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Discovery of potent and selective Spleen Tyrosine Kinase inhibitors for the topical treatment of inflammatory skin disease

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ABSTRACT

The discovery and lead optimisation of a novel series of SYK inhibitors is described. These were optimised for SYK potency and selectivity against Aurora B. Compounds were profiled in a human skin penetration study to identify a suitable candidate molecule for pre-clinical development. Compound **44** (GSK2646264) was selected for progression and is currently in Phase I clinical trials.

Spleen Tyrosine Kinase (SYK) is a 72 kDa cytosolic non-receptor tyrosine kinase that is involved in signal transduction in a variety of cell types, including B lymphocytes, mast cells and macrophages.[1] SYK and Zeta-chain-associated protein kinase 70 (ZAP-70) are the only members of the SYK family of protein tyrosine kinases and share a similar domain organisation with two N-terminal SH2 domains and a C-terminal kinase domain. ZAP-70 has much lower intrinsic enzyme activity and its expression is mainly restricted to T-cells and NK cells.[2] SYK plays a key role in coupling activated immunoreceptors to downstream events that mediate diverse cellular responses, including proliferation, differentiation and phagocytosis. Inhibition of SYK mediated immunoreceptor (Ig Fcε, Ig Fcγ and B-cell receptors) signalling leads to the inhibition of mast cell, macrophage and B-cell activation and subsequent release of inflammatory modulators.[3] Therefore, the discovery of safe small molecule SYK inhibitors has attracted much attention in a number of therapeutic areas, including the treatment of rheumatoid arthritis, B-cell lymphoma and asthma / rhinitis.[4-10]

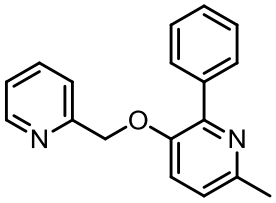
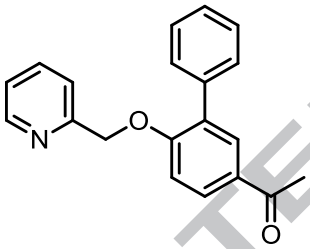
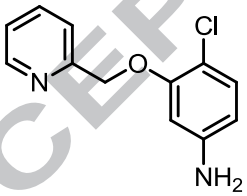
The treatment of several skin diseases such as chronic urticaria, atopic dermatitis and rosacea are inadequately treated by topically applied medication and the development of a SYK inhibitor which should reduce the overall inflammatory response could be beneficial if topically applied. Topical administration was preferred over an oral treatment as drug is applied locally to disease tissue, leading to higher drug levels in the skin whilst minimising the systemic exposure of drug and hence reducing any potential safety risks.

GSK has investigated several chemical series previously, including the pyrimidine carboxamides[11] and the azanaphthyridines.[12] Both templates had developability issues, with several analogues from each series being positive

in the AMES mutagenicity assay.[13-14] Additional chemical equity was required to find alternative templates that could be optimised towards selective SYK inhibitors. To find novel chemotypes, a HTS was run against SYK, using the SYK lysate assay.[15] This is a cell free assay to assess SYK signal transduction with lysates from Ramos B cells. Concomitantly, a high concentration fragment screen was performed in single shot format at a concentration of 667 μM, using an in-house set of lower molecular weight "reduced complexity" molecules. Hits were followed up by full curve screening in the SYK lysate assay. With previous series, Aurora B activity was evident and this has been difficult to optimise against during lead optimisation. As this was a potential liability, compounds were screened in the Aurora B assay too. Hits obtained from the full curve SYK lysate assay were prioritised based on selectivity over Aurora B, ligand efficiency, novelty and tractability.

From the HTS, a group of novel, ligand efficient compounds were discovered to have SYK activity as exemplified by compounds **1** and **2**. In addition, compound **3** was discovered form the fragment set screening. This was one of the few fragment hits that didn't appear more potent at Aurora B and has similar pharmacophoric features to the hits from the HTS (Table 1).

Table 1. *In vitro* profile of initial hits

Compound		SYK lysate pIC_{50}[a,b] / ligand efficiency (LE)[c]	Aurora B pIC_{50}[a,b]	cLogP / MW
1		5.3 / 0.35	4.4	3.4 / 276
2		5.6 / 0.33	4.0	3.4 / 303
3		4.3 / 0.37	3.9	2.0 / 234

[a] Enzyme inhibition assay[15]

[b] pIC_{50} values are reported as a mean

[c] LE= (1.37*pIC_{50})/n heavy atoms[16]

Molecular modelling of the compounds in the SYK active site indicated that the likely binding mode was a monodentate hinge interaction of the pyridine nitrogen with the Ala451 of the hinge region.

