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Microwave assisted novel synthesis and antibacterial evaluation of 2-[(5-{[(*Z*)-phenylmethylidene/phenylethylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione derivatives

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ABSTRACT

As a continued research towards the thiadiazole derivatives, we explored here synthesis of 2-[(5-{[(Z)-phenylmethylidene/phenylethylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1H-isoindole-1,3 (2H)-dione Derivatives ***(3a-3j)*** *from 2-[(5-amino-1,3,4-thiadiazol-2-yl)methyl]-1H-isoindole-1,3(2H)-dione* ***(2)*** *by using different aldehyde/substituted acetophenone in glacial acetic acid by microwave irradiation. All the synthesized compounds were characterised on the basis IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis, also synthesized compounds were screened for their antibacterial activity against Gram positive and Gram negative bacteria. Some of the synthesized compounds have potent activity as compared to that of the standard streptomycin.*

Key words: Thiadiazole, Microwave, Antibacterial activity.

INTRODUCTION

Chemistry of heterocycles has been of importance in understanding the formation of bioactive molecules as well as having industrial applications especially in pharmaceuticals [1]. The majority of Bio- active compounds and agrochemicals contain N and S heterocyclic system. The 1, 3, 4-thiadiazole motif demonstrates numerous biological properties such as anti-parkinsonism [2], anticancer [3], anti-inflammatory [4] etc and acquire unique position in the area of pharmaceutical research. In addition electron- deficient nature and good electron accepting property of 1, 3, 4-thiadiazole promotes its application in field of Electrochemistry. However, some studies revealed that thalidomide drug with phthalimide moiety were efficient in the treatment of erythema nodosum leprosum (ENL), a sharp manifestation of the Hansen's disease [5-6]. It has been reported to be efficient in inflammatory process [7] and used in the agrochemical industry. So we are interested in synthesis of phthalimide derivatives with thiadiazole moiety.

In the last few years Microwave-induced Organic Reaction Enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid synthesis [8] and many researchers have described accelerated organic reactions and a large number of papers has appeared proving the synthetic utility of MORE chemistry in routine organic synthesis [8, 9].In view of development of environmentally benign protocols, we report herein a Microwave assisted novel synthesis of 2-[(5-{[(*Z*)-phenylmethylidene/phenylethylidene]amino}-1,3,4-thiadiazol-2-yl) methyl] -1*H*-isoindole-1,3(2*H*)-dione Derivatives and evaluated their antibacterial activities.

EXPERIMENTAL SECTION

Solvents and reagents were commercially sourced from Sigma Aldrich and used without further purification. Melting points were determined in an open capillary and are uncorrected. Products were recrystalized from ethanol as a solvent. The purity of compound checked by the TLC on silica gel G plates. The microwave used for the synthesis is of ONIDA Company and domestic type. The Infrared spectra were obtained on Perkin Elmer FT-IR spectrometer. The samples were examined as KBr discs 5%w/w. All the compounds were analysed for C, H and N

on Carlo-Erba elemental analyser.^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avon 300MHz spectrometer using $CDCl_3$/ DMSO as solvent and TMS as internal standard, the chemical shifts are reported in ppm. Multiplicities are indicated by's' (singlet),'d' (doublet),'t' (triplet),'q (quartet),'m' (multiplet), bs (broad singlet).

General procedure for preparation of (1, 3-dioxo-1, 3-dihydro-2H-isoindol-2-yl) acetic acid (1)
An equimolar mixture of phthalic anhydride (0.02 mol) and glycine (0.02 mol) was taken in borocil beaker and irradiated to the microwave radiation for 3min.[10].Resulted reaction mixture was poured into water to remove unreacted glycine, filtered, dried and recrystallized from ethanol.

