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An improved microwave assisted one-pot synthesis, and biological investigations of some novel aryldiazenyl chromeno fused pyrrolidines

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ABSTRACT

An improved microwave assisted one-pot method for the synthesis of twelve new aryldiazenylchromeno [4,3-*b*] pyrrolidines via intramolecular azomethine ylide cycloaddition route is described. The method is efficient and advantageous over conventional and solvent-free thermal methods. The stereochemistry of the compounds was confirmed on the basis of various NMR experiments, and finally by single crystal X-ray diffraction data. *N*-Methyl or ethyl pyrrolidine based heterocycles gave good biological activities.

In last couple of decades, an impressive development has been achieved to afford complex organic compounds of biological interest. Aim of the modern synthetic management lies in seeking an environmentally benign, time-resolved, chemo-regio- and stereo-selective transformations. Accordingly, a microwave assisted and solvent-free thermal procedures, for example, have come up with alternatives to conventional heating,[1] which offered advantages like higher yields, milder reaction conditions and shorter reaction time.

Five- and six-membered nitrogen heterocycles belong to a largest class of heterocyclic compounds possessing a diverse biological activities.[1,2] A pyrrolidine unit, specifically, is a structural subunit of many alkaloids and of pharmaceutically important compounds.[3] Out of many synthetic routes, the one involving in situ generated an azomethine ylide is efficient to assemble pyrrodine with many heterocycles. Its highly regio- and stereocontrolled intramolecular version has afforded a variety of fused nitrogen containing bicyclic systems.[4] Many of related cyclic amines form a core structure of variety of alkaloid and natural products.[5] Aziridine tethered alkenes, and *O*-allyl, *O*-prenyl, or *O*-propargyl tethered aldehydes and others have been developed to afford important bicyclic, tricycic and even more complex ring systems.[3,4] There are many reports on chromeno fused pyrrolidines. Nevertheless a work on analogues amino precursors is desirable and interesting to search new bioactive molecule. New scaffolds thus assessed are expected to display both the photochromic[6] and biological[7] properties.

Inspired by our earlier work,[8] we have continued our search to afford new aryldiazenylchromeno annulated heterocycles. In the presence work, we have designed and biologically evaluated aryldiazenylchromeno fused pyrrolidine, a precursor to an amino chromeno [4,3-*b*] pyrrolidines.

This new scaffold may possess interesting bioprofiles.[5,7] Besides, this microwave-assisted method for preparation of these heterocycles was compared with conventional and thermal neat procedures.[4d–e]

A substrate *O*-allyl-5-phenyldiazenylsalicylaldehyde **1** was prepared by a method reported elsewhere.[8] Amino acid esters **2a–d** were prepared by incrementally adding corresponding chloro acetic ester, within 2 h, to a vigorously stirred anhydrous benzylamine solution in acetonitrile, in the presence of catalyst triethylamine, followed by further 4 h room temperature stirring. Other amines **2e–l** (Table 1) were prepared in the same way but in the presence of K_2CO_3 at room temperature (Scheme 1). Colorless oily products **2a–l** which left after solvent evaporation were collected and then used in the subsequent step without any purification.

In our quest to search an optimal reaction condition, we examined substrate **1** first with amino acid ester **2a**, employing conventional, microwave-assisted and solvent-free thermal procedures. The reaction was monitored with or without additives $MgSO_4$ or Na_2SO_4 under refluxing xylene, toluene, decaline, DMF, DMSO, dioxane and MeCN. The result showed that the yields **3a** was in the 50–83% range. But it required a longer reaction time. Refluxing toluene (entry 1), however, gave good results in this category

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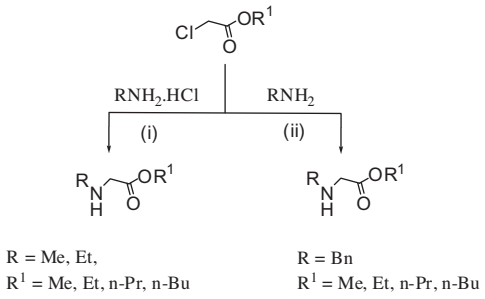
Table 1
Synthesis of various amino acid esters **2a–l**

