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Antifungal Activity of Aniline-Enfolded Substituted Thiourea Derivatives

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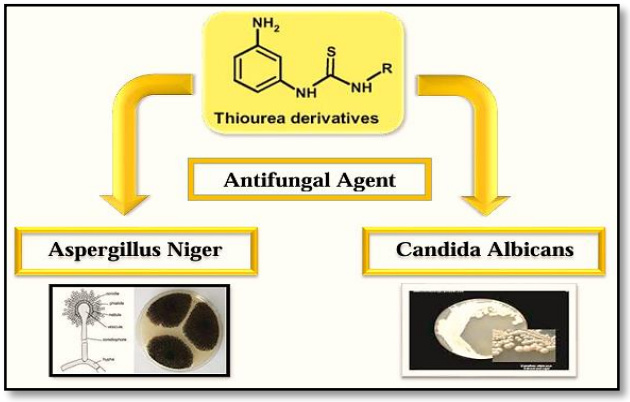
Abstract

Antifungal fugal activity of substituted thiourea derivatives enfolded with aniline tested against fungal strain Aspergillus Niger and Candida albicans. New series of thiourea derivatives were synthesized from aniline reflux with substituted thiourea. The antifungal activity of compounds was confirmed by Zone Inhibition Method in concentration of 50–1000 µg/mL. Substituted thiourea derivatives enfolded with aniline exhibited the most potent antifungal activity against fungal strain Aspergillus Niger, Candida albicans. These alkyl and acyl thioureas derivatives had significant inhibitory effect on the fungal strain. Minimum inhibition concentration (MIC) values in mm of antifungal thioureas derivative at max. Conc. 1000 µg/mL against Aspergillus niger strain were 13.67, 15, 12 while against Candida albicans strain were 7.33, 11 and 13.7 respectively. The initial structure-function link suggests that allyl and aromatic groups enhanced antifungal activities.

Graphical Abstract



Introduction

Heterocycles are an important class of molecules and thioureas constitute main heterocyclic compounds made up of nitrogen and sulfur the fact that are currently demonstrating possibilities in medical research. Because of the rapid rise of antibiotic resistance to currently available antimicrobial agents, diseases caused by bacteria and fungi continue to be a major global health problem after numerous significant developments in antibiotic treatment[1-3]. In addition, the rise in utilization and overuse of the available antimicrobial medicines has culminated in the growth of resistant infections.

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Due to their enzymatic activities and genetic information transfer, thioureas compounds can be especially significant to biological functions[4-5]. Also they used in several fields such as chemistry, medicine industry, and agriculture. Thiourea derivatives are effective against fungi like fusarium, aspergillus, and candida because they may interfere with enzymes produced by fungi and damage the structure of cell membranes. The compound's usefulness and specificity can be improved through replacing the thioureas base[6-8].

Fungal infections have become an increasing serious health problem due to its comparatively abundance and rapid growth of tolerance to the commonly used antifungal agents. Treatments with increased bioavailability and lower toxicity have also been developed. The distinction between contamination and infection can be difficult to make, and difficulties in diagnosing infection may delay the initiation of antifungal treatment [9-11]. Human fungal infections may be categorized into three types: (a) allergic reactions to fungal proteins, (b) toxic reactions to toxins present in specific fungi, and (c) infections (mycoses). Endogenous (Candida infections) or acquired from the environment (Cryptococcus, Aspergillus infections), are responsible for many fungal diseases. C. albicans, which is generally found in the oral cavity and gastrointestinal system of humans, and Aspergillus niger filamentous fungus that grows aerobically on organic materials create an illness black mould. Drug resistance evolved as a result of increasing consumption of antibiotics against fungi. Currently, toxicity and low effectiveness rates can limit the use of common antifungal treatments. Antifungal resistance develops through a variety of ways. Searching for a new heterocycle with distinct activity or versatile therapy has been stimulated by this [12-15].

A number of research groups have been interested in thiourea derivatives due to their potential in medicinal chemistry. Thiourea derivatives have been studied for their wide range of biological activity and fungicides. We present here our results about the antifungal assessment of thioureas against a variety of fungal strains, as part of our interest in the synthesis and screening of potential bioactive compounds. Based on the above considerations and as extension of our discovery for potential antimicrobial agents, we attempted to synthesize a new class of thioureas derivatives[16-17].

