Arch Pharm Res Vol 26, No 10, 773-777, 2003

Archives of Pharmacal Research
http://apr.psk.or.kr

Synthesis and Antimicrobial Activities of Some New Nitroimidazole Derivatives

Kadriye BENKLİ, Ahmet Çağrı KARABURUN, Nalan GÜNDOĞDU-KARABURUN, Şeref DEMİRAYAK, and Kıymet GÜVEN[1]

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Anadolu, 26470 Eskişhir, Turkey and [1]Department of Microbiology, Faculty of Science, University of Anadolu, 26470 Eskişhir, Turkey

(Received June 29, 2003)

In this study, some new nitroimidazole derivatives were obtained from 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethylamine dihydrochloride (**4**) and 1-(2-bromoethyl)-2-methyl-5-nitroimidazole (**5**), which were prepared using metronidazole. Compound **4** was reacted with arylisothiocyanates (**6**) to obtain 1-[2-(2-methyl-5-nitroimidazol-1-yl)ethyl]-3-arylthioureas (**7**) and the latter with *α-bromoacetophenones* (**8**) to give 3-[2-(2-methyl-5-nitroimidazol-1-yl)ethyl]-2-arylimino-4-aryl-4-thiazolines (**9**). Also 1-[2-(2-methyl-5-nitroimidazol-1-yl)ethyl]-2-phenyl-4-arylideneimidazolin-5-ones (**11**) were prepared by reaction of **4** with 2-phenyl-4-arylidene-5-oxazolones (**10**). The reaction of the other starting material **5** with 5-arylidenethiazolidin-2,4-dione (**12**) gave 3-[2-(2-methyl-5-nitroimidazol-1-yl)ethyl]-5-arylidenethiazolidin-2,4-dione (**13**) derivatives. Structural elucidation of the compounds was performed by IR, ^{1}H-NMR and MASS spectroscopic data and elemental analysis results. Antimicrobial activities of the compounds were examined and moderate activity was obtained.

Key words: Metronidazole, Nitroimidazoles, Antibacterial and antifungal activity

INTRODUCTION

Metronidazole is not only the leading and most important member, but also the most commonly studied compound of 5-nitroimidazoles, possessing strong anti protozoal and antibacterial activity (Carganico and Cozzi, 1991; Wolf, 1997). In order to improve the pharmacokinetic properties of the molecule, efforts have been made to obtain prodrugs (Bowden and Izadi, 1998; Mahfouz *et al.*, 1998; Mahfouz and Hasan, 2001) and also novel different nitroimidazole derivatives.

The antimicrobial activities, obtained from the compounds of our previous research on the synthesis of metronidazole derivatives, encouraged us to perform the synthesis of some new compounds using the active bromo or amino functional group replaced on metronidazole as previously described (Demirayak and Kiraz, 1993; Demirayak *et al.*, 1995). Hence, the metronidazole molecule was planned to be furnished with thiourea (Griffin *et al.*, 1974), 2-iminothiazoline (Turan-Zitouni, *et al.*, 2002), 5-arylidenethiazolidine-2,4-dione (Lima *et al.*, 1992) and 3-aryl-5-benzylidene-2-phenyl-4-imidazolone (Hanna *et al.*, 1994; Patel *et al.*, 1997; Allimony *et al.*, 1999) residues in order to add activity properties against aerobic prokaryotes and eukaryotes. In continuation of our study on nitroimidazoles we prepared a series of compounds and tested their antimicrobial and antifungal activities on a number of bacteria and fungi.

Correspondence to: Kadriye Benkli, Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Eskişehir 26470, Turkey
Tel: 90-222-3350581/3635, Fax: 90-222-3350750
E-mail: kbenkli@anadolu.edu.tr

MATERIALS AND METHODS

Chemistry

Melting points were determined by using an Electrothermal 9100 digital melting point apparatus and were uncorrected. Spectroscopic data were recorded on the following instruments: IR, Schimadzu 435 IR spectrophotometer; ^{1}H-NMR, Bruker DPX 400 NMR spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as internal standard. Elemental analyses were performed on a Leco CHNS analyser and all the analyses for C, H, and N were within ±0.4% of the theoretical values.

