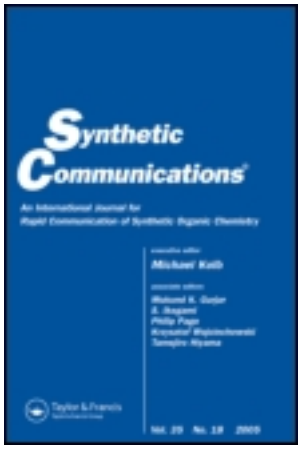

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Synthesis and Molecular Structure of New Macro Acyclic Mannich Derivatives: Symmetrical and Unsymmetrical 2-[(E)-(Benzylideneamino)(aryl)methyl]cyclododecanone

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SYNTHESIS AND MOLECULAR STRUCTURE OF NEW MACRO ACYCLIC MANNICH DERIVATIVES: SYMMETRICAL AND UNSYMMETRICAL 2-[(E)-(BENZYLIDENEAMINO)(ARYL)METHYL] CYCLODODECANONE

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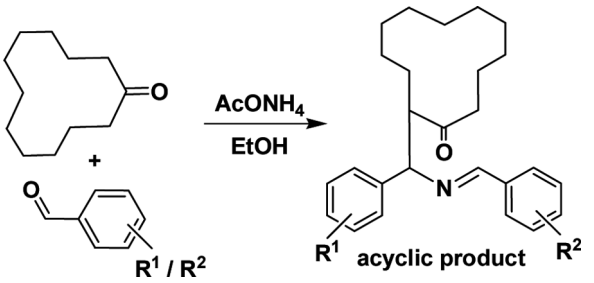
GRAPHICAL ABSTRACT



Abstract *In an effort to provide a green synthetic route for heterocyclic scaffolds, new macro analogs of acyclic Mannich derivatives have been synthesized in good yields in a one-pot, efficient fashion. The acyclic symmetrical and unsymmetrical 2-[(E)-(benzylideneamino)(aryl)methyl]cyclododecanones have been synthesized by condensation of cyclododecanone, aromatic aldehyde, and ammonium acetate in ethanolic media. By infrared, NMR, and mass spectral analyses, their structures were determined. Examination of crystal structure of a* p-*Cl and* o-*Br analogs reveals the minimum energy [3333] square conformation of cyclododecanone ring. In the crystal, molecules aggregate in dimeric subunits formed by C-Cl*$\ldots\pi$ *and C-H..*π *interactions. The reported one-pot, multichain reaction of macrocycles is the first synthetic attempt of acyclic compounds in this type of Mannich reaction involving ketones containing active methylene groups.*

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Keywords Ammonium acetate; cyclododecanone; Mannich reaction; MCR

