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Electrochemical behaviour of some alkyl substituted N-hydroxy-2,6-diarylpiperidin-4-one thiosemicarbazone and the antifungal studies of the products

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ABSTRACT

A series of 3-ethyl-2,6-diarylpiperidin-4-one thiosemicarbazone and 3,5-dimethyl-2,6-diarylpiperidin-4-one thiosemicarbazone were synthesised. The thiosemicarbazones were subjected to cyclic voltammetric study using graphite electrode with variable scan rate at moderate acidic conditions maintained in the electrolytic solution. The reduction takes place by two electron transfer and the reaction is pH dependent. The reduced products were isolated and purified by column chromatography. The structure was proved by ^{1}H and ^{13}C NMR spectroscopy. The electrode process was found to be irreversible and diffusion controlled. Further the products were analysed for anti fungal activity in which nitro substituted compound showed high inhibition towards the fungi Asperillus niger.

Keywords

Piperidone thiosemicarbazone, Cyclic voltammetry, ^{1}H and ^{13}C NMR, Antifungal activity.

1.INTRODUCTION

Thiosemicarbazone are of considerable interest due to their antimicrobial activity. The thiosemicarbazones widely act as intermediates in several organic syntheses. Occasionally on the other hand, their versatile structural features make them as excellent ligands with transition metal ions bonding through the sulphur[1-6]. The heterocyclic thiosemicarbazones is of great interest in the areas of research because of their applications in antimicrobial activity is very wide as compared to those with heteroaromatic ring substitutions[4-11].

In this paper we have reported the electrochemical reduction of 2,6-diaryl-3,5-dimethylpiperidin-4-one thiosemicarbazones and 2,6-diaryl-3-ethylpiperidin-4-one thiosemicarbazones. The cyclic voltammetric study of the title compound was carried out in mixed solvent of 0.1M of ethanol and distilled water in the potential range -2200mV to 2200mV. The variable scan rate used were $100mVs^{-1}$, $150mVs^{-1}$ and $200mVs^{-1}$ at the graphite electrode surface. The reduction process and numerical parameters, such as diffusion coefficients and charge transfer coefficients are also reported[8-14]. The reduced products after subjected Cyclic voltammetric were screened for anti-fungal activity.

2.MATERIALS AND METHODS

2.1.Reagents and Chemicals

All the chemicals were used for the synthesis of compounds of high purity. The thiosemicarbazones used in this research work were prepared in the laboratory and purified by earlier methods. The AR grade of ethanol is used as solvent(Merck). Completion of reactions has been monitored by Thin Layer Chromatography on silica gel coated Aluminium sheet (Type 60 GF 254, Merck). The melting points were measured with open capillaries and uncorrected. ^{1}H NMR spectra (in DMSO-d_6/$CDCl_3$) on Varian 270MHz instrument using TMS as the internal standard.

2.2.Preparation of N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one(1a–c) and N-hydroxy-2,6-diaryl-3,5-dimethylpiperidin-4-one(1d–g)

The respective 3-ethyl-2,6-diarylpiperidin-4-one, 2,6-diaryl-3,5-dimethylpiperidin-4-one[1] and m-chloroperbenzoic acid (1:1) were mixed in 20ml chloroform at 0°C. The mixture was extracted and washed with 10% sodium bicarbonate solution. The chloroform layer was dried with anhydrous sodium sulphate and evaporated. The separated solid was subjected to column chromatography. The column was packed with silica gel(100–200mesh) in hexane. The eluting solvents used were benzene, and benzene-pet-ether (40:60) (8:2). The compound was found to be separated in benzene -pet-ether (8:2).

2.3.Preparation of N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one thiosemicarbazone(2a–c) and N-hydroxy-2,6-diaryl-3,5-dimethylpiperidin-4-one thiosemicarbazone(2d–g)

A mixture of N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one(1gm,0.0027mol), N-hydroxy-2,6-diaryl-3,5-dimethylpiperidin-4-one(1gm,0.0027mol), thiosemicarbazide hydrochloride(0.316gm,0.0027mol) and sodium acetate(0.75gm) were dissolved in ethanol(40ml) and refluxed for two hours on a steam bath and cooled. The separated solid was filtered and washed with water and recrystallised from ethanol. The physical data of the entire synthesised compounds (2a–g) are given in table 1 and their reaction is represented in scheme 1.

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Table 1: Physical Data of the Compound(2a–g)

Compound	Molecular Formula	Molecular Weight Kg/Kmol	Melting Point °C	Yield %
2a	$C_{20}H_{22}F_2N_4OS$	441	131-133	86
2b	$C_{20}H_{21}N_6O_5S$	457	140-142	84
2c	$C_{20}H_{21}Cl_2N_4OS$	420	141-143	82
2d	$C_{20}H_{22}N_4OSCl_2$	421	127-129	73
2e	$C_{22}H_{28}N_4OS$	396	139-141	81
2f	$C_{20}H_{22}N_4OSCl_2$	421	124-125	79
2g	$C_{20}H_{22}F_2N_4OS$	442	135-137	83

2.4.Preparation of Media

Sabouraud's Dextrose agar is used to culture the fungi. Peptone water (1%) is used for fresh culture of all the fungi and is maintained by periodic sub-culture in fresh Sabouraud's Dextrose medium under in vitro disc diffusion method. Plates for Sabouraud's Dextrose medium are prepared with inocula by adding 1 ml of dilute culture of the test organism. The respective hydrochlorides of thiosemicarbazones are dissolved in water in the concentration of 10mg/ml. The solution was maintained as a stock solution of variable concentrations(100ppm, 200ppm,300ppm). Sterile paper disc of 5mm diameter is saturated with the three different concentrations and such discs are placed in each seeded agar plates. The petri plates are incubated at 30°C for 70hrs. The inhibition zone are measured excluding the diameter of the paper disc(5mm). At 500 µg/ml concentration of the conventional standard antifungal drug ketoconazole exhibited 20±5mm zone of inhibition against all the test fungi.

