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Discovery of 5-(arenethynyl) hetero-monocyclic derivatives as potent inhibitors of BCR–ABL including the T315I gatekeeper mutant

Mathew Thomas *, Wei-Sheng Huang, David Wen, Xiaotian Zhu, Yihan Wang, Chester A. Metcalf, Shuangying Liu, Ingrid Chen, Jan Romero, Dong Zou, Raji Sundaramoorthi, Feng Li, Jiwei Qi, Lisi Cai, Tianjun Zhou, Lois Commodore, Qihong Xu, Jeff Keats, Frank Wang, Scott Wardwell, Yaoyu Ning, Joseph T. Snodgrass, Marc I. Broudy, Karin Russian, John Iuliucci, Victor M. Rivera, Tomi K. Sawyer, David C. Dalgarno, Tim Clackson, William C. Shakespeare

ARIAD Pharmaceuticals Inc., 26 Lansdowne Street, Cambridge, MA 02139, USA

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ABSTRACT

Ponatinib (AP24534) was previously identified as a pan-BCR–ABL inhibitor that potently inhibits the T315I gatekeeper mutant, and has advanced into clinical development for the treatment of refractory or resistant CML. In this study, we explored a novel series of five and six membered monocycles as alternate hinge-binding templates to replace the 6,5-fused imidazopyridazine core of ponatinib. Like ponatinib, these monocycles are tethered to pendant toluanilides via an ethynyl linker. Several compounds in this series displayed excellent in vitro potency against both native BCR–ABL and the T315I mutant. Notably, a subset of inhibitors exhibited desirable PK and were orally active in a mouse model of T315I-driven CML.

Imatinib (Gleevec, ST1571), a small molecule BCR–ABL inhibitor is a proven and effective frontline therapy for the treatment of chronic myeloid leukemia (CML).[1] Despite the impressive clinical success of imatinib in treating early phase CML, acquired resistance has surfaced as an important limitation of the drug. Such resistance is often associated with the emergence of point mutations in the ABL kinase domain that impede inhibitor binding.[2] To address these mutations, two second generation inhibitors nilotinib (Tasigna, AMN107) and dasatinib (Sprycel, BMS-354825) have been developed.[3] Despite the effectiveness of these newer agents which successfully target most imatinib failures, pockets of resistance still remain, and neither compound inhibits the T315I mutant, which constitutes ~15–20% of all clinically observed mutations.[4] To identify next-generation inhibitors capable of overcoming resistance, we focused on compounds which target not only BCR–ABL^{T315I} but also the native (unmutated) form of the protein, and all other known resistant mutations. Such a pan-BCR–ABL inhibitor should exert high levels of disease control in patients resistant or refractory to current agents, and have the potential to thwart all resistance if used early in disease treatment.

As a part of our ongoing program targeting DFG-out based ABL inhibitors, we have previously described a series of purine based, ATP competitive dual Src/ABL inhibitors[5] which displayed modest cellular potency against BCR–ABL^{T315I}. Subsequent structure guided optimization led to the discovery of ponatinib,[6] a highly potent and orally bioavailable pan-BCR–ABL inhibitor including T315I. Ponatinib has advanced into clinical trials for the treatment of CML patients with resistance to prior therapy. A full description of the medicinal chemistry strategy leading to the discovery of this compound has been described in a recent publication.[7]

To further probe ponatinib SAR, particularly in the hinge region, efforts were undertaken to explore replacing the 6,5-fused imidazopyridazine core with small subsets of potential five and six membered monocyclic hinge-binding moieties such as **7** and **8** tethered to pendant toluanilides via an ethynyl linker (Fig. 1).[8] Monocycles capable of forming one or two hinge region H-bonds were included, and the effects on potency, PK and kinase selectivity were monitored relative to ponatinib. A recent report highlights a similar strategy where low nM inhibitors of BCR–ABL^{T315I} exemplifying both mono and bicyclic hinge-binding templates were disclosed.[9]

To guide our design efforts, we first conducted docking studies to elucidate key molecular recognition elements between prototype inhibitor **8h** and the ABL^{T315I} kinase domain. The model was built based on the recently published crystal structure of ponatinib[6,10] in complex with ABL^{T315I} (RCSB code: 3OY3).

