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Graphical Abstract

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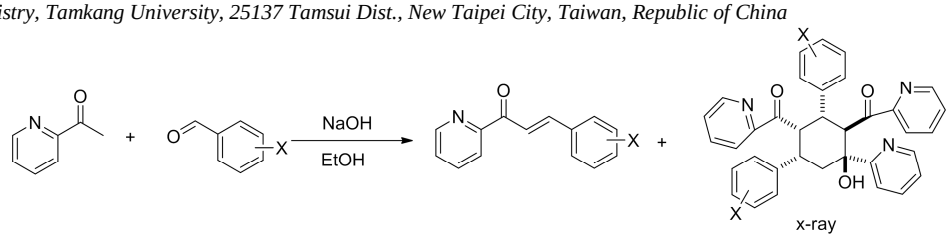

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ABSTRACT

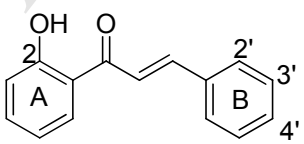
A systematic study of the synthesis of halo-substituted azachalcones was conducted. During the reaction course, we obtained not only the target azachalcones, but also penta-substituted cyclohexanols, which are seldom reported in the literatures. The formation of penta-substituted cyclohexanols was dependent on equivalents of base used and reaction time. Their formation followed a tandem reaction: Claisen-Schmidt condensation, three Michael reactions, retro-aldol reaction, and intramolecular aldol cyclization.

1. Introduction

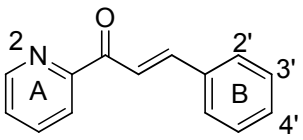
Chalcones are precursors in the synthesis of flavonoids and are found pervasively in natural plants. They exhibit a wide variety of biological activity such as antibacterial[1], antifungal[1b], antimalarial[2], antioxidant[3], antitumor[4] and antiinflammatory[5] properties. Chalcones possess a 1,3-diphenyl-2*E*-propene-1-one framework (Figure 1). The most common and widely used strategy in synthesis of chalcones or their analogues is Claisen-Schmidt condensation.

Another non-naturally occurring chalcone-like family is the azachalcones in which annular carbons in either the A or B ring are replaced by nitrogen atom(s) (Figure 1). Azachalcones exhibit biological properties similar to those of chalcones.[6] Further, they have been used in studies of asymmetric Diels-Alder reactions.[7] The target azachalcones synthesized in this article are from 2-acetylpyridine with a series of halobenzaldehydes under Claisen-Schmidt condensation. We obtained not only the target azachalcones but also unexpected products. These unexpected products were later confirmed to be unusual penta-substituted cyclohexanols by NMR experiments or X-ray analysis. There have been very few reports that mention these cyclohexanol derivatives.[8] In order to clarify their formation, herein we reinvestigate their syntheses and discuss their formation mechanism.

Figure 1 Representative structures of chalcone and C-2 azachalcone



Chaclone



Azachaclone

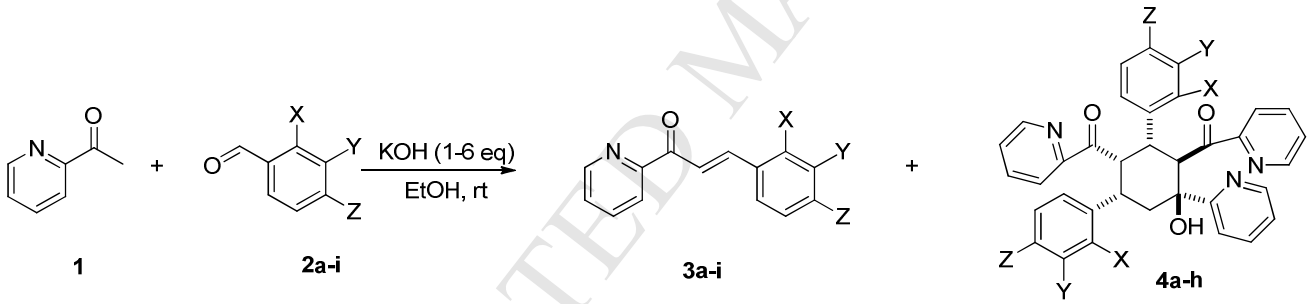
2. Results and discussion

We synthesized a series of B-ring halo-substituted chalcones for evaluation of their biological activity.[9] The synthesis of azachalcones using Claisen-Schmidt condensation[6a,7d,e,8,10,11] (Scheme 1) can be carried out either under catalytic conditions[8,11] or in the presence of a slightly excess amount of base (1–3 equivalent of NaOH or KOH).[6a,10] Either MeOH or EtOH was used as a solvent. Reaction temperature was kept either at 0 to 10 ^{o}C for 2–5h[7d,e,10d,e] or at room temperature overnight.[6a,10b,c] Some reports describe procedures but without providing yields[6a,10]; others describe procedure whereby the expected azachalcones are obtained at moderate[10f] to high yields.[7d,e,11]

We tried to replicate the above-mentioned conditions using stoichiometric amounts of base; however, we were not able to obtain the expected azachalcones at as high yields as described. Only moderate to low yields were obtained. We therefore carefully surveyed the amounts of base used in the reaction. Initially, the mixture concentration was 0.35M based on **1** in EtOH and an aqueous 8M KOH solution (1 equivalent) was used as a base (Table 1, entry 1). Reaction completed within an hour and compounds **3a-c** were obtained at moderate to low yields. We observed longer reaction times to result in much lower yields of **3a-c** (Table 1, entry 2). When two equivalents of base were used, not only chalcone **3a** but also an unexpected penta-substituted cyclohexanol **4a** were obtained (Table 1, entry 3). A structure similar to that of **4a** has been reported as a side product at a low yield (8%) or as a major product during the preparation of 4'-*p*-Tolyl-2,2':6',2"-terpyridine.[8a] However, neither detailed mechanisms nor procedures have been explicitly described. This penta-substituted cyclohexanol **4a** was well-resolved by NMR spectroscopy. Normally, an equatorial hydrogen is more deshielding than a gemenial axial hydrogen in cyclohexane. However, the opposite result was observed for H_{5a} and H_{5e} of **4a** (Figure 2), which was probably due to the equatorial hydrogen being in a shielding position on an aromatic ring. Also, the NOESY spectrum observed between H_3 and H_{5a} was as indicated in Figure 2. The structure of compound **4a** was further confirmed by X-ray crystallography[12] (Figure 3). We conclude from Table 1 that higher concentrations of base and shorter reaction times produced the target azachalcones at moderate yields (entries 3, 5, 7). Once the reaction time was extended to 4-5h, the yields of isolated azachalcones dropped dramatically, and the penta-substituted **4a-c** were isolated as major products (Table 1, entries 6, 8).

A plausible mechanism for the formation **4a** is depicted in Figure 4. Its formation involved tandem Claisen-Schmidt condensation, three Michael reactions (**3a–7**), a retro-aldol reaction (**8**) and an intramolecular aldol reaction (**9**).

