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Synthesis and Characterization of Novel 1-(Morpholin-4-yl-methyl)-3-alkyl(aryl)-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones

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Abstract: In this study, six novel 1-(morpholin-4-yl-methyl)-3-alkyl(aryl)-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-one (2) compunds were synthesized from a reaction of type 1 compunds with formaldehyde and morpholine. The finally part contains that synthesis of new compounds. The structures of these novel compounds were characterized by using, IR, ^{1}H NMR and ^{13}C NMR spectral data.

Keywords: Schiff bases, Mannich bases, Synthesis, Characterization

Introduction

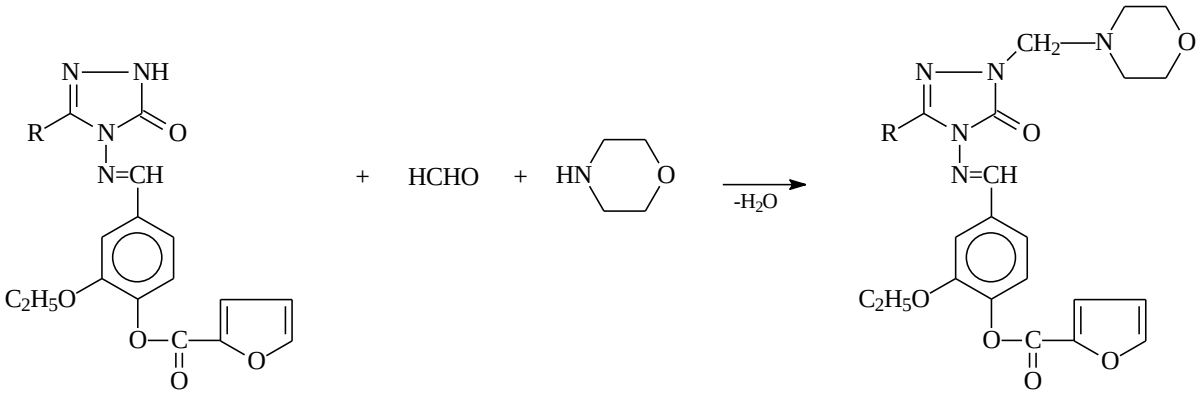
1,2,4-triazole nucleus is one of the active ingredients found in many standard drugs and is known to increase the pharmacological activity of the molecules. Compounds containing the morpholine moiety are effective in contributing to the net biological activity of a system. It has been found that some of the compounds having 1,2,4-triazole ring have antimicrobial activity against various microorganisms (Demirbas et al., 2009).

In a recent study, pyrimidine alkyne-derived Mannich bases were synthesized and their neuroprotection and neurotoxicity activities were evaluated (Triloknadh et al., 2018). Mannich bases containing 5-mercapto-1,2,4-triazole derivative were synthesized and screened for a panel of 60 cell lines derived from seven cancer types, such as lung, colon, melanoma, renal, ovarian, CNS and leukemia, for their anticancer activity (Holla et al., 2003). Some Mannich bases carrying morpholine fragment showed good anti-inflammatory and analgesic activity (Nithinchandra et al., 2012). The antimicrobial activities of the triazole compounds containing Mannich base were screened; some have shown good or moderate activity against tested microorganisms (Bektaş et al., 2010). Anti-lipase and anti-urease activities of some 1,2,4-triazole derived compounds were investigated. Some of these have shown moderate to good lipase inhibitory effects (Bekircan et al., 2014). Some heterocyclic compounds containing morpholine showed good and moderate antimicrobial activity (Bayrak et al., 2009).

A series of compounds containing 1,2,4-triazole and morpholine were synthesized. Some of them showed significant anti-inflammatory activity. They have also been tested for analgesic activities and gastric ulceration studies. Important analgesic activity was detected in the compounds containing morpholine rings without causing any stomach irritation. Most of the compounds were found to exhibit moderate antimicrobial activity (Alam et al., 2012). Recently, some 1,2,4-triazole derived compounds have been tested for antimicrobial and anti-lipase inhibitory activities (Ozdemir et al., 2017).

- Selection and peer-review under responsibility of the Organizing Committee of the Conference

In the present study, six novel compounds 1-(morpholin-4-yl-methyl)-3-alkyl(aryl)-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (2a-f) were synthesized from the reactions of 3-alkyl(aryl)-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (1a-f) with formaldehyde and morpholine (Scheme 1).



1 **2**

1-2	R
a	CH_3
b	CH_2CH_3
c	$CH_2C_6H_5$
d	$CH_2C_6H_4CH_3$(*p*-)
e	$CH_2C_6H_4Cl$(*p*-)
f	C_6H_5

Scheme 1

Method

Chemicals and Apparatus

Chemical reagents and all solvents used in this study were purchased from Merck AG, Aldrich and Fluka. Melting point was determined in open glass capillary using a Stuart melting point SMP30 apparatus and is uncorrected. The IR spectra were obtained on an ALPHA-P BRUKER 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 Plus Biospin spectrometer at 400 MHz and 100 MHz, respectively.

