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One - pot Reformatsky-Imine addition reaction-leading to the synthesis of structurally diverse β-lactams

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The Reformatsky-imine addition reaction of α-bromoethylacetate with aldimines derived from 3,4-methylenedioxy benzaldehyde and α-methylcinnamaldehyde has provided an efficient and practical access to structurally diverse β-lactams. All the new β-lactams have been identified as 1,4-diaryl-2-azetidinones through their detailed spectral studies. Further it also reveals that the styryl bond of α-methylcinnamylideneanilines does not participate in the reaction and gives β-lactams contrary to their analogues cinnamylideneanilines[15] and *o*-nitrocinnamylideneanilines[16] which gave δ-lactams.

Keywords: Reformatsky reaction, β-lactams, Imines, α-bromoethylacetate, α-methylcinnamaldehyde

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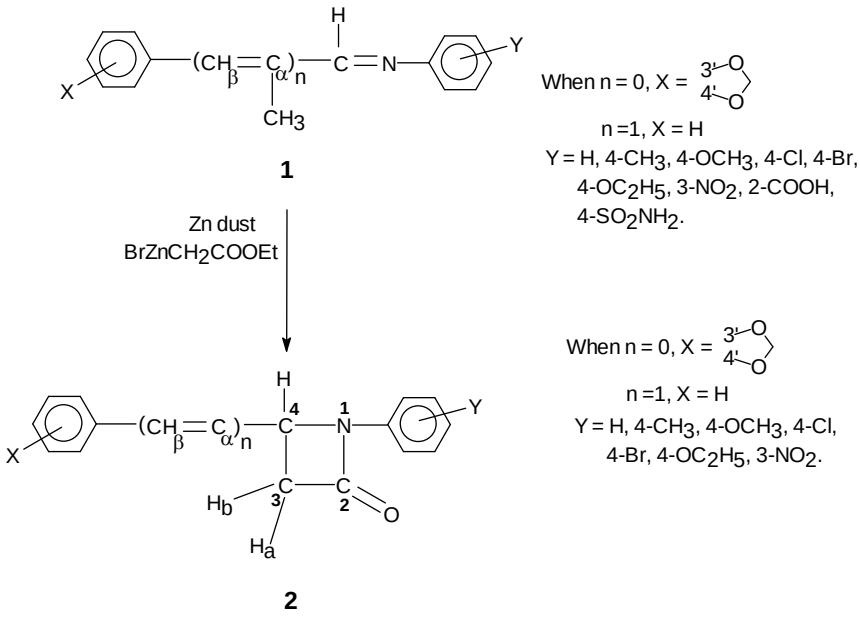
β-Lactams and their derivatives have potential biological activity as antibiotics[1]. Reformatsky reaction is the part of the large and rapidly expanding field of enolate chemistry, where specific mode of metal-enolate formation is from halo carbonyl compounds[2,3]. Improvements in the yields of Reformatsky reaction have been achieved when freshly prepared zinc powder[4], a heated column of zinc dust[5], a trimethylborate-THF solvent system[6], a zinc-copper couple[7], acid washed zinc[8], trimethyl-chlorosilane[9], ultrasonic irradiation[10-13], microwave irradiation[14] were utilized.

In continuation to this research a convenient one-pot thermal method for the preparation of β-lactams **2** from the Reformatsky-Imine addition reaction of 1 equiv. of aldimines **1** with 1.8 equiv. of zinc dust and 1.5 equiv of α-bromoethylacetate (**Scheme I**) is described. The aldimines (eighteen in number) have been obtained by condensation of 3,4-methylene-dioxybenzaldehyde and α-methylcinnamaldehyde with a series of nine aromatic amines having various substituents at *o*, *m*, *p*-positions. These aldimines are evaluated as potential electrophiles for the Reformatsky-Imine addition reactions.

