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Design and synthesis of new 1,2,4-triazole derivatives containing morpholine moiety as antimicrobial agents

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2-Morpholine-4ylethyl-3*H*-1,2,4-triazole-3-ones (**2a, 2b**) were obtained from the condensation between the corresponding ethoxycarbonylhydrazones and 2-morpholinoethanamine. **2a** was converted to acetohydrazide (**4**) via the formation of an ester derivative (**3**). Treatment of **2a** and **2b** with several aryl sulfonyl chlorides afforded the corresponding 2-arylsulfonyl-1,2,4-triazole-3-ones (**5a-c** and **6**). The reaction of hydrazide (**4**) with benzyl iso- and benzyl isothiocyanate produced the corresponding carboxamide (**8a**) and carbothioamide (**8b**). The basic treatment of **8b** yielded 5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**10**). The synthesis of 1,3-thiazol-2(3*H*)-ylidene-1,2,4-triazol-1-ylacetohydrazide (**11**) and 1,3-oxazole-2(3*H*)-ylidene-1,2,4-triazole-1-yl)acetohydrazide (**9**) derivatives was performed from the reaction of **8a** and **8b** with substituted phenacyl bromides.

All the newly synthesized compounds were screened for their antimicrobial activities and some of them were found to possess good or moderate antimicrobial activity.

Key Words: 1,2,4-Triazole, 1,3-oxazole, 1,3-thiazole, morpholine, antimicrobial activity

Introduction

The development of drug resistance towards the clinically used antibacterial agents has increased the demand for the design and synthesis of new chemical scaffolds possessing antimicrobial activity. The growing number of immuno-compromised patients as a result of cancer chemotherapy, organ transplantation, and HIV infection are

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the major factors contributing to this increase. Moreover, in some cases, especially in patients with impaired liver or kidney functions, the use of antimicrobial drugs to treat infections causes several problems.[1,2]

Thus, these trends have required the urgent need for new, more effective antibacterial agents with lack of side effects. For this purpose, 2 attractive approaches have been developed. One of them involved the development of structurally new classes of antimicrobial agents with novel mechanism of action; the other contained structural modification or optimization of the existing agents by improving both the binding affinity and spectrum of activity while retaining bioavailability and safety profile. However, in recent years, another strategy employing a combination of 2 different active fragments in 1 molecule has emerged.[3] In this strategy, each drug moiety is designed to bind independently to 2 different biological targets and synchronously accumulate at both target sites. Such dual-action drugs, or hybrid drugs, offer the possibility to overcome the current resistance and reduce the appearance of new resistant strains.[2,4]

1,2,4-Triazole derivatives have consistently attracted scientific and practical interest because of their widely varying chemical properties, synthetic versatility, and pharmacological activities, such as antibacterial,[5−11] antifungal,[8−12] antitubercular,[13−15] analgesic,[16,17] anti-inflammatory,[17−19] anticancer,[20,21] anticonvulsant,[22,23] antiviral,[24,25] insecticidal,[26] and antidepressant[27] antiviral properties. Moreover, the 1,2,4-triazole compounds carrying sulfone moiety or imine bond have been reported as antibacterial and antifungal, antihypertensive, analgesic, anti-inflammatory, or antitumoral agents.[28−36]

Another important pharmacophore group is the morpholine nucleus incorporated in a wide variety of therapeutically important drugs, one of which is linezolid, which belongs to the oxazolidinone class of antibiotics and is used for the treatment of infections caused by gram-positive bacteria.[37−39] In addition, 4-phenylmorpholine derivatives have been reported to possess antimicrobial, anti-inflammatory, and central nervous system activities.[40]

Oxazolidinones are a new and promising class of synthetic antibiotics that have activity against numerous multidrug-resistant gram-positive pathogens. Oxazolidinones have been thought to be not cross resistant with other types of antibiotics due to their different mode of action mechanism that includes the interaction with the bacterial ribosome to inhibit bacterial growth.[41−45] Thiazolidinones, being bioisosters of oxazolidinones, have been reported to possess diverse pharmacological properties such as antibacterial, antifungal, anticonvulsant, anticancer, antituberculosis, and anti-human immunodeficiency virus type 1 (HIV-1) activities.[46−52]

Over 10 years our interest has focused on the synthesis of novel heterocyclic systems that have antimicrobial activity. In the present study, as a part of our ongoing research, we designed and synthesized new hybrid molecules containing different pharmacophores in a single structure.

Experimental

All the chemicals were purchased from Fluka Chemie AG Buchs (Switzerland) and used without further purification. Melting points of the synthesized compounds were determined in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. The reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminum sheets. The mobile phase was ethyl acetate:ether (1:1) and detection was performed using UV light. IR spectra were recorded as potassium bromide pellets using a Perkin Elmer 1600 series FTIR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a BRUKER AVENE II 400 MHz

NMR Spectrometer (chemical shift in ppm downfield from TMS as an internal reference). The elemental analysis was performed on a Costech Elemental Combustion System CHNS-O elemental analyzer. All the compounds gave C, H, and N analyses within ±0.4% of the theoretical values. The mass spectra (except compound **5**) were obtained on a Quattro LC-MS (70 eV) Instrument. Compounds **1a** and **1b** were prepared following a previously reported literature procedure.[53]

General method for the synthesis of compounds 2a and 2b

Method 1: A mixture of the corresponding compound **1** (10 mmol) and 2-morpholinoethanamine (10 mmol) was heated at 110-120 °C in an oil bath for 2 h. (The progress of the reaction was monitored by TLC). Then *n*-butyl acetate-diethyl ether (1:2) was added and the reaction mixture was kept overnight in cold conditions. The solid formed was filtered off and recrystallized several times with suitable solvents to afford the target compounds.

Method 2: A solution of the corresponding compound **1** (10 mmol) in water was refluxed with 2-morpholinoethanamine (10 mmol) for 5 h (the progress of the reaction was monitored by TLC). The solvent was evaporated under reduced pressure and an oily product was obtained. *n*-Butyl acetate-diethyl ether (1:2) was added to it and it was kept overnight in cold conditions. The solid formed was filtered off and recrystallized several times from suitable solvents to afford the target compounds.

5-Methyl-4-(2-morpholine-4ylethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-one (2a). Yield 65%, mp 146-148 °C. IR (KBr, υ, cm^{-1}): 3185 (NH), 1693 (C=O), 1589 (C=N); Anal. Calcd (%) for $C_9H_{16}N_4O_2$: C, 50.93; H, 7.60; N, 26.40. Found: C, 50.92; H, 7.65; N, 25.75. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.00 (3H, s, CH_3), 2.16-2.51 (6H, m, $3CH_2$), 3.52-3.65 (6H, m, $3CH_2$), 11.31 (1H, brs, NH, exch. D_2O); ^{13}C-NMR (DMSO-d_6, δ ppm): 16.99 (CH_3), 58.73 ($2CH_2$), 62.08 ($2CH_2$), 71.61 ($2CH_2$), 150.17 (triazole C-5), 160.43 (triazole C-3); EI MS m/z (%): 212.98 ($[M]^+$, 69), 125.87 (29), 113.92 (100).