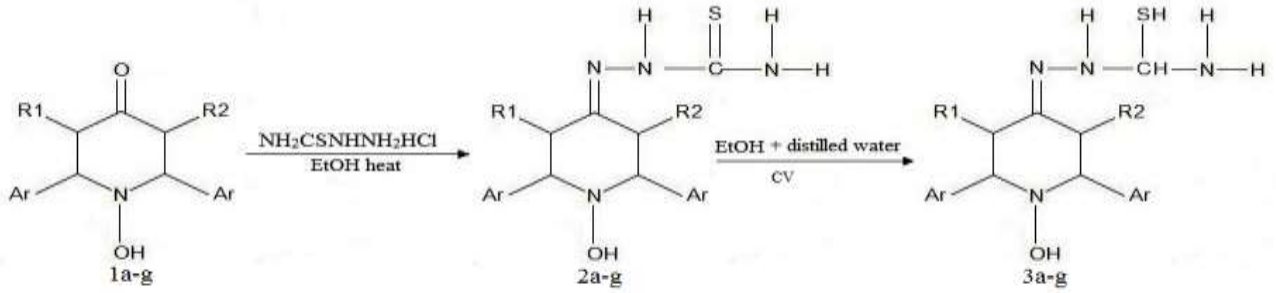
2.5.Instrumentation

The Cyclic voltammetric data were recorded with a fully computer controlled Electrochemistry System. A three electrode combination system was used. This consisted of graphite working electrode and saturated calomel (SCE) as reference electrode and platinum as an auxiliary electrode. The working electro potential was fixed slightly more than that was required for micro electrolysis using cyclic voltammetry technique. The cyclic voltammogram behaviour of 0.01M thiosemicarbazone dissolved in mixed solvent of 0.1M of ethanol and distilled water was studied with cyclic voltammetric technique in the potential range -2200mV to 2200mV and scan rate range of $100mVs^{-1}$, $150mVs^{-1}$ and $200mVs^{-1}$. The solution was deoxygenated by passage of nitrogen gas for five minutes and then voltammogram data was recorded. The PC controlled method was used to record the potentiostat cyclic voltammetric curves.

All the chemicals used in the preparation of semicarbazone derivatives are of very high purity. Completion of reactions was monitored by thin layer chromatography on silica gel coated Aluminium sheet (Type 60 GF 254, Merck). The melting points were measured with open capillaries and uncorrected. ^1H NMR spectra (in DMSO-d_6/$CDCl_3$) on Varian 270 MHz instrument using TMS as the internal standard.

3.RESULTS AND DISCUSSION

The appropriate N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one(table 2) and thiosemicarbazide are refluxed in the presence of sodium acetate for two hours. The product obtained is piperidin-4-one thiosemicarbazone(2a–c). Similarly N-hydroxy-2,6-diaryl-3,5-dimethyl piperidin-4-one are obtained(2d–g). Then the thiosemicarbazones(2a–g) are subjected to CV study[19-23]. The reactions are represented in Scheme 1.



3a–Amino(2-(N-hydroxy-3-ethyl-2,6-bis(p-flurophenyl)piperidin-4-one ylidene)hydrazinyl)thiol
3b–Amino(2-(N-hydroxy-3-ethyl-2,6-bis(m-nitrophenyl)piperidin-4-one ylidene)hydrazinyl)thiol
3c–Amino(2-(N-hydroxy-3-ethyl-2,6-bis(p-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol
3d–Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol
3e–Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-methylphenyl)piperidin-4-one ylidene)hydrazinyl)thiol
3f–Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol
3g–Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-flurophenyl)piperidin-4-one ylidene)hydrazinyl)thiol

Scheme 1

Table 2: List of synthesised N-hydroxy-piperidin-4-one thiosemicarbazone

Compound	1a-3a	1b-3b	1c-3c	1d-3d	1e-3e	1f-3f	1g-3g
R1	C_2H_5	C_2H_5	C_2H_5	CH_3	CH_3	CH_3	CH_3
R2	H	H	H	CH_3	CH_3	CH_3	CH_3
Ar	p-FC_6H_4	m-$NO_2C_6H_4$	p-ClC_6H_4	o-ClC_6H_4	p-$CH_3C_6H_4$	p-ClC_6H_4	p-FC_6H_4

3.1. The Electrochemical behaviour of N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one thiosemicarbazone(2a–c)

The voltammetric data were analysed in the potential range of -2200mV to 2200mV for the thiosemicarbazone(2a–c)[13-18]. The voltammogram(Figure 1–3) of the compounds 2a–c showed two cathodic peaks and single anodic peak during the reverse scan. It was quite interesting and most fascinating to probe that the compounds(2a–c) were exhibited irreversible reduction mechanism with the observed peak potential values are shown in the table 3. It also be noted that the change in scan rate is more significant in shifting the peak potential values to more negative[17]. Thus in the compounds(2a–c) is confirmed that the peak potential values shifted to the more negative potential with increase in the scan rate(v) indicating the electrochemical processes are quite irreversible. Further the potential shift and the peak current(I_{pc}) was higher when the scan rate is increased. The current function($I_{pc}/v^{1/2}$) has been found to be fairly constant with respect to the sweep rate indicated and the electrode process is found to be diffusion controlled[16-24].

Further it also been observed for the compounds(2a–c) exhibited the irreversible reduction mechanism with higher shifts potential only if the reaction is carried out in moderate acidic condition is sustained in the electrolytic solution of 0.01M thiosemicarbazone dissolved in mixed solvent of 0.1M of ethanol and distilled water. Beside this the compound (2a–c) has been observed that the number of stop crossing level is increased the number of peaks have not changed. This in evidence that, all the compounds were studied and have undergone for the electro chemical reduction process and confirmed that irreversible reduction mechanism has clearly taken place at the active thionyl group with two electron transfer mode. The dependence of the voltammetric response of compounds(2a–c) on the scan rate is typical to the chemical reaction coupled between two charge transfer processes. The results represented in table 3 shows that $I_{pc}/v^{1/2}$ increases with increasing scan rate for the compounds(2a–c) representing the electrochemical reaction has taken place. Similarly the dependence of the peak current on the square root of the scan rate($v^{1/2}$) suggests the diffusion controlled electrochemical processes[21]. Diffusion controlled means that the electron transfer from the organic compound to the electrode surface is much faster than the mass transfer to the surface of the electrode. The calculated values of Diffusion Coefficient follow the same range of values even with increase in scan rate as illustrated in table 3[22-33]. Thus, the Kinetic parameters such as Charge transfer coefficient($D_0^{1/2}$)and diffusion coefficient have been calculated for irreversible and diffusion controlled reduction by using following equations and reported in table 3.

