Supporting Information

Exploration of a Series of 5-Arylidene-2-thioxoimidazolidin-4-ones as Inhibitors of the Cytolytic Protein Perforin

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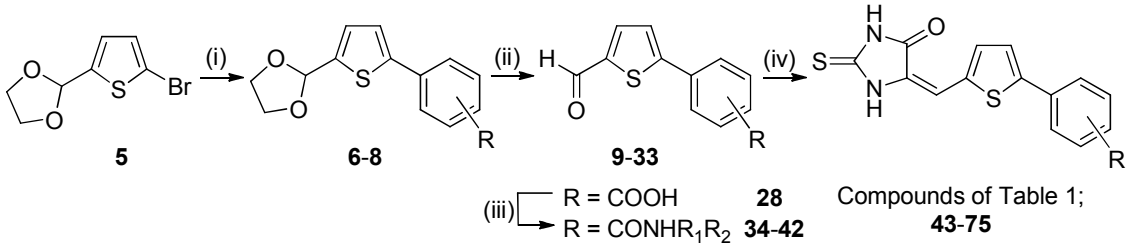
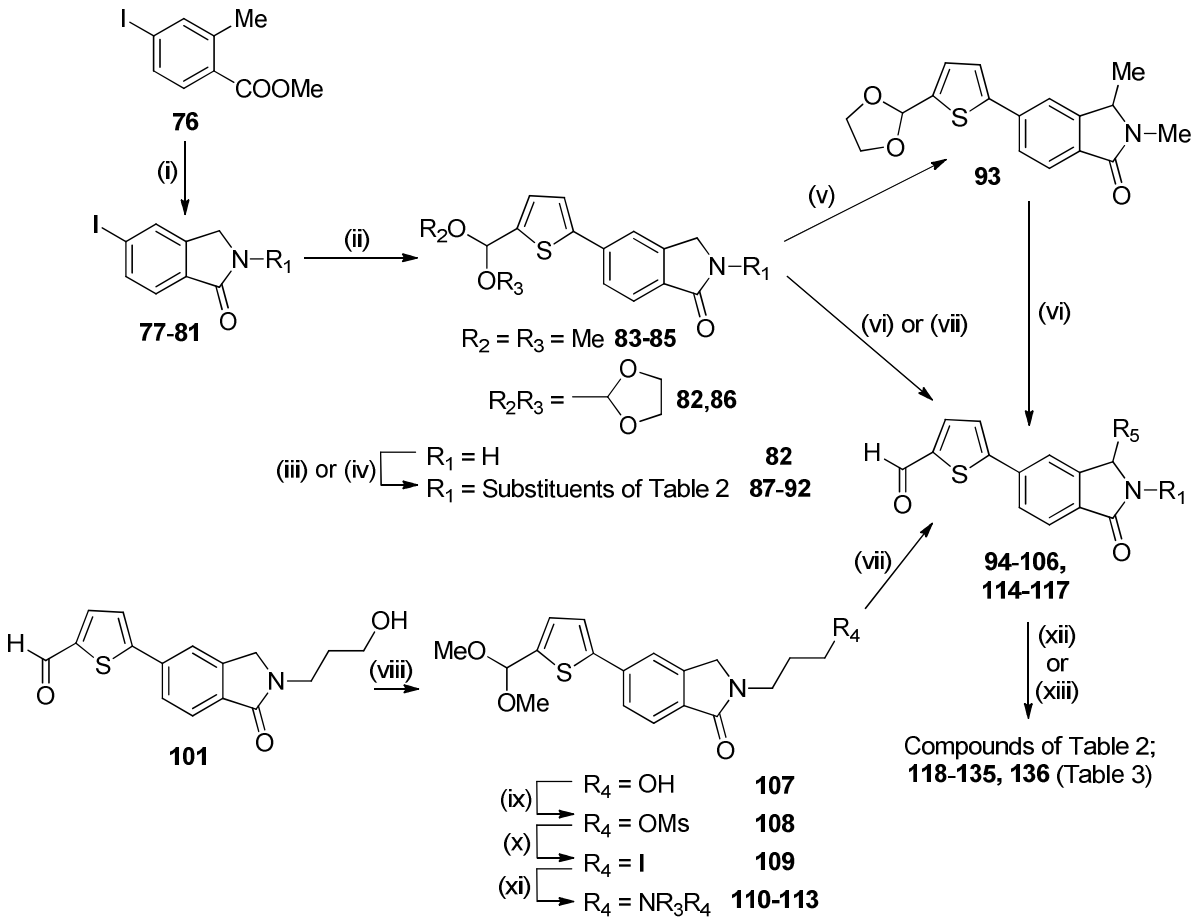
Contents:

Scheme 1/ Table 1. Individual Compound Numbering



Substituent	Dioxolanes (6-8)	Aldehydes (9-42)	Final Compounds
4-CH_2OH	**6**	**9**	**58**
3-$CONH_2$	**7**	**10**	**60**
4-$CONH_2$	**8**	**11**	**61**
H		**12**	**43**
2-Cl		**13**	**44**
3-Cl		**14**	**45**
4-Cl		**15**	**46**
3-F		**16**	**47**
4-F		**17**	**48**
3,4-diF		**18**	**49**
3-CF_3		**19**	**50**
4-CF_3		**20**	**51**
3-CN		**21**	**52**
4-OH		**22**	**53**
3-CF_3,4-Cl		**23**	**54**
4-Br		**24**	**55**
4-SMe		**25**	**56**
4-Ac		**26**	**57**
4-COOMe		**27**	**59**
4-COOH		**28**	
3-Me,4-COOMe		**29**	**62**
4-SO_2Me		**30**	**63**
4-$NHSO_2Me$		**31**	**64**
3-pyridyl		**32**	**65**
4-pyridyl		**33**	**66**
4-CONHMe		**34**	**67**
4-$CONMe_2$		**35**	**68**
4-COmorph		**36**	**69**
4-$CONH(CH_2)_2$morph		**37**	**70**
4-$CONH(CH_2)_3$morph		**38**	**71**
4-$CONH(CH_2)_2OH$		**39**	**72**
4-$CONH(CH_2)_3OH$		**40**	**73**
4- $CONHCH_2CH(CH_3)OH$		**41**	**74**
4-$CONHCH_2CH(OH)CH_2OH$		**42**	**75**

Scheme 2/ Table 2. Individual Compound Numbering.

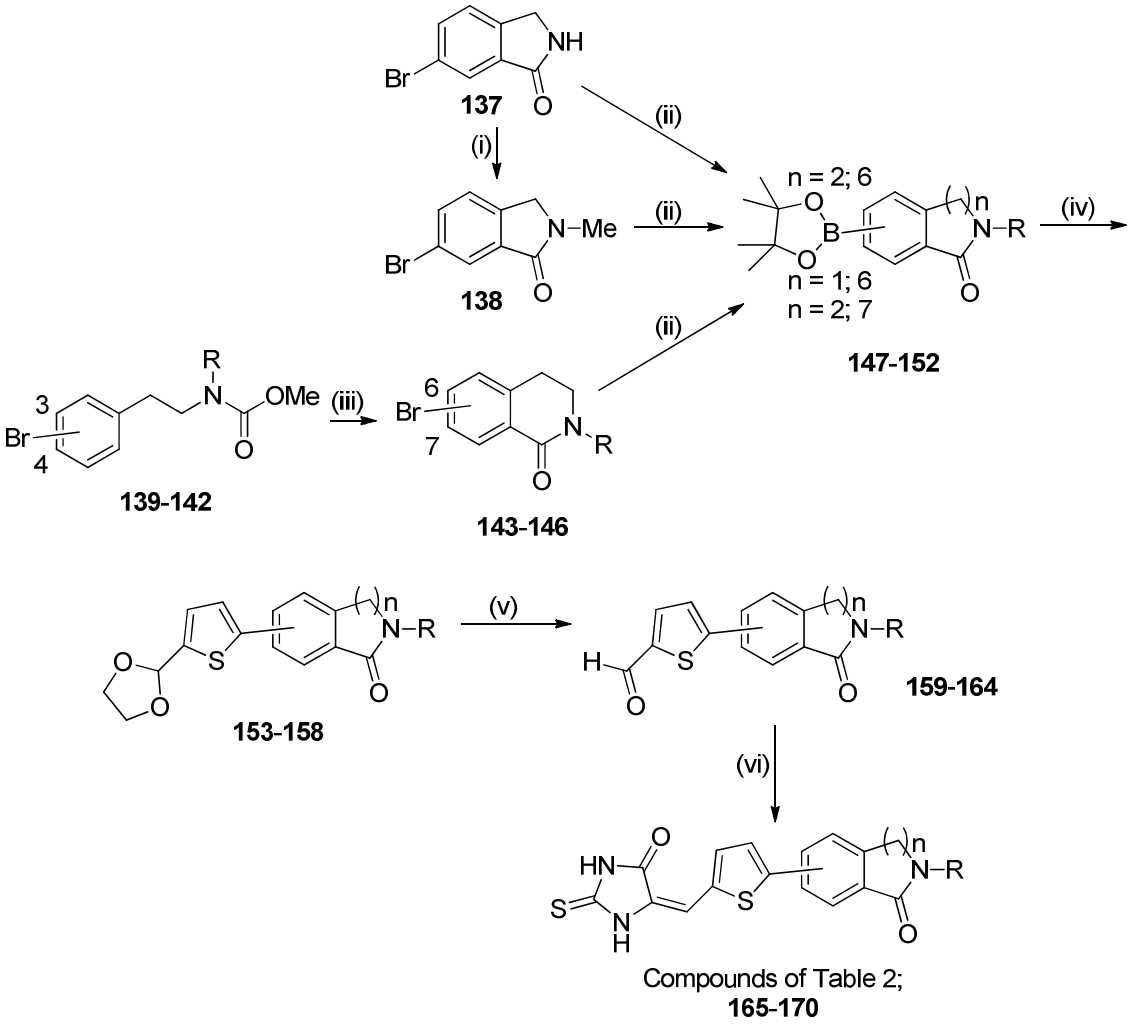


Compound	R_1	R_2	R_3	R_4	R_5
77	H				
78	$(CH_2)_2OH$				
79	$(CH_2)_3OH$				
80	$CH_2CH(OH)CH_2OH$				
81	$(CH_2)_2$morph				
82	H	dioxolane			
83	$(CH_2)_2OH$	Me	Me		
84	$(CH_2)_3OH$	Me	Me		
85	$CH_2CH(OH)CH_2OH$	Me	Me		
86	$(CH_2)_2$morph	dioxolane			
87	Me	dioxolane			
88	Et	dioxolane			
89	nPr	dioxolane			
90	nBu	dioxolane			
91	Ac	dioxolane			
92	C(O)OEt	dioxolane			
93	Me	dioxolane			Me
94	H				
95	Me				

Compound	R_1	R_2	R_3	R_4	R_5
96	Et				
97	nPr				
98	nBu				
99	iPr				
100	$(CH_2)_2OH$				
101	$(CH_2)_3OH$				
102	$CH_2CH(OH)CH_2OH$				
103	Ac				
104	C(O)OEt				
105	$(CH_2)_2$morph				
106	Me				Me
107	$(CH_2)_3R_4$	Me	Me	OH	
108	$(CH_2)_3R_4$	Me	Me	OMs	
109	$(CH_2)_3R_4$	Me	Me	I	
110	$(CH_2)_3R_4$	Me	Me	NMe_2	
111	$(CH_2)_3R_4$	Me	Me	Piperidine	
112	$(CH_2)_3R_4$	Me	Me	NMepiperazine	
113	$(CH_2)_3R_4$	Me	Me	pyrrolidine	
114	$(CH_2)_3NMe_2$				
115	$(CH_2)_3$piperidine				
116	$(CH_2)_3$NMepiperazine				
117	$(CH_2)_3$pyrrolidine				
118	H				
119	Me				
120	Et				
121	nPr				
122	nBu				
123	iPr				
124	$(CH_2)_2OAc$				
125	$(CH_2)_2OH$				
126	$(CH_2)_3OH$				
127	$CH_2CH(OH)CH_2OH$				
128	Ac				
129	C(O)OEt				
130	$(CH_2)_2$morph				
131	$(CH_2)_3NMe_2$				
132	$(CH_2)_3$piperidine				
133	$(CH_2)_3$NMepiperazine				
134	$(CH_2)_3$pyrrolidine				
135	Me				Me
136*	H				

* Imidazolidine-2,4-dione A-subunit

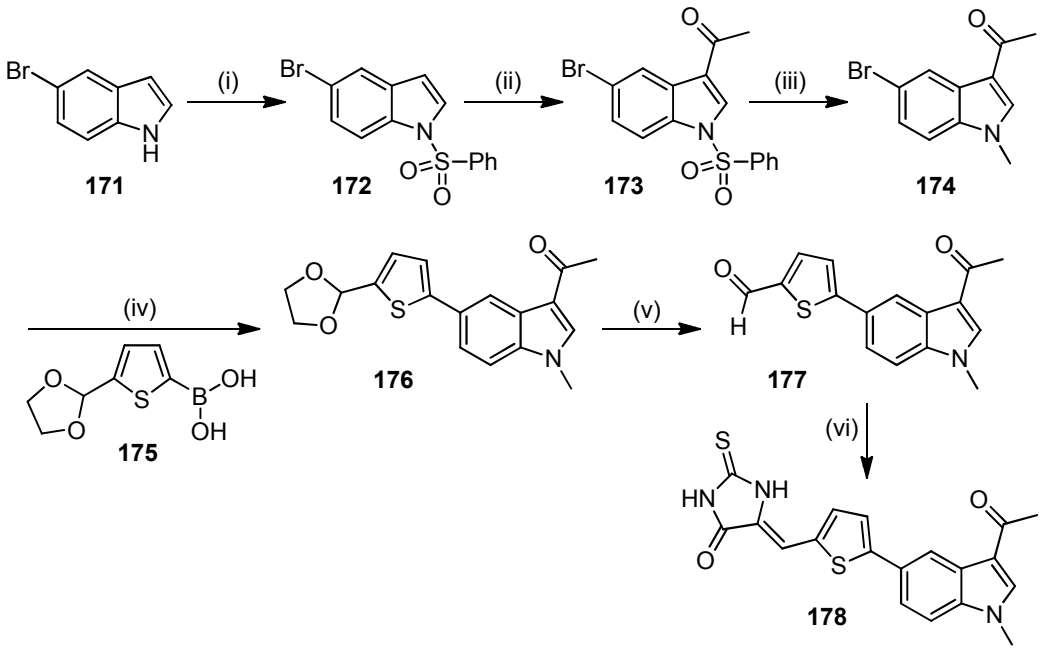
Scheme 3/ Table 3. Individual Compound Numbering.



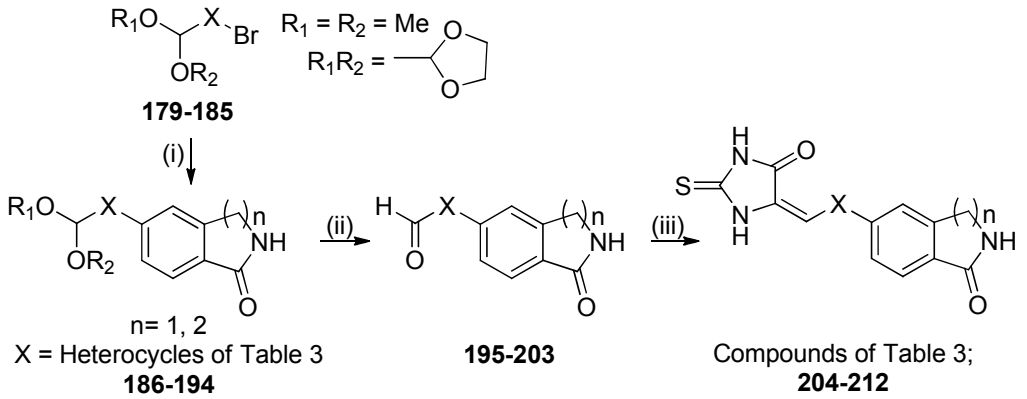
Compound	Substituent Position	R	n
139	3-Br	H	
140	4-Br	H	
141	3-Br	Me	
142	4-Br	Me	
143	6-Br	H	2
144	7-Br	H	2
145	6-Br	Me	2
146	7-Br	Me	2
147	6-boronate	H	1
148	6-boronate	Me	1
148	6-boronate	H	2
150	7-boronate	H	2
151	6-boronate	Me	2
152	7-boronate	Me	2
153	6-(thiophene-dioxolane)	H	1
154	6-(thiophene-dioxolane)	Me	1

Compound	Substituent Position	R	n
155	6-(thiophene-dioxolane)	H	2
156	7-(thiophene-dioxolane)	H	2
157	6-(thiophene-dioxolane)	Me	2
158	7-(thiophene-dioxolane)	Me	2
159	6-(thiophene-aldehyde)	H	1
160	6-(thiophene-aldehyde)	Me	1
161	6-(thiophene-aldehyde)	H	2
162	7-(thiophene-aldehyde)	H	2
163	6-(thiophene-aldehyde)	Me	2
164	7-(thiophene-aldehyde)	Me	2
165	6-	H	1
166	6-	Me	1
167	6-	H	2
168	7-	H	2
169	6-	Me	2
170	7-	Me	2

Scheme 4. Individual Compound Numbering.

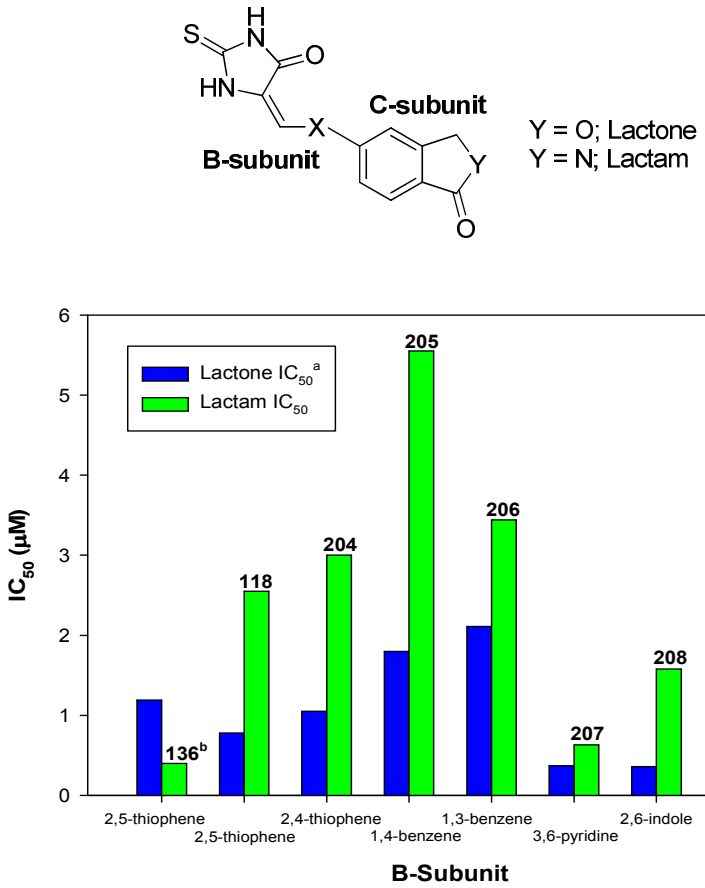


Scheme 5/ Table 4. Individual Compound Numbering.



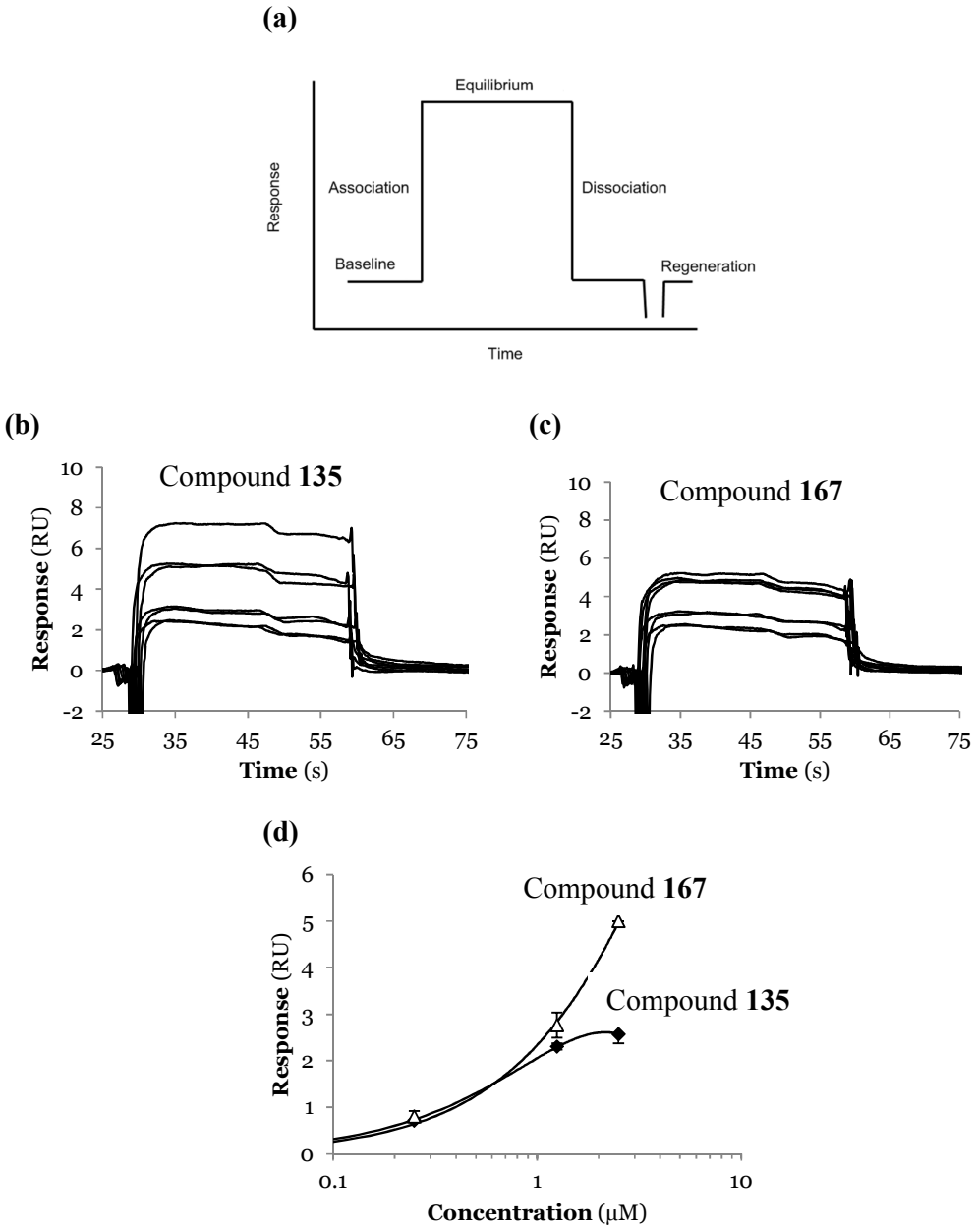
Compound	X	R_1	R_2	n
179	2,4-thiophene	Me	Me	
180	1,4-benzene	Me	Me	
181	1,3-benzene	Me	Me	
182	3,6-pyridine	Me	Me	
183	2,6-(1*H*-indole)	Me	Me	
184	2,5-(1*H*-indole)	Me	Me	
185	2,6-quinoline	dioxolane		
186	2,4-thiophene	Me	Me	1
187	1,4-benzene	Me	Me	1
188	1,3-benzene	Me	Me	1
189	3,6-pyridine	Me	Me	1
190	2,6-(1*H*-indole)	Me	Me	1
191	2,5-(1*H*-indole)	Me	Me	1
192	2,6-(1*H*-indole)	Me	Me	2
193	2,5-(1*H*-indole)	Me	Me	2
194	2,6-quinoline	dioxolane		2
195	2,4-thiophene			1
196	1,4-benzene			1
197	1,3-benzene			1
198	3,6-pyridine			1
199	2,6-(1*H*-indole)			1
200	2,5-(1*H*-indole)			1
201	2,6-(1*H*-indole)			2
202	2,5-(1*H*-indole)			2
203	2,6-quinoline			2
204	2,4-thiophene			1
205	1,4-benzene			1
206	1,3-benzene			1
207	3,6-pyridine			1
208	2,6-(1*H*-indole)			1
209	2,5-(1*H*-indole)			1
210	2,6-(1*H*-indole)			2
211	2,5-(1*H*-indole)			2
212	2,6-quinoline			2

Figure 1. Comparison of Lactone and Lactam Activities



[a]IC_{50}s for corresponding lactones (blue) previously reported in reference 30. [b]Compound **136** contains a a imidazolidine-2,4-dione A-subunit, while all others (**118**, **204**-**209**) contain a 2-thioxoimidazolidin-4-one A-subunit.

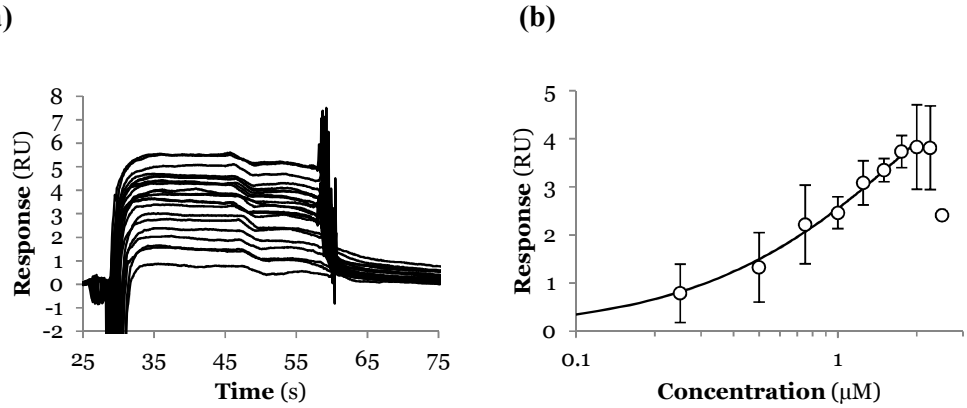
Figure 2. Binding of Compounds **135** and **167** to Perforin Protein by SPR[a]



[a]**(a)** Features of a typical sensorgram for low molecular weight analytes: The association phase of the interaction, when the analyte binds to the immobilised biomolecular target, generates an increase in response. Equilibrium is then achieved as association and dissociation occur at an equal rate. Following the end of injection, the dissociation of the complex can be measured and information on the stability of the complex collected. After this the surface is regenerated by disrupting any ligand-analyte complexes by mild acidic or basic washing conditions, which yields a fully functional surface that can be re-used. **(b)**, **(c)** SPR binding response of compounds **135** and **167 (**0, 0.25, 1.25 and 2.5 μM) and **(d)** resulting dose-response curves of binding to surface immobilised wildtype perforin monomers (4,257 RU), fitted to a single site specific binding model (R^2 = 0.5943). Samples were injected in duplicate at a flow rate of 50 μl/min at 25°C. Data are as mean ± standard deviation. The calculated R_{max} for binding of **135** was 1.23 ± 0.10 RU and the calculated K_D was 1.79 ± 0.55 μM.

The sodium salts of compounds **135** and **167** had relatively poor solubility in running buffer containing 5% DMSO and were only soluble up to 2.5 μM. Both compounds were injected across the immobilised perforin at 0, 0.25, 1.25 and 2.5 μM [(b) and (c), Figure 2]. At these low concentrations there was a linear concentration response for binding of **167** to immobilised perforin. Determination of the maximum binding appears to be limited by solubility. However, at the same low concentrations, saturable binding of **135** to immobilised perforin was observed above 1 μM. A further dilution series [0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25 and 2.5 μM (n=2)] was then injected over the biosensor chip (Figure 3). The sudden decrease in binding response at 2.5μM is suggestive of a solubility issue at this concentration. The data were then fitted to a single site specific binding model (R^2 = 0.8506). The calculated R_{max} was 8.66 ± 2.81 RU and the calculated K_D was 2.39 ± 1.23 μM.

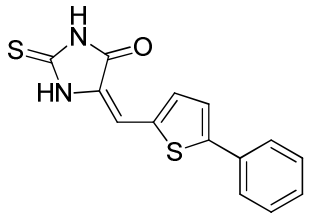
Figure 3. SPR Binding and Dose-Response Curve of Compound **135**[a]



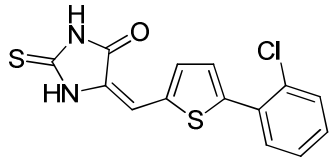
[a]**(a)** SPR binding response and **(b)** the dose-response curve of compound **135** (0 – 2.5 μM) binding to surface immobilised wildtype perforin monomers (4,257 RU), fitted to a single site specific binding model (R^2 = 0.5943). Samples were injected in triplicate at a flow rate of 50 μl/min at 25°C. Data are shown as mean ± standard deviation. The calculated R_{max} for binding of **135** was 8.66 ± 2.81 RU and the calculated K_D was 2.39 ± 1.23 μM (R^2 = 0.8506).

Experimental For Target Compounds

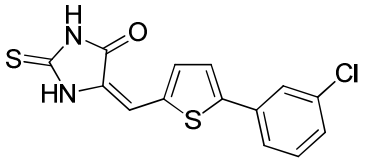
The general procedures referred to below are described in the published article. Reference numbers as in the published article and given below.



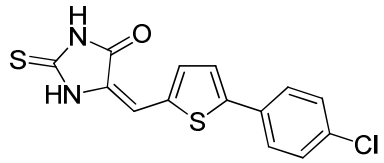
(*E,Z*)-5-((5-Phenylthiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (43). Reaction of 5-phenylthiophene-2-carbaldehyde (**9**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **43** as a bright orange solid (89%), mp (AcOH) 290-294°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.35 (br s, 1 H), 11.95 (br s, 1 H), 7.83 (d, *J* = 4.0 Hz, 1 H), 7.69-7.75 (m, 2 H), 7.64 (d, *J* = 4.0 Hz, 1 H), 7.42-7.49 (m, 2 H), 7.33-7.39 (m, 1 H), 6.63 (s, 1 H). LRMS ($APCI^+$) calcd for $C_{14}H_{11}N_2OS_2$ 287 (MH^+), found 287. Anal. ($C_{14}H_{10}N_2OS_2$), C, H, N.



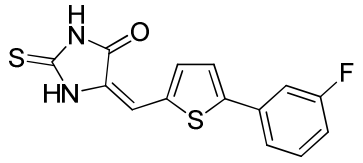
(*E,Z*)-5-((5-(2-Chlorophenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (44). Reaction of 5-(2-chlorophenyl)thiophene-2-carbaldehyde (**10**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **44** as a dark yellow solid (41%), mp (AcOH) 269-271°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.32 (s, 1 H), 12.02 (s, 1 H), 7.85 (d, *J* = 3.3 Hz, 1 H), 7.72 (dd, *J* = 2.0, 7.5 Hz, 1 H), 7.62 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.55 (d, *J* = 3.9 Hz, 1 H), 7.43 (m, 2 H), 6.63 (s, 1 H). Anal. ($C_{14}H_9ClN_2OS_2.0.5H_2O$) C, H, N.



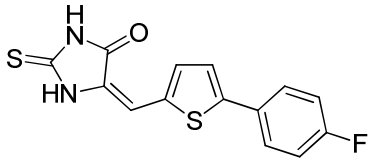
(*E,Z*)-5-((5-(3-Chlorophenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (45). Reaction of 5-(3-chlorophenyl)thiophene-2-carbaldehyde (**11**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **45** as a brown solid (45%), mp (AcOH) 281-283°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.33 (s, 1 H), 11.96 (s, 1 H), 7.81 (d, *J* = 3.7 Hz, 1 H), 7.79 (t, *J* = 1.7 Hz, 1 H), 7.73 (d, *J* = 3.9 Hz, 1 H), 7.66 (d, *J* = 6.6 Hz, 1 H), 7.48 (t, *J* = 7.9 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 6.63 (s, 1 H). Anal. ($C_{14}H_9ClN_2OS_2.0.25H_2O$) C, H, N.



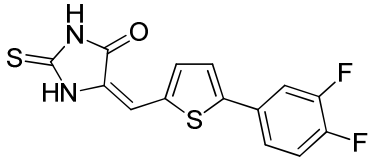
(*E,Z*)-5-((5-(4-Chlorophenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (46). Reaction of 5-(4-chlorophenyl)thiophene-2-carbaldehyde (**12**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **46** as a yellow solid (75%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.36 (s, 1 H), 11.96 (s, 1 H), 7.81 (d, *J* = 3.9 Hz, 1 H), 7.73 (d, *J* = 8.6 Hz, 2 H), 7.66 (d, *J* = 3.9 Hz, 1 H), 7.49 (d, *J* = 8.6 Hz, 2 H), 6.62 (s, 1 H). Anal. ($C_{14}H_9ClN_2OS_2$) C, H, N.



(*E,Z*)-5-((5-(3-Fluorophenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (47). Reaction of 5-(3-fluorophenyl)thiophene-2-carbaldehyde (**13**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **47** as an orange solid (75%), mp (AcOH) 285-289°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.35 (s, 1 H), 11.96 (s, 1 H), 7.82 (d, *J* = 4.0 Hz, 1 H), 7.72 (d, *J* = 4.0 Hz, 1 H), 7.48-7.60 (m, 3 H), 7.19 (t, *J* = 9.0 Hz, 1 H), 6.62 (s, 1 H). Anal. ($C_{14}H_9FN_2OS_2.1.25H_2O$) C, N, H; + 0.5.

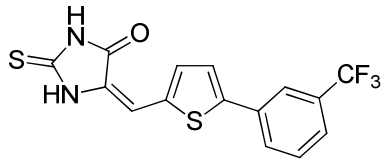


(*E,Z*)-5-((5-(4-Fluorophenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (48). Reaction of 5-(4-fluorophenyl)thiophene-2-carbaldehyde (**14**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **48** as an orange solid (87%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.27 (s, 1 H), 11.96 (s, 1 H), 7.74-7.81 (m, 3 H), 7.60 (d, *J* = 4.0 Hz, 1 H), 7.29 (t, *J* = 8.8 Hz, 2 H), 6.60 (s, 1 H). Anal. ($C_{14}H_9FN_2OS_2$) C, H, N.

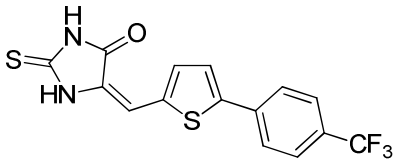


(*E,Z*)-5-((5-(3,4-Difluorophenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (49). Reaction of 5-(3,4-difluorophenyl)thiophene-2-carbaldehyde (**15**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **49** as an orange solid (75%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.33 (s, 1 H),

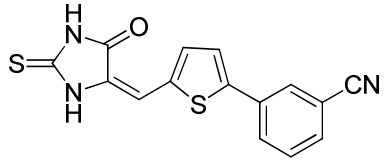
11.95 (s, 1 H), 7.81-7.87 (m, 2 H), 7.68 (d, *J* = 4.0 Hz, 1 H), 7.48-7.56 (m, 2 H), 6.61 (s, 1 H). Anal. ($C_{14}H_8F_2N_2OS_2.0.25H_2O$) C, H, N.



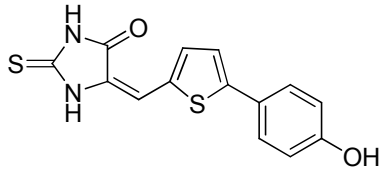
(*E,Z*)-2-thioxo-5-((5-(3-(trifluoromethyl)phenyl)thiophen-2-yl)methylene)imidazolidin-4-one (50). Reaction of 5-(3-(trifluoromethyl)phenyl)thiophene-2-carbaldehyde (**16**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **50** as a brown solid (85%), mp (AcOH) 308-312°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.30 (s, 1 H), 12.00 (s, 1 H), 7.98-8.01 (m, 2 H), 7.81-7.83 (m, 2 H), 7.67-7.72 (m, 2 H), 6.64 (s, 1 H). HRMS (ESI-TOF) calcd for $C_{15}H_8F_3N_2OS_2$ 353.0036 (M-H), found 353.0032.



(*E,Z*)-2-Thioxo-5-((5-(4-(trifluoromethyl)phenyl)thiophen-2-yl)methylene)imidazolidin-4-one (51). Reaction of 5-(4-(trifluoromethyl)phenyl)thiophene-2-carbaldehyde (**17**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **51** as an orange solid (55%), mp (AcOH) 291-294°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.36 (s, 1 H), 12.01 (s, 1 H), 7.92 (d, *J* = 8.2 Hz, 2 H), 7.86 (d, *J* = 3.9 Hz, 1 H), 7.79-7.81 (m, 3 H), 6.64 (s, 1 H). Anal. ($C_{15}H_9F_3N_2OS_2$) C, H, N.

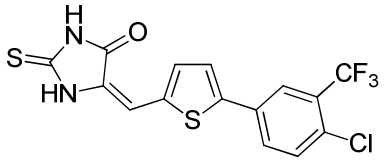


(*E,Z*)-3-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzonitrile (52). Reaction of 3-(5-formylthiophen-2-yl)benzonitrile (**18**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **52** as a brown solid (39%), mp (AcOH) 278-281°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.06 (br s, 2 H), 8.21 (t, *J* = 1.5 Hz, 1 H), 8.00 (ddd, *J* = 9.0, 1.8, 1.0 Hz, 1 H), 7.76-7.84 (m, 3 H), 7.65 (t, *J* = 7.9 Hz, 1 H), 6.60 (s, 1 H). Anal. ($C_{15}H_9N_3OS_2.0.75H_2O$) C, H. N; +0.5.

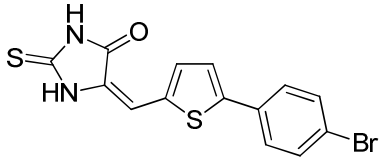


(*E,Z*)-5-((5-(4-Hydroxyphenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (53). Reaction of 5-(4-hydroxyphenyl)thiophene-2-carbaldehyde (**19**) with 2-

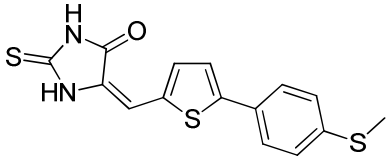
thioxoimidazolidin-4-one according to general procedure C gave **53** as a red-purple solid (88%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.32 (s, 1 H), 11.88 (s, 1 H), 9.78 (s, 1 H), 7.78 (d, *J* = 4.0 Hz, 1 H), 7.54 (d, *J* = 8.7 Hz, 2 H), 7.44 (d, *J* = 4.0 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 2 H), 6.61 (s, 1 H). Anal ($C_{14}H_{10}N_2O_4S_2$) C, H, N.



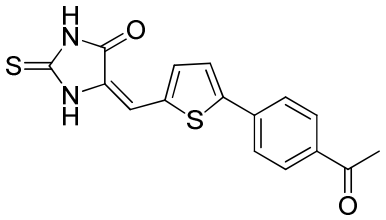
(*E,Z*)-5-((5-(4-Chloro-3-(trifluoromethyl)phenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (54). Reaction of 5-(4-chloro-3-(trifluoromethyl)phenyl)thiophene-2-carbaldehyde (**20**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **54** as a yellow solid (77%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.34 (s, 1 H), 12.00 (s, 1 H), 8.07 (d, *J* = 1.5 Hz, 1 H), 7.99 (dd, *J* = 1.9, 8.4 Hz, 1 H), 7.76-7.84 (m, 3 H), 6.64 (s, 1 H). Anal. ($C_{15}H_8ClF_3N_2OS_2.0.5H_2O$) C, H, N.



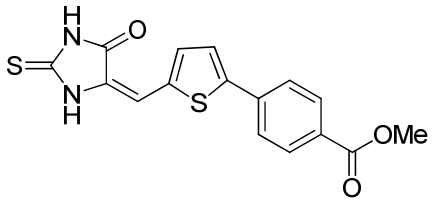
(*E,Z*)-5-((5-(4-Bromophenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (55). Reaction of 5-(4-bromophenyl)thiophene-2-carbaldehyde (**21**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **55** as a yellow solid (72%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.12 (s, 1 H), 11.99 (s, 1 H), 7.79 (m, 1 H), 7.62-7.68 (m, 5 H), 6.60 (s, 1 H). HRMS (ESI-TOF) calcd for $C_{14}H_8BrN_2OS_2$ 362.9267, 364.9246 (M-H), found 362.9256, 364.9230.



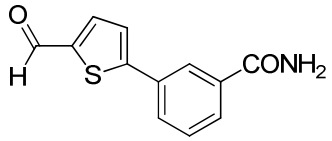
((*E,Z*)-5-((5-(4-(Methylthio)phenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (56). Reaction of 5-(4-(methylthio)phenyl)thiophene-2-carbaldehyde (**22**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **56** as a bright orange solid (80%), mp (AcOH) 289-293°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.34 (s, 1 H), 11.96 (s, 1 H), 7.79 (d, *J* = 3.9 Hz, 1 H), 7.65 (d, *J* = 8.5 Hz, 2 H), 7.60 (d, *J* = 4.0 Hz, 1 H), 7.32 (td, *J* = 2.3, 8.5 Hz, 2 H) , 6.61 (s, 1 H), 2.53 (s, 3 H). Anal. ($C_{15}H_{12}N_2OS_3$) C, H, N.



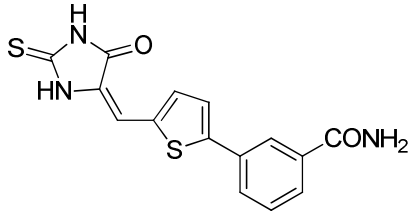
(*E*,*Z*)-5-((5-(4-Acetylphenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (57). Reaction of 5-(4-acetylphenyl)thiophene-2-carbaldehyde (**23**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **57** as a pale brown solid (79%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (br s, 1 H), 12.00 (br s, 1 H), 8.02 (d, *J* = 8.5 Hz, 2 H), 7.83-7.89 (m, 3 H), 7.81 (d, *J* = 4.0 Hz, 1 H), 6.65 (s, 1 H), 2.60 (s, 3 H). Anal. ($C_{16}H_{12}N_2O_2S_2.0.25H_2O$) C, H, N.



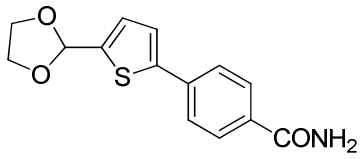
(*E*,*Z*)-Methyl 4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzoate (59). Reaction of methyl 4-(5-formylthiophen-2-yl)benzoate (**25**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **59** as a bright orange solid (75%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.37 (br s, 1 H), 12.00 (br s, 1 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 7.83-7.88 (m, 3 H), 7.79 (d, *J* = 4.0 Hz, 1 H), 6.65 (s, 1 H), 3.87 (s, 3 H). Anal. ($C_{16}H_{12}N_2O_3S_2$) C, H, N.



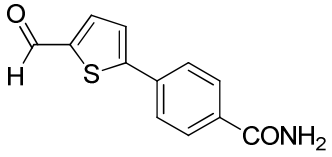
3-(5-Formylthiophen-2-yl)benzamide (26). Bromo-2-thiophenecarboxaldehyde was protected as the cyclic acetal **5** according to a literature procedure,[44] then reacted with 3-aminocarbonylphenylboronic acid according to general procedure A. This gave the intermediate 3-(5-(1,3-dioxolan-2-yl)thiophen-2-yl)benzamide (**7**) which was purified by flash column chromatography on silica gel (10% acetone/CH_2Cl_2 as eluant) and deprotected directly according to general procedure B to give **26** as a brown solid (73%, 2 steps). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.26 (s, 1 H), 8.13 (s, 1 H), 8.07 (d, *J* = 2.9 Hz, 1 H), 7.93 (t, *J* = 8.8 Hz, 2 H), 7.81 (d, *J* = 3.1 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.48 (s, 1 H). LRMS (APCI$^+$) calcd for $C_{12}H_9NO_2S$ 232 (MH^+), found 232.



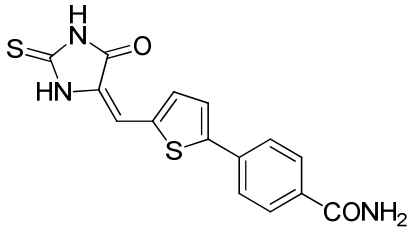
(*E,Z*)-3-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (60). Reaction of **26** with 2-thioxoimidazolidin-4-one according to general procedure C gave **60** as a brown solid (91%), mp (AcOH) > 295˚C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.34 (s, 1 H), 11.99 (s, 1 H), 8.19 (s, 1 H), 8.09 (s, 1 H), 7.77-7.86 (m, 3 H), 7.71 (d, *J* = 3.8 Hz, 1 H), 7.53 (t, *J* = 7.1 Hz, 1 H), 7.46 (s, 1 H), 6.64 (s, 1 H). Anal. ($C_{15}H_1N_3O_2S_2.0.5H_2O$) C, H. N; +0.5.



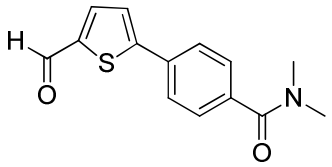
4-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)benzamide (8). Bromo-2-thiophenecarboxaldehyde was protected as the cyclic acetal **5** according to a literature procedure,[44] then reacted with 4-aminocarbonylphenylboronic acid according to general procedure A. Purification by flash column chromatography on silica gel (10% acetone/CH_2Cl_2 as eluant) gave **8** as an off-white solid (64%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.97 (br s, 1 H), 7.91 (d, *J* = 8.5 Hz, 2 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.52 (d, *J* = 3.7 Hz, 1 H), 7.34 (br s, 1 H), 7.24 (d, *J* = 3.7 Hz, 1 H), 6.05 (s, 1 H), 4.02-4.10 (m, 2 H), 3.92-4.00 (m, 2 H). LRMS (APCI$^+$) calcd for $C_{14}H_{14}NO_3S$ 276 (MH^+), found 276.



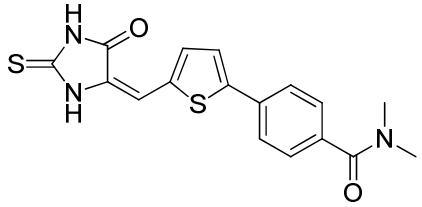
4-(5-Formylthiophen-2-yl)benzamide (27). Deprotection of **8** according to general procedure B gave **27** as a white solid (90%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.07 (d, *J* = 4.0 Hz, 1 H), 8.05 (br s, 1 H), 7.97 (d, *J* = 8.6 Hz, 2 H), 7.89 (d, *J* = 8.6 Hz, 2 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 7.43 (br s, 1 H). LRMS (APCI$^-$) calcd for $C_{12}H_9NO_2S$ 231 (M), found 231.



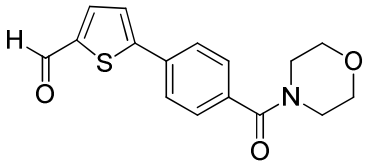
(*E,Z*)-4-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (61). Reaction of **27** with 2-thioxoimidazolidin-4-one according to general procedure C gave **61** as an orange solid (92%), mp (AcOH) >300^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (br s, 1 H), 11.97 (br s, 1 H), 8.00 (br s, 1 H), 7.94 (d, *J* = 8.5 Hz, 2 H), 7.85 (br s, 1 H), 7.79 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 4.0 Hz, 1 H), 7.37 (br s, 1 H), 6.64 (s, 1 H). LRMS (APCI$^+$) calcd for $C_{15}H_{12}N_3O_2S_2$ 330 (MH^+), found 330. Anal. ($C_{15}H_{11}N_3O_2S_2$) C, H, N.



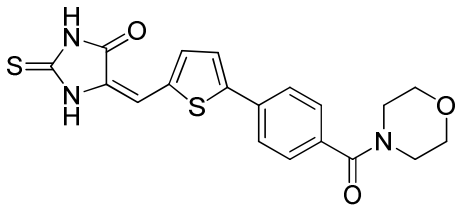
4-(5-Formylthiophen-2-yl)-*N,N*-dimethylbenzamide (35). 4-(5-Formylthiophen-2-yl)benzoic acid (**28**) was reacted with PFP-TFA, followed by 40% dimethylamine in water according to general procedure D, to give **35** as a pale yellow solid (100%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.93 (s, 1 H), 8.06 (d, *J* = 4.0 Hz, 1 H), 7.86 (d, *J* = 8.5 Hz, 2 H), 7.81 (d, *J* = 4.0 Hz, 1 H), 7.51 (d, *J* = 8.5 Hz, 2 H), 2.51 (s, 6 H). LRMS (APCI$^+$) calcd for $C_{14}H_{14}NO_2S$ 260 (MH^+), found 260.



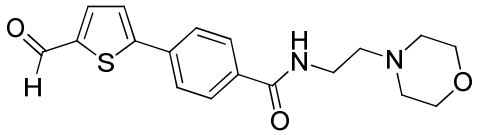
(*E,Z*)-*N,N*-Dimethyl-4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (68). Reaction of **35** with 2-thioxoimidazolidin-4-one according to general procedure C gave **68** as a brown-orange solid (62%), mp (AcOH) >295^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (br s, 1 H), 11.97 (br s, 1 H), 7.85 (d, *J* = 3.8 Hz, 1 H), 7.77 (d, *J* = 8.4 Hz, 2 H), 7.71 (d, *J* = 4.0 Hz, 1 H), 7.48 (d, *J* = 2 H), 6.64 (s, 1 H), 2.97 (s, 6 H). LRMS (APCI$^-$) calcd for $C_{17}H_{14}N_3O_2S_2$ 356 (M-H), found 356. Anal. ($C_{17}H_{15}N_3O_2S_2$) C, H, N.



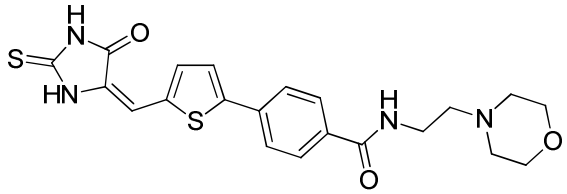
5-(4-(Morpholine-4-carbonyl)phenyl)thiophene-2-carbaldehyde (36). 4-(5-Formylthiophen-2-yl)benzoic acid (**28**) was reacted with PFP-TFA, followed by morpholine according to general procedure D. Purification by flash column chromatography on silica gel (50% EtOAc/hexanes) gave **36** as a yellow-orange solid (68%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.93 (s, 1 H), 8.07 (d, *J* = 4.0 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 4.0 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 3.55-3.67 (v br s, 8 H). LRMS (APCI$^+$) calcd for $C_{16}H_{16}NO_3S$ 302 (MH^+), found 302.



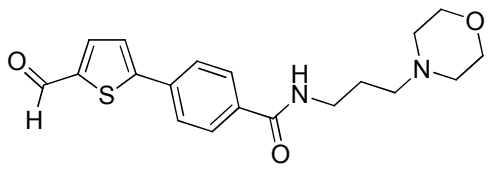
(*E,Z*)-5-((5-(4-(Morpholine-4-carbonyl)phenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (69). Reaction of **36** with 2-thioxoimidazolidin-4-one according to general procedure C gave **69** as an orange solid (56%), mp (AcOH) 278-281°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (br s, 1 H), 11.97 (br s, 1 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 2 H), 7.72 (d, *J* = 4.0 Hz, 1 H), 7.49 (d, *J* = 8.2 Hz, 2 H), 6.64 (s, 1 H), 3.40-3.61 (v br s, 8 H). LRMS (APCI$^-$) calcd for $C_{19}H_{16}N_3O_3S_2$ 398 (M-H), found 398. Anal. ($C_{19}H_{17}N_3O_3S_2$) C, H, N.



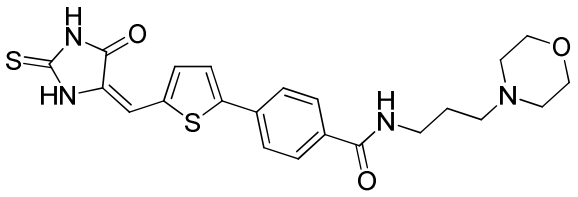
4-(5-Formylthiophen-2-yl)-*N*-(2-morpholinoethyl)benzamide (37). 4-(5-Formylthiophen-2-yl)benzoic acid (**28**) was reacted with PFP-TFA, followed by 4-(2-aminoethyl)morpholine according to general procedure D, to give **37** as a pale yellow solid (100%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.49 (t, *J* = 5.6 Hz, 1 H), 8.07 (d, *J* = 4.0 Hz, 1 H), 7.93 (d, *J* = 8.8 Hz, 2 H), 7.90 (d, *J* = 8.8 Hz, 2 H), 7.84 (d, *J* = 4.0 Hz, 1 H), 3.51-3.66 (m, 4 H), 3.41 (dd, *J* = 12.9, 6.7 Hz, 4 H), 2.45 (m, 4 H). LRMS (APCI$^+$) calcd for $C_{18}H_{21}N_2O_3S$ (MH^+) 345, found 345.



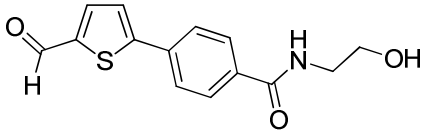
(*E,Z*)-*N*-(2-Morpholinoethyl)-4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (70). Reaction of **37** with 2-thioxoimidazolidin-4-one according to general procedure C gave **70** as an orange powder (38%), mp (AcOH) 248-252°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.32 (s, 1 H), 11.94 (s, 1 H), 8.45 (t, *J* = 5.5 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 2 H), 7.84 (d, *J* = 3.9 Hz, 1 H), 7.80 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 4.0 Hz, 1 H), 6.63 (s, 1 H), 3.51-3.67 (m, 4 H), 3.41 (dd, *J* = 12.8, 6.6 Hz, 4 H), 2.45 (m 4 H). Anal. ($C_{21}H_{22}N_4O_3S_2 \cdot 1.5$ H_2O) C, H, N.



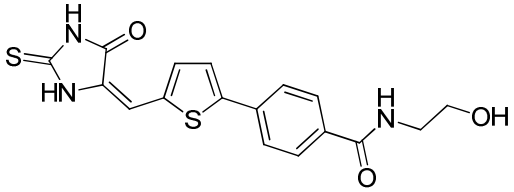
4-(5-Formylthiophen-2-yl)-*N*-(3-morpholinopropyl)benzamide (38). 4-(5-Formylthiophen-2-yl)benzoic acid (**28**) was reacted with PFP-TFA, followed by 4-(3-aminopropyl)morpholine according to general procedure D, to give **38** as a pale yellow solid (100%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.56 (t, *J* = 5.6 Hz, 1 H), 8.07 (d, *J* = 4.0 Hz, 1 H), 7.93 (d, *J* = 8.8 Hz, 2 H), 7.90 (d, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 3.62-3.54 (m, 4 H), 3.31 (dd, *J* = 12.7, 6.9 Hz, 4 H), 2.44-2.30 (m, 4 H), 1.71 (m, 2 H). LRMS (APCI$^+$) calcd for $C_{19}H_{23}N_2O_3S$ 359 (MH^+), found 359.



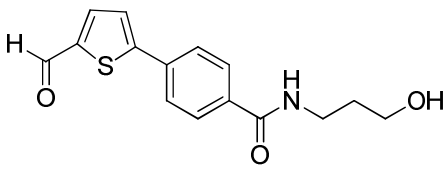
(*E,Z*)-*N*-(3-Morpholinopropyl)-4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (71). Reaction of **38** with 2-thioxoimidazolidin-4-one according to general procedure C gave **71** as an orange powder (9%), mp (AcOH) 287°C dec. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 12.18 (m, 2 H), 8.52 (t, *J* = 5.5 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 2 H), 7.80 (m, 3 H), 7.74 (d, *J* = 4.0 Hz, 1 H), 6.83 (s, 0.2 Hz), 6.62 (s, 0.8 Hz), 3.54-3.61 (m, 4 H), 3.32 (m, 2 H), 2.35 (m, 6 H), 1.70 (m, 2 H). HRMS (ESI-TOF) calcd for $C_{22}H_{25}N_4O_3S_2$ 457.1363 (MH^+), found 457.1369.



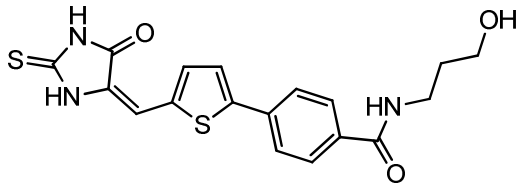
4-(5-Formylthiophen-2-yl)-*N*-(2-hydroxyethyl)benzamide (39). 4-(5-Formylthiophen-2-yl)benzoic acid (**28**) was reacted with PFP-TFA, followed by ethanolamine according to general procedure D, giving **39** as a pale yellow solid (40%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.52 (t, *J* = 5.50 Hz, 1 H), 8.07 (d, *J* = 4.0 Hz, 1 H), 7.96 (d, *J* = 8.7 Hz, 2 H), 7.90 (d, *J* = 8.7 Hz, 2 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 4.71 (s, 1 H), 3.53 (t, *J* = 6.2 Hz, 2 H), 3.35 (dd, *J* = 12.0, 6.1 Hz, 2 H). LRMS ($APCI^+$) calcd for $C_{14}H_{14}NO_3S$ 276 (MH^+), found 276.



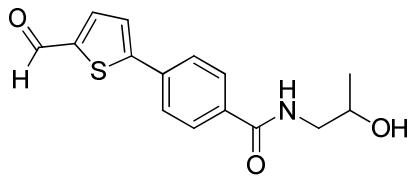
(*E,Z*)-*N*-(2-Hydroxyethyl)-4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (72). Reaction of **39** with 2-thioxoimidazolidin-4-one according to general procedure C gave **72** as an orange powder (61%), mp (AcOH) 281-284°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (s, 1 H), 11.97 (s, 1 H), 8.47 (t, *J* = 5.6 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 2 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 7.80 (d, *J* = 8.5 Hz, 2 H), 7.75 (d, *J* = 4.0 Hz, 1 H), 6.65 (s, 1 H), 4.70 (t, *J* = 5.6 Hz, 1 H), 3.53 (q, *J* = 6.0 Hz, 2 H), 3.35 (q, *J* = 6.0 Hz, 2 H). HRMS (ESI-TOF) calcd for $C_{17}H_{14}N_3O_3S_2$ 372.0477 (M-H), found 372.0465. Anal. ($C_{17}H_{15}N_3O_3S_2$) C, H, N.



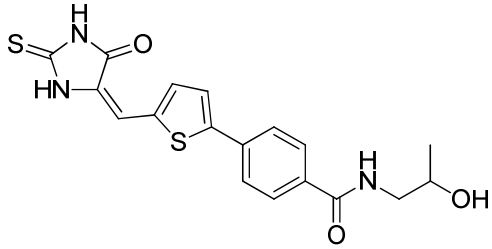
4-(5-Formylthiophen-2-yl)-*N*-(3-hydroxypropyl)benzamide (40). 4-(5-Formylthiophen-2-yl)benzoic acid (**28**) was reacted with PFP-TFA, followed by 3-aminopropanol according to general procedure D, to give **40** as a pale yellow solid (72%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.49 (t, *J* = 5.6 Hz, 1 H), 8.07 (d, *J* = 4.0 Hz, 1 H), 7.93 (d, *J* = 8.8 Hz, 2 H), 7.90 (d, *J* = 8.8 Hz, 2 H), 7.84 (d, *J* = 4.0 Hz, 1 H), 3.66-3.51 (m, 3 H), 3.41 (dd, *J* = 12.9, 6.7 Hz, 2 H), 2.45 (m, 2 H). LRMS (APCI$^+$) calcd for $C_{18}H_{21}N_2O_3S$ 345 (M+H), found 345.



(*E,Z*)-*N*-(3-Hydroxypropyl)-4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (73). Reaction of **40** with 2-thioxoimidazolidin-4-one according to general procedure C gave **73** as an orange powder (55%), mp (AcOH) 282-285^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.39 (s, 0.5 H), 12.28 (s, 0.5 H), 12.10 (s, 0.5 H), 11.97 (s, 0.5 H), 8.51-8.43 (m, 1 H), 7.95-7.88 (m, 2 H), 7.86 (d, *J* = 4.1 Hz, 1 H), 7.83-7.73 (m, 2 H), 7.67 (d, *J* = 4.0 Hz, 1 H), 6.83 (s, 0.5 H), 6.65 (s, 0.5 H), 4.45 (t, *J* = 4.2 Hz, 1 H), 3.48 (dd, *J* = 9.9, 5.8 Hz, 2 H), 3.33 (dd, *J* = 13.1, 6.8 Hz, 2 H), 1.69 (m, 2 H). Anal. ($C_{19}H_{17}N_3O_3S_2$) C, H, N.

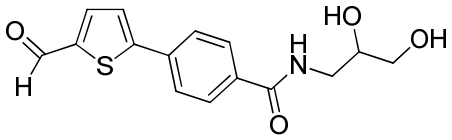


4-(5-Formylthiophen-2-yl)-*N*-(2-hydroxypropyl)benzamide (41). 4-(5-Formylthiophen-2-yl)benzoic acid (**28**) was reacted with PFP-TFA, followed by 1-aminopropan-2-ol according to general procedure D, to give **41** as a pale yellow solid (58%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.54 (t, *J* = 5.7 Hz, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 7.96 (d, *J* = 8.6 Hz, 2 H), 7.91 (d, *J* = 8.6 Hz, 2 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 3.84-3.75 (m, 1 H), 3.22 (ddd, *J* = 9.9, 6.8, 4.0 Hz, 2 H), 1.07 (d, *J* = 8.0 Hz, 3 H); OH too broad to integrate. LRMS (APCI$^+$) calcd for $C_{15}H_{16}NO_3S$ 290 (MH^+), found 290.

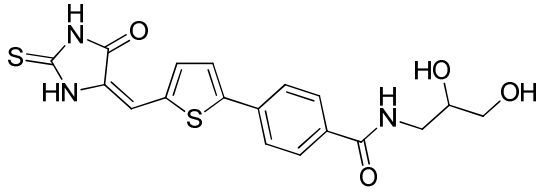


(*E,Z*)-*N*-(2-Hydroxypropyl)-4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (74). Reaction of **41** with 2-thioxoimidazolidin-4-one according to general procedure C gave **74** as an orange powder (26%), mp (AcOH) 277^{o}C dec. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*-

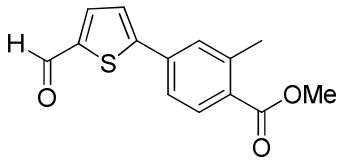
and *Z*- isomers separately. δ 12.44 (s, 0.5 H), 12.33 (s, 0.5 H), 12.16 (s, 0.5 H), 12.03 (s, 0.5 H), 8.49 (dt, *J* = 5.9, 5.7, 3.4 Hz, 1 H), 7.95-7.90 (m, 2 H), 7.87 (d, *J* = 4.0 Hz, 0.5 H), 7.83-7.75 (m, 3 H), 7.68 (d, *J* = 4.0 Hz, 0.5 H), 6.84 (s, 0.5 H), 6.66 (s, 0.5 H), 4.88-4.65 (m, 1 H), 3.97-3.61 (m, 1 H), 3.21 (dd, *J* = 9.8, 6.0 Hz, 2 H), 1.07 (d, J = 8.0 Hz, 3 H). Anal. ($C_{18}H_{17}N_3O_3S_2$) C, H, N.



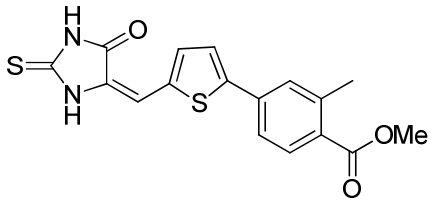
***N*-(2,3-Dihydroxypropyl)-4-(5-formylthiophen-2-yl)benzamide (42).** 4-(5-Formylthiophen-2-yl)benzoic acid (**28**) was reacted with PFP-TFA, followed by 3-aminopropane-1,2-diol according to general procedure D, to give **42** as a pale yellow solid (45%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.47 (t, *J* = 5.5 Hz, 1 H), 8.07 (d, *J* = 4.0 Hz, 1 H), 7.96 (d, *J* = 8.5 Hz, 2 H), 7.90 (d, *J* = 8.5 Hz, 2 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 4.78 (d, *J* = 5.0 Hz, 1 H), 4.54 (t, *J* = 5.8 Hz, 1 H), 3.71-3.60 (m, 1 H), 3.48-3.32 (m, 3 H), 3.23 (m, 1 H). LRMS (APCI$^+$) calcd for $C_{15}H_{16}NO_4S$ 306 (MH^+), found 306.



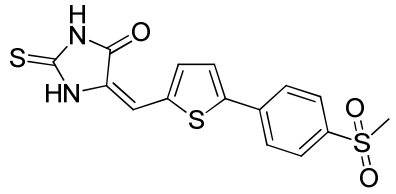
(*E,Z*)-*N*-(2,3-Dihydroxypropyl)-4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzamide (75). Reaction of **42** with 2-thioxoimidazolidin-4-one according to general procedure C gave **75** as an orange powder (32%), mp (AcOH) 287°C dec. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (s, 1 H), 11.98 (s, 1 H), 8.43 (t, *J* = 5.7 Hz, 1 H), 7.93 (d, *J* = 8.6 Hz, 2 H), 7.85 (d, *J* = 4.0 Hz, 2 H), 7.80 (d, *J* = 8.6 Hz, 2 H), 7.76 (d, *J* = 4.0 Hz, 2 H), 6.65 (s, 1 H), 4.78 (d, *J* = 5.0 Hz, 1 H), 4.54 (t, *J* = 5.8 Hz, 1 H), 3.66 (tt, *J* = 10.5, 5.3 Hz, 1 H), 3.36 (t, *J* = 5.6 Hz, 1 H), 3.21 (m, 1 H). HRMS (ESI-TOF) calcd for $C_{18}H_{18}N_3O_4S_2$ 404.0733 (MH^+), found 404.0713. Anal. ($C_{18}H_{17}N_3O_4S_2$) C, H, N.



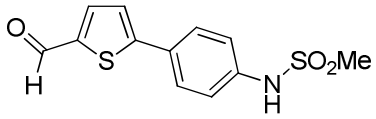
Methyl 4-(5-formylthiophen-2-yl)-2-methylbenzoate (29). Methyl 4-bromo-2-methylbenzoate and 5-formyl-2-thiopheneboronic acid were reacted according to general procedure A, followed by purification by flash column chromatography on silica gel (10% EtOAc/hexanes as eluant), to give **29** as a pale yellow solid (19%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.07 (d, *J* = 4.0 Hz, 1 H), 7.91 (d, *J* = 8.2 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.78-7.81 (m, 1 H), 7.74 (dd, *J* = 8.2, 1.7 Hz, 1 H), 3.85 (s, 3 H), 2.59 (s, 3 H). LRMS (APCI$^+$) calcd for $C_{14}H_{13}O_3S$ 261 (MH^+), found 261.



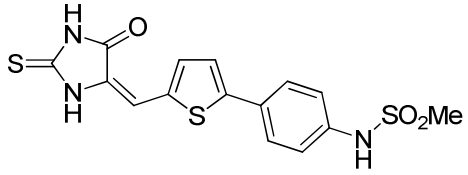
(*E,Z*)-Methyl 2-methyl-4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)benzoate (62). Reaction of **29** with 2-thioxoimidazolidin-4-one according to general procedure C gave **62** as an orange solid (57%), mp (AcOH) 289°C (dec.). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.37 (br s, 1 H), 11.99 (br s, 1 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.84 (d, *J* = 3.8 Hz, 1 H), 7.76 (d, *J* = 4.0 Hz, 1 H), 7.68 (br s, 1 H), 7.64 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.65 (s, 1 H), 3.84 (s, 3 H), 2.58 (s, 3 H). Anal. ($C_{17}H_{14}N_2O_3S_2$) C, H, N.



(*E,Z*)-5-((5-(4-(Methylsulfonyl)phenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (63). Reaction of 5-(4-(Methylsulfonyl)phenyl)thiophene-2-carbaldehyde (**30**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **63** as a brown solid (73%), mp (AcOH) 301-304°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.31 (s, 1 H), 11.97 (s, 1 H), 7.97 (s, 4 H), 7.75-7.85 (m, 2 H), 6.64 (s, 1 H), 3.24 (s, 3 H). HRMS (FAB^+) calcd for $C_{15}H_{13}N_2O_3S_3$ 365.0088 (MH^+), found 365.0089.

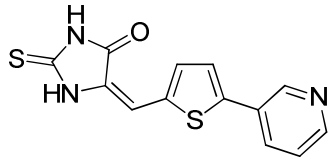


***N*-(4-(5-Formylthiophen-2-yl)phenyl)methanesulfonamide (31).** Reaction of 5-bromothiophen-2-carboxaldehyde and 4-(methylsulfonamido)phenylboronic acid according to general method A gave **31** as a brown solid (11%). [400 MHz, $(CD_3)_2SO$] δ 10.07 (s, 1 H), 9.89 (s, 1 H), 8.01 (d, *J* = 4.0 Hz, 1 H), 7.78 (d, *J* = 8.9 Hz, 2 H), 7.65 (d, *J* = 4.0 Hz, 1 H), 7.27 (d, *J* = 8.7 Hz, 2 H), 3.04 (s, 3 H). LRMS ($APCI^+$) calcd for $C_{12}H_{12}NO_3S_2$ 282 (MH^+), found 282.

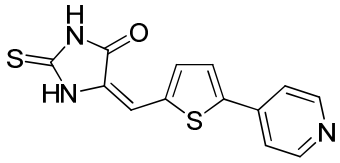


(*E,Z*)-*N*-(4-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)phenyl)methanesulfonamide (64). Reaction of **31** with 2-thioxoimidazolidin-4-one according to general procedure C gave **64** as a brown solid (56%), mp (AcOH)

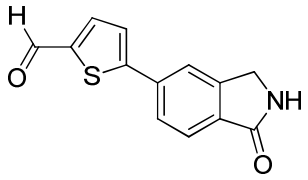
>295°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.31 (s, 1 H), 11.94 (s, 1 H), 9.93 (s, 1 H), 7.80 (d, *J* = 3.8 Hz, 1 H), 7.66-7.70 (m, 2 H), 7.56 (d, *J* = 4.0 Hz, 1 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 6.61 (s, 1 H), 3.04 (s, 3 H). Anal. ($C_{15}H_{13}N_3O_3S_3$) C, H, N.



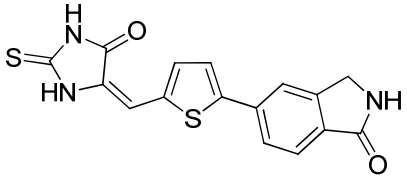
(*E*,*Z*)-5-((5-(Pyridin-3-yl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (65). Reaction of 5-(pyridin-3-yl)thiophene-2-carbaldehyde (**32**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **65** as an orange solid (66%), mp (AcOH) >295°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.34 (s, 1 H), 11.98 (s, 1 H), 8.95 (d, *J* = 1.8 Hz, 1 H), 8.54 (dd, *J* = 1.5, 4.8 Hz, 1 H), 8.07-8.10 (m, 1 H), 7.86 (d, *J* = 3.9 Hz, 1 H), 7.76 (d, *J* = 3.9 Hz, 1 H), 7.46-7.49 (m, 1 H), 6.64 (s, 1 H). Anal. ($C_{13}H_9N_3OS_2.0.25H_2O$) C, H, N.



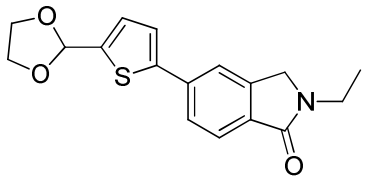
(*E*,*Z*)-5-((5-(Pyridin-4-yl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (66). Reaction of 5-(pyridin-4-yl)thiophene-2-carbaldehyde (**33**) with 2-thioxoimidazolidin-4-one according to general procedure C gave **66** as a brown solid (63%), mp (AcOH) >295°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.45 (s, 1 H), 12.05 (s, 1 H), 8.64 (d, *J* = 4.9 Hz, 2 H), 7.97 (d, *J* = 3.9 Hz, 1 H), 7.90 (d, *J* = 3.9 Hz, 1 H), 7.77 (d, *J* = 5.9 Hz, 2 H), 6.66 (s, 1 H). Anal. ($C_{13}H_9N_3OS_2.1.5H_2O$) C, H, N.



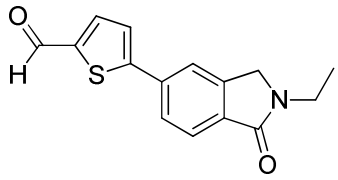
5-(1-Oxoisoindolin-5-yl)thiophene-2-carbaldehyde (94). Deprotection of **82** was carried out according to general procedure B to give **94** as a pale yellow solid (100%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.64 (br s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.02 (br s, 1 H), 7.92 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 3.54 (s, 2 H). LRMS (APCI$^+$) calcd for $C_{13}H_{10}NO_2S$ 244 (MH^+), found 244.



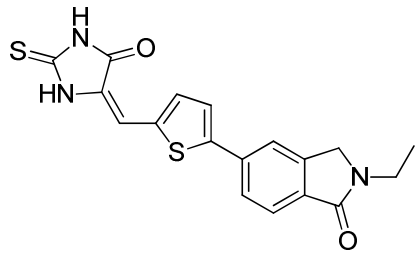
(*E,Z*)-5-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (118). Reaction of **94** with 2-thioxoimidazolidin-4-one according to general procedure C gave **118** as an orange solid (57%), mp (DMSO/H_2O) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (s, 1 H), 11.98 (s, 1 H), 8.57 (s, 1 H), 7.91 (s, 1 H), 7.86 (d, *J* = 3.9 Hz, 1 H), 7.83 (dd, *J* = 1.4, 7.9 Hz, 1 H), 7.76 (d, *J* = 3.9 Hz, 1 H), 7.71 (d, *J* = 7.9 Hz, 1 H), 6.65 (s, 1 H), 4.43 (s, 2 H). Anal. ($C_{16}H_{11}N_3O_2S_2.1.5H_2O$) C, H, N; + 0.5.



5-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-2-ethylisoindolin-1-one (88). Alkylation of **82** with NaH and ethyl iodide according to general procedure F gave **88** as a pale yellow solid (58%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.87 (d, *J* = 0.8 Hz, 1 H), 7.76 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.53 (d, *J* = 3.7 Hz, 1 H), 7.26 (d, *J* = 3.7 Hz, 1 H), 6.07 (s, 1 H), 4.51 (s, 2 H), 4.02-4.09 (m, 2 H), 3.94-4.01 (m, 2 H), 3.55 (q, *J* = 7.3 Hz, 2 H), 1.18 (t, *J* = 7.3 Hz, 3 H). LRMS (APCI$^+$) calcd for $C_{17}H_{18}NO_3S$ 316 (MH^+), found 316.

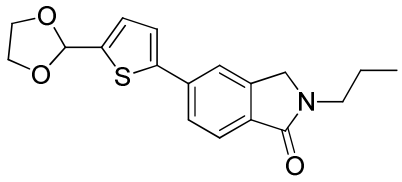


5-(2-Ethyl-1-oxoisoindolin-5-yl)thiophene-2-carbaldehyde (96). Deprotection of **88** according to general procedure B gave **96** as a pale yellow-orange solid (78%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.06 (d, *J* = 4.0 Hz, 1 H), 8.04 (d, *J* = 0.8 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 4.55 (s, 2 H), 3.56 (q, *J* = 7.3 Hz, 2 H), 1.19 (t, *J* = 7.3 Hz, 3 H). LRMS (APCI$^+$) calcd for $C_{15}H_{14}NO_2S$ 272 (MH^+), found 272.

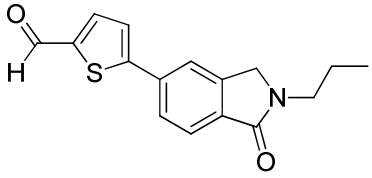


(*E,Z*)-2-Ethyl-5-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (120). Reaction of **96** with 2-thioxoimidazolidin-4-one according to general procedure C gave **120** as an orange solid (64%), mp (AcOH) 267-270°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.98-12.37 (m, 2 H), 7.93 (d, *J* = 0.7 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 0.85 H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.75-7.78 (m, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 7.68 (d, *J* = 4.0 Hz, 0.15 H),

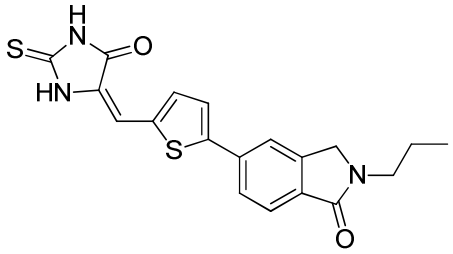
6.84 (s, 0.15 H), 6.65 (s, 0.85 H), 4.53 (s, 2 H), 3.56 (q, *J* = 7.2 Hz, 2 H), 1.19 (t, *J* = 7.2 Hz, 3 H). LRMS (APCI$^-$) calcd for $C_{18}H_{14}N_3O_2S_2$ 368 (M-H), found 368.



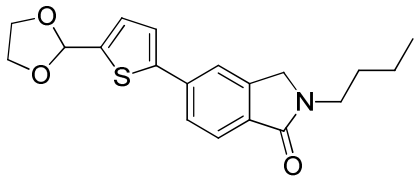
5-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-2-propylisoindolin-1-one (89). Alkylation of **82** with NaH and propyl iodide according to general procedure F gave **89** as a pale yellow solid (45%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.87 (d, *J* = 0.7 Hz, 1 H), 7.76 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.68 (d, *J* = 8.2 Hz, 1 H), 7.53 (d, *J* = 3.7 Hz, 1 H), 7.26 (d, *J* = 3.8 Hz, 1 H), 6.07 (s, 1 H), 4.50 (s, 2 H), 4.02-4.09 (m, 2 H), 3.94-4.01 (m, 2 H), 3.48 (t, *J* = 7.2 Hz, 2 H), 1.62 (pentet, *J* = 7.3 Hz, 2 H), 0.88 (t, *J* = 7.4 Hz, 3 H). LRMS (APCI$^+$) calcd for $C_{18}H_{20}NO_3S$ 330 (MH^+), found 330.



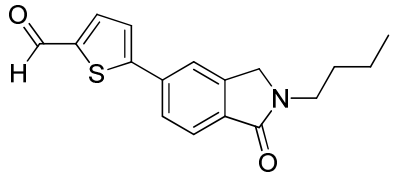
5-(1-Oxo-2-propylisoindolin-5-yl)thiophene-2-carbaldehyde (97). Deprotection of **89** according to general procedure B gave **97** as a pale yellow solid (65%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.03 (d, *J* = 0.8 Hz, 1 H), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.86 (d, *J* = 3.9 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 4.54 (s, 2 H), 3.50 (t, *J* = 7.2 Hz, 2 H), 1.63 (pentet, *J* = 7.3 Hz, 2 H), 0.88 (t, *J* = 7.4 Hz, 3 H). LRMS (APCI$^+$) calcd for $C_{16}H_{16}NO_2S$ 286 (MH^+), found 286.



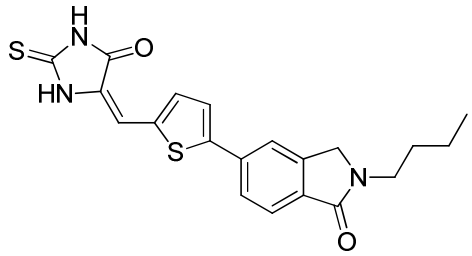
(*E,Z*)-5-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)-2-propylisoindolin-1-one (121). Reaction of **97** with 2-thioxoimidazolidin-4-one according to general procedure C gave **121** as an orange solid (64%), mp (AcOH) 275-278^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.98-12.38 (m, 2 H), 7.92 (br s, 1 H), 7.67-7.87 (m, 4 H), 6.82 (s, 0.4 H), 6.65 (s, 0.6 H), 4.52 (s, 2 H), 3.48 (t, *J* = 7.2 Hz, 2 H), 1.63 (pentet, *J* = 7.3 Hz, 2 H), 0.89 (t, *J* = 7.4 Hz, 3 H). LRMS (APCI$^-$) calcd for $C_{19}H_{16}N_3O_2S_2$ 382 (M-H), found 382. HRMS (ESI$^-$) calcd for $C_{19}H_{16}N_3O_2S_2$ 382.0689 (M-H), found 382.0697.



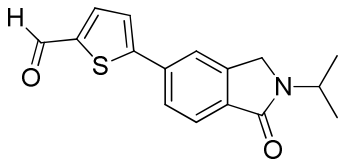
5-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-2-butylisoindolin-1-one (90). Alkylation of **82** with NaH and butyl iodide according to general procedure F (except in this case the solution of anion was added to a solution of the butyl iodide in DMF) gave **90** as a pale yellow solid (49%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.86 (br d, *J* = 0.7 Hz, 1 H), 7.77 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.53 (d, *J* = 3.9 Hz, 1 H), 7.25 (d, *J* = 3.9 Hz, 1 H), 6.07 (s, 1 H), 4.50 (s, 2 H), 4.02-4.09 (m, 2 H), 3.94-4.01 (m, 2 H), 3.52 (t, *J* = 7.1 Hz, 2 H), 1.59 (pentet, *J* = 7.3 Hz, 2 H), 1.30 (sextet, *J* = 7.4 Hz, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H). LRMS (APCI$^+$) calcd for $C_{19}H_{22}NO_3S$ 344 (MH^+), found 344.



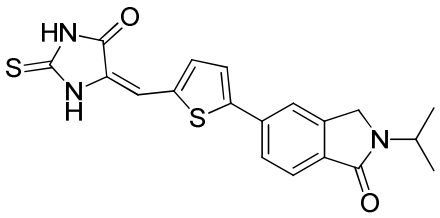
5-(2-Butyl-1-oxoisoindolin-5-yl)thiophene-2-carbaldehyde (98). Deprotection of **90** according to general procedure B gave **98** as a yellow solid (88%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.03 (br d, *J* = 0.7 Hz, 1 H), 7.92 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.86 (d, *J* = 3.9 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 4.53 (s, 2 H), 3.53 (t, *J* = 7.1 Hz, 2 H), 1.60 (pentet, *J* = 7.3 Hz, 2 H), 1.30 (sextet, *J* = 7.4 Hz, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H). LRMS (APCI$^+$) calcd for $C_{17}H_{18}NO_2S$ 300 (MH^+), found 300.



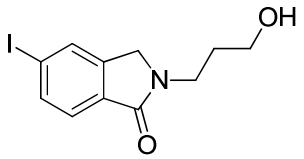
(*E*,*Z*)-2-Butyl-5-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (122). Reaction of **98** with 2-thioxoimidazolidin-4-one according to general procedure C gave **122** as an orange solid (67%), mp (AcOH) 278-281^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.91-12.39 (br m, 2 H), 7.92 (br d, *J* = 0.7 Hz, 1 H), 7.87 (d, *J* = 4.1 Hz, 0.9 H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.77 (d, *J* = 4.0 Hz, 1 H), 7.71 (d, *J* = 7.9 Hz, 1 H), 7.68 (d, *J* = 4.0 Hz, 0.1 H), 6.85 (s, 0.1 H), 6.65 (s, 0.9 H), 4.52 (s, 2 H), 3.53 (t, *J* = 7.1 Hz, 2 H), 1.60 (pentet, *J* = 7.3 Hz, 2 H), 1.30 (sextet, *J* = 7.40 Hz, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H). LRMS (APCI$^-$) calcd for $C_{20}H_{18}N_3O_2S_2$ 396 (M-H), found 396.



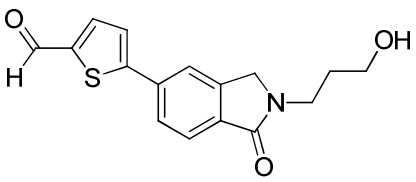
5-(2-Isopropyl-1-oxoisoindolin-5-yl)thiophene-2-carbaldehyde (99). 5-Bromo-2-isopropylisoindolin-1-one (prepared according to a literature procedure[47]) was reacted with 5-formylthiophen-2-ylboronic acid according to general procedure A. Purification by flash column chromatography on silica gel (50% EtOAc/hexanes) gave **99** as a pale yellow solid (44%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.03 (d, *J* = 0.8 Hz, 1 H), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.85 (d, *J* = 4.0 Hz, 1 H), 7.74 (d, *J* = 7.6 Hz, 1 H), 4.50 (s, 2 H), 4.48-4.39 (m, 1 H), 1.26 (s, 3 H), 1.24 (s, 3 H). LRMS (APCI$^+$) calcd for $C_{16}H_{16}NO_2S$ 286 (MH^+), found 286.



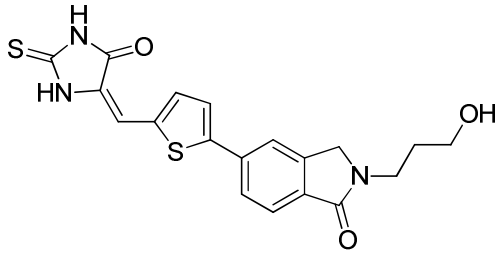
(*E*,*Z*)-2-Isopropyl-5-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (123). Reaction of **99** with 2-thioxoimidazolidin-4-one according to general procedure C gave **123** as a red powder (23%), mp (AcOH) 285-290^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 12.39 (s, 1 H), 11.99 (s, 1 H), 7.92 (d, *J* = 0.70 Hz, 1 H), 7.87 (d, *J* = 4.0 Hz, 1 H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.76 (d, *J* = 4.0 Hz, 1 H), 7.71 (d, *J* = 7.9 Hz, 1 H), 6.65 (s, 1 H), 4.48 (s, 2 H), 4.43 (td, *J* = 13.5, 6.8 Hz, 1 H), 1.26 (s, 3 H), 1.24 (s, 3 H). HRMS (ESI-TOF) calcd for $C_{19}H_{18}N_3O_2S_2$ 384.0835 (MH^+), found 384.0821.



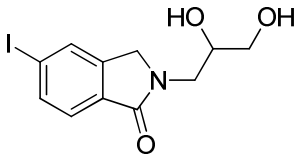
2-(3-Hydroxypropyl)-5-iodoisoindolin-1-one (79). Reaction of methyl 4-iodo-2-methylbenzoate[45] **76** and 3-amino-1-propanol according to general procedure G gave **79** as a crystalline white solid (65%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 8.02 (d, *J* = 0.7 Hz, 1 H), 7.84 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 4.48 (t, *J* = 5.1 Hz, 1 H), 4.45 (s, 2 H), 3.55 (t, *J* = 7.2 Hz, 2 H), 3.43 (q, *J* = 5.9 Hz, 2 H), 1.70-1.77 (m, 2 H). LRMS (APCI$^+$) calcd for $C_{11}H_{13}INO_2$ 318 (MH^+), found 318.



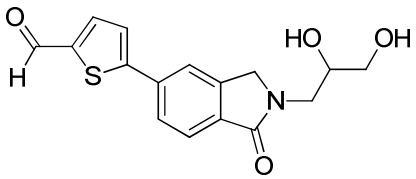
5-(2-(3-Hydroxypropyl)-1-oxoisoindolin-5-yl)thiophene-2-carbaldehyde (101). 2-Thiophenecarboxaldehyde was protected as the dimethyl acetal based on a literature procedure[46] then reacted with **79** according to general procedure E. Deprotection of **84** directly to the aldehyde according to general procedure H gave **101** as a yellow solid (50%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.03 (d, *J* = 0.8 Hz, 1 H), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 4.55 (s, 2 H), 4.50 (t, *J* = 5.2 Hz, 1 H), 3.58 (q, *J* = 7.5 Hz, 2 H), 3.46 (q, *J* = 5.8 Hz, 2 H), 1.76 (pentet, *J* = 6.3 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{16}H_{16}NO_3S$ 302 (MH^+), found 302.



(*E,Z*)-2-(3-Hydroxypropyl)-5-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (126). Reaction of **101** with 2-thioxoimidazolidin-4-one according to general procedure C, followed by hydrolysis of the crude *O*-acetate according to general procedure I, gave **126** as an orange solid (64%), mp (MeOH) 240-243°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*-isomers separately. δ 11.98-12.40 (m, 2 H), 7.93 (br s, 1 H), 7.87 (d, *J* = 4.0 Hz, 0.9 H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.77 (d, *J* = 4.0 Hz, 1 H), 7.71 (d, *J* = 8.1 Hz, 1 H), 7.68 (d, *J* = 4.0 Hz, 0.1 H), 6.84 (s, 0.1 H), 6.65 (s, 0.9 H), 4.54 (s, 2 H), 4.50 (t, *J* = 5.1 Hz, 1 H), 3.58 (t, *J* = 7.2 Hz, 2 H), 3.46 (q, *J* = 5.8 Hz, 2 H), 1.77 (pentet, *J* = 6.7 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{19}H_{18}N_3O_3S_2$ 400 (MH^+), found 400.

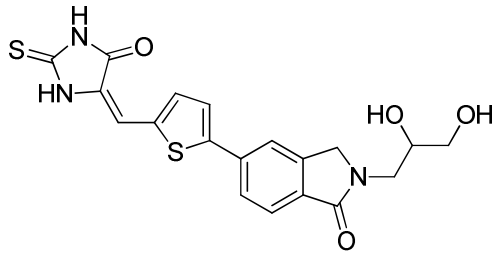


2-(2,3-Dihydroxypropyl)-5-iodoisoindolin-1-one (80). Reaction of methyl 4-iodo-2-methylbenzoate[45] **76** and 3-amino-1-propanol according to general procedure G gave **80** as a crystalline cream solid (58%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 8.03 (d, *J* = 0.7 Hz, 1 H), 7.84 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.46 (d, *J* = 7.9 Hz, 1 H), 4.88 (d, *J* = 5.2 Hz, 1 H), 4.47-4.64 (m, 3 H), 3.69-3.77 (m, 1 H), 3.61-3.66 (m, 1 H), 3.30-3.43 (m, 3 H). LRMS (APCI$^+$) calcd for $C_{11}H_{13}INO_3$ 334 (MH^+), found 334.

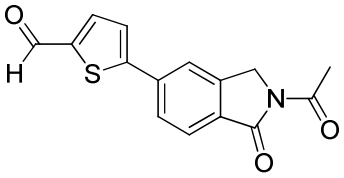


5-(2-(2,3-Dihydroxypropyl)-1-oxoisoindolin-5-yl)thiophene-2-carbaldehyde (102). 2-Thiophenecarboxaldehyde was protected as the dimethyl acetal based on a literature

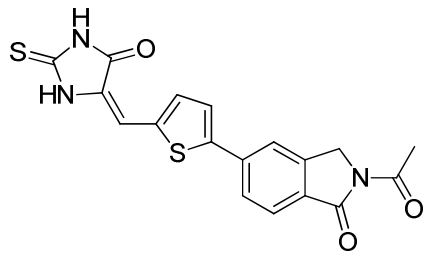
procedure,[46] then reacted with **80** according to general procedure E. Deprotection of **85** directly to the aldehyde according to general procedure H gave **102** as a yellow solid (38%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.05 (d, *J* = 0.7 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 4.91 (t, *J* = 5.2 Hz, 1 H), 4.57-4.71 (m, 3 H), 3.73-3.81 (m, 1 H), 3.65-3.71 (m, 1 H), 3.31-3.47 (m, 3 H). LRMS (APCI$^+$) calcd for $C_{16}H_{16}NO_4S$ 318 (MH^+), found 318.



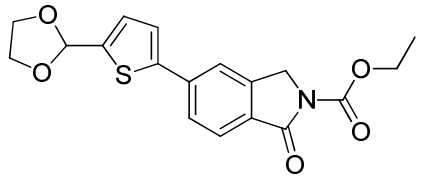
(*E,Z*)-2-(2,3-Dihydroxypropyl)-5-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (127). Reaction of **102** with 2-thioxoimidazolidin-4-one according to general procedure C, followed by hydrolysis of the crude *O,O*-diacetate according to general procedure I, gave **127** as an orange solid, (18%); mp (DMSO/water) 260-263^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 12.02-12.41 (m, 2 H), 7.94 (br s, 1 H), 7.87 (br d, *J* = 3.9 Hz, 0.7 H), 7.83 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.77 (d, *J* = 4.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 4.0 Hz, 0.3 H), 6.84 (s, 0.3 H), 6.65 (s, 0.7 H), 4.93 (t, *J* = 5.2 Hz, 1 H), 4.56-4.59 (m, 3 H), 3.72-3.80 (m, 1 H), 3.63-3.70 (m, 1 H), 3.33-3.46 (m, 3 H). LRMS (APCI$^-$) calcd for $C_{19}H_{16}N_3O_4S_2$ 414 (M-H), found 414.



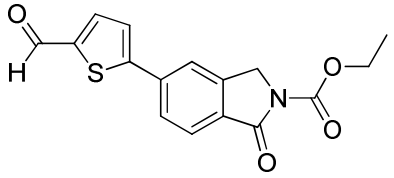
5-(2-Acetyl-1-oxoisoindolin-5-yl)thiophene-2-carbaldehyde (103). Compound **82** (150 mg, 0.52 mmol) was suspended in acetic anhydride (10 mL) and heated at reflux temperature for 2 h. The solvent was removed under reduced pressure to afford a residue which was dissolved in CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ (2x50 mL) and brine (50 mL). The organic fraction was dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give **91** as a brown solid which was deprotected directly according to general procedure B. Purification by flash column chromatography on silica gel (2% acetone/CH_2Cl_2 as eluant), gave **103** as a pale yellow solid (84%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.96 (s, 1 H), 8.11-8.13 (br m, 1 H), 8.10 (d, *J* = 4.0 Hz, 1 H), 8.00 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.89-7.93 (m, 2 H), 4.84 (s, 2 H), 2.56 (s, 3 H). LRMS (APCI$^+$) calcd for $C_{15}H_{12}NO_3S$ 286 (MH^+), found 286.



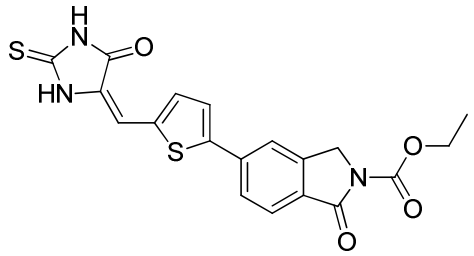
(*E,Z*)-2-Acetyl-5-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (128). Reaction of **103** with 2-thioxoimidazolidin-4-one according to general procedure C gave **128** as an orange solid (79%), mp (AcOH) 336-339°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.91-12.39 (m, 2 H), 7.99 (br s, 1 H), 7.91 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.85-7.89 (m, 1.85 H), 7.83 (d, *J* = 4.0 Hz, 0.85 H), 7.78 (br d, *J* = 4.4 Hz, 0.15 H), 7.75 (d, *J* = 4.0 Hz, 0.15 H), 6.84 (s, 0.15 H), 6.65 (s, 0.85 H), 4.83 (s, 2 H), 2.55 (s, 3 H). LRMS ($APCI^-$) calcd for $C_{18}H_{12}N_3O_3S_2$ 382 (M-H), found 382.



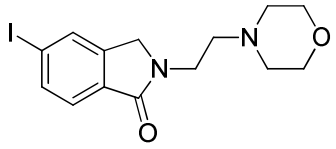
Ethyl 5-(5-(1,3-dioxolan-2-yl)thiophen-2-yl)-1-oxoisoindoline-2-carboxylate (92). Alkylation of **82** with NaH and ethyl chloroformate according to general procedure F gave **92** as an off-white solid (60%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.93 (br d, *J* = 0.7 Hz, 1 H), 7.84 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.59 (d, *J* = 3.9 Hz, 1 H), 7.28 (d, *J* = 4.0 Hz, 1 H), 6.08 (s, 1 H), 4.86 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 4.02-4.11 (m, 2 H), 3.93-4.01 (m, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H). LRMS ($APCI^+$) calcd for $C_{18}H_{18}NO_5S$ 360 (MH^+), found 360.



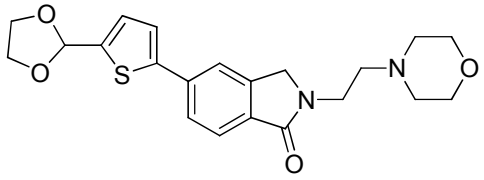
Ethyl 5-(5-formylthiophen-2-yl)-1-oxoisoindoline-2-carboxylate (104). Deprotection of **92** according to general procedure B gave **104** as a cream solid (100%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.96 (s, 1 H), 8.08-8.11 (m, 2 H), 7.98 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.90 (d, *J* = 4.0 Hz, 1 H), 7.87 (d, *J* = 8.2 Hz, 1 H), 4.89 (s, 2 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H). LRMS ($APCI^-$) calcd for $C_{16}H_{13}NO_4S$ 315 (M^+), found 315.



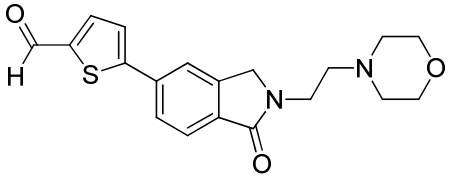
(*E,Z*)-Ethyl 1-oxo-5-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindoline-2-carboxylate (129). Reaction of **104** with 2-thioxoimidazolidin-4-one according to general procedure C gave **129** as an orange solid (98%), mp (AcOH) 274-277°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.91-12.39 (m, 2 H), 7.97 (br s, 1 H), 7.86-7.91 (m, 1.8 H), 7.80-7.85 (m, 1.8 H), 7.78 (br d, *J* = 4.4 Hz, 0.2 H), 7.73 (d, *J* = 4.0 Hz, 0.2 H), 6.84 (s, 0.2 H), 6.65 (s, 0.8 H), 4.88 (s, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.31 (t, *J* = 7.1 Hz, 3 H). LRMS (APCI$^-$) calcd for $C_{19}H_{14}N_3O_4S_2$ 412 (M-H), found 312.



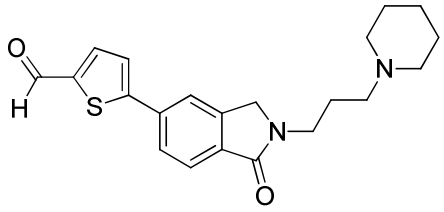
5-Iodo-2-(2-morpholinoethyl)isoindolin-1-one (81). Reaction of methyl 4-iodo-2-methylbenzoate[45] **76** and 4-(2-aminoethyl)morpholine, according to general procedure G gave **81** as a white solid (61%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 8.02 (d, *J* = 0.7 Hz, 1 H), 7.84 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 4.52 (s, 2 H), 3.63 (t, *J* = 6.3 Hz, 2 H), 3.53 (t, *J* = 4.6 Hz, 4 H), 2.53 (t, *J* = 6.4 Hz, 2 H), 2.41 (t, *J* = 4.4 Hz, 4 H). LRMS (APCI$^+$) calcd for $C_{14}H_{18}IN_2O_2$ 373 (M+H), found 373.



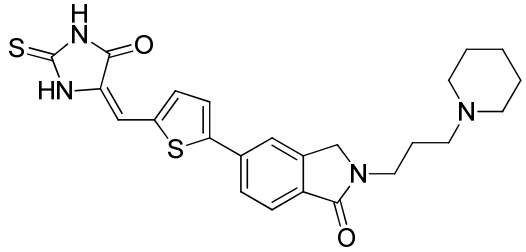
5-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-2-(2-morpholinoethyl)isoindolin-1-one (86). 2-Thiophenecarboxaldehyde was protected as the cyclic acetal according to a literature procedure,[44] then reacted with **81** according to general procedure E giving **86** as a yellow-orange foam (50%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 7.88 (d, *J* = 0.7 Hz, 1 H), 7.76 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.68 (dd, *J* = 7.9, 0.3 Hz, 1 H), 7.54 (d, *J* = 3.7 Hz, 1 H), 7.26 (dd, *J* = 3.8, 0.4 Hz, 1 H), 6.07 (s, 1 H), 4.58 (s, 2 H), 4.02-4.10 (m, 2 H), 3.93-4.01 (m, 2 H), 3.65 (t, *J* = 6.3 Hz, 2 H), 3.55 (t, *J* = 4.6 Hz, 4 H), 2.56 (t, *J* = 6.3 Hz, 2 H), 2.39-2.46 (m, 4 H). LRMS (APCI$^+$) calcd for $C_{21}H_{25}N_2O_4S$ 401 (M+H), found 401.



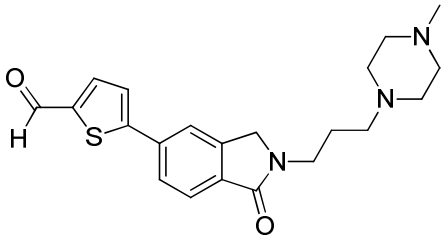
5-(2-(2-Morpholinoethyl)-1-oxoisoindolin-5-yl)thiophene-2-carbaldehyde (105). Deprotection of **86** according to general procedure B gave **105** as a yellow solid (81%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.05 (d, *J* = 0.8 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 4.62 (s, 2 H), 3.67 (t, *J* = 6.3 Hz, 2 H), 3.55 (t, *J* = 4.6 Hz, 4 H), 2.56 (t, *J* = 6.2 Hz, 2 H), 2.40-2.47 (m, 4 H). LRMS (APCI$^+$) calcd for $C_{19}H_{21}N_2O_3S$ 357 (M+H), found 357.



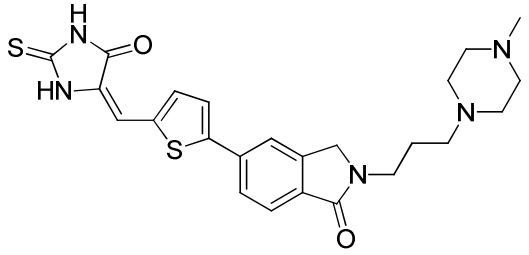
5-(1-Oxo-2-(3-(piperidin-1-yl)propyl)isoindolin-5-yl)thiophene-2-carbaldehyde (115). Reaction of iodide **109** with piperidine according to general procedure K, followed by deprotection of **111** according to general procedure H gave **115** as a yellow solid (73%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.03 (br s, 1 H), 7.92 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 4.55 (s, 2 H), 3.56 (t, *J* = 7.2 Hz, 2 H), 2.22-2.34 (m, 6 H), 1.77 (pentet, *J* = 7.0 Hz, 2 H), 1.45 (pentet, *J* = 5.3 Hz, 4 H), 1.31-1.38 (m, 2 H). LRMS (APCI$^+$) calcd for $C_{21}H_{25}N_2O_2S$ 369 (MH^+), found 369.



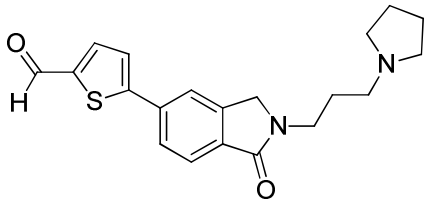
(*E,Z*)-5-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)-2-(3-(piperidin-1-yl)propyl)isoindolin-1-one (132). Reaction of **115** with 2-thioxoimidazolidin-4-one according to general procedure C, followed by isolation according to general procedure J, gave **132** as an orange solid (48%), mp (dioxane) 221-224^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.47 (v br s, 2 H), 7.91 (br s, 1 H), 7.82 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.77 (d, *J* = 4.4 Hz, 0.15 H), 7.67-7.72 (m, 2.85 H), 6.84 (s, 0.15 H), 6.52 (s, 0.85 H), 4.53 (s, 2 H), 3.51 (t, *J* = 6.9 Hz, 2 H), 2.44-2.57 (m, 6 H), 1.83 (pentet, *J* = 7.1 Hz, 2 H), 1.53 (pentet, *J* = 5.4 Hz, 4 H), 1.35-1.43 (m, 2 H). HRMS (ESI$^+$) calcd for $C_{24}H_{27}N_4O_2S_2$ 467.1570 (MH^+), found 467.1567.



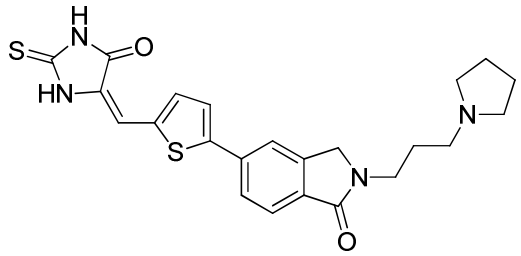
5-(2-(3-(4-Methylpiperazin-1-yl)propyl)-1-oxoisoindolin-5-yl)thiophene-2-carbaldehyde (116). Reaction of iodide **109** with 1-methylpiperazine according to general procedure K, followed by deprotection of **112** according to general procedure H gave **116** as a yellow solid (78%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.03 (d, *J* = 0.7 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.86 (d, *J* = 3.9 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 4.54 (s, 2 H), 3.55 (t, *J* = 7.1 Hz, 2 H), 2.20-2.38 (m, 10 H), 2.11 (s, 3 H), 1.76 (pentet, *J* = 7.0 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{21}H_{26}N_3O_2S$ 384 (MH^+), found 384.



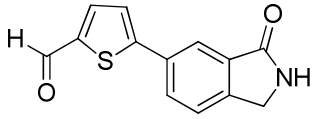
(*E,Z*)-2-(3-(4-Methylpiperazin-1-yl)propyl)-5-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (133). Reaction of **116** with 2-thioxoimidazolidin-4-one according to general procedure C, followed by isolation according to general procedure J, gave **133** as a dark orange solid (81%), mp (MeOH) 197-201°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.75 (br s, 2 H), 7.90 (br s, 1 H), 7.82 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.77 (d, *J* = 4.4 Hz, 0.2 H), 7.65-7.72 (m, 2.8 H), 6.84 (s, 0.2 H), 6.51 (s, 0.8 H), 4.52 (s, 2 H), 3.54 (t, *J* = 7.0 Hz, 2 H), 2.29-2.42 (m, 10 H), 2.16 (s, 3 H), 1.75 (pentet, *J* = 7.1 Hz, 2 H). HRMS (ESI$^+$) calcd for $C_{24}H_{28}N_5O_2S_2$ 482.1679 (MH^+), found 482.1675.



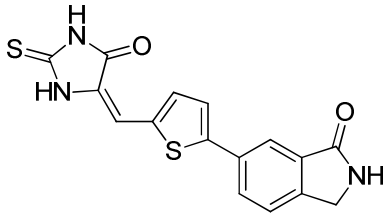
5-(1-Oxo-2-(3-(pyrrolidin-1-yl)propyl)isoindolin-5-yl)thiophene-2-carbaldehyde (117). Reaction of iodide **109** with pyrrolidine according to general procedure K, followed by deprotection of **113** according to general procedure H gave **117** as a beige solid (78%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.94 (s, 1 H), 8.08 (d, *J* = 4.0 Hz, 1 H), 8.03 (d, *J* = 0.7 Hz, 1 H), 7.92 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.86 (d, *J* = 4.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 4.55 (s, 2 H), 3.57 (t, *J* = 7.2 Hz, 2 H), 2.40-2.46 (m, 6 H), 1.79 (pentet, *J* = 7.1 Hz, 2 H), 1.64-1.70 (m, 4 H). LRMS (APCI$^+$) calcd for $C_{20}H_{23}N_2O_2S$ 355 (MH^+), found 355.



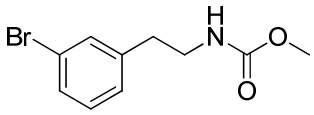
(*E,Z*)-5-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)-2-(3-(pyrrolidin-1-yl)propyl)isoindolin-1-one (134). Reaction of **117** with 2-thioxoimidazolidin-4-one according to general procedure C, followed by isolation according to general procedure J, gave **134** as a dark orange solid (67%), mp (acetone) 206-210 ^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.36 (v br s, 2 H), 7.92 (br s, 0.2 H), 7.90 (br s, 0.8 H), 7.82 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.77 (d, *J* = 3.9 Hz, 0.2 H), 7.65-7.72 (m, 2 H), 7.60 (d, *J* = 3.9 Hz, 0.8 H), 6.84 (s, 0.2 H), 6.47 (s, 0.8 H), 4.53 (s, 2 H), 3.57 (t, *J* = 6.9 Hz, 2 H), 2.58-2.74 (m, 6 H), 1.85 (pentet, *J* = 7.2 Hz, 2 H), 1.70-1.78 (m, 4 H). LRMS (APCI$^+$) calcd for $C_{23}H_{25}N_4O_2S_2$ 453 (MH^+), found 453.



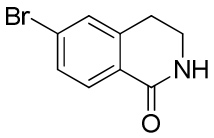
5-(3-Oxoisoindolin-5-yl)thiophene-2-carbaldehyde (159). 6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one (**147**) was reacted with 2-(5-bromothiophen-2-yl)-1,3-dioxolane (**5**) according to general procedure A, to give **153** which was deprotected directly to the aldehyde according to general procedure B, affording **159** as an off-white solid (84%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.93 (s, 1 H), 8.68 (br s, 1 H), 8.07 (d, *J* = 3.9 Hz, 1 H), 8.00-8.04 (m, 2 H), 7.87 (d, *J* = 3.9 Hz, 1 H), 7.70 (br d, *J* = 8.5 Hz, 1 H), 4.44 (s, 2 H). LRMS (APCI$^+$) calcd for $C_{13}H_{10}NO_2S$ 244 (MH^+), found 244.



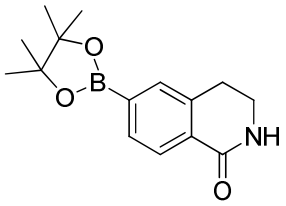
(*E,Z*)-6-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)isoindolin-1-one (165). Reaction of **159** with 2-thioxoimidazolidin-4-one according to general procedure C gave **164** as an orange solid (60%), mp (DMSO/water) >320^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.97-12.37 (m, 2 H), 8.63 (br s, 1 H), 7.93-7.97 (m, 2 H), 7.83 (br d, *J* = 4.0 Hz, 1 H), 7.76 (br d, *J* = 4.0 Hz, 1 H), 7.75 (d, *J* = 8.5 Hz, 1 H), 6.84 (s, 0.05 H), 6.66 (s, 0.95 H), 4.42 (s, 2 H). LRMS (APCI$^-$) calcd for $C_{16}H_{10}N_3O_3S_2$ 340 (M-H), found 340.



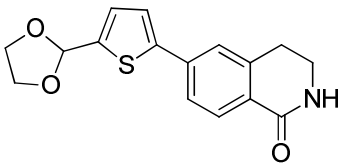
Methyl 3-bromophenethylcarbamate (139). Adaption of a literature procedure[38] gave **139** as a pale yellow oil (96%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.33-7.38 (m, 2 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.11 (d, *J* = 7.7 Hz, 1 H), 4.68 (bs, 1 H), 3.67 (s, 3 H), 3.42 (q, *J* = 6.6 Hz, 2 H), 2.78 (t, *J* = 7.0 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{10}H_{13}BrNO_2$ 259 (MH^+), found 259.



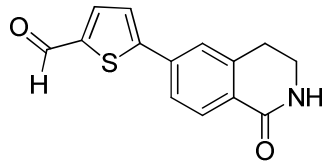
6-Bromo-3,4-dihydroisoquinolin-1(2*H*)-one (143). Cyclisation of **139** was carried out by adaption of a literature procedure[39] to give **143** as a white solid (30%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.93 (d, *J* = 8.3 Hz, 1 H), 7.49 (dd, *J* = 8.3, 1.9 Hz, 1 H), 7.39 (d, *J* = 1.7 Hz, 1 H), 5.98 (bs, 1 H), 3.57 (dt, *J* = 6.6, 2.9 Hz, 2 H), 2.99 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for C_9H_9BrNO 227 (MH^+), found 227.



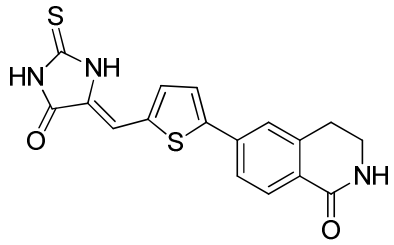
6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (149). Reaction of **143** with bis(pinacolato)diboron according to general procedure L gave **149** as a light brown solid (26%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.06 (d, *J* = 7.7 Hz, 1 H), 7.79 (d, *J* = 7.7 Hz, 1 H), 7.66 (s, 1 H), 5.95 (bs, 1 H), 3.55 (dt, *J* = 6.6, 2.9 Hz, 2 H), 3.01 (t, *J* = 6.7 Hz, 2 H), 1.36 (s, 12 H). LRMS (APCI$^+$) calcd for $C_{15}H_{21}BNO_3$ 274 (MH^+), found 274.



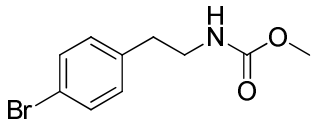
6-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (155). Reaction of 2-(5-bromothiophen-2-yl)-1,3-dioxolane (**5**) with **149** according to general procedure A gave **155** as a light orange solid (44%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.07 (d, *J* = 8.1 Hz, 1 H), 7.57 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.42 (d, *J* = 1.8 Hz, 1 H), 7.27 (d, *J* = 3.7 Hz, 1 H), 7.15 (dd, *J* = 3.6, 0.4 Hz, 1 H), 6.11 (s, 1 H), 6.02 (bs, 1 H), 4.03-4.21 (m, 4 H), 3.59 (dt, *J* = 6.6, 2.9 Hz, 2 H), 3.03 (t, *J* = 6.7 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{16}H_{16}NO_3S$ 302 (MH^+), found 302.



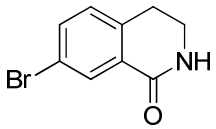
5-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)thiophene-2-carbaldehyde (161). Deprotection of **155** was carried out according to general procedure B to give **161** as an orange solid (97%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 9.92 (s, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 7.77 (d, *J* = 4.0 Hz, 1 H), 7.66 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.52 (d, *J* = 1.0 Hz, 1 H), 7.48 (d, *J* = 3.9 Hz, 1 H), 6.01 (bs, 1 H), 3.62 (dt, *J* = 6.6, 2.9 Hz, 2 H), 3.07 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{14}H_{12}NO_2S$ 258 (MH^+), found 258.



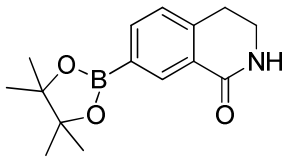
(*E,Z*)-6-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (167). Reaction of **161** with 2-thioxoimidazolidin-4-one according to general procedure C gave **167** as a brown solid (65%); mp (AcOH) 341-344^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.98-12.30 (br m, 2 H), 7.93 (br s, 1 H), 7.88 (d, *J* = 8.1 Hz, 1 H), 7.83 (d, *J* = 3.9 Hz, 1 H), 7.77 (d, *J* = 4.4 Hz, 0.2 H), 7.74 (d, *J* = 4.0 Hz, 0.8 H), 7.64-7.70 (m, 2 H), 6.83 (br s, 0.2 H), 6.63 (br s, 0.8 H), 3.40 (dt, *J* = 6.6, 2.5 Hz, 2 H), 2.96 (t, *J* = 6.5 Hz, 2 H). HRMS (ESI$^-$) calcd for $C_{17}H_{12}N_3O_2S_2$ 354.0376 (M-H), found 354.0368.



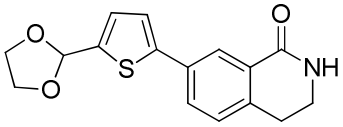
Methyl 4-bromophenethylcarbamate (140). Adaption of a literature procedure[38] gave **140** as a pale yellow oil (94%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.43 (d, *J* = 8.4 Hz, 2 H), 7.06 (d, *J* = 8.3 Hz, 2 H), 4.65 (bs, 1 H), 3.65 (s, 3 H), 3.41 (q, *J* = 6.3 Hz, 2 H), 2.77 (t, *J* = 7.0 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{10}H_{13}BrNO_2$ 259 (MH^+), found 259.



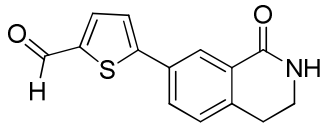
7-Bromo-3,4-dihydroisoquinolin-1(2*H*)-one (144). Cyclisation of **140** was carried out by adaption of a literature procedure[39] to give **144** as a white solid (20%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.20 (d, *J* = 2.1 Hz, 1 H), 7.55 (dd, *J* = 8.1, 2.2 Hz, 1 H), 7.09 (d, *J* = 8.1 Hz, 1 H), 6.12 (bs, 1 H), 3.55 (dt, *J* = 6.2, 2.9 Hz, 2 H), 2.94 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for C_9H_9BrNO 227 (MH^+), found 227.



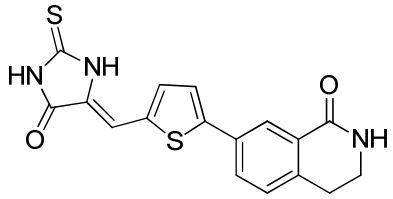
7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (150). Reaction of **144** with bis(pinacolato)diboron according to general procedure L gave **150** as a light brown solid (47%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.53 (s, 1 H), 7.86 (dd, *J* = 7.5, 1.3 Hz, 1 H), 7.21 (d, *J* = 7.4 Hz, 1 H), 5.88 (bs, 1 H), 3.55 (dt, *J* = 6.6, 2.9 Hz, 2 H), 3.01 (t, *J* = 6.6 Hz, 2 H), 1.33 (s, 12 H). LRMS (APCI$^+$) calcd for $C_{15}H_{21}BNO_3$ 274 (MH^+), found 274.



7-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (156). Reaction of 2-(5-bromothiophen-2-yl)-1,3-dioxolane (**5**) with **150** according to general procedure A gave **156** as a brown solid (41%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.31 (d, *J* = 2.0 Hz, 1 H), 7.65 (dd, *J* = 7.9, 2.1 Hz, 1 H), 7.27 (d, *J* = 3.6 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 1 H), 7.13 (d, *J* = 3.8 Hz, 1 H), 6.11 (s, 1 H), 6.01 (bs, 1 H), 4.03-4.16 (m, 4 H), 3.59 (dt, *J* = 6.7, 2.9 Hz, 2 H), 3.01 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{16}H_{16}NO_3S$ 302 (MH^+), found 302.

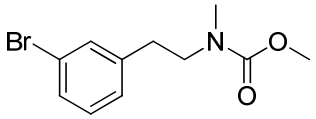


5-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)thiophene-2-carbaldehyde (162). Deprotection of **156** was carried out according to general procedure B to give **162** as an orange solid (84%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 9.90 (s, 1 H), 8.40 (d, *J* = 2.0 Hz, 1 H), 7.75 (d, *J* = 3.9 Hz, 1 H), 7.73 (d, *J* = 2.0 Hz, 1 H), 7.49 (d, *J* = 3.9 Hz, 1 H), 7.30 (d, *J* = 7.9 Hz, 1 H), 6.12 (bs, 1 H), 3.61 (dt, *J* = 6.6, 2.8 Hz, 2 H), 3.05 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{14}H_{12}NO_2S$ 258 (MH^+), found 258.

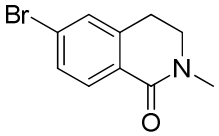


(*E,Z*)-7-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (168). Reaction of **162** with 2-thioxoimidazolidin-4-one according to general procedure C gave **168** as a brown solid (72%); mp (AcOH)

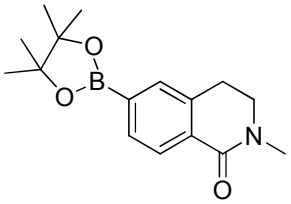
>310°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 12.35-12.69 (br m, 2 H), 8.12 (d, *J* = 2.0 Hz, 0.9 H), 8.10 (d, *J* = 2.0 Hz, 0.1 H), 8.03 (m, 1 H), 7.86 (dd, *J* = 7.9, 2.1 Hz, 1 H), 7.79 (d, *J* = 3.9 Hz, 0.9 H), 7.74 (d, *J* = 4.0 Hz, 0.1 H), 7.66 (d, *J* = 4.0 Hz, 0.9 H), 7.59 (d, *J* = 4.0 Hz, 0.1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 6.65 (br s, 0.9 H), 6.60 (br s, 0.1 H), 3.40 (dt, *J* = 6.6, 2.5 Hz, 2 H), 2.93 (t, *J* = 6.5 Hz, 2 H). HRMS (ESI$^+$) calcd for $C_{17}H_{14}N_3O_2S_2$ 356.0516 (MH^+), found 356.0522.



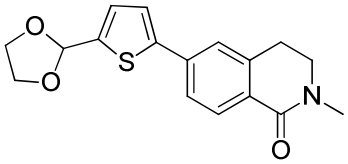
Methyl 3-bromophenethyl(methyl)carbamate (141). Adaption of a literature procedure[38] gave **141** as a pale yellow oil (88%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.32-7.38 (m,1 H), 7.30 (d, *J* = 7.4 Hz, 1 H), 7.16-7.24 (m, 2 H), 3.69 (s, 3 H), 3.48 (s, 3 H), 2.72-2.91 (m, 4 H). LRMS (APCI$^+$) calcd for $C_{11}H_{14}BrNO_2$ 273 (MH^+), found 273.



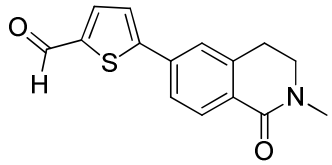
6-Bromo-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (145). Cyclisation of **141** was carried out by adaption of a literature procedure[39] to give **145** as a pale orange oil (13%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.94 (d, *J* = 8.3 Hz, 1 H), 7.46 (dd, *J* = 8.3, 1.8 Hz, 1 H), 7.34 (d, *J* = 1.8 Hz, 1 H), 3.56 (t, *J* = 6.8 Hz, 2 H), 3.14 (s, 3 H), 2.98 (t, *J* = 6.9 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{10}H_{10}BrNO$ 241 (MH^+), found 241.



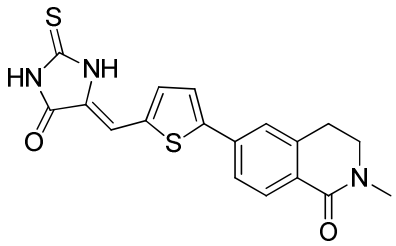
2-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (151). Reaction of **145** with bis(pinacolato)diboron according to general procedure L gave **151** as a yellow oil (0.26 g, 86%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.09 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.76 (d, *J* = 7.6 Hz, 1 H), 7.61 (s, 1 H), 3.57 (t, *J* = 6.8 Hz, 2 H), 3.16 (s, 3 H), 3.01 (t, *J* = 6.6 Hz, 2 H), 1.35 (s, 12 H). LRMS (APCI$^+$) calcd for $C_{16}H_{22}BNO_3$ 288 (MH^+), found 288.



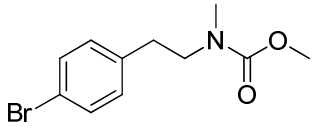
6-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (157). Reaction of 2-(5-bromothiophen-2-yl)-1,3-dioxolane (**5**) with **151** according to general procedure A gave **157** as an orange-brown solid (88%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.08 (d, *J* = 8.1 Hz, 1 H), 7.55 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.37 (s, 1 H), 7.25 (d, *J* = 3.6 Hz, 1 H), 7.14 (d, *J* = 3.6 Hz, 1 H), 6.11 (s, 1 H), 4.01-4.21 (m, 4 H), 3.61 (t, *J* = 6.7 Hz, 2 H), 3.18 (s, 3 H), 3.03 (t, *J* = 6.7 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{17}H_{17}NO_3S$ 316 (MH^+), found 316.



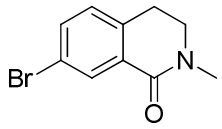
5-(2-Methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)thiophene-2-carbaldehyde (163). Deprotection of **157** was carried out according to general procedure B to give **163** as an orange solid (75%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 9.91 (s, 1 H), 8.14 (d, *J* = 8.1 Hz, 1 H), 7.75 (d, *J* = 4.0 Hz, 1 H), 7.64 (dd, *J* = 8.1, 1.9 Hz, 1 H), 7.47 (s, 1 H), 7.46 (d, *J* = 4.0 Hz, 1 H), 3.61 (t, *J* = 6.6 Hz, 2 H), 3.18 (s, 3 H), 3.07 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{15}H_{13}NO_2S$ 272 (MH^+), found 272.



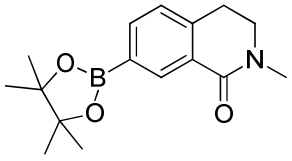
(*E*,*Z*)-2-Methyl-6-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (169). Reaction of **163** with 2-thioxoimidazolidin-4-one according to general procedure C gave **169** as an orange-brown solid (60%); mp (AcOH) >300^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 12.40 (s, 0.4 H), 12.28 (s, 0.6 H), 12.10 (s, 0.6 H), 11.98 (s, 0.4 H), 7.90 (d, *J* = 8.1 Hz, 1 H), 7.86 (d, *J* = 4.1 Hz, 0.4 H), 7.76 (d, *J* = 4.4 Hz, 0.6 H), 7.74 (d, *J* = 4.0 Hz, 0.4 H), 7.69 (dd, *J* = 8.0, 2.0 Hz, 0.4 H), 7.67 (dd, *J* = 8.1, 1.9 Hz, 0.6 H), 7.65 (d, *J* = 4.1 Hz, 0.6 H), 7.64 (s, 0.4 H), 7.62 (s, 0.6 H), 6.83 (s, 0.6 H), 6.65 (s, 0.4 H), 3.57 (t, *J* = 6.6 Hz, 2 H), 3.05 (t, *J* = 6.6 Hz, 2 H), 3.04 (s, 3 H). HRMS (ESI$^-$) calcd for $C_{18}H_{14}N_3O_2S_2$ 368.0533 (M-H), found 368.0542.



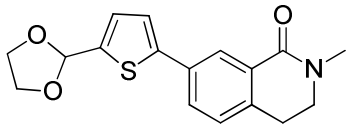
Methyl 4-bromophenethyl(methyl)carbamate (142). Adaption of a literature procedure[38] gave **142** as an orange oil (89%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.42 (d, *J* = 8.4 Hz, 2 H), 7.04-7.09 (m, 2 H), 3.65 (s, 3 H), 3.45 (s, 3 H), 2.72-2.81 (m, 4 H). LRMS (APCI$^+$) calcd for $C_{11}H_{14}BrNO_2$ 273 (MH^+), found 273.



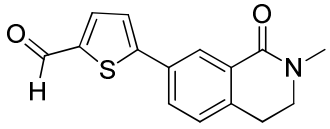
7-Bromo-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (146). Cyclisation of **142** was carried out by adaption of a literature procedure[39] to give **146** as an orange oil (55%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.21 (d, *J* = 2.1 Hz, 1 H), 7.52 (dd, *J* = 8.1, 2.2 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 3.56 (t, *J* = 6.7 Hz, 2 H), 3.15 (s, 3 H), 2.95 (t, *J* = 6.7 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{10}H_{10}BrNO$ 241 (MH^+), found 241.



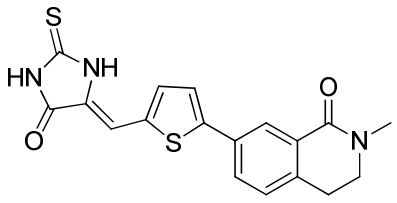
2-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (152). Reaction of **146** with bis(pinacolato)diboron according to general procedure L gave **152** as a pale yellow oil (58%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.53 (s, 1 H), 7.82 (dd, *J* = 7.5, 1.3 Hz, 1 H), 7.16 (d, *J* = 7.5 Hz, 1 H), 3.55 (t, *J* = 6.7 Hz, 2 H), 3.15 (s, 3 H), 3.01 (t, *J* = 6.6 Hz, 2 H), 1.33 (s, 12 H). LRMS (APCI$^+$) calcd for $C_{16}H_{22}BNO_3$ 288 (MH^+), found 288.



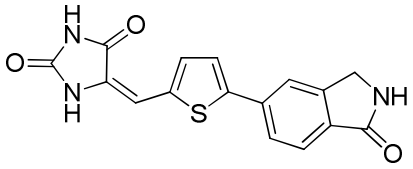
7-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (158). Reaction of 2-(5-bromothiophen-2-yl)-1,3-dioxolane (**5**) with **152** according to general procedure A gave **158** as a yellow oil (41%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.32 (d, *J* = 2.0 Hz, 1 H), 7.61 (dd, *J* = 7.8, 2.0 Hz, 1 H), 7.25 (d, *J* = 3.6 Hz, 1 H), 7.17 (d, *J* = 7.8 Hz, 1 H), 7.12 (d, *J* = 3.6 Hz, 1 H), 6.11 (s, 1 H), 4.01-4.17 (m, 4 H), 3.58 (t, *J* = 6.7 Hz, 2 H), 3.17 (s, 3 H), 3.01 (t, *J* = 6.7 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{17}H_{17}NO_3S$ 316 (MH^+), found 316.



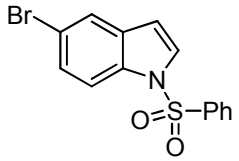
5-(2-Methyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)thiophene-2-carbaldehyde (164). Deprotection of **158** was carried out according to general procedure B to give **164** as a yellow-orange solid (99%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 9.89 (s, 1 H), 8.41 (d, *J* = 2.0 Hz, 1 H), 7.74 (d, *J* = 4.0 Hz, 1 H), 7.69 (dd, *J* = 7.8, 2.1 Hz, 1 H), 7.48 (d, *J* = 4.0 Hz, 1 H), 7.24 (s, 1 H), 3.60 (t, *J* = 6.7 Hz, 2 H), 3.19 (s, 3 H), 3.05 (t, *J* = 6.7 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{15}H_{13}NO_2S$ 272 (MH^+), found 272.



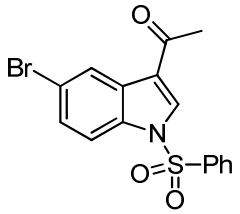
(*E*,*Z*)-2-Methyl-7-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (170). Reaction of **164** with 2-thioxoimidazolidin-4-one according to general procedure C gave **170** as a red-brown solid (66%); mp (AcOH) >320°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*-isomers separately. δ 11.72-12.49 (br m, 2 H), 8.13 (d, *J* = 2.0 Hz, 0.7 H), 8.12 (d, *J* = 2.0 Hz, 0.3 H), 7.84 (dd, *J* = 7.9, 2.2 Hz, 0.7 H), 7.83 (dd, *J* = 7.9, 2.2 Hz, 0.3 H), 7.79 (d, *J* = 4.0 Hz, 0.7 H), 7.73 (d, *J* = 4.0 Hz, 0.3 H), 7.65 (d, *J* = 3.9 Hz, 0.7 H), 7.58 (d, *J* = 4.0 Hz, 0.3 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 6.84 (s, 0.3 H), 6.64 (s, 0.7 H), 3.58 (t, *J* = 6.7 Hz, 2 H), 3.06 (s, 3 H), 3.01 (t, *J* = 6.6 Hz, 2 H). HRMS (ESI$^-$) calcd for $C_{18}H_{14}N_3O_2S_2$ 368.0533 (M-H), found 368.0529.



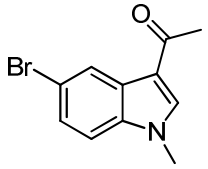
(*E*,*Z*)-5-((5-(1-Oxoisoindolin-5-yl)thiophen-2-yl)methylene)imidazolidine-2,4-dione (136) . Reaction of **94** with hydantoin according to general procedure C gave **136** as a yellow-brown solid (41%), mp (DMSO/H_2O) >295°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 11.27 (s, 1 H), 10.39 (s, 1 H), 8.55 (s, 1 H), 7.87 (s, 1 H), 7.80 (dd, *J* = 1.4, 7.9 Hz, 1 H), 7.71 (m, 2 H), 7.62 (d, *J* = 4.2 Hz, 1 H), 6.59 (s, 1 H), 4.42 (s, 2 H). Anal. ($C_{16}H_{11}N_3O_3S.1.25H_2O$) C, H, N.



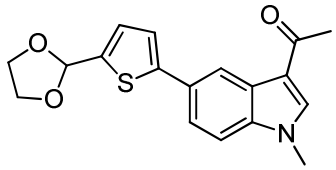
5-Bromo-1-(phenylsulfonyl)-1*H*-indole (172).[40] To a stirred suspension of powdered sodium hydroxide (7.18 g, 180 mmol), and $(n\text{-Bu})_4.HSO_4$ (505 mg, 1.48 mmol) in CH_2Cl_2 (180 mL) at 0°C was added 5-bromoindole (**171**) (10.0 g, 51.0 mmol). After 3 hours the mixture was filtered through a pad of silica and washed with CH_2Cl_2. The eluant was removed under reduced pressure to give **172** as an oil which solidified on standing (17.0 g, 95%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 7.83-7.89 (m, 3 H), 7.66 (d, *J* = 1.9 Hz, 1 H), 7.53-7.58 (m, 2 H), 7.41 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.43-7.48 (m, 2 H), 6.60 (dd, *J* = 3.7, 0.7 Hz, 1 H). LRMS (APCI$^+$) calcd for $C_{14}H_{11}BrNO_2S$ 336 (MH^+), found 336.



1-(5-Bromo-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanone (173).[41] To a stirred solution of $AlCl_3$ (13.9 g, 105 mmol), and Ac_2O (4.58 g, 44.8 mmol) in CH_2Cl_2 (180 mL) at RT was added a dropwise solution of **172** (5.03 g, 14.9 mmol). The reaction was stirred for 3 h and then poured onto ice, and extracted with CH_2Cl_2. The solvent was dried with $MgSO_4$, concentrated, and the crude was purified by trituration with CH_2Cl_2/hexanes to give **173** as a brown solid (3.62 g, 64%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.88 (s, 1 H), 8.32 (d, *J* = 2.0 Hz, 1 H), 8.13-8.17 (m, 2 H), 7.93 (d, *J* = 8.6 Hz, 1 H), 7.75-7.79 (m, 2 H), 7.62-7.68 (m, 1 H), 7.58 (dd, *J* = 8.9, 2.1 Hz, 1 H), 2.59 (s, 3 H). LRMS (APCI$^+$) calcd for $C_{16}H_{13}BrNO_3S$ 378 (MH^+) found 378.

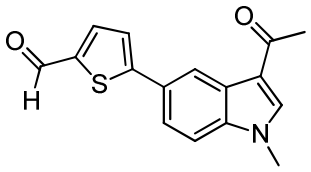


1-(5-Bromo-1-methyl-1*H*-indol-3-yl)ethanone (174). An oven dried 50 mL round bottom flask was charged with **173** (812 mg, 2.09 mmol), MeOH (100 mg, 3.14 mmol), $CsCO_3$ (751 mg, 2.31 mmol), and tetra-*n*-butylammonium bromide (34 mg, 0.104 mmol), and the mixture was suspended in dry toluene (20 mL). After heating to 65°C overnight, the reaction was quenched with saturated NH_4Cl (20 mL), extracted with CH_2Cl_2, dried over $MgSO_4$ and then evaporated to dryness. The crude material was purified by silica gel chromatography, eluting with CH_2Cl_2/MeOH 98:2, to afford **174** as a colourless oil which solidified upon standing (520 mg, 98%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.38 (s, 1 H), 8.31 (dd, *J* = 2.0, 0.4 Hz, 1 H), 7.54 (dd, *J* = 8.8, 0.4 Hz, 1 H), 7.41 (dd, *J* = 8.8, 0.4 Hz, 1 H), 3.86 (s, 3 H), 2.43 (s, 3 H). LRMS (APCI$^+$) calcd for $C_{11}H_{11}BrNO$ 252 (MH^+), found 252.

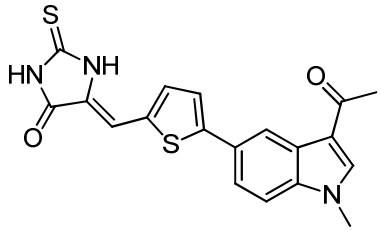


1-(5-(5-(1,3-Dioxolan-2-yl)thiophen-2-yl)-1-methyl-1*H*-indol-3-yl)ethanone (176). A 50 mL round bottom flask was charged with (5-(1,3-dioxolan-2-yl)thiophen-2-yl)boronic acid (**175**) (494 mg, 2.47 mmol), **174** (520 mg, 2.06 mmol) and $Pd(dppf)Cl_2$ (20.0 mg, 0.03 mmol). The mixture was suspended in DMF (12 mL) and 2 M $KHCO_3$ (3 mL), degassed and then heated to 70°C for 3 h. The reaction was diluted with saturated NH_4Cl, extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent removed under reduced pressure to give a black solid. Chromatography with silica gel eluting with CH_2Cl_2/MeOH 98:2 gave **176** as a cream coloured solid (318 mg, 47%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 9.84 (s, 1 H), 8.76 (dd, *J* = 6.4, 0.4 Hz, 1

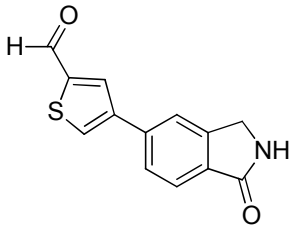
H), 7.76 (d, *J* = 0.4 Hz, 1 H), 7.74 (br s, 1 H), 7.63 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.50 (d, *J* = 4.0 Hz, 1 H), 7.38 (dd, *J* = 8.8, 0.8 Hz, 1H), 3.89 (s, 3 H), 2.54 (s, 3 H), 1.57 (s, 4 H). LRMS (APCI$^+$) calcd for $C_{16}H_{14}NO_2S$ 284 (MH – $C_2H_4O^+$), found 284.



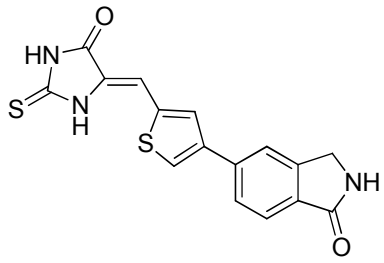
5-(3-Acetyl-1-methyl-1*H*-indol-5-yl)thiophene-2-carbaldehyde (177). Deprotection of **176** according to general procedure B gave **177** as a colourless solid (270 mg, 98%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 9.90 (s, 1 H), 8.57 (d, *J* = 1.6 Hz, 1 H), 8.42 (s, 1 H), 8.04 (d, *J* = 4.0 Hz, 1 H), 7.75 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.70 (d, *J* = 4.0 Hz, 1 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 3.90 (s, 3 H), 2.46 (s, 3 H). LRMS (APCI$^+$) calcd for $C_{16}H_{14}NO_2S$ 284 (MH^+), found 284.



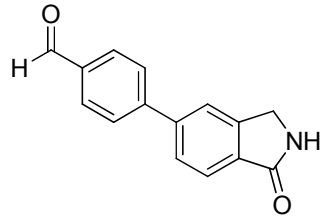
5-((5-(3-Acetyl-1-methyl-1*H*-indol-5-yl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (178). Reaction of **177** with 2-thioxoimidazolidin-4-one according to general procedure C gave **178** isolated as a cream solid (73%); mp (AcOH) 309-313°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.37 (s, 1 H), 12.03 (s, 1 H), 8.51-8.51 (m, 1 H), 8.38 (s, 1 H), 7.83 (dd, *J* = 4.0, 0.5 Hz, 1 H), 7.70 (dd, *J* = 8.6, 1.9 Hz, 1 H), 7.63 (d, *J* = 8.3 Hz, 1 H), 7.59 (d, *J* = 4.0 Hz, 1 H), 6.67 (s, 1 H), 3.88 (s, 3 H), 2.45 (s, 3 H). Anal. calcd for ($C_{19}H_{15}N_3O_2S_2.H_2O$) C, H, N.



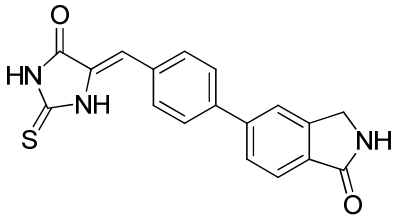
4-(1-Oxoisoindolin-5-yl)thiophene-2-carbaldehyde (195). 4-Bromo-2-thiophenecarboxaldehyde was protected as the dimethyl acetal **179** according to a literature procedure,[46] then reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one[48] according to general procedure A. In this case deprotection of the product **179** occurred *in situ*, affording the aldehyde directly. Purification by flash column chromatography on silica gel (EtOAc as eluant) gave **195** as a cream solid (74%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 10.00 (d, *J* = 1.2 Hz, 1 H), 8.53-8.59 (m, 3 H), 7.98 (s, 1 H), 7.89 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.74 (d, *J* = 7.9 Hz, 1 H), 4.43 (s, 2 H). LRMS (APCI$^+$) calcd for $C_{13}H_{10}NO_2S$ 244 (MH^+), found 244.



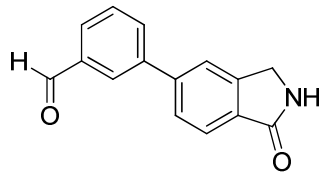
(*E,Z*)-5-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-3-yl)isoindolin-1-one (204). Reaction of **195** with 2-thioxoimidazolidin-4-one according to general procedure C gave **204** as a yellow solid (58%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.41 (br s, 1 H), 12.27 (br s, 1 H), 8.55 (br s, 1 H), 8.32 (s, 1 H), 8.24 (d, *J* = 1.0 Hz, 1 H), 8.01 (s, 1 H), 7.97 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.75 (d, *J* = 7.9 Hz, 1 H), 6.55 (s, 1 H), 4.45 (s, 2 H). HRMS (FAB$^+$) calcd for $C_{16}H_{12}N_3O_2S_2$ 342.0371 (MH^+), found 342.0372.



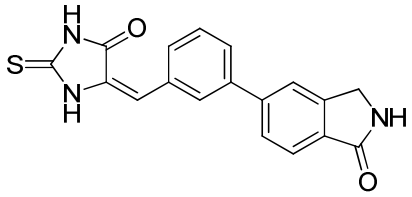
4-(1-Oxoisoindolin-5-yl)benzaldehyde (196). 4-Bromobenzaldehyde was protected as the dimethyl acetal **180** according to a literature procedure,[46] then reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one[48] according to general procedure A. Deprotection of **180** directly to the corresponding aldehyde according to general procedure H gave **196** as a cream solid (78%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 10.08 (s, 1 H), 8.60 (br s, 1 H), 8.03 (d, *J* = 8.5 Hz, 2 H), 7.95-8.00 (m, 3 H), 7.84-7.89 (m, 1 H), 7.78 (d, *J* = 7.9 Hz, 1 H), 4.46 (s, 2 H). LRMS (APCI$^+$) calcd for $C_{15}H_{12}NO_2$ 238 (MH^+), found 238.



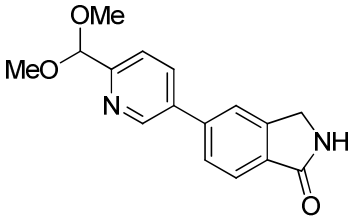
(*E,Z*)-5-(4-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)phenyl)isoindolin-1-one (205). Reaction of **196** with 2-thioxoimidazolidin-4-one according to general procedure C gave **205** as a yellow solid (66%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (br s, 1 H), 12.22 (br s, 1 H), 8.56 (br s, 1 H), 7.93 (s, 1 H), 7.89 (d, *J* = 8.5 Hz, 2 H), 7.84 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.80 (d, *J* = 8.5 Hz, 2 H), 7.76 (d, *J* = 7.9 Hz, 1 H), 6.54 (s, 1 H), 4.45 (s, 2 H). LRMS (APCI$^-$) calcd for $C_{18}H_{12}N_3O_2S$ 334 (M-H), found 334. Anal. ($C_{18}H_{13}N_3O_2S$.0.5AcOH) C, H, N.



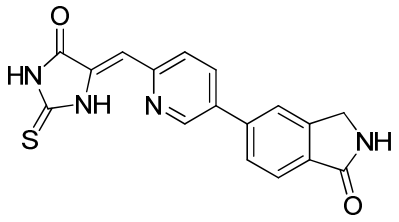
3-(1-Oxoisoindolin-5-yl)benzaldehyde (197). 3-Bromobenzaldehyde was protected as the dimethyl acetal **181** according to a literature procedure,[46] then reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one[48] according to general procedure A. Deprotection of **188** directly to the corresponding aldehyde according to general procedure H gave **197** as a cream solid (87%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 10.12 (s, 1 H), 8.58 (br s, 1 H), 8.28 (t, *J* = 1.6 Hz, 1 H), 8.08 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1 H), 7.93-7.98 (m, 2 H), 7.85 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.78 (d, *J* = 7.9 Hz, 1 H), 7.74 (t, *J* = 7.7 Hz, 1 H), 4.46 (s, 2 H). LRMS (APCI$^+$) calcd for $C_{15}H_{12}NO_2$ 238 (MH^+), found 238.



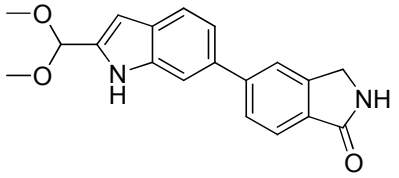
(*E,Z*)-5-(3-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)phenyl)isoindolin-1-one (206). Reaction of **197** with 2-thioxoimidazolidin-4-one according to general procedure C gave **206** as a yellow solid (81%), mp (AcOH) >300^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.38 (br s, 1 H), 12.30 (br s, 1 H), 8.56 (br s, 1 H), 8.01 (s, 1 H), 7.93 (s, 1 H), 7.85 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.74-7.79 (m, 2 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.55 (t, *J* = 7.8 Hz, 1 H), 6.59 (s, 1 H), 4.45 (s, 2 H). LRMS (APCI$^-$) calcd for $C_{18}H_{12}N_3O_2S$ 334 (M-H), found 334. Anal. ($C_{18}H_{13}N_3O_2S$.0.5AcOH) C, H, N.



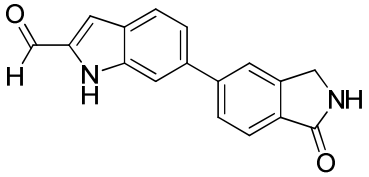
5-(6-(Dimethoxymethyl)pyridin-3-yl)isoindolin-1-one (189). 5-Bromopyridinecarboxaldehyde was protected as the dimethyl acetal **182** according to a literature procedure,[46] then reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one[48] according to general procedure A, followed by purification by flash column chromatography on silica gel (5% MeOH/CH_2Cl_2 as eluant) to give **189** as a cream solid (63%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 8.92 (dd, *J* = 2.4, 0.7 Hz, 1 H), 8.59 (br s, 1 H), 8.19 (dd, *J* = 8.2, 2.4 Hz, 1 H), 7.94 (d, *J* = 0.7 Hz, 1 H), 7.84 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.78 (d, *J* = 7.7 Hz, 1 H), 7.61 (d, *J* = 8.2 Hz, 1 H), 5.36 (s, 1 H), 4.48 (s, 2 H), 3.35 (s, 6 H). LRMS (APCI$^+$) calcd for $C_{16}H_{17}N_2O_3$ 285 (MH^+), found 285.



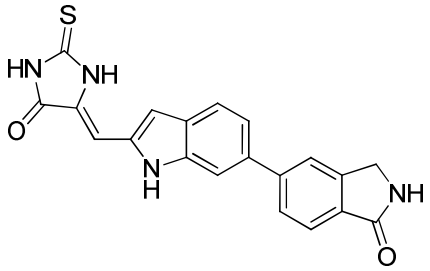
(*E*,*Z*)-5-(6-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)pyridin-3-yl)isoindolin-1-one (207). Deprotection of **189** was carried out according to general method H to give the corresponding aldehyde **198** as an off-white solid which was then used directly in a reaction with 2-thioxoimidazolidin-4-one according to general procedure C. The title compound **207** was obtained as a dark green solid (50% over 2 steps), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.53 (s, 1 H), 11.50 (s, 1 H), 9.13 (d, *J* = 2.4 Hz, 1 H), 8.62 (s, 1 H), 8.25 (dd, *J* = 8.2, 2.4 Hz, 1 H), 7.99 (s, 1 H), 7.89 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.85 (d, *J* = 8.1 Hz, 1 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 6.68 (s, 1 H), 4.46 (s, 2 H). LRMS (APCI$^-$) calcd for $C_{17}H_{11}N_4O_2S$ 335 (M-H), found 335. Anal. ($C_{17}H_{12}N_4O_2S.0.5H_2O$) C, H, N.



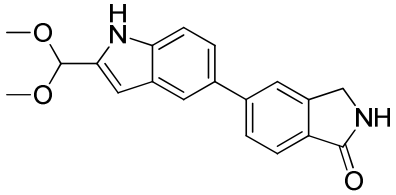
5-(2-(Dimethoxymethyl)-1*H*-indol-6-yl)isoindolin-1-one (190). 6-Bromo-1*H*-indole-2-carbaldehyde was protected as the dimethyl acetal **183** according to a literature procedure,[46] then reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one[48] according to general procedure A to give **190** as a pale yellow solid (61%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.55 (bs, 1 H), 7.93 (d, *J* = 7.6 Hz, 1 H), 7.75 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.71 (d, *J* = 0.6 Hz, 1 H), 7.69 (d, *J* = 8.3 Hz, 1 H), 7.59-7.63 (m, 1 H), 7.39 (dd, *J* = 8.2, 1.6 Hz, 1 H), 6.57-6.59 (m, 1 H), 6.47 (bs, 1 H), 5.68 (d, *J* = 0.8 Hz, 1 H), 4.52 (s, 2 H), 3.41 (s, 6 H). LRMS (APCI$^+$) calcd for $C_{19}H_{19}N_2O_3$ 323 (MH^+), found 323.



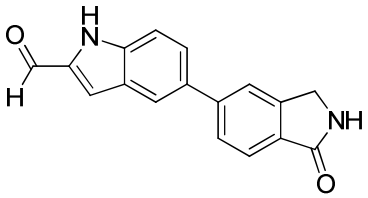
6-(1-Oxoisoindolin-5-yl)-1*H*-indole-2-carbaldehyde (199). Deprotection of **190** according to general procedure H gave **199** as a pale yellow solid (74%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.14 (br s, 1 H), 9.88 (s, 1 H), 8.57 (br s, 1 H), 7.85-7.90 (m, 2 H), 7.79 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.76 (dd, *J* = 7.9, 0.6 Hz, 1 H), 7.70-7.73 (m, 1 H), 7.49 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.45 (dd, *J* = 2.1, 0.8 Hz, 1 H), 4.45 (s, 2 H). LRMS (APCI$^+$) calcd for $C_{17}H_{13}N_2O_2$ 277 (MH^+), found 277.



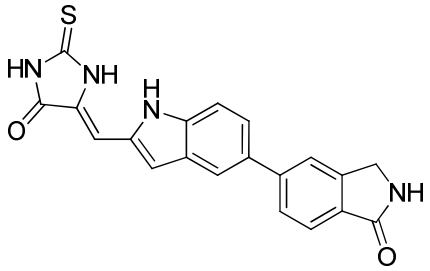
(*E,Z*)-5-(2-((5-oxo-2-Thioxoimidazolidin-4-ylidene)methyl)-1H-indol-6-yl)isoindolin-1-one (208). Reaction of **199** with 2-thioxoimidazolidin-4-one according to general procedure C gave **208** as a red solid (67%); mp >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 12.56 (br s, 0.8 H), 12.40 (br s, 0.2 H), 12.29 (br s, 0.8 H), 12.15 (br s, 0.2 H), 12.00 (br s, 0.8 H), 11.56 (br s, 0.2 H), 8.54 (br s, 1 H), 7.78-7.96 (m, 3 H), 7.65-7.77 (m, 2 H), 7.41-7.48 (m, 1 H), 7.38 (s, 0.2 H), 7.16 (s, 0.8 H), 6.72 (s, 0.8 H), 6.60 (s, 0.2 H), 4.44 (s, 2 H). LRMS (APCI$^-$) calcd for $C_{20}H_{13}N_4O_2S$ 373 (M-H), found 373. Anal. ($C_{20}H_{14}N_4O_2S$.0.50AcOH) C, H, N.



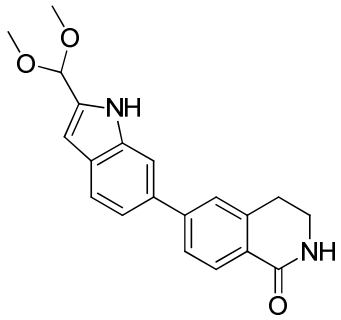
5-(2-(Dimethoxymethyl)-1*H*-indol-5-yl)isoindolin-1-one (191). 5-Bromo-1*H*-indole-2-carbaldehyde was protected as the dimethyl acetal **184** according to a literature procedure,[46] then reacted with 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-1-one[48] according to general procedure A to give **191** as a pale brown solid (65%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.50 (bs, 1 H), 7.93 (d, *J* = 7.9 Hz, 1 H), 7.86 (d, *J* = 0.7 Hz, 1 H), 7.76 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.72 (d, *J* = 0.7 Hz, 1 H), 7.45-7.50 (m, 2 H), 6.59-6.62 (m, 1 H), 6.60 (bs, 1 H), 5.68 (d, *J* = 0.4 Hz, 1 H), 4.52 (s, 2 H), 3.41 (s, 6 H). LRMS (APCI$^+$) calcd for $C_{19}H_{19}N_2O_3$ 323 (MH^+), found 323.



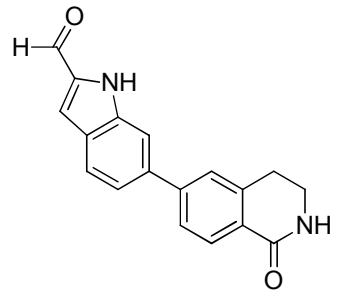
5-(1-Oxoisoindolin-5-yl)-1*H*-indole-2-carbaldehyde (200). Deprotection of **191** according to general procedure H gave **200** as a pink solid (61%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.09 (br s, 1 H), 9.89 (s, 1 H), 8.53 (br s, 1 H), 8.09-8.13 (m, 1 H), 7.88 (d, *J* = 0.6 Hz, 1 H), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.72 (dd, *J* = 8.8, 1.9 Hz, 1 H), 7.57 (d, *J* = 8.7 Hz, 1 H), 7.48 (d, *J* = 1.3 Hz, 1 H), 4.44 (s, 2 H). LRMS (APCI$^+$) calcd for $C_{17}H_{13}N_2O_2$ 277 (MH^+), found 277.



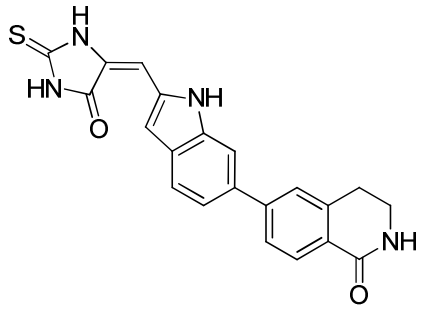
(*E*,*Z*)-5-((5-(1-Oxoisoindolin-5-yl)-1*H*-indol-2-yl)methylene)imidazolidine-2,4-dione (208). Reaction of **200** with 2-thioxoimidazolidin-4-one according to general procedure C gave **208** as a red solid (99%); mp >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 12.56 (br s, 0.7 H), 12.39 (br s, 0.3 H), 12.29 (br s, 0.7 H), 11.96 (br s, 1.0 H), 11.54 (br s, 0.3 H), 8.51 (br s, 1 H), 7.94 (s, 0.7 H), 7.91 (s, 0.3 H), 7.87 (s, 1 H), 7.77-7.82 (m, 1 H), 7.73 (d, *J* = 7.8 Hz, 0.3 H), 7.72 (d, *J* = 7.9 Hz, 0.7 H), 7.65 (d, *J* = 8.7 Hz, 0.7 H), 7.56-7.62 (m, 1 H), 7.52 (d, *J* = 8.7 Hz, 0.3 H), 7.39 (s, 0.3 H), 7.21 (s, 0.7 H), 6.73 (s, 0.7 H), 6.58 (s, 0.3 H), 4.43 (s, 2 H). LRMS (APCI$^-$) calcd for $C_{20}H_{13}N_4O_2S$ 373 (M-H), found 373. Anal. ($C_{20}H_{14}N_4O_2S$.0.80AcOH) C, H, N.



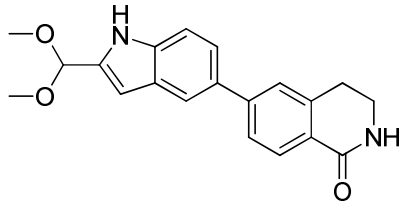
6-(2-(Dimethoxymethyl)-1*H*-indol-6-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (192). 6-Bromo-1*H*-indole-2-carbaldehyde was protected as the dimethyl acetal **183** according to a literature procedure,[46] then reacted with **149** according to general procedure A to give **192** as a brown oil (43%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.51 (bs, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 7.68 (d, *J* = 8.3 Hz, 1 H), 7.63 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.61 (t, *J* = 0.7 Hz, 1 H), 7.49 (d, *J* = 1.2 Hz, 1 H), 7.39 (dd, *J* = 8.2, 1.6 Hz, 1 H), 6.57 (quint, *J* = 1.0 Hz, 1 H), 5.91 (bs, 1 H), 5.67 (d, *J* = 0.8 Hz, 1 H), 3.62 (dt, *J* = 6.6, 2.8 Hz, 2 H), 3.41 (s, 6 H), 3.08 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{20}H_{21}N_2O_3$ 337 (MH^+), found 337.



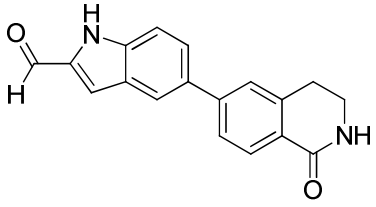
6-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-1*H*-indole-2-carbaldehyde (201). Deprotection of **192** according to general procedure H gave **201** as a dark orange solid (72%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.11 (br s, 1 H), 9.87 (s, 1 H), 7.95 (br s, 1 H), 7.94 (d, *J* = 7.9 Hz, 1 H), 7.86 (d, *J* = 8.3 Hz, 1 H), 7.71 (s, 1 H), 7.66 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.64 (s, 1 H), 7.48 (dd, *J* = 8.5, 1.6 Hz, 1 H), 7.44 (s, 1 H), 3.42 (dt, *J* = 6.6, 2.7 Hz, 2 H), 3.00 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{18}H_{15}N_2O_2$ 291 (MH^+), found 291.



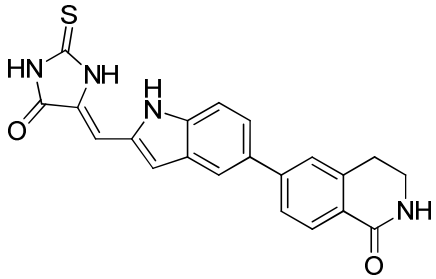
(*E*,*Z*)-6-(2-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)-1*H*-indol-6-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (210). Reaction of **201** with 2-thioxoimidazolidin-4-one according to general procedure C gave **210** as a red-brown solid (76%); mp >310^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 11.60-12.60 (br m, 2 H), 12.01 (s, 0.6 H), 11.55 (s, 0.4 H), 7.88-7.94 (m, 3 H), 7.65-7.74 (m, 3 H), 7.41-7.48 (m, 1 H), 7.33 (s, 0.4 H), 7.14 (s, 0.6 H), 6.71 (s, 0.6 H), 6.56 (s, 0.4 H), 3.42 (dt, *J* = 6.3, 2.6 Hz, 2 H), 2.96-3.01 (m, 2 H). LRMS (APCI$^-$) calcd for $C_{21}H_{15}N_4O_2S$ 387 (M-H), found 387. Anal. ($C_{21}H_{16}N_4O_2S.1.40H_2O$) C, H, N.



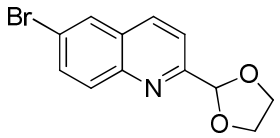
6-(2-(Dimethoxymethyl)-1*H*-indol-5-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (193). 5-Bromo-1*H*-indole-2-carbaldehyde was protected as the dimethyl acetal **184** according to a literature procedure,[46] then reacted with **149** according to general procedure A to give **193** as a yellow oil (50%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.47 (bs, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 7.86 (d, *J* = 0.8 Hz, 1 H), 7.63 (dd, *J* = 8.1, 1.8 Hz, 1 H), 7.42-7.51 (m, 3 H), 6.58-6.61 (m, 1 H), 5.90 (bs, 1 H), 5.67 (d, *J* = 0.8 Hz, 1 H), 3.61 (dt, *J* = 6.6, 2.8 Hz, 2 H), 3.40 (s, 6 H), 3.08 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{20}H_{21}N_2O_3$ 337 (MH^+), found 337.



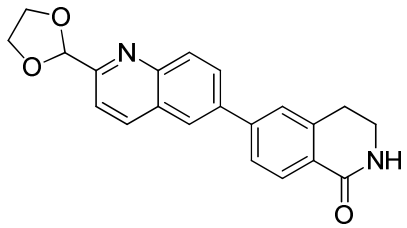
5-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-1*H*-indole-2-carbaldehyde (202). Deprotection of **193** according to general procedure H gave **202** as a pink solid (72%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.09 (br s, 1 H), 9.88 (s, 1 H), 8.11 (d, *J* = 0.8 Hz, 1 H), 7.91 (d, *J* = 7.9 Hz, 1 H), 7.90 (br s, 1 H), 7.72 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.64-7.69 (m, 2 H), 7.54 (d, *J* = 8.7 Hz, 1 H), 7.47 (dd, *J* = 2.0, 0.7 Hz, 1 H), 3.42 (dt, *J* = 6.6, 2.7 Hz, 2 H), 2.99 (t, *J* = 6.5 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{18}H_{15}N_2O_2$ 291 (MH^+), found 291.



(*E,Z*)-6-(2-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)-1H-indol-5-yl)-3,4-dihydroisoquinolin-1(2H)-one (211). Reaction of **202** with 2-thioxoimidazolidin-4-one according to general procedure C gave **211** as an orange solid (76%); mp >315^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] Observe *E*- and *Z*- isomers separately. δ 12.11-12.72 (br m, 1.6 H), 11.96 (s, 1 H), 11.52 (s, 0.4 H), 7.86-7.95 (m, 3 H), 7.48-7.69 (m, 4 H), 7.36 (s, 0.4 H), 7.20 (s, 0.6 H), 6.72 (s, 0.6 H), 6.57 (s, 0.4 H), 3.37-3.45 (m, 2 H), 2.95-3.01 (m, 2 H). LRMS (APCI$^-$) calcd for $C_{21}H_{15}N_4O_2S$ 387 (M-H), found 387. Anal. ($C_{21}H_{16}N_4O_2S$.0.80AcOH) C, H, N.

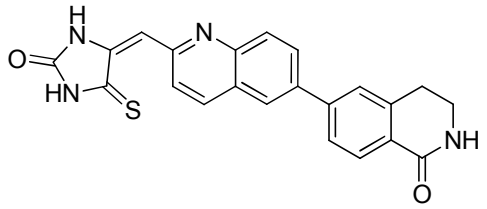


6-Bromo-2-(1,3-dioxolan-2-yl)quinolone (185). 6-Bromoquinoline-2-carbaldehyde was protected as the cyclic acetal according to a literature procedure[44] to give **185** as an orange solid (91%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.13 (d, *J* = 8.6 Hz, 1 H), 8.02 (d, *J* = 9.0 Hz, 1 H), 8.00 (d, *J* = 2.2 Hz, 1 H), 7.79 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.68 (d, *J* = 8.5 Hz, 1 H), 5.96 (s, 1 H), 4.11-4.19 (m, 2 H), 4.20-4.28 (m, 2 H). LRMS (APCI$^+$) calcd for $C_{12}H_{11}BrNO_2$ 281 (MH^+), found 281.



6-(2-(1,3-Dioxolan-2-yl)quinolin-6-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (194). Reaction of **185** and **149** according to general procedure A gave **194** as a pale brown solid (74%). ^{1}H NMR [400 MHz, $CDCl_3$] δ 8.28 (d, *J* = 8.5 Hz, 1 H), 8.24 (d, *J* = 8.8 Hz, 1 H), 8.20 (d, *J* = 8.1 Hz, 1 H), 8.06 (d, *J* = 2.0 Hz, 1 H), 8.00 (dd, *J* = 8.8, 2.2 Hz, 1 H), 7.72 (dd, *J* = 8.0, 1.9 Hz, 1 H), 7.70 (d, *J* = 5.5 Hz, 1 H), 7.58 (d, *J* = 1.2 Hz, 1

H), 6.01 (bs, 2 H), 4.15-4.20 (m, 2 H), 4.22-4.28 (m, 2 H), 3.64 (dt, *J* = 6.6, 2.8 Hz, 2 H), 3.18 (t, *J* = 6.6 Hz, 2 H). LRMS (APCI$^+$) calcd for $C_{21}H_{19}N_2O_3$ 347 (MH^+), found 347.



(*E,Z*)-6-(2-((2-Oxo-5-thioxoimidazolidin-4-ylidene)methyl)quinolin-6-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (212). Deprotection of **194** according to general procedure B gave aldehyde **203** as a brown solid which was reacted directly with 2-thioxoimidazolidin-4-one according to general procedure C. The desired product **212** was isolated as a green solid (71%); mp >310^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.60 (br s, 1 H), 11.88 (br s, 1 H), 8.48 (d, *J* = 8.6 Hz, 1 H), 8.45 (d, *J* = 9.0 Hz, 1 H), 8.37 (d, *J* = 2.0 Hz, 1 H), 8.21 (dd, *J* = 8.8, 2.1 Hz, 1 H), 7.95-8.01 (m, 2 H), 7.82-7.89 (m, 3 H), 6.75 (s, 1 H), 3.44 (dt, *J* = 6.6, 2.6 Hz, 2 H), 3.03 (t, *J* = 6.5 Hz, 2 H). LRMS (APCI$^-$) calcd for $C_{22}H_{15}N_4O_2S$ 399 (M-H), found 300. Anal. ($C_{22}H_{16}N_4O_2S$) C, H, N.

References

(38) Ortwine, D. F.; Malone, T. C.; Bigge, C. F.; Drummond, J. T.; Humblet, C.; Johnson, G.; Pinter, G.W. Generation of *N*-methyl-D-aspartate agonist and competitive antagonist pharmacophore models. Design and synthesis of phosphonoalkyl-substituted tetrahydroisoquinolines as novel antagonists. *J. Med. Chem.* **1992**, *35*, 1345-70.

(39) Wang, X.-J.; Tan, J.; Grozinger, K. A significantly improved condition for cyclization of phenethylcarbamates to *N*-alkylated 3,4-dihydroisoquinolones. *Tetrahedron Lett.* **1998**, *39*, 6609-6612.

(40) Fraser, H. L. and Gribble, G. W. A synthesis of 6,11-disubstituted benzo[*b*]carbazoles. *Can. J. Chem.* **2001**, *79*, 1515-21.

(41) Ran, J. –Q.; Huang, N.; Xu, H.; Yang, L., -M.; Min Lv, M.; Zheng, Y. –T. Anti HIV-1 agents 5: Synthesis and anti-HIV-1 activity of some *N*-arylsulfonyl-3-acetylindoles *in vitro*. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 3534-3536.

(44) Lu, T. -J.; Yang, J. -F.; Sheu, L. -J. An efficient method for the acetalisation of α,β-unsaturated aldehydes. *J. Org. Chem.*, **1995**, *60*, 2931-2934.

(45) Menet, C. J. M., Blanc, J., Hodges, A. J., Burli, R. W., Breccia, P., Blackaby, W. P., Van Rompaey, L. J. C., Fletcher, S. R. Preparation of [1,2,4]triazolo[1,5-a]pyridines as JAK inhibitors for the treatment of degenerative and inflammatory diseases. WO 2010010184 A1.

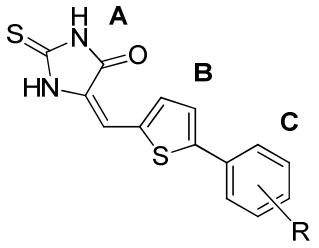
(46) Kumar, R. and Chakraborti, A. K. Copper(II) tetrafluoroborate as a novel and highly efficient catalyst for acetal formation. *Tetrahedron Lett*., **2005**, *46*, 8319-8323.

(47) Tsuritani, T.; Kii, S.; Akao, A.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. A short and efficient synthesis of isoindolin-1-ones. *Synlett*, **2006**, 801-803.

(48) Dally, R. D.; Dodge, J. A.; Hummel, C. W.; Jones, S. A.; Shepherd, T.A.; Wallace, O. B.; Weber, W. W. Selective estrogen receptor modulators. WO 2005073205 A1.

Biological Activity for Other Selected Compounds

Table 5. *in vitro* Perforin-Inhibitory Activity for Selected Compounds



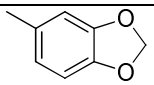
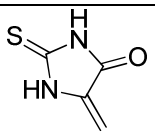
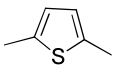
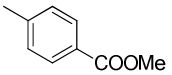
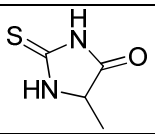
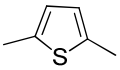
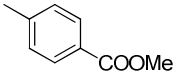
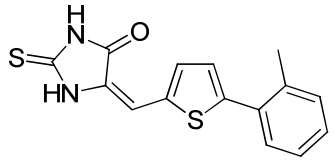
Cmpd	R	Jurkat IC_{50} (μM)
205	2-Me	>20
206	3-Me	>20
207	4-Me	>20
208	2-OMe	>20
209	3-OMe	>20
210	4-OMe	8.93
211	4-NHAc	>20
212		>20

Table 6. Effect of Double Bond Reduction

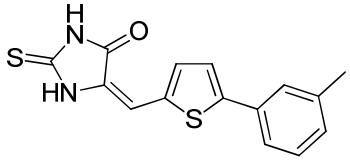
Cmpd	A-Subunit	B-Subunit	C-Subunit	Jurkat IC_{50} (μM)
59				1.62
213				>20

Further Experimental for Selected Compounds

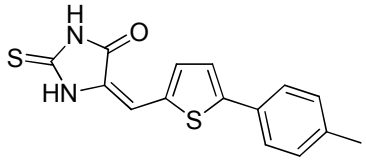
The general procedures referred to below are described in the published article.



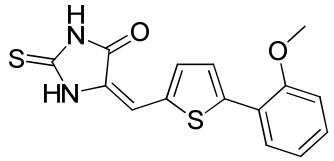
(*E,Z*)-2-Thioxo-5-((5-*o*-tolylthiophen-2-yl)methylene)imidazolidin-4-one (213). Reaction of 5-*o*-tolylthiophene-2-carbaldehyde with 2-thioxoimidazolidin-4-one according to general procedure C gave **213** as a dark red solid (37%), mp (AcOH) 224-226^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.32 (s, 1 H), 11.95 (s, 1 H), 7.82 (d, *J* = 3.8 Hz, 1 H), 7.46 (dd, *J* = 1.5, 6.8 Hz, 1 H), 7.31 (m, 4 H), 6.64 (s, 1 H), 2.45 (s, 3 H). Anal. ($C_{15}H_{12}N_2OS_2.0.2H_2O$) C, H, N.



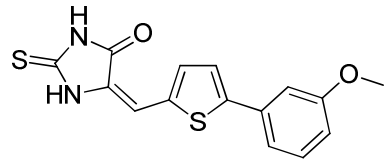
(*E,Z*)-2-Thioxo-5-((5-*m*-tolylthiophen-2-yl)methylene)imidazolidin-4-one (214). Reaction of 5-*m*-tolylthiophene-2-carbaldehyde with 2-thioxoimidazolidin-4-one according to general procedure A gave **214** as a brown solid (31%), mp (AcOH) >295^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.34 (s, 1 H), 11.94 (s, 1 H), 7.81 (d, *J* = 3.9 Hz, 1 H), 7.62 (d, *J* = 3.9 Hz, 1 H), 7.50-7.73 (m, 2 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 6.63 (s, 1 H), 2.34 (s, 3 H). Anal. ($C_{15}H_{12}N_2OS_2.H_2O$) C, N, H; + 0.5.



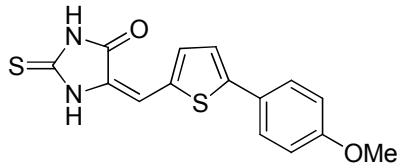
(*E,Z*)-2-Thioxo-5-((5-*p*-tolylthiophen-2-yl)methylene)imidazolidin-4-one (215) . Reaction of 5-*p*-tolylthiophene-2-carbaldehyde with 2-thioxoimidazolidin-4-one according to general procedure A gave **215** as an orange solid (78%), mp (AcOH) >300^{o}C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.35 (s, 1 H), 11.91 (s, 1 H), 7.80 (d, *J* = 3.9 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 2 H), 7.58 (d, *J* = 3.9 Hz, 1 H), 7.26 (d, *J* = 7.9 Hz, 2 H) , 6.61 (s, 1 H), 2.33 (s, 3 H). Anal. ($C_{15}H_{12}N_2OS_2.0.2H_2O$) C, H, N.



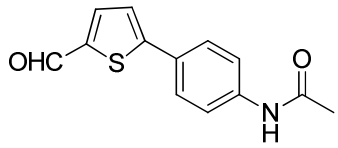
(*E,Z*)-5-((5-(2-Methoxyphenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (216). Reaction of 5-(2-methoxyphenyl)thiophene-2-carbaldehyde with 2-thioxoimidazolidin-4-one according to general procedure A gave **216** as a red solid (54%), mp (AcOH) 255-258°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.30 (s, 1 H), 11.96 (s, 1 H), 7.85 (d, *J* = 3.9 Hz, 1 H), 7.82 (dd, *J* = 1.3, 7.8 Hz, 1 H), 7.72 (d, *J* = 4.0 Hz, 1 H), 7.35 (t, *J* = 8.6 Hz, 1 H), 7.17 (d, *J* = 8.0 Hz, 1 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 6.59 (s, 1 H), 3.83 (s, 3 H). Anal. ($C_{15}H_{12}N_2O_2S_2$) C, H, N.



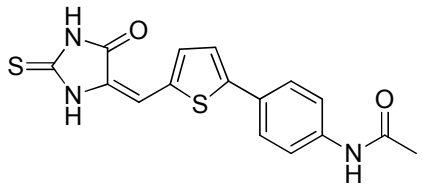
(*E,Z*)-5-((5-(3-Methoxyphenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (217). Reaction of 5-(3-methoxyphenyl)thiophene-2-carbaldehyde with 2-thioxoimidazolidin-4-one according to general procedure A gave **217** as an orange solid (64%), mp (AcOH) 267-270°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.34 (s, 1 H), 11.94 (s, 1 H), 7.81 (d, *J* = 3.9 Hz, 1 H), 7.66 (d, *J* = 3.9 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.27 (m, 2 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 6.62 (s, 1 H), 3.84 (s, 3 H). Anal. ($C_{15}H_{12}N_2O_2S_2$) C, H, N.



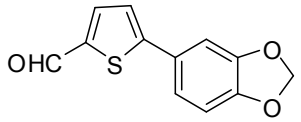
(*E,Z*)-5-((5-(4-Methoxyphenyl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (218). Reaction of 5-(4-methoxyphenyl)thiophene-2-carbaldehyde with 2-thioxoimidazolidin-4-one according to general procedure A gave **218** as a purple-brown solid (38%), mp (AcOH) 288-293°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.32 (br s, 1 H), 11.90 (br s, 1 H), 7.79 (d, *J* = 4.0 Hz, 1 H), 7.65 (d, *J* = 8.8 Hz, 2 H), 7.51 (d, *J* = 4.0 Hz, 1 H), 7.02 (d, *J* = 8.9 Hz, 2 H), 6.61 (s, 1 H), 3.81 (s, 3 H). HRMS (EI^+) calcd for $C_{15}H_{12}N_2O_2S_2$ 316.0340 (M^+), found 316.0338.



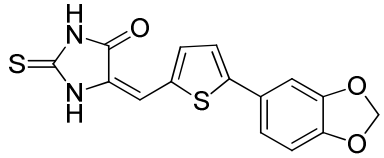
***N*-(4-(5-Formylthiophen-2-yl)phenyl)acetamide**. *N*-(4-Iodophenyl)acetamide and 5-formyl-2-thiopheneboronic acid were reacted according to general procedure B, followed by purification by flash column chromatography on silica gel (20% EtOAc/hexanes as eluant) to give *N*-(4-(5-formylthiophen-2-yl)phenyl)acetamide as a yellow solid (40%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 10.14 (br s, 1 H), 9.88 (s, 1 H), 8.01 (d, *J* = 4.0 Hz, 1 H), 7.75 (d, *J* = 8.8 Hz, 2 H), 7.68 (d, *J* = 8.8 Hz, 2 H), 7.64 (d, *J* = 3.9 Hz, 1 H), 2.07 (s, 3 H). LRMS ($APCI^+$) calcd for $C_{13}H_{12}NO_2S$ 246 (MH^+), found 246.



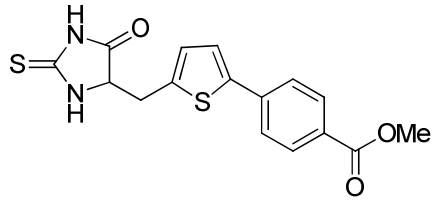
(*E,Z*)-*N*-(4-(5-((5-Oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-yl)phenyl)acetamide (219). Reaction of *N*-(4-(5-formylthiophen-2-yl)phenyl)acetamide with 2-thioxoimidazolidin-4-one according to general procedure A gave **219** as an orange solid (39%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.30 (br s, H), 11.80 (br s, 1 H), 10.07 (s, 1 H), 7.80 (br d, *J* = 3.8 Hz, 1 H), 7.65 (br s, 4 H), 7.54 (d, *J* = 4.0 Hz, 1 H), 6.61 (s, 1 H), 2.06 (s, 3 H). Anal. ($C_{16}H_{13}N_3O_2S_2.0.5H_2O$) C, H, N.



5-(Benzo[*d*][1,3]dioxol-5-yl)thiophene-2-carbaldehyde. 4-Bromo-1,2-(methylenedioxy)benzene and 5-formyl-2-thiopheneboronic acid were reacted according to general procedure B, followed by purification by flash column chromatography on silica gel (10% EtOAc/hexanes as eluant) to give 5-(benzo[*d*][1,3]dioxol-5-yl)thiophene-2-carbaldehyde as a yellow solid (13%). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 9.87 (s, 1 H), 7.99 (d, *J* = 4.0 Hz, 1 H), 7.63 (d, *J* = 4.0 Hz, 1 H), 7.41 (d, *J* = 1.8 Hz, 1 H), 7.31 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.01 (d, *J* = 8.1 Hz, 1 H), 6.10 (s, 2 H). LRMS (APCI$^+$) calcd for $C_{12}H_9O_3S$ 233 (MH^+), found 233.



(*E,Z*)-5-((5-(Benzo[*d*][1,3]dioxol-5-yl)thiophen-2-yl)methylene)-2-thioxoimidazolidin-4-one (220). Reaction of 5-(benzo[*d*][1,3]dioxol-5-yl)thiophene-2-carbaldehyde with 2-thioxoimidazolidin-4-one according to general procedure A gave **220** as a red-orange solid (84%), mp (AcOH) >300°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 12.34 (br s, 1 H), 11.88 (br s, 1 H), 7.78 (d, *J* = 4.0 Hz, 1 H), 7.53 (d, *J* = 4.0 Hz, 1 H), 7.32 (d, *J* = 1.8 Hz, 1 H), 7.20 (dd, *J* = 8.1, 1.9 Hz, 1 H), 6.99 (d, *J* = 8.1 Hz, 1 H), 6.60 (s, 1 H), 6.08 (s, 2 H). Anal. ($C_{15}H_{10}N_2O_3S_2.0.25H_2O$) C, H, N.



Methyl 4-(5-((5-oxo-2-thioxoimidazolidin-4-yl)methyl)thiophen-2-yl)benzoate (221). (*E,Z*)-Methyl 4-(5-((5-oxo-2-thioxoimidazolidin-4-ylidene)methyl)thiophen-2-

yl)benzoate (**59**) (105 mg, 0.31 mmol) was dissolved in DMSO (1.5 ml), to which was added AcOH (3.0 mL). This mixture was heated to 105°C, Zn powder (100 mg, 1.53 mmol) added, and heating and stirring continued for 3 h. The mixture was then allowed to cool, then partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was washed with further water (2x50 mL), and all fractions filtered to collect the precipitated product which was washed well with water and dried under vacuum. The title compound **221** was isolated as a pale brown solid (75 mg, 71%), mp (AcOH) 240-244°C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ 11.55 (s, 1 H), 10.09 (s, 1 H), 7.96 (d, *J* = 8.5 Hz, 2 H), 7.72 (d, *J* = 8.6 Hz, 2 H), 7.52 (d, *J* = 3.7 Hz, 1 H), 6.92 (d, *J* = 3.7 Hz, 1 H), 4.59 (t, *J* = 4.5 Hz, 1 H), 3.86 (s, 3 H), 3.22-3.34 (m, 2 H). LRMS ($APCI^+$) calcd for $C_{16}H_{15}N_2O_3S_2$ 347 (MH^+), found 347. Anal. ($C_{16}H_{14}N_2O_3S_2.0.25H_2O$) C, H, N.

Table 7. Elemental Analysis Results for Target Compounds

Cmpd		Calcd			Found		
		C	H	N	C	H	N
43	$C_{14}H_{10}N_2OS_2$	58.7	3.5	9.8	58.9	3.6	9.8
44	$C_{14}H_9ClN_2OS_2.0.5H_2O$	51.0	3.1	8.5	51.0	2.8	8.7
45	$C_{14}H_9ClN_2OS_2.0.25H_2O$	51.7	2.9	8.6	51.4	2.8	8.7
46	$C_{14}H_9ClN_2OS_2$	52.4	2.8	8.7	52.3	2.9	8.6
47	$C_{14}H_9FN_2OS_2.1.25H_2O$	51.4	3.2	8.6	51.5	2.9	8.6
48	$C_{14}H_9FN_2OS_2$	55.3	3.0	9.2	55.0	3.0	9.2
49	$C_{14}H_8F_2N_2OS_2.0.25H_2O$	51.4	2.6	8.6	51.5	2.6	8.5
50	$C_{15}H_9F_3N_2OS_2$	50.8	2.6	7.9	50.7	2.7	8.1
51	$C_{15}H_9F_3N_2OS_2$	50.8	2.6	7.9	50.8	2.6	7.8
52	$C_{15}H_9N_3OS_2.0.75H_2O$	55.5	3.3	12.9	55.6	3.3	12.4
53	$C_{14}H_{10}N_2O_2S_2$	55.6	3.3	9.3	55.9	3.5	9.3
54	$C_{15}H_8ClF_3N_2OS_2$	45.2	2.3	7.0	45.0	2.2	6.9
55	$C_{14}H_9BrN_2OS_2.0.5H_2O$	44.9	2.7	7.5	44.5	2.5	7.4
56	$C_{15}H_{12}N_2OS_3$	54.2	3.6	8.4	54.3	3.8	8.6
57	$C_{16}H_{12}N_2O_2S_2.0.25H_2O$	57.9	3.7	8.7	57.7	3.8	8.4
58	$C_{17}H_{14}N_2O_3S_2$	57.0	3.9	7.8	57.0	4.0	7.8
59	$C_{16}H_{12}N_2O_3S_2$	55.8	3.5	8.1	55.7	3.4	8.1
60	$C_{15}H_{11}N_3O_2S_2.0.5H_2O$	53.2	3.6	12.4	53.1	3.5	11.9
61	$C_{15}H_{11}N_3O_2S_2$	54.7	3.4	12.8	55.0	3.5	12.6
67	$C_{16}H_{13}N_3O_2S_2$	56.0	3.8	12.2	55.9	3.9	12.2
68	$C_{17}H_{15}N_3O_2S_2$	57.1	4.2	11.8	57.2	4.2	11.6
69	$C_{19}H_{17}N_3O_3S_2$	57.1	4.3	10.5	56.9	4.2	10.4
70	$C_{21}H_{22}N_4O_3S_2.1.5H_2O$	53.7	5.4	11.9	53.6	5.1	11.9
72	$C_{17}H_{15}N_3O_3S_2$	54.7	4.1	11.3	54.4	4.1	11.2
73	$C_{18}H_{17}N_3O_3S_2$	55.8	4.4	10.8	56.1	4.6	10.6
74	$C_{18}H_{17}N_3O_3S_2$	55.8	4.4	10.8	55.5	4.6	10.9
75	$C_{18}H_{17}N_3O_4S_2$	53.6	4.3	10.4	53.3	4.4	10.3
62	$C_{17}H_{14}N_2O_3S_2$	57.0	3.9	7.8	56.9	4.0	7.9
64	$C_{15}H_{13}N_3O_3S_3$	47.5	3.5	11.1	47.2	3.5	11.2
65	$C_{13}H_9N_3OS_2.0.25H_2O$	53.5	3.3	14.4	53.6	3.4	14.3
66	$C_{13}H_9N_3OS_2.1.25H_2O$	49.6	3.8	13.4	49.7	3.4	13.2
118	$C_{16}H_{11}N_3O_2S_2.1.5H_2O$	52.2	3.8	11.4	52.2	3.7	10.9
119	$C_{17}H_{13}N_3O_2S_2$	57.5	3.7	11.8	57.6	3.7	11.6
120	$C_{18}H_{15}N_3O_2S_2.0.25H_2O$	57.8	4.2	11.2	57.5	4.1	11.4
122	$C_{20}H_{19}N_3O_2S_2$	60.4	4.8	10.6	60.2	4.9	10.5
124	$C_{20}H_{17}N_3O_4S_2.0.5H_2O$	55.0	4.2	9.6	55.1	4.0	9.6
125	$C_{18}H_{15}N_3O_3S_2.0.75H_2O$	54.2	4.2	10.5	54.2	4.3	10.2
126	$C_{19}H_{17}N_3O_3S_2.0.5H_2O$	55.9	4.4	10.3	55.8	4.2	10.2
127	$C_{19}H_{17}N_3O_4S_2.0.75H_2O$	53.2	4.4	9.8	53.2	4.3	9.6
128	$C_{18}H_{13}N_3O_3S_2.0.25AcOH$	55.8	4.2	10.6	56.2	3.9	10.3
129	$C_{19}H_{15}N_3O_4S_2.0.25H_2O$	54.6	3.7	10.1	54.5	3.8	9.7
131	$C_{21}H_{22}N_4O_2S_2.H_2O$	56.8	5.4	12.6	56.9	5.5	12.8
134	$C_{23}H_{24}N_4O_2S_2.0.5H_2O$	59.8	5.5	12.1	59.5	5.3	11.8
135	$C_{18}H_{15}N_3O_2S_2$	58.5	4.1	11.4	58.3	4.1	11.4

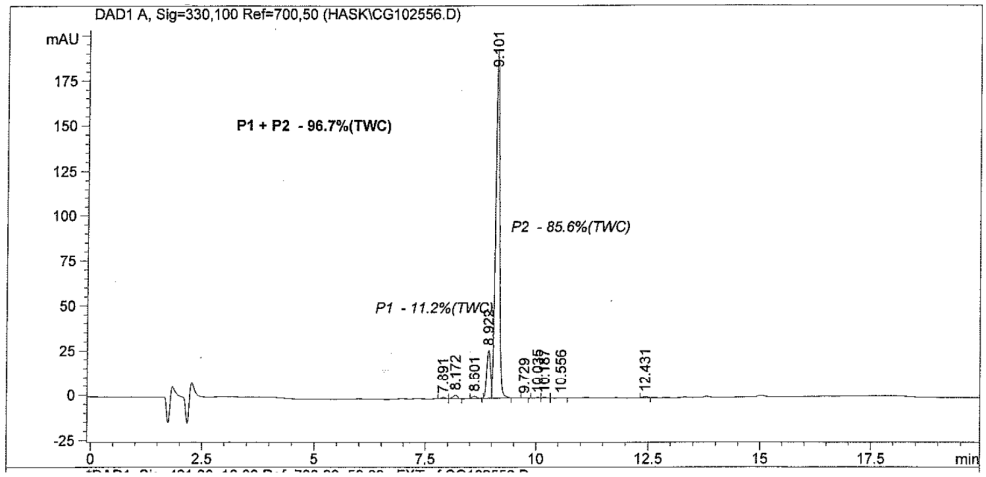
136	$C_{16}H_{11}N_3O_3S.1.25H_2O$	55.2	3.9	12.0	55.52	3.60	11.6
165	$C_{16}H_{11}N_3O_2S_2$	56.3	3.3	12.3	56.2	3.3	12.2
166	$C_{17}H_{13}N_3O_2S_2$	57.5	3.7	11.8	57.5	3.7	11.9
167	$C_{17}H_{13}N_3O_2S_2.0.4H_2O$	56.3	3.8	11.6	56.0	3.8	11.8
168	$C_{17}H_{13}N_3O_2S_2.0.5H_2O$	56.0	3.9	11.5	55.8	3.9	11.6
169	$C_{18}H_{15}N_3O_2S_2.0.1H_2O$	58.2	4.1	11.3	57.9	4.0	11.3
170	$C_{18}H_{15}N_3O_2S_2.H_2O$	55.8	4.4	10.8	55.8	4.4	10.4
178	$C_{19}H_{15}N_3O_2S_2.H_2O$	57.1	4.3	10.5	57.4	4.2	10.4
205	$C_{18}H_{13}N_3O_2S.0.5AcOH$	62.5	4.1	11.5	62.7	4.2	11.5
206	$C_{18}H_{13}N_3O_2S.0.5AcOH$	62.5	4.1	11.5	62.8	4.3	11.5
207	$C_{17}H_{12}N_4O_2S.0.5H_2O$	59.1	3.8	16.2	59.4	3.6	16.0
208	$C_{20}H_{14}N_4O_2S.0.50AcOH$	62.4	4.0	13.9	62.2	4.3	14.1
209	$C_{20}H_{14}N_4O_2S.0.75AcOH$	61.6	4.1	13.4	61.5	4.3	13.1
210	$C_{21}H_{16}N_4O_2S.1.5H_2O$	60.7	4.6	13.5	60.8	4.5	13.4
211	$C_{21}H_{16}N_4O_2S.0.75AcOH$	62.3	4.4	12.9	62.0	4.4	13.2
212	$C_{22}H_{16}N_4O_2S$	65.7	4.1	13.7	66.0	4.0	14.0
213	$C_{15}H_{12}N_2OS_2.0.25H_2O$	59.1	4.1	9.2	59.1	4.1	9.5
214	$C_{15}H_{12}N_2OS_2.H_2O$	56.6	4.4	8.8	56.9	3.9	8.9
215	$C_{15}H_{12}N_2OS_2.0.25H_2O$	59.1	4.1	9.2	59.5	4.1	9.3
216	$C_{15}H_{12}N_2O_2S_2$	56.9	3.8	8.9	56.8	3.8	8.9
217	$C_{15}H_{12}N_2O_2S_2$	56.9	3.8	8.9	57.2	3.8	8.9
219	$C_{16}H_{13}N_3O_2S_2.0.5H_2O$	54.5	4.0	11.9	54.5	4.0	11.9
220	$C_{15}H_{10}N_2O_3S_2.0.25H_2O$	53.9	3.2	8.4	53.8	3.2	8.4
221	$C_{16}H_{14}N_2O_3S_2.0.25H_2O$	54.8	4.2	8.0	54.7	4.3	7.9

Table 8. HRMS and HPLC for Target Compounds

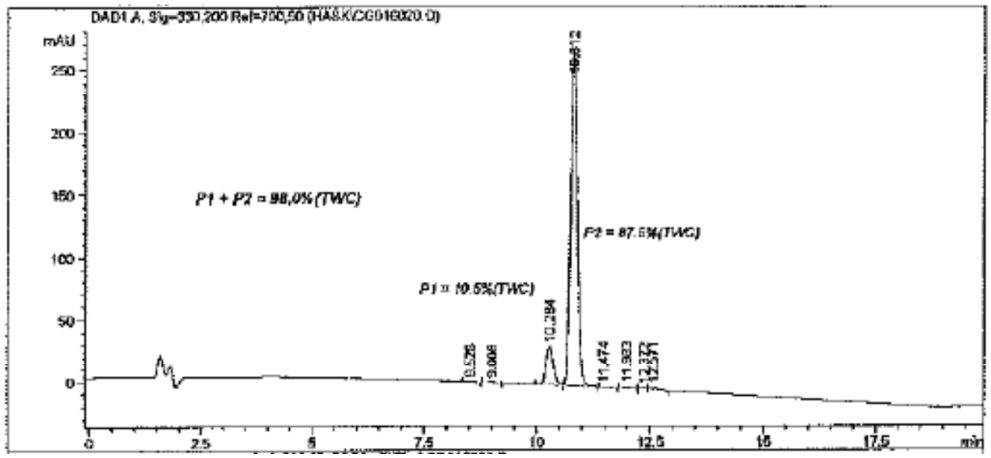
	HRMS			**HPLC**
Cmpd	**Formula**	**Calcd.**	**Found**	
71	$C_{22}H_{25}N_4O_3S_2$ (MH^+)	457.1363	457.1369	96.7%
63	$C_{15}H_{11}N_2O_3S_3$ (M-H)	362.9937	362.9922	96.9%
121	$C_{19}H_{16}N_3O_2S_2$ (M-H)	382.0689	382.0697	96.6%
123	$C_{19}H_{18}N_3O_2S_2$ (MH^+)	384.0835	384.0821	98.3%
130	$C_{22}H_{23}N_4O_3S_2$ (MH^+)	455.1206	455.1201	94.7%
132	$C_{24}H_{27}N_4O_2S_2$ (MH^+)	467.1570	467.1567	98.1%
133	$C_{24}H_{28}N_5O_2S_2$ (MH^+)	482.1679	482.1675	95.1%
204	$C_{16}H_{12}N_3O_2S_2$ (MH^+)	342.0371	342.0372	99.8%
218	$C_{15}H_{12}N_2O_2S_2$ (M^+)	316.0340	316.0338	96.7%

HPLC Traces For Selected Compounds

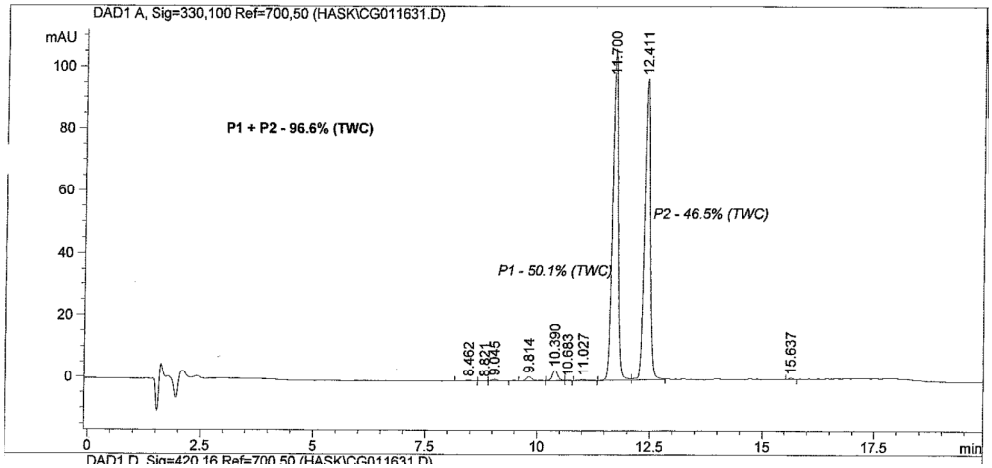
Compound **71**:



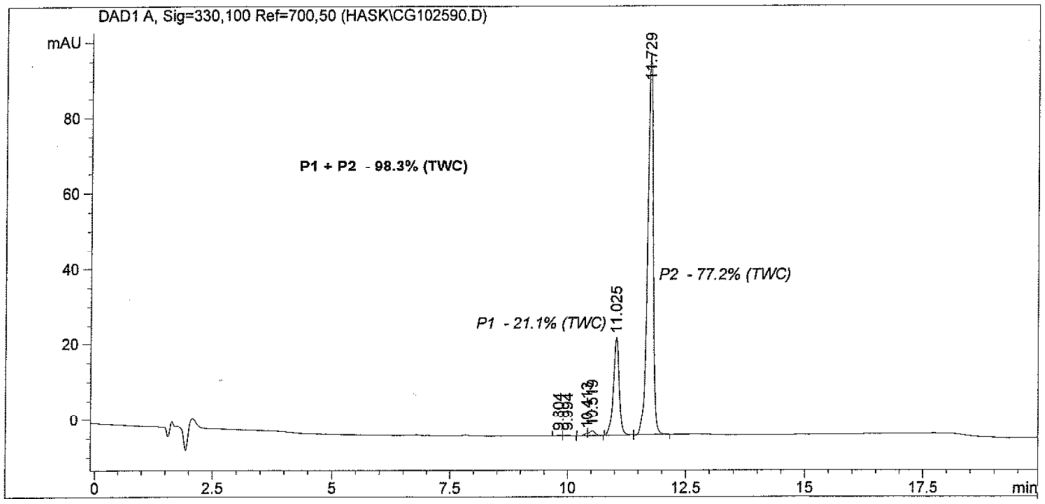
Compound **63**:



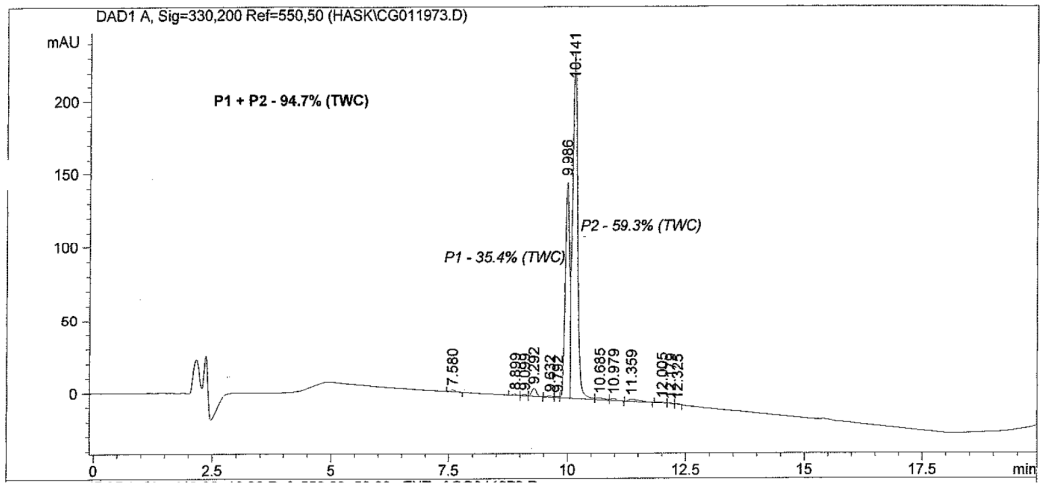
Compound **121**:



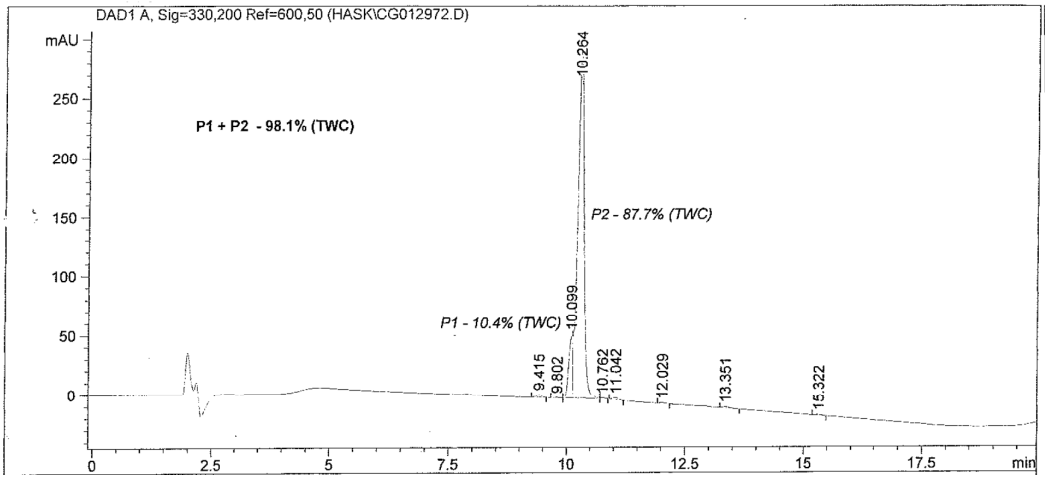
Compound **123**:



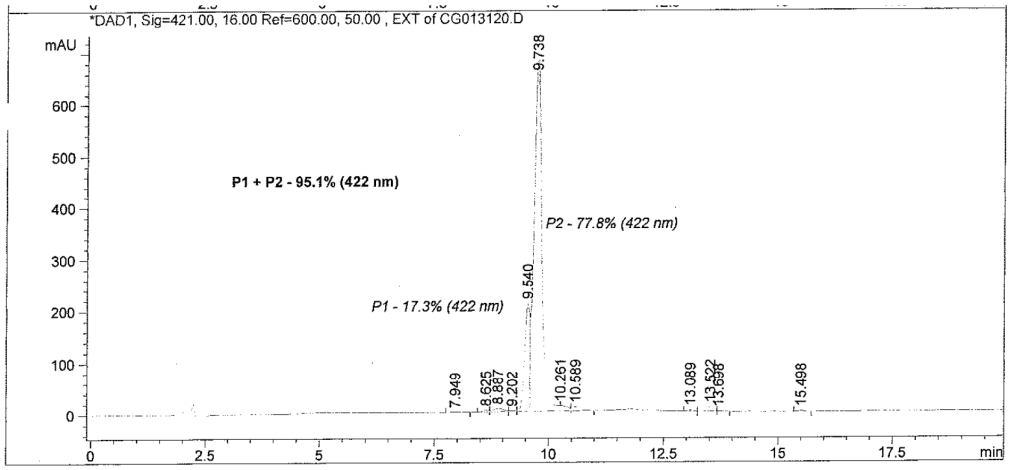
Compound **130**:



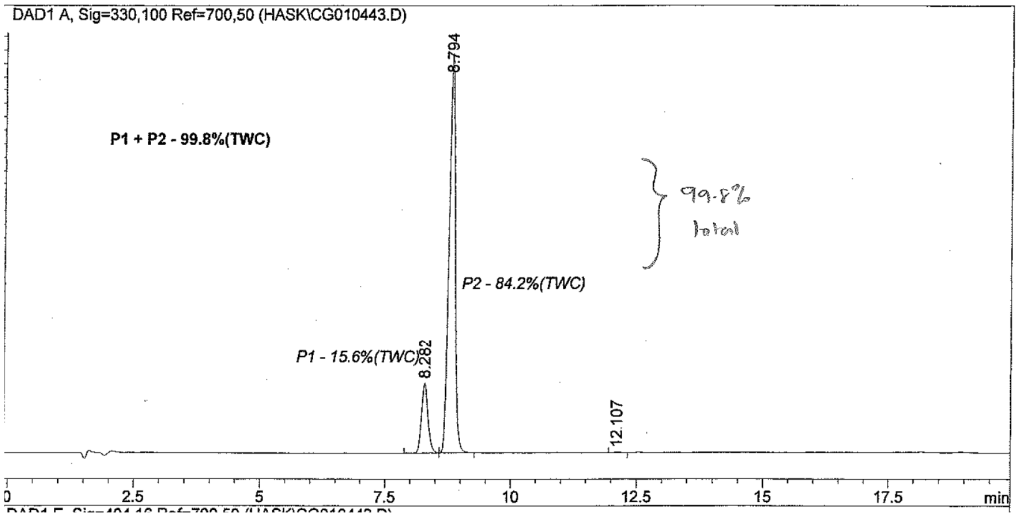
Compound **132**:



Compound **133**:



Compound **204**:



Compound **218**: