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Tetrahydropyrrolo[3,2-*c*]azepin-4-ones as a new class of cytotoxic compounds

Roberto Martínez,[a,*] J. Gustavo Ávila,[b] Ma. Teresa Ramírez,[a] Araceli Pérez[a] and Ángeles Martínez[a]

[a]*Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, 04510 Coyoacán, México, DF, Mexico*
[b]*Facultad de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, 04510 Coyoacán, México, DF, Mexico*

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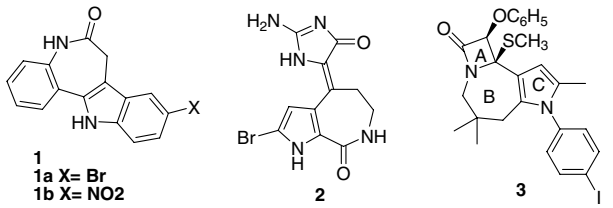
Abstract—Pyrroloazepinones **8a**–**j** and **9a**–**j** were designed by structural modification of lead compound **3**. These compounds were tested on five tumor cell lines to determine the role of the azeto ring and the 2-methyl substituent in the cytotoxicity of compound **3**. Our results show that compounds **8a**–**j** ($R_1 = CH_3$) have dramatically reduced cytotoxicity, resulting from the loss of the azeto moiety of lead compound **3**. By contrast, azepinones **9a**–**j** (R_1 = 4-nitrophenyl) inhibited the proliferation of almost all cancer cell lines tested even though they lack the azeto ring. Preliminary SAR studies with these compounds revealed the importance of halogens at the *para*- or *meta*-position of the 1-phenyl moiety. Additionally, derivatives **9a** (R_2 = H), **9e** (R_2 = 4-F), and **9g** (R_2 = 4-OMe) were selectively cytotoxic to U-251 cells. However, none of the pyrroloazepinones inhibited the enzymatic activity of CDK1/cyclin B, CDK5/p25, and GSK-3.

1. Introduction

The cyclin-dependent kinases (CDKs) are a family of enzymes that drive the cell cycle.[1] Inhibitors of CDK have been shown to disrupt the cell cycle and to have potential value in the treatment of cancer.[2] Some of the most potent CDK inhibitors include 7,12-dihydroindolo[3,2-*d*]benzazepin-6(5*H*)-ones **1** (paullones)[3] and (*Z*)-4-(2-amino-4-oxo-1*H*-imidazol-5(4*H*)-ylidene)-2-bromo-4,5,6,7-tetrahydropyrrolo[2,3-*c*]azepin-8 (1*H*)-one **2** (hymenialdisine; HD).[4] Kenpaullone and HD act by competitive inhibition of ATP binding, and molecular modeling shows that kenpaullone can bind to the ATP-binding site of CDK2 with residue contacts similar to those observed in the crystal structures of other CDK2-inhibitor complexes (Fig. 1).[5] HD, by contrast, belongs to a new class of small molecules that act as tight binding inhibitors of CDK due to the formation of strong, specific hydrogen bonds and a short-range electrostatic interaction between the acidic Asp145 and the basic guanidinium ring of the inhibitor (Fig. 2).[6] Within the paullone family, kenpaullone **1a** and alsterpaullone **1b** are two outstanding examples in terms of anticancer activity.[7] The paullones and HD have been intensively investigated as inhibitors of cellular proliferation.[8]



In this light, we are currently engaged in a program aimed at synthesizing original heterocyclic compounds that inhibit the growth of cancer cells.[9] One of these compounds is azetopyrroloazepinone **3**, which shows in vitro cytotoxic activity against PC-3 (prostate) and U251 (central nervous system) cancer cell lines.[10] This molecule is composed of three units: an azeto ring (A), an azepine ring (B), and a five-membered heterocyclic

Keywords: Pyrroloazepinones; Cytotoxic activity; CDK1/cyclin B; CDK5/p25; GSK-3 activity.
* Corresponding author. Tel.: +52 56 22 44 41; fax: +52 16 22 03; e-mail: robmar@servidor.unam.mx

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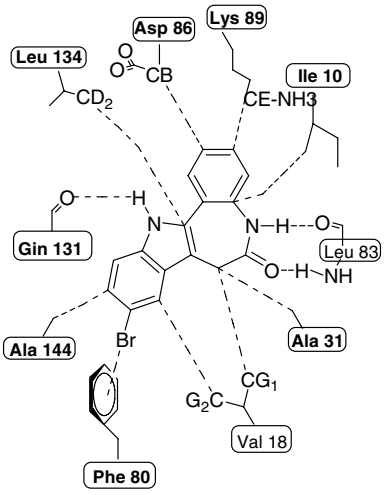


Figure 1. Possible interactions between kenpaullone and CDK2.[5]

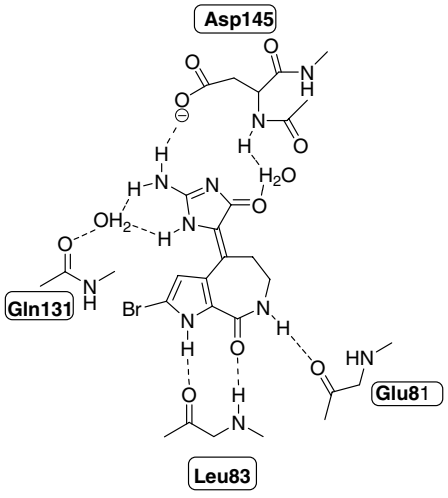


Figure 2. Possible interactions between Hymenialdisine and CDK2.[6]

ring (C). Because structural modification is an effective approach for understanding the mechanism of drug action and for designing better drugs,[11] an exploration of structural changes of compound **3** and cytotoxic activity evaluation of generated compounds should help determine the mechanism of its antiproliferative activity. As a first approach, we substituted the pyrrolo ring of **3** with a thiophene (series **4**), a furan (series **5**), or a benzene ring (series **6**) by using bioisosteric modification (Fig. 3). The cytotoxic activities of the new compounds corresponded to their C ring aromaticities.[12] We recently explored the role of the substituents attached to the 3-phenyl ring of compound **3** (compound series **7**) in the inhibition of cancer cell growth (Fig. 3).[13] The results indicated an apparent relationship between the cytotoxic activity of the 3-halogen derivatives and both the electronegativity and size of the halogen.

We removed the azeto ring from compound **3** (generating compound series **8**) to determine its role in the cytotoxic activity. These compounds have part of the pharmacophore found in the paullones and HD. In other CDK2-inhibitor complexes, the 2-bromine substituent of HD is an aromatic group, and alsterpaullone **1b** contains a 9-nitro group. Because both of these retain potent CDK inhibitory and cytotoxicity activity, we speculated that similarly substituted 2-nitrophenylipyrroloazepinone derivatives (compound series **9**) would exhibit potent antiproliferative activity.

