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ORIGINAL ARTICLE

Green synthesis and anxiolytic activity of some new dibenz-[1,4] diazepine-1-one analogues

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KEYWORDS

Dibenz [1,4] diazepine-1-ones;
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Oxalic acid catalyst;
Anxiolytic activity

Abstract A facile, green approach for the synthesis of some new dibenz[1,4]-diazepine-1-one by a three component reaction of Diamine, 1,3 diketone and aromatic aldehyde using oxalic acid as catalyst in water is described. The products are formed in good yields (92–94%). Newly synthesized dibenz [1,4]-diazepine-1-one analogues were evaluated for the anxiolytic activity by the elevated plus maze method. From the activity data it is observed that compounds, **4g**, **4h** and **4k** show promising anxiolytic activity.

1. Introduction

Dibenz-[1,4] diazepine-1-ones constitute an important class of bioactive compounds due to their central nervous system depressing effect. They are widely prescribed as psychotropic drugs (Ator and Griffith, 1997; Nabih et al., 2003). Dibenzodiazepine derivatives are one of the most known atypical neuroleptic agents which possess antimuscarinic, antiserotonergic, sedative and weak antidopaminergic properties (Liegeois et al., 1993, 1995). Benzodiazepine derivatives bind to the gamma subunit of the γ-aminobutyric acid ($GABA_A$) receptor. Their binding causes an allosteric modification of the receptor activity, which leads to an increase in the chloride conductance and inhibition of the action potential (Falco et al., 2005; Nash and Nutt, 2004). The $GABA_A$ receptors are pentameric ligand gated chloride ion channels assembled from at least 16 subunits from seven different classes (α_{1-6}, β_{1-3}, γ_{1-3}, δ, ε, Π, and θ) (Sieghart, 2006; Johnston, 2005; Olsen and Sieghart, 2009). The benzodiazepine-binding site (BZDR) is believed to be located at an interface between α and γ subunit and ligands of the receptor are believed to mediate their pharmacological effect predominately through interactions at the $\alpha_1\beta x\gamma_2$, $\alpha_2\beta x\gamma_2$, $\alpha_3\beta x\gamma_2$, and $\alpha_5\beta x\gamma_2$ subtype assemblies. Studies with transgenic mice and subtype selective compounds clearly

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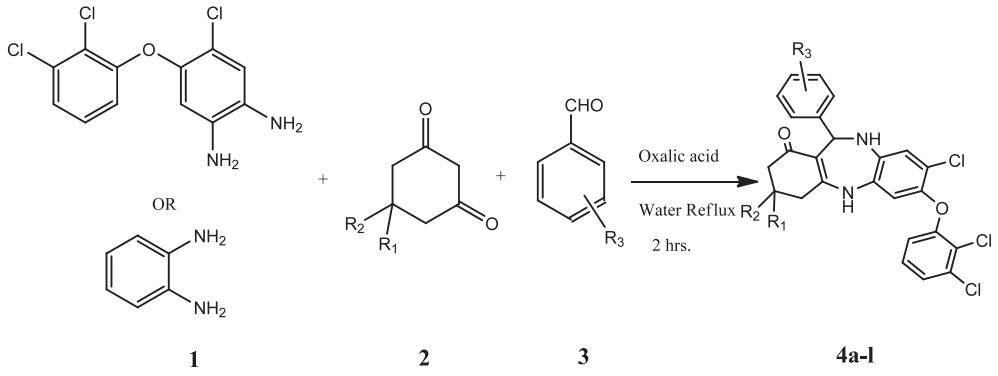
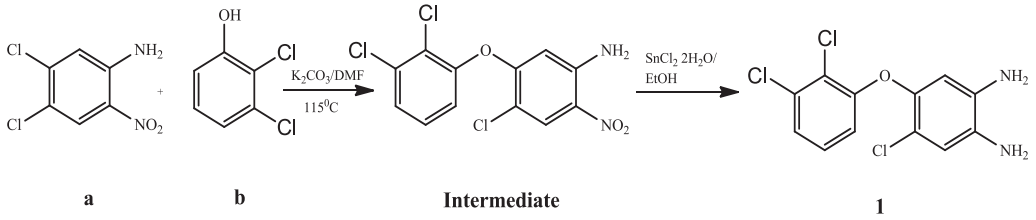


Scheme 1 Synthesis of Dibenz [1, 4]-diazepine-1-one catalyzed by Oxalic acid in water.



