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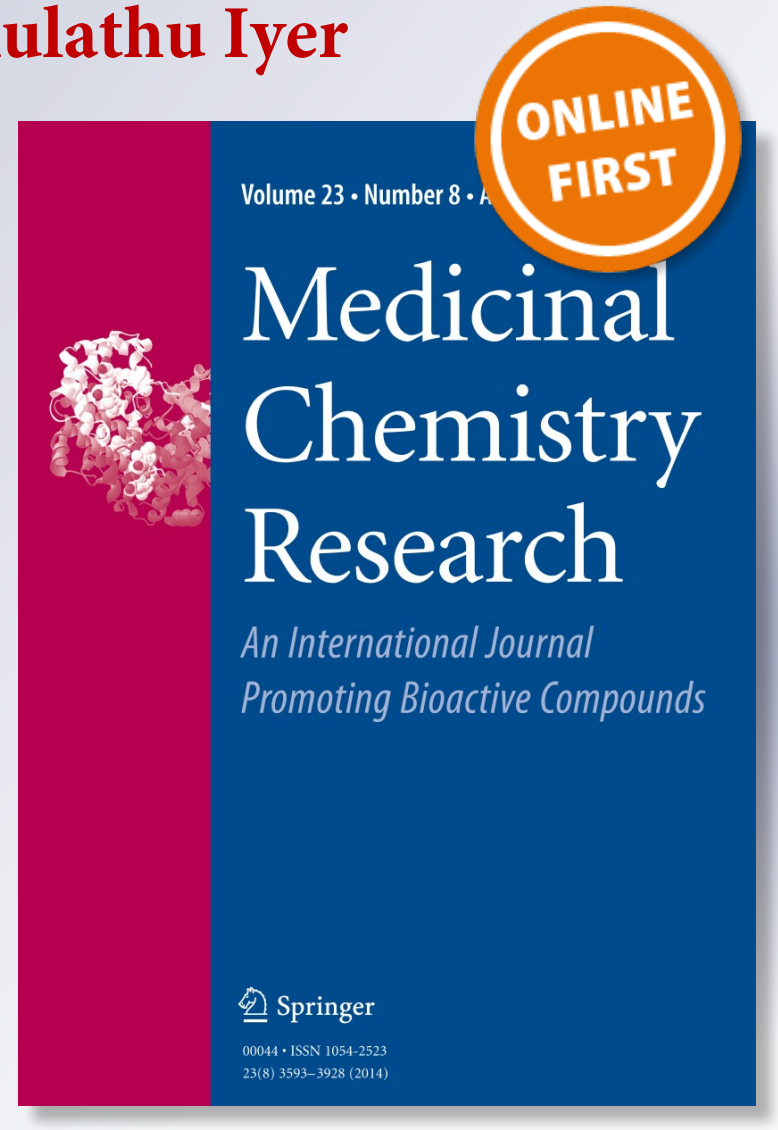

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A mild and efficient one-pot three-component synthesis of anti-β-amino-carbonyl compounds catalyzed by NH_4OAc and their anticancer activities

Sathesh Venkatesan · Natesan Sundaramoorthy Karthikeyan · Ravindranath S. Rathore · Periyasamy Giridharan · Kulathu Iyer Sathiyanarayanan

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Abstract The diastereoselective direct one-pot three-components Mannich reaction of cyclododecanone (CDD), which has a unique conformation with aromatic aldehydes and anilines in the presence of catalytic amount of ammonium acetate was studied. The catalyzed reaction offered high yield, high diastereoselectivity, and simple workup. The addition of aniline to the aldol product took place, and this addition was made to the less hindered α-side. The Mannich derivatives were found to exhibit anti-cancer activities against six human cancer cell lines. This was observed using the CCK-8 nonradioactive colorimetric assay and the results were compared with MCFA10 normal breast epithelium cell line. A significant difference was observed in anti-cancer activity of anti (**7f–7h**) and syn (**7ff–7hh**) isomers in human cancer cell lines.

Electronic supplementary material The online version of this article (doi:10.1007/s00044-014-1065-2) contains supplementary material, which is available to authorized users.

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Keywords Cyclododecanone (CDD) · Diastereoselectivity · Anti-Mannich-type · Aldol and Michael · NH_4OAc-catalyzed · Steric strain and anti-cancer activity

Introduction

In the past few decades, Mannich and Mannich-type reactions have become very useful platforms for the development of biologically active compounds for C–C bond formation (List *et al.*, 2002; Joshi *et al.*, 2004). Several reports have disclosed significant advantages of cyclododecanone (CDD) as a precursor to the synthesis of β-hydroxy carbonyl compounds and natural products containing macrocyclic ring systems such as the rosphellin (anti-cancer agent) (Trost and Doherty, 2000; Salamone and Dudley, 2005). CDD is the precursor of 12-formyldodecanonic acid, which is a main building block in the total synthesis of altohyrtin C. These have been identified as being potent against human colon (HCT116) cell line (Zoorob *et al.*, 2011; Carl *et al.*, 2008). Methyl jasmonate and jasmonic acid have also been found to induce death in lymphoblastic leukemia cells and it has been observed that they cause suppression of cell proliferation in other human cancer calls (Fingrut and Flescher, 2002) and also to some extent for the agrochemical, flavor, and fragrances industries (Trost and Doherty, 2000; Salamone and Dudley, 2005; Zoorob *et al.*, 2011; Carl *et al.*, 2008; Tombo and Bellus, 1991). Enantiomers play a major role in biological activity. For example, the (*R*)-(+)-enantiomer of the herbicide dichloprop is an active enantiomer in killing the weeds, whereas the (*S*)-(−)-enantiomer is inactive as a herbicide (Lewis *et al.*, 1999; Hegeman and Laane, 2002). Methyl jasmonate is a unique example of plant growth

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regulator, valuable fragrance material whose stereoisomers have remarkably different odor intensities (Kobayashi *et al.*, 1980; Acree *et al.*, 1985). There are a quite large number of reports of one diastereoisomer having biological activity and the other isomers not having biological activity. For example, timberol is mainly composed of four racemic diastereoisomer and shows a powdery-woody odor (Schulte-Elte *et al.*, 1985; Brenna *et al.*, 2003) with animal, steroid type undertones and it was further established that the woody animal note was due to the only anti-diastereomer. Similarly (1*R*,2*R*)-(−)-methyl(*Z*)-jasmonate (1*R*,2*R*) and its diastereoisomer (+)-(1*R*,2*S*) occur in nature in the proportions of 97:3 for the odor of jasmine flower oil (*Jasminium grandiflorum* L.) whereas their enantiomers are nearly odorless (Demole *et al.*, 1962; Demole, 1982).

Nowadays, many new single diastereomeric or enantiomeric drugs with a well-timed chiral switch are being produced to enhance therapy with more predictable pharmacologically active isomers (Xiaodong *et al.*, 2011). In pharmacology, chirality is an important factor in drug efficacy. About 56 % of the drugs are chiral compounds, and about 88 % of these chiral synthetic drugs are used therapeutically as racemates (Rentsch, 2002; Leffingwell, 2003). Enantiomers can be prepared either via a synthetic approach or by the separation of racemates (Noyori, 1994; Schuur *et al.*, 2011). Enantiomerically pure compounds can be obtained through the synthetic routes using either natural compounds or asymmetric synthesis.

Several groups have reported catalytic Mannich reactions and have stated that these produce β-amino-carbonyl compounds by the coupling of three different components (Cordova, 2004; Ollevier and Nadeau, 2004). Recently, the three-component (MCRs) reactions of Mannich and Mannich-type reactions have been catalyzed by lanthanide triflates (Kobayashi *et al.*, 1995, 1999), bismuth triflates (Gaspard-Iloughmane and Le Roux, 2004), phenylboronic acid (Santosh *et al.*, 2013), zinc tetrafluoroborate (Brindadan *et al.*, 2002), and Cu-nanoparticles (Mazaahir *et al.*, 2009) to get sole diastereomers. Although these methodologies are useful, most of the methods encounter some limitations, such as the requirement of expensive catalysts or longer reaction time, and poor diastereoselectivity.

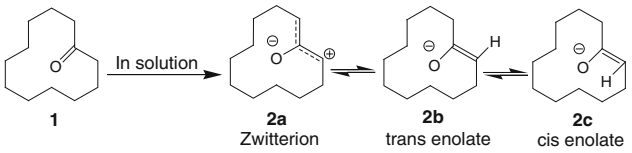
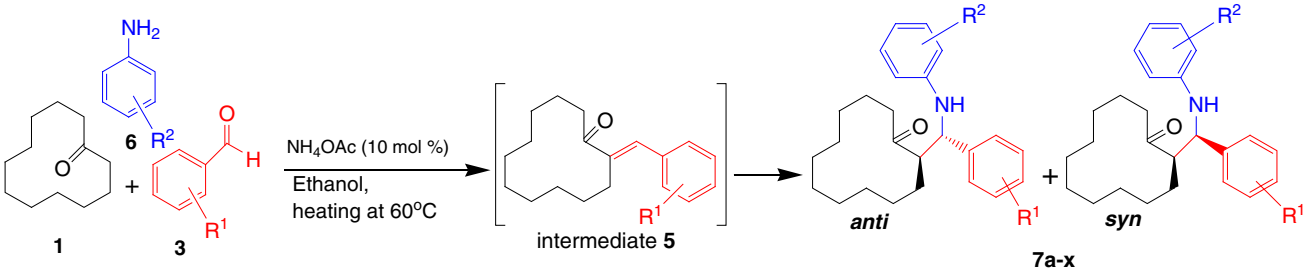


Fig. 1 The formation of zwitter ion cyclododecanone (CDD)

Hence there exists wide scope for the development of new methodologies for the preparation of β-amino-carbonyl compounds through more suitable and environmental friendly methods. Many attempts have been made in the past few decades to improve the selectivity based on two-component reactions, where the imine (Brindadan *et al.*, 2002; Uraguchi *et al.*, 2008; Ueno *et al.*, 2002; Handa *et al.*, 2010) as electrophile is pre-formed and then it reacts with nucleophile such as enolate and enol ethers (Ollevier and Nadeau, 2004; Enders *et al.*, 1996; Palomo *et al.*, 2000). The Mannich reaction had been well studied in cases of cyclohexanone (Wang *et al.*, 2007), silyl enol ethers of cyclic (Ueno *et al.*, 2002), acyclic ketones (Ollevier and Nadeau, 2004; Ueno *et al.*, 2002), and unmodified propiophenone (Zhang *et al.*, 2006). The diastereoselectivity was very poor in all these cases. However, such extensive study of Mannich reaction in CDD has not been carried out so far.

The conformation of CDD is different from other cyclic (cyclohexanone) and acyclic ketones, since it (CDD) suffers from ring strain and bad transannular interaction (Sathesh *et al.*, 2012; Goodman *et al.*, 1995; Rawdah, 1991), which are observed in higher cyclic ketones ($n > 7$) (Rawdah, 1990; Ledaal, 1968) as shown in Fig. 1. Ketone is supposed to play a major role in diastereoselectivity. The CDD takes part in the reaction in the form of a W-shaped zwitter ion with dynamic equilibrium in [3333]-2-one square conformation (Sathesh *et al.*, 2012; Goodman *et al.*, 1995).

