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Discovery of novel tricyclic indole derived inhibitors of HCV NS5B RNA dependent RNA polymerase

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ABSTRACT

The characterization of HCV genome has identified various vital functional proteins involved in the life cycle of hepatitis C virus. This has resulted in many novel enzymatic targets that are potential for development of therapeutic agents. The HCV RNA dependent RNA polymerase (HCV NS5B) is one such essential enzyme for HCV replication that has been well characterized and studied by various groups to develop novel therapies for hepatitis C. In this paper, we describe our efforts towards the identification and structure–activity relationship (SAR) of novel tricyclic indole derivatives that bind close to the palm site of the NS5B polymerase. X-ray crystal structure of an inhibitor bound to the polymerase is also described.

1. Introduction

Approximately 3% of world population has been infected with hepatitis C virus (HCV) which belongs to the *hepacivirus* genus and *Flaviviridae* family.[1,2] The vast majority (~80%) of these infections turn chronic, resulting in cirrhosis of the liver and hepatocellular carcinoma. HCV infections are the primary causes of liver transplantation in the United States. Current standard of care for the treatment of patients with gt1 infections is a combination of pegylated interferon, ribavirin and a protease inhibitor which has resulted in improved management of the disease. About 60–70% of the patients infected with the major genotype 1 virus demonstrate sustained virologic response (SVR).[3,4] The suboptimal response obtained in treating genotype 1 infected patients and non-responders has prompted experimental new therapies for the treatment of HCV. Characterization of HCV genome has resulted in identification of various proteins and their functions in the viral life cycle, providing many novel targets for drug interference. Of these, the quintessential enzyme HCV NS3 protease[5,6] has been widely studied and many novel inhibitors have been identified and progressed to clinical evaluation including Boceprevir,[7] Narlaprevir[8] and Vaniprevir[9] from our laboratories. HCV NS5B polymerase is a RNA dependent RNA polymerase enzyme which is essential for viral replication that has been extensively studied as a potential target for therapeutic intervention. Numerous non-nucleoside (NNI) and nucleotide (NI) inhibitors targeting various sites of the enzyme have been identified and progressed to clinical evaluation. Proof of concept was initially demonstrated with NS5B inhibitor Nesbuvir[10] (HCV-796) resulting in significant viral load reductions in humans. However, it was discontinued from further development due to its adverse side effects. Many nonnucleoside inhibitors such as filibuvir[11], GS-9190,[12] ANA598,[13] VCH-759[14] A837093[15] are currently undergoing or completed clinical evaluations and have demonstrated robust viral load reductions. Nucleoside derived polymerase inhibitors such has GS7977[16] and INX-189[17] have demonstrated clinical efficacy and are currently undergoing phase-2 studies. We recently disclosed novel indole derived inhibitors of HCV NS5B polymerase.[18,19] These compounds bind to the NS5B enzyme close to the palm site. The X-ray structure of the inhibitor bound to enzyme indicated novel interactions that contributed to its specific binding (Fig. 1). 5-Chloroindole derivative **1**, functionalized with a pyridone at C(3) and benzyl acylsulfonamide at C(2) demonstrated good enzyme potency (IC_{50} = 10 nM) and modest replicon cellular potency (EC_{50} = 1.0 μM). The corresponding C(2) carboxylic acid analog containing N1 2,4-difluorobenzyl moiety

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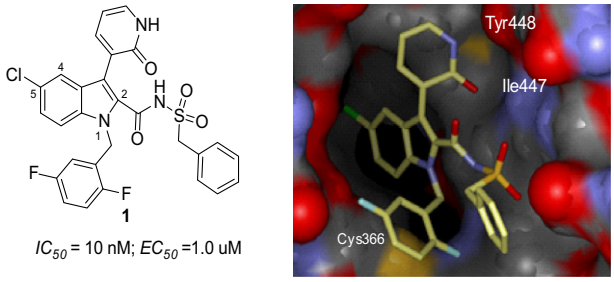


Figure 1.

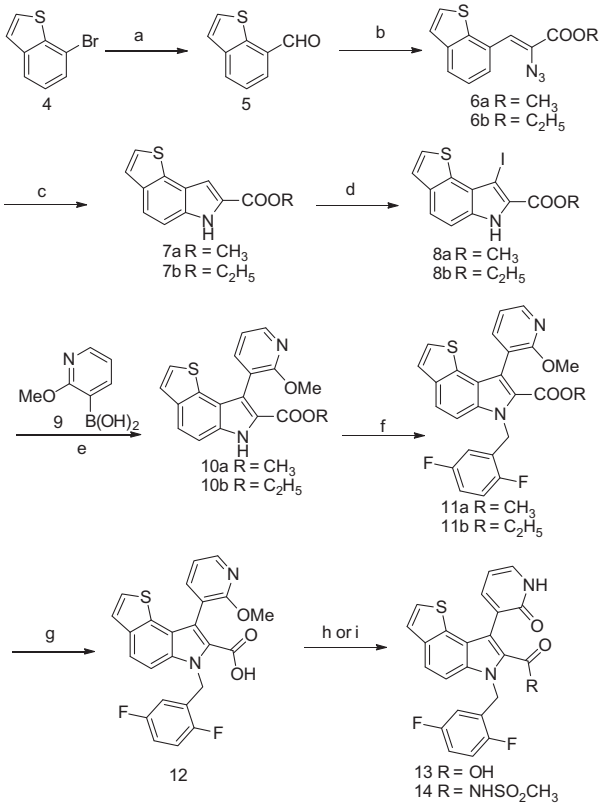
displayed an IC_{50} = 35 nM and EC_{50} = 10 μM). The X-ray structure of **1** bound in the enzyme revealed characteristic hydrogen bonding interactions of C(3)-pyridone to the protein backbone. The pyridone oxygen atom accepts a hydrogen bond from tyr448, whereas the pyridone NH donates hydrogen bond to Ile447. In addition to these interactions, the chlorine atom at the C(5) position is buried into a lipophilic channel and the aryl ring of the 2, 5-difluorophenyl makes close contact with Cys366.

It was clear from the soaked X-ray structure of **1** that the pocket occupied by the C(5) chlorine was large and could be replaced with other substitutions, potentially improving potency. We envisioned syntheses of novel tricyclic indole derivatives by fusing an additional ring at C(4)–C(5) positions to improve potency. In this paper, we describe the syntheses and evaluation of NS5B polymerase inhibitors that culminated in the identification of a novel furan derived tricyclic indoles resulting in improved enzyme binding and cellular activity.

2. Chemistry

Syntheses of inhibitors used to construct tricyclic ring systems are outlined in schemes below. Scheme 1 outlines the syntheses of inhibitors derived from the 6*H*-thieno[2,3-*e*]indole core.

Commercially available 7-bromobenzo[*b*]thiophene (**4**) was converted to aldehyde **5** by treatment with *n*-butyl lithium at −78 °C to affect bromine–lithium exchange followed by treatment with DMF. Aldehyde **5** was then subjected to Hemetsberger–Knittel[20] reaction to assemble the indole core. Condensation of aldehyde **5** with ethyl azidoacetate using sodium methoxide resulted in azido acrylate derivatives **6a** and **6b**. Azido compounds **6a** and **6b** were identified as methyl and ethyl esters arising from *trans*-esterification of the ethyl ester with sodium methoxide. The mixtures of esters were heated in refluxing xylenes to induce indole formation. Upon cooling the desired indole products precipitated from the reaction mixture yielding 6*H*-thieno[2,3-*e*]indole-7-carboxylate esters (**7a** and **7b**). The facile access to aldehyde **5** followed by scalability of the Hemetsberger–Knittel synthesis made this method desirable and robust for syntheses of indoles. Tricyclic indoles (**7a** and **7b**) were converted to inhibitor **14** by functionalizing the indole at C(3) position using Suzuki coupling followed by nitrogen alkylation. Thus, a mixture of **7a** and **7b** were selectively iodinated at C(3) with NIS to form iodoindoles **8a** and **8b**. Coupling of iodo compounds with 2-methoxypyridin-3-ylboronic acid (**9**) using Pd(dppf)Cl_2 installed methoxypyridine, as a masked pyridone moiety.[21] N(1) alkylation of indoles **10a** and **10b** was accomplished by treatment with 2,5-difluorobenzyl bromide and Cs_2CO_3 which were subsequently hydrolyzed to the acid **12** using aqueous lithium hydroxide. Demethylation of pyridine methyl ether **12** with refluxing 4 M HCl in dioxane yielded pyridone analog **13**. Alternatively, carboxylic acid **12** was coupled with methyl sulfonamide using carbonyl diimidazole followed by demethylation with 4 M HCl in dioxane to yield methyl acyl sulfonamide analog **14**.[22]

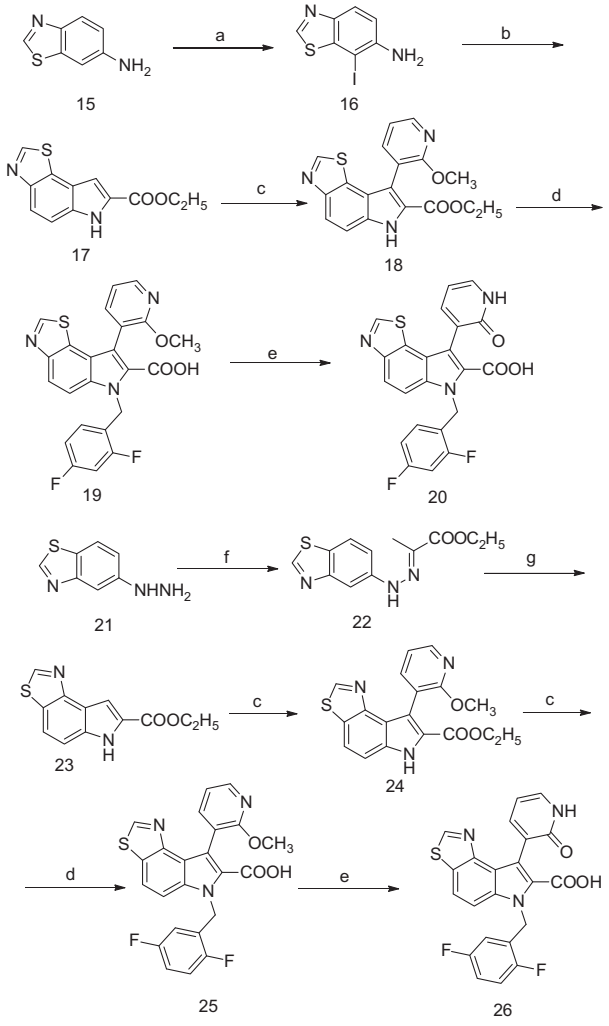


Scheme 1. Reagents and conditions: (a) (i) *n*-BuLi, ether, −78 °C, 15 min; (ii) DMF, −78 °C → rt; (b) $N_3CH_2COOC_2H_5$, NaOMe, methanol, 0 °C → rt; (c) xylenes, reflux; (d) NIS, DMF, 0 °C → rt; (e) Pd(dppf)Cl_2, K_2CO_3, H_2O, DME, reflux (f) Cs_2CO_3, DMF, 2,5-difluorobenzyl bromide, (g) aq LiOH, THF, reflux; (h) 4 M HCl, dioxane, reflux (i) (i) $CH_3SO_2NH_2$, CDI, DBU reflux; (ii) 4 M HCl, dioxane.

