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SYNTHESIS, CHARACTERIZATION AND EVALUATION OF NOVEL 2-ARYL BENZOTHIAZOLE DERIVATIVES AS POTENTIAL ANTIFUNGAL AGENTS

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ABSTRACT: In the present study a series of novel 2-aryl substituted benzothiazoles were synthesized. The synthesized benzothiazole (BTA) derivatives were characterized physicochemically, by elemental analysis and spectral (IR and 1H-NMR) analysis. The synthesized compounds were screened for their *in-vitro* antifungal activity against *Candida albicans*, *Aspergillus niger* and *Cryptococcus neoformans* by cup plate method. The results revealed that three compounds namely BTA-3, BTA-9 and BTA-10 have better or equal antifungal activity compared to the standard fluconazole. Further research on benzothiazoles can warrant more consideration on benzothiazoles as prospective antifungal agents.

INTRODUCTION: Over the past two decades, the incidence of invasive fungal infections (IFIs) has markedly increased. It has been observed that in immunocompromised patients, such as patients undergoing organ transplants or anticancer chemotherapy and patients with AIDS have high morbidity and mortality rate associated with IFIs. This increase in IFIs has been combated by treating patients with potent pharmacologic immuno-modulators and broad-spectrum antibiotics [1, 2, 3, 4].

The clinically available antifungal agents can be divided into four categories including the polyenes (*e.g.*, Amphotericin B and Nystatin) [5], echinocandins (*e.g.*, Caspofungin and Micafungin) [6], anti-metabolites (*e.g.*, 5-fluorocytosine) [7], and azoles (*e.g.*, Fluconazole, Voriconazole and Itraconazole) [8].

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Azole antifungal agents are used as first-line antifungal drugs. They act by inhibiting fungal lanosterol 14α-demethylase (CYP51), which plays a central role in ergosterol biosynthesis [9, 10, 11]. Among these agents, fluconazole, the first triazole alcohol antifungal drug has narrow antifungal spectrum and has suffered severe drug resistance [12, 13]. In the search for better antifungal compounds, the structure of fluconazole has been modified and a variety of its analogues like itraconazole, voriconazole and ketoconazole were developed [14, 15, 16]. However, they have narrow antifungal spectrum, low bioavailability and faced the problem of drug resistance [17]. Thus, there was scope to develop better azole antifungal agents. As benzothiazoles serve as unique and versatile scaffolds for experimental drug design, in the present study various benzothiazole derivatives were synthesized, characterized by ^{1}HNMR and ATR IR techniques and were evaluated for their antifungal activity.

MATERIALS AND METHODS: All chemicals and solvents were supplied by Sigma Aldrich,

Merck, and CDH under certificate of purity. The melting range of the synthesized compounds was measured by Scientech-2211 digital auto melting/ boiling point apparatus. Proton magnetic resonance (^{1}HNMR) spectra were recorded on Bruker 400 MHz NMR spectrometer using $CDCl_3$ as solvent. Chemical shifts were reported in parts per million relative to internal standard tetra-methylsilane (TMS). IR spectra were recorded on Bruker- Alpha 1005151/06 ATIR spectrophotometer.

Reaction progress was checked by TLC using Merck Silica gel 60 F-254 coated glass plates. The solvent system used was n-Hexane: Ethyl acetate in the ratio of 2:3.

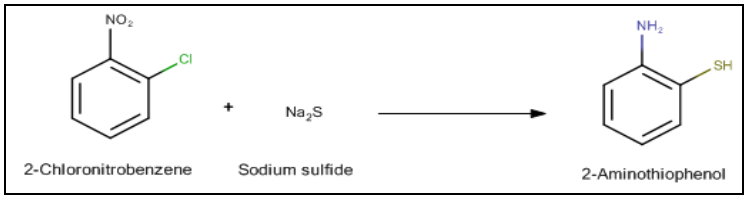
Synthetic Procedure:

