CHAPTER 2

A FACILE AND EFFICIENT MULTICOMPONENT ULTRASOUND-ASSISTED "ON WATER" SYNTHESIS OF BENZODIAZEPINE RING

A facile and efficient multicomponent ultrasound-assisted “on water” synthesis of benzodiazepine ring

2.1 Introduction

Recently, ultrasound irradiation has emerged as a clean and green method to speed up organic synthetic transformations [1-3]. The prominent advantages of ultrasound-assisted synthesis are high reaction rates, short reaction time, high yield, and mild reaction conditions. Actually, ultrasound radiation gives rise to acoustic cavitations to overcome the molecular attractive forces and to stimulate the mixing of molecules. This increases intimate contact among different molecules to form a highly reactive species and results in the acceleration of the reaction and improved product yields. This procedure is accomplished to stimulate several organic reactions [4-6] . In contrast to the conventional method, which affords thermal energy to the macro-system, the ultrasound-assisted process lessens reaction time, rises yield, reduces waste, and conserves energy by affording the activation energy to the microenvironment accentuates its greener impact.

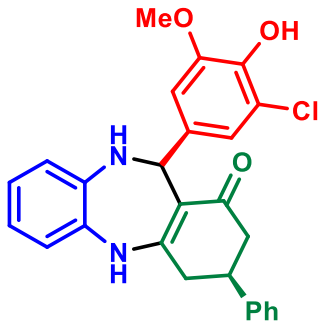
Water has attracted considerable attention from organic chemists as it is a nonhazardous, inexpensive, ecologically benign, readily available, non-flammable, harmless, and versatile solvent for many chemical reactions. The isolation of the product becomes very easy in water solvents because maximum organic compounds are not soluble in water. They may be obtained in pure form only by filtration and/or recrystallization without column

chromatography to avoid using hazardous solvents. “On water” synthesis is a distinctive theory of the increasing rate of organic reaction in the aqueous medium. Commonly, reactions in aqueous media involve the vigorous stirring of water-insoluble reagents due to the absence of organic co-solvents. The reason for higher yield in water is its dual behavior, i.e., as a solvent as well as a catalyst in organic reaction [7-11].

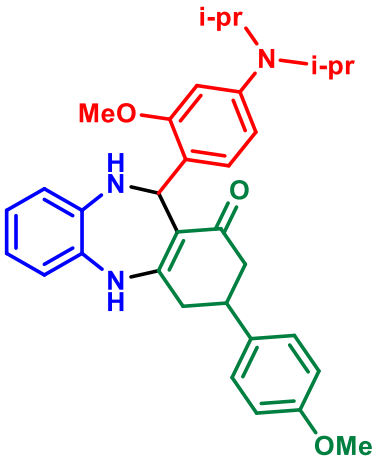
Due to their valued properties, multicomponent reactions have evolved as an effective and powerful tool in modern synthetic organic chemistry. Multicomponent reactions, which lead to fascinating heterocyclic scaffolds, are especially beneficial for developing various "drug-like" molecules [12].

Spiro compounds are an essential group of naturally occurring substances with high biological characteristics. The framework of spirooxindole is a fundamental component of many pharmacological agents and natural alkaloids such as horsfiline, mitraphylline, spirotryprotatin, gelsemine, and others [13-19]. Spirooxindoles act as anti-cancer, anti-viral, antibacterial, and anti-fungal agents. These are the major concerns for medicinal, modern organic, and natural product chemistry. The structural rigidity of spirooxindole and spirocarbon conformation induces biological activities, i.e., NITD 609 and MI77301 are used in malaria diagnosis and cancer therapy, respectively.

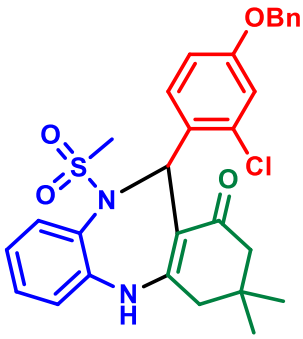
Among *N*-heterocyclic compounds, benzodiazepines are the most significant compounds, which developed extensive attention in medicinal chemistry due to their well-known biological and pharmacological activities [20-27] (**Figure 2.1**).



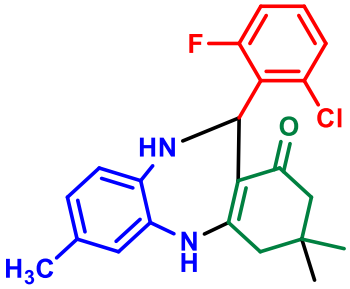
HIV protease inhibitor



Cystathionine Synthase inhibitor



HCV NS5B polymerase inhibitor



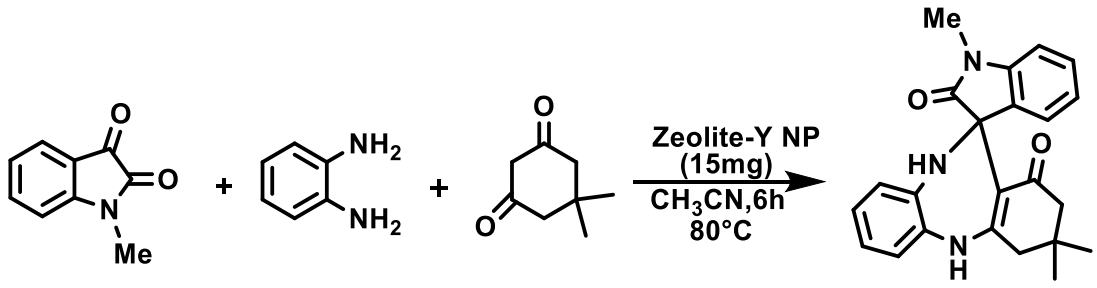
Neoromedin B receptor antagonist

Figure 2.1 Some biologically active compounds having 1, 4-benzodiazepine scaffold

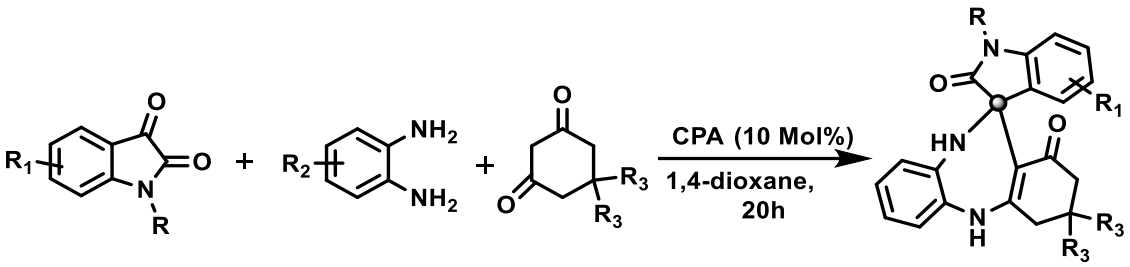
Benzodiazepine rings are one of the most extensively recommended classes of psychotropics due to their significant central nervous system (CNS) sedative activity [28]. Furthermore, benzodiazepine rings containing moiety has found to possess encouraging pharmacological properties and biological activities such as sedative, HIV-1 protease inhibiting [29, 30], anti-

inflammatory [31], anti-depressive [32-35], antibiotic [36], antifungal [37, 38], insecticidal [39], anticoagulant [40-43], analgesic [44], and antiepileptic [45]. 1,4-Benzodiazepines are used to treat anxiety, insomnia, muscle spasms, alcohol withdrawal syndrome, and avoid seizures [46]. Such compounds are also used as dyes for acrylic fibres [47, 48] and in photography. Due to their great importance, several synthetic approaches have been developed **(Scheme 2.1 and 2.2)**. Previously O. S. Popovaa et al. [49] described a successive two-step reaction for synthesizing benzodiazepine rings using trifluoroacetic acid as a catalyst. Recently, Wang Shulianga et al. [50] developed a green synthesis of such a ring via a microwave-assisted multi-component reaction of isatin, diphenylamine, and tetronic acid using water as a solvent and acetic acid as a catalyst. Though, this method is associated with the use of catalyst, i.e., acetic acid.

