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A new efficient synthetic strategy for *N*-(dialkylamino)azacycle as a tetrasubstituted hydrazine derivative using sodium triacyloxyborohydride

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ABSTRACT

A new efficient and convergent method has been developed to construct a *N*-(dialkylamino)azacyclic system as a tetrasubstituted hydrazine via reductive alkylation of the corresponding hydrazone using sodium triacyloxyborohydride [$NaBH(OCOR)_3$], which is tolerant of various substituents (e.g., phenol, conjugated olefin, amide, and thioamide) on the substrate and useful for organization of the *N*-amino-azacycle array.

1. Introduction

N-(Dialkylamino)azacycle is a tetrasubstituted hydrazine derivative bearing a dialkylamino moiety at the nitrogen atom of aliphatic cyclic amine, and has often been installed to various bioactive substances. For example, in a new drug discovery program based on natural products, podophyllotoxin analogue **1**[1] having *N*-aminopiperazine moiety has been studied as an antitumor agent with DNA topoisomeraze II inhibition; and 9-azamorphinan **2**[2] has been identified as an analgesic with antagonist effect of morphine analgesia. In order to identify other new drug candidates, a series of *N*-aminopiperazine derivatives **3**[3] have been investigated as new compounds to treat multi-drug-resistant tuberculosis; and naphthalene derivative **4**[4] with *N*-aminomorpholine has been studied as an oral-administrative antifungal agent. In addition, although the *N*-amino moiety was not substituted, the *N*-aminorhodanine system has been found as a framework of sialyl Lewis X (sLe^x) biosynthesis inhibitor **5a**[5] as well as other rhodanine derivatives, such as compound **5b**. Therefore, an extension of the *N*-aminorhodanine library by alkylation of the amino moiety could be interesting to explore a new drug candidate (Fig. 1).

Such a *N*-(dialkylamino)azacyclic system has been prepared via alkylation[1–4] of a *N*-(monoalkylamino)azacycle as a trisubstituted hydrazine compound, derived by reduction[2,4] of the corresponding hydrazone, reduction[6] of the amido moiety in *N*-(acylamino)azacycle, or alkylation of a protected *N*-aminoazacycle.[7] Thus, the conventional methods require step-by-step alkylation reactions from non-substituted *N*-aminoazacycle to avoid the formation of a symmetrical *N*-dialkyl compound. Therefore, in order to carry out effectively both medicinal and process research programs on a new drug candidate bearing *N*-(dialkylamino)azacycle, an efficient and convergent method to construct the ring system as a tetrasubstituted hydrazine system has been demanded.

On the other hand, G. W. Gribble and co-workers have explored an unique alkylation method[8a–d] of amine or imine derivatives using sodium triacyloxyborohydride [$NaBH(OCOR)_3$] since their first report[8e] on the reductive ethylation of indole with $NaBH_4$ and acetic acid in 1974. Although his and other groups have contributed to expansion of the chemistry, the reductive alkylation of hydrazine moiety has received less attention. To our knowledge, there is only one report[9] regarding alkylation of the protected phenylhydrazine derivative. Herein, we report a new efficient and convergent strategy for preparation of the *N*-(dialkylamino)azacyclic system, as a tetrasubstituted hydrazine, utilizing $NaBH(OCOR)_3$ alkylation. According to our new synthetic strategy, shown in Scheme 1, the target compound (A) would be prepared by $NaBH(OCOR)_3$ alkylation of hydrazone derivative (B), which would be easily converted from *N*-aminoazacycle (C) and carbonyl compounds (D).

2. Results and discussion

First, reductive ethylation of hydrazone derivatives **7a–e**, easily prepared from various *N*-aminoazacycles **6a–e** and piperonal, was investigated by employing commercially available $NaBH(OAc)_3$ in acetic acid at room temperature (Scheme 2, Table 1, entries 1–5).

