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Synthesis of highly functionalized β-lactam substituted pyrroloisoquinoline and indolizinoindole system by sequential intermolecular 1,3-dipolar cycloaddition reaction and Pictet-Spengler cyclization

Natarajan Arumugam, Raghavachary Raghunathan *

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600025, India

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ABSTRACT

Synthesis of novel pyrroloisoquinoline and indolizinoindole derivatives with β-lactam unit has been achieved by sequential intermolecular 1,3-dipolar cycloaddition reaction and Pictet-Spengler cyclization. The azomethine ylide derived from β-lactam imine of α-amino ester in the presence of silver acetate reacted with nitrostyrenes to give pyrrolidinyl β-lactam, which underwent Pictet-Spengler cyclization in presence of trifluoroacetic acid to give pyrroloisoquinolines and indolizinoindoles.

1. Introduction

1,3-Dipolar cycloaddition is one of the most powerful methods for the construction of highly substituted five membered heterocycles.[1] More specifically, 1,3-dipolar cycloaddition of azomethine ylides and alkenes afford pyrrolidines with high stereoselectivity. The pyrrolidine based heterocycles is ever fascinating since they promise a wide spectrum of pharmacological activities like preventing and treating rheumatoid arthritis, asthma, allergies, rhinitis, and related diseases as they inhibit the production of prostaglandin E2 and intracellular phospholipase A2.[2] Furthermore, pyrrolidines are important building blocks in organic synthesis and in the past years have emerged as privileged organocatalysts.[3]

Azomethine ylides are unstable and have to be prepared in situ. Several methods have been developed for the synthesis of azomethine ylides, including ring opening of aziridines,[4] 1,2-proton shift of *N*-arylidene-benzylamines,[5] and deprotonation of iminium salts[6] or metalated imino esters (metallo-azomethine ylides),[7] the last one being the most commonly used in organic chemistry.

Grigg et al.[8] reported sequential intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylide generated through N-metalation route followed by Pictet-Spengler cyclization, which resulted in the formation of biologically important pyrroloisoquinoline and indolizinoindole derivatives. The pyrroloisoquinoline ring system is a key subunit of *Erythrina* alkaloids,[9] which have been widely applied in folk medicine in tropical, sub-tropical regions.[10] Moreover, the pyrroloisoquinoline alkaloid (+)-crispine A, isolated from *Clathrus crispus* by Zhao et al., shows important biological activity against SKOV3, KB, and HeLa human cancer cell lines.[11] Likewise, indolizinoindole ring systems are of interest to the pharmaceutical industry. They have been used as intermediates in the preparation of diuretic compounds and are also known to exhibit analgesic and *anti*-inflammatory activity in their own right.[12]

Our research group has been largely involved in the synthesis of pyrrolidine,[13–15] pyrroloisoquinoline,[16] and indolizinoindole[17,18] derivatives by 1,3-dipolar cycloaddition reactions which are found in many naturally occurring alkaloids and known to possess significant biological activity as discussed.

On the other hand, β-lactam as synthetic intermediate has been widely recognized in organic synthesis[19] because it is an active moiety present in most widely used antibiotics such as penicillin,[20] cephalosporins[21] etc. Besides, these antibiotics also shows many other interesting biological properties such as cholesterol absorption inhibitors, human cytomegalovirus protease inhibitors, thrombin inhibitors, *anti*-hyperglycemic, *anti*-tumor, *anti*-HIV, *anti*-inflammatory, analgesic activities.[22] Recently, we reported the synthesis of β-lactam substituted pyrrolidine[23] and pyrrolizidine derivatives by intermolecular 1,3-dipolar cycloaddition and macrocylic bis

* Corresponding author. Fax: +91 44 22352494
E-mail address: ragharaghunathan@yahoo.com (R. Raghunathan).

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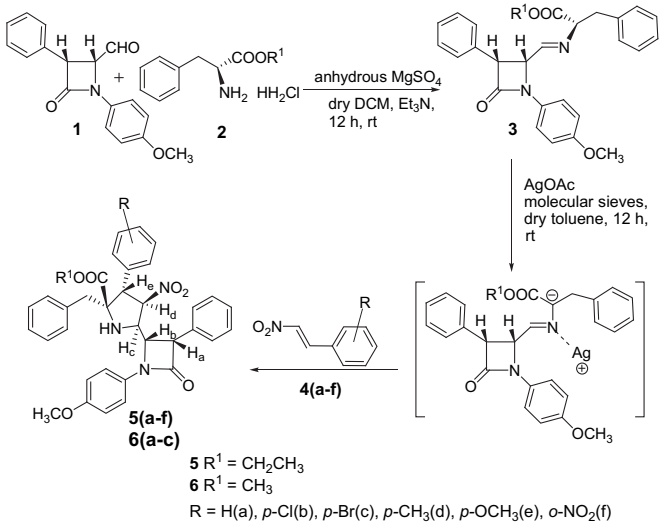
β-lactam through [2+2] Staudinger reaction.[24] Alcaide et al.[25] reported pyrrolidinyl β-lactam derived from 4-formyl β-lactam through 1,3-dipolar cycloaddition reaction of *N*-metallo azomethine ylide. Despite the versatility of the β-lactam ring, there are only a few reports on the subject of 1,3-dipolar cycloaddition involving 4-formyl β-lactam as substrate. To the best of our knowledge to date there has been no reports in literature for the synthesis of pyrroloisoquinoline and indolizinoindole incorporating β-lactam heterocycles. In this article, we focused our study on the reactivity of *N*-metallo azomethine ylide generated from β-lactam aldehyde and α-amino esters in order to broaden the scope of 1,3-dipolar cycloaddition reactions for the construction of pyrrolidinyl β-lactam and pyrroloisoquinoline and indolizinoindole incorporating β-lactam ring system.

2. Results and discussion

Our synthetic study started with the substrates 4-formyl β-lactam **1**, α-amino ester **2** and nitroalkenes **4a–f**. First, β-lactam aldehyde **1** was reacted with phenylalanine ester hydrochloride **2** and triethylamine in dry dichloromethane at room temperature. After stirring for 12 h, filtering the reaction mixture and evaporation of organic layer yielded crude imine. The imine **3** was used for the next step without further purification. The azomethine ylide generated by the imines in presence of silver acetate and triethylamine in acetonitrile at room temperature, was reacted with various substituted nitrostyrenes to yield a series of novel pyrrolidinyl β-lactam derivatives **5a–f** and **6a–c** as single diasteromers with overall yields of 30–45% (Scheme 1).



Scheme 1.

