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Synthesis and Antimicrobial and Antitumor Activity of Some New [1,2,4] Triazole-5-one Derivatives

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4-[Arylidene-amino]-3-thiophen-2-ylmethyl-4,5-dihydro[1,2,4]triazole-5-one compounds **(3a-g)** with Schiff base character were obtained from the reaction of 4-amino-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-one **(2)** with various aldehydes. 1-(2-Oxo-2-phenyl-ethyl)-4-[arylidene-amino]-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-ones **(4a-g)** were synthesized from the reaction of corresponding compounds **3a-g** with bromoacetophenone. 1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[aryl-amino]4,5-dihydro-1H-[1,2,4]triazole-5-ones **(5a-g)** and 1-(2-hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[arylidene-amino]4,5-dihydro-1H-[1,2,4]triazole-5-ones **(6b,d,e)** were obtained from the selective reduction of 1-(2-oxo-2-phenyl-ethyl)-4-[arylidene-amino]-3-thiophen-2ylmethyl-4,5-dihydro-1H-[1,2,4] triazole-5-ones **(4)** with $NaBH_4$. They were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analyses.

Compounds **2, 3a, 3c, 3g, 4f, 5b,** and **5g** showed good antifungal activity against yeast-like fungi. Compounds selected by the National Cancer Institute (NCI, USA) were investigated for antitumor activity.

Key Words: Triazole-5-one, acetophenone, $NaBH_4$, antimicrobial and antitumor activity.

Introduction

Wide-ranging pharmacological activity of 1,2,4-triazole derivatives has been reported in the scientific literature. Two main types of their activity are antiviral, antibacterial, and antifungal activity, and central nervous system (CNS) activity. The first type of activity is exhibited, for example, by fluotrimazole, ribavirine, and furazonal, while the second type of activity is exhibited by estazolam,[1−2] alrazolam,[3] and rizatriptane.[4]

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Moreover, some bi-heterocyclic compounds incorporating a [1,3,4] thiadiazole and [1,2,4] triazole ring have been produced as antimicrobial agents.[5−10] Compounds incorporating a 1,2,4-triazol ring with diverse pharmacological effects have been reported as therapeutic agents in medicinal chemistry[11−15] and several of these compounds have been shown to be antitumor agents.[16−21] The need for safe and effective systemic antifungal agents has intensified due to the rapid growth in the number of immunocompromised patients. Azole antifungal agents, such as fluconazole, are most widely used today.[22]

In the present study, prompted by these observations, a series of new [1,2,4]triazole-5-ones incorporating a Schiff base structure **(3),** N-1 substitute [1,2,4] triazole-5-ones **(4)**, and selective reduction compounds of [1,2,4] triazole-5-one derivatives **(5** and **6)** was synthesized. In addition, we report their antimicrobial and antitumor activity, and geometric optimization.

Experimental

Chemistry

Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR 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. Elemental analysis was carried out on a C, H, N-O rapid elemental analyzer (Hewlett-Packard 185) for C, H, and N; results were within 0.4% of the theoretical values. All the chemicals were obtained from Fluka Chemie AG Buchs (Switzerland). Compounds **1** and **2** were synthesized using the published method.[23,24] Compounds **3c** and **4g** are published at Acta Crystallographica.[25,26]

General Method for the Synthesis of 4-[arylidene-amino]-4,5-dihydro-1H-1,2,4-triazole-5-ones (3)

The corresponding 4-amino-3-thiophen-2-yl-methyl4,5-dihydro-1H-[1,2,4] triazole-5-one **(2)** (0.01 mol) and aldehyde (0.01 mol) were heated at 160 °C in an oil bath for 2 h. After cooling to room temperature, a solid appeared and was recrystallized from an appropriate solvent to afford the desired compound.

3-Thiophen-2-ylmethyl-4-[(thiophen-2-yl-methylene)-amino]-4,5-dihydro-1H- [1,2,4]triazole-5-one (3a)

Recrystallized from ethanol/water (1:1) (yield: 75.00%). mp: 183-184 °C. Analysis (calc/found %): for $C_{12}H_{10}N_4OS_2$ C: 58.80/58.78, H: 3.95/3.98, N: 13.72/13.75; IR (KBr) (ν, cm^{-1}) 3159 (NH), 1708 (triazole-C=O), 1670 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.29 (s, 2H, thiophen-CH_2), 6.93-7.03 (m, 2H, arH), 7.18-7.83 (m, 4H, arH), 9.85 (s, 1H, N=CH),12.04 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 25.69 (thiophen-CH_2), thiophen-C: [125.44(CH), 126.78(CH), 126.97(CH), 137.21(C)], ar-C: [128.37(CH), 131.17(CH), 134.03(CH), 138.04(C)], 145.32 (triazole-C-3), 148.70 (-N=CH), 151.16 (triazole-C-5).

4-[(Furan-2-yl-methylene)-amino]-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4] triazole-5-one (3b)

Recrystallized from ethanol (yield: 78.33%). mp: 175-176 °C. Analysis (calc/found %) for $C_{12}H_{10}N_4O_2S$ C: 52.54/52.56, H: 3.67/3.68, N: 20.43/20.45; IR (KBr) (ν, cm^{-1}) 3179 (NH), 1708 (triazole-C=O), 1630

(C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.21 (s, 2H, thiophen-CH_2), 6.72 (s, 2H, arH), 6.95-7.01 (m, 1H, arH), 7.19 (s, 1H, arH), 7.38 (d, 1H, J=4 Hz, arH), 7.98 (s, 1H, arH), 9.60 (s, 1H, N=CH), 12.04 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.56 (thiophen-CH_2), thiophen-C: [125.40 (CH), 126.80 (CH), 126.99 (CH), 137.12 (C)], ar-C: [112.73 (CH), 117.84 (CH), 143.06 (CH), 148.31 (C)], 145.53 (triazole-C-3), 146.83 (N=CH), 151.17 (triazole-C-5).