Step I: For Synthesis of 2-aminothiophenol: A clear solution of sodium sulphide nonahydrate (4.8g, 0.02M) in water (20 ml) was prepared. 2-chloronitrobenzene (1.28g, 0.008M) was added to it in one single portion and the mixture was refluxed for 8 h. After 4 h, small amount of yellow coloured oil appeared in the reaction mixture due to the formation of 2-chloroaniline as the by-product. The reaction mixture was cooled after 8 hrs and then extracted with ether to remove 2-chloroaniline. The aqueous layer containing sodium salt of 2-aminothiophenol was saturated with sodium chloride and then acidified with glacial acetic acid. Addition of acetic acid should be done carefully to get the maximum yield of 2-amino-thiophenol [18].

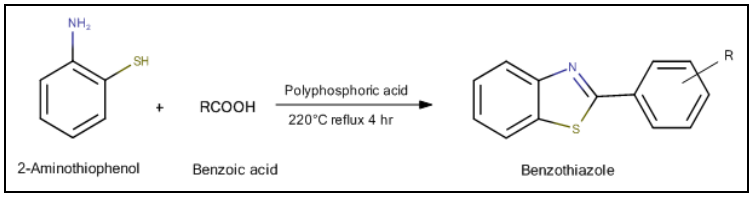
Step II: For Synthesis of Benzothiazoles:

Using 2-aminothiophenol and Benzoic Acid: Scheme II Equimolar quantities of 2-amino-thiophenol and substituted benzoic acid were added to 15g of polyphosphoric acid and refluxed for 4 h at 220 ºC. The reaction mixture was cooled and poured into a large volume of rapidly stirred ice cold water. The slurry was made alkaline with 50% sodium hydroxide solution. The progress of the reaction was monitored by TLC, using *n*-hexane: ethyl acetate in the ratio of 2:3 as the mobile phase. During the basification, ice was added to prevent an excessive rise in temperature. The crude product was obtained by extracting the reaction mixture with toluene and subsequent evaporation of the solvent in rotary vacuum evaporator followed by recrystallization from ethanol [19].

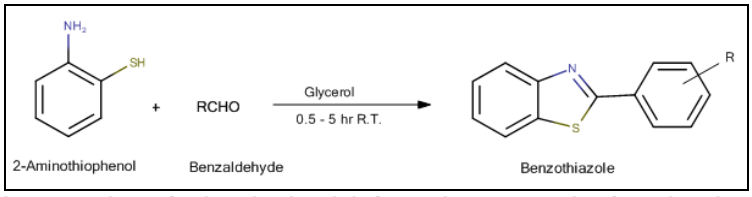
Using 2-aminothiophenol and Benzaldehyde: Equimolar quantities of 2-aminothiophenol (1.25 g, 10 mmol) and the appropriate aldehyde (10 mmol) in glycerol (10 ml) were heated until a clear solution was obtained and then left at room temperature for 0.5-5 h (TLC control). The reaction mixture was quenched with water and the resulting solid product was collected by filtration, dried and recrystallized from ethanol to afford final compounds [20].