Previous methodology

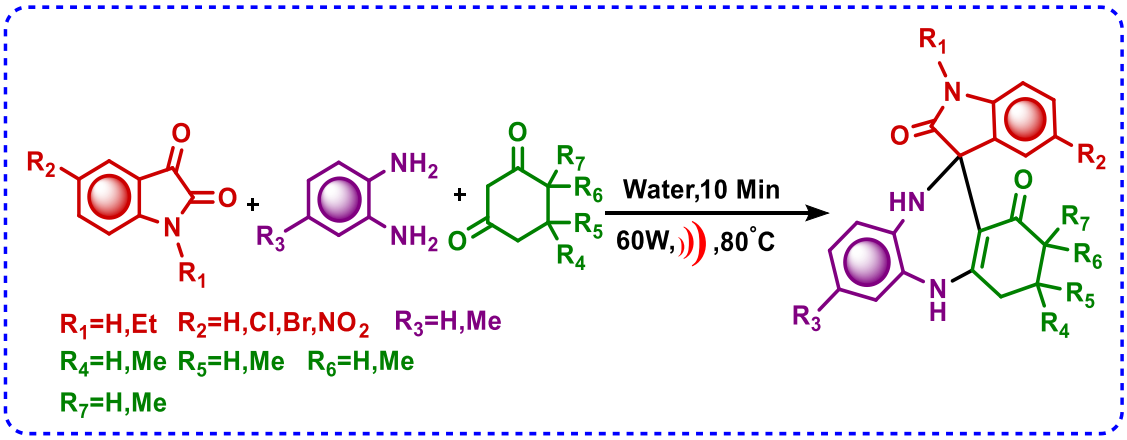


Scheme 2.1 Kajal De et al.—ChemCatChem https://doi.org/10.1002/cctc.201701487



Scheme 2.2 Wang, Shi et al.—Chem. Eur. J. https://doi.org/10.1002/chem.201403868

Current Work:



Scheme 2.3 Current procedure for the synthesis of 1, 4- benzodiazepine ring

In spite of their potential utility, most of these synthetic processes suffer from one or more serious drawbacks, such as substantial amounts of waste materials, laborious and complex work-up and purification, strongly acidic conditions, the occurrence of side reactions, low yields, high temperature, prolonged reaction time and the use of expensive reagents and a metal catalyst.

So far, the literature survey does not reveal any green protocol via ultrasonic-assisted "on water" synthesis of benzodiazepine ring. However, there is a necessity for the development of a highly efficient synthetic protocol to construct benzodiazepine ring-containing compounds.

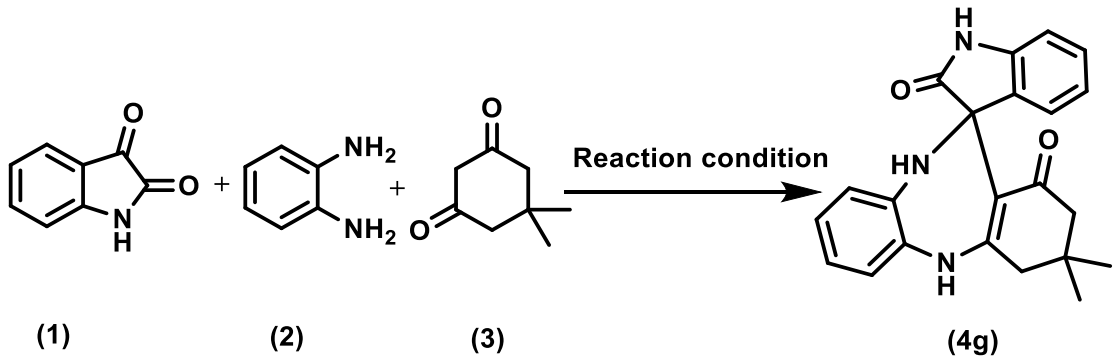
In continuation to our research work on the synthesis of biologically interesting heterocyclic moieties [51-55] and in view of the above, it was thought worthwhile to synthesize some benzodiazepine rings by multicomponent reaction of isatin, diphenylamine, and 1,3-diketone under ultrasound irradiation in water with excellent yield (95%) **(Scheme 2.3)**.

2.2 Results and discussion

Our study was commenced by carrying out a one-pot multicomponent reaction of isatin **1** (1 mmol), 1,2-phenylenediamine **2** (1 mmol), and 5,5-dimethylcyclohexane-1,3-dione **3** (1 mmol) under conventional heating at 100°C in water without using any catalyst and amazingly 68 % yield was obtained. Surprisingly, when a similar reaction was carried out under ultrasonic irradiation (instrument model 750W, 220V), the product was achieved with an excellent yield of 95%. To find the optimized reaction condition, various reaction parameters such as solvent effect, type of catalyst, and molar ratio were investigated by taking model reaction of isatin **1** (1 mmol) 1, 2-phenylenediamine **2** (1 mmol), and 5,5-dimethyl cyclohexane-1,3-dione **3** (1 mmol) under ultrasound irradiation at 80° C in water. First, the reaction was carried out without solvent and catalyst; as expected, no product was obtained

even after 24 hrs. To investigate the solvent effect, the reaction was carried out in both non-polar and polar solvents (**Table 2.1**). A perusal of the table indicates that the product was not obtained with a non-polar solvent. In contrast, the product was obtained with a polar solvent like ethanol, methanol, and acetonitrile to a few extents. Furthermore, the product yield was good when the EtOH and EtOH:H_2O in ratio 1:1 and1:2 were used as solvents system, but there was a decrease in yield when the EtOH:H_2O ratio was 2:1 **(Table 2.1, Entries 5,6,7 and 8)**. This result encouraged us to do the reaction in water. The effect of various catalysts was examined, and the results are summarized **(Table 2.1)**. None of the catalysts improved the yield of the product. The results demonstrate the catalytic role of water in this reaction.

Table 2.1 Optimization reaction for the model reaction **4g**[a]



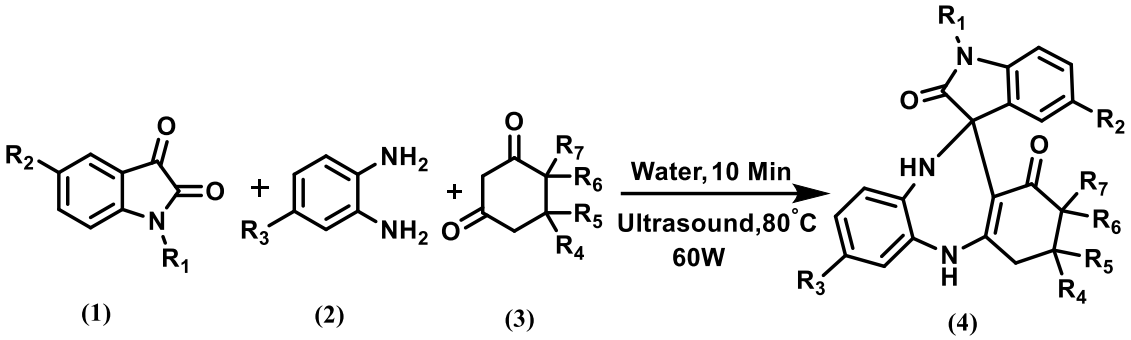
Entry	Catalyst(10mol%)	Solvent	Time (min)	Yield %[b]
1.	-	-	24 h	No reaction
2.	-	n-Hexane	50	No reaction
3.	-	Xylene	40	No reaction
4.	-	CCl_4	40	No reaction
5.	-	CH_3CH_2OH	15	38
6.	-	$C_2H_5OH:H_2O$ 1:1	15	48
7.	-	1:2	15	55
8.	-	2:1	15	43
9.	-	CH_3OH	15	35
10.	-	CH_3CN	15	26
11.	HOAc	H_2O	15	50
12.	p-TSA	H_2O	15	59
13.	TFA	H_2O	15	61

