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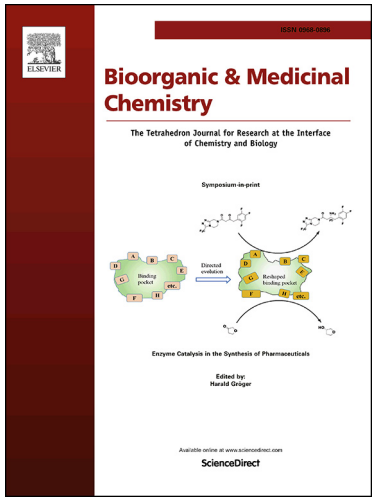

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Anticancer profile of newly synthesized BRAF inhibitors possess 5-(pyrimidin-4-yl)imidazo[2,1-b]thiazole scaffold

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Abstract

In this work, a new series of imidazo[2,1-*b*]thiazole was designed and synthesized. The new compounds are having 3-fluorophenyl at position 6 of imidazo[2,1-*b*]thiazole and pyrimidine ring at position 5. The pyrimidine ring containing either amide or sulphonamide moiety attached to a linker (ethyl or propyl) at position 2 of the pyrimidine ring. The final compounds were selected by NCI for in vitro cytotoxicity screening. Most derivatives showed cytotoxic activity against colon cancer and melanoma cell lines. In addition, IC_{50}s of the target compounds were determined over A375 and SK-MEL-28 cell lines using sorafenib as positive control. Compounds**12b, 12c, 12e, 12f, 15a, 15d, 15f, 14g and 15h** exhibited superior activity when compared to sorafenib. The most potent compounds were tested against wild type BRAF, v600e BRAF, and CRAF. Compound **15h** exhibited a potential inhibitory effect against^{V600E}BRAF (IC_{50} = 9.3 nM).

Keywords

Imidazo[2,1-*b*]thiazole; Anticancer; Colon cancer; Melanoma; BAF inhibitors

Introduction

Cancer is a type of disease that causes threat to human health as well as human life.[1-6] In recent years, the morbidity rate of cancer is increased.[2-4, 7] Cell proliferation is triggered through the activation of MAPK signalling pathway.[8-10]The activation of MAPK signalling pathway is regulated by a cascade of protein kinases phosphorylated successively and control a number of cellular activities such as; cell proliferation, differentiation and migration.[10-13]

RAF kinases (ARAF, BRAF and CRAF) play an important role in MAPK signalling pathway activation.[14] High frequency of RAF kinases mutation was investigated to cause cancer disease.[15] Among the RAF kinase subtypes, BRAF is the major activator of MAPK signalling pathway. [16-

[18]The most common mutation in BRAF is the substitution of valine (V) by glutamate (E) at residue 600 in the BRAF kinase domain (^{V600E}BRAF)[14, 19, 20].^{V600E}BRAF was identified in 8% of all cancer types, such as; thyroid cancer (30-70%), melanoma (60%) and colorectal cancer (10%).[15,20-25] Therefore, BRAF kinase enzyme is considered a crucial biological target in treating and controlling the cancer disease.[26, 27]

Both vemurafenib (**I**) and sorafenib (**II**) (**Figure 1**) are FDA-approved drugs in the treatment of melanoma through inhibition of mutated BRAF kinase enzyme (^{V600E}BRAF).[28-33]On the other hand, imidazothiazole-based scaffold (compounds **III**, and **IV**) (**Figure 1**) has an attracted significant interest as lead compounds for molecular optimization to have potent anticancer activity. Where, they exert their action through inhibiting ^{V600E}BRAF kinase enzyme.[34-36]

In the present research, based on the aforementioned data, a new series of imidazo[2,1-*b*]thiazole derivatives was designed and synthesized. The final target compounds possess the sub-structures found in compounds **III** and **IV** in order to enhance their anticancer activity and increase their BRAF inhibitory effect to add more drug candidates to the medicinal chemistry library in the field of anticancer agents especially in the area of BRAF kinase inhibitors. The new compounds are having 3-fluorophenyl at position 6 of imidazo[2,1-*b*]thiazole and pyrimidine ring at position 5. The pyrimidine ring containing either amide or sulphonamide moiety attached to a linker (ethyl or propyl) at position 2 of the pyrimidine ring.

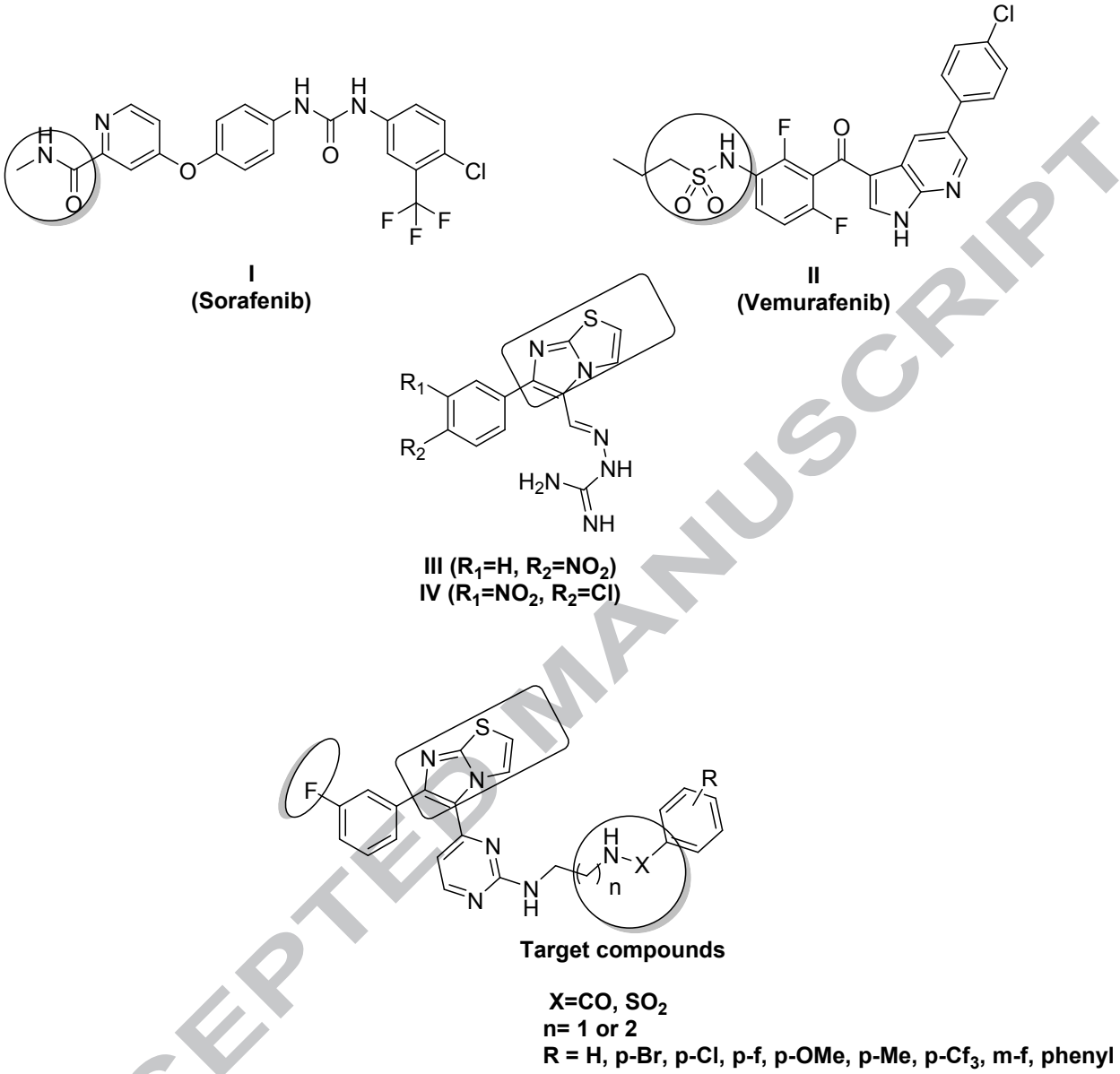


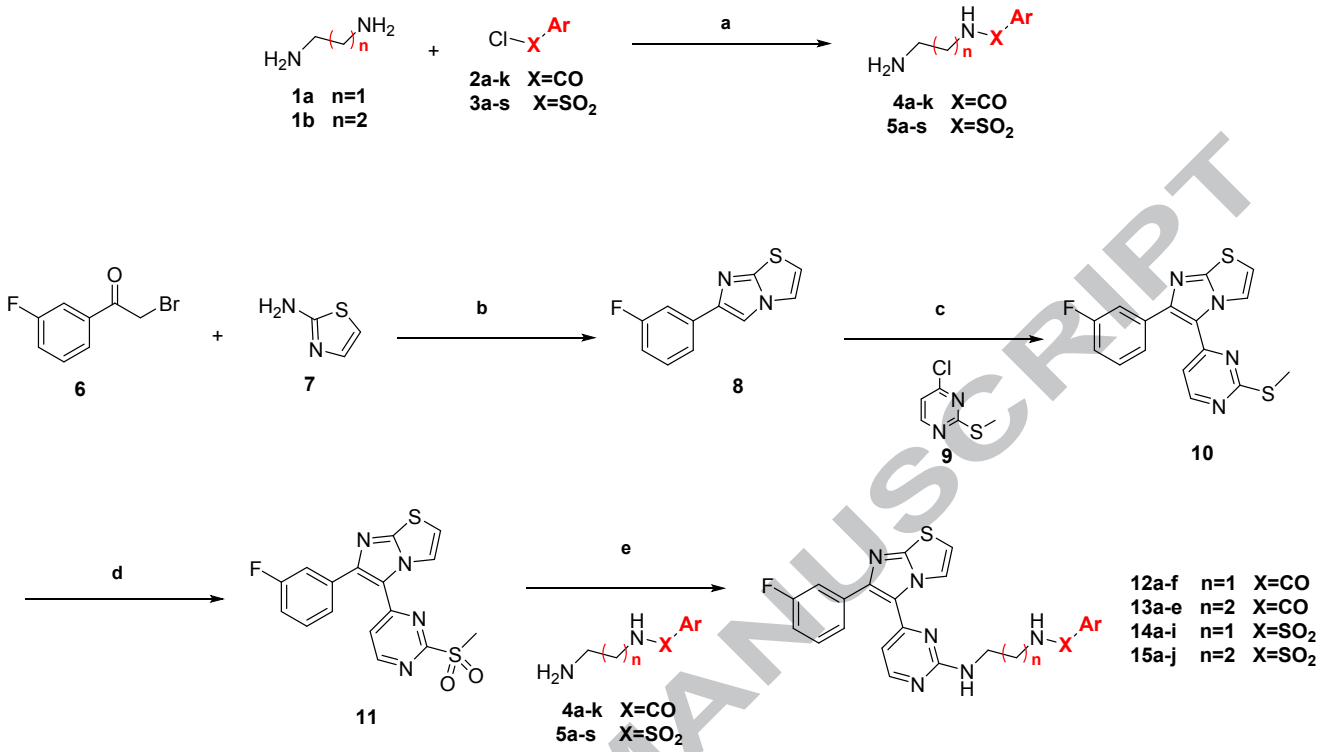
Fig.1. Chemical structure of reported BRAF inhibitors and final target compounds

