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Synthesis of Some New Benzimidazole Carbamate Derivatives for Evaluation of Antifungal Activity

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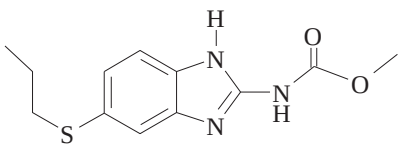
The synthesis and structure elucidation of methyl 5(6)-fluoro-6(5)-substituted-1H-benzimidazole carbamate derivatives are performed and their antifungal activities evaluated against *Candida albicans*.

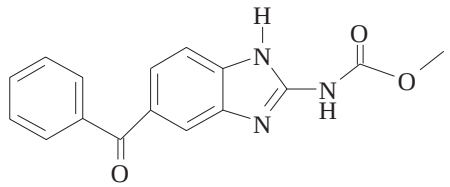
Key Words: Benzimidazole carbamates, synthesis, antifungal activity.

Introduction

Microtubules, which are found in all eucaryotic cells, are very important because of their role in cell mitosis. Benzimidazole derivatives have a broad antifungal spectrum and display their antifungal activities by blocking the polymerization of α- and β-tubulin subunits[1,2]. Antitubulin agents, especially benzimidazoles, disrupt microtubule function in eucaryotic organisms such as fungi, protozoa and helminths. So far many benzimidazole carbamate derivatives having a substituent at the 5(6) position have been reported and some of them, albendazole (I) and mebendazole (II), are approved as chemotherapeutic agents for human use.



(I)



(II)

Benzimidazole carbamates are useful for the treatment of *Giardia lamblia*[3], *Cryptococcus neoformans*[4], *Trichomonas vaginalis*[5], *Pneumocystis carinii*[6,7] and *Encephalitozoon intestinalis*[8]. They are also known to have antihelmintic activities. In connection with these studies, it was planned to synthesize some new

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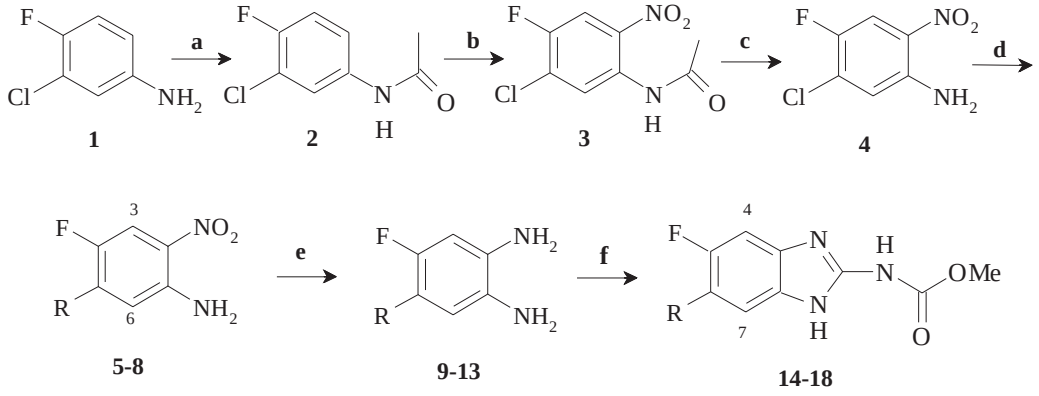
methyl benzimidazole carbamate derivatives having 5(6)-fluoro-6(5)-substituted heterocyclic rings and to investigate their antifungal activities against *C. albicans.*

Results and Discussion

The synthetic pathway for the preparation of the benzimidazoles listed in the Table is shown in the Scheme. The precursor **4** was synthesized as described by El-Abadelah et al.[9]. Nucleophilic substitution of the chlorine atom of **4** with morpholine gave compound **5**[10]. Unknown compounds **6-8** were synthesized by us using similar methods. Reduction of these compounds with tin (II) chloride/hydrochloric acid produced o-phenylenediamine derivatives **9-13,** which were used for the next step without purification. The reaction of **9-13** with 1,3-dicarbomethoxy-S-methyl-isothiourea[11,12] gave the desired benzimidazole carbamate derivatives **14-18**.



4	**9**	**14**	R = Cl
5	**10**	**15**	R = 4-morpholinyl
6	**11**	**16**	R = 1-pyrrolidinyl
7	**12**	**17**	R = 3-methylpiperidin-1-yl
8	**13**	**18**	R = (pyridin-3-ylmethyl)-amino

Scheme. Synthesis of the benzimidazole carbamates (**14-18**).

a: Acetic anhydride/pyridine, **b**: conc. H_2SO_4/conc. HNO_3, **c**: H_2SO_4/H_2O, **d**: appropriate amines, **e:** $SnCl_2$/HCl, **f**: 1,3-dicarbomethoxy-S-methylisothiourea/EtOH.

