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Research Article

Synthesis and Biological Evaluation of Thiosemicarbazone Analogues of Ornidazole as Antifungal Agents

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ABSTRACT

To synthesize a series of ornidazole thiosemicarbazone analogs based on literature reviews of 2-Methyl-5-nitroimidazoles and thiosemicarbazones and to evaluate all the analogs *in vitro* for their activity against *Aspergillus niger* and *fumigatus.* Thiosemicarbazone analogs were synthesized from oxidizing ornidazole with potassium dichromate and refluxing the oxidized product with substituted thiosemicarbazide using ethanol as a solvent in the acidic medium overnight. All the synthesized analogs of ornidazole showed good antifungal action against *fumigatus* and *niger* except compound C-4. Unsubstituted amine analog C-2 has shown highest percentage inhibition (96.6%, 500 µg/mL) against *fumigatus* while aromatic amine with or without electronegative atom analogs C-3 and C-5 has shown highest activity against *Aspergillus niger* which is two times than standard drug ornidazole (100%, 1000 µg/mL).

Introduction

A 5-Nitroimidazoles are well-established heterocyclic moieties for their anti-protozoal and antibacterial potential.[1] Numerous nitroimidazole derivatives are used clinically as potent antiprotozoal drugs as well as antifungal agents such as metronidazole, nimorazole, and ornidazole.[2] The pharmacological potential depends upon the position of the nitro group as 5-nitro compounds are more active than 4-nitro derivatives.[3,4]

The effectiveness of these compounds is due to its electron acceptance tendency in the endogenous reduction reaction. Since it has redox potential lower than the protein ferrodoxin, which is found in an anaerobic organism, its nitro group is reduced. This reduced form then causes interference in carbohydrate metabolism and nucleic acid synthesis.[2]

Nitroimidazoles have a wide spectrum of activity along with numerous side effects like hepatotoxicity, skin rashes, gastrointestinal disorder, vomiting, nausea etc. Thus an attempt has been made to synthesis a new bioactive series of 5-nitroimidazole derivatives.

Ornidazole[1-(2-hydroxy-3-chloroproryl)-2-methyl-5-nitroimidazole] (1) is a synthetic derivative of 5-nitroimidazole which possesses anti-protozoan,[5] antimycotic[6] and antibacterial potential[2,7] due to inhibition of microbial DNA synthesis and degradation of existing DNA through generation of more reactive amine group from the nitro group.[8-11]

In 1966, Hoffman-La-Roche synthesized the drug. [9,11] It has similarity to metronidazole in terms of molecular structure and pharmacological action,[1] but certain therapeutic advantages over metronidazole which results in dosage frequency reduction as well as duration

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of treatment (longer half-life–12–14 hours and 6–8 hours, respectively) in most clinical infections and this becomes the reason to select it for further research and modifications to enhance its therapeutic effect.[11]

Ornidazole releases chlorinated side chain during metabolism in male animals and exerts antifertility action reversibly[6] through conversion into 3-chlorolactaldehyde which possess the capacity to inhibit the ATP synthesis in sperm through inhibition of the glycolytic enzyme (3-GPD) glyceraldehydes-3-phosphate dehydrogenase.[8]

Thiosemicarbazones (2) have been known for their antiviral, anticancer, and parasiticidal action.[12,13] The effectiveness of thiosemicarbazone analogs has been reported due to its action against cysteine proteinases. [12] In addition, numerous thiosemicarbazone derivatives possess antifungal,[14] antioxidant, antiproliferative, and many other biological properties.[12,15] By changing the chemical substituent at the 1 and 2-positions of the 5-nitroimidazole, it is possible to synthesize molecules that are active against a broader range of microorganisms.[16-18] Demirayak *et al*., (1999) synthesized some 1-[2-(substituted pyrrol-1-yl)ethyl]-2-methyl-5-nitroimidazole derivatives and check the antibacterial and antifungal activity. As compared to metronidazole (*i.e.* > 1024 mg/ml), the compounds 3a-d showed highest activity (MIC against *S. aureus* (*i.e.* 8mg/mL) and entirely found ineffective for antifungal activity.[19]