* Corresponding author.
E-mail address: Mathew.thomas@ariad.com (M. Thomas).

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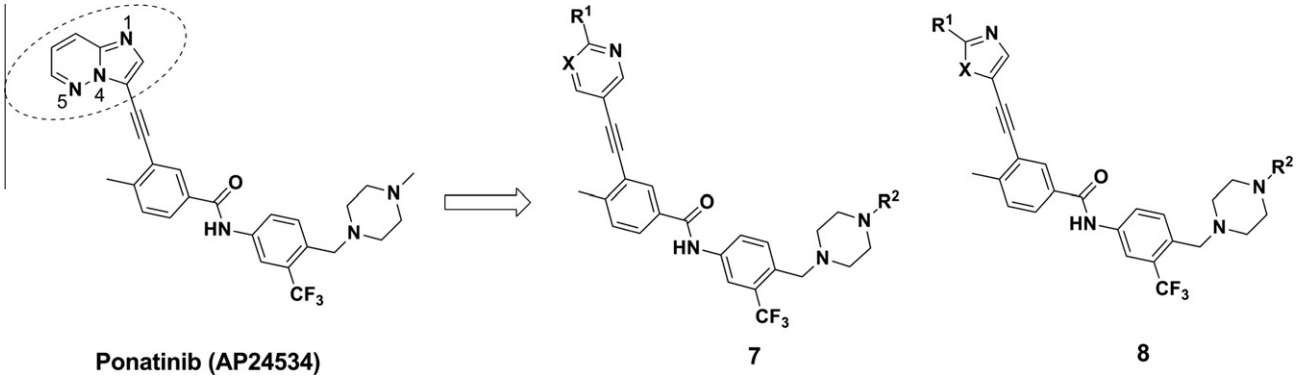


Figure 1. Evolution of hetero-monocyclic BCR–ABL^{T315I} inhibitors from ponatinib (AP24534).

As shown in the docked model, **8h** binds to ABL^{T315I} through a DFG-out mode (Fig. 2). The monocyclic core of **8h** forms two H-bonds with the backbone of M318 in the kinase hinge region. Additionally, three more hydrogen bond contacts arise between the amide of the ligand and the backbone of D381 and the side chain of E286, as well as between the backbone of I360 and the basic hydroxyethyl piperazine tail stretching into the solvent front. In addition, extensive van der Waals molecular contacts are made throughout the entire molecule, particularly around F382 of the DFG motif. These include the contacts of F382 with the tolyl moiety, the ethynyl linkage and the monocyclic core of **8h**. The ethynyl group of **8h** makes favorable hydrophobic interactions with the mutated gatekeeper isoluceine residue subjugating this highly restricted structural requirement for this mutation. The *N*-methyl substituent of the imidazole core also makes additional van der Waals interactions with the hinge region compared with ponatinib.[10]

In contrast to ponatinib, the P-loop of ABL^{T315I} adopts a more open conformation in ABL^{T315I} when bound with **8h** making limited van der Waals interactions with the inhibitor. This is most likely caused by the change of the 6,5-fused bicyclic core in ponatinib compared to the monocyclic core in **8h** resulting in the loss of edge-to-face aromatic interactions between Y253 located in the P-loop and the hinge binding core of **8h**. Overall, the model suggests that **8h** binds similar to ponatinib in ABL^{T315I} but with the ability to make an additional hinge region H-bond while forfeiting close van der Waals interactions with the P-loop.

