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Synthesis and antimicrobial evaluation of some new hydrazone derivatives of 6-(4-nitrophenyl)imidazo[2,1-*b*]thiazole-3-acetic acid hydrazide

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Abstract: In this study, some novel *N2*-arylidene/cycloalkylidene-(6-(4-nitrophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetic acid hydrazides (**2a-d**) were synthesized from (6-(4-nitrophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetic acid hydrazide (**1**). The newly synthesized compounds were characterized by IR, 1H NMR, mass and elemental analysis. Their antibacterial and antifungal activities were evaluated against *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *C. albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258, *T. mentagrophytes var. erinacei* NCPF 375, *M. gypseum* NCPF 580 and *T. tonsurans* NCPF 245. *N*2-Cyclohexylidene-(6-(4-nitrophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetic acid hydrazide (**2c**) and *N*2-(3-methylcyclohexylidene)-(6-(4-nitrophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetic acid hydrazide (**2d**) showed the highest antibacterial activity. Particularly **2c** showed the highest antifungal activity against tested fungi.

Key words: Imidazo[2,1-*b*]thiazole, arylidene/cycloalkylidenehydrazides, antibacterial activity, antifungal activity

Introduction

The problem of multi-drug resistant microorganisms has reached on alarming level around the world and for the treatment of microbial infections; the synthesis of new antiinfectious compounds has become an urgent need. Recently, considerable attention has been paid to the design

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and the biological activity of compounds bearing imidazo[2,1-*b*]thiazole scaffolds due to their broad spectrum of pharmacological activities, such as antifungal (Dangi et al., 2011; Juspin et al., 2010; Atta et al., 2011), antibacterial (Shetty et al., 2008; Lamani et al., 2009), anti-inflammatory (Jadhav et al., 2008) and antihypertensive properties (Budriesi et al., 2008), as well as being used as cystic fibrosis transmembrane conductance regulator (CFTR)-selective potentiators (Budriesi et al., 2011). In particular, many imidazo[2,1-*b*]thiazole derivatives have been reported to display potential antitumor activities against a variety of human cancer cell lines (Noolvi et al., 2011; Park & Oh, 2010; Kamal et al., 2010; Meriç et al., 2008; Andreani et al., 2008). Tetramisole (Raeymaekers et al., 1966) (Fig. 1) is one of the broad spectrum anthelmintic drug, whose discovery led to the search of different condensed imidazo[2,1-*b*]thiazole systems.

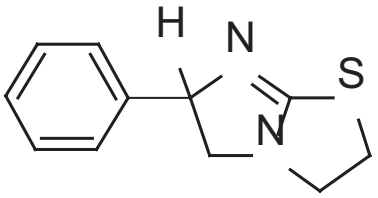

Figure 1. Chemical structure of Tetramisole.

In view of these facts and as a continuation of our research on the biological properties of imidazo[2,1-*b*]thiazole containing derivatives (Çapan et al., 1999; Ulusoy et al., 2000; Ulusoy, 2002; Ulusoy et al., 2002; Gürsoy & Ulusoy Güzeldemirci, 2007; Ulusoy Güzeldemirci & Küçükbasmacı, 2010; Ulusoy Güzeldemirci et al., 2013), we have designed and synthesized a number of arylidenehydrazides fused imidazo[2,1-*b*] thiazole systems, as potential antibacterial and antifungal agents.

Materials and methods

Chemistry

Melting points were determined by using a Büchi 530 melting point apparatus in open capillary tubes and are uncorrected. Elemental analyses

were performed on a Carlo Erba 1106 elemental analyzer. IR spectra were recorded on KBr discs, using a Perkin Elmer 1600 FT-IR

spectrophotometer. 1H NMR (*DMSO*-d_6/*TMS*) spectra were measured on a Bruker AC 200 (200 MHz) spectrometer. EI mass spectra were recorded on a VG Zab Spec (70 eV) instrument. The starting materials were either commercially available or synthesized according to the references cited.

Synthesis of N^2-arylidene/cycloalkylidene-(6-(4-nitrophenyl) imidazo[2,1-b]thiazol-3-yl)acetic acid hydrazides (2a-d)

A solution of appropriate aromatic aldehyde/cyclic ketone (0.005 mol) and (6-(4-nitrophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetic acid hydrazide (0.005 mol) (**1**) in absolute ethanol (30 ml) was refluxed for 6h and allowed to stand overnight. The precipitate obtained was purified either by recrystallization from EtOH or by washing with hot EtOH.

