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ARTICLE TYPE

Efficient synthesis of some new antiproliferative *N*-fused indoles and isoquinolines via 1,3-dipolar cycloaddition reaction in 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 *N*-fused indole/isoquinoline–heterocyclic framework as one of their integral structural units constitute an important class of bioprofiles, and have attracted interest of many in the research fields of medicines and pharmaceuticals.[1] Containing 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 interest of many chemists and biochemists.[7]

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

Finally, the pyrrolizidine occurring 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 inhibition 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 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 the medicinal chemistry. Development and enlargement of a molecular library of these heterocycles is thus desirable and worth studying too.

<< Figure: 1 Some biologically active heterocycles containing pyrrolo-indole and pyrrolo-isoquinoline units >>

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 kind of this heterocycles. [19] The protocol is highly atom economic, and.used so far for many complex heterocyclic systems. It is witness of many aldehyde reacted with amino acid derivatives[20] to design 6-5 fused-ring systems. Indole-based substrates however remained

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with a very few in number in the protocol for designing of 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 synthesis of many pyran−heterocycles.[20-h] 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.[23-c] 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] Teterahydroisoquinolines **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 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) K_2CO_3, allyl bromide, DMF, 10 – 12 h, room temp. >>

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, 6), in 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 under solvent−free environment at 100 ℃. 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 ℃ that were improved further at 100 ℃ (entry 9). Above 100 ℃, however no further improvement was seen. This improved method was then generalised to receive other products, too (Scheme 2, Table 2). Advantage of the present protocol is that it takes relatively less reaction times (3 h) than others[24c]. It should be noted further that the present combination allows pyrrolizidine as highly significant, bioactive unit to incorporate effectively into *N*-fused indole/isoquinoline heterocycles.

<< Table 1: Optimization of conditions of the reaction between amine 3a and aldehyde 1>>

<<**Scheme 2**: Synthesis of all newly pyrrolo-fused-indoles and isoquinolines (1) TEAA, 100 ^oC>>

<<**Table 2:** Synthesis of all newly pyrrolo-fused-indoles and isoquinolines >>

A plausible mechanism of the reaction has been depicted in Scheme 3. Addition of electron from the tethered-alkene terminal carbon on imine follows the addition of the enolized ester on the other end of the alkene *via* semi bicyclic transition state that may force 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 3:** A plausible mechanism of the reaction between aldehyde **1** and secondary amine *via* 1,3-dipolar cycloaddition reaction >>

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 **7a** showed a multiplet in the region δ 2.93–4.09 ppm, due to diastereotopic methylene protons of the pyrrolidine ring. In **7a**, instead *N*-methyl proton appeared as a singlet at δ ~2.75 ppm. The carbonyl group in **7-10** showed a characteristic IR band at ~1730 cm^{-1}, and a ^{13}C NMR signal ~δ 173 ppm. In all compounds, a doublet in the δ 4.00–4.80 ppm range, with *J* value in the 7.6–8.4 Hz range, can be attributed to a bridge-head proton **10b** or **12b,** suggestive of the *cis*-fusion between central pyrrolidine rings. Another bridge-head proton **3a** or **5a** appeared as a multiplet at δ ~3.80 ppm is therefore orientated *cis* to this **10b** or **12 b** 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), the 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,** appeared at δ 4.00–4.40 ppm, except in 11'a-b. In 11'a-b, it is c*is* oriented.

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

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

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

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

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 more potent drug. Analyzing results in terms of maximum how many bacterium species a compound can kill effectively, it revealed the compound can cover a maximum five species at least with the potency equivalent to **ampicillin.** Examples include **7c**, **9c**, **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 to 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 had good results against *Bacillus subtilis* and *Salmonella typhi* bacteria respectively. It is noted that both **ciprofloxacin** and compound **7d** recorded similar MIC value 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.

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 (mmo/100 gm), indicating that they are moderate in **anti-oxidant** power. However, compound **10b** revealed remarkable activity.

<< **Table 3:** Antimicrobial, antitubercular and antioxidant activities test result. >>

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 4:** Antiproliferative activity (GI_{50}) against human solid tumor cells. >>

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 with resembling Chloramphenicol in activity with MIC 62.5 μg/L. Antiproliferative activity of **11b**, on the other hand, found excellent against all cell lines, with GI_{50} values laying in the 9.5–18 μM range, comparable with standard drugs used. Besides, **10b**, with FRAP value of 225 (mmol/100 gm), 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 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 Shimadzu LCMS-2010 spectrometer. Elemental analysis (% C, H, N) was carried out by 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 ℃ and completion of the reaction was confirmed through the 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 diethyl ether portions. It yielded crude products in quantitative amounts on 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. The TEAA was recovered quantitatively by heating the aqueous layer–left after the ether extraction of product–under the reduced presser at 80 ℃. The recovered ionic liquid can be used again for the same. It was noticed that TEAA can be recycled at least four-time with its unaltered efficiency.