Based on these hits demonstrating some selectivity over Aurora B, possessing good ligand efficiency, being novel starting points and having tractable chemistry, the series was selected for optimisation.

Initial SAR investigations were carried out on **2**, varying substitution on the pendant phenyl ring (Table 2).

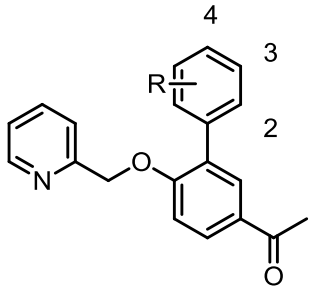


Table 2. SAR around the pendant phenyl ring

Compound	R	SYK pIC_{50}	LE	Aurora B pIC_{50}	cLogP / ChromLogD[a] (pH=7.4)
2	H	5.6	0.33	4.0	3.4 / 5.0
4	2-Me	<4.6	0.26	<4.6	3.6 / 5.9
5	3-Me	5.6	0.32	<4.6	3.9 / 6.0
6	4-Me	6.1	0.34	<4.6	3.9 / 6.1
7	4-F	5.5	0.31	<4.6	3.6 / 5.6
8	4-OMe	6.4	0.35	4.8*	3.3 / 5.3
9	3-OMe	5.8	0.32	<4.6	3.3 / 5.4

[a] ChromLogD (pH=7.4) is the chromatographic LogD obtained at pH=7.4, and is derived from the CHILogD

* 1 value <4.6

The data showed a preference for the phenyl group carrying substitution at the 4-position. Electron donating substituents at the 4-position, such as the methoxyl depicted in **8**, gave the compounds with good potency in the SYK lysate assay. A 2-substituted analogue, exemplified by **4**, was significantly less potent than having the substituent at the 3- or 4- positions (**5** and **6**). In addition to the clogP, the chromatographic LogD at pH 7.4 is shown. This is a high throughput experimental measurement of lipophilicity based on the retention time of the molecule on a reverse phase HPLC column.

The core aromatic ring was also investigated (Table 3):

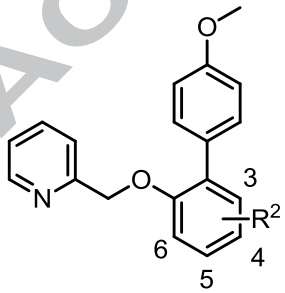


Table 3. SAR around the core phenyl ring

Compound	R^2	SYK pIC_{50}	LE	Aurora B pIC_{50}	cLogP / ChromLogD (pH=7.4)

8	4-C(O)Me	6.4	0.35	4.8*	3.3 / 5.3
10	H	5.5	0.34	5.0	3.6 / 6.2
11	3-OMe	5.8	0.34	<4.6	3.1 / 5.8
12	4-OMe	6.1	0.35	<4.6	3.7 / 6.0
13	5-OMe	5.5	0.31	<4.6	3.7 / 6.2
14	3-F	5.5	0.33	<4.6	3.9 / 6.2
15	4-F	5.5	0.33	<4.6	3.9 / 6.4
16	5-F	4.9	0.29	<4.6	3.9 / 6.6
17	3-Me	5.5	0.33	<4.6	3.8 / 6.7
18	4-Me	6.0	0.35	<4.6	4.1 / 6.8

* 1 value <4.6

Substituents were tolerated at the 3-, 4- and 5- positions, but most potency was obtained by substitution at the 3- or 4-positions, particularly with a methoxyl group.

One of the original hits, **1**, contained a pyridine core and so a matched pair was synthesised to investigate the effect of replacing the phenyl group with a pyridyl group (Table 4).

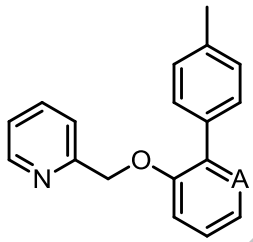


Table 4. Core phenyl replacement

Compound	A	SYK pIC_{50}	LE	Aurora B pIC_{50}	cLogP / ChromLogD (pH=7.4)
19	CH	5.5	0.36	<4.6	4.2 / 7.0
20	N	5.5*	0.36	4.7*	3.4 / 4.9

* 1 value <4.6

As can be seen for compounds **19** and **20**, the potency of the phenyl and pyridyl core were the same, but the pyridyl core was significantly more polar as measured by the ChromLogD. This would give us the option to investigate a wider range of polarities for our target molecules.