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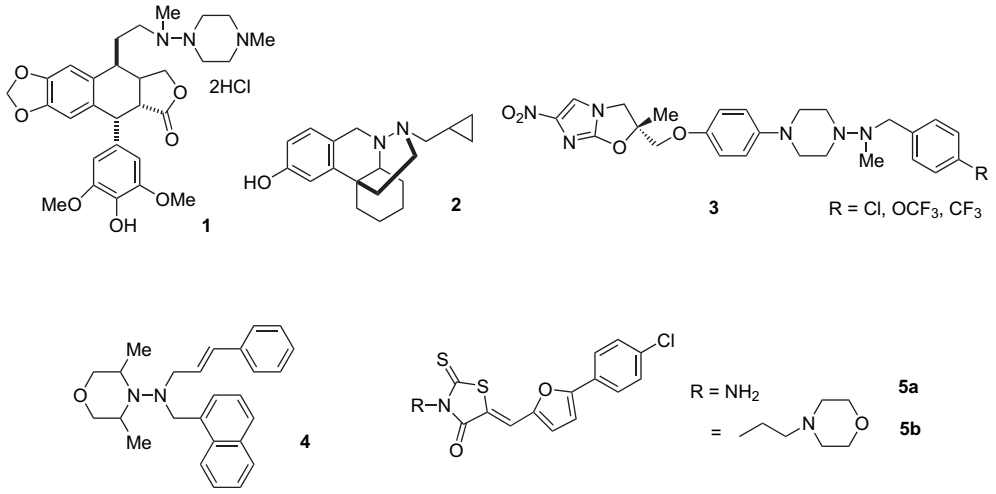
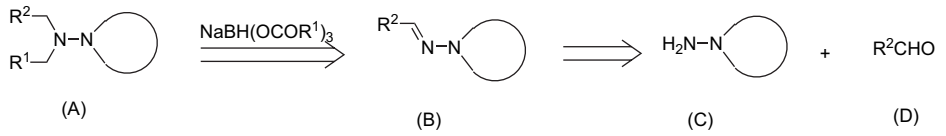
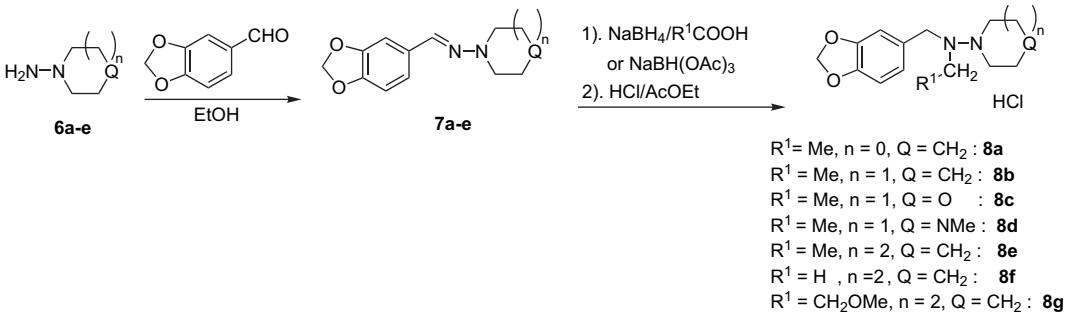


Figure 1.



Scheme 1.



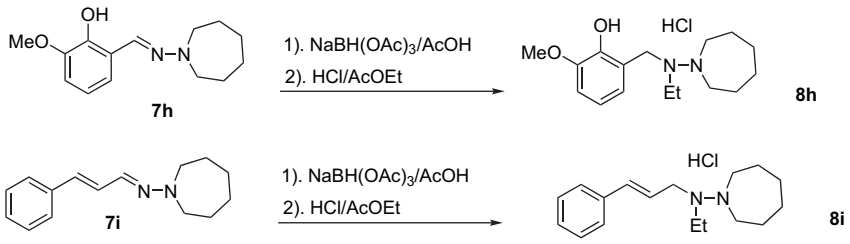
Scheme 2.

Table 1
Syntheses of various *N*-(dialkylamino)azacycles **8a**–**g** by sodium triacyloxyborohydride

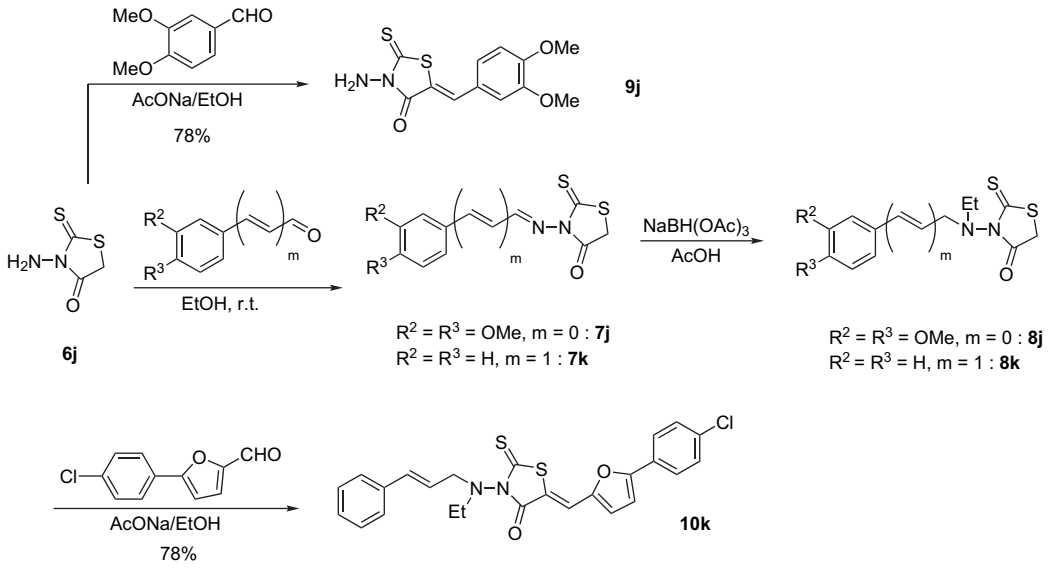
Entry	*N*-Aminoazacycle	Product	Yield (%)	$NaBH_4/R^4COOH$ or $NaBH(OCOR^4)_3$	Product	Yield (%)
1	*N*-Aminopyrrolidine (**6a**)	**7a**	78	$NaBH(OAc)_3$	**8a**	77
2	*N*-Aminopiperidine (**6b**)	**7b**	72	$NaBH(OAc)_3$	**8b**	91
3	*N*-Aminomorpholine (**6c**)	**7c**	74	$NaBH(OAc)_3$	**8c**	80
4	*N*-Amino-*N*′-methylpiperazine (**6d**)	**7d**	80	$NaBH(OAc)_3$	**8d**	67
5	*N*-Aminohomopiperidine (**6e**)	**7e**	79	$NaBH(OAc)_3$	**8e**	84
6				$NaBH_4$/HCOOH	**8f**	82
7				$NaBH_4/MeOCH_2COOH$	**8g**	78