2-(2-Methyl-5-nitro-1*H*-imidazol-1-yl)ethylamine dihydrochloride (**4**), 1-(2-bromoethyl)-2-methyl-5-nitroimidazole (**5**), which was obtained from the reaction of **2** with KBr in DMF (M.p. 80-81°C, Lit. (Tovarna Zdravil, 1969) M.p. 79.5-80°C), α-bromoacetophenones (Cawper, 1943) (**8**), 2-aryl-4-arylideneoxazol-5-ones (Turcki, 1986) (**10**), and 5-arylidenethiazolidine-2,4-diones (Lima *et al.*, 1992) (**12**) were prepared according to the methods given in the literature.

1-[2-(2-Methyl-5-nitroimidazol-1-yl)ethyl]-3-arylthioureas (7)

A mixture of **4** (10 mmol), sodium acetate (20 mmol) and a suitable arylisothiocyanate (**6**) (10 mmol) in 50 mL of ethanol was stirred in a boiling water bath for 30 min. The precipitate formed was filtered and recrystallised from ethanol. **7a** IR(KBr) ν_{max} (cm^{-1}): 3158 (N-H), 1581-1420 (C=N, C=C), 1526, 1360 (N=O). ^{1}H-NMR δ (ppm) (DMSO-d_6): 2.44 (s, 3H), 3.91 (q, 2H), 4.41 (t, 2H), 7.14-7.51 (m, 5H), 7.73 (bs, 1H), 8.03 (s, 1H), 9.66 (bs, 1H). EI-MS: *m/z*: 259.78, 258.34, 176.69, 134.81, 91.37, 49.80 (%100). **7d** IR(KBr) ν_{max}(cm^{-1}): 3350, 3158 (N-H), 1592-1420 (C=N, C=C), 1545, 1358 (N=O). ^{1}H-NMR δ (ppm) (DMSO-d_6): 2.28 (s, 3H), 3.85 (q, 2H), 4.52 (t, 2H), 7.22 (d, 2H, J:8.64 Hz), 7.36 (d, 2H, J:8.62 Hz), 7.75 (bs, 1H), 8.12 (s, 1H), 9.70 (bs, 1H).

3-[2-(2-Methyl-5-nitroimidazol-1-yl)ethyl]-2-arylimino-4-aryl-4-thiazolines (9)

A mixture of **7** (10 mmol), sodium bicarbonate (10 mmol) and a suitable α-bromoacetophenone (**8**) (10 mmol) in 50 mL of ethanol was stirred in a boiling water bath for 4 h. The precipitate formed was filtered and recrystallised from ethanol. **9b** IR(KBr) ν_{max} (cm^{-1}): 1608-1423 (C=N), 1579, 1359 (N=O). ^{1}H-NMR δ (ppm) (DMSO-d_6): 2.22 (s, 3H), 2.35 (s, 3H), 4.38 (t, 2H), 4.53 (t, 2H), 6.27 (s, 1H), 7.00 (d, 2H, j: 7.99), 7.05-7.16 (m, 3H), 7.21 (d, 2H, j: 7.97), 7.38-7.44 (m, 2H), 7.86 (s, 1H). **9c** IR(KBr) ν_{max} (cm^{-1}): 1607-1426 (C=N), 1565, 1361 (N=O). ^{1}H-NMR δ (ppm) (DMSO-d_6): 2.20 (s, 3H), 4.36 (t, 2H), 4.55 (t, 2H), 6.25 (s, 1H), 7.05-7.18 (m, 5H), 7.22 (d, 2H J:7.85 Hz) 7.40-7.46 (m, 2H), 7.83 (s, 1H). EI-MS: *m/z*: 441.28 (M+2), 439.36 (M^+), 438.22, 284.98, 79.82, 40.41 (%100). **9e** IR(KBr) ν_{max} (cm^{-1}): 1612-1420 (C=N), 1569, 1360 (N=O). ^{1}H-NMR δ (ppm) (DMSO-d_6): 2.22 (s, 3H), 2.31 (s, 3H), 4.35 (t, 2H), 4.53 (t, 2H), 6.25 (s, 1H), 6.94-7.00 (m, 2H), 7.10 (d, 2H, j: 7.85), 7.20 (d, 2H, j: 7.99), 7.36-7.47 (m, 3H), 7.83 (s, 1H).