Here we report the synthesis of pyrrolo[3,2-*a*]azepinone derivatives **8a**–**j** and pyrrolo[3,2-*a*]azepinone compounds **9a**–**j**. Both series lack the azeto moiety found in **3**. In addition, in **9a**–**j**, the 2-methyl substituent is replaced by a 2-(*p*-nitrophenyl) group (Chart 1). We also report on the cytotoxic activity and the CDK1/cyclin B, CDK5/p25, and GSK-3 inhibitory activity of these compounds.

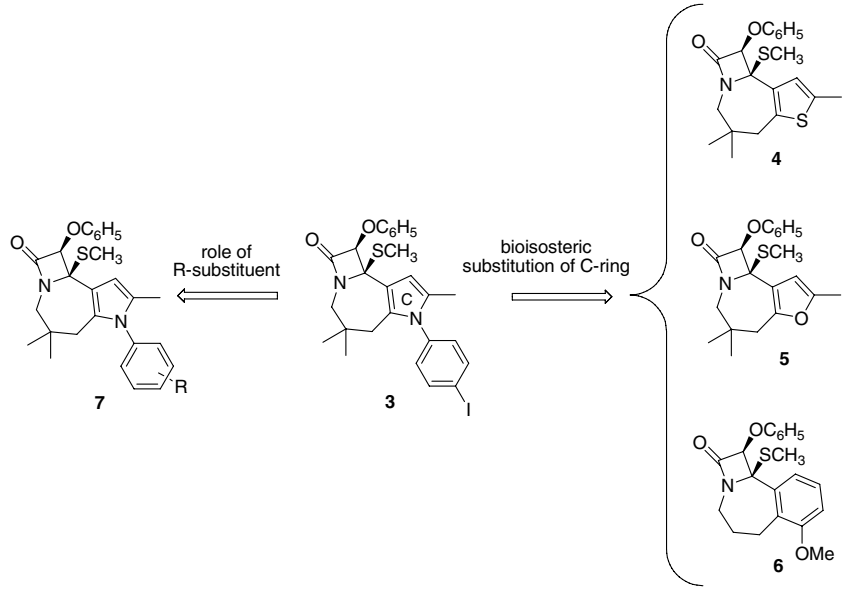


Figure 3. Exploration of the azetopyrroloazepinone **3** pharmacophore.

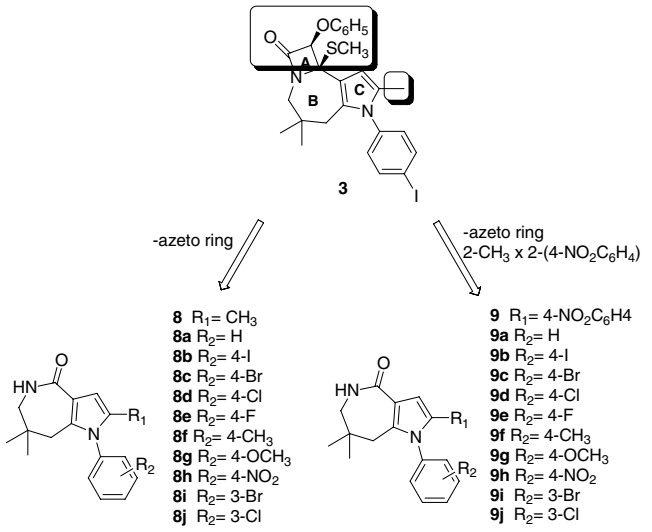
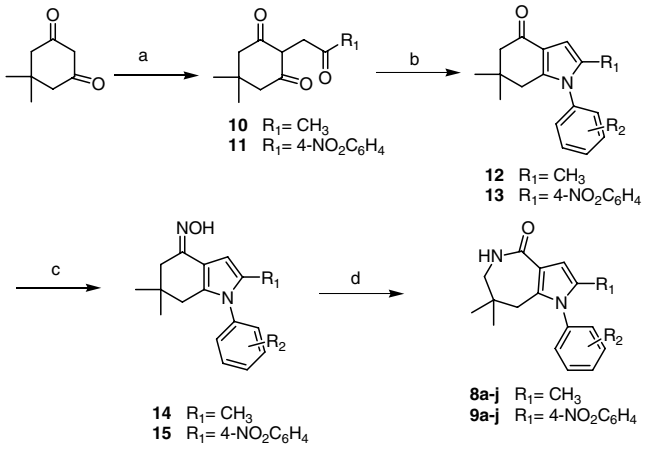


Chart 1. Structural modification of lead compound **3**.

2. Chemistry

The preparation of compounds **8a-j** and **9a-j** involves a four-step procedure starting from commercially available 5,5-dimethyl-1,3-cyclohexanodione (dimedone) as we have described previously (Scheme 1).[14] The first step involves alkylation of dimedone with 1-chloro-2-propanone ($R_1 = CH_3$) or 2-bromo-4-nitroacetophenone ($R_1 = 4\text{-}NO_2\text{-}C_6H_4$) to provide tricarbonyl compounds **10** and **11** in good yields. The second step involves ring closure in compounds **10** and **11** to indol-4-ones **12a-j** and **13a-j** under Paal–Knor conditions using different substituted anilines as amines. In the third step, quantitative oximation of compounds **12a–j** and **13a–j** was achieved with hydroxylamine hydrochloride in ethanol and in the presence of sodium carbonate to give oximes **14a–j** and **15a–j**. Finally, regioselective Beckmann rearrangement of the *syn*- and *anti*-oximes **14a–j** and **15a–j** gave azepinones **8a–j** and **9a–j** as the sole products. It is commonly assumed the group that migrates in the Beckmann rearrangement is the one *anti* to the hydroxyl and here should be formed both azepinones **9a–j** and **16a–j** (Scheme 2). One possible explanation to observe regioselectivity is that *anti* oximes undergo isomerization to *syn* oximes under the reaction conditions before migration takes place. To test this assertion, an ^1H NMR experiment with the *syn*/*anti* oxime mixture **14b** in the presence of polyphosphoric acid at 80 °C was carried out. As can be seen in Figure 4 *anti*-oxime isomerizes to *syn*-oxime instead of furnishing azepinone **10b**.



Scheme 1. Synthesis of tetrahydropyrroloazepinones **8a–j** and **9a–j**. Reagents and conditions: (a) K_2CO_3, R_1COCH_2Cl, $CHCl_3$, rt, 48 h; (b) $R_2C_6H_4NH_2$, CH_3CO_2H, reflux, 12 h; (c) $NH_2OH.HCl$, NaOH aq, EtOH, reflux, 2 h; (d) PPA, 80 °C, 3 h.