Scheme 2 Synthesis of 4-chloro-5-(3,4-dichlorophenoxy)benzene-1,2-diamine (Campos et al., 2002).

Table 1 The effect of catalyst on model reaction **4a**[a].

Entry	Catalyst[b]	Time (min)	Yield (%)[c]
1.	No catalyst	240	40
2.	CH_3COOH	120	76
3.	Sulfamic acid	130	80
4.	Oxalic acid	120	94

[a] Reaction condition diamine (1) (1.0 mmol), substituted aldehyde (2) (1.0 mmol), water (5 mL), 1,3diketone (3) (1.0 mmol) and oxalic acid (40 mol%) refluxed at 100 °C.
[b] 40 mol% Of catalyst were used for standardization of catalyst.
[c] Isolated yields of two runs.

Table 2 Effect of concentration of oxalic acid on model reaction **4a**[a].

Entry	mol%	Time (min)	Yield (%)[b]
1.	10	135	88
2.	20	135	89
3.	30	120	91
4.	40	120	94
5.	50	120	94

[a] Reaction condition diamine (1) (1.0 mmol), substituted aldehyde (2) (1.0 mmol), water (5 mL), 1,3diketone (3) (1.0 mmol) and oxalic acid (40 mol%) refluxed at 100 °C.
[b] Isolated yields of two runs.

suggest that $GABA_A$ receptors with different subtype composition are associated with different physiological effects, α_1-containing receptors mediate sedative and anterograde amnesic effects, α_2, and α_3 containing receptors are involved in the anxiolytic activity, while α_5 containing receptors might be associated with cognition and memory (Rudolph et al., 1999, 2001).

The most common approaches for the preparation of dibenz-[1,4] diazepine-1-one involve internal mannich reaction (Tonkikh et al., 2004), cyclization, condensation (Wang et al., 2011), and C aryl–N bond construction, accomplished by a palladium-catalyzed intramolecular *N*-arylation (Susana et al., 2011). However, most of these involve multi-step procedures and have significant drawbacks such as long reaction times, low yields of the products, harsh reaction conditions, difficult work-up and the use of expensive and environmentally toxic catalysts, reagents or media. The development of simple and efficient methods for the synthesis of dibenz-[1,4] diazepine-1-ones is therefore strongly desirable.

Table 3 Screening of solvent for model reaction **4a**[a].

Entry	Solvent	Time (min)	Yield (%)[b]
1.	Acetonitrile	180	60
2.	Iso-propylalcohol	180	65
3.	Methanol	120	90
4.	Ethanol	120	94
5.	Ethanol–Water (50%)	120	94
6.	Water	120	94

[a] Reaction condition diamine (1) (1.0 mmol), substituted aldehyde (2) (1.0 mmol), water (5 mL), 1,3 diketone (3) (1.0 mmol) and oxalic acid (40 mol%) refluxed at 100 °C.
[b] Isolated yields of two runs.

Based on the above facts and due to our interest in establishing the synthetic strategies for new biologically active heterocycles (Sangshetti et al., 2009, 2011a,b; Sangshetti and Shinde, 2010a,b, 2011), we have reported a facile methodology

Table 4 Synthesis of Dibenz [1,4]-diazepine-1-one derivatives using oxalic acid as catalyst in water[a].

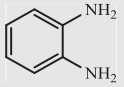
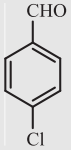
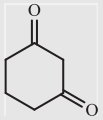
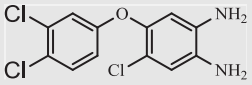
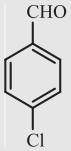
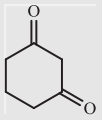
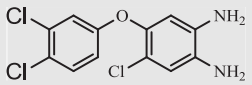
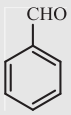
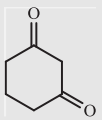
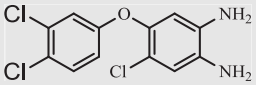
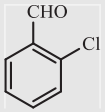
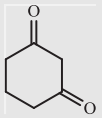
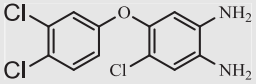
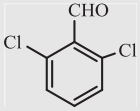
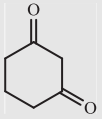
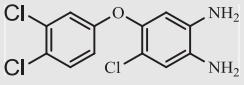
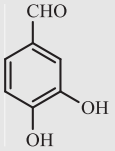
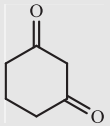
Entry	Diamine (1)	Aldehyde (2)	1,3 diketone (3)	Time (min)	Yield (%)[b]	Melting Point in °C*
4a				120	94	250–253
4b				120	92	273–275
4c				130	93	268–270
4d				130	90	258–260
4e				120	94	264–266
4f				125	92	275–277

