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Dibenzo[*b*,*e*][1,4]diazepin-1-ones and their Ring-Opened Derivatives: Revisited Synthesis, 2D NMR and Crystal Structure

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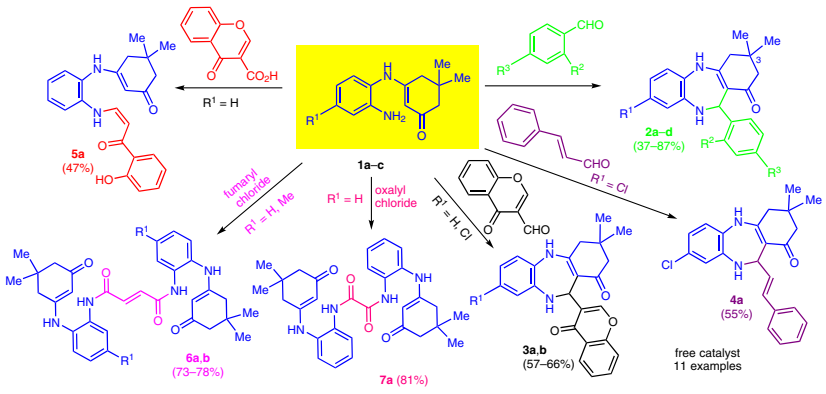

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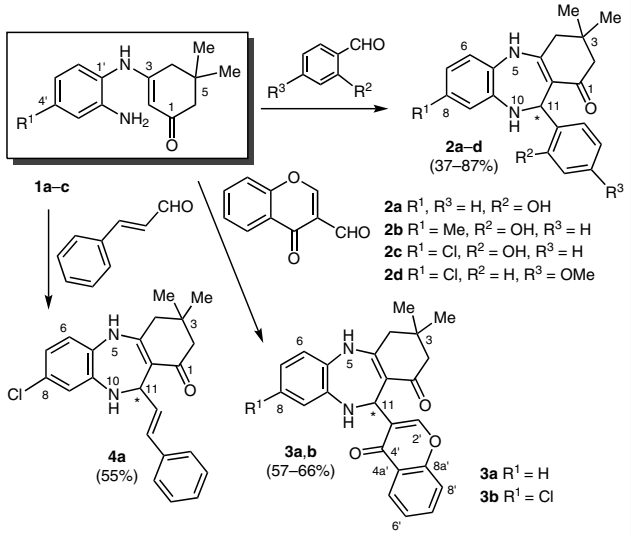
Abstract The synthesis of 2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones was revisited and a catalyst-free method was established, by exploring the reactivity of 3-[(2-aminoaryl)amino]dimedones towards carbonylated electrophiles. 2D NMR and single-crystal X-ray diffraction studies were used to characterize the structures unequivocally and to review the mechanism leading to the formation of supposed positional isomers. The action of 3-[(2-aminoaryl)amino]dimedones on chromene-3-carboxylic acid, fumaryl, and oxalyl chloride has led to dibenzo[*b*,*e*][1,4]diazepin-1-one ring opening to produce novel *Z*-configured enaminone and linear diamides.

Key words 3-[(2-aminoaryl)amino]dimedones, carbonylated electrophiles, dibenzo[*b*,*e*][1,4]diazepin-1-ones, reaction mechanism, 2D NMR, single-crystal X-ray diffraction

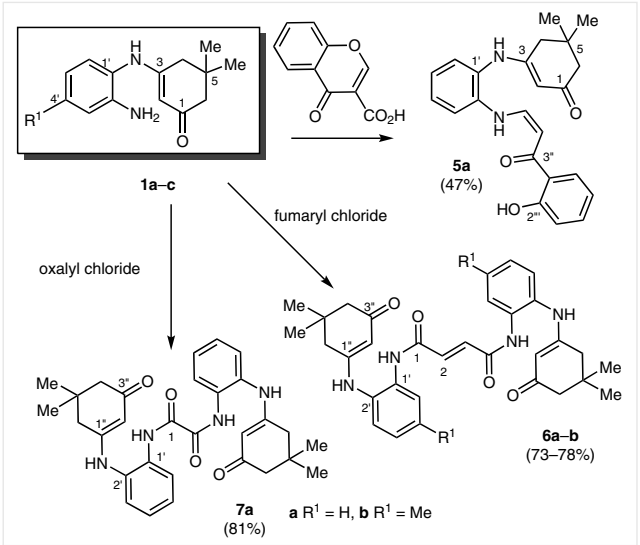
Nitrogen-containing heterocycles occupy an important position in synthetic organic chemistry due to their multitude of applications in medicine, agriculture, and industry.[1,2] Several attractive chemotypes thereof have been reported, such as benzodiazepine derivatives, which are a common group of compounds in the area of psychoactive drugs. Benzodiazepines are to date present in more than forty approved medicines with a range of therapeutic properties.[3] This class of compounds is still the subject of in vivo clinical trials associated with the treatment of several diseases, such as insomnia, anxiety, seizures, agitation, alcohol withdrawal, muscle spasms, and premedication for medical or dental procedures.[4] The main biological activity of benzodiazepines is their action as stimulators of the central nervous system. They usually reduce the activity of nerves in the brain and the spinal cord, thus enhancing the effects of the neurotransmitter γ-aminobutyric acid (GABA).[5]

