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PAPER

The synthesis of novel heteroaryl-fused 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indoles, 4-oxo-2,3-dihydro-1*H*-[1,4]diazepino[1,7-*a*]indoles and 1,2,4,5-tetrahydro-[1,4]oxazepino[4,5-*a*]indoles. Effective inhibitors of HCV NS5B polymerase†

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Three synthetic approaches have been developed that allow efficient access to novel heteroaryl fused indole ring systems, including: 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indoles, 4-oxo-2,3-dihydro-1*H*-[1,4]diazepino[1,7-*a*]indoles and 1,2,4,5-tetrahydro-[1,4]oxazepino[4,5-*a*]indoles. Each strategy is fully exemplified and the relative merits and limitations of the approaches are discussed. The hepatitis C virus (HCV) non-structural 5B (NS5B) polymerase inhibitory activities of select examples from each molecular class are briefly presented.

Introduction

Recent literature reports[1–3] have disclosed a number of tricyclic indole analogs, see Fig. 1, that display potent activity against the non-structural 5B (NS5B) RNA dependant RNA polymerase of the hepatitis C virus (HCV).[4] This enzyme is a key component of the viral replicase complex, and its function is essential for proliferation of the pathogen. Later work by our group[5] and others[6,7] evaluated more conformationally constrained tetracyclic indole derivatives as exemplified by compound **2**, and subsequently demonstrated that these systems generally displayed improved potency against NS5B.

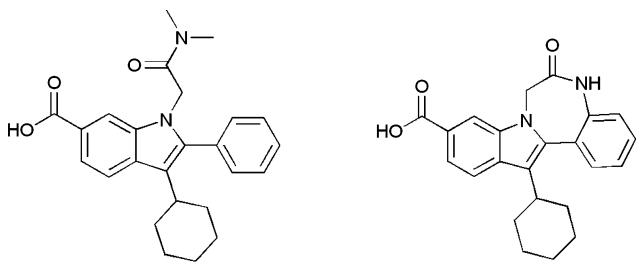

Fig. 1 Indole and indolo-fused NS5B inhibitors.

In our laboratories we became interested in exploring a number of related indole ring systems in which the fused aryl moieties in **2** (and related structures) are replaced with a variety of heterocycles in an attempt to significantly extend the known structure activity relationships (SARs) in this area.

Correspondingly, we discuss here a number of routes that can be employed for the syntheses of five- and six-membered heterocycles fused to the indolo systems shown in Fig. 2. These include: 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indoles **3**, 4-oxo-2,3-dihydro-1*H*-[1,4]diazepino[1,7-*a*]indoles **4**, and

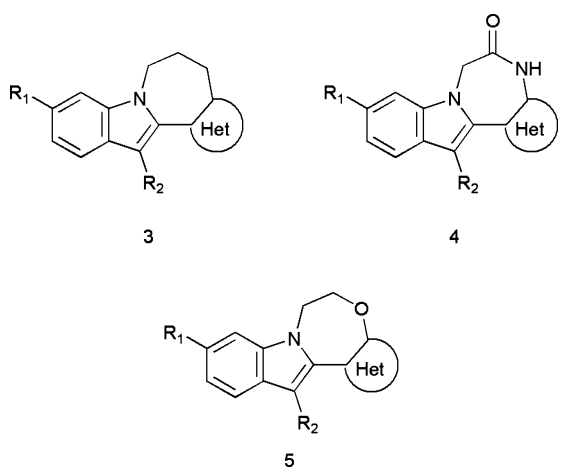

Fig. 2 Novel heteroaryl fused tetracyclic indoles.

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† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra for compounds **7**, **9–16**, **18** and **20–27**. See DOI: 10.1039/c1ob05525a

1,2,4,5-tetrahydro-[1,4]oxazepino[4,5-*a*]indoles **5**. We comment on the relative advantages and limitations of each of the strategies evaluated, and briefly present the NS5B inhibitory activities of select examples from each of these classes of heterocycles.

In reviewing approaches to these systems we primarily considered the routes depicted by the disconnections shown in Scheme 1. Each retrosynthetic analysis is to some extent complementary. Route 1 is most appropriate for the synthesis of a number of fused 1,3-azoles. These can be assembled in the penultimate step from suitably functionalized bromo-ketones using standard alkylation-condensation chemistries. In Route 2, the fused-heterocycle and bridging moiety are introduced in a more convergent manner, with the key step involving an intramolecular coupling reaction. Lastly, in Route 3, what will ultimately be the fused heterocycle is introduced at an early stage, and the bridging moiety is constructed towards the end of the synthesis using a variety of chemistries dictated by the functionality required in the bridge.

Results and discussion

Route 1

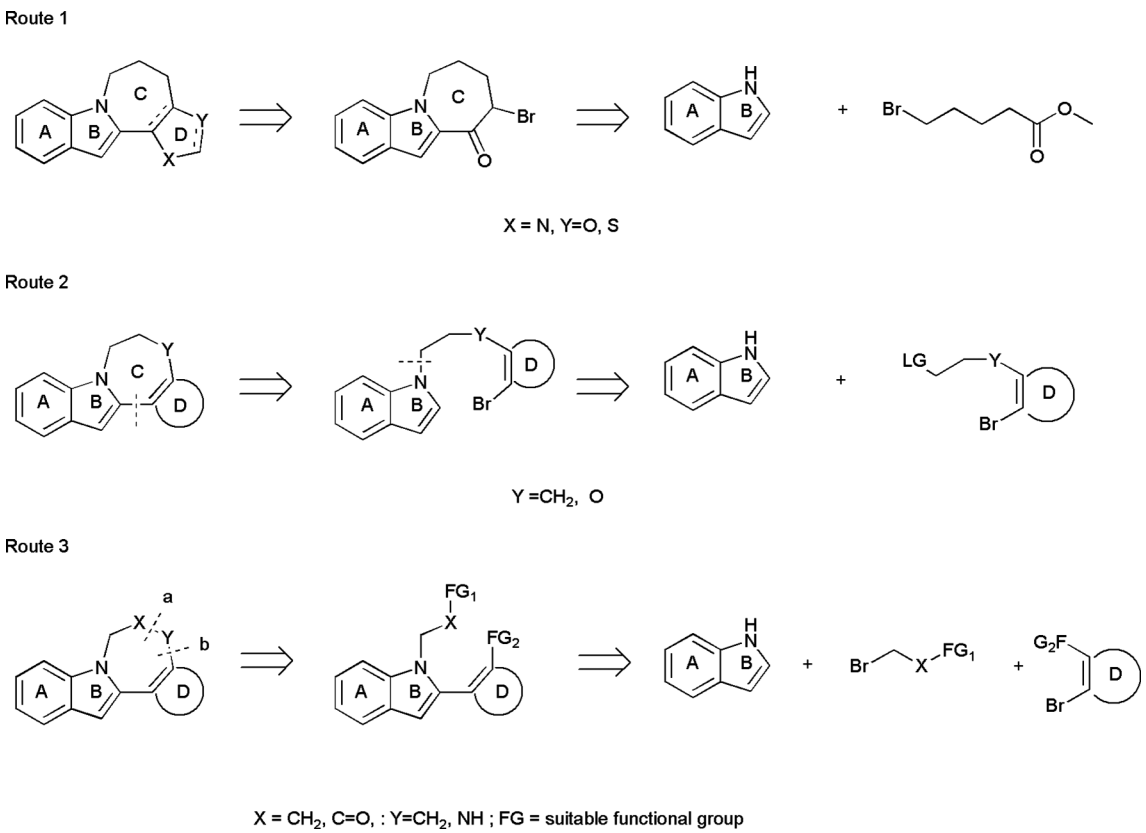
As outlined above, the most obvious route to access a diversity of five-membered heterocycles fused to the indolo-systems of the current discussion involves the syntheses of intermediate bromo-ketones of the type shown in Route 1 of Scheme 1. This strategy is exemplified in Scheme 2 by the syntheses of the oxazole and thiazole derivatives **11** and **12**.

