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Carboxamide Spleen Tyrosine Kinase (Syk) Inhibitors: Leveraging Ground State Interactions to Accelerate Optimization

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Spleen tyrosine kinase, intramolecular hydrogen bond, structure-based drug design

ABSTRACT: Optimization of a series of highly potent and kinome selective carbon-linked carboxamide Spleen Tyrosine Kinase (Syk) inhibitors with favorable drug-like properties is described. A pervasive Ames liability in an analogous nitrogen-linked carboxamide series was obviated by replacement with a carbon-linked moiety. Initial efforts lacked on-target potency, likely due to strain induced between the hinge binding amide and solvent front heterocycle. Consideration of ground state and bound state energetics allowed rapid realization of improved solvent front substituents affording subnanomolar Syk potency and high kinome selectivity. These molecules were also devoid of mutagenicity risk as assessed via the Ames test the using the TA97a *Salmonella* strain.

The advancement of kinase inhibitors as oncology therapeutics has resulted in approval of a number of effective drugs over the past two decades. Recently, efforts have been directed toward the treatment of autoimmune disorders, particularly rheumatoid arthritis (RA), via kinase inhibition. RA is a chronic inflammatory disease that presents with pathophysiology including synovial hyperplasia, inflammation, and joint destruction. RA is characterized by up-regulation of cytokines and chemokines ultimately leading to inflammation. Treatment paradigms have consisted of palliative therapies to mitigate symptoms including pain and disease-modifying antirheumatic drugs (DMARDs) or biologics with the goal to slow or stop disease progression. Existing therapies are not universally effective for all RA patients, underscoring the need for additional treatment options.

Spleen tyrosine kinase (Syk) is a well-studied enzyme that plays a critical role in immune signaling via Fc and B cell receptors (BCR).[1] Preclinical studies demonstrated that pharmacological modulation of Syk (R788 (**1**), PRT-062607 (**2**), RO9021 (**3**), and GS-9973 (**4**)) is efficacious in preclinical RA models (Figure 1).[2,3,4,5] Further, poorly selective Syk inhibitor **1** (52% of 100 kinases tested >100X Syk IC_{50}) has demonstrated efficacy in human clinical trials, however dosing was limited by observations of hypertension and diarrhea.[6] We aimed to develop a selective Syk inhibitor that would obviate the clinical side effects and could be useful for autoimmune and oncological disorders.[7,8,9,10,11]. As previously described,[12] a picolinamide series of Syk inhibitors we developed was halted by mutagenicity risk as indicated by positive results in the Ames assay. Described herein are the design considerations employed to overcome this liability via a scaffold modification affording novel Syk inhibitors consistent with our objective.

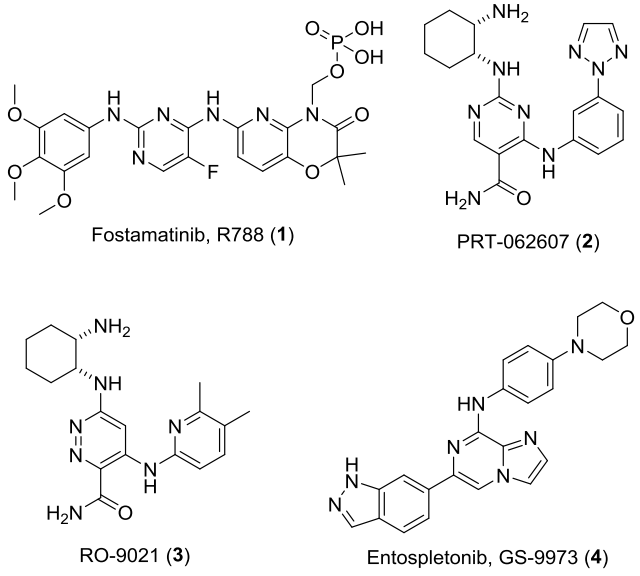
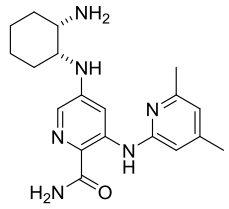


Figure 1. Diverse Published Syk Inhibitors.