14.	$ZnCl_2$	H_2O	15	46
15.	HCl	H_2O	15	43
16.	Fe_2O_3	H_2O	15	64
17.	TiO_2	H_2O	15	51
18.	$AlCl_3$	H_2O	15	68
19.	NH_2SO_3H	H_2O	15	74
20.	**–**	**H_2O**	**10**	**95**

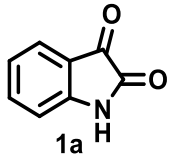
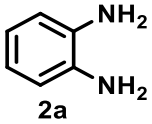
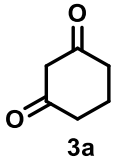
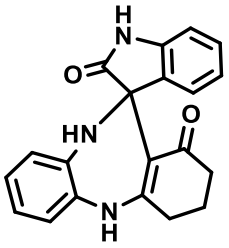
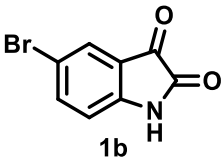
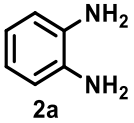
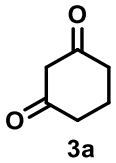
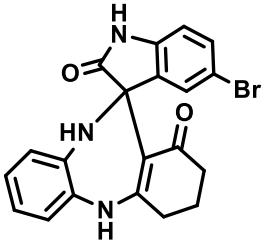
[a]Reaction condition: Isatin(1mmol), 1,2-phenylenediamine(1mmol),and 5,5-dimethylcyclohexane-1,3- dione (1mmol), under ultrasonication.
[b]Isolated yield after recrystallization.

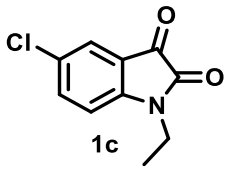
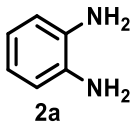
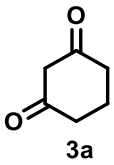
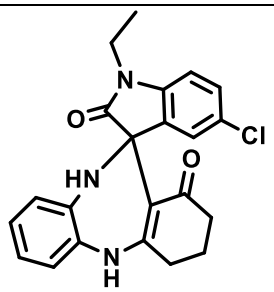
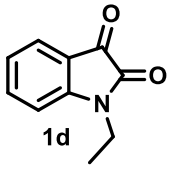
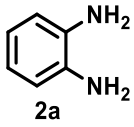
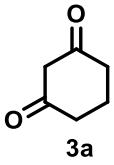
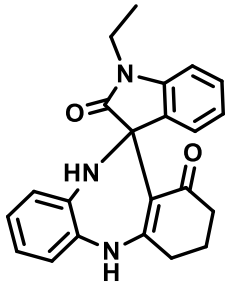
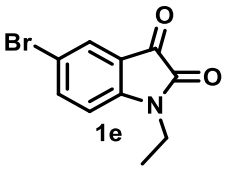
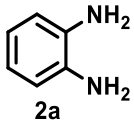
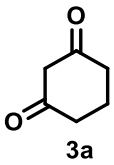
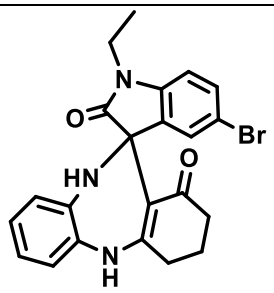
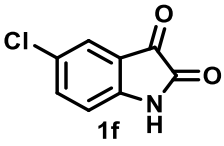
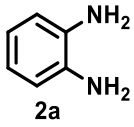
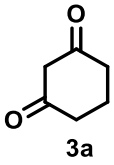
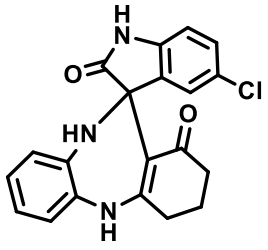
Several isatin derivatives such as isatin (**1a**), 5-bromoisatin **(1b)**, 5-chloro-1-ethylisatin **(1c)**, 1-ethylisatin **(1d)**, 5-bromo-1-ethylisatin **(1e)**, 5-chloroisatin **(1f)**, 5-nitroisatin **(1g)**, 1, 2-phenylenediamine **(2a)** 4-methyl-phenylenediamine (**2b)** were allowed to react with 1,3-cyclohexanedione (**3a)** 5,5-dimethylcyclohexane-1,3-dione **(3b)** and 4,4-dimethylcyclohexane-1,3-dione **(3c)** to validate the general applicability of this procedure under the optimized reaction condition. The results are summarized in **(Table 2.2)**. In most cases, the yield of products was good.

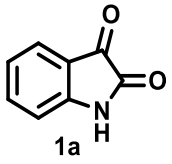
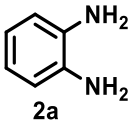
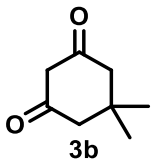
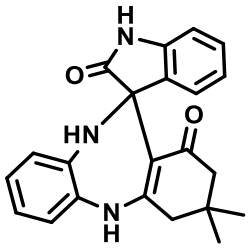
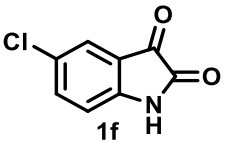
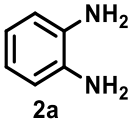
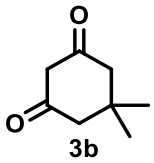
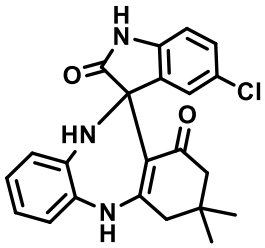
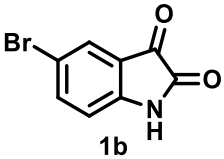
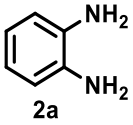
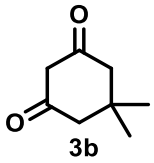
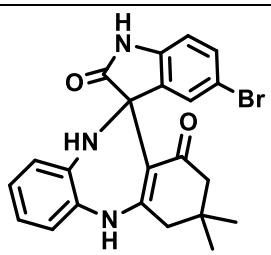
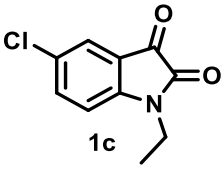
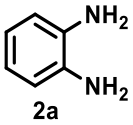
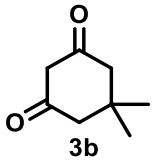
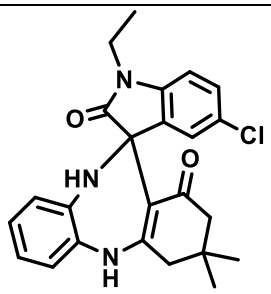
Table 2.2 Investigation of substrate scope for the synthesis of 1,4-benzodiazepine ring[a].