Starting from the suitably functionalized indole **6**,[3] treatment with methyl 5-bromovalerate afforded the N-alkylated methyl ester, hydrolysis of which resulted in the formation of the related di-acid **8**. This on treatment with a mixture of TFAA and TFA[8] efficiently underwent an intramolecular Friedel–Crafts reaction to give the tricyclic azepinone intermediate **9**. Bromination with copper(II) bromide[9] gave the key α-bromoketo compound **10**. The desired fused heterocyclic products **11** and **12** could then be generated by reacting **10** with either formamide or thioacetamide. A key advantage of this methodology is that a diversity of functionalized heterocyclic systems can be accessed from a common intermediate, and this methodology can be applied efficiently to array synthesis due to the heterocycle being constructed toward the conclusion of the syntheses.

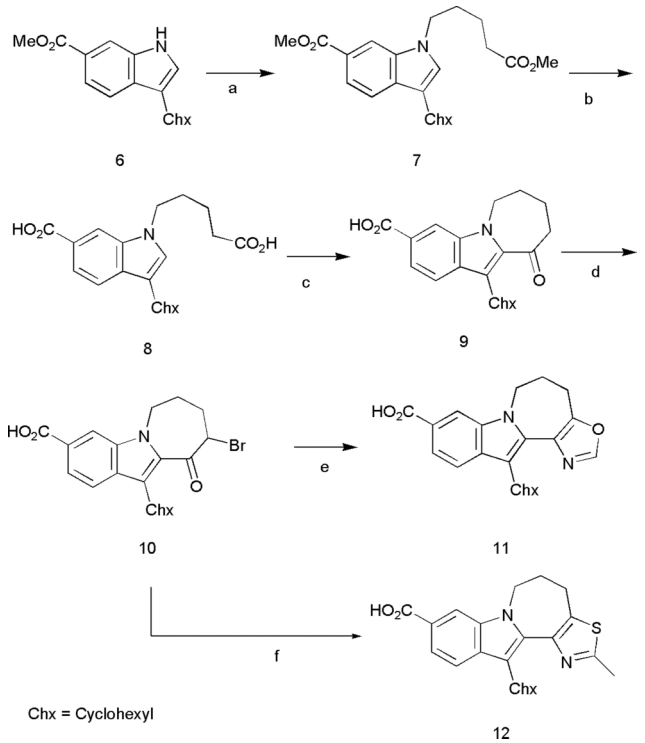
Route 2

A potentially more convergent approach to these polycyclic indole systems employs the methodology depicted in Scheme 3 that describes the synthesis of the pyrido[2′,3′:6,7][1,4]oxazepino[4,5-*a*]indole derivative **16**. The key step in this reaction sequence involves an intramolecular coupling reaction, a step that we envisioned could be best accomplished using Heck-type conditions.[10]

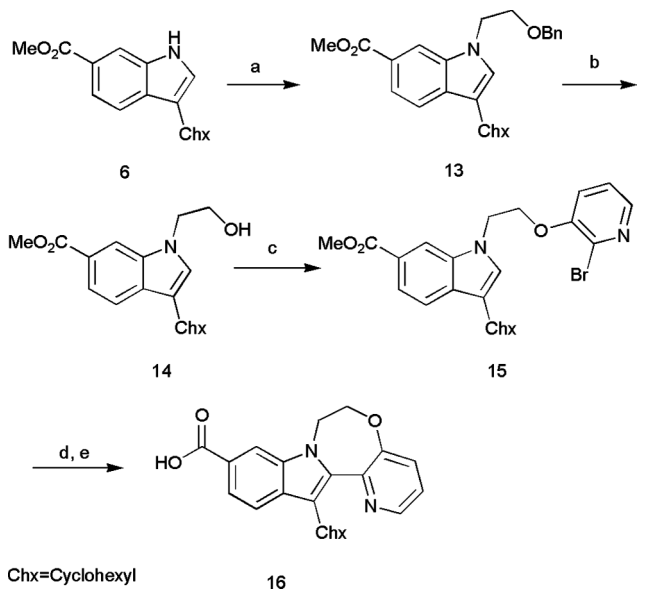
Starting from methyl 3-cyclohexylindole-6-carboxylate **6**,[3] alkylation with benzyl 2-bromoethyl ether using sodium hydride as base gave an N-alkylated intermediate **13** which on hydrogenation provided the indoylethanol **14**. Mitsunobu reaction of this intermediate with 2-bromo-3-pyridinol afforded the pyridyl ether **15**. The subsequent intramolecular Heck reaction followed



Scheme 1 Considered disconnections in the retrosynthetic analysis of targeted heterocycles.



Scheme 2 Reagents and conditions: (a) methyl 5-bromovalerate, NaH, DMF, 57%; (b) NaOH, THF–MeOH–H_2O; (c) TFAA–TFA, 85% (two steps b and c); (d) $CuBr_2$, EtOAc–$CHCl_3$, 64%; (e) formamide, DMF, 150 °C, 21%; (f) thioacetamide, ethanol, reflux, 56%.

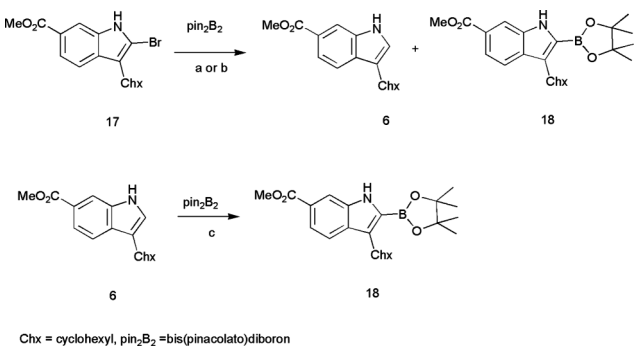


Scheme 3 Reagents and conditions: (a) NaH, benzyl 2-bromoethyl ether, DMF, 76%; (b) H_2, Pd/C, 98%; (c) 2-bromo-3-pyridinol, PPh_3, DBAD, THF, 58%; (d) $Pd(PPh_3)_4$, KOAc, DMA, 160 °C; (e) NaOH, THF–MeOH–H_2O, 42%(two steps d and e).

by base-catalyzed hydrolysis using sodium hydroxide gave the targeted pyrido[2′,3′:6,7][1,4]oxazepino[4,5-*a*]indole **16** in good overall yield. However, in our hands, the intramolecular Heck reaction[11] was sensitive to the position of the halogen on the pyridyl moiety: When 3-bromo-2-pyridinol was reacted with **14** and the Mitsunobu reaction product subjected to the same Heck conditions no cyclization product was formed, and attempts to use more forcing conditions only resulted in dehalogenation of the starting material. Therefore, although it may be envisioned that this approach offers the possibility of the introduction of a variety of fused heterocycles and bridging elements, the compatibility of the relevant intermediates with the Heck coupling conditions is key to the successful deployment of this methodology. The efficiency of the key annulation can be expected to be strongly influenced by the product ring size, the tether flexibility in analogs of type **15**, and the exact electronic character of the halogenated heterocycle.

Route 3

Within the scope of the work presented here, the most general approach for accessing the tetracyclic indoles discussed above employs the strategy depicted in Route 3 of Scheme 1. This approach is characterized by the early introduction of the heterocycle that will ultimately be fused to the polycyclic indole ring system. In order to maximize the generality of this methodology, we desired to use the 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole **18** as a partner in a key Suzuki type coupling step. We anticipated that this reagent would be suitably reactive with a wide array of halo-substituted heteroaryls and would obviate the need to employ potentially difficult to access heteroaryl boronic acids or related stannyl compounds. In addition, reagent **18** exploits the intrinsic electron rich nature of the indole ring system that should facilitate its coupling to a range of electron deficient heterocycles. Given the importance of this intermediate, efforts were directed at optimizing its synthesis, as shown in Scheme 4 and Table 1.