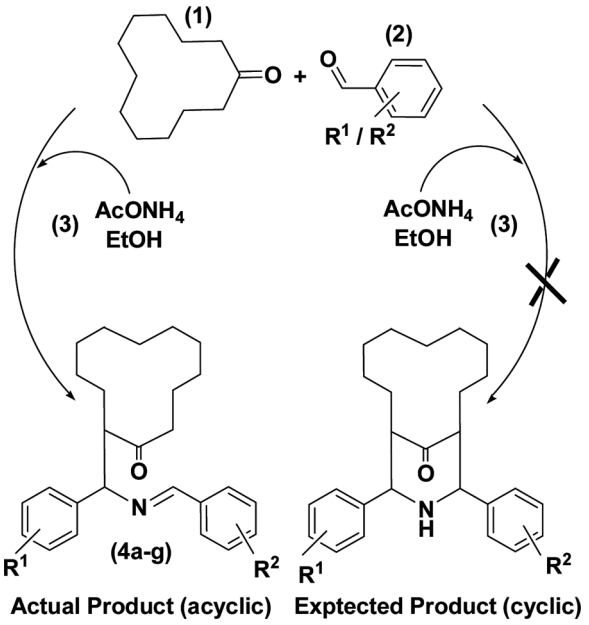
INTRODUCTION

The concept of ideal synthesis was first put forth by Wender et al.[1] Multicomponent reactions (MCRs) are efficient synthetic routes to perform near-ideal synthesis. MCRs are now being tailored and fine-tuned for synthesizing various compounds including many heterocyclic scaffolds.[2] The one-pot MCR has emerged as an attractive tool for atom-economical and benign synthesis by virtue of convergence, productivity, facile execution, and generation of diverse compounds from easily available starting materials in a single operation.[3–8] Our goal is to provide a rapid and green synthetic route for new representative title compounds. We had earlier reported efficient synthesis of several such compounds in a one-pot fashion using ammonium acetate.[9–13] Here, we report the Mannich synthesis of macro analogs of acyclic symmetrical ($R^1 = R^2$) and unsymmetrical ($R^1 \neq R^2$) 2-[(*E*)-(benzylidene amino)(aryl)-methyl]cyclododecanones. Our interest in compounds containing medium to large alicyclic rings (in the C_{10}–C_{20} range) began with the discovery of their importance in many natural products and biologically active compounds. Macromolecules containing hetero-atoms have gained considerable interest in recent years, and particularly the ligands containing N or O macro systems are of special interest as natural products. Moreover, they also demonstrate a broad spectrum of biological activities with unusual pharmacological properties.[14–17]

The development of synthetic methods for the formation of acyclic compounds has increased enormously. However, the construction of a large ring with appropriately situated functional groups poses a great synthetic challenge. Various piperidones and bicyclic analogs were synthesized earlier by Noller, Jeyaraman, and coworkers.[18,19] Although the Mannich procedure for the preparation of such azabicyclic system was published more than a half-century ago, the applications of this versatile skeleton of acyclic derivatives have not been investigated. To the best of our knowledge, despite the intensive chemical and pharmacological investigations of various acyclic symmetrical Mannich dervatives, studies on unsymmetrical Mannich compounds remain scarce. In this article, we report successful synthesis of libraries of acyclic symmetrical and unsymmetrical 2-[(E)-(benzylideneamino)(aryl)methyl]cyclododecanone in good purity and good yield, targeting the diversity of Mannich derivatives for further activity screening.

RESULTS AND DISCUSSION

The title compounds were readily synthesized in good yields by the reaction of cyclododecaone (**1**) and aromatic aldehdye (**2**) in the presence of ethanolic ammonium acetate (**3**), and the strategy is depicted in the Scheme 1. Surprisingly, the condensation reaction does not lead to the cyclic Mannich adduct, but the C-C and C-N bond formation gave the acyclic adduct. We got only the acyclic product. Presumably, formation of the quaternary center is avoided in this case because of ring strain in the large annulated ring of cyclododecanone (absence of planarity). Even though the expected product is a six-membered ring, we are getting acyclic product.



Scheme 1. General synthesis of 2-[(*E*)-(benzylideneamino)(aryl)methyl]cyclododecanone (**4a–g**).

This may be due to the prevention of the formation of six-membered ring by ring stain already present in cyclododecanone ring. This is very clear from the formation of six-membered ring in the case of cyclohexanone instead of cyclododecanone.

Because it is a new product, this method can be applied to higher cyclic ketones to test whether we are getting the six-membered ring product. We were excited to learn that the method was applicable to a broad spectrum of substrates on various substituted benzaldehydes (**2**), even though we are not getting a cyclic Mannich product. In this way, we used two different aromatic aldehydes for the synthesis of unsymmetrical acyclic analogs without the protection of α-carbon in ketone.

This protocol can be applied not only to electron-withdrawing groups (such as halide groups) but also to electron-donating groups (such as alkyl groups) under the same conditions. In most of the cases, the reaction proceeded smoothly and gave the products in good yields. However, we failed to get the products in a few aromatic aldehydes, such as *p*-ethyl, *p*-ethoxy, *o*-methyl, and *o*-methoxy. Presumably, the long carbon chain in *para*-substituted benzaldehydes (*p*-ethyl, *p*-ethoxy) decreases the electrophilicity of the imine carbon. The reduced reactivity diminishes the product formation. Similarly the electron-donating group on the *ortho* position (*o*-methyl, *o*-methoxy, *o*-ethyl, *o*-ethoxy) fails in the product formation because of the steric effect. This principle was also successfully applied to two different aldehydes ($R^1 \neq R^2$). We are getting unsymmetrical product only in the case of the electron-donating group (Me ≠ MeO) on the *para* position of benzaldehyde. The reaction is stopped halfway without leading to ring closure. The results are summarized in Table 1.