Table 4 *(continued)*

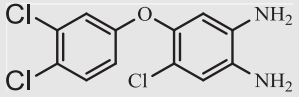
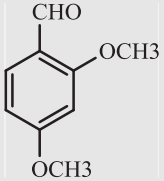
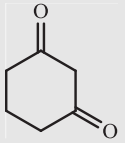
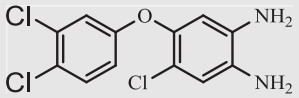
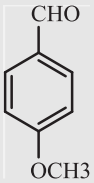
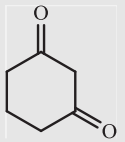
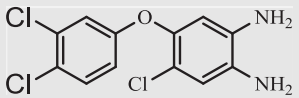
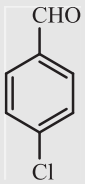
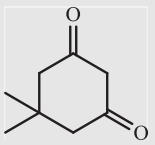
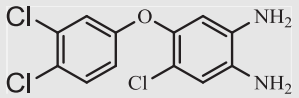
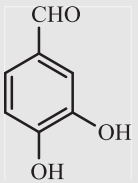
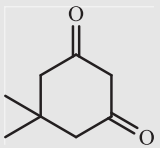
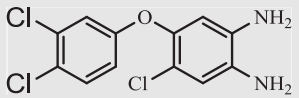
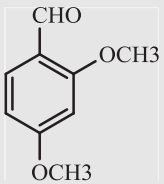
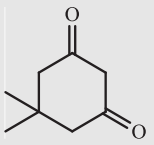
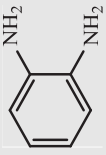
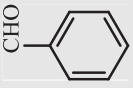
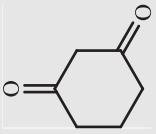
4g				120	93	263–264
4h				130	92	258–216
4i				120	91	280–281
4j				120	89	274–276
4k				120	92	268–270

Table 4 *(continued)*

4l				92	255–257

[a] Reaction condition diamine (1) (1.0 mmol), substituted aldehyde (2) (1.0 mmol), water (5 mL), 1,3diketone (3) (1.0 mmol) and oxalic acid (40 mol%) refluxed at 100 °C.
[b] Isolated yields of two runs.
[*] Melting point uncorrected.

for the synthesis of some new dibenz-[1,4] diazepine-1-one derivatives by three component reaction of diamine, substituted aldehydes and 1,3-diketones by using oxalic acid as a catalyst in water. The newly synthesized compounds have further been tested for the anxiolytic activity.

2. Result and discussion

2.1. Chemistry

All dibenz-[1,4] diazepine-1-one derivatives prepared in this study are new compounds. Dibenz-[1,4] diazepine-1-one scaffold (**4a–4l**) was synthesized by using synthetic route outlined in Scheme 1 by cyclocondensation of diamine (**1**) 1,3-diketone (**2**) and aromatic aldehydes (**3**) in the presence of oxalic acid in good yield. 4-chloro-5-(3,4-dichlorophenoxy) benzene-1,2-diamine (**1**) is prepared by using 4,5-dichloro-2-nitro aniline (**a**) and 2,3-dichlorophenol (**b**) giving an intermediate nitro compound. The nitro compound on further reduction with $SnCl_2$ gives 4-chloro-5-(3,4-dichlorophenoxy) benzene-1,2-diamine (**1**) as shown in Scheme 2 (Campos et al., 2002). Optimization of the reaction has been carried out using different catalyst considering a model reaction **4a**. The results are presented in Table 1. From the data it is observed that use of oxalic acid is more favorable. The reaction has also been optimized for concentration of oxalic acid. Use of 40 mol% oxalic acid is suitable for maximum yield (Table 2). Reaction has also been tried with different solvent; the effect of different solvent on yield of the reaction was evaluated. The results are summarized in Table 3. The yield and physical constant data of all the newly synthesized compounds have been represented in Table 4.

