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# Synthesis of Pharmacologically Active Hexahydroacridine-1, 8 *(2H, 5H)*-diones using Nickel (II) Fluoride Tetrahydrate as a New Heterogeneous Catalyst

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**Abstract** *There are several reactions used in synthesis of dihydropyrimidines, but one of the simplest and most economical method for the synthesis of pharmacologically active acridine-1,8 (2H,5H)-dione derivatives is the classical Hantzsch reaction. Nickel (II) fluoride tetrahydrate catalyzed efficient Hantzsch reaction via one-pot three–component condensation of aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and ammonium acetate refluxing in water was described for the preparation of hexahydroacridine-1,8 (2H,5H)-dione derivatives. The products obtained were characterized on the basis of their melting-points, $^{1}H$ NMR, $^{13}C$ NMR, UV, IR, EI-MS, and HR-MS. Diethyl malonate and ethyl methyl ketone were observed to serve only as solvent and not reagent as proposed in solvent free synthesis of dihydropyrimidines. The attractive features of this environmentally benign protocol are excellent yields, cost-effective, simplicity and easy work-up. The higher catalytic activity of $NiF_2.4H_2O$ is due to its high acidity, thermal stability and water tolerance.*

***Key words:*** *Acridinedione; ethanol; Hantzsch reaction; nickel (II) fluoride tetrahydrate; water*.

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## 1.0 Introduction

Multi-component reactions allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the creation of molecular diversity and complexity (Aswin *et al*., 2012). Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents (Mansoor *et al*., 2016). For example, in this research, it was observed that adjusting the amount of solvent to equal the scale of the reaction (that is, if the reaction is carried out in 1 mmol scale, the amount of solvent was adjusted to 1 ml) resulted in a faster reaction rate and high yield of acridine-1,8 (*2H,5H*)-diones (95 to 100 %) without impurities.

Nitrogen-containing heterocyclic compounds such as acridinediones, have attracted interest of many researchers because their derivatives exhibit a broad spectrum of biological activities, such as antibacterial, antifungal, antimicrobial, anticonvulsant, anti-inflammatory, anti-HIV, anti-tubercular, antihistamine, antimalarial, analgesic etc. (Satheeshkumar *et al*., 2017; Aly *et al*., 2010; Kumar and Rajput, 2009; Dahiya *et al*., 2008; Kidwai *et al*., 2005; Alagarsamy *et al*., 2000; Ghorab *et al*., 2000). Acridinediones also exhibit DNA binding properties which make them useful as drugs for cardiovascular diseases such as angina

pectoris and hypertension, and they are employed as DNA-intercalating anticancer drugs (Nasresfahani and Kassaee, 2015).

In view of the various biological activities of hexahydroacridine-1, 8 *(2H, 5H)*-diones, many researchers have developed various methods for the synthesis of this class of heterocycle using various catalysts such as mesoporous silica nanoparticles (Nasresfahani and Kassaee, 2015), silica iodide (Ramesh and Pasha, 2014), silica-supported sulphuric acid (Mansoor *et al*., 2014), cetyltrimethyl ammonium bromide (CTAB) (Xia and Zhang, 2012), and microwave irradiation (Abdelhamid *et al*., 2014; Gündüz *et al*., 2014; Ladani *et al*., 2011). Although most of these procedures offer several advantages, there are also related disadvantages, such as longer reaction times, unsatisfactory yields, harsh reaction conditions and use of high cost or toxic catalysts and difficult, time and energy consuming methods of purification of the final product.

The use of metal salts that are less toxic, as efficient heterogeneous catalysts, have been adopted in recent years by most synthetic organic chemists as a powerful synthetic tools for the synthesis of many organic compounds (Dutta *et al*., 2017; *Abdolmohammadi* and Karimpour, 2016; Banothu *et al*., 2014; Hashim *et al* ., 2014; Kumar *et al*., 2010). To the best of our knowledge, however, with the exception to that reported by our research team (Isaac *et al*., 2018; Isaac *et al*., 2019; Ali *et al*., 2019), there is limited information on the use nickel (II) fluoride tetrahydrate as efficient catalyst for synthesis of hexahydroacridine-1, 8 *(2H, 5H)*-diones. Hence, the aim of this research is to investigate the role of $NiF_2.4H_2O$ as an inexpensive, easy work-up, environmentally benign, short reaction time, ease of manipulation and high yielding heterogeneous catalyst for the synthesis of acridinediones (**4**) via a Hantzsch one-pot multi-component condensation of aromatic aldehydes (**1**), dimedone (**2**) as active methylene compound and ammonium acetate (**3**) in refluxing water or ethanol respectively (**Scheme 1)**.

Our intention also was to extend the above method to different 1,3-dicarbonyl compounds for the synthesis of novel unsymmetrically substituted 1,4-dihydropyridines such as hexahydroquinoline-3-carboxylate (**6**) and tetrahydroquinolin-*5(1H)*-one (**8**) derivatives from solvent free multi-component reaction of diethyl malonate and ethyl methyl ketone respectively with dimedone, aromatic aldehydes and ammonium acetate based on the reaction **scheme 2** using nickel (II) fluoride tetrahydrate as efficient catalyst. But $^1$H NMR, EI-MS and HREI-MS results showed that the products were hexahydroacridine-1, 8 *(2H, 5H)*-diones and not as suggested in **scheme 2**. However, synthesis of hexahydroquinoline derivatives from the reaction of dimedone, aromatic aldehydes, ammonium acetate and malonitrile promoted by a catalytic amount of melamine trisulfonic acid (5 mol%) under solvent free conditions at 60 $^0$C have been reported (Aswin *et al*., 2012). We ended up discovering two more green solvents that could be used in Hantzsch reaction via one-pot three –component condensation of aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione, and ammonium acetate promoted by nickel (II) trifluoride tetrahydrate.

## 2.0 Materials and Methods

### *2.1 Reagents and apparatus*

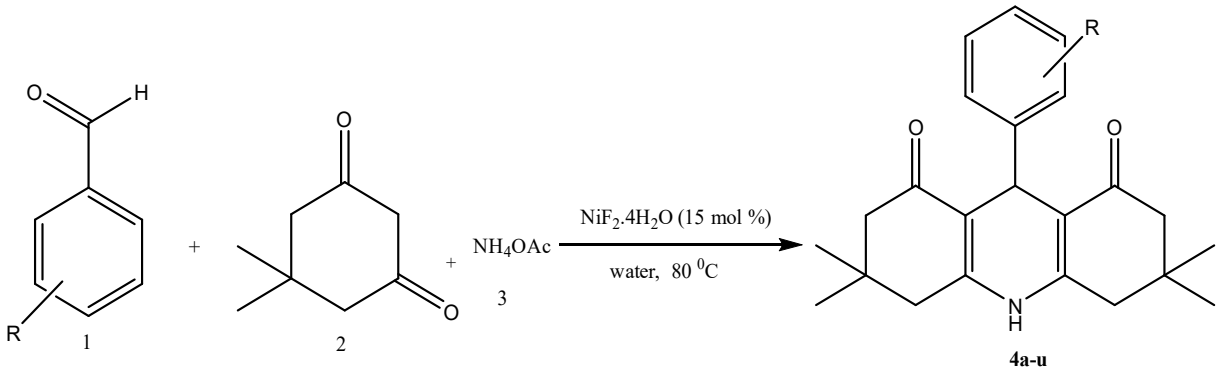
All commercial grade reagents and chemicals used in this work were purchased from Acros Organics, Scharlau, Merck or Sigma–Aldrich Chemicals Ltd and used without further purification. The melting point was determined using Automated BUCHI M-560 melting point apparatus with microscope. The UV and IR spectra were recorded on a THERMO ELECTRON-VISIONproVA.10 spectrophotometer using methanol as the solvent and RX-1 PerkinElmer spectrophotometer with samples prepared as KBr pellets respectively. EI-MS and HR-MS mass spectra were recorded on JEOL MS 600H-1 mass spectrometer. The NMR spectra were carried out using a Bruker AVANCE AV-400 MHz spectrometer in DMSO-$d_6$ as solvent. All reactions were followed by TLC developed in an ethyl acetate:hexane solvent system, with detection by UV light.