A structural evaluation of the new benzimidazole carbamate derivatives and the intermediates synthesized in this study was performed using various spectroscopic techniques. The IR spectra of carbamate derivatives **14-18** disclosed sharp bands at around 1698-1733 cm^{-1} (NHCOOH) and around 3336-3420 cm^{-1} (NH). The spectra of compounds **6** and **8** had two sharp bands at about 3439 cm^{-1}, 3305 cm^{-1} and 3477 cm^{-1}, 3365 cm^{-1} (NH_2), respectively. In the ^1H NMR spectra of the F-carrying compounds, the magnitude of the F-H coupling constant (J) and in the mass spectra of **14,** isotopes of chlorine atoms were seen as expected. All spectral data were in accordance with assumed structures. Physical and spectral data of compounds **5-8,14-18** are shown in Table 1.

Compounds **14-18** were tested for their in vitro antifungal activity against *C. albicans* by the agar diffusion technique[13] using a 1500 μg/ml solution in propylene glycol. Compound **18** exhibited slight activity against *C. albicans*, however, when their activity was compared with the standards, none of the new

Table. Physical and spectral data of compounds **5-8,14-18,** and antifungal activity[a] of compounds **14-18.**

Comp.	Mp (ºC)	Yield (%)	Formulae Calculated Found	^{1}H NMR (δ ppm)	Mass (70 eV , EI) ($M^{+\cdot}$, %)	*C.albicans*[a] IZ (mm)
5	180-181[b]					
6	177-179	85	$C_{10}H_{12}FN_3O_2$	(CDCl$_3$) 1.8 (4H, pyrrolidine CH_2), 3.3 (4H, pyrrolidine CH_2), 5.9(3H, H_6 and NH_2), 7.5 (d, 1H, J_{H3-F} =14).	225 ($M^{+\cdot}$,5), 194 (7), 178 (3), 157 (2), 107 (10), 41 (100).	
7	117-119[c]					
8	185-187	32	$C_{12}H_{11}FN_4O_2$ .0.1EtOH C: 54.91 H: 4.35 N: 21.0 C:55.33 H: 4.21 N:20.7	(CDCl$_3$) 4.3 (d, 2H, CH_2), 4.9 (1H, NH), 5.7 (d, 1H, J_{H5-F} =7), 6.02 (2H, NH_2), 7.25 (q,1H, pyridin H), 7.55 (1H, pyridin H), 7.7(d,1H, J_{H3-F} =13), 8.5 (dd, 1H, J_o=4.8, J_m =1.6, pyridin H), 8.6 (d, 1H, J_m =1.6, pyridin H).	262 ($M^{+\cdot}$, 1), 236 (6), 177 (9), 149 (2), 122 (2), 28 (100).	
14	>250	65	$C_9H_7ClFN_3O_2$ C: 44.37 H: 2.87 N:17.25 C: 44.58 H: 2.48 N:17.02	(DMSO-d$_6$ + CDCl$_3$) 3.79 (s, 3H, OCH_3), 7.27 (d, 1H, J_{H4-F} = 9.7), 7.45 (d, 1H, J_{H7-F} = 7), 10.49 (br.s, 2H, NH).	243 ($M^{+\cdot}$, 4.3), 245 (1.4), 211 (4.47), 213 (1.17), 183 (6), 156 (9), 121 (6), 95 (8), 59 (50), 28 (100).	9
15	>250	61	$C_{13}H_{15}FN_4O_3$ C:53.06 H: 5.14 N: 19.04 C:52.86 H: 4.74 N:18.77	(DMSO-d$_6$ + CDCl$_3$) 2.95 (4H, morpholine CH_2), 3.76 (7H, morpholine CH_2 and OCH_3), 6.94 (d, 1H, J_{H7-F} = 8), 6.98 (d,1H, J_{H4-F} = 13), 11.9 (br.s, 2H, NH).	294 ($M^{+\cdot}$, 75), 262 (16), 236 (46), 204 (58), 177 (24), 121 (19), 94 (18), 58 (38), 29 (100).	10
16	>250	58	$C_{13}H_{15}FN_4O_2$ C:56.08 H:5.43 N: 20.13 C: 55.64 H: 5.16 N: 19.88	(DMSO-d$_6$ + CDCl$_3$) 1.9 (4H, pyrrolidine CH_2), 3.2 (4H, pyrrolidine CH_2), 3.7 (s, 3H, OCH_3), 6.8 (d, 1H, J_{H7-F} = 8), 7.05 (d, 1H, J_{H4-F} = 13), 10.5 (br.s, 2H, NH).	278 ($M^{+\cdot}$, 22), 245 (53), 203 (19), 190 (30), 149 (12), 95 (21), 76 (21), 59(58), 32(100).	11
17	228	55	$C_{15}H_{19}FN_4O_2$. 1.4 H_2O C:54.34 H:6.58 N:16.9 C:54.08 H:6.18 N:17.3	(DMSO-d$_6$) 0.9 (d, 3H, C-CH_3), 1.1-3.3 (9H, piperidine H), 3.8 (s, 3H, OCH_3), 7.1 (d, 1H, J_{H7-F} = 8), 7.2 (d, 1H, J_{H4-F} =12), 11.5 (br.s, 2H, NH).	306 ($M^{+\cdot}$, 100), 273 (31), 219 (21), 204 (26), 177 (12), 59 (78).	11
18	239-241	38	$C_{15}H_{14}FN_5O_2$. 0.1 EtOH C: 57.07 H: 4.57 N: 21.90 C: 56.72 H: 4.42 N: 21.86	(DMSO-d$_6$ + CDCl$_3$) 3.6 (s, 3H, OCH_3), 4.3 (d, 2H, C$\underline{H_2}$-N), 5.4 (1H, CH_2-N$\underline{H}$), 6.5 (d, 1H, J_{H7-F} =8), 6.9 (d, 1H, J_{H4-F} = 12), 7.1 (1H, pyridin H), 7.6 (1H, pyridin H), 8.3 (1H, pyridin H), 8.4 (1H, pyridin H), 11(br.s, 2H, NH).	315 ($M^{+\cdot}$,22), 223 (26), 191 (29), 152 (11), 137 (12), 109 (15), 92 (100), 65 (56), 59 (54).	12
F						20
M						26