1-[2-(2-Methyl-5-nitroimidazol-1-yl)ethyl]-2-phenyl-4-arylidene-imidazolin-5-ones (11)

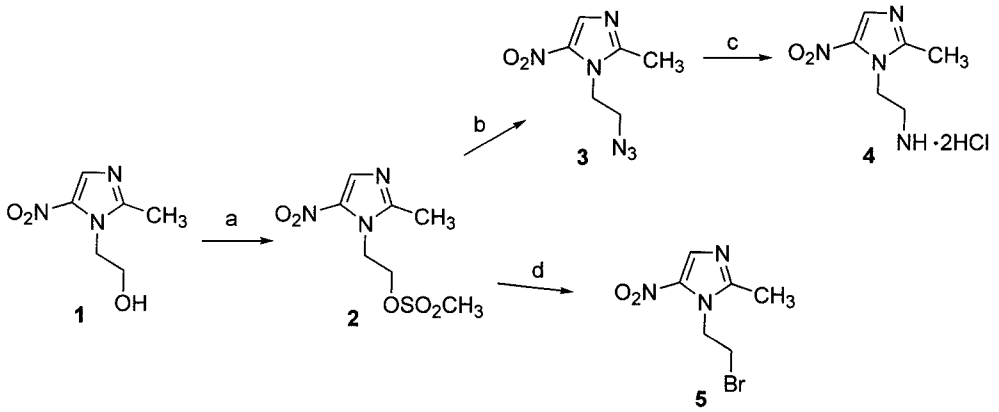
A mixture of **4** (10 mmol), sodium acetate (20 mmol) and **10** (10 mmol) in 50 mL of acetic acid was stirred in a boiling water bath for 30 min, poured into water and neutralised with $NaHCO_3$. The precipitate formed was filtered and crystallised from ethanol. **11a** IR(KBr) ν_{max} (cm^{-1}): 1662 (C=O), 1617-1427 (C=N, C=C), 1525, 1365 (N=O). ^{1}H-NMR δ (ppm) (DMSO-d_6): 2.24 (s, 3H), 3.65 (t, 2H), 4.40 (t, 2H), 7.21 (s, 1H), 7.30-7.64 (m, 5H), 7.78-8.11 (m, 5H), 8.82 (s, 1H). **11d** IR(KBr) ν_{max} (cm^{-1}): 1711 (C=O), 1631-1425 (C=N, C=C), 1523, 1383 (N=O). ^{1}H-NMR δ (ppm) (DMSO-d_6): 2.46 (s, 3H), 3.56 (t, 2H), 4.40 (t, 2H), 7.14 (s, 1H), 7.43 (d, 2H, j: 8.55), 7.49-8.03 (m, 7H), 9.94 (s, 1H). EI-MS: *m/z*: 437.63 (M+2), 436.88 (M+1), 435.03 (M^+), 388.83, 104.36 (%100). **11e** IR(KBr) ν_{max} (cm^{-1}): 1652 (C=O), 1619-1424 (C=N, C=C), 1524, 1384 (N=O). ^{1}H-NMR δ (ppm) (DMSO-d_6): 2.21 (s, 3H), 4.25 (t, 2H), 4.45 (t, 2H), 7.36 (s, 1H), 7.51-7.81 (m, 8H), 8.89 (bs, 1H).

3-[2-(2-Methyl-5-nitroimidazol-1-yl)ethyl]-5-arylidene-thiazolidine-2,4-diones (13)

A mixture of **5** (10 mmol), a suitable **12** (10 mmol) and potassium carbonate (10 mmol) in 100 mL of acetone was refluxed for 12 h. The solvent was evaporated to dryness, the residue was washed with water and the raw product was crystallised in ethanol/DMF. **13a** IR(KBr) ν_{max} (cm^{-1}): 1715, 1685 (C=O), 1630-1450 (C=N, C=C), 1526, 1374 (N=O). ^{1}H-NMR δ (ppm) ($CDCl_3$): 2.33 (s, 3H), 4.13 (t, 2H), 4.53 (t, 2H), 7.38-7.41 (m, 5H), 7.79 (s, 1H), 7.87 (s, 1H). EI-MS: *m/z*: 358.8 (M), 277.06, 133.95 (100%). **13c** IR(KBr) ν_{max} (cm^{-1}): 1732, 1690 (C=O), 1621-1425 (C=N, C=C), 1517, 1382 (N=O). ^{1}H-NMR δ (ppm) ($CDCl_3$): 2.34 (s, 3H), 4.14 (t, 2H), 4.54 (t, 2H), 7.33 (d, 2H, j:8.64 Hz), 7.36 (d, 2H, j:8.73 Hz), 7.74 (s, 1H), 7.88 (s, 1H). **13e** IR(KBr) ν_{max} (cm^{-1}): 1727, 1687 (C=O), 1630-1432 (C=N, C=C), 1525, 1375 (N=O). ^{1}H-NMR δ (ppm) ($CDCl_3$): 2.17 (s, 3H), 3.97 (t, 2H), 4.37 (t, 2H), 6.97 (t, 1H), 7.18 (d, 1H, j:5.03 Hz), 7.47 (d, 1H, j:3.67 Hz), 7.72 (s, 1H), 7.81 (s, 1H).