General procedure for preparation of 2-[(5-amino-1, 3, 4-thiadiazol-2-yl)methyl]-1H-isoindole-1,3(2H)-dione (2)
A mixture of thiosemicarbazide (0.02mol), (1, 3-dioxo-1, 3-dihydro-2H-isoindol-2-yl) acetic acid **(1)** (0.02mol) and conc. H_2SO_4 (10ml) was taken in borocil beaker and subjected to the microwave irradiation for 2-3 min. After completion of the reaction as checked by TLC(EA: Pet ether::40:60), reaction mixture poured into the ice cold water and treated with the saturated solution of $NaHCO_3$ to neutralise acid left behind[11]. Product of the reaction filtered and recrystallized from hot water.

General procedure for preparation of 2-[(5-{[(Z)-phenylmethylidene/phenylethylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1H-isoindole-1,3(2H)-dione (3a-3j)
The compounds **(3a-3j)** were synthesized as per reported in literature [12]. Equimolar quantity of (**2)** (1mmol) and substituted aromatic aldehydes /acetophenone(1mmol) were dissolved in ethanol containing few drops of glacial acetic acid, taken in borocil beaker and subjected to the microwave radiation for 3 min; after completion of reaction, reaction mixture cooled and then poured into crushed ice. The solid obtained thus filtered, and washed with water and recrystallized from ethanol

Antimicrobial activity
Method of testing: Cup plate method
The compounds were screened for their antibacterial activity using cup plate method [13].Sterile nutrient agar media was poured into the sterilised Petri dishes. The poured agar media was allowed to solidify for 30 min, on the surface of the media microbial suspension were spread with help of sterilised spreader and there after cups were made into the agar surface with help of sterile cork borer. The test compound solution 0.1 ml was placed into these cups with the help of micro pipette. The plates were kept in freeze for diffusion, for one hr. For antibacterial studies, incubation was carried out at 37^0C for 24 hr. The test solution was prepared using DMSO as solvent. Clinically antimicrobial drug streptomycin was used as the positive control and DMSO for blank. The solution was diffuses trough agar around its cup and produces clear zone of inhibition which was measured in mm and the results were recorded.

Spectral data of representative compounds:
(1, 3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl) acetic acid (1)
IR (KBr) :υ_{max} = 3418.34 (-OH), 3057.68(Ar-H), 1714.003(>C=O), 1612.3 (Ar- C=C<) cm^{-1}.
^{1}H NMR (400 MHz, DMSO) : δ = 4.48 (s, 2H, $-CH_2$), 7.81-7.94(m, 4H, Ar-H), 13.2 (bs, 1H, OH) ppm.
^{13}CNMR(100MHz, DMSO): δ=56.18($-CH_2$), 123.52, 131.87, 132.73, 155.86 (>C=O), 167.30(>C=O), 167.66 (>C=O) ppm.

2-[(5-amino-1,3,4-thiadiazol-2-yl)methyl]-1H-isoindole-1,3(2H)-dione (2)
IR(KBr): υ_{max} = 3392.563, 3252($-NH_2$), 3072(-Ar-H), 2879(-CH), 1705.611(>C=O), 1603.551(Ar-C=C<), 1515.179 (-C=N-), 750(-C-S-)cm^{-1}.
^{1}H NMR (400 MHz, DMSO): δ= 4.59 (s, 2H, $-CH_2$), 4.99 (s, 2H, $-NH_2$), 7.7 – 7.9 (m, 4H, Ar-H) ppm.
^{13}CNMR (100 MHz, DMSO): δ=56.54($-CH_2$), 123.60, 132.40, 132.78, 162.10, 167.60(>C=O), 167.86 (>C=O), 169.06 ppm.

2-[(5-{[(*E*)-(4-chlorophenyl)methylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione(3d)
IR(KBr): υ_{max}=3092.072(-Ar-H), 2956.922(-C-H), 1706.002(>C=O), 1596.054(Ar-C=C<), 1515.642(-C=N-), 750(-C-S-), 725 (C-Cl) cm^{-1}.
^{1}H NMR(400 MHz, DMSO): δ = 4.590(s, 2H, $-CH_2$), 6.998-7.962 (m, 8H, Ar-H), 8.884 (s, 1H, =CH) ppm.
^{13}CNMR(100MHz, DMSO): δ= 57.54($-CH_2$), 129.22, 129.59, 130.11, 131.40, 131.78, 132.02, 134.73, 152.86, 162.18, 165.06, 167.29(>C=O), 167.64(>C=O)ppm.
MS (EI): m/z =382(M+).

