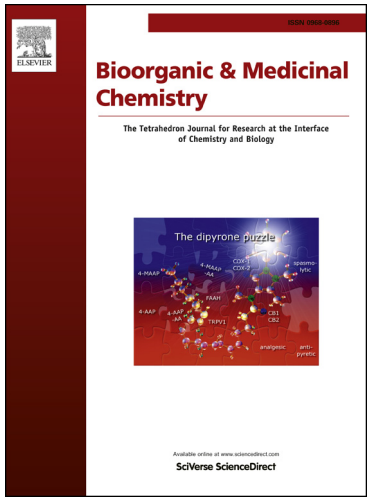

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PII: S0968-0896(16)30062-1
DOI: http://dx.doi.org/10.1016/j.bmc.2016.01.047
Reference: BMC 12790

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 26 November 2015
Revised Date: 19 January 2016
Accepted Date: 26 January 2016

Please cite this article as: Leung, E., Pilkington, L.I., Rensburg, M.v., Jeon, C.Y., Song, M., Arabshahi, H.J., Zoysa, G.H.D., Sarojini, V., Denny, W.A., Reynisson, J., Barker, D., Synthesis and cytotoxicity of thieno[2,3-*b*]quinoline-2-carboxamide and cycloalkyl[*b*]thieno[3,2-*e*]pyridine-2-carboxamide derivatives, *Bioorganic & Medicinal Chemistry* (2016), doi: http://dx.doi.org/10.1016/j.bmc.2016.01.047

Synthesis and cytotoxicity of thieno[2,3-*b*]quinoline-2-carboxamide and cycloalkyl[*b*]thieno[3,2-*e*]pyridine-2-carboxamide derivatives

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Abstract: Seventy nine derivatives of thieno[2,3-*b*]quinolines, tetrahydrothieno[2,3-*b*]quinoline, dihydrocyclopenta[*b*]thieno[3,2-*e*]pyridine, cyclohepta[*b*]thieno[3,2-*e*]pyridine and hexahydrocycloocta[*b*]thieno[3,2-*e*]pyridine were either synthesized or obtained commercially and tested for their antiproliferative activity against HCT116, MDA-MB-468 and MDA-MB-231 human cancer cell lines. The most potent eight compounds were active against all cell lines with IC_{50} values in the 80-250 nM range. In general hexahydrocycloocta[*b*]thieno[3,2-*e*]pyridines were most active with increasing activity observed as larger cycloalkyl rings were fused to the pyridine ring.

Keywords: thieno[2,3-*b*]pyridines; thieno[3,2-*e*]pyridines; thieno[2,3-*b*]quinolones; antiproliferative

1. Introduction

Thienopyridine derivatives have been reported to have significant antiproliferative activity against a range of human cancer cell lines [1-8]. In tests against the National Cancer Institute's human tumour cell line panel (NCI60) [2,4,5], and later verified using thymidine uptake assays, thienopyridines have been shown to be growth inhibitory to triple negative breast cancer cell lines (those lacking the oestrogen and progesterone receptors and HER2) such as MDA-MB-231/468, with GI_{50} values in the nanomolar range [3]. Thienopyridine

derivatives have been reported to have numerous effects on cell growth and development; these include severe growth restriction, rounding with accompanying blebbing of the plasma membrane, cell cycle arrest in G_2/M-phase and slowed proliferation in scratch assays. Many of the cellular effects induced by thienopyridines resemble behaviour seen in phospholipase C – δ1 (PLC-δ1) and δ3 isoforms knockdown cells for MDA-MB-231 [9], indicating that these compounds may bind with PLC. Additionally, inhibition of copper trafficking of Atox1 and CCS proteins has also been reported with this class of compound [10].

We have previously shown that thieno[2,3-*b*]pyridines, such as **1**, which lack an additional ring fused to the pyridine ring, have lower anti-proliferative activity than the tetrahydrothieno[2,3-*b*]quinolones **2** (Fig. 1) [5]. However, compounds with a large substituent at C-5 (e.g. **1b**) or C-6 (e.g. **3**) have greater activity than those without (e.g. **1a**) showing that substituents attached to the pyridine ring can increase activity. Compounds where the 2-carboxamide and 3-amino groups were modified to form a cyclic structure (e.g. **4**) were generally less active than those without modification. Whilst these effects have been investigated, less was known about the effect of changing the ring(s) fused to the pyridine at positions C-5 and C-6.

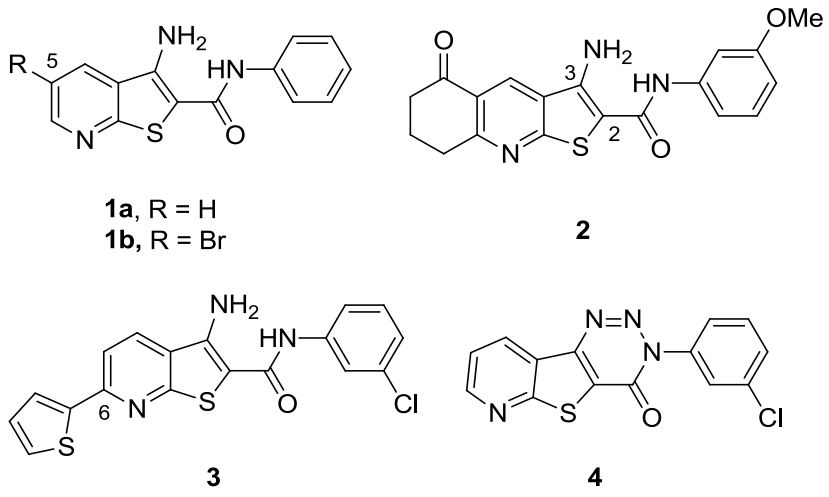
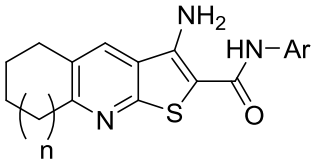


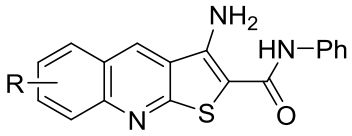
Figure 1. Previously prepared anti-proliferative thieno[2,3-*b*]pyridines

To investigate the effect of changing the ring fused to the pyridine ring, a range of compounds were prepared. Firstly, a series of cycloalkyl-fused derivatives, dihydrocyclopenta[*b*]thieno[3,2-*e*]pyridines **5**, tetrahydrothieno[2,3-*b*]quinolines **6**, cyclohepta[*b*]thieno[3,2-*e*]pyridines **7** and hexahydrocycloocta[*b*]thieno[3,2-*e*]pyridines **8**

investigate the change of ring size on activity, whilst thieno[2,3-*b*]quinolones explore the effect of adding a further fused aromatic ring (Fig. 2)



5, n = 0, dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridines
6, n = 1, tetrahydrothieno[2,3-*b*]quinolines
7, n = 2, tetrahydro-5*H*-cyclohepta[*b*]thieno[3,2-*e*]pyridines
8, n = 3, hexahydrocycloocta[*b*]thieno[3,2-*e*]pyridines



thieno[2,3-*b*]quinoline-2-carboxamides

Figure 2. Compounds prepared and evaluated.

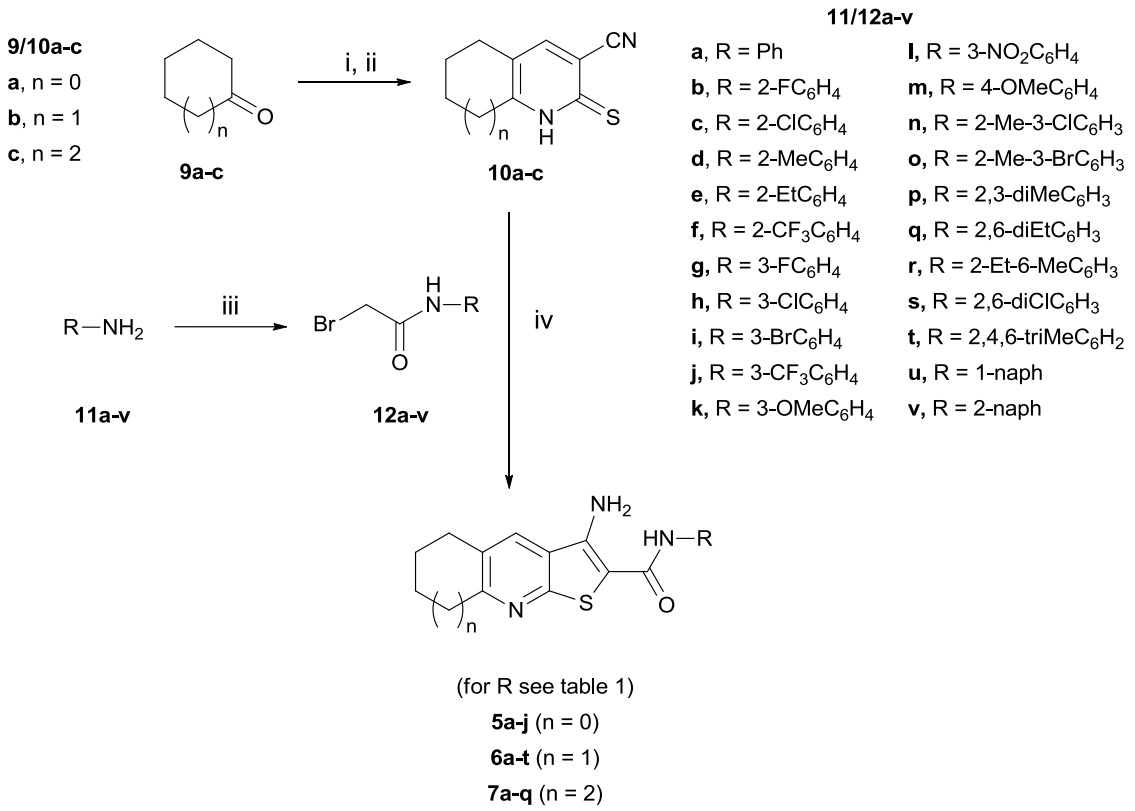
2. Results and Discussion

2.1 Chemistry

Thieno[2,3-*b*]quinolines **6** and cycloalkyl[*b*]thieno[3,2-*e*]pyridines **5** and **7** were prepared in an efficient three step process from the corresponding cyclic ketones **9a-c**. The first step involved the formation of the corresponding hydroxymethylene salts, which were obtained by the reaction of ketones **9a-c** with freshly-prepared sodium methoxide and methyl formate [11]. These salts were then immediately heated at reflux with cyanothioacetamide and piperidinium acetate, followed by acidification with acetic acid, which provided bicyclic thiocarbonitriles **10a-c** [12].

Anilines **11a-v** were converted to 2-bromo-*N*-phenylacetamides **12a-v** using 1 equivalent of bromoacetyl bromide in the presence of Et_3N and were not optimised if sufficient material for further reactions was obtained [13]. The reactions These bromoacetamides **12a-v** were then coupled with the required bicyclic thiocarbonitrile **10a-c** by heating at reflux with sodium

carbonate, which also effected concomitant cyclisation to give cycloalkyl[*b*]thieno[3,2-*e*]pyridines, **5a-j** and **7a-q** and thieno[2,3-*b*]quinolines, **6a-t** [5]. Again reactions were not optimised if sufficient material for biological tesing was obtained.

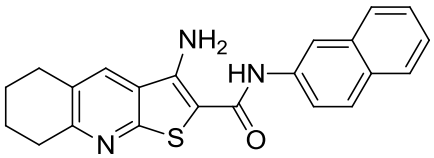


Scheme 1. Reagents and conditions: (i) Na, MeOH, methyl formate, 52-67 %; (ii) cyanothioacetamide (1.1 equiv.), piperidinium acetate, water, reflux, 4 h, AcOH, r.t., 12 h, **10a-c** 30-59 %; (iii) bromoacetyl bromide (1 equiv.), Et_3N (1.1 equiv.), 0 ºC, 1 h, **12a-v** 16-100 %; (iv) Na_2CO_3 (1.06 equiv.), EtOH, 100 ºC, 18 h, **5a-j**, **6a-t**, **7a-q** 6-100 %.

2.2 Anti-proliferative activity of synthesised and commercially obtained compounds

The anti-proliferative activity of the synthesised cycloalkyl[*b*]thieno[3,2-*e*]pyridines **5a-j** and **7a-q**, and thieno[2,3-*b*]quinolines **6a-t**, along with a series of related commercially-obtained compounds (Fig. 3), was measured against three cancer cell-lines, HCT116, MDA-MB-468 and MDA-MB-231 with all compounds being initially tested at 1 μM concentration (Table 1). These cell lines were chosen based on favourable results in previous studies against the entire National Cancer Institute 60 human cell line panel [1-5]. The testing concentration of 1 μM was chosen as previous studies, on structurally similar compounds, have shown this concentration, and higher, to be non-toxic in whole animal murine studies [14]. Furthermore,

testing of thieno[2,3-*b*]pyridine analogues for *in vitro* antibacterial activity against *E. coli, P. aeruginosa* and *S. aureus* pathogens showed no, or marginal, activity against these three bacterial strains. This indicate that the ligands are not generally toxic, e.g., forming DNA adducts via the aryl amine moiety [15].