The products obtained by Reformatsky-Imine addition reaction were identified as 1,4-diaryl-2-azetidinones **2** on the basis of their IR, ^{1}H NMR and mass spectra. The infrared spectrum of these azetidinones (β-lactams) displayed sharp and strong absorption bands in the region 1731-1748 cm^{-1}, which have been assigned to amidocarbonyl group of the β-lactams.

^{1}H NMR spectrum of these azetidinones exhibited that the two geminal protons H_{3a} and H_{3b} appear as separate signals. The H_{3b} appears at δ 2.83-2.92 as double doublet having coupling constant $J$$H_{3b}$-$H_4$ ≈ 2.5 and $J$$H_{3b}$-$H_{3a}$ ≈ 15.2 Hz. Whereas the proton H_{3a} appears downfield at δ 3.28-3.52 as double doublet having coupling constant $J$$H_{3a}$-$H_4$ ≈ 5.5 and $J$$H_{3a}$-$H_{3b}$ ≈ 15.2 Hz. Out of the two geminal protons H_{3a} and H_{3b}, the proton H_{3a} shows downfield shift as compared to proton H_{3b} because of orientation of carbonyl group[1]. As a result proton H_{3a} comes in the deshielding zone of the π-bond electron cloud of the carbonyl group attached to it. Therefore in all the β-lactams the H_{3a} proton appears (δ 3.28-3.52) down-field as compared to proton H_{3b} (δ 2.85-2.92). The H_4 proton appears at δ 4.58-4.82 as quartet having coupling constant $J$$H_4$-$H_{3b}$ ≈ 5.4 Hz and $J$$H_4$-$H_{3a}$ ≈ 2.4 Hz. The same proton in aldimines appeared downfield at δ 8.5-8.6 due to its association with a double bond.



Scheme I

Further it is confirmed that the styryl bond of the α-methylcinnamylideneanilines do not participate in the reaction and here occur 1,2 addition only to form β-lactams contrary to their analogues cinnamylideneanilines where this styryl bond participate in the addition reaction and gave 1,4 adduct named δ-lactams[15]. This is shown by their ^{1}H NMR spectra in which a singlet appeared at δ 6.7 due to H_β proton in β-lactams as well as in α-methylcinnamylideneanilines proves that this styryl bond does not participate in reaction. Also the IR data support this fact because a sharp and strong absorption band occur in the range 1731-1748 cm^{-1} indicating the formation of 4-membered β-lactam instead of 6-membered δ-lactam which should appear at 1640-1670 cm^{-1}.

The 70 ev mass spectrum of 1-(4-ethoxyphenyl)-4-(3′,4′ methylenedioxy phenyl)-2-azetidinone **2f** showed molecular ion peak at *m/z* 311. The fission of this molecular ion occurs by two pathways 'a' and 'b'. Fission by path 'a' gives peak at *m/z* 163 due to formation of *p*-ethoxyphenyl isocyanate and a base peak at *m/z* 148. Whereas the fission by path 'b' gives a peak at *m/z* 269 assigned to its imine analogue along with ketene (**Chart I**). The analytical and spectral data of all the products have been given in **Tables I** and **II**.

This Reformatsky-Imine addition reaction is probably affected by substituents in the *N*-phenyl ring of the aldimines. The electron withdrawing functions seem to inhibit this reaction as no product obtained with aldimines having a 2-COOH and 4-SO_2NH_2 function at *N*-phenyl ring. Further the 3-NO_2 function in this ring gives very poor yield even after 3 hr refluxing. Also to a certain extent the yield of the reaction is solubility dependent, as the highly soluble 4-bromo substituted aldimine gives high yield.

