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Research Article

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Synthesis and Characterization of Some Novel Potential Biologically Active 2-Ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonates

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Abstract In this study, because of potential biological activity, five new 2-ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonates (**2a-e**) were synthesized by the reactions of2-ethoxy-4-[(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenylbenzenesulfonates(**1a-e**) with formaldehyde and 4-piperidinecarboxamide. The structures of five new compounds characterized from the mass, IR, ^{1}H-NMR, ^{13}C-NMR spectral data.

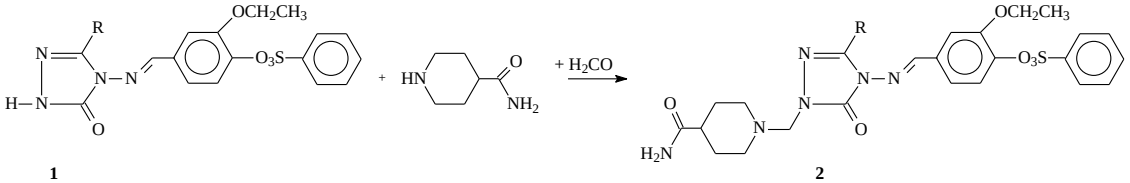
Keywords 4,5-Dihydro-1*H*-1,2,4-triazol-5-one, Schiffbase, Mannih base, Synthesis

Introduction

1,2,4-Triazole and 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives are reported to possess a broad spectrum of biological activities such as antifungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiviral, antiinflammatory, antitumor, antioxidant and anti-HIV properties [1-13]. In addition, several articles reporting the synthesis of some *N*-arylidenamino-4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives have been published [8-13].

On the other hand, a lot of literatures have shown that Mannich bases posses potent biological activities [12-19].

In the present paper, five new 2-ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonates (**2a-e**) were synthesized by the reactions of 2-ethoxy-4-[(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenylbenzenesulfonates (**1a-e**) with formaldehyde and 4-piperidinecarboxamide (Scheme 1).



1 **2**

a) R = CH_3, b) R = CH_2CH_3, c) R = $CH_2C_6H_5$, d) R = $CH_2C_6H_4CH_3$ (*p*-), e) $CH_2C_6H_4Cl$ (*p*-)

Scheme 1: *Synthetic route of compounds**2***

Materials and Methods

Chemical reagents and all solvents used in this study were purchased from Merck AG, Aldrich and Fluka. Melting points which were uncorrect were determined in open glass capillaries using an Electrothermal 9100 digital melting point apparatus. The IR spectra were obtained on a Perkin-Elmer Instruments Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in deuterated dimethyl sulfoxide with TMS as internal standard using a Bruker Ultrashield spectrometer at 400 MHz and 100 MHz, respectively. Electrospray ionisation mass spectrometry (ESI-MS) was performed on a TSQ Quantum Access Max Triple Stage Quadrupole Mass Spectrometer. The starting compounds **1a-e** were prepared according to the literature [20].

General procedure for the synthesis of 2-ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonates (2a-e)

2-Ethoxy-4-[(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenylbenzenesulfonates(**1**) (5 mmol) dissolved in ethanol was treated with formaldehyde (10 mmol) and 4-piperidinecarboxyamide (6 mmol). The reaction mixture was refluxed for 3 h. Then the reaction mixture were cooled and filtrated. Several recrystallizations of the residue from an appropriate solvent gave pure compounds **2a-e** as colourless crystals.

2-Ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-methyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonate(2a): Yield 63 %, m.p. 120 °C. IR: 3367 and 3191 (NH_2), 1704, 1648 (C=O), 1600 (C=N), 1374 and 1198 (SO_2), 752 and 699 (monosubstituted benzenoid ring) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.11 (t, 3H, OCH_2CH_3, *J*=6.80 Hz), [1.49-1.53 (m, 2H, CH_2), 1.66-1.68 (m, 2H, CH_2), 1.99 (m, 1H, CH), 2.25-2.31 (m, 2H, CH_2), 2.89-2.92 (m, 2H, CH_2)] (piperidine-H), 2.30 (s, 3H, CH_3), 3.84 (q, 2H, OCH_2CH_3, *J*=6.80 Hz), 4.52 (s, 2H, NCH_2N), 6.70 (s, 1H, NH), 7.14 (s, 1H, NH), 7.31 (d, 1H, ArH, *J*=8.00 Hz), 7.45-7.48 (m, 2H, ArH), 7.65-7.69 (m, 2H, ArH), 7.80-7.86 (m, 3H, ArH), 9.66 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 10.89 (CH_3), 14.04 ($OCH_2\underline{C}H_3$), 28.40 ($2CH_2$), 41.08 (CH), 49.71 (CH_2NCH_2), 64.08 ($O\underline{C}H_2CH_3$), 66.35 (NCH_2N), [112.82, 119.99, 124.26, 128.12 (2C), 129.47 (2C), 133.55, 134,83, 135.18, 139.63, 150.89] (arom-C), 143.46 (triazole C_3), 150.13 (N=CH), 153.00 (triazole C_5), 176.37 ($CONH_2$). MS: m/z 545 (M+2, 5), 544 (M+1, 15), 543 (M, 60), 173 (25), 159 (8), 141 (100), 129 (34).