N^2-(4-Methoxybenzylidene)-(6-(4-nitrophenyl)imidazo[2,1-b]thiazol-3-yl)acetic acid hydrazide (2a)

IR (KBr, ν, cm^{-1}): 3210 (N-H), [1]655 (C=O); ^{1}H NMR (200 MHz, δ, ppm, DMSO-d_6): 3.79 (s, 3H, OCH_3), 3.92, 4.34 (2s, 2H, CH_2CO), 6.99 (d, 2H, J = 8.67 Hz, ar), 7.15 (s, 1H, C_2-H), 7.67 (d, 2H, J = 8.64 Hz, ar), 8.01-8.28 (m, 5H, =CH and ar), 8.55 (s, 1H, C_5-H), 11.64 (s, 1H, CONH); EIMS (70 eV) *m/z* (%): 435 (M^+, 100), 302 (14), 286 (82), 259 (89), 133 (13).

N2-Cyclopentylidene-(6-(4-nitrophenyl)imidazo[2,1-b]thiazol-3-yl) acetic acid hydrazide (2b)

IR (KBr, ν, cm^{-1}): 3210 (N-H), 1655 (C=O).

N2-Cyclohexylidene-(6-(4-nitrophenyl)imidazo[2,1-b]thiazol-3-yl) acetic acid hydrazide (2c)

IR (KBr, ν, cm-1): 3176 (N-H), 1668 (C=O); ^{1}H NMR (200 MHz, δ, ppm, DMSO-d_6): 1.60 (s, 6H, cyclohexylidene), 2.26, 2.41 (2s, 4H, cyclohexylidene), 3.89, 4.20 (2s, 2H, CH_2CO), 7.09 (s, 1H, C_2-H), 8.08 (d, 2H, J = 8.68 Hz, ar), 8.25 (d, 2H, J = 8.36 Hz, ar), 8.47 (s, 1H, C_5-H), 10.53 (s, 1H, CONH); EIMS (70 eV) *m/z* (%): 397 (M^+, 100), 302 (4), 286 (88), 259 (58), 96 (9).

N2-(3-Methylcyclohexylidene)-(6-(4-nitrophenyl)imidazo[2,1-b] thiazol-3-yl)acetic acid hydrazide (2d)

IR (KBr, ν, cm^{-1}): 3173 (N-H), 1665 (C=O).

Microbiology

Compounds to be tested were dissolved in DMSO at a stock concentration of 3200 µg.cm-3. The final desired concentration were prepared with RPMI 1640 medium for *Candida* species and dermatophytes and with Mueller-Hinton broth of bacteria. The final DMSO concentration was reduced to 1%.

Antibacterial activity

MICs were determined by the microbroth dilution method using the National Committee for Clinical Laboratory Standards (NCCLS) recommendations (CLSI, 2005). Mueller-Hinton broth (Oxoid, Hemakim, Turkey) was used as the test medium. An inoculum of approximately 5x105 CFU. cm^{-3} was delivered per well. Serial twofold dilutions of the test compounds (64-0.25µg. cm-3) and extra dilutions (0.12-0.015µg. cm-3) for antibiotic standards were prepared. Plates were incubated for 16-20h at 35oC in an ambient air incubator. The lowest concentration of the test compounds inhibiting visible growth was taken as the MIC value.

Antifungal activity

Antifungal activity for Candida species

MICs were determined by the microbroth dilution method using the NCCLS recommendations (NCCLS, 2002). RPMI broth was prepared from RPMI 1640 medium (Sigma, St. Louis, Mo, USA) supplemented with 0.3gof glutamine per dm3 , bufferred with 3- (N-morpholino)-propanesulfonic acid (MOPS) , and adjusted to pH 7.0. A working suspension of the inoculum was prepared by a 1:100 dilution of the 0.5 McFarland standards yeast suspension in 0.85% saline followed by a 1:20 dilution in RPMI broth.