Having determined the key structural features required for optimal protein interaction, we prepared a series of five and six membered monocyclic derivatives for testing in enzymatic and cellular assays. Based on our previously described synthetic route to this chemical class,[7] we first introduced the acetylenic side chain by subjecting commercially available hetero-aryl bromides **1a**–**f** to standard Songashira coupling conditions followed by protodesilylation to afford **2a**–**f** in good yields (Scheme 1). Similarly, the acetylenic azole precursors **5a**–**c**, **5k** and **5l** required for compounds **8a**–**c**, **8k** and **8l** were all prepared in an analogous fashion (Scheme 1).

For the remaining azole alkynyl derivatives **5d**–**f** a slightly different strategy was adopted in order to install the necessary C2 amides. Commercially available 5-bromo *N*-methyl imidazole was first converted into a common protected acetylenic derivative **3** via the process outlined above. Subsequent deprotonation with *n*-butyllithium led to C-2 lithioimidazole intermediacy followed by quenching with trimethyl isocyanate furnished the respective primary amide precursor which on protodesilylation under basic conditions provided **5d**.[11] In case of amides **4e** and **4f**, acetylenic precursor **3** was likewise treated with *n*-butyllithium and quenched with dry ice to yield the corresponding acid derivative which was further coupled with either methylamine or 2-aminoethanol produced the required amides. Consequent release of the silyl group from the amide precursors under basic conditions provided terminal alkynes **5e** and **5f** in quantitative yields (Scheme 2).

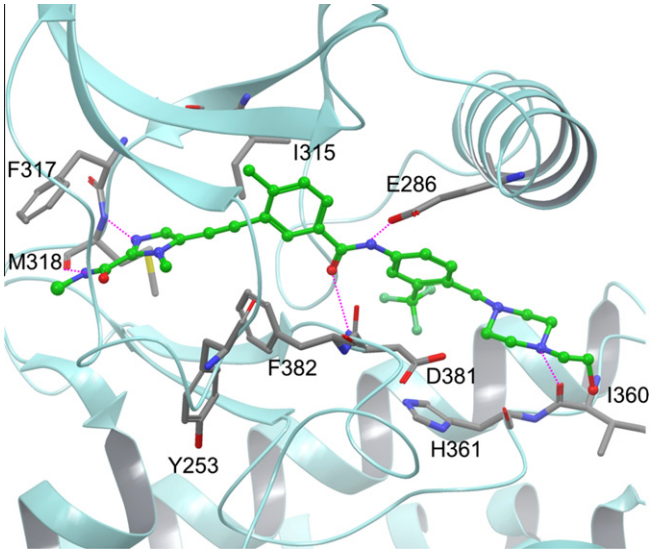
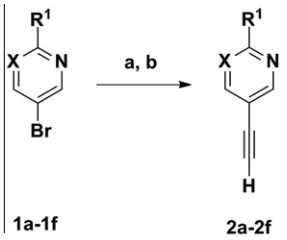
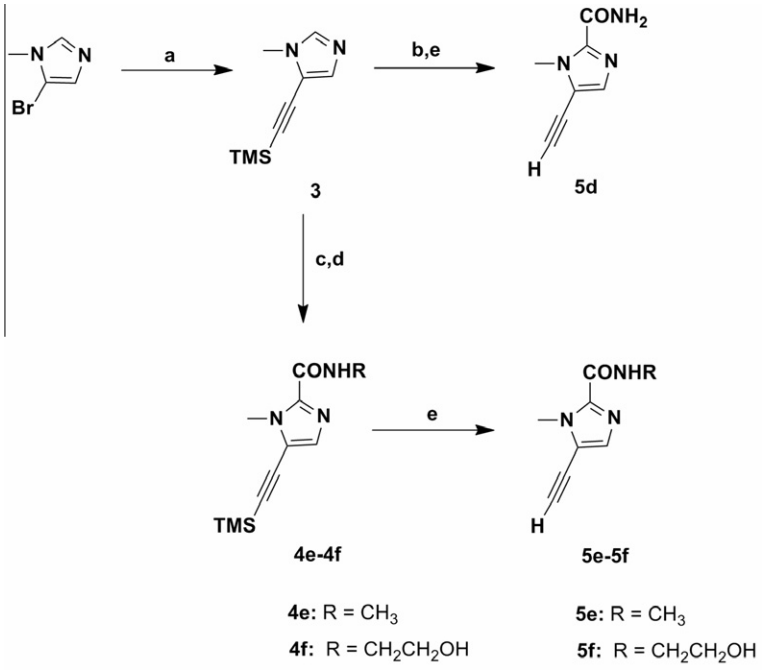


Figure 2. Model of inhibitor **8h** bound to ABL^{T315I} kinase.