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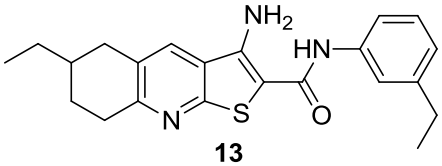

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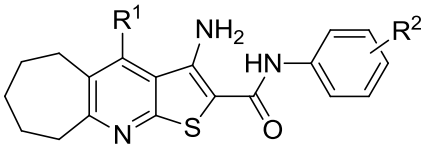
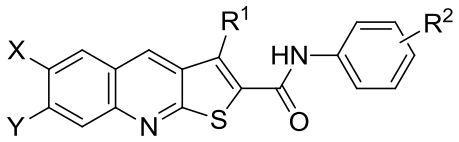
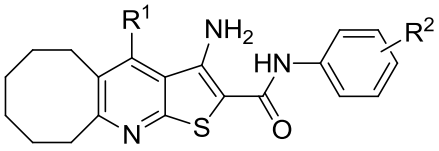


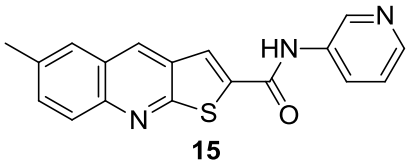
7r: R^1 = 2-furyl, R^2 = H
7s: R^1 = H, R^2 = 2-Cl, 5-CF_3
7t: R^1 = H, R^2 = 3,4-di-OMe
7u: R^1 = H, R^2 = 2,5-di-OMe
7v: R^1 = H, R^2 = 3,4-di-Cl
7w: R^1 = H, R^2 = 3-butoxy



14a: X = Me, Y = H, R^1 = H, R^2 = 2,5-di-Me
14b: X = Me, Y = H, R^1 = H, R^2 = 3-Me
14c: X = Me, Y = H, R^1 = H, R^2 = 3-F
14d: X = Me, Y = H, R^1 = H, R^2 = 2-Me
14e: X = Me, Y = H, R^1 = H, R^2 = H
14f: X, Y = H, R^1 = NH_2, R^2 = 4-OMe
14g: X, Y = H, R^1 = NH_2, R^2 = 4-acetyl
14h: X = OEt, Y = H, R^1 = NH_2, R^2 = 4-acetyl
14i: X = OMe, Y = H, R^1 = NH_2, R^2 = 2-OMe, 5-Cl
14j: X = OEt, Y = H, R^1 = NH_2, R^2 = 4-Cl
14k: X = H, Y = Me, R^1 = NH_2, R^2 = 2-NO_2



8a: R^1 = CF_3, R^2 = 2-Cl
8b: R^1 = H, R^2 = 2-F
8c: R^1 = H, R^2 = 3-acetyl
8d: R^1 = H, R^2 = 4-F
8e: R^1 = H, R^2 = 4-Cl
8f: R^1 = H, R^2 = 4-OMe
8g: R^1 = H, R^2 = 3,4-di-OMe
8h: R^1 = H, R^2 = 2,4-di-OMe
8i: R^1 = H, R^2 = 2,5-di-OMe
8j: R^1 = H, R^2 = 2,3-di-Me



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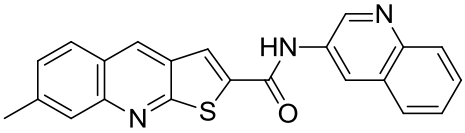

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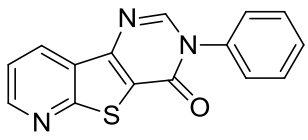

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Figure 3. Structures of commercially-obtained compounds.

Table 1. Anti-proliferative activity of cycloalkyl[*b*]thieno[2,3-*e*]pyridines and thieno[2,3-*b*]quinolines.

Compound	n	R	Relative growth (%) at 1 μM		
			HCT116[a]	MDA-MB-468[a]	MDA-MB-231[a]
5a	0	Ph	94	76	90
5b	0	3-ClC_6H_4	87	53	92
5c	0	3-BrC_6H_4	93	53	94
5d	0	3-$CF_3C_6H_4$	90	58	100
5e	0	3-$OMeC_6H_4$	92	63	95
5f	0	3-$NO_2C_6H_4$	79	46	79
5g	0	2-Me-3-ClC_6H_3	3	4	11
5h	0	2-Me-3-BrC_6H_3	5	5	16
5i	0	1-naphthalene	92	67	80
5j	0	2-naphthalene	94	64	81
6a	1	Ph	5	8	22
6b	1	2-FC_6H_4	84	48	92
6c	1	2-ClC_6H_4	94	95	119
6d	1	2-MeC_6H_4	84	53	70
6e	1	2-EtC_6H_4	86	63	89
6f	1	2-$CF_3C_6H_4$	104	93	128
6g	1	3-FC_6H_4	11	11	30
6h	1	3-ClC_6H_4	80	58	98
6i	1	3-BrC_6H_4	85	45	101
6j	1	3-$CF_3C_6H_4$	82	41	108
6k	1	3-$NO_2C_6H_4$	75	44	71
6l	1	4-$OMeC_6H_4$	99	84	98
6m	1	2-Me-3-ClC_6H_3	3	6	15
6n	1	2-Me-3-BrC_6H_3	5	3	5
6o	1	2,3-di-MeC_6H_3	5	3	4
6p	1	2,6-di-EtC_6H_3	108	116	115
6q	1	2-Et-6-MeC_6H_3	96	67	84
6r	1	2,6-di-ClC_6H_3	100	82	93
6s	1	2,4,6-tri-MeC_6H_2	101	93	97
6t	1	1-naphthalene	37	8	60
6u[b]	1	2-naphthalene	100	76	120
7a	2	Ph	6	5	26
7b	2	2-FC_6H_4	15	11	46
7c	2	2-ClC_6H_4	92	73	89
7d	2	2-MeC_6H_4	66	25	43
7e	2	2-$CF_3C_6H_4$	112	100	124
7f	2	3-FC_6H_4	29	10	28
7g	2	3-ClC_6H_4	86	39	95
7h	2	3-BrC_6H_4	83	45	92
7i	2	3-$CF_3C_6H_4$	108	92	94
7j	2	3-$OMeC_6H_4$	6	3	19
7k	2	3-$NO_2C_6H_4$	51	18	67
7l	2	2-Me-3-ClC_6H_3	10	3	13
7m	2	2-Me-3-BrC_6H_3	8	3	12
7n	2	2,3-di-MeC_6H_3	6	4	6
7o	2	2,4,6-tri-MeC_6H_2	99	89	98

7p	2	1-naphthalene	93	91	106
7q	2	2-naphthalene	103	97	118
7r[b]		see figure 3	65	71	89
7s[b]	2	2-Cl-5-$CF_3C_6H_3$	98	106	105
7t[b]	2	3,4-di-$OMeC_6H_3$	98	77	114
7u[b]	2	2,5-di-$OMeC_6H_3$	98	94	117
7v[b]	2	3,4-di-ClC_6H_3	103	77	115
7w[b]	2	3-$O^nBuC_6H_4$	97	53	100
8a[b]		see figure 3	112	100	116
8b[b]		see figure 3	5	5	24
8c[b]		see figure 3	85	72	117
8d[b]		see figure 3	82	65	100
8e[b]		see figure 3	94	82	117
8f[b]		see figure 3	106	84	107
8g[b]		see figure 3	106	107	102
8h[b]		see figure 3	109	110	119
8i[b]		see figure 3	107	94	131
8j[b]		see figure 3	6	4	3
13[b]		see figure 3	73	12	73
14a[b]		see figure 3	98	77	103
14b[b]		see figure 3	100	84	105
14c[b]		see figure 3	98	91	103
14d[b]		see figure 3	99	89	104
14e[b]		see figure 3	95	81	92
14f[b]		see figure 3	97	68	101
14g[b]		see figure 3	93	70	95
14h[b]		see figure 3	96	87	97
14i[b]		see figure 3	100	104	86
14j[b]		see figure 3	100	93	97
14k[b]		see figure 3	102	101	90
15[b]		see figure 3	102	101	81
16[b]		see figure 3	99	87	97
17[b]		see figure 3	96	101	107

[a] Values represent relative growth (%) versus control. All compounds were tested at 1μM against the specified cell lines. Experiments were performed in duplicate; stated values are the averages of two independent determinations. [b] Compound was obtained commercially, see Figure 3 for structures.

From the results from the bioactivity tests against the three cancer cell line, general trends can be made. Firstly, the triple negative MDA-MB-468 cell line was the most susceptible to the tested compounds with an average relative growth of 60% over the 79 compounds tested versus 76% and 82% for HCT116 and MDA-MB-231, respectively. This result is in line with previous observations of the susceptibility of triple negative breast cancer cell lines to thienopyridines [3].

With the aryl carboxamide moiety of both the thieno[2,3-*b*]quinolines and cycloalkyl[*b*]thieno[3,2-*e*]pyridines, it can be seen that 2,3-disubstitution on the aryl ring is more favoured over others (as can be seen in compounds **5g**, **5h**, **6m**, **6n**, **6o**, **7l**, **7m**, **7n** and **8j**).

It was noted that a decrease in cell growth was observed as the size of the ring fused to the pyridine ring increased, regardless of substitution on the aryl carboxamide. This can be seen when comparing the data for most susceptible cell line (MDA-MB-468); for example compounds **5f** (46% relative growth), **6k** (44%), and **7k** (18%); compounds **5a** (76%), **6a** (8%) and **7a** (5%); and compounds **6b** (48%), **7b** (11%) and **8b** (5%).

The presence of a benzene ring fused to the pyridine ring (as in **14a-k**, **15**, **16**) results in inactive compounds. All compounds lacking the 2-aryl carboxamide and 3-amino moieties were found to be inactive (e.g. **14a-e**, **15**, **16** and **17**), a trend previously observed on smaller thienopyridines [5].

From this screen of 79 compounds, 17 of the most active compounds were further tested to obtain IC_{50} values. The previously used cancer cell lines along with leukaemia cell line K562, which has been shown to be susceptible to this class of compounds[2] (Table 2). The IC_{50} results further validate the trends seen initially in terms of increased activity as the size of the ring fused to the pyridine increase, as well as the importance of 2,3-disubstitution in the aryl carboxamide for activity. The most active eight compounds were generally active against all four cell lines with IC_{50} values in the 80-250 nM range.

Table 2. IC_{50} values of cycloalkyl[*b*]thieno[2,3-*e*]pyridines and thieno[2,3-*b*]quinolines.

Compound	IC_{50} (nM)[a]			
	HCT116	**MDA-MB-468**	**MDA-MB-231**	**K562**
5g	218 ± 22	546 ± 16	593 ±1	197 ± 2
5h	161 ± 4	79 ± 24	84 ± 14	83 ± 9
6a	594 ± 2	407 ± 50	617 ± 8	526 ± 33
6g	563 ± 14	398 ± 23	632 ± 28	554 ± 13
6m	191 ± 9	134 ± 31	221 ± 8	153 ± 6
6n	207 ± 1	185 ± 9	233 ± 16	185 ± 3
6o	199 ± 4	148 ± 46	204 ± 9	152 ± 6
6t	720 ± 4	447 ± 76	854 ± 104	576 ± 24
7a	606 ± 29	383 ± 21	508 ± 56	570 ± 71
7b	798 ± 202	528 ± 15	672 ± 67	575 ± 90
7f	543 ± 47	351 ± 56	448 ± 47	558 ± 63
7j	601 ± 64	391 ± 16	524 ± 46	580 ± 60
7l	266 ± 62	160 ± 25	190 ± 5	210 ± 19

7m	442 ± 74	199 ± 22	198 ± 33	223 ± 20
7n	204 ± 9	121 ± 26	198 ± 1	167 ± 1
8b	599 ± 6	372 ± 61	587 ± 8	562 ± 17
8j	183 ± 1	83 ± 16	170 ± 10	83 ± 6

[a]Experiments were performed in triplicate; stated values are the averages of three independent determinations.

3. Conclusions

In summary seventy nine synthetic or commercially obtained compounds all containing a thienopyridine motif were tested for their antiproliferative activity against a range of human cancer cell lines. The most susceptible cell line tested was MDA-MB-468 and the most active compounds having IC_{50} values ~80 nM. In general hexahydrocycloocta[*b*]thieno[3,2-*e*]pyridines were most active series of compounds with increasing activity observed as larger cycloalkyl rings were fused to the pyridine ring. These results show that further modifications to thienopyridine scaffolds, in particular changing the pyridine-fused ring, led to improved cytotoxicity and shows that along with substitution of the aryl carboxamide are sites for further investigations in this class of compound. The low IC_{50} values in selected cell lines along with tolerance in animal toxicity studies show thienopyridines as a promising class of novel antiproliferative agents.

4. Experimental Details and Methodology

4.1 Synthesis of Compounds

4.1.1 General Details: All reactions were carried out under a nitrogen atmosphere in dry, freshly distilled solvents unless otherwise noted. All NMR spectra were recorded on either Bruker Avance DRX 300 MHz or 400 MHz spectrometers at ambient temperatures. Chemical shifts are reported relative to the solvent peak of chloroform (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C), DMSO (δ 2.50 for ^{1}H and δ 39.5 for ^{13}C) or acetone (δ 2.05 for ^{1}H and δ 29.8 for ^{13}C). ^{1}H NMR data is reported as position (δ), relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of triplets; dd, doublet of doublets; tt, triplet of triplets; m, multiplet; br, broad peak; qd, quartet of doublets), coupling constant (*J*, Hz), and the assignment of the atom. ^{13}C NMR data are reported as position (δ) and assignment of the atom. All NMR assignments were performed using HSQC and HMBC experiments. High-resolution mass spectroscopy (HRMS) was carried out by either chemical ionization (CI) or

electrospray ionization (ESI) on a MicroTOF-Q mass spectrometer. Unless noted, chemical reagents were used as purchased.

4.1.2 General Procedure for the synthesis of thieno[2,3-b]pyridine-2-carboxamides ***5-7***

A mixture of 2-bromoacetamides **12a-v** (1 equiv), carbonitrile **10a-c** (1 equiv) and anhydrous sodium carbonate (1.06 equiv) in absolute ethanol or methanol was stirred at reflux for 18 h. The mixture was cooled to room temperature and the solvent removed *in vacuo* to give the crude product which was washed with small amounts of ice water before being recrystallized from methanol to give the *thieno[2,3-b]pyridine-2-carboxamides* **5-7**.

