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Diverse synthesis of natural product inspired fused and spiro-heterocyclic scaffolds *via* ring distortion and ring construction strategy

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2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole, 1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one, Pictet-Spengler Lactamization, MCF7.

ABSTRACT. Several natural product inspired fused and spiro-heterocyclic scaffolds were prepared by ring distortion and ring construction strategies and evaluated for anti-breast cancer activity. A facile domino Pictet-Spengler lactamization (PSL) afforded nine natural product inspired indolo[2,3-a]quinolizidine and indolo[8, 7-b]indolizidine scaffolds which are converted to seven other scaffolds by functional group transformation, ring distortion and ring construction strategies. *In vitro* screenings of this library of sixteen scaffolds with six distinct architectures against MCF7 cell lines afforded two compounds (**10** and **21**) with modest activity. Principal component analysis of this library against databases of FDA approved drugs, commercial compounds and FDA approved breast cancer compounds indicated an eclectic mix of structures among the molecules.

Introduction

Conventional genetic approaches have been used to examine biological systems by generating random mutations which were then screened in search of a precise cellular phenotype.[1a and g] Analogous to the genetic approach, large random collections of small molecules can be screened to identify bioactive compounds which can elucidate the roles of specific proteins in many biological pathways. The crux of this "chemical genetic" approach is the design and synthesis of scaffold libraries with diverse architectures that span large tracts of biologically relevant chemical space.[1] The criticality of diverse architectures stems from the fact that small molecules interact superficially with biological macromolecules like protein, DNA and RNA.[2-3]

By virtue of binding to both their biosynthetic enzymes and their targets, natural products necessarily reside in biologically relevant chemical space[4] and in that sense natural product families are libraries of pre-validated, functionally diverse structures known to bear three

dimensional features that are desirable to make molecules active towards diverse biological targets.[5] They are rich in sp3 carbon content (i.e. three dimensional surface) and stereogenicity, which has been correlated with better clinical success of drug candidates.[6] However, the paucity of effective synthetic and scale-up strategies in accessing the natural products opened avenues for generating scaffolds inspired from natural products as suitable alternatives.[7] Hence, it is not surprising that the recent years have observed a stark rise in the development of synthetic strategies to access such scaffolds that could be used therapeutically to: (a) investigate and develop small molecules with better efficacy on known targets and (b) interrogate novel mode of action on previously unexploited targets.[8]

The indolo[2,3-a]quinolizidine, indolo[8, 7-b]indolizidine and 3,3′-pyrrolidinylspirooxoindole ring systems are of great interest since they elucidate the characteristic structural motifs of large family alkaloids with conspicuous and diverse biological activities including: (a) Hirsutine **1**, isolated from *Uncaria rhychnophylia* that inhibits neurotoxicity mediated by inflammation and microglial activation; (b) spirooxoindole MI-219 **2**, that binds to MDM2 with K_i = 5nM, with an oral bioavailability of 65% in rats and much better exposure in pharmacokinetics (PK) studies in rats; (c) (-)-Vincatine **3**, a member of *Aspidosperma* alkaloids, a complex natural product that is biologically active and encrusted with chiral centers and functional moieties which makes the system extremely challenging for synthesis; and (d) **4** containing the indolo[8, 7-b]indolizidino framework that exhibited high binding affinity and selectivity of CCK1 receptors and also acted as β-turn mimics (Figure 1).[9-13] Despite the synthetic challenge, individual syntheses of these natural products encompassed various chiral auxiliary mediated as well as catalytic enantioselective strategies.[14]

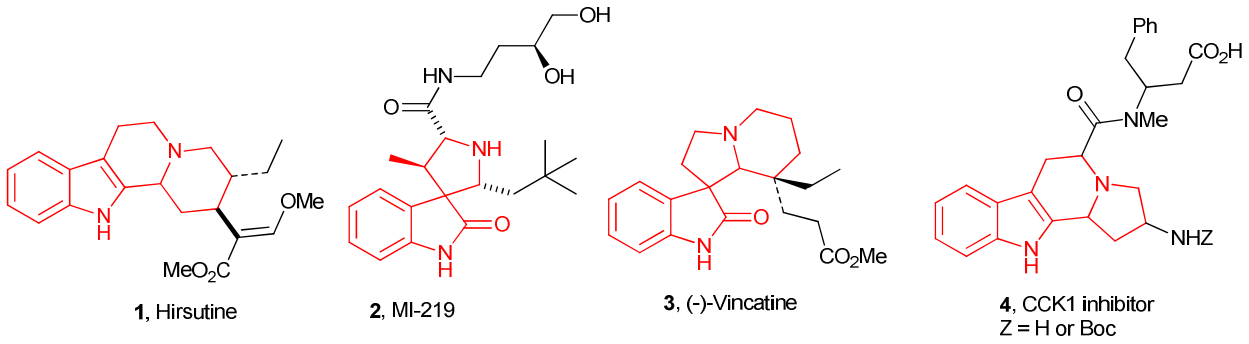
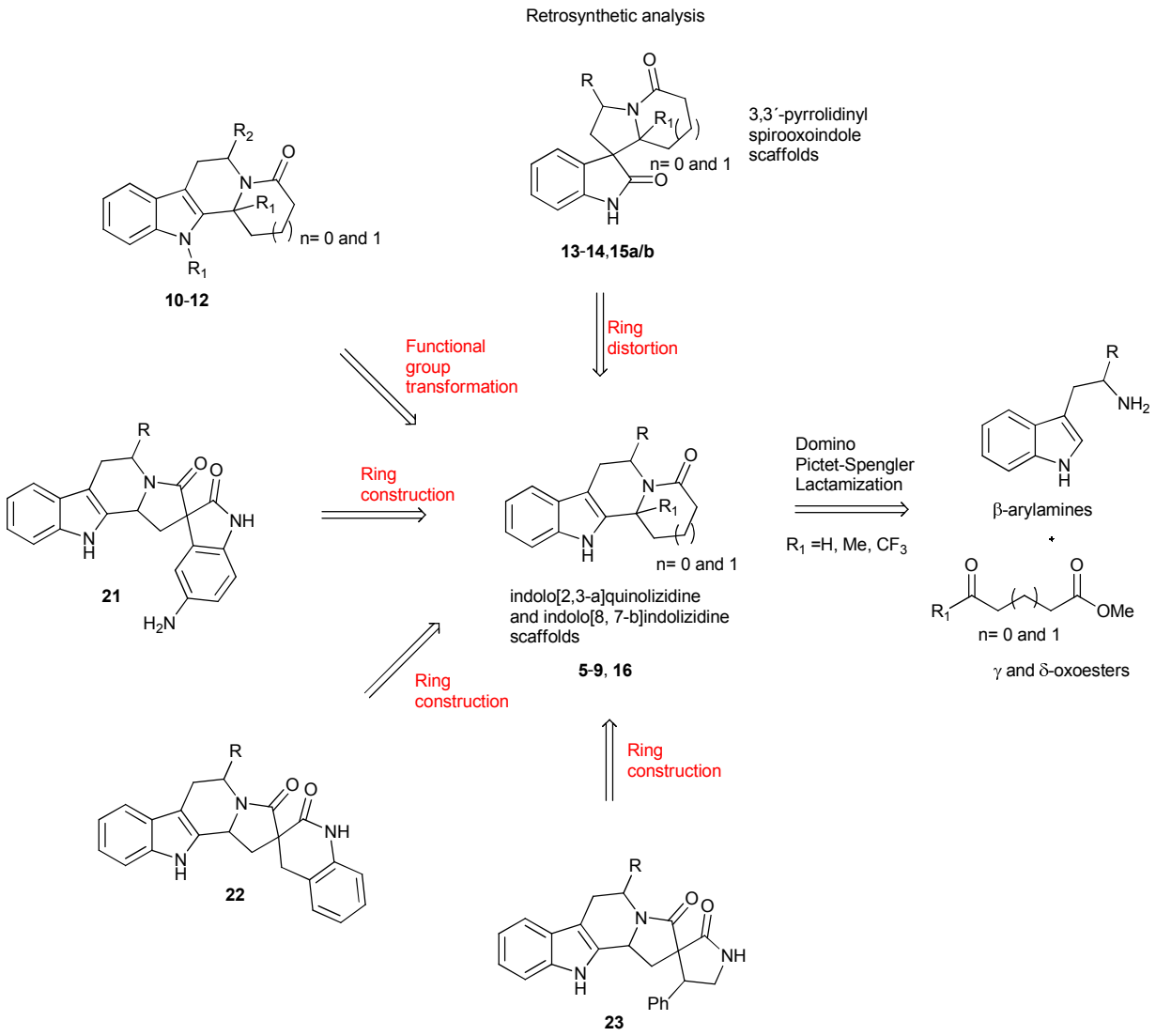


Figure 1. The natural products that influenced our scaffolds;

Here we describe a modular synthetic strategy involving domino Pictet-Spengler lactamization of β-aryl amines with γ- and δ-oxoesters to generate a library of indolo[2,3-a]quinolizidine and indolo[8, 7-b]indolizidine scaffolds (Scheme 1). Functional group transformation, ring distortion *via* oxidative ring contraction (to afford the 3, 3′-pyrrolidinyl oxoindoles) and ring construction *via* directed enolate-addition/substitution followed by a ring-closure onto the built-in scaffold electrophile, afforded carbocycles and spirocycles (Scheme 1). Cellular evaluation yielded 2 candidates that inhibit the proliferation of MCF7 cells moderately when compared with the reference drug etoposide. These compounds exhibited no cytotoxicity against the healthy COS-7 cells at similar concentration as that for MCF-7 cells. The diversity of the library was assessed *via* a principal component analysis (PCA) against FDA approved drugs, breast cancer drugs and a commercial compound database.