2-[(5-{[(*E*)-(4-methoxyphenyl)methylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (3e)

IR(KBr): υ_{max}=3078.318(-Ar-H), 2970.990(-C-H), 1703.735(>C=O), 1596.054(Ar-C=C<), 1510.418 (-C=N-), 740(-C-S-)cm^{-1}.

^{1}HNMR(400MHz, DMSO):δ =4.49(s, 3H, -OCH_3), 4.96(s, 2H, -CH_2), 6.6-7.812(m, 8H, Ar-H), 8.8(s, 1H, =CH) ppm.

^{13}CNMR(100MHz, DMSO): δ= 56.21(-OCH_3), 56.99(-CH_2), 114.18, 116.51, 123.54, 131.18, 132.23, 134.53, 139.24, 152.29, 162.15, 165.55, 167.75(>C=O), 167.85 (>C=O) ppm.

2-[(5-{[(1*E*)-1-(2-hydroxyphenyl)ethylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (3h)

IR(KBr):υ_{max}=3218.312(-OH), 3070.319(Ar-H), 2930.319(C-H), 1705.707(>C=O), 1610.312(Ar-C=C), 1517.039(-C=N-), 750(-C-S-) cm^{-1}.

^{1}HNMR(400MHz, DMSO): δ=2.1(s, 3H, -CH_3), 4.4(s, 2H, -CH_2), 6.959-7.947(m, 8H, Ar-H), 9.88 (bs, 1H, -OH) ppm.

^{13}CNMR(100MHz, DMSO): δ=19.15(-CH_3), 56.10(-CH_2), 117.50, 118.83, 120.84, 123.11, 128.15, 131.78, 131.86, 133.73, 162.20, 163.25, 165.30, 165.35, 167.50(>C=O), 167.68 (>C=O) ppm.

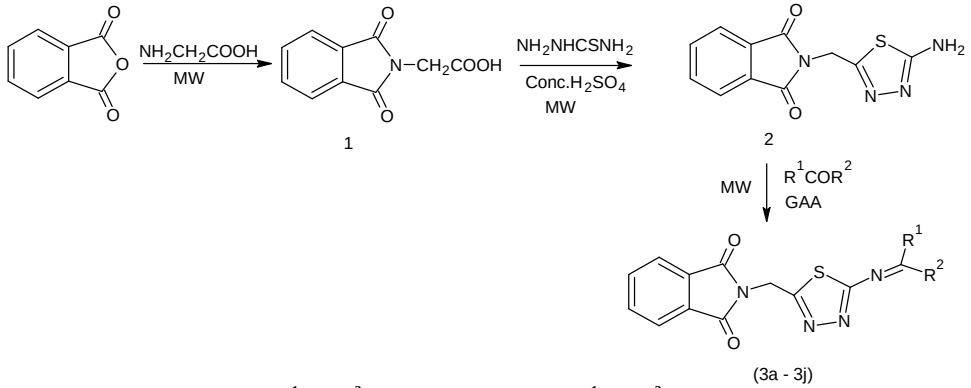
2-[(5-{[(*E*)-(4-fluorophenyl)methylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione(3g)

^{1}HNMR(400MHz, DMSO): δ =4.4(s, 2H, CH_2), 7.4-7.9(m, 8H, Ar-H), 8.8(s, 1H ,-=CH) ppm.

^{13}CNMR(100MHz, DMSO): δ=56.14(-CH_2), 123.76, 129.26, 129.57, 130.10, 131.40, 131.76, 132.12, 134.70, 134.80, 152.80, 162.26, 165.06, 167.22, 167.60ppm.

MS (EI): m/z =365(M+).

