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Efficient synthesis of some new antiproliferative N-fused indoles and isoquinolines *via* 1,3-dipolar cycloaddition reaction in an ionic liquid†

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Syntheses of some new pyrrolo-fused pyrrolo[1,2-*a*] indole derivatives have been achieved by combining *N*-allyl-indole-2-carbaldehyde with a variety of *N*-alkyl-glycine esters as well as tetrahydroisoquinolines in an ionic liquid, triethylammonium acetate (TEAA), a recyclable reaction medium, *via* intramolecular [3+2] cycloaddition reaction. This new method is highly efficient, and the ionic liquid employed is recyclable. The stereochemistry of all the compounds was confirmed by 2D NMR NOESY and in some cases single crystal X-ray diffraction data. The *in vitro* screening of all new candidates against various bacterial strains and representative human solid tumor cell lines, A549 (lung), HeLa (cervix), SW1573 (lung), T-47D (breast) and WiDr (colon), revealed that many of them have good antibacterial, antifungal and antitubercular and antiproliferative activities.

Introduction

The heterocycles with a N-fused indole/isoquinoline-heterocyclic framework as one of their integral structural units constitute an important class of bioprofiles, and have attracted the interest of many in the research fields of medicines and pharmaceuticals.[1] Containing the pyrrolo-indole nucleus, terpenoidal alkaloids[2] and mitomycins exhibited antitumor activity (Fig. 1A).[3] With pyrrolo[1,2-*a*]indole as a specific fusion, cyclopropamitosenes revealed cytotoxicity through bacterial cell division and DNA alkylation.[4] Likewise, antimalarial Flinderole B,[5] bioactive Isatisine A (Fig. 1B)[6] and hallucinogenic Yuremamine (Fig. 1C), which are potential candidates of this class have attracted the interest of many chemists and biochemists.[7]

Pyrrolo-isoquinoline alkaloids, on the other hand, showed promising results for depression in animals, with the pyrrolo-isoquinoline nucleus.[8] A tricyclic hydropyrrolo [2,1-*a*] isoquinoline is a key fused-ring system with (2)-trolline structure, which

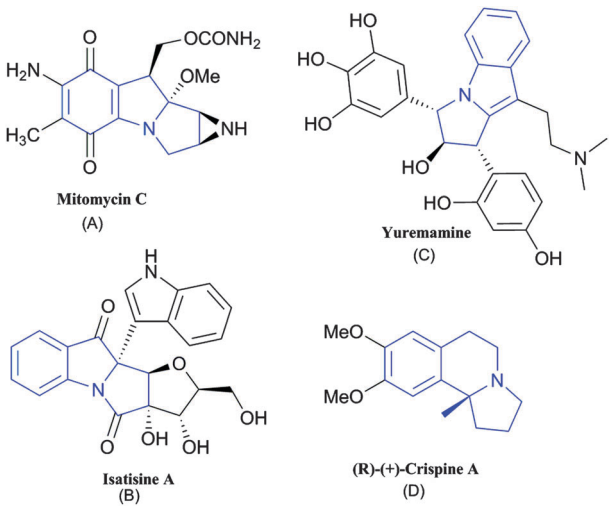

Fig. 1 Some biologically active heterocycles containing pyrrolo-indole and pyrrolo-isoquinoline units.

can be derived from *Trollius* Chinese flowers[9] and its *Portulaca oleracea* L weed-derived antipode (+)-oleracein E.[10,11] Studies showed that (2)-trolline has remarkable activity against influenza viruses A and B, and so revealed antiviral properties. (+)-Oleracein E displayed DPPH-radical scavenging activity.[10] In addition, the members of the trolline family are active against respiratory *Staphylococcus aureus* and pneumonia bacteria.[9] Like trolline, (+)-crispine A (Fig. 1D) also incorporates an analogous heterocyclic framework and has potential anti-proliferative activity against SKOV3, KB, and HeLa human cancer lines.[12]

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Finally, pyrrolizidine present in many heterocycles represents another useful framework of biological interest. In addition to anti-inflammatory and analgesic properties, it confers heterocycles with effective aromatase and tumour growth inhibitory action.[13] Besides, 5-HT_{2c} receptor agonists, known to be effective in hyperglycaemia and other diseases, come from the same family and make it an interesting source of bioactive scaffolds.[14]

In view of the above, it follows that incorporation of N-fused indole, N-fused isoquinoline and pyrrolizidine into a molecular assembly helps generate a new and useful class of heterocycles, finding a great importance in medicinal chemistry. Development and enlargement of a molecular library of these heterocycles is thus desirable and worth studying too.

Intermolecular alkylation,[15] radical cyclization,[16] *trans* annulation reaction,[17] carbene-based rearrangement,[18] *etc.* are general synthetic approaches for N-fused indoles. Cycloaddition reaction involving *in situ* azomethine ylide generation, nevertheless, seems to be seldom studied for such heterocycles.[19] This protocol is highly atom economic, and has been used so far for many complex heterocyclic systems. Many aldehydes reacted with amino acid derivatives[20] to afford 6–5 fused-ring systems. Indole-based substrates however are very few in number for designing 5–5 fused-ring systems.[21] The ring system exists in biotin, an important naturally occurring heterocycle.[21d]

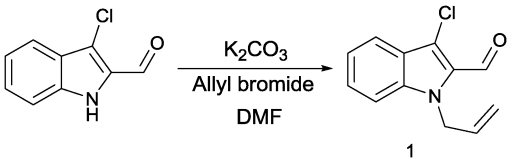
As part of our research program, we have reported the synthesis of many pyran-heterocycles.[20h] including aminobenzopyrans[20h,i] *via* 1,3 dipolar cycloaddition. Here, we describe pyrroloindole and pyrrolo-isoquinoline derivatives as new bioprofiles, constructed from *N*-allyl-3-chloro-indole-2-carbaldehyde **1** with a variety of α-amino acid esters as well as tetrahydroisoquinolines, in ionic liquid TEAA as an effective reaction medium.

Use of ionic liquids (ILs) helped translate many synthetic routes into green methodologies, with adopting requisite practice not only as economic one, but as environmentally friendly too.[22] To the best of our knowledge, very few reports appeared on use of ionic liquid in 1,3-dipolar cycloaddition reaction.[23] And those reported in ILs still suffer from preparation cost, use and recyclability of ILs, and, of course, promotion of the reaction.[23c] Conventional methods in general suffers from many disadvantages like use of conventional solvent, longer reaction time and tedious work-up procedure.[24]

Results and discussion

Chemistry

All requisite secondary amines **2–6**, except tetrahydro-isoquinolines **6**; *N*-methyl/ethyl/benzyl/(4-morpholinyl) ethyl glycine esters, are liquids and prepared by methods reported elsewhere.[25] Tetrahydroisoquinolines **6** were used as received from commercial sources. The substrate, *N*-allyl-3-chloro-indole-2-carbaldehyde **1**, was obtained by reacting 3-chloro-indole-2-carbaldehyde with ally bromide in the presence of anhydrous K_2CO_3, suspended in DMF (dimethylformamide) solution (Scheme 1), in 95% yield. 3-Chloro-indole-2-carbaldehyde was obtained as the Vilsmeier–Haack product of (phenylglycine)-*O*-carboxylic acid, with excellent purity.[26]



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Scheme 1 Synthesis of *N*-allyl-3-chloro-indole-2-carbaldehyde **1**, the reagents and conditions (**1**) K_2CO_3, allyl bromide, DMF, 10–12 h, room temp.

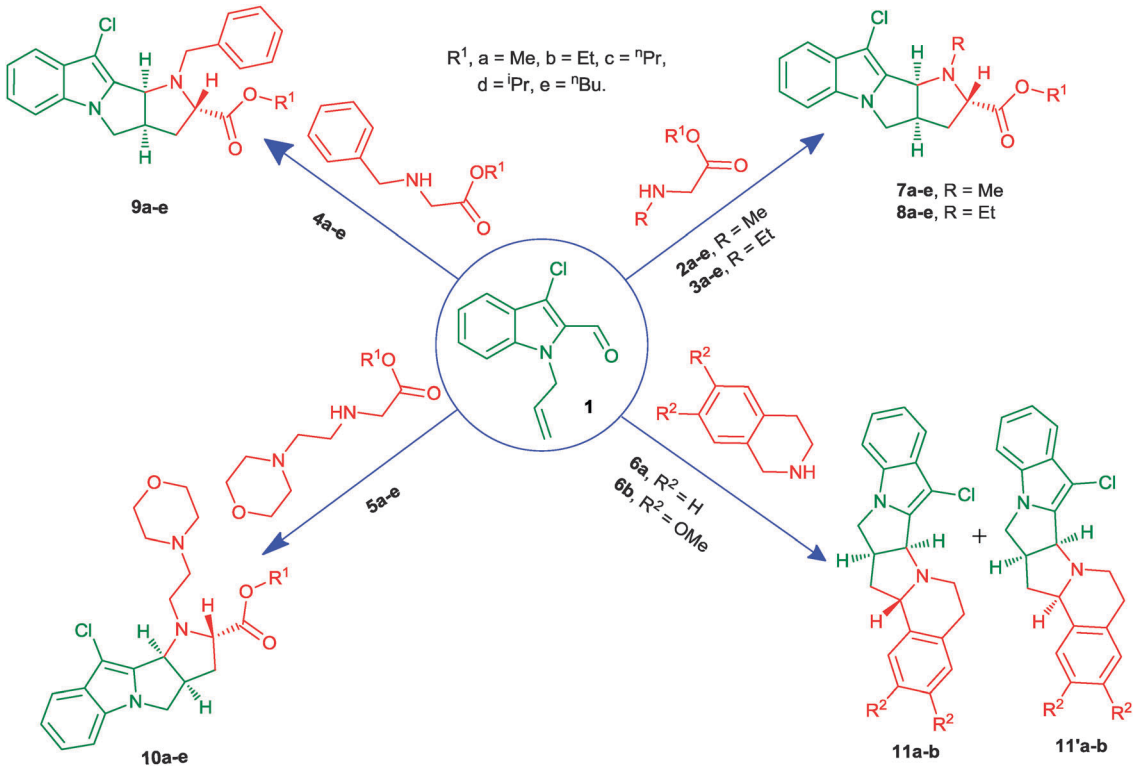
Table 1 Optimization of the reaction conditions between amine **3a** and aldehyde **1**

Entry	Solvent (reflux)	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1	MeOH	—	Reflux	24	Trace
2	ACN	—	Reflux	10	40
3	Toluene	—	Reflux	6.0	68
4	Toluene	Na_2SO_4	Reflux	6.0	72
5	Xylene	—	Reflux	5.5	70
6	Xylene	Na_2SO_4	Reflux	5.0	75
7	—	—	100[a]	4	70
8	TEAA	TEAA	80	3.5	78
9	TEAA	TEAA	100	2.5	85

[a] Solvent free.