During the prolonged reaction course, we observed gradually increasing amounts of a polar mixture once the target chalcones were formed (Table 1, *vide infra* Tables 2 and 3). This polar mixture was purified by column chromatography to isolate **4a-h** along with a complex mixture that could not be identified. The unidentified complex mixture was assumed to be a combination of incomplete Michael reaction and uncyclized products which resulted in the low yields of **3a-i** as well as **4a-h**. We do not exclude the possibility of the formation of **4'a-i**[8a] (Figure 2), however, we were not able to isolate any of these compounds.



a. X=H, Y=H, Z=F **d.** X=H, Y=F, Z=H **g.** X=F, Y=H, Z=H
b. X=H, Y=H, Z=Cl **e.** X=H, Y=Cl, Z=H **h.** X=Cl, Y=H, Z=H
c. X=H, Y=H, Z=Br **f.** X=H, Y=Br, Z=H **i.** X=Br, Y=H, Z=H

Scheme 1. Synthesis of azachaclones **3a-i** and penta-substituted cyclohexanols **4a-h**.

Table 1. Synthesis of 4'-haloazachaclones **3a-c** and penta-substituted cyclohexanols **4a-c**

Entry	KOH (eq)	3a:4a (%)	Time	3b:4b (%)	Time	3c:4c (%)	Time
1	1	51:0[a]	30 min	35:0[a]	45 min	32:0[a]	1 h
2	1	35:0	4 h	19:0	5 h	12:0	5 h
3	2	57:1[a]	35 min	43:2[a]	40 min	15:6[a]	75 min
4	2	22:3	4 h	21:5	5 h	4:12	5 h
5	4	50:9[a]	15 min	44:4[a]	20 min	15:3[a]	45 min
6	4	9:9	4 h	0:13	5 h	0:23	5 h
7	6	54:4[a]	15 min	41:4[a]	15 min	37:20[a]	15 min
8	6	0:6	4 h	0:11	5 h	0:18	5 h

[a] Isolated yields all based on the complete consumption of **1**.

Figure 2 Stereochemistry confirmation by NOESY

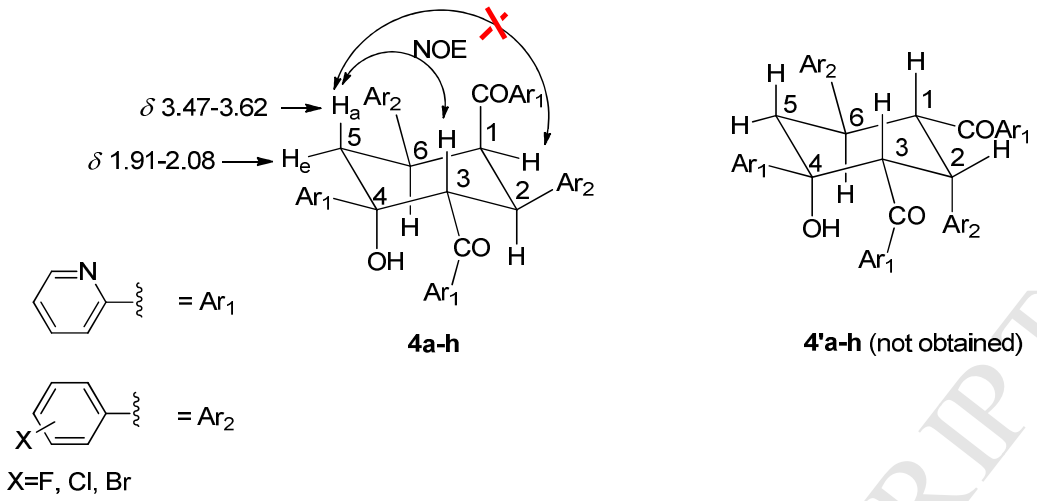
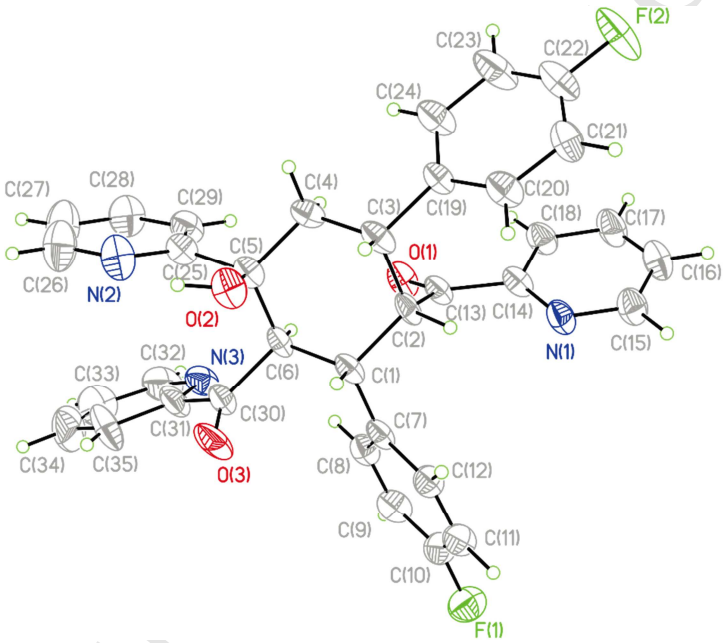


Figure 3 Structure of **4a** obtained by X-ray diffraction analysis



***** Table Correlating NMR and X-ray carbon numbers

NMR	C_1	C_2	C_3	C_4	C_5	C_6
X-ray	=C(2)	=C(1)	=C(6)	=C(5)	=C(4)	=C(3)

The same conditions were applied to synthesis of 3'-haloazachalcones (Table 2). With one equivalent of base and relatively short times, compounds **3d-f** were obtained at moderate to low yields (entry 1). No penta-substituted cyclohexanols were obtained with longer reaction times except **4f** (entry 2). When two or more equivalents of base were used, yields of **3d-f** decreased and **4d-f** increased with longer reaction times (entry 3–8). The results show a similar to that trend in Table 1.

We also studied the 2'-haloazachalcones' synthesis (Table 3). Our observations were consistent with the trends shown in Tables 1 and 2. Yields of **4g** and **4h** increased under extended reaction times with 2, 4, and 6 equivalents base used (entries 4, 6, 8). No penta-substituted cyclohexanol derivative **4i** was formed from condensation between **1** and **2i** even when six equivalents of base were used, probably owing to the larger atom size of bromine in the vicinity of the reaction center restricting cyclization.