Researchers have paid much attention to novel benzodiazepines that are linked to other bioactive organic motifs.[6] A synthetic literature survey underlined the availability of various procedures towards the synthesis of 1,4- and 1,5-benzodiazepines.[7] For instance, one piece of work has disclosed the use of binucleophilic enaminones as key starting materials in the reaction with diverse aromatic/heterocyclic aldehydes to generate novel benzodiazepine frameworks.[7f] Most of the reported methods are, however, time-consuming and multistep catalytic procedures.[7b–e,7g] Because of these drawbacks, it is pertinent to develop efficient and simple processes for the preparation of benzodiazepine-based drugs. Elaborating a molecular system containing dimedone, benzodiazepine, phenolic, and chromone moieties all in one scaffold is a promising strategy to create unprecedented new biologically active agents.

A study on the reactivity of 3-[(2-aminoaryl)amino]-5,5-dimethylcyclohex-2-en-1-ones **1** towards benzaldehydes has already been disclosed, leading to the production of useful dibenzo[*b*,*e*][1,4]diazepin-1-one structures.[8] However, we decided to revisit the reaction in order to simplify the experimental procedure, to prepare further novel derivatives, and to establish the obtained structures unequivocally. Compounds **1a–c**[8d] were used as enaminone derivatives for the preparation of 11-substituted 2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones **2a–d**, **3a**,**b**, and **4a** through their reaction with benzaldehydes,[8a–c,8e] cinnamaldehyde, and chromone-3-carbaldehyde, respectively. Contrary to the reported procedures,[8a–c,8e] our reaction proceeded in ethanol under catalyst-free conditions at room temperature for 4–5 hours. The reaction is worked up by simple filtration of the formed precipitate showing a high purity of the products **2–4**, isolated in moderate-to-good yields (37–87%) after simple washing with ethanol; thus avoiding any chromatographic purification (Scheme 1).[9] Under similar conditions, we further investigated the reaction of **1a–c** with other electrophiles, such as chromone-3-carboxylic acid, fumaryl chloride, and oxalyl chloride, to afford new (*Z*)-3-[(2-{[3-(2-hydroxyphenyl)-3-oxoprop-1-en-1-yl]amino}phenyl)amino]-5,5-dimethylcyclohex-2-en-1-one (**5a**) and linear diamides **6a**,**b** and **7a**, respectively, in 47–81% yield (Scheme 2).[9]



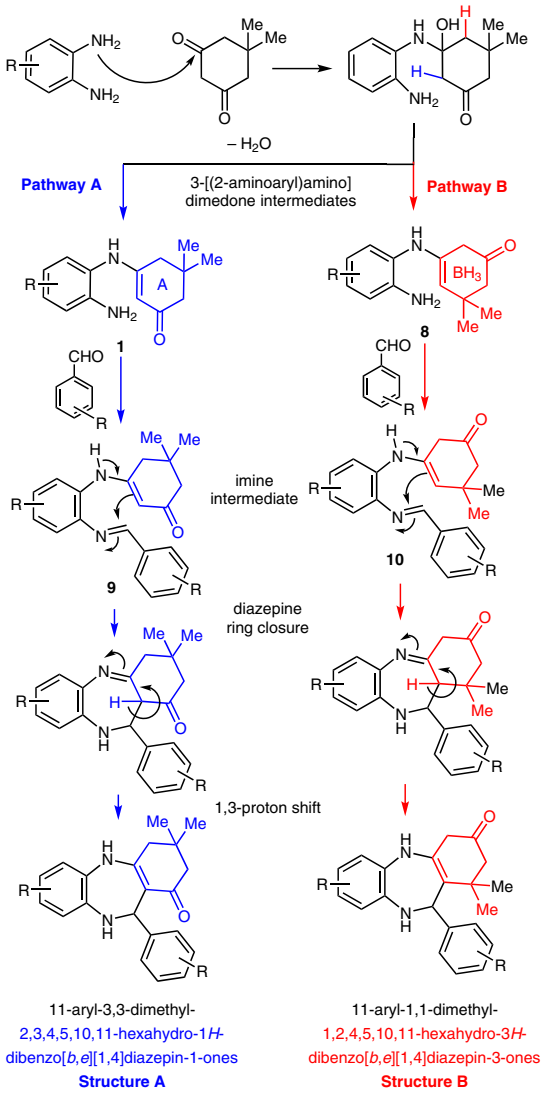
Scheme 1 Synthesis of 11-substituted 2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones **2a–d** and **4a**, and of **3a**,**b**. *Reagents and conditions*: EtOH, r.t., 4–5 h.