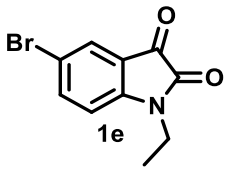
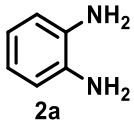
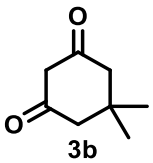
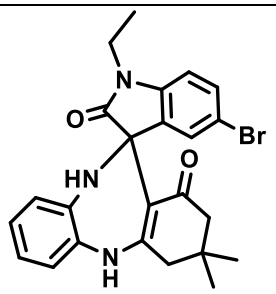
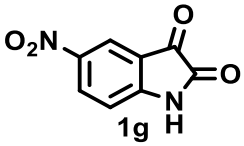
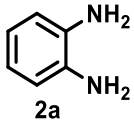
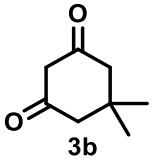
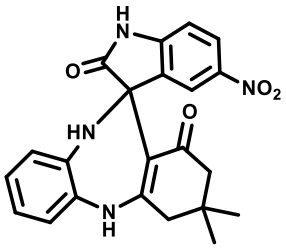
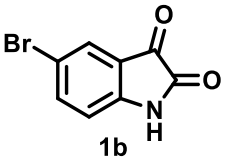
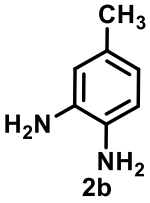
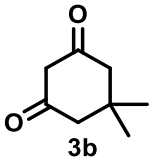
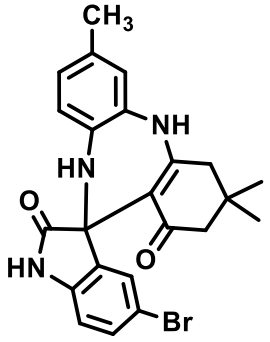
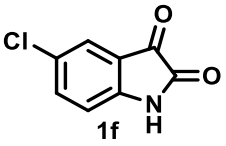
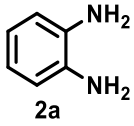
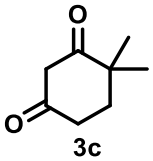
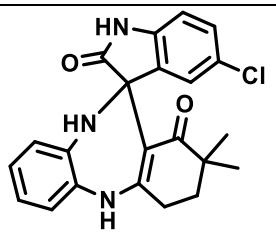


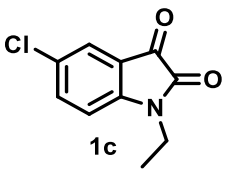
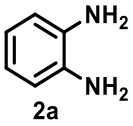
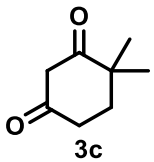
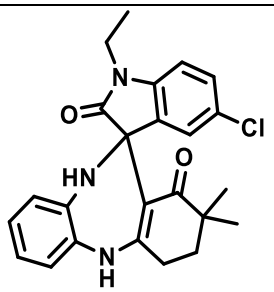
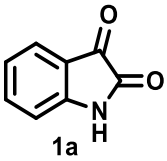
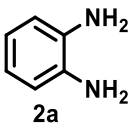
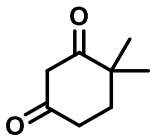
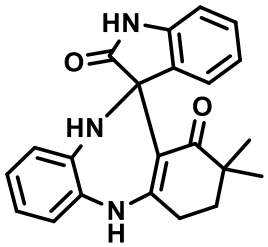
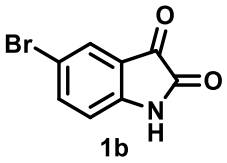
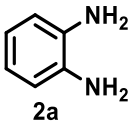
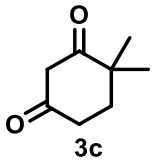
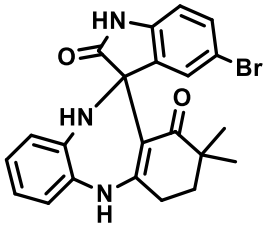
(1) (2) (3) (4)

Entry	1	2	3	4[a]	Yield[b] (%)
4a					89
4b					89

4c	 1c	 2a	 3a		90
4d	 1d	 2a	 3a		89
4e	 1e	 2a	 3a		90
4f	 1f	 2a	 3a		87

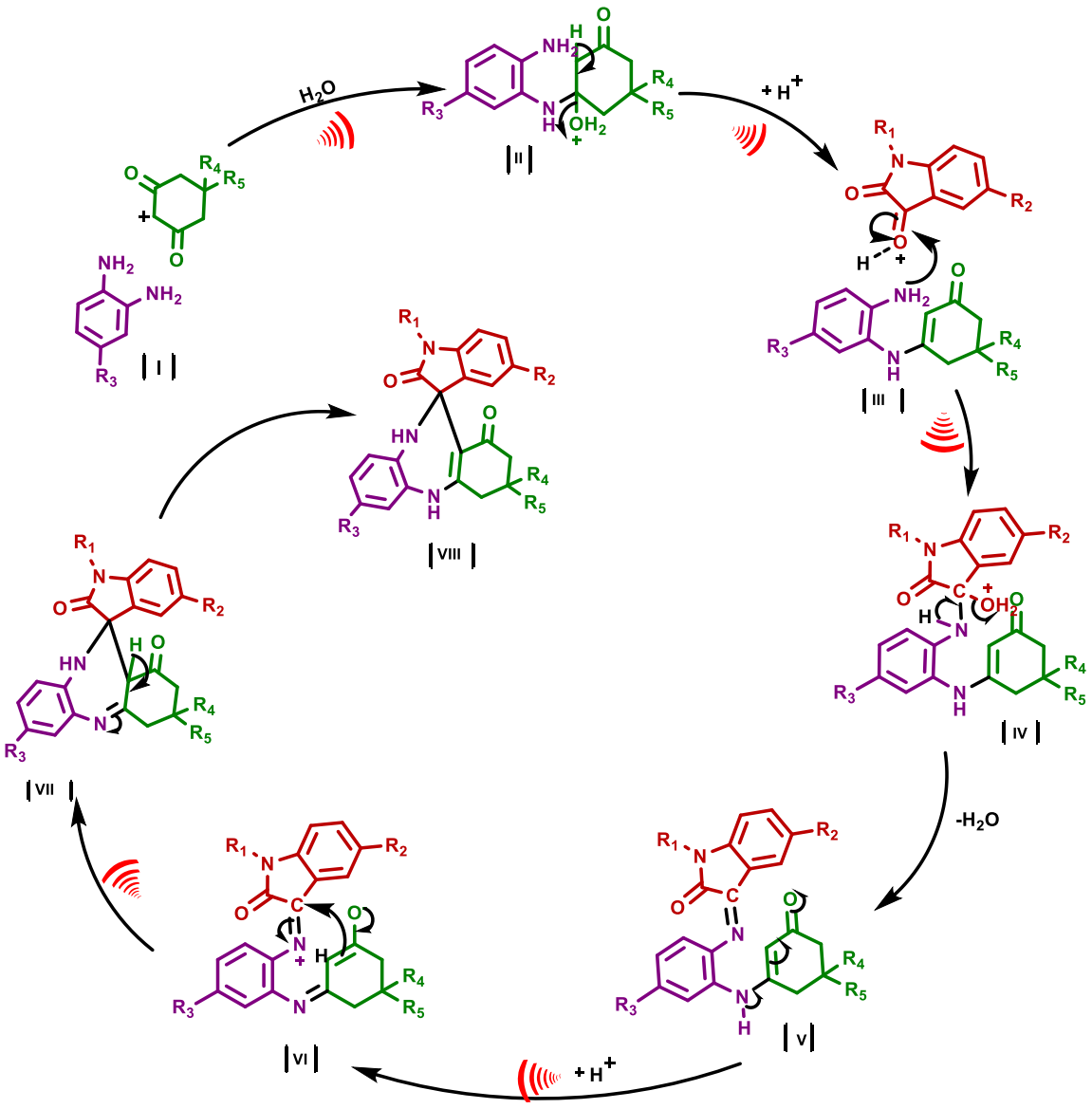
4g	 1a	 2a	 3b		95
4h	 1f	 2a	 3b		92
4i	 1b	 2a	 3b		94
4j	 1c	 2a	 3b		90

