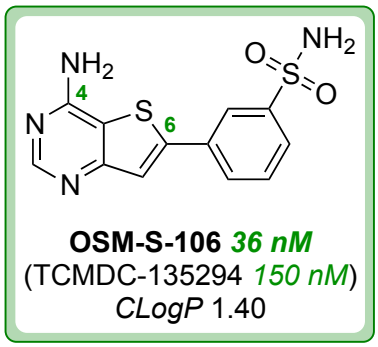
OSDDMalaria Open Consultation on Aminothienopyrimidines
Summary Document

The OSDDMalaria team held an open meeting on Monday 13th May to discuss the next molecules for synthesis and evaluation. This document is going to be circulated to a team of expert medicinal chemists who will guide the team's decision regarding which compounds to synthesise next. This draft may be edited and refined following guidance from MMV and +Matthew Todd prior to circulation.
All of the data contained in this summary can be found on the various websites/blog sites used by the OSDDMalaria team, this document has been compiled to summarise the data in a single document for those generous enough to offer their advice.

Introduction

In 2010, GlaxoSmithKline (GSK) released chemical and biological data pertaining to some 13,500 compounds that displayed potent antimalarial activity *in vitro* (Nature paper). Medicinal chemists at the Medicines for Malaria Venture (MMV) identified several compounds present in this dataset, which they believed to be excellent hits. These compounds had the combination of a drug-like profile (polar, low molecular weight, amenable to structural variation), high potency, low cytotoxicity, no known intellectual property issues, and to the best of their knowledge they were not the subject of antimalarial research by any other group, and hence suitable for an open source project.



OSM-S-106 ***36 nM***
(TCMDC-135294 *150 nM*)
CLogP 1.40

One such compound was TCMDC-135294, which was found to have an IC50 of 150 nM against *P. falciparum* 3D7. The high throughput nature of the GSK screen carried the possibility of a false positive, and thus the first step was to resynthesise the hit compound and confirm its antimalarial activity. TCMDC-135294 was resynthesised (project identifier: OSM-S-106) and its potent activity was confirmed (36 nM).

To see if the compound's activity could be further optimised, the team are currently exploring the druggability (solubility, metabolic degradation etc.) of the hit compound. Additionally, the synthesis of small sets of diverse analogs is currently underway, to see if an interesting structure-activity relationship can be found, in the hope that the compound might be suitable for lead optimisation. MMV has developed a set of compound progression criteria, which are being used to inform the project.

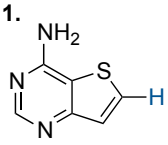
First Round

A number of compounds, both synthetic and commercial (including designed compounds and their intermediates as well as unanticipated by products and side products) have been evaluated to date. So far, most compounds tested have been inactive (>40 000 nM) although some interesting observations have been noted (all data can be found in on at the end of this document pages x–x).

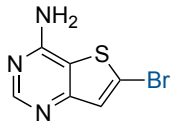
1. Changing the C-6 substituent to H, Br, Ph or a selection of *para*-substituted phenyls kills activity.
2. Replacing the amino group at C-4 with a morpholine group kills activity
3. Replacing the *ortho*-sulfonamide with an amide kills activity.
4. Replacing the amino group at C-4 with a (4-fluorobenzyl)piperazine results in moderate levels of activity (OSM-S-137, 1700 nM).

It should be noted that the synthesis of OSM-S-137 was inspired by another molecule found in the TCAMS data set. TCMDC-132385 was found to display activity of 1015 nM. The team postulated that substituting the C-6 phenyl group with benzene sulphonamide would lead to increased activity, however the activities were comparable. TCMDC-132385 is currently being resynthesised in the Sydney lab in order to confirm the accuracy of the result from the HTS.

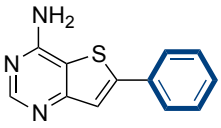
1.



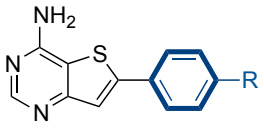
OSM-S-71
>40 000 nM
CLogP 1.10



OSM-S-139
to be sent
CLogP 1.97

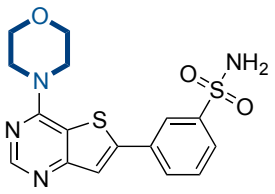


OSM-S-123
>40 000 nM
CLogP 3.20



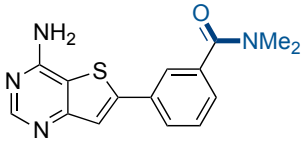
OSM-S-128–132
and
OSM-S-134
>40 000 nM

2.

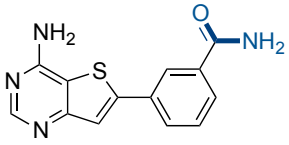


OSM-S-127
42% @ 40 000 nM
CLogP 1.60

3.