Synthesis of Compounds 2: The General Procedure

The corresponding compound 1 (0.01 mol) was dissolved in ethanol (40 mL) and was treated with morpholine (0.01 mol) and formaldehyde (%37) (0.02 mol) and then the mixture was refluxed for 2 h and filtered. The filtrate evaporated *in vacuo*, and the crude product was recrystallized from ethanol to afford compound 2.

Results and Discussion

1-(Morpholin-4-yl-methyl)-3-methyl-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-one (2a)

Yield: 3.18 g (70%), m.p. 146 °C. IR (KBr, υ, cm^{-1}): 1741, 1704 (C=O), 1573 (C=N), 1505, 1463 (C=C), 1298 (COO), 1159 (C-O, furan), 856 (1,4-disubstituted benzenoid ring) cm^{-1}; ^{1}H NMR (400MHz, DMSO–d_6): δ 1.24 (t, 3H, OCH_2CH_3, *J* = 6.80 Hz), 2.33 (s, 3H, CH_3), 2.59 (t, 4H, CH_2NCH_2, *J* = 4.40 Hz), 3.56 (t, 4H, CH_2OCH_2, *J* = 4.40 Hz), 4.14 (q, 2H, OCH_2CH_3, *J* = 6.80 Hz), 4.54 (s, 2H, NCH_2N), 6.82 (dd, 1H, Ar-H, *J* = 3.60, 1.60 Hz), 7.38 (d, 1H, Ar-H, *J* = 8.40 Hz), 7.50 (dd, 1H, Ar-H, *J* = 8.40, 1.60 Hz), 7.59 (dd, 1H, Ar-H, *J* = 3.60, 0.80 Hz), 7.64 (d, 1H, Ar-H, *J* = 1.60 Hz), 8.12 (dd, 1H, Ar-H, *J* = 1.60, 0.80 Hz), 9.71 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.94 (CH_3), 14.38 ($OCH_2\underline{CH_3}$), 49.97 (CH_2NCH_2), 64.34 ($O\underline{CH_2}CH_3$), 65.93

(NCH_2N), 66.03 (CH_2OCH_2), 112.70 (CH), 112.76 (CH), 120.33 (CH), 120.70 (CH), 123.62 (CH), 132.56 (C), 141.46 (C), 142.66 (C), 148.75 (CH), 150.53 (arom-C), 143.15 (triazol C_3), 150.22 (triazol C_5), 153.63 (N=CH), 155.48 (COO).

1-(Morpholin-4-yl-methyl)-3-ethyl-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-one (2b)

Yield: 3.90 g (83.33%), m.p. 142 °C. IR (KBr, υ, cm^{-1}): 1731, 1691 (C=O), 1575 (C=N), 1509, 1471 (C=C), 1282 (COO), 1165 (C-O, furan), 859 (1,4-disubstituted benzenoid ring) cm^{-1}; ^{1}H NMR (400MHz, DMSO–d_6): δ 1.22-1.26 (m, 6H, $2CH_2\underline{CH_3}$), 2.59 (t, 4H, CH_2NCH_2, *J* = 4.40 Hz), 2.73 (q, 2H, CH_2CH_3, *J* = 7.20 Hz), 3.57 (t, 4H, CH_2OCH_2, *J* = 4.40 Hz), 4.14 (q, 2H, OCH_2CH_3, *J* = 7.20 Hz), 4.55 (s, 2H, NCH_2N), 6.81 (dd, 1H, Ar-H, *J* = 3.60, 1.60 Hz), 7.38 (d, 1H, Ar-H, *J* = 8.40 Hz), 7.50 (dd, 1H, Ar-H, *J* = 8.40, 1.60 Hz), 7.60 (dd, 1H, Ar-H, *J* = 3.60, 0.80 Hz), 7.63 (d, 1H, Ar-H, *J* = 1.60 Hz), 8.12 (dd, 1H, Ar-H, *J* = 1.60, 0.80 Hz), 9.71 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.99 ($CH_2\underline{CH_3}$), 14.37 ($OCH_2\underline{CH_3}$), 18.39 ($\underline{CH_2}CH_3$), 49.99 (CH_2NCH_2), 64.32 ($O\underline{CH_2}CH_3$), 65.98 (NCH_2N), 66.04 (CH_2OCH_2), 112.74 (2CH), 120.32 (CH), 120.59 (CH), 123.65 (CH), 132.60 (C), 141.45 (C), 142.67 (C), 148.75 (CH), 150.58 (arom-C), 146.86 (triazol C_3), 150.35 (triazol C_5), 153.60 (N=CH), 155.48 (COO).