The products obtained through this protocol had the inherent advantage of precipitating out the insoluble product. Thus, the reaction could be monitored

Table 1. Three-component reaction of cyclododecanone (**1**), aromatic aldehyde (**2**), and ammonium acetate (**3**)

Entry	RCHO (R^1)	RCHO (R^2)	Product	Yield (%)	Mp (°C)
1	H	H	**4a**	67	118–120
2	*p*-F	*p*-F	**4b**	86	116–118
3	*p*-Cl	*p*-Cl	**4c**	77	114–116
4	*p*-Br	*p*-Br	**4d**	74	242–244
5	*m*-Br	*m*-Br	**4e**	68	150–152
6	*o*-F	*o*-F	**4f**	84	158–160
7	*o*-Br	*o*-Br	**4g**	82	142–144
8	*p*-MeO	*p*-MeO	**4h**	74	132–134
9	*p*-Me	*p*-Me	**4i**	69	142–144
10	*p*-Me	*p*-MeO	**4j**	70	110–112
11	*p*-OEt	*p*-OEt	**4k**	–	–
12	*p*-Et	*p*-Et	**4l**	–	–
13	*o*-OMe	*o*-MeO	**4m**	–	–
14	*o*-Me	*o*-Me	**4n**	–	–
15	*o*-OEt	*o*-OEt	**4o**	–	–
16	*o*-Et	*o*-Et	**4p**	–	–
17	*o*-Br	*p*-Br	**4q**	–	–
18	*o*-Br	*p*-Cl	**4r**	–	–
19	o-Br	*p*-MeO	**4s**	–	–

visually by the formation of pale white precipitate, indicating the completion of the reaction. Therefore, the purity of the obtained product was consistently better.

Spectroscopic Characterization

The structures of synthesized compounds were unequivocally identified with the aid of spectroscopic means. The Fourier transform–infrared (FT-IR) spectrum of the compounds, **4a–j** had a sharp band at 1695–1711 cm^{-1} (C=O stretch); 1618–1646 cm^{-1} (N=CH stretch), clearly indicating the formation of acyclic (open) structure. In the ^{1}H NMR spectrum of the compounds **4a–j**, the N=CH protons occur as singlets, ranging from δ 8.11–8.75 ppm. The mass spectrum of the compounds **4a–j** showed their respective peaks (spectra available in the supplementary data). The structures of crystalline compounds **4c** and **4g** were also confirmed by single-crystal x-ray analysis (Figs. 1a and 1b, respectively).

Based on IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry, it can be concluded that the reaction affords a sole product. The selectivity of the desired products thus obtained was consistently high, probably because the reaction took place under mild conditions. These structures were further validated by x-ray crystallographic studies.

Crystal Structure Analyses of Representative Compounds 4c and 4g

These compounds are noncrystalline in nature, and diffraction data for only **4c** and 4g could be obtained. The overall structures of **4c** and **4g** are illustrated in Fig. 1a and 1b, respectively. In the reported structures of the centrosymmetric crystal of **4b**, the stereogenic centers (C2 and C13) adopt *R* and *S* configurations, respectively. In **4g**, C13 adopts *S* configuration. C2 possess *S* configuration in the major component,

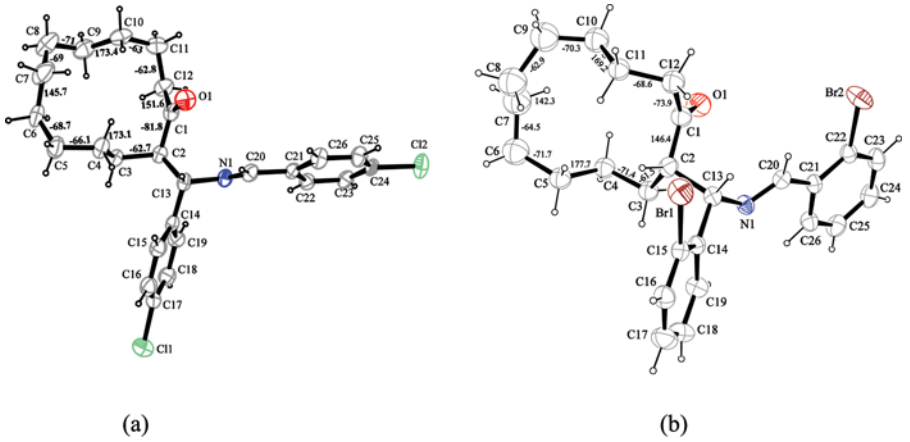


Figure 1. (a) Molecular structure of **4c**; (b) molecular structure of **4g**. (Figure is provided in color online.)

whereas in minor component it assumes *R* configuration.[20] The molecules **4c** and **4g** adopt an *E* configuration with respect to the imine C=N, with C13—N1—C20—C21 torsion angles of 175.5(2)° and −178.4(3)°, respectively.