2. Results & discussion

2.1. Chemistry

The final target compounds **12a-f**, **13a-e**, **14a-i** and **15a-j** were synthesized as depicted in **Scheme 1**. The first step is condensation and cyclization of 2-bromo-1-(3-fluorophenyl)ethan-1-one(**6)** with 2-aminothiazole (**7)** in absolute ethanol under refluxed condition to provide6-(3-

fluorophenyl)imidazo[2,1-b]thiazole(**8)**. ^{1}H NMR showed an additional signals at δ 6.99 and 6.85 ppm attributed to the thiazole protons. In addition to disappearance of methyl protons signals of compound **6** at δ 4.56 ppm. C. Mizoroki-Heck cross-coupling[40] of compound **8** with 4-chloro-2-(methylthio)pyrimidine(**9)** was accomplished in presence of palladim acetate as a catalyst, triphenyl phosphine as a ligand and potassium carbonate as a base and at 80 °C to give 6-(3-fluorophenyl)-5-(2-(methylthio)pyrimidin-4-yl)imidazo[2,1-b]thiazole (**10)**. Oxidation of thiomethyl group of compound **10** was achieved by reaction with oxone to afford 6-(3-fluorophenyl)-5-(2-(methylsulfonyl)pyrimidin-4-yl)imidazo[2,1-b]thiazole(**11)**. ^{1}H NMR showed deshielded signals at δ 3.47 ppm attributed to the methyl sulfonyl group ($-SO_2CH_3$). The second part was the synthesis of the side chain. Reaction of excess (10 mole equivalent) ethylene diamine (**1a**) or propylene diamine (**1b**) with appropriate acid chloride **2a-k** or benzene sulfonyl chloride **3a-s** lead to formation of amide side chain **4a-k** and sulfonamide side chain **5a-s.**Final target compounds **12a-f**, **13a-e**, **14a-i** and **15a-j** were provided by reaction of compound **11** with appropriate side chains **4a-k** and **5a-s** in DMSO and in presence of DIPEA at 80 °C .



Reagents and conditions: a) MC, 0 °C-rt, 18 h., 60-80%; b) EtOH, reflux, 18 h., 75%; c) $Pd(OAc)_2$, K_2CO_3, Ph_3P, DMF, 80 °C, 18 h., 30%; d) Oxone, $MeOH/H_2O$, rt, 18 h., 90%; e) DIPEA, DMSO, 100 °C, 18 h., 45-80%

Scheme 1. Synthesis of compounds 12a-f, **13a-e**, **14a-i** and **15a-j.**

2.2. Biological evaluation

2.2.1. NCI 60 cell lines one dose test

The final target compounds were submitted to the NCI, USA for in vitro antiproliferative screening against a 60 cell lines panel belonging to nine cancer types (leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer) and compounds **12a,b,d-f, 13a-c,e, 14a, b, d, f-i** and **15a-e, g-j** were selected to be tested at single dose of 10 μM. The mean % inhibition of each of the tested compounds against the cancer cell lines are shown in **Figure 2** and **Table 2s**.

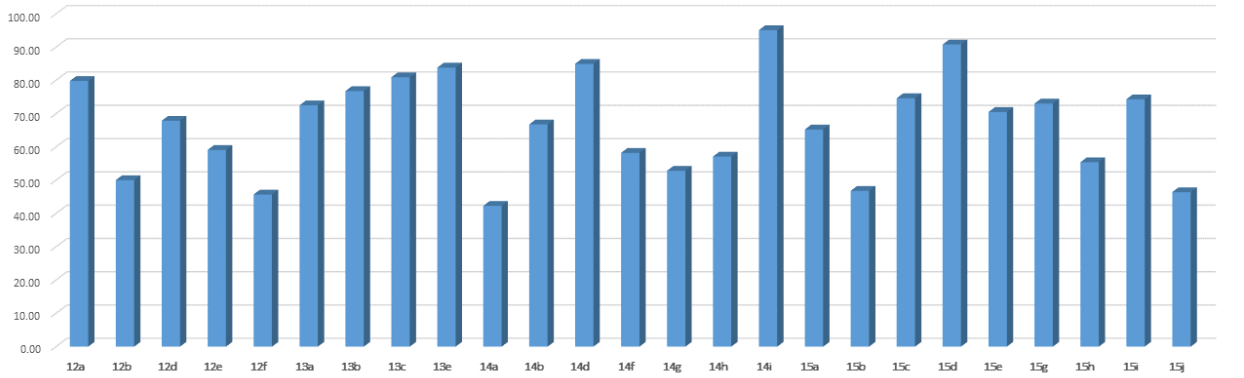


Fig. 2. Mean growth percent of the final target compounds against NCI 60 cell lines.

All final target compounds reduced the mean growth of cancer cell lines. In the amide series, compounds with ethyl linker between pyrimidine ring and amide group were more potent compared to compounds with propylene linker. Compounds **12b** (unsubstituted phenyl) and **12f** (2,6-diflourophenyl) inhibited the mean growth percentage to half the control value. Compound **12e** (p-Cl phenyl) reduced cell growth by 40%. Regarding the final compounds possess sulfonamide moiety, compounds **14a** (unsubstitutedphenyl) showed the highest percent inhibition among all compound with value 60% followed by **15b** (m-f phenyl) with 55% growth inhibition. Similarly, to amide containing compounds, sulfonamide derivatives with ethylene linker were more potent comparing to their propylene analogues. Also, compounds with electron withdrawing group **14f, 14g,14h** and **15b** or unsubstituted **14a** were stronger compared to one with bulky group such as naphthyl**14i** Figure 2.

The sub-panel deep analysis (Table 2s) showed interesting results, the highest percent inhibition was exhibited against two sub-panel colon cancer sub-panel and melanoma sub-panel. Compounds **12b, 12e, 12f, 15b** and **15h** exhibited the highest percent inhibition against melanoma cell lines with mean percent inhibition 63%, 55%, 65%, 62% and 53%, respectively. On the other hand, compounds **14a, 14f, 14g, 14h** and **15j** had the highest percent inhibition against colon cancer cell lines with mean percent inhibition 66%, 52%, 56%, 53%, and 77%, respectively.

The individual cell line activities of compounds **12b, 12f, 14a, 15b,** and **15j** are represented in **Table 1**. Compound **12b** showed the highest percent inhibition against COLO 205, MALME-3M and M14 with percent inhibitions 89.59%, 76.29% and 71.56%. Compound **12f** exhibited 82.85% inhibition against MDA-MB-435. Compound **14a** inhibited 95.1% of IGROV1 growth and 82.5 % against MDA-MB-435. Compound **15b** showed a lethal effect on T-47D cell line with percent inhibition 102% and inhibited UACC-62, SK-MEL-5 and MOLT-4 with percent inhibition 93.64%, 86.49%, and 90.06%, respectively. Finally, compound **15j** inhibited 98.03% and 95.95% of HT29 and MDA-MB-231/ATCC cell lines.

Table 1: *In vitro* cytotoxic activity (%inhibition) of the most active compounds **12b**,**f**, **14a** and **15b,j** against different human cancer cells.

Cell name	**Compound No.**				
	12b	**12f**	**14a**	**15b**	**15j**
Leukemia					
CCRF-CEM	59.07	57.25	66.42	75.33	61.54
HL-60(TB)	16.32	13.59	36.91	59.53	46.1
K-562	55.98	59.79	76.06	79.92	84.75
MOLT-4	53.49	64.12	83.43	**90.06**	70.7

Non-Small Cell Lung Cancer					
A549/ATCC	73.27	70.86	74.83	50.73	54.38
NCI-H226	55.69	59.33	65.49	76.76	63.23
NCI-H460	71.18	75.23	74.11	41.68	80.15
Colon Cancer					
COLO 205	**89.59**	80.76	75.85	76.59	78.46
HCC-2998	26.15	29.63	33.65	ND	83.67
HCT-116	74.39	75.13	77.29	52.03	67.58
HCT-15	65.37	68.91	74.20	77.45	81.95
HT29	74.19	79.63	76.84	69.40	**98.03**
Melanoma					
LOX IMVI	64.92	67.62	63.70	61.01	79.08
MALME-3M	**76.29**	68.43	31.49	36.76	21.26
M14	**71.56**	70.70	58.60	71.37	57.32
MDA-MB-435	73.04	**82.65**	82.58	75.96	77.38
SK-MEL-5	74.40	82.85	80.92	**86.49**	68.17
UACC-62	88.82	89.70	75.06	**93.64**	75.67
Ovarian Cancer					
IGROV1	83.48	87.93	**95.10**	81.11	77.73
OVCAR-4	44.57	39.14	60.01	73.22	59.85
OVCAR-8	53.16	55.83	66.12	81.57	61.50
NCI/ADR-RES	35.08	43.09	53.74	82.39	52.90
Renal Cancer					
786-0	52.65	55.81	52.61	33.73	47.14
ACHN	70.95	73.99	74.02	57.46	65.32
CAKI-1	63.60	65.45	60.94	58.46	70.89
UO-31	77.25	79.17	84.64	71.76	79.97

Prostate Cancer					
PC-3	37.14	42.97	66.86	72.91	58.80
Breast Cancer					
MCF7	76.29	82.53	78.26	66.32	62.63
MDA-MB-231/ATCC	34.93	18.80	34.03	24.14	**95.95**
T-47D	65.49	73.30	81.18	**102.25**	81.63

