# Design and Synthesis of New Heterocyclic Bcr-Abl Inhibitors

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**ABSTRACT**

Herein, a series of heterocyclic Bcr-Abl kinase inhibitors with different structural scaffolds were designed and synthesized. HTScan Abl1 kinase assay kit was used for the inhibitory test. Some modest inhibitors were obtained.

**Keywords**: CML, benzo[δ]imidazoles, kinase, and cancer

## INTRODUCTION

The Bcr-Abl gene is the results of Philadelphia translocation (reciprocal translocation between chromosome 9 and 22), which is associated with chronic myelogeneous leukemia (CML). The end product is a tyrosine kinase.[1-2] Inhibitors of this kinase are potential drugs against CML. The success of using STI-571 (imatinib, Gleevec) to bring complete remission in CML patients has spurred a great deal of interest in developing new inhibitors of this tyrosine kinase as potential drugs.[3-5] In addition, drug resistance development is a major issue associated with Gleevec.[6] Therefore, there is truly a need for new inhibitors in order to overcome drug resistant problems. Several new Bcr-abl kinase inhibitors have been evaluated in clinical trials.[7-8] However, the need for new inhibitors has not diminished because drug resistance is a continuous issue. Herein, we are interested in the development of Bcr-abl kinase inhibitors using structural scaffolds that are completely different from existing inhibitors. The hope was that such compounds might offer advantage in overcoming drug resistant problems.

In carrying out the work, we first were interested in building a pharmacophore model using existing inhibitors including AMN-107 (**1**), AP-23464 (**2**), AZD-0530 (**3**), BMS-354825 (**4**), CGP-076030 (**5**), STI-571 (**6**), SKI-606 (**7**) and PD-173955 (**8**) (**Figure 1**). In this study, the closed conformation (PDB entry: 1IEP) of the enzyme was selected as the docking model. The 3D structure of STI-571 was derived from X-ray structure (PDB entry: 1IEP). Other 3D structures were generated by AM1 semi-empirical quantum mechanics calculation. All ligands were then assigned with

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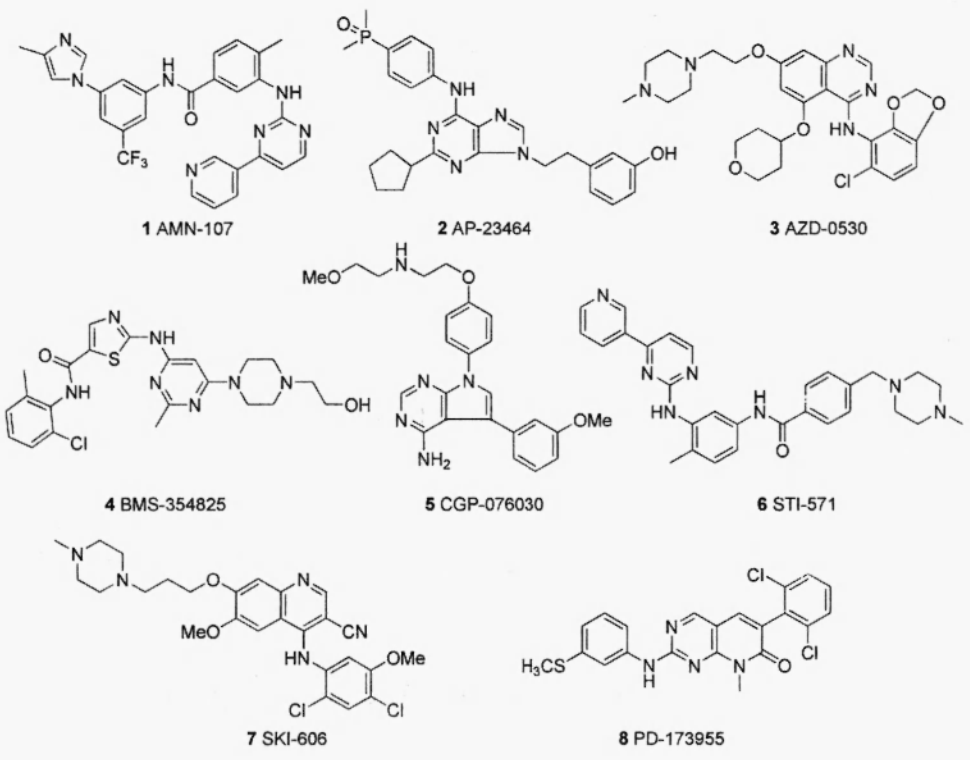



**Fig. 1:** Known inhibitors for Bcr-Abl kinase used in this study

Gastiger-Hückel partial charges using SYBYL. DOCK 5.2 was used to dock these ligands into active site against Bcr-Abl kinase. **Figure 2** shows the docking conformations of these ligands against Bcr-Abl kinase. **Figure 3** depicts these ligands in the active site surface.

**Fig. 2:** The docking conformations of ligands described in **Fig. 1** against Bcr-Abl kinase. Kinase is represented as ribbon.

From **Figure 3**, one can see that these ligands have mainly hydrophobic interaction with at least two hydrophobic pockets around the active site. Another important factor is hydrogen bond with Thr 315. According to the docking results, we can postulate three pharmacophoric features for ligands from the viewpoint of the receptor. The first one is an aromatic hydrophobic group, which can strongly interact with a hydrophobic pocket lined by Phe 382, Val 270, Leu 370, Tyr 253, Leu 248, Phe 317 and Gly 321. Another is also an aromatic hydrophobic group interacting with Phe 313, Ala 380, Ala 269 and Lys 271. There is also a hydrogen bond donor feature for these ligands, which can have hydrogen bond interactions with Thr 315. The analysis of STI-571-Abl kinase X-ray structure also supports such findings (**Figure 4**). Based on all these features, we have designed the compounds in **Figure 5** as potential inhibitors.

