Synthesis and Characterizations of Some New 4H-1,2,4-Triazole Derivatives

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3-[(5-Amino-1,3,4-thiadiazol-2-yl)methyl]-4-ethoxycarbonylamino-5-alkyl-4H-1,2,4-triazoles (2a,b) were obtained from the reaction of 3-cyanomethyl-5-alkyl-4-ethoxycarbonylamino-4H-1,2,4-triazoles (1a,b) with thiosemicarbazide in the presence of trifluoroacetic acid. The treatment of the obtained compounds (2a,b) with acetic anhydride for 1 h afforded 3-[(5-acetylamino-1,3,4-thiadiazol-2-yl)methyl]-4-ethoxycarbonylamino-5-alkyl-4H-1,2,4-triazoles (3a,b). The synthesis of 4-ethoxycarbonylamino-3-[(2,3-dihydro-1,3-benzoxazol-2-yl)methyl]-5-(4-methylbenzyl)-4H-1,2,4-triazole (4) was performed by the treatment of 3-[(5-acetylamino-1,3,4-thiadiazol-2-yl)methyl]-4-ethoxycarbonylamino-5-(4-methylbenzyl)-4H-1,2,4-triazole (3a) with o-aminophenol under nitrogen atmosphere for 50 h. The reaction of compounds 1a,b with salicylaldehyde in the presence of sodium ethoxide yielded 2-{4-[(ethoxycarbonyl)amino]-5-alkyl-4H-1,2,4-triazol-3-yl}-3-(2-hydroxyphenyl)acrylonitriles (5a,b). The acetylations of compounds 5a,b with acetic anhydride for 5 h resulted in the formation of 2-{4-[acetyl(ethoxycarbonyl)amino]-5-alkyl-4H-1,2,4-triazol-3-yl}-3-[(2-acetylxy)phenyl]-acrylic acids (6a,b). On the other hand, the treatment of compounds 5a,b with methyl iodide in the presence of NaOH produced 2-{4-[ethoxycarbonyl]amino}-5-alkyl-4H-1,2,4-triazol-3-yl}-3-(2-methoxyphenyl)acrylic acids (7a,b).

Key Words: 4H-1,2,4-triazole, 1,3,4-thiadiazole, 1,3-benzoxazole, salicyl aldehyde, acetylation, acrylonitrile, acrylic acid.

Introduction

The synthesis of 1,2,4-triazole derivatives has been attracting widespread attention due to their diverse biological activities such as antimicrobial, antiinflammatory, and analgesic antitumoral activities.1−8 There are some antimicrobial drugs containing a triazole moiety. For instance, fluconazole and itraconazole are used in medical therapy.9,10 In addition, Vorozole, Letrozole, Fadrozole, and Anastrozole are nonsteroidal drugs used for the treatment of estrogen dependent breast cancer.11 In this connection, we have synthesized some of the 1,2,4-triazole derivatives possessing antimicrobial or antitumoral activity, some of which are also...
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containing the 1,3,4-thiadiazole ring\textsuperscript{1,4,12−18} in their structures. Besides, the compounds containing 1,3,4-thiadiazole or benzoxazole ring have been reported to possess several biological properties such as analgesic, fungicidal, insecticidal, nematocidal and antitumoral activities and their antibacterial properties were largely described.\textsuperscript{19−21}

Several methods have been described for the synthesis of 1,3,4-thiadiazoles.\textsuperscript{22,23} Among these, the cyclization of thiosemicarbazide derivatives in acidic media has reported to be a good strategy resulting in good yields.\textsuperscript{22} Another way leading to the formation of 1,3,4-thiadiazoles have been containing the reaction of cyano compounds with thiosemicarbazide in the presence of trifluoroacetic acid.\textsuperscript{23}

