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Research Article

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Structure–Activity Relationship Study of Thiosemicarbazones on the Fungi *Candida Albicans*

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ABSTRACT
The work aimed at synthesizing and studying the structure-activity relationship of some thiosemicarbazones on *Candida abicans* MHMR. After their synthesis, thiosemicarbazones of fifteen aldehydes and ketones were confirmed by their IR, ^{1}H and ^{13}C NMR spectra and in mass spectrometry.The biological activity of these compounds was tested *in vitro* against the growth of strains of *Candida abicans* MHMR. it appears that the presence of a benzene ring in R_2 and that of a hydrogen, a methyl group or phenyl in R_1 thiosemicarbazone are favorable for the inhibition of *Candida abicans*.

KEYWORDS: Thiosemicarbazones; spectrometric confirmation; antifungal; structure-activity relationship

INTRODUCTION

Candida albicans is a yeast found in human mucous membranes. This saprophyte, which is usually harmless to humans, is however responsible for important oral fungal and gynecological infections in certain immunocompromised patients [1, 2, 3]. In recent decades, candidiasis caused by this yeast is a real public health problem because of the spread of diseases such as AIDS and diabetes that weaken the immune system of affected people [4]. Antifungal medications commonly used against Candida albicans are becoming less effective [5]. It is then necessary to develop new antifungal molecules active on Candida albicans. We chose thiosemicarbazones because they have many biological activities such as: antiviral [6], antibacterial [7-9], antimalarial [10], antitumor [11-17].

Thiosemicarbazones are also known for their antifungal properties [20, 21]. However, the

structure-activity relationship of thiosemicarbazones on Candida albicans has not yet been studied extensively. Furthermore, the cost of thiosemicarbazones synthesis is not expensive. In addition, thiosemicarbazones are important intermediates in drugs synthesis, formation of metal complexes and heterocycles such as thiadiazolines preparation [7, 22].

The aim of this work is to study the structure–activity relationships of thiosemicarbazones of ketones and aldehydes on *Candida albicans* in order to develop new active molecules in a safer chemotherapeutic approach.

MATERIALS AND METHODS

Chemistry

Ketones, aldehydes, and thiosemicarbazide hydrochloride used for synthesis of thiosemicarbazones are sold by Acros Organics and Aldrich. TLC analyses were performed using silica gel-precoated plates. The solvent used is dichloromethane / ethyl acetate (v/v 2/1). Thiosemicarbazones were purified by recrystallization in ethanol. Compounds purity was confirmed by LC/MS in mode APCI on column C18. The melting points were taken on a fusionometer eletrothermal 1A 9000. The spectrometric data were recorded with the following instruments: IR, Perkin Elmer FT-IR 286; ^{1}H NMR and ^{13}C NMR, Bruker 400. To synthesize thiosemicarbazones: a mixture of ketone or aldehyde (20 mmol dissolved in 100 mL of ethanol) and thiosemicarbazide (20 mmol dissolved in 20 ml of 1 N hydrochloric acid) is stirred until the thiosemicarbazone precipitates. The precipitate is filtered, dried, and recrystallized in ethanol (96°) to give thiosemicarbazone crystals

Microbiology

Determination of Minimal Inhibitory Concentration (MIC)

It is *Candida albicans* MHMR strain that was used for this study. MIC was determined by the liquid macro-dilution method described by Delarras (1998) [23] with visual assessment of growth in microorganisms. One milliliter of sterile distilled water was introduced into a series of 11 test tubes numbered from T1 to T11. One milliliter of the stock solution of thiosemicarbazone concentration 20 mg / ml was added to tube T1 from which successive (half) dilutions were made up to tube T10 to have concentrations of thiosemicarbazone of 10 mg / ml; 5 mg / mL; 2.5 mg / mL; 1.25 mg mL; 0.625 mg / mL; 0.312 mg / mL; 0.156 mg / mL; 0.078 mg / mL and 0.039 mg / mL. All tubes (T1-T11) inoculated with 1 mL of inoculum (106 CFU / mL) were incubated at 37 ° C for 24 h and examined for bacterial growth resulting in turbidity. The tube T11 is considered as a control. Nystatin, in serial dilutions of 50-0.02 µg/mL, was used as positive control. The MIC of a compound against a given strain is the smallest of the concentrations showing no visible growth of the seed with the naked eye.