5-Benzyl-4-(2-morpholine-4ylethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-one (2b). Yield 55%, mp 124-126 °C. IR (KBr, υ, cm^{-1}): 3167 (NH), 1697 (C=O), 1675 (C=N); Anal. Calcd (%) for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.42; H, 7.03; N, 19.92. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.17-2.49 (6H, m, $3CH_2$), 3.35-3.49 (6H, m, $3CH_2$), 3.95 (2H, s, CH_2), 7.26-7.31 (5H, m, arH), 11.52 (1H, s, NH, exch.D_2O); ^{13}C-NMR (DMSO-d_6, δ ppm): 31.34 (CH_2), 53.05 ($3CH_2$), 55.90 ($3CH_2$), 65.97 ($3CH_2$), ar C: [126.76 (CH), 128.48 (2CH), 128.51 (2CH), 135.41 (C)], 146.29 (triazole C-5), 154.98 (triazole C-3); EI MS m/z (%): 311.42 ($[M+Na]^+$, 99), 289.41 ($[M+1]^+$, 59), 288.40 ($[M]^+$, 64), 202.23 (97), 114.18 (34), 113.18 (84).

Ethyl [3-methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl]acetate (3). Compound **2a** (10 mmol) was refluxed with 1 equiv. of sodium in absolute ethanol for 2 h. Then ethyl bromoacetate (10 mmol) was added, followed by refluxing for an additional 8 h (the progress of the reaction was monitored by TLC). After the solvent was evaporated under reduced pressure, a solid appeared. The crude product was recrystallized from ethanol:water (1:1) to afford the target compound **3**.

Yield 43%, mp 94 °C. IR (KBr, υ, cm^{-1}): 1743 and 1713 (2C=O), 1581 (C=N), 1215 (C-O); Anal. Calcd (%) for $C_{13}H_{22}N_4O_4$: C, 52.34; H, 7.43; N, 18.78. Found: C, 52.38; H, 7.39; N, 18.71. ^{1}H-NMR (DMSO-d_6, δ ppm): 1.19 (3H, t, J = 7.2 Hz, CH_3), 2.22 (3H, s, CH_3), 2.35-2.52 (6H, m, $3CH_2$), 3.54 (4H, t, J = 4.2 Hz, $2CH_2$), 3.68 (2H, t, J = 6.0 Hz, CH_2), 4.12 (2H, q, J = 7.2 Hz, CH_2), 4.49 (2H, s, CH_2);

^{13}C-NMR (DMSO-d_6, δ ppm): 11.25 (CH_3), 13.90 (CH_3), 45.89 (CH_2), 53.18 ($2CH_2$), 56.35 (CH_2), 60.91 ($2CH_2$), 66.04 ($2CH_2$), 144.21 (triazole C-5), 153.45 (triazole C-3), 167.86 (C=O). EI MS m/z (%): 321.23 ($[M+Na]^+$, 100), 299.22 ($[M+1]^+$, 69), 211.98 (23), 113.93 (78).

2-[3-Methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl] acetohydrazide (4). A solution of compound **3** (10 mmol) in ethanol was allowed to reflux in the presence of hydrazine hydrate (25 mmol) for 5-8 h (the progress of the reaction was monitored by TLC). After cooling to room temperature, acetone was added to the mixture and it was kept overnight in cold conditions. The resulting solid that separated was collected by filtration and recrystallized from ethyl acetate to afford the desired product.

Yield 36%, mp 146-148 °C. IR (KBr, υ, cm^{-1}): 3313 and 3169 ($NH+NH_2$), 1692 and 1654 (C=O), 1585 (C=N), 1112 (C-O); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.18 (3H, s, CH_3), 2.30-2.50 (6H, m, $3CH_2$+DMSO), 3.50-3.60 (4H, m, $2CH_2$), 3.64 (2H, t, J = 6.0 Hz, CH_2), 4.17 (2H, s, CH_2), 4.50 (2H, brs, NH_2), 9.17 (1H, s, NH); ^{13}C-NMR (DMSO-d_6, δ ppm): 16.83 (CH_3), 43.62 (CH_2), 51.39 (CH_2), 58.77 ($2CH_2$), 62.04 (CH_2), 71.62 ($2CH_2$), 149.42 (triazole C-5), 156.14 (triazole C-3), 171.49 (C=O); EI MS m/z (%): 325.32 ($[M+2+K]^+$, 53), 285.26 ($[M+1]^+$, 69), 114.06 (100).

General method for the synthesis of compounds 5a-c and 6. A solution of compound **4** (10 mmol) in dichloromethane was refluxed in the presence of metallic sodium (10 mmol) until the metallic sodium disappeared completely (about 7-8 h). Then a suitable aryl sulfonylchloride was added, followed by refluxing for an additional 8 h (the progress of the reaction was monitored by TLC). Water was added to the reaction mixture, and the organic phase was separated and dried on sodium sulfate. After evaporation of the solvent under reduced pressure, an oily product was obtained. This crude product was recrystallized from an appropriate solvent to afford the desired compound.

5-Methyl-4-(2-morpholine-4-ylethyl)-2-[(4-nitrophenyl)sulfonyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-one (5a). Recrystallized from ethanol:water (1:2). Yield 31%, mp 190-192 °C. IR (KBr, υ, cm^{-1}): 1742 (C=O), 1605 (C=N), 1186 (C-O); Anal. Calcd (%) for $C_{15}H_{19}N_5O_6S$: C, 45.33; H, 4.82; N, 17.62. Found: C, 45.48; H, 4.96; N, 17.47. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.26 (3H, s, CH_3), 3.20-3.37 (12H, m, $6CH_2$), 7.85 (1H, d, J =8.6 Hz, arH), 8.18 (2H, d, J =8.9 Hz, arH), 8.51 (1H, d, J =8.6 Hz, arH); ^{13}C-NMR (DMSO-d_6, δ ppm): 12.26 (CH_3), 38.69-41.17 (DMSO-d_6 +$4CH_2$), 50.22 (CH_2), arC: [123.91 (CH), 125.66 (CH), 126.20 (C), 127.43 (CH), 129.86 (CH), 130.04 (C)], 140.18 (triazole C-3), 150.22 (triazole C-5); EI MS m/z (%): 436 ($[M+K]^+$, 14), 399 ($[M+2]^+$, 11), 398 ($[M+1]^+$, 49), 336 (14), 216 (14), 215 (70), 154 (16), 153 (100), 120 (30), 114 (42).

5-Methyl-4-(2-morpholine-4-ylethyl)-2-[(4-bromophenyl)sulfonyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-one (5b). Recrystallized from ethyl acetate:petroleum ether (1:1). Yield 35%, mp 179-181 °C. IR (KBr, υ, cm^{-1}): 1722 (C=O), 1600 (C=N), 1186 (C-O); Anal. Calcd (%) for $C_{15}H_{19}N_4O_4S$: C, 41.77; H, 4.44; N, 12.99. Found: C, 41.77; H, 4.49; N, 12.71. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.22 (3H, s, CH_3), 3.31-3.52 (8H, m, $4CH_2$), 3.60 (4H, t, J = 5.6 Hz, $2CH_2$), 7.87-7.94 (4H, m, arH); ^{13}C-NMR (DMSO-d_6, δ ppm): 11.63 (CH_3), 38.07-40.16 (DMSO-d_6 +CH_2), 52.94 (CH_2), 55.28 ($2CH_2$), 65.91 ($2CH_2$), arC: [129.20 (2CH), 130.42 (C), 132.80 (2CH), 135.52 (C)], 149.59 (triazole C-3), 151.11 (triazole C-5); EI MS m/z (%): 114 (96), 215 (99), 216 (19), 431 ($[M]^+$, 76), 433 (72), 434 (16), 453 (40), 455 ($[M+1+Na]^+$, 32).