### *2.2 General Procedure for Preparation of Hexahydroacridine-1, 8 (2H, 5H)-dione Derivatives 4a-4u*

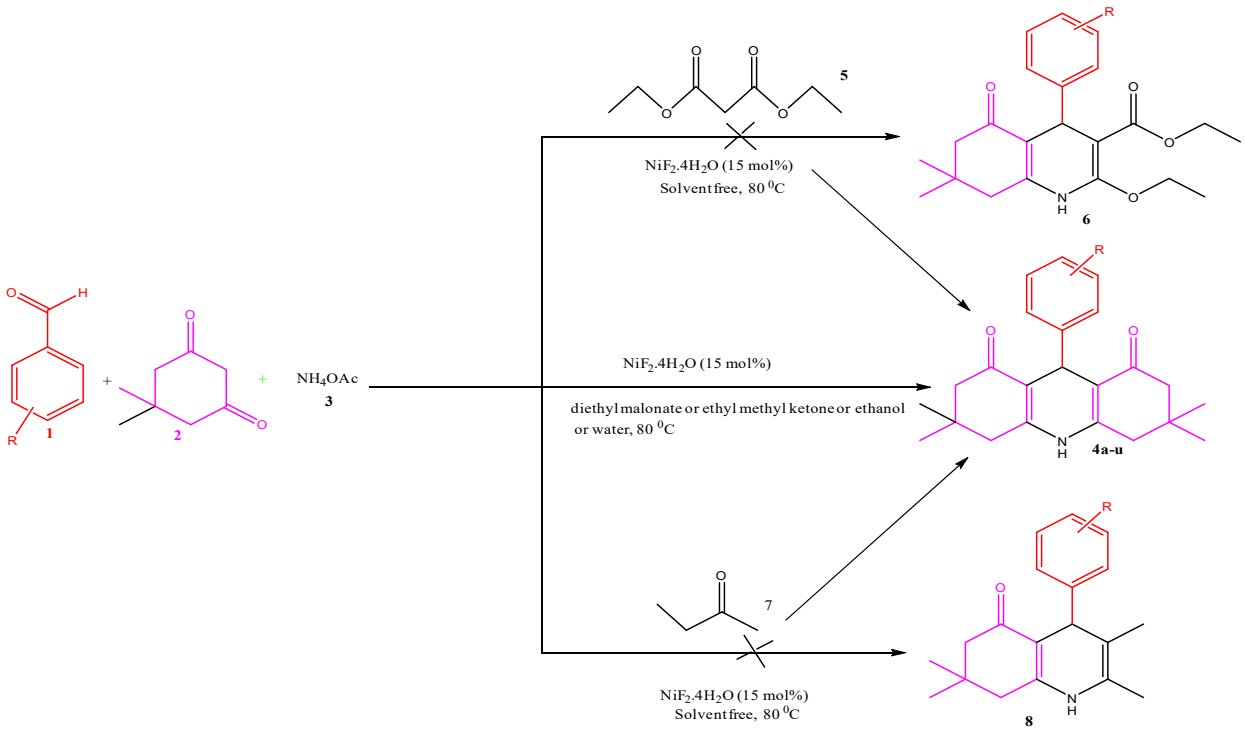
A mixture of aromatic aldehyde (0.6 equiv.), active methylene compound-dimedone (2 equiv.), ammonium acetate (2 equiv.), nickel (II) fluoride tetrahydrate (15 mol %) and water (the quantity of water was based on the mmol scale in which the reaction was performed, for 2 mmol reaction, water was 2 ml) was placed in a 25 ml round bottom flask charged with magnetic stirrer, heated at 80 $^0$C under

stirring for the appropriate time as monitored by thin-layer chromatography (TLC) using ethyl acetate:hexane (3:7) solvent system. After completion of the reaction as indicated by TLC, methanol was added to obtain a homogenous mixture which was then poured into a beaker charged with crushed ice and magnetic stirrer and kept under stirring for 30 mins. The solid was filtered, dried but not recrystallized to afford the pure product **4a -4u** (**Scheme 1**).

All the products were fully characterized on the basis of their melting -points, IR, UV, and $^{1}$H NMR, $^{13}$C NMR, EI-MS and HR-MS.




**Scheme 1: Synthesis of hexahydroacridine-1,8 *(2H, 5H)*-dione derivatives, 4a-u, by the reactions of aryl aldehydes, dimedone and ammonium** acetate




**Scheme 2**. Synthesis of hexahydroacridine-1,8(2H, 5H)-dione derivatives by the reactions of aryl aldehydes, dimedone and ammonium acetate

***2.3 Spectral data for the synthesized compounds***

***2.3.1 9-(3-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4a)***

IR (KBr, $cm^{-1}$): 3390.0, 31723.0, 2959.0, 2870.0, 1621.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.87 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.01 (s, 1H, NH), 6.39 – 6.92 (m, 4H, Ar-H), 4.72 (s, 1H, CH), 9.22 (s, 1H, OH), 1.96 – 2.49 (m, 8H, 2×$CH_2$); $^{13}$C NMR (400 MHz, DMSO-$d_6$) δ: 26.56, 29.08, 32.12, 32.56, 39.12, 40.16, 50.32, 111.48, 114.97, 118.21, 128.32, 148.47, 149.16, 156.65, 194.31; EI-MS: m/z (rel. abund. %), 365.1 [$M^+$] (19.4), 273.1 (23.1), 348.1 (2.9), 272.1 (100.0), 216.1 (2.9); HREI-MS: m/z calcd for $C_{23}H_{27}O_3N_1$ [$M^+$] 365.1991, found 365.1986; Anal. calcd for $C_{23}H_{27}O_3N_1$: C, 75.59; H, 7.45; O, 13.13; N, 3.83; Found: C, 75.58; H, 7.39; O, 13.14; N, 3.83. The $^1$H NMR spectrum of **4a** is given in **Appendix 1**.

***2.3.2 9-(4-Fluoro-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H, 5H)-dione (4b)***

IR (KBr, $cm^{-1}$): 3280.0, 3074.0, 2956.0, 2360.0, 1643.0, 1610.0, $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.87 (s, 6H, 2×$CH_3$), 1.00 (s, 6H, 2×$CH_3$), 9.29 (s, 1H, NH), 6.63 – 6.99 (m, 3H, Ar-H), 4.79 (s, 1H, CH), 3.72 (s, 3H, $OCH_3$), 1.98 – 2.49 (m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 397.1 [$M^+$] (86.8), 396.2 (18.4), 382.2 (14.0), 273.1 (72.6), 272.1 (100.0), 216.1 (9.0), 188.1 (8.4); HREI-MS: m/z calcd for $C_{24}H_{28}O_3N_1F_1$ [$M^+$] 397.2053, found 397.2072; Anal. calcd for $C_{24}H_{28}O_3N_1F_1$: C, 72.52; H, 7.10; O, 12.08; N, 3.52; F, 4.78; Found: C, 72.51; H, 7.05; O, 12.08; N, 3.53; F, 4.78.

***2.3.3 9-(4-(1-Hydroxyethoxy)-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H, 5H)-dione (4c)***

IR (KBr, $cm^{-1}$): 3699.0, 3420.0, 3196.0, 3069.0, 2926.0, 1856.0, 1743.0, 1624.0, 1609.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.87 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 8.54 (s, 1H, NH), 6.50 – 6.85 (m, 3H, Ar-H), 4.70 (s, 1H, CH), 3.65 (s, 3H, $OCH_3$), 9.19 (s, 1H, OH), 2.45 (s, 1H, OCH), 2.40-2.44 (s, 3H, $CH_3$), 1.96 – 2.36 (m, 8H, 2×$CH_2$); $^{13}$C NMR (500 MHz, DMSO-$d_6$) δ: 20.39, 26.38, 28.97, 29.16, 31.87, 32.18, 32.57, 50.21, 55.49, 111.16, 112.21, 114.75, 119.75, 121.92, 148.96, 149.53, 156.65, 194.44; EI-MS: (rel. abund. %), 437.3 [$M^+$] (27.7), 396.2 (12.9), 395.2 (39.4), 378.3 (14.3), 273.1 (20.4), 272.1 (100.0), 216.1 (4.2); 188.1 (3.8); HREI-MS: m/z calcd for $C_{26}H_{31}O_5N_1$ [$M^+$] 437.2202, found 437.2192; Anal. calcd for $C_{26}H_{31}O_5N_1$: C, 71.37; H, 7.14; O, 18.28; N, 3.20; Found: C, 71.36; H, 7.09; O, 18.30; N, 3.20. **Appendix 2** shows the $^1$H NMR spectrum of compound **4c.**

