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Modification of imidazothiazole derivatives gives promising activity in B-Raf kinase enzyme inhibition; synthesis, *in vitro* studies and molecular docking

Usama M. Ammar[a,b,c], Mohammed S. Abdel-Maksoud[d], Karim I. Mersal[a,b], Eslam M. H. Ali[a,b], Kyung Ho Yoo[e], Hong Seok Choi[f], Jae Kyun Lee[g], Sun Young Cha[h], Chang-Hyun Oh[a,b,*]

[a]*Center for Biomaterials, Korea Institute of Science & Technology (KIST School), Seoul, Seongbuk-gu, 02792, Republic of Korea*
[b]*University of Science & Technology (UST), Daejeon, Yuseong-gu, 34113, Republic of Korea*
[c]*Pharmaceutical Chemistry Department, Faculty of Pharmacy, Ahram Canadian University, Giza, 12566, Egypt*
[d]*Medicinal & Pharmaceutical Chemistry Department, Pharmaceutical and Drug Industries Research Division, National Research Centre (NRC), Dokki, Giza, 12622, Egypt*
[e]*Chemical Kinomics Research Center, Korea Institute of Science and Technology, Seoul, Republic of Korea*
[f]*College of Pharmacy, Chosun University, Gwangju 61452, Republic of Korea*
[g]*Center for Neuro-Medicine, Korea Institute of Science & Technology (KIST School), Seoul, Seongbuk-gu, 02792, Republic of Korea*
[h]*Department of Beauty Science, Hanseo University, Seosan 31962, Republic of Korea*
[*]*Corresponding author*

Abstract

B-Raf mutation was identified as a key target in cancer treatment. Based on structural features of dabrafenib (potent FDA approved B-Raf inhibitor), the design of new NH_2-based imidazothiazole derivatives was carried out affording new highly potent derivatives of imidazothiazole-based scaffold with amino substitution on the terminal phenyl ring as well as side chain with sulfonamide group and terminal substituted phenyl ring. *In vitro* enzyme assay was investigated against V600E B-Raf kinase. Compounds **10l**, **10n** and **10o** showed higher inhibitory activities (IC_{50} = 1.20, 4.31 and 6.21 nM, respectively). *In vitro* cytotoxicity evaluation was assessed against NCI-60 cell lines. Most of tested derivatives showed cytotoxic activities against melanoma cell line. Compound **10k** exhibited most potent activity (IC_{50} = 2.68 μM). Molecular docking study revealed that the new designed derivatives preserved the same binding mode of dabrafenib with V600E B-Raf active site. It was investigated that the new modification in the synthesized derivatives

(substituted with NH_2) had a significant inhibitory activity towards V600E B-Raf. This core scaffold is considered a key compound for further structural and molecular optimization.

Keywords

Antitumor agents; cancer; imidazo[2,1-*b*]thiazole; V600E B-Raf.

Cancer is one of the most prevalent diseases worldwide[1-6]. Both cell growth and proliferation are controlled through MAPK signaling pathway[7-12]. B-Raf kinase enzyme is considered an important element in MAPK cascade. Mutation of B-Raf lead to uncontrolled cell proliferation and potentiation of cancer particularly melanoma[2]. At present, a number of small molecule-based inhibitors have been approved by FDA as B-Raf kinase inhibitors such as vemurafenib (**I**)[13] and dabrafenib (**II**)[14] (**Figure 1**).

