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ORIGINAL ARTICLE OPEN ACCESS

Ionic liquid $[Et_3NH][HSO_4]$ promoted One-pot Synthesis of 1, 3-Benzoxazoles with Substituted Thiazolidinone Moiety

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ABSTRACT
A significant, One-pot Synthesis of 1, 3-benzoxazoles with substituted thiazolidinone moiety using 2-(4-amino phenyl) benzoxazole, substituted aromatic aldehyde, and thioglycolic acid under $[Et_3NH][HSO_4]$ ionic liquid. Ionic liquid has been used as a rupid, greener, and reusesionic liquid for the synthesis of 1, 3-benzoxazoles with substituted thiazolidinonesunder solvent-free conditions.This methodology's numerous advantages are non-corrosiveness, safety, little waste, generality, simplicity, ease of isolation, short reaction times, better yields, and environmental friendliness.
Keywords: *$[Et_3NH][HSO_4]$, Ionic liquid, 1, 3-benzoxazoles,thiazolidinone,multicomponent reactions.*

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INTRODUCTION

Multi-component reactions have proven to an extremely effective at producing compounds in a single step and development of new MCRs, as well as the improvement of existing multi-component reactions, is a hot topic right now [1-4].MCRs contribute significantly to the convergence synthesis of organic compounds' simple, commonly available starting components [5-7].

Sulfur heterocycles, such as the thiazole, have been labeled "privileged structures" because of their presence in biologically active natural compounds, medicines, and a variety of synthetic intermediates[8]. During the process of probing structural activity relationships (SAR) for lead optimization, thiazole can also be employed as an amide isostere or in a scaffold hopping strategy. As a result, thiazoles are commonly used as the main structure in the synthesis of chemical library resources or in drug design. Many thiazole compounds have been produced in recent decades and tested for a variety of biological activities[9]. Among these numerous classes, thiazolidine-4-ones are of special interest to researchers due to their efficacy in several biologically active compounds such as anti-bacterial[10-14], anti-tumor[15], anti-tubercular[16],anti-fungal[17],anti-viral[18], anti-inflammatory [19], and etc. Several of these procedures, however, limitations are extended reaction durations, dangerous organic solvent, high acidic conditions, time-consuming workups, and the use of significant amounts of catalyst.

ILshaveenvironmentally acceptable solvents, catalysts, and reagents for chemical transformations due to their exceptional properties such as superior chemical stability, lack of flammability, and low volatility [21-27].They have notable qualities such as low vapour pressure, nonflammability, recyclable capabilities, and organic substances. Because of their fascinating physical and chemical features, ionic liquids have been used in a variety of applications. ILs have been successfully employed in cyclo condensation reactions, Prins reactions, and Oxa-Michael additions, among other chemical reactions [28-30]. As a result, we developed a moderate generalized to synthesis 1, 3-benzoxazoles with substituted thiazolidinone moiety using ionic liquid $[Et_3NH][HSO_4]$ under solvent-free environments.

MATERIAL AND METHODS

The chemicals were bought in a store and used without purification. The melting points were measured in an open capillary tube with no corrections. CDCl3 was used as the solvent for ^1H and ^{13}C-NMR on a Bruker Avance II 400 spectrometer. The IR spectra were captured in KBr using a Perkin-Elmer RXI spectrometer.

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General Procedure for Preparation [Et_3NH] [HSO_4] Ionic liquid.

H_2SO_4 (98 percent, 9.79 g, 0.1mmol) was dropped into Et_3N at 60 °C for 60 minutes (9.99 g, 0.1mmol). Following the addition, the reaction mixture was agitated for an extra 60 minutes at 80 °C to ensure that the reaction was complete. The remaining water is removed by heating, Yielding 98 percent, 18.5 g of IL [Et_3NH][HSO_4].

General Procedure for Synthesis of 3-[4-(1,3-benzoxazol-2-yl)phenyl]-2-aryl-1,3-thiazolidin-4-one.

A reaction mixture 2-(4-amino phenyl) benzoxazole 1a (1 mmol), substituted aromatic aldehyde 2a (1 mmol) and thioglycolic acid 3a (1 mmol) under ionic liquid [Et_3NH] [HSO_4] and the reaction mixture heated 80°C with constant string. Progress of the reaction is monitored byusing TLC. After completing the reaction product was quenched into ice-cold water, the product was separated through filtration and characteristics data compared to literature. By removing the water under reduced pressure, the [Et_3NH] [HSO_4] was recycled.

Spectral Data.

3-[4-(1,3-benzoxazol-2-yl)phenyl]-2-(4-chlorophenyl)-1,3-thiazolidin-4-one(4e): Solid;m. p. 119-122 °C; Yield: 94%;IR(KBr):υ_{max}=3052(-Ar-H),2885(-C-H),1685(>C=O), 751(C-S-C) cm^{-1};13C-NMR(100 MHz, DMSO-d^6):δ 34.3(C2),68.5(C5), 110.4 (C23), 113.8 (C8,C12), 119.9(C26),124.2(C24),124.9 (C25), 127.5(C10), 128.6(C17), 129.6(C14,C18), 129.5 (C15),131.3(C9,C11), 135.17.(C16), 139.3(C13), 141.1(C21), 144.7(C7),150.1(C20),164.4(C19),170.9(>C=O) ; 1H-NMR(DMSO):δ 3.71 (d,*J* = 15.9 Hz,1H,C2-H), 3.97 (d,*J* = 15.9 Hz,1H,C2-H), 6.47 (s,1H,C5-H), 7.26(ddd,J=8.55,7.56,1.76,1H, C24-H), 7.33(ddd, J=7.92, 1.60, 0.45, 1H,C25), 7.54(ddd,J=8.41, 1.54, 0.55,2H,C15,17-H),7.65(ddd,J=8.41, 1.49, 0.55, 2H,C14,18), 7.71(ddd,J=8.55, 160,0.51, 1H,C23-H), 7.72(ddd,J= 8.19,1. 58,0.44,2H,C9,11-H), 7.84(ddd,J=8.19, 1.93, 0.45, 2H,C8,12-H), 7.89 (ddd, J=7.92, 1.76,0.51,1H,C26-H) ppm.).

3-[4-(1,3-benzoxazol-2-yl)phenyl]-2-(4-nitrophenyl)-1,3-thiazolidin-4-one(4f): Solid;m. p. 175-178 °C; Yield: 92%;IR (KBr):υ_{max}= 3066(Ar-H),2933(CH),1650(>C=O),1519.274(Ar-C=C<),1423(-C=N-),775(C-S-C)cm^{-1}.; 13C-NMR(100 MHz, DMSO-d^6):δ 33.4(C2),68.5(C5), 110.4(C24), 113.8 (C8,C12), 119.9 (C27),124.2(C24),124.9 (C25), 127.5(C10), 127.8 (C14,C18), 124.6 (C15,C17), 131.3(C9,C11),139.3(C13), 141.1 (C21), 143.3 (C16),144.7(C7), 150.1 (C20), 164.4(C19), 170.9(>C=O);^{1}H-NMR(DMSO): δ 3.72 (d,*J* = 15.9 Hz,1H), 3.97 (d,*J* = 15.9 Hz,1H), 6.50(s,1H), 7.25(ddd,J=7.93, 2.25,0.44,1H, C24H),7.33(ddd,J=7.92,0.56,1.60,1H,C25H),7.41(ddd,J=7.93,2.225,0.55,2H, C14,18H), 7.71 (ddd, J=8.55, 1.60,0.51,2H,C23-H),7.72(ddd,J=8.19,1.59,0.44,2H,C9,11H),7.84(ddd,J=8.19. 1.93, 0.45,2H,C8, 12-H), 7.89 [ddd,J=7.92,1.76,0.51,1H,C26H),8.16(ddd,J=7.93,1.86,0.44,2H,C15,17-H)

RESULT AND DISCUSSIONS

Here, we revealed an effective and greener route for the one pot Synthesis of 1, 3-Benzoxazoles with Substituted thiazolidinone moiety, 2-(4-amino phenyl) benzoxazole(1a, 1 mmol), substituted aromatic aldehyde (2a,1 mmol) and thioglycolic acid(3a,1 mmol) in the presence of [Et3NH][HSO4] act as a catalyst plus solvent[Scheme 1].

The several ILs and model reaction was carried out 2-(4-amino phenyl) benzoxazole(1a, 1 mmol), benzaldehyde (2a,1 mmol), and thioglycolic acid (3a,1 mmol) under [Et_3NH][HSO_4] ionic liquid. All of the ILs tested were shown to be capable of initiating the product3-[4-(1,3-benzoxazol-2-yl) phenyl]-2-phenyl-1,3-thiazolidin-4-one derivatives (4a-h). However, a yield of the corresponding 1, 3-Benzoxazoles with Substituted thiazolidinone moiety was outstanding(Table 1,entry 6). Formerly, several reaction parameters were examined, including temp., and IL quantity (Table 1).

With these results in hand, we were inspired to make a variety of 1, 3-Benzoxazoles with substituted thiazolidinone moiety (4a-h) and the synthesis (4a) compound shows shorter time 35 min and 95 % yield. Table 2 shows the results, which show that the product 3-[4-(1,3-benzoxazol-2-yl) phenyl] contains both electron-poor and electron-rich substituents. The simple and easy to make -2-phenyl-1,3-thiazolidin-4-one analogs, all were obtained with excellent yields. [Et_3NH][HSO_4]] catalyst for ionic liquid. In the reaction to synthesize 3-[4-(1,3-benzoxazol-2-yl) phenyl], the reusability of the [Et_3NH][HSO_4] catalyst were investigated. Under ideal reaction conditions, (4a). When the reaction was finished and cool to room temp. After being added to water, and precipitated mixture was filtered andseparated the crude components. The water and [Et_3NH][HSO_4] were evaporated in the presence of decreasing pressure after completely washing the solid products, and the catalyst was retrieved and utilized for the next round. Without losing any activity, the recovering catalyst was reapplied for at least four runs.(Figure 1&2)

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Scheme: 1 One-pot Synthesis of 1, 3-Benzoxazoles with Substituted Thiazolidinone Moiety

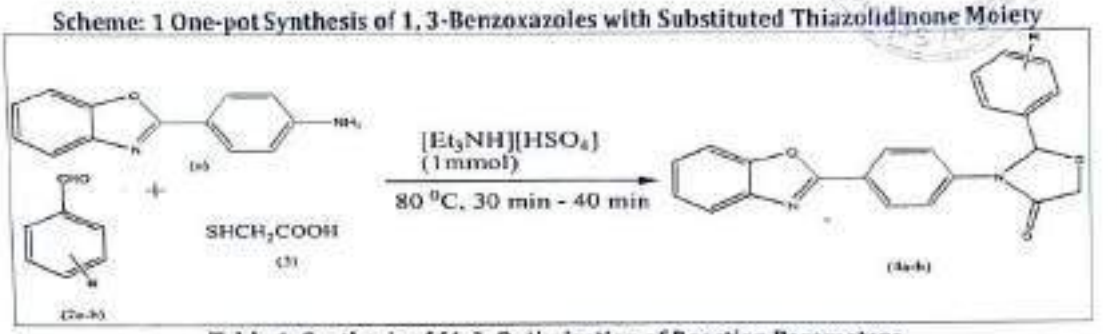

Table 1: Synthesis of (4a): Optimization of Reaction Parameters

Entry	Catalyst (mmol)	Temperature (°C)	Time (min)	[a]Yield (%)
1	Solvent-free	120	20h	35
2	EtOH	80	16h	35
3	[DBUH][Im] (1)	80	40	75
4	[DBUH][OAc]	80	40	79
5	[Et3NH][HSO4] (0.5)	80	35	85
6	**[Et3NH][HSO4] (1)**	**80**	**35**	**95**
7	[Et3NH][HSO4] (1.5)	80	35	95
8	[Et3NH][HSO4] (2)	80	35	95

Table 2: One-pot Synthesis of 1, 3-Benzoxazoles with Substituted Thiazolidinone Moiety

Entry	Aromatic aldehyde	Time (min)	[a]Yield (%)	[b]Melting point
4a	-H	35	95	150-153
4b	-4-F	35	92	109-111
4c	-2-OH	35	94	248-250
4d	-2-OH-OMe	38	93	209-211
4e	-4-Cl	38	94	119-122
4f	-4-NO2	40	92	175-178
4g	-3-Br	35	94	279-281
4h	-2-NO2	40	94	178-180

[a]Isolated yields. [b]All m.p. compared with literature[31].

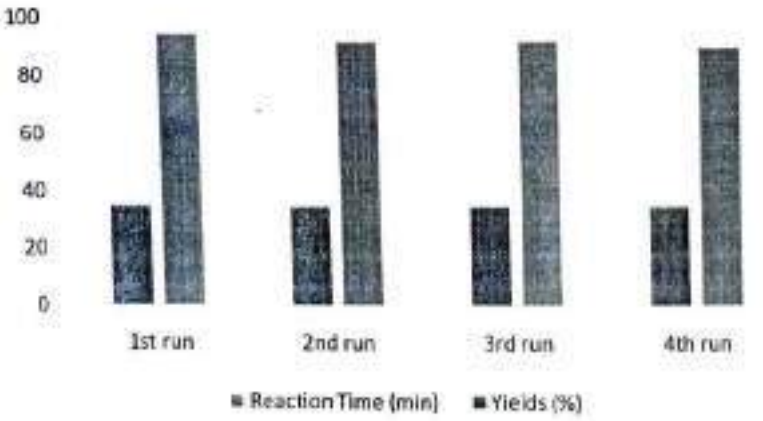

Figure 1: Recycling of ionic liquid [Et3NH][HSO4] of synthesis (4a) compound.

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Figure 2: IR Spectra shows reusability of ionic liquid $[Et_3NH][HSO_4]$.

CONCLUSION

A conclusion, one-pot Synthesis of 1, 3-benzoxazoles with substituted thiazolidinone moiety by using ionic liquid $[Et_3NH][HSO_4]$. Every one of the reactions were carried out at 80°C with 1 mmol $[Et_3NH][HSO_4]$, and the desired products were generated with excellent yield in shorter reaction times. This approach is environmentally sustainable, with benefits such as strong yields, facile catalyst preparation/separation, high catalytic activity, catalyst recyclability, and ease of use.

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ORIGINAL ARTICLE **OPEN ACCESS**

Ultrasound Assisted One-Pot Green Synthesis of Highly Substituted Pyrazoles Catalyzed by [DBUH][OAc] Ionic Liquid

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ABSTRACT

A significant, one-pot synthesis of highly substituted pyrazoles derivativevia three-component condensations of Aromatic aldehyde, Malononitrile, along with Phenylhydrazine in the presence of ionic liquid [DBUH][OAc]. The present technique provides significant advantages, including reduced environmental impact, simple procedure, shorter reaction time, mild condition, and ease of product recovery. The ionic liquid reusability and recovery make the protocol eco-friendly. Also, a series for 5-amino-1,3-diphenylpyrazole-4-carbonitrile analogues were synthesised. For the comparison between conventional and ultrasound techniques. It was observed that the ultrasound irradiation technique gave excellent yield and shorter reaction time than the conventional technique.

Keywords: pyrazole, multicomponent reaction, ionic liquid, [DBUH][OAc], ultrasound irradiation.

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INTRODUCTION

In pharmaceutical research, five-membered N-linked heterocyclic molecules have attracted much interest. For synthesizing five-membered heterocyclic compounds, the condensation reaction suitable sequential compound is the most popular alternative approach [1-4]. Pyrazole ring is a prominent motif which among the provide reported as having outstanding pharmacological and biological activity such as antimicrobial [5], antiviral [6], anti-inflammatory [7], anticonvulsant [8], anti-depressant [9], antitumor [10], as well as fungicidal properties [11,12]. Several pyrazole derivatives exhibit significant pharmacological properties and are valuable materials in pharmaceutical research. Some of the pyrazole-containing drugs like Antipyrine, Celecoxib, Mepirizole, Rimonabant, Lonazolac, and Tepoxalin, etc. The structure of drugs has been shown in Figure 1[13-18].

Multicomponent reactions (MCRs) is the preferable approach because it allows for high throughput chemical synthesis at a low cost and in a shorter reaction time. Because it generates significant compounds in a single step by forming multiple new bonds in a one-opt, the approach has prompted a lot of interest in organic chemistry. In both drug discovery and green chemistry [19,20]. In the last decade, the growth of three and four-component reaction has been considerable and there is still a lot of effort being put into developing new MCRs [21,22].In currentcenturies, ionic liquids (ILs) have obtained a noteworthy attention in the context of eco-friendly green synthesis since they can also be used as effective media for organic synthesis [23-25]. Non-volatility, non-explosive, low vapour pressure, reusable, easily operated, as well as thermally stable over a wide temperature range are only several of the physicochemical features of ILs. Due to their specific ionic character and structural organization, ionic liquids can be regarded as alternative greener solvents [26,27]. In organic synthesis, there are numerous reports about the application of ILs such as Biginelli reaction [28], Friedel-Crafts reaction [29], Beckmann rearrangement [30], Diels-Alder reaction [31], Heck reaction [32], Pechmann condensation [33], and more reactions [34-38].Recently, the technique of synthesizing organic molecules using ultrasound irradiation is very effective and attractive. Ultrasound irradiation is used to increase the rate of a chemical reaction by ultrasonic cavitation mechanism, mass transfer in the microenvironment can be accelerated, which is the formation of microbubbles, growth, and impulsive collapse. High temperature and pressure are generated by collapsing bubbles, resulting in hot spots with enough energy to promote chemical reactions [39-43]. This method is considered in terms of conserving energy, reducing reaction time, improving yield and waste minimization [44,45]. In the current work, effective implementation of

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[DBUH][OAc] ionic liquid and ultrasound has been established for synthesis of highly substituted pyrazoles [Scheme 1]. Use of the catalyst [DBUH][OAc] is associated with ultrasound irradiation technique for the synthesis substituted pyrazoles is investigated for first time. A comparative study by conventional as well as ultrasonication technique.

MATERIALS AND METHODS

Analytical grade of all chemicals and were purchased from a commercial source. Merck 60 F250 TLC analytical silica gel plat is used to monitor reaction progress and purity of compounds. Bondelin sonorex (frequency of 40 MHz and 100W) was used to ultrasound bath. Using of Avance-II(Bruker) instrument for ^{1}H-NMR and ^{13}C-NMR their frequency 400MHz and 100 MHz, recorded in Dimethyl sulfoxide-d6. RZX (Perkin Elmer) spectrometer using KBr, IR spectra were recorded. The melting points were determined by using the open capillary tube is uncorrected.

General procedure for the preparation of I.L.[DBUH][OAc]

In a round bottom flask add acetic acid (1 eq.) was added over a time span of 5 min. to DBU (1 eq.) in an ice bath under ultrasound at 5°C. At normal temperature, the reaction mixture was irradiated with ultrasound for an increased 30 minutes. As result, the lightyellow viscous liquid of [DBUH][OAc] was obtained.

General experimental procedure for the synthesis of 5-amino-1,3-diphenylpyrazole-4-carbonitrile 4(a-j)

Conventional Method

A mixture of Aromatic aldehydes (**1a-j**, 1mmol), Malononitrile (**2**, 1mmol), along with Phenylhydrazine (**3**, 1mmol), and 20 mol % [DBUH]OAc] in 5 mL ethanol was placed in a round bottom flask. At 80 °C, the mixture was heated. TLC (eluent: pet ether/ethyl acetate, 7:3)by using the progress of a reaction. After that, the reaction was completed and the reaction mixture was cooled to normal temp. and poured over ice-cold water and the product obtained was isolated by filtration. The obtained product was crystallized in ethanol to get pure products. The catalyst [DBUH] [OAc] is recovered from the water below reduced pressure and reused. All the products are confirmed by melting point and compared with the literature **[Scheme 1]**.