3. Pharmacology

3.1. Anxiolytic activity

Anxiety behavior was induced and assessed in albino mice using an elevated plus maze (EPM) apparatus (Sheibania et al., 2011). The animals were randomly assigned to different experimental and control groups. Grouped mice were brought into the testing room and allowed to acclimatize to the new environment for 30 min. The experiments were carried out in a dimly-lit room (44-lux). A trained observer scored the parameters. After each trial, the maze was cleaned with ethanol solution (10% v/v). The mice were placed in the center of EPM and were allowed to explore EPM for 5 min. Diazepam (DZP) was used as the reference standard. Animals were given the test compound **4a–4l** (2 mg/kg, i. p.), DZP (2 mg/kg, i.p.) and vehicle (Tween 20, 5%, i.p.). The anxiolytic activity was evaluated through the number of entries and the average time spent in seconds in the arms of EPM during the test. These were used to calculate percent open arm entry (% OAE, [open arm entries/(open + closed arm entries)] × 100), percent closed arm entry (% OCE, [close arm entries/(open + closed arm entries)] × 100), percent time spent in open arm (% TOA, (open arm time/300) × 100), percent time spent in close arm (% TCA, (close arm time/300) × 100).

The effect of compounds **(4a–4l)**, DZP and vehicle on the time spent and number of entries into the arms of EPM are shown in Table 5 and Figs. 1 and 2 Increase in the OAE and percent TOA indicates the anti-anxiety activity. All the

Table 5 Effect of Dibenz [1,4]-diazepine-1-one derivatives (**4a–4l**) on the relative parameters in the EPM for measurement of anxiolytic activity.

DV	VEH	DZP	4a	4b	4c	4d	4e	4f	4 g	4 h	4i	4j	4 k	4 l
OAE	3.3 ± 0.6	10.3 ± 1.3*	7.6 ± 1.6*	8.1 ± 0.5*	8.6 ± 0.6*	7.6 ± 1.8*	7.5 ± 0.9*	6.8 ± 0.4*	10.6 ± 0.4*	12.0 ± 0.5*	6.3 ± 0.7 ns	5.3 ± 0.4 ns	13.0 ± 0.5*	9.0 ± 0.3*
CAE	13.0 ± 0.6	5.5 ± 0.9*	6.0 ± 1.2*	5.3 ± 0.8*	7.6 ± 0.8*	9.5 ± 1.9*	8.0 ± 1.0*	6.0 ± 0.0*	7.1 ± 0.4*	6.1 ± 0.4*	6.3 ± 0.6*	4.1 ± 0.3*	7.5 ± 0.4*	7.8 ± 0.3*
TOA	17 ± 2.0	120.0 ± 5.1*	129.8 ± 1.5*	151.5 ± 9.8*	136.5 ± 5.3*	105.5 ± 1.3*	120.0 ± 8.6*	76.5 ± 2.3*	80.8 ± 1.2*	88.5 ± 2.1*	39.3 ± 1.4ns	18.0 ± 1.0ns	74.0 ± 1.9*	100.7 ± 1.2*
TCA	223.0 ± 1.1	95.0 ± 1.6*	99.3 ± 2.1*	68.6 ± 8.2*	100.5 ± 1.3*	67.0 ± 8.2*	102.8 ± 3.6*	145.2 ± 1.6*	167.0 ± 2.6*	157.5 ± 2.1*	209.8 ± 4.3ns	233.2 ± 1.6ns	170.5 ± 1.3*	126.5 ± 5.0*
% OAE	19.3 ± 2.7	65.0 ± 4.4*	56.9 ± 4.7*	61.8 ± 3.6*	53.4 ± 1.1*	45.7 ± 8.1*	48.3 ± 0.7*	52.8 ± 1.8*	59.7 ± 2.2*	65.9 ± 2.7*	49.9 ± 0.8*	56.0 ± 2.1*	63.3 ± 1.5*	53.4 ± 0.4*
% CAE	80.6 ± 2.7	34.9 ± 4.4*	42.8 ± 4.6*	38.0 ± 3.6*	46.4 ± 1.1*	54.2 ± 8.1*	51.6 ± 0.7*	47.0 ± 1.8*	40.1 ± 2.2*	33.9 ± 2.7*	49.6 ± 1.1*	43.9 ± 2.1*	36.5 ± 1.5*	46.4 ± 0.4*
% TOA	5.6 ± 0.6	40.1 ± 1.7*	43.2 ± 0.5*	50.4 ± 3.2*	45.4 ± 1.7*	35.1 ± 0.4*	40 ± 2.8*	25.4 ± 0.7*	26.9 ± 0.4*	29.4 ± 0.7*	13 ± 0.5*	5.9 ± 0.3ns	24.6 ± 0.6*	33.5 ± 0.3*
% TCA	74.3 ± 4.7	31.6 ± 3.5*	33 ± 0.7*	22.8 ± 2.7*	33.4 ± 0.4*	22.3 ± 2.7*	34.2 ± 1.2*	48.3 ± 0.5*	55.6 ± 0.8*	52.4 ± 0.7*	69.9 ± 1.4*	76.8 ± 4.0ns	56.8 ± 0.4*	42.1 ± 1.7*