Ammonium acetate (NH_4OAc) is a readily available, inexpensive catalyst used in many of MCR's like preparation of phenanthridine (Sathiyanarayanan *et al.*, 2009), cross-aldol reaction (Karthikeyan *et al.*, 2009), Betti's base reaction (Karthikeyan *et al.*, 2012), and 1,4-dihyropyridine derivatives (Tewari *et al.*, 2004), synthesis of trifluoromethylated cyclopenta[*b*]pyran derivatives (Cao *et al.*, 2012), synthesis of *N*-methylpiperidin-4-one oxime esters



Scheme 1 Ammonium acetate catalyzed Mannich reaction in cyclododecanone

(Salakatte *et al.*, 2013), and synthesis of teichoic acid fragments (Hogendorf *et al.*, 2012). NH_4OAc has been used as a catalyst because of its dual behavior of acting as catalyst and a reactant. The Mannich-type reaction in the synthesis of 2-[(*E*)-(benzylideneamino)(aryl)methyl] CDD using NH_4OAc as a catalyst (Karthikeyan *et al.*, 2011a, b) was recently reported from our laboratory. Hence, in continuation of our earlier research, we used NH_4OAc as a mild and efficient catalyst for the green transformation of CDD into Mannich product.

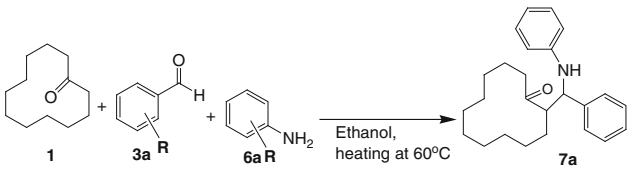
In this paper, we report the synthesis and anti-cancer evaluation of highly diastereoselective novel direct one-pot Mannich reaction of benzaldehyde (0.01 mol), aniline (0.01 mol) with CDD (0.01 mol). This has special properties involving diastereoselectivity with the use of ammonium acetate as catalyst as shown in Scheme 1. The β-amino-carbonyl compounds were synthesized via Mannich approach in order to investigate the role of hetero atoms and aromatic ring substitution on the anti-cancer activities of those analogues. The analogues were evaluated for anti-cancer activity utilizing six different human cancer cell lines using CCK-8 non radioactive colorimetric assay, via Panc1 (pancreas), ACHN (renal), HCT116 (colon), H460 (non small cell lung), Calu1 (lung), and MCF7 (breast cancer). These results were then compared with MCF10A, normal breast epithelium cell line.

Results and Discussion

Chemistry

In order to find out the optimal catalyst loading, the Mannich reaction was carried out using benzaldehyde (0.01), aniline (0.01), and CDD (0.01) as representative reactants with 10 mol% of Lewis acids such as CAN, $LaCl_3{\cdot}7H_2O$, $ZnCl_2$ and mild base catalyst like ammonium acetate (Table 1). However, the best results were obtained with 10 mol% ammonium acetate. The reaction took 12 h, and the yield was 92 %. However, with an increase in the amount of ammonium acetate the reaction time decreased, but it also showed a corresponding decrease in yield.

Table 1 Optimization of catalyst in diastereoselective Mannich reactions of **1**, **3a**, and **6a**



1 3a 6a 7a

Entry	Catalyst	Cat. load (mol%)	*t* (h)	Yield (%)[a]
1	CAN	10	22	58
2	$LaCl_3{\cdot}7H_2O$	10	24	55
3	$ZnCl_2$	10	17	66
4	NH_4OAc	10	12	92
5	NH_4OAc	15	10	80

To a solution of parent benzaldehyde (0.01 mol), aniline (0.01 mol) CDD (0.01 mol) in C_2H_5OH (3–4 ml) and catalyst (10 %) were added, and the mixture was heated at 60 °C

[a] Isolated yield

The solvent was the next factor for consideration to study the reaction. Hence, the reaction was tried with various solvents. Out of these solvents, ethanol was found to be effective in terms of the time taken and the yield produced. In continuation, further derivatives were synthesized using 10 mol% of NH_4OAc in ethanol. The optimum conditions for the one-pot multi-component Mannich reaction for the synthesis of β-amino-carbonyl compounds at 60 °C and its results are summarized in Table 2.

In the case of ammonium acetate catalyst (10 mol%) the anti-product (98 %) was obtained with 92 % yield. The products were obtained in pure form when parent and para-substituted benzaldehydes were used, whereas when ortho- and meta-substituted benzaldehydes were used, column chromatography was required for purification. Even though the product formation was diastereoselective in the case of a majority of benzaldehydes (ammonium acetate catalyzed), the deviation occurred in the case of sterically congested ortho and meta substituted aromatic aldehydes. The yield was found to be excellent, but the diastereoselectivity decreased in 2-Br, 2-CF_3, and 4-OC_3H_5 (Table 3, entries 4, 5, and 14). This was due to the bulkiness of the substituents. With 3-F, 2-OMe, and 3-Me (Table 3, entries 6–8) syn (**7ff**, **7gg**, **7hh**) and anti (**7f**, **7g**, **7h**) diastereoisomers could be isolated separately through the normal column chromatography. The separation was confirmed by NMR and melting points as shown in ESI.

To elucidate the three-dimensional details, attempts were made to crystallize these compounds and examine their structures. Suitable single crystals could be grown for compound entry 5 (**7e**), and the crystal structures of entries 5 (**7e**) have been discussed. In order to study the effects of substituents on the aniline side, the reaction was carried out with 2-OH aniline with various benzaldehydes. However, less diastereoselectivity was got. Hence, the reaction was not tried with anilines other than 2-OH and 3-Cl anilines.

In this study, it was found that the reaction mechanism of this one-pot reaction was complex, and it involved more than one pathway. In the first step, ammonium acetate reacted with benzaldehyde to form aldimine (**4**), which was less stable and it further reacted with enolate of CDD (**2**) to form deaminated product (**5**), i.e., monobenzylidene CDD intermediate. The deaminated product reacted with aniline

(**6**) via aza-Michael reaction to give the Mannich product. The mechanism is shown in Fig. 2. There is evidence for the formation of deaminated product using with NH_4OAc as a catalyst (Tan and Weaver, 2002).

The same reaction was tested starting from intermediate (**5**), which was obtained through another reaction. (The details of NMR spectra and m.p. have been given in the experimental section) We found that it perfectly reacted with aniline to give the same product, and the mechanism has been proved beyond any doubt. Hence, the aza-Michael reaction can be performed in one-pot fashion without isolating α,β-unsaturated ketone. This unique reaction was produced only by CDD and not by any other cyclic ketone. In the formation of anti-aldol product (Sathesh *et al.*, 2012) and aldol product involving pinacol coupling reaction (Tsuritani *et al.*, 2000) CDD gives only anti-diastereoselective products. This was possible by ammonium acetate because of its dual nature. There is one more evidence for the dual nature of ammonium acetate in the synthesis of α,β-unsaturated ketone ((3*E*,5*E*)-1-benzyl-3,5-dibenzylidenepiperidin-4-one) using ammonium acetate as a catalyst (Karthikeyan *et al.*, 2009).

Crystal structures of representative compounds, **7e**

A view of structure of **7e** is shown in Fig. 3. In the reported models of the centrosymmetric crystal of **7e**, the stereogenic centers (C2 and C13) adopt *R* and *S* configurations, respectively (Cahn *et al.*, 1966). Aniline –NH group is in pyramidal configurations. The CDD ring adopts [3333] square conformation (422 symmetry) in all the three compounds (Sathesh *et al.*, 2012; Anet, 1974; Dale, 1976). The numbers in the square brackets indicate the number of ring bonds between the four corner atoms of the CDD ring. The [3333] square conformation is the most favoured conformation of the cyclododecane. Based on theoretical calculations, the other three lowest energy conformation for the 12-membered ring were found to be [2334], [1434], and [2343] (Kolossváry and Guida, 1993). Crystal packing in **7e** was characterized by intermolecular (aniline) N1–H1···O1=C1 (CDD) hydrogen bonded molecular dimers as shown in Figure S2 (ESI). Short intermolecular C–H···F and C–H···O contacts stabilize structures of **7e** (Table 4). Significant short halogen···halogen contacts were observed in **7e** [F1B···FIB^{i}, symmetry code (i): $1 - x$, y, $1/2 - z$, F···F distance = 2.54(3) Å].

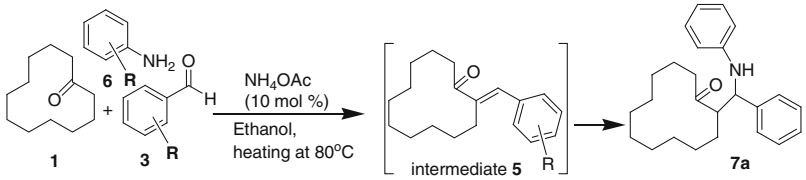
In Fig. 3, the molecular structure of **7e** shows the adopted atom-numbering scheme. Displacement ellipsoids are drawn at 30 % probability level and H atoms are shown as small spheres of arbitrary radii. Only major components of the trifluromethane group in **7e** are shown.

Biological studies

Anti-cancer activity of β-amino-carbonyl analogues

Earlier CDD derivatives have been reported to exhibit anti-cancer activities (Trost and Doherty, 2000;

Table 2 Screening of solvents



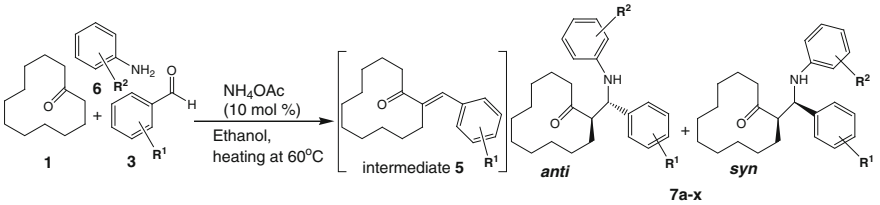
Entry	Solvents[a]	Time (h)	Yield (%)[b]
1	C_2H_5OH	12	92
2	CH_3OH	14	82
3	CH_2Cl_2	14	86
4	THF	16	68
5	*i*PrOH	19	72
6	$CHCl_3$	15	78
7	CH_3CN	17	60
8	H_2O	22	85
9	$CH_3COOC_2H_5$	24	46

[a] Reaction condition: a solution of parent benzaldehyde (0.1 mmol), aniline (0.1 mmol), and CDD (0.1 mmol) and a catalyst (NH_4OAc) in a solvent (3–4 ml) was heated on water bath at 60 °C

[b] Isolated yield

Salamone and Dudley, 2005). Hence, it was judicious to test the present compounds for anti-cancer screening. Anti-cancer studies were carried out at two different concentrations of 1 and 10 μM against a panel of six human cancer cell lines. The human tumor cell lines of Panc1 (pancreas), ACHN (renal cancer), HCT116 (colon), H460 (non-small cell lung) and Calu1 (lung), MCF7 (breast cancer), and MCF10A (normal breast epithelium) were used for evaluating anticancer activity on the high throughput screening platform using Cell

Table 3 Anti-/syn-Mannich-type reaction of cyclododecanone catalyzed by ammonium acetate (10 mol%)



	R^1	R^2	Product (**7**)	*t* (h)	Yield (%)[a]	Anti/syn[c]
1	H	H	**7a**	12	92	98/2
2	2-Cl	H	**7b**	18	78	94/6
3	2-OEt	H	**7c**	20	75	99/1
4	2-Br	H	**7d**	18.5	80	80/20
5	2-CF_3	H	**7e**	17	82	33/67[d]
6	2-OMe	H	**7f**	19.5	57[b]	100/0[d]
			7ff	19.5	29[b]	100/0
7	3-Me	H	**7g**	19	58[b]	100/0
			7gg	19	26[b]	100/0
8	3-F	H	**7h**	18	57[b]	100/0[d]
			7hh	18	25[b]	100/0
9	3-Br	H	**7i**	21	80	99/1
10	4-Me	H	**7j**	15	84	98/2
11	4-OEt	H	**7k**	22	74	99/1
12	4-Cl	H	**7l**	19.5	86	100/0
13	4-Br	H	**7m**	16	84	100/0
14	4-OC_3H_5	H	**7n**	23	66	73/27
15	4-F	H	**7o**	18	90	100/0
16	4-NO_2	H	**7p**	17.5	92	94/6
17	H	2-OH	**7q**	23	65	60/40
18	α-Methyl-*trans*-cinna.	4-Cl	**7r**	22.5	68	100/0
19	4-Me	2-OH	**7s**	24	59	67/33
20	2-F	2-OH	**7t**	26	55	70/30
21	3-OH	2-OH	**7u**	26	Trace	n.d[e]
22	4-Et	2-NO_2	**7v**	28	Trace	n.d[e]
23	3-NO_2	4-Cl	**7w**	27	Trace	n.d[e]
24	2-Cl	3-Cl	**7x**	25.5	65	100/0

Reaction condition: benzaldehyde (0.01 mol), aniline (0.01 mol), and CDD (0.01 mol) and NH_4OAc (10 mol%) in ethanol (3–4 ml) were heated on water bath at 60 °C

[a] Isolated yield

[b] Anti and syn products were separated by column chromatography

[c] The anti/syn ratio as determined by ^{1}H-NMR analysis

[d] The crystal structures of compounds **5**–**6** and **8** (**7e**, **7f**, and **7h**) were examined

[e] Not determined

Counting Kit (CCK8) (Ramachandran *et al.*, 2012; Karthikeyan *et al.*, 2011a, b) cell proliferation and cytotoxicity assays.