Statistical analysis

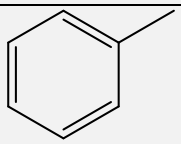
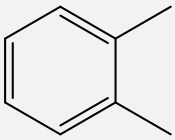
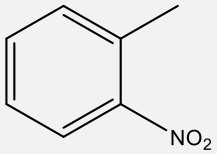
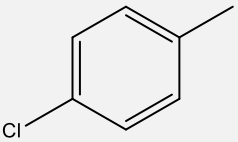
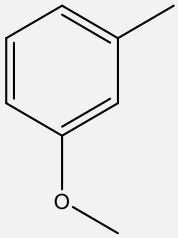
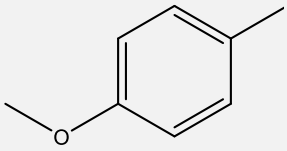
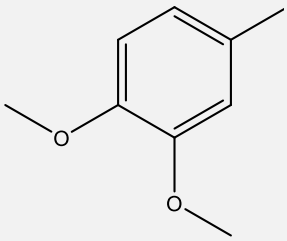
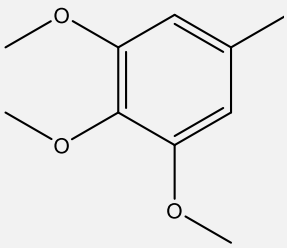
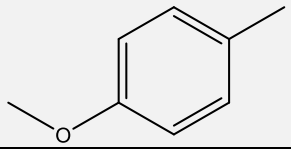
Student's t-test was used to test the significance of differences between results obtained for different samples, and between results for samples and controls (GraphPad Prism 4.0; GraphPad Software Inc., San Diego, USA). Statistical significance was set at $P < 0.05$ [24-25].

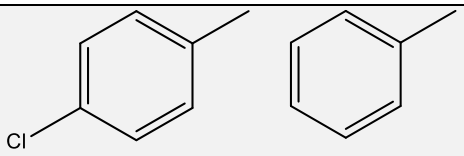
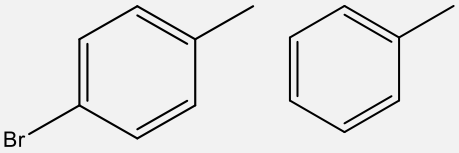
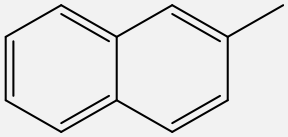
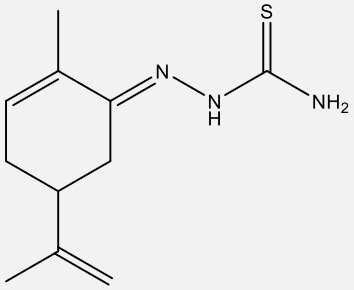
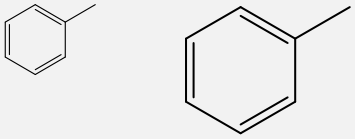
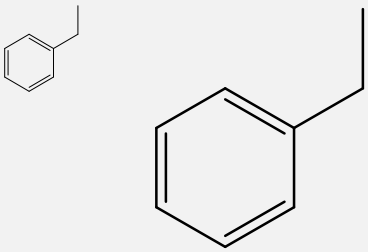
RESULTS AND DISCUSSION

Chemistry

Fifteen thiosemicarbazones were synthesized with yields going from 45 to 90 %.The use of a polar protic solvent such as ethanol, is good for the reaction. Yields are generally greater than 70 % except with the 2'-chloroacetophenone-thiosemicarbazone (45 %). This is generally the case of 2-substituted aryl ketones [26]. The physical data of these compounds are reported in Table 1. Thin layer chromatography (TLC) shows that thiosemicarbazones have Rf ranging from 0.62 to 0.98.