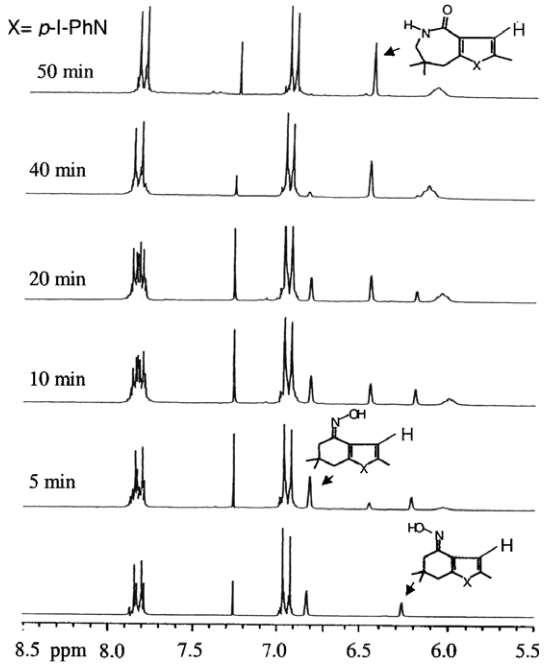
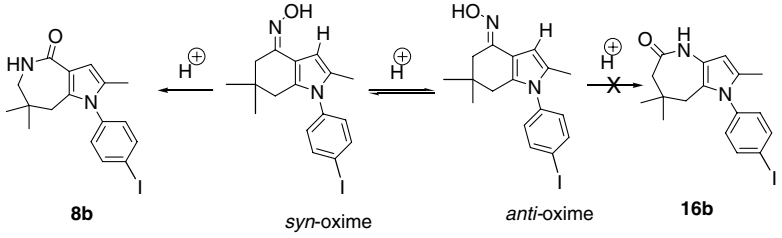


Figure 4. ^1H NMR experiments of Beckmann rearrangement reaction of *syn*/*anti* oximes **16b**.



Scheme 2. Proposed reaction mechanism for the Beckmann rearrangement of *syn*/*anti* oximes **14b**.

3. Biological activity

Azeto-pyrroloazepinones **8a–j** and **9a–j** were evaluated in vitro for their ability to inhibit the growth of PC-3 prostate, U251 central nervous system, K652 leukemia, HCT-15 colon, and MFC7 breast cancer cells. The percent inhibition of growth of these five cell lines after treatment with compounds **8a–j** (100 μM) or **9a–j** (50 μM) is given in Tables 1 and 2, respectively.[15]

As shown in Table 1, the 2-methylpyrroloazepinones **8a–j** ($R_1 = CH_3$) did not inhibit the proliferation of the five cancer cell lines, indicating that the azeto ring is necessary for cytotoxic activity for this series of compounds. However, replacement of the 2-methyl substituent of **8a–j** ($R_1 = CH_3$) with a 2-(4-nitrophenyl) moiety (compounds **9a–j**) improved their cytotoxic potency. Notably, the 1-(3-chlorophenyl) derivative **9j** ($IC_{50} = 6.3$ μM) was 10-fold more cytotoxic than lead compound **3** ($IC_{50} = 87$ μM) against PC-3 prostate cancer cells. Also, compounds **9b**, **9c**, **9d**, **9h**, and **9i** were more active than **3** against this cell line (Table 3). The most active compounds against the proliferation of K-562 cells were **9d** ($R_2 = 4$-Cl; $IC_{50} = 15$ μM), **9i** ($R_2 = 3$-Br; $IC_{50} = 13$ μM), and **9j** ($R_2 = 3$-Cl; $IC_{50} = 14$ μM). Interestingly, the azetopyrroloazepinones **7** demonstrated a similar tendency [13] against K-562 cells. In the U-251 central nervous system cancer cell line, all the **9a–j** compounds, except for **9e** (($R_2 = 4$-F), **9f** ($R_2 = 4$-CH_3) and **9g** ($R_2 = 4$-OMe), were significantly more potent than lead compound **3**. In particular, the 1-(4-nitrophenyl) derivative **9h** was the most active compound, and the unsubstituted derivatives **9a** and **9e** ($R_2 = 4$-F) were selectively cytotoxic to these cells. The HCT-15 cell line was sensitive to several of the pyrroloazepinones (**9b**, **9d**, **9h**, **9i**, and **9j**). The halogen

Table 1. % Inhibition of compounds **8a–j** to the five cancer cell lines (100 μM)

Compound	R_2	PC-3 (prostate)	U-251 (CNS)	K-562 (leukemia)	HCT-15 (colon)	MCF-7 (breast)
8a	4-H	7.55	14.73	10.86	−9.92	19.31
8b	4-I	20.43	19.98	30.59	−29.33	23.20
8c	4-Br	−2.38	14.25	17.16	−20.43	−3.73
8d	4-Cl	31.01	28.46	22.43	−3.87	13.73
8e	4-F	−9.59	−5.40	−18.78	−21.20	−3.85
8f	4-CH_3	−13.29	21.79	1.25	−23.47	−4.12
8g	4-OCH_3	−25.77	10.52	12.30	10.23	−4.26
8h	4-NO_2	23.76	24.30	−3.45	−15.80	27.70
8i	3-Br	41.40	41.13	42.21	17.0	28.87
8j	3-Cl	23.38	39.47	42.27	12.04	24.34

Table 2. % Inhibition of compounds **9a–j** to the five cancer cell lines (50 μM)

Compound	R_2	PC-3 (prostate)	U-251 (CNS)	K-562 (leukemia)	HCT-15 (colon)	MCF-7 (breast)
9a	H	37.36	62.41	42.90	9.79	37.60
9b	4-I	113.30	117.70	22.87	66.52	74.81
9c	4-Br	108.66	115.97	46.51	48.40	39.03
9d	4-Cl	117.44	114.54	94.76	97.94	133.27
9e	4-F	−5.43	52.30	−31.09	18.21	40.42
9f	4-CH_3	−16.73	17.56	−40.31	9.90	43.39
9g	4-OCH_3	11.80	57.02	−23.50	21.79	46.28
9h	4-NO_2	84.24	110.92	34.00	51.84	31.10
9i	3-Br	111.3	100.60	88.62	103.36	125.93
9j	3-Cl	134.91	117.29	85.91	81.87	82.89

Table 3. The IC_{50} values (μM) of compounds **9a–j** to the five cancer cell lines[a]

Compound	R_2	PC-3 (prostate)	U-251 (CNS)	K-562 (leukemia)	HCT-15 (colon)	MCF-7 (breast)
3	NA	87.0 ± 8.6	40.0 ± 3.6	>100	>100	>100
9a	H	>100	12.4 ± 0.2	>100	>100	>100
9b	4-I	10.13 ± 0.56	15.5 ± 4.1	>100	63.3 ± 12.5	14.3 ± 1.3
9c	4-Br	21.1 ± 2.1	25.6 ± 4.5	>100	>100	>100
9d	4-Cl	17.44 ± 1.87	28.82 ± 3.7	15.10 ± 3.9	20.04 ± 4.7	51.66 ± 3.6
9e	4-F	>100	35.1 ± 7.3	>100	>100	>100
9f	4-CH_3	>100	>100	>100	>100	>100
9g	4-OMe	>100	87.0 ± 17.0	>100	>100	>100
9h	4-NO_2	14.3 ± 3.1	8.7 ± 1.2	>100	57.3 ± 10.4	>100
9i	3-Br	10.11 ± 0.73	14.8 ± 0.12	12.6 ± 2.3	10.5 ± 1.3	13.3 ± 2.1
9j	3-Cl	6.3 ± 0.5	20.7 ± 0.9	13.7 ± 1.5	33.6 ± 4.5	11.8 ± 3.8
Doxo		0.32 ± 0.02	0.09 ± 0.02	0.28 ± 0.01	0.23 ± 0.01	0.14 ± 0.01