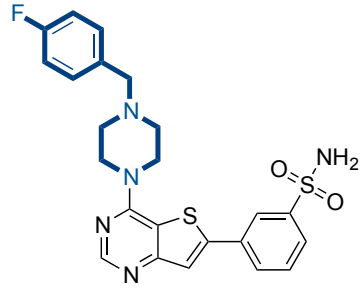


OSM-S-133
73% @ 40 000 nM
CLogP 1.68

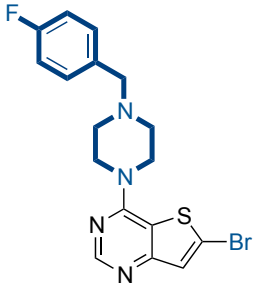


OSM-S-135
>40 000 nM
CLogP 1.74

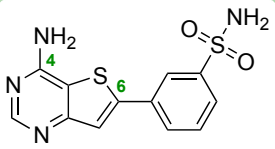
4.



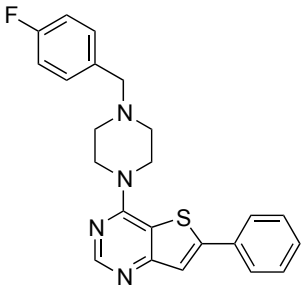
OSM-S-137
1700 nM
CLogP 4.03



OSM-S-136
15 000 uM
CLogP 4.59



OSM-S-106 ***36 nM***
(TCMDC-135294 *150 nM*)
CLogP 1.40

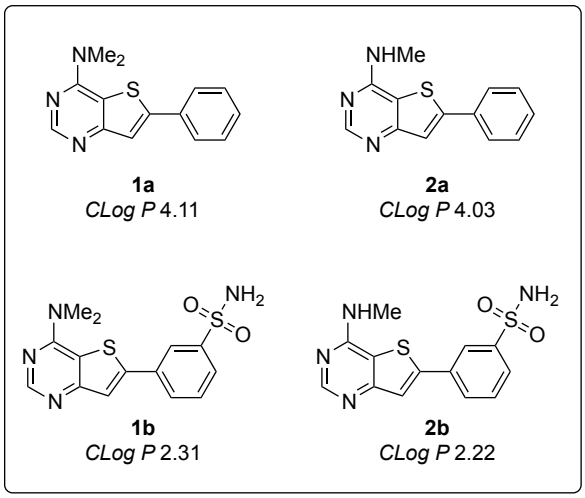


TCMDC-132385
1015 nM
CLogP 5.83

Second Round

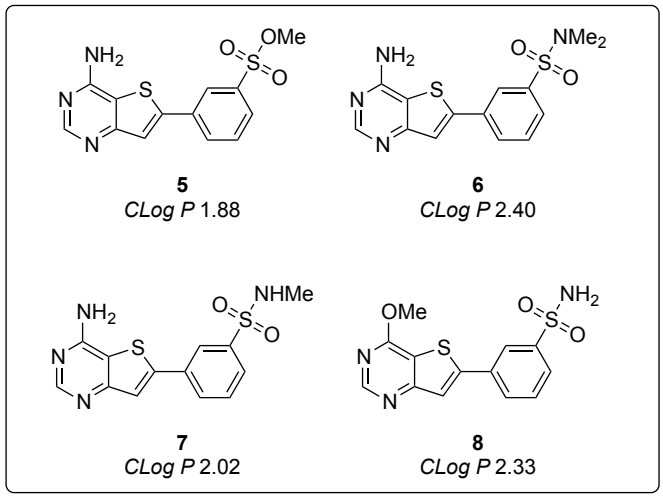
These early results could suggest that OSM-S-106 is a singleton, but the team feel that there is still space around the core that should be explored. The team have therefore proposed the following sets of molecules for the next round of synthesis. It is hoped that consultation with the medicinal chemistry community may help to refine this list of 'Wanted Compounds'. Additionally the team would be delighted to hear suggestions of other analogs based on this series.