Table 1: Chemical structure, yield, and melting point of synthesized compounds (1-15)

Compounds	R_1	R_2	R_3	Yield (%)	*Rf*	M. P (°C)
1	H		H	65	0.80	162-163
2	H		H	55	0.87	180-181
3	H		H	90	0.78	254-255
4	H		H	78	0.82	212-213
5	H		H	85	0.78	192-193
6	$-CH_3$		H	89	0.82	180-181
7	$-CH_3$		H	82	0.75	224-225
8	$-CH_3$		H	74	0.62	215-216
9	$-CH_2-CH_3$		H	78	0.80	126-127

10	-CH_3			90	--	155-156
11	-CH_3			80	--	154-155
12	-CH_3		H	89	0.83	182-183
13				65	0.91	111-112
14			H	45	0.98	169-170
15			H	88	0.90	161-162

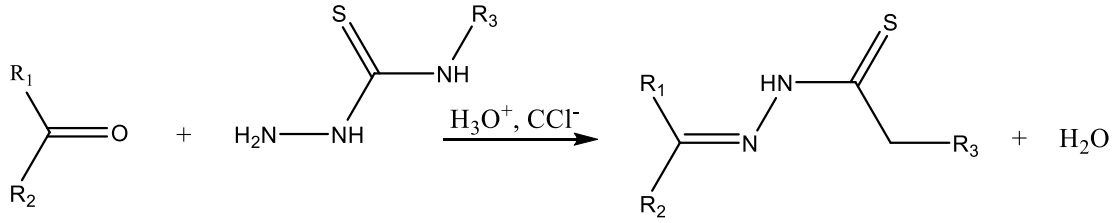


Fig. 1: Synthesis of thiosemicarbazones(1-15)

The spectrometric data are reported in below and are in conformity with the structures suggested for the products. Thus, IR spectra of thiosemicarbazones show bands in range of 3,455–3,139 cm^{-1} due to the stretching vibration of NH of thiosemicarbazones. In the ^{1}H NMR spectra this most deshielded proton, which is linked to the central nitrogen atom appears as a broadened singlet between 8.9 and 11.70 ppm.

The C=N bond; the junction between semicarbazide and the carbonyl compound that forms thiosemicarbazone stretching band appears at 1,588 or 1,587 cm^{-1}. In ^{13}C NMR spectra, this C=N bond is indicated by chemical shifts between 145 and 149 ppm. The presence of the vibration band of the C = N bond in the infrared spectra, as well as the confirmed chemical shift of the carbon of this bond in all

the ^{13}C NMR spectra of the synthesized thiosemicarbazones, prove that the condensation reaction between thiosemicarbazone and the carbonyl compound has worked well. Confirmation of the presence of this link is an important asset in the structural confirmation of thiosemicarbazones. While the chemical shift of the C=S bond appears between 176 and 180 ppm.

Spectrometric data

Benzaldehyde-thiosemicarbazone (1)

IR m (KBr cm^{-1}): 3401, 3145 (NH), 1600, 1584 (C=N).

^1H NMR d (DMSO-d_6 ppm): 7.39–7.79 (5H, several signals, ArH), 8.00 (1H, s, NH_2), 8.06 (1H, s, CH=N); 8.21 (1H, s, NH_2), 11.44 (1H, s, NH).

^{13}C NMR d (DMSO-d_6 ppm): 127.26–134.15 (Aromatic C), 142.24 (C=N), 177.97 (C=S).

2'-Methylbenzaldehyde-thiosemicarbazone (2)

IR m (KBr cm^{-1}): 3420, 3257, 3156 (NH), 1592 (C=N, C=C).

