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Synthesis of tetrahydro-3-benzazepines

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ABSTRACT

A synthetic route toward tetrahdro-3-benzazepines **1a**–**f** starting with **2a** and **2b** in modest total yield is described. The facile route was carried by Henry reaction of aldehydes **3a**–**e** with nitroalkanes and NH_4OAc at reflux, reduction of the resulting nitroalkenes **4a**–**h** with LAH at rt followed by protection with K_2CO_3 and $PhSO_2Cl$ at rt, one-pot oxidative cleavage annulation of olefins **5a**–**h** with the one-pot combination of $OsO_4/NaIO_4$ at reflux, and hydrogenation of the corresponding enamines **6a**–**f**. Aldehydes **3a**–**e** was prepared from **2a** and **2b** in moderate yield of three-step.

1. Introduction

An interesting functionalized tetrahydro-3-benzazepine ring system has become a versatile class of compounds that have found use in drug discovery.[1,2] The unique framework of 3-benzazepine has also been found to be widespread among benzindenoazepine and rhoeadine alkaloids and a considerable number of attempts have been developed to the skeleton.[3] The adopted synthetic routes are described in Fig. 1. Basically, the key transformations include condensation of ketoacid with a nitrogen atom or amino-acid,[4] intramolecular ring expansion or rearrangement reaction,[5] electrophilic aromatic substitution reaction,[6] Heck cross-coupling reaction,[1a,b,7] and Pummerer cyclization.[8]

2. Results and discussion

With our experience in using the one-pot combination of $OsO_4/NaIO_4$ for the synthesis of substituted isoquinolines[9a] and benzo[*g*]indazoles,[9b] we believed that it may be possible to develop this methodology for preparing the skeleton of tetrahydro-3-benzazepine **1** (see Fig. 2). As shown in Scheme 1, a facile synthetic route was employed to create the skeleton **1**, starting with isovanillin (**2a**) and 3-hydroxybenzaldehyde (**2b**) via (1) a Claisen rearrangement of 3-*O*-allyl compound, (2) a Henry (nitroaldol) reaction of 2-allylbenzaldehydes **3**, followed by LAH-mediated reduction and sulfonation with $PhSO_2Cl$, and then (3) an oxidative cleavage annulation with the combination of $OsO_4/NaIO_4$ followed by hydrogenation.

Four 2-allylbenzaldehydes **3a**–**b** and **3d**–**e** were easily provided from commercially available compound **2a** in moderate overall three-step yields, according to reported procedures, with a reaction sequence of O-allylation and a Claisen rearrangement followed by O-methylation.[10] **3c** was prepared from one-pot *ortho*-metalative $PhBCl_2$-mediated double alkylation of compound **2b** with LDA,

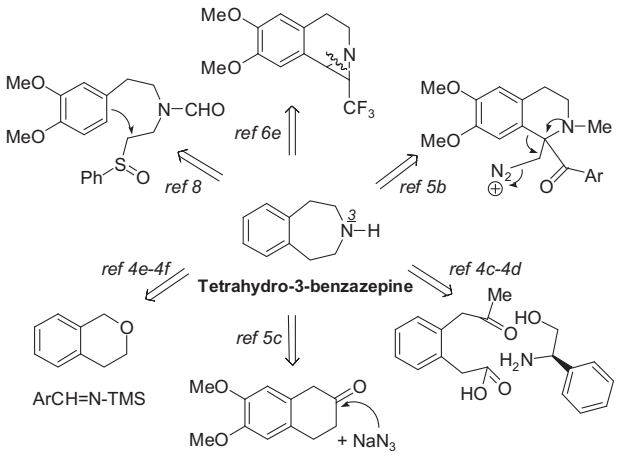

Fig. 1. Synthetic strategies toward tetrahydro-3-benzazepine.

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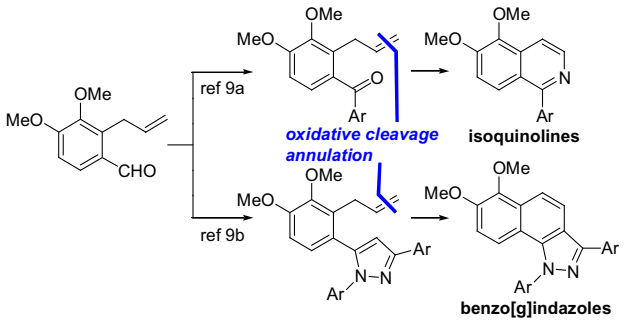
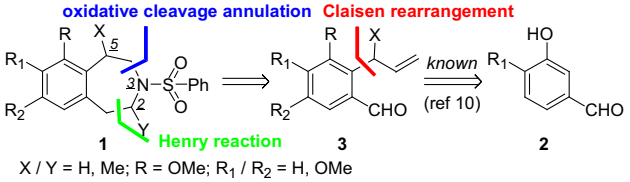


Fig. 2. Synthetic route of isoquinolines and benzo[*g*]indazoles.



Scheme 1. Synthetic route of tetrahydro-3-benzazepines **1**.

followed by O-methylation in a moderate yield.[11] Next, a NH_4OAc-mediated Henry (nitroaldol) reaction of skeleton **3** was employed to create the skeleton of (*E*)-nitroalkenes **4a**–**h** with nitromethane or nitroethane.[12] Compounds **4a**–**d** with (*E*)-form and compounds **4e**–**h** with (*E*,*E*)-form were synthesized in 80–92% yields by the NH_4OAc-mediated Henry condensation of compounds **3a**–**e** ($R/R_1/R_2$=H or OMe; X/Y=H, Me or Ph) with nitromethane and nitroethane. We found that compounds **4c**, **4f**, and **4h** (Y=Me) also provided similar yields (86%, 80%, and 82%) to the others at reflux for 2 h. However, a NH_4OAc-mediated Henry reaction of compound **3a** with nitromethylbenzene failed to isolate the desired nitroalkene product and compound **3a** was recovered as the major product under the above reaction conditions. Furthermore, compounds **5a**–**h** were obtained as a single isomer with the 60–80% yields via the reduction of compounds **4a**–**h** with LAH in THF placed in an ice bath for 2 h, followed by treatment of the corresponding primary amine with $PhSO_2Cl$ and K_2CO_3 at rt for 4 h, as shown in Scheme 2. With the previous synthetic experience,[9] we attempted to construct the bicyclic skeleton of 3-benzazepines **1** by the combination of $OsO_4/NaIO_4$/HOAc via the facile one-pot oxidative cleavage of compounds **5a**–**h** and subsequent hydrogenation of the corresponding compounds **6a**–**f**.

condition was treated at rt, compound **6a** provided a 75% yield within a period of 4 h. After adjusting the reaction temperature from rt to 60 °C and overall reaction time from 4 h to 2 h, the desired compound **6a**, with a similar yield (73%), was observed. Under the abovementioned one-pot combination $OsO_4/NaIO_4$/HOAc condition, compounds **6b**–**f** provided 58–75% yields, as shown in Table 1.

The possible mechanism for the formation of compound **6a** is described in Scheme 3. The initial event may be considered as the formation of intermediate **I** with the proton/oxocarbenium ions from HOAc-mediated annulation. Intermediate **II**, with a seven-membered ring, is yielded via the nitrogen lone pair promoted intramolecular ring-closure on intermediate **I**. After a proton exchange of intermediate **II** and sequential dehydration of intermediate **III**, the bicyclic tetrahydro-3-benzazepine **6a** was produced. Finally, compounds **1a**–**f** were accomplished with 80–94% yields by the hydrogenation of compounds **6a**–**f** with hydrogen in the presence of a catalytic amount of 10% palladium on activated carbon (Table 1).