Proposed Compounds



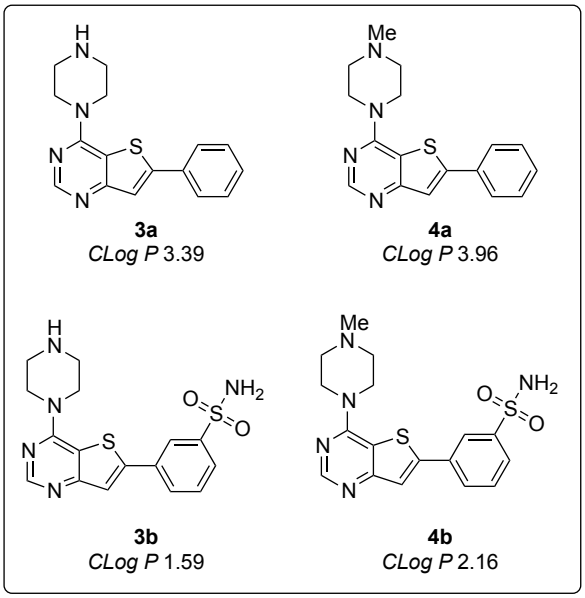
1a *CLog P* 4.11 | **2a** *CLog P* 4.03

1b *CLog P* 2.31 | **2b** *CLog P* 2.22



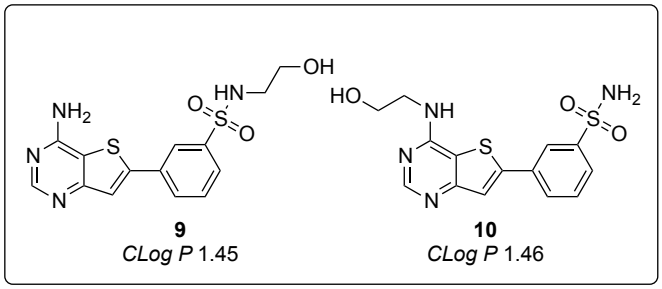
5 *CLog P* 1.88 | **6** *CLog P* 2.40

7 *CLog P* 2.02 | **8** *CLog P* 2.33



3a *CLog P* 3.39 | **4a** *CLog P* 3.96

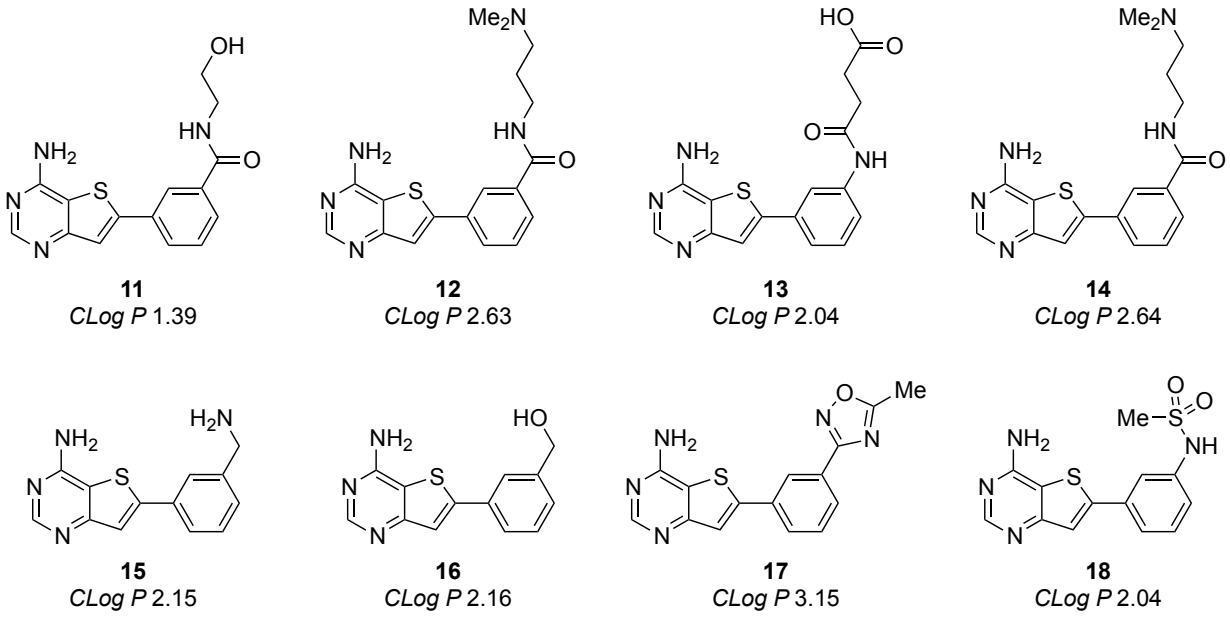
3b *CLog P* 1.59 | **4b** *CLog P* 2.16



9 *CLog P* 1.45 | **10** *CLog P* 1.46

- The first set of compounds (**1–2**) are designed to explore the effect of *N*-methylation on activity for both phenyl and benzene sulphonamide substituted compounds.
- The second (**3–4**) will probe the effect piperazine ring substitution.
- The third (**5–8**) should give insight into the importance of the hydrogen donor extending from the *meta*-position of the C-6 aryl group.
- The fourth (**9** and **10**) are designed to increase the number of interactions at the active site.