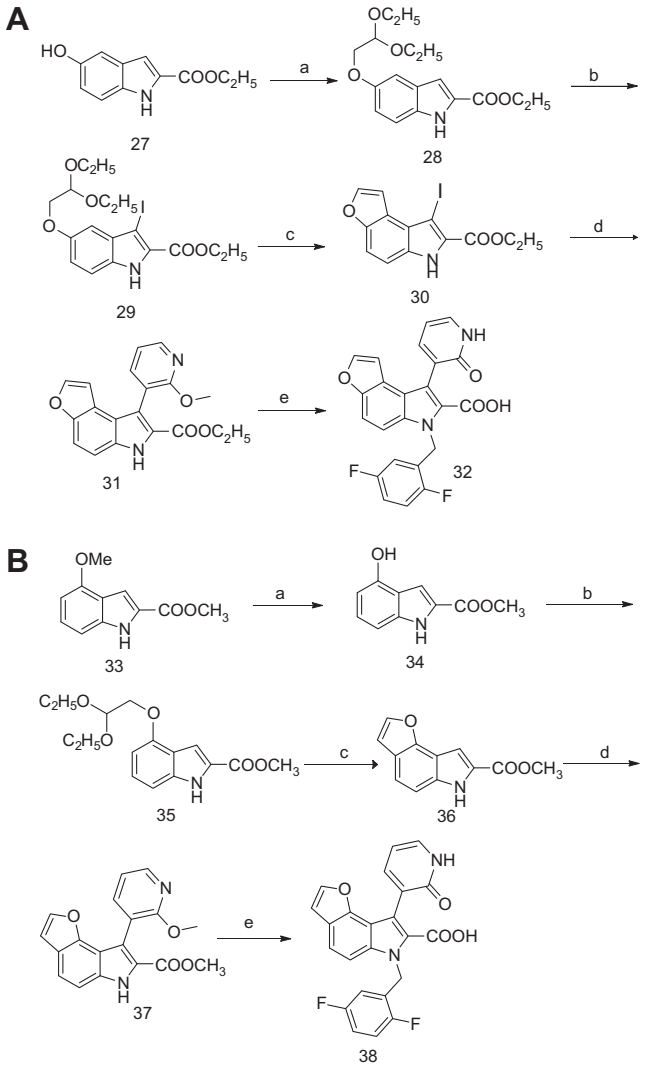
Isomeric thiazole fused indole derived inhibitors **20** and **26** were synthesized using palladium catalyzed Heck cyclization and Fischer indole synthesis,[23] as outlined in Scheme 2. Regioselective iodination of 6-aminobenzothiazole (**15**) with iodine and silver sulfate resulted in formation of 7-iodobenzo[*d*]thiazol-6-amine (**16**) in modest yields.[24] The iodinated aniline **16** was converted to ethyl 6*H*-thiazolo[5,4-*e*]indole-7-carboxylate (**17**) by heating with ethyl pyruvate and palladium acetate in the presence of DABCO.[25] Indole **17** was then converted to inhibitor **20** following iodination, Suzuki coupling, N-alkylation and demethylation in a similar sequence as outlined in scheme 1. The regioisomeric thiazole compound **26** was initiated from hydrazide **21**. Condensation of **21** with ethylpyruvate followed by acid catalyzed cyclization using HCl in ethanol[26] resulted in the formation of indole **23** that was converted to inhibitor **26** using similar reactions described in Scheme 1.

Scheme 3 outlines syntheses of 4,5-furan fused indole derivatives. Alkylation of commercially available ethyl 5-hydroxy-1*H*-indole-2-carboxylate (**27**) with bromoacetaldehyde diethyl acetal resulted in O-alkylated intermediate **28**. Attempts to induce furan cyclization with intermediate **28** only resulted in polymerization and intractable mixtures. However, iodination of indole **28** with NIS resulted in iodo derivative **29** which underwent smooth cyclization to form ethyl 8-iodo-6*H*-furo[3,2-*e*]indole-7-carboxylate **30** upon heating with polyphosphoric acid. The furan-derived indole **30** was converted to target **32** following similar reactions previously described.

The regioisomeric furan fused indole **36** was synthesized starting from commercially available methyl 4-methoxy-1*H*-indole-2-carboxylate (**33**). Demethylation of **33** with BBr_3 resulted in hydroxy indole **34**, which was alkylated with bromoacetaldehyde



Scheme 2. Reagents and conditions: (a) (i) Ag_2SO_4, I_2, ethanol, 47%; (b) ethyl pyruvate, $Pd(OAc)_2$, DABCO, tetramethylene hexammine, DMF, 33%; (c) (i) NIS, DMF; (ii) **9**, $Pd(dppf)Cl_2$, K_2CO_3, H_2O, DME, reflux; (d) (i) Cs_2CO_3, DMF, 2,5-difluorobenzyl bromide or 2,4 difluorobenzyl bromide; (ii) aq LiOH, THF, reflux; (e) 4 M HCl/dioxane reflux, 71% (f) ethylpyruvate, HCl; (g) HCl in ethanol reflux.



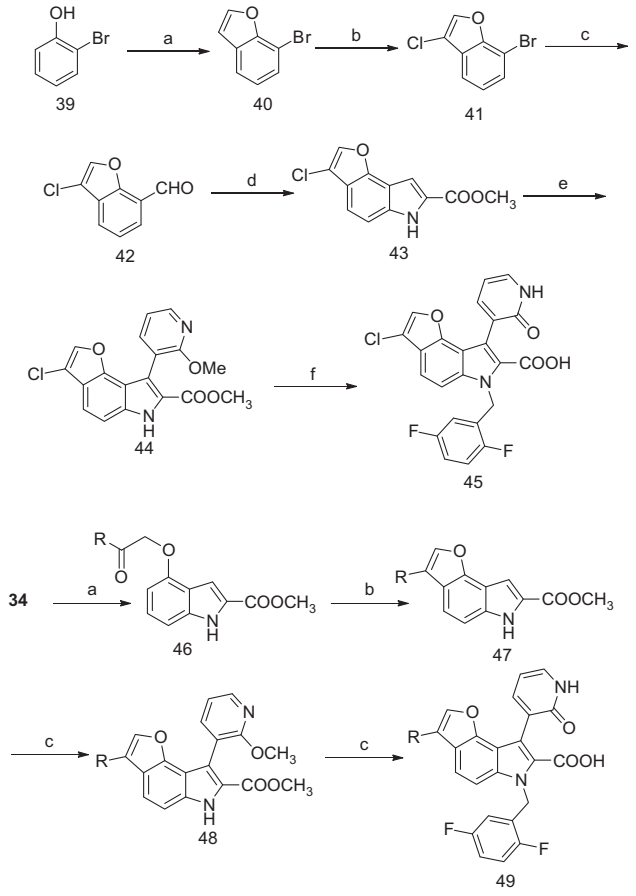
Scheme 3. (A) Reagents and conditions: (a) $BrCH(OC_2H_5)_2$, Cs_2CO_3, DMF, 150 °C; (b) NIS, DMF; (c) PPA, benzene, reflux, 1 h; (d) **9**, $Pd(dppf)Cl_2$, K_2CO_3, H_2O, DME, reflux; (e) (i) 2,5-difluorobenzyl bromide, Cs_2CO_3, DMF; (ii) aq LiOH, THF; (iii) 4 M HCl/dioxane reflux. (B) Reagents and conditions: (a) BBr_3, CH_2Cl_2, −78 → 0 °C; (b) $BrCH(OC_2H_5)_2$, Cs_2CO_3, DMF, 150 °C; (c) Amberlyst-15, benzene, reflux; (d) (i) NIS, DMF; (ii) **9**, $Pd(dppf)Cl_2$, K_2CO_3, H_2O, DME, reflux; (e) (i) 2,5-difluorobenzyl bromide, Cs_2CO_3, DMF; (ii) aq LiOH, THF; (iii) 4 M HCl/dioxane reflux.

diethylacetal using conditions previously described. Cyclization of **35** to methyl 6*H*-furo[2,3-*e*]indole-7-carboxylate was accomplished by refluxing **35** in benzene with strongly acidic resin amberlyst-15 to obtain indole **36**. Tricyclic indole **36** was converted to inhibitor **38** using similar set of reactions outlined in scheme 1.

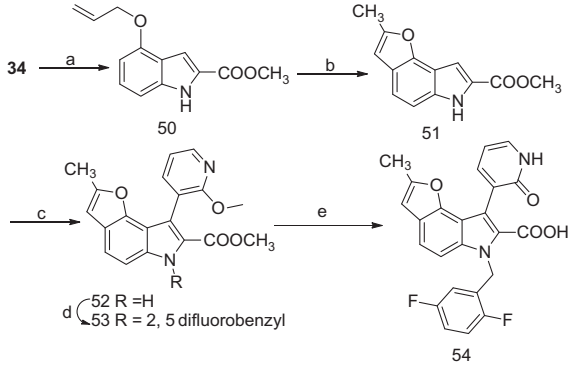
Furan fused indoles bearing substitutions at two and three positions of furan were synthesized using methodology outlined in schemes 4 and 5. The synthesis of methyl 3-chloro-6*H*-furo[2,3-*e*]indole-7-carboxylate (**43**) was initiated from 2-bromophenol (**39**). Alkylation of **39** with 2-bromoacetaldehyde diethylacetal, followed by acid catalyzed cyclization afforded 7-bromobenzofuran **40**. Chlorination of **40** with chlorine gas followed by treatment with sodium hydroxide provided 7-bromo-3-chlorobezofuran **41**. Halogen metal exchange of **41** followed by treatment with DMF yielded aldehyde **42** that was converted to indole **43** using Hemetsberger–Knittel synthesis. Indole **43** was converted to inhibitor **45** using similar protocol previously described. Syntheses of 3-alkyl substituted indoles were accomplished starting from methyl 4-hydroxyindole-2-carboxylate **34**. Alkylation of phenolic oxygen with bromo acetone or 1-bromobutane-2-one followed by acid catalyzed cyclization resulted in 3-alkyl substituted indoles of type **47**, which were converted to inhibitors of type **49** using methodology previously described.