Microbiology

The antibacterial and antifungal activities of the compounds were determined *in vitro* by using the tube dilution technique (Finegold *et al.*, 1978; Mc Ginnis *et al.*, 1991). The MIC values were given in μg/mL. The stock solutions of the compounds were prepared in DMSO. Metronidazole, chloramphenicol and fluconazole were used as control antibacterial and antifungal agents, respectively. The standard bacteria and fungi strains used were: *Escherichia coli* ATCC 25922, *Proteus vulgaris* NRRL B-123, *Enterobacter aerogenes* NRRL B-3567, *Enterobacter faecalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853, *Salmonella typhimurium* NRRL B-4420, *Staphylococcus aureus* NRRL B-767, *Staphylococcus epidermidis* ATCC 12228, *Candida albicans** and *Rhodotorula**. (*: University of Osmangazi, Eskisehir, TURKEY).

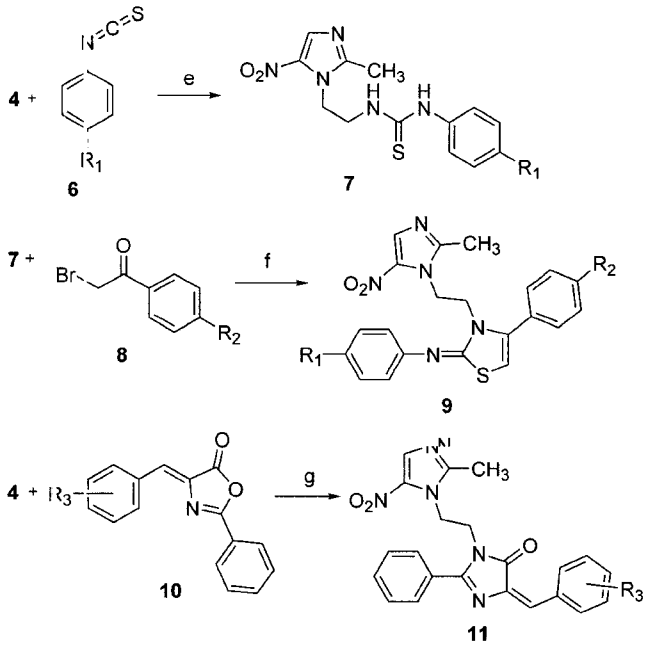


Scheme 1. Preparation of the starting compounds. a: CH_3SO_2Cl/Pyridine; b: NaN_3/DMF; c: *i:* PPh_3/THF, *ii:* HCl / H_2O; d: KBr/ DMF.