In this work, the β-amino-carbonyl analogue was identified as a biologically active molecule, which had two adjacent stereogenic centers. Of the 21, 13 analogues were

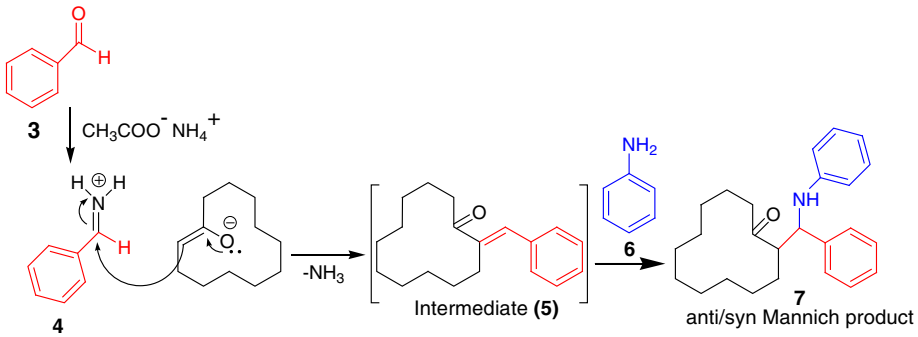


Fig. 2 Plausible reaction mechanistic path way in NH_4OAc catalytic cycle for the formation Mannich product via aldol and aza-Michael reaction in one-pot manner

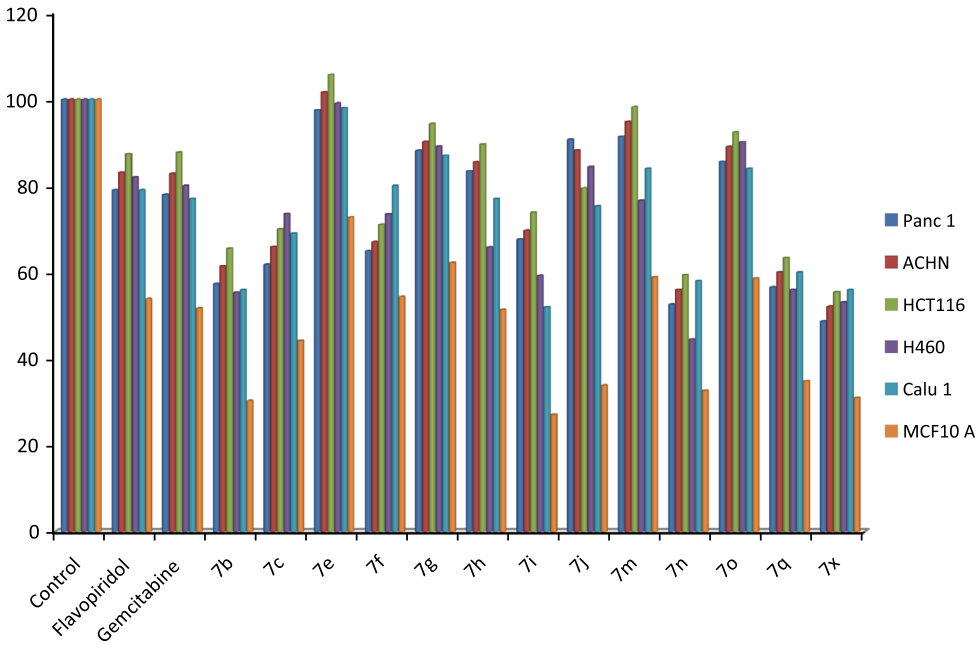


Fig. 3 The ORTEP diagram of **7e**

Table 4 Observed intermolecular interactions in **7e**

Interaction	D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H A(°)
(**7e**)	N1–H1···O1[i]	0.86 (3)	2.31 (3)	3.137 (3)	162 (2)
	C13–H13···F1A	0.98	2.30	3.016 (7)	129
	C16–H16A···F3A	0.93	2.27	2.623 (8)	102
	C21–H21···F1A	0.93	2.46	3.383 (8)	170

Symmetry code [i]: 1/2 − *x*,3/2 − *y*,−*z*, [ii] 1 − *x*,−*y*,1 − *z*, [iii] 2 − *x*,2 − *y*,2 − z, [iv] *x*, 3/2 − *y*,−1/2 + *z*. Cg2 is the centroid of (C20–C25) ring. Intermolecular N–H···O hydrogen bonded molecular dimers observed in (a) **7e**, (b) **7f**, and (c) **7h** as shown in Fig. S2 (supporting information)

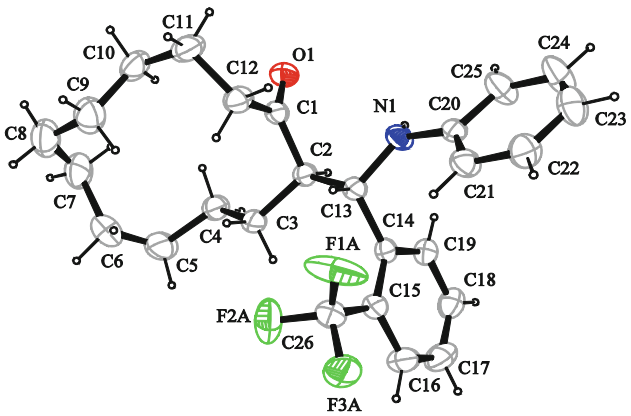


Fig. 4 Cytotoxic activity of active compound at 10 μM concentration against cancer cell lines

Table 5 IC_{50} values of in vitro anti-cancer activity of β-amino-carbonyl analogue against six different cancer cell lines

S. no	Product	Concentration (IC_{50} in μM)[a]						
		Panc1 (pancreas)	ACHN (renal)	HCT116 (colon)	H460 (non small cell lung)	CALU1 (lung)	MCF7 (breast cancer)	MCF10A (normal breast epithelium)
1	**7b**	5.6 ± 0.72	4.8 ± 0.72	3.3 ± 0.42	6.1 ± 0.91	6.7 ± 0.86	5.3 ± 0.79	>10
2	**7c**	2.8 ± 0.36	5.3 ± 0.79	2.2 ± 0.28	3.5 ± 0.52	4.2 ± 0.54	6.8 ± 1.01	>10
3	**7e**	0.4 ± 0.04	0.3 ± 0.04	0.2 ± 0.02	0.4 ± 0.06	0.5 ± 0.07	0.4 ± 0.06	2.8 ± 0.42
4	**7f**	5.7 ± 0.73	5.2 ± 0.78	3.3 ± 0.43	7.0 ± 1.04	6.9 ± 0.89	6.0 ± 0.89	9.87 ± 1.47
5	**7g**	3.7 ± 0.48	5.9 ± 0.88	2.5 ± 0.32	3.7 ± 0.55	5.0 ± 0.64	7.8 ± 1.16	8.7 ± 1.30
6	**7h**	5.5 ± 0.71	4.8 ± 0.72	2.9 ± 0.37	6.6 ± 0.98	6.9 ± 0.88	5.7 ± 1.16	8.7 ± 1.30
7	**7i**	4.8 ± 0.62	7.2 ± 1.07	6.1 ± 0.78	7.8 ± 1.16	9.3 ± 1.19	8.7 ± 1.30	>10
8	**7j**	3.7 ± 0.36	4.7 ± 0.43	5.5 ± 0.36	4.5 ± 0.28	3.6 ± 0.61	5.6 ± 0.83	>10
9	**7m**	4.3 ± 0.56	6.1 ± 0.91	3.4 ± 0.44	4.6 ± 0.69	5.7 ± 0.73	7.9 ± 1.18	9.3 ± 1.39
10	**7n**	6.3 ± 0.81	5.8 ± 0.86	3.2 ± 0.41	7.0 ± 1.04	7.8 ± 1.00	6.4 ± 0.96	>10
11	**7o**	6.7 ± 0.86	6.4 ± 0.96	3.3 ± 0.42	7.0 ± 1.05	8.3 ± 1.07	7.3 ± 1.08	8.2 ± 1.22
12	**7q**	4.6 ± 0.59	6.6 ± 0.99	4.4 ± 0.56	5.5 ± 0.81	6.5 ± 0.84	8.1 ± 1.22	>10
13	**7x**	5.9 ± 0.76	5.2 ± 0.78	3.1 ± 0.40	6.6 ± 0.99	7.5 ± 0.96	6.6 ± 0.99	>10
Gemcitabine		0.38 ± 0.04	0.78 ± 0.07	1.15 ± 0.21	1.23 ± 0.23	0.98 ± 0.11	0.85 ± 0.16	>10
Flavopiridol		0.62 ± 0.05	0.56 ± 0.08	0.91 ± 0.11	0.73 ± 0.08	0.82 ± 0.09	0.79 ± 0.19	>10

[a] The experiment was performed in triplicate for three repeats and IC_{50} values were expressed as mean ± SEM

found to have moderate to good anti-cancer activity against human tumor cell lines in preliminary screening as shown in Table S1 (ESI), and the pictorial representation of an active compound against these cancer cell lines at 10 μM concentration is shown in Fig. 4. The compound **7e** showed highest potent activity in the initial screening at 1 μM concentration. The anti-isomers **7f**, **7g**, and **7h** analogues were biologically active whereas the syn-isomers **7ff**, **7gg**, and **7hh** analogues were biologically inactive. The results are expressed in percentage inhibition with respect to positive control flavopiridol and gemcitabine.

We evaluated IC_{50} value of primary active analogue to study the activity against six different cancer cell lines. Compound **7e** showed potent activity against these cancer cell lines with very less cytotoxicity in 10 μM concentration. Analogues of **7g**, **7h**, **7j**, **7m**, and **7o** showed good activity with less cytotoxicity, whereas all other analogues like **7b**, **7c**, **7f**, **7i**, **7n**, **7q**, and **7x** showed moderate activity against these cancer cell lines with moderate cytotoxicity. The results revealed that the compound **7e** showed potent IC_{50} in the range of 0.2–0.5 μM concentrations in all the cancer cell lines, whereas the IC_{50} for MCF10A was 2.8 μM (normal breast epithelium cells). Analogue of **7e** was highly active toward proliferating cells and even other compounds **7c**, **7g**, **7h**, and **7q** were found to be potentially active against cancer cell lines with less cytotoxicity on normal breast epithelium cells. The optimum concentration to inhibit 50 % of cells was found to be IC_{50} value for each compound. All the data have been expressed as mean ± SEM of three independent experiments. The results obtained for the active analogues are reported in Table 5. In most of the cases, these analogues were found to possess good activity against cancer cells, when the aromatic aldehydes contained electron-withdrawing groups.