Scheme



3a: R^1=H; R^2=C_6H_5, **3b: R^1=H; R^2= 2-OH- C_6H_5,**
3c: R^1=H; R^2=4-OH-C_6H_5 **3d: R^1=H; R^2=4-Cl-C_6H_5**
3e: R^1=H; R^2=4-OCH_3-C_6H_5 **3f: R^1=H; R^2=4-NO_2-C_6H_5**
3g: R^1=H; R^2=4-F-C_6H_5 **3h: R^1=CH_3; R^2=2-OH-C_6H_5**
3i : R^1=CH_3; R^2=C_6H_5 **3j: R^1= CH_3; R^2=4-NH_2-C_6H_5**

RESULTS AND DISCUSSION

In the present chapter, we have carried out novel synthesis of 2-[(5-{[(*Z*)-phenylmethylidene/phenylethylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione **(3a-3j)** in 82-84% yield by using 2-[(5-amino-1, 3, 4-thiadiazol-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione **(2)** as per outlined in **scheme 2.8**. Initially, (1, 3-dioxo-1, 3-dihydro-2*H*-isoindol-2-yl) acetic acid **(1)** were prepared by microwave method as per reported[10] which on condensation with the thiosemicarbazide in presence of concentrated H_2SO_4 yields the desired thiadiazole derivative **(2)** by the microwave radiation, followed by treatment of the different aromatic aldehydes/acetophenones in glacial acetic acid under the microwave radiation for 3 min predicts thiadiazole derivatives **(3a-3j)**.The mechanism of formation of target compound is as shown in **Fig.2.1.**

The structures of the synthesized compounds were confirmed unambiguously using IR, NMR and Mass spectral methods. In IR spectra of the entire synthesized compounds **(3a-3j)**, presence of characteristic absorption band at 1706-1703 cm^{-1} due to stretching vibration of carbonyl groups. The absorption band observed at 1610-1596, 1515 cm^{-1}assigned to the stretching vibration of -C=C and -C=N- (Thiadiazole ring) groups respectively. Also absorption band at 750 cm^{-1} is showing presence of -C-S stretch which supports thiadiazole ring. Compound **2** exhibit absorption band at 3392-3252cm^{-1} due to -NH_2 stretching vibration which is disappear in the compounds **(3a-3j)**

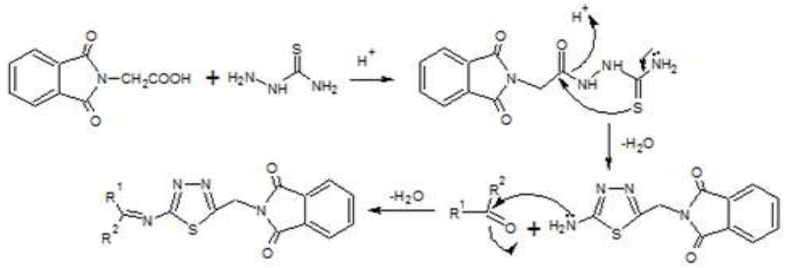


Fig.2.1 Mechanism for formation of Thiadiazole and Schiff base

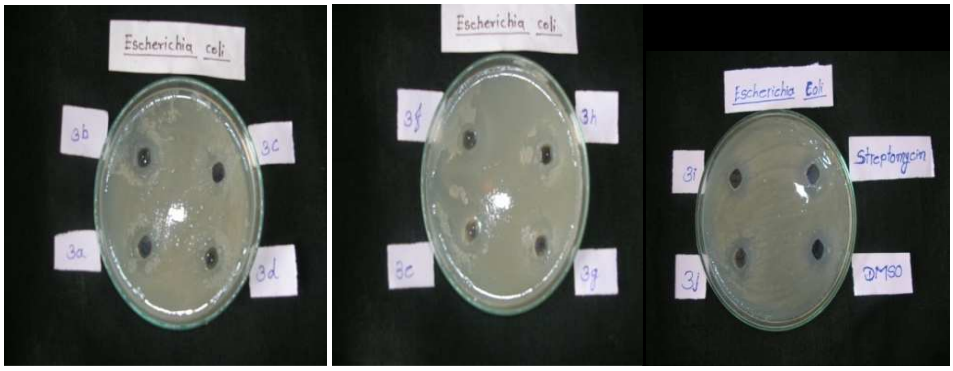
^{1}HNMR spectra of compounds **(3a-3g)** exhibit singlet at δ 4.5 ppm corresponds to $–CH_2$ protons, while multiplets due to aromatic protons observed at δ 6.9-7.9 ppm and singlet of olefinic –CH proton at δ 8.8 ppm. While the compounds **(3h-3j)** shows presence of singlet at δ 2.1 ppm due to $–CH_3$ protons, singlet at δ 4.4 ppm corresponds to the $–CH_2$ protons and multiplets due to aromatic proton observed at δ 6.9-7.9 ppm. ^{13}C NMR spectra of all synthesized compound **(3a-3j)** shows distinct peaks in agreement with the synthesized compounds.