2-Methyl substituted indole **51** was synthesized using metal catalyzed Claisen rearrangement methodology. Thus, alkylation of methyl 4-hydroxy indole 2-carboxylate **34** with allyl bromide, formed O-allylated compound **50**. Refluxing **50** with $Pd(CH_3CN)_2Cl_2$ and benzophenone in the presence of potassium carbonate induced cyclization to tricyclic indole **51**, by a metallo-Claisen rearrangement followed by intramolecular ring closure reaction.[27] Versatile intermediate **51** was progressed to inhibitor **54**, following reaction conditions previously outlined

Synthesized inhibitors were evaluated in NS5B enzyme assay[28] for their ability to inhibit the initiation of polymerization using a NS5BΔCT21 polymerase enzyme by 50%. Potent compounds in this assay were evaluated in the cellular based replicon assay[29] to obtain EC_{50} defined as the concentration required reducing 50% of viral RNA levels in replicon infected hepatoma cells. Cellular toxicity of inhibitors was evaluated using GAPDH as the internal control and/or using MTS toxicity assays. Compounds demonstrating



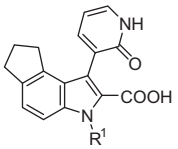
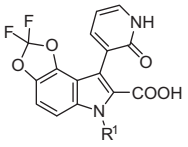
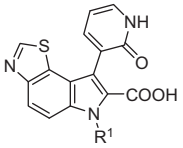
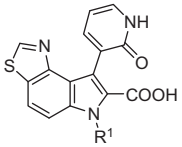
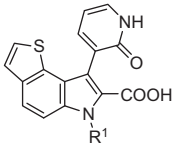
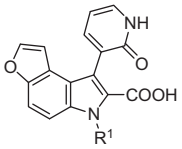
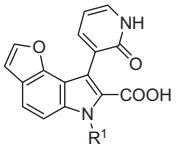
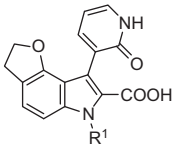
Scheme 4. Reagents and conditions: (i) Cs_2CO_3, $BrCH(OC_2H_5)_2$, DMF, 150 °C; (ii) PPA, toluene reflux; (b) Cl_2 gas, acetic acid, 0 °C → rt, (ii) NaOH, methanol; (c) (i) BuLi, ether, −78 °C; (ii) DMF, −78 °C → rt; (d) $N_3CHCOOC_2H_5$, NaOMe, MeOH; (ii) xylenes, reflux; (e) (i) NIS, DMF; (ii) $Pd(dppf)Cl_2$, K_2CO_3, H_2O, DME, reflux; (f) (i) 2,5-difluorobenzyl bromide, Cs_2CO_3, DMF; (ii) aq LiOH, THF; (iii) 4 M HCl/dioxane reflux.



Scheme 5. Reagents and conditions: (a) Cs_2CO_3, allylbromide, DMF, 63%; (b) $Pd(CH_3CN)_2Cl_2$, benzoquinone, K_2CO_3, THF, reflux, 32%; (c) (i) NIS, DMF, (ii) **9**, $Pd(dppf)Cl_2$, K_2CO_3, H_2O, DME reflux; (d) 2,5-difluorobenzyl bromide, Cs_2CO_3, DMF, (e) (i) aq LiOH/THF/MeOH, (ii) 4 M HCl/dioxane reflux.

potent inhibition in enzyme assay and replicon based cellular assay were evaluated for oral exposure using a rapid rat assay.[30] The area under the curve integrated over 0–6 h after single oral administration of 10 mg/kg was defined as $AUC_{0-6\ h}$ enabling ranking of compounds for further evaluation.

Table 1

Entry	Compound	IC_{50} (nM)	EC_{50} (nM)	AUC[a] (μM h)
55		27	3.5	104
56		7	2.0	
20		1700[c]	—	104
26		9	0.7	
14		67	5.2	63
32		34	3.1	
38		31	0.16	146
57		8	0.46	11

[b] All compounds demonstrated CC_{50} >10 μM.
[a] 10 mg/Kg of compound in 0.4% HPMC was dosed to rats orally.
[c] R^1 = 2, 4 difluorobenzyl.

3. Discussion

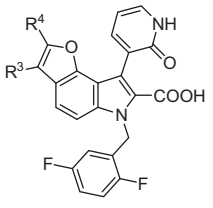
Table 1 summarizes tricyclic indole inhibitors that were synthesized as initial screen for the inhibition of HCV NS5B polymerase. Previous N(1) SAR studies had shown that a 2,5 difluorobenzyl group and C(2) carboxylic acid as preferred moieties. Synthesis of cyclopentyl fused indole resulted in compound **55** (IC_{50} = 27 nM and EC_{50} = 3.5 μM), with loss in enzyme and replicon activity poorer than **1**. Even though the activity was lower than **1** this clearly demonstrated that introduction of a five-membered fused ring at C(4)–C(5) was tolerated and could be optimized to obtain compound with acceptable activity. Replacement of cyclopentyl ring in **55** with difluorodioxolane ring resulted in analog **56** that

demonstrated improved potency IC_{50} = 7 nM and EC_{50} = 2 μM. This was a marginal improvement compared to the cyclopentane analog **55**. We next evaluated incorporation of a series of five-membered heterocycles. Incorporation of a 6*H*-thiazolo[5,4-*e*]indole into the inhibitor scaffold resulted in analog **20** (IC_{50} = 1700 nM) that was not well tolerated. However, the introduction of a regioisomeric thiazole resulted in analog **26** (IC_{50} = 9 nM; EC_{50} = 0.7 μM) that was more potent than the chloro derivative **1**.

We next evaluated the introduction of thiophene and furans at this position. The thiophene derived analog **14** demonstrated acceptable potency with IC_{50} = 67 nM and EC_{50} = 5.2 μM. Even though the enzyme potency of this analog was good its potency in the cellular assay was modest. The introduction of furan rings resulted in analogs **32** and **38**. Inhibitor **32** derived from 6*H*-furo[3,2-*e*]indole-7-carboxylic acid was potent in the enzyme assay with IC_{50} = 34 nM, but demonstrated poor cellular activity with EC_{50} = 3.1 μM whereas, the regio isomeric furan containing compound **38** demonstrated much improved cellular potency. Thus, analog **38** containing 6*H*-furo[2,3-*e*]indole-7-carboxylic acid had a potency an IC_{50} = 31 nM and an EC_{50} = 0.16 μM. This was a significant improvement in cellular potency compared to the chloro analog **1**. The furan derived analog **38** was further reduced to the dihydrofuran derivative **57** that improved potency but had a weaker cellular potency (IC_{50} = 8 nM; EC_{50} = 0.46 μM). From the activity of compounds in Table 1, it is clear that the presence of oxygen at the four position of the indole is important for potency. Replacement of this group with a sulfur (analog **14**) or CH (analog **32**) resulted in reduced cellular activity. It is unclear if this loss in activity is an electronic or steric effect. Tricyclic indole derived analogs were evaluated for plasma exposure in rats dosed orally at 10 mg/kg in methyl cellulose. The tricyclic inhibitors were readily absorbed in rats and demonstrated excellent plasma exposure. The furan derivative **38** demonstrated excellent $AUC_{0-6\ h}$ = 146 μM h and the dihydrofuran derivative had an $AUC_{0-6\ h}$ = 11 μM h. Having identified the furan fused analog **38** as a potential lead with improved enzyme and cellular activity we evaluated the effect of substitutions on the furan ring.

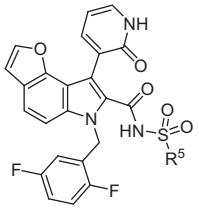
The syntheses of substituted furan fused indoles are outlined in scheme 4 and their inhibitory activities are described in Table 2. Incorporation of a methyl or ethyl substitution at C(3) position of the furan ring resulted in analogs **58** (IC_{50} = 2900 nM) and **59** (IC_{50} >5000 nM) with significant loss in enzyme potency compared to the hydrogen analog 38; clearly demonstrating alkyl substitution was not tolerated at this position. However, the introduction of a chlorine group (compound **45**) displayed high potencies (IC_{50} = 7 nM) and potent cellular activity (EC_{50} = 0.12 μM. This is an interesting observation given the fact that both chlorine and

Table 2



Entry	R^3	R^4	IC_{50} (nM)	EC_{50} (nM)
58	CH_3	H	2900	—
59	C_2H_5	H	>5000	—
45	Cl	H	7	0.12
53	H	CH_3	21	2.00

Table 3



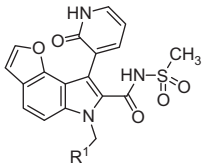
Entry	R^5	IC_{50} (nM)	EC_{50} (nM)	AUC (μM h)
60	CH_3	9	0.05	11
61	C_2H_5	6	0.11	0.7
62	$(CH_3)_2CH$	8	0.05	1.0
63	^cPr	16	0.05	—

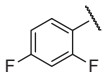
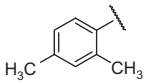
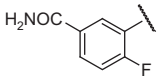
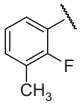
methyl groups are similar in size and display similar lipophilic properties. The chlorine substituted compound **45** also demonstrated good oral pharmacokinetics in the rapid rat assay with an $AUC_{0-6\ h}$ = 16 μM h when dosed at 10 mg/kg. We next evaluated the activity of 2-methyl substituted furano-indole resulting in compound **53**. The methyl substitution at 2-postion was well tolerated with compound **53** inhibiting the polymerase enzyme with IC_{50} = 21 nM, however it had a weak cellular activity (EC_{50} = 2 μM); an 18-fold loss in activity compared to unsubstituted compound **38** (see Table 3.)

