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Microwave-assisted multi-component reaction in water leading to highly regioselective formation of benzo[*f*]azulen-1-ones

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ABSTRACT

Microwave-assisted three-component reaction has been established for the regioselective synthesis of benzo[*f*]azulen-1-ones. The reaction was performed in aqueous media under microwave irradiation by using readily available and inexpensive starting materials. A total of 38 examples were examined to show a broad substrate scope and good overall yields (70–89%). The present new synthesis shows attractive green chemistry characteristics, such as the use of water as reaction media, concise one-pot conditions, short reaction periods (7–24 min), easy work-up/purification, and reduced waste production without the use of any strong acids or metal promoters.

1. Introduction

Heterocycles containing benzodiazepine rings belong to important building blocks because of their remarkable depressant activity in central nervous system[1] and their being one of the most widely prescribed class of psychotropics.[1h,i] In addition, some of these compounds also possess bioactivities on analgesic, sedative, and antidepressive as well as hypnotic activities.[2] On the other hand, the derivatives of tetronic acid (tetrahydrofuran-2,4-dione) play an essential role in medicinal chemistry[3] by serving as HIV-1 protease inhibiting,[4] anti-inflammatory,[5] antifungal,[6] antibiotic,[7] insecticidal,[8] analgesic,[9] anticoagulant,[10] and antiepileptic[11] agents. Consequently, benzoazulen-1-one derivatives containing both benzodiazepine and tetronic acid motifs would provide novel leading structures for combinatorial drug-discovery research.

A careful literature survey revealed that benzo[*f*]azulen-1-one derivatives have been synthesized by the condensation reaction of 4-(2-aminophenylamino)furan-2(5*H*)-one with aldehyde in normal organic solvents.[12] However, the substrate scope of this reaction is limited. It also suffered by other shortcomings, such as multiple steps, long reaction times, low overall yields, and environmental unfriendly and uneconomical. So far, there have been a few benzo[*f*]azulen-1-one compounds produced via this method. The continuing search for new efficient approaches to benzo[*f*]azulen-1-ones in terms of mild reaction conditions, operational simplicity, economic viability, eco-friendliness, and selectivity remains challenging.

In the past several years, our groups and several others have developed a series of multi-component domino reactions (MDRs) that can provide easy accesses to multi-functionalized heterocyclic structures of chemical and pharmaceutical interest.[13–16] Especially, we established a new four-component domino reaction for an efficient synthesis of multi-functionalized quinazoline derivatives.[13a] The reaction is easily performed by simply mixing readily available starting materials, aromatic aldehydes, cyclopentanone, and cyanoacetamide with K_2CO_3 in ethylene glycol under microwave (MW) irradiation. Interestingly, when aliphatic aldehydes were employed to replace their aromatic counterparts for the above MDR reaction, the reaction was found to undergo along another pathway leading to the formation of multi-functionalized tricyclo[6.2.2.0^{1,6}]dodecanes.[13b] Recently, we have also found that the MDR of Meldrum's acid, aromatic aldehydes, and electron-rich heteroaryl-amines in aqueous phase under microwave (MW) irradiation led to the multi-functionalized spiro{[1,3]dioxanes-pyridine}-4,6-dione with high chemo,- regio,- and stereoselectivity and good yields.[13d]

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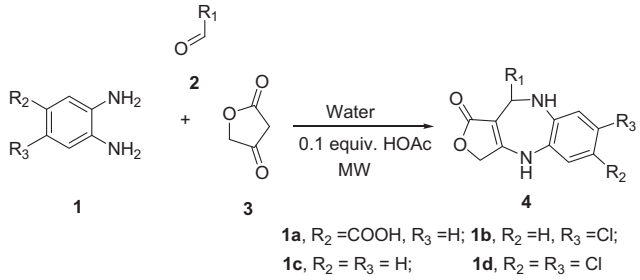
As a continuation of our research devoted to the development of multi-component domino reactions,[13–15] in this communication we would like to report a new green chemistry approach to benzo[*f*]azulen-1-one derivatives that are of chemical and biomedical importance (Scheme 1). This reaction was achieved by reacting benzene-1,2-diamines, tetronic acid, and aldehydes in aqueous phase under microwave irradiation without use of any metal catalyst as represented in Scheme 1.



Scheme 1. The synthesis of benzoazulen-1-one derivatives.

2. Results and discussion

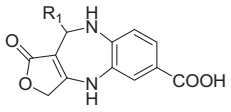
We started this methodology by subjecting 3,4-diaminobenzoic acid **1a** to the reaction with 4-chlorobenzaldehyde **2a** and tetronic acid **3** as the model case for condition optimization. As shown in Table 1, the use of glacial acetic acid (HOAc) as reaction media at 90 °C allowed the direct conversion of 3,4-diaminobenzoic acid **1a** into the corresponding benzo[*f*]azulen-1-ones **4a** in a chemical yield of 55% under microwave irradiation (Table 1, entry 4). Other organic solvents, such as benzene, DCE, DMF, THF, ethanol and glycol gave much lower yields of 10%–45% at the same temperature (Table 1, entries 1–3); this is due to the fact that the benzo[*d*]imidazoles **5** were generated as by-products. Since water is an efficient absorber for microwave irradiation, it often leads to many successful reactions under environmentally friendly conditions.[17,18] Under this aqueous system, the three-component reaction of **1a** with **2a** and **3** resulted in benzo[*f*]azulen-1-ones **4a** with a chemical yield of 51%. The reaction proceeded rapidly to completion at 110 °C within a few minutes. Increasing reaction temperature did not improve chemical yields. Pleasantly, we found that a higher yield of **4a** (86%) was obtained when the reaction was conducted in presence of 0.1 equiv of HOAc at 110 °C.

Table 1
Optimization of solvent and temperature for the synthesis of **4a**

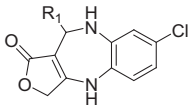
Entry	Solvent	*T* (°C)	Time (min)	Yield (%)	
				4a	**5**
1	Benzene	90	16	10	61
2	DCE	90	16	15	57
3	THF	90	16	24	48
4	DMF	90	16	34	26
5	EtOH	90	16	45	21
6	Glycol	90	16	40	24
7	HOAc	90	14	55	Trace
8	Water	90	16	51	Trace

We then investigated the substrate scope of this reaction by subjecting a series of aromatic aldehyde **2b**–**i** to the reaction with 3,4-diaminobenzoic acid **1a** under the optimal condition. As shown in Table 2, the reaction of thiophene-2-carbaldehyde with 3,4-diaminobenzoic acid **1a** was finished within 12 min to give thienyl-substituted benzo[*f*]azulen-1-ones **4h** in 85% yield. Similarly, benzo[*f*]azulen-1-ones **4b**–**g** were formed within 12–15 min in good to excellent yields of 74–89% (Table 2, entries 2–7). Moreover, aliphatic aldehydes, such as 2-phenylacetaldehyde (Table 2, entry 9) still displayed high reactivity and clean conversion under this condition. The similar situation exists for the use of 4-chlorobenzene-1,2-diamine **1b** for reactions that occurred rapidly to give the desired products **4j**–**n** in 76–84% yields (Table 2, entries 10–14). It is worth noting that these reactions showed high regioselectivity; only one single regioisomer was generated when 3,4-diaminobenzoic acid and 4-chlorobenzene-1,2-diamine were employed as substrates. The reason for this excellent selectivity is that the amino group attached on *meta*-position of carboxyl group on the phenyl ring shows higher nucleophilic than that on *para* position, favoring to condense with tetronic acid. While the halogen substitution has an *ortho*–*para* directing effect, the amino group on the *para* position of chloro group shows higher reactivity than that on *meta*-position, preferring to form enaminones from the reaction with tetronic acid.

Table 2
Regioselective synthesis of product **4a**–**n** under MW



4a-4i



4j-4n

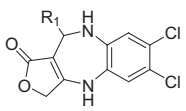
Entry	**4**	R_1	Time (min)	Yield (%)
1	**4a**	4-Chlorophenyl (**2a**)	12	86
2	**4b**	4-Bromophenyl (**2b**)	12	85
3	**4c**	2,4-Dichlorophenyl (**2c**)	12	83
4	**4d**	4-Nitrophenyl (**2d**)	11	89
5	**4e**	4-Methylphenyl (**2e**)	15	83
6	**4f**	4-Methoxyphenyl (**2f**)	15	81
7	**4g**	2,3-Dimethoxyphenyl (**2g**)	15	78
8	**4h**	2-Thienyl (**2h**)	12	74
9	**4i**	Benzyl (**2i**)	16	70
10	**4j**	4-Chlorophenyl (**2a**)	10	87
11	**4k**	2,4-Dichlorophenyl (**2b**)	10	84
12	**4l**	4-Methylphenyl (**2e**)	13	81
13	**4m**	2-Thienyl (**2h**)	11	80
14	**4n**	Benzyl (**2i**)	15	76

After we achieved the above mono-substituted benzene-1,2-diamine-based multi-component reaction, we then subjected symmetric benzene-1,2-diamine (including **1c** and **1d**) to the reaction with aromatic aldehydes **2** and tetronic acid under the similar conditions. As shown in Table 3, the corresponding products **4** were generated in good to excellent yields of 81–92% (Scheme 2). The reaction is compatible with various substrates including aldehydes with aromatic, heteroaromatic, and aliphatic ones and aromatic diamine component with both Cl and COOH substituents. The products have been unambiguously determined by X-ray structural analysis of single crystals of **4g** and **4u**, which were obtained by carefully evaporating solvents (Figs. 1 and 2).

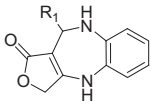
To expand the substrate scope of this reaction, the 2-formylbenzoic acid **2v** and 2-formyl-4,5-dimethoxybenzoic acid **2w** were employed to react with benzene-1,2-diamine (**1c**, **1d**, or 4,5-dimethylbenzene-1,2-diamine **1e**) and tetronic acid **3** (Scheme 3). To our delight, under the above optimized conditions, these reactions proceeded smoothly to give pentacyclic isoindole-fused furo[1,4]diazepines **5a**–**f** in good to excellent yields (Table 4, entries 1–6). Excellent regioselectivity was observed in this three-component reaction involving 3,4-diaminobenzoic acid and 2-formylbenzoic acid (Table 4, entries 7 and 8). It is worth noting that this result is significant with no literature precedent regarding the synthesis of highly functionalized isoindole-fused furo[1,4]diazepines.