Benkli *et al*., (2003) carried out synthesis of some 3-[2-(2-Methyl-5-nitroimidazol-1-yl) ethyl]-5-arylidene-thiazolidine-2,4-diones (5) and evaluated antifungal and antibacterial activity. All the synthesized were found moderately active (MIC = 62.5 µg/mL) against *staphylococcus* in comparison to fluconazole.[20] Frank *et al*, (2005) synthesized a series of 1,3,4-oxadiazoles derivatives of imidazole (6) and tested their antifungal and antibacterial potential. Most of the derivatives showed most promising antifungal and antibacterial action (MIC = 0.25 µg/mL) when compared with fluconazole.[21] Frank *et al*, (2007) carried out the microwave-assisted synthesis of 5-substituted-2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxazoles (7) with nitroimidazole nucleus and their anti-inflammatory, antifungal, and antibacterial activity. Compounds (7a-d) show good antifungal activity. The zone of inhibition (mm) was found to be 12–14mm for *Trichophyton* at 10 mg/mL concentration as compared with standard Ciclopiroxolamine (20 mm).[22] Olender *et al*., (2009) synthesized nitroimidazole derivatives by reacting epichlorohydrin, epoxypropane, or phenacyl bromide with 4,5-dinitro and 2-methyl-4,5-nitroimidazoles in alkylation reactions.[3] 4-Aminoimidazole derivatives were also synthesized and compounds were analyzed as anti-fungal and antioxidant.[23,24] Amongst those, compounds (8a-b) exhibited very significant fungistatic activity (ED_{50} < 25) against *Sclerophoma pityophila.*[3] Kumar *et al*, (2010) also synthesized imidazole derivatives and compound 2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethyl dimethylcarbamodithioate (9) showed remarkable *anti-trichomonas* (MIC = 1.14 ± 0.20 µM) along with mild antifungal action.[25] All the reported derivatives of nitroimidazole with antifungal activity have been illustrated in Fig. 1.

A survey of chemical literature revealed that ornidazole and thiosemicarbazones have antifungal activity and ornidazole (Fig. 2) analogs have not been reported at position 2.