5-Methyl-4-(2-morpholine-4-ylethyl)-2-[(4-chlorophenyl)sulfonyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-one (5c). Recrystallized from ethanol. Yield 27%, mp 167-169 °C. IR (KBr, υ, cm^{-1}): 1721 (C=O),

1599 (C=N), 1186 (C-O). Anal. Calcd (%) for $C_{15}H_{19}N_4O_4S$: C, 46.57; H, 4.95; N, 14.48. Found: C, 46.84; H, 5.12; N, 14.21. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.22 (3H, s, CH_3), 2.27 (2H, t, J = 4.4 Hz, CH_2), 2.40 (2H, t, J =5.6 Hz, CH_2), 2.51 (2H, m, CH_2), 3.38-3.43 (4H, m, $2CH_2+H_2O$), 3.60 (2H, t, J =5.8 Hz , CH_2), 7.77 (2H, d, J = 8.6 Hz, arH), 7.94 (2H, d, J = 9.0 Hz, arH); ^{13}C-NMR (DMSO-d_6, δ ppm): 11.66 (CH_3), 52.98 ($2CH_2$), 55.33 ($2CH_2$), 65.95 ($2CH_2$), arC:[129.25 (2CH), 129.88 (2CH), 135.11 (C), 140.01 (C)], 149.60 (triazole C-3), 151.12 (triazole C-5); EI MS m/z (%): 411 (38), 409 ([M+Na]$^+$, 87), 389 (28), 387 ([M+1]$^+$, 100), 229 (61), 114 (91).

5-Benzyl-4-(2-morpholine-4-ylethyl)-2-[(4-nitrophenyl)sulfonyl]-2,4-dihydro-3*H*-1,2,4-triazole-3-one (6). Recrystallized from ethyl acetate. Yield 53%, mp 144-146 °C. IR (KBr, υ, cm^{-1}): 1743 (C=O), 1604 (C=N), 1186 (C-O); Anal. Calcd (%) for $C_{21}H_{23}N_5O_6S$: C, 53.27; H, 4.90; N, 14.79. Found: C, 53.27; H, 4.89; N, 14.85. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.12 (4H, brs, $2CH_2$), 2.49 (2H, brs, CH_2), 3.32-3.35 (4H, m, $2CH_2+H_2O$), 3.54 (2H, t, J = 6.4 Hz, CH_2), 4.03 (2H, s, CH_2), 8.18-8.26 (5H, m, arH), 8.46-8.50 (2H, m, arH), 8.52-8.55 (2H, m, arH); ^{13}C-NMR (DMSO-d_6, δ ppm): 31.16 (CH_2), 52.87 ($2CH_2$), 54.92 ($2CH_2$), 65.92 ($2CH_2$), arC: [125.03 (3CH), 127.22 (CH), 128.63 (3CH), 128.70 (2CH), 133.68 (C), 141.20 (C), 150.96 (C)], 151.29 (triazole C-3), 151.51 (triazole C-5); EI MS m/z (%): 496 (20), 475 (25), 474 ([M+1]$^+$, 100), 458 (11), 216 (12), 215 (50), 202 (12), 153 (19), 114 (41).

General method for the synthesis of compounds 7a-c. A solution of the corresponding compound **4** (10 mmol) in absolute ethanol was refluxed with appropriate aldehyde (10 mmol) for 3 h. On cooling the mixture to room temperature, a white solid appeared. This crude product was recrystallized from ethanol to afford the desired product.

2-[3-Methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl]-*N*'-[phenylmethylene]acetohydrazide (7a). Yield 84%, mp 190-191 °C. IR (KBr, υ, cm^{-1}): 3126 (NH), 1709 and 1681 (C=O). Anal. Calcd (%) for $C_{18}H_{24}N_6O_3$: C, 57.99; N, 22.55; H, 6.44. Found: C, 57.68; N, 22.33; H, 6.71. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.23 (3H, s, CH_3), 2.41-2.51 (8H, m, $4CH_2$+DMSO-d_6), 3.36-3.66 (2H, m, CH_2+H_2O), 3.70 (2H, t, J = 6.2 Hz, CH_2), 4.41 and 4.81 (2H, s, CH_2, cis/trans amide conformers), 7.40-750 (3H, m, arH), 7.71 (2H, d, J = 3.4 Hz, arH), 7.99 and 8.21 (1H, s, N=CH, cis/trans amide conformers), 11.67 (1H, s, NH); ^{13}C-NMR (DMSO-d_6, δ ppm): 12.09 (CH_3), 39.74 (CH_2), 46.66 (CH_2), 54.01 ($2CH_2$), 57.23 (CH_2), 66.86 ($2CH_2$), arC:[127.64 (CH), 127.82 (2CH), 129.50 (CH), 130.68 (CH), 134.62 (C)], 144.53 (CH), 144.67 (triazole C-5), 154.68 (triazole C-3), 168.83 (C=O); EI MS m/z (%): 373 ([M+1]$^+$, 100), 395 ([M+Na]$^+$, 50), 374 (24), 114 (56).

2-[3-Methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl]-*N*'-[(4-nitrophenyl)methylene]acetohydrazide (7b). Yield 94%, mp 200-203 °C. IR (KBr, υ, cm^{-1}): 3193 (NH), 1703 and 1679 (C=O). Anal. Calcd (%) for $C_{18}H_{23}N_7O_5$: C, 53.63; N, 23.45; H, 5.06. Found: C, 53.26; N, 23.18; H, 5.37. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.23 (3H, s, CH_3), 2.40-2.60 (4H, m, $2CH_2$+DMSO-d_6), 3.55 (4H, t, J = 5.0 Hz, $2CH_2$), 3.70 (2H, t, J = 6.4 Hz, CH_2), 4.86 (2H, s, CH_2), 7.94-8.03 (2H, m, arH), , 8.10 (1H, s, N=CH), 8.24-8.33 (2H, m, arH), 11.94 (1H, s, NH); ^{13}C-NMR (DMSO-d_6, δ ppm): 11.30 (CH_3), 38.92 (CH_2), 45.89 (CH_2), 53.20 ($2CH_2$), 56.41 (CH_2), 66.05 ($2CH_2$), arC: [121.85 (C), 123.89 (2CH), 127.84 (2CH), 140.13 (C)], 141.55 (N=CH), 143.84 (triazole C-5), 158.75 (triazole C-3), 167.07 (C=O); EI MS m/z (%): 419.27 (21), 418.27 ([M+1]$^+$, 100), 284.37 (54), 259.59 (22).

***N*'-[1*H*-Indol-3-ylmethylene]-2-[3-methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-**

1,2,4-triazole-1-yl]acetohydrazide (7c). Yield 92%, mp 130 °C. IR (KBr, υ, cm^{-1}): 3217 (NH), 1690 (C=O). Anal. Calcd (%) for $C_{20}H_{25}N_7O_3$: C, 52.28; N, 21.35; H, 5.45. Found: C, 52.41; N, 21.17; H, 5.63. ^{1}H-NMR (DMSO-d_6, δ ppm): 2.24 (3H, s, CH_3), 2.43-2.51 (4H, m, $2CH_2$+DMSO-d_6), 3.56 (4H, m, $2CH_2$+H_2O), 3.67 (2H, t, J =6.2 Hz, CH_2), 3.70 (2H, m, CH_2), 4.87 (2H, s, CH_2), 7.12-7.25 (2H, m, arH), 7.45 (1H, d, J =8.0 Hz, arH), 7.83 (1H, s, arH), 8.20 and 8.38 (1H, s, N=CH, *cis/trans* amide conformers), 11.60 (1H, s, NH); ^{13}C-NMR (DMSO-d_6, δ ppm): 11.30 (CH_3), 38.92 (CH_2), 45.86 (CH_2), 53.23 ($2CH_2$), 56.49 (CH_2), 60.07 ($2CH_2$), arC: [120.30 (CH), 121.53 (CH), 122.54 (CH), 123.91 (C), 130.53 (CH), 136.88 (C)], 141.34 (N=CH), 143.91 (triazole C-5), 144.38 (N-CH), 153.93 (triazole C-3), 162.22 (indole C-3) 167.07 (C=O); EI MS m/z (%): 434.28 (31), 413.32 (28), 412.32 ($[M+1]^+$, 100], 284.30 (41), 113.92 (69).