Data represent mean values ± SEM; $n = 6$. **DV** – Dependent Variable, **VEH**- Vehicle Tween 20 (5%), **DZP** – Diazepam, **OAE** – Open Arm Entry, **CAE** – Closed Arm Entry, **TE** – Total Entry**TOA** – Time in Open Arm, **TCA**- Time in Closed Arm, **TT** – Total Time, **%OAE** – % Open Arm Entry, **%CAE** – % Closed Arm Entry, **%TOA** – % Time in Open Arm, **%TCA** – % Time in Closed Arm.

ns Non significant.

* The mean difference is significant at the 0.05 level.

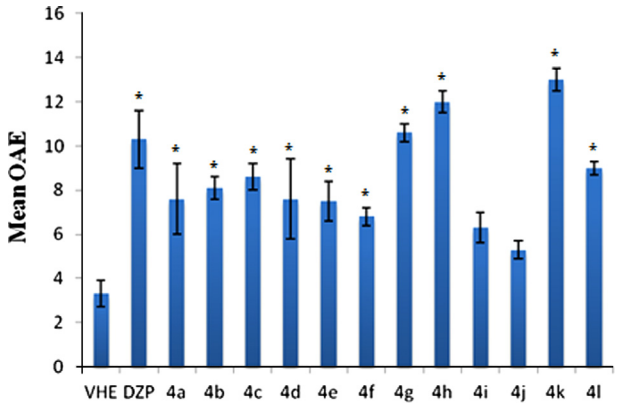


Figure 1 Mean open arm entries of drug in mice by using diazepam as standard drug and tween 80 as vehicle.

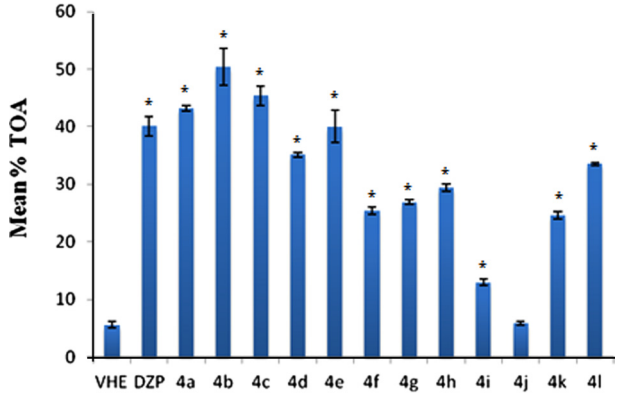


Figure 2 % Time spent in open arm entries of drug in mice by using diazepam as standard drug and tween 80 as vehicle.

synthesized compounds **(4a–4l)** that were subjected to the anxiolytic activity by EPM method showed significant anxiolytic activity. Compounds **4h** and **4k** are found to be more potent than DZP whereas **4g** is equipotent to DZP.