Spectroscopy data of compounds (7-11)

Methyl (2S,3aS,10bS)-10-chloro-1-methyl-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4]pyrrolo[1,2-a]indole-2-carboxylate (7a). yield 82%, mp 118-120 ℃, 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 = 5.8Hz, 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 (2S,3aS,10bS)-10-chloro-1-methyl-1,2,3,3a,4,10b hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate(7b). yield 82%, mp 102-104℃, 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 (2S,3aS,10bS)-10-chloro-1-methyl-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate(7c). yield 77%, mp 106-108℃, 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, -$COOCH_2CH_2\underline{CH_3}$), 1.75(2H, m, -$COOCH_2\underline{CH_2}CH_3$), 2.19(1H, m, H-3'), 2.42(1H, ddd, J = 13.8, 8.2, 5.4 Hz, H-3), 2.74(3H, s, -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 -$COO\underline{CH_2}CH_2CH_3$, 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 (2S,3aS,10bS)-10-chloro-1-methyl-1,2,3,3a,4,10b-hexahydropyrrolo [2',3':3,4]pyrrolo[1,2-a]indole-2-carboxylate(7d). yield 84%, mp 107-109℃; 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 = 5.8Hz, 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 (2S,3aS,10bS)-10-chloro-1-methyl-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate(7e). yield 77%, mp 92-94℃, 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 (2S,3aS,10bS)-10-chloro-1-ethyl-1,2,3,3a,4,10b-hexahydropyrrolo [2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate(8a); yield 85%, mp 84-86℃, 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 = 8Hz, 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 (2S,3aS,10bS)-10-chloro-1-ethyl-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate(8b); yield 82%, mp 92-94℃, 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 (2S,3aS,10bS)-10-chloro-1-ethyl-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate(8c); yield 84%, mp 64-66℃, 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 (2S,3aS,10bS)-10-chloro-1-ethyl-1,2,3,3a,4,10b hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate (8d); yield 78%, mp 62-63℃, IR (νmax, 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 (2S,3aS,10bS)-10-chloro-1-ethyl-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate (8e); yield 89%, mp 60-62℃, 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 (2S,3aS,10bS)-1-benzyl-10-chloro-1,2,3,3a,4,10b-hexahydropyrrolo [2',3':3,4]pyrrolo[1,2-a]indole-2-carboxylate (9a); yield 80%, mp 154-156℃, IR (ν_{max}, cm^{-1}): 3055, 2980, 1723, 1581, 1455, 1369, 1195, 1028, 739, 705, 598; ^{1}H 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 (2S,3aS,10bS)-1-benzyl-10-chloro-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate(9b); yield 82%, mp 124-125℃, IR (ν_{max}, cm^{-1}): 3053, 2982, 1720, 1582, 1455, 1371, 1194, 1027, 739, 700, 599; ^{1}H 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 (2S,3aS,10bS)-1-benzyl-10-chloro-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate (9c); yield 78%, mp 126-128℃, IR (νmax, cm^{-1}): 3054, 2981, 1725, 1582, 1457, 1369, 1196, 1029, 738, 702, 601; ^{1}H 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 (2S,3aS,10bS)-1-benzyl-10-chloro-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate (9d); yield 76%, mp 132-134℃, IR (ν_{max}, cm^{-1}): 3055, 2984, 1719, 1579, 1458, 1369, 1192, 1028, 740, 702, 602; ^{1}H 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 (2S,3aS,10bS)-1-benzyl-10-chloro-1,2,3,3a,4,10b-hexahydropyrrolo[2',3':3,4] pyrrolo[1,2-a]indole-2-carboxylate (9e); yield 74%, mp 96-98℃, IR (ν_{max}, cm^{-1}): 3052, 2981, 1722, 1584, 1453, 1372, 1194, 1028, 741, 702, 597; ^{1}H 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(-$COOCH_2CH_2CH_2CH_3$), 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 (2S,3aS,10bS)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3a,4,10b-hexahydro pyrrolo[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; ^{1}H 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 (2S,3aS,10bS)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3a,4,10b-hexahydro pyrrolo[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; ^{1}H 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 (2S,3aS,10bS)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3a,4,10b-hexahydro pyrrolo[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 (2S,3aS,10bS)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3a,4,10b-hexahydro pyrrolo[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 (2S,3aS,10bS)-10-chloro-1-(2-morpholin-4-ylethyl)-1,2,3,3a,4,10b-hexahydro pyrrolo[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(-$COO(CH2)_2CH_2CH_3$), 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.