The chemistry of 1,2,4-triazol-3-ones was studied in detail. For instance, \textit{N}-alkylated derivatives of some 1,2,4-triazol-3-one compounds were obtained in our laboratory as antimicrobial agents by the reaction of corresponding 5-alkyl-1,2,4-triazol-3-one with the corresponding alkyl halide in the presence of sodium ethoxide. The \textit{O}-alkylation reactions could be achieved in the presence of sodium ethoxide or sodium hydroxide in the 1,2,4-triazole derivatives.\textsuperscript{13} In addition, acylation, nitration, and bromination of 1,2,4-triazol-3-one derivatives were performed in our laboratories along with their conversion into Schiff bases.\textsuperscript{12,13,24}

There are antimicrobial agents having different structures are frequently used in treatment of microbial infections. However, there is an increasing resistance to these drugs. Moreover, some of azole derivatives used as common antibiotics such as Amphotericin B posses a toxic effect on humans as well as their antimicrobial effects.\textsuperscript{25} To overcome the development of drug resistance, it is crucial to synthesize a new class of antimicrobials possessing different chemical properties from those of used commonly.

In view of these facts, the aim of this present study is to obtain the compounds containing 1 or 2 azole rings.

\textbf{Results and Discussion}

3-Cyanomethyl-5-alkyl-4-ethoxycarbonylamino-4\textit{H}-1,2,4-triazoles (1\textit{a},\textit{b}) were prepared by the method reported by us earlier [1]. The synthesis of compounds 2\textit{a},\textit{b} was performed by the treatment of compounds 1\textit{a},\textit{b} with thiosemicarbazide in the presence of trifluoroacetic acid in good yields.

The IR spectra of compounds 2\textit{a},\textit{b} displayed no signals belonging to cyano group; instead, new signals derived from amino structure appeared at 3360-3252 cm\textsuperscript{-1}. The \textit{NH\textsubscript{2}} group at position-5 on 1,3,4-thiadiazole ring resonated at 3.40 ppm integrating for 2 protons (exchangeable with D\textsubscript{2}O) in the \textit{\textit{1H}} NMR spectra, while the signal due to CN group disappeared in the \textit{\textit{13C}} NMR spectra of compounds 2\textit{a},\textit{b}.

The synthesis of monoacetylated derivatives (3\textit{a},\textit{b}) of compounds 2\textit{a},\textit{b} was achieved by the treatment with acetic anhydride for 1 h. There exists an additional carbonyl stretching in the IR spectra of compounds 3\textit{a},\textit{b}. Moreover, the \textit{\textit{1H}} and \textit{\textit{13C}} NMR spectra of 3-[5-acetylamino-1,3,4-thiadiazol-2-yl]methyl]-4-ethoxycarbonylamino-5-alkyl-4\textit{H}-1,2,4-triazoles (3\textit{a},\textit{b}) displayed additional signals belonging to acetyl group at 1.98-2.32 ppm and 20.50-22.56 ppm, respectively. Beside this, the \textit{NH\textsubscript{2}} signals disappeared in the IR and \textit{\textit{1H}} NMR spectra of compounds 3\textit{a},\textit{b}, while an additional signal originated from second \textit{NH} group (exchangeable with D\textsubscript{2}O) was recorded at 11.03-11.16 ppm in the \textit{\textit{1H}} NMR spectrum.

The reaction of compound 1\textit{a} with o-amino phenol under nitrogen atmosphere in the acidic media afforded 4-ethoxycarbonylamino-3-\textit{[(2,3-dihydro-1,3-benzoxazol-2-yl)methyl]-5-(4-methylbenzyl)-4\textit{H}-1,2,4-triazole (4)}. The signal belonging to cyano group was absent in the IR and \textit{\textit{13C}} NMR spectra of compound 4. The aromatic protons of benzoxazole moiety resonated in the same region with the aromatic protons of
4-methylbenzyl group, between 7.20-7.31 ppm, integrating 8 protons, as expected. On the other hand, the signal due to benzoxazole C-2-H appeared at 162.61 ppm in the $^{13}$C NMR spectrum.