3.2. Statistics

Data obtained in the test were compared against the control group by using the one-way analysis of variance method followed by post hoc Dunnett's test. For all statistical analyses, alpha was set to 0.05. Statistical analysis was performed using the SPSS 16 software package.

4. Structure activity relationship

Structure activity relationship reveals that newly synthesized dibenz-[1,4] diazepine-1-one scaffold shows significant anxiolytic activity. Aromatic substitution at 11 position of dibenz-[1,4] diazepine-1-one favors the anxiolytic activity. 4-methoxy (**4h**) and 2,4-dimethoxy (**4g**, **4k**) substitution on the aromatic ring gives most potent compounds in the series. Other aromatic substitutions like 4-Cl (**4a**, **4b**), 3,4-di-OH (**4f**), 2,6di-Cl (**4e**), 2-Cl (**4d**) also show significant anxiolytic activity. Introduction of dimethyl group at third position of dibenz-[1,4] diazepine-1-one (**4i–4j**) generally reduces the anxiolytic activity

except in compound with 2,4dimethoxy aromatic substitution (**4k**). Analogues synthesized from *o*-phenylene diamine (**4a**, **4l**) are less potent as compared to analogues synthesized from 4-chloro-5-(3,4-dichlorophenoxy)benzene-1,2-diamine (**4b**–**4k**).

5. Conclusion

A new series of dibenz[1,4]-diazepine-1-one has been synthesized by a one pot green method. The reaction has been completed with good to excellent yield in short reaction time. Newly synthesized compounds were subjected to anxiolytic activity. Compounds (**4g**), (**4h**) and (**4k**) are the most active compounds showing significant anxiolytic activity. The highlighting advantages of this method are a catalytic process for the synthesis of dibenz[1,4]-diazepine-1-one catalyzed by oxalic acid as catalyst using water as a media by one pot three component condensation of aromatic aldehydes, 1,3-diketones, diamines. Water is used as a reaction medium which is eco-friendly, inexpensive and abundantly available. Other advantages of this method are good yield, short reaction time, easy work-up, simplicity in operation, use of green solvents, mild reaction conditions.

6. Experimental

The substituted aldehydes, *o*-phenylene diamine, 1,3-diketone and oxalic acid were commercially available. Melting points were recorded on Thiele's tube apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz BRUKER spectrometer and ^{13}C NMR spectra were recorded on a 100 MHz BRUKER spectrometer and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used, singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micro mass-QUATTRO-II of WATER mass spectrometer.

6.1. General procedure for the synthesis of Dibenz[1,4]-diazepine-1-one derivatives

In a 50 ml reaction flask, the diamine (1 mmol), (**1**) 1,3-diketone (1mmole) (**2**), oxalic acid (40 mol%), and water (5 ml) were mixed and then stirred for 30 min. Subsequently aldehyde (**3**) (1 mmol) was added to the reaction mixture, and the mixture was refluxed for 120 min. Upon completion monitored by TLC (Ethylacetate 30%-n-Hexane 70%), the reaction mixture was cooled to room temperature, filtered to give the crude product which was further recrystallized using ethanol to give pure product.

6.2. Spectral characterization

*6.2.1. 11-(4-chlorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4a**)*

Pale Yellow Solid, ES-MS *m*/*z* (%): 325 (M + H) ^{1}HNMR (400 MHz, CDCl3); 7.85–7.34 (m, 4H), 6.85–6.51(m, 4H), 6.00(d, 1H), 4.51(s, 1H), 4.51(s, 1H), 3.94 (t, 2H), 2.96(t, 2H), 1.97(m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$); 199.9, 144.4, 136.5, 134.2, 132.3, 128.6, 118.9, 119.5, 105.1, 53.3, 36.8, 27. 3, 25.6.

*6.2.2. 8-chloro-11-(4-chlorophenyl)-7-(3,4-dichlorophenoxy)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4b**)*

White Solid, ES-MS *m*/*z* (%): 521(M + H) ^{1}H NMR (400 MHz, CDCl3); 7.98–7.18(m, 3H), 7.37–7.34(m, 4H), 6.49–6.05(m, 2H), 5.50(d, 1H), 4.5(s, 1H), 4.4 (s, 1H), 3.98(t, 2H), 2.96(t, 2H), 1.97(m, 2H) ^{13}C NMR (100 MHz, CDCl3); 195.9, 155.5, 148.1, 135.3, 133.1, 126.5, 119.6, 129.0, 141.4, 119.7, 117.4, 126.3, 131.0, 128.6, 104.8, 117.0, 128.6, 127.1, 53.3, 36.0, 25.1.