$|E_p-E_{P/2}|=1.85RT/F\alpha_n=(47.7/\alpha_n)mV$---------(1)

$I_p=3.01x10^5xn(\alpha_n)^{1/2}$ A C $D_0^{1/2}v^{1/2}$----------(2)

It is evident from the voltammetric data shows that the degree of irreversibility improves in the order of 3b>3a>3c. The experimental data reveals the dependence of the scan rate on ΔE_p values, and this confirms the hydrogen transfer takes

place at the electron deficient thionyl site[31-34]. Hence it is inferred that a new reduced compound(3a–c) is formed[35-36].

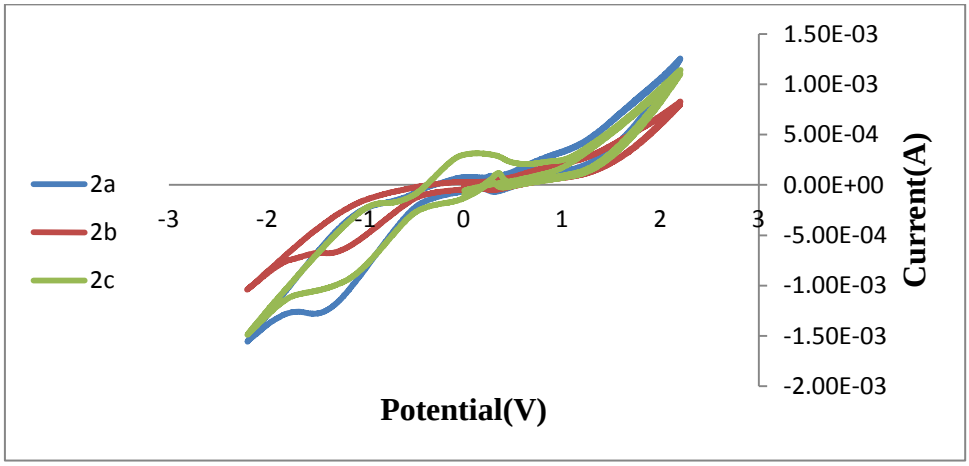


Figure 1: Cyclic Voltammogram of 0.01M of N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one thiosemicarbazone(2a–c) dissolved with 0.1M of ethanol and distilled water at 100mVs^{-1}

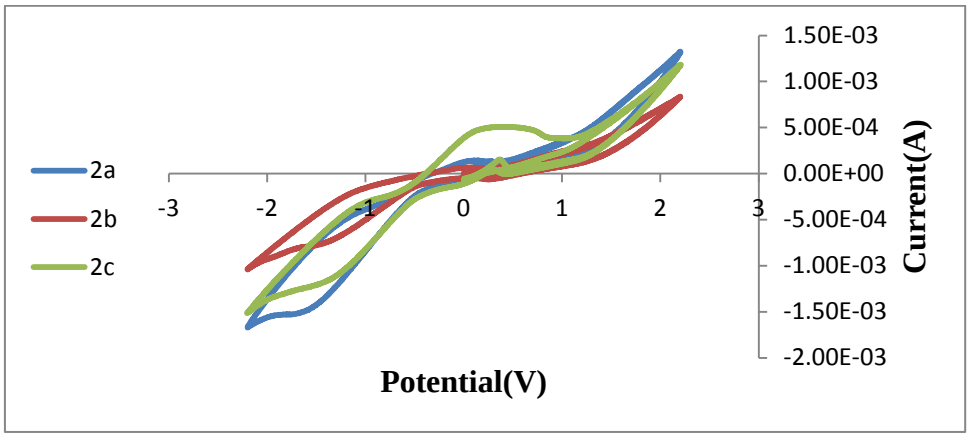


Figure 2: Cyclic Voltammogram of 0.01M of N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one thiosemicarbazone(2a–c) dissolved with 0.1M of ethanol and distilled water at 150mVs^{-1}

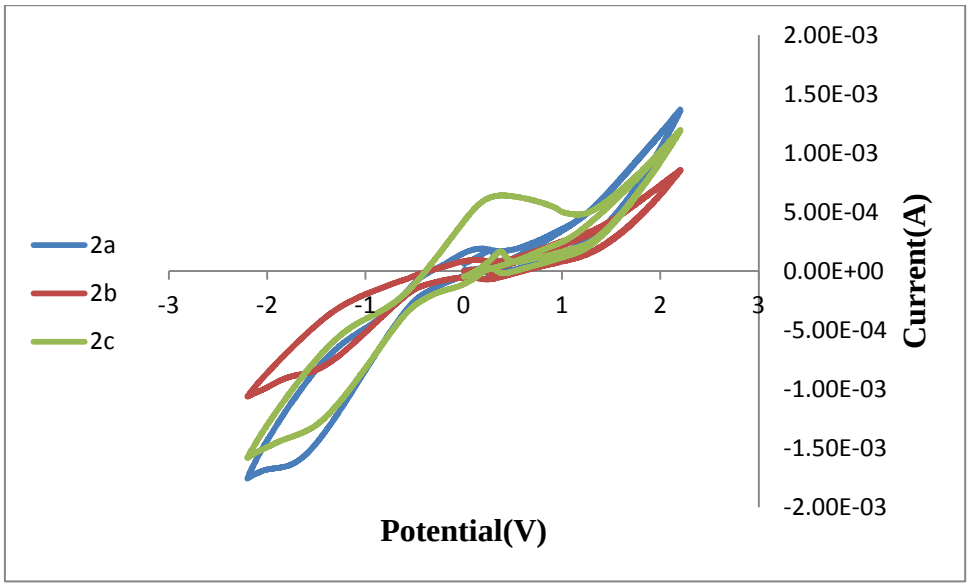


Figure 3: Cyclic Voltammogram of 0.01M of N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one thiosemicarbazone(2a–c) dissolved with 0.1M of ethanol and distilled water at 200mVs^{-1}