The cyclododecanone ring adopts [3333] square conformation in both compounds possessing 422 symmetry.[21,22] The numbers in the square brackets indicate the number of ring bonds between the four corner atoms of cyclododecanone ring. The [3333] square conformation is the most favored conformation of cyclododecanone. Based on theoretical calculations, the other three lowest energy conformations for the 12-membered ring were [2334], [1434], and [2343].[23] Upon examination of the structures of cyclododecanone ring in Cambridge Structural Database (version 5.31), 38 structures were retrieved. Their refcodes are as follows: BRDECO, DESNUL, DESPAT, DIFJEH, EJEJEI, ETIBAK, EVIPEE, FEYYEO, FOMYAH, FOMYEL, FONBAL, GEFMAG, HABWUC, HABXAJ, HABXOX, HABYIS, HABYUE, HABZUF, HIBLIN, HIHPOD, IJUTIQ, KOQHON, NILMOK, NIVROZ, OMIWUC, QAYKAD, QIXFUY, QIXFUY01, TOCFAS, UNOCEF, VASDAU, VASKUV, VASLOQ, VASQAH, VASQEL, XEXYAA, ZOGRIW, and ZUMLIC. In all, the cyclododecanone ring assumes the lowest energy [3333] square conformation with very few exceptions (in the cases of ETIBAK, IJUTIQ, NILMOK, and QAYKAD), where the additionally fused cyclic ring imposes severe restraints, leading to preference for other minimum-energy conformations. To calculate the average geometry of the cyclododecanone ring, we selected only those structures having a cyclododecanone ring without any associated fused cyclic ring (refcodes: BRDECO, DESNUL, EJEJEI, EJEJEI, GEFMAG, HABXAJ, HABXOX, HABYIS, HABYUE, HABZUF, HIBLIN, HIHPOD, XEXYAA, and ZOGRIW). The average intra-annular bond distance and angles are 1.53(2) Å and 114 (2)°, respectively. The observed values in **4c** [1.52(1) Å and 115(2)°] and **4g** [1.51(1) Å and 114(3)°] are in agreement with the mean values. The absolute value of average torsion angles corresponding to the synclinal and antiperiplanar conformations are 69(5)° and 161(8)°, respectively, for a cyclododecanone ring. In the present case, out of 12 torsion angles, eight are in -synclinal conformations having average values of 68.1° and 68.1°, in **4c** and **4g**. The other four torsion angels are in

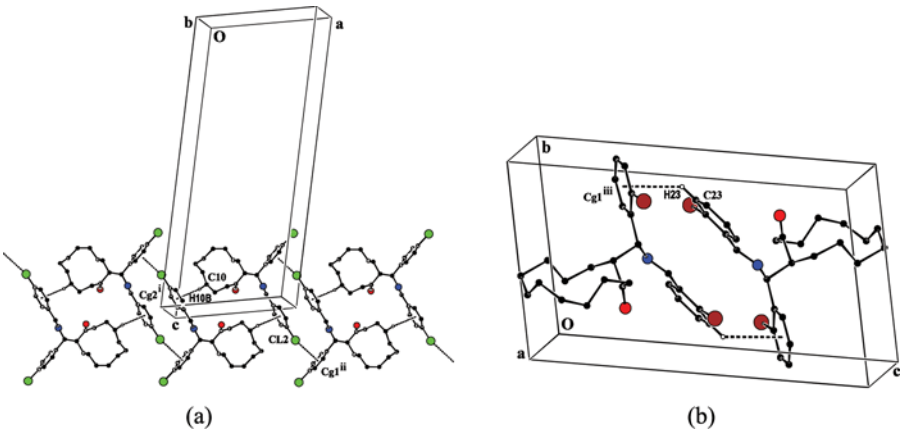


Figure 2. (a) Crystal packing in **4c**; (b) C-H. . .π bonded dimer in **4g**. (Figure is provided in color online.)

antiperiplanar conformations with average values of 161.0° and 158.7° (in **4c** and **4g**). The internal torsion angles of the cyclododecanone ring are listed in Fig. 1.