***2.3.4 9-(3-Bromo-4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H, 5H)-dione (4d)***

IR (KBr, $cm^{-1}$): 3779.0, 3464.0, 3282.0, 2959.0, 2359.0, 1642.0, 1614.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.87 (s, 6H, 2×$CH_3$), 1.00 (s, 6H, 2×$CH_3$), 9.28 (s, 1H, NH), 6.89 – 7.26 (m, 3H, Ar-H), 4.71 (s, 1H, CH), 3.74 (s, 3H, $OCH_3$), 1.96-2.49 (m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 457.0 [$M^+$] (57.3), 442.0 (4.1), 378.1 (5.4), 374.0 (4.2), 273.1 (40.4); 272.0 (100.0), 216.1 (5.8), 188.1 (5.6); HREI-MS: m/z calcd for $C_{24}H_{28}O_3N_1Br_1$ [$M^+$] 457.1253, found 457.1260; Anal. calcd for $C_{24}H_{28}O_3N_1Br_1$: C, 62.88; H, 6.16; O, 10.47; N, 3.06; Br, 17.43; Found: C, 63.00; H, 6.13; O, 10.50; N, 3.06; Br, 17.50.

***2.3.5 9-(2,6-Dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H,5H)-dione (4e)***

IR (KBr, $cm^{-1}$): 3779.0, 3444.0, 3072.0, 2952.0, 2359.0, 1625.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.79 (s, 6H, 2×$CH_3$), 0.97 (s, 6H, 2×$CH_3$), 9.00 (s, 1H, NH), 6.44 – 6.95 (m, 3H, Ar-H), 5.38 (s, 1H, CH), 3.69 (s, 6H, $OCH_3$), 1.80 – 2.49 (m, 8H, 2×$CH_2$); $^{13}$C NMR (400 MHz, DMSO-$d_6$) δ: 24.05, 25.77, 29.36, 31.84, 38.91, 39.12, 39.95, 40.03, 50.72, 104.12, 109.80, 122.62, 126.33, 149.90, 193.65; EI-MS: (rel. abund. %), 409.1 [$M^+$] (100.0), 394.1 (23.4), 379.1 (24.8), 378.1 (89.3), 273.1 (11.7), 272.1 (59.6), 271.1 (15.5); 256.1 (14.2); HREI-MS: m/z calcd for $C_{25}H_{31}O_4N_1$ [$M^+$] 409.2253, found 409.2260; Anal. calcd for $C_{25}H_{31}O_4N_1$: C, 73.32; H, 7.63; O, 15.63; N, 3.42; Found: C, 72.31; H, 7.58; O, 15.64; N, 3.42. The $^1$H NMR spectrum of **4e** is shown in **Appendix 3**.

***2.3.6 2-(3,3,6,6-Tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl)benzoic acid (4f)***

IR (KBr, $cm^{-1}$): 3275.0, 3178.0, 2955.0, 2590.0, 1598.0, 1480.0, 1376.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.84 (s, 6H, 2×$CH_3$), 1.01 (s, 6H, 2×$CH_3$), 9.72 (s, 1H, NH), 7.13 – 7.40 (m, 4H, Ar-H), 5.12 (s, 1H, CH), 13.86 (s, 1H, OH), 1.96 – 2.53

(m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 393.1 [$M^+$] (57.9), 391.1 (10.2), 346.1 (64.9), 309.1 (32.2), 292.1 (40.9), 291.0 (100.0), 272.1 (81.5); HREI-MS: m/z calcd for $C_{24}H_{27}O_4N_1$ [$M^+$] 393.1940, found 393.1928; Anal. calcd for $C_{24}H_{27}O_4N_1$: C, 73.26; H, 6.92; O, 16.26; N, 3.56; Found: C, 73.25; H, 6.87; O, 16.28; N, 3.56.

***2.3.7 3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4g)***

IR (KBr, $cm^{-1}$): 3421.0, 3185.0, 3065.0, 2959.0, 1647.0, 1609.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 1.00 (s, 6H, 2×$CH_3$), 9.45 (s, 1H, NH), 7.47 – 7.95 (m, 4H, Ar-H), 4.91 (s, 1H, CH), 1.96 – 2.49 (m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 394.1 [$M^+$] (19.2), 378.1 (16.3), 377.1 (48.6), 347.1 (15.3), 272.0 (100.0), 216.0 (5.4), 188.0 (4.6); HREI-MS: m/z calcd for $C_{23}H_{26}O_4N_2$ [$M^+$] 394.1893, found 394.1898; Anal. calcd for $C_{23}H_{26}O_4N_2$: C, 70.03; H, 6.64; O, 16.22; N, 7.10; Found: C, 70.02; H, 6.60; O, 16.24 N, 7.10.

***2.3.8 9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4h)***

IR (KBr, $cm^{-1}$): 3276.0, 3199.0, 2958.0, 2814.0, 2359.0, 1612.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 8.95 (s, 1H, NH), 6.50 – 6.92 (m, 4H, Ar-H), 4.69 (s, 1H, CH), 9.16 (s, 1H, OH), 1.94 – 2.43 (m, 8H, 2×$CH_2$); EI-MS: m/z (rel. abund. %), 365.3 [$M^+$] (39.9), 348.3 (4.0), 281.2 (3.8), 280.2 (4.7), 273.2 (18.9), 272.2 (100.0), 216.1 (4.7), 215.1 (4.0), 188.1 (3.4); HREI-MS: m/z calcd for $C_{23}H_{27}O_3N_1$ [$M^+$] 365.1991, found 365.2013; Anal. calcd for $C_{23}H_{27}O_3N_1$: C, 75.59; H, 7.45; O, 13.13; N, 3.83; Found: C, 75.57; H, 7.39; O, 13.14; N, 3.83.

***2.3.9 9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4i)***

IR (KBr, $cm^{-1}$): 3712.0, 3421.0, 3178.0, 3052.0, 2957.0, 2358.0, 1619.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.29 (s, 1H, NH), 6.93 – 7.15 (m, 4H, Ar-H), 4.79 (s, 1H, CH), 1.95 – 2.45 (m, 8H, 2×$CH_2$); EI-MS: m/z (rel. abund. %), 367.1 [$M^+$] (44.4), 352.1 (4.1), 350.1 (3.0), 296.1 (4.8), 283.1 (3.7), 282.1 (7.0), 274.1 (4.2), 273.1 (29.8), 272.0 (100.0), 216.1 (8.5), 198.1 (6.4), 188.1 (8.8); HREI-MS: m/z calcd for $C_{23}H_{26}O_2N_1F_1$ [$M^+$] 367.1942, found 367.1948; Anal. calcd for $C_{23}H_{26}O_2N_1F_1$: C, 75.18; H, 7.13; O, 8.71; N, 3.81; F, 5.17 Found: C, 75.17; H, 7.08; O, 8.72; N, 3.81, F, 5.17.

***2.3.10 9-(2-Chloro-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H, 5H)-dione (4j)***

IR (KBr, $cm^{-1}$): 3448.0, 32183.0, 3066.0, 2959.0, 2359.0, 1645.0, 1612.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.26 (s, 1H, NH), 6.75 – 7.08 (m, 3H, Ar-H), 5.11 (s, 1H, CH), 3.75 (s, 3H, $OCH_3$), 1.87 – 2.45 (m, 8H, 2×$CH_2$); EI-MS: m/z (rel. abund. %), 413.3 [$M^+$] (20.0), 380.3 (9.7), 379.3 (67.9), 378.2 (100.0), 376.3 (21.0), 274.2 (9.2), 273.2 (69.5), 272.1 (100.0), 256.2 (10.8), 216.1 (11.7), 188.1 (10.9), 160.6 (8.2); HREI-MS: m/z calcd for $C_{24}H_{28}O_3N_1Cl_1$ [$M^+$] 413.1758, found 413.1773; Anal. calcd for $C_{24}H_{28}O_3N_1Cl_1$: C, 69.64; H, 6.82; O, 11.60; N, 3.38; Cl, 8.56 Found: C, 69.70; H, 6.78; O, 11.62; N, 3.39, Cl, 8.59.