All the synthesized compounds were evaluated for their antibacterial activity against *E.coli* and *S.aureus* using cup plate method, at 100µg/ml using DMSO as a control and streptomycin standard. Most of the synthesized compounds showed moderate to good antibacterial potential as compared to the standard (**Table 2.4).**Literature survey showed that incorporation of the electron withdrawing and electron donating groups into the heterocyclic compounds increases lipophilicity of the compounds, which results in easier penetration of lipid membranes and compounds showed better antibacterial potential. Out of the synthesized compounds **3c, 3h**, **3j** with hydroxyl; amino substituents have good activity and **3b, 3f, 3i,** have moderate antibacterial activities against *S.aureus.* However **3b, 3e, 3i, 3j** compounds showed moderate activity against *E.coli.* Result of the screening indicates that most of the compounds showed good inhibitory activity against *S.aureus* as compared to against E.coli.

Antibacterial activity of 2-[(5-{[(Z)-phenylmethylidene/phenylethylidene]amino}-1,3,4-thiadiazol-2-yl)methyl] -1H-isoindole-1,3(2H)-dione (3a-3j)

Against *Staphylococcus aureus*

Against *Escherichia coli*



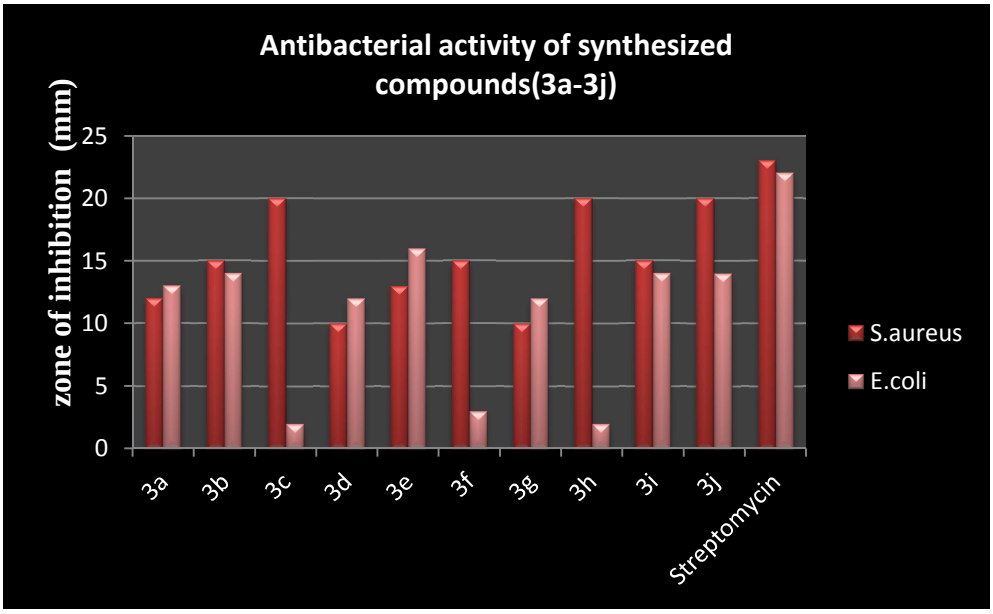


Table 1: Antibacterial activity of Synthesized Compounds (3a-3j)