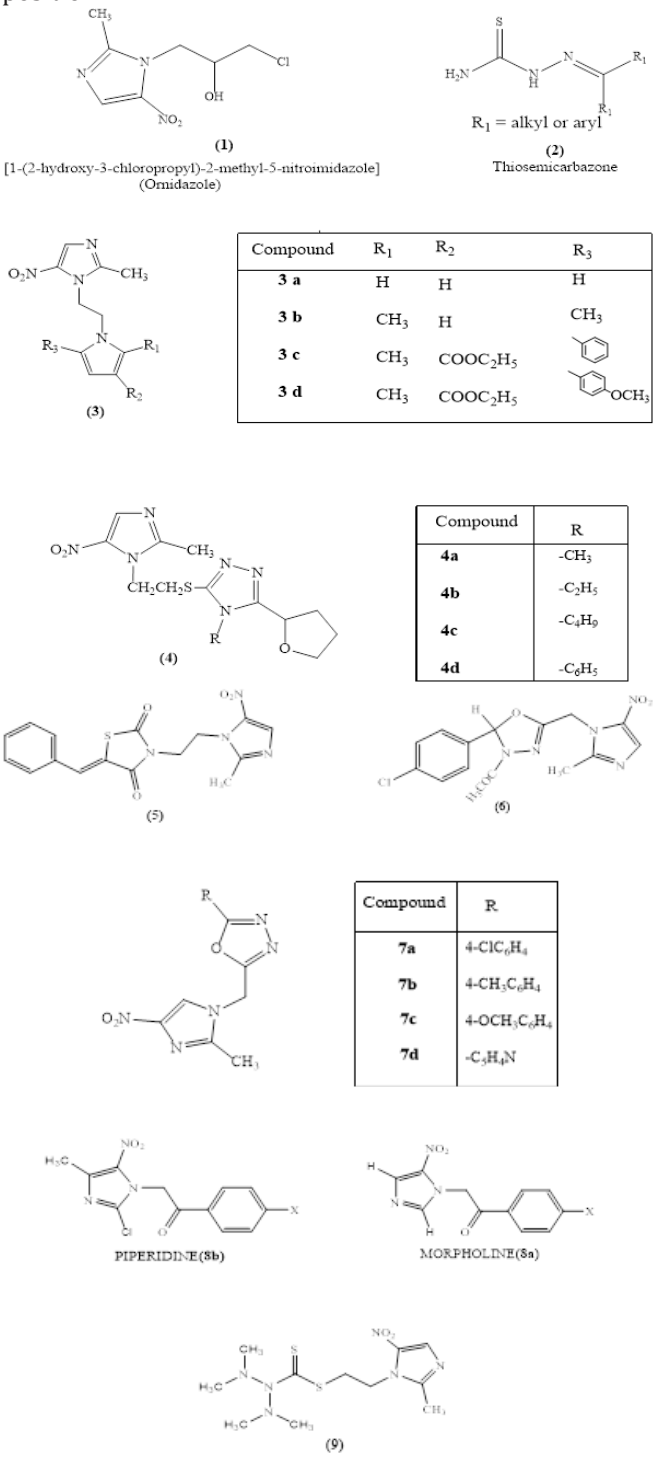


Fig. 1: Representative structure of derivatives of nitroimidazole with antifungal activity

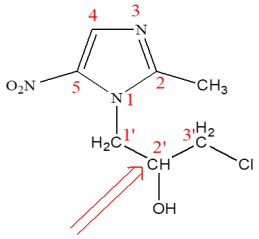


Fig. 2: Ornidazole moiety

From a literature survey, it has been concluded that 5-nitroimidazole with thiosemicarbazone results in a compound with potent antifungal activity. So we decided to synthesize ornidazole thiosemicarbazone analogs at position 2/ of ornidazole.

Materials and Methods

Chemicals and Instruments

The chemical used in our experimental work was procured from Loba Chemie Pvt. Ltd., Mumbai, India, and Qualikems Fine Chem Pvt. Ltd. Vadodara, India.

The melting point was determined using an open capillary method and were uncorrected. Fourier-transform infrared spectroscopy (FTIR) spectra were recorded using Shimadzu 8400 Co. Ltd., Singapore, and the samples were analyzed using potassium bromide (KBr) pellets. ^{1}H-NMR spectra were collected on Bruker Avance II 400 NMR spectrometer. Thin layer chromatography (TLC) analysis was done to check the purity of the compounds on pre-coated aluminum plates (Silica gel 60 F_{254} Merck-Germany).

Synthetic Procedures (Fig. 3)

- For the preparation of 1-(3-chloro-propan-2-one)-2-methyl-5-nitroimidazole(C-1)

To a stirred solution of ornidazole (0.0045mol, 1gm) in 10 N H_2SO_4 (5 mL) a warm solution of $Na_2Cr_2O_7{\cdot}2H_2O$ (0.0046 mol, 1.41 gm) in 4.1 mL of H_2O was added dropwise with stirring over 30 minutes at room temperature. The mixture was allowed to stir overnight. Reaction completion was monitored by TLC and extracted with ethyl acetate. The crude product was dried and recrystallized from ethanol to give compound.

- For the preparation of 1-[(3-Chloropropyl)-2-methyl-5-nitroimidazole]thiosemicarbazone (C-2)

1-(3-chloro-propan-2-one)-2-methyl-5-nitroimidazole (C-1) (0.29 gm, 0.001 mol) and thiosemicarbazide (0.182 gm, 0.002 mol) in ethanol (50 mL) by adding HCl to acidic medium was refluxed overnight and the reaction was monitored by TLC after refluxing the mixture was cooled over ice-bath. The crude product was recrystallized from ethanol and water to give compound.

- For the preparation of Methyl phenyl carbamodithioate (MPC)

To a solution of aniline (1.9 gm, 0.02 mol) in DMSO (20 mL), carbon disulfide (1.5 gm, 0.02 mol), and 20 M aqueous NaOH solution (1.2 mL) were added dropwise over 30 minutes with stirring at 5–10°C. The stirring was continued for 5 hrs. Reaction completion was monitored by TLC. Then, dimethyl sulfate (2.5 gm, 0.02 mol) was added dropwise with stirring at 0-5°C and stirring was continued for another 3 hours. After 3 hours, the reaction mixture was poured into ice-water. The product was filtered, dried in a vacuum desiccator, and recrystallized from benzene to give compound MPC.

