Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supplementary Information

Index

Table S1. The calculated molecular descriptors for the thieno[2,3-*b*]pyridines.

Molecule	MW	Log P	donorHB	accptHB	PSA	Rot. Bond.
1	385.9	3.0	2	5.5	95.9	3
2	371.8	2.7	2	5.5	96.7	3
3	355.4	2.4	2	5.5	97.6	3
4	367.4	2.4	2	6.3	103.6	4
5	406.3	3.1	2	5.5	96.6	3
6	405.4	3.1	2	5.5	94.7	3
7	351.4	2.5	2	5.5	97.6	3
8	355.4	2.4	2	5.5	97.6	3
9	371.8	2.7	2	5.5	97.4	3
10	416.3	2.7	2	5.5	97.4	3
11	365.4	2.9	2	5.5	92.7	3
12	397.4	2.5	2	7.0	111.6	5
13	397.4	2.5	2	7.0	111.4	5
14	406.3	3.1	2	5.5	97.6	3
15	379.4	1.7	2	7.5	126.0	4
16	387.5	3.1	2	5.5	96.2	3
17	343.4	2.4	2	5.5	97.8	3
18	344.4	1.3	2	7.0	110.7	3
19	341.4	1.9	2	6.0	108.8	4

Table S2. The results of the scoring functions for derivatives 1 -19.

Deriv.	GoldScore	ChemScore	ChemPLP	ASP
1	56.4	31.2	69.6	35.8
2	62.6	30.3	68.4	34.4
3	62.3	30.6	74.1	36.6
4	56.7	27.8	63.1	34.4
5	55.4	30.7	70.5	34.9
6	53.7	30.2	66.5	34.6
7	58.4	29.7	63.6	32.4
8	62.5	34.5	72.6	38.1
9	58.8	29.0	61.5	31.7
10	57.7	29.2	60.1	30.3
11	59.2	30.9	66.0	35.7
12	60.2	28.3	61.3	34.1
13	59.4	28.2	68.8	36.7
14	64.2	34.7	67.2	33.0
15	61.9	31.0	71.0	37.7
16	57.6	33.1	79.3	39.6
17	48.1	33.2	67.3	26.5
18	61.3	34.1	73.6	36.2
19	57.9	34.3	81.9	39.1

Table S3. The results from the virtual screen.

Number	NCI Total (%)	Leukaemia Average (%)	Ratio	ChemBridge ID
20	97.7	91.1	1.1	5152889
21	99.2	89.3	1.1	5656310
22	80.7	55.6	1.5	5890847
23	99.6	82.6	1.2	7653771
24	95.9	69.8	1.4	7677433
25	96.0	74.9	1.3	7724791
26	94.3	33.6	2.8	7725570
27	71.6	50.1	1.4	7754704
28	96.7	86.1	1.1	7779675
29	77.1	33.9	2.3	7816934
30	100.3	75.6	1.3	7975398
31	95.2	79.9	1.2	7989630
32	87.7	57.2	1.5	7996756
33	87.9	70.6	1.2	9009888
34	97.9	87.1	1.1	9023708
35	88.7	36.4	2.4	9030551
36	97.4	89.8	1.1	9033852
37	99.0	88.0	1.1	9040504
38	84.6	61.6	1.4	9114228
39	85.1	37.6	2.3	9116933

Table S4 Criteria of lead-like, drug-like and known drug space (KDS) in terms of molecular descriptors.

	Lead-like Space	Drug-like Space	Known Drug Space
Molecular weight (g mol^{-1})	300	500	800
Lipophilicity (Log P)	3	5	6.5
Hydrogen bond donors (HD)	3	5	7
Hydrogen bond acceptors (HA)	3	10	15
Polar surface area ($Å^2$) (PSA)	60	140	180
Rotatable bonds (RB)	3	10	17

Table S5. Length of the pyridines and the NCI mean growth inhibition.

