Chapter 6

A Catalyst-Free Expeditious Green Synthesis of Quinoxaline, Oxazine, Thiazine, and Dioxin Derivatives in Water under Ultrasound Irradiation

6.1 Introduction

Quinoxaline, 1,4-oxazine, 1,4-thiazine and 1,4-dioxin derivatives are an important class of heterocycles gaining considerable attention due to their biological activities and pharmacological importance (Das et al. 2012, Sindhu et al. 2013, Soliman 2013, Vincent et al. 2014, Mohsen et al. 2015, Cheng et al. 2016, El-Zahabi 2017, Gu et al. 2017, Paliwal et al. 2017). These heterocyclic compounds are also the basic scaffold for the synthesis of solar cells (Shen et al. 2018), dyes (Katoh et al. 2000), pigments (Dietz et al. 1994), organic semiconductors (Dailey et al. 2001) and chemical switches (Crossley et al. 2002). There are many drugs possessing these core structural units like Quinacilline (penicillin drug), Ragaglitazar (anti-hypertensive drug), Chlorpromazine (antipsychotic drug), WB-4101 (α_{1B}-adrenergic receptor), D 106669 (PI3K inhibitor), Ofloxacin (antibiotic) etc. (**Figure 6.1**). Due to their wide range of biological activities many synthetic strategies have been reported in the literature. Synthesis of quinoxaline derivatives have been achieved by using different synthons with *o*-phenylenediamine like 1,2-dicarbonyl compounds, epoxides (Antoniotti et al. 2002), phenacyl bromide (Sarmah et al. 2017), α-acylthioformanilide (El-Sharief et al. 2009) etc. Among these 1,2-dicarbonyl compounds and *o*-phenylenediamines are the best starting materials for quinoxaline synthesis.

Conventionally, quinoxaline derivatives were synthesized by the reaction of 1,2-dicarbonyl compound and *o*-phenylenediamine using different catalysts such as acetic acid (Islami et al. 2008, Han et al. 2017), molecular iodine (Bhosale et al. 2005, More et al. 2005), *o*-iodoxybenzoic acid (Heravi et al. 2006), montmorillonite K-10 clay (Huang et al. 2008), polyaniline sulfate (Srinivas et al. 2007), nitrilotris (methylenephosphonic acid) (Fathi et al. 2015), aqueous HF (Shekhar et al. 2014), sulfamic acid (Darabi et al. 2007, Hegade et al. 2014), NH_4Cl (Darabi et al. 2008), Amberlyst-15 (Liu et al. 2010) and metal catalysts such as cerium(IV) ammonium nitrate (CAN) (More et al. 2006), gallium(III) triflate (Cai et al. 2008), silica-supported antimony(III) chloride (Darabi et al. 2009), zirconium(IV) chloride (Aghapoor et al. 2010), $SnCl_2/SiO_2$ (Darabi et al. 2011), ZnO (Hosseini-Sarvari 2012), $FeCl_3$ (Bardajee et al. 2013), Keplerate $\{Mo_{132}\}$ nanoballs (Rezaeifard et al. 2015) and sulfated polyborate (Indalkar 2017). Synthesis of quinoxalines have also been reported under microwave irradiation (Kidwai et al. 2005, Dwivedi et al. 2014), ultrasound irradiation (Guo et al. 2009, Aghapoor et al. 2011) and using ball mill (Kaupp et al. 2002, Etman et al. 2011, Bhutia et al. 2017).

Synthesis of the 1,4-oxazines were reported by the reaction of 1,2-aminophenol with 1,2-dicarbonyl compound (Moghaddam et al. 2016) and phenacyl bromide (Anguiano et al. 2013) while 1,4-thiazines were synthesized by 1,2-aminothiophenol and 1,2-dicarbonyl compound (Jadamus, Fernando and Freiser 1964), phenacyl bromide (Yang et al. 2013), chalcones (Lin et al. 2016), maleic anhydride (Jangir et al. 2015) etc. and some other

methods were also utilized which involves the sulphur insertion (Zhang et al. 2001, Gu et al. 2014). Similar to the quinoxalines, the best method of 1,4-oxazine and 1,4-thiazine synthesis involves the reaction of 1,2-aminophenol/ 1,2-aminothiophenol with 1,2-dicarbonyl compounds under different experimental conditions like THF-MW, *p*-TSA etc. There are only few reports on the synthesis of indenoxazines and indenothiazines from the reaction of ninhydrin with *o*-aminophenol and *o*-aminothiophenol respectively (Schönberg et al. 1978, Simakov et al. 2001, Kaupp 2002); but the reaction of ninhydrin with catechol and 3-hydroxy-2-aminopyridine leading to the formation of 4b,10a-dihydroxy-4b*H*-benzo [*b*]indeno[1,2-*e*][1,4]dioxin-11(10a*H*)-one and 5a-hydroxyindeno[2,1-*b*] pyrido[2,3-*e*][1,4]oxazin-6(5a*H*)-one has not been reported till now. These reported methods for synthesis of quinoxaline, oxazine, thiazine and dioxin have some drawbacks such as harsh reaction conditions, longer reaction time, expensive catalysts, toxic solvents or tedious workup. Green synthesis of biologically active heterocyclic compounds is always on the priority of the synthetic organic chemists. Therefore, the development of facile and energy-efficient greener methods for synthesis of these heterocyclic compounds is necessary.

The use of appropriate solvents in organic synthesis is also very important from the green chemistry point of view. In this regard the use of water as solvent has attracted great deal of interest in recent years. Indeed, water offers many advantages because it is cheap, readily available, nontoxic, nonflammable and can be more selective than organic solvents (Lindstrom 2008, Gawande et al. 2013). Catalyst-free syntheses are in full agreement with

the idea of green chemistry because they reduce pollutant production, use of hazardous chemicals, and cost. The reaction occurs under mild conditions and usually requires easier workup procedures.