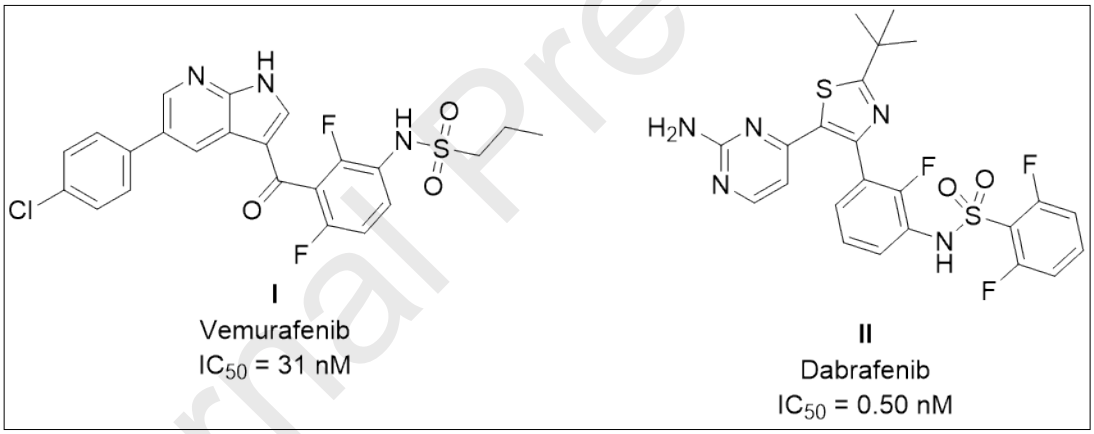


Figure 1. FDA approved V600E B-Raf inhibitors with their IC_{50} values.

However, these approved drugs have been acquired a number of resistances[15, 16]. As a result, it is necessary to develop a more efficient and selective agents against mutated B-Raf kinase enzyme. Imidazothiazole derivatives exhibit a wide range of biological activities including anti-cancer, anti-inflammatory and anti-bacterial effect[17]. Recently, the medicinal research era focus on the development of imidazothiazole-based derivatives in the treatment of cancer[18-21].

In previous studies, we synthesized a number of imidazothiazole-based small molecules. These derivatives exhibited inhibitory activities against V600E B-Raf kinase enzyme in a

range of nanomolar level[22]. In the present study, based on the structural features of dabrafenib (**II**), we designed a number of new imidazothiazole-based derivatives in order to enhance the potency towards V600E B-Raf kinase enzyme. Molecular docking screening of dabrafenib has been identified to investigate the potential pharmacophores which bind to conserved amino acids in B-Raf active site.

A new imidazothiazole derivatives was designed, where, the terminal phenyl ring was substituted with NH_2 group. In addition, the other key chemical features in dabrafenib (sulphonamide group and terminal phenyl ring) were kept in the designed compounds in order to afford the same binding mode of dabrafenib in B-Raf binding site (sulphonamide group, Lys 483; terminal phenyl ring, Leu 505 and Phe 595) (**Figure 2**). The new incorporated NH_2 group affords both polarity as well as H-bond contribution (donor and acceptor) with the biochemical environment of B-Raf active site. The new proposed interactions (of NH_2 group) was supposed to significantly contribute in the inhibitory activity.