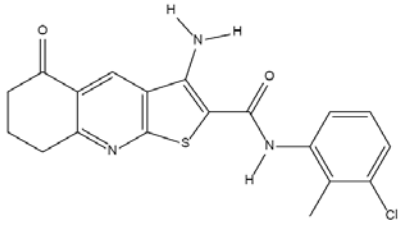
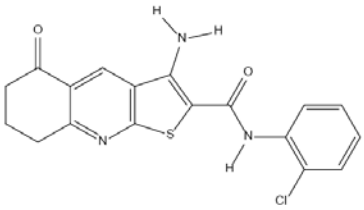
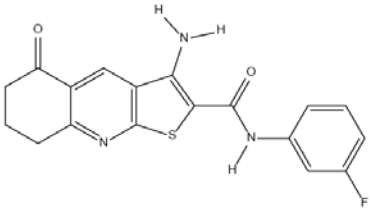
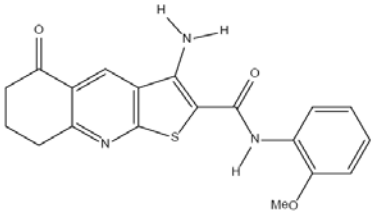
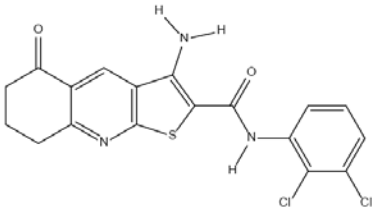
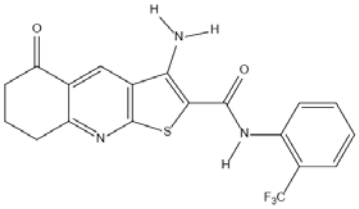
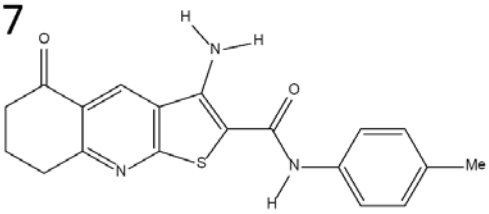
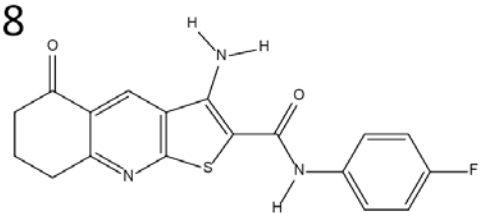
	NCI Mean (%)	Length A
1	16.4	13.465
2	48.3	13.506
3	31.4	13.516
4	61.3	13.518
5	74.8	13.537
6	81.6	13.536
7	75.6	15.061
8	89.8	14.887
9	100.2	15.258
10	100.1	15.421
11	73.5	13.517
12	99.2	15.604
13	82.5	13.505
14	101.6	15.245
15	97.9	15.030
16	20.8	13.649
17	99.2	13.194
18	100.4	13.082
19	103.1	12.474
1[a]	30.2	13.486
2[a]	33.3	13.487
3[a]	36.3	13.736
4[a]	23.1	15.014
5[a]	42.0	13.491
6[a]	59.2	13.492
7[a]	103.0	15.736
8[a]	105.4	15.036
9[a]	102.4	15.033
10[a]	99.9	16.120
11[a]	101.7	16.522
12[a]	109.8	16.354
13[a]	107.6	16.732
14[a]	110.2	15.347
15[a]	87.4	16.445
16[a]	104.5	16.230
1a[a]	111.9	13.302
2a[a]	102.6	15.286

[a] Values from: L. Feng, I. Reynisdóttir and J. Reynisson, *Eur. J. Med. Chem.*, 2012, **54**, 463-469.