General method for the synthesis of compounds 8a and 8b.

A mixture of compound **4** (10 mmol) and benzylisocyanate (10 mmol) (for **8a**) or benzylisothiocyanate (10 mmol) (for **8b**) was stirred under reflux in ethanol for 3 h (the progress of the reaction was monitored by TLC). After evaporating the solvent under reduced pressure an oily product appeared; this was recrystallized from ethanol to afford the desired products.

***N*-Benzyl-2-{[3-methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl] acetyl}hydrazinecarboxamide (8a).** Yield 70%, mp 178-180 °C. IR (KBr, υ, cm^{-1}): 3278 (2NH), 3020 (NH), 1720 (C=O), 1690 (C=O), 1667 (C=O); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.19 (3H, s, CH_3), 2.30-2.53 (6H, m, $3CH_2$+DMSO-d_6), 3.40-3.50 (4H, m, $2CH_2$), 3.66 (2H, t, J = 5.6 Hz, CH_2), 4.23 (2H, d, J = 5.6 Hz, CH_2), 4.33 (2H, s, CH_2), 7.05 (1H, brs, NH), 7.25-7.30 (5H, m, arH),7.99 (1H, s, NH), 9.83 (1H, s, NH); ^{13}C-NMR (DMSO-d_6, δ ppm): 12.02 (CH_3), 38.74 (CH_2), 43.07 (CH_2), 46.70 ($2CH_2$), 53.93 ($2CH_2$), 57.14 (CH_2), 66.77 (CH_2), arC: [127.26 (CH), 127.51 (2CH), 128.84 (2CH), 141.04 (C)], 144.85 (triazole C-5), 154.46 (triazole C-3), 158.66 (C=O), 167.52 (C=O); EI MS m/z (%): 456.25 (50), 440.29 (47), 418.27 ($[M+1]^+$,59), 246.07 (34), 232.06 (23).

***N*-Benzyl-2-{[3-methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl] acetyl}-phenylhydrazinecarbothioamide (8b).** Yield 57%, mp 180-181 °C. IR (KBr, υ, cm^{-1}): 3371 (3NH), 1734 (C=O), 1681 (C=N), 1180 (C-O). Anal. Calcd (%) for $C_{19}H_{27}N_7O_3S$: C, 52.64; H, 6.28; N, 22.62. Found: C, 53.08; H, 6.35; N, 22.49. 2.19 (3H, s, CH_3), 2.42-2.51 (2H, m, CH_2+DMSO-d_6), 3.38 (4H, brs, $2CH_2$), 3.41 (4H, brs, $2CH_2$), 3.47 (2H, brs, CH_2), 4.36 (2H, s, CH_2), 4.72 (2H, brs, CH_2), 7.22-7.30 (5H, m, arH), 8.57 (1H, brs, NH), 9.50 (1H, s, NH), 10.13 (1H, s, NH); ^{13}C-NMR (DMSO-d_6, δ ppm): 12.06 (CH_3), 38.92-41.43 (CH_2+DMSO-d_6), 46.77 (CH_2), 47.31 (CH_2), 54.01 ($2CH_2$), 57.21 (CH_2), 66.86 ($2CH_2$), arC:[127.35 (2CH), 127.63 (CH), 128.77 (2CH), 139.85 (C)], 144.80 (triazole C-5), 154.46 (triazole C-3), 167.28 (C=O), 182.48 (C=S); EI MS m/z (%): 472.14 (53), 456.18 (28), 434.22 ($[M+1]^+$, 53), 285.12 (38), 284.24 (65), 238.06 (91), 113.86 (100).

***N*'-[3-Benzyl-4-(4-nitrophenyl)-1,3-oxazole-2(3*H*)-ylidene]-2-(3-methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl)acetohydrazide (9).** 4-Nitrophenacyl bromide (10 mmol) was added to the solution of compound **8a** (10 mmol) in ethanol and the mixture was refluxed in the presence of dried sodium acetate (30 mmol) for 11 h (the progress of the reaction was monitored by TLC). Then the mixture was cooled to room temperature, poured into ice-cold water while stirring, and left overnight in

cold conditions. The formed solid was filtered off, washed with water 3 times, and recrystallized from dimethyl sulfoxide to afford the pure compound. Yield 48%, mp 238-240 °C. IR (KBr, υ, cm^{-1}): 3288 (NH), 1661 (C=O), 1572 (C=O); EI MS m/z (%): 134.76 (100), 137.89 (51), 337.06 (41), 423.10 (81), 563.39 ($[M+1]^+$, 15).

2-[(4-Benzyl-5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-5-methyl-4-(2-morpholin-4-ylethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (10). A solution of compound **8b** (10 mmol) in ethanol:water (1:1) was refluxed in the presence of 2 N NaOH for 3 h. Then the resulting solution was allowed to cool to room temperature and acidified to pH 3-4 with 37% HCl. The precipitate formed was filtered off, washed with water, and recrystallized from ethanol to afford the desired compound. Yield 30%, mp 162-163 °C. IR (KBr, υ, cm^{-1}): 2854 (SH), 1703 (C=O), 1587 (C=N). Anal. Calcd (%) for $C_{19}H_{25}N_7O_2S$: C, 54.88; N, 23.59; H, 6.01; S, 7.70. Found: C, 54.56; N, 23.19; H, 6.24; S, 7.35. ^{1}H-NMR (DMSO-d_6, δ ppm): 1.96 (3H, s, CH_3), 2.23-2.34 (4H, m, $2CH_2$), 3.29 (4H, t, J = 6.2 Hz, $2CH_2$), 3.50 (4H, brs, $2CH_2$), 4.91 (2H, s, CH_2), 5.19 (2H, s, CH_2), 6.92-6.99 (2H, m, arH), 7.22-7.27 (2H, m, arH), 13.95 (1H, s, SH); ^{13}C-NMR (DMSO-d_6, δ ppm): 11.81 (CH_3), 38.80-40.97 ($2CH_2$+DMSO-d_6), 46.50 (CH_2), 53.93 ($2CH_2$), 56.97 (CH_2), 66.80 ($2CH_2$), arC:[126.53 (2CH), 127.88 (CH), 128.76 (2CH), 135.38 (C)], 145.14 (triazole C-5), 149.01 (triazole C-3), 153.28 (C=O), 168.89 (C=S); EI MS m/z (%): 229 (81), 438 (38), 416 ($[M+1]^+$, 100).

