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Synthesis of New 3, 5-Disubstituted-1, 2, 4-Triazoles and Evaluation of Antimicrobial Activities

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Abstract
The chemistry of heterocyclic compounds containing five membered 1, 2, 4-triazole nucleus has been an intresting field of study recently. The five membered 1, 2, 4-triazole ring includes two tautomeric forms i.e., 1H-1, 2, 4-triazole, 4H-1, 2, 4-triazole. The triazole derivatives possess extensive spectrum of biological activities such as antibacterial, antifungal, antitubercular, anxiolytic, anticonvulsant, anti-inflammatory, analgesic, anticancer, antioxidant activities. The present review is determined view of pharmacological activity of compounds bearing 1, 2, 4-triazole nucleus. First, a series of acylhydrazones **1(a-d)** were synthesized by the condensation of iminoester hydrochlorides with acyl hydrazines. The treatment of acylhydrazones with hydrazine hydrate afforded 4-amino-(3, 5-diaryl-4-yl)-4H-1,2, 4-triazoles **2(a-d).** A series of new (3, 5-diaryl-4-yl)-4-(arylmethylenamino)-4H-1, 2, 4-triazole derivatives **3(a-d)** were prepared in good yields by treatment of 4-amino-(3, 5-diaryl-4-yl)-4H-1, 2, 4-triazoles **2(a-d)** with selected aldehydes. Sodium borohydride reduction of 4-arylidenamino derivatives afforded 4-alkylamino-3, 5-dialkyl-1, 2, 4- triazoles **4(a-d).** The present review, eight new compounds have been synthesized and characterized by elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectral data. A series of compounds have been evaluated for their antimicrobial activities. The results show that the synthesized new compounds had effective antimicrobial activities.
Keywords: Acyl hydrazone, 1, 2, 4-triazole, Schiff base, reduction, antimicrobial activity, antifungal activity.

Yeni 3, 5- Disubstitue-1, 2, 4-Triazoller'in Sentezi ve Antimikrobiyal Aktivitelerinin Değerlendirilmesi

Özet
Beş üyeli 1, 2, 4 triazol halkası içeren heterosiklik bileşiklerin çalışma alanı son yıllarda giderek dikkat çekmektedir. Bu triazol halkası 1H-1, 2, 4-triazol ve 4H-1, 2, 4-triazol olmak üzere iki tautomerik formu içerir. Triazol türevleri, antibakteriyel, antifungal, antitüberküloz, anksiyolitik, antikonvulsan, anti-inflamatuar, analjezik, antikanser, antioksidan gibi geniş spektrumlu biyolojik aktivitelere sahiptirler. Bu çalışmada 1, 2, 4-triazol halkası taşıyan bileşiklerin farmakolojik aktivite gösterdiği belirlenmiştir. Öncelikle, iminoester hidroklorürlerin açil hidrazinlerle reaksiyonundan açil hidrazon **1(a-d)**' lar sentezlenmiştir. Daha sonra açil hidrazonların hidrazin hidrat ile muamelesinden 4-amino-(3,5-diaril-4-il)-4H-1, 2, 4-triazol **2(a-d)** bileşikleri elde edilmiştir. Yeni (3,5-diaril-4-il)-4-(arilmetilenamino)-4H-1, 2, 4-triazol **3(a-d)**'ler, 4-amino-(3,5-diaril-4-il)-4H-1, 2, 4-triazoller **2(a-d)**'in bazı aldehitlerle reaksiyonlarından yüksek verimlerle elde edilmiştir. 4-arilidenamino türevlerinin sodyumborhidrür ile indirgenmesinden ise 4-alkillamino-3,5-dialkil-1, 2, 4- triazol **4(a-d)** bileşikleri sentezlenmiştir. Bu çalışmada 8 yeni bileşik sentezlendi ve yapıları elemental analiz, IR, ^{1}H NMR, ^{13}C NMR spektral verilerle aydınlatıldı. Bileşik serilerinin antimikrobiyal aktiviteleri değerlendirildi. Sonuçlar sentezlenen yeni bileşiklerin etkili antimikrobiyal aktiviteye sahip olduğunu göstermektedir.
Anahtar kelimler: Açil hidrazon, 1, 2, 4-triazol, Schiff bazı, İndirgenme, Antimikrobiyal aktivite, Antifungal aktivite.

