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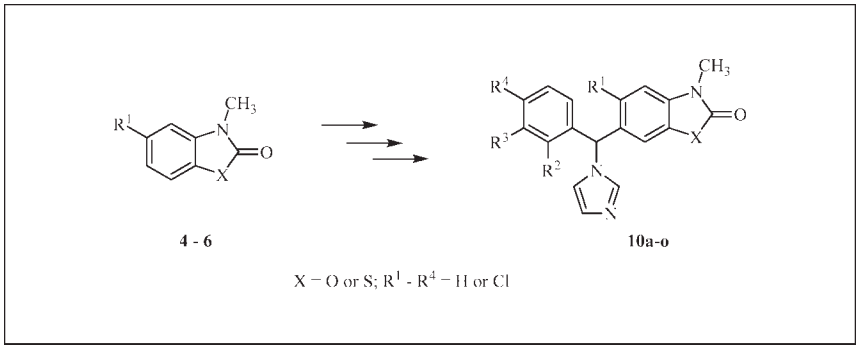

A series of new imidazole derivatives containing 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone ring were synthesized as analogues of the antifungal drug bifonazole. All compounds were tested *in vitro* against *Candida albicans*, *Candida parapsilosis*, and *Candida krusli*.

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INTRODUCTION

As a result of the dramatic increase in fungal infections, in recent years serious attention has been directed toward the discovery and development of new antifungal drugs. Mostly caused by *Candida albicans*, these infections are often spread through the use of broad-spectrum antibiotics, immunosuppressive agents, anticancer, and anti-AIDS drugs [1]. The main problem in the treatment of fungal infections is the increasing prevalence of drug resistance especially in patients chronically subjected to antimycotic therapy such as persons infected with HIV [2].

Azoles (imidazole and triazole) are presented in many effective antifungal drugs widely used for the treatment of topical or inner mycoses, in particular AIDS-related mycotic pathologies [3]. Their main effect is to block fungal ergosterol biosynthesis by preventing the access of natural substrate lanosterol to the active site of the cytochrome P-450-dependent enzyme 14α-lanosterol demethylase [4,5]. Since the identification of clotrimazole in 1972 [6], a number of antifungal imidazole agents have been studied and now are used in clinical practice: miconazole, bifonazole, *etc* [7]. Fluconazole is one of the most important drugs in the triazole family (Fig. 1).

In searching for new compounds with potential antifungal activity, we synthesized a number of imidazole derivatives, containing 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone moiety. These compounds could be examined as heterocyclic analogues of bifonazole, in which the biphenyl moiety could be replaced with benzoxazole or benzothiazole ring. A chlorine atom was introduced at different position on benzene cycle.

In this article, we present the synthesis and the results of the initial biological investigations of series bifonazole-like imidazole derivatives.

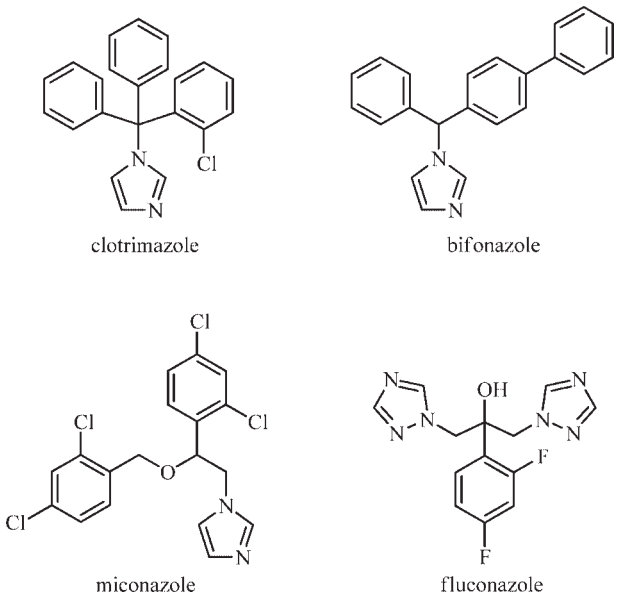


Figure 1. The structures of azole antifungal drugs used in clinical practice.

RESULTS AND DISCUSSION

A series of new imidazole derivatives **10a–o** with 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone moiety were prepared as potential antifungal agents as shown in Scheme 1.

