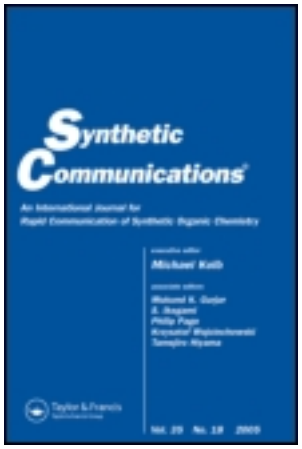

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Natarajan Arumugam [a] & Raghavachary Raghunathan [a]

[a] Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai, India

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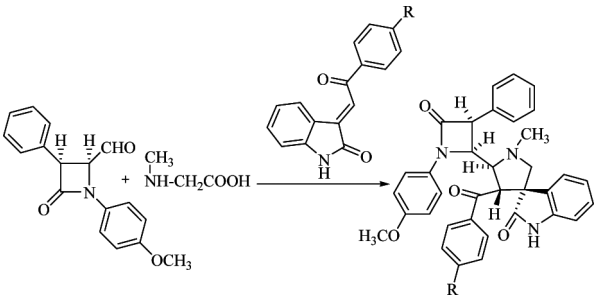
FACILE SYNTHESIS OF β-LACTAM-GRAFTED SPIROOXINDOLOPYRROLIDINE THROUGH REGIOSELECTIVE 1,3-DIPOLAR CYCLOADDITION REACTION

Natarajan Arumugam and Raghavachary Raghunathan
Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai, India

GRAPHICAL ABSTRACT



Abstract *One-pot synthesis of novel β-lactam-grafted spiropyrrolidines has been accomplished in good yield* via *a facile [3 + 2] cycloaddition reaction of azomethine ylides, derived from β-lactam aldehyde and sarcosine, with various* p-*substituted (*E*)-2-oxoindoline-3-ylidene acetophenone derivatives as dipolarophiles. The reaction gave excellent yields of the products when carried out under microwave irradiation.*

Keywords Azomethine ylide; β-lactam; cycloaddition; microwave; spiropyrrolidine

INTRODUCTION

The 1,3-dipolar cycloaddition of azomethine ylides with olefinic and acetylenic dipolarophiles has resulted in a number of novel heterocyclic scaffolds, which are particularly useful for the creation of diverse chemical libraries of druglike molecules for biological screening.[1,2] Functionalized pyrrolidines and oxindoles are the central skeletons for numerous alkaloids and constitute classes of compounds with significant biological activity.[3,4] Derivatives of spirooxindole find very wide biological applications as antimicrobials; anti-inflammatory, antitumoral, and antibiotic agents, and inhibitors of human NK-1 receptors.[5] They are also found to be potent

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Address correspondence to Raghavachary Raghunathan, Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India. E-mail: ragharaghunathan@yahoo.com

aldose reductase inhibitors (ARIs), which help to treat and prevent diabetic complications arising from elevated levels of sorbitol.[6] Spiropyrrolidinyloxindole ring systems are found in a number of alkaloids such as horsifiline, spirotryprostatine A and B, and elacomine.[7]

β-Lactam forms a class of antibiotic characterized by the presence of an azetidine-2-one ring, with biological activity.[8] The azetidine-2-one ring system is a common structural feature of a number of broad-spectrum β-lactam antibiotics such as pencillins, cephalosporins, carbapenems, nocardicins, and monobactams, which have been widely used as chemotherapeutic agents for treating microbial diseases.[9] It also shows many other interesting biological properties, such as cholesterol absorption inhibitory,[10] human cytomegalovirus protease inhibitory,[11] thrombin inhibitory,[12] antihyperglycemic,[13] antitumor,[14] anti-HIV,[15] anti-inflammatory, and analgesic activities.[16] Hence, there has been renewed interest in the synthesis of β-lactam-based heterocycles.