^1H NMR d (DMSO-d_6 ppm): 2.34 (1H, s, CH_3), 7.19–7.26 and 8.03 (4H, several signals, ArH), 7.83 (1H, s, NH_2), 8.19 (1H, s, NH_2), 8.40 (1H, s, CH=N), 11.34 (1H, s, NH).

^{13}CNMR d (DMSO-d_6 ppm): 18.83 (CH_3) from 125.96 to 136.75 and 159.54 (Aromatic C), 141.08 (C=N), 177.82 (C=S).

2'-Nitrobenzaldehyde-thiosemicarbazone (3)

IR m (KBr cm^{-1}): 3424, 3245, 3159 m (NH), 1539 (C=N, C=C).

^1H NMR d (DMSO-d_6 ppm): 7.63–8.02 and 8.41 (4H, several signals, ArH), 8.11 (1H, s, NH_2), 8.39 (1H, s, NH_2), 8.47 (1H, s, CH=N), 11.74 (1H, s, NH). ^{13}C NMR d (DMSO-d_6 ppm): 124.44–137.19 (Aromatic C), 148.22 (C=N), 178.45 (C=S).

4'-Chlorobenzaldehyde-thiosemicarbazone (4)

IR m (KBr cm^{-1}): 3437, 3281, 3165 m (NH), 1600, 1525 (C=N).

^1H NMR d (DMSO-d_6 ppm): 7.43–7.84 (4H, several signals, ArH), 8.03 (1H, s, CH=N), 8.07 (1H, s, NH_2); 8.24 (1H, s, NH), 11.49 (1H, s, NH).

^{13}C NMR d (DMSO-d_6 ppm): 128.65–134.22 (Aromatic C), 140.85 (C=N), 178.06 (C=S).

3'-methoxybenzaldehyde-thiosemicarbazone (5)

IR m (KBr cm^{-1}): 3396, 3279, 3155 (NH), 1576 (C=N, C=C).

^1H NMR d (DMSO-d_6 ppm): 3.80 (1H, s, OCH_3), 6.94–7.44 (4H, several signals, ArH), 8.02 (1H, s, CH=N); 8.06 (1H, s, NH_2), 8.22 (1H, s, NH_2), 11.43 (1H, s, NH).

^{13}C NMR d (DMSO-d_6 ppm): 55.25 (OCH_3), 110.91–135.57 and 159.54 (Aromatic C), 142.12 (C=N), 177.94 (C=S).

4-Methoxyacetophenone-thiosemicarbazone (6)

IR m (KBr cm^{-1}): 3400, 3247, 3162 (NH), 1588 (C=N).

^1H NMR d (DMSO-d_6 ppm): 2.26 (3H, s, CH_3), 3.78 (3H, s, O–CH_3), 7.39–7.52 (several signals, 4H of ArH and 1H of NH_2) 8.19 (1H, s, NH_2) 10.10 (1H, s, NH).

^{13}C NMR d (DMSO-d_6 ppm): 13.24 (CH_3) 54.59 (O– CH_3) from 112.94 to 129.45 and 159.61 (Aromatic C), 147.21 (C=N), 178.02 (C=S).

3',4'-Dimethoxyacetophenone-thiosemicarbazone (7)

IR m (KBr cm-1): 3376, 3267, 3155 (NH), 1588 (C=N).

1H NMR d (DMSO-d_6 ppm): 2.27 (3H, s, CH_3), 3.78 (3H, s, O– CH_3), 3.82 (3H, s, O– CH_3), 6.92–7.51 (3H, several signals, ArH), 7.88 (1H, s, NH_2), 8.22 (1H, s, NH_2), 10.06 (1H, s, NH).

13C NMR d (DMSO-d_6 ppm): 12.95 (CH_3) 54.45 (O– CH_3) 54.65 (O– CH_3) from 108.60 to 129.19 and 149.12, 147.49 (Aromatic C), 147.19 (C=N), 177.52 (C=S).