Experimental Section

α-Bromoethylacetate and α-methylcinnamaldehyde were purchased from Merck. 3, 4-Methylenedioxy benzaldehyde was purchased from Fluka. Aromatic amines were obtained from commercial sources and used without additional treatment. IR spectra were recorded with FT IR Perkin-Elmer RX-I instrument using nujol. NMR (^{1}H and ^{13}C) spectra were recorded on 300 MHz Bruker AC-300F instrument with TMS as internal standard and deuteriochloroform as solvent and mass spectra were recorded on VG-70 S instrument at SAIF, Chandigarh. All melting points have been determined by Gallen-Kamp apparatus and are uncorrected.

General procedure for the preparation of 1,4-diaryl-2-azetidinones 2a-2r. A 50 mL three necked flask equipped with a magnetic stirrer and a reflux condensor was flushed with nitrogen for several minutes and kept under nitrogen throughout the reaction. Zinc dust (1.18 g, 18 mmole) and half of the benzene (12.5 mL) was added and stirring was initiated. The aldimine (10 mmole) and α-bromoethylacetate (15 mmole) were added followed by

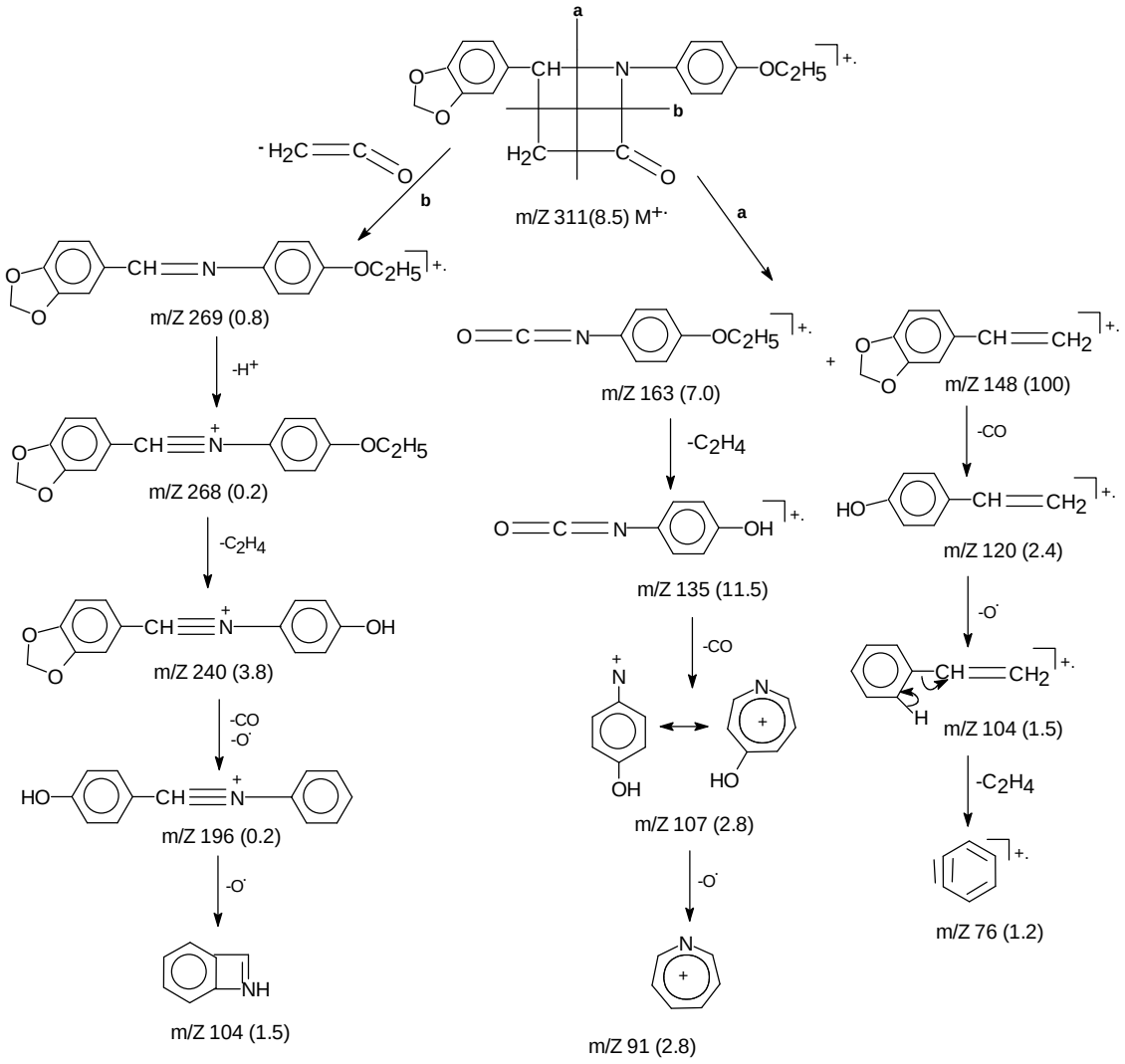


Chart I

Table I — Physical and analytical data of 1, 4 diphenyl-2-azetidinones **2a-r**

Compd	X	Y	n	m.p. (°C)	Yield (%)	Mol. Formula	Found % (Calcd) C	H	N
2a	3',4'-O-CH$_2$-O	H	0	110-12	60	$C_{16}H_{13}NO_3$	71.90 (71.91	4.80 4.86	5.20 5.24)
2b	3',4'-O-CH$_2$-O	4-CH_3	0	145	65	$C_{17}H_{15}NO_3$	72.01 (72.5	5.31 5.33	4.78 4.98)
2c	3',4'-O-CH$_2$-O	4-OCH_3	0	140-42	62	$C_{17}H_{15}NO_4$	68.69 (68.68	4.97 5.05	4.68 4.71)

— Contd

Table I — Physical and analytical data of 1, 4 diphenyl-2-azetidinones **2a-r** — *Contd*

Compd	X	Y	n	m.p. (°C)	Yield	Mol. Formula	Found % (Calcd)		
2d		4-Cl	0	148-49	63	$C_{16}H_{12}NO_3Cl$	62.78 (63.68	3.87 3.98	4.61 4.64)
2e		4-Br	0	152-53	78	$C_{16}H_{12}NO_3Br$	54.79 (55.49	3.32 3.46	3.98 4.04)
2f		4-OC_2H_5	0	155	67	$C_{18}H_{17}NO_4$	69.12 (69.45	5.41 5.46	4.42 4.50)
2g		3-NO_2	0	143-45	20	$C_{16}H_{12}N_2O_5$	60.82 (61.50	3.72 3.84	8.72 8.97)
2h		2-COOH	0	-	-	No reaction	-	-	-
2i		4-SO_2NH_2	0	-	-	No reaction	-	-	-
2j	H	H	1	105	63	$C_{18}H_{17}NO$	82.2 (82.11	6.21 6.46	5.22 5.32)
2k	H	4-CH_3	1	140-42	64	$C_{19}H_{19}NO$	81.98 (82.31	6.74 6.85	5.12 5.05)
2l	H	4-OCH_3	1	130-35	63	$C_{19}H_{19}NO_2$	77.73 (77.81	6.32 6.48	4.65 4.77)
2m	H	4-Cl	1	145-46	66	$C_{18}H_{16}NOCl$	72.43 (72.60	5.26 5.37	4.68 4.70)
2n	H	4-Br	1	149-51	68	$C_{18}H_{16}NOBr$	63.05 (63.15	4.71 4.67	3.89 4.09)
2o	H	4-OC_2H_5	1	150-53	60	$C_{20}H_{21}NO_2$	77.89 (78.17	6.72 6.84	4.41 4.56)
2p	H	3-NO_2	1	153	18	$C_{18}H_{17}N_2O_3$	69.89 (70.12	5.62 5.51	8.92 9.09)
2q	H	2-COOH	1	-	-	No reaction	-	-	-
2r	H	2-SO_2NH_2	1	-	-	No reaction	-	-	-