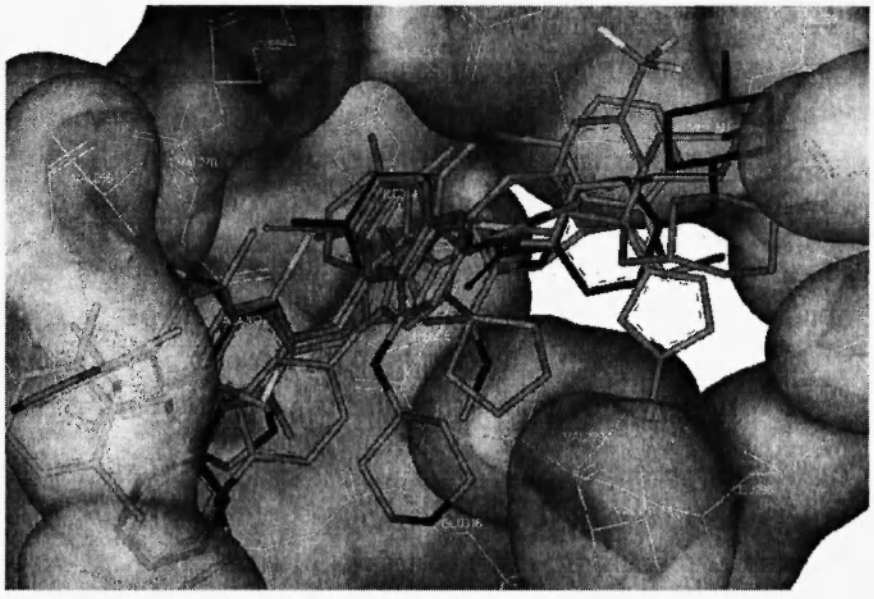


**Fig. 3:** The docking conformations depicted in the active site surface of Bcr-Abl kinase. Ligands are shown in stick and STI-571 is in red stick. Residues around the active site are represented in blue line. Hydrogen bond is shown in green line.

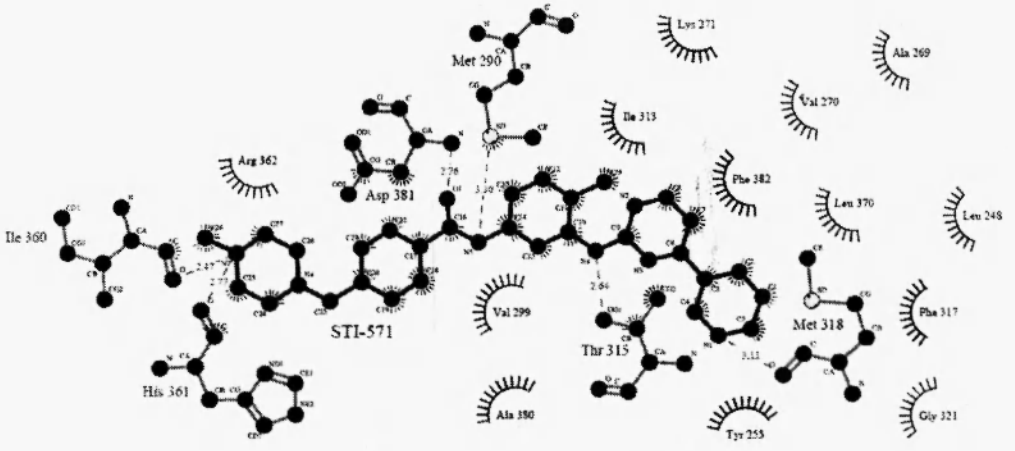
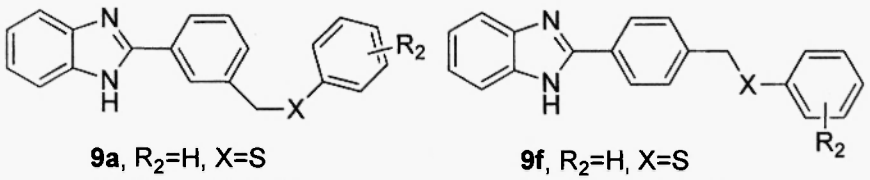
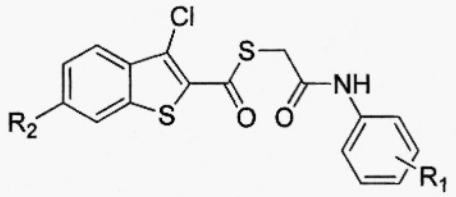



**Fig. 4:** An interaction diagram of STI-571 with Bcr-Abl



**9a**, $R_2$=H, X=S
**9b**, $R_2$=*p*-Cl, X=S
**9c**, $R_2$=*p*-$NO_2$, X=O
**9d**, $R_2$=H, X=O
**9e**, $R_2$=*o*-$NO_2$, X=O

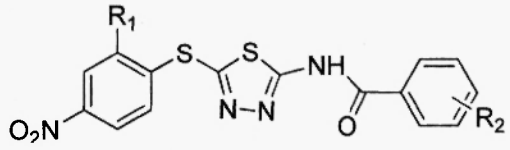
**9f**, $R_2$=H, X=S
**9g**, $R_2$=*p*-Cl, X=S
**9h**, $R_2$=*p*-$NO_2$, X=O
**9i**, $R_2$=H, X=O
**9j**, $R_2$=*o*-$NO_2$, X=O



**10a**, $R_2$=H, $R_1$=H
**10b**, $R_2$=H, $R_1$=*o*-Cl
**10c**, $R_2$=H, $R_1$=*m*-Cl
**10d**, $R_2$=H, $R_1$=*p*-Cl
**10e**, $R_2$=H, $R_1$=*p*-Br
**10f**, $R_2$=H, $R_1$=*p*-$CH_3$
**10g**, $R_2$=H, $R_1$=*p*-$OCH_3$
**10h**, $R_2$=H, $R_1$=*p*-$OC_2H_5$