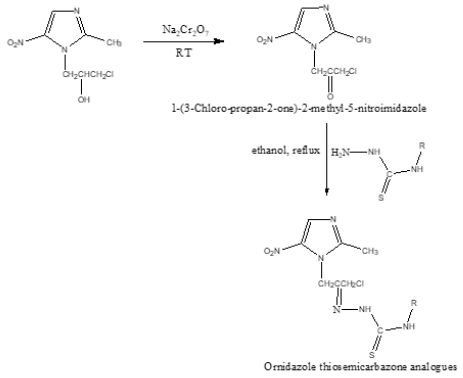
- For the preparation of 4-Phenyl thiosemicarbazide (PT)

Methyl phenyl carbamodithioate (MPC) (1.5 gm, 0.01 mol) was dissolved in absolute ethanol (50 ml) and hydrazine hydrate (0.5 gm, 0.01 mol) was added dropwise with stirring at 5–10°C. Stirring was further continued for 5 hours at 50°C, and then the reaction mixture was poured into ice-water. The solid obtained was filtered, dried, and recrystallization was done using ethanol.

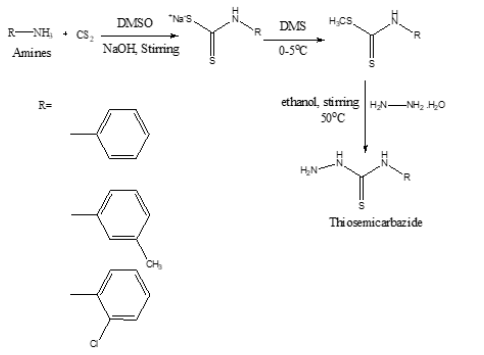
- For the preparation of 1-[(3-chloropropyl)-2-methyl-5-nitroimidazole]-4-phenyl-3-thiosemicarbazone (C-3)

1-(3-chloro-propan-2-one)-2-methyl-5-nitroimidazole (C-1) (0.65 gm, 0.003 mol) and 4-phenyl thiosemicarbazide (1.003 gm, 0.006 mol) in ethanol (50 mL) by adding HCl to acidic medium was refluxed overnight and the mixture was cooled over ice-bath. The crude product obtained was recrystallized from ether.

- For the preparation of methyl (3-methylphenyl) carbamodithioate (MMPC)



Scheme:1 Synthesis of ornidazole thiosemicarbazone analogues



Scheme:2. Synthesis of Thio-semicarbazides

Fig. 3: Synthetic schemes for the synthesis of derivatives of ornidazole.

To a solution of m-toluidine (2.1 gm, 0.02 mol) in DMSO (20 mL), carbon disulfide (1.52 gm, 0.02 mol), and 20 Molar aqueous NaOH solution (1.2 mL) were added dropwise simultaneously over 30 minutes with stirring at 5–10°C. The mixture was further allowed to stir for 5 hours. TLC monitored reaction completion. To the reaction mixture, dimethyl sulfate (2.5 gm, 0.02 mol) was added dropwise with stirring at 0-5°C and stirring was continued for another 3 hours. After 3 hours, the reaction mixture was poured into ice-water. The solid obtained was filtered, dried in vacuum desiccator, and recrystallized from ethanol to give compound.

- For the preparation of 4-(3-Methylphenyl)thiosemicarbazide (MPT)

Methyl (3-methylphenyl) carbamodithioate (1.5 gm, 0.01 mol) was dissolved in absolute ethanol (50 mL) and hydrazine hydrate (0.5 gm, 0.01 mol) was added dropwise with stirring while maintaining the temperature at 5-10°C. Stirring was further continued for 5 hours at 50°C and then the reaction mixture was poured into ice-water. The solid obtained was filtered, dried, and recrystallized from ethanol to give compound.

- For the preparation of 1-[(3-chloropropyl)-2-methyl-5-nitroimidazole]-4-(3-methylphenyl) thiosemicarbazone (C-4)

1-(3-chloro-propan-2-one)-2-methyl-5-nitroimidazole (C-1) (0.65 gm, 0.003 mol) and 4-(3-MethylPhenyl) thiosemicarbazide (1.08 gm, 0.006 mol) in ethanol (50mL) by adding HCl to acidic medium was refluxed overnight and after refluxing the mixture was cooled over ice-bath. The crude obtained was recrystallized from ethanol to give compound.