The reaction between amine **3a** and aldehyde **1** was taken as a model to optimize the reaction conditions (Table 1). Initially, we heated the aldehyde and amine in refluxing methanol (entry 1), acetonitrile (entry 2), toluene (entries 3 and 4) and xylene (entries 5 and 6), in the presence and absence of Na_2SO_4. Although results in toluene and xylene using Na_2CO_3 were good, prolonged heating was discouraging to accept this method (6 h). Even when tried reported methods, they failed to run present conversion effectively.[22c,d] Thus, we opted for heating in a solvent-free environment at 100 °C. Here, the reaction time could be improved but not the yields (entry 7). The conventional way was thus abandoned in favour of the TEAA promoted one (entry 8). It showed improved results in yield and reaction time at 80 °C that were improved further at 100 °C (entry 9). Above 100 °C, however no further improvement was seen. This improved method was then generalised to receive other products, too (Scheme 2 and Table 2). The advantage of the present protocol is that it takes relatively less reaction time (3 h) than others.[24c] It should be noted further that the present combination allows pyrrolizidine to act as a highly significant bioactive unit to incorporate effectively into N-fused indole/isoquinoline heterocycles.

A plausible mechanism of the reaction has been depicted in Scheme 3. Addition of electrons from the tethered-alkene terminal carbon on imine follows the addition of the enolized ester on the other end of the alkene *via* a semi bicyclic transition state that may force the system to adopt the most favoured *cis*-fusion product. The *exo* or *endo* attack of dipolarophile alkene on azomethine ylide dipole determines the stereoselectivity of the reaction. The spectral data support the *cis*-fusion between central pyrrolidine rings in all heterocycles, hence favouring the *endo* transition state. In **11′a–b**, however, the *cis*-fusion may involve a further isomerization of the ylide.[27]



Scheme 2 Synthesis of all newly pyrrolo-fused indoles and isoquinolines (**1**) TEAA, 100 °C.

Table 2 Synthesis of all pyrrolo-fused-indoles and isoquinolines

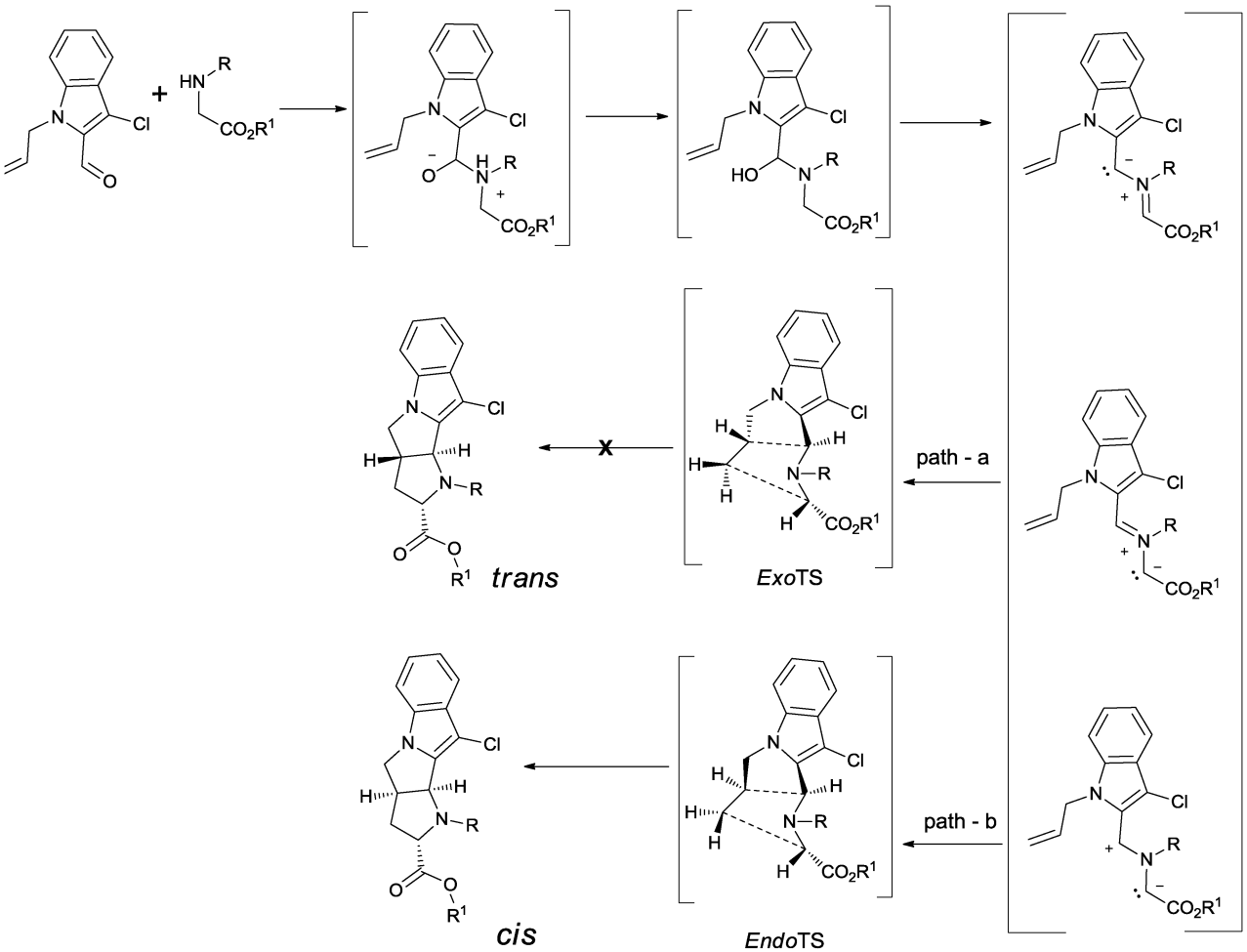
Entry	Compound	R	R^1	R^2	Time (h)	Yield (%)
1	**7a**	Me	Me	—	2.75	82
2	**7b**	Me	Et	—	2.75	80
3	**7c**	Me	*n*Pr	—	3.0	77
4	**7d**	Me	iPr	—	3.0	84
5	**7e**	Me	*n*Bu	—	3.5	77
6	**8a**	Et	Me	—	2.5	85
7	**8b**	Et	Et	—	2.75	82
8	**8c**	Et	*n*Pr	—	3.0	84
9	**8d**	Et	iPr	—	3.0	78
10	**8e**	Et	*n*Bu	——	3.0	79
11	**9a**	Bn	Me	—	2.5	80
12	**9b**	Bn	Et	—	3.0	82
13	**9c**	Bn	*n*Pr	—	3.0	78
14	**9d**	Bn	iPr	—	3.5	76
15	**9e**	Bn	*n*Bu	—	3.5	74
16	**10a**	Mp	Me	—	3.0	76
17	**10b**	Mp	Et	—	3.0	78
18	**10c**	Mp	*n*Pr	—	3.0	72
19	**10d**	Mp	iPr	—	3.5	74
20	**10e**	Mp	*n*Bu	—	3.0	75
21	**11a**	—	—	H	2.75	45
22	**11′a**	—	—	H	2.75	37
23	**11b**	—	—	OMe	3.0	46
24	**11′b**	—	—	OMe	3.0	38

The proposed structures of all newly synthesized heterocycles fully agreed with the observed elemental analyses, mass, IR and NMR spectral data. In the ^{1}H NMR spectra, all compounds except **7** showed a multiplet in the region δ 2.93–4.09 ppm, due to diastereotopic methylene protons of the pyrrolidine ring. In **7**, instead the *N*-methyl proton appeared as a singlet at $\delta \sim 2.75$ ppm. The carbonyl group in **7–10** showed a characteristic IR band at $\sim$1730 cm^{-1}, and a ^{13}C NMR signal $\sim\delta$ 173 ppm. In all compounds, a doublet in the δ 4.00–4.80 ppm range, with the *J* value in the 7.6–8.4 Hz range, can be attributed to a bridge-head proton **10b** or **12b**, suggestive of *cis*-fusion between central pyrrolidine rings. Another bridge-head proton **3a** or **5a** appeared as a multiplet at $\delta \sim 3.80$ ppm is therefore orientated *cis* to this **10b** or **12b** proton. Analysing cross-peaks in 2D NMR NOESY (nuclear Overhauser effect spectroscopy) and DQF-COSY (double quantum filtered correlation spectroscopy) of representative **8a** (Fig. 2 and 3), a similar relationship between these protons could be confirmed. The bridge-head proton **2** or **4b** is however *trans* with respect to proton **10b** or **12b**, appearing at δ 4.00–4.40 ppm, except in **11′a–b**. In **11′a–b**, it is *cis* oriented.

Finally, with the single-crystal X-ray diffraction data of **9b** and **11′b**, we could be able to establish important stereochemical considerations (Fig. 4).

Biological results

Table 3 summarizes *in vitro* antimicrobial screening test results of all the compounds. The majority of compounds displayed good resistance against bacteria, at least, in line with one of the standard reference drugs ampicillin. The activity of some of them was found to be equal to that of a more potent drug. Analyzing results in terms of maximum how many bacterium species a compound can kill effectively revealed that the compound can cover a maximum of five species at least with the potency equivalent to ampicillin. Examples include **7c**, **9c**,



Scheme 3 A plausible mechanism of the reaction between aldehyde **1** and secondary amine *via* 1,3-dipolar cycloaddition reaction.