2-Ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-ethyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonate (2b): Yield 69 %, m.p. 86 °C IR: 3364 and 3218 (NH_2), 1711, 1658 (C=O), 1619 (C=N), 1378 and 1175 (SO_2), 768 and 682 (monosubstituted benzenoid ring) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 1.10 (t, 3H, OCH_2CH_3, *J*=7.20 Hz), 1.21 (t, 3H, CH_2CH_3, *J*=7.20 Hz), [1.49-1.52 (m, 2H, CH_2), 1.65-1.68 (m, 2H, CH_2), 1.94-1.98 (m, 1H, CH), 2.24-2.29 (m, 2H, CH_2), 2.90-2.92 (m, 2H, CH_2)] (piperidine-H), 2.71 (q, 2H, CH_2CH_3, *J*=7.20 Hz), 3.84 (q, 2H, OCH_2CH_3, *J*=7.20 Hz), 4.53 (s, 2H, NCH_2N), 6.69 (s, 1H, NH), 7.14 (s, 1H, NH), 7.31 (d, 1H, ArH, *J*=8.40 Hz), 7.45-7.48 (m, 2H, ArH), 7.65-7.69 (m, 2H, ArH), 7.81-7.86 (m, 3H, ArH), 9.66 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 9.98 ($CH_2\underline{C}H_3$), 14.03 ($OCH_2\underline{C}H_3$), 18.32 ($\underline{C}H_2CH_3$), 28.39 ($2CH_2$), 41.08 (CH), 49.72 (CH_2NCH_2), 64.05 ($O\underline{C}H_2CH_3$), 66.37 (NCH_2N), [112.92, 120.02, 124.31, 128.12 (2C), 129.49 (2C), 133.62, 134,85, 135.17, 139.61, 150.89] (arom-C), 146.66 (triazole C_3), 150.27 (N=CH), 153.05 (triazole C_5), 176.41 ($CONH_2$). MS: m/z 559 (M+2, 5), 558 (M+1, 18), 557 (M, 80), 281 (8), 173 (25), 159 (12), 141 (100), 129 (68).

2-Ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-benzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonate (2c): Yield 65 %, m.p. 80 °C. IR: 3379 and 3190 (NH_2), 1699, 1672 (C=O), 1594 (C=N), 1371and 1197 (SO_2), 753 and 698 (monosubstitutedbenzenoid ring) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 1.13 (t, 3H, OCH_2CH_3, *J*=6.80 Hz), [1.51-1.55 (m, 2H, CH_2), 1.67-1.70 (m, 2H, CH_2), 1.94-1.98 (m, 1H, CH), 2.27-2.30 (m, 2H, CH_2), 2.92-2.95 (m, 2H, CH_2)] (piperidine-H), 3.83 (q, 2H, OCH_2CH_3, *J*=6.80 Hz), 4.09 (s, 2H, CH_2Ph), 4.58 (s, 2H, NCH_2N), 6.72 (s, 1H, NH), 7.18 (s, 1H, NH), 7.23-7.39 (m, 8H, ArH), 7.65-7.69 (m, 2H, ArH), 7.81-7.85 (m, 3H, ArH), 9.62 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 14.01 ($OCH_2\underline{C}H_3$), 28.41 ($2CH_2$), 30.99 (CH_2Ph),

41.09 (CH), 49.74 (CH_2NCH_2), 64.02 ($O\underline{C}H_2CH_3$), 66.48 (NCH_2N), [112.00, 120.68, 124.25, 126.75, 128.11 (2C),128.49 (2C), 128.55 (2C), 129.45 (2C), 133.54, 134,82, 135.18, 135.69, 139.64, 150.83] (arom-C), 144.67 (triazole C_3), 150.16 (N=CH), 152.39 (triazole C_5), 176.38 ($CONH_2$). MS: m/z 621 (M+2, 4), 620 (M+1, 12), 619 (M, 34), 159 (15), 141 (100), 129 (86).