Similar to our previous multi-component domino processes,[13] the present reaction also showed the following attractive characteristics:

Table 3
Synthesis of products **4o**–**ll** under MW

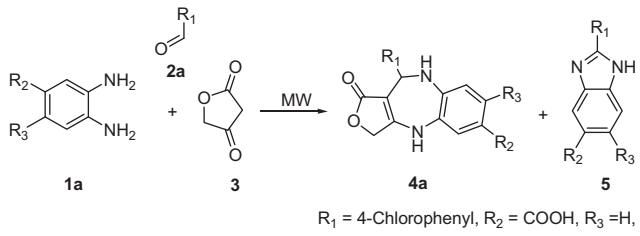


4o-4s



4t-4ll

Entry	4	R_1	Time (min)	Yield (%)
1	**4o**	2,4-Dichlorophenyl (**2c**)	10	81
2	**4p**	4-Nitrophenyl (**2d**)	9	83
3	**4q**	4-Methylphenyl (**2e**)	13	78
4	**4r**	2-Thienyl (**2h**)	12	80
5	**4s**	Benzyl (**2i**)	15	75
6	**4t**	4-Chlorophenyl (**2a**)	9	86
7	**4u**	4-Bromophenyl (**2b**)	9	86
8	**4v**	2,4-Dichlorophenyl (**2c**)	8	88
9	**4w**	4-Nitrophenyl (**2d**)	7	85
10	**4x**	2-Chlorophenyl (**2j**)	9	84
11	**4y**	3-Nitrophenyl (**2k**)	7	87
12	**4z**	4-Cyanophenyl (**2l**)	8	89
13	**4aa**	Phenyl (**2m**)	11	83
14	**4bb**	4-Methylphenyl (**2e**)	12	82
15	**4cc**	2-Methoxyphenyl (**2n**)	12	79
16	**4dd**	3,4,5-Trimethoxyphenyl (**2o**)	15	76
17	**4ee**	4-Dimethylaminophenyl (**2p**)	14	73
18	**4ff**	2-Thienyl (**2h**)	11	79
19	**4gg**	Benzyl (**2i**)	15	73
20	**4hh**	Isobutyl (**2q**)	16	72
21	**4ii**	*sec*-Butyl (**2r**)	16	70
22	**4jj**	1-Methylbutyl (**2s**)	17	72
23	**4kk**	Cyclohexyl (**2t**)	17	76
24	**4ll**	Isopropyl (**2u**)	16	75



Scheme 2.

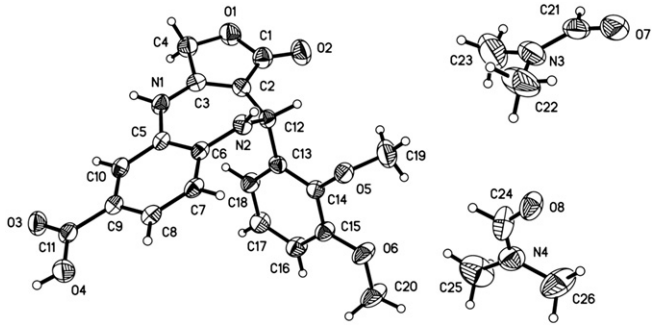


Fig. 1. ORTEP diagram of **4g**.

(1) fast reaction rates, which enable the reaction to be completed within 7–17 min, which can save energy and manpower for future industrial production; (2) the environmentally friendly process in which water is used as a solvent; (3) the convenient work-up, which only needs simple filtration since the products directly precipitate out after the reaction is finished, which belongs to GAP

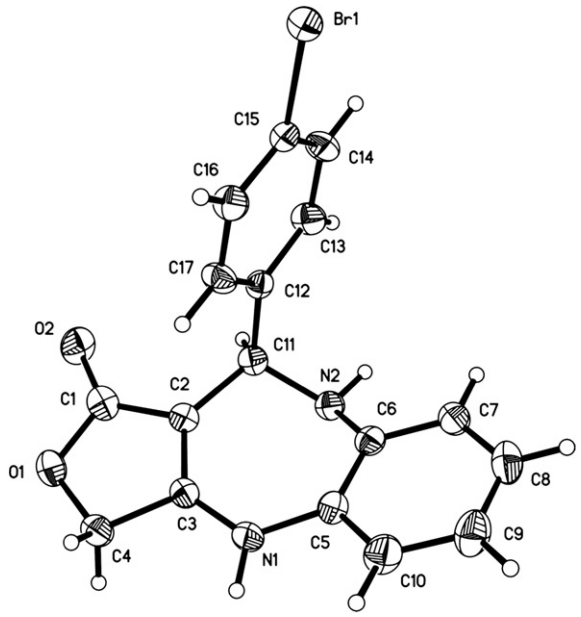
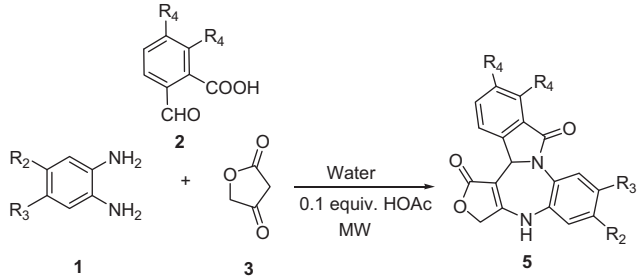


Fig. 2. ORTEP diagram of **4u**.



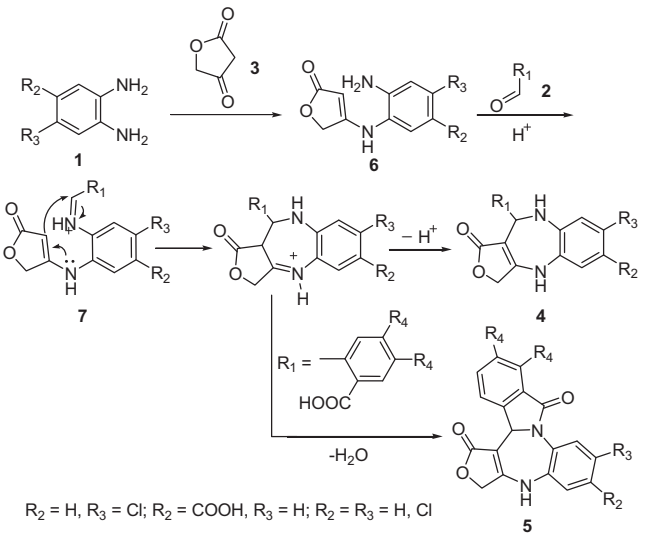
Scheme 3.

chemistry;[19–20] (4) readily available starting materials of aldehydes, substituted benzene-1,2-diamine and tetronic acid.

In according to a similar mechanism,[12] the formation of **4** is likely to proceed via initial condensation of benzene-1,2-diamine **1** and tetronic acid **3** to give enaminone **6**. The following addition of aldehydes **2** to enaminone **6** furnishes the formation of intermediate **7**, which is then converted into the final product **4** through intramolecular cyclization (Scheme 4). The carbonyl substituent on the aromatic ring **2** was dehydrated upon the treatment with amino group, leading to the formation of pentacyclic isoindole-fused furo[1,4]diazepines. Based on this mechanism, the regioselectivity is controlled by the strong nucleophilicity of amino group on starting material **1**, i.e., the formation of **4a**–**n** depends on the higher nucleophilicity of the amino group in the *meta*-position of carboxyl group than in that on *para* position.

Table 4
Synthesis of products **5** under MW

Entry	Product	Time (min)	Yield (%)
1	**5a**, R_4=R_2=R_3=H	15	85
2	**5b**, R_4=OMe, R_2=R_3=H	18	83
3	**5c**, R_4=H, R_2=R_3=Me	20	88
4	**5d**, R_4=OMe, R_2=R_3=Me	24	86
5	**5e**, R_4=H, R_2=R_3=Cl	18	84
6	**5f**, R_4=OMe, R_2=R_3=Cl	18	82
7	**5g**, R_4=H, R_2=COOH, R_3=H	15	81
8	**5h**, R_4=OMe, R_2=COOH, R_3=H	16	80



Scheme 4.

3. Conclusion

In conclusion, a new microwave-assisted multi-component reaction have been established to afford benzo[*f*]azulen-1-one and isoindole-fused furo[1,4]diazepine derivatives that can serve as versatile building blocks for both organic and medicinal research. The reactions were conducted in aqueous solution under microwave irradiation using readily available and inexpensive starting materials. The directing effects of substituents on benzene-1,2-diamine ring have been proven to control regioselectivity efficiently. This green synthesis shows several attractive characteristics, such as the use of water as reaction media, concise conditions, short reaction periods, easy work-up, and reduced waste production without the use of any strong acids or metal promoters.

4. Experimental section

4.1. General

Microwave irradiation was carried out with microwave oven Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on an FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in parts per million relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-Q II HRMS/MS instrument (Bruker).X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

4.2. General procedure for the synthesis of benzo[*f*]azulen-1-ones 4a

In a 10-mL reaction vial, the benzene-1,2-diamine **1a** (1 mmol), tetronic acid **3** (1 mmol), acetic acid (0.1 mmol), and water (2 mL) were mixed and then stirred for 30 min. Subsequently, the aldehydes **2a** (1 mmol) was added to the reaction mixture, and the reaction vial was capped and pre-stiring for 20 s. The mixture was subjected to microwave irradiation at 200 W (initial power 100 W, maximum power 200 W) at 110 °C, for a given time. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature, filtered to give the crude product, which was further washed by 50% EtOH to give pure product **4a**.

4.2.1. 10-(4-Chlorophenyl)-1-oxo-3,4,9,10-tetrahydro-1H-2-oxa-4,9-diaza-benzo[f]azulene-6-carboxylic acid ***4a***. Pale white solid, mp: 281–282 °C; IR (KBr): 3373, 3323, 3134, 1725, 1691, 1672, 1601, 1571, 1390, 1197, 1164, 1133, 1051, 1012, 832, 820 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.53 (s, 1H, COOH), 10.10 (s, 1H, NH), 7.57 (d, J=1.6 Hz, 1H, ArH), 7.31–7.27 (m, 3H, ArH), 7.16 (d, J=8.8 Hz, 2H, ArH), 6.71–6.68 (m, 2H, ArH and NH), 5.08 (d, J=4.4 Hz, 1H, CH), 4.91 (s, 2H, CH_2). HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{18}H_{14}ClN_2O_4$: 357.0637; found: 357.0649.