**10i**, $R_2$=$OCH_3$, $R_1$=*p*-Cl
**10j**, $R_2$=$OCH_3$, $R_1$=*p*-$OCH_3$
**10k**, $R_2$=$OCH_3$, $R_1$=*p*-Br

**10l**, $R_2$=Cl, $R_1$=H
**10m**, $R_2$=Cl, $R_1$=*o*-Cl
**10n**, $R_2$=Cl, $R_1$=*m*-Cl
**10o**, $R_2$=Cl, $R_1$=*p*-Cl
**10p**, $R_2$=Cl, $R_1$=*p*-Br
**10q**, $R_2$=Cl, $R_1$=*p*-$CH_3$
**10r**, $R_2$=Cl, $R_1$=*p*-$OCH_3$
**10s**, $R_2$=Cl, $R_1$=*p*-$OC_2H_5$



**11a**, $R_1$=$NO_2$, $R_2$=H
**11b**, $R_1$=$NO_2$, $R_2$=*o*-Cl
**11c**, $R_1$=$NO_2$, $R_2$=*m*-Cl
**11d**, $R_1$=$NO_2$, $R_2$=*p*-Cl
**11e**, $R_1$=$NO_2$, $R_2$=*m*-Br
**11f**, $R_1$=$NO_2$, $R_2$=*p*-Br
**11g**, $R_1$=$NO_2$, $R_2$=*m*-F
**11h**, $R_1$=$NO_2$, $R_2$=*p*-F
**11i**, $R_1$=$NO_2$, $R_2$=*m*-Cl, *p*-Cl
**11j**, $R_1$=$NO_2$, $R_2$=*p*-$CH_3$

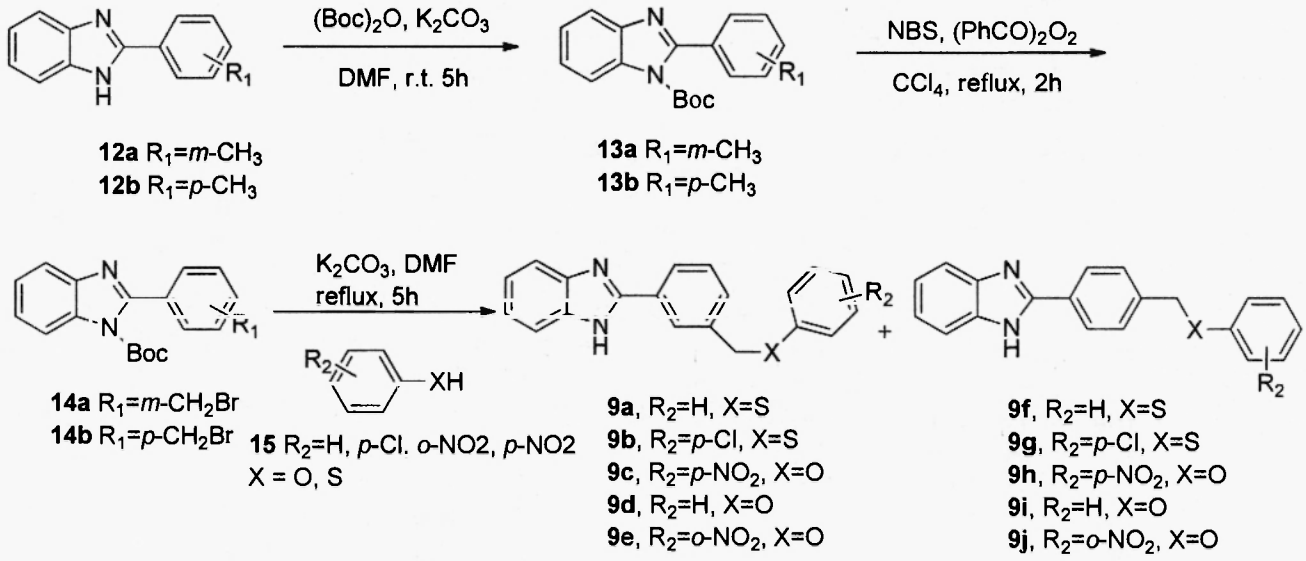
**11k**, $R_1$=CN, $R_2$=H
**11l**, $R_1$=CN, $R_2$=*o*-Cl
**11m**, $R_1$=CN, $R_2$=*m*-Cl
**11n**, $R_1$=CN, $R_2$=*p*-Cl
**11o**, $R_1$=CN, $R_2$=*m*-Br
**11p**, $R_1$=CN, $R_2$=*p*-Br
**11q**, $R_1$=CN, $R_2$=*m*-F
**11r**, $R_1$=CN, $R_2$=*p*-F
**11s**, $R_1$=CN, $R_2$=*m*-Cl, *p*-Cl
**11t**, $R_1$=CN, $R_2$=*p*-$CH_3$

**Fig. 5:** Structures of all the designed compounds

## RESULTS AND DISCUSSION

**Scheme 1** describes the synthesis of analogs of benzo[δ]imidazoles (**9a-9j**). Specifically, starting from **12** the bromo-substituted compounds (**14a, 14b**) were generated in two steps through *tert*-butyl carbamate protection (**13a. 13b**) and bromination (**14a, 14b**) according to general literature procedures.[9-11] The final compounds (**9a-9j**) were obtained

through nucleophilic substitution of **14** with phenol/benzenethiol. It was interesting to note the unexpected cleavage of the Boc group during the last step. Though the original intention of the Boc protection was to minimize side reactions in the last step, this unexpected deprotection did not seem to present a significant problem.

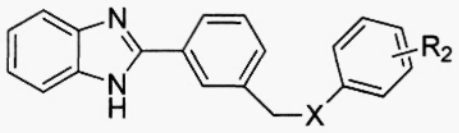



**Scheme 1.** The synthesis of compounds (**9a**–**9j**)

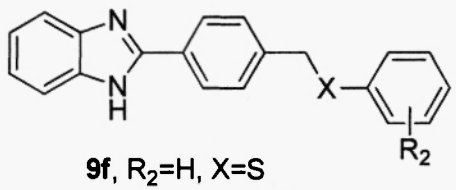
Benzo[β]thiophene-2-carbothioates **10a**-s were synthesized starting with the amidation of aniline **16** (**Scheme 2**). Acyl chlorides **20** were synthesized from the α, β-unsaturated carboxylic by reacting with thionyl chloride (**17**) under reflux conditons.[12-13] Reaction of acylchloride **20** and phenylacetamides **18** in presence of $Et_3N$ in benzene gave the final products (**10a-10s**) 81-95% yields.