Crystal packing in **4c** is characterized by two kinds of adjacent dimers (Fig. 2a). Short intermolecular C10–H10B . . . π(Cg2)^{i} [symmetry code (i): 1-x, 1-y, 2-z] contacts stabilize the dimeric subunit (H . . . π = 2.98 Å; C-H . . . π = 137°). An adjacent dimer is also formed by a C24–Cl2. . .π(Cg1)^{ii} [symmetry code (ii): 2-x, -y, 2-z] contact. Cg1 and Cg2 are the centroids of (C14–C19) and (C21–C26) rings, respectively. The Cl . . . π distance and C-Cl . . . π angle are 3.368(2) Å and 157.3(1)°, respectively, whereas the minimum atomic distance, in Cl . . . π, is 3.569(3) Å. These dimeric subunits in tandem generate a one-dimensional chain along crystal [1-1 0]-direction. The C-Hal . . . π–dimer interactions, which have also been referred to as PHD (π-halogen–dimer) interactions, have recently been shown to play an important role in host–guest chemistry.[24,25] Aromatic–aromatic stacking interactions are also observed in the packing with Cg2 . . . Cg2^{i} [symmetry code (i): 2-x, -y, 2-z] centroid . . . centroid distance of 3.892(2) Å, an interplanar distance of 3.608(1) Å, and a slippage of 1.457 Å. Cg2 is the center of the (C21–C26) ring. In the crystal of **4g**, intermolecular C23-H23 . . . π(Cg1)^{i} [symmetry code (i): 1-x, 1-y, 1-z] short contact stabilizes the dimeric subunit (H . . . π = 2.97 Å; C-H . . . π = 133°). Cg1 is the center of the (C14–C19) ring (Fig. 2b).

CONCLUSION

A multicomponent Mannich reaction has been successfully used as the key step for the synthesis of the first representatives of the new class of stable macro acyclic analogs. These structures were established by spectroscopic and x-ray crystallographic methods. The proposed one-pot synthetic method is green, efficient, and rapid. The starting materials are easily available, and the chemical diversity of products can be conveniently manipulated. The reported one-pot synthesis serves as an interesting example of efficient and rapid green synthetic route for designing other macro molecules.

EXPERIMENTAL

All chemicals purchased were of reagent grade and were used without further purification. Melting points were determined in open capillary tubes with a Dalal melting-point apparatus (100 watts) and are uncorrected. IR spectra were recorded in the range 4000–400 cm^{-1} on a Thermo Nicolet Avatar 330 FT-IR spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded in chloroform-d using a Bruker AMX 500 FT, while the mass spectrum was obtained with an Agilent instrument. Chemical shifts are reported as parts per million (ppm) relative to tetramethylsilane (TMS). LC-MS (liquid chromatography–mass spectrometry) data were obtained using an Agilent 1200 series LC and Micromass zQ 4000 spectrometer. Spectral data are reported as supplementary data.

General Procedure for the Preparation of Synthesis of Products 4a–j

A mixture of cyclododecanone (0.01 mol) and the respective aldehyde (0.02 mol) was added to a warm solution of ammonium acetate (0.01 mol) in absolute ethanol (15 ml). The mixture was gently warmed on a water bath for 2–3 min and was stirred at room temperature. The completion of the reaction was identified with thin-layer chromatography (TLC). The solid obtained was separated, and the crude compound was purified by silica-gel column chromatography (hexane and ethyl acetate as elutant). The desired product precipitated out in the reaction mixture because of the poor solubility in ethanol at room temperature. Hence, the reaction could also be monitored for its completeness by the visual inspection of the formation of pale white precipitates.

