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Investigation of Biological Properties of New 1-(2,6-Dimetilmorfolin-4-yl-metil)-3-alkyl(aryl)-4-[3-ethoxy-(4-benzenesulfonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones

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Abstract: In this study, six new 1-(2,6-dimethylmorpholin-4-yl-methyl)-3-alkyl(aryl)-4-[3-ethoxy-(4-benzenesulfonyloxy)-benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones were obtained from the reactions of 3-alkyl(aryl)-4-[3-ethoxy-(4-benzenesulfonyloxy)-benzylideneamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones with 2,6-dimethylmorpholine and formaldehyde. Characterization of new compounds obtained was carried out by IR, ^{1}H-NMR, ^{13}C-NMR spectral data. Antibacterial properties of the synthesized novel compounds were evaluated by agar well method against Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Bacillus cereus and Klepsiella pneumoniae strains.

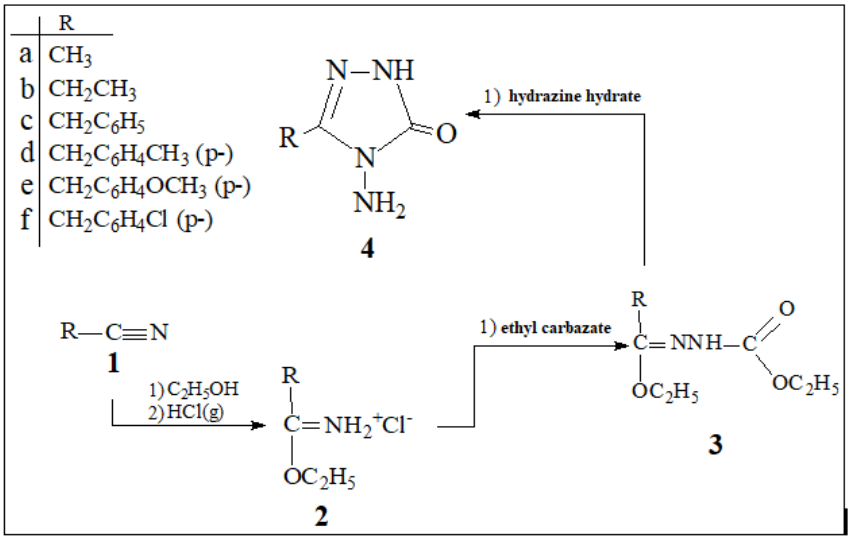
Keywords: 1,2,4-triazol-5-one, Schiff base, Mannich base, Synthesis, Antimicrobial actvitiy

Introduction

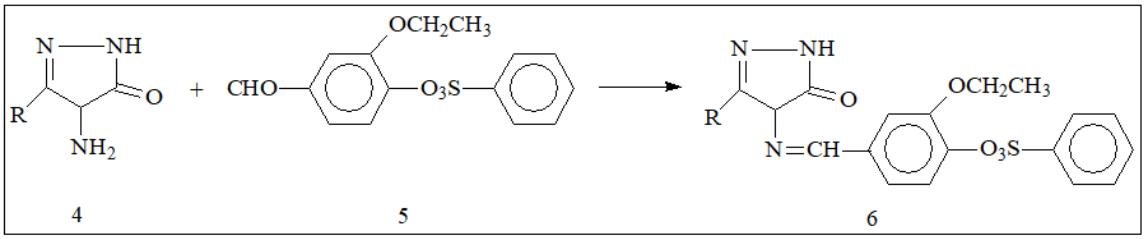
Biochemical properties of rings containing triazole ring or triazole derivative ring, which are important members of heterocyclic compounds, have a wide range of academic work (Ure, 2010; Manap, 2009; Kardaş, 2006). Recently, antitumor (Ikizler et al., 1998), anti-HIV, antihypertensive, diuretic properties (Gursoy et al., 2013; Yuksek et al., 2004; Yuksek et al., 2008), antimicrobial, antioxidant, antiinflammatory and pharmacological properties of the triazole ring, (Ikizler et al., 1997), antioxidants, antiinflammatory, anticonvulsant, antiparasitic, analgesic, antiviral and antibiotic effects of the triazole rings to have a broad spectrum of biological activities (Yuksek, 2001; Ocak, 2004; Gursoy Kol et al., 2012) have been reported. In addition, several articles have been published concerning the synthesis of some N-arylideneamino-4,5-dihydro-1H-1,2,4-triazol-5-one derivatives.