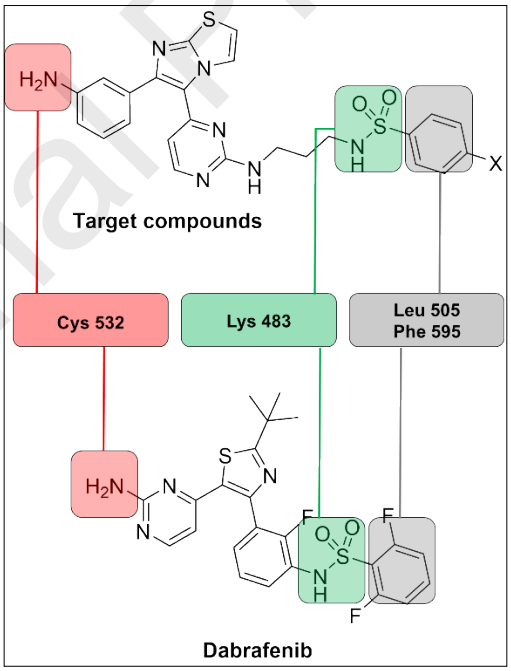
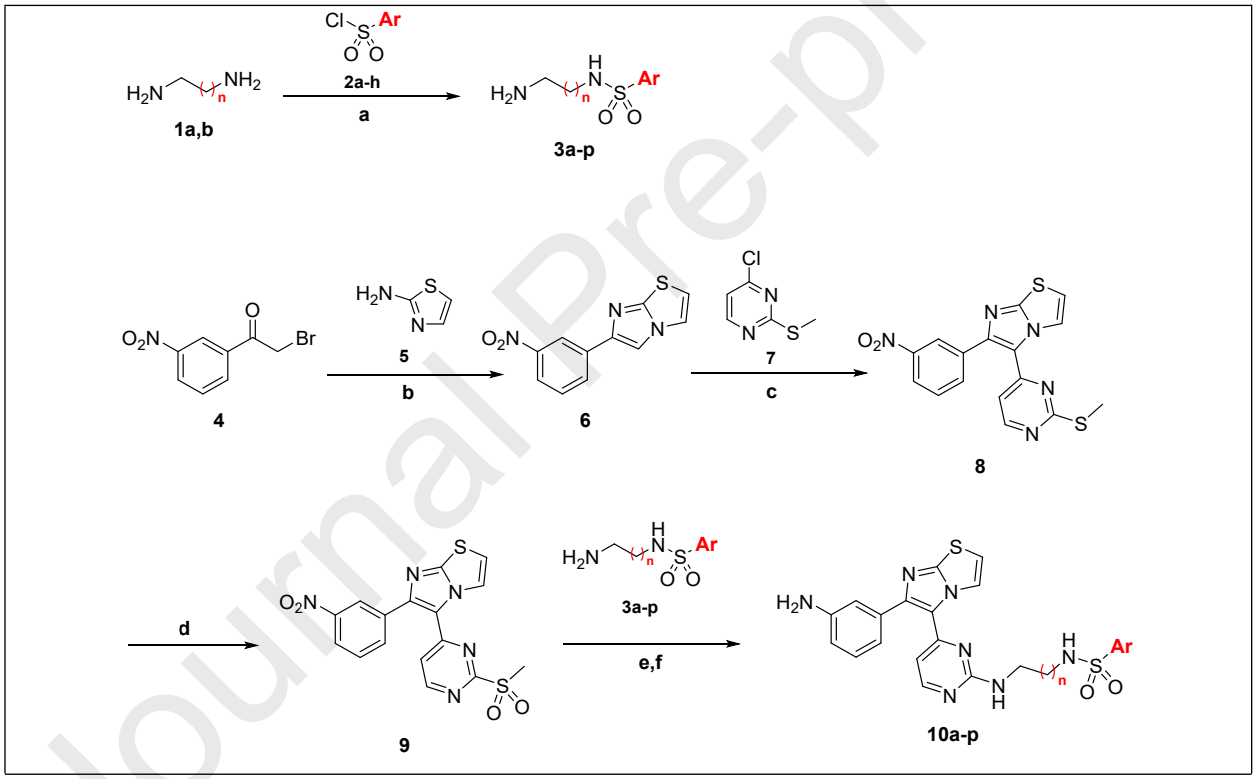


Figure 2. Rational design of new imidazothiazole derivatives (**10a-p**) in regard to dabrafenib (**II**). Both scaffolds maintained the same binding mode with conserved amino acids in V600E B-Raf active site (Lys 483, Leu 505, Cys 532 and Phe 595).

The synthesis of new derivatives (**10a-p**) is shown in **Scheme 1**. The incorporated side chain (**3a-p**) were prepared by reaction of appropriate diamines (**1a,b**) and different substituted benzene sulfonyl chlorides (**2a-h**) though nucleophilic substitution reaction mechanism[23]. Compound **6** was obtained by condensation of compound **4** with 2-aminothiazole (**5**). Cross-coupling reaction of compound **6** with aryl halide compound (**7**) is accomplished through Heck reaction[24, 25] to give compound **8**. Treatment of compound **8** with oxone led to oxidation of SMe moiety to afford the key intermediate (**9**). Final target compounds (**10a-p**) were provided by reaction of compound **9** with appropriate amine-based side chain (**3a-p**) in presence of base followed by reduction of NO_2 group in presence of Pd/C under H_2 atmosphere.



Scheme 1. Reagents and conditions. a,TEA, DCM, 0 °C-rt, 8 h; **b,** EtOH, reflux, 18 h; **c,** $Pd(OAc)_2$, Ph_3P, K_2CO_3, DMF, 80 °C, 8 h; **d,** Oxone, $MeOH/H_2O$, rt, 9 h; **e,** DIPEA, DMSO, 90 °C, 8 h; **f,** H_2, Pd/C, MeOH, rt,9 h.