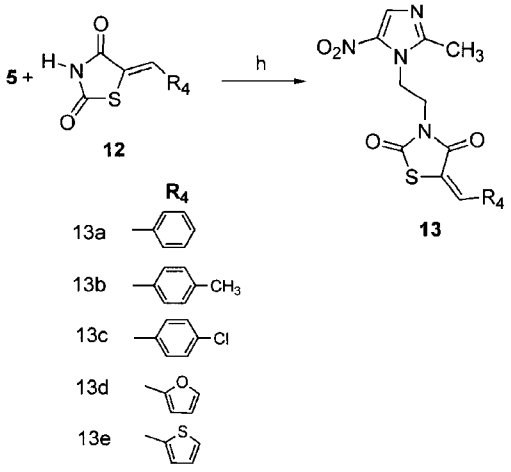
RESULTS AND DISCUSSION

Chemistry

Preparation of the starting compounds **4** and **5** has previously been reported and outlined in Scheme 1. The ethylamine derivative (**4**) was used in the syntheses of 2-iminothiazoline (**9**) and imidazolidinone (**11**) derivatives. The reaction sequences are outlined in Scheme 2. 1,3-Disubstituted thioureas are often prepared by reaction of an appropriate amine with an alkyl or arylisothiocyanate in ethanol (Griffin *et al.*, 1974). In the present study, 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethylamine dihydrochloride (**4**) was reacted with 4-substituted arylisothiocyanates (**6**), in the presence of sodium bicarbonate to give thioureas (**7**). The compounds **7** were characterised by IR spectra exhibiting the presence of amide N-H bands. Treatment of compounds **7** with α-bromoacetophenones (**8**) furnished the corresponding 2-iminothiazoline derivatives (**9**). The characteristic N-H stretching bands originating from thioureas (**7**) are no longer present in the IR spectra of the compounds **9**, after cyclization. The intermediate 4-arylidene-2-aryl-5(4*H*)oxazolones (**10**) were prepared by condensation of aryl aldehydes with hippuric acid in the presence of sodium acetate in acetic anhydride (Turcki, 1986). These oxazolones were converted into compounds **11**, by reacting with the ethylamine (**4**). The other starting material ethyl bromide (**5**) was used for preparing the thiazolidinedione derivatives (**13**) of Scheme 3. Thus, the mentioned compounds were reacted with the corresponding 5-arylidenethiazolidin-2,4-dione derivative in the presence of potassium carbonate in acetone. IR spectra of **11** and **13** exhibited characteristic carbonyl bands due to imidazolones and thiazolidinediones, respectively. In the NMR spectra methyl, ethylene and imidazole-4-H protons



Scheme 2. Syntheses of 2-iminothiazoline and imidazolidinone derivatives. e: CH_3COONa/C_2H_5OH/Reflux; f: $NaHCO_3/C_2H_5OH$/Reflux; g: CH_3COONa/CH_3COOH/Reflux.



Scheme 3. Syntheses of thiazolidinedione derivatives. h: K_2CO_3/ Acetone/Reflux.

that are common for all compounds were resonated at expected regions (Silverstein *et al.*, 1991).

Some characteristics of the compounds are shown in Table I.

Microbiology

Compounds **7**, **9**, **11** and **13** were evaluated for antibacterial and antifungal activity against representative bacteria – gram (-) bacteria; *Escherichia coli*, *Proteus vulgaris*, *Enterobacter aerogenes*, *Enterobacter faecalis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* and gram (+) bacteria; *Staphylococcus aureus*, *Staphylococcus epidermidis* – and fungi – *Candida albicans*, *Rhodotorula* – as shown in Table II. Two antibacterial agents, metronidazole and chloramphenicol, and an antifungal agent were used as control. As we have indicated before (Demirayak *et al.*, 1999), metronidazole itself is not effective against aerobe bacteria (MIC > 1000 μg/mL), which is understandable considering metronidazole is an antianaerobic agent. The most sensitive microorganisms for the control of antibacterial chloramphenicol appeared to be *Proteus vulgaris* and *Enterobacter aerogenes* (MIC 7.81 μg/mL) and for the control of antifungal fluconazole, *Candida albicans* (MIC 1.95 μg/mL).

As we have emphasised, the aim of this work was primarily to make the molecule effective against aerobic

Table I. Some characteristics of the synthesised compounds

Compounds	M.p. (°C)	Yield (%)	Molecular Formulae	Mol. Weight (g)
7a	186-187	68	$C_{13}H_{15}N_5O_2S$	305
7b	197-198	72	$C_{14}H_{17}N_5O_2S$	319
7c	200-201	70	$C_{14}H_{17}N_5O_3S$	335
7d	182-183	73	$C_{13}H_{14}ClN_5O_2S$	339.5
9a	148-149	77	$C_{21}H_{19}N_5O_2S$	405
9b	187-189	79	$C_{22}H_{21}N_5O_2S$	419
9c	191-193	75	$C_{21}H_{18}ClN_5O_2S$	439.5
9d	199-200	82	$C_{21}H_{18}N_6O_4S$	450
9e	195-196	69	$C_{22}H_{21}N_5O_2S$	419
9f	181-182	73	$C_{22}H_{21}N_5O_3S$	435
9g	140-142	82	$C_{21}H_{18}ClN_5O_2S$	439.5
9h	165-167	80	$C_{22}H_{20}ClN_5O_2S$	453.5
11a	171-172	47	$C_{22}H_{19}N_5O_3$	401
11b	120-121	50	$C_{23}H_{21}N_5O_4$	431
11c	209-210	52	$C_{22}H_{18}ClN_5O_3$	435.5
11d	198-199	48	$C_{22}H_{18}ClN_5O_3$	435.5
11e	71-73	50	$C_{22}H_{17}Cl_2N_5O_3$	470
11f	111-113	45	$C_{22}H_{17}Cl_2N_5O_3$	470
13a	165-166	69	$C_{16}H_{14}N_4O_4S$	358
13b	197-198	75	$C_{17}H_{16}N_4O_4S$	372
13c	208-209	83	$C_{16}H_{13}ClN_4O_4S$	392.5
13d	161-162	66	$C_{14}H_{12}N_4O_5S$	348
13e	148-149	62	$C_{14}H_{12}N_4O_4S_2$	364

