



Cite this: *New J. Chem.*, 2015, 39, 2657

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

Tushar R. Sutariya,^a Balvantsingh M. Labana,^a Narsidas J. Parmar,^{*a} Rajni Kant,^b Vivek K. Gupta,^b Gabriela B. Plata^c and José M. Padrón^c

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.

Received (in Montpellier, France)
15th December 2014,
Accepted 23rd January 2015

DOI: 10.1039/c4nj02308k

www.rsc.org/njc

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 alkaloids² 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 hydroxy pyrrolo [2,1-*a*] isoquinoline is a key fused-ring system with (2)-trolline structure, which

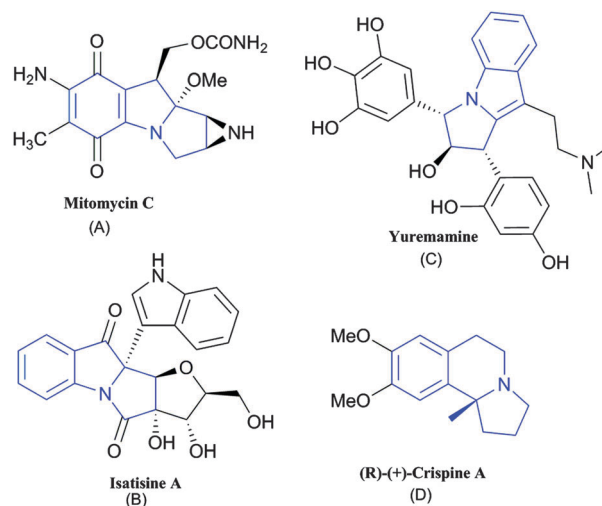


Fig. 1 Some biologically active heterocycles containing pyrrolo-indole and pyrrolo-isoquinoline units.

can be derived from *Trollius* Chinese flowers⁹ 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

^a Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar-388120. Dist. Anand, Gujarat, India. E-mail: njchemdeptspu@yahoo.co.in; Fax: +91-2692-236475; Tel: +91-2692-226858

^b Post-Graduate Department of Physics, University of Jammu, Jammu, Tawi-180006, India

^c BioLab, Instituto Universitario de Bio-Organica "Antonio González" (IUBO-AG), Centro de Investigaciones Biomédicas de Canarias (CIBICAN), C/Astrofísico Francisco Sánchez 2, 38206 La Laguna, Spain

† Electronic supplementary information (ESI) available. CCDC 960921 and 1018001. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4nj02308k



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 derivatives²⁰ 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}

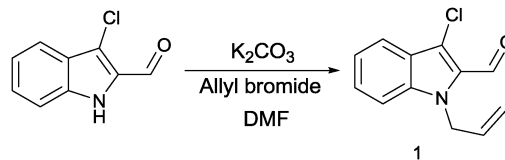
As part of our research program, we have reported the synthesis of many pyran-heterocycles,^{20h} including aminobenzopyrans^{20h,i} *via* 1,3 dipolar cycloaddition. Here, we describe pyrrolo-indole and pyrrolo-isoquinoline derivatives as new bioprofiles, constructed from *N*-allyl-3-chloro-indole-2-carbaldehyde **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 allyl bromide in the presence of anhydrous K₂CO₃, 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



Scheme 1 Synthesis of *N*-allyl-3-chloro-indole-2-carbaldehyde **1**, the reagents and conditions (**1**) K₂CO₃, allyl bromide, DMF, 10–12 h, room temp.

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

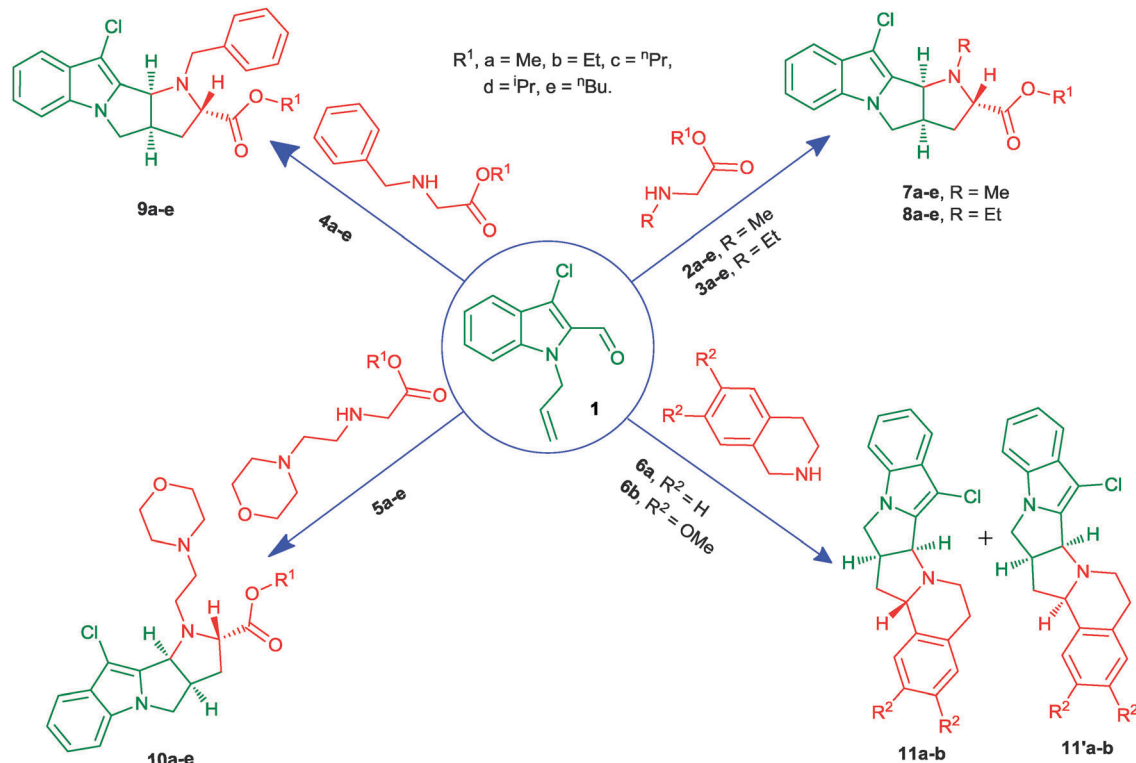
Entry	Solvent (reflux)	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1	MeOH	—	Reflux	24	Trace
2	ACN	—	Reflux	10	40
3	Toluene	—	Reflux	6.0	68
4	Toluene	Na ₂ SO ₄	Reflux	6.0	72
5	Xylene	—	Reflux	5.5	70
6	Xylene	Na ₂ SO ₄	Reflux	5.0	75
7	—	—	100 ^a	4	70
8	TEAA	TEAA	80	3.5	78
9	TEAA	TEAA	100	2.5	85