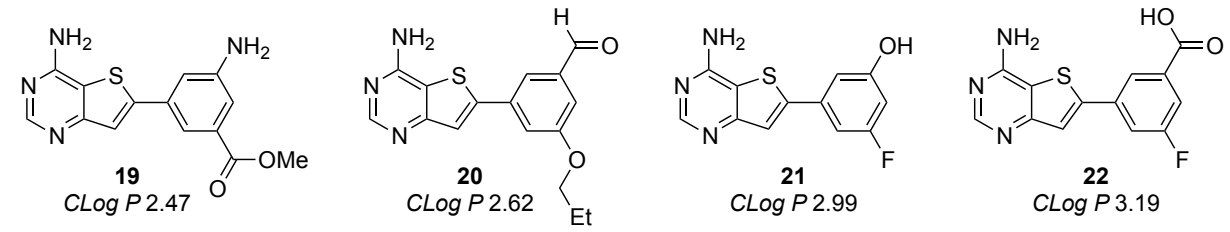
Following open consultation, the team also decided to look at some more *meta*-substituted boronic acids that could be incorporated to modified analogs of OSM-S-106. The compounds have below have been proposed in the hope that additional binding sites might be accessed (**11**–**14**), the importance of the hydrogen bond donor on the C-6 aryl group might be explored (**15** and **16**) and additionally that different functional groups might be explored (**17** and **18**). In particular, the team are keen to explore the properties of the reverse sulphonamide (**18**).



11 *CLog P* 1.39 | **12** *CLog P* 2.63 | **13** *CLog P* 2.04 | **14** *CLog P* 2.64

15 *CLog P* 2.15 | **16** *CLog P* 2.16 | **17** *CLog P* 3.15 | **18** *CLog P* 2.04

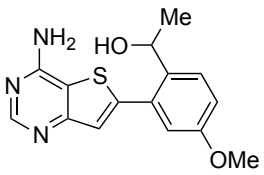
Additionally, a search of commercially available di-*meta* substituted boronic acids and esters was performed. The team considered the possibility that some singly *meta*-substituted compounds might orient themselves in a position where a hydrogen bond donating or accepting *meta*-substituent is unable to interact with the binding pocket. It was suggested therefore that design and evaluation of appropriate di-*meta* substituted analog would be of interest. Those commercially available di-*meta* compounds containing one or more polar group were highlighted as potential targets (**19**–**22**).



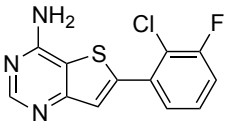
19 *CLog P* 2.47 | **20** *CLog P* 2.62 | **21** *CLog P* 2.99 | **22** *CLog P* 3.19

Third Round

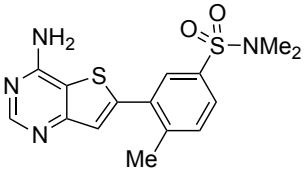
Some solubility issues were flagged in previous rounds of testing for the aminothienopyrimidines. This was surprising owing to the favourable CLogP values calculated for the compounds. Paul Willis suggested that this might be a result of their highly planar structure leading to favourable stacking interactions. He proposed that the team synthesise some *ortho*-substituted derivatives, as a bulky group in the *ortho*-position could force the aryl ring to twist out of plane and therefore perhaps reduce the propensity of the molecule to stack, leading to more favourable solubility's. Very few *ortho*,*meta*-substituted boronic esters/acids are available and the majority are prohibitively expensive. However, depending on the result from the second round of testing, some of the analogs proposed below could be of great interest. Additionally, some *ortho*-substituted boronic acids/esters could be used to make singly *ortho*-substituted analogs.



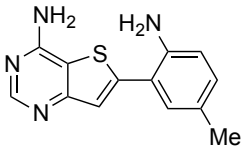
23
CLog P 2.11



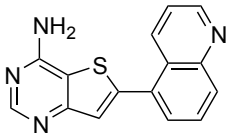
24
CLog P 3.81



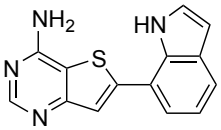
25
CLog P 2.60



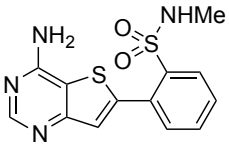
26
CLog P 2.51



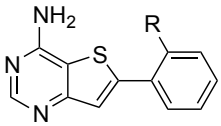
27
CLog P 3.09



28
CLog P 3.19



29
CLog P 2.02

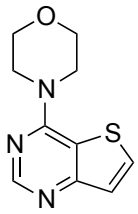


30
Many Possibilites

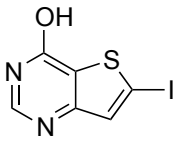
Appeal for assistance

Need to write this part.