The condensation of compounds 1a,b with salicylaldehyde in the presence of sodium ethoxide yielded 2-{4-[ethoxycarbonyl]amino}-5-alkyl-1H,1,2,4-triazol-3-yl}-3-(2-hydroxyphenyl) acrilonitriles (5a,b). The stretching band belonging to CN group is present in the IR spectra of compounds 5a,b. Moreover, the CN signal belonging to acrylonitril moiety was observed at 114.41 ppm (compound 5a,) or 114.40 ppm (compound 5b), while ethylenic C was seen at 116.35 ppm in the $^{13}$C NMR spectra of compounds 5a,b. On the other hand, ethylenic CH of acrylonitril moiety resonated at 138.5 ppm due to the mesomeric effect. The ethylenic CH appeared at 6.94-7.13 ppm in the $^1$H NMR spectra of compound 5a,b. When NaOH, primary or secondary amine was used, no reaction took place between compounds 1a,b and salicyl aldehyde.

The acetic anhydride treatment of compounds 5a,b for 5 h resulted in the acetylation of both –NH-groups at the same time with the hydrolysis of cyano group to carboxyl group, thus, 2-{4-[acetyl(ethoxycarbonyl)amino]-5-alkyl-1H,1,2,4-triazol-3-yl}-3-[2-(acetyloxy)phenyl]-acrylic acids (6a,b) were obtained. The peak derived from cyano group disappeared in the IR and $^{13}$C NMR spectra of compounds 6a,b. On the other hand, the signal due to carboxyl group was observed at 3360 cm$^{-1}$ in the IR spectra. In addition, the carboxyl group resonated at 14.77 ppm and 178.90-178.92 ppm in the $^1$H and $^{13}$C NMR spectra of compounds 6a,b, respectively. Moreover, -NH and -OH signals were absent in the $^1$H NMR spectra of compounds 6a,b.

The reactions of compounds 5a,b with methyl iodide in the presence of sodium hydroxide produced 2-{4-[ethoxycarbonyl]amino}-5-alkyl-1H,1,2,4-triazol-3-yl}-3-[2-methoxyphenyl]acrylic acids (7a,b). In the $^1$H NMR spectra of compounds 7a,b, the signal belonging to phenolic –OH disappeared. Instead, a new signal derived from methoxy group was observed at 3.79 ppm integrating for 3 protons. This group appeared at 59.27 ppm in the $^{13}$C NMR spectra. Furthermore, the presence of NaOH in this reaction afforded the conversion of cyano group to carboxyl group, as expected. In the IR, $^1$H NMR and $^{13}$C NMR spectra of compounds 7a,b peaks originating from carboxyl group were observed at 3365-3367 cm$^{-1}$, 14.82 ppm, and 178.46 ppm, respectively, while the signal representing cyano group was absent.

The elemental analyses of newly synthesized compounds are consistent with the assigned structures.

**Experimental**

Melting points were determined on a Gallenkamp melting point apparatus and were uncorrected. $^1$H NMR and $^{13}$C NMR (as APT) spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrometer. Combustion analysis was performed on a Carlo Erba 1106 elemental analyzer. All the chemicals were obtained from Fluka Chemie AG Buchs (Switzerland).