***N*'-[3-Benzyl-4-(4-chlorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-2-[3-methyl-4-(2-morpholin-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide (11).** 4-Chlorophenacyl bromide (10 mmol) was added to the solution of compound **8b** in ethanol and the mixture was allowed to reflux in the presence of dried sodium acetate for 8 h (the progress of the reaction was monitored by TLC). Then the mixture was cooled to room temperature, poured into ice-cold water while stirring, and left overnight in cold conditions. The formed solid was filtered off, washed with water 3 times, and recrystallized from ethylacetate-ethyl ether (1:2) to afford the target compound. Yield 33%, mp 138-140 °C. IR (KBr, υ, cm^{-1}): 3386 (NH), 1702 (C=O). 1587 (C=N). ^{1}H-NMR (DMSO-d_6, δ ppm): 2.02 (3H, s, CH_3), 2.08-2.49 (6H, m, $3CH_2$), 3.39-3.52 (6H, m, $3CH_2$), 4.88 (2H, s, CH_2), 5.02 (2H, s, CH_2), 5.25 (1H, s, CH), 6.84 (2H, d, J = 5.4 Hz, arH), 7.28 (3H, d, J = 7.0 Hz, arH), 7.62 (2H, d, J = 7.0 Hz, arH), 8.0 (2H, d, J = 8.6 Hz, arH), 11.23 (1H, s, NH). ^{13}C-NMR (DMSO-d_6, δ ppm): 11.00 (CH_3), 37.29 (CH_2), 38.49-40.17 (CH_2+DMSO-d_6), 45.72 (CH_2), 52.66 ($2CH_2$), 55.52 (CH_2), 65.38 ($2CH_2$), 104.36 (thiazole C-5), arC: [125.74 (2CH), 127.14 (CH), 127.99 (2CH), 128.85 (2CH), 130.40 (CH), 131.41 (CH), 134.61 (2C), 136.50 (C)], 144.27 (triazole C-5+thiazole C-4), 148.16 (triazole C-3), 152.57 (thiazole C-2), 164.50 (C=O); EI MS m/z (%): 570.31 (34), 568.29 ($[M]^+$, 72), 238.17 (44), 152.71 (31), 113.88 (100).

Antimicrobial activity assessment. All test microorganisms were obtained from the Refik Saydam Hygiene Institute (Ankara, Turkey) and were as follows: *E. coli* ATCC35218, *E. aerogenes* ATCC13048, *Y. pseudotuberculosis* ATCC911, *P. aeruginosa* ATCC43288, *S. aureus* ATCC25923, *E. faecalis* ATCC29212, *B. cereus* 709 Roma, *M. smegmatis* ATCC607, *C. albicans* ATCC60193, *C. tropicalis* ATCC 13803, *A. niger* RSKK 4017, and *S. cerevisiae* RSKK 251. All the newly synthesized compounds were weighed and dissolved in dimethylsulphoxide to prepare extract stock solution of 5 mg/mL. Agar-well diffusion method screening test using agar-well diffusion[54] as adapted earlier[55] was used for all newly synthesized compounds. Each microorganism was suspended in Mueller Hinton (MH) (Difco Detroit, MI, USA) broth and diluted approximately to 10^6 colony forming units (cfu)/mL. They were "flood-inoculated" onto the surface of MH

agar and Sabouraud Dextrose Agar (SDA) (Difco, Detriot, MI, USA) and then dried. For *C. albicans* and *C. tropicalis*, SDA were used. Five millimeter diameter wells were cut from the agar using a sterile cork-borer, and 50 mL of the extract substances was 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. Ampicillin (10 mg), streptomycin (10 mg), and fluconazole (5 mg) were the standard drugs. Dimethyl sulfoxide and ethanol were used as solvent controls. The antimicrobial activity results are summarized in the Table.

Table. Screening for antimicrobial activity of the compounds.

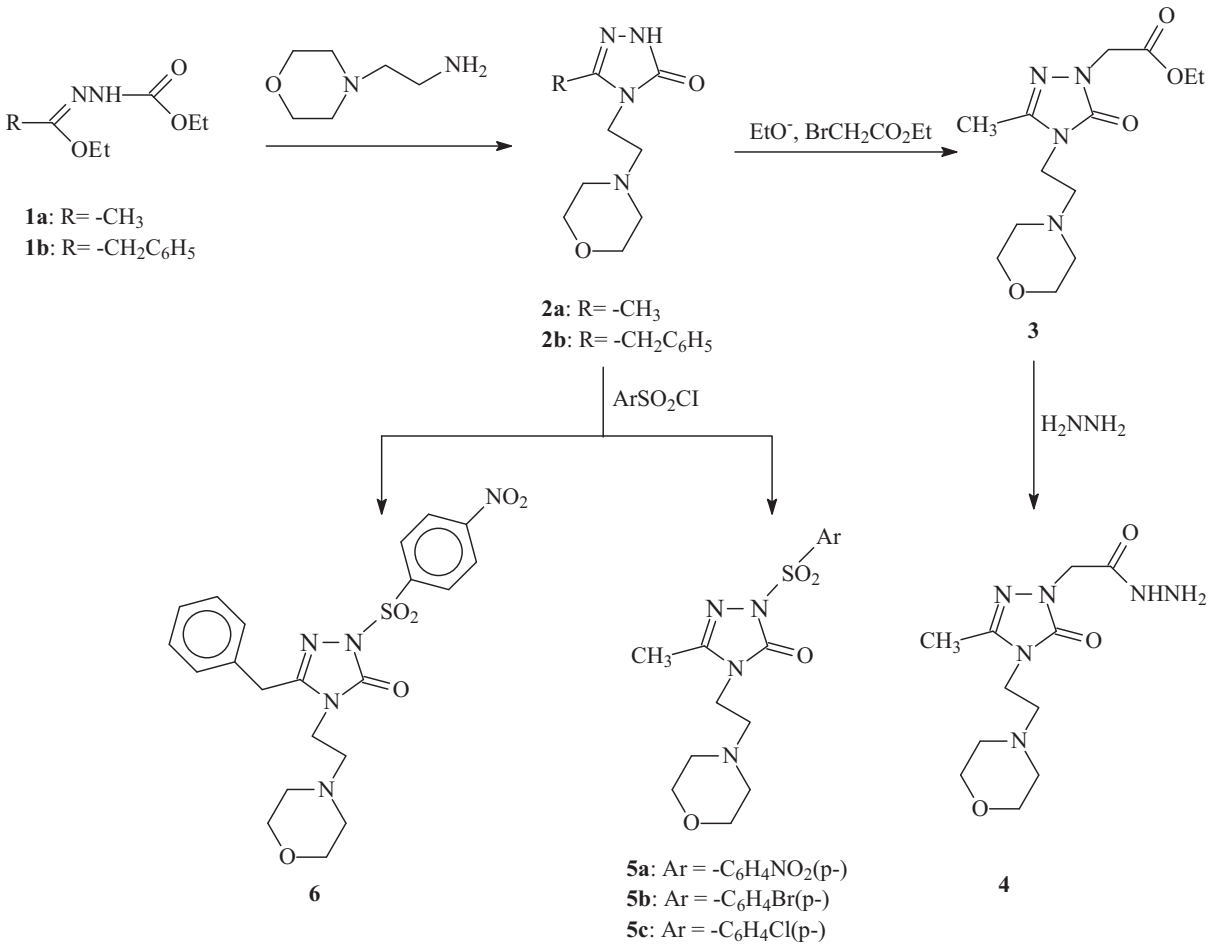
Comp.	Microorganisms and inhibition zone (mm)													
no.	Ec	Ea	Yp	Kp	Pa	Sa	Ef	Li	Bc	Ms	Ca	Ct	Sc	An
2a	-	-	-	-	-	20	8	7	15	15	-	-	-	-
2b	-	-	-	-	-	15	8	6	6	10	-	-	-	-
3	-	-	-	-	-	7	-	-	7	-	8	-	-	-
6	30	30	25	15	30	40	6	-	6	10	9	7	-	-
7a	15	15	15	10	10	25	15	10	10	20	-	-	-	-
7b	10	10	12	15	15	15	6	10	15	20	-	-	-	-
7c	15	15	12	12	-	25	15	20	30	20	-	-	-	-
Amp.	10	10	>18	18	>18	35	10	10	15					
Strep.										35				
Flu.											25	25	>25	ND