NCI's 60-cell line panel growth inhibition assay

The NCI's human 60-cell lines were grown in RPMI 1640 medium containing 5% FBS and 2mM L-glutamine. Cells were inoculated into 96-well plates at plating densities 5000–40 000 cells per well, based on the doubling time of individual cell lines. Plates were then incubated at 37 °C, 5% CO_2, 95% air and 100% relative humidity for 24 h prior to addition of tested compounds. After 24 h, two plates of each cell line were fixed *in situ* with trichloroacetic acid (TCA), to represent a measurement of the cell population for each cell line at the time of tested compound addition. Tested compounds were solubilized in DMSO at a concentration 400 times that of the desired final maximum test concentration and stored frozen prior to use. An aliquot of each frozen tested concentrate was thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 μg mL^{-1} gentamicin. 100 μL aliquot of the tested drug diluted solution was added to appropriate wells containing 100 μL of medium, resulting in the required final drug doses. Following tested compound addition, plates were incubated for additional 48 h. The assay was terminated by the addition of cold TCA for adherent cells. Cells were fixed *in situ* by addition of 50 μL of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 min at 4 °C. The supernatant was discarded, and plates were washed 5 times with water and air dried. Sulforhodamine B (SRB) solution (100 μL), 0.4%(w/v) in 1% acetic acid was added to each well, and plates were incubated for 10 min at rt. After staining, the unbound dye was removed by washing five times with 1% acetic acid and plates were air dried. The bound stain was subsequently solubilized with 10 mM Trizma base, and the absorbance was measured on a plate reader at 515 nm. For suspension cells, the methodology was identical except the assay termination by fixing settled cells at the bottom of each well by adding 50 μL of 80%TCA (final concentration, 16% TCA).
Taken from: K. A. El Sayed, A. I. Foudah, A. M. S. Mayer, A. M. Crider and D. Song, *Med. Chem. Comm.*, 2013, **4**, 1231-1238.

Table S6. Structures of all the tested pyridines.

1  3-amino-N-(3-chloro-2-methylphenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide	2  3-amino-N-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide
3  3-amino-N-(3-fluorophenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide	4  3-amino-N-(2-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide
5  3-amino-N-(2,3-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide	6  3-amino-5-oxo-N-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide
7  3-amino-5-oxo-N-p-tolyl-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide	8  3-amino-N-(4-fluorophenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide

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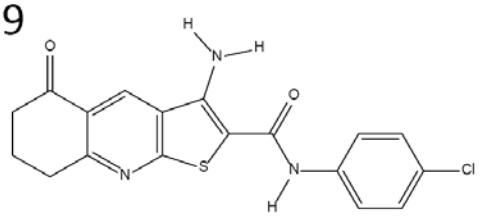

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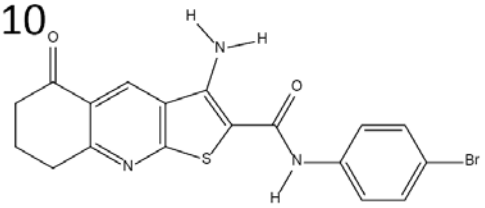

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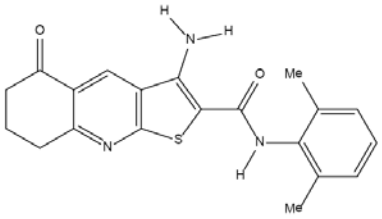

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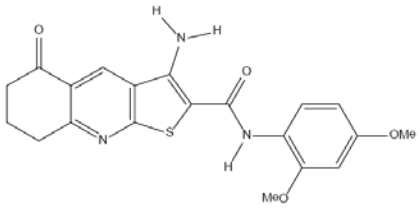
12



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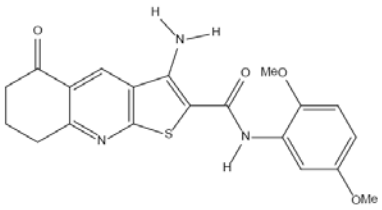
13



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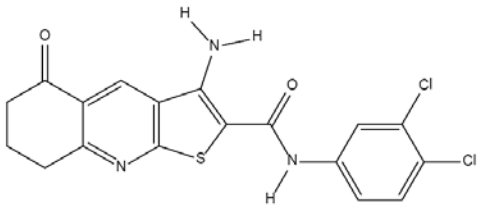

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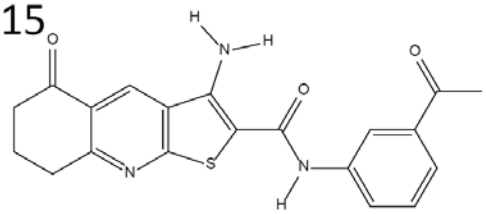