Amino esters	R	R^1	2° Amine
2a	Bn	Et	$BnNHCH_2COOEt$
2b	Bn	Me	$BnNHCH_2COOMe$
2c	Bn	*n*-Bu	$BnNHCH_2COOn$-Bu
2d	Bn	*n*-Pr	$BnNHCH_2COOn$-Pr
2e	Me	Et	$MeNHCH_2COOEt$
2f	Me	Me	$MeNHCH_2COOMe$
2g	Me	*n*-Bu	$MeNHCH_2COOn$-Bu
2h	Me	*n*-Pr	$MeNHCH_2COOn$-Pr
2i	Et	Et	$EtNHCH_2COOEt$
2j	Et	Me	$EtNHCH_2COOMe$
2k	Et	*n*-Bu	$EtNHCH_2COOn$-Bu
2l	Et	*n*-Pr	$EtNHCH_2COOn$-Pr



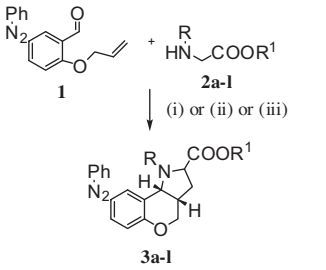
Scheme 1. Reagents and conditions: (i) K_2CO_3/MeCN at room temprature; (ii) TEA/MeCN at room temperature.

Table 2
Optimization of the reaction conditions between amine **2a** and aldehyde **1**

Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1	Toluene	—	110	5.5	76[a]
2	Toluene	Na_2SO_4	110	4.0	80[a]
3	Toluene	$MgSO_4$	110	4.0	78[a]
4	*p*-Xylene	—	138	4.0	79[a]
5	*p*-Xylene	Na_2SO_4	138	3.5	82[a]
6	*p*-Xylene	$MgSO_4$	138	3.5	83[a]
7	Decaline	—	190	2.0	69[a]
8	Decaline	Na_2SO_4	190	1.5	75[a]
9	Decaline	$MgSO_4$	190	1.5	72[a]
10	Decaline	—	120	3.5	73[a]
11	Decaline	—	150	3.0	77[a]
12	DMF	—	153	3.0	66[a]
13	DMSO	—	189	2.0	59[a]
14	Dioxane	—	100	40	50[a]
15	MeCN	—	81	32	55[a]
16	b	—	130	0.75	78[b]
17	c	—	280 W	10 min	90[c]

[a] Concentional.
[b] Solvent-free.
[c] Micro-wave.

(Table 2, entries 1–15). When the reaction was performed at higher temperature under a solvent-free environment, we noticed improvement in the reaction taking only 0.75 h to yield maximum 78% yield (entry 16). Finally, it showed a dramatic improvement that is in the yield the reaction time (10 min), when we employed a microwave-assisted method. Thus this protocol effectively worked for the affording new aryldiazenylchromeno [4,3-*b*] pyrrolidines (Scheme 2), a precursor to amino analogues frameworks, than the others exploited so far in the literature.[4d–e] Results are summarized in Table 2. Compounds bearing this structural motif are known to act as noncompetitive antagonists of muscular



3a-d; R = Bn, R^1 = Me, Et, n-Pr, n-Bu
3e-h; R = Me, R^1 = Me, Et, n-Pr, n-Bu
3i-l; R = Et, R^1 = Me, Et, n-Pr, n-Bu

Scheme 2. The synthesis of phenyldiazenylchromeno fused pyrrolidines **3.** Reagents an conditions: (i) Solvent-free, (ii) conventional and (iii) microwave-assisted.

nicotine receptor.[9] The plausible mechanism of this reaction is depicted in Scheme 3.