STEP I: SYNTHESIS OF 2-AMINOTHIOPHENOL



SCHEME I: SYNTHESIS OF BENZOTHIAZOLES USING 2-AMINOTHIPHENOL AND SUBSTITUTED BENZOIC ACIDS



SCHEME II: SYNTHESIS OF BENZOTHIAZOLES USING 2-AMINOTHIPHENOL AND SUBSTITUTED BENZALDEHYDE

TABLE 1: LIST OF SYNTHESIZED COMPOUNDS

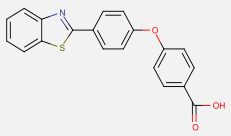
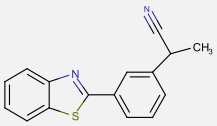
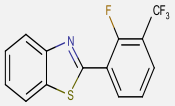
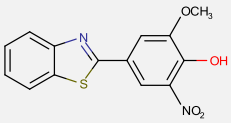
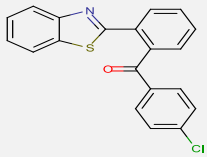
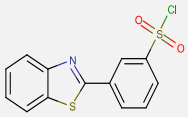
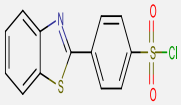
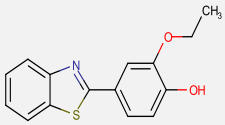
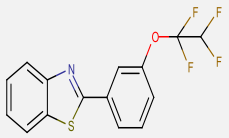
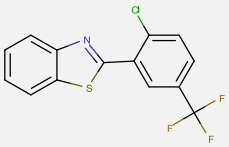
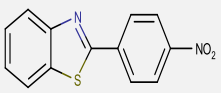
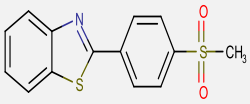
Name	Structure	IUPAC name
BTA-1		4-[4-(1,3-benzothiazol-2-yl) phenoxy] benzoic acid
BTA-2		2-[3-(1,3-benzothiazol-2-yl) phenyl] propanenitrile
BTA-3		2-[2-fluoro-3-(trifluoromethyl) phenyl]-1,3-benzothiazole
BTA-4		4-(benzothiazol-2-yl)-2-methoxy-6-nitrophenol
BTA-5		2-[2-(4-chlorobenzoyl) phenyl]-1,3-benzothiazole
BTA-6		3-(1,3-benzothiazol-2-yl)benzene-1-sulfonyl chloride
BTA-7		4-(1,3-benzothiazol-2-yl)benzene-1-sulfonyl chloride
BTA-8		4-(1,3-benzothiazol-2-yl)-2-ethoxyphenol
BTA-9		2-[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-1,3-benzothiazole
BTA-10		2-[2-chloro-5-(trifluoromethyl) phenyl]-1,3-benzothiazole
BTA-11		2-(4-nitrophenyl) benzothiazole
BTA-12		2-(4-methanesulfonyl phenyl)-1,3-benzothiazole

TABLE 2: PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

Name	Molecular formula	Molecular weight (g)	Melting point (˚C)	Yield (%)	Solubility
BTA-1	$C_{20}H_{13}NO_3S$	347.39	121-123	62	Chloroform, DMSO, Ethanol, Methanol
BTA-2	$C_{16}H_{12}N_2S$	264.34	114-120	71	Chloroform, DMSO, Ethanol
BTA-3	$C_{14}H_7F_4NS$	298	115-120	74	Chloroform, DMSO, Ethanol, Methanol
BTA-4	$C_{14}H_{10}N_2O_4S$	303.31	118-121	56	Chloroform, DMSO, Ethanol, Methanol
BTA-5	$C_{20}H_{12}ClNOS$	349.83	115-117	82	Chloroform, DMSO, Ethanol, Methanol
BTA-6	$C_{13}H_{18}ClNO_2S_2$	309.79	116-121	65	Chloroform, DMSO, Ethanol
BTA-7	$C_{13}H_{18}ClNO_2S_2$	309.79	117-119	83	Chloroform, DMSO, Ethanol, Methanol
BTA-8	$C_{15}H_{13}NO_2S$	271.22	125-127	70	Chloroform, DMSO, Ethanol, Methanol
BTA-9	$C_{15}H_8F_4NOS$	327.3	112-116	56	Chloroform, DMSO, Ethanol, Methanol
BTA-10	$C_{14}H_7ClF_3NS$	313.73	115-119	70	Chloroform, DMSO, Ethanol, Methanol
BTA-11	$C_{13}H_8N_2O_2S$	256.28	116-118	54	Chloroform, DMSO, Ethanol, Methanol
BTA-12	$C_{14}H_{11}NO_2S_2$	289.37	120-125	69	Chloroform, DMSO, Ethanol, Methanol

RESULTS AND DISCUSSION:

Chemistry: The benzothiazole derivatives were synthesized from cost effective materials like Sodium Sulphide and ortho chloro nitro benzene. All compounds were synthesized in appreciable yield. The structures of the synthesized compounds were established on the basis of ATR IR and ^{1}HNMR spectrophotometry. The result obtained from spectral analysis was found to be in accordance with the data reported in literature [19]. The major peaks were recorded at 1728-1605 cm^{-1} for C=N group, at 1365 - 1305 cm^{-1} and 722 - 640 cm^{-1} for C-S group, Absorption peaks for other functional groups were also observed in the respective derivatives. ^{1}HNMR: NMR peak for CH_3 group was found at δ1.53-3.99 ppm and for aromatic hydrogens (Ar-H) in the range δ6.99-8.32 ppm.