In vitro inhibitory activity on mutated B-Raf kinase enzyme (V600E B-Raf) was evaluated for the synthesized derivatives. The test was measured at 10 doses of tested compounds with serial dilution (3-fold) at 1 μM. An IC_{50} value higher than 1 μM was estimated based on the best curve fitting available. The IC_{50} values were summarized in **Table 1**.

The results showed that all the synthesized compounds exhibited potent inhibitory activities against V600E B-Raf kinase enzyme in nanomolar level. Compounds **10l**, **10n** and **10o** exhibited more potent inhibitory activities (IC_{50} = 1.20, 4.31 and 6.21 nM, respectively) than that of other synthesized derivatives as well as vemurafenib (**I**, IC_{50} = 31 nM). Moreover, they approached the inhibitory activity of dabrafenib (**II**, IC_{50} = 0.5 nM). The results revealed that the new substituted group (NH_2) has a potential biological impact in inhibiting V600E B-Raf enzyme. Moreover, compounds with electron withdrawing substitution in the terminal phenyl ring of side chain enhanced the enzyme inhibitory effect (**10e**, 4-Cl; **10g**, 4-F; **10i**, 3-F; **10k**, 4-CF_3; **10n**, 4-Br and **10o**, 4-F). In addition, compounds with propylene spacer-based side chain (**10i-p**) showed higher activities than that of ethylene linker-based derivatives (**10a-h**). It was suggested that the propylene linker affords a proper molecular distance between the central scaffold and the phenyl ring of side chain in order to be brought into the hydrophobic pocket of V600E B-Raf kinase enzyme active site.

Table 1. *In vitro* enzyme assay data of target compounds.

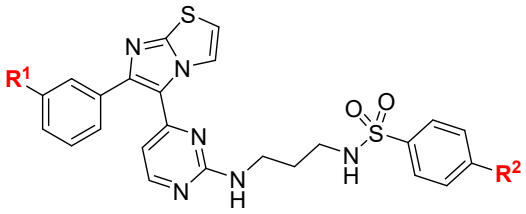
Compound	n	Ar	V600E B-Raf IC_{50}[a]
10a	1	3-FPh	28.30
10b	1	4-MePh	59.10
10c	1	4-CF_3Ph	141.00
10d	1	4-OMePh	23.40
10e	1	4-ClPh	16.70
10f	1	4-BrPh	73.70
10g	1	4-FPh	12.70
10h	1	1-Naph	152.00
10i	2	3-FPh	13.50
10j	2	4-MePh	ND[b]
10k	2	4-CF_3Ph	11.40
10l	2	4-OMePh	1.20
10m	2	4-ClPh	20.40

Compound	n	Ar	V600E B-Raf IC_{50}[a]
10n	2	4-BrPh	4.31
10o	2	4-FPh	6.21
10p	2	1-Naph	24.50
Vemurafenib (**I**)	-	-	31.00
Dabrafenib (**II**)	-	-	0.50

[a]nM
[b]Not determined

In addition, the results revealed that the amino-based derivatives were more potent than the previously reported imidazothiazole derivatives (fluoro-based[22] and nitro-based[26], **Table 2**). The results showed that substitution at position 3 of terminal phenyl ring with electron donating group (NH_2) afforded greater inhibitory activities than electron withdrawing groups (F and NO_2). From these findings, it can be suggested that the electron donation at that position is important in V600E B-Raf inhibition. Moreover, The high activity of the most active compound (**10l**, IC_{50} = 1.20 nM) can be referred to the propylene spacer along with 4-methoxy phenyl ring in the side chain which afford an outstanding chemical environment for that compound to possess high affinity and stable complex with B-Raf active site.

Table 2. *In vitro* enzyme assay data of most active compounds (**10l**, **10n** and **10o**) and previously reported imidazothiazole derivatives with similar side chains against V600E B-Raf kinase.



R^2	V600E B-Raf IC_{50} (nM)		
	R^1		
	NH_2	F[a]	NO_2[b]
OMe	1.20 (**10l**)	25.10	131.00
Br	4.31 (**10n**)	9.30	20.00
F	6.21 (**10o**)	ND[c]	35.00

[a][22]
[b][26]
[c]Not determined

In vitro cellular activity was identified for the synthesized compounds. All target derivatives were tested initially at a single high dose (10 μM) in the full NCI-60 cancer cell line panel. The mean percent inhibition were summarized in **Table 1s-10s**.