Next, boron trifluoride etherate promoted the efficient addition of compound **6a** with trimethylsilyl cyanide and *N*-bromosuccinimide (1.2 equiv) resulting in compound **7** (82%) via a bromination reaction of enamine, as shown in Scheme 4. A lone-pair of nitrogen atoms promoted the ring-opening of the brominium ion. Then, the cyanide ion can trap the formed iminium ion and eliminate bromide by α-proton abstraction. The α-amino nitrile and related derivatives with an important bioactive component are key ingredients in therapeutic agents for pharmaceutical research.[14,15]

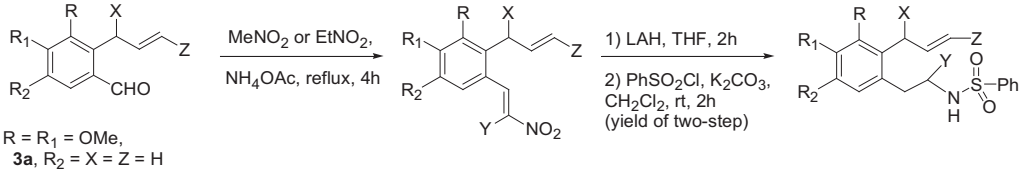
3. Conclusion

In summary, we have successfully presented a synthetic route for the synthesis of tetrahydro-3-benzazepines **1a**–**f** via Henry nitroaldol condensation, reduction, sulfonation, and oxidative cleavage annulation with the one-pot combination of $OsO_4/NaIO_4$/HOAc. This synthesis begins from simple starting materials and reagents, and provides a new synthetic route toward the skeleton of 3-benzazepines.

4. Experimental section

4.1. General

All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were



R = R_1 = OMe,
3a, R_2 = X = Z = H
3b, R_2 = Z = H, X = Me
R = OMe,
3c, R_1 = R_2 = X = Z = H
R_1 = R_2 = OMe,
3d, R = X = H, Z = Ph
3e, R = X = H, Z = Me

R = R_1 = OMe,
4a, R_2 = X = Y = Z = H (88%)
4b, R_2 = Y = Z = H, X = Me (92%)
4c, R_2 = X = Z = H, Y = Me (86%)
R = OMe,
4d, R_1 = R_2 = X = Y = Z = H (80%)

R_1 = R_2 = OMe, Z = Ph
4e, R = X = Y = H (89%)
4f, R = X = H, Y = Me (80%)
R_1 = R_2 = OMe, Z = Me
4g, R = X = Y = H (90%)
4h, R = X = H, Y = Me (82%)

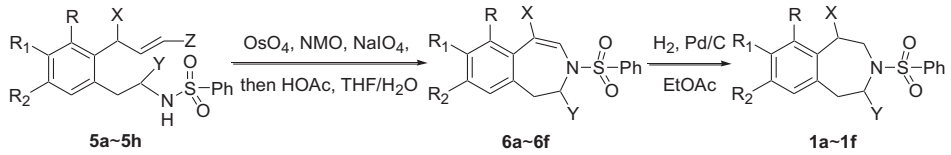
5a (70%) **5e** (78%)
5b (68%) **5f** (63%)
5c (60%) **5g** (80%)
5d (73%) **5h** (66%)

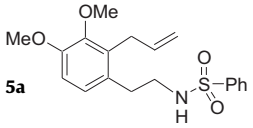
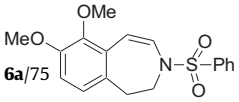
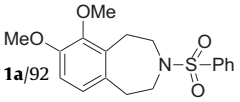
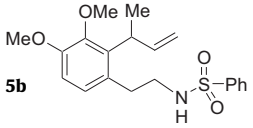
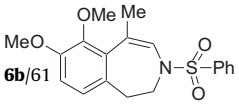
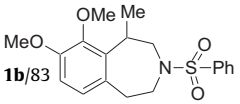
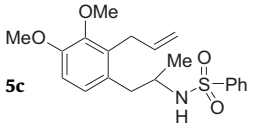
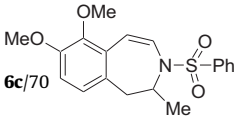
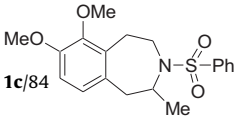
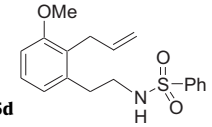
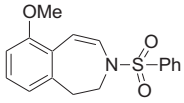
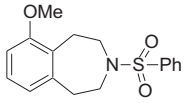
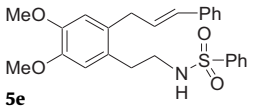
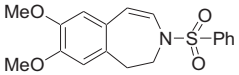
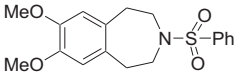
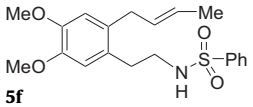
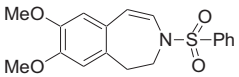
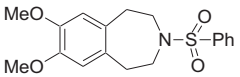
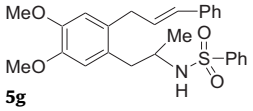
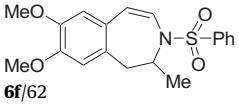
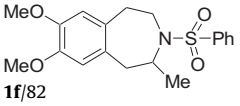
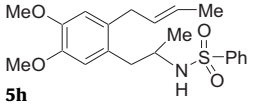
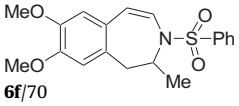
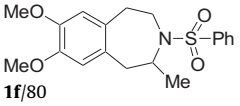
Scheme 2. Reaction of skeleton **5**.

Reports in the literature have described the improved procedure for the oxidative cleavage of olefins by the OsO_4–$NaIO_4$ system.[13] In order to initiate the work, one-pot oxidative cleavage of the olefinic group of compound **5a** was first examined. When the reaction

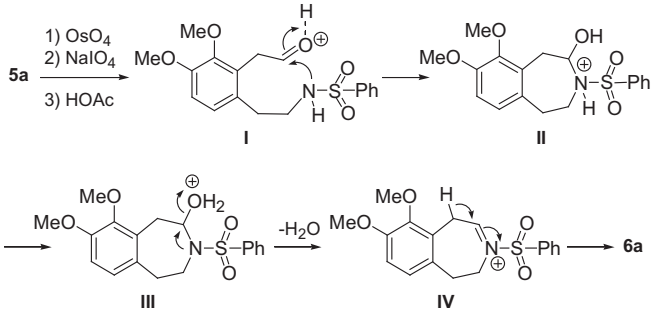
routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous $MgSO_4$ before concentration in vacuo. Melting points were determined with a SMP3 melting apparatus. ^1H and ^{13}C NMR

Table 1
Synthesis of tetrahdro-3-benzazepines **1a**–**f**[a–c]

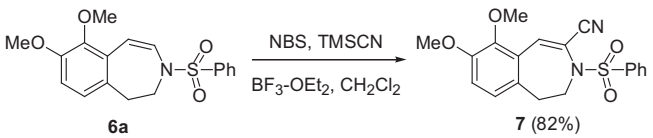


Entry	Reactants **5**	Products **6**/Yield[a] (%)	Products **1**/Yield[b] (%)
1	 **5a**	 **6a**/75	 **1a**/92
2	 **5b**	 **6b**/61	 **1b**/83
3	 **5c**	 **6c**/70	 **1c**/84
4	 **5d**	 **6d**/58	 **1d**/90
5	 **5e**	 **6e**/66	 **1e**/94
6	 **5f**	 **6e**/72	 **1e**/94
7	 **5g**	 **6f**/62	 **1f**/82
8	 **5h**	 **6f**/70	 **1f**/80

[a] For the optimal reaction conditions: (i) compounds **5a**–**h** (1.0 mmol), OsO_4 (2.5% in THF, 1 mL), NMO (50% in H_2O, 2.2 mmol), THF/H_2O (v/v=1/1, 20 mL), rt, 2 h, (ii) $NaIO_4$ (1.2 mmol), rt, 1 h, (iii) HOAc (1 mL), rt, 1 h.
[b] Compounds **6a**–**f** (0.5 mmol), 10% Pd on charcoal (15 mg), EtOAc (10 mL), rt, 4 h.
[c] The isolated products were >95% pure as determined by ^1H NMR analysis.