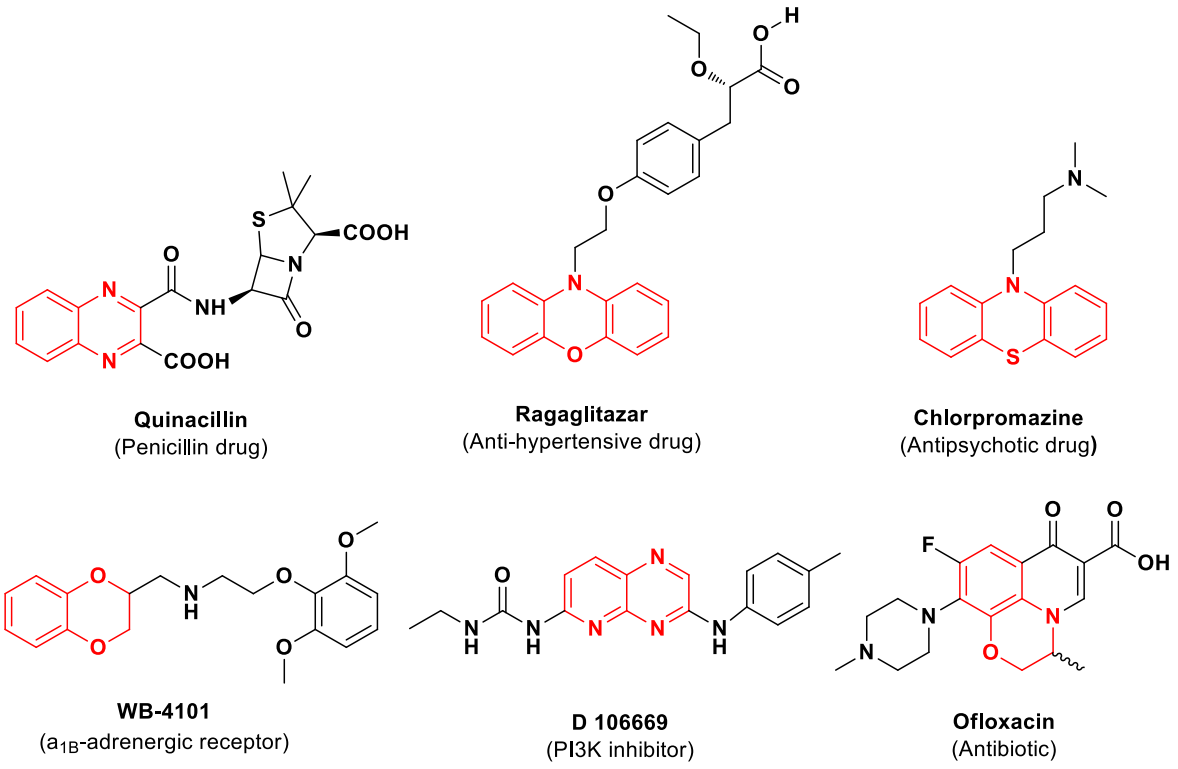


Figure 6.1: Structures of some pharmacologically active compounds containing quinoxaline, oxazine, thiazine or dioxin core moieties.

In this context, ultrasound assisted reactions have gained much attention because they offer milder reaction conditions, higher reaction rates, excellent yields and low energy consumption. Many organic transformations have been successfully achieved with the help of ultrasound irradiation. Therefore, ultrasound assisted organic synthesis, as a green

synthetic approach, is considered to be a powerful technique (Banerjee 2017, Nishtala et al. 2017, Ghomi et al. 2018).

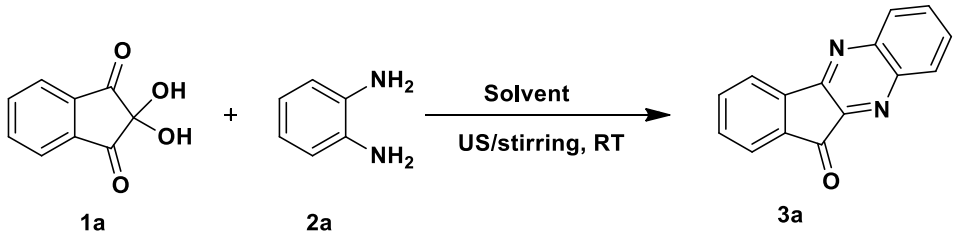
The fascinating nature of water and the beneficial effects of ultrasound have prompted us to undertake the synthesis of quinoxaline, oxazine, thiazine and dioxin derivatives. Herein, we report the catalyst-free reaction of ninhydrin and isatin derivatives with 1,2-difunctionalized benzene/ pyridine for the first time in water under ultrasound irradiation.

6.2 Results and Discussion

In order to optimize reaction conditions, the reaction of ninhydrin and *o*-phenylenediamine was chosen as a model reaction for the synthesis of quinoxaline derivatives (**Scheme 6.1**). The reaction was carried out in various solvents under conventional and ultrasound irradiation methods. The reaction was performed at room temperature with 1.0 mmol of ninhydrin and 1.0 mmol *o*-phenylenediamine in 5.0 mL of solvent without any catalyst. The progress of the reaction was monitored by TLC. It was observed that under ultrasound irradiation the reaction was completed in shorter time with excellent yield (**Table 6.1**). Among the polar solvents tested (ethanol, methanol, isopropanol, water, acetonitrile, acetic acid, THF and dioxane) water was found to be the best, which gave 98% yield in 50 seconds under ultrasound irradiation (**Table 6.1, Entry 4**) while no product was detected at room temperature in case of nonpolar solvents (benzene and toluene) (**Table 6.1, Entries 9 & 10**). Pure product was separated as solid and collected by filtration. There was no requirement for further purification.

The rate of reaction was faster under ultrasound irradiation. This is attributed to the cavitation phenomena occurring during sonication. Cavitation results in formation of micro bubbles which adiabatically collapse and gives local hotspots. These hotspots generate high temperature and pressures of several thousand atmosphere which cause the reaction to proceed rapidly (Banerjee 2017).

To examine the effect of ultrasound energy on reaction time and yield, the model reaction was carried out at different energies from 500 to 11000 J, and the results are shown in **Table 6.2**. The maximum yield of the product was obtained at 2000 J ultrasound energy (**Table 6.2, Entry 4)**. An increase in the ultrasound energy above 2000 J did not show any significant improvement in terms of yield and reaction time. So, 2000 J ultrasound energy is considered as the optimum energy condition. In order to examine the effect of ultrasound amplitude on reaction rate we carried out this reaction at different ultrasound amplitudes from 20–50% at room temperature. The maximum yield (98%) of the product (**3a**) was obtained at 20% amplitude. The increase in amplitude did not affect the yield of the reaction.



Scheme 6.1: Reaction of ninhydrin with *o*-phenylenediamine.

Table 6.1: Effect of solvents on the yield of the product **3a** under conventional and ultrasound irradiation methods.

Entry	Solvent	Conventional[a]		Ultrasonication[b]	
		Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
1	Ethanol	15	80	10	84
2	Methanol	30	75	12	77
3	Isopropanol	35	72	15	75
4	**Water**	**10**	**85**	**50 sec**	**98**
5	Acetonitrile	60	60	40	72
6	Acetic acid	30	78	10	80
7	THF	NR	--	NR	--
8	Dioxane	NR	--	NR	--
9	Benzene	NR	--	NR	--
10	Toluene	NR	--	NR	--

Reaction conditions: [a] Mixture of **1a** (1.0 mmol) and **2a** (1.0 mmol) in 5.0 mL of solvent was stirred at room temperature (30 ^{0}C). [b] Mixture of **1a** (1.0 mmol) and **2a** (1.0 mmol) in 5.0 mL of solvent was irradiated at 750 W, 2000 J, 20% amplitude, 30 ^{0}C. [c] Pure isolated yield.

Table 6.2: Effect of ultrasound energy on the yield of the product **3a**[a]

Entry	US Energy (Joule)	Time (sec)	Yield (%)[b]
1	500	260	90
2	1000	180	92
3	1500	100	95
4	**2000**	**50**	**98**
5	5000	45	95
6	7500	35	96
7	11000	35	95

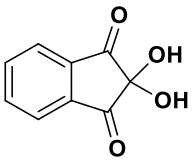
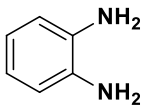
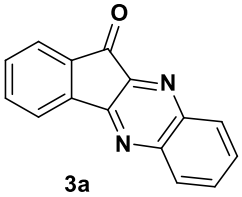
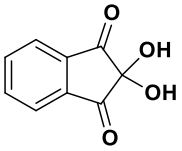
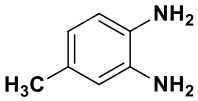
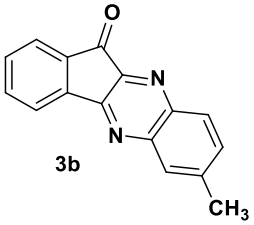
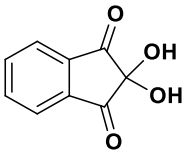
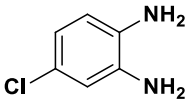
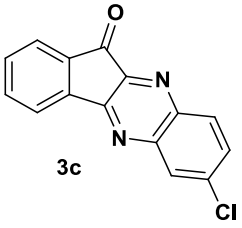
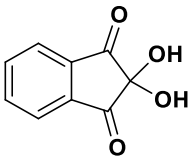
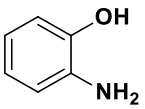
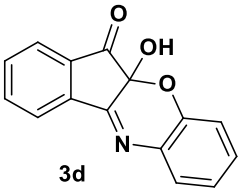
[a] **Reaction condition**: Mixture of ninhydrin **1a** (1.0 mmol) and *o*-phenylenediamine **2a** (1.0 mmol) in 5 mL of water irradiated at 750 W, 20% amplitude at room temperature (30 ^{0}C). [b] Pure isolated yield.