Introduction

Resistance to antimicrobial agents has become an increasingly important and pressing global problem. Lots of people who acquire bacterial infections in hospitals each year, 70% of cases now involve strains that are resistant to at least one drug (Adcock, 2002). Structural modification of antimicrobial drugs to which resistance has developed has proven to be an effective means of extending the lifespan of antifungal agents such as the azoles (Jeu *et al*., 2003), antiviral agents such as the non-nucleoside reverse transcriptase inhibitors (De Clercg, 2001), and various antibacterial agents including β-lactams and quinolones (Poole, 2001).

The synthesis of 1, 2, 4-triazole derivatives has attracted widespread attention due to their diverse biological activities, including antimicrobial, anti_inflammatory, analgesic, and antitumoral (Awad and El Ashry, 1998; Palaska *et al*., 2002; Holla *et al*., 2002; Amir and Shikha, 2004). Schiff bases and their complexes have some different chemical properties such as reversible oxygen bindings (Park *et al*., 1998; Lu *et al*., 2003), catalytic activities on olefins that getting hydrogenic (Olive and Olive, 1984), electrochemical electron transfer (Rahaman *et al*., 2005), photocromic features (Kunkely and Vogler, 2001), and to form a complex with some toxic metals (Mederos *et al*., 1999; Gumrukcuoglu *et al*., 2013).

In our studies we have reported that 1,2 4-triazole ligands showed antiurease, antioxidant activities, ion extraction selectivity, fluorescent chemosensor and complex stability constant (Ocak *et al*., 2008; Caglar *et al*., 2012; Gumrukcuoglu *et al*., 2012; Sokmen Bilgin *et al*., 2015). These biological data prompted us to synthesize new 1, 2, 4-triazole derivatives. The synthesized compounds were evaluated for antimicrobial activity.

Material and Methods

General information for chemicals

Melting points were determined on a Barnstead Electrothermal melting point apparatus and were uncorrected. The IR spectra (υ, cm^{-1}) was obtained with a Perkin-Elmer 1600 FTIR spectrometer in KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra (δ, ppm) were recorded on a Varian-Mercury 200 MHz spectrophotometer using

tetramethylsilane as the 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 analysis results within ± 0. 4 % of the theoretical values. The necessary chemicals were purchased from Merck and Fluka. Compounds **1(a-d)** were synthesized using literature procedure (Milcent and Redeuilh, 1977). Ethyl benzimidate hydrochlorides **1(a-d)** and amino compounds **2(a-d)** were synthesized using a published method (Un and Ikizler, 1975; Gumrukcuoglu et al., 2016).

Synthesis of compounds 3(a-d).

The corresponding aldehyde (0.01 mol) was added to a solution of compounds **2(a-d)** (0.005 mol) in glacial acetic acid (20 mL) and the mixture was refluxed for 4 h. After cooling, the mixture was poured into a beaker containing ice-water (100 mL). The precipitate formed was filtered. After drying in vacuo, the product was recrystallized from an appropriate solvent to give the desired compound.

3-(4-Chlorophenyl)-5-(methyl-4-yl)-4-(2,4,6-trimethoxy-benzylidenamino)-4H-1,2,4-triazole (3a)*:* Yield 78%, m. p. 165-166 ◦C. IR (KBr): 1610-1569 (C=N), 816, 833 (arom. ring) cm^{-1}. ^{1}H-NMR (DMSO-d6) δ (ppm): 2.39 (s, 3H, CH_3), 3.85 (s, 6H, 2O-CH_3), 3.86 (s, 3H, O-CH_3), Ar-H [6.33 (s, 2H), 7.55 (d, 2H), 8.04 (d, 2H)], 8.69 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d6) δ (ppm): 163.29 (N=CH), 148.91 (triazole C_3), 148. 21 (triazole C_5), Ar-C: [165.88 (C), 162.24 (2C), 134.79 (C), 129.80 (2CH), 129.34 (2CH), 126.80 (C), 102. 42 (C), 91.93 (2CH)], 57.06 (2 O-CH_3), 56.49 (O-CH_3), 11.61 (CH_3); Anal. for $C_{19}H_{19}N_4O_3Cl$ (386.83): calcd. C 58.99, H 4.95, N 14.48; found C 58.97, H 4.98, N 14.54.