[a] The tumoral cell lines were supplied by the National Cancer Institute. The cytotoxic assay were carried out at 5000–7500 cells/mL using the sulforhamide B (SRB) protein assay to estimate cell growth. The percentage growth was evaluated spectrophotometrically in a Bio kinetics reader spectrophotometer. Values are means of three experiments, standard deviation is given in parentheses (>100, not active). Doxo, doxorubicine.

derivatives **9b** (R_2 = 4-I; IC_{50} = 14 μM), **9i** (R_2 = 3-Br; IC_{50} = 13 μM), and **9j** (R_2 = 3-Cl; IC_{50} = 12 μM) were effective in killing breast cancer cell lines (MFC-7) with moderate micromolar cytotoxicity, suggesting that derivatization of N-phenyl group with these halogens is suitable to obtain best anticancer compounds. Thus, the antiproliferative activity of **9i** in HCT-15 and MCF-7 cells resembles its potency in the PC-3, U-251, and K-562 cancer cell lines.

Because it was reported that the HCT-116 cancer cell line was the most sensitive to the growth inhibitory activity of paullones **1** and compounds **9a–j** were tested on its parental HCT-15 cancer cell line, a comparison of their cytotoxic activity was made . Compounds **9a–j** exhibit a similar antiproliferative activity (IC_{50} in the low micromolar range) as kenpaullone **1a** (GI_{50} 20 μM). In contrast, alsterpaullone **1b** (R = NO_2; GI_{50} 0.2 μM)) shows a more than 10-fold higher potency compared to **9a–j** compounds. Unfortunately, compounds **8c**, **8d**, **8i**, **8j**, and **9a–j** did not inhibit the protein kinase activity of CDK1/cyclin B, CDK5/p25, and GSK-3 CDK1 (IC_{50} > 10 μM),[16] and these results do not allow it to give a reasonable mechanistic explanation of cytotoxic behavior of **9a–j**.

4. Conclusion

The present results indicate that removal of the azeto moiety from lead compound **3** (compounds **8a–j**; $R_1 = CH_3$) dramatically reduces the cytotoxic activity. However, this is less clear in the case of azepinones **9a–j** (R_1 = 4-nitrophenyl) which, in most cases, inhibited the proliferation of all five cancer cell lines despite lacking the azeto ring. The preliminary SAR for these compounds also revealed the importance of halogens in *para* or *meta* positions on the 1-phenyl moiety. Additionally, derivatives **9a** (R_2 = H), **9e** (R_2 = 4-F), and **9g** (R_2 = 4-OMe) were selectively cytotoxic to U-251 cells. Therefore, our results indicate that these new cytotoxic compounds may be useful as lead compounds for the development of novel anticancer agents. Unfortunately, compounds **9a–j** did not inhibit protein kinase activity. Therefore, future studies will focus on determining the mechanism by which these new pyrroloazepinones inhibit tumor growth and investigating the effect of combinations of appropriately positioned substituents.

5. Experimental

5.1. Chemistry

Melting points were determined on a Melt-Tem II melting points apparatus and are uncorrected. The IR spectra were determined in a Nicolet FT Magna-IR 750 spectrometer. The H1 and ^{13}C NMR were determined in Varian Gemini 200 and UNITY-300 spectrometers in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with AX505-HA and SX-100 Jeol mass spectrometers. Reaction mixtures and chromatography fractions were concentrated by using a rotary evaporator (ca. 20 °C/20 Torr). For column chromatography, the Merck silica gel 60 F254 was employed. Commercial grade reagents were used without further purification except when indicated.

5.1.1. General procedure for the synthesis of cyclohex-1-ones (10 and 11). A slurry of dimedone (0.01 equiv), chloroketone (0.01 equiv), and anhydrous potassium carbonate (0.01 equiv) in chloroform was kept stirred at room temperature for 48 h. The mixture was filtered; the insoluble salts were dissolved in water and the filtered solution was made acidic with concentrated HCl. The precipitate was filtered off, washed with water, and crystallized from aqueous alcohol.

3-Hydroxy-5,5-dimethyl-2-(2-oxopropyl)-2-cyclohex-1-one **10**: yield 70% as a white solid; mp 133–134 °C. (lit.[17] 135–137 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.08 (6H, s), 2.16 (3H, s), 2.35 (4H, s), 3.41(2H, s), 9.0 (1H, s, br).

3-Hydroxy-5,5-dimethyl-2-[2-(4-nitrophenyl)-2-oxoethyl]-2-cyclohex-1-one **11**: yield 75% as a white solid; mp 198–200 °C (lit.[18] 202–204 °C); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07 (6H, s), 2.30 (4H, s), 3.92 (2H, s), 8.12 (2H, m), 8.27 (2H, m).

5.1.2. Synthesis of 1-(R_2-phenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-ones (12a–j). General procedure (R_2 = H): To a vigorously stirred suspension of triketone **10** (0.20 mmol) in acetic acid (5 mL) was added aniline (0.25 mmol). The resulting slurry was refluxed overnight until no more starting material was observed by TLC and then the reaction mixture was allowed to warm to room temperature and spilled over ice-water (10 mL). The aqueous solution was treated with a 10% sodium bicarbonate solution until a precipitate appeared. Purification by flash column chromatography on silica using hexane/ethyl acetate (7:3) as the eluent liquid afforded **12a** as a colorless solid (70% yield), mp: 135–137 °C, mp lit.,[19] 135–138 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1648; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (H-9,9′), 2.04 (H-8), 2.35 (H-5), 2.37 (H-7), 6.36 (H-3), 6.9–7.2 (Ar-H); MS (EI) *m/z* 253.

5.1.3. 1-(4-Iodophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12b). Yield: 84%; mp: 170–172 °C; mp lit.,[13] 172–173 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1648; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (H-9,9′), 2.04 (H-8), 2.35 (H-5), 2.38 (H-7), 6.36 (H-3), 6.9–7.87 (Ar-H); MS (EI) *m/z* 379.

5.1.4. 1-(4-Bromophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12c). Yield: 86%; mp: 171–173 °C, mp lit.,[13] 171–173 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1648; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05 (H-9,9′), 2.04 (H-8), 2.35 (H-5), 2.37 (H-7), 6.37 (H-3), 7.08–7.67 (Ar-H); MS (EI) *m/z* 331.

