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Research Article

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW IMIDAZO [2, 1-*B*] THIAZOLE DERIVATIVES

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ABSTRACT

A series of arylidenehydrazides (3a–3i) were synthesized from [6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetic acid hydrazide. The structures of new compounds were determined by analytical and spectral (IR, ^{1}H NMR, ^{13}C NMR, EIMS) methods. The synthesized compounds (3a–3i) were evaluated the antimicrobial activities. Their antimicrobial activities against *Escherichia coli* (NRRL B-3704), *Staphylococcus aureus* (NRLL B-767), *Salmonella typhimurium* (NRRL B-4420), *Bacillus cereus* (NRRL B-3711), *Streptococcus faecalis* (NRRL B-14617), *Aeromonas hydrophila*, *Candida albicans* and *Candida glabrata* were investigated. A significant level of activity was observed.

Keywords: Imidazo [2, 1-*b*] thiazole; Arylidenehydrazide; antimicrobial; antifungal;

INTRODUCTION

Recently much interest has been focused on the chemistry and the biological activity of imidazo[2,1-*b*]thiazoles and their derivatives. The imidazo[2,1-*b*]thiazole derivatives have been reported in the literature as antibacterial[1], antifungal[2], antihelmintic[3,4] and antitumour[5-9,] agents. The imidazo[2,1-*b*]thiazole system constitutes the main part of the well-known antihelmintic and immunomodulatory agent levamisole, which is 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole. Andreani et al.[10] studied a series of imidazo[2,1-*b*]thiazole guanyl hydrazones which were active against various cancer cell lines. In view of these observations, we planned the synthesis of novel [6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetic acid arylidenehydrazides to evaluate their primary cytotoxicity.

In this paper we described new arylidenehydrazides bearing imidazo[2,1-*b*]thiazole moiety. The antitumour activity of all new compounds was evaluated on three human tumour cell lines according to the protocols available in the National Cancer Institute (NCI, Bethesda, MD), and the active compounds were tested on the 60 tumour cell lines as well.

EXPERIMENTAL

Chemistry

The synthetic route of the compounds is outlined in Scheme 1. Ethyl 6-(4-bromophenyl)imidazo[2,1-*b*]thiazole-3-acetate (1)[11] was refluxed with hydrazine hydrate to obtain [6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetic acid hydrazide (2)[12-16]. Condensation of 2 with appropriate aromatic aldehydes yielded the corresponding hydrazide hydrazones (3a–3i). The structures of the synthesized compounds were confirmed by analytical (Table 1) and spectral data (IR, ^{1}H NMR, ^{13}C NMR,EIMS). Melting points were determined with a Büchi B-540 melting point apparatus (Flawil, Switzerland) in open capillaries and are uncorrected. Elemental analyses were performed on a LECO CHNS 932 elemental analyser (St. Joseph, Michigan). IR spectra were recorded on KBr discs, using a Perkin–Elmer Model 1600 FT-IR spectrophotometer (Norwalk, Connecticut, USA). ^{1}H NMR spectra were obtained on Bruker DPX 400 (400 MHz) spectrophotometer (Rheinstetten, Germany) using DMSO-d_6. EIMS were determined on a VG Zabspec MS (70 eV) mass spectrometer (Manchester, England).

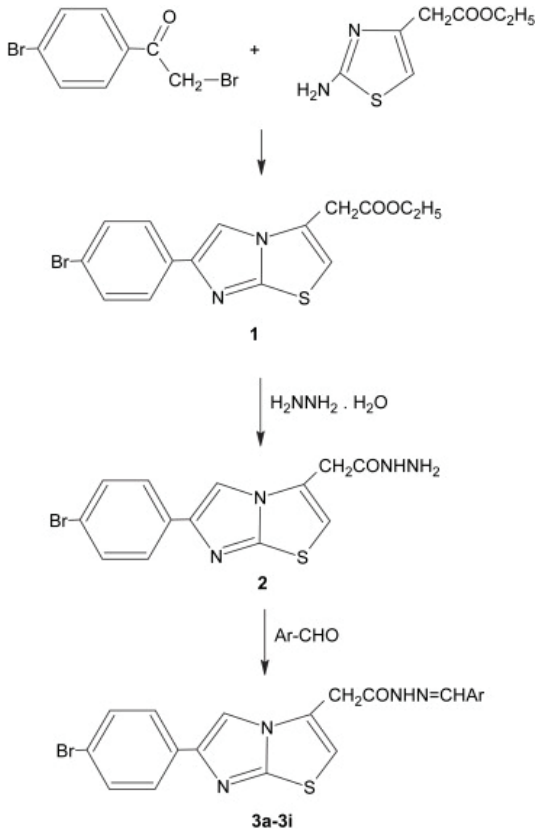
General procedure for the synthesis of [6-(4-bromophenyl)imidazo[2,1-*b*]thiazol-3-yl]acetic acid arylidenehydrazides (3a–3i)