The acylation of 3-methyl-2(3*H*)-benzoxazolone (**4**), 5-chloro-3-methyl-2(3*H*)-benzoxazolone (**5**), and 3-methyl-2(3*H*)-benzothiazolone (**6**) was carried out in polyphosphoric acid (PPA) with unsubstituted and various chloro-substituted benzoic acids and led to the corresponding 6-benzoyl derivatives **7a–o**.

The acylation of 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone was previously studied and was found to proceed with high regioselectivity [8–10]. The precise position of acylation was unequivocally assigned by X-ray single-crystal diffraction in the case of 6-benzoyl-2(3*H*)-benzoxazolone and 6-benzoyl-2(3*H*)-benzothiazolone [11,12].

Compounds **8a–o** were obtained in high yields and purity by a sodium borohydride reduction of the corresponding ketones **7a–o**. The reaction was carried out at room temperature in methanol and afforded the desired hydroxyl derivatives, which were the starting materials for the imidazole series.

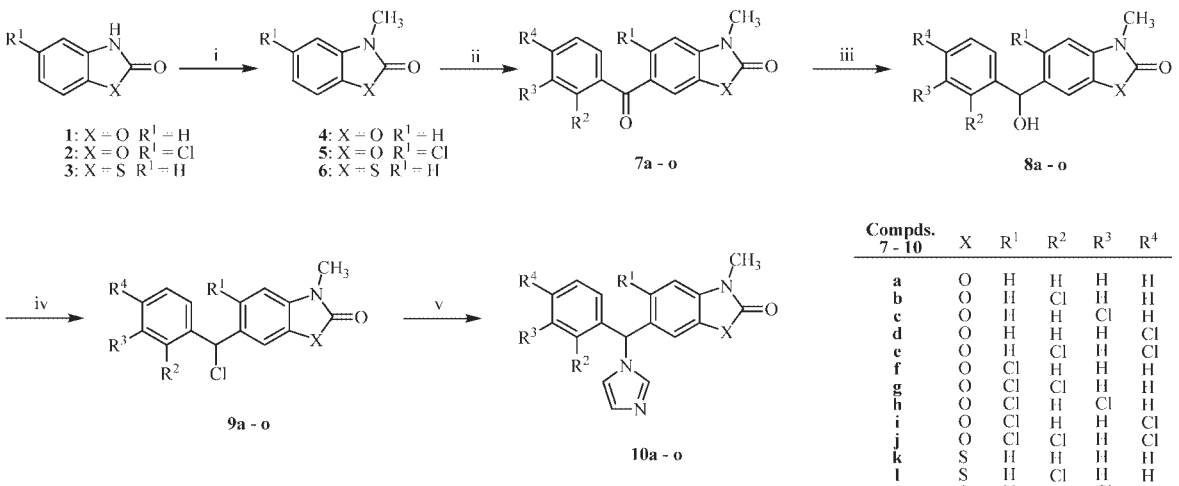
Two general approaches can be used for the synthesis of imidazole derivatives **10a–o**: by reaction of carbinols **8a–o** with *N,N′*-carbonyldiimidazole (CDI) [13] or *N,N′*-sulfinyldiimidazole (SDI) [14] or by conversion of corresponding hydroxyl derivatives **8a–o** *via* their chlorides to the desired heterocycles **10a–o**. Our early experiments showed that the use of the first method of approach (CDI or SDI) brought low yields or in any case did not form the expect imidazole derivative. It may be possible, instead of the desired compounds **10a–o**, imidazole-*N*-carboxylic ester intermediates are formed [13]. Therefore, we followed the second approach: the compounds **8a–o** were converted to the corresponding chlorides **9a–o** by refluxing with thionyl chloride in toluene. This reaction afforded sufficiently pure chlorides **9a–o**, which were used without further purification. The condensation of crude chlorides **9a–o** with two equivalents of 1*H*-imidazole provided target imidazole derivatives **10a–o** and the formation of imidazole hydrochloride as a by-product. Compounds **10a–o** were isolated in good yields (Table 1) and purified by recrystallization.

The imidazole derivatives **10a–o** have one asymmetric carbon atom; however, we did not make any efforts for the separation of individual enantiomers in view of the fact that both enantiomers of bifonazole have been reported to possess the same antimycotic profile and potency [15].