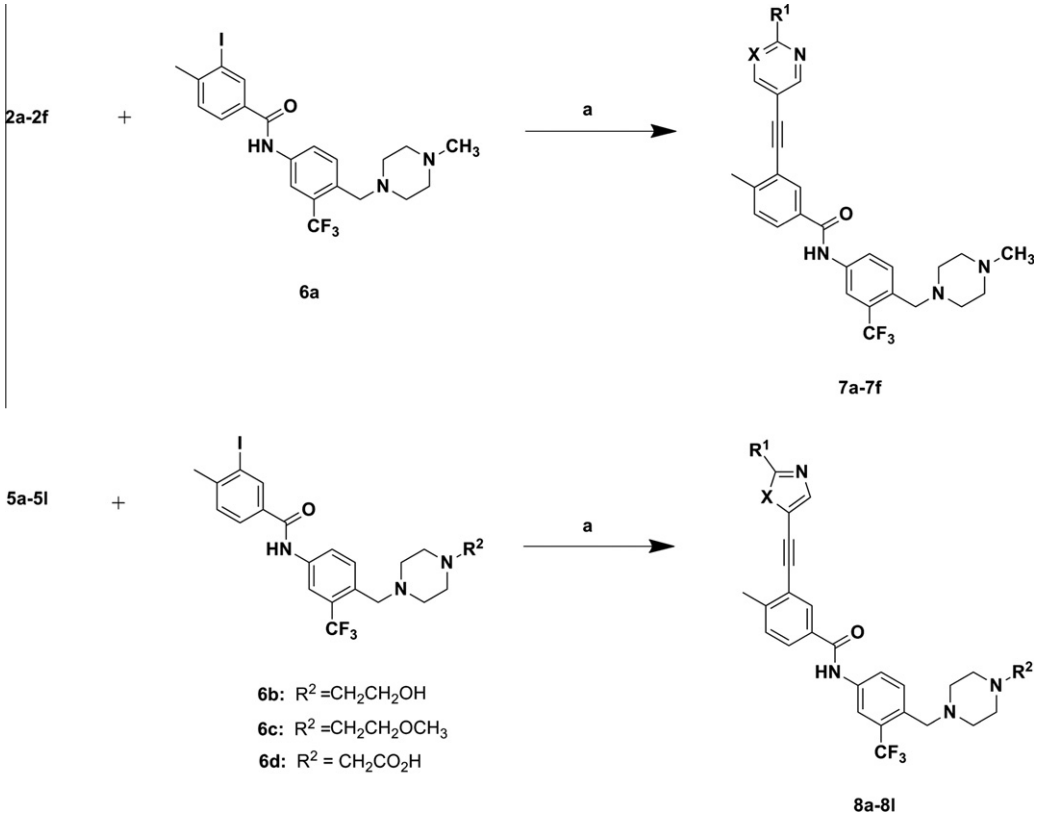


2a: X = CH, R^1 = H
2b: X = N, R^1 = H
2c: X = CH, R^1 = $NHCOCH_3$
2d: X = CH, R^1 = $NHCOCH_2CH_3$
2e: X = CH, R^1 = $CONH_2$
2f: X = N, R^1 = HN–cyclopropyl

Scheme 1. Reagents and conditions: (a) TMS acetylene, $Pd(PPh_3)_4$, CuI, DMF, 80 °C; (b) K_2CO_3, MeOH–THF.