Three possible intermediates (Scheme 3) namely *cis*-fused, *trans*-fused and one with no stereocontrol are possible candidates to give cyclized products. Electrophilic addition occurs from the tethered alkene on the formed imine followed by addition of the enolized ester on the other end of the alkene. All the products are *Cis*-fused as confirmed by spectral analysis. Therefore, one can assume the concerted reaction, without a real carbonation intermediate, taking place where the steric bias that imposed from the semi bicyclic transition state forces the system to adopt a most favored *Cis*-fusion via an *endo* transition state. A very minor product that formed via an *exo* route could not be isolated. Thus, the intermediates that involved in the present reaction are both *Exo* and *Endo* transition states.

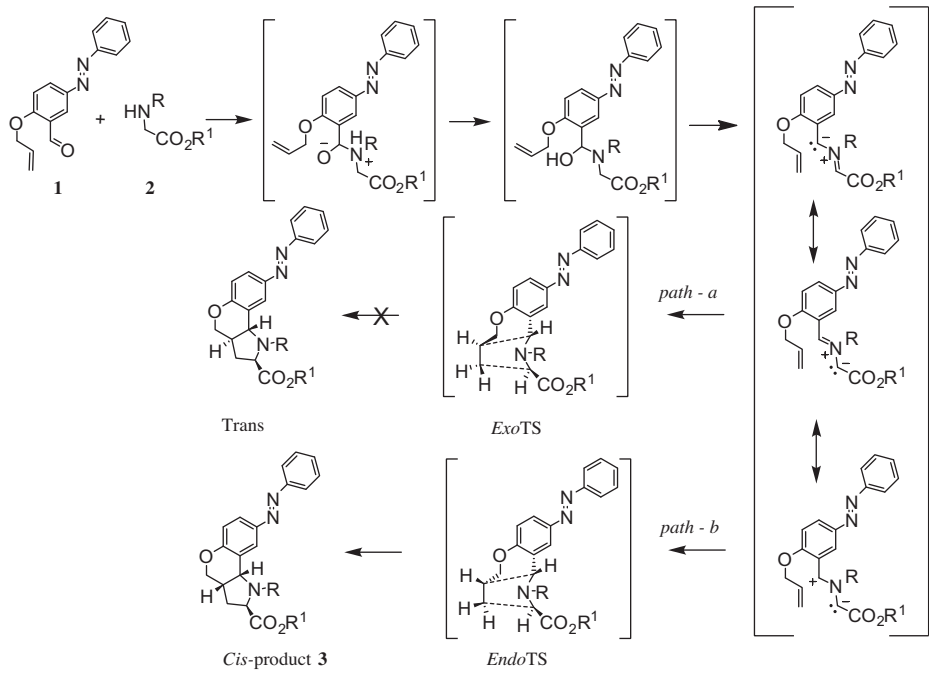
Other products **3a–l** were synthesized by a microwave assisted as well as by optimal solvent-free condition (entry 16 and 17).[12]

Analyzed also an optimized reaction condition in terms of amino acid esters used. Over all, a performance was in the order microwave-assisted > solvent-free > toluene reflux. The residue left after completion of the reaction, as confirmed by TLC, was passed through silica bed to isolate pure product **3**.

O-Allyl-5-phenyldiazenylsalicylaldehyde **1** was reacted with various freshly prepared ester **2a–l** to give 8-phenyldiazenyl-hexahydrobenzopyrano [4,3-*b*] pyrroles **3a–l** in moderate to good yields (79–90%) (Table 3).

The structure of cycloadduct was confirmed by various spectral data. IR of **3a** showed a sharp peak at 1724 cm^{-1} attributable to ester carbonyl. ^1H NMR of **3a** showed a doublet of doublets for pyranyl ring OCH_2 protons each at δ 4.18 ppm. Due to the overlap of ester OCH_2 protons, unresolved spectral peak could not allow its *J* value calculation in this region. The pyrrolidine ring CH_2 protons appeared as a doublet of doublet of doublets, one at δ 1.95 ppm (J = 11.6, 8.6, 3.2) and second at δ 2.20 ppm (J = 10.2, 8.4, 3.6). One of the ring junction protons appeared as a doublet at δ 4.44 ppm (J = 5.6) and second as a multiplate at δ 2.68 ppm. The similar characteristic pattern was appeared in all the compounds **3a–l** except N-substituent protons. The benzylic NCH_2 showed a doublet at δ 3.91, and δ 4.35 ppm (J = 13.2) in **3a–d**. Singlet N-CH_3 appeared at δ 2.61 ppm in **3e–h**. Multiplate *N*-CH_2CH_3 observed at δ 2.80, and 3.08 ppm in **3i–l**. The structure of **3a** was also confirmed by its mass spectrometry, which showed a peak at *m*/*z* 442.2 (M+1).