All attempts to improve cellular potencies of these inhibitors by incorporating substitutions on the furan ring only lead to compounds that were less potent than the hydrogen derivative. We therefore decided to investigate acid isostere modifications at C(2) carboxylic acid of indole ring. Various alkyl derived acyl sulfonamides of the lead compound **38** were synthesized and evaluated in the binding and cellular assays (Table 3). Thus, functionalization of C(2) carboxylic acid with methyl acylsulfonamide resulted in analog **60** which demonstrated an enzyme activity of IC_{50} = 9 nM and cellular activity of EC_{50} = 0.05 μM. This analog also demonstrated acceptable oral rat PK with an $AUC_{0-6\ h}$ = 11 μM h, when dosed at 10 mg/Kg. Homologation of methyl to ethyl acyl sulfonamide resulted in analog **61** (IC_{50} = 6 nM, EC_{90} = 0.11 μM) which demonstrated low oral PK ($AUC_{0-6\ h}$ = 0.7 μM h). The incorporation of branched acyl sulfonamide groups had a positive effect on binding with isopropyl acyl sulfonamide and cyclopropyl acyl sulfonamides compounds **62** and **63** having IC_{50}'s of 8 and 16 nM and EC_{50}'s of 0.05 μM respectively. This is a 20-fold improvement in comparison to analog 1.

Having identified methylacyl sulfonamide as desirable moiety at C(2) position of indole, we next explored replacement of N(1) 2,5-difluorobenzyl group with other benzylic moieties. Table 4 outlines the results of these modifications. Replacement of 2,5-difluorobenzyl group of **60** with 2,4 difluoro benzyl moiety resulted in analog **64** (IC_{50} = 31 nM, EC_{50} = 0.08 μM) demonstrating diminished cellular potency compared to 2,5-difluoro analog **60**. Introduction of the 2-fluorobenzyl moiety resulted in inhibitor **65** with excellent enzyme inhibition (IC_{50} = 8 nM) and modest cellular activity (EC_{50} = 0.1 μM). The 2-fluorobenzyl analog had a better oral exposure in rats ($AUC_{0-6\ h}$ = 9.5 μM h) than the corresponding 2,4 difluorobenzyl analog **64**. Introduction of 2,4 dimethylbenzyl group resulted in analog **66** (IC_{50} = 6 nM; EC_{50} = 0.06 μM) which had a similar activity to the 2,5-difluorobenzyl analogs. We next evaluated the replacement of 2,5-difluorobenzyl group with 2-methylbenzyl group resulting in compound **67** (IC_{50} = 10 nM;

Table 4



Entry	R^1	IC_{50} (nM)	EC_{50} (nM)	AUC (μM h)
64		31	0.08	2.4
65		8	0.10	9.5
66		6	0.06	—
67		10	0.05	1.2
68		10	0.03	
69		3	0.03	0.3
70		3	0.05	

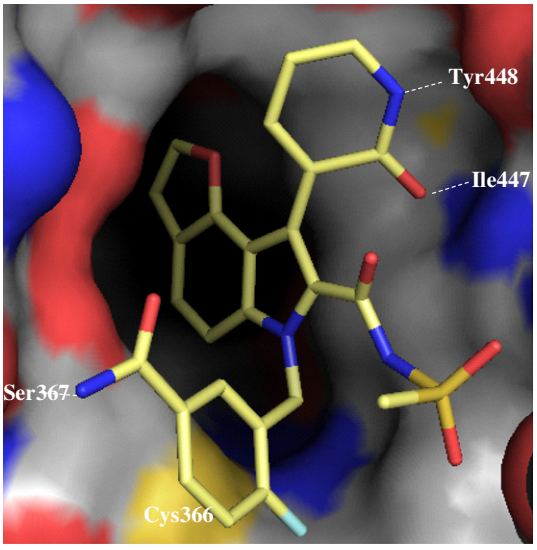


Figure 2. X-ray structure of **68** bound to HCV NS5B polymerase.

EC_{90} = 0.05 μM). The replacement of N(1) 2, 5-fluorobenzyl moiety of **60** with primary carboxamide derivative yielded inhibitor **68** (IC_{50} = 10 nM; EC_{50} = 0.03 μM); with improved cellular potency relative to 2,5-difluorobenzyl derivatives. Replacement of N(1) with 2-fluoro-3-methylbenzyl and 2-chlorobenzyl moieties yielded compounds **69** (IC_{50} = 3 nM; EC_{50} = 0.03 μM) and inhibitor **70** (IC_{50} = 3 nM; EC_{50} = 0.05 μM) that had improved enzyme and cellular profiles than **60**. However, the oral exposure of **67** and **69** were poor with an $AUC_{0-6\ h}$ = 1.2 and 0.3 μM h, possibly due to increased metabolism of the methyl group.

The X-ray structure of inhibitor **68** bound to HCV NS5B polymerase was solved and characteristic interactions responsible for specific binding with the enzyme were identified (Fig. 2). The inhibitor bound close to the palm region of the enzyme. The oxygen of the pyridone at C(3) accepted a hydrogen bond from NH of Ile447 and NH of pyridone in turn donated a hydrogen bond to Tyr448 making these interactions specific. The aryl ring of the indole was oriented orthogonal to the pyridone ring and formed lipophilic interactions with the protein. The C(3)–C(4) fused furan ring was buried in a lipopholic pocket and was in close proximity to Tyr415, Met414, Pro197 and Leu384.

The aryl ring of the N(1) benzyl group made lipophilic contact with the sulfur of cys366 and the carboxamide group interacts with side chain hydroxyl of Ser367. In addition oxygen of an amide interacted with Tyr415 and Arg386 via a water molecule.

4. Conclusions

In an effort to improve potency and cellular activity of indole derived inhibitor **1**, novel tricyclic indole scaffolds were synthesized and evaluated for inhibition of HCV NS5B polymerase. C(4)–C(5) ring fused indoles were prepared and incorporated into inhibitor scaffold. Five-membered C(4)–C(5) ring fusion was well-tolerated and yielded compounds with good enzyme activities and modest cellular potencies. Expanding the SAR of the fused five-membered rings identified **38**, a 6*H*-furo[2,3-*e*]indole-7-carboxylic acid derived compound that contained a C(4)–C(5) fused furan with good potency (IC_{50} = 31 nM) and cellular activity (EC_{50} = 0.16 μM). Further SAR exploration of substitution on the furan demonstrated that chlorine at C(3) was tolerated. Investigation of substitutions at indole C(2) showed acyl sulfonamide derivatives were more potent than corresponding carboxylic acids. It was discovered that methyl acyl sulfonamide was equipotent to cyclopropyl acyl sulfonamide derivatives. A systematic investigation of N(1) substitutions in C(2) methyl acyl sulfonamide series identified N(1) benzyl groups substituted with 2-fluoro and 5-carboxamide, compounds **68** (EC_{50} = 0.03 μM) demonstrating excellent enzyme activities and cellular potencies.

The X-ray structure of **68** bound to the HCV polymerase enzyme revealed key hydrogen bonding interactions to the backbone, which correlated with the enhancement of potency. The interaction of the carboxamide with hydroxyl of Ser367, and oxygen to Tyr415 and Arg386 via a bound water molecule is worth mention. We have demonstrated the identification of a novel tricyclic indole scaffold that inhibits HCV NS5B polymerase in low nanomolar concentration and display excellent cellular activities and acceptable PK. Further optimization of the furan scaffold leading to potent inhibitors with excellent PK and developable clinical candidates will be disclosed in future communications.

5. Experimental

5.1. General

Dry solvents were purchased from Aldrich or Acros and used without further purification. Other solvents or reagents were used as obtained except when otherwise noted. Analytical thin layer chromatographies (TLC) were performed on pre-coated silica gel plates available from Analtech. Column chromatography were performed using Merck silica gel 60 (particle size 0.040–0.055 μm, 230–400 mesh), or using Biotage or Isco chromatographic systems

with prepacked silica columns. Final compounds were purified by reverse phase HPLC using C_{18} column in a Varian HPLC instrument. Elution was achieved using water, and acetonitrile or water containing 0.1% TFA and THF system. (Column: Waters: Delta Pk, P/No 11805, Wat 011805, 300 mm × 30 mm (L/ID) C18, 15 μM, 300 Å, 343K16006 (W): 30 mL/min flow; 30–70% ramp water/acetonitrile; 0 → 40 min). Visualization was accomplished with UV light or by staining with basic $KMnO_4$ solution, methanolic H_2SO_4 or Vaughn's reagent. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 unless otherwise noted either in a 400 or 500 MHz (^{1}H NMR), or 100 or 125 MHz (^{13}C NMR). Mass spectra were obtained using electron spray ionization methods. Where applicable ^{13}C NMRs are reported as fluorine coupled spectra unless otherwise indicated.

5.1.1. Benzo[b]thiophene-7-carbaldehyde (5)

A solution of commercially available 7-bromobenzo[*b*]thiophene (8.0 g, 37.5 mmol) in ether (50.0 mL) was cooled to −78 °C was and treated dropwise with BuLi (1.6 M solution in Hexanes, 21 mL, 37.5 mmol) and stirred at −78 °C for 20 min. The reaction mixture was treated with DMF (5.4 g, 67.4 mmol) and stirred at −78 °C for 1 h. The reaction mixture was diluted with water and extracted with ether. The combined organic layer were washed with water, dried ($MgSO_4$) filtered concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/Hexanes) to yield **5** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.12 (d, 1 H, J = 7.6 Hz), 7.90 (d, 1H, J = 7.2 Hz), 7.67 (d, 1H, J = 5.6 Hz), 7.59 (t, 1H, J = 7.6 Hz), 7.45 (d, 1H, J = 5.6 Hz).

5.1.2. (*Z*)-Methyl 2-azido-3-(benzo[*b*]thiophen-7-yl)acrylate (6)

A solution of freshly made sodium methoxide by dissolving (1.42 g, 62.0 mmol) of sodium in methanol (30 mL) was added dropwise to a solution of ethylazido acetate (7.99 g, 62 mmol), and 5.1 g (31 mmol) of aldehyde **5** in methanol (30 mL) at −20 °C. The reaction mixture was slowly warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated in vacuo and diluted with EtOAc. The organic layers were washed with water and dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography using SiO_2 (EtOAc/hexanes) to yield **6** (3 g) of yellow solid. It was further purified by crystallization using ether and hexanes to yield pure product (1.95 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 1H, J = 7.6 Hz), 7.81 (d, 1H, J = 8.4 Hz), 7.44 (d, 1H, J = 6.0 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.38 (d, 1H, J = 5.6 Hz), 7.19 (s, 1H), 3.97 (s, 3H).