Scheme 3. The possible mechanism of compound **6a**.



Scheme 4. Synthesis of compound **7**.

spectra were recorded on a Varian INOVA-400 spectrometer operating at 200/400 and at 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in Hertz. High resolution mass spectra (HRMS) were

measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD). Elemental analyses were carried out with Heraeus Vario III-NCSH, Heraeus CHN–OS-Rapid Analyzer or Elementar Vario EL III.

4.2. A representative procedure of skeleton 4 is as follows

Ammonium acetate (NH_4OAc, 390 mg, 5.0 mmol) was added to a solution of skeleton **3** (5.0 mmol) in nitromethane or nitroethane ($MeNO_2$ or $EtNO_2$, 10 mL) at rt. The reaction mixture was stirred at reflux for 6 h. The reaction mixture was cooled to rt. Saturated $NaHCO_{3(aq)}$ (5 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc=10/1–6/1) afforded skeleton **4**.

*4.2.1. 2-Allyl-3,4-dimethoxy-1-(2-nitrovinyl)benzene (**4a**).* Yield=88% (1.09 g); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{13}H_{16}NO_4$ 250.1079, found 250.1080; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J=13.2 Hz, 1H, C*H*=CHNO$_2$), 7.45 (d, J=13.2 Hz, 1H, CH=C*H*NO$_2$), 7.35 (d, J=8.8 Hz, 1H, aromatic C*H*), 6.86 (d, J=8.8 Hz, 1H, aromatic C*H*), 6.01–5.91 (m, 1H, C*H*=CH$_2$), 5.07 (dq, J=1.6, 10.4 Hz, 1H, *cis*-CH=CH$_2$), 4.90 (dq, J=1.6, 17.2 Hz, 1H, *trans*-CH=CH$_2$), 3.92 (s, 3H, OC*H*$_3$), 3.81 (s, 3H, OC*H*$_3$), 3.61 (dt, J=1.6, 5.2 Hz, 2H, CH$_2$CH=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.75 (*C*q), 147.68 (*C*q), 136.92 (*C*H), 136.16 (2×, *C*H), 135.09 (*C*q), 123.97 (*C*H), 122.34 (*C*q), 116.27 (*C*H$_2$), 110.76 (*C*H), 60.99 (*C*H$_3$), 55.79 (*C*H$_3$), 30.12 (*C*H$_2$); Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.81; H, 6.32; N, 5.90.

*4.2.2. 1,2-Dimethoxy-3-(1-methylallyl)-4-(2-nitrovinyl)benzene (**4b**).* Yield=92% (1.21 g); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1240; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, J=13.6 Hz, 1H, C*H*=CHNO$_2$), 7.35 (d, J=13.6 Hz, 1H, CH=C*H*NO$_2$), 7.28 (d, J=8.4 Hz, 1H, aromatic C*H*), 6.84 (d, J=8.4 Hz, 1H, aromatic C*H*), 6.14 (ddd, J=4.4, 10.4, 17.2 Hz, 1H, C*H*=CH$_2$), 5.17 (ddd, J=1.2, 2.4, 10.4 Hz, 1H, *cis*-CH=CH$_2$), 5.10 (ddd, J=1.2, 2.4, 17.2 Hz, 1H, *trans*-CH=CH$_2$), 4.30–4.26 (m, 1H, CH$_2$CH=CH$_2$), 3.92 (s, 3H, OC*H*$_3$), 3.81 (s, 3H, OC*H*$_3$), 1.43 (d, J=7.2 Hz, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.70 (*C*q), 147.56 (*C*q), 141.86 (*C*H), 140.42 (*C*q), 138.23 (*C*H), 135.70 (*C*H), 124.57 (*C*H), 122.09 (*C*q), 114.27 (*C*H$_2$), 110.62 (*C*H), 61.07 (*C*H$_3$), 55.81 (*C*H$_3$), 34.66 (*C*H), 19.59 (*C*H$_3$).

*4.2.3. 2-Allyl-3,4-dimethoxy-1-(2-nitropropenyl)benzene (**4c**).* Yield=86% (1.13 g); yellowish oil; HRMS (ESI, M^++1) calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1238; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H, C*H*=C(CH$_3$)NO$_2$), 7.02 (d, J=8.4 Hz, 1H, aromatic C*H*), 6.86 (d, J=8.8 Hz, 1H, aromatic C*H*), 5.93–5.84 (m, 1H, C*H*=CH$_2$), 5.02 (dq, J=1.6, 10.0 Hz, 1H, *cis*-CH=CH$_2$), 4.90 (dq, J=1.6, 17.2 Hz, 1H, *trans*-CH=CH$_2$), 3.91 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 3.47 (dt, J=1.6, 6.0 Hz, 2H, CH$_2$CH=CH$_2$), 2.32 (d, J=0.8 Hz, 3H, CH=C(C*H*$_3$)NO$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.86 (*C*q), 147.47 (*C*q), 135.77 (2×, *C*q), 133.88 (*C*q), 132.48 (*C*H), 125.29 (*C*H), 125.01 (*C*H), 115.76 (*C*H$_2$), 110.13 (*C*H), 60.95 (*C*H$_3$), 55.71 (*C*H$_3$), 31.09 (*C*H$_2$), 13.91 (*C*H$_3$).

*4.2.4. 2-Allyl-1-methoxy-3-(2-nitrovinyl)benzene (**4d**).* Yield=80% (880 mg); colorless solid; mp=55–57 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{12}H_{14}NO_3$ 220.0974, found 220.0977; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J=13.6 Hz, 1H, C*H*=CHNO$_2$), 7.48 (d, J=13.6 Hz, 1H, CH=C*H*NO$_2$), 7.26 (t, J=7.6 Hz, 1H, aromatic C*H*), 7.13 (d, J=7.6 Hz, 1H, aromatic C*H*), 7.00 (d, J=7.6 Hz, 1H, aromatic C*H*), 5.98–5.88 (m, 1H, C*H*=CH$_2$), 5.03 (dq, J=1.6, 2.8, 10.0 Hz, 1H, *cis*-CH=CH$_2$), 4.91 (dq, J=1.6, 2.8, 16.8 Hz, 1H, *trans*-CH=CH$_2$), 3.85 (s, 3H, OC*H*$_3$), 3.58 (dt, J=1.6, 5.6 Hz, 2H, CH$_2$CH=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.91 (*C*q), 138.26 (*C*q), 136.95 (*C*H), 135.75 (*C*q), 130.33 (*C*q), 129.41 (*C*q), 127.80 (*C*H), 119.27 (*C*H), 115.66 (*C*H$_2$), 113.47 (*C*H), 55.84 (*C*H$_3$), 29.83 (*C*H$_2$); Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.98; H, 6.16; N, 6.50.