**General method for the synthesis of compounds 2a,b**

The solution of corresponding compound 1 (10 mmol) in trifluoroacetic acid was refluxed with thiosemicarbazide (10 mmol) at 60-80 °C for 10 h. After neutralizing with NH$_3$ solution, excess amount of water was added into it. The formed white solid was filtered off, washed with water, and recrystallized from ethanol-water (1:2) to afford the desired compound.
H-1,2,4-triazole (2a): This compound was obtained as white needles (yield: 3.19 g, 86%); M.P. 214 °C; IR (KBr) (v, cm⁻¹): 3360-3252 (NH+NH₂), 1733 (C=O), 1515 and 1487 (4C=N), 1255 (C-O); ¹H NMR (DMSO-d₆, δ ppm): 1.34 (t, 3H, CH₃, J = 6.1 Hz), 2.27 (s, 3H, CH₃), 3.40 (s, 2H, NH₂), 4.02 (s, 4H, 2CH₂), 4.60 (q, 2H, CH₂, J = 6.1 Hz), 7.18-7.20 (m, 2H, arom-H), 7.22-7.24 (m, 2H, arom-H), 11.03 (s, NH); ¹³C NMR (DMSO-d₆, δ ppm): 14.03 (CH₃), 20.05 (CH₃), 25.13 (CH₂), 28.56 (CH₂), 61.66 (OCH₂CH₃), arom-C: [128.22 (2CH), 130.50 (2CH), 131.35 (C), 134.17 (C)], 150.83 (triazole-C-3), 151.35 (thiadiazole-C-2), 153.58 (triazole-C-5), 166.27 (thiadiazole-C-5), 169.45 (C=O).


H-1,2,4-triazole (2b): This compound was obtained as white needles (yield: 3.39 g, 86%); M.P. 216 °C; IR (KBr) (v, cm⁻¹): 3363-3269 (NH+NH₂), 1733 (C=O), 1515 and 1491 (4C=N), 1257 (C-O); ¹H NMR (DMSO-d₆, δ ppm): 1.34 (t, 3H, CH₃, J = 6.5 Hz), 3.40 (s, 2H, NH₂), 3.98 (s, 2H, CH₂), 4.16 (s, 2H, CH₂), 4.51 (q, 2H, CH₂, J = 6.1 Hz), 7.18 (d, 2H, arom-H, J = 8.2 Hz), 7.35 (d, 2H, arom-H, J = 8.2 Hz), 10.94 (s, NH); ¹³C NMR (DMSO-d₆, δ ppm): 14.03 (CH₃), 25.10 (CH₂), 28.74 (CH₂), 61.98 (OCH₂CH₃), arom-C: [128.24 (2CH), 130.52 (2CH), 131.34 (C), 134.29 (C)], 150.91 (triazole-C-3), 151.26 (thiadiazole-C-2), 153.16 (triazole-C-5), 165.50 (thiadiazole-C-5), 169.35 (C=O).

Anal. Calcd. (%) for C₁₆H₁₉ClN₇O₂S: C, 54.75; H, 4.09; N, 24.89. Found; C, 45.79; H, 4.19; N, 24.92.

General method for the synthesis of compounds 3a,b

The corresponding compound 2 (10 mmol) was refluxed with acetic anhydride for 1 h. Then, the mixture was cooled to room temperature and, after 40 mL ethanol was added, it was refluxed for an additional 30 min. On cooling the mixture in a deep freeze, a solid appeared. This crude product was recrystallized from ethanol-water (1:1) to give pure compound.

3-[5-Amino-1,3,4-thiadiazol-2-yl)methyl]-4-ethoxycarbonylamino-5-(4-chloro-benzyl)-4

H-1,2,4-triazole (3a): This compound was obtained as white needles (yield: 3.46 g, 84%); M.P. 186 °C; IR (KBr) (v, cm⁻¹): 3158 and 3137 (2NH), 1780 and 1733 (2C=O), 1622, 1538, 1497 and 1480 (4C=N), 1257 (C-O); ¹H NMR (DMSO-d₆, δ ppm): 1.56 (t, 3H, CH₃, J = 6.5 Hz), 2.32 (bs, 6H, 2CH₃), 3.37 (s, 4H, 2CH₂), 4.52 (q, 2H, CH₂, J = 6.1 Hz), 7.20-7.23 (m, 2H, arom-H), 7.31-7.34 (m, 2H, arom-H), 10.27 (s, 1H, NH), 11.03 (s, 1H, NH); ¹³C NMR (DMSO-d₆, δ ppm): 14.03 (CH₃), 20.12 (CH₃), 25.13 (CH₂), 28.56 (CH₂), 61.66 (OCH₂CH₃), arom-C: [127.67 (2CH), 130.11 (2CH), 132.33 (C), 134.62 (C)], 148.80 (triazole-C-3), 152.26 (thiadiazole-C-2), 154.05 (triazole-C-5), 165.55 (C=O), 167.78 (thiadiazole-C-5), 169.43 (C=O), 169.87 (C=O).