2-[(E)-(Benzylideneamino)(aryl)methyl]cyclododecanone (4a)

Pale white solid; mp 118–120 °C; yield 67%; IR (KBr): 2930, 2857, 1706 (C=O), 1632 (N=CH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30–8.18 (1H, N=CH), 7.77–7.20 (10H, ArH), 4.46–4.36 (1H, Ali-CH), 3.60–3.43 (1H, Ali-CH), 3.60–1.14 (20H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 213.63 (C=O), 160.64 (N=CH), 142.41, 141.79, 141.50, 136.20, 130.72, 130.64, 128.58, 128.52, 128.49, 128.43, 128.36, 128.32, 127.89, 127.74, 127.42, 127.34, 126.84, 70.64, 59.66, 58.22, 41.18, 28.21, 27.62, 26.45, 26.28, 25.95, 25.86, 24.55, 23.20, 23.03, 22.31; MS: $m/z = 376$ (M + 1); HRMS: calculated 375.5463; found 375.5462.

2-[(E)-(4-Fluorobenzylideneamino)(4-fluorophenyl)methyl] cyclododecanone (4b)

White solid; mp 116–118 °C; yield 86%; IR (KBr): 2937, 2850, 1711 (C=O), 1642 (N=CH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24–8.12 (1H, N=CH), 7.68–6.97 (8H, ArH), 4.44–4.42 (1H, Ali-CH), 3.37–3.35 (1H, Ali-CH), 2.27–1.14 (20H, Ali-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.97 (C=O), 165.60, 163.29, 163.11, 160.85 (N=CH), 159.58, 137.50, 137.47, 132.34, 132.31, 130.24, 130.16, 129.32, 129.24, 115.69, 115.57, 115.47, 115.36, 57.72, 41.59, 27.45, 26.27, 25.85, 24.57, 24.40, 22.95, 22.22, 21.89; HRMS: calculated 411.5272; found 411.5271.

2-[(E)-(4-Chlorobenzylideneamino)(4-chlorophenyl)methyl] cyclododecanone (4c)

Crystalline solid; mp 114–116 °C; yield 77%; IR (KBr): 2930, 2857, 1710 (C=O), 1638 (N=CH) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.23 (1H, N=CH), 7.69–7.24 (8H, ArH), 4.45–4.43 (1H, Ali-CH), 3.40–3.34 (1H, Ali-CH), 2.77–1.15 (20H, Ali-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.69 (C=O), 159.92 (N=CH), 140.09, 136.80, 134.46, 133.21, 129.50, 129.16, 128.80, 128.79, 58.20, 57.54, 41.61, 27.91, 27.41, 26.43, 26.28, 25.89, 24.53, 24.37, 24.34, 22.89, 22.59, 22.24, 21.87; HRMS: calculated 444.4364; found 444.4362.

2-[(E)-(4-Bromobenzylideneamino)(4-bromophenyl)methyl] cyclododecanone (4d)

White solid; mp 242–244 °C; yield 74%; IR (KBr): 2926, 2855, 1701 (C=O), 1638 (N=CH), 639 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.22–8.11 (1H, N=CH), 7.62–7.25 (m, 8H, Ar-H), 4.43–4.36 (1H, Ali-CH), 3.39–2.69 (1H, Ali-CH), 2.44–1.26 (20H, Ali-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.65 (C=O), 160.08 (N=CH), 141.31, 140.56, 134.85, 131.84, 131.76, 129.76, 129.72, 129.53, 125.38, 125.28, 121.35, 121.26, 58,14, 57.46, 41.62, 41.10, 27.40, 26.28, 25.89, 24.52, 24.36, 24.33, 24.29, 22.27, 22.24, 21.86, 21.80; HRMS: calculated 533.3384; found 533.3381.

2-[(E)-(3-Bromobenzylideneamino)(3-bromophenyl)methyl] cyclododecanone (4e)

White solid; mp 150–152 °C; yield 68%; IR (KBr): 2935, 2864, 1700 (C=O), 1620 (N=CH) cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 8.25 (1H, N=CH), 7.97–7.26 (8H, ArH), 4.04–4.02 (2H, Ali-CH), 2.82–1.04 (20H, Ali-CH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 212.97 (C=O), 162.95 (N=CH), 134.46, 131.08, 130.89, 130.78, 130.60, 127.07, 56.19, 26.45, 24.08, 22.37, 21.65; MS: HRMS: calculated 533.3384; found 533.3179.