Thiadiazole benzamides (**11a-11t**) were prepared starting with the substitution of the chloride in **21** with thiadiazole thiol (**22**). This was followed by amidation to give the final products **11a-t** in 50-73% yields.

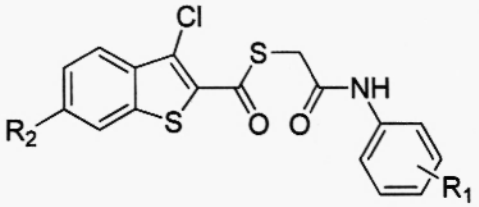
For the inhibitor assay, an HTScan Abl1 kinase assay kit (#7905 from cell signaling technology) was used. Among all the compounds tested, **9** were observed to have inhibition activities against Abl kinase with $IC_{50}$ below 1 mM (**9b, 9g, 10d, 10c, 10k, 10p, 10q, 11j,** and **11n**), and compound **10q** showed $IC_{50}$ below 100 μM (**Table 1**). In analyzing the inhibition results, we were interested in achieving some basic understanding of the structural features, which are important for future optimization work. From the compounds listed above, one can see that the benzo[β]thiophene-2-carbothioate core structure seem to confer better inhibition effect than the thiadiazol-benzamides and benzo[δ]imidazoles. For example, compounds **10p** and **10q** have the best inhibitory effects. There are five benzo[β]thiophene-2-carbothioate compounds (**10d, 10e, 10k, 10p,** and **10q**) with $IC_{50}$ values below 1 mM, while the thiadiazol-benzamide and the benzo[δ]imidazole scaffolds combined only have four compounds (**9b, 9g, 11j,** and **11n**) with $IC_{50}$ in the range of 500-1000 μM.



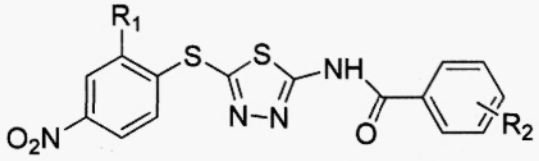
**9a**, $R_2$=H, X=S
**9b**, $R_2$=*p*-Cl, X=S
**9c**, $R_2$=*p*-$NO_2$, X=O
**9d**, $R_2$=H, X=O
**9e**, $R_2$=*o*-$NO_2$, X=O



**9f**, $R_2$=H, X=S
**9g**, $R_2$=*p*-Cl, X=S
**9h**, $R_2$=*p*-$NO_2$, X=O
**9i**, $R_2$=H, X=O
**9j**, $R_2$=*o*-$NO_2$, X=O



**10a**, $R_2$=H, $R_1$=H
**10b**, $R_2$=H, $R_1$=*o*-Cl
**10c**, $R_2$=H, $R_1$=*m*-Cl
**10d**, $R_2$=H, $R_1$=*p*-Cl
**10e**, $R_2$=H, $R_1$=*p*-Br
**10f**, $R_2$=H, $R_1$=*p*-$CH_3$
**10g**, $R_2$=H, $R_1$=*p*-$OCH_3$
**10h**, $R_2$=H, $R_1$=*p*-$OC_2H_5$
**10i**, $R_2$=$OCH_3$, $R_1$=*p*-Cl
**10j**, $R_2$=$OCH_3$, $R_1$=*p*-$OCH_3$
**10k**, $R_2$=$OCH_3$, $R_1$=*p*-Br
**10l**, $R_2$=Cl, $R_1$=H
**10m**, $R_2$=Cl, $R_1$=*o*-Cl
**10n**, $R_2$=Cl, $R_1$=*m*-Cl
**10o**, $R_2$=Cl, $R_1$=*p*-Cl
**10p**, $R_2$=Cl, $R_1$=*p*-Br
**10q**, $R_2$=Cl, $R_1$=*p*-$CH_3$
**10r**, $R_2$=Cl, $R_1$=*p*-$OCH_3$
**10s**, $R_2$=Cl, $R_1$=*p*-$OC_2H_5$



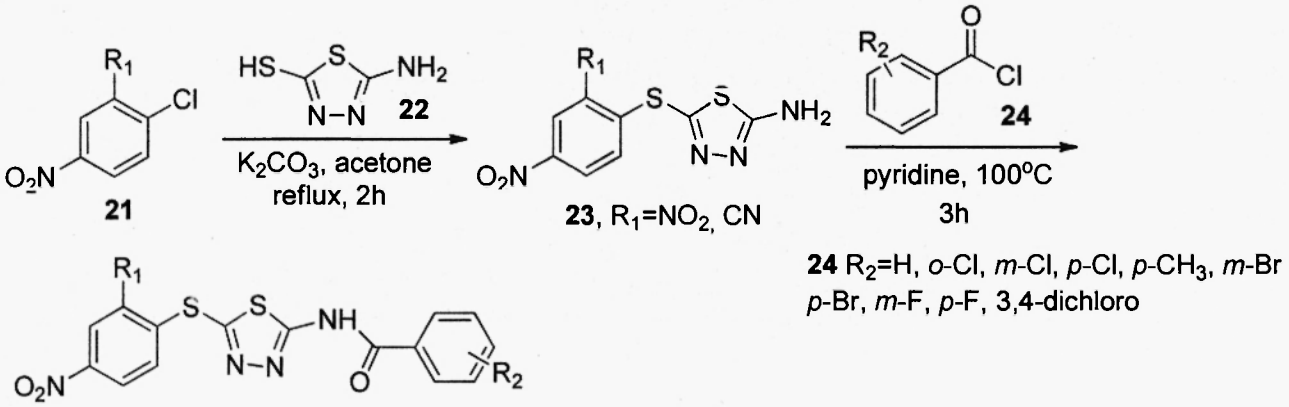
**11a**, $R_1$=$NO_2$, $R_2$=H
**11b**, $R_1$=$NO_2$, $R_2$=*o*-Cl
**11c**, $R_1$=$NO_2$, $R_2$=*m*-Cl
**11d**, $R_1$=$NO_2$, $R_2$=*p*-Cl
**11e**, $R_1$=$NO_2$, $R_2$=*m*-Br
**11f**, $R_1$=$NO_2$, $R_2$=*p*-Br
**11g**, $R_1$=$NO_2$, $R_2$=*m*-F
**11h**, $R_1$=$NO_2$, $R_2$=*p*-F
**11i**, $R_1$=$NO_2$, $R_2$=*m*-Cl, *p*-Cl
**11j**, $R_1$=$NO_2$, $R_2$=*p*-$CH_3$
**11k**, $R_1$=CN, $R_2$=H
**11l**, $R_1$=CN, $R_2$=*o*-Cl
**11m**, $R_1$=CN, $R_2$=*m*-Cl
**11n**, $R_1$=CN, $R_2$=*p*-Cl
**11o**, $R_1$=CN, $R_2$=*m*-Br
**11p**, $R_1$=CN, $R_2$=*p*-Br
**11q**, $R_1$=CN, $R_2$=*m*-F
**11r**, $R_1$=CN, $R_2$=*p*-F
**11s**, $R_1$=CN, $R_2$=*m*-Cl, *p*-Cl
**11t**, $R_1$=CN, $R_2$=*p*-$CH_3$