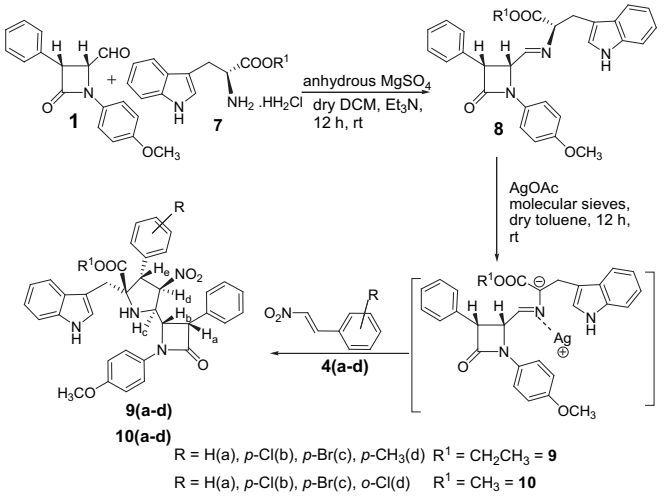
The structure and regiochemistry of cycloadducts were confirmed by spectral and elemental analysis. The stereochemistry of the product **6a** was ascertained by single crystal X-ray diffraction analysis.[26]

To improve the yield of the products, we carried out the reaction in various organic solvents. We found that using dichloromethane and benzene as solvents was not fruitful and gave a mixture of inseparable byproducts. The cycloaddition with other solvents like dioxane under the same reaction condition did not give the expected results. However, we observed substantial increase in the yield of the products with a decrease in reaction time when the reaction was carried out in toluene (Table 1).

A similar reaction protocol was extended for the synthesis of pyrrolidinyl β-lactam **9** and **10** by replacing phenylalanine ester hydrochloride with tryptophan ester hydrochloride to afford **9a–d** and **10a–d** in good to excellent yield (Scheme 2).

Table 1
Cycloaddition reaction under the two different solvent conditions

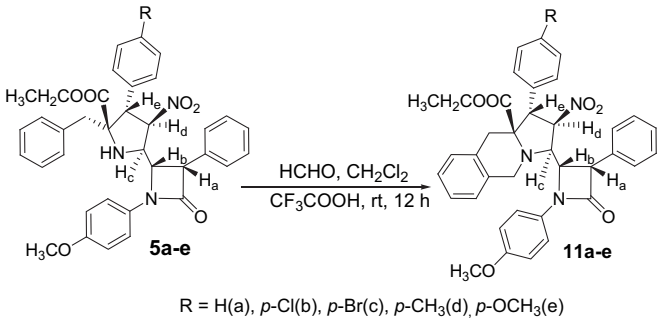
Entry	Compounds	Acetonitrile (12 h) Yield %	Toluene (12 h) Yield %
1	**5a**	42	85
2	**5b**	45	89
3	**5c**	43	87
4	**5d**	32	85
5	**5e**	30	82
6	**5f**	37	80
7	**6a**	33	86
8	**6a**	40	89
9	**6c**	39	86
10	**9a**	40	85
11	**9b**	44	90
12	**9c**	45	88
13	**9d**	35	84
14	**10a**	39	86
15	**10b**	44	86
16	**10c**	32	80
17	**10d**	37	81



Scheme 2.

The cycloadducts were characterized by spectral and elemental analysis. Moreover, the structure of the compounds **9d**,[27] **10c**,[28] and **10d**[29] were unambiguously established by its single crystal X-ray analysis. The cycloaddition proceeded stereo- and regiospecifically in toluene at room temperature to afford *syn-endo* cycloadducts via metallo-azomethine ylide cycloadditions. The stereochemistry of the cycloadducts **5**(**a–f**), **6**(**a–c**), **9**(**a–d**), and **10**(**a–d**) are based on the usual facial selectivity and *endo*-transition state observed.[30] Thus, in all the cases the cycloadducts are formed via *endo*-trasition state.

Having fascinated by the structural and therapeutics diversities of isoquinoline ring such as *inter alia* antibacterial and antiplasmodial activity as well as cardiovascular and neuromodulating



Scheme 3.

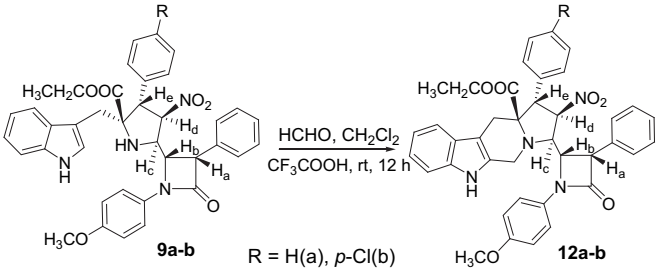
effects,[31] pyrrolidinyl β-lactam fused isoquinoline ring was conceived as targets on the design and synthesis of new heterocycles. Thus, pyrrolidinyl β-lactam **5** was reacted with paraformaldehyde in the presence of catalytic amount of trifluoroacetic acid in dry dichloromethane to give pyrroloisoquinoline incorportated β-lactam **11a**–**e** in good to excellent yields (Scheme 3) (Table 2).

Table 2
Pictet-Spengler cyclization under the three different acid catalyst conditions

Entry	Compounds	TFA 12 h Y (%)	H_2SO_4 12 h Y (%)	PTSA 12 h Y (%)
1	**11a**	90	64	45
2	**11b**	95	69	48
3	**11c**	92	67	46
4	**11d**	89	65	42
5	**11e**	87	62	40
6	**12a**	85	59	39
7	**12b**	89	60	45

The Pictet-Spengler cyclized products were confirmed by spectral and elemental analysis. The structure of the cyclized product was further ascertained on the basis of 2D NMR spectrum (^1H–^1H cosy). Furthermore, the structure of the products **11b**[32] and **11e**[33] were unambiguously determined by single crystal X-ray diffraction analysis.

Molecules with indolizinoindole motif have shown a wide spectrum of bioactivities. Anticipating a better bioactivity by incorporating aforesaid biologically potent moiety, a series of β-lactam substituted indolizinoindole heterocycles were synthesized from cycloadduct **9** by Pictet-Spengler cyclization reaction (Scheme 4). Thus, the cycloadducts **9a**–**b** when reacted with paraformaldehyde in dry dichloromethane in the presence of TFA for 12 h gave the target molecules **12a**–**b** in moderate to good yield (Table 2).



Scheme 4.