All compounds showed relative cytotoxic activities over NCI-60 cancer cell lines. However, a number of tested compounds exhibited potent values against melanoma cell line (UACC-62,V600E B-Raf-based human cancer cell line, **Table 3**). In addition, derivatives with propylene spacer exhibited better potencies than that of ethylene spacer (**Figure 3**).

Table 3. *In vitro* one-dose cytotoxic assay of most active compounds (**10i-o**) against NCI-melanoma cell line (UACC-62).

Compound	UACC-62 (%)
10i	78.07
10j	59.62

Compound	UACC-62 (%)
10k	100.00
10l	47.03
10m	13.40
10n	3.91
10o	77.80
10p	57.39

Compound **10k** showed the most potent cytotoxic activity among the tested compounds. It showed mean percent inhibition value of 100% over melanoma cell lines. The relative potencies of the synthesized compounds over NCI-60 cancer cell lines were suggested to be referred to the polarity of the new substituted group (NH_2) which may be incorporated in the poor cell penetrating properties. This type of polarity can be masked in a form of prodrug in future molecular and structural optimization.

Compound **10k** (most potent derivative in single dose assay) was selected to be tested in five-dose assay to evaluate its mean GI_{50} values against NCI-60 cell lines (**Table 11s** and **4**). The results showed that compound **10k** showed high inhibitory activities in micromolar level all over the NCI-60 cell lines. It exhibited higher inhibitory activities against breast, leukemia, melanoma and prostate cancer (mean GI_{50} = 3.28, 3.03, 3.80 and 3.34 μM, respectively).

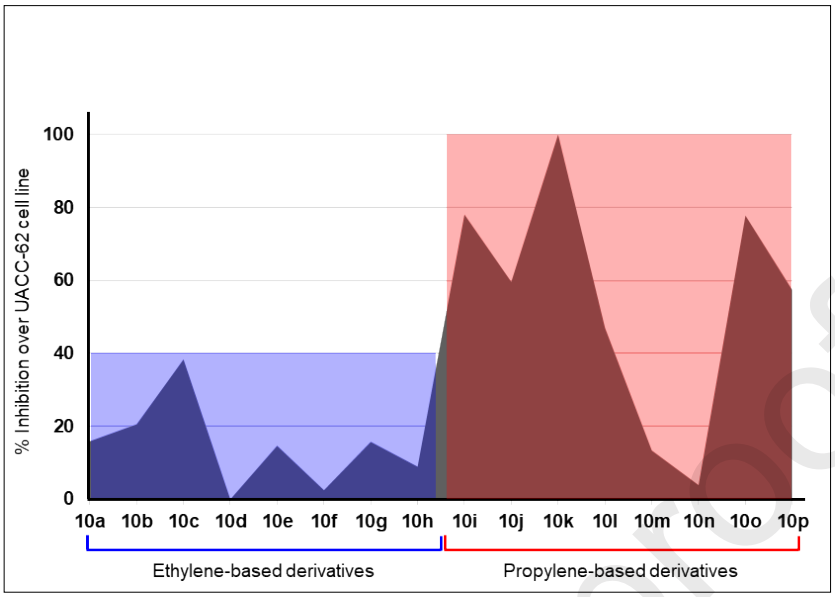


Figure 3. % Inhibition of compounds with ethylene spacer (blue color) and propylene spacer (red color) against NCI melanoma cell line (UACC-62).

Table 4. *In vitro* five-dose cytotoxic assay (mean GI_{50} and mean TCI values in μM) of compound **10k** against NCI-60 cancer cell lines.

NCI-60 cell lines	**Mean GI_{50}**	**Mean TGI**
Breast cancer	3.28	28.46
CNS cancer	5.58	29.77
Colon cancer	4.28	32.17
Leukemia	3.03	17.41
Melanoma	3.80	19.70
Non-small cell lung cancer	5.61	52.43
Ovarian cancer	5.26	44.42
Prostate cancer	3.34	23.75
Renal cancer	5.08	44.05

In order to investigate the binding mode of the new designed compounds in V600E B-Raf kinase active site, molecular docking study was conducted for both dabrafenib (**II**) and the most active derivatives (**10i,k,l,n** and **10o**) into the V600E B-Raf pocket using Molecular Operating Evnvironment (MOE 2014).