Compound 2, 0.005 mol was refluxed with 0.005 mol of the appropriate aromatic aldehyde in 30 ml ethanol for 5 h. The precipitate obtained was purified by washing with hot ethanol.

Compound 3a

IR (ν cm^{-1}, KBr): 3198, 3149 (N–H), 1683 (C-O), 1598 (hydrazone C-N). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 3.76, 4.18 (2s, 2H, CH_2CO), 6.95 (s, 1H, C_2-H), 7.27–7.30 (m, 3H, ar $C_{3,4,5}$-H), 7.40, 7.42 (2d, 2H, J = 8.49, 8.56 Hz, Br–Ph $C_{3,5}$-H), 7.56–7.65 (m, 4H, Br–Ph $C_{2,6}$-H, ar $C_{2,6}$-H), 7.91, 8.08 (2s, 1H, NCH), 8.13, 8.16 (2s, 1H, C_5-H), 11.51, 11.62 (2s, 1H, CONH). EIMS (70 eV) m/z (%): 337 (1.7), 336 (1.9), 335 (2.3), 334 (2.4), 294 (1.4), 292 (3.8), 211 (31.3), 182 (3.4), 180 (2.9), 169 (1.1), 167 (1.7), 125 (1.7), 120 (2.6), 119 (44.4), 114

(8.6), 111 (24.7), 110 (60.4), 104 (16.3), 103 (57.6), 102 (1.4), 100 (4.0), 99 (3.2), 91 (18.2), 90 (15.2), 89 (50.7), 85 (4.2), 84 (3.0), 77 (100), 73 (11.6), 72 (5.6), 65 (54.2), 59 (4.9), 58 (3.0), 51 (35.4), 43 (34.9), 42 (29.3).



Scheme 1. The general synthesis reactions

Compound 3b

IR (ν cm^{-1}, KBr): 3139 (N–H), 1685 (CO), 1618 (hydrazone CN). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 3.93, 4.31 (2s, 2H, CH_2CO), 6.84, 6.88 (2d, 1H, J = 7.38, 7.58 Hz, ar C_5-H), 6.91 (d, 1H, J = 8.00 Hz, ar C_3-H), 7.08, 7.11 (2s, 1H, C_2-H), 7.23–7.30 (m, 1H, ar C_4-H), 7.53–7.59 (m, 2H, Br–Ph $C_{3,5}$-H), 7.72–7.81 (m, 3H, Br–Ph $C_{2,6}$-H, ar C_6-H), 8.28, 8.29 (2s, 1H, C_5-H), 8.36, 8.45 (2s, 1H, NCH), 10.05, 10.97 (2s, 1H, ar C_2-OH), 11.56, 11.92 (2s, 1H, CONH).

Compound 3c

IR (ν cm^{-1}, KBr): 3102 (N–H), 1663 (CO), 1616 (hydrazone CN). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 3.72, 4.13 (2s, 2H, CH_2CO), 6.66 (d, 2H, J = 8.64 Hz, ar $C_{3,5}$-H), 6.93 (s, 1H, C_2-H) 7.36–7.43 (m, 4H, Br–Ph $C_{3,5}$-H, ar $C_{2,6}$-H), 7.59–7.64 (m, 2H, Br–Ph $C_{2,6}$-H), 7.80, 7.96 (2s, 1H, NCH), 8.12, 8.14 (2s, 1H, C_5-H), 9.76, 9.78 (2s, 1H, ar C_4-OH), 11.30, 11.40 (2s, 1H, CONH).