Scheme 2. Reagents and conditions: (a) TMS acetylene, $Pd(PPh_3)_4$, CuI, DMF, 80 °C; (b) *n*-BuLi, TMSNCO, THF −78 °C; (c) *n*-BuLi, CO_2, THF −78 °C; (d) $MeNH_2$ or 2-amino ethanol, CDI, THF; (e) K_2CO_3, MeOH–THF.

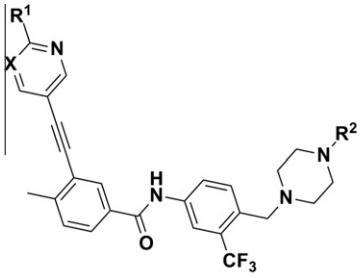


Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, DMF, 80 °C.

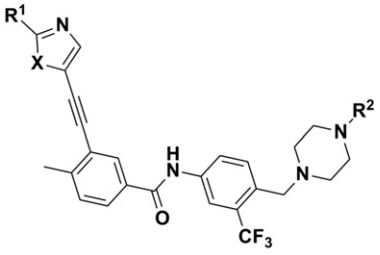
As depicted in Scheme 3, the fully elaborated compounds were then prepared individually by executing a second Sonagashira coupling reaction between precursors **2a–f** with the previously described iodo benzamide **6a**[7] to furnish the corresponding target compounds **7a–f**. Similarly, compounds **8a–l** were obtained via the same route outlined for **7a–f** using the appropriate substituted iodobenzamides **6b–d**, respectively.

Compounds were evaluated for their kinase inhibitory activity against both native and mutant (T315I) ABL as previously described.[7] Cellular activity was assessed with Ba/F3 cells transfected

Table 1
Structure–activity relationship for inhibitors **7** and **8** (IC_{50}s in nM)



7a -7f



8a -8l

Compd	X	R^1	R^2	ABL kinase[a]	ABL^{T315I} kinase[a]	BCR–ABL (Ba/F3)	$BCR–ABL^{T315I}$ (Ba/F3)	Parental (Ba/F3)
Ponatinib			CH_3	8.6	40	1.2	8.8	1219
7a	CH	H	CH_3	40.3	123	4.1	45.5	2038
7b	N	H	CH_3	62.7	435	3.1	65	2818
7c	CH	$NHCOCH_3$	CH_3	18	121	2.2	9.6	1787
7d	CH	$NHCOCH_2CH_3$	CH_3	28.6	104	2.5	13.4	1659
7e	CH	$CONH_2$	CH_3	48.7	321	2.6	18	1021
7f	N		CH_3	49.7	457	195	519	607
8a	NH	H	CH_3	1000	3717	730	5738	6549
8b	NCH_3	H	CH_3	129	550	43	709	5647
8c	NCH_3	CH_3	CH_3	72.6	362	8.5	69	1793
8d	NCH_3	$CONH_2$	CH_3	3.6	25	1.3	7.6	787
8e	NCH_3	$CONHCH_3$	CH_3	17.4	18	1.7	4	1583
8f	NCH_3	$CONHCH_2CH_2OH$	CH_3	55	301	3.9	64	1603
8g	NCH_3	$CONH_2$	CH_2CH_2OH	3.6	36	0.61	5.8	1320
8h	NCH_3	$CONHCH_3$	CH_2CH_2OH	17.2	60.2	1.3	8.4	3093
8i	NCH_3	$CONH_2$	$CH_2CH_2OCH_3$	4.8	140	0.65	10.8	2378
8j	NCH_3	$CONH_2$	CH_2CO_2H	4.3	106	7.6	64	10000
8k	S	NH_2	CH_3	29	139	2.8	17.5	1269
8l	S	$NHCOCH_3$	CH_3	12	27	0.67	5.5	97

[a] All data in this study were obtained from in-house assays. In a different enzymatic assay conducted by Reaction Biology Corporation,[12] the IC_{50}s of ponatinib were determined to be 0.37 (ABL) and 2.0 nM (ABL^{T315I}), as previously reported.[6]

with native BCR–ABL or $BCR–ABL^{T315I}$ using inhibition of parental, non-transfected Ba/F3 cells as a control (Table 1).