Synthesis

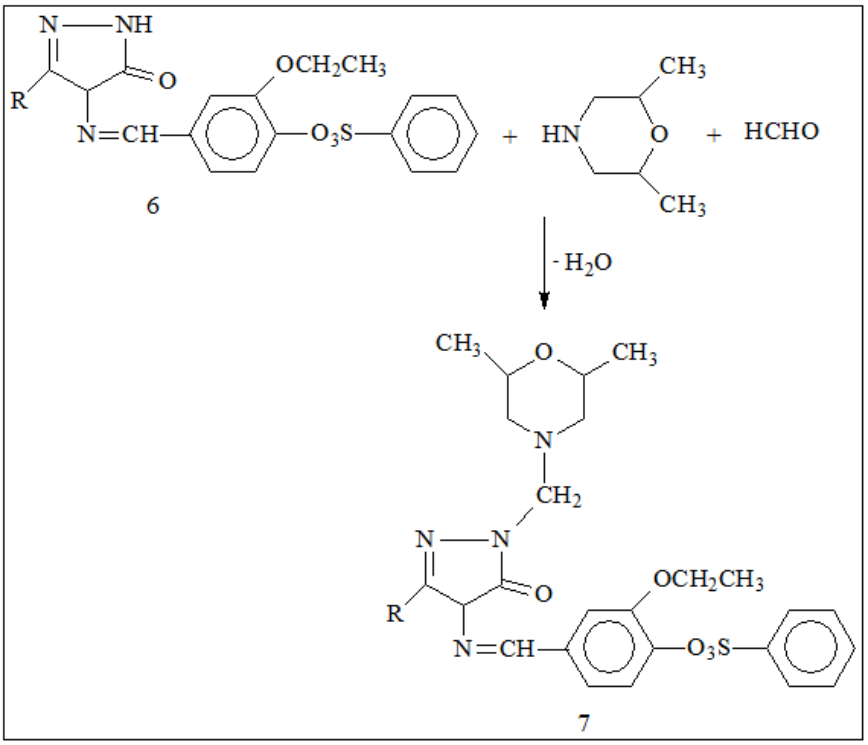
The Pinner method was used as an appropriate method for synthesizing the starting compounds used in the work (Pinner, 1892) (Equation 1). The compounds 4 obtained according to this method were reacted with 3-ethoxy-4-benzenesulfonyloxybenzaldehyde to provide synthesis of 6 type Schiff bases (Equation 2). Subsequently, six Mannich bases were synthesized (Equation 3) from the reactions of compounds 6 with 2,6-dimethylmorpholine and formaldehyde.



Equation-1



Equation-2



Equation-3

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 7: The General Procedure

3-Ethoxy-4-hydroksibenzaldehyde (0,01 mol) dissolved in ethylacetate (20 mL) was treated with benzenesulphonyl chloride (0,01 mol) and to this solution was slowly added triethylamine (0.01 mol) with stirring at 0-5 °C. The process of stirring continued for 2 h, and then the mixture was refluxed for 3 h and filtered. The filtrate evaporated *in vacuo*, and the crude product was washed with water and recrystallized from ethanol to afford compound **5.** The corresponding compound **4** (0.01 mol) was dissolved in acetic acid (20 mL) and treated with 3-ethoxy-4-benzenesulphonyloksibenzaldehyde (0.01 mol). The mixture was refluxed for 2 h and then evaporated at 50-55 °C in vacuo. Several recrystallizations of the residue from ethanol gave pure compounds 3-alkyl(aryl)-4-[3-ethoxy-(4-benzenesulfonyloxy)-benzylidenamino]-4,5-dihydro-1*H*-1,2,4-triazol-5-ones **6** as crystals (Özdemir, 2016).

In the final step, the corresponding **6** type Schiff Base (5 mmol), 2,6-dimethylmorpholine (6 mmol) and formaldehyde (10 mmol) was refluxed **6** hours. Obtained mixture was filtered and crystalliazed from approprivate solvents and pure 7 type compounds were synthesized.