Scheme 1. The retrosynthetic analysis involving ring distortion, functional group transformation and ring construction strategy

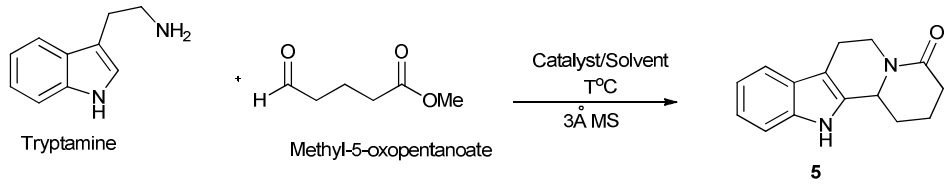
Results and discussion

Design and synthesis of various heterocyclic scaffolds

Tryptamine and methyl-5-oxopentanoate were chosen as the reaction partners to optimize the domino Pictet-Spengler lactamization reaction.[15a-c] The synthesis of such indolo[2,3-

a]quinolizidine and indolo[8, 7-b]indolizidine scaffolds were previously synthesized by Allin et al. *via* ring transformation reactions of bicyclic lactams.[15d-f] All the reactions were executed in presence of 3 Å molecular sieves (MS). Initially the reactions were carried out in toluene under reflux in presence of various acid catalysts (~10 mol %) to produce **5** (Table 1, entry 1-5). Under these conditions, trifluoroacetic acid (TFA) produced the best result (82% yield of **5**) (entry 5, Table 1). In a bid to further improve the efficiency of the reaction by lowering the catalyst concentration,

Table 1. Optimization of Domino Pictet-Spengler lactamization



Entry	Solvent	Temperature (T°C)	Conditions	Yield (%)[a]
1	Toluene	Reflux	Acetic Acid (10 mol%)	42
2	Toluene	Reflux	Polyphosphoric acid (10 mol%)	38
3	Toluene	Reflux	*p*-toluenesulfonic acid (10 mol%)	69
4	Toluene	Reflux	Methane sulfonic acid (10 mol%)	41
5	**Toluene**	**Reflux**	**Trifluoroacetic acid (10 mol%)**	**82**
6	Toluene	Reflux	Trifluoroacetic acid (1 mol%)	25
7	CH_3CN	-5→20°C	$TiCl_4$ (1 mol%)	-[b]
8	CH_3CN	-5→20°C	BF_3-Et_2O (1 mol%)	-[b]
9	CH_3CN	-5→20°C	$Sc(OTf)_3$ (1 mol%)	-[b]
10	CH_3CN	-5→20°C	$Yb(OTf)_3$ (1 mol%)	-[b]
11	CH_3CN	-5→20°C	$TiCl_4$ (1 mol%)/ 1eq. 2,6-lutidine)	56
12	CH_3CN	-5→20°C	BF_3-Et_2O (1 mol%/ 1eq. 2,6-lutidine)	59

13	CH_3CN	-5→20°C	$Sc(OTf)_3$ (1 mol%)/ 1eq. 2,6-lutidine	72
14	**CH_3CN**	**-5→20°C**	**$Yb(OTf)_3$ (1 mol%)/ 1eq. 2,6-lutidine**	**90**

[a] Isolated yields after column chromatography. [b] Isolated unreacted tryptamine

1 mol % of TFA (entry 6) proved disappointing, generating **5** in ~25% yield. Consequently the next set of procedures were applied using diverse Lewis acid catalysts *viz.* titanium chloride ($TiCl_4$), boron trifluoride-diethyl ether ($BF_3.OEt_2$), scandium triflate ($Sc(OTf)_3$) and ytterbium triflate ($Yb(OTf)_3$) at much milder reaction conditions than before (15→20°C) in acetonitrile (CH_3CN) (entry 7-10). Unfortunately none of these conditions could generate the desired product, but careful scrutiny of the literature prompted us to use one equivalent of 2, 6-lutidine as base in all the above reactions along with the catalysts (entry 11-14). To our utmost delight this subtle change of conditions generated the desired product **5** in 56-90% yield in all the reactions, with the best with $Yb(OTf)_3$ (entry 14).[16]

Applying the optimized procedure, several other scaffolds *viz*. **6**-**9** and **16** were synthesized with appropriate starting combos. **7** was synthesized from D-tryptophan methyl ester and methyl levulinate. **8** and **9** were synthesized from L-tryptophan methyl ester with methyl levulinate and methyl-5-oxopentanoate respectively (Figure 2). Tryptamine when reacted with methyl levulinate and methyl 5,5,5-trifluoro-4-oxopentanoate afforded scaffolds **6** and **16** respectively (Scheme 2). The average yields ranged from 49-84%. For the chiral scaffolds the diastereomeric ratio ranged from 60:40 to 88:12.

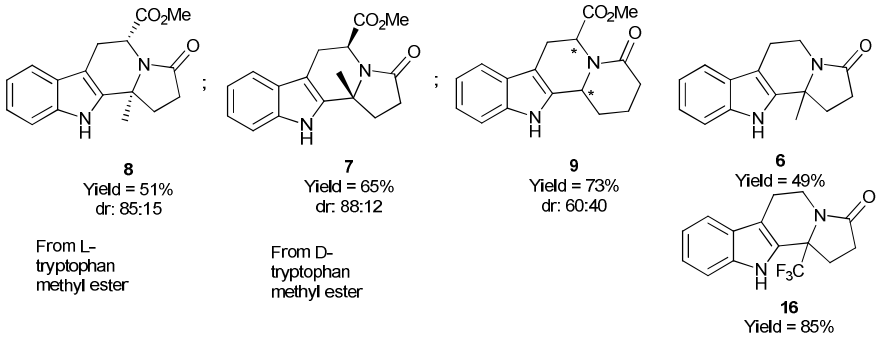
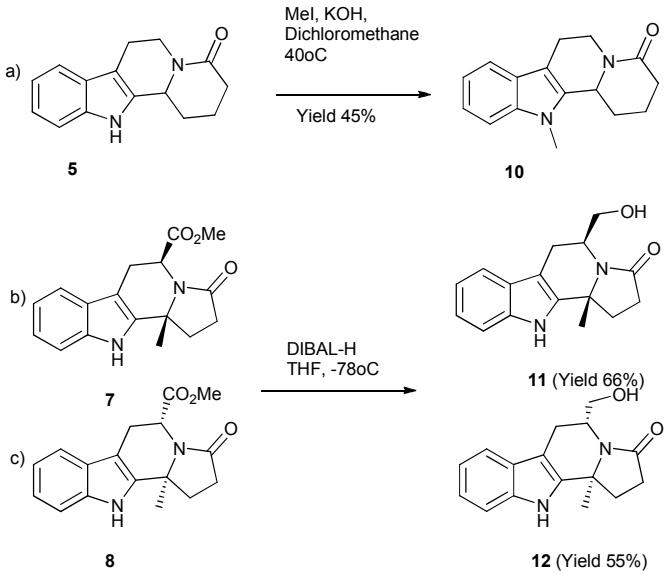


Figure 2. Synthesis of fused scaffolds

Compounds **5**, **7**-**8** were further derivatized *via N*-alkylation of the indole nitrogen and reduction of the ester functionality. Compound **10** was obtained in ~45% yield by methylating **5** at the indole nitrogen with methyl iodide (MeI) and dichloromethane (DCM) under reflux in presence of potassium hydroxide (KOH) (Scheme 2).

