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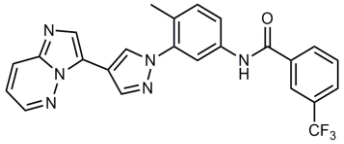

16a

BCR-ABL IC_{50} = 8.5 nM

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ABSTRACT

A series of 4-(pyrazolo[1,5-a]pyrimidin-6-yl)-1H-pyrazol-1-yl)phenyl-3-benzamide derivatives and 4-(imidazo[1,2-b]pyridazin-3-yl)-1H-pyrazol-1-yl-phenyl-3-benzamide derivatives were designed, synthesized as new BCR-ABL tyrosine kinase inhibitors by using combinational strategies of scaffold hopping and conformational constraint. These new compounds were screened for BCR-ABL1 kinase inhibitory activity, and most of them appeared good inhibitory activity against BCR-ABL1 kinase. One of the most potent compounds **16a** strongly suppressed BCR-ABL1 kinase with IC_{50} value of 8.5 nM. The tested compounds **16a** and **16i** showed strong inhibitory activities against K562 with IC_{50} value of less than 2nM. Molecular docking studies indicated that these compounds fitted well with the active site of BCR-ABL1 protein. The results showed these inhibitors may serve as lead copounds for further developing new drugs targeted BCR-ABL kinase.

Protein kinases are involved in multiple signaling pathways in the cellular processes including growth, survival, invasion and angiogenesis during tumour initiation and progression.[1] ABL tyrosine kinase inhibitors, the most successful TKIs, have been used for the treatment of chronic myeloid leukaemia (CML) which is a haematological cancer caused by the Philadelphia positive(Ph+) human leukaemias as a consequence of the t(9;22)(q34;q11) chromosome translocation.[2-4] The ABL kinase which is a proto-oncogene protein tyrosine kinase involved in cell differentiation, migration and signaling suffers an oncogenic activation in Ph+ human leukaemias where generating a breakpoint cluster region–Abelson (BCR-ABL) fusion protein with constitutive tyrosine kinase activity.[5] According to BCR-ABL fusion oncoprotein, several mechanisms are involved in the malignant transformation.[6] First, the speed of cell division is accelerated because of the activations of some cell cycle controlling enzymes and proteins caused by BCR-ABL. Subsequently, mitogenic signaling pathways are constitutively activated by the BCR-ABL fusion oncoprotein such as the janus kinase (JAK)/signal transduction and transcription (STAT) pathway, phosphaditylinositide-3 (PI3) kinase pathway, RAS/mitogen-activated protein kinase (MAPK) pathways, and the myc pathway.[7]

Since the BCR–ABL protein exists in greater than 90% of CML cases, it has become a well-validated and novel target for designing small molecular inhibitors to treat CML.[8] Following the identification of the disease mechanism, imatinib, the first approved tyrosine kinase inhibitor, was developed and used to treat CML targeting the inhibition of BCR-ABL kinase (Fig. 1).[9] As a first-generation Bcr-Abl kinase inhibitor, imatinib has achieved great clinical success and became the first-line drug for the treatment of CML. However, multiple drug resistance of tumor cells against the existing BCR-ABL TKIs has emerged due to the mutations in the ABL kinase domain or other reasons.[10] $BCR\text{-}ABL^{T315I}$ is the most common mutation which occurs from the replacement of the so-called "gatekeeper" threonine residue at position 315 with isoleucine, where it sacrifices a favourable hydrogen bonding interaction between imatinib and Thr 315 and imposes an unfavourable steric clash due to the bulky isoleucine side chain.[11] The emergence of resistance leads to the development of a second generation of BCR-ABL tyrosine kinase inhibitors such as nilotinib, dasatinib, and bosutinib.[12-14] These TKIs have been approved as second-line drugs to treat adult patients in all phases of CML with resistance to imatinib. Many other inhibitors, such as bafetinib, have also been developed in late-stage clinical trials (Figure 1).[15] Although these BCR-ABL inhibitors have been synthesized or approved to be second-line drugs, drug resistance remains an unmet clinical challenge for CML treatment.[16]

Asp381-Phe382-Gly383, known as the "DFG-motif" (derived from the single letter amino acid code) was three highly conserved amino acid residues in the binding region between the