*6.2.3. 8-chloro-7-(3,4-dichlorophenoxy)-11-phenyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4c**)*

Yellowish brown Solid, ES-MS *m*/*z* (%): 485 (M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 7.89–7.38 (m,3H), 7.83–7.23 (m,5H), 6.49–6.05 (m,2H), 5.8 (d,1H), 4.4 (s,1H), 4.7 (s,1H), 3.94 (t,2H), 3.96 (t,2H), 1.87 (m,2H) ^{13}C NMR (100 MHz, CDCl3); 196.5, 153.5, 130.2, 128.1, 126.5, 129.0, 123.3, 131.7, 119.7, 114.4, 131.0, 115.8, 107.8, 104.9, 128.9, 126.7, 36.0, 27.3, 53.3, 24.5.

*6.2.4. 8-chloro-11-(2-chlorophenyl)-7-(3,4-dichlorophenoxy)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4d**)*

Off-white Solid, ES-MS *m*/*z* (%): 521 (M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 8.71–7,58 (m, 3H), 7.65–7.39 (m, 4H), 6.49–6.13 (m, 2H), 5.56 (d, 1H), 4.5 (s, 1H), 4.34 (s, 1H), 3.94 (t, 2H), 2.96 (t, 2H), 2.67 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$); 188.9, 154.5, 141.1, 133.1, 131.2, 129.0, 126.2, 142.8, 119.7, 128.6, 114.4, 120.3, 36.0, 27.3.

*6.2.5. 8-chloro-7-(3,4-dichlorophenoxy)-11-(2,6-dichlorophenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4e**)*

Pale Yellow Solid, ES-MS *m*/*z* (%): 554 (M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 8.89–7.45(m, 4H), 7.53–7.25 (m, 3H), 6.49–6.05 (m, 2H), 5.00 (d, 1H), 4.0 (s, 1H), 4.0 (s, 1H), 2.94 (t, 2H), 1.96 (t, 2H), 1.67 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$); 198.9, 152.5, 143.2, 133.6, 126.3, 124.7, 116.6, 109.8, 101.1, 53.6, 26.9, 27.9, 26.3.

*6.2.6. 8-chloro-7-(3,4-dichlorophenoxy)-11-(3,4-dihydroxyphenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4f**)*

Yellowish brown Solid, ES-MS *m*/*z* (%): 517 (M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 7.71–7.48 (m,3H),7.60–6.62 (m,3H), 6.49–6.25 (m,2H), 5.38 (s,1H), 5.20 (s,1H), 5.00 (d,1H), 4.4 (s,1H), 4.7 (s,1H), 2.98 (t,2H), 1.96 (t,2H), 1.97 (m,2H) ^{13}CNMR (100 MHz, $CDCl_3$); 192.9, 153.5, 145.5, 140.1, 137.3, 133.1, 129.7, 126.5, 121.7, 120.0, 117.9, 115.8, 114.9, 111.0, 109.5, 101.1, 53.0, 36.9, 27.9, 24.5.

*6.2.7. 8-chloro-7-(3,4-dichlorophenoxy)-11-(2,4-dimethoxyphenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4g**)*

Yellow Solid, ES-MS *m*/*z* (%): 545 (M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 8 .71–7.28 (m,3H), 7.61–7.45 (m,3H), 6.49–6.05 (m,2H), 5.2 (d,1H), 4.2 (s,1H), 4.6 (s,1H), 3.98 (s,3H), 3.93 (s, 3H), 3.94 (t, 2H), 2.96 (t,2H), 1.67 (m,2H)

^{13}C NMR (100 MHz, $CDCl_3$); 191.9, 159.6,157.5, 151.5, 142.1, 140.1, 131.0, 129.0, 126.5, 121.8, 117.5, 116.6, 114.9, 113.5, 106.6, 105.0, 101.1, 100.0, 55.3, 47.9, 29.4, 27.9, 25.0.