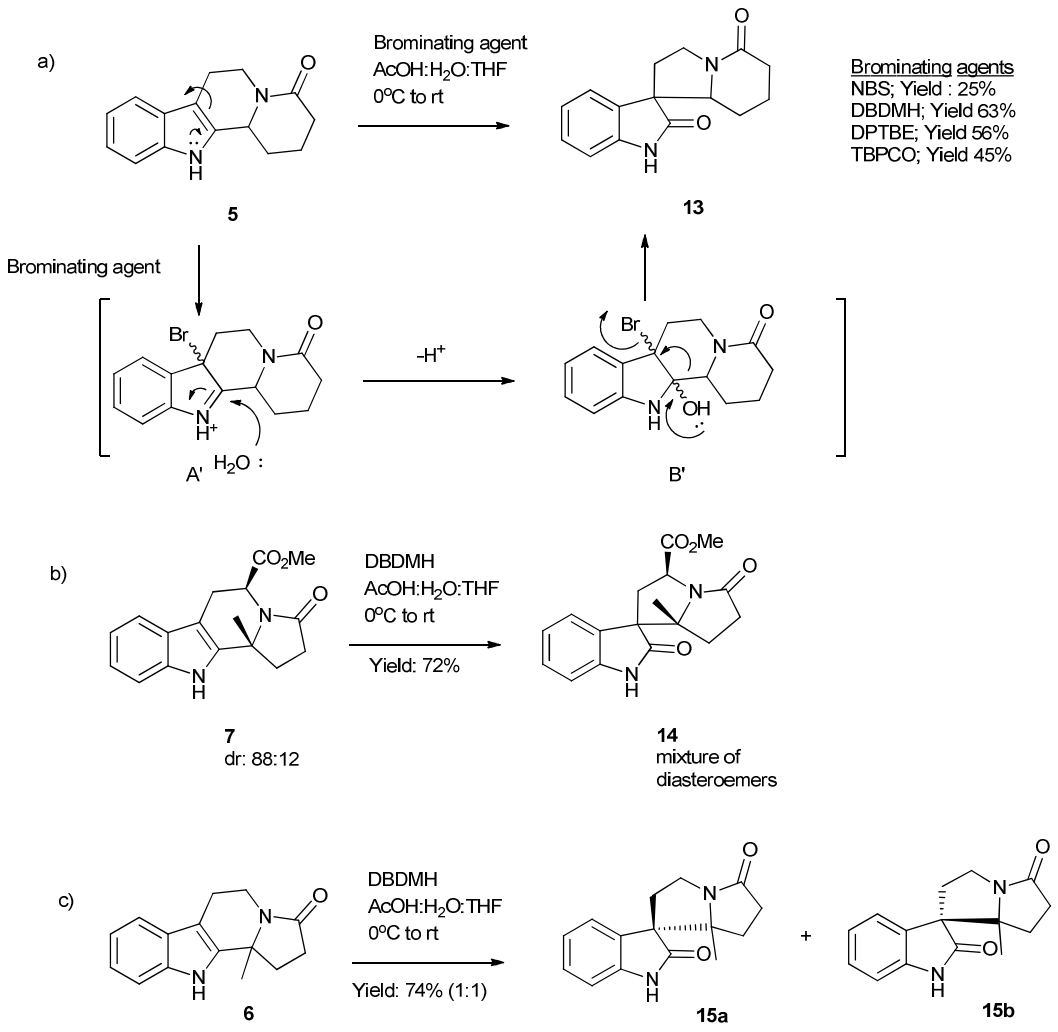


Scheme 2. Functionalization of scaffolds **5**, **7** and **8**

The ester moieties in compounds **7** and **8** were reduced with diisobutyl aluminum hydride (DIBAL-H) in THF at -78°C to their corresponding alcohols **11** and **12**. The major diastereomers of **11** and **12** were isolated by flash chromatography and their relative configurations were

determined by single crystal X-ray analysis (Figure 2a and b). This in turn also confirmed the relative configuration of the major diastereomers of **7** and **8** respectively.

Next, the ring distortion strategy was utilized by transforming the fused scaffolds to their spiro analogs *via* oxidative ring contraction. Observed first by Irikawa et al. in 1989 the reaction is believed to initiate *via* electrophilic bromination from NBS in presence of water, acetic acid and tetrahydrofuran as solvent, resulting in a bromo-hydroxy intermediate which undergoes ring



Scheme 3. Synthesis of spiro scaffolds

contraction to provide the spiral-motifs (Scheme 3).[17a] We optimized the protocol further by using a variety of electrophilic brominating agents scouted from the literature *viz*. DBDMH (1,3-dibromo-5,5-dimethylhydantoin), TBPCO (2,4,4,6-tetrabromo-3-*n*-pentadecyl-2,5-cyclohexadienone) and DPTBE (1,2-dipyridiniumditribromide-ethane).[17b-d] Starting from **5**, with DBDMH, we could improve the yields of the desired product **13** from 25→63% (Scheme 3). Hence **14** and racemic diastereomers **15a**/**b** were synthesized similarly from **7** and **6** (Scheme 3). The structure of **15a** and **b** were confirmed by the single crystal X-ray of **15a** (Figure 3c).

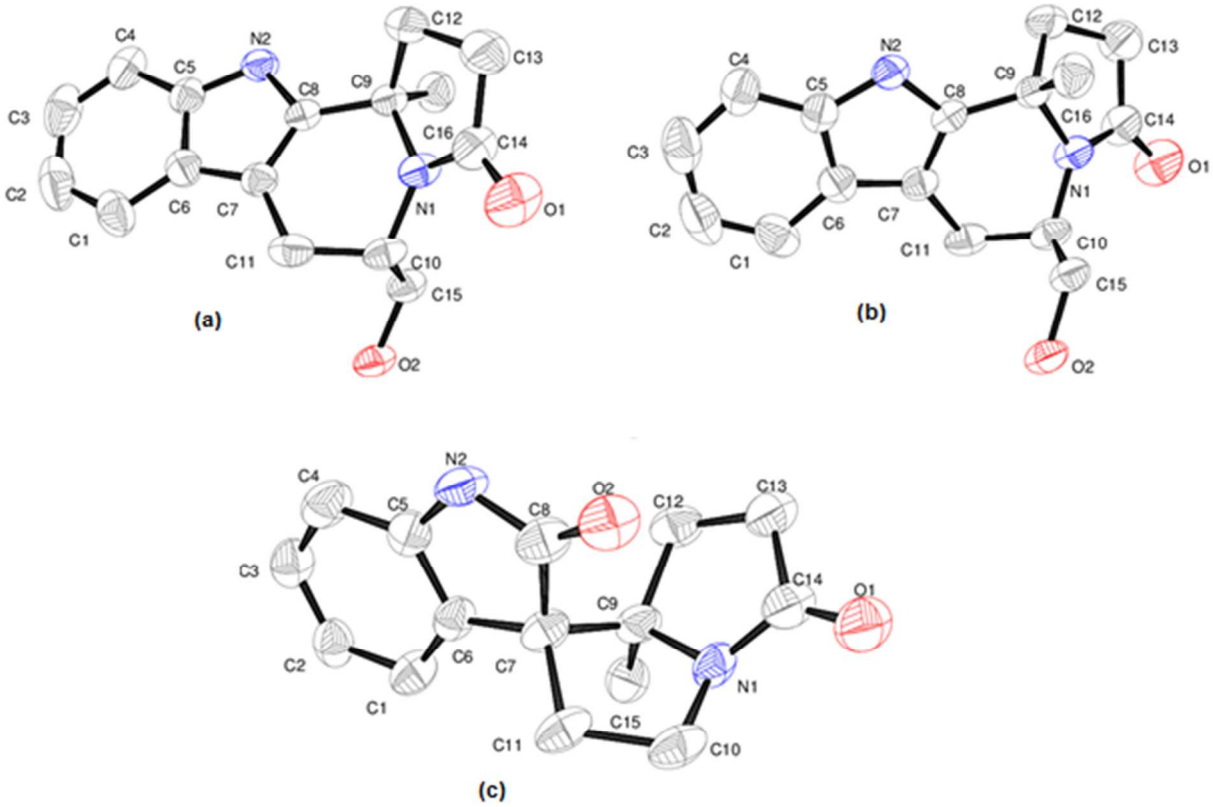
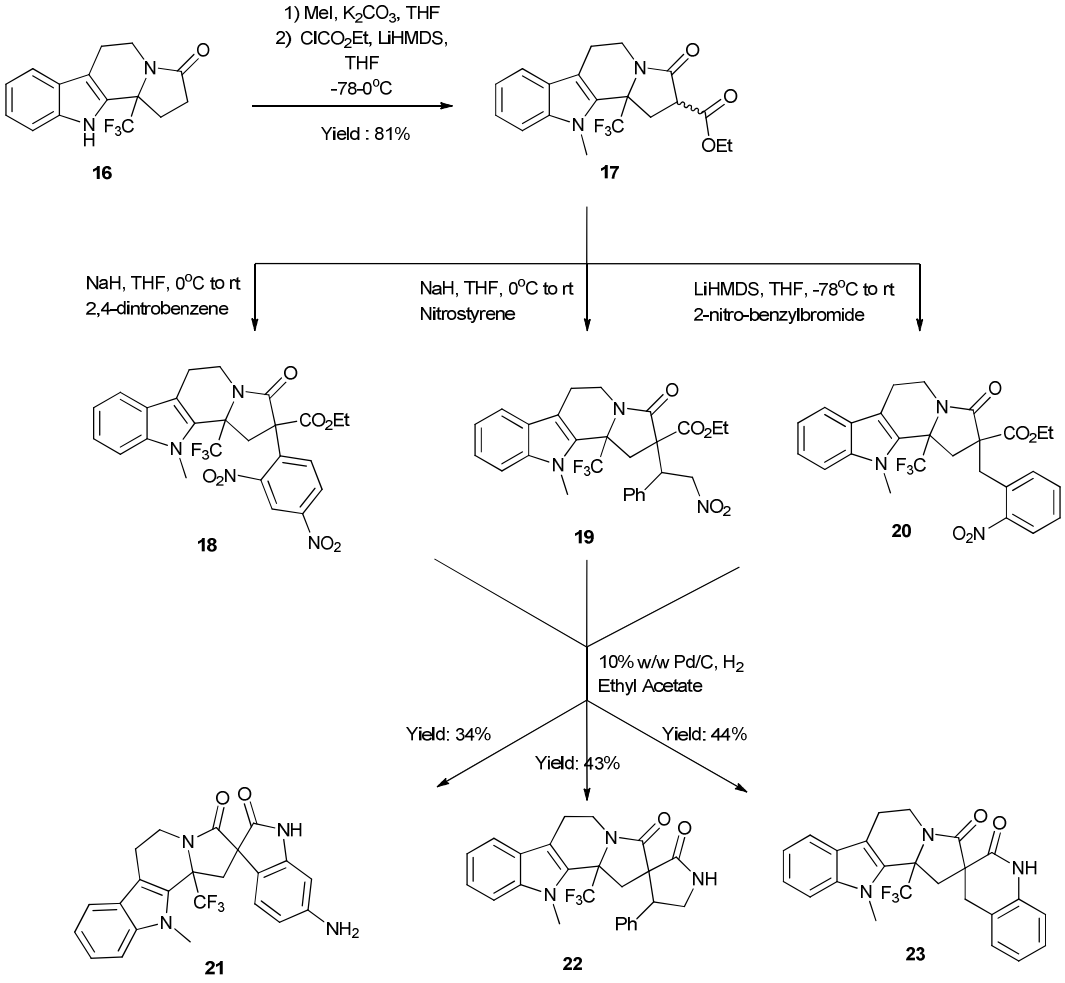


