan, S. Tsymbalov, C.R. Dorn, B.S. Pitzele, D.W.J. Hansen, J. Med. Chem. 45 (2002) 1686; f) P.M. O'Brien, D.R. Sliskovic, A. Bernabei, T. Hurley, M.K. Anderson, R.F. Bousley, B.R. Krause, R.L. Stanfield, Biorg. Med. Chem. Lett. 5 (1995) 295.

[20] a) Sankyo Co., Ltd. Jpn. (C1. C07D261/12), 1980; Chem. Abstr. 94 (1981) P 139781q; b) M.J. Kurth, L.A.A. Randall, K. Takenouchi, J. Org. Chem. 61 (1996) 8755; c) B.A. Lorsbach, R.B. Miller, M.J. Kurth, J. Org. Chem. 61 (1996) 8716; d) E.J. Kantorowski, M.J. Kurth, J. Org. Chem. 62 (1997) 6797; e) A.F. Hegarty, P.J. Tuohey, J. Chem. Soc. Perkin Trans 2, 1980, 1313 and references cited therein (128.5-129 °C, 130 °C also reported in *Beilstein* for *E-p*-nitrobenzaldoxime); f) M.O. Froster, F.P. Dunn, J. Chem. Soc. 95 (1909) 425 (also reported in *Beilstein* for *E-m*-nitrobenzaldoxime); g) D.R. Dalton, H.G. Foley, J. Org. Chem. 24 (1973) 4200.

[21] For conversion of aldoximes to the corresponding nitrile oxides using sodium hypochlorite see: a) A.L. Smith, C.-K. Hwang, E. Pitsinos, G.R. Scarlato, K.C. Nicolaou, J. Am. Chem. Soc. 114 (1992) 3134; b) C. Grundman, J.M. Dean, J. Org. Chem. 30 (1965) 2809 and references cited therein; c) A. Hassner, K.S.K. Murty, J. Org. Chem. 54 (1989) 5277.

[22] P.G. Baraldi, A. Barco, S. Benetti, F. Moroder, G.P. Pollini, D. Simmon, J. Org. Chem. 48 (1983) 1297.

[23] a) The melting point and also the NMR spectra were consistent with the reported one. T. Isida, T. Akiyama, K. Nabika, K. Sisido, S. Kozima, Bull. Chem. Soc. Jpn. 46 (1973) 2176 and references cited therein; b) R.N. Butler, V.C. Garvin, T.M. McEvoy, J. Chem. Soc. Perkin Trans 2 (1984) 721 and references cited therein; c) R.N. Butler, V.C. Garvin, T.M. McEvoy, J. Chem. Soc. (Synop) 6 (1981) 174; d) W. Fuhrer, F. Ostermayer, M. Zimmermann, Eur. Pat. Appl. EP 39892 (Cl. C07D233/64), 1981; Chem. Abstr. 96 (1981) P 122404n; d) A.V. Moskvin, A.V. Ostrovskii, I.Y. Shirobokov, G.I. Koldobskii, B.V. Gidaspov, Zh. Org. Khim. 14 (1978) 2440.

[24] The melting point and also the NMR spectra were consistent with the reported one.

[25] a) K. Tsuszuki, Y. Nakajima, T. Walanabe, M. Yanajiya, T. Matsumoto, Tetrahedron Lett. 11 (1978) 989; b) I. Kawasaki, K. Matsuda, T. Kaneko, T. Bull. Chem. Soc. Jpn. 14 (1971) 1986.

[26] a) J.J. Hansen, P. Krogsgaard-Larsen, J. Chem. Soc. Perkin Trans. I. (1980) 1826; b) T.N. Johansen, B. Ebert, H. Braeuner-Osborne, M. Didriksen, I.T. Christensen, K.K. Søby, U. Madsen, P. Krogsgaard-Larsen, L. Brehm, J. Med. Chem. 41 (1998) 930; c) Y. Watanabe, H. Iida, C. Kibayashi, J. Org. Chem. 54 (1989) 4088; d) This compound was prepared earlier, E.

Mugnani, P. Grünanger, Atti Accad. Nazl. Lincei, Rend, Classe Sci. Fis., Mat. Nat. 14 (1953) 95; Chem. Abstr. 48 (1954) 2685.

[27] Y.R. Mirzaei, S.B. Tabrizi, L. Edjlali, Acta Chim. Slov. 55 (2008) 554.

[28] K. Hayakawa, M. Yodo, S. Ohsuki, K. Kanematsu, J. Am. Chem. Soc. 106 (1984) 6735.

[29] This compound was prepared in a different method without any characterization: H.G. Sen, D. Seth, D.U.N. Joshi, P. Rajagopalan, J. Med. Chem. 9 (1966) 431.