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A new synthetic approach towards isoquinobenzazepinone and isoindolinobenzazepinone using acid-mediated cyclisation and Heck reaction

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ABSTRACT

Six-membered ring cyclisation of *N*-ethylbenzazepinone, prepared from the condensation of benzazepinone with phenethyl iodide under basic conditions, smoothly provided the corresponding product, isoquino[1,2-*b*][3]benzazepinone, under acid-mediated conditions. On the other hand, the attempted direct five-membered ring cyclisation using the acid-mediated conditions failed to give the 7,5 fused ring isoindolinobenzazepinone from *N*-benzylbenzazepinone, but the 7,6 fused ring product was instead obtained. However, five-membered ring cyclisation of *N*-benzylbenzazepinone could be effected efficiently by employing the Heck reaction followed by catalytic hydrogenation to furnish the desired isoindolinobenzazepinone.

1. Introduction

Lennoxamine **1** is the prominent representative of the isoindolobenzazepine alkaloids and it was isolated from the Chilean plant *Berberis darwinii* Hook.[1] Despite its lack of important biological activities reported in the literature, its unique structural feature of the five- and seven-membered ring system fused with the aromatic moieties renders this molecule an attractive and synthetically challenging target. *C*-Homoprotoberberine is structurally related to lennoxamine containing the unique framework of the six- and seven-membered ring joined with the respective aromatic parts. Hediamine **2**, the prototype of *C*-homoprotoberberine, has been recently isolated from a natural source.[2]

Lennoxamine has been the target of many synthetic endeavours [3–14] including our own work[15] employing a wide variety of approaches. *C*-Homoprotoberberine could be obtained from phenylethyl phenylacetamide by tin(IV) chloride-promoted reaction with oxalyl chloride.[16] While the *C*-homoprotoberberine and lennoxamine both share a fused tetracyclic system, their frameworks differ in the sizes of the fused lactam rings (seven-five in lennoxamine versus seven-six in *C*-homoprotoberberine). The lactam carbonyl group in the *C*-homoprotoberberine resides on the benzazepine moiety whereas that in the lennoxamine on the five-membered ring of the indoline unit (Fig. 1).

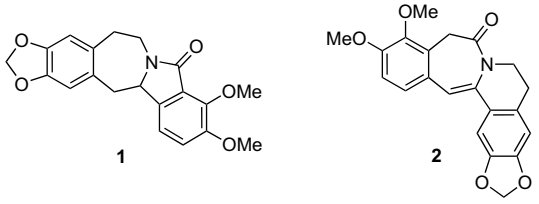

Figure 1. Structures of lennoxamine **1** and hediamine **2**.

Significantly, it was found that the benzazepinone ring played a crucial role for bradycardic activity from the structure–activity relationships study.[17] In addition, some *C*-homoprotoberberines exhibited significant cytotoxicity against some human breast carcinoma cell lines.[16]

As shown retrosynthetically in Scheme 1, we now wish to report the total synthesis of both isoindolinobenzazepinone **9a**, via Heck reaction,[18] (n=1, forming a five-membered ring) and *C*-homoprotoberberine **9b** via acid-mediated cyclisation[19] (n=2, forming a six-membered ring) from the common synthon benzazepinone **4**. We envisioned that *N*-alkylbenzazepinones **8** and **6** could serve as the key intermediates for **9a** and **9b**, respectively, since both compounds could be formed by the corresponding N-alkylation reactions of benzazepinone **4** with derivatives of either phenethyl iodide **5** or benzyl bromide **7**. Both *N*-alkylbenzazepinones **6** and **8** share the common synthon in benzazepinone **4**.

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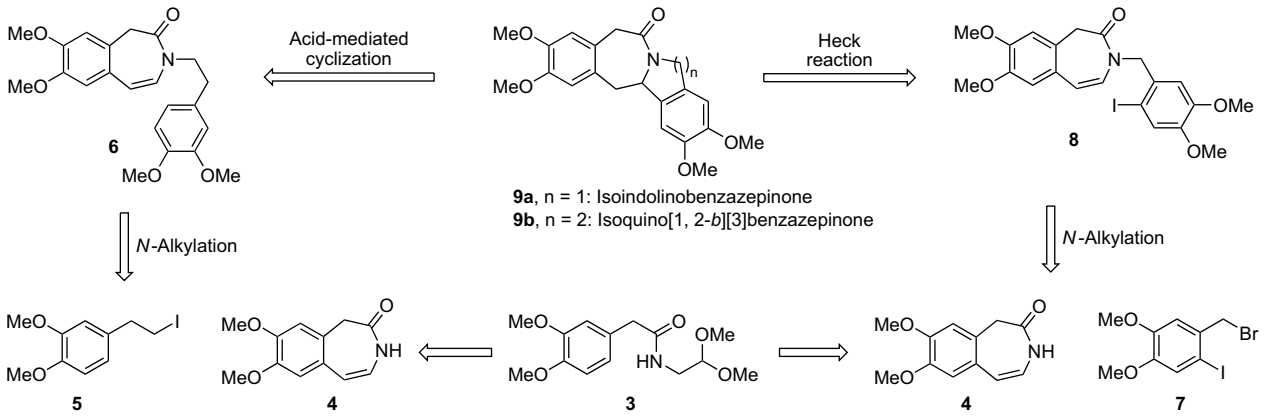