Figure 4 Plausible mechanism for formation, for example, of penta-substituted cyclohexanol **4a**

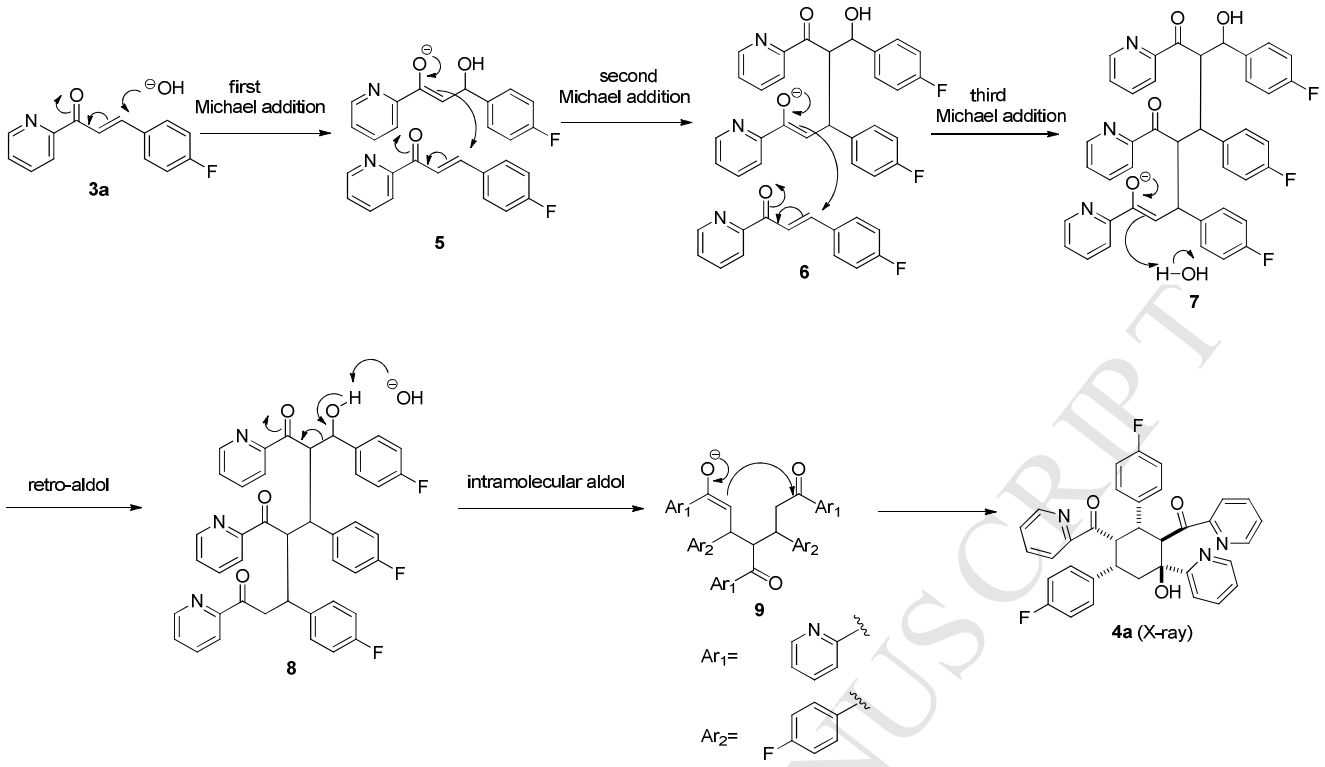


Table 2. Synthesis of 3'-haloazachalcones **3d-f** and penta-substituted cyclohexanols **4d-f**

Entry	KOH (eq)	3d:4d (%)	Time	3e:4e (%)	Time	3f:4f (%)	Time
1	1	28:0[a]	100 min	46:0[a]	30 min	46:0[a]	20 min
2	1	12:0	8 h	43:0	3 h	24:10	5 h
3	2	25:2[a]	1 h	44:0[a]	45 min	52:0[a]	40 min
4	2	0:13	7 h	36:6	3 h	0:18	5 h
5	4	37:5[a]	20 min	27:2[a]	20 min	48:2[a]	10 min
6	4	0:16	6 h	21:14	3 h	0:30	5 h
7	6	17:4[a]	20 min	36:1[a]	30 min	44:1[a]	5 min
8	6	0:9	6 h	10:10	3 h	0:26	5 h

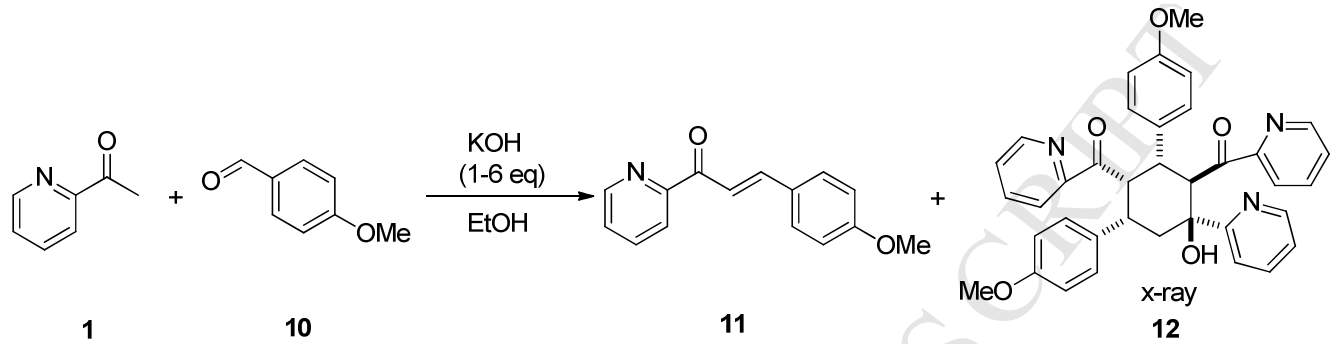
[a] Isolated yields all based on the complete consumption of **1**

Table 3. Synthesis of 2'-haloazachaclones **3g-i** and penta-substituted cyclohexanols **4g,h**

Entry	KOH (eq)	3g:4g (%)	Time	3h:4h (%)	Time	3i:4i (%)	Time
1	1	35:0[a]	45 min	56:0[a]	1 h	41:0[a]	20 min
2	1	26:0	8 h	38:0	8 h	63:0	5 h
3	2	43:6[a]	45 min	58:4[a]	50 min	51:0[a]	20 min
4	2	21:21	8 h	20:20	8 h	62:0	5 h
5	4	28:4[a]	25 min	42:5[a]	15 min	54:0[a]	15 min
6	4	19:12	5 h	0:31	8 h	65:0	5 h
7	6	45:4[a]	10 min	47:2[a]	20 min	50:0[a]	10 min
8	6	15:14	5 h	0:20	8 h	44:0	5 h

[a] Isolated yields all based on the complete consumption of **1**.

In order to test whether the inductive effect might influence the formation of penta-substituted cycloheanol, we replaced the para-halo substituents in B ring with an electron-donating group (OMe, **10**) and reacted under the same conditions as in Scheme 1 (Scheme 2). Compound **11** was received in high yields (87–94%) once compound **1** was completely reacted (Table 4, entries 1, 4, 7, and 10). Unlike the results in Tables 1–3, the extended reaction time (4–8 h) did not reduce too much amount of **11,** which received in moderate yields (Table 4, entries 2, 3, 5, 6, 8, 9, 11 and 12)**.** The penta-substituted cyclohexanol **12** was also obtained but in low yields (6–11%) and its structure was confirmed by x-ray crystallography (Figure 5).[13] Apparently penta-substituted cyclohexanols **4a-h** and **12** were inevitable formation under slightly excess basic conditions but were always in low yields. It is also noticed that halo-substituted azachalcones **3a-i** were proceeded subsequent Michael reaction faster than that of **11** thus led to low yields of **3a-i**. This might be due to the inductive effect of halo substituent in increasing the electron deficiency of β-carbon for accelerating Michael reaction.