2.2.2. Antiproliferative activity against A375 and SK-MEL-28

In order to determine the potency of the final target compounds,**12b-f**, **13d-f**, **14a-h**, **15a-d** and **15f-I** were evaluated for their antiproliferative (IC_{50}) effect against melanoma cell lines (A375 and SK-MEL-28) using sorafenib as positive control. The IC_{50} values (μM) of the tested compounds against melanoma cell lines are showed in **Table 2**. The tested compounds exhibited significant inhibitory effect against both A375 melanoma cell line (2.57-15.44 μM) and Skmel28 melanoma cell line (6.60-19.02 μM) compared to sorafenib (7.88 and 9.45 μM, respectively). Regarding A375 cell line, compounds **12b** (unsubstituted phenyl), **12c** (p-methyl), **12e** (p-Cl), **12f** (2,6-diflouro), **14d** (p-CF3), **15a** (unsubstitutedphenyl), **15d** (p-CF3), **15f** (p-OMe), **15g** (p-Cl) and **15h**(p-Br) were more potent thensorafenib with IC_{50}s 5.06, 5.88, 2.57, 2.70, 7.44, 6.60, 4.09, 5.51, 5.90 and 7.04 μM. Generally, compounds with amide moiety were more potent then compounds with sulfonamide. Among amide derivatives, compounds with ethylene linker showed lower IC_{50}s then compounds with propylene linker and compounds with electron withdrawing substitution were more potent then electron donating group. Compound **12e** is the most active compound with IC_{50} 2.57 μM. For sulfonamide derivatives, compounds with propylene linker were more potent then compounds containing ethylene linker. Similarly,

compounds with electron withdrawing groups were more potent then compounds having electron donating group and compound **15d** was the most potent compound among these derivatives with IC_{50} 4.09 μM.

On the other hand, compounds **12d, 12e, 14d, 14h, 15a, 15b, 15f, 15g** and **15h** were more potent thensorafenib against SK-MEL-28 cell line with IC50s 9.26, 8.16, 8.45, 9.45, 6.85, 8.55, 8.98, 8.45 and 9.40 μM. As in A375 cell line compounds with amide moiety and ethylene linker were more potent compared to propylene derivatives. While for sulfonamide compounds, propylene derivatives were more potent then ethylene compounds. There was no significant difference between both amide and sulfonamide derivatives on SK-MEL-28 cell line.

Table 2: *In vitro* cytotoxic activity (IC_{50} μM) of target compounds **12b-f**, **13d-f**, **14a-h**, **15a-d** and **15f-i** against human melanoma cell lines (**A375** and **SK-MEL-28**) using sorafenib as standards.

Compound	A375	SK-MEL-28	Compound	A375	SK-MEL-28
Sorafenib	7.88	9.45	**14e**	12.63	12.63
12b	**5.06**	17.04	**14f**	18.57	18.57
12c	**5.88**	18.77	**14g**	13.52	13.52
12d	8.71	**9.26**	**14h**	9.45	**9.45**
12e	**2.57**	**8.16**	**15a**	**6.60**	**6.85**
12f	**2.70**	11.44	**15b**	13.72	**8.55**
13d	13.72	> 20	**15c**	8.38	9.50
13e	14.90	> 20	**15d**	**4.09**	11.65

13f	11.21	13.67	**15f**	**5.51**	**8.98**
14a	11.02	19.02	**15g**	**5.90**	**8.45**
14b	14.91	18.28	**15h**	**7.04**	**9.40**
14c	15.44	> 20	**15i**	14.48	> 20
14d	**7.44**	**8.45**			

Finally, in order to check the toxicity of the new synthesized compounds, the most potent compounds were tested over L132 cell line (as normal human embryonic epithelial cells). All tested compounds had higher IC_{50} over normal cell line then cancer cell lines. All compounds had an IC_{50} more then 150 uM. The most potent compound against normal cell line was compound **12f** with IC_{50} 198 uM , which is 18 folds compared to its IC50 over A375 and SK-MEL-28 cell lines (Table 3)

Table 3: IC_{50} of most potent compound over the normal cell line (L132)

Compound	IC_{50} (uM)
12b	200
12c	245
12f	198
15a	>400
15d	320

2.2.3. In vitro kinase assay

As the imidazthiazole-based derivatives were reported as BRAF kinase inhibitors[35, 36, 40], among the most potent antiproliferative compounds, compounds **12b**, **15c,d** and **15f-h** were evaluated

for their *in vitro* kinase assay against ^{WT}BRAF, ^{V600E}BRAF and CRAF. The results are depicted in **Table 4**.

The results revealed that the tested compounds exhibited more inhibitory effect against ^{V600E}BRAF (9.30-89.00 nM) than that of ^{WT}BRAF (22.90-182.00 nM) and CRAF (18.60-312.00 nM).Moreover, all tested compound showed nanomolar IC_{50} and compound **15h** showed that most potential inhibitory effect against ^{V600E}BRAF (9.30 nM). Compounds with sulfonamide moiety were more potent then compounds with amide side chain over the three enzymes. In addition , the presence of electron withdrawing groups enhanced the inhibitory effect compared to unsubstituted derivatives. The order of activity was bromo>chloro>triflouromethyl. Compound 15f with para methoxy group showed similar activity against both v600e BRAF and CRAF. Amide containing derivatives exhibited high selectivity for mutant BRAF compared to wild type and CRAF.

Table 4: Kinase inhibitory effect (IC_{50}nM) of target compounds **12b**, **15c,d** and **15f-h** against ^{WT}BRAF, ^{V600E}BRAF and CRAF.

Compound	^{WT}BRAF	^{V600E}BRAF	CRAF
12b	162.00	37.00	312.00
12e	105.02	27.20	120.1
12f	95.30	33.10	102.00
14d	85.20	22.30	88.40
15c	182.00	89.00	143.00
15d	63.00	26.00	40.00
15f	55.10	25.10	26.10

15g	49.60	16.20	34.00
15h	22.90	9.30	18.60

2.3. Molecular docking

The X-ray crystal structure of BRAF kinase enzyme domain with dabrafenib (PDB ID: 5CSW)was identified (**Figure 3**). Analysis of the docking results revealed that the dabrafenib-BRAF kinase domain complex had low root mean square deviation, RMSD (0.4737) that proved valid docking protocol with dock score (-17.8199 kcal/mol, **Table 5**).The native ligand (dabrafenib) showed H-bonding with Lys 483, Cys 532 and Phe 595 amino acids. In addition, it exhibited both arene-cation and arene-arene interactions with Lys 483 and Phe 583 amino acids, respectively. The binding affinity of the ligand was evaluated with energy score (S, Kcal/mol) (**Table 5**). Low dock score energy indicates good affinity.

Table 5: Docking results of target compounds **12b**, **15c**, **15d, 15f, 15g**and **15h** with BRAF kinase enzyme domain (PDB ID: 5CSW):

Compound	**Energy score S (Kcal/mol)**	**Amino acid**	**Binding group**	**Interaction**	**Hydrogen bond length (Å)**
Native ligand	-17.8199	Lys 483	SO_2	H-bond	2.74
		Lys 483	Phenyl ring	Arene cation	
		Cys 532	NH_2	H-bond	2.95
		Cys 532	N pyrimidine	H-bond	2.87
		Phe 583	Pyrimidine ring	Arenearene	
		Phe 595	SO_2	H-bond	3.04
12b	-27.9025	Lys 483	Phenyl ring	Arene cation	

		Gly 534	NH amide	H-bond	1.89
		Phe 583	Pyrimidine ring	Arenearene	
		Cys 532	N pyrimidine	H-bond	3.15
		Gly 534	NH amide	H-bond	1.76
15c	-25.1258	Lys 483	SO_2	H-bond	2.86
		Phe 583	Pyrimidine ring	Arenearene	
		Phe 595	SO_2	H-bond	2.65
15d	-20.6763	Lys 483	SO_2	H-bond	2.74
		Phe 583	Pyrimidine ring	Arenearene	
		Asp 594	SO_2	H-bond	2.77
15f	-23.6009	Trp 531	Phenyl ring	Arenearene	
15g	-24.4202	Phe 583	Pyrimidine ring	Arenearene	
		Asp 594	SO_2	H-bond	2.43
15h	-27.4217	Asn 580	NH sulphonamide	H-bond	1.58
		Phe 583	Imidazole ring	Arenearene	

The docking study revealed that most of the target compounds mad molecular interactions with Lys 483, Leu 514, Trp 531, Cys 532, Gly 534, Lys 578, Asn 580, Phe 583, Asp 594 and Phe 595 amino acids. Moreover, all the target compounds shared the same binding groups towards BRAF kinase enzyme active site with H-bonding interaction (amide, sulphonamide and N pyrimidine chemical moieties) as well as arene-arene and arene-cation interactions (phenyl, naphthyl, imidazolyl and pyrimidinyl rings).

Analysis of the docking results revealed that most of the target compounds showed more molecular interactions with the BRAF active site than the native ligand. Moreover, target

compounds **12e**, **13a**, **14b**, **14h**, **14i**, **15e**, **15i** and **15j** exhibited four to five visible interactions with BRAF active site (-29.4200, -27.2361, -23.4021, -30.2736, -26.8178, -30.89.75, -25.4579 and -20.4652 kcal/mol) (**Figure 3**). In addition, it was revealed that the target compounds bearing sulphonamide chemical moiety (**14a-i** and **15a-j**) showed additional molecular interactions with the BRAF active site than that bearing amide group (**12a-f** and **13a-e**).