4.1.2.1 3-Amino-N-phenyl-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5a***. The reaction was carried out according to general procedure C using 2-bromo-*N*-phenylacetamide **12a** (0.06 g, 0.28 mmol), carbonitrile **10a** (0.05 g, 0.26 mmol) and sodium carbonate (0.03 g, 0.28 mmol) in ethanol (2 mL) to give the *title product* **5a** (0.04 g, 55%) as a black solid. m.p. 213-216 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.19-2.27 (2H, m, H-6), 3.07-3.14 (4H, m, H-5 and H-7), 7.13-7.18 (1H, m, H-4'), 7.38-7.42 (4H, m, NH_2 and H-3' and H-5'), 7.77-7.79 (2H, m, H-2' and H-6'), 8.37 (1H, s, H-4), 9.43 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 95.7 (C-2), 121.0 (C-2' and C-6'), 123.3 (C-4'), 124.1 (C-3a), 128.4 (C-3' and 5'), 128.7 (C-4), 133.3 (C-3), 139.0 (C-4a), 147.0 (C-1'), 159.3 (C-8a), 164.0 (C=O), 167.8 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3410, 3288, 3042, 2954, 1677, 1590, 1509, 1430, 1226; *m/z* (ESI$^+$): 377 (MNa$^+$, 100%), 355 (MH$^+$, 52%); HRMS (ESI$^+$) found (MNa$^+$): 332.0815, $C_{17}H_{15}N_3NaOS$ requires 377.0679. The spectroscopic data was consistent with literature values [16].

4.1.2.2 3-Amino-N-(3'-chlorophenyl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5b.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-chlorophenyl)acetamide **12c** (0.08 g, 0.31 mmol), carbonitrile **10a** (0.05 g, 0.28 mmol) and sodium carbonate (0.03 g, 0.31 mmol) in methanol (2 mL) to give the *title product* **5b** (0.10 g, 100%) as a black solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.14-2.20 (2H, m, H-6), 2.99-3.05 (4H, m, H-5 and H-7), 7.11-7.14 (1H, m, H-4'), 7.33-7.37 (1H, m, H-5'), 7.39 (2H, br s, NH_2), 7.65-7.68 (1H, m, H-6'), 7.94 (1H, s, H-2'), 8.31 (1H, s, H-4), 9.52 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 95.2 (C-2), 119.1(C-6'), 120.1 (C-2'), 122.8 (C-4'), 124.0 (C-4a), 126.2 (C-4), 130.0 (C-

5'), 132.7 (C-3a), 133.1 (C-3), 140.7 (C-3'), 147.6 (C-1'), 157.3 (C-8a), 164.1 (C=O), 168.1 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3426, 3323, 2952, 1673, 1586, 1522, 1497, 1474, 1253, 770, 675; *m/z* (ESI$^+$): 368 (^{37}ClMNa$^+$, 8%), 366 (^{35}ClMNa$^+$, 22%), 253 (MNa$^+$-Cl, 100%); HRMS (ESI$^+$) found (^{37}ClMNa$^+$): 368.0431, $C_{17}H_{14}{}^{37}ClN_3NaOS$ requires 368.0412. Found (^{35}ClMNa$^+$): 366.0447, $C_{17}H_{14}{}^{35}ClN_3NaOS$ requires 366.0438.

4.1.2.3 3-Amino-N-(3'-bromophenyl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5c.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-bromophenyl)acetamide **12i** (0.09 g, 0.37 mmol), carbonitrile **10a** (0.05 g, 0.34 mmol) and sodium carbonate (0.04 g, 0.37 mmol) in ethanol (2 mL) to give the *title product* **5c** (0.09 g, 87%) as a black solid. m.p. 214-216 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.12-2.20 (2H, m, H-6), 2.99-3.01 (4H, m, H-5 and H-7), 7.24-7.31 (2H, m, H-4' and H-5'), 7.39 (2H, br s, NH_2), 7.70-7.72 (1H, m, H-6'), 8.08 (1H, s, H-2'), 8.31 (1H, s, H-4), 9.51 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 95.7 (C-2), 119.4 (C-2' and C-6'), 121.2 (C-3a), 123.0 (C-3'), 126.1 (C-4), 130.3 (C-5'), 130.7 (C-3), 133.4 (C-4'), 140.3 (C-4a), 140.8 (C-1'), 147.6 (C-3'), 157.3 (C-8a), 164.1 (C=O), 168.1 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3430, 3329, 2929, 1677, 1585, 1451, 1395, 1259, 1078; *m/z* (ESI$^+$): 412 (^{81}BrMNa$^+$, 28%), 410 (^{79}BrMNa$^+$, 26%), 393 (MNa$^+$-Br, 100%); HRMS (ESI$^+$) found (^{81}BrMNa$^+$): 411.9920, $C_{17}H_{14}{}^{81}BrN_3NaOS$ requires 411.9913. Found (^{79}BrMNa$^+$): 409.9939, $C_{17}H_{14}{}^{79}BrN_3NaOS$ requires 409.9933.

4.1.2.4 3-Amino-N-(3'-(trifluoromethyl)phenyl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5d.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-(trifluoromethyl)phenyl)acetamide **12j** (0.09 g, 0.31 mmol), carbonitrile **10a** (0.05 g, 0.28 mmol) and sodium carbonate (0.03 g, 0.31 mmol) in methanol (2 mL) to give the *title product* **5d** (1.0 g, 100%) as a black solid. m.p. 215-216 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.12-2.20 (2H, m, H-6), 2.99-3.06 (4H, m, H-5 and H-7), 7.40-7.42 (3H, m, H-4' and NH_2), 7.55-7.59 (2H, m, H-5' and H-6'), 8.23 (1H, s, H-4), 8.32 (1H, s, H-2'), 9.67 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 95.0 (C-2), 116.8 (q, $^3J_{F/C}$ 3.6 Hz, C-2'), 119.4 (q, $^3J_{F/C}$ 3.8 Hz, C-4'), 124.0 (C-3a), 124.1 (q, $^1J_{F/C}$ 274.6 Hz, CF_3), 124.2 (C-6'), 126.2 (C-5'), 129.6 (q, $^2J_{F/C}$ 39.0 Hz, C-3'), 129.9 (C-3), 133.4 (C-4), 140.0 (C-4a), 147.8 (C-1'), 157.3 (C-8a), 164.3 (C=O), 168.1 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3433, 3332, 2953, 1686, 1595, 1556, 1496, 1260, 1164, 1115; *m/z* (ESI$^+$): 400

(MNa^+, 27%), 378 (MH^+, 100%); HRMS (ESI^+) found (MH^+): 378.0895, $C_{18}H_{15}F_3N_3OS$ requires 378.0882.

4.1.2.5 3-Amino-N-(3'-methoxyphenyl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5e.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-methoxyphenyl)acetamide **12k** (0.09 g, 0.37 mmol), carbonitrile **10a** (0.06 g, 0.34 mmol) and sodium carbonate (0.04 g, 0.37 mmol) in methanol (2 mL) to give the *title product* **5e** (0.11 g, 91%) as a black solid. m.p. 215-218 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.11-2.19 (2H, m, H-6), 2.99-3.06 (4H, m, H-5 and H-7), 3.76 (3H, s, OCH_3), 6.64-6.67 (1H, dd, J = 8.6, 2.4 Hz, H-4'), 7.22 (1H, t, J = 8.1 Hz, H-5'), 7.32-7.35 (3H, m, NH_2 and H-6'), 7.40 (1H, s, H-2'), 8.30 (1H, s, H-4), 9.31 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 54.9 (OCH_3), 95.7 (C-2), 106.5 (C-2'), 108.9 (C-4'), 113.1 (C-5'), 124.1 (C-3), 126.1 (C-4), 129.1 (C-6'), 133.3 (C-4a), 140.3 (C-1'), 147.1 (C-3a), 157.2 (C-8a), 159.3 (C-3'), 164.0 (C=O), 167.8 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3435, 3327, 3000, 2951, 2827, 1671, 1590, 1527, 1448, 1255, 1160; *m/z* (ESI^+): 362 (MNa^+, 100%), 340 (MH^+, 46%); HRMS (ESI^+) found (MNa^+): 362.0934, $C_{18}H_{17}N_3NaO_2S$ requires 362.0934.

4.1.2.6 3-Amino-N-(3'-nitrophenyl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5f.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-nitrophenyl)acetamide **12l** (0.10 g, 0.37 mmol), carbonitrile **10a** (0.06 g, 0.34 mmol) and sodium carbonate (0.04 g, 0.37 mmol) in methanol (2 mL) to give the *title product* **5f** (0.09 g, 75%) as a black solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.12-2.20 (2H, m, H-6), 2.99-3.06 (4H, m , H-5 and H-7), 7.47 (2H, br s, NH_2), 7.62 (1H, t, J = 8.2 Hz, H-5'), 7.91-7.94 (1H, dd, J = 8.1, 1.9 Hz, H-6'), 8.16 (1H, d, J = 7.8 Hz, H-4'), 8.34 (1H, s, H-4), 8.80 (1H, s, H-2'), 9.84 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 94.8 (C-2), 114.7 (C-2'), 117.5 (C-6'), 123.2 (C-3a), 126.2 (C-4), 126.5 (C-4'), 129.7 (C-5'), 133.4 (C-3), 138.5 (C-4a), 140.5 (C-1'), 148.1 (C-3'), 157.4 (C-8a), 164.3 (C=O), 168.3 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3424, 3328, 2951, 1683, 1582, 1498, 1349, 1290; *m/z* (ESI^+): 377 (MNa^+, 30%), 355 (MNa^+-NO_2, 100%); HRMS (ESI^+) found (MNa^+): 377.0683, $C_{17}H_{14}N_4NaO_3S$ requires 377.0679.

4.1.2.7 3-Amino-N-(3'-chloro-2'-methylphenyl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5g.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-chloro-2'-methylphenyl)acetamide **12n** (0.1 g, 0.37 mmol), carbonitrile

10a (0.06 g, 0.34 mmol) and sodium carbonate (0.04 g, 0.37 mmol) in methanol (2 mL) to give the *title product* **5g** (0.03 g, 30%) as a black solid. m.p. 216-217 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.14-2.20 (2H, m, H-6), 2.25 (3H, s, CH_3), 2.99-3.05 (4H, m, H-5 and H-7), 7.18-7.26 (3H, m, NH_2 and H-5'), 7.29-7.31 (1H, m, H-6'), 7.34-7.38 (1H, m, H-4'), 8.29 (1H, s, H-4), 9.32 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 15.4 (CH_3), 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 95.6 (C-2), 109.7(C-6'), 124.2 (3a), 126.1 (C-4), 126.2 (C-4'), 126.5 (C-6'), 126.7 (C-5'), 132.5 (C-3), 133.2 (C-4a), 133.6 (C-2'), 137.6 (C-3'), 146.8 (C-1'), 164.2 (C-8a), 167.8 (C=O), 174.9 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3380, 3291, 2970, 1708, 1639, 1607, 1459, 1426, 1254; *m/z* (ESI$^+$): 382 (^{37}ClMNa$^+$, 38%), 380 (^{35}ClMNa$^+$, 100%); HRMS (ESI$^+$) found (^{37}ClMNa$^+$): 382.0547, $C_{18}H_{16}{}^{37}ClN_3NaOS$ requires 382.0569. Found (^{35}ClMNa$^+$): 380.0580, $C_{18}H_{16}{}^{35}ClN_3NaOS$ requires 380.0595.

4.1.2.8 3-Amino-N-(3'-bromo-2'-methylphenyl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5h.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-bromo-2'-methylphenyl)acetamide **12o** (0.1 g, 0.31 mmol), carbonitrile **10a** (0.05 g, 0.28 mmol) and sodium carbonate (0.03 g, 0.31 mmol) in methanol (2 mL) to give the *title product* **5h** (0.84 g, 74%) as a black solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.10-2.20 (2H, m, H-6), 2.28 (3H, s, CH_3), 2.99-3.05 (4H, m, H-5 and H-7), 7.11-7.19 (1H, m, H-5'), 7.23 (2H, s, NH_2), 7.31-7.33 (1H, m, H-4'), 7.51-7.53 (1H, m, H-6'), 8.29 (1H, s, H-4), 9.34 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 18.5 (CH_3), 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 95.5 (C-2), 124.2(C-2'), 124.5 (C-3a), 126.1 (C-4), 126.9 (C-4'), 127.2 (C-5'), 129.8 (C-6'), 133.3 (C-3), 134.2 (C-3'), 138.0 (C-4a), 146.9 (C-1'), 157.2 (C-8a), 164.2 (C=O), 167.8 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3402, 3294, 2945, 1695, 1605, 1545, 1432, 1254; *m/z* (ESI$^+$): 426 (^{81}BrMNa$^+$, 64%), 424 (^{79}BrMNa$^+$, 63%), 313 (MNa$^+$-Br, 100%); HRMS (ESI$^+$) found (^{81}BrMNa$^+$): 426.0076, $C_{18}H_{16}{}^{81}BrN_3NaOS$ requires 426.0070. Found (^{79}BrMNa$^+$): 424.0091, $C_{18}H_{16}{}^{79}BrN_3NaOS$ requires 426.0090.

4.1.2.9 3-Amino-N-(naphthalen-1'-yl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5i.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(naphthalene-1'-yl)acetamide **12u** (0.1 g, 0.31 mmol), carbonitrile **10a** (0.05 g, 0.28 mmol) and sodium carbonate (0.03 g, 0.31 mmol) in methanol (2 mL) to give the *title product* **5i** (0.84 g, 74%) as a black solid. m.p. 213-215 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.14-2.21 (2H, m, H-6), 3.01-3.07 (4H, m, H-5 and H-7), 7.23 (2H, s, NH_2), 7.54-7.57 (4H, m, H-3', H-4', H-7' and H-8'), 7.93-7.99 (3H, m, H-2', H-5' and H-6'), 8.30 (1H, s, H-4), 9.65

(1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 96.0 (C-2), 123.5 (C-2'), 124.3 (C-3a), 125.5, 125.8, 125.9, 126.2 (C-3', C-4', C-7' and C-8'), 126.1 (C-4), 128.0 and 128.1 (C-1a' and C-5a'), 133.2 (C-3), 133.7 and 134.0 (C-5' and C-6'), 136.8 (C-4a), 146.7 (C-1'), 157.3 (C-8a), 164.9 (C=O), 167.7 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3295, 2936, 1713, 1605, 1525, 1501; *m/z* (ESI$^+$): 382 (MNa$^+$, 100%), 360 (MH$^+$, 31%); HRMS (ESI$^+$) found (MNa$^+$): 382.0991, $C_{21}H_{17}N_3NaOS$ requires 382.0985.