4-[Benzylidene-amino]-3-thiophen-2-yl-methyl-4,5-dihydro-1H-[1,2,4]triazole-5-one (3d)

Recrystallized from ethanol (yield: 83.45%). mp: 198-199 °C. Analysis (calc/found %): for $C_{14}H_{12}N_4OS$ C: 59.14/59.16, H: 4.25/4.22, N: 19.70/19.72; IR (KBr) (ν, cm^{-1}) 3174 (NH), 1705 (triazole-C=O), 1625 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.29 (s, 2H, thiophen-CH_2), 6.94-7.05 (m, 2H, arH), 7.37-7.54 (m, 4H, arH), 7.84-7.89 (m, 2H, arH), 9.77 (s, 1H, N=CH), 12.14 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.51 (thiophen-CH_2), thiophen-C: [125.49 (CH), 126.68 (CH), 126.85 (CH), 137.16 (C)], ar-C: [120.23 (CH), 125.31 (CH), 137.08 (CH), 149.81 (CH), 152.36(C)], 145.49 (triazole-C-3), 150.93 (N=CH).152.72 (triazole-C-5).

4-[(3-Bromo-benzylidene)-amino]-3-thiophen-2-yl-methyl-4,5-dihydro-1H-[1,2,4]triazole-5-one (3e)

Recrystallized from ethanol/water (1:2) (yield: 83.75%). mp: 225-226 °C. Analysis (calc/found %): for $C_{14}H_{11}BrN_4OS$ C: 46.29/46.31, H: 3.05/3.02, N: 15.42/15.43; IR (KBr) (ν, cm^{-1}) 3172 (NH), 1715 (triazole-C=O), 1618 (C=N); ^{1}H-NMR (DMSO-d_6) δ (ppm) 4.30 (s, 2H, thiophen-CH_2), 6.94-7.04 (m, 2H, arH), 7.38-7.50 (m, 2H, arH), 7.60-7.70 (m, 2H, arH), 8.06 (s, 1H, arH), 9.72 (s, 1H, N=CH), 12.08 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ (ppm) 25.58 (thiophen-CH_2), thiophen-C: [125.27 (CH), 126.56 (CH), 126.82 (CH),137.25 (C)], ar-C: [122.23 (C), 127.01 (CH), 129.67 (CH), 131.02 (CH), 133.87 (CH),135.80 (C)], 145.49 (triazole-C-3), 150.89 (N=CH), 151.38 (triazole-C-5).

4-[(2-Chloro-6-flouro-benzylidene)-amino]-3-thiophen-2-ylmethyl-4,5dihydro-1H-[1,2,4] triazole-5-one (3f)

Recrystallized from ethanol/water (1:2) (yield: 85.42%). mp: 160-161 °C. Analysis (calc/found %): for $C_{14}H_{10}ClFN_4OS$ C: 49.93/49.92, H: 2.99/3.00, N: 16.64/16.65; IR (KBr) (ν, cm^{-1}) 3188 (NH), 1706 (triazole-C=O), 1591 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.18 (s, 2H, thiophen-CH_2), 6.91-6.95 (m, 2H, arH), 7.34-7.47 (m, 4H, arH), 10.05 (s, 1H, N=CH), 12.15 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.29 (thiophen-CH_2), thiophen-C: [125.21 (CH), 126.35 (CH), 126.42 (CH), 136.97(C)], ar-C: [115.77 (CH), 119.55 (CH), 126.50 (CH), 132.88 (CH), 134.26 (C), 157.89 (C)], 145.46 (triazole-C-3), 147.07 (-N=CH),150.86 (triazole-C-5).

4-[(2,4-Dichloro-benzylidene)-amino]-3-thiophen-2-ylmethyl-4,5dihydro-1H-[1,2,4] triazole-5-one (3g)

Recrystallized from ethanol/water (1:1) (yield: 84.14%). mp: 209-210 °C. Analysis (calc/found %): for $C_{14}H_{10}Cl_2N_4OS$ C: 47.60/47.61, H: 2.85/2.87, N: 15.86/15.84; IR (KBr) (ν, cm^{-1}) 3177 (NH), 1704 (triazole-C=O), 1601 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.30 (s, 2H, thiophen-CH_2), 6.94-7.04 (m, 2H, arH), 7.37-7.40 (m, 1H, arH), 7.56-7.61 (m, 1H, arH), 7.80 (d, 1H, J=9 Hz, arH), 8.01 (d, 1H, J=2 Hz, arH), 10.13 (s, 1H, N=CH), 12.15 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.44 (thiophen-CH_2), thiophen-C:

[125.25 (CH), 126.60 (CH), 126.82 (CH), 1367.08(C)], ar-C: [127.96 (CH), 128.08 (CH), 129.51 (C), 129.80-(CH), 134.98(C), 136.54(C)], 145.46 (triazole-C-3), 147.37 (N=CH), 150.92 (triazole-C-5).

General Method for the Synthesis of 1-(2-oxo-2-phenyl-ethyl)-4-[(arylidene-amino)]-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-ones (4)

The corresponding 3-thiophen-2-yl-methyl-4-aryliden-amino-4,5-dihydro-1H-1,2,4-triazole-5-one (**3**) (0.01 mol) was refluxed with an equivalent amount of natrium in absolute ethanol for 1 h. Then, bromo acetophenone (0.01 mol) was added and refluxed for an additional 5 h. The precipitate was filtered off, washed with H_2O, and recrystallized from an appropriate solvent to afford the desired compound.

1-(2-Oxo-2-phenyl-ethyl)-4-[(thiophen-2-yl-methylene)-amino]-3-thiophen-2-yl methyl-4,5-dihydro-1H-[1,2,4]triazole-5-one (4a)

Recrystallized from methanol (yield: 66.00%). mp: 152-153 °C. Analysis (calc/found %): for $C_{20}H_{16}N_4O_2S_2$ C: 58.80/58.79, H: 3.95/3.96, N: 13.72/13.74; IR (KBr) (ν, cm^{-1}) 1693 (acetophenone-C=O), 1708 (triazole-C=O), 1601 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.28 (s, 2H, thiophen-CH_2), 5.45 (s, 2H, NCH_2), 6.95-7.42 (m, 4H, arH), 7.39-7.42 (m, 1H, arH), 7.54-7.88 (m, 5H, arH), 8.03-8.10 (m, 1H, arH), 9.83 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.60 (thiophen-CH_2), 51.99 (NCH_2), thiophen-C: [125.67 (CH), 126.99 (CH), 127.11 (CH), 134.53 (C)], ar-C: [128.26 (CH), 131.60 (CH), 134.35 (CH), 136.92 (C)], benzene-C: [128.51 (CH), 129.11-(CH), 131.60 (C), 134.10 (CH)], 144.71 (triazole-C-3), 149.34 (N=CH), 150.25 (triazole-C-5), 192.88 (acetophenone-C=O).