4.2.2. 10-(4-Bromophenyl)-1-oxo-3,4,9,10-tetrahydro-1H-benzo[b]furo[3,4-e][1,4]diazepine-6-carboxylic acid ***4b***. Pale white solid, mp: 272–273 °C; IR (KBr): 3360, 3294, 1726, 1705, 1650, 1570, 1516, 1505, 1418, 1406, 1357, 1232, 1184, 1125, 1111, 1039, 1008, 827 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.55 (s, 1H, COOH), 10.10 (s, 1H, NH), 7.58 (1H, d, J=1.6 Hz, ArH), 7.41 (2H, d, J=8.4 Hz, ArH), 7.30 (dd, J=1.6, 16.0 Hz, 1H, ArH), 7.10 (d, J=8.4 Hz, 2H, ArH) 6.71–6.69 (m, 2H, ArH and NH), 5.07 (d, J=4.4 Hz, 1H, CH), 4.91 (s, 2H, CH_2). HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{18}H_{14}BrN_2O_4$: 401.0132; found: 401.0105.

4.2.3. 10-(2,4-Dichlorophenyl)-1-oxo-3,4,9,10-tetrahydro-1H-benzo[b]furo[3,4-e][1,4]diazepine-6-carboxylic acid ***4c***. Pale white solid, mp: 285–287 °C; IR (KBr): 3379, 3322, 1724, 1692, 1660, 1571, 1511, 1463, 1392, 1358, 1198, 1167, 1137, 1046, 880, 855, 821, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.58 (s, 1H, COOH), 10.21 (s, 1H, NH), 7.61 (d, J=1.6 Hz, 2H, ArH), 7.29 (dd, J=1.6, 16.8 Hz, 1H, ArH), 7.17 (dd, J=2.0, 16.8 Hz, 1H, ArH), 6.83 (d, J=8.4 Hz, 1H, ArH), 6.72 (d, J=8.4 Hz, 1H, ArH), 6.36 (d, J=4.4 Hz, 1H, NH), 5.45 (d, J=4.4 Hz, 1H, CH), 4.94 (s, 2H, CH_2). HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{18}H_{13}Cl_2N_2O_4$: 391.0247; found: 391.0219.

4.2.4. 10-(4-Nitrophenyl)-1-oxo-3,4,9,10-tetrahydro-1H-2-oxa-4,9-diazabenzo[f]azulene-6-carboxylic acid ***4d***. Pale white solid, mp: >300 °C; IR (KBr): 3358, 3316, 3137, 1727, 1686, 1667, 1602, 1572, 1521, 1509, 1240, 1199, 1185, 1163, 1129, 1049, 1017, 820 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.58 (s, 1H, COOH), 10.21 (s, 1H, NH), 8.10 (d, J=8.8 Hz, 1H, ArH), 7.62 (s, 1H, ArH), 7.41 (d, J=8.8 Hz, 2H, ArH), 7.31 (d, J=8.4Hz, 1H, ArH), 6.84 (d, J=4.4 Hz, 1H, NH), 6.72 (d, J=8.4 Hz, 1H, ArH), 5.21 (d, J=4.0 Hz, 1H, CH), 4.94 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 172.9, 167.3, 159.2, 151.7, 146.8, 141.3, 130.4, 128.6, 124.8, 124.0, 122.5, 122.5, 121.8, 96.0, 66.7, 57.0. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{18}H_{14}N_3O_6$: 368.0878; found: 368.0865.

4.2.5. 1-Oxo-10-p-tolyl-3,4,9,10-tetrahydro-1H-2-oxa-4,9-diazabenzo[f]azulene-6-carboxylic acid ***4e***. Pale white solid, mp: 278–280 °C; IR (KBr): 3361, 1724, 1702, 1650, 1570, 1513, 1359, 1186, 1170, 1123, 1039, 1008, 754 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.49 (s, 1H, COOH), 10.02 (s, 1H, NH), 7.56 (s, 1H, ArH), 7.28 (d, J=8.0 Hz, 1H, ArH), 7.02 (t, J=8.4 Hz, 4H, ArH), 6.69 (d, J=8.4 Hz, 1H, ArH), 6.65 (d, J=4.0 Hz, 1H, NH), 5.05 (d, J=4.0 Hz, 1H, CH), 4.90 (s, 2H, CH_2), 2.19 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.1, 167.3, 158.7, 142.2, 141.2, 136.3, 130.5, 129.2, 127.2, 124.6, 122.7, 122.4, 121.5, 97.3, 66.5, 57.1, 21.0. HRMS (ESI) m/z: calcd for $[M+Na^+]$ $C_{19}H_{16}NaN_2O_4$: 359.1003; found: 359.0991.

4.2.6. 10-(4-Methoxyphenyl)-1-oxo-3,4,9,10-tetrahydro-1H-benzo[b]furo[3,4-e][1,4]diazepine-6-carboxylic acid ***4f***. Pale white solid, mp: 251–253 °C; IR (KBr): 3361, 3079, 1724, 1651, 1570, 1511, 1410, 1347, 1252, 1177, 1114, 1038, 1008, 831, 760 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.46 (s, 1H, COOH), 10.02 (s, 1H, NH), 7.55 (d, 1H, J=1.6 Hz, ArH), 7.27 (dd, J=1.6, 16.8 Hz, 1H, ArH), 7.05 (d, J=8.8 Hz, 2H, ArH), 6.75 (d, J=8.8 Hz, 1H, ArH), 6.68 (d, J=8.4 Hz, 1H, ArH), 6.63 (d, J=4.4 Hz, 1H, NH), 5.02 (d, J=4.4 Hz, 1H, CH), 4.89 (s, 2H,

CH_2), 3.65 (s, 3H, CH_3). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{19}H_{17}N_2O_5$: 353.1132; found: 353.1119.

4.2.7. 10-(2,3-Dimethoxyphenyl)-1-oxo-3,4,9,10-tetrahydro-1H-benzo[b]furo[3,4-e][1,4]diazepine-6-carboxylic acid ***4g***. Pale white solid, mp: >300 °C; IR (KBr): 3366, 3326, 3250, 3074, 2973, 1720, 1643, 1574, 1514, 1484, 1415, 1393, 1348, 1280, 1259, 1053, 1041, 1000, 852 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.51 (s, 1H, COOH), 10.10 (s, 1H, NH), 7.60 (d, 1H, *J*=1.6 Hz, ArH), 7.25 (dd, *J*=2.0, 16.4 Hz, 1H, ArH), 6.86–6.83 (m, 1H, ArH), 6.77 (t, *J*=8.0 Hz, 1H, ArH), 6.66 (d, *J*=8.4 Hz, 1H, ArH), 6.26–6.24 (m, 1H, ArH), 6.12 (d, *J*=4.4 Hz, 1H, NH), 5.42 (d, *J*=4.4 Hz, 1H, CH), 4.91 (s, 2H, CH_2), 3.89 (s, 3H, CH_3), 3.78 (s, 3H, CH_3). HRMS (ESI) *m*/*z*: calcd for [M+Na^+] $C_{20}H_{18}NaN_2O_6$: 405.1058; found: 405.1073.

4.2.8. 1-Oxo-10-thien-2-yl-3,4,9,10-tetrahydro-1H-2-oxa-4,9-diazabenzo[f]azulene-6-carboxylic acid ***4h***. Pale white solid, mp: 285–286 °C; IR (KBr): 3336, 3305, 1720, 1696, 1652, 1572, 1508, 1404, 1353, 1267, 1227, 1144, 1043, 1007, 891, 828 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.56 (s, 1H, COOH), 10.07 (s, 1H, NH), 7.55 (d, *J*=0.8Hz, 1H, Thienyl-H), 7.35–7.33 (m, 1H, ArH), 7.26–7.25 (m, 1H, ArH), 6.85 (t, *J*=4.0 Hz, 2H, Thienyl-H), 6.80 (d, *J*=8.4 Hz, 1H, ArH), 6.77 (d, *J*=4.8 Hz, 1H, NH), 5.30 (d, *J*=4.4 Hz, 1H, CH), 4.88 (dd, *J*=15.6, 17.8 Hz, 2H, CH_2). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{16}H_{12}N_2NaO_4S$: 351.0410; found: 351.0409.

4.2.9. 10-Benzyl-1-oxo-3,4,9,10-tetrahydro-1H-2-oxa-4,9-diazabenzo[f]azulene-6-carboxylic acid ***4i***. Pale white solid, mp: 249–250 °C; IR (KBr): 3524, 3350, 3299, 3132, 1688, 1637, 1573, 1516, 1497, 1422, 1353, 1277, 1252, 1231, 1190, 1129, 1047, 1027, 980 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 12.46 (s, 1H, COOH), 9.81 (s, 1H, NH), 7.51 (d, *J*=1.6 Hz, 1H, ArH), 7.37 (dd, *J*=2.0, 8.0 Hz, 1H, ArH), 7.24–7.21 (m, 2H, ArH), 7.18–7.14 (m, 1H, ArH), 7.03 (d, *J*=7.2 Hz, ArH), 6.78 (1H, d, *J*=8.4 Hz, ArH), 6.22 (1H, d, *J*=4.4 Hz, 2H, NH), 4.80 (d, *J*=15.2 Hz, CH_2), 4.69 (d, *J*=15.2 Hz, CH_2), 4.15–4.11 (m, 1H, CH), 2.85–2.81 (m, 1H, CH_2), 2.71–2.65 (m, 1H, CH_2). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{19}H_{17}N_2O_4$: 337.1183; found: 337.1190.

4.2.10. 7-Chloro-10-(4-chlorophenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4j***. Pale white solid, mp: 250–252 °C; IR (KBr): 3345, 3273, 3140, 3095, 1715, 1666, 1621, 1563, 1499, 1420, 1398, 1363, 1186, 1057, 1031, 1014, 999, 872 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 10.00 (s, 1H, NH), 7.31–7.29 (m, 2H, ArH), 7.15–7.13 (m, 2H, ArH), 6.90 (d, *J*=8.4 Hz, 1H, ArH), 6.80–6.78 (m, 1H, ArH), 6.68–6.67 (m, 1H, ArH), 6.36 (d, *J*=4.4 Hz, 1H, NH), 5.05 (d, *J*=4.0 Hz, 1H, CH), 4.90 (s, 2H, CH_2). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{17}H_{13}Cl_2N_2O_2$: 347.0349; found: 347.0343.