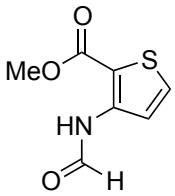
1. Tested OSM Compounds



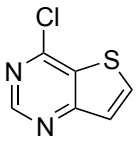
OSM-S-64
>40 000 nM
CLogP 1.30



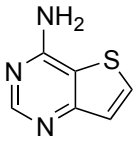
OSM-S-65
>40 000 nM
CLogP 2.86



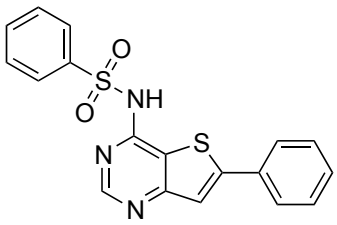
OSM-S-69
>40 000 nM
CLogP 0.26



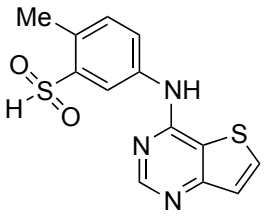
OSM-S-70
>40 000 nM
CLogP 1.83



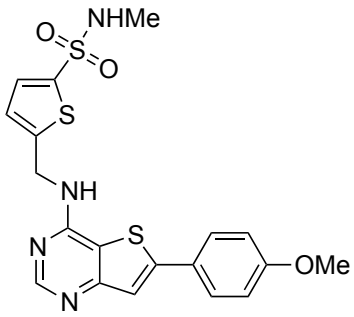
OSM-S-71
>40 000 nM
CLogP 1.10



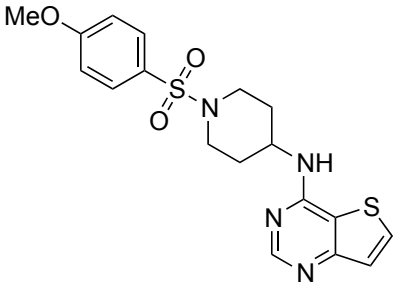
OSM-S-72
>40 000 nM
CLogP 4.50



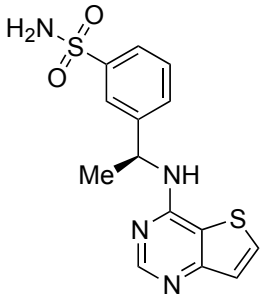
OSM-S-73
>40 000 nM
CLogP 2.43



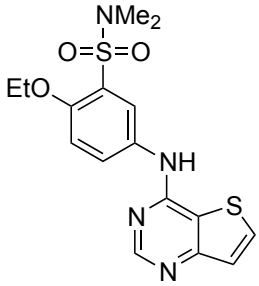
OSM-S-74
17 600 nM
CLogP 4.10



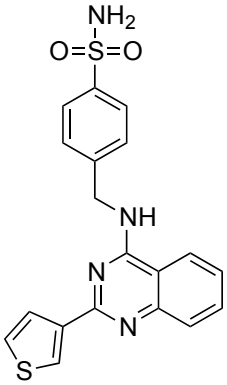
OSM-S-75
>40 000 nM
CLogP 3.30



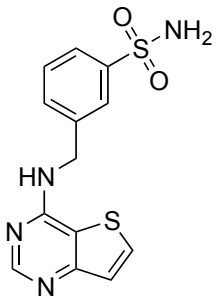
OSM-S-76
>40 000 nM
CLogP 1.85



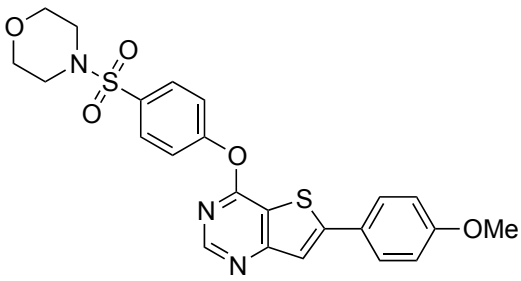
OSM-S-77
>40,000 nM
CLogP 3.20



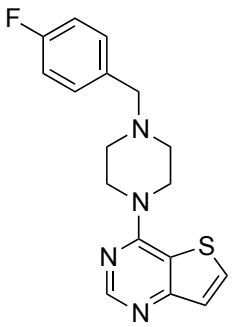
OSM-S-78
>40 000 nM
CLogP 3.29



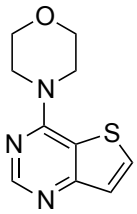
OSM-S-79
>40,000 nM
CLogP 1.54



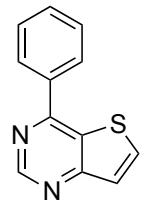
OSM-S-80
80% @ 40 uM
CLogP 4.37



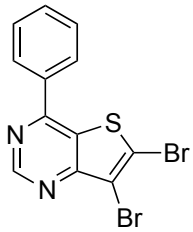
OSM-S-107
92% @ 40 000 nM
CLogP 3.73



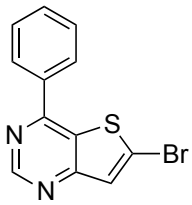
OSM-S-117
>40,000 nM
CLogP 1.30



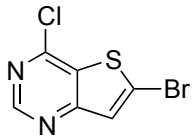
OSM-S-118
>40,000 nM
CLogP 3.19