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Table 3: Cyclic Voltammogram values of 0.01M of series of N-hydroxy-3-ethyl-2,6-diarylpiperidin-4-one thiosemicarbazone(3a–c) dissolved with 0.1M of ethanol and distilled water with variable scan rate of 100mV s^{-1}, 150mVs^{-1} and 200mVs^{-1}

Compound (3a-c)	Scan rate(mV/s)	E_{pc} (mV)	I_{pc} (μA)	$E_{p/2}$ (mV)	$I_{pc}/v^{1/2}$	α_n	$D_0^{1/2} \times 10^{-5}$ $cm^2.s^{-1}$
3a	100	-240	0.23	-120	0.023	0.396	1.2
	150	-218	0.39	-109	0.031	0.437	1.5
	200	-202	0.71	-101	0.050	0.472	2.2
3b	100	-202	2.89	-101	0.289	0.472	12.7
	150	-160	4.45	-80	0.360	0.596	12.6
	200	-125	6.71	-63	0.475	0.757	13.0
3c	100	-240	0.28	-120	0.028	0.398	1.5
	150	-226	0.41	-113	0.033	0.422	1.6
	200	-214	0.56	-107	0.039	0.445	1.8

3.2. The Electrochemical behaviour of N-hydroxy-2,6-diaryl-3,5-dimethylpieridin-4-one thiosemicarbazone (2d–g)

The cyclic voltammogram(figure 4–6) of the compounds(2d–g) showed a single cathodic peak and no anodic peak is observed during the reverse scan at variable scan rates of 100mVs^{-1},150mVs^{-1} and 200mVs^{-1}. Thus the inclusion of the analysed voltammetry data(table 6–8) is based on the above justification of the compounds(2d–g) have undergone irreversible reduction. The degree of irreversibility improves in the order of 2d>2e>2g>2f and the diffusion coefficient is also invariable with increase in scan rate as recorded in table 4[36-41]. It was interesting to observe that the compound does not produce any anodic wave in reverse scan with increase in scan rate, number of stop crossing level and maintaining moderate pH conditions. All these observation indicating the diffusion controlled nature of the electro chemical process is sustained for the electrolytic solution of the compounds(2d–g). The cyclic voltammogram of completely reduced solution did not produce any peak and indicated that no electro active species remind in the solution after electro chemical reduction. Thus the kinetic parameter have been calculated for the electro chemical reaction of same irreversible reduction of the compounds (2g–d) and reported in table 3. The physical data of the compound 3d–g are represented in table 4[41].

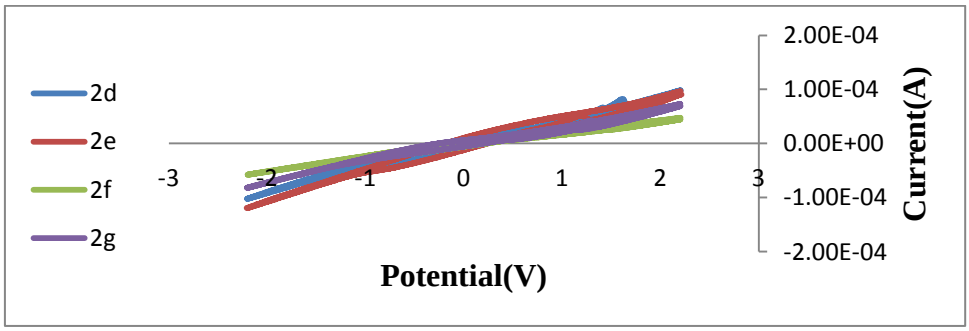

Figure 4: Cyclic Voltammogram of 0.01M of N-hydroxy-2,6-diaryl-3,5-dimethylpieridin-4-one thiosemicarbazone(2d-g) dissolved with 0.1M of ethanol and distilled water at 100mVs^{-1}

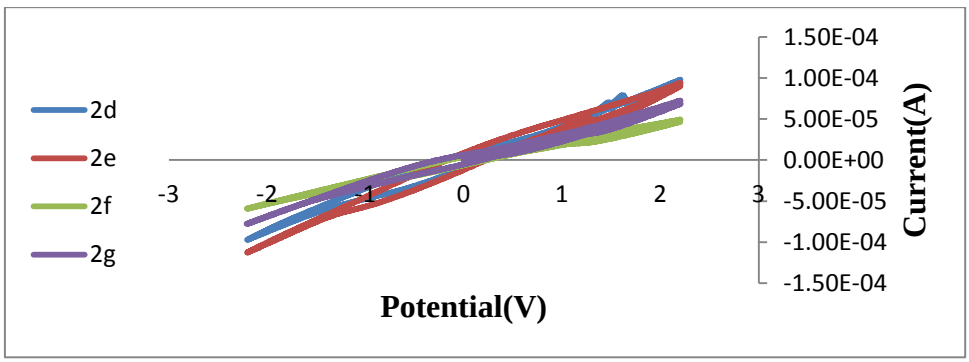

Figure 5: Cyclic Voltammogram of 0.01M of N-hydroxy-2,6-diaryl-3,5-dimethylpieridin-4-one thiosemicarbazone(2d-g) dissolved with 0.1M of ethanol and distilled water at 150mVs^{-1}