5.1.5. 1-(4-Chlorophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12d). Yield: 86%; mp: 171–172 °C, mp lit.,[20] 170–172 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1649;

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07(H-9, 9′), 2.05 (H-8), 2.36 (H-5), 2.39 (H-7), 6.36 (H-3),7.14–7.65 (Ar-H); MS (EI) *m*/*z* 287.

5.1.6. 1-(4-Fluorophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12e). Yield: 83%; mp: 156–158 °C, mp lit.,[19] 155–157 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1648; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (H-9,9′), 2.04 (H-8), 2.35 (H-5), 2.37 (H-7), 6.36 (H-3), 6.9–7.2 (Ar-H); MS (EI) *m*/*z* 271.

5.1.7. 1-(4-Methylphenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12f). Yield: 80%; mp: 170–171 °C, mp lit.,[20] 170–172 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1648; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (H-9,9′), 2.04 (H-8), 2.35 (H-5), 2.37 (H-7), 2.44 (4-CH_3-Ar), 6.36 (H-3), 6.9–7.22 (Ar-H); MS (EI) *m*/*z* 267.

5.1.8. 1-(4-Methoxyphenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12g). Yield: 81%; mp: 143–145 °C, mp lit.,[20] 142–144 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1648; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06 (H-9,9′), 2.04 (H-8), 2.35 (H-5), 2.37 (H-7), 2.42 (4-CH_3-Ar), 6.36 (H-3), 3.81 (4-OCH_3-Ar), 7.0–7.22 (Ar-H); MS (EI) *m*/*z* 283.

5.1.9. 1-(4-Nitrophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12h). Yield 75%; mp: 178–180 °C, mp lit.,[20] 177–179 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1649; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (H-9, 9′), 2.05 (H-8), 2.36 (H-5), 2.39 (H-7), 6.39 (H-3), 7.14–8.02 (Ar-H); MS (EI) *m*/*z* 298.

5.1.10. 1-(3-Bromophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12i). Yield 70%; mp 134–136 °C, mp lit.,[20] 134–135 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1649; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (H-9, 9′), 2.05 (H-8), 2.35 (H-5), 2.39 (H-7), 6.36 (H-3), 7.09–7.48 (Ar-H); MS (EI) *m*/*z* 331.

5.1.11. 1-(3-Chlorophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (12j). Yield 70%; mp 130–132 °C, mp lit.,[13] 129–131 °C; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1649; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (H-9, 9′), 2.05 (H-8), 2.36 (H-5), 2.39 (H-7), 6.36 (H-3),7.14–7.65 (Ar-H); MS (EI) *m*/*z* 287.

5.2. Synthesis of 6,6-dimethyl-2-(4-nitrophenyl)-1-(R_2-phenyl)-1,5,6,7-tetrahydroindol-4-ones (13a–j)

General procedure (R_2 = H). To a reaction vessel with a reflux condenser were successively added 5,5-dimethyl-2[2-(4-nitrophenyl)-2-oxoethyl]cyclohexane-1.3-diona (0.20 mmol), zirconium sulfate (0.080 g), aniline (0.02 mL), and toluene (3 mL). After the resulting mixture was stirred at 100 °C for 3 h, the zirconium sulfate was separated by filtration. The filtrate was concentrated and subjected to column chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (3:1) giving **13a** as a colorless solid (80% yield), mp: 246–248 °C, mp lit.,[21] 245–246 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8′), 2.43 (H-5), 2.54 (H-7), 6.97 (H-3), 7.16 - 8.01 (Ar-H); MS *m*/*z* 360.

5.2.1. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-iodophenyl)-1,5,6,7-tetrahydroindol-4-one (13b). Yield 60%; mp: 174–175 °C, mp lit.,[21] 173–175 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8′), 2.43 (H-5), 2.52 (H-7), 6.95 (H-3), 7.10–8.05 (Ar-H). MS: *m*/*z* 486.

5.2.2. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-bromophenyl)-1,5,6,7-tetrahydroindol-4-one (13c). Yield 65%; mp: 227–228 °C, mp lit.,[21] 224–225 °C^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8′), 2.43 (H-5), 2.51 (H-7), 6.95 (H-3), 7.04–8.08 (Ar-H). MS: *m*/*z* 438.

5.2.3. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-chlorophenyl)-1,5,6,7-tetrahydroindol-4-one (13d). Yield 67%; mp: 251–253 °C, mp lit.[21] 246–247 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8′), 2.43 (H-5), 2.53 (H-7), 6.95 (H-3), 7.12–8.07 (Ar-H). MS: *m*/*z* 394.

5.2.4. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-fluorophenyl)-1,5,6,7-tetrahydroindol-4-one, (13e). Yield 66%; mp: 277–279 °C, mp lit.,[21] 280–281 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8′), 2.43 (H-5), 2.51 (H-7), 6.96 (H-3), 7.16–8.07 (Ar-H). MS: *m*/*z* 378.

5.2.5. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-methylphenyl)-1,5,6,7-tetrahydroindol-4-one (13f). Yield 65%; mp: 262–264 °C, mp. lit.,[21] 260–262 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (H-8,8′), 2.42 (4-CH_3-Ar), 2.44 (H-5), 2.52 (H-7), 6.96 (H-3), 7.02–8.05 (Ar-H). MS: *m*/*z* 374.

5.2.6. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-methoxylphenyl)-1,5,6,7-tetrahydroindol-4-one (13g). Yield 70%; mp: 200–202 °C, mp lit.,[21] 205–207 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.11 (H-8,8′), 2.42 (H-5), 2.51 (H-7), 3.78 (4-OCH_3-Ar), 6.95 (H-3), 6.94–8.05 (Ar-H). MS: *m*/*z* 390.

5.2.7. 6,6-Dimethyl-bis-1,2-(4-nitrophenyl)-1,5,6,7-tetrahydroindol-4-one (13h). Yield 55%; mp: 275–277 °C, mp lit.,[21] 269–270 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.12 (H-8,8′), 2.45 (H-5), 2.57 (H-7), 6.99 (H-3), 7.18–8.36 (Ar-H). MS: *m*/*z* 405.

5.2.8. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(3-bromophenyl)-1,5,6,7-tetrahydroindol-4-one (13i). Yield 60%; mp: 223–225 °C, mp lit.,[21] 226–227 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.12 (H-8,8′), 2.43 (H-5), 2.45 (H-7), 6.95 (H-3), 7.09–8.08 (Ar-H). MS: *m*/*z* 438.

5.2.9. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(3-chlorophenyl)-1,5,6,7-tetrahydroindol-4-one (13j). Yield 65%; mp: 224–225 °C, mp lit.,[21] 225–227 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.12 (H-8,8′), 2.43 (H-5), 2.54 (H-7), 6.96 (H-3), 7.04–8.08 (Ar-H). MS: *m*/*z* 394.

5.2.10. Synthesis of 1-(R_2-phenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one (*syn*/*anti*) oximes (14a–j) and 1-(R_2-phenyl)-6,6-dimethyl-2-(4-nitrophenyl)-1,5,6,7-tetrahydro-indol-4-one (*syn*/*anti*) oximes (15a–j). General procedure (R_2 = H). To a solution of **12a** (1.26 mmol) dissolved in 50 mL of ethanol was added a solution of hydroxylamine hydrochloride(5.5 mmol) dissolved in 30 mL of 5 M sodium hydroxide and the mixture was

stirred on a steam bath for two hours. Removal of the solvent under reduced pressure gave an amorphous solid that was purified by column chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (6:4) giving **14a** as a colorless solid (97% yield); mp: 188–190 °C, mp lit.,[14] 186–190 °C; δ 0.91–0.93 (H-9,9′), 2.04–2.27 (H-8), 2.58–2.25 (H-5), 2.24 (H-7), 6.24–6.81 (H-3), 7.17–7.45 (Ar-H); MS (EI) *m*/*z* 268.

5.2.10.1. 1-(4-Iodophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14b). Yield 98%; mp: 210–212 °C, mp lit.,[13] 210–212 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92–0.96 (H-9,9′), 2.05–2.35 (H-8), 2.37 (H-7), 2.25–2.58 (H-5), 2.37 (H-7), 6.23–6.82 (H-3), 6.9–7.87 (Ar-H); MS (EI) *m*/*z* 394.

5.2.10.2. 1-(4-Bromophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14c). Yield 97%; mp: 209–210 °C, mp lit.,[14] 208–210 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91–0.94 (H-9,9′), 2.06–2.28 (H-8), 2.25–2.58 (H-5), 2.24 (H-7), 6.25–6.83 (H-3), 7.08–7.62 (Ar-H); MS (EI) *m*/*z* 346.

5.2.10.3. 1-(4-Chlorophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14d). Yield 99%; mp: 186–188 °C, mp lit.,[13] 185–187 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90–0.93 (H-9,9′), 2.06–2.25 (H-8), 2.27–2.58 (H-5), 2.28 (H-7), 6.25–6.82 (H-3), 7.11–7.48 (Ar-H); MS (EI) *m*/*z* 302.

5.2.10.4. 1-(4-Fluorophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14e). Yield 95%; mp: 212–214 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.93–0.95 (H-9,9′), 2.04–2.22 (H-8), 2.57(H-7), 2.27–2.58 (H-5), 6.21–6.80 (H-3), 7.18–7.26 (Ar-H); MS (EI) *m*/*z* 286. $C_{17}H_{19}FN_2O$; Anal. Calcd: C, 71.31; H, 6.69; N, 9.78. Found C, 71.25; H, 6.65; N, 9.73.

5.2.10.5. 1-(4-Methylphenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14f). Yield 96%; mp: 220–222 °C, mp lit.,[14] 220–225 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92–0.94 (H-9,9′), 2.03–2.24 (H-8); 2.24 (H-7), 2.25–2.56 (H-5), 6.19–6.78 (H-3), 7.05–7.24 (Ar-H); MS (EI) *m*/*z* 282.

5.2.10.6. 1-(4-Methoxyphenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14g). Yield 97%; mp: 213–215 °C, mp lit.,[14] 212–213 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.93–0.91 (H-9,9′), 2.05–2.26 (H-8); 2.26 (H-7), 2.28–2.59 (H-5), 6.23–6.70 (H-3), 6.97–7.10 (Ar-H); MS (EI) *m*/*z* 298.

5.2.10.7. 1-(4-Nitrophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14h). Yield: 95%; mp: 256–258 °C, mp lit.,[10] 255–258 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92–0.94 (H-9,9′), 2.10–2.29 (H-8); 2.26 (H-7), 2.12–2.37 (H-5), 6.30–6.90 (H-3), 7.30–8.40 (Ar-H); MS (EI) *m*/*z* 313.

5.2.10.8. 1-(3-Bromophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14i). Yield 95%; mp: 174–176 °C, mp lit.,[13] 174–175 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.03–1.04 (H-9, 9′), 2.07 (H-8), 2.29–2.61 (H-5), 2.36 (H-7), 6.33–6.82 (H-3), 7.12–7.62 (Ar-H); MS (EI) *m*/*z* 346.

5.2.10.9. 1-(3-Chlorophenyl)-2,6,6-trimethyl-4,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (14j). Yield 99%; mp: 175–180 °C, mp lit.,[14] 185–187 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.99–1.02 (H-9,9′), 1.96–2.26 (H-8), 2.21–2.61 (H-5), 2.12 (H-7), 6.23–6.83 (H-3), 7.25–7.84 (Ar-H); MS (EI) *m*/*z* 302.

5.2.10.10. 6,6-Dimethyl-2-(4-nitrophenyl)-1-phenyl-1,5,6,7-tetrahydro-indol-4-one oximes (*syn*/*anti*) (15a). Yield 80%; mp: 240–242 °C, IR ($CHCl_3$, cm^{-1}) 3587; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.034–1.045 (H-8,8′), 2.36 (H-7), 2.39–2.59 (H-5), 6.86 (H-3), 7.06–8.04 (Ar-H); MS 375.

5.2.10.11. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-iodophenyl)-1,5,6,7-tetrahydroindol- 4-one oximes (*syn*/*anti*) (15b). Yield 75%; mp: 265–267 °C, IR ($CHCl_3$, cm^{-1}) 3587; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.034–1.045 (H-8,8′), 2.36 (H-7), 2.39–2.59 (H-5), 6.86 (H-3), 7.06–8.04 (Ar-H); MS 501.

5.2.10.12. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-bromophenyl)-1,5,6,7-tetrahydroindol-4-one oximes *syn*/*anti*) (15c). Yield 89%; mp: 265–267 °C, IR ($CHCl_3$, cm^{-1}) 3587; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.034–1.045 (H-8,8′), 2.36 (H-7), 2.39–2.59 (H-5), 6.86 (H-3), 7.06–8.04 (Ar-H); MS 453.

5.2.10.13. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-chlorophenyl)-1,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (15d). Yield 95%; mp: 231–233 °C, IR ($CHCl_3$, cm^{-1}) 3587; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06–1.07 (H-8,8′), 2.39 (H-7), 2.43–2.70 (H-5), 6.91 (H-3), 7.07–8.05 (Ar-H); MS 409.

5.2.10.14. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-fluorophenyl)-1,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (15e). Yield 86%; mp: 255–257 °C, IR ($CHCl_3$, cm^{-1}) 3588; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.01 (H-8,8′), 2.38 (H-7), 2.41–2.69 (H-5), 7.05 (H-3), 7.13–8.04 (Ar-H); MS 393.

5.2.10.15. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-methylphenyl)-1,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (15f). Yield 89%; mp: 224–225 °C, IR ($CHCl_3$, cm^{-1}) 3587; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.06–1.07 (H-8,8′), 2.39 (H-7), 2.43–2.66 (H-5), 6.94 (H-3), 2.42 (H-R), 7.0–8.0 (Ar-H); MS 389.

