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ORIGINAL RESEARCH

Design, synthesis, and biological evaluation of chalcone-linked thiazole-imidazopyridine derivatives as anticancer agents

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Abstract

A novel library of chalcone linked thiazole-imidazopyridine (**12a–j**) derivatives were designed, synthesized, and their structures were characterized by ^{1}H NMR, ^{13}C NMR and mass spectral studies. Further, all compounds were tested for their anticancer effects on four human cancer cell lines including MCF-7 (breast carcinoma), A549 (lung carcinoma), DU-145 (prostate carcinoma) and MDA MB-231 (breast carcinoma) by employing MTT method, using etoposide as the positive control. Among them, compound **12b** displayed more potent anticancer activity against four cancer cell lines when compared to the positive control.

Keywords Imidazo[4,5-b]pyridine · Zolpidine · Licochalcone A · Chalcone and anticancer activity

Introduction

Now days, cancer is the second leading cause of death after heart disease in developed and undeveloped countries (John and Ross 2010), which is initiated by external (Park et al. 2010; Meffert et al. 2003; Clemens 1991) and internal factors (Mantovani et al. 2008; Clayton et al. 2011; Porta et al. 2011). Cancer treatment has become an important and challenging therapeutic task in medicinal chemistry. The three main treatment strategies employed are surgery, radiation therapy, and chemotherapy. Of these, chemotherapy is one of the important therapy used for the treatment of cancer, which employs chemotherapeutic agents. However, this is associated with various side effects. Hence, the discovery of potent anticancer agents without side effects is a challenge in development of cancer chemotherapeutics for the future generations.

Nitrogen-containing heterocyclic molecules has always attracted significant interest in pharmaceutical industry because of their biological applications. Nitrogen containing imidazo[4,5-b]pyridines are versatile nitrogenized fused hetero-aromatic units that have exhibited potent anticancer properties against a panel of cell lines (Agarwal et al. 2016; Ahsan et al. 2015; Durgesh et al. 2018a, 2018b, 2018c; Hatti et al. 2015a, 2015b; Madhavi et al. 2017b; Murthy et al. 2019; Pragathi et al. 2019; Rao et al. 2019; Reddy et al. 2016a, 2016b; Reddy et al. 2019; Shahinshavali et al. 2019; Spandana et al. 2018a, 2018b; Sreenivasulu et al. 2017; 2018; 2019; 2020; Subramanyam et al. 2018; Suma et al. 2019; Yakantham et al. 2019). It is a structural analog of a purine base. Its derivatives easily interact with the proteins of DNA and RNA. They also show a variety of biological properties like antimitotic (Temple 1990),

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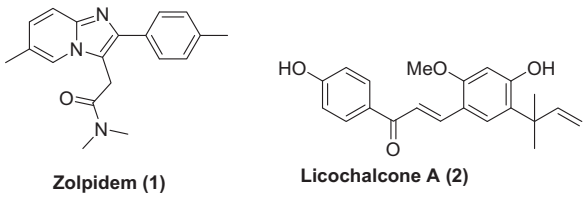


Fig. 1 Structure of Zolpidem (**1**) and Licochalcone A (**2**)

anticancer (Byth et al. 2006; Kamal et al. 2015, 2010), antifungal (Rival et al. 1991), antiviral (Gudmundsson et al. 2003; Gueiffier et al. 1998), anti-inflammatory (Lacerda et al. 2009), antimicrobial (Al-Tel et al. 2011), antiulcer (Starrett et al. 1989), anti tuberculotic (Bukowski and Kaliszan 1991) and hypnotic (Kercher et al. 2007). Among these, the drug candidate, Zolpidine (**1**, Fig. 1) contains imidazo[4,5-b]pyridine core as a backbone of the structure and is used for the treatment of anxiety (antianxiolytic) (Harrison and Keating 2005; Lancel and Steiger 1999; Langer et al. 1990).

On the other hand, chalcones are the unique class of α, β-unsaturated ketones and are precursors of flavonoids and isoflavonoids (Rozmer and Perjési 2016). The unsaturated (–COCH=CH–) system is responsible for biological activity exhibited by this class of compounds. These derivativs possess a broad spectrum of biological activities including antimitotic (Ducki et al. 1998), anticancer (Modzelewska et al. 2006), antimalarial (Larsen et al. 2005), antifungal (Lahtchev et al. 2008), antioxidant (Nowakowska 2007), antituberclosis (Lin et al. 2002), antioncogenic (Go et al. 2005), antileishmanial (Nielsen et al. 1998), anti-inflammatory (Rojas et al. 2003), antiviral (Cheenpracha et al. 2006), antibacterial (Liaras et al. 2011) activities and exhibit hyper glycaemic (Satyanarayana et al. 2004) cardiovascular (Furman et al. 2001) properties, induce apoptosis, are cytotoxic (Dimmock et al. 1998). Chalcone functionality is also present in anticancer agents like Licochalcone A (**2**) (2012), which is first isolated from the root of *Glycyrrhiza glabra* (Yoon et al. 2007; Fu et al. 2004). It acts as a human DNA topoisomerase-I inhibitor.

Based on the above information and our continuous efforts, we have synthesized a new series of structurally modified chalcone incorporated thiazole-imidazopyridine (**12a–j**) derivatives and investigated their anticancer activities against a panel of four human cancer cell lines.

Results and discussion

Chemistry

The synthetic route for these compounds **12a–j** is outlined in Scheme 1. Compound pyridin-2-amine (**3**) undergoes cyclization reaction with 4-methyl cinnamaldehyde (**4**) in the presence of CuBr in ethanol solvent at 60 °C for 8 h to afford 2-p-tolylH-imidazo[1,2-a]pyridine-3-carbaldehyde (**5**). This was then reacted with hydroxyl amine hydrochloride in DMSO solvent and reaction mixture was stirred at 90 °C for 2 h to afford pure 2-p-tolylH-imidazo[1,2-a] pyridine-3-carbonitrile (**6**). This intermediate 5 was converted into thioamide group by reacting with NaSH, $MgCl_2.6H_2O$ in dry DMF and was stirred at 40 °C for 90 min to provide pure 2-p-tolylH-imidazo[1,2-a]pyridine-3-carbothioamide (**7**). Compound **7** undergoes cyclization with 2-bromo-1-(3,4,5-trimethoxyphenyl)ethanone (**8**) in absolute ethanol at room temperature for 1 h, then stirred at reflux for 20 min to give 3-(4-(3,4,5-trimethoxyphenyl) thiazol-2-yl)-2-p-tolylH-imidazo[1,2-a]pyridine (**9**). Compound **9** was reacted with selenium dioxide in ethanol and reaction mixture was stirred at reflux for 24 h to afford 4-(3-(4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)H-imidazo[1,2-a] pyridin-2-yl)benzaldehyde (**10**). Furthermore, aldehyde **9** undergoes to Claisen-schmidt condensation reaction with substituted acetophenones (**11a–j**) in the presence of aq KOH base in ethanol at room temperature for 12 h to provide pure chalcones **12a–j**.

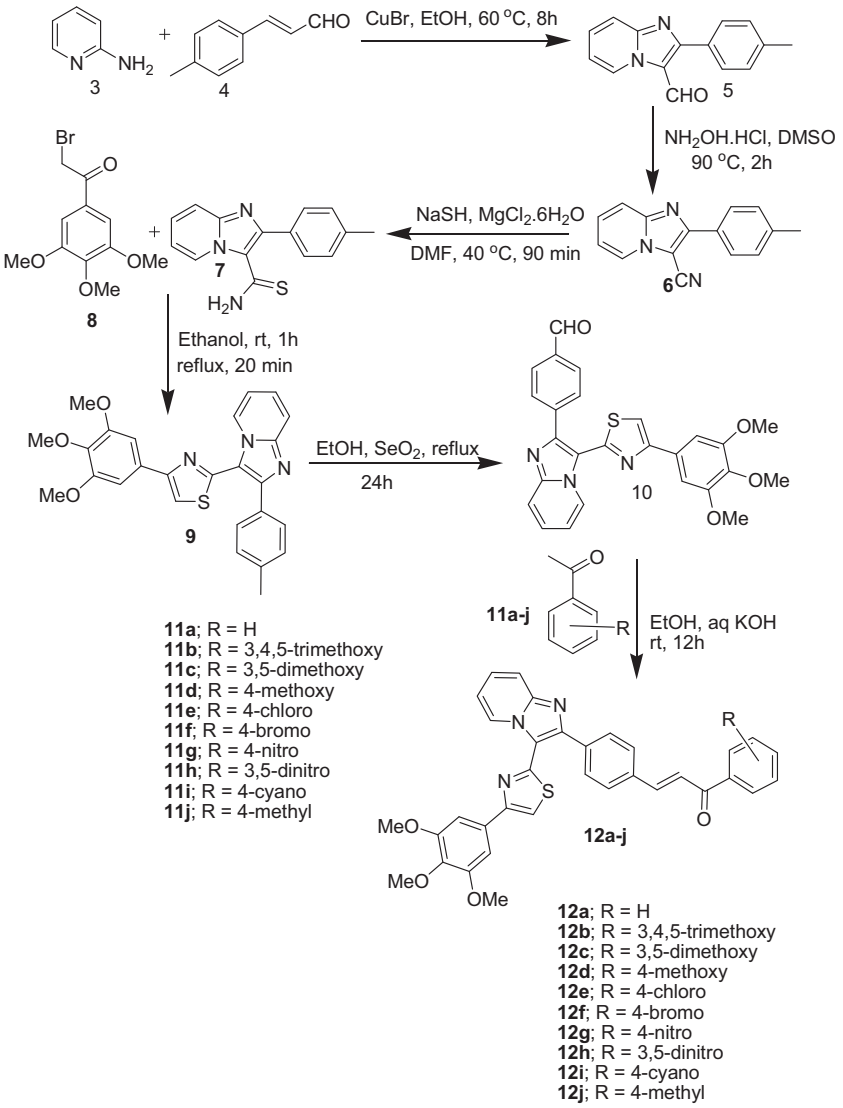
Biological evaluation

In vitro cytotoxicity

The developed compounds (**12a–j**) were screened for their anticancer activity against four human cancer cell lines viz, MCF-7 (breast carcinoma), A549 (lung carcinoma), DU-145 (prostate carcinoma), and MDA MB-231 (breast carcinoma) by using MTT method, and clinical drug etoposide was used as the positive control. Etoposide is employed in chemotherapy medication for the treatment of different types of cancers. Etoposide has 3,5-dimethoxy-4-hydroxy phenyl active scaffold. In the present research, we synthesized different derivatives by varying the substituents on the phenyl ring. Hence we selected Etoposide as standard drug.

Previously reported chalcone derivatives showed medium-to-less anticancer activities against a panel of cancer cell lines (Madhavi et al. 2016, 2017a). But chalcone linked thiazole-imidazopyridine derivatives exhibited potent anticancer activities against four specified cancer cell lines. It can be explained on the basis of insertion of active scaffold "thiazole-imidazopyridine". Among the ten screened compounds, five compounds (**12b, 12c, 12d, 12i** and **12j**) have exhibited superior potency in anticancer activity on four cell lines. Structure-activity relationship studies indicated that the compound **12b** with electron-rich (3,4,5-trimethoxy) group on the phenyl ring displayed the

Scheme 1 Synthesis chalcone linked thiazole-imidazopyridine derivatives



highest anticancer activity amongst all the compounds screened, with IC_{50} values MCF-7 = 0.18 ± 0.094 μM, A549 = 0.66 ± 0.071 μM, DU-145 = 1.03 ± 0.45 μM and MDA MB-231 = 0.065 ± 0.0082 μM. Compound **12c** with 3,5-dimethoxy group exhibited slightly lower activity (MCF-7 = 0.44 ± 0.018 μM, A549 = 1.23 ± 0.37 μM, DU-145 = 1.12 ± 0.25 μM and MDA MB-231 = 0.95 ± 0.066 μM) compared to compound **12b**. Similarly, compound **12d** having only one methoxy substituent (4-methoxy) also showed decreased activity on four cell lines (MCF-7 = 1.98 ± 0.52 μM, A549 = 2.10 ± 1.66 μM, DU-145 = 2.44 ± 1.32 μM and MDA MB-231 = 1.81 ± 0.84 μM) than **12b** and **12c**.Replacement of 4-methoxy substituent with electron-withdrawing substituent's 4-chloro (**12e**), 4-bromo (**12 f**), 4-nitro (**12 g**) and 3,5-dinitro (**12 h**) declined the biological activity further. Interestingly, compound **12i** with 4-cyano group on the phenyl ring has shown considerable anticancer activity (MCF-7 = 2.33 ± 1.73 μM, A549 = 2.17 ± 1.50 μM, DU-145 = 1.90 ± 0.88 μM and MDA MB-231 = 2.02 ± 0.99 μM) than **12e–h**. Whereas, compound **12j** having weaker electron-rich group has demonstrated improved anticancer activity on three cell lines like MCF-7 = 1.73 ± 0.11 μM, A549 = 1.69 ± 0.32 μM, DU-145 = 1.33 ± 0.45 μM. compound **12a** which has no substituent, exhibited lesser activity.

From the SAR studies, it could be concluded that the presence of three electron donating $–OCH_3$ group at 3,4,5 positions on phenyl ring displayed excellent potent anticancer activities against four specified cancer cell lines. Decrease the number of electron donating $–OCH_3$ groups on phenyl ring would decreases the activity against all specified cancer cell lines. The presence of strong withdrawing group $–NO_2$ at 3, 5 positions on phenyl ring displayed very less anticancer activity against specified cancer cell lines. Consequently, weak electron-withdrawing groups like bromo and chloro on phenyl ring showed low

Table 1 In vitro cytotoxicity of newly synthesized compounds 12a-j with IC_{50} in μM[a]

Compound	[b]MCF-7	[c]A549	[d]DU-145	[e]MDA MB-231
12a	3.29 ± 2.66	4.88 ± 2.87	7.13 ± 3.14	3.86 ± 2.10
12b	0.18 ± 0.094	0.66 ± 0.071	1.03 ± 0.45	0.065 ± 0.0082
12c	0.44 ± 0.018	1.23 ± 0.37	1.12 ± 0.25	0.95 ± 0.066
12d	1.98 ± 0.52	2.10 ± 1.66	2.44 ± 1.32	1.81 ± 0.84
12e	4.25 ± 2.11	ND	5.89 ± 3.23	3.57 ± 2.59
12f	6.36 ± 3.56	10.33 ± 5.48	6.68 ± 3.11	ND
12g	14.85 ± 5.98	16.03 ± 6.19	ND	ND
12h	17.68 ± 6.32	11.55 ± 5.42	9.42 ± 4.62	15.61 ± 5.22
12i	2.33 ± 1.73	2.17 ± 1.50	1.90 ± 0.88	2.02 ± 0.99
12j	1.73 ± 0.11	1.69 ± 0.32	1.33 ± 0.45	3.22 ± 2.48
Etoposide	2.11 ± 0.024	3.08 ± 0.135	1.97 ± 0.45	1.91 ± 0.84

ND not determined

[a]Each data is represented as mean ± SD values from three different experiments performed in triplicates.

[b]MCF-7: human breast cancer cell line

[c]A549: human lung cancer cell line

[d]DU-145: human prostate cancer cell line

[e]MDA MB-231: human breast cancer cell line

anticancer activities. In this series of derivatives, cytotoxicity effect decreases as the electron donating group is replaced with electron-withdrawing groups Table 1.

Molecular docking studies

The docking studies of all the imidazopyridine analogs (**12a–j**) were carried against three potential targets, protein kinases CLK1 (5X8I), EGFR (2J5F) and tubulin (1SA0) to know the putative mechanism of actions of these new analogs. The docking studies showed the docking scores were found to be comparatively more against the CLK1. The results of molecular docking studies are shown in Table 2. The docking score of compounds **12c** and **12d** were found to be −9.264 and −9.115 respectively showed significant in vitro cytotoxicity. The comparative docking results against the protein kinases, CLK1, EGFR and tubulin are given in Table 1S (Supplementary information). The imidazopyridine analogs were also reported as protein kinases CLK1 inhibitor (Patent WO2017222285A1). The imidazopyridine analogs were well accommodated in the active site of protein kinase CLK1. The binding mode of all the imidazopyridine analogs against the protein kinase CLK1 is shown in Fig. 2. All the analogs bind in a similar ways (Fig. 3a) except compound, **12g**, which is shown in Figs. 2 and 3b with specific saffron color. The carbonyl functions of ligands, **12b**, **12c**, **12f**, and **12i** showed H-bonding with residues Lys191. The carbonyl function of ligand, **12h** showed H-bonding with the residue Lys191 and nitro function showed slat bridges with the residues Asp288, Asp325, and Lys290. The respective carbonyl and methoxy functions of ligands, **12a**, **12e**, and **12j**, showed

Table 2 Molecular docking studies of the title compounds, 12a-j against protein kinase, CLK1

S. No.	Compounds	Molecular docking studies	
		D Score	Emodel
1	**12a**	−8.795	−105.360
2	**12b**	−9.264	−115.063
3	**12c**	−9.115	−111.646
4	**12d**	−8.548	−109.363
5	**12e**	−8.885	−106.392
6	**12f**	−9.017	−107.381
7	**12g**	−8.619	−111.476
8	**12h**	−9.705	−122.674
9	**12i**	−8.955	−108.793
10	**12j**	−8.794	−105.595

H-bonding with the residue Lys191 and Lys290, respectively. However the carbonyl function of ligand, **12g**, showed H-bonding with the residue Lys290. The methoxy function of ligand, 12d showed H-bonding with the residue Lys290. The imidazopyridine fragments of analogs, **12a–f** lies in the hydrophobic cavity of protein kinase CLK1 surrounded by the residues, Phe326, Val324, Phe241, Leu243, Leu244. The compounds **12b** and **12c** showed significant in vitro cytotoxicity and their binding mode against the active site of protein kinase CLK1 is shown in Figs. 4 and 5. They showed similar type of binding in the active site of CLK1. The binding modes of imidazopyridine analogs, **12a**, and **12d–f** are shown in Fig. 1S, while the binding modes of imidazopyridine analogs, **12g–j** are shown in Fig. 2S (Supplementary information).

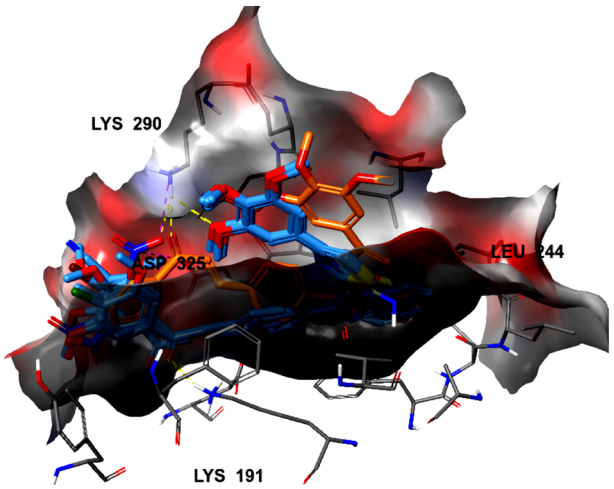


Fig. 2 The binding mode of all the imidazopyridine analogs (**12a-j**) against the active site

Experimental section

All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra were recorded on Gemini Varian-VXR-unity (400 MHz, 300 MHz) instrument. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI + software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electro thermal melting point apparatus, and are uncorrected.

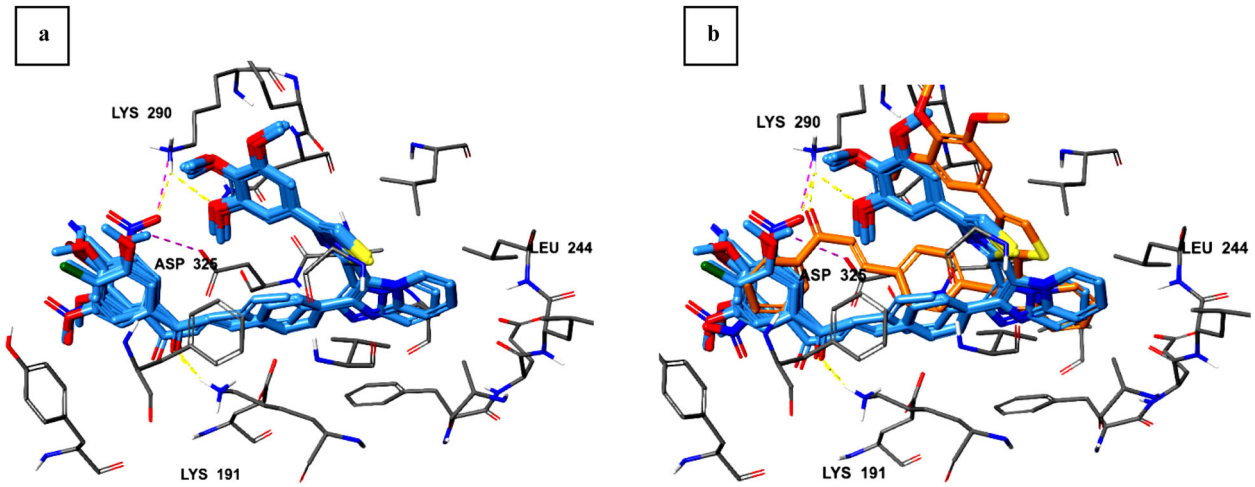


Fig. 3 **a** Binding mode of imidazopyridine analogs **12a–j** except **12g**. **b**. Binding mode of imidazopyridine analogs **12a–j** including **12g**

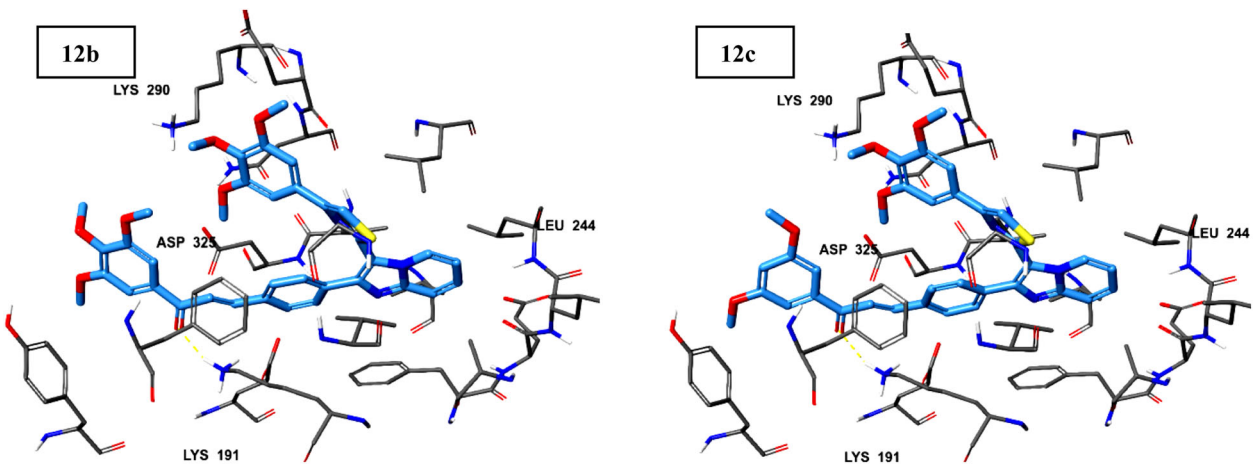


Fig. 4 Binding mode of ligand **12b** and **12c** against the active site of protein kinase CLK1

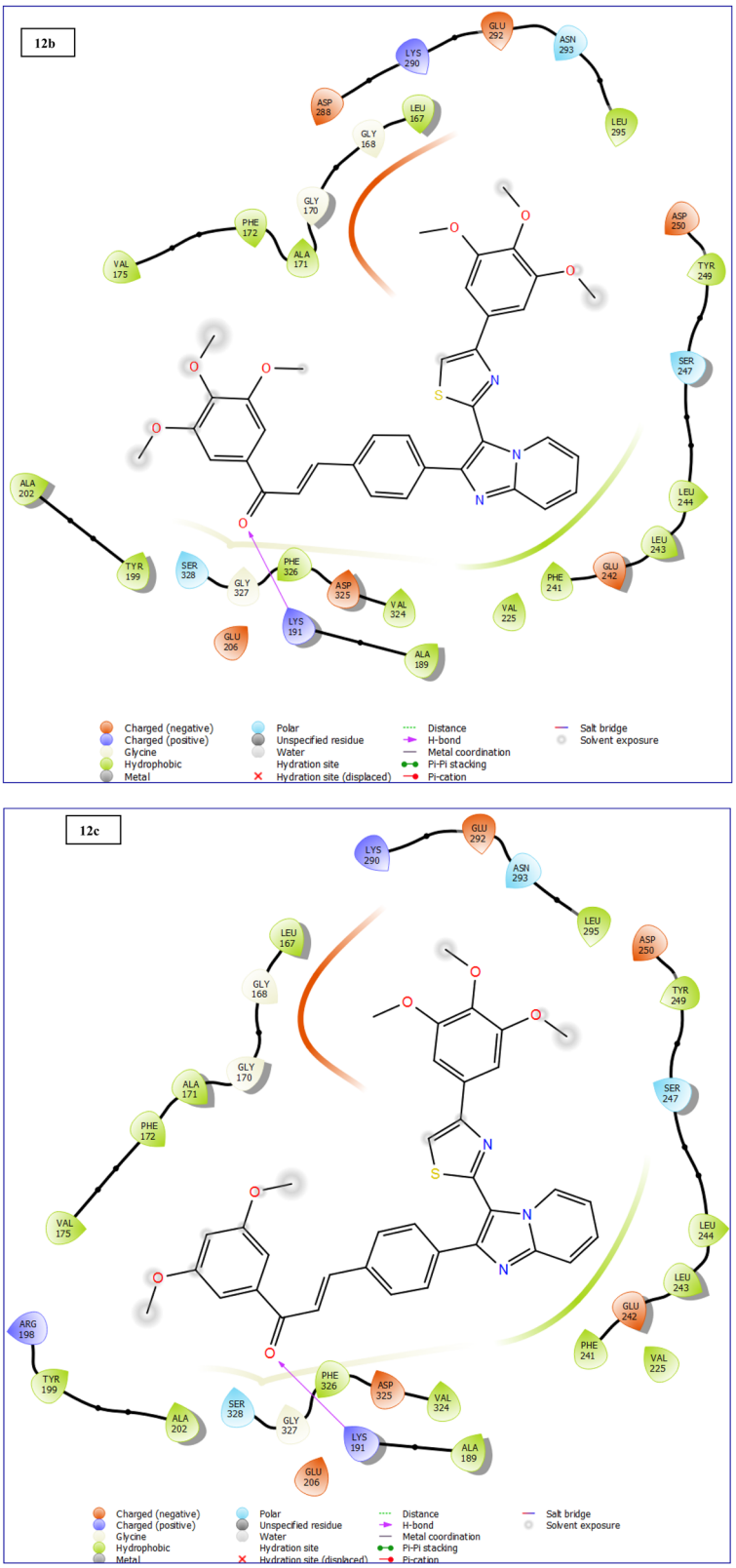


Fig. 5 Binding mode of ligand **12b** and **12c** against the active site of protein kinase CLK1

2-p-TolylH-imidazo[1,2-a]pyridine-3-carbaldehyde (5)

To the mixture of 2-amino pyridine (**3**)(13 g, 0.138 mmol) and (E)-3-p-tolylacrylaldehyde (**4**) (24. 2 g, 0.166 mmol) taken in ethanol, 10 mol% CuBr (1.98 g, 0.0138 mmol) was added and the reaction mixture was stirred at 60 °C for 8 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered using the Whatman paper. The filtrate was dried on rotavapor and was then extracted with water and ethyl acetate. Ethyl acetate layer was dried over anhydrous sodiumsulfate and evaporated on vacuum rotavapor to give crude product. The crude product was purified by column chromatography using n-hexane and ethyl acetateto provide pure colorless product **5** as yellow color solid, in 23.8 g with 61% yield. mp: 168–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 7.08 (d, 2H, $J = 8.1$ Hz), 7.13 (t, 1H), 7.56 (t, 1H), 7.81 (d, 2H, $J = 8.1$ Hz), 7.85 (d, 1H, $J = 8.0$ Hz), 9.68 (d, 1H, $J = 8.0$ Hz), 10.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 115.3, 117.8, 120.3, 128.8, 129.5, 130.1, 130.8, 141.0, 147.9, 158.9, 179.6; MS (ESI): *m/z* 237 $[M + H]^+$; Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.03; H, 4.99; N, 11.71.

2-p-TolylH-imidazo[1,2-a]pyridine-3-carbonitrile (6)

A mixture of 2-p-tolylH-imidazo [1,2-a]pyridine-3-carbaldehyde (**5**) (23 g, 0.097 mmol) and $NH_2OH{\cdot}HCl$ (7.45 g, 0.107 mmol) in DMSO (50 ml) was stirred at 90 °C for 2 h. After completion of the reaction as confirmed by TLC (20% EtOAc in hexane), the mixture was cooled and diluted with H_2O. The solid precipitated was collected by filtration, washed with H_2O and dried under suction to afford pure nitrile compound **6** as half white color solid, in 16.2 g with 71% yield. mp: 160–162 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.47 (s, 3H), 7.10 (d, 2H, $J = 8.2$ Hz), 7.15 (t, 1H), 7.57 (t, 1H), 7.83 (d, 2H, $J = 8.2$ Hz), 7.85 (d, 1H, $J = 8.0$ Hz), 9.68 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 93.3, 113.2, 114.8, 118.6, 125.9, 127.5, 128.2, 129.10129.8, 140.6, 146.9, 153.6; MS (ESI): m/z 236 $[M + H]^+$; Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.06; H, 4.63; N, 17.85.

2-p-TolylH-imidazo[1,2-a]pyridine-3-carbothioamide (7)

To a slurry of 70% sodium hydrosulfide hydrate (7 g, 0.125 mmol) and magnesium chloride hexahydrate (12.97 g, 0.0638 mmol) in 45 ml of DMF, 2-p-tolylH-imidazo[1,2-a]pyridine-3-carbonitrile (**6**) (15 g, 0.0638 mmol) was added in one portion, and the mixture was stirred at room temperature for 90 min. The resulting green slurry was poured into 100 ml of water, and the precipitates obtained were collected by filtration. The crude product was suspended in 1 N HCl and stirred for 20 min, then filtered and washed with water to afford pure compound **7** as half white color solid, in 12.9 g with 76% yield. mp: 211–214 °C, ^{1}H NMR (300 MHz, DMSO-d_6):δ 2.47 (s, 3H), 7.11 (d, 2H, $J = 8.3$ Hz), 7.16 (t, 1H), 7.58 (t, 1H), 7.84 (d, 2H, $J = 8.3$ Hz), 7.86 (d, 1H, $J = 8.1$ Hz), 9.33 (s, 2H), 9.66 (d, 1H, $J = 8.1$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.3, 113.4, 114.6, 116.3, 121.2, 125.6, 130.8, 132.0, 138.9, 140.2, 148.6, 178.3; MS (ESI): *m/z* 268 $[M + H]^+$; Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.22; H, 4.78; N, 15.55.

3-(4-(3,4,5-Trimethoxyphenyl)thiazol-2-yl)-2-p-tolylH-imidazo[1,2-a]pyridine (9):

The compounds 2-bromo-1-(3,4,5-trimethoxyphenyl)ethanone (**8**) (13 g, 0.045 mmol) and 2-p-tolylH-imidazo[1,2-a] pyridine-3-carbothioamide (**7**) (12 g, 0.045 mmol) were dissolved in absolute ethanol and reaction mixture was stirred at room temperature for 1 h and then refluxed for 20 min. After cooling, the precipitate obtained was filtered and neutralized with sodium acetate base, recovered from the HBr salts. The crude product was recrystallized twice from ethanol solvent to afford pure compound **9** as half white color solid, 14.3 g with 70% yield. mp: 201–203 °C; ^{1}H NMR (300 MHz, DMSO-d_6):δ 2.47 (s, 3H), 3.87 (s, 6H), 3.90 (s, 3H), 7.13 (d, 2H, $J = 8.4$ Hz), 7.17 (t, 1H), 7.38 (s, 2H), 7.59 (t, 1H), 7.85 (d, 2H, $J = 8.5$ Hz), 7.88 (d, 1H, $J = 8.2$ Hz), 8.23 (s, 1H), 9.69 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.6, 56.3, 61.1, 103.6, 108.9, 114.6, 120.1, 127.6, 128.0, 130.1, 131.1, 131.8, 132.5, 135.3, 139.1, 140.6, 145.9, 149.0, 154.1, 159.1; MS (ESI): *m/z* 458 $[M + H]^+$; Anal. Calcd for $C_{26}H_{23}N_3O_3S$: C, 68.25; H, 5.07; N, 9.18. Found: C, 68.42; H, 4.91; N, 9.36.

4-(3-(4-(3,4,5-Trimethoxyphenyl)thiazol-2-yl)H-imidazo[1,2-a]pyridin-2-yl)benzaldehyde (10)

A mixture of compound (**9**) (13 g, 0.0284 mmol), SeO_2 (15.8 g, 0.142 mmol) and 70 ml ethanol was stirred at reflux for 24 h. After completion of the reaction, the mixture was cooled to room temperature and filtered through a celite pad. The filtrate was evaporated by vacuum and diluted with 50 ml water and extracted with 150 ml of CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ solution, dried over anhydrous sodium sulfate. The crude product was purified by column chromatography by using hexane:ethyl acetate (4:6) as eluent to afford pure aldehyde **10**, as half white color solid, in 10.8 g with 81% yield. mp: 224 −226 °C. ^{1}H NMR (300 MHz, DMSO-d_6):δ 3.87 (s, 6H), 3.90 (s, 3H), 7.18 (d, 2H, $J = 8.5$ Hz), 7.20 (t, 1H), 7.38 (s, 2H), 7.60 (t, 1H), 7.86 (d, 2H, $J = 8.5$ Hz), 7.89 (d, 1H, $J = 8.2$ Hz), 8.24 (s, 1H), 9.69 (d, 1H, $J = 8.2$ Hz), 10.35 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.1, 60.9, 103.4, 108.6,

109.8, 114.6, 120.1, 126.9, 128.0, 130.3, 131.1, 132.6, 138.1, 138.9, 139.3, 145.7, 148.3, 154.1, 158.9, 191.4; MS (ESI): *m/z* 472 $[M + H]^+$; Anal. Calcd for $C_{26}H_{21}N_3O_4S$: C, 66.23; H, 4.49; N, 8.91. Found: C, 66.06; H, 4.36; N, 8.78.

(2E)-3-(4-(3-(4-(3,4,5-Trimethoxyphenyl)thiazol-2-yl) H-imidazo[1,2-a]pyridin-2-yl)phenyl)-1-phenylprop-2-en-1-one (12a)

A mixture of acetophenone (**11a)** (0.13 ml,0.001 mmol) and 4-(3-(4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)H-imidazo [1,2-a]pyridin-2-yl)benzaldehyde **(10)**(500 mg, 0.001 mmol) was dissolved in 20 ml ethanol. To this mixture, potassium hydroxide (40%, 1 ml) was added at 0–5 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was poured over crushed ice and acidified with dil HCl. The light yellow solid thus obtained was filtered, washed with water and dried. The residue was purified on column chromatography by using ethyl acetate/hexane (7:3) to afford compound **12a** as half white color solid, 212.6 mg with 35% yield. mp: 254–256 °C; ^{1}H NMR (300 MHz, DMSO-d_6):δ 3.87 (s, 6H), 3.90 (s, 3H), 7.10 (d, 1H, $J = 15.6$ Hz), 7.18 (d, 2H, $J = 8.5$ Hz), 7.20 (t, 1H), 7.38 (s, 2H), 7.42 (t, 1H), 7.61 (t, 1H), 7.87–8.00 (m, 4H), 8.24 (s, 1H), 9.69 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6):δ 57.4, 61.5, 104.7, 109.2, 115.6, 120.3, 122.4, 127.6, 127.9, 128.3, 129.7, 131.2, 131.6, 134.5, 135.6, 135.8, 139.6, 146.3, 149.6, 154.2, 159.7, 170.5; MS (ESI): *m/z* 574 $[M + H]^+$; Anal. Calcd for $C_{34}H_{27}N_3O_4S$: C, 71.19; H, 4.74; N, 7.32. Found: C, 71.06; H, 4.63; N, 7.47.

(2E)-1-(3,4,5-Trimethoxyphenyl)-3-(4-(3-(4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)H-imidazo[1,2-a] pyridin-2-yl)phenyl)prop-2-en-1-one (12b)

This compound **12b** was prepared following the method described for the preparation of the compound **12a**, employing **10** (500 mg, 0.001 mmol) with 1-(3,4,5-trimethoxyphenyl)ethanone(**11b**) (210 mg, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 8:2) to afford pure compound **12b** as half white color solid, 233.4 mg with 33% yield. mp: 276–278 °C, ^{1}H NMR (300 MHz, DMSO-d_6):δ 3.79 (s, 6H), 3.87 (s, 6H), 3.90 (s, 3H), 3.94 (s, 3H), 7.09 (d, 1H, $J = 15.7$ Hz), 7.17 (d, 2H, $J = 8.3$ Hz), 7.19 (t, 1H), 7.30 (s, 2H), 7.38 (s, 2H), 7.60 (t, 1H), 7.84–7.95 (m, 4H), 8.24 (s, 1H), 9.69 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6):δ 57.4, 57.8, 61.5, 61.7, 104.5, 107.3, 109.3, 115.6, 120.4, 124.6, 127.5, 127.9, 128.3, 128.7, 131.4, 131.7, 134.6, 134.8, 135.7, 139.5, 140.6, 145.3, 145.9, 146.3, 149.6, 152.4, 154.3, 159.7, 171.3; MS (ESI): *m/z* 664 $[M + H]^+$; Anal. Calcd for $C_{37}H_{33}N_3O_7S$: C, 66.95; H, 5.01; N, 6.33. Found: C, 66.82; H, 4.88; N, 6.46.

(2E)-1-(3,5-Dimethoxyphenyl)-3-(4-(3-(4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)H-imidazo[1,2-a] pyridin-2-yl)phenyl)prop-2-en-1-one (12c)

This compound **12c** was prepared following the method described for the preparation of the compound **12a**, employing **10** (500 mg, 0.001 mmol) with 1-(3,5-dimethoxyphenyl)ethanone(**11c**) (180 mg, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 8:2) to afford pure compound **12c** as half white color solid, 248.7 mg with 37% yield. mp: 267–269 °C,^{1}H NMR (300 MHz, DMSO-d_6):δ 3.69 (s, 6H), 3.87 (s, 6H), 3.90 (s, 3H), 6.88 (s, 1H), 7.11 (d, 1H, $J = 15.6$ Hz), 7.18 (d, 2H, $J = 8.4$ Hz), 7.19 (t, 1H), 7.34 (s, 2H), 7.38 (s, 2H), 7.60 (t, 1H), 7.88–7.97 (m, 4H), 8.25 (s, 1H), 9.69 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6):δ 56.4, 57.5, 61.5, 104.5, 109.4, 110.5, 112.4, 115.6, 120.6, 124.7, 127.5, 127.9, 128.5, 128.8, 131.5, 131.7, 134.6, 134.8, 135.7, 139.5, 144.5, 145.8, 146.3, 149.6, 154.2, 159.3, 160.5, 171.4; MS (ESI): m/z634 $[M + H]^+$; Anal. Calcd for $C_{36}H_{31}N_3O_6S$: C, 68.23; H, 4.93; N, 6.63. Found: C, 68.06; H, 4.81; N, 6.49.

(2E)-1-(4-Methoxyphenyl)-3-(4-(3-(4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)H-imidazo[1,2-a] pyridin-2-yl)phenyl)prop-2-en-1-one (12d):

This compound **12d** was prepared following the method described for the preparation of the compound **12a**, employing **10**(500 mg, 0.001 mmol) with 1-(4-methoxyphenyl)ethanone(**11d**) (150 mg, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 8:2) to afford pure compound **12d** as half white color solid, 220.6 mg with 34% yield. mp: 260–262 °C,^{1}H NMR (300 MHz, DMSO-d_6):δ 3.87 (s, 6H), 3.90 (s, 3H), 3.93 (s, 3H), 6.88 (s, 1H), 7.08–7.13 (m, 3H), 7.18 (d, 2H, $J = 8.5$ Hz), 7.20 (t, 1H, c7), 7.38 (s, 2H), 7.43 (d, 2H, $J = 8.7$ Hz), 7.61 (t, 1H), 7.85–7.98 (m, 4H), 8.25 (s, 1H), 9.12 (d, 2H, $J = 8.7$ Hz), 9.69 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6):δ 56.5, 57.5, 61.6, 104.6, 109.5, 114.5, 115.7, 120.5, 122.4, 127.5, 127.8, 128.4, 128.7, 129.4, 131.5, 131.7, 134.6, 134.8, 135.7, 139.6, 145.4, 146.8, 149.4, 154.6, 159.7, 164.8, 171.7; MS (ESI): *m/z* 604 $[M + H]^+$; Anal. Calcd for $C_{35}H_{29}N_3O_5S$: C, 69.64; H, 4.84; N, 6.96. Found: C, 69.81; H, 4.72; N, 7.12.

(2E)-1-(4-Chlorophenyl)-3-(4-(3-(4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)H-imidazo[1,2-a] pyridin-2-yl)phenyl)prop-2-en-1-one (12e)

This compound **12e** was prepared following the method described for the preparation of the compound **12a**, employing **10** (500 mg, 0.001 mmol) with 1-(4-chlorophenyl)ethanone(**11e**)

(0.13 ml, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 7:3) to afford pure compound **12e** as half white color solid, 342.7 mg with 53% yield. mp: 287–289 °C,^{1}H NMR (300 MHz, DMSO-d_6):δ 3.87 (s, 6H), 3.90 (s, 3H), 7.12 (d, 1H, J = 15.8 Hz), 7.19 (d, 2H, J = 8.6 Hz), 7.21 (t, 1H), 7.38 (s, 2H), 7.51 (d, 2H, J = 8.8 Hz), 7.61 (t, 1H), 7.87-8.03 (m, 4H), 8.27 (s, 1H), 9.18 (d, 2H, J = 8.8 Hz), 9.69 (d, 1H, J = 8.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6):δ 57.6, 61.7, 104.6, 109.7, 115.6, 120.4, 122.3, 127.6, 127.9, 128.4, 128.7, 130.4, 131.5, 131.8, 132.3, 134.6, 134.8, 135.7, 137.6, 139.5, 140.6, 145.7, 146.3, 149.7, 154.3, 159.6, 172.6; MS (ESI): m/z 608 $[M + H]^+$; Anal. Calcd for $C_{34}H_{26}ClN_3O_4S$: C, 67.15; H, 4.31; N, 6.91. Found: C, 67.03; H, 4.44; N, 7.07.

(2E)-1-(4-Bromophenyl)-3-(4-(3-(4-(3,4,5-trimethoxyphenyl)thiazol-2-yl)H-imidazo[1,2-a] pyridin-2-yl)phenyl)prop-2-en-1-one (12f)

This compound **12f** was prepared following the method described for the preparation of the compound **12a**, employing **10** (500 mg, 0.001 mmol) with 1-(4-bromophenyl) ethanone (**11f**) (199 mg, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 7:3) to afford pure compound **12f** as half white color solid, 289.7 mg with 42% yield. mp: 293–295 °C,^{1}H NMR (300 MHz, DMSO-d_6):δ 3.87 (s, 6H), 3.90 (s, 3H), 7.11 (d, 1H, J = 15.7 Hz), 7.18 (d, 2H, J = 8.6 Hz), 7.20 (t, 1H), 7.38 (s, 2H), 7.56 (d, 2H, J = 8.7 Hz), 7.61 (t, 1H), 7.86-7.94 (m, 4H), 8.26 (s, 1H), 9.10 (d, 2H, J = 8.7 Hz), 9.69 (d, 1H, J = 8.2 Hz);^{13}C NMR (75 MHz, DMSO-d_6):δ 57.5, 61.6, 104.6, 109.7, 115.6, 120.5, 122.4, 127.5, 127.9, 128.5, 128.7, 129.3, 131.5, 131.7, 132.5, 132.7, 134.5, 134.8, 136.5, 137.2, 139.5, 145.3, 146.5, 149.7, 154.4, 159.7, 171.7; MS (ESI): m/z 654 $[M + H]^+$; Anal. Calcd for $C_{34}H_{26}BrN_3O_4S$: C, 62.58; H, 4.02; N, 6.44. Found: C, 62.41; H, 4.16; N, 6.59.

(2E)-3-(4-(3-(4-(3,4,5-Trimethoxyphenyl)thiazol-2-yl) H-imidazo[1,2-a]pyridin-2-yl)phenyl)-1-(4-nitrophenyl)prop-2-en-1-one (12 g):

This compound **12g** was prepared following the method described for the preparation of the compound **12a**, employing **10** (500 mg, 0.001 mmol) with 1-(4-nitrophenyl) ethanone (**11g**) (165 mg, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 7:3) to afford pure compound **10 g** as half white color solid, 365.4 mg with 56% yield. mp: 300–302 °C,^{1}H NMR (300 MHz, DMSO-d_6):δ 3.87 (s, 6H), 3.90 (s, 3H), 7.15 (d, 1H, J = 15.7 Hz), 7.17-7.25 (m, 3H), 7.38 (s, 2H), 7.62 (t, 1H), 7.86-7.94 (m, 4H), 8.15 (d, 2H, J = 8.9 Hz), 8.27 (s, 1H), 9.32 (d, 2H, J = 8.9 Hz), 9.69 (d, 1H, J = 8.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6):δ 57.6, 61.7, 104.5, 109.7, 115.6, 120.5, 122.7, 124.6, 127.5, 127.9, 128.5, 128.7, 131.6, 131.9, 132.4, 134.6, 134.7, 136.5, 139.6, 144.5, 145.5, 146.3, 149.6, 153.4, 154.7, 159.6, 171.7; MS (ESI): m/z 619 $[M + H]^+$; Anal. Calcd for $C_{34}H_{26}N_4O_6S$: C, 66.01; H, 4.24; N, 9.06. Found: C, 66.17; H, 4.39; N, 9.22.

(2E)-3-(4-(3-(4-(3,4,5-Trimethoxyphenyl)thiazol-2-yl) H-imidazo[1,2-a]pyridin-2-yl)phenyl)-1-(3,5-dinitrophenyl)prop-2-en-1-one (12 h)

This compound **12h** was prepared following the method described for the preparation of the compound **12a**, employing **10** (500 mg, 0.001 mmol) with 1-(3,5-dinitrophenyl)ethanone(**11h**) (210 mg, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 7:3) to afford pure compound **12h** as half white color solid, 410.3 mg with 58% yield. mp: 343–345 °C,^{1}H NMR (300 MHz, DMSO-d_6):δ 3.87 (s, 6H), 3.90 (s, 3H), 7.16 (d, 1H, J = 15.8 Hz), 7.19–7.28 (m, 3H), 7.38 (s, 2H), 7.62 (t, 1H), 7.88-7.97 (m, 4H), 8.27 (s, 1H), 9.44 (s, 2H), 9.69 (d, 1H, J = 8.2 Hz), 9.73 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6):δ 57.6, 61.7, 104.6, 109.8, 115.7, 120.5, 122.7, 125.6, 127.6, 127.9, 128.5, 128.7, 129.3, 131.6, 131.8, 134.6, 134.8, 136.8, 139.4, 145.6, 146.7, 149.6, 151.7, 154.8, 159.7, 171.8; MS (ESI): m/z 664 $[M + H]^+$; Anal. Calcd for $C_{34}H_{25}N_5O_8S$: C, 61.53; H, 3.80; N, 10.55. Found: C, 61.39; H, 3.93; N, 10.72.

4-((2E)-3-(4-(3-(4-(3,4,5-Trimethoxyphenyl)thiazol-2-yl)H-imidazo[1,2-a]pyridin-2-yl)phenyl)acryloyl) benzonitrile (12i):

This compound **12i** was prepared following the method described for the preparation of the compound **12a**, employing **10** (500 mg, 0.001 mmol) with 4-acetylbenzonitrile (**11i**) (145 mg, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 7:3) to afford pure compound **12i** as half white color solid, 106.8 mg with 17% yield. mp: 295–297 °C,^{1}H NMR (300 MHz, DMSO-d_6):δ 3.87 (s, 6H), 3.90 (s, 3H), 7.14 (d, 1H, J = 15.6 Hz), 7.17–7.26 (m, 3H), 7.38 (s, 2H), 7.62 (t, 1H), 7.87–7.96 (m, 4H), 8.13 (d, 2H, J = 8.8 Hz), 8.27 (s, 1H), 9.51 (d, 2H, J = 8.8 Hz), 9.69 (d, 1H, J = 8.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6):δ 57.6, 16.7, 104.6, 109.8, 115.6, 116.4, 118.7, 120.5, 122.7, 127.6, 127.9, 128.5, 128.8, 131.5, 131.7, 132.4, 133.7, 134.7, 134.9, 136.5, 139.6, 142.5, 145.7, 146.4, 149.7, 154.6, 159.7, 171.8; MS (ESI): m/z 599$[M + H]^+$; Anal. Calcd for $C_{35}H_{26}N_4O_4S$: C, 70.22; H, 4.38; N, 9.36. Found: C, 70.09; H, 5.00; N, 9.51.

(2E)-3-(4-(3-(4-(3,4,5-Trimethoxyphenyl)thiazol-2-yl) H-imidazo[1,2-a]pyridin-2-yl)phenyl)-1-p-tolylprop-2-en-1-one (12j)

This compound **12j** was prepared following the method described for the preparation of the compound **12a**, employing **10** (500 mg, 0.001 mmol) with 1-p-tolylethanone (**11j**) (0.13 ml, 0.001 mmol) and crude product was purified by column chromatography (ethyl acetate/hexane: 7:3) to afford pure compound **12j** as half white color solid, 241.7 mg with 39% yield. mp: 270–272 °C, ^{1}H NMR (300 MHz, DMSO-d_6):δ 2.48 (s, 3H), 3.87 (s, 6H), 3.90 (s, 3H), 7.12 (d, 1H, $J = 15.5$ Hz), 7.18 (d, 2H, $J = 8.6$ Hz), 7.21 (t, 1H), 7.32-7.41 (m, 4H), 7.62 (t, 1H), 7.85-7.94 (m, 4H), 8.26 (s, 1H), 9.69 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6):δ 24.8, 57.6, 61.7, 104.7, 109.7, 115.6, 120.7, 122.6, 127.5, 127.8, 128.5, 128.9, 129.5, 130.2, 131.6, 131.7, 1134.6, 134.8, 136.5, 136.8, 139.6, 144.5, 145.9, 146.4, 149.7, 154.6, 159.7, 170.6; MS (ESI): m/z 588 $[M + H]^+$; Anal. Calcd for $C_{35}H_{29}N_3O_4S$: C, 71.53; H, 4.97; N, 7.15. Found: C, 71.66; H, 4.85; N, 7.03.

MTT assay

Individual wells of a 96-well tissue culture micro titer plate were inoculated with 100 µL of complete medium containing 1×10^4 cells. The plates were incubated at 37 °C in a humidified 5% CO_2 incubator for 18 h prior to the experiment. After medium removal, 100 µL of fresh medium containing the test compounds and etoposide (Eto) at different concentrations such as 0.5, 1, and 2 µM were added to each well and incubated at 37 °C for 24 h. Then the medium was discarded and replaced with 10 µL MTT dye. Plates were incubated at 37 °C for 2 h. The resulting formazan crystals were solubilized in 100 µL extraction buffer. The optical density (OD) was read at 570 nm with the micro plate reader (Multi-mode Varioskan Instrument-Themo Scientific). The percentage of DMSO in the medium never exceeded 0.25%.

Molecular docking studies

The X-ray crystal structure protein kinase CLK1 (PDB: 5X8I), with resolution 1.91 A°; *R*-value: 0.168 (obs.) was obtained from the protein data bank www.rcsb.org/structure/5×8I. The ligands were saved as mol file. The molecular docking studies were performed as per the reported protocol (Sun et al. 2017; ElHady et al. 2017).

Conclusion

In conclusion, A new library of chalcone linked thiazole-imidazopyridine (**12a–j**) were synthesized and screened their anticancer effects on four human cancer cell lines including MCF-7 (breast carcinoma), A549 (lung carcinoma), DU-145 (prostate carcinoma), and MDA MB-231 (breast carcinoma) by employing MTT method and etoposide used as positive control. Among them, compound **12b** exhibited potent anticancer activities against four cancer cell lines than positive control. This compound may act as drug lead one in cancer chemotherapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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