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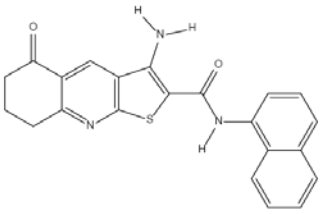

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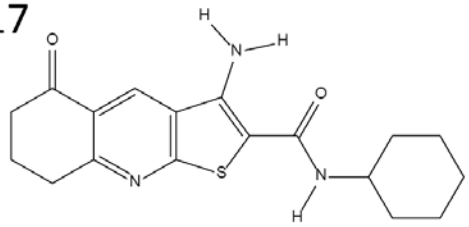

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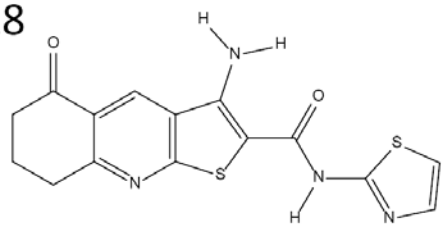

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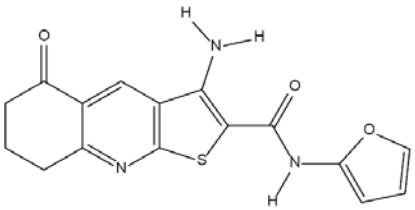

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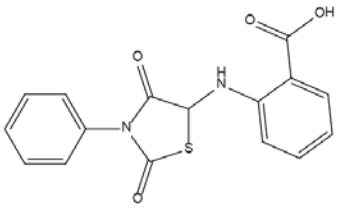

3-chloro-N-phenethyl-1H-indole-2-carboxamide

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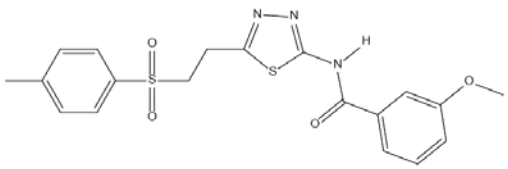

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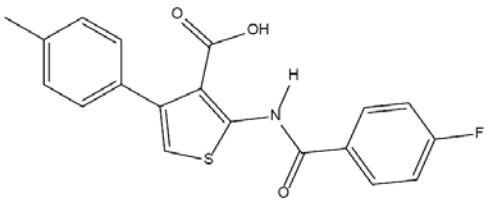

2-(4-fluorobenzamido)-4-p-tolylthiophene-3-carboxylic acid

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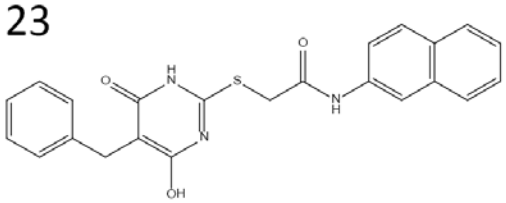

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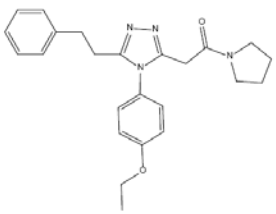
24



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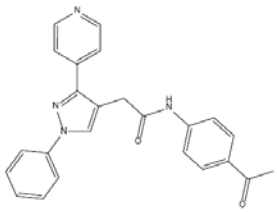

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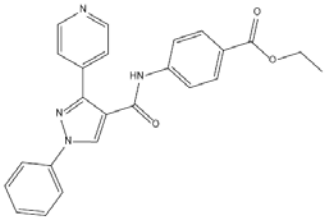
26



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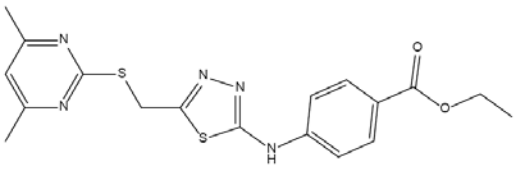
27