Scheme 2. Synthesis of azachaclone **11** and penta-substituted cyclohexanol **12**.

Table 4. Synthesis of 4'-methoxyazachaclone **11** and penta-substituted cyclohexanol **12**

Entry	KOH (eq)	11:12 (%)	Time
1	1	94:0[a]	10 min
2	1	83:6	4 h
3	1	68:9	8 h
4	2	89:0[a]	3 min
5	2	64:7	4 h
6	2	62:9	8 h
7	4	94:0[a]	2 min
8	4	79:10	4 h
9	4	64:11	8 h
10	6	87:0[a]	1 min
11	6	64:10	4 h
12	6	64:11	8 h

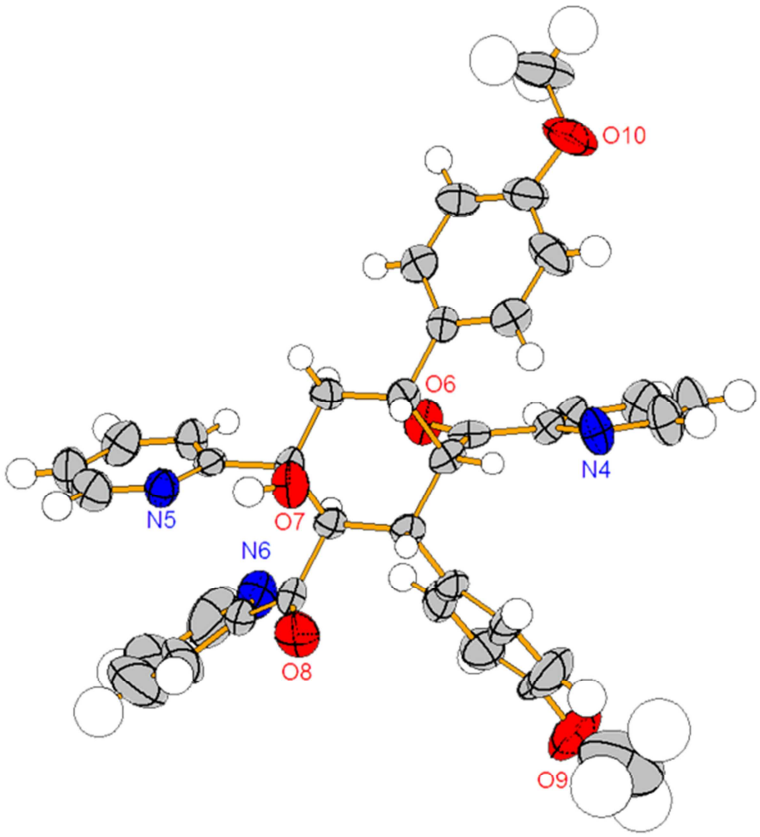
[a] Isolated yields all based on the complete consumption of **1**.

Conclusion

Little attention has been paid to the formation of penta-substituted cyclohexanols during the synthesis of azachalcones *via* Claisen-Schmidt condensation under stoichiometric conditions or in the presence of a slightly excess amount of base. In our systematic studies, the more equivalents of base and prolonged reaction times might be needed to obtain the distinctive structures **4a-h** and **12.** We also observed that yields of **4a-h** and **12** were not improved even after reaction stirring for 24h. It is clear that compounds **4a-h** were obtained from a tandem reaction of **3a-i** once they were formed that ultimately led to low yields of **3a-i**. This same mechanism as in Figure 4 also occurred during the course in synthesis of **11** and **12**. The differences between Scheme 1 and Scheme 2 were the substituted groups in B ring as well as the yields of **3a-i** and **11**. We believe that more equivalents of base induced this tandem reaction, resulting in products **4a-h** and **12** which may have been neglected in reports of synthesis of azachalcones owing to their low yields. These products are distinctive because we do not obtain penta-substituted cyclohexanols when we synthesize chalcones. Thus the nitrogen atom at 2-position of A ring must play an important

directing role of formation of cyclized adducts. This is the first time that the mechanism of formation of these unique structures **4a-h** and **12** has been clearly demonstrated.

Figure 5 Structure of **12** obtained by X-ray diffraction analysis



* Table Correlating NMR and X-ray carbon numbers

NMR	C_1	C_2	C_3	C_4	C_5	C_6
X-ray	=C(2)	=C(1)	=C(6)	=C(5)	=C(4)	=C(3)

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

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3. Experimental

All chemicals were purchased from either Alfa or Aldrich and used without purification except where otherwise stated. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Bruker 600 spectrometer. Chemical shifts were reported in ppm and referenced to the residue of solvent: ($CDCl_3$: 7.26 ppm for ^{1}H; 77.0 ppm for ^{13}C). Melting points were determined on a Fargo MP-2D apparatus and not corrected. HRMS were recorded on a Finnigan MAT-95S instrument. The IR spectra were recorded
on Bruker Tensor 27 in KBr.

4.1 General procedure of Claisen-Schmidt condensation

To a stirred solution of 2-acetylpyridine (0.100 mL, 0.108 g, 0.890 mmol), for example, in EtOH (2.5 mL) was added aqueous 8M KOH (1 to 6 equivalent). This mixture was stirred at 0 ^{o}C for 10 min, followed by addition of the corresponding aldehyde (1.5 equivalent) dropwise at the same temperature. The mixture was gradually warmed up to room temperature until 2-acetylpyridine was completely consumed according to TLC

analysis. At the end of the reaction time, the mixture was quenched by 2N HCl, diluted with H_2O and extracted with CH_2Cl_2. **Method A**: The organic layer was dried over $MgSO_4$ and purified by flash column chromatography.

Method B: An alternative method for purification of **4a-h** and **12**: The above-mentioned CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated. To this mixture was added 95% EtOH and this mixture was sonicated for a few minutes until the solution turned from clear to turbid. The mixture was filtrated and the solid washed with 95% EtOH. The resulting sticky solid was collected and dissolved in EtOAc then sonicated for a few minutes until a white solid formed. The solid was collected to give pure **4a-h** without column chromatography. Slightly lower yields of **4a-h** were obtained to compare with purification by column chromatography.

4.2 (*E*)-3-(4-Fluorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3a). Purification by flash column chromatography (230–400 mesh SiO_2, CH_2Cl_2:Hexanes = 1:3, R_f = 0.3) provided compound **3a** as a white solid. Mp 90–92 °C (*lit.*[10e] 84–86 °C). The eluent was changed (EtOAc:Hexanes = 1:4) to produce **4a** (EtOAc:Hexanes=1:4, R_f = 0.25) as a solid which was recrystallized from EtOAc/Hexanes. The solid was filtrated and washed with hexanes and CH_2Cl_2 to give **4a** as a white crystalline solid. IR (cm^{-1}) 3082, 1687, 1638, 1522, 1422, 1346, 1247, 1038, 803. For (**3a**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (ddd, *J* = 4.7, 1.7, 1.0 Hz, 1H), 8.23 (d, *J* = 16.0 Hz, 1H), 8.18 (ddd, *J* = 5.3, 2.0, 1.0 Hz, 1H), 8.04–7.85 (m, 2H), 7.75–7.70 (m, 2H), 7.50–7.47 (m, 1H), 7.10 (t, *J* = 11.5 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.2, 164.1 ($^1J_{C\text{-}F}$ = 251.0 Hz), 154.1, 148.8, 143.4 (X2), 137.1, 131.3 ($^4J_{C\text{-}F}$ = 3.0 Hz), 130.7 ($^3J_{C\text{-}F}$ = 9.0 Hz, X2), 126.9, 122.9, 120.6, 116.0 ($^2J_{C\text{-}F}$ = 22.5 Hz). HRMS (ESI) calculated for $C_{14}H_{10}FNO$ $[M]^+$ 227.0746. Found: 227.0744.