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core of these BCR-ABL kinase inhibitors and the ATP-binding region. These inhibitors can be divided into two types depending on their modes of binding.[2,17] The bindings between Type 1 kinase inhibitors and the "DFG-in" conformation as the active form of the kinase are similar to ATP-binding. So the inhibitors can prevent phosphorylation through competitive inhibition of the ATP-binding site. By contrast, the bindings between Type 2 inhibitors and a hydrophobic pocket adopting the inactive "DFG-out" conformation are directly adjacent to the ATP-binding site. As a result, the kinase is locked in a conformation that it is unable to bind ATP and preventing catalysis. Inhibitor selectivity is therefore achieved by binding to regions where the structure is less conserved in the inactive form of the kinase. Imatinib demonstrates the selectivity achieved by a Type 2 inhibitor, so does some second generation of BCR-ABL tyrosine kinase inhibitors such as nilotinib, bafetinib. Recently, the third-generation BCR-ABL inhibitors such as GNF-7 and ponatinib were also reported as Type 2 inhibitors.[13]

Based on chemical features of the inhibitors, cocrystal structural analysis of different Type 2 third-generation inhibitors with BCR-ABL kinase showed that most of the compounds possessed four key structural elements which formed crucial interactions with the protein: (1) "head region", a heterocyclic moiety interacting via hydrogen bond with the hinge region; (2) "middle part", a methylphenyl group occupying the back cavity influenced by gatekeeper residue; (3) "tail region", an additional hydrophobic group bringing hydrophobic interactions within the allosteric site induced by the DFG-out conformation; (4) "linker part", a suitable linker between the head region and the middle skirting the bulk of Ile315 side chain.[4,12,18-20] According to the previous work by our group[21], the phenyl-pyrazole derivatives displayed good inhibitory activity to BCR-ABL kinase. Among them, PPBA-1 (showed in Figure 2) displayed the most potent activity with IC_{50} value of 14.2 nM. By the analysis of the chemical structures of PPBA-1 and ponatinib, a new series of phenyl-pyrazole derivatives were designed as BCR-ABL kinase inhibitors with the pyrazole linker between the head region and the middle part retained and two different groups as the head region part (imidazo[1,2-b]pyridazine group and pyrazolo[1,5-a]pyrimidine group) attached as shown in Figure 2.

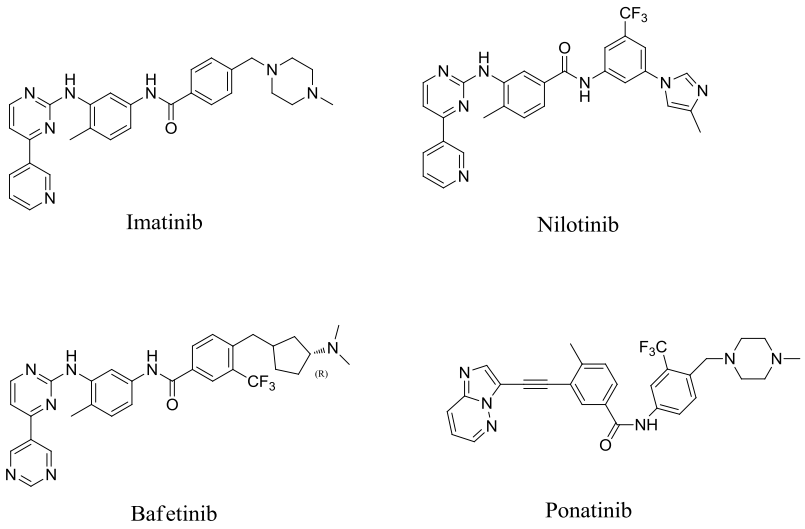


Figure 1. Chemical structures of typical Bcr-Abl inhibitors.