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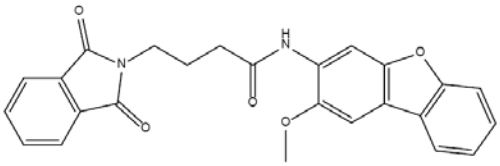
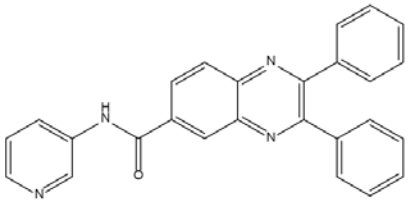
28



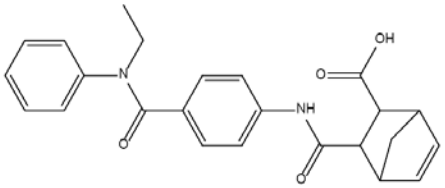
4-(1,3-dioxoisoindolin-2-yl)-N-(2-methoxydibenzo[b,d] furan-3-yl)butanamide

29



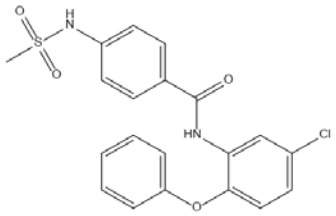
2,3-diphenyl-N-(pyridin-3-yl)quinoxaline-6-carboxamide

30



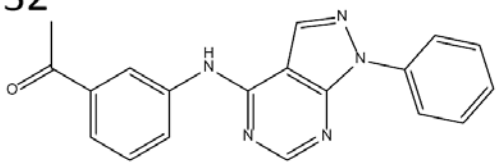
3-(4-(ethyl(phenyl)carbamoyl)phenylcarbamoyl) bicyclo[2.2.1]hept-5-ene-2-carboxylic acid

31



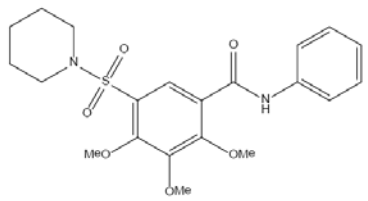
N-(5-chloro-2-phenoxyphenyl)-4-(methylsulfonamido) benzamide

32



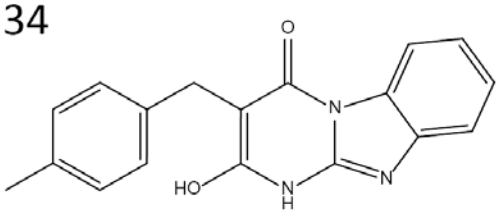
1-(3-(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino) phenyl)ethanone

33



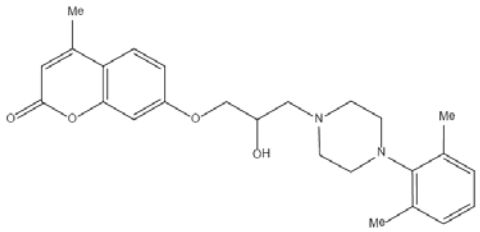
2,3,4-trimethoxy-N-phenyl-5-(piperidin-1-ylsulfonyl) benzamide

34



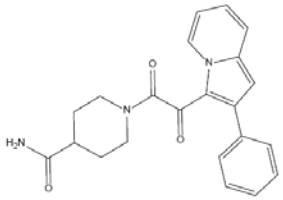
2-hydroxy-3-(4-methylbenzyl)pyrimido[1,2-a] benzimidazol-4(1H)-one

35



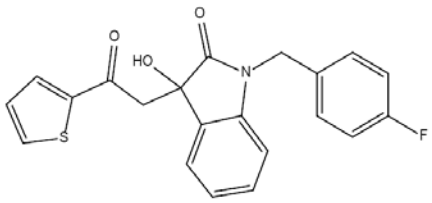
7-(3-(4-(2,6-dimethylphenyl)piperazin-1-yl)-2-hydroxypropoxy)-4-methyl-2H-chromen-2-one