Ec*: Escherichia coli* ATCC 25922, Ea: *Enterobacter aeruginosa* ATCC 13048, Yp: *Yersinia pseudotuberculosis* ATCC 911, Kp: *Klebsiella pneumoniae* ATCC 13883, Pa: *Pseudomonas aeruginosa* ATCC 43288, Sa: *Staphylococcus aureus* ATCC 25923, Ef: *Enterococcus faecalis* ATCC 29212, Li: *Listeria monocytogenes* ATCC 43251, Bc: *Bacillus cereus* 702 Roma, Ms: *Mycobacterium smegmatis* ATCC607, Ca: *Candida albicans* ATCC 60193, Ct: *Candida tropicalis* ATCC 13803, Sc: *Saccharomyces cerevisiae* RSKK 251, An: *Aspergillus niger* RSKK 4017, Amp.: Ampicillin, Flu.: Fluconazole, (-): No activity.

Results and discussion

The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1 and 2. In the present study, the synthesis of 5-alkyl-4-(2-morpholine-4ylethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-ones (**2a, 2b**) was achieved by cyclocondensation of ester ethoxycarbonylhydrazones (**1a, 1b**) with 2-morpholinoethanamine. In the IR and NMR spectra of compounds **2a** and **2b**, the absence of any signals pointing to ester functionality has supported the ring closure. More evidence for cyclization is the presence of [M^+] or [M+1] ion peak in the EI-MS spectra.

The reaction of **2a** with ethyl bromoacetate in the presence of sodium ethoxide produced ethyl [3-methyl-4-(2-morpholine-4-ylethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazole-1-yl]acetate (**3**). In the ^{1}H- and ^{13}C-NMR spectra of compound **3**, additional signals originating from ester moiety were recorded at the related chemical shift values, while the signal due to ring NH disappeared. The treatment of compound **3** with hydrazine



Scheme 1. Synthetic pathway for the preparation of compounds **2-6**.

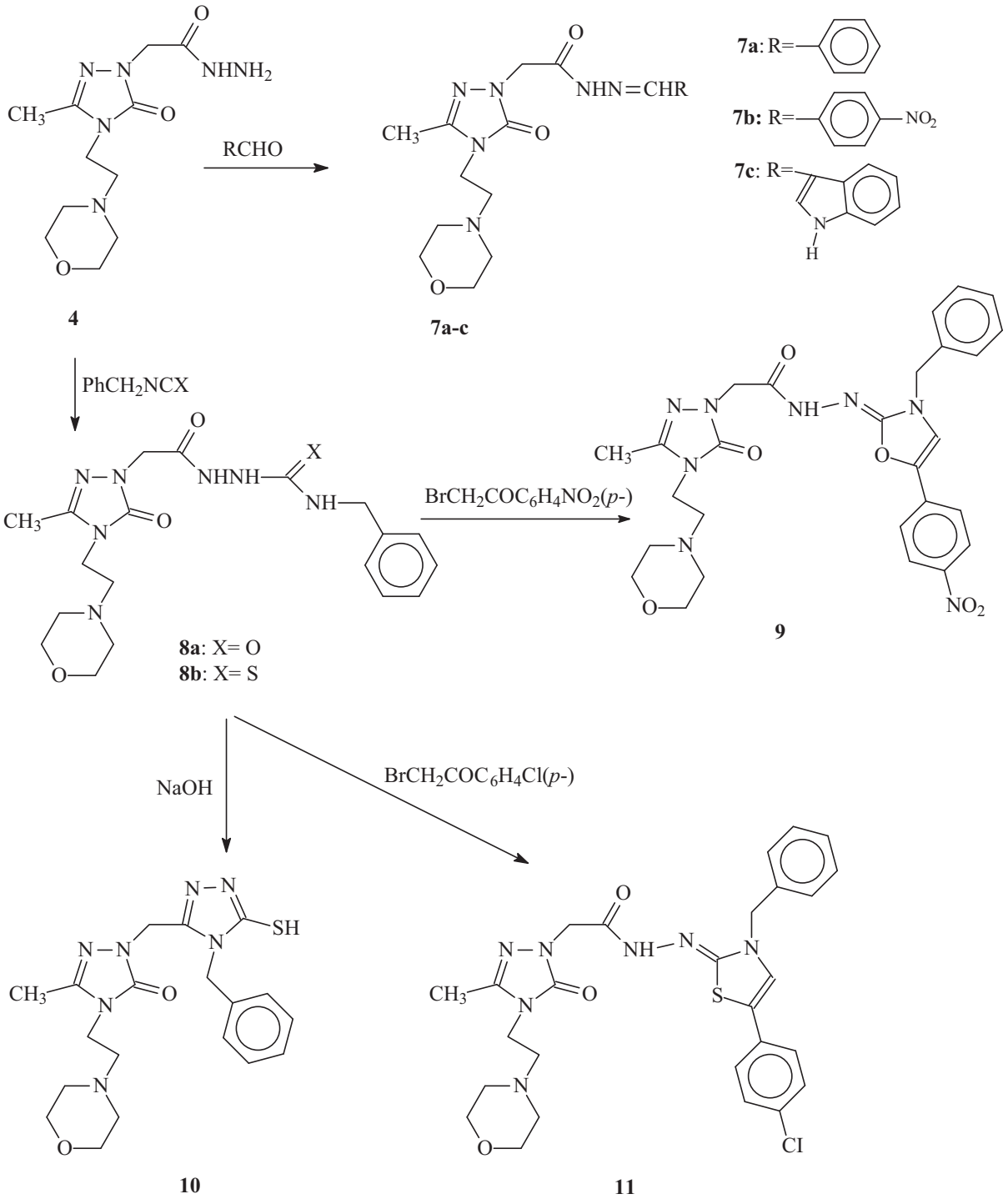
hydrate in ethanolic solution caused the conversion of the ester group to hydrazide function in good yield. The IR and NMR spectra of hydrazide compound **4** displayed signals belonging to a -NHNH$_2$ group. Moreover, compounds **3** and **4** exhibited MS spectral and elemental analysis data consistent with the assigned structures.

The condensation of compounds **2a,b** with several aryl sulfonyl chlorides in ethanol in the presence of metallic sodium generated the corresponding cyclic sulfon amides (**5a-c** and **6**). The structures of these compounds were confirmed on the basis of IR, NMR, and mass spectroscopic methods and elemental analysis.

The synthesis of arylmethyleneacetohydrazides (**7a-c**) was achieved from the reaction of compound **4** with several aromatic aldehydes in ethanolic solution in good yields.

The evidence for the formation of compounds **7a-c** can be obtained by ^{1}H-NMR, ^{13}C-NMR, IR, mass spectroscopic methods and elemental analysis. In the ^{1}H-NMR spectra of compounds **7a-c,** additional signals originating from arylidene moiety were observed in the aromatic region, and an additional signal was recorded at 9.66 ppm derived from –N=CH- bond, whereas the signal due to –NH<u>NH</u>$_2$ amino group disappeared that had been observed at 4.50 ppm in the ^{1}H-NMR spectrum of the parent compound, **4**.