Conclusions

A novel one-pot three-component Mannich reaction involving CDD, aniline, and benzaldehyde in the presence of NH_4OAc was developed. We got an overall anti-β-amino-carbonyl compound as the predominant one. The mechanism of this reaction is unique. When the ammonium acetate (10 mol%) was used as catalyst, a mixture of anti- and syn-products were obtained. These products were formed via aldol/aza-Michael reaction in one-pot manner, and the intermediate (**5**) of deaminated product was isolated. There are numerous benefits of using ammonium acetate as a catalyst. These benefits include mild reaction condition, easy work up procedure, and high yield.

Several β-amino-carbonyl scaffolds containing CDD derivatives were potent against human tumor cells. The significant difference was observed between anti- and syn-isomers of **7f–h** and **7ff–hh** derivatives. The preliminary study showed a foundation for the further development of new single diastereomer anti-cancer drugs, even though diastereoisomeric mixture of **7e** was found to be more

potent in all the cancer cell lines. We also studied the crystal structures of **7e**, and observed intermolecular N–H···O hydrogen bonded molecular dimers.

Experimental

General information

All chemicals were purchased from commercial sources, and they were used without further purification unless otherwise specified. TLC—thin layer chromatography was performed on pre-coated silica gel on alumina plates. Melting points were recorded by microprocessor digital melting point apparatus and are uncorrected. IR spectra were recorded in the range 4,000–400 cm^{-1} using KBr pellet technique. The solution IR spectra were recorded at 4,000–560 cm^{-1} using analytical grade dichloromethane as solvent. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 and 400 MHz using $CDCl_3$ as the solvent with TMS as an internal standard. HRMS analysis was obtained from double focusing electron impact method.

The catalytic amount of NH_4OAc in 3–4 ml of ethanol was mixed with aromatic benzaldehydes (**3a**–**x**) 0.01 mol, gently warmed in a water bath followed by addition of CDD (**1**) (0.01 mol) and it was further warmed gently for 5 min. After the subsequent addition of aniline (**4**) 0.01 mol the resulting mixture was gently warmed for 15 min until the color changed from yellow to orange. The reaction was monitored by TLC and the period of time is listed in Table 3. Column chromatography was performed on silica gel using *n*-hexane and EtOAc as elutant. The isolated final product was recrystallized using ethanol and THF in 1:1 ratio.

Cell Line Maintenance

A panel of six cancer cells representing multiple cancers of clinical relevance were selected, namely; ACHN (human renal cell, ATCC, CRL-1611), Panc-1 (human pancreatic, ATCC, CRL-1469) cultured on MEM with 2 mM L-glutamine and 10 % FBS, H460 (human non small cell lung carcinoma, ATCC, HTB-177), Calu-1 (human lung carcinoma, ATCC, HTB-54) and MCF7 (human breast adenocarcinoma, ATCC HTB-22) cultured on RPMI, 2 mM L-glutamine and 10 % FBS, HCT-116 (human colon cancer, ATCC, CCL-247) cultured on McCoy's **5a** medium and 10 % FBS and MCF10A (normal breast epithelium cells) cultured on MEM with 2 mM L-glutamine and 10 % FBS.

Crystallography details

Single crystals for data collection were grown from a mixture of THF and ethanol in (1:1) ratio. Data were obtained from a Bruker SMART diffractometer. Crystals were stable during data collection. Structures were solved by applying the direct phase-determination technique using SHELXS-97, and refined by full-matrix least square on F2 using SHLEXL-97 (Bruker, 2004). All the structure calculations were performed with WinGX suit of programs (version 1.70.01) (Sheldrick, 2008; Farrugia, 1999). The trifluromethane group in **7e** possesses conformational disorder with contribution of major and minor components of 0.67(2) and 0.33(2), respectively. All C–F atomic distances were restrained to be the same using SADI options in SHELX-97. The hydrogens were placed in the geometrically expected positions and refined with the riding options. N–H hydrogens were isotropically refined. The distances with hydrogen atoms are: aromatic/sp2 C–H = 0.93 Å, methyl C–H = 0.96 Å, methylene C–H = 0.97 Å, methine C–H = 0.98 Å, N–H = 0.84(2)–0.91(3) Å, and Uiso = 1.2 Ueq (parent)/1.5 Ueq(CH3). Essential crystal data are listed in Table S2 (see supporting information). Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre having following accession number—CCDC 876363 (**7e**). 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 email: deposit@ccdc.cam.ac.uk).

(E)-1-(2-Chlorobenylidene)cyclododecanone ***5*** *intermediate for mechanism proof using* NH_4OAC *as catalyst*

The crude, light yellow viscous oil was subjected to column chromatography on silica gel (4:1 *n*-hexane:EtOAc) to afford **7b** Mannich product and monobenzylidene intermediate **5** *E*/*Z* = 96/4, R_f 0.4 (4:1 hexane:EtOAc); white crystalline solid; M.P: 93–95 °C; FT-IR (KBr) υ = 3066.8, 2940.0, 2855.7, 1661.7, 1465.4, 1361.7, 1239.9, 1157.7, 939.2, 870.3, 767.8, 692.5; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.46 (s, 1H, CH vinylic); 7.44–7.42 (td, 4.4, 1.2 Hz, 1H, CHAr); 7.28–7.25 (m, 3H, CHAr); 2.87–2.84 (m, 2H, $CH2_{ali}$); 2.54–2.51 (t, 12 Hz, 2H, $CH2_{ali}$); 1.86 (s, 2H, $CH2_{ali}$); 1.32 (s, 11H, $CH2_{ali}$); 1.24 (s, 1H, CH_{ali}); 1.13–1.11 (t, J = 10.4 Hz, 2H, $CH2_{ali}$). ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 205.0_{(C=O)}$, 143.2, 136.0, 134.7, 133.8, 130.3, 129.4, 129.2, 126.4, 38.8, 26.5, 26.4, 25.4, 24.4, 24.2, 24.1, 23.9, 23.1, 22.5; GC–MS *m*/*z*: Calc. for C19H25ClO; 304.1593 $[M]^+$; Found 305.2032 $[M]^{+1}$.

*2-(Phenylamino)-phenyl-methyl)-cyclododecanone (****7a****)*

The crude, colorless solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture of solvents (THF and ethanol 1:1 ratio) to afford anti-Mannich product

(**7a** was prepared by benzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml) (3.343 g, 92 %; anti/syn 98:2); Mp: 167–169 °C; FT-IR (KBr): ν cm^{-1} $3385.0_{NH\ peak}$, 3059.1, 3026.3, 2939.5, 2920.2, 2843.0, $1695.4_{C=O}$, 1604.8, 1321.2, 1284.5, 970.2, 866.0, 750.3; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.33–7.19 (m, 5H), 7.08–7.04 (m, 2H), 6.65–6.61 (t, $J = 14$ Hz, 1H), 6.49–6.48 (d, $J = 7.6$ Hz, 1H), 4.57–4.55 (d, $J = 6.4$ Hz, $1H_{CH^*}$), 4.22 (s, $1H_{\ NH}$), 3.23–3.17 (qd, $J = 17.2$, 8.6, 2.8 Hz, 1H), 2.62–2.55 (qd, $J = 26.4$, 13.2, 3.2 Hz 1H), 2.17–1.29 (m, 19H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 213.3(C=O, C-1), 147.1 (C, C-20), 141.5 (C, C-14), 129.0 (CH, C-15,16,18,19), 128.6 (CH, C-22,24), 127.2 (CH, C-17), 126.9 (CH, C-23), 113.6 (CH, C-23), 58.7 (CH*, C-13), 56.6 (CH*, C-12), 40.7 (CH_2, C-2) 25.6 (CH_2, C-3), 25.4 (CH_2, C-4), 25.3 (CH_2, C-5), 25.2 (CH_2, C-6), 25.0 (CH_2, C-7), 24.4 (CH_2, C-8), 23.5 (CH_2, C-9), 22.5 (CH_2, C-10), 22.3 (CH_2, C-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{33}NO$, 363.2562 $[M]^+$; Found 363.2558.

*2-[(Phenylamino)-2-chlorophenyl-methyl]-cyclododecanone (**7b**)*

The crude, light yellow viscous oil was subjected to column chromatography on silica gel (4:1 *n*-hexane:EtOAc) to afford anti-Mannich product (**7b** was prepared by 2-chlorobenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.096 g, 78 %; dr 94:6); R_f 0.48 (4:2 *n*-hexane EtOAc); Mp: 140–142 °C; FT-IR (KBr): ν cm^{-1} 3350.4_{NHpeak}, 3052.3, 3029.3, 2924.0, 2872.2, $1697.4_{C=O}$, 1602.9, 1259.5, 1139.9, 952.9, 688.6; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.38–7.36 (d, $J = 3.6$ Hz, 1H), 7.27–7.25 (t, $J = 6$ Hz, 1H), 7.17–7.14 (t, $J = 9$ Hz, 2H), 7.09–7.04 (t, $J = 15.6$ Hz, 2H), 6.64–6.59 (t, $J = 14.4$ Hz, 1H), 6.48–6.46 (d, $J = 7.5$ Hz, 2H), 4.99 (s, $1H_{CH^*}$) 4.79 (s, $1H_{NH}$), 3.10–3.08 (t, $J = 7.2$ Hz, 1H), 2.39–2.36 (d, $J = 9.6$ Hz, 1H), 2.14–1.28 (m, 19H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 214.9 (C=O, C-1), 146.2 (C, C-20), 138.2 (C, C-14), 133.4 (C–Cl, C-15), 129.7 (CH, C-19), 129.2 (CH, C-22,24), 128.6 (CH, C-16), 127.8 (CH, C-17), 127.4 (CH, C-18), 117.5 (CH, C-23), 113.0 (CH, C-21,25), 57.0 (CH*, C-13), 55.9 (CH*, C-12), 40.9 (CH_2, C-2), 28.4 (CH_2, C-3), 26.3 (CH_2, C-3,4), 25.7 (CH_2, C-5,6), 24.5 (CH_2, C-7), 24.4 (CH_2, C-8,9), 22.7(CH_2, C-10), 21.9 (CH_2, C-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}ClNO$, 397.2172 $[M]^+$; Found 397.2172.

*2-[(Phenylamino)-2-ethoxyphenyl-methyl]-cyclododecanone (**7c**)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (7:3 *n*-hexane:EtOAc) to afford anti-Mannich product (**7c** was prepared by 2-ethoxybenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.058 g, 75 % dr 99:1); R_f 0.52 (8:2 *n*-hexane EtOAc); Mp: 121–123 °C; FT-IR (KBr): ν cm^{-1} 3348.4_{NH}, 3069.4, 3033.2, 2947.2, 2867.0, $1695.4_{C=O}$, 16047, 1324.3, 1035.8, 867.0, 756.1; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.17–7.13 (m, 2H), 7.06–7.02 (m, 2H), 6.86–6.80 (m, 2H), 6.60–6.56 (t, $J = 14.8$ Hz, 1H), 6.518–6.50 (d, $J = 7.6$ Hz, 2H), 4.88–4.87 (d, $J = 6.4$ Hz, $1H_{\ CH^*}$), 4.65 (s, $1H_{NH}$) 4.17–4.12 (q, $J = 13.6$, 6.8 Hz, 2H), 3.21–3.16 (dd, $J = 13.6$, 2.4 Hz, 1H), 2.53–2.47 (t, 24.4 Hz, 1H), 2.20–2.15 (dd, $J = 16.8$, 4 Hz, 1H), 1.89–1.52 (m, 2H), 1.50 (s, 3H), 1.48(m, 16H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 215.1(C=O, C-1), 156.4 (C–C, C-20), 147.0 (C–C, C-14), 129.0, 128.8, 128.2, 120.6, 117.2, 113.2, 111.3 (CH, C-15-19, 21–25), 63.4 (OCH_2), 56.6(CH*, C-13,12), 28.3, 26.2, 25.7, 24.4, 24.2, 23.9, 22.5, 21.8 (CH_2, C-2-11), 15.0 (CH_3); HRMS (EI) *m/z*: Calc. for $C_{27}H_{37}NO_2$, 407.2824 $[M]^+$; Found 407.2824.