4.3 (*E*)-3-(4-Chlorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3b). Purification: same as for **3a**. Mp 92–94 °C (*lit.*[10e] 100–102 °C). A white solid. IR (cm^{-1}) 3025, 1687, 1631, 1515, 1356, 1038, 806. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.29 (d, *J* = 16.2 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.88 (d, *J* = 16.2 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.50 (ddd, *J* = 7.3, 4.6, 0.9 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.2, 154.0, 148.8, 143.2, 137.1, 136.4, 133.7, 129.9 (X2), 129.1 (X2), 127.0, 123.0, 121.4. HRMS (ESI) calculated for $C_{14}H_{10}ClNO$ $[M]^+$ 243.0451. Found: 243.0449

4.4 (*E*)-3-(4-Bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3c). Purification: same as for **3a**. Mp 99–100 °C (*lit.*[10e] 97–99 °C). A white solid. IR (cm^{-1}) 3102, 1687, 1631, 1595, 1515, 1346, 1308, 803. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.4 Hz, 1H), 8.29 (d, *J* = 16.1 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 7.88 (td, *J* = 7.7, 1.4 Hz, 1H), 7.85 (d, *J* = 16.1 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.49 (ddd, *J* = 7.3, 4.8, 1.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.2, 154.0, 148.8, 143.2, 137.1, 134.1, 132.1 (X2), 130.1 (X2), 127.0, 124.8, 123.0, 121.4. HRMS (ESI) calculated for $C_{14}H_{10}BrNO$ $[M]^+$ 286.9946. Found: 286.9945.

4.5 (*E*)-3-(3-Fluorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3d). Purification: same as for **3a**. Mp 74–77 °C (*lit.*[10e] 72–74 °C). A pale yellow solid. IR (cm^{-1}) 3092, 1687, 1641, 1499, 1459, 1041, 793. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.5 Hz, 1H), 8.29 (d, *J* = 16.0 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.89–7.86 (m, 2H), 7.51–7.47 (m, 2H), 7.43 (d, *J* = 9.8 Hz, 1H), 7.38 (dd, *J* = 13.7, 7.9 Hz, 1H), 7.10 (td, *J* = 8.2, 1.9 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.3, 163.1 ($^1J_{C\text{-}F}$ = 244.5 Hz), 153.9, 148.9, 143.1, 137.4 ($^3J_{C\text{-}F}$ = 7.5 Hz), 137.0, 130.3 ($^4J_{C\text{-}F}$ = 6.0 Hz), 127.0, 124.8, 123.0, 122.2, 117.3 ($^2J_{C\text{-}F}$ = 21.0 Hz), 114.8 ($^2J_{C\text{-}F}$ = 21.0 Hz). HRMS (ESI) calculated for $C_{14}H_{10}FNO$ $[M]^+$ 227.0746. Found: 227.0745.

4.6 (*E*)-3-(3-Chlorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3e). Purification: same as for **3a**. Mp 89–91 °C (*lit.*[10e] 92–93 °C). A pale yellow solid. IR (cm^{-1}) 3098, 1691, 1628, 1535, 1459, 1416, 1353, 1058, 793. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (d, *J* = 7.9 Hz,1H), 8.30 (d, *J* = 16.0 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 16.0 Hz, 1H), 7.72 (s, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.50 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.2, 153.9, 148.9, 142.9, 137.1, 137.0, 134.9, 130.3, 130.1, 128.2, 127.1, 127.0, 123.0, 122.2. HRMS (ESI) calculated for $C_{14}H_{10}ClNO$ $[M]^+$ 243.0451. Found: 243.0452.

4.7 (*E*)-3-(3-Bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3f). Purification: same as for **3a**. Mp 88–92 °C (*lit.*[10e] 84–86 °C). A white solid. IR (cm^{-1}) 3075, 1691, 1634, 1532, 1349, 1263, 1005, 783. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (d, *J* = 5.1 Hz, 1H), 8.29 (d, *J* = 16.1 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.90–7.86 (m, 2H), 7.83 (d, *J* = 16.1 Hz, 1H), 7.62 (d, *J* =7.7 Hz, 1H), 7.53–7.48 (m, 2H), 7.28 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.1, 153.9, 148.9, 142.9, 137.3 (X2), 137.1, 133.2, 131.2, 130.3, 127.6, 127.1, 123.0, 122.2. HRMS (ESI) calculated for $C_{14}H_{10}BrNO$ $[M]^+$ 286.9946. Found: 286.9946.

4.8 (*E*)-3-(2-Fluorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3g). Purification: same as for **3a**. Mp 65–66 °C (*lit.*[10e] 72–74 °C). A pale yellow-green solid. IR (cm^{-1}) 3079, 1697, 1638, 1502, 1353, 1008, 783. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.3, 0.6 Hz, 1H), 8.36 (d, *J* = 16.2 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 16.2 Hz, 1H), 7.86 (dt, *J* = 9.5, 1.7 Hz, 1H), 7.78 (d, *J* = 9.2, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.39–7.34 (m, 1H), 7.17 (td, *J* = 15.1, 0.8 Hz, 1H), 7.10 (ddd, *J* = 10.5, 8.3, 1.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.4, 161.8, 154.0, 148.8, 137.0, 136.9, 131.9 ($^3J_{C\text{-}F}$ = 9.0 Hz), 129.2, 126.9 124.3 ($^4J_{C\text{-}F}$ = 3.0 Hz), 123.3, 123.1 ($^2J_{C\text{-}F}$ = 21.0 Hz), 123.0 ($^2J_{C\text{-}F}$ = 15.0 Hz), 116.1 ($^2J_{C\text{-}F}$ = 21.0 Hz). HRMS (ESI) calculated for $C_{14}H_{10}FNO$ $[M]^+$ 227.0746. Found: 227.0745.

4.9 (*E*)-3-(2-Chlorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3h). Purification: same as for **3a**. Mp 98–99 °C (*lit.*[10e] 92–96 °C) (decomposed). A white solid. IR (cm^{-1}) 3102, 1687, 1631, 1512, 1346, 1310, 1008, 763. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.3 Hz, 1H), 8.35 (d, *J* = 16.0 Hz, 1H), 8.28 (d, *J* = 16.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 7.6, 1.6 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 1H), 7.48 (td, *J* = 6.0, 4.8 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.34–7.28 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.2, 154.0, 148.9, 143.0, 137.1, 135.8, 133.4, 131.2, 130.2, 128.1, 127.0 (X2), 123.3, 123.0. HRMS (ESI) calculated for $C_{14}H_{10}ClNO$ 243.0451. Found: 243.0449.