Compound 3d

IR (ν cm^{-1}, KBr): 3208, 3136 (N–H), 1660 (CO), 1605 (hydrazone CN). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 3.64 (s, 3H, ar C_4-OCH_3), 3.73, 4.15 (2s, 2H, CH_2CO), 6.83 (d, 2H, J = 8.75 Hz, ar $C_{3,5}$-H), 6.94 (s, 1H, C_2-H), 7.40, 7.42 (2d, 2H, J = 8.58, 8.57 Hz, ar $C_{2,6}$-H), 7.49, 7.51 (2d, 2H, J = 8.91, 9.58 Hz, Br–Ph $C_{3,5}$-H), 7.61, 7.63 (2d, 2H, J = 8.55, 8.54 Hz, Br–Ph $C_{2,6}$-H), 7.84, 8.01 (2s, 1H, NCH), 8.13, 8.15 (2s, 1H, C_5-H), 11.37, 11.48 (2s, 1H, CONH).

^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 32.71, 34.21 (CH_2), 56.16 (ar OCH_3), 109.86, 110.17 (C_5), 111.10, 111.35 (C_2), 115.18 (ar $C_{3,5}$), 120.55, 120.66 (Br–Ph C_4), 127.29 (ar C_1), 127.45, 127.51 (Br–Ph $C_{2,6}$), 127.29, 127.67 (C_3), 129.38, 129.60 (ar $C_{2,6}$), 132.38, 132.43 (Br–Ph $C_{3,5}$), 134.39, 134.50 (Br–Ph C_1), 149.62, 149.71 (C_{7a}), 145.52, 145.66 (C_6), 144.40, 147.78 (NCH), 161.57, 161.74 (ar C_4), 163.87, 169.65 (CONH). EIMS (70 eV) m/z (%): 470 (M + 2, 62.4), 468 (M^+, 61.7), 337 (22.4), 336 (5.1), 335 (23.4), 334 (2.0), 322 (10.8), 321 (60.3), 320 (13.5), 319 (68.1), 294 (62.0), 292 (63.0), 240 (15.9), 211 (42.4), 199 (5.4), 198 (2.7), 182 (4.1), 180 (3.4), 169 (6.8), 167 (4.7), 150 (11.5), 149 (13.5), 134 (19.0), 133 (14.6), 125 (10.2), 120 (9.8), 114 (14.6), 111 (13.2), 110 (5.4), 107 (9.8), 102 (4.7), 101 (9.5), 100 (100), 99 (25.8), 89 (8.1), 85 (21.7), 84 (8.8), 73 (4.1), 72 (6.1), 59 (2.7), 58 (37.3).

Compound 3e

IR (ν cm^{-1}, KBr): 3353, 3143 (N–H), 1681 (CO), 1603 (hydrazone CN). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6):

3.75, 4.18 (2s, 2H, CH_2CO), 6.94 (s, 1H, C_2-H), 7.12 (t, 2H, J = 8.78 Hz, ar $C_{3,5}$-H), 7.40, 7.42 (2d, 2H, J = 8.43, 6.84 Hz, Br–Ph $C_{3,5}$-H), 7.60–7.66 (m, 4H, Br–Ph $C_{2,6}$-H, ar $C_{2,6}$-H), 7.90, 8.08 (2s, 1H, NCH), 8.13, 8.15 (2s, 1H, C_5-H), 11.51, 11.62 (2s, 1H, CONH). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 33.17, 34.71 (CH_2), 110.29, 110.55 (C_5), 111.62, 111.85 (C_2), 117.20 (d, J = 21.9 Hz, ar $C_{3,5}$), 121.06, 121.16 (Br–Ph C_4), 127.65, 128.03 (C_3), 127.95, 128.00 (Br–Ph $C_{2,6}$), 130.44, 130.64 (2d, J = 8.5, 8.8 Hz, ar $C_{2,6}$), 132.04 (d, J = 2.8 Hz, ar C_1), 132.84, 132.89 (Br–Ph $C_{3,5}$), 134.87, 134.97 (Br–Ph C_1), 143.93, 147.37 (NCH), 146.06, 146.21 (C_6), 150.14, 150.22 (C_{7a}), 164.37, 164.48 (2d, J = 247.7, 247.0 Hz, ar C_4), 164.66, 170.36 (CONH). EIMS (70 eV) m/z (%): 458 (M + 2, 83.8), 456 (M^+, 81.7), 337 (31.1), 336 (7.8), 335 (32.4), 334 (3.4), 322 (15.5), 321 (87.8), 320 (20.9), 319 (100), 294 (85.9), 292 (85.5), 240 (16.2), 211 (78.7), 199 (2.0), 198 (6.1), 182 (5.4), 180 (4.7), 169 (8.1), 167 (6.1), 138 (6.4), 137 (17.6), 125 (6.8), 122 (10.9), 121 (5.4), 114 (4.7), 111 (5.4), 110 (18.9), 108 (13.2), 102 (4.7), 101 (4.1), 100 (6.8), 99 (9.5), 95 (19.2), 89 (3.4), 85 (19.6), 84 (5.4), 73 (4.7), 72 (23.0), 59 (27.7), 58 (6.1).