4.2.11. 7-Chloro-10-(2,4-dichlorophenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4k***. Pale white solid, mp: 272–274 °C; IR (KBr): 3387, 3274, 3088, 1722, 1710, 1628, 1569, 1501, 1464, 1411, 1354, 1331, 1237, 1184, 1103, 1046, 967, 868 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 10.13 (s, 1H, NH), 7.64 (d, *J*=2.0 Hz, 1H, ArH), 7.19 (dd, *J*=2.0, 8.4 Hz, 1H, ArH), 6.96 (d, *J*=8.8 Hz, 1H, ArH), 6.84 (dd, *J*=2.4, 8.6 Hz, 1H, ArH), 6.82 (d, *J*=8.4 Hz, 1H, ArH), 6.72 (d, *J*=2.4 Hz, 1H, ArH), 6.05 (d, *J*=4.4 Hz, 1H, NH), 5.41 (d, *J*=4 Hz, 1H, CH), 4.94 (s, 2H, CH_2). HRMS (ESI) *m*/*z*: calcd for [M+Na^+] $C_{17}H_{11}Cl_3N_2NaO_2$: 402.9779; found: 402.9796.

4.2.12. 7-Chloro-10-p-tolyl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4l***. Pale white solid, mp: 287–289 °C; IR (KBr): 3346, 3248, 3092, 1716, 1667, 1654, 1564, 1499, 1420, 1405, 1364, 1331, 1187, 1057, 1032, 998, 867 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.94 (s, 1H, NH), 7.04–6.99 (m, 4H, ArH), 6.88 (d, *J*=8.4 Hz, 1H, ArH), 6.77–6.75 (m, 1H, ArH), 6.66 (s, 1H, ArH), 6.31 (d, *J*=4.4 Hz, 1H, NH), 5.01 (d, *J*=4.0 Hz, 1H, CH), 4.90 (s, 2H, CH_2), 2.21 (s, 3H, CH_3). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{18}H_{16}ClN_2O_2$: 327.0895; found: 327.0878.

4.2.13. 7-Chloro-10-(2-methoxyphenyl)-3,4,9,10-tetrahydro-1H-benzo[b]furo[3,4-e][1,4]diazepin-1-one ***4m***. Pale white solid, mp: 248–251 °C; IR (KBr): 3357, 3248, 3154, 1717, 1672, 1617, 1572, 1503, 1408, 1368, 1064, 1053, 1013, 1000, 777 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.96 (s, 1H, NH), 7.18–7.12 (m, 1H, ArH), 7.00 (d, *J*=8.0 Hz, 1H, ArH), 6.87 (d, *J*=8.4 Hz, 1H, ArH), 6.75 (dd, *J*=8.4, 2.0 Hz, 1H, ArH), 6.68–6.60 (m, 3H, ArH), 5.75 (d, *J*=4.4 Hz, 1H, NH), 5.34 (d, *J*=4.4 Hz, 1H, CH), 4.98–4.89 (m, 2H, CH_2), 3.90 (s, 3H, CH_3). HRMS (ESI) *m*/*z*: calcd for [M+Na^+] $C_{18}H_{15}ClN_2O_3Na$ 365.0664; found: 365.0654.

4.2.14. 7-Chloro-10-thien-2-yl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4n***. Pale yellow solid, mp: 294–296 °C; IR (KBr): 3337, 3244, 3069, 1716, 1667, 1617, 1567, 1499, 1413, 1365, 1190, 1000, 868, 849, 808 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.99 (s, 1H, NH), 7.28–7.27 (m, 1H, ArH), 6.90–6.86 (m, 2H, ArH), 6.83–6.79 (m, 3H, Thienyl-H), 6.77–6.69 (m, 2H, ArH), 6.43 (d, *J*=4.4 Hz, 1H, NH), 5.27 (d, *J*=4.4 Hz, 1H, CH), 4.87 (dd, *J*=15.6, 20.0 Hz, 2H, CH_2). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{15}H_{12}ClN_2O_2S$: 319.0303; found: 319.0290.

4.2.15. 10-Benzyl-7-chloro-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4o***. White solid, mp: 234–235 °C; IR (KBr): 3379, 3276, 3107, 3027, 1721, 1637, 1569, 1496, 1490, 11,417, 1362, 1339, 1190, 1037, 1028, 983 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.77 (s, 1H, NH),7.27 (t, *J*=7.2 Hz, 2H, ArH), 7.19 (t, *J*=7.8 Hz, 1H, ArH), 7.06 (d, *J*=7.2 Hz, 2H, ArH), 6.87 (d, *J*=8.4 Hz, 1H, ArH), 6.82–6.78 (m, 2H, ArH), 5.87 (d, *J*=4.4 Hz, 1H, NH), 4.77 (dd, *J*=15.2, 20.2 Hz, 2H, CH_2), 4.11–4.06 (m, 1H, CH), 2.79–2.75 (m, 1H, CH_2), 2.68–2.63 (m, 1H, CH_2). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{18}H_{16}ClN_2O_2$: 327.0895; found: 327.0911.

4.2.16. 6,7-Dichloro-10-(2,4-dichloro-phenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4p***. Pale white solid, mp: 211–213 °C; IR (KBr): 3371, 3242, 3074, 1724, 1643, 1563, 1483, 1342, 1183, 1148, 1105, 1042, 1013, 879, 868 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 10.21 (s, 1H, NH), 7.64 (d, 1H, *J*=2.0 Hz, ArH), 7.21 (dd, *J*=2.0, 16.8 Hz, 1H, ArH), 7.13 (s, 1H, ArH), 6.91 (s, 1H, ArH), 6.83 (d, *J*=8.4 Hz, 1H, ArH), 6.19 (d, *J*=4.4 Hz, 1H, NH), 5.41 (d, *J*=4.4 Hz, 1H, CH), 4.95 (dd, *J*=15.6, 17.4 Hz, 2H, CH_2). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{17}H_{11}Cl_4N_2O_2$: 414.9570; found: 414.9551.

4.2.17. 6,7-Dichloro-10-(4-nitro-phenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4q***. Pale yellow solid, mp: 296–297 °C; IR (KBr): 3367, 3256, 3093, 1721, 1647, 1570, 1518, 1488, 1405, 1348, 1244, 1185, 1152, 1049, 1017, 875, 861 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 10.21 (s, 1H, NH), 8.13 (d, *J*=8.4 Hz, 2H, ArH), 7.40 (d, *J*=8.8 Hz, 2H, ArH), 7.12 (s, 1H, ArH), 6.89 (s, 1H, ArH), 6.64 (d, *J*=4.4 Hz, 1H, NH), 5.21 (d, *J*=4.0 Hz, 1H, CH), 4.96 (dd, *J*=15.6, 18.6 Hz, 2H, CH_2). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{17}H_{12}Cl_2N_3O_4$: 392.0200; found: 392.0178.

4.2.18. 6,7-Dichloro-10-p-tolyl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4r***. Pale white solid, mp: 282–284 °C; IR (KBr): 3350, 3286, 3093, 1724, 1646, 1566, 1487, 1403, 1344, 1328, 1242, 1183, 1149, 1044, 1008, 873 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 10.03 (s, 1H, NH), 7.05–6.98 (m, 5H, ArH), 6.83 (s, 1H, ArH), 6.44 (d, *J*=4.4 Hz, 1H, NH), 5.01 (d, *J*=4.4 Hz, 1H, CH), 4.91 (s, 2H, CH_2), 2.21 (s, 3H, CH_3). HRMS (ESI) *m*/*z*: calcd for [M+H^+] $C_{18}H_{15}Cl_2N_2O_2$: 361.0506; found: 361.0495.

4.2.19. 6,7-Dichloro-10-thien-2-yl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4s***. Pale white solid, mp: 261–263 °C; IR

(KBr): 3335, 3247, 3096, 2943, 1718, 1665, 1639, 1561, 1487, 1407, 1342, 1255, 1227, 1177, 1143, 1039, 1006, 876 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 10.08 (s, 1H, NH), 7.29 (d, 1H, J=5.2 Hz, Thienyl-H), 7.06 (s, 1H, ArH), 6.96 (s, 1H, ArH), 6.88 (m, 1H, Thienyl-H), 6.83 (d, J=2.8 Hz, 1H, ArH), 6.55 (d, J=4.4 Hz, 1H, NH), 5.28 (d, J=4.4 Hz, 1H, CH), 4.89 (dd, J=15.2, 23.6 Hz, 2H, CH_2). HRMS (ESI) m/z: calcd for $[M+Na^+]$ $C_{15}H_{10}Cl_2NaN_2O_2S$: 374.9733; found: 374.9731.

4.2.20. 10-Benzyl-6,7-dichloro-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4t***. White solid, mp: 276–277 °C; IR (KBr): 3353, 3299, 3141, 3100, 3028, 1715, 1647, 1602, 1566, 1486, 1416, 1338, 1246, 1187, 1140, 1043, 1028, 987, 870 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.83 (s, 1H, NH), 7.27–7.23 (m, 2H, ArH), 7.20–7.17 (m, 1H, ArH), 7.05 (d, J=7.2 Hz, 2H, ArH), 7.01 (s, 1H, ArH), 6.93 (s, 1H, ArH), 6.03 (d, J=4.4 Hz, 1H, NH), 4.78 (dd, J=15.2, 23.6 Hz, 2H, CH_2), 4.12–4.08 (m, 1H, CH), 2.82–2.77 (m, 1H, CH_2), 2.70–2.65 (m, 1H, CH_2). HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{18}H_{15}Cl_2N_2O_2$: 361.0506; found: 361.0491.

4.2.21. 10-(4-Chlorophenyl)-3,4,9,10-tetrahydro-2-oxa-4,5,9-triazabenzo[f]azulen-1-one ***4u***. White solid, mp: 262–264 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1568, 1508, 1478, 1390, 1365, 1062, 1052, 1032, 1011 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.87 (s, 1H, NH), 7.25 (d, J=8.0 Hz, 2H, ArH), 7.15 (d, J=8.4 Hz, 2H, ArH), 6.90 (d, J=7.6 Hz, 1H, ArH), 6.77–6.69 (m, 2H, ArH), 6.59 (d, J=7.2 Hz, 1H, ArH), 6.09 (d, J=4.4 Hz, 1H, NH), 5.06 (d, J=4.0 Hz, 1H, CH), 4.90 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.2, 159.5, 143.1, 137.5, 132.1, 131.7, 129.4, 128.4, 123.5, 123.4, 121.4, 120.1, 96.7, 66.6, 57.2. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{17}H_{14}ClN_2O_2$: 313.0739; found: 313.0712.