In molecular docking analysis, the X-ray structure of V600E B-Raf with dabrafenib (**II**) as native ligand (PDB ID: 4XV2)[27] was used. The X-ray structure of B-Raf kinase domain consists of two lobes, small N-terminal lobe (orients the ATP molecule by antiparallel β-sheet structure) and large C-terminal lobe (binds to MEK). The catalytic site is located between these two lobes that were occupied by most B-Raf kinase inhibitors. Most B-Raf kinase mutation (Val600Glu) occur in the activation segment (P-loop)[28].

The docking protocol of dabrafenib (**II**) in the enzyme active site was validated with route mean square deviation (RMSD) of 1.8883 and virtual ligand screening (VLS) score of -16.0501 kcal/mol.

The tested derivatives showed distinct interactions (arene and H-bonding interactions) with the conserved amino acids (Lys 483, Leu 505, Cys 532, Phe 583 and Phe 595) (**Table 5**).

Table 5. Molecular docking results of tested compounds and dabrafenib into V600E B-Raf kinase domain

Compound	**Binding score**[a]	**Amino acids**[b]				
		Lys 483	**Leu 505**	**Cys 532**	**Phe 583**	**Phe 595**
Dabrafenib (**II**)	-16.0501	SO_2 (2.88 Å)	DiFPh (π)	NH_2 (3.06 Å) N Pyrimid (2.91 Å)	-	SO_2 (2.87 Å)
10i	-16.0956	-	-	-	-	SO_2 (2.98 Å)
10k	-16.3698	NH (3.43 Å) SO_2 (2.72 Å)	-	-	Pyrimid (π)	4-CF_3Ph (π)
10l	-15.4919	NH (3.27 Å) SO_2 (2.80 Å)	4-OMePh (π)	NH_2 (3.15 Å)	-	4-OMePh (π)
10n	-15.3194	SO_2 (3.50 Å) SO_2 (2.59 Å)	-	NH_2 (2.94 Å)	-	4-BrPh (π)
10o	-14.1222	SO_2 (2.78 Å)	4-FPh (π)	-	Pyrimid (π)	-

[a]kcal/mol

[b]π, arene interaction

The results showed that most of the tested compounds preserved the same binding mode with that of dabrafenib. Most of compounds showed H-bond interactions between sulfonamide moiety in the side chain and Lys 483 amino acid residue.