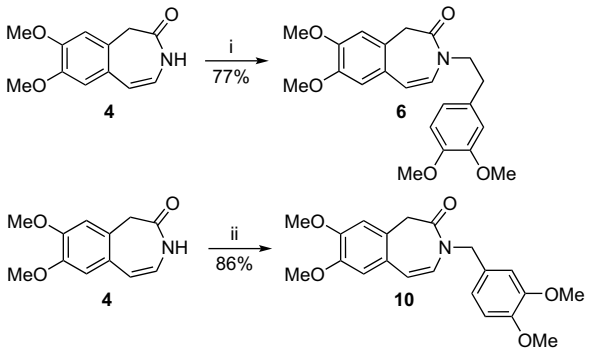
Scheme 1. Retrosynthetic strategies of isoindolinobenzazepinone **9a** and isoquino[1,2-*b*][3]benzazepinone **9b** via a common intermediate benzazepinone **4**.

2. Results and discussion

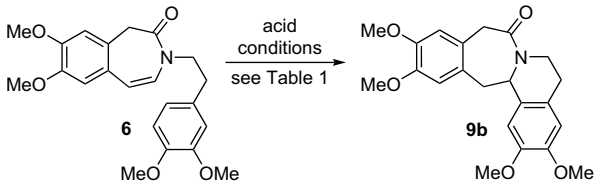
Our synthesis commenced with the preparation of the starting material benzazepinone[17] **4** from the acid-mediated cyclisation of acetal amide **3**. Cyclisation of acetal amide **3** with HCl/AcOH gave benzazepinone **4** in 75% yield. The cyclisation could also be accomplished by H_2SO_4/AcOH or HCO_2H, albeit in lower yield of 45% and 40%, respectively.

N-Alkylation of benzazepinone **4** using sodium hydride as a base in DMF at 0 °C for 30 min, followed by the addition of 3,4-dimethoxyphenethyl iodide **5** was first employed. However, our initial attempt to carry out the reaction using sodium hydride did not proceed to give the desired product **6**, but rather gave 3,4-dimethoxystyrene from the elimination reaction of **5** and recovered starting material benzazepinone **4**. Potassium *tert*-butoxide has been used as base in the N-alkylation reactions in polar solvents (DMF or DMSO).[17] Thus, treatment of benzazepinone **4** with 1.5 equiv of potassium *tert*-butoxide in DMF at 0 °C for 30 min, followed by the addition of 3,4-dimethoxyphenethyliodide **5** furnished, after purification, *N*-alkylbenzazepinone **6** in 77% yield as shown in Scheme 2. From this experiment, it was apparent that bulky base was critical for this N-alkylation reaction. Similar treatment of benzazepinone **4** with potassium *tert*-butoxide in DMF at 0 °C followed by the addition of 3,4-dimethoxybenzyl chloride gave *N*-alkylbenzazepinone **10** in 86% yield (Scheme 3).

After the key intermediate *N*-alkylbenzazepinones **6** and **10** were prepared, the acid-mediated cyclisation to convert *N*-alkylbenzazepinone **6** to isoquino[1,2-*b*][3]benzazepinone **9b** was explored. Table 1 summarises the results of our investigation employing different acidic conditions. It is apparent that longer reaction time or changing HCl to H_2SO_4 in the mixed acid system



Scheme 2. Reagents and conditions: (i) (a) Bu^{t}OK (1.5 equiv), DMF, 0 °C, (b) **5**; (ii) (a) Bu^{t}OK (1.5 equiv), DMF, 0 °C, (b) 3,4-dimethoxybenzyl chloride.



Scheme 3. Acid-mediated cyclisation of *N*-alkylbenzazepinone **6**.

with AcOH resulted in better yields of the product (entries 1–6 compared with entries 7–12). However, the best results were obtained when formic acid, a weaker acid, was employed, furnishing the desired isoquino[1,2-*b*][3]benzazepinone product **9b** in 72–85% yields and in much shorter reaction times (1–2 h).