1-(Morpholin-4-yl-methyl)-3-benzyl-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-one (2c)

Yield: 3.75 g (70.68%), m.p. 105 °C. IR (KBr, υ, cm^{-1}): 1744, 1700 (C=O), 1573 (C=N), 1500, 1432 (C=C), 1290 (COO), 1159 (C-O, furan), 856 (1,4-disubstituted benzenoid ring), 772 and 694 (monosubstituted benzenoid ring) cm^{-1}; ^{1}H NMR (400MHz, DMSO–d_6): δ 1.26 (t, 3H, OCH_2CH_3, *J* = 6.80 Hz), 2.61 (t, 4H, CH_2NCH_2, *J* = 4.40 Hz), 3.58 (t, 4H, CH_2OCH_2, *J* = 4.40 Hz), 4.09 (s, 2H, CH_2Ph), 4.11 (q, 2H, OCH_2CH_3, *J* = 6.80 Hz), 4.59 (s, 2H, NCH_2N), 6.82 (dd, 1H, Ar-H, *J* = 3.60, 1.60 Hz), 7.24-7.25 (m, 1H, Ar-H), 7.31-7.37 (m, 5H, Ar-H), 7.42 (dd, 1H, Ar-H, *J* = 8.00, 1.60 Hz), 7.53 (d, 1H, Ar-H, *J* = 1.60 Hz), 7.59 (d, 1H, Ar-H, *J* = 3.20 Hz), 8.12 (dd, 1H, Ar-H, *J* = 1.60, 0.80 Hz), 9.67 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.36 ($OCH_2\underline{CH_3}$), 31.04 (CH_2Ph), 50.01 (CH_2NCH_2), 64.25 ($O\underline{CH_2}CH_3$), 66.06 (NCH_2N + CH_2OCH_2), 111.84 (CH), 112.76 (CH), 120.33 (CH), 121.23 (CH), 123.60 (CH), 132.52 (C), 141.47 (C), 142.65 (C), 148.75 (CH), 150.52 (arom-C), 126.78 (CH), 128.51 (2CH), 128.66 (2CH), 135.72 (C_3-arom-C), 144.91 (triazol C_3), 150.24 (triazol C_5), 153.00 (N=CH), 155.47 (COO).

1-(Morpholin-4-yl-methyl)-3-p-methylbenzyl-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-one (2d)

Yield: 4.15 g (76.27%), m.p. 154 °C. IR (KBr, υ, cm^{-1}): 1741, 1703 (C=O), 1573 (C=N), 1507, 1468 (C=C), 1291 (COO), 1156 (C-O, furan), 858 (1,4-disubstituted benzenoid ring) cm^{-1}; ^{1}H NMR (400MHz, DMSO–d_6): δ 1.26 (t, 3H, OCH_2CH_3, *J* = 6.80 Hz), 2.25 (s, 3H, $PhCH_3$), 2.60 (t, 4H, CH_2NCH_2, *J* = 4.40 Hz), 3.57 (t, 4H, CH_2OCH_2, *J* = 4.40 Hz), 4.06 (s, 2H, CH_2Ph), 4.12 (q, 2H, OCH_2CH_3, *J* = 6.80 Hz), 4.59 (s, 2H, NCH_2N), 6.82 (dd, 1H, Ar-H, *J* = 3.60, 1.60 Hz), 7.12 (d, 2H, Ar-H, *J* = 7.60 Hz), 7.23 (d, 2H, Ar-H, *J* = 8.00 Hz), 7.36 (d, 1H, Ar-H, *J* = 8.00 Hz), 7.42 (m, 1H, Ar-H), 7.53 (d, 1H, Ar-H, *J* = 1.60 Hz), 7.59 (dd, 1H, Ar-H, *J* = 3.60, 0.80 Hz), 8.12 (dd, 1H, Ar-H, *J* = 1.60, 0.80 Hz), 9.66 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.37 ($OCH_2\underline{CH_3}$), 20.57 ($PhCH_3$), 30.65 (CH_2Ph), 50.01 (CH_2NCH_2), 64.23 ($O\underline{CH_2}CH_3$), 66.04 (NCH_2N + CH_2OCH_2), 111.83 (CH), 112.76 (CH), 120.34 (CH), 121.25 (CH), 123.61 (CH), 132.59 (C), 141.47 (C), 142.66 (C), 148.75 (CH), 150.52 (arom-C), 128.49 (2CH), 129.00 (2CH), 132.54 (C), 135.87 (C_3-arom-C), 146.06 (triazol C_3), 150.24 (triazol C_5), 152.97 (N=CH), 155.48 (COO).