Ultrasound method

A mixture of Aromatic aldehydes (**1a-j**, 1mmol), Malononitrile (**2**, 1mmol), along with Phenylhydrazine (**3**, 1mmol), and 20 mol % [DBUH]OAc] in 5 mL ethanol was placed in a round bottom flask. At 50 °C, the mixture was irradiated with ultrasound. TLC (eluent: pet ether/ethyl acetate, 7:3) by using the progress of a reaction. After that, the reaction mixture was cooled to normal temp. and poured over ice-cold water and the solid product obtained was isolated by filtration. The obtained products were crystallized in ethanol to get pure products. The catalyst [DBUH] [OAc] is recovered from the water below reduced pressure and reused. All the products are confirmed by melting point and compared with the literature **[Scheme 1]**.

Spectral data of synthesized compounds

5-amino-3-(4-chlorophenyl)-1-phenylpyrazole-4-carbonitrile(4d): chrome yellow crystal. melting point 127-130°C. yield 95%.^{1}H-NMR (DMSO-d6, 400MHz) δ 7.5 (J=5.65Hz, d, 2H), 7.46 (J=6.6Hz, t, 2H), 7.32 (t, 1H), 7.42 (J=4.5Hz, d, 2H), 7.43 (J=5.31Hz, d, 2H), 5.40 (s, 2H). ^{13}C NMR (DMSO-d6, 100MHz) δ 158.80, 148.87, 139.62, 135.11, 133.83, 130.12, 129.93; 129.83, 129.41, 129.12, 128.39, 126.69, 126.3, 118.92, 117.98, 96.05. M.S. (m/z) (M$^+$) Calculated $C_{16}H_{11}ClN_4$ (294.0676 and (M+2)$^+$ 296.0682, found 294.0678. & 296.0685).

5-amino-3-(4-methoxyphenyl)-1-phenylpyrazole-4-carbonitrile(4e): light-yellow crystal. melting point. 107-109°C. yield 96%. ^{1}H-NMR (DMSO-d6, 400MHz) δ 7.24 (t, 1H), 7.37 (J=3.33 Hz, t, 2H), 7.54 (J=3.11 Hz, t, 2H), 7.45 (J=5.11 Hz, d, 2H), 6.89 (J=2.13 Hz, d, 2H) 4.58 (s, 2H), 3.77 (s, 3H). ^{13}C-NMR (DMSO-d6, 100MHz) δ 160.10, 148.55, 139.69, 132.16, 129.19, 128.45, 124.98, 124.32, 121.89, 121.46, 121.01, 118.96, 117.91, 114.69, 113.80, 94.79, 56.24. M.S. (m/z) Calculated $C_{17}H_{14}N_4O$ ((M$^+$) 290.0653, found 290.0650).

5-amino-3-(4-bromophenyl)-1-phenylpyrazole-4-carbonitrile(4g): creamy-white crystal. melting point 165-167°C. yield 94%.^{1}H-NMR (DMSO-d6, 400MHz) δ 6.91 (t, 1H), 7.35 (J=2.15Hz, t, 2H), 7.77 (J=2.25Hz, t, 2H), 7.43 (J=3.35Hz, d, 2H), 7.48 (J=3.55Hz, d, 2H), 5.89 (s, 2H). ^{13}C-NMR (DMSO-d6, 100MHz) δ 158.23, 147.96, 138.01, 137.52, 134.99, 132.26, 129.91, 129.09, 128.76, 126.46, 123.29, 118.93, 118.12, 98.94. M.S. (m/z) Calculated $C_{16}H_{11}BrN_4$ ((M$^+$) 338.1021 and (M+2)$^+$ 340.1023, found 338.1020 and 340.1022).

5-amino-3-(4-hydroxyphenyl)-1-phenylpyrazole-4-carbonitrile(4h): Pale-yellow, melting point 175-177°C. yield 95%.^{1}H-NMR (DMSO-d6, 400MHz) δ 7.62 (J=4.35Hz, d, 2H), 7.43 (J=4.25Hz, t, 2H), 7.25 (t, 1H), 7.35 (J=6.1Hz, d, 2H), 6.75 (J=2.4Hz, d, 2H), 5.52 (s, 2H), 5.15 (s, 1H). ^{13}C-NMR (DMSO-d6, 100MHz, δ

ppm): 165.65, 155.97, 147.98, 139.31, 138.26, 135.47, 130.05, 129.87, 129.49, 129.28, 128.36, 128.08, 128.01, 118.78, 118.09, 116.34, 96.92. M.S. (m/z) Calculated $C_{16}H_{12}N_4O$ ((M+) 276.1016, found 276.1012). **1,8-diazabicyclo [5,4,0] undec-7-enium acetate [DBUH][OAc]:** light-yellow viscous liquid, ^{1}H-NMR (DMSO-d6, 400MHz, δ) δ=3.53-3.22 (m, 6H), 2.53 (J = 3.16 Hz, d, 2H), 1.83 (J = 5.11 Hz, d, 2H), 1.85 – 1.75 (m, 3H), 1.70 – 1.43 (m, 7H). IR (potassium bromide), υ_{max}/cm^{-1}, 2928 – 2856, 1643, 1549, 1445, 1379, 1310, 1192, 1113, 1073, 911, 685. The spectral data is in according to literature [38,48].

RESULTS AND DISCUSSION

In view of the diverse pharmacological activity of substituted pyrazoles, we have planned to develop an eco-friendly synthetic protocol. Also, it was assumed worthwhile to investigate the catalytic role of [DBUH][OAc] for the synthesis of highly substituted pyrazole derivatives *via* a 3-component reaction involving Aromatic aldehydes (1a-j, 1mmol), Malononitrile (2, 1mmol), along with Phenylhydrazine (3, 1mmol) under the conventional and ultrasound technique [Scheme 1].

In order to optimize the reaction conditions and to obtain the finest catalytic activity of [DBUH][OAc], the reaction of benzaldehyde (1a, 1mmol), malononitrile (2, 1mmol), and phenylhydrazine (3, 1mmol) was used model reaction. The model reaction was initially performed in a variety of solvents, including H_2O, EtOH, MeOH, Acetone, and solvent free conditions, using the conventional method to study the efficiency of the catalyst (Table 1, entries 1-5). In this study, it was experiential that ethanol was preferred solvent with respect to reaction time and yield (Table 1, entry 3).To determine the suitable conc. of [DBUH][OAc], the model reaction was investigated at different concentrations such as 5, 10, 15, 20, and 25 mol%. The product was found in trace, 60, 70, 82, 85, and 85% yield, respectively (Table 2, entries 1-5). This indicates that 20 mol% of [DBUH][OAc] is sufficient to carry out the reaction efficiently (Table 2, entry 4). To demonstrate the result of ultrasound irradiation the same reaction was done under the ultrasound method. It was observed that in ultrasonic irradiations the reaction rate decreased and product yield was increased. Evidently, the sonochemical effect might be a key factor to the high efficiency for the synthesis of substituted pyrazoles derivative which was superior to conventional method with respect to yields, reaction times, easiness, and safeties. A comparative study by conventional as well as ultrasonication technique whereas the conventional condition observed that 4a compound gave 89% yield within 60 min. and ultrasound irradiation condition gave 97% yield within 35 min. In order to the extremely interesting scope of the reaction. We intended to apply our methodology to a wide range of aromatic aldehydes in presence of [DBUH][OAc] 20 mol% under the conventional and ultrasound methods. As expected, satisfactory results were obtained for both electron-donating (-OCH_3, -O,) as well as electron-withdrawing (-NO_2 -Cl, -Br,) groups (Table 3). We herein proposed a mechanism for condensation aromatic aldehyde (1a-j), malononitrile (2), and phenylhydrazine (3) in presence of [DBUH][OAc]. The reaction proceeds throughout condensations of aromatic aldehyde along with malononitrile by using Knoevenagel condensation (5), by adding phenylhydrazine the reaction carried out Michael addition (6), along with intramolecular cyclization, followed by air oxidation was converted into the final product (4a-j) [Scheme 2]. The reusability and recovery of the ILs [DBUH][OAc] significant advantage. For reason, we've chosen the model reaction Benzaldehyde (1a), Malononitrile (2), and Phenylhydrazine (3) in[DBUH][OAc] 20 mol% under conventional heating. After the completions reaction product was poured into ice-cold water and filtration of the product was isolated. Below the reduced pressure, the ILs was recovered for recycling at least 5 times. In terms of the product, the catalytic activity is decreasing (Figure 2). Recovered IR spectra of ionic liquid after 5th cycles we are equated with the 1st cycle. As confirmed shown in Figure 3. Recovered IR spectra of ionic liquid shown to be close to identical to the 1st cycle.

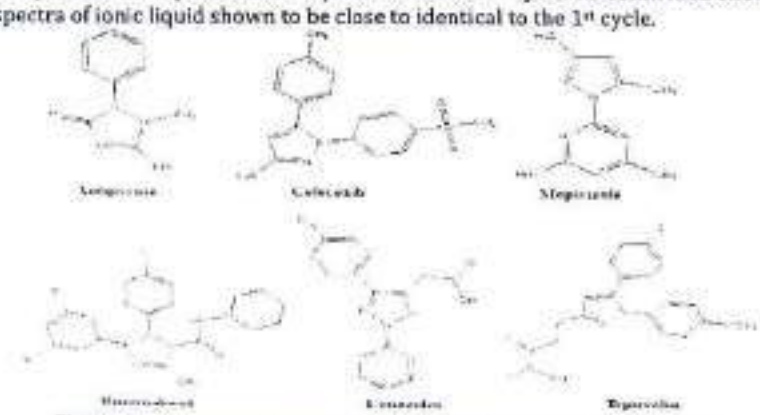
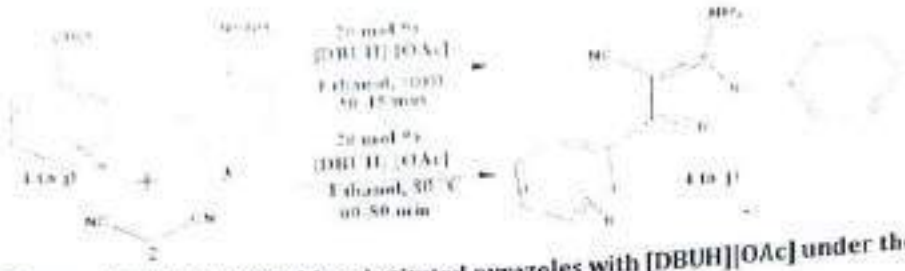


Figure 1: pyrazole derivatives containing pharmacological drug.



Scheme 1: synthesis of highly substituted pyrazoles with [DBUH]|OAc] under the ultrasound and conventional methods.

Table 1: Screening of Solvents[a]

Entry	Solvents	Time(min.)	[b]Yield(%)
1	Solvent free	60	76
2	Water	60	70
3	Ethanol	60	85
4	Methanol	60	74
5	Acetone	60	75

[a]Reaction condition: Benzaldehyde (1a, 1mmol), Malononitrile (2, 1mmol), along with Phenylhydrazine (3, 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under conventional heating.[b]Isolated yields.

Table 2: Effect of Catalyst Concentration[a]

Entry	[DBUH][OAc] mol (%)	Time (min.)	Yield[b](%)
1	5	150	60
2	10	120	70
3	15	90	82
4	20	60	85
5	25	60	85

[a]Reaction condition: Benzaldehyde (1a, 1mmol), Malononitrile (2, 1mmol), along with Phenylhydrazine (3, 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under conventional heating.[b]Isolated yields.

Table 3. Synthesis of highly substituted pyrazoles in presence of [DBHU][OAc] 20 mol% under the Conventional and ultrasound methods. 4(a-j)

Entry	R	[a]Ultrasound Method		[a]Conventional Method		M.P. (℃)	
		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)	Found	[c]Literature
4a	-H	35	97	60	89	158-160	159-161
4b	2-OH	38	94	60	87	159-162	160-162
4c	3,4-OCH_3	40	92	75	85	119-121	120-123
4d	4-Cl	35	95	50	87	127-130	128-130
4e	4-OCH_3	45	96	60	88	107-109	106-108
4f	4-NMe_2	40	93	60	85	156-158	157-159
4g	4-Br	35	94	60	88	165-167	164-166
4h	4-OH	35	95	60	86	207-209	208-210
4i	4-NO_2	45	92	60	85	163-165	164-165
4j	4-CH_3	38	94	60	88	115-117	117-118

[a]Reaction condition: Aromatic aldehydes (1a-j, 1mmol), Malononitrile (2, 1mmol), along with Phenylhydrazine (3, 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under ultrasound method and conventional method. [b]Isolated yields.
[c]All the product was confirmed by melting point and compared with the literature [46,47,49]

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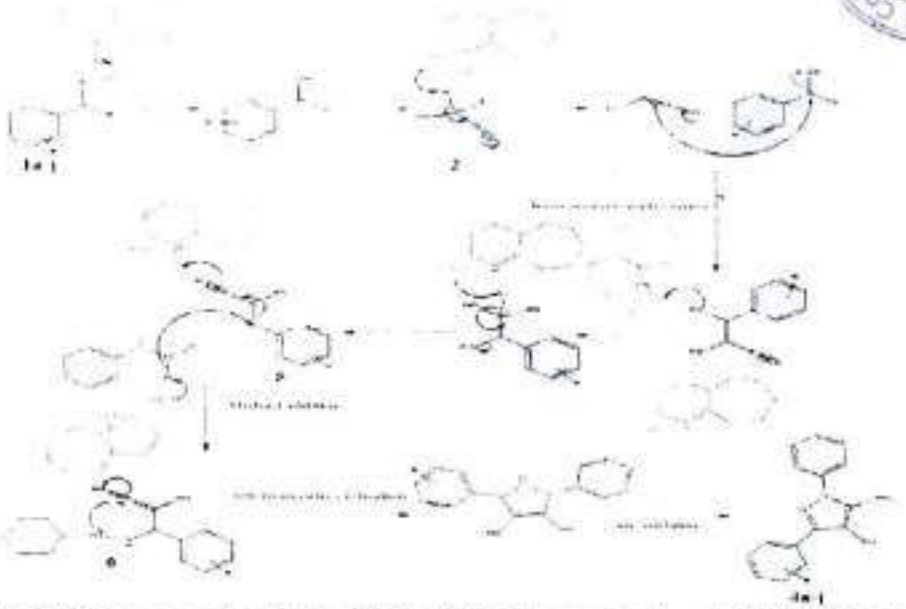

Scheme 2: Propose a mechanism for highly substituted pyrazoles by using[DBUH][OAc] ionic liquid.

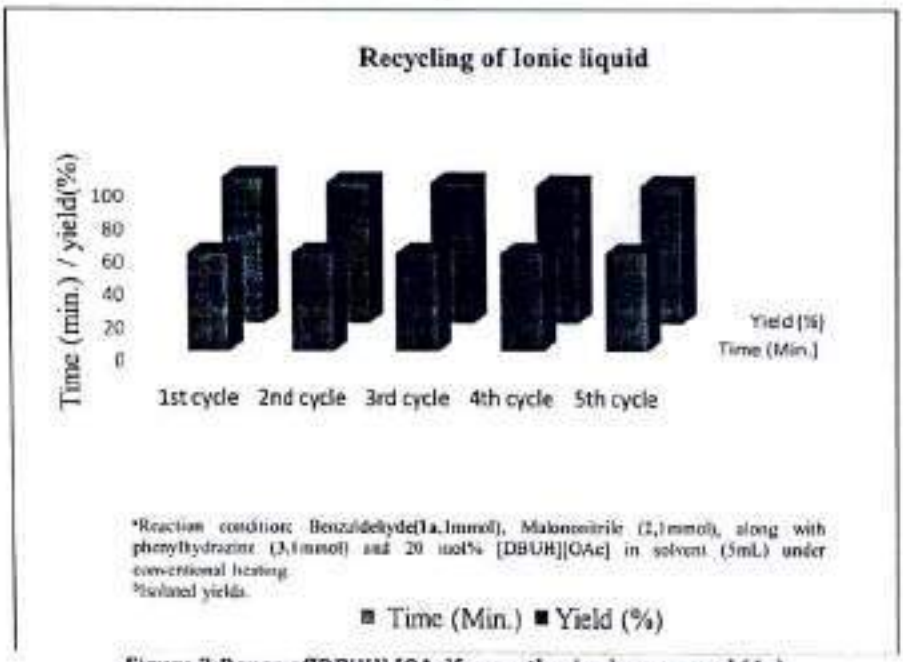

Figure 2:Reuse of[DBUH] [OAc]for synthesized compound (4a).

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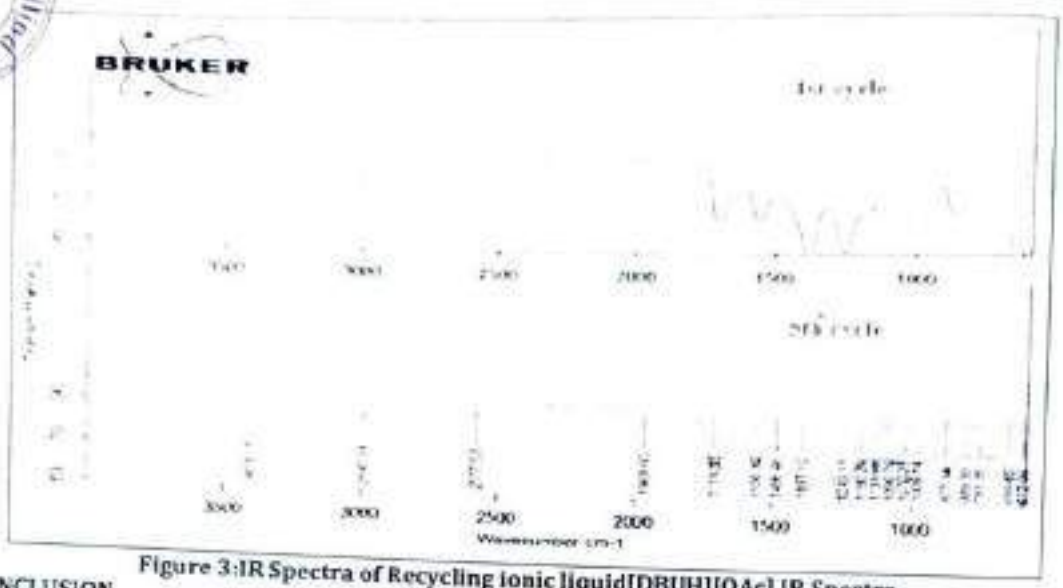

Figure 3:IR Spectra of Recycling ionic liquid[DBUH][OAc] IR Spectra.

CONCLUSION

Finally, we have developed an efficient technique for synthesizing highly substituted pyrazole derivatives. The producers described here are simple, mild and efficient, which gives this synthesis strategy a significant advantage over others. The benefits of using an ionic liquid catalyst include increased rate and reactivity, as well as ease of product recovery and recycling. The use of ultrasonication of non-classical energy sources provides better energy stability to conventional methods. The ultrasound irradiation technique gave excellent yield, shorter reaction time, and simplified work procedure than the conventional technique. Present work is the reported first time forsynthesis of highly substituted pyrazoles using [DBUH][OAc] ionic liquid under ultrasound irradiation technique.

