Discovery of Potent and Selective Tricyclic Inhibitors of Bruton’s Tyrosine Kinase with Improved Druglike Properties

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ABSTRACT: In our continued effort to discover and develop best-in-class Bruton’s tyrosine kinase (Btk) inhibitors for the treatment of B-cell lymphomas, rheumatoid arthritis, and systemic lupus erythematosus (SLE), multiple sclerosis (MS) as well as B-cell lymphomas. Accordingly, there have been significant efforts from the pharmaceutical community toward identifying Btk inhibitors for clinical evaluation. Of these, the most advanced compound to date is ibrutinib, recently approved for the treatment of Mantle Cell Lymphoma (MCL), chronic lymphocytic leukemia (CLL), and Waldenstrom’s macroglobulinemia and under evaluation in additional indications. We have previously reported on the discovery of several series of novel and potent Btk inhibitors that possess exquisite selectivity for Btk over other kinases. Their high potency and selectivity stems from the ability of compounds such as 1 to create an induced binding fit in the protein via a rearrangement of the activation loop. Other kinases, including members of the tyrosine kinase family, cannot rearrange in the exact same way due to differences in the amino acid sequence within this loop. The tetrahydrobenzothiophene moiety within 1, held rigidly in place by other contacts the inhibitor makes with the protein, presents a hydrophobic surface that “attracts and sequesters” Y551, ultimately creating a lipophilic specificity pocket (“H3”). A common feature in this series is the incorporation of a secondary amide that tethers the distal bicyclic ring to the central benzene. We set out to address metabolism and permeability liabilities associated with the amide moiety.

In particular, we hypothesized that molecules with an amide tethered back onto the tetrahydrobenzothiophene, such as 2a, would offer a molecule with one less exposed N–H donor and reduce the number of rotatable bonds, potentially improving potency and permeability. Crystal structures of related compounds bound to Btk indicated the amide N–H was not interacting with the protein. Additionally, we incorporated a hydroxyl group in the central benzene ring that was well positioned to interact with nearby K430 and D539 residues, with the hope of improving binding affinity. Table 1 shows the potencies of these compounds for Btk in a biochemical assay, as well as their potencies in an in vitro mouse splenocyte CD86 cell based assay that was used as a downstream pharmacodynamic marker for Btk activity (assay protocols in SI). Pleasingly, the newly generated tricyclic compound 2a was roughly 4-fold more potent against Btk than the uncyclized precursor 1. Compound 2b, which includes a hydroxymethyl group on the central benzene ring, had a ~10-fold increase in Btk binding potency than 2a and was roughly 40-fold more potent than...
The success of our initial attempts at creating improved Btk inhibitors by the employment of a tricyclic moiety encouraged us to explore additional tricycles at this position as well as carefully designed bicycles. Table 2 shows a selected subset of such compounds. Compounds 2b–6 are examples of inhibitors that contain distal 6−5−6 tricyclic ring systems. Since the H3 site is lipophilic, with nonpolar residues flanking much of this pocket, it is not surprising that the most potent compounds, 2b and 3 (Btk IC₅₀ = 0.001 and 0.006 μM respectively), contain all-carbon fused cyclohexane rings.

Table 1. Improved Properties of Tricyclic H3 Btk Inhibitors

| ID | IC₅₀ (μM)ᵃ | LLEᵇ | hPPBᶜ | CLᵈ | F%ᵉ |
|----|------------|------|-------|-----|-----|
| 1  | 0.042      | 3.6  | 99%   | 2   | 45% |
| 2a | 0.011      | 4.2  | 99%   |     |     |
| 2b | 0.001      | 0.087| 5.8   | 2   | 90% |

ᵃAssay protocols in Supporting Information (SI), n ≥ 2.ᵇLLE = pIC₅₀(Btk) − cgLogD.ᶜHuman plasma protein binding.ᵈTotal clearance (mL/min/kg) at 1 mg/kg i.v. dose formulated using a mixture of EtOH/Cremophor/water for 1 (solution) or PEG400/EtOH/water for 2b (solutions).ᵉF% = oral bioavailability after a 5 mg/kg oral dose (n = 3) formulated using a mixture of EtOH and Cremophor for 1 (solution) or PEG400/EtOH/Tween80/water for 2b (suspension).