A crystal structure of **20** in human SYK was solved (Figure 1). This confirmed that the pyridine nitrogen is acting as a monodentate hinge binder to Ala451 as predicted from the modelling. The pendant phenyl group is heading into the ribose binding pocket of the active site.

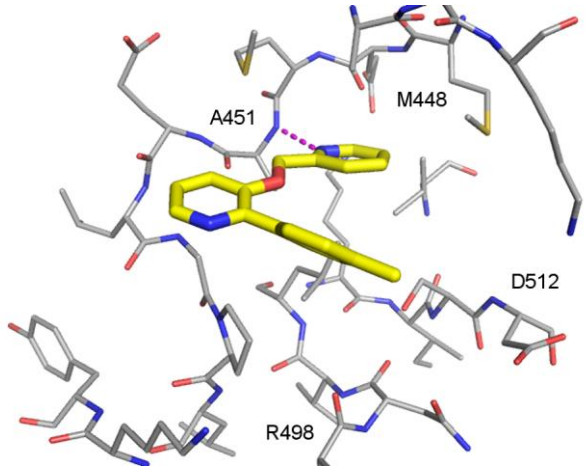


Figure 1. X-ray crystal structure of the complex of **20** in the kinase domain of human Spleen Tyrosine Kinase (PDB code 6HM6)

Substitution of the hinge binding group was carried out to investigate the effects on SYK potency (Table 5).

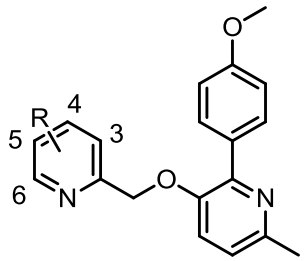


Table 5. SAR around the hinge binding group

Compound	R	SYK (LE) / pERK pIC_{50}[a]	Aurora B pIC_{50}	cLogP / ChromLogD (pH=7.4)
21	H	5.9 (0.35) / -	<4.6	3.4 / 5.0
22	3-Me	<4.6 / -	<4.6	3.8 / 5.3
23	4-Me	6.8 (0.39) / 5.0	4.7	3.9 / 5.4
24	5-Me	4.9 (0.28) / -	4.8	3.9 / 5.5
25	6-Me	<4.6 / -	<4.6	3.9 / 5.5

[a] Inhibition of anti-IgM induced Erk1/2 phosphorylation in Ramos cells[15]

Variation around the pyridine hinge binding group showed that a methyl group adjacent to the pyridine nitrogen in **25** is not tolerated. The space here in the active site is restricted due to a clash with the carbonyl of Glu449. Compound **22**, with the methyl group adjacent to the linker methyloxy chain, was also inactive. This could be due to the preferred conformation of **22** being twisted and so not being able to bind into the active site in a low energy conformation. The most potent compound contained the 4-methyl substituent, **23**, showing an order of magnitude increase over the 4-H analogue, **21**. This was the most potent and ligand efficient analogue to date and demonstrated 100-fold selectivity over Aurora B. It was tested in the pERK cellular assay.[15] This assay detects the inhibition of anti-IgM induced Erk1/2 phosphorylation in Ramos B cells, the same cell type that is used in the primary SYK lysate assay. Unfortunately, **23** had a large drop off in activity in the cell assay compared to the enzyme assay, almost 2 orders of magnitude.

The effect of adding an additional nitrogen to the pyridine hinge binding motif was carried out to look not only at the effects on the SYK potency, but also to reduce the lipophilicity of the molecules, as many of the analogues synthesised so far had been relatively lipophilic (Table 6). There are little data in the literature relating to the optimal physicochemical space for dermal compounds to penetrate the skin and so it was of interest to span a wider range of polarities to investigate this.