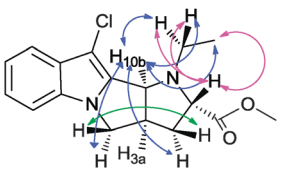


Fig. 2 Characteristic NOESY interactions in **8a**.

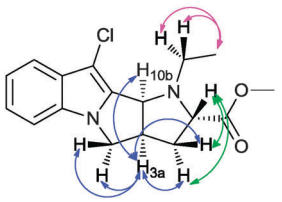


Fig. 3 Characteristic COSY interactions in **8a**.

10e and **11b**. Among them, **7c** revealed excellent activity against Gram-positive *Clostridium tetani* (reaching to potency of even more potent norfloxacin) and Gram-negative *Escherichia coli* bacteria (reaching the potency of even more potent chloramphenicol). Similarly, compound **9c** resembled more potent standard norfloxacin drug in activity, against Gram-positive *Bacillus subtilis* bacteria. Compounds **7a**, **7d**, **8a**, **8c**, **8d**, **9e**, **10a**, **10b**, **10c** and **11a**, on the other hand, had recorded better resistance against at least four types of bacteria. Among them, **7a**, **7d**, **8c**, and **10a** registered excellent activity against Gram-positive *Clostridium tetani* bacteria, with MIC values in line with ciprofloxacin which is more potent than ampicillin. Compounds **7d** and **10a** with chloramphenicol-equivalent potency showed good results against *Bacillus subtilis* and *Salmonella typhi* bacteria respectively. It is noted that both ciprofloxacin and compound **7d** recorded similar MIC values against *Bacillus subtilis* bacteria. Next, those with at least activity against three types of bacterium species include **7b**, **7e**, **8b**, **8e**, **9b**, **9d** and **10d**. Among them **8b**, **8c** and **9d** are very close to standard ciprofloxacin in potency, against *Clostridium tetani* bacteria. Further, a few of the compounds showed good antifungal activity, particularly against *Candida albicans* fungus. Examples include **7a**, **7e**, **8c**, **8e**, **9c** and **10d** all having griseofulvin-equivalent power. As anti-fungal agents, compounds **7d**, **10a** and **10b** are relatively more active.

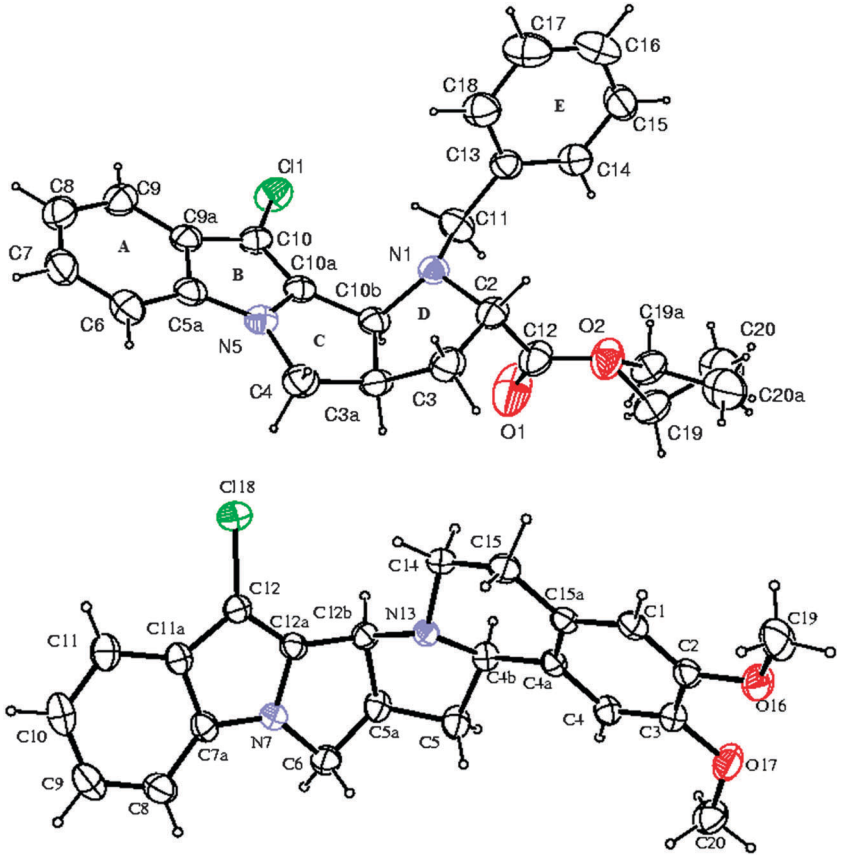


Fig. 4 The ORTEP views of compounds **9b** and **11′b**, with displacement ellipsoids at the 40% probability level.

Anti-tubercular activity study shows that compounds **9d** and **10b** have highest *M. tuberculosis* H37Rv bacterial resistance, with growth inhibition in the 90–100% range. Compounds **8a**, **9a**, **9c**, **10a** and **11′b** have growth inhibition in the 80–90% range.

FRAP values of majority of the heterocycles are around 225 (mmol per 100 g), indicating that they are moderate in antioxidant power. However, compound **10b** revealed remarkable activity.

The antiproliferative activity of **7–11** was evaluated against a panel of representative human tumor cell lines including A549 (lung), HeLa (cervix), SW1573 (lung), T-47D (breast) and WiDr (colon), using the SRB assay.[28] The experimental GI_{50} values are summarized in Table 4 and compared to those of cisplatin, etoposide and camptothecin after 48 h of treatment. Taken as a whole, pyrrolo-fused-indoles **7–8** was the most active class of compounds, with activity against all cell lines tested. In this particular context, compounds **7–8** showed more activity against HeLa cells, with GI_{50} values in the range 3.1–14 μM and comparable to those of cisplatin (2.0 μM) or etoposide (3.3 μM).

No significant differences were observed between methyl and ethyl ester derivatives. In contrast, the presence of a benzyl group (**9**) or a morpholine substituent (**10**) on the pyrrol nitrogen produced a severe loss in activity. From the pyrrolo-fused-isoquinolines **11** obtained in our investigations, the best results of antiproliferative activity were obtained for adduct **11b**, which showed active against all the cell lines with GI_{50} values in the range 9.5–18 μM. This is a relevant result, since the class of adduct correlates to selectivity towards cancer cell lines.

Analysing N-fused indoles derived from amino acid esters, structurally, it reveals that methyl at pyrolidine nitrogen confers heterocycles with enhanced resistivity against *Clostridium tetani* and *Escherichia coli* bacteria, when carbpropoxy moiety is present at carbon next to this nitrogen. Pyrrolidin with morpholine or ethyl moieties at nitrogen in combination with carbmethoxy group also had a similar effect against these bacteria. Carbbutoxy moiety, on the other hand, had very less effect on activity, irrespective of substituent present at pyrrolidine nitrogen. Antiproliferative activity, nevertheless, seemed to be altered very less taking any ester component with *N*-methyl/*N*-ethyl pyrrolidine ring, against HeLa (cervix) cell lines. In addition, *N*-ethyl pyrrolidine with any ester component had similar effect against Widr(colon) cell lines. The N-fused indoles derived from tetrahydreoisoquinolines showed remarkable bioactivities as well. In general, heterocycles derived from electron releasing methoxy substituted-tetrahyderoisoquinoline are excellent in antibacterial, antitubercular, antioxidant and antiproliferative activities, compared to the ones derived from simple tetrahydro isoquinoline.

Table 3 Antimicrobial, antitubercular and antioxidant activity test results

	Antimicrobial activity (MIC μg mL^{-1})									
	Gram-positive bacteria			Gram-negative bacteria			Fungi		Anti TB[a] (%) inhibition	Antioxidant activity[b] FRAP[c]
Compound	S.p.	C.t.	B.s.	S.t.	V.c.	E.c.	A.f.	C.a.		
7a	250	**100**	**250**	250	**125**	**100**	>500	**500**	46	225.11
7b	200	**125**	**100**	500	**100**	200	>500	>500	20	220.49
7c	250	**62.5**	**200**	**125**	**125**	**62.5**	>500	>500	13	215.27
7d	**100**	**100**	**62.5**	200	200	**100**	>500	**250**	47	216.87
7e	**100**	**250**	**100**	250	250	250	>500	**500**	57	227.32
8a	**125**	**200**	**200**	200	250	**62.5**	>500	>500	**84**	219.28
8b	**125**	**100**	**250**	200	200	200	>500	>500	59	217.28
8c	**100**	**100**	**250**	250	250	**125**	>500	**500**	58	210.25
8d	**125**	**200**	**250**	250	250	**125**	>500	>500	33	213.26
8e	200	**125**	**200**	200	250	**100**	>500	**500**	47	222.90
9a	200	**200**	**125**	250	250	200	>500	>500	80	213.46
9b	250	**250**	**200**	250	200	**100**	>500	>500	33	228.72
9c	**100**	**250**	**100**	100	**125**	200	>500	**500**	**87**	234.95
9d	250	**100**	**200**	100	200	250	>500	>500	**91**	236.35
9e	200	**250**	**100**	**100**	**125**	250	>500	>500	12	245.99
10a	**125**	**125**	**100**	**62.5**	200	200	500	**250**	**84**	232.14
10b	200	**200**	**100**	**125**	**125**	250	500	**250**	**92**	**285.15**
10c	500	**250**	**250**	**125**	250	**100**	>500	>500	25	236.15
10d	200	**250**	**100**	**125**	250	250	>1000	**500**	74	239.37
10e	500	**200**	**250**	**125**	**125**	**100**	500	>500	65	241.37
11a	**100**	**200**	**250**	**100**	200	250	500	**500**	65	224.51
11′a	500	**250**	**100**	200	250	200	250	**500**	78	252.22
11b	200	**125**	**125**	**125**	**100**	**100**	>500	>500	58	254.23
11′b	250	**200**	**200**	200	250	250	500	>500	**88**	217.28
[A]	0.5	5	1	5	5	0.05	—	—	—	—
[B]	100	250	250	100	100	100	—	—	—	—
[C]	50	50	50	50	50	50	—	—	—	—
[D]	50	100	50	25	25	25	—	—	—	—
[E]	10	50	100	10	10	10	—	—	—	—
[F]	—	—	—	—	—	—	100	100	—	—
[G]	—	—	—	—	—	—	100	500	—	—
[H]	—	—	—	—	—	—	—	—	99	—

S.p.: *Streptococcus pneumoniae*, C.t.: *Clostridium tetani*, B.s.: *Bacillus subtilis*, S.t.: *Salmonella typhi*, V.c.: *Vibrio cholerae*, E.c.: *Escherichia coli*, A.f.: *Aspergillus fumigatus*, C.a.: *Candidaalbicans*; [A]: gentamycin, [B]: ampicillin, [C]: chloramphenicol, [D]: ciprofloxacin, [E]: norfloxacin, [F]: nystatin, [G]: griseofulvin, [H]: isoniazide.[a] Concentration of compounds used against *M. tuberculosis* H37Rv bacteria = 250 μg mL^{-1}, standard antimicrobials used: isoniazide (0.2 μg mL^{-1}). [b] Concentration of compounds = 200 μg mL^{-1} and standard: A.A. (ascorbic acid) = 176 μg mL. [c] A.A. mm per 100 g sample.