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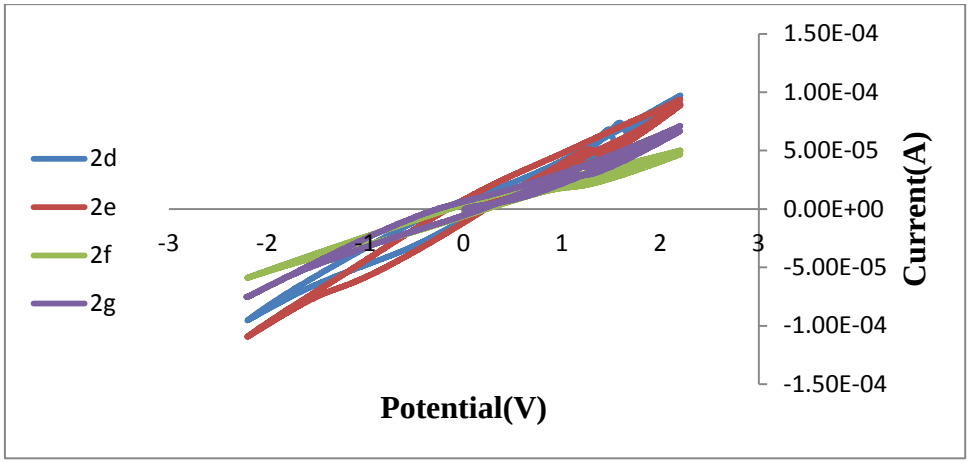

Figure 6: Cyclic Voltammogram of 0.01M of N-hydroxy-2,6-diaryl-3,5-dimethylpieridin-4-one thiosemicarbazone(2d-g) dissolved with 0.1M of ethanol and distilled water at 200mVs^{-1}

Table 4: Cyclic Voltammogram values of 0.01M of N-hydroxy-2,6-diaryl-3,5-dimethylpieridin-4-one thiosemicarbazone(3d-g) dissolved with 0.1M of ethanol and distilled water with variable scan rate of 100mVs^{-1}, 150mVs^{-1} and 200mVs^{-1}

Compound (3d-g)	Scan rate(mV/s)	E_{pc} (mV)	I_{pc} (µA)	Ep/2 (mV)	$I_{pc}/v^{1/2}$	α_n	$D_0$1/2 x 10-5 cm^2.s^{-1}
3d	100	-1740	0.66	-870	0.066	0.055	5.84
	150	-1690	0.69	-845	0.056	0.056	4.94
	200	-1580	0.71	-790	0.050	0.060	4.25
3e	100	-1230	0.32	-615	0.032	0.078	3. 72
	150	-1050	0.36	-525	0.029	0.091	3.59
	200	-1020	0.39	-510	0.028	0.094	3.42
3f	100	-1030	0.22	-515	0.022	0.093	1.50
	150	-1030	0.26	-515	0.021	0.093	1.45
	200	-940	0.27	-320	0.019	0.149	1.03
3g	100	-1273	0.31	-637	0.031	0.075	2.35
	150	-1261	0.36	-631	0.029	0.076	2.21
	200	-1240	0.46	-620	0.033	0.077	2.43

Table 5: Physical Data of the Compounds(3a–g)

Compound	Molecular Formula	Molecular Weight Kg/Kmol	Melting Point °C	Yield %
3a	$C_{20}H_{24}F_2N_4OS$	443	129-131	81
3b	$C_{20}H_{23}N_6O_5S$	459	142-144	77
3c	$C_{20}H_{23}Cl_2N_4OS$	422	143-145	76
3d	$C_{20}H_{24}N_4OSCl_2$	423	122-124	71
3e	$C_{22}H_{30}N_4OS$	398	134-136	77
3f	$C_{20}H_{24}N_4OSCl_2$	423	131-132	74
3g	$C_{20}H_{24}F_2N_4OS$	444	133-136	80

3.3.^{1}H NMR and ^{13}C NMR analysis of the products(3a–g)

The structure of the compounds 3a–g is confirmed by comparing[23-31] the ^{1}H NMR and ^{13}C NMR spectra of the compounds 2a–g.

In the ^{1}H NMR spectra of 3a–g, two new signals appeared corresponding to the reduction of thionyl group to secondary alcohol and a signal to the methine proton. The ^{13}C NMR showed the disappearance of signal due to thionyl group and a new signal due to C-SH carbon owing to the reduction of thionyl group[28-32]. The physical data of the reduced products after CV are shown in the table 7.

3.3.1.The analytical data of N-hydroxy-3-ethyl-2,6-bis(p-flurophenyl)piperidin-4-one thiosemicarbazone(2a) before subjection to CV

The structure of N-hydroxy-3-ethyl-2,6-bis(p-flurophenyl)piperidin-4-one thiosemicarbazone(2a) is confirmed by ^{1}H NMR and ^{13}C NMR spectral data. ^{1}H-NMR (DMSO-d_6): ∂ 4.17(s,N-OH), 3.73-3.75(d,2H,6H), 2.79-2.83(m,3H,5H), 7.32-7.35(s,ph), 8.86(s,NH_2), 1.01(d,3-CH_3), 1.36-1.42(d,3-CH_2), 2.19(s,NH) and ^{13}C NMR ∂ value: 74.23(2C,6C), 164.86(s,SZ-CS), 125.12-128.48(ph), 43.52 (3C,5C), 13.5(3-CH_3), 17.6 (3-CH_2).

3.3.2.The analytical data of the N-hydroxy-3-ethyl-2,6-bis(p-flurophenyl)piperidin-4-one thiosemicarbazone(2a) after subjection to CV

The structure of the reduction product Amino(2-(N-hydroxy-3-ethyl-2,6-bis(p-fluro)piperidin-4-one ylidene)hydrazinyl)thiol(3a) is established by comparing the ^{1}H NMR and ^{13}C NMR with the reactant N-hydroxy-3-ethyl-2,6-bis(p-flurophenyl)piperidin-4-one thiosemicarbazone(2a).^{1}H-NMR (DMSO-d_6): ∂ 4.65(s,N-OH), 4.13-4.65(d,2H,6H), 2.92-2.97(m,3H,5H), 7.35-7.47(s,ph), 8.32(s,NH_2), 1.12(d,3-CH_3), 1.86-1.91(d,3-CH_2), 1.27(s,NH) and ^{13}C NMR ∂ value: 61.56(2C,6C), 90.57(s,SZ-CSH), 126.75-129.27(ph), 51.67(3C,5C), 10.67(3-CH_3), 20.63(3-CH_2).