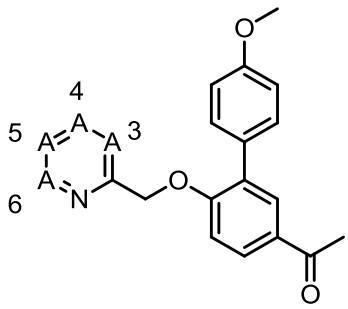


Table 6. SAR around the heterocyclic hinge binder

Compound	A	SYK (LE) / pERK pIC_{50}	Aurora B pIC_{50}	cLogP / ChromLogD (pH=7.4)	CLND Solubility (μg/ml)[a]
8	CH	6.4 (0.35) / <4.3	4.8*	3.3 / 5.3	3
26	3 aza	4.9 (0.27) / -	<4.6	2.4 / 4.5	110
27	4 aza	6.4 (0.35) / -	<4.6	2.4 / 4.7	11
28	5 aza	5.5 (0.30) / -	4.7	2.4 / 4.5	5
29	6 aza	<4.6 / -	<4.6	2.1 / 4.1	7

[a] Kinetic solubility measured by CLND

* 1 value <4.6

The pyrazine head group, **27**, is equipotent with the pyridine head group, **8**, and so offers an alternative hinge binder that contributes to reducing the lipophilicity of the series. Despite the aza analogues decreasing the lipophilicity of the series, the kinetic solubility as determined in the CLND assay was still only low to moderate. An increase in solubility is required for the dermal mode of administration.

From the crystal structure, it was apparent that there was additional space and potential interactions that could be explored in the ribose binding pocket. Previous lead series[11,12] had exploited this by targeting a polar triad of residues with a basic group in an attempt to increase the potency of the compounds. In addition, this change should provide the enhanced solubility required for a dermal topical formulation.

Initially, an aminoalkyl group was added to the 4-position of the pendant phenyl group to target the polar residues in the ribose binding pocket (Asp512, Asn499 and Arg498). Disappointingly, the activity against SYK was reduced compared to the 4-methyl analogue (Table 7). However, the compounds did have reduced lipophilicity and improved solubility, as expected.

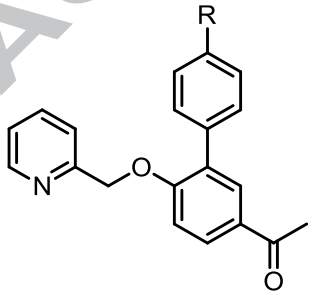


Table 7. Investigation of basic centre on potency

Compound	R	SYK pIC_{50} (LE)	cLogP / ChromLogD	CLND Solubility (μg/ml)

			(pH=7.4)	
6	Me	6.1 (0.34)	3.9 / 6.1	3
30	CH_2NH_2	5.6 (0.31)	2.4 / 1.9	53
31	$CH_2CH_2NH_2$	5.5 (0.29)	2.7 / 2.1	97

Due to the open-chain amino analogues decreasing the ligand efficiency, modelling work was undertaken to investigate a variety of constrained amines to see which might target 2 of the 3 polar residues in the ribose binding pocket. Compounds were prioritised and synthesised according to the best fit in the docking studies (Table 8).

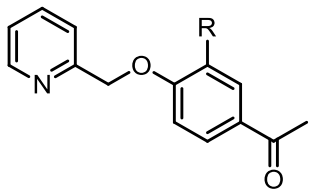
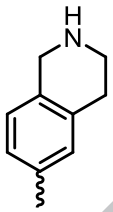
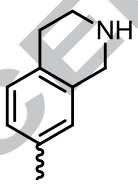
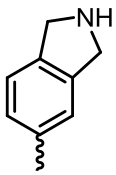
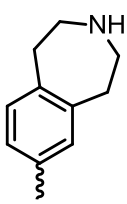
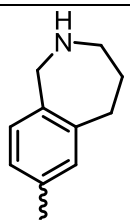
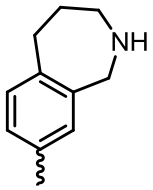


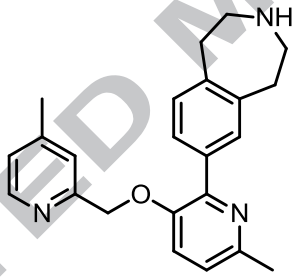
Table 8. Investigation of constrained amines

Compound	R	SYK pIC_{50} (LE)	Aurora B pIC_{50}	cLogP / ChromLogD (pH=7.4)	CLND Solubility (μg/ml)
32		5.7 (0.29)	<4.6	2.3 / 2.1	104
33		5.5 (0.28)	<4.6	2.9 / 2.2	>=123
34		6.6 (0.35)	<4.6	2.9 / 2.1	109
35		6.7 (0.33)	<4.6	3.3 / 2.3	69

36		5.5 (0.27)	<4.6	3.3 / 2.3	>=129
37		5.7 (0.28)	<4.6	3.3 / 2.3	67

This shows that constraining the amine in **34** and **35** gave higher potency compared to the equivalent open chain analogues **30** and **31** (around 1 order of magnitude increase). Additionally, the constrained amine analogues gave compounds with moderate / high solubility (Table 8).