1-(2-Oxo-2-phenyl-ethyl)-4-[(furan-2-yl-methylene)-amino]-3-thiophen-2-ylmethyl -4,5-dihydro-1H-[1,2,4]triazole-5-one (4b)

Recrystallized from ethanol (yield: 65.90%). mp: 129-130 °C. Analysis (calc/found %): for $C_{20}H_{16}N_4O_3S$ C: 61.21/61.23, H: 4.11/4.12, N: 14.28/14.29; IR (KBr) (ν, cm^{-1}) 1698 (acetophenone-C=O), 1709 (triazole-C=O), 1595 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.30 (s, 2H, thiophen-CH_2), 5.46 (s, 2H, NCH_2), 6.72-7.05 (m, 4H, arH), 7.24-7.42 (m, 2H, arH), 7.54-8.03 (m, 5H, arH), 9.59 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.45 (thiophen-CH_2), 51.95 (NCH_2), thiophen-C: [125.58 (CH), 126.95-(CH), 127.04-(CH), 136.78 (C)], ar-C: [112.83 (CH), 118.39 (CH), 143.46 (CH), 148.26 (C)], benzene-C: [128.23 (CH),129.06 (CH),134.07 (C), 134.31 (CH)], 144.84 (triazole-C-3), 147.09 (N=CH), 150.18 (triazole-C-5), 192.86 (acetophenone-C=O).

1-(2-Oxo-2-phenyl-ethyl)-4-[(pyridine-2-yl-methylene)-amino]-3-thiophen-2-yl methyl-4,5-dihydro-1H-[1,2,4] triazole-5-one (4c)

Recrystallized from ethanol (yield: 68.49%). mp: 137-138 °C. Analysis (calc/found %): for $C_{21}H_{17}N_5O_2S$ C: 62.52/62.51, H: 4.25/4.23, N: 17.36/14.35; IR (KBr) (ν, cm^{-1}) 1689 (acetophenone-C=O), 1716 (triazole-C=O), 1610 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.35 (s, 2H, thiophen-CH_2), 5.45 (s, 2H, NCH_2), 6.94-7.63 (m, 8H, arH), 7.71-8.07 (m, 4H, arH), 10.33 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.45 (thiophen-CH_2), 51.78 (NCH_2), thiophen-C: [126.06 (CH), 126.58 (CH), 126.81 (CH), 136.97 (C)], ar-C: [116.31 (CH), 119.22 (CH), 119.41 (CH), 125.35 (CH), 157.56 (C)], benzene-C: [128.58 (CH), 128.83 (CH), 133.07 (C), 134.00 (CH)], 144.73 (triazole-C-3), 150.04 (N=CH), 150.76 (triazole-C-5), 192.74 (acetophenone-C=O).

1-(2-Oxo-2-phenyl-ethyl)-4-[(benzylidene)-amino]-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-one (4d)

Recrystallized from ethanol (yield: 69.40%). mp: 133-134 °C. Analysis (calc/found %): for $C_{22}H_{18}N_4O_2S$ C: 65.65/65.64, H: 4.51/4.53, N: 13.92/13.94; IR (KBr) (ν, cm^{-1}) 1693 (acetophenone-C=O), 1717 (triazole-C=O), 1590 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.27 (s, 2H, thiophen-CH_2), 5.45 (s, 2H, NCH_2), 6.73-6.93 (m, 3H, arH), 7.37-7.60 (m, 7H, arH), 8.01-8.04 (m, 3H, arH) 10.04 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 26.16 (thiophen-CH_2), 52.54 (NCH_2), thiophen-C: [126.15 (CH), 127.43 (CH), 127.61 (CH), 137.65 (C)], ar-C: [128.58 (CH), 129.60 (CH), 132.37 (CH), 133.83 (C)], benzene-C: [128.81 (CH), 129.69 (CH), 134.72 (C), 134.83 (CH)], 145.56 (triazole-C-3), 150.74 (N=CH), 154.68 (triazole-C-5), 193.44 (acetophenone-C=O).

1-(2-Oxo-2-phenyl-ethyl)-4-[(3-bromo-benzylidene)-amino]-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-one (4e)

Recrystallized from ethanol (1:2) (yield: 61.33%). mp: 126-127 °C. Analysis (calc/found %): for $C_{22}H_{17}BrN_4O_2S$ C: 54.89/54.88, H: 3.56/3.57, N: 11.64/11.65; IR (KBr) (ν, cm^{-1}) 1689 (acetophenone-C=O), 1713 (triazole-C=O), 1585 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.38 (s, 2H, thiophen-CH_2), 5.47 (s, 2H, NCH_2), 6.96-7.04 (m, 2H, arH), 7.40-7.62 (m, 4H, arH), 7.72-7.88 (m, 3H, arH), 8.03-8.10 (m, 3H, arH), 9.69 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.41 (thiophen-CH_2), 51.82 (-NCH_2), thiophen-C: [125.42 (CH), 126.68 (CH), 126.86 (CH), 136.88 (C)], ar-C: [122.24 (C), 127.13 (CH), 129.85 (CH), 131.06 (CH), 133.87 (CH), 135.56 (C)], benzene-C: [128.09 (CH), 128.85 (CH), 133.98 (C), 134.07 (CH)], 144.82 (triazole-C-3), 149.87 (N=CH), 152.00 (triazole-C-5), 144.82 (triazole-C-3), 149.87 (-N=CH), 192.66 (acetophenone-C=O).