Five- to seven-membered aliphatic cyclic amine derivatives **8a**–**e**, including bisheteroatom-containing types such as morpholine and piperazine, were conveniently obtained as *N*-ethylated derivatives of crystalline hydrochloride in good yield. The other reductive alkylations of hydrazone **6e** were then studied using $NaBH(OCOR)_3$, generated in-situ from $NaBH_4$ and appropriate carboxylic acid (Table 1, entries 6 and 7). Dropwise-addition of formic acid to a suspension of $NaBH_4$ and **6e** in toluene at 0–25 °C gave *N*-methylated hydrazine derivative **8f**. In the same manner, use of methoxyacetic acid introduced the methoxyethyl moiety into *N*-(dialkylamino)homopiperidine **8g**.

Next, our interest focused on the compatibility of various substituents on hydrazones with reductive alkylation methodology (Schemes 3 and 4, Table 2). *N*-(Dialkylamino)homopiperidine **8h** bearing a phenol moiety was furnished from the corresponding hydrazone derivative **7h** by reductive ethylation using $NaBH(OAc)_3$ in acetic acid, the transformation of which was superior to S_N2-type alkylation due to no protective group for the phenol moiety (Table 2, entry 1). The reductive alkylation of α,β-unsaturated hydrazone derivative **7i**, derived from *N*-aminohomopiperidine **6e** and *trans*-cinnamaldehyde, afforded *N*-cinnamyl hydrazine derivative **8i** chemoselectively (Table 2, entry 2). Although it is



Scheme 3.



Scheme 4.

Table 2
Syntheses of various *N*-(dialkylamino)azacycles **8h–k** by sodium triacyloxyborohydride

Entry	*N*-Aminoazacycle	Aldehyde	Product	Yield (%)	$NaBH_4/R^4COOH$ or $NaBH(OCOR^4)_3$	Product	Yield (%)
1	**6e**	*o*-Vaniline	**7h**	77	$NaBH(OAc)_3$	**8h**	67[a]
2	**6e**	Cinnamaldehyde	**7i**	—	$NaBH(OAc)_3$	**8i**	65[b]
3	*N*-Aminorhodanine (**6j**)	Veratraldehyde	**7j**	92	$NaBH(OAc)_3$	**8j**	64[c]
4	**6j**	Cinnamaldehyde	**7k**	94	$NaBH(OAc)_3$	**8k**	72[c]

[a] Isolated yield as a hydrochloride salt.
[b] Isolated yield as a hydrochloride salt based on *N*-aminohomopiperidine (without isolation of **7i**).
[c] Isolated yield as a free base.

reported[4] that alkylation of trisubstituted hydrazine with cinnamyl chloride gave a mixture of the target *N*-cinnamyl derivatives and *N*-(3-phenylpropynilidene-1-yl)-substituted compound, migration of the olefin bond was not observed in our process for **8i**.

Furthermore, our methodology has contributed to the organization of highly molecular diversity of the *N*-aminorhodanine scaffold (Scheme 4, Table 2). Namely, although condensation of *N*-aminorhodanine **6j** and an aldehyde in the presence of a base or by heating under reflux gave *C*5-alkylidene product **9j**, the condensation reaction without a base at room temperature selectively afforded *N*-alkylidene product[10] **7j** and **7k**. The reductive alkylation of **7j** and **7k** using $NaBH(OAc)_3$ provided *N*-(dialkylamino)rhodanine **8i** and **8k** (Table 2, entries 3 and 4), without reduction of their carbonyl and thiocarbonyl moiety. The Knoevenagel reaction of **8k** and 2-furaldehyde derivative afforded *N*-(dialkylamino)rhodanine **10k**, further functionalized at its 5-positon.

3. Conclusion

In conclusion, we have developed a new efficient and convergent method for the preparation of a *N*-(dialkylamino)azacyclic system via reductive alkylation of *N*-(alkylideneamino)azacyclic derivative using sodium triacyloxyborohydride [$NaBH(OCOR)_3$], which is tolerant of various substituents (e.g., phenol, conjugated olefine, amide, and thioamide). Furthermore, the method will contribute to establish a *N*-(dialkylamino)azacyclic library with high molecular diversity.

4. Experimental

4.1. General remarks

Melting points were recorded on Buchi B-540 micromelting apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR Prestige-21 spectrophotometer. ^1H NMR spectra were

recorded on a Bruker DPX-300 spectrometer. Elemental analyses and mass spectra were analyzed by Takeda Analytical Research Ltd. HPLC conditions: Inertsil ODS-2 column (150 mm×4.6 mm I.D.) with 0.05 M KH_2PO_4 in water and acetonitrile (50:50) at 25 °C. Detection was effected with a Hitachi spectrophotometric detector at 254 nm.