4.1.2.10 3-Amino-N-(naphthalen-2'-yl)-6,7-dihydro-5H-cyclopenta[b]thieno[3,2-e]pyridine-2-carboxamide ***5j.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(naphthalene-2'-yl)acetamide **12v** (0.1 g, 0.31 mmol), carbonitrile **10a** (0.05 g, 0.28 mmol) and sodium carbonate (0.03 g, 0.31 mmol) in methanol (2 mL) to give the *title product* **5j** (0.84 g, 74%) as a black solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 2.15-2.20 (2H, m, H-6), 3.00-3.06 (4H, m, H-5 and H-7), 7.43-7.51 (4H, m, H-5', H-8' and NH_2), 7.83-7.94 (4H, m, H-3', H-4', H-6' and H-7'), 8.32 (1H, s, H-4), 8.35 (1H, s, H-2'), 9.57 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 23.2 (C-6), 29.6 (C-5), 33.6 (C-7), 95.7 (C-2), 117.0 (C-2'), 121.6 (C-8'), 124.1 (C-5'), 124.6 (C-3a), 126.1 (C-4), 126.2 (C-3'), 127.3 (C-4'), 127.4 (C-6'), 127.8 (C-6a'), 129.8 (C-7'), 133.2 (C-2a'), 133.3 (C-3), 136.8 (C-4a), 147.2 (C-1'), 157.3 (C-8a), 164.2 (C=O), 167.9 (C-7a); IR: υ_{max} (film)/cm^{-1}: 3424, 3358, 3306, 1713, 1603, 1542, 1499; *m/z* (ESI$^+$): 382 (MNa$^+$, 45%), 360 (MH$^+$, 100%); HRMS (ESI$^+$) found (MH$^+$): 360.1165, $C_{21}H_{18}N_3OS$ requires 360.1165. The spectroscopic data was consistent with literature values [10].

4.1.2.11 3-Amino-N-phenyl-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6a.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-phenylacetamide **12a** (105 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6a** (136 mg, 86%) as a green solid. m.p. > 230 ºC. lit. m.p. 267 ºC [16]. ^{1}H NMR (300 MHz, d_6-DMSO) 1.76-1.89 (4H, m, H-6 and H-7), 2.88 (2H, t, J = 6.3 Hz, H-5), 2.95 (2H, t, J = 6.2 Hz, H-8), 7.06 (1H, tt, J = 7.2, 1.2 Hz, H-4'), 7.28-7.34 (4H, m, NH_2, H-3' and H-5'), 7.66-7.70 (2H, m, H-2' and H-6'), 8.18 (1H, s, H-4), 9.33 (1H, s, NH); ^{13}C NMR (75 MHz, d_6-DMSO) 22.3 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.8 (C-2), 121.1 (C-2' and C-6'), 123.3 (C-4'), 124.4 (C-3a), 128.3 (C-8a), 128.3 (C-3' and C-5'), 130.8 (C-4), 139.0 (C-1'), 146.8 (C-3), 155.9 (C-9a), 159.1 (C-4a), 164.1 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3448, 3333, 3180, 2943, 1607, 1590, 1522, 1495, 1318, 1166. *m/z* (ESI$^+$): 346 (MNa$^+$, 37%), 324 (MH$^+$,

100%); HRMS (ESI^+) found (MH^+): 324.1161, $C_{18}H_{18}N_3OS$ requires 324.1165. Found (MNa^+): 346.0977, $C_{18}H_{17}N_3NaOS$ requires 346.0985. The ^1H NMR data was in agreement with the literature values [16].

4.1.2.12 3-Amino-N-(2'-fluorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6b.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-fluorophenyl)acetamide **12b** (114 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6b** (85 mg, 51%) as a green solid. m.p. > 230 ºC. lit. m.p. 280-285 ºC [16]. ^1H NMR (400 MHz, d_6-DMSO) 1.80-1.91 (4H, m, H-6 and H-7), 2.88 (2H, t, J = 6.4 Hz, H-5), 2.95 (2H, t, J = 6.4 Hz, H-8), 7.17-7.28 (5H, m, H-3', H-4', H-5' and NH_2), 7.51 (1H, t, J = 7.8 Hz, H-6'), 8.18 (1H, s, H-4), 9.22 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.3 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.5 (C-2), 115.6 (d, $^2J_{F/C}$ 19.9 Hz, C-3'), 124.1 (d, $^4J_{F/C}$ 3.1 Hz, C-5'), 124.4 (C-3a), 125.8 (d, $^2J_{F/C}$ 12.3 Hz, C-1'), 126.7 (d, $^3J_{F/C}$ 7.7 Hz, C-4'), 127.5 (C-6'), 128.3 (C-4a), 130.9 (C-4), 146.8 (C-3), 156.2 (d, $^1J_{F/C}$ 245.4 Hz, C-2'), 156.0 (C-9a), 159.1 (C-8a), 163.9 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3411, 3275, 2938, 1645, 1606, 1507, 1447, 1319, 1244, 1186; *m/z* (ESI^+): 342 (MH^+, 100%); HRMS (ESI^+) found (MH^+): 342.1081, $C_{18}H_{17}FN_3OS$ requires 342.1071. The ^1H NMR data was in agreement with the literature values [16].

4.1.2.13 3-Amino-N-(2'-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6c.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-chlorophenyl)acetamide **12c** (261 mg, 1.10 mmol), carbonitrile **10b** (200 mg, 1.10 mmol) and anhydrous sodium carbonate (0.12 g, 1.1 mmol) in absolute ethanol (4 ml) to give the *title compound* **6c** (292 mg, 78%) as a brown solid, m.p. 228-229 ºC. ^1H NMR (400 MHz, d_6-DMSO) 1.77-1.91 (4H, m, H-6 and H-7), 2.88 (2H, t, J = 6.2 Hz, H-5), 2.95 (2H, t, J = 6.2 Hz, H-8), 7.22-7.27 (3H, m, H-4' and NH_2), 7.36 (1H, dt, J = 7.8, 1.2 Hz, H-5'), 7.53 (1H, dd, J = 8.0, 1.2 Hz, H-3'), 7.66 (1H, dd, J = 7.9, 1.1 Hz, H-6'), 8.18 (1H, s, H-4), 9.05 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.3 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.7 (C-2), 124.5 (C-3a), 126.7 (C-4'), 127.4 and 127.5 (C-5' and C-6'), 128.4 (C-2'), 128.7 (C-4a), 129.4 (C-3'), 130.9 (C-4), 135.2 (C-1'), 146.8 (C-3), 155.9 (C-9a), 159.2 (C-8a), 163.8 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3404, 3283, 2928, 1645, 1585, 1504, 1432, 1303, 1187, 746, 691; *m/z* (ESI^+): 360($^{37}ClMH^+$, 38%), 358 ($^{35}ClMH^+$, 100%); HRMS (ESI^+) found

($^{37}ClMH^+$): 360.0759, $C_{18}H_{17}{}^{37}ClN_3OS$ requires 360.0750. Found ($^{35}ClMH^+$): 358.0788, $C_{18}H_{17}{}^{35}ClN_3OS$ requires 358.0775.

4.1.2.14 3-Amino-N-(2'-methylphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6d.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(*o*-tolyl)acetamide **12d** (112 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6d** (130 mg, 79%) as a brown solid. m.p. > 250 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.79-1.89 (4H, m, H-6 and H-7), 2.22 (3H, s, CH_3), 2.88 (2H, t, J = 6.4 Hz, H-5), 2.95 (2H, t, J = 6.4 Hz, H-8), 7.12-7.21 (4H, m, H-5', H-4' and NH_2), 7.25 (1H, d, J = 7.2 Hz, H-3'), 7.31 (1H, dd, J = 7.6, 1.2 Hz, H-6'), 8.16 (1H, s, H-4), 9.03 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 17.9 (CH_3), 22.3 and 22.5 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 96.2 (C-2), 124.5 (C-3a), 125.7 (C-5'), 125.9 (C-4'), 126.8 (C-6'), 128.2 (C-4a), 130.1 (C-3'), 130.7 (C-4), 133.9 (C-2'), 136.5 (C-1'), 146.2 (C-3), 155.9 (C-9a), 158.8 (C-8a), 164.0 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3412, 3281, 2928, 1642, 1583, 1506, 1446, 1241, 1188; *m/z* (ESI$^+$): 338 (MH^+, 100%); HRMS (ESI$^+$) found (MH^+): 338.1332, $C_{19}H_{20}N_3OS$ requires 338.1322.

4.1.2.15 3-Amino-N-(2'-ethylphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6e.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-ethylphenyl)acetamide **12e** (135 mg, 0.56 mmol), carbonitrile **10b** (100 mg, 0.56 mmol) and anhydrous sodium carbonate (63 mg, 0.59 mmol) in absolute ethanol (2 ml) to give the *title compound* **6e** (159 mg, 81%) as a brown solid. m.p. 177-180 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.14 (3H, dt, J = 7.6, 2.4 Hz, CH_2CH_3), 1.80-1.88 (4H, m, H-6 and H-7), 2.61 (2H, dq, J = 7.6, 2.0 Hz, CH_2CH_3), 2.88-2.89 (2H, m, H-5), 2.94-2.95 (2H, m, H-8), 7.16 (2H, br s, NH_2), 7.19-7.28 (4H, m, H-3', H-4', H-5' and H-6'), 8.15 (1H, s, H-4), 9.02 (1H, br s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 14.0 (CH_2CH_3), 22.3 and 22.5 (C-6 and C-7), 24.0 (CH_2CH_3), 28.3 (C-5), 32.5 (C-8), 96.1 (C-2), 124.6 (C-3a), 125.9 (C-6'), 126.2 and 127.7 (C-4' and C-5'), 128.2 (C-4a), 128.3 (C-3'), 130.7 (C-4), 135.8 (C-1'), 139.9 (C-2'), 146.2 (C-3), 155.9 (C-9a), 158.8 (C-8a), 164.4 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3419, 3354, 2957, 1677, 1583, 1528, 1436, 1262, 1145; *m/z* (ESI$^+$): 352 (MH^+, 100%), 374 (MNa^+, 76%); HRMS (ESI$^+$) found (MH^+): 352.1470, $C_{20}H_{22}N_3OS$ requires 352.1478. Found (MNa^+): 374.1288, $C_{20}H_{21}N_3NaOS$ requires 374.1298.

4.1.2.16 3-Amino-N-(2'-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6f.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-(trifluoromethyl)phenyl)acetamide **12f** (138 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6f** (124 mg, 65%) as a brown solid. m.p. 188-190 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.78-1.91 (4H, m, H-6 and H-7), 2.88 (2H, t, *J* = 6.4 Hz, H-5), 2.95 (2H, t, *J* = 6.4 Hz, H-8), 7.21 (2H, s, NH_2), 7.49 (1H, t, *J* = 7.6 Hz, H-4'), 7.58 (1H, d, *J* = 7.6 Hz, H-6'), 7.71 (1H, t, *J* = 8.0 Hz, H-5'), 7.76 (1H, d, *J* = 8.0 Hz, H-3'), 8.18 (1H, s, H-4), 9.12 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.2 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.4 (C-2), 123.7 (q, $^{1}J_{F/C}$ 271.9 Hz, CF_3), 124.4 (C-3a), 125.7 (q, $^{2}J_{F/C}$ 28.9 Hz, C-2'), 126.4 (q, $^{3}J_{F/C}$ 4.8 Hz, C-3'), 126.8 (C-4'), 128.3 (C-4a), 130.6 (C-6'), 130.9 (C-4), 132.9 (C-5'), 135.9 (C-1'), 146.8 (C-3), 155.9 (C-9a), 159.1 (C-8a), 164.6 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3435, 3305, 2931, 1653, 1588, 1525, 1453, 1290, 1167, 1106; *m/z* (ESI^{+}): 392 (MH^{+}, 100%); HRMS (ESI^{+}) found (MH^{+}): 392.1052, $C_{19}H_{17}F_3N_3OS$ requires 392.1039.

4.1.2.17 3-Amino-N-(3'-fluorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6g.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-fluorophenyl)acetamide **12g** (114 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6g** (110 mg, 66%) as a green solid. m.p. 244-247 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.78-1.90 (4H, m, H-6 and H-7), 2.87 (2H, t, *J* = 6.4 Hz, H-5), 2.95 (2H, t, *J* = 6.4 Hz, H-8), 6.87 (1H, dt, *J* = 8.4, 2.4 Hz, H-4'), 7.30-7.36 (3H, m, H-5' and NH_2), 7.52 (1H, d, *J* = 8.8 Hz, H-6'), 7.68 (1H, dt, *J* = 12.0, 2.0 Hz, H-2'), 8.19 (1H, s, H-4), 9.51 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.3 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.2 (C-2), 107.4 (d, $^{2}J_{F/C}$ 26.0 Hz C-2'), 109.6 (d, $^{2}J_{F/C}$ 20.9 Hz C-4'), 116.4 (d, $^{4}J_{F/C}$ 1.9 Hz C-6'), 124.3 (C-3a), 128.4 (C-4a), 129.9 (d, $^{3}J_{F/C}$ 9.4 Hz C-5'), 130.9 (C-4), 141.0 (d, $^{3}J_{F/C}$ 11.0 Hz C-1'), 147.4 (C-3), 156.0 (C-9a), 160.1 (d, $^{1}J_{F/C}$ 143.1 Hz C-3'), 163.2 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3442, 3331, 2957, 1599, 1525, 1484, 1433, 1312, 1246, 1166; *m/z* (ESI^{+}): 342 (MH^{+}, 100%); HRMS (ESI^{+}) found (MH^{+}): 342.1073, $C_{18}H_{17}FN_3OS$ requires 342.1071.