Scheme 2 Synthesis of enaminone **5a** and diamides **6a**,**b** and **7a**. *Reagents and conditions*: EtOH, r.t., 4–5 h.

Several mechanistic proposals have been described for the formation of 11-aryl-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones **2–4** (Scheme 3, pathway A).[8a–c,8e] Maleki and Kamalzare described, however, the unexpected formation of different isomers, 11-aryl-1,1-dimethyl-1,2,4,5,10,11-hexahydro-3*H*-dibenzo[*b*,*e*][1,4]diazepin-3-ones (Scheme 3, pathway B), via a one-pot catalytic three-component reaction of *o*-phenylenediamines (OPDA), dimedone, and various benzaldehydes.[8e] The mechanistic difference between the pathways A and B is the initial formation of the two key intermediates, namely: 3-[(2-aminoaryl)amino]-5,5-dimethyl-cyclohex-2-en-1-ones **1** and 3-[(2-aminoaryl)amino]-5,5-dimethylcyclohex-3-en-1-ones **8** (Scheme 3). These intermediates are formed by nucleophilic attack of the amino group of OPDA onto one of the dimedone carbonyl groups. After loss of water, it is most likely to form the cyclohex-2-en-1-one **1** from deprotonation of the more acidic α-carbonyl proton compared to that at the γ position, which generates the cyclohex-3-en-1-one **8** (Scheme 3). Compounds **1**, reported as isolable products in this work and others,[8a–c] can also be formed in situ during multicomponent processes.[8e] Following the mechanistic pathways A and B that involve an intramolecular diazepine ring closure of imine intermediates (**9** or **10**) and 1,3-proton shift (Scheme 3), two totally different structures **A** and **B** are formed. We found, however, that the reported structure **B**[8e] has been compared to **A**[8a–c] in terms of their physical characteristics, namely the melting point. Although the resulting products structures are distinct, there is a high probability to reach quasi similar values of melting points for the two isomers **A** and **B**

(Scheme 3). This fact requires a careful review of the spectroscopic data relating to compounds featuring structure **B** as reported in the literature.[8e]



Scheme 3 Mechanism for the formation of 1,4-benzodiazepines **2–4**

^{1}H NMR and ^{13}C NMR spectroscopic analysis of compounds **2–4**[10–12] clearly reveal the cyclic portions of the 11-aryl-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one scaffold, including the benzodiazepine ring featuring the asymmetric C-11 (δ_H = 5.64–5.90 ppm and δ_C = 49.2–55.1 ppm). The 1,4-diamino protons are easily assigned, the 10-NH proton appearing as a doublet (J = 5.9–5.5 Hz) at δ = 5.28–5.85 ppm by coupling with H-11, while the 5-NH proton can be assigned to a singlet appearing at δ = 8.76–9.00 ppm. Due to the close proximity of the C-11 asymmetric center to the dimedone methylene protons, the latter appear as *AB* spin systems at δ = 2.02–2.21 ppm for H-2 and δ = 2.57–2.75 ppm for H-4. The protons attributed to the 3,3-dimethyl groups are also affected by the presence of the asymmetric center and appear at different chemical shifts around δ = 1.03–109 ppm. Carbon assignments were based on HSQC and HMBC correlations. For instance in the case of compounds **2b**[10] and **3a**:[11] the four diazepine quaternary carbons C-4a (δ = 155.1–155.7 ppm), C-5a (δ = 125.0–130.2 ppm), C-9a (δ = 137.8–140.2 ppm), and C-11a (δ = 106.5–110.7 ppm) have been assigned based on the HMBC correlations C-4a/H-11, C-5a/10-NH, C-9a/H-11/10-NH, and C-11a/H-4/5-N*H*, respectively (Figure 1). The structure **A** 2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]-diazepin-1-one can be clearly distinguished from its reported positional isomer 1,2,4,5,10,11-hexahydro-3*H*-dibenzo[*b*,*e*][1,4]diazepin-3-one structure **B**: the existing HMBC connectivity between the carbonyl carbon C-1 and H-11 in the structure **A** will not be observed in the structure **B** between C-3 and H-11 due to the distance between them (Figure 1). Furthermore, both carbonyls C-1 and C-4′ (δ = 192.1–192.2 and 176.1–176.4 ppm, respectively) of the newly synthetized 11-chromone-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones **3a** and **3b** have been assigned through HMBC connectivities of C-4′/H-2′/H-11 and C-1/H-11, respectively (Figure 1, compound **3a**).[11]