^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 Na₂SO₄. Although results in toluene and xylene using Na₂CO₃ 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	<i>n</i> Pr	—	3.0	77
4	7d	Me	<i>i</i> Pr	—	3.0	84
5	7e	Me	<i>n</i> Bu	—	3.5	77
6	8a	Et	Me	—	2.5	85
7	8b	Et	Et	—	2.75	82
8	8c	Et	<i>n</i> Pr	—	3.0	84
9	8d	Et	<i>i</i> Pr	—	3.0	78
10	8e	Et	<i>n</i> Bu	—	3.0	79
11	9a	Bn	Me	—	2.5	80
12	9b	Bn	Et	—	3.0	82
13	9c	Bn	<i>n</i> Pr	—	3.0	78
14	9d	Bn	<i>i</i> Pr	—	3.5	76
15	9e	Bn	<i>n</i> Bu	—	3.5	74
16	10a	Mp	Me	—	3.0	76
17	10b	Mp	Et	—	3.0	78
18	10c	Mp	<i>n</i> Pr	—	3.0	72
19	10d	Mp	<i>i</i> Pr	—	3.5	74
20	10e	Mp	<i>n</i> 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 ¹H 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

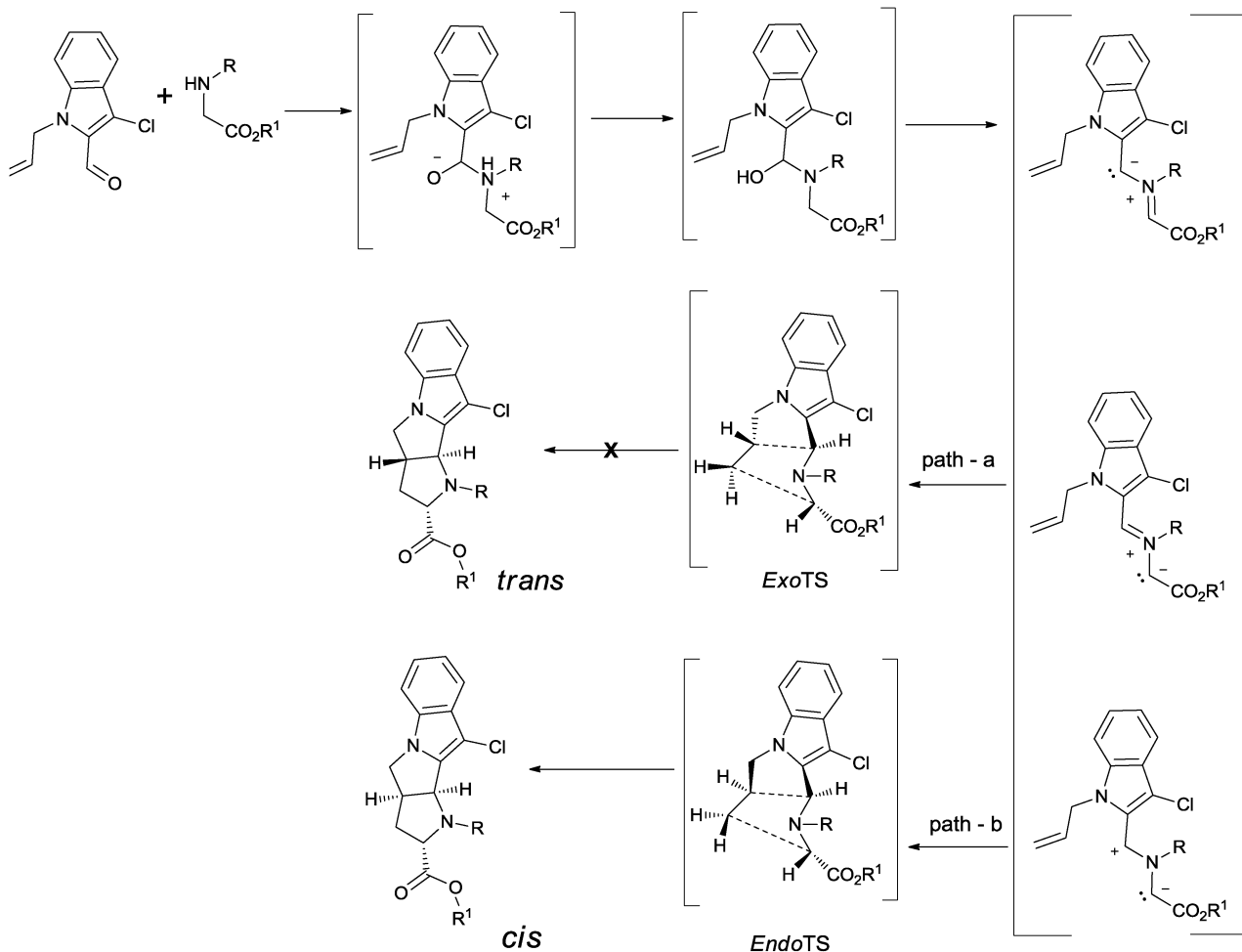
as a singlet at $\delta \sim 2.75$ ppm. The carbonyl group in **7–10** showed a characteristic IR band at ~ 1730 cm⁻¹, and a ¹³C NMR signal $\sim \delta$ 173 ppm. In all compounds, a doublet in the δ 4.00–4.80 ppm range, with the *J* value in the 7.6–8.4 Hz range, can be attributed to a bridge-head proton **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.

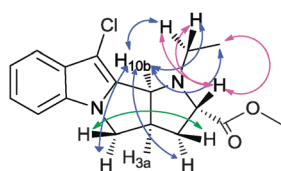


Fig. 2 Characteristic NOESY interactions in **8a**.