Table 2. SAR for H3 Groups

| ID | R | IC₅₀ (μM)ᵃ | Sol η (μM)b |
|----|----|------------|-------------|
| 2b |    | 0.001      | 0.087       |
| 3  |    | 0.006      | 0.2         |
| 4  |    | 0.081      | 0.48        |
| 5  |    | 2.6        | 48.6        |
| 6  |    | 16.7       | >50         |
| 7  |    | 0.002      | 0.064       |
| 8  |    | 0.002      | 0.057       |
| 9  |    |            | 0.051       |
| 10 |    | 0.003      | 0.193       |
| 11 |    | 0.139      | NT          |
| 12 |    | 0.003      | 1.2         |
| 13 |    | 0.004      | 0.171       |
| 14 |    | 0.005      | 0.23        |

ᵃAssay protocol in SI, n ≥ 2.ᵇKinetic solubility was measured at pH 7.4.十七
Table 3. Combination of the Best H2 and H3 Moieties for Optimal Potency and Druglike Properties

| ID | X   | Y   | Z   | IC50 (μM) | HHep/RHep | Sol. (μM) | Perm. | Rat |
|----|-----|-----|-----|-----------|-----------|----------|-------|-----|
|    |     |     |     | Btk | CD86 | WB CD69 |       |     |
| 7  | H   | n/a |     | 0.002 | 0.064 | 0.087   | 11 / <10 | 1.4 | MOD | 16 | 41 |
| 15 | H   | Me  |     | 0.003 | 0.025 | -       | <6.2 / <10 | 18 | -   | 29 | 37 |
| 16 | H   | ox  |     | 0.004 | 0.006 | 0.089   | 8.8 / <10 | 1  | MOD | -  | -  |
| 17 | H   | Me  |     | 0.004 | 0.107 | 0.045   | 10 / 12 | 115 | MOD | 40 | 20 |
| 18 | H   | ox  |     | 0.008 | 0.137 | 0.069   | <6 / <10 | 99 | MOD | 14 | 46 |
| 19 | F   | Me  |     | 0.002 | 0.022 | 0.029   | <6.2 / <10 | 71 | MOD | 37 | 52 |
| 20 | F   | ox  |     | 0.004 | 0.010 | 0.035   | <6 / <10 | 73 | HIGH | 20 | 27 |

aAssay protocol in SI, n ≥ 2. bProjected hepatic clearance using human or rat hepatocytes. cKinetic solubility was measured at pH 7.4. dMeasured permeability using Madin-Darby Canine Kidney (MDCK) Epithelial cell lines, A to B: MOD: 1–10 (10⁻⁶ cm/s) and HIGH: >10 (10⁻⁵ cm/s).

With a variety of novel tricyclic compounds in hand that had excellent potency for Btk, we focused our efforts on designing compounds with improved physiochemical properties. As demonstrated in Table 2, although compounds 2b, 7, 8, and 9 had the best cellular potency (CD86 IC50 < 100 nM), they unfortunately all had low kinetic solubility (≤ 2 μM) at physiological pH. Kinetic solubility as measured in an internal high throughput assay was used as an initial gauge of intrinsic solubility. Low solubility is a primary cause of reduced oral bioavailability of the crystalline materials preferred for clinical development, and often presents formulation challenges in dose escalations for safety studies. This was indeed the case for many compounds in this chemical series. To find compounds with improved solubility, modifications of the left-hand portion of the inhibitor that extends into a partially solvent exposed area of the protein region (“H2”, Figure 1) were explored and found to be well tolerated. Of the many compounds generated, we determined that compounds with a substituted pyridinopiperazine group (Table 3), as opposed to the pyrimidine of the previous compounds (Table 2), offered an exciting new subseries with much improved kinetic solubility.