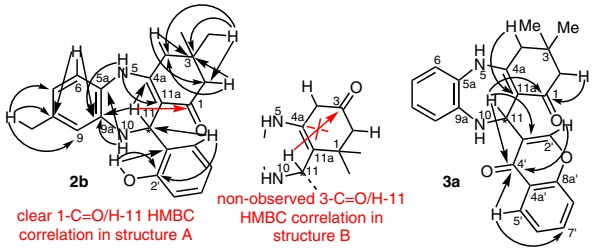
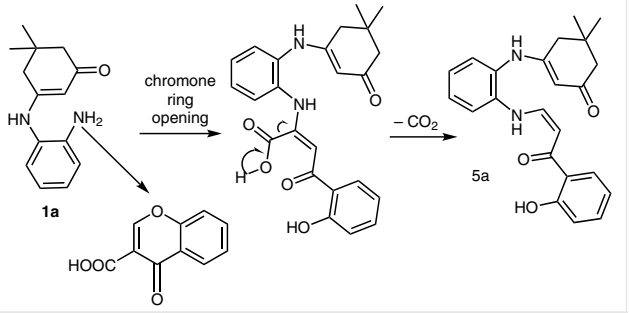


Figure 1 Main HMBC correlations of 11-substituted-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones **2b** and **3a**

The reaction of **1a–c** with chromone-3-carboxylic acid resulted in the open-chain enaminone, (*Z*)-3-[(2-{[3-(2-hydroxyphenyl)-3-oxoprop-1-en-1-yl]amino}phenyl)amino]-5,5-dimethylcyclohex-2-en-1-one (**5a**)[13] through a decarboxylative 1,4-conjugate addition and chromone ring opening (Scheme 4). ^{1}H NMR, ^{13}C NMR, HMBC, and NOESY spectroscopic analyses of **5a** were used to confirm the *Z* configuration ($^3J_{H-1''H-2''}$ = 8.0 Hz) of the enaminone olefin which was unequivocally proved based on the strong NOE effects observed between the protons H-1″ and H-2″ (Figure 2). The reaction of **1a–c** with fumaryl chloride or oxalyl chloride afforded linear diamides **6** and **7**,[14,15] respectively, even when using equimolar mixtures of the starting reagents.



Scheme 4 Reaction mechanism for the synthesis of **5a**

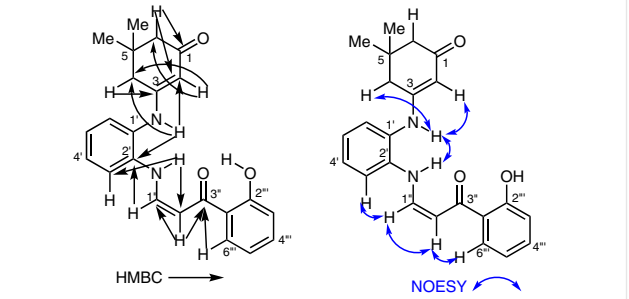


Figure 2 Main HMBC and NOESY correlations observed in **5a**

Single-crystal X-ray diffraction studies were used to reveal the spatial arrangement of structure **A** of compounds **2b**, **3a**, and **5a**, which is in good agreement with the aforementioned 2D NMR studies. These studies show that the polycyclic 2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one fragment approaches planarity (Figure 3) with the maximum atomic deviation for the average plane being of 0.537(2) and 0.673(1) Å for compounds **2b** and **3a** (both distances correspond to NH groups of the seven-membered rings composing the molecules).[16,17] We also note that it was not uncommon for the crystalline dibenzo[*b*,*e*][1,4]diazepin-1-ones to contain crystallization solvent. This is observed for compounds **2b·EtOH** and **3a·5H$_2$O**. This phenomenon affects the melting-point measurement for **2a** (170–172 °C determined in this work, see Supporting Information), which is taken as an example when compared to its reported non-crystalline amorphous material which, supposedly, does not contain solvent molecules (158–159 °C).[18]