Anal. Calcd. (%) for C₁₆H₁₉ClN₇O₂S: C, 52.04; H, 5.09, N, 23.60. Found; C, 52.19; H, 5.13; N, 23.56.

3-[5-Acetamino-1,3,4-thiadiazol-2-yl)methyl]-4-ethoxycarbonylamino-5-(4-methylbenzyl)-4

H-1,2,4-triazole (3b): This compound was obtained as white needles (yield: 3.79 g, 87%); M.P. 188 °C; IR (KBr) (v, cm⁻¹): 3155 and 3141 (2NH), 1783 and 1728 (2C=O), 1622, 1538, 1497 and 1480 (4C=N), 1257 (C-O); ¹H NMR (DMSO-d₆, δ ppm): 1.58 (t, 3H, CH₃, J = 6.4 Hz), 1.98 (s, 3H, CH₃), 4.09 (bs, 4H, 2CH₂), 4.62 (q, 2H, CH₂, J = 6.4 Hz), 7.23 (d, 2H, arom-H, J = 8.0 Hz), 7.31 (d, 2H, arom-H, J = 8.2 Hz), 10.74 (s, 1H, NH), 11.16 (bs, 1H, NH); ¹³C NMR (DMSO-d₆, δ ppm): 14.45 (CH₃), 22.56 (CH₃), 25.51 (CH₂), 29.07 (CH₂), 63.78 (OCH₂CH₃), arom-C: [127.67 (2CH), 130.11 (2CH), 132.33 (C), 134.62 (C)], 146.26 (triazole-C-3), 151.67 (thiadiazole-C-2), 153.48 (triazole-C-5), 165.54 (thiadiazole-C-5), 169.83 (C=O), 171.35 (C=O).
The synthesis of 4-ethoxycarbonylamino-3-[(2,3-dihydro-1,3-benzoxazol-2-yl)methyl]-5-(4-methylbenzyl)-4H-1,2,4-triazole (4): The corresponding compound 1a (10 mmol) was refluxed with o-amino-phenol (10 mmol) in the presence of dilute hydrochloric acid (20 mL of Conc. HCl in 200 mL of water) under nitrogen atmosphere for 50 h. After cooling to room temperature, the reaction content was extracted with 20 mL of CHCl₃ 3 times. Then, chloroform extract was washed with three 20 mL of 4N NaOH solution. On evaporating the chloroform layer under reduced pressure, an oily product was obtained. This was recrystallized from isobutyl acetate-petroleum ether (1:1). This compound was obtained as white needles (yield: 1.39 g, 35.61%); M.P. 166 °C.

The synthesis of 4-ethoxycarbonylamino-3-[(2,3-dihydro-1,3-benzoxazol-2-yl)methyl]-5-(4-methylbenzyl)-4H-1,2,4-triazole (5): This compound was obtained as white needles (yield: 1.39 g, 35.61%); M.P.166 °C; IR (KBr) (v, cm⁻¹): 3155 (NH), 1716 (C=O), 1607 and 1514 (2C=N), 1252 (C-O); 1³C NMR (DMSO-d₆, δ ppm): 17.45 (CH₃), 24.35 (CH₃), 28.62 (CH₂), 33.63 (CH₂), 62.48 (OCH₂CH₃), C₁=C₂: [123.88 (2CH), 125.31 (2CH), 127.26 (2CH), 128.04 (2CH), 129.61 (C), 134.60 (C), 141.37 (C), 145.11 (triazole-C-3), 153.42 (triazole-C-5), 160.73 (C=O), 163.21 (benzoxadiazole-C-2).