(4bR, 5aS, 12bS)-12-chloro-4b,5,5a,12b,14,15-hexahydro-6H-benzo[5',6']pyrrolizino [2',1':4,5]pyrrolo[2,1-a]isoquinoline(11a); yield 45%, mp 118-120℃, 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.

(4bS, 5aS, 12bS)-12-chloro-4b,5,5a,12b,14,15-hexahydro-6H-benzo[5',6']pyrrolizino [2',1':4,5]pyrrolo[2,1-a]isoquinoline(11'a). yield 37%, mp 152-154℃ 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.

(4bR, 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(11b); yield 46%, mp 162-164℃ 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.

(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℃ IR (ν_{max}, cm^{-1}): 3002, 2935, 2818, 1608, 1518, 1454, 1325, 1218, 1012, 748, 672; ^{1}H 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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Notes and references

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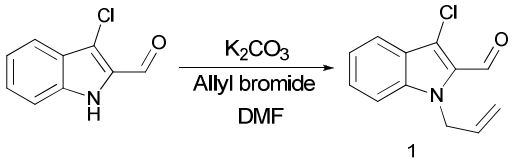
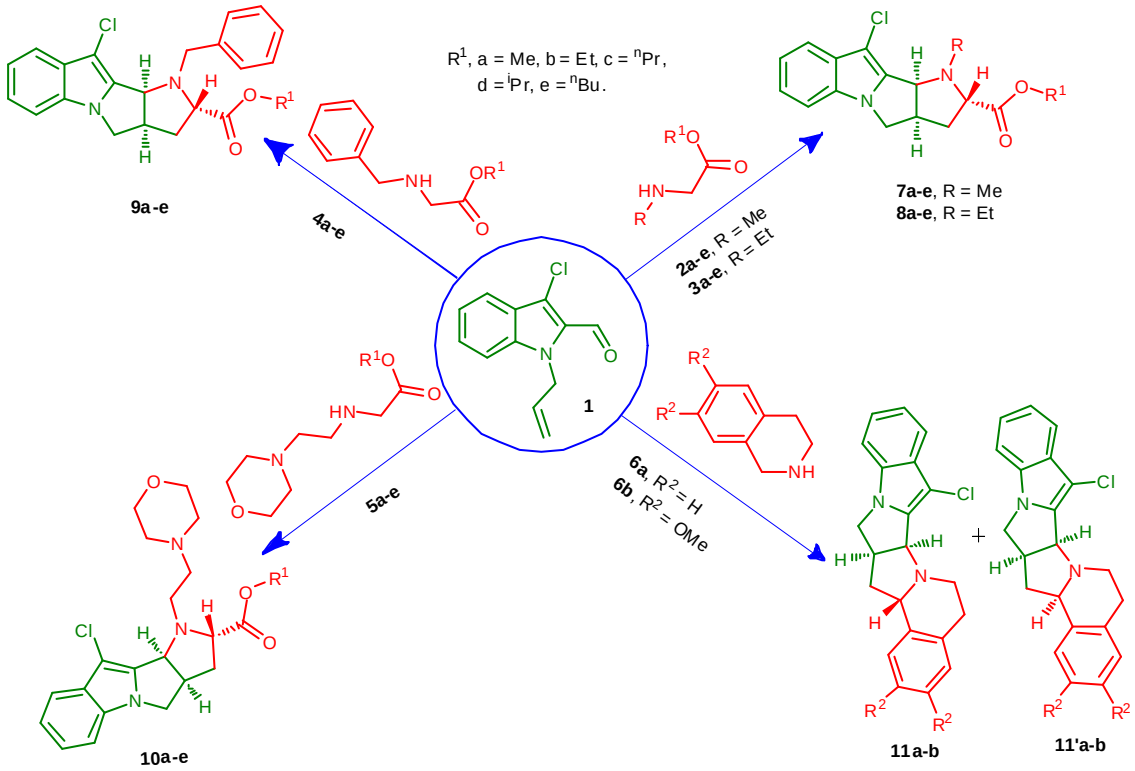
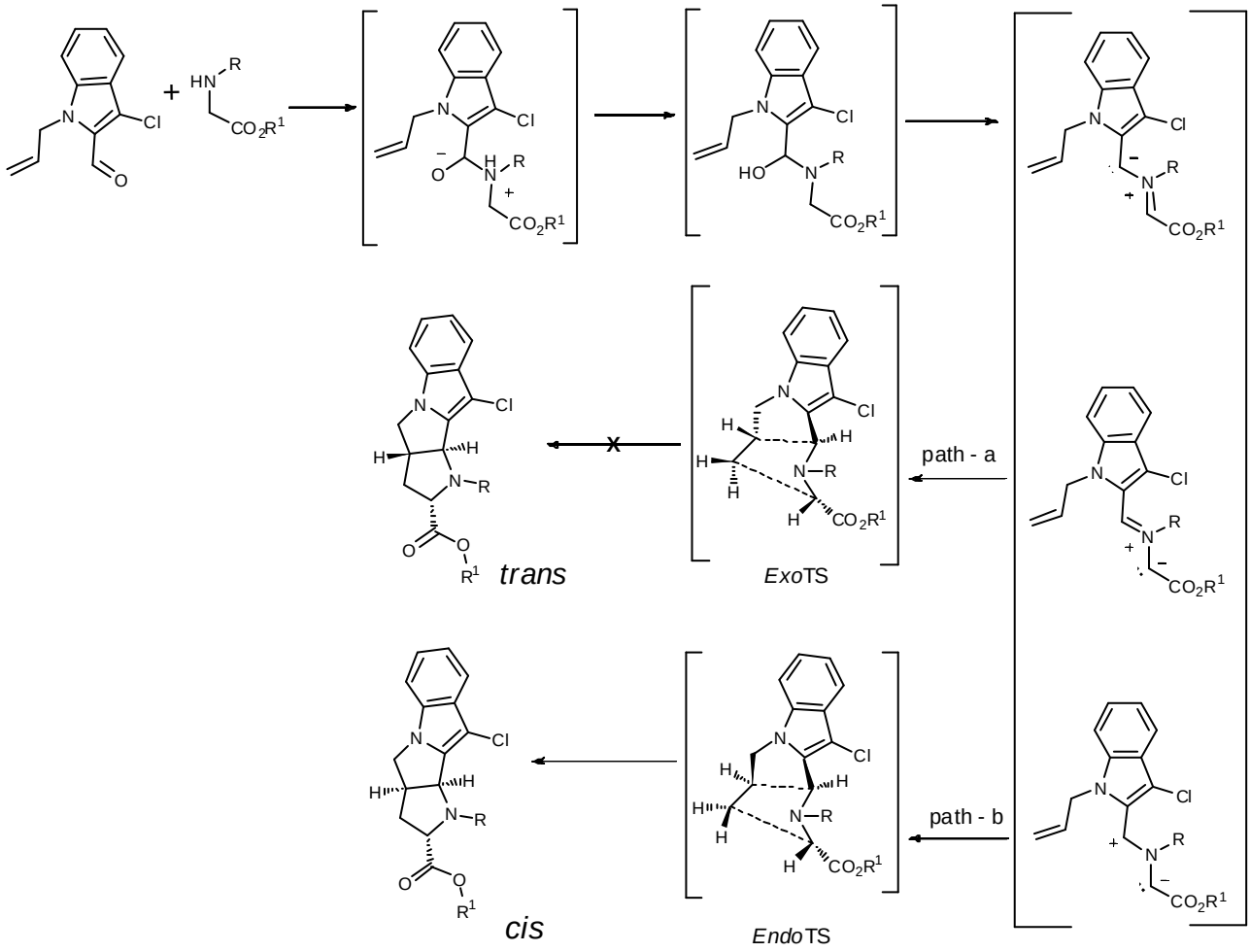


Scheme 1: Synthesis of N-allyl-3-chloro–indole-2-carbaldehyde **1**, The reagents and conditions (1) K_2CO_3, allyl bromide, DMF, 10 – 12 h, room temp.