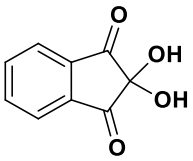
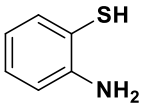
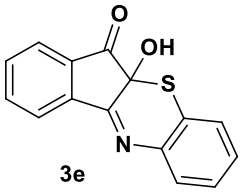
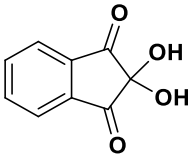
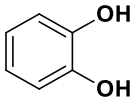
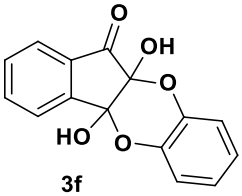
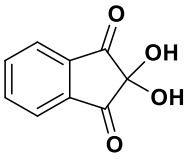
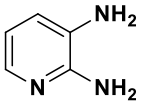
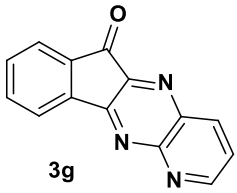
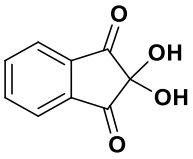
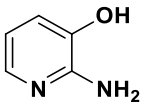
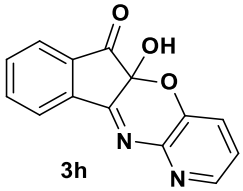
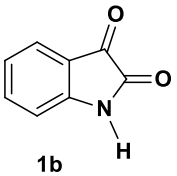
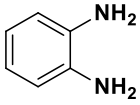
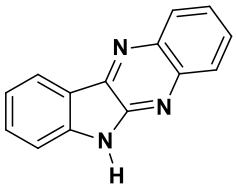
To explore the applicability of the optimized reaction conditions, various derivatives of the quinoxaline, oxazine, thiazine, and dioxin were synthesized by the reaction of ninhydrin and isatin derivatives (**1**) *viz.* ninhydrin (**1a**), isatin (**1b**) 1-ethylindoline-2,3-dione (**1c**), 1-propylindoline-2,3-dione (**1d**), 1-benzylindoline-2,3-dione (**1e**), ethyl 2-(2,3-dioxoindolin-1-yl)acetate (**1f**) and ethyl 2-(5-chloro-2,3-dioxoindolin-1-yl)acetate (**1g**) with several 1,2-difuncionalized benzenes and pyridines (**2**) *viz*. *o*-phenylenediamine (**2a**), 4-methyl-*o*-phenylenediamine (**2b**), 4-chloro-*o*-phenylenediamine (**2c**), *o*-aminophenol (**2d**), *o*-aminothiophenol (**2e**), catechol (**2f**), 2,3-diaminopyridine (**2g**) and 3-hydroxy-2-aminopyridine (**2h**) to give compound (**3**) *viz.* 11H-indeno[1,2-b]quinoxalin-11-one **(3a),** 7-methyl-11H-indeno[1,2-b]quinoxalin-11-one (**3b**),

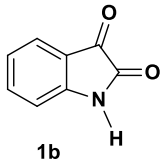
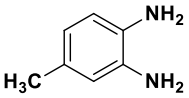
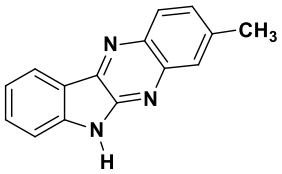
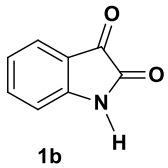
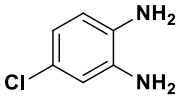
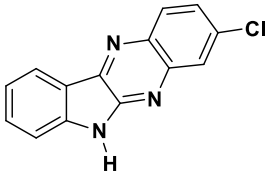
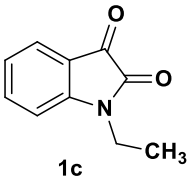
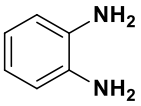
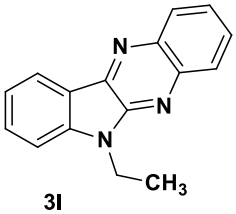
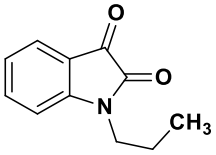
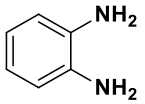
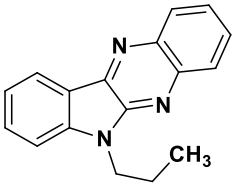
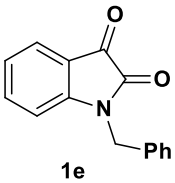
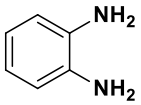
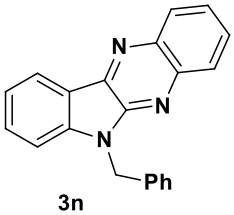
7-chloro-11H-indeno[1,2-b] quinoxalin-11-one (**3c**), 10a-hydroxybenzo[b]indeno[1,2-e][1,4]oxazin-11(10aH)-one (**3d**), 10a-hydroxybenzo[e]indeno[2,1-b][1,4]thiazin-11(10aH)-one (**3e**), 4b,10a-dihydroxy-4bH-benzo[b]indeno[1,2-e][1,4]dioxin-11(10aH)-one (**3f**), 6H-indeno[1,2-b]pyrido[3,2-e]pyrazin-6-one (**3g**), 5a-hydroxyindeno[2,1-b]pyrido[2,3-e][1,4]oxazin -6(5aH)-one (**3h**), 6H-indolo[2,3-b]quinoxaline (**3i**), 3-methyl-6H-indolo[2,3-b] quinoxaline (**3j**), 3-chloro-6H-indolo[2,3-b]quinoxaline (**3k**), 6-ethyl-6H-indolo [2,3-b]quinoxaline (**3l**), 6-propyl-6H-indolo[2,3-b]quinoxaline (**3m**), 6-benzyl-6H-indolo [2,3-b]quinoxaline (**3n**), ethyl 2-(6H-indolo[2,3-b]quinoxalin-6-yl)acetate (**3o**) and ethyl 2-(9-chloro-6H-indolo[2,3-b]quinoxalin-6-yl)acetate (**3p**) in good to excellent yield. The chemical structures of the synthesized compounds were established from their spectral data. The structure of the products along with their reaction time, m.p. and yields are summarized in (**Table 6.3**).