*4.2.5. 2-Cinnamyl-3,4-dimethoxy-1-(2-nitrovinyl)benzene (**4e**).* Yield=89% (1.45 g); colorless solid; mp=129–130 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{19}H_{20}NO_4$ 326.1392, found 326.1398; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J=13.6 Hz, 1H, C*H*=CHNO$_2$), 7.49 (d, J=13.6 Hz, 1H, CH=C*H*NO$_2$), 7.34–7.19 (m, 5H, aromatic C*H*), 7.00 (s, 1H, aromatic C*H*), 6.81 (s, 1H, aromatic C*H*), 6.39–6.25 (m, 2H, C*H*=C*H*Ph), 3.93 (s, 3H, OC*H*$_3$), 3.92 (s, 3H, OC*H*$_3$), 3.67 (d, J=5.6 Hz, 2H, CH$_2$CH=CHPh); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.73 (*C*q), 148.07 (*C*q), 136.87 (*C*q), 136.28 (*C*q), 136.02 (*C*H), 135.74 (*C*H), 131.81 (*C*H), 128.52 (2×, *C*H), 128.04 (*C*H), 127.43 (*C*H), 126.15 (2×, *C*H), 120.72 (*C*q), 113.24 (*C*H$_2$), 109.15 (*C*H), 56.06 (*C*H$_3$), 56.03 (*C*H$_3$), 36.36 (*C*H$_2$); Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.37; H, 6.22; N, 4.47.

*4.2.6. 1-Cinnamyl-4,5-dimethoxy-2-((E)-2-nitroprop-1-enyl)benzene (**4f**).* Yield=80% (1.36 g); colorless gum; HRMS (ESI, M^++1) calcd for $C_{20}H_{22}NO_4$ 340.1549, found 340.1550; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H, C*H*=C(CH$_3$)NO$_2$), 7.33–7.24 (m, 5H, aromatic C*H*), 6.83 (s, 1H, aromatic C*H*), 6.78 (s, 1H, aromatic C*H*), 6.36 (d, J=15.6 Hz, 1H CH=C*H*Ph), 6.23 (dt, J=6.4, 15.6 Hz, 1H, C*H*=CHPh), 3.92 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 3.55 (dd, J=1.2, 6.4 Hz, 2H, C*H*$_2$CH=CHPh), 2.36 (d, J=0.8 Hz, 3H, CH=C(C*H*$_3$)NO$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.39 (*C*q), 147.35 (*C*q), 137.04 (*C*q), 133.52 (*C*q), 132.52 (*C*H), 131.59 (*C*H), 128.52 (2×, *C*H), 127.72 (*C*H), 127.33 (*C*H), 126.14 (2×, *C*H), 126.10 (*C*H), 123.38 (*C*q), 112.99 (*C*H$_2$), 112.18 (*C*H), 56.15 (*C*H$_3$), 55.98 (*C*H$_3$), 36.86 (*C*H$_2$), 14.04 (*C*H$_3$).

*4.2.7. 1-But-2-enyl-4,5-dimethoxy-2-(2-nitrovinyl)benzene (**4g**).* Yield=90% (1.18 g); colorless solid; mp=110–111 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1244; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J=13.2 Hz, 1H, C*H*=CHNO$_2$), 7.47 (d, J=13.2 Hz, 1H, CH=C*H*NO$_2$), 6.96 (s, 1H, aromatic C*H*), 6.73 (s, 1H, aromatic C*H*), 5.56–5.40 (m, 2H, C*H*=C*H*CH$_3$), 3.93 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 3.44 (dt, J=1.2, 5.6 Hz, 2H, CH$_2$CH=CHCH$_3$), 1.67 (ddd, J=1.6, 3.2, 6.4 Hz, 3H, CH$_2$CH=CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.68 (*C*q), 147.88 (*C*q), 137.02 (*C*q), 136.57 (*C*H), 135.53 (*C*H), 129.09 (*C*H), 127.43 (*C*H), 120.53 (*C*q), 113.16 (*C*H$_2$), 109.09 (*C*H), 56.06 (*C*H$_3$), 55.99 (*C*H$_3$), 36.16 (*C*H$_2$), 17.87 (*C*H$_3$); Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.01; H, 6.34; N, 5.58.

*4.2.8. 1-But-2-enyl-4,5-dimethoxy-2-(2-nitropropenyl)benzene (**4h**).* Yield=82% (1.14 g); colorless gum; HRMS (ESI, M^++1) calcd for $C_{15}H_{20}NO_4$ 278.1392, found 278.1389; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H, C*H*=C(CH$_3$)NO$_2$), 6.76 (s, 1H, aromatic C*H*), 6.75 (s, 1H, aromatic C*H*), 5.50–5.40 (m, 2H, C*H*=C*H*CH$_3$), 3.91 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.28 (dd, J=1.6, 5.6 Hz, 2H, CH$_2$CH=CHCH$_3$), 2.35 (d, J=0.8 Hz, 3H, CH$_2$CH=CHC*H*$_3$), 1.65 (d, J=5.6 Hz, 3H, CH=C(C*H*$_3$)NO$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.30 (*C*q), 147.07 (2×, *C*q), 134.52 (*C*q), 132.73 (*C*H), 128.63 (*C*H), 127.05 (*C*H), 123.10 (*C*q), 112.83 (*C*H$_2$), 112.10 (*C*H), 56.10 (*C*H$_3$), 55.89 (*C*H$_3$), 36.55 (*C*H$_2$), 17.83 (*C*H$_3$), 13.99 (*C*H$_3$).

4.3. A representative procedure of skeleton 5 is as follows

Lithium aluminum hydride ($LiAlH_4$, 300 mg, 8.0 mmol) was added to a solution of skeleton **4** (2.0 mmol) in THF (20 mL) at rt. The reaction mixture was stirred at rt for 4 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added to the reaction mixture and the solvent was

concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Without further purification, potassium carbonate (K_2CO_3, 420 mg, 3.0 mmol) was added to the resulting product in CH_2Cl_2 (20 mL) at rt. Then, phenylsulfonyl chloride ($PhSO_2Cl$, 430 mg, 2.4 mmol) was added to the reaction mixture at rt. The reaction mixture was stirred at rt for 4 h. Water (5 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc=8/1–4/1) afforded skeleton **5**.

*4.3.1. N-[2-(2-Allyl-3,4-dimethoxyphenyl)ethyl]benzenesulfonamide (**5a**).* Yield=70% (505 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_4S$ 362.1426, found 362.1434; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.80 (m, 2H, aromatic C*H*), 7.59–7.55 (m, 1H, aromatic C*H*), 7.51–7.47 (m, 2H, aromatic C*H*), 6.77 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.72 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 5.90–5.80 (m, 1H, CH_2CH=CH_2), 4.90 (dq, *J*=2.0, 10.4 Hz, 1H, *cis*-CH=CH_2), 4.78 (dq, *J*=2.0, 17.6 Hz, 1H, *trans*-CH=CH_2), 4.52 (t, *J*=6.4 Hz, 1H, N*H*), 3.83 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.33 (dt, *J*=2.0, 6.0 Hz, 2H, CH_2CH=CH_2), 3.14 (q, *J*=7.2 Hz, 2H, CH_2CH_2NH), 2.71 (t, *J*=7.2 Hz, 2H, CH_2CH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.58 (*C*q), 147.58 (*C*q), 139.91 (*C*q), 136.99 (*C*q), 132.58 (*C*H), 132.03 (*C*q), 129.06 (2×, *C*H), 128.92 (*C*H), 127.00 (2×, *C*H), 124.89 (*C*H), 115.03 (CH_2), 110.48 (*C*H), 60.74 (CH_3), 55.62 (CH_3), 43.75 (CH_2), 32.36 (CH_2), 30.34 (CH_2).