Scheme 2: Synthesis of all newly pyrrolo-fused indoles and isoquinolines (1) TEAA, 100 ºC



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

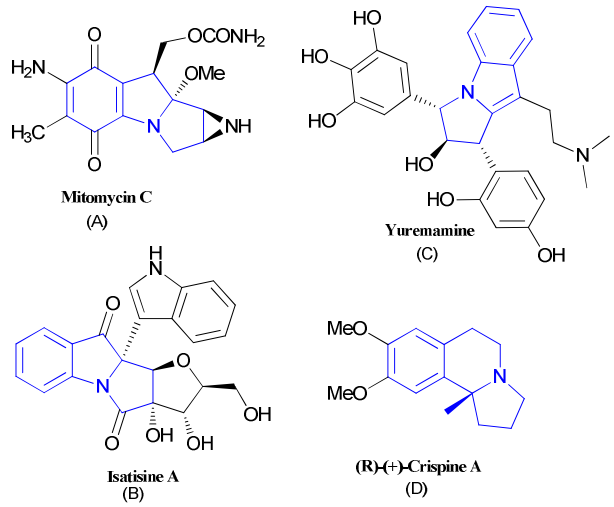


Figure 1. Some biologically active heterocycles containing pyrrolo-indole and pyrrolo-isoquinoline units

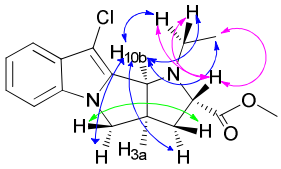


Figure 2.Characteristic NOESY interactions in **8a**.

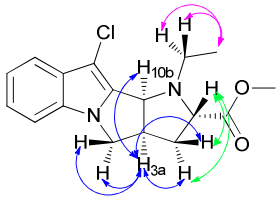
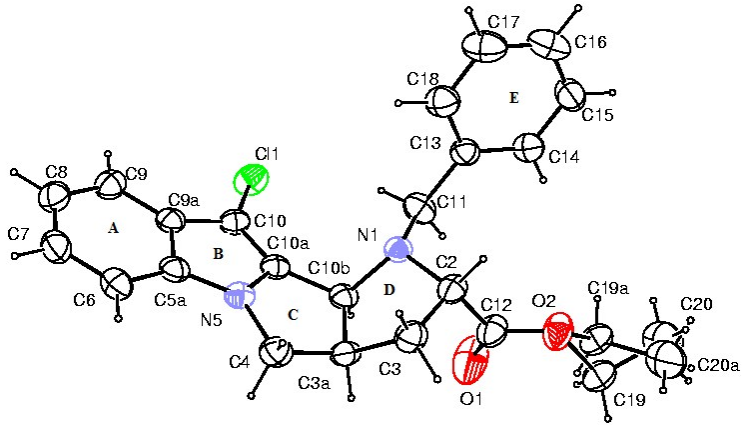


Figure 3. Characteristic COSY interactions in **8a**.



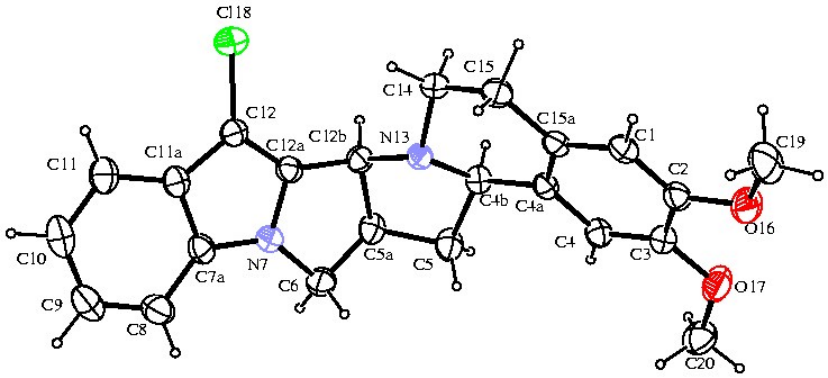


Figure 4. The ORTEP views of compounds **9b** and **11'b,** with displacement ellipsoids at the 40% probability level.

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

Entry	Solvent(reflux)	Catalyst	Temp(℃)	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

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	nPr	–	3.0	77
4	7d	Me	iPr	–	3.0	84
5	7e	Me	nBu	–	3.5	77
6	8a	Et	Me	–	2.5	85
7	8b	Et	Et	–	2.75	82
8	8c	Et	nPr	–	3.0	84
9	8d	Et	iPr	–	3.0	78
10	8e	Et	nBu	–	3.0	79
11	9a	Bn	Me	–	2.5	80
12	9b	Bn	Et	–	3.0	82
13	9c	Bn	nPr	–	3.0	78
14	9d	Bn	iPr	–	3.5	76
15	9e	Bn	nBu	–	3.5	74
16	10a	Mp	Me	–	3.0	76
17	10b	Mp	Et	–	3.0	78
18	10c	Mp	nPr	–	3.0	72
19	10d	Mp	iPr	–	3.5	74
20	10e	Mp	nBu	–	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

Table. 3 Antimicrobial, antitubercular and antioxidant activities test result.

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

Table. 4. Antiproliferative activity (GI_{50}) 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] Only was experiment was done