1-(2-Oxo-2-phenyl-ethyl)-4-[(2-chloro-6-floro-benzylidene)-amino]-3-thiophen-2- ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-one (4f)

Recrystallized from ethanol (1:2) (yield: 72.47%). mp: 128-129 °C. Analysis (calc/found %): for $C_{22}H_6ClFN_4O_2S$ C: 58.09/58.08, H: 3.55/3.57, N: 12.32/12.31; IR (KBr) (ν, cm^{-1}) 1695 (acetophenone-C=O), 1709 (triazole-C=O), 1597 (C=N); ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.36 (s, 2H, thiophen-CH_2), 5.46 (s, 2H, NCH_2), 6.95-7.05 (m, 2H, arH), 7.39-7.73 (m, 5H, arH), 7.89-8.05 (m, 4H, arH), 10.07 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.15 (thiophen-CH_2), 51.78 (NCH_2), thiophen-C: [125.36 (CH), 126.35 (CH), 126.61 (CH), 136.57 (C)], ar-C: [115.99 (CH), 119.45 (C), 129.82 (CH), 133.26 (CH), 134.38 (C), 150.65 (C)], benzene-C: [128.06 (CH), 128.82 (CH), 133.93 (C), 134.06 (CH)], 144.73 (triazole-C-3), 147.55 (N=CH), 149.79 (triazole-C-5), 192.59 (acetophenone-C=O).

General method for the synthesis of 1-(2-hydroxy-2-phenyl-ethyl)-3 thiophen-2-ylmethyl-4-[aryl-amino]4,5-dihydro-1H-[1,2,4]triazole-5-ones (5)

A mixture of corresponding compound (**4**) (0.01 mol) and $NaBH_4$ (0.04 mol) in absolute ethanol (50 mL) was refluxed for 4 h. After cooling to room temperature, ice water was added with vigorous stirring. The solid obtained was filtered off and recrystallized from an appropriate solvent to afford the desired compound.

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[(thiophen-2-ylmethyl)-amino]-4,5-dihydro-1H-[1,2,4]-triazole-5-one (5a)

Recrystallized from ethanol/water (1:3) (yield: 81.55%). mp 113-114 °C. Analysis (calc/found %): for $C_{20}H_{20}N_4O_2S_2$ C: 58.23/58.24, H: 4.89/4.87, N: 13.58/13.57; IR (KBr) (ν, cm^{-1}) 3377 (OH), 3230 (NH),

1685 (triazole-C=O), 1568 (C=N), 1203 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 3.71 (s, 2H, thiophen-CH_2), 3.79-3.90 (m, 2H, NCH_2), 4.18 (t, 2H, J= 4 Hz, NH-C$\underline{H}_2$), 4.86 (q, 1H, J= 5 Hz, C$\underline{H}$-OH,), 5.58 (d, 1H, J= 5 Hz, OH), 6.66 (t, 1H, J= 4 Hz, NH), 6.80-6.98 (m, 4H, arH), 7.27-7.51 (m, 7H, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 24.63 (thiophen-CH_2), 46.50 (NH-CH_2), 51.87 (N-CH_2), 70.06 (CH-OH); thiophen-C: [125.01 (CH), 126.01 (CH), 126.28 (CH), 137.09 (C)], ar-C: [126.28 (CH), 126.80 (CH), 127.32 (CH), 139.22 (C)], benzene-C: [126.70 (CH), 127.20 (CH), 127.98 (CH), 142.50 (C)], 145.47 (triazole-C-3), 151.95 (triazole-C-5).

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[(furan-2-yl-methyl)-amino]-4,5-dihydro-1H-[1,2,4]triazole-5-one (5b)

Recrystallized from ethanol/water (1:2) (yield: 80.70%). mp: 109-110 °C. Analysis (calc/found %): for $C_{20}H_{20}N_4O_3S_2$ C: 60.59/60.58, H: 5.08/5.09, N: 14.13/14.11; IR (KBr) (ν, cm^{-1}) 3361 (OH), 3236 (NH), 1687 (triazole-C=O), 1569 (C=N), 1201 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 3.61 (s, 2H, thiophen-CH_2), 3.70-3.89 (m, 2H, NCH_2), 3.99 (t, 2H, J= 3 Hz, NH-C$\underline{H}_2$), 4.85 (q, 1H, J= 5 Hz, C$\underline{H}$-OH), 5.57 (d, 1H, J=5 Hz, OH), 6.60 (t, 1H, J= 3Hz, NH), 6.15 (d, 1H, arH), 6.39-6.93 (m, 3H, arH), 7.27-7.65 (m, 7H, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 24.23 (thiophen-CH_2), 44.61 (NH-CH_2), 51.90 (N-CH_2), 70.10 (CH-OH), thiophen-C: [125.01 (CH), 126.00 (CH), 126.37 (CH), 136.96 (C)], ar-C: [109.37 (CH), 110.56 (CH), 142.88 (CH), 150.48 (C)], benzene-C: [126.98 (CH), 127.19 (CH), 127.29 (CH), 142.54 (C)], 145.46 (triazole-C-3), 151.89 (triazole-C-5).

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[(pyridine-2-yl-methyl)- amino]-4,5-dihydro-1H-[1,2,4]triazole-5-one (5c)

Recrystallized from ethanol/water (1:2) (yield: 67.16%). mp: 87-88 °C. Analysis (calc/found %): for $C_{21}H_{21}N_5O_2S$ C: 61.90/61.89, H: 5.19/5.17, N: 17.19/17.17; IR (KBr) (ν, cm^{-1}) 3291 (OH), 3234 (NH), 1686 (triazole-C=O), 1563 (C=N), 1201 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 3.80 (s, 2H, thiophen-CH_2), 3.64-3.72 (m, 2H, NCH_2), 4.09 (t, 2H, J= 4 Hz, NH-C$\underline{H}_2$,), 4.87 (q, 1H, J= 4.6 Hz, C$\underline{H}$-OH), 5.59 (d, 1H, J=4.6 Hz, OH), 6.60 (t, 1H, J=4 Hz, NH), 6.83-6.95 (m, 2H, arH), 7.29-7.76 (m, 9H, arH), 8.50 (d, 1H, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 24.73 (thiophen-CH_2), 52.02 (NH-CH_2), 53.96 (N-CH_2), 70.10 (CH-OH) thiophen-C: [125.02 (CH), 125.98 (CH), 126.31 (CH), 136.60 (C)], ar-C: [122.57 (CH), 123.11 (CH), 137.22 (CH), 156.70 (C)], benzene-C: [126.72 (CH), 127.19 (CH), 127.99 (CH), 142.53 (C)], 145.38 (triazole-C-3), 152.11 (triazole-C-5).