Our research group has been largely involved in the synthesis of spiropyrrolidine subsitituted oxindole and β-lactam heterocycles[17–20] by 1,3-dipolar cycloaddition, which are found in many naturally occurring alkaloids with significant biological activity. We had recently reported the synthesis of macrocyclic bis-β-lactam[21] through [2 + 2] Staudinger reaction and the synthesis of β-lactam-substituted spiropyrrolidine/pyrrolizidines.[22] And, also we reported the synthesis of β-lactam-substituted pyrroloisoquinoline and indolizinoindole ring system by intermolecular 1,3-dipolar cycloaddition.[23]

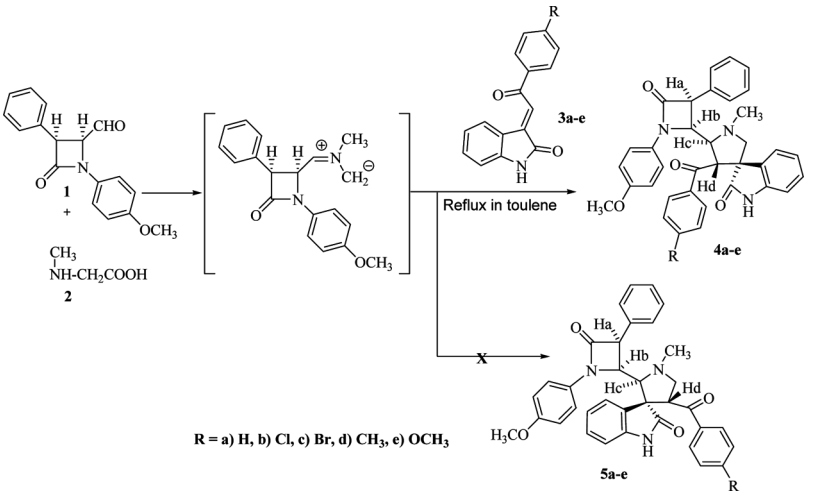
In continuation of our efforts[24] and in anticipation of the high bioactive potential of pyrrolidine-based heterocycles, we herein report the synthesis of some spirooxindolopyrrolidine with β-lactam moiety. Although there are reports available for the synthesis of substituted spiropyrrolidine, there seem to be no reports for the synthesis of β-lactam-grafted spiropyrrolidine with oxindole derivative. Consequently, integration of the β-lactam moiety with spirooxindolopyrrolidine derivatives may increase their biological activities or create new medicinal properties.

RESULTS AND DISCUSSION

In a one-pot cycloaddition reaction, the azomethine ylide generated from β-lactam and sarcosine was reacted with (*E*)-2-oxoindoline-3-ylidene acetophenones **3a–e** in refluxing toluene to afford a series of spiropyrrolidine **4a–e** with overall yield of 45–50% (Scheme 1). The required dipolarophile (*E*)-2-oxoindoline-3-ylidene acetophenones **3a–e** were prepared by the base-catalyzed condensation of isatin with various acetophenones according to the literature procedure.[25]

The cycloadducts **4a–e** were confirmed by spectroscopic techniques and elemental analysis.

The infrared (IR) spectrum of compound **4d** exhibited a peak at 3192 cm^{-1} characteristic of oxindole NH stretch. The presence of an amide carbonyl group was confirmed by an absorption band at 1706 cm^{-1}. The absorption bands at 1739 cm^{-1} and 1630 cm^{-1} showed the presence of β-lactam carbonyl and benzoyl carbonyl groups respectively. The ^1H NMR spectrum of compound **4d** showed a sharp singlet at δ 2.24 ppm due to *N*-methyl protons, and the *N*-CH_2 protons of the pyrrolidine ring appeared as two doublets at δ 2.92 ppm ($J = 10.3$ Hz) and

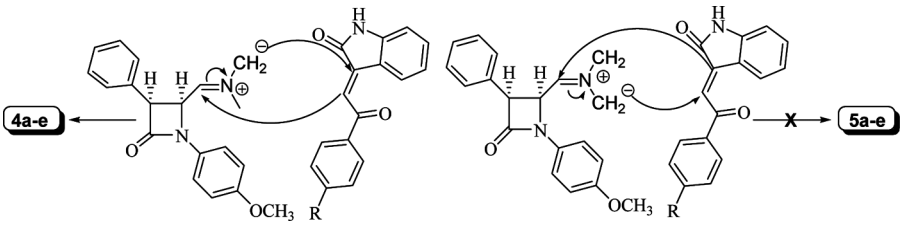


Scheme 1. Synthesis of spiropyrrolidines.