Picolinamide **5** was designed via analysis of X-ray crystallographic data with a focus on ligand binding efficiency and ensuring favorable physicochemical properties (Figure 2). Carboxamide **5** possessed desirable intrinsic (Syk IC_{50} = 60 pM) and human whole blood potency (hWB CysLT IC_{50} = 58 nM). Additionally, kinome selectivity was high (99% of 265 kinases tested >100X Syk IC_{50}),[13] and the oral pharmacokinetic profile (rat plasma Cl_p (Cl_u) = 33 (710) mL/min/kg, rat $T_{1/2}$ = 2.7 h, F = 19%) enabled testing in the rat collagen-induced arthritis model, where the compound demonstrated therapeutic efficacy at doses as low as 3 mg/kg QD (C_{max} = 0.2 μM, C_{min} = 0.007 μM). However, this molecule, and this series of diaminopicolinamides, was plagued with positive results in the Ames test using TA97a *Salmonella* strain. Since mutation in this strain often reflects intercalation of the test molecule into DNA, we developed a docking model leveraging DNA cocrys-

tals with acridine. Based upon this model, an approach we pursued to ameliorate this activity involved changing the two-dimensional shape of how the molecules are presented, aimed at disrupting the favorable interactions with DNA.

Figure 2. Lead Molecule Picolinamide **5**.



5

Our initial foray into changing two-dimensional shape focused on altering the vector at which the "solvent front" group was presented; this strategy involved carbon-linking to replace the previous nitrogen-linked moiety. To this end, picolinamide **6** was quickly prepared via Suzuki coupling[14] of available intermediates to replace the aminoheterocycle with a *C*-linked 3-methylpyrazole analog (Figure 3). However, picolinamide **6** was inactive in our enzymatic assay (Syk IC_{50} >10 μM, 9% inhibition at 10 μM). We hypothesized that the 3-methylpyrazole may introduce torsional strain with the carbonyl oxygen of the carboxamide, disfavoring the planar geometry desired for efficient interaction with the hinge domain of Syk, and kinases in general. To probe this theory, we pursued computational quantum mechanical approaches to estimate the lowest energy dihedral angles about these two substituents and the energetic penalty required to achieve a fully flat conformation (amide dihedral = 0 ° and aryl solvent front dihedral = 0 °) for binding.[15] For picolinamide **6**, calculations suggest that the preferred ground state conformation positions the two critical substituents ~30 ° and -30 ° out of plane, resulting in an estimated penalty of 2–4 kcal/mol to adopt the planar bound-state conformation, which is reflected in the lack of potency for this analog.

Considering rational structural modifications that could be implemented to further favor the flat ground state conformation, minimizing the motion and associated energetic penalty required to achieve the flat bioactive state, calculations were executed to examine the roles of different heteroatom substituted cores and solvent fronts. Among those surveyed, the pyrazinecarboxamide core was predicted to favor a smaller dihedral angle, and corresponding lower energetic penalty (0–2 kcal/mol) than the picolinamide. In the picolinamide **9**, there is likely increased torsional strain resulting from the two CH's in close proximity compared to the pyrazine **10**, where this strain is removed and the conformation may be reinforced by an additional intramolecular hydrogen bond (Figure 4). Pyrazinecarboxamide **7** was prepared to test this hypothesis and showed improved potency (Syk IC_{50} = 1.6 μM). It is worth noting that the cyclohexyldiamine generally introduces a ~10X potency enhancement versus the propanyldiamine, though this matched pair was never made with the methypyrazole solvent front.

Hoping to parlay the potency gain achieved moving from the picolinamide to the pyrazinecarboxamide with a solvent front group predicted to further favor a planar disposition, indole **8** was synthesized.[16] Calculations suggested that the indole substituted pyrazinecarboxamide should strongly favor a flat ground state conformation, resulting in a 0–0.5 kcal/mol energetic penalty to adopt the bound conformation. In addition, the energy minimum at the presumed bound conformation is predicted to become much deeper than alternative states, which likely reduces entropic penalties as well. This is likely influenced by an intramolecular hydrogen bond between the more polarized NH of the indole and the carbonyl of the carboxamide. Gratifyingly, indole **8**'s doubly-stabilized planarity afforded a significantly improved intrinsic potency (Syk IC_{50} = 5 nM). Interestingly, the predicted ground-state geometry for **8** suggests a pseudo 7-membered ring where the angles open up to accommodate an intramolecular hydrogen bond between the indole NH and the carboxamide carbonyl (Figure S1).[15]

Figure 3. Initial *C*-linked carboxamides and predicted quantum mechanical potential energy landscape for rotation about the aryl and amide dihedral angles. (0, 0) represents the presumed planar bioactive conformation in the orientation as drawn. White regions represent configurations with severe intramolecular clashes and thus no energy was computed. This figure was prepared with MATLAB.