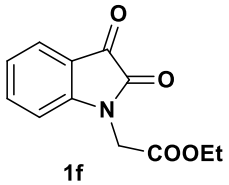
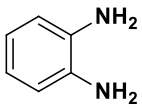
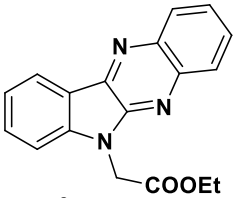
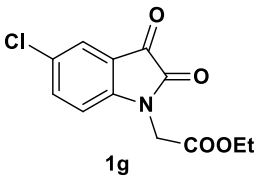
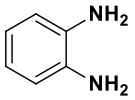
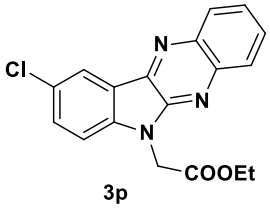
The results shown in **Table 6.3** reveal that in case of electron donating substituent (-CH_3) on the *o*-phenylenediamine ring reaction goes faster (**Entries 2 & 10**) than electron withdrawing substituent (-Cl) (**Entries 3 & 11**). The reaction of ninhydrin with *o*-substituted amines were completed within a minute in excellent yields >90% while isatin derivatives require longer time. The lower reactivity of the isatin derivatives is attributed to the presence of the amidic carbonyl group in these compounds. It is worth noting that the ultrasound irradiation facilitates nucleophilic addition-elimination reactions leading to the formation of fused quinoxaline, oxazine, thiazine, and dioxin derivatives.

Table 6.3: Reaction of 1,2-diketones with 1,2-difunctionalized benzene/pyridine in water under ultrasound irradiation[a]

Entry	Diketone (1)	1,2-difunctionalized benzene/pyridine (2)	Product (3)	Time (sec)	Yield (%)[b]	MP (^{0}C)
1	 1a	 2a	 3a	50	98	217-18
2	 1a	 2b	 3b	35	99	175-76
3	 1a	 2c	 3c	55	96	235-36
4	 1a	 2d	 3d	60	92	255

5	 1a	 2e	 3e	55	95	225-26
6	 1a	 2f	 3f	55	86	233-34
7	 1a	 2g	 3g	55	92	>300
8	 1a	 2h	 3h	50	95	252-53
9	 1b	 2a	 3i	230	92	295-96

10	 1b  2b  3j	200	95	257-58
11	 1b  2c  3k	250	90	275-77
12	 1c  2a  3l	225	87	247-48
13	 1d  2a  3m	220	88	218-19
14	 1e  2a  3n	230	91	170-71

15	 1f  2a  3o	210	90	185-86
16	 1g  2a  3p	220	92	275-76

[a] **Reaction condition:** Mixture of 1,2-diketone (1.0 mmol) and 1,2-difunctionalized benzene/pyridine (1.0 mmol) in 5 mL of water was irradiated at 750 W, 2000 J energy, 20% ultrasound amplitude at room temperature. [b] Isolated yield.

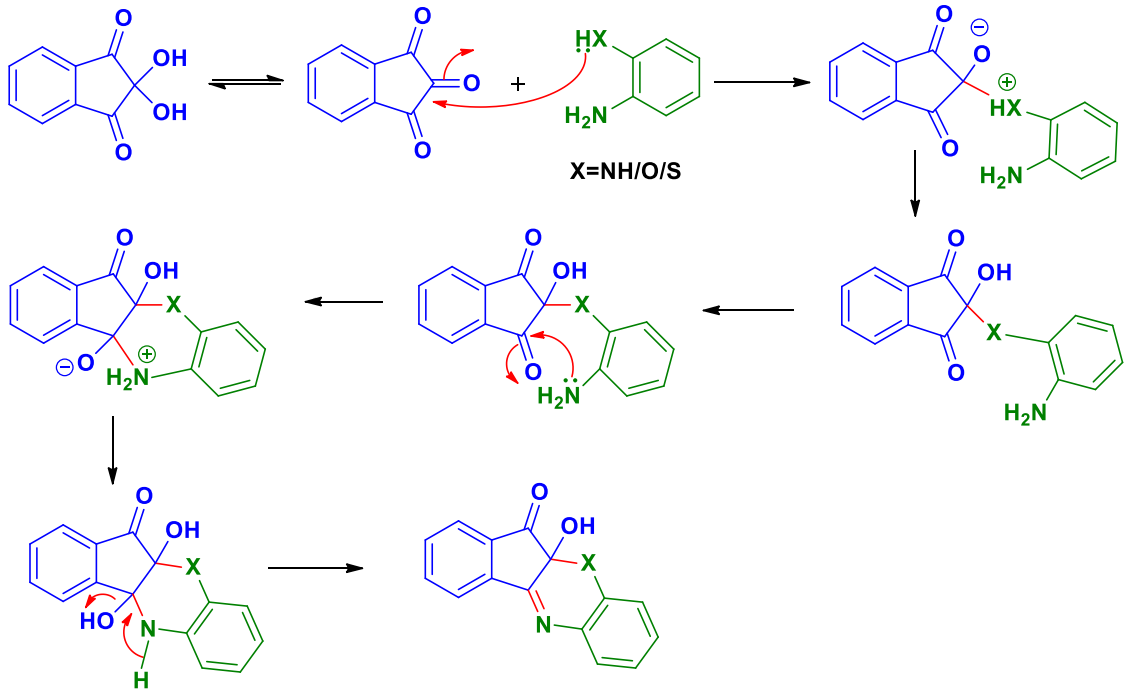


Figure 6.2: Plausible mechanism of synthesis of Quinoxaline, Oxazine and Thiazine derivatives.

6.3 Experimental section

6.3.1 General procedure for synthesis of products (3a-p).

The equimolar amount of 1,2-diketone (1.0 mmol) and the corresponding 1,2-difunctionalized benzene/ pyridine (1.0 mmol) were mixed in 5.0 ml of water. The reaction mixture was irradiated under ultrasonication at 750 W power, 2000 J energy, 20% amplitude at room temparature for the required time. The progress of the reaction was monitered using thin layer chromatography (ethyl acetate: *n*-hexane, 1:4). After completion of reaction solid product was separated by filtration, washed with disstilled water and recrystallized with appropiate solvents ethanol/toluene to obtain pure products (**3a-p**).

6.4 Analytical data of the products

11H-Indeno[1,2-b]quinoxalin-11-one (3a): Yellow solid; yield 98%; m.p. 217-18 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3036, 2358, 1790, 1728, 1607, 1565, 1509, 1462, 1336, 1247, 1190, 1118, 1040, 1001, 939, 867, 825, 775, 740; **^{1}H NMR** (500 MHz, DMSO–d_6) δ (ppm): 8.21 – 8.01 (m, 3 H), 7.92 – 7.82 (m, 4 H), 7.71 (t, 1 H); **^{13}C NMR** (126 MHz, DMSO–d_6) δ (ppm): 189.29, 156.44, 149.81, 142.12, 141.82, 140.94, 136.93, 136.62, 132.76, 132.43, 130.95, 130.35, 129.35, 124.21, 122.27.

7-Methyl-11H-indeno[1,2-b]quinoxalin-11-one (3b): Yellow solid; yield 99%; m.p. 175-76 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3040, 2910, 1974, 1726, 1609, 1564, 1506, 1462, 1332, 1244, 1188, 1150, 1113, 1041, 1001, 965, 903, 834, 766, 731; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.12 – 7.90 (m, 4 H), 7.77 – 7.57 (m, 3 H), 2.53 (d, 3 H); **^{13}C NMR** (126 MHz,

$CDCl_3$) δ (ppm): 190.24, 156.97, 143.86, 143.37, 141.73, 141.26, 136.88, 136.80, 134.81, 132.62, 132.50, 131.26, 130.75, 129.29, 129.01, 124.83, 122.54, 22.19.