**Scheme 2.** The synthesis of compounds **10a**–s

As for the core thiadiazol-benzamide structure, *para* substitution on the phenyl group seems to favor activities. For example, adding a bromo group at the *para*- position of the phenyl ring resulted in significantly improved activities from an $IC_{50}$ of 1 mM (**10l**) to 175 μM (**10p**). However, no improvement was observed if the substituent was at the *meta*- or *ortho*- position. This seems to be true for all the compounds tested. All the active compounds have *para*-

substituent on the phenyl ring. Meanwhile, bulky groups also do not seem to favor the inhibitory effects. Such are the cases with compounds **10r** and **10s**.

In comparing between the phenoxy and phenylthiol groups in the benzo[δ]imidazole compounds, higher inhibition activities of the phenylthiol compound were observed. For example, both compounds **9b** and **9g** have lower $IC_{50}$ (<1 mM) compared to compounds **9d** and **9i**, though *para*-Cl probably also played some important roles as discussed above.




**11a**, $R_1$=$NO_2$, $R_2$=H
**11b**, $R_1$=$NO_2$, $R_2$=*o*-Cl
**11c**, $R_1$=$NO_2$, $R_2$=*m*-Cl
**11d**, $R_1$=$NO_2$, $R_2$=*p*-Cl
**11e**, $R_1$=$NO_2$, $R_2$=*m*-Br
**11f**, $R_1$=$NO_2$, $R_2$=*p*-Br
**11g**, $R_1$=$NO_2$, $R_2$=*m*-F
**11h**, $R_1$=$NO_2$, $R_2$=*p*-F
**11i**, $R_1$=$NO_2$, $R_2$=*m*-Cl, *p*-Cl
**11j**, $R_1$=$NO_2$, $R_2$=*p*-$CH_3$

**11k**, $R_1$=CN, $R_2$=H
**11l**, $R_1$=CN, $R_2$=*o*-Cl
**11m**, $R_1$=CN, $R_2$=*m*-Cl
**11n**, $R_1$=CN, $R_2$=*p*-Cl
**11o**, $R_1$=CN, $R_2$=*m*-Br
**11p**, $R_1$=CN, $R_2$=*p*-Br
**11q**, $R_1$=CN, $R_2$=*m*-F
**11r**, $R_1$=CN, $R_2$=*p*-F
**11s**, $R_1$=CN, $R_2$=*m*-Cl, *p*-Cl
**11t**, $R_1$=CN, $R_2$=*p*-$CH_3$

**Scheme 3.** The synthesis of compounds (**11a–11t**)

**Table 1**

$IC_{50}$ Values

| Compound number | **9b** | **9g** | **10d** | **10e** | **10k** | **10p** | **10q** | **11j** | **11n** |
|---|---|---|---|---|---|---|---|---|---|
| $IC_{50}$ (μM) | 571 | 842 | 205 | 460 | 763 | 175 | 76 | 839 | 914 |

Though only modest inhibitors were obtained, considering that these compounds were based on *de novo* design the results are very significant and lay a foundation for future optimization in search of new Bcr-abl kinase inhibitors with a structural scaffold that is completely different from other known inhibitors.

## EXPERIMENTAL SECTION

### Enzyme assay

All the test compounds were dissolved in DMSO to the concentration 20 mM as stock solution. The compounds were tested by using the HTScan Abl1 kinase assay kit (cell signaling technology #7905). The experiment was performed according to the standard protocol described in the brochure for the kit. Briefly, the tested compounds were diluted to the test concentration and added to 96-well plates. This was followed by the addition of ATP, substrate, and the enzyme. After incubation and washing, primary and secondary antibodies were added. Fluorescence intensity was detected by using a Perkin-Elmer microplate reader ($\lambda_{ex}$ 340 nm, $\lambda_{em}$ 615 nm). $IC_{50}$ values were estimated based on the concentration that caused 50% reduction of in fluorescence.

### Chemistry

Triethylamine and pyridine were distilled over KOH pellets and stored in a septum-sealed flask. Solvents were dried by heating under refluxing for at least 12 h over $P_2O_5$ (dichloromethane) or sodium/benzophenone (benzene, THF), and were freshly distilled prior to use. All new compounds gave satisfactory 1H NMR (400 or 300 MHz) 13C NMR (100 or 75 MHz) and high resolution mass spectra (ESI). Melting points were determined on an XT–4 melting point apparatus and were uncorrected.