3-(phenyl)-5-(furan-4-yl)-4-(2,4,6-trimethoxy-benzylidenamino)-4H-1,2,4-triazole 3b): Yield 75%, m. p. 236– 237 ◦C. IR (KBr): 1602, 1560 (C=N), 766-693, 818 (arom. ring) cm^{-1}. ^{1}H-NMR (DMSO-d6) δ (ppm): 3.78 (s, 6H, 2O-CH_3), 3.89 (s, 3H, O-CH_3), Ar-H [6.30 (s, 2H), 7.38 (d, 2H), 7.40-7.60 (m, 3H), 7.80-8.00 (m, 3H)], 8.45 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d6) δ (ppm): 163.87 (N=CH), 150.00 (triazole C_3), 149.37 (triazole C_5), Ar-C: [165.14 (C), 161.42 (2C), 139.14 (C), 129.42 (CH), 129.18 (2CH), 128.61 (2CH), 128.06 (2CH), 127.00 (C), 101.98 (C), 90.95 (2CH)], 56.02 (2 O-CH_3),

55.66 (O-CH_3); Anal. for $C_{22}H_{20}N_4O_4$ (404.43): calcd. C 65.34, H 4.98, N 13.85; found C 65.37, H 4.96, N 13.92.

***3-(phenyl)-5-(p-tolyl-4-yl)-4-(4-N,N-dimethylamino-benzylidenamino)-4H-1,2,4-triazole (3c)*:** Yield 63%, m. p. 248-249 ◦C; IR (KBr): 1613- 1589 (C=N), 826, 767-696 (arom. ring) cm^{-1}. ^{1}H-NMR (DMSO-d6) δ (ppm): 1.77 (s, 3H, CH_3), 2.45 (s, 6H, 2 N-CH_3), Ar-H [7.02 (d, 1H), 7.19-7.26 (m, 1H), 7.33 - 7.41 (m, 3H), 7.52-7.55 (m, 2H), 7.84 (d, 4H), 7.93-7.96 (m, 2H)], 8.60 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d6) δ (ppm): 161.72 (N=CH), 149.94 (triazole C_3), 149.73 (triazole C_5), Ar-C: [139.51(C), 139.16 (C), 129.93 (CH), 129.72 (C), 129.41 (CH), 128.97 (CH), 128.82 (CH), 128.38 (CH), 128.23 (CH), 128.14 (CH), 127.13 (CH), 127.08 (CH), 126.58 (C), 125.26 (CH), 124.35 (C), 123.69 (CH), 115.66 (2CH)], 20.89 (N-CH_3), 20.81(N-CH_3), 15.95 (CH_3); Anal. for $C_{24}H_{23}N_5$ (381.47): calcd. C 75.57, H 6.08, N 18.36; found C 75.59, H 6.13, N 18.24.

3-(phenyl)-5-(p-methoxyphenyl-4-yl)-4-(2,6-diflouro-benzylidenamino)-4H-1,2,4-triazole (3d): Yield 73%, m. p. 126-127 ◦C. IR (KBr): 1618-1580 (C=N), 816, 778-756, 771-694 (arom. ring) cm^{-1}. ^{1}H-NMR (DMSO-d6) δ (ppm): 3.69 (s, 3H, O-CH_3), Ar-H [6.83 (d, 2H), 7.16-7.28 (m, 4H), 7.40-7.60 (m, 3H), 7.78-8.00 (m, 3H)], 8.70 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d6) δ (ppm): 159.62 (N=CH), 151.01 (triazole C_3), 150.23 (triazole C_5), Ar-C: [159.13 (C), 158.79 (C), 156.47 (C), 136.16 (CH), 130.38 (2CH), 129.46 (2CH), 128.80 (2CH), 128.26 (2C), 127.29 (C), 114.66 (2CH), 113.65 (CH), 113.27 (CH), 111.91 (CH)], 55.71 (O-CH_3); Anal. for $C_{22}H_{16}N_4OF_2$ (390.40): calcd. C 67.68, H 4.13, N 14.35; found C 67.65, H 4.06, N 14.49.