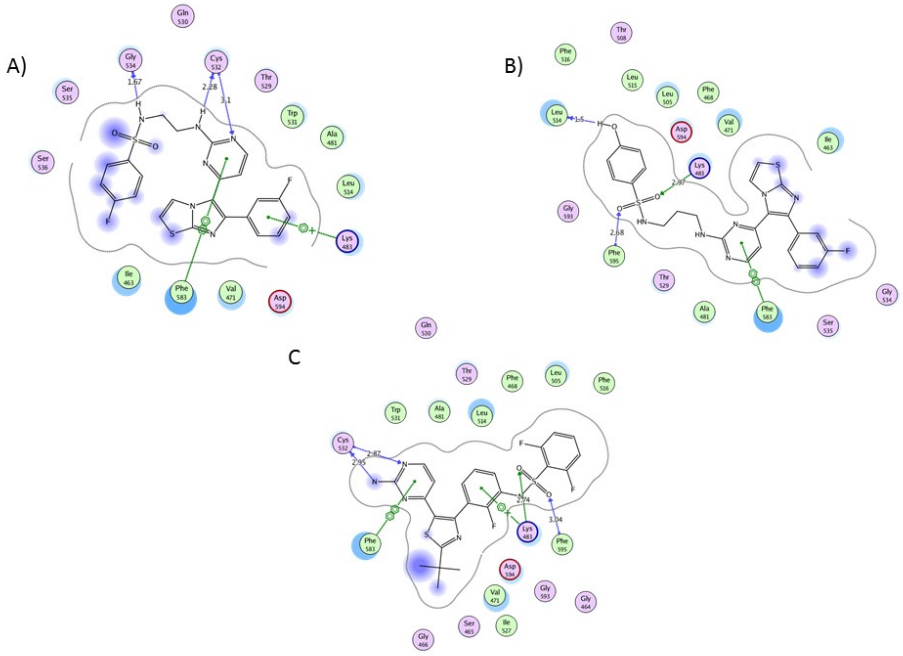


Fig.3. 2D representation of docking study output (PDB ID: 5CSW) A) 2D interaction of **14h** (native ligand) with BRAF kinase enzyme domain; B) 2D interaction of **15e** (native ligand) with BRAF kinase enzyme domain C) 2D interaction of dabrafenib (native ligand) with BRAF kinase enzyme domain.

3. Experimental

3.1. Chemistry

3.1.1. General

The intermediate compounds **8** and **11** as well as the target compounds **12a-f**, **13a-e**, **14a-i** and **15a-j** were purified by flash column chromatography using silica gel 60 (0.040-0.063 mm, 230-

400 mesh ASTM) and technical grade solvents. ^{1}H NMR and ^{13}C NMR analyses were carried out on a Bruker Avance 400 spectrometer using tetramethylsilane (TMS) as an internal standard. Melting points were measured on a Walden Precision Apparatus Electrothermal 9300 apparatus and were uncorrected. LC-MS analysis was conducted using the following system: Waters 2998 photodiode array detector, Waters 3100 mass detector, Waters SFO system fluidics organizer, Waters 2545 binary gradient module, Waters reagent manager, Waters 2767 sample manager, Sunfire™ C18 column (4.6 × 50 mm, 5 µm particle size); Solvent gradient = 95% A at 0 min, 1% A at 5 min; solvent A: 0.035% trifluoroacetic acid (TFA) in water; solvent B: 0.035% TFA in MeOH; flow rate = 3.0 mL/min; the AUC was calculated using Waters MassLynx 4.1 software. The solvents and liquid reagents were transferred using hypodermic syringes. All the solvents and reagents were purchased from commercial companies, and used as such.

3.1.2. Synthesis of N^{1}-sustituted ethane(propane)-1,2(3)diamine ***(4a-k and 5a-s):***

Synthesis of side chains (**4a-k** and **5a-s**) was carried out through a pathway previously reported[37].

3.1.3. Synthesis of 6-(3-fluorophenyl)imidazo[2,1-b]thiazole ***(8)***

A mixture of 2-bromo-1-(3-fluorophenyl)ethan-1-one (**6**, 9.6 g, 44.6 mmol) and 2-aminothiazole (**5**, 4.46 g, 44.6 mmol, 1 Eq) in absolute ethanol (60 ml) was dissolved, stirred and refluxed for 18 h. The reaction mixture was concentrated under reduced pressure. Ice-cold water (50 ml) was added followed by ammonia solution (30%, 100 ml). The reaction mixture was stirred at rt for 2 h. The formed precipitate was filtered off, washed with water (2 × 20 ml) and dried to give the crude solid product. The crude product was purified by column chromatography (hexane:ethyl acetate; 5:1) to give the titled product **8**.

Yield: 75%. m.p.: 91-2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H, Ar-H), 7.59 (d, J = 8.0 Hz, 1H, Ar-H), 7.56 (d, J = 8.0 Hz, 1H, Ar-H), 7.44 (d, J = 4.0 Hz, 1H, Ar-H), 7.37

(q, *J* = 8.0 Hz, 1H, Ar-H), 6.99 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.85 (d, *J* = 4.0 Hz, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.48 (Ar-C), 162.04 (Ar-C), 150.29 (Ar-C), 146.52 (Ar-C), 136.25 (Ar-C), 130.15 (Ar-C), 120.76 (Ar-C), 118.51 (Ar-C), 114.14 (Ar-C), 112.45 (Ar-C), 111.97 (Ar-C), 108.5 (Ar-C).LC-MS (m/z) calculated for $C_{11}H_7FN_2S$ (m/z): 218.03 found: 218.9 $(M + H)^+$.

3.1.4. Synthesis of 6-(3-fluorophenyl)-5-(2-(methylthio)pyrimidin-4-yl)imidazo[2,1-b]thiazole ***(10)***

In a three neck flask, 4-chloro-2-(methylthio)pyrimidine (**7**, 70.7 mg, 0.44 mmol, 1 Eq), potassium carbonate (60.8 mg, 0.44 mmol, 1 Eq), palladium acetate (19.8 mg, 0.09 mmol, 0.2 Eq) and triphenylphosphine (34.6 mg, 0.13 mmol, 0.3 Eq) were mixed with compound **8** (96 mg, 0.44 mmol, 1 Eq). Air was replaced by nitrogen. Anhydrous DMF (10 ml) was added and the mixture was purged with nitrogen several times. The reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was cooled and extracted between EA (20 ml) and water (10 ml). The organic layer was separated, dried over anhydrous sodium sulfate and evaporated. The crude residue was used in the next step without further purification.

3.1.5. Synthesis of 6-(3-fluorophenyl)-5-(2-(methylsulfonyl)pyrimidin-4-yl)imidazo[2,1-b]thiazole ***(11)***

To a solution of compound **10** (103 mg, 0.44 mmol) in methanol (10 ml), a solution of oxone (0.9 g, 1.32 mmol) in water (10 ml) was added dropwise at rt. The mixture was stirred at rt for 48 h. The reaction mixture was concentrated under reduced pressure. The reaction mass was extracted with dichloromethane (20 ml) and the organic layer was separated. The aqueous layer was extracted with dichloromehane (3 × 10 ml). The combined organic layers were dried over

anhydrous sodium sulfate and evaporated under reduced pressure. The crude residue was purified by column chromatography (hexane:ethyl acetate; 2:1) to give the titled products **11**.

Yield: 90%. m.p.: 188-90 °C. ^{1}H NMR (400 MHz, DMSO- d_6) δ 8.83 (d, J = 5.2 Hz, 1H, Ar-H), 8.63 (d, J = 4.4 Hz, 1H, Ar-H), 7.65 (d, J = 4.4 Hz, 1H, Ar-H), 7.55 (m, 3H, Ar-H), 7.43 (d, J = 5.6 Hz, 1H, Ar-H), 7.37 (t, J = 8.8 Hz, 1H, Ar-H), 3.47 (s, 3H, SO_2CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.92 (Ar-H), 163.96 (Ar-H), 161.53 (Ar-H), 158.89 (Ar-H), 156.74 (Ar-H), 153.75 (Ar-H), 150.23 (Ar-H), 136.72 (Ar-H), 131.58 (Ar-H), 125.58 (Ar-H), 122.24 (Ar-H), 119.95 (Ar-H), 118.91 (Ar-H), 116.62 (Ar-H), 116.51 (Ar-H), 116.41 (Ar-H), 116.26 (Ar-H), 116.04 (Ar-H), 40.01 (SO_2CH_3). LC-MS (m/z) calculated for $C_{16}H_{11}FN_4S_2$(m/z):374.03 found: 375.0 $(M + H)^+$.

3.1.6. General procedure for synthesis of 4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)-N-substituted pyrimidin-2-amine ***(12a-f, 13a-e, 14a-i and 15a-j)****:*

To a solution of compound **11** (0.26 mmol) in DMSO (3 ml), compounds **4a-k** and **5a-s** (0.39 mmol) (**Scheme 1, Table 1s**) and DIPEA (300 mg, 2.34 mmol) were added. The reaction mixture was stirred at 100 °C for 18 h. The reaction mixture was cooled and extracted between EA (20 ml) and water (10 ml)). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude residue was purified by column chromatography (hexane:ethyl acetate; 1:1) to give the titled products **12a-f**, **13a-e**, **14a-i** and **15a-j**.

N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)cyclohexanecarboxamide **(12a);**Yield: 75%. m.p.: 202-3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 2.3 Hz, 1H, Ar-H), 8.04 (d, J = 1.2 Hz, 1H, Ar-H), 7.35 (m, 3H, Ar-H), 7.07 (m, 1H, Ar-H), 6.95 (d, J = 2.2 Hz, 1H, Ar-H), 6.73 (s, 1H, NH), 6.48 (d, J = 3.1 Hz, Ar-H), 6.05 (s, 1H, NH), 3.61 (m, 2H, Aliph-H), 3.49 (m, 2H, Aliph-H), 2.02 (m, 1H, cyclohexyl), 1.70

(m, 4H, cyclohexyl), 1.23 (m, 2H, cyclohexyl), 1.19 (m, 4H, cyclohexyl).^{13}C NMR (100 MHz, $CDCl_3$) δ 177.06 (C=O), 162.54 (Ar-C), 157.55 (Ar-C), 156.77 (Ar-C), 152.08 (Ar-C), 148.30 (Ar-C), 136.90 (Ar-C), 130.18 (Ar-C), 124.97 (Ar-C), 122.04 (Ar-C), 121.02 (Ar-C), 116.15 (Ar-C), 115.44 (Ar-C), 112.94 (Ar-C), 107.39 (Ar-C), 45.41 (Aliph-C), 40.89 (Aliph-C), 29.62 (Aliph-C), 25.69 (Aliph-C).LC-MS (m/z) calculated for $C_{24}H_{25}FN_6OS$ (m/z):464.18 found: 465.0 $(M + H)^+$.