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SYNTHESIS AND ANTIMICROBIAL STUDY OF METAL COMPLEXES OF SM (III), EU (III) AND ASYMMETRICAL LIGAND DERIVED FROM DEHYDROACETIC ACID

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Keywords:

Tetradentate schiff base, Salicylaldehyde, Powder X-ray diffraction, TGA/DSC spectral analysis and antimicrobial activity

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ABSTRACT: Tetradentate Schiff bases are synthesized from o-phenylenediamine, 5-bromo Salicylaldehyde, and 3-Acetyl-6-methyl-pyran-2, 4-dione, and then its colored complexes of Sm (III) and Eu (III) are formed. The structure of ligand and complexes are characterized by elemental analysis, magnetic susceptibility, thermal analysis, X-ray diffraction, 1H-NMR, mass, IR, UV-visible spectra, and conductometry. TGA/DSC spectral and kinetic parameter of the complexes was studied eagerly. The x-ray diffraction data proposes Tetragonal crystal system for Sm (III) complexes and orthorhombic for Eu (III) complexes. The ligand and their metal complexes were subjected for antibacterial activity against Escherichia coli, *Staphylococcus aureus*, Pseudomonas Aeruginosa using the agar cup-plate method, and antifungal activity was observed by poison plate method against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*. The results obtained above are in good agreement with previous findings with respect to the comparative activity of the free ligand and its complexes. The result of an investigation of antimicrobial activity indicates that all the ligands show an inhibitory effect against all the pathogens.

INTRODUCTION: In the present investigation, study of various colored complexes of Sm(III), Eu(III) with tetradentate ligands (Schiff Base)were synthesized and characterized. The novel series of lanthanides of tetradentate Schiff bases formed by the reaction of o-phenylenediamine, dehydroacetic Acid (DHA) and 5-bromo salicylaldehyde.

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MATERIALS AND METHODS:

Experiments: The reagents, solvents, DHA, o-phenylenediamine and 5-bromo salicylaldehyde of AR grade supplied by Merck were used for the synthesis of ligand. All metal chlorides used for synthesis of complexes are also AR grade.

Instrumentation: ^{1}H-NMR was recorded on FT NMR spectrometer (400 MH_2) model Advance-II (Bruker) in $CDCl_3$ as a solvent and tetramethylsilane as the internal standard. C, H, N was carried out on Thermo Scientific (FLASH 2000) CHN elemental analyzer. IR study has been carried out on Perkin Elmer-Spectrum RX-I FTIR spectrometer using KBr pellets.

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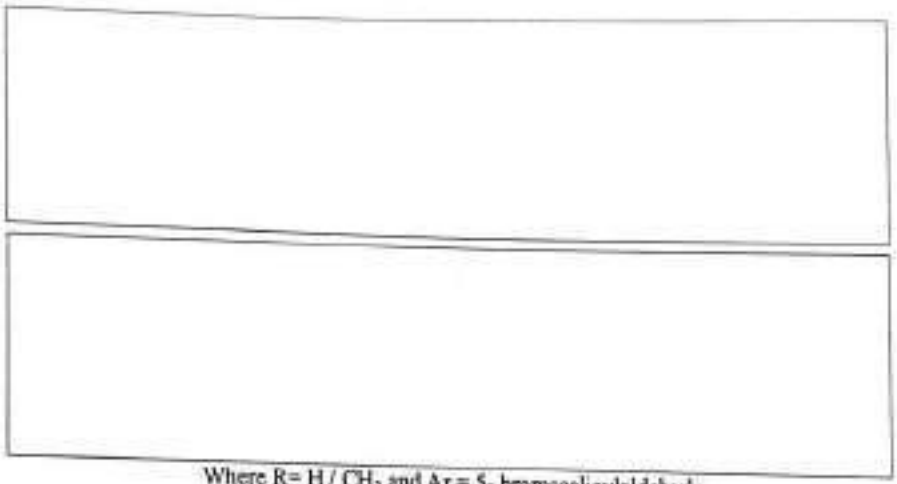
The TGA/DSC and XRD were recorded on TA Inc. SDT-2790 and Pananalytical X'Pert Pro, respectively. All electronic absorption spectra of the complexes and ligand were chronicled on Shimadzu 1800 spectrometer.

Molar conductance of complexes was probed on Elico CM 180 conductivity meter using 10^{-3} M solution in DMF.

Synthesis of Ligand: The synthesis was carried out in two steps; first step is a synthesis of mono-Schiff base, which was prepared by refluxing 50 ml solution of (10 mmol) of DHA and (10m mol) o-phenylenediamine in absolute ethanol for about 3 h. The progress of the reaction was monitored with TLC. Thus formed mono-Schiff base then refluxed with 10 mmol of 5-bromo Salicylaldehyde to form tetradentate Schiff base. Obtained solid was then cooled at room temperature and collected by filtration and recrystallization using super dry ethanol (Yield: 76%).



Where R= H / CH_3 and Ar = 5- bromosalicylaldehyde

FIG. 1: SYNTHESIS OF LIGAND

Synthesis of Metal Complexes: A solutions of (1:1) ratio of ligand (0.01mol) and metal chloride (0.01 mol) were prepared in methanol and mixed in hot conditions with continuous stirring to form metal complexes. The mixture was refluxed for 3-4 h. Heat on water bath till the volume of the reaction mixture is reduced to half. After cooling solid metal complex is appeared. Obtained solid metal complex was purified by petroleum ether and dried over vacuum desiccator (yield: 78%).

RESULTS AND DISCUSSION: Physical characterization, analytical and molar conductance data of compounds are given in **Table 1**. From the data it was analysis that, equimolar stoichiometry (metal: ligand) is formed and it also satisfying general formula as $ML(H_2O)_2$ (where M =, Sm (III), Eu(III).

The study of magnetic properties indicates octahedral geometry for Sm(III), Eu (III) at room temperature and two water molecules are coordinated to the metal ion. Existence of two coordinated water molecules was further confirmed by weight loss before 270 °C in TGA-DSC analysis.

^{1}H-NMR Spectra of Ligand: From ^{1}H NMR spectral data it shows the following signals 2.07 δ (s, 3H, C_6-CH_3), 2.13 δ (s, 3H, N=C-CH_3), 5.83 δ (s, 1H, C_5-H), 6.73-7.04 δ (m, aromatic protons), 8.96 δ (s, 1H, N=C-H),9.98 (phenolic (-OH) hydrogen of phenyl ring) and 15.89 δ (s, 1H, enolic OH of DHA moiety) [1, 2, 3].

IR Spectra: The IR data of ligand (H_2L) and its metal complexes are listed in Table 2. It depicts prominent bands at 3360, 1685, 1660, 1353, and 1230 cm^{-1} assignable to υ OH, υ C=O (lactone carbonyl), υ C=N (azomethine), υ C-N (aryl azomethine) and υ C-O (phenolic) stretching modes respectively [4]. The presence of a strong, broadband in the 3360 cm^{-1} regions in the spectra of the ligand, which is not observed in complexes, elucidates coordination of phenolic oxygen to the metal ion by deprotonation [5].

Resulting upswing to an extent of 40-60 cm^{-1} in the υ C-O (phenolic) band [6]. This shift further confirms the involvement of the enolic oxygen in C-O-M bond. Chelation by nitrogen of azomethine (C=N) is confirmed by observing band at 1660 cm^{-1} in the spectra of ligand, which find at lower frequency 1612-1556 cm^{-1}whencomplex formed [7].

This change can be supported by transfer of electrons from nitrogen to the vacant d-orbitals of the metal. Finding new bands in the 521-525 and 461-477 cm^{-1} regions confirms the M-O and M-N bonding, respectively [8]. No any change in skeletal vibrations (C=C) upon complexation. The presence of coordinated water is confirmed by the appearance of a strong band in the 3363-3416 cm^{-1} region in case of Sm(III) and Eu(III)which is also supported by the appearance of a non-ligand band in 825-846 cm^{-1} region, quoted for a rocking mode of water [9].

Magnetic Susceptibility and Electronic Absorption Spectra: The electronic absorption spectrum of Sm (III) complex contains three bands at 24700, 24000 and 21505 cm^{-1} assignable to the transitions $^6H_{5/2} \rightarrow {}^2P_{9/2}$, $^6H_{5/2} \rightarrow {}^2P_{5/2}$ and $^6H_{5/2} \rightarrow {}^3P_{13/2}$ charge transfer respectively. The electronic absorption spectra of Eu(III) complex show three strong bands at 17500, 24500, and 27800 cm^{-1} which may be assigned to the transitions $^8S_{7/2} \rightarrow {}^6P_{5/2}$, $^8S_{7/2} \rightarrow {}^4P_{7/2}$, and charge transfer, respectively. Electronic transitions together with magnetic moment value 1.50 B.M. of Sm(III) complex and 7.92 B.M. for Eu(III) complex suggest high spin octahedral geometry for complex [10, 11].

TABLE 1: PHYSICAL CHARACTERIZATION, ANALYTICAL AND MOLAR CONDUCTANCE DATA OF COMPOUNDS

Compound Molecular formula	Mol. Wt.	M.P / Decomp Temp. °C	Color	Molar conduc. Mho cm^2 mol^{-1}	Found (calculated) C	H	N	M
(H_2L) $C_{28}H_{27}N_3O_4$	433.50	189	Dark Saffron	----	69.23 (69.27)	6.24 (6.28)	9.67 (9.69)	----
[LSm(H_2O)$_2$]	617.87	286	Dark Brown	26.21	48.60 (48.55)	4.73 (4.69)	6.80 (6,76)	24.34 (24.30)
[L Eu(H_2O)$_2$]	619.48	285	Dark Brown	23.10	48.47 (48.40)	4.70 (4.65)	6.78 (6.72)	24.53 (24.49)

TABLE 2: IR DATA OF LIGAND AND METAL COMPLEXES

Compound	IR band frequency (cm^{-1}) ν(OH)	ν(C=O)	ν(C=N)	C=C	C-N	C-O	M-O	M-N
L	3360	1685	1660	1519	1353	1230	-	-
Sm-L	3363	1655	1612	1556	1384	1256	521	461
Eu-L	3416	1654	1595	1571	1399	1250	525	477

Thermal Analysis: The TG/DSC analysis of Sm (III) and Eu (III) complexes was done from ambient temperature to 1000°C in a nitrogen atmosphere using α-Al_2O_3 as reference. In the TG curve of Sm (III) complex, the first weight loss 6.834 % occurred at a temperature between 150-200°C indicating coordinated water in these complexes supported by an endotherm at ΔT_{min} = 214. 22°C. The second step slowed decomposition from 200-600 °C with a mass loss 29.83%. This can be further confirmed by observing broad exothermic peak in DSC with $\Delta T_{max.}$ = 373. 61°C indicates to the removal of the coordinated part of ligand [12, 13]. The TG-DSC curve of Eu (III) complex show first mass loss 6.893% begins between the range 150-250°C and an endothermic peak in this region ΔT_{min} = 313.71°C, indicating loss of two coordinated water molecules. The second step slowed decomposition from 250-600 °C with 27.99% mass loss (calcd. 26.32%). This can be further confirmed by observing exothermic peaks in DSC with $\Delta T_{max.}$ = 397.97°C indicates decomposition of non-coordinated part of ligand. The second slow step from 600-800°C with mass loss 18% corresponds to the removal of the coordinated part of the ligand. A broad endotherm in DSC is observed for this step [14].

Kinetic Calculations: The kinetic and thermodynamic parameters *viz* ΔG (free energy change), ΔS, z (pre-exponential factor), E_a, and n (order of reaction), together with correlation coefficient (r) for non-isothermal decomposition of metal complexes have been determined by

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Horowitz-Metzer (HM) approximation method and Coats-Redfern integral method The data is arranged in **Table 3**. The results show that the values obtained by the two methods are analogous.

Low Ea values of the complexes indicate the autocatalytic effect of metal ion after thermal decomposition [15, 16].

TABLE 3: THE KINETIC PARAMETER OF METAL COMPLEXES CALCULATED BY THE METHODS HOROWITZ-METZGER (HM) AND COATS-REDFERN (CR)

Complex	Step	n	Method	E_a	Z	ΔS	ΔG	Correlation coefficient (r)
Sm(III)	I	1.80	HM	40.18	14492	-155.10	48.39	0.9998
			CR	38.98	172113	-152.85	44.98	0.9985
	II	1.20	HM	60.58	83114	-150.34	78.74	0.9993
			CR	55.00	362280	-157.15	48.47	0.9984
Eu(III)	I	1.18	HM	47.55	15365	-135.23	55.45	0.9984
			CR	32.55	47183215	-128.45	45.89	0.9989
	II	1.20	HM	28.20	85456	-154.96	40.54	0.9989
			CR	36.98	35088264	-145.62	49.65	0.9987

Ea in kJ mol-1, Z in S-1, ΔS in JK-1mol-1and ΔG in kJ mol

Powder X-ray Diffraction: Scanning of x-ray diffract gram of Sm(III), Eu (III), and metal complexes of L is done at wavelength 1.543 Å in the range 5-100°. The x-ray diffraction pattern of these complexes compared with major peaks of relative intensity greater than 10% has been indexed to their hkl value by using the computer program [17]. The diffract gram of Sm(III) complex of L had ten reflections with maxima at 2θ = 21.356°, corresponding to d value of 3.93521Å.The unit cell of Sm(III) complex of L yielded values of lattice constants, a=9.26993 Å, b= 9.22178 Å, c = 7.71860 Å and unit cell volume V=470.6505(Å) ^{3} [18]. The diffract gram of Eu(III) complex of L shows eleven reflections with maxima at 2θ = 17.256° corresponding to d value 5.47562 Å. The unit cell of Eu(III) complex of L yielded values of lattice constants, a=18.264632 Å, b=8.18910Å, c = 5.983770Å and unit cell volume V=532.72466(Å) ^{3}. In respect of these cell parameters, the condition such as a ≠ b ≠ c and α = γ = β = 90° required for sample to be tetragonal were tested and found to be satisfactory in Sm(III) complex. While a ≠ b ≠ c and α = β= γ = 90° for sample to be orthorhombic were tested and found to be satisfactory for Eu (III). Density values of the complexes were determined practically using a specific gravity method and found to be 1.9706, 2.9800gcm-3 for Sm(III) and Eu (III) complexes, respectively. Theoretical density was found to be 1.98241, 2.8582 gcm-3 for respective complexes and found near experimental value. By using experimental density values, the molecular weight of complexes, Avogadro's number and volume of the unit cell were computed [19].

Antimicrobial Activity: Ligand and metal complexes are subjected for antimicrobial activity against bacteria such as *Escherichia coli* and *Staphylococcus aureus, Pseudomonas aeruginosa* by Agar Cup Method [20, 21]. The compounds were tested at the concentration of 1% in DMSO and Ciproflaxin as standard **Table 4**. For fungicidal activity Poison plate method is used, compounds were tested against *Aspergillus niger, Aspergillus flavus, Penicillium chrysogenum.* Potato Dextrose Agar is used as a medium, and depicted in **Table 5** by comparison with Griseofulvin as standard. Observing **Table 4** and **5**, the conclusion made that the inhibition by metal complexes is more than a ligand. Solubility of metal complexes in organic solvents increases its activity. Hydrogen bonding with the active center of cell may be responsible for enhanced activity [22].

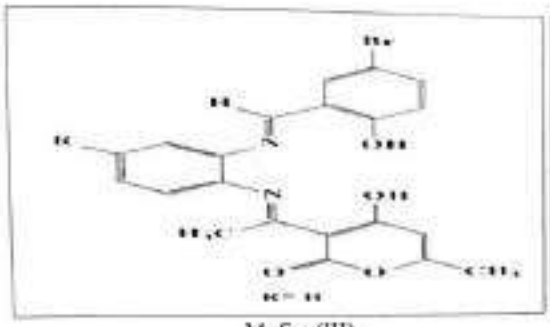
TABLE 4: ANTIBACTERIAL ACTIVITY OF COMPOUNDS

Test Compound	Diameter of inhibition zone (mm)		
	E. coli	*S. aureus*	*Ps. aeruginosa*
Ciprofloxacin	25	50	25
L	09	10	11
L-Sm	12	14	15
L-Eu	13	13	14

TABLE 5: ANTIFUNGAL SCREENING OF LIGAND AND THEIR METAL COMPLEXES

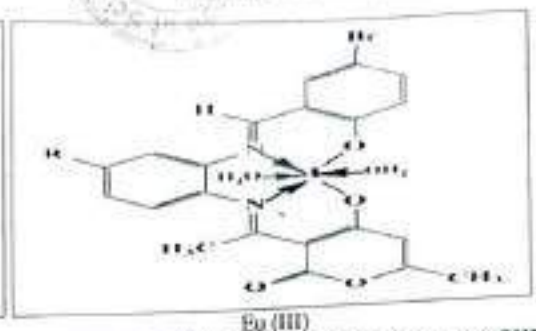
Test Compound	Microorganisms		
	Asp. niger	*Asp. flavus*	*Pen. chrysogenum*
L	-ve	-ve	-ve
L-Sm	RG	-ve	-ve
L-Eu	-ve	+ve	-ve
DMSO	+ve	+ve	+ve
Griseofulvin	-ve	-ve	-ve

-ve -No growth Antifungal activity present , +ve -Growth Antifungal activity absent RG -Reduced growth.



M=Sm (III)

FIG. 2: THE STRUCTURE OF THE LIGAND



Eu (III)

FIG. 3: PROPOSED STRUCTURE OF THE COMPLEXES

CONCLUSION: In the present investigation tetradentated ligand of Schiff Base and its transition metal complexes of Sm(III) and Eu (III) was synthesized. Spectral analysis studies suggest that azomethine nitrogen and phenolic oxygen are involved in the coordination with metal ions **Fig. 1**. Proposing octahedral geometry for Sm (III) and Eu (III) complexes also concluded that the ligand is dibasic and ONNO tetra dentate metal complexes. A study of Microbial activity shows that complexes have enhanced antimicrobial activities as compared to their free ligand. The x-ray diffraction data proposes Tetragonal crystal system for Sm (III) complexes and orthorhombic for Eu (III) complexes. From Thermal data, it predicts the thermal behavior of complexes.

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CONFLICTS OF INTEREST: The author declares that there are no conflicts of interest in submitting this manuscript.

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SYNTHESIS, CHARACTERIZATION AND QSAR STUDY OF 2-(5-METHYL-4-PHENYLTHIAZOL-2-YL)-4-OXOTHIAZOLIDINE-5-CARBOXYLIC ACID DERIVATIVES

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ABSTRACT

In this present work, we report a green and eco-friendly procedure for the synthesis of various different derivatives of Schiff bases N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline. These derivatives were synthesised by 5-methyl-4-phenylthiazole-2-carbaldehyde, substituted anilines, and reaction mixture was irradiated with microwave at 20% power to furnish Schiff bases N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline derivatives. The products react with 2-Mercapto-malonic acid, dry dioxane in scientific microwave oven (20%, 140 watts), on cyclocondensation gave different 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid derivatives with good yield. Library of such 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid derivatives has been generated and the structures were exposed to PASS to check probabilities of biological activity. QSAR study of the library was carried out to find the most active molecules.

Key words: cyclocondensation; 2-Mercapto-malonic acid; microwave; Schiff bases

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1. Introduction:

The 4-oxo-thiazolidine is an important class of heterocyclic compounds had wide spectrum of biological activities. The 4-oxo -thiazolidines occupies significant place in medicinal field.[1] Initially 4-oxothiazolidine are

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derivatives having a carbonyl group at 4-posotion are prepared by intermolecular cyclization followed elimination of water. Literature survey tells that 4-oxo-thiozolidinederivatives has shown Anti-HIV,[2] enzyme murB,[3] antimicrobial activity,[4] antituberculosis,[5] antiproliferative agent,[6] CNS activity,[7] cytotoxic agent,[8] anticonvulsant activity,[9] antibacterial activity,[10] analgesic agent [11] antiinflammetry agent,[12] antihypertensive agent, [13] and hypolipidemic agent [14] properties.