Anal. Calcd. (%) for C₂₁H₂₄N₅O₃: C, 64.44; H, 5.41, N, 17.89. Found; C, 64.58; H, 5.50; N, 17.69.

General method for the synthesis of compounds 5a,b
The corresponding compound 1 (10 mmol) was refluxed with equalent amount of sodium in absolute ethanol for 2 h. Then, salicylaldehyde (10 mmol) was added and refluxed for an additional 8 h. After neutralizing with HCl, a solid appeared. This crude product was filtered off, washed with water and recrystallized from ethyl acetate to afford the desired compound.

2-{4-[Ethyoxycarbonylamino]-5-(4-methylbenzyl)-4H-1,2,4-triazol-3-yl}-3-(2-hydroxyphenyl)acrylonitril (5a): This compound was obtained as white needles (yield: 2.71 g, 67 %); M.P.190 °C; IR (KBr) (v, cm⁻¹): 3450 (OH), 3117 (NH), 2261 (CN), 1735 (C=O), 1607 and 1517 (2C=N); ¹H NMR (DMSO-d₆, δ ppm): 1.53 (bs, 3H, CH₃), 2.54 (s, 3H, CH₃), 3.33 (s, 2H, CH₂), 3.84 (s, 2H, CH₂), 4.20 (s, 2H, CH₂), 7.20-7.31 (m, 8H, arom-H), 10.76 (s, 1H, NH); ¹³C NMR (DMSO-d₆, δ ppm): 17.45 (CH₃), 24.35 (CH₃), 28.62 (CH₂), 33.63 (CH₂), 62.48 (OCH₂CH₃), C₁=C₂: [123.88 (2CH), 125.31 (2CH), 127.26 (2CH), 128.04 (2CH), 129.61 (C), 134.60 (C), 141.37 (C), 145.11 (triazole-C-3), 153.42 (triazole-C-5), 160.73 (C=O), 163.21 (benzoxadiazole-C-2).


2-{4-[Ethyoxycarbonylamino]-5-(4-chlorobenzyl)-4H-1,2,4-triazol-3-yl}-3-(2-hydroxyphenyl)acrylonitril (5b): This compound was obtained as white needles (yield: 2.77 g, 66 %); M.P. 178 °C; IR (KBr) (v, cm⁻¹): 3453 (OH), 3116 (NH), 2260 (CN), 1733 (C=O), 1607 and 1514 (2C=N), 1252 (C=O); ¹H NMR (DMSO-d₆, δ ppm): 1.45 (t, 3H, CH₃,J= 7.0 Hz), 3.35 (s, 2H, CH₂), 4.00 (q, 2H, CH₂,J= 7.0 Hz), 6.94 (bs, 1H, ethylenic CH), 7.17 (s, 3H, arom-H), 7.50-7.65 (m, 3H, arom-H), 7.82 (m, 1H, arom-H), 8.48 (s, 1H, arom-H), 11.08 (bs, 2H, NH+OH); ¹³C NMR (DMSO-d₆, δ ppm): 14.63 (CH₃), 29.39 (CH₂), 62.03 (OCH₂CH₃), 114.40 (CN), 116.35 (ethylenic C), arom-C: [for o-hydroxyphenyl ring: 118.13 (CH), 125.16 (C), 128.67 (CH), 132.08 (CH), 133.68 (CH), 156.60 (C); for p-methylphenyl ring: 129.16 (2CH), 129.45 (2CH), 135.80 (C), 135.83 (C), 146.66 (triazole-C-3), 138.54 (ethylenic CH), 153.74 (triazole-C-5), 157.66 (C=O).

General method for the synthesis of compounds 6a,b

The corresponding compound 5 (10 mmol) was refluxed with acetic anhydride for 5 h. Then, the mixture was cooled to room temperature and after 40 mL of ethanol was added, it was refluxed for an additional 60 min. On cooling the mixture in a deep freeze, a solid appeared. This crude product was recrystallized from ethanol-water (1:1) to give the desired compound.