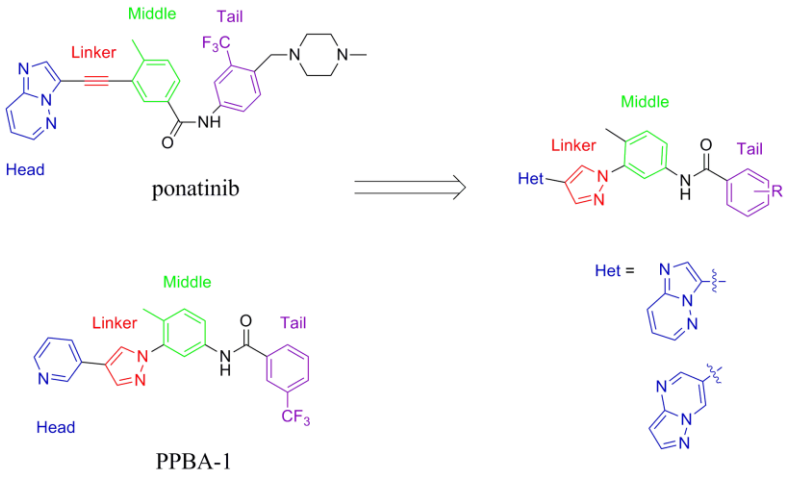
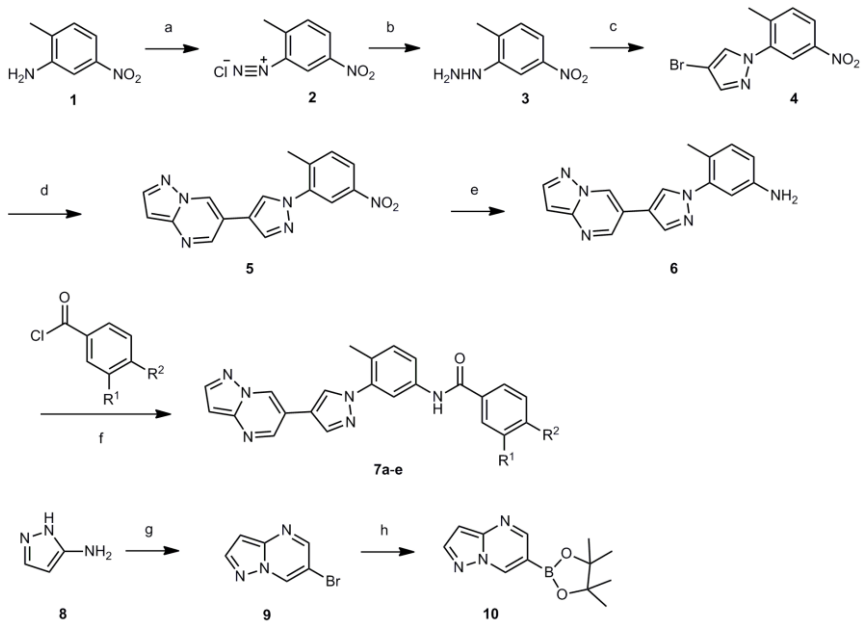
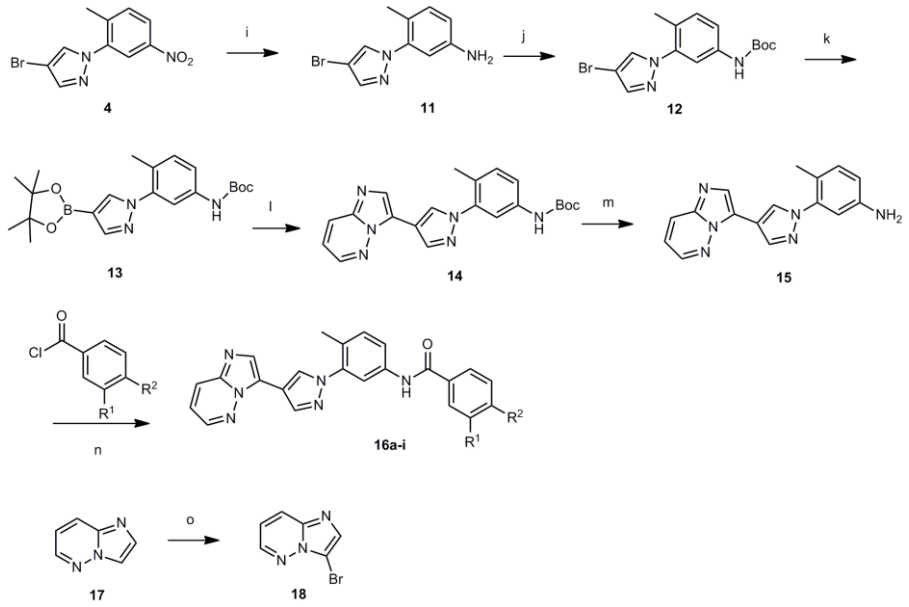


Figure 2. Design of phenyl-pyrazole heterocyclic derivatives as new BCR–ABL inhibitor.