Single-crystal X-ray studies also provided additional structural insights on compound **5a·EtOH**. Crystals of this material were isolated by slow evaporation at 6 °C of an ethanol solution. The existence of two cooperative intramolecular hydrogen bonds as depicted in Figure 3 promotes considerable structural planarity. Indeed, the maximum atomic deviation for the average plane being just of 0.132(3) Å, which is attributed to the hydroxyl group. As shown in Figure 3, the two intramolecular O–H···O and N–H···O hydrogen bonds are considerably strong with the interatomic distances being of 2.535(5) and 2.884(5) Å, respectively (the latter even has an interaction angle of 171° which approaches linearity).[19] Noteworthy, the dimedone moiety subtends an angle of 72.20(12)° with the average plane of the remaining portion of the molecular unit.

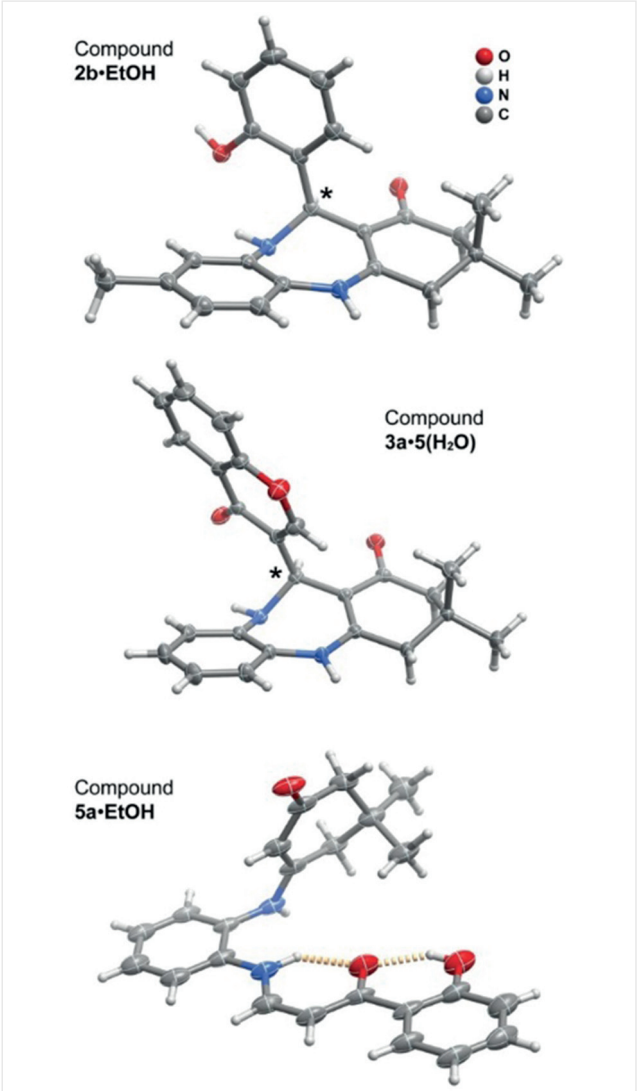


Figure 3 Schematic representation of the molecular units present in crystal structures of compounds **2b·EtOH**, **3a·5H$_2$O**, and **5a·EtOH**. Asymmetric centers are depicted by an asterisk and intramolecular hydrogen-bonding interactions as dashed gold lines. Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level and hydrogen atoms as small spheres with arbitrary radii. The solvent molecules present in the crystal structures have been omitted for clarity purposes.

In summary, the versatile reactivity of 3-[(2-aminoaryl)amino]dimedones towards carbonylated electrophiles is described. This constitutes an efficient, simple, and economic method for the preparation of dibenzo[*b*,*e*][1,4]diazepin-1-ones and their ring-opened derivatives. Clear advan-

tages are noticeable in our free-catalyst synthetic protocol, such as mild reaction conditions, and simple workup procedure to isolate pure 11-substituted-dibenzo[*b*,*e*][1,4]diazepin-1-ones in optimal yields. 2D NMR spectroscopy and single-crystal X-ray techniques were very helpful to differentiate between the two possible isomers **A** and **B** described in the literature (the latter should be carefully reviewed) and support the favorable formation of dibenzo[*b*,*e*][1,4]diazepin-1-ones. We have further explored the action of 3-[(2-aminoaryl)amino]dimedones on different active carbonylated electrophiles to generate a novel *Z*-enaminone and linear diamide molecules bearing chelating groups which may find suitable application in coordination chemistry.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590306.