Although the constrained amino analogues didn't always offer a significant increase in potency in the SYK lysate assay over the monosubstituted phenyl analogues, they did however offer improved cellular potency in the pERK mechanistic assay as demonstrated by the comparison of **38** with **23** (Table 9). The high artificial membrane permeability data indicate that the drop-off in activity from enzyme to the cell for **23** is not due to passive permeability. Pleasingly, **38** also maintained the ca. 100-fold selectivity over Aurora B.



38

Table 9. Effect of the constrained amine on the cellular potency

	SYK pIC_{50}	pERK pIC_{50}	Aurora B	Artificial membrane Permeability (nm/s)	CLND solubility (μg/ml)
23	6.8	5.0	4.7	330	5
38	6.7	6.3	4.8*	435	>=153

* 3 values <4.6

Based on these promising cellular data, further combinations with constrained amines were synthesised to investigate enhancing the cellular potency of the molecules (Table 10).

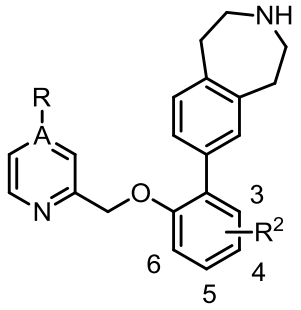


Table 10. Combination of constrained amine and substitution around the hinge and core groups

Compound	A	R	R^2	SYK pIC_{50} (LE)	pERK pIC_{50}	Aurora B pIC_{50}	cLogP / ChromLogD (pH=7.4)
35	C	H	4-(CO)CH_3	6.7 (0.33)	-	<4.6	3.3 / 2.3
39	C	Me	4-(CO)CH_3	7.4 (0.35)	6.9	5.0	3.8 / 2.5
40	C	Et	4-(CO)CH_3	7.4 (0.34)	6.6	4.9	4.3 / 2.8
41	C	OEt	4-(CO)CH_3	6.7 (0.30)	6.2	5.4	4.2 / 2.7
42	C	Me	4-CN	6.5 (0.31)	6.0	4.6	3.8 / 2.8
43	C	Me	4-(CO)NHMe	7.0 (0.32)	6.5	4.7	3.0 / 1.9
44	C	Me	3-OMe	7.1 (0.35)	6.7	<4.6	3.6 / 3.1
45	C	Me	4-OMe	7.2 (0.35)	6.5	4.6*	4.1 / 3.0
46	C	Me	5-OMe	7.1 (0.35)	6.2	4.7^	4.1 / 3.0
47	N	-	3-OMe	6.4 (0.32)	-	<4.5	2.1 / 2.2
48	N	-	4-OMe	6.7 (0.34)	6.4	<4.6	2.7 / 2.4

* 8 values <4.6; ^ 2 values <4.6

Table 10 shows that these constrained analogues are generally potent in the cell assay. The optimal R group for balancing the SYK lysate potency, the cellular potency and the physicochemical properties is the methyl (compare compounds **39**-**41**). The R^2 group is somewhat more accommodating, and good cellular activity was obtained with both 3- and 4- substituted analogues such as the methoxyl group in examples **44** and **45**.

An X-ray crystal structure of compound **44** in human SYK was solved (Figure 2). This confirmed the hypothesised interaction between the cyclic amino group with the aspartate residue (Asp512) that forms part of the ribose pocket in the ATP binding site of SYK.