The *cis*-stereochemistry can be assigned to the ring junction of all the cycloadducts by analogy with the stereochemistry observed in the similar systems.[4] The *cis*-junction of the pyran and pyrrolidine rings in all the isolated products follows from a characteristic spin coupling constant of protons, H3a and H9b lying in 4.8–6.4 Hz range. It is in well agreement with *cis*-5,6-fused ring systems. The



Scheme 3. Mechanism of the 1,3-cycloaddition reaction of aldehyde substrate **1** with ester **2**.

Table 3
The synthesis of 8-phenyldiazenylchromeno [4, 3-*b*] pyrrolidines **3a-l**

Compound	R	R^1	Solvent free (130 °C)		Under toluene reflux		Solvent free microwave[a] yield (%)
			Time (h)	Yield (%)	Time (h)	Yield (%)	
3a	Bn	Et	0.75	78	5.5	76	90
3b	Bn	Me	1.0	82	6.0	77	89
3c	Bn	*n*-Bu	1.5	71	8.0	67	86
3d	Bn	*n*-Pr	1.5	73	7.5	72	87
3e	Me	Et	1.0	83	7.0	69	86
3f	Me	Me	1.5	80	7.0	71	88
3g	Me	*n*-Bu	2.0	72	9.5	66	84
3h	Me	*n*-Pr	2.0	76	9.0	73	83
3i	Et	Et	1.0	81	6.5	71	87
3j	Et	Me	1.5	70	7.5	70	81
3k	Et	*n*-Bu	2.5	73	9.5	68	79
3l	Et	*n*-Pr	2.0	76	8.0	62	83

[a] Time taken 10 min in each of the cases.

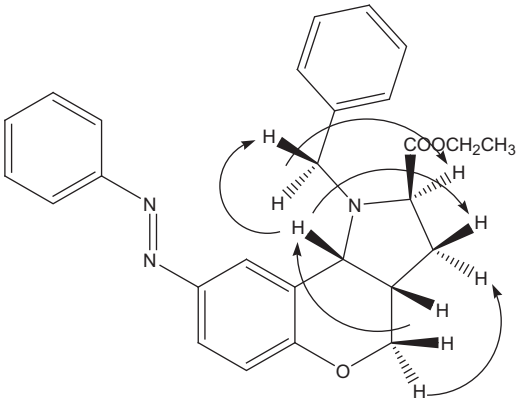


Figure 1. Characteristic NOE's of **3a**.

same was also confirmed by cross peaks in the 2D nuclear Over hauser effect spectroscopy (NOESY) and the double quantum filtered correlation spectroscopy (DQFCOSY) data (Fig. 1).

A solid state structure of compound **3d** was also determined by single crystal X-ray diffraction analysis. An ORTEP view of compound **3d** has been depicted in Figure 2.

As part of our ongoing interest, we wished to introduce an amino group in chromeno [4,3-*b*] pyrrolidine unit. Starting with amino aldehyde substrate could not give good results due to regiochemical issues. Therefore, we used aryldiazenyl salicylaldehyde substrate. Subsequent acidic tin chloride reduction of cycloadduct **3a** afforded amino compound **4a** (Scheme 4).[13] The same was also assessed from nitro aldehyde substrate **3m**. The synthesis of novel amino product **4a** was confirmed by spectroscopic data. Further development in this direction is continued.