36



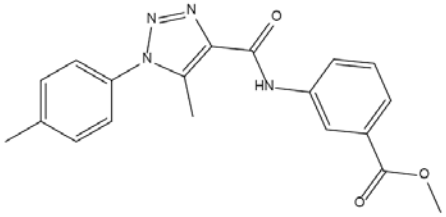
1-(2-oxo-2-(2-phenylindolizin-3-yl)acetyl)piperidine-4-carboxamide

37



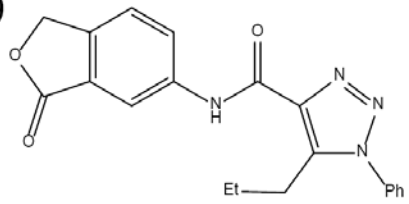
1-(4-fluorobenzyl)-3-hydroxy-3-(2-oxo-2-(thiophen-2-yl)ethyl)indolin-2-one

38



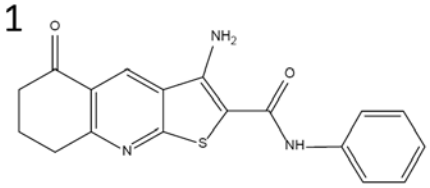
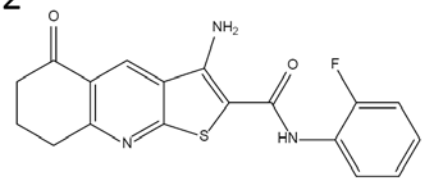
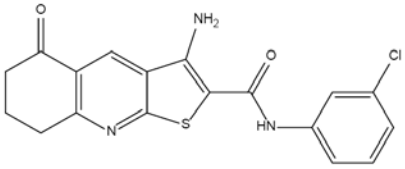
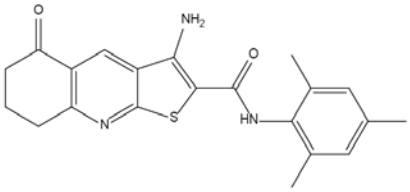
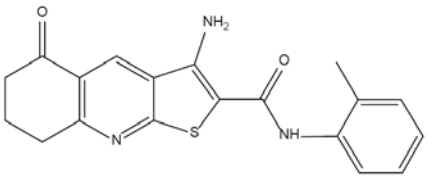
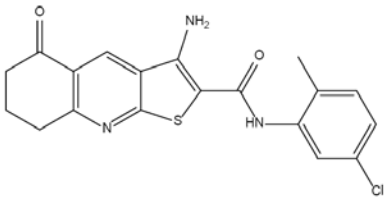
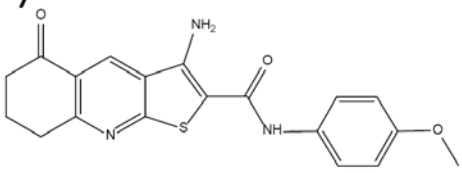
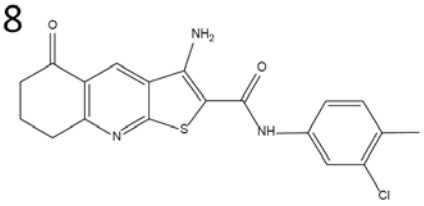
methyl 3-(5-methyl-1-p-tolyl-1H-1,2,3-triazole-4-carboxamido)benzoate

39

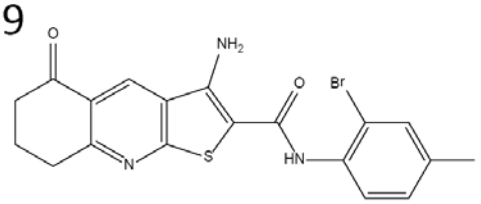


N-(3-oxo-1,3-dihydroisobenzofuran-5-yl)-1-phenyl-5-propyl-1H-1,2,3-triazole-4-carboxamide

Table S7. Structures from Feng et al. (L. Feng, I. Reynisdóttir and J. Reynisson, *Eur. J. Med. Chem.*, 2012, **54**, 463-469) used in the QSAR analysis.