Synthesis of compounds 4(a-d).

The corresponding compounds **3(a-d)** (0.005 mol) was dissolved in dried methanol (50 mL) and $NaBH_4$ (0.01 mol) was added in small portions to this solution. The mixture was refluxed for 20 min and then allowed to cool. After evaporation at 30-35 °C under reduced pressure, the solid residue was washed with cold water. After drying *in vacuo*, the solid product was recrystallized from an appropriate solvent (1:1 ethanol-water, unless otherwise noted) to afford the desired compounds **4(a-d)**.

3-(4-Chlorophenyl)-5-(methyl-4-yl)-4-(2,4,6-trimethoxy-benzylamino)-4H-1,2,4-triazole (4a): Yield 88%, m. p. 129-130 ◦C. IR (KBr): 3324 (NH), 1560 –1603 (C=N), 823, 800 (arom. ring) cm^{-1}. ^{1}H-NMR (DMSO-d6) δ (ppm): 2.33 (s, 3H, CH_3), 3.61 (s, 6H, 2O-CH_3), 3.72 (s, 3H, O-CH_3), 3.90 (d, 2H, CH_2), Ar-H [6.04 (s, 2H), 7.46 (d, 2H), 7.99 (d, 2H)], 6.55 (t, 1H, NH); ^{13}C-NMR (DMSO-d6) δ (ppm): 153.48 (triazole C_3), 151.21 (triazole C_5), Ar-C: [161.81 (C), 159.97 (2C), 134.41 (C), 129.53 (2CH), 128.84 (2CH), 127.08 (C), 104.33 (C), 90.97 (2CH)], 56.18 (2O-CH_3), 55.91 (O-CH_3), 43.04 (CH_2), 10.18 (CH_3); Anal. for $C_{19}H_{21}N_4O_3Cl$ (388.85): calcd. C 58.69, H 5.44, N 14.41; found C 58.65, H 5.41, N 14.54.

3-(phenyl)-5-(furan-4-yl)-4-(2,4,6-trimethoxy-benzylamino)-4H-1,2,4-triazole (4b): Yield 82 %, m. p. 215 – 216 ◦C. IR (KBr): 3316 (NH), 1589 –1617 (C=N), 815, 765-693, (arom. ring) cm^{-1}. ^{1}H-NMR (DMSO-d6) δ (ppm): 3.29 (s, 6H, 2O-CH_3), 3.68 (s, 3H, O-CH_3), 3.85 (d, 2H, CH_2), Ar-H [5.94 (s, 2H), 6.70 (t, 1H), 7.28 (d, 1H), 7.44 (t, 3H), 7.88-7.92 (m, 3H)], 6.70 (t, 1H, NH); ^{13}C-NMR (DMSO-d6) δ (ppm): 153.67 (triazole C_3), 147.63 (triazole C_5), Ar-C: [161.66 (C), 159.83 (2C), 142.13 (C), 130.04 (CH), 128.94 (2CH), 128.82 (2CH), 128.52 (CH), 127.49 (C), 112.32 (CH), 111.80 (CH), 104.02 (C), 90.85 (2CH)], 55.93 (2O-CH_3), 55.86 (O-CH_3), 43.02 (CH_2); Anal. for $C_{22}H_{22}N_4O_4$ (406.44): calcd. C 65.01, H 5.45, N 13.79; found C 65.07, H 5.42, N 13.84.