There appeared a new singlet as around 3.52ppm for Amino(2-(N-hydroxy-3-ethyl-2,6-bis(p-flurophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3a), which is due to the reduction of thionyl group to secondary alcohol group. The multiplet as around 2.37 ppm is assigned to the methine proton.

In ^{13}C NMR of Amino(2-(N-hydroxy-3-ethyl-2,6-bis(p-flurophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3a) , there appeared a signal at 164.86ppm assigned to C-SH and the thionyl group disappeared. Elemental analysis of the compound(3a) shows excellent agreement with the experimental and calculated values viz., C 76.09%(78.11%), H 7.24% (7.89%) and N 8.11%(8.95%).

3.3.3.The analytical data of N-hydroxy-3-ethyl-2,6-bis(m-nitrophenyl)piperidin-4-one thiosemicarbazone(2b) before subjection to CV

The structure of N-hydroxy-3-ethyl-2,6-bis(m-nitrophenyl)piperidin-4-one thiosemicarbazone(2b) is confirmed by ^{1}H NMR and ^{13}C NMR spectral data. ^{1}H-NMR (DMSO-d_6): ∂ 3.99(s,N-OH), 3.55-3.71(d,2H,6H), 2.86-2.91(m,3H,5H), 7.41-7.45(s,ph), 8.76(s,NH_2), 1.66(d,3-CH_3), 1.35-1.39(d,3-CH_2), 1.89(s,NH) and ^{13}C NMR ∂ value: 75.92(2C,6C), 164.33 (s,SZ-CS), 125.66-129.80(ph), 41.02(3C,5C), 9.46(3-CH_3), 16.4(3-CH_2).

3.3.4.The analytical data of the N-hydroxy-3-ethyl-2,6-bis(m-nitrophenyl)piperidin-4-one thiosemicarbazone(2b) after subjection to CV

The structure of the reduction product Amino(2-(N-hydroxy-3-ethyl-2,6-bis(m-nitrophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3b) is established by comparing the ^{1}H NMR and ^{13}C NMR with the reactant N-hydroxy-3-ethyl-2,6-bis(m-nitrophenyl)piperidin-4-one thiosemicarbazone(2b). ^{1}H-NMR (DMSO-d_6): ∂ 4.26(s,N-OH), 4.25-4.56(d,2H,6H), 2.81-2.85(m,3H,5H), 7.25-7.46(s,ph), 7.85(s,NH_2), 1.11(d,3-CH_3), 1.36-1.39(d,3-CH_2), 1.28(s,NH) and ^{13}C NMR ∂ value: 62.77(2C,6C), 91.54(s,SZ-CSH), 127.73-129.27(ph), 51.60(3C,5C), 10.22(3-CH_3), 20.56(3-CH_2).

There appeared a new singlet as around 3.57ppm for Amino(2-(N-hydroxy-3-ethyl-2,6-bis(m-nitrophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3b), which is due to the reduction of thionyl group to secondary alcohol group. The multiplet as around 2.36ppm is assigned to the methine proton.

In ^{13}C NMR of Amino(2-(N-hydroxy-3-ethyl-2,-6bis(m-nitrophenyl)piperidin-4-oneylidene)hydrazinyl)thiol(3b), there appeared a signal at 164.33ppm assigned to C-SH and the thionyl group disappeared. Elemental analysis of the compound(3b) shows excellent agreement with the experimental and calculated values viz., C 71.32%(72%), H 7.52% (7.87%) and N 9.65%(10.01%).

3.3.5.The analytical data of N-hydroxy-3-ethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone(2c) before subjection to CV

The structure of N-hydroxy-3-ethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone(2c) is confirmed by ^{1}H NMR and ^{13}C NMR spectral data. ^{1}H-NMR (DMSO-d_6): ∂ 4.06(s,N-OH), 3.63-3.70(d,2H,6H), 2.74-2.83(m,3H,5H), 7.23-7.31(s,ph), 8.65(s,NH_2), 1.32(d,3-CH_3), 1.29-1.38(d,3-CH_2), 2.10(s,NH) and ^{13}C NMR ∂ value: 76.50(2C,6C), 163.76(s,SZ-CS), 123.86-130.90(ph), 40.17(3C,5C), 9.89(3-CH_3), 16.76(3-CH_2).

3.3.6.The analytical data of the N-hydroxy-3-ethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone(2c) after subjection to CV

The structure of the reduction product Amino(2-(N-hydroxy-3-ethyl-2,6bis(p-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3c) is established by comparing the ^{1}H NMR and ^{13}C NMR with the reactant N-hydroxy-3-ethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone(2c). ^{1}H-NMR (DMSO-d_6): ∂ 4.15(s,N-OH), 3.70-3.75(d,2H,6H), 2.85-3.50(m,3H,5H), 7.21-7.39(s,ph), 7.90(s,NH_2), 1.16(d,3-CH_3), 1.33-1.41(d,3-CH_2), 2.16(s,NH), 2.33(m-CH) and ^{13}C NMR ∂ value: 61.48(2C,6C), 88.56(s,SZ-CSH), 125.6-127.8(ph), 51.43(3C,5C), 10.57(3-CH_3), 21.63(3-CH_2).

There appeared a new singlet as around 3.51ppm for Amino(2-(N-hydroxy-3-ethyl-2,6bis(p-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3c), which is due to the reduction of thionyl group to secondary alcohol group. The multiplet as around 2.56ppm is assigned to the methine proton.

In ^{13}C NMR of Amino(2-(N-hydroxy-3-ethyl-2,6bis(p-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3c) , there appeared a signal at 164.86ppm assigned to C-SH and the thionyl group disappeared. Elemental analysis of the compound(3c) shows excellent agreement with the experimental and calculated values viz., C 72.29%(73.10%), H 6.82%(7.21%) and N 3.86%(3.93%).