4.2. General procedure for the synthesis of *N*-(alkylindeneamino)azacycle, represented by *N*-(1,3-benzodioxol-5-ylmethylene)azepan-1-amine (7e) (method A)

A mixture of 1-aminohomopiperidine (**6e**) (1.78 g, 15.6 mmol), piperonal (2.34 g, 15.6 mmol), and ethanol (23 ml) was stirred under reflux for 7.5 h. After cooling to room temperature and then ice-cold temperature, the resulting crystals were filtered and dried in vacuo at 40 °C to give the title compound (2.87 g). From the mother liquor, the second crop (149 mg) was obtained as a colorless crystalline powder: total yield 79%, mp 79–80 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.6–1.9 (8H, m), 3.59 (4H, t, J=5.7 Hz), 6.02 (2H, s), 6.84 (1H, d, J=8.0 and 1.5 Hz), 7.14 (1H, s), 7.28 (1H, d, J=1.4 Hz); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 27.91, 28.79, 53.83, 101.62, 104.50, 109.04, 119.98, 127.08, 133.51, 146.67, 148.47; MS (EI, m/z): (M^+) 246. Elemental analysis: calcd for $C_{14}H_{18}N_2O_2$; C: 68.27, H: 7.37, N: 11.37; found, C: 68.38, H: 7.25, N: 11.44.

4.2.1. *N*-(1,3-Benzodioxol-5-ylmethylene)pyrrolidin-1-amine (**7a**)

Following method A, compound **6a** (738 mg, 6.02 mmol) was treated with piperonal (904 mg, 6.02 mmol) to give the title compound (1.01 g, yield 78%) as a colorless crystalline powder: mp 101–103 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.9–2.0 (4H, m), 3.33 (4H, t, J=6.6 Hz), 5.96 (2H, s), 6.77 (1H, d, J=8.0 Hz), 6.91 (1H, dd, J=8.0 and 1.5 Hz), 7.14 (1H, s), 7.20 (1H, d, J=1.5 Hz); IR (ATR, cm^{-1}): 1604, 1560, 1498, 1382, 1338, 1253, 1036; MS (EI, m/z): (M^+) 218. Elemental analysis: calcd for $C_{12}H_{14}N_2O_2$, C: 66.04, H: 6.47, N: 12.84; found, C: 66.10, H: 6.46, N: 12.90.

4.2.2. *N*-(1,3-Benzodioxol-5-ylmethylene)piperidin-1-amine (**7b**)

Following method A, compound **6b** (615 mg, 6.02 mmol) was treated with piperonal (904 mg, 6.02 mmol) to give the title compound (1.04 g, yield 74%) as a colorless crystalline powder: mp 64–65 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.5–1.8 (6H, m), 3.14 (4H, t, J=5.6 Hz), 5.97 (2H, s), 6.79 (1H, d, J=8.0 Hz), 6.95 (1H, dd, J=8.0 and 1.6 Hz), 7.27 (1H, d, J=1.5 Hz), 7.50 (1H, s); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 24.57, 25.55, 52.59, 101.87, 105.18, 109.07, 121.58, 132.26, 134.83, 147.87, 148.55; MS (EI, m/z): (M^+) 232. Elemental analysis: calcd for $C_{13}H_{16}N_2O_2$, C: 67.22, H: 6.94, N: 12.06; found, C: 67.26, H: 6.89, N: 12.10.

4.2.3. *N*-(1,3-Benzodioxol-5-ylmethylene)morpholin-4-amine (**7c**)

Following method A, compound **6c** (603 mg, 6.02 mmol) was treated with piperonal (904 mg, 6.02 mmol) to give the title compound (1.01 g, yield 72%) as a colorless crystalline powder: mp 76–78 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 3.15 (4H, t, J=4.8 Hz), 3.90 (4H, t, J=4.8 Hz), 5.98 (2H, s), 6.80 (1H, d, J=8.0 Hz), 6.97 (1H, dd, J=8.0 and 1.6 Hz), 7.27 (1H, d, J=1.5 Hz), 7.50 (1H, s); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 52.63, 66.55, 101.99, 105.35, 109.13, 122.07, 131.63, 136.60, 148.27, 148.61; MS (EI, m/z): (M^+) 234. Elemental analysis: calcd for $C_{12}H_{14}N_2O_3$, C: 61.53, H: 6.02, N: 11.96; found, C: 61.38, H: 5.94, N: 12.01.

4.2.4. *N*-(1,3-Benzodioxol-5-ylmethylene)-4-methylpiperazin-1-amine (**7d**)

Following method A, compound **6d** (693 mg, 6.02 mmol) was treated with piperonal (904 mg, 6.02 mmol) to give the title compound (1.19 g, yield 74%) as a colorless crystalline powder: mp 108–110 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 2.44 (3H, s), 2.70 (4H, t, J=5.0 Hz), 3.27 (4H, t, J=5.2 Hz), 6.00 (2H, s), 6.86 (1H, d, J=8.0 Hz), 7.04 (1H, dd, J=8.0 and 1.5 Hz), 7.34 (1H, d, J=1.5 Hz), 7.57 (1H, s); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 46.41, 51.67, 54.87, 101.93, 105.26, 109.10, 121.85, 131.89, 136.06, 148.09, 148.57; MS (EI, m/z): (M^+) 247. Elemental analysis: calcd for $C_{13}H_{17}N_3O_2$, C: 63.14, H: 6.93, N: 16.99; found, C: 63.05, H: 6.89, N: 17.07.