Scheme 4 Synthesis of **18**. Reagents and conditions: (a) $PdCl_2$(dppf), NaOAc, CH_3CN, 150 °C; (b) $Pd(dba)_2$, PCy_3, KOAc, dioxane, 80 °C; (c) $[(Ir(OMe)(cod)]_2$, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy), THF, 30 °C, 41%. cod = 1,5-cyclooctadiene.

To access **18**, we examined a palladium catalyzed reaction between the bromo indole **17**[3] and bis(pinacolato)diboron (pin_2B_2). In our hands under a variety of conditions, we could only obtain **18** as a mixture with the dehalogenated by-product **6** and unreacted starting material **17**, as reported in Table 1. These mixtures proved difficult to fractionate and required that a mixture be used in the subsequent coupling reaction, where the desired products were typically easier to isolate.

In an attempt to address this issue we looked for alternative boronylation conditions that might obviate the use of the 2-bromo indole **17**, and therefore facilitate the isolation of the boronate ester **18**. In this regard, the recently reported[12]

Table 1 Product ratios for boronylation of indole **6**

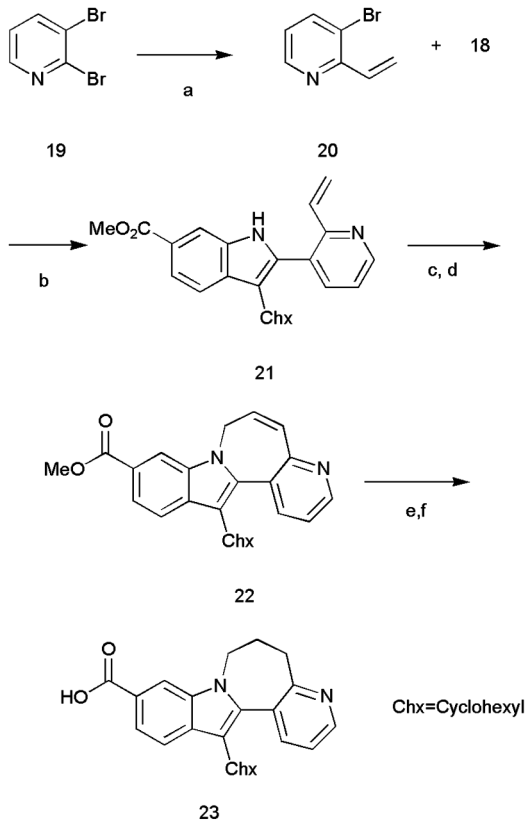
Coupling conditions	Relative ratios of products			HPLC per cent yield of **18**
	17	**6**	**18**	
$PdCl_2(dppf)$, NaOAc, CH_3CN, 150 °C	1.8	3.4	1	16
$Pd(dba)_2$, PCy_3, KOAc, dioxane, 80 °C	0.28	1	2.1	62

iridium-catalyzed direct boronylation of aromatic C–H moieties was of particular interest. Iridium complexes of the type, iridium(I)-2,2′-bipyridine prepared from [{Ir(OMe)(cod)}$_2$] and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy), have been shown to be highly active catalysts for the boronylation of a range of aromatic substrates using stoichiometric amounts of pin_2B_2 at room temperature in non-polar, inert solvents (typically hexanes or octanes).[12] In our studies, attempts to convert **6** to **18** proved unsuccessful due to the limited solubility of **6** in non-polar solvents. However, the use of 1,3,5-trimethylbenzene, in which **6** is significantly more soluble resulted in approximately 40% conversion of **6** to **18**, as estimated by LCMS analysis. Even more encouraging was the observation that in THF at 30 °C for three hours and using one equivalent of pin_2B_2, the conversion improved to 70–80%. Importantly, the crude reaction mixture could simply be concentrated, whereupon **18** could be isolated as a crystalline material by trituration with a mixture of 1 : 4 ethyl acetate–hexanes. (The filtrand from these processes could be recycled to obtain further quantities of **18**.) This methodology was then applied to the synthesis of multi-gram quantities of **18**.

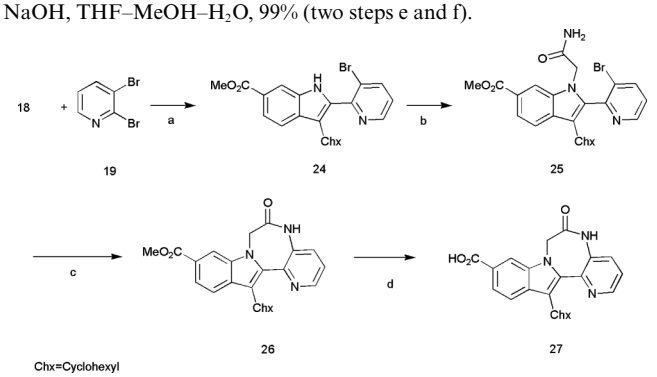
With an efficient route to the boronate in hand, we sought to evaluate the strategy depicted in Route 3 of Scheme 1 to access a range of tetracyclic indole systems using a variety of D-ring heterocycles in combination with a range of bridging functionality. This is exemplified in the synthesis of the fused pyridyl systems shown in Schemes 5 and 6, in which both hydrocarbon and lactam bridges are constructed in the syntheses of the two heterocyclic ring systems: 7*H*-pyrido[3′,2′:3,4]azepino[1,2-*a*]indole and 5*H*-pyrido[3′,2′:5,6][1,4]diazepino[1,7-*a*]indol-6(7H)-one.

The synthesis of the indoloazepine **23** proceeded as shown in Scheme 5. A Stille coupling[13] of 2, 3-dibromopyridine **19** with tributylvinyltin was found to give exclusively the 3-bromo-2-vinylpyridine **20**. Suzuki coupling of **20** with **18** provided the (2-vinylpyridin-3-yl)-1*H*-indole **21** in good yield. Subsequent alkylation with allyl bromide gave the N-alkylated derivative, which was then subjected to a ring-closing metathesis reaction using Grubbs' second generation catalyst[14] to provide the unsaturated tetracyclic indole derivative **22**. Sequential hydrogenation and hydrolysis then afforded the targeted indole, 13-cyclohexyl-6,7-dihydro-5*H*-pyrido[3′,2′:3,4]azepino[1,2-*a*] indole-10-carboxylic acid **23**. A further example of this methodology involving the synthesis of a more highly functionalized bridging element is shown in Scheme 6.

In this synthesis, 2,3-dibromopyridine **19** was coupled with **18** to provide exclusively, methyl 2-(3-bromopyridin-2-yl)-3-cyclohexyl-1*H*-indole-6-carboxylate **24** in good yield. Alkylation with 2-bromoacetamide gave the N-alkylated intermediate **25**. This compound was subjected to a palladium catalyzed intramolecular N-arylation reaction[15] that efficiently provided the lactam **26**. Hydrolysis of this intermediate gave the targeted acid, 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-pyrido[3′,2′:5,6][1,4]-



Scheme 5 Reagents and conditions: (a) tributylvinyltin, $PdCl_2(PPh_3)_2$, LiCl, DMF, 100 °C, 53%; (b) $Pd(PPh_3)_4$, LiCl, Na_2CO_3, EtOH–toluene, 80 °C, 65%;(c) NaH, allyl bromide, DMF; (d) Grubbs catalyst 2nd generation, CH_2Cl_2, reflux, 58% (two steps c and d); (e) H_2/Pd–C; (f) NaOH, THF–MeOH–H_2O, 99% (two steps e and f).