Table 4 Antiproliferative activity (GI_{50}) against human solid tumor cells

	Antiproliferative activity (GI_{50})[a]				
	Cell line (origin)				
Compound	A549 (lung)	HeLa (cervix)	SW1573 (lung)	T-47D (breast)	WiDr (colon)
7a	>100	3.3 (±0.4)	68 (±45)	67 (±47)	66 (±48)
7b	61 (±18)	5.7 (±1.6)	92 (±11)	84 (±29)	76 (±37)
7c	>100	3.9 (±1.2)	53 (±26)	66 (±49)	62 (±54)
7d	41[b]	8.3 (±3.2)	29 (±0.2)	26 (±6.5)	22 (±4.0)
7e	32 (±8.8)	9.9 (±5.2)	32 (±2.3)	25 (±5.8)	23 (±4.1)
8a	33 (±3.0)	14 (±1.4)	25 (±3.3)	27 (±4.8)	24 (±1.7)
8b	43 (±19)	3.4 (±0.7)	33 (±4.6)	29 (±16.0)	28 (±10)
8c	47 (±19)	3.6 (±0.3)	41 (±4.3)	37 (±13.0)	35 (±7.8)
8d	28 (±6.9)	13 (±2.8)	27 (±3.5)	25 (±9.4)	27 (±4.3)
8e	40 (±20)	3.1 (±0.4)	32 (±2.5)	26 (±4.7)	24 (±8.9)
9c	>100	41 (±30)	>100	54 (±21)	>100
9d	>100	48 (±36)	>100	57 (±43)	89 (±15)
9e	>100	>100	>100	>100	>100
10a	>100	>100	>100	>100	>100
11a	89 (±16)	33 (±6.8)	>100	53 (±14)	73 (±39)
11′a	>100	84 (±21)	>100	>100	>100
11b	18 (±14)	9.5 (±7.1)	17 (±1.9)	15 (±7.3)	14 (±2.4)
[A]	—	2.0 (±0.3)	3.0 (±0.4)	15 (±2.3)	26 (±5.3)
[B]	—	3.3 (±1.6)	14 (±1.5)	22 (±5.5)	23 (±3.1)
[C]	—	0.6 (±0.4)	0.25 (±0.12)	2.0 (±0.5)	1.8 (±0.7)

[A]: cisplatin, [B]: etoposide, [C]: camptothecin. [a] Values are given in μM and are means of two to four experiments; standard deviation is given in parentheses. [b] One experiment was done.

Conclusions

Thus, we synthesized N-fused indole and isoquinoline derivatives as new bioactive compounds *via* 1,3-dipolar cycloaddition reaction, using an ionic liquid, TEAA as inexpensive, environmentally friendly and recyclable reaction medium. The resistance power of **7c**, **7d**, **8a** and **10a** at least against one of the bacterial species studied is highest resembling chloramphenicol in activity with MIC 62.5 μg L^{-1}. The antiproliferative activity of **11b**, on the other hand, was found to be excellent against all cell lines, with GI_{50} values lying in the 9.5–18 μM range, comparable to standard drugs used. Besides, **10b**, with the FRAP value of 225 (mmol per 100 g), showed excellent ferric reducing antioxidant power.

Experimental

Materials and methods

All solvents and reagents were used as supplied from commercial sources. The recorded melting points are uncorrected. IR spectra were recorded in KBr on a Shimadzu FT-IR 8401 spectrometer and are reported in wave numbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR as solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts are reported as parts per million (ppm, d) and referenced to the residual protic solvent. Coupling constants are reported in Hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. The degree of substitution (C, CH, CH_2, and CH_3) was determined by the DEPT-135 method. The ESI mass spectra were measured on a Shimadzu LCMS-2010 spectrometer. Elemental analysis (% C, H, N) was carried out using a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA). TLC was performed on Merck 60 F254 precoated silica plates, spots were detected either by UV (254 nm, 366 nm) or dipping into a permanganate [$KMnO_4$ (3 g), K_2CO_3 (20 g), NaOH (5 mL, 5% in H_2O), H_2O (300 mL)] or an anisaldehyde solution [3% *p*-methoxybenzaldehyde and 1% H_2SO_4 in MeOH] or 2,4-dinitro phenyl hydrazine solution [2,4-DNP (12 g), conc. H_2SO_4 (6 mL), water (8 mL), EtOH (20 mL)] followed by heating.

General procedure for the synthesis of N-fused indoles and isoquinolines

A mixture of an aldehyde 1 (1 equiv.) and an acyclic secondary amine **2–5** (1 equiv.) or isoquinoline **6a–b** (1 equiv.) in 2 mL of ionic liquid TEAA in a round bottom flask was heated at 100 °C and completion of the reaction was confirmed through TLC. The reaction mass was cooled to room temperature and poured into ice species. The oily product thus emulsified was then extracted with three 10 mL of diethyl ether portions. It yielded crude products in quantitative amounts upon removal of ether. Finally, the product was purified by column chromatography using a 90 : 10 *n*-hexane-ethyl acetate mixture as an eluent. The yields were in the 75–85% range. TEAA was recovered quantitatively by heating the aqueous layer-left after the ether extraction of the product-under the reduced presser at 80 °C. The recovered ionic liquid can be used again for the same. It was noticed that TEAA can be recycled at least four-times with its unaltered efficiency.

Spectroscopy data of compounds (7–11)

Methyl (2*S*,3*aS*,10*bS*)-10-chloro-1-methyl-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (7a). Yield 82%, mp 118–120 °C, IR (ν_{max}, cm^{-1}): 3058, 2983, 1732, 1630, 1455, 1178, 1039, 731, 600; ^1H NMR (400 MHz, $CDCl_3$): δ 2.20 (1H, m, H-3′), 2.41 (1H, ddd, J = 13.6, 8.2, 5.6 Hz, H-3), 2.76 (3H, s, $-NCH_3$), 3.68 (1H, t, J = 5.8 Hz, H-2), 3.78 (4H, m, 3H of $-COOCH_3$, 1H, H-3a), 3.97 (1H, ddd, J = 9.8, 4.2, 1.4 Hz, H-4), 4.19 (1H, m, H-4′), 4.81 (1H, d, J = 7.4 Hz, H-10b), 7.17 (3H, m, Ar–H), 7.70 (1H, dd, J = 7.6, 1.0 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.7 (C-3), 37.1 ($-NCH_3$), 45.3 (C-3a), 50.8 (C-4), 51.3 ($-COOCH_3$), 64.8 (C-10b), 67.0 (C-2), 98.2 (C-10), 110.0 (C-6), 118.6, 120.1, 122.2, 130.2, 131.9, 138.5 (Ar–C), 172.87 (C═O). ESI-MS (m/z): 304.97 $(M)^+$, anal. calcd for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19; found: C, 63.35; H, 5.27; N, 9.42.

Ethyl (2*S*,3*aS*,10*bS*)-10-chloro-1-methyl-1,2,3,3*a*,4,10*b* hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (7b). Yield 82%, mp 102–104 °C, IR (ν_{max}, cm^{-1}): 3059, 2983, 1730, 1631, 1455, 1177, 1038, 732, 602; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 6.4 Hz, $-OCH_2CH_3$), 2.21 (1H, m, H-3′), 2.40 (1H, ddd, J = 13.2, 8.4, 5.2 Hz, H-3), 2.75 (3H, s, N–CH_3), 3.66 (1H, t, J = 5.6 Hz, H-2), 3.79 (1H, m, H-3a), 3.96 (1H, ddd, J = 9.9, 4.0, 1.2 Hz, H-4), 4.18–4.28 (3H, m, 2H of $-COOCH_2CH_3$ and 1H of H-4′), 4.82 (1H, d, J = 7.6 Hz, H-10b), 7.18 (3H, m, Ar–H.), 7.6 (1H, dd, J = 7.8, 0.8 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (OCH_2CH_3), 36.7 (C-3), 37.1 (NCH_3), 45.3 (C-3a), 50.8 (C-4), 60.6 (OCH_2CH_3), 64.8 (C-10b), 67.0 (C-2), 98.2 (C-10), 110.0 (C-6), 118.6, 120.1, 122.2, 130.2, 131.9, 138.5 (Ar–C), 172.8 (C═O). ESI-MS (m/z): 319.10 $(M)^+$, anal. calcd for $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79; found: C, 64.21; H, 6.17; N, 8.62.

