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Design, synthesis, DFT, molecular modelling studies and biological evaluation of novel 3-substituted (*E*)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-ones with potent cytotoxic activities against breast MCF-7, liver HepG2, and lung A549

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ABSTRACT

We report the synthesis of novel 3-substituted (*E*)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-ones **6-11**, and their biological evaluation. Based on structural and pharmacophore analyses of known inhibitors such as fluorouracil (5-FU), we envisioned interesting 2-thioxoimidazolidin-4-one compounds, 3-substituted (*E*)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-ones **6-11** that would be expected to well match the structural features in 5-FU. Efficient synthesis of twenty-four target compounds **6-11** were achieved through the synthetic pathway of **5** → **6** → **7** → **10** → **11**, established after consideration of several plausible synthetic pathways. A series of (*E*)-5-(arylidene)-1-methyl-2-thioxoimidazolidinoneones **5a-d** were synthesized *via* the reaction of 1-methyl-2-thioxoimidazolidin-4-one (**3**), which in turn was prepared *via* the reaction of *N*-methyl glycine (**2**) with NH_4SCN, followed by Knoevenagel condensation. *N*-alkylation and *N*-glycosylation were carried *via* the reaction of **5a-d** with alkyl bromides and α-glycopyranosyl bromides **9a,b** under alkaline and glycoside conditions, respectively. The *N*-alkylated and *N*-glycosylated structures have been selected for the products. Conformational analysis has been studied by homonuclear and heteronuclear two-dimensional NMR methods (DQF-COSY, HMQC, and HMBC). The *N* site of alkylation and glycosylation were determined from the ^{1}H, ^{13}C heteronuclear multiple-quantum coherence (HMQC) experiments. Molecular modelling and DFT calculations using B3LYP/6-31+G (d, p) level were performed to study the electronic and geometric properties obtained from the stable structure of the investigated compounds. A good correlation between the quantum chemical descriptors and experimental observations was found. The synthesized derivatives exhibited good binding interactions towards the cyclin-dependent kinase 2, especially compound **11b**, which have better key interactions than the co-crystallized ligand. Additionally, it had potent cytotoxic activities with IC_{50} = 4.30, 5.53, 9.43 against MCF-7, HepG2, and A549, respectively.

1. Introduction

2-Thioxo-4-imidazolidinones were surveyed as biologically relevant moieties against different cancer cell lines, so in the present study, we analyzed novel derivatives as target-oriented chemotherapeutic anticancer drugs. 2-Thioxo-4-imidazolidinone compounds [1,2] and their 2-alkylthioxo-4-imidazolidinone derivatives are a biologically important class of compounds in the fields of drugs, pharmaceutical intermediates, and agrochemicals. As examples, the isatinylidene derivative **I** (Fig. 1) exhibit immunosuppressive activity [3] and the thioglycosyl hydantoin [4] **II** possesses a broad-spectrum antitumor activity against a wide range of different human cell lines from nine tumor subpanels causing both cytostatic and cytotoxic effects. The 5-arylmethylene-2-methylthio-4-imidazolidinones **III** substituted with a biphenyl tetrazole (BTP) group at the C-2 position show activities as angiotensin **II** receptor antagonists [5] and the 3-morpholinomethyl-5,5-dimethyl-2-thioglycosyl-4-imidazolidinone **IV** has been also identified as a potential AZT analogue [6]. The 2-thioxo-4-imidazolidinone derivatives have not only been used in medicinal chemistry but have

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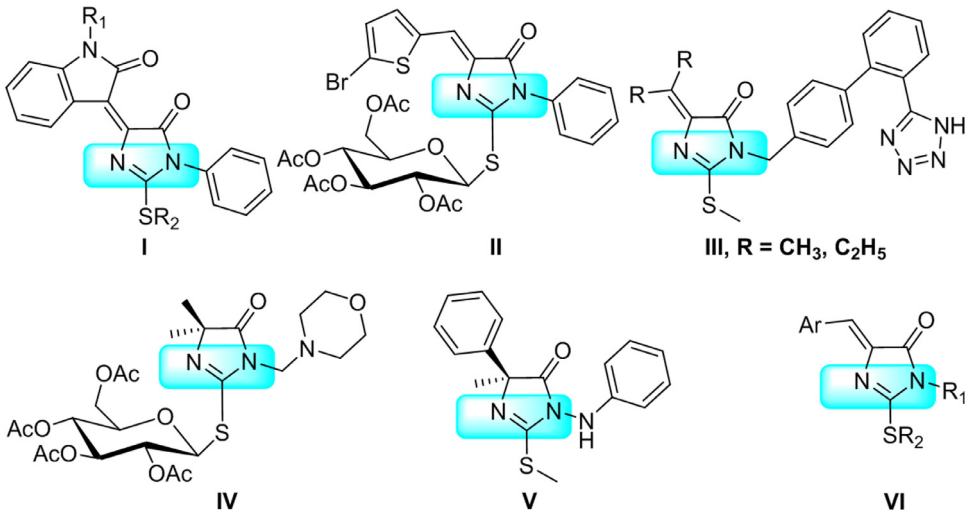