Scheme 6 Reagents and conditions: (a) $Pd(PPh_3)_4$, LiCl, Na_2CO_3, EtOH–toluene, 80 °C, 70%; (b) KH, DMF, bromoacetamide, 76%; (c) $Pd_2(dba)_3$, Xantphos, Cs_2CO_3, 1,4-dioxane, 100 °C, 57%; (d) LiI, pyridine, 180 °C, 98%.

diazepino[1,7-*a*]indole-10-carboxylic acid **27**. This reaction required the use of LiI in pyridine[16] in order to obviate the hydrolysis

Table 2 Enzymatic and replicon inhibition data

Compound	HCV NS5B Genotype 1b IC_{50} (μM)	Replicon Genotype 1b EC_{50} (μM)	Replicon Mutant P495L EC_{50} (μM)
11	>12.5	>10	>10
12	8.3 ± 3.2	>10	>10
16	0.39 ± 0.23	0.98	>10
23	0.45 ± 0.04	0.52 ± 0.15	>10
27	0.28 ± 0.04	1.8	>10
1	0.43		

Note: The reported IC_{50} and EC_{50} values (μM) equal the concentration of each compound that inhibits HCV NS5B enzyme activity (genotype 1b derived from Con 1) by 50%. The IC_{50} values were determined in assays described previously using poly A and/or poly C templates.[17] Reported values are the mean from at least 2 independent test occasions. The EC_{50} values were determined in the Luciferase assay.[18]

of the lactam moiety which proved to be sensitive to a range of base-catalyzed hydrolysis conditions.

As can be seen from the preceding two schemes, the strategy outlined in Route 3 of Scheme 1 is highly flexible, both in regard to the range of heterocycles that can be incorporated, as well as the type of functionality that can be introduced into the bridging element that constitutes Ring C. An important aspect in the successful execution of this chemistry was developing an efficient preparation of the boronate intermediate, methyl 3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-6-carboxylate **18**, and our use of an iridium catalyzed procedure was key to the successful synthesis and isolation of this compound.

Determination of NS5B Inhibitory Activities

All of the final targets of the above syntheses were assayed for their inhibitory activities against the HCV NS5B genotype 1b enzyme.[17] In addition, the compounds activities were also assessed in a cell-based HCV genotype 1b replicon system[18] as well as a mutant replicon containing a P495L mutation in the NS5B gene.[18] The results from these experiments are shown in Table 2.

It is apparent that the 5-membered heterocycles examined here are significantly less active than the fused pyridino analogs explored, all of which displayed similar levels of enzyme activity to the acyclic analog **1**, discussed in the introduction. In addition, these activities are mostly reproduced in the replicon assay, suggesting that the incorporation of the heterocycle does not prevent or significantly impair cellular penetration. In addition, the reduced activities observed in the mutant replicon system suggest that all of the analogs examined bind in the "thumb" domain of the NS5B polymerase, proximal to the P495L mutation, as has been described with related analogs.[1–3,5]

Conclusion

We have presented three general routes for the syntheses of series of novel tetracyclic indole ring systems. The advantages and limitations of each of the strategies have been outlined, and taken collectively these procedures provide a comprehensive set of methodologies that can be used to access a number of functionalized derivatives of these heterocyclic ring systems. Additionally, we have briefly presented the activity of compounds of this type against the NS5B polymerase of the hepatitis C virus, and the further characterization and optimization of this property will be the subject of future manuscripts.

Experimental section

General

Solvents and reagents unless otherwise noted, were obtained from commercial suppliers and were used without further purification. Melting point was recorded on an EZ-Melt Automated Melting Point Apparatus and was not calibrated. Infrared spectra data were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer as solid neat sample or film in $CHCl_3$. NMR spectra were recorded on Bruker spectrometers (300, 400 or 500 MHz for ^{1}H NMR and 100 or 125 MHz for ^{13}C NMR). Chemical shifts for observed signals are reported in parts per million downfield from tetramethylsilane and are measured using the residual resonance from the deuterated solvent as reference. Compound **6** was synthesized according to the procedure reported in reference 3 [{Ir(OMe)(cod)}$_2$] was prepared by a published protocol.[19] Reverse Phase Preparative HPLC was performed on a Shimadzu instrument with a Sunfire column C18 19 mm X 150 mm using acetonitrile–water–0.1% TFA as the mobile solvent system. Low resolution mass spectra were measured on a Shimadzu LC-MS with Waters Micromass ZQ in positive ESI mode. High resolution mass spectrometry (HRMS) analyses were performed on a hybrid linear ion trap LTQ XL Fourier transform Orbitrap mass spectrometer (Thermo Fisher Scientific) in positive ionization electrospray mode operating at 30,000 resolution (full width at half height maximum, FWHM).

Methyl 3-cyclohexyl-1-(5-methoxy-5-oxopentyl)-1*H*-indole-6-carboxylate 7

To a suspension of NaH (85.5 mg of 60% dispersion in mineral oil, 2.14 mmol) in DMF (5 mL), **6** (500 mg, 1.94 mmol) was added and the reaction mixture was stirred at room temperature for 15 min. Methyl 5-bromovalerate (0.305 mL, 2.14 mmol) was then added. The reaction mixture was stirred at room temperature overnight. It was then quenched with ice, extracted with ethyl acetate (2 × 50 mL) and the organic layers were combined. It was then washed with 1 N HCl solution, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, hexanes to 25% ethyl acetate in hexanes) to give a colorless thick oil as the desired product. (0.41 g, 57% yield) IR (film, ν_{max}/cm^{-1}): 2924, 2851, 1736, 1709, 1615, 1472, 1434, 1274, 1239, 1200, 1089. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17–1.95 (m, 12 H), 1.99–2.18 (m, 2 H), 2.34 (t, J = 7.32 Hz, 2 H), 2.73–2.92 (m, 1 H), 3.67 (s, 3 H), 3.94 (s, 3 H), 4.15 (t, J = 6.95 Hz, 2 H), 7.01 (s, 1 H), 7.64 (d, J = 8.42 Hz, 1 H), 7.76 (dd, J = 8.42, 1.10 Hz, 1 H), 8.05 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 22.35, 26.41, 26.84, 29.79, 33.47, 34.14, 35.26, 46.00, 51.57, 51.88, 111.63, 118.99, 119.42, 122.34, 122.82, 126.66, 130.72, 135.59, 168.31, 173.56. LRMS *m/z* 372.3 (M + H). HRMS calcd for $C_{22}H_{30}O_4N$ (M + H): 372.2169, found: 372.2156.

1-(4-Carboxybutyl)-3-cyclohexyl-1*H*-indole-6-carboxylic acid 8

To a solution of **7** (410 mg, 1.1 mmol) in THF–methanol mixture (5.0 mL/5.0 mL), 2 N NaOH solution (5.0 mL) was added. The reaction mixture was heated at 100 °C under microwave conditions for 15 min. It was then concentrated and acidified with 1 N HCl solution. The diacid product precipitated and was collected by filtration. This crude material was used as is, in the preparation of **9**.

11-Cyclohexyl-10-oxo-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indole-3-carboxylic acid 9

A mixture of TFA (1.0 mL) and TFAA (469 mg, 2.232 mmol) was added dropwise to the above acid **8** at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 4 h. Water was added slowly to quench the reaction and a light yellow solid was collected as the desired product. (305 mg, 85% yield) IR (neat, ν_{max}/cm^{-1}): 2922, 1670, 1610, 1557, 1421, 1332, 1302, 1263, 1240, 1210. ^{1}H NMR (500 MHz, CD_3OD) δ 1.32–1.55 (m, 3 H), 1.71–1.83 (3 H, m, 3 H), 1.82–2.05 (m, 6 H), 2.05–2.17 (m, 2 H), 2.78–2.92 (m, 2 H), 3.38–3.49 (m, 1 H), 4.32–4.60 (m, 2 H), 7.71 (dd, *J* = 8.70, 1.37 Hz, 1 H), 7.96 (d, *J* = 8.55 Hz, 1 H), 8.18 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.28, 26.28, 26.95, 27.02, 33.01, 35.78, 41.94, 43.48, 113.22, 120.21, 122.96, 124.91, 128.38, 129.64, 136.82, 137.34, 172.17, 197.67. LRMS *m/z* 326.2 (M + H). HRMS calcd for $C_{20}H_{24}O_3N$ (M + H): 326.1751, found: 326.1750.