4.1.2.18 3-Amino-N-(3'-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6h.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-chlorophenyl)acetamide **12h** (122 mg, 0.49 mmol), carbonitrile **10b** (93 mg,

0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6h** (90 mg, 51%) as a dark brown solid. m.p. > 250 ºC. ^{1}H NMR (300 MHz, d_6-DMSO) 1.80-1.88 (4H, m, H-6 and H-7), 2.87 (2H, t, *J* = 6.3 Hz, H-5), 2.95 (2H, t, *J* = 6.0 Hz, H-8), 7.10 (1H, d, *J* = 7.8 Hz, H-4'), 7.30-7.37 (3H, m, H-5' and NH_2), 7.64 (1H, d, *J* = 8.4 Hz, H-6'), 7.91 (1H, t, *J* = 2.1 Hz, H-2'), 8.20 (1H, s, H-4), 9.49 (1H, br s, NH); ^{13}C NMR (75 MHz, d_6-DMSO) 22.2 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.1 (C-2), 119.1 (C-6'), 120.2 (C-2'), 122.8 (C-4'), 124.3 (C-3a), 128.3 (C-8a), 130.0 (C-5'), 130.9 (C-4), 132.7 (C-3'), 140.7 (C-1'), 147.4 (C-3), 156.0 (C-9a), 159.3 (C-4a), 164.2 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3432, 3328, 2957, 1607, 1584, 1518, 1417, 1251, 1166; *m/z* (ESI$^+$): 360 (^{37}ClMH$^+$, 39%), 358 (^{35}ClMH$^+$, 100%); HRMS (ESI$^+$) found (^{37}ClMH$^+$): 360.0756, $C_{18}H_{17}{}^{37}ClN_3OS$ requires 360.0750. Found (^{35}ClMH$^+$): 358.0786, $C_{18}H_{17}{}^{35}ClN_3OS$ requires 358.0775.

4.1.2.19 3-Amino-N-(3'-bromophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6i.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-bromophenyl)acetamide **12i** (143 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6i** (0.114 mg, 58%) as an orange solid. m.p. 244-245 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.79-1.89 (4H, m, H-6 and H-7), 2.87 (2H, t, *J* = 6.4 Hz, H-5), 2.95 (2H, t, *J* = 6.0 Hz, H-8), 7.24 (1H, dt, *J* = 8.0, 1.6 Hz, H-4'), 7.28 (1H, t, *J* = 8.0 Hz, H-5'), 7.38 (2H, br s, NH_2), 7.69 (1H, dt, *J* = 8.0, 1.6 Hz, H-6'), 8.05 (1H, t, *J* = 1.6 Hz, H-2'), 8.20 (1H, s, H-4), 9.48 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.3 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.1 (C-2), 119.5 (C-6'), 121.2 (C-3'), 123.0 (C-2'), 124.3 (C-3a), 125.7 (C-4'), 128.4 (C-4a), 130.3 (C-5'), 130.9 (C-4), 140.8 (C-1'), 147.5 (C-3), 156.0 (C-9a), 159.4 (C-8a), 164.2 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3432, 3328, 2923, 1606, 1581, 1515, 1471, 1291, 1163; *m/z* (ESI$^+$): 404 (^{81}BrMH$^+$, 100%), 402 (^{79}BrMH$^+$, 96%); HRMS (ESI$^+$) found (^{81}BrMH$^+$): 404.0244, $C_{18}H_{17}{}^{81}BrN_3OS$ requires 404.0251. Found (^{79}BrMH$^+$): 402.0264, $C_{18}H_{17}{}^{79}BrN_3OS$ requires 402.0270.

4.1.2.20 3-Amino-N-(3'-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6j.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-(trifluoromethyl)phenyl)acetamide **12j** (138 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6j** (43 mg, 22%) as a yellow solid. m.p. 193-194 ºC. ^{1}H

NMR (300 MHz, $(CD_3)_2CO$) 1.79-1.95 (4H, m, H-6 and H-7), 2.87-2.98 (4H, m, H-5 and H-8), 7.09 (2H, br s, NH_2), 7.40 (1H, dt, *J* = 7.7, 0.7 Hz, H-4'), 7.54 (1H, t, *J* = 7.9 Hz, H-5'), 7.99 (1H, dt, *J* = 8.8, 0.6 Hz, H-2'), 8.04 (1H, s, H-4), 8.27 (1H, s, H-6'), 8.87 (1H, br s, NH); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) 23.5 and 23.6 (C-6 and C-7), 29.5 (C-5), 33.7 (C-8), 97.3 (C-2), 117.8 (q, $^3J_{F/C}$ 4.0 Hz, C-2'), 120.5 (q, $^3J_{F/C}$ 3.9 Hz, C-4'), 124.7 (q, $^5J_{F/C}$ 1.0 Hz, C-6'), 125.3 (q, $^1J_{F/C}$ 270.0 Hz, CF_3), 125.4 (C-3a), 129.6 (C-4a), 130.3 (C-5'), 131.1 (C-4), 131.2 (q, $^2J_{F/C}$ 31.6 Hz, C-3'), 141.0 (C-1'), 148.5 (C-3), 157.4 (C-9a), 160.6 (C-8a), 165.4 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3441, 3326, 2940, 1591, 1541, 1482, 1439, 1331, 1250, 1165; *m/z* (ESI$^+$): 392 (MH^+, 100%), 381 (22%); HRMS (ESI$^+$) found (MH^+): 392.1033, $C_{19}H_{17}F_3N_3OS$ requires 392.1039.

4.1.2.21 3-Amino-N-(3'-nitrophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6k.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-nitrophenyl)acetamide **12l** (127 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6k** (157 mg, 87%) as a brown solid. m.p. > 250 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.81-1.91 (4H, m, H-6 and H-7), 2.90 (2H, t, *J* = 6.4 Hz, H-5), 2.98 (2H, t, *J* = 6.4 Hz, H-8), 7.48 (2H, br s, NH_2), 7.63 (1H, t, *J* = 8.4 Hz, H-5'), 7.93 (1H, dd, *J* = 7.6, 1.6 Hz, H-4'), 8.16 (1H, dd, *J* = 8.0, 1.2 Hz, H-6'), 8.25 (1H, s, H-4), 8.80 (1H, t, *J* = 2.0 Hz, H-2'), 9.83 (1H, br s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.2 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 94.7 (C-2), 114.7 (C-2'), 117.5 (C-4'), 124.2 (C-3a), 126.6 (C-6'), 128.4 (C-4a), 129.7 (C-5'), 131.0 (C-4), 140.5 (C-1'), 147.8 and 147.9 (C-3 and C-3'), 156.1 (C-9a), 159.5 (C-8a), 164.4 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3388, 2948, 1649, 1584, 1496, 1427, 1523, 1344, 1250, 1062; *m/z* (ESI$^+$): 391 (MNa^+, 64%), 381 (58%), 369 (MH^+, 100%); HRMS (ESI$^+$) found (MNa^+): 391.0825, $C_{18}H_{16}N_4NaO_3S$ requires 391.0835. Found (MH^+): 369.1007, $C_{18}H_{17}N_4O_3S$ requires 369.1016.

4.1.2.22 3-Amino-N-(4'-methoxyphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6l.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(4'-methoxyphenyl)acetamide **12m** (120 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6l** (10 mg, 6%) as a yellow solid. m.p. > 250 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.79-1.91 (4H, H-6 and H-7), 2.87 (2H, t, *J* = 6.3 Hz, H-5), 2.95 (2H, t, *J* = 6.3 Hz, H-8), 3.74 (3H, s, CH_3), 6.89 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 7.23 (2H, br s, NH_2),

7.56 (2H, d, *J* = 9.0 Hz, H-2' and H-6'), 8.16 (1H, s, H-4), 9.23 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.3 and 22.5 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 55.1 (CH_3), 95.6 (C-2), 113.5 (C-3' and C-5'), 122.9 (C-2' and C-6'), 124.5 (C-3a), 128.2 (C-4a), 130.7 (C-4), 131.9 (C-1'), 146.4 (C-3), 155.4 (C-4'), 155.9 (C-9a), 159.0 (C-8a), 163.9 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3421, 3316, 2945, 1597, 1509, 1497, 1390, 1315, 1235, 1041; *m/z* (ESI$^+$): 376 (MNa^+, 100%), 354 (MH^+, 21%); HRMS (ESI$^+$) found (MNa^+): 376.1083, $C_{19}H_{19}N_3NaO_2S$ requires 376.1090. Found (MH^+): 354.1258, $C_{19}H_{20}N_3O_2S$ requires 354.1271.

4.1.2.23 3-Amino-N-(3'-chloro-2'-methylphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6m.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-chloro-2'-methylphenyl)acetamide **12n** (129 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6m** (34 mg, 19%) as a yellow solid. m.p. > 250 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.79-1.89 (4H, m, H-6 and H-7), 2.23 (3H, s, CH_3), 2.88 (2H, t, *J* = 6.4 Hz, H-5), 2.95 (2H, t, *J* = 6.4 Hz, H-8), 7.20-7.28 (4H, m, H-4' or H-6', H-5' and NH_2), 7.34 (1H, d, *J* = 8.0 Hz, H-4' or H-6'), 8.17 (1H, s, H-4), 9.30 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 15.5 (CH_3), 22.3 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.5 (C-2), 124.4 (C-3a), 126.2 and 126.7 (C-4' and C-6'), 126.5 (C-5'), 128.3 (C-4a), 130.8 (C-4), 132.5 (C-2'), 133.6 (C-3'), 138.2 (C-1'), 146.7 (C-3), 156.0 (C-9a), 159.1 (C-8a), 164.2 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3421, 3315, 2931, 1590, 1427, 1294, 1012; *m/z* (ESI$^+$): 374 ($^{37}ClMH^+$, 37%), 372 ($^{35}ClMH^+$, 100%); HRMS (ESI$^+$) found ($^{37}ClMH^+$): 374.0893, $C_{19}H_{19}{}^{37}ClN_3OS$ requires 374.0907. Found ($^{35}ClMH^+$): 372.0923, $C_{19}H_{19}{}^{35}ClN_3OS$ requires 372.0932.

4.1.2.24 3-Amino-N-(3'-bromo-2'-methylphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6n.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-bromo-2'-methylphenyl)acetamide **12o** (171 mg, 0.56 mmol), carbonitrile **10b** (100 mg, 0.56 mmol) and anhydrous sodium carbonate (63 mg, 0.59 mmol) in absolute ethanol (2 ml) to give the *title compound* **6n** (176 mg, 76%) as a brown solid. m.p. > 230 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.79-1.89 (4H, m, H-6 and H-7), 2.26 (3H, s, CH_3), 2.87 (2H, t, *J* = 6.4 Hz, H-5), 2.95 (2H, t, *J* = 6.4 Hz, H-8), 7.15 (1H, t, *J* = 8.0 Hz, H-5'), 7.21 (2H, br s, NH_2), 7.30 (1H, d, *J* = 8.0 Hz, H-4'), 7.50 (1H, d, *J* = 8.0 Hz, H-6'), 8.17 (1H, s, H-4), 9.33 (1H, br s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 18.5 (CH_3), 22.3 and 22.4 (C-6 and

C-7), 28.3 (C-5), 32.5 (C-8), 95.5 (C-2), 124.4 (C-3'), 124.5 (C-3a), 126.9 (C-4'), 127.2 (C-5'), 128.2 (C-4a), 129.8 (C-6'), 130.8 (C-4), 134.2 (C-2'), 138.1 (C-1'), 146.7 (C-3), 156.0 (C-9a), 159.0 (C-8a), 164.2 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3314, 3207, 2933, 1614, 1588, 1504, 1428, 1296, 1162; *m/z* (ESI$^+$): 440 (^{81}BrMNa$^+$, 38%), 438 (^{79}BrMNa$^+$, 38%), 418 (^{81}BrMH$^+$, 26%), 416 (^{79}BrMH$^+$, 26%); HRMS (ESI$^+$) found (^{81}BrMNa$^+$): 440.0208, $C_{19}H_{18}{}^{81}BrN_3NaOS$ requires 440.0227. Found (^{79}BrMNa$^+$): 438.0232, $C_{19}H_{18}{}^{79}BrN_3NaOS$ requires 438.0246. Found (^{81}BrMH$^+$): 418.0391, $C_{19}H_{19}{}^{81}BrN_3OS$ requires 418.0407. Found (^{79}BrMH$^+$): 416.0413, $C_{19}H_{19}{}^{79}BrN_3OS$ requires 416.0427.

4.1.2.25 3-Amino-N-(2',3'-dimethylphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6o.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2',3'-dimethylphenyl)acetamide **12p** (119 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6o** (132 mg, 77%) as a green solid. m.p. 249-250 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.79-1.89 (4H, m, H-6 and H-7), 2.09 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.88 (2H, t, J = 6.0 Hz, H-5), 2.95 (2H, t, J = 6.0 Hz, H-8), 7.05-7.11 (3H, m, H-4', H-5' and H-6'), 7.15 (2H, s, NH_2), 8.15 (1H, s, H-4), 9.09 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 14.3 (CH_3), 20.1 (CH_3), 22.3 and 22.5 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 96.1 (C-2), 124.5 (C-3a), 125.0 and 125.1 (C-4' and C-5'), 127.3 (C-6'), 128.1 (C-4a), 130.7 (C-4), 133.0 (C-2'), 136.3 (C-1'), 136.8 (C-3'), 146.2 (C-3), 156.0 (C-9a), 158.8 (C-8a), 164.2 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3429, 3322, 2945, 1601, 1519, 1493, 1471, 1267, 1165; *m/z* (ESI$^+$): 352 (MH$^+$, 100%); HRMS (ESI$^+$) found (MH$^+$): 352.1492, $C_{20}H_{22}N_3OS$ requires 352.1478.