*6.2.8. 8-chloro-7-(3,4-dichlorophenoxy)-11-(4-methoxyphenyl)-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4] diazepin-1-one (**4h**)*

White Solid, ES-MS *m/z* (%): 515 (M + H) ^{1}H NMR (400 MHz,$CDCl_3$); 7.71–7.28 (m,3H), 7.12–6.87 (m,4H), 6.49–6.05 (m,2H), 5.00 (d,1H), 4.0 (s,1H), 4.0 (s,1H), 3.91 (s,3H), 2.94 (t,2H), 1.96 (t,2H), 1.67 (m,2H) ^{13}C NMR (100 MHz, $CDCl_3$); 191.9, 158.6, 156.5, 144.1, 135.6, 133.2, 133.1, 131.0, 129.0, 128.5, 126.3, 125.1, 120.8, 117.1, 116.6, 114.9, 109.5, 101.1, 58.8, 53.0, 39.4, 27.6, 26.8.

*6.2.9. 8-chloro-11-(4-chlorophenyl)-7-(3,4-dichlorophenoxy)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4i**)*

Yellow Solid, ES-MS *m/z* (%): 549 (M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 8.71–7.28 (m,3H), 7.37–7.34 (m,4H), 6.49–6.05 (m,2H), 5.00 (d,1H), 4.9 (s,1H), 4.2 (s,1H), 2.29 (d2H), 1.88 (d,2H), 0.94 (s,3H), 0.91 (s,3H) ^{13}C NMR (100 MHz, $CDCl_3$); 192.9, 151.5, 145.4, 141.1, 137.0, 126.0, 128.5, 126.1, 120.9, 116.6, 114.9, 109.5, 101.1, 53.0, 50.1, 42.8, 32.7, 27.9.

*6.2.10. 8-chloro-7-(3,4-dichlorophenoxy)-11-(3,4-dihydroxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4j**)*

Yellowish brown Solid, ES-MS *m/z* (%): 517(M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 7.71–7.28 (m,3H), 6.80–6.62 (m,3H), 6.49–6.05 (m,2H), 5.35 (s,1H), 5.35 (s,1H), 5.00 (d,1H), 4.7 (s,1H), 4.3 (s,1H), 3.97 (t,2H), 2.66 (t,2H), 1.97 (t,2H) ^{13}C NMR (100 MHz, $CDCl_3$); 196.1, 157.5, 155.5, 148.1, 137.3, 133.1, 131.0, 126.5, 121.7, 121.0, 117.9, 115.8, 114.9, 111.0, 109.5, 101.1, 53.0, 36.9, 27.9, 24.0.

*6.2.11. 8-chloro-7-(3,4-dichlorophenoxy)-11-(2,4-dimethoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (**4k**)*

Brown Solid, ES-MS *m/z* (%): 573(M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 7.71–7.28 (m,3H), 7.01–6.43 (m,3H), 6.49–6.05 (m,2H), 5.00 (d,1H), 4.0 (s,1H), 4.0 (s,1H), 3.83 (s,3H), 3.83 (s,3H), 2.94 (t,2H), 1.96 (t,2H), 1.67 (t,2H), 0.89 (s,3H), 0.85 (s,3H) ^{13}C NMR (100 MHz, $CDCl_3$); 194.9, 159.6, 152.5, 147.1, 143.1, 139.7, 129.0, 126.5, 120.7, 116.6, 114.9, 113.5, 106.4, 105.0, 101.1, 100.0, 56.1, 50.1, 47.0, 42.0, 32.7, 31.2, 27.0.

6.2.12. 11-phenyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (4l)

Pale Yellow Solid, ES-MS *m/z* (%): 291(M + H) ^{1}H NMR (400 MHz, $CDCl_3$); 7.93–7.23 (m,5H), 7.85–6.51 (m,4H), 5.45 (d,1H), 4.5 (s,1H), 4.1 (s,1H), 2.94 (t,2H), 2.26 (t,2H), 1.97 (m,2H) ^{13}C NMR (100 MHz, $CDCl_3$) 187.9, 143.3, 141.5, 133.2, 128.3, 126.2, 120.5, 116.5, 115.1, 101.1, 53.0, 39.0, 27.9, 22.6.

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