3.3.7.The analytical data of N-hydroxy-3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one thiosemicarbazone(2d) before subjection to CV

The structure of N-hydroxy-3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one thiosemicarbazone(2d) is confirmed by ^{1}H NMR and ^{13}C NMR spectral data.^{1}H-NMR (DMSO-d_6): ∂4.04(s,N-OH), 3.72-3.76(d,2H,6H), 2.67-2.76(m,3H,5H), 7.27-7.40(s,ph), 8.74(s,NH_2), 1.19(d,3CH_3,5CH_3), 2.11(s,NH) and ^{13}C NMR ∂ value: 74.70(2C,6C), 161.21(s,SZ-CS), 122.58-128.78(ph), 15.74-20.71(3,5-CH_3), 43.92(3C,5C).

3.3.8.The analytical data of the N-hydroxy-3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one thiosemicarbazone(2d) after subjection to CV

The structure of the reduction product Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3d) is established by comparing the ^{1}H NMR and ^{13}C NMR with the reactant N-hydroxy-3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one thiosemicarbazone(2d). ^{1}H-NMR (DMSO-d_6): ∂ 3.99(s,N-OH), 3.77-4.10(d,2H,6H), 2.62-2.76(m,3H,5H), 7.27-7.44(s,ph), 8.21(s,NH_2), 2.25(m,C-H), 2.30(d,3CH_3,5CH_3), 3.49(s,C-SH), 2.10(d,NH) and ^{13}C NMR ∂ value: 60.30(2C,6C), 90.49(s,SZ-C-SH), 124.09-126.26(ph), 15.88-16.01(3,5-CH_3), 50.6(3C,5C).

There appeared a new singlet as around 3.49ppm for Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3d), which is due to the reduction of thionyl group to secondary alcohol group. The multiplet as around 2.45ppm is assigned to the methine proton.

In ^{13}C NMR of Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(o-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3d), there appeared a signal at 161.21ppm assigned to C-SH and the thionyl group disappeared. Elemental analysis of the compound(3d) shows excellent agreement with the experimental and calculated values viz., C 68.87%(69.26%), H 6.14% (6.71%) and N 7.27%(7.87%).

3.3.9.The analytical data of N-hydroxy-3, 5-dimethyl -2,6-bis(p-methylphenyl)piperidin-4-one thiosemicarbazone (2e) before subjection to CV

The structure of N-hydroxy-3,5-dimethyl-2,6-bis(p-methylphenyl)piperidin-4-one thiosemicarbazone(2e) is confirmed by ^{1}H NMR and ^{13}C NMR spectral data.^{1}H-NMR (DMSO-d_6): ∂ 4.07(s,N-OH), 3.55-3.67(d,2H,6H), 2.79-2.82(m,3H,5H), 7.15-7.203(s,ph), 1.26(s,ph-CH_3), 7.68(s,NH_2), 1.26(d,3CH_3,5CH_3), 1.99(s,NH) and ^{13}C NMR ∂ value: 73.50(2C,6C), 161.36(s,SZ-CS), 125.34-127.65(ph), 15.18-17.56(3,5-CH_3), 40.37(3C,5C), 21.38(ph-CH_3).

3.3.10.The analytical data of the N-hydroxy-3,5-dimethyl-2,6-bis(p-methylphenyl) piperidin-4-one thiosemicarbazone (2e) after subjection to CV

The structure of the reduction product Amino(2-(N-hydroxy-3,5-dimethyl-2,6-diphenylpiperidin-4-one-ylidene)hydrazinyl)thiol(3e) is established by comparing the ^{1}H NMR and ^{13}C NMR with the reactant N-hydroxy-3,5-dimethyl-2,6-bis(p-methylphenyl) piperidin-4-one thiosemicarbazone(2e). ^{1}H-NMR (DMSO-d6): ∂ 4.14(s,N-OH), 3.61-3.72(d,2H,6H), 2.16-2.86 (m,3H,5H), 7.27-7.31(s,ph), 1.243(s,ph-CH3), 7.67(s,NH2), 2.29(m,C-H), 1.25 (d,3CH3,5CH3), 3.51(s,C-SH), 1.85(d,NH) and ^{13}C NMR ∂ value: 73.77(2C,6C), 89.96 (s,SZ-C-SH), 124.42-125.89(ph), 15.15-16.56(3,5-CH3), 40.22(3C,5C), 21.61(ph-CH3).

There appeared a new singlet as around 3.51ppm for Amino(2-(N-hydroxy-3,5-dimethyl-2,6-diphenylpiperidin-4-one-ylidene)hydrazinyl)thiol(3e), which is due to the reduction of thionyl group to secondary alcohol group. The multiplet as around 2.42ppm is assigned to the methine proton.

In 13C NMR of Amino(2-(N-hydroxy-3,5-dimethyl-2,6-diphenylpiperidin-4-one-ylidene)hydrazinyl)thiol(3e), there appeared a signal at 161.36ppm assigned to C-SH and the thionyl group disappeared. Elemental analysis of the compound(3e) shows excellent agreement with the experimental and calculated values viz., C 67.77%(70.12%), H 6.22%(6.91%) and N 7.87%(8.01%).

3.3.11.The analytical data of N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone(2f) before subjection to CV

The structure of N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone(2f) is confirmed by ^{1}H NMR and ^{13}C NMR spectral data.^{1}H-NMR (DMSO-d_6): ∂ 4.67(s,N-OH), 3.55-3.67(d,2H,6H), 2.86-2.89(m,3H,5H), 7.26-7.56(s,ph), 8.89(s,NH_2), 1.56(d,3CH_3,5CH_3), 1.81(s,NH) and ^{13}C NMR ∂ value: 71.67(2C,6C), 161.46(s,SZ-CS), 125.77-130.95(ph), 15.26-19.93(3,5-CH_3), 29.86(3C,5C).