7-Chloro-11H-indeno[1,2-b]quinoxalin-11-one (3c): Yellow solid; yield 96%; m.p. 245-46 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3069, 2958, 2916, 2852, 2322, 1721, 1609, 1555, 1496, 1329, 1256, 1182, 1017, 946, 877, 792; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.05 (t, 4 H), 7.84 – 7.48 (m, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 189.53, 157.53, 149.46, 143.62, 141.24, 137.06, 133.04, 132.65, 131.29, 128.92, 124.98, 122.90.

10a-Hydroxybenzo[b]indeno[1,2-e][1,4]oxazin-11(10aH)-one (3d): White solid; yield 92%; m.p. 255-56 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3735, 2924, 2644, 2484, 1738, 1641, 1586, 1460, 1414, 1347, 1291, 1201, 1147, 1112, 1062, 966, 919, 855, 755, 712; **^{1}H NMR** (500 MHz, DMSO–d_6) δ (ppm): 8.55 (s, 1 H, D_2O exchangeable), 8.18 (d, 1 H), 8.00 (dd, 2 H), 7.90 – 7.81 (m, 1 H), 7.61 (dd, 1 H), 7.37 – 7.13 (m, 3 H); **^{13}C NMR** (126 MHz, DMSO–d_6) δ (ppm): 192.22, 157.98, 144.79, 141.64, 137.55, 135.93, 134.01, 133.90, 128.94, 127.57, 124.83, 123.70, 123.38, 118.04, 85.90.

10a-Hydroxybenzo[e]indeno[2,1-b][1,4]thiazin-11(10aH)-one (3e): Green solid; yield 95%; m.p. 225-26 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3738, 2949, 2701, 1728, 1635, 1636, 1585, 1458, 1398, 1340, 1251, 1165, 1114, 1074, 1005, 953, 854, 820,762, 709; **^{1}H NMR** (500 MHz, DMSO–d_6) δ (ppm): 8.22 (d, 1 H), 8.08 – 7.97 (m, 2 H), 7.87 (t, 1 H), 7.80 (s, 1 H, D_2O exchangeable), 7.68 (dd, 1 H), 7.57 (dd, 1 H), 7.41 (m, 1 H), 7.30 (m, 1 H); **^{13}C NMR** (126 MHz, DMSO–d_6) δ (ppm): 195.42, 155.79, 142.95, 142.23, 137.94, 134.99, 134.22, 129.42, 128.31, 127.31, 127.23, 124.86, 124.01, 120.86, 70.94.

4b,10a-Dihydroxy-4bH-benzo[b]indeno[1,2-e][1,4]dioxin-11(10aH)-one (3f): White solid; yield 86%; m.p. 233-34 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3742, 3615, 3380, 3312, 3187, 2356, 1706, 1597, 1496, 1400, 1275, 1217, 1149, 1084, 941, 874, 762,722; **^{1}H NMR** (500 MHz, DMSO–d_6) δ (ppm): 9.45 (s, 1 H, D_2O exchangeable), 8.03 – 7.84 (m, 4 H), 7.76 – 7.57 (m, 2 H), 6.94 – 6.79 (m, 1 H), 6.77 – 6.65 (m, 2 H), 6.58 (s, 1 H, D_2O exchangeable); **^{13}C NMR** (126 MHz, DMSO–d_6) δ (ppm): 199.38, 149.23, 144.54, 141.73, 136.58, 133.90, 130.90, 126.55, 125.20, 122.79, 121.55, 117.52, 115.43, 110.16, 82.97. **Elemental analysis:** (Found: C, 66.59; H, 3.64. Calc. for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73%).

6H-Indeno[1,2-b]pyrido[3,2-e]pyrazin-6-one (3g): Yellow solid; yield 92%; m.p.>300 ^{0}C; **IR** (KBr) ν (cm^{-1}): 2912, 2350, 1914, 1714, 1555, 1490, 1375, 1331, 1233, 1152, 1094, 1027, 934, 873, 781; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 9.16 (d, 1 H), 8.60 (d, 1 H), 8.25 (d, 1 H), 7.96 (d, 1 H), 7.88 – 7.60 (m, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 188.86, 155.70, 140.35, 137.45, 133.56, 125.58, 125.08, 123.79.

5a-Hydroxyindeno[2,1-b]pyrido[2,3-e][1,4]oxazin-6(5aH)-one (3h): White solid; yield 95%; m.p. 252-53 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3027, 2647, 1723, 1643, 1596, 1537, 1460, 1411, 1334, 1245, 1195, 1145, 1084, 1036, 950, 868, 737; **^{1}H NMR** (500 MHz, DMSO–d_6) δ (ppm): 8.18 – 7.35 (m, 4 H), 6.88 (d, 2 H), 6.37 (d, 1 H), 5.41 (s, 1 H, D_2O exchangeable); **^{13}C NMR** (126 MHz, DMSO–d_6) δ (ppm): 197.05, 150.46, 145.98, 139.26, 137.21, 136.09, 123.88, 123.43, 119.08, 118.52, 114.02, 112.37. **Elemental analysis:** (Found: C, 66.48; H, 3.25; N, 11.23 Calc. for $C_{14}H_8N_2O_3$: C, 66.67; H, 3.20; N, 11.11%).

6H-Indolo[2,3-b]quinoxaline (3i): Yellow solid; yield 92%; m.p. 295-96 ^{0}C; **IR** (KBr) ν(cm^{-1}): 3071, 3007, 2831, 2779, 2682, 1945, 1710, 1608, 1461, 1406, 1333,1245, 1206, 1132, 1010, 924, 829, 748 ; **^{1}H NMR** (500 MHz, DMSO–d_6) δ (ppm): 12.04 (s, 1 H), 8.35 (d, 1 H), 8.24 (d, 1 H), 8.07 (d, 1 H), 7.80 (t, 1 H), 7.71 (dd, 2 H), 7.59 (d, 1 H), 7.37 (t, 1 H); **^{13}C NMR** (126 MHz, DMSO–d_6) δ (ppm): 145.88, 144.04, 140.17, 139.82, 138.61, 131.38, 129.11, 129.01, 128.81, 127.55, 127.46, 126.03, 122.33, 122.24, 120.81, 120.75, 118.99, 112.04.

3-Methyl-6H-indolo[2,3-b]quinoxaline (3j): Yellow Solid; yield 95%; m.p. 257-58 ^{0}C; **IR** (KBr) ν(cm^{-1}): 3065, 2916, 2850, 2353, 1895, 1737, 1595, 1459, 1399, 1331, 1242, 1195, 1129, 1021, 816, 738; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 9.56 (s, 1 H), 8.38 (t, 2 H), 8.19 – 7.78 (m, 2 H), 7.67 – 7.25 (m, 4 H), 2.57 (d, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 165.44, 136.67, 131.43, 131.16, 131.00, 129.88, 129.12, 128.84, 128.54, 126.97, 126.48, 122.90, 122.75, 121.46, 121.40, 111.64, 21.77.