δ 3.53 ($J = 10.3$ Hz). The H_a proton exhibited a doublet at δ 5.15 ppm ($J = 2.1$ Hz). The H_b proton resonated as a doublet of doublets in the range δ 4.40–4.42 ppm ($J = 4.8$, 2.4 Hz). The H_c proton exhibited a doublet of doublet at δ 4.22–4.26 ppm ($J = 8.1$, 4.8 Hz). The H_d proton appeared as doublet at δ 4.53 ppm ($J = 8.4$ Hz), which clearly showed the regiochemistry of the cycloaddition. The NH proton of the oxindole appeared as a singlet at δ 8.14. If the other possible regio-isomer **5d** had been formed, a triplet for H_d proton would have been observed.

The ^{13}C NMR spectrum of cycloadduct **4d** showed peaks at 195.62 ppm and 181.29 ppm due to the benzoyl carbonyl carbon and oxindole amide carbonyl carbon respectively. β-Lactam amide carbonyl carbon showed a peak at δ 166.17 ppm. The *N*-methyl carbon exhibited a peak at δ 40.99 ppm. The spirocarbon showed a peak at δ 68.50 ppm. The mass spectrum of **4d** showed a peak at m/z 571.25 (M^+), which confirmed the structure of the cycloadduct. The regioselective cycloaddition of the dipoles is shown in Scheme 2.

Finally, the regio- and stereochemical outcome of the cycloaddition reaction was unambiguously ascertained by single-crystal x-ray diffraction analysis of the cycloadduct **4d** and **4e** [26] (Figs. 1and 2). The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number



Scheme 2. Regioselective cycloaddition of the dipoles.

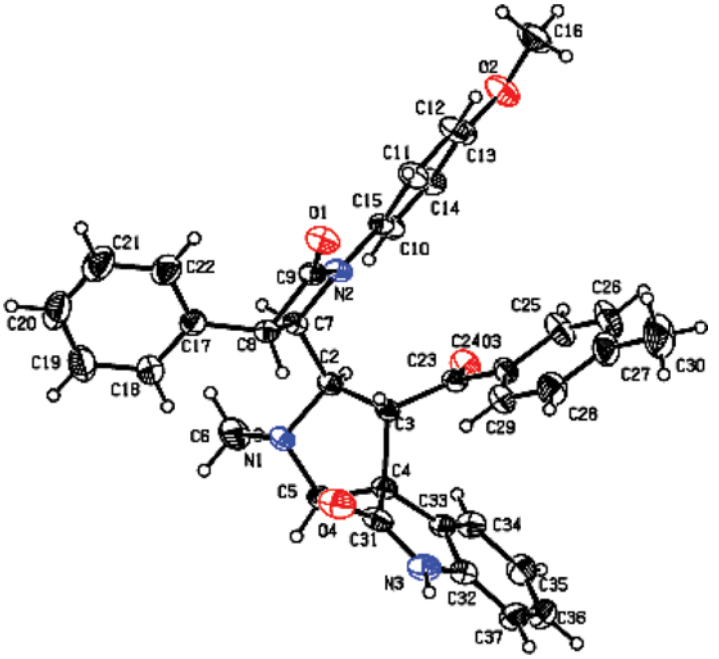


Figure 1. ORTEP diagram of **4d**.

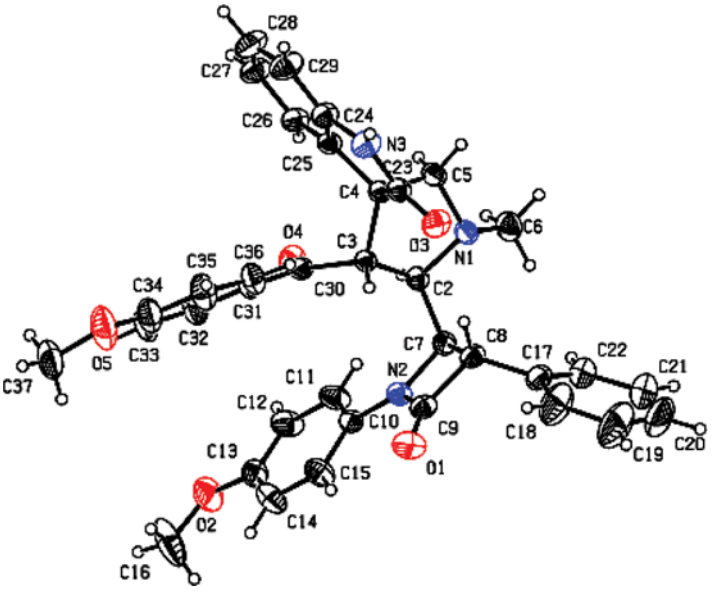


Figure 2. ORTEP diagram of **4e**.