2-[4-(Acetyl(ethoxycarbonylamino)-5-(4-methylbenzyl)-4H-1,2,4-triazol-3-yl]-3-[2-(acetoxyl)phenyl]acrylic acid (6a): This compound was obtained as white needles (yield: 4.45 g, 88%);
M.P.159 °C; IR (KBr) (v, cm⁻¹): 3360 (COOH), 1723 (3C=O), 1608 and 1576 (2C=N), 1231 (C-O);¹H NMR (DMSO-d₆, δ ppm): 1.27 (t, 3H, CH₃, J=6.8 Hz), 2.18 (s, 3H, CH₃), 2.52 (bs, 6H, 2CH₃), 3.33 (bs, 2H, CH₂), 4.51 (q, 2H, CH₂, , J=6.8 Hz), 6.87 (bs, 1H, ethylenic CH), 7.15 (bs, 2H, arom-H), 7.50 (m, 2H, arom-H), 7.68-7.82 (m, 4H, arom-H); ¹³C NMR (DMSO-d₆, δ ppm): 14.10 ppm) 90.28 (C), 124.96 (C), 131.26 (C), 147.68 (ethylenic-CH), 154.14 (triazole-C-5), 157.21 (esteric-C=O), 167.89 and 168.11 (acetyl-C=O), 178.90 (COOH).

Anal. Calcd. (%) for C₉H₁₂ClN₂O₇: C, 61.65; H, 5.17 N, 11.06. Found: C, 61.82; H, 5.34; N, 10.92.

2-[4-(Acetyl(ethoxy carbonyl)amino)-5-(4-chlorobenzyl)-4H-1,2,4-triazol-3-yl]-3-[2-(acetoxyl)phenyl]acrylic acid (6b): This compound was obtained as white needles (yield: 4.58 g, 87%);
M.P.150 °C; IR (KBr) (v, cm⁻¹): 3360 (COOH), 1723 and 1730 (3C=O), 1612 and 1575 (2C=N), 1231 (C-O);¹H NMR (DMSO-d₆, δ ppm): 1.26 (t, 3H, CH₃, , J=6.6 Hz), 2.50 (s, 3H, CH₃), 2.74 (s, 3H, CH₃), 3.37 (bs, 2H, CH₂), 4.51 (q, 2H, CH₂, , J=6.6 Hz), 6.96 (bs, 1H, ethylenic CH), 7.20-7.37 (m, 4H, arom-H), 7.53 (m, 2H, arom-H), 7.82 (m, 2H, arom-H), 14.77 (bs, 1H, COOH); ¹³C NMR (DMSO-d₆, δ ppm): 20.61 (CH₃), 22.65 (CH₃), 24.83 (CH₃), 29.32 (CH₂), 62.41 (OCH₂CH₃), 124.96 (ethylenic-C), arom-C: [for o-(O-acetylphenyl) ring: 118.13 (CH), 128.61 (CH), 129.45 (CH), 125.24 (C), 132.08 (CH), 156.17 (c); for p-methylphenyl ring: 129.16 (2CH), 130.34 (2CH), 133.68 (C), 135.83 (C)], 146.66 (triazole-C-3), 147.28 (ethylenic-CH), 153.74 (triazole-C-5), 157.66 (esteric-C=O), 166.25 and 166.37 (acetyl-C=O), 178.92 (COOH).


General method for the synthesis of compounds 7a,b

The corresponding compound 6 (10 mmol) was refluxed with equivalent amount of sodium hydroxide in absolute ethanol for 2 h. Then, methyl iodide (10 mmol) was added and refluxed for additional 8 h. After neutralization with HCl, a solid appeared. This crude product was filtered off, washed with water and recrystallized from isobutyl acetate-petroleum ether (1:1) to afford the desired compound.