***2.3.11 9-(2,4-Dichlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4k)***

IR (KBr, $cm^{-1}$): 3416.0, 3314.0, 3066.0, 2959.0, 2879.0, 2360.0, 1639.0, 1611.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.35 (s, 1H, NH), 7.22 – 7.29 (m, 3H, Ar-H), 5.02 (s, 1H, CH), 1.89 – 2.41 (m, 8H, 2×$CH_2$); EI-MS: m/z (rel. abund. %), 417.1 [$M^+$] (30.0), 384.1 (36.2), 383.1 (32.7), 382.1(95.9), 273.1 (45.6), 272.0 (100.0), 272.2 (100.0), 188.1 (9.4); HREI-MS: m/z calcd for $C_{23}H_{25}O_2N_1Cl_2$ [$M^+$] 417.1262, found 417.1273; Anal. calcd for $C_{23}H_{25}O_2N_1Cl_2$: C, 66.03; H, 6.02; O, 7.65; N, 3.35, Cl, 16.95; Found: C, 66.17; H, 5.99; O, 7.67; N, 3.37; Cl, 17.02.

***2.3.12 3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4l)***

IR (KBr, $cm^{-1}$): 3384.0, 3073.0, 2956.0, 2359.0, 1646.0, 1514.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.84 (s, 6H, 2×$CH_3$), 1.00 (s, 6H, 2×$CH_3$), 9.43 (s, 1H, NH), 7.39 – 8.06 (m, 4H, Ar-H), 4.89 (s, 1H, CH), 1.95 – 2.49 (m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 394.1 [$M^+$] (100.0), 392.2 (6.6), 379.2 (8.6), 378.2 (7.6), 377.2 (16.0), 364.2 (9.7), 348.2 (5.9), 347 (11.7), 274.1 (11.0), 273.1 (94.4), 272.0 (100.0), 216.1 (18.3), 188.1 (16.6); HREI-MS: m/z calcd for $C_{23}H_{26}O_4N_2$ [$M^+$] 394.1893, found 394.1889; Anal. calcd for $C_{23}H_{26}O_4N_2$: C, 70.03; H,

6.64; O, 16.22; N, 7.10; Found: C, 70.02; H, 6.60; O, 16.24 N, 7.10.

***2.3.13 9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4m)***

IR (KBr, $cm^{-1}$): 3446.0, 3280.0, 3176.0, 3059.0, 2956.0, 2879.0, 2360.0, 1649.0, 1610.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.31 (s, 1H, NH), 7.13 – 7.21 (m, 4H, Ar-H), 4.77 (s, 1H, CH), 1.95 – 2.46 (m, 8H, 2×$CH_2$); $^{13}$C NMR (400 MHz, DMSO-$d_6$) δ: 26.45, 28.99, 32.09, 38.88, 39.30, 39.59, 39.92, 40.13, 50.14, 111.01, 127.48, 129.40, 129.90, 146.04, 149.44; EI-MS: m/z (rel. abund. %), 383.3 [$M^+$] (69.1), 368.2 (5.2), 366.3 (4.3), 312.12 (4.2), 298.2 (4.8), 274.2 (6.5), 273.2 (54.6), 272.0 (100.0), 216.1 (7.7), 272.0 (100.0), 188.1 (6.4); HREI-MS: m/z calcd for $C_{23}H_{26}O_2N_1Cl_1$ [$M^+$] 383.1652, found 383.1643; Anal. calcd for $C_{23}H_{26}O_2N_1Cl_1$: C, 71.96; H, 6.83; O, 8.33; N, 3.65; Cl, 9.23 Found: C, 72.03; H, 6.79; O, 8.35; N, 3.65, Cl, 9.26.

***2.3.14 3,3,6,6-Tetramethyl-9-p-tolyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4n)***

IR (KBr, $cm^{-1}$): 3280.0, 3185.0, 3067.0, 2956.0, 2873.0, 1650.0, 1608.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.84 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.21 (s, 1H, NH), 6.92 – 7.02 (m, 4H, Ar-H), 4.74 (s, 1H, CH), 2.16 (s, 3H, $CH_3$), 1.93 – 2.44 (m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 363.2 [$M^+$] (86.2), 362.2 (20.5), 348.2 (12.1), 346.2 (7.0), 279.2 (6.2), 278.2 (9.5), 274.2 (7.6), 273.2 (57.9), 272.0 (100.0), 256.1 (5.3), 188.1 (7.0); HREI-MS: m/z calcd for $C_{24}H_{29}O_2N_1$ [$M^+$] 363.2198, found 363.2206; Anal. calcd for $C_{24}H_{29}O_2N_1$: C, 79.30; H, 8.04; O, 8.80; N, 3.85; Found: C, 79.29; H, 7.98; O, 8.81; N, 3.85.

***2.3.15 3-(3,3,6,6-Tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8,9,10-decahydroacridin-9-yl)benzonitrile (4o)***

IR (KBr, $cm^{-1}$): 3783.0, 3694.0, 3301.0, 3067.0, 2957.0, 2369.0, 2234.0, 1644.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.84 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.39 (s, 1H, NH), 7.39 – 7.52 (m, 4H, Ar-H), 4.82 (s, 1H, CH), 1.97 – 2.49 (m, 8H, 2×$CH_2$); EI-MS: m/z (rel. abund. %), 374.2 [$M^+$] (94.3), 373.2 (22.7), 359.2 (9.2), 303.2 (7.8), 274.1 (10.2), 273.1 (79.8), 272.0 (100.0), 216.1 (15.7), 188.1 (12.2); HREI-MS: m/z calcd for $C_{24}H_{26}O_2N_2$ [$M^+$] 374.1994, found 374.1998; Anal. calcd for $C_{24}H_{26}O_2N_2$: C, 76.98; H, 7.00; O, 8.54; N, 7.48; Found: C, 76.96; H, 6.95; O, 8.55; N, 7.48.

***2.3.16 9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4p)***

IR (KBr, $cm^{-1}$): 3782.0, 3448.0, 3207.0, 3071.0, 2956.0, 2370.0, 1642.0, 1608.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.21 (s, 1H, NH), 6.68 – 7.04 (m, 4H, Ar-H), 4.73 (s, 1H, CH), 3.64 (s, 3H, $OCH_3$), 1.94 – 2.44 (m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 379.3 [$M^+$] (52.6), 378.3 (15.0), 377.2 (4.3), 362.2 (5.9), 295.2 (4.6), 294.2 (6.5), 273.2 (19.6), 272.2 (100.0), 216.1 (4.6); 188.1 (4.1); HREI-MS: m/z calcd for $C_{24}H_{29}O_3N_1$ [$M^+$] 379.2147, found 379.2141; Anal. calcd for $C_{24}H_{29}O_3N_1$: C, 75.96; H, 7.70; O, 12.65; N, 3.69; Found: C, 75.95; H, 7.65; O, 12.66; N, 3.69.

***2.3.17 9-(3-Bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4q)***

IR (KBr, $cm^{-1}$): 3885.0, 3694.0, 3429.0, 3272.0, 3177.0, 3065.0, 2955.0, 2369.0, 1886.0, 1731.0, 1642.0, 1602.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.86 (s, 6H, 2×$CH_3$), 1.00 (s, 6H, 2×$CH_3$), 9.35 (s, 1H, NH), 7.12 – 7.28 (m, 4H, Ar-H), 4.76 (s, 1H, CH), 2.01 – 2.49 (m, 8H, 2×$CH_2$); EI-MS: m/z (rel. abund. %), 427.0 [$M^+$] (14.2), 273.1 (21.8), 272.1 (100.0), 216.0 (4.0), 84.9 (4.3), 84.0 (5.8), 82.9 (6.7), 44.0 (6.3); HREI-MS: m/z calcd for $C_{23}H_{26}O_2N_1Br_1$ [$M^+$] 427.1147, found 427.1130; Anal. calcd for $C_{23}H_{26}O_2N_1Br_1$: C, 64.49; H, 6.12; O, 7.47; N, 3.27; Br, 18.65 Found: C, 64.62; H, 6.09; O, 7.49; N, 3.28, Br, 18.71.