Table 1. Synthesis of spirooxindolopyrrolodines (**5a–e**)

Entry	Compounds	R	Conventional method yield in 4 h (%)	Microwave method in toluene in 10 min yield (%)
1	**6a**	H	50	86
2	**6b**	Cl	52	89
3	**6c**	Br	45	87
4	**6d**	Me	55	85
5	**6e**	OMe	54	84

CCDC 271093 for compound **4d**. In the molecular structure of **4d**, the pyrrolidine ring adopts a twist conformation. The molecular structure is stabilized by intramolecular C–H···O interaction, and the crystal packing also involves weak C–H···O interactions. The β-lactam ring is planar with its internal angles in the range 85.7(1) to 94.5(1)°. The oxindole moiety is planar, is nearly orthogonal to the pyrrolidine and the β-lactam rings, and makes a dihedral angle of 67.3(1)° with the benzoyl plane.

To achieve greater yield of the cycloadducts, reactions were carried out under two different conditions. Thus, the reaction of β-lactam aldehyde and sarcosine, when reacted with dipolarophiles in toluene under reflux, afforded cycloadducts **4a–e** in moderate yields in all cases but required long reaction times and higher temperature. When the same reactions were carried out under microwave irradiation in a toluene solvent, there was a dramatic increase in the yields of the products with a decrease in reaction time. Under these conditions, cycloadducts were obtained in good yields (84–89%) with high regio- and stereoselectivity. The results are summarized in Table 1.

CONCLUSION

In conclusion, the synthesis of a series of β-lactam-grafted spirooxindolopyrrolidines has been accomplished in a simple one-pot reaction with high regioselectivity. Microwave irradiation was found to be synthetically useful in achieving good yields of the products with reduced reaction time as compared to the conventional method. The bioactive studies on the synthesized β-lactam-grafted spiropyrrolidines are in progress.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Shimadzu IR-8300 series Fourier transform (FT)-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Jeol 300 instruments in $CDCl_3$ solvent with tetramethylsilane (TMS) as a standard. Mass spectra were recorded by Jeol-DX303 HF mass spectrophotometer. Elemental analyses were carried out on a Perkin-Elmer CHNS 2400 instrument. Single-crystal x-ray diffraction analyses were performed by

a Bruker Smart Apex CCD area–detector diffractometer and Bruker Smart Apex II CCD area–detector diffractometer.

Column chromatography was performed on silica gel (ACME, 100–200 mesh). Routine monitoring of the reaction was done using thin-layer chromatography (TLC) developed on glass plates coated with silica gel G (ACME) 25 mm thick and visualized with iodine.

General Procedure for Synthesis of Cycloadducts (4a–e)

A solution of *cis*-4-formyl-2 azetidinones (200 mg, 0.71 mmol), sarcosine (63 mg, 0.71 mmol), and 4-(*E*)-3-phenacylidene oxindole (176 mg, 0.71 mmol) was refluxed in dry toluene for 12 h at 110 °C using a Dean–Stark apparatus. After the completion of reaction as indicated by TLC, toluene was evaporated under reduced pressure. The crude product was purified by column chromatography using hexane–EtOAc (8:2) as eluent. The product was recrystallized from EtOAc to reveal the cycloadduct as colorless crystals.

General Procedure for Synthesis of Cycloadducts Under Microwave Method (4a–e)

A mixture of *cis*-4-formyl-2 azetidinones (200 mg, 0.71 mmol), sarcosine (63 mg, 0.71 mmol), and 4-(*E*)-phenacylideneoxindole (176 mg, 0.71 mmol) in toluene was subjected to microwave irradiation for 10 min. After completion of the reaction as evidenced by TLC analysis, the crude product was subjected to column chromatography using petroleum ether/EtOAc (8:2) as eluent. The cycloadduct was obtained exclusively.