Comp. No.	Antibacterial activity(mm)	
(100µg/ml)	***S.aureus***	***E.coli***
3a	12	13
3b	**15**	**14**
3c	**20**	02
3d	10	12
3e	13	**16**
3f	**15**	03
3g	10	12
3h	**20**	02
3i	**15**	**14**
3j	**20**	**14**
Streptomycin	**23**	**22**

Table 2: Physical and Elemental analysis of synthesized compound (3a-3j)

Comp. No.	Molecular Formula	MP (^{0}C)	Yield (%)	Elemental Analysis (%)		
				C	H	N
3a	$C_{18}H_{12}N_4O_2S$	160[162][12]	82	62.05	3.41	16.1
3b	$C_{18}H_{12}N_4O_3S$	150[154][12]	83	59.33	3.3	15.35
3c	$C_{18}H_{12}N_4O_3S$	143[140][14]	85	59.32	3.3	15.34
3d	$C_{18}H_{11}N_4O_2SCl$	270	86	56.46	2.88	14.66
3e	$C_{19}H_{14}N_4O_3S$	159[160][12]	84	60.32	3.71	14.82
3f	$C_{18}H_{11}N_5O_4S$	259	85	54.97	2.77	17.82
3g	$C_{18}H_{11}N_4O_2SF$	244	86	59.18	3.02	15.33
3h	$C_{19}H_{14}N_4O_3S$	98	83	62.3	3.82	15.31
3i	$C_{19}H_{14}N_4O_2S$	123[124][12]	84	62.91	3.88	15.47
3j	$C_{19}H_{15}N_5O_2S$	290	83	60.46	3.98	18.55

CONCLUSION

Here we have carried out operationally simple microwave assisted synthesis of 2-[(5-{[(Z)-phenylmethylidene/ phenylthylidene]amino}-1,3,4-thiadiazol-2-yl)methyl]-1H-isoindole-1,3(2H)–dione. This synthetic protocol operates in short reaction time, atom economy and has benefit of easy workup. All the synthesized compounds were showed moderate to good antibacterial activity.

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REFERENCES

[1]E. Couladourous; A. T. Strongilos. *Angew. Chem. Int. Ed.*, **2002**, 41, 3677.
[2]F. Azam; I. Ibn-Rajab; A. Alruiad. *Pharmazi* ,**2009**, 64, 771.
[3]C. Parkanyi; H.Yuan ; B. Stromberg; A. Evenzahav. *J. Heterocycl. Chem.*, **1992**, 29, 749.
[4]D. Boschelli; D.Connor; D. Bornemeier; R.Dyer; J.Kennedy; P. Kuipers; Okonkwo; G. D. Schrier; C. Wright. *J. Med. Chem*., **1993**, 36, 1802.
[5]J. Sheskin. *J. Clin.Pharmacol.Ther*.,**1965**, 6, 303.
[6]C.L. Crawford. *Adv. Drug. React. Toxicol. Rev*., **1994**, 13,177.
[7]G.W. Muller; L. G. Corral; M.G. Shire; H. Wang; A. Moreira; G. Kaplan; D.I. Stirling *J.Med.Chem*., **1996**,39,3238.
[8]R. Varma. *Green Chemistry*, **1999**, 1, 43.
[9]R.Borah; D.Kalita; J. Sarma. *Indian J. Chem. (Sec. B)*, **2002**, 41B, 1032.
[10] R. Antunes; H. Batista; R. Srivastava; G.Thomas; C. Araujo; Longo, R.; H. Magalhaes; M. Leao; A. Pavao. *J. Mol. Struct*., **2003,** 660, 1.
[11] A. Nayak; N. Madhav. *Acta Chim. Pharm. Indica*, **2014**, 4(1), 63.
[12] R. Mahendrasinh; H. Patel; L. Raj; N. Patel. *Int. J. Res. Chem. Environ.*, **2013**, 3(3), 9.
[13] R.Chuickshank; Dugid; D. Marmon; R.Swain; *In medicinal microbiology. Churchill-livingstone, Edinburg***, 1975**, 2.
[14] P. Sah; N.Saraswat; M. Seth. *E-Journal of Chem.* **2011**, 8(1), 427.