9-Bromo-11-cyclohexyl-10-oxo-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indole-3-carboxylic acid 10

To a refluxing suspension of $CuBr_2$ (80 mg, 0.36 mmol) in ethyl acetate (3.0 mL), a solution of **9** (78 mg, 0.24 mmol) in chloroform (3.0 mL) was added. The reaction mixture was heated under reflux for 4 h. It was then cooled down and filtered to remove the solids. The filtrate was then concentrated and the residue was purified by Reverse Phase Preparative HPLC to give a light yellow solid as the desired product. (62 mg, 64% yield) IR (neat, ν_{max}/cm^{-1}): 2934, 2854, 1673, 1344, 1253, 1056, 1033. ^{1}H NMR (500 MHz, CD_3OD) δ 1.32–1.54 (m, 3 H), 1.66–2.07 (m, 7 H), 2.14–2.27 (m, 1 H), 2.27–2.52 (m, 3 H), 3.04–3.22 (m, 1 H), 4.08 (ddd, *J* = 14.65, 9.31, 2.59 Hz, 1 H), 4.59–4.71 (m, 1 H), 5.01 (dd, *J* = 5.95, 2.90 Hz, 1 H), 7.73 (dd, *J* = 8.54, 1.53 Hz, 1 H), 7.94 (d, *J* = 8.54 Hz, 1 H), 8.18 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.87, 26.22, 26.91, 26.94, 31.67, 32.65, 33.02, 36.13, 44.98, 55.40, 113.37, 120.48, 122.80, 125.33, 129.64, 131.09, 135.27, 137.31, 171.34, 191.11. LRMS *m/z* 404.2 (M + H), 406.2 (M + 2 + H). HRMS calcd for $C_{20}H_{23}O_3NBr$ (M + H): 404.0856, found: 404.0851.

12-Cyclohexyl-5,6-dihydro-4*H*-oxazolo[4′,5′:3,4]azepino[1,2-*a*]indole-9-carboxylic acid 11

To a solution of **10** (80 mg, 0.198 mmol) in DMF (3.0 mL), formamide (1.5 mL) was added. The reaction mixture was heated at 150 °C for 2 h. The reaction was added to water and extracted with ethyl acetate (2 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated. The residue was then purified by Reverse Phase Preparative HPLC column to afford an orange solid as the desired product. (15 mg, 21% yield) IR (film, ν_{max}/cm^{-1}): 3325 (br), 2943, 2834, 1650, 1449, 1434, 1413, 1110, 1019. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.27–1.46 (m, 3 H), 1.67–1.87 (m, 5 H), 1.91–2.05 (m, 2 H), 2.10–2.18 (m, 2 H), 3.12 (t, *J* = 6.71 Hz, 2 H), 3.88–4.04 (m, 1 H), 4.29–4.40 (m, 2 H), 7.57 (dd, *J* = 8.54, 1.53 Hz, 1 H), 7.83 (d, *J* = 8.54 Hz, 1 H), 8.10 (s, 1 H), 8.47 (s, 1 H), 12.57 (s, br, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.27, 25.71, 25.77, 26.89, 32.28, 34.95, 43.20, 111.42, 119.18, 119.48, 120.20, 123.04, 127.72, 129.01, 129.50, 135.67, 148.84, 151.04, 168.28. LRMS *m/z* 351.3 (M + H). HRMS calcd for $C_{21}H_{23}O_3N_2$ (M + H): 351.1703, found: 351.1696.

12-Cyclohexyl-5,6-dihydro-2-methyl-4*H*-thiazolo[4′,5′:3,4]-azepino[1,2-*a*]indole-9-carboxylic acid 12

To a solution of **10** (20 mg, 0.049 mmol) in ethanol (5.0 mL), thioacetamide (5.6 mg, 0.074 mmol) was added. The reaction mixture was heated under reflux overnight. The ethanol was evaporated and the residue was then purified by Reverse Phase Preparative HPLC column to afford a light yellow solid as product. (10.5 mg, 56% yield) IR (film, ν_{max}/cm^{-1}): 3393 (br), 2927, 2850, 1676, 1610, 1449, 1434, 1206, 1012. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.23–1.50 (m, 3 H), 1.65–1.88 (m, 5 H), 1.88–2.04 (m, 2 H), 2.18–2.32 (m, 2 H), 2.69 (s, 3 H), 2.98 (t, *J* = 7.17 Hz, 2 H), 3.41–3.58 (m, 1 H), 4.13–4.30 (m, 2 H), 7.60 (dd, *J* = 8.55, 1.22 Hz, 1 H), 7.83 (d, *J* = 8.54 Hz, 1 H), 8.12 (s, 1 H), 12.54 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 19.01, 22.92, 25.74, 26.85, 28.98, 32.38, 35.64, 42.03, 111.55, 119.29, 119.49, 120.15, 123.07, 129.39, 133.60, 133.73, 135.66, 143.24, 162.01, 168.27. LRMS *m/z* 381.3 (M + H). HRMS calcd for $C_{22}H_{25}O_2N_2S$(M + H): 381.1631, found: 381.1624.

Methyl 1-(2-(benzyloxy)ethyl)-3-cyclohexyl-1*H*-indole-6-carboxylate 13

To a suspension of NaH (192 mg of 60% dispersion in mineral oil, 4.8 mmol) in DMF (8 mL), **6** (1.029 g, 4.0 mmol) was added, and the reaction mixture was stirred at room temperature for 15 min. Benzyl 2-bromoethyl ether (0.7 mL, 4.4 mmol) was then added. The reaction mixture was stirred at room temperature for 2 h. It was then quenched with water, extracted with ethyl acetate (2 × 50 mL) and the organic layers were combined. It was then washed with 1 N HCl solution, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, 3 : 1 hexanes : ethyl acetate) to give a colorless thick oil as the desired product. (1.19 g, 76% yield) IR (film, ν_{max}/cm^{-1}): 2924, 2851, 1709, 1615, 1470, 1277, 1240, 1090. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26–1.38 (m, 1 H), 1.42–1.56 (m, 4 H), 1.77–1.93 (m, 3 H), 2.06–2.16 (m, 2 H), 2.81–2.90 (m, 1 H), 3.81 (t, *J* = 5.49 Hz, 2 H), 3.95 (s, 3 H), 4.35 (t, *J* = 5.49 Hz, 2 H), 4.47 (s, 2 H), 7.14 (s, 1 H), 7.19–7.24 (m, 2 H), 7.25–7.32 (m, 3 H), 7.68 (d, *J* = 8.55 Hz, 1 H), 7.80 (d, *J* = 8.55 Hz, 1 H), 8.10 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.42, 26.84, 34.11, 35.22, 46.27, 51.83, 69.08, 73.15, 111.68, 118.91, 119.50, 122.27, 122.76, 127.42, 127.60, 127.69, 128.30, 130.83, 135.71, 137.77, 168.30. LRMS *m/z* 392.3 (M + H). HRMS calcd for $C_{25}H_{30}O_3N$ (M + H): 392.2220, found: 392.2204.

