

## Antifungal Activity of Novel C-6 Methyl Substituted Benzothiazole Derivatives against *Candida albicans*

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### Abstract

**Background:** *Candida* species, especially *C. albicans* has commonly colonized the human skin surface and cause infection. However, skin barrier level defence mechanisms are very efficient. Therefore, the skin is an effective barrier against fungal infection.

**Methods:** C-6 methyl substituted benzothiazole derivatives were synthesized by reaction of methyl-chloro substituted aniline with potassium thiocyanate under temperature control and presence of bromine in glacial acetic acid and ammonia. Substituted nitrobenzamides then synthesized by condensation of C-6 methyl, 7-chloro and 2-amino substituted benzothiazole with 2 (3 or 4)-nitrobenzoylchloride acid in presence of dry pyridine and acetone.

Finally, newly synthesized derivatives (D-01 to D-09) were synthesized through replacing at 7<sup>th</sup> position chlorine by reaction with 2-nitroaniline, 3-nitroaniline, and 4-nitroaniline in presence of DMF. Antifungal activity was performed against *C. albicans* by cup plate method (diffusion technique) using Griseoflavin as standard.

**Results:** Compound D-02 and D-08 showed potent antifungal activity against *C. albicans* while compound D-01 and D-04 showed moderate inhibitory activity at both concentrations 50 µg/mL and 100 µg/mL as compared to standard.

**Conclusion:** Present work was based on the synthesis of substituted benzothiazole derivatives in order to find out the antifungal activity against *C. albicans*, since *Candida albicans* is mainly responsible for skin infection, especially in the epithelial cells of the vagina. The present work focused on the synthesis of newer derivatives having methyl substitution at a C-6 position of benzothiazole while 2-(3 or 4)-aryl-NO<sub>2</sub> considered as rotating substitution at C-2 and C-7 position of benzothiazole nucleus.

**Keywords:** *Candida albicans*; Skin infection; Vaginal infection; Benzothiazole; Antifungal activity; 2-substituted benzothiazole; 7-substituted benzothiazole; Nitro-benzothiazole; Cyclization of benzothiazole nucleus; Cup plate method (diffusion technique)

### Introduction

In the current scenario, different fungi especially *C. albicans* has been identified as human skin commensals that colonized on human skin [1,2]. Around 20%-25% of the world population is affected by symptomatic fungal skin infections caused by *C. albicans* [3]. The common symptoms of symptomatic fungal skin infections caused by *C. albicans* are thickening of the skin, hyperkeratosis, and erythema. The skin and mucosal surface infection caused by *C. albicans* is referred to as chronic mucocutaneous candidiasis, which occurs mainly in individuals with primary or acquired immunodeficiencies [4,5]. In the commensal, non-invasive state, *C. albicans* exists in the yeast form on the tissue surface. Yeast cells can be detected through the dectin-1 receptor (Dec1) that is expressed by Langerhans cells in the epidermis [6-11]. Interleukin-6 (IL-6)-dependent Th17 response was achieved by activation of Langerhans cells (LCs) and antimicrobial peptide production by keratinocytes and superficial antifungal defence. Commensal skin bacteria are also involved in preventing invasion of *C. albicans* into the skin by direct and indirect mechanisms [12-18]. *C.*

*albicans* invading the epidermis can moreover be detected by sensory neurons that promote IL-23 secretion by dermal dendritic cells and subsequent proliferation and IL-17 secretion of skin resident  $\gamma\delta$  T cells. Upon breaching of the epidermis, *C. albicans* is detected in the dermis by dermal dendritic cells which induce an IL-12- dependent Th1 response required for systemic immunity against the fungus. Antimicrobial defence supported by dermal fibroblasts directly in the dermis upon activation through TLR2 by *C. albicans* and IL-1 $\beta$  secretion and autoactivation. Secretion of IL-1 $\beta$  by dermal fibroblasts requires an additional yet unidentified signal from CD4<sup>+</sup> T cells [19-24].

Benzothiazole is a therapeutically important privileged bicyclic ring system contains sulphur and nitrogen as a heteroatom. Synthesis and screening of benzothiazole derivatives have great importance in heterocyclic chemistry because of its potent and significant biological activities [25-29]. Substitution at C-2, C-6 and C-7 at benzothiazole nucleus has emerged in its usage as a core structure in the diversified therapeutically applications [30-36]. As per reported biological activities of benzothiazole derivatives it was found that change of the structure of substituent group at C-2 and C-7 position commonly results in the change of its bioactivities. Commonly change of substitution at C-2 and C-7 at benzothiazole nucleus especially with methyl at C-6 has already been proven its therapeutic importance. Till