4.2.5. 2-(Azepan-1-ylimino)methyl-6-methoxyphenol (**7h**)

Following method A, compound **6h** (687 mg, 6.02 mmol) was treated with piperonal (904 mg, 6.02 mmol) to give the title compound (1.15 g, yield 77%) as a colorless crystalline powder: mp 78–79 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.6–1.9 (8H, m), 3.58 (4H, t, J=5.7 Hz), 3.99 (3H, s), 6.7–6.9 (3H, m), 7.31 (1H, s), 12.0 (1H, s); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 27.44, 28.53, 53.58, 56.66, 111.74, 119.38, 120.82, 122.11, 131.21, 146.10, 148.48; MS (EI, m/z): (M^+) 248. Elemental analysis: calcd for $C_{14}H_{18}N_2O_2$, C: 67.71, H: 8.12, N: 11.28; found, C: 67.67, H: 8.06, N: 11.29.

4.3. General procedure for the synthesis of *N*-(dialkylamino)-azacycle, represented by *N*-(1,3-benzodioxol-5-ylmethyl)-*N*-methylazepan-1-amine hydrochloride (8f) (method B)

To a stirred suspension of **7e** (500 mg, 2.03 mmol), toluene (5 ml), and $NaBH_4$ (768 mg, 20.3 mmol) was added formic acid (3 ml) dropwise at ice-cold temperature under N_2 atmosphere. After stirring at the same temperature for 1 h, the mixture was stirred at room temperature for 2 days. After the addition of $NaBH_4$ (386 mg, 10.2 mmol) and formic acid (2.5 ml), stirring was continued for more than 1 day. To the reaction mixture were added 4 M NaOH (35 ml) and water (20 ml), followed by extraction with ethyl acetate three times. The combined organic layers were washed with water (150 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo. To the residue were added ethyl acetate (7.5 ml) and 4 M HCl/ethyl acetate (1.02 ml, 4.08 mmol). After the resulting slurry was stirred at ice-cold temperature, the crystals were filtered, washed with cold ethyl acetate, and dried in vacuo at room temperature to give the title compound (496 mg, yield 82%) as a colorless crystal: mp 194 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.6–1.9 (6H, m), 2.3–2.4 (2H, br), 2.56 (3H, s), 3.2–3.3 (2H, m), 3.7–3.9 (2H, m), 4.14 (2H, s), 5.95 (2H, s), 6.7–6.9 (3H, m), 13.6 (1H, br); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 22.78, 26.10, 35.50, 51.61, 56.10, 101.19, 108.19, 109.42, 122.56, 129.56, 147.01, 147.52; MS (EI, m/z): (M^+) 262. Elemental analysis: calcd for $C_{16}H_{25}N_2O_2Cl$; C: 60.29, H: 7.76, N: 9.38; found, C: 60.19, H: 7.82, N: 9.36.

4.3.1. *N*-(1,3-Benzodioxol-5-ylmethyl)-*N*-(2-methoxyethyl)azepan-1-amine hydrochloride (**8g**)

Following method B, compound **7e** (500 mg, 2.03 mmol) was treated with $NaBH_4$ (768 mg, 20.3 mmol) and methoxyacetic acid (5 ml) at room temperature for 4 days to give the title compound (541 mg, yield 78%) as a colorless crystalline powder: mp 148–149 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.6–2.1 (6H, m), 2.3–2.4 (2H, br), 3.0–3.4 (9H, m), 3.6–3.9 (2H, m), 4.29 (2H, s), 5.95 (2H, s), 6.7–6.9 (3H, m), 13.3 (1H, br); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 23.74, 26.53, 51.64, 53.99, 56.50, 58.89, 70.76, 101.92, 108.88, 110.14, 123.00, 131.26, 147.69, 148.19; MS (EI, m/z): (M^+) 306. Elemental analysis: calcd for $C_{16}H_{25}N_2O_2Cl$, C: 59.55, H: 7.94, N: 8.17; found, C: 59.33, H: 7.81, N: 8.04.

4.4. General procedure for the synthesis of *N*-(dialkylamino)-azacycle, represented by *N*-(1,3-benzodioxol-5-ylmethyl)-*N*-ethylazepan-1-amine hydrochloride (8e) (method C)

To a stirred suspension of **7e** (500 mg, 2.03 mmol) and AcOH (10 ml) was added sodium triacetoxyborohydride (4.30 g,