Fig. 1. Select 4-imidazolone derivatives with biological activities.

also been developed as fungicides [7] [e. g., fenamidone (**V**) [8,9] and herbicides [10]. Recent work [11] by Wang's group has established that esters of 5-(4-hydroxybenzyl)-2-thioxoimidazolidin-4-ones exhibit good herbicidal activity against *Zea mays* and *Arabidopsis thaliana*.

On the other hand, the synthesis, and biological properties of 2-alkylthio-5-arylidene-4-imidazolidinone derivatives **VI** has rarely been the subject of detailed investigations reported in the literature. A 25-year-old study of Unangst and co-workers only reported the preparation of (5*Z*)-[(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-1,5-dihydro-1-methyl-2-methylthio-4*H*-imidazol-4-one for an inflammation therapy program [12]. In 1993, a report described the biological activity of the same compound as a potent antiviral agent for the human immunodeficiency virus (HIV) [13]. More recently, the use of 5-arylidene-1-methyl-1,5-dihydro-4*H*-imidazol-4-one as a convenient synthetic intermediate in a sulfur/nitrogen displacement has been studied with one example [14,15]. As the first part of this study, we at this moment report the synthesis and spectroscopy of a new series of *N*-alkylated bearing 1-methal-2-thioxoimidazolidin-4-ones as potential antiviral and antitumor activities (Schemes 1 and 2). Moreover, nucleoside analogs constitute an important class of therapeutic agents in the treatment of cancers and viral infections [16,17]. The mode of action of these derivatives is based upon their intracellular conversation to their phosphorylated forms (nucleotides), which can interact with different cell biosynthesis. During the last decades, intensive research was dedicated to the discovery of more effective, selective, and non-toxic new nucleoside derivatives [18-21]. Glycosides of structurally similar heterocyclic systems have been reported before and in continuation of our work on the synthesis of novel nucleosides as potential antiviral, antitumor agents and keeping in mind the biological significance of imidazolidin-2,4-diones, 2-thioxoimidazolidin-4-ones, 2-thioxopyrimidin-4-ones, 2-thioxothiazolidin-4-ones, 2-thioxopyridines and 2-thioxoquinazolin-4-ones [22-55]. As the second part of this study, we at this moment report the synthesis and spectroscopy of a new series of *N*-glycosylated bearing (*E*)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-one bases as potential antiviral and antitumor activities (Scheme 3). This is the first time to prepare *N*-glycosides of (*E*)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-ones *via* new synthetic strategies. In the last few decades, computational chemistry has progressed from a rarity to become a full partner with an experiment in the investigation of organic and biochemical structures and reactions. Computations have become essential to elucidate structures, properties of molecules, mechanisms, and selectivity of reactions [56]. The density functional theory (DFT) is one of the most popular theoretical methods used in calculating a great variety of molecular properties such as molecular structures, vibrational frequencies, chemical shifts, non-linear optical (NLO) effects, natural bond orbital (NBO) analysis, molecular electrostatic potential, frontier molecular orbitals and thermodynamic properties [56-60]. The present work aims to perform the density functional theory to study the effect of the molecular and electronic structure changes on the biological activity of the investigated compounds and try to find a good correlation between the theoretical data with the experimental observations.