date various biological activities for benzothiazole derivatives have been reported as antitumor, antitubercular, antimalarial, anticonvulsant, anthelmintic, analgesic, anti-inflammatory, antibacterial and antifungal, a topical carbonic anhydrase inhibitor and an antihypoxic [37-39]. 2-substituted benzothiazole derivatives were first discovered in 1887 by A. W. Hofmann as simple cyclization mechanism and number of the synthetic scheme has been reported. The most common and classical method was reported as direct method that involved condensation of an ortho-amino thiophenol with a substituted aromatic aldehyde, carboxylic acid, acyl chloride or nitrile to synthesize C-2 substituted benzothiazoles, but it was found that this method is not appropriate for majority of substituted C-2 aryl benzothiazoles because main difficulty encountered in synthesis of the readily oxidisable 2-amino thiophenols bearing substituent groups. For above said reason some other methods were reported and extensively used in the laboratories that based on the use of the potassium ferricyanide radical cyclization of thiobenzanilides. This method was named as Jacobsen cyclization and popularized because it produced only one product. As per reported method, it involved cyclization onto either carbon atom ortho to the anilido nitrogen.

Because of selective product synthesis, the Jacobsen cyclization was considered as a highly effective strategy for benzothiazole synthesis e.g. for the synthesis of C-6 substituted benzothiazoles, radical cyclization of the 3-fluoro-or 3,4-difluoro-substituted thiobenzanilides. The literature review also reveals that change of substituents at C-2, C-6 and C-7 interestingly changed bioactivity and considered to established structure-activity relationship [40-42].

## Materials and Methods

### Synthesis of substituted benzothiazole (compound code 1-SB)

Synthesis of substituted benzothiazole nucleus was achieved by adding 8 gm (0.08 mol) of potassium thiocyanate and 1.45 g (0.01 mol) of substituted aniline into 20 mL cooled glacial acetic acid in such a way that the temperature not exceeded above room temperature. Freezing mixture of ice and salt was used to control the temperature of reaction with continuous mechanical stirring. Again temperature control was maintained during the addition of a solution of 1.6 mL of bromine in 6 mL of glacial acetic acid using dropping funnel. The time of addition of bromine also considered to take around 105 mins to control temperature. During the addition of bromine, temperature was controlled to never rise beyond the room. As the addition of bromine was completed the solution stirred for 2 h but below room temperature. After that solution was again stirred at room temperature for 10 h and allowed to stand overnight to get precipitate followed by heating at 850°C on a steam bath after addition of 6 mL water and filtered hot (Filtrate-01). In the resulting precipitate 10 mL of glacial acetic acid was added and heated with at 850°C and filtered hot (Filtrate-02). Finally, both filtrate combined and cooled at room temperature followed by neutralization with concentrated ammonia solution to pH-6 to get precipitate. The resulting product treated with animal charcoal and recrystallized from benzene, ethanol of (1:1) to get substituted benzothiazole (1-SB, 66% yield).

### Synthesis of nitrobenzamide (compound code 2-SB, 3-SB, and 4-SB)

5.36 g (0.026 mol) of 2-(3 or 4)-nitrobenzoylchloride was dissolved in dry acetone. Product 1-SB separately dissolved in dry pyridine and added drop wise into the solution of 2-(3 or 4)-nitro-benzoylchloride with continuous stirring at room temperature. After complete addition stirring was continued for another 30 mins then transferred into 200 mL ice cold water. Finally recrystallized with ethanol to get intermediate nitrobenzamide compound 2-SB, 3-SB and 4-SB

### Synthesis of compound D-01 to D-09

0.008 mol of 2 (3 or 4) nitro-substituted aniline was refluxed with 2.7 g (0.0075 mol) of compound 2-SB, 3-SB and 4-SB separately for 2 h in the presence of DMF (Dimethylformamide). After 2 h reflux, mixture cooled at room temperature and poured into crushed ice. The solid was separated, dried and recrystallized with super dry alcohol to get novel benzothiazole derivatives D-01 to D-09 (Figure 1).