4k	 1e	 2a	 3b		91
4l	 1g	 2a	 3b		85
4m	 1b	 2b	 3b		90
4n	 1f	 2a	 3c		87

4o	 1c	 2a	 3c		89
4p	 1a	 2a	 3c		91
4q	 1b	 2a	 3c		90

[a]Reaction condition: Isatin(1mmol), 1,2-phenylenediamine(1mmol),and 5,5-dimethylcyclohexane-1,3- dione (1mmol), in water under ultrasonication.
[b]Isolated yield after recrystallization

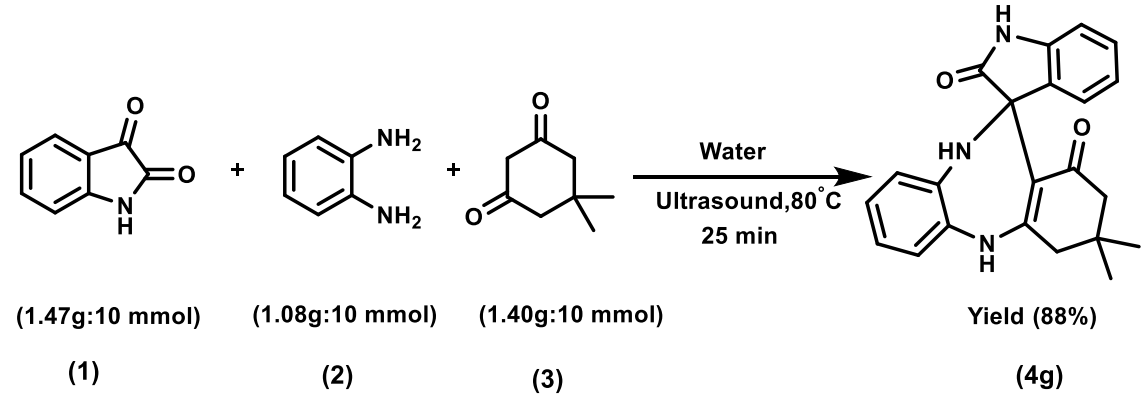
The mechanism is proposed **(Scheme 2.4)** on the basis of product isolation and reported literature. The condensation reaction of 1, 2-phenylenediamine with 1, 3-diketone in the presence of water results in intermediate formation **[III]**. This intermediate attacks at carbonyl carbon -3 of isatin to give intermediate **[IV]**, which on intramolecular cyclization gives the final product **[VIII]**.



Scheme 2.4 Proposed mechanism for the synthesis of benzodiazepine ring

2.3 Gram-Scale synthesis of benzodiazepine ring

Moreover, the practicality was validated by carrying out the model reaction on a gram scale (**Scheme 2.5**). The reaction mixture of isatin **1**(10 mmol, 1.47 g) 1,2-phenylenediamine **2**(10 mmol, 1.08 g), and 5,5-dimethyl cyclohexane-1,3- dione **3**(10 mmol, 1.40 g) in water was stirred and heated at 80°C for 25 min under ultrasonic irradiations (monitored by TLC). The ice-cold water was added to this reaction mixture and stirred for five minutes. A solid precipitate was obtained, which was washed with water and recrystallized with ethanol to give a pure product.



Scheme 2.5 Gram-scale synthesis of benzodiazepine ring under ultrasound irradiation

2.4 Conclusion

In conclusion, green and efficient synthesis of benzodiazepine ring was developed *via* multicomponent reaction of isatin, 1, 2-phenylenediamine, 5,5-dimethylcyclohexane-1,3-

dione under ultrasonic irradiation in water. The present method provides good to excellent yield in a short reaction time. This method is also valid for gram-scale reactions.

2.5 Experimental section

2.5.1 Typical procedure for preparation of compound (4)

A mixture of isatin **1**(1 mmol), 1,2 phenylenediamine **2**(1 mmol), and dimedone **3**(1 mmol) was mixed with a minimum amount of water in a 50-ml beaker and subjected to ultrasound irradiation with 60 Watt power at 80 ˚C for 10 min (model no.PKS-750F) . The progress of the reaction was measured by thin-layer chromatography (ethyl acetate: hexane 1:3). After the completion of the reaction, the ice-cold water was added to the reaction mixture and stirred for 5 min. The solid precipitate was collected by filtration, washed with water, and recrystallized with ethanol to give the desired product in good yield.

2.5.2 Analytical Data

3,4,5,10-Tetrahydrospiro[dibenzo[b,e][1, 4]diazepine-11, 3′-indoline]-1,2′(2H)-dione [4a]

White solid, yield 89%, m. p. 258 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.17 (s, 1H), 9.12 (s, 1H), 7.12 (d, J=7.8 Hz, 1H), 7.00 (t, J=7.6 Hz, 1H), 6.85 (t, J=7.5 Hz, 1H), 6.74 (d, J=7.7 Hz, 2H), 6.64 (d, J=7.8 Hz, 1H), 6.54 (t, J=7.5 Hz, 1H), 6.19 (d, J=7.3 Hz, 1H), 5.44 (s, 1H), 2.71 (d, 2H), 2.16–1.83 (m, 4H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 192.89, 176.64,

156.79, 143.29, 137.98, 135.49, 133.57, 127.54, 123.67, 123.14, 122.21, 121.99, 120.34, 120.27, 109.79, 109.28, 66.19, 40.44, 40.36, 40.27, 40.20, 40.11, 39.94, 39.77, 39.61, 39.44, 36.72, 32.02, 21.09. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3242, 1954, 1661, 1583, 1475, 1252, 1184, 889 cm^{-1}; **Anal. calc. for $C_{20}H_{17}N_3O_2$**: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.62; H, 5.25; N, 12.81.

5′-Bromo-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4b]

White solid, yield 89%, m. p. 236 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.31 (s, 1H), 9.16 (s, 1H), 7.19 (m, J=8.2 Hz, 1H), 7.14 (d, J=7.9 Hz, 1H), 6.90 (t, J=7.6 Hz, 1H), 6.79 (t, J=7.5 Hz, 1H), 6.72 (d, J=8.2 Hz, 1H), 6.66 (d, J=7.7 Hz, 1H), 6.25 (s, 1H), 5.54 (s, 1H), 2.74–2.70 (m, 2H), 2.09–2.07 (m, 2H), 1.89–1.85 (m, 2H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 193.23, 176.21, 157.33, 142.64, 137.81, 137.67, 133.59, 130.11, 124.94, 124.62, 123.21, 122.45, 120.55, 112.02, 111.07, 109.04, 66.39, 40.46, 40.30, 40.13, 39.96, 39.79, 39.63, 39.46, 36.62, 31.96, 20.99. **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3266, 1946, 1662, 1578, 1456, 1258, 1195, 866 cm^{-1}; **Anal. Calc. for $C_{20}H_{16}N_3O_2Br$**: C, 58.55; H, 3.93; N, 10.24 Found: C, 58.65.; H, 3.98; N, 10.31.

5′-Chloro-1′-ethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4c]

White solid, yield 90%, m. p. 225 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.20 (s, 1H), 7.22–7.10 (m, 2H), 6.97 (d, J=8.3 Hz, 1H), 6.91 (s, 1H), 6.80 (s, 1H), 6.63 (d, J=7.8 Hz, 1H), 6.16

(s, 1H), 5.53 (s, 1H), 2.73 (t, 2H), 2.07 (m, 2H), 1.89–1.85 (m, 2H), 1.22 (m, 2H), 1.06 (t, 3H).**^{13}C NMR (126 MHz, DMSO-d^6)** δ 193.20, 174.39, 157.31, 142.69, 137.58, 136.71, 133.56, 127.73, 127.35, 124.71, 123.07, 122.35, 122.10, 121.81, 120.62, 109.07, 65.88, 56.50, 40.46, 40.30, 40.13, 39.96, 39.79, 39.63, 39.46, 31.95, 19.07, 18.95, 12.00. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3211, 1965, 1625, 1549, 1448, 1381, 1118, 866 cm^{-1}. **Anal. Calc. for $C_{22}H_{20}N_3O_2Cl$**: C, 67.09; H, 5.12; N, 10.67. Found: C, 67.18; H, 5.22; N, 10.72.