Spektral Data

Table 1. Spectral data of compound 7a

IR (KBr) cm^{-1}	**^{1}H-NMR**	**^{13}C –NMR**
1705 (C=O) **1603, 1577 (C=N)** **1375 ve 1171 (SO_2)** **754 ve 695 (monosubstitue ring**	δ 1.03 (d, 6H, $2CH_3$; J:6.40 Hz) δ 1.10 (T, 3H, OCH_2CH_3; J:6.40 Hz) δ 2.01 (T, 2H, CH_2; J:11.20 Hz) δ 2.31 (S, 3H, CH_3) δ 2.75 (d, 2H, CH_2; J:10.40 Hz) δ 3.50-3.55 (m, 2H, 2CH) δ 3.83 (q, 2H, OCH_2CH_3; J: 8.80 Hz) δ 4.54 (s, 2H, NCH_2) δ 7.31 (d, 1H, ArH; J: 8.40 Hz) δ 7.46-7.49 (m, 2H, ArH) δ 7.67 (t, 2H,ArH; J: 8.00 Hz) δ 7.83-7.85 (m, 3H, ArH) δ 9.66 (s, 1H, N=CH)	10.94 (CH_3) 14.04 (OCH_2CH_3) 18.92 ($2CH_3$) 55.57 ($2CH_2$) 64.05 (OCH_2CH_3) 71.02 ($2CH_2$) 112.91, 120.08, 124.30, 128.14, 129.48, 133.59, 134.85, 135.12, 139.58, 150,87 (ArC) 143.13 (Triazol C_3) 150.15 (N=CH) 150.00 (Triazol C_5)

Table 2. Spectral data of compound 7b

IR (KBr) cm^{-1}	^{1}H-NMR	^{13}C –NMR
1673 (C=O) **1603, 1576 (C=N)** **1373 ve 1159 (SO_2)** **749 ve 696 (monosubstitue aromatic ring)**	δ 1.03 (d, 6H, $2CH_3$; *J*=6.40 Hz) δ 1.11 (t, 3H, OCH_2CH_3; *J*=6.80 Hz) δ 1.21 (t, 3H, CH_2CH_3; *J*=7.60 Hz) δ 2.00 (t, 2H, CH_2; *J*=10.80 Hz) δ 2.72 (d, 2H, CH_2CH_3; *J*=7.60 Hz) δ 2.75 (t, 2H, CH_2; *J*=12.40 Hz) δ 3.51 – 3.54 (m, 2H, 2CH)) δ 3.93 (q, 2H, OCH_2CH_3; *J*=7.20 Hz) δ 4.55 (s, 2H, NCH_2) δ 7.31 (d, 1H, ArH; *J*=8.00 Hz) δ 7.46-7.49 (m, 2H, ArH) δ 7.67 (t, 2H, ArH; *J*=8.00 Hz) δ 7.82-7.85 (m, 3H, ArH) δ 9.62 (s, 1H, N=CH)	δ 10.01 ($CH_2\underline{CH_3}$) δ 14.03 ($OCH_2\underline{CH_3}$) δ 18.40 ($\underline{CH_2}CH_3$) δ 18.93 ($2CH_3$) δ 55.60 ($2CH_2$) δ 64.03 ($O\underline{CH_2}CH_3$) δ 65.50 (NCH_2) δ 71.02 ($2CH_2$) δ 112.95; 118.98; 124.33; 128.14(2C); 128.49(2C); 133.62; 134.86; 135.14; 139.58; 150;87 (ArC) δ 146.84 (Triazol C_3) δ 150.29 (N=CH) δ 153.03 (Triazol C_5)