Selected Data

1-*N*-Methyl-2-[1′-*N*-(*p*-methoxyphenyl)-3′-phenylazetidine-2′-one]-3-benzoyl spiro[4.3″]oxindole pyrrolidine, 4a. White solid, 86% (0.45 g); mp 238–240 °C; IR (KBr): 1738, 1708 and 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.24 (s, 3H, NCH_3), 2.87 (d, 1H, NCH_2, $J = 10.3$ Hz), 3.49 (d, $J = 10.3$ Hz, 1H, NCH_2), 3.78 (s, 3H, OCH_3), 4.20–4.24 (dd, 1H, $J = 8.1$, 4.8 Hz), 4.38–4.40 (dd, 1H, $J = 4.8$, 2.4 Hz), 4.52 (d, 1H, $J = 8.4$ Hz), 5.13 (d, 1H, $J = 2.1$ Hz), 6.50–7.44 (m, Ar-H, 18H), 8.20 (s, 1H, N-H); ^{13} C NMR ($CDCl_3$, 75 MHz): δ 40.75, 52.98, 54.36, 55.38, 55.64, 60.84, 68.29, 68.47, 109.41, 114.02, 118.83, 122.45, 126.39, 127.27, 127.66, 128.12, 128.38, 128.81, 128.79, 130.67, 134.20, 135.76, 140.26, 143.69, 156.12, 166.15, 181.25 and 195.58. Mass spectrum (EI, 70 eV): *m/z,* 557.23 (M^+). Anal. calcd. for $C_{35}H_{31}N_3O_4$: C, 75.38; H, 5.60; N, 7.54%. Found: C, 75.48; H, 5.68; N, 7.45%.

1-*N*-Methyl-2-[1′-*N*-(*p*-methoxyphenyl)-3′-phenylazetidine-2′-one]-3-(*p*-chlorobenzoyl) spiro[4.3″]oxindolo pyrrolidine, 4b. White solid, 87% (0.5 g); mp: 282–285 °C; IR (KBr): 1739, 1708 and 1628 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.26 (s, 3H, NCH_3), 2.91 (d, 1H, NCH_2, $J = 10.3$ Hz), 3.54 (d, 1H, NCH_2, $J = 10.3$ Hz), 3.78 (s, 3H, OCH_3), 4.25–4.29 (dd, 1H, $J = 8.1$, 4.8 Hz),

4.39–4.41 (dd, 1H, $J = 4.8$, 2.4 Hz), 4.55 (d, 1H, $J = 8.4$ Hz), 5.17 (d, 1H, $J = 2.1$ Hz), 6.58–7.40 (m, Ar-H, 17H), 8.24 (s, 1H, N-H); ^{13} C NMR ($CDCl_3$, 75 MHz): δ 41.97, 53.48, 54.36, 55.40, 55.68, 61.09, 68.35, 68.45, 109.17, 114.07, 118.95, 122.53, 126.36, 127.35, 127.68, 128.05, 128.47, 128.96, 129.02, 130.69, 134.31, 135.78, 140.38, 143.94, 156.26, 166.25, 181.32 and 195.74. Mass spectrum (EI, 70 eV): m/z 591.19 (M^+). Anal. calcd. for $C_{35}H_{30}ClN_3O_4$: C, 71.00; H, 5.11; N, 7.10%. Found: C, 71.16; H, 5.20; N, 7.02%.