4.1.2.26 3-Amino-N-(2',6'-diethylphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6p.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-ethylphenyl)acetamide **12q** (135 mg, 0.56 mmol), carbonitrile **10b** (100 mg, 0.56 mmol) and anhydrous sodium carbonate (63 mg, 0.59 mmol) in absolute ethanol (2 ml) to give the *title compound* **6p** (159 mg, 81%) as a brown solid. m.p. 111-114 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.13 (6H, t, J = 7.6 Hz, CH_2CH_3), 1.82-1.90 (4H, m, H-6 and H-7), 2.57 (4H, q, J = 7.6 Hz, CH_2CH_3), 2.90-2.91 (2H, m, H-5), 2.95-2.97 (2H, m, H-8), 7.13-7.15 (4H, m, H-3', H-5' and NH_2), 7.21-7.24 (1H, m, H-4'), 8.16 (1H, s, H-4), 8.90 (1H, br s, NH); ^{13}C NMR (125 MHz, d_6-DMSO) 14.4 (CH_2CH_3), 22.3 and 22.5 (C-6 and C-7), 24.5 (CH_2CH_3), 28.4 (C-5), 32.5 (C-8), 96.0 (C-2), 124.7 (C-3a), 125.8 (C-3' and C-5'), 127.2

(C-4'), 128.2 (C-4a), 130.7 (C-4), 134.4 (C-1'), 142.0 (C-2' and C-6'), 146.0 (C-3), 155.9 (C-9a), 158.8 (C-8a), 164.6 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3411, 3298, 2936, 1682, 1598, 1504, 1448, 1253, 1185; *m/z* (ESI$^+$): 402 (MNa$^+$, 100%), 380 (MH$^+$, 11%); HRMS (ESI$^+$) found (MNa$^+$): 402.1598, $C_{22}H_{25}N_3NaOS$ requires 402.1611. Found (MH$^+$): 380.1772, $C_{22}H_{26}N_3OS$ requires 380.1791.

4.1.2.27 3-Amino-N-(2'-ethyl-6'-methylphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6q.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-ethyl-6'-methylphenyl)acetamide **12r** (125 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6q** (118 mg, 66%) as a tan solid. m.p. 150-152 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.11 (3H, t, *J* = 7.6 Hz, $CH_2C\mathit{H}_3$), 1.80-1.88 (4H, m, H-6 and H-7), 2.18 (3H, s, CH_3), 2.55 (2H, q, *J* = 7.6 Hz, $C\mathit{H}_2CH_3$), 2.88-2.95 (4H, m, H-5 and H-8), 7.07-7.14 (5H, m, H-3', H-4', H-5' and NH_2), 8.14 (1H, s, H-4), 8.89 (1H, br s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 14.4 ($CH_2\mathit{C}H_3$), 18.2 (CH_3), 22.3 and 22.5 (C-6 and C-7), 24.4 ($\mathit{C}H_2CH_3$), 28.3 (C-5), 32.5 (C-8), 95.9 (C-2), 124.6 (C-3a), 125.8 (C-3'), 126.8 (C-4'), 127.5 (C-5'), 128.1 (C-4a), 130.6 (C-4), 134.9 (C-1'), 136.3 (C-6'), 141.8 (C-2'), 146.0 (C-3), 155.9 (C-9a), 158.7 (C-8a), 164.3 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3372, 3292, 2936, 1598, 1489, 1394, 1266, 1077; *m/z* (ESI$^+$): 388 (MNa$^+$, 69%), 366 (MH$^+$, 100%); HRMS (ESI$^+$) found (MNa$^+$): 388.1446, $C_{21}H_{23}N_3NaOS$ requires 388.1454. Found (MH$^+$): 366.1628, $C_{21}H_{24}N_3OS$ requires 366.1635.

4.1.2.28 3-Amino-N-(2',6'-dichlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6r.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2',6'-dichlorophenyl)acetamide **12s** (139 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6r** (161 mg, 84%) as a brown solid. m.p. > 250 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.78-1.91 (4H, m, H-6 and H-7), 2.88 (1H, t, *J* = 6.0 Hz, H-5), 2.96 (1H, t, *J* = 6.4 Hz, H-8), 7.23 (2H, br s, NH_2), 7.37 (1H, t, *J* = 8.0 Hz, H-4'), 7.56 (2H, d, *J* = 8.0 Hz, H-3' and H-5'), 8.17 (1H, s, H-4), 9.40 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.3 and 22.4 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 94.8 (C-2), 124.3 (C-3a), 128.3 (C-4a), 128.4 (C-3' and C-5'), 129.2 (C-4'), 130.9 (C-4), 133.5 (C-1'), 134.7 (C-2' and C-6'), 147.0 (C-3), 156.1 (C-9a), 159.2 (C-8a), 163.90 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3398, 3308, 2940, 1600, 1499, 1473, 1243, 1197; *m/z* (ESI$^+$): 396 ($^{37,37}Cl_2MH^+$, 13%), 394 ($^{35,37}Cl_2MH^+$, 71%), 392

($^{35,35}Cl_2MH^+$, 100%); HRMS (ESI^+) found ($^{37,37}Cl_2MH^+$): 396.0322, $C_{18}H_{16}{}^{37,37}Cl_2N_3OS$ requires 396.0333. Found ($^{35,37}Cl_2MH^+$) 394.0356, $C_{18}H_{16}{}^{35,37}Cl_2N_3OS$ requires 394.0358. Found ($^{35,35}Cl_2MH^+$): 392.0383, $C_{18}H_{16}{}^{35,35}Cl_2N_3OS$ requires 392.0386.

4.1.2.29 3-Amino-N-(2',4',6'-trimethylphenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6s.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-mesitylacetamide **12t** (125 mg, 0.49 mmol), carbonitrile **10b** (93 mg, 0.49 mmol) and anhydrous sodium carbonate (55 mg, 0.52 mmol) in absolute ethanol (2 ml) to give the *title compound* **6s** (108 mg, 60%) as a light tan solid. m.p. > 250 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.79-1.88 (4H, m, H-6 and H-7), 2.13 (6H, s, 2'-CH_3 and 6'-CH_3), 2.25 (3H, s, 4'-CH_3), 2.88 (2H, t, J = 6.0 Hz, H-5), 2.95 (2H, t, J = 5.6 Hz, H-8), 6.90 (2H, s, H-3' and H-5'), 7.11 (2H, s, NH_2), 8.13 (1H, s, H-4), 8.81 (1H, s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 18.1 (2'-CH_3 and 6'-CH_3), 20.5 (4'-CH_3), 22.3 and 22.5 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 96.0 (C-2), 124.8 (C-3a), 128.2 (C-3', C-5' and C-4a), 130.6 (C-4), 132.8 (C-1'), 135.4 (C-4'), 135.6 (C-2' and C-6'), 145.9 (C-3), 155.9 (C-9a), 158.7 (C-8a), 164.0 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3371, 3314, 2937, 1599, 1505, 1489, 1247, 1162; *m/z* (ESI^+): 388 (MNa^+, 62%), 366 (MH^+, 100%); HRMS (ESI^+) found (MNa^+): 388.1441, $C_{21}H_{23}N_3NaOS$ requires 388.1454. Found (MH^+): 366.1623, $C_{21}H_{24}N_3OS$ requires 366.1635.

4.1.2.30 3-Amino-N-(naphthalen-1'-yl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide ***6t.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(naphthalen-1'-yl)acetamide **12u** (139 mg, 0.56 mmol), carbonitrile **10b** (100 mg, 0.56 mmol) and anhydrous sodium carbonate (63 mg, 0.59 mmol) in absolute ethanol (2 ml) to give the *title compound* **6t** (162 mg, 81%) as a dark green solid. m.p. 206-207 ºC. ^{1}H NMR (400 MHz, d_6-DMSO) 1.83-1.92 (4H, m, H-6 and H-7), 2.89 (2H, t, J = 6.0 Hz, H-5), 2.97 (2H, t, J = 6.4 Hz, H-8), 7.21 (2H, br s, NH_2), 7.52-7.55 (4H, m, H-5', H-6', H-8' and H-9'), 7.83-7.85 (1H, m, H-10'), 7.91-7.97 (2H, m, H-3' and H-4'), 8.18 (1H, s, H-4), 9.62 (1H, br s, NH); ^{13}C NMR (100 MHz, d_6-DMSO) 22.3 and 22.5 (C-6 and C-7), 28.3 (C-5), 32.5 (C-8), 95.9 (C-2), 124.3 (C-3a), 124.5 (C-8'), 123.5, 125.5, 125.8, 125.9, 126.2 and 128.0 (C-3', C-4', C-5', C-6', C-9' and C-10'), 128.2 (C-1'), 129.7 (C-4a), 130.8 (C-4), 133.7 (C-7'), 134.0 (C-2'), 146.6 (C-3), 156.0 (C-9a), 158.9 (C-8a), 164.9 (C=O); IR: υ_{max}(ATR)/cm^{-1}: 3437, 3323, 2947, 1668, 1603, 1501, 1433, 1254, 1098; *m/z* (ESI^+): 374 (MH^+, 25%), 144 (100%); HRMS (ESI^+) found (MH^+): 374.1334, $C_{22}H_{20}N_3OS$ requires 374.1322.

4.1.2.31 3-Amino-N-phenyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7a.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-phenylacetamide **12a** (0.07 g, 0.34 mmol), carbonitrile **10c** (0.07 g, 0.34 mmol) and anhydrous sodium carbonate (0.04 g, 0.38 mmol) in absolute ethanol (1.8 mL) to give the *title product* **7a** (0.11 g, 91%) as a brown solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.91 (2H, m, H-5), 3.08-3.11 (2H, m, H-9), 7.08 (1H, tt, *J* = 7.3, 1.0 Hz, H-4'), 7.29 (2H, s, NH_2), 7.34 (2H, td, *J* = 8.0, 2.0 Hz, H-3' and H-5'), 7.71 (2H, dd, *J* = 8.5, 1.0 Hz, H-2' and H-6'), 8.21 (1H, s, H-4), 9.36 (1H, s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.5 (C-5), 38.8 (C-9), 96.1 (C-2), 121.1 (C-2' and C-6'), 123.3 (C-4'), 124.3 (C-3), 128.4 (C-3' and C-5'), 130.4 (C-4), 134.1 (C-4a), 139.0 (C-1'), 147.0 (C-3a), 155.45 (C-9a), 164.04 (C=O), 164.76 (C-10a); IR: υ_{max} (film)/cm^{-1}: 3382, 3287, 3033, 2916, 2848, 1647, 1596, 1531, 1494, 1435, 1320; *m/z* (ESI$^+$): 360 (MNa^+, 36%), 338 (MH^+, 100%); HRMS (ESI$^+$) found (MH^+): 338.1311, $C_{19}H_{20}N_3OS$ requires 338.1322. The spectroscopic data was consistent with literature values [17].

4.1.2.32 3-Amino-N-(2'-fluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7b.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-fluorophenyl)acetamide **12b** (0.11 g, 0.49 mmol), carbonitrile **10c** (0.10 g, 0.49 mmol) and anhydrous sodium carbonate (0.06 g, 0.54 mmol) in absolute ethanol (2.5 mL) to give the *title product* **7b** (0.14 g, 82%) as a brown solid. m.p. 228-230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.91 (2H, m, H-5), 3.09-3.11 (2H, m, H-9), 7.18-7.30 (5H, m, NH_2, H-3', H-5' and H-4'), 7.54 (1H, t, *J* = 7.7 Hz, H-6'), 8.21 (1H, s, H-4), 9.24 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.4 (C-5), 38.8 (C-9), 95.9 (C-2), 115.6 (d, $^{2}J_{F/C}$ 20.1 Hz, C-3'), 124.1 (d, $^{4}J_{F/C}$ 3.4 Hz, C-5'), 124.3 (C-3a), 125.8 (d, $^{2}J_{F/C}$ 12.0 Hz, C-1'), 126.7 (d, $^{3}J_{F/C}$ 7.2 Hz, C-4'), 127.5 (C-6'), 130.5 (C-4), 134.1 (C-4a), 146.9 (C-3), 155.5 (C-10a), 158.5 (d, $^{1}J_{F/C}$ 210.1 Hz, C-2'), 163.9 (C=O), 164.8 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3423, 3286, 2930, 2853, 1644, 1518, 1445, 1322, 1245; *m/z* (ESI$^+$): 378 (MNa^+, 30%), 356 (MH^+, 100%); HRMS (ESI$^+$) found (MH^+): 356.1224, $C_{19}H_{19}FN_3OS$ requires 356.1227.

4.1.2.33 3-Amino-N-(2'-chlorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7c.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-chlorophenyl)acetamide **12c** (0.08 g, 0.34 mmol), carbonitrile **10c** (0.07

g, 0.34 mmol) and anhydrous sodium carbonate (0.04 g, 0.38 mmol) in absolute ethanol (2 mL) to give the *title product* **7c** (0.09 g, 86%) as a dark brown solid. m.p. 228-230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.91 (2H, m, H-5), 3.09-3.11 (2H, m, H-9), 7.23-7.29 (3H, m, NH_2 and H-4'), 7.38 (1H, td, *J* = 7.7, 1.5 Hz, H-5'), 7.55 (1H, dd, *J* = 8.0, 2.5 Hz, H-3'), 7.68 (1H, dd, *J* = 8.0, 2.0 Hz, H-6'), 8.22 (1H, s, H-4), 9.09 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.4 (C-5), 38.7 (C-9), 96.1 (C-2), 124.4 (C-3a), 126.8 (C-5'), 127.4 (C-4'), 127.5 (C-3'), 128.7 (C-6'), 129.4 (C-2'), 130.5 (C-4), 134.2 (C-4a), 135.2 (C-1'), 146.9 (C-3), 155.4 (C-10a), 163.8 (C=O), 164.9 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3423, 3392, 3302, 2921, 1651, 1589, 1522, 1434, 1307; *m/z* (ESI$^+$): 396 (^{37}ClMNa$^+$, 12%), 394 (^{35}ClMNa$^+$, 33%), 374 (^{37}ClMH$^+$, 37%), 372 (^{35}ClMH$^+$, 100%); HRMS (ESI$^+$) found (^{37}ClMNa$^+$): 374.0896, $C_{19}H_{19}{}^{37}ClN_3OS$ requires 374.0907. Found (^{35}ClMH$^+$): 372.0924, $C_{19}H_{19}{}^{35}ClN_3OS$ requires 372.0932.