[a] Growth-inhibition zone diameter (mm) [b] Ref[10]: 182-183 ºC , [c] Ref[15]: 117-119 ºC , M: miconazole, F: fluconazole

benzimidazole carbamate derivatives exhibited significant antifungal activity against *C. albicans*. Inhibition zones (IZ) are listed in the Table.

Experimental

Silica gel plates (Merck F_{254}) and silica gel 60 (Merck; 230-400 mesh ATSM) were used for analytical and column chromatography, respectively. Melting points (uncorrected) were determined with a Büchi SMP-20 melting point apparatus. IR spectra were recorded on a Jasco FT/IR 420 spectrophotometer as potassium bromide disks. Microanalyses were performed on a Leco CHNS 932 analyzer and satisfactory results ± 0.4% of calculated values (C, H, N) were obtained. ^{1}H NMR spectra were measured on a Bruker AC400 NMR spectrophotometer. All chemical shifts were reported as ppm and coupling constants (J) were given in Hz. AN MS analysis was carried out on a VG Platform II mass spectrometer (70 eV) with EI methods. (TÜBİTAK Instrumental Analysis Lab., Ankara). N-(3-chloro-4-fluorophenyl)acetamide (**2**)[9], N-(5-chloro-4-fluoro-2-nitro-phenyl)acetamide (**3**)[9], and 4-chloro-5-fluoro-1,2-phenylenediamine (**9**)[14] were synthesized according to the literature methods.

Synthesis of 5-8

A solution of **4** (1 mmol) in a mixture of triethylamine (1 ml) and appropriate piperidine, pyridine derivatives, morpholine or pyrrolidine (2 mmol) was stirred at 60°C overnight. The resulting suspension was partitioned between water and ethyl acetate (1:2). The organic layer was dried over anhydrous sodium sulfate and evaporated. All of the compounds were recrystallized from ethanol, except compound **7,** which was purified by cc using chloroform:n-hexane (1:2) as the eluent before recrystallization.

Synthesis of 9-13

A solution of **4-8** (1 mmol) in concentrated hydrochloric acid (5 ml) was treated portionwise with tin (II) chloride (6 mmol) and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and neutralized with 10% sodium hydroxide solution, extracted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and evaporated and used for the next step without further purification.

Synthesis of benzimidazole carbamates 14-18

1,3-dicarbomethoxy-S-methylisothiourea (2 mmol) was added to a solution of **9-13** (1 mmol) in ethanol (15 ml) and refluxed for 8 h under nitrogen atmosphere. The reaction mixture was cooled and the separated solid was filtered out and crystallized from ethanol.

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