1-*N*-Methyl-2-[1′-*N*-(*p*-methoxyphenyl)-3′-phenylazetidine-2′-one]-3-(*p*-bromobenzoyl) spiro[4.3″]oxindolo pyrrolidine, 4c. White solid, 85% (0.54 g); mp 265–267 °C; IR (KBr): 1738, 1708 and 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s, 3H, NCH_3), 2.95 (d, 1H, NCH_2, $J = 10.3$ Hz), 3.57 (d, 1H, NCH_2, $J = 10.3$ Hz), 3.79 (s, 3H, OCH_3), 4.23–4.27 (dd, 1H, $J = 8.1$, 4.8 Hz), 4.41–4.43 (dd, 1H, $J = 4.8$, 2.4 Hz), 4.56 (d, 1H, $J = 8.4$ Hz), 5.15 (d, 1H, $J = 2.1$ Hz), 6.57–7.37 (m, Ar-H, 17H), 7.85 (s, 1H, N-H); ^{13} C NMR ($CDCl_3$, 75 MHz): δ 42.26, 53.52, 54.36, 55.49, 55.83, 60.03, 68.26, 68.55, 109.57, 114.04, 119.06, 122.61, 126.21, 127.22, 127.34, 128.04, 128.30, 128.90, 129.74, 130.77, 132.58, 137.09, 140.47, 143.89, 156.17, 166.27, 181.39 and 195.60. Mass spectrum (EI, 70 eV): m/z 635.14 (M^+). Anal. calcd. for $C_{35}H_{30}BrN_3O_4$: C, 66.04; H, 4.75; N, 6.60%; Found: C, 66.12; H, 4.68; N, 6.69%.

1-*N*-Methyl-2-[1′-*N*-(*p*-methoxyphenyl)-3′-phenylazetidine-2′-one]-3-(*p*-methylbenzoyl) spiro[4.3″]oxindolo pyrrolidine, 4d. Colorless crystals, 75% (0.42 g); mp 263–265 °C; IR (KBr): 1739, 1706 and 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.24 (s, 3H, NCH_3), 2.43 (s, 3H, CH_3), 2.92 (d, 1H, NCH_2, $J = 10.3$ Hz), 3.53 (d, 1H, NCH_2, $J = 10.3$ Hz), 3.75 (s, 3H, OCH_3), 4.22–4.26 (dd, 1H, $J = 8.1$, 4.8 Hz), 4.40–4.42 (dd, 1H, $J = 2.4$, 4.8 Hz), 4.53 (d, 1H, $J = 8.4$ Hz), 5.15 (d, 1H, $J = 2.1$ Hz), 6.56–7.41 (m, Ar-H, 17H), 8.14 (s, 1H, N-H); ^{13} C NMR ($CDCl_3$, 75 MHz): δ 21.53, 40.99, 53.42, 54.38, 55.42, 55.73, 60.94, 68.24, 68.50, 109.37, 113.93, 118.93, 122.52, 126.31, 127.37, 127.76, 128.00, 128.37, 128.82, 128.98, 130.77, 134.21, 135.73, 140.31, 143.86, 156.16, 166.17, 181.29 and 195.62. Mass spectrum (EI, 70 eV): m/z 571.25 (M^+). Anal. calcd. for $C_{36}H_{33}N_3O_4$: C, 75.64; H, 5.82; N, 7.35%. Found: C, 75.73; H, 5.96; N, 7.27%.

1-*N*-Methyl-2-[1′-*N*-(*p*-methoxyphenyl)-3′-phenylazetidine-2′-one]-3-(*p*-methoxybenzoyl) spiro[4.3″]oxindolo pyrrolidine, 4e. Colorless crystals, 84% (0.42 g); mp 255–258 °C; IR (KBr): 1738, 1708 and 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.44 (s, 3H, NCH_3), 2.95 (d, 1H, NCH_2, $J = 10.3$ Hz), 3.56 (d, 1H, $J = 10.3$ Hz), 3.72 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.26–3.30 (dd, 1H, $J = 8.1$, 4.8 Hz), 4.42–4.44 (dd, 1H, $J = 4.8$, 2.4 Hz), 4.53 (d, 1H, $J = 8.4$ Hz), 6.49–7.41 (m, Ar-H, 17H), 9.15 (s, 1H, N-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 40.98, 52.87, 54.57, 55.27, 55.42, 56.57, 60.84, 68.31, 68.71, 109.67, 113.92, 118.88, 122.52, 126.34, 127.42, 127.82, 128.09, 128.34, 128.48, 128.85, 129.98, 130.67, 133.56, 135.72, 140.57, 156.31, 166.18, 181.97 and 194.28. Mass spectrum (EI, 70 eV): m/z 587.24 (M^+). Anal. calcd. for $C_{36}H_{33}N_3O_5$: C, 73.58; H, 5.66; N, 7.15%. Found: C, 73.65; H, 5.78; N, 7.06%.

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