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Design and Synthesis of Thiadiazoles and Thiazoles Targeting the Bcr-Abl T315I Mutant: from Docking False Positives to ATP-Noncompetitive Inhibitors

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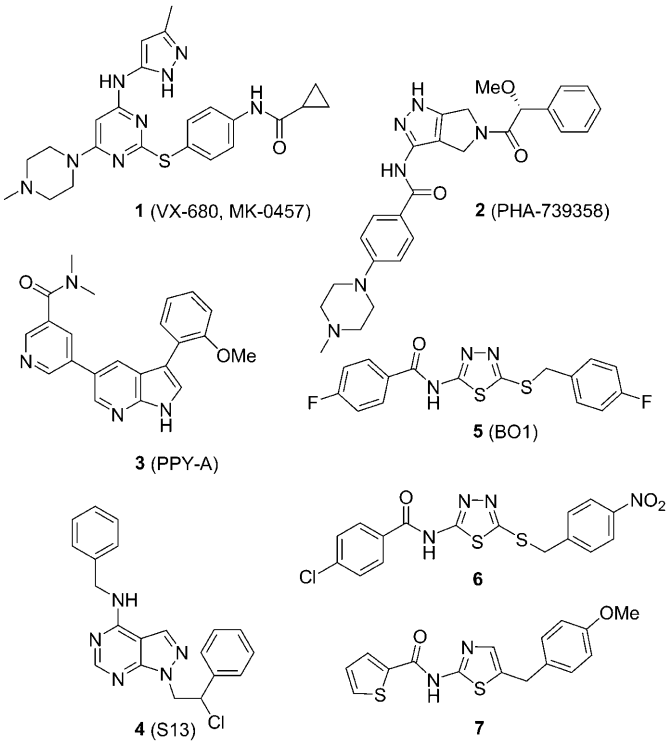
Chronic myeloid leukemia (CML) was the first neoplastic disease for which the knowledge of the molecular pathogenesis led to the development of a curative therapy. Imatinib mesylate (Gleevec; Novartis, Basel, Switzerland), the first targeted drug for the treatment of CML, has a high rate of remission and is currently used as frontline therapy.[1] However, patients treated with imatinib (IM) can develop resistance to the drug leading to leukemia progression.[2] Multiple mechanisms of resistance have been identified, though the dominant mechanism seems to be represented by amino acid point mutations within the kinase domain of Bcr-Abl.

Second generation Bcr-Abl inhibitors (such as dasatinib and nilotinib) are capable of inhibiting many IM-resistant forms of the kinase but not the form in which threonine is mutated to isoleucine at the highly conserved gatekeeper residue Thr315 (T315I). This specific mutation accounts for 15% of all point mutations and confers complete resistance to all ATP-competitive Bcr-Abl inhibitors currently on the market.[3] The mutation of the gatekeeper residue in Bcr-Abl (Thr315) to a bulkier hydrophobic residue (such as isoleucine) often causes the loss of an important hydrogen bond necessary for high-affinity inhibitor binding and creates steric hindrance that could interfere with inhibitor binding within the ATP-binding pocket.[4] In addition, recent studies showed that bulkier hydrophobic residues in position 315 tend to stabilize a “hydrophobic spine”, shifting the equilibrium towards the active conformation of Bcr-Abl.[5] For this reason, targeting Bcr-Abl with compounds able to avoid unfavorable clashes with Ile315 is becoming an effective strategy in the search for new drugs active on the highly resistant T315I mutant. The aurora kinase/Abl inhibitors VX-680 (**1**), PHA-739358 (**2**) and the Abl inhibitor PPY-A (**3**) are rare examples of ATP-competitive inhibitors that are also able to inhibit those enzymes with the T315I mutation.[6]



The pyrazolo[3,4-*d*]pyrimidines (such as **4**), synthesized by our research group, have recently shown promising inhibitory activity against the T315I mutant enzyme and have also exhibited potent cytotoxicity to cells isolated from IM-resistant patients.[7] Another recently explored strategy to overcome T315I drug resistance involves the development of small molecules targeting enzyme regions outside the ATP binding site (ATP-noncompetitive inhibitors) leading to agents that should be unaffected by mutations in the kinase domain that cause resistance to the common ATP-competitive inhibitors (e.g., imatinib, nilotinib and dasatinib).[8] A few ATP-noncompetitive inhibitors have already been identified (e.g., GNF2,[9] ON012380,[10] DCC-2036[11]) and proven to be unaffected by the Bcr-Abl T315I mutation.