2-[(E)-(2-Fluorobenzylideneamino)(2-fluorophenyl)methyl] cyclododecanone (4f)

White solid; mp 158–160 °C; yield 84%; IR (KBr): 2930, 2859, 1705 (C=O), 1639 (N=CH) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.53 (1H, N=CH), 7.97–7.00 (8H, ArH), 4.98–4.96 (1H, Ali-CH), 3.49–3.47 (1H, Ali-CH), 2.43–1.17 (20H, Ali-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.32 (C=O), 155.16 (N=CH), 132.32, 129.31, 128.87, 128.79, 127.84, 124.47, 124.18, 115.73, 115.60, 115.50, 69.06, 40.67, 27.26, 26.30, 25.90, 24.35, 24.29, 23.01, 22.27, 21.92; HRMS: calculated 411.5272; found 411.5269.

2-[(E)-(2-Bromobenzylideneamino)(2-bromophenyl)methyl] cyclododecanone (4g)

White solid; mp 142–144 °C; yield 82%; IR (KBr): 2935, 2856, 1700 (C=O), 1638 (N=CH), 678 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ 8.75–8.65 (1H, N=CH),

7.98–7.07 (8H, ArH), 5.24–5.13 (1H, Ali-CH), 3.52–3.47 (1H, Ali-CH), 2.41–1.24 (20H, Ali-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.85 (C=O), 160.91 (N=CH), 140.07, 134.59, 133.14, 132.96, 131.96, 129.85, 129.10, 128.83, 127.73, 127.53, 125.20, 123.84, 72.59, 56.90, 38.97, 26.59, 26.15, 25.78, 24.15, 24.12, 24.04, 22.66, 22.32, 22.03; MS: $m/z = 534$ ($M^+ + 1$); HRMS: calculated 533.3384; found 533.3382.

2-[(E)-(4-Methoxybenzylideneamino)(4-methoxyphenyl)methyl] cyclododecanone (4h)

White solid; mp 132–134 °C; yield 74%; IR (KBr): 2927, 2855, 1700 (C=O), 3420, 1636 (N=CH) cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.24–8.11 (1H, N=CH), 7.57–7.13 (8H, ArH), 4.38–4.36 (1H, Ali-CH), 3.44–3.39 (1H, Ali-CH), 2.36–2.28(6H, OCH_3), 2.75–1.12 (20H, Ali-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.57 (C=O), 160.53 (N=CH), 140.83, 138.90, 136.96, 133.69, 129.24, 129.12, 128.28, 127.75, 57.69, 41.67, 27.70, 26.26, 25.83, 24.87, 24.62, 24.48, 23.33, 22.29, 22.00, 21.47, 21.11; HRMS: calculated 435.5983; found 435.5981.

2-[(E)-(4-Methylbenzylideneamino)(4-methylphenyl)methyl] cyclododecanone (4i)

White solid; mp 142–144 °C; yield 69%; IR (KBr): 2929, 2858, 1695 (C=O), 1627 (N=CH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (1H, N=CH), 7.57–7.13 (8H, ArH), 4.39–4.36 (1H, Ali-CH), 3.45–3.39 (1H, Ali-CH), 2.36–2.28(6H, OCH_3), 2.75–1.12 (20H, Ali-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.56 (C=O), 160.54 (N=CH), 140.83, 138.90, 136.96, 133.69, 129.24, 129.13, 128.28, 127.76, 57.70, 41.67, 27.71, 26.27, 25.84, 24.87, 24.62, 24.49, 23.34, 22.29, 22.00, 21.47, 21.11; MS: $m/z = 404$ ($M^+ + 1$); HRMS: calculated 403.5995; found 403.5992.

2-[(E)-(4-Methoxybenzylideneamino)(4-methylphenyl)methyl] cyclododecanone (4j)

White solid; mp 110–112 °C; yield 70%; IR (KBr): 2931, 2858, 1707 (C=O), 1646 (N=CH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11–8.07 (1H, N=CH), 7.61–6.84 (8H, ArH), 4.36–4.33 (1H, Ali-CH), 3.78–3.75 (3H, OCH_3), 3.41–3.38 (1H, Ali-CH), 2.36–2.28(6H, CH_3), 2.74–1.11 (20H, Ali-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.67 (C=O), 161.58 (N=CH), 159.90, 158.79, 140.84, 139.00, 138.88, 136.93, 133.66, 129.85, 129.25, 128.84, 128.28, 127.74, 113.79, 57.72, 41.62, 27.69, 26.25, 25.82, 24.84, 24.61, 24.47, 23.31, 22.25, 22.00, 21.09; HRMS: calculated 419.5989; found 419.5981.