Propyl (2*S*,3*aS*,10*bS*)-10-chloro-1-methyl-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (7c). Yield 77%, mp 106–108 °C, IR (ν_{max}, cm^{-1}): 3059, 2984, 1732, 1630, 1457, 1179, 1039, 730, 599; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J = 7.8 Hz, $-COOCH_2CH_2CH_3$), 1.75 (2H, m, $-COOCH_2CH_2CH_3$), 2.19 (1H, m, H-3′), 2.42 (1H, ddd, J = 13.8, 8.2, 5.4 Hz, H-3), 2.74 (3H, s, $-NCH_3$), 3.70 (1H, t, J = 5.4 Hz, H-2), 3.79 (1H, m, H-3a), 3.98 (1H, ddd, J = 9.6, 4.0, 1.6 Hz, H-4), 4.17 (3H, m, 2H of $-COOCH_2CH_2CH_3$, 1H of H-4′), 4.83 (1H, d, J = 7.8 Hz, H-10b), 7.16 (3H, m, Ar–H), 7.71 (1H, dd, J = 7.6, 1.0 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 ($-COOCH_2CH_2CH_3$), 22.1 ($-COOCH_2CH_2CH_3$), 36.6 (C-3), 37.0 ($-NCH_3$), 45.3 (C-3a), 50.7 (C-4), 64.8 (C-10b), 66.7 ($-COOCH_2CH_2CH_3$), 67.0 (C-2), 98.2 (C-10), 110.0 (C-6), 118.5, 120.1, 122.2, 130.2, 131.9, 138.1 (Ar–C), 172.8 (C═O). ESI-MS (m/z): 332.92 $(M)^+$, anal. calcd for $C_{18}H_{21}ClN_2O_2$: C, 64.96; H, 6.36; N, 8.42; found: C, 64.75; H, 6.47; N, 8.62.

Isopropyl (2*S*,3*aS*,10*bS*)-10-chloro-1-methyl-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (7d). Yield 84%, mp 107–109 °C; IR (ν_{max}, cm^{-1}): 3058, 2984, 1732, 1632, 1456, 1179, 1038, 732, 599; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, d, J = 2.4 Hz, CH_3 of isopropyl), 1.32 (3H, d, J = 2.4 Hz,

CH_3 of isopropyl), 2.20 (1H, m, H-3′), 2.39 (1H, ddd, J = 12.8, 8.2, 5.0 Hz, H-3), 2.74 (3H, s, N–CH_3), 3.67 (1H, t, J = 5.8 Hz, H-2), 3.80 (1H, m, H-3a), 3.96 (1H, ddd, J = 9.8, 4.0, 1.2 Hz, H-4), 4.18 (1H, dd, J = 16.8, 7.8 Hz, H-4′), 4.81 (1H, d, J = 7.4 Hz, H-10b), 5.12 (1H, septet, J = 6.4 Hz, –$CH(CH_3)_2$), 7.18 (3H, m, Ar–H), 7.61 (1H, dd, J = 7.6, 0.8 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (–$OCH(CH_3)_2$), 36.7 (C-3), 37.0 (–NCH_3), 45.2 (C-3a), 50.7 (C-4), 64.8 (C-10b), 67.0 (C-2), 68.0 (–$CH(CH_3)_2$), 98.2 (C-10), 110.0 (C-6), 118.5, 120.1, 122.2, 130.2, 131.9, 138.6 (Ar–C), 172.87 (C═O). ESI-MS (m/z): 332.94 $(M)^+$, anal. calcd for $C_{18}H_{21}N_2O_2$, C, 64.96; H, 6.36; N, 8.42; found: C, 64.88; H, 6.25; 8.34.

Butyl (2*S*,3a*S*,10b*S*)-10-chloro-1-methyl-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (7e). Yield 77%, mp 92–94 °C, IR (ν_{max}, cm^{-1}): 3060, 2982, 1732, 1630, 1456, 1178, 1039, 731, 600; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J = 7.8 Hz, –$COO(CH_2)_3CH_3$), 1.43 (2H, sextet, J = 7.6 Hz, –$COO(CH_2)_2CH_2CH_3$), 1.68 (2H, quintet, J = 7.2 Hz, –$COOCH_2CH_2CH_2CH_3$), 2.22 (1H, m, H-3′), 2.39 (1H, ddd, J = 13.6, 8.4, 5.6 Hz, H-3), 2.73 (3H, s, –NCH_3), 3.70 (1H, t, J = 5.4 Hz, H-2), 3.78 (1H, m, H-3a), 3.97 (1H, ddd, J = 9.4, 4.2, 1.8 Hz, H-4), 4.19 (3H, m, 2H of –$COOCH_2$ $(CH_2)_2CH_3$, 1H of H-4′), 4.81 (1H, d, J = 7.6 Hz, H-10b), 7.17 (3H, m, Ar–H), 7.70 (1H, dd, J = 7.4, 1.2 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 (–$COO(CH_2)_3CH_3$), 19.2 (–$COOC(CH_2)_2CH_2CH_3$), 30.7 (–$COOCH_2CH_2CH_2CH_3$), 36.7 (C-3), 37.1 (–NCH_3), 45.3 (C-3a), 50.7 (C-4), 64.7 (C-10b), 66.7 (–$COOCH_2$ $(CH_2)_2CH_3$), 67.0 (C-2), 98.2 (C-10), 110.0 (C-6), 118.5, 120.1, 122.2, 130.2, 131.9, 138.5 (Ar–C), 172.8 (C═O). ESI-MS (m/z): 347.04 $(M)^+$, anal. calcd for $C_{19}H_{23}ClN_2O_2$: C, 65.79; H, 6.68; N, 8.08; found: C, 65.55; H, 6.57; N, 8.22.

Methyl (2*S*,3a*S*,10b*S*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (8a). Yield 85%, mp 84–86 °C, IR (ν_{max}, cm^{-1}): 3051, 2975, 1728, 1631, 1453, 1197, 1169, 738, 650; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (3H, t, J = 7.2 Hz, –NCH_2CH_3), 2.19 (1H, m, H-3′), 2.40 (1H, ddd, J = 12.8, 9.4, 3.2 Hz, H-3), 2.95 (1H, m, one of N$\underline{CH_2}$$CH_3$), 3.35 (1H, m, another of –NCH_2CH_3), 3.78 (4H, m, 3H of –$COOCH_3$, and 1H of H-3a), 3.96 (2H, m, 1H of H-2, and 1H of H-4), 4.18 (1H, dd, J = 10, 8.4 Hz, H-4′), 4.82 (1H, d, J = 8 Hz, H-10b), 7.20 (3H, m, Ar–H), 7.60 (1H, dd, J = 7.6, 1.6 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (–NCH_2CH_3), 35.9 (C-3), 44.2 (–NCH_2CH_3), 45.0 (C-3a), 50.5 (C-4), 51.3 (CH_3), 63.9 (C-2), 64.1 (C-10b), 97.7 (C-10), 110.0 (C-6), 118.5, 120.0, 122.1, 130.1, 131.8, 139.4 (Ar–C), 173.8 (C═O); ESI-MS (m/z): 319.10 $(M)^+$, anal. calcd for $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79; found: C, 63.88; H, 6.23; N, 8.94.

Ethyl (2*S*,3a*S*,10b*S*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (8b). Yield 82%, mp 92–94 °C, IR (ν_{max}, cm^{-1}): 3053, 2973, 1730, 1630, 1450, 1248, 1198, 1170, 739, 652; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J = 7.2 Hz, –NCH_2CH_3), 1.32 (3H, t, J = 6.8 Hz, –$COOCH_2CH_3$), 2.20 (1H, m, H-3′), 2.42 (1H, ddd, J = 12.4, 9.6, 3.4 Hz, H-3), 2.94 (1H, m, 1H of –NCH_2CH_3), 3.32 (1H, m, 1H –NCH_2CH_3), 3.79 (1H, m, H-3a), 3.98 (2H, m, 1H of H-2 and 1H of H-4), 4.18–4.22 (3H, m, 1H of H-4′ and 2H of –$COOCH_2$), 4.80 (1H, d, J = 8.2 Hz, H-10b), 7.22 (3H, m, Ar–H), 7.62 (1H, dd, J = 7.8, 1.4 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (–NCH_2CH_3), 14.3 (–$COOCH_2CH_3$) 35.9 (C-3), 44.2 (–NCH_2CH_3), 45.0 (C-3a), 50.4 (C-4), 60.3 ($COOCH_2CH_3$), 63.9 (C-2), 64.1 (C-10b), 97.7 (C-10), 112.0 (C-6), 118.5, 120.0, 122.1, 130.1, 131.8, 139.4 (Ar–C), 173.8 (C═O); ESI-MS (m/z): 332.82 $(M)^+$, anal. calcd for $C_{18}H_{21}ClN_2O_2$: C, 64.96; H, 6.36; N, 8.42; found: C, 64.86; H, 6.53; N, 8.74.

Propyl (2*S*,3a*S*,10b*S*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (8c). Yield 84%, mp 64–66 °C, IR (ν_{max}, cm^{-1}): 3050, 2976, 1730, 1632, 1452, 1198, 1168, 739, 648; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J = 7.4 Hz, –$COO(CH_2)_2CH_3$), 1.21 (3H, t, J = 7.4 Hz, –NCH_2CH_3), 1.72 (2H, m, –$COOCH_2CH_2CH_3$), 2.22 (1H, m, H-3′), 2.41 (1H, ddd, J = 12.6, 9.2, 3.4 Hz, H-3), 2.95 (1H, m, 1H of –NCH_2CH_3), 3.30 (1H, m, 1H of –NCH_2CH_3), 3.78 (1H, m, H-3a), 3.97 (2H, m, 1H of H-2 and 1H of H-4), 4.16–4.21 (3H, m, 1H of H-4′ and 2H of –$COOCH_2$), 4.79 (1H, d, J = 7.8 Hz, H-10b), 7.21 (3H, m, Ar–H), 7.62 (1H, dd, J = 7.4, 1.6 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 (–$COO(CH_2)_2CH_3$), 13.8 (–NCH_2CH_3), 22.1 (–$COOCH_2CH_2CH_3$) 35.9 (C-3), 44.2 (–NCH_2CH_3), 45.0 (C-3a), 50.5 (C-4), 63.9 (C-2), 64.1 (C-10b), 66.3 (–$COOCH_2CH_2CH_3$), 97.7 (C-10), 112.0 (C-6), 118.5, 120.0, 122.1, 130.1, 131.8, 139.4 (Ar–C), 173.8 (C═O); ESI-MS (m/z): 346.87 $(M)^+$, anal. calcd for $C_{19}H_{23}ClN_2O_2$: C, 65.79; H, 6.68; N, 8.08; found: C, 65.89; H, 6.43; N, 7.89.