***2.3.18 3,3,6,6-Tetramethyl-9-(4-(methylthio)phenyl)-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4r)***

IR (KBr, $cm^{-1}$): 3914.0, 3790.0, 3661.0, 3439.0, 3277.0, 3180.0, 3066.0, 2956.0, 2869.0, 1878.0, 1648.0, 1608.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.26 (s, 1H, NH), 7.06 (s, 4H, Ar-H), 4.74 (s, 1H, CH), 2.38 – 2.41 (m, 3H, $SCH_3$), 1.94 – 2.38 (m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 395.3 [$M^+$] (51.7), 393.3 (8.3), 380.3 (3.6), 348.3 (3.9), 310.2 (3.1), 274.2 (3.1), 273.2 (16.2), 272.2 (100.0), 216.1 (4.7), 188.1 (3.5); HREI-MS: m/z calcd for $C_{24}H_{29}O_2N_1S_1$ [$M^+$] 395.1919, found 395.1921; Anal. calcd for $C_{24}H_{29}O_2N_1S_1$: C, 72.87; H, 7.39; O, 8.09; N, 3.54; S, 8.11; Found: C, 72.88; H, 7.34; O, 8.10 N, 7.09; S, 8.10.

***2.3.19 9-(3-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4s)***

IR (KBr, $cm^{-1}$): 3448.0, 3275.0, 3187.0, 3067.0, 2959.0, 2836.0, 1645.0, 1610.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.86 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.25 (s, 1H, NH), 6.59 – 7.07 (m, 4H, Ar-H), 4.78 (s, 1H, CH), 3.64 (s, 3H, $OCH_3$), 1.96 – 2.45 (m, 8H, 2×$CH_2$); EI-MS: (rel. abund. %), 379.3 [$M^+$] (21.0), 377.3 (3.7), 274.2 (3.0), 273.2 (18.1), 272.2 (100.0), 216.1 (3.6); 188.1 (3.7); HREI-MS: m/z calcd for $C_{24}H_{29}O_3N_1$ [$M^+$] 379.2147, found 379.2151; Anal. calcd for $C_{24}H_{29}O_3N_1$: C, 75.96; H, 7.70; O, 12.65; N, 3.69; Found: C, 75.95; H, 7.65; O, 12.66; N, 3.69.

***2.3.20 9-(3-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4t)***

IR (KBr, $cm^{-1}$): 3707.0, 3420.0, 3274.0, 3180.0, 3066.0, 2954.0, 2927.0, 2885.0, 2370.0, 1731.0, 1643.0, 1606.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.86 (s, 6H, 2×$CH_3$), 1.00 (s, 6H, 2×$CH_3$), 9.34 (s, 1H, NH), 7.09 – 7.19 (m, 4H, Ar-H), 4.77 (s, 1H, CH), 1.97 – 2.35 (m, 8H, 2×$CH_2$); EI-MS: m/z (rel. abund. %), 383.3 [$M^+$] (17.0), 274.2 (3.2), 273.2 (22.4), 272.2 (100.0), 216.2 (4.2), 188.2 (3.5); HREI-MS: m/z calcd for $C_{23}H_{26}O_2N_1Cl_1$ [$M^+$] 383.1647, found 383.1633; Anal. calcd for $C_{23}H_{26}O_2N_1Cl_1$: C, 71.96; H, 6.83; O, 8.33; N, 3.65; Cl, 9.23 Found: C, 72.03; H, 6.79; O, 8.35; N, 3.65, Cl, 9.26.

***2.3.21 9-(3-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8(2H,5H)-dione (4u)***

IR (KBr, $cm^{-1}$): 3784.0, 3451.0, 3281.0, 3071.0, 2957.0, 2875.0, 1636.0, 1616.0; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 0.85 (s, 6H, 2×$CH_3$), 0.99 (s, 6H, 2×$CH_3$), 9.34 (s, 1H, NH), 6.85 – 7.20 (m, 4H, Ar-H), 4.81 (s, 1H, CH), 1.97 – 2.41 (m, 8H, 2×$CH_2$); EI-MS: m/z (rel. abund. %), 367.3 [$M^+$] (54.9), 352.2 (4.1), 350.3 (3.0), 296.2 (4.3), 283.2 (3.0), 282.2 (5.2), 274.2 (6.4), 273.2 (56.5), 272.0 (100.0), 216.2 (9.8), 198.1 (3.9), 188.1 (9.2), 83.1 (3.2); HREI-MS: m/z calcd for $C_{23}H_{26}O_2N_1F_1$ [$M^+$] 367.1948, found 367.1951; Anal. calcd for $C_{23}H_{26}O_2N_1F_1$: C, 75.18; H, 7.13; O, 8.71; N, 3.81; F, 5.17 Found: C, 75.16; H, 7.08; O, 8.71; N, 3.81, F, 5.17.

## 3.0 Results and Discussion

In this work, we present a versatile and environmentally benign strategy, one-pot multi-component reaction for synthesis of acridine 1,8(*2H,5H*)-diones by the reaction of aromatic aldehydes, dimedone, and ammonium acetate under reflux in water with nickel (II) fluoride tetrahydrate as the catalyst (**Scheme 1)**. Other solvents like ethanol, diethyl malonate and ethyl methyl ketone were also used in the synthesis of this novel compounds. Diethyl malonate and ethyl methyl ketone were initially selected as one of the reagents for solvent free one-pot multi-component synthesis of hexahydroquinoline-3-carboxylate (**6**) and tetrahydroquinolin-*5(1H)*-one (**8**) derivatives (**Scheme 2**) respectively which did not yield the target compounds but rather acridine1,8 *(2H,5H)*-diones. This showed that they were acting as solvents.

The optimization of the reaction conditions using a model reaction of 3-hydroxybenzaldehyde (0.6 equiv.), dimedone (2 equiv.) and ammonium acetate (1.5 equiv.) in 1 mmol scale to afford the corresponding product **4a** under various reaction conditions was studied. The results are summarized in **Tables 1 and 2**. The efficiency of $NiF_2.4H_2O$ as a heterogeneous catalyst using different amounts of $NiF_2.4H_2O$ and water as solvent was first examined. The results in **Table 1** showed that using just 15 mol% catalyst affected the efficiency of the reaction (**Table 1,** entries 1- 5) , at catalyst amount >15 mol%, the decreased in yield by >5 % was observed (**Table 1**, entries 6-7). To examine the effect of reaction media, several solvents were screened (ethanol, ethyl methyl ketone, diethyl malonate, methanol and water). The best yield of product (99 %) was obtained in ethanol and water (**Table 2**, entries 1 and 5), followed by diethyl malonate and ethyl methyl ketone (**Table 2**, entries 2-3). Hence, water and ethanol were the best media for this reaction, but water was used as solvent for subsequent reactions due to its environmental benign nature, easy work-up and availability. This observation collaborates the literature report (Mansoor *et al*., 2014). During optimization, we also discovered that solvent amount affects the efficiency of the reaction. The efficiency of reaction was inversely proportional to the amount of the

Table 1
The reaction of aromatic aldehyde, dimedone, and ammonium acetate: optimization of the amount of catalyst.[a]

| Entry | Catalyst | Amount of catalyst (mol%) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $NiF_2.4H_2O$ | 0.0 | 10.0 | 46 |
| 2 | $NiF_2.4H_2O$ | 2.0 | 9.5 | 58 |
| 3 | $NiF_2.4H_2O$ | 5.0 | 7.0 | 62 |
| 4 | $NiF_2.4H_2O$ | 10.0 | 3.0 | 70 |
| 5 | $NiF_2.4H_2O$ | 15.0 | 1.5 | 99 |
| 6 | $NiF_2.4H_2O$ | 20.0 | 1.5 | 92 |
| 7 | $NiF_2.4H_2O$ | 25.0 | 1.5 | 87 |

[a] Reaction conditions: aromatic aldehydes (0.6 equiv), dimedone (2 equiv), and ammonium acetate (1.5 equiv) at 80 $^0$C in water

[b] Isolated yields.

Table 2
The reaction of aromatic aldehyde, dimedone, and ammonium acetate: effect of solvent.[a]

| Entry | Solvent | Amount of catalyst (mol%) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Ethanol | 15.0 | 2.0 | 99 |
| 2 | Ethyl methyl ketone | 15.0 | 2.0 | 70 |
| 3 | Diethyl malonate | 15.0 | 3.0 | 88 |
| 4 | Methanol | 15.0 | 3.0 | 65 |
| 5 | Water | 15.0 | 1.5 | 99 |

[a] Reaction conditions: aromatic aldehydes (0.6 equiv), dimedone (2 equiv), and ammonium acetate (1.5 equiv) in the presence of $NiF_2.4H_2O$ (15 mol%) at 80 $^0$C in solvent
[b] Isolated yields.

solvent. That is, increase in the amount of solvent, decreases the efficiency of reaction. For reactions in 1 mmol scale, 1 ml of solvent was required for efficient and fast reaction, while reaction in 2 mmol scale also required 2 ml of solvent as compared to 4 ml widely reported in most literature (Mansoor *et al*., 2014; Xia and Zhang, 2012).