The product formation was established by spectroscopic data. The Pictet-Spengler cyclization was investigated with a series of acid catalysts such as H_2SO_4, PTSA, and TFA in different solvents to find the best reaction conditions. Among the acid catalysts used TFA in chlorinated solvent was found to be the best in terms of yield and reaction time (Table 2). Further, we observed that electronic factors of aromatic ring substitutions did not affected Pictet–Spengler cyclization.

3. Conclusion

In conclusion, for the first time we have accomplished the synthesis of novel pyrroloisoquinoline and indolizinoindole grafted β-lactam derivatives by sequential intermolecular 1,3-dipolar cycloaddition reaction via *N*-metallo azomethine ylide and Pictet-Spengler cyclization.

4. Experimental

4.1. General considerations

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU IR-8300 series FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker 300 MHz instruments in $CDCl_3$ and DMSO-d_6 solvent with TMS as a standard. Mass spectra were recorded on JEOL-DX303 HF mass spectrophotometer. Elemental analyses were carried out using Perkin–Elmer CHNS 2400 and Carlo Erba 1106 instruments. Single crystal X-ray diffraction analyses were performed on Bruker SMARTAPEX CCD area-detector diffractometer and Bruker SMART APEXII CCD area-detector diffractometer.

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

4.2. General procedure for synthesis of pyrrodinyl β-lactams 5, 6, 9, and 10

β-lactam aldehyde (281.0 mg, 1 mmol) was treated with phenylalanine ester hydrochloride (244.7 mg, 1 mmol) /tryptophan ester hydrochloride (285.8 mg, 1 mmol) in the presence of Et_3N (0.35 ml, 2.5 mmol) and anhydrous $MgSO_4$ in dry dichloromethane (10 mL) at room temperature for 12 h to give the imine. The solution was washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum to get the imine. The imine (456.5 mg, 1 mmol) was then stirred with silver (I) acetate and nitrostyrene (1 mmol) in the presence of Et_3N (0.167 mL, 1.2 mmol) and molecular sieves in dry toluene (30 mL) at room temperature for 12 h. The reaction mixture was filtered through Celite. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (100–200 mesh), with hexane–ethylacetate (7:3) as eluent to give the product. The compounds were recrystallized from ethylacetate by slow evaporation method.

4.2.1. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-phenyl-2-ethoxy carbonyl-2-benzylpyrrolidine, ***5a***. Yield (510 mg, 85%) as a colorless crystal; Mp: 168–170 °C; [Found: C, 71.49; H, 5.88; N, 6.87. $C_{36}H_{35}N_3O_6$ requires: C, 71.39; H, 5.82; N, 6.94%]; R_f (30% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.18 (3H, t, CH_3), 1.97 (1H, d, J=13.5 Hz), 2.04 (1H, d, J=13.5 Hz), 2.95 (1H, d, J=11.7 Hz), 3.67–3.76 (1H, m), 3.82 (3H, s, OCH_3), 4.00–4.03 (2H, q, CH_2), 4.16 (1H, s, NH), 4.24–4.29 (1H, dd, J=5.4, 9.7 Hz), 4.45 (1H, dd, J=4.5 Hz), 4.87 (1H, d, J=5.4 Hz), 6.49–7.69 (19H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 40.8, 55.5, 56.4, 57.4, 57.6, 61.6, 64.4, 73.4, 92.6, 114.3, 121.6, 126.4, 127.5, 127.7, 128.3, 128.5, 128.7, 129.1, 129.8, 130.0, 130.5, 132.5, 135.7, 136.0, 157.2, 165.2, 173.0 ppm EIMS m/z 605.25 (M^+).

4.2.2. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-Chlorophenyl)-2-ethoxy carbonyl-2-benzylpyrrolidine, ***5b***. Yield (570 mg, 89%) as a colorless crystal; Mp: 207–209 °C; [Found: C, 67.69; H, 5.43; N, 6.45. $C_{36}H_{34}ClN_3O_6$ requires: C, 67.55; H, 5.35; N, 6.56%]; R_f (30% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 1.16 (3H, t, CH_3), 1.97 (1H, d, J=13.5 Hz) 1.99 (1H, d, J=13.5 Hz), 2.92 (1H, d, J=11.7 Hz), 3.61–3.70 (1H, m), 3.82 (3H, s, OCH_3), 4.00–4.10 (2H, q, CH_2), 4.14 (1H, s, NH), 4.23–4.28 (1H, dd, J=5.4, J=9.7 Hz), 4.38 (1H, dd, J=4.5 Hz), 4.88 (1H, d, J=5.4 Hz), 6.41–7.69 (18H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 40.8, 55.5, 55.6, 57.3, 57.5, 61.7, 64.3, 73.3, 92.3, 114.3, 121.5, 126.6, 127.5, 128.7, 128.8, 129.2, 129.6, 129.7, 130.0, 130.5, 132.5, 133.7, 134.7, 135.7, 157.2, 165.1, 172.8 ppm EIMS m/z 640.12 (M^+).

4.2.3. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-bromophenyl)-2-ethoxy carbonyl-2-benzylpyrrolidine, ***5c***. Yield (590 mg, 87%) as a white solid; Mp: 212–214 °C; [Found: C, 63.27; H, 5.11; N, 6.19. $C_{36}H_{34}BrN_3O_6$ requires: C, 63.16; H, 5.01; N, 6.14%]; R_f (30% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, t, CH_3), 1.98 (1H, d, J=13.5 Hz) 1.99

(1H, d, J=13.5 Hz), 2.92 (1H, d, J=11.7 Hz), 3.61–3.69 (1H, m), 3.82 (3H, s, OCH_3), 3.99–4.10 (2H, q, CH_2), 4.13 (1H, s, NH), 4.23–4.28 (1H, dd, J=5.4, 9.7 Hz), 4.38 (1H, dd, J=4.5 Hz), 4.87 (1H, d, J=5.4 Hz), 6.35–7.69 (18H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$,) 13.9, 40.8, 55.5, 56.4, 57.4, 57.6, 61.6, 64.4, 73.4, 92.6, 114,3, 121.6, 126.4, 127.5, 127.7, 128.3, 128.5, 128.7, 129.1, 129.8, 130.0, 130.5, 132.5, 135.7, 136.0, 157.2, 165.2, 173.0 ppm EIMS m/z 683.16 (M^+).