Table 3. Spectral data of compound 7c

IR (KBr) cm^{-1}	^{1}H-NMR	^{13}C –NMR
1708 (C=O) **1587 (C=N)** **1391 ve 1166 (SO_2)** **850 (1,4-disubstitue aromatic ring)** **760 ve 698 (monosubstitue aromatic ring)**	δ 1.03 (d, 6H, $2CH_3$; *J*=6.40 Hz) δ 1.12 (t, 3H, OCH_2CH_3; *J*=6.80 Hz) δ 2.01 (t, 2H, CH_2; *J*=11.20 Hz) δ 2.78 (d, 2H, ArH_2; *J*=10.40 Hz) δ 3.51 – 3.55 (m, 2H, 2CH)) δ 3.80 (q, 2H, OCH_2CH_3; *J*=6.80 Hz) δ 4.55 (s, 2H, CH_2Ph) δ 4.59 (s, 2H, NCH_2) δ 7.28-7.32 (m, 6H, ArH) δ 7.37-7.40 (m, 2H, ArH) δ 7.66 (t, 2H, ArH; *J*=8.00 Hz) δ 7.81-7.85 (m, 3H, ArH) δ 9.61 (s, 1H, N=CH)	δ 14.03 ($OCH_2\underline{CH_3}$) δ 18.93 ($2CH_3$) δ 30.94 (CH_2Ph) δ 55.64 ($2CH_2$) δ 63.99 ($O\underline{CH_2}CH_3$) δ 65.60 (NCH_2) δ 71.01 ($2CH_2$) δ 112.04; 120.68; 124.29; 128.14; 128.47(2C); 128.60(2C); 129.48(2C); 133.54; 134.86; 135.11; 135.71; 139.60; 150.81 (ArC) δ 144.86 (Triazol C_3) δ 150.17 (N=CH) δ 152.45 (Triazol C_5)

Table 4. Spectral data of compound 7d

IR (KBr) cm^{-1}	^{1}H-NMR	^{13}C –NMR
1709 (C=O) **1589 (C=N)** **1349 ve 1167 (SO_2)** **849 (1,4-disubstitue aromatic ring)** **763 ve 697 (monosubstitue aromatic ring)**	δ 1.03 (d, 6H, $2CH_3$; *J*=6.40 Hz) δ 1.12 (t, 3H, OCH_2CH_3; *J*=6.80 Hz) δ 2.01 (t, 2H, CH_2 *J*=10.80 Hz) δ 2.25 (t, 3H, $PhCH_3$) δ 2.78 (d, 2H, CH_2 *J*=10.40 Hz) δ 3.51 – 3.55 (m, 2H, 2CH) δ 3.81 (q, 2H, OCH_2CH_3; *J*=6.80 Hz) δ 4.03 (s, 2H, CH_2Ph) δ 4.59 (s, 2H, NCH_2) δ 7.10 (d, 2H, ArH; *J*=8.00 Hz) δ 7.20 (d, 2H, ArH; *J*=8.00 Hz) δ 7.30 (d, 1H, ArH; *J*=8.00 Hz) δ 7.38-7.41 (m, 2H, ArH) δ 7.67 (t, 2H, ArH; *J*=8.00 Hz) δ 7.81-7.85 (m, 3H, ArH) δ 9.62 (s, 1H, N=CH)	δ 14.03 ($OCH_2\underline{CH_3}$) δ 18.92 ($2CH_3$) δ 20.56 ($PhCH_3$) δ 30.55 (CH_2Ph) δ 55.65 ($2CH_2$) δ 63.98 ($O\underline{CH_2}CH_3$) δ 65.50 (NCH_2) δ 71.00 ($2CH_2$) δ 112.03; 120.68; 124.29; 128.14(2C); 128.48(2C); 129.03(2C); 129.47(2C); 132.57; 133.56; 134.84; 135.13; 135.87; 139.60; 150.81 (ArC) δ 145.00 (Triazol C_3) δ 150.17 (N=CH) δ 150.38 (Triazol C_5)

Table 5. Spectral data of compound 7e

IR (KBr) cm^{-1}	^{1}H-NMR	^{13}C –NMR
1700 (C=O) [1] **1612 ve 1576 (C=N)** **1365 ve 1162 (SO_2)** **811 (1,4-disubstitue aromatic ring)** **752 ve 688 (monosubstitue aromatic ring)**	δ 1.03 (d, 6H, $2CH_3$; *J*=6.40 Hz) δ 1.12 (t, 3H, OCH_2CH_3; *J*=6.80 Hz) δ 2.00 (t, 2H, ArH; *J*=11.20 Hz) δ 2.77 (d, 2H, ArCH; *J*=10.00 Hz) δ 3.51 – 3.55 (m, 2H, 2CH) δ 3.71 (s, 3H, OCH_3) δ 3.82 (q, 2H, OCH_2CH_3; *J*=6.80 Hz) δ 4.02 (s, 2H, CH_2Ph) δ 4.58 (s, 2H, NCH_2) δ 6.86 (d, 2H, ArH; *J*=8.40 Hz) δ 7.23 (d, 2H, ArH; *J*=8.80 Hz) δ 7.31 (d, 1H, ArH; *J*=8.00 Hz) δ 7.40-7.43 (m, 2H, ArH) δ 7.67 (t, 2H, ArH; *J*=8.00 Hz) δ 7.83-7.85 (m, 3H, ArH) δ 9.62 (s, 1H, N=CH)	δ 14.03 ($OCH_2\underline{CH_3}$) δ 18.92 ($2CH_3$) δ 30.10 (CH_2Ph) δ 55.02 (OCH_3) δ 55.65 ($2CH_2$) δ 63.99 ($O\underline{CH_2}CH_3$) δ 65.50 (NCH_2) δ 71.01 ($2CH_2$) δ 112.15; 120.60; 127.43; 128.14(2C); 129.47(2C); 129.68(2C); 133.57; 134.84; 135.13; 139.60; 150;82 151.12 (ArC) δ 145.15 (Triazol C_3) δ 150.18 (N=CH) δ 150.47 (Triazol C_5)