In the search for new molecular scaffolds active on Bcr-Abl, our research group has recently identified a family of 1,3,4-thiadiazole derivatives as interesting inhibitors of Bcr-Abl (e.g., compounds **5** and **6**).[12] The lead compound **5** showed interesting inhibitory activity on murine myeloid clones transduced with IM-sensitive or resistant Bcr-Abl. Kinetic studies showed

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that compound **5** acts as a Bcr-Abl ATP-competitive inhibitor, and the subsequent docking simulations on the active form of the enzyme allowed structure–activity relationships to be suggested for this family of compounds.[12]

In the proposed binding mode, both compounds **5** and **6** failed to establish any contacts with the gatekeeper residue Thr315 (Figure 1a and b) and could therefore represent an interesting starting point for the design of novel analogues targeting the T315I Bcr-Abl mutant. Subsequent molecular modeling studies suggested that the nitrogen atom in the 4-position of the thiadiazole ring may not be necessary for interaction with Met318 and that the phenyl ring of the benzamido moiety could be profitably functionalized. The thiazole derivatives **7** showed an improved affinity towards wild-type (wt) Bcr-Abl.[13] However, the common drawback of the hits **5**–**7** was represented by their high lipophilicity. Accordingly, the present study has been focused on the synthesis of new 1,3,4-thiadiazole and thiazole analogues (general structure I, Figure 1) endowed with a less lipophilic character and potentially active on the T315I mutant.

In the first part of this work, we focused on the synthesis of 1,3,4-thiadiazole analogues endowed with a predicted solubility profile better than that of hits **5** and **6** (set 1). The highest probability of reducing lipophilicity of a series of compounds can be obtained by replacing lipophilic carbon atoms for nitrogen atoms thus reducing Log *D* with minimal impact on molecular mass. As recently reported, the latter two parameters are the most important factors in determining the permeability of a drug candidate and are also connected with a variety of parameters affecting drug-likeness and efficiency.[14] With this concept in mind we decided to maintain the 4-F- and 4-NO_2 benzylthio chain in the 5-position of the thiadiazole and to introduce an additional nitrogen on the solvent-exposed benzamido moiety (**10a** and **11a**,**b**; Scheme 1). In addition, the superimposition of the leads **5** and **6** within the Bcr-Abl binding site (figure S1, Supporting Information) suggests that the introduction of a hydrogen-bond acceptor (a carbonyl moiety) between the sulfur and the substituted phenyl ring could give additional hydrogen-bonding interactions with the hinge region for those compounds bearing a 4-nitrobenzylthio moiety in C2-position of the thiadiazole (**11e**; Scheme 1; see also figure S1c in the Supporting Information).

Following a previously reported protocol,[12] the commercially available 5-amino-1,3,4-thiadiazole-2-thiol (**8**) was reacted with the selected alkylating agents in the presence of the resin Amberlite® IRA-67 (acting both as a base and as an acid scavenger) to give the intermediates **9a**–**e** in high yield and purity. The final compound **10a** was then obtained by coupling **9a** with 3-amino-4-chlorobenzoic acid in the presence of EDC and HOBt and purified by simple trituration in dichloromethane and petroleum ether. To obtain compounds **11a**–**e**, the intermediates **9a**–**e** were dissolved in anhydrous THF and treated with nicotinoyl chloride hydrochloride in the presence of an excess of pyridine. The final products **11a**–**e** were precipitated by addition of water to the reaction mixtures and isolated as pure compounds via filtration (Scheme 1).

Taking into account the hit-to-lead optimization process that led to the discovery of Dasatinib, we also decided to introduce