5.1.3. Methyl 6*H*-thieno[2,3-*e*]indole-7-carboxylate (7)

A solution of azido ester **6** (1.9 g, 7.4 mmol) in xylenes was heated at reflux for 30 min, when the starting material completely disappears as indicated by TLC. On cooling the solution to room temperature and partial concentration of the xylenes, indole **7** (1.1 g) precipitated out of solution as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ, 7.72 (d, 1H, J = 8.8 Hz), 7.57 (d, 1H, J = 5.2 Hz), 7.48 (d, 1H, J = 5.2 Hz), 7.44 (d, 1H, J = 8.8 Hz), 7.33 (s, 1H), 3.87 (s, 3H).

5.1.4. Methyl, 8-(2-methoxypyridin-3-yl)-6*H*-thieno[2,3-*e*]indole-7-carboxylate (10)

A solution of indole **7** (1.00 g, 4.33 mmol) in DMF (20 mL) was treated with N-iodosuccinimide (1.07 g, 4.76 mmol) and stirred at rt for 12 h. The reaction mixture was concentrated in vacuo, diluted with water, and extracted in EtOAc (300 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and purified by chromatography (SiO2, EtOAc/hexanes) to yield iodinated compounds **8a** and **8b** as a colorless solid.

A solution of iodide (1.2 g, 3.35 mmol) in DME (25 mL) was treated with 2-methoxypyridin-3-ylboronic acid **9** (1.52 g, 10 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (324 mg) and stirred at rt under nitrogen for 0.25 h. The reaction mixture was treated with a solution of potassium carbonate (2.77 g, 20.1 mmol) in 25 mL of water and heated at 90 °C. After 1 h, analysis of TLC of reaction mixture indicated complete consumption of starting material. The reaction mixture was diluted with EtOAc (300 mL), and washed with water. The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo and purified by chromatography using EtOAc/hexanes (0 → 70%) to yield **10a** and **10b**.

5.1.5. 6-(2,5-Difluorobenzyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-thieno[2,3-*e*]indole-7-carboxylic acid (13)

A solution of **10a** and **10b** (300 mg, 0.90 mmol) in DMF (10 mL) were treated with cesium carbonate (585 mg, 1.80 mmol), 2,5-difluorobenzyl bromide (372 mg, 1.80 mmol) and stirred at rt for 12 h. The reaction mixture was diluted with EtOAc (250 mL) and washed with brine (2 × 100 mL). The EtOAc layer was dried ($MgSO_4$), filtered, concentrated in vacuo and purified by chromatography using SiO_2 (EtOAc/hexanes) and once again with acetone/CH_2Cl_2 to yield N(1) alkylated products **10a** and **10b** as a colorless solid. The solid were taken in THF (20 mL) and water (20 mL), treated with lithium hydroxide and refluxed. The disappearance of starting material was followed by TLC. On complete consumption of starting material the mixture was diluted with EtOAc (200 mL) washed with water, brine and dried ($MgSO_4$), filtered concentrated in vacuo to yield **12** that was used as is.

A solution of the acid **12** (100 mg, 0.23 mmol) in HCl (4 M solution in dioxane, 5.0 mL) was treated with 1 mL of methanol and heated at 90 °C for 3 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc. On treatment with hexanes a colorless solid separated out which was filtered (45 mg) to yield 6-(2,5-difluorobenzyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-thieno[2,3-*e*]indole-7-carboxylic acid (**13**) ^{1}H NMR (500 MHz in DMSO-d_6), δ 12.88 (b, 1H), 11.78 (s, 1H), 7.81 and 7.62 (AB, 2H, J = 9.0 Hz), 7.61 (dd, 1H, J = 6.5 and 2.0 Hz), 7.51 and 7.48 (AB, 2H, J = 5.3 Hz), 7.52–7.48 (m, 1 H), 7.33 (dt, 1 H, J = 4.5 and 9.5 Hz), 7.18–7.13 (m, 1H), 6.37–6.33 (m, 2H), 6.04 and 5.95 (AB, 2H, J = 17.5 Hz).^{13}C NMR (125 MHz in DMSO-d_6) δ 162.6, 161.4, 158.1 (d, J_{C-F} = 242 Hz), 156.0 (d, J_{C-F} = 242 Hz), 140.8, 134.7, 131.5, 124.1, 123.8, 121.2, 120.4, 118.4, 116.9 (dd, J_{C-F} = 24 and 8.8 Hz), 115.3 (dd, J_{C-F} = 24 and 8.4 Hz), 113.9 (dd, J_{C-F} = 24 and 6 Hz), 108.9, 104.7, 41.9 (dd, J_{C-F} = 4.1 Hz). LR MS (ESI) 437 [$(M+1)^+$, 44], 493 [$(M+1-CO_2)^+$, 100].

5.1.6. Ethyl-6*H*-thiazolo[5,4-*e*]indole-7-carboxylate (17)

A solution of 7-iodobenzo[*d*]thiazol-6-amine[31] (**16**) (1.7 g, 6.16 mmol) in DMF (15 mL) was extensively degassed and treated with ethylpyruate (0.965 g, 8.4 mmol), DABCO, $Pd(OAc)_2$ (139 mg, 0.616 mmol) and heated at 105 °C for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate (an emulsion was formed which was painstakingly separated). The organic layer was dried ($MgSO_4$) filtered concentrated in vacuo and purified by chromatography SiO_2 (EtOAc/hexanes 0–70%) to yield indole **17** (500 mg) as a tan colored solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.63 (s, 1H), 8.93 (s, 1H), 8.06 (s, 1H, J = 8.8 Hz), 7.57 (d, 1H, J = 8.8 Hz), 7.41 (br d, 1H, J = 1.7 Hz), 4.46 (q, 2H, J = 7.3 Hz), 1.44 (t, 3H, J = 7.3 Hz); LR-MS (ESI): calcd for $C_{12}H_{11}N_2O_2S$ $[M+H]^+$ 247, found 247 (100), 201 (50%).

5.1.7. Methyl-6*H*-furo[2,3-*e*]indole-7-carboxylate (36)

A solution of methyl-4-hydroxy indole carboxylate **34** (2.5 g, 13.1 mmol) in DMF (50 mL) was treated with Cs_2CO_3 (5.12 g, 15.72 mmol), bromoacetaldehye diethyl acetal (12.90 g, 65.6 mmol) and stirred at reflux for 2 h. The reaction mixture was cooled to room temperature, treated with aq NaOH (1 M, 50 mL) and extracted into EtOAc (250 mL). The organic layers were

dried (MgSO4), filtered, concentrated in vacuo (high vacuum to distill out DMF and bromoacetaldehyde) and purified by chromatography (SiO_2, hexanes/EtOAc 0 → 100%) to yield methyl 4-(2,2-diethoxyethoxy)-1*H*-indole-2-carboxylate **35** (3.5 g, 88%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.96 (s, 1H), 7.17 (t, 1H, J = 7.6 Hz), 7.08 (dd, 1H, J = 1.0 and 2.2 Hz), 7.05 (d, 1H, J = 8.2 Hz), 6.57 (d, 1H, J = 7.6 Hz), 4.91 (t, 1H, J = 5.1 Hz), 4.07 (d, 2H, J = 5.0 Hz), 3.87 (s, 3H), 3.76–3.61 (m, 4H), 1.17 (t, 6*H*, J = 7.0 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4, 152.5, 138.7, 125.7, 118.0, 105.7, 104.8, 100.5, 100.0, 68.3, 62.1, 51.6, 15.2.

A solution of methyl 4-(2,2-diethoxyethoxy)-1*H*-indole-2-carboxylate **35** (4.5 g, 14.7 mmol) in benzene (60 mL) was treated with strongly acidic resin amberlyst-15 (4.5 g) and heated at 70 °C. The reaction mixture was monitored by TLC (10% EtOAc/hexanes). After 4 h, the reaction mixture was cooled, diluted with EtOAc (300 mL) and washed with saturated aq NaHCO3. The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and purified by chromatography (SiO2) EtOAc/Hexanes (0 → 30%) to yield indole **36** (1.2 g). ^{1}H NMR (400 MHz, DMSO-d_6), δ, 12.31 (s, 1H), 7.93 (d, 1H, J = 2.1 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.37 (d, 1H, J = 8.1 Hz), 7.32 (d, 1H, J = 2.0 Hz), 7.00 (br d, 1H), 3.89 (s, 3H).

5.1.8. 3-Chloro-7-bromobenzofuran (41)

A solution of 7-bromobenzofuran **40** (20 g, 101 mmol) in acetic acid (150 mL) was cooled to 15 °C and a gentle stream of chlorine was passed through the mixture for 0.5 h. The reaction mixture was concentrated in vacuo, diluted with water and extracted with ether (1 L). The ether layer was washed with water, dried (MgSO4), filtered and concentrated in vacuo. KOH (28 g) was dissolved in methanol (300 mL) and a solution of the crude dichlorinated compound was added dropwise into the base. The reaction mixture was stirred at room temperature for 20 min. The reaction mixture was concentrated in vacuo when a colorless solid precipitated out. The solid was filtered washed with water and dried to yield **41** (14 g, 60%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ, 7.72 (s, 1H), 7.55 (d, 1H, J = 7.6 and 1.2 Hz), 7.53 (d, 1H, J = 7.6 and 1.2 Hz), 7.21 (t, 1H, J = 7.6 Hz).

5.1.9. 3-Chloro-benzofuran-7-carbaldehyde (42)

A solution of 3-chloro-7-bromobenzo furan **41** (10 g, 43.2 mmol) in ether (100 mL) at −78 °C was treated with BuLi (15.5 mL, 38.9 mmol, 2.5 M soln.) and stirred −78 °C. After 10 min, dimethylformamide (9 g, 123 mmol) was added to the mixture and stirred for 0.5 h. The reaction was quenched with a solution of saturated ammonium chloride and aq HCl (30 mL) and extracted into ether (700 mL). The combined organic layers were dried (MgSO4) filtered concentrated in vacuo and purified by chromatography (SiO2, EtOAc/hexanes) to yield aldehyde **42**. ^{1}H NMR (400 MHz, $CDCl_3$), δ, 10.42 (s, 1 H), 7.90–7.87 (m, 2 H), 7.80 (s, 1 H), 7.49 (t, 1 H, J = 7.6 Hz).