3-Chloro-6H-indolo[2,3-b]quinoxaline (3k): Yellow solid; yield 90%; m.p. 275-77 ^{0}C; **IR** (KBr) ν(cm^{-1}): 3052, 2918, 2851, 2766, 1937, 1740, 1580, 1482, 1452, 1401, 1331, 1234, 1182, 1107, 1068, 1021, 939, 824, 783, 737; **^{1}H NMR** (500 MHz, DMSO–d_6) δ (ppm): 12.17 (s, 1 H), 8.35 (d, 1 H), 8.27 (d, 1 H), 8.12 (d, 1 H), 7.79 – 7.70 (m, 2 H), 7.60 (d, 1 H), 7.39 (t, 1 H); **^{13}C NMR** (126 MHz, DMSO–d_6) δ (ppm): 146.14, 144.15, 140.58, 137.10, 132.96, 131.67, 130.72, 126.37, 126.09, 122.36, 121.00, 118.79, 112.12.

6-Ethyl-6H-indolo[2,3-b]quinoxaline (3l): White solid; yield 87%; m.p. 247-48 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3054, 2923, 2856, 2217, 1896, 1727, 1579, 1462, 1405, 1354, 1279, 1235, 1116, 1009, 932, 860, 808, 740; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.49 (d, 1 H), 8.30 (d, 1 H), 8.14 (d, 1 H), 7.72 (m, 3 H), 7.49 (d, 1 H), 7.38 (t, 1 H), 4.57 (q, 2 H), 1.53 (t, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.42, 144.22, 140.73, 140.33, 139.36, 131.11, 129.47, 128.88, 127.86, 126.04, 122.98, 120.94, 119.68, 109.48, 36.33, 13.79.

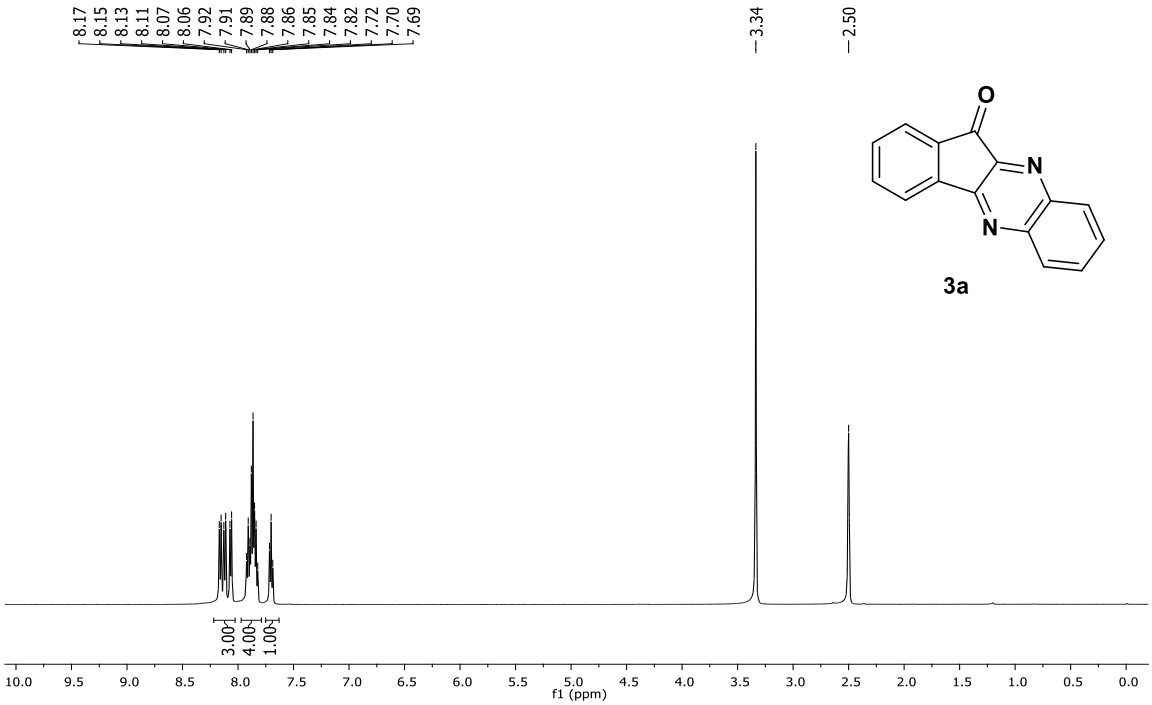
6-Propyl-6H-indolo[2,3-b]quinoxaline (3m): Yellow solid; yield 88%; m.p. 218-19 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3056, 2922, 2856, 2359, 1729, 1579, 1461, 1405, 1363, 1276, 1203, 1116, 1071, 983, 942, 893, 743; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.49 (d, 1 H), 8.30 (d, 1 H), 8.14 (d, 1 H), 7.80 – 7.63 (m, 3 H), 7.48 (d, 1 H), 7.38 (t, 1 H), 4.46 (t, 2 H), 2.00 (dd, 2 H), 1.03 (t, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.87, 144.68, 140.79, 140.18, 139.36, 131.05, 129.44, 128.83, 127.92, 126.02, 122.90, 120.89, 119.58, 109.67, 43.20, 21.96, 11.74.

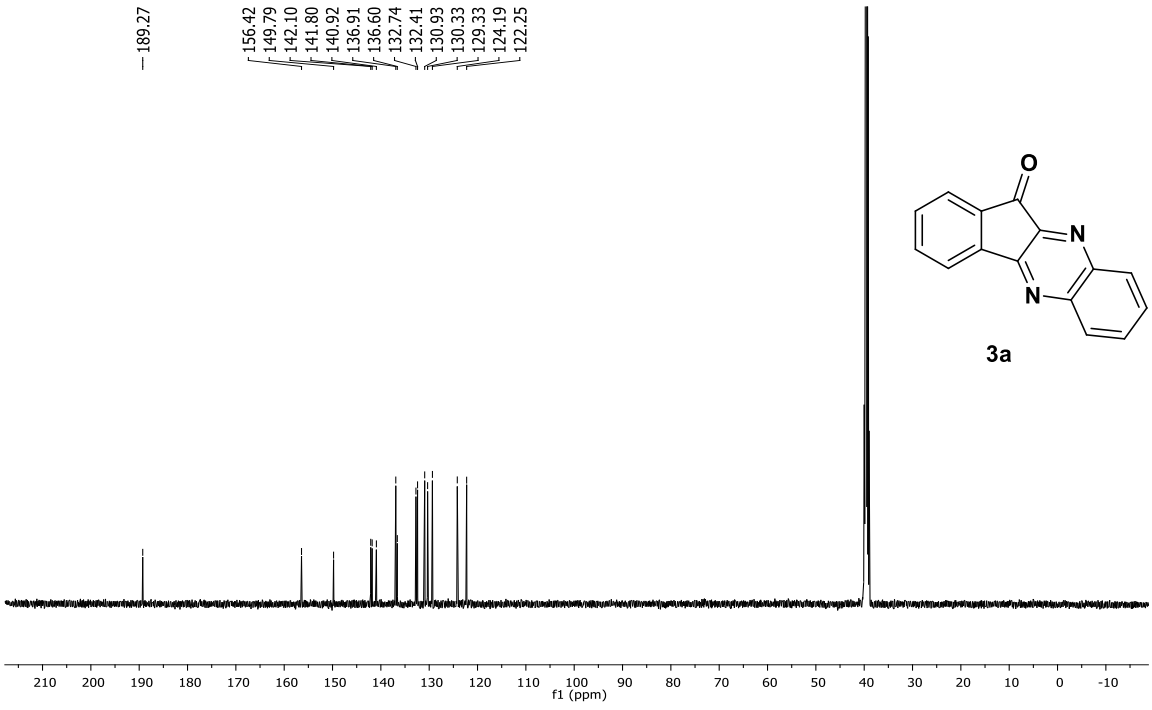
6-Benzyl-6H-indolo[2,3-b]quinoxaline (3n): Yellow solid; yield 91%; m.p. 140-41 ^{0}C; **IR** (KBr) ν (cm^{-1}): 2920, 2856, 1729, 1574, 1459, 1396, 1344, 1274, 1186, 1117, 1069, 982, 940, 850, 813, 736; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.49 (d, 1 H), 8.32 (d, 1 H), 8.14 (d, 1 H), 7.83 – 7.54 (m, 3 H), 7.48 – 7.19 (m, 7 H), 5.71 (s, 2 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 145.94, 144.40, 140.79, 140.17, 139.65, 136.63, 131.14, 129.47, 128.96, 128.93, 128.01, 127.81, 127.32, 126.26, 122.84, 121.30, 119.79, 110.28, 45.13.