*4.3.2. N-{2-[3,4-Dimethoxy-2-(1-methylallyl)phenyl]ethyl}benzenesulfonamide (**5b**).* Yield=68% (510 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{26}NO_4S$ 376.1583, found 376.1580; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.81 (m, 2H, aromatic C*H*), 7.59–7.55 (m, 1H, aromatic C*H*), 7.52–7.47 (m, 2H, aromatic C*H*), 6.74 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.70 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.08 (ddd, *J*=1.6, 10.4, 17.2 Hz, 1H, CH(CH_3)C*H*=CH_2), 4.91 (dt, *J*=1.6, 10.8 Hz, 1H, *cis*-CH=CH_2), 4.88 (dt, *J*=1.6, 17.2 Hz, 1H, *trans*-CH=CH_2), 4.49 (br t, *J*=6.4 Hz, 1H, N*H*), 3.86–3.80 (m, 2H, CH_2CH_2NH), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.15–3.09 (m, 1H, C*H*(CH_3)CH=CH_2), 2.77 (t, *J*=7.2 Hz, 2H, CH_2CH_2NH), 1.31 (d, *J*=7.2 Hz, 3H, CH(CH_3)CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.04 (*C*q), 148.06 (*C*q), 142.90 (*C*q), 139.80 (*C*q), 137.69 (*C*q), 132.61 (*C*H), 129.08 (2×, *C*H), 127.98 (*C*H), 127.03 (2×, *C*H), 125.51 (*C*H), 112.86 (*C*H), 110.45 (*C*H), 60.57 (CH_3), 55.59 (CH_3), 44.14 (CH_2), 36.80 (CH_2), 33.28 (*C*H), 19.29 (CH_3).

*4.3.3. N-[2-(2-Allyl-3,4-dimethoxyphenyl)-1-methylethyl]benzenesulfonamide (**5c**).* Yield=60% (450 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{26}NO_4S$ 376.1583, found 376.1586; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.67 (m, 2H, aromatic C*H*), 7.53–7.49 (m, 1H, aromatic C*H*), 7.42–7.38 (m, 2H, aromatic C*H*), 6.69 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.64 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 5.86–5.76 (m, 1H, CH_2CH=CH_2), 4.94 (dq, *J*=1.6, 10.0 Hz, 1H, *cis*-CH=CH_2), 4.79 (dq, *J*=1.6, 17.2 Hz, 1H, *trans*-CH=CH_2), 4.59 (br d, *J*=6.8 Hz, 1H, N*H*), 3.83 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.45–3.41 (m, 1H, $CH_2CH(CH_3)$N), 3.29–3.24 (m, 2H, CH_2CH=CH_2), 2.67 (dd, *J*=7.2, 14.0 Hz, 1H, CH_2CH(CH_3)N), 2.56 (dd, *J*=7.2, 14.0 Hz, 1H, CH_2CH(CH_3)N), 1.13 (d, *J*=6.4 Hz, 3H, $CH_2CH(CH_3)$N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.47 (2×, *C*q), 147.44 (*C*q), 140.42 (*C*q), 137.11 (*C*q), 132.28 (*C*H), 132.08 (*C*H), 128.83 (2×, *C*H), 126.87 (2×, *C*H), 125.55 (*C*H), 115.05 (CH_2), 110.22 (*C*H), 60.67 (CH_3), 55.56 (CH_3), 50.71 (*C*H), 40.15 (CH_2), 30.35 (CH_2), 21.78 (CH_3); Anal. Calcd for $C_{20}H_{25}NO_4S$: C, 63.97; H, 6.71; N, 3.73. Found: C, 64.12; H, 6.92; N, 3.55.

*4.3.4. N-[2-(2-Allyl-3-methoxyphenyl)ethyl]benzenesulfonamide (**5d**).* Yield=73% (480 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1323; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.79 (m, 2H, aromatic C*H*), 7.59–7.54 (m, 1H, aromatic C*H*), 7.51–7.46 (m, 2H, aromatic C*H*), 7.11 (t, *J*=7.6 Hz, 1H, aromatic C*H*), 6.76 (dd, *J*=0.8, 7.6 Hz, 1H, aromatic C*H*), 6.67 (dd, *J*=0.8, 7.6 Hz, 1H, aromatic C*H*), 5.89 (m, 1H, CH_2CH=CH_2), 4.87 (dq, *J*=1.6, 10.0 Hz, 1H, *cis*-CH=CH_2), 4.79 (dq, *J*=1.6, 17.2 Hz, 1H, *trans*-CH=CH_2), 4.60 (br t, *J*=5.6 Hz, 1H, N*H*), 3.79 (s, 3H, OCH_3), 3.33 (dt, *J*=1.6, 5.6 Hz, 2H, CH_2CH=CH_2), 3.18 (dt, *J*=7.6, 13.6 Hz, 2H, CH_2CH_2N), 2.78 (t, *J*=7.6 Hz, 2H, CH_2CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.81 (*C*q), 139.89 (*C*q), 137.22 (*C*q), 136.67 (*C*q), 132.55 (*C*H), 129.05 (2×, *C*H), 127.21 (*C*H), 127.00 (2×, *C*H), 126.59 (*C*H), 121.88 (*C*H), 114.50 (CH_2), 109.12 (*C*H), 55.58 (CH_3), 43.68 (CH_2), 32.85 (CH_2), 29.86 (CH_2).

*4.3.5. N-[2-(2-Cinnamyl-3,4-dimethoxyphenyl)-1-methylethyl]benzenesulfonamide (**5e**).* Yield=78% (680 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{25}H_{28}NO_4S$ 438.1739, found 438.1743; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.74 (m, 2H, aromatic C*H*), 7.49–7.46 (m, 1H, aromatic C*H*), 7.39–7.35 (m, 2H, aromatic C*H*), 7.31–7.16 (m, 5H, aromatic C*H*), 6.66 (s, 1H, aromatic C*H*), 6.59 (s, 1H, aromatic C*H*), 6.29–6.18 (m, 2H, CH_2CH=*CH*Ph), 5.05 (t, *J*=6.0 Hz, 1H, N*H*), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.39 (d, *J*=4.8 Hz, 2H, CH_2CH=CHPh), 3.13 (dd, *J*=7.2, 14.4 Hz, 2H, CH_2CH_2NH), 2.77 (t, *J*=7.2 Hz, 2H, CH_2CH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.64 (*C*q), 147.37 (*C*q), 139.76 (*C*q), 137.13 (*C*q), 132.39 (*C*H), 130.57 (*C*H), 130.07 (*C*q), 129.06 (*C*H), 128.91 (2×, *C*H), 128.38 (2×, *C*H), 127.82 (*C*H), 127.02 (*C*q), 126.77 (2×, *C*H), 125.96 (2×, *C*H), 113.21 (CH_2), 112.88 (*C*H), 55.84 (CH_3), 55.80 (CH_3), 43.91 (CH_2), 35.69 (CH_2), 32.66 (CH_2).

*4.3.6. (E)-N-(2-(But-2-enyl)-4,5-dimethoxyphenethyl)benzenesulfonamide (**5f**).* Yield=63% (472 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{20}H_{26}NO_4S$ 376.1583, found 376.1588; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J*=8.0 Hz, 2H, aromatic C*H*), 7.59–7.47 (m, 3H, aromatic C*H*), 6.62 (s, 1H, aromatic C*H*), 6.53 (s, 1H, aromatic C*H*), 5.49–5.32 (m, 2H, CH_2CH=*CH*CH_3), 4.47 (br t, *J*=6.4 Hz, 1H, N*H*), 3.84 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.17–3.13 (m, 4H, CH_2CH=*CH*CH_3+CH_2CH_2NH), 2.74 (t, *J*=7.2 Hz, 2H, CH_2CH_2NH), 1.62 (dd, *J*=1.2, 6.0 Hz, 3H, CH_2CH=CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.76 (*C*q), 147.32 (*C*q), 139.90 (*C*q), 132.57 (*C*q), 131.15 (*C*H), 129.93 (*C*q), 129.05 (2×, *C*H), 126.97 (2×, *C*H), 126.40 (*C*H), 126.30 (*C*H), 113.24 (CH_2), 112.78 (*C*H), 55.95 (CH_3), 55.90 (CH_3), 43.90 (CH_2), 35.51 (CH_2), 32.39 (CH_2), 17.81 (CH_3).