Methyl 3-cyclohexyl-1-(2-hydroxyethyl)-1*H*-indole-6-carboxylate 14

To a solution of **13** (1.19 g, 3.04 mmol) in ethyl acetate (50 mL), 10% Pd on carbon (0.12 g) was added. Next, about five drops of 1 N HCl solution were added to the reaction mixture which was stirred at room temperature under a hydrogen balloon for three days. It was then filtered through celite and washed with ethyl acetate. The filtrate was concentrated to give a light yellow solid as the desired product. (0.9 g, 98% yield) IR (neat, ν_{max}/cm^{-1}): 3386 (br), 2922, 2849, 1698, 1614, 1544, 1439, 1335, 1289, 1274, 1240, 1128, 1087. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22–1.37 (m, 1 H), 1.38–1.54 (m, 4 H), 1.73–1.93 (m, 4 H), 2.03–2.14 (m, 2 H), 2.78–2.88 (m, 1 H), 3.94 (s, 3 H), 3.97 (t, J = 5.19 Hz, 2H), 4.29 (t, J = 5.19 Hz, 2 H), 7.09 (s, 1 H), 7.66 (d, J = 8.39 Hz, 1 H), 7.77 (dd, J = 8.39, 1.37 Hz, 1 H), 8.08 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.39, 26.83, 34.07, 35.24, 48.62, 51.92, 62.00, 111.67, 119.10, 119.69, 122.67, 123.02, 127.33, 130.93, 135.80, 168.28. LRMS m/z 302.3 (M + H). HRMS calcd for $C_{18}H_{24}O_3N$ (M + H): 302.1751, found: 302.1748.

Methyl 1-(2-(2-bromopyridin-3-yloxy)ethyl)-3-cyclohexyl-1*H*-indole-6-carboxylate 15

To a solution of 2-bromo-3-pyridinol (173 mg, 0.995 mmol) in THF (10 mL), PPh_3 (261 mg, 0.995 mmol) and di-*tert*-butyl azodicarboxylate (229 mg, 0.995 mmol) were added. The reaction mixture was stirred at room temperature for 0.5 h. Next, a solution of **14** (200 mg, 0.66 mmol) in THF (3 mL) was added. The reaction mixture was stirred at room temperature overnight. The solvent was then evaporated to give a brownish oil as crude product. The brownish oil solidified upon standing. It was then triturated with methanol to give a grayish solid as product. (175 mg, 58% yield) IR (neat, ν_{max}/cm^{-1}): 2923, 2852, 1699, 1612, 1564, 1470, 1446, 1417, 1294, 1276, 1246, 1205, 1128, 1076, 1052, 987. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17–1.56 (m, 5 H), 1.67–1.93 (m, 3 H), 1.98–2.15 (m, 2 H), 2.75–2.90 (m, 1 H), 3.95 (s, 3 H), 4.31 (t, J = 4.94 Hz, 2 H), 4.64 (t, J = 4.94 Hz, 2 H), 6.96 (dd, J = 8.05, 1.46 Hz, 1 H), 7.13 (dd, J = 8.23, 4.57 Hz, 1 H), 7.32 (s, 1 H), 7.65 (d, J = 8.42 Hz, 1 H), 7.78 (dd, J = 8.42, 1.46 Hz, 1 H), 7.98 (dd, J = 4.76, 1.46 Hz, 1 H), 8.12 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.40, 26.83, 34.04, 35.20, 45.37, 51.94, 68.01, 111.26, 119.17, 119.27, 119.83, 122.82, 123.07, 123.25, 128.24, 131.12, 132.91, 135.42, 141.74, 151.73, 168.28. LRMS m/z 457.2 (M + H), 459.2 (M + 2 + H). HRMS calcd for $C_{23}H_{26}O_3N_2Br$ (M + H): 457.1121, found: 457.1102.

13-Cyclohexyl-6,7-dihydropyrido[2′,3′:6,7][1,4]oxazepino[4,5-*a*]indole-10-carboxylic acid 16

To a mixture of **15** (174 mg, 0.38 mmol), KOAc (75 mg, 0.76 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.019 mmol) in a sealed tube, dimethylacetamide (3 mL) was added. The reaction mixture was heated at 160 °C for 5 h. It was then filtered to remove the Pd precipitate and washed with ethyl acetate. The filtrate was concentrated and the residue was purified by Reverse Phase Preparative HPLC to afford a light yellow solid as the cyclized product. The solid was then dissolved in a THF–methanol mixture (1.5 mL/1.5 mL), and 2 N NaOH solution (1.0 mL) was added. The reaction mixture was heated at 100 °C under microwave conditions for 15 min. It was then concentrated and adjusted pH to 4–5 with 1 N HCl solution. The light yellow solid was collected as product. (58 mg, 42% yield) IR (neat, ν_{max}/cm^{-1}): 2500–3500 (br), 2933, 2853, 1685, 1611, 1467, 1426, 1245, 1181, 1122, 1107, 1033. ^{1}H NMR (500 MHz, CD_3OD) δ 1.32–1.47 (m, 3 H), 1.74–1.81 (m, 1 H), 1.82–1.94 (m, 4 H), 1.96–2.12 (m, 2 H), 3.33–3.40 (m, 1 H), 4.47 (t, J = 5.49 Hz, 2 H), 4.56 (t, J = 5.49 Hz, 2 H), 7.50 (dd, J = 8.24, 4.88 Hz, 1 H), 7.72 (dd, J = 8.09, 1.37 Hz, 1 H), 7.75 (dd, J = 8.55, 1.53 Hz, 1 H), 7.95 (d, J = 8.55 Hz, 1 H), 8.22 (s, 1 H), 8.55 (dd, J = 4.73, 1.37 Hz, 1 H).^{13}C NMR (125 MHz, CD_3OD) δ 27.57, 28.46, 34.25, 37.43, 42.43, 75.85, 112.76, 121.13, 122.41, 123.85, 125.62, 126.09, 131.68, 133.11, 135.94, 137.02, 145.66, 146.57, 152.98, 171.15. LRMS m/z 363.3 (M + H). HRMS calcd for $C_{22}H_{23}O_3N_2$ (M + H): 363.1703, found: 363.1699.

Methyl 3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-6-carboxylate 18

In a flame-dried flask equipped with magnetic stirrer was added $[Ir(OMe(cod)]_2$ (150 mg, 0.225 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (120 mg, 0.45 mmol), and bis(pinacolato)diboron (7.62 g, 30 mmol). The flask was flushed with N_2 and sealed with a septum. Anhydrous THF (45 mL) was added and the solution was stirred at room temperature for 10 min. The solution turned dark purple. **6** (7.71 g, 30 mmol) was then added in one portion under nitrogen. The reaction mixture was stirred at 30 °C for 3 h. The solution turned red–brown. The solvents were then removed under reduced pressure, and the residue was treated with hexane (10 mL). The crystalline product was collected and washed with ethyl acetate–hexanes (1 : 3) and air dried to give a white solid as the desired product. (4.7 g, 41% yield) The mother liquor was also concentrated. Hexanes were added and the crystalline solid was collected to give 3.3 g of material as a mixture of **18** and **6**, which was recycled. mp: 195–197 °C (decomp.). IR (neat, ν_{max}/cm^{-1}): 3384, 2977, 2922, 2850, 1695, 1439, 1333, 1292, 1247, 1138, 1087. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 12H), 1.39–1.51 (m, 3H), 1.75–1.92 (m, 5 H), 1.92–2.07 (m, 2 H), 3.20–3.40 (m, 1 H), 3.96 (s, 3 H), 7.71 (dd, J = 8.54, 1.53 Hz, 1 H), 7.85 (d, J = 8.55 Hz, 1H), 8.08 (1 H, s), 8.51 (s, br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.86, 26.34, 27.33, 33.70, 36.87, 51.92, 83.99, 113.74, 119.37, 120.96, 124.65, 130.34, 134.77, 137.52, 168.11. HRMS calcd for $C_{22}H_{31}O_4N_{10}B$ (M + H): 383.2377, found: 383.2378.