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2ylmethyl-4-(benzyl-amino)-4,5-dihydro-1H-[1,2,4]triazole-5-one (5d)

Recrystallized from ethanol/water (1:2) (yield: 79.06%). mp: 123-124 °C. Analysis (calc/found %): for $C_{22}H_{22}N_4O_2S$ C: 65.00/65.01, H: 5.46/5.45, N: 13.78/13.79; IR (KBr) (ν, cm^{-1}) 3384 (OH), 3234 (NH), 1685 (triazole-C=O), 1569 (C=N), 1203 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 3.63 (s, 2H, thiophen-CH_2), 3.72-3.87 (m, 2H, NCH_2), 3.95 (t, 2H, J= 3 Hz NH-C$\underline{H}_2$), 4.88 (q, 1H, J= 4 Hz C$\underline{H}$-OH), 5.58 (d, 1H, J= 4 Hz OH), 6.53 (t, 1H, J= 3 Hz, NH), 6.80-6.92 (m, 2H, arH), 7.18-7.38 (m, 11H, arH), ^{13}C-NMR (DMSO-d_6)δ (ppm) 24.69 (thiophen-CH_2), 51.87 (-NHCH_2), 52.38 (N-CH_2), 70.12 (CH-OH), thiophen-C: [125.00 (CH), 126.06 (CH), 126.26 (CH), 136.87 (C)], ar-C: [127.47 (CH), 128.26 (CH), 129.20 (CH), 137.16 (C)], benzene-C: [126.69 (CH), 127.22 (CH), 128.00 (CH), 142.57 (C)], 145.37 (triazole-C-3), 152.11 (triazole-C-5).

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[(3-bromobenzyl)-amino]-4,5-dihydro-1H-[1,2,4]-triazole-5-one (5e)

Recrystallized from ethanol/water (1:2) (yield: 82.35%). mp: 103-105 °C. Analysis (calc/found %): for $C_{22}H_{21}BrN_4O_2S$ C: 54.44/54.43, H: 4.36/4.35, N: 11.54/11.56; IR (KBr) (ν, cm^{-1}) 3408 (OH), 3236 (NH), 1697 (triazole-C=O), 1567 (C=N), 1202 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 3.80 (s, 2H, thiophen-CH_2), 3.64-3.74 (m, 2H, NCH_2), 3.95 (t, 2H, J= 5 Hz, NH-C<u>H</u>$_2$,), 4.88 (q, 1H, J= 4 Hz C<u>H</u>-OH), 5.59 (d, 1H, J= 4 Hz, OH), 6.60 (t, 1H, J=5Hz, NH), 6.94-7.51 (m, 11H, arH), 8.83 (d, 1H, J= 6 Hz, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 24.89 (thiophen-CH_2), 51.84 (NH-CH_2), 51.98 (N-CH_2), 70.10 (CH-OH), thiophen-C: [125.04 (CH), 126.01 (CH), 126.22 (CH), 137.21 (C)], ar-C: [121.46 (C), 130.27 (CH), 130.37 (CH), 131.65 (CH), 133.67 (CH), 139.73 (C)], benzene-C: [126.74 (CH), 127.22 (CH), 128.01 (CH), 142.54 (C)], 145.19 (triazole-C-3), 152.10 (triazole-C-5).

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[(2-chloro-6-flourobenzyl)-amino]-4,5-dihydro-1H-[1,2,4] triazole-5-one (5f)

Recrystallized from ethanol/water (1:2) (yield: 83.62%). mp: 185-186 °C. Analysis (calc/found %): for $C_{20}H_{18}ClFN_4O_2S$ C: 55.49/55.47, H: 4.19/4.20, N: 12.94/12.97; IR (KBr) (ν, cm^{-1}) 3345 (OH), 3242 (NH), 1688 (triazole-C=O), 11605 (C=N), 1200 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 3.53 (s, 2H, thiophen-CH_2), 3.64-3.83 (m, 2H, NCH_2), 4.24 (bs, 2H, NH-C<u>H</u>$_2$), 4.87 (q, 1H, J= 4 Hz C<u>H</u>-OH), 5.54 (d, 1H, J= 4 Hz, OH), 6.63 (t, 1H, J= 4.6 Hz, NH), 6.68-6.92 (m, 3H, arH), 7.22-7.42 (m, 8H, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 24.20 (thiophen-CH_2), 43.23 (NH-CH_2), 52.12 (N-CH_2), 70.12 (CH-OH), thiophen-C: [125.40 (CH), 126.24 (CH), 126.03 (CH), 136.75 (C)], ar-C: [114.19 (CH), 122.61 (C), 125.40 (CH), 130.81 (CH), 135.21 (C), 149.86 (C)], benzene-C: [126.64 (CH), 127.20 (CH), 128.00 (CH), 142.59 (C)], 144.98 (triazole-C-3), 152.12 (triazole-C-5).

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2ylmethyl-4-[(2,4-dichlorobenzyl)-amino]-4,5-dihydro-1H-[1,2,4]triazol-5-one (5g)

Recrystallized from ethanol/water (1:2) (yield: 80.42%). mp: 119-120 °C. Analysis (calc/found %): for $C_{20}H_{20}CI_2N_4O_2S$ C: 55.58/55.57, H: 4.24/4.26, N: 11.79/11.80; IR (KBr) (ν, cm^{-1}) 3391 (OH), 3235 (NH), 1696 (triazole-C=O), 1587 (C=N), 1203 (C-O) ^{1}H-NMR (DMSO-d_6)δ (ppm) 3.69 (s, 2H, thiophen-CH_2), 3.74-3.88 (m, 2H, NCH_2), 4.10 (t, 2H, J= 4.4 Hz, NH-C<u>H</u>$_2$), 4.87 (q, 1H, J= 4.6 Hz, CH-OH), 5.59 (d, 1H, J= 4.6 Hz OH), 6.70 (t, 1H, J= 4.4 Hz NH), 7.21-7.37 (m, 10H, arH), 7.59 (d, 1H, J=6 Hz, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 24.48 (thiophen-CH_2), 49.00 (NH-CH_2), 51.87 (N-CH_2), 70.14 (CH-OH) thiophen-C: [125.03 (CH), 126.06 (CH), 126.20 (CH), 136.98 (C)], ar-C: [128.74 (CH), 132.64 (CH), 133.04 (C), 133.49 (CH), 134.31 (C), 136.64 (C)], benzene-C: [126.67 (CH), 127.27 (CH), 128.02 (CH), 142.52 (C)], 145.24 (triazole-C-3), 152.12 (triazole-C-5).