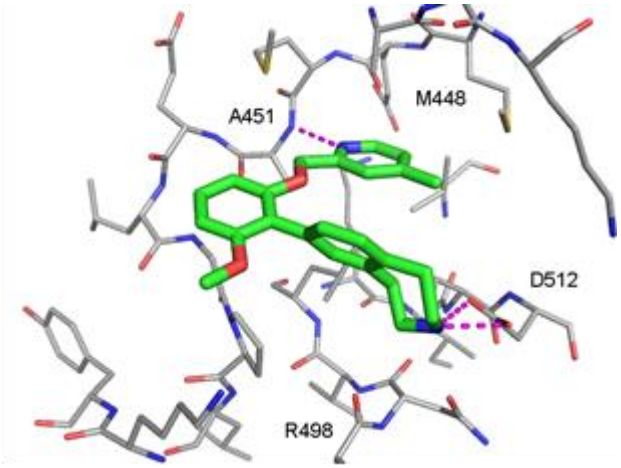


Figure 2. X-ray crystal structure of the complex of **44** in the kinase domain of human Spleen Tyrosine Kinase (PDB code 6HM7)

Several compounds were profiled in more detail to investigate their suitability as a topical dermal agent. One assay that was developed to assist with prioritisation was an *in vitro* human skin penetration assay. The permeability (percutaneous flux) of two SYK inhibitors **39** and **44** through intact human skin was measured, by applying a 1% solution of the inhibitors in ethanol: PBS (60:40, v/v) to sections of human skin. Compound **44** was penetrable into the epidermis and dermis of the skin and showed a 1.5-fold higher concentration in the epidermis compared to **39**. The calculated dermal concentration of compound **44** was 60 μM. No significant differences in dermal concentrations were noted (Figure 3).

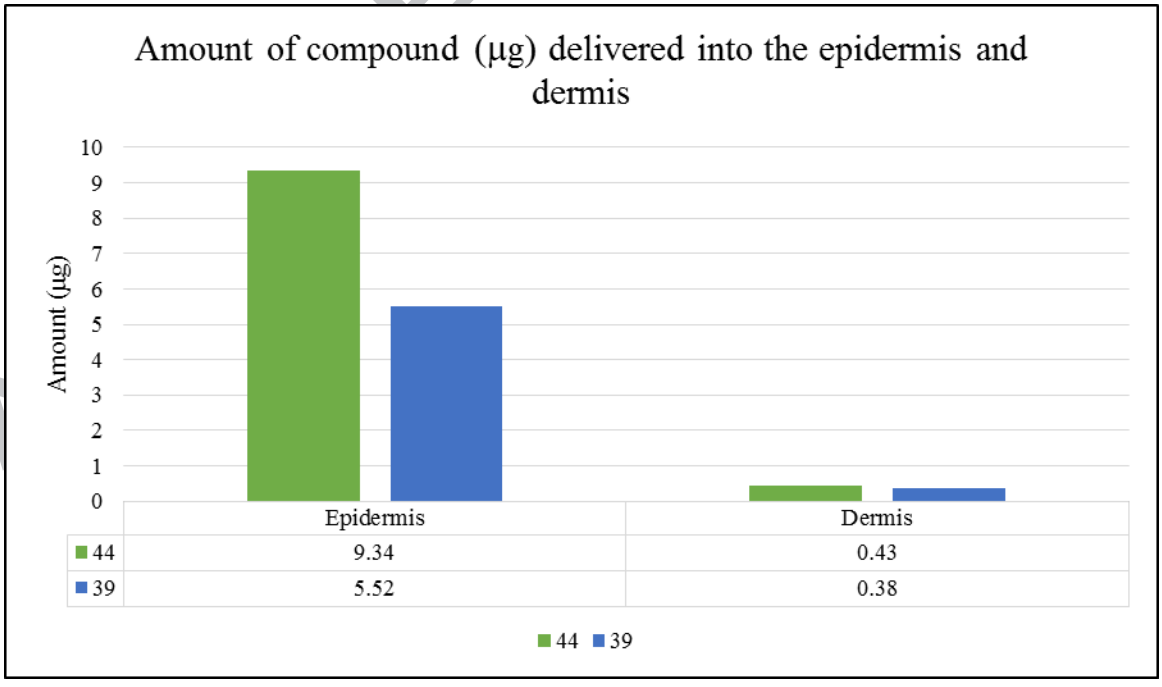


Figure 3. Total amounts of **44** and **39** measured in the epidermis and dermis 6h after topical application. *The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol*.

