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Research Article

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Synthesis and Characterization of Novel 2-Methoxy-6-[(1-acetyl-3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]phenyl-4-Methoxybenzoates

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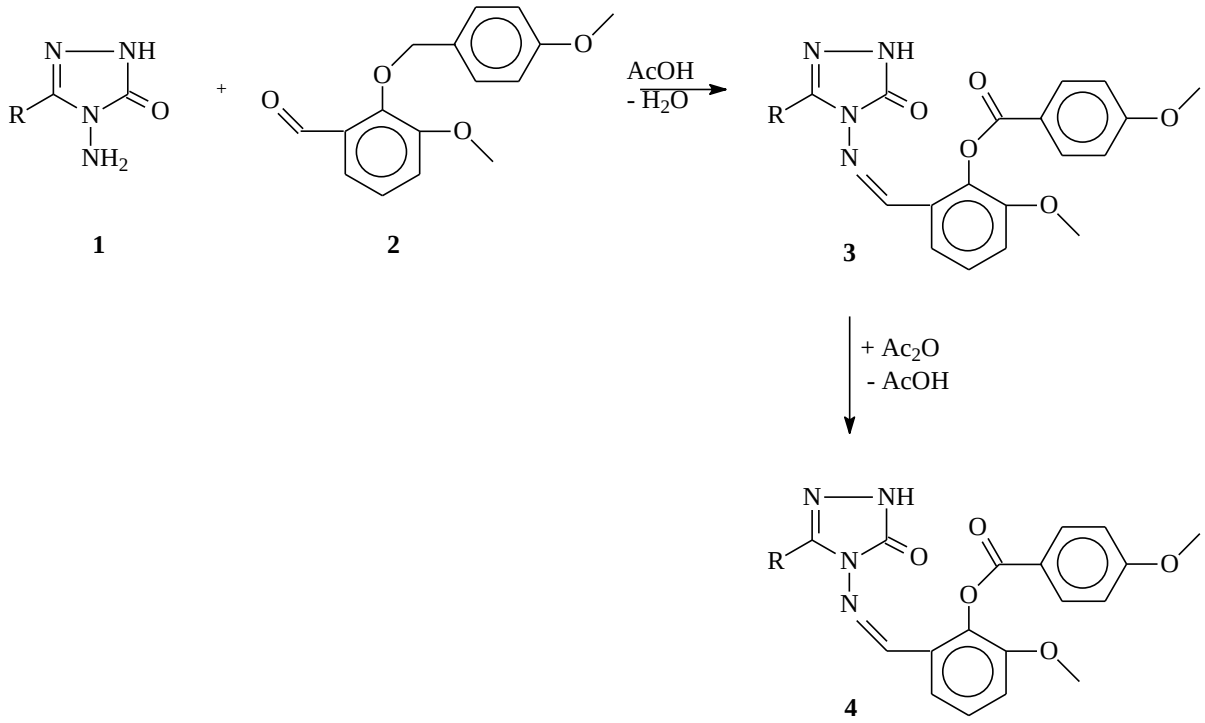
Abstract A series of novel 2-methoxy-6-[(1-acetyl-3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]phenyl 4-methoxybenzoates **(4)** were synthesized from the reactions of 2-methoxy-6-[(3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]phenyl 4-methoxybenzoates (**3**), which were obtained by the reactions of 3-substituted-4-amino-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (**1**) with 2-methoxy-3-(4-methoxybenzoxy)-benzaldehyde (**2**), with acetic anhydride. The structures of nine new compounds were characterized from IR, ^{1}H NMR, ^{13}C NMR and UV spectral data.