*2-[(Phenylamino)-2-bromophenyl-methyl]-cyclododecanone **7d** mixture of anti/syn (72/28)*

The crude, light yellow viscous oil was subjected to column chromatography on silica gel (7:3 *n*-hexane:EtOAc) to afford anti-Mannich product (**7d** was prepared by 2-bromobenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.524 g, 80 %; dr 72/28); R_f 0.50 (8:2 *n*-hexane EtOAc); Mp: 132–134 °C; FT-IR (KBr): ν cm^{-1} for anti-/syn-isomers: $3414.0_{NH\ peak}$, 3350.4_{NH}, 3115.0, 3099.8, 3063.0, 3022. 6, 2939.5, 2922.2, 2845.0, $1697.4_{C=O}$, $1693.4_{C=O}$, 1668.4, 1602.9, 1323.2, 952.8, 746.5, 734.9, 688.6, 603.7; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.72–7.54 (m, 1H), 7.43–7.40 (d, $J = 6$ Hz, 1H), 7.26–7.06 (m, 4H), 6.63–6.61 (d, $J = 7.2$ Hz, 1H), 6.47–6.45 (d, $J = 7.8$ Hz, 1H), 6.38–6.35 (d, $J = 7.5$ Hz, 1H), 4.95–4.93 (anti-isomer d, $J = 6.3$ Hz, $1H_{\ CH^*}$), 4.47 (s, $1H_{NH}$), 3.72–3.62 (m, 1H), 3.16–3.01 (m, 1H), 2.87–2.86 (d, $J = 6.8$ Hz, 1H), 2.53 (s, 1H), 2.47–2.29 (m, 2H), 2.12–1.32 (m, 15H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ for anti-/syn-isomers: 215.0(C=O, C-1), 214.1(C=O, C-1), 146. 8 (C–C, C-20), 146.3 (C–C, C-14), 140.3 (C–Br, C-15), 133.4, 133.1, 129.2, 129.0, 128.1, 127.5, 123.8, 122.3, 117.9, 117.5, 113.6, 113.1 (CH, C-16-19 and CH, C-21-25), 58.3 (CH*, C-13), 58.0 (CH*, C-13), 56.6 (CH*, C-12), 41.7 (α-CH_2, C-2), 28.7, 26.5, 26.3, 25.6, 24.8, 24.5, 23.8, 23.2, 22.7, 22.4, 22.0 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}BrNO$, 441.1667 $[M]^+$; Found 441.1664.

*2-[(Phenylamino)-2-trifluoromethylphenyl-methyl]-cyclododecanone **7e** mixture of anti/syn 33/67)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (7:3 *n*-hexane:EtOAc) to afford

a mixture anti/syn-Mannich product (**7e** was prepared by 2-trifluoromethylbenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (534 g, 82 %; dr 67/33; R_f 0.38 (4:1 *n*-hexane:EtOAc); Mp: 143–145 °C; FT-IR (KBr): ν cm^{-1} $3415.9_{NH\ peak}$, 3059.1, 3032.0, 2943.4, 2856.6, $1699.3_{C=O}$, 1602.9, 1379.1, 1323.2, 1035.8, 871.9, 777.3, 748.9, 696.3; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.76–7.69 (q, $J = 8$, 18.8 Hz, 2H), 7.48–7.24 (m, 2H), 7.07–7.01 (q, $J = 16$, 8 Hz, 2H), 6.65–6.48 (m, 1H), 6.40–6.38 (d, $J = 7.6$ Hz, 1H), 5.16–5.14 (d, $J = 6.8$ $Hz_{anti\text{-}isomerCH^*}$), 5.04 (s, $1H_{NH}$), 4.96–4.93 (t, $J = 12$ Hz, $1H_{CH^*}$), 4.50–4.49 (d, $J = 2.4$ Hz, $1H_{syn\text{-}isomer}$), 3.48–3.45 (dt, $J = 12$, 2.8 Hz, 1H), 3.21–3.16 (m, 1H), 3.00–2.92 (m, 1H), 2.33–2.26 (m, 1H), 2.15–2.04 (m, 2H), 1.78–1.71 (m, 2H), 1.60–1.07 (m, 15H), 0.95–0.90 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 215.1(C=O, C-1), 214.1(C=O, C-1), 146.6 (C–C, C-20), 146.3 (C–C, C-14), 139.8 (C-Cf_3, C-15), 132.4, 131.9, 129.5, 129.1, 129.0, 127.6, 127.5, 126.9, 126.8, 126.6, 117.9, 117.4, 113.5,113.0 (CH, C-16-19 and CH, C-21-25), 54.4 (CH*, C-13), 51.4 (CH*, C-12), 41.8 (α-CH_2, C-2), 30.1, 26.7, 326.29, 26.21, 25.5, 24.9, 24.8, 24.6, 24.5, 24.4, 23.9, 23.7, 22.8, 22.7, 22.5 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{26}H_{32}F_3NO$, 431.2436 $[M]^+$; Found 431.2436.

*2-[(Phenylamino)-2-methoxyphenyl-methyl]-cyclododecanone (**7f** anti and **7ff** syn)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (8:2 *n*-hexane: EtOAc) to afford anti and syn-Mannich product (**7f** was prepared by 2-methoxybenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml).

*Anti-Mannich product (**7f**)* 2.245 g 57 %; anti/syn 100:0; R_f 0.50 (4:1 *n*-hexane:EtOAc); Mp: 104–106 °C; FT-IR (KBr): ν cm^{-1} 3381.2_{anti} NH, 2927.9, 2860.4, 1697.4_{anti} C=O, 1604.8, 1352.1, 1290.4, 869.9, 746.5; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.24–7.24 (d, $J = 1.6$ Hz, 1H), 7.22–7.20 (d, $J = 7.6$ Hz, 1H), 7.10–7.06 (m, 2H), 6.93–6.91 (d, $J = 7.6$ Hz, 1H), 6.89–6.87 (d, $J = 7.8$ Hz, 1H), 6.65–6.61 (t, $J = 14.8$ Hz, 1H), 6.57–6.54 (d, $J = 7.6$ Hz, 2H), 4.93–4.91 (d, $J = 8$ Hz, $1H_{CH^*}$), 4.69 (s, $1H_{NH}$), 3.96 (s, $3H_{OCH3}$), 3.19–3.15 (t, $J = 16.8$ Hz, 1H), 2.62–2.56 (dd, $J = 16.4$, 6.8 Hz, 1H), 2.28–2.21 (dq, $J = 23.6$, 6.8, 2.8 Hz, 1H), 1.89 (s, 2H), 1.50–1.21 (m, 16H); ^{13}C-NMR (100 MHz, CDCl3): δ 215.0 (C=O, C-1), 157.2 (C–C, C-20), 146.9 (C–C, C-14), 129.0, 128.3, 120.8, 117.3, 113.4, 110.7 (CH, C-16-19 and CH, C-21-25), 57.1 (OCH_3), 55.4 (CH*, C-12,13), 28.2, 26.3, 25.8, 24.4, 24.0, 22.6, 21.7 (CH_2, C-2-11); HRMS (EI) *m/z*: Calc. for $C_{26}H_{35}NO_2$, 393.2667 $[M]^+$; Found 393.2667.

*Syn-Mannich product (**7ff**)* 1.065 g; anti/syn 0:100; R_f 0.50 (4:1 *n*-hexane:EtOAc); Mp: 144–146 °C; FT-IR (KBr): ν cm^{-1} $3352.3_{syn\text{-}NH}$, 3059.1, 3023.9, 2939.5, 2858.6, $1695.4_{syn\text{-}C=O}$, 1604.8, 1363.7, 1240.2, 873.8, 752.2; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.28–7.19 (m, 2H), 7.11–7.05 (m, 2H), 6.94–6.86 (s, 2H), 6.66–6.63 (t, $J = 12$ Hz, 1H), 6.53–6.51 (d, $J = 8$ Hz, 1H), 4.90–4.89 (d, $J = 4$ Hz, $1H_{CH^*}$), 4.42 (s, $1H_{NH}$), 3.97 (s, $1H_{OCH3}$), 3.60–3.55 (m, 1H), 2.77–2.70 (m, 1H), 2.22–2.214 (m, 1H), 2.09–2.00 (m, 1H), 1.76–1.70 (m, 2H), 1.43–1.06 (m, 15H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 213.8(C=O, C-1), 157.3 (C–C, C-20), 156.4 (C–C, C-14), 129.0, 128.9, 128.8, 128.6, 128.2, 120.6, 113.6, 110.7 (CH, C-16-19 and CH, C-21-25), 55.4 (OCH_3), 54.7 (CH*, C-13), 52.3 (CH*, C-12), 40.8 (α-CH_2, C-2), 26.3, 25.8, 25.6, 25.5, 24.9,24.59, 24.52, 24.4, 23.5, 22.7, 22.6, 22.4, 21.7 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{26}H_{35}NO_2$, 393.2667 $[M]^+$; Found 393.2667.

*2-[(Phenylamino)-3-tolyl-methyl]-cyclododecanone (**7g** anti and **7gg** syn)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (8:2 *n*-hexane:EtOAc) to afford anti-/sin-Mannich product (**7g** was prepared by 3-methylbenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml).

*Anti-Mannich product for **7g*** 2.192 g, 58 %; dr 100; R_f 0.50 (8:2 *n*-hexane:EtOAc); Mp: 151–153 °C; FT-IR (KBr): ν cm^{-1} $3337.2_{anti\text{-}NHpeak}$, 3051.8, 3031.6 2913.2, 2837.7, $1698.0_{anti\text{-}C=O}$, 1599.7, 1359.6, 992.2; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.28–7.20 (m, 1H), 7.14–7.05 (m, 5H), 6.66–6.62 (t, $J = 14.4$ Hz, 1H), 6.55–6.52 (d, $J = 7.8$ Hz, 2H), 4.52–4.49 (d, $J = 6.9$ Hz, $1H_{CH^*}$), 4.46 (s, $1H_{NH\ overlapping\ for\ NH\ and\ Chiral\ CH^*\ peaks}$), 2.92–2.86 (t, $J = 17.1$ Hz, 1H), 2.64–2.55 (m, 1H), 2.35 (s, $3H_{Me}$), 2.24–2.16 (dq, $J = 23.7$, 8.8, 2.4 Hz, 1H), 1.89–1.86 (t, $J = 9.6$ Hz, 3H), 1.33 (s, 15H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 214.5(C=O, C-1), 146.7 (C–C, C-20), 141.4 (C–C, C-14), 138. 2 (C–CH_3, C-17), 129.1, 128.4, 128.2, 127.4, 124.1, 117.4, 113.3 (CH, C-15,16,18,19 and CH, C-21-25), 60.5 (CH*, C-13), 59.6 (CH*, C-12), 37.3 (α-CH_2, C-2), 28.6, 26.5, 25.9, 24.3, 24.1, 23.9, 22.5, 21.7 (CH_2, C-3-11), 21.5 (CH_3); HRMS (EI) *m/z*: Calc. for $C_{26}H_{35}NO$, 337.2718 $[M]^+$; Found 337.2718.