Compound 3f

IR (ν cm^{-1}, KBr): 3133 (N–H), 1681 (CO), 1604 (hydrazone CN). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 3.76, 4.18 (2s, 2H, CH_2CO), 6.94 (s, 1H, C_2-H), 7.40, 7.42 (2d, 2H, J = 8.42, 6.95 Hz, ar $C_{3,5}$-H), 7.47–7.55 (m, 4H, Br–Ph $C_{3,5}$-H, ar $C_{2,6}$-H), 7.61, 7.63 (2d, 2H, J = 8.46, 8.49 Hz, Br–Ph $C_{2,6}$-H), 7.88, 8.05 (2s, 1H, NCH), 8.12, 8.14 (2s, 1H, C_5-H), 11.57, 11.68 (2s, 1H, CONH). EIMS (70 eV) m/z (%): 337 (2.1), 336 (1.8), 335 (1.5), 334 (1.5), 321 (1.5), 319 (1.2), 294 (1.5), 292 (1.2), 240 (1.5), 211 (3.8), 200 (7.7), 199 (8.0), 198 (8.9), 197 (8.9), 185 (2.9), 184 (3.5), 183 (4.4), 182 (4.1), 181 (3.2), 180 (2.7), 170 (2.9), 169 (4.1), 168 (3.9), 167 (3.5), 157 (3.5), 155 (5.0), 125 (7.6), 114 (3.0), 111 (15.5), 102 (1.5), 101 (1.1), 100 (1.6), 99 (4.2), 89 (4.6), 85 (28.2), 76 (2.8), 73 (4.0), 72 (8.0), 59 (15.5), 43 (100).

Compound 3g

IR (ν cm^{-1}, KBr): 3151 (N–H), 1672 (CO), 1600 (hydrazone CN). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 2.95 (s, 6H, ar C_4-N(CH_3)$_2$), 3.85, 4.27 (2s, 2H, CH_2CO), 6.71, 6.73 (2d, 2H, J = 8.85, 7.60 Hz, ar $C_{3,5}$-H), 7.07 (s, 1H, C_2-H), 7.49–7.58 (m, 4H, Br–Ph $C_{3,5}$-H, ar $C_{2,6}$-H), 7.75, 7.79 (2d, 2H, J = 8.53, 8.52 Hz, Br–Ph $C_{2,6}$-H), 7.92, 8.09 (2s, 1H, NCH), 8.26, 8.28 (2s, 1H, C_5-H), 11.37 (s, 1H, CONH).

Compound 3h

IR (ν cm^{-1}, KBr): 3201 (N–H), 1664 (CO), 1598 (hydrazone CN). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 3.71 (s, 3H, ar C_5-OCH_3), 3.80 (s, 3H, ar C_2-OCH_3), 3.88, 4.33 (2s, 2H, CH_2CO), 7.00 (dd, 1H, J = 9.06, 2.90 Hz, ar C_4-H), 7.04–7.09 (m, 2H, C_2-H, ar C_3-H), 7.30, 7.40 (2d, 1H, J = 2.85, 2.90 Hz, ar C_6-H), 7.55, 7.57 (2d, 2H, J = 8.44, 10.01 Hz, Br–Ph $C_{3,5}$-H), 7.76, 7.79 (2d, 2H, J = 8.37, 8.41 Hz, Br–Ph $C_{2,6}$-H), 8.27, 8.28 (2s, 1H, C_5-H), 8.36, 8.55 (2s, 1H, NCH), 11.58, 11.73 (2s, 1H, CONH). ^{13}C NMR (100 MHz, δ, ppm, DMSO-d_6): 32.80, 34.26 (CH_2), 56.29, 56.32 (ar C_5-OCH_3), 57.06, 57.11 (ar C_2-OCH_3), 109.87, 110.10 (C_5), 109.94, 110.56 (ar C_6), 111.12, 111.43 (C_2), 114.13, 114.29 (ar C_3), 117.92, 118.63 (ar C_4), 120.56, 120.67 (Br–Ph C_4), 123.39, 123.55 (ar C_1), 127.15, 127.69 (C_3), 127.44, 127.50 (Br–Ph $C_{2,6}$), 132.36, 132.42 (Br–Ph $C_{3,5}$), 134.39, 134.49 (Br–Ph C_1), 139.98, 143.25 (NCH), 145.55, 145.68 (C_6), 149.64, 149.72 (C_{7a}), 153.01, 153.14 (ar C_5), 154.09, 154.12 (ar C_2), 163.97, 169.86 (CONH).