1′-Ethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4d]

White solid, yield 89%, m. p. 281 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.15 (s, 1H), 7.12 (d, J=7.9 Hz, 1H), 7.08 (t, J=7.6 Hz, 1H), 6.91 (d, J=7.7 Hz, 1H), 6.85 (t, J=7.5 Hz, 1H), 6.73 (t, J=7.4 Hz, 1H), 6.59 (t, J=7.5 Hz, 2H), 6.21 (d, J=7.2 Hz, 1H), 5.39 (s, 1H), 3.69 (m, 2H), 2.71 (t, 2H), 2.50 (s, 2H), 1.85–1.83 (m, 2H), 1.23 (t, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.64, 174.39, 156.52, 143.34, 137.51, 134.41, 133.16, 127.39, 123.43, 122.73, 121.77, 121.71, 120.41, 109.46, 107.88, 65.42, 40.01, 39.84, 39.67, 39.51, 39.34, 39.17, 39.01, 36.24, 34.13, 31.65, 30.79, 20.70, 11.84. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3145, 1925, 1645, 1523, 1446, 1224, 1121, 872 cm^{-1}; **Anal. Calc. for $C_{22}H_{21}N_3O_2$**: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.61; H, 5.95; N, 11.76.

5′-Bromo-1′-ethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4e]

White solid, yield 90%, m. p. 225 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 9.22 (s, 1H), 7.18–7.11 (m, 2H), 6.97 (d, J=8.3 Hz, 1H), 6.93–6.88 (m, 1H), 6.79 (dd, J=7.4, 6.3 Hz, 1H), 6.62 (dd, J=7.9, 1.2 Hz, 1H), 6.15 (d, J=2.2 Hz, 1H), 5.56 (s, 1H), 3.71 (m, 2H), 2.73 2.06–1.93 (m, 1H), 1.87 (d, 2H), 1.21 (t, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 193.15, 174.35, 157.26, 142.66, 137.58, 136.70, 133.53, 127.31, 124.68, 124.02, 123.18, 122.41, 121.94, 120.60, 109.58, 109.05, 65.85, 40.46, 40.38, 40.29, 40.21, 40.12, 40.05, 39.96, 39.79, 39.62, 39.46, 36.51, 34.64, 31.94, 20.97, 12.09). . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3173, 1981, 1676, 1577, 1467, 1245, 1137, 858 cm^{-1}. **Anal. Calc. for $C_{22}H_{20}N_3O_2Br$**: C, 60.28; H, 4.60; N, 9.59. Found: C, 60.38; H, 4.72; N, 9.65.

5′-Chloro-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4f]

White solid, yield 87%, m. p. 189 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.33 (s, 1H), 9.18 (s, 1H), 7.14 (d, J=7.8 Hz, 1H), 7.06 (dd, J=8.2, 2.2 Hz, 1H), 6.89 (d, J=7.2 Hz, 1H), 6.79 (t, J=7.2 Hz, 2H), 6.66 (d, J=7.7 Hz, 1H), 6.13 (d, J=2.0 Hz, 1H), 5.58 (s, 1H), 2.73– 2.71 (m, 2H), 2.51 (s, 2H), 1.88–1.86 (m, 2H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 193.25, 176.32, 157.30, 142.23, 137.40, 133.56, 127.26, 124.17, 123.96, 123.24, 122.33, 122.05, 120.53, 114.29, 110.57, 109.03, 66.37, 36.62, 31.95, 20.98. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3242, 1942, 1656, 1572, 1442, 1252, 1185, 887 cm^{-1}. **Anal. Calc. for $C_{20}H_{16}N_3O_2Cl$**: C, 65.67; H, 4.41; N, 11.49. Found: C: 65.72; H: 4.45; N: 11.55.

3,3-Dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4g]

White solid, yield 95%, m. p. 275 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.21 (s, 1H), 9.10 (s, 1H), 7.18 (d, J=7.9 Hz, 1H), 7.05 (t, J=7.6 Hz, 1H), 6.90 (t, J=7.5 Hz, 1H), 6.79 (t, J=9.0 Hz, 2H), 6.69 (d, J=7.8 Hz, 1H), 6.59 (t, J=7.4 Hz, 1H), 6.24 (d, J=7.3 Hz, 1H), 5.52 (s, 1H), 2.65 (d, 2H), 2.15–1.91 (m, 2H), 1.15 (s, 3H), 1.01 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 192.68, 176.57, 159.79, 154.87, 143.34, 137.84, 135.54, 133.60, 127.56, 123.68, 123.14, 122.08, 121.96, 120.37, 120.23, 109.35, 108.66, 66.40, 50.19, 45.37, 40.43, 40.27, 40.10, 39.93, 39.76, 39.60, 39.43, 31.90, 28.06**.** . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3259, 1947, 1629, 1551, 1487, 1233, 1145, 861 cm^{-1}. **Anal. Calc. for $C_{22}H_{21}N_3O_2$**: C, 73.52; H, 5.89; N, 11.69. Found: C, 73.58; H, 5.96; N, 11.78.

5′-Chloro-3,3-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4h]

White solid, yield 92%, m. p. 285 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.32 (s, 1H), 9.11 (s, 1H), 7.18 (dd, J=8.2, 2.0 Hz, 1H), 7.13 (d, J=7.9 Hz, 1H), 6.89 (s, 1H), 6.78 (s, 1H), 6.71 (d, J=8.2 Hz, 1H), 6.66 (d, J=7.9 Hz, 1H), 6.21 (s, 1H), 5.58 (s, 1H), 2.61 (d, 2H), 1.96 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 192.53, 175.69, 154.92, 142.27, 137.44, 137.13, 133.19, 129.67, 124.22, 123.53, 122.88, 121.90, 120.14, 111.50, 110.82, 107.45, 66.18, 49.60, 44.81, 40.11, 40.02, 39.94, 39.85, 39.78, 39.68, 39.61, 39.52, 39.35, 39.18, 39.02, 31.34, 27.85, 27.28, 18.61. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3244, 1951, 1637,

1546, 1557, 1264, 1171, 852 cm^{-1};**Anal. Calc. for $C_{22}H_{21}N_3O_2$**: C, 67.09; H, 5.12; N, 10.67. Found: C, 67.18; H, 5.22; N, 10.74.

5′-Bromo-3,3-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4i]

White solid, yield 94%, m. p. 295 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.32 (s, 1H), 9.11 (s, 1H), 7.16 (m, 2H), 6.90 (t, J=7.3 Hz, 1H), 6.79 (s, 1H), 6.72 (d, J=8.1 Hz, 1H), 6.66 (d, J=7.6 Hz, 1H), 6.22 (s, 1H), 5.57 (s, 1H), 2.62 (s, 2H), 1.97 (m, 2H), 1.10 (s, 3H), 0.99 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.97, 176.13, 155.36, 142.69, 137.87, 137.55, 133.63, 130.10, 124.66, 123.97, 123.32, 122.34, 120.57, 111.94, 111.26, 107.89, 66.62, 56.50, 50.04, 40.45, 40.29, 40.21, 40.12, 39.95, 39.79, 39.62, 39.45, 31.77, 27.72, 19.02. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3266, 1948, 1644, 1551, 1478, 1251, 1165, 859 cm^{-1}; **Anal. Calc. for $C_{22}H_{20}N_3O_2Br$**: C, 60.28; H, 4.60; N, 9.59. Found: C, 60.35; H, 4.73; N, 9.68.