3-(phenyl)-5-(p-tolyl-4-yl)-4-(4-N,N-dimethylamino-benzylamino)-4H-1,2,4-triazole (4c): Yield 85 %, m. p. 230 – 231 ◦C; IR (KBr): 3298 (NH), 1614- 1589 (C=N), 825, 767- 697 (arom. ring) cm^{-1}. ^{1}H-NMR (DMSO-d6) δ (ppm): 1.77 (s, 3H, CH_3), 2.45 (s, 6H, 2 N-CH_3), 3.80 (d, 2H, CH_2), Ar-H [7.02 (d, 1H), 7.19-7.26 (m, 1H), 7.33 - 7.41 (m, 3H), 7.52-7.55 (m, 2H), 7.84 (d, 4H), 7.93-7.96 (m, 2H)], 7.65 (t, 1H, NH); ^{13}C-NMR (DMSO-d6) δ (ppm): 149.88 (triazole C_3), 149.67 (triazole C_5), Ar-C: [139.48 (C), 129.89 (C), 129.69 (CH), 129.38 (C), 128.94 (CH), 128.81 (CH), 128.36 (CH), 128.18 (CH), 128.09 (CH), 127.08 (CH), 127.03 (CH), 126.54 (CH), 125.21 (C), 123.66 (CH), 115.60 (2CH)], 54.12 (CH_2), 20.89 (N-CH_3), 20.80 (N-CH_3), 15.94 (CH_3). Anal. for $C_{24}H_{25}N_5$ (383.49): calcd. C 75.17, H 6.57, N 18.26; found C 75.21, H 6.59, N 18.19.

3-(phenyl)-5-(p-methoxyphenyl-4-yl)-4-(2,6-diflouro-benzylamino)-4H-1,2,4-triazole (4d): Yield 84%, m. p. 148-149 ◦C. IR (KBr): 3290 (NH), 1608-1579 (C=N), 816,

812-781, 793-698 (arom. ring) cm^{-1}. ^{1}H-NMR (DMSO-d6) δ (ppm): 3.69 (s, 3H, O-CH_3), 4.22 (d, 2H, CH_2), Ar-H [6.90 (d, 2H), 7.29 (d, 2H), 7.46-7.58 (m, 3H), 7.72 (d, 2H), 7.80-7.96 (m, 3H)], 7.38 (t, 1H, NH); ^{13}C-NMR (DMSO-d6) δ (ppm): 152.18 (triazole C_3), 151.46 (triazole C_5), Ar-C: [147.97 (C), 146.09 (C), 138.93 (C), 129.93 (CH), 129.86 (2CH), 129.36 (2CH), 128.58 (2CH), 127.85 (2CH), 127.16 (C), 125.74 (C), 124.25 (C), 120.95 (CH), 114.50 (CH) 112.18 (CH)], 55.00 (O-CH_3), 53.80 (CH_2). Anal. for $C_{22}H_{18}N_4OF_2$ (392.41): calcd. C 67.34, H 4.62, N 14.28; found C 67.25, H 4.56, N 14.49.

Microbiology

Antibacterial activity

All test microorganisms were obtained from the Refik Saydam Hıfzıssıhha Institute (Ankara, Turkey), which included Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 10145, Yersinia pseudotuberculosis ATCC 911, Klepsiella pneumonia ATCC 13883, Enterococcus faecalis ATCC 29212, Staphylococcus aureus ATCC 25923, Bacillus cereus 709 ROMA, Candida albicans ATCC 60193, and Candida tropicalis ATCC 13803. The chemicals were weighed and dissolved in dimethylsulfoxide (DMSO) to prepare extract stock solutions of 10 mg/mL.

Agar well diffusion method

A simple susceptibility screening test using agar-well diffusion as adapted earlier (Ahmad *et al*., 1998) was used. Each microorganism was suspended in Mueller Hinton (Difco, Detroit, MI, USA) broth and diluted to ca. 10^6 colony forming units (cfu) per mL. They were flood-inoculated onto the surface of Mueller Hinton agar and Sabouraud dextrose agar (SDA) (Difco), which were then dried. For *C. albicans* and *C. tropicalis*, SDA was used. From the agar, 5-mm diameter wells were cut using a sterile cork-borer and 500 μg/50 μL (10 mg/mL) 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. Ampicillin (10 μg/50 μL) served as the control antibiotic. Triflucan (5 μg/50 μL) served as the control fungicide. DMSO served as the solvent control. The results are shown in the Table 1.

Results and Discussion

In this study, a convenient method has been established for the synthesis in good yields of new triazole schiff bases **3(a-d)** and corresponding amino triazole compounds **4(a-d)**. Eight new 4H-1, 2, 4-triazole derivatives synthesized in the study exhibit some biological activities and these results are reported.

Compounds **1(a-d)** were synthesized from the reaction of corresponding iminoester hydrochlorides with acyl hydrazines and compounds **2(a-d)** were obtained by treatment of compounds **1(a-d)** with hydrazine hydrate, which were obtained by a literature method (Un and Ikizler, 1975; Gumrukcuoglu *et al*., 2016).