Compound 3i

IR (ν cm^{-1}, KBr): 3132 (N–H), 1688 (CO), 1616 (hydrazone CN). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6): 3.78, 4.20 (2s, 2H, CH_2CO), 6.94, 6.96 (2s, 1H, C_2-H), 7.34 (dd, 1H, J = 8.53, 2.08 Hz, ar C_5-H), 7.39, 7.43 (2d, 2H, J = 8.55, 8.49 Hz, Br–Ph $C_{3,5}$-H), 7.57–7.65 (m, 3H, Br–Ph $C_{2,6}$-H, ar C_3-H), 7.79, 7.90 (2d, 1H, J = 8.58, 8.58 Hz, ar C_6-H), 8.13, 8.14 (2s, 1H, C_5-H), 8.24, 8.41 (2s, 1H, NCH), 11.73, 11.84 (2s, 1H, CONH). EIMS (70 eV) m/z (%): 512 (M + 6, 7.4), 510 (M + 4, 40.5), 508 (M + 2, 80.4), 506 (M^+, 49.7), 337 (30.4), 336 (6.7), 335 (33.8), 334 (3.4), 322 (19.2), 321 (98.0), 320 (21.6), 319 (100), 294 (90.5), 292 (89.5), 240 (16.2), 211 (77.7), 199 (4.7), 198 (2.0), 192 (0.7), 191 (0.7), 190 (2.0), 189 (2.7), 188 (1.3), 187 (3.4), 182 (4.4), 180 (3.4), 176 (3.4), 175 (3.7), 174 (10.8), 173 (9.1), 172 (9.1), 171 (4.4), 169 (4.7), 167 (3.4), 162 (1.3), 160 (2.7), 158 (2.7), 149 (2.0), 147 (3.4), 145 (5.1), 125 (6.1), 114 (4.7), 111 (6.8), 110 (5.4), 102 (4.7), 101 (7.4), 100 (58.4), 99 (10.1), 89 (4.1), 85 (9.5), 84 (4.7), 73 (4.1), 72 (11.1), 59 (4.7), 58 (14.9).

RESULT AND DISCUSSION

In the IR spectra, the NH, CO and CN bands were observed in the 3353–3102 cm^{-1}, 1688–1660 cm^{-1} and 1618–1598 cm^{-1} regions, respectively. In the ^{1}H NMR spectra of hydrazide hydrazones (3a–3i), the absence of the NH_2 absorptions of the hydrazide 2 (δ = 4.38 ppm) and the presence of new resonances assigned to the –CH proton of 3 provided evidence for hydrazone formation. The ^{1}H NMR spectra of 3a–3i revealed the presence of two geometric isomers as concluded from the NH, NCH and CH_2 protons resonating as double singlets at about δ 11.73–11.30/11.92–11.40, 8.36–7.80/8.55–7.96 and 3.93–3.72/4.33–4.13 ppm, respectively[13]. It is assumed that the NCH double bond restricted rotation and gave rise to the formation of *E* and *Z* isomers. ^{13}C NMR spectra of 3d, 3e and 3h chosen as prototypes verified the proposed hyrazide–hydrazone structure. EIMS spectra of 3d, 3e and 3i displayed molecular ions which confirmed their molecular weights. Major fragmentation routes involved the breaking of the CO–NH and NH–N bonds of the hydrazide moiety.