12.5 mL of benzene. The reaction mixture was refluxed for appropriate time till the zinc dust changes to brownish slurry. The reaction mixture was allowed to stay overnight at room temperature and then filtered. The filtrate was first washed with aqueous ammonia and then with dilute hydrochloric acid. Finally it was washed with distilled water and dried over anhydrous sodium sulphate. The solvent was then removed under vacuum and the crude product was recrystallised to give crystalline solid. **2f**: yield 67%, m.p. 155-56°C (Found: C, 69.12; H, 5.41; N, 4.42. $C_{18}H_{17}NO_4$ requires: C, 69.45; H, 5.46; N, 4.50%). IR (nujol): 1744, 1377, 1230, 1050 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$): δ 1.33 (d, 3H, OCH_2CH_3), 2.85 (dd, $1H_{3b}$, JH_{3b}-H_{3a}=14.99 Hz, JH_{3b}-H_4=2.62 Hz), 3.45 (dd, $1H_{3a}$, JH_{3a}-H_4=5.43 Hz, JH_{3a}-H_{3b}=15.01 Hz), 3.92 (q, 2H, OCH_2CH_3), 4.86 (q, $1H_4$, JH_4-H_{3a}=5.42 Hz, JH_4-H_{3b}=2.27 Hz), 5.94 (d, 2H, >CH_2),

Table II — Infrared and ^{1}H NMR spectral data of 1, 4-diphenyl-2-azetidinones **2a-2p**