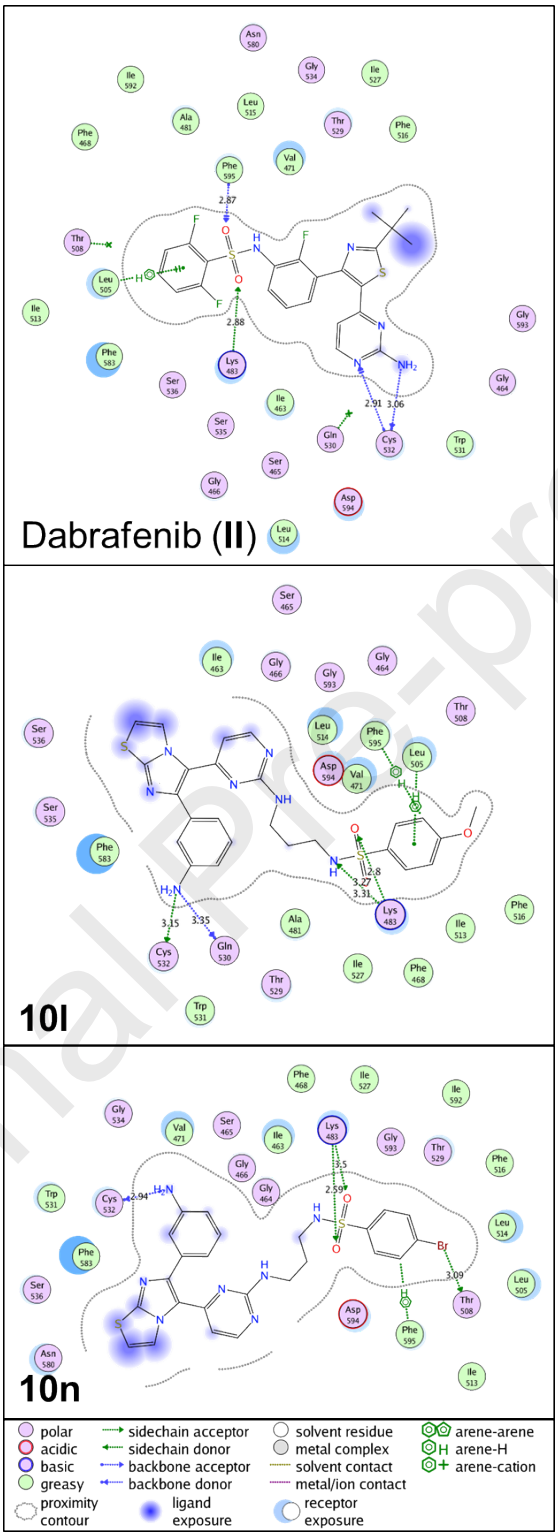


Figure 4. 2D ligand interaction of dabrafenib (**II**) and tested compounds (**10l** and **10n**) with V600E B-Raf kinase domain.

In addition, the terminal phenyl ring of side chain exhibited hydrophobic interactions with Leu 505 and Phe 595 amino acids in the active site. Moreover, the central pyrimidine ring of the tested compounds contributed the molecular binding through arene interaction with Cys 532. Furthermore, the most active compounds, **10l** and **10n** (IC_{50} = 1.20 and 4.31 nM, respectively), showed additional H-bond interaction between the new substitution (NH_2 group) and Cys 532 amino acid residue of V600E B-Raf kinase active site (**Figure 4**). From the molecular docking study, it was revealed that the tested derivatives conserved the binding interactions of dabrafenib.

In summary, a number of new series of NH_2-based imidazothiazole derivatives was synthesized and evaluated for their *in vitro* enzyme inhibitory effect as well as *in vitro* cytotoxic activity. It was investigated that the new NH_2-substituted derivatives preserved the V600E B-Raf kinase enzyme inhibitory activity. Compounds **10l**, **10n** and **10o** were the most potent compounds against V600E B-Raf kinase enzyme. In addition, compound **10k** (*p*-CF_3 substituted phenyl ring with propylene linker-based side chain) was the most active compounds among the synthesized derivatives against *in vitro* human cancer cell lines. Both *in vitro* biological assays showed that derivatives with propylene spacer in the incorporated side chain had a greater activities than that of ethylene spacer-based derivatives. Moreover, derivatives with 4-OMe, 4-Br and 4-F substituted phenyl ring in side chain (**10l**, **10n** and **10o**, respectively) had higher enzyme inhibitory activities among the synthesized compounds. Furthermore, the potent enzyme inhibitory activities of new NH_2-based derivatives were explained by the additional binding to V600E B-Raf kinase enzyme active site *via* additional H-bond interaction(s) with Cys 532 amino acid residue. Finally, these results afforded a new NH_2-based imidazothiazole derivatives for further molecular and structural optimization.

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Maryland, USA, for testing the antiproliferative activity of the target compounds against 60 cancer cell lines of nine different cancer types.

Conflict of Interest

The authors declare no conflict of interest.

Appendix A – Supplementary data

The supplementary data (the experimental details of synthesis, *in vitro* cytotoxicity assay, *in vitro* enzyme assay, molecular docking and characterization data of all synthesized compounds) related to this article can be found online at https://doi.org/××.××××/j.bmcl.×

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Highlights

- New imidazothiazole derivatives were designed and synthesized.
- *In vitro* enzyme inhibitory assay was evaluated on V600E B-Raf kinase.
- *In vitro* cytotoxicity studies was performed over NCI-60 cancer cell lines.
- Molecular docking was conducted to explore the mode of interactions with enzyme.
- Compounds **10l**, **10n** and **10o** showed potent inhibitory activities.

Graphical abstract