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(9) **General Procedure for the Synthesis of Compounds 2–7**
To a solution of 3-[(2-aminoaryl)amino]dimedone derivative **1a–c** (0.001 mol) in EtOH (20 mL), the carbonylic derivative (0.001 mol) was added, and the resulting reaction mixture was stirred at r.t. for 4–5 h. In all the cases, a precipitate formed which was filtered-off, dried, and recrystallized from EtOH to give pure products **2–7**.
Note: In the case of the synthesis of the diamides **6** and **7**, 2 molar equiv of the 3-[(2-aminoaryl)amino]dimedones **1a–c** (0.002 mol) were used for 1 molar equiv of oxalyl chloride or fumaryl chloride. The reaction also works with an equimolar mixture of the reagent but excess of **1a–c** remain in the reaction mixture.
(10) **11-(2-Hydroxyphenyl)-3,3,8-trimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (2b)**
$C_{22}H_{24}N_2O_2$ (colorless crystals, 0.30 g, 87%, mp 175–177 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.06 and 1.08 (2 s, 6 H, 3-CH_3), 1.99 (s, 3 H, 8-CH_3), 2.04 and 2.19 (AB, *J* = 15.9 Hz, 2 H, H-2), 2.60 (s, 2 H, H-4), 5.28 (d, *J* = 5.6 Hz, 1 H, 10-NH), 5.89 (d, *J* = 5.6 Hz, 1 H, H-11), 6.26 (d, *J* = 1.1 Hz, 1 H, H-9), 6.38 (dd, *J* = 8.0, 1.1 Hz, 1 H, H-7), 6.39–6.45 (m, 1 H, H-5′), 6.57 (dd, *J* = 7.5, 1.3 Hz, 1 H, H-6′), 6.71–6.74 (m, 1 H, H-3′), 6.82 (d, *J* = 8.0 Hz, 1 H, H-6) 6.84–6.91 (m, 1 H, H-4′), 8.76 (s, 1 H, 5-NH), 9.70 (s, 1 H, 2′-OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.2 (8-CH_3), 27.4 and 28.6 (3-CH_3), 31.8 (C-3), 44.2 (C-4), 49.6 (C-2), 52.1 (C-11), 108.9 (C-11a), 114.8 (C-3′), 118.0 (C-5′), 119.9 (C-6), 120.5 and 120.6 (C-7, C-9), 126.6 (C-6′), 127.4 (C-4′), 128.4 (C-5a), 129.9 (C-1′), 131.3 (C-8), 138.3 (C-9a), 155.1 and 155.3 (C-4a, C-2′), 191.8 (C-1, C=O) ppm. HRMS (ESI$^+$): *m/z* calcd for $[C_{22}H_{24}N_2O_2 + Na]^+$: 371.1730; found: 371.1721.
(11) **3,3-Dimethyl-11-(4-oxo-4*H*-chromen-3-yl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (3a)**
$C_{24}H_{22}N_2O_3$ (colorless crystals, 0.22 g, 57%, mp 183–184 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.06 and 1.08 (2 s, 6 H, 3-CH_3), 2.13 and 2.19 (AB, *J* = 16.2 Hz, 2 H, H-2), 2.52 and 2.75 (AB, *J* = 16.2 Hz, 2 H, H-4), 5.46 (d, *J* = 5.5 Hz, 1 H, 10-NH), 5.78 (d, *J* = 5.5 Hz, 1 H, H-11), 6.47 (dd, *J* = 7.6, 1.7 Hz, 1 H, H-9), 6.52–6.70 (m, 2 H, H-7, H-8), 7.01 (dd, *J* = 7.7, 1.6 Hz, 1 H, H-6), 7.41–7.55 (m, 3 H, H-6′, H-8′, H-2′), 7.74 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1 H, H-7′), 8.09

(dd, J = 8.0, 1.7 Hz, 1 H, H-5′), 8.95 (s, 1 H, 5-NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.4 and 28.6 (3-CH_3), 31.7 (C-3), 44.0 (C-4), 49.3 (C-2), 49.8 (C-11), 106.5 (C-11a), 118.3 (C-8′), 120.4, 120.7 and 120.8 (C-6, C-7, C-9), 123.0 (C-8), 123.1 (C-4a′), 124.8 and 125.0 (C-5′, C-3′), 125.5 (C-6′), 131.0 (C-5a), 134.2 (C-7′), 137.8 (C-9a), 152.5 (C-2′), 155.7 and 155.9 (C-4a, C-8a′), 176.4 (C-4′), 192.1 (C-1) ppm. HRMS (ESI$^+$): m/z calcd for [$C_{24}H_{22}N_2O_3$ + H]$^+$: 387.1703; found: 387.1729.