Twofold dilutions of test compounds from 64 to 0.25 µg. cm^{-3} were prepared with the working suspension of the inoculum. Extra dilutions (0.12-0.015mg.cm-3) were added for itraconazole. The plates were incubated at

35oC for 48h in ambient air. The MIC is the lowest concentration of a compound that inhibits growth of the organism as detected visually.

Antifungal activity for dermatophytes

Microdilution method was used according to a standard protocol by NCCLS (CLSI, 2005). RPMI 1640 broth with L-glutamine without sodium bicarbonate was and 0.165 M MOPS buffer (34.54g/lt) and used. The medium was adjusted to pH 7.0 at 25°C. Preparation of inoculum suspensions of dermatophytes were based according to the NCCLS guidelines (NCCLS, 2002). and previously described procedure (Fernandez-Torres et al., 2002).

The isolates were subcultured on to potato dextrose agar (PDA) plates at 28°C, during 7-14 days. The fungal colonies were covered with 1 ml of sterile 0,85 % saline, and suspensions were made by gently probing the surface with the tip of Pasteur pipette. The resulting mixture of conidia and hyphal fragments was withdrawn and transferred to a sterile tube. Heavy particles were allowed to settle for 15-20 min at room temperature; the upper suspension was mixed with a vortex for 15 sec. The turbidity of supernatants was measured spectrophotometrically at a wavelength of 530 nm, and transmission was adjusted to 65 to 75 %. These stock suspensions were diluted 1:50 in RPMI medium to obtain the final inoculum sizes, which range from $0,4x10^4$ to $5x10^4$ CFU/ml. Microdilution plates were prepared and frozen at –70°C until needed. Rows from 2 to 12 contained the series of drug dilutions in 100 µl volumes and first row contained 100 µl of drug-free medium, which served as the growth control. Each well was inoculated on the day of the test with 100 µl of the corresponding inoculum. This step brought the drug dilutions and inoculum size to the final test concentrations given above. The microplates of dermatophytes were incubated at 28°C during 7 days. The microplates were read visually with the aid to an inverted reading mirror after 7 days for dermatophytes. For all drugs, the MIC was defined as the lowest concentration showing 100 % inhibition of growth.

Results and discussion

The target compounds were prepared from (6-(4-nitrophenyl) imidazo[2,1-*b*]thiazol-3-yl)acetic acid hydrazide (**1**) (Harraga et al., 1994),

by a three step synthesis as shown in Figure 2. Condensation of **1** with appropriate aromatic aldehyde/cyclic ketone afforded the corresponding *N2*-arylidene/cycloalkylidene-(6-(4-nitrophenyl)imidazo[2,1-*b*]thiazol-3-yl)acetic acid hydrazides (**2a-d**). The structures of the synthesized compounds were confirmed by physical (Table 1) and spectral data (IR, ^{1}H NMR, and EIMS).

Table 1. Some physical and analytical data of compounds **2a-d**.

Compd.	Formula (MW)	M.p. (°C)	Yield (%)	Analysis (%) (calc./found)		
				C	H	N
2a	$C_{21}H_{17}N_5O_4S.H_2O$ (453.49)	270	83	55.61 55.92	4.22 3.66	15.44 15.83
2b	$C_{18}H_{17}N_5O_3S.0,5H_2O$ (392.45)	267-268	74	55.08 55.32	4.62 4.76	17.84 18.09
2c	$C_{19}H_{19}N_5O_3S.1,5H_2O$ (424.48)	270	73	53.75 53.29	5.22 4.54	16.50 17.28
2d	$C_{20}H_{21}N_5O_3S$ (411.49)	269-270	85	58.37 57.67	5.14 4.96	17.02 16.96