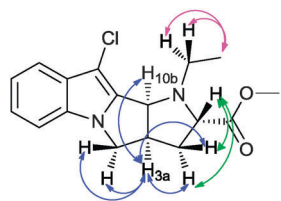


Fig. 3 Characteristic COSY interactions in **8a**.

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.



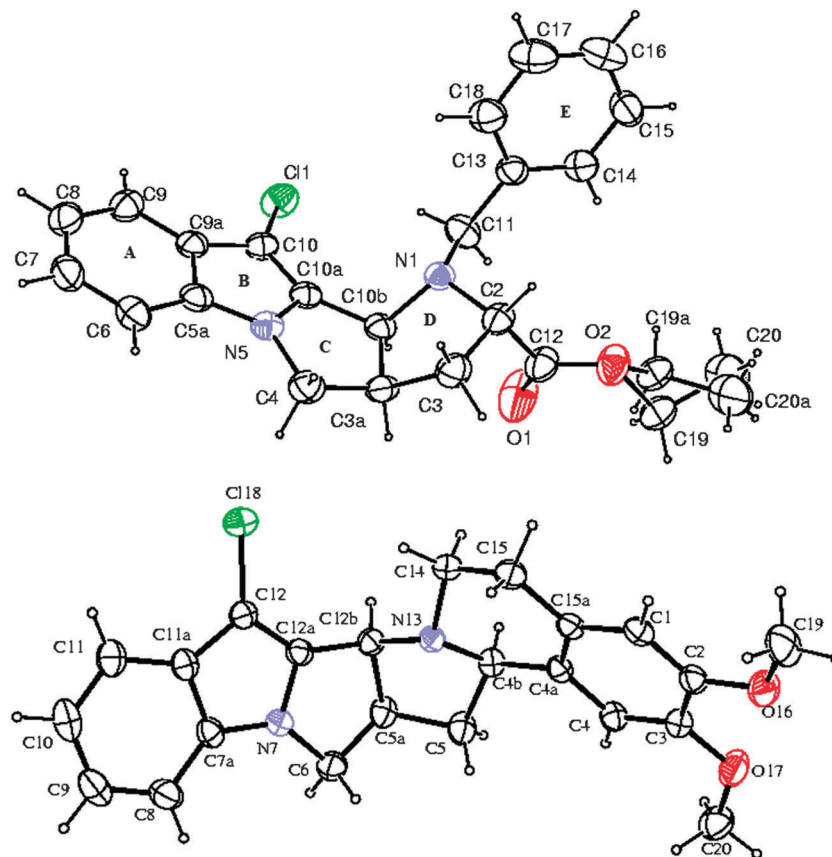


Fig. 4 The ORTEP views of compounds **9b** and **11b**, with displacement ellipsoids at the 40% probability level.

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 **11b** 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 pyrrolidine 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 carb-methoxy 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 tetrahydroisoquinolines showed remarkable bioactivities as well. In general, heterocycles derived from electron releasing methoxy substituted-tetrahydroisoquinoline 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

Compound	Antimicrobial activity (MIC $\mu\text{g mL}^{-1}$)								Anti TB ^a (%) inhibition	Antioxidant activity ^b FRAP ^c
	Gram-positive bacteria			Gram-negative bacteria			Fungi			
	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.: *Candida albicans*; [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 $\mu\text{g mL}^{-1}$, standard antimicrobials used: isoniazide (0.2 $\mu\text{g mL}^{-1}$).^b Concentration of compounds = 200 $\mu\text{g mL}^{-1}$ and standard: A.A. (ascorbic acid) = 176 $\mu\text{g mL}^{-1}$.^c A.A. mm per 100 g sample.

Table 4 Antiproliferative activity (GI₅₀) against human solid tumor cells

Compound	Antiproliferative activity (GI ₅₀) ^a				
	Cell line (origin)				
	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 $\mu\text{g L}^{-1}$. 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 anti-oxidant 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 pre-coated 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*-hexahydroindolo[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, $-\text{NCH}_3$), 3.68 (1H, t, $J = 5.8$ Hz, H-2), 3.78 (4H, m, 3H of $-\text{COOCH}_3$, 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 ($-\text{NCH}_3$), 45.3 (C-3a), 50.8 (C-4), 51.3 ($-\text{COOCH}_3$), 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 $\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{O}_2$: 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*-hexahydroindolo[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, $-\text{OCH}_2\text{CH}_3$), 2.21 (1H, m, H-3'), 2.40 (1H, ddd, $J = 13.2, 8.4, 5.2$ Hz, H-3), 2.75 (3H, s, $-\text{NCH}_3$), 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 $-\text{COOCH}_2\text{CH}_3$ 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 $\text{C}_{17}\text{H}_{19}\text{ClN}_2\text{O}_2$: 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*-hexahydroindolo[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, $-\text{COOCH}_2\text{CH}_2\text{CH}_3$), 1.75 (2H, m, $-\text{COOCH}_2\text{CH}_2\text{CH}_3$), 2.19 (1H, m, H-3'), 2.42 (1H, ddd, $J = 13.8, 8.2, 5.4$ Hz, H-3), 2.74 (3H, s, $-\text{NCH}_3$), 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 $-\text{COOCH}_2\text{CH}_2\text{CH}_3$, 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 ($-\text{COOCH}_2\text{CH}_2\text{CH}_3$), 22.1 ($-\text{COOCH}_2\text{CH}_2\text{CH}_3$), 36.6 (C-3), 37.0 ($-\text{NCH}_3$), 45.3 (C-3a), 50.7 (C-4), 64.8 (C-10b), 66.7 ($-\text{COOCH}_2\text{CH}_2\text{CH}_3$), 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 $\text{C}_{18}\text{H}_{21}\text{ClN}_2\text{O}_2$: 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*-hexahydroindolo[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,



CH₃ 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-CH₃), 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(CH₃)₂), 7.18 (3H, m, Ar-H), 7.61 (1H, dd, *J* = 7.6, 0.8 Hz, H-9); ¹³C NMR (100 MHz, CDCl₃): δ 21.2 (-OCH(CH₃)₂), 36.7 (C-3), 37.0 (-NCH₃), 45.2 (C-3a), 50.7 (C-4), 64.8 (C-10b), 67.0 (C-2), 68.0 (-CH(CH₃)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 C₁₈H₂₁N₂O₂, C, 64.96; H, 6.36; N, 8.42; found: C, 64.88; H, 6.25; 8.34.