The compounds having arylidene-hydrazide structure may exist as E/Z geometrical isomers about a



Scheme 2. Preparation of compounds 7-11.

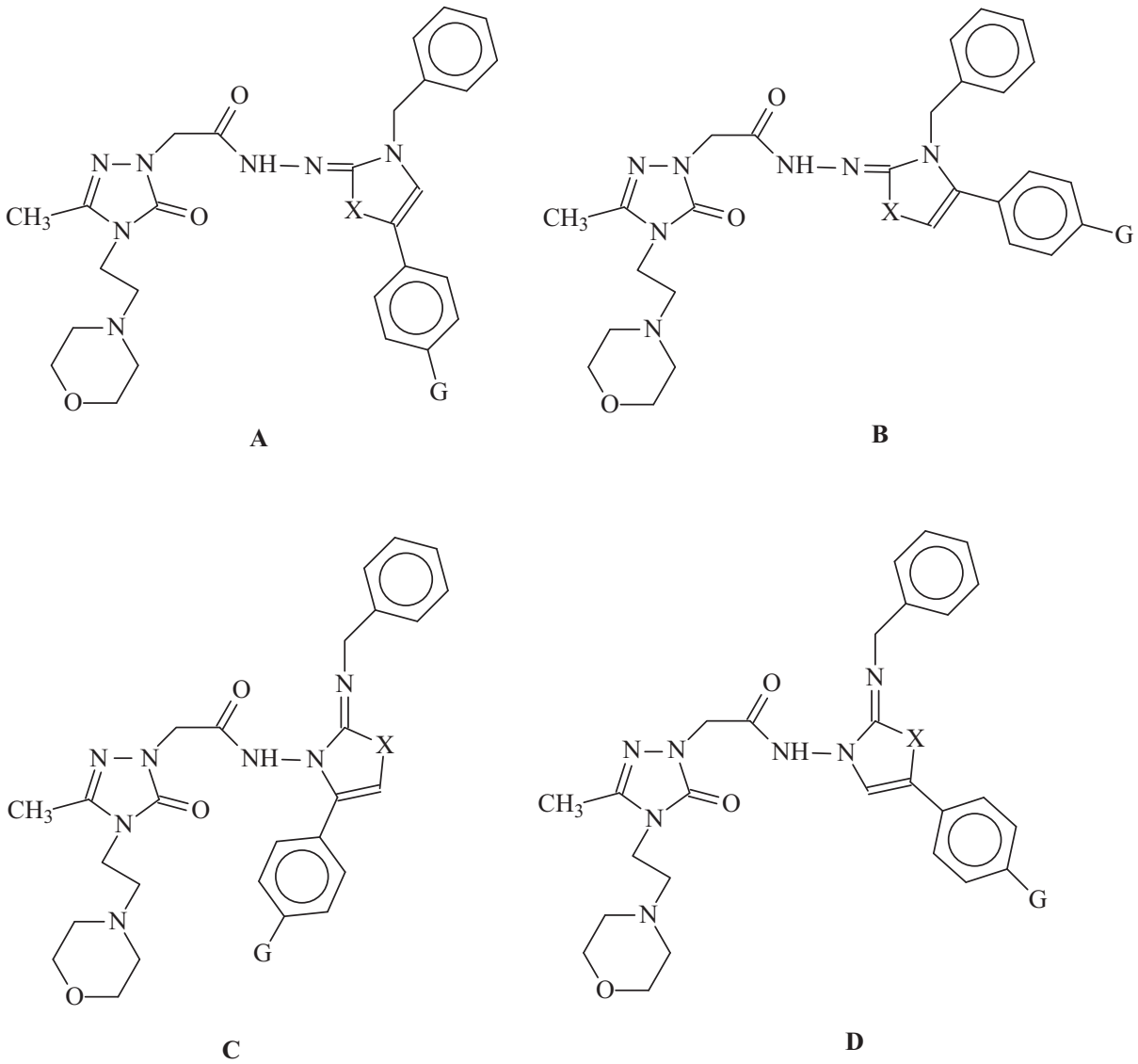
–C=N double bond and *cis*/*trans* amide conformers.[37,56,57] According to the literature, compounds containing an imine bond are present in higher percentages in dimethyl-d_6 sulfoxide solution in the form of geometrical *E* isomer about a –C=N double bond.[37,56,57] The *Z* isomer can be stabilized in less polar solvents by an intramolecular hydrogen bond. In the present study, the spectral data were obtained in dimethyl-d_6 sulfoxide solution and no signal belonging to *Z* isomer was observed. On the other hand, the *cis-trans* conformers of *E* isomer were present in the dimethyl-d_6 sulfoxide solution of compounds **7a** and **7b**. In the ^{1}H-NMR spectra of compounds **7a** and **7c,** 2 sets of signals each belonging to the N=CH group of *cis-* and *trans-* conformers were observed at 7.99 (for **7a**) or 8.20 (for **7c**) ppm and 8.21 (for **7a**) or 8.38 (for **7c**) ppm, respectively. The upfield lines of N=CH protons were assigned to *cis-* conformer of the amide structure and downfield lines of the protons of the same group to *trans-* conformer of the amide structure.

Iso(thio)cyanates are known as useful tools for the synthesis of nitrogen-, sulfur-, or oxygen-containing compounds. In the present study, carboxamide (**8a**) and carbothioamide (**8b**) were obtained by the nucleophilic addition of hydrazide (**4**) to benzyl isocyanate (for **8a**) or benzylisothiocyanate (for **8b**). In the ^{13}C-NMR spectrum of compound **8a**, the signal derived from urea carbonyl resonated at 158.66 ppm, while the C=S function of **8b** appeared at a lower field, 182.48 ppm. Their molecular structures were confirmed by mass spectroscopic method and elemental analysis, as well.