5.1.10. Methyl-3-chloro-6*H*-furo[2,3-*e*]indole-7-carboxylate (43)

Metallic sodium (1.43 g, 61.9 mmol) was added carefully to methanol (60 mL) and stirred for 20 min till a homogenous solution was obtained. This was added dropwise to a solution of aldehyde **42** (5.00 g, 27.68 mmol) and ethyl azido acetate (8 g, 61.9 mmol) in 30 mL of methanol at −20 °C. The reaction mixture was stirred at rt for 2 h and quenched with aq saturated ammonium chloride and concentrated in vacuo. The mostly aqueous layer was extracted with EtOAc (700 mL) and purified by chromatography (SiO_2, EtOAc/hexanes) to yield azido ester as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ, 8.29 (td, 1H, J = 7.6, 0.4 and 0.4 Hz), 7.68 (s, 1H), 7.58 (dd, 1H, J = 8.0 and 1.2 Hz), 7.42 (s, 1H), 7.37 (t, 1H, J = 7.6 and 0.4 Hz), 4.41 (q, 2H, J = 7.2 Hz), 1.43 (t, 3H, J = 7.2 Hz). A solution of the azido ester (2.8 g, 10.8 mmol) in xylenes (20 mL) was heated at reflux for 20 min until all the ester was consumed as indicated by TLC (20% EtOAc/hexanes). On cooling the solution to rt, indole **43** crystallized out, which was filtered and washed with hexanes (500 mg, ∼ 20%). ^{1}H NMR (400 MHz, DMSO-d_6), δ, 12.47 (s, 1H), 8.26 (s, 1H), 7.50 and 7.46 (AB, 2H, J = 9.0 Hz), 7.35–7.34 (m, 1H), 4.37 (q, 2 H, J = 7.2 Hz), 1.36 (t, 3H).

5.1.11. Methyl-3-ethyl-6*H*-furo[2,3-*e*]indole-7-carboxylate (47, R = C2H5)

A solution of methyl 4-hydroxy indole 2-carboxylate (**34**, 500 mg, 2.62 mmol) in DMF (4.00 mL) was treated with bromobutanone (789 mg, 5.20 mmol) and Cs_2CO_3 (936 mg, 2.88 mmol) and heated at 70 °C for 3 h. The reaction mixture was diluted with water (100 mL) and extracted into EtOAc (200 mL). The combined organic layers were dried ($MgSO_4$), filtered concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/hexanaes) to yield **46** (320 mg, 47%). A solution of ketone **46** (3.5 g, 13.4 mmol) in toluene (30.00 mL) was treated with 6.5 g of Amberlyst-15 strongly acidic resin and heated at 80 °C for 3 h. The reaction mixture was diluted with EtOAc (300 mL), filtered, washed with aq sodium bicarbonate, dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by chromatography to yield indole **47** as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ, 9.11 (s, 1H), 7.48 (d, 1H, J = 8.5 Hz), 7.45 (dd, 1 H, J = 1.0 and 1.0 Hz), 7.43 (t, 1H, J = 1.0 Hz), 7.30 (dd, 1 H, J = 8.5 and 1.0 Hz), 3.97 (s, 3 H), 2.75 (dq, 2 H, J = 7.5 and 1.5 Hz), 1.36 (t, 3 H, J = 7.5 Hz).

5.1.12. Methyl-4-(allyloxy)-1*H*-indole-2-carboxylate (50)

A solution of methyl-4-hydroxy-1*H*-indole-2-carboxylate, **34** (2.9 g, 15 mmol) and Cs_2CO_3 (5.4 g, 16 mmol) in DMF (45 mL), was treated with allyl bromide (1.6 mL, 18 mmol) and heated at 60 °C for 2 h. The reaction mixture was concentrated in vacuo and the residue diluted with EtOAc (200 mL). The organic layer was washed with water, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude mixture was purified by chromatography (SiO_2 EtOAc/Hexanes) to yield methyl 4-(allyloxy)-1*H*-indole-2-carboxylate **50** (2.2 g, 63%). ^{1}H NMR (400 MHz, CH_3OH-d_4), δ, 7.22 (s, 1H), 7.15 (t, 1H, J = 7.3 Hz), 7.02 (d, 1H, J = 7.0 Hz), 6.50 (d, 1H, J = 8.1 Hz), 6.19–6.01 (m, 1H), 5.47 (td, 1H, J = 19 and 1.5 Hz), 5.28 (td, 1H, J = 11.6 and 1.6 Hz) 4.66 (s, 2H, J = 5.1 Hz), 3.90 (s, 3H). LR-MS (ESI), relative intesity 312 (40), 272 (20), 232 [(M+1)$^+$, 100], 199 (20).

5.1.13. Methyl-2-methyl-6*H*-furo[2,3-*e*]indole-7-carboxylate (51)

A solution of methyl-4-(allyloxy)-1*H*-indole-2-carboxylate **50** (2.2 g, 9.5 mmol), *p*-benzoquinone (1.00 g, 9.5 mmol) and K_2CO_3 (1.3 g, 9.5 mmol) in dioxane (15.0 mL) was degassed and treated with bis(acetonitrile)palladium(II) chloride (200 mg, 0.9 mmol) and heated at reflux for 5 h. The reaction mixture was diluted with water and extracted into EtOAc (300 mL). The combined organic layers were washed with aq NaOH (1 M, 300 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo and purified by chromatography (SiO_2, EtOAc/hexanes) to yield methyl-2-methyl-6*H*-furo[2,3-*e*]indole-7-carboxylate **51** (702 mg, 32%) as a colorless solid ^{1}H NMR (400 MHz, CD_3OD) δ, 7.35 (d, 1H, J = 8.8 Hz), 7.27 (d, 1 H, J = 8.1 Hz), 7.25 (s, 1H), 6.44 (s, 1H), 3.92 (s, 3H), 2.47 (s, 3H).

5.1.14. 6-(2,5-Difluorobenzyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-thiazolo[5,4-*e*]indole-7-carboxylic acid (20)

^{1}H NMR (400 MHz in DMSO-d_6) δ, 9.17 (s, 1 H), 8.01 and 7.79 (AB, 2 H, J = 9.00 Hz), 7.60 (dd, 1H, J = 7.0 and 2.5 Hz), 7.51 (dd, 1H, J = 6.5 and 2.0 Hz), 7.32–7.27 (m, 1H), 6.97 (dt, 1H, J = 8.5 and 2.0 Hz), 6.76–6.71 (m, 1H), 6.37 (t, 1H, J = 6.5 Hz), 6.06–5.95 (AB, 2 H, J = 15.8 Hz); ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled), δ

162.5, 162.4, 162.3, 161.2, 160.5, 160.4, 160.3, 158.5, 158.4, 152.3, 149.2, 141.1, 135.1, 134.8, 129.0, 128.96, 128.93, 128.88, 126.9, 125.3, 125.1, 121.7, 121.6, 121.53, 121.50, 120.1, 119.7, 118.4, 111.59, 111.56, 111.42, 111.39, 110.5, 104.9, 104.1, 103.9, 103.8, 103.6, 41.7, 41.65, LR-MS (ESI): calcd for $C_{22}H_{14}F_2N_3O_3S$ $[M+H]^+$ 438, found 438 (100), 394 (30)

5.1.15. 3-(2,5-Difluorobenzyl)-1-(2-oxo-1,2-dihydropyridin-3-yl)-3,6,7,8-tetrahydrocyclopenta[*e*]indole-2-carboxylic acid (55)

^{1}H NMR (400 MHz, DMSO-d_6) δ above 12 (1 H), 11.6 (s, broad, 1H), 7.43 (dd, 1H, J = 2 and 6.5 Hz), 7.39 (dd, 1H, J = 2 and 6.5 Hz), 7.30 (d, 1H, J = 8.5 Hz), 7.27 (dt, 1H, J = 4.5, 9.3 and 9.3 Hz), 7.20 (d, 1H, J = 8.5 Hz), 7.11 (m, 1H), 6.36 (m, 1H), 6.27 (t, 1H, J = 6.5 Hz), 5.85 (br, 2 H), 2.86 (t, J = 7.6 Hz, 2 H), 2.72 (br, 2 H), 1.98 (br, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled spectra), δ, 162.8, 161.8, 158.9, 157.0, 156.4, 154.5, 140.5, 136.9, 136.1, 135.9, 134.1, 127.8, 127.7, 127.67, 127.6, 126.9, 126.2, 123.3, 121.6, 118.6, 116.8, 116.7, 116.6, 116.5, 115.2, 115.1, 115.0, 114.9, 114.04, 114.0, 113.84, 113.80, 108.5, 104.6, 41.51, 41.48, 39.9, 39.8, 39.6, 39.4, 39.2, 39.1, 38.9, 31.6, 31.2, 24.5. HR-MS (ESI): calcd. for $C_{24}H_{19}F_2N_2O_3$ $[M+1]^+$ 421.1363, found 421.1360.

5.1.16. 6-(2,5-Difluorobenzyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[3,2-*e*]indole-7-carboxylic acid (32)

^{1}H NMR (400 MHz, in DMSO-d_6): δ above 12 (1H), 11.81 (br s, 1H), 7.95 (s, 1H), 7.60 (d, 2H, J = 8.8 Hz), 7.5 (d, 1H, J = 9.5 Hz), 7.46 (d, 1H, J = 6.6 Hz), 7.30 (ddd, 1H, J = 4.4, 8.8, 9.5 Hz), 7.13 (m, 1H), 6.57 (s, 1H), 6.36–6.31 (m, 2 H), 5.95 (s, 2 H); LR-MS (ESI): calcd for $C_{23}H_{15}F_2N_2O_4$ $[M+H]^+$ 421, found 421.

5.1.17. 6-(2,5-Difluorobenzyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxylic acid (38)

^{1}H NMR (400 MHz, DMSO-d_6), δ 12.8 (s, 1H), 11.74 (s, 1H), 7.85 (d, 1H, J = 1.5 Hz), 7.68 (dd, 1H, J = 2.2 and 6.6 Hz), 7.56 and 7.47 (AB, 2 H, J = 8.8 Hz), 7.40 (d, 1H, J = 5.2 Hz), 7.30 (dt, 1H, J = 4.4 and 5.0 Hz), 7.16–7.11 (m, 1H), 6.97 (d, 1H, J = 2.2 Hz), 6.36–6.31 (m, 2H), 5.93 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled spectra), δ 162.7, 161.4, 158.9, 157.0, 156.4, 154.5, 147.8, 143.5, 140.4, 136.0, 134.1, 127.59, 127.53, 127.4, 127.3, 126.3, 126.0, 120.2, 118.3, 117.0, 116.9, 116.8, 116.7, 115.4, 115.39, 115.32, 115.27, 115.20, 114.08, 114.05, 113.88, 113.85, 112.7, 107.1, 106.8, 104.9, 41.97, 41.94 LR-MS (ESI): calcd for $C_{23}H_{15}F_2N_2O_4$ $[M+H]^+$ 421, found 421 (50), 377 (100).