General method for the synthesis of 1-(2-hydroxy-2-phenyl-ethyl)-3-thiophen-2-yl methyl-4-[arylidene-amino]-4,5-dihydro-1H-[1,2,4]triazole-5-ones (6)

A mixture of corresponding compounds **4** (0.01 mol) and $NaBH_4$ (0.02 mol) in absolute ethanol (50 mL) was stirred for 4 h at –5 °C. Ice water was then added with vigorous stirring. The solid obtained was filtered off and recrystallized from an appropriate solvent to afford the desired compound

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[(furan-2-ylmethylene-amino]-4,5-dihydro-1H-[1,2,4] triazole-5-one (6b)

Recrystallized from ethanol/water (1:2) (yield: 82.75%). mp: 110-111 °C. Analysis (calc/found %): for $C_{20}H_{18}N_4O_3S$ C: 60.90/60.91, H: 4.60/4.63, N: 14.20/14.18; IR (KBr) (ν, cm^{-1}) 3403 (OH), 1706 (triazole-C=O), 1610 (-C=N), 1254 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.25 (s, thiophen-CH_2), 3.68-3.97 (m, -NCH_2), 4.90-4.95 (m, CH-OH), 5.62 (d, OH, J=4.4 Hz), 9.55 (s, N=CH), 6.72-7.41 (m, 10H, arH), 7.98 (s, 1H, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.20 (thiophen-CH_2), 51.87 (N-CH_2), 69.87 (CH-OH) thiophen C: [125.24 (CH), 125.86(CH), 126.62(CH), 136.79 (C)], ar-C: [112.48 (CH), 117.63 (CH), 143.72 (CH), 148.08 (C)], benzene C: [126.73 (CH), 127.23 (CH), 127.99 (CH), 142.67 (C)], 149.33 (triazole-C-5), 142.19 (triazole-C-3), 146.71 (N=CH).

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2ylmethyl-4-[(benzylidene)-amino]-4,5-dihydro-1H-[1,2,4] triazole-5-one (6d)

Recrystallized from ethanol/water (1:2) (yield: 79.25%). mp: 139-140 °C. Analysis (calc/found %): for $C_{22}H_{20}N_4O_3S$ C: 65.32/65.30, H: 4.98/4.97, N: 13.85/13.87; IR (KBr) (ν, cm^{-1}) 3382 (OH), 1710 (triazole-C=O), 1590 (-C=N), 1203 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.30 (s, thiophen-CH_2), 3.77-3.82 (m, -NCH_2), 4.94 (s, CH-OH), 5.63 (s, OH,), 9.67 (s, N=CH), 7.00 (bs, 4H, arH), 7.41-7.84 (m, 4H, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.00 (thiophen-CH_2), 52.10 (N-CH_2), 69.80 (CH-OH) thiophen C: [125.27 (CH), 125.91 (CH), 126.58 (CH), 137.10 (C)], ar-C: [128.03 (CH), 128.88 (CH), 131.45 (C), 1433.16 (C)], benzene C: [126.78 (CH), 127.26 (CH), 127.70 (CH), 142.25 (C)], 153.36 (triazole-C-5), 143.93 (triazole-C-3), 149.35 (N=CH).

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2ylmethy-4-[(3-bromobenzylidene)-amino]-4,5-dihydro-1H-[1,2,4]triazole-5-one (6e)

Recrystallized from ethanol/water (1:2) (yield: 77.88%). mp: 150-151 °C. Analysis (calc/found %): for $C_{22}H_{19}BrN_4O_2S$ C: 54.66/54.54.65, H: 3.96/3.98, N: 11.59/11.58; IR (KBr) (ν, cm^{-1}) 3361 (OH), 1716 (triazole-C=O), 1607 (-C=N), 1200 (C-O), ^{1}H-NMR (DMSO-d_6)δ (ppm) 4.33 (s, thiophen-CH_2), 3.69-3.95 (m, -NCH_2), 4.94 (s, CH-OH), 5.64 (s, OH), 9.67 (s, N=CH), 6.95-7.50 (m, 9H, arH), 7.72-7.84 (m, 2H, arH), 8.05 (s, 1H, arH); ^{13}C-NMR (DMSO-d_6)δ (ppm) 25.34 (thiophen-CH_2), 51.95 (N-CH_2), 69.84 (CH-OH) thiophen C: [125.23 (CH), 125.87 (CH), 126.53 (CH), 136.79 (C)], ar-C: [122.16 (C), 126.99 (CH), 126.63 (CH), 133.88 (CH), 135.57 (C)], benzene C: [126.75 (CH), 127.24 (CH), 127.99 (CH), 142.19 (C)], 151.41 (triazole-C-5), 143.99 (triazole-C-3), 149.19 (N=CH).

Antimicrobial Activity

All test microorganisms were obtained from the Hıfzıssıha Institute of Refik Saydam (Ankara, Turkey) and were as follows; Ec: *Escherichia coli* ATCC 25922; Pa: *Pseudomonas aeruginosa* ATCC 10145; Yp: *Yersinia pseudotuberculosis* ATCC 911; Kp: *Klebsiella pneumoniae* ATCC 13883; Ef: *Enterococcus faecalis* ATCC 29212; Sa: *Staphylococcus aureus* ATCC 25923; Bc: *Bacillus cereus* 709 roma; Ca: *Candida albicans* ATCC 60193; Ct: *Candida tropicalis* ATCC 13803. Some of the new compounds were dissolved in dimethylsulphoxide (DMSO) to prepare extract stock solutions.