N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzamide ***(12b);*** Yield: 70%. m.p.: 177-8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.1 Hz, 1H, Ar-H), 8.05 (d, *J* = 4.2 Hz, 1H, Ar-H), 7.83 (d, *J* = 16.0 Hz, 1H, NH), 7.73 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.38 (m, 3H, Ar-H), 7.32 (m, 3H, Ar-H), 7.09 (m, 1H, Ar-H), 6.91 (d, *J* = 4.4 Hz, 1H, A-H), 6.48 (d, *J* = 5.2 Hz, 1H, Ar-H), 6.30 (s, 1H, NH), 3.72 (s, 4H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.07 (C=O), 183.95 (Ar-C), 162.65 (Ar-C), 161.50 (Ar-C), 157.53 (Ar-C), 152.07 (Ar-C), 148.32 (Ar-C), 136.84 (Ar-C), 134.31 (Ar-C), 131.35 (Ar-C), 130.16 (Ar-C), 128.31 (Ar-C), 126.92 (Ar-C), 124.95 (Ar-C), 121.94 (Ar-C), 120.97 (Ar-C), 116.10 (Ar-C), 115.42 (Ar-C), 112.93 (Ar-C), 41.42 (Aliph-C), 40.85 (Aliph-C).LC-MS (m/z) calculated for $C_{24}H_{19}FN_6OS$ (m/z):458.13 found: 459 $(M+H)^+$.

N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-4-methylbenzamide ***(12c);***Yield: 70%. m.p.: 180-1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.05 (d, *J* = 8.0 Hz,1H, Ar-H), 7.70 (t, *J* = 4.0 Hz, 1H, Ar-H), 7.60 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.36 (m, 3H, Ar-H), 7.09 (m, 2H, Ar-H), 6.89 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.48 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.25 (s, 1H, NH), 3.71 (s, 4H, Aliph-H), 2.29 (s, 3H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.09 (C=O), 163.96 (Ar-C), 162.66 (Ar-C), 161.52 (Ar-C), 152.09 (Ar-C), 148.35 (Ar-C), 141.81 (Ar-C), 136.82 (Ar-C), 131.39 (Ar-C), 130.19 (Ar-C), 129.09 (Ar-C),

127.00 (Ar-C), 124.99 (Ar-C), 116.18 (Ar-C), 115.51 (Ar-C), 112.92 (Ar-C), 107.47 (Ar-C), 41.45 (Aliph-C), 40.86 (Aliph-C), 21.34 (CH_3).LC-MS (m/z) calculated for $C_{25}H_{21}FN_6OS$ (m/z):472.15 found: 473.3 $(M + H)^+$.

N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-4-(trifluoromethyl)benzamide ***(12d)*****;**Yield: 65%. m.p.: 167-8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.10 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.83 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.59 (d, *J* = 4.0 Hz, 2H, Ar-H), 7.40 (m, 2H, Ar-H), 7.33 (m, 1H, Ar-H), 7.12 (m, 1H, Ar-H), 6.93 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.56 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.76 (m, 4H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 166.66 (C=O), 164.01 (Ar-C), 162.75 (Ar-C), 161.56 (Ar-C), 152.25 (Ar-C), 148.73 (Ar-C), 137.60 (Ar-C), 136.73 (Ar-C), 133.26 (Ar-C), 132.94 (Ar-C), 130.26 (Ar-C), 127.33 (Ar-C), 125.44 (Ar-C), 124.93 (CF_3), 121.76 (Ar-C), 120.78 (Ar-C), 116.13 (Ar-C), 115.62 (Ar-C), 113.02 (Ar-C), 107.88 (Ar-C), 42.49 (Aliph-C), 41.22 (Aliph-C).LC-MS (m/z) calculated for $C_{25}H_{18}F_4N_6OS$ (m/z): 526.12 found: 527.5 $(M + H)^+$.

4-Chloro-N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzamide ***(12e);***Yield: 80%. m.p.: 170-1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 4.0 Hz, 1H, Ar-H), 8.06 (d, J = 8.0 Hz, 1H, Ar-H), 7.71 (d, J = 8.0 Hz, 2H, Ar-H), 7.34, (m, 5H, Ar-H), 7.10 (m, 1H, Ar-H), 6.91 (d, J = 4.0 Hz, 1H, Ar-H), 6.49 (d, J = 4.0 Hz, 1H, Ar-H), 6.18 (s, 1H, NH), 3.73 (s, 4H, Aliph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.99 (C=O), 162.69 (Ar-C), 161.54 (Ar-C), 157.56 (Ar-C), 152.12 (Ar-C), 148.42 (Ar-C), 136.85 (Ar-C), 134.29 (Ar-C), 131.41 (Ar-C), 130.20 (Ar-C), 128.35 (Ar-C), 126.89 (Ar-C), 124.99 (Ar-C), 121.92 (Ar-C), 120.95 (Ar-C), 116.13 (Ar-C), 115.55 (Ar-C), 112.97 (Ar-C), 107.55 (Ar-C), 41.44 (Aliph-C), 40.88 (Aliph-C).;LC-MS (m/z) calculated for $C_{24}H_{18}ClFN_6OS$ (m/z): 492.09 found: 493.3 $(M+H)^+$.

2,6-Difluoro-N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzamide ***(12f);*** Yield: 70%. m.p.: 185-7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.05 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.41 (m, 3H, Ar-H), 7.34 (m, 1H, Ar-H), 7.13 (m, 1H, Ar-H), 6.95 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.87 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.52 (d, *J* = 4.0 Hz, 1H, Ar-H), 5.82 (s, 1H, NH), 3.76 (s, 4H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 164.01 (C=O), 162.52 (Ar-C), 161.56 (Ar-C), 160.85 (Ar-C), 152.09 (Ar-C), 148.35 (Ar-C), 136.84 (Ar-C), 131.64 (Ar-C), 130.20 (Ar-C), 124.92 (Ar-C), 121.68 (Ar-C), 120.86 (Ar-C), 116.18 (Ar-C), 115.55 (Ar-C), 112.96 (Ar-C), 111.84 (Ar-C), 107.87 (Ar-C), 41.10 (Aliph-C), 40.94 (Aliph-C).LC-MS (m/z) calculated for $C_{24}H_{17}F_3N_6OS$ (m/z): 494.11 found: 495.2 $(M+H)^+$.

*N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)cyclohexanecarboxamide****(13a)*****;** Yield: 75%. m.p.: 187-9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H, NH), 8.09 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.41 (m, 3H, Ar-H), 7.12 (m, 1H, Ar-H), 6.98 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.54 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.34 (s, 1H, NH), 5.73 (t, *J* = 8.0 Hz, 1H, Ar-H), 3.55 (m, 2H, Aliph-H), 3.40 (m, 2H, Aliph-H), 2.11 (m, 8H, Cyclohexyl), 2.79 (m, 2H, Aliph-H), 1.68 (m, 1H, Cyclohexyl), 1.45 (m, 2H, Cyclohexyl).^{13}C NMR (100 MHz, $CDCl_3$) δ 176.58 (C=O), 164.03 (Ar-C), 162.42 (Ar-C), 161.59 (Ar-C), 157.57 (Ar-C), 152.05 (Ar-C), 148.38 (Ar-C), 137.00 (Ar-C), 130.18 (Ar-C), 125.02 (Ar-C), 122.02 (Ar-C), 121.08 (Ar-C), 116.20 (Ar-C), 115.41 (Ar-C), 112.80 (Ar-C), 107.27 (Ar-C), 45.68 (Aliph-C), 38.31 (Aliph-C), 36.11 (Aliph-C), 35.20 (Aliph-C), 30.02(Aliph-C), 29.80 (Aliph-C), 25.76 (Aliph-C).LC-MS (m/z) calculated for $C_{25}H_{27}FN_6OS$ (m/z):478.20 found: 479.4 $(M + H)^+$.

N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)benzamide ***(13b);***Yield: 65% m.p.: 190-1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.02 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.78 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.35 (m, 5H, Ar-H), 7.06 (m, 1H, Ar-H), 6.87 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.44 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.01 (t, *J* = 7.75 Hz, 1H, Ar-H), 3.56 (m, 4H, Aliph-H), 1.89 (t, *J* = 7.75 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 167.82 (C=O), 163.95 (Ar-C), 162.48 (Ar-C), 161.50 (Ar-C), 151.97 (Ar-C), 134.74 (Ar-C), 131.28 (Ar-C), 130.14 (Ar-C), 128.38 (Ar-C), 126.97 (Ar-C), 125.00 (Ar-C), 122.04 (Ar-C), 116.12 (Ar-C), 115.14 (Ar-C), 112.78 (Ar-C), 107.05 (Ar-C), 40.89 (Aliph-C), 38.39 (Aliph-C), 29.66 (Aliph-C). LC-MS (m/z) calculated for $C_{25}H_{21}FN_6OS$ (m/z):472.15 found: 473.4 $(M+H)^+$.

N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-4-(trifluoromethyl)benzamide ***(13c);***Yield; 60%. m.p.: 173-4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.00 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.92 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.35 (m, 3H, Ar-H), 7.05 (m, 1H, Ar-H), 6.89 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.43 (d, *J* = 4.0 Hz, 1H, Ar-H), 3.55 (m, 4H, Aliph-H), 1.89 (m, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 166.42 (C=O), 163.92 (Ar-C), 162.45 (Ar-C), 161.47 (Ar-C), 157.40 (Ar-C), 151.99 (Ar-C), 138.10 (Ar-C), 136.87 (Ar-C), 132.93 (Ar-C), 130.18 (Ar-C), 127.58 (Ar-C), 125.32 (CF_3), 124.96 (Ar-C), 122.01 (Ar-C), 116.11 (Ar-C), 115.50 (Ar-C), 112.82 (Ar-C), 107.05 (Ar-C), 40.85 (Aliph-C), 38.37 (Aliph -C), 29.41 (Aliph -C).LC-MS (m/z) calculated for $C_{26}H_{20}F_4N_6OS$ (m/z):540.14 found: 541.0 $(M+H)^+$.

4-Chloro-N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)benzamide ***(13d)*****;** Yield; 75%. m.p.: 104-6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.01 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.78 (d, *J* = 8.0 Hz, 2H, Ar-H),

7.37 (m, 5H, Ar-H), 7.06 (m, 1H, Ar-H), 6.88 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.44 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.02 (s, 1H, NH), 3.55 (m, 4H, Aliph-H), 1.90 (t, J = 7.74 Hz, 2H, Aliph-H).LC-MS (m/z) calculated for $C_{25}H_{20}ClFN_6OS$ (m/z):506.11 found: 507.2 $(M+H)^+$.