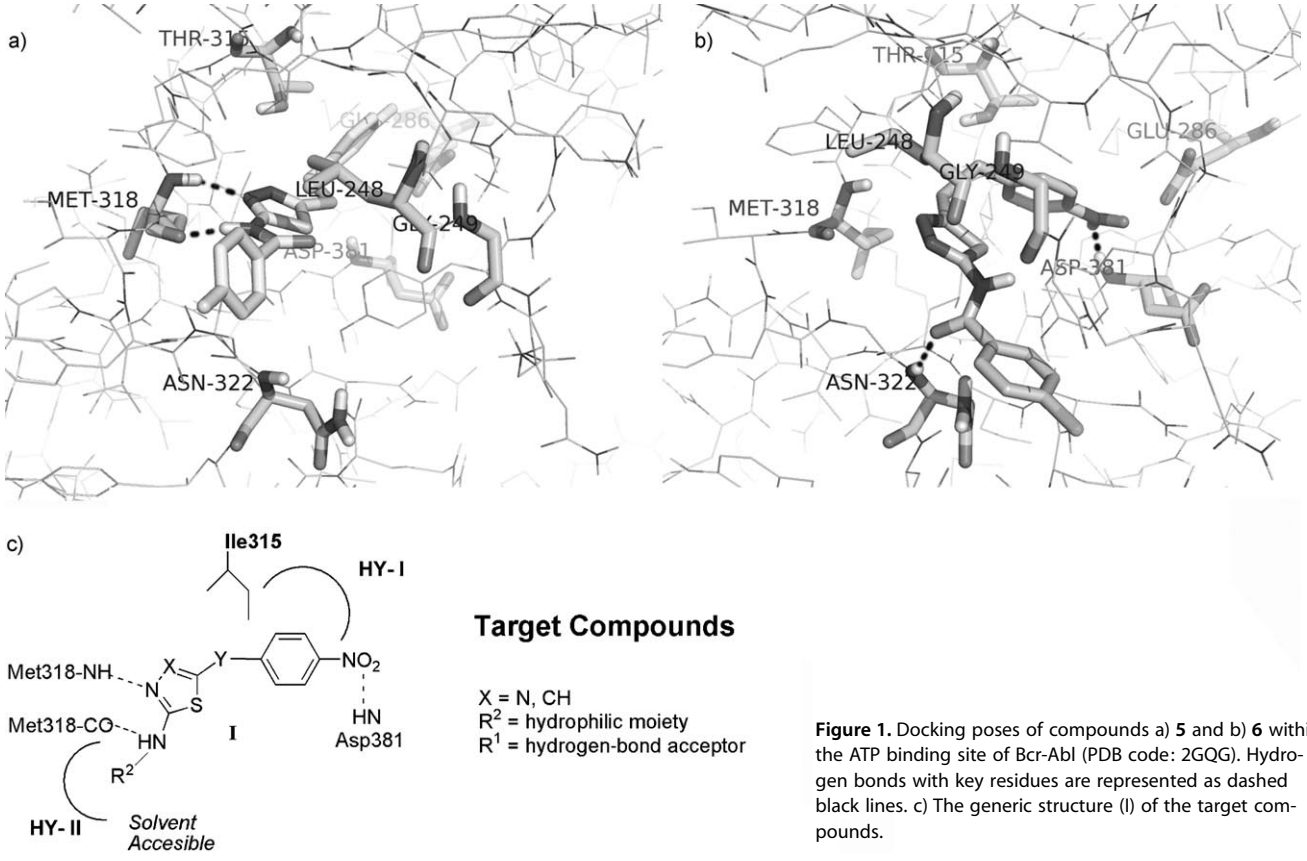
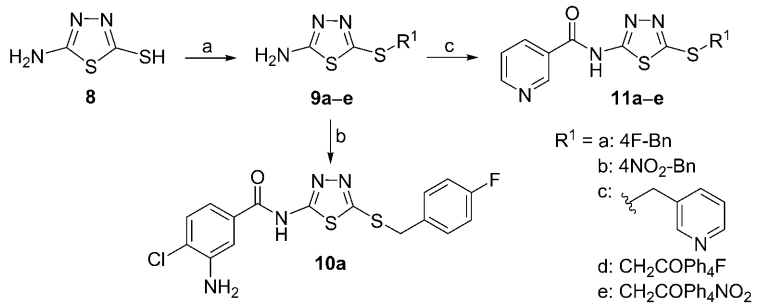


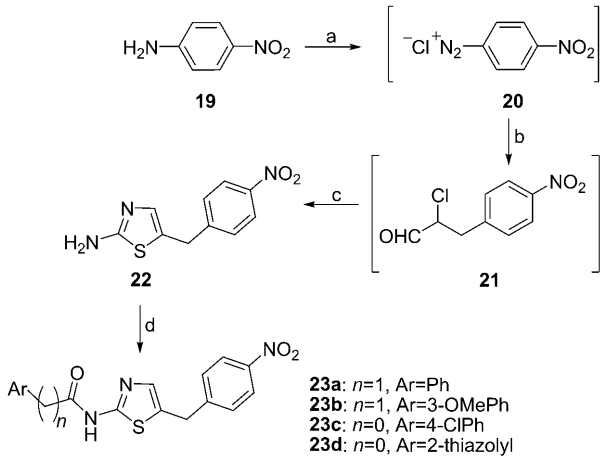
Figure 1. Docking poses of compounds a) **5** and b) **6** within the ATP binding site of Bcr-Abl (PDB code: 2GQG). Hydrogen bonds with key residues are represented as dashed black lines. c) The generic structure (I) of the target compounds.



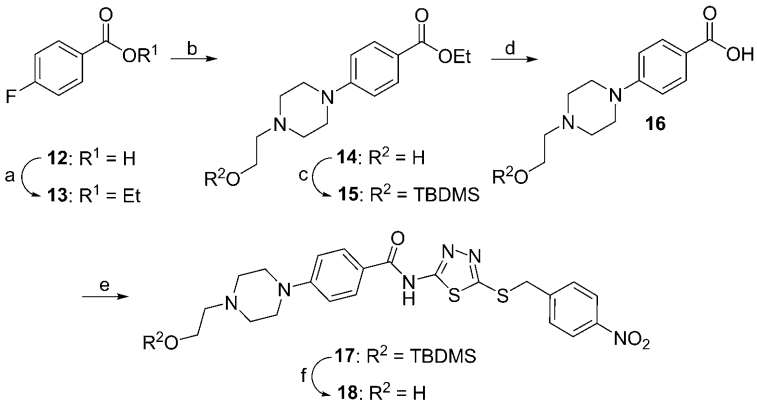
Scheme 1. *Reagents and conditions*: a) R^1Cl or R^1Br, Amberlite® IRA-67, CH_3CN, RT, 24 h (for **9a**,**b**); or THF, reflux, 48 h (for **9c**); or DMF, RT, 1.5 h (for **9d**,**e**); b) EDC, HOBT, DMAP, DMF, RT, overnight; c) nicotinoyl chloride hydrochloride, THF, pyridine, 60 °C, 48 h.

a piperazinyl ethanol moiety (characteristic of Dasatinib) on the solvent-exposed benzamido phenyl ring of hit **6**, trying to improve its solubility profile. The target compound **18** was synthesized starting from commercial 4-F-benzoic acid **12**, which was initially converted into the corresponding ethyl ester **13** and then submitted to a nucleophilic substitution with hydroxyethyl piperazine[15] to give compound **14**. Protection of the free hydroxy group of **14** with TBDMSCl and subsequent deprotection of the ester moiety gave the carboxylic acid **16**. Coupling of this product with 5-(4-nitrobenzylthio)-1,3,4-thiadiazol-2-amine (**9b**) and deprotection with TBAF gave the desired product **18** (Scheme 2).