Figure 3. X-Ray crystal structures of (a) **11**; (b) **12**; (c) **15a.** ORTEP view along with the atom labels are shown at 50% probability level. H-atoms are omitted for clarity.

In a bid to diversify the 3D binding surface of racemic, **16** the next endeavor focused on constructing heterocyclic rings *viz.* indole, pyrrolidinone and pyrroloisoquinolinone at the carbon

adjacent to the amide carbonyl of **16** (Scheme 4). The diversification strategy involved methylation of indole nitrogen followed by acylation of **16** with ethyl chloroformate to afford **17**. The crude **17** underwent: (a) S_NAr reaction with 2, 4-dinitrofluorobenzene in presence of NaH, at 0°C in THF to generate **18**; (b) Michael addition with nitrostyrene to provide **19**; and finally (c) alkylation with *o*-nitrobenzyl bromide to generate **20**. The crude intermediates **18-20** were hydrogenated in presence of 10% Pd-C in hydrogen at atmospheric pressure that facilitated the synthesis of the final compounds **21-23** (which were purified by column chromatography) (Scheme 4).



Scheme 4. Diversification of **16** *via* ring construction strategy

Evaluation of anti-breast cancer activity

One of the purposes of this investigation was to develop methodology to generate compounds that have the potential to be biologically active. We accept the fact that it is an unrealistic expectation to generate potent molecules *via* synthetic efforts unbiased towards any particular biological target. However, we hoped that our scaffolds may provide hits that could be used for further elaboration into drug leads. Therefore we focused our attention on *in vitro* screening of our scaffold library against the proliferation of MCF-7 (Michigan Cancer Foundation-7), a breast cancer cell line employing the MTT, [3-(4, 5-dimethylthiazol-2-yi)-2, 5-diphenyltetrazolium bromide] assay, according to the method developed by Mosmann.[18] All the stock solutions of the test compounds were prepared in DMSO. MCF-7 cells were seeded in a 96 well microtitre plate and were allowed to adhere and stretch overnight. The grown cells were then treated with 50 μM compounds in 200 μL overall volume. After 24 hours of compound treatment, 10 μl of MTT (5mg/mL) was added to each well and subsequently the plate was incubated at 37°C in the dark for about 4 h. The reduction of MTT (rate of color developed) was quantified by measuring the absorbance at 570 nm in a spectrophotometer (Model: Spectra MAX Plus; Molecular Devices; supported by SOFTmax PRO-3.0). The assay was also carried out with etoposide, a well-known anti-breast cancer compound as positive control. Treatment with DMSO alone was taken as negative control. All the experiments were done in triplicate. It was gratifying to see that two scaffolds (**10** and **21**) showed 27-31% inhibition of cell proliferation of the MCF-7 cells compared to 42% by Etoposide (Table 2). Screening the most active compounds **10 and 21** in a 48h screen against the proliferation of MCF7 cells exhibited inhibition in the range of 35-40% (refer supplementary material). Cytotoxicity studies of **10** and **21** on non-carcinoma COS-7 cell

line *via* MTT assay at the same concentration used for screening i.e. 50 μM indicated no toxicity. (refer supplementary material).

Table 2. *In vitro* screening of the scaffolds

Entry	Compound Code	% inhibition[a]
1	**control**	-
2	**etoposide**	42.12
3	**5**	1.92
4	**10**	27.61
5	**13**	10.84
6	**7**	-16.11
7	**8**	-9.80
8	**14**	-8.25
9	**11**	4.92
10	**6**	12.44
11	**15a**	-3.45
12	**15b**	-4.86
13	**9**	-4.48
14	**16**	7.31
15	**12**	-3.16
16	**21**	33.45
17	**22**	12.07
18	**23**	-23.90

[a.] Experiments ran in triplicates

To computationally evaluate the structural diversity of our library, we executed principal component analysis (PCA) study of a set of various shape based and charge based molecular

surface descriptors for our library and three reference compound collections from one thousand five hundred and fifty FDA approved drugs, seven hundred and forty six Chembridge Screen compounds and twenty four FDA-approved breast cancer drugs. PCA utlizes definite medicinal chemistry descriptors to determine the overall chemical space. All the descriptors calculation and analysis was done in Molecular Operating environment software.

In Figure 4, the first two PCA components i.e PCA1 & PCA2 were plotted on X and Y axis. In this plot it was very clear that chemical space shared by FDA approved drugs and Chembridge Screen Compounds were very much similar. The well represented chemical space in the plot was covered by FDA approved compounds, Chembridge Screen Compounds, twenty three FDA approved breast cancer drugs and six (**14-15a/b**, **21-23**) of our library compounds. The fact that scaffold **21** tracts the chemical space similar to the breast cancer drugs, further corroborates our screening results (Table 2). Compounds **5-10** and **12** were lying in the underrepresented area where except few of FDA approved and Chembridge screening compounds only one of the breast cancer drugs were present. This indicated a diverse scaffold library, where two distinct regions in the chemical space were occupied by several scaffolds.