5′-Chloro-1′-ethyl-3,3-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4j]

White solid, yield 90%, m. p. 240 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.14 (s, 1H), 7.19–7.12 (m, 2H), 6.98 (d, J=8.3 Hz, 1H), 6.94–6.88 (m, 1H), 6.80 (t, J=6.9 Hz, 1H), 6.63 (d, J=6.9 Hz, 1H), 6.14 (d, J=2.1 Hz, 1H), 5.55 (s, 1H), 3.71 (m, 2H), 2.63 (s, 2H), 1.90-2.03 (m, 2H), 1.23 (t, 3H), 1.10 (s, 3H), 0.98 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.99, 174.32, 155.37, 142.73, 137.47, 136.78, 133.58, 127.36, 124.67, 123.95, 123.36, 121.93, 121.65, 120.66, 109.76, 107.95, 66.09, 49.94, 45.27, 40.46, 40.30, 40.13, 39.96, 39.80, 39.63, 39.46, 31.84, 28.15, 27.85, 27.72, 12.01. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3261, 1968, 1642, 1547,

1465, 1237, 1165, 891 cm^{-1}. **Anal. Calc. for $C_{24}H_{24}N_3O_2Cl$**: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.39; H, 5.88; N, 9.98.

5′-Bromo-1′-ethyl-3,3-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4k]

White solid, yield 91%, m. p. 225 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.15 (s, 1H), 7.34–7.06 (m, 2H), 6.97 (d, J=8.3 Hz, 1H), 6.90 (s, 1H), 6.79 (s, 1H), 6.64 (s, 1H), 6.13 (d, J=2.1 Hz, 1H), 5.58 (s, 1H), 3.80–3.61 (m, 2H), 2.62 (s, 2H), 1.99–1.89 (m, 2H), 1.22 (t, 3H), 1.09 (s, 3H), 0.97 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.96, 174.30, 155.34, 142.71, 137.48, 136.78, 133.57, 127.34, 124.66, 124.05, 123.21, 122.40, 121.78, 120.66, 109.69, 107.93, 66.08, 49.94, 45.25, 40.46, 40.29, 40.13, 39.96, 39.79, 39.62, 39.46, 34.65, 31.85, 28.20, 27.78, 12.10. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3271, 1958, 1647, 1537, 1455, 1232, 1169, 888 cm^{-1};**Anal. Calc. for $C_{24}H_{24}N_3O_2Br$**: C, 61.81; H, 5.19; N, 9.01. Found: C, 61.95; H, 5.59; N, 9.78.

3,3-Dimethyl-5′-nitro-3,4,5,10-tetrahydrospiro- [dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4l]

White solid, yield 85%, m. p. 240 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.95 (s, 1H), 9.23 (s, 1H), 8.04 (m, J=8.6, Hz, 1H), 7.18 (d, J=7.8 Hz, 1H), 6.98–6.95 (m, 2H), 6.92 (t, J=7.5 Hz, 1H), 6.78 (t, J=7.4 Hz, 1H), 6.63 (d, J=7.7 Hz, 1H), 5.73 (s, 1H), 2.69 – 2.61 (m, 2H), 1.97 (m, 2H), 1.10 (s, 3H), 0.99 (s, 3H). **^{13}CNMR (126 MHz, DMSO-d^6) δ** 192.85, 176.33, 155.53, 149.69, 140.51, 136.92, 135.73, 133.31, 124.99, 123.84, 122.92, 122.27, 120.41, 116.50, 108.93, 106.88, 65.84, 49.41, 44.73, 40.02, 39.85, 39.78, 39.69, 39.52, 39.35, 39.19,

39.02, 31.34, 27.94, 27.11. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3296, 1988, 1674, 1581, 1498, 1279, 1191, 876 cm^{-1}; **Anal. calcd. for $C_{22}H_{20}N_4O_4$**; C: 65.34; H: 4.98; N: 13.85%. Found: C: 65.42; H: 4.88; N: 13.94%.

5′-Bromo-7-methyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4m]

White solid, yield 90%, m. p. 185 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.29 (s, 1H), 9.20–9.03 (m, 1H), 7.18 (m, 1H), 7.01 (d, J=8.1 Hz, 1H), 6.70 (m, 2H), 6.48 (s, 1H), 6.27 (m, 1H), 5.46 (s, 1H), 2.70 (t, 2H), 2.08 (s, 3H), 2.01 (m, 2H), 1.87–1.85 (m, 2H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 193.00, 176.28, 157.20, 142.66, 137.86, 137.46, 132.83, 131.00, 130.09, 124.82, 123.29, 122.96, 120.48, 112.01, 111.16, 108.73, 66.36, 40.47, 40.40, 40.30, 40.23, 40.14, 40.06, 39.97, 39.80, 39.64, 39.47, 36.64, 31.95, 20.99, 20.85. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3215, 1921, 1689, 1579, 1443, 1251, 1187, 876 cm^{-1}; **Anal. calcd. for $C_{21}H_{18}N_3O_2Br$**; C: 59.45; H: 4.28; N: 9.90%. Found: C: 59.62; H: 4.38; N: 9.98%.

5′-Chloro-2,2-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indo line]-1,2′(2H)-dione [4n]

White solid, yield 87%, m. p. 286 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.31 (s, 1H), 9.10 (s, 1H), 7.18 (m, J=8.2, Hz, 1H), 7.14 (m, J=8.0 Hz, 1H), 6.91– 6.87 (m, 1H), 6.79 (d, J=1.3 Hz, 1H), 6.72 (d, J=8.2 Hz, 1H), 6.68–6.65 (m, 1H), 6.22 (d, J=2.0 Hz, 1H), 5.57 (s, 1H), 2.61 (d, 2H), 1.97 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.97, 176.13, 155.36, 142.69, 137.86, 137.55, 133.63, 130.10, 124.65, 123.96, 123.32,

122.34, 120.57, 111.94, 111.26, 107.89, 66.62, 50.04, 45.26, 40.45, 40.37, 40.28, 40.21, 40.12, 40.04, 39.95, 39.78, 39.61, 39.45, 31.77, 27.72, 18.99. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3289, 1975, 1655, 1561, 1535, 1227, 1147, 878 cm^{-1}; **Anal. calcd. for $C_{22}H_{20}N_3O_2Cl$**; C: 67.09; H: 5.12; N: 10.67%. Found: C: 67.16; H: 5.18; N: 10.73%.

5′-Chloro-1′-ethyl-2,2-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4o]

White solid, yield 89%, m. p. 225 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 9.14 (s, 1H), 7.22–7.11 (m, 3H), 6.97 (d, J=8.3 Hz, 1H), 6.93–6.87 (m, 1H), 6.79 (m, J=7.7 Hz, 1H), 6.63 (m, J=7.9 Hz, 1H), 6.13 (d, J=2.2 Hz, 1H), 5.55 (s, 1H), 3.70–3.58 (m, 2H), 2.62 (s, 2H), 1.96 (m, 2H), 1.22 (t, 3H), 1.10 (s, 3H), 0.97 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.97, 174.29, 155.35, 142.70, 137.45, 136.76, 133.56, 127.33, 124.65, 124.04, 123.21, 122.41, 121.77, 120.64, 109.68, 107.93, 66.08, 49.94, 45.53, 40.45, 40.28, 40.20, 40.11, 40.04, 39.95, 39.78, 39.61, 39.44, 34.66, 31.84, 28.18, 12.09. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3251, 1978, 1646, 1537, 1448, 1257, 1175, 893 cm^{-1}. **Anal. Calc. for $C_{24}H_{24}N_3O_2Cl$**: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.35; H, 5.79; N, 9.99.