Agar Well Diffusion Method

Simple susceptibility screening tests using the agar-well diffusion method,[27] as adapted earlier,[28] were employed. Each microorganism was suspended in brain heart infusion (BHI) (Difco, Detroit, MI, USA) broth and diluted to 10^6 colony forming units (cfu) per mL. They were flood-inoculated onto the surface of BHI agar and Sabouraud dextrose agar (SDA) (Difco), and then dried. For *C. albicans*, *C. tropicalis*, *Penicillium* spp., and *Aspergillus* spp., SDA was used. Wells 5 mm in diameter were cut from the agar using a sterile cork borer and 250-5000 μg/50 $\mu\mu$L of the chemical substances were delivered into the wells. The plates were incubated for 18 h at 35 °C. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ceftazidime (Fortum) (10 μg) and Triflucan (5 μg) were the standard drugs. DMSO served as the solved control. The results are shown in Table 1.

Table 1. Antibacterial and antifungal activity of the synthesized compounds (10 mg/mL).

Compounds	Microorganisms and Inhibition Zones (mm)								
	Ec	Pa	Yp	Kp	Ef	Sa	Bc	Ca	Ct
2	5	5	5	5	5	5	5	**12**	**12**
3a	5	5	5	5	5	5	5	**13**	**8**
3b	5	5	5	5	5	5	5	5	5
3c	5	5	5	5	5	5	5	5	**10**
3d	5	5	5	5	5	5	5	5	5
3e	5	5	5	5	5	5	5	5	5
3f	5	5	5	5	5	5	5	5	5
3g	5	5	5	5	5	5	5	**10**	**10**
4a	5	5	5	5	5	5	5	5	5
4b	5	5	5	5	5	5	5	5	5
4c	5	5	5	5	5	5	5	5	5
4d	5	5	5	5	5	5	5	5	5
4e	5	5	5	5	5	5	5	5	5
4f	5	5	5	5	5	5	5	**12**	**11**
4g	5	5	5	5	5	5	5	5	5
5a	5	5	5	5	5	5	5	5	5
5b	5	5	5	5	5	5	5	**8**	**13**
5c	5	5	5	5	5	5	5	5	5
5d	5	5	5	5	5	5	5	5	5
5e	5	5	5	5	5	5	5	5	5
5f	5	5	5	5	5	5	5	5	5
5g	5	5	5	5	5	5	5	**6**	**8**
DMSO	5	5	5	5	5	5	5	5	5
Ampicillin	**8**	**5**	**5**	**5**	**11**	**15**	**14**		
Fortum	**45**	**45**	**45**	**20**	**30**	**30**	**35**		
Triflucan								**25**	**25**
Control PDA									

Results were interpreted in terms of the diameter of the inhibition zone (5 mm: no antimicrobial activity; > 5 mm: positive antimicrobial activity). Ec: *Escherichia coli* ATCC 25922; Pa: *Pseudomonas aeruginosa* ATCC 10145; Yp: *Yersinia pseudotuberculosis* ATCC 911; Kp: *Klebsiella pneumoniae* ATCC 13883; Ef: *Enterococcus faecalis* ATCC 29212; Sa: *Staphylococcus aureus* ATCC 25923; Bc: *Bacillus cereus* 709 ROMA; Ca: *Candida albicans* ATCC 60193; Ct: *Candida tropicalis* ATCC 13803.

Pharmacology

The screening experiments were performed by the Therapeutic Development Program of the National Cancer Institute (NCI), Bethesda MD, USA. Compounds **2**, **3a**, **3b**, **3c**, **3g**, **4a**, **4g, 5a**, and **5g** were selected by the NCI for screening against 3 human cell lines: breast cancer (MCF7), non-small-cell lung cancer (NCI-H460), and CNS (SF-268). Each cell line was inoculated and pre-incubated on a microtiter plate. Test agents were then added at a single concentration and the cultures were incubated for 48 h. End-point determinations were performed using Alamar blue.[29]

Compounds selected by the NCI were investigated for antitumor activity. The obtained results are presented in Table 2.

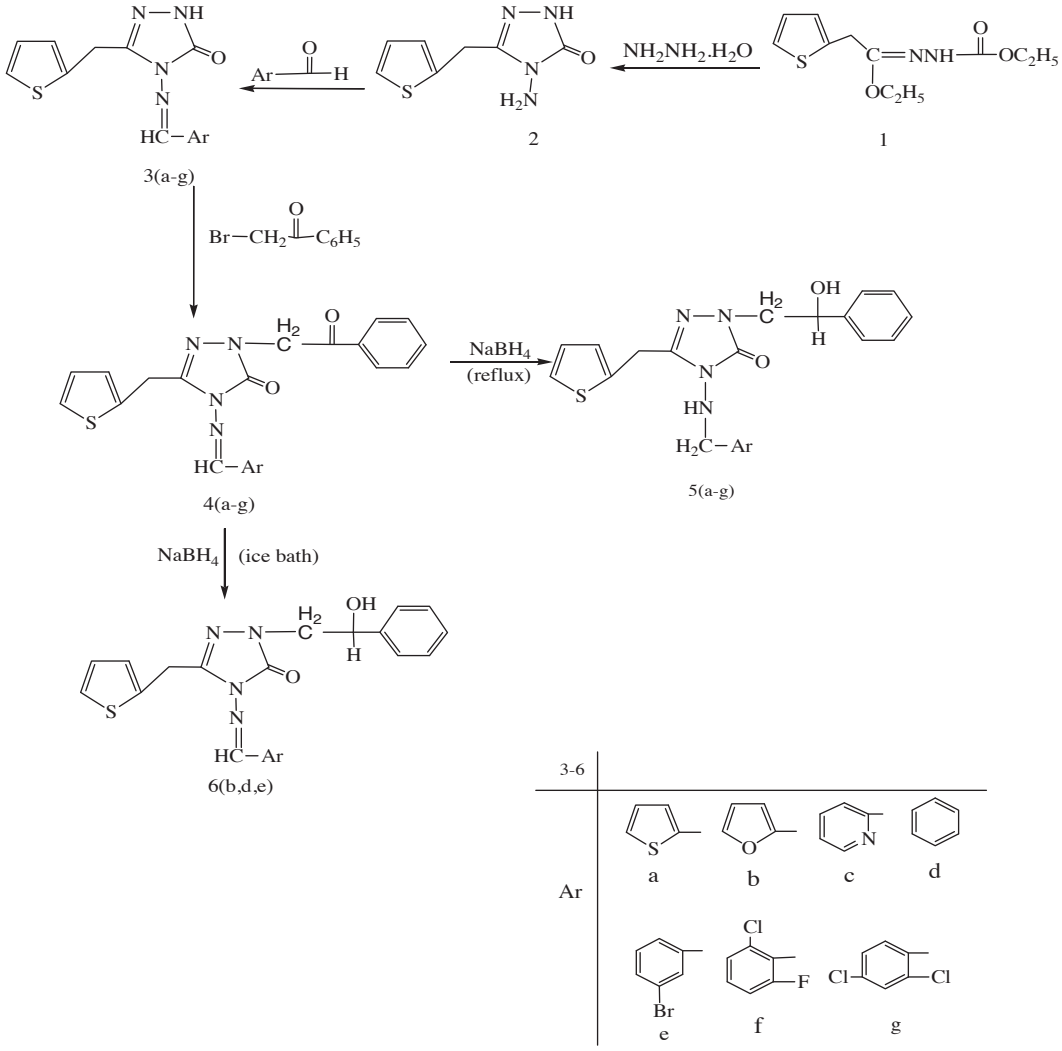
Table 2. Screening for cancer activity of some of the selected compounds.