Butyl (2*S*,3*aS*,10*bS*)-10-chloro-1-methyl-1,2,3,3*a*,4,10*b*-hexahydroindolo[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; ¹H NMR (400 MHz, CDCl₃): δ 0.99 (3H, t, *J* = 7.8 Hz, -COO(CH₂)₃CH₃), 1.43 (2H, sextet, *J* = 7.6 Hz, -COO(CH₂)₂CH₂CH₃), 1.68 (2H, quintet, *J* = 7.2 Hz, -COOCH₂CH₂CH₂CH₃), 2.22 (1H, m, H-3'), 2.39 (1H, ddd, *J* = 13.6, 8.4, 5.6 Hz, H-3), 2.73 (3H, s, -NCH₃), 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 -COOCH₂(CH₂)₂CH₃, 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); ¹³C NMR (100 MHz, CDCl₃): δ 10.4 (-COO(CH₂)₃CH₃), 19.2 (-COOCH₂(CH₂)₂CH₃), 30.7 (-COOCH₂CH₂CH₂CH₃), 36.7 (C-3), 37.1 (-NCH₃), 45.3 (C-3a), 50.7 (C-4), 64.7 (C-10b), 66.7 (-COOCH₂(CH₂)₂CH₃), 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 C₁₉H₂₃ClN₂O₂: C, 65.79; H, 6.68; N, 8.08; found: C, 65.55; H, 6.57; N, 8.22.

Methyl (2*S*,3*aS*,10*bS*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b*-hexahydroindolo[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; ¹H NMR (400 MHz, CDCl₃): δ 1.20 (3H, t, *J* = 7.2 Hz, -NCH₂CH₃), 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 -NCH₂CH₃), 3.35 (1H, m, another of -NCH₂CH₃), 3.78 (4H, m, 3H of -COOCH₃, 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); ¹³C NMR (100 MHz, CDCl₃): δ 13.8 (-NCH₂CH₃), 35.9 (C-3), 44.2 (-NCH₂CH₃), 45.0 (C-3a), 50.5 (C-4), 51.3 (CH₃), 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 C₁₇H₁₉ClN₂O₂: C, 64.05; H, 6.01; N, 8.79; found: C, 63.88; H, 6.23; N, 8.94.

Ethyl (2*S*,3*aS*,10*bS*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b*-hexahydroindolo[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; ¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, *J* = 7.2 Hz, -NCH₂CH₃), 1.32 (3H, t, *J* = 6.8 Hz, -COOCH₂CH₃), 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 -NCH₂CH₃), 3.32 (1H, m, 1H -NCH₂CH₃), 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 -COOCH₂), 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); ¹³C NMR (100 MHz, CDCl₃): δ 13.8 (-NCH₂CH₃), 14.3 (-COOCH₂CH₃), 35.9 (C-3), 44.2 (-NCH₂CH₃), 45.0 (C-3a), 50.4 (C-4), 60.3 (COOCH₂CH₃), 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 C₁₈H₂₁ClN₂O₂: C, 64.96; H, 6.36; N, 8.42; found: C, 64.86; H, 6.53; N, 8.74.

Propyl (2*S*,3*aS*,10*bS*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b*-hexahydroindolo[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; ¹H NMR (400 MHz, CDCl₃): δ 0.99 (3H, t, *J* = 7.4 Hz, -COO(CH₂)₂CH₃), 1.21 (3H, t, *J* = 7.4 Hz, -NCH₂CH₃), 1.72 (2H, m, -COOCH₂CH₂CH₃), 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 -NCH₂CH₃), 3.30 (1H, m, 1H of -NCH₂CH₃), 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 -COOCH₂), 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); ¹³C NMR (100 MHz, CDCl₃): δ 10.4 (-COO(CH₂)₂CH₃), 13.8 (-NCH₂CH₃), 22.1 (-COOCH₂CH₂CH₃), 35.9 (C-3), 44.2 (-NCH₂CH₃), 45.0 (C-3a), 50.5 (C-4), 63.9 (C-2), 64.1 (C-10b), 66.3 (-COOCH₂CH₂CH₃), 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 C₁₉H₂₃ClN₂O₂: C, 65.79; H, 6.68; N, 8.08; found: C, 65.89; H, 6.43; N, 7.89.

Isopropyl (2*S*,3*aS*,10*bS*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b* hexahydroindolo[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; ¹H NMR (400 MHz, CDCl₃): δ 1.2 (3H, t, *J* = 7.2 Hz, -CH₂CH₃), 1.31 (3H, d, *J* = 2.4 Hz, CH₃ of isopropyl), 1.32 (3H, d, *J* = 2.4 Hz, CH₃ 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 -NCH₂CH₃), 3.37 (1H, m, 1H of -NCH₂CH₃), 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(CH₃)₂), 7.19 (3H, m, Ar-H), 7.59 (1H, dd, *J* = 7.8, 1.2 Hz, H-9); ¹³C NMR (100 MHz, CDCl₃): δ 13.5 (-NCH₂CH₃), 21.2 (Me of iso propyl), 35.9 (C-3), 44.6 (-NCH₂CH₃), 45.7 (C-3a), 50.7 (C-4), 64.1 (C-2), 64.2 (C-10b), 68.0 (-OCH(CH₃)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 C₁₉H₂₃ClN₂O₂: C, 65.79; H, 6.68; N, 8.08; found: C, 65.88; H, 6.73; N, 8.16.