In the second part of this work, we focused on the synthesis of thiazole analogues specifically designed to target the ATP binding pocket of the T315I mutant (set 2). A cross docking study was conducted on the three available crystal structures of the Bcr-Abl enzyme bearing the T315I mutation (PDB: 2Z60, 2V7A, 3K7) to design new analogues potentially endowed with a specificity for the gatekeeper mutant (See Supporting Information, figure S2). This study prompted us to synthesize a family of thiazole analogues characterized by a 4-NO_2-benzyl group in the 5-position of the thiazole scaffold (general structure I; X = CH, Y = CH_2) and bearing different functional groups bound to the 2-position of the same scaffold (**23a**–**d**, **29a**,**b** and **33a**,**b**). The common precursor 5-[(4-nitrophenyl)methyl]-2-thiazolamine (**22**) was synthesized following the Meerwein protocol reported by Obushak et al. (Scheme 3).[16] Commercially available 4-NO_2-aniline (**19**) was converted into the corresponding diazonium salt **20**, which was directly added to a toluene solution of acrolein in the presence of a cupric salt ($CuCl_2 \cdot 2H_2O$) as the catalyst to obtain the unstable α-chloro aldehyde **21**. This intermediate was treated, without further purification, with thiourea in refluxing ethanol to give the desired thiazole derivative **22** as a brown solid. A first set of final compounds (**23a**–**d**) was then obtained by acylation of **22** with a series of selected acyl chlorides following a previously reported protocol.[12]

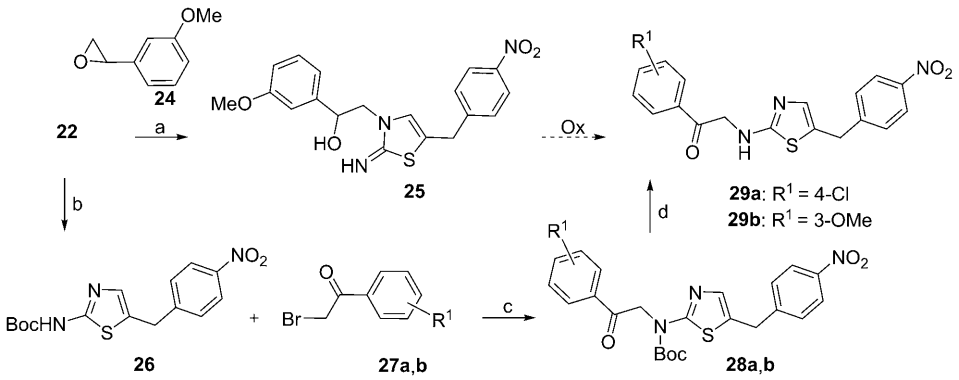


Scheme 3. *Reagents and conditions*: a) $NaNO_2$, HCl (3 N), 0 °C, 40 min; b) acrolein, $CuCl_2 \cdot 2H_2O$, toluene, 3 h, RT; c) thiourea, EtOH, 5 d, reflux; d) Ar-$(CH_2)_n$COCl, Amberlite® IRA-67, THF, 24 h, 60 °C.



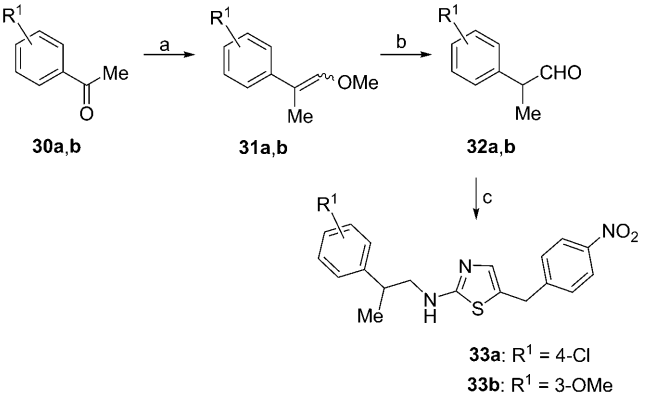
Scheme 2. *Reagents and conditions*: a) EtOH, H_2SO_4 (cat), 24 h, 80 °C; b) 1-(2-hydroxyethyl)piperazine, CH_3CN, 60 h, 80 °C; c) TBDMSCl, imidazole, DMF, 15 min, RT; d) NaOH 1 M, CH_3OH, 30 min, 65 °C; e) **9b**, $POCl_3$, DMAP, toluene, 15 min, 130 °C; f) TBAF, DMF, 96 h, RT.