Comp. No.	Number Assigned by NCI	Sample Concentration $\times 10^{-4}$	Percentage of Growth of Tumor Cells		
			MCF7	NCI-H460	SF-268
2	737033	1.00	96	74	84
3a	37034	1.00	97	91	89
3b	736261	1.00	108	98	105
3c	736212	1.00	113	120	109
3g	737038	1.00	109	108	100
4a	736728	1.00	91	109	113
4g	736727	1.00	89	115	98
5a	736729	1.00	101	124	117
5g	736730	1.00	96	118	121

Results and Discussion

In the first part of this study compounds **3a-g**, including both thiophen and 1,2,4-triazole-5-one, ring-linked to each other via a methylene group, were synthesized via the reaction of compound **2** with aromatic aldehydes (Scheme). In the IR and ^{1}H-NMR spectra of compounds **3a-g** no signals derived from the amino function were observed. In the ^{1}H-NMR spectra of compounds **3a-g** the proton signals due to N=CH were recorded at 9.02-10.13 ppm, integrating for 1 proton. The peaks belonging to the same group were observed at 147.07-150.95 ppm in the ^{13}C-NMR spectra.

The NH proton at position 1 of the 4,5-dihydro-1H-1,2,4-triazole-5-one ring is adequately acidic for further reactions. In the new study, some new 1-(2-oxo-2-phenyl-ethyl)-4-[arylidene-amino]-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-ones **(4a-g)** were obtained from the reaction of [arylidene-amino]-3-thiophen-2-ylmethyl-4,5-dihydro-1H-[1,2,4]triazole-5-ones **(3a-g)** with bromo acetophenone in reasonably good yields (Scheme). The IR spectra of compounds **4a-g** showed 2 sharp absorption bands; one at 1703-1713 cm^{-1} was attributed to the carbonyl function of the 1,2,4-triazole-5-one ring and the other observed at 1689-1698 cm^{-1} was assigned to the C=O stretching frequency corresponding to the ketone carbonyl. The NH signal disappeared in the ^{1}H-NMR and IR spectra of compounds **4a-g**. In the ^{1}H-NMR spectra of compounds **4a-g** a new additional signal belonging to methylene protons of acetophenone was recorded at 5.45-5.52 ppm. The signal belonging to the carbonyl carbon of the benzoyl group was seen at 192.56-193.44 ppm in the ^{13}C-NMR spectra of compounds **4**.



Scheme. Synthetic pathway for the preparation of target compounds **3, 4, 5,** and **6.**

The synthesis of 1-(2-hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[aryl-amino] 4,5-dihydro-1H-[1,2,4] triazole-5-ones **(5a-g)** was performed by the reaction of compounds **4** with $NaBH_4$ at the reflux temperature in the presence of absolute ethanol (Scheme). In the IR spectra of compounds **5** only 1 carbonyl function (C=O) belonging to the 1,2,4-triazole-5-one ring was observed at 1685-1696 cm^{-1}. The N=CH proton signals of compounds **4** were recorded at 9.59-10.12 ppm. These signals disappeared when compounds **5** formed. Instead, new signals at 3.95-4.18 ppm belonging to methylenic protons of the NH-CH_2 group of compounds **5** were seen and a C=O carbon signal belonging to acetophenone of compounds **4** was recorded at 192.88-192.56 ppm. These signals disappeared and new signals at 4.87-4.88 and 5.54-5.59 ppm belonging to CH and OH protons of the CH-OH group of compounds **5** were seen. The signals of the reduced (NH-CH_2 and CH-OH) carbon atoms of compounds **5** were observed at 43.23-51.87 and 70.12-70.14 ppm in the ^{13}C-NMR spectra, respectively. The spectral data suggest carbonyl belonging to both the acetophenone and azomethine groups was reduced by $NaBH_4$.

1-(2-Hydroxy-2-phenyl-ethyl)-3-thiophen-2ylmethyl-4-[arylidene-amino]4,5-dihydro-1H-[1,2,4] triazole-5-ones (6b, d, e) were synthesized via the reaction of compounds 4 with $NaBH_4$ at –5 °C in the presence of absolute ethanol (Scheme). In the IR spectra of compounds 6 only 1 carbonyl function (C=O) belonging to the 1,2,4-triazole-5-one ring appeared at 1706-1716 cm^{-1}. The C=O carbon signals belonging to the acetophenone of compounds 4 were recorded at 192.88-192.56 ppm. These signals disappeared and new signals at 4.90-4.94 and 5.62-5.64 ppm, belonging to the –CH and –OH protons of the CH-OH group of compounds 6, were seen. In the ^{1}H-NMR spectra of compounds 6 an N=CH proton signal was recorded at 9.55-9.67 ppm. The peaks belonging to the same group were observed at 147.07-150.95 ppm in the ^{13}C-NMR spectra. We can therefore say that the carbonyl group belonging to acetophenone was reduced by $NaBH_4$. Compounds **2, 3a, 3c, 3g, 4f, 5b, 5f**, and **5g** showed good antifungal activity against *Candida albicans* ATCC 60193 and *Candida tropicalis* ATCC 13803, while none of the compounds showed antimicrobial activity against bacteria.

Compounds selected by NCI were investigated for antitumor activity and they were not found to be active.

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