Compd	cm^{-1} (nujol)	(300MHz, $CDCl_3$, δ)
2a	1740 (>C=O), 1378, 1320 (C-N), 922 (C-O)	2.83 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.25 Hz, $J_{3b\text{-}4}$=2.61 Hz), 3.52 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.51 Hz, $J_{3a\text{-}3b}$=15.21Hz), 4.82 (q, 1H_4, $J_{4\text{-}3a}$=5.38Hz, $J_{4\text{-}3b}$=2.59Hz), 5.94 (d, 2H, >CH_2), 6.73-7.12 (m, 8H, aromatic)
2b	1748 (>C=O), 1375, 1320 (C-N), 930 (C-O)	2.25 (s, 3H, CH_3), 2.85 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.19 Hz, $J_{3b\text{-}4}$=2.52 Hz), 3.45 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.43 Hz, $J_{3a\text{-}3b}$=15.23Hz), 4.87 (q, 1H_4, $J_{4\text{-}3a}$=5.42Hz, $J_{4\text{-}3b}$=2.51Hz), 5.92 (d, 2H, >CH_2), 6.76-7.17 (m, 7H, aromatic)
2c	1741 (>C=O), 1374, 1320 (C-N), 925 (C-O), 1245,1050 (OCH_3)	2.84 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.21 Hz, $J_{3b\text{-}4}$=2.56 Hz), 3.51 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.65 Hz, $J_{3a\text{-}3b}$=15.21Hz), 3.68 (s, 3H, OCH_3), 4.87 (q, 1H_4, $J_{4\text{-}3a}$=5.39Hz, $J_{4\text{-}3b}$=2.61Hz), 5.94 (d, 2H, >CH_2), 6.91-7.86 (m, 7H, aromatic)
2d	1748 (>C=O), 1381, 1325 (C-N), 924 (C-O), 702 (Ar-Cl)	2.83 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.24 Hz, $J_{3b\text{-}4}$=2.58 Hz), 3.52 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.67 Hz, $J_{3a\text{-}3b}$=15.18Hz), 4.85 (q, 1H_4, $J_{4\text{-}3a}$=5.41Hz, $J_{4\text{-}3b}$=2.55Hz), 5.94 (d, 2H, >CH_2), 7.28-8.27 (m, 7H, aromatic)
2e	1746 (>C=O), 1380, 1322 (C-N), 922 (C-O), 692 (Ar-Br)	2.84 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.18 Hz, $J_{3b\text{-}4}$=2.58 Hz), 3.50 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.46 Hz, $J_{3a\text{-}3b}$=15.24Hz), 4.86 (q, 1H_4, $J_{4\text{-}3a}$=5.39Hz, $J_{4\text{-}3b}$=2.48Hz), 5.94 (d, 2H, >CH_2), 7.2$_4$-8.19 (m, 7H, aromatic)
2f	1744 (>C=O), 1377, 1321 (C-N), 924 (C-O), 1230, 1050 (O-C_2H_5)	1.33 (t, 3H, OCH_2CH_3), 2.85 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=14.99 Hz, $J_{3b\text{-}4}$=2.62 Hz), 3.45 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.43 Hz, $J_{3a\text{-}3b}$=15.01Hz), 3.92 (q, 2H, OCH_2CH_3), 4.86 (q, 1H_4, $J_{4\text{-}3a}$=5.42Hz, $J_{4\text{-}3b}$=2.27Hz), 5.94 (d, 2H, >CH_2), 6.7$_4$-7.19 (m, 7H, aromatic)
2g	1740 (>C=O), 1371, 1316 (C-N), 924 (C-O), 1526, 1360 (C-NO_2)	2.81 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.02 Hz, $J_{3b\text{-}4}$=2.56 Hz), 3.58 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.45 Hz, $J_{3a\text{-}3b}$=15.09Hz), 4.78 (q, 1H_4, $J_{4\text{-}3a}$=5.41Hz, $J_{4\text{-}3b}$=2.59Hz), 5.93 (d, 2H, >CH_2), 7.28-8.82 (m, 7H, aromatic)