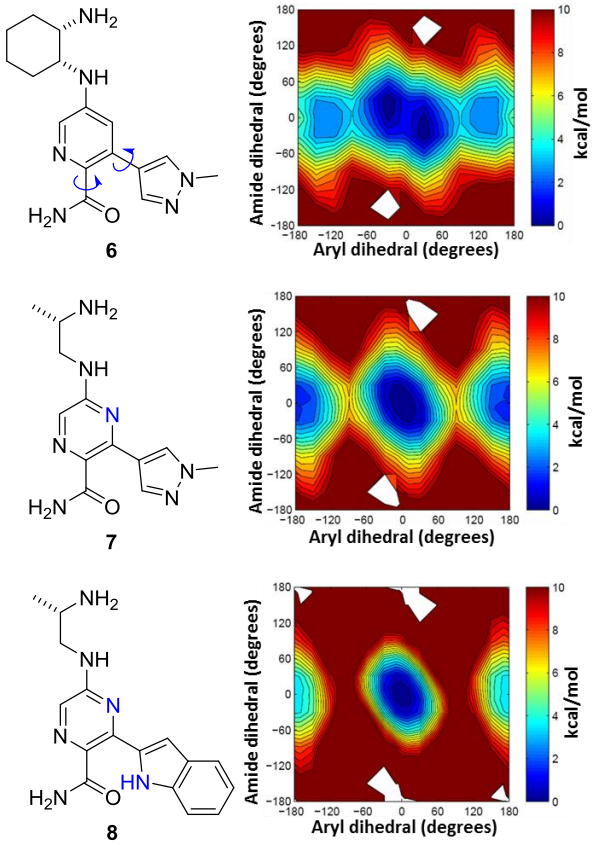
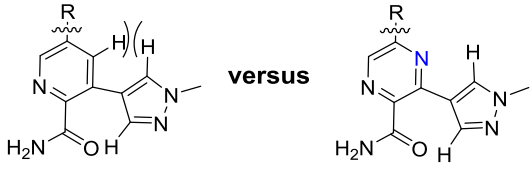


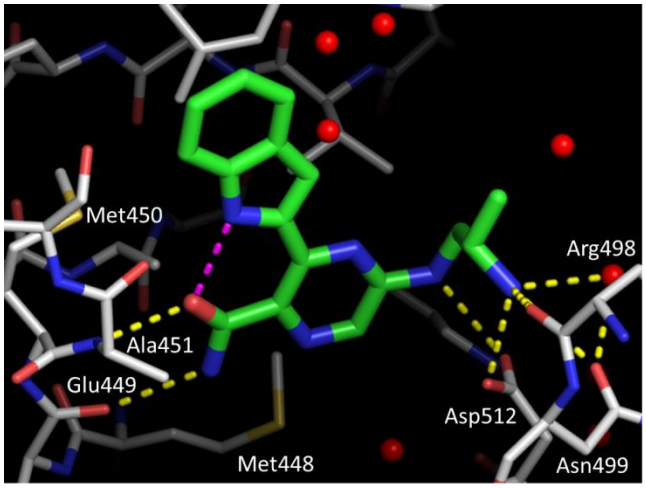
Figure 4. Rationale for picolinamide and pyrazinecarboxamide ground state dihedral angles and resultant intrinsic potencies.