4.2.4. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-methylphenyl)-2-ethoxy carbonyl-2-benzylpyrrolidine, ***5d****.* Yield (530 mg, 85%) as a white solid; Mp: 227–229 °C; [Found: C, 71.84; H, 6.11; N, 6.88. $C_{37}H_{37}N_3O_6$ requires: C, 71.71; H, 6.02; N, 6.78%]; R_f (30% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.18 (3H, t, CH_3), 2.00 (1H, d, J=13.5 Hz), 2.01 (1H, d, J=13.5 Hz), 2.30 (3H, s, CH_3), 2.94 (1H, d, J=11.7 Hz), 3.67–3.74 (1H, m), 3.82 (3H, s, OCH_3), 3.99–4.09 (2H, q, CH_2), 4.12 (1H, s, NH), 4.23–4.28 (1H, dd, J=5.4, 9.7 Hz), 4.43 (1H, dd, J=4.5 Hz), 4.86 (1H, d, J=5.4 Hz), 6.37–7.69 (18H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 20.9, 40.7, 55.5, 56.1, 57.4, 57.6, 61.5, 64.3, 73.4, 92.7, 114.3, 121.6, 126.4, 127.4, 128.1, 128.7, 129.1, 129.2, 129.8, 130.1, 130.5, 132.5, 132.6, 136.1, 137.5, 157.2, 165.3, 173.0. EIMS m/z 619.27 (M^+).

4.2.5. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-methoxyphenyl)-2-ethoxy carbonyl-2-benzylpyrrolidine, ***5e****.* Yield (530 mg, 82%) as a white solid; Mp: 218–220 °C; [Found: C, 70.36; H, 6.18; N, 6.56. $C_{38}H_{39}N_3O_7$ requires: C, 70.25; H, 6.05; N, 6.47%]; R_f (30% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$,) 1.24 (3H, t, CH_3), 1.97 (1H, d, J=13.5 Hz), 2.06 (1H, d, J=13.5 Hz), 2.93 (1H, d, J=11.7 Hz), 3.64 (1H, s, NH), 3.67–3.70 (1H, m), 3.76 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.10 (2H, q, CH_2), 4.23–4.28 (1H, dd, J=5.4, 9.6 Hz), 4.37 (1H, dd, J=4.5 Hz), 4.83 (1H, d, J=5.4 Hz), 6.41–7.67 (18H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1, 21.0, 40.8, 55.4, 56.6, 57.4, 57.6, 60.3, 64.2, 73.4, 92.7, 114.2, 121.7, 126.4, 127.5, 128.3, 128.7, 129.1, 129.2, 129.6, 130.0, 130.5, 132.5, 136.1, 136.2, 157.2, 159.0, 165.3, 176.3 ppm EIMS m/z 649.28 (M^+).

4.2.6. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(2-nitrophenyl)-2-ethoxy carbonyl-2-benzylpyrrolidine, ***5f****.* Yield (520 mg, 80%) as a pale yellow solid; Mp: 196–198 °C; [Found: C, 66.53; H, 5.37; N, 8.69. $C_{36}H_{34}N_4O_8$ requires: C, 66.45; H, 5.27; N, 8.61%]; R_f (30% EtOAc/Hexane) 0.55; IR (KBr): 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.15 (3H, t, CH_3), 1.77 (1H, d, J=13.5 Hz), 2.08 (1H, d, J=13.5 Hz), 3.14 (1H, d, J=11.7 Hz), 3.68–3.77 (1H, m), 3.82 (3H, s), 3.94–4.12 (2H, q, CH_2), 4.28–4.33 (1H, dd, J=5.4, 9.7 Hz), 4.39 (1H, dd, J=4.5 Hz), 4.89 (1H, d, J=5.4 Hz), 5.90–7.77 (18H, m, Ar-H); ^{13}C NMR (75 MHz $CDCl_3$) 13.6, 39.8, 49.5, 55.5, 57.2, 57.4, 62.3, 65.2, 73.6, 93.6, 114.3, 121.7, 125.4, 126.7, 127.5, 128.7, 128.8, 128.9, 129.1, 129.4, 129.9, 130.6, 132.0, 132.6, 135.1, 150.4, 157.3, 165.0 and 171.6 ppm EIMS m/z 650.24 (M^+).

4.2.7. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-phenyl-2-methoxy carbonyl-2-benzylpyrrolidine, ***6a****.* Yield (500 mg, 86%) as a white solid; Mp: 175–177 C; [Found: C, 71.18; H, 5.72; N, 7.18. $C_{35}H_{33}N_3O_6$ requires: C, 71.05; H, 5.62; N, 7.10%] 0.6; R_f (30% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.98 (1H, d, J=14.1 Hz), 2.03 (1H, d, J=14.1 Hz), 2.94 (1H, d, J=11.7 Hz), 3.66 (3H, s, OCH_3), 3.71–3.76 (1H, m), 3.82 (3H, s, OCH_3), 4.16 (1H, s, NH), 4.24–4.30 (1H, dd, J=5.4, 9.7 Hz), 4.44 (1H, dd, J=4.5 Hz), 4.87 (1H, d, J=5.4 Hz), 6.50–7.69 (19H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 40.9, 52.5, 55.5, 56.1, 57.4, 57.6, 64.4, 73.5, 92.5, 114.3, 121.6, 126.5, 127.6, 127.8, 128.3, 128.6, 128.7, 129.2, 129.6, 130.0, 130.5, 132.5, 135.6, 135.9, 157.9, 165.3, 173.5 ppm EIMS m/z 591.24 (M^+).

4.2.8. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-chlorophenyl)-2-methoxy carbonyl-2-benzylpyrrolidine, ***6b****.* Yield (550 mg, 89%) as a white solid; Mp: 180–182 °C; [Found: C, 67.23; H, 5.27; N, 6.79. $C_{35}H_{32}ClN_3O_6$ requires: C, 67.14; H, 5.15; N, 6.71%]; R_f (30% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 1.98 (2H, s, CH_2), 2.91 (1H, d, J=11.5 Hz), 3.64 (3H, s, OCH_3), 3.67–3.68 (1H, m), 3.82 (3H, s, OCH_3), 4.14 (1H, s, NH), 4.24–4.28 (1H, dd, J=5.6, 9.7 Hz), 4.37 (1H, dd, J=4.5 Hz), 4.86 (1H, d, J=5.6 Hz), 6.42–7.68 (18H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) 40.9, 52.6, 55.3, 55.5, 57.4, 57.4, 64.3, 73.3, 92.2, 114.3, 121.6, 126.6, 127.6, 128.3, 128.7, 128.8, 129.2, 129.6, 129.9, 130.5, 132.5, 133.7, 134.0, 135.6, 157.2, 165.1, 173.3 ppm EIMS m/z 625.2 (M^+).