2',3',4'-Trimethoxyacetophenone-thiosemicarbazone (8)

IR m (KBr cm^{-1}): 3341, 3264, 3173 (NH), 1585 (C=N).

^1H NMR d (DMSO-d_6 ppm): 2.30 (3H, s, CH_3), 3.68 (3H, s, O– CH_3), 3.84 (6H, s, 2-O CH_3) 7, 12 (2H, s, ArH), 7.92 (1H, s, NH_2), 8.27 (1H, s, NH_2), 10.10 (1H, s, NH).

^{13}C NMR d (DMSO-d_6 ppm): 12.25 (CH3) 53.98 (2 O– CH_3) 57.91 (O– CH_3), 102.24 to 136.70 and 150.51 (Aromatic C), 146.12 (C=N), 176.60 (C=S).

4'-Methoxypropiophenone-thiosemicarbazone (9)

IR m (KBr cm^{-1}): 3433, 3278 (NH), 1596 (C=N).

^{1}H NMR d (DMSO-d_6 ppm): 1.01 (3H, t, CH_3), 2.83 (2H, q, CH_2), 3.78 (3H, s, O–CH_3), 6.92–7.87 (4H, several signals, ArH), 7.85 (1H, s, NH_2), 8.18 (1H, s, NH_2), 10.19 (1H, s, NH).
^{13}C NMR d (DMSO-d6 ppm): 11.01 (CH_3) 19.11 (CH_2) 55.17 (O–CH_3) from 112.96 to 128.06 and 160.17 (Aromatic C) 151, 78 (C=N), 178.70 (C=S).

1-(4-Chlorophenyl) ethylidene-4-phenylthiosemicarbazide (10)
IR m (KBr cm^{-1}): 3303, 3256 (NH), 1590, 1520 (C=N).
^{1}H NMR d (DMSO-d_6 ppm): 2.39 (3H, s, CH_3), 7.23–8.07 (9H, several signals, ArH), 10.10 (1H, s, NHArH); 10.65 (1H, s, NH).
^{13}C NMR d (DMSO-d_6 ppm): 14.22 (CH_3) from 125.36 to 139.40 (Aromatic C), 147.54 (C=N), 177.07 (C=S).

1-(4-Bromophenyl) ethylidene-4-phenylthiosemicarbazide (11)
IR m (KBr cm^{-1}): 3303, 3225 (NH), 1587, 1518 (C=N).
^{1}H NMR d (DMSO-d6 ppm): 2.38 (3H, s, CH3), 7.22–7.90 (9H, several signals, ArH), 10.10 (1H, s, NHArH); 10.65 (1H, s, NH).
^{13}C NMR d (DMSO-d_6 ppm): 14.23 (CH_3) from 122.93 to 139.13 (Aromatic C), 147.67 (C=N), 177.01(C=S).

Acetonaphthone-thiosemicarbazone (12)
IR m (KBr cm^{-1}): 3435, 3193 (NH), 1606 (C=N).
^{1}H NMR d (DMSO-d_6 ppm): 2.4 (3H, s, CH_3), 7.54–7.88 (7H, several signals, ArH), 8.00 (1H, s, NH_2) 8.38 (1H, s, NH_2), 10.30 (1H, s, NH).
^{13}C NMR d (DMSO-d_6 ppm): 11.89 (CH_3) from 122.18 to 133.19 (Aromatic C), 145.71 (C=N), 177.05 (C=S).

Carvone-thiosemicarbazone (13)
IR m (KBr cm^{-1}): 3415, 3259 (NH), 1598 (C=N).
^{1}H NMR d (DMSO-d_6 ppm): 1.82 (3H, s, CH_3), 1.9 (3H, s, CH_3) 2, 28 (4H, m, 2CH_2), 2.68 (1H, q, CH_2–CH_2–CH), 4.8 (2H, s, =CH_2), 5.1 (1H, t, CH=C), 6.3 (1H, s, NH_2), 7.81 (1H, s, NH_2) 10.3 (1H, s, NH).
^{13}C NMR d (DMSO-d_6 ppm): 19–22 (CH_3) 29–42 (CH_2CH and carvone) 109–150 (=CH and =CH_2), 148.29 (C=N), 176.16 (C=S).