9 **10**

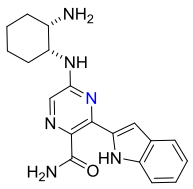
In order to further understand the binding interactions of these compounds, as well as interrogate the computational predictions, we solved the X-ray crystal structure of compound **8** bound to the kinase domain of human Syk (Figure 5). Similar to other carboxamide-based Syk inhibitors,[17,18,1920] **8** binds to the hinge region via bidentate hydrogen bonding to the backbone of Glu449 and Ala451. The indole region extends toward solvent and packs against the side chain of Met450 at the top of the hinge, while NH groups of the diamine region form interactions with the catalytic Asp512 and surrounding backbone carbonyls from Arg498 and Asn499. As predicted, the core is planar with a pseudo 7-membered ring geometry stabilized by an intramolecular hydrogen bond between the indole NH and the carboxamide oxygen with a short N-O distance of 2.6 Å (Figure 5, magenta dashed line).

Figure 5. Binding site view of the crystal structure of **8** bound to the human Syk kinase domain. The carbon atoms of Syk protein are shown in white and carbon atoms of **8** are in green. Modeled water molecules are shown as red spheres, an intramolecular hydrogen bond in **8** is shown in magenta dashes, and polar interactions between **8** and protein are shown as yellow dashes. This figure was prepared with PyMOL.



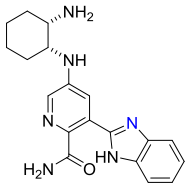
Seeking to further optimize the *C*-linked carboxamides, introduction of the cyclohexyldiamine moiety to afford pyrazinecarboxamide **11** delivered the expected potency enhancement (Syk IC_{50} = 500 pM) approaching the previously achieved intrinsic activity of the *N*-linked picolinamide **5**. Further, indole **11** featured excellent kinase selectivity (99% of 101 kinases tested >100X Syk IC_{50}, LRRK2 IC_{50} = 30 nM) and human whole blood potency (hWB CysLT IC_{50} = 130 nM) with a favorable pharmacokinetic profile in rat Cl_p (Cl_u) = 44 (255) mL/min/kg, rat $T_{1/2}$ = 2.8 h, F = 19%). As previously described, all molecules tested from the *C*-linked carboxamides were negative in the mutagenicity assay in strain TA97a *Salmonella* with rat S9 up to testable concentrations.[12] Additional data to support the effectiveness of the shape change in ablating interaction with DNA were gathered via consistent results in a UV-Vis perturbation assay and a DNA unwinding assay. We subsequently examined a nitrogen transposition of pyrazinecarboxamide **11** to afford benzimidazole **12**. Interestingly, picolinamide **12** showed a loss in intrinsic potency (Syk IC_{50} = 7 nM), but a maintained selectivity (97% of 101 kinases tested >100X Syk IC_{50}, LRRK2 IC_{50} = 130 nM, CHK2 IC_{50} = 160 nM, TSSK3 IC_{50} = 420 nM), human whole blood potency (hWB CysLT IC_{50} = 93 nM), and rat pharmacokinetic (Cl_p (Cl_u) = 134 (277) mL/min/kg, rat $T_{1/2}$ = 4.8 h) profile.

Figure 6. Advanced *C*-linked carboxamides.



11

Syk IC_{50}: 0.5 nM
hWB CysLT IC_{50}: 130 nM
Kinases >100X: 99% (100)
Rat Cl_p (Cl_u): 44 (255) mL/min/kg
Rat $T_{1/2}$: 2.8 h, 19% F

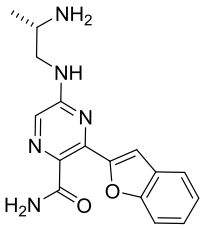
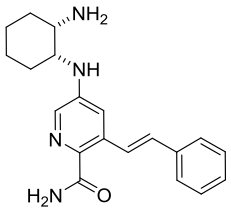
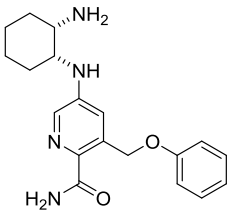


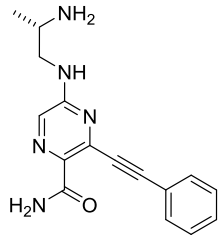
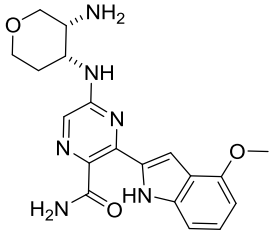
12