5.1.18. 6-(2,5-Difluorobenzyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-3,6-dihydro-2*H*-furo[2,3-*e*]indole-7-carboxylic acid (57)

^{1}H NMR (400 MHz, in DMSO-d_6): δ 12.92 (1H, br s), 11.67 (1H, br s), 7.50 (1H, dd, J = 1.5, 6.6 Hz), 7.34 (1H, d, J = 5.1 Hz), 7.30 (1H, dt, J = 4.4, 8.8 Hz), 7.18 (1H, d, J = 8.8 Hz), 7.14 (1H, m), 6.99 (1H, d, J = 8.8 Hz), 6.34 (1H, m), 6.27 (1H, t, J = 6.6 Hz), 5.79 (2H, s), 4.54 (2H, t, J = 8.8 Hz), 3.16 (2H, t, J = 8.8 Hz); ^{13}C NMR (125 MHz, in DMSO-d_6): δ 162.9, 161.5, 158.0 (d, J_{C-F} = 240.4 Hz), 155.5 (d, J_{C-F} = 240.4 Hz), 153.2, 140.6, 138.8, 133.7, 127.6 (dd, J_{C-C-F} = 17.5 Hz, $J_{C-C-C-F}$ = 7.3 Hz), 126.6, 125.9, 121.7, 116.9 (dd, J_{C-C-F} = 24.0 Hz, $J_{C-C-C-F}$ = 8.3 Hz), 116.8, 115.5, 115.3 (dd, J_{C-C-F} = 24.0 Hz, $J_{C-C-C-F}$ = 8.3 Hz), 114.0 (dd, J_{C-C-F} = 24.9 Hz, J_{C-C-F} = 5.5 Hz), 112.1, 104.8, 102.2, 71.9, 41.7 (d, J_{C-C-F} = 3.6 Hz), 28.7 ppm. LR-MS (ESI): calcd for $C_{23}H_{17}F_2N_2O_4$ $[M+H]^+$ 423.12, found 422.99.

5.1.19. 6-(2,5-Difluorobenzyl)-3-methyl-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxylic acid (58)

^{1}H NMR (400 MHz, DMSO-d_6), δ above 12 (s, 1H), 11.94 (s, 1H), 7.77 (dd, 1H, J = 2.0 and 8.5 Hz), 7.54 and 7.47 (AB, 2 H, J = 8.8 Hz), 7.54–7.44 (m, 2 H), 7.33–7.27 (m, 1H), 7.17–7.08 (m, 1 H), 6.35 (t, 1H, J = 6.8 Hz), 6.15–6.10 (m, 1H), 5.96 (s, 2H), 2.28 (s, 3H); LR-MS (ESI): calcd for $C_{24}H_{17}F_2N_2O_4$ $[M+H]^+$ 435, found 435 (100).

5.1.20. 6-(2,5-Difluorobenzyl)-3-ethyl-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxylic acid (59)

^{1}H NMR (400 MHz, DMSO-d_6), δ 13.2 (s, 1H), 11.92 (s, 1H), 7.75 (d, 1H, J = 6.6 Hz), 7.57 and 7.44 (AB, 2 H, J = 8.8 Hz), 7.50 (d, 1H, J = 6.6 Hz), 7.47 (s, 1H), 7.30 (dt, 1H, J = 4.4 and 4.3 Hz), 7.15–7.09 (m, 1H), 6.35 (t, 1H, J = 6.6 Hz), 6.16–6.13 (m, 1H), 6.00 (s, 2H), 2.77 (q, 2H, J = 7.3 Hz), 1.18 (t, 3 H, J = 7.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled), δ 162.3, 159.9, 159.0, 157.1, 156.4, 154.5, 147.1, 145.5, 141.0, 138.0, 136.0, 127.7, 127.5, 121.8, 120.3, 117.4, 116.99, 116.92, 116.8, 116.7, 115.34, 115.28, 115.0, 113.6, 113.4, 111.8, 106.5, 105.8, 104.9, 41.8, 17.2, 14.5. LR-MS (ESI): calcd for $C_{25}H_{19}F_2N_2O_4$ $[M+H]^+$ 449, found 449 (100)

5.1.21. 3-Chloro-6-(2,5-difluorobenzyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxylic acid (45)

^{1}H NMR (400 MHz, DMSO-d_6), δ 13.11 (s, 1H), 11.76 (s, 1H), 8.18 (s, 1H), 7.69 (dd, 1H, J = 2.2 and 4.4 Hz), 7.63 and 7.49 (AB, 2H, J = 8.8 Hz), 7.41 (d, 1H, J = 5.5 Hz), 7.30 (dt, 1H, J = 4.4 and 4.3 Hz), 7.17–7.11 (m, 1H), 6.38–6.33 (m, 1H), 6.32 (t, 1H, J = 6.6 Hz), 5.95 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled), δ 162.6, 161.3, 159.0, 157.1, 157.1, 156.5, 156.5, 154.6, 147.5, 140.4, 139.5, 136.6, 134.3, 127.4, 127.3, 127.2, 127.1, 125.6, 118.3, 117.0, 116.98, 116.85, 116.78, 115.5, 115.5, 115.3, 115.3, 115.0, 114.1, 114.08, 113.9, 113.87, 112.7, 112.0, 108.2, 104.8, 42.1, 42.1. LR-MS (ESI): calcd for $C_{23}H_{14}ClF_2N_2O_4$ $[M+H]^+$ 455, found 455 (30), 411 (100)

5.1.22. 6-(2,5-Difluorobenzyl)-2-methyl-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxylic acid (53)

^{1}H NMR (400 MHz, DMSO-d_6), δ above 12.97 (s, 1H), 11.75 (s, 1H), 7.70 (dd, 1H, J = 1.8 and 6.8 Hz), 7.44 and 7.38 (AB, 2 H, J = 8.7 Hz), 7.45–7.36 (m, 1H), 7.29 (dt, 1H, J = 4.6 and 9.1 Hz), 7.15–7.10 (m, 1H), 6.57 (d, 1H, J = 0.9 Hz), 6.34 (t, 1H, J = 6.8 Hz), 6.35–6.30 (m, 1H), 5.89 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled), δ 162.8, 161.5, 158.0 (d, J_{C-F} = 238 Hz), 155.5 (d, J_{C-F} = 238 Hz), 152.4, 147.1, 140.4, 135.5, (dd, J_{C-F} = 24 and 8.3 Hz), 126.4, 125.9, 121.6, 117.6, 116.9 (d, J_{C-F} = 24 and 9.3 Hz), 114.7, 114.0 (dd, J_{C-F} = 25.9 and 5.5 Hz), 112.4, 106.3, 104.9, 103.0, 41.8 (dd, J_{C-F} = 3.7 Hz), 13.5. LR-MS (ESI): calcd for $C_{24}H_{17}F_2N_2O_4$ $[M+H]^+$ 435, found 435 (100), 391 (50).

5.1.23. 6-(2,5-Difluorobenzyl)-*N*-(methylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (60)

^{1}H NMR (400 MHz, DMSO-d_6), δ 12.6 (s, 1H), 12.7 (s, 1H), 7.99 (d, 1H, J = 6.6 Hz), 7.85 (s, 1H), 7.69–7.65 (m, 1H), 7.60 and 7.49 (AB, 2H, J = 8.8 Hz), 7.33–7.24 (m, 1H), 7.18–7.13 (m, 1H), 6.99 (s, 1H), 6.63–6.53 (m, 2H), 5.78 (s, 2H), 3.24 (s, 3H) LR-MS (ESI): calcd for $C_{24}H_{18}F_2N_3O_5S$ $[M+H]^+$ 498, found 498 (30), 435 (100), 377 (30).

5.1.24. 6-(2,5-Difluorobenzyl)-*N*-(ethylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (61)

^{1}H NMR (400 MHz, DMSO-d_6) δ above 12 (2H), 8.00 (d, 1H, J = 7.2 Hz), 7.84 (dd, 1H, J = 2.0 and 7.2 Hz), 7.69 (t, 1H, J = 6.4 Hz), 7.61 and 7.53 (AB, 2H, J = 9.2 Hz), 7.30 (dt, 1H, J = 4.0 and 8.8 Hz), 7.18–7.13 (m, 1H), 6.99 (dd, 1H, J = 1.2 and 2.4 Hz), 6.64 (t, 1H, J = 7.6 Hz), 6.57–6.53 (m, 1H), 5.79 (s, 2H), 3.35 (q, 2H, J = 8.0 Hz), 1.04 (d, 3H, J = 7.6 Hz). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled spectra), δ 163.5, 161.7, 159.9, 158.0, 157.6, 155.6,

148.5, 145.9, 144.6, 140.8, 137.1, 136.8, 129.0, 127.8, 127.8, 127.7, 127.6, 124.0, 121.6, 119.8, 117.9, 117.7, 117.8, 116.7, 116.7, 116.5, 115.7, 115.7, 115.5, 115.5, 113.7, 113.6, 108.2, 108.1, 108.0, 47.7, 43.0, 43.0, 8.2. LR-MS (ESI): calcd for $C_{25}H_{20}F_2N_3O_5S$ $[M+H]^+$ 512, found 512 (30), 435 (50), 402 (30), 377 (100).

5.1.25. 6-(2,5-Difluorobenzyl)-*N*-(isopropylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (62)

^{1}H NMR (400 MHz, DMSO-d_6), δ above 12 (2H), 8.00 (td, 1H, J = 1.6 and 6.8 Hz), 7.84 (m, 1H), 7.71 (t, 1H, J = 6.8 Hz), 7.62 and 7.54 (AB, 2 H, J = 8.8 Hz), 7.30 (dt, 1H, J = 4.4 and 8.8 Hz), 7.18–7.13 (m, 1H), 6.99–6.98 (m, 1H), 6.64 (t, 1H, J = 7.2 Hz), 6.54–6.49 (m, 1H), 5.80 (s, 2H), 3.63–3.55 (m, 1H), 1.14 (d, 6 H, J = 7.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled spectra), δ 162.6, 160.7, 159.0, 157.1, 154.7, 147.6, 145.1, 143.7, 136.2, 135.9, 128.0, 126.9, 126.8, 123.0, 120.7, 118.9, 117.1, 117.0, 116.9, 115.7, 115.6, 115.5, 114.7, 114.5, 112.8, 112.6, 107.4, 107.3, 107.2, 107.1, 52.6, 42.1, 42.0, 15.1. LR-MS (ESI): calcd for $C_{26}H_{22}F_2N_3O_5S$ $[M+H]^+$ 526, found 526 (100), 377 (60).