The 4-oxo-thiozolidine derivatives has biological potential and essay synthetic protocols attracted the attention of many researchers. [15-17] Organic reaction induced by microwave irradiation are environmentally friendly and proceed with short time. [18-20] M.W. assisted method is termed as e-chemistry because easy, effective, economical and eco-friendly.[21] This method is more significant than conventional methods.[22]

Schiff bases are synthesised by condensation of aldehyde and ketones and amines or anilines. [23] Schiff bases has wide application in biological and medicinal field. [24] QSAR study done by using Pass online is software application used for prediction of 565 possible biological activities of compounds. The biological activity spectrum shows intrinsic properties of compounds based on structure. Pass online tool is used to design drug with high probable activity. [25-29]

Recent literature survey reports successful attempt made for the preparation of 4-oxo-thiozolidine derivatives phthalimido[2-aryl-3-(5'-(4"-pyridyl)-1',3',4'-thiadiazol-2'-yl)-4-oxothiazolidin-5-yl]ethanoates,[30]2-[5-(arylidene)-2-imino-4-oxo-thiazolidin-yl]benzothiazole-6-carboxylic acid, N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide,[31] 2-(aryl)-3-[2-(benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines,[32] N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide,[33]4-oxo-thiazolidine derivatives have been obtained by cyclisation of various Schiff's base with thiomalic acid, and N-(2-(4-substituted phenyl)-4-oxothiazolidin-3-yl)isonicotin-amide[34]etc.

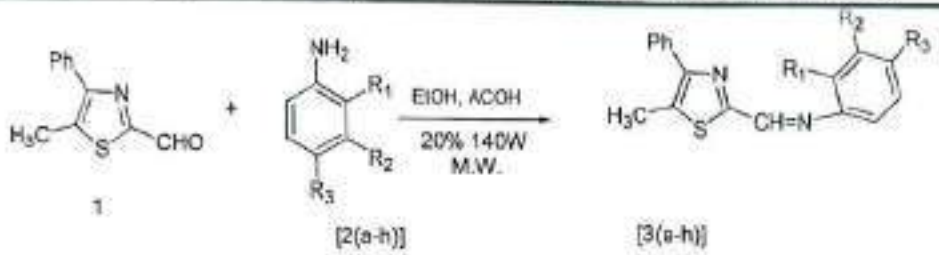
In continuation of this, we had carried out microwave assisted synthesis different of 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid in two steps. In first step formation of Schiff base by reacting 5-Methyl-4-phenyl-thiazole-2-carbaldehyde with different substituted anilines. Second step consists cyclocondensation of different Schiff bases with 2- Mercapto-malonic acid gives desired products using green chemistry.

2. Materials and Methods:

The melting points of the compounds were determined in open capillary tubes are uncorrected. The purity of compound was checked on silica gel G plates. FT-IR spectra were recorded on a Shimadzu Miracle 10 ATR spectrometer. ^{1}H NMR spectra were recorded on a Bruker 500 MHz spectrometer with $CDCl_3$ as the solvent and TMS as the internal reference. ^{13}C NMR spectra were recorded on Bruker 125 MHz spectrometer with $CDCl_3$ as the solvent. Elemental analysis carried out using CHN elemental analyser. All chemicals were analytical grade.

2.1 Synthesis of Schiff bases N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline

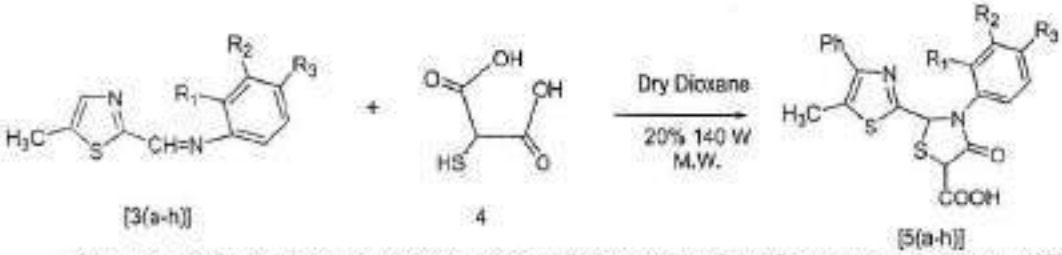
Schiff bases are prepared by mixture of 5-methyl-4-phenylthiazole-2-carbaldehyde (0.02 mol) [1], substituted anilines (0.02 mol) [2(a-h)], 10 ml ethanol and 1 ml acetic acid added in microwave tube. The contents were subjected to 20 % microwave power (140 W) for 3-5 min. The progress of reaction was monitored on TLC (Ethyl acetate: Hexane 1:9). After completion of the reaction, solid product obtained in reaction was poured into crushed ice filtered and recrystallised in methanol gives solid product [3(a-h)] **Scheme-I**.



Scheme I- Synthesis of Schiff bases N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline [3(a-h)] derivatives

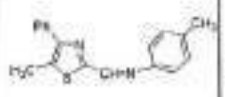
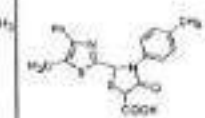
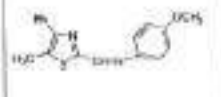
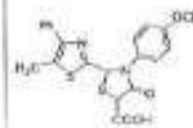
2.2 Synthesis of 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid

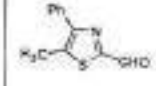
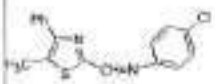
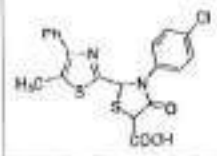
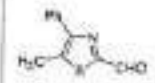
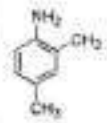
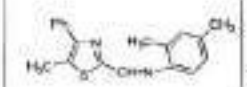
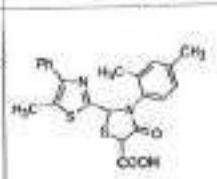
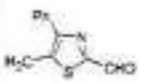
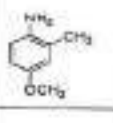
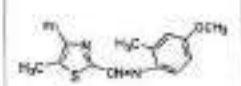
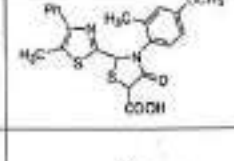
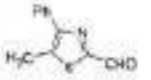
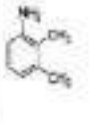
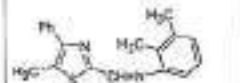
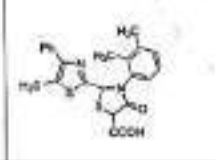
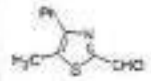
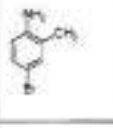
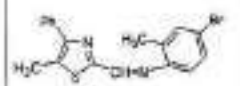
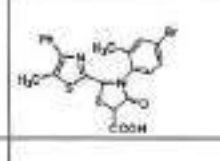
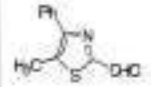
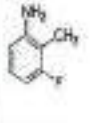
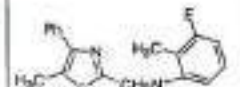
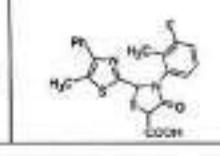
A mixture of (1mmol) of Schiff base N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline[3(a-h)] and 2- Mercapto-malonic acid (15ml) [4] in 30 ml Dry dioxane was added in small round bottom flask at room temperature then mixture was exposed to microwave power 20% 140W for 3-5 min. The progress was monitored on TLC (Ethyl acetate: Hexane 1:9). The resultant solution was cooled and poured into crushed ice. The separated solid was filtered, recrystallised from ethanol gives solid product [5(a-h)] **Scheme-II summarised in Table -1.**



Scheme II- Synthesis of 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid derivatives [5(a-h)]

TABLE-I
PREPARATION OF SUBSTITUTED OXOTHIAZOLIDINE UNDER MICROWAVE IRRADIATION

Comp.	Substrate			Product	Time (min)	M.P. (°C)	Yield (%)
	1	2	3				
5a					4	682-683	84
5b					3	704-705	79

5c					4	701-702	78
5d					5	706-707	86
5e					5	728-730	83
5f					4	706-707	82
5g					4	754-755	85
5h					5	695-696	80

Spectral data of compounds [5(a-h)]

5'-Methyl-4-oxo-4'-phenyl-3-p-tolyl-2,3,4,5-tetrahydro- [2,2'] bithiazolyl-5-carboxylic acid 5(a): IR (KBr) ν_{max}: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) cm^{-1}. H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s, 1H, CH), 2.35(s, 6H, 2× CH_3), 4.35(s, 1H, CH), 6.98 (d, 2H,2×CH), 7.11(d, 2H,2×CH),7.22-7.48(m, 5H, C_6H_5),11.0(s,1H, OH) ppm.^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 166.50(=C<), 152.60(=C<), 128.50(=C<), 56.60(>C<), 7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<), 20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<). Anal. calcd. (%) for $C_{21}H_{18}N_2O_3S_2$: C, 61.44; H, 4.42; N, 6.82; O,11.69; S,15.62. Found (%): C, 61.41; H, 4.48; N, 16.27; O,11.72; S,15.68. M.P. 682^{0}C; mass(M+) 410.

3-(4-Methoxy-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2']bithiazolyl-5-carboxylic acid 5(b): IR (KBr) vmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3)cm^{-1}.H^1 NMR (CDCl3, 200.13 MHz): δ 5.92(s, 1H, CH), 2.35(s, 6H, 2× CH_3), 4.35(s,1H,CH),6.98(d,2H,2×CH),7.11(d,2H,2×CH),7.22-7.48(m,5H,C_6H_5),11.0(s,1H,OH),3.73(s,3H)ppm.^{13}C

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NMR(CDCl3, 50.32 MHz): δ 166.50(=C<), 152.60(=C<), 128.50(=C<), 56.60(>C<), 7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=), 120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00 (=C<),56.00(>C<). Anal. calcd. (%) for $C_{21}H_{18}N_2O_4S_2$: C, 59.14; H, 4.25; N, 6.57; O,15.00; S,15.04. Found (%): C, 59.10; H, 4.29; N,6.55; O,15.01; S,15.04. M.P. 704^{0}C; mass(M+)426.

3-(4-Chloro-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2']bithiazolyl-5-carboxylic acid 5(c):IR (KBr) vmax: 1440(C-CH3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3), 650(-Cl)cm^{-1}.H^1 NMR (CDCl3, 200.13 MHz): δ 5.92(s, 1H, CH), 2.35(s, 6H, 2×CH_3), 4.35(s,1H,CH),6.98(d,2H,2×CH), 7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH)ppm.^{13}CNMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60 (=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),13 3.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<).Anal.calcd.(%)forC_{20} $H_{15}ClN_2O_3S_2$:C,55.74; H,3.51; Cl,8.23; N, 6.50; O,11.14; S,14.88. Found (%): C, 55.70; H, 3.50; Cl,8.23; N,6.55; O,11.12; S,14.90. M.P. 701^{0}C; mass(M+1)430.

5'-Methyl-4-oxo-4'-phenyl-3-p-tolyl-2,3,4,5-tetrahydro- [2,2'] bithiazolyl-5-carboxylic acid 5(d): IR (KBr) vmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH3),750(CH_3), 820(CH_3) cm^{-1}. H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s, 1H, CH), 2.35(s,6H,2×CH_3),4.35(s,1H, CH),6.98(d,2H,2×CH), 7.11(d,2H,2×CH),7.227.48(m,5H, C_6H_5),11.0(s,1H, OH),8(s,3H, CH_3),1.0(s,3H, CH_3) ppm.

^{13}CNMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166. 70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C <),128.50(=C<),129.00(=C<),21.2(>C<),12.4(>C<).Anal.calcd.(%)for $C_{22}H_{20}N_2O_3S_2$:C,62.24; H, 4.75; N, 6.60; O,11.31; S,15.11. Found (%): C,62.20; H, 4.72; N,6.64; O,11.33; S,15.12. M.P. 706^{0}C; mass(M+) 424.

3-(4-Methoxy-2-methyl-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2']bithiazolyl-5-carboxylic acid 5(e):IR (KBr) vmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3),750(CH_3),1240(OCH_3) cm^{-1}. H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s,1H,CH), 2.35(s,6H,2×CH_3),4.35(s,1H,CH), 6.98(d,2H,2×CH),7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH),8(s,3H,CH_3),3.6(s,3H,OCH_3)ppm.^{13}C NMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<), 128.50(=C<),129.00(=C<),12.4(>C<).Anal.calcd.(%)for $C_{22}H_{20}N_2O_4S_2$:C,59.98; H, 4.58; N, 6.36; O,14.56; S,14.56. Found (%): C,59.96; H, 4.60; N,6.34; O,14.54; S,14.57. M.P. 728^{0}C; mass(M+) 440.

3-(2,3-Dimethyl-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2']bithiazolyl-5-carboxylic acid 5(f): IR (KBr) vmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3),750(CH_3) , 880(CH_3) cm-1.H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s,1H,CH),2.35(s,6H,2×CH_3),4.35(s,1H,CH), 6.98 (d,2H,2×CH), 7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH),8(s,3H,CH_3),2.35(s,3H,CH_3)ppm.^{13}CNMR($CDCl_3$,50.3 2MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=

),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<),14.4(>C<).Anal.calcd.(%)for $C_{22}H_{20}N_2O_3S_2$: C,62.24; H, 4.75; N, 6.60; O,11.31; S,15.11. Found (%): C,62.22; H, 4.77; N,6.61; O,11.30; S,15.11. M.P. 706°C; mass(M+)424.

3-(4-Bromo-2-methyl-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2'] bithiazolyl-5-carboxylic acid 5(g): IR (KBr) vmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3),750(CH_3) , 1075(Br) cm-1.H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s,1H,CH), 4.35(s,1H,CH), 2.35(s,6H,2×CH_3), 6.98(d,2H,2×CH),7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH),8(s,3H,CH_3)ppm.^{13}CNMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<).Anal.calcd.(%) for $C_{21}H_{17}BrN_2O_3S_2$: C,51.54; H, 3.50; Br,16.33,N, 5.72; O,9.81; S,13.10. Found (%): C,51.52; H, 3.52; Br,16.32; N,5.73; O,9.80; S,13.11. M.P. 754°C; mass(M+1)489, (M+2) 491.

3-(3-Fluoro-2-methyl-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2'] bithiazolyl-5-carboxylic acid 5(h): IR (KBr) vmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3),750(CH_3) , 1250(F) cm-1.H^1 NMR ($CDCl_3$, 200.13 MHz): 5.92(s,1H,CH), 4.35(s,1H,CH), 2.35(s,6H,2×CH_3), 6.98(d,2H,2×CH),7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH),8(s,3H,CH_3)ppm.^{13}CNMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<).Anal.calcd.(%)for $C_{21}H_{17}FN_2O_3S_2$: C,58.86; H, 4.00; F,4.43,N, 6.54; O,11.20; S,14.97. Found (%): C,58.54; H, 4.02; F,4.42; N,6.55; O,11.19; S,14.98. M.P. 695°C; mass(M+) 428.

3. Result and Discussion

In the present work, we Synthesised rapid and efficient various 4-oxo thiazolidines *viz.* 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid derivatives were achieved (Scheme-I and scheme-II) by using microwave method gives good yield. The synthesized compounds were characterized by analysing their H^1NHR & ^{13}C NMR, IR, Mass spectra. It was observed that substituted Schiff bases cyclocondensation with 2-mercaptomalonic acid yields 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid [5(a-h)]. The structures of [5(a-h)] were confirmed by elemental analysis and IR spectra showing an absorption band at 1595 (C=C) and signals at), 6.9-7.1 (d, 2H, =CH),7.2-7.4(m,5H =CH) 11.0 (s, 1H, COOH) in H^1NMR representative of the completion of the reaction and formation of the desired product. Similarly, absorption bands at 1595 (C=C), 1690 (C=O), 1600 (C=N) in IR spectra and signal at 11.0 (s, 1H, OH) in H^1NMR of [5(a-h)] confirmed the structures assigned to 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid [5(a-h)]. The structures assigned to 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid [5(a-h)] were supported by the elemental analysis and IR spectra showing an absorption band at 1690 (C=O), 1595 (C=C).

QSAR Analysis of Activities with PASS:

To obtain the predicted biological activity profile for synthesized compounds the structures of derivatives [5(a-h)] were added to Pass online computer Programme. The predictions of their probabilities active [Pa] and inactive [Pi] for the set of biological activities studied. The subsequent three activities were predicted with highest probability for the series of compounds [5(a-h)]

1. Follicle-stimulating hormone agonist
2. Antiinfertility, female
3. Muramoyltetrapeptide carboxypeptidase inhibitor

Table 2

Predictions Of Biological Activities By Pass Online Programme

Compound	Follicle-stimulating hormone agonist **Pa**	Antiinfertility, female **Pa**	Muramoyltetrapeptide carboxypeptidase inhibitor **Pa**
5-a	**0.916**	**0.724**	**0.684**
5-b	0.904	0.704	0.626
5-c	0.903	0.709	0.626
5-d	0.901	0.693	0.643
5-e	0.886	0.671	0.565
5-f	0.907	0.697	0.664
5-g	0.891	0.660	0.560
5-h	0.886	0.687	0.582

Follicle-stimulating hormone agonist:

The follicle-stimulating hormone receptor (FSHR) is a glycoprotein plays important role in mammalian reproduction and development. Follicle-stimulating hormone agonist is chemical substance which binds to specific hormone receptors stimulates the function of the endocrine glands the biosynthesis of their secreted hormones, or the action of hormones upon their specific sites. It helps control the menstrual cycle and stimulates the growth of eggs in the ovaries. The said compounds may acts as drug.

Antiinfertility, female:

Infertility is a disease in which women are unable to get pregnant due to many problems associated with uterus, fallopian tubes and ovulation. These compounds may be used as Antiinfertility agents.

Muramoyltetrapeptide carboxypeptidase inhibitor:

Muramoyltetrapeptide carboxypeptidase is an enzyme also referred as carboxypeptidase IIW belongs to hydrolases. It is involved in peptidoglycan synthesis, catalyzing both decarboxylation and transpeptization. The substance used as thiol blocking agent and stimulated by Ca^{2+} and Mg^{2+} not affected by penicillin. The catalytic activity of the enzyme in the organism is probably inhibited by the compounds under study.

We can conclude that, all compounds have moderately all three activities. Out of [5a-5h] compounds only 5a has highest Pa values for all three activities shown in Table 2.

4. Conclusion:

The synthesis of eight 4-oxo-thiozolidines viz 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid by microwave assisted method. These synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass Spectroscopy. All compounds were screened for antimicrobial activities, we found that, all compounds have moderately all three activities such as Antiinfertility in female, Follicle stimulating hormone agonist and Muramoyltetrapeptide carboxypeptidase inhibitor. The compound **5a** found highest all three activities can serve as potent antimicrobial lead for further studies.

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ELECTRICAL PROPERTIES AND HYDROGEN ADSORPTION OF MULTIWALLED CARBON NANOTUBES OBTAINED FROM *AZADIRACHTA INDICA OIL*

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ABSTRACT

Neem oil *(Azadirachta indica)* is a vegetable low cost nonedible oil obtained from its fruits and seeds. Due to easily available in nature with plenty of abundance, and being a rich source of carbon, it can be used as organic precursor for the synthesis of Multiwalled carbon nanotubes (MWCNTs). In this study, we experimented the synthesis MWCNTs by using spray pyrolysis of neem oil over cobalt catalyst under the influence of argon atmosphere at 850°C. As synthesized MWCNTs were purified using acid treatment and characterized for structural confirmation. The electronic properties of as synthesized and purified MWCNTs was studied using four probe method. We studied the influence of acid treatment to MWCNTs on Surface area, Electrical properties and Hydrogen gas adsorption.

Keywords: Adsorption, spray pyrolysis, BET, Semiconductor

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times and dried at 200°C for 3hrs in muffle furnace.

Characterization of MWCNTs:

Purified MWCNTs were characterized by X-ray diffraction (XRD) analysis which was performed using Phillips analytical X-ray diffractometer with Cu Kα radiation running at 45 KV/40 mA in the 2θ range 2°–100° with step size of 0.02. Specific surface areas were measured using SmartSorb-92/93 model of Smart Instruments Co. Pvt. Ltd. by low temperature nitrogen adsorption using the Brunauer-Emmett-Teller (BET) single point method. The samples were degassed at 150°C for 2 hours prior to analysis. The morphological analysis was performed with a Phillips SEM 505 scanning electron microscope.