(12) **(*E*)-8-Chloro-3,3-dimethyl-11-styryl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (4a)**

$C_{23}H_{23}ClN_2O$ (beige solid, 0.21 g, 55%, mp 160–161 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.00 and 1.05 (2 s, 6 H, 3-CH_3), 2.08 and 2.20 (AB, J = 15.9 Hz, 2 H, H-2), 2.51 (s, 2 H, H-4), 5.25 (dd, J = 6.0, 5.9 Hz, 1 H, H-11), 6.03 (dd, J = 15.8, 6.0 Hz, 1 H, H-1′), 6.20 (d, J = 15.8 Hz, 1 H, H-2′), 6.26 (d, J = 5.9 Hz, 1 H, 10-NH), 6.70 (dd, J = 8.6, 2.4 Hz, 1 H, H-7), 6.83 (d, J = 2.4 Hz, 1 H, H-9), 7.01 (d, J = 8.6 Hz, 1 H, H-6), 7.11–7.29 (m, 5 H, H-2″,6″, H-3″,5″ H-4″), 8.86 (s, 1 H, 5-NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.3 and 28.5 (3-CH_3), 31.9 (C-3), 44.0 (C-4), 49.5 (C-2), 53.2 (C-11), 110.3 (C-11a), 119.0 and 119.1 (C-7, C-9), 121.6 (C-6), 126.0 and 126.2 (C-2″,6″, C-8), 127.3 (C-4″), 128.73 and 128.74 (C-3″,5″, C-2′), 129.6 (C-5a), 131.8 (C-1′), 136.6 (C-1″), 140.0 (C-9a), 154.0 (C-4a), 192.2 (C-1) ppm. HRMS (ESI$^+$): m/z calcd for [$C_{23}H_{23}ClN_2O$ + H]$^+$: 379.1572; found: 379.1586.

(13) **(*Z*)-3-[(2-{[3-(2-Hydroxyphenyl)-3-oxoprop-1-en-1-yl]amino}phenyl)amino]-5,5-dimethylcyclohex-2-en-1-one (5a)**

$C_{23}H_{24}N_2O_3$ (yellow crystals, 0.18 g, 47%, mp 234–235 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.09 (2 s, 6 H, 5-CH_3), 2.03 (s, 2 H, H-6), 2.53 (s, 2 H, H-4), 4.46 (s, 1 H, H-2), 6.28 (d, J = 8.0 Hz, 1 H, H-2″), 6.86–6.94 (m, 2 H, H-5‴, H-3‴), 7.14–7.26 (m, 2 H, H-5′, H-6′), 7.36–7.49 (m, 2 H, H-4‴, H-4′), 7.71 (d, J = 8.0 Hz, 1 H, H-3′), 7.90–7.93 (m, 1 H, H-6‴), 8.10 (dd, J = 12.8, 8.0 Hz, 1 H, H-1″), 8.74 (s, 1 H, 3-NH), 11.82 (d, J = 12.8 Hz, 1 H, 1″-NH), 13.12 (s, 1 H, 2‴-OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.1 (5-CH_3), 32.3 (C-5), 41.6 (C-4), 50.2 (C-6), 93.2 (C-2″), 96.6 (C-2), 114.9 (C-3′), 117.8 (C-3‴), 118.9 (C-5‴), 119.8 (C-1‴), 124.3 (C-5′), 126.9 (C-1′), 128.6 and 128.8 (C-4′, C-6′), 129.0 (C-6‴), 134.9 (C-4‴), 136.1 (C-2′), 146.5 (C-1″), 161.6 (C-2‴), 162.3 (C-3), 193.1 (C-3″), 195.0 (C-1) ppm. HRMS (ESI$^+$): m/z calcd for [$C_{23}H_{24}N_2O_3$ + H]$^+$: 377.1860; found: 377.1871.