Isopropyl (2*S*,3a*S*,10b*S*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b* hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (8d). Yield 78%, mp 62–63 °C, IR (ν_{max}, cm^{-1}): 3054, 2967, 1733, 1631, 1456, 1373, 1185, 1107, 737, 656; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.2 (3H, t, J = 7.2 Hz, –CH_2CH_3), 1.31 (3H, d, J = 2.4 Hz, CH_3 of isopropyl), 1.32 (3H, d, J = 2.4 Hz, CH_3 of isopropyl), 2.19 (1H, m, H-3′), 2.39 (1H, ddd, J = 13.4, 9.2, 2.8 Hz, H-3), 2.93 (1H, m, 1H of –NCH_2CH_3), 3.37 (1H, m, 1H of –NCH_2CH_3), 3.81 (1H, m, H-3a), 3.93 (1H, dd, J = 7.2, 2.8 Hz, H-4), 3.98 (1H, dd, J = 10.2, 4.0 Hz, H-2), 4.20 (1H, dd, J = 17.2, 8.0 Hz, H-4′), 4.82 (1H, d, J = 8.4 Hz, H-10b), 5.12 (1H, septet, J = 6.4 Hz, –$OCH(CH_3)_2$), 7.19 (3H, m, Ar–H), 7.59 (1H, dd, J = 7.8, 1.2 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (–NCH_2CH_3), 21.2 (Me of iso propyl), 35.9 (C-3), 44.6 (–NCH_2CH_3), 45.7 (C-3a), 50.7 (C-4), 64.1 (C-2), 64.2 (C-10b), 68.0 (–$OCH(CH_3)_2$) 97.4 (C-10), 110.0, 118.1, 120.1, 122.2, 130.1, 131.6, 139.6 (Ar–C), 173.4 (C═O); ESI-MS (m/z): 346.00 $(M)^+$, anal. calcd for $C_{19}H_{23}ClN_2O_2$: C, 65.79; H, 6.68; N, 8.08; found: C, 65.88; H, 6.73; N, 8.16.

Butyl (2*S*,3a*S*,10b*S*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (8e). Yield 89%, mp 60–62 °C, IR (ν_{max}, cm^{-1}): 3052, 2976, 1729, 1630, 1451, 1198, 1170, 1130, 740, 648; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, J = 7.6 Hz, –$COO(CH_2)_3CH_3$), 1.19 (3H, t, J = 7.8 Hz, –NCH_2CH_3), 1.42 (2H, sextet, J = 7.2 Hz, –$COO(CH_2)_2CH_2CH_3$), 1.68 (2H, quintet, J = 7.2 Hz, –$COOCH_2CH_2CH_2CH_3$), 2.21 (1H, m, H-3′), 2.41 (1H, ddd, J = 12.8, 9.6, 3.2 Hz, H-3), 2.94 (1H, m, 1H of –NCH_2CH_3), 3.32 (1H, m, 1H of –NCH_2CH_3), 3.79 (1H, m, H-3a), 3.96 (2H, m, 1H of H-2, and 1H of H-4), 4.18–4.21 (3H, m, 1H of H-4′ and 2H of –$COOCH_2$), 4.80 (1H, d, J = 7.6 Hz, H-10b), 7.20 (3H, m, Ar–H), 7.61 (1H, dd, J = 7.2, 1.8 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 (–$COO(CH_2)_3CH_3$), 13.8 (–NCH_2CH_3), 19.2 (–$COO(CH_2)_2CH_2CH_3$),

30.7 (–$COOCH_2CH_2CH_2CH_3$) 35.9 (C-3), 44.2 (–NCH_2CH_3), 45.0 (C-3a), 50.5 (C-4), 63.9 (C-2), 64.1 (C-10b), 66.8 (–$COOCH_2$-$(CH_2)_2CH_3$), 97.7 (C-10), 112.0 (C-6), 118.5, 120.0, 122.1, 130.1, 131.8, 139.4 (Ar–C), 173.8 (C═O); ESI-MS (*m*/*z*): 360.88 $(M)^+$, anal. calcd for $C_{20}H_{25}ClN_2O_2$: C, 66.56; H, 6.98; N, 7.76; found: C, 66.78; H, 6.54; N, 7.98.

Methyl (2*S*,3*aS*,10*bS*)-1-benzyl-10-chloro-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (9a). Yield 80%, mp 154–156 °C, IR (ν_{max}, cm^{-1}): 3055, 2980, 1723, 1581, 1455, 1369, 1195, 1028, 739, 705, 598; ^1H NMR (400 MHz, $CDCl_3$): δ 2.16 (1H, m, H-3′), 2.35 (1H, ddd, *J* = 12.4, 9.0, 3.2 Hz, H-3), 3.67 (1H, t, *J* = 6.2 Hz, H-2), 3.77 (3H, s, –$COOCH_3$), 3.84 (1H, m, H-3a), 4.06 (2H, m, –NCH_2Ph), 4.21 (1H, m, H-4), 4.79 (1H, d, *J* = 13.4 Hz, H-4′), 5.01 (1H, d, *J* = 8.2 Hz, H-10b), 7.25 (8H, m, Ar–H), 7.62 (1H, d, *J* = 7.4 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.8 (C-3), 45.4 (C-3a), 50.1 (C-4), 51.3 (–$COOCH_3$), 54.0 (–NCH_2Ph), 63.9 (C-10b), 64.4 (C-2), 97.2 (C-10), 110.0 (C-6), 118.6, 120.0, 122.1, 127.1, 128.2, 129.0, 130.2, 131.7, 138.8, 140.3 (Ar–C), 173.4 (–C═O); ESI-MS (*m*/*z*): 380.87 $(M)^+$, anal. calcd for $C_{22}H_{21}ClN_2O_2$: C, 69.38; H, 5.56; N, 7.36; found: C, 69.54; H, 5.68; N, 7.42.

Ethyl (2*S*,3*aS*,10*bS*)-1-benzyl-10-chloro-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (9b). Yield 82%, mp 124–125 °C, IR (ν_{max}, cm^{-1}): 3053, 2982, 1720, 1582, 1455, 1371, 1194, 1027, 739, 700, 599; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* = 7.2 Hz, –$COOCH_2CH_3$), 2.17 (1H, m, H-3′), 2.34 (1H, ddd, *J* = 12.6, 9.2, 3.0 Hz, H-3), 3.68 (1H, t, *J* = 6.0 Hz, H-2), 3.85 (1H, m, H-3a), 4.05 (2H, m, –NCH_2Ph), 4.2 (3H, m, 2H of –$COOCH_2CH_3$, and 1H of H-4), 4.8 (1H, d, *J* = 13.6 Hz, H-4′), 5.0 (1H, d, *J* = 8.0 Hz, H-10b), 7.23 (8H, m, Ar–H), 7.63 (1H, d, *J* = 7.6 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (–$COOCH_2CH_3$), 35.8 (C-3), 45.4 (C-3a), 50.1 (C-4), 54.0 (–NCH_2Ph), 60.3 (–$COOCH_2CH_3$), 63.9 (C-10b), 64.4 (C-2), 97.2 (C-10), 110.0 (C-6), 118.6, 120.0, 122.1, 127.1, 128.2, 129.0, 130.2, 131.7, 138.8, 140.3 (Ar–C), 173.4 (–C═O); ESI-MS (*m*/*z*): 395.30 $(M)^+$, anal. calcd for $C_{23}H_{23}ClN_2O_2$: C, 69.95; H, 5.87; N, 7.09; found: C, 69.74; H, 5.68; N, 7.23.

Propyl (2*S*,3*aS*,10*bS*)-1-benzyl-10-chloro-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (9c). Yield 78%, mp 126–128 °C, IR (ν_{max}, cm^{-1}): 3054, 2981, 1725, 1582, 1457, 1369, 1196, 1029, 738, 702, 601; ^1H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, t, *J* = 7.4Hz, –$COO(CH_2)_2CH_3$), 1.76 (2H, m, –$COOCH_2CH_2CH_3$), 2.18 (1H, m, H-3′), 2.33 (1H, ddd, *J* = 12.8, 9.0, 3.0 Hz, H-3), 3.69 (1H, t, *J* = 5.8 Hz, H-2), 3.86 (1H, m, H-3a), 4.09 (4H, m, 2H of –NCH_2Ph and 2H of –$COOCH_2CH_2CH_3$), 4.19 (1H, m, H-4), 4.81 (1H, d, *J* = 13.6 Hz, H-4′), 5.01 (1H, d, *J* = 7.8 Hz, H-10b), 7.24 (8H, m, Ar–H), 7.64 (1H, d, *J* = 7.2 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 (–$COO(CH_2)_2CH_3$), 22.1 (–$COOCH_2CH_2CH_3$), 35.8 (C-3), 45.4 (C-3a), 50.1 (C-4), 54.0 (–NCH_2Ph), 63.9 (C-10b), 64.4 (C-2), 66.7 (–$COOCH_2CH_2CH_3$), 97.2 (C-10), 110.0 (C-6), 118.6, 120.0, 122.1, 127.1, 128.2, 129.0, 130.1, 131.7, 138.8, 140.3 (Ar–C), 173.4 (–C═O); ESI-MS (*m*/*z*): 408.92 $(M)^+$, anal. calcd for $C_{24}H_{25}ClN_2O_2$: C, 70.49; H, 6.16; N, 6.85; found: C, 70.54; H, 6.38; N, 6.72.