20.3 mmol) at room temperature under N_2 atmosphere. After stirring at the same temperature for 34 h, water (20 ml) and 4 M NaOH (75 ml) were added to the reaction mixture and extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with water (100 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a free base as yellow oil. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.03 (3H, t, J=7.0 Hz), 1.5–1.6 (8H, m), 2.41 (2H, t, J=7.0 Hz), 2.81 (4H, t, J=5.9 Hz), 3.52 (2H, s), 5.9 (2H, s), 6.6–6.8 (2H, m), 6.89 (1H, m); ^{13}C NMR ($CDCl_3$, TMS, 75.5 MHz) δ (ppm): 13.97, 27.31, 29.01, 45.50, 51.60, 54.36, 101.05, 107.94, 109.56, 121.84, 135.11, 146.43, 147.75. To the residual free base were added ethyl acetate (3 ml) and 4 M HCl/ethyl acetate (1.02 ml, 4.08 mmol). After the resulting slurry was stirred at ice-cold temperature, the crystals were filtered, washed with cold ethyl acetate, and dried in vacuo at room temperature to give the title compound (534 mg, yield 84%) as a colorless crystalline powder: mp 198 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 0.99 (3H, t, J=6.3 Hz), 1.4–1.9 (7H, m), 2.2–2.4 (1H, br), 2.9–3.4 (5H, m), 3.7–3.9 (1H, br), 4.1–4.3 (2H, m), 5.95 (2H, s), 6.7–7.0 (2H, m), 7.1–7.4 (1H, m), 13.3 (1H, br); IR (ATR, cm^{-1}): 1490, 1444, 1382, 1255, 1242, 1041; MS (EI, m/z): (M^+) 276. Elemental analysis: calcd for $C_{16}H_{25}N_2O_2Cl$, C: 61.43, H: 8.05, N: 8.95; found, C: 61.15, H: 7.91, N: 8.74.

4.4.1. *N-(1,3-Benzodioxol-5-ylmethyl)-N-ethylpyrrolidin-1-amine hydrochloride (**8a**)*

Following method C, compound **7a** (450 mg, 2.06 mmol) was treated with sodium triacetoxyborohydride and acetic acid at room temperature for 48 h, to give the title compound (453 mg, yield 77%) as a colorless crystalline powder: mp 160–161 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.13 (3H, t, J=6.8 Hz), 1.8–2.2 (4H, m), 3.10 (3H, t, J=6.9 Hz), 3.0–3.5 (2H, br), 3.7–3.9 (1H, br), 4.1 (2H, br), 5.95 (2H, s), 6.7–7.0 (3H, m), 13.6 (1H, br); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 13.52, 23.59, 47.02, 51.69, 54.38, 101.94, 109.01, 109.85, 122.83, 131.32, 147.61, 148.26; MS (EI, m/z): (M^+) 248. Elemental analysis: calcd for $C_{14}H_{21}N_2O_2Cl$, C: 59.05, H: 7.43, N: 9.84; found, C: 59.03, H: 7.28, N: 9.79.

4.4.2. *N-(1,3-Benzodioxol-5-ylmethyl)-N-ethylpiperidin-1-amine hydrochloride (**8b**)*

Following method C, compound **7b** (500 mg, 2.15 mmol) was treated with sodium triacetoxyborohydride and acetic acid at room temperature for 33 h, to give the title compound (583 mg, yield 91%) as a colorless crystalline powder: mp 200 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.0–2.1 (8H, br), 2.60 (1H, br), 2.8–3.2 (5H, br), 3.58 (1H, br), 4.18 (2H, br), 5.95 (2H, s), 6.79 (1H, d, J=7.5 Hz), 6.7–7.4 (2H, m), 13.4 (1H, br); IR (ATR, cm^{-1}): 1490, 1448, 1255, 1041; MS (EI, m/z): (M^+) 262. Elemental analysis: calcd for $C_{15}H_{23}N_2O_2Cl$, C: 60.29, H: 7.76, N: 9.38; found, C: 60.20, H: 7.66, N: 9.35.

4.4.3. *N-(1,3-Benzodioxol-5-ylmethyl)-N-ethylmorpholin-4-amine hydrochloride (**8c**)*

Following method C, compound **7c** (500 mg, 2.13 mmol) was treated with sodium triacetoxyborohydride and acetic acid at room temperature for 22 h, to give the title compound (583 mg, yield 80%) as a colorless crystalline powder: mp 165 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.48 (3H, br), 3.0–3.4 (2H, br), 3.76 (4H, br), 4.1–4.4 (2H, br), 5.98 (2H, s), 6.79 (1H, d, J=8.0 Hz), 7.0–7.3 (2H, m), 13.7 (1H, br); IR (ATR, cm^{-1}): 1494, 1444, 1255, 1238, 1101, 1035; MS (EI, m/z): (M^+) 264. Elemental analysis: calcd for $C_{16}H_{27}N_2O_2Cl$; C: 55.91, H: 7.04, N: 9.31; found, C: 55.45, H: 7.04, N: 9.14.

4.4.4. *N-(1,3-Benzodioxol-5-ylmethyl)-N-ethyl-4-methylpiperazin-1-amine hydrochloride (**8d**)*

Following method C, compound **7d** (500 mg, 2.02 mmol) was treated with sodium triacetoxyborohydride and acetic acid at room temperature for 24 h to give the title compound (435 mg, yield 67%) as a colorless crystalline powder: mp 157 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.24 (3H, br), 2.7–3.0 (7H, m), 3.1–3.7 (6H, m), 3.92 (2H, br), 5.97 (2H, s), 6.7–7.1 (3H, m), 13.0 (1H, br); IR (ATR, cm^{-1}): 1502, 1444, 1259, 1236, 1035; MS (EI, m/z): (M^+) 277. Elemental analysis: calcd for $C_{15}H_{24}N_3O_2Cl\cdot 2.5H_2O$, C: 50.20, H: 8.15, N: 11.71; found, C: 50.49, H: 8.09, N: 11.68.