X-Ray Diffraction

Suitable single crystals for data collection were grown from a mixture of ethanol and tetrahydrofuran in a 1:1 ratio. Data were obtained from a Bruker SMART and Oxford Diffraction Xcalibur Eos Gemini diffractometers.[26] Crystals were stable during data collection. The structure was solved by applying the direct phase-determination technique using SHELXS-97 and refined by full-matrix least square

on F2 using SHLEXL-97.[27] All structural calculations were performed with the WinGX suit of programs (version 1.70.01).[28] These compounds are mostly noncrystalline, and suitable crystals for **4c** and **4g** could be grown. The cyclododecanone ring in **4g** had a conformational disorder with contribution of major and minor components of 0.79(1) and 0.21(3), respectively. Ring atoms (excluding oxygen O1 and anchor atom C2) were refined isotropically and their equivalent distances and displacement parameters were restrained to be the same using SADI and EADP options in SHELX-97. Distance restraints were also applied to C7–C8 and C6–C7 distances. The hydrogens were placed in the geometrically expected positions and refined

Table 2. Crystal data for **4c** and **4g**

Parameter	**4c**	**4g**
Crystal data		
Empirical formula	$C_{26}H_{31}Cl_2NO$	$C_{26}H_{31}Br_2NO$
Molecular weight	444.42	533.34
Morphology	Colorless, rectangular	Colorless, block
Crystal size (mm)	$0.42 \times 0.22 \times 0.20$	$0.38 \times 0.35 \times 0.35$
Cell parameters		
a (Å)	13.5193(13)	7.9961(5)
b (Å)	5.5858(5)	9.6617(7)
c (Å)	31.994(3)	16.890(1)
a, β, γ (°)	90.0, 98.268(5), 90.0	102.312(6), 91.493(5), 106.857(6)
V (Å^3)	2390.9(4)	1214.7(1)
Cell measuring reflection	2532	12186
θ range (°)	2.6–21.8	2.7–29.2
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	P1 bar
Z/Z'	4/1	2/1
Dx(cal.) (g/cm^3)	1.235	1.455
μ (mm^{-1})	0.289	3.354
Absorption correction	Multiscan	Multiscan
F (000)	944	542
Data collection		
Radiation	MoK_α	MoK_α
Temperature (K)	298(2)	295(2)
θ range (°)	2.3–28.4	2.7–29.3
Index ranges	$-18 <= h <= 16$ $-6 <= k <= 6$ $-37 <= l <= 42$	$-10 <= h <= 10$ $-13 <= k <= 12$ $-23 <= l <= 22$
Scan type	φ and ω scans	φ and ω scans
Independent reflections	5586	6082
Observed [$I > 2\sigma(I)$]	2379	2995
Refinement		
Final R [$F^2 > 2(F^2)$]	0.0578	0.0510
$wR(F^2)$_all	0.1716	0.1428
Goodness of fit (S)	0.998	1.103
$(\Delta/\sigma)_{max}$	0.002	0.001
$\Delta\rho_{max}$ and $\Delta\rho_{min}$(e Å^{-3})	0.413 and −0.286	0.767 and −0.440
Data/restraints/parameter	5586/0/271	6082/12/241

Note: $w = 1/[\sigma^2(F_0^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$; parameters a and b are 0.0701, 0.3657 (**4c**), and 0.0651, 0.000 (**4g**), respectively.

with the riding options. The distances with hydrogen atoms are aromatic/sp2 C—H = 0.93 Å, methylene C—H = 0.97 Å, methine C—H = 0.98 Å, and Uiso = 1.2 Ueq (parent). Essential crystal data are listed in Table 2. Crystallographic data for the structures in this article have been deposited with the Cambridge Crystallographic Data Centre with the following accession numbers: CCDC 801979 (**4c**) and CCDC 801980 (**4g**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Database Study

Cambridge Structural Database (version 5.31) searches were carried out using *Conquest* (version 1.12) and analyzed with *VISTA* (version 2.1).

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