TABLE 3: SPECTRAL STUDY OF SYNTHESIZED COMPOUNDS

Name	IR spectra data	^{1}HNMR spectra data ($CDCl_3$)
BTA-1	1710.98ν (C=O), 1690.08 ν (C=N), 1515.41 ν (C-C), 1411.45ν (C=C), 1058.96 ν (C-O-C), 754.78 ν (Ar C-H), 686.54 ν (C-S)	δ11.0 (s, 1H, COOH), 8.32-8.00 (m, 4H, Ar-H), 7.55 (t, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.13 (d, 2H, Ar-H), 6.72 (d, 2H, Ar-H)
BTA-2	2303.91 ν (C≡N),1665.11 ν (C=N), 1585.15 ν (C-C), 1431.68 ν (C=C), 759.19 ν (Ar C-H), 645.11 ν (C-S)	δ 8.20-8.05 (d, 2H, Ar-H), 7.52 (t, 2H, Ar-H), 7.33-6.99 (m, 4H, Ar-H), 3.46 (m, 1H, CH), 1.57 (d, 3H, CH_3)
BTA-3	1607.75 ν (C=N), 1515.50 ν (C-C), 1465.28 ν (C=C), 1050.58 ν (C-F), 745.14 ν (Ar C-H), 692.81 ν (C-S)	δ 8.25-8.12 (d, 2H, Ar-H), 7.56 (t, 2H, Ar-H), 7.46 (d, 1H, Ar-H), 7.34 (d, 1H, Ar-H), 7.02 (t, 1H, Ar-H)
BTA-4	3376.99 ν (OH), 1615.35 ν (C=N), 1549.28 ν (C-C), 1468.13 ν (C=C), 1318.19 ν (C-N), 1041.48 ν (C-O-C), 799.98 ν (Ar C-H), 672.07 ν (C-S)	δ 8.32-8.00 (d, 2H, Ar-H), 7.88 (s, 1H, Ar-H), 7.52 (t, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 5.08 (s, 1H, OH), 3.99 (s, 3H, CH_3)
BTA-5	1801.85 ν (C=O), 1650.31 ν (C=N), 1515.40 ν (C-C), 1435.28 ν (C=C), 756.63 ν (Ar C-H), 722.64 ν (C-Cl), 692.40 ν (C-S)	δ 8.03-8.00 (d, 2H, Ar-H), 7.85 (d, 1H, Ar-H), 7.70 (d, 2H, Ar-H), 7.59-7.32 (m, 7H, Ar-H)
BTA-6	1610.16 ν (C=N), 1544.62 ν (C-C), 1409.12 ν (C=C), 1199.10 ν (SO_2Cl), 796.71 ν (Ar C-H), 679.41 ν (C-S)	δ 8.32-8.05 (m, 3H, Ar-H), 7.72 (d, 1H, Ar-H), 7.69 (d, 1H, Ar-H), 7.55 (m, 3H, Ar-H)
BTA-7	1605.61ν (C=N), 1506.82 ν (C-C), 1439.52 ν (C=C), 1204.16 ν (SO_2Cl), 754.50 ν (Ar C-H), 670.11 ν (C-S)	δ 8.15 (d, 1H, Ar-H), 8.12 (d, 1H, Ar-H), 7.99 (d, 2H, Ar-H), 7.72 (d, 2H, Ar-H), 7.54 (t, 2H, Ar-H)
BTA-8	3367.45 ν (OH), 1601.01 ν (C=N), 1508.41 ν (C-C), 1437.38 ν (C=C), 1039.98 ν (C-O-C), 750.17 ν (Ar C-H), 655 ν (C-S)	δ 8.59-8.05 (d, 2H, Ar-H), 7.49 (d, 2H, Ar-H), 6.97-6.68 (m, 3H, Ar-H), 4.65 (s, 1H, OH), 3.97 (m, 2H, CH_2), 1.53 (t, 3H, CH_3)
BTA-9	1728.86 ν (C=N), 1596.70 ν (C-C), 1439.12 ν (C=C), 1192.42 ν (C-F), 832.32 ν (Ar C-H), 722.53 ν (C-S)	δ 8.25 (d, 1H, Ar-H), 8.12 (d, 1H, Ar-H), 7.56 (t, 2H, Ar-H), 7.21 (t, 1H, Ar-H), 7.04- 6.73 (m, 3H, Ar-H)
BTA-10	1698.40 ν (C=N), 1515.09 ν (C-C), 1404.36 ν (C=C), 1077.57 ν (C-F), 789.28 ν (C-Cl), 742.04 ν (Ar C-H), 641.72 ν (C-S)	δ 8.32- 8.00 (d, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 7.55 (t, 2H, Ar-H), 7.40 (d, 1H, Ar-H), 6.72 (d, 1H, Ar-H)
BTA-11	1669.26 ν (C=N), 1586.48 ν (NO_2), 1516.91 ν (C-C), 1417.09 ν (C=C), 752.05 ν (Ar C-H), 657.15 ν (C-S)	δ 8.28- 8.04 (m, 4H, Ar-H), 7.73 (d, 2H, Ar-H), 7.51 (t, 2H, Ar-H)
BTA-12	1647.80 ν (C=N), 1523.76 ν (C-C), 1440.49 ν (C=C), 1022.14 (S=O), 802.37 ν (Ar C-H), 690.53 ν (C-S)	δ 8.31- 8.09 (d, 2H, Ar-H), 7.97 (d, 2H, Ar-H), 7.68(d, 2H, Ar-H) 7.55 (t, 2H, Ar-H), 2.41 (s, 3H, CH_3)