Keywords 4,5-Dihydro-1*H*-1,2,4-triazol-5-one, Schiff base, synthesis, acetylation

1. 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.[3, 7, 11-19] The acylation of 4,5-dihydro-1*H*-1,2,4-triazol-5-one derivatives has also been reported.[3, 11-14, 16-20]

In the present study, we present the synthesis of a series of novel 2-methoxy-6-[(1-acetyl-3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]phenyl 4-methoxybenzoates **(4)** were synthesized from the reactions of 2-methoxy-6-[(3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]phenyl 4-methoxybenzoates (**3**) with acetic anhydride. The starting compounds 3-substituted-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones **(1)** were prepared as described in the literatüre [20, 21]. In addition, compounds **3** were synthesized from the reactions of compounds **1** with 2-methoxy-3-(4-methoxybenzoxy)-benzaldehyde (**2**), which was synthesized by the reaction of 2-hydroxy-3-methoxybenzaldehyde with 4-methoxybenzoyl chloride by using triethylamine according to the literature [22] (Scheme 1). The structures of new compounds were identified by using IR, ^{1}H NMR, ^{13}C NMR and UV spectral data.



1 **2** **3** **4**

a) R = CH_3, b) R = $CH_2CH_2CH_3$, c) R = $CH_2C_6H_5$, d) R = $CH_2C_6H_4CH_3$ (*p*-),
e) R = $CH_2C_6H_4Cl$ (*p*-), f) R = C_6H_5

*Scheme 1: Synthetic route of compounds **4***

2. Materials and Methods

Chemical reagents used in the study were supplied from Sigma (Sigma-Aldrich GmbH, Germany), Fluka (Switzerland) and Merck AG, (Germany). Melting points were identified using a Stuart SMP30 melting point apparatus with open glass capillaries (United Kingdom). 1H and 13C-NMR spectra were recorded in deuterated dimethyl sulfoxide (DMSO-d6) using a Bruker Avance III spectrophotometer at 400 MHz and 100 MHz, respectively.

General procedure for the synthesis of 2-methoxy-6-[(1-acetyl-3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]phenyl 4-methoxybenzoates (4)

The corresponding compound **3** (0.01 mol) was refluxed with acetic anhydride (15 mL) for 0.5 h. After addition of absolute ethanol (50 mL), the mixture was refluxed for 1 h. Evaporation of the resulting solution at 40-45 °C *in vacuo* and several recrystallizations of the residue from an appropriate solvent gave pure compounds **4**.

2-Methoxy-6-[(1-acetyl-3-methyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenyl 4-methoxybenzoate (4a): Yield: 76%, m.p. 160 °C; IR (cm^{-1}) υ_{max}: 1775, 1724 (C=O), 1604,1577 (C=N), 1253 (COO), 832 (1,4-disubstituted benzenoid ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,23 (s, 3H, CH_3), 2,41 (s, 3H, $COCH_3$), 3,82 (s, 3H, OCH_3), 3,91 (s, 3H, OCH_3), 7,16 (d, 2H, ArH, *J* = 9.2 Hz), 7,38 (d, 1H, ArH, *J* = 8.4 Hz), 7,44 (t, 1H, ArH, *J* = 8.0 Hz), 7,62 (d, 1H, ArH, *J* = 8.0 Hz), 8,13 (d, 2H, ArH, *J* = 9.2 Hz), 9,74 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11,03 (CH_3), 23,36 ($CO\underline{C}H_3$), 55,69 (OCH_3), 56,19 (OCH_3), [114,46 (2C), 115.73, 117.96, 120.03, 126.80, 126.93, 132.23 (2C), 139.50, 149.81, 163.95] (ArC), 144,18 (Triazole C-3), 148,13 (N=CH), 151,61 (Triazole C-5), 164,02 (COO), 166,05 ($\underline{C}OCH_3$); UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 296 (13.680), 258 (27.820), 230 (21.100), 216 (22.430).

2-Methoxy-6-[(1-acetyl-3-*n*-propyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenyl 4-methoxybenzoate (4b):