2-Ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-(*p*-methylbenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonate (2d): Yield 69 %, m.p. 85 °C. IR: 3401 and 3213 (NH_2), 1711, 1667 (C=O), 1587 (C=N), 1348 and 1155 (SO_2), 805 (1,4-disubstituted benzenoid ring), 765 and 697 (monosubstituted benzenoid ring) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.13 (t, 3H, OCH_2CH_3, *J*=7.20 Hz), [1.50-1.54 (m, 2H, CH_2), 1.66-1.69 (m, 2H, CH_2), 1.95-2.00 (m, 1H, CH), 2.26-2.31 (m, 2H, CH_2), 2.91-2.94 (m, 2H, CH_2)] (piperidine-H), 2.25 (s, 3H, $PhCH_3$), 3.81 (q, 2H, OCH_2CH_3, *J*=7.20 Hz), 4.03 (s, 2H, CH_2Ph), 4.57 (s, 2H, NCH_2N), 6.71 (s, 1H, NH), 7.10-7.20 (m, 5H, ArH+NH), 7.29 (d, 1H, ArH, *J*=8.00 Hz), 7.37-7.39 (m, 2H, ArH), 7.65-7.69 (m, 2H, ArH), 7.81-7.85 (m, 3H, ArH), 9.61 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 14.03 ($OCH_2\underline{C}H_3$), 20.56 ($PhCH_3$), 28.41 ($2CH_2$), 30.59 (CH_2Ph), 41.09 (CH), 49.74 (CH_2NCH_2), 64.04 ($O\underline{C}H_2CH_3$), 66.45 (NCH_2N), [112.01, 120.70, 124.26, 128.12 (2C), 128.43 (2C), 129.05 (2C), 129.47 (2C), 132.57, 133.56, 134.82, 135.18, 135.83, 139.64, 150.83] (arom-C), 144.82 (triazole C_3), 150.16 (N=CH), 152.37 (triazole C_5), 176.37 ($CONH_2$). MS: m/z 634 (M+1, 5), 633 (M, 14), 173 (28), 159 (10), 141 (100), 129 (32).

2-Ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-(*p*-chlorobenzyl)-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonate (2e): Yield 81 %, m.p. 135 °C. IR: 3383 and 3193 (NH_2), 1700, 1671 (C=O), 1596 (C=N), 1370 and 1197 (SO_2), 806 (1,4-disubstituted benzenoid ring), 751 and 698 (monosubstituted benzenoid ring) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.13 (t, 3H, OCH_2CH_3, *J*=7.20 Hz), [1.51-1.54 (m, 2H, CH_2), 1.67-1.70 (m, 2H, CH_2), 1.98-2.02 (m, 1H, CH), 2.26-2.29 (m, 2H, CH_2), 2.91-2.94 (m, 2H, CH_2)] (piperidine-H), 3.80 (q, 2H, OCH_2CH_3, *J*=7.20 Hz), 4.10 (s, 2H, CH_2Ph), 4.57 (s, 2H, NCH_2N), 6.72 (s, 1H, NH), 7.17 (s, 1H, NH), 7.28-7.39 (m, 7H, ArH), 7.65-7.69 (m, 2H, ArH), 7.81-7.85 (m, 3H, ArH), 9.62 (s, 1H, N=CH). ^{13}C NMR (DMSO-d_6): δ 14.03 ($OCH_2\underline{C}H_3$), 28.39 ($2CH_2$), 30.32 (CH_2Ph), 41.05 (CH), 49.71 (CH_2NCH_2), 64.02 ($O\underline{C}H_2CH_3$), 66.51 (NCH_2N), [112.07, 120.68, 124.26, 128.11 (2C), 129.45 (2C), 130.46 (2C), 130.60 (2C), 131.46, 133.48, 134.70, 134.82, 135.17, 139.68, 150.84] (arom-C), 144.32 (triazole C_3), 150.15 (N=CH), 152.57 (triazole C_5), 176.38 ($CONH_2$). MS: m/z 655 (M+2, 4), 557 (M, 10), 173 (28), 159 (12), 141 (100), 129 (62).

Results and Discussion

In this study, the structures of five new 2-ethoxy-4-{[1-(4-piperidinecarboxyamide-1-yl-methyl)-3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl]-azomethine}-phenylbenzenesulfonates(**2a-e**), which were synthesized by the reactions of 2-ethoxy-4-[(3-alkyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenylbenzenesulfonates(**1a-e**) with formaldehyde and 4-piperidinecarboxyamide, were identified using the mass, IR, ^{1}H-NMR, ^{13}C-NMR spectral data, and the observed spectral values were seen to be compatible with literature values [17-19].

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