A small subset of compounds containing combinations of the best H2 and H3 groups are highlighted in Table 3. Installing a tertiary basic amine containing left-hand H2, which is primarily protonated at neutral pH, indeed helped improve the solubility from 1.4 μM (7) to 18 μM (15). Reducing the basicity from a calculated pKₐ of 7.8 (15) to 6.3 (16, substituted with an oxetane) abrogated the improved solubility. This prompted...
us to focus on H3 groups with higher polarity than that of 7. Gratifyingly, all four compounds containing a more polar tetrahydroindole H3 group (17-20) maintained high kinetic solubility regardless of the amine basicity. However, the moderate CD86 cellular potencies of 17 and 18 (IC$_{50}$’s of 0.107 and 0.137 μM, respectively) mirrored that of the 0.2 μM potency seen for 3, which bears the same polar H3 group. A potency breakthrough was realized when a single fluorine atom was added to the middle linker benzene ring (19-20). This fluorine is well positioned to engage the backbone carbonyl carbon of G409 in a dipole-dipole interaction (Figure s1 in the SI), further stabilizing the binding orientation of these inhibitors in the Btk catalytic domain. The resultant CD86 cellular potency improved 5-fold and 13-fold for the two pairs 17 → 19 and 18 → 20, respectively.

All compounds in Table 3, except 17, were low to moderately cleared and had reasonable bioavailability in in vivo rat PK studies. In vitro hepatic clearance represented by RHEP data underestimated the in vivo clearance; however, the relative stability trend was consistent from in vitro to in vivo studies. It was also pleasing to see that human hepatic clearance ranged from low to moderate. Given the totality of data including safety assessment (not discussed here), compounds 7 (G-744) and 20 rose to the top of the list with the most balanced overall profile.

In addition to potency and druglike properties, a prominent goal of developing a clinically viable kinase inhibitor lies in controlling selectivity. Poor selectivity may have a profound effect on drug safety, especially for nononcology indications where chronic dosing requires an exquisitely clean safety profile. Therefore, both G-744 and 20 were profiled against a panel of 285 active recombinant human kinases. In particular, G-744 demonstrated >1000-fold Btk biochemical selectivity against all kinases tested except for EphA7 and Fgr, against which it still showed robust selectivity of 428-fold and 868-fold, respectively (Figure s3 in the SI). Due to G-744’s superb kinase selectivity (superior to 20), we realized it could be an excellent tool molecule to probe the biology of Btk, as the results would not be confounded by off-target activity and the need for interpretation. Thus, we performed a full characterization of this molecule, with key data summarized in Table 4. In addition to preventing cellular functions in murine B-cells such as B-cell receptor (BCR)-mediated CD86 induction with an EC$_{50}$ of 64 nM, G-744 also inhibited BCR-stimulated B-cell proliferation in human B-cells (EC$_{50}$ = 22 nM). In human monocytes, production of the inflammatory cytokine TNFα following activation with immune complexes was abrogated by G-744 (EC$_{50}$ = 33 nM). In human whole blood, G-744 demonstrated potent inhibition of BCR-stimulated CD69 expression on B-cells with an EC$_{50}$ of 87 nM.

In pharmacokinetic experiments, G-744 exhibited low to moderate clearance in four preclinical species (Table 5). Sufficient oral exposures were achievable using a crystalline formulation in both mouse and rat despite low kinetic solubility.

| Species | In vitro | In vivo |
|---------|----------|---------|
|         | CL (μM)  | CL (μM) |
| mouse   | 35       | 2       | 45$^{−}$ 77$^{−}$ |
| rat     | 18       | 3       | 23$^{−}$ 37$^{−}$ |
| dog     | 15       | 1       | 7        |
| cyno    | 18       | 31      | 17       |
| human   | 8        | 11      |          |

$^{a}$Projected hepatic clearance using liver microsomes (mL/min/kg).
$^{b}$Projected hepatic clearance using hepatocytes (mL/min/kg). *Total clearance in vivo (mL/min/kg). 2F% = oral bioavailability after 5 (amorphous) or 100 mg/kg (crystalline) dose in mouse; 5 (amorphous) or 100 mg/kg (crystalline) dose in rat; 5 mg/kg dose in dog (n = 3). *Methylcellulose/Tween80/water suspension of crystalline free base material. *Hydroxypropylmethylcellulose/Na citrate/water pH 3 suspension of amorphous material.