We focused initially on a discrete subset of azine scaffolds **7** that could recapitulate the key hinge H-bond while conserving all elements of molecular recognition that contributed to the potency of ponatinib including the tolyl moiety and the trifluoromethyl phenyl group bearing the *N*-methyl piperazine moiety.

In general, comparison of prototype azines **7a** and **7b** versus ponatinib revealed decreased ABL^{T315I} kinase activity (3 and 10 fold, respectively) and 4–7 fold potency reduction in Ba/F3 cells expressing $BCR–ABL^{T315I}$. In part this may be attributed to the inability of both inhibitors to form close van der Waals contacts with the P-loop as seen with ponatinib.

Introduction of an acetamido group at position C2 yielded compounds **7c** and **7d** both with significantly increased enzymatic and cellular potencies relative to the parent **7a** (Table 1). The potency gain presumably arises from the additional hydrogen bond between the exocyclic NH of the template and M318 in the kinase hinge region notwithstanding the aforementioned loss of P-loop interactions. Despite the increased potency, previous experience with similar molecules targeting alternate kinases suggested they would be rapidly metabolized in vivo and so they were no longer pursued.

Given the importance of the paired hinge region H-bonds, we sought alternative ways to maintain these interactions but with increased metabolic stability. Thus we tested inhibitor **7e** bearing a stable primary carboxamide. Compound **7e** exhibited similar in vitro potency (Table 1) relative to **7c** and **7d**, however, when tested in the presence of physiological concentrations of human serum albumin,[5] cellular potency against $BCR–ABL^{T315I}$ was markedly shifted by 29 fold (18–513 nM) suggesting that **7e** was highly protein bound. Next we capped the C2 exocyclic primary amine with a cyclopropyl group yielding **7f**. Although we have previously used this functionality to identify compounds with good oral bioavailability and attenuated protein binding in an alternate series[5] surprisingly, this modification markedly reduced both kinase and cellular activities >10 fold (IC_{50} of 457 and 519 nM, respectively) relative to both ponatinib and **7c–e**.

In parallel to our investigation of azine derivatives we also explored a series of azole moieties **8** and evaluated them for activity. Compared to ponatinib, the imidazole prototype inhibitor **8a** was essentially inactive in both kinase and cellular assays, likely due to significantly decreased hydrophobic contact between the inhibitor core and the protein. The *N*-methyl imidazole analog **8b** improved potency relative to **8a** suggesting that the *N*-1 methyl substituent on the imidazole ring occupies a similar position to *N*-5 of the ponatinib bicyclic core. Interestingly, the dimethyl analog **8c** exhibited two fold increased kinase activity relative to **8b** but was 10 fold more active in cells against $BCR–ABL^{T315I}$.

Analogously to the approach with azine analogues, carboxyamide substituents at C2 were installed to serve as acyclic surrogates for a purine template whereby the NH_2 of the carboxy amide is expected to be equivalent to the exocyclic 6-amino group of the adenine core, preserving the required paired H-bonds to the kinase hinge region.[5] Inhibitor **8d** was synthesized, tested and indeed, displayed comparable potency to ponatinib in the ABL^{T315I} kinase and $BCR–ABL^{T315I}$ mutant Ba/F3 cell assays (IC_{50}s of 25 and 7.6 nM, respectively). Encouraged by these results, further SAR around this series was explored. The simple N-methylated carboxamide analog **8e**, also exhibited similar