Table 6. Spectral data of compound 7f

IR (KBr) cm^{-1}	^{1}H-NMR	^{13}C –NMR
1705 (C=O) **1577 (C=N)** **1373 ve 1162 (SO_2)** **749 ve 694 (1,3-monobstitue aromatic ring)**	δ 1.03 (d, 6H, $2CH_3$; *J*=6.40 Hz) δ 1.11 (t, 3H, OCH_2CH_3; *J*=6.80 Hz) δ 2.00 (t, 2H, CH_2 *J*=?) δ 3.51 – 3.55 (m, 2H, 2CH) δ 3.79 (q, 2H, OCH_2CH_3; *J*=6.80 Hz) δ 4.11 (s, 2H, CH_2Ph) δ 4.55 (s, 2H, NCH_2) δ 7.29 (d, 1H, ArH; *J*=8.00 Hz) δ 7.34 – 7.40 (m, 6H, ArH) δ 7.66 (t, 2H, ArH; *J*=8.00 Hz) δ 7.82 – 7.85 (m, 3H, ArH) δ 9.62 (s, 1H, N=CH)	δ 14.04 (OCH_2CH_3) δ 18.92 (CH_3) δ 30.29 (CH_2Ph) δ 55.62 ($2CH_2$) δ 63.99 (O CH_2CH_3) δ 65.50 (NCH_2) δ 71.02 ($2CH_2$) δ 112.10; 120.68; 124.30; 128.14(2C); 128.41(2C); 129.48(2C); 130.53(2C); 131.45; 133.49; 134.73; 134.86; 135.10; 139.63; 150.82 (ArC) δ 144.53 (Triazol C_3) δ 150.17 (N=CH) δ 152.60 (Triazol C_5) δ 162.27 (COO)

Antibacterial Properties

Antibacterial properties of the synthesized type 7 compounds against bacterial strains of B. *subtilis*, B. *cereus*, P. *aeruginosa*, K. *pneumoniae*, S. *aureus* and E. *coli* were investigated and the results are presented in Table 7.

Table 7. Antibacterial Properties of Compounds 7a-f

	B. subtilis	B. cereus	P. aeruginosa	K. pneumoniae	S. aureus	E. coli
7a	-	14	18	7	-	21
7b	-	10	12	7	8	17
7c	-	17	9	8	9	14
7d	-	12	14	7	11	18
7e	-	18	13	8	8	13
7h	-	14	17	9	7	20

0-5,5 mm negative effect; 5,5-10 mm (+) low effect; 11-16 (++) modarate effect; 17 and upper (+++) high effect (Perez et al., 1990; Ahmad et al., 1998)

Result and Discussion

There was no compound effect against B. *subtilis* strain. For B. *cereus*; compound 7b is at a low level, compound 7a, 7b, 7d and 7h is moderate and compounds 7c and 7e have a high level of activity. Different result obtained from P. *aeruginosa*. While compounds 7c-e were moderately active, compounds 7a and 7h had a high level of activity. All of the compounds have shown low effect for K. *pneumoniae*. For *aureus*, a gram-positive bacterium, while compounds 7a, 7b, 7c, 7e and 7f showed low activity, only compound 7d had moderate activity. The bacterium in which the highest activity was observed is E. *coli*. While compounds 7c and 7e were moderately effective, other compounds were highly active.

As a result, it has been concluded that the synthesized 7a-f type Mannich Some type of compounds acted at various levels against gram negative and gram positive bacteria. This situation draws attention to further research.

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