4.1.2.34 3-Amino-N-(2'-methylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7d.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-methylphenyl)acetamide **12d** (0.08 g, 0.34 mmol), carbonitrile **10c** (0.07 g, 0.34 mmol) and anhydrous sodium carbonate (0.04 g, 0.38 mmol) in absolute ethanol (2 mL) to give the *title product* **7d** (0.09 g, 84%) as a brown solid. m.p. 195-197 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.24 (3H, s, CH_3), 2.88-2.91 (2H, m, H-5), 3.08-3.11 (2H, m, H-9), 7.14-7.23 (4H, m, NH_2, H-4' and H-5'), 7.27 (1H, dd, *J* = 7.5, 1.5 Hz, H-6'), 7.33 (1H, dd, *J* = 7.5, 1.5 Hz, H-3'), 8.19 (1H, s, H-4), 9.05 (1H, s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 17.9 (CH_3), 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.4 (C-5), 38.5 (C-9), 96.6 (C-2), 124.4 (C-3a), 125.87 (C-4'), 125.93 (C-5'), 126.8 (C-3'), 130.2 (C-4), 130.3 (C-6'), 133.9 (C-2'), 134.2 (C-4a), 136.3 (C-1'), 146.3 (C-3), 155.3 (C-10a), 164.1 (C=O), 164.7 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3423, 3392, 3306, 2922, 2851, 1650, 1587, 1521, 1434, 1307, 1195; *m/z* (ESI$^+$): 374 (MNa$^+$, 70%), 352 (MH$^+$, 100%); HRMS (ESI$^+$) found (MH$^+$): 352.1473, $C_{20}H_{22}N_3OS$ requires 352.1478.

4.1.2.35 3-Amino-N-(2'-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7e.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2'-(fluoromethyl)phenyl)acetamide **12f** (0.10 g, 0.34 mmol), carbonitrile **10c** (0.07 g, 0.34 mmol) and anhydrous sodium carbonate (0.04 g, 0.38 mmol) in absolute ethanol (2 mL) to give the *title product* **7e** (0.12 g, 86%) as a

dark yellow solid. m.p. 210-212 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.91 (2H, m, H-5), 3.09-3.11 (2H, m, H-9), 7.20 (2H, s, NH_2), 7.51 (1H, t, *J* = 7.7 Hz, H-4'), 7.60 (1H, d, *J* = 7.7 Hz, H-6'), 7.72 (1H, t, *J* = 7.7 Hz, H-5'), 7.78 (1H, d, *J* = 7.7 Hz, H-3'), 8.20 (1H, s, H-4), 9.09 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.3 (C-8), 28.0 (C-6), 31.6 (C-7), 34.4 (C-5), 38.7 (C-9), 95.8 (C-2), 124.3 (C-3a), 125.8 (q, $^{2}J_{F/C}$ 27.0 Hz, C-2'), 126.1 (q, $^{1}J_{F/C}$ 284.8 Hz, CF_3), 126.4 (q, $^{3}J_{F/C}$ 4.2 Hz, C-3'), 126.8 (C-4'), 130.5 (C-4), 130.6 (C-6'), 132.9 (C-5'), 134.1 (C-4a), 135.9 (C-1'), 146.9 (C-3), 155.5 (C-10a), 164.6 (C=O), 164.8 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3432, 3316, 2930, 2847, 1603, 1320, 1290, 1165, 1121; *m/z* (ESI^{+}): 428 (MNa^{+}, 42%), 406 (MH^{+}, 100%); HRMS (ESI^{+}) found (MNa^{+}): 428.1001, $C_{20}H_{18}F_3N_3NaOS$ requires 428.1015.

4.1.2.36 3-Amino-N-(3'-fluorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7f.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-fluorophenyl)acetamide **12g** (0.08 g, 0.34 mmol), carbonitrile **10c** (0.07 g, 0.34 mmol) and anhydrous sodium carbonate (0.04 g, 0.38 mmol) in absolute ethanol (2 mL) to give the *title product* **7f** (0.10 g, 85%) as a brown solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.91 (2H, m, H-5), 3.09-3.11 (2H, m, H-9), 6.89 (1H, td, *J* = 8.5, 2.0 Hz, H-4'), 7.32-7.38 (3H, m, NH_2 and H-5'), 7.55 (1H, dd, *J* = 8.0, 2.0 Hz, H-6'), 7.70 (1H, dt, *J* = 12.0, 2.3 Hz, H-2'), 8.23 (1H, s, H-4), 9.54 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.5 (C-5), 38.5 (C-9), 96.6 (C-2), 107.3 (d, $^{2}J_{F/C}$ 26.1 Hz, C-2'), 109.4 (d, $^{2}J_{F/C}$ 20.9 Hz, C-4'), 116.4 (C-6'), 124.2 (C-3a), 129.9 (d, $^{3}J_{F/C}$ 9.6 Hz, C-5'), 130.5 (C-4), 134.2 (C-4a), 141.0 (d, $^{3}J_{F/C}$ 11.5 Hz, C-1'), 147.5 (C-3), 155.5 (C-10a), 163.8 (d, $^{1}J_{F/C}$ 140.2 Hz, C-3'), 164.2 (C=O), 165.0 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3385, 3292, 2914, 2848, 1650, 1597, 1531, 1435, 1280; *m/z* (ESI^{+}): 378 (MNa^{+}, 41%), 356 (MH^{+}, 100%); HRMS (ESI^{+}) found (MH^{+}): 356.1221, $C_{19}H_{19}FN_3OS$ requires 356.1227.

4.1.2.37 3-Amino-N-(3'-chlorophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7g.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-chlorophenyl)acetamide **12h** (0.05 g, 0.20 mmol), carbonitrile **10c** (0.04 g, 0.20 mmol) and anhydrous sodium carbonate (0.02 g, 0.22 mmol) in absolute ethanol (1.3 mL) to give the *title product* **7g** (0.10 g, 100%) as a brown solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.91 (2H, m, H-5), 3.08-3.11 (2H, m, H-9), 7.13 (1H, dt, *J* = 8.0, 1.3 Hz, H-4'), 7.35 (3H, m, H-5'

and NH_2), 7.67 (1H, dq, *J* = 8.5, 1.0 Hz, H-6'), 7.93-7.94 (1H, m, H-2'), 8.23 (1H, s, H-4), 9.52 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.5 (C-5), 38.6 (C-9), 95.5 (C-2), 119.1 (C-6'), 120.2 (C-2'), 122.8 (C-4'), 124.2 (C-3a), 130.0 (C-5'), 130.5 (C-4), 132.7 (C-1'), 134.2 (C-4a), 140.7 (C-3'), 147.6 (C-3), 155.6 (C-10a), 164.1 (C=O), 165.0 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3429, 3320, 3197, 2924, 2852, 1668, 1584, 1497, 1479, 1300; *m/z* (ESI$^+$): 396 (^{37}ClMNa$^+$, 11%), 394 (^{35}ClMNa$^+$, 30%), 374 (^{37}ClMH$^+$, 38%), 372 (^{35}ClMH$^+$, 100%); HRMS (ESI$^+$) found (^{37}ClMH$^+$): 374.0890, $C_{19}H_{19}{}^{37}ClN_3OS$ requires 374.0907. Found (^{35}ClMH$^+$): 372.0920, $C_{19}H_{19}{}^{35}ClN_3OS$ requires 372.0932.

4.1.2.38 3-Amino-N-(3'-bromophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7h.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-bromophenyl)acetamide **12i** (0.06 g, 0.20 mmol), carbonitrile **10c** (0.04 g, 0.20 mmol) and anhydrous sodium carbonate (0.02 g, 0.22 mmol) in absolute ethanol (1.5 mL) to give the *title product* **7h** (0.06 g, 79%) as a tan solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.90 (2H, m, H-5), 3.08-3.11 (2H, m, H-9), 7.24-7.31 (2H, m, H-4' and H-5'), 7.37 (2H, s, NH_2), 7.71 (1H, dt, *J* = 8.0, 1.5 Hz, H-6'), 8.08 (1H, t, *J* = 1.8 Hz, H-2'), 8.23 (1H, s, H-4), 9.51 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.5 (C-5), 38.6 (C-9), 95.5 (C-2), 119.5 (C-6'), 121.2 (C-3'), 123.0 (C-2'), 124.2 (C-3a), 125.7 (C-4'), 130.3 (C-4), 130.5 (C-5'), 134.2 (C-4a), 140.8 (C-1'), 147.6 (C-3), 155.6 (C-10a), 164.1 (C=O), 165.0 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3435, 3323, 3198, 2919, 2851, 1674, 1579, 1515, 1497, 1474, 1396, 1301; *m/z* (ESI$^+$): 467 (100%), 440 (^{81}BrMNa$^+$, 13%), 438 (^{79}BrMNa$^+$, 11%); HRMS (ESI$^+$) found (^{81}BrMNa$^+$): 440.0224, $C_{19}H_{18}{}^{81}BrN_3NaOS$ requires 440.0227. Found (^{79}BrMNa$^+$): 438.0243, $C_{19}H_{18}{}^{79}BrN_3NaOS$ requires 438.0246.

4.1.2.39 3-Amino-N-(3'-(trifluoromethyl)phenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7i.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-(trifluoromethyl)phenyl)acetamide **12j** (0.06 g, 0.20 mmol), carbonitrile **10c** (0.04 g, 0.20 mmol) and anhydrous sodium carbonate (0.02 g, 0.22 mmol) in absolute ethanol (1.3 mL) to give the *title product* **7i** (0.07 g, 90%) as a tan solid. m.p. 220-222 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.90 (2H, m, H-5), 3.09-3.11 (2H, m, H-9), 7.40-7.43 (3H, m, NH_2 and H-4'), 7.57 (1H, t, *J* = 8.0 Hz, H-5'), 8.01 (1H, d, *J* = 8.0 Hz, H-6'), 8.24 (2H, br s, H-2' and H-4), 9.68 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-

6), 31.6 (C-7), 34.5 (C-5), 38.8 (C-9), 95.3 (C-2), 116.8 (q, $^{3}J_{F/C}$ 3.7 Hz, C-2'), 119.4 (q, $^{3}J_{F/C}$ 3.9 Hz, C-4'), 124.1 (C-3a), 124.2 (d, $^{1}J_{F/C}$ 273.6 Hz, CF_3), 124.2 (q, $^{5}J_{F/C}$ 4.46 Hz, C-6'), 129.2 (d, $^{2}J_{F/C}$ 31.2 Hz, C-3'), 129.6 (C-5'), 130.6 (C-4), 134.2 (C-4a), 140.0 (C-1'), 147.8 (C-3), 155.6 (C-10a), 164.3 (C=O), 165.1 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3396, 3309, 2922, 2854, 1649, 1597, 1541, 1439, 1165, 1114; *m/z* (ESI^{+}): 428 (MNa^{+}, 20%), 406 (MH^{+}, 100%); HRMS (ESI^{+}) found (MH^{+}): 406.1190, $C_{20}H_{19}F_3N_3OS$ requires 406.1195.

4.1.2.40 3-Amino-N-(3'-methoxyphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7j.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-methoxyphenyl)acetamide **12k** (0.04 g, 0.15 mmol), carbonitrile **10c** (0.03 g, 0.15 mmol) and anhydrous sodium carbonate (0.02 g, 0.16 mmol) in absolute ethanol (1 mL) to give the *title product* **7j** (0.04g, 78%) as a dark brown solid. m.p. 220-222 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.90 (2H, m, H-5), 3.08-3.11 (2H, m, H-9), 3.76 (3H, s, OCH_3), 6.66 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, H-4'), 7.22 (1H, t, *J* = 8.0 Hz, H-5'), 7.30-7.35 (3H, m, NH_2 and H-6'), 7.41 (1H, t, *J* = 2.0 Hz, H-2'), 8.21 (1H, s, H-4), 9.32 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.5 (C-5), 38.4 (C-9), 55.0 (OCH_3), 96.0 (C-2), 106.5 (C-2'), 108.9 (C-4'), 113.1 (C-6'), 124.3 (C-3a), 129.1 (C-5'), 130.4 (C-4), 134.1 (C-4a), 140.3 (C-1'), 147.1 (C-3), 155.4 (C-10a), 159.3 (C-3'), 164.0 (C=O), 164.8 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3441, 3330, 3185, 3031, 2926, 1668, 1590, 1490, 1301, 1278; *m/z* (ESI^{+}): 390 (MNa^{+}, 63%), 368 (MH^{+}, 100%); HRMS (ESI^{+}) found (MH^{+}): 368.1420, $C_{20}H_{22}N_3O_2S$ requires 368.1427.

4.1.2.41 3-Amino-N-(3'-nitrophenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7k.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-nitrophenyl)acetamide **12l** (0.05 g, 0.20 mmol), carbonitrile **10c** (0.04 g, 0.20 mmol) and anhydrous sodium carbonate (0.02 g, 0.22 mmol) in absolute ethanol (1.3 mL) to give the *title product* **7k** (0.06 g, 75%) as a light brown solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.90 (2H, m, H-5), 3.09-3.11 (2H, m, H-9), 7.45 (2H, s, NH_2), 7.62 (1H, t, *J* = 7.9 Hz, H-5'), 7.92 (1H, d, *J* = 7.9 Hz, H-4'), 8.16 (1H, d, *J* = 7.9 Hz, H-6'), 8.25 (1H, s, H-4), 8.80 (1H, s, H-2'), 9.85 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.2 (C-8), 27.9 (C-6), 31.6 (C-7), 34.5 (C-5), 38.8 (C-9), 95.1 (C-2), 114.7 (C-2'), 117.5 (C-4'), 124.1 (C-3a), 126.6 (C-6'), 129.7 (C-5'), 130.6 (C-4), 134.2 (C-4a), 140.5 (C-1'), 147.8 and 148.0 (C-3 and C-3'), 155.7 (C-10a), 164.3 (C=O), 165.2 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3431, 3384, 3328, 3144, 2925, 2848, 1652,

1594, 1519, 1344, 1328; *m/z* (ESI^+): 405 (MNa^+, 70%), 383 (MH^+, 86%), 381 ($[M-H]^+$, 100%); HRMS (ESI^+) found (MH^+): 383.1161, $C_{19}H_{19}N_4O_3S$ requires 383.1172.