Table 2
Pharmacokinetic profile for selected compounds

	Rat[a]									Mouse[b]
	iv					po				po
Compd	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (h/ng/mL)	*Vd* (L/kg)	CI (L/h/kg)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (h/ng/mL)	*F* (%)	C_{6h} (ng/mL)
7b	822	6.2	5308	8.5	0.94	900	10	13,559	85.0	771
8d	627	7.0	5445	9.3	0.92	258	8.0	4144	25.3	358
8g	598	3.5	2320	11	2.15	61.4	6.3	962	14.0	333
8h	200	5.6	970	8.2	1.03	344	10	6586	45	1148

[a] Dosed iv in rats @ 5 mg/kg, po dosed @ 15 mg/kg.
[b] Dosed po in mice @ 30 mg/kg.

kinase and cellular activities. However, further attempts to increase potency through incorporation of a more hydrophilic amide **8f** resulted in reduced kinase and cellular activity relative to **8d** and **8e**.

Next we briefly explored piperazine ring SAR, both as a means to increase potency and modify the ADME properties of this series. For this purpose, we simultaneously prepared matched sets of both **8d** and **8e** by further substituting the basic *N*-methyl group with more hydrophilic side chains, yielding **8g** and **8h**. When tested, both compounds exhibited similar potencies relative to their parent compounds **8d** and **8e**. Since, inhibitor **8g** was slightly more active it was further modified to ether **8i** and acid **8j**, however, these analogues offered no significant advantage relative to **8g** or were less potent.

Lastly, we also explored alternate azole moieties such as aminothiazole derivatives **8k** and **8l** as potential bioisosteres of pyrimidine inhibitor **7f**. Both analogues retained potency against the native and mutated forms of BCR–ABL with the caveat that **8l** potently inhibited the Ba/F3 parental cell line with an IC_{50} of 97 nM, suggesting a loss of selectivity.

To probe the ADME properties of this series, we evaluated several potent compounds in a rat pharmacokinetic model in parallel with the in vitro assays. In general, potent compounds from both series displayed good clearance properties and modest to excellent oral bioavailability. Among those analogues, **7b** exhibited the highest oral exposure and longest half-life ($t_{1/2}$) (Table 2). The remaining inhibitors, ranked as follows: **8h** > **8d** > **8g**.

In preparation for efficacy studies, mouse PK data were also determined at a single 6 h time point. Notably, **8h** demonstrated the highest plasma concentration when dosed orally at 30 mg/kg (Table 2).

Several inhibitors possessing desirable in vitro potency and with favorable pharmacokinetic profiles were further evaluated for their anti-tumor activity in an aggressive mouse model of CML driven by the T315I mutation.[6] In this survival model, mice were injected intravenously with Ba/F3 BCR–ABL^{T315I} cells. After three days, the animals were dosed orally, once-daily with inhibitors at 10 mg/kg for 19 consecutive days. The level of increased overall survival of treated mice relative to untreated control was used to assess efficacy. The median survival time for vehicle-treated mice was 15 days. Among all the inhibitors tested, **8h** demonstrated the greatest increased overall survival (Fig. 3) and was comparable to the ponatinib control.

In a second study, **8h** exhibited excellent dose-dependency and significantly prolonged median survival to 37 days at the highest dose tested (30 mg/kg) representing 130% increase in overall survival relative to vehicle control group with no signs of overt toxicity (Fig. 4). This potency is similar to that previously observed with ponatinib.[6]

To assess the kinase selectivity profile and examine the effects of an additional hinge-region H-bond on specificity, **8h** was screened against a broad kinase panel using enzyme assays as previously described.[6] Similar to ponatinib, the incorporation of the alkyne moiety adjacent to the gatekeeper residue imparts a degree of kinase promiscuity, despite the additional hinge region H-bond in the monocyclic template (Table 3). **8h** inhibited the ephrin, FGFR, FLT, PDGFR and Src family of kinases with IC_{50}s within 10 fold of that for the ABL T315I mutant. Notably, all of these kinases contain small to medium size gatekeeper residues that are more easily accommodated by the linear acetylene linkage. Like ponatinib, **8h** was completely inactive against Aurora A, CDK2 and the insulin receptor tyrosine kinase.