2,2-Dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indoline]-1,2′(2H)-dione [4p]

White solid, yield 91%, m. p. 270 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.14 (s, 1H), 9.03 (s, 1H), 7.12 (m, J=8.0 Hz, 1H), 7.00 (m, 1H), 6.89–6.80 (m, 1H), 6.73 (m, J=8.6 Hz, 2H), 6.64 (m, J=7.9 Hz, 1H), 6.54 (m, 1H), 6.19 (d, J=7.3 Hz, 1H), 5.43 (s, 1H), 2.60 (d, 2H), 1.96

(m, 2H), 1.09 (s, 3H), 0.96 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.66, 176.56, 154.84, 143.33, 137.83, 135.54, 133.60, 127.54, 123.66, 123.14, 122.07, 121.94, 120.36, 120.28, 109.34, 108.66, 66.41, 50.20, 45.39, 40.45, 40.37, 40.28, 40.21, 40.12, 40.04, 39.95, 39.78, 39.62, 39.45, 31.89, 28.06, 19.01. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3251, 1977, 1658, 1542, 1493, 1223, 1155, 879 cm^{-1}; **Anal. calcd. for $C_{22}H_{21}N_3O_2$**; C: 73.52; H: 5.89; N: 11.69%. Found: C: 73.65; H: 5.88; N: 11.75%.

5′-Bromo-2,2-dimethyl-3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3′-indo line]-1,2′(2H)-d ione [4q]

White solid, yield 90%, m. p. 287 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.30 (s, 1H), 9.10 (s, 1H), 7.14 (m, *J* = 8.0 Hz, 1H), 7.06 (m, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 0.7 Hz, 1H), 6.77 (m, *J* = 7.8, 2H), 6.67 (d, 1H), 6.10 (d, *J* = 7.2 Hz, 1H), 5.57 (s, 1H), 2.61 (s, 2H), 1.97 (m, 2H), 1.09 (s, 3H), 0.98 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 192.97, 176.13, 155.36, 142.69, 137.86, 137.55, 133.63, 130.10, 124.65, 123.96, 123.32, 122.34, 120.57, 111.94, 111.26, 107.89, 66.62, 50.04, 45.26, 40.45, 40.37, 40.28, 40.21, 40.12, 40.04, 39.95, 39.78, 39.61, 39.45, 31.77, 18.99. . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3280, 1942, 1652, 1558, 1465, 1273, 1183, 861 cm^{-1}; **Anal. calcd. for $C_{22}H_{20}N_3O_2Br$**; C: 60.28; H: 4.60; N: 9.59%. Found: C: 60.24; H: 4.52; N: 9.53%.

2.5.3 Spectral Data of Product 3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3'-indoline]-1,2'(2H)-dione (4a)

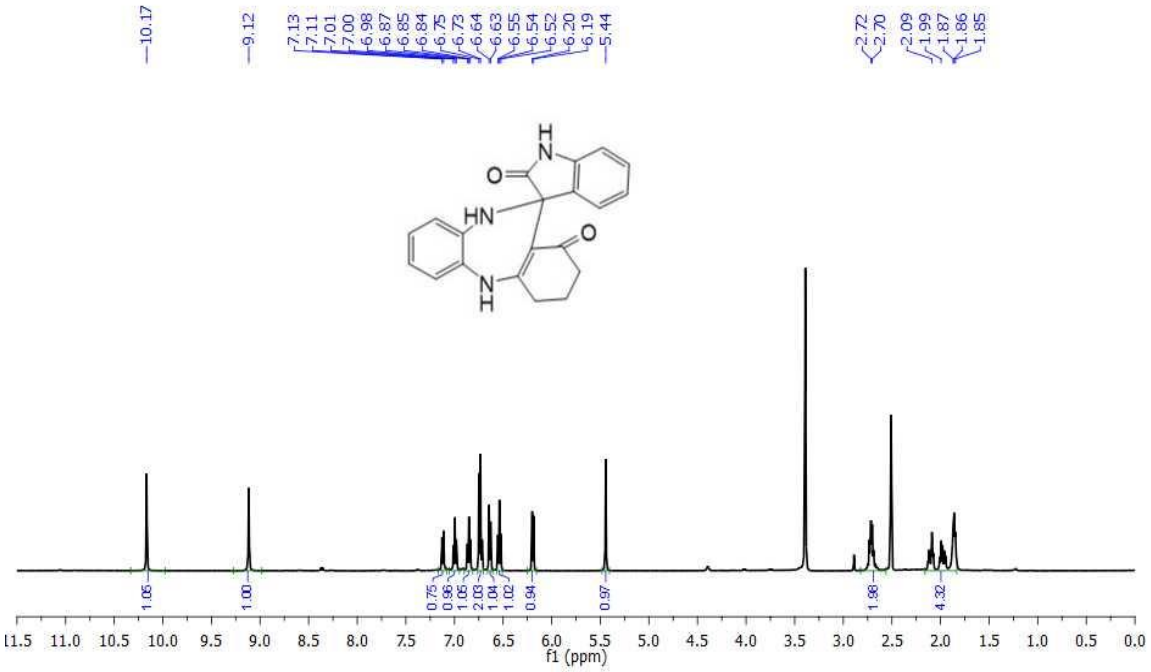


Figure 2.2 ^{1}H NMR of 3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3'-indoline]-1,2'(2H)-dione **(4a)**

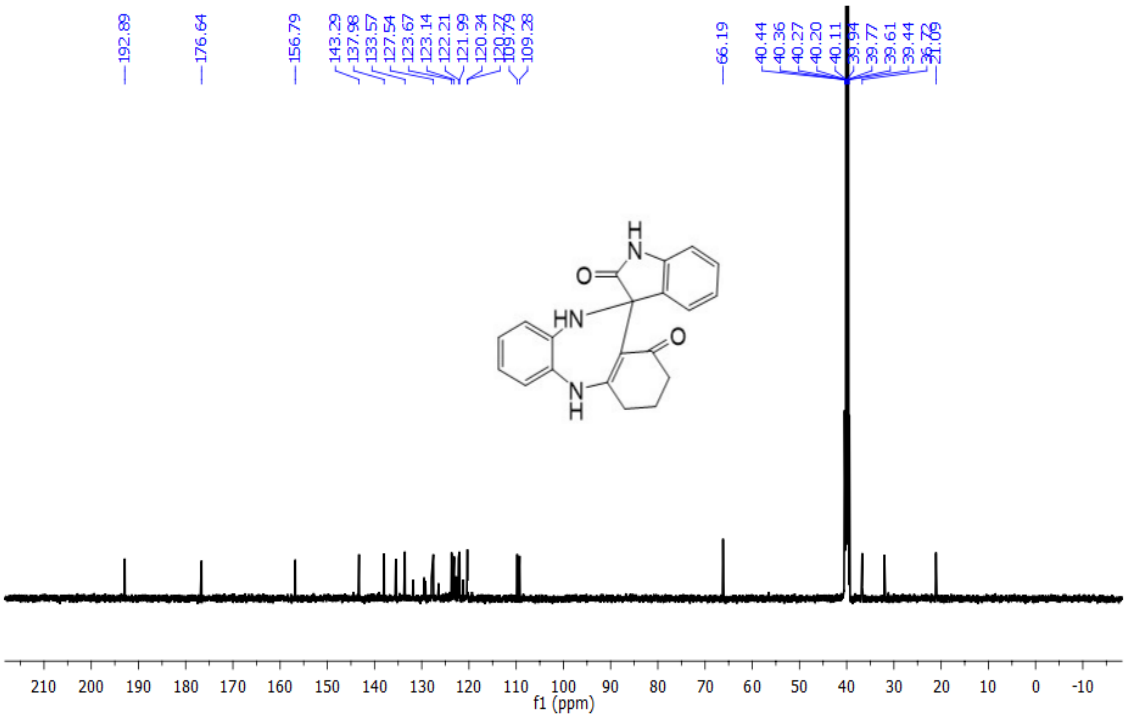


Figure 2.3 ^{13}C NMR of 3,4,5,10-tetrahydrospiro[dibenzo[b,e][1,4]diazepine-11,3'-indoline]-1,2'(2H)-dione **(4a)**

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