4.2.9. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-bromophenyl)-2-methoxy carbonyl-2-benzylpyrrolidine, ***6c****.* Yield (570 mg, 86%) as a white solid; Mp: 210–212 °C; [Found: C, 62.78; H, 4.88; N, 6.36. $C_{35}H_{32}BrN_3O_6$ requires: C, 62.69; H, 4.81; N, 6.27%]; R_f (30% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1727 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.99 (2H, s, CH_2), 2.91 (1H, d, J=11.4 Hz), 3.65 (3H, s, OCH_3), 3.69 (1H, m), 3.82 (3H, s, OCH_3), 4.13 (1H, s, NH), 4.24–4.29 (1H, dd, J=5.4, 9.7 Hz), 4.37 (1H, dd, J=4.5 Hz), 4.87 (1H, d, J=5.4 Hz), 6.35–7.37 (18H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 40.9, 52.6, 55.3, 55.5, 57.4, 57.5, 64.3, 73.3, 92.1, 114.3, 121.6, 121.9, 126.6, 127.6, 128.7, 128.8, 129.2, 129.6, 129.9, 130.5, 131.7, 132.5, 134.5, 135.6, 157.2, 165.1, 173.3 ppm EIMS m/z 669.15 (M^+).

4.2.10. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-phenyl-2-ethoxy carbonyl-2-methyl indolylpyrrolidine, ***9a****.* Yield (540 mg, 85%) as a white solid; Mp: 217–219 °C; [Found: C, 70.87; H, 5.70; N, 8.75. $C_{38}H_{36}N_4O_6$ requires: C, 70.79; H, 5.63; N, 8.69%]; R_f (30% EtOAc/Hexane) 0.4; IR (KBr): 3358, 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 0.97 (3H, t, CH_3), 2.08 (1H, d, J=14.4 Hz), 2.28 (1H, d, J=14.4 Hz), 3.23 (1H, d, J=12.6 Hz), 3.65–3.71 (1H, m), 3.79 (3H, s, OCH_3), 3.94 (2H, q, CH_2), 4.13 (1H, s, NH), 4.21 (1H, dd, J=4.2 Hz), 4.46–4.51 (1H, dd, J=5.7, 9.6 Hz), 4.91(1H, d, J=5.7 Hz), 6.49–7.67 (19H, m, Ar-H), 10.56 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 13.4, 30.0, 55.3, 56.3, 56.9, 57.1, 61.8, 63.7, 72.5, 92.9, 108.4, 110.9, 113.7, 117.6, 117.8, 120.3, 121.7, 123.9, 127.2, 127.3, 128.1, 128.3, 128.5, 128.8, 130.4, 130.5, 132.8, 135.3, 136.3, 156.4, 165.5, 172.9 ppm EIMS m/z 644.26 (M^+).

4.2.11. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-Chlorophenyl)-2-ethoxy carbonyl-2-methyl indolylpyrrolidine, ***9b****.* Yield (610 mg, 90%) as a white solid; Mp: 285–287 °C; [Found: C, 67.29; H, 5.27; N, 8.16. $C_{38}H_{35}ClN_4O_6$ requires: C, 67.20; H, 5.19; N, 8.25%]; R_f (30% EtOAc/Hexane) 0.4; IR (KBr): 3359, 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 0.98 (3H, t, CH_3), 2.11 (1H, d, J=14.4 Hz), 2.34 (1H, d, J=14.4 Hz), 3.24 (1H, d, J=12.6 Hz), 3.68–3.72 (1H, m), 3.80 (3H, s, OCH_3), 3.94 (2H, q, CH_2), 4.13 (1H, dd, J=4.2 Hz), 4.18 (1H, s, NH), 4.48–4.53 (1H, dd, J=5.7, 9.6 Hz), 4.91 (1H, d, J=5.7 Hz), 6.50–7.67 (18H, m, Ar-H), 10.59 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 13.4, 30.1, 55.3, 55.6, 56.9, 57.0, 60.8, 63.7, 72.4, 92.7, 108.3, 110.0, 113.7, 117.7, 117.9, 120.3, 121.7, 124.0, 127.2, 128.0, 128.4, 128.9, 130.4, 130.5, 130.6, 132.1, 132.7, 135.3, 135.5, 156.4, 165.5, 172.8 ppm EIMS m/z 678.22 (M^+).

4.2.12. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-bromophenyl)-2-ethoxy carbonyl-2-methyl indolylpyrrolidine, ***9c****.* Yield (630 mg, 88%) as a white solid; Mp: 237–239 °C; [Found: C, 63.14; H, 4.96; N, 7.80. $C_{38}H_{35}BrN_4O_6$ requires: C, 63.07; H, 4.88; N, 7.74%]; R_f (30% EtOAc/Hexane) 0.4; IR (KBr): 3358, 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 0.97 (3H, t, CH_3), 2.08 (1H, d, J=14.4 Hz), 2.32 (1H, d, J=14.4 Hz), 3.22 (1H, d, J=12.6 Hz), 3.64–3.70 (1H, m), 3.79 (3H, s, OCH_3), 3.93 (2H, q, CH_2), 4.10 (1H, dd, J=4.2 Hz), 4.15 (1H, s, NH), 4.49–4.54 (1H, dd, J=5.7, 9.6 Hz), 4.90 (1H, d, J=5.7 Hz), 6.50–7.67 (18H, m, Ar-H), 10.58 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 13.4, 30.1, 55.3, 55.6, 56.9, 57.0, 60.6, 63.7, 72.4, 92.6, 108.3, 110.9, 113.7, 117.7, 117.9, 120.3, 120.6, 121.6, 124.0, 127.2, 128.4, 128.9, 130.3, 130.4, 130.7, 131.0, 132.7, 135.3, 135.9,

156.4, 165.5, 172.7 ppm EIMS *m*/*z* 722.17 (M^+). Anal. Calcd for $C_{38}H_{35}BrN_4O_6$: C, 63.07; H, 4.88; N, 7.74%. Found: C, 63.14; H, 4.96; N, 7.80%.