*Syn-Mannich product for **7gg*** 0.984 g, 26 %, dr 100; R_f 0.50 (8:2 *n*-hexane:EtOAc); Mp 148–151 °C; FT-IR (KBr): ν cm^{-1} $3398.9_{syn\text{-}Nhpeak}$, 3054.7, 3022.9, 2923.5, 2859.9, $1697.1_{syn\text{-}C=O}$, 1600.8 1363.4, 991.2; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.28 (s, 1H), 7.23–7.18 (t, $J = 15.3$ Hz, 1H), 7.14–7.032(m, 4H), 6.68–6.64 (t, $J = 14.4$ Hz, 1H), 6.53–6.51 (d, $J = 8.1$ Hz, 2H), 4.55–4.52 (d, $J = 6.6$ Hz, $1H_{CH^*}$), 4.23 (s, 1H), 3.23–3.18 (t, $J = 14.7$ Hz, 1H), 2.64–2.55 (dq, $J = 23.7$, 8.2, 3HZ, 1H), 2.34 (s, 3H), 2.20–1.

31 (m, 19H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 213.4(C=O, C-1), 147.3 (C–C, C-20), 141.5 (C–C, C-14), 138.1 (C–CH_3, C-17), 129.0, 128.4, 128.0, 127.5, 124.0, 117.5, 113.6 (CH, C-15,16,18,19 and CH, C-21-25), 58.8 (CH*, C-13), 56.7 (CH*, C-12), 25.6, 25.5, 25.3, 25.1, 24.4, 23.6, 22.5, 22.3 (CH_2, C-3-11), 21.5 (CH_3); HRMS (EI) *m/z*: Calc. for $C_{26}H_{35}NO$, 337.2718 $[M]^+$; Found 337.2718.

*2-[(Phenylamino)-3-fluoro-phenyl-methyl]-cyclododecanone (**7h** and **7hh**)*

The crude, light orange viscous oil was subjected to column chromatography on silica gel (7:3 *n*-hexane:EtOAc) to afford anti/syn-Mannich product (**7h** was prepared by 3-fluorobenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml).

*Anti-Mannich product for **7h*** 2.175 g, 57 %; anti/syn 100:0; R_f 0.47 (4:2 *n*-hexane:EtOAc); Mp: 174–176 °C; FT-IR (KBr): ν cm^{-1} 3390.9$_{antiNH}$, 3059.1, 3020.5, 2943.4, 2856.6, 1697.4$_{anti\ C=O}$, 1602.9, 1315.5, 947.0, 796.6, 748.4; ^{1}H-NMR ($CDCl_3$; 300 MHz): 7.35–7.04 (m, 6H), 6.69–6.64 (t, J = 14.7 Hz, 1H), 6.53–6.50 (d, J = 7.8 Hz, 1H), 4.53 (s, 1H$_{NH\ overlapping\ for\ NH\ and\ Chiral\ CH^*\ peaks}$), 4.53–4.50 (d, J = 8.4 Hz, 1H$_{CH^*}$), 2.93–2.87 (t, J = 17.1 Hz, 1H), 2.59–2.53 (m, 1H), 2.20–2.17 (m, 1H), 1.95–1.79 (m, 2H) 1.68–1.33 (m, 16H); ^{13}C-NMR (75 MHz in $CDCl_3$): δ 214.1(C=O, C-1), 164.7 (C–C-F, C-17), 146.3 (C–C, C-20), 144.5 (C–C, C-14), 144.5, 130.3, 130.1, 129.1, 122.5, 117.7, 114.6, 114.3, 113.8, 113.6, 113.3 (CH-, C-15,16,18,19 and CH, C-21-25), 59.5 (CH*, C-13), 59.3 (CH*, C-12), 37.7 (α-CH_2, C-2), 28.7, 26.5, 25.9, 24.3, 24.1, 24.0, 22.5, 21.7 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}FNO$, 381.2467 $[M]^+$; Found 381.2467.

*Syn-Mannich product for **7hh*** 0.958 g, 25 %, anti/syn 0:100; R_f 0.50 (8:2 *n*-hexane:EtOAc); Mp 159–161 °C; FT-IR (KBr): ν cm^{-1} 3331.0$_{syn\ NH}$, 3054.3, 3018.3, 2941.4, 2929.6, 2850.8, 1693.5$_{syn\ C=O}$, 1600.9, 1311.6, 952.8, 750.3; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.33–7.26 (m, 1H), 7.16–7.08 (m, 4H), 6.96–6.91 (t, J = 15.6 Hz, 1H), 6.71–6.66 (t, J = 14.1 Hz, 1H), 6.51–6.49 (d, J = 7.8 Hz, 2H), 4.60–4.58 (d, J = 6 Hz, 1H$_{CH^*}$) 4.26 (s, 1H$_{NH}$), 3.24–3.19 (t, J = 13.8 Hz, 1H), 2.72–2.65 (m, 1H), 2.16–2.01 (m, 2H), 1.76–1.32 (m, 17H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 212.8 (C=O, C-1), 146.8 (C–C–F, C-17), 144.6 (C–C, C-20), 144.5 (C–C, C-14), 130.1, 130.0, 129.1, 122.6, 117.9, 144.3, 114.1, 113.9, 113.6 (CH, C-15,16,18,19 and CH, C-21-25), 58.2 (CH*, C-13), 56.2(CH*, C-12), 41.13 (α-CH_2, C-2), 25.5, 25.4, 25.2, 25.0, 24.4, 23.3, 22.5, 22.8; HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}FNO$, 381.2467 $[M]^+$; Found 381.2467.

*2-[(Phenylamino)-3-bromo-phenyl-methyl]-cyclododecanone (**7i**)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (7:3 *n*-hexane:EtOAc) to afford anti-Mannich product (**7i** was prepared by 3-bromobenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.545 g; 80 %; anti/sin 100:0; R_f 0.6 (4:2 *n*-hexane:EtOAc); Mp: 162–164 °C; FT-IR (KBr): ν cm^{-1} 3396.4$_{NH}$, 3076.5, 3023.2, 2943.4, 2924.2, 2848.9, 1679.5$_{C=O}$, 1600.9, 1317.4, 995.3, 792.7; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.48 (s, 1H), 7.36–7.34 (d, J = 7.5 Hz, 1H), 7.28–7.26 (d, J = 8 Hz, 1H), 7.20–7.15 (t, J = 15 Hz, 1H), 7.11–7.06 (t, J = 15 Hz, 2H), 6.69–6.64 (t, J = 14.4 Hz, 1H), 6.48–6.45 (d, J = 7.8 Hz, 2H), 4.54–4.52 (d, J = 6 Hz, 1H$_{CH^*}$), 4.23 (s, 1H$_{NH}$), 3.17–3.15 (d, J = 6.6 Hz, 1H), 2.71–2.63 (m, 1H), 2.20–1.60 (m, 6H), 1.29 (s, 15H); ^{13}C-NMR (75 M Hz in $CDCl_3$): δ 212.7(C=O, C-1), 146.8 (C–C–Br, C-17), 144.3 (C–C, C-20), 130.4 (C–C, C-14), 130.1, 129.7, 129.1, 125.8, 117.9, 113.6 (CH, C-15,16,18,19 and CH, C-21-25), 58.0 (CH*, C-13), 56.3 (CH*, C-12), 41.1 (α-CH_2, C-2), 25.4, 25.2, 25.1, 24.9, 24.3, 23.2, 22.4, 22.2 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}BrNO$, 441.1667 $[M]^+$; Found 441.1667.

*2-[(Phenylamino)-4-toluyl-methyl]-cyclododecanone (**7j**)*

The crude, colorless solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture solvent (THF and ethanol 1:1 ratio) to afford anti-Mannich product (**7j** was prepared by 4-methylbenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.168 g, 84 %; anti/syn 98:2); Mp: 175–177 °C; FT-IR (KBr): ν cm^{-1} 3383.1, 3053.6, 3022.5, 2941.4, 2922.2, 2852.7, 1697.4, 1602.9, 1319.3, 1282.7, 1053.1, 1370.2, 815.9, 748.3; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.26 (s, 1H), 7.20–7.18 (d, J = 8 Hz, 2H), 7.10 (m, 3H), 6.64–6.61 (t, J = 14.4 Hz, 1H), 6.50–6.48 (d, J = 8 Hz, 2H), 4.53–4.52 (d, J = 6.8 Hz, 1H$_{CH^*}$), 4.21 (s, 1H$_{NH}$), 3.18–3.15 (td, J = 14, 10.8, 3.6 Hz, 1H), 2.60–2.53 (dq, J = 24, 8.4, 3.2 Hz, 1H), 2.30 (s, 3H), 2.14–2.07 (dq, J = 25, 9.2, 3.6 Hz, 1H), 2.03–1.97 (m, 1H), 1.68–1.50 (m, 3H), 1.29 (m, 15H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 213.3(C=O, C-1), 147.2 (C–C–CH_3, C-18), 138.4 (C–C, C-20), 136.7 (C–C, C-14), 129.2, 129.0, 126.7, 117.5, 113.6 (CH, C-15-17,19 and CH, C-21-25), 58.4 (CH*, C-13), 56.8 (CH*, C-12), 25.59, 25.50, 25.3, 25.0, 24.4, 23.5, 22.5 (CH_2, C-2-11), 22.2 (CH_3); HRMS (EI) *m/z*: Calc. for $C_{26}H_{35}NO$, 377.2715 $[M]^+$; Found 377.2715.

*2-[(Phenylamino)-4-ethoxyphenyl-methyl]-cyclododecanone (**7k**)*

The crude, colorless solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture solvent (THF

and ethanol 1:1 ratio) to afford anti-Mannich product (**7k** was prepared by 4-methoxybenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.015 g, 74 %; anti/syn 99:1); Mp: 156–158 °C; FT-IR (KBr): ν cm^{-1} 3381.2_{NH}, 3051.4, 3026.3, 2931.8, 2864.3, $1697.4_{C=O}$, 1602.9, 1386.8, 1242.2, 831.3, 748.4; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.28–7.22 (t, $J = 19.2$ Hz, 2H), 7.11–7.06 (t, $J = 14.7$ Hz, 2H), 6.85–6.82 (d, $J = 7.8$ Hz, 2H), 6.67–6.63 (t, $J = 14.1$ Hz, 1H), 6.53–6.50 (d, $J = 7.8$HZ, 2H), 4.53–4.51 (d, $J = 6.3$ Hz, $1H_{CH^*}$), 4.19 (s, $1H_{NH}$), 4.02–3.98 (q, $J = 13.2$, 6 Hz, 2H), 3.20–3.15 (t, $J = 14.4$ Hz, 1H), 2.60–2.53 (m, 1H), 2.14–2.02 (m, 2H), 1.67 (s, 3H), 1.43–1.31 (m, 17H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 213.4(C=O, C-1), 158.0 (C–C–C_2H_5, C-18), 147.2 (C–C, C-20), 133.3 (C–C, C-14), 129.0, 127.9, 117.5, 114.4, 113.6 (CH, C-15-17,19 and CH, C-21-25), 65.3 (OCH_2), 58.3 (CH*, C-13), 57.0 (CH*, C-12), 41.0 (α-CH_2, C-2), 25.6, 25.5, 25.1, 24.4, 23.6, 22.4, 22.3 (CH_2, C-3-11), 14.8 (OCH_2 –CH_3); HRMS (EI) *m/z*: Calc. for $C_{27}H_{37}NO_2$, 407.2818 $[M]^+$; Found 407.2818.