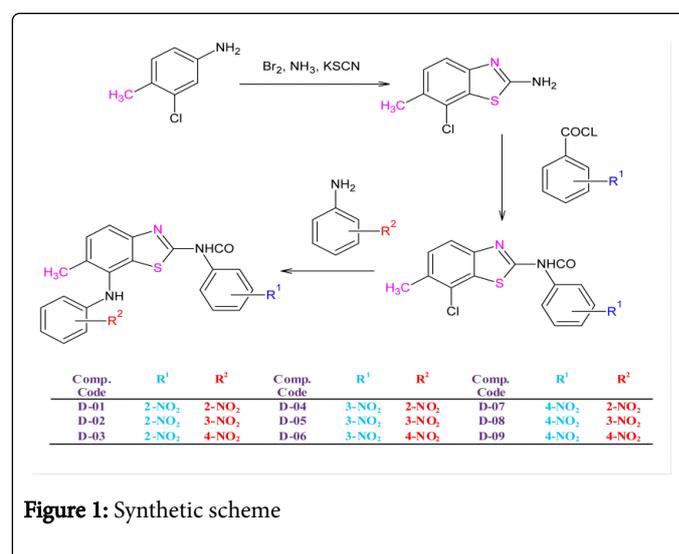


Figure 1: Synthetic scheme

### Analytical characterization

Thin layer chromatography (TLC) was used to monitor reaction progress, completion and identification of newly synthesized compounds from starting material using solvent system butanol: ethyl acetate: benzene (1:2:1) and detection performed by exposing them to iodine vapors. The melting point of compounds was determined using open capillaries method. Structure elucidation of compounds was done by IR and <sup>1</sup>HNMR spectral study.

SHIMADZU (8400S) used for IR spectral study (KBr pellet technique). For the structure elucidation using IR, frequency range for Ar-C=C, C=O, C-S, C-NO<sub>2</sub> were considered. Bruker AM 400 1H NMR instrument (at 400 MHz) was used using CDCl<sub>3</sub> as a solvent and tetramethylsilane (TMS) as an internal standard. For structure elucidation by <sup>1</sup>HNMR, NH proton that characterized benzothiazole was considered.

### Antifungal activity against *C. albicans*

The synthesized compounds are screened against selected fungal strains *C. albicans* by using diffusion method and griseofulvin as a standard drug. Under the aseptic condition, 48 h old fungal culture

was inoculated into the nutrient broth and incubated for 48 h at 37°C ± 20°C in an incubator. Potato-dextrose agar media (20%) mixed with inoculated culture and poured into petri plates. Five bores are made at an equal distance by using sterile steel cork borer (8 mm in diameter) after solidification. Different concentrations (50 µg/mL and 100 µg/mL) of standard drug and synthesized compounds along with control (Dimethyl formamide) introduced in this plates and placed in a refrigerator at 8°C-100°C as cold incubation for two hours that allowed proper diffusion of the drug and synthesized compounds. The petri plates were transferred to the incubator and maintained at 37°C ± 20°C for 24-36 h after cold incubation. Zone of inhibition was observed by using vernier scale. The mean value of the zone of inhibition was measured in millimeter of two preparation of synthesized compounds (D-01 to D-09) and standard drug.

## Result and Discussion

The skin is similar to mucosal surfaces such as the oral and vaginal mucosa, as they are all stratified squamous epithelia. Yet there are also substantial differences, like different degrees of cornification in these tissues, and importantly, their local environment. The mechanisms underlying skin colonization and invasion by *Candida species* as well as host defense mechanisms are consequently overlapping with those found for mucosal surfaces. These findings have revealed both mechanisms of fungal recognition as well as immunological networks required to control these infections. Simple, often unicellular *in vitro* models furthermore have revealed initial mechanisms of pathogenesis in *Candida* infections. Recently, complex 3D tissue models of human

origin containing defined elements of the immune system have been shown to be particularly amenable for identifying and Modelling aspects of the antifungal defence of the human skin. These recent advances in setting up complex 3D-tissue models have shown great promise already and therefore will most likely offer additional approaches to dissect and study *Candida*-skin interactions in great detail in the near future. Benzothiazole contains sulphur and nitrogen as hetero atom but imparts biological activity while substitution at C-2, C-6 and C-7 position. In the present work, methyl substitution was at the C-6 position while 2-(3 or 4)-aryl-nitro considered as rotating substitution at C-2 and C-7 position of benzothiazole nucleus. The novel derivatives (D-01 to D-09) evaluated for antifungal activity against *C. albicans*. In the present work nitro group consider as rotating basis on ortho, meta and para position. The reason behind considering nitro group as substituent is the fungi rarely acquire resistance. TLC, melting point, IR and <sup>1</sup>HNMR were used for analytical characterization. In the TLC, the distance traveled by compound D-01 to D-09 was found to be different from that of the starting compound that proved synthesized compounds were different from parent one, even during TLC performance every time single spot was obtained, hence it also reveals that synthesized compounds were free from impurity as well as reaction was completed. Structure elucidation by IR spectroscopy frequency range for Ar C=C, C=O, C-S, C-NO<sub>2</sub> was considered. In case of structure elucidation of by <sup>1</sup>HNMR sharp characteristic signal at 7.14-7.60 ppm is observed and consider as NH proton (benzothiazole) in all the synthesized compounds (Table 1).