4.2.22. 10-(4-Bromophenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4v***. White solid, mp: >300 °C; IR (KBr): 3352, 3247, 3150, 3104, 1716, 1670, 1617, 1595, 1568, 1508, 1478, 1454, 1403, 1390, 1365, 1334, 1062, 1052, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.88 (s, 1H, NH), 7.39 (d, J=8.0 Hz, 2H, ArH), 7.09 (d, J=8.4 Hz, 2H, ArH), 6.90 (d, J=7.6 Hz, 1H, ArH), 6.77–6.69 (m, 2H, ArH), 6.59 (d, J=7.6 Hz, 1H, ArH), 6.09 (d, J=4.4 Hz, 1H, NH), 5.04 (d, J=4.0 Hz, 1H, CH), 4.90 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.2, 159.5, 143.6, 137.5, 132.1, 131.3, 129.8, 123.5, 123.4, 121.4, 120.2, 120.1, 96.7, 66.6, 57.3. HRMS (ESI) m/z: calcd for $[M+Na^+]$ $C_{17}H_{13}BrNaN_2O_2$: 379.0053; found: 379.0037.

4.2.23. 10-(2,4-Dichlorophenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4w***. White solid, mp: 204–205 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1568, 1508, 1478, 1403, 1390, 1365, 1334, 1062, 1032, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 10.00 (s, 1H, NH),7.60 (s, 1H, ArH), 7.14 (d, J=8.0 Hz, 1H, ArH), 6.96 (d, J=8 Hz, 1H, ArH), 6.81 (m, 2H, ArH), 6.71 (t, J=7.6 Hz, 1H, ArH), 6.58 (d, J=7.6 Hz, 1H, ArH), 5.71 (d, J=4.0 Hz, 1H, NH), 5.41 (d, J=4.4 Hz, 1H, CH), 4.94 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 172.7, 160.4, 139.6, 136.6, 134.6, 132.7, 132.7, 129.3, 129.3, 127.2, 123.8, 122.2, 120.1, 96.0, 66.8, 54.8. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{17}H_{13}Cl_2N_2O_2$: 347.0349; found: 347.0347.

4.2.24. 10-(4-Nitrophenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4x***. Yellow solid, mp: 219–220 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1568, 1508, 1478, 1403, 1390, 1365, 1334, 1062, 1032, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.99 (s, 1H, NH), 8.08 (d, J=8.0 Hz, 2H, ArH), 7.40 (d, J=8.4 Hz, 2H, ArH), 6.94 (d, J=7.6 Hz, 1H, ArH), 6.78 (t, J=7.2 Hz, 1H, ArH), 6.72 (d, J=7.2 Hz, 1H, ArH), 6.61 (d, J=7.6 Hz, 1H, ArH), 6.26 (d, J=4.4 Hz, 1H, NH), 5.18 (d, J=4.4 Hz, 1H, CH), 4.94 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.1, 159.7, 151.8, 146.7, 137.1, 132.0, 128.7, 123.7, 123.7, 123.3, 121.7, 120.3, 96.0, 66.7, 57.4. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{17}H_{14}N_3O_4$: 324.0979; found: 324.0956.

4.2.25. 10-(2-Chlorophenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4y***. White solid, mp: 233–235 °C; IR (KBr): 3395, 3156, 3063, 2989, 2952, 2930, 2899, 1725, 1652, 1574, 1506, 1484, 1444, 1398, 1363, 1233, 1122, 1046, 985 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.98 (s, 1H, NH),7.43 (d, J=4.0 Hz, 1H, ArH), 7.16 (t, J=7.2 Hz, 1H, ArH), 7.03 (t, J=7.6 Hz, 1H, ArH), 6.96 (d, J=7.6 Hz, 1H, ArH), 6.79 (t, J=7.6 Hz, 2H, ArH), 6.68 (t, J=7.2 Hz, 1H, ArH), 6.56 (d, J=7.6 Hz, 1H, ArH), 5.63 (d, J=4.4 Hz, 1H, NH), 5.47 (d, J=4.4 Hz, 1H, CH), 4.95 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 172.8, 160.4, 140.4, 136.7, 133.7, 132.6, 130.0, 129.2, 128.0, 127.1, 123.7, 123.6, 122.0, 120.0, 96.4, 66.7, 55.3. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{17}H_{14}ClN_2O_2$: 313.0739; found: 313.0724.

4.2.26. 10-(3-Nitrophenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4z***. Yellow solid, mp: 252–255 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1568, 1478, 1454, 1438, 1403, 1365, 1062, 1032, 1011, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.97 (s, 1H, NH), 8.09 (s, 1H, ArH), 8.00 (d, J=8.0 Hz, 1H, ArH), 7.55–7.47 (m, 2H, ArH), 6.94 (d, J=7.6 Hz, 1H, ArH), 6.79–6.70 (m, 2H, ArH), 6.62 (d, J=8.0 Hz, 1H, ArH), 6.25 (d, J=4.4 Hz, 1H, NH), 5.22 (d, 1H, J=4 Hz, CH), 4.95 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.2, 159.9, 148.1, 146.4, 137.1, 133.9, 132.2, 130.0, 123.7, 123.4, 122.4, 122.2, 121.8, 120.3, 96.1, 66.7, 57.4. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{17}H_{14}N_3O_4$: 324.0979; found: 324.0957.

4.2.27. 4-(1-Oxo-3,4,9,10-tetrahydro-1H-2-oxa-4,9-diazabenzo[f]azulen-10-yl)-benzonitrile ***4aa***. Pale white solid, mp: 279–281 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1508, 1478, 1454, 1438, 1390, 1365, 1334, 1062, 1032, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.96 (s, 1H, NH),7.68 (d, J=8.4 Hz, 2H, ArH), 7.32 (d, J=8.0 Hz, 2H, ArH), 6.93 (d, J=7.2 Hz, 1H, ArH), 6.79–6.70 (m, 2H, ArH), 6.59 (d, J=7.6 Hz, 1H, ArH), 6.22 (d, J=4.0 Hz, 1H, NH), 5.12 (d, J=4 Hz, 1H, CH), 4.92 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.1, 159.7, 149.7, 137.2, 132.5, 132.0, 128.5, 123.6, 123.3, 121.6, 120.2, 119.2, 109.9, 96.0, 66.7, 57.6. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{18}H_{14}N_3O_2$: 304.1081; found: 304.1071.

4.2.28. 10-Phenyl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4bb***. White solid, mp: 290–291 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1568, 1508, 1478, 1403, 1390, 1334, 1062, 1052, 1011, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.83 (s, 1H, NH), 7.20–7.09 (m, 5H, ArH), 6.89 (d, J=7.8 Hz, 1H, ArH), 6.75–6.66 (m, 2H, ArH), 6.59 (d, J=6.8 Hz, 1H, ArH), 6.07 (d, J=4.4 Hz, 1H, NH), 5.05 (d, J=4.4 Hz, 1H, CH), 4.90 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.3, 159.2, 144.2, 137.8, 131.9, 128.4, 127.5, 127.0, 123.3, 123.3, 121.1, 120.0, 97.2, 66.5, 57.8. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{17}H_{15}N_2O_2$: 279.1129; found: 279.1127.

4.2.29. 10-p-Tolyl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4cc***. White solid, mp: 287–288 °C; IR (KBr): 3351, 3246, 3202, 3149, 3102, 3083, 2965, 1717, 1645, 1639, 1568, 1509, 1487, 1387, 1197, 1061, 1033, 995, 851, 845 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.81 (s, 1H, NH), 7.00 (dd, J=8.0, 14.4 Hz, 4H, ArH), 6.89 (d, J=7.6 Hz, 1H, ArH), 6.74–6.66 (m, 2H, ArH), 6.58 (d, J=7.2 Hz, 1H, ArH), 6.03 (d, J=4.0 Hz, 1H, NH), 5.02 (d, J=4.0 Hz, 1H, CH), 4.89 (s, 2H, CH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.2, 159.5, 143.6, 137.5, 132.1, 131.3, 129.8, 123.5, 123.4, 121.4, 120.2, 120.1, 96.7, 66.6, 57.3. HRMS (ESI) m/z: calcd for $[M+H^+]$ $C_{18}H_{17}N_2O_2$: 293.1285; found: 293.1279.

4.2.30. 10-(2-Methoxyphenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4dd***. White solid, mp: 247–259 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1568,

1508, 1478, 1438, 1403, 1390, 1062, 1052, 1032, 1011, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.88 (s, 1H, NH), 7.39 (d, J=8.0 Hz, 2H, ArH), 7.09 (d, J=8.4 Hz, 2H, ArH), 6.90 (d, J=7.6 Hz, 1H, ArH), 6.77–6.69 (m, 2H, ArH), 6.59 (d, J=7.6 Hz, 1H, ArH), 6.09 (d, J=4.4 Hz, 1H, NH), 5.04 (d, J=4.0 Hz, 1H, CH), 4.90 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.2, 159.5, 143.6, 137.5, 132.1, 131.3, 129.8, 123.5, 123.4, 121.4, 120.2, 120.1, 96.7, 66.6, 57.3. HRMS (ESI) m/z: calcd for [M+H^+] $C_{18}H_{17}N_2O_3$: 309.1234; found: 309.1220.

4.2.31. 10-(3,4,5-Trimethoxyphenyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4ee***. Pale white solid, mp: 259–260 °C; IR (KBr): 3323, 3301, 3105, 2994, 2945, 2832, 1716, 1661, 1627, 1603, 1565, 1485, 1418, 1390, 1305, 1252, 1153, 1047, 783 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.83 (s, 1H, NH), 6.91–6.89 (m, 1H, ArH), 6.78–6.71 (m, 2H, ArH), 6.67–6.64 (m, 1H, ArH), 6.41 (s, 2H, ArH), 6.01 (d, J=4.4 Hz, 1H, NH), 4.97 (d, J=4.0 Hz, 1H, CH), 4.90 (d, J=15.6 Hz, 1H, CH_2), 4.86 (d, J=15.6 Hz, 1H, CH_2), 3.58 (s, 6H, CH_3), 3.55 (s, 3H, CH_3). HRMS (ESI) m/z: calcd for [M+Na^+] $C_{20}H_{20}NaN_2O_5$: 391.1265; found: 391.1262.