Isopropyl (2*S*,3*aS*,10*bS*)-1-benzyl-10-chloro-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (9d). Yield 76%, mp 132–134 °C, IR (ν_{max}, cm^{-1}): 3055, 2984, 1719, 1579, 1458, 1369, 1192, 1028, 740, 702, 602; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, d, *J* = 2.4 Hz, Me of isopropyl), 1.33 (3H, d, *J* = 2.4 Hz, Me of isopropyl), 2.18 (1H, m, H-3′), 2.36 (1H, ddd, *J* = 12.8, 9.2, 3.2 Hz, H-3), 3.69 (1H, t, *J* = 6.0 Hz, H-2), 3.84 (1H, m, H-3a), 4.03 (2H, m, –NCH_2Ph), 4.20 (1H, m, H-4), 4.82 (1H, d, *J* = 13.4 Hz, H-4′), 5.02 (1H, d, *J* = 8.4 Hz, H-10b), 5.14 (1H, septet, *J* = 6.4 Hz, –$CH(CH_3)_2$), 7.25 (8H, m, Ar–H), 7.65 (1H, d, *J* = 7.8 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3 (–$COOCH(CH_3)_2$), 35.8 (C-3), 45.4 (C-3a), 50.2 (C-4), 54.0 (–NCH_2Ph), 63.8 (C-10b), 64.3 (C-2), 68.0 (–$CH(CH_3)_2$), 97.2 (C-10), 110.0 (C-6), 118.6, 120.0, 122.1, 127.1, 128.2, 129.0, 130.1, 131.7, 138.8, 140.3 (Ar–C), 173.4 (–C═O); ESI-MS (*m*/*z*): 408.90 $(M)^+$, anal. calcd for $C_{24}H_{25}ClN_2O_2$: C, 70.49; H, 6.16; N, 6.85; found: C, 70.54; H, 6.28; N, 6.73.

Butyl (2*S*,3*aS*,10*bS*)-1-benzyl-10-chloro-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (9e). Yield 74%, mp 96–98 °C, IR (ν_{max}, cm^{-1}): 3052, 2981, 1722, 1584, 1453, 1372, 1194, 1028, 741, 702, 597; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.8 Hz, –$COO(CH_2)_3CH_3$), 1.46 (2H, sextet, *J* = 7.6 Hz, –$COO(CH_2)_2CH_2CH_3$), 1.66 (2H, quintet, *J* = 6.8 Hz, –$COOCH_2CH_2CH_2CH_3$), 2.16 (1H, m, H-3′), 2.34 (1H, ddd, *J* = 12.6, 8.8, 3.2 Hz, H-3), 3.68 (1H, t, *J* = 6.2 Hz, H-2), 3.87 (1H, m, H-3a), 4.06 (2H, m, –NCH_2Ph), 4.17 (3H, m, 1H of H-4 and 2H of –$COOCH_2CH_2CH_2CH_3$), 4.79 (1H, d, *J* = 13.4 Hz, H-4′), 4.99 (1H, d, *J* = 7.6 Hz, H-10b), 7.25 (8H, m, Ar–H), 7.62 (1H, d, *J* = 7.6 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 (–$COO(CH_2)_3CH_3$), 19.2 (–$COO(CH_2)_2CH_2CH_3$), 30.7 (–$COOCH_2$-$CH_2CH_2CH_3$), 35.8 (C-3), 45.4 (C-3a), 50.1 (C-4), 54.0 (–NCH_2Ph), 63.9 (C-10b), 64.4 (C-2), 66.7 (–$COOCH_2CH_2CH_2CH_3$), 97.2 (C-10), 110.0 (C-6), 118.6, 120.0, 122.1, 127.1, 128.2, 129.0, 130.2, 131.7, 138.8, 140.3 (Ar–C), 173.4 (–C═O); ESI-MS (*m*/*z*): 422.95 $(M)^+$, anal. calcd for $C_{25}H_{27}ClN_2O_2$: C, 70.99; H, 6.43; N, 6.62; found: C, 70.64; H, 6.58; N, 6.92.

Methyl (2*S*,3*aS*,10*bS*)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (10a). Yield 76%, IR (ν_{max}, cm^{-1}): 3060, 2956, 1727, 1684, 1456, 1338, 1158, 1029, 745, 702, 664, 608; ^1H NMR (400 MHz, $CDCl_3$): δ 2.24 (1H, m, H-3′), 2.40–2.62 (7H, m, 1H of H-3 and 6H of –CH_2–N–$(CH_2)_2$–), 3.12 (1H, m, 1H of CH_2-11), 3.52 (1H, m, 1H of CH_2-11), 3.70 (5H, m, 1H of H-3a, and 4H of –CH_2–O–CH_2–), 3.79 (3H, s, –$COOCH_3$), 3.96 (1H, dd, *J* = 10.2, 4.0 Hz, H-2), 4.07 (2H, m, H-4 and H-4′), 4.86 (1H, d, *J* = 8.4 Hz, H-10b), 7.21 (3H, m, Ar–H), 7.59 (1H, d, *J* = 7.6 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.1 (C-3), 44.8 (C-3a), 46.4 (C-11), 50.3 (C-4), 51.3 (–$COOCH_3$), 53.7 (C-14), 57.7 (C-12), 64.6 (C-10b), 64.7 (C-2), 66.2 (C-15), 97.3 (C-10), 110.0, 118.4, 120.0, 122.1, 130.0, 131.7, 139.7 (Ar–C), 173.5 (–C═O); ESI-MS (*m*/*z*): 404.02 $(M)^+$, anal. calcd for $C_{21}H_{26}ClN_3O_3$: C, 62.45; H, 6.49; N, 10.40; found: C, 62.64; H, 6.38; N, 10.02.

Ethyl (2*S*,3*aS*,10*bS*)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (10b). Yield 78%, IR (ν_{max}, cm^{-1}): 3059, 2954, 1729, 1685, 1454, 1336, 1151, 1028, 742, 700, 662, 612; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.6 Hz, –$COOCH_2CH_3$), 2.23 (1H, m, H-3′), 2.38–2.63 (7H, m, 1H of H-3, and 6H of –CH_2–N–$(CH_2)_2$–), 3.13 (1H, m, 1H of CH_2-11), 3.51 (1H, m, 1H of

CH_2-11), 3.71 (5H, m, 1H of H-3a, and 4H of $-CH_2-O-CH_2-$), 3.97 (1H, dd, J = 10, 4.2 Hz, H-2), 4.07–4.15 (4H, m, 2H of $-COOCH_2CH_3$, and 2H of H-4 and H-4′), 4.85 (1H, d, J = 8.2 Hz, H-10b), 7.20 (3H, m, Ar–H), 7.58 (1H, d, J = 7.4 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 ($-COOCH_2CH_3$), 36.1 (C-3), 44.8 (C-3a), 46.4 (C-11), 50.3 (C-4), 53.7 (C-14), 57.7 (C-12), 60.5 ($-COOCH_2CH_3$), 64.6 (C-10b), 64.7 (C-2), 66.2 (C-15), 97.3 (C-10), 110.0, 118.4, 120.0, 122.1, 130.0, 131.7, 139.7 (Ar–C), 173.6 (–C═O); ESI-MS (m/z): 417.90 $(M)^+$, anal. calcd for $C_{22}H_{28}ClN_3O_3$: C, 63.22; H, 6.75; N, 10.05; found: C, 63.54; H, 6.58; N, 10.22.

Propyl (2*S*,3*aS*,10*bS*)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (10c). Yield 72%, IR (ν_{max}, cm^{-1}): 3059, 2952, 1728, 1632, 1455, 1308, 1116, 1026, 743, 701, 612; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (3H, t, J = 7.6 Hz, $-COOCH_2CH_2CH_3$), 1.74 (2H, m, $-COOCH_2CH_2CH_3$), 2.25 (1H, m, H-3′), 2.40–2.65 (7H, m, 1H of H-3, and 6H of $-CH_2-N-(CH_2)_2-$), 3.12 (1H, m, 1H of CH_2-11), 3.50 (1H, m, 1H of CH_2-11), 3.7 (5H, m, 1H of H-3a, and 4H of $-CH_2-O-CH_2-$), 3.97 (1H, dd, J = 10, 4.4 Hz, H-2), 4.15 (4H, m, 2H of $-COOCH_2CH_2CH_3$, and 2H of H-4 and H-4′), 4.84 (1H, d, J = 8.0 Hz, H-10b), 7.21 (3H, m, Ar–H), 7.58 (1H, d, J = 7.6 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 ($-COO(CH_2)_2CH_3$), 22.1 ($-COOCH_2CH_2CH_3$), 36.1 (C-3), 44.8 (C-3a), 46.8 (C-11), 50.3 (C-4), 53.7 (C-14), 57.7 (C-12), 64.6 (C-10b), 64.8 (C-2), 66.1 (C-15), 66.7 ($-COOCH_2$), 97.3 (C-10), 110.0, 118.4, 120.0, 122.2, 130.0, 131.7, 139.7 (Ar–C), 173.5 (–C═O); ESI-MS (m/z): 430.90 $(M)^+$, anal. calcd for $C_{23}H_{30}ClN_3O_3$: C, 63.95; H, 7.00; N, 9.73; found: C, 63.74; H, 6.78; N, 9.96.

Isopropyl (2*S*,3*aS*,10*bS*)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (10d). Yield 74%, IR (ν_{max}, cm^{-1}): 3060, 2950, 1729, 1632, 1454, 1309, 1117, 1028, 741, 702, 614; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, d, J = 2.4 Hz, Me of $-COOCH(CH_3)_2$), 1.34 (3H, d, J = 2.4 Hz, Me of $-COOCH(CH_3)_2$), 2.24 (1H, m, H-3′), 2.40–2.66 (7H, m, 1H of H-3 and 6H of $-CH_2-N-(CH_2)_2-$), 3.12 (1H, m, 1H of CH_2-11), 3.51 (1H, m, 1H of CH_2-11), 3.71 (5H, m, 1H of H-3a and 4H of $-CH_2-O-CH_2-$), 3.98 (1H, dd, J = 10.2, 4.6 Hz, H-2), 4.15–4.18 (2H, m, H-4 and H-4′), 4.85 (1H, d, J = 8.2 Hz, H-10b), 5.14 (1H, m, $-CH(CH_3)_2$), 7.20 (3H, m, Ar–H), 7.59 (1H, d, J = 7.6 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3 ($-COOCH(CH_3)_2$), 36.1 (C-3), 44.8 (C-3a), 46.8 (C-11), 50.3 (C-4), 53.7 (C-14), 57.7 (C-12), 64.6 (C-10b), 64.8 (C-2), 66.1 (C-15), 66.1 ($-CH(CH_3)_2$), 97.3 (C-10), 110.0, 118.4, 120.0, 122.2, 130.0, 131.7, 139.7 (Ar–C), 173.6 (–C═O); ESI-MS (m/z): 430.94 $(M)^+$, anal. calcd for $C_{23}H_{30}ClN_3O_3$: C, 63.95; H, 7.00; N, 9.73; found: C, 63.86; H, 6.81; N, 9.86.