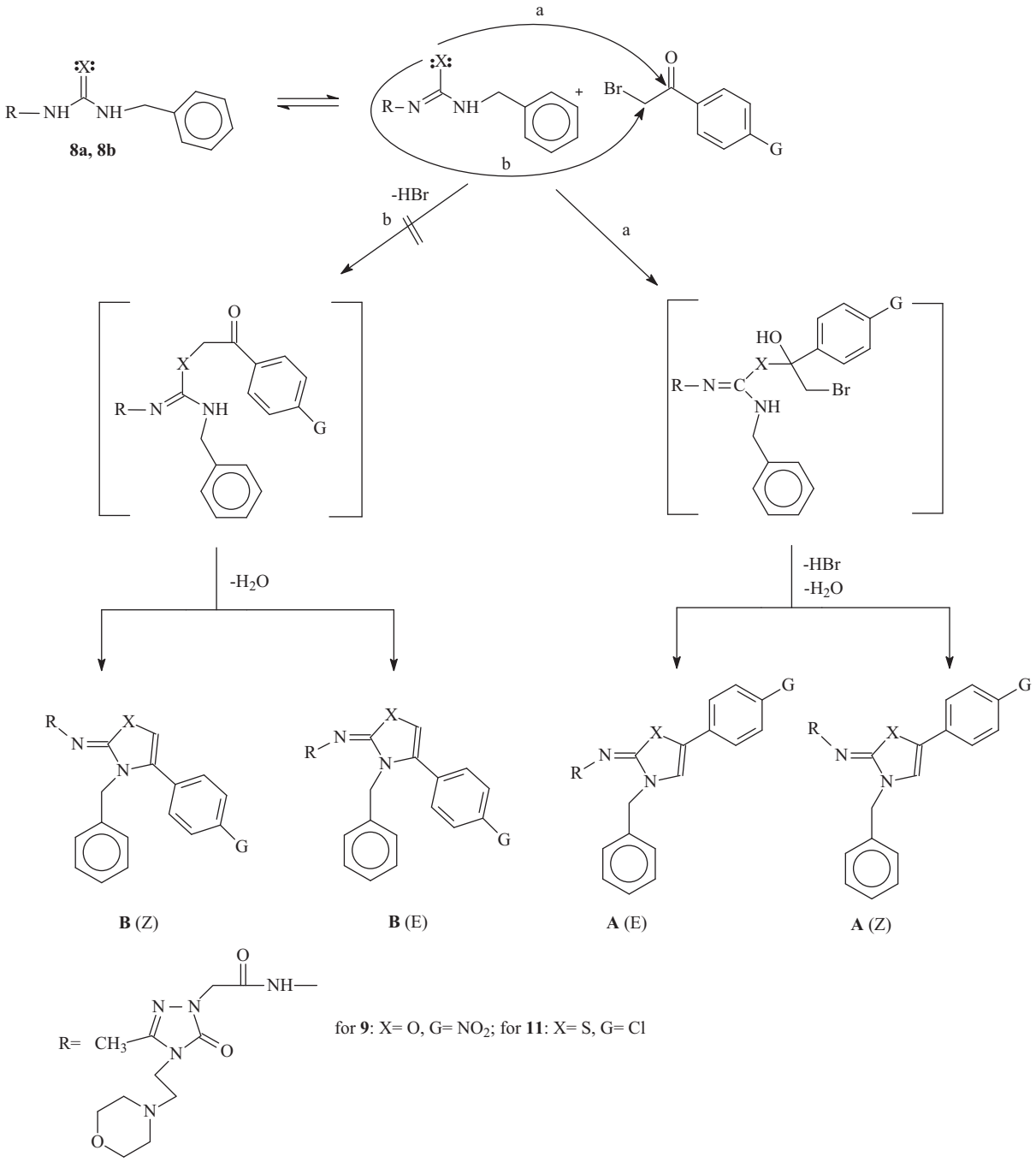
The intramolecular cyclization of compound **8b** in the presence of 2 N NaOH resulted in the formation of 2-[(4-benzyl-5-mercapto-4*H*-1,2,4-triazol-3-yl)methyl]-5-methyl-4-(2-morpholin-4-ylethyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (**10**). On the other hand, the cyclocondenzation of the same intermediate (**8b**) with 4-chlorophenacylbromide yielded *N*'-[3-benzyl-4-(4-chlorophenyl)-1,3-thiazol-2(3*H*)-ylidene]-2-[3-methyl-4-(2-morpholin-4-yl ethyl)-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl]acetohydrazide **(11).** Similarly, the treatment of **8a** with 4-nitrophenacylbromide led to the formation of the corresponding 1,3-oxazole derivative (**9**). In the ^{1}H-NMR spectrum of compound **10** the absence of any signal pointing to a NH proton confirmed the cyclization at the side chain of 1,2,4-triazol-3-one ring in compound **8a.** It has been reported that type of compounds **10** can be present in their thioxo-mercapto tautomeric forms. In the ^{1}H-NMR spectrum of compound **10,** the presence of a singlet peak at 14.00 representing the presence of a –SH proton showed that the dominant form is mercapto form for compound **10.**

So far, several methods have been developed for the preparation of 1,3-thiazole derivatives, the most commonly applied of which is Hantzsch synthesis, involving the reaction of α-halocarbonyl compounds with thioamides.[58,59] It has been agreed that a Hantzsch reaction starts by the attack of the sulfur atom of thioamide that is present in its ene-thiol form on the halogene-containing atom of phenacyl bromide, followed by HBr and H_2O elimination, leading to a 1,3-thiazole ring.[58] In the present study, as compounds **8a** and **8b** possess more than 1 nucleophilic center and also phenacyl bromide has 2 positions for nucleophilic attacks, there are at least 4 different possibilities leading to the formation of 4 different structural isomers (Scheme 3). In our previous studies submitted for publication, to identify the exact structure of the products obtained from the reaction between catbo(thio)amide and phenacyl bromide, full geometric optimizations of the possible products were obtained by DFT/B3LYP (density functional theory with B3LYP-the hybrid Becke's 3 parameter functional and Lee-Yang-Parr exchange-correlation potential)[60,61] method with the 6-31G (d, p) basis set and the structure of the molecules was also investigated in detail. The obtained results (unpublished data) showed that among the possible Hantzsch products (A-D) the most stable one is **A** isomer due to its *Z* geometrical isomer about the

N=C double bond. Taking into account these data, it can be speculated that the strongly probable structure for compounds **9** and **11** is structure **A**. In the present study, contrary to the description in the literature,[60–63] the reaction between carbo(thio)amide (**8a, 8b**) and substituted phenacyl bromide started by the attack of sulfur atom on carbonyl carbon of phenacyl bromide instead of halogen bearing carbon atom of acyl component, because the latter attack leads to the formation of **9** or **11**, which is thermodynamically a less favorable isomer (Scheme 4). The *Z* rearrangement of groups in these reactions is likely due to the steric hindrance of the bulky R group and benzyl moiety in the intermediate **E**. In the reaction media, the presence of dried sodium acetate is necessary to accelerate the reaction by catching H_2O and HBr furnishing during the reaction.



Scheme 3. Possible structural isomers for compounds 9 and 11.



Scheme 4. The mechanism leading to the formation of compounds **9** and **11**.

The IR and ^{1}H-NMR spectra of compounds **9** and **11** showed no signal representing the –SH group. Instead, the signals derived from phenacyl moiety were observed in the aromatic region in the ^{1}H- and ^{13}C-NMR spectra of compound **11**. Due to the slight solubility in any NMR solvent, a satisfactory NMR spectrum could not be obtained for compound **9**. In addition, elemental analyses are consistent with the assigned structures for compounds **9, 10,** and **11**, and the mass spectra of the cyclization products (**9-11**) showed $[M]^+$ or $[M+1]^+$

ion peaks consistent with their molecular formulae.

The antimicrobial activity results are presented in Table 1. The compounds displaying no activity are not incorporated in this table. Among the newly synthesized compounds, compound **6,** a cyclic sulfonamide derivative containing 4-nitrophenyl sulfonyl moiety in position 2 beside a benzyl group at position 5 of the 1,2,4-triazole skeleton, was the most active against most of the test microorganisms, whereas other sulfonamides (**5a-c**) containing a methyl group instead of a benzyl group showed no activity towards the test microorganisms. Compounds **2a** and **2b**, which are unsubstituted 1,2,4-triazole compounds at position 2, exhibited activity against the gram-positive bacteria *Staphylococcus aureus* (Sa), *Enterococcus faecalis* (Ef), *Listeria monocytogenes* (Li), and *Bacillus cereus* (Bc), and one nonpigmented rapidly growing mycobacterium leading to morbidity and mortality, *Mycobacterium smegmatis* (Ms). Arylidenehydrazides (**7a-c**) are the other most potent group synthesized in this study. They displayed good antibacterial activity against gram-positive and gram-negative bacterial strains and *Mycobacterium smegmatis*.

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