Antifungal Activity: All the synthesized compounds were evaluated for *in-vitro* antifungal activity against *Candida albicans*, *Aspergillus niger* and *Cryptococcus neoformans* at concentrations of

60µg/ml, 80µg/ml and 100µg/ml by cup plate method using DMSO as solvent control and fluconazole as standard. Sabouraud agar was employed as culture media. After 48 h of incubation at 37 ºC, the zone of inhibition was measured in mm.

Procedure: The Sabouraud agar medium was prepared by dissolving 40 g of dextrose, 10g of peptone, 15g of agar in 1000 ml distilled water. The pH was adjusted to 5.6 with hydrochloric acid. The Sabouraud agar so prepared was allowed to boil, after that it was autoclaved at 121 ºC, 15 Psig for 30 min and cooled to 45-50 °C. The medium was then inoculated aseptically with 0.5 ml of strains of *Candida albicans, Aspergillus niger* and *Cryptococcus neoformans* at room temperature.

The petriplates were sterilized by autoclaving. Into each sterile petridish about 15 ml of inoculated molten medium was poured. The plates were left at room temperature for solidification. After solidification, the cups of 6 mm diameter were made by scooping out the medium with the sterilized corn borer and were labelled.

All the synthesized compounds and reference were dissolved in DMSO to get required concentration of 60µg/ml, 80µg/ml and 100µg/ml. The solution of each compound, reference and a control (DMSO) were added separately into each cup. The plates were incubated for period of 48 h. The diameter of zone of inhibition was measured with the help of antibiotic zone reader.

RESULTS:

Antifungal Activity: All the 12 newly synthesized compounds were screened for antifungal activity at a concentration of 60µg/ml, 80µg/ml and 100µg/ml by cup-plate method against *Candida albicans, Aspergillus niger and cryptococcus neoformans*. Fluconazole was used as the standard drug. The results are summarized in the **Table 4**, **5** and **6**.