4-Fluoro-N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)benzamide ***(13e);*** Yield: 70%. m.p.: 161-3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.09 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.82 (s, 2H, Ar-H), 7.43 (m, 3H, Ar-H), 7.10 (m, 3H, Ar-H), 6.92 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.53 (d, *J* = 4.0 Hz, 1H, Ar-H), 3.62 (m, 4H, Aliph-H), 1.93 (m, 2H, Aliph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.68 (C=O), 164.03 (Ar-C), 163.37 (Ar-C), 162.55 (Ar-C), 161.58 (Ar-C), 157.08 (Ar-C), 152.14 (Ar-C), 148.58 (Ar-C), 136.88 (Ar-C), 130.25 (Ar-C), 129.13 (Ar-C), 125.00 (Ar-C), 121.87 (Ar-C), 120.81 (Ar-C), 116.22 (Ar-C), 115.63 (Ar-C), 112.83 (Ar-C), 107.43 (Ar-C), 38.34 (Aliph-C), 36.90 (Aliph-C), 29.97 (Aliph-C).LC-MS (m/z) calculated for $C_{25}H_{20}F_2N_6OS$ (m/z): 590.14 found: 591.6 $(M+H)^+$.

N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzenesulfonamide ***(14a);*** Yield: 50%. m.p.: 225-7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H, NH), 7.85 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.78 (d, *J* = 8.1 Hz, 3H, Ar-H), 7.68 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.62 (m, 5H, Ar-H), 7.45 (t, *J* = 9.2 Hz, 1H, Ar-H), 7.32 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.40 (s, 1H, NH), 3.45 (s, 2H, Aliph-H), 3.02 (t, *J* = 4.8 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, DMSO-d_6) δ 168.08 (Ar-C), 163.96 (Ar-C), 162.66 (Ar-C), 161.51 (Ar-C), 157.53 (Ar-C), 152.07 (Ar-C), 148.32 (Ar-C), 136.86 (Ar-C), 134.31 (Ar-C), 131.36 (Ar-C), 130.18 (Ar-C), 128.31 (Ar-C), 126.92 (Ar-C), 124.95 (Ar-C), 121.95 (Ar-C), 120.97 (Ar-C), 116.15 (Ar-C), 115.45 (Ar-C), 112.93 (Ar-C), 107.43 (Ar-C), 41.42 (Aliph-C), 40.86 (Aliph-C); HRMS (m/z) calculated for $C_{23}H_{19}FN_6O_2S_2$(m/z): 494.0995 found: 495.1073 $(M+H)^+$.

3-Fluoro-N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzenesulfonamide ***(14b)*****;**Yield: 65%. m.p.: 188-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.4 Hz, 1H, Ar-H), 8.04 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.62 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.52 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.39 (t, *J* = 16.4 Hz, 3H, Ar-H), 7.24 (d, *J* = 17.2 Hz, 2H, Ar-H), 7.10 (s, 1H, Ar-H), 6.94 (d, *J* = 4.4 Hz, 1H, Ar-H), 6.54 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.45 (s, 1H, Ar-H), 3.62 (s, 2H, Aliph-H), 3.25 (d, *J* = 4.8 Hz, 2H, Aliph-H). LC-MS (m/z) calculated for $C_{23}H_{19}F_2N_6O_2S_2$(m/z): 512.09 found: 513.0 $(M+H)^+$.

N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-4-methylbenzenesulfonamide ***(14c)*****;**Yield: 60%. m.p.: 200-1 °C. ^{1}H NMR (400 MHz, MeOH) δ 8.36 (s, 1H, Ar-H), 8.01 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.89 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.72 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.52 (m, 1H, Ar-H), 7.44 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.35 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.31 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.23 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.47 (d, *J* = 4.0 Hz, 1H, Ar-H), 3.53 (s, Aliph-H), 3.14 (t, *J* = 4.0 Hz, 2H, Aliph-H), 2.36 (s, 3H, CH_3). HRMS (m/z) calculated for $C_{24}H_{21}FN_6O_2S_2$(m/z): 508.1151 found: 509.1229 $(M+H)^+$.

*N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-4-(trifluoromethyl)benzenesulfonamide****(14d)*****;**Yield: 55%. m.p.: 73-5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 4.0 Hz, 1H, Ar-H), 8.89 (t, *J* = 8.0 Hz, 3H, Ar-H), 7.63 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.27 (t, *J* = 8.0 Hz, 3H, Ar-H), 7.18 (s, 1H, Ar-H), 6.83 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.40 (d, *J* = 4.0 Hz, 1H, Ar-H), 5.60 (s, 1H, NH), 3.52 (s, 2H, Aliph-H), 3.14 (d, *J* = 4.0 Hz, 2H, Aliph-H).^{13}C NMR (101 MHz, $CDCl_3$) δ 162.10 (Ar-C), 157.30 (Ar-C), 156.90 (Ar-C), 152.26 (Ar-C), 148.56 (Ar-C), 143.71 (Ar-C), 136.77 (Ar-C), 130.25 (Ar-C), 127.45 (Ar-C), 126.23 (Ar-C), 124.97 (CF_3), 121.94 (Ar-C), 116.11 (Ar-C), 115.66 (Ar-C), 113.03 (Ar-C), 107.76 (Ar-C),

43.50 (Ar-C), 41.47 (Ar-C). HRMS calculated for $C_{24}H_{18}F_4N_6O_2S_2$(m/z): 562.0869 found: 563.0948 $(M+H)^+$.

*N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-4-methoxybenzenesulfonamide**(14e);***Yield: 55%. m.p.: 203-4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 7.99 (d, *J* = 4.4 , 1H, Ar-H), 7.81 (m, 2H, Ar-H), 7.41 (m, 3H, Ar-H), 7.13 (m, 1H, Ar-H), 7.99 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.93 (m, 2H, Ar-H), 6.51 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.10 (s, 1H, NH), 3.82 (s, 3H, OCH_3), 3.65 (d, *J* = 8.0 Hz, 2H, Aliph-H), 3.24 (d, *J* = 8.0 Hz, 2H, Aliph-H).LC-MS (m/z) calculated for $C_{24}H_{24}FN_6O_3S_2$(m/z): 524.11 found: 525.3 $(M+H)^+$.

*4-Chloro-N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzenesulfonamide**(14f);***Yield: 75%. m.p.: 183-5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H, NH), 8.49 (s, 1H, NH), 8.14 (d, *J* = 4.8 Hz, 1H, Ar-H), 7.85 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.64 (q, *J* = 6.8 Hz, 3H, Ar-H), 7.55 (t, *J* = 6.8 Hz, 2H, Ar-H), 7.47 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.32 (s, 1H, Ar-H), 6.41 (s, 1H, Ar-H), 3.02 (s, 2H, Aliph-H), 2.56 (s, 2H, Aliph-H). LC-MS (m/z) calculated for $C_{23}H_{18}ClFN_6O_2S_2$(m/z): 528.06 found: 529.08 $(M+H)^+$.

*4-Bromo-N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzenesulfonamide**(14g)***;Yield: 70%. m.p.: 160-2 °C. ^{1}H NMR (400 MHz, MeOH) δ 8.37 (s, 1H, Ar-H), 8.01 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.65 (t, *J* = 6.8 Hz, 1H, Ar-H), 7.55 (m, 5H, Ar-H), 7.44 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.36 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.24 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.48 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.55 (s, 2H, Aliph-H), 3.15 (t, *J* = 4.0 Hz, 2H, Aliph-H).; LC-MS (m/z) calculated for $C_{23}H_{18}BrFN_6O_2S_2$(m/z): 572.01 found: 573 $(M + 1)^+$.

*4-Fluoro-N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzenesulfonamide**(14h)***;Yield: 70%. m.p.: 220-2 °C. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.56 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 7.91 (m, 2H, Ar-H), 7.53 (m, 1H, Ar-H), 7.47 (m, 2H, Ar-H), 7.37 (m, 1H, Ar-H), 7.18 (d, *J* = 8.0 Hz, 3H, Ar-H), 7.12 (s, 1H, NH), 6.58 (d, *J* = 8.0 Hz, 1H, Ar-H). HRMS (m/z) calculated for $C_{23}H_{18}F_2N_6O_2S_2$(m/z): 512.0901 found: 513.0978 $(M+H)^+$.

N-(2-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)naphthalene-2-sulfonamide ***(14i):***Yield: 45%. m.p.: 166-8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 4.8 Hz, 2H, Ar-H), 7.94 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.78 (m, 4H, Ar-H), 7.51 (m, 2H, Ar-H), 7.32 (m, 3H, Ar-H), 6.85 (d, *J* = 4.0 Hz, 1H, Ar-H), 6.41 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.68 (s, 1H, NH), 3.58 (d, *J* = 5.2 Hz, 2H, Aliph-H), 3.28 (t, *J* = 4.8 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 157.24 (Ar-C), 156.71 (Ar-C), 152.13 (Ar-C), 148.48 (Ar-C), 136.67 (Ar-C), 134.67 (Ar-C), 132.05 (Ar-C), 130.19 (Ar-C), 129.22 (Ar-C), 128.42 (Ar-C), 127.51 (Ar-C), 124.98 (Ar-C), 122.15 (Ar-C), 116.2 (Ar-C), 115.51 (Ar-C), 112.80 (Ar-C), 107.52 (Ar-C), 43.50 (Aliph-C), 41.23 (Aliph-C).LC-MS (m/z) calculated for $C_{27}H_{21}FN_6O_2S_2$(m/z): 544.12 found: 545.2 $(M+H)^+$.

N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)benzenesulfonamide ***(15a);***Yield: 60%. m.p.: 144-5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.4 Hz, 1H, Ar-H), 8.01 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.81 (t, *J* = 8.0 Hz, 4H, Ar-H), 7.50 (m, 6H, Ar-H), 6.45 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.57 (s, 1H, NH), 3.54 (q, *J* = 6.4 Hz, 2H, Aliph-H), 3.04 (d, *J* = 5.6 Hz, 2H, Aliph-H), 1.78 (t, *J* = 6.0 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (Ar-C), 157.4 (Ar-C), 156.91 (Ar-C), 152.23 (Ar-C), 148.43 (Ar-C), 140 (Ar-C), 136.92 (Ar-C), 132.6 (Ar-C), 130.21 (Ar-C), 129.15 (Ar-C), 126.89 (Ar-C), 125.02 (Ar-C), 121.95 (Ar-C), 120.91 (Ar-C), 116.22 (Ar-C), 115.51 (Ar-C), 113.13 (Ar-C), 107.29

(Ar-C), 40.28 (Aliph-C), 39.82 (Aliph-C), 29.87 (Aliph-C). HRMS (m/z) calculated for $C_{24}H_{21}FN_6O_2S_2$(m/z): 508.1151 found: 509.1229 $(M+H)^+$.