4.1.2.42 3-Amino-N-(3'-chloro-2'-methylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7l.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-chloro-2'-methylphenyl)acetamide **12n** (0.09 g, 0.34 mmol), carbonitrile **10c** (0.07 g, 0.34 mmol) and anhydrous sodium carbonate (0.04 g, 0.38 mmol) in absolute ethanol (1.8 mL) to give the *title product* **7l** (0.09 g, 86%) as a dark beige solid. m.p. 228-230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.28 (3H, s, CH_3), 2.88-2.91 (2H, m, H-5), 3.09-3.11 (2H, m, H-9), 7.21-7.30 (3H, m, NH_2, H-5' and H-4'), 7.36 (1H, d, J = 7.6 Hz, H-6'), 8.20 (1H, s, H-4), 9.33 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 15.4 (CH_3), 26.3 (C-8), 28.0 (C-6), 31.6 (C-7), 34.5 (C-5), 38.8 (C-9), 95.9 (C-2), 124.3 (C-3a), 126.2 (C-5'), 126.5 and 126.7 (C-4' and C-6'), 130.4 (C-4), 132.5 (C-2'), 133.6 (C-3'), 134.1 (C-4a), 138.2 (C-1'), 146.8 (C-3), 155.5 (C-10a), 164.2 (C=O), 164.7 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3448, 3332, 3139, 2927, 2849, 1673, 1501, 1464, 1432, 1289; *m/z* (ESI^+): 410 ($^{37}ClMNa^+$, 30%), 408 ($^{35}ClMNa^+$, 80%), 388 ($^{37}ClMH^+$, 38%), 386 ($^{35}ClMH^+$, 100%); HRMS (ESI^+) found ($^{37}ClMH^+$): 388.1054, $C_{20}H_{21}{}^{37}ClN_3OS$ requires 388.1064. Found ($^{35}ClMH^+$): 386.1081, $C_{20}H_{21}{}^{35}ClN_3OS$ requires 386.1088.

4.1.2.43 3-Amino-N-(3'-bromo-2'-methylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7m.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(3'-bromo-2'-methylphenyl)acetamide **12o** (0.07 g, 0.25 mmol), carbonitrile **10c** (0.05 g, 0.25 mmol) and anhydrous sodium carbonate (0.03 g, 0.27 mmol) in absolute ethanol (1.5 mL) to give the *title product* **7m** (0.03 g, 46%) as a brown solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.89 (2H, m, H-7), 2.28 (3H, s, CH_3), 2.88-2.90 (2H, m, H-5), 3.08-3.11 (2H, m, H-9), 7.14-7.20 (3H, m, H-5' and NH_2), 7.33 (1H, d, J = 7.4 Hz, H-6'), 7.51 (1H, d, J = 7.4 Hz, H-4'), 8.19 (1H, s, H-4), 9.35 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 18.5 (CH_3), 26.3 (C-8), 28.0 (C-6), 31.6 (C-7), 34.4 (C-5), 38.5 (C-9), 95.9 (C-2), 124.3 (C-3a), 124.5 (C-3'), 126.9 (C-6'), 127.2 (C-5'), 129.9 (C-4'), 130.4 (C-4), 134.1 (C-4a), 134.2 (C-2'), 138.0 (C-1'), 146.8 (C-3), 155.5 (C-10a), 164.2 (C=O), 164.7 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3446, 3333, 3137, 2926, 2849, 1682, 1500, 1462, 1432, 1288; *m/z* (ESI^+) : 454 ($^{81}BrMNa^+$, 75%), 452 ($^{79}BrMNa^+$, 73%), 432 ($^{81}BrMH^+$, 100%), 430 ($^{79}BrMH^+$, 99%); HRMS (ESI^+)

found ($^{81}BrMH^+$): 432.0557, $C_{20}H_{21}{}^{81}BrN_3OS$ requires 432.0564. Found ($^{79}BrMH^+$): 430.0577, $C_{20}H_{21}{}^{79}BrN_3OS$ requires 430.0583.

4.1.2.44 3-Amino-N-(2',3'-dimethylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7n.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2',3'-dimethylphenyl)acetamide **12p** (0.08 g, 0.34 mmol), carbonitrile **10c** (0.07 g, 0.34 mmol) and anhydrous sodium carbonate (0.04 g, 0.38 mmol) in absolute ethanol (1.5 mL) to give the *title product* **7n** (0.12 g, 97%) as a deep brown solid. m.p. 223-225 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.10 (3H, s, 2'-CH_3), 2.29 (3H, s, 3'-CH_3), 2.88-2.91 (2H, m, H-5), 3.08-3.11 (2H, m, H-9), 7.06-7.11 (3H, m, H-4', H-5' and H-6'), 7.15 (2H, br s, NH_2), 8.18 (1H, s, H-4), 9.12 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 14.3 (2'-CH_3), 20.1 (3'-CH_3), 26.3 (C-8), 28.0 (C-6), 31.6 (C-7), 34.5 (C-5), 38.8 (C-9), 96.5 (C-2), 124.4 (C-6'), 125.0 (C-3a), 125.1 (C-5'), 127.4 (C-4'), 130.3 (C-4), 133.0 (C-2'), 134.0 (C-4a), 136.3 (C-1'), 136.8 (C-3'), 146.3 (C-2), 155.4 (C-10a), 164.2 (C=O), 164.5 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3440, 3324, 3160, 2924, 2839, 1683, 1516, 1471, 1292, 1195; *m/z* (ESI$^+$): 388 (MNa^+, 98%), 366 (MH^+, 100%); HRMS (ESI$^+$) found (MH^+): 366.1629, $C_{21}H_{24}N_3OS$ requires 366.1635.

4.1.2.45 3-Amino-N-(2',4',6'-trimethylphenyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7o.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(2',4',6'-trimethylphenyl)acetamide **12t** (0.09 g, 0.34 mmol), carbonitrile **10c** (0.07 g, 0.34 mmol) and anhydrous sodium carbonate (0.04 g, 0.38 mmol) in absolute ethanol (2 mL) to give the *title product* **7o** (0.09 g, 48%) as a dark brown solid. m.p. 212-214 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.64-1.69 (4H, m, H-8 and H-6), 1.84-1.89 (2H, m, H-7), 2.15 (6H, s, 2'-CH_3 and 6'-CH_3), 2.26 (3H, s, 4'-CH_3), 2.88-2.90 (2H, m, H-5), 3.08-3.10 (2H, m, H-9), 6.92 (2H, s, H-3'and H-5'), 7.10 (2H, br s, NH_2), 8.16 (1H, s, H-4), 8.83 (1H, br s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 18.1 (2'-CH_3 and 6'-CH_3), 20.5 (4'-CH_3), 26.3 (C-8), 28.0 (C-6), 31.6 (C-7), 34.4 (C-5), 38.8 (C-9), 96.4 (C-2), 124.1 (C-3a), 128.2 (C-3' and C-5'), 130.2 (C-4), 132.8 (C-1'), 134.0 (C-2' and C-6'), 135.4 (C-4a), 135.6 (C-4'), 146.0 (C-3), 155.3 (C-10a), 164.4 (C=O), 165.2 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3352, 3285, 2925, 2851, 1659, 1597, 1506, 1437, 1283, 1194. *m/z* (ESI$^+$): 402 (MNa^+, 67%), 380 (MH^+, 100%); HRMS (ESI$^+$) found (MH^+): 380.1780, $C_{22}H_{26}N_3OS$ requires 380.1791.

4.1.2.46 3-Amino-N-(naphthalen-1'-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7p.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(naphthalen-1'-yl)acetamide **12u** (0.06 g, 0.25 mmol), carbonitrile **10c** (0.05 g, 0.25 mmol) and anhydrous sodium carbonate (0.03 g, 0.27 mmol) in absolute ethanol (1.5 mL) to give the title product **7p** (0.08 g, 86%) as a brown solid. m.p. 208-210 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.66-1.72 (4H, m, H-8 and H-6), 1.85-1.91 (2H, m, H-7), 2.89-2.92 (2H, m, H-5), 3.10-3.13 (2H, m, H-9), 7.21 (2H, s, NH_2), 7.54-7.57 (4H, m, H-2', H-3', H-6' and H-7'), 7.87 (1H, dd, J = 6.0, 3.5 Hz, H-4'), 7.92-7.99 (2H, m, H-5' and H-8'), 8.21 (1H, s, H-4), 9.64 (1H, s, NH); ^{13}C NMR (100 MHz; d_6-DMSO) 26.3 (C-8), 28.0 (C-6), 31.6 (C-7), 34.5 (C-5), 38.6 (C-9), 96.3 (C-2), 123.5, 126.2 and 128.0 (C-3', C-6' and C-7'), 124.3 (C-3a), 124.4, 125.5, 125.9 and 125.9 (C-2', C-4', C-5' and C-8'), 129.7 (C-8a'), 130.4 (C-4), 133.7 (C-4a'), 134.0 (C-4a), 146.7 (C-3), 150.0 (C-1'), 155.6 (C-10a), 164.7 (C=O), 164.9 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3431, 3316, 3159, 3049, 2921, 2848, 1668, 1518, 1497, 1283; m/z (ESI$^+$): 410 (MNa$^+$, 70%), 388 (MH$^+$, 100%); HRMS (ESI$^+$) found (MH$^+$): 388.1473, $C_{23}H_{22}N_3OS$ requires 388.1478.

4.1.2.47 3-Amino-N-(naphthalen-2'-yl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]thieno[3,2-e]pyridine-2-carboxamide ***7q.*** The reaction was carried out according to general procedure C using 2-bromo-*N*-(naphthalen-2'-yl)acetamide **12v** (0.06 g, 0.25 mmol), carbonitrile **10c** (0.05 g, 0.25 mmol) and anhydrous sodium carbonate (0.03 g, 0.27 mmol) in absolute ethanol (1.5 mL) to give the *title product* **7q** (0.06 g, 67%) as a tan solid. m.p. > 230 °C. ^{1}H NMR (400 MHz; d_6-DMSO) 1.65-1.70 (4H, m, H-8 and H-6), 1.84-1.90 (2H, m, H-7), 2.88-2.91 (2H, m, H-5), 3.09-3.11 (2H, m, H-9), 7.37 (2H, br s, NH_2), 7.41-7.44 (1H, m, H-5'), 7.47-7.51 (1H, m, H-6'), 7.83-7.89 (4H, m, H-2', H-7', H-3' and H-4'), 8.23 (1H, s, H-8'), 8.35 (1H, s, H-4), 9.57 (1H, s, NH); ^{13}C NMR (100MHz; d_6-DMSO) 26.2 (C-8), 28.0 (C-6), 31.6 (C-7), 34.5 (C-5), 38.6 (C-9), 96.0 (C-2), 117.0 (C-1'), 121.7 (C-3'), 124.3 (C-3), 124.6 (C-6'), 126.2 (C-7'), 127.3 (C-8'), 127.4 (C-5'), 127.8 (C-4'), 129.8 (C-4a'), 130.4 (C-4), 133.3 (C-8a'), 134.1 (C-4a), 136.8 (C-2'), 147.2 (C-2), 155.5 (C-10a), 164.2 (C=O), 164.8 (C-9a); IR: υ_{max} (film)/cm^{-1}: 3440, 3383, 3312, 3044, 2916, 2848, 1651, 1582, 1532, 1354, 1276; *m/z* (ESI$^+$) : 410 (MNa$^+$, 91%), 388 (MH$^+$, 100%); HRMS (ESI$^+$) found (MH$^+$): 388.1470, $C_{23}H_{22}N_3OS$ requires 388.1478.

4.2 Cell proliferation assay

As described in detail previously [3], cell proliferation was measured using a thymidine incorporation assay by seeding 3000 cells in each well using 96 well plates with varying concentrations of inhibitors for three days. Experiments were performed in triplicate with a minimum of two experimental repeats. Briefly, 0.04 μCi of ^{3}H-thymidine was added to each well and incubated for five hours, after which the cells were gathered onto glass fibre filters using an automated TomTec harvester. The filters were incubated with Betaplate Scint and thymidine incorporation determined with a Trilux/Betaplate counter showing the percentage of cells incorporated with ^{3}H-thymidine into the DNA helix.

Acknowledgements

Funding for this work was obtained from the Faculty Research Development Fund from University of Auckland. This work is also supported by the Auckland Medical Research Foundation, Auckland Cancer Society and the Auckland Cancer Society Research Centre.

Supplementary Data

Experimental details for the synthesis of compounds **10a-c** and **12a-v** and antibacterial testing results.

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Graphical Abstract

Synthesis and cytotoxicity of thieno[2,3-*b*]quinoline-2-carboxamide and cycloalkyl[*b*]thieno[3,2-*e*]pyridine-2-carboxamide derivatives

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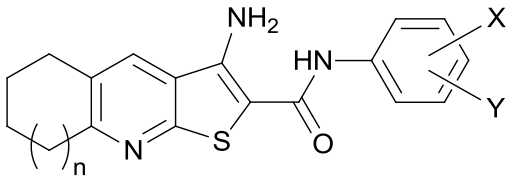

n = 0,1,2,3
activity improves
with increasing
ring size

X,Y = various groups
most active
compounds have
2,3-disubstitution