The reaction was carried out in 1-propanol at refluxing temperature for 24 h and the desired 4-amino-3,5-dialkyl-1, 2, 4-triazoles **2(a-d)** were yielded. 4-Amino-1, 2, 4-triazoles **2(a-d)** were converted to their Schiff bases **3(a-d)** by refluxing with 2, 4, 6-trimethoxy benzaldehyde, 4-N,N-dimethylaminobenzaldehyde and 2, 6-diflourobenzaldehyde in acetic acid. Previously, we obtained the Schiff bases of 1, 2, 4-triazole derivatives. The synthesis of compounds **4(a-d)** were performed by the reduction of only the exocyclic azomethine bond of the Schiff bases **3(a-d)** (Scheme 1). These reduction reactions were conducted in considerably milder conditions. The structures of these compounds were confirmed on the basis of FT-IR, ^{1}H-NMR, ^{13}C-NMR spectroscopic methods, and elemental analysis.

In the IR spectra of compounds **3(a-d)** the characteristic absorption bands appeared at around 1620-1560 cm^{-1} attributed to the C=N groups. In the ^{1}H- NMR spectra of **3(a-d)**, the signal derived from NH_2 group disappeared; instead, new signals originated from aldehyde moiety were recorded at the related chemical shift values in the ^{1}H-NMR and ^{13}C-NMR spectra. Moreover, these compounds exhibited elemental analysis data consistent with the proposed structures. The ^{1}H-NMR signals for the -N=CH group were observed between δ 8.60-8.70 ppm. The ^{13}C-NMR signals for the –N=CH- group were recorded at δ 160-163 ppm. Reduced compounds **4(a-d)** showed IR absorption bands around 3324-3290 cm^{-1} (υNH). The ^{1}H-NMR signals for the -NH-CH_2- group of these compounds were observed as a doublet at around δ 3.85-4.22 ppm and the proton signals of –NH-CH_2- groups were recorded as a triplet or strong singlet between δ 6.55-7.65 ppm. In the ^{13}C-NMR the triazole C_3 and C_5 of the schiff base derivatives **3 (a-d)** were observed between δ 151.01-148.21 ppm and the triazole C_3 and