Surface area measurement by MBA (Methylene Blue Dye Adsorption) and BET method:

In MBA measurement the dye used was 'Methylene blue, (MB)from qualigens fine Chemicals'. Aqueous Solutions of different concentrations of MB are prepared ranging from 0.25 to 5.0 ppm and the absorbance of these solutions are measured using a UV-visible spectrophotometer at a fixed wavelength of 662 nm. This wavelength is selected for absorption measurement as MB solution shows highest absorbance at 662nm. Linearity curve of concentration v/s absorbance is plotted; the absorbance was found to be linear with regression factor 0.999. Weighed exactly 100 mg of test sample (MWCNTs) in 500 ml round bottom flask and added 100 ml of 5 ppm MB solution, shaken to mix properly then this solution is refluxed at 260 °C temperature for 1 hr. Allowed to cool the solution in same flask and kept for 24 hrs to absorb the MB on test sample. The absorbance of this solution is measured by UV-vis spectrophotometer at 662nm wavelength and found the amount of MB dye adsorbed on the test sample from linearity curve and by using formula the specific surface area was calculated. Similarly, the surface area of same test sample was determined using well known scientific apparatus called BET surface area analyzer from SMART instruments and both the results obtained by BET and MBA method were compared.

Electrical properties of MWCNTs:

Different weight % of MWCNTs were mixed with HDPE and prepared its chip using hydraulic press. Inserted the prepared chips of different weight % of MWCNTs in four probe instrument to measure the respective resistivity The schematic representation of four probe instrument to measure the resistivity is as shown in below **Figure 1.**

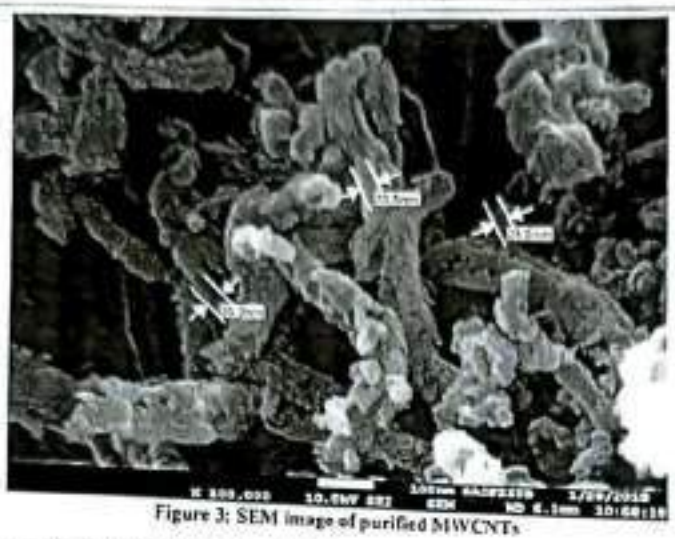

Figure 3: SEM image of purified MWCNTs

Table 1: Percentage Loading of MWCNTs with HDPE and volume resistivity

Sr No	% Loading of MWCNTs with HDPE	Volume Resistivity (Ohm-cm)
1	2	17
2	4	11
3	6	8
4	8	5
5	10	4
6	12	3
7	14	3.2
8	16	3.1
9	18	3.2

Figure 4: Plot of % loading of MWCNTs with HDPE v/s volume Resistivity

Table 2: The surface area and Hydrogen storage capacity of MWCNTs

Sample Details	Surface Area (m^2/g)		Hydrogen Gas Storage	
	BY MB Adsorption	By BET	At 11 kg/cm^3	At 100 kg/cm^3
MWCNTs (Obtained from Neem Oil)	112	118	1.20	5.25

measured by using Sieverts apparatus. It found that the hydrogen adsorption capacity of MWCNTs is 1.20 wt. % at 11 kg/cm^3 and 3.25wt% at 100kg/cm^3

Resistivity of MWCNTs shows the highest conductance capacity of MWCNTs when spiked with HDPE in higher concentration. i.e. obtained MWCNTs are conducting. The Surface area by MBA method and BET method as obtained is tabulated below along with Hydrogen Gas storage capacity of MWCNTs obtained from Neem oil shown in **Table 2.**

The surface area of MWCNTs measured by in-house MBA method is found to be comparable to that of BET method and also shows relative Hydrogen gas storage.

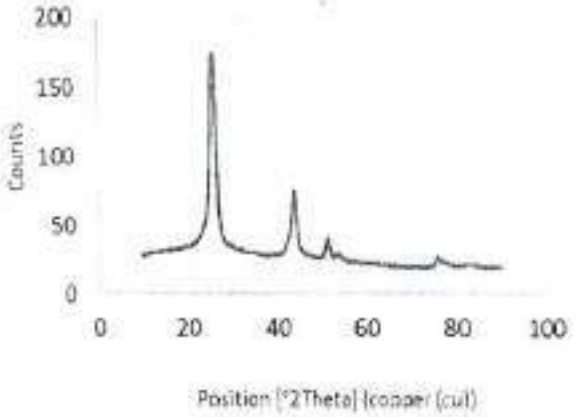

Figure 2(a): X-Ray Diffractogram of As obtained MWCNTs (Impure)

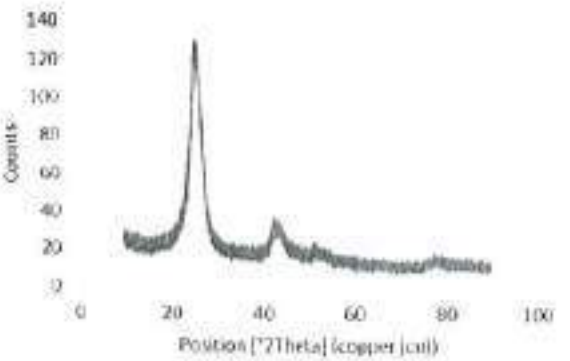

Figure 2(b): X-Ray Diffractogram of purified MWCNTs

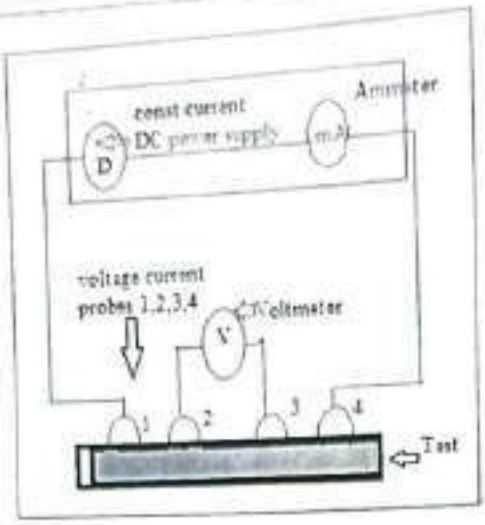

Figure 1: Schematic Diagram of four-point probe method

Hydrogen gas Adsorption Measurement

Adsorption of hydrogen gas on MWCNTs is carried out using low pressure Sieverts apparatus; this apparatus enables us to measure the hydrogen adsorption of MWCNTs by measuring decrease in hydrogen pressure. A detailed about apparatus, leak test and hydrogen adsorption measurement is discussed elsewhere [10].

RESULTS AND DISCUSSION

The Diffractogram of as obtained MWCNTs (impure) and Acid treated MWCNTs (purified) shows the reduction of peaks due to metallic impurities present in test sample. **Figure 2** (a) represents the major peak at around 26° is due to carbon i.e. MWCNT and the other two peaks at around 44.4° and 51.3° mainly due to metallic impurities i.e. presence of cobalt catalyst in test sample. Intensity of peaks due to metallic impurities gets reduced after purification which represents the purification of MWCNTs with acid treatment.

Scanning Electron Microscope image of purified MWCNTs show the formation of MWCNTs with tube diameter ranging from 28nm to 35 nm size (**Figure 3**).

The different concentration of MWCNTs with HDPE w/w were exposed to four probe method and the volume resistivity obtained is plotted against concentration as shown in **Table 1.**

The plot of percentage loading of MWCNTs with HDPE and its volume resistivity is shown below in **Figure 4.** The Resistivity decreases with the increase in MWCNTs loading with HDPE. Confirms that the MWCNTs are electrically conductive.

The optimal hydrogen storage capacity of purified MWCNTs at different pressure was

CONCLUSION

Naturally occurring precursor i.e. Neem oil is used for the synthesis of MWCNTs. The obtained MWCNTs were purified and characterized using different analytical tools and also studied its applications in Hydrogen gas adsorption and electrical property i.e. resistivity. Along with surface area measurement of MWCNTs with in-house Methylene Blue Adsorption and existing BET method which are found to be comparable and in-house MBA method can be replaced to that of existing BET method of surface area measurement. The results of resistivity measurement shows that the MWCNTs are electrically conducting.

Acknowledgement

The authors owe their sincere thanks to Department of Chemistry, Milind College of Science, Aurangabad, M.S. and Nano Technology Research Laboratory of B. K. Birla College (Autonomous) Kalyan, M.S for their research guidance and motivational inputs to shape up the presented research.

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INTRODUCTION

Azadirachta indica, a key member of botanical family is widely known as Neem oil in urban language [1]. Neem is considered to be a part of India's genetic diversity [2]. It is a vegetable oil obtained from its fruits and seeds. It is easily available in nature with plenty of abundance and also known as margosa oil. Neem tree is indigenous to the Indian subcontinent and has been introduced to many others areas in the tropics [3]. Multiwalled carbon nanotubes has built a concrete platform for a variety of applications across all the fields on globe. Not a single domain has left over where nanotechnology based products are unaware. The literature has witnessed plenty of methodologies for the synthesis MWCNTs by several ways [4]. Some of the methods are based on the chemical synthesis under different experimental conditions. However, these methods had reported afterwards that having costly affair from economic and environmental view point. Therefore, a new arena of green synthesis had come up with efficient methodologies followed by benchmarking end product with desired quality and quantity [5]. Neem is the key element of nature and pretty rich in anti-oxidant property [6]. It is enriched with carbon storage which on exposure to high temperature under catalytic climate yields MWCNTs. Researchers had reported the synthesis of MWCNTs from different natural precursors [7], functionalization with different functional groups [8] In this study, we have discussed the spray pyrolysis of neem oil with cobalt catalyst as reaction stimulator. A vertical spray pyrolysis furnace equipped with inert gas and water circulator with elevated temperature chamber having temperature range maximum of 1150°C.

Experimental

Preparation of Cobalt catalyst

The economical and qualitative cobalt Nanoparticles was obtained using in-house green method and used as catalyst for synthesis of MWCNTs. The details of this green method is described elsewhere in [9].

Synthesis of MWCNTs

The MWCNTs was synthesized from Neem oil using a cobalt catalyst, by vertical tube spray pyrolysis method at 850°C in an inert atmosphere of argon gas. Details about synthesis of MWCNTs is discussed elsewhere [10].

Purification of MWCNTs

The as obtained MWCNTs from boats was purified by soaking in 50% Hydrochloric acid followed by 50% Nitric acid solution for 24 h and later it was sonicated for 2h. Further MWCNTs were washed with water for several

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AN OUTLOOK FOR SAMPLE PREPARATION IN XRD ANALYSIS OF PHARMACEUTICAL SOLIDS

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ABSTRACT

Evaluation of polymorphic forms of sample specimens has secured an inevitable importance across the pharmaceutical industry as it is scientifically proven that, the alteration of small change in polymorphic form of drug substance and/or drug product may end up with significant changes in physico-chemical properties of solids. The aforesaid polymorphic evaluation can be achieved by powder XRD technique which is primary analytical tool globally used by crystallographers for the determination of polymorphic forms. However sample preparation is key attribute while using powder XRD tool for said evaluation. The illegitimate sample preparation may lead to ambiguous data and falsification of conclusion. As sample specimens meant for polymorphic assessment may have different physical nature, a practical and enriched skill-set is required to reach to the desired goal. In this paper, we focused on various sample types, their physical nature, polymorphic targets and road map for sample preparations. Also we covered expectations of regulatory agencies from pharmaceutical industries as far polymorphic data is concerned.

Keywords: Powder XRD, Regulatory agency, Ointments, DPIs, Suspensions

1.0. INTRODUCTION

Sample preparation is vital step in almost all the analytical techniques because the techniques are often not responsive to the analyte in its in-situ form or the results are distorted by interfering species [1]. Sometimes pre-treatment is done to prepare the sample into a form ready for analysis by specified analytical equipment. Pharmaceutical industries are performing polymorphic evaluations of various drug substances and drug products and generate an inevitable data which is required during product filing.

The polymorphic data is the requirement of various regulatory agencies like USFDA (USA), MHRA (UK), TGA (Australia), CDSCO (India), HEALTH CANADA (CANADA), MCC (South Africa), ANVISA (Brazil), EMEA (European Union), SFDA (China), NAFDAC (Nigeria), MEDSAFE (New Zeland), MHLW (Japan), MCAZ (Zimbabwe), SWISSMEDIC (Switzerland), KFDA (Korea), MoH (Sri Lanka) [2].

The physical nature of drug substances which are subjected to polymorphic evaluations may be either solids or powders and semi-solids also. However the nature of drug products may vary from solids/powders to suspensions, nasal sprays, ointments, creams, gels and foams. It becomes challenging task when the sample nature varies from analysis to analysis.

Powder X-ray diffraction (XRPD or p-XRD) technique is the gold standard for the evaluation of polymorphic form of any drug substance and drug product [3].

The sample preparation is the most crucial part involved in the aforesaid evaluation. Since powder XRD is the surface phenomenon, the selection of appropriate sample holder and sampler accessories is immensely important and it relies with expertise of concerned analytical scientist.

In this paper, we focused on the various types of samples and relevant sampler accessories.

2.0.MATERIALS USED IN THE STUDY:

The materials i.e. the types of sample holders used in the proposed study are basically of two types of available for XRD analysis as [1],

i. Back Loading Holder and
ii. Top Loading Holder or Zero Background Holder.
iii. Back loading holder is primarily used for the solid samples provided adequate sample quantity must be available whereas the top loading holder or zero background holder is used in the case when less sample quantity is available like in nasal

spray samples and when the targeted sample bears hydroscopic nature.

Semi-solid nature of samples specifically creams, ointments, suspensions, gels etc.

Figure 1 and **Figure 2** respectively are the representative figures of back loading and top loading holders.

Figure1: Pictorial Presentation of Backloading Holder (Courtesy: Malvern-Panalytical X-ray diffraction manual and X'Press magazine)

Figure 2: Pictorial Presentation Toploading Holder

3.0. SAMPLE PREPARATION ETHICS:

As XRD is surface phenomena, the surface of sample must be smooth enough so as to obtain pretty intense 2-theta reflections. The word 'smooth' herewith refers to uniform. If sample surface is not uniform then expected XRD profile may not obtain and data may end up with misleading conclusion.

To make the sample surface uniform, analyst must use either a 'glass slide' or 'metallic spatula' to avoid distortion of peaks [4].

Figure 3a indicate the practical way of sample preparation methodology to achieve the desired goal and Figure 3b indicates the back loading holder with uniform sample surface.

For the hygroscopic samples, cut silicon single crystal zero background holder provided with kapton film is preferred. The kapton film is nothing but a poly-imide film which is used to cover the sample throughout analysis in order to prevent the sample from atmospheric conditions.

This activity enables the crystallographer to gather the key knowledge about the hydrate polymorphic form of sample, if any [5].

Figure 4 shows representative silicon cut silicon single crystal zero background holder with kapton film.

Figure 3a: Practical Sample Preparation Technique

Figure 3b: Uniform Sample Surface in back loading holder

Figure 4: Silicon Cut Silicon Single Crystal Zero Background holder with Kapton film

If hygroscopic sample are being analyzed without kapton film then there will be conversion of solid nature of sample into semi-solid and may be liquid also if the analysis time is longer. The outcome of such analysis leads to generation of additional 2-theta peaks in XRD profile which may not be the part of actual crystal lattice of solid

sample but due to exposure of sample to atmospheric moisture during analysis. Thus scientist will obtain false crystallographic data [6].

4.0.SAMPLE PREPARATION IN DRUG PRODUCTS:

To analyze the samples like creams, ointments and suspensions, the zero back ground holder with kapton film is again suitable way forward. The semi-solid samples can be gently spread inside the groove of zero back ground holder and covered with kapton film to avoid spillage of sample due to rotation mode of XRD configuration. The crucial operation during preparation of such samples is uniform distribution of sample with smoothening of its surface. Broadening of peaks can be overcomes by better smoothened surface of these samples. Due to broadened peaks there may be shifting in 2-theta values from lot to lot of same product or may be shifting in comparison with reference data base [1, 7].

5.0.SAMPLE NATURE AND SAMPLE PREPARATION HURDLES:

Every times it is not mandatory that, analyst will get powder sample for XRD analysis. Since the sample nature solely depends on the route of synthesis adapted in particular. It is quite possible, the sample may be mixture of lumps or may have plate like shape or maybe needle shaped [8].

If samples of above said nature are used for XRD analysis without pre-treatment then sample will not be appropriately fitted into holder and lead to broadening of XRD bands resulting into amorphicity of sample [9, 10]. Figure 5shows different nature of solid samples for XRD analysis [11].

Figure 6 shows amorphous voids and broadening of XRD bands and due to non-uniformity of samples.

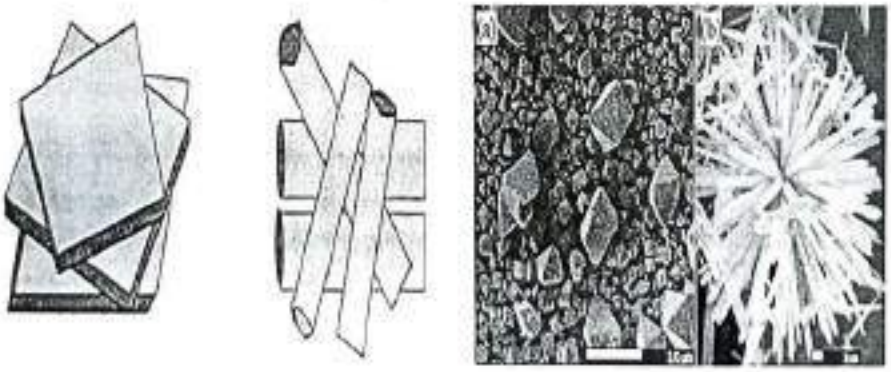

Figure 5: Different Nature of Solid Samples for XRD analysis

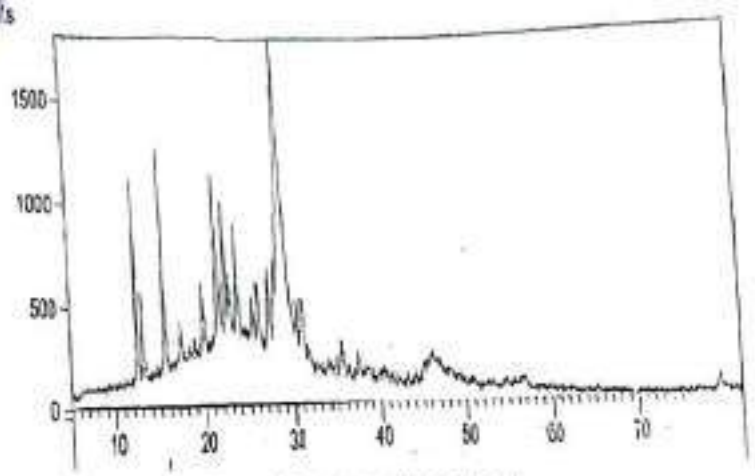

Figure 6: Broadening of XRD Peak Pattern

The broadening of XRD bands also result in absence of some 2-theta peaks which may be the characteristic of polymorphic form in particular [12, 13].