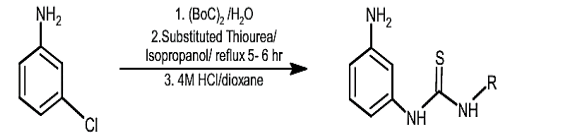
Method And Material

1. General

All chemicals are used of analytical grade. The melting points were determined on an open capillary tube and are uncorrected. Progress of the reaction was using thin-layer chromatography (TLC) in hexane: ethyl acetate (10:1) solvent system. IR spectra were recorded using FTIR Perkin Elmer (400 MHz) Spectrophotometer KBr disc.^{1}H NMR spectra were recorded using Brucker Avance (500 MHz) NMR Spectrometer instrument using $CDCl_3$ solvent and TMS as an internal standard, LCMS spectra were recorded by Waters Corporation (Alliance II-2795) micro mass spectrometer and CHNS analysis were done by Thermo Scientific (Flash 2000) elemental analyser.

2. Synthesis of 1-(3-aminophenyl)-3-substitutedthiourea:

3-chloroaniline and sustitutedthiourea were used for synthesized new series of 1-(3-aminophenyl)-3-substitutedthiourea. 3-chloroaniline (5 mmol) magnetic stirred with di-tert-butyl dicarbonate **(***BOC*) for protection of amino group, then resulting compound reflux with substitutedthiourea (5 mmol) in isopropanol about 5-6 hrs. Finally deprotection of amino group in acidic condition (4M HCl in methanol) to yield 1-(3-aminophenyl)-3-sustitutedthiourea derivatives. After that, it was rinsed with cold water and left to dry. Ethyl alcohol was utilized for additional recrystallize. applying single spot TLC in a mobile phase of hexane-ethyl acetate (10:1 volume ratio) helps monitor the reaction's progress.



3-chloroaniline — 3-(thiosubstitutedcarbamido) aniline

Spectral Analysis:

1-(3-aminophenyl)-3-ethylthiourea:

M.F. $C_9H_{13}N_3S$, *M.P.:* 73-75 ^{0}C,

I.R. (KBr pellets, ν in cm^{-1}): (N-$H_{stret.}$) 3438.16, (C-H) 2927.02, (C=C) 1600.93, (N-C=S) 1398.48, (N N >C=S) 1314.46, (C-N) 1088.79.

^{1}H-NMR (500MHz, $CDCl_3$, δ in ppm): 2.430-2.457 (t, 3H, CH_3), 4.458-4.481 (q, 2H, CH_2), 7.038-8.136 (m, 4H, Ar-H), 5.757 (s, 2H, Ar-NH_2), 8.143 (s, 1H, NH_2), 10.975 (s, 1H, N-H)

^{13}C NMR (500MHz, $CDCl_3$, δ in ppm): 16.61 (CH_3), 77.03 ($CDCl_3$), 43.48 (CH_2), 110.65-136.96, 147.78 (Ar-C), 178.57 (C=S)

CHNS Analysis: C, H, N % calc. 55.35, 21.52, 16.42. *Found* 55.34, 21.50, 16.40

Mass: m/z (M$^+$) 195.03, *M.W.* 195.08

3. Anti-fungal Susceptibility test:

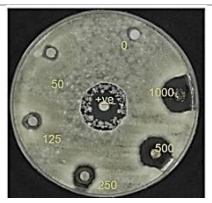
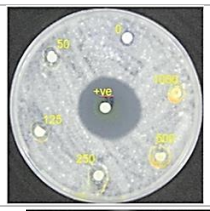
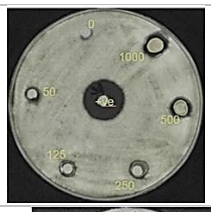
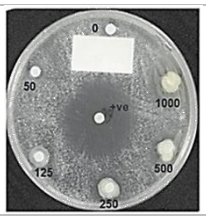
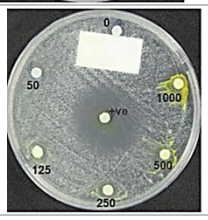
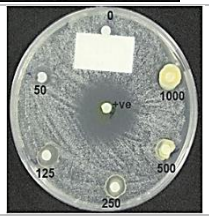
The antifungal activity was checked by following

Zone Inhibition Method. The MHA plates were inoculated by spreading with compound 100 µl of fungal strains A. niger (MTCC-281), C. albicans (MTCC-854) (adjusted to 0.5 McFarl and Unit Approx cell density (1.5 X 108 CFU/mL) and followed by placing the discs containing 10 µl of different concentration (0 to 100 mg/ml). 10 % of the compound was taken and serially diluted to achieve the required amount to be loaded on the disc. One disc in each plate was loaded with solvent (DMSO) alone which served as vehicle control and Amphotericin B (Amphocare)-5 mg/ml were taken as positive control. The plates were incubated at 37 °C for 24 hrs. A clear zone created around the disc were measured and recorded.