4.2.32. 10-(4-Dimethylaminophenyl)-3,4,9,10-tetrahydro-2-oxa-4,5,9-triazabenzo[f]azulen-1-one ***4ff***. Pale white solid, mp: 273–276 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1568, 1508, 1454, 1438, 1390, 1365, 1334, 1062, 1011, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.74 (s, 1H, NH), 6.94 (d, J=8.4 Hz, 2H, ArH), 6.87 (d, J=7.2 Hz, 1H, ArH), 6.73–6.66 (m, 2H, ArH), 6.60 (d, J=7.2 Hz, 1H, ArH), 6.53 (d, J=8.8 Hz, 2H, ArH), 5.94 (d, J=4.4 Hz, 1H, NH), 4.96 (d, J=4.0 Hz, 1H, CH), 4.87 (s, 2H, CH_2), 2.79 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.4, 158.9, 149.6, 138.2, 132.0, 128.2, 123.3, 123.2, 119.8, 112.4, 197.9, 66.4, 57.2. HRMS (ESI) m/z: calcd for [M+H^+] $C_{19}H_{20}N_3O_2$: 322.1551; found: 322.1551.

4.2.33. 10-Thien-2-yl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4gg***. Pale yellow solid, mp: 282–283 °C; IR (KBr): 3352, 3247, 3150, 3104, 3083, 1716, 1670, 1617, 1595, 1508, 1478, 1454, 1403, 1390, 1365, 1062, 1052, 1032, 774 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.88 (1H, s, NH),7.39 (d, J=8.0 Hz, 2H, ArH), 7.09 (d, J=8.4 Hz, 2H, ArH), 6.90 (d, J=7.6 Hz, 1H, ArH), 6.77–6.69 (m, 2H, ArH), 6.59 (d, J=7.6 Hz, 1H, ArH), 6.09 (d, J=4.4 Hz, 1H, NH), 5.04 (d, J=4.0 Hz, 1H, CH), 4.90 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 173.0, 159.1, 148.6, 137.6, 132.1, 127.0, 125.1, 123.7, 123.5, 121.6, 120.1, 98.2 66.5, 53.3. HRMS (ESI) m/z: calcd for [M+Na^+] $C_{15}H_{12}N_2NaO_2S$: 307.0512; found: 307.0513.

4.2.34. 10-Benzyl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4hh***. White solid, mp: 229–231 °C; IR (KBr): 3349, 3287, 3154, 3101, 1720, 1640, 1568, 1507, 1489, 1438, 1396, 1335, 1192, 1047, 766, 747, 702 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.66 (s, 1H, NH), 7.28 (t, J=7.4 Hz, 2H, ArH), 7.20 (t, J=7.2 Hz, 1H, ArH), 7.09 (d, J=7.2 Hz, 2H, ArH), 6.90 (d, J=7.2 Hz, 1H, ArH), 6.86–6.78 (m, 2H, ArH), 6.72 (d, J=7.2 Hz, 1H, ArH), 5.43 (d, J=4.0 Hz, 1H, NH), 4.76 (dd, J=15.2, 4.0 Hz, 2H, CH_2), 2.78–2.73 (m, 1H, CH_2), 2.64–2.58 (m, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6 25 °C) (δ, ppm): 173.1, 158.5, 139.1, 137.3, 131.8, 129.8, 128.7, 126.6, 123.7, 123.2, 121.0, 120.1, 98.6, 66.5, 55.7, 44.3. HRMS (ESI) m/z: calcd for [M+H^+] $C_{18}H_{17}N_2O_2$: 293.1285; found: 293.1287.

4.2.35. 10-Isobutyl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4ii***. White solid, mp: 208–210 °C; IR (KBr): 3346, 2952, 2926, 1737, 1666, 1560, 1502, 1475, 1390, 1363, 1337, 1186, 1030, 1011, 969, 758, 647 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.64 (s, 1H, NH), 6.88 (d, J=7.2 Hz, 2H, ArH), 6.83–6.76 (m, 2H, ArH), 5.69 (d, J=4.4 Hz, 1H, NH), 4.77 (dd, J=15.2, 18.8 Hz, 2H, CH_2), 3.92–3.87 (m, 1H, CH), 1.72–1.65 (m, 1H, CH), 1.28–1.22 (m, 1H, CH_2), 1.12–1.05 (m, 1H, CH_2), 0.88 (d, J=6.4 Hz, 3H, CH_3), 0.83 (d, J=6.4 Hz, 3H, CH_3). HRMS (ESI) m/z: calcd for [M+Na^+] $C_{15}H_{18}NaN_2O_2$: 281.1261; found: 281.1274.

4.2.36. 10-sec-Butyl-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4jj***. White solid, mp: 173–175 °C; IR (KBr): 3355, 3293, 3109, 2963, 2929, 2874, 1731, 1651, 1567, 1490, 1437, 1393, 1359, 1335, 1186, 1151, 1122, 1043, 772 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.65 (s, 1H, NH), 6.90–6.84 (m, 2H, ArH), 6.82–6.78 (m, 1H, ArH), 6.75–6.72 (m, 1H, ArH), 5.83–5.80 (m, 1H, NH), 4.77 (s, 2H, CH_2), 3.92–3.87 (m, 1H, CH), 3.60–3.54 (m, 1H, CH), 1.56–1.26 (m, 2H, CH_2), 1.17–0.94 (m, 1H, CH), 0.81–0.72 (m, 6H, CH_3). HRMS (ESI) m/z: calcd for [M+Na^+] $C_{15}H_{18}N_2NaO_2$: 281.1261; found: 281.1276.

4.2.37. 10-(1-Methylbutyl)-3,4,9,10-tetrahydro-2-oxa-4,9-diazabenzo[f]azulen-1-one ***4kk***. White solid, mp: 173–174 °C; IR (KBr): 3352, 2963, 2930, 2871, 1731, 1651, 1566, 1488, 1436, 1393, 1360, 1333, 1186, 1153, 1042, 1030, 986, 772, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.66 (s, 1H, NH), 6.91–6.85 (m, 2H, ArH), 6.82–6.79 (m, 1H, ArH), 6.77–6.73 (m, 1H, ArH), 5.82 (d, 1H, J=4.8 Hz, NH), 4.76 (m, 2H, CH_2), 3.56–3.53 (m, 1H, CH), 1.51–1.26 (m, 3H, CH and CH_2), 1.13–0.96 (m, 2H, CH_2), 0.80–0.71 (m, 6H, CH_3). HRMS (ESI) m/z: calcd for [M+Na^+] $C_{16}H_{20}N_2NaO_2$: 295.1417; found: 295.1410.

4.2.38. 10-Cyclohexyl-3,4,9,10-tetrahydro-2-oxa-4,9-diaza-benzo[f]azulen-1-one ***4ll***. White solid, mp: 256–257 °C; IR (KBr): 3483, 3350, 3325, 3058, 2934, 2853, 1731, 1706, 1654, 1616, 1565, 1508, 1486, 1434, 1393, 1191, 1178, 1041, 801 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.64 (s, 1H, NH), 6.89–6.84 (m, 2H, ArH), 6.80 (t, J=7.6 Hz, 1H, ArH), 6.76–6.72 (m, 1H, ArH), 5.83 (d, J=4.8 Hz, 1H, NH), 4.78 (d, J=15.2 Hz, 1H, CH_2), 4.73 (d, J=15.2 Hz, 1H, CH_2), 3.49 (dd, J=4.8, 15.2 Hz, 1H, CH), 1.85–1.84 (m, 1H, CH), 1.62–1.39 (m, 4H, CH_2), 1.15–0.98 (m, 4H, CH_2), 0.94–0.87 (m, 2H, CH_2). HRMS (ESI) m/z: calcd for [M+H^+] $C_{17}H_{21}N_2O_2$: 285.1598; found: 285.1595.

4.2.39. 10-Isopropyl-3,4,9,10-tetrahydro-2-oxa-4,9-diaza-benzo[f]azulen-1-one ***4mm***. White solid, mp: 254–256 °C; IR (KBr): 3469, 3329, 3276, 3152, 3101, 2960, 1708, 1652, 1570, 1508, 1479, 1435, 1395, 1364, 1333, 1232, 1045, 998, 849 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.66 (s, 1H, NH), 6.91–6.85 (m, 2H, ArH), 6.82–6.79 (m, 1H, ArH), 6.77–6.73 (m, 1H, ArH), 5.82 (d, J=4.8 Hz, 1H, NH), 4.77 (s, 2H, CH_2), 3.46 (dd, J=4.8, 8.4 Hz, 1H, CH), 1.53–1.44 (m, 1H, CH), 0.86 (d, J=6.4 Hz, 3H, CH_3), 0.82 (d, J=6.8 Hz, 3H, CH_3). HRMS (ESI) m/z: calcd for [M+Na^+] $C_{14}H_{17}N_2O_2$: 245.1285; found: 245.1289.

4.3. General procedure for the synthesis of products 5a

In a 10-mL reaction vial, the benzene-1,2-diamine **1a** (1 mmol), tetronic acid **3** (1 mmol), acetic acid (0.1 mmol), and water (2 mL) were mixed and then stirred for 10 min. Subsequently, the 2-formylbenzoic acids **2** (1 mmol) was added to the reaction mixture, and the reaction vial was capped and pre-stirred for 20 s. The mixture was subjected to microwave irradiation at 200 W (initial power 100 W, maximum power 200 W) at 150 °C, for 15 min. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature, filtered to give the crude product, which was further washed by 50% EtOH to give pure product **5a**.

4.3.1. 4bH-Benzo[2,3]furo[3′,4′:5,6][1,4]diazepino[7,1-a]isoindole-5,14(7H,8H)-dione ***5a***. White solid, mp: 286–289 °C; IR (KBr): 3277, 3220, 3147, 3108, 1734, 1704, 1688, 1730, 1595, 1543, 1506, 1397, 1348, 1194, 1045, 1023, 766 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): 9.99 (s, 1H, NH), 8.41 (d, 1H, J=8.0 Hz, ArH), 7.78 (d, 1H, J=7.6 Hz, ArH), 7.70–7.66 (m, 1H, ArH), 7.59–7.55 (m, 1H, ArH), 7.40–7.34 (m,

2H, ArH), 7.21–7.14 (m, 2H, ArH), 5.74 (s, 1H, CH), 4.83 (d, J=15.2 Hz, 1H, CH_2), 4.78 (d, J=15.2 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 171.8, 165.8, 158.5, 143.9, 136.8, 131.6, 130.7, 130.6, 128.8, 128.2, 126.3, 123.3, 123.1, 119.4, 94.4, 66.6, 59.3. HRMS (ESI) m/z: calcd for [M−H$^+$] $C_{18}H_{11}N_2O_3$:303.0764; found: 303.0761.