4.4.5. *2-{[Azepan-1-yl(ethyl)amino]methyl}-6-methoxyphenol hydrochloride (**8h**)*

Following method C, compound **7h** (500 mg, 2.01 mmol) was treated with sodium triacetoxyborohydride and acetic acid at room temperature for 32 h to give the title compound (420 mg, yield 67%) as a colorless crystalline powder: mp 131 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 0.6–2.1 (9H, br), 3.0–3.6 (6H, br), 3.89 (3H, s), 4.3 (2H, br), 6.0–7.8 (4H, br), 12.9 (1H, br); IR (ATR, cm^{-1}): 1496, 1448, 1244, 1203, 1070; MS (EI, m/z): (M^+) 258. Elemental analysis: calcd for $C_{16}H_{27}N_2O_2Cl$, C: 61.04, H: 8.64, N: 8.90; found, C: 60.72, H: 8.30, N: 8.79.

4.4.6. *N-Ethyl-N-[(2E)-3-phenylprop-2-en-1-yl]piperidin-1-amine hydrochloride (**8i**)*

A mixture of 1-aminohomopiperidine (687 mg, 6.02 mmol), *trans*-cinnamaldehyde (796 mg, 6.02 mmol), and ethanol (8 ml) was stirred under reflux for 8 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The crude hydrazone compound was treated with sodium triacetoxyborohydride and acetic acid at room temperature for 3 days, following method C, to give the title compound (1.16 g, yield 65% based on 1-aminohomopiperadine) as a colorless crystalline powder: mp 127 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.1–2.5 (11H, m), 3.0–3.5 (4H, m), 3.6–4.2 (2H, m), 6.1–6.8 (2H, m), 7.2–7.6 (5H, m), 13.1–13.6 (1H, br); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 26.37, 27.60, 47.53, 51.20, 53.60, 120.66, 127.42, 129.29, 129.67, 136.63, 137.68; MS (EI, m/z): (M^+) 258. Elemental analysis: calcd for $C_{17}H_{27}N_2Cl$, C: 69.25, H: 9.23, N: 9.50; found, C: 69.06, H: 9.18, N: 9.42.

4.4.7. *3-Amino-5-(3,4-dimethoxybenzylidene)-2-thioxo-1,3-thiazolidin-4-one (**9j**)*

A mixture of **6j** (892 mg, 6.02 mmol), 3,4-dimethoxybenzaldehyde (1.00 g, 6.02 mmol), sodium acetate (19.7 mg, 0.24 mmol), and ethanol (23 ml) was stirred under reflux for 3 h. After cooling to room temperature, the resulting crystals were filtered, washed with ethanol and water, and then dried in vacuo at room temperature to give the title compound (1.39 g, yield 78%) as an orange crystalline powder: mp 175 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) (ppm): 3.86 (3H, s), 3.88 (3H, s), 5.98 (2H, s), 7.1–7.3 (3H, m), 7.83 (1H, s); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 56.50, 56.69, 113.16, 114.60, 117.87, 125.92, 126.60, 134.89, 150.00, 152.41, 164.60, 188.03; MS (EI, m/z): (M^+) 296. Elemental analysis: calcd for $C_{12}H_{12}N_2O_3S_2$; C: 48.63, H: 4.08, N: 9.45; found, C: 48.99, H: 4.05, N: 9.34.

4.4.8. *3-{[(3,4-Dimethoxyphenyl)methylene]amino}-2-thioxo-1,3-thiazolidin-4-one (**7j**)*

A mixture of **6j** (892 mg, 6.02 mmol), 3,4-dimethoxybenzaldehyde (1.00 g, 6.02 mmol), and ethanol (10 ml) was stirred at room temperature for 5 h. The resulting crystals were filtered, washed with ethanol and water, and dried in vacuo at room temperature to give the title compound (1.07 g, yield 94%) as a yellow crystalline powder: mp 152–154 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 3.94 (6H, s), 4.06 (2H, s), 6.91 (1H, d, J=8.3 Hz), 7.29 (1H, dd, J=8.3 and 1.9 Hz), 7.57 (1H, d, J=1.9 Hz); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 35.16, 56.07, 56.31, 109.89, 112.07, 124.87, 125.38, 149.66, 153.69, 170.29, 171.11, 197.26; MS (EI,

m/*z*): (M^+) 296. Elemental analysis: calcd for $C_{12}H_{12}N_2O_3S_2$, C: 48.63, H: 4.08, N: 9.45; found, C: 48.76, H: 4.18, N: 9.49.