Scheme 1. Reagents and conditions: (a) $NaNO_2$, HCl, H_2O, 0-5 ^oC; (b) $SnCl_2 \cdot 2H_2O$, HCl, H_2O, 0-5 ^oC, 70-75 %; (c) 2-bromomalonaldehyde, EtOH, 55-65 ^oC, 2h, 30-40 %; (d) **10**, $Pd(PPh_3)_4$, Na_2CO_3, dioxane / H_2O(3:1), reflux, 6 h, 65%; (e) Zn dust, CH_3COOH, r.t.; 1 h; (f) $(CH_3CH_2)_3N$, CH_2Cl_2, 0 ^oC, r.t., 4 h, 70-75%; (g) 2-bromomalonaldehyde, EtOH, reflux, 2 h, 30% (h) Bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, toluene, 100 ^oC, 5 h, 65%.



Scheme 2. Reagents and conditions: (i) Fe, NH_4Cl, EtOH, H_2O, reflux, 3 h, 90%; (j) $(Boc)_2O$, THF, reflux, 3 h, 90%; (k) Bis(pinacolato)diboron, KOAc, $Pd(pph_3)_2Cl_2$, Dioxane, 100^oC, 15 h, 65%; (l) **18**, $Pd(PPh_3)_4$, Na_2CO_3, dioxane / H_2O(3:1), reflux, 6 h, 65%; (m) CF_3COOH, CH_2Cl_2, r.t., 5 h, 85%; (n) $(CH_3CH_2)_3N$, CH_2Cl_2, r.t., 3 h, 80%; (o) NBS, $CHCl_3$, reflux, 2 h, 75%.

Inspired by combinational strategies of scaffold hopping and conformational constraint based on PPBA-1 and ponatinib, a series of 4-(pyrazolo[1,5-a]pyrimidin-6-yl)-1H-pyrazol-1-yl)p-henyl-3-benzamide derivatives and 4-(imidazo[1,2-b]pyridazin-2-yl)-1H-pyrazol-1-yl)phenyl-3-benzamide derivatives have been designed, synthesized and characterized. All compounds were screened for BCR-ABL1 kinase inhibitory activity, and most of all appeared good inhibitory activity to BCR-ABL kinase.

The synthetic route of **7a-e** was illustrated in Scheme 1, and that of **16a-i** was outlined in Scheme 2. The synthetic details were presented in Supplementary material. Compound **4** was prepared by the literature method.[21] Via the ring-closure reaction of 2-bromomalonaldehyde with 3-aminopyrazole, refluxing in ethanol, compound **9** was prepared. Compound **10** was obtained by the borylation reaction between 6-bromopyrazolo[1,5-a]pyri-midine and bis(pinacolato)diboron catalyzed by $PdCl_2$(dppf) in toluene at 100 ^oC. After the Suzuki coupling reaction between intermediate **4** and compound **10**, 6-(1-(2-methyl-5-nitrophenyl)-1H-pyrazol-4-yl)pyrazolo[1,5-a]py-rimidine (**5**) was obtained. Through the reduction reaction of the intermediate **5** with Zn dust in the presence of acetate acid, 4-methyl-3-(4-(pyrazolo[1,5-a]pyrimidin-6-yl)-1H-pyrazol-1-yl)aniline (**6**) was produced. Finally, the target products **7a-e** were prepared by the acylation reaction of variable substituted benzoylchlorides in anhydrous dichloromethane at 0 ^oC in the presence of triethylamine.

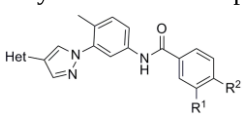
The synthetic route of **16a-i** was illustrated in Scheme 2. Firstly, amido-protecting reaction was conducted by compound **11** and $(Boc)_2O$ and succeeded to Miyaura-Ishiyama-Hartwig Borylation to product **13**. Secondly, compound **14** obtained from the Suzuki coupling reaction between the borylation product **13** and 3-bromoimidazo[1,2-b]pyridazine (**18**). Finally, the target products **16a-i** were prepared by the acylation reaction of variable substituted benzoylchlorides in anhydrous dichloromethane at 0 ^oC in the presence of triethylamine.