4.3.2. 1,2-Dimethoxy-4bH-benzo[2,3]furo[3′,4′:5,6][1,4]diazepino [7,1-a]isoindole-5,14(7H,8H)-dione ***5b***. White solid, mp: 291–293 °C; IR (KBr): 3251, 3201, 3141, 3092, 1752, 1677, 1655, 1596, 1557, 1497, 1376, 1337, 1272, 1062, 1040, 1011, 773 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 9.93 (s, 1H, NH), 8.06 (d, 1H, J=8.4 Hz, ArH), 7.37–7.32 (m, 3H, ArH), 7.19–7.13 (m, 2H, ArH), 5.58 (s, 1H, CH), 4.87 (d, J=15.2 Hz, CH_2), 4.83 (d, J=15.2 Hz, CH_2), 4.87 (d, J=15.2 Hz, 1H, CH_2), 4.85 (d, J=15.2 Hz, 1H, CH_2), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 171.8, 163.9, 158.3, 152.4, 146.3, 137.1, 136.8, 130.9, 128.1, 126.4, 123.0, 121.6, 119.4, 116.8, 95.1, 66.5, 61.6, 58.0, 56.4. HRMS (ESI) m/z: calcd for [M−H$^+$] $C_{20}H_{15}N_2O_5$:363.0975; found: 363.0976.

4.3.3. 10,11-Dimethyl-4bH-benzo[2,3]furo[3′,4′:5,6][1,4]diazepino [7,1-a]isoindole-5,14(7H,8H)-dione ***5c***. White solid, mp: >300 °C; IR (KBr): 3270, 3186, 3124, 3082, 1753, 1687, 1653, 1614, 1510, 1398, 1362, 1340, 1211, 1195, 1141, 1115, 1065, 1024, 760 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 9.94 (s, 1H, NH), 8.40 (d, 1H, J=7.6 Hz, ArH), 7.75 (d, 1H, J=7.2 Hz, ArH), 7.67 (t, 1H, J=7.6 Hz, ArH), 7.58–7.54 (m, 1H, ArH), 7.14 (s, 1H, ArH), 6.95 (s, 1H, ArH), 5.67 (s, 1H, CH), 4.84 (d, J=15.2 Hz, 1H, CH_2), 4.74 (d, J=15.2 Hz, 1H, CH_2), 2.24 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). HRMS (ESI) m/z: calcd for [M−H$^+$] $C_{20}H_{15}N_2O_3$:331.1077; found: 331.1075.

4.3.4. 1,2-Dimethoxy-10,11-dimethyl-4bH-benzo[2,3]furo[3′,4′:5,6] [1,4]diazepino[7,1-a]isoindole-5,14(7H,8H)-dione ***5d***. White solid, mp: >300 °C; IR (KBr): 3255, 3196, 3127, 3088, 3001, 1749, 1682, 1667, 1620, 1557, 1448, 1400, 1270, 1197, 1117, 1060, 1015, 958 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 9.77 (s, 1H, NH), 8.05 (d, J=8.4 Hz, 1H, ArH), 7.34 (d, J=8.4 Hz, 1H, ArH), 7.11 (s, 1H, ArH), 6.93 (s, 1H, ArH), 5.51 (s, 1H, CH), 4.83 (d, J=15.2 Hz, 1H, CH_2), 4.72 (d, J=15.2 Hz, 1H, CH_2), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.23 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 171.9, 163.9, 158.4, 152.3, 146.2, 138.8, 136.4, 134.5, 131.1, 131.0, 123.8, 123.0, 121.6, 120.0, 116.6, 94.4, 66.4, 61.6, 58.0, 56, 4, 19.1, 18.5. HRMS (ESI) m/z: calcd for [M−H$^+$] $C_{22}H_{19}N_2O_5$: 391.1288; found: 391.1284.

4.3.5. 10,11-Dichloro-4bH-benzo[2,3]furo[3′,4′:5,6][1,4]diazepino [7,1-a]isoindole-5,14(7H,8H)-dione ***5e***. Pale white solid, mp: >300 °C; IR (KBr): 3330, 3281, 3134, 3102, 1747, 1715, 1662, 1626, 1597, 1557, 1487, 1408, 1259, 1179, 1135, 1014, 871 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 10.18 (s, 1H, NH), 8.41 (d, J=7.6 Hz, 1H, ArH), 7.80 (d, J=7.6 Hz, 1H, ArH), 7.73–7.69 (m, 2H, ArH), 7.61–7.57 (m, 1H, ArH), 7.39 (s, 1H, ArH), 5.76 (s, 1H, CH), 4.91 (d, J=15.2 Hz, 1H, CH_2), 4.79 (d, J=15.2 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 171.6, 165.9, 157.8, 143.7, 137.1, 132.1, 132.0, 130.2, 130.5, 129.0, 126.3, 124.0, 123.5, 120.4, 112.7, 95.6, 66.6, 59.0. HRMS (ESI) m/z: calcd for [M−H$^+$] $C_{18}H_9Cl_2N_2O_3$: 370.9984; found: 370.9982.

4.3.6. 10,11-Dichloro-1,2-dimethoxy-4bH-benzo[2,3]furo[3′,4′:5,6] [1,4]diazepino[7,1-a]isoindole-5,14(7H,8H)-dione ***5f***. Pale white solid, mp: 263–265 °C; IR (KBr): 3249, 1747, 1681, 1672, 1592, 1537, 1489, 1474, 1393, 1342, 1194, 1134, 1111, 1055, 1027, 742 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 10.10 (s, 1H, NH), 8.06 (d, J=8.4 Hz, 1H, ArH), 7.68 (s, 1H, ArH), 7.39–7.37 (m, 2H, ArH), 5.59 (s, 1H, CH), 4.90 (d, J=15.2 Hz, 1H, CH_2), 4.76 (d, J=15.2 Hz, 1H, CH_2), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 171.5, 163.9, 157.6, 152.4, 146.4, 137.3, 136.5, 132.3, 129.9, 126.1, 123.9, 122.5, 121.6, 120.3, 117.2, 96.2, 66.6, 61.6, 57.6, 56.4. HRMS (ESI) m/z: calcd for [M−H$^+$] $C_{20}H_{13}Cl_2N_2O_5$: 432.0196; found: 432.0199.

4.3.7. 5,14-Dioxo-5,7,8,14-tetrahydro-4bH-benzo[2,3]furo[3′,4′:5,6] [1,4]diazepino[7,1-a]isoindole-10-carboxylic acid ***5g***. Pale white solid, mp: >300 °C; IR (KBr): 3340, 3116, 1748, 1701, 1687, 1616, 1562, 1516, 1404, 1390, 1342, 1268, 1314, 1182, 1058, 1023, 771 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 13.21 (s, 1H, COOH), 10.17 (s, 1H, NH), 8.43 (d, 1H, J=7.6 Hz, ArH), 7.83 (d, 1H, J=2.0 Hz, ArH), 7.80 (d, 1H, J=7.6 Hz, ArH), 7.73–7.68 (m, 2H, ArH), 7.61–7.57 (m, 1H, ArH), 7.52 (d, 1H, J=8.0 Hz, ArH), 5.80 (s, 1H, CH), 4.90 (d, J=15.2 Hz, 1H, CH_2), 4.81 (d, J=15.2 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 171.6, 166.4, 165.9, 158.3, 143.9, 136.7, 135.9, 131.9, 131.0, 130.4, 130.3, 130.0, 128.9, 126.4, 123.4, 120.5, 94.7, 66.5, 59.2. HRMS (ESI) m/z: calcd for [M−H$^+$] $C_{19}H_{11}N_2O_5$: 347.0662; found: 347.0659.

4.3.8. 1,2-Dimethoxy-5,14-dioxo-5,7,8,14-tetrahydro-4bH-benzo[2,3] furo[3′,4′:5,6][1,4]diazepino[7,1-a]isoindole-10-carboxylic acid ***5h***. Pale white solid, mp: 277–280 °C; IR (KBr): 3313, 3138, 1750, 1689, 1672, 1558, 1499, 1400, 1275, 1061, 1047, 783, 774, 755 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 13.18 (s, 1H, COOH), 10.11 (s, 1H, NH), 8.08 (d, 1H, J=8.4 Hz, ArH), 7.81 (s, 1H, ArH), 7.68–7.66 (m, 1H, ArH), 7.51–7.49 (m, 1H, ArH), 7.38 (d, 1H, J=8.4 Hz, ArH), 5.62 (s, 1H, CH), 4.89 (d, J=15.2 Hz, 1H, CH_2), 4.78 (d, J=15.2 Hz, 1H, CH_2), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 171.7, 166.4, 163.9, 158.1, 152.4, 146.4, 136.9, 136.7, 131.1, 130.3, 130.1, 123.3, 122.8, 121.7, 120.5, 117.0, 95.2, 66.5, 61.6, 57.8, 56.4. HRMS (ESI) m/z: calcd for [M−H$^+$] $C_{21}H_{15}N_2O_7$: 407.0874; found: 407.0880.

Crystal data for **4g**: $C_{26}H_{32}N_4O_8$, pale white, crystal dimension 0.40×0.35×0.14 mm, monoclinic, space group $P2(1)/c$, a=11.9237(11) Å, b=14.1491(13) Å, c=16.7626(14) Å, α=γ=90 °C, β=99.5980(10) °C, V=2788.4(4) Å^3, M_r=528.56, Z=4, D_c=1.259 Mg/m^3, λ=0.71073, μ(Mo Kα)=0.094 mm^{-1}, F (000)=1120, R=0.0552, wR_2=0.1182, S=1.036, largest diff. Peak and hole: 0.508 and −0.324 e/Å^3. CCDC-823409 contains the supplementary crystallographic data for this paper.

Crystal data for **4u**: $C_{17}H_{13}BrN_2O_2$, pale white, crystal dimension 0.35×0.20×0.11 mm, monoclinic, space group $P2(1)/c$, a=14.6324(15) Å, b=12.0632(12) Å, c=8.5627(9) Å, α=γ=90 °C, β=94.7470(10) °C, V=1506.2(3) Å^3, M_r=357.20, Z=4, D_c=1.575 Mg/m^3, λ=0.71073, μ (Mo Kα)=2.737 mm^{-1}, F (000)=720, R=0.0320, wR_2=0.0630, S=1.011, largest diff. Peak and hole: 0.279 and −0.343 e/Å^3. CCDC-823410 contains the supplementary crystallographic data for this paper.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.05.002.