To prepare **29a**,**b**, we initially envisioned the regioselective opening of a substituted styrene epoxide by reaction with **22** in the presence of indium tribromide ($InBr_3$)[17] to give a β-amino alcohol that could have been oxidized to give the desired compounds (Scheme 4). The 2-(3-methoxyphenyl)oxirane (**24**), prepared by oxidation of 3-vinylanisole with mCPBA,[18] was reacted with **22** in the presence of $InBr_3$ to give the undesired β-amino alcohol **25** resulting from the epoxide opening via the *endo*-N of **22**. The structure of compound **25** was further confirmed by NOE experiments. Although certain electrophiles (e.g., alkyl halides) are known to react at the *endo*-N of thiazoles, others (such as acid chlorides and anhydrides) react preferentially at the *exo*-N.[19] Accordingly, compound **22** was initially protected at the *exo*-N (compound **26**, Scheme 4) and subsequently treated with the substituted 2-bromoacetophenones **27a**,**b** to give a mixture of *endo*-*N*- and *exo*-*N*-alkyl products in a 1:1 ratio. These derivatives (**28a**,**b**) were isolated by chromatographic pu-



Scheme 4. *Reagents and conditions*: a) $InBr_3$, CH_2Cl_2, RT, 24 h; b) $(Boc)_2O$, DMAP, THF, 1 h, 60 °C; c) NaH, DMF, 1 h, 0 °C then 24 h, RT; d) HCl/AcOEt (1:1), 24 h, RT.

rification and deprotected to give the final compounds **29a**,**b**. The thiazole derivatives **33a**,**b** were prepared from the commercially available acetophenones. Wittig homologation of compounds **30a**,**b** gave the aldehydes **32a**,**b**, which were finally reacted with the 2-aminothiazole **22** under reductive amination conditions to give the desired final products **33a**,**b** (Scheme 5).



Scheme 5. *Reagents and conditions*: a) $(Ph)_3PCH_2OMeCl$, *n*BuLi (1.6 M in THF), THF, 24 h; b) HBr (48%), acetone/H_2O (4:1), RT, 2 h; c) **22**, $NaBH(OAc)_3$, AcOH, DME, RT, 72 h.

As recently reported by Johnson and co-workers, molecular weight (MW) and liphophilicity (Log *D* at pH 7.4) act as surrogates of many different molecular descriptors and have been used to develop a useful visualization tool—the Golden Triangle.[20] According to this tool, drug candidates with good permeability and low clearance (drug-like space) should be positioned close to the center of the Golden Triangle (Log *D* = 1.5; MW = 350). In order to obtain some preliminary insight into the drug-likeness of the synthesized compounds, the Log *D* values of the final compounds and the lead **5** were calculated using the web version of the ToxBoxes software[21] (see Table 1) and were plotted against the corresponding molecular weights (Figure 2). As expected, the compounds synthesized to decrease the lipophilicity (set 1) are located close to or within the center of the Golden Triangle showing a marked improvement with respect to the lead **5**. On the other hand, compounds belonging to set 2 were designed with the sole intention of improving the affinity of the agent for the T315I mutant and, unfortunately, were predicted to show a behavior similar to or worse than that of the lead **5**. According to the Golden Triangle predictions, it would therefore be easier to identify potential drug candidates among the compounds belonging to set 1.

Table 1. Enzymatic activity and selected molecular descriptors of the target compounds.

Entry	Compd	MW	c Log *D*[a]	K_i[b] [μM]		
				Src	Abl wt	Abl T315I
1	**5** (BO1)	363.4	3.92	0.55	0.10	0.40
2	**6**	406.9	4.36	0.17[c]	0.10[c]	ND
3	**7**	330.4	3.81	ND	0.02[c]	ND
4	**10a**	394.9	3.56	NA	1.40	NA
5	**11a**	346.4	2.81	NA	1.22	NA
6	**11b**	373.4	2.55	NA	0.20	17.20
7	**11c**	329.4	1.39	2.50	NA	NA
8	**11d**	374.4	2.47	0.47	0.41	13.90
9	**11e**	401.4	2.16	NA	0.20	15.20
10	**18**	500.6	2.19	NA	2.95	ND
11	**23a**	353.4	3.74	1.13	0.90	28.14
12	**23b**	383.4	3.71	3.00	1.30	ND
13	**23c**	373.8	4.43	1.30	0.80	16.00
14	**23d**	345.4	3.63	1.11	0.80	28.80
15	**29a**	387.8	4.37	3.10	0.55	NA
16	**29b**	383.4	3.96	2.00	0.60	NA
17	**33a**	387.9	6.17	0.31	0.36	18.50
18	**33b**	383.5	5.57	NA	1.20	NA

[a] Predicted lipophilicity; values calculated at pH 7.4 using the web version of the ToxBoxes software.[21] [b] Values are the mean of at least two experiments. [c] These activity values were obtained from previous experiments as reported in References [12, 13].