- For the preparation of Methyl-(2-chlorophenyl) carbamodithioate (MCC):

To a solution of chloroaniline (2.55 gm, 0.02 mol) in DMSO (20 mL), carbon disulfide (1.5 gm, 0.02 mol) and 20 Molar aqueous NaOH solution (1.2 mL) were added dropwise simultaneously over 30 minutes with stirring at 5–10°C. The mixture was further allowed to stir for 5 hrs. To the reaction mixture, dimethyl sulfate (2.5 gm, 0.02 mol) was added dropwise with stirring at 0–5°C and stirring was continued for another 3 hours. After 3 hours, the reaction mixture was poured into ice-water. The solid obtained was filtered, dried in a vacuum desiccator, and recrystallized from benzene to give compound.

- For the preparation of 4-(2-Chlorophenyl) thiosemicarbazide (ClPT)

Methyl-(2-chlorophenyl) carbamodithioate (2.1gm, 0.01 mol) was dissolved in absolute ethanol (50 mL) and hydrazine hydrate (0.5 gm, 0.01 mol) was added dropwise with stirring by keeping the reaction mixture at 5-10°C. Stirring was further continued for 5 hours at 50°C, and then the reaction mixture was poured into ice-water. The solid obtained was filtered, dried, and recrystallized from ethanol to give compound.

- For the preparation of 1-[(3-Chloropropyl)-2-methyl-5-nitroimidazole]-4-(2-chlorophenyl) thiosemicarbazone (C-5)

1-(3-chloro-propan-2-one)-2-methyl-5-nitroimidazole (C-1) (0.65 gm, 0.003 mol) and 4-(2-chloro) phenyl thiosemicarbazide (1.2 gm, 0.006 mol) in ethanol (50 mL) by adding HCl to acidic medium was refluxed overnight and after refluxing the mixture was cooled over ice-bath. The crude obtained was recrystallized from ethanol to give compound.

Characterisation (Fig. 4) includes structure of all synthesized compounds:

1-(3-Chloro-propan-2-one)-2-methyl-5-nitroimidazole (C-1)

Chemical formula: $C_7H_8ClN_3O_3$; molecular mass: 217; elemental fnalysis: C, 38.64; H, 3.71; Cl, 16.29; N, 19.31; O, 22.06; Yield 30%; Rf value: 0.36; M.P: 109-111°C; 1H NMR (400MHz, DMSO): δ = 8.01(1H, s), 5.42(2H, s), 4.58(2H, s), 2.36(3H, s); IR (KBr, cm-1): 2929, 1751, 1637, 1560, 1373, 1273, 1143, 1193, 837, 740; MS m/z: 217.32 (MH^+).

1-[(3-Chloropropyl)-2-methyl-5-nitroimidazole] thiosemicarbazone (C-2)

Chemical formula: $C_8H_{11}ClN_6O_2S$; molecular mass:290; element alanalysis: C, 33.05; H, 3.81; Cl, 12.19; N, 28.91; O, 11.01; S, 11.03; Yield30%; Rf value: 0.7; M.P: 120–130°C; 1H NMR (400MHz, DMSO): δ = 9.65(1H, s); 7.94(1H, s); 3.89(2H, s); 3.73(2H, s); 1.97(2H, s); 1.95(3H, s); IR (KBr, cm-1): 3371, 3261, 3176, 1645, 1622, 1527, 1373, 804, 705; MS m/z: 290.04 (MH^+).

Methylphenylcarbamodithioate (MPC)

Chemical formula: $C_8H_9NS_2$; molecular mass: 183 ; elemental analysis: C, 52.42; H, 4.95; N, 7.64; S, 34.99; Yield 40%; Rf value: 0.7; M.P: 92-93°C; 1H NMR (400MHz, DMSO): δ = 7.48-7.23(5H, m); 4(1H, s); 2.07(3H, s); IR (KBr, cm-1): 3149, 2949, 1510, 1247, 1141, 810, 704.MS m/z: 183.04 (MH^+).