Benzophenone-thiosemicarbazone (14)
IR m (KBr cm^{-1}): 3412, 3248, 3153 (NH), 1609 (C=N).
^{1}H NMR d (DMSO-d6 ppm): 7.35–7.47 (10H, several signals, ArH), 7.86 (1H, s, NH_2), 7.87 (1H, s, NH_2) 8, 65 (1H, s, NH).
^{13}C NMR d (DMSO-d_6 ppm): 127.55–136.29 (Aromatic C), 149.06 (C=N), 177.85 (C=S).

1,3-Diphenylacetone-thiosemicarbazone (15)
IR m (KBr cm^{-1}): 3336, 3296, 3228, 3138 (NH), 1601 (C=N).
^{1}H NMR d (DMSO-d_6 ppm): 3.48 (1H, s, CH_2), 3.75 (1H, s, CH_2), 7.12–7.25 (10H, several signals, ArH), 7, 43 (1H, s, NH_2), 8.21 (1H, s, NH2), 10.43 (1H, s, NH).
^{13}C NMR d (DMSO-d_6 ppm): 34.41 (CH_2) 42.35 (CH_2) 126.53–137.04 (Aromatic C), 152.36 (C=N), 179.03 (C=S).

Microbiology
The thiosemicarbazones synthesized were then tested on the pathogenic strain *Candida albicans* MHMR. The results are shown in Table 2. Thiosemicarbazones 1, 2, 5, 6, 7, 10, 11 and 14, more than half of the compounds synthesized were found to be active on *Candida Albicans* MHMR with MIC less than or equal to 5 mg / mL. Other thiosemicarbazones (3, 4, 8, 9, 12, 13 and 15) were less active with MIC greater than 6 mg / mL. Thiosemicarbzone 6 was the most active compound with a MIC of 0.625 mg / mL. But statistical analysis showed that this activity was significantly different on that of Nystatin (MIC = 6.24±0.01 µg / mL) the reference compound used in this test.

Table 2: Minimal inhibitory concentration (MIC) of synthesized compounds (mean ± sd, n = 3)

Compounds	IMC (mg/mL)
1	5.02±0.03[e]
2	2.50±0.01[d]
3	> 6
4	> 6
5	1.25±0.02[c]
6	0.625±0.05[b]
7	5.01±0.06[e]
8	> 6
9	> 6
10	1.25±0.02[c]
11	2.50±0.06[d]
12	> 6
13	> 6
14	1.25±0.05[c]
15	> 6
Nystatin	6.24±0.01[a*]

*Nystatin was used as positive control and the MIC value is given in µg/mL; *Means with different letters in exponent, differ significantly by *Newman-Keuls* test ($p \leq 0.05$)