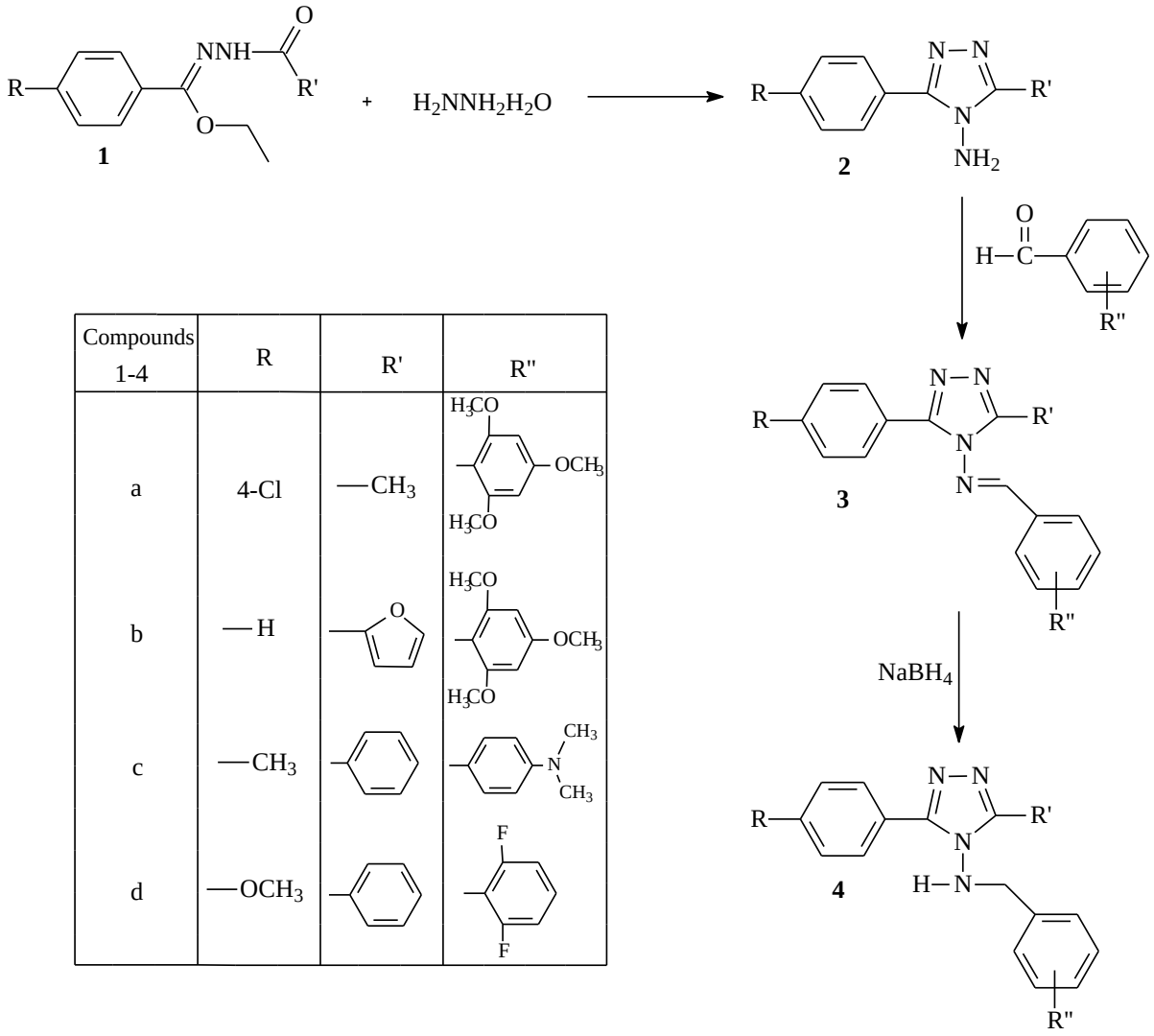
C_5 signals of the reduced compounds **4(a-d)** were observed between δ 153.67-147.63 ppm. The NH-CH_2- carbon signals of compounds **4(a-d)** were recorded between δ 43-54. Chemical shift values consistent with the literature (Gumrukcuoglu *et al.* 2016). In addition, these compounds gave reasonable elemental analysis data.

The best activity was observed against *C. albicans* ATCC 60193 by compound **3d**. Compound **3a** was effective on both *P. aeruginosa* ATCC 10145 and *S. aureus* ATCC 25923. Compounds **3c**, and **4c** showed good antifungal activity only against yeast-like fungi, while compounds **4a**, **4d** showed antimicrobial activity against bacteria and yeast-like fungi. Compounds **3b**, and **4b** were only effective on the gram-positive bacteria, *S. aureus* ATCC 25923.

Table 1. Antimicrobial activities of the synthesized compounds in DMSO (dimethylsulfoxide) solvent (10 mg/mL).

Compound no	Microorganisms and inhibition zone (mm)								
	E	Pa	Yp	Kp	Ef	Sa	Bc	Ca	Ct
3a	5	**10**	5	5	5	**10**	5	5	5
3b	5	5	5	5	5	**11**	5	5	5
3c	5	5	5	5	5	5	5	5	**9**
3d	5	5	5	5	5	**8**	5	**20**	**18**
4a	5	**25**	5	**10**	5	5	5	**15**	**9**
4b	5	5	5	5	5	**10**	5	5	5
4c	5	5	5	5	5	5	5	5	**10**
4d	5	**10**	5	5	5	5	5	5	**10**
DMSO	5	5	5	5	5	5	5	5	**5**
Ampicillin	8	5	5	5	11	15	14	5	5
Triflucan								**25**	**25**

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 pneumonia* 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.



Compounds 1-4	R	R'	R"
a	4-Cl	—CH_3	H_3CO, OCH_3, H_3CO
b	—H	O	H_3CO, OCH_3, H_3CO
c	—CH_3		CH_3, N, CH_3
d	—OCH_3		F, F

Scheme 1. Synthetic pathway for preparation of compounds 1-4.

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