4-Phenylthiosemicarbazide (PT)

Chemical Formula: $C_7H_9N_3S$; molecular mass: 167; elemental Analysis: C, 50.27; H, 5.42; N, 25.13; S, 19.17; Yield 68.96%; Rf value: 0.5; M.P:130-132°C; 1H NMR (400MHz, DMSO): δ = 6.8-7.7(5H, m); 4(1H, s); 2(3H, s); IR (KBr, cm-1): 3304, 3167, 2970, 1529, 1494, 1286, 1068; MS m/z: 167.04 (MH^+).

1-[(3-Chloropropyl)-2-methyl-5-nitroimidazole]-4-phenyl-3-thiosemicarbazone(C-3)

Chemical formula: $C_{14}H_{15}ClN_6O_2S$; molecular mass:366; elemental snalysis: C, 45.84; H, 4.12; Cl, 9.66; N, 22.91; O, 8.72; S, 8.74; Yield30%; Rf value: 0.92; M.P:210-213 °C; 1H NMR (400MHz, DMSO): δ =10.56(1H, s); 8.07 (1H, s); 7.48-7.23 (5H, m); 4.07(1H, s); 3.54(2H, s); 3.32(2H,

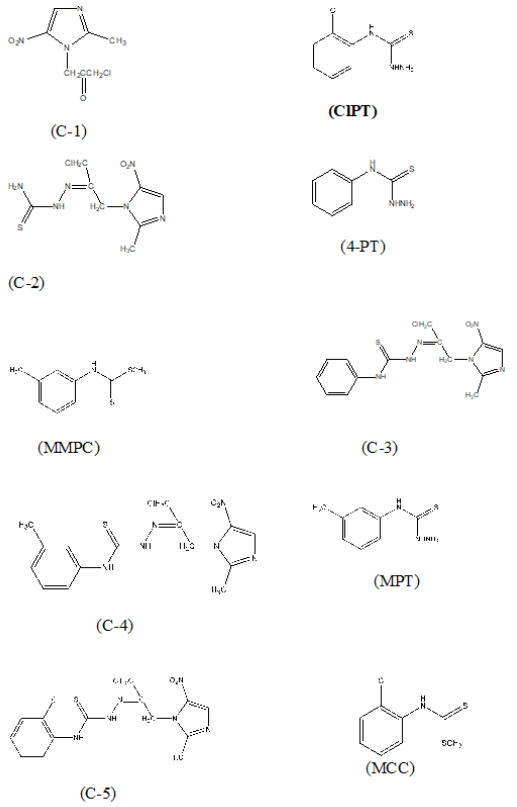


Fig. 4: Structures of synthesized compounds

s); 2.07(3H, s); IR (KBr, cm-1): 3302, 2972, 1641, 1529, 1498, 1446, 1286, 1068, 896, 736.MS m/z: 366.07 (MH^+)

Methyl-(3-methylphenyl)carbamodithioate (MMPC)

Chemical formula: $C_9H_{11}NS_2$; molecular mass: 197.32; elemental analysis: C, 54.78; H, 5.62; N, 7.10; S, 32.50; Yield 60%; Rf value: 0.6; M.P:78-80°C; 1H NMR (400MHz, DMSO): δ= 7.08-6.59(4H, m); 4(1H,s); 2.55(3H,s); 2.34(3H,s); IR (KBr, cm-1): 3122, 2918, 1637, 1558, 1496, 1313, 1035, 956,792, 692, 605; MS m/z: 197 (MH^+)

4-(3-MethylPhenyl)thiosemicarbazide (MPT)

Chemical formula: $C_8H_{11}N_3S$; molecular mass: 181.26; elemental analysis: C, 53.01; H, 6.12; N, 23.18; S, 17.69 Yield 69.89%; Rf value: 0.5; M.P:88-90°C; 1H NMR (400MHz, DMSO): δ= 6.8-7.7(4H, m); 4(1H, s); 2.34(3H, s); 2(3H, s); IR (KBr, cm-1): 3309, 3234, 2916, 1610, 1543, 1492, 1311, 1068, 777, 731; MS m/z: 181 (MH^+).