The yields, melting points, and molecular formula of imidazole derivatives **10a–o** are listed in Table 1. All spectral data are in accordance with the assumed structures. In addition to the signals for aromatic protons, ^{1}H NMR spectra of the compounds **10a–o** reveal singlet at 3.39–3.47 ppm for the N-CH_3 protons from 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone ring. Furthermore, the spectra show singlet for methyne proton at the asymmetric carbon atom in range 6.53–6.92 ppm.

IR spectra of compounds **10a–o**, containing 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone ring showed carbonyl bands at 1750–1795 cm^{-1} and 1650–1680 cm^{-1}, respectively.

Scheme 1



Compds. 7 - 10	X	R^1	R^2	R^3	R^4
a	O	H	H	H	H
b	O	H	Cl	H	H
c	O	H	H	Cl	H
d	O	H	H	H	Cl
e	O	H	Cl	H	Cl
f	O	Cl	H	H	H
g	O	Cl	Cl	H	H
h	O	Cl	H	Cl	H
i	O	Cl	H	H	Cl
j	O	Cl	Cl	H	Cl
k	S	H	H	H	H
l	S	H	Cl	H	H
m	S	H	H	Cl	H
n	S	H	H	H	Cl
o	S	H	Cl	H	Cl

Reagents and conditions: (i) $(CH_3)_2SO_4$, NaOH; (ii) benzoic acid or chloro substituted benzoic acid, PPA, 140°C; (iii) $NaBH_4$, CH_3OH; (iv) $SOCl_2$, toluene, reflux; (v) imidazole, toluene, reflux.

Table 1

Yields and physical data of compounds **10a-o**.

Compd	X	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)	Molecular formula
10a	O	H	H	H	H	80	144-145	$C_{18}H_{15}N_3O_2$
10b	O	H	Cl	H	H	82	143-144	$C_{18}H_{14}ClN_3O_2$
10c	O	H	H	Cl	H	60	124-125	$C_{18}H_{14}ClN_3O_2$
10d	O	H	H	H	Cl	68	108-110	$C_{18}H_{14}ClN_3O_2$
10e	O	H	Cl	H	Cl	50	167-168	$C_{18}H_{13}Cl_2N_3O_2$
10f	O	Cl	H	H	H	69	195-196	$C_{18}H_{14}ClN_3O_2$
10g	O	Cl	Cl	H	H	70	189-190	$C_{18}H_{13}Cl_2N_3O_2$
10h	O	Cl	H	Cl	H	55	232-234	$C_{18}H_{13}Cl_2N_3O_2$
10i	O	Cl	H	H	Cl	52	119-121	$C_{18}H_{13}Cl_2N_3O_2$
10j	O	Cl	Cl	H	Cl	53	208-210	$C_{18}H_{12}Cl_3N_3O_2$
10k	S	H	H	H	H	64	132-133	$C_{18}H_{15}N_3OS$
101	S	H	Cl	H	H	84	182-184	$C_{18}H_{14}ClN_3OS$
10m	S	H	H	Cl	H	78	149-150	$C_{18}H_{14}ClN_3OS$
10n	S	H	H	H	Cl	75	188-189[a]	$C_{18}H_{14}ClN_3OS \times HNO_3$
10o	S	H	Cl	H	Cl	70	196-197	$C_{18}H_{13}Cl_2N_3OS$

[a] Compound was isolated as a nitrate.

The new imidazole derivatives **10a–o** were evaluated *in vitro* against several pathogenic fungi responsible for human diseases using the twofold agar dilution method [16]. The results of this biological investigation did not report any significant activity against yeast. The most active compounds in the series showed weak antimicrobial activity against *Candida albicans*, *Candida parapsilosis*, and *Candida krusli* with MIC values 100–400 μM.

The results of the biological tests revealed that the replacement of the biphenyl portion of the bifonazole with 2(3*H*)-benzoxazolone or 2(3*H*)-benzothiazolone moiety afforded heterocyclic analogues, which are inactive as antimycotic agents toward *Candida* strains.

EXPERIMENTAL

Melting points were determined on a Boetius hot-stage microscope and are uncorrected. IR spectra (nujol) were recorded on a Specord 71 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker DRX 300 spectrometer operating at 300 MHz in $CDCl_3$. Chemical shifts were reported in δ units (ppm) relative to $(CH_3)_4Si$ as internal standard. Coupling constants (*J*) were reported in Hz. Elemental analyses (C, H, N, S) for final compounds were performed on a Vario III microanalyzer. Obtained results were within 0.4% of theoretical values. Thin layer chromatography (TLC) was carried out on Silica gel plates (Merck 60 F_{254}) using toluene–chloroform–ethyl acetate (3:1:1) and ethyl acetate–isopropanol (3:1) as eluent.