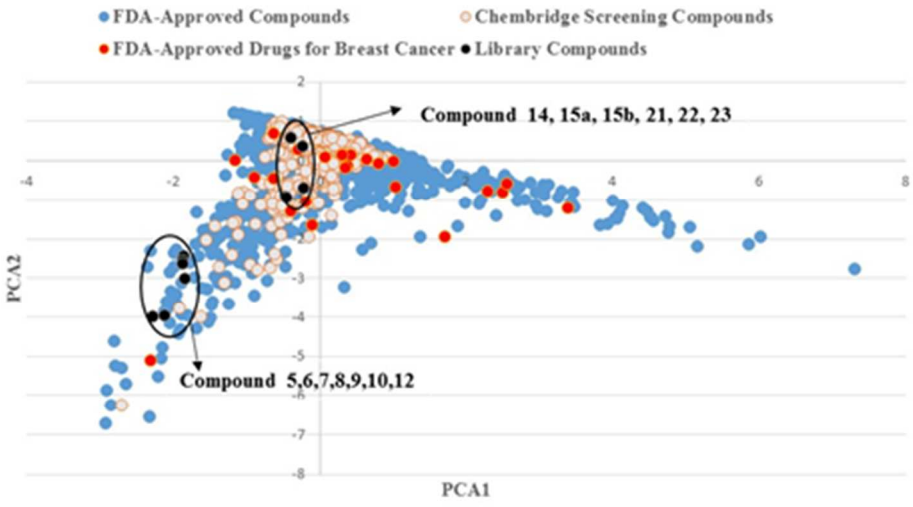
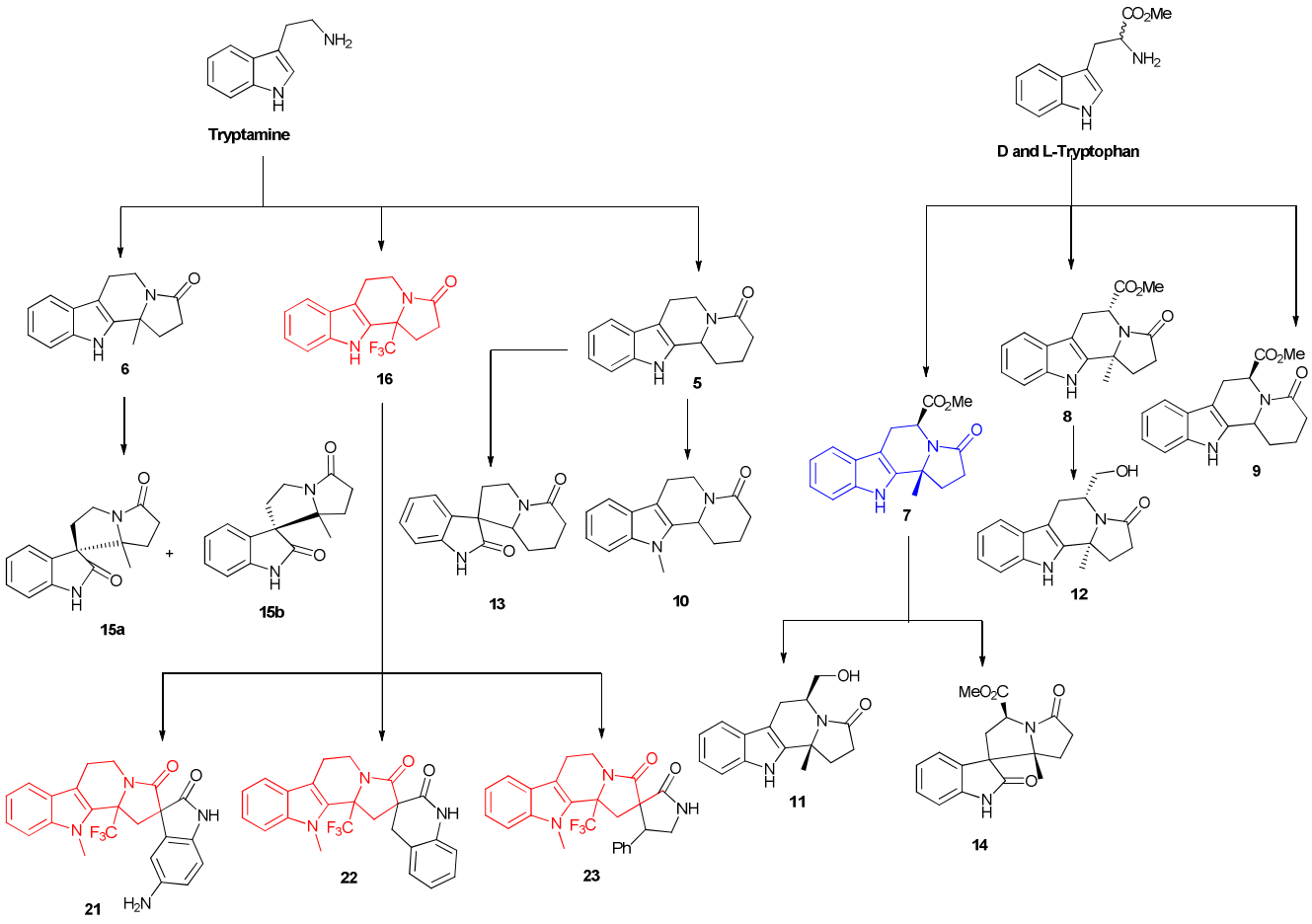


Figure 4. Sixteen library compounds (black), one thousand five hundred and fifty five FDA approved drugs (blue), seven hundred and forty six Chembridge Screening compounds (orange) and FDA approved breast cancer drugs were used for the PCA analyses

Conclusion

Here in we have demonstrated a diverse synthesis of a library of scaffolds (**5**-**16** and **21**-**23**) using domino Pictet Spengler Lactamization (PSL) reaction, followed by various ring distortion, construction and functional group transformations (Scheme 5). During this we have developed a novel condition based on catalytic (1 mol %) ytterbium triflate for the domino Pictet Spengler lactamization. We also revisited an oxidative ring contraction protocol to generate new spiro scaffolds and improved the protocol by doubling the yield *via* commercially available brominating reagent DBDMH. Beginning from simple starting materials like tryptamine and D/L-tryptophan, this synthetic strategy with steps/scaffold ratio of 1 is extremely efficient in building the scaffold library. *In vitro* screening against the proliferation of MCF-7 cells identified two scaffolds with moderate activity that could be refined into better molecules through structure activity relationship studies (SAR). Finally diversity assessment of this library through PCA analysis indicated an eclectic mix of scaffolds that also tracts new area of chemical space.



Scheme 5. The complete library of scaffolds (**5-16** and **21-23**) developed from simple starting materials viz. Tryptamine and D/L-Tryptophan.

EXPERIMENTAL

Chemistry

General Methods. Unless otherwise noted, all reactions were carried out in flame-dried glassware under a static nitrogen atmosphere in anhydrous solvent. All reagents were obtained from commercially available sources and used without purification. ^{1}H and ^{13}C spectra were recorded using Varian 300/400 and JEOL JNM-ECX500 MHz, using $CDCl_3$ and DMSO-D_6 as a

solvents. The chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (δ 0.00 ppm for proton NMR and δ 77.0 ppm for carbon NMR) and DMSO-D_6 (δ 2.50 ppm for proton NMR and δ 39.50 ppm for carbon NMR). Coupling constants are reported in hertz (Hz). The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS spectra acquired via Reverse-phase 6540 UHD Accurate-Mass Q-Tof LCMS, Agilent Technologies (Milford, MA). It is to be noted that the several crystallization experiments with various solvents and at different conditions always resulted in poor quality crystals of compound **15a**. As a result the refined structure of **15a** as reported here is with relatively high R-factor. However, it certainly confirms the correct geometry and proper conformation of the molecule.

General Procedure for the synthesis of indolo[2,3-a]quinolizidine and indolo[8, 7-b]indolizidine scaffolds (**5-9** and **16**)

Appropriate β-aryl amines (0.5 mmol, 1 equiv) and δ or γ-oxo esters (0.5 mmol, 1 equiv) were dissolved in CH_3CN (22 mL) and activated 3 Å molecular sieves were added to the resulting solution. Next 2,6-lutidine (0.07 ml, 0.5 mmol) and $Yb(OTf)_3$ (5 mg, 0.005 mmol) were added and the resulting mixture was then stirred under argon at an ambient temperature of 15-20°C for 10-16h. Once thin layer chromatography (TLC) confirms the complete consumption of the starting materials, the reaction was cooled to room temperature (rt), quenched with water and was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate (Na_2SO_4) and was evaporated to obtain the desired crude compounds as yellow to colorless solids. The crude solids were purified by flash column chromatography (FCC) using ethyl acetate-hexane as the mobile phase, to provide the final compounds as solid or semi solid,

which were characterized by ^{1}H-NMR, ^{13}C-NMR and QTof-HRMS. Single crystal X-ray structures were obtained for few of them.

1, 2, 3, 6, 7, 12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one (**5**). Yield: 97 mg, 81%; colorless solid. ^{1}H NMR (400 MHz, DMSO-D_6): δ 10.91 (s, 1H), 7.40 and 7.32 (2 X d, J = 8 Hz, 2H), 7.06 and 6.97 (2 X t, J = 7.2 Hz, 2H), 4.91 and 4.78 (2 X m, 2H), 2.78 (m, 1H), 2.65 (m, 3H), 2.28 (m, 2H), 1.79 (m, 2H), 1.63 (m, 1H). ^{13}C NMR (125 MHz, DMSO-D_6) 168.6, 137.5, 125.8, 121.2, 118.9, 117.9, 109.4, 108.4, 53.8, 31.8, 31.2, 29.3, 21.2, 18.9. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{15}H_{16}N_2O$ 241.1335, found 241.1376.

11b-methyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**6**). Yield: 59 mg, 49%; colorless solid. ^{1}H NMR (300 MHz, DMSO-D_6): δ 11.01 (s, 1H), 7.39 and 7.28 (d, J = 8 Hz, 2H), 7.05 and 6.95 (t, J = 7.2 Hz, 2H), 4.21 (m, 1H), 3.01 (m, 1H), 2.78 (m, 1H), 2.61 (m, 2H), 2.25 (m, 2H), 2.02 (t, J = 8 Hz, 1H), 1.48 (s, 3H). ^{13}C NMR (125 MHz, DMSO-D_6) 169.2, 136.3, 133.2, 126.1, 121.3, 118.7, 117.9, 111.2, 104.5, 52.3, 51.9, 49.3, 31.7, 28.9, 22.4, 19.3, 14.1. Q-Tof LCMS(MS ESI): $[M + H]^+$calcd for $C_{15}H_{16}N_2O$ 241.1335, found 241.1346.