All final compounds were then screened in a cell-free assay against recombinant human c-Src, Abl and T315I Abl using **5** as a reference compound (Table 1). Unexpectedly, most of the derivatives belonging to set 1 (Table 1, entries 4–10) completely lost their activity towards Src, despite their high structural similarity to the hit compounds **5** and **6**. However, in the same subset of compounds, **11c**,**d** represent exceptions (Table 1, entries 7–8); while **11c** was found to be active towards Src only, compound **11d** behaved as a dual Src/Abl inhibitor (as does **5**) and showed also an appreciable activity against the mutant T315I. The most interesting compounds **11b**,**e** were completely inactive against Src and maintained the activity of the lead **5** towards Abl (wt) while showing an appreciable activity against

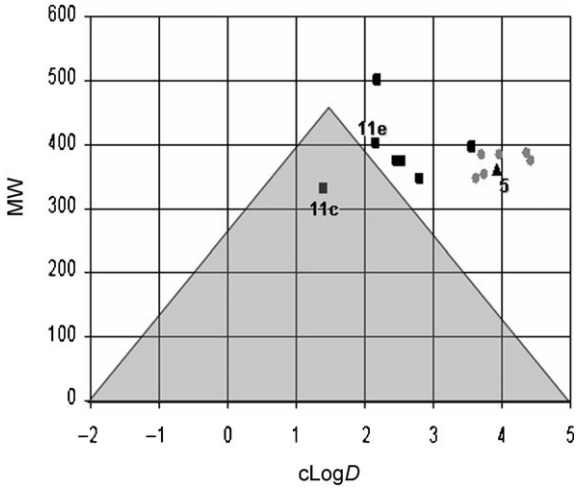


Figure 2. The Golden Triangle. Compounds of set 1 are depicted as black squares, compounds of set 2 are depicted as grey circles, reference compound **5** is depicted as black triangle.

the T315I mutant. Unfortunately, the docking simulations were not able to explain the loss of activity against Src observed for most of the compounds belonging to set 1. On the other hand, the thiazole derivatives suggested by the cross docking study (set 2) and specifically designed to target the T315I mutants (Table 1, entries 11–18) were found to be much less active against the mutant than predicted and generally acted as dual Src/Abl inhibitors.

A thorough kinetic study has been conducted on the lead compound **5**.[22] Surprisingly, this study showed that **5** acts on the wild-type and mutated T315I Abl enzyme with two different mechanisms-of-action (Table 2): 1) In the case of wt Abl, compound **5** targeted both the free enzyme and the enzyme–peptide complex, preventing ATP binding with a competitive or mixed mechanism-of-action; 2) in the case of T315I Abl, compound **5** acted only as a non-competitive inhibitor with respect to both ATP and the peptide substrates. These results may explain the overestimated activity for the set 2 compounds, which were designed for the optimal interaction with the ATP binding pocket of the mutated T315I Abl but that could interact with a different allosteric site in the presence of such mutation.

We initially speculated that the T315I mutation could force our compounds to bind in the deep allosteric pocket on the back of the gatekeeper residue, which is partially exploited by

Table 2. Inhibition of wild-type (wt) Abl and T315I Abl by compound **5**.

Abl	K_i[a] [μM]	Variable substrate	Type of inhibition
wt	0.1 ± 0.01	ATP	competitive
wt	0.12 ± 0.01	peptide	mixed
T315I	0.4 ± 0.1	ATP	noncompetitive
T315I	0.45 ± 0.1	peptide	noncompetitive

[a] Values are the mean of at least two experiments. Further details can be found in the Supporting Information.

the inhibitor AP24534 (PDB code: 3K3).[23] Unfortunately, docking simulations conducted on this site were unable to rationalize the activity of our inhibitors against the T315I mutant. Another known allosteric pocket of Bcr-Abl is represented by the myristate binding site.[8] A co-crystal structure of Bcr-Abl (PDB code: 3K5V) bound by an ATP-competitive inhibitor (IM) and an allosteric inhibitor (GNF-2) has been recently released.[24] This represents the first structure of an allosteric inhibitor bound to the myristate pocket.

Docking simulations on the myristate binding site showed that, among the synthesized compounds, only compound **5** showed a profitable interaction pattern within the pocket. The 4-fluorobenzylthio chain completely fill the hydrophobic tunnel defined by the residues Leu 448, Phe 512, Ala 363, Ile 451, Ile 521, Ala 356, Leu 360 and Val 487, while an hydrogen bond with Ala 452 and edge-to-face aromatic interactions with Tyr 452 contribute to maintain compound **5** in a binding orientation similar to that of the original ligand GNF-2 (Figure 3). The other synthesized compounds, especially those characterized by a polar 4-nitrophenyl substituent, showed less profitable interactions with the myristate pocket, fitting only partially within the hydrophobic tunnel and remaining mostly solvent