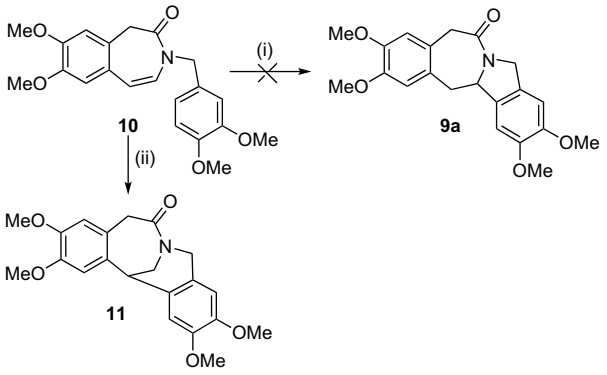
Our attempts to induce an acid-mediated cyclisation of *N*-alkylbenzazepinone **10**, using the mixed acid systems (HCl or H_2SO_4 and AcOH) or refluxed formic acid failed to produce the desired product **9a**. However upon treating with triflic acid in refluxed dichloromethane for 2 h, **10** underwent an extremely smooth cyclisation to the tetracyclic ring system **11** via a 7,6 annulation in 64% yield (Scheme 4).

Under the mixed acid systems (HCl or H_2SO_4 in AcOH) or refluxed formic acid, **10** did not provide the product **9a** presumably due to the angle strain present for the unfavoured anti-Baldwin 5-*endo-trig* cyclisation[20] of the resulting iminium Pictet–Spengler-

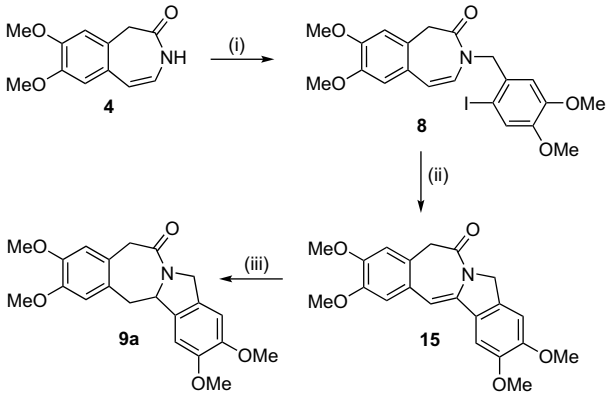
Table 1
Effect of acids and reaction time on the cyclisation of *N*-alkylbenzazepinone **6** to homoprotoberberine **9b**

Entry	Acid	Temperature	Time (h)	Yield[a] (%)
1	HCl/AcOH[b]	rt	2	41
2	HCl/AcOH[b]	rt	4	46
3	HCl/AcOH[b]	rt	6	48
4	HCl/AcOH[b]	rt	8	52
5	HCl/AcOH[b]	rt	10	54
6	HCl/AcOH[b]	rt	17	68
7	H_2SO_4/AcOH[c]	rt	2	46
8	H_2SO_4/AcOH[c]	rt	4	62
9	H_2SO_4/AcOH[c]	rt	6	70
10	H_2SO_4/AcOH[c]	rt	8	75
11	H_2SO_4/AcOH[c]	rt	10	76
12	H_2SO_4/AcOH[c]	rt	17	80
13	HCO_2H	Reflux	1	72
14	HCO_2H	Reflux	2	85

[a] Isolated yield after chromatography on silica gel.
[b] All reactions were performed with HCl/AcOH (1:1).
[c] All reactions were performed with H_2SO_4/AcOH (1:5).[11]



Scheme 4. Reagents and conditions: (i) HCl/AcOH or H_2SO_4; (ii) triflic acid (4 equiv), CH_2Cl_2, reflux, 2 h, 64%.



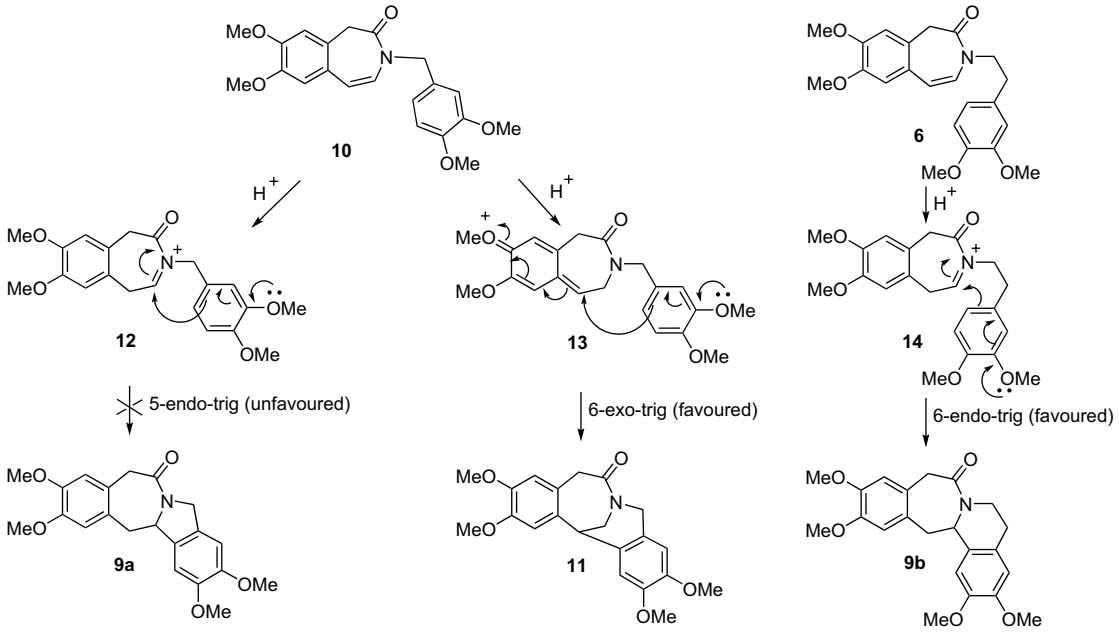
Scheme 6. Reagents and conditions: (i) (a) Bu^{t}OK, DMF, 0 °C, (b) **7**, 96%; (ii) $Pd(OAc)_2$, K_2CO_3, Bu_4NBr, DMF, 110 °C, 7 h, 91%; (iii) H_2/Pd/C, 83%.

type intermediate **12**. On the other hand, as shown in Scheme 5, the isolation of **11** under strong acid condition suggests that the initial step in the conversion of **10** to **11** involves the intermediacy of the corresponding *para*-quinone methide **13**, which underwent the favoured 6-*exo*-*trig* cyclisation.[21] Similarly, compound **9b** could be formed from the corresponding benzazepinone **6** via intermediacy of the iminium ion **14** undergoing the favoured *6-endo-trig* cyclisation.[22]

As a result of the undesirable acid-mediated cyclisation of **10** to **11**, we now envisioned that the desired compound **9a** could be more readily prepared from the *N*-alkylbenzazepinone **8** via Heck reaction. We decided to investigate the use of Heck reaction of *N*-alkylbenzazepinone **8**. Compound **8** was synthesised by the corresponding alkylation reaction of benzazepinone **4** with potassium *tert*-butoxide and 2-iodo-3,4-dimethoxybenzyl bromide **7**[23] as outlined in Scheme 6. Firstly, we examined the use of Pd(0) in the Heck reaction of *N*-alkylbenzazepinone **8** to form the dehydroisoindolinobenzazepinone **15**. Initially, conditions employing $Pd(PPh_3)_4$, Et_3N in DMF at 110 °C for 24 h was explored for the Heck reaction of benzazepinone **8**. Unfortunately, the reaction did not provide the desired product **15**. We then attempted to use Pd(II) in the presence of $Bu_4N^+Br^-$ as an additive.[6,24] Treatment of *N*-alkylbenzazepinone **8** with $Pd(OAc)_2$ in DMF containing K_2CO_3 (2 equiv) and $Bu_4N^+Br^-$ (1 equiv) at 110 °C for 2 h provided the desired tetracyclic ring structure of dehydroisoindolinobenzazepinone **15** in 91% yield. Subsequent palladium-catalysed hydrogenation of the dehydroisoindolinobenzazepinone **15** readily furnished the corresponding isoindolinobenzazepinone **9a** in 83% yield.

3. Conclusion

Isoindolinobenzazepinone **9a** and isoquino[1,2-*b*][3]benzazepinone **9b** were successfully synthesised in three and two steps from benzazepinone **4** with either benzyl bromide **7** or phenethyl iodide **5** in 74% and 66% overall yields, respectively. The key step for **9a** was the Heck reaction that produced dehydroisoindolinobenzazepinone **15** in 91% yield, which, upon catalytic hydrogenation, furnished isoindolinobenzazepinone **9a**. On the other hand, acid-mediated cyclisation reaction of *N*-alkylbenzazepinone **6** proceeded to provide homoprotoberberine **9b** in 85% yield. Both benzazepinone alkaloids were synthesised from the same key intermediate **4**, and both phenethyl iodide **5** and benzyl bromide **7** were easily prepared from commercially available starting materials.



Scheme 5. Proposed mechanism for tetracycles **9b** and **11**.

4. Experimental

4.1. General

Melting points were determined on a Electrothermal 9100 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 using deuterochloroform and dimethyl sulfoxide-d_6 as solvents. IR spectra were run on a Perkin Elmer system 2000 FT-IR and JASCO A-302 spectrometers. Mass spectra were recorded on a Finnigan INCOS 50 and Bruker Daltonics (microTOF). Elemental analyses were performed on Perkin Elmer Elemental Analyzer 2400 CHN. Column and preparative thin layer chromatographic purifications were carried out using silica gel (70–230 mesh ASTM) and on a silica gel E. Merck PF_{254}, respectively.

4.2. 7,8-Dimethoxy-1,3-dihydro-2*H*-benzazepin-2-one (4)

Oxalyl chloride (3.25 mL, 38.4 mmol) was added slowly to a stirred solution of homoveratric acid (5.00 g, 25.5 mmol) and *N*,*N*-dimethylformamide (3 drops) in benzene (20 mL). The reaction mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure to give the crude acid chloride. To a mixture of aminoacetaldehyde dimethyl acetal (2.75 mL, 25.5 mmol) in CH_2Cl_2 (50 mL) and Na_2CO_3 (5.40 g, 25.5 mmol) in water (15 mL) was added the solution of acid chloride in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 2 h. Water (50 mL) was added and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to give the crude acetal amide **3**, which was used in the next step without further purification.

When HCl/AcOH was utilised, the crude acetal amide **3** was dissolved in glacial AcOH (15 mL) and concd HCl (15 mL) was then added dropwise. The reaction mixture was allowed to stir at room temperature for 17 h. The reaction mixture was then poured into a mixture of ice and water, stirred for 30 min, filtered and washed with water. Benzazepinone **4** (4.16 g, 19.1 mmol, 75%) was obtained as a white solid.

When H_2SO_4/AcOH was used, the crude acetal amide **3** was dissolved in glacial AcOH (20 mL) and concd H_2SO_4 (4 mL) was then added dropwise. The reaction mixture was allowed to stir at room temperature for 17 h. The reaction mixture was then poured into a mixture of ice and water, stirred for 30 min, filtered and washed with water. Benzazepinone **4** (2.53 g, 11.5 mmol, 45%) was obtained.

When HCO_2H was used, the crude acetal amide **3** was refluxed in HCO_2H (20 mL) for 4 h. The reaction mixture was poured into water containing crushed ice and the aqueous phase was then extracted with CH_2Cl_2 (3×15 mL). The combined organic solution was washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a yellow solid, which was recrystallised in ethyl acetate to give benzazepinone **4** (2.24 g, 10.2 mmol, 40%).

Benzazepinone **4** (white solid). Mp 236–238 °C (lit.[17] 235–237 °C); IR (KBr) ν_{max} 1667, 1634, 1514, 1414 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.27 (s, 2H, CH_2CO), 3.73 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.16 (dd, J=9.2, 4.0 Hz, 1H, CH=C*H*NH), 6.23 (d, J=9.2 Hz, 1H, C*H*=CHNH), 6.83 (s, 1H, Ar*H*), 6.84 (s, 1H, Ar*H*), 9.45 (d, J=4.0 Hz, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 42.6, 55.56, 55.61, 110.3, 112.0, 114.4, 123.4, 124.2, 127.2, 147.6, 149.1, 168.7; LRMS (EI) m/z (rel intensity) 220 (M+H$^+$, 14), 219 (M$^+$, 100), 176 (54); HRMS (TOF) calcd for $C_{12}H_{14}NO_3$[M+H]$^+$ 220.0968, found: 220.0972.

4.3. General procedure for the synthesis of *N*-alkylbenzazepinones (6), (8) and (10)

Benzazepinone **4** dissolved in DMF was slowly added into a solution of potassium *tert*-butoxide in DMF (10 mL) at 0 °C and then stirred at this temperature for 30 min. To the reaction mixture was slowly added phenethyl iodide **5**, benzyl bromide **7** or 3,4-dimethoxybenzyl chloride as a solution in DMF (5 mL) and then the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured on crushed ice containing NH_4Cl (50 mL). The aqueous phase was extracted with EtOAc, washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude product, which was further purified by column chromatography on silica (40% EtOAc/hexane), to provide the corresponding product *N*-alkylbenzazepinones.

When 7,8-dimethoxy-1,3-dihydro-2*H*-benzazepinone **4** (1.00 g, 4.56 mmol), potassium *tert*-butoxide (0.77 g, 6.84 mmol), and phenethyl iodide **5** (2.62 g, 6.84 mmol) were reacted, 3-[2-(3,4-dimethoxyphenyl)ethyl]-7,8-dimethoxy-1,3-dihydrobenzo-[*d*]azapin-2-one **6** (1.35 g, 3.51 mmol, 77%) was obtained as a viscous oil. IR (KBr) ν_{max} 1651, 1516, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.76 (t, J=7.2 Hz, 2H, CH_2CH$_2$N), 3.43 (s, 2H, CH_2CO), 3.73 (s, 3H, OCH_3), 3.76 (t, J=7.2 Hz, 2H, CH$_2$CH_2N), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.01 (d, J=9.1 Hz, 1H, C*H*=CHN), 6.21 (d, J=9.1 Hz, 1H, CH=C*H*N), 6.56 (d, J=1.7 Hz, 1H, Ar*H*), 6.62 (dd, J=8.1, 1.7 Hz, 1H, Ar*H*), 6.68 (s, 1H, Ar*H*), 6.71 (d, J=8.1 Hz, 1H, Ar*H*), 6.80 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.3, 43.2, 50.3, 55.6, 55.8, 55.9, 109.4, 111.1, 112.1, 116.7, 120.7, 124.6, 126.4, 128.6, 131.1, 147.5, 147.9, 148.7, 149.8, 167.5; LRMS (EI) m/z (rel intensity) 385 (M$^+$+2, 10), 384 (M+H$^+$, 44), 383 (M$^+$, 100), 219 (87), 176 (29); HRMS (TOF) calcd for $C_{22}H_{26}NO_5$[M+H]$^+$ 384.1805, found: 384.1810.

When 7,8-dimethoxy-1,3-dihydro-2*H*-benzazepinone **4** (0.20 g, 0.91 mmol), potassium *tert*-butoxide (0.15 g, 1.37 mmol), and bromomethyl-2-iodo-4,5-dimethoxybenzene **7** (0.49 g, 1.37 mmol) were reacted, 3-(2-iodo-4,5-dimethoxybenzyl)-7,8-dimethoxy-1,3-dihydrobenzo[*d*]-azepin-2-one **8** (0.45 g, 0.89 mmol, 98%) was obtained as a white solid. Mp 150–151 °C; IR (KBr) ν_{max} 1670, 1507, 867 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.18 (s, 3H, OCH_3), 3.48 (s, 2H, CH_2CO), 3.73 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2N), 5.96 (s, 1H, Ar*H*), 6.12 (d, J=9.0 Hz, 1H, C*H*=CHN), 6.34 (d, J=9.0 Hz, 1H, CH=C*H*N), 6.66 (s, 1H, Ar*H*), 6.79 (s, 1H, Ar*H*), 7.10 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.8, 54.9, 55.2, 55.98, 56.02, 56.1, 85.3, 109.4, 109.9, 111.2, 118.4, 121.4, 124.8, 126.3, 128.3, 131.2, 148.1, 148.5, 149.5, 150.0, 167.9; LRMS (EI) m/z (rel intensity) 496 (M+H$^+$, 3), 495 (M$^+$, 5), 369 (25), 368 (100), 277 (39). Anal. Calcd for $C_{21}H_{22}NO_5I$: C, 50.92; H, 4.48; N, 2.83. Found: C, 50.94; H, 4.21; N, 2.40.

When 7,8-dimethoxy-1,3-dihydro-2*H*-benzazepinone **4** (1.00 g, 4.56 mmol), potassium *tert*-butoxide (0.77 g, 6.84 mmol), and 3,4-dimethoxybenzyl chloride (1.28 g, 6.84 mmol) were reacted, 3-(3,4-dimethoxybenzyl)-7,8-dimethoxy-1,3-dihydrobenzo[*d*]azapin-2-one **10** (1.43 g, 3.87 mmol, 86%) was obtained as a white solid. Mp 61–63 °C; IR (KBr) ν_{max} 1667, 1518, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.53 (s, 2H, CH_2CO), 3.66 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2N), 6.20 (d, J=9.1 Hz, 1H, C*H*=CHN), 6.36 (d, J=9.1 Hz, 1H, CH=C*H*N), 6.54 (d, J=1.7 Hz, 1H, Ar*H*), 6.69 (dd, J=8.1, 1.7 Hz, 1H, Ar*H*), 6.72 (s, 1H, Ar*H*), 6.77 (d, J=8.1 Hz, 1H, Ar*H*), 6.84 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.0, 50.3, 55.2, 55.4, 55.7, 55.9, 109.3, 110.3, 110.9, 111.1, 117.6, 119.5, 124.6, 126.3, 128.0, 129.4, 147.9, 148.1, 148.9, 149.8, 167.8; LRMS (EI) m/z (rel intensity) 370 (M$^+$+1, 16), 369 (M$^+$, 66), 151 (100); HRMS (FAB) calcd for $C_{21}H_{23}NO_5$[M+H]$^+$ 369.1576, found: 369.1585.

4.4. 2,3,11,12-Tetramethoxy-5,9,14,14a-tetrahydro-6*H*-benzo[4,5]azepino[2,1-*a*]isoquinolin-8-one (9b)

When HCl/AcOH was used, 3-[2-(3,4-dimethoxoyphenyl)ethyl]-7,8-dimethoxy-1,3-dihydrobenzo[*d*]azapin-2-one **6** (0.50 g, 1.30 mmol) was dissolved in acetic acid (5 mL). To this mixture, concd HCl (5 mL) was

then slowly added dropwise and the entire reaction mixture was subsequently stirred for different amounts of time (2, 4, 6, 8, 10 and 17 h). After that, the reaction was quenched with water, neutralised with 25% NH_4OH and the aqueous phase extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered and the solvent evaporated under reduced pressure to give the crude product ,which was purified by preparative TLC (60% EtOAc/hexane) to give the desired isoquinolinobenzazepinone **9b**. Similarly, when H_2SO_4/AcOH was utilised, concd H_2SO_4 (1 mL) was employed instead of concd HCl for 2, 4, 6, 8, 10 and 17 h. When formic acid was used, compound **6** was refluxed in formic acid (10 mL) for 1 and 2 h. From all cases, the desired product **9b** was obtained from the crude product by preparative TLC (60% EtOAc/hexanes) as a white solid (see Table 1 for yields). Mp 185 °C; IR (KBr) ν_{max} 1645, 1521, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.85 (t, J=6.0 Hz, 2H, CH_2CH$_2$N), 3.20 (dd, J=11.4, 3.5 Hz, 1H, CH_2CHN), 3.27 (dd, J=11.4, 3.5 Hz, 1H, CH_2CHN), 3.44 (d, J=15.0 Hz, 1H, CH_2CO), 3.61 (dt, J=13.0, 6.0 Hz, 1H, CH$_2$CH_2N), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.03 (dt, J=13.0, 6.0 Hz, 1H, CH$_2$CH_2N), 4.50 (d, J=15.0 Hz, 1H, CH_2CO), 5.43 (dd, J=11.4, 3.5 Hz, 1H, CH$_2$CHN), 6.57 (s, 1H, ArH), 6.66 (s, 1H, ArH), 6.70 (s, 1H, ArH), 6.73 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.1, 37.8, 41.0, 42.6, 54.2, 55.82, 55.85, 55.88, 56.04, 109.6, 111.2, 113.1, 114.0, 123.0, 127.3, 127.7, 147.2, 147.8, 147.9, 148.0, 171.8; LRMS (EI) m/z (rel intensity) 384 ($M+H^+$, 21), 383 (M^+, 79), 355 (23), 192 (100), 190 (84). Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.88; H, 6.64; N, 3.49.

4.5. 2,3,10,11-Tetramethoxy-5,13-dihydro-8*H*-6,13-methanodibenzo[*c*,*f*]azonin-7-one (11)

3-(3,4-Dimethoxybenzyl)-7,8-dimethoxy-1,3-dihydrobenzo[*d*]azepin-2-one **10** (0.30 g, 0.81 mmol) was refluxed in triflic acid (0.30 mL, 3.44 mmol) in CH_2Cl_2 (5 mL) for 2 h. At that time water (20 mL) was added and then the mixture was extracted with CH_2Cl_2 (2×20 mL). The combined CH_2Cl_2 layers were washed with 10% sodium carbonate and water, and dried (Na_2SO_4). After evaporation of the solvent, the obtained solid was recrystallised from methanol/diethyl ether and CH_2Cl_2 to give colourless needles of tetracycle **11** (0.18 g, 0.49 mmol) in 64% yield. Mp 306 °C (decomposed); IR (KBr) ν_{max} 1656, 1521, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.42 (d, J=15.0 Hz, 1H, CH_2N), 3.69 (dd, J=14.5, 3.4 Hz, 1H, CHCH_2N), 3.83 (s, 6H, 2×OCH_3), 3.90 (s, 3H, OCH_3), 3.93 (d, J=3.4 Hz, 1H, CHCH$_2$N), 3.94 (s, 3H, OCH_3), 4.07 (d, J=15.8 Hz, 1H, CH_2CO), 4.48 (d, J=15.0 Hz, 1H, CH_2N), 4.57 (d, J=14.5 Hz, 1H, CHCH_2N), 5.38 (d, J=15.8 Hz, 1H, CH_2CO), 6.56 (s, 1H, ArH), 6.60 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.06 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 40.3, 42.3, 46.5, 47.6, 55.84, 55.88, 55.94, 56.00, 109.2, 112.0, 113.8, 114.7, 122.9, 127.1, 129.6, 132.4, 147.5, 147.6, 147.7, 148.0, 174.9; LRMS (EI) m/z (rel intensity) 370 (M^++H^+, 25), 369 (M^+, 100), 340 (43), 309 (43), 281 (54). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.42; H, 6.52; N, 3.60.

4.6. 2,3,10,11-Tetramethoxy-5,8,13,13a-tetrahydrobenzo-[4,5]azepino[2,1-*a*]isoindol-7-one (15)

A mixture of 3-(2-iodo-4,5-dimethoxybenzyl)-7,8 dimethoxy-1,3-dihydrobenzo[*d*]azepin-2-one **8** (0.10 g, 0.20 mmol), $Pd(OAc)_2$ (0.0045 g, 0.02 mmol, 10 mol %), K_2CO_3 (0.056 g, 0.40 mmol), and $Bu_4N^+Br^-$ (0.065 g, 0.2 mmol) in dry DMF (10 mL) was heated at 110 °C for 2 h. The reaction mixture was quenched with aq NH_4Cl (10 mL), filtered and the aqueous phase was then extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure to dryness. The crude product was purified by preparative TLC (60% EtOAc/hexanes) to afford dehydroisoindolinobenzazepinone **15** (67 mg, 0.18 mmol, 91%) as a white solid. Mp 214–215 °C; IR (KBr) ν_{max} 1655, 1608, 1517 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.46 (s, 2H, CH_2CO), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.77 (s, 2H, CH_2N), 6.54 (s, 1H, CH=C–N), 6.73 (s, 2H, ArH), 6.77 (s, 1H, ArH), 7.02 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.7, 53.1, 55.97, 56.0, 56.2, 102.4, 104.2, 105.4, 109.8, 112.0, 121.7, 127.6, 128.4, 129.2, 139.0, 148.2, 149.3, 149.8, 150.7, 168.0; LRMS (EI) m/z (rel intensity) 369 (M^++2, 4), 368 ($M+H^+$, 26), 367 (M^+, 100), 353 (15), 352 (60). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.51; H, 5.36; N, 3.52.

4.7. 2,3,10,11-Tetramethoxy-5,8,13,13a-tetrahydrobenzo-[4,5]azepino[2,1-*a*]isoindol-7-one (9a)

To a stirred solution of dehydroindolinobenzazepinone **15** (0.05 g, 0.14 mmol) in CH_2Cl_2 containing AcOH (10 drops), 10% Pd on charcoal (0.054 g) was added. The mixture was hydrogenated with a hydrogen balloon at 1 atm by stirring at room temperature for 20 h. Catalyst residue was removed by filtration and the residue was washed with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), filtered and concentrated to give the crude product, which was purified by preparative TLC (60% EtOAc/hexanes) to provide isoindolinobenzazepinone **9a** (0.042 g, 0.12 mmol, 83%) as a white solid. Mp 264.0 °C (decomposed); IR (KBr) ν_{max} 1635, 1611, 1523, 1465, 1451, 1433 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.02 (dd, J=16.9, 12.0 Hz, 1H, CH_2CHN), 3.40 (d, J=16.9 Hz, 1H, CH_2CHN), 3.46 (d, J=15.0 Hz, 1H, CH_2CO), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.31 (d, J=15.0 Hz, 1H, CH_2CO), 4.69 (d, J=15.4 Hz, 1H, CH_2N), 4.85 (d, J=15.4 Hz, 1H, CH_2N), 5.53 (d, J=12.0 Hz, 1H, CH$_2$CHN), 6.57 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.78 (s, 1H, ArH), 6.82 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 40.7, 43.0, 51.0, 55.81, 55.84, 56.04, 56.10, 61.4, 105.0, 105.7, 113.2, 114.0, 122.6, 126.8, 127.2, 132.0, 147.2, 147.8, 149.2, 149.6, 170.5; LRMS (EI) m/z (rel intensity) 371 (M^++2, 2), 370 ($M+H^+$, 14), 369 (M^+, 58), 178 (22), 177 (100), 165 (21). HRMS (TOF) Calcd for $C_{21}H_{24}NO_5[M+H]^+$ 370.1649, found: 370.1656.

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