To determine the utility of this protocol, we examined some substituted aromatic benzaldehydes for the reaction with dimedone and ammonium acetate to obtain the desired products under optimized conditions (**Table 3**). The isolated compounds (**4a-u**) were characterized by IR, $^1$H NMR, $^{13}$C NMR, EI-MS, HREI-MS, elemental analysis and melting point determination. The spectroscopic, analytical and physical data collaborates with those reported in the literature.

Among the 21 acridinedione compounds synthesized, **4b, 4c**, **4e**, and **4f** were novel and are reported in this work for the first time. The low yield (41%) of **4e** may be attributed to steric hindrance by the two methoxy groups attached at positions 2 and 6 on the aromatic aldehyde ring. Compound **4c** was unique as it exhibited keto-enol tautomerism (**Figure 1**).

This was observed during the interpretation of the EI-MS and $^1$H NMR results respectively. EI-MS spectra that was obtained in solid state gave the

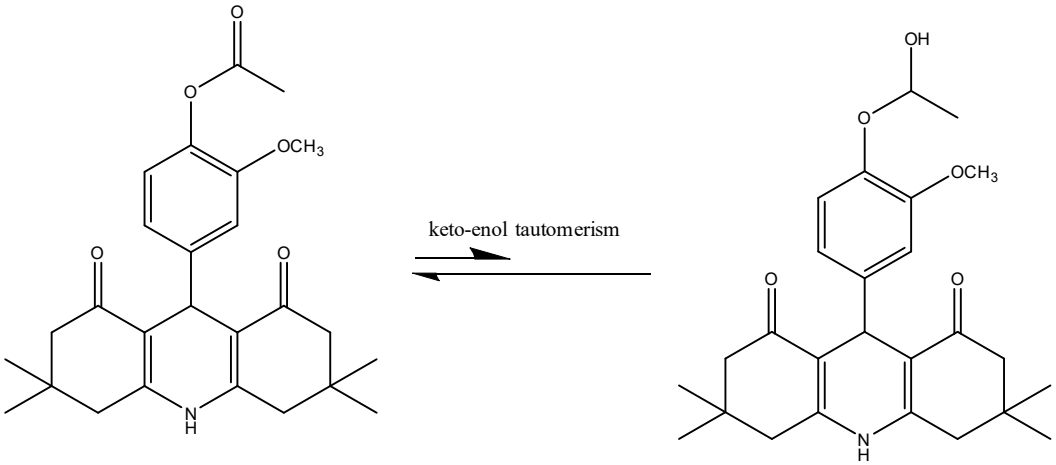
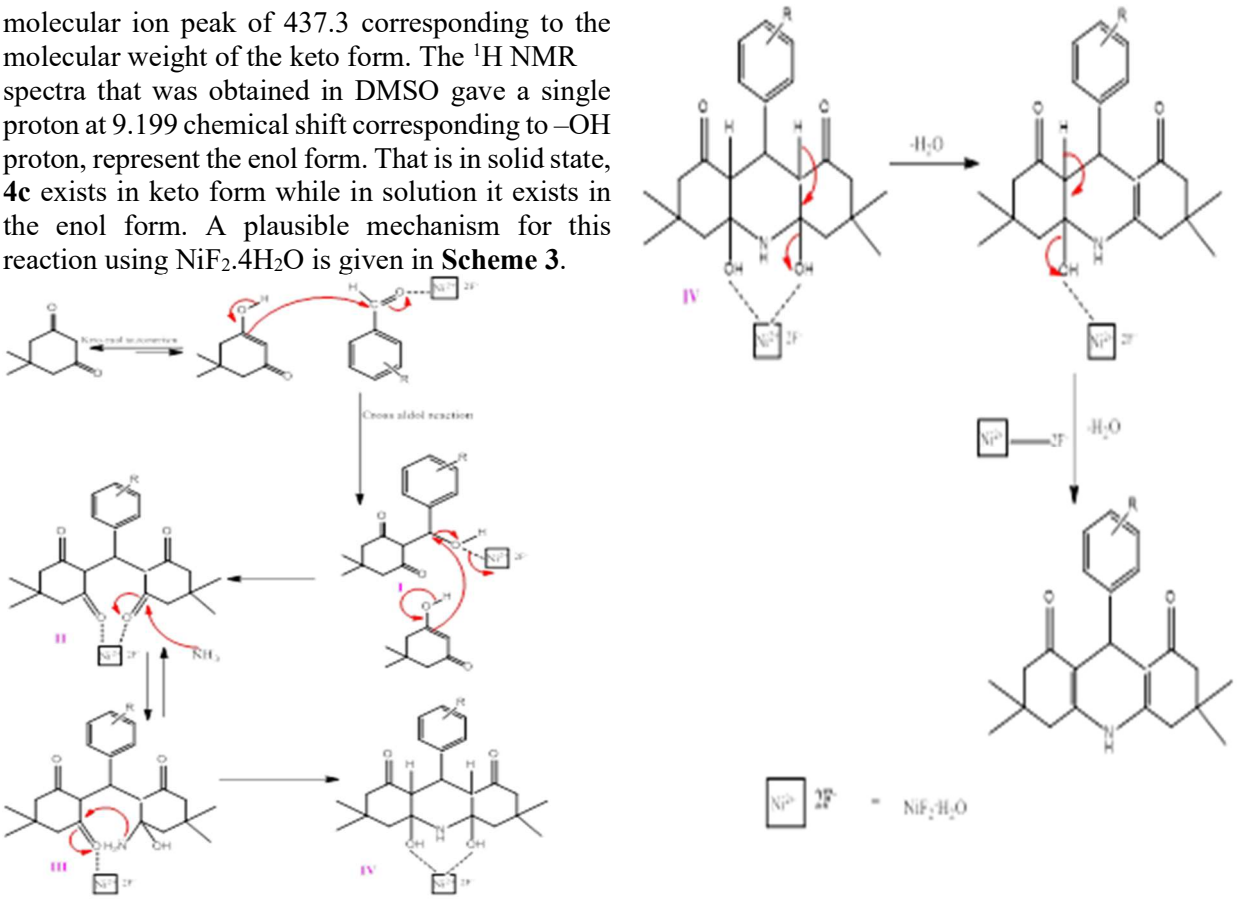



**Figure 1: Keto-enol tautomerism of 4c**

molecular ion peak of 437.3 corresponding to the molecular weight of the keto form. The $^1$H NMR spectra that was obtained in DMSO gave a single proton at 9.199 chemical shift corresponding to –OH proton, represent the enol form. That is in solid state, **4c** exists in keto form while in solution it exists in the enol form. A plausible mechanism for this reaction using $NiF_2.4H_2O$ is given in **Scheme 3**.