4.2.13. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-methylphenyl)-2-ethoxy carbonyl-2-methyl indolylpyrrolidine, ***9d***. Yield (550 mg, 84%) as a colorless crystals; Mp: 227–229 °C; [Found: C, 71.21; H, 5.88; N, 8.48. $C_{39}H_{38}N_4O_6$ requires: C, 71.11; H, 5.81; N, 8.51%]; R_f (30% EtOAc/Hexane) 0.4; IR (KBr): 3359, 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 0.98 (3H, t, CH_3), 2.14 (1H, d, *J*=14.4 Hz), 2.27 (3H, s, CH_3), 2.30 (1H, d, *J*=14.4 Hz), 3.22 (1H, d, *J*=12.6 Hz), 3.68–3.78 (1H, m), 3.80 (3H, s, OCH_3), 3.92–3.95 (2H, q, CH_2), 4.10 (1H, s, NH), 4.21 (1H, dd, *J*=4.2 Hz, *J*=4.5 Hz), 4.46–4.51 (1H, dd, *J*=5.7, 9.6 Hz), 4.91 (1H, d, *J*=5.7 Hz), 6.51–7.67 (18H, m, Ar-H), 10.58 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 13.4, 20.5, 30.0, 55.3, 55.2, 56.8, 57.0, 60.8, 63.7, 72.6, 93.0, 108.5, 111.0, 113.7, 117.7, 117.9, 120.3, 121.7, 123.9, 127.2, 128.3, 128.7, 128.8, 130.4, 132.7, 133.3, 135.3, 136.6, 156.4, 165.6, 173.0 ppm EIMS *m*/*z* 658.28 (M^+).

4.2.14. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-phenyl-2-methoxy carbonyl-2-methyl indolylpyrrolidine, ***10a***. Yield (540 mg, 86%) as a white solid; Mp: 188–190 °C; [Found: C, 70.39; H, 5.37; N, 8.92. $C_{37}H_{34}N_4O_6$ requires: C, 70.46; H, 5.43; N, 8.88%]; R_f (30% EtOAc/Hexane) 0.4; IR (KBr): 3354, 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 2.11(1H, d, *J*=14.4 Hz), 2.29 (1H, d, *J*=14.4 Hz), 3.15 (1H, d, *J*=12.6 Hz), 3.82–3.89 (1H, m), 3.44 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.15 (1H, s, NH), 4.22 (1H, dd, *J*=4.2 Hz), 4.43–4.48 (1H, dd, *J*=5.7, 9.6 Hz), 4.90 (1H, d, *J*=5.7 Hz), 6.48–7.66 (19H, m, Ar-H), 10.58 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 29.3, 30.5, 52.1, 55.3, 56.8, 57.3, 63.7, 72.5, 92.4, 107.8, 110.1, 113.5, 117.5, 118.1, 120.4, 122.0, 124.1, 127.0, 128.0, 128.3, 128.7, 130.2, 130.4, 130.6, 132.0, 132.5, 135.2, 135.3, 156.3, 164.5, 172.2 ppm EIMS *m*/*z* 630.25 (M^+).

4.2.15. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-Chlorophenyl)-2-methoxy carbonyl-2-methyl indolylpyrrolidine, ***10b***. Yield (570 mg, 86%) as a white solid; Mp: 237–239 °C; [Found: C, 66.76; H, 5.12; N, 8.36. $C_{37}H_{33}ClN_4O_6$ requires: C, 66.81; H, 5.00; Cl, 5.33; N, 8.42%]; R_f (30% EtOAc/Hexane) 0.4; IR (KBr): 3352, 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 2.11(1H, d, *J*=14.4 Hz), 2.35 (1H, d, *J*=14.4 Hz), 3.19 (1H, d, *J*=12.6 Hz), 3.45 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.90–3.99 (1H, m), 4.13 (1H, dd, *J*=4.2 Hz), 4.20 (1H, s, NH), 4.47–4.52 (1H, d, *J*=5.7, 9.6 Hz), 4.90 (1H, d, *J*=5.7 Hz), 6.49–7.67 (18H, m, Ar-H), 10.60 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 30.3, 30.6, 52.1, 55.3, 56.9, 57.2, 63.6, 72.5, 92.5, 108.2, 11.0, 113.7, 117.7, 118.0, 120.3, 121.9, 124.0, 127.1, 128.1, 128.4, 128.9, 130.4, 130.4, 130.5, 132.1, 132.7, 135.4, 135.4, 156.4, 165.6, 173.3. EIMS *m*/*z* 664.21 (M^+).

4.2.16. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-bromophenyl)-2-methoxy carbonyl-2-methyl indolylpyrrolidine, ***10c***. Yield (560 mg, 80%) as a colorless crystals; Mp: 240–242 °C; [Found: C, 62.6; H, 4.62; N, 7.84. $C_{37}H_{33}BrN_4O_6$: $C_{37}H_{33}BrN_4O_6$: C, 62.63; H, 4.69; N, 7.90%]; R_f (30% EtOAc/Hexane) 0.4; IR (KBr): 3359, 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 2.10 (1H, d, *J*=14.4 Hz), 2.34 (1H, d, *J*=14.4 Hz), 3.18 (1H, d, *J*=12.6 Hz), 3.43 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.96–4.05 (1H, m), 4.12 (1H, dd, *J*=4.2 Hz), 4.18 (1H, s, NH), 4.46–4.51 (1H, dd, *J*=5.7, 9.6 Hz), 4.90 (1H, d, *J*=5.7 Hz), 6.48–7.67 (18H, m, Ar-H), 10.60 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 30.3, 52.1, 55.3, 55.4, 56.9, 57.1, 63.6, 72.4, 92.5, 108.2, 111.0, 113.7, 117.7, 118.0, 120.3, 120.6, 121.7, 124.1, 127.0, 128.4, 128.9, 130.4, 130.5, 130.7, 131.0, 132.7, 135.3, 135.8, 156.4, 165.6, 173.3. EIMS *m*/*z* 708.16 (M^+).

4.2.17. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(2-chlorophenyl)-2-methoxy carbonyl-2-methyl indolylpyrrolidine, ***10d***. Yield (530 mg, 81%) as a colorless crystals; Mp: 220–222 °C; [Found: C, 66.90; H, 5.11; N, 8.36. $C_{37}H_{33}ClN_4O_6$ requires: C, 66.81; H, 5.00; N, 8.42%]; R_f (30% EtOAc/Hexane) 0.4; IR (KBr): 3359, 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 2.26 (1H, d, *J*=14.4 Hz), 2.36 (1H, d, *J*=14.4 Hz), 3.24 (1H, d, *J*=12.6 Hz), 3.50 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.96–4.05 (1H, m), 4.12 (1H, dd, *J*=4.2 Hz), 4.18 (1H, s, NH), 4.46–4.51 (1H, dd, *J*=5.7, 9.6 Hz), 4.90 (1H, d, *J*=5.7 Hz), 6.48–7.67 (18H, m, Ar-H), 10.60 (1H, br s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 30.3, 52.1, 55.3, 55.5, 56.9, 57.2, 63.6, 72.4, 92.5, 108.3, 111.0, 113.7, 117.8, 118.1, 120.4, 120.6, 121.7, 124.2, 127.1, 128.4, 128.9, 130.4, 130.5, 130.8, 131.0, 132.7, 135.4, 135.9, 156.4, 165.8, 173.5 ppm EIMS *m*/*z* 664.21 (M^+).