6.0.SCIENTIFIC APPROACH FOR XRD SAMPLE PREPARATION:

Analytical scientist cannot restrict the sample nature receiving from process development team. However he can establish the approach of sample pre-treatment before XRD analysis so that to avoid peak broadening followed by generation of amorphicity in XRD pattern and absence of characteristic 2-theta bands.One way is the trituration of sample with the help of mortar-pestle before applying to XRD exposure. The term 'trituration' herewith refers to gentle operation so that to make the sample uniform and not grinding the sample which may end with alteration in polymorphic form [8, 9].

The triturated sample must be filled into the cavity of sample holder in such way that the sample surface sould be closely packed and smooth. The trituration followed by closed packing of sample into the holder overcomes the preferred orientation effect in XRD pattern. Figure 7, 7a and 7b shows the sequential process of sample trituration, filling of sample into holder and sharpening of XRD peaks due to this process [1, 7]. In Figure 7b comparison of XRD patterns before (above graph) and after (below graph) following the suggested scientific approach is shown [14, 15, 16].

Figure 7: Sample Trituration in Mortar-Pestle

Figure 7a: Sample Filling in Holder and Surface Smoothening

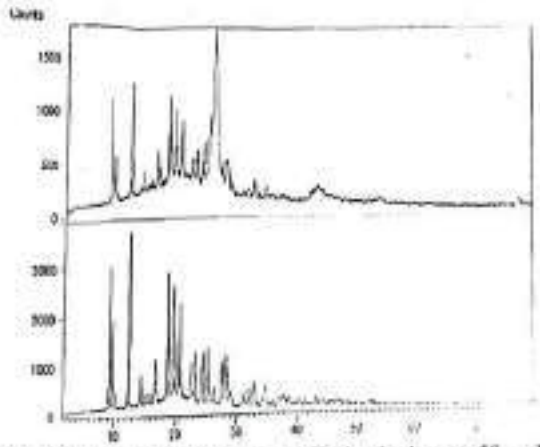

Figure 7b: Comparative XRD Peak Profile showing impact of Sample Trituration and appropriate Sample Preparation on Peak broadening (above graph) and peak sharpening (below graph)

7.0. DISCUSSION

The scientific approach suggested by us is an inevitable practice to obtain more precise and rugged XRD data. Figure 7 and 7a indicates the procedure to overcome the problems arises due to varying sample nature. Figure 7b clearly shows the difference in XRD peak profile obtained before and after implementing the recommended approach. Figure 3a and 3b exhibits the accurate methodology for sample loading into cavity of holder followed by surface smoothening to get reproducible results. The regulatory bodies expect the precise and robust data from pharmaceutical industries which shall be reproducible during product life cycle. The sample preparation approach attempted in this article will surely add values to the crystallographer to achieve the desired goal.

8.0. CONCLUSION

The scientific approaches defined in these experiments are the road maps to get improved XRD profiles of different types of drug substances and drug products. The sample nature will not be the hurdle for analytical scientist to get more robust and precise XRD data if recommended approach has been followed. A special precaution has to be taken while analyzing hygroscopic samples to maintain exactness of conclusion about hydrate form. The expertise of end-user or crystallographer plays an important role during selection of appropriate sample holder and sampler accessory depending on the nature of sample meant for polymorphic assessment. Finally, perfection of data leads to minimize the queries of regulatory bodies.

9.0. ACKNOWLEDGMENT

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(2021-22)

A GREEN AND EFFICIENT ONE-POT SYNTHESIS OF POLYHYDROQUINOLINE DERIVATIVES CATALYZED BY AMMONIUM CHLORIDE UNDER AQUEOUS MEDIA

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ABSTRACT

An efficient and eco-friendly one-pot four component synthesis of polyhydroquinoline derivatives from dimedone, aromatic aldehydes, ethylacetoacetate and ammonium acetate in the presence of catalytic amount of ammonium chloride under aqueous media is reported.The present approach of this protocol offeruse of green solvent, short reaction time, high yields, operational simplicity and simple workup.

Keywords: *Polyhydroquinoline, one-pot synthesis, eco-friendly, aqueous media*

Introduction

Heterocyclic compounds particularly containing nitrogen have attracted considerable attention in modern synthetic chemistry as these compounds play a key role in the fields of natural products, medicinal chemistry and materials chemistry. Among the important heterocyclic compounds, Quinolines having 1,4-dihydropyridine nucleus has attracted the enormous attention of organic and pharmaceutical chemists because of their significant biological activity and pharmacological properties[1-2].1,4-Dihydropyridines possess a range of biological activities, some of the biological activities exhibited by them are anti-atherosclerotic, bronchodilator, vasdilator, hepatoprotective, anti-hypertensive, anti-diabetic, geroprotective and antitumor agents[3-6]. 1,4- DHPs exhibit variety of pharmacological and medicinal properties and have been found to be effective as calcium channel blockers [7] and thus used in the therapeutic treatment of cardiovascular diseases [8]such as hypertension, angina pectoris, supraventricular tachycardia [9]. Literature have disclosed that these compounds also exhibits certain medicinal applications such as chemo sensitizer in tumor therapy, memory enhancing power, platelet anti-aggregatory activity, neuroprotectant, anti-inflammatory activity, antithrombotic activity [10-12].

In recent years, from the environmental and economic view point it is advisable to develop environmentally benign processes and avoid the use of solvents which are hazardous, responsible for environmental pollution and suspected human carcinogens. The use of water as an eco-friendly and easily available solvent in chemical reaction is the new trend in organic synthesis and important area of research. The use of water as a solvent shows valuable gains as it is most abundant and non-toxic. Water is polar solventhence immiscible with majority of organic compounds, therefore the water soluble by-products stays and isolation of organic compound is easy. Multicomponent reaction (MCR) is one of the most powerful and efficient tools in organic synthesis for the fabrication of biologically important compounds in the perspective of green chemistry. Multicomponent reactions offer advantages of atom economy, high yields and one-pot operation and aregreatly influenced by selection of suitable solvent and efficient catalyst [13-15].

Commonly used method reported for the synthesispolyhydroquinoline derivatives involves the one-pot, four component reaction of dimedone, aromatic aldehydes, ethyl acetoacetate and ammonium acetate in the presence of a variety of catalyst. The synthesis of these heterocyclic molecules is therefore extensively studied in the presence of organic solvents and catalysts [16-21].Recently the synthesis of polyhydroquinoline derivatives have been carried out using microwaves [22], ionic liquids [16], TMSCl-NaI [23], metal triflates [24], molecular iodine [25], SiO_2/$NaHSO_4$[26], SiO_2/$HClO_4$[27], ceric ammonium nitrate [28], tetrabutylammonium hydrogen sulfate [29], fermenting baker's yeast [30], organocatalyst [31]. Many of these methods are unsatisfactory as they suffer from

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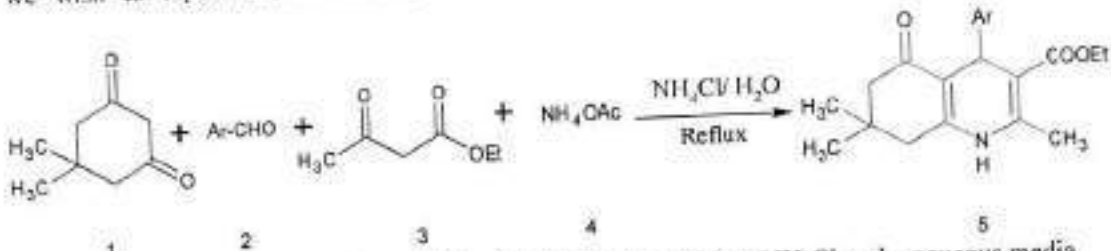
disadvantages such a use of toxic organic solvents, longer reaction times, low yield, and tedious workup procedures.Therefore the development of a new green and convenient method using a readily available catalyst in aqueous media for the synthesis of 1,4-Dihydropyridines is highly desirable. Herein, we wish to report an efficient, green and ammonium chloride catalyzed synthesis of polyhydroquinoline derivatives via one-pot four component condensation reaction between dimedone, aromatic aldehydes, ethyl acetoacetate and ammonium acetate in the presence of ammonium chloride in refluxing water (Scheme 1).



1 2 3 4 5

Scheme1. Synthesis of polyhydroquinoline derivatives catalyzed by NH_4Cl under aqueous media

Experimental
Materials and Methods

All the chemicals were purchased from LOBA Chemie and used as received without any further purification. All the reactions were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel using petroleum ether and ethyl acetate (60/40) as eluent and visualized with either UV light or an iodine chamber. Melting points were recorded by melting point apparatus. IR spectra were recorded onKBr disc on a Perkin-Elmer FTIR Spectrophotometer. The ^{1}H NMR spectrawere recorded in $CDCl_3$at room temperature on a VARIAN USA, Mercury plus 300 NMR Spectrometer using TMS as an internal standard.

Typical experimental procedure for the synthesis of polyhydroquinoline derivatives

In a typical experimental procedure a mixture of aromatic aldehyde (10 mmol), dimedone(10 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (10 mmol) and ammonium chloride (20 mol %) in water was refluxed for the appropriate time as summarized in Table 1. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and poured in ice cold water. The solid product obtained was filtered, washed with water and dried. Further purification was accomplished by recrystallization from ethanol to obtain pure polyhydroquinoline derivatives.

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(phenyl)-5-(*6H*)-oxoquinolin-3-carboxylate (5a)

M.P.: 200-202 ^{0}C. IR (KBr): 3290, 3076, 2969, 1698, 1608, 1060, 690 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ 0.96 (s, 3H), 1.05 (s, 3H), 1.21 (t, J=7.3Hz, 3H), 2.12-2.30 (m, 4H), 2.30 (s, 3H), 4.08 (q, J=7.1Hz, 2H), 5.09 (s, 1H), 6.62 (s, 1H), 7.06-7.212 (m, 1H), 7.20-7.24 (m, 2H), 7.28-7.33 (m, 2H).

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(4-chlorophenyl)-5-(*6H*)-oxoquinolin-3-carboxylate (5b)

M.P.: 247-248^{0}C. IR (KBr): 3274, 3190, 3076, 1706, 2961, 1603, 1492, 1214, 849 cm^{-1}; ^{1}HNMR ($CDCl_3$ 300 MHz): δ0.95 (s, 3H), 1.06 (s, 3H), 1.16 (t, J=7.1Hz, 3H), 2.11-2.33 (m, 4H), 2.35(s, 3H), 4.02 (q, J=7.1Hz, 2H), 5.02 (s, 1H), 6.48 (s, 1H), 7.12-7.20 (m, 2H), 7.25-7.28 (m, 2H).

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(4-methoxyphenyl)-5-(*6H*)-oxoquinolin-3-carboxylate (5c)

M.P.: 258-260^{0}C. IR (KBr): 3276, 3201, 3076, 2951, 1701, 1605, 1492, 1215, 847 cm^{-1}; ^{1}HNMR ($CDCl_3$ 300 MHz): δ0.92 (s, 3H), 1.02 (s, 3H), 1.22 (t, J=6.9Hz, 3H), 2.10-2.30 (m, 4H), 2.35 (s, 3H), 3.75 (s, .3H), 4.02 (q,

J=7.1Hz, 2H), 4.98 (s, 1H), 6.39 (s, 1H), 6.69 (d, J=8.5, 2H),7.20 (d J=8.5, 2H).

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(3-nitrophenyl)-5-(6*H*)-oxoquinolin-3-carboxylate (5d)

M.P.: 180-182 °C. IR (KBr): 3290, 2969, 1607, 1532, 1160, 752 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ0.91 (s, 3H), 1.04 (s, 3H), 1.22 (t, J=7.1Hz, 3H), 2.09-2.30 (m, 4H), 2.36 (s, 3H), 4.02 (q, J=7.1Hz, 2H), 4.90 (s, 1H), 6.32 (s, 1H), 6.72 (d, 1H), 7.22-7.15 (m, 2H),7.38(d, 1H).

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(4-hydroxyphenyl)-5-(6*H*)-oxoquinolin-3-carboxylate (5e)

M.P.: 226-228 °C. IR (KBr): 3365, 2968, 1710, 1640, 1590, 1480, 1385, 1220, 782 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ 0.93 (s, 3H), 1.04 (s, 3H), 1.26 (t, J=7.1Hz, 3H), 2.15-2.33 (m, 4H), 2.40 (s, 3H), 4.06 (q, J=7.1Hz, 2H), 4.95 (s, 1H), 5.36 (s, 1H), 6.45(s, 1H), 6.75-6.78 (m, 2H), 7.03-7.06 (m, 2H).

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(4-hydroxy-3-methoxyphenyl)-5-(6*H*)-oxoquinolin-3-carboxylate(5f)

M.P.: 214-216 °C. IR (KBr): 3392, 3291, 3098, 1690, 1612, 1020, 732 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ0.90 (s, 3H), 1.02 (s, 3H), 1.21 (t, J=7.1Hz, 3H), 2.11-2.30 (m, 4H), 2.35 (s,3H), 4.02 (q, J=7.1Hz, 2H), 4.92 (s, 1H), 5.36 (s, 1H), 6.45(s, 1H), 6.68-6.70 (d, 2H), 7.5 (m, 1H).

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(5-bromo-2-hydroxyphenyl)-5-(6*H*)-oxoquinolin-3-carboxylate (5g)

M.P.: 210-212 °C. IR (KBr): 3316, 3107, 2962, 1736, 1616, 1475, 1230, 777 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ 0.92 (s, 3H), 1.02 (s, 3H), 1.22 (t, J=7.1Hz, 3H), 2.13-2.32 (m, 4H), 2.42 (s, 3H), 4.05 (q, J=7.1Hz, 2H), 4.96 (s, 1H), 5.38 (s, 1H), 6.55(s, 1H), 7.7(m, 1H), 6.72 (m, 1H), 7.8 (d, 1H)

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(4-methylphenyl)-5-(6*H*)-oxoquinolin-3-carboxylate (5h)

M.P.: 264-266 °C. IR (KBr): 3280, 3099, 2962, 1698, 1610 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ0.91 (s, 3H), 1.06 (s, 3H), 1.21 (t, J=7.1Hz, 3H), 2.21-2.39 (m, 4H), 2.12 (s, 3H), 4.025(q, J=7.1Hz, 2H), 5.00 (s, 1H), 6.41 (s, 1H), 6.96 (d, 2H), 7.02 (d, 2H).

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(2,4-dimethoxyphenyl)-5-(6*H*)-oxoquinolin-3-carboxylate (5i)

M.P.: 198-200 °C. IR (KBr): 3280, 3200, 3098, 1698, 1610, 1020 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ0.92 (s, 3H), 1.05 (s, 3H), 1.21 (t, J=7.1Hz, 3H), 2.08-2.30 (m, 4H), 2.34 (s, 3H), 4.02 (q, J=7.1Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H), 4.98 (s, 1H), 6.40 (s, 1H), 6.69 (m, 1H), 6.01 (d, 1H), 7.02 (m, 1H).

Ethyl 1,4,7,8-tetrahydro-2,7,7-4-(2-thienyl)-5-(6*H*)-oxoquinolin-3-carboxylate (5j)

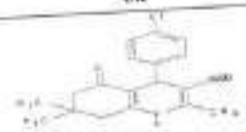
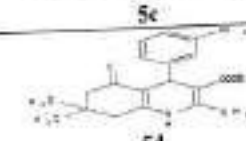
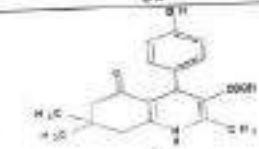
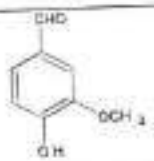
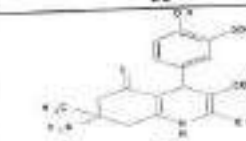
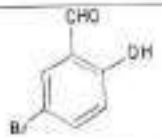
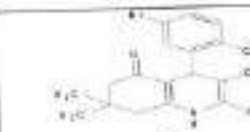
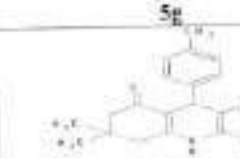
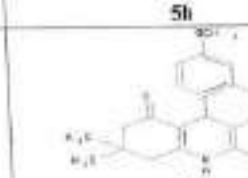
M.P.: 280-282 °C. IR (KBr): 3292, 3211, 3065, 1689, 1602, 1067, 685 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ 0.95 (s, 3H), 1.07 (s, 3H), 1.25 (t, J=7.1Hz, 3H), 2.10-2.30 (m, 4H), 2.36 (s,3H), 4.03 (q, J=7.1Hz, 2H), 4.95 (s, 1H), 6.439 (s, 1H), 7.12(m, 1H), 7.2 (m, 1H), 7.8 (m, 1H).

Results and Discussion

Synthesis of polyhydroquinoline derivatives (**5a-5j**) was studied via one-pot four component reaction of dimedone**1**, an aldehyde **2**, ethyl acetoacetate **3** and ammonium acetate **4** in presence ammonium chloride as a catalyst in water (Table 1).In order to investigate the optimal loading of ammonium chloride catalyst, a catalytic performance was surveyed on the model reaction. For optimization, we have synthesized polyhydroquinoline derivative (5a) fromdimedone (10 mmol), benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol) and ammonium acetate (10 mmol) under reflux inwater with different amount of catalyst as a model reaction.To generalize the scope of present method, reaction was studied by using different aldehydes bearing electron withdrawing to electron donating groups under the optimized conditions. The reaction under the influence of ammonium chloride in aqueous media proceeds smoothly in all cases to yield corresponding products with very good to excellent yields with reduced reaction time. As a result of this improved protocol, it was confirmed that the reaction time is significantly reduced from hours to minutes. The reproducibility of the result and purity of the compound was checked by TLC. The easy

workup of reaction in which pouring the reaction mixture in ice water to get solid product in good yield and sufficiently pure. The present method is found better to the available methods in regards with environmentally benign, inexpensive and commercially available catalyst and simplicity of workup.

Table 1. Synthesis of polyhydroquinoline derivatives with various aldehydes using NH_4Cl catalyst

Entry	Ar-CHO	Product[a]	Time (min)	Yield[b] (%)	M.P. (°C)
1		 **5a**	35	95	200-202
2		 **5b**	65	87	247-248
3		 **5c**	40	92	258-260
4		 **5d**	90	86	180-182
5		 **5e**	100	86	226-228
6		 **5f**	20	88	214-216
7		 **5g**	50	84	210-212
8		 **5h**	80	95	264-266
9		 **5i**	130	90	198-200
10		 **5j**	110	92	280-282

[a] Products were characterized by IR and ^1H NMR spectroscopy
[b] Isolated yield

Conclusion

In conclusion, we have developed a simple, rapid, efficient and green method for the preparation of polyhydroquinoline derivatives using ammonium chloride catalyst under aqueous medium. The notable features of this one-pot protocol are the short reaction time, high yield, green solvent and operational simplicity. This method does not involve the use of organic solvents and thus is an environmentally benign, useful and attractive process.

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Research Article

SYNTHESIS, CHARACTERIZATION, THERMAL, X-RAY AND ANTIMICROBIAL STUDY OF ZN (II) METAL COMPLEXES OF DEHYDROACETIC ACID BASED NEW SCHIFF BASES

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ABSTRACT

Tetradentate complexes of Zn (II) of Schiff bases derived from DHA, o-phenylenediamine, 4- N, N, Diethyl amino Salicylaldehyde (L1) and Dehydroacetic Acid (DHA), 4-methyl-o-phenylenediamine, 5-bromo Salicylaldehyde (L2) have been synthesized and characterized by elemental analysis, magnetic susceptibility, thermal analysis, X-ray diffraction, ^{1}H-NMR, Mass, IR, UV visible spectra and conductometry. The ligand field parameters have been characterized and found to have octahedral geometry. Thermal behavior (TG/DSC) of the complexes was studied. X-Ray diffraction study reveals monoclinic crystal system. The ligand and its complexes were subjected for antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* and fungicidal activity against *Trichoderma and Aspergillus Niger*.