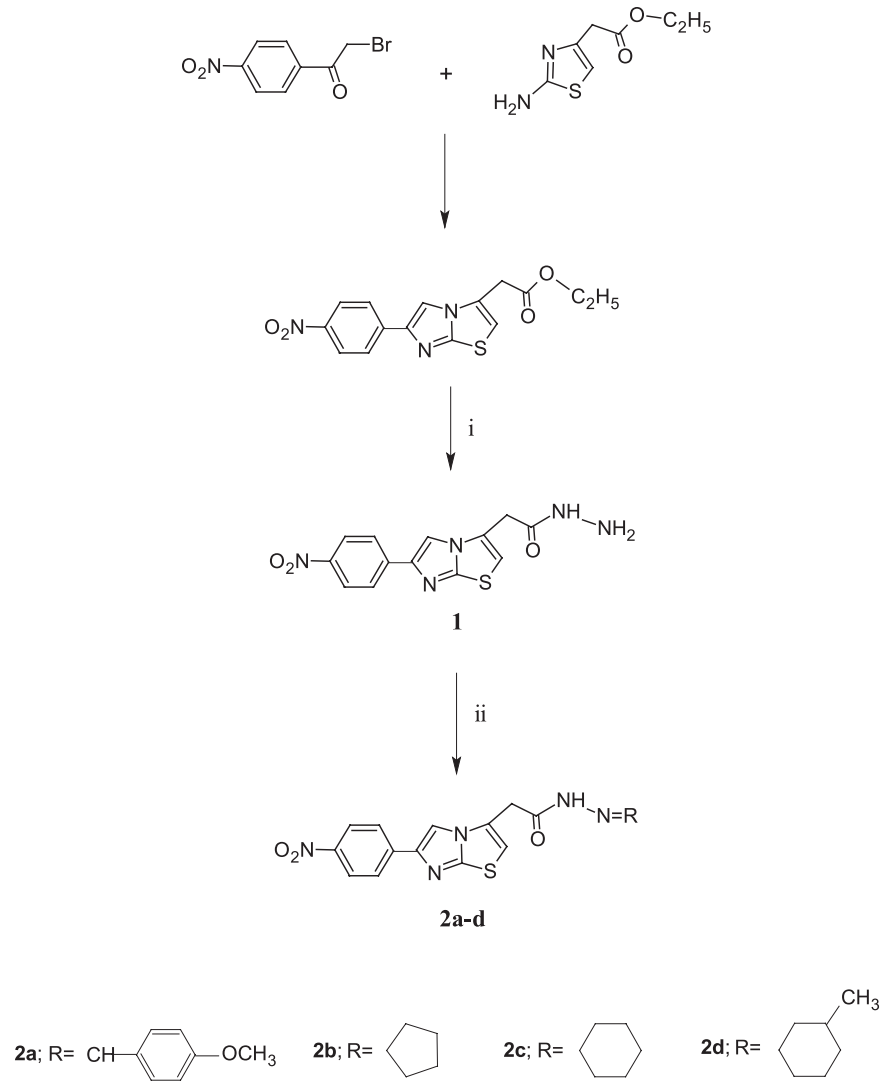

Figure 2. Synthesis of the title compounds. (i) $NH_2NH_2.H_2O$ (ii) ArCHO/cyclic ketone

The IR spectra of **2a-d** exhibited two separate bands resulting from the NH and CO bands of the amide function at about regions 3210-3173 and 1668-1655 cm^{-1} respectively (Çapan et al., 1996; Hogale et al., 1991). In the ^{1}H-NMR spectra of **2a** ve **2c** the CH_2 (δ 4.34-3.89 ppm) of the acetylamino moiety were observed as a double singlet presumably due

to the partial double bond character of the C-N bond and the bulk of the attached cyclohexyl structure which can disrupt free rotation about the cited bond (Somogyi, 1985). The protons of the imidazo[2,1-*b*]thiazole nucleus and the other protons resonated at the expected regions (Gürsoy & Ulusoy Güzeldemirci, 2007) The EIMS of compounds **2a** and **2c** displayed molecular ions which confirmed their molecular weights. Fragmentation followed the route in accordance with literature (Fig. 3) (Ulusoy, 2002).