*4.4.9. 3-[(3,4-Dimethoxybenzyl)(ethyl)amino]-2-thioxo-1,3-thiazolidin-4-one (**8j**)*

To a stirred suspension of **7j** (634 mg, 2.14 mmol) and AcOH (8 ml) was added sodium triacetoxyborohydride (4.54 g, 21.4 mmol) at room temperature under N_2 atmosphere. After stirring at the same temperature for 5 days, sodium triacetoxyborohydride (10.2 g, 48.1 mmol) and acetic acid (7 ml) were added. After an additional reaction at room temperature for 5 days, water (15 ml) and 4 M NaOH (50 ml), 2 M NaOH (50 ml) and NaOH (3.00 g) were added to the reaction mixture to give precipitates. After stirring at ice-cold temperature for 1 h, the resulting crystals were filtered and washed with water and dried in vacuo at room temperature to give the title compound (456 mg, yield 64%) as a yellow crystalline powder: mp 92–94 °C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.07 (3H, t, J=7.2 Hz), 3.2–3.4 (2H,m), 3.74 (1H, dd, J=32 and 18 Hz), 3.84 (2H, s), 3.86 (2H, s), 4.38 (1H, dd, J=54 and 12 Hz), 6.74 (1H, d, J=8.1 Hz), 6.86 (1H, dd, J=8.1 and 1.6 Hz), 7.16 (1H, d, J=1.7 Hz); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 12.98, 32.62, 46.93, 55.83, 55.95, 58.04, 111.75, 113.22, 121.34, 129.77, 148.68, 148.93, 173.92, 203.00; MS (EI, *m*/*z*): (M^+) 326. HRMS: calcd for $C_{14}H_{18}N_2O_3S_2$, 325.06866; found, 325.06866.

*4.4.10. 3-{[(2E)-3-Phenylprop-2-en-1-ylidene]amino}-2-thioxo-1,3-thiazolidin-4-one (**7k**)*

A mixture of compound **6k** (892 mg, 6.02 mmol), *trans*-cinnamaldehyde (796 mg, 6.02 mmol), and ethanol (8 ml) was stirred at room temperature for 5 h. The resulting crystals were filtered and dried in vacuo at room temperature to give the title compound (1.45 g, yield 92%) as a yellow crystalline powder: mp 144 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 3.94 (6H, s), 4.06 (2H, s), 6.91 (1H, d, J=8.3 Hz), 7.29 (1H, dd, J=8.3 and 1.9 Hz), 7.57 (1H, d, J=1.9 Hz); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 35.61, 124.16, 129.08, 129.89, 131.31, 135.71, 148.56, 170.59, 173.04, 197.71; MS (FAB, *m*/*z*): (M^+) 262. Elemental analysis: calcd for $C_{12}H_{10}N_2OS_2$, C: 54.94, H: 3.84, N: 10.68; found, C: 54.89, H: 3.81, N: 10.75.

*4.4.11. 3-{Ethyl[(2E)-3-phenylprop-2-en-1-yl]amino}-2-thioxo-1,3-thiazolidin-4-one (**8k**)*

To a stirred suspension of **7k** (500 mg, 1.91 mmol) and AcOH (10 ml) was added sodium triacetoxyborohydride (4.05 g, 19.1 mmol) at room temperature under N_2 atmosphere. After stirring at the same temperature for 40 h, water (70 ml) and NaOH (10 g) were added to the reaction mixture and extracted with ethyl acetate (2×50 ml). The combined organic layers were washed with water (100 ml), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting residual solid was dried in vacuo at room temperature to give the title compound (400 mg, yield 72%) as yellow wax: HPLC purity: 94.5%; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.10 (3H, t, J=7.2 Hz), 3.45 (2H, t, J=7.2 Hz), 3.77 (2H, dd, J=26.9 and 18.1 Hz), 4.0–4.2 (2H, m), 6.1–6.3 (1H, m), 6.56 (1H, d, J=15.8 Hz), 7.2–7.4 (5H, m); MS (FAB, *m*/*z*): (M^+) 293. Elemental analysis: calcd for $C_{14}H_{16}N_2OS_2$, C: 57.50, H: 5.52, N: 9.58; found, C: 57.65, H: 5.42, N: 9.51.

*4.4.12. 5-{[5-(4-Chlorophenyl)-2-furyl]methylene}-3-{ethyl[(2E)-3-phenylprop-2-en-1-yl]amino}-2-thioxo-1,3-thiazolidin-4-one (**10k**)*

A mixture of **8k** (338 mg, 1.16 mmol), 5-(4-chlorophenyl)furfural (240 mg, 1.16 mmol), sodium acetate (3.8 mg, 0.0464 mmol), and ethanol (23 ml) was stirred under reflux for 1.5 h. After cooling to room temperature, the resulting crystals were filtered, washed with ethanol and dried in vacuo at room temperature to give the title compound (435 mg, yield 78%) as an orange crystalline powder: mp 89–91 °C (decomposed); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ (ppm): 1.13 (2H, t, J=7.2 Hz), 3.4–3.7 (2H, m), 4.1–4.2 (2H, m), 6.2–6.4 (2H, m), 6.56 (2H, d, J=15.8 Hz), 6.81 (1H, d, J=3.7 Hz), 6.90 (1H, d, J=3.7 Hz), 7.2–7.5 (8H, m), 7.66 (2H, d, J=8.6 Hz); ^{13}C NMR (DMSO-d_6, TMS, 75.5 MHz) δ (ppm): 13.36, 48.42, 56.80, 111.68, 116.51, 119.25, 124.10, 126.01, 126.92, 127.12, 128.23, 128.58, 129.51, 130.30, 133.96, 134.64, 137.23, 150.45, 157.85, 166.37, 194.32; MS (EI *m*/*z*): (M^+) 480. Elemental analysis: calcd for $C_{25}H_{21}N_2O_2SCl$, C: 62.42, H: 4.40, N: 5.82; found, C: 62.06, H: 4.36, N: 5.67.

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