*4.3.7. (E)-N-(1-(2-Cinnamyl-4,5-dimethoxyphenyl)propan-2-yl)benzenesulfonamide (**5g**).* Yield 80% (721 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{26}H_{30}NO_4S$ 452.1896, found 452.1900; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.74 (m, 2H, aromatic C*H*), 7.50–7.46 (m, 1H, aromatic C*H*), 7.40–7.36 (m, 2H, aromatic C*H*), 7.35–7.30 (m, 5H, aromatic C*H*), 6.73 (s, 1H, aromatic C*H*), 6.61 (s, 1H, aromatic C*H*), 6.32–6.30 (m, 2H, CH_2CH=*CH*Ph), 5.25 (t, *J*=6.0 Hz, 1H, N*H*), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.56–3.50 (m, 2H, CH_2CH=CHPh), 3.46–3.40 (m, 1H, $CH_2CH(CH_3)$NH), 2.99 (t, *J*=7.2 Hz, 2H, CH_2CH(CH_3)NH), 1.62 (dd, *J*=1.2, 6.0 Hz, 3H, $CH_2CH(CH_3)$NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.65 (*C*q), 147.83 (*C*q), 139.92 (*C*q), 137.44 (*C*q), 133.01 (*C*H), 131.32 (*C*H), 130.22 (*C*q), 129.59 (*C*H), 128.30 (2×, *C*H), 128.34 (2×, *C*H), 127.28 (*C*H), 127.32 (*C*q), 126.37 (2×, *C*H), 125.26 (2×, *C*H), 113.81 (CH_2), 112.91 (*C*H), 55.44 (CH_3), 556.12 (CH_3), 43.94 (CH_2), 35.12 (CH_2), 34.21 (CH_2), 18.28 (CH_3).

*4.3.8. (E)-N-(1-(2-(But-2-enyl)-4,5-dimethoxyphenyl)propan-2-yl)-benzenesulfonamide (**5h**).* Yield 66% (515 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{21}H_{28}NO_4S$ 390.1739, found 390.1744; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65–7.62 (m, 2H, aromatic C*H*), 7.50–7.46 (m, 1H, aromatic C*H*), 7.38–7.34 (m, 2H, aromatic C*H*), 6.53 (s, 1H, aromatic C*H*), 6.40 (s, 1H, aromatic C*H*), 5.45–5.33 (m,

2H, CH_2CH=$CHCH_3$), 4.92 (br s, 1H, N*H*), 3.83 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.44–3.37 (m, 1H, $CH_2CH(CH_3)NH$), 3.16–3.04 (m, 2H, CH_2CH=$CHCH_3$), 2.68 (dd, *J*=8.0, 14.0 Hz, 1H, $CH_2CH(CH_3)NH$), 2.55 (dd, *J*=6.8, 14.0 Hz, 1H, $CH_2CH(CH_3)NH$), 1.65 (d, *J*=5.2 Hz, 3H, CH_2CH=$CHCH_3$), 1.16 (d, *J*=6.4 Hz, 3H, $CH_2CH(CH_3)NH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.54 (*C*q), 146.92 (*C*q), 140.30 (*C*q), 132.12 (*C*H), 130.94 (*C*q), 130.05 (*C*q), 128.68 (2×, *C*H), 127.34 (*C*H), 126.73 (2×, *C*H), 126.34 (*C*H), 113.20 (CH_2), 112.87 (*C*H), 55.75 (CH_3), 55.72 (CH_3), 51.04 (*C*H), 39.83 (CH_2), 35.40 (CH_2), 21.95 (CH_3), 17.78 (CH_3).

4.4. A representative procedure of skeleton 6 is as follows

A solution of 2.5% osmium tetraoxide (OsO_4, 1 mL, in THF) was added to a solution of skeleton **5** (1.0 mmol) in the co-solvent of THF (10 mL) and water (10 mL). *N*-Methylmorpholine-*N*-oxide (NMO, 50% in water, 500 mg, 2.2 mmol) was added to the reaction mixture at rt. The reaction mixture was stirred at rt for 2 h. Then, sodium periodate ($NaIO_4$, 257 mg, 1.2 mmol) was added to the reaction mixture at rt. The reaction mixture was stirred at rt for 1 h. Acetic acid (1 mL) were added to the reaction mixture at rt. The reaction mixture was stirred at rt for 1 h. The overall synthetic procedure had to be monitored by TLC until the reaction was completed. 10% $NaHSO_{3(aq)}$ (5 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield crude compound. Purification on silica gel (hexanes/EtOAc=7/1–4/1) afforded skeleton **6**.

*4.4.1. 3-Benzenesulfonyl-6,7-dimethoxy-2,3-dihydro-1H-benzo[d] azepine (**6a**).* Yield=75% (260 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{20}NO_4S$ 346.1113, found 346.1120; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.81 (m, 2H, aromatic C*H*), 7.60–7.56 (m, 1H, aromatic C*H*), 7.53–7.49 (m, 2H, aromatic C*H*), 6.97 (d, *J*=11.2 Hz, 1H, C*H*=CHN), 6.67 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.63 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.10 (d, *J*=11.2 Hz, 1H, CH=C*H*N), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.75 (dt, *J*=4.8, 9.2 Hz, 2H, CH_2CH_2N), 2.73 (dt, *J*=4.8, 9.2 Hz, 2H, CH_2CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.28 (*C*q), 146.45 (*C*q), 138.44 (*C*q), 133.05 (*C*H), 132.79 (*C*q), 129.29 (2×, *C*H), 128.43 (*C*q), 126.98 (2×, *C*H), 125.78 (*C*H), 123.76 (*C*H), 110.05 (*C*H), 102.46 (*C*H), 60.67 (CH_3), 55.84 (CH_3), 47.76 (CH_2), 35.36 (CH_2); Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.67; H, 5.58; N, 4.18.

*4.4.2. 3-Benzenesulfonyl-6,7-dimethoxy-5-methyl-2,3-dihydro-1H-benzo[d]azepine (**6b**).* Yield=61% (220 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1277; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.63 (m, 2H, aromatic C*H*), 7.50–7.45 (m, 1H, aromatic C*H*), 7.40–7.35 (m, 2H, aromatic C*H*), 6.84 (d, *J*=8.0 Hz, 1H, aromatic C*H*), 6.74 (d, *J*=8.0 Hz, 1H, aromatic C*H*), 6.28 (br q, *J*=1.2 Hz, 1H, $C(CH_3)$=C*H*N), 3.84 (t, *J*=6.0 Hz, 2H, CH_2CH_2N), 3.83 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 2.68 (t, *J*=6.0 Hz, 2H, CH_2CH_2N), 2.09 (d, *J*=1.2 Hz, 3H, $C(CH_3)$=CHN); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.84 (*C*q), 146.61 (*C*q), 138.96 (*C*q), 132.33 (*C*q), 132.28 (*C*q), 131.75 (*C*q), 131.15 (*C*H), 128.76 (2×, *C*H), 126.91 (2×, *C*H), 123.21 (*C*H), 122.44 (*C*H), 111.45 (*C*H), 60.38 (CH_3), 56.74 (CH_3), 55.85 (CH_2), 31.78 (CH_2), 19.53 (CH_3).