(5S,11bR)-methyl 11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-5-carboxylate (**7**). Yield: 96 mg, 65%; yellow solid. ^{1}H NMR (500 MHz, DMSO-D_6): δ 11.10 (s, 1H), 7.42 (d, J = 7.55 Hz, 1H), 7.31 (d, J = 8.25 Hz, 1H), 7.07 and 6.99 (t, J = 7.6 Hz, 2H), 5.27 (d, J = 6.9 Hz, 1H), 3.59 (s, 3H), 2.78 (m, 2H), 2.51 (m, 1H), 2.35 (m, 3H), 2.01 (m, 1H), 1.48 (s, 3H). ^{13}C NMR (125 MHz, DMSO-D_6) 172.9, 171.5, 137.8, 136.1, 126.1, 121.2, 118.7, 118.2, 111.2, 102.5, 58.9, 52.1, 47.8, 34.5, 29.9, 25.4, 21.4. Q-Tof LCMS(MS ESI): $[M + H]^+$calcd for $C_{17}H_{18}N_2O_3$299.1390, found 299.1395.

(5R,11bS)-methyl 11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-5-carboxylate (**8**). Yield: 83 mg, 51%; lemon yellowsolid. ^{1}H NMR (500 MHz, DMSO-D_6): δ 11.11 (s, 1H), 7.42 and 7.30 (d, J = 8.25 Hz, 2H), 7.07 and 6.99 (t, J = 7.6 Hz, 2H), 4.34 (m,1H), 3.67 (s, 3H), 2.98 and 2.82 (m, 2H), 2.63 (m, 1H), 2.46 (m, 3H), 2.19 and 2.08 (m, 1H), 1.65 (s, 3H). ^{13}C NMR (125 MHz, DMSO-D_6)176.1, 170.5, 138.2, 136.1, 126.3, 121.3, 118.7, 118.0, 111.2, 105.8, 61.4, 51.7, 51.0, 31.6, 29.0, 26.8, 22.0. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{17}H_{18}N_2O_3$ 299.1390, found 299.1395.

methyl 4-oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-6-carboxylate (**9**). Yield: 73 mg, 49%; grey semi solid. ^{1}H NMR (500 MHz, DMSO-D_6): δ 10.99 (s, 1H), 7.43 (d, J = 7.55 Hz, 1H), 7.31 (d, J = 8.25 Hz, 1H) 7.07 and 6.98 (t, J_1 = 7.55 Hz and J_2 = 8.25, 2H), 5.91(d, J = 6.15 Hz, 1H), 4.85 (d, J = 10.3 Hz, 1H), 3.56 (s, 3H), 3.30 (m, 1H), 2.91 (m, 1H), 2.61 (m, 1H), 2.51 (m, 1H), 2.42 (m, 1H), 1.91 (m, 2H), 1.58 (m, 1H).^{13}C NMR (125 MHz, DMSO-D_6) 171.3, 169.2, 136.3, 133.2, 126.1, 121.3, 118.7, 117.9, 111.2, 104.5, 55.0, 52.4, 51.9, 49.3, 31.7, 28.9, 22.4, 19.3. Q-Tof LCMS(MS ESI): $[M + H]^+$calcd for $C_{17}H_{18}N_2O_3$ (299.1397), found 299.1387.

11b-(trifluoromethyl)-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**16**). Yield: 125 mg, 85%; pale yellow solid. ^{1}H NMR (400 MHz, DMSO-D_6): δ 11.3 (s, 1H), 7.48 (d, J = 7.68 Hz, 1H), 7.39 (d, J = 8.04 Hz, 1H), 7.16 (t, J = 6.92 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 4.38 (m, 1H), 3.32 (m, 1H), 2.85 (m, 1H), 2.67 (m, 3H), 2.46 (m, 1H), 2.29 (m, 1H). ^{13}C NMR (75 MHz, DMSO-D_6) 173.5, 136.7130.6, 127.7, 127.5, 125.5, 124.8, 122.4, 122.0, 119.1, 118.6, 111.7, 109.2, 63.4, 63.1, 62.9, 62.6, 62.1, 35.7, 29.7, 26.9, 19.9. LCMS (MS ESI): $[M + H]^+$ calcd for $C_{15}H_{13}F_3N_2O$ 295.1050, found 294.9500.

12-methyl-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one (**10**). Compound **5** (120 mg, 0.5 mmol) was dissolved in dichloromethane (10 mL) and was treated with potassium hydroxide (38 mg, 0.7 mmol) and methyl iodide (210 mg, 1.5 mmol) and the resulting solution was heated at 40°C for 6h. Once TLC confirms the complete consumption of the starting material the reaction was cooled to rt, diluted with water (10 mL) and extracted with ethyl acetate (2 X 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and was evaporated to generate the crude compound. It was purified by flash chromatography to provide the desired compound. Yield: 57 mg, 45%; white solid. ^{1}H NMR (500 MHz, DMSO-D_6): δ 7.42 (m, 2H), 7.39 (m, 1H), 7.04 (m, 1H), 4.93 (m, 2H), 3.72 (s, 3H), 2.61 (m, 4H), 2.27 (m, 2H), 1.83 (m, 1H), 1.51 (m, 1H). ^{13}C NMR (125 MHz, DMSO-D_6) 168.6, 137.5, 135.6, 125.8, 121.2, 118.9, 117.9, 109.4, 108.4, 53.8, 31.8, 31.2, 29.3, 21.2, 19.0. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{16}H_{18}N_2O$ 255.1492, found 255.1478.

General Procedure for the synthesis of hydroxymethyl indolizino indolones 11 and **12.**

Appropriate indolizino indolone esters **7** and **8** (0.5 mmol, 1equiv) were dissolved in THF (10 mL) and cooled to -78°C and were treated with diisobutyl aluminum hydride (0.5 mmol, 1 equiv). The reactions were then slowly warmed to rt and stirred for 8-12h. Once thin layer chromatography (TLC) confirmed the complete consumption of the starting materials, the reactions were quenched with water and was extracted with ethyl acetate. The organic layers were separated, dried over anhydrous sodium sulphate (Na_2SO_4) and evaporated to obtain the desired crude compounds as white to light yellow solids. The crude solids were purified by flash chromatography using ethyl acetate-hexane as the mobile phase, to provide the final compounds as solid or semi solid, which were characterized by ^{1}H-NMR, ^{13}C-NMR and Q-Tof LCMS (MS ESI). Single crystal X-ray structures were obtained for them.

(5S, 11bR)-5-(hydroxymethyl)-11b-methyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**11**). Yield: 89 mg, 66%; light yellow solid. ^{1}H NMR (500 MHz, DMSO-D_6): δ 11.01 (s, 1H), 7.39 (d, J = 7.55 Hz, 1H), 7.36 (d, J = 8.25 Hz, 1H), 4.98 (t, J = 4.2 Hz, 1H), 4.09 (m, 2H), 3.59 (m, 1H), 2.76 (m, 2H), 2.58 (m, 1H), 2.21 (m, 3H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, DMSO-D_6) 174.9, 138.6, 136.1, 126.3, 121.0, 118.6, 117.9, 111.1, 105.7, 62.1, 61.7, 54.8, 32.2, 30.5, 25.3, 24.0. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{16}H_{18}N_2O_2$ 271.1441, found 271.1453.

(5R, 11bS)-5-(hydroxymethyl)-11b-methyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indol-3(2H)-one (**12**). Yield: 65 mg, 55%; white solid. ^{1}H NMR (500 MHz, DMSO-D_6): δ 11.1 (s, 1H), 7.39 (d, J = 7.64 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.98 (t, J = 7.32 Hz, 1H), 4.92 (m, 1H), 4.54 (m, 1H), 3.31 (m, 1H), 2.92 (d, J = 8.28 Hz, 1H), 2.69 (m, 2H), 2.26 (m, 2H), 1.90 (m, 1H). ^{13}C NMR (125 MHz, DMSO-D_6) 172.8, 137.5, 136.2, 126.7, 121.0, 118.5, 118.1, 111.1, 102.2, 61.7, 58.4, 48.6, 35.1, 30.3, 26.8, 21.3. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{16}H_{18}N_2O_2$ 271.1441, found 271.1454.

General Procedure for the synthesis of 3, 3´-pyrrolidinylspirooxoindole (13-15a/b).

To a solution of indolo[2,3-a]quinolizidine and indolo[8, 7-b]indolizine scaffolds (0.5 mmol, 1 equiv) in H_2O: acetic acid : THF (1:1:1) at 0°C was added DBDMH (1.2 equiv) in portions. The reaction mixture was stirred at same temperature and after TLC indicates complete consumption of starting material, saturated sodium bicarbonate ($NaHCO_3$) solution was added to the reaction mixture and then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide the crude material, which was purified by flash chromatography with EtOAc-Hexane (4:1) as eluent.