Compound Code	%Yield	Melting point (°C)	TLC (RF-value)	IR	<sup>1</sup> HNMR (400 Hz, DMSO-d6)
D-01	74	265	0.48	1469 cm <sup>-1</sup> Ar C=C, 1648 cm <sup>-1</sup> C=O, 1255 cm <sup>-1</sup> C-S, 1540 cm <sup>-1</sup> C-NO <sub>2</sub> .	δ 7.61, 7.64(s, 2H, NH), δ 3.37(s, 3H, CH <sub>3</sub> ), δ 7.19-7.76 (m, 10H, Ar-H)
D-02	71	259	0.52	1424 cm <sup>-1</sup> Ar C=C, 1634 cm <sup>-1</sup> C=O, 1265 cm <sup>-1</sup> C-S, 1547 cm <sup>-1</sup> C-NO <sub>2</sub> .	δ 7.58, 7.62(s, 2H, NH), δ 3.35(s, 3H, CH <sub>3</sub> ), δ 7.15-7.70 (m, 10H, Ar-H)
D-03	65	268	0.51	1423cm <sup>-1</sup> Ar C=C, 1622cm <sup>-1</sup> C=O, 1215cm <sup>-1</sup> C-S, 1534cm <sup>-1</sup> C-NO <sub>2</sub> .	δ 7.63, 7.75(s, 2H, NH), δ 3.33(s, 3H, CH <sub>3</sub> ), δ 7.17-7.72 (m, 10H, Ar-H)
D-04	68	270	0.55	1421cm <sup>-1</sup> Ar C=C, 1665cm <sup>-1</sup> C=O, 1243cm <sup>-1</sup> C-S, 1537cm <sup>-1</sup> C-NO <sub>2</sub> .	δ 7.65, 7.79(s, 2H, NH), δ 3.39(s, 3H, CH <sub>3</sub> ), δ 7.13-7.65 (m, 10H, Ar-H)
D-05	66	256	0.59	1440 cm <sup>-1</sup> Ar C=C, 1629 cm <sup>-1</sup> C=O, 1217cm <sup>-1</sup> C-S, 1532cm <sup>-1</sup> C-NO <sub>2</sub> .	δ 7.59, 7.55(s, 2H, NH), δ 3.31(s, 3H, CH <sub>3</sub> ), δ 7.23-7.71 (m, 10H, Ar-H)
D-06	70	269	0.48	1421cm <sup>-1</sup> Ar C=C,	δ 7.65, 7.81(s, 2H, NH),

				1615cm <sup>-1</sup> C=O, 1212cm <sup>-1</sup> C-S, 1554cm <sup>-1</sup> C-NO <sub>2</sub>	δ 3.34(s, 3H, CH <sub>3</sub> ), δ 7.22-7.77 (m, 10H, Ar-H)
D-07	55	264	0.65	1443cm <sup>-1</sup> Ar C=C, 1626cm <sup>-1</sup> C=O, 1222cm <sup>-1</sup> C-S, 1543cm <sup>-1</sup> C-NO <sub>2</sub>	δ 7.62, 7.66(s, 2H, NH), δ 3.37(s, 3H, CH <sub>3</sub> ), δ 7.17-7.70 (m, 10H, Ar-H)
D-08	65	255	0.62	1421cm <sup>-1</sup> Ar C=C, 1621cm <sup>-1</sup> C=O, 1258cm <sup>-1</sup> C-S, 1523cm <sup>-1</sup> C-NO <sub>2</sub>	δ 7.62, 7.81(s, 2H, NH), δ 3.41(s, 3H, CH <sub>3</sub> ), δ 7.21-7.70 (m, 10H, Ar-H)
D-09	58	267	0.54	1467cm <sup>-1</sup> Ar C=C, 1660cm <sup>-1</sup> C=O, 1244cm <sup>-1</sup> C-S, 1521cm <sup>-1</sup> C-NO <sub>2</sub>	δ 7.61, 7.74(s, 2H, NH), δ 3.32(s, 3H, CH <sub>3</sub> ), δ 7.13-7.79 (m, 10H, Ar-H)

**Table 1:** Analytical characterization of newly synthesized compounds

Antifungal activity performed at two concentration 50 and 100 µg/mL using griseofulvin as a standard drug against *C. albicans*. Compound D-02 and D-08 showed potent antifungal activity against *C. albicans* while compound D-01 and D-04 showed moderate inhibitory activity at both concentrations 50 µg/mL and 100 µg/mL as compared to standard (Table 2).

Compound code	<i>C. albicans</i>	
	50 µg/mL	100 µg/mL
Griseofulvin	18	28
D-1	07	12
D-2	17	26
D-3	09	16
D-4	10	18
D-5	11	21
D-6	10	18
D-7	11	19
D-8	17	25
D-9	13	22

**Table 2:** Result of antifungal activity

## Conclusion

In the present work C-6, methyl substituted novel benzothiazole derivatives were synthesized and screened for antifungal activity against *C. albicans*. The paucity of data showed that compound D-02 and D-08 showed potent activity and could be considered for further clinical trials as antifungal agents.

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