1-[(3-Chloropropyl)-2-methyl-5-nitroimidazole]-4-(3-methylphenyl) thiosemicarbazone (C-4)

Chemical Formula: $C_{15}H_{17}ClN_6O_2S$; molecular mass: 380.85; elemental Analysis: C, 47.30; H, 4.50; Cl, 9.31; N, 22.07; O, 8.40; S, 8.42; Yield 46%; Rf value: 0.85; M.P: 40-41°C; 1H NMR (400MHz, DMSO): δ = 10.04(1H, s); 8.11(1H, s); 8.01-7.99(1H, d); 7.38-7.31(1H, t); 7.17-7.13(1H, d); 6.87(1H,s); 5.35(1H, s); 3.87(2H, s); 3.56(2H, s); 2.43(3H, s); 2.34(3H, s); IR (KBr, cm-1): 3302, 2918, 1666, 1531, 1492, 1373, 1193, 827, 781, 690; MS m/z: 380 (MH^+).

Methyl-(2-chlorophenyl)carbamodithioate (MCC)

Chemical formula: $C_8H_8ClNS_2$; molecular mass: 217.74; elemental analysis: C, 44.13; H, 3.70; Cl, 16.28; N, 6.43; S, 29.45Yield 70%; Rf value: 0.8; M.P: 72-73°C; 1H NMR (400MHz, DMSO): δ= 7.4-6.75(4H, m); 4(1H, s); 2.55(3H, s); IR (KBr, cm-1): 3115, 2922, 1573, 1506, 1467, 1323, 1037, 868, 761; MS m/z: 217 (MH^+).

4-(2-Chlorophenyl)thiosemicarbazide (CIPT)

Chemical formula: $C_7H_8ClN_3S$; molecular mass: 201.68; elemental analysis: C, 41.69; H, 4.00; Cl, 17.58; N, 20.84; S, 15.90Yield 69.89%; Rf value: 0.4; M.P:109°C; 1H NMR (400MHz, DMSO): δ = 7.4-6.75(4H, m); 4(1H, s); 2(3H, s); IR (KBr, cm-1): 3311, 3279, 1612, 1550, 1523, 1440, 1290, 1074, 908, 744; MS m/z: 201 (MH^+).

1-[(3-Chloropropyl)-2-methyl-5-nitroimidazole]-4-(2-chlorophenyl)thiosemicarbazone (C-5)

Chemical Formula: $C_{14}H_{14}Cl_2N_6O_2S$; molecular mass: 401.27; elemental Analysis: C, 41.90; H, 3.52; Cl, 17.67; N, 20.94; O, 7.97; S, 7.99; Yield 46%; Rf value: 0.85; M.P: 40-41°C; 1H NMR (400MHz, DMSO): δ = 10.19(1H, s); 7.97(1H, s); 7.85-7.82(1H, d); 7.44-7.22(2H, t); 6.88(1H, d); 4.53(1H, s); 3.76(2H, s); 3.28(2H, s); 2.48(3H, s); IR (KBr, cm-1): 3149, 2945, 1641, 1585, 1510, 1342, 1246, 1139, 1020, 950, 810, 704; MS m/z: 401 (MH^+).

Results and Discussion

Biological Activity

The *in vitro* antifungal activity of compounds C-1, C-2, C-3, C-4 and C-5 were tested using the standard cup plate agar diffusion method[26] against *Aspergillus niger* and *fumigatus*. These fungus species display the highest risk of invasive infections in the recipients of liver and lung transplant.[25] The concentration of test compounds used in the study was 5% using DMSO as a solvent. Ornidazole was tested as a standard drug for the fungi. The results of the antifungal activity are shown in Table 1. Figs. 5 and 6.

The minimum inhibitory concentration (MIC) required for antifungal activity has been detailed in Table 2.

A series of ornidazole thiosemicarbazone analogues were synthesized on the basis of literature review on 2-Methyl-5-nitroimidazoles and thiosemicarbazones. The synthesized compounds were elucidated by ^1H NMR and IR aspectra.