5.2.10.16. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(4-methoxyphenyl)-1,5,6,7-tetrahydro-indol-4-one oximes (*syn*/*anti*) (15g). Yield 88%; mp: 267–269 °C, IR ($CHCl_3$, cm^{-1}) 3587; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.067–1.07 (H-8,8′), 2.39 (H-7), 2.44–2.66 (H-5), 6.95 (H-3), 3.87 (H-R), 7.04–8.02 (Ar-H); MS 405.

5.2.10.17. 6,6-Dimethyl-1,2-bis-(4-nitrophenyl)-1,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (15h). Yield 77%; mp: 227–229 °C, IR ($CHCl_3$, cm^{-1}) 3586; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05–1.06 (H-8,8′), 2.40

(H-7), 2.43–2.63 (H-5), 6.94 (H-3), 7.19–8.34 (Ar-H); MS 420.

5.2.10.18. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(3-bromophenyl)-1,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (15i). Yield 88%; mp: 248–250 °C, IR ($CHCl_3$, cm^{-1}) 3586; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.047–1.057 (H-8,8′), 2.33 (H-7), 2.38–2.59 (H-5), 6.87 (H-3), 7.17–8.04 (Ar-H); MS 453.

5.2.10.19. 6,6-Dimethyl-2-(4-nitrophenyl)-1-(3-chlorophenyl)-1,5,6,7-tetrahydroindol-4-one oximes (*syn*/*anti*) (15j). Yield 89%; mp: 245–246 °C, IR ($CHCl_3$, cm^{-1}) 3587; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04–1.05 (H-8,8′), 2.32 (H-7), 2.39–2.58 (H-5), 6.85 (H-3), 7.07–8.04 (Ar-H); MS 409.

5.2.11. Synthesis of 5,6,7,8-tetrahydro-2,7,7-trimethyl-1-(R_2- phenyl)pyrrolo[3,2-*c*]azepin-4 (1*H*)-ones (8a–j) and 5,6,7,8-tetrahydro-7,7-dimethyl-2-(4-nitro-phenyl)-1-(R_2-phenyl) pyrrolo[3,2-*c*]azepin-4(1*H*)-ones (9a–j). General procedure (R_2 = H): To a mixture of phosphorus pentoxide (7 mmol) and phosphoric acid (10 ml) was added **14a** (3 mmol) and the mixture was mechanically stirred at 80–90 °C for 2 h. The mixture was treated with ice-water, neutralized with sodium carbonate and extracted with methylene chloride (3× 20 mL), and dried (sodium anhydrous sulfate). Removal of the solvent under reduced pressure gave an amorphous solid that was separated by column chromatography (silica gel, hexane/ethyl acetate 6:4) to give **8a** as a colorless solid (95% yield); mp: 238–240 °C, mp lit.,[14] 237–238 °C; IR ($CHCl_3$ cm−1) 1631; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (H-10,10′), 1.96 (H-9), 2.33 (H-8), 3.0 (H-6), 5.98 (exchangeable with D_2O, N–H), 6.46 (H-3), 7.19–7.49 (Ar-H); MS (EI) *m*/*z* 268.

5.2.11.1. 6*H*-1-(4-Iodophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one (8b). Yield 96%; mp: 264–265 °C, mp lit.,[13] 264–2265 °C; IR ($CHCl_3$, cm^{-1}) 1631; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (H-10-10′), 1.96 (H-9), 2.31 (H-8), 2.98 (H-6), 6.30 (exchangeable with D_2O, N–H), 6.46 (H-3), 6.91–7.85 (Ar-H); MS (EI) *m*/*z* 394.

5.2.11.2. 6*H*-1-(4-Bromophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one (8c). Yield 94%; mp: 248–250 °C, mp lit.,[14] 247–248 °C; IR ($CHCl_3$, cm^{-1}) 1631; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.97 (H-10-10′), 1.96 (H-9), 2.32 (H-8), 3.0 (H-6), 6.32 (exchangeable with D_2O, N–H), 6.46 (H-3), 7.07–7.65 (Ar-H); MS (EI) *m*/*z* 346.

5.2.11.3. 6*H*-1-(4-Chlorophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one (8d). Yield 95%; mp: 249–250 °C, mp lit.,[13] 247–249 °C; IR ($CHCl_3$, cm^{-1}) 1635; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (H-10-10′), 1.96 (H-9), 2.33 (H-8), 3.0 (H-6), 6.02 (exchangeable with D_2O, N-H), 6.46 (H-3), 7.09-7.51 (Ar-H); MS (EI) 302.

5.2.11.4. 6*H*-1-(4-Fluorophenyl)-2,7,7-trimethyl-4,5,7,8- tetrahydropyrrolo[3,2-*c*]azepin-4-one (8e). Yield 90%; mp: 156–158 °C; IR ($CHCl_3$, cm^{-1}) 1637; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (H-10,10′), 1.94 (H-9), 2.34 (H-8), 3.0 (H-6), 6.19 (exchangeable with D_2O, N–H), 6.47 (H-3), 7.10–7.601 (Ar-H); MS *m*/*z* 286, $C_{17}H_{19}FN_2O$; Anal. Calcd: C, 71.31; H, 6.69; N, 9.78. Found: C,71.26; H, 6.66; N, 9.72.

5.2.11.5. 6*H*-1-(4-Methylphenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one (8f). Yield 95%; mp: 251–252 °C, mp lit.,[14] 250–251 °C; IR ($CHCl_3$, cm^{-1}) 1629; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (H-10-10′), 1.95 (H-9), 2.32 (H-8), 2.44 (CH_3-Ar), 3.0 (H-6), 5.90 (exchangeable with D_2O, N–H), 6.44 (H-3), 7.04–7.28 (Ar-H); MS (EI) 282.

5.2.11.6. 6*H*-1-(4-Methoxylphenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one (8g). Yield 95%; mp: 231–232 °C, mp lit.,[14] 230–231 °C; IR ($CHCl_3$, cm^{-1}) 1628; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (H-10-10′), 1.95 (H-9), 2.32 (H-8), 2.44 (CH_3-Ar), 3.0 (H-6), 3.88 (CH_3O-Ar), 6.0 (exchangeable with D_2O, N–H), 6.44 (H-3), 7.0-7.1 (Ar-H); MS (EI) 298.

5.2.11.7. 6*H*-1-(4-Nitrophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one (8h). Yield 93%; mp: 253–255 °C, mp lit.,[10] 250–255 °C; IR ($CHCl_3$, cm^{-1}) 1638; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.98 (H-10-10′), 2.0 (H-9), 2.34 (H-8), 3.03 (H-6), 6.22 (exchangeable with D_2O, N-H), 6.52 (H-3), 7.41-8.40 (Ar-H); MS (EI) 313.

5.2.11.8. 6*H*-1-(3-Bromophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one (8i). Yield 94%; mp: 179–180 °C, mp lit.,[13] 178–180 °C; IR ($CHCl_3$, cm^{-1}) 1630; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.97 (H-10-10′), 1.97 (H-9), 2.32 (H-8), 3.02 (H-6), 6.22 (exchangeable with D_2O, N–H), 6.46 (H-3), 7.11–7.64 (Ar-H); MS (EI) *m*/*z* 346.