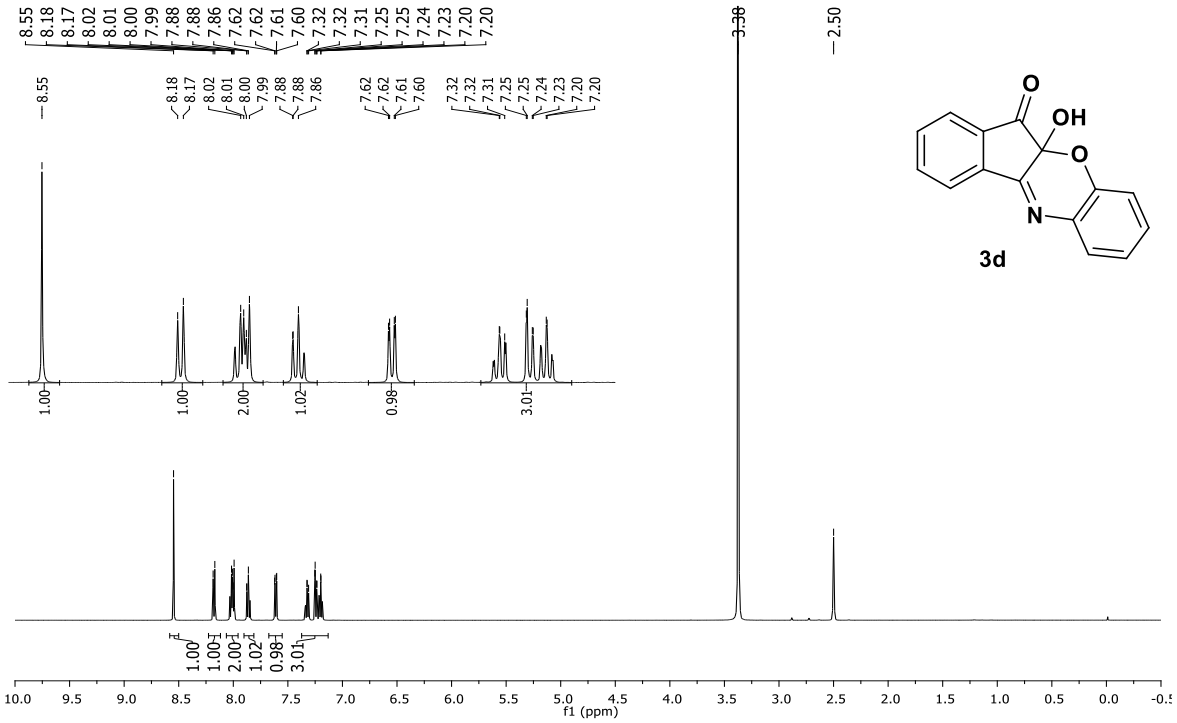
Ethyl 2-(6H-indolo[2,3-b]quinoxalin-6-yl)acetate (3o): White solid; yield 90%; m.p. 185-86 ^{0}C; **IR** (KBr) ν (cm^{-1}): 3054, 2976, 2359, 1950, 1732, 1587, 1475, 1417, 1357, 1213, 1112, 1019, 925, 866, 771, 737; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.49 (d, 1 H), 8.31 (d, 1 H), 8.11 (d, 1 H), 7.83 – 7.61 (m, 3 H), 7.49 – 7.30 (m, 2 H), 5.24 (s, 2 H), 4.24 (d, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 168.21, 145.70, 144.38, 140.55, 140.31, 139.87, 131.27, 129.50, 129.05, 127.92, 126.48, 122.99, 121.74, 119.97, 109.42, 62.00, 42.81, 14.27.

Ethyl 2-(9-chloro-6H-indolo[2,3-b]quinoxalin-6-yl)acetate (3p): White solid; yield 92%; m.p. 275-76 ^{0}C; **IR** (KBr) ν (cm^{-1}): 921, 2854, 2346, 2213, 1733, 1577, 1460, 1362, 1275, 1209, 1120, 1019, 952, 871, 811, 739; **^{1}H NMR** (500 MHz, $CDCl_3$) δ (ppm): 8.46 (s, 1 H), 8.29 (d, 1 H), 8.11 (d, 1 H), 7.83 – 7.60 (m, 3 H), 7.29 (d, 1 H), 5.22 (s, 2 H), 4.24 (q, 2 H), 1.26 (t, 3 H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ (ppm): 167.95, 145.78, 142.55, 140.79, 140.05, 139.15, 131.10, 129.67, 129.53, 128.00, 127.45, 126.81, 122.75, 121.19, 110.57, 62.12, 42.85, 14.27.