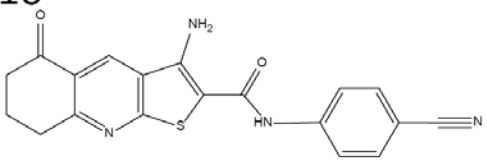
1  3-amino-5-oxo-N-phenyl-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide	2  3-amino-N-(2-fluorophenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-
3  3-amino-N-(3-chlorophenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide	4  3-amino-N-mesityl-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide
5  3-amino-5-oxo-N-o-tolyl-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide	6  3-amino-N-(5-chloro-2-methylphenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide
7  3-amino-N-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide	8  3-amino-N-(3-chloro-4-methylphenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide

9



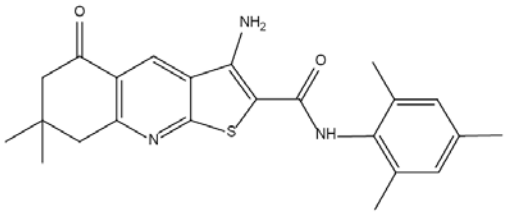
3-amino-N-(2-bromo-4-methylphenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide

10



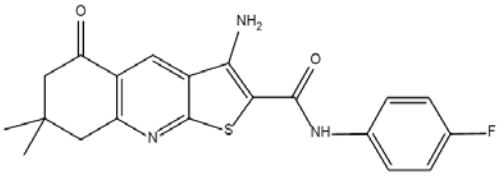
3-amino-N-(4-cyanophenyl)-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide

11



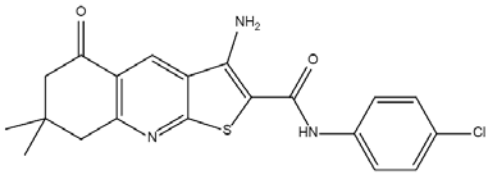
3-amino-N-mesityl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide

12



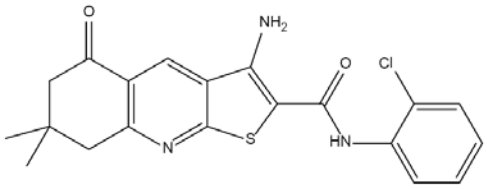
3-amino-N-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide

13



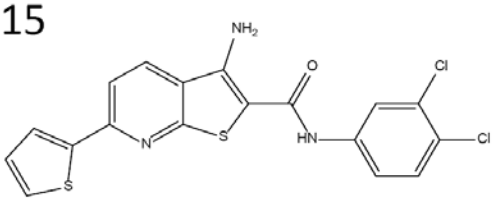
3-amino-N-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide

14



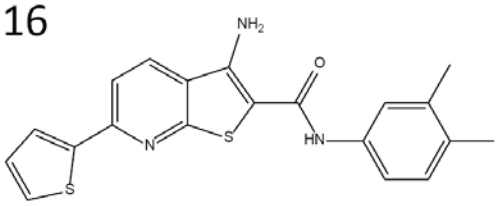
3-amino-N-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b]quinoline-2-carboxamide

15

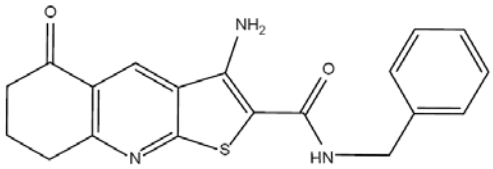
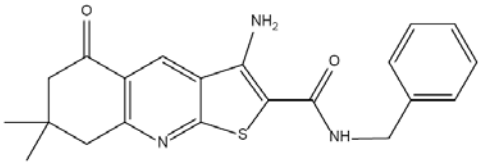


3-amino-N-(3,4-dichlorophenyl)-6-(thiophen-2-yl) thieno[2,3-b]pyridine-2-carboxamide

16



3-amino-N-(3,4-dimethylphenyl)-6-(2-thienyl) thieno[2,3-b]pyridine-2-carboxamide

1a	2a
	
3-amino-N-benzyl-5-oxo-5,6,7,8-tetrahydrothieno[2,3-b] quinoline-2-carboxamide	3-amino-N-benzyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-thieno[2,3-b]quinoline-2-carboxamide