4.3. Representative procedure for the preparation Pictet-Spengler cyclized products (11) and (12)

To a stirred solution of cycloadduct **5** (605.7 mg, 1 mmol) and **9** (644.2 mg, 1 mmol) in 20 mL of dry dichloromethane was added paraformaldehyde (30 mg, 1 mmol) followed by trifluoroacetic acid (0.007 mL, 0.1 mmol) at 0 °C. After completion of the reaction the mixture was washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was subjected to column chromatography with hexane–ethylacetate (9:1) to obtain pure cyclized product. The compounds were recrystallized from ethylacetae by slow evaporation method.

4.3.1. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidin-2′-one]-4-nitro-3-phenyl-2-ethoxy carbonyl-pyrrolo (1,2-b)isoquinoline, ***11a***. Yield (550 mg, 90%) as a white solid; Mp: 132–134 °C; [C, 71.99; H, 5.79; N, 6.74. $C_{37}H_{35}N_3O_6$ requires: C, 71.94; H, 5.71; N, 6.80%]; R_f (10% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.27 (3H, t, OCH_3), 2.38 (1H, d, *J*=15.3 Hz), 2.61 (1H, d, *J*=15.6 Hz), 3.42 (1H, d, *N*-CH, *J*=14.7 Hz), 3.50 (1H, d, *N*-CH, *J*=14.7 Hz), 3.56–3.62 (1H, dd, *J*=7.8, 9.9 Hz), 3.81 (3H, s, OCH_3), 4.24 (2H, q, CH_2), 4.40–4.44 (1H, dd, *J*=5.1, 7.3 Hz), 4.47–4.52 (1H, dd, *J*=5.4, 7.3 Hz), 4.61 (1H, d, *J*=5.7 Hz), 4.68 (1H, d, *J*=5.1 Hz), 6.45–7.93 (18H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.2, 34.0, 51.5, 54.5, 55.5, 57.8, 58.4 61.7, 66.7, 73.4, 89.7, 114.0, 119.8, 126.1, 126.3, 127.2, 127.4, 127.7, 128.3, 128.3, 128.6, 128.8, 130.5, 131.6, 132.2, 134.1, 134.7, 136.0, 156.5, 166.6, 174.8 ppm EIMS *m*/*z* 617.25 (M^+).

4.3.2. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-(4-chlorophenyl)-2-ethoxy carbonyl-pyrrolo(1,2-b)isoquinoline, ***11b***. Yield (644 mg, 95%) as a colorless crystal; Mp: 204–206 °C; [Found: C, 68.24; H, 5.33; N, 6.52. $C_{37}H_{34}ClN_3O_6$ requires: C, 68.14; H, 5.26; N, 6.44%]; R_f (10% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (3H t, OCH_3), 2.38 (1H, d, *J*=15.3 Hz), 2.62 (1H, d, *J*=15.6 Hz), 3.43 (1H, d, *N*-CH, *J*=14.7 Hz), 3.48 (1H, d, *N*-CH, *J*=14.7 Hz), 3.50–3.55 (1H, dd, *J*=7.8, 9.9 Hz), 3.82 (3H, s, OCH_3), 4.26 (2H, q, CH_2), 4.32–4.36 (1H, dd, *J*=5.7, 8.1 Hz), 4.44–4.50 (1H, dd, J_1=5.4, 7.3 Hz), 4.62 (1H, d, *J*=5.7 Hz), 4.65 (1H, d, *J*=6 Hz), 6.34–7.91 (17H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.2, 33.8, 51.3, 53.7, 55.5, 57.8, 58.2, 61.9, 66.5, 73.3, 89.4, 114.0, 119.7, 126.3, 126.4, 127.5, 128.4, 128.7, 128.8, 129.5, 130.4, 131.5, 132.1, 133.1, 133.2, 133.8, 133.8, 136.0, 156.6, 166.4, 174.6 ppm EIMS *m*/*z* 651.21 (M^+).

4.3.3. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidin-2′-one]-4-nitro-3-(4-bromophenyl)-2-ethoxy carbonyl-pyrrolo(1,2-b)isoquinoline, ***11c***. Yield (628 mg, 92%) as a white solid; Mp: 209–211 °C; [Found: C, 63.88; H, 4.99; N, 6.12. $C_{37}H_{34}BrN_3O_6$ requires: C, 63.80; H, 4.92; N, 6.03%]; R_f (10% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 1.29 (3H, t, OCH_3), 2.38 (1H, d, *J*=15.6 Hz), 2.60 (1H, d, *J*=15.3 Hz), 3.43 (1H, d, *N*-CH, *J*=14.7 Hz), 3.45 (1H, d, *N*-CH, *J*=14.7 Hz), 3.51–3.55 (1H, dd, *J*=7.8, 5.4 Hz), 3.82 (3H, s, OCH_3), 4.26 (2H, q, CH_2), 4.31–4.36 (1H, dd, *J*=5.7, 8.1 Hz), 4.44–4.49 (1H, dd, *J*=5.4, 7.3 Hz,), 4.62 (1H, d, *J*=5.7 Hz), 4.63 (1H,

d, J=5.1 Hz), 6.27–7.91 (17H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 33.8, 51.3, 53.8, 55.5, 57.8, 58.2, 61.9, 66.5, 73.3, 89.3, 114.0, 119.7, 121.8, 126.3, 126.4, 127.1, 127.5, 128.4, 128.8, 129.8, 130.4, 131.5, 131.6, 132.1, 133.7, 133.8, 135.9, 156.6, 166.4, 174.6 ppm EIMS m/z 695.16 (M^+).