*4.4.3. 3-Benzenesulfonyl-6,7-dimethoxy-2-methyl-2,3-dihydro-1H-benzo[d]azepine (**6c**).* Yield=70% (251 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1276; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.83 (m, 2H, aromatic C*H*), 7.58–7.48 (m, 3H, aromatic C*H*), 6.98 (dd, *J*=1.6, 11.2 Hz, 1H, C*H*=CHN), 6.66 (s, 2H, aromatic C*H*), 6.09 (d, *J*=10.8 Hz, 1H, CH=C*H*N), 4.69–4.62 (m, 1H, $CH_2CH(CH_3)$N), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.72 (dd, *J*=6.4, 15.2 Hz, 1H, $CH_2CH(CH_3)$N), 2.25 (d, *J*=15.2 Hz, 1H, $CH_2CH(CH_3)$N), 0.79 (d, *J*=6.4 Hz, 3H, $CH_2CH(CH_3)$N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.06 (*C*q), 145.69 (*C*q), 138.73 (*C*q), 132.90 (*C*H), 129.18 (3×, 2CH+*C*q), 128.97 (*C*H), 126.89 (2×, *C*H), 125.03 (*C*H), 123.94 (*C*H), 110.10 (*C*H), 101.21 (*C*H), 60.57 (CH_3), 55.65 (CH_3), 51.95 (*C*H), 40.00 (CH_2), 17.44 (CH_3); Anal. Calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.55; H, 6.11; N, 4.10.

*4.4.4. 3-Benzenesulfonyl-6-methoxy-2,3-dihydro-1H-benzo[d]azepine (**6d**).* Yield=58% (183 mg); colorless solid; mp=109–111 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{17}H_{18}NO_3S$ 316.1007, found 316.1011; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.81 (m, 2H, aromatic C*H*), 7.59–7.48 (m, 3H, aromatic C*H*), 7.03 (t, *J*=8.0 Hz, 1H, aromatic C*H*), 6.95 (d, *J*=11.2 Hz, 1H, C*H*=CHN), 6.72 (dd, *J*=0.8, 8.0 Hz, 1H, aromatic C*H*), 6.60 (d, *J*=7.6 Hz, 1H, aromatic C*H*), 6.15 (d, *J*=11.2 Hz, 1H, CH=C*H*N), 3.83 (s, 3H, OCH_3), 3.78–3.75 (m, 2H, CH_2CH_2N), 2.79–2.77 (m, 2H, CH_2CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.62 (*C*q), 141.05 (*C*H), 138.41 (*C*q), 132.99 (*C*H), 129.27 (2×, *C*H), 127.97 (2×, *C*H), 126.89 (*C*q), 124.90 (*C*H), 123.00 (*C*q), 121.15 (*C*H), 108.66 (*C*H), 102.32 (*C*H), 55.68 (CH_3), 47.61 (CH_2), 35.92 (CH_2); Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.95; H, 5.62; N, 4.68.

*4.4.5. 3-Benzenesulfonyl-7,8-dimethoxy-2,3-dihydro-1H-benzo[d] azepine (**6e**).* For compound **5e**: yield=66% (228 mg); For compound **5f**: yield=72% (248 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{20}NO_4S$ 346.1113, found 346.1119; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.80 (m, 2H, aromatic C*H*), 7.60–7.49 (m, 3H, aromatic C*H*), 6.81 (d, *J*=10.4 Hz, 1H, CH=C*H*N), 6.64 (s, 1H, aromatic C*H*), 6.50 (s, 1H, aromatic C*H*), 5.59 (d, *J*=10.4 Hz, 1H, C*H*=CHN), 3.84 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.78–3.74 (m, 2H, CH_2CH_2N), 2.74–2.72 (m, 2H, CH_2CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.31 (*C*q), 147.21 (*C*q), 138.52 (*C*H), 133.01 (2×, *C*q), 131.75 (*C*H), 129.29 (2×, *C*H), 126.95 (2×, *C*H), 123.79 (*C*H), 113.47 (*C*H), 112.43 (*C*H), 109.87 (*C*H), 55.92 (2×, CH_3), 47.16 (CH_2), 35.76 (CH_2).

*4.4.6. 7,8-Dimethoxy-2-methyl-3-(phenylsulfonyl)-2,3-dihydro-1H-benzo[d]azepine (**6f**).* For compound **5g**: yield=62% (223 mg); for compound **5h**: yield=70% (250 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1276; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.82 (m, 2H, aromatic C*H*), 7.58–7.48 (m, 3H, aromatic C*H*), 6.81 (dd, *J*=1.6, 10.8 Hz, 1H, CH=C*H*N), 6.65 (s, 1H, aromatic C*H*), 6.48 (s, 1H, aromatic C*H*), 5.59 (d, *J*=10.8 Hz, 1H, CH=C*H*N), 4.71–4.64 (m, 1H, $CH_2CH(CH_3)$N), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.71 (dd, *J*=6.0, 15.6 Hz, 1H, $CH_2CH(CH_3)$N), 2.27 (d, *J*=15.6 Hz, 1H, $CH_2CH(CH_3)$N), 0.79 (d, *J*=6.8 Hz, 3H, $CH_2CH(CH_3)$N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.26 (2×, *C*q), 138.76 (*C*q), 132.87 (*C*H), 129.18 (2×, *C*H), 128.14 (*C*q), 127.85 (*C*q), 126.95 (2×, *C*H), 121.72 (*C*H), 113.36 (*C*H), 112.58 (*C*H), 108.94 (*C*H), 55.82 (2×, CH_3), 51.21 (*C*H), 40.43 (CH_2), 17.34 (CH_3).

4.5. A representative procedure of skeleton 1 is as follows

Palladium on activated carbon (10%, 15 mg) was added to a solution of skeleton **6** (0.5 mmol) in EtOAc (10 mL) at rt. Then hydrogen was bubbled into the mixture for 10 min, and stirring occurred at rt for 20 h. The reaction mixture was filtered and evaporated to yield crude product. Purification on silica gel (hexanes/EtOAc=7/1–4/1) afforded skeleton **1**.

*4.5.1. 3-Benzenesulfonyl-6,7-dimethoxy-2,3,4,5-tetrahydro-1H-benzo-[d]azepine (**1a**).* Yield=92% (160 mg); colorless solid; mp=90–91 °C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_4S$ 348.1270, found 349.1273; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.74 (m, 2H, aromatic C*H*), 7.55–7.45 (m, 3H, aromatic C*H*), 6.77 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.64 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 3.80 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.29–3.27 (m, 4H,

CH_2CH_2N), 3.12–3.09 (m, 2H, CH_2CH_2N), 2.95–2.92 (m, 2H, CH_2CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.42 (*C*q), 146.44 (*C*q), 138.15 (*C*q), 134.37 (*C*q), 133.91 (*C*q), 132.45 (*C*H), 129.01 (2×, *C*H), 127.15 (2×, *C*H), 124.40 (*C*H), 109.80 (*C*H), 60.96 (CH_3), 55.68 (CH_3), 48.68 (CH_2), 48.38 (CH_2), 36.47 (CH_2), 27.27 (CH_3); Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.35; H, 6.28; N, 4.31.

*4.5.2. 3-Benzenesulfonyl-8,9-dimethoxy-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**1b**).* Yield=83% (150 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_4S$ 362.1426, found 362.1430; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78–7.75 (m, 2H, aromatic C*H*), 7.51–7.42 (m, 3H, aromatic C*H*), 6.73 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.66 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 4.45–4.41 (m, 1H, $CH(CH_3)CH_2N$), 4.11–4.10 (m, 1H, $CH(CH_3)CH_2N$), 3.81 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.22 (dd, *J*=2.8, 14.8 Hz, 1H, $CH(CH_3)CH_2N$), 3.11–3.05 (m, 1H, CH_2CH_2N), 2.93–2.89 (m, 1H, CH_2CH_2N), 2.70–2.66 (m, 1H, CH_2CH_2N), 2.55 (dd, *J*=6.4, 14.8 Hz, 1H, CH_2CH_2N), 0.79 (d, *J*=6.8 Hz, 3H, $CH(CH_3)CH_2N$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.78 (*C*q), 147.32 (*C*q), 141.39 (*C*q), 134.88 (*C*q), 132.23 (*C*H), 130.92 (*C*H), 129.04 (2×, *C*H), 126.90 (2×, *C*H), 126.12 (*C*q), 1010.32 (*C*H), 61.02 (CH_3), 52.17 (CH_3), 48.18 (*C*H), 44.12 (CH_2), 40.87 (CH_2), 28.42 (CH_2), 16.01 (CH_3).