3-Fluoro-N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)benzenesulfonamide ***(15b);***Yield: 65%. m.p.: 155-7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.4 Hz, 1H, Ar-H), 8.04 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.60 (d, *J* = 7.6 Hz, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.42 (m, 3H, Ar-H), 7.36 (m, 1H, Ar-H), 7.23 (q, *J* = 8.0 Hz, 1H, Ar-H), 7.11 (q, *J* = 7.6 Hz, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 6.48 (d, *J* = 5.6 Hz, 1H, Ar-H), 3.55 (d, *J* = 6.0 Hz, 2H, Aliph-H), 3.06 (s, 2H, Aliph-H), 1.80 (d, *J* = 5.6 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.33 (Ar-C), 157.69 (Ar-C), 152.19 (Ar-C), 147.99 (Ar-C), 146.79 (Ar-C), 136.61 (Ar-C), 130.89 (Ar-C), 130.19 (Ar-C), 125.01 (Ar-C), 122.62 (Ar-C), 121.93 (Ar-C), 119.51 (Ar-C), 116.22 (Ar-C), 115.66 (Ar-C), 114.21 (Ar-C), 112.99 (Ar-C), 107.33 (Ar-C), 40.33 (Aliph-C), 38.03 (Aliph-C), 30.28 (Aliph-C).LC-MS (m/z) calculated for $C_{24}H_{20}F_2N_6O_2S_2$(m/z): 526.11 found: 527.2 $(M+H)^+$.

N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-4-methylbenzenesulfonamide ***(15c);***Yield: 60%. m.p.: 171-3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.41 (d, *J* = 4.4 Hz, 1H, Ar-H), 7.93 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.59 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.25 (m, 3H, Ar-H), 7.13 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.00 (t, *J* = 7.6 Hz, 1H, Ar-H), 6.87 (s, 1H, Ar-H), 6.37 (d, *J* = 5.6 Hz, 1H, Ar-H), 5.63 (s, 1H, NH), 3.44 (d, *J* = 6.0 Hz, 2H, Aliph-H), 2.93 (d, *J* = 5.2 Hz, 2H, Aliph-H), 2.27 (s, 3H, CH_3), 1.69 (t, *J* = 5.2 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.31 (Ar-C), 161.53 (Ar-C), 157.42 (Ar-C), 156.81 (Ar-C), 152.16 (Ar-C), 148.31 (Ar-C), 143.23 (Ar-C), 137.17 (Ar-C), 136.91 (Ar-C), 130.18 (Ar-C), 129.66 (Ar-C), 126.90 (Ar-C), 125.01 (Ar-C), 122.01 (Ar-C), 120.97 (Ar-C), 116.30 (Ar-C), 115.41 (Ar-C),

113.07 (Ar-C), 107.14 (Ar-C), 40.30 (Aliph-C), 38.32 (Aliph-C), 29.77 (Aliph-C), 21.44 (CH_3). LC-MS (m/z) calculated for $C_{25}H_{23}FN_6O_2S_2$(m/z): 522.13 found: 523.4 $(M+H)^+$.

N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-4-(trifluoromethyl)benzenesulfonamide ***(15d):***Yield: 55%. m.p.: 107-8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H, Ar-H), 7.95 (m, 3H, Ar-H), 7.70 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.31 (m, 3H, Ar-H), 7.09 (s, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 6.47 (d, *J* = 4.8 Hz, 1H, Ar-H), 5.60 (s, 1H, NH), 3.55 (s, 2H, Aliph-H), 3.06 (s, 2H, Aliph-H), 1.79 (s, 2H, Aliph-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.00 (Ar-C), 162.32 (Ar-C), 157.38 (Ar-C), 156.94 (Ar-C), 152.26 (Ar-C), 148.48 (Ar-C), 144.04 (Ar-C), 130.26 (Ar-C), 127.36 (Ar-C), 126.23 (Ar-C), 124.98 (CF3), 121.85 (Ar-C), 116.13 (Ar-C), 115.65 (Ar-C), 113.11 (Ar-C), 107.38 (Ar-C), 40.24 (Aliph-C), 38.19 (Aliph-C), 29.96 (Aliph-C).LC-MS (m/z) calculated for $C_{25}H_{20}F_4N_6O_2S_2$(m/z): 576.10 found: 577.2 $(M+H)^+$.

*N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-4-hydroxybenzenesulfonamide****(15e);***Yield: 75%. ^{1}H NMR (400 MHz, MeOH) δ 8.75 (s, 1H, OH), 7.95 (d, *J* = 4.0 Hz, 1H, Ar-H), 7.68 (d, *J* = 8.0 Hz, 3H, Ar-H), 7.52 (m, 2H, Ar-H), 7.48 (m, 1H, Ar-H), 7.34 (m, 1H, Ar-H), 7.25 (t, *J* = 8.0 Hz, 1H, Ar-H), 6.86 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.43 (d, *J* = 4.0 Hz, 1H, Ar-H), 3.52 (s, 2H, Aliph-H), 2.98 (t, *J* = 4.0 Hz, 2H, Aliph-H), 1.87 (t, *J* = 8.0 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, MeOH) δ 163.99 (Ar-C), 161.42 (Ar-C), 158.72 (Ar-C), 153.92 (Ar-C), 150.60 (Ar-C), 136.13 (Ar-C), 130.61 (Ar-C), 129.71 (Ar-C), 128.97 (Ar-C), 125.34 (Ar-C), 124.97 (Ar-C), 120.55 (Ar-C), 116.04 (Ar-C), 115.82 (Ar-C), 115.26 (Ar-C), 105.42 (Ar-C), 40.13 (Aliph-C), 38.66 (Aliph-C), 28.60 (Aliph-C).LC-MS (m/z) calculated for $C_{24}H_{21}FN_6O_3S_2$(m/z): 524.11 found: 525.2 $(M+H)^+$.

*N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-4-methoxybenzenesulfonamide**(15f)***;Yield: 55%. m.p.: 110-2 °C. $_1$H NMR (400 MHz, $CDCl_3$) δ 8.53 (t, *J* = 4.0 Hz, 1H, Ar-H), 8.07 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.76 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.38 (m, 3H, Ar-H), 7.13 (m, 1H, Ar-H), 7.11 (m, 2H, Ar-H), 6.95 (m, 1H, Ar-H), 6.53 (t, *J* = 8.0 Hz, 1H, Ar-H), 3.84 (s, 3H, OCH_3), 3.58 (q, *J* = 8.0 Hz, 2H, Aliph-H), 3.06 (q, *J* = 8.0 Hz, 2H, Aliph-H), 1.82 (t, *J* = 8.0 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.43 (Ar-C), 152.24 (Ar-C), 131.67 (Ar-C), 130.21 (Ar-C), 129.02 (Ar-C), 125.04 (Ar-C), 121.94 (Ar-C), 120.92 (Ar-C), 116.22 (Ar-C), 115.55 (Ar-C), 114.23 (Ar-C), 107.33 (Ar-C), 55.57 (OCH3), 40.21 (Aliph-C), 38.27 (Aliph-C), 29.87 (Aliph-C).LC-MS (m/z) calculated for $C_{25}H_{23}FN_6O_3S_2$(m/z): 538.13 found: 539.2 $(M+H)^+$.

*4-Chloro-N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)benzenesulfonamide**(15g);***Yield: 70%. m.p.: 120-1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 3.6 Hz, 1H, Ar-H), 8.02 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.81 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.51 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.39 (d, *J* = 2.4 Hz, 1H, Ar-H), 7.33 (d, *J* = 9.2 Hz, 1H, Ar-H), 7.10 (t, *J* = 8.8 Hz, 1H, Ar-H), 6.98 (d, *J* = 3.3 Hz, 1H, Ar-H), 6.47 (d, *J* = 5.2 Hz, 1H, Ar-H), 5.62 (s, 1H, NH), 3.54 (q, *J* = 6.0 Hz, 2H, Aliph-H), 3.04 (d, *J* = 3.6 Hz, 2H, Aliph-H), 2.25 (s, 1H, NH), 1.78 (t, *J* = 5.6 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 163.99 (Ar-C), 162.31 (Ar-C), 161.54 (Ar-C), 157.43 (Ar-C), 156.88 (Ar-C), 152.18 (Ar-C), 148.38 (Ar-C), 140.22 (Ar-C), 136.95 (Ar-C), 136.87 (Ar-C), 132.45 (Ar-C), 130.20 (Ar-C), 129.10 (Ar-C), 126.84 (Ar-C), 125.02 (Ar-C), 121.96 (Ar-C), 120.95 (Ar-C), 116.21 (Ar-C), 115.51 (Ar-C), 113.04 (Ar-C), 107.25 (Ar-C), 40.47 (Aliph-C), 38.23 (Aliph-C), 29.83 (Aliph-C).LC-MS (m/z) calculated for $C_{24}H_{20}ClFN_6O_2S_2$(m/z): 542.08 found: 543.1 $(M+H)^+$.

4-Bromo-N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)benzenesulfonamide ***(15h);*** Yield: 60%. m.p.: 159-60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.80 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.51 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.38 (d, *J* = 2.8 Hz, 2H, Ar-H), 7.32 (d, *J* = 9.6 Hz, 1H, Ar-H), 7.1 (m, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 6.46 (d, *J* = 5.6 Hz, 1H, Ar-H), 5.55 (s, 1H, NH), 3.54 (m, 2H, Aliph-H), 3.04 (d, *J* = 5.2 Hz, 2H, Aliph-H), 1.77 (t, *J* = 6.0 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 163.99 (Ar-C), 162.32 (Ar-C), 161.55 (Ar-C), 157.42 (Ar-C), 156.91 (Ar-C), 152.21 (Ar-C), 148.44 (Ar-C), 140.16 (Ar-C), 136.86 (Ar-C), 132.50 (Ar-C), 130.19 (Ar-C), 129.08 (Ar-C), 126.85 (Ar-C), 125.02 (Ar-C), 124.99 (Ar-C), 121.93 (Ar-C), 120.91 (Ar-C), 116.25 (Ar-C), 115.51 (Ar-C), 113.05 (Ar-C), 107.31 (Ar-C), 40.26 (Aliph-C), 38.22 (Aliph-C), 29.92 (Aliph-C).LC-MS (m/z) calculated for $C_{24}H_{20}BrFN_6O_2S_2$(m/z): 586.03 found: 587.2 $(M+H)^+$.