Yield: 84%, m.p. 157 °C; IR (cm^{-1}) υ_{max}: 1770, 1732, 1695 (C=O), 1604,1575 (C=N), 1249 (COO), 817 (1,4-disubstituted benzenoid ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0,93 (t, 3H, $CH_2CH_2CH_3$, *J* = 7.6 Hz), 1,65 (sext, 2H, $CH_2CH_2CH_3$, *J* = 7.6 Hz), 2,42 (s, 3H, $COCH_3$), 2,57 (t, 3H, $CH_2CH_2CH_3$, *J* = 7.6 Hz), 3,82 (s, 3H, OCH_3), 3,91 (s, 3H, OCH_3), 7,16 (d, 2H, ArH, *J* = 9.2 Hz), 7,39 (d, 1H, ArH, *J* = 8.4 Hz), 7,45 (t, 1H, ArH, *J* = 8.4 Hz), 7,59 (d, 1H, ArH, *J* = 8.0 Hz), 8,13 (d, 2H, ArH, *J* = 8.8 Hz), 9,73 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13,34 ($CH_2CH_2CH_3$), 18,28 ($CH_2CH_2CH_3$), 23,40 ($COCH_3$), 26,49 ($CH_2CH_2CH_3$), 55,69 (OCH_3), 56,21 (OCH_3), [114,46 (2C), 115.75, 118.21, 120.07, 126.80, 127.14, 132.23 (2C), 139.42, 150.23, 163.38] (ArC), 147,95 (Triazole C-3), 148,80 (N=CH), 151,64 (Triazole C-5), 164,02 (COO), 166,02 ($COCH_3$); UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 296 (13.000), 258 (27.740), 228 (21.190), 218 (23.480).

2-Methoxy-6-[(1-acetyl-3-benzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenyl 4-methoxybenzoate (4c):

Yield: 87%, m.p. 143 °C; IR (cm^{-1}) υ_{max}: 1761, 1734, 1699 (C=O), 1604 (C=N), 1249 (COO), 817 (1,4-disubstituted benzenoid ring), 788 and 703 (monosubstituted benzenoid ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,42 (s, 3H, $COCH_3$), 3,81 (s, 3H, OCH_3), 3,89 (s, 3H, OCH_3), 4,05 (s, 2H, CH_2Ph), 7,15 (d, 2H, ArH, *J* = 9.2 Hz), 7.27-7.29 (m, 1H, ArH), 7.32-7.34 (m, 4H, ArH), 7.35-7.38 (m, 1H, ArH), 7,43 (t, 1H, ArH, *J* = 8.0 Hz), 7,55 (d, 1H, ArH, *J* = 8.0 Hz), 8,12 (d, 2H, ArH, *J* = 9.2 Hz), 9,73 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23,45 ($COCH_3$), 30,84 (CH_2Ph), 55,68 (OCH_3), 56,21 (OCH_3), [114,48 (2C), 115.77, 117.69, 119.94, 126.79, 126.94, 132.23 (2C), 139.62, 151.58, 163.40] (ArC), [127.12, 128.40 (2C), 128.77 (2C), 134.54] (ArC linked C-3), 148,06 (Triazole C-3), 149,52 (N=CH), 151,58 (Triazole C-5), 164,04 (COO), 166,00 ($COCH_3$); UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 292 (13.140), 260 (26.320), 230 (20.500), 218 (22.050).

2-Methoxy-6-[(1-acetyl-3-*p*-methylbenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenyl 4-methoxybenzoate (4d):

Yield: 80%, m.p. 150 °C; IR (cm^{-1}) υ_{max}: 1752, 1735, 1718 (C=O), 1605, 1577 (C=N), 1247 (COO), 806 (1,4-disubstituted benzenoid ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,28 (s, 3H, $PhCH_3$), 2,42 (s, 3H, $COCH_3$), 3,81 (s, 3H, OCH_3), 3,89 (s, 3H, OCH_3), 3,99 (s, 2H, CH_2Ph), 7,13-7.17 (m, 4H, ArH), 7,21 (d, 2H, ArH, *J* = 8.0 Hz), 7,37 (d, 1H, ArH, *J* = 8.4 Hz), 7,43 (t, 1H, ArH, *J* = 8.0 Hz), 7,56 (d, 1H, ArH, *J* = 8.0 Hz), 8,11 (d, 2H, ArH, *J* = 9.2 Hz), 9,72 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.61 ($PhCH_3$), 23,45 ($COCH_3$), 30,45 (CH_2Ph), 55,67 (OCH_3), 56,20 (OCH_3), [114,47 (2C), 115.75, 117.70, 119.95, 126.80, 127.12, 132.23 (2C), 139.62, 149.50, 163.40] (ArC), [128.63 (2C), 128.82 (2C), 131.38, 136.05] (ArC linked C-3), 147,94 (Triazole C-3), 148,40 (N=CH), 151,58 (Triazole C-5), 164,04 (COO), 166,00 ($COCH_3$); UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 300 (14.475), 258 (24.025), 228 (27.810).