*4.5.3. 3-Benzenesulfonyl-6,7-dimethoxy-2-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**1c**).* Yield=84% (152 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_4S$ 362.1426, found 362.1428; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79–7.76 (m, 2H, aromatic C*H*), 7.53–7.42 (m, 3H, aromatic C*H*), 6.70 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 6.63 (d, *J*=8.4 Hz, 1H, aromatic C*H*), 4.49–4.45 (m, 1H, $CH_2CH(CH_3)N$), 4.12–4.06 (m, 1H, CH_2CH_2N), 3.81 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.31 (ddd, *J*=1.6, 6.4, 15.2 Hz, 1H, CH_2CH_2N), 3.11 (dd, *J*=2.8, 14.4 Hz, 1H, $CH_2CH(CH_3)N$), 2.98 (ddd, *J*=1.6, 10.4, 14.4 Hz, 1H, $CH_2CH(CH_3)N$), 2.66–2.59 (m, 1H, CH_2CH_2N), 2.62 (dd, *J*=6.0, 14.4 Hz, 1H, CH_2CH_2N), 0.78 (d, *J*=6.8 Hz, 3H, $CH_2CH(CH_3)N$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.45 (*C*q), 146.30 (*C*q), 141.40 (*C*q), 133.71 (*C*q), 132.08, 130.41 (*C*H), 128.94 (2×, *C*H), 126.78 (2×, *C*H), 125.62 (*C*q), 109.63 (*C*H), 60.88 (CH_3), 55.57 (CH_3), 49.89 (*C*H), 42.10 (CH_2), 41.00 (CH_2), 27.47 (CH_2), 15.45 (CH_3).

*4.5.4. 3-Benzenesulfonyl-6-methoxy-2,3,4,5-tetrahydro-1H-benzo[d]-azepine (**1d**).* Yield=90% (143 mg); colorless gum; HRMS (ESI, M^++1) calcd for $C_{17}H_{20}NO_3S$ 318.1164, found 318.1166; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77–7.74 (m, 2H, aromatic C*H*), 7.59–7.44 (m, 3H, aromatic C*H*), 7.06 (d, *J*=7.6 Hz, 1H, aromatic C*H*), 6.72 (d, *J*=7.6 Hz, 1H, aromatic C*H*), 6.68 (d, *J*=7.6 Hz, 1H, aromatic C*H*), 3.76 (s, 3H, OCH_3), 3.31–3.28 (m, 2H, CH_2CH_2N), 3.26–2.24 (m, 2H, CH_2CH_2N), 3.12–3.10 (m, 2H, CH_2CH_2N), 3.00–2.97 (m, 2H, CH_2CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.59 (*C*q), 142.49 (*C*q), 132.67 (*C*q), 132.43 (*C*H), 128.99 (2×, *C*H), 127.66 (*C*q), 127.21 (2×, *C*H), 127.14 (*C*H), 121.61 (*C*H), 109.14 (*C*H), 55.65 (CH_3), 48.20 (CH_2), 48.13 (CH_2), 36.69 (CH_2), 26.00 (CH_2).

*4.5.5. 3-Benzenesulfonyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-benzo-[d]azepine (**1e**).* For compound **5e** → **6e**, yield=94% (163 mg); for compound **5f** → **6e**, yield=94% (163 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_4S$ 348.1270, found 348.1270; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75–7.73 (m, 2H, aromatic C*H*), 7.54–7.44 (m, 3H, aromatic C*H*), 6.59 (s, 2H, aromatic C*H*), 3.80 (s, 6H, OCH_3), 3.29–3.27 (m, 4H, CH_2CH_2N), 2.93–2.90 (m, 4H, CH_2CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.92 (2×, *C*q), 138.05 (*C*q), 132.46 (*C*q), 132.41 (*C*H), 128.95 (2×, *C*q), 127.02 (2×, *C*H), 126.21 (*C*H), 113.13 (2×, *C*H), 55.88 (2×, CH_3), 48.53 (2×, CH_2), 36.42 (2×, CH_2).

*4.5.6. 7,8-Dimethoxy-2-methyl-3-phenylsulfonyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine (**1f**).* For compound **5g** → **6f**, yield=82% (148 mg); for compound **5h** → **6f**, yield=80% (144 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{24}NO_4S$ 362.1426, found 362.1428; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76–7.74 (m, 2H, aromatic C*H*), 7.50–7.43 (m, 3H, aromatic C*H*), 6.52 (s, 1H, aromatic C*H*), 6.51 (s, 1H, aromatic C*H*), 4.47–4.43 (m, 1H, $CH_2CH(CH_3)N$), 4.09–4.03 (m, 1H, CH_2CH_2N), 3.81 (s, 6H, OCH_3), 3.12 (dd, *J*=2.8, 14.8 Hz, 1H, CH_2CH_2N), 3.08–3.01 (m, 1H, $CH_2CH(CH_3)N$), 2.95–2.88 (m, 1H, $CH_2CH(CH_3)N$), 2.71–2.66 (m, 1H, CH_2CH_2N), 2.59 (dd, *J*=6.4, 14.8 Hz, 1H, CH_2CH_2N), 0.80 (d, *J*=6.8 Hz, 3H, $CH_2CH(CH_3)N$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.09 (*C*q), 146.99 (*C*q), 141.38 (*C*q), 132.05 (*C*H), 131.83 (*C*q), 129.11 (*C*H), 128.90 (2×, *C*H), 126.75 (2×, *C*H), 114.20 (*C*H), 112.98 (*C*H), 55.97 (CH_3), 55.85 (CH_3), 50.02 (*C*H), 42.13 (CH_2), 40.94 (CH_2), 36.51 (CH_2), 14.47 (CH_3).

4.6. 3-Benzenesulfonyl-8,9-dimethoxy-4,5-dihydro-3*H*-benzo-[*d*]azepine-2-carbonitrile (7)

N-Bromosuccinimide (NBS, 90 mg, 0.5 mmol) was added to a solution of compound **6a** (173 mg, 0.5 mmol) with trimethylsilyl cyanide (TMSCN, 3 mL) in CH_2Cl_2 (10 mL) at rt. The reaction mixture was stirred at rt for 5 min. Boron trifluoride etherate ($BF_3{\cdot}OEt_2$, ~0.1 mL) was added to the reaction mixture. The reaction mixture was stirred at rt for 3 h. Saturated $NaHCO_{3(aq)}$ solution (2 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate=6/1–3/1) afforded compound **7**. Yield=82% (152 mg); colorless oil; HRMS (ESI, M^++1) calcd for $C_{19}H_{19}N_2O_4S$ 371.1066, found 371.1070; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91–7.88 (m, 2H, aromatic C*H*), 7.57–7.53 (m, 1H, aromatic C*H*), 7.49–7.44 (m, 2H, aromatic C*H*), 7.37 (s, 1H, C*H*=C(CN)N), 6.82 (br s, 2H, aromatic C*H*), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.81 (t, *J*=5.2 Hz, 2H, CH_2CH_2N), 2.99 (d, *J*=5.2 Hz, 2H, CH_2CH_2N); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.95 (*C*q), 147.74 (*C*q), 138.57 (*C*q), 133.30 (*C*H), 132.32 (*C*q), 130.53 (*C*H), 129.09 (2×, *C*H), 127.38 (2×, *C*H), 125.78 (*C*q), 124.73 (*C*H), 116.96 (*C*q), 114.11 (*C*H), 111.72 (*C*q), 61.29 (CH_3), 55.89 (CH_3), 50.91 (CH_2), 35.61 (CH_2).

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Supplementary data

Scanned photocopies of ^1H and ^{13}C NMR spectral data were supported. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.10.017.

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