6.5 Spectral data of products



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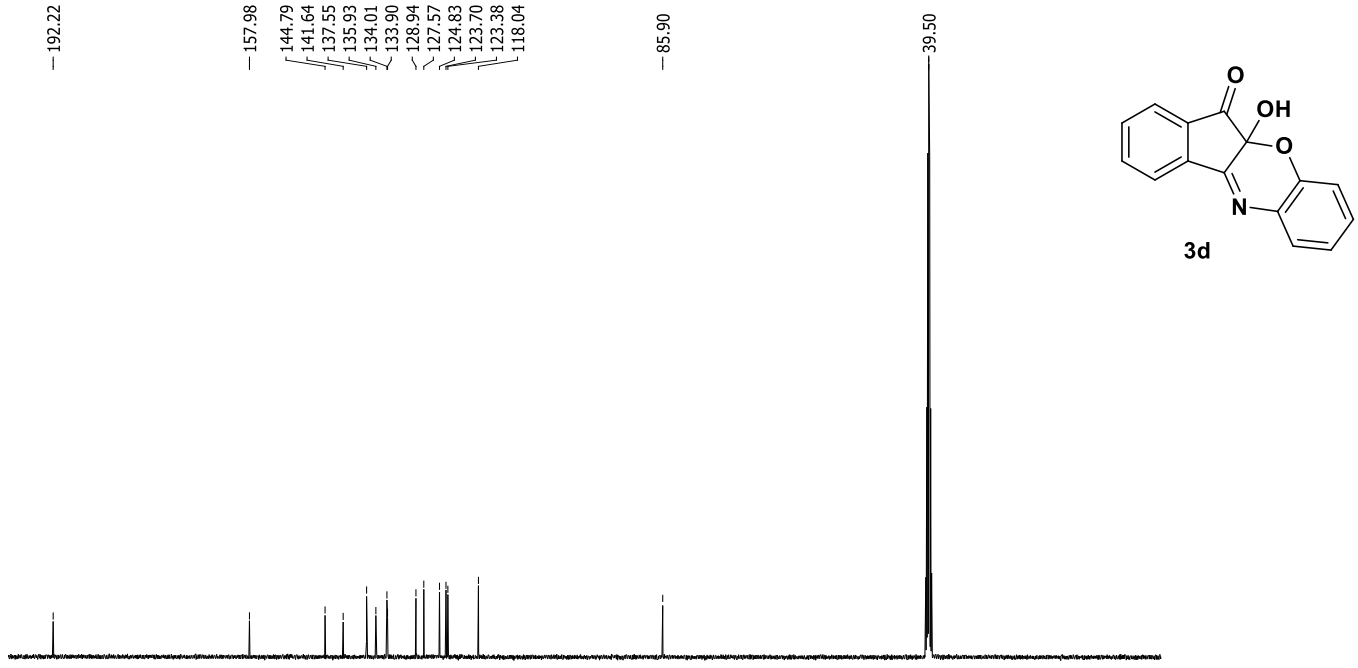
8.17
8.02
8.01
8.00
7.99
7.88
7.88
7.86
7.62
7.62
7.61
7.60
7.32
7.32
7.31
7.25
7.25
7.24
7.23
7.20
7.20
3.38
2.50
1.00
1.00
2.00
1.02
0.98
3.01
f1 (ppm)
O
OH
O
N
3d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157.98
144.79
141.64
137.55
135.93
134.01
133.90
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127.57
124.83
123.70
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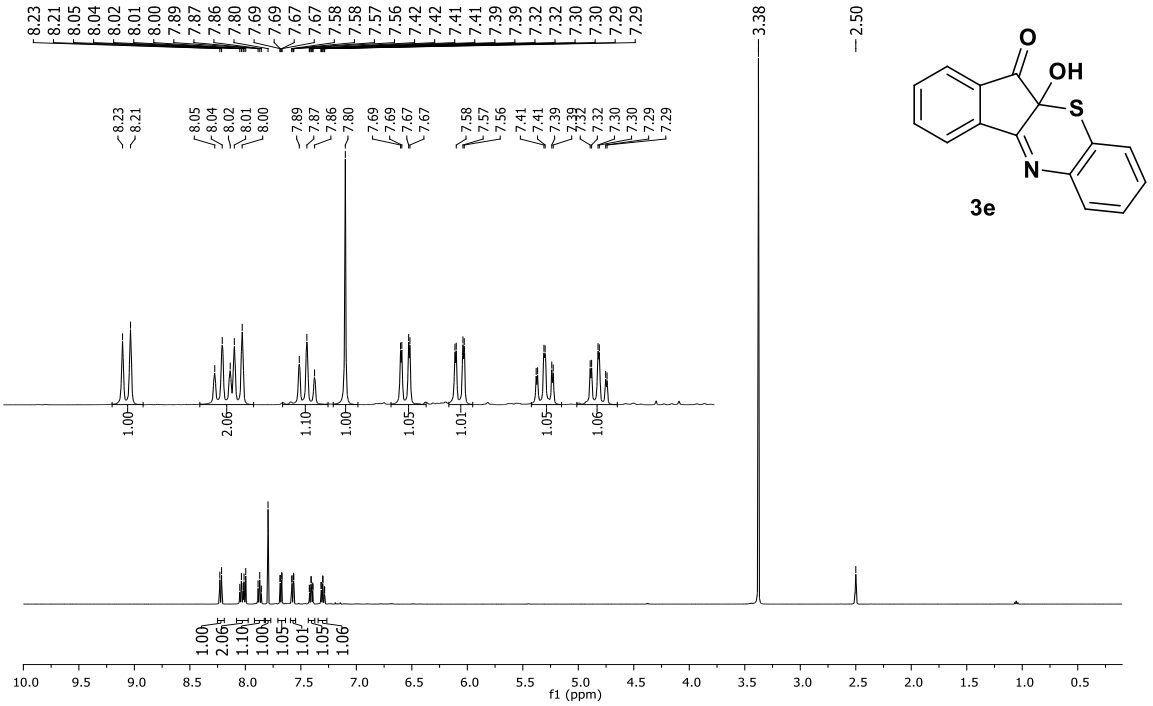
85.90
39.50
O
OH
O
N
3d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8.05
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8.02
8.01
8.00
7.89
7.87
7.86
7.80
7.69
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7.67
7.67
7.58
7.58
7.57
7.56
7.42
7.41
7.41
7.39
7.32
7.32
7.30
7.30
7.29
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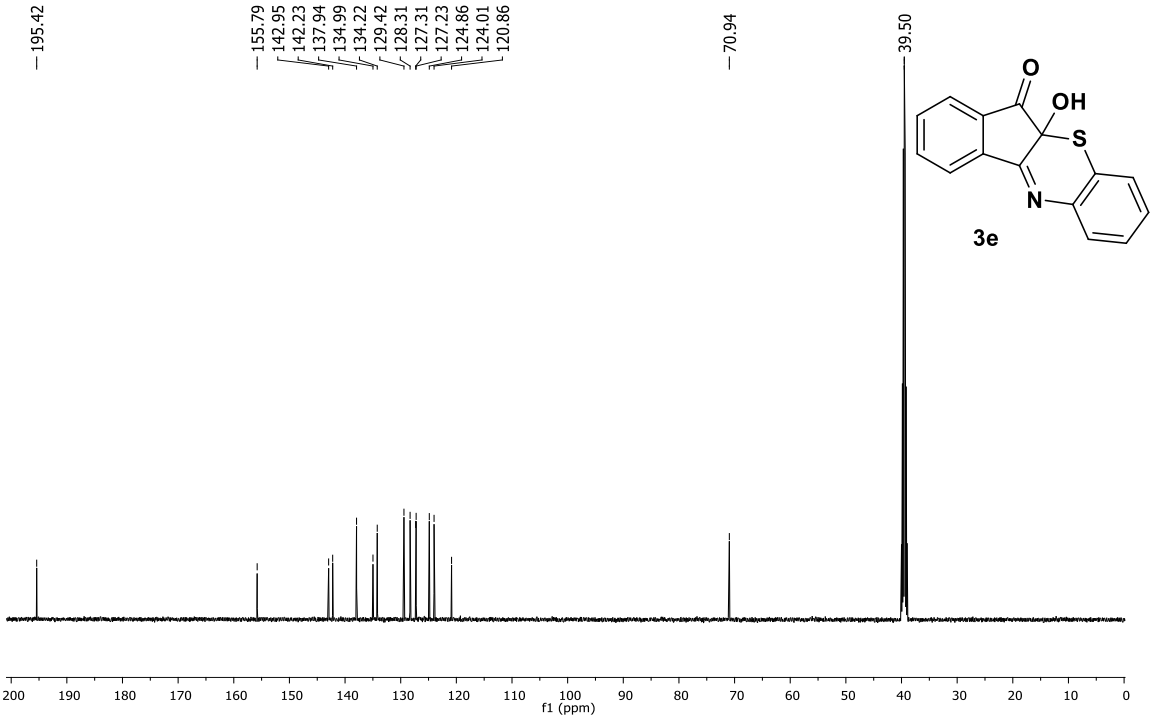
1.06
f1 (ppm)
O
OH
S
N
3e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142.95
142.23
137.94
134.99
134.22
129.42
128.31
127.31
127.23
124.86
124.01
120.86
70.94
39.50
f1 (ppm)
O
OH
S
N
3e

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