3-Bromo-2-vinylpyridine 20

To a solution of 2,3-dibromopyridine (2.0 g, 8.44 mmol) in DMF (10 mL), tributyl(vinyl)tin (2.94 g, 9.29 mmol), LiCl (1.07 g, 25.32 mmol) and $PdCl_2(PPh_3)_2$ (0.296 g, 0.422 mmol) were added. The reaction mixture was heated at 100 °C overnight. It was then added to a saturated solution of KF and stirred for 4 h. Next, it was extracted with hexanes (3 × 50 mL) and the organic layers were combined. It was then washed with 1 N HCl solution. The aqueous layer was separated, neutralized with 1 N NaOH solution, and extracted with hexanes. The organic layer was separated, dried ($MgSO_4$) and concentrated to give a yellowish oil as product. (0.83 g, 53% yield) IR (film, ν_{max}/cm^{-1}): 2946, 2832, 1442, 790, 735, 702. ^{1}H NMR (400 MHz, CD_3OD) δ 5.57 (dd, J = 10.88, 1.83 Hz, 1 H), 6.38 (dd, J = 17.12, 1.96 Hz, 1 H), 7.19 (dd, J = 8.07, 4.65 Hz, 1H), 7.25 (dd, J = 16.87, 10.76 Hz, 1H), 8.00 (dd, J = 8.07, 1.47 Hz, 1 H), 8.48 (dd, J = 4.65, 1.47 Hz, 1 H).^{13}C

NMR (100 MHz, CD_3OD) δ (ppm) 121.77, 122.19, 125.52, 134.77, 142.63, 149.34, 154.32. LRMS m/z 184.0 (M + H), 186.0 (M + 2 + H). HRMS calcd for C_7H_7NBr (M + H): 183.9756, found: 183.9752.

Methyl 3-cyclohexyl-2-(2-vinylpyridin-3-yl)-1*H*-indole-6-carboxylate 21

To a mixture of **18** (2.5 g, 6.52 mmol), **20** (1.56 g, 8.48 mmol) and LiCl (553 mg, 13.04 mmol), ethanol (20 mL) and toluene (20 mL) were added. 2 M Na_2CO_3 (8.15 mL, 16.3 mmol) aqueous solution was then added, and the mixture was degassed with N_2. $Pd(PPh_3)_4$ (377 mg, 0.326 mmol) was added and the reaction mixture was heated at 80 °C for 3 h. The reaction mixture was filtered and concentrated. It was then extracted with ethyl acetate (2 × 50 mL). The organic layers were combined, washed with brine and dried ($MgSO_4$). Evaporation of solvent gave a brownish oil which was purified by flash column chromatography (silica gel, hexanes to ethyl acetate) to afford a light yellow solid as product (1.52 g, 65% yield). IR (neat, ν_{max}/cm^{-1}): 2923, 2850, 1712, 1433, 1288, 1217, 1105, 985. ^{1}H NMR (500 MHz, CD_3OD) δ 1.17–1.39 (m, 3 H), 1.60–1.95 (m, 7 H), 2.45–2.58 (m, 1 H), 3.91 (s, 3 H), 5.41 (dd, J = 10.99, 1.83 Hz,1 H), 6.30 (dd, J = 17.09, 1.83 Hz, 1 H), 6.65 (dd, J = 17.24, 10.83 Hz, 1 H), 7.42 (dd, J = 7.63, 4.88 Hz, 1 H), 7.71 (dd, J = 8.39, 1.37 Hz, 1 H), 7.76–7.84 (m, 2 H), 8.07 (s, 1 H), 8.62 (dd, J = 4.88, 1.53 Hz, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 27.42, 28.34, 34.49, 38.15, 52.52, 114.68, 120.53, 120.78, 120.99, 121.82, 123.70, 124.15, 129.70, 131.91, 135.05, 135.36, 137.56, 141.13, 150.55, 155.34, 170.12. LRMS m/z 361.3 (M + H). HRMS calcd for $C_{23}H_{25}O_2N_2$ (M + H): 361.1911, found: 361.1904.

Methyl 13-cyclohexyl-7*H*-pyrido[3′,2′:3,4]azepino[1,2-*a*]indole-10-carboxylate 22

To a suspension of NaH (230 mg of 60% dispersion oil, 5.77 mmol) in DMF (10 mL), **21** (1.6 g, 4.44 mmol) was added and the reaction mixture was stirred at room temperature for 15 min. Allyl bromide (0.46 mL, 5.33 mmol) was then added. The reaction mixture was stirred at room temperature for 2 h. It was then quenched with water, and extracted with ethyl acetate (100 mL). The organic layer was separated, washed with 1 N HCl solution, dried ($MgSO_4$) and concentrated to give an orange oil. It was then dissolved in dichloromethane (500 mL) and Grubbs Catalyst 2nd generation (377 mg, 0.444 mmol) was added. The reaction mixture was heated under reflux overnight. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 1 : 1 hexanes : ethyl acetate) to give an off-white solid as product. (0.95 g, 58% yield) IR (neat, ν_{max}/cm^{-1}): 1702, 1427, 1380, 1323, 1279, 1248, 1104. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.12–2.14 (m, 10 H), 2.60–2.75 (m, 1 H), 3.89 (s, 3 H), 4.26 (s, br, 1 H), 5.23 (s, br, 1 H), 6.64 (dt, J = 10.45, 6.68 Hz, 1 H), 6.91 (d, J = 10.68 Hz, 1 H), 7.53 (dd, J = 7.63, 4.58 Hz, 1 H), 7.63 (d, J = 8.24 Hz, 1 H), 7.85–7.98 (m, 2 H), 8.30 (s, 1 H), 8.69 (d, J = 3.66 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.45, 26.59, 32.55, 36.29, 51.83, 111.69, 118.98, 119.51, 120.69, 121.92, 122.28, 126.53, 129.34, 133.54, 134.47, 134.94, 135.26, 138.14, 148.81, 153.22, 167.06. LRMS m/z 373.2 (M + H). HRMS calcd for $C_{24}H_{25}O_2N_2$ (M + H): 373.1911, found: 373.1903.

13-Cyclohexyl-6,7-dihydro-5*H*-pyrido[3′,2′:3,4]azepino[1,2-*a*]indole-10-carboxylic acid 23

To a solution of **22** (1.0 g, 2.68 mmol) in ethyl acetate (500 mL), 10% Pd on carbon (100 mg) was added. The reaction mixture was stirred under a hydrogen balloon at room temperature for 4 h. It was then filtered through celite, washed with ethyl acetate, and the filtrate was concentrated. The residue was then dissolved in THF–MeOH (10 mL/10 mL), and 2 N NaOH solution (15 mL) was added. Next, the reaction mixture was heated at 100 °C under microwave conditions for 15 min. The reaction was then concentrated and the pH was adjusted 4–5 with 1 N HCl solution. An off-white solid was collected as product. (0.96 g, 99% yield) IR(neat, ν_{max}/cm^{-1}): 2500–3500 (br), 2925, 2850, 1685, 1612, 1418, 1379, 1253, 1185. ^{1}H NMR (500 MHz, CD_3OD) δ 1.22–1.54 (m, 3 H), 1.60–1.71 (m, 1 H), 1.75–2.30 (m, 7 H), 2.42–2.56 (m, 1 H), 2.65–2.79 (m, 1 H), 2.85 (tt, J = 12.25, 3.62 Hz, 1 H), 2.89–2.98 (m, 1 H), 3.60–3.75 (m, 1 H), 4.53–4.67 (m, 1 H), 7.50 (dd, J = 7.63, 5.19 Hz, 1 H), 7.72 (dd, J = 8.54, 1.22 Hz, 1 H), 7.82–7.90 (m, 2 H), 8.14 (s, 1 H), 8.51 (dd, J = 5.04, 1.68 Hz, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 27.44, 28.34, 31.05, 34.31, 34.71, 38.12, 41.48, 112.34, 120.79, 121.00, 121.62, 123.73, 126.97, 130.00, 130.79, 137.15, 137.20, 139.02, 149.44, 160.29, 172.65. LRMS m/z 361.1 (M + H). HRMS calcd for $C_{23}H_{25}O_2N_2$(M + H): 361.1911, found: 361.1906.