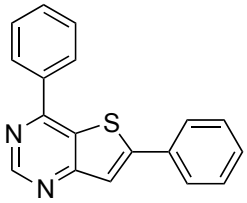
OSM-S-119
>40,000 nM
CLogP 4.73
opaque



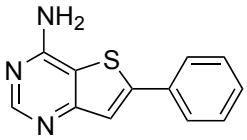
OSM-S-120
>40,000 nM
CLogP 4.07
opaque



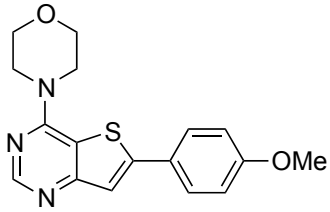
OSM-S-121
95% @ 40 000 nM
CLogP 2.69
opaque



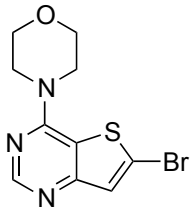
OSM-S-122
>40 000 nM
CLogP 5.29
opaque
minor floating specks



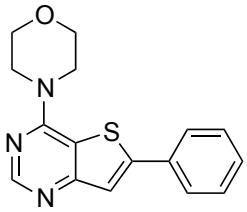
OSM-S-123
>40 000 nM
CLogP 3.20
opaque
minor floating specks



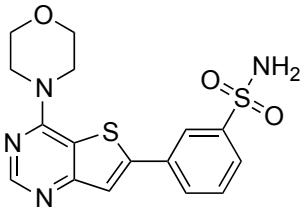
OSM-S-124
62% @ 40 000 nM
CLogP 3.34



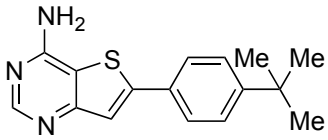
OSM-S-125
>40 000 nM
CLogP 2.16



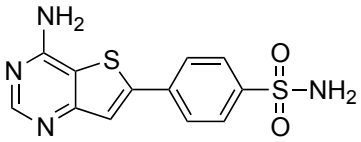
OSM-S-126
39% @ 40 000 nM
CLogP 3.40



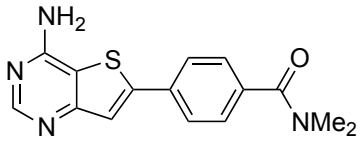
OSM-S-127
42% @ 40 000 nM
CLogP 1.60



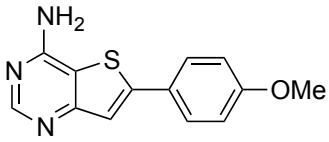
OSM-S-128
54% @ 40 000 nM
CLogP 5.03



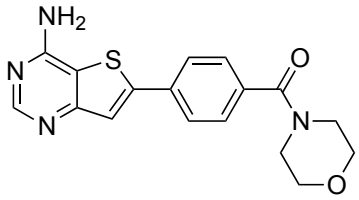
OSM-S-129
>40 000 nM
CLogP 1.40
opaque



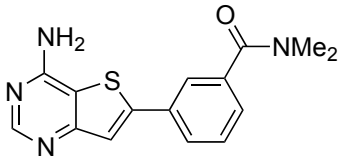
OSM-S-130
>40 000 nM
CLogP 1.68



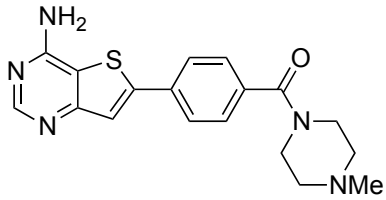
OSM-S-131
>40 000 nM
CLogP 3.14



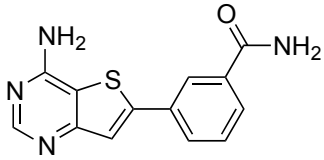
OSM-S-132
>40 000 nM
CLogP 1.84



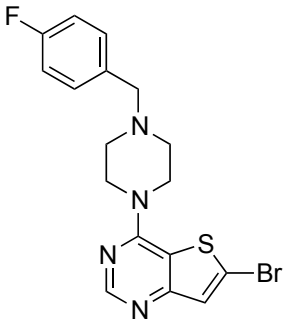
OSM-S-133
73% @ 40 000 nM
CLogP 1.68



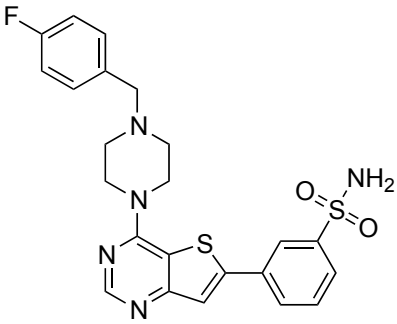
OSM-S-134
>40 000 nM
CLogP 2.40
not fully dissolved
(many needle-like chrystals)