Ketones **7a–o** and corresponding alcohols **8a–o** were prepared according to the method described previously [17,18].

6-[(1*H*-Imidazol-1-yl)phenylmethyl]-3-methyl-2(3*H*)-benzoxazolone (10a). A solution of hydroxyl derivative **8a** (1.28 g, 5 mmol) in toluene (10 mL) and thionyl chloride (1 mL, 14 mmol) was refluxed for 30 min and then the excess of thionyl chloride was evaporated under reduced pressure. The obtained oil of **9a** was dissolved in toluene (15 mL) and imidazole (0.68 g, 10 mmol) was added. The mixture was refluxed for 6 h, until the chloride **9a** was no longer detectable (TLC). After cooling of the reaction mixture, 5% aqueous NaOH (10 mL) was added. The organic layer was washed with water and extracted with 10% HCl. The aqueous layer was neutralized with 10% NaOH, extracted with dichloromethane, dried ($MgSO_4$), and evaporated under reduced pressure. The obtained crude product **10a** crystallized slowly. Yield 1.22 g (80%), mp 144–145 °C (ethyl acetate); ir (nujol): 1765 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.41 (s, 3H, NCH_3), 6.56 (s, 1H, CH), 6.84–7.11 (m, 7H, ArH and ImH), 7.36–7.42 (m, 4H, ArH and ImH). Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C 70.81; H 4.95; N 13.76. Found: C 70.56; H 4.98; N 13.46.

6-[(2-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10b). This compound was obtained according to the procedure for **10a**, using compound **8b** as a starting material. Yield: 1.36 g (82%), mp 143–144 °C (hexane–ethyl acetate 1:1); ir (nujol): 1780 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.43 (s, 3H, NCH_3), 6.79–6.85 (m, 2H, ArH and ImH), 6.92 (s, 1H, CH), 6.95–6.96 (m, 3H, ArH and ImH), 7.14 (s, 1H, ArH), 7.28 (dt, 1H, ArH, J = 1.8 Hz, J = 7.8 Hz), 7.35 (dt, 1H, ArH, J = 1.8 Hz, J = 7.8 Hz), 7.42 (s, 1H, ImH), 7.45 (dd, 1H, ArH, J = 1.8 Hz, J = 7.8 Hz). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C 63.63; H 4.15; N 12.37. Found: C 63.90; H 4.18; N 12.44.

6-[(3-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10c). This compound was obtained according to the procedure for **10a**, using compound **8c** as a starting material. Yield: 1.02 g (60%), mp 124–125 °C (hexane–ethyl acetate, 1:1); ir (nujol): 1780 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.43 (s, 3H, NCH_3), 6.54 (s, 1H, CH), 6.85 (s, 1H, ImH), 6.96–7.08 (m, 5H, ArH and ImH), 7.14 (s, 1H, ArH), 7.33–7.36 (m, 2H, ArH), 7.44 (s, 1H, ImH). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C 63.63; H 4.15; N 12.37. Found: C 63.86; H 4.18; N 12.45.

6-[(4-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10d). This compound was obtained according to the procedure for **10a**, using compound **8d** as a starting material. Yield: 1.16 g (68%), mp 108–110 °C (cyclohexane–ethyl acetate, 1:1); ir (nujol): 1760 (C=O) cm^{-1}; ^{1}H

NMR ($CDCl_3$): δ 3.43 (s, 3H, NCH_3), 6.55 (s, 1H, CH), 6.84 (s, 1H, ImH), 6.95–6.96 (m, 3H, ArH and ImH), 7.02 (d, 2H, ArH, J = 8.4 Hz), 7.14 (s, 1H, ArH), 7.34 (d, 2H, ArH, J = 8.4 Hz), 7.44 (s, 1H, ImH). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C 63.63; H 4.15; N 12.37. Found: C 63.96; H 4.10; N 12.56.

6-[(2,4-Dichlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10e). This compound was obtained according to the procedure for **10a**, using compound **8e** as a starting material. Yield: 0.94 g (50%), mp 167–168 °C (ethyl acetate); ir (nujol): 1750 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.43 (s, 3H, NCH_3), 6.7 (d, 1H, ArH, J = 7.4 Hz), 6.81 (s, 1H, ImH), 6.85 (s, 1H, CH), 6.93–6.98 (m, 3H, ArH and ImH), 7.15 (s, 1H, ArH), 7.27 (dd, 1H, ArH, J = 2.0 Hz, J = 7.4 Hz), 7.39 (s, 1H, ImH), 7.48 (d, 1H, ArH, J = 2.0 Hz). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C 57.77; H 3.50; N 11.23. Found: C 57.68; H 3.62; N 11.07.

5-Chloro-6-[(1*H*-imidazol-1-yl)phenylmethyl]-3-methyl-2(3*H*)-benzoxazolone (10f). This compound was obtained according to the procedure for **10a**, using compound **8f** as a starting material. Yield: 1.17 g (69%), mp 195–196°C (ethyl acetate); ir (nujol): 1790 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.41 (s, 3H, NCH_3), 6.70 (s, 1H, CH), 6.81 (s, 1H, ImH), 6.91 (s, 1H, ArH), 7.05–7.07 (m, 3H, ArH and ImH), 7.13 (s, 1H, ArH), 7.34–7.40 (m, 4H, ArH and ImH). Anal. Calcd. for $C_{18}H_{14}ClN_3O_2$: C 63.63; H 4.15; N 12.37. Found: C 63.88; H 4.16; N 12.56.

5-Chloro-6-[(2-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10g). This compound was obtained according to the procedure for **10a**, using compound **8g** as a starting material. Yield: 1.31 g (70%), mp 189–190 °C (ethyl acetate); ir (nujol): 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.42 (s, 3H, NCH_3), 6.63 (s, 1H, CH), 6.76 (dd, 1H, ArH, J = 1.5 Hz, J = 7.5 Hz), 6.81 (s, 1H, ImH), 7.10 (s, 1H, ArH), 7.15 – 7.17 (m, 2H, ArH and ImH), 7.23 (dt, 1H, ArH, J = 1.5 Hz, J = 7.5 Hz), 7.33–7.39 (m, 2H, ArH and ImH), 7.46 (dd, 1H, ArH, J = 1.5 Hz, J = 7.5 Hz). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C 57.77; H 3.50; N 11.23. Found: C 57.83; H 3.49; N 10.86.

5-Chloro-6-[(3-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10h). This compound was obtained according to the procedure for **10a**, using compound **8h** as a starting material. Yield: 1.03 g (55%), mp 232–234 °C (toluene); ir (nujol): 1790 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.39 (s, 3H, NCH_3), 6.65 (s, 1H, CH), 6.81 (s, 1H, ImH), 6.89 (s, 1H, ArH), 6.93–6.96 (m, 1H, ArH), 7.04–7.15 (m, 3H, ArH and ImH), 7.31–7.41 (m, 3H, ArH and ImH). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C 57.77; H 3.50; N 11.23. Found: C 57.93; H 3.41; N 11.36.

5-Chloro-6-[(4-chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10i). This compound was obtained according to the procedure for **10a**, using compound **8i** as a starting material. Yield: 0.97 g (52%), mp 119–121 °C (cyclohexane–ethyl acetate, 2:1); ir (nujol): 1795 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.42 (s, 3H, NCH_3), 6.67 (s, 1H, CH), 6.80 (s, 1H, ImH), 6.88 (s, 1H, ArH), 6.99 (d, 2H, ArH, J = 7.0 Hz), 7.07 (s, 1H, ArH), 7.14 (s, 1H, ImH), 7.35–7.39 (m, 3H, ArH and ImH). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C 57.77; H 3.50; N 11.23. Found: C 58.09; H 3.72; N 11.27.

5-Chloro-6-[(2,4-dichlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzoxazolone (10j). This compound was obtained according to the procedure for **10a**, using compound **8j** as a starting material. Yield: 1.04 g (53%), mp 208–210 °C (toluene); ir (nujol): 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.42 (s, 3H, NCH_3), 6.61 (s, 1H, CH), 6.69 (d, 1H, ArH, J = 8.4 Hz), 6.79 (s, 1H, ImH), 7.09–7.15 (m, 3H, ArH and ImH), 7.27 (dd, 1H, ArH, J = 2.1 Hz, J = 8.4 Hz), 7.37 (s, 1H, ImH), 7.49 (d, 1H, ArH, J = 2.1 Hz). Anal. Calcd. for $C_{18}H_{12}Cl_3N_3O_2$: C 52.90; H 2.96; N 10.28. Found: C 52.79; H 3.22; N 10.33.