Methyl 2-(3-bromopyridin-2-yl)-3-cyclohexyl-1*H*-indole-6-carboxylate 24

To a mixture of **18** (1000 mg, 2.61 mmol), 2,3-dibromopyridine (742 mg, 3.13 mmol) and LiCl (221 mg, 5.22 mmol), ethanol (15 mL) and toluene (15 mL) were added. 2 M Na_2CO_3 (3.26 mL, 6.52 mmol) aqueous solution was then added and the mixture was degassed with N_2. $Pd(PPh_3)_4$ (151 mg, 0.13 mmol) was added and the reaction mixture was heated at 80 °C overnight. The reaction mixture was then filtered and concentrated. Next, it was extracted with ethyl acetate (2 × 80 mL). The organic layers were combined, washed with brine and dried ($MgSO_4$). Evaporation of solvent gave a brownish oil which was purified by flash column chromatography (silica gel, hexanes to 50% ethyl acetate in hexanes) to afford a light yellow solid as the desired product. (750 mg, 70% yield) IR(neat, ν_{max}/cm^{-1}): 3305, 2924, 2849, 1693(br), 1619, 1505, 1434, 1407, 1319, 1282, 1216, 1095. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26–1.38 (m, 3 H), 1.70–1.98 (m, 7 H), 2.71–2.82 (m, 1 H), 3.95 (s, 3 H), 7.25 (dd, J = 8.24, 4.58 Hz, 1 H), 7.79 (dd, J = 8.54, 1.53 Hz, 1 H), 7.88 (d, J = 8.54 Hz, 1 H), 8.04 (dd, J = 8.24, 1.53 Hz, 1 H), 8.11 (s, 1 H), 8.42 (s, br, 1 H), 8.68 (dd, J = 4.58, 1.53 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.26, 27.09, 32.72, 36.96, 51.94, 113.59, 120.04, 120.80, 121.89, 121.94, 123.98, 124.24, 130.37, 133.87, 135.56, 141.05, 148.10, 151.88, 168.04. LRMS m/z 413.0 (M + H), 415.0 (M + 2 + H). HRMS calcd for $C_{21}H_{22}O_2N_2Br$: 413.0859, found: 413.0850.

Methyl 1-(2-amino-2-oxoethyl)-2-(3-bromopyridin-2-yl)-3-cyclohexyl-1*H*-indole-6-carboxylate 25

To a suspension of NaH (25.5 mg of 60% dispersion oil, 0.64 mmol) in DMF (3 mL), **24** (220 mg, 0.53 mmol) was added and the reaction mixture was stirred at room temperature for 15 min. Next, 2-bromoacetamide (80 mg, 0.583 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. It was then

quenched with water, extracted with ethyl acetate (2 × 50 mL), and the organic layers were combined. Next, the organic layers were washed with 1 N HCl solution, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, ethyl acetate) to give a colorless thick oil as the desired product.(190 mg, 76% yield) IR (film, ν_{max}/cm^{-1}): 3362 (br), 2928, 2852, 1696 (br), 1435, 1382, 1282, 1255, 1242, 1020. ^1H NMR (500 MHz, $CDCl_3$) δ 1.18–1.36 (m, 3 H), 1.67–1.89 (m, 6 H), 2.03–2.11 (m, 1 H), 2.45–2.59 (m, 1 H), 3.96 (s, 3 H), 4.41 (d, J = 17.70 Hz, 1 H), 4.70 (d, J = 17.70 Hz, 1 H), 5.37 (s, br, 1 H), 6.19 (s, br, 1 H), 7.35 (dd, J = 8.24, 4.58 Hz, 1 H), 7.85–7.91 (m, 2 H), 8.08–8.14 (m, 2 H), 8.70 (dd, J = 4.73, 1.37 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.14, 26.91, 27.02, 32.31, 33.10, 37.22, 47.78, 52.08, 111.91, 121.00, 121.10, 122.25, 124.00, 124.72, 125.17, 130.15, 135.58, 136.36, 141.11, 148.40, 150.72, 167.66, 170.39. LRMS m/z 470.2 (M + H), 472.2 (M+2+H). HRMS calcd for $C_{23}H_{25}O_3N_3Br$ (M + H): 470.1074, found: 470.1069.

Methyl 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-pyrido[3′,2′:5,6][1,4]-diazepino[1,7-*a*]indole-10-carboxylate 26

In a microwave reactor tube, **25** (500 mg, 1.063 mmol), Xantphos (92 mg, 0.159 mmol), $Pd_2(dba)_3$ (97 mg, 0.1063 mmol) and Cs_2CO_3 (518 mg, 1.59 mmol) were added. The reaction was then flushed with nitrogen and sealed. 1,4-dioxane (10 mL) was added and the mixture was heated at 100 °C under microwave conditions for 5 h. Next, water was added and the reaction was extracted with ethyl acetate (2 × 75 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, 20% ethyl acetate in hexanes to 60% ethyl acetate in hexanes) to give a yellowish solid as the desired product. (235 mg, 57% yield) IR (neat, ν_{max}/cm^{-1}): 2924, 1708, 1686, 1613, 1443, 1389, 1255, 1044. ^1H NMR (500 MHz, DMSO-d_6) δ 1.20–1.47 (m, 3H), 1.66–1.86 (m, 5 H), 1.89–2.05 (m, 2 H), 3.33–3.42 (m, 1 H), 3.90 (s, 3 H), 4.91 (s, br, 2 H), 7.52 (dd, J = 8.09, 4.43 Hz, 1 H), 7.64 (dd, J = 8.09, 1.37 Hz, 1 H), 7.69 (dd, J = 8.54, 1.22 Hz, 1 H), 7.99 (d, J = 8.55 Hz, 1 H), 8.30 (s, 1 H), 8.61 (dd, J = 4.42, 1.37 Hz, 1 H), 10.44 (s, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.64, 26.75, 32.31, 35.35, 47.02, 51.92, 111.59, 119.60, 120.99, 121.03, 122.93, 123.74, 129.40, 130.08, 133.90, 134.36, 134.75, 141.72, 145.70, 166.94, 167.98. LRMS m/z 390.3 (M + H). HRMS calcd for $C_{23}H_{24}O_3N_3$ (M + H): 390.1812, found: 390.1811.

13-Cyclohexyl-6-oxo-6,7-dihydro-5*H*-pyrido[3′,2′:5,6][1,4]diazepino[1,7-*a*]indole-10-carboxylic acid 27

To a solution of **26** (180 mg, 0.462 mmol) in pyridine (7 mL), LiI (186 mg, 1.387 mmol) was added. The reaction mixture was heated at 180 °C under microwave conditions for 2.5 h. Water was added and the reaction mixture was adjusted to pH 4–5 with 1 N HCl solution. A light brownish solid was collected as product. (170 mg, 98% yield) IR (neat, ν_{max}/cm^{-1}): 2500–3500 (br), 2923, 2847, 1685, 1671, 1438, 1401, 1252, 1202, 1136. ^1H NMR (500 MHz, DMSO-d_6) δ 1.17–1.49 (m, 3 H), 1.64–1.86 (m, 5 H), 1.89–2.04 (m, 2 H), 4.89 (s, br, 2 H), 7.51 (dd, J = 8.09, 4.42 Hz, 1 H), 7.64 (dd, J = 8.24, 1.53 Hz, 1 H), 7.68 (dd, J = 8.54, 1.53 Hz, 1 H), 7.96 (d, J = 8.55 Hz, 1 H), 8.26 (d, J = 1.22 Hz, 1 H), 8.61 (dd, J = 4.58, 1.53 Hz, 1 H), 10.44 (s, 1 H), 12.76 (s, br, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.67, 26.79, 32.34, 35.38, 47.03, 111.64, 119.92, 120.86, 120.94, 123.70, 124.12, 129.19, 130.08, 133.87, 134.44, 141.84, 145.70, 168.04. LRMS m/z 376.3 (M + H). HRMS calcd for $C_{22}H_{22}O_3N_3$ (M + H): 376.1656, found: 376.1652.

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