*2-[(Phenylamino)-4-chlorophenyl-methyl]-cyclododecanone (**7l**)*

The crude, colorless solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture solvent (THF and ethanol 1:1 ratio) to afford anti-Mannich product (**7l** was prepared by 4-chlorobenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.425 g, 86 %; anti/syn 100:0); Mp: 178–180 °C; FT-IR (KBr): ν cm^{-1} 3385.1, 3058.2, 3024.4, 2937.6, 2852.7, 1697.4, 1602.9, 1317.38, 1278.8, 821.6, 746.5, 690.5; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.30 (s, 4H), 7.12–7.07 (t, $J = 15.6$ Hz, 2H), 6.71–6.66 (t, $J = 14.7$ Hz, 1H), 6.50–6.47 (d, $J = 7.8$ Hz, 2H), 4.59–4.57 (d, $J = 6.6$ Hz, $1H_{CH^*}$), 4.24 (s, 1H), 3.21–3.17 (t, $J = 14.4$ Hz, 1H), 2.71–2.63 (dq, $J = 21.9$, 9.6, 2.7 Hz, 1H), 2.09–1.45 (m, 4H), 1.31 (s, 13H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 212.8(C=O, C-1), 146.8 (C–C–Cl, C-18), 140.2 (C–C, C-20), 132.8 (C–C, C-14), 129.1, 128.8, 128.3, 117.9, 113.6 (CH, C-15-17,19 and CH, C-21-25), 57.9 (CH*, C-13), 56.4 (CH*, C-12), 41.0 (α-CH_2, C-2), 25.4, 25.2, 25.0, 24.3, 23.3, 22.4, 22.2 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}ClNO$, 397.2172 $[M]^+$; Found 397.2175.

*2-[(Phenylamino)-4-bromophenyl-methyl]-cyclododecanone (**7m**)*

The crude, colorless solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture solvent (THF and ethanol 1:1 ratio) to afford anti-Mannich product (**7m** was prepared by 4-bromobenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.710 g, 84 %, anti/sin 100:0); Mp: 176–178 °C; FT-IR (KBr): ν cm^{-1} 3383.5, 3052.5, 3028.8, 2935.7, 2922.2, 2868.0, 1697.7, 1603.2, 1319.3, 1280.7, 821.7, 746.5, 690.5; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.46–7.44 (d, $J = 7.8$ Hz, 2H), 7.28–7.23 (t, $J = 15.9$ Hz, 2H), 7.12–7.07 (t, $J = 13.8$ Hz, 2H), 6.71–6.66 (t, $J = 13.8$ Hz, 1H), 6.50–6.47 (d, $J = 7.5$ Hz, 1H), 4.58–4.56 (d, $J = 5.4$ Hz, $1H_{CH^*}$), 4.24 (s, $1H_{NH}$), 3.19 (s, 1H), 2.71–2.64 (t, $J = 22.2$ Hz, 1H), 2.17–2.03 (m, 2H), 1.77–1.32 (m, 17H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 212.8(C=O, C-1), 146.8 (C–C–Br), 140.8 (C–C, C-20), 131.7 (C–C, C-14), 129.1, 128.7, 121.0, 117.9, 113.6 (CH, C-15-17,19 and CH*, C-21-25), 57.4 (CH*, C-13), 56.4 (CH*, C-12), 41.0 (α-CH_2, C-2), 25.4, 25.2, 25.0, 24.3, 23.2, 22.4, 22.2 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}BrNO$ 441.1667 $[M]^+$; Found 441.1664.

*2-[(Phenylamino)-4-alloxyphenyl-methyl]-cyclododecanone **7n** a mixture of anti/syn (73/27)*

The crude, colorless solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture solvent (THF and ethanol 1:1 ratio) to afford anti-Mannich product (**7n** was prepared by 4-alloxybenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (2.7 g, 66 %, anti/syn 100:0); Mp: 143–145 °C; Anti-isomer of **7n**: FT-IR (KBr): ν cm^{-1} 3383.1, 3067.2, 3032.3, 2941.4, 2856.5, 1697.4, 1602.9, 1321.2, 1247.9, 1026.1, 922.0, 746.5; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.26 (s, 1H), 7.22–7.20 (d, $J = 8.8$ Hz, 1H), 7.08–7.04 (t, $J = 15.6$ Hz, 2H), 6.85–6.83 (d, $J = 8.4$ Hz, 2H), 6.65–6.61 (t, $J = 14.4$ Hz, 1H), 6.50–6.48 (d, $J = 7.6$ Hz, 2H), 6.09–5.99 (m, $1H_{CH=CH2\ for\ sin\ isomer}$), 5.42–5.37 (dd, $J = 17.2$, 1.6 Hz, 1H), 5.28–5.25 (dd, $J = 10.4$, 1.2 Hz, 1H), 4.51–4.49 (d, $J = 6.8$ Hz, $1H_{CH^*for\ anti}$), 4.48–4.48 (d, $J = 1.2$ Hz, $2H_{OCH2}$), 4.33 (s, $1H_{NH\ for\ anti\text{-}isomer}$), 3.18–3.13 (m, 1H), 2.57–2.51 (m, 1H), 2.11–1.96 (m, 2H), 1.85–1.49 (3H), 1.28–1.12 (m, 15H); syn-isomer of **7n**: ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.26 (s, 1H), 7.22–7.20 (d, $J = 8.8$ Hz, 1H), 7.08–7.04 (t, $J = 15.6$ Hz, 2H), 6.85–6.83 (d, $J = 8.4$ Hz, 2H), 6.65–6.61 (t, $J = 14.4$ Hz, 1H), 6.50–6.48 (d, $J = 7.6$ Hz, 2H), 5.42–5.37 (dd, $J = 17.2$, 1.6 Hz, 1H), 5.28–5.25 (dd, $J = 10.4$, 1.2 Hz, 1H), 4.15–4.09 (m, $1H_{CH=CH2\ for\ sin\ isomer}$) 3.76–3.71 (d, $J = 13.6$, 6.4 Hz, $1H_{CH^*for\ syn}$), 4.48–4.48 (d, $J = 1.2$ Hz, $2H_{OCH2}$), 4.23 (s, $1H_{NH\ for\ syn\text{-}isomer}$), 3.18–3.13 (m, 1H), 2.57–2.51 (m, 1H), 2.11–1.96 (m, 2H), 1.85–1.49 (3H), 1.28–1.12 (m, 15H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 213.4 X2 (C=O), 157.7 X2 (C–C-alloxy, C-18), 147.1 X2 (C–C, C-20), 133.6 (C–C, C-14), 133.2, 129.0, 127.9 X2, 117.7, 117.5, 114.7, 113.6 (CH, C-15-17,19 and CH, C-21-25), 68.7 (OCH_2), 67.9 (OCH_2), 58.2 (CH*, C-13), 56.9 (CH*, C-12), 41.0 X2 (α-CH_2, C-2), 25.6, 25.5, 25.4, 25.2, 25.0,

24.4 X2, 23.5 X2, 22.4, 22.2 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{28}H_{37}NO_2$, 419.2824 $[M]^+$; Found 419.2820.

*2-[(Phenylamino)-4-fluorophenyl-methyl]-cyclododecanone (**7o**)*

The crude, colorless solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture solvent (THF and ethanol 1:1 ratio) to afford anti-Mannich product (**7o** was prepared by 4-fluorobenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.44 g, 90 %, anti/syn 100:0); Mp: 169–171 °C; FT-IR (KBr): *v* cm^{-1} 3385.1_{NH}, 3058.8, 3028.3, 2937.6, 2862.7, $1695.4_{C=O}$, 1604.8, 1512.2, 1321.2, 1057.0, 970.2, 835.2, 748.4; ^{1}H-NMR ($CDCl_3$; 300 MHz): δ 7.32–7.26 (m, 2H), 7.20–7.04 (t, $J = 15.3$ Hz, 2H), 7.02–6.99 (t, $J = 17.1$ Hz, 2H), 6.68–6.63 (t, $J = 14.7$ Hz, 1H), 6.48–6.45 (d, $J = 8.1$ Hz, 2H), 4.56–4.54 (d, $J = 6.3$ Hz, 1H), 4.21 (s, 1H), 3.16–3.11 (t, $J = 15.3$ Hz, 1H), 2.63–2.57 (td, 15.6, 6.9, 3 Hz, 1H), 2.11–1.46 (m, 3H), 1.29 (s, 13H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 213.0(C=O, C-1), 146.9 (C–C-F, C-18), 137.3 (C–C, C-20), 129.0 (C–C, C-14), 128.5, 128.4, 117.8, 115.6, 115.3, 113.6 (C–C, C-15-17,19 and CH, C-21-25), 57.9 (CH*, C-13), 56.7 (CH*, C-12), 41.1 (α-CH_2, C-2), 25.5, 25.2, 25.1, 24.3, 23.3, 22.4, 22.2 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}FNO$ 381.2467 $[M]^+$; Found 381.2467.

*2-[(Phenylamino)-4-nitrophenyl-methyl]-cyclododecanone (**7p**)*

The crude, colorless solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture solvent (THF and ethanol 1:1 ratio) to afford anti-Mannich product (**7p** was prepared by 4-nitrobenzaldehyde, CDD, and aniline in the presence of NH_4OAC in ethanol 3–4 ml). (3.72 g, 92 %, anti/syn 96:4); Mp: 184–186 °C; FT-IR (KBr): *v* cm^{-1} 3385.1, 3051.4, 3025.3, 2941.4, 2862.3, 1697.4, 1600.9, 1346.3, 1263.4, 970.2, 858.3, 740.7; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 8.20–8.17 (d, $J = 8$ Hz, 1H), 8.15–8.15 (d, $J = 2.4$ Hz, 1H), 7.54–7.49 (m, 2H), 7.09–7.05 (td, $J = 16.2$, 7, 1.6 Hz, 2H), 6.69–6.66 (t, 14.8 Hz, 1H), 6.45–6.43 (d, $J = 7.6$ Hz, 2H), 4.72–4.70 (d, $J = 6.8$ Hz, $1H_{CH^*}$), 4.30 (s, $1H_{NH}$), 3.24–3.20 (m, 1H), 2.91–2.72 (m, 1H), 2.63–2.60 (m, 1H), 2.13–2.02 (m, 1H), 1.83–1.70 (m, 2H), 1.59–1.55 (m, 1H), 1.48–1.43 (m, 14H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 212.1(C=O, C-1), 149.7 (C–C-NO_2), 147.1 (C–C, C-20), 146.3 (C–C, C-14), 129.2, 127.9, 127.8, 124.0, 123.8, 118.3, 113.6 (CH, C-15-17,19 and CH, C-21-25), 57.6 (CH*, C-13), 56.0 (CH*, C-12), 40.9 (α-CH_2, C-2), 25.4, 25.1, 24.9, 24.8, 24.2, 22.7, 22.3, 22.1 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}N_2O_3$, 408.2412 $[M]^+$; Found 408.2412.