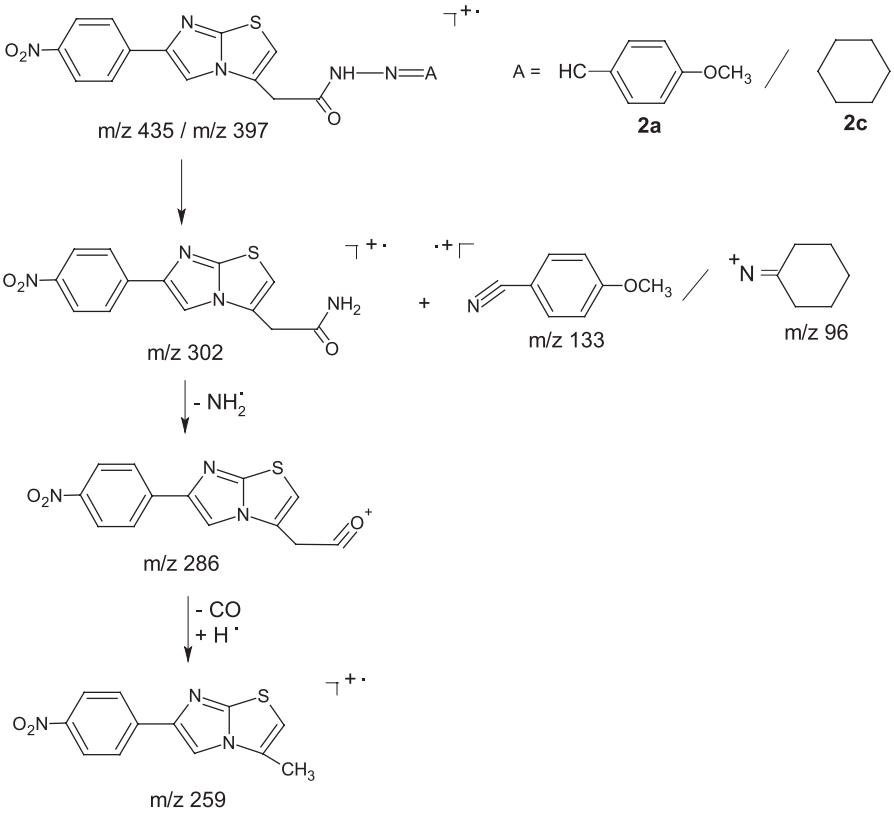

Figure 3. Proposed mass fragmentation pattern of **2a** and **2c**

Compounds **2a-d** were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 as well as for antifungal activity against *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258, *Trichophyton mentagrophytes var. erinacei* NCPF 375, *Microsporum gypseum* NCPF 580 and *Trichophyton*

tonsurans NCPF 245 using the microbroth dilution method (Clinical and Laboratory Standards Institute, 2005). As can be seen in Table 2, **2c** showed the highest activity against *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 (*MIC* = 32 μg.cm^{-3}). **2d** showed the highest activity against *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 (*MIC* = 32 μg.cm^{-3}).

Table 2. Antibacterial activity of compounds **2a-d** (MIC μg/mL)

Comp./ *microorg.	**30. A**	**31. B**	**32. C**
2a	64	>64	64
2b	n.t.	n.t.	n.t.
2c	32	>64	32
2d	64	32	32
Levofloxacin	0.12	0.5	0.015

***A=** *S. aureus* ATCC 29213, **B=** *P. aeruginosa* ATCC 27853,
C= *E. coli* ATCC 25922 n.t.= not tested

Compounds **2a** showed the highest activity against *Candida albicans* ATCC 10231, *Trichophyton mentagrophytes var. erinacei* NCPF 375 and *Trichophyton tonsurans* NCPF 245 (*MIC* = 16 μg.cm^{-3}). Compounds **2c** showed the highest activity against *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258, *Microsporum gypseum* NCPF 580 and *Trichophyton tonsurans* NCPF 245 (*MIC* = 16 μg.cm^{-3}). On the other hand, compound **2d** showed the highest activity against *Candida parapsilosis* ATCC 22019 (*MIC* = 16 μg.cm^{-3}). (Table 3).

Table 3. Antifungal activity of compounds **2a-d** (MIC µg/mL)

Comp./ *microorg.	**A**	**B**	**C**	**D**	**E**	**F**
2a	16	32	32	16	32	16
2b	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
2c	32	16	16	32	16	16
2d	32	16	32	32	32	32
Itraconazole	0.12	0.06	0.12	n.t.	n.t.	n.t.
Amphotericin B	n.t.	n.t.	n.t.	0.5	0.5	0.25

***A=** *C. albicans* ATCC 10231, **B=** *C. parapsilosis* ATCC 22019, **C=** *C. krusei* ATCC 6258,
D= *T. mentagrophytes var. erinacei* NCPF 375, **E=** *M. gypseum* NCPF 580, **F=** *T. tonsurans* NCPF 245

n.t.= not tested

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