Candida albicans:

- BTA-3 at 100µg/ml showed better activity than the standard Fluconazole at 80µg/ml.
- BTA-3 and BTA-9 at 80µg/ml showed equal activity to the standard Fluconazole at 60µg/ml.
- BTA-9 and BTA-10 at 100µg/ml showed equal activity to the standard Fluconazole at 80µg/ml.

Aspergillus niger:

- BTA-10 at 100µg/ml showed better activity than the standard Fluconazole at 80µg/ml.
- BTA-9 and BTA-10 at 80µg/ml showed equal activity to the standard Fluconazole at 60µg/ml.
- BTA-3 and BTA-9 at 100µg/ml showed equal activity to the standard Fluconazole at 80µg/ml.

Cryptococcus neoformans:

- BTA-9 at 80µg/ml showed better activity than the standard Fluconazole at 60µg/ml.
- BTA-3 and BTA-9 at 100µg/ml showed better activity than the standard Fluconazole at 80µg/ml.
- BTA-9 at 100µg/ml showed better activity than the standard Fluconazole at 80µg/ml. BTA-3 and BTA-10 at 80µg/ml showed equal activity to the standard Fluconazole at 60µg/ml.

TABLE 4: DIAMETER OF ZONE OF INHIBITION (mm) OF COMPOUNDS AGAINST *CANDIDA ALBICANS*

Compound	Dilutions µg/ml		
	60µg/ml	80µg/ml	100µg/ml
BTA-1	-	-	8
BTA-2	-	9	10
BTA-3	12	20	30
BTA-4	10	14	20
BTA-5	-	-	10
BTA-6	8	12	18
BTA-7	-	12	16
BTA-8	6	10	14
BTA-9	14	20	26
BTA-10	12	18	26
BTA-11	-	8	12
BTA-12	-	6	10
Fluconazole	20	26	34

TABLE 5: DIAMETER OF ZONE OF INHIBITION (mm) OF COMPOUNDS AGAINST *ASPERGILLUS NIGER*

Compound	Dilutions µg/ml		
	60µg/ml	80µg/ml	100µg/ml
BTA-1	-	-	6
BTA-2	-	10	12
BTA-3	12	18	26
BTA-4	10	14	18
BTA-5	-	-	8
BTA-6	8	10	16
BTA-7	10	14	17
BTA-8	6	8	10
BTA-9	14	22	26
BTA-10	12	22	28
BTA-11	-	10	14
BTA-12	-	8	10
Fluconazole	20	26	34

TABLE 6: DIAMETER OF ZONE OF INHIBITION (mm) OF COMPOUNDS AGAINST *CRYPTOCOCCUS NEOFORMANS*

Compound	Dilutions µg/ml		
	60µg/ml	80µg/ml	100µg/ml
BTA-1	-	-	10
BTA-2	-	8	10
BTA-3	10	20	28
BTA-4	8	12	16
BTA-5	-	-	10
BTA-6	8	10	16
BTA-7	-	12	18
BTA-8	6	8	10
BTA-9	12	24	28
BTA-10	10	20	26
BTA-11	-	6	10
BTA-12	-	8	12
Fluconazole	20	26	34

From the results it can be concluded that three compounds namely BTA-3, BTA-9 and BTA-10 showed better or equal activity at slightly higher dose than the standard fluconazole.

CONCLUSION: All of the synthesized compounds (BTA-1 to BTA-12) were evaluated for their antifungal activity (MIC) *in-vitro* by cup plate method against fungal strains *Candida albicans, Aspergillus niger* and *Cryptococcus neoformans* taking fluconazole as standard drug. The results indicated that three compounds namely BTA-3, BTA-9 and BTA-10 showed better or equal antifungal activity compared to the standard Fluconazole. Probably the activity of these three compounds can be attributed to the presence of fluoro, trifluoromethyl and tertrafluoroethoxy groups at position C-2, C-3 and C-5 on the phenyl ring of 2-aryl benzothiazole nucleus. Keeping this fact in mind further research can be taken up in synthesizing fluoro based more benzothiazole derivatives to develop better antifungal drugs.