1-(Morpholin-4-yl-methyl)-3-p-chlorobenzyl-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-one (2e)

Yield: 4.24 g (75%), m.p. 129 °C. IR (KBr, υ, cm^{-1}): 1735, 1704 (C=O), 1595 (C=N), 1493, 1469 (C=C), 1297 (COO), 1161 (C-O, furan), 853 (1,4-disubstituted benzenoid ring) cm^{-1}; ^{1}H NMR (400MHz, DMSO–d_6): δ 1.26 (t, 3H, OCH_2CH_3, *J* = 6.80 Hz), 2.60 (t, 4H, CH_2NCH_2, *J* = 4.40 Hz), 3.57 (t, 4H, CH_2OCH_2, *J* = 4.40 Hz), 4.11 (q, 2H, OCH_2CH_3, *J* = 6.80 Hz), 4.14 (s, 2H, CH_2Ph), 4.58 (s, 2H, NCH_2N), 6.82 (dd, 1H, Ar-H, *J* = 3.60, 2.00 Hz), 7.37 (d, 1H, Ar-H, *J* = 8.00 Hz), 7.41-7.44 (m, 5H, Ar-H), 7.51 (d, 1H, Ar-H, *J* = 2.00 Hz), 7.59 (dd, 1H,

Ar-H, *J* = 3.60, 0.80 Hz), 8.12 (dd, 1H, Ar-H, *J* = 1.60, 0.80 Hz), 9.67 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.36 ($OCH_2\underline{CH_3}$), 30.37 (CH_2Ph), 49.99 (CH_2NCH_2), 64.25 ($O\underline{CH_2}CH_3$), 66.04 (CH_2OCH_2), 66. 11 (NCH_2N), 111.89 (CH), 112.75 (CH), 120.33 (CH), 121.24 (CH), 123.61 (CH), 132.48 (C), 141.51 (C), 142.66 (C), 148.75 (CH), 150.54 (arom-C), 128.45 (2CH), 130.71 (2CH), 131.48 (C), 134.72 (C_3-arom-C), 144.57 (triazol C_3), 150.23 (triazol C_5), 153.16 (N=CH), 155.47 (COO).

1-(Morpholin-4-yl-methyl)-3-phenyl -4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1H-1,2,4-triazol-5-one (2f)

Yield: 4.91 g (95.12%), m.p. 191 °C. IR (KBr, *υ*, cm^{-1}): 1733, 1697 (C=O), 1574 (C=N), 1499, 1469 (C=C), 1280 (COO), 1133 (C-O, furan), 856 (1,4-disubstituted benzenoid ring) cm^{-1}; ^{1}H NMR (400MHz, DMSO–d_6): δ 1.24 (t, 3H, OCH_2CH_3, *J* = 6.80 Hz), 2.67 (t, 4H, CH_2NCH_2, *J* = 4.40 Hz), 3.59 (t, 4H, CH_2OCH_2, *J* = 4.40 Hz), 4.12 (q, 2H, OCH_2CH_3, *J* = 6.80 Hz), 4.71 (s, 2H, NCH_2N), 6.82 (dd, 1H, Ar-H, *J* = 3.60, 1.60 Hz), 7.39 (d, 1H, Ar-H, *J* = 8.00 Hz), 7.47 (m, 1H, Ar-H), 7.55-7.57 (m, 3H, Ar-H), 7.60 (dd, 1H, Ar-H, *J* = 3.60, 0.80 Hz), 7.62 (d, 1H, Ar-H, *J* = 1.60 Hz), 7.93-7.95 (m, 2H, Ar-H), 8.12 (dd, 1H, Ar-H, *J* = 1.60, 0.80 Hz), 9.66 (s, 1H, N=CH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.33 ($OCH_2\underline{CH_3}$), 49.98 (CH_2NCH_2), 64.23 ($O\underline{CH_2}CH_3$), 66.07 (CH_2OCH_2), 112.60 (CH), 112.76 (CH), 120.37 (CH), 120.98 (CH), 123.76 (CH), 132.42 (C), 141.63 (C), 142.64 (C), 148.76 (CH), 150.57 (arom-C), 126.12 (C), 128.17 (2CH), 128.54 (2CH), 130.37 (C_3-arom-C), 143.23 (triazol C_3), 150.40 (triazol C_5), 156.08 (N=CH), 155.47 (COO).

Conclusion

In this study, the structures of six novel 1-(morpholin-4-yl-methyl)-3-alkyl(aryl)-4-[3-ethoxy-4-(2-furylcarbonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (2a-f) were characterized with IR, ^{1}H NMR and ^{13}C NMR spectral data and these were in parallel with previously published reports. *In vitro* antioxidant and antimicrobial properties of these novel compounds are currently under investigation and will be reported in the near future.

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