2-Methoxy-6-[(1-acetyl-3-*p*-chlorobenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenyl 4-methoxybenzoate (4e):

Yield: 83%, m.p. 158 °C; IR (cm^{-1}) υ_{max}: 1762, 1734, 1698 (C=O), 1604, 1574 (C=N), 1249 (COO), 788 (1,4-disubstituted benzenoid ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,42 (s, 3H, $COCH_3$), 3,81 (s, 3H, OCH_3), 3,89 (s, 3H, OCH_3), 4,06 (s, 2H, CH_2Ph), 7,14 (d, 2H, ArH, *J* = 9.2 Hz), 7,34-7.41 (m, 5H, ArH), 7,43 (t, 1H, ArH, *J* = 8.0 Hz), 7,54 (d, 1H, ArH, *J* = 8.0 Hz), 8,11 (d, 2H, ArH, *J* = 8.8 Hz), 9,73 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23,43 ($COCH_3$), 30,15 (CH_2Ph), 55,67 (OCH_3), 56,20 (OCH_3), [114,47 (2C), 115.79, 117.75, 119.94, 126.75, 127.12, 132.23 (2C), 139.61, 149.61, 163.39] (ArC), [128.38 (2C), 130.87 (2C), 131.67, 134.59] (ArC linked C-3), 147,76 (Triazole C-3), 147,93 (N=CH), 151,59 (Triazole C-5), 164,04 (COO), 165,97 ($COCH_3$); UV [Etanol, λ_{max}, nm (ε, $L.mol^{-1}.cm^{-1}$)]: 298 (11.260), 260 (22.210), 218 (26.990).

2-Methoxy-6-[(1-acetyl-3-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]-phenyl 4-methoxybenzoate (4f):

Yield: 90%, m.p. 202 °C; IR (cm^{-1}) υ_{max}: 1770, 1725, 174 (C=O), 1603, 1574 (C=N), 1261 (COO), 788 (1,4-disubstituted benzenoid ring), 761 and 694 (monosubstituted benzenoid ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2,51 (s, 3H, $COCH_3$), 3,81 (s, 3H, OCH_3), 3,90 (s, 3H, OCH_3), 7,13 (d, 2H, ArH, *J* = 8.8 Hz), 7,34-7.43 (m, 2H,

ArH), 7,51-7.61 (m, 4H, ArH), 7,87-7.93 (m, 2H, ArH), 8,10 (d, 2H, ArH, *J* = 8.8 Hz), 9,70 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23,47 ($CO\underline{C}H_3$), 55,66 (OCH_3), 56,21 (OCH_3), [114,40 (2C), 115.91, 117.51, 119.99, 126.71, 127.20, 132.21 (2C), 139.64, 151.26, 163.44] (ArC), [126.50, 128.00 (2C), 128.60 (2C), 130.08] (ArC linked C-3), 148,03 (Triazole C-3), 150,33 (N=CH), 151,63 (Triazole C-5), 163,98 (COO), 166,20 ($\underline{C}OCH_3$); UV [Etanol, λ_{max}, nm (ε, L.mol^{-1}.cm^{-1})]: 308 (9.730), 282 (18.150), 254 (21.755), 226 (17.060).

3. Results and discussion

In the present work, 2-methoxy-6-[(3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]phenyl 4-methoxybenzoates (**3**) reacted with acetic anhydride to obtain six novel 2-methoxy-6-[(1-acetyl-3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-azomethine]phenyl 4-methoxybenzoates **(4)**. The structures of compounds **4** were identified by using IR, ^{1}H-NMR, ^{13}C-NMR and UV spectral data, and the observed spectral values were seen to be compatible with literature values [3, 11-19].

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