*2-[(2-Hydroxyphenylamino)-phenyl-methyl]-cyclododecanone (**7q**)*

The crude, light brown solid was washed with *n*-hexane (5 ml) twice and recrystallized from mixture solvent (THF and ethanol 1:1 ratio) to afford anti-Mannich product (**7q** was prepared by benzaldehyde, CDD, and 2-hydroxyaniline in the presence of NH_4OAC in ethanol 3–4 ml). (2.470 g, 65 %, anti/syn 60:40); Mp: 219–221 °C; FT-IR (KBr): *v* cm^{-1} $3648.2_{ar\text{-}OHpeak}$, 3348.4_{NHpeak}, 3047.0, 3024.5, 2926.0, 2846.9, $1705.0_{C=O\text{-}peak}$, 1591.2, 1504.4, 842.8, 819.7, 758.0; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.71–7.66 (m, 1H), 7.42–7,21 (m, 6H), 6.73–6.71 (d, $J = 8$ Hz, 1H), 6.39–6.35 (m, 1H), 6.14 (s, $1H_{OH}$), 6.07 (s, $1H_{NH}$), 4.71–4.67 (t, $J = 16$ Hz, $1H_{CH^*anti\text{-}isomer}$), 4.65–4.61 (t, $J = 16$ Hz, $1H_{CH^*syn\text{-}isomer}$), 3.27–3.22 (td, 14.8, 7.6, 1.2 Hz, $1H_{isomer}$), 3.15–3.10 (td, 12.8, 5.6, 1.2 Hz, $1H_{isomer}$), 2.49–2.41 (m, 1H), 2.33–2.30 (m, 1H), 2.00–1.98 (m, 1H), 1.93–1.77 (m, 2H), 1.72–1.58 (m, 2H), 1.45–1.41 (m, 1H), 1.45–1.21 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$): 212.9 (C=O, C-1) 180.2 (C–C–OH, C-21), 149.2 (C–C, C-20), 148.3 (C–C, C-14), 144.5, 129.2, 128.9, 128.8, 128.5, 127.2, 126.8, 115.9 (CH, C-15-19 and CH*, C-22-25), 97.9 (CH*, C-13), 57.4 (CH*, C-12), 40.9 (α-CH_2, C-2), 26.9, 25.6, 25.2, 24.8, 24.8, 24.1, 22.7, 22.5, 21.8 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{33}NO_2$, 379.2511 $[M]^+$; Found 379.2507.

*2-[(4-Chlorophenylamino)-α-methyl-trans-cinnamaldehyde-methyl]-cyclododecanone (**7r**)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (7:3 *n*-hexane:EtOAc) to afford anti-Mannich product (**7r** was prepared by α-methyl-*trans*-cinnamaldehyde, CDD, and 4-chloroaniline in the presence of NH_4OAC in ethanol 3–4 ml). (2.98 g, 68 %; anti/sin 100:0; R_f 0.56 (4:1 *n*-hexane:EtOAc); Mp: 178–180 °C; FT-IR (KBr): *v* cm^{-1} 3396.6, 3057.3, 3028.4, 2926.0, 2856.6, 1695.4, 1600.9, 1323.2, 1288.5, 1091.7, 810.1, 700.2; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.23–7.17 (m, 4H), 7.165(s, $1H_{CH=C\text{–}CH_3}$), 7.16–7.13 (m, 2H), 6.94–6.90 (m, 2H), 6.34–6.32 (d, $J = 8.4$ Hz, 2H), 4.44–4.43 (d, $J = 6.4$ Hz, $1H_{CH^*}$), 4.22 (s, $1H_{NH}$), 3.12 (s, 1H), 2.52–2.49 (qd, $J = 24.8$, 9.2, 3.2 Hz, 1H), 2.017–1.917 (m, 2H), 1.65–1.54 (m, 2H), 1.51 (s, $3H_{CH3}$), 1.41–1.04 (m, 15H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 213.2(C=O, C-1), 145.7 (C–C–Cl, C-25), 141.0 (C–C, C-21), 128.8 (C–C, C-16), 128.6, 127.4, 126.8, 122.3, 114.7 (CH, C-17-21 and CH, C-22-26), 58.8 (CH*, C-13), 56.4 (CH*, C-12), 41.1 (α-CH_2, C-2), 25.6, 25.4, 25.3, 25.2, 25.0, 24.4, 23.5, 22.4 (CH_2, C-3-11), 22.3 (CH_3); HRMS (EI) *m/z*: Calc. for $C_{28}H_{36}ClNO$, 437.2485 $[M]^+$; Found 437.2485.

*2-[(2-Hydroxyphenylamino)-4-toluyl-methyl]-cyclododecanone (**7s**)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (7:3 *n*-hexane:EtOAc) to afford mixture of anti/syn-Mannich product (**7s** was prepared by 4-methylbenzaldehyde, CDD and 2-hydroxyaniline in the presence of NH_4OAC in ethanol 3–4 ml). (2.325, 59 %; anti/sin: 67/33; R_f 0.58 (4:1 *n*-hexane:EtOAc) Mp: 207–209 °C; FT-IR (KBr): ν cm^{-1} 3586.5, 3331.1, 3055.2, 3024.2, 2941.4, 2921.5, 2846.9, 1705.1, 1620.2, 1338.6, 1273.0, 1022.3, 895.0, 814.0; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.69 (s, 1H), 7.41–7.30 (m, 5H), 7.24–7.20 (t, $J = 15.2$ Hz, 4H), 7.16–7.08 (t, 16.2 Hz, 4H), 6.98–6.94 (td, 14.8, 7.6, 1.2 Hz, 1H), 6.72–6.70 (d, $J = 8$ Hz, 1H), 6.41–6.36 (t, 17.6 Hz, 2H), 6.17 (s, $1H_{NH}$), 6.11 (s, $1H_{OH}$), 4.64–4.61 (d, $J = 8$ Hz, 1H), 4.60–4.57 (d, $J = 8.4$ Hz, 1H), 3.12 (s, 1H), 2.451 (s, 1H), 2.38–2.35 (t, $J = 11.6$ Hz, 1H), 2.33 (s, $3H_{CH3}$), 2.30 (s, $3H_{CH3}$), 2.28 (s, 1H), 1.77–1.23 (m, 15H); ^{13}C-NMR (100 MHz in $CDCl_3$) δ 213.0(C=O, C-1), 180.1 (C–C–OH, C-21), 149.7 (C–C-CH_3, C-18), 144.6 (C–C, C-20), 142.5 (C–C, C-14), 137.7, 136.1, 130.1, 129.6, 129.5, 129.1, 129.0, 128.3, 127.1, 126.7, 125.3, 125.2, 115.9, 103.9, 103.8 (CH, C-15-17,19 and CH*, C-22-25), 97.9, 58.3 (CH*, C-13), 57.9, 57.6 (CH*, C-12), 57.2, 39.5 (α-CH_2), 28.6, 26.9, 26.4, 26.0, 25.8, 24.3, 24.2, 24.0, 23.4, 22.4, 21.8 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{26}H_{35}NO_2$, 393.2667 $[M]^+$; Found 393.2667.

*2-[(2-Hydroxyphenylamino)-4-fluorophenyl-methyl]-cyclododecanone (**7t**)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (4:2 *n*-hexane:EtOAc) to afford mixture of anti/sin-Mannich product (**7t** was prepared by 4-fluorobenzaldehyde, CDD, and 2-hydroxyaniline in the presence of NH_4OAC in ethanol 3–4 ml). 2.19, 55 %; anti/sin 60:40; R_f 0.52 (4:1 *n*-hexane:EtOAc) Mp: 203–205 °C; FT-IR (KBr): ν cm^{-1} 3417.9 $_{OH\ peak}$, 3352.3, 3057.8, 3025.4, 2927.9, 2846.9, 1691.6, 1595.1, 1317.4, 1271.1, 937.4, 864.1, 760.0; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.73–7.68 (td, $J = 15.6$, 7.2, 2 Hz, 1H), 7.42–7.20 (m, 4H), 7.13–7.03 (m, 1H), 6.74–6.72 (d, 8.4 Hz, 1H), 6.39–6.36 (t, $J = 13.2$ Hz, 1H), 6.22 (s, $1H_{NH}$), 6.13 (s, NH_{OH}), 5.00–4.97 (d, $J = 8.4$ Hz, 1H), 3.49–3.44 (td, $J = 17.6$, 8.8, 2.8 Hz, 1H), 3.30–3.25 (t, 21.2 Hz, 1H), 2.70–2.62 (dq, $J = 26.4$, 9.6, 3.2 Hz, 1H), 2.43–2.27 (m, 1H), 2.12–1.98 (m, 1H), 1.85–1.76 (m, 2H), 1.62–1.60 (m, 1H), 1.56–1.43 (m, 1H), 1.30–1.23 (m, 11H); ^{13}C-NMR (100 MHz in $CDCl_3$) δ 212.7(C=O, C-1), 211.0(C=O, C-1), 180.0 (C–C–OH, C-21), 149.6 (C–C-F, C-18), 148.4 (C–C-F, C-18), 144.5 (C–C, C-20), 144.4 (C–C, C-20), 142.6 (C–C, C-14), 133.9, 129.7, 129.6, 129.28, 129.23, 128.5, 128.4, 125.3, 125.2, 124.7, 116.0, 115.9, 103.98, 103.91 (CH, C-15-17,19 and CH, C-22-25), 97.8 (CH*, C-13), 97.5 (CH*, C-13), 52.5 (CH*, C-12), 39.7 (α-CH_2, C-2), 28.3, 26.3, 26.0, 25.9, 25.8, 24.2, 24.0, 23.9, 23.3, 22.4, 22.18, 22.1, 21.9, 21.6 (CH_2, C-3-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{32}FNO_2$, 397.2417 $[M]^+$; Found 397.2417.

*2-[(2-Chlorophenylamino)-3-chloro-methyl]-cyclododecanone (**7x**)*

The crude, colorless viscous oil was subjected to column chromatography on silica gel (4:2 *n*-hexane:EtOAc) to afford mixture of anti/syn-Mannich product (**7x** was prepared by 3-chlorobenzaldehyde, CDD, and 2-chloroaniline in the presence of NH_4OAC in ethanol 3–4 ml). 2.81, 65 %; anti/syn 100:0; R_f 0.48 (4:2 *n*-hexane:EtOAc) Mp: 168–170 °C; FT-IR (KBr): ν cm^{-1} 3338.78, 3084.18, 3037.89, 2951.09, 2948.27, 2859.12, 1693.50, 1602.85, 1315.45, 889.18, 763.81, 736.81, 736.81, 626.87, 611.43; ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.408–7.377 (td, $J = 9.2$, 4,4, 2.8 Hz, 1H), 7.257–7.159 (m, 3H), 6.981–6.940 (t, $J = 16.4$ Hz, 1H), 6.591–6.568 (dd, $J = 8$, 1.2 Hz, 1H), 6.471–6.461 (t, $J = 4$ Hz, 1H), 6.341–6.316 (dd, $J = 8$, 2 Hz, 1H), 5.051 (s, $1H_{NH}$), 4.949–4.934 (d, $J = 6$ Hz, $1H_{CH*}$), 3.151 (s, 1H), 2.350–2.289 (m, 1H), 2.152–1.985 (m, 2H), 1.718–1.650 (m, 1H), 1.554–1.482 (m, 1H), 1.428–1.231 (m, 15H); ^{13}C-NMR (100 MHz in $CDCl_3$) δ 215.0(C=O. C-1), 147.4 (C–C, C-20), 138.1 (C–C, C-14), 134.8 (C–Cl, C-15), 134.8 (C–Cl, C-15), 133.3 (CH, C-22), 130.1 (CH, C-17), 129.8 (CH, C-22), 128.8 (CH, C-24), 127.7 (CH, C-19), 127.5 (CH, C-16), 117.4 (CH, C-23), 112.9 (CH, C-25), 111.1 (CH, C-23), 56.3 (CH*, C-13), 55.8 (CH*, C-12), 28.5, 26.2, 25.6, 24.5, 24.4, 24.38, 24.32, 22.6, 21.8 (CH_2, C-2-11); HRMS (EI) *m/z*: Calc. for $C_{25}H_{31}Cl_2NO$, 431.1782 $[M]^+$; Found 431.1782.

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