4.10 (*E*)-3-(2-Bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (3i). Purification: same as for **3a**. Mp 109–110 °C (*lit.*[10e] 95–97 °C). A white solid. IR (cm^{-1}) 3098, 1687, 1631, 1475, 1349, 1038, 763. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.7, 0.5 Hz, 1H), 8.30 (d, *J* = 16.0 Hz, 1H), 8.23 (d, *J* = 16.0 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.47 (td, *J* = 6.6, 0.7 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.23 (td, *J* = 7.9, 1.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.0, 154.0, 148.8, 142.8, 137.0,

135.1, 133.4, 131.3, 128.2, 127.6, 127.0, 126.2, 123.5, 123.0. HRMS (ESI) calculated for $C_{14}H_{10}BrNO$ $[M]^+$ 286.9946. Found: 286.9946.

4.11 (±)-((1*S*,2*S*,3*R*,4*S*,6*S*)-2,6-Bis(4-fluorophenyl)-4-hydroxy-4-(pyridin-2-yl)cyclohexane-1,3-diyl)-bis(pyridin-2-ylmethanone) (4a). Mp 249–253 °C. A white solid. IR (cm^{-1}) 3105, 1707, 1667, 1525, 1495, 1253, 1194. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.3 Hz, 1H), 8.21 (d, *J* = 4.3 Hz, 1H), 8.15 (d, *J* = 4.3 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.52–7.46 (m, 2H), 7.44 (td, *J* = 7.6, 1.6 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.26–7.15 (m, 5H), 7.10–7.07 (m, 1H), 6.87 (td, *J* = 7.4, 0.7 Hz, 1H), 6.70 (t, *J* = 8.7 Hz, 2H), 6.49 (t, *J* = 7.5 Hz, 2H), 6.26 (d, *J* = 12.5 Hz, 1H), 5.77 (s, -OH), 5.51 (t, *J* = 5.0 Hz, 1H), 4.44 (dd, *J* = 12.5, 5.0 Hz, 1H), 4.16 (dt, *J* = 12.7, 4.0 Hz, 1H), 3.50 (t, *J* = 13.0 Hz, 1H), 1.97 (dd, *J* = 13.0, 3.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ205.4, 203.4, 162.5, 161.2 ($^1J_{C\text{-}F}$ = 242.8 Hz), 161.1 ($^1J_{C\text{-}F}$ = 242.5 Hz), 154.1, 152.9, 148.0 (X2), 147.0, 137.8, 136.4, 136.2, 136.1, 136.0, 130.0 (X2, $^3J_{C\text{-}F}$ = 7.8 Hz), 129.2 (X2, $^3J_{C\text{-}F}$ = 7.8 Hz), 126.1, 126.0, 121.9, 121.7, 121.1, 120.9, 114.5 (X2, $^2J_{C\text{-}F}$ = 20.4 Hz), 114.4 (X2, $^2J_{C\text{-}F}$ = 20.4 Hz), 75.8, 48.7, 48.2, 44.7, 40.5, 38.2. HRMS (ESI) calculated for $C_{35}H_{28}F_2N_3O_3$ $[M+H]^+$ 576.2100. Found: 576.2095.

4.12 (±)-((1*S*,2*S*,3*R*,4*S*,6*S*)-2,6-Bis(4-chlorophenyl)-4-hydroxy-4-(pyridin-2-yl)cyclohexane-1,3-diyl)-bis(pyridin-2-ylmethanone) (4b). Mp 245–248 °C. A white solid. IR (cm^{-1}) 3168, 1711, 1664, 1608, 1502, 1452, 1025, 763. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.8 Hz, 1H), 8.20 (d, *J* = 4.8 Hz, 1H), 8.15 (d, *J* = 4.2 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.51 (dd, 7.7, 1.6 Hz, 1H),7.50 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.44 (td, *J* = 7.7, 1.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.17–7.14 (m, 1H), 7.10 (ddd, *J* = 7.3, 4.7, 0.8 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 6.9, 4.9 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.24 (d, *J* = 12.5 Hz, 1H), 5.75 (s, 1H), 5.52 (t, *J* = 5.0 Hz, 1H), 4.44 (dd, *J* = 12.5, 5.0 Hz, 1H), 4.15 (dt, *J* = 13.0, 4.0 Hz, 1H), 3.49 (t, *J* = 13.1 Hz, 1H), 1.95 (dd, *J* = 13.1, 3.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ205.1, 203.1, 162.3, 154.0, 153.8, 148.07, 148.02, 147.0, 140.6, 139.2, 136.2, 136.1, 131.9, 129.9, 129.2 (X2), 127.9 (X2), 127.8 (X2), 126.12, 126.05, 121.9, 121.7, 121.1, 121.0, 75.6, 48.5, 47.9, 44.8, 40.6, 38.0. HRMS (ESI) calculated for $C_{35}H_{27}Cl_2N_3O_3$ $[M]^+$ 607.1429. Found: 607.1428.

4.13 (±)-((1*S*,2*S*,3*R*,4*S*,6*S*)-2,6-Bis(4-bromrophenyl)-4-hydroxy-4-(pyridin-2-yl)cyclohexane-1,3-diyl)-bis(pyridin-2-ylmethanone) (4c). Mp 242–246 °C. A white solid. IR (cm^{-1}) 3198, 1707, 1658, 1512, 1452, 846, 760. ^{1}H NMR (600 MHz, $CDCl_3$) δ8.60 (d, *J* = 4.2 Hz, 1H), 8.33 (d, *J* = 4.0 Hz, 1H), 8.28 (d, *J* = 4.2 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.65–7.60 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.30–7.28 (d, *J* = 8.5 Hz, 3H), 7.27–7.23 (m, 5H), 7.05 (t, *J* = 8.4, 2H), 7.0 (t, *J* = 7.0 Hz, 1H), 6.37 (d, *J* = 12.5 Hz, 1H), 5.92 (s, –OH, 1H), 5.65 (dd, *J* = 12.9, 2.6 Hz, 1H), 4.56 (dd, *J* = 12.4, 4.9 Hz, 1H), 4.29–4.25 (m, 1H), 3.62 (t, *J* = 12.9 Hz, 1H), 2.08 (dd, *J* = 12.9, 2.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.6, 203.1, 162.2, 154.0, 153.8, 148.10, 148.03, 147.0, 141.1, 139.8, 136.2, 136.1, 130.86, 130.73, 130.3, 129.6, 126.12, 126.07, 121.9, 121.7, 121.2, 121.03, 119.98, 75.6, 48.5, 47.8, 44.9, 40.7, 38.0. HRMS (ESI) calculated for $C_{35}H_{28}{}^{79}Br^{79}BrN_3O_3$ $[M+H]^+$ 696.0497. Found: 696.0499. $C_{35}H_{28}{}^{79}Br^{81}BrN_3O_3$ $[M+H]^+$ 698.0477. Found: 696.0482.