**Scheme 3: A plausible mechanism for the formation of acridinediones**

Table 3. Synthesis of products **4a - 4u** by the reactions of aromatic aldehydes with dimedone and ammonium acetate[a]

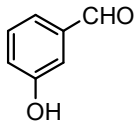
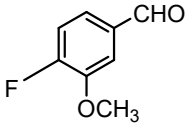
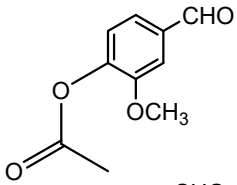
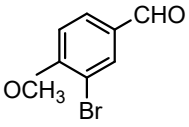
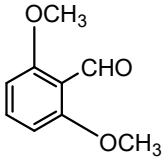
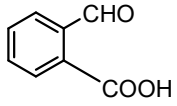
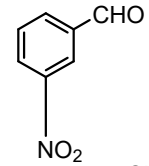
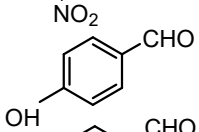
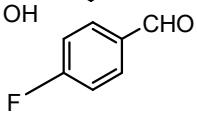
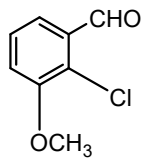
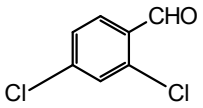
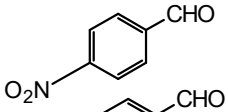
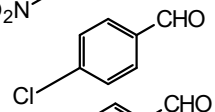
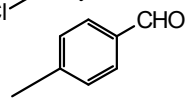
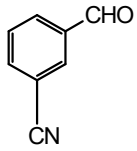
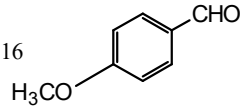
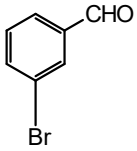
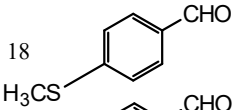
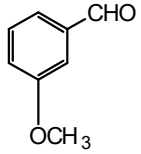
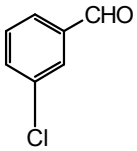
| Entry | Aromatic aldehyde | Nitrogen source | Product source | Time (h) | Yield (%)[b] | Mp ($^0$C) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Found | Reported |
| 1 |  | $NH_4OAC$ | **4a** | 1.5 | 99 | 309-312 | — |
| 2 |  | $NH_4OAC$ | **4b** | 3.0 | 80 | 258-260 | — |
| 3 |  | $NH_4OAC$ | **4c** | 3.0 | 91 | 270-274 | — |
| 4 |  | $NH_4OAC$ | **4d** | 3.0 | 92 | 313-317 | 238-241 (Ramesh and Pasha, 2014) |
| 5 |  | $NH_4OAC$ | **4e** | 2.0 | 41 | 265-268 | — |
| 6 |  | $NH_4OAC$ | **4f** | 2.0 | 54 | 325-327 | — |
| 7 |  | $NH_4OAC$ | **4g** | 2.0 | 70 | 289-294 | 290-293 (Nasresfahani and Kassaee,2015) |
| 8 |  | $NH_4OAC$ | **4h** | 1.0 | 92 | 362-364 | >300 (Mansoor *et al.,* 2014) |
| 9 |  | $NH_4OAC$ | **4i** | 1.0 | 96 | 262-265 | 274-276 (Mansoor *et al.,* 2014) |
| 10 |  | $NH_4OAC$ | **4j** | 3.0 | 72 | 373-376 | — |

Table 3 (*Continued*)

| Entry | Aromatic aldehyde | Nitrogen source | Product source | Time (h) | Yield (%)[b] | Mp ($^0$C) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Found | Reported |
| 11 |  | $NH_4OAC$ | **4k** | 3.0 | 71 | 352-355 | — |
| 12 |  | $NH_4OAC$ | **4l** | 2.0 | 75 | 287-290 | 284-287 (Dutta *et al.*, 2017) |
| 13 |  | $NH_4OAC$ | **4m** | 2.0 | 99 | 296-298 | 298-301 (Dutta *et al.*, 2017) |
| 14 |  | $NH_4OAC$ | **4n** | 2.5 | 95 | 317-320 | 320-325 (Nasresfahani and Kassaee, 2015) |
| 15 |  | $NH_4OAC$ | **4o** | 1.0 | 96 | 303-307 | — |
| 16 |  | $NH_4OAC$ | **4p** | 1.0 | 96 | 273-288 | 270-280 (Nasresfahani and Kassaee, 2015) |
| 17 |  | $NH_4OAC$ | **4q** | 1.5 | 79 | 317-320 | 286-288 (Satheeshkumar *et al.*, 2017) |
| 18 |  | $NH_4OAC$ | **4r** | 1.0 | 99 | 284-287 | — |
| 19 |  | $NH_4OAC$ | **4s** | 1.5 | 86 | 307-310 | — |
| 20 |  | $NH_4OAC$ | **4t** | 1.0 | 96 | 281-284 | 280-282 (Satheeshkumar *et al.*, 2017) |
| 21 |  | $NH_4OAC$ | **4u** | 1.0 | 91 | 263-266 | 262-264 (Satheeshkumar *et al.*, 2017) |

[a] Reaction conditions: aromatic aldehydes (0.6 equiv), dimedone (2 equiv), and ammonium acetate (1.5 equiv) in the presence of $NiF_2.4H_2O$ (15 mol%) at 80 $^0$C in water

[b] Isolated yield.

## 4.0 Conclusion

We have developed an efficient and environmentally benign strategy for synthesis of substituted acridinediones through one-pot multi-component condensation of aromatic aldehyde, dimedone, and ammonium acetate in an aqueous medium with nickel (II) fluoride tetrahydrate as efficient catalyst. The experimental simplicity, compatibility with various functional groups, the mildness of the conversion, easy work-up procedure and excellent product yield make this strategy attractive for synthesis of a variety of such compounds. Ethyl methyl ketone and diethyl malonate were also discovered as suitable solvents for synthesis of these compounds with excellent product yield.