Structure–Activity Relationship

Starting from benzaldehyde-thiosemicarbazone (1) as a reference with a MIC of 5 mg / mL, it was found that the presence of a donor methyl group in *ortho* position on the nucleus of the 2'-methylbenzadéhyde-thiosemicarbazone (2) doubles the activity with a MIC of 2.5 mg / mL. In addition, the presence of a donor activating group (methoxy) in the *meta* position in the compound 3'-methoxybenzaldehyde-thiosemicarbazone (5), further enhances the activity (MIC = 1.25 mg / mL). However, the presence of an acceptor nitro group in place of the methyl group in 2'- nitrobenzaldehyde-thiosemicarbazone (3) leads to a loss of inhibitory activity (MIC > 6 mg / mL). This same loss of activity was also observed with a disabling group (Cl) in the *para* position of the nucleus in 4'-Chlorobenzaldehyde-thiosemicarbazone (4, MIC > 6 mg / mL). A donor or activating group seemed to enhance the antifungal activity while an acceptor or disabling group showed opposite effect in *ortho*, *meta* or *para* position of the nucleus of the compound benzaldehyde-thiosemicarbazone (1). With a methoxy group in the *meta* position on the nucleus of 3'-methoxybenzadéhyde-thiosemicarbazone (5, MIC = 1.25 mg / mL) there is a four-fold greater inhibition than that of benzaldehyde-thiosemicarbazone (1, MIC = 5.02 mg / mL). The inhibition becomes eight times greater when the methoxy group goes to the *para* position on the nucleus and the hydrogen in R_1 is replaced by a methyl in 4'-methoxyacetophenone-thiosemicarbazone (6, MIC = 0.625 mg / mL). This considerable increase in the activity could be due to the mesomer donor effect of the *para* methoxy group which makes appear a negative charge on the nitrogen of the C= N group, increasing the proton exchange, the acidity of the compound and the antifungal activity. The inductive donor effect of the methyl group at R1 which destabilizes the negative charge on the nitrogen (C=N), seems to compete with the increase of the activity in the compound 6. This competition becomes visible in the compound 4'-

methoxypropiophenone-thiosemicarbazone (9) in which the ethyl group at R1, has a donor effect sufficient to cancel the activity (9, MIC > 6 mg / mL). The presence of an additional methoxy group in *mata* position of the nucleus of the compound 6 in the compound 3',4'-Dimethoxyacetophenone-thiosemicarbazone (7) leads to the loss of the activity (7, MIC = 5.01 mg / mL), which is not significantly different from that of the starting compound 1.

The binding of a third methoxy group in the second *mata* position of the nucleus of compound 6 in the compound 2',3',4'-trimethoxyacetophenone-thiosemicarbazone (8), enhances the loss of activity (8, MIC > 6 mg / mL). The methoxy groups in the *mata* positions exert non-conjugated mesomeric effects with the (C = N) group, which seems to compete with the conjugated effect of the methoxy in *para* and thus seems to be at the basis of the decrease of the antifungal activity.

The benzene ring also seems to play an important role in the inhibition because its replacement by a non-aromatic or bicyclic aromatic ring leads in cases to a loss of activity in the compounds acetonaphthone-thiosemicarbazone (12) and carvone-thiosemicarbazone (13) (12 and 13, MIC > 6 mg / mL). The substitution of the hydrogen R1 of the compound 1 by a second benzene ring in the compound benzophenone-thiosemicarbazone (14), increases the mesomeric effect conjugated with the C = N group and enhances the activity (14, MIC = 1,25 mg / mL). But when the two phenyl radicals of compound 14 are replaced by benzyl radicals with loss of conjugation with the C = N group, in compound 1,3-diphenylacetone-thiosemicarbazone (15), the activity strongly decrease (15, MIC > 6 mg / mL). These observations confirm the positive impact of the mesomeric effects conjugated with the C = N group, on the increase of the antifungal activity. In addition, the comparison of the inhibitory activity at the level of the compounds 1-(4-Chlorophenyl) ethylidene-4-phenylthiosemicarbazide (10) and 1-(4-Bromophenyl) ethylidene-4-phenylthiosemicarbazide (11) with the compoud 4 showed that the presence of phenyl group in R3 position increases the mesomeric effect conjugated with the C = S, and offset the negative impact of the presence of disabling (Cl and Br on the nucleus R2) on the studied activity. In this condition, the presence of chlorine (10, MIC = 1,25 mg / mL) is more beneficial than that of bromine (11, MIC = 2,25 mg / mL).

CONCLUSION

From this work which consisted in highlighting the structure-activity relationship of some thiosemicarbazones on *Candida abicans*, it appears that the presence of a benzene ring in R_2 or R_3 and that of a hydrogen, a methyl group or phenyl in R_1 of thiosemicarbazone are favorable for the inhibition of *Candida abicans*. This activity is enhanced by the presence of electron donor groups on the benzene ring, particularly in the ortho and para positions.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in this research article.

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