2-[4-((Ethoxycarbonyl)amino)-5-(4-methyl benzyl)-4H-1,2,4-triazol-3-yl]-3-[2-methoxypHENYL]acrylic acid (7a): This compound was obtained as white needles (yield: 2.73 g, 63%); M.P.152 °C; IR (KBr) (v, cm⁻¹): 3367 (COOH), 3125 (NH), 1723 and 1745 (2C=O), 1613 and 1549 (2C=N), 1238 (C-O);¹H NMR (DMSO-d₆, δ ppm): 1.31 (t, 3H, CH₃, , J=6.6 Hz), 2.50 (s, 3H, CH₃), 3.79 (s, 3H, CH₃), 3.32 (bs, 2H, CH₂), 4.14 (q, 2H, CH₂, , J=6.5 Hz), 6.84 (bs, 1H, ethylenic CH), 7.15 (bs, 2H, arom-H), 7.32 (m, 1H, arom-H), 7.50 (m, 1H, arom-H), 7.64 (m, 2H, arom-H), 7.82 (m, 1H, arom-H), 8.13 (s, 1H, arom-H), 11.16 (bs, 1H, NH), 14.82 (bs, 1H, COOH); ¹³C NMR (DMSO-d₆, δ ppm): 15.67 (CH₃), 21.38 

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(CH₃), 29.35 (CH₂), 59.27 (OCH₃), 61.66 (OCH₂CH₃), 115.41 (ethylenic-C), arom-C: [for o-methoxyphenyl ring: 118.24 (CH), 125.67 (CH), 129.43 (C), 131.36 (CH), 156.85 (C); for p-methylphenyl ring: 129.45 (2CH), 130.24 (2CH), 132.30 (C), 134.25 (C)], 144.71 (triazole-C-3), 135.80 (ethylenic-CH), 152.11 (triazole-C-5), 157.74 (esteric-C=O), 178.46 (COOH).

Anal. Calcd. (%) for C₂₃H₂₄N₄O₅: C, 63.29; H, 5.54, N, 12.84. Found; C, 63.42; H, 5.68; N, 12.81.

2-{(4-(Ethoxycarbonyl)amino)-5-(4-chlorobenzyl)-4H-1,2,4-triazol-3-yl}-3-(2-methoxyphenyl)acrylic acid (7b): This compound was obtained as white needles (yield: 2.98 g, 65%); M.P. 167 °C; IR (KBr) (υ, cm⁻¹): 3365 (COOH), 3112 (NH), 1737 (2C=O), 1611 and 1553 (2C=N), 1237 (C-O); ¹H NMR (DMSO-d₆, δ ppm): 1.20 (t, 3H, CH₃, J=6.7 Hz), 3.39 (bs, 2H, CH₂), 3.89 (s, 3H, CH₃), 4.03 (q, 2H, CH₂, J=6.6 Hz), 6.84 (bs, 1H, ethylenic CH), 7.15 (bs, 2H, arom-H), 7.32 (m, 1H, arom-H), 7.50 (m, 1H, arom-H), 7.64 (m, 2H, arom-H), 7.82 (m, 1H, arom-H), 8.13 (s, 1H, arom-H), 11.16 (bs, 1H, NH), 14.82 (bs, 1H, COOH); ¹³C NMR (DMSO-d₆, δ ppm): 16.28 (CH₃), 29.35 (CH₂), 61.03 (OCH₃), 61.65 (OCH₂CH₃), 117.41 (ethylenic-C), arom-C: [for o-methoxyphenyl ring: 112.21 (CH), 123.85 (CH), 126.91 (CH), 129.34 (CH), 130.62 (C), 157.03 (C); for p-chlorophenyl ring: 128.17 (2CH), 132.37 (2CH), 134.45 (C), 135.86 (C)], 145.85 (ethylenic-CH), 144.70 (triazole-C-3), 152.27 (triazole-C-5), 157.16 (esteric-C=O), 178.42 (COOH).


Scheme. Synthetic pathway for the preparation of compounds 1-7.

References
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