(14) **N^1,N^4-Bis{2-[(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino]phenyl}fumaramide (6a)**

$C_{32}H_{36}N_4O_4$ (brown solid, 0.40 g, 73%, mp 219–221 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.04 (s, 12 H, 5″-CH_3), 2.28 (s, 4 H, H-4″), 2.56 (s, 4 H, H-6″), 5.36 (s, 2 H, H-2″), 7.30 (s, 2 H, H-2), 7.31–7.35 (m, 4 H, H-3′, H-4′), 7.36–7.49 (m, 2 H, H-5′), 7.84 (d, J = 8.0 Hz, 2H, H-6′), 10.41 (s, 2 H, N^1H), 10.70 (s, 2 H, N^4H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 27.7 (5-CH_3), 32.6 (C-5″), 41.3 (C-6″), 46.1 (C-4″), 95.6 (C-2″), 125.0 (C-6′), 125.9 (C-3′) 127.1 (C-4′), 128.0 (C-5′), 129.5 (C-1′), 132.8 (C-2′), 134.0 (C-2), 162.3 (C-1), 170.6 (C-1″), 191.2 (C-3″) ppm. HRMS (ESI$^+$): m/z calcd for [$C_{32}H_{36}N_4O_4$ + H]$^+$: 541.2815; found: 541.2776.

(15) **N^1,N^2-Bis{2-[(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amino]phenyl}oxalamide (7a)**

$C_{30}H_{34}N_4O_4$ (white solid, 0.42 g, 81%, mp 200–202 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.03 (s, 12 H, 5″-CH_3), 2.02 (s, 4 H, H-4″), 2.39 (s, 4 H, H-6″), 4.70 (s, 2 H, H-2″), 7.27–7.40 (m, 6 H, H-3′, H-4′, H-5′), 7.96 (d, J = 7.9 Hz, 2 H, H-6′), 8.58 (s, 2 H, N^2H), 9.96 (s, 2 H, N^1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.0 (5-CH_3), 32.5 (C-5″), 41.6 (C-6″), 50.1 (C-4″), 96.8 (C-2″), 123.2 (C-6′), 126.3 (C-3′) 127.2 (C-4′), 127.6 (C-5′), 130.5 (C-1′), 131.9 (C-2′), 157.6 (C-1″), 162.3 (C-1), 195.2 (C-3″) ppm. HRMS (ESI$^+$): m/z calcd for [$C_{30}H_{34}N_4O_4$ + Na]$^+$: 537.2472; found: 537.2449.

(16) **Crystal Data for Compound 2b·EtOH**

$C_{24}H_{30}N_2O_3$, M = 394.50, monoclinic, space group $P2_1/c$, Z = 4, a = 9.5603(7) Å, b = 18.5619(12) Å, c = 12.7403(11) Å, β = 111.863(3), V = 2098.3(3) Å^3, μ(MoKα) = 0.082 mm^{-1}, D_c = 1.249 g cm^{-3}, colorless needle, crystal size of 0.13 × 0.05 × 0.04 mm^3. Of a total of 20015 reflections collected, 3827 were independent (R_{int} = 0.0548). Final $R1$ = 0.0455 [$I > 2\sigma(I)$] and $wR2$ = 0.1092 (all data). Data completeness to θ = 25.24°, 99.6%. CCDC 1531504 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures..

(17) **Crystal Data for Compound 3a·5H_2O**

$C_{24}H_{32}N_2O_8$, M = 476.51, triclinic, space group $P\bar{1}$, Z = 2, a = 9.3720(6) Å, b = 11.4969(8) Å, c = 13.0910(9) Å, α = 113.510(2), β = 90.028(2), γ = 92.865(2), V = 1291.51(15) Å^3, μ(Mo Kα) = 0.092 mm^{-1}, D_c = 1.225 g cm^{-3}, colorless plate, crystal size of 0.12 × 0.12 × 0.04 mm^3. Of a total of 26256 reflections collected, 6884 were independent (R_{int} = 0.0266). Final $R1$ = 0.0501 [$I > 2\sigma(I)$] and $wR2$ = 0.1459 (all data). Data completeness to θ = 25.24°, 99.7%. CCDC 1531506 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(18) Maleki, A.; Kamalzare, M. *Tetrahedron Lett.* **2014**, *55*, 6931.

(19) **Crystal Data for Compound 5a·EtOH**

$C_{25}H_{30}N_2O_4$, M = 422.51, monoclinic, space group $P2_1/c$, Z = 4, a = 13.8692(12) Å, b = 15.4961(10) Å, c = 11.3368(12) Å, β = 113.249(6), V = 2238.6(4) Å^3, μ(MoKα) = 0.085 mm^{-1}, D_c = 1.254 g cm^{-3}, yellow plate, crystal size of 0.17 × 0.15 × 0.13 mm^3. Of a total of 12149 reflections collected, 4011 were independent (R_{int} = 0.1114). Final $R1$ = 0.0764 [$I > 2\sigma(I)$] and $wR2$ = 0.2393 (all data). Data completeness to θ = 25.24°, 98.3%. CCDC 1531505 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.