References and notes

1. (a) Kumar, R.; Chaudhary, P.; Nimesh, S.; Verma, A. K.; Chandra, R. *Green Chem.* **2006**, *8*, 519–521; (b) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Org. Lett.* **2007**, *9*, 1687–1690; (c) Hart, B. R.; Rush, D. J.; Shea, K. J. *J. Am. Chem. Soc.* **2000**, *122*, 460–465; (d) Shaabani, A.; Maleki, A.; Mofakham, H. *J. Comb. Chem.* **2008**, *10*, 595–598; (e) Murai, K.; Nakatani, R.; Kita, Y.; Fujioka, H. *Tetrahedron* **2008**,

64, 11034–11040; (f) Ookura, R.; Kito, K.; Ooi, T.; Namikoshi, M.; Kusumi, T. *J. Org. Chem.* **2008**, *73*, 4245–4247; (g) Tonkikh, N. N.; Strakovs, A.; Rizhanova, K. V.; Petrova, M. V. *Chem. Heterocycl. Compd.* **2004**, *40*, 949–955; (h) Michelini, S.; Cassano, G. B.; Frare, F.; Perugi, G. *Pharmacopsychiatry* **1996**, *29*, 127–134; (i) Harry, M. G.; Lawrence, L. M.; Charles, A. C.; Frederick, W. D.; Daniel, B. E.; Hansjoerg, K.; Linda, L. S.; Manfred, W. *J. Med. Chem.* **1982**, *25*, 340–346.

2. (a) Schutz, H. *Benzadiazepines*; Springer: Heidelberg, 1982; Vol. 2; p 240; (b) Smalley, R. K. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 4, p 600; (c) Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*; Katritzk, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 1; p 166.
3. (a) Neelakantan, S.; Seshadri, T. R. *Curr. Sci.* **1959**, *28*, 476–480; (b) Haynes, L. J.; Plimmer, J. R. *Q. Rev.* **1960**, *14*, 292–315; (c) Brodersen, R.; Kjaer, A. *Acta Pharmacol. Toxicol.* **1946**, *2*, 109–120.
4. (a) Roggo, B. E.; Petersen, F.; Delmendo, R.; Jenny, H. B.; Peter, H. H.; Roesel, J. *J. Antibiot.* **1994**, *47*, 136–142; (b) Chrusciel, R. A.; Maggiora, L. L.; Thaisrivongs, S.; Tustin, J. M.; Tommasi, R. A.; Aristoff, P. A.; Skulnick, H. I.; Howe, W. J.; Bundy, G. L. WO 9507901, 1995; *Chem. Abstr.* **1995**, *123*, 55683p.
5. Foden, F. R.; McCormick, J.; O'Mant, D. M. *J. Med. Chem.* **1975**, *18*, 199–203.
6. (a) Vishwakarma, R. A.; Kapil, R. S.; Popli, S. P. *Indian J. Chem., Sect. B* **1987**, *26*, 486–487; (b) Luk, K.; Readshaw, S. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1641–1644.
7. (a) Ley, S. V.; Trudell, M. L.; Wadsworth, D. J. *Tetrahedron* **1991**, *47*, 8285–8296; (b) Vanwagenen, B. E.; Cardellina, J. H. *Tetrahedron* **1986**, *42*, 1117–1122; (c) Cappon, R. J.; Macleod, J. K. *Aust. J. Chem.* **1987**, *40*, 1327–1330; (d) Matsumoto, M.; Kawamura, Y.; Terui, Y.; Nakai, H.; Yoshida, T.; Shoji, J. *J. Antibiot.* **1990**, *43*, 739–747.
8. Ibi, A.; Yaniguchi, E.; Maekawa, K. *Agric. Biol. Chem.* **1979**, *43*, 1641–1646.
9. (a) Dal Pozzo, A.; Dansi, A.; Neneghini, E. *Bull. Chim. Farm.* **1974**, *113*, 280–285; (b) Dal Pozzo, A.; Dansi, A.; Neneghini, E. *Bull. Chim. Farm.* **1974**, *113*, 324–327; (c) Foden, F. R.; McCormick, J.; O'Mant, D. M. British Patent 1,358,382, 1974; *Chem. Abstr.* **1974**, *81*, 120438t.
10. (a) Rehse, K.; Wagenknecht, J.; Rietbrock, N. *Arch. Pharm. (Weinheim, Ger.)* **1978**, *311*, 986–992; (b) Rehse, K.; Emisch, U. *Arch. Pharm. (Weinheim, Ger.)* **1983**, *316*, 115–120; (c) Rehse, K.; Rothe, M.; Kuhn, M. *Arch. Pharm. (Weinheim, Ger.)* **1982**, *315*, 52–56; (d) Witiak, D.; Kokrady, S. S.; Patel, S. T.; Akbar, H. D.; Feller, R.; Newmann, H. A. I. *J. Med. Chem.* **1982**, *25*, 90–93.
11. Zhang, C.-L.; Chatterjee, S. S.; Stein, U.; Heinemann, U. *Naunyn-Schmiedebergs Arch. Pharmakol.* **1992**, *345*, 85–92.
12. (a) Amari, M.; Fodili, M.; Kolli, B. N. *J. Heterocycl. Chem.* **2002**, *39*, 811–816; (b) Savina, S. A.; Lyubchanskaya, V. M.; Alekseeva, L. M.; Shashkov, A. S.; Granik, V. G. *Russ. Chem. Bull.* **2007**, *56*, 2298–2304; (c) Matsuo, K.; Tanaka, K. *Chem. Pharm. Bull.* **1984**, *32*, 3724–3729.
13. (a) Jiang, B.; Tu, S.-J.; Parminder, K.; Walter, W.; Li, G. *J. Am. Chem. Soc.* **2009**, *131*, 11660–11661; (b) Jiang, B.; Li, C.; Shi, F.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. *J. Org. Chem.* **2010**, *75*, 2962–2965; (c) Jiang, B.; Wang, X.; Shi, F.; Tu, S.-J.; Li, G. *J. Org. Chem.* **2009**, *74*, 9486–9489; (d) Ma, N.; Jiang, B.; Zhang, G.; Tu, S.-J.; Wever, W.; Li, G. *Green Chem.* **2010**, *12*, 1357–1361.
14. (a) Tu, S.-J.; Cao, X.-D.; Hao, W.-J.; Zhang, X.-H.; Yan, S.; Wu, S.-S.; Han, Z.-G.; Shi, F. *Org. Biomol. Chem.* **2009**, *7*, 557–563; (b) Jiang, B.; Hao, W.-J.; Zhang, J.-P.; Tu, S.-J.; Shi, F. *Org. Biomol. Chem.* **2009**, *7*, 1171–1175; (c) Hao, W.-J.; Jiang, B.; Tu, S.-J.; Cao, X.-D.; Wu, S.-S.; Yan, S.; Zhang, X.-H.; Han, Z.-G.; Shi, F. *Org. Biomol. Chem.* **2009**, *7*, 1410–1414; (d) Jiang, B.; Hao, W.-J.; Zhang, J.-P.; Tu, S.-J.; Shi, F. *Org. Biomol. Chem.* **2009**, *7*, 2195–2201; (e) Jiang, B.; Shi, F.; Tu, S.-J. *Curr. Org. Chem.* **2010**, *14*, 357–378.
15. (a) Tu, S.-J.; Zhang, X.-H.; Han, Z.-G.; Cao, X.-D.; Wu, S.-S.; Yan, S.; Hao, W.-J.; Ma, N. *J. Comb. Chem.* **2009**, *11*, 428–432; (b) Jiang, B.; Cao, L.-J.; Tu, S.-J.; Zheng, W.-R.; Yu, H.-Z. *J. Comb. Chem.* **2009**, *11*, 612–616; (c) Jiang, B.; Hao, W.-J.; Wang, X.; Shi, F.; Tu, S.-J. *J. Comb. Chem.* **2009**, *11*, 846–850.
16. (a) Cleator, E.; Baxter, C.; O'Hagan, M.; O'Riordan, T.; Sheen, F.; Stewart, G. *Tetrahedron Lett.* **2010**, *51*, 1079–1082; (b) Enders, D.; Wang, C.; Mukanova, M.; Greb, A. *Chem. Commun.* **2010**, *46*, 2447–2449; (c) Adib, M.; Ansari, S.; Fatemi, S.; Bijanzadeh, H.; Zhu, L. *Tetrahedron* **2010**, *66*, 2723–2727; (d) Kumar, A.; Sharma, S.; Maurya, R. *Tetrahedron Lett.* **2009**, *50*, 5937–5940.
17. (a) Ju, Y.-H.; Rajender, S. V. *J. Org. Chem.* **2006**, *71*, 135–141; (b) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Mathews, NC, 2002, pp 29–36; (c) Gellis, A.; Boufatah, N.; Vanelle, P. *Green Chem.* **2006**, *8*, 483–487; (d) Ju, Y.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409–2411; (e) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101–2104; (f) Skouta, R.; Varma, R. S.; Li, C.-J. *Green Chem.* **2005**, *7*, 571–575; (g) Wu, X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327–3329.
18. (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3165; (b) Herreroas, C. I.; Yao, X.-Q.; Li, Z.-P.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546–2562; (c) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581–590; (d) Macleod, D. P.; Li, Z.-P.; Li, C.-J. *Tetrahedron* **2010**, *66*, 1045–1050; (e) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.
19. (a) Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. *Chem. Commun.* **2010**, *46*, 4330–4332; (b) Kaur, P.; Pindi, S.; Wever, W.; Rajale, T.; Li, G. *J. Org. Chem.* **2010**, *75*, 5144–5150; (c) Kattuboina, A.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 1573–1577; (d) Kattuboina, A.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216–223; (e) Kattuboina, A.; Kaur, P.; Nguyen, T.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 3722–3724.
20. (a) Kaur, P.; Nguyen, T.; Li, G. *Eur. J. Org. Chem.* **2009**, 912–916; (b) Han, J.; Ai, T.; Li, G. *Synthesis* **2008**, *16*, 2519–2526; (c) Han, J.; Chen, Z.-X.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2009**, *73*, 203–208; (d) Chen, Z.-X.; Ai, T.; Kaur, P.; Li, G. *Tetrahedron Lett.* **2009**, *50*, 1079–1081; (e) Ai, T.; Li, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3967–3969.