Keywords: Tetradentate ligand, Dehydroacetic acid, TGA/DSC, X-Ray diffraction.

1. INTRODUCTION

Dehydroacetic Acid (DHA) has antimicrobial effect against bacteria, yeast and molds and used as preservative in food factories & as fungicide with virtuous co-ordination properties [1]. So researchers are infatuated to synthesize metal complexes of Schiff bases choosing it as nucleus. Indicated metal complexes are used in Catalysis [2], DNA cleavage [3], antifungal [4], antitumor [5], antibacterial agents [6]. Zinc has decent co-ordination with N_2O_2 donor Schiff bases. In the present study, tetradentate Zn (II) complexes derived from, DHA, o-phenylenediamine, 4-N, N Diethyl amino Salicylaldehyde (L1) and DHA, 4-methyl-o-phenylenediamine, 5-bromo Salicylaldehyde (L_2) have been synthesized and characterized.

2. MATERIAL AND METHODS

2.1. Reagents and solvents

Dehydroacetic Acid (DHA), o-phenylenediamine, 4-N,N-Diethylamino Salicylaldehyde, 4-methyl-o-phenylene diamine, 5-bromo Salicylaldehyde from Merrk of AR grade were used as supplied for synthesis of ligand. AR grade Zinc chlorides used for the synthesis of complexes.

2.2. Synthesis of ligand

In the first step, mono-Schiff base compound was prepared by refluxing 50 ml solution of 10mmol of DHA and 10mmol o-phenylenediamine, 4-methyl-o-phenylenediamine in super dry ethanol for about 3h. The progress of reaction was monitored by thin layer chromatography. Mono-Schiff base thus formed was then refluxed with 10mmol 4-N, N Diethyl amino Salicylaldehyde/5-bromo Salicylaldehyde to prepare asymmetric ligand. Product was then cooled at room temperature and collected by filtration, and recrystallized by ethanol (Yield: L1-87, L2-85 %).

2.3. Synthesis of metal complexes

To a hot methanolic solution (25ml) of the ligand (0.01 mol), methanolic solution (25ml) of zinc chloride (0.01 mol) was added with constant stirring and refluxed for about 3 h. The pH of reaction mixture was adjusted to 7.5-8.5 by adding 10 % alcoholic ammonia. The precipitated solid colored metal complexes was filtered off in hot condition and washed with hot methanol, petroleum ether (40°-60°) and dried over calcium chloride in vacuum desiccators (yield: 65 %).

2.4. Instrumentation

The carbon, hydrogen and nitrogen contents were determined on Perkin Elmer (2400) CNS analyzer. FTIR spectra were recorded on Jasco FTIR-4100 spectrometer using KBr pellets. ^{1}H NMR spectra of ligand were measured in $CDCl_3$ using TMS as internal standard. The TG/DTA and XRD were recorded on Perkin Elmer TA/SDT-2960 and Philips 3701, respectively. The UV-visible spectra of the complex were recorded on JascoUV-530 spectrometer. Magnetic susceptibility measurements of the metal chelates were determined on a Guoy balance at room temperature using $Hg[Co(SCN)_4]$ as calibrant.

2.5. Antimicrobial Analysis

Metal and Ligand complexes were screened for their antimicrobial activity by disc plate method. Antimicrobial activity was tested by disc plate technique involving the cultures of the selected organisms. The test solutions of metal ligand complexes were prepared in sterile dimethyl sulfoxide (DMSO) solvent for the study. The synthesized metal ligand complexes were tested at different concentrations to find out the minimum concentration of the metal complexes required for inhibiting the growth of microbes. The zone of inhibition for the test samples, standard and control (DMSO) was measured.

3. RESULTS AND DISCUSSION

Table 1 indicates physical characteristics, micro analytical and molar conductance data of ligand and metal complexes. Molar ratio of (metal: ligand) is 1:1 and found in good relevance with the general formula $[ML(H_2O)_2]$. Where L= L1, L2.

3.1. ^{1}H-NMR spectra of ligand

The ^{1}H NMR spectra of free ligand, in $CDCl_3$ at room temperature shows the following signals. L_1 -1.04-1.09 δ (t, 6H, 2×CH_3-CH_2-N), 1.11-1.16 δ (q, 4H, 2×N-CH_2-CH_3), 2.12 δ (s, 3H, C6-CH_3), 2.51 δ (s, 3H, N=C-CH_3), 5.79 δ (s, 1H, C5-), 6.75-7.16 δ (m, aromatic protons), 8.59 δ (s, 1H, N=C-H), 6.18 δ (s), phenolic (OH) hydrogen of phenyl ring) and 9.50 δ (s, 1H, enolic (OH/NH) of DHA moiety) [7]. L_2 - 2.09 δ (s,3H,C6-CH_3),2.11 δ (s, 3H, N=C-CH_3),2.25 δ (s,3H, C4-methyl of phenylring) 5.77 δ (s, 1H, C5-), 6.73-7.03 δ (m, aromatic protons), 8.88 δ (s, 1H, N=C-H),9.76 δ(s), phenolic (OH) hydrogen of phenyl ring) and 15.88 δ (s, 1H, enolic (OH) ofDHA moiety).

3.2. FTIR Spectra

A comparative study of IR data of ligand and its metal complexes is listed in Table 2. It shows major band at 3227-3419, 1687-1690, 1640-1658, 1502-1561, 1351-1353, 1214-1230 cm-1 of L_1 and L_2 are assignable to υ OH, υ C=O (lactone carbonyl), υ C=N (azomethine), C=C, υ C-N (aryl azomethine) and υ C-O (phenolic) stretching modes respectively [8]. Lack of broad band in region of 3200-3400 cm^{-1} in the spectra of metal complexes reveals chelation of phenolic oxygen to the metal ion [9]. Difference of 10-40 cm^{-1} in frequency is observed in case of azomethine υ (C=N) band in metal complexes, with compared to ligand which is 1640-1658 cm^{-1} indicating involvement of azomethine nitrogen in coordination to metal [10]. Metal complexes shows new band in the 530-532 and 471-477 cm^{-1} region can be assigned to υ M-O and M-N vibrations respectively. While (C=C) ring skeletal band is constant in all metal complexes. The presence of coordinated water in metal complexes is confirmed by observing broad band in 3067-3088 cm^{-1} region and a new band at 860 cm^{-1} that may be assigned for O-H stretching vibration and out of plane bending of water molecule coordinated to complexes [11]. Hence, it is concluded that the coordination takes place via phenolic oxygen and azomethine nitrogen of ligand molecule to the zinc metal ions.

Table 1: Physical characterization, analytical and molar conductance data of compounds

Compound Molecular formula	Mol. Wt.	M.P./ Decomp Temp. ^{0}C	Color	Molar conductance Mho cm^2mol^{-1}	Found (calculated) C	H	N	M
(H_2L1) $C_{23}H_{32}N_2O_4$	433.50	87	Dark Red	----	68.25 (69.27)	6.06 (6.28)	5.23 (9.69)	----
(H_2L2) $C_{23}H_{19}N_2O_4Br$	454.30	173	Dark Yellow	----	57.44 (58.04)	4.09 (4.21)	6.08 (6.15)	----
$[L1Zn(H_2O)_2]$	496.87	263	Faint Brown	25.35	60.89 (60.43)	5.21 (5.07)	5.35 (5.46)	13.10 (13.16)
$[L_2Zn(H_2O)_2]$	518.68	267	Faint Yellow	29.54	51.25 (50.94)	3.15 (3.30)	5.34 (5.40)	11.56 (12.61)

Table 2: IR and UV data of ligand and metal complexes

Compound	IR band frequency (cm⁻¹)								λmax (nm)	Magnetic Moment (BM)
	ν(OH)	ν(C=O)	ν(C=N)	C=C	C-N	C-O	M-O	M-N		
L1	3227	1687	1640	1502	1353	1230	---	---	261, 332	---
Zn-L1	3056	1685	1621	1502	1360	1214	532	472	328, 447, 613	Diamagnetic
L2	3419	1690	1658	1561	1360	1214	---	---	274, 338	---
Zn-L2	3054	1685	1612	1519	1351	1167	530	477	340, 421, 621	Diamagnetic

3.3. Electronic absorption spectra and Magnetic susceptibility

The electronic absorption spectrum of L1, L2 and its complexes in 10^{-3} M DMSO solution at room temperature along with magnetic susceptibility are listed in Table 2. L1 shows two bands at 263,332 nm these absorption bands assigned for π-π*, n-π*transitions. L2 shows two bands at 274,338 nm suggested the π-π*, n-π* transitions. Both ligands show the value for -C=O, in 263-274 region, and -C=N azomethine π- π* transition in 332-338 nm. Zn (II) complex of L1 shows three bands at 613,447,328 assigned for 6A1g → 4T1g, 6A1g → 4T2g and charge transfer respectively. Zn (II) complex of L2 absorbs at 623, 423,340, for 6A1g → 4T1g, 6A1g → 4T2g and charge transfer respectively. Both complexes are Diamagnetic in nature for d^{10}configuration of Zn (II) [12]. Electronic absorption data along with magnetic properties are in good agreement with high spine octahedral geometry for both Zn (II) complexes.

3.4. Powder X-ray diffraction

Scanning of x-ray diffractogram of Zn(II) metal complexes of L1 and L2 is done at wavelength 1.543 Å in the range 5-100°. The x-ray diffraction pattern of these complexes compared with major peaks of relative intensity greater than 10% has been indexed to their hkl value by using computer program. The diffractogram of Zn(II) complex of L1 had twenty reflections with maxima at 2θ=4.14° corresponding to d value 4.8017Å, lattice constants, a=7.3662 Å, b=9.5623 Å, c = 11.7895 Å and unitcell volume V=718.43318 Å^3. The diffractogram of Zn (II) complex of L2 had twenty one reflections with maxima at 2θ = 10.48° corresponding to d value 4.16Å, lattice constants, a=8.9665 Å, b=9.4879 Å, c =16.7895 Å and unit cell volume V=1284.546 Å^3. In concurrence with these cell parameters, the condition such as a ≠ b ≠ c and α =γ = 90° ≠ β required for sample to be monoclinic were tested and found to be satisfactory. Hence it can be concluded that Zn (II), complex of L1, L2 has monoclinic crystal system [13].

3.5. Thermal analysis

The TG/DSC analysis of both Zn (II) complexes was done from ambient temperature to 1000°C in nitrogen atmosphere using α-Al2O3 as reference. The TG curve of Zn-L1 complex show first mass loss 7.91% (calcd.7.45%) in the range 185-220°C and an endothermic peak in this region ΔT min. is 200°C, indicate removal of two coordinated water molecules [14]. The first step is slow decomposition from 220-505°C with 27% mass loss. This can be further confirmed by observing broad exotherm in DSC with ΔTmax. = 434°C indicates non coordinated part of complex. In second step, 37.19 % losses confirmed by ΔTmax. = 690.17°C indicate removal of coordinated part. The TG curve of Zn-L2 show first mass loss 11.91 % (calcd.11.45%) in the range 165-200°C and an endothermic peak in this region ΔTmin. = 190°C, The first step is slow decomposition from 200-450°C with 37% mass loss. This can be further confirmed by observing broad exotherm in DSC with ΔTmax. = 385°C indicates removal of non-coordinated part of complex. In second step 27.29% loss confirmed by ΔTmax. = 630.25°C by stable residue formation.

3.6. Antimicrobial activity

The antimicrobial activity of ligand and metal complexes were tested in vitro against bacteria such as Staphylococcus aureus and Escherichia coli by paper disc plate method [15]. The compounds were tested at the concentration 500ppm and 1000ppm. DMF and compared with known antibiotics viz. Ciprofloxin (Table 3). For fungicidal activity, compounds were screened in vitro against Aspergillus Niger and Trichoderma by mycelia dry weight method [16] with glucose nitrate media. The compounds were tested at the concentration 250 and 500 ppm in DMF and compared with control (Table 4)

From Table 3 and 4, it is clear that the inhibition by metal chelates is higher than that of a ligand and results are in good agreement with previous findings with respect to comparative activity of free ligand and its complexes. Such enhanced activity of metal chelates is due to the increased lipophilic nature of the metal ions in complexes. The increase in activity with concentration is due to the effect of metal ions on the normal cell process.

Table 3: Antibacterial activity of compounds

Test Compound	Inhibition Zone (mm)			
	E.Coli		*Staphylococcus*	
	500 ppm	1000 ppm	500 ppm	1000 ppm
Ciprofloxin	29	32	31	35
(H_2L_1)	09	12	12	15
$[L_1Zn(H_2O)_2]$	13	17	17	19
(H_2L_2)	15	18	17	18
$[L_2Zn(H_2O)_2]$	19	23	21	24

Table 4: Yield of Mycelial dry weight in mg (% inhibition)

Test Compound	*Aspergillus Niger*		*Trichoderma*	
	250 ppm	500 ppm	250 ppm	500 ppm
Control	79	79	70	70
(H_2L_1)	61	24	40	19
$[L_1Zn(H_2O)_2]$	53	18	34	08
(H_2L_2)	43	17	24	15
$[L_2Zn(H_2O)_2]$	32	10	22	04

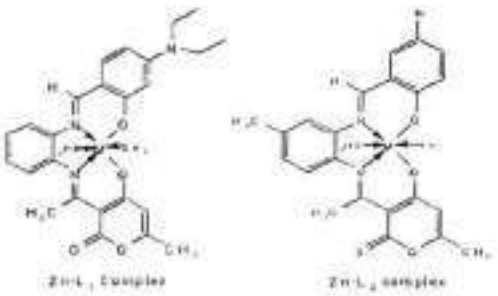

Fig. 1: The proposed structure of the complexes, Where M= Zn

4. CONCLUSION

In the present investigation we have reported synthesis of two asymmetrical ligand and its Zn (II) metal complexes. Spectral study proves chelation by azomethine nitrogen and phenolic oxygen are involved in the coordination with metal ions, proposing high spine octahedral geometry for both Zn (II) complexes. It is assumed that the ligands behave as dibasic and are biologically active and show enhanced antimicrobial activities compared to free ligand. Thermal study reveals thermal stability of complexes. The XRD study suggests monoclinic crystal system. Study based on transition metal complexes is an under-developed area of research and is full of opportunities for further progress as Metal Complexation and its significant effects on biological activities.

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Conflict of interest

The authors certify that there is no conflict of interests with any financial organization regarding the material discussed in the paper.

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None declared

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ORIGINAL ARTICLE **OPEN ACCESS**

Ultrasound Assisted One-Pot Green Synthesis of Highly Substituted Pyrazoles Catalyzed by [DBUH][OAc] Ionic Liquid

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ABSTRACT

A significant, one-pot synthesis of highly substituted pyrazoles derivativevia three-component condensations of Aromatic aldehyde, Malononitrile, along with Phenylhydrazine in the presence of Ionic liquid [DBUH][OAc]. The present technique provides significant advantages, including reduced environmental impact, simple procedure, shorter reaction time, mild condition, and ease of product recovery. The ionic liquid reusability and recovery make the protocol eco-friendly. Also, a series for 5-amino-1,3-diphenylpyrazole-4-carbonitrile analogues were synthesised. For the comparison between conventional and ultrasound techniques. It was observed that the ultrasound irradiation technique gave excellent yield and shorter reaction time than the conventional technique.

Keywords: *pyrazole, multicomponent reaction, ionic liquid, [DBUH][OAc], ultrasound irradiation.*

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INTRODUCTION

In pharmaceutical research, five-membered N-linked heterocyclic molecules have attracted much interest. For synthesizing five-membered heterocyclic compounds, the condensation reaction suitable sequential compound is the most popular alternative approach [1-4]. Pyrazole ring is a prominent motif which among the provide reported as having outstanding pharmacological and biological activity such as antimicrobial [5], antiviral [6], anti-inflammatory [7], anticonvulsant [8], anti-depressant [9], antitumor [10], as well as fungicidal properties [11,12]. Several pyrazole derivatives exhibit significant pharmacological properties and are valuable materials in pharmaceutical research. Some of the pyrazole-containing drugs like Antipyrine, Celecoxib, Mepirizole, Rimonabant, Lonazolac, and Tepoxalin, etc. The structure of drugs has been shown in Figure 1[13-18].

Multicomponent reactions (MCRs) is the preferable approach because it allows for high throughput chemical synthesis at a low cost and in a shorter reaction time. Because it generates significant compounds in a single step by forming multiple new bonds in a one-opt, the approach has prompted a lot of interest in organic chemistry. In both drug discovery and green chemistry [19,20]. in the last decade, the growth of three and four-component reaction has been considerable and there is still a lot of effort being put into developing new MCRs [21,22].In currentcenturies, ionic liquids (ILs) have obtained a noteworthy attention in the context of eco-friendly green synthesis since they can also be used as effective media for organic synthesis [23-25]. Non-volatility, non-explosive, low vapour pressure, reusable, easily operated, as well as thermally stable over a wide temperature range are only several of the physicochemical features of ILs. Due to their specific ionic character and structural organization, ionic liquids can be regarded as alternative greener solvents [26,27]. In organic synthesis, there are numerous reports about the application of ILs such as Biginelli reaction [28], Friedel-Crafts reaction [29], Beckmann rearrangement [30], Diels-Alder reaction [31], Heck reaction [32], Pechmann condensation [33], and more reactions [34-38].Recently, the technique of synthesizing organic molecules using ultrasound irradiation is very effective and attractive. Ultrasound irradiation is used to increase the rate of a chemical reaction by ultrasonic cavitation mechanism, mass transfer in the microenvironment can be accelerated, which is the formation of microbubbles, growth, and impulsive collapse. High temperature and pressure are generated by collapsing bubbles, resulting in hot spots with enough energy to promote chemical reactions [39-43]. This method is considered in terms of conserving energy, reducing reaction time, improving yield and waste minimization [44,45]. In the current work, effective implementation of

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[DBUH][OAc] ionic liquid and ultrasound has been established for synthesis of highly substituted pyrazoles [Scheme 1]. Use of the catalyst [DBUH][OAc] is associated with ultrasound irradiation technique for the synthesis substituted pyrazoles is investigated for first time. A comparative study by conventional as well as ultrasonication technique.

MATERIALS AND METHODS

Analytical grade of all chemicals and were purchased from a commercial source. Merck 60 F250 TLC analytical silica gel plat is used to monitor reaction progress and purity of compounds. Bondelin sonorex (frequency of 40 MHz and 100W) was used to ultrasound bath. Using of Avance-II(Bruker) instrument for ^{1}H-NMR and ^{13}C-NMR their frequency 400MHz and 100 MHz, recorded in Dimethyl sulfoxide-d6. RZX (Perkin Elmer) spectrometer using KBr, IR spectra were recorded. The melting points were determined by using the open capillary tube is uncorrected.

General procedure for the preparation of I.L.[DBUH][OAc]

In a round bottom flask add acetic acid (1 eq.) was added over a time span of 5 min. to DBU (1 eq.) In an ice bath under ultrasound at 5°C. At normal temperature, the reaction mixture was irradiated with ultrasound for an increased 30 minutes. As result, the lightyellow viscous liquid of [DBUH][OAc] was obtained.