### General procedure for synthesis of tert-butyl 2-aryl -1H-benzo[d]imidazole-1-carboxylate

To a solution of 2-arylbenzimidazole (10 mmol) in DMF (30 mL) was added $K_2CO_3$ (12 mmol). Then the mixture was stirred for 40 min. A solution of di-*tert*-butyl dicarbonate (11 mmol) in DMF (10 mL) was added to the reaction mixture, and the reaction was allowed to continue for 5 h until no starting material remained. The solvent was removed, and the residue was dissolved in EtOAc, washed with 5% HCl, saturated $NaHCO_3$ and brine, dried with anhydrous $Na_2SO_4$. It was purified by column chromatography (petroleum ether/ethyl acetate = 1/6) to afford the desired products.

***tert*-Butyl 2-*m*-tolyl-1*H*-benzo[*d*]imidazole-1-carboxylate**

Colorless oil (96% yield); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 (dd, $J$ = 6.4, 2.8 Hz, 1H), 7.79 (dd, $J$ = 8.0, 2.4 Hz, 1H), 7.47–7.24 (m, 6H), 2.42 (s, 3H), 1.41 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.0, 148.6, 142.6, 137.6, 133.8, 132.3, 130.3, 129.7, 127.8, 126.3, 124. 9, 124.4, 120.1, 114.6, 85.1, 27.6, 21.4.

***tert*-Butyl 2-*p*-tolyl-1*H*-benzo[*d*]imidazole-1-carboxylate**

White solid (98% yield); mp 117–118 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (dd, $J$ = 7.6, 2.4 Hz, 1H), 7.80 (dd, $J$ = 7.6, 2.4Hz, 1H), 7.55 (d, $J$ = 8.0 Hz, 2H), 7.38 (m, 2H), 7.28 (d, $J$ = 7.6 Hz, 2H), 2.44 (s, 3H), 1.46 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.1, 148.7, 142.7, 139.6, 133.8, 129.4, 129.1, 124. 8, 128.6, 124.3, 120.1, 114.6, 85.2, 27.6, 21.5.

**Bromination of *tert*-butyl 2-aryl -1*H*-benzo[*d*]imidazole-1-carboxylate**

A stirred solution of *tert*-butyl 2-aryl-1*H*-benzo[*d*]imidazole-1-carboxylate (5 mmol) and benzoyl peroxide (1mmol) in $CCl_4$ (50 mL) was refluxed for 2 h. The solution was cooled, filtered, and concentrated under reduced pressure. The

crude product was purified by column chromatography (petroleum ether/ethyl acetate = 1/6) to afford the desired products.

***tert*-Butyl 2-(3-(bromomethyl)phenyl)-1*H*-benzo[*d*]imidazole-1-carboxylate**

White solid (83% yield); mp 78–79 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J$ = 8.4 Hz, 1H), 7.77 (d, $J$ = 8.0 Hz, 1H), 7.65 (s, 1H), 7.54 (d, $J$ = 7.6 Hz, 1H), 7.46 – 7.35 (m, 4H), 4.51 (s, 2 H), 1.39 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 152.8, 148.1, 142.2, 137.4, 133.5, 132.9, 129.9, 129.5, 128.9, 128.2, 124.9, 124.3, 119.9, 114.5, 85.2, 32.6, 27.3.

***tert*-Butyl 2-(4-(bromomethyl)phenyl)-1*H*-benzo[*d*]imidazole-1-carboxylate**

White solid (85% yield); mp 122–123 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (dd, $J$ = 8.0, 2.0 Hz, 1H), 7.80 (dd, $J$ = 8.0, 2.4 Hz, 1H), 7.62 (d, $J$ = 8.4 Hz, 2H), 7.50 (d, $J$ = 8.0 Hz, 2H), 7.40 (m, 2H), 4.56 (s, 2H), 1.43 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.1, 148.5, 142.6, 139.2, 133.8, 132.6, 129. 7, 128.6, 125.1, 124.5, 120.2, 114.7, 85.5, 32.8, 27.6.

**General procedure for the synthesis of compounds 9a-j**

To the solution of phenol or benzenethiol (5 mmol) in DMF (5 mL) was added $K_2CO_3$ (6 mmol). The mixture was stirred for 30 min, then a solution of *tert*-butyl 2-(4-(bromomethyl)phenyl)-1*H*-benzo[*d*]imidazole-1-carboxylate or *tert*-butyl 2-(3-(bromomethyl)phenyl)-1*H*-benzo[*d*]imidazole -carboxylate (1 mmol) in DMF (2 mL) was added. The mixture was refluxed for 5 h until no starting material remained. The mixture was poured into cold water (50 mL), extracted with EtOAc, and the extract was dried with anhydrous $Na_2SO_4$, filtered, and purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to give the desired products.

**2-(3-(Phenylthiomethyl)phenyl)-1*H*-benzo[*d*]imidazole (9a)**

White solid (71% yield); mp 168–169 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.94 (d, $J$ = 8.0 Hz, 2H), 7.92–7.17 (m, 11H), 4.11 (s, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 151.4, 138.9, 136.4, 130.8, 130.7, 129. 5, 128. 8, 127.4, 126.4, 125.5, 123.0, 122.2, 119.3, 111.8, 37.0; IR (KBr) 3436, 3043, 2876, 2790, 1583, 1474, 1447, 1402, 1364, 1315, 1277, 1231, 1106, 742, 690 cm$^{-1}$; MS (EI) *m/z* 316, HRMS (ESI) calcd for $C_{20}H_{17}N_2S$ $[M + H]^+$: 317.1107, found: 317.1105.