Butyl (2*S*,3*aS*,10*bS*)-10-chloro-1-ethyl-1,2,3,3*a*,4,10*b*-hexahydroindolo[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; ¹H NMR (400 MHz, CDCl₃): δ 0.98 (3H, t, *J* = 7.6 Hz, -COO(CH₂)₃CH₃), 1.19 (3H, t, *J* = 7.8 Hz, -NCH₂CH₃), 1.42 (2H, sextet, *J* = 7.2 Hz, -COO(CH₂)₂CH₂CH₃), 1.68 (2H, quintet, *J* = 7.2 Hz, -COOCH₂CH₂CH₂CH₃), 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 -NCH₂CH₃), 3.32 (1H, m, 1H of -NCH₂CH₃), 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 -COOCH₂), 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); ¹³C NMR (100 MHz, CDCl₃): δ 10.4 (-COO(CH₂)₃CH₃), 13.8 (-NCH₂CH₃), 19.2 (-COO(CH₂)₂CH₂CH₃),



30.7 (–COOCH₂CH₂CH₂CH₃), 35.9 (C-3), 44.2 (–NCH₂CH₃), 45.0 (C-3a), 50.5 (C-4), 63.9 (C-2), 64.1 (C-10b), 66.8 (–COOCH₂–(CH₂)₂CH₃), 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 C₂₀H₂₅ClN₂O₂: 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, CDCl₃): 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, –COOCH₃), 3.84 (1H, m, H-3a), 4.06 (2H, m, –NCH₂Ph), 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); ¹³C NMR (100 MHz, CDCl₃): δ 35.8 (C-3), 45.4 (C-3a), 50.1 (C-4), 51.3 (–COOCH₃), 54.0 (–NCH₂Ph), 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 C₂₂H₂₁ClN₂O₂: 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, CDCl₃): δ 1.30 (3H, t, *J* = 7.2 Hz, –COOCH₂CH₃), 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, –NCH₂Ph), 4.2 (3H, m, 2H of –COOCH₂CH₃, 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); ¹³C NMR (100 MHz, CDCl₃): δ 14.4 (–COOCH₂CH₃), 35.8 (C-3), 45.4 (C-3a), 50.1 (C-4), 54.0 (–NCH₂Ph), 60.3 (–COOCH₂CH₃), 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 C₂₃H₂₃ClN₂O₂: 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, CDCl₃): δ 1.02 (3H, t, *J* = 7.4 Hz, –COO(CH₂)₂CH₃), 1.76 (2H, m, –COOCH₂CH₂CH₃), 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 –NCH₂Ph and 2H of –COOCH₂CH₂CH₃), 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); ¹³C NMR (100 MHz, CDCl₃): δ 10.4 (–COO(CH₂)₂CH₃), 22.1 (–COOCH₂CH₂CH₃), 35.8 (C-3), 45.4 (C-3a), 50.1 (C-4), 54.0 (–NCH₂Ph), 63.9 (C-10b), 64.4 (C-2), 66.7 (–COOCH₂CH₂CH₃), 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 C₂₄H₂₅ClN₂O₂: 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, CDCl₃): 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, –NCH₂Ph), 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(CH₃)₂), 7.25 (8H, m, Ar–H), 7.65 (1H, d, *J* = 7.8 Hz, H-9); ¹³C NMR (100 MHz, CDCl₃): δ 21.3 (–COOCH(CH₃)₂), 35.8 (C-3), 45.4 (C-3a), 50.2 (C-4), 54.0 (–NCH₂Ph), 63.8 (C-10b), 64.3 (C-2), 68.0 (–CH(CH₃)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 C₂₄H₂₅ClN₂O₂: 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, CDCl₃): δ 0.99 (3H, t, *J* = 7.8 Hz, –COO(CH₂)₃CH₃), 1.46 (2H, sextet, *J* = 7.6 Hz, –COO(CH₂)₂CH₂CH₃), 1.66 (2H, quintet, *J* = 6.8 Hz, –COOCH₂CH₂CH₂CH₃), 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, –NCH₂Ph), 4.17 (3H, m, 1H of H-4 and 2H of –COOCH₂CH₂CH₂CH₃), 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); ¹³C NMR (100 MHz, CDCl₃): δ 10.4 (–COO(CH₂)₃CH₃), 19.2 (–COO(CH₂)₂CH₂CH₃), 30.7 (–COOCH₂–CH₂CH₂CH₃), 35.8 (C-3), 45.4 (C-3a), 50.1 (C-4), 54.0 (–NCH₂Ph), 63.9 (C-10b), 64.4 (C-2), 66.7 (–COOCH₂CH₂CH₂CH₃), 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 C₂₅H₂₇ClN₂O₂: 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, CDCl₃): δ 2.24 (1H, m, H-3'), 2.40–2.62 (7H, m, 1H of H-3 and 6H of –CH₂–N–(CH₂)₂–), 3.12 (1H, m, 1H of CH₂–11), 3.52 (1H, m, 1H of CH₂–11), 3.70 (5H, m, 1H of H-3a, and 4H of –CH₂–O–CH₂–), 3.79 (3H, s, –COOCH₃), 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); ¹³C NMR (100 MHz, CDCl₃): δ 36.1 (C-3), 44.8 (C-3a), 46.4 (C-11), 50.3 (C-4), 51.3 (–COOCH₃), 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 C₂₁H₂₆ClN₃O₃: 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, CDCl₃): δ 1.32 (3H, t, *J* = 7.6 Hz, –COOCH₂CH₃), 2.23 (1H, m, H-3'), 2.38–2.63 (7H, m, 1H of H-3, and 6H of –CH₂–N–(CH₂)₂–), 3.13 (1H, m, 1H of CH₂–11), 3.51 (1H, m, 1H of