All the ornidazole analogs were subjected to antifungal evaluation by cup and plate method, and they showed good antifungal activity against *Fumigatus* and *Niger* except compound C-4. Unsubstituted amine analog C-2 has shown highest percentage inhibition (96.6%, 500 µg/mL)against *Fumigatus* while aromatic amine with or without electronegative atom; analogs C-3 and C-5 have shown highest activity against *Niger* which is two times than standard drug ornidazole (100%, 1000

Table 1: Zone of inhibition, mean ad standard deviation on the data of antifungal activity of synthesized compounds:

		Zone of inhibition (mm)						*Mean*		*SD*	
S. No	*Compound*	*A. fumigatus*			*A. niger*			*A. fumigatus*	*A. niger*	*A. fumigatus*	*A. niger*
1	C-1	28	28	27	25	26	26	27.67	25.67	0.58	0.58
2	C-2	28	29	29	26	25	25	28.67	25.33	0.58	0.58
3	C-3	24	23	24	27	28	27	23.67	27.33	0.58	0.58
4	C-4	10	10	9	13	15	14	9.67	14.00	0.58	1.00
5	C-5	26	27	26	27	28	26	26.33	27.00	0.58	1.00
6	DMSO (control)	0	0	0	0	0	0	0.00	0.00	0.00	0.00
7	Ornidazole (10%) (std.)	30	30	30	29	29	29	30.00	29.00	0.00	0.00

Table 2: Minimum inhibitory concentration of ornidazole derivatives; MIC (µg/mL)

		MIC (µg/mL)	
S. No	*Compound*	*Aspergillus fumigatus*	*Aspergillus niger*
1	C-1	100	200
2	C-2	50	100
3	C-3	500	50
4	C-4	1000	>1000
5	C-5	200	100
6	DMSO (control)	0	0
7	Ornidazole (10%) (std.)	500	200

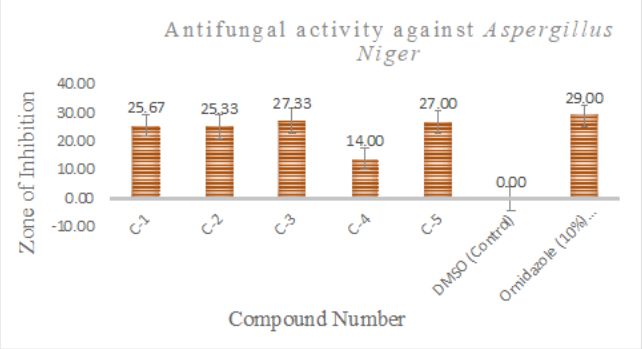


Fig. 5: Antifungal activities of synthesized compounds against *Aspergillus fumigatus* using ornidazole as standard and DMSO as control

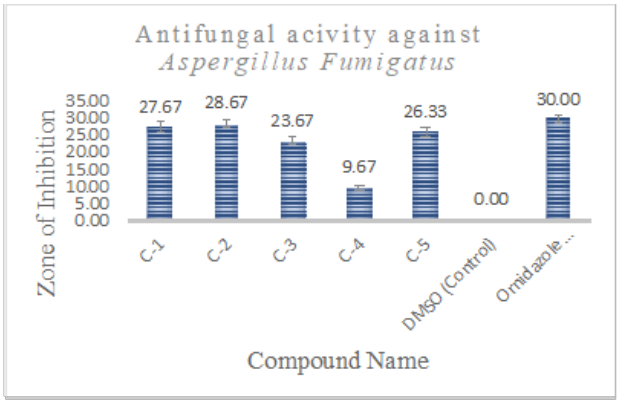


Fig. 6: Antifungal activity of synthesized compounds against *Aspergillus niger*

µg/mL). Thus, the synthesis of a number of ornidazole thiosemicarbazone analogs has been reported in this study. Substituted anilines on reaction with carbon disulfide in aqueous sodium hydroxide solution and dimethyl sulfate afforded methyl aryl carbamodithioate, which on reacting with hydrazine hydrate yielded 4-aryl thiosemicarbazide. Condensation of different thiosemicarbazides with keto group of oxidized ornidazole in acidic medium afforded ornidazole thiosemicarbazone analogs.

The compounds were characterized by melting points, R_f values, FTIR, and ^{1}H NMR. IR and ^{1}H NMR spectral data confirmed the identity of all the compounds. All the compounds were checked for their antifungal activity using ornidazole as the standard drug. All the compounds exhibited good result against a test organism.

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