6',7',8',8a'-tetrahydro-2'H-spiro[indoline-3,1'-indolizine]-2,5'(3'H)-dione (**13**). Yield: 81 mg, 63%; colorless solid. ^{1}H NMR (500 MHz, DMSO-D_6): δ 10.67 (s, 1H), 7.39 (t, J = 8.25 Hz, 1H), 7.09 (t, J = 7.55 Hz, 1H), 6.91 (d, J = 7.68 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 3.76 (m, 2H), 3.63 (m, 1H), 2.22 (m, 2H), 2.06 (m, 1H), 1.93 (m, 1H), 0.70 (m, 1H). ^{13}C NMR (125 MHz, DMSO-D_6). 176.6, 168.0, 141.4, 130.1, 128.2, 123.3, 121.9, 109.9, 64.3, 56.5, 32.6, 31.2, 30.8, 29.0, 23.4, 22.1, 19.8, 14.0. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{15}H_{16}N_2O_2$ 257.1288, found 257.1288.

(3'S, 7a'R)-methyl-7a'-methyl-2,5'-dioxo-2',3',5',6',7',7a'-hexahydrospiro[indoline-3,1'-pyrrolizine]-3'-carboxylate (**14**). Yield: 113 mg, 72%; grey solid. ^{1}H NMR (500 MHz, DMSO-D_6): δ 7.39 (d, J = 6.9 Hz, 1H), 7.23 (t, J = 7.55 Hz, 1H), 6.98 (t, J = 7.55 Hz, 1H), 6.84 (d, J = 7.55 Hz, 1H), 4.54 (t, J = 8.95 Hz, 1H), 4.13 (t, J = 5.5 Hz, 2H), 3.70 (s, 3H), 2.75 (m, 1H), 2.67 (m, 2H), 2.16 (m, 1H), 1.78 (m, 1H), 1.67 (m, 2H), 1.47 (s, 3H), 1.36 (m, 1H). ^{13}C NMR (125 MHz, DMSO-D_6) 179.6, 175.8, 171.9, 167.0, 142.6, 131.7, 131.6, 128.7, 126.3, 125.9, 121.4, 109.6, 71.7, 67.4, 58.3, 54.0, 52.2, 29.8, 28.4, 23.2, 22.4, 13.9, 10.8. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{17}H_{18}N_2O_4$ 315.1339, found 315.1353.

7a'-methyl-2',3',7',7a'-tetrahydrospiro[indoline-3,1'-pyrrolizine]-2,5'(6'H)-dione (+/-**15a**) and (+/-**15b**). Yield: 94 mg, 74% (combined yield); yellow solid. (+/-) **15a**: ^{1}H NMR (400 MHz, DMSO-D_6): δ 10.41 (s, 1H), 7.35 (d, J = 7.55 Hz, 1H), 7.21 (t, J = 8.25 Hz, 1H), 7.01 (t, J = 7.55 Hz, 1H), 6.81 (d, J = 7.55 Hz, 1H), 3.65 (m, 1H), 3.17 (m, 1H), 2.61 (m, 2H), 2.25 (m, 1H), 2.18 (m, 1H), 1.79 (m, 1H), 1.59 (m, 1H), 1.39 (s, 3H). ^{13}C NMR (75 MHz, DMSO-D_6) 180.1, 174.8, 142.7, 128.4, 127.6, 125.6, 121.2, 109.4, 71.5, 57.4, 34.6, 33.0, 28.0, 25.6. Q-Tof LCMS (MS ESI): MS ESI): $[M + H]^+$ calcd for $C_{15}H_{16}N_2O_2$ 257.1285, found 257.1290.

(+/-) **15b**. ^{1}H NMR (400 MHz, DMSO-D_6): δ 10.45 (s, 1H), 7.21 (t, J = 8.25 Hz, 1H), 6.95 (t, J = 7.55 Hz, 1H), 6.83 (d, J = 7.55 Hz, 1H), 6.65 (d, J = 7.55 Hz, 1H), 3.65 (m, 1H), 3.35 (m, 1H), 2.71 (m, 2H), 2.15 (m, 1H), 1.95 (m, 1H), 1.59 (m, 1H), 1.39 (s, 3H), 1.28 (m, 1H). ^{13}C NMR (75 MHz, DMSO-D_6) 176.5, 173.4, 141.4, 132.3, 128.2, 122.8, 121.7, 109.5, 72.7, 57.1, 35.2, 33.1, 27.4, 23.9. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{15}H_{16}N_2O_2$ 257.1285, found 257.1299.

Ethyl 11-methyl-3-oxo-11b-(trifluoromethyl)-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole-2-carboxylate (**17**). Compound **16** (200 mg, 0.68 mmol) was dissolved in dichloromethane (10 mL) and was treated with 10% KOH, methyl iodide (142 mg, 1 mmol) and catalytic amount of tetrabutyl ammonium bromide (TBAB) and the resulting mixture was stirred at rt overnight. Once TLC indicated complete consumption of starting material, the reaction was quenched with water, the organic layer was separated and washed with brine. It was then dried over magnesium sulphate and evaporated to generate crude solid, which was taken to the next step without further purification.

The crude compound from the previous step was dissolved in THF (10 mL), cooled to -78°C and was treated with *n*-BuLi (1M in THF) (0.65 mL, 0.65 mmol). The resulting mixture was stirred for 0.5h and was treated with ethyl chloroformate (71 mg, 0.65 mmol). The reaction was warmed to -40°C and when LCMS indicated formation of 70% of desired compound (if the reaction is continued longer, then the diacylated product starts to form which makes purification difficult) the reaction was quenched with brine and was extracted with ethyl acetate. The organic layer was further washed with brine and was dried over magnesium sulphate. The solvent was evaporated and the crude was purified by 20% EtOAc-hexane as eluent to generate the desired compound **17** as 1:1 epimeric mixture. Yield: 210 mg, 81% (combined yield); colorless liquid.

^{1}H NMR (400 MHz, DMSO-D_6):): δ 7.55-7.51 (t, J = 16 Hz, 2H), 7.30-7.26 (t, J = 15.2 Hz, 1H), 7.14-7.10 (t, J = 15.2 Hz, 1H), 4.40-4.37 (m, 1H), 4.17-4.10 (m, 2H), 3.78 (s, 3H), 3.46-3.42 (m, 1H), 3.00-2.95 (m, 1H), 2.82-2.80 (m, 1H), 2.79-2.78 (m, 1H), 1.26-1.20 (m, 2H), 1.19 (m, 3H). ^{13}C NMR (75 MHz, DMSO-D_6) 173.1, 172.3, 137.56, 134.4, 128.0, 127.8, 127.1, 126.8, 126.6, 125.6, 125.2, 122.8,122.5, 119.4, 119.1, 118.5, 111.3, 111.1, 109.8, 109.7, 58.7, 57.8, 51.5, 48.1, 44.0, 42.7, 35.7, 31.7, 31.3, 29.0, 28.7, 19.5, 19.3. LCMS (MS ESI): $[M + H]^+$ calcd for $C_{19}H_{19}F_3N_2O_3$ 381.1421, found 381.9700.

6-amino-11'-methyl-11b'-(trifluoromethyl)-1',5',6',11b'-tetrahydrospiro[indoline-3,2'-indolizino[8,7-b]indole]-2,3'(11'H)-dione (**21**). Compound **17** (100 mg, 0.26 mmol) was dissolved in THF (10mL), cooled to -78°C and was treated with LiHMDS in 1M solution in THF (0.3 mL, 0.30 mmol). The resulting mixture was stirred for 0.5h and was treated with 2,4-dinitrofluorobenzene (48.36 mg, 0.26 mmol). The reaction was warmed to rt and when LCMS indicated complete conversion to the desired intermediate the reaction was quenched with brine and was extracted with ethyl acetate. The organic layer was further washed with brine and was dried over Na_2SO_4. The solvent was evaporated and the crude was subjected to hydrogenation.

To a solution of the above crude material in EtOAc (10 mL) was added Pd/C (50% moist) followed by ammonium formate and stirring was continued at ambient temperature. Once TLC indicates completion of the reaction, the reaction mixture was filtered over celite, washed the celite with EtOAc (2x20mL). The filtrate collected was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude, which was purified by 20% EtOAc-hexane as eluent to generate the desired compound **21**. Yield: 39 mg, 34%; light yellow semi-solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.60- 7.54 (dd, J_1 = 7.32 Hz, J_2 = 8.08 Hz, 2H), 7.32-7.30 (t, J_1 = 7.6Hz, J_2 = 15.2 Hz, 1H), 7.17- 7.13 (t, J_1 = 7.48 Hz, J_2 = 15.28 Hz, 1H),

6.10 (s, 1H), 5.75-5.73 (d, *J* = 8.2 Hz, 1H), 5.50- 5.48 (dd, *J* = 8.2 Hz, 1H), 5.18 (s, 2H), 4.34-4.30 (m, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) 175.5, 171.6, 162.9, 149.9, 143.3, 138.1, 127.7, 125.2, 123.2, 122.2, 119.7, 118.9, 117.7, 111.6, 110.27, 107.0, 96.0, 63.4, 63.1, 56.5, 36.9, 34.9, 31.7, 29.0, 19.8, 18.0. LCMS (MS ESI): $[M + H]^+$ calcd for $C_{23}H_{19}F_3N_4O_2$ 441.1533, found 441.1819.