Given the favorable DMPK profile of G-744 in rat, we examined its efficacy in the developing collagen-induced arthritis (CIA) model in Lewis rat$^{1,2,3}$ Oral dosing with G-744 at 6.25, 12.5, and 25 mg/kg b.i.d. maintained plasma concentrations above the IC$_{50}$, IC$_{70}$, and IC$_{90}$ respectively, for inhibition of Btk Y223 phosphorylation in whole blood (Figure s2 in the SI). As shown in Figure 2, all three doses resulted in a significant dose-dependent inhibition of ankle thickness between day 10 and day 17 (onset of increase in ankle diameter on day 9). The 25 mg/kg dose (97% inhibition of the area under the ankle thickness vehicle curve) showed comparable efficacy to dexamethasone. In naïve rats treated with vehicle, the ankle diameters did not change over the course of the study and ankles from normal rats were significantly (by ANOVA) reduced toward normal for all drug-treated rats (significant days 10–17) as compared to the vehicle control.
In summary, orally bioavailable Btk inhibitors with novel tricyclic head groups were discovered through structure and property-based drug design. Improved molecules were discovered, and an outstanding tool molecule, G-744, was identified with excellent potency, favorable DMPK properties, and superb kinase selectivity. G-744 demonstrated efficacy equivalent to Dexamethasone in a rat CIA model at 25 mg/kg b.i.d. dosing. Such findings further solidified our commitment to Btk as a therapeutic target. The chemistry culminating in a clinical candidate will be described in a subsequent manuscript.

**ASSOCIATED CONTENT**

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00103.

Physiochemical properties, experimental procedures, compound characterization, assay protocols, PK–PD relationship, and full kinase data (PDF)

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**Notes**

The authors declare no competing financial interest.

**Biographies**

Xiaojing Wang received a B.S. degree from Peking University, a Ph.D. in Organic Chemistry from University of Florida under the supervision of Kenan Professor Alan R. Katritzky, and was a Postdoctoral Fellow at RTI International with Dr. C. Edgar Cook. Since then, Xiaojing has pursued drug discovery of various disease indications at ISIS (now Ionis), Scios/Johnson and Johnson, and Genentech/Roche. Xiaojing is currently a Senior Scientist of Discovery Chemistry at Genentech and has led multidisciplinary teams into nominating several clinical candidates as a project team lead. Xiaojing is an inventor and author of over 40 patents and research publications.

Wendy B. Young received a B.A./M.S. in chemistry from WFU under the direction of E. C. Taylor, and was a Postdoctoral Fellow at Sloan-Kettering in the laboratory of Samuel Danishefsky. Since then, Wendy has led drug discovery efforts at both small biotech firms (Axys/Cela) and larger pharma companies (Genentech/Roche). Wendy is currently Vice President of Discovery Chemistry at Genentech where her teams have produced numerous drug candidates in multiple disease indications. She is listed as an inventor or author on over 70 patents and research publications. Wendy is currently the 2017 elected Chair of the ACS MEDI division.

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**ABBREVIATIONS**

Btk, Bruton’s tyrosine kinase; RA, Rheumatoid arthritis; SLE, systemic lupus erythematosus; MS, multiple sclerosis; MCL, mantle cell lymphoma; CLL, chronic lymphocytic leukemia; BCR, B-cell receptor; DMPK, drug metabolism and pharmacokinetics; CIA, collagen-induced arthritis; b.i.d., twice a day; SEM, standard error of the mean

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