3.3.12.The analytical data of the N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone(2f) after subjection to CV

The structure of the reduction product Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3f**)** is established by comparing the ^{1}H NMR and ^{13}C NMR with the reactant N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one thiosemicarbazone(2f). ^{1}H-NMR (DMSO-d_6): ∂ 4.71(s,N-OH), 3.86-4.12(d,2H,6H), 3.41-3.45(m,3H,5H), 7.43-7.45(s,ph), 8.86(s,NH_2), 2.15(m,C-H), 2.29(d,3CH_3,5CH_3), 3.4(s,C-SH), 1.39(d,NH) and ^{13}C NMR ∂ value: 64.90(2C,6C), 90.98(s,SZ-C-SH), 125.65-128.59(ph), 16.50-16.62(3,5-CH_3), 51.61(3C,5C).

There appeared a new singlet as around 3.4ppm for Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3f), which is due to the reduction of thionyl group to secondary alcohol group. The multiplet as around 3.5ppm is assigned to the methine proton.

In ^{13}C NMR of Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one-ylidene)hydrazinyl)thiol(3f), there appeared a signal at 161.46ppm assigned to C-SH and the thionyl group disappeared. Elemental analysis of the compound (3f) shows excellent agreement with the experimental and calculated values viz., C 70.27%(71.38%), H 6.76% (6.89%) and N 10.52%(10.86).

3.3.13.The analytical data of N-hydroxy-3,5-dimethyl-2,6-bis(p-flurophenyl)piperidin-4-one thiosemicarbazone(2g) before subjection to CV

The structure of N-hydroxy-3,5-dimethyl-2,6-bis(p-flurophenyl)piperidin-4-one thiosemicarbazone(2g) is confirmed by ^{1}H NMR and ^{13}C NMR spectral data.^{1}H-NMR (DMSO-d_6): ∂ 4.23(s,N-OH), 3.72-3.75(d,2H,6H), 2.76-2.81(m,3H,5H), 7.23-7.35(s,ph), 8.79(s,NH_2), 1.36(d,3CH_3,5CH_3), 2.12(s,NH) and ^{13}C NMR ∂ value: 71.27(2C,6C), 161.28(s,SZ-CS), 126.5-128.8(ph), 16.71-18.70(3,5-CH_3), 29.62(3C,5C).

3.3.14.The analytical data of the N-hydroxy-3,5-dimethyl-2,6-bis(p-flurophenyl)piperidin-4-one thiosemicarbazone(2g) after subjection to CV

The structure of the reduction product Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-chlorophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3g) is established by comparing the ^{1}H NMR and ^{13}C NMR with the reactant N-hydroxy-3,5-dimethyl-2,6-bis(p-flurophenyl)piperidin-4-one thiosemicarbazone(2g). ^{1}H-NMR (DMSO-d_6): ∂ 4.70(s,N-OH), 3.74-4.09(d,2H,6H), 2.79-2.89(m,3H,5H), 7.24-7.40(s,ph), 8.34(s,NH_2), 2.86(m,C-H), 2.27(d,3CH_3,5CH_3), 3.52(s,C-SH), 1.24(d,NH) and ^{13}C NMR ∂ value: 64.11(2C,6C), 90.55(s,SZ-C-SH), 125.61-129.32(ph), 17.20-17.95(3,5-CH_3), 54.58(3C,5C).

There appeared a new singlet as around 3.52ppm for Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-flurophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3g), which is due to the reduction of thionyl group to secondary alcohol group. The multiplet as around 3.01ppm is assigned to the methine proton.

In ^{13}C NMR of Amino(2-(N-hydroxy-3,5-dimethyl-2,6-bis(p-flurophenyl)piperidin-4-one ylidene)hydrazinyl)thiol(3g), there appeared a signal at 165.31ppm assigned to C-SH and the thionyl group disappeared. Elemental analysis of the compound(3g) shows excellent agreement with the experimental and calculated values viz., C 70.25%(69.85%), H 6.62% (6.72%) and N 10.26%(10.52%).

3.4.Antifungal Activity

The thiosemicarbazones (3b-e) were screened for their antifungal activity. The method used for this study is disc diffusion method.The fungal strains used in this study are Aspergillus flavus, Aspergillus niger, Mucor, Microsporum gypseum, Candida albicans and Rhizopus.The results of the antifunagal activity are tabulated in table 8.Each values is an average of three determinations. The table 8 reveals that the compounds (3b, 3c and 3d) and 3g are slight moderate active against all the bacteria, but for the compound 3b is more active for the fungi Aspergillus niger when compared to other three compounds[41].

Table 8: The invitro zone of inhibition profile of the N-hydroxy piperidone thiosemicarbazone against test fungi

Organisms	Compound 3b (µg/ml)			Compound 3c (µg/ml)			Compound 3d (µg/ml)			Compound 3e (µg/ml)		
	100	200	500	100	200	500	100	200	500	100	200	500
Aspergillus flavuspus	12	14	13	17	19	21	9	13	14	11	14	17

Aspergillus niger	21	23	24	17	18	18	12	14	18	12	17	18
Aspergillus fumigates	14	15	18	18	19	20	8	10	11	12	13	16
Mucor	13	16	17	12	16	17	8	11	16	11	18	19
Microsporum gypseum	11	13	17	13	17	18	11	15	16	12	17	19
Candida albicans	10	12	16	14	18	19	12	13	17	13	15	17
Rhizopus	15	16	16	17	17	19	15	17	17	16	18	19

All values are in millimetre (mm), representing the diameter of the zone of inhibition.

4.CONCLUSION

The result obtained shows that the compounds 2a–c and 2d–g undergo irreversible reduction. The diffusion coefficient values obtained for all the compounds are found to be consistent and also have good with the voltametric data. The electrochemical analysis was carried out in mild conditions with minimum working current of μA. The degree of irreversibility was ascertained and the order is 2b>2a>2c for 3-ethyl substituted compounds and 2d>2e>2g>2f for 3,5-dimethyl substituted compounds. The values obtained for charge transfer coefficient (α_n) and diffusion coefficient($D_0^{1/2}$) of all the compounds are discussed. Further the structure of the products was proved by ^{1}H NMR and ^{13}C NMR studies. The results of antifungal activity reveal maximum inhibition against the Aspergillus niger by the compound Amino(2-(N-hydroxy-3-ethyl-2,6bis(p-nitrophenyl)piperidin-4-one-ylidene)hydrazinyl)thiol(3f).

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