2. Results and Discussion

2.1. Chemistry

The synthetic pathway for the described compounds is illustrated in Scheme 1. The synthesis started with the preparation of 1-methyl-2-thioxoimidazolidin-4-one (**3**) [61,72] by the fusion of methyl amino acetic acid (**1**) with ammonium thiocyanate at 140-150 °C through the formation of 1-(methylthioureido)-acetic acid (**2**) as intermediate. Compound **3** was then condensed with the appropriate aryl carboxaldehydes namely benzaldehyde (**4a**), 4-methylbenzaldehyde (**4b**), 4-methoxybenzaldehyde (**4c**) and finally 4-chlorobenzaldehyde (**4d**) to yield the corresponding (*E/Z*)-5-(benzylidene)-1-methyl-2-thioxoimidazolidin-4-one **5a** (*E/Z* ratio, 1.3:1.0), respectively and (*E*)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-ones **5b-d** (Scheme 1). The structures of compounds **5a-d** were established and confirmed by elemental analyses and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, and MS). The IR absorption spectra of **5a–d** were characterized the presence of a signal for NH group at ν_{max} 3094-3230 cm^{-1} and the presence of a signal for the thiocarbonyl group at ν_{max} 1314-1386 cm^{-1}. ^{1}H–NMR(500 MHz, DMSO-d_6) spectrum of compound **5a** (*E*-form) showed a singlet at δ_H 3.47 ppm assigned to the methyl proton of N_1-CH$_3$, a multblet at δ_H 7.35-7.43 ppm assigned to 2′-H, 6'-H, 3′-H, 5'-H, a multblet at δ_H 7.82-8.02 ppm assigned to 4′-H, a singlet at 6.63 ppm assigned to the =CH and a broad singlet at δ_H 12.13 ppm assigned to NH. ^{1}H–NMR(500 MHz, DMSO-d_6) spectrum of compound **5a** (*Z*-form) showed a singlet at δ_H 3.20 ppm assigned to the methyl proton of N_1-CH$_3$, a multblet at δ_H 7.35-7.43 ppm assigned to 2′-H, 6'-H, 3′-H, 5'-H, a mult-

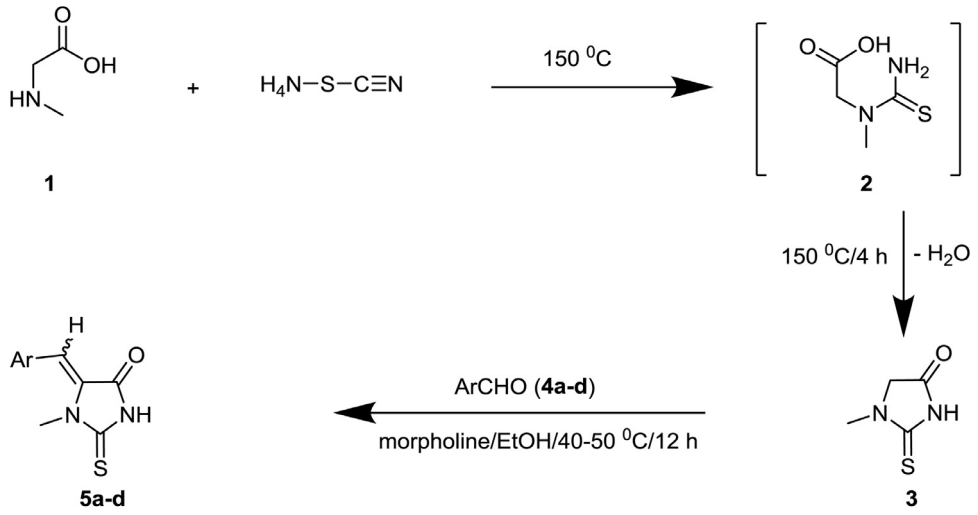
Fig. 2. NOE spectrum of compound **5b**.

blet at δ_H 7.82-8.02 ppm assigned to 4′-H, a singlet at 6.66 ppm assigned to the =CH and a broad singlet at δ_H 12.13 ppm assigned to NH. This agrees with the ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum of 5-(*Z*)-5-(1,3-benzodioxol-5-ylmethylene)-1-methyl-2-thioxoimidazolin-4-one [61], whose N_1-CH_3 appears at δ_H 3.18 ppm, =CH appears at 6.54 ppm and NH appears at δ_H 12.22 ppm, respectively. ^{1}H–NMR (500 MHz, DMSO-d_6) spectrum of compound **5b** showed a singlet at δ_H 2.33 ppm assigned to the methyl proton, a singlet at 3.47 ppm assigned to the methyl proton of N_1-CH_3, a doublet at δ_H 7.22 ppm (J = 7.50 Hz) assigned to 2′-H, 6′-H, a doublet at δ_H 8.02 ppm (J = 8.00 Hz) assigned to 3′-H, 5′-H, a singlet at 6.65 ppm assigned to the =CH and a singlet at δ_H 12.50 ppm assigned to NH. This agrees with the ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum of (*E*)-5-(benzylidene)-1-methyl-2-thioxoimidazolin-4-one (**5a** *E*-form), whose =CH appears at 6.66 ppm and NH appears at δ_H 12.40 ppm, respectively. The ^{13}C-NMR (75 MHz, DMSO-d_6) spectrum of compound **5d** showed an absorption at δ 118.62, 163.55, 177.15 ppm assigned to the vinyl, carbonyl and thiocarbonyl groups, respectively, likewise indicