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RESEARCH ARTICLE

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Novel imidazo[2,1-*b*]thiazole-based anticancer agents as potential focal adhesion kinase inhibitors: Synthesis, in silico and in vitro evaluation

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Abstract

The purpose of this study was to synthesize imidazo[2,1-*b*]thiazole derivatives, characterize them with spectroscopical techniques and investigate for cytotoxic and apoptotic effects on glioma C6 cancer cell line. The in vitro anticancer activities were also investigated against focal adhesion kinase. Most of the compounds, particularly the derivatives carrying 3-oxo-1-tiya-4-azaspiro[4.5]decane moiety, exhibited higher or comparable activities in comparison with the reference drug, cisplatin. Compounds with methyl, propyl, phenyl moieties at the eighth and second position of the spirothiazolidinone ring showed high FAK inhibitory activities. In addition, molecular docking studies shed light on the binding modes of the synthesized compounds. The critical interactions with amino acid residues located in the active site were revealed. The results obtained from both biological assay data and computational results might provide insight into developing new inhibitors against focal adhesion kinase.

KEYWORDS

focal adhesion kinase, Imidazo[2,1-*b*]thiazole, molecular docking

1 | INTRODUCTION

Cancer (carcinoma) is one of the serious diseases that are still being studied extensively. Among the most aggressive human cancers are gliomas, a type of primary malignant brain tumour. Despite advances in regular therapy, patients with gliomas have a low prognosis. At the present day, adjuvant chemotherapy and radiotherapy are administered to glioma patients after surgery. The efficacy of chemotherapy is limited because of problems in drug delivery and inherent radio, and chemoresistance (Lin et al., 2017; Patil et al., 2013). Therefore, the development of novel anticancer drugs that possess good biological activity and fewer side-effects are required.

In medicinal chemistry, imidazo[2,1-*b*]thiazoles have a broad spectrum of pharmacological activities including antiviral (Conti et al., 2019), antibacterial (Atta et al., 2011; Gadad et al., 2000; Mohan & Kiran, 1991), antifungal (Çapan et al., 1999; Juspin et al., 2010; Ulusoy et al., 2002) and

antitumor (Andreani et al., 1982; Andreani et al., 1992, 1993) activities. Moreover, the clinical efficacies of tiazofurin, dasatinib and bleomycins have indicated the importance of incorporating the thiazole moiety in antitumor drug design (Paunescu et al., 2015; Rouf & Tanyeli, 2015).

Focal adhesion kinase (FAK) is a tyrosine kinase that plays a major role in cellular survival and movement pathways. FAK is a potential target for the prevention and treatment of both primary cancers and tumour metastasis (Frisch et al., 1996; Ilic et al., 1995; Mitra et al., 2005). Only in the past decade, phase I and II clinical trials have been initiated for small molecule inhibitors of FAK (Infante et al., 2012; Shanthi et al., 2014; Yoon et al., 2015). Therefore, inhibition of FAK activity may be a novel strategy for cancer therapy.

Previous studies reported that compounds carrying imidazole and thiazole rings display anticancer activity by inhibiting FAK (Dao et al., 2015; Jain et al., 2013; Lv et al., 2018).

The present study aims to investigate the synthesis of a series of novel imidazo[2,1-*b*]thiazole derivatives, which include either N-cyclohexylidene or 3-oxo-1-thia-4-azaspiro[4.5] decan-4-yl that could have potential anticancer activity. The characterization of these compounds with spectroscopic techniques was also carried out, and in vitro anticancer activities were evaluated. Additionally, computational studies were employed to gain new insights into interaction modes of the compounds with the active site of FAK.

2 | METHODS AND MATERIALS

2.1 | Experimental

Details for general synthesis procedure for the compounds are given in supplementary data. All synthesized compounds were recrystallized from 96% ethanol. After the purification, white solid powders were obtained with good yield.

Elemental analyses were carried out on a Thermo Finnigan Flash EA 1,112 elemental analyser. Melting points were examined using a Büchi B-540 melting point apparatus in open capillary tubes and are uncorrected. FT-IR spectra were recorded on KBr discs, using a Shimadzu IR Affinity-1 FT-IR spectrophotometer. ^{1}H-NMR, ^{13}C-NMR (APT), ^{13}C-NMR (DEPT) and HSQC (^{1}H-^{13}C) spectra were measured on a Varian UNITY INOVA (500 MHz) spectrometer using DMSO-D_6. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage Max instrument.

2.2 | Biochemistry

2.2.1 | Cell culture method

In Dulbecco's Modified Eagle's Medium (DMEM - Sigma, Deisenhofen, Germany) supplemented with 10% foetal bovine serum (Gibco, Paisley, UK), NIH/3T3 mouse embryonic fibroblast cells and Glioma C6 rat cancer cells were brooded. All of the media were put in with 100 IU/ml penicillin-streptomycin (Gibco, Paisley, UK), and the cells were incubated at 37°C in a humidified atmosphere of 5% CO2 and 95% air. Exponentially growing cells were plated at 2 × 104 cells/mL into 96-well microtiter tissue culture plates (Nunc, Roskilde, Denmark) and were incubated for 24 hr before the supplementation of the compounds. The stock solutions of compounds were prepared with DMSO (dimethyl sulfoxide), and extra dilutions were done using the fresh culture medium. Finally, DMSO's concentration in the last culture medium was less than 0.1% (Ciftci et al., 2015).

2.2.2 | MTT assay for cytotoxicity of compounds

The level of cellular reduction of tetrazolium salt, 3-(4,5 -dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to formazan by mitochondrial succinate dehydrogenase was quantified as previously described in the literature with small modifications (Scheuber et al., 1983). After 24 hr of preincubation, the tested compounds and cisplatin (positive control) were added to give final concentration in the range 3.9–500 μg/ml, and the cells were incubated for 24 hr. Then, MTT was added to a final concentration of 0.5 mg/ml, and the cells were incubated for further four hours at 37℃. After the medium was removed, the formazan crystals were solubilized by the addition of 200 μl DMSO to each well and absorbance was read at 540 nm with a microtitre plate spectrophotometer (Bio-Tek plate reader, Winooski, VT, USA). Every concentration was repeated in three wells, and IC_{50} values were defined as the drug concentrations that reduced absorbance to 50% of the control values (Ciftci et al., 2015).

In the present study, the degree of selectivity index (SI) of the synthetic compounds is expressed as follows:

SI = IC50 of pure compound in a normal cell line / IC50 of the same pure compound in cancer cell line, where IC50 is the concentration required to kill 50% of the cell population.

2.2.3 | Flow cytometric analyses of apoptosis

After cells were incubated with compounds **4g, 4k, 5c, 5d, 5e, 6a-6f** and cisplatin at IC_{50} concentrations, phosphatidylserine externalization which indicates early apoptosis was measured by Annexin V-PI (BD, Pharmingen) on a flow cytometer (BD FACS Aria) (Ciftci et al., 2015) for 24 hr. Annexin V staining protocol was applied according to the manufacturer's instructions (BD, Pharmingen). The cells were processed for

data acquisition and analysed on a Becton-Dickinson FACS Aria, which uses FACSDiva version 6.1.1. Software (Ciftci et al., 2015).

2.2.4 | FAK (Phospho-Tyr397) activity detection by ELISA

Initially, C6 cancer glioma cells were administrated by IC_{50} concentrations of compounds **4c, 4h, 4l, 5d, 6b, 6d, 6e, 6f** and cisplatin for 24 hr. FAK (Phospho-Tyr397) effectiveness of compounds was examined by Colorimetric Cell-Based ELISA FAK (Phospho-Tyr397) activity kit (Aviva Systems Biology, San Diego, USA) according to manufacturer's instructions (Altintop et al., 2018).

2.3 | Computational section

2.3.1 | Ligand and protein preparation

Prior to computational studies, all compounds must be prepared for calculations. Accordingly, all compounds were prepared using the LigPrep (Ligand preparation) module of the Schrödinger suite (Schrödinger, 2016a). OPSL2005 (optimized potential liquid simulations) force field was used for minimizations (Jorgensen et al., 1996; Jorgensen & Tirado-Rives, 1988; Shivakumar et al., 2010). All probable states of the compounds at pH 7.0 ± 2.0 were generated.

The molecular docking studies were performed using high resolution (2.3 Å) X-ray crystal structure of focal adhesion kinase domain (PDB ID: 2ETM) in complex with 7H-Pyrrolo[2,3-*d*]pyrimidine derivative (7PY, native ligand). The raw crystal structure was also prepared using PrepWizard (Protein Preparation Wizard) (Sastry et al., 2013) in Maestro of Schrödinger-2016 software package (Schrödinger, 2016b). As a first step, the PrepWizard was used for adding missing hydrogen atoms and removing all water molecules and heteroatoms. The native ligand was kept for binding site detection. Then, the protein structure was refined by assigning the bond orders and revising the missing side-chains. In the final step, the steric clashes between the atoms were removed by minimizing whole structure using OPLS2005 force field.

2.3.2 | Molecular docking

The docking calculations were carried out using Glide SP (standard precision) module (Friesner et al., 2004; Halgren et al., 2004). A grid that illustrated the binding pocket was generated. The native ligand, 7PY, was used as reference to identify the size and centre of the receptor grid.

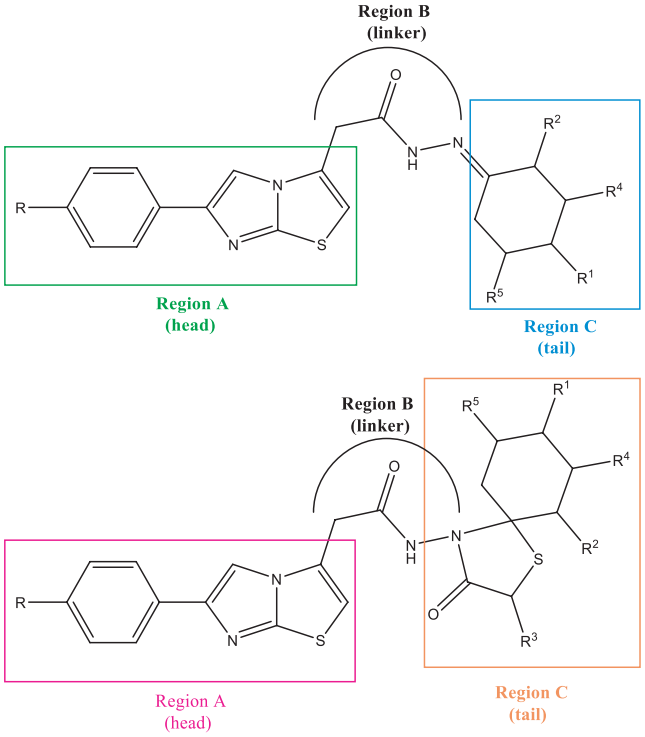
2.3.3 | Calculation of the molecular properties

Some selected physicochemical properties of the synthesized compounds were calculated using the Qik-Prop module of Maestro (Table 4) (Schrödinger, 2016c).

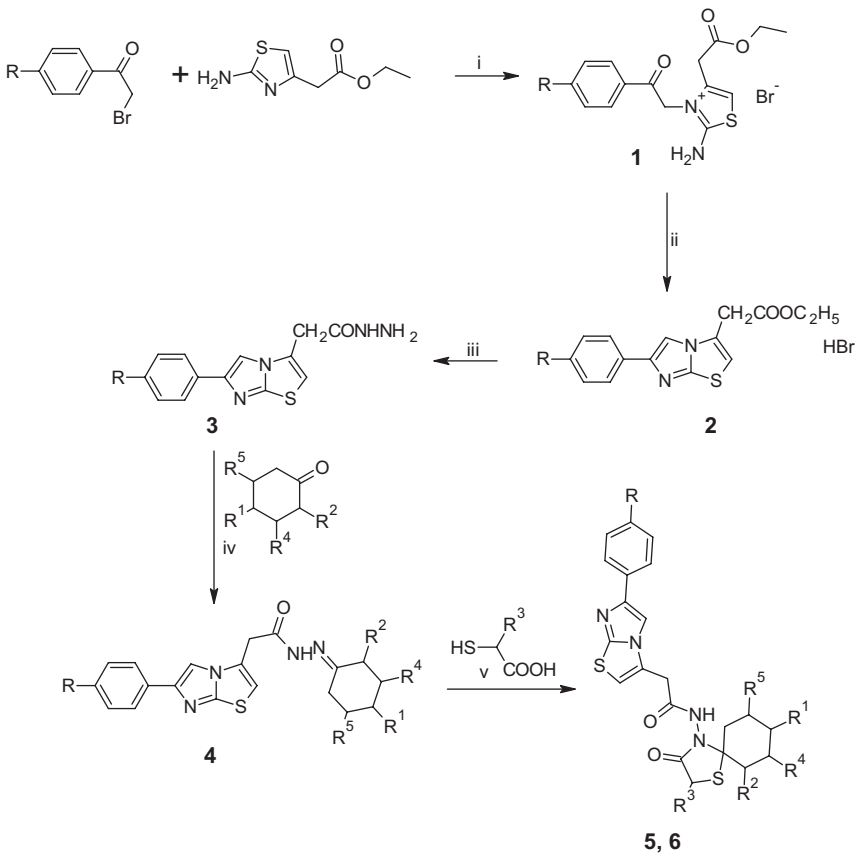
3 | RESULTS AND DISCUSSION

3.1 | Chemistry

The rationale for the design and synthesis of N^2-(substituted cyclohexylidene)-6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-acetohydrazides and 2-[6-(phenyl/4-chlorophenyl)imidazo[2,1-b]thiazol-3-yl]-N-(2-nonsubstituted/methyl-6,7,8,9-alkyl/aryl-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl)acetamides derivatives are based on previous studies that showed efficient anticancer potency. Both imidazo[2,1-b]thiazoles and thiazolidinone scaffolds are known to possess many various anticancer activities (Ali et al., 2014; Deep et al., 2015; Deng et al., 2019; Jain et al., 2012; Manasa et al., 2020; Romagnoli et al., 2015; Szychowski et al., 2017; Szychowski et al., 2017; Tahmasvand et al., 2020). Additionally, Levamisole containing imidazo[2,1-*b*]thiazole nucleus was approved by FDA in 1990 and has been used in cancer treatment since then (FDA, 2021; Moertel et al., 1995; Vacchelli et al., 2012) Those imidazo[2,1-*b*]thiazole



SCHEME 1 Rationally designed template for the targeted compounds as potential anticancer agents [Colour figure can be viewed at wileyonlinelibrary.com]



SCHEME 2 General synthetic pathway of the imidazo[2,1-*b*]thiazole derivatives (**4a-m, 5a-5f, 6a-6f**). Reagents and conditions: (i) acetone, **36h**; (ii) 99% ethanol, reflux, 20 min; (iii) 99% ethanol, 98% $NH_2NH_2.H_2O$, reflux, **5h**; (iv) 99% ethanol, cyclic ketone derivatives, reflux, **6h**; (v) toluene, mercaptoacetic acid or 2-mercaptopropionic acid, reflux, **7h**

Comp.	R	R^1	R^2	R^3	R^4	R^5
4a	H	H	Me	-	H	H
4b	H	Pr	H	-	H	H
4c	Cl	H	Me	-	H	H
4d	Cl	H	2-CNEt	-	H	H
4e	Cl	H	COOEt	-	H	H
4f	Cl	H	H	-	diMe	Me
4g	Cl	H	H	-	diMe	diMe
4h	Cl	Pr	H	-	H	H
4i	Cl	H	*ter*-butyl	-	H	H
4j	Cl	*ter*-butyl	H	-	H	H
4k	Cl	H	Ph	-	H	H
4l	Cl	Cl	Ph	-	H	H
4m	Cl	4-OHPh	H	-	H	H
5a	Cl	H	Me	H	H	H
5b	Cl	H	H	H	diMe	Me
5c	Cl	Pr	H	H	H	H
5d	Cl	*ter*-butyl	H	H	H	H
5e	Cl	Ph	H	H	H	H
5f	Cl	4-OHPh	H	H	H	H
6a	H	Pr	H	Me	H	H
6b	Cl	H	Me	Me	H	H
6c	Cl	H	H	Me	diMe	H
6d	Cl	Pr	H	Me	H	H
6e	Cl	*ter*-butyl	H	Me	H	H
6f	Cl	Ph	H	Me	H	H

TABLE 1 IC50 values of the synthesized compounds on C6 cancer cells and NIH/3T3 cell lines

	IC_{50} (μM)				IC_{50} (μM)		
Comp.	**C6 cell line**	**NIH/3T3 cell line**	**SI value**	**Comp.**	**C6 cell line**	**NIH/3T3 cell line**	**SI values**
4a	>500	>500	–	**5a**	68.33 ± 12.58	>500	>7.32
4b	>500	>500	–	**5b**	>500	>500	-
4c	>500	>500	–	**5c**	13.66 ± 2.08	140.0 ± 28.28	10.24
4d	275 ± 35.35	>500	>1.82	**5d**	12.66 ± 0.57	25.67 ± 6.03	2.03
4e	>500	>500	–	**5e**	19.83 ± 0.76	32.5 ± 3.54	1.64
4f	>500	>500	–	**5f**	>500	>500	-
4g	8.33 ± 2.08	>500	>60.02	**6a**	12.66 ± 0.57	156.67 ± 40.41	12.38
4h	>500	>500	–	**6b**	28.33 ± 2.88	57.5 ± 3.54	2.03
4i	>500	>500	–	**6c**	18.00 ± 2.00	39.0 ± 1.41	2.17
4j	106.66 ± 2.88	>500	>4.69	**6d**	10.83 ± 1.25	223.33 ± 25.17	20.62
4k	4.83 ± 0.28	>500	>103.5	**6e**	19.66 ± 3.21	25.0 ± 7.07	1.27
4l	>500	>500	–	**6f**	16.33 ± 1.52	62.5 ± 3.24	3.83
4m	>500	>500	–	**Cisplatin**	36 ± 8.48	ND	

Abbreviations: ND, not determined; SI, selectivity index.

TABLE 2 Percentages of typical quadrant analysis of Annexin V FITC/Propidium iodide flow cytometry of C6 cancer cells treated with Cisplatin and most active compounds

Comp.[a]	**Early apoptotic cells%**	**Late apoptotic cells%**	**Viable cells%**	**Necrotic cells%**
Control	4.8	3.7	87.4	4.1
Cisplatin	2.2	10.6	75.1	12.1
4g	8.4	7.8	63.6	20.3
4k	12.9	23.4	29.0	34.7
5c	2.5	24.5	11.6	61.9
5d	7.1	6.3	77.9	13.5
5e	0.2	1.6	33.4	64.8
6a	4.7	14.9	22.0	58.5
6b	3.5	3.9	85.5	7.2
6c	4.0	7.7	79.3	9.0
6d	5.7	30.6	14.2	49.5
6e	5.6	4.0	84.3	6.1
6f	2.1	7.3	77.0	13.5

[a]C6 cancer cells were cultured for 24 hr in medium with active compounds (**4g**, **4k**, **5c**, **5d**, **5e**, **6a-f and cisplatin**) at IC50 values. At least 10,000 cells were examined for each sample, and quadrant analysis was achieved.

TABLE 3 FAK inhibitory effects of the compounds **4c**, **4h**, **4l**, **5d**, **6b**, **6d**, **6e**, **6f** and Cisplatin on C6 cell line

	Inhibition %
Compounds	**FAK**
4c (>500 μM)	20.58 ± 3.31
4h (>500 μM)	21.74 ± 2.87
4l (>500 μM)	5.93 ± 0.04
5d (12.66 ± 0.57 μM)	37.29 ± 2.85
6b (28.33 ± 2.88 μM)	68.71 ± 0.73
6d (10.83 ± 1.25 μM)	47.78 ± 3.93
6e (19.66 ± 3.21 μM)	46.64 ± 8.59
6f (16.33 ± 1.52 μM)	72.55 ± 3.63
Cisplatin (36 ± 8.48 μM)	32.03 ± 0.21

derivatives were synthesized by extremely easy method with a high yield (Guzeldemirci & Kucukbasmaci, 2010).

In the current study, the target novel compounds were designed as the head group (region A), the linker chain (region B) and the tail group (region C) to shed light on future research (Scheme 1). The head group was considered as an imidazo[2,1-*b*]thiazole derivative. The tail group was planned as either *N*-cyclohexylidene or 3-oxo-1-thia-4-azaspiro[4.5] decan-4-yl, and the linker between the head and tail groups was designed as hydrazone and hydrazide, respectively. The tail group that was expected to be key important for the anticancer activity consists of 2-methylcyclohexyliden, 4-propylcyclohexyliden, 2-(2-cyanoethyl)cyclohexyliden, 2-ethoxycarbonylcyclohexyliden,3,3,5-trimethylcyclohexyliden, 2-ter-butylcyclohexyliden, 2-phenylcyclohexyliden,4-pheny lcyclohexyliden, 4-(4-hydroxyphaneyl) cyclohexyliden and their spirothiazolidinone derivatives.

Over and above that, substituents with different electronegativity and size were also considered. Therefore, some small and bulky substitutions that have low electronegativity

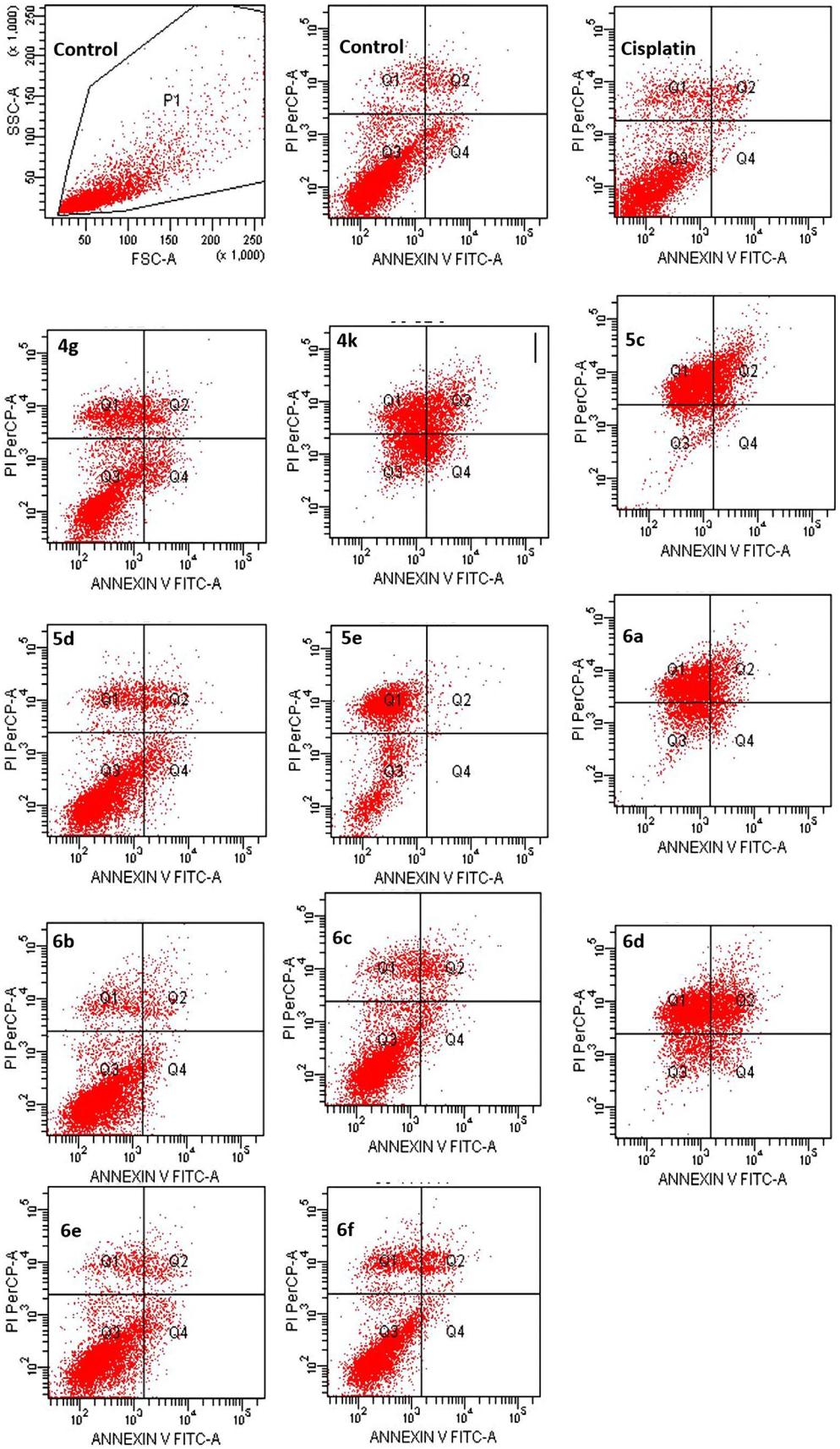


FIGURE 1 Flow cytometric analysis of C6 cancer cells treated with IC50 values of compounds **4g, 4k, 5c, 5d, 5e, 6a-6f** and cisplatin for 24 hr. At least 10,000 cells were examined for each sample, and quadrant analysis was carried out [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Binding energies and selected molecular properties of the native ligand and compounds **4a-4m**, **5a-5f**, **6a-6f**

Compound	MW[a]	%HOA[b]	PSA[c]	QPlogP$_0$/w[d]	DS[e]	MM/GBSA[f]
4a	366.4	100	69.06	5.39	−5.441	−52.572
4b	394.5	100	71.11	6.13	−5.606	−62.942
4c	400.9	100	68.13	5.52	−4.490	−50.817
4d	439.9	94.2	93.93	5.16	−4.651	−40.530
4e	548.9	100	94.07	5.52	−4.844	−61.477
4f	428.9	100	69.60	6.46	−5.382	−59.494
4g	443.0	100	68.83	6.78	−5.035	−67.270
4h	428.9	100	71.17	6.56	−4.801	−61.831
4i	443.0	100	64.45	6.84	−4.894	−65.487
4j	443.0	100	71.01	6.66	−5.151	−53.405
4k	462.9	100	68.20	7.17	−4.781	−42.677
4l	462.9	100	71.04	7.10	−4.637	−61.928
4m	478.9	100	94.75	6.46	−5.692	−64.445
5a	475.0	100	73.19	5.57	−6.060	−78.772
5b	503.0	100	73.27	6.06	−4.587	−45.650
5c	503.0	100	76.98	6.36	−6.617	−76.899
5d	517.1	100	76.99	6.53	−5.977	−82.917
5e	537.0	100	76.97	6.95	−5.459	−57.943
5f	553.0	89.07	99.51	6.26	−5.588	−60.849
6a	482.6	100	73.62	6.24	−4.443	−55.226
6b	489.0	100	68.23	5.88	−6.622	−81.730
6c	517.1	95.76	69.62	5.98	−5.432	−50.252
6d	517.1	100	74.95	6.75	−6.715	−78.799
6e	531.1	100	74.86	6.92	−5.762	−69.911
6f	551.1	100	74.94	7.64	−5.558	−70.194
NL	377.4	100	65.14	3.90	−7.740	−71.812

[a]Molecular weight (g/mol) (recommended value <500).

[b]Percentage oral absorption (<25% weak and >85% strong).

[c]Polar surface area (Å) (recommended value ≤140 Å).

[d]Logarithm of the octanol/water ratio coefficient of compound (recommended value <5).

[e]Docking Score (kcal/mol).

[f]MM/GBSA dG Bind Energy (kcal/mol).

such as methyl, propyl, *tert*-butyl and phenyl were chosen. Additionally, to investigate the electronegativity effect on activity, more electronegative substituents such as 2-cyanoethyl, ethoxycarbonyl and 4-hydroxyphenyl were chosen.

The synthesis of the heretofore unlisted compounds (**4a-m**, **5a-f**, **6a-f**) is outlined in Scheme 1. N^2-(substituted cyclohexylidene)-6-(4-chlorophenyl/phenyl)imidazo[2,1-*b*]thiazol-3-acetohydrazides (**4a-4m**) was synthesized starting from 2-[6-(4-chlorophenyl/phenyl)imidazo[2,1-*b*]thiazol-3-yl]acetohydrazides and then 2-[6-(phenyl / 4-chlorophenyl) imidazo[2,1-*b*]thiazol-3-yl]-*N*-(2-nonssbstited/methyl-6,7,8,9-alkyl/aryl-3-oxo-1-thia-4-azaspiro[4.5]decan-4-yl) acetamides (**5a-5f, 6a-6f**) were synthesized by the reaction of compounds **4a-m** with thioglycolic acid or thiolactic acid. All novel imidazo[2,1-*b*]thiazole derivatives are reported in Scheme 2. The structures of the compounds were characterized by several spectroscopic methods.

MTT assay was used to figure out antiproliferative effectiveness of the synthesized compounds on rat glioma C6 cancer cell lines (Table 1). To investigate whether the compounds possess either non-toxic or toxic to healthy (normal) cells, the cytotoxic effects of imidazo[2,1-*b*]thiazole derivatives (**4a-4m, 5a-5f, 6a-6f**) on NIH/3T3 mouse embryonic fibroblast cell line were evaluated as well by MTT assay.

Because compound **6d** had critical inhibitory effects on C6 cell line with 10.83 ± 1.25 μg/ml, it was identified to be the most encouraging anticancer agent among the series of the synthesized compounds. This result showed that the propyl substituent on the cyclohexane ring at the 4th position of the azaspiro[4.5]decane moiety considerably increased

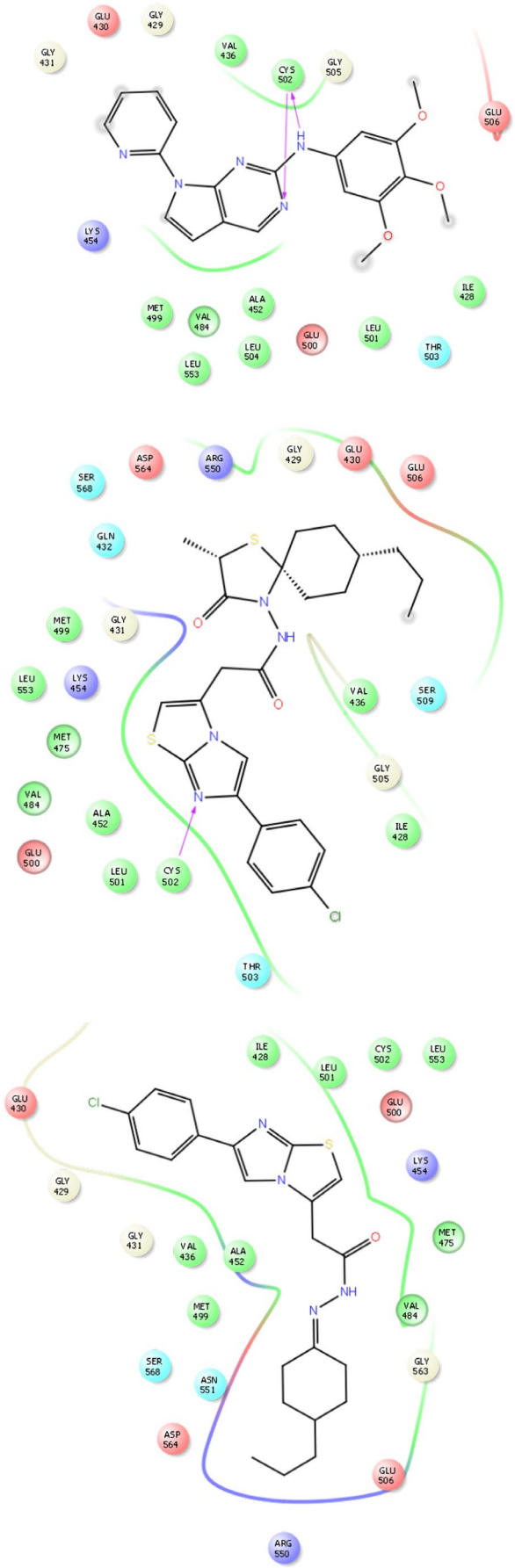


FIGURE 2 2D ligand interaction diagram for NL (Top), active compound **6d** (middle) and inactive compound **4h** (bottom). H-bond is represented purple arrow [Colour figure can be viewed at wileyonlinelibrary.com]

anticancer activity against the C6 cancer cell line by inducing apoptosis. Also, this compound had selectivity by its low toxic effect on towards the NIH/3T3 cell line.

The ketone-hydrazone derivatives (except compound **4d, 4j, 4g** and **4k**) among the synthesized compounds did not exhibit cytotoxic activity against C6 cancer cell line (IC_{50} > 500 μM). Compounds **4d** and **4j** expressed cytotoxic activity with IC_{50} values of 275 ± 35.35 and 106.66 ± 2.88 μM, respectively. However, compounds **4g** and **4k** exhibited considerable cytotoxic effect with IC_{50} values of 8.33 ± 2.08 and 4.83 ± 0.28 μM, respectively. Also, the cytotoxicity of the compounds was low against NIH/3T3 cell line (Table 1).

As the SI demonstrates the differential activity of compounds, the greater the SI value is, the more selective it is. According to the calculated SI data shown in Table 1, the selectivity index rankings are as follow; **4k>4g>6d>6a>5c>5a>4j>6f>6c>6b=5d**. The rest of the compounds displayed very low selectivity.

The apoptotic effects of the most effective anticancer agents among the new series were evaluated for C6 cancer cell lines based on Annexin V-PI binding capacities in flow cytometry. The early apoptotic effects of compound **6d** and cisplatin on the C6 cancer cell line were identified as 5.7 and 2.2%, respectively, while their late apoptotic effects were observed as 30.6 and 10.6%, respectively (Table 2 and Figure 1). The results showed that compound **6d** possessed more apoptotic activity against the C6 cancer cell line than cisplatin. Moreover, the significance of the imidazo[2,1-*b*] thiazole scaffold for apoptotic activity against the C6 cell line was clearly observed.

We should note that FAK also known as PTK2, which has been identified as a crucial regulator of growth factor receptor, is either prompted or overexpressed in various cancers (Altintop et al., 2018). Hence, FAK has been known to be a pharmacological target for preventing carcinoma, and numerous compounds that have FAK inhibitory activity have been designed and synthesized (Cao et al., 2016; Lee et al., 2015; Roy-Luzarraga & Hodivala-Dilke, 2016; Yoon et al., 2015; Zhao & Guan, 2011). Also, the significance of imidazole and thiazole derivatives as FAK inhibitors (Dao et al., 2015; Jain et al., 2013) prompted us to evaluate the inhibitory effects of compounds **4c, 4h, 4l, 5d, 6b, 6d, 6e, 6f** on FAK (Phospho-Tyr397) activity (Table 3). According to the assay, we administered IC50 values of these compounds to C6 cell lines. Then, the OD450 values obtained for the phosphorylated FAK were normalized using the OD450 values that were obtained for GAPDH after 24 hr. Mean per

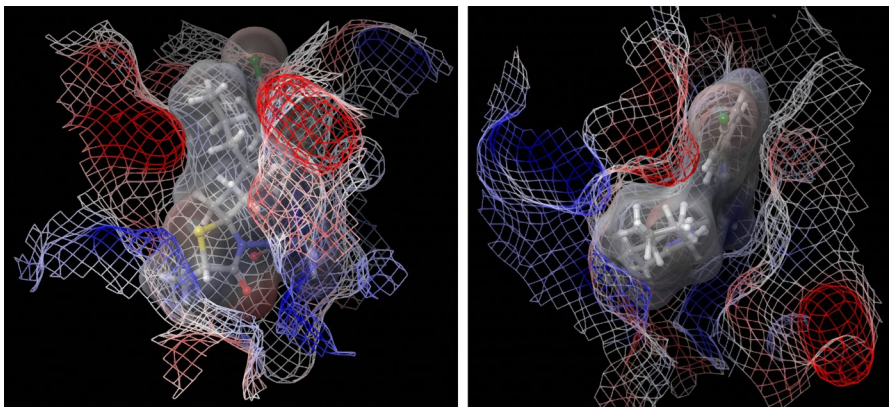


FIGURE 3 Electrostatic potential at the binding site mapped onto the molecular surface of FAK in complexed with docked **6d** (left) and **4h** (right) [Colour figure can be viewed at wileyonlinelibrary.com]

cent absorbance of untreated control cells were assumed to be 0%. Then, % inhibition rates of compounds and cisplatin administered C6 cells were calculated. Data points represent means for three independent wells. According to the assay, the most effective FAK inhibitor on C6 cancer line was determined to be compound **6f** (72.54925 ± 3.63%) followed by compounds **6b** (68.71 ± 0.73%), **6d** (47.78 ± 3.93%) and **6e** (46.64 ± 8.59%) (IC_{50} concentrations were 16.33 ± 1.52, 28.33 ± 2.88, 10.83 ± 1.25 and 19.66 ± 3.21 μM, respectively). However, compounds **4c, 4h, 4l** and **5d** (20.58 ± 3.31%, 21.74 ± 2.87%, 5.93 ± 0.04% and 37.29 ± 2.85%, respectively) did not show considerable FAK inhibition in C6 cancer cells. These results pointed out the importance of the phenyl, propyl, tert-butyl, methyl moieties at the eighth and second position of the spirothiazolidinone ring for FAK inhibitory activity.

When all results are evaluated, spirothiazolidinone derivatives seem to have higher anticancer activity than hydrazone derivatives, and interestingly, the hydrazone derivatives carrying tetramethyl and phenyl substitutions show great anticancer activity. Propyl substitution at 8th position on spirothiazolidinone ring increases activity. Additionally, small alkyl groups such as methyl boost the activity. 4-Chlorophenyl and phenyl derivatives show slightly different anticancer activity. Electronegativity might affect anticancer activity, especially for hydrazone derivatives.

In our recent studies, we have used a number of computational approaches against some important therapeutic targets (Chan et al., 2020; Ece, 2020; Ece & Pejin, 2015; Mustafa Er et al., 2018; Maryam et al., 2020; Maryam et al., 2020; Yamali et al., 2021). Hence, molecular docking simulations were implemented to see probable binding modes of the synthesized compounds. A high resolution (2.3 Å) X-ray crystal structure of focal adhesion kinase domain (PDB ID: 2ETM) in complex with 7H-Pyrrolo[2,3-*d*]pyrimidine derivative (7PY, native ligand) was used in calculations. As an internal validation, co-crystallized native ligand was docked in the binding site and then both conformations were overlayed. The RMSD value between the docked pose and the crystal conformation of the native ligand was found as 0.651 Å. Although the docking programmes perform well in generating pharmacological active conformations of the ligands and detecting the binding modes to the receptor, the current scoring functions are not predicted to distinguish between inactive and active compounds with a high success rate (Ece & Fatma, 2013; Mascarenhas & Ghoshal, 2008; Tahtaci et al., 2018). However, we have obtained good results with Glide software previously (Er et al., 2017; Hou et al., 2011; Tahtaci et al., 2018). The docking scores of the synthesized compounds (**4a-4m, 5a-5f, 6a-6f**) are given together with 7PY in Table 4.

Glide docking performed well in classifying active compounds, for example **6d**, which had a higher docking score among other compounds (**4a-m, 5a-f, 6a-f**). The native ligand, 7PY, had the highest docking score, and it fitted the target by making hydrogen bonds with Cysteine 502 of FAK (Figure 2). As a comparison, 2D binding interaction diagrams were also depicted for one active and one inactive compound, **6d** and **4h**, respectively. As can be seen from the Figure 2, 6d makes the same hydrogen bond with the amino acid residue, CYS 502.

In order to get more insight into the difference between the binding modes of the active and inactive compounds, the electrostatic potential map surface of the receptor and the binding surface of the ligands were drawn (Figure 3). Blue colour indicates low electron density regions, while red colour illustrates high electron density zones. The binding conformation of active compound **6d** and inactive compound **4h** look thoroughly different. The active compound **6d** has favourable electrostatic interactions with the receptor. For instance, high electron density oxygen atom of carbonyl group interacts with low electron density region of the target (Figure 3).

The binding free energies of macromolecules were calculated by MM/GBSA (Molecular Mechanics/Generalized Born Surface Area) methods using combining continuum solvation models and molecular mechanics calculations to

perform more rigorous binding affinity calculations (Hou et al., 2011). Hou et al. (2011) assessed the performance of MM/GBSA on the binding free energies. The authors reported MM/GBSA to serve as a powerful tool in ranking of inhibitors (Hou et al., 2011).

The combination of computational study and experimental findings on SAR works disclosed that the presence of spiro[4.5]decane scaffold with -CH_3 at 2nd position and lipophilic groups at 8th position on spiro[4.5]decane ring has significant effects on the anticancer activity.

The calculated molecular descriptors related to drug likeness and absorption, distribution, metabolism and excretion (ADME) were all in acceptable ranges (Table 4).

4 | CONCLUSION

The fact that focal adhesion kinase signalling pathways can accelerate tumour progression and metastasis formation that makes it a promising therapeutic target prompted us to study novel small molecule inhibitors of this target. In the present study, novel imidazo[2,1-*b*]thiazole derivatives were obtained using simple and practical methods. Their structure was characterized using various spectroscopic methods such as FT-IR, ^{1}H-NMR, ^{13}C-NMR, HSQC, elemental analysis and mass spectroscopy. The in vitro anticancer activities were also investigated against focal adhesion kinase. Most of the compounds, especially the derivatives which carry 3-oxo-1-tiya-4-azaspiro[4.5] decane moiety, showed considerable anticancer activity. Furthermore, compounds **6b**, **6d**, **6f** carrying methyl, propyl, phenyl moieties at the eighth and second position of the spirothiazolidinone ring, showed high FAK inhibitory activities. Additionally, according to the results, compound **4k** can also be considered as a promising anticancer lead compound due to its high SI value and apoptotic effect. However, it does not show anticancer activity by inhibiting FAK. Molecular docking studies were implemented for all synthesized compounds to evaluate the probable binding modes.

The biological assay data, along with the computational results that shed light on the binding motifs and critical interactions, might provide insight into designing new inhibitors against focal adhesion kinase.

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Novel imidazo[2,1-*b*]thiazole-based anticancer agents as potential focal adhesion kinase inhibitors: Synthesis, in silico and in vitro evaluation

Faika Başoğlu, Nuray Ulusoy-Güzeldemirci, Gülşen Akalın-Çiftçi, Serap Çetinkaya, Abdulilah Ece

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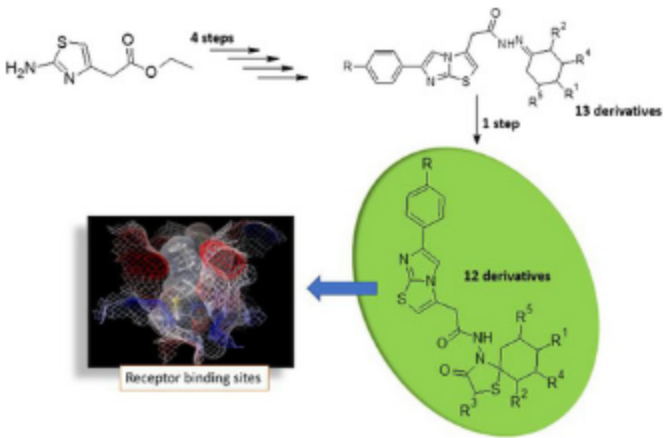

Focal adhesion kinase inhibition effects of novel synthesized imidazo[2,1-*b*]thiazole derivatives were investigated by in vitro and in silico studies. Promising anticancer imidazo[2,1-*b*]thiazole derivatives have been reported as a result of the study.

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