## 5.0 Acknowledgements.

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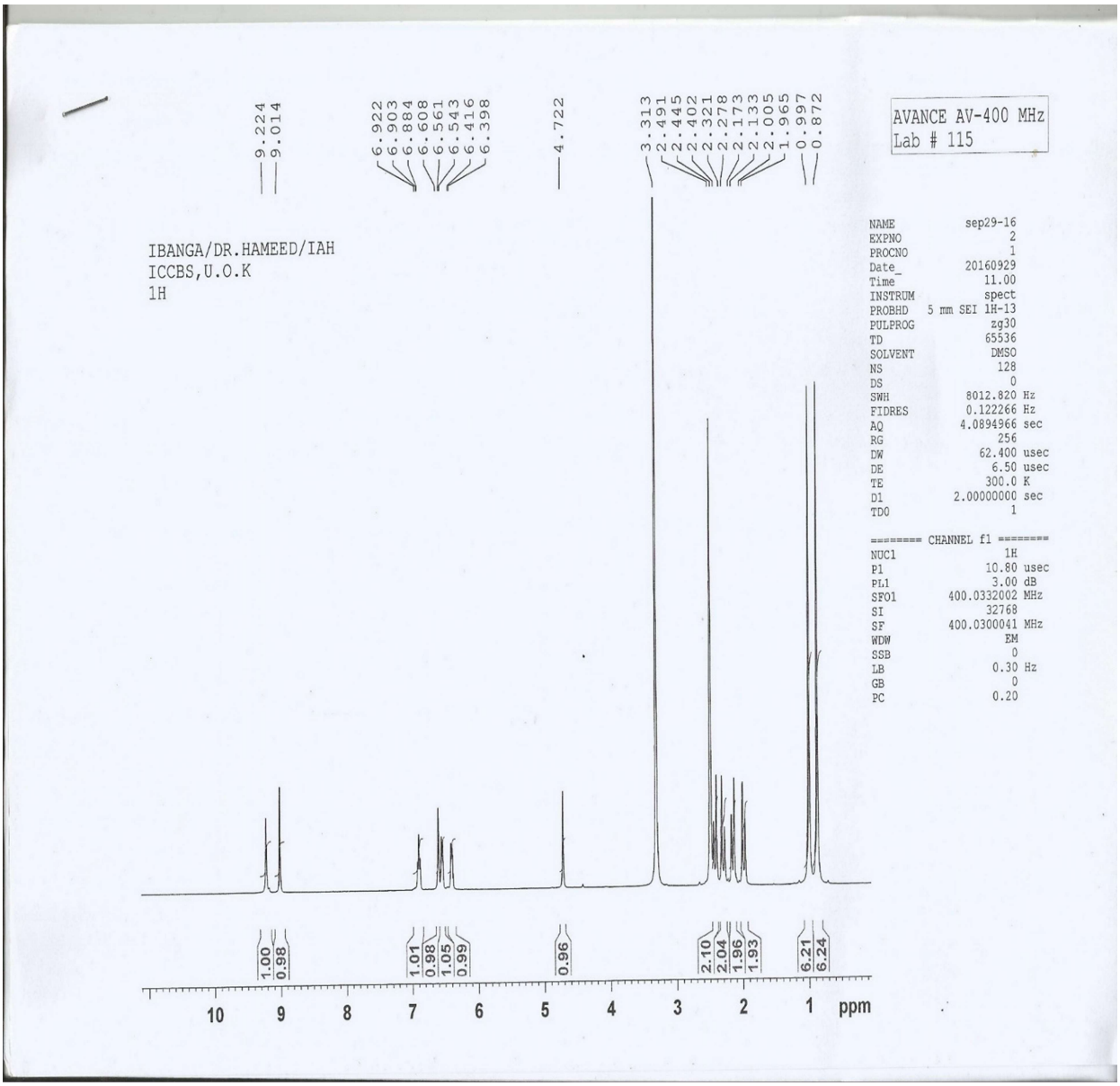
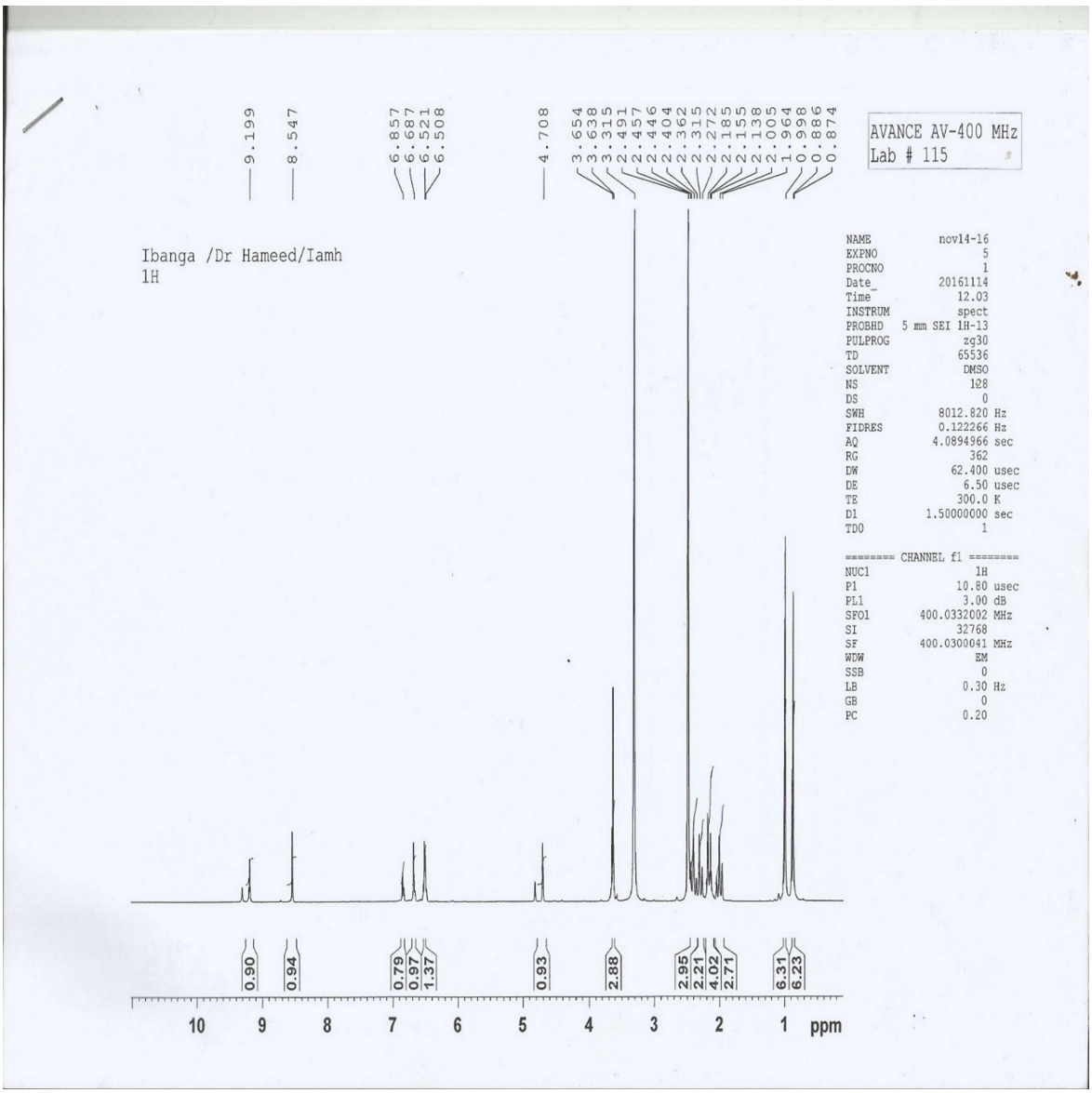
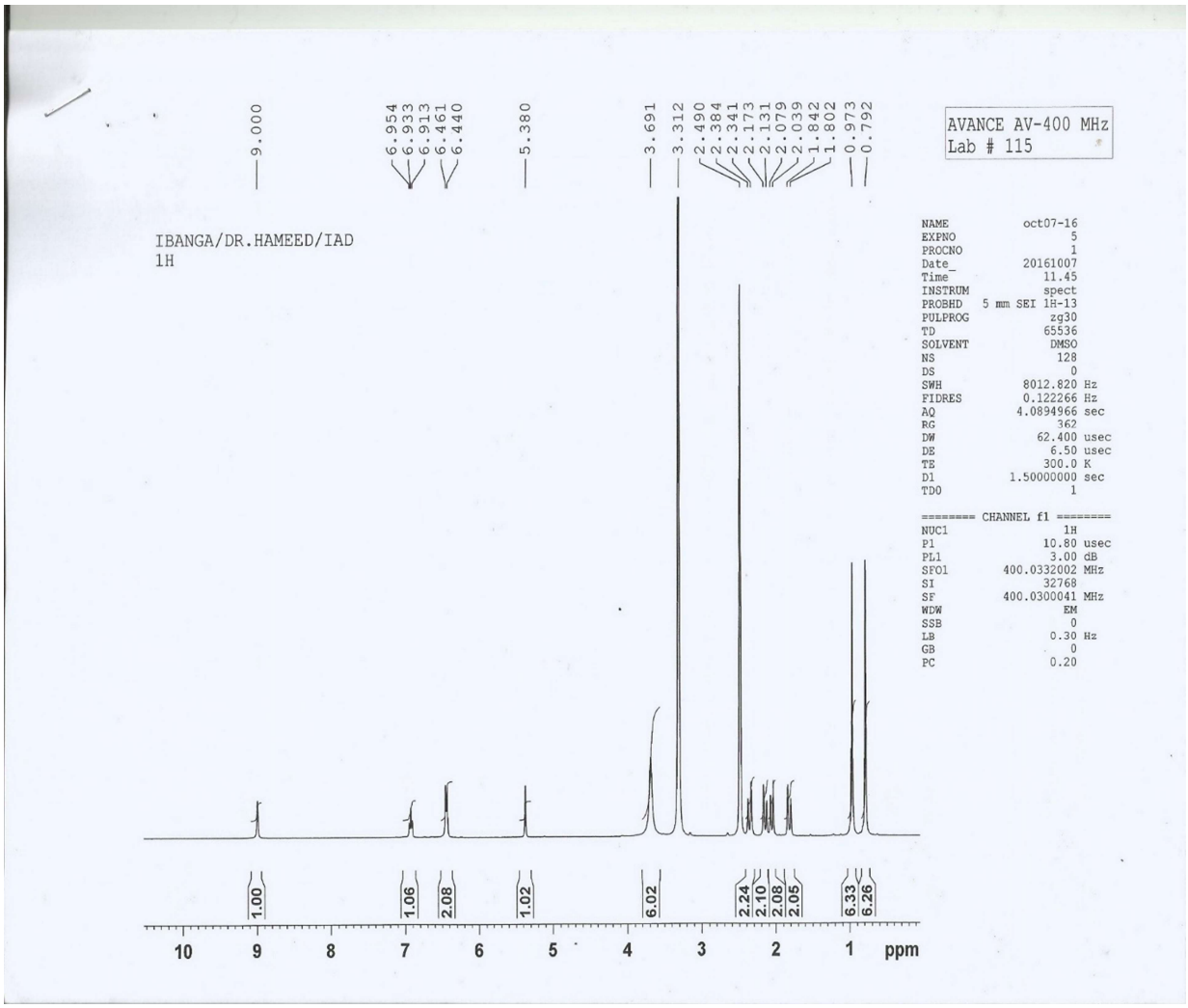



**Appendix 1: $^{1}$H NMR spectrum of sample 4a**




**Appendix 2: $^{1}$H NMR spectrum of sample 4c**




**Appendix 3: $^{1}$H NMR spectrum of sample 4e**