6-[(1*H*-Imidazol-1-yl)phenylmethyl]-3-methyl-2(3*H*)-benzothiazolone (10k). This compound was obtained according to the procedure for **10a**, using compound **8k** as a starting material. Yield: 1.03 g (64%), mp 132–133 °C (ethyl acetate); ir (nujol): 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.44 (s, 3H, NCH_3), 6.54 (s, 1H, CH), 6.84 (s, 1H, ImH), 6.99–7.13 (m, 6H, ArH and ImH), 7.35–7.43 (m, 4H, ArH and ImH). Anal. Calcd. for $C_{18}H_{15}N_3OS$: C 67.23; H 4.70; N 13.07. Found: C 67.09; H 4.55; N 13.43.

6-[(2-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzothiazolone (10l). This compound was obtained according to the procedure for **10a**, using compound **8l** as a starting material. Yield: 1.49 g (84%), mp 182–184 °C (cyclohexane–ethyl acetate, 1:1); ir (nujol): 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.47 (s, 3H, NCH_3), 6.81–6.84 (m, 2H, ArH and ImH), 6.91 (s, 1H, CH), 7.02–7.13 (m, 4H, ArH and ImH), 7.29 (dt, 1H, ArH, J = 1.8 Hz, J = 7.8 Hz), 7.34 (dt, 1H, ArH, J = 1.8 Hz, J = 7.8 Hz), 7.39 (s, 1H, ImH), 7.45 (dd, 1H, ArH, J = 1.8 Hz, J = 7.8 Hz). Anal. Calcd. for $C_{18}H_{14}ClN_3OS$: C 60.76; H 3.97; N 11.81. Found: C 60.87; H 3.99; N 11.62.

6-[(3-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzothiazolone (10m). This compound was obtained according to the procedure for **10a**, using compound **8m** as a starting material. Yield: 1.39 g (78%), mp 149–150 °C (ethyl acetate); ir (nujol): 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.47 (s, 3H, NCH_3), 6.53 (s, 1H, CH), 6.85 (s, 1H, ImH), 6.96–7.16 (m, 6H, ArH and ImH), 7.32–7.35 (m, 2H, ArH), 7.43 (s, 1H, ImH). Anal. Calcd. for $C_{18}H_{14}ClN_3OS$: C 60.76; H 3.97; N 11.81. Found: C 60.53; H 4.02; N 11.81.

6-[(4-Chlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzothiazolone nitrate (10n). This compound was obtained according to the procedure for **10a**, using compound **8n** as a starting material. The crude product **10n**, obtained as a viscous oily residue was dissolved in isopropanol and conc. HNO_3 was added. The obtained precipitate was collected by filtration and washed with cold isopropanol. Yield: 1.57 g (75%), mp 188–189 °C (isopropanol); ir (nujol): 2770–2250 (NH^+), 1660 (C=O) cm^{-1}. Anal. Calcd. for $C_{18}H_{14}ClN_3OS \times HNO_3$: C 51.62; H 3.61; N 13.38. Found: C 52.00; H 4.01; N 13.10.

6-[(2,4-Dichlorophenyl)(1*H*-imidazol-1-yl)methyl]-3-methyl-2(3*H*)-benzothiazolone (10o). This compound was obtained according to the procedure for **10a**, using compound **8o** as a starting material. Yield: 1.37 g (70%), mp 196–197 °C (ethyl acetate); ir (nujol): 1650 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.47 (s, 3H, NCH_3), 6.75 (d, 1H, ArH, J = 8.4 Hz), 6.81 (s, 1H, ImH), 6.85 (s, 1H, CH), 7.02–7.16 (m, 4H, ArH and ImH), 7.27 (dd, 1H, ArH, J = 1.8 Hz, J = 8.4 Hz), 7.38 (s, 1H, ImH), 7.48 (d, 1H, ArH, J = 1.8 Hz). Anal. Calcd. for $C_{18}H_{13}Cl_2N_3OS$: C 55.39; H 3.36; N 10.77. Found: C 55.78; H 3.46; N 10.55.

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