Results And Discussion

Table 1: Antifungal activity of 1-(3-aminophenyl)-3-substitutedthiourea against standard Antibiotic (Amphotericin B) and A. niger, C. albicans fungi

Compound code	Substitutedthiourea Compounds	Zone of inhibition(mm) Antifungal Activity (µg./disc)	
		A. niger	C. albicans
3(c)	*-Et*	*13.67*	*7.33*
3(d)	*-allyl*	*15*	*11*
3(e)	*-Ph*	*12*	*13.7*
Standard Antibiotic	*Amphotericin B*	*21.7*	*24*

Compounds / Fungal Strain	**3(c)**	**3(d)**	**3(e)**
Aspergillus Niger			
Candida albicans			

(Amount present on disk per µg, disperse volume 10 µl, positive control 10 µg)

Figure 1: Antifungal activity against test organisms

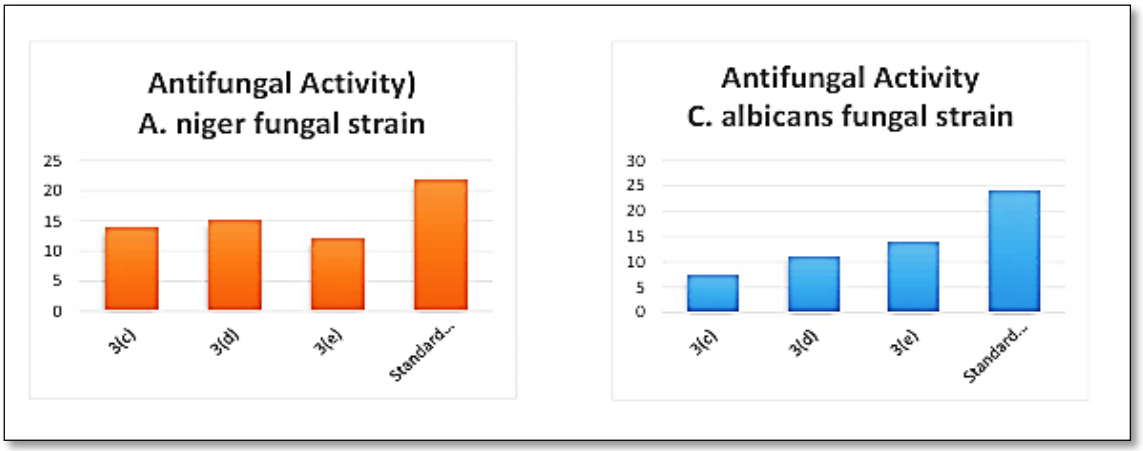


Figure 2: Graphical representation of Antifungal activity against test organisms

The results of the present investigation, a few new thiourea derivatives were evaluated for their antifungal activity against the fungus organisms Aspergillus Niger and Candida albicans. The standard drug Amphotericin B (Amphocare) was used to compare the antifungal activity of the compounds. The 1-(3-aminophenyl)-3-substitutedthiourea solution exhibited antifungal effects against Aspergillus Niger and Candida albicans when exposed to a range of 50–1000 µg/mL of disks on an agar plate. Compare this to the positive control's 21.7 mm diameter zone at a dose of 10 µg, the experimental study's zone of inhibition, 1-(3-aminophenyl)-3-allylthiourea, indicated 15 mm around the disk at the maximal dose of 1000 µg/mL. While compare this to the positive control's 24 mm diameter zone at a dose of 10 µg at a max. dose of 1000 µg/mL, 1-(3-aminophenyl)-3-phenylthiourea reported a maximal zone of inhibition of 13.7 mm against Candida albicans.

Conclusion

The thiourea derivatives displayed antifungal activity against Candida albicans and Aspergillus niger in the present studies. Although the molecule comprised a thiourea moiety, it exhibited an antifungal effect. As the compound 1-(3-aminophenyl)-3-substituted thiourea was investigated against a variety of fungi, it was shown to have a strong antifungal effect, as it responded effectively against Aspergillus niger and Candida albicans. The research results show potential thiourea compounds may be used in the development of antifungal drugs.For an understanding of the biological processes responsible for this antifungal response as well as assess these drugs' potential in clinical trials, further investigation is needed. Also, modifying the structure of thiourea derivatives could result in more potent antifungal agents in the future.

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Ethical Approval: This has not been published elsewhere and is not currently under consideration for publication elsewhere. This study does not involve experiments on animals or human subjects.

Conflict of interest: The authors declare that they have no conflict of interest.

Informed consent: Written informed consent was obtained from all individual participants included in the study.

Data and materials availability: All data associated with this study are present in the paper.

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