General experimental procedure for the synthesis of 5-amino-1,3-diphenylpyrazole-4-carbonitrile 4(a-j)

Conventional Method

A mixture of Aromatic aldehydes (**1a-j**, 1mmol), Malononitrile (**2**, 1mmol), along with Phenylhydrazine (**3**, 1mmol), and 20 mol % [DBUH]OAc] in 5 mL ethanol was placed In a round bottom flask. At 80 °C, the mixture was heated. TLC (eluent: pet ether/ethyl acetate, 7:3)by using the progress of a reaction. After that, the reaction was completed and the reaction mixture was cooled to normal temp. and poured over ice-cold water and the product obtained was isolated by filtration. The obtained product was crystallized in ethanol to get pure products. The catalyst [DBUH] [OAc] is recovered from the water below reduced pressure and reused. All the products are confirmed by melting point and compared with the literature **[Scheme 1]**.

Ultrasound method

A mixture of Aromatic aldehydes (**1a-j**, 1mmol), Malononitrile (**2**, 1mmol), along with Phenylhydrazine (**3**, 1mmol), and 20 mol % [DBUH]OAc] in 5 mL ethanol was placed In a round bottom flask. At 50 °C, the mixture was irradiated with ultrasound. TLC (eluent: pet ether/ethyl acetate, 7:3) by using the progress of a reaction. After that, the reaction mixture was cooled to normal temp. and poured over ice-cold water and the solid product obtained was isolated by filtration. The obtained products were crystallized in ethanol to get pure products. The catalyst [DBUH] [OAc] is recovered from the water below reduced pressure and reused. All the products are confirmed by melting point and compared with the literature **[Scheme 1]**.

Spectral data of synthesized compounds

5-amino-3-(4-chlorophenyl)-1-phenylpyrazole-4-carbonitrile(4d): chrome yellow crystal. melting point 127-130°C. yield 95%.^{1}H-NMR (DMSO-d6, 400MHz) δ 7.5 (J=5.65Hz, d, 2H), 7.46 (J=6.6Hz, t, 2H), 7.32 (t, 1H), 7.42 (J=4.5Hz, d, 2H), 7.43 (J=5.31Hz, d, 2H), 5.40 (s, 2H). ^{13}C NMR (DMSO-d6, 100MHz) δ 158.80, 148.87, 139.62, 135.11, 133.83, 130.12, 129.93; 129.83, 129.41, 129.12, 128.39, 126.69, 126.3, 118.92, 117.98, 96.05. M.S. (m/z) (M$^+$) Calculated $C_{16}H_{11}ClN_4$ (294.0676 and (M+2)$^+$ 296.0682, found 294.0678. & 296.0685).

5-amino-3-(4-methoxyphenyl)-1-phenylpyrazole-4-carbonitrile(4e): light-yellow crystal. melting point. 107-109°C. yield 96%. ^{1}H-NMR (DMSO-d6, 400MHz) δ 7.24 (t, 1H), 7.37 (J=3.33 Hz, t, 2H), 7.54 (J=3.11 Hz, t, 2H), 7.45 (J=5.11 Hz, d, 2H), 6.89 (J=2.13 Hz, d, 2H) 4.58 (s, 2H), 3.77 (s, 3H). ^{13}C-NMR (DMSO-d6, 100MHz) δ 160.10, 148.55, 139.69, 132.16, 129.19, 128.45, 124.98, 124.32, 121.89, 121.46, 121.01, 118.96, 117.91, 114.69, 113.80, 94.79, 56.24. M.S. (m/z) Calculated $C_{17}H_{14}N_4O$ ((M$^+$) 290.0653, found 290.0650).

5-amino-3-(4-bromophenyl)-1-phenylpyrazole-4-carbonitrile(4g): creamy-white crystal. melting point 165-167°C. yield 94%.^{1}H-NMR (DMSO-d6, 400MHz) δ 6.91 (t, 1H), 7.35 (J=2.15Hz, t, 2H), 7.77 (J=2.25Hz, t, 2H), 7.43 (J=3.35Hz, d, 2H), 7.48 (J=3.55Hz, d, 2H), 5.89 (s, 2H). ^{13}C-NMR (DMSO-d6, 100MHz) δ 158.23, 147.96, 138.01, 137.52, 134.99, 132.26, 129.91, 129.09, 128.76, 126.46, 123.29, 118.93, 118.12, 98.94. M.S. (m/z) Calculated $C_{16}H_{11}BrN_4$ ((M$^+$) 338.1021 and (M+2)$^+$ 340.1023, found 338.1020 and 340.1022).

5-amino-3-(4-hydroxyphenyl)-1-phenylpyrazole-4-carbonitrile(4h): Pale-yellow. melting point 175-177°C. yield 95%.^{1}H-NMR (DMSO-d6, 400MHz) δ 7.62 (J=4.35Hz, d, 2H), 7.43 (J=4.25Hz, t, 2H), 7.25 (t, 1H), 7.35 (J=6.1Hz, d, 2H), 6.75 (J=2.4Hz, d, 2H), 5.52 (s, 2H), 5.15 (s, 1H). ^{13}C-NMR (DMSO-d6, 100MHz, δ

ppm): 165.65, 155.97, 147.98, 139.31, 138.26, 135.47, 130.05, 129.87, 129.49, 129.28, 128.36, 128.08, 128.01, 118.78, 118.09, 116.34, 96.92. MS. (m/z) Calculated $C_{16}H_{12}N_4O$ ([M⁺] 276.1016, found 276.1012). **1,8-diazabicyclo [5,4,0] undec-7-enium acetate [DBUH][OAc]:** light-yellow viscous liquid, ^{1}H-NMR (DMSO-d6, 400MHz, δ) 8-3.53-3.22 (m, 6H), 2.53 (J = 3.16 Hz, d, 2H), 1.83 (J = 5.11 Hz, d, 2H), 1.85 – 1.75 (m, 3H), 1.70 – 1.43 (m, 7H). IR (potassium bromide), ν_{max}/cm^{-1}, 2928 – 2856, 1643, 1549, 1445, 1379, 1310, 1192, 1113, 1073, 911, 685. The spectral data is in according to literature [38,48]

RESULTS AND DISCUSSION

In view of the diverse pharmacological activity of substituted pyrazoles, we have planned to develop an eco-friendly synthetic protocol. Also, it was assumed worthwhile to investigate the catalytic role of [DBUH][OAc] for the synthesis of highly substituted pyrazole derivatives *via* a 3-component reaction involving Aromatic aldehydes (1a-j, 1mmol), Malononitrile (2, 1mmol), along with Phenylhydrazine (3, 1mmol) under the conventional and ultrasound technique [Scheme 1].

In order to optimize the reaction conditions and to obtain the finest catalytic activity of [DBUH][OAc], the reaction of benzaldehyde (1a, 1mmol), malononitrile (2, 1mmol), and phenylhydrazine (3, 1mmol) was used model reaction. The model reaction was initially performed in a variety of solvents, including H_2O, EtOH, MeOH, Acetone, and solvent free conditions, using the conventional method to study the efficiency of the catalyst (Table 1, entries 1-5). In this study, it was experiential that ethanol was preferred solvent with respect to reaction time and yield (Table 1, entry 3).To determine the suitable conc. of [DBUH][OAc], the model reaction was investigated at different concentrations such as 5, 10, 15, 20, and 25 mol%. The product was found in trace, 60, 70, 82, 85, and 85% yield, respectively (Table 2, entries 1-5). This indicates that 20 mol% of [DBUH][OAc] is sufficient to carry out the reaction efficiently (Table 2, entry 4). To demonstrate the result of ultrasound irradiation the same reaction was done under the ultrasound method. It was observed that in ultrasonic irradiations the reaction rate decreased and product yield was increased. Evidently, the sonochemical effect might be a key factor to the high efficiency for the synthesis of substituted pyrazoles derivative which was superior to conventional method with respect to yields, reaction times, easiness, and safeties. A comparative study by conventional as well as ultrasonication technique whereas the conventional condition observed that 4a compound gave 89% yield within 60 min. and ultrasound irradiation condition gave 97% yield within 35 min. In order to the extremely interesting scope of the reaction. We intended to apply our methodology to a wide range of aromatic aldehydes in presence of [DBUH][OAc] 20 mol% under the conventional and ultrasound methods. As expected, satisfactory results were obtained for both electron-donating (-OCH_3, -O,) as well as electron-withdrawing (-NO_2 -Cl, -Br,) groups (Table 3). We herein proposed a mechanism for condensation aromatic aldehyde (1a-j), malononitrile (2), and phenylhydrazine (3) in presence of [DBUH][OAc]. The reaction proceeds throughout condensations of aromatic aldehyde along with malononitrile by using Knoevenagel condensation (5), by adding phenylhydrazine the reaction carried out Michael addition (6), along with intramolecular cyclization, followed by air oxidation was converted into the final product (4a-j) [Scheme 2]. The reusability and recovery of the ILs [DBUH][OAc] significant advantage. For reason, we've chosen the model reaction Benzaldehyde (1a), Malononitrile (2), and Phenylhydrazine (3) in[DBUH][OAc] 20 mol% under conventional heating. After the completions reaction product was poured into ice-cold water and filtration of the product was isolated. Below the reduced pressure, the ILs was recovered for recycling at least 5 times. In terms of the product, the catalytic activity is decreasing (Figure 2). Recovered IR spectra of ionic liquid after 5th cycles we are equated with the 1st cycle. As confirmed shown in Figure 3. Recovered IR spectra of ionic liquid shown to be close to identical to the 1st cycle.

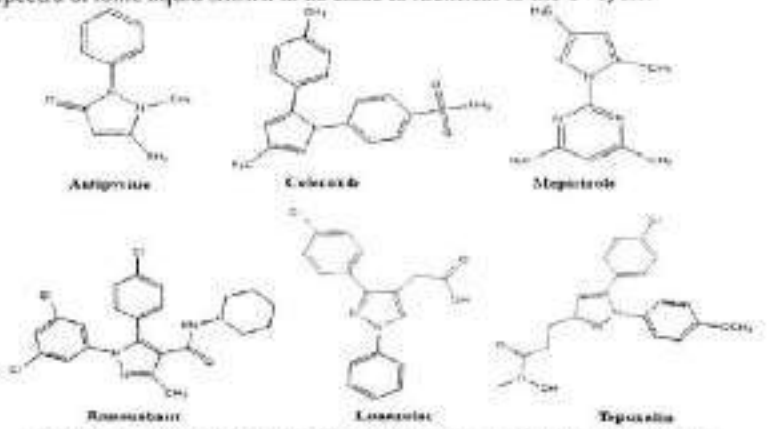
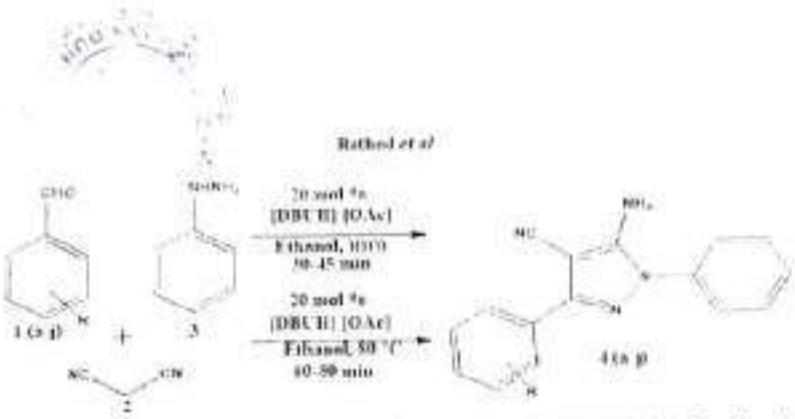


Figure 1: pyrazole derivatives containing pharmacological drug.



Scheme 1: synthesis of highly substituted pyrazoles with [DBUH][OAc] under the ultrasound and conventional methods.

Table 1: Screening of Solvents[a]

Entry	Solvents	Time(min.)	[b]Yield(%)
1	Solvent free	60	76
2	Water	60	70
3	**Ethanol**	**60**	**85**
4	Methanol	60	74
5	Acetone	60	75

[a]Reaction condition: Benzaldehyde (**1a**, 1mmol), Malononitrile (2, 1mmol), along with Phenylhydrazine (3, 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under conventional heating[b]Isolated yields.

Table 2: Effect of Catalyst Concentration[a]

Entry	[DBUH][OAc] mol (%)	Time (min.)	Yield[b] (%)
1	5	150	60
2	10	120	70
3	15	90	82
4	**20**	**60**	**85**
5	25	60	85

[a]Reaction condition: Benzaldehyde (**1a**, 1mmol), Malononitrile (**2**, 1mmol), along with Phenylhydrazine (**3**, 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under conventional heating[b]Isolated yields.

Table 3. Synthesis of highly substituted pyrazoles in presence of [DBHU][OAc] 20 mol% under the Conventional and ultrasound methods. 4(a-j)

Entry	R	[a]Ultrasound Method		[a]Conventional Method		M.P. (°C)	
		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)	Found	[c]Literature
4a	-H	35	97	60	89	158-160	159-161
4b	2-OH	38	94	60	87	159-162	160-162
4c	3,4-OCH_3	40	92	75	85	119-121	120-123
4d	4-Cl	35	95	50	87	127-130	128-130
4e	4-OCH_3	45	96	60	88	107-109	106-108
4f	4-NMe_2	40	93	60	85	156-158	157-159
4g	4-Br	35	94	60	88	165-167	164-166
4h	4-OH	35	95	60	86	207-209	208-210
4i	4-NO_2	45	92	60	85	163-165	164-165
4j	4-CH_3	38	94	60	88	115-117	117-118

[a]Reaction condition: Aromatic aldehydes (**1a-j**, 1mmol), Malononitrile (**2**, 1mmol), along with Phenylhydrazine (**3**, 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under ultrasound method and conventional method. [b]Isolated yields.

[c]All the product was confirmed by melting point and compared with the literature [46,47,49]

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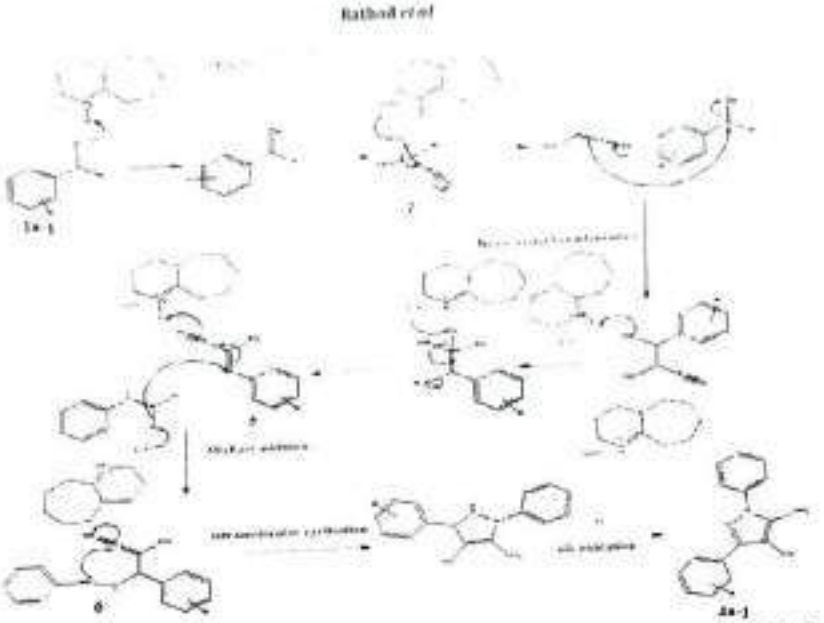

Scheme 2: Propose a mechanism for highly substituted pyrazoles by using[DBUH][OAc] Ionic liquid.

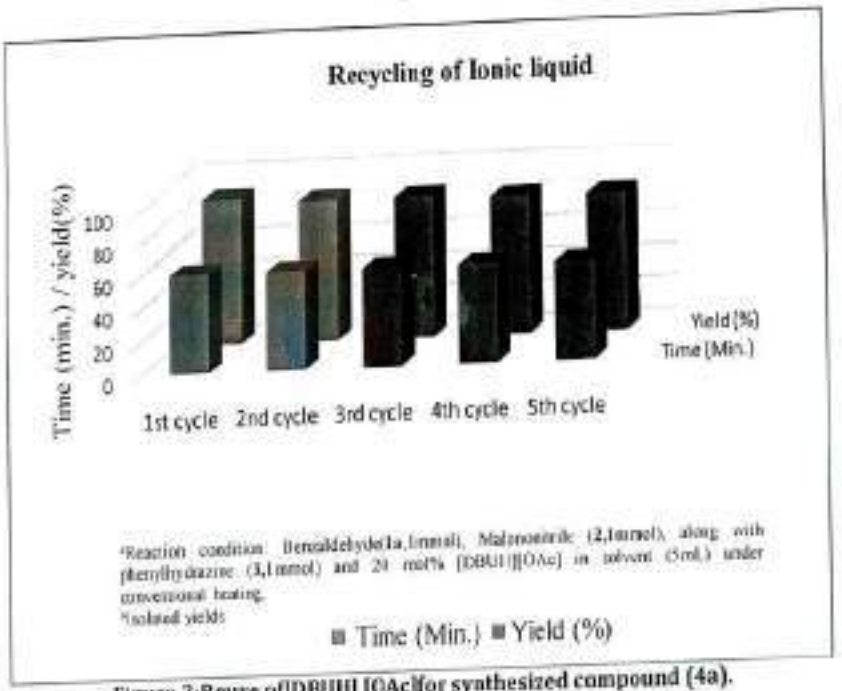

Figure 2:Reuse of[DBUH] [OAc]for synthesized compound (4a).

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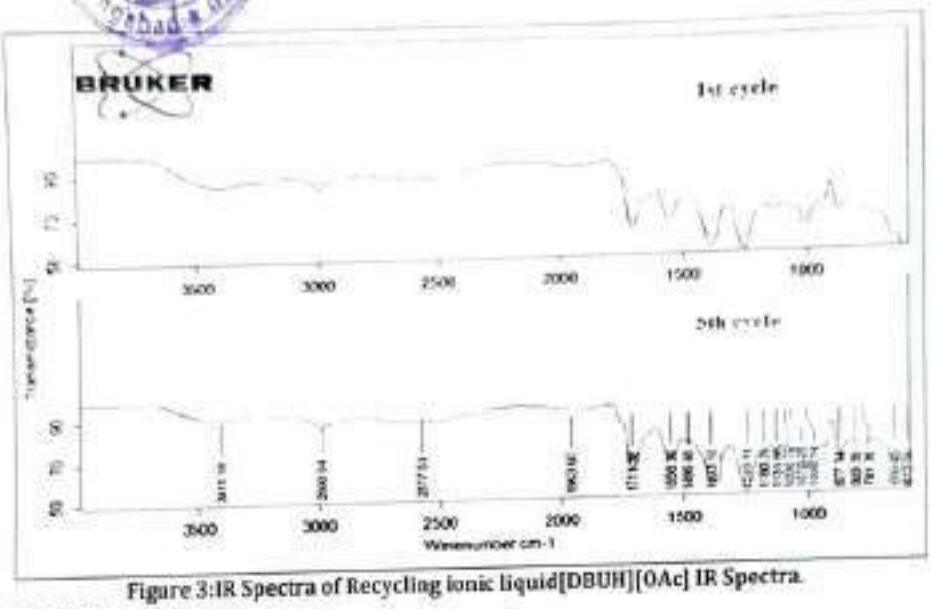

Figure 3:IR Spectra of Recycling ionic liquid[DBUH][OAc] IR Spectra.

CONCLUSION

Finally, we have developed an efficient technique for synthesizing highly substituted pyrazole derivatives. The producers described here are simple, mild and efficient, which gives this synthesis strategy a significant advantage over others. The benefits of using an ionic liquid catalyst include Increased rate and reactivity, as well as ease of product recovery and recycling. The use of ultrasonication of non-classical energy sources provides better energy stability to conventional methods. The ultrasound irradiation technique gave excellent yield, shorter reaction time, and simplified work procedure than the conventional technique. Present work is the reported first time forsynthesis of highly substituted pyrazoles using [DBUH][OAc] ionic liquid under ultrasound irradiation technique.

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