Syk IC_{50}: 7 nM
hWB CysLT IC_{50}: 93 nM
Kinases >100X: 97% (100)
Rat Cl_p (Cl_u): 134 (277) mL/min/kg
Rat $T_{1/2}$: 4.8 h

Encouraged by the successes of exploiting intramolecular hydrogen bonds, we investigated the use of weaker *H*-bond donors and other configurations predicted to maintain a planar geometry. Benzofuran **13** lost ~100X potency (Syk IC_{50} = 530 nM) versus its indole analog **8.** Styrene **14** had comparable intrinsic affinity, ~3X loss (Syk IC_{50} = 24 nM) versus the corresponding benzimidazole **12**. Aryl ether **15**, interestingly predicted to prefer a planar configuration affords an equipotent inhibitor (Syk IC50 = 9 nM) to benzimidazole **12**. Alkyne **16** was readily prepared, but demonstrated a substantial potency loss (Syk IC_{50} = 990 nM), likely due to negative interaction of the phenyl moiety with the hinge region of Syk.

Table 1. Additional *C*-linked carboxamide SAR

Analog	Structure	Syk IC_{50} (nM)[a]
13		530
14		24
15		9

16		990
17		0.7

[a] See supporting information for details.

The combined efforts of this scaffold re-design ultimately delivered pyrazinecarboxamide **17**,[21] which possessed the overall profile we were seeking (Syk IC_{50} = 700 pM) including high selectivity (99% of kinases >100X, 101 kinases tested, LRRK2 IC_{50} = 33 nM), potent cell functional activity (hWB CysLT IC_{50} = 62 nM) and a favorable pharmacokinetic profile in preclinical species (Rat Plasma Clp (Clu) = 25 (100) mL/min/kg, Rat $T_{1/2}$ = 3.5 h, 29 %F). Further, indole **17** posed low risk for ion channel activity and DNA interaction as assessed by preclinical safety assays (hERG IC_{50} = 22 μM and UV-Vis = Negative). In summary, careful consideration of designs to bias toward the bioactive conformation delivered alternative chemotypes that maintained favorable drug-like properties while overcoming several safety issues.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures for synthesis of final compounds and intermediates, descriptions of assays performed, computational methods with additional results, and crystallographic details. The complex between the human Syk kinase domain and compound **8** has been deposited in the Protein Data Bank (PDB) with accession code 5TIU. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

Syk, Spleen tyrosine kinase; RA, rheumatoid arthritis; DMARD, disease-modifying antirheumatic drug; Fc, fragment, crystallizable; BCR, B cell receptor; Syk IC_{50}, recombinant human Syk IC_{50}; hWB, human whole blood; PEG, polyethylene glycol.

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[13] Zap70 IC_{50}: 5.3 nM (Zap70 IC_{50}/Syk IC_{50} = 90X), which was consistent with the general selectivity index versus this structurally homologous kinase

[14] Miyaura, N.; Yamada, K.; Suzuki, A. A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.

[15] Model compounds were employed where the diamine portion of the molecule was truncated leaving behind only the heterocyclic ring, primary carboxamide, and C-linked aryl substituent. To calculate potential energy surfaces, initial geometries were generated stepping through the two relevant dihedral angles at +/- 0, 5, 10, 30, 60, 90, 120, 150, 170, 175, and 180 degrees. Dihedral angles of (0, 0) were defined to be the presumed planar bioactive conformation. Geometries were then optimized using GAUSSIAN 09 rev. D01 at the B3LYP/6-31G* level of theory keeping the two dihedral angles fixed at their initial values. Relative electronic energies across the geometries were then used to generate potential energy surface maps in MATLAB. Prediction of planar ground state geometries, such as for the compounds in Table 1, were performed similarly. Geometries of model compounds were generated through systematic enumeration of dihedral angles in 30 degree increments followed by unconstrained optimization. Compounds where the lowest-energy optimized structure was planar were considered for synthesis and experimental study.

[16] Predicted ground state geometry for the core of **8** depicting the pseudo 7-membered ring formed through intramolecular hydrogen bonding can be found in Figure S1 of the supporting information.

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[21] A detailed account of the design considerations affording carboxamide **17** with a favorable in vitro, including mitigation of ion channel activity, and in vivo profile can be found in reference 12.

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