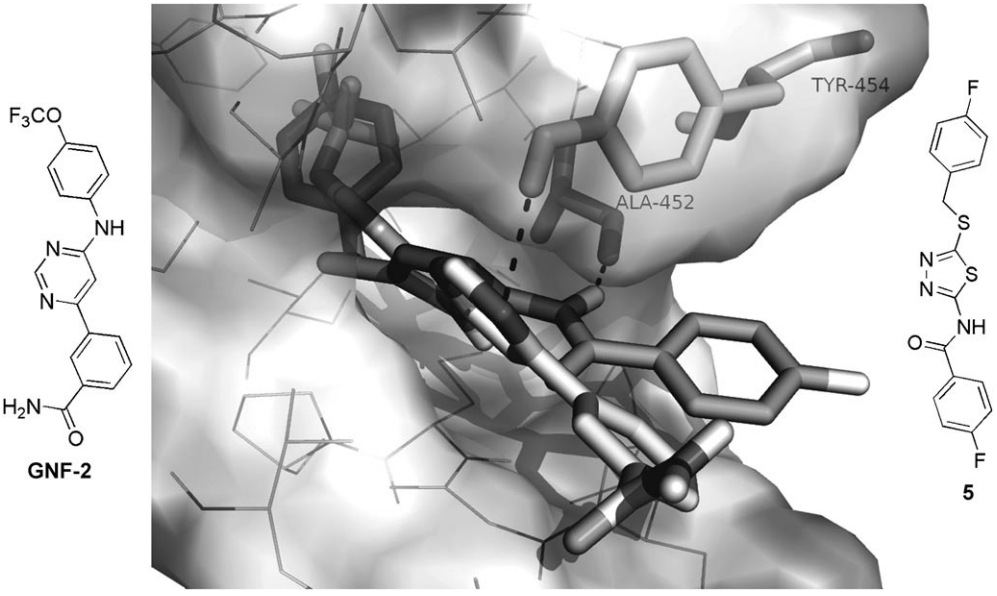


Figure 3. Superimposition of the energetically preferred docked conformation of **5** (sticks, gray carbons) and the crystallized inhibitor GNF-2 (sticks, white carbons) within the myristate binding pocket of Bcr-Abl (PDB code: 3K5V). Intermolecular hydrogen bonds are highlighted by black dashed lines.

exposed. These findings, although speculative in nature, may support the kinetic studies conducted on the lead compound **5** and suggest the myristate pocket as a possible binding site. Further experimental data are, however, needed to confirm this hypothesis.

The work described here is focused on the hit optimization of previously identified dual Src/Abl inhibitors based on 1,3,4-thiadiazole and thiazole scaffolds. Two different set of compounds were designed to solve the two major issues: the high lipophilicity of the hits and their low affinity for the T315I mutant. A few interesting inhibitors, endowed with better predicted drug-like properties, were identified among the compounds of set 1. Compounds **11 c** and **11 e**, with significant affinity for Src and Abl, respectively, will be further explored to better understand the molecular determinants required for the inhibition of these two enzymes.

Surprisingly, the compounds designed to target the T315I mutants (set 2) showed an overestimated predicted activity against this mutant and a dual Src/Abl profile comparable to that of the hit compound **5**. A kinetic enzymatic study conducted on the lead **5** showed that this compound was able to inhibit the drug-resistant T315I Abl mutant by adapting its mechanism-of-action to the specific enzymatic form of Abl. At the same time, compound **5** was shown to be an ATP-competitive inhibitor of wt Abl (targeting the free enzyme) and a purely noncompetitive-ATP inhibitor in the case of Abl T315I (targeting all enzymatic forms). In an attempt to speculate on a possible binding site for our compounds, docking simulations suggested the myristate binding pocket as a possible site that could be target by compound **5** in the presence of the T315I mutation. Besides providing an explanation for the false positive docking results on the designed T315I inhibitors, these data pave the way for the synthesis of novel allosteric inhibitors of the Abl T315I mutant. Further studies are ongoing in our laboratories and will be reported in due course.

Experimental Section

Representative and general experimental procedures, compound characterization data (^{1}H and ^{13}C NMR, elemental analysis), details of the enzymatic assays and modeling simulations are available in the Supporting Information.

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Keywords: Bcr-Abl · chronic myeloid leukemia · T315I · thiadiazoles · thiazoles