**2-(3-((4-Chlorophenylthio)methyl)phenyl)-1*H*-benzo[*d*]imidazole (9b):** White solid (70% yield); mp 159–160 °C.
**2-(3-((4-Nitrophenoxy)methyl)phenyl)-1*H*-benzo[*d*]imidazole (9c):** Yellowish solid (60% yield); mp 213–214 °C.
**2-(3-(Phenoxymethyl)phenyl)-1*H*-benzo[*d*]imidazole (9d):** White solid (65% yield); mp 164–165 °C.
**2-(3-((2-Nitrophenoxy)methyl)phenyl)-1*H*-benzo[*d*]imidazole (9e):** Yellowish solid (50% yield); mp 229–231 °C.
**2-(4-(Phenylthiomethyl)phenyl)-1*H*-benzo[*d*]imidazole (9f):** White solid (73% yield); mp 211–212 °C.
**2-(4-((4-Chlorophenylthio)methyl)phenyl)-1*H*-benzo[*d*]imidazole (9g):** White solid (70% yield); mp 210–211 °C.
**2-(4-((4-Nitrophenoxy)methyl)phenyl)-1*H*-benzo[*d*]imidazole (9h):** Yellowish solid (53% yield); mp 220–221 °C.
**2-(4-(Phenoxymethyl)phenyl)-1*H*-benzo[*d*]imidazole (9i):** White solid (60% yield); mp 202–203 °C .
**2-(4-((2-Nitrophenoxy)methyl)phenyl)-1*H*-benzo[*d*]imidazole (9j):** Yellowish solid (59% yield); mp 217–218 °C.

**General procedure for the synthesis of compounds 10a**

s. $\alpha$–Mercaptoacetanilide (1 mmol) was dissolved in benzene (5 mL), then triethylamine (1.5 mmol) and benzo[*b*]thiophene-2-carboxyl chloride (1 mmol) were added to the solution. The reaction mixture was stirred for 5 h at room temperature, filtered, and the solid was dissolved in chloroform, washed with water, dried and concentrated to give the desired products.

**2-Oxo-2-(phenylamino)ethyl 3-chlorobenzo[*b*]thiophene-2-carbothioate (10a)**

White solid (95% yield); mp 168–169 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.37 (s, 1H), 7.99 (d, $J$ = 7.6 Hz, 1H), 7.84 (d, $J$ = 7.6 Hz, 1H), 7.56 (m, 3H), 7.32 (t, $J$ = 7.6 Hz, 2H), 7.12 (d, $J$ = 7.2Hz, 1H), 3.93 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 185.2, 166.0, 138.7, 137.6, 137.0, 133.4, 129.0, 126.0, 125.8, 124.6, 124.3, 122.9, 119.9, 34.6; IR (KBr) 3455, 3299, 3056, 2912, 1672, 1629, 1598, 1531, 1498, 1439, 1322, 1251, 1181, 948, 804, 756 cm$^{-1}$; MS (EI) *m/z* 361; HRMS (ESI) calcd for $C_{17}H_{13}ClNO_2S_2$ [M + H]$^+$: 362.0071, found :362.0069.

**2-(2-Chlorophenyiamino)-2-oxoethyl 3-chlorobenzo[*b*]thiophene-2-carbothioate (10b):** White solid (93% yield); mp 160–161 °C.

**2-(3-Chlorophenylamino)-2-oxoethyl 3-chlorobenzo[*b*]thiophene-2-carbothioate (10c):** White solid (89% yield), mp 170–171 °C.

**2-(4-Chlorophenylamino)-2-oxoethyl 3-chlorobenzo[*b*]thiophene-2-carbothioate (10d):** White solid (90% yield); mp 192–193 °C.

**2-(4-Bromophenylamino)-2-oxoethyl 3-chlorobenzo[*b*]thiophene-2-carbothioate (10e):** White solid (90% yield); mp 192–194 °C.

**2-(*p*-Toluidino)-2-oxoethyl 3-chlorobenzo[*b*]thiophene-2-carbothioate (10f):** White solid (92% yield); mp 182–183 °C

**2-(4-Methoxyphenylamino)-2-oxoethyl 3-chlorobenzo[*b*]thiophene-2-carbothioate (10g):** White solid (93%); mp 188–189 °C.

**2-(4-Ethoxyphenylamino)-2-oxoethyl 3-chlorobenzo[*b*]thiophene-2-carbothioate (10h):** White solid (92% yield); mp 188–190 °C.

**2-(4-Chlorophenylamino)-2-oxoethyl 3-chloro-6-methoxybenzo[*b*]thiophene-2-carbothioate (10i):** Yellowish solid (83% yield); mp 172–174 °C.

**2-(4-Methoxyphenylamino)-2-oxoethyl 3-chloro-6-methoxybenzo[*b*]thiophene-2-carbothioate (10j):** Yellowish solid (89%); mp 175–176 °C.

**2-(4-Bromophenylamino)-2-oxoethyl 3-ehloro-6-methoxybenzo[*b*]thiophene-2-carbothioate (10k):** White solid (81% yield); mp 189–190 °C.

**2-Oxo-2-(phenylamino)ethyl 3,6-dichlorobenzo[*b*]thiophene-2-carbothioate (10l):** White solid (95% yield); mp 183–184 °C.

**2-(2-Chlorophenylamino)-2-oxoethyl 3,6-dichlorobenzo[*b*]thiophene-2-carbothioate (10m):**
White solid (93% yield); mp 173–174 °C.

**2-(3-Chlorophenylamino)-2-oxoethyl 3,6-dichlorobenzo[*b*]thiophene-2-carbothioate (10n):**
White solid (89% yield); mp 184–185 °C.

**2-(4-Chlorophenylamino)-2-oxoethyl 3,6-dichlorobenzo[*b*]thiophene-2-carbothioate (10o):** White solid (90% yield);

mp 204–205 °C.

**2-(4-Bromophenylamino)-2-oxoethyl 3,6-dichlorobenzo[*b*]thiophene-2-carbothioate (10p):** White solid (90% yield); mp 208–209 °C.

**2-(*p*-Toluidino)-2-oxoethyl 3,6-dichlorobenzo[*b*]thiophene-2-carbothioate (10q):** White solid (92% yield); mp 191–192 °C.

**2-(4-methoxyphenylamino)-2-oxoethyl 3,6-dichlorobenzo[*b*]thiophene-2-carbothioate (10r):** White solid (90% yield); mp 191–192 °C.

**2-(4-Ethoxyphenylamino)-2-oxoethyl 3,6-dichlorobenzo[*b*]thiophene-2-carbothioate (10s):** White solid (92% yield); mp 204–205 °C.