4-Fluoro-N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)benzenesulfonamide **(*15i*);** Yield: 50%. m.p.: 82-3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.4 Hz, 1H, Ar-H), 8.03 (d, *J* = 4.8 Hz, 1H, Ar-H), 7.83 (d, *J* = 5.2 Hz, 2H, Ar-H), 7.36 (m, 3H, Ar-H), 7.13 (t, *J* = 8.4 Hz, 3H, Ar-H), 7.01 (s, 1H, NH), 6.46 (d, *J* = 5.6 Hz, 1H, Ar-H), 5.92 (d, *J* = 5.6 Hz, 1H, Ar-H), 3.52 (d, *J* = 5.6 Hz, 2H, Aliph-H), 3.00 (s, 2H, Aliph-H), 1.79 (d, *J* = 5.2 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 165.98 (Ar-C), 163.90 (Ar-C), 162.23 (Ar-C), 161.45 (Ar-C), 157.41 (Ar-C), 156.68 (Ar-C), 152.01 (Ar-C), 148.12 (Ar-C), 136.85 (Ar-C), 136.49 (Ar-C), 130.14 (Ar-C), 129.50 (Ar-C), 124.97 (Ar-C), 122.03 (Ar-C), 121.01 (Ar-C), 116.11 (Ar-C), 115.44 (Ar-C), 113.00 (Ar-C), 106.97 (Ar-C), 40.27 (Aliph-C), 38.28 (Aliph-C), 29.45 (Aliph-C).LC-MS (m/z) calculated for $C_{24}H_{20}F_2N_6O_2S_2$(m/z): 526.11 found: 527.3 $(M+H)^+$.

N-(3-((4-(6-(3-fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)propyl)naphthalene-2-sulfonamide ***(15j):***Yield: 40%. m.p.: 88-90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (m, 2H, Ar-H), 8.01 (m, 2H, Ar-H), 7.82 (m, 3H, Ar-H), 7.55 (m, 2H, Ar-H), 7.32 (m, 3H, Ar-H), 7.09 (d, *J* = 4.4 Hz, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 6.43 (d, *J* = 4.8 Hz, 1H, Ar-H), 5.58 (s, 1H, NH), 3.53 (d, *J* = 5.6 Hz, 2H, Aliph-H), 3.09 (s, 2H, Aliph-H), 1.78 (d, *J* = 5.2 Hz, 2H, Aliph-H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.29 (Ar-C), 161.55 (Ar-C), 157.46 (Ar-C), 156.86 (Ar-C), 152.18 (Ar-C), 136.93 (Ar-C), 134.67 (Ar-C), 132.10 (Ar-C), 130.23 (Ar-C), 129.45 (Ar-C), 129.11 (Ar-C), 128.69 (Ar-C), 128.16 (Ar-C), 127.81 (Ar-C), 127.49 (Ar-C), 125.02 (Ar-C), 122.16 (Ar-C), 120.89 (Ar-C), 116.22 (Ar-C), 115.64 (Ar-C), 113.02 (Ar-C), 107.27 (Ar-C), 40.35 (Aliph-C), 38.26 (Aliph-C), 29.87 (Aliph-C). HRMS (m/z) calculated for $C_{28}H_{23}FN_6O_2S_2$(m/z): 558.1308 found: 559.1388 $(M+H)^+$.

3.2. Biological evaluation

3.2.1. Antitumor screening

Screening against the cancer cell lines was carried out for compounds **12a,b,d-f**, **13a-c,e**, **14a,b,d,f-i** and **15a-e,g-j** at the National Cancer Institute (NCI), Bethesda, Maryland, USA, applying the standard protocol of the NCI. While, compounds **12b-f**, **13d-f**, **14a-h**, **15a-d** and **15f-i** were evaluated for their antiproliferative activity against melanoma cell lines (A375 and Skmel28) using MTT (3-(4,5dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay[38].

3.2.2. In vitro kinase assay

Reaction Biology Corp. Kinase HotSpot^{SM} service was used for screening of compounds **12b**, **15c,d** and **15f-h**. Assay protocol: as reported on Reaction Biology Corp. website using 1 μM concentration of ATP.

3.3. Molecular docking

The molecular docking of the target compounds **12a-f**, **13a-e**, **14a-i** and **15a-j** with BRAF kinase enzyme domain (PDB ID: 5CSW)[39]was investigated using Molecular Operating Environment (MOE) software. The X-ray crystal structure of BRAF kinase enzyme with dabrafenib (PDB ID: 5CSW) was downloaded from the protein data bank (www.rcsb.org) in PDB format. The enzyme was prepared for the molecular docking procedure by applying 3D protonation of both enzyme amino acids and the native ligand (dabrafenib). In addition, water of crystallization was removed from both BRAF kinase enzyme domains. Moreover, the BRAF kinase enzyme active site was isolated.

The docking simulation of native ligand (debrafenib) with the BRAF kinase enzyme active site (PDB ID: 5CSW) was investigated in order to validate the docking protocol.

The 2D structure of the target compounds were assembled using ChemDraw software. Both 3D protonation and energy minimization were performed for the target compounds using MOE software.

The docking of the *in silico*-prepared target compounds was performed with the isolated active site of BRAF kinase enzyme domain. The most stable conformer of each target compound (the conformer that showed best score) was selected to identify the possible molecular interaction(s) between the target compounds binding groups and the BRAF kinase enzyme active site.

4. Conclusion

In conclusion, a new a new series of imidazo[2,1-*b*]thiazole derivatives was designed and synthesized. The new compounds having 3-fluorophenyl at position 6 of imidazo[2,1-*b*]thiazole and pyrimidine ring at position 5. The pyrimidine ring containing either amide or sulphonamide moiety attached to a linker (ethyl or propyl) at position 2 of the pyrimidine ring. The initial

screening by NCI 60 cell lines assay showed that the highest percent inhibition was exhibited against two melanoma cell lines and colon cancer cell lines. Compounds having amide moiety and ethyl linker were more potent when compared to amide compounds with propyl linker. Compounds having sulfonamide moiety and propyl linker followed the amide ethyl compounds in the activity.Compounds**12b, 12f, 14a, 15b,** and **15j**the highest percent inhibition among the final target compounds. Compounds **12b** (unsubstituted phenyl), **12c** (p-methyl), **12e** (p-Cl), **12f** (2,6-diflouro), **14d** (p-CF3), **15a** (unsubstitutedphenyl), **15d** (p-CF3), **15f** (p-OMe), **15g** (p-Cl) and **15h**(p-Br) were more potent thensorafenib with IC_{50}s 5.06, 5.88, 2.57, 2.70, 7.44, 6.60, 4.09, 5.51, 5.90 and 7.04 μM. The final compounds showed a potent enzyme activity against ^{WT}BRAF, ^{V600E}BRAF and CRAF. Compound **15h** showed that most potential inhibitory effect against ^{V600E}BRAF (9.30 nM).

Overall, the synthesized imidazo[2,1-*b*]thiazole derivatives represent a therapeutically promising scaffold for future structural and molecular optimization.

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Conflict of interest

Authors declare no conflict of interest.

Supporting information

Supporting information related to this article including the NCI result charts, representative ^{1}H NMR and ^{13}C NMR charts and detailed docking resultsare available online.

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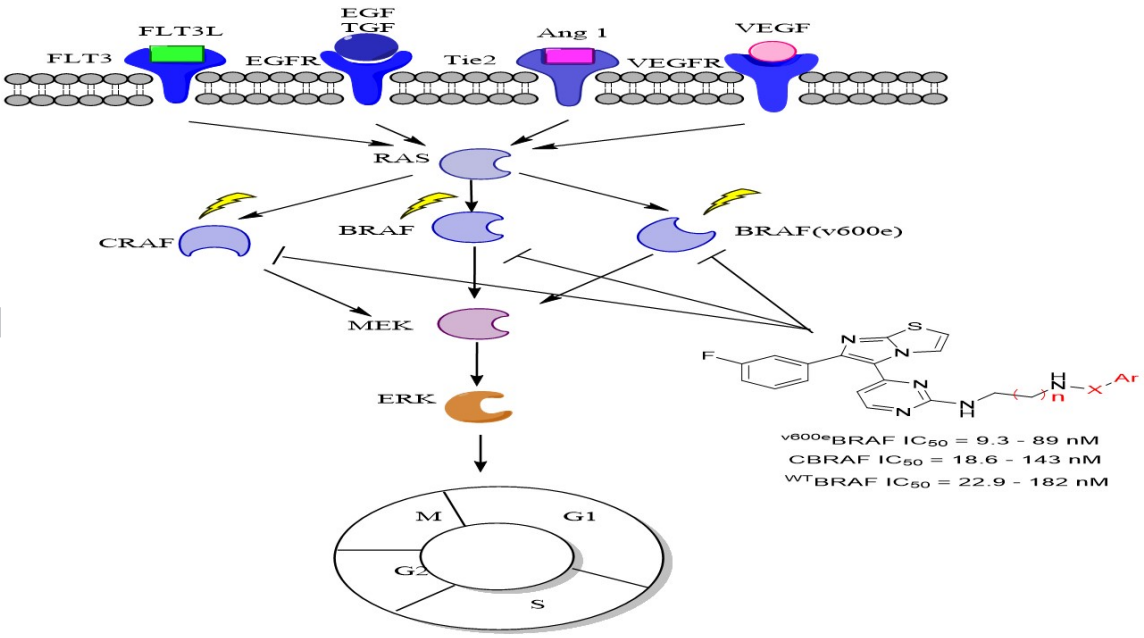
Graphical abstract



Highlights

- A new series of imidazo[2,1-b]thiazole was designed and synthesized.
- The final target compounds were tested against NCI 60 cancer cell lines.
- Compounds **12b, 12c, 12e, 12f, 15a, 15d, 15f** and **15h** showed higher activity compared to sorafenib.
- RAF Kinases inhibitory effects of the most potent compounds were determined.
- Molecular modeling study for the final compounds were performed.