All new aryldiazenylchromeno[4,3-*b*]pyrrolidine derivatives **3a–l** were screened for their in vitro antibacterial activities against three Gram-positive (*Streptococcus pneumoniae*, *Clostridium tetani, Bacillus subtilis*) and three Gram-negative (*Salmonella typhi, Vibrio cholerae, Escherichia coli*) bacteria, and for antifungal activity against two fungus; *Aspergillus fumigatus* and *Candida albicans*, by the macro-broth dilution[10,11] assay. These compounds were also intended to have their antitubercular activity against *M. Tuberculosis H37RV* bacteria. Table 4 displays the results of antibacterial and antifungal tests, and Table 5 of antitubercular activity. Except **3h** and **3j**, all new chromeno fused pyrrolidins showed good to moderate antimicrobial properties. Notably, compounds **3e** and **3l** found active against all three Gram-negative bacteria with MIC values lying in the 50–125 μg/mL range. Both compounds **3e** and **3l** were found as potent as a standard reference drug Chloramphenicol against *E. coli* bacteria. Additionally compound **3e** also showed same potency against *Salmonella typhi* bacteria. While compound **3l** resembled with a standard Ampicillin drug against both *Salmonella typhi* and *Vibrio cholerae* bacteria with a MIC value (100 μg/mL), compound **3e** remained very close to this against *V. cholerae* bacteria. More exceptional result was due to **3c** which showed activity against Gram-positive *S. pneumonia* bacteria with a MIC value of 25 μg/mL, a more potency then all other reference drugs used in the study. Though a majority of compounds showed

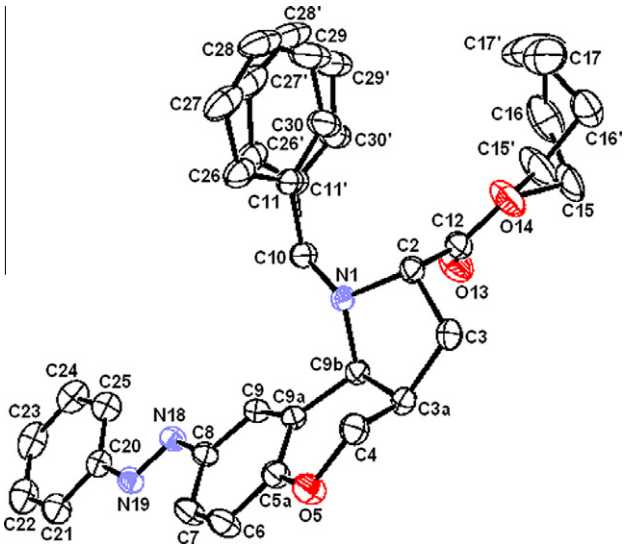
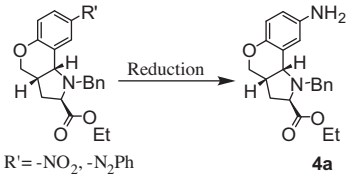


Figure 2. ORTEP view of compound **3d**.



Scheme 4. Reduction of **3a** or **3m** to aminochromeno [4,3-*b*] pyrrolidine **4a**.

poor activity against fungus *A. fumigatus*, compounds **3b**, **3f** and **3k** among them displayed impressive results against *Candida albicans* fungus with a MIC value even less than that of standard Griseofulvin. Antitubercular activity test results are given in Table 5. Compounds **3b**, **3c**, **3i** and **3l** are found very active against *M. Tuberculosis H37RV* bacteria with Growth inhibition in the 87–98% range. Thus it reveals that these compounds are more potent than the standard drugs Metronidazole, Fluconazole and Miconazole. From structural variation, it may conclude that replacement of benzyl group by either methyl or ethyl at pyrrolidin nitrogen allowed improvement in the biological properties. This trend however, decrease with increase in the size of ester group in the chromeno[4,3-*b*]pyrrolidine.