2j	1734 (>C=O), 1379, 1320 (C-N)	1.86 (s, 3H, α-CH_3), 2.93 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.21 Hz, $J_{3b\text{-}4}$=2.17 Hz), 3.31 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.47 Hz, $J_{3a\text{-}3b}$=15.20Hz), 4.61 (q, 1H_4, $J_{4\text{-}3a}$=5.68Hz, $J_{4\text{-}3b}$=2.55Hz), 6.71 (s, 1H_β), 7.04 (m, 10H, aromatic)
2k	1732 (>C=O), 1378, 1322 (C-N)	1.84 (s, 3H, α-CH_3), 2.01 (s, 3H, CH_3), 2.91 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.25 Hz, $J_{3b\text{-}4}$=2.62 Hz), 3.32 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.51 Hz, $J_{3a\text{-}3b}$=15.14Hz), 4.67 (q, 1H_4, $J_{4\text{-}3a}$=5.64Hz, $J_{4\text{-}3b}$=2.59Hz), 6.71 (s, 1H_β), 6.98-7.17 (m, 9H, aromatic)
2l	1740 (>C=O), 1378, 1314 (C-N), 1296, 1032, 1015 (OCH_3)	1.84 (s, 3H, α-CH_3), 2.90 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.13 Hz, $J_{3b\text{-}4}$=2.33 Hz), 3.28 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.45 Hz, $J_{3a\text{-}3b}$=15.21Hz), 3.76 (s, 3H, OCH_3), 4.56 (q, 1H_4, $J_{4\text{-}3a}$=5.56Hz, $J_{4\text{-}3b}$=2.41Hz), 6.69 (s, 1H_β), 6.82-7.38 (m, 9H, aromatic)
2m	1731 (>C=O), 1375, 1321 (C-N), 701 (Ar-Cl)	1.86 (s, 3H, α-CH_3), 2.92 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.01 Hz, $J_{3b\text{-}4}$=2.19 Hz), 3.39 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.41 Hz, $J_{3a\text{-}3b}$=15.21Hz), 4.58 (q, 1H_4, $J_{4\text{-}3a}$=5.40Hz, $J_{4\text{-}3b}$=2.20Hz), 6.72 (s, 1H_β), 7.2$_4$-7.31 (m, 9H, aromatic)
2n	1742 (>C=O), 1380, 1328 (C-N), 695 (Ar-Br)	1.83 (s, 3H, α-CH_3), 2.89 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.09 Hz, $J_{3b\text{-}4}$=2.23 Hz), 3.32 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.45 Hz, $J_{3a\text{-}3b}$=15.19Hz), 4.47 (q, 1H_4, $J_{4\text{-}3a}$=5.48Hz, $J_{4\text{-}3b}$=2.35Hz), 6.72 (s, 1H_β), 7.1$_4$-7.39 (m, 9H, aromatic)
2o	1739 (>C=O), 1382, 1322 (C-N), 1235, 1080, 1016 (OC_2H_5)	1.31 (t, 3H, OCH_2CH_3), 1.88 (s, 3H, α-CH_3), 2.89 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.31 Hz, $J_{3b\text{-}4}$=2.21 Hz), 3.45 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.43 Hz, $J_{3a\text{-}3b}$=15.23Hz), 3.87 (q, 2H, OCH_2CH_3), 4.59 (q, 1H_4, $J_{4\text{-}3a}$=5.42Hz, $J_{4\text{-}3b}$=2.36Hz), 6.70 (s, 1H_β), 6.75-7.28 (m, 9H, aromatic)
2p	1743 (>C=O), 1374, 1318 (C-N), 1524, 1518, 1352 (NO_2)	1.86 (s, 3H, α-CH_3), 2.83 (dd, 1H_{3b}, $J_{3b\text{-}3a}$=15.23 Hz, $J_{3b\text{-}4}$=2.24 Hz), 3.41 (dd, 1H_{3a}, $J_{3a\text{-}4}$=5.31 Hz, $J_{3a\text{-}3b}$=15.22Hz), 4.54 (q, 1H_4, $J_{4\text{-}3a}$=5.38Hz, $J_{4\text{-}3b}$=2.29Hz), 6.71 (s, 1H_β), 7.12-7.49 (m, 9H, aromatic)