Compound **44** showed a > 6-fold increase in the cumulative amount of drug material in the receiving fluid after 6 h compared to **39**, indicating that there was a flow of **44** through the skin, reducing the likelihood of accumulation. (Figure 4)

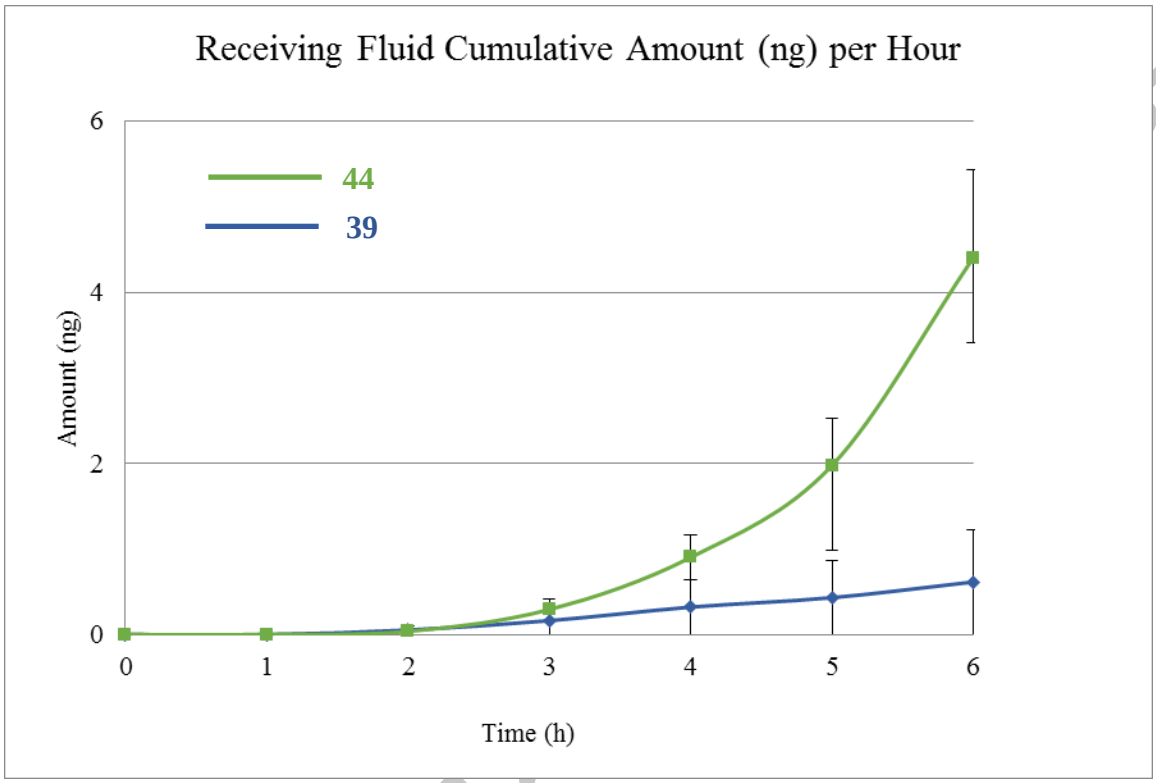


Figure 4. Cumulative concentration of **44** and **39** after topical application onto the skin (Error bars represent SEM from n=3 donors with 6 replicates per donor). *The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol*.

Compound **44** was screened through a number of kinase assays (Table 11) and demonstrated good selectivity (at least 30-fold) against the other kinases shown.

Table 11. Kinase selectivity of **44**

Kinase	pIC50	Fold selectivity (by IC_{50})
SYK	7.1	-
Aurora A	<4.3	>630
Aurora B	<4.6	>316
VEGFR2	4.5	398
JAK2	5	125
GSK3β	5.3	63
LCK	5.4	39
LRRK2	5.4	50

Based on the optimal balance of properties, GSK2646264 (**44**) was chosen as our molecule to progress into pre-clinical studies.

In summary, we have described a novel series of SYK inhibitors, containing a pyridine or pyrazine hinge binding group. The compounds demonstrated good SYK lysate potency that transferred well into a mechanistic cellular assay, as well as demonstrating very good selectivity over a key liability target, Aurora B. A pre-clinical candidate was identified from this series that has progressed into Phase I clinical studies, and will be the subject of further publications.

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Supplementary data

Supplementary data associated with this article, including preparation of **44**, crystallography, skin penetration assay and physicochemical assay protocols, can be found in the online version.

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- A novel series of SYK inhibitors was identified through fragment and HTS screening
- This was optimised to give selective inhibitors with good cellular potency
- Skin penetration studies were carried out to assess permeability
- A pre-clinical candidate was identified that is currently in Phase I clinical studies