4.14 (±)-((1*S*,2*S*,3*R*,4*S*,6*S*)-2,6-Bis(3-fluorophenyl)-4-hydroxy-4-(pyridin-2-yl)cyclohexane-1,3-diyl)-bis(pyridin-2-ylmethanone) (4d). Mp 229–233 °C. A white solid. IR (cm^{-1}) 3168, 1714, 1658, 1552, 1422, 1177, 710. ^{1}H NMR (600 MHz, $CDCl_3$) δ8.48 (dd, *J* = 4.8, 4.8 Hz, 1H), 8.20 (d, *J* = 4.6 Hz, 1H), 8.15 (dt, *J* = 4.7, 1.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.51 (td, *J* = 7.7, 1.3 Hz, 1H), 7.46 (td, *J* = 7.7, 1.8 Hz, 1H), 7.43 (td, *J* = 7.3, 1.7 Hz, 1H), 7.39 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.15 (ddd, *J* = 7.1, 4.7, 1.4 Hz, 1H), 7.08–7.04 (m, 4H), 7.00–6.94 (m, 2H), 6.87 (dd, *J* = 7.1, 5.1 Hz, 1H), 6.77 (dt, *J* = 14.0, 6.2 Hz, 1H), 6.59 (td, *J* = 8.3, 2.2 Hz, 1H), 6.39 (td, *J* = 8.5, 2.7 Hz, 1H), 6.25 (d, *J* = 12.4 Hz, 1H), 5.80 (br s, 1H), 5.56 (t, *J* = 5.0 Hz, 1H), 4.47 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.18 (dt, *J* = 13.0, 4.0 Hz, 1H), 3.51 (t, *J* = 13.0 Hz, 1H), 1.99 (dd, *J* = 13.0, 3.3 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ204.9, 203.1, 162.4 ($^1J_{C\text{-}F}$ = 243.7 Hz), 162.2 ($^1J_{C\text{-}F}$ = 243.7 Hz), 162.1, 154.0, 153.9, 148.1, 148.0, 144.6 ($^3J_{C\text{-}F}$ = 7.0 Hz), 143.2 ($^3J_{C\text{-}F}$ = 7.0 Hz), 136.3, 136.0, 135.9, 129.2 ($^3J_{C\text{-}F}$ = 8.0 Hz), 129.1 ($^3J_{C\text{-}F}$ = 8.0 Hz), 126.0 (X2), 124.3, 123.6 (X2), 122.0, 121.6, 121.2, 121.0, 115.5 ($^2J_{C\text{-}F}$ = 21.6 Hz), 114.7 ($^2J_{C\text{-}F}$ = 21.4 Hz), 113.0, 112.9, 75.6, 48.4, 47.6, 45.1, 40.9, 38.0. HRMS (ESI) calculated for $C_{35}H_{28}F_2N_3O_3$ $[M+H]^+$ 576.2099. Found: 576.2100.

4.15 (±)-((1*S*,2*S*,3*R*,4*S*,6*S*)-2,6-Bis(3-chlorophenyl)-4-hydroxy-4-(pyridin-2-yl)cyclohexane-1,3-diyl)-bis(pyridin-2-ylmethanone) (4e). Mp 174–178 °C. A white solid. IR (cm^{-1}) 3125, 1711, 1644, 1449, 1005, 803. ^{1}H NMR (600 MHz, $CDCl_3$) δ8.52 (d, *J* = 4.5 Hz, 1H), 8.23 (d, *J* = 4.5 Hz, 1H), 8.18 (dd, *J* = 4.6, 0.7 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.53 (td, *J* = 7.7, 1.3 Hz, 1H), 7.50 (td, *J* = 7.8, 1.6 Hz, 1H), 7.45 (td, *J* = 7.5, 1.6 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.33 (s, 1H), 7.24 (s, 1H), 7.18 (dd, *J* = 6.2, 1.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7. 13 (s, 1H), 7.08 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 2H), 6.73 (t, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.26 (d, *J* = 12.4 Hz, 1H), 5.73 (s, 1H), 5.55 (t, *J* = 5.0 Hz, 1H), 4.43 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.16 (dt, *J* = 13.0, 4.1 Hz, 1H), 3.49 (t, *J* = 13.0 Hz, 1H), 1.99 (dd, *J* = 13.0, 3.3 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ204.8, 203.4, 162.3, 154.0, 148.1, 148.0, 147.0, 144.1, 142.5, 136.3, 136.1, 136.0, 133.7, 133.5, 129.1 (X2), 129.0, 128.9 (X2), 128.1, 126.7, 126.3, 126.1, 126.0 (X2), 122.0, 121.6, 121.2, 121.1, 75.7, 48.2, 47.6, 45.2, 40.9, 37.9. HRMS (ESI) calculated for $C_{35}H_{28}{}^{35}Cl^{35}ClN_3O_3$ $[M+H]^+$ 608.1508. Found: 608.1510. $C_{35}H_{28}{}^{35}Cl^{37}ClN_3O_3$ $[M+H]^+$ 610.1479. Found: 610.1498.

4.16 (±)-((1*S*,2*S*,3*R*,4*S*,6*S*)-2,6-Bis(3-bromrophenyl)-4-hydroxy-4-(pyridin-2-yl)cyclohexane-1,3-diyl)-bis(pyridin-2-ylmethanone) (4f). Mp 155–158 °C. A white solid. IR (cm^{-1}) 3108, 1707, 1641, 1528, 1449, 1012, 803. ^{1}H NMR (600 MHz, $CDCl_3$) δ8.52 (dd, *J* = 2.5, 2.2 Hz, 1H), 8.22 (t, *J* = 2.9 Hz, 1H), 8.18 (t, *J* = 0.7 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.67 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.53–7.49 (m, 3H), 7.45–7.42 (m, 1H), 7.41–7.37 (m, 2H), 7.20 (t, *J* = 8.8 Hz, 1H), 7.18–7.15 (m, 1H), 7.09–7.06 (m, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.88 (td, *J* = 7.9, 2.4 Hz, 2H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.66 (td, *J* = 7.9, 2.3 Hz, 1H), 6.26 (d, *J* = 12.0 Hz, 1H), 5.71 (br s, 1H), 5.45 (t, *J* = 5.0 Hz, 1H), 5.28 (t, *J* = 1.4 Hz, 1H), 4.41 (dd, *J* = 12.4, 5.0 Hz, 1H), 4.15 (dt, *J* = 13.0, 3.9 Hz, 1H), 3.47 (t, *J* = 13.0 Hz, 1H), 1.98 (dd, *J* = 13.0, 3.1 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ204.7, 203.4, 162.3, 153.9, 148.1, 148.0, 147.0, 144.4, 142.8, 136.3, 136.0, 135.9, 131.9, 131.0, 129.4, 129.23, 129.21, 129.18, 127.1, 126.5, 126.1, 121.98, 121.95, 121.8, 121.6, 121.07, 121.05, 75.7, 48.0, 47.5, 45.1, 40.8, 37.9. HRMS (ESI) calculated for $C_{35}H_{28}{}^{79}Br^{79}BrN_3O_3$ $[M+H]^+$ 696.0497. Found: 696.0494. $C_{35}H_{28}{}^{79}Br^{81}BrN_3O_3$ $[M+H]^+$ 698.0477. Found: 696.0474.