CH₂-11), 3.71 (5H, m, 1H of H-3a, and 4H of -CH₂-O-CH₂-), 3.97 (1H, dd, *J* = 10, 4.2 Hz, H-2), 4.07–4.15 (4H, m, 2H of -COOCH₂CH₃, 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); ¹³C NMR (100 MHz, CDCl₃): δ 14.4 (-COOCH₂CH₃), 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 (-COOCH₂CH₃), 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 C₂₂H₂₈ClN₃O₃: 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; ¹H NMR (400 MHz, CDCl₃): δ 1.01 (3H, t, *J* = 7.6 Hz, -COOCH₂CH₂CH₃), 1.74 (2H, m, -COOCH₂CH₂CH₃), 2.25 (1H, m, H-3'), 2.40–2.65 (7H, m, 1H of H-3, and 6H of -CH₂-N-(CH₂)₂-), 3.12 (1H, m, 1H of CH₂-11), 3.50 (1H, m, 1H of CH₂-11), 3.7 (5H, m, 1H of H-3a, and 4H of -CH₂-O-CH₂-), 3.97 (1H, dd, *J* = 10, 4.4 Hz, H-2), 4.15 (4H, m, 2H of -COOCH₂CH₂CH₃, 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); ¹³C NMR (100 MHz, CDCl₃): δ 10.4 (-COO(CH₂)₂CH₃), 22.1 (-COOCH₂CH₂CH₃), 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 (-COOCH₂), 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 C₂₃H₃₀ClN₃O₃: 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; ¹H NMR (400 MHz, CDCl₃): δ 1.32 (3H, d, *J* = 2.4 Hz, Me of -COOCH(CH₃)₂), 1.34 (3H, d, *J* = 2.4 Hz, Me of -COOCH(CH₃)₂), 2.24 (1H, m, H-3'), 2.40–2.66 (7H, m, 1H of H-3 and 6H of -CH₂-N-(CH₂)₂-), 3.12 (1H, m, 1H of CH₂-11), 3.51 (1H, m, 1H of CH₂-11), 3.71 (5H, m, 1H of H-3a and 4H of -CH₂-O-CH₂-), 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(CH₃)₂), 7.20 (3H, m, Ar-H), 7.59 (1H, d, *J* = 7.6 Hz, H-9); ¹³C NMR (100 MHz, CDCl₃): δ 21.3 (-COOCH(CH₃)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(CH₃)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 C₂₃H₃₀ClN₃O₃: 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; ¹H NMR (400 MHz, CDCl₃): δ 0.98 (3H, t, *J* = 8.0 Hz, -O(CH₂)₃CH₃), 1.44 (2H, sextet, *J* = 7.6 Hz, -COO(CH₂)₂CH₂CH₃), 1.67 (2H, quintet, *J* = 7.2 Hz, -OCH₂CH₂CH₂CH₃), 2.24 (1H, m, H-3'), 2.35–2.65 (7H, m, 1H of H-3 and 6H of -CH₂-N-(CH₂)₂-), 3.12

(1H, m, 1H of CH₂-11), 3.50 (1H, m, 1H of CH₂-11), 3.69 (5H, m, 1H of H-3a and 4H of -CH₂-O-CH₂-), 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 -COOCH₂- 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); ¹³C NMR (100 MHz, CDCl₃): δ 10.4 (-COO(CH₂)₃CH₃), 19.2 (-COO(CH₂)₂CH₂CH₃), 30.7 (-COOCH₂CH₂CH₂CH₃), 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 (-COOCH₂), 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 C₂₄H₃₂ClN₃O₃: 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; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₁H₁₉ClN₂: 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; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₁H₁₉ClN₂: 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; ¹H NMR (400 MHz, CDCl₃): 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, -OCH₃), 3.87 (3H, s, -OCH₃), 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₃H₂₃ClN₂O₂: C, 69.95; H, 5.87; N, 7.09; found: C, 69.81; H, 5.93; N, 7.02.

(4bS,5aS,12bS)-12-Chloro-2,3-dimethoxy-4b,5,5a,12b,14,15-hexahydro-6H-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, CDCl₃): 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 -OCH₃ and 1H of H-6), 3.88 (3H, s, -OCH₃), 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); ¹³C NMR (100 MHz, CDCl₃): 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 C₂₃H₂₃ClN₂O₂: C, 69.95; H, 5.87; N, 7.09; found: C, 69.91; H, 5.90; N, 7.04.

Acknowledgements

We sincerely express our thanks to Head, Department of Chemistry, Sardar Patel University, for providing necessary research facilities. One of the authors, TRS, specially thanks the UGC, New Delhi, India, for providing financial assistance under the UGC Scheme of RFSMS. We thank DST, New Delhi, in general, and the PURSE central facility for mass analysis (vide sanction letter DO. No. SR/59/Z-23/2010/43 dated 16th march 2011). J.M.P. thanks the EU Research Potential (FP7-REGPOT-2012-CT2012-31637-IMBRAIN), the European Regional Development Fund (FEDER), and the Spanish Instituto de Salud Carlos III (PI11/00840) for financial support. G.B.P. thanks Fundación CajaCanarias for a postgraduate grant.