**General procedure for the synthesis of 5-(2,4-dinitrophenylthio)-1,3,4- thiadiazol-2-amine and 2-(5-amino-1,3,4-thiadiazol-2-ylthio)-5-nitrobenzonitrile**

The solution of 2-amino-5-mercapto-1,3,4-thiadiazole (20 mmol ) and $K_2CO_3$ (25 mmol) in acetone (150 mL) was stirred for 30 min. The solution of 1-chloro-2,4-dinitrobenzene or 2- chloro-5-nitrobenzonitrile (25 mmol) dissolved in acetone (20 mL) was added to the reaction while refluxing until the reaction was accomplished for 2 h. The reaction mixture was filtered, and the solid was washed with water and acetone, dried under reduced pressure to afford the desired products.

**2-(5-Amino-1,3,4-thiadiazol-2-ylthio)-5-nitrobenzonitrile:** Green solid (67% yield); mp 243–244 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.78 (d, $J$ = 2.0 Hz, 1H), 8.46 (dd, $J$ = 8.8, 2.0 Hz, 1H), 7.90 (s, 2H), 7.41 (d, $J$ = 8.8 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 174.0, 148.0, 146.4, 141.2, 129.7, 129.3, 129.1, 115.1, 111.2.

**5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-amine**

Yellow solid (73% yield); mp 268–269 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.89 (d, $J$ = 2.4 Hz, 1H), 8.45 (dd, $J$ = 8.8, 2.4 Hz, 1H), 7.90 (s, 2H), 7.85 (d, $J$ = 8.4 Hz, 1H), 7.32 (d, $J$ = 8.8 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 174.5, 145.6, 144.5, 143.8, 142.5, 129.5, 128.9, 121.8.

**General procedure for the synthesis of compounds 11a–t.**

The solution of 5-(2,4-dinitrophenythio)-1,3,4-thiadiazol-2-ylamine or 2-(5-amino-1,3,4-thiadiazol-2-ylthio)-5-nitrobenzonitrile (0.5 mmol) in pyridine (5 mL) was treated with substituted benzoyl chloride (0.6 mmol), heated at 100 °C for 3 h, and the reaction mixture was poured into ice water containing concentrated hydrochloride acid (5 mL). The precipitate was filtered. The solid was purified by column chromatography (petroleum ether/ethyl acetate = 2/1) to afford the desired products.

***N*-[5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl]-benzamide (11a)**

Yellow solid (63% yield), mp 243–244 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 13.61 (s, 1H), 8.91(s, 1H), 8.35 (dd, $J$ = 7.2, 1.6 Hz, 1H), 8.11 (d, $J$ = 7.6 Hz, 2H), 7.68 (t, $J$ = 7.2 Hz, 1H), 7.57 (dd, $J$ = 7.6, 7.2 Hz, 2H), 7.33 (d, $J$ = 8.8 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 166.2, 164.9, 151.7, 145.7, 144.8, 142.8, 133.9, 131.3, 130.1, 129.3, 128.9, 128.8, 121.7; IR (KBr) 3424, 3257, 3109, 2922, 1675, 1661, 1596, 1521, 1343, 1302, 1240, 1070, 1042, 890, 704 cm$^{-1}$;

MS (ESI) *m/z* $[M + H]^+$ 404; HRMS (ESI) calcd for $C_{15}H_{10}N_5O_5S_2$ $[M + H]^+$: 404.0118, found: 404.0122.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-2-chlorobenzamide (11b):** Yellowish solid (50% yield); mp 240–241 °C.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-3-chlorobenzamide (11c):** Yellow solid (60% yield); mp 232–233 °C.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-4-chlorobenzamide (11d):** Yellowish solid (60% yield); mp 238–239 °C.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-3-bromobenzamide (11e):** Yellowish solid (52% yield); mp 222–223 °C.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-4-bromobenzamide (11f):** Yellowish solid (57% yield); mp 239–240 °C.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-3-fluorobenzamide (11g):** Yellowish solid (50%); mp 233–234 °C.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-4-fluorobenzamide (11h):** Yellowish solid (51% yield); mp 224–225 °C.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-3,4-dichlorobenzamide (11i):** Yellow solid (53% yield); mp 235–236 °C.

***N*-(5-(2,4-Dinitrophenylthio)-1,3,4-thiadiazol-2-yl)-4-methylbenzamide (11j):** Yellowish solid (73% yield); mp 246–247 °C.

***N*-[5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl]-benzamide (11k):** Yellowish solid (66% yield); mp 231–232 °C.

***N*-(5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl)-2-chlorobenzamide (11l):** Yellow solid (50% yield); mp 231–233 °C.

***N*-(5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl)-3-chlorobenzamide (11m):** Yellow solid (60% yield); mp 231–233 °C.

***N*-(5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl)-4-chlorobenzamide (11n):** Yellow solid (63% yield); mp 244–245 °C.

***N*-(5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl)-3-bromobenzamide (11o):** Yellow solid (57% yield); mp 232–233 °C.

***N*-(5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl)-4-bromobenzamide (11p):** Yellow solid (61% yield); mp 242–244 °C.

***N*-(5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl)-3-fluorobenzamide (11q):** Yellowish solid (53% yield); mp 247–248 °C.

***N*-(5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl)-4-fluorobenzamide (11r):** Yellow solid ( 60% yield); mp 234–235 °C.

**3,4-Dichloro-*N*-[5-(2-cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl]-benzamide (11s):** Yellowish solid (54% yield); mp 224–225 °C.

***N*-[5-(2-Cyano-4-nitrophenylthio)-1,3,4-thiadiazol-2-yl]-4-methyl-benzamide (11t):** Yellow solid (68% yield); mp 230–231 °C.

## CONCLUSIONS

Based on pharmacophore modeling, a series of heterocylic inhibitors of Bcr-Abl kinase was designed and synthesized. Although only modest inhibition activities were obtained, future optimization of the new structural scaffold identified could lead potent inhibitors effect against Bcr-Abl kinase.

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