4.17 (±)-((1*S*,2*S*,3*R*,4*S*,6*S*)-2,6-Bis(2-fluorophenyl)-4-hydroxy-4-(pyridin-2-yl)cyclohexane-1,3-diyl)-bis(pyridin-2-ylmethanone) (4g). Mp 236–243 °C. A white solid. IR (cm^{-1}) 3118, 1711, 1671, 1512, 1479, 1349, 1257, 780. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.4 Hz, 1H), 8.23 (d, *J* = 4.4 Hz, 1H), 8.16 (d, *J* = 4.2 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.42–7.38 (m, 2H), 7.30–7.24 (m, 1H), 7.17 (t, *J* = 5.3 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 7.00 (dd, *J* = 6.3, 4.9 Hz, 1H), 6.87 (dd, *J* = 7.1, 4.7 Hz, 2H), 6.80 (t, *J* = 9.5 Hz, 1H), 6.74–6.69 (m, 3H), 6.45–6.41 (m, 1H), 6.27 (d, *J* = 12.6 Hz, 1H), 5.83 (s, 1H), 5.67 (t, *J* = 4.9 Hz, 1H), 4.89 (dd, *J* = 12.7, 4.7 Hz, 1H), 4.58 (dd, *J* = 9.5, 3.8 Hz, 1H), 3.58 (t, *J* = 13.0 Hz, 1H), 1.90 (dd, *J* = 13.0, 2.9 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.1, 203.1, 162.7, 161.7 ($^1J_{C\text{-}F}$ = 245.0 Hz), 161.0 ($^1J_{C\text{-}F}$ = 245.0 Hz), 154.1 ($^3J_{C\text{-}F}$ = 8.4 Hz), 148.2, 148.0, 147.1, 136.2, 136.1, 135.7, 129.2, 129.1, 129.0, 127.9, 127.8, 127.6, 127.5 ($^3J_{C\text{-}F}$ = 7.0 Hz), 126.0, 125.8, 123.1, 123.0, 121.8, 121.7, 121.0, 120.7, 114.8 ($^2J_{C\text{-}F}$ = 22.4 Hz), 114.7 ($^2J_{C\text{-}F}$ = 22.4 Hz), 75.8, 48.8, 44.3, 37.3, 37.0, 33.8. HRMS (ESI) calculated for $C_{35}H_{28}F_2N_3O_3$ $[M+H]^+$ 576.2100. Found: 576.2102.

4.18 (±)-((1*S*,2*S*,3*R*,4*S*,6*S*)-2,6-Bis(2-chlorophenyl)-4-hydroxy-4-(pyridin-2-yl)cyclohexane-1,3-diyl)-bis(pyridin-2-ylmethanone) (4h). IR (cm^{-1}) 3171, 1707, 1658, 1492, 1452, 1018, 770. Mp 263–266 °C. A white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, *J* = 3.8 Hz, 1H), 8.29 (s, 1H), 8.16 (d, *J* = 3.9 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.56 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 2.1 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 3.9 Hz, 1H), 6.99 (dd, *J* = 6.6, 5.1 Hz, 1H), 6.92 (br s, 1H), 6.84 (t, *J* = 3.7 Hz, 2H), 6.67 (t, *J* = 7.4 Hz, 1H), 6.57 (t, *J* = 7.5 Hz, 1H), 6.27 (d, *J* = 11.7 Hz, 1H), 6.05 (br s, 1H), 5.89 (t, *J* = 4.2 Hz, 1H), 5.01 (dd, *J* = 12.3, 3.8 Hz, 1H), 4.69 (d, *J* = 13.1 Hz, 1H), 3.61 (t, *J* = 13.0 Hz, 1H), 1.91 (d, *J* = 12.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.0, 202.9, 162.8, 154.2, 154.1, 148.4, 147.9, 147.0, 139.3, 138.0, 136.4, 136.2, 135.6, 135.3, 135.0, 129.3, 129.2 (X2), 128.9, 127.7, 127.2, 126.1, 126.0, 125.9, 125.7, 121.9, 121.8, 121.1, 120.7, 75.9, 49.8, 42.5, 41.2, 37.8, 37.6. HRMS (ESI) calculated for $C_{35}H_{28}{}^{35}Cl^{35}ClN_3O_3$ $[M+H]^+$ 608.1508. Found: 608.1503. $C_{35}H_{28}{}^{35}Cl^{37}ClN_3O_3$ $[M+H]^+$ 610.1479. Found: 610.1486.

4.18 (*E*)-3-(4-Methoxyphenyl)-1-(pyridin-2-yl)prop-2-en-1-one (11). Method B. Mp 83–88 °C (*lit.*[14a] 126 °C; *lit.*[14b] 81–82 °C). A white solid. IR (cm^{-1}) 3026, 1681, 1631, 1525, 1495, 1320, 1277, 1058, 806. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (d, *J* = 3.8 Hz, 1H), 8.18 (d, *J* = 16.0 Hz, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 16.0 Hz, 1H), 7.87 (t, *J* = 6.4 Hz, 1H), 7.69 (d, *J* = 8.6 Hz , 2H), 7.47 (dd, *J* = 6.7, 6.2 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.3, 161.8, 154.4, 148.7, 144.8, 137.1, 130.7 (X2), 128.0, 126.7, 122.9, 118.5, 114.3 (X2), 55.4. HRMS (ESI) calculated for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1025. Found: 240.1027.

4.19 ((1S,2S,3R,4S,6S)-4-hydroxy-2,6-bis(4-methoxyphenyl)-4-(pyridin-2-yl)cyclohexane-1,3-diyl)bis(pyridin-2-ylmethanone) (12). Method B. Mp 223–227 °C. A white solid. IR (cm^{-1}) 3178, 1707, 1661, 1525, 1495, 1267, 1214. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 3.8 Hz, 1H), 8.22 (s, 1H), 8.13 (d, *J* = 2.3 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.0 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.17–7.13 (m, 5H), 7.02 (t, *J* = 7.0 Hz, 1H), 6.87 (t, *J* = 5.6 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 2H), 6.23 (d, J = 12.3 Hz, 1H), 5.81 (br s, 1H), 5.48 (t, J = 4.6 Hz, 1H), 4.38 (dd, *J* = 12.3, 4.6 Hz, 1H), 4.13–4.10 (m, 1H), 3.59 (s, 3H), 3.50 (t, *J* = 13.0 Hz, 1H), 3.46 (s, 3H), 1.96 (d, *J* = 12.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 203.7, 162.9, 157.7, 157.6, 154.2, 154.1, 147.9 (X2), 146.9, 136.2, 136.0, 135.7, 134.4, 132.9, 129.5 (X2), 128.7 (X2), 125.9, 125.7, 121.8, 121.7, 121.2, 121.0, 113.2 (X2), 113.0 (X2), 75.9, 55.0, 54.8, 49.1, 48.6, 44.7, 40.5, 38.4. HRMS (ESI) calculated for $C_{37}H_{34}N_3O_5$ $[M+H]^+$ 600.2498. Found: 600.2498.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR data) for all of the compounds associated with this article can be found in the online version.

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