[1] R. Hehlmann, A. Hochhaus, M. Baccarani, *Lancet* **2007**, *370*, 342 – 350.
[2] a) J. F. Apperley, *Lancet Oncol.* **2007**, *8*, 1018 – 1029; b) J. F. Apperley, *Lancet Oncol.* **2007**, *8*, 1116 – 1128.
[3] S. Storey, *Nat. Rev. Drug Discovery* **2009**, *8*, 447 – 448.
[4] A. Hochhaus, S. Kreil, A. S. Corbin, P. La Rosee, M. C. Muller, T. Lahaye, B. Hanfstein, C. Schoch, N. C. Cross, U. Berger, H. Gschaidmeier, B. J. Druker, R. Hehlmann, *Leukemia* **2002**, *16*, 2190 – 2196.
[5] a) A. P. Kornev, N. M. Haste, S. S. Taylor, L. F. T. Eyck, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 17783 – 17788; b) M. Azam, M. A. Seeliger, N. S. Gray, J. Kuriyan, G. Q. Daley, *Nat. Struct. Mol. Biol.* **2008**, *15*, 1109 – 1118.
[6] a) T. Zhou, L. Parillon, F. Li, Y. Wang, J. Keats, S. Lamore, Q. Xu, W. Shakespeare, D. Dalgarno, X. Zhu, *Chem. Biol. Drug Des.* **2007**, *70*, 171; b) M. A. Young, N. P. Shah, L. H. Chao, M. Seeliger, Z. V. Milanov, W. H. Biggs III, D. K. Treiber, H. K. Patel, P. P. Zarrinkar, D. J. Lockhart, C. L. Sawyers, J. Kuriyan, *Cancer Res.* **2006**, *66*, 1007 – 1014; c) M. Modugno, E. Casale, C. Soncini, P. Rosettani, R. Colombo, R. Lupi, L. Rusconi, D. Fancelli, P. Carpinelli, A. D. Cameron, A. Isacchi, J. Moll, *Cancer Res.* **2007**, *67*, 7987 – 7990.
[7] a) M. A. Santucci, V. Corradi, M. Mancini, F. Manetti, M. Radi, S. Schenone, M. Botta, *ChemMedChem* **2009**, *4*, 118 – 126; b) M. A. Santucci, M. Mancini, V. Corradi, I. Iacobucci, G. Martinelli, M. Botta, S. Schenone, *Invest. New Drugs* **2009**; DOI: 10.1007/s10637-009-9294-9.
[8] a) M. A. Bogoyevitch, D. P. Fairlie, *Drug Discovery Today* **2007**, *12*, 622 – 633; b) L. O. Kirkland, C. McInnes, *Biochem. Pharmacol.* **2009**, *77*, 1561 – 1571.
[9] F. J. Adrián, Q. Ding, T. Sim, A. Velentza, C. Sloan, Y. Liu, G. Zhang, W. Hur, S. Ding, P. Manley, J. Mestan, D. Fabbro, N. S. Gray, *Nat. Chem. Biol.* **2006**, *2*, 95 – 102.
[10] K. Gumireddy, S. J. Baker, S. C. Cosenza, P. John, A. D. Kang, K. A. Robell, M. V. Reddy, E. P. Reddy, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 1992 – 1997.
[11] R. A. Van Etten, W. W. Chan, V. M. Zaleskas, P. Evangelista, K. Lazarides, C. Peng, S. Li, S. C. Wise, P. Petillo, D. L. Flynn, *Blood* (ASH Annual Meeting Abstracts) **2007**, *110*, 463.
[12] M. Radi, E. Crespan, G. Botta, F. Falchi, G. Maga, F. Manetti, V. Corradi, M. Mancini, M. A. Santucci, S. Schenone, M. Botta, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1207 – 1211.
[13] F. Manetti, F. Falchi, E. Crespan, S. Schenone, G. Maga, M. Botta, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4328 – 4331.
[14] M. J. Waring, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2844 – 2851.
[15] F. Nobs, (Novartis, AG., Basel, Switzerland), WO/2007/025696, **2007**.
[16] N. D. Obushak, V. S. Matiichuk, R. Ya. Vasylyshin, Yu. V. Ostapyuk, *Russ. J. Org. Chem.* **2004**, *40*, 383 – 389.
[17] J. R. Rodriguez, A. Navarro, *Tetrahedron Lett.* **2004**, *45*, 7495 – 7498.
[18] Data not shown.
[19] R. Barone, M. Chanon, R. Gallo, in *Thiazole and Its Derivatives, Part 2*, (Ed.: J. V. Metzger), Wiley, New York, **1979**, Chapter 6.
[20] T. W. Johnson, K. R. Dress, M. Edwards, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5560 – 5564.
[21] Pharma Algorithms 1, ADME/Tox WEB, http://www.pharma-algorithms.com/webboxes/ (Last accessed: May 4, 2010).
[22] E. Crespan, M. Radi, S. Zanoli, S. Schenone, M. Botta, G. Maga, *Bioorg. Med. Chem.* **2010**; DOI: 10.1016/j.bmc.2010.04.024.
[23] T. O'Hare, W. C. Shakespeare, X. Zhu, C. A. Eide, V. M. Rivera, F. Wang, L. T. Adrian, T. Zhou, W. S. Huang, Q. Xu, C. A. Metcalf III, J. W. Tyner, M. M. Loriaux, A. S. Corbin, S. Wardwell, Y. Ning, J. A. Keats, Y. Wang, R. Sundaramoorthi, M. Thomas, D. Zhou, J. Snodgrass, L. Commodore, T. K. Sawyer, D. C. Dalgarno, M. W. Deininger, B. J. Druker, T. Clackson, *Cancer Cell* **2009**, *16*, 401 – 412.
[24] J. Zhang, F. J. Adrián, W. Jahnke, S. W. Cowan-Jacob, A. G. Li, R. E. Iacob, T. Sim, J. Powers, C. Dierks, F. Sun, G. R. Guo, Q. Ding, B. Okram, Y. Choi, A. Wojciechowski, X. Deng, G. Liu, G. Fendrich, A. Strauss, N. Vajpai, S. Grzesiek, T. Tuntland, Y. Liu, B. Bursulaya, M. Azam, P. W. Manley, J. R. Engen, G. Q. Daley, M. Warmuth, N. S. Gray, *Nature* **2010**, *463*, 501 – 506.

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