11-methyl-4'-phenyl-11b-(trifluoromethyl)-1,5,6,11b-tetrahydrospiro[indolizino[8,7-b]indole-2,3'-pyrrolidine]-2',3(11H)-dione (**22**). Compound **17** (100 mg, 0.26 mmol) was dissolved in THF (10mL), cooled to -0°C and was treated with NaH (60% dispersion in mineral oil) (15 mg, 0.3 mmol). The resulting mixture was stirred for 0.5h and was treated with 2-nitrostyrene (40 mg, 0.26 mmol). The reaction was warmed to rt and when LCMS indicated complete conversion to the desired compound **19**, the reaction was quenched with brine and was extracted with ethyl acetate. The organic layer was further washed with brine and was dried over magnesium sulphate. The solvent was evaporated and the crude was taken subjected to hydrogenation.

To a crude ethyl acetate (EtOAc) (10 mL) solution of the above intermediate, was added Pd/C (10% *w*/*w*) followed by ammonium formate and stirring was continued at ambient temperature. Once TLC indicates completion of the reaction, the reaction mixture was filtered over celite, washed the celite with EtOAc (2x20mL). The filtrate collected was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude, which was purified by 20% EtOAc-hexane as eluent to generate the desired compound **22**. Yield: 51 mg, 43%; white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48-8.44 (d, *J* = 14.8 Hz, 1H), 7.55-7.50 (m, 1H), 7.48-7.19 (m, 2H), 7.12-7.05 (m, 1H), 6.87-6.85 (d, *J* = 7.64 Hz, 1H), 6.77-6.73 (t, *J* = 15 Hz, 1H), 6.63-6.52 (m, 2H), 6.35-6.32 (t, *J* = 15.24 Hz, 1H), 4.02-3.97 (m, 1H), 3.89 (s, 3H), 3.63-3.61 (m, 2H), 3.03-2.96 (m, 1H), 2.82-2.81 (m, 1H), 2.69-2.50 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ172.3,

137.6, 134.4, 128.0, 127.8, 127.0, 126.8, 126.6, 125.6, 122.8, 122.5, 119.3, 119.1, 118.5, 111.3, 111.1, 109.8, 109.7, 58.7, 57.8, 51.5, 48.1, 44.0, 42.7, 40.2, 35.7, 31.7, 29.0, 28.7, 19.5, 19.3. Q-Tof LCMS (MS ESI): $[M + H]^+$ calcd for $C_{25}H_{22}F_3N_3O_2$ 454.1737, found 454.2038.

11-methyl-11b-(trifluoromethyl)-1,5,6,11b-tetrahydro-1'H-spiro[indolizino[8,7-b]indole-2,3'-quinoline]-2',3(4'H,11H)-dione (**23**). Compound **17** (100 mg, 0.26 mmol) was dissolved in THF (10mL), cooled to -0°C and was treated with NaH (60% dispersion in mineral oil) (15 mg, 0.3 mmol). The resulting mixture was stirred for 0.5h and was treated with 2-nitrobenzyl bromide (56 mg, 0.26 mmol). The reaction was warmed to rt and when LCMS indicated complete conversion to the desired compound, the reaction was quenched with brine and was extracted with ethyl acetate. The organic layer was further washed with brine and was dried over magnesium sulphate. The solvent was evaporated and the crude was taken subjected to hydrogenation.

To an EtOAc (10 mL) solution of the above crude, was added Pd/C (10% *w*/*w*) followed by ammonium formate and stirring was continued at ambient temperature. Once TLC indicates completion of the reaction, the reaction mixture was filtered over celite, washed the celite with EtOAc (2x20mL). The filtrate collected was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude, which was purified by 20% EtOAc-hexane as eluent to generate the desired compound **23**. Yield: 50 mg, 44%; colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.58-7.56 (d, J = 7.88 Hz, 1H), 7.35-7.34 (d, J = 3.24 Hz, 2H), 7.23-7.21 (d, J = 6Hz, 2H), 7.02-6.96 (m, 2H), 6.84-6.82 (d, J = 7.8 Hz, 1H), 4.68-4.63 (dd, J_1 = 7.2 Hz, J_2 = 6.64 Hz, 1H), 3.75 (s, 3H), 3.70-3.49 (m, 1H), 3.43-3.39 (d, J = 15.8 Hz, 1H), 3.23-3.19 (d, 1H), 3.02-2.85 (m, 2H), 2.64-2.60 (d, J = 16 Hz, 1H), 2.41-2.39 (d, J = 16 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 171.9, 168.7, 138.4, 136.6, 128.7, 128.6, 128.4, 126.7, 125.9, 123.9,

123.8, 123.7, 120.9, 121.0, 119.2, 115.6, 111.6, 109.7, 63.3, 63.0, 51.0, 37.6, 37.0, 36.1, 32.1, 32.0, 30.3, 29.8, 29.7, 29.5, 29.3, 22.8, 20.4, 14.34, 14.3, 1.2. LCMS (MS ESI): $[M + Na]^+$ calcd for $C_{24}H_{20}F_3N_3O_2$ 462.1402, found 462.1686.

ASSOCIATED CONTENT

Supporting Information. ^1H, ^{13}C, LCMS and single crystal X-ray structures of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

S_NAr, Aromatic nucleophilic substitution; CAD, caspase activated deoxyribonuclease; NBS, N-Bromosuccinimide; MCF-7, Michigan Cancer Foundation-7.

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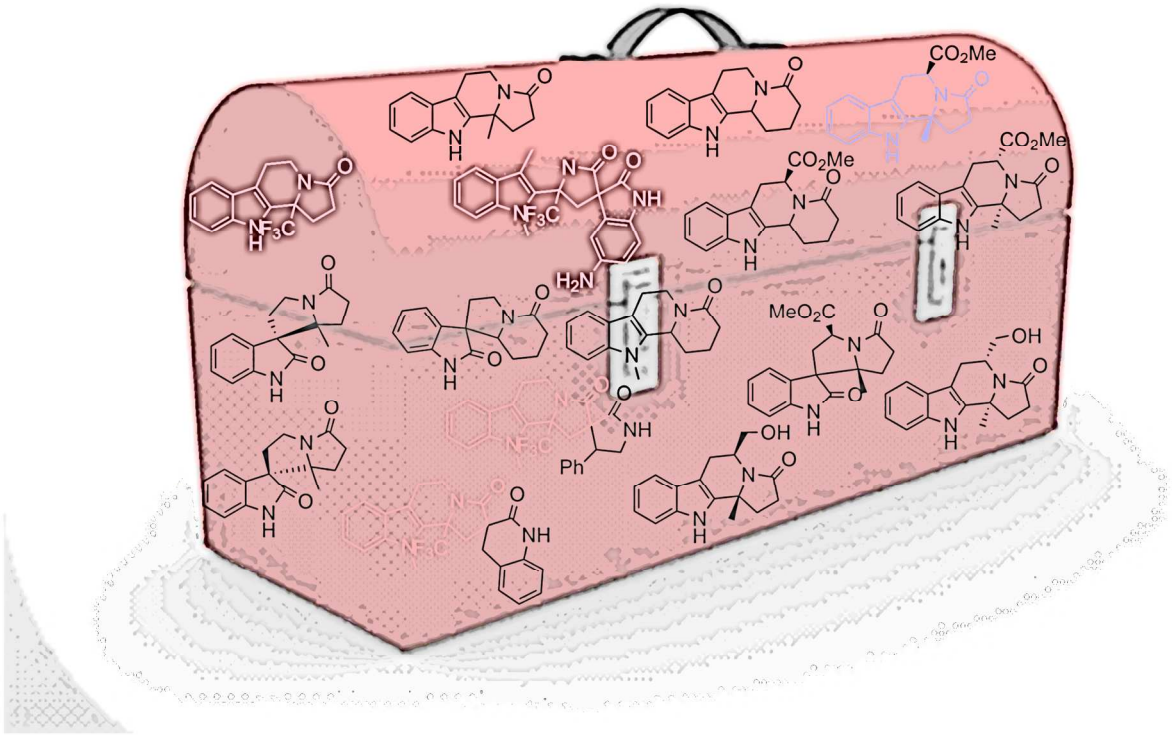
Graphical Abstract



A toolkit of indole scaffolds inspired from natural products