Notes and references

- (a) F. Nakataubo, A. J. Cocuzza, D. E. Keeley and Y. Kishi, *J. Am. Chem. Soc.*, 1977, **99**, 4835–4836; (b) F. Nakatsubo, T. Fukuyama, A. J. Cocuzza and Y. Kishi, *J. Am. Chem. Soc.*, 1977, **99**, 8115–8116; (c) Y. J. Kishi, *Nat. Prod.*, 1979, **42**, 549–568; (d) L. Hao, Y. Pan, T. Wang, M. Lin, L. Chen and Z. P. Zhan, *Adv. Synth. Catal.*, 2010, **352**, 3215–3222; (e) S. E. Wolkenberg and D. L. Boger, *Chem. Rev.*, 2002, **102**, 2477–2496; (f) D. Crich and A. Banerjee, *Acc. Chem. Res.*, 2007, **40**, 151–161; (g) S. W. Pelletier, John Wiley & Sons, New York, 1988, vol. 6, pp. 1–74; (h) G. R. Allen, J. F. Poletto and M. J. Weiss, *J. Am. Chem. Soc.*, 1964, **86**, 3877–3878; (i) E. O. M. Orlemans, W. Verboom, M. W. Scheltinga, D. N. Reinhoudt, P. Lelieveld, H. H. Fiebig, B. R. Winterhalter, J. A. Double and M. C. Bibby, *J. Med. Chem.*, 1989, **32**, 1612–1620; (j) J. J. Vepsäläinen, S. Auriola, M. Tukiainen, N. Ropponen and J. C. Callaway, *Planta Med.*, 2005, **71**, 1053–1057; (k) U. Galm, M. H. Hager, S. G. Van Lanen, J. Ju, J. S. Thorson and B. Shen, *Chem. Rev.*, 2005, **105**, 739–758.
- (a) I. S. Marcos, R. F. Moro, I. Costales, P. Basabe and D. Díez, *Nat. Prod. Rep.*, 2013, **30**, 1509–1526; (b) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73–103; (c) X. Yu, X. Xie and S. M. Li, *Appl. Microbiol. Biotechnol.*, 2011, **92**, 737–748; (d) *Modern Alkaloids: Structure, Isolation, Synthesis, and Biology*, ed. F. Fattorusso and O. T. Scafati, Wiley-VCH, 2008; (e) *Marine Pharmacognosy: Trends and Applications*, ed. S. M. Kim, CRC Press, 2012.
- (a) S. T. Crooke and A. W. Prestayko, Academic Press, New York, 1981, vol. 3, p. 49; (b) S. Alcaro, F. Ortuso and R. S. Coleman, *J. Med. Chem.*, 2002, **45**, 861–870; (c) N. Zein, W. Solomon, K. L. Colson and D. R. Schroeder, *Biochemistry*, 1995, **34**, 11591–11597; (d) W. A. Remers and R. T. Dorr, in *In Alkaloids Chemical and Biological Perspectives*, ed. S. W. Pelletier, John Wiley & Sons, New York, 1988, vol. 6, pp. 1–74; (e) R. S. Coleman, C. H. Burk, A. Navarro, R. W. Brueggemeier and E. S. Diaz-Cruz, *Org. Lett.*, 2002, **4**, 3545–3548.
- (a) W. Verboom, D. N. Reinhoudt, B. H. M. Lammerink, E. O. M. Orlemans, F. C. J. M. Van Veggel and P. Lelieveld, *Anti-Cancer Drug Des.*, 1987, **2**, 271–277; (b) W. Verboom, E. O. M. Orlemans, M. W. Scheltinga, D. N. Reinhoudt, P. Lelieveld, H. H. Fiebig, B. R. Winterhalter, J. A. Double and M. C. Bibby, *J. Med. Chem.*, 1989, **32**, 1612–1620; (c) M. Maliepaard, N. J. de Mol, L. H. M. Janssen, J. C. Hoogvliet, W. van der Neut, W. Verboom and D. N. Reinhoudt, *J. Med. Chem.*, 1993, **36**, 2091–2097.
- (a) L. S. Fernandez, M. F. Jobling, K. T. Andrews and V. M. Avery, *Phytother. Res.*, 2008, **22**, 1409–1412; (b) D. H. Dethe, R. D. Erande and A. Ranjan, *J. Am. Chem. Soc.*, 2011, **133**, 2864–2867; (c) L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y. J. Feng, R. J. Quinn and V. M. Avery, *Org. Lett.*, 2009, **11**, 329–332; (d) L. S. Fernandez, M. L. Sykes, K. T. Andrews and V. M. Avery, *Int. J. Antimicrob. Agents*, 2010, **36**, 275–279; (e) R. Vallakati and J. A. May, *J. Am. Chem. Soc.*, 2012, **134**, 6936–6939; (f) R. M. Zeldin and F. D. Toste, *Chem. Sci.*, 2011, **2**, 1706–1709.
- (a) C. V. Suneel Kumar, V. G. Puranik and C. V. Ramana, *Chem. – Eur. J.*, 2012, **18**, 9601–9611; (b) Q. Yin and S. L. You, *Chem. Sci.*, 2011, **2**, 1344–1348; (c) P. Patel and C. V. Ramana, *Org. Biomol. Chem.*, 2011, **9**, 7327–7334; (d) A. Karadeolian and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2010, **49**, 1133–1135; (e) J. F. Liu, Z. Y. Jiang, R. R. Wang, Y. T. Zeng, J. J. Chen, X. M. Zhang and Y. B. Ma, *Org. Lett.*, 2007, **9**, 4127–4129; (f) A. Karadeolian and M. A. Kerr, *J. Org. Chem.*, 2010, **75**, 6830–6841; (g) X. Zhang, T. Mu, F. Zhan, L. Ma and G. Liang, *Angew. Chem., Int. Ed.*, 2011, **50**, 6164–6166.
- J. J. Vepsäläinen, S. Auriola, M. Tukiainen, N. Ropponen and J. C. Callaway, *Planta Med.*, 2005, **71**, 1053–1057.
- (a) A. R. Battersby, R. Binks and R. Huxtable, *Tetrahedron Lett.*, 1968, **9**, 6111–6115; (b) J. Lundstrom, in *The Alkaloids*, ed. A. Brossi, Academic, New York, NY, 1983, vol. 21, p. 312; (c) K. W. Bentley, *Nat. Prod. Rep.*, 2003, **20**, 342–365;