5.1.26. *N*-(Cyclopropylsulfonyl)-6-(2,5-difluorobenzyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (63)

^{1}H NMR (400 MHz, DMSO-d_6), δ above 12 (2H), 7.98 (dd, 1H, J = 2.0 and 7.2 Hz), 7.84 (d, 1H, J = 2.0 Hz), 7.69 (t, 1H, J = 5.2 Hz), 7.61 and 7.52 (AB, 2 H, J = 8.4 Hz), 7.30 (dt, 1H, J = 5.2 and 9.6 Hz), 7.19–7.13 (m, 1H), 6.99 (d, 1H, J = 2.0 Hz), 6.63 (t, 1H, J = 6.4 Hz), 6.60–6.56 (m, 1H), 5.80 (s, 2 H), 2.96–2.89 (m, 1H), 0.96 (d, 4 H, J = 6.4 Hz). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled spectra), δ 162.5, 160.6, 159.0, 157.1, 154.8, 147.6, 144.9, 143.7, 136.1, 135.8, 128.1, 123.1, 120.6, 118.8, 117.0, 116.9, 116.8, 115.8, 115.8, 115.6, 115.6, 114.9, 114.8, 114.7, 114.6, 112.6, 112.6, 107.2, 107.1, 41.9, 30.5, 5.3. LC-MS (ESI, water [0.1% TFA]/acetonitrile): calcd for $C_{26}H_{20}F_2N_3O_5S$ $[M+H]^+$ 524, found 524 (100).

5.1.27. 6-(2,4-Difluorobenzyl)-*N*-(methylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (64)

^{1}H NMR (400 MHz, DMSO-d_6), δ 12.8 (s, 1H), 12.9 (s, 1H), 7.96 (d, 1H, J = 6.6 Hz), 7.84 (d, 1H, J = 2.2 Hz), 7.66 (bt, 1H), 7.59 and 7.51 (AB, 2 H, J = 8.8 Hz), 7.28 (dt, 1H, J = 2.2 and 8.8 Hz), 6.98 (d, 1H, J = 2.2 Hz), 6.98–6.87 (m, 2H), 6.61 (t, 1H, J = 6.6 Hz), 5.77 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.4, 160.9, 160.5, 160.4, 158.8, 158.74, 147.6, 144.6, 143.6, 136.1, 135.6, 129.9, 129.8, 128.2, 123.2, 121.1, 121.0, 120.6, 118.7, 112.6, 111.6, 111.4, 107.2, 107.1, 104.1, 103.9, 103.8, 41.7, 41.1. LR-MS (ESI): calcd for $C_{24}H_{18}F_2N_3O_5S$ $[M+H]^+$ 498, found 498 (30), 377 (15), 337 (25), 169 (40), 107 (100).

5.1.28. 6-(2-Fluorobenzyl)-*N*-(methylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (65)

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (br s, 1H), 12.61 (br s, 1H), 7.98 and 7.96 (d, J = 6.04 Hz, 2H), 7.86–7.83 (m, 1H), 7.67 (s, 1H), 7.60 and 7.58 (d, J = 7.7 Hz, 1H), 7.51 and 7.49 (d, J = 8.3 Hz, 1H), 7.32–7.27 (m, 1H), 7.21 (t, J = 8.8 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.82 (t, J = 7.7 Hz, 1H), 6.67–6.60 (m, 1H), 5.81 (s, 2H), 3.22 (s, 3H). ^{13}C NMR, (125 MHz, DMSO-d_6, F-coupled spectra), δ 162.4, 160.8, 160.4, 158.5, 147.5, 144.5, 143.5, 136.1, 135.5, 129.3, 129.2, 128.4, 128.4, 124.6, 124.5, 124.4, 120.5, 118.5, 115.2, 115.1, 112.5, 112.4, 107.2, 107.1, 107.0, 42.0, 41.0; LR-MS (ESI): calcd for $C_{24}H_{19}FN_3O_5S$ $(M+1)^+$: 480.3; Found 502 [$(M+Na)^+$, 5], 480 (10), 417 (10), 359 (25), 251 (100).

5.1.29. 6-(2,4-Dimethylbenzyl)-*N*-(methylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (66)

^{1}H NMR (400 MHz, DMSO-d_6), δ 12.70 (s, 1H), 12.59 (d, 1H, J = 5.4 Hz), 7.99 (dd, 1H, J = 1.9 and 4.9 Hz), 7.85 (t, 1H, J = 1.5 Hz), 7.66 (t, 1H, J = 4.9 Hz), 7.54 and 7.35 (AB, 2H, J = 8.8 Hz), 7.00 (br s, 1H), 6.98 (d, 1H, J = 2.5 Hz), 6.76 (d, 1H, J = 7.8 Hz), 6.62 (t, 1H, J = 6.4 Hz), 6.14 (d, 1H, J = 7.8 Hz), 5.66 (s, 2H), 3.10 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H). LR-MS (ESI): calcd for $C_{26}H_{24}N_3O_5S$ $(M+1)^+$ 490, found 490 (60), 427(60), 395 (35), 369 (100).

5.1.30. 6-(2-Methylbenzyl)-*N*-(methylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (67)

^{1}H NMR (400 MHz, DMSO-d_6), δ 12.69 (s, 1H), 12.60 (s, 1H), 8.00 (dd, 1H, J = 1.5 and 5.4 Hz), 7.85 (d, 1H, J = 2.5 Hz), 7.66 (t, 1H, J = 5.9 Hz), 7.55 and 7.36 (AB, 2H, J = 8.8 Hz), 7.19 (d, 1H, J = 7.3 Hz), 7.10 (t, 1H, J = 7.3 Hz), 6.98 (d, 1H, J = 2.0 Hz), 6.95 (t, 1H, J = 7.8 Hz), 6.62 (t, 1H, J = 6.8 Hz), 6.22 (d, 1H, J = 7.8 Hz), 5.71 (s, 2H), 3.09 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 173.8, 173.3, 172.7, 172.2, 159.2, 155.9, 154.9, 154.8, 151.2, 147.8, 147.5, 147.7, 146.9, 145.9, 145.8, 141.2, 138.0, 137.3, 138.1, 136.1, 135.2, 131.6, 129.9, 129.7, 126.3, 118.8, 118.6, 62.8, 30.1, 30.0; LR-MS (ESI): calcd for $C_{25}H_{22}N_3O_5S$ $[M+H]^+$ 476. found 498 [$(M+Na)^+$ 10]. 476 (50). 355 (100).

5.1.31. 6-(5-Carbamoyl-2-fluorobenzyl)-*N*-(methylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (68)

^{1}H NMR (400 MHz, DMSO-d_6), δ above 12 (2H), 7.98 (dt, 1H, J = 2.4 and 7.2 Hz), 7.86 (s, 1H), 7.82–7.80 (m, 2H), 7.68 (t, 1H, J = 6.0 Hz), 7.59, 7.52 (AB, 2H, J = 3.2 Hz), 7.53–7.51 (m, 1H), 7.33 (s, 1H), 7.30 (t, 1H, J = 9.2 Hz), 6.98–6.96 (m, 1H), 6.63 (t, 1H, J = 7.2 Hz), 5.81 (s, 2H), 3.25 (s, 3H). LR-MS (ESI): calcd. for $C_{25}H_{20}FN_4O_6S$ $[M+H]^+$ 523, found 523 (100).

5.1.32. 6-(2-Fluoro-3-methylbenzyl)-*N*-(methylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (69)

^{1}H NMR (400 MHz, DMSO-d_6), δ above 12 (2H), 7.97 (dd, 1H, J = 1.6 and 6.8 Hz), 7.84–7.83 (m, 1H), 7.66 (t, 1H, J = 6.4 Hz), 7.58 and 7.48 (AB, 2 H, J = 8.8 Hz), 7.16 (t, 1H, J = 8.5 Hz), 6.98–6.97 (m, 1H), 6.92 (t, 1H, J = 7.6 Hz), 6.61 (t, 1H, J = 6.8 Hz), 6.57 (t, 1H, J = 7.2 Hz), 5.79 (s, 2H), 3.22 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6, F-coupled spectra), δ 162.4, 160.9, 158.9, 157.0, 147.5, 144.5, 143.5, 136.1, 135.6, 130.5, 128.2, 125.7, 124.4, 124.2, 123.9, 123.2, 120.5, 118.5, 112.4, 107.3, 107.2, 107.0, 42.2, 42.1, 41.0, 13.9, LR-MS (ESI): calcd for $C_{25}H_{21}FN_3O_5S$ $[M+H]^+$ 494, found 494 (30), 373 (100).

5.1.33. 6-(2-Chlorobenzyl)-*N*-(methylsulfonyl)-8-(2-oxo-1,2-dihydropyridin-3-yl)-6*H*-furo[2,3-*e*]indole-7-carboxamide (70)

^{1}H NMR (500 MHz, DMSO-d_6), δ 12.77 (br s, 1H) 12.67 (d, 1H, J = 6.5 Hz), 8.02 (dd, 1H, J = 2.5 and 7 Hz), 7.87 (d, 1H, J = 2.5 Hz), 7.68 (dt, 1H, J = 2 and 6 Hz), 7.57 (d, 1H, J = 9 Hz), 7.51 and 7.33 (AB, 2 H, J = 8.5 Hz), 7.29 (dt, 1H, J = 8 and 2.0 Hz), 7.15 (dt, 1H, J = 7.5 and 1.0 Hz), 7.01 (d, 1H, J = 2.0 Hz), 6.64 (t, 1H, J = 7 Hz), 6.40 (d, 1H, J = 8.0 Hz), 5.79 (s, 2H), 3.17 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6), δ 162.5, 160.8, 147.6, 144.7, 143.7, 136.2, 135.7, 135.2, 130.1, 129.2, 128.8, 127.4, 127.1, 120.7, 118.9, 113.1, 112.5, 107.2, 107.1, 46.0, 41.0. LR-MS (ESI): calcd for $C_{24}H_{19}ClN_3O_5S$ $[M+H]^+$ 496, found 496 (20), 400 (10) 375 (100).

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