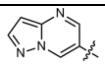
Preliminary structure-activity relationships (SARs) were explored when pyrazolo[1,5-a]pyrimidine group and imidazo[1,2-b]pyridazine were introduced as the head region group respectively. As shown in Table 1, the compounds with the head region composed of imidazo[1,2-b]pyridazine group exhibited dramatically lower IC_{50} values ranging from 8.5 to 108.6 nM against BCR-ABL1 kinase than those composed of pyrazolo[1,5-a]pyrimidine group exceeding 621 nM. For instance, compound **16h** (IC_{50}= 108.6 nM against BCR-ABL1 kinase) displayed superior activity to compound **7d** (IC_{50} = 2.4 μM against BCR-ABL1 kinase). It may be that imidazo[1,2-b] pyridazine group was better in forming hydrogen bond or pi-pi interaction with the hinge region. Moreover, the modification of the substituent in tail region had some effect on their bioactivities. Further investigation about the potential influence of the tail region was made by introducing different groups in phenyl ring. In the case of the head region composed of imidazo[1,2-b]pyridazine group, the substituents on 3-position of phenyl ring (such as **16a**, **16e**) in tail region showed better potency against BCR-ABL1 kinase than the electron withdrawing group substituents on 4-position (such as **16b**, **16d**). In particular, by introducing trifluoromethyl group on 3-position of phenyl ring, compound **16a** showed the best performance on BCR-ABL1 kinase inhibitory activity probably owing to the favorable conformation to fit into the ATP bind site of ABL protein. Interestingly, the electron donating group substituents on 4-position (**16g)** showed the IC_{50} value as low as 19.4 nM against BCR-ABL1 kinase. Finally, most of these compounds (**16a**, **16b**, **16d**, **16e**, **16g**, **16h** and **16i**) displayed lower IC_{50} values than the control compound Staurosporine (STSP), especially compound **16a** whose IC_{50} value was 14.3-fold lower than that of STSP showing the great promising potential as novel BCR-ABL1 inhibitors.

Antiproliferative activities of the compounds are also examined against K562 and U937 leukemia cell lines. the results were summarized in Table 2. Consistent with their kinase inhibitory activities, most of the compound showed promising antiproliferative activies. For instance, the most promising compound **16a** strongly inhibited the proliferation of K562 and U937 leukemia cells with IC_{50} values of 2nM and 13.68μM,respectively, which showed more strong inhibitory activity to K562 cells than that of control compound Imatinib and similar to that of control compound Imatinib fof U937 cells. Most of the compounds were tested at multiple doses to study the viability of 293T cell, As shown in Table 3, The median cytotoxic concentration (CC_{50}) showed that the tested compounds displayed almost no cytotoxicity.

In order to investigate the possible bonding mechanism, compounds **16a** and **7c** were selected for docking studies. The binding mode of selected molecules was studied by autodock 4.0 with the help of atuodockTools. BCR-ABL tyrosine kinase (PDB:3cs9) was selected as the receptor for docking study. The best docking conformation was selected for the analysis and the docking results were shown in Figure 3. Our docking study has suggested

Table 1. Inhibitory activities of compounds **7a-e** and **16a-i**.



Compd	Het	R^1	R^2	BCR-ABL IC_{50} (nM)
7a		H	4-OMe	766.6
7b		H	4-CF_3	803.7
7c		H	4-F	> 10000
7d		H		2436.0
7e		H		621.0
16a		3-CF_3	H	8.5
16b		H	4-CF_3	74.1
16c		3-F	H	ND[a]
16d		H	4-F	80.9
16e		3-Cl	H	22.2
16f		H	4-OMe	ND
16g		H	4-Et	19.4
16h		H		108.6
16i		H		26.07
STSP				121.8

[a] ND : not determined.

Table 2. Antiproliferative assay in vitro[a]

Compound	K562 IC_{50} (μM)	U937 IC_{50} (μM)
7a	19.7	16.32
7b	6.93	13.11
7e	5.88	6.83
16a	<0.002	13.68
16b	10.53	>20
16d	12.37	>20
16e	5.08	>20
16g	7.54	>20
16h	8.25	12.42
16i	<0.002	10.78
Imatinib	7.38	12.44

[a] Values are means of at least two experiment.