Antimicrobial activity

Antimicrobial activities of compounds were tested using microbroth dilution method[17, 18]. Tested microorganism strains were: *Escherichia coli* (NRRL B-3704), *Staphylococcus aureus* (NRLL B-767), *Salmonella typhimurium* (NRRL B-4420), *Bacillus cereus* (NRRL B-3711), *Streptococcus faecalis* (NRRL B-14617), *Aeromonas hydrophila* (Ankara Uni. Fac. of Veterinary), *Candida albicans* and *Candida glabrata* (isolates obtained from Osmangazi Uni. Fac. of Medicine). Chloramphenicol and flucanazole were used as control drugs. The observed data on the antimicrobial activity of the compounds and control drugs are given in Table 2.

Table 1: Physical and analytical data of compounds Synthesized

Compound	Ar	Yield (%)	M.p. (°C)	Formula (M. wt.)	Analysis, calc./found		
					C	H	N
3a	C_6H_5	91	249–251	$C_{20}H_{15}BrN_4OS$ (439.329)	54.68/55.15	3.44/3.46	12.75/12.77
3b	C_6H_4OH(2-)	95	268–270	$C_{20}H_{15}BrN_4O_2S$ (455.329)	52.76/52.48	3.32/3.00	12.30/12.27
3c	C_6H_4OH(4-)	91	265–266	$C_{20}H_{15}BrN_4O_2S$ (455.329)	52.76/53.03	3.32/3.24	12.30/12.17
3d	$C_6H_4OCH_3$(4-)	92	243–245	$C_{21}H_{17}BrN_4O_2S$ (469.355)	53.74/54.01	3.65/3.52	11.94/11.97
3e	C_6H_4F(4-)	93	253–255	$C_{20}H_{14}BrFN_4OS$ (457.320)	52.53/52.80	3.09/2.66	12.25/12.31
3f	C_6H_4Br(4-)	92	255–256	$C_{20}H_{14}Br_2N_4OS$ (518.226)	46.35/46.75	2.72/2.35	10.81/10.84
3g	$C_6H_4N(CH_3)_2$(4-)	57	262–263	$C_{22}H_{20}BrN_5OS$ (482.397)	54.78/54.14	4.18/3.49	14.52/14.36
3h	$C_6H_3(OCH_3)_2$(2,5-)	95	236–237	$C_{22}H_{19}BrN_4O_3S$ (499.381)	52.91/52.42	3.83/3.45	11.22/11.14
3i	$C_6H_3(Cl)_2$(2,4-)	99	245–247	$C_{20}H_{13}BrCl_2N_4OS$ (508.219)	47.27/47.87	2.58/2.19	11.02/10.61

Table 2: MIC values (µg/mL) of compounds 3a–3i

Compound	A	B	C	D	E	F	G	H
3a	250	15.6	62.5	31.25	31.25	31.25	250	250
3b	250	125	125	62.5	250	125	125	125
3c	125	125	125	62.5	250	125	62.5	62.5
3d	125	62.5	62.5	62.5	62.5	62.5	125	62.5
3e	125	125	125	62.5	250	125	125	125
3f	250	125	250	250	250	250	250	250
3g	250	125	125	125	250	250	125	125
3h	250	250	125	250	250	125	125	125
3i	250	250	250	3.9	125	250	250	250
Reference-2	–	–	–	–	–	–	250	250

Reference-1: Chloramphenicol, Reference-2: flucanazole; A: *Escherichia coli* (NRRL B-3704); B: *Staphylococcus aureus* (NRRL B-767); C: *Salmonella typhimurium* (NRRL B-4420); D: *Bacillus cereus* (NRRL B-3711); E: *Streptococcus faecalis* (NRRL B-14617); F: *Aeromonas hydrophila* (Ankara Uni. Fac. of Veterinary); G: *Candida albicans* (isolates obtained from Osmangazi Uni. Fac. of Medicine); H: *Candida glabrata* (isolates obtained from Osmangazi Uni. Fac. of Medicine).

Microdilution broth susceptibility assay was used for the antibacterial evaluation of the compounds[17], whereas antifungal susceptibility of the fungus yeasts was examined according to NCCLS reference method for broth dilution antifungal susceptibility testing of yeasts[18]. Chloramphenicol was used as standard antibacterial agent whereas flucanazol was used as antifungal agent and both are prepared as described in the related references.

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