- (d) S. H. Chung, J. Yook, B. J. Min, J. Y. Lee, Y. S. Lee and C. Jin, *Arch. Pharmacol. Res.*, 2000, **23**, 353–359.
- 9 R. F. Wang, X. W. Yang, C. M. Ma, S. Q. Cai, J. J. Nong and Y. Shoyama, *Heterocycles*, 2004, **63**, 1443–1448.
- 10 L. Xiang, D. Xing, W. Wang, R. Wang, Y. Ding and L. Du, *Phytochemistry*, 2005, **66**, 2595–2601.
- 11 (a) X. J. Zhang, Y. B. Ji, Z. Y. Qu, J. Ch. Xia and L. Wang, *Chin. J. Microecol.*, 2002, **14**, 277–280; (b) K. Chan, M. W. Islam, M. Kamil, R. Radhakrishnan, M. N. M. Zakaria, M. Habibullah and A. Attas, *J. Ethnopharmacol.*, 2000, **73**, 445–451; (c) O. Parry, F. Okwuasaba and C. Ejike, *J. Ethnopharmacol.*, 1987, **19**, 247–253; (d) A. N. Rashed, F. U. Afifi and A. M. Disi, *J. Ethnopharmacol.*, 2003, **88**, 131–136.
- 12 Q. Zhang, G. Tu, Y. Zhao and T. Cheng, *Tetrahedron*, 2002, **58**, 6795–6798.
- 13 (a) S. Zhang, X. Zhao, W. Kao and J. Wang, *U.S. Pat.*, US 566604, 1997 (*Chem. Abstr.* 1997, **126**, P305533m); (b) P. Sonnet, P. Dallemagne, J. Guillon, C. Enguehard, S. Stiebing, J. Tanguy, R. Bureau, S. Rault, P. Auvray, S. Moslemi, P. Sourdain and G. E. Seralini, *Bioorg. Med. Chem.*, 2000, **8**, 945–955; (c) W. K. Anderson and R. H. Mach, *J. Heterocycl. Chem.*, 1990, **27**, 1025–1030.
- 14 (a) C. J. Fong, J. Addo, M. Dukat, C. Smith, N. A. Mitchell, K. Herrick-Davis, M. Teitler and R. A. Glennon, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 155–158; (b) M. Bos, F. Jenck, J. R. Martin, J. L. Moreau, V. Mutel, A. J. Sleight and U. Widmer, *Eur. J. Med. Chem.*, 1997, **32**, 253–261.
- 15 (a) R. Peters, P. Waldmeier and A. Joncour, *Org. Process Res. Dev.*, 2005, **9**, 508–512; (b) J. S. Shiue and J. M. Fang, *Chem. Commun.*, 1993, 1277–1278; (c) M. Ishikura, W. Ida and K. Yanada, *Tetrahedron*, 2006, **62**, 1015–1024.
- 16 (a) S. Caddick, K. Aboutayab, K. Jenkins and R. I. West, *J. Chem. Soc., Perkin Trans. 1*, 1996, 675–682; (b) M. L. Bennasar, T. Roca and F. Ferrando, *Org. Lett.*, 2004, **6**, 759–762; (c) S. F. Wang and C. P. Chuang, *Tetrahedron Lett.*, 1997, **38**, 7597–7598; (d) E. Z. Frederick and G. H. Patrick, *J. Org. Chem.*, 1993, **58**, 2168–2773.
- 17 K. Tsuboike, D. J. Guerin, S. M. Mennen and S. J. Miller, *Tetrahedron*, 2004, **60**, 7367–7374.
- 18 D. T. Richard, G. O. Stephane, A. R. Robert, J. J. G. Edward and J. R. Paul, *J. Am. Chem. Soc.*, 2000, **122**, 1215–1216.
- 19 (a) M. B. Egle, B. Gianluigi, L. R. Concetta, P. Daniele, P. Tullio, T. Alberto and Z. Gaetano, *J. Org. Chem.*, 2000, **65**, 8924–8932; (b) S. Kathiravan and R. Raghunathan, *Synlett*, 2010, 952–954.
- 20 (a) S. Majumder and P. J. Bhuyan, *Tetrahedron Lett.*, 2012, **53**, 762–764; (b) W. Zhang, Y. Lu and S. Geib, *Org. Lett.*, 2005, **7**, 2269–2272; (c) M. Ghandi, A. Taheri, A. H. Bozcheloei, A. Abbasi and R. Kia, *Tetrahedron*, 2012, **68**, 3641–3648; (d) M. Bakthadoss, N. Sivakumar, G. Sivakumar and G. Murugan, *Tetrahedron Lett.*, 2008, **49**, 820–823; (e) N. Sirisha and R. Raghunathan, *Tetrahedron Lett.*, 2010, **51**, 2515–2518; (f) S. Kathiravan, D. Vijayarajan and R. Raghunathan, *Tetrahedron Lett.*, 2010, **51**, 3065–3070; (g) E. M. Beccalli, G. Broggini, C. L. Rosa, D. Passarella, T. Pilati, A. Terraneo and G. Zecchi, *J. Org. Chem.*, 2000, **65**, 8924–8932; (h) N. J. Parmar, B. R. Pansuriya, H. A. Barad, R. Kant and V. K. Gupta, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4075–4079; (i) N. J. Parmar, B. R. Pansuriya, B. M. Labana, R. Kant and V. K. Gupta, *RSC Adv.*, 2013, **3**, 17527–17539.
- 21 (a) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765–2810; (b) M. Poornachandran and R. Raghunathan, *Tetrahedron Lett.*, 2005, **46**, 7197–7200; (c) S. Kathiravan and R. Raghunathan, *Synlett*, 2010, 952–954; (d) G. B. Jones, C. J. Moody, A. Padwa and J. M. Kassirb, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1721–1727; (e) *Stereochemistry of carbon compounds*, ed. E. L. Eliel, Tata McGraw-Hill Publishing Co. Ltd., New Delhi, 1975, reprint 2003, p. 274.
- 22 (a) J. M. Khurana and D. Magoo, *Tetrahedron Lett.*, 2009, **50**, 7300–7303; (b) D. Chaturvedi, *Curr. Org. Synth.*, 2011, **8**, 438–471; (c) J. R. Harjani, S. J. Nara and M. M. Salunkhe, *Tetrahedron Lett.*, 2002, **43**, 1127–1130; (d) V. V. Namboodiri and R. S. Varma, *Chem. Commun.*, 2002, 342–343; (e) R. Sheldon, *Chem. Commun.*, 2001, 2399–2407.
- 23 (a) I. Coldham, B. C. Dobson, A. I. Franklin and S. R. Fletcher, *Tetrahedron Lett.*, 2007, **48**, 873–875; (b) S. Kathiravan, D. Vijayarajan and R. Raghunathan, *Tetrahedron Lett.*, 2010, **51**, 3065–3070; (c) M. Bakthadoss, N. Sivakumar, G. Sivakumar and G. Murugan, *Tetrahedron Lett.*, 2008, **49**, 820–823; (d) S. Purushothaman, R. Prasanna, P. Niranjana, R. Raghunathan, S. Nagaraj and R. Rengasamy, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7288–7291.
- 24 (a) J. F. Dubreuil and J. P. Bazureau, *Tetrahedron Lett.*, 2000, **41**, 7351–7355; (b) C. P. Frizzo, D. P. Moreira and M. A. P. Martins, in *In Ionic Liquids Applications in Heterocyclic Synthesis, Ionic Liquids Applications and Perspectives*, ed. K. Alexander, InTech, 2011, ISBN 978-953-307-248-7, DOI: 10.5772/15343; (c) A. Hazra, Y. P. Bharitkar, A. Maity, S. Mondal and N. B. Mondal, *Tetrahedron Lett.*, 2013, **54**, 4339–4342.
- 25 (a) A. J. Speziale and E. G. Jaworski, *J. Org. Chem.*, 1960, **25**, 728–732; (b) J. L. Moore, S. M. Taylor and V. A. Soloshonok, *ARKIVOC*, 2005, 287–292.
- 26 V. J. Majo and P. T. Perumal, *J. Org. Chem.*, 1996, **61**, 6523–6525.
- 27 (a) S. Kanemasa, K. Sakamoto and O. Tsuge, *Bull. Chem Soc. Jpn.*, 1989, **62**, 1960; (b) A. F. Khlebnikov, M. S. Novikov, R. R. Kostikov and J. Kopl, *Russ. J. Org. Chem.*, 2005, **41**, 1341–1348.
- 28 P. O. Miranda, J. M. Padrón, J. I. Padrón, J. Villar and V. S. Martín, *ChemMedChem*, 2006, **1**, 323–329.