4.3.4. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidin-2′-one]-4-nitro-3-(4-methylphenyl)-2-ethoxy carbonyl-pyrrolo(1,2-b)isoquinoline, ***11d***. Yield (579 mg, 89%) as a colorless crystals; Mp: 198–200 °C; [Found: C, 72.33; H, 5.97; N, 6.72. $C_{38}H_{37}N_3O_6$ requires: C, 72.25; H, 5.90; N, 6.65%]; R_f (10% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.25 (3H, t, CH_3), 2.27 (3H, s, CH_3), 2.36 (1H, d, J=15.6 Hz), 2.61 (1H, d, J=15.3 Hz), 3.40 (1H, d, N-CH, J=14.7 Hz), 3.49 (1H, d, N-CH, J=14.7 Hz), 3.55–3.61 (1H, dd, J_1=7.8, 5.4 Hz), 3.81 (3H, s, OCH_3), 4.22 (2H, q, CH_2), 4.38–4.42 (1H, dd, J_1=5.7, 8.1 Hz), 4.50–4.55 (1H, dd, J=5.4, 7.3 Hz), 4.61 (1H, d, J=6 Hz), 4.66 (1H, d, J=5.7 Hz), 6.41–7.93 (17H, m, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.2, 20.9, 33.9, 51.6, 54.3, 55.5, 57.8, 58.4, 61.7, 66.6, 73.3, 89.6, 113.9, 119.8, 126.1, 126.3, 127.2, 127.3, 128.1, 128.3, 128.8, 129.3, 130.5, 131.5, 131.6, 132.2, 134.2, 135.9, 137.6, 156.5, 166.6, 174.7 ppm EIMS m/z 651.21 (M^+).

4.3.5. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidin-2′-one]-4-nitro-3-(4-methoxyphenyl)-2-ethoxy carbonyl-pyrrolo(1,2-b)isoquinoline, ***11e***. Yield (563 mg, 87%) as a colorless crystals; Mp: 147–149 °C; [Found: C, 70.55; H, 5.82; N, 6.39. $C_{38}H_{37}N_3O_7$ requires: $C_{38}H_{37}N_3O_7$: C, 70.46; H, 5.76; N, 6.49%]; R_f (10% EtOAc/Hexane) 0.6; IR (KBr): 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.26 (3H, t, CH_3), 2.39 (1H, d, J=15.6 Hz), 2.62 (1H, d, J=15.3 Hz), 3.40 (1H, d, N-CH, J=15 Hz), 3.48 (1H, d, N-CH, J=14.7 Hz), 3.53–3.59 (1H, dd, J=7.8, 5.4 Hz), 3.76 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.23 (2H, q, CH_2), 4.33–4.38 (1H, dd, J=5.7, 8.1 Hz), 4.52–4.58 (1H, dd, J=5.4, 7.3 Hz,), 4.60 (1H, d, J=5.7 Hz), 4.66 (1H, d, J=5.7 Hz), 6.45–7.89 (17H, m, Ar-H); ^{13}C NMR (75 MHz, CDCl3) 14.2, 33.6, 51.5, 54.0, 55.2, 55.5, 57.8, 58.4, 61.7, 66.4, 73.2, 89.5, 113.9, 119.9, 126.3, 126.4, 127.2, 127.4, 128.3, 128.8, 129.2, 129.3, 129.5, 130.5, 131.4, 132.1, 134.2, 136.0, 156.5, 159.1, 166.6, 174.6 ppm EIMS m/z 647.26 (M^+).

4.3.6. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidine-2′-one]-4-nitro-3-phenyl-2-ethoxycarbonyl-indolizino(6,7-b)indole, ***12a***. Yield (557 mg, 85%) as a white solid; Mp: 197–199 °C; [Found: C, 71.42; H, 5.62; N, 8.47. $C_{39}H_{36}N_4O_6$ requires: C, 71.33; H, 5.53; N, 8.53%]; R_f (10% EtOAc/Hexane) 0.55; IR (KBr): 3360, 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$) 1.08 (3H, t, CH_3), 2.35 (1H, d, J=16 Hz), 2.70 (1H, d, J=16 Hz), 3.48 (1H, d, N-CH, J=17.7 Hz), 3.74–3.80 (1H, dd, J=7.8, 9.9 Hz), 3.83 (3H, s, OCH_3), 3.96 (1H, d, N-CH, J=17.7 Hz), 4.06 (2H, q, CH_2), 4.65–4.69 (1H, dd, J=5.7, 7.8 Hz), 4.72–4.78 (1H, dd, J=5.7, 7.3 Hz), 4.83 (1H, d, J=5.7 Hz), 4.89 (1H, d, J=5.7 Hz), 6.95–7.34 (18H, m, Ar-H), 7.88 (1H, br s, NH); ^{13}C NMR (75 MHz $CDCl_3$) 14.1, 23.1, 42.2, 53.4, 55.5, 58.1, 61.1, 61.6, 66.2, 68.1, 86.9, 107.0, 108.8, 114.0, 118.0, 120.4, 122.0, 127.1, 128.3, 128.4, 128.7, 128.8, 128.9, 130.2, 130.7, 130.8, 131.5, 131.7, 136.5, 156.7, 161.0, 167.7, 171.3 ppm EIMS m/z 656.26 (M^+).

4.3.7. 5-[1′-N-(p-Methoxyphenyl)-3′-phenylazetidin-2′-one]-4-nitro-3-(4-chlorophenyl)-2-ethoxycarbonyl-indolizino(6,7-b)indole, ***12b***. Yield (614 mg, 89%) as a colorless solid; Mp: 218–220 °C; [Found: C, 67.87, H, 5.19, N, 8.01. $C_{39}H_{35}ClN_4O_6$ requires: C, 67.77; H, 5.10; Cl, 5.13; N, 8.11%]; R_f (10% EtOAc/Hexane) 0.55; IR (KBr): 3362, 1745, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.06 (3H, t, CH_3), 2.33 (1H, d, J=16 Hz), 2.67 (1H, d, J=16 Hz), 3.48 (1H, d, N-CH, J=17.7 Hz), 3.70–3.79 (1H, dd, J=7.8, 9.9 Hz), 3.83 (3H, s, OCH_3), 3.97 (1H, d, N-CH, J=17.7 Hz), 4.06 (2H, q, CH_2), 4.63–4.67 (1H, dd, J=5.7, 7.8 Hz), 4.71–4.79 (1H, dd, J=5.7, 7.3 Hz), 4.82 (1H, d, J=5.7 Hz), 4.87 (1H, d, J=5.7 Hz), 6.94–7.33 (17H, m, Ar-H), 7.95 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1, 23.3, 43.1, 54.6, 55.5, 58.0, 61.2, 61.7, 66.2, 67.9, 86.8, 106.7, 108.8, 114.0, 118.0, 120.4, 122.1, 127.0, 128.4, 128.9, 129.0, 129.6, 130.2, 130.3, 130.6, 130.7, 131.5, 134.8, 136.5, 156.7, 162.6, 167.1, 171.2 ppm EIMS m/z 690.22 (M^+).

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Supplementary data

The spectral discussion of compound **5b**, **9b**, **11b**, **12b**, and ORTEP diagram of compounds **6a**, **9d**, **10c**, **10d**, **11b**, and **11e** are provided. Supplementary data associated with this article can be found in the online version, doi:10.1016/j.tet.2009.11.085.

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