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REFERENCES:

1. Enoch DA, Ludlam HA and Brown NM: Invasive fungal infections: a review of epidemiology and management options. J Med Microbiol 2006; 55: 809-818.
2. Brown GD, Denning DW and Levitz SM: Tackling Human Fungal Infections. Science 2012; 336: 647-647.
3. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG and Chiller TA: Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. Aids 2009; 23: 525-530.
4. Jain, Jain S and Rawat S: Emerging fungal infections among children: A review on its clinical manifestations, diagnosis and prevention. J Pharm Bioall Sci 2010; 2: 314-320.
5. Arikan S, Rex JH, Nystatin LF: (Aronex/Abbott) Curr Opin Investig Drugs (London, England: 2000) 2001; 2: 488-495.
6. Denning DW: Echinocandin antifungal drugs. Lancet 2003; 362: 1142-1151.
7. Moudgal V and Sobel J: Antifungals to treat *Candida albicans*. Exp Opin Pharmacother 2010; 11: 2037-2048.
8. Heeres J, Meerpoel L and Lewi P: Conazoles. Molecules 2010; 15: 4129-4188.
9. Kathiravan MK, Salake AB, Chothe AS, Dudhe, Watode RP and Mukta MS: The biology and chemistry of anti-fungal agents: A review. Bioorg Med Chem 2013; 21: 1367-1367.
10. Aoyama Y, Yoshida Y and Sato R: Yeast cytochrome P-450 catalyzing lanosterol 14 alpha-demethylation. II. Lanosterol metabolism by purified P-450(14) DM and by intact microsomes. J Biol Chem 1984; 259: 1661-1666.
11. Jiang Z, Wang Y, Wang W, Wang S, Xu B and Fan G: Discovery of highly potent triazole antifungal derivatives by heterocycle-benzene bioisosteric replacement. Eur J Med Chem 2013; 64: 16-22.
12. Loeffler J and Stevens DA: Antifungal drug resistance. Clin Infect Dis 2003; 36: S31-S41.
13. Prasad R, Shah AH and Rawal MK: Antifungals: Mechanism of action and drug resistance. Adv Exp Med Biol 2016; 892: 327-349.
14. Jiang Z, Gu J, Wang C, Wang S, Liu N and Jiang Y: Design, synthesis and antifungal activity of novel triazole derivatives containing substituted 1,2,3-triazole-piperdine side chains. Eur J Med Chem 2014; 82: 490-497.
15. Cao X, Xu Y, Cao Y, Wang R, Zhou R and Chu W: Design, synthesis and structure-activity relationship studies of novel thienopyrrolidone derivatives with strong antifungal activity against *Aspergillus fumigates*. Eur J Med Chem 2015; 102: 471-476.
16. Sheehan DJ, Hitchcock CA and Sibley CM: Current and emerging azole antifungal agents. Clin Microbiol Rev 1999; 12: 40-79.
17. Castelli VM, Butassi E, Monteiro CM, Svetaz LA, Vicente F and Zacchino SA: Novel antifungal agents: a patent review (2011-present). Expert Opin. Ther Pat. 2014; 24: 323-338.
18. Mahajan SS and Miranda SJ: Studies on the synthesis of 2-Aminothiophenol. Ind J Pharm Sci 1998; 60(4): 196-198.
19. Likhar R, Perumal P, Kolhe N, Bhaskar VH and Daroi P: Synthesis and antioxidant activity of novel 2-Aryl Substituted benzothiazole derivatives. Int J Curr Pharm Res 2015; 7: 34-37.
20. Sadek KU, Mekheimer RA, Hameed AMA, Elnahas F AND Elnagdi MH: Green and highly efficient synthesis of 2-Arylbenzothisazoles using glycerol without catalyst at ambient temperature. Molecules 2012; 17: 6011-6019.

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