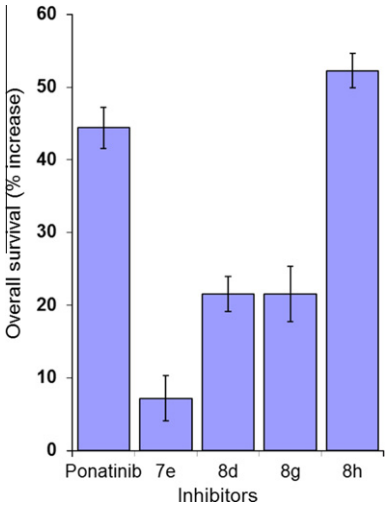


Figure 3. Comparative in vivo efficacy in a Ba/F3 BCR–ABL^{T315I} survival model following 19 daily oral doses (10 mg/kg, error bars represent SD).

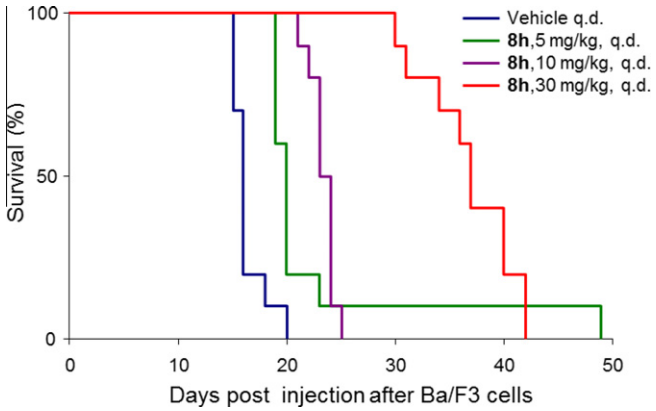


Figure 4. In vivo efficacy of **8h** in a Ba/F3 BCR–ABL^{T315I} survival model following 19 daily oral doses.

Table 3
Kinase inhibition profile of **8h** against selected kinases

Kinase	IC_{50} (nM)	Kinase	IC_{50} (nM)
ABL	0.2	FGFR3	10.5
ABL(T315I)	0.4	FGFR4	34
BRAF	20	VEGFR1	5.2
BRAF (V599E)	26	VEGFR2	2.3
Aurora A	>3000	VEGFR3	2.6
CDK2/cycline E	6.4	FMS	7.2
c-Kit	>3000	IR	>3000
c-Met	>3000	JAK1	55.3
EGFR	736	JAK2	536
EGFR (L858R)	231	JAK3	57.5
EGFR (L858R T790M)	>3000	FLT3	2.0
EGFR (T790M)	>3000	LYN	<0.15
EPHA2	0.6	PDGFRα	1.3
EPHA3	1.2	PDGFRβ	2.6
EPHA7	4.2	RET	0.2
FGFR1	1.8	Tie2/TEK	2.2
FGFR2	1.5	Src	4.0

In summary, we describe a strategy to design an orthogonal series of BCR–ABL inhihitors bearing monocyclic hinge-binding templates, evolved from our clinical candidate and pan-BCR–ABL inhibitor, ponatinib. Lead compounds from this series potently inhibit ABL kinase activity and proliferation of Ba/F3 cells expressing both native BCR–ABL and BCR–ABL^{T315I} with low nM IC_{50}s. Multiple compounds in the series exhibited favorable rat and mouse pharmacokinetic profiles, and **8h** exhibited efficacy similar to ponatinib in an aggressive mouse model of CML driven by the T315I mutant of BCR–ABL. The additional hinge region H-bond appears to compensate for the decreased hydrophobic interactions of the monocycle relative to the 6,5-fused bicycle in ponatinib in terms of in vitro and in vivo activity, and has almost no effect on kinase selectivity. Monocyclic derivatives such as **8h** may be useful for targeting multiple kinases, including those bearing gatekeeper mutations, and therefore could prove useful in the treatment of tumor types where these kinases play a key role.

Acknowledgments

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