5.2.11.9. 6*H*-1-(3-Chlorophenyl)-2,7,7-trimethyl-4,5,7,8-tetrahydropyrrolo[3,2-*c*]azepin-4-one (8j). Yield 96%; mp: 168–170 °C, mp lit.,[14] 169–170 °C; IR ($CHCl_3$, cm^{-1}) 1635; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (H-10-10′), 1.96 (H-9), 2.33 (H-8), 3.0 (H-6), 6.02 (exchangeable with D_2O, N–H), 6.46 (H-3), 7.09–7.51 (Ar-H); MS (EI) 302.

5.2.11.10. 7,7-Dimethyl-2-(4-nitro-phenyl)-1-phenyl-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9a). Yield 69%; mp: 250–252 °C; IR ($CHCl_3$, cm^{-1}) 1637; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (H-9,9′), 2.47 (H-8), 3.09 (H-6), 6.19 (exchangeable with D_2O, N–H), 7.11 (H-3), 7.14–8.01 (Ar-H); MS (EI) 375. $C_{22}H_{21}N_3O_3$; Anal. Calcd: C, 70.38; H, 5.64; N, 11.19. Found: C,70.34; H, 5.63; N, 11.13.

5.2.11.11. 1-(4-Iodophenyl)-7,7-dimethyl-2-(4-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9b). Yield 70%; mp: 305–307 °C; IR ($CHCl_3$, cm^{-1}) 1638; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.03 (H-9,9′), 2.43 (H-8), 3.12 (H-6), 6.45 (exchangeable with D_2O, N–H), 7.08 (H-3), 7.02–8.06 (Ar-H); MS 501. $C_{22}H_{20}IN_3O_3$; Anal. Calcd: C, 52.71; H, 4.02; N, 8.38. Found C, 52.72; H, 4.03; N, 8.33.

5.2.11.12. 1-(4-Bromophenyl)-7,7-dimethyl-2-(4-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9c). Yield 70%; mp: 301–302 °C; IR ($CHCl_3$, cm^{-1}) 1639; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (H-9,9′), 2.44 (H-8), 3.09 (H-6), 6.41 (exchangeable with D_2O, N–H), 7.08 (H-3), 7.03–8.04 (Ar-H); MS (EI) 453. $C_{22}H_{20}$ BrN^3O_3; Anal. Calcd: C, 58.16; H, 4.44; N, 9.25. Found: C, 58.20; H, 4.43; N, 9.23.

5.2.11.13. 1-(4-Chloro-phenyl)-7,7-dimethyl-2-(4-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9d). Yield 80%; mp: 272–274 °C; IR ($CHCl_3$, cm^{-1}) 1638; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (H-9,9′), 2.44 (H-8), 3.09 (H-6), 6.48 (exchangeable with D_2O, N–H), 7.13 (H-3), 7.15–8.04 (Ar-H); MS (EI) 409. $C_{22}H_{20}ClN_3O_3$; Anal. Calcd: C, 64.47; H, 4.92; N, 10.25. Found: C,64.44; H, 4.90; N, 10.23.

5.2.11.14. 1-(4-Fluoro-phenyl)-7,7-dimethyl-2-(4-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9e). Yield 72% yield); mp: 283–284 °C; IR ($CHCl_3$, cm^{-1}) 1637; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05 (H-9,9′), 2.45 (H-8), 3.11 (H-6), 6.45 (exchangeable with D_2O, N–H), 7.10 (H-3), 7.16–8.04 (Ar-H); MS (EI) 393. $C_{22}H_{20}$ FN_3O_3; Anal. Calcd: C, 67.17; H, 5.12; N, 10.68. Found: C,67.20; H, 5.10; N, 10.63.

5.2.11.15. 1-(4-Methylphenyl)-7,7-dimethyl-2-(4-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9f). Yield 72%; mp: 278–279 °C; IR ($CHCl_3$, cm^{-1}) 1637; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.03 (H-9,9′), 2.45 (H-8), 2.43 (H-CH_3), 3.09 (H-6), 6.39 (exchangeable with D_2O, N–H), 7.09 (H-3), 7.03–8.01 (Ar-H); MS (EI) 389. $C_{23}H_{23}N_3O_3$; Anal. Calcd: C, 70.93; H, 5.95; N, 10.79. Found: C,70.95; H, 5.96; N, 10.73.

5.2.11.16. 1-(4-Methoxy-phenyl)-7,7-dimethyl-2-(4-nitro-phenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9g). Yield 70%; mp: 295–296 °C; IR ($CHCl_3$, cm^{-1}) 1634; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (H-9,9′), 2.47 (H-8), 3.09 (H-6), 3.87(H-OCH_3), 6.27 (exchangeable with D_2O, N–H), 7.10 (H-3), 6.94–8.02 (Ar-H); MS (EI) 405. $C_{23}H_{23}N_3O_4$; Anal. Calcd: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.15; H, 5.72; N, 10.33.

5.2.11.17. 7,7-Dimethyl-1,2-bis(4-nitro-phenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9h). Yield 69%; mp: 307–308 °C; IR ($CHCl_3$, cm^{-1}) 1630; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (H-9,9′), 2.47 (H-8), 3.12 (H-6), 6.50 (exchangeable with D_2O, N-H), 7.12 (H-3), 7.12–8.35 (Ar-H); MS (EI) 420. $C_{22}H_{20}N_4O_5$; Anal. Calcd: C, 62.85; H, 4.79; N, 13.33. Found C,62.87; H, 4.76; N, 13.34.

5.2.11.18. 1-(3-Bromo-phenyl)-7,7-dimethyl-2-(4-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9i). Yield 75%; mp: 252–253 °C; IR ($CHCl_3$, cm^{-1}) 1639; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (H-9,9′), 2.46 (H-8), 3.09 (H-6), 6.27 (exchangeable with D_2O, N–H), 7.27 (H-3), 7.12–8.05 (Ar-H); MS (EI) 453. $C_{22}H_{20}$ BrN_3O_3; Anal. Calcd: C, 58.16; H, 4.44; N, 9.25. Found C, 58.18; H, 4.43; N, 9.26.

5.2.11.19. 1-(3-Chloro-phenyl)-7,7-dimethyl-2-(4-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (9j). Yield 78%; mp: 253–255 °C; IR ($CHCl_3$, cm^{-1}) 1638; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.06 (H-9,9′), 2.46 (H-8), 3.10 (H-6), 6.65 (exchangeable with D_2O, N–H), 7.27 (H-3), 7.05–8.08 (Ar-H); MS (EI) 409. $C_{22}H_{20}$ ClN_3O_3; Anal. Calcd: C, 64.47; H, 4.92; N, 10.25. Found: C,64.45; H, 4.90; N, 10.22.

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