Table 3. The median cytotoxic concentration (CC_{50}) of tested compounds

Compound	CC50 (μM)
7a	>80
7b	43.23
7e	20.53
16a	40.34
16b	>80
16d	>80
16e	>80
16g	>80
16h	9.04
16i	23.80
Imatinib	27.54

that compound **16a** could form hydrogen bond with the NH of Met 318 in the hinge region of BCR–ABL (Figure 3). The amide moiety formed two additional hydrogen bonds with E 286 and D 381, and the trifluoromethylphenyl group bounded deeply in to the hydrophobic pocket. Moreover, imidazo[1,2-b]pyridazine group formed pi–pi interaction with F317 of BCR–ABL protein, which was similar to ponatinib. The fact that compound **7c** only formed two hydrogen bond with Met 318 and E 286, and no pi-pi stacking interaction might be the main reason why 4-(imidazo[1,2-b]pyridazin-2-yl)-1H-pyrazol-1-yl)phenyl-3-benzamide derivatives showed stronger inhibitory activities than 4-(pyrazolo[1,5-a]pyrimidin-6-yl)-1H-pyrazol-1-yl)phenyl-3-benzamide derivatives.

In summary, we have successfully designed, synthesized and characterized a series of 4-(pyrazolo[1,5-a]pyrimidin-6-yl)-1H-pyrazol-1-yl)phenyl-3-benzamide derivatives and 4-(imid-azo [1,2-b]pyridazin-2-yl)-1H-pyrazol-1-yl)phenyl-3-benzamide derivatives. These new compounds were screened for BCR-ABL1 kinase inhibitory activity, most of them appeared good inhibitory activity to BCR-ABL kinase. In particular, compound **16a** displayed the most potent activity with IC_{50} value of 8.5 nM. The compounds **16a** and **16i** displayed excellent antiproliferative activities to K562 leukemia cells. Most of the tested compounds showed almost no cytotoxicity in vitro against 293T cell compared to the positive control imatinib. Molecular docking studies indicated that these novel compounds fitted well with the active site of BCR-ABL protein. The results above showed the great promising potential of these compounds as novel BCR-ABL inhibitors.

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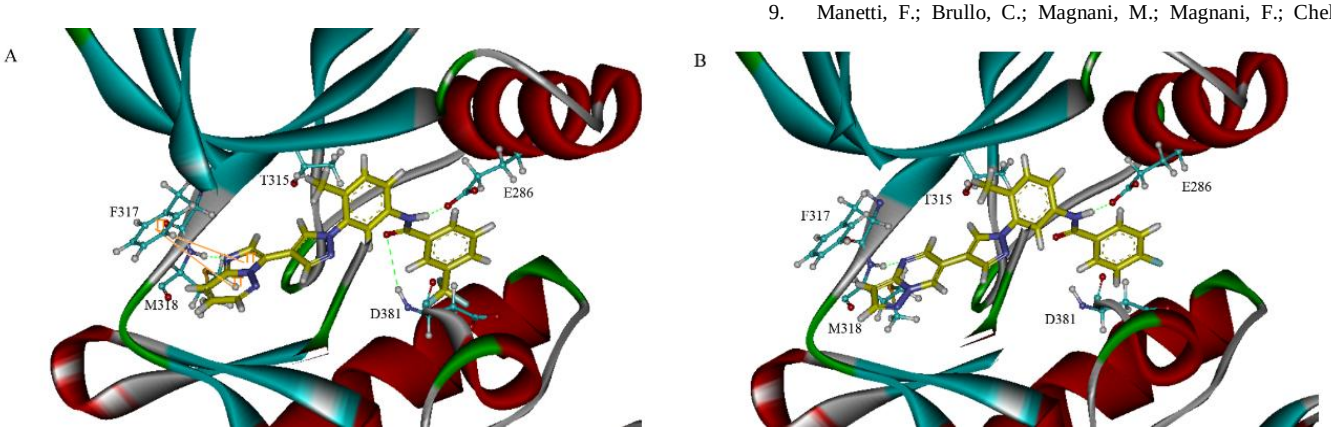

Figure 3. A and B show the binding model of inhibitor **16a** and **7c** to BCR-ABL protein. Oxygen atom (red stick), nitrogen atom (blue stick), H-bond (green dash line), pi-pi stack (orange line).

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