Butyl (2*S*,3*aS*,10*bS*)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3*a*,4,10*b*-hexahydropyrrolo[2′,3′:3,4]pyrrolo[1,2-*a*]indole-2-carboxylate (10e). Yield 75%, IR (ν_{max}, cm^{-1}): 3060, 2955, 1728, 1685, 1455, 1337, 1152, 1028, 744, 701, 663, 613; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, J = 8.0 Hz, $-O(CH_2)_3CH_3$), 1.44 (2H, sextet, J = 7.6 Hz, $-COO(CH_2)_2CH_2CH_3$), 1.67 (2H, quintet, J = 7.2 Hz, $-OCH_2CH_2CH_2CH_3$), 2.24 (1H, m, H-3′), 2.35–2.65 (7H, m, 1H of H-3 and 6H of $-CH_2-N-(CH_2)_2-$), 3.12 (1H, m, 1H of CH_2-11), 3.50 (1H, m, 1H of CH_2-11), 3.69 (5H, m, 1H of H-3a and 4H of $-CH_2-O-CH_2-$), 3.98 (1H, dd, J = 10.0, 4.0 Hz, H-2), 4.06 (1H, dd, J = 7.6, 2.4 Hz, H-4), 4.18 (3H, m, 2H of $-COOCH_2-$ and 1H of H-4′), 4.84 (1H, d, J = 8.4 Hz, H-10b), 7.19 (3H, m, Ar–H), 7.58 (1H, d, J = 7.6 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.4 ($-COO(CH_2)_3CH_3$), 19.2 ($-COO(CH_2)_2CH_2CH_3$), 30.7 ($-COOCH_2CH_2CH_2CH_3$), 36.1 (C-3), 44.8 (C-3a), 46.3 (C-11), 50.3 (C-4), 53.7 (C-14), 57.7 (C-12), 64.4 (C-10b), 64.6 (C-2), 64.9 (C-15), 66.7 ($-COOCH_2$), 97.3 (C-10), 109.9, 118.4, 120.0, 122.2, 130.0, 131.7, 139.7 (Ar–C), 173.6 (–C═O); ESI-MS (m/z): 446.10 $(M)^+$, anal. calcd for $C_{24}H_{32}ClN_3O_3$: C, 64.63; H, 7.23; N, 9.42; found: C, 64.74; H, 7.48; N, 9.76.

(4*bR*,5*aS*,12*bS*)-12-Chloro-4*b*,5,5*a*,12*b*,14,15-hexahydro-6*H*-benzo[5′,6′]pyrrolizino[2′,1′:4,5]pyrrolo[2,1-*a*]isoquinoline (11a). yield 45%, mp 118–120 °C, IR (ν_{max}, cm^{-1}): 3054, 2939, 2817, 1637, 1455, 1321, 1220, 740, 642, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (1H, m, H-5′), 2.40 (1H, m, H-5), 2.90 (1H, m, 1H of C-14), 3.15 (2H, m, 1H of C-15 and 1H of C-14), 3.66 (2H, m, 1H of C-14 and 1H of H-5a), 4.00 (1H, t, J = 7.6 Hz, H-4b), 4.10 (1H, dd, J = 10.2, 3.2 Hz, H-6), 4.28 (1H, t, J = 10.0 Hz, H-6′), 4.93 (1H, d, J = 7.6 Hz, H-12b), 7.20 (7H, m, Ar–H), 7.61 (1H, d, J = 8.0 Hz, H-11); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9 (C-15), 34.6 (C-5), 44.2 (C-14), 48.4 (C-5a), 51.5 (C-6), 59.6 (C-4b), 64.4 (C-12b), 99.0 (C-12), 109.3, 119.3, 121.3, 122.5, 123.2, 125.0, 126.8, 128.2, 128.9, 129.9, 130.8, 137.4, 139.5 (Ar–C); ESI-MS (m/z): 334.20 $(M)^+$, anal. calcd for $C_{21}H_{19}ClN_2$: C, 75.33; H, 5.72; N, 8.37; found: C, 75.41; H, 5.63; N, 8.42.

(4*bS*,5*aS*,12*bS*)-12-Chloro-4*b*,5,5*a*,12*b*,14,15-hexahydro-6*H*-benzo[5′,6′]pyrrolizino[2′,1′:4,5]pyrrolo[2,1-*a*]isoquinoline (11′a). Yield 37%, mp 152–154 °C IR (ν_{max}, cm^{-1}): 3055, 2938, 2818, 1638, 1454, 1321, 1222, 1138, 742, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (1H, m, H-5′), 2.78 (1H, m, H-5), 2.88 (2H, m, two H of C-15), 3.16 (1H, m, 1H of C-14), 3.72 (2H, m, 1H of C-14 and 1H of H-5a), 3.89 (1H, dd, J = 10.8, 7.2 Hz, H-6), 3.97 (1H, dd, J = 10.0, 6.4 Hz, H-6′), 4.12 (1H, d, J = 8.4 Hz, H-12b), 4.39 (1H, t, J = 9.6 Hz, H-4b), 7.16 (7H, m, Ar–H), 7.61 (1H, dd, J = 7.6, 1.2 Hz, H-11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0 (C-15), 34.6 (C-5), 44.2 (C-14), 48.2 (C-5a), 51.5 (C-6), 59.6 (C-4b), 64.5 (C-12b), 98.9 (C-12), 109.3, 119.3, 121.3, 122.5, 123.2, 125.2, 127.0, 128.2, 128.9, 130.0, 130.8, 137.4, 139.8 (Ar–C); ESI-MS (m/z): 334.20 $(M)^+$, anal. calcd for $C_{21}H_{19}ClN_2$: C, 75.33; H, 5.72; N, 8.37; found: C, 75.39; H, 5.61; N, 8.45.

(4*bR*,5*aS*,12*bS*)-12-Chloro-2,3-dimethoxy-4*b*,5,5*a*,12*b*,14,15-hexahydro-6*H*-benzo[5′,6′]pyrrolizino[2′,1′:4,5]pyrrolo[2,1-*a*]isoquinoline (11b). Yield 46%, mp 162–164 °C IR (ν_{max}, cm^{-1}): 2998, 2934, 2820, 1608, 1516, 1452, 1323, 1219, 1014, 746, 674; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (2H, m, H-5 and H-5′), 2.80 (1H, m, 1H of C-15), 3.13 (1H, m, 2H, 1H of C-15 and 1H of C-14), 3.65 (2H, m, 1H of C-14 and 1H of H-5a), 3.85 (3H, s, $-OCH_3$), 3.87 (3H, s, $-OCH_3$), 4.01 (1H, t, J = 7.2 Hz, H-4b), 4.09 (1H, dd, J = 10.4, 3.6 Hz, H-6), 4.27 (1H, dd, J = 10.2, 8.4 Hz, H-6′), 4.90 (1H, d, J = 7.6 Hz, H-12b), 6.56 (1H, s, H-1), 6.64 (1H, s, H-4), 7.20 (3H, m, Ar–H), 7.60 (1H, dd, J = 7.0, 1.2 Hz, H-11); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2 (C-15), 36.8 (C-5), 40.9 (C-14), 45.7 (C-5a), 50.6 (C-6), 55.8 (–OMe), 56.5 (–OMe), 60.4 (C-4b),

64.6 (C-12b), 98.4 (C-12), 109.7, 111.9, 117.0, 118.6, 121.8, 123.2, 125.2, 128.7, 130.0, 130.3, 132.5, 147.0, 147.5 (Ar–C); ESI-MS (m/z): 394.54 $(M)^+$, anal. calcd for $C_{23}H_{23}ClN_2O_2$: C, 69.95; H, 5.87; N, 7.09; found: C, 69.81; H, 5.93; N, 7.02.

(4*bS*,5*aS*,12*bS*)-12-Chloro-2,3-dimethoxy-4*b*,5,5*a*,12*b*,14,15-hexahydro-6*H*-benzo[5′,6′] pyrrolizino[2′,1′:4,5] pyrrolo[2,1-*a*]-isoquinoline (11′b). Yield 38%, mp 202–204 °C IR (ν_{max}, cm^{-1}): 3002, 2935, 2818, 1608, 1518, 1454, 1325, 1218, 1012, 748, 672; ^1H NMR (400 MHz, $CDCl_3$): δ 1.90 (1H, m, H-5′), 2.79 (3H, m, 1H of H-5 and 2H of C-15), 3.07 (1H, m, 1H of C-14), 3.68 (2H, m, 1H of C-14 and 1H of H-5a), 3.83 (4H, m, 3H of $-OCH_3$ and 1H of H-6), 3.88 (3H, s, $-OCH_3$), 3.98 (1H, dd, J = 9.6, 6.4 Hz, H-6′), 4.13 (1H, d, J = 8.0 Hz, H-12b), 4.40 (1H, t, J = 9.6 Hz, H-4b), 6.58 (1H, s, H-1), 6.63 (1H, s, H-4), 7.18 (3H, m, Ar–H), 7.60 (1H, d, J = 7.6 Hz, H-11); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2 (C-15), 36.9 (C-5), 41.0 (C-14), 45.7 (C-5a), 50.5 (C-6), 56.0 (–OMe), 56.6 (–OMe), 60.4 (C-4b), 64.5 (C-12b), 99.0 (C-12), 110.1, 112.0, 117.0, 118.6, 121.8, 123.3, 125.2, 128.7, 130.0, 130.4, 132.6, 147.2, 147.8 (Ar–C); ESI-MS (m/z): 394.54 $(M)^+$, anal. calcd for $C_{23}H_{23}ClN_2O_2$: C, 69.95; H, 5.87; N, 7.09; found: C, 69.91; H, 5.90; N, 7.04.

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