Table II. Antibacterial and antifungal activities of the compounds

Compounds	A	B	C	D	E	F	G	H	I	J
7a	500	250	500	250	250	1000	250	500	62.5	31.25
7b	500	250	250	250	250	500	250	500	125	250
7c	250	62.5	250	250	500	125	250	500	250	250
7d	500	250	500	250	250	250	250	500	250	250
9a	250	500	500	250	250	250	250	250	250	250
9b	125	500	500	250	250	250	250	250	250	250
9c	500	500	250	250	250	250	250	250	250	125
9d	250	500	250	250	250	250	125	250	250	125
9e	250	500	250	250	250	125	250	250	250	250
9f	250	250	250	250	250	125	250	250	250	250
9g	250	250	250	250	250	250	125	250	500	250
9h	250	250	250	250	250	500	125	125	250	250
11a	500	500	500	250	250	250	250	250	250	250
11b	500	500	500	250	500	500	250	250	250	125
11c	500	500	500	125	250	125	250	125	250	250
11d	500	250	250	250	250	250	250	250	125	250
11e	500	500	500	250	250	250	250	250	250	250
11f	500	500	500	250	250	250	250	250	250	250
13a	250	250	250	31.25	125	250	125	62.5	125	125
13b	250	250	250	250	500	250	250	500	125	125
13c	250	250	250	125	250	250	250	250	125	125
13d	250	250	250	250	250	250	250	250	125	125
13e	250	250	250	125	125	250	250	125	125	125
Metronidazole	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Chloramphenicole	250	7.81	7.81	250	250	250	15.62	125	250	250
Fluconazole	250	500	500	250	250	500	250	250	1.95	3.90

A: *Escherichia coli* **B**: *Proteus vulgaris* **C**: *Enterobacter aerogenes* **D**: *Enterobacter faecalis* **E**: *Pseudomonas aeruginosa* **F**: *Salmonella typhimurium* **G**: *Staphylococcus aureus* **H**: *Staphylococcus epidermidis* **I**: *Candida albicans* **J**: *Rhodotorula*

bacteria and fungi. Therefore, the newly synthesised compounds were tested against representative aerobic bacteria and fungi. We had confirmed in our two recent works (Demirayak and Kiraz, 1993; Demirayak *et al.*, 1999) that some of the 1-[2-(5-substituted benzazol-2-yl)thioethyl]-2-methyl-5-nitroimidazole and 1-[2-(substituted pyrrol-1-yl)ethyl]-2-methyl-5-nitroimidazole derivatives are highly effective against aerobic bacteria. On the contrary to metronidazole, in this work, the failure of our compounds sustain this effectiveness may be attributed to the greater volumes of the new compounds than those of the above mentioned ones.

When the MIC values of our compounds in Table II were taken into consideration, in regard to the effects of the control antibacterial chloramphenicol, it was seen that the values obtained against *Escherichia coli*, *Enterobacter faecalis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* and *Staphylococcus epidermidis* were quite closer. Nevertheless, the situation was not the same against *Proteus vulgaris* *Enterobacter aerogenes* and *Staphylococcus aureus*. Although moderately low MIC values were obtained for some of the compounds, i.e. for compound **7c**, 62.5 µg/mL against *Proteus vulgaris*, and for **13a**, 31.25 and 62.5 µg/mL against *Enterobacter faecalis* and *Staphylococcus epidermidis*, respectively, it was not possible to classify the results according to either compound groups or substituents.

Considering antifungal activity, MIC values obtained from the control antifungal agent, fluconazole, were 1.95 µg/mL against *Candida albicans* and 3.90 µg/mL against *Rhodotorula* and it was evident that the most noteworthy result was obtained from compound **7a**. This compound carries a thiourea residue and the result was therefore understandable because the thiourea derivatives are an important group for antimicrobial activity. For antifungal activity, no other significant results could be obtained from the other group of compounds.

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