In conclusion, we have developed an improved method to synthesize aryldiazenylchromeno [4,3-*b*]pyrrolidines via intramolecular 1,3-dipolar cycloaddition of azamethine ylide from a new aldehyde substrate *O*-allyl-5-aryldiazenyl salicylaldehyde. Present method is efficient and could be applied usefully to aryldiazenylsalicaldehyde substrate containing unactivated allylic dienophile in the side chain with amino acid ester. All new synthesized compounds are good antibacterial as well as antitubercular. While compounds **3e** and **3l** exhibited potency as close as a standard drug chloramphenicol against all three Gram-negative bacteria, compound **3c** even more then all reference drugs against Gram-positive S. *pneumonia* bacteria. Moreover, all the compounds act as precursors to amino analogus framework. A preliminary work on

Table 5
Antitubercular test results

compound[a]	Growth of inhibition (%)
3a	20
3b	87
3c	90
3d	84
3e	64
3f	72
3g	25
3h	41
3i	98
3j	55
3k	68
3l	95
Standard[b]	99

Fluconazole (>256 μg/mL), Miconazole (>256 μg/mL).
[a] A concentration 250 μg/mL of each was used against *M. Tuberculosis H37RV* bacteria.
[b] Standard antimicrobials and their effective concentration to inhibit 100% growth: Isoniazid (0.2 μg/mL), Metronidazole (>256 μg/mL).

Table 4
Antibacterial and antifungal test results (MIC μg/mL)

Compound	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	S.p. MTCC 1936	*C.t.* MTCC 449	*B.s.* MTCC 441	*S.t.* MTCC 98	*V.c.* MTCC 3906	*E.c.* MTCC 443	*A.f.* MTCC 3008	*Ca.* MTCC 227
3a	250	200	250	>250	200	>250	>250	>250
3b	250	200	250	250	>250	125	>250	200
3c	**25**	>250	250	100	250	200	>250	>250
3d	200	250	250	250	100	250	>250	250
3e	250	200	>250	50	125	50	>250	>250
3f	**125**	>250	125	200	100	200	>250	250
3g	250	100	50	250	200	250	>250	>250
3h	250	>250	250	250	250	250	>250	>250
3i	**100**	250	>250	250	250	>250	250	>250
3j	200	>250	200	>250	>250	200	>250	>250
3k	>250	250	100	100	>250	200	>250	200
3l	>250	200	200	100	100	50	>250	>250
[A]	100	250	250	100	100	100	–	–
[B]	10	50	100	10	10	10	–	–
[C]	50	50	50	50	50	50	–	–
[D]	50	100	50	25	25	25	–	–
[E]	–	–	–	–	–	–	100	500
[F]	–	–	–	–	–	–	100	100

S.p.: *Streptococcus pneumoniae*, C.t.: *Clostridium tetani*, B.s.: *Bacillus subtilis*, S.t.: *Salmonella typhi*, Vc.: *Vibrio cholerae*, E.c.: *Escherichia coli*, A.f.: *Aspergillus fumigatus*, C.a.: *Candida albicans*, [A]: Ampicillin, [B]: Norfloxacin,[C]: Chloramphenicol, [D]: Ciprofloxacin, [E]: Griseofulvin, [F]: Nystatin.

this has been set and it will be efficiently developed to assess new bioprofiles.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.04.070.

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12. *Synthesis of aryldiazenylhexahydrochromeno [4,3-b] pyrroles* ***3a–3m****:* A mixture of an aldyhyde **1** (0.5 g, 1.88 mmol) and an amine **2** (1 equiv) was heated in a round bottom flask equipped with preheated air condenser from 0.75 to 2.5 h. After confirming the completion of reaction by TLC, it was cooled to room temperature. The resulted reaction mass was passed through silica bed column to get pure product. The same reaction was performed under microwave irradiation at 280 W for 10 min. Compound **3a**: yellow Solid, yield 90%, 0.746 g, mp 104–106 °C; IR (ν_{max}, cm^{-1}): 3081, 3022, 2950,1724 (C=O), 1681, 1575, 1493, 1244, 1032, 852, 768, 749, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 1.95 (ddd, $^2J_{3',3}$ = 11.6, $^3J_{3',2}$ = 8.6, $^3J_{3',3a}$ = 3.2 Hz, 1 H, H-3′), 2.20 (ddd, $^2J_{3,3'}$ = 10.2, $^3J_{3,3a}$ = 8.4, $^3J_{3,2}$ = 3.6 Hz, 1 H, H-3), 2.68 (m, 1 H, H-3a), 3.62 (dd, $^3J_{2,3'}$ = 9.0, $^3J_{2,3}$ = 3.2 Hz, 1 H, H-2), 3.91 (d, ^2J = 13.2 Hz, 1 H, one of NCH_2Ph), 4.18 (m, 2 H of H-4 and 2 H of OCH_2CH_3), 4.35 (d, ^2J = 13.2, 1 H, the other of NCH_2Ph),,4.44 (d, $^3J_{9b,3a}$ = 5.6 Hz, 1 H, H-9b) 7.0–7.93 (m, 13 H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.27 (OCH_2CH_3), 29.99 (C-3), 34.45 (C-3a), 51.22 (NCH_2Ph), 57.92 (C-2), 59.45 (C-9b), 60.48 (OCH_2CH_3), 67.86 (C-4), 117.92, 122.57, 122.84, 123.46, 127.23, 128.22, 128.76, 129.03, 129.38, 130.34, 138.91, 146.45, 152.81, 158.32 (arom.), 173.78 (C=O); ESI-MS: *m*/*z*: 442.2 $(M+H)^+$,Anal Calcd for $C_{27}H_{27}N_3O_3$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.08; H, 6.46; N, 9.27.
13. *Synthesis of (2R,3aS,9bR)-ethyl-8-amino-1-benzyl-1,2,3,3a,4,9b-hexahydrochromeno [4,3-b]pyrrole-2-carboxylate* ***4a****:* A solution of diazenylcompound **3a** (0.5 g, 1.87 mmol), prepared in 20 ml hot concentrated HCl, was added drop wise a solution of 2 g tin (ll) chloride in 5 ml same acid until it decolorized the resulted reaction mass. It was then cooled and added 10% sodium hydroxide solution until tin hydroxide precipitates redissolved. Four 20 ml ether extracts of this cold solution were combined and dried with anhydrous sodium sulphate followed by ether evaporation. A crude amino derivative obtained as a residue, was then purified by column chromatography. Compound **4a**: Brown Solid, yield 62%, 0.247 g, mp = 88–90 °C IR (ν_{max}, cm^{-1}): 3432, 3205, 3018, 2946, 1732 (C=O), 1608, 1535, 1491, 1214, 1020, 822, 761, 749, 689; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 1.87 (ddd, $^2J_{3',3}$ = 7.2, $^3J_{3',2}$ = 5.0, $^3J_{3',3a}$ = 4.0 Hz, 1 H, H-3′), 2.00 (ddd, $^2J_{3,3'}$ = 11.6, $^3J_{3,3a}$ = 9.2, $^3J_{3,2}$ = 3.2 Hz, 1 H, H-3), 2.70 (m, 1 H, H-3a), 3.40 (dd, $^3J_{2,3'}$ = 8.8, $^3J_{2,3}$ = 3.2 Hz, 1 H, H-2), 3.69 (d, ^2J = 13.6 Hz, 1 H, one of NCH_2Ph), 3.81 (dd, $^2J_{4,4}$ = 18.2, $^3J_{4,3a}$ = 10.4 Hz, 1 H, one of H-4), 3.86 (dd, $^2J_{4,4}$ = 10.8, $^3J_{4,3a}$ = 4.8 Hz, 1 H, the other of H-4), 4.06 (m, 1 H, H-9b and 2 H of OCH_2CH_3), 4.19 (d, $^3J_{9b,3a}$ = 13.6 Hz, 1 H, the other of NCH_2Ph), 4.65 (s, 2 H, NH_2), 7.45–7.27 (m, 8 H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.63 (OCH_2CH_3), 30.21 (C-3), 35.25 (C-3a), 51.22 (NCH_2Ph), 58.21 (C-2), 59.55 (C-9b), 60.18 (OCH_2CH_3), 67.70 (C-4), 115.57, 117.19, 117.29, 122.61, 127.32, 128.45, 128.64, 139.39, 142.10, 146.93, (arom.), 173.85 (C=O); ESI-MS: *m*/*z*: 352.8 $(M+H)^+$, Anal Calcd $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.46; H, 6.98; N, 8.02.