6.74-7.19 (m, 7H, aromatic); ^{13}C NMR (300 MHz) $CDCl_3$: δ_C 20.785, 26.876, 46.931, 50.952, 53.826, 101.248, 105.779, 108.566, 116.725, 119.724, 129.456, 132.128, 133.344, 135.310, 145.456, 147.756, 148.446, 164.242; MS: *m/z* 311 (8.5) $M^{+\cdot}$, 148 (100) and other prominent mass ion peaks are 248 (3.8), 163 (7.0), 135 (11.5), 120 (2.4), 107 (2.8) 91 (4.3). **2j**: Yield 63%, m.p. 105°C (Found: C, 82.2; H, 6.21; N, 5.22. $C_{18}H_{17}NO$ requires C, 82.1; H, 6.46; N, 5.32%). IR (nujol): 1734, 1377 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$): δ 1.86 (s, 3H, CH_3), 2.93 (dd, 1H_{3b}, $J$$H_{3b}$-$H_{3a}$=15.21 Hz, $J$$H_{3b}$-$H_4$=2.17 Hz), 3.31 (dd,

$1H_{3a}$, JH_{3a}-H_4=5.47 Hz, JH_{3a}-H_{3b}=15.20 Hz), 4.61 (q, $1H_4$, JH_4-H_{3a}=5.65 Hz, JH_4-H_{3b}=2.55 Hz), 6.71 (s, $1H_\beta$), 7.04 (m, 10H, aromatic); ^{13}C NMR 300 MHz ($CDCl_3$): δ 12.042, 42.390, 57.868, 116.362, 123.781, 126.993, 128.214, 128.856, 129.032, 134.450, 136.545, 138.492, 164.211; MS: *m/z* 263 (23.3) $M^{+\cdot}$, 129 (100), 144 (66.1), 77 (15.6).

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