OSM-S-135
>40 000 nM
CLogP 1.74

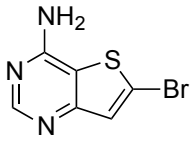


OSM-S-136
15 000 uM
CLogP 4.59
opaque

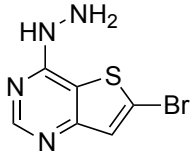


OSM-S-137
1700 nM
CLogP 4.03
opaque

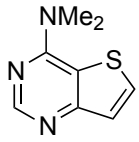
2. Compounds ready to be sent for testing



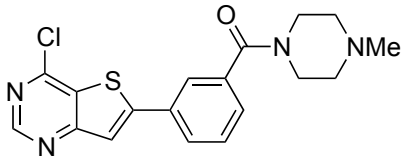
OSM-S-139
to be sent
CLogP 1.97



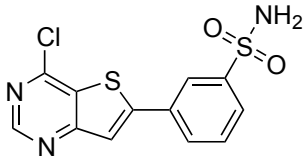
OSM-S-140
to be sent
CLogP 2.42



OSM-S-141
to be sent
CLogP 2.01

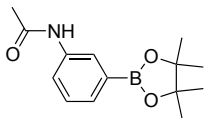


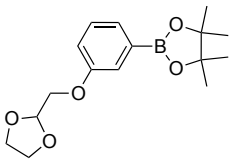
OSM-S-142
to be sent
CLogP 3.13

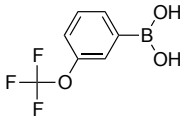


OSM-S-143
to be sent
CLogP 2.12

3. Commercially available *meta*-substituted boronic acids/esters


1


2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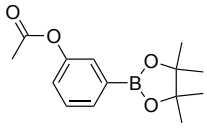
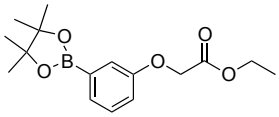
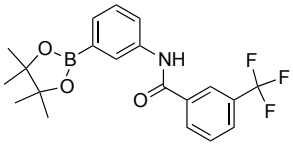

4


5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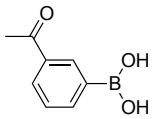
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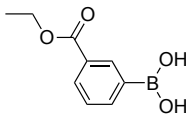
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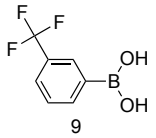
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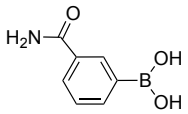
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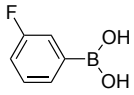
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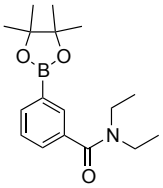
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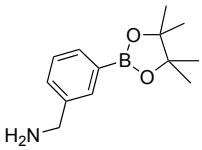
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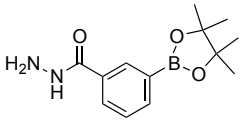
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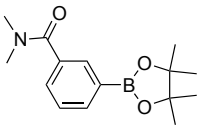
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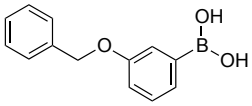
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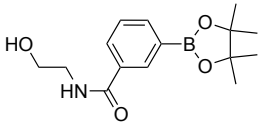
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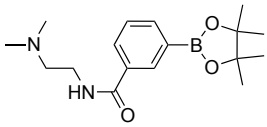
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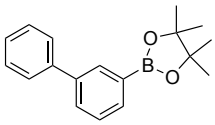
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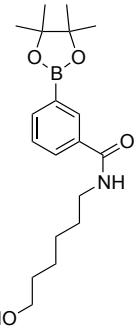
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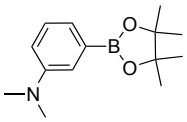
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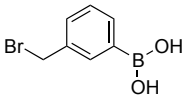
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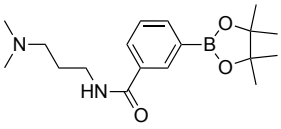
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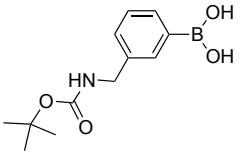
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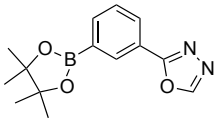
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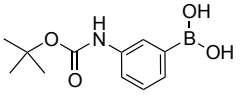
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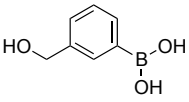
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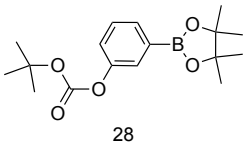
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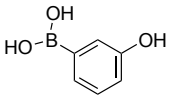
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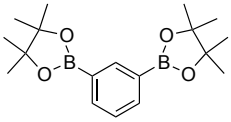
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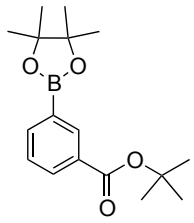

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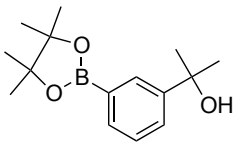

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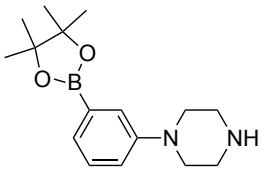

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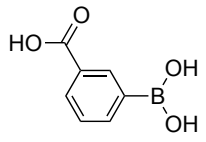

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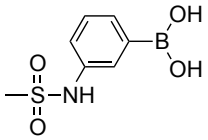

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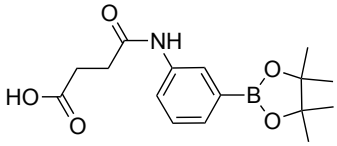

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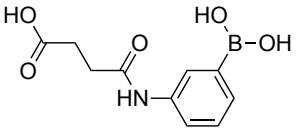

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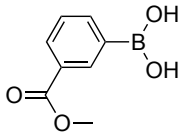

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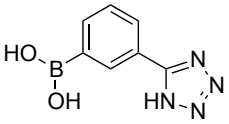

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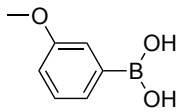

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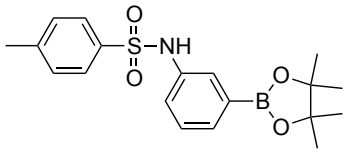

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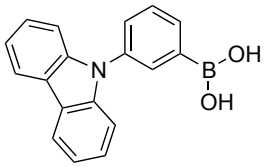

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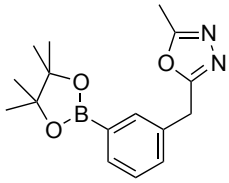

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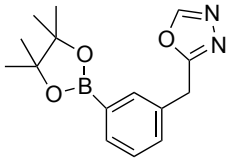

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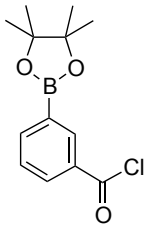

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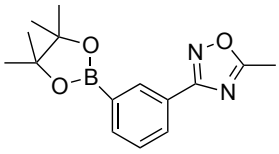

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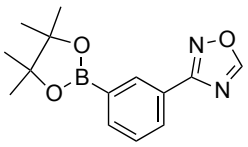

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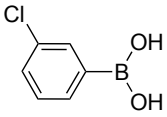

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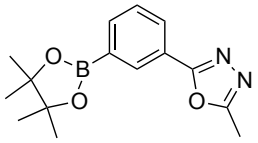

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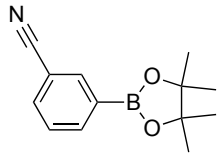

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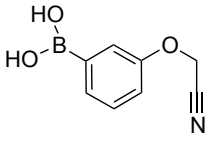

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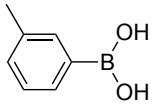

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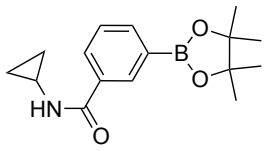

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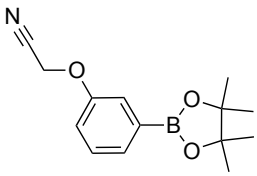

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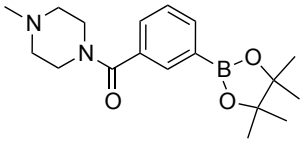

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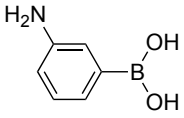

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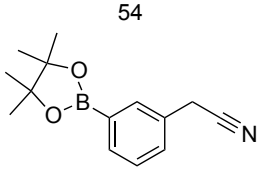

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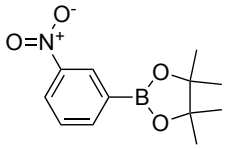

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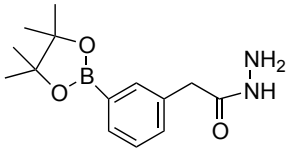

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5. Commercially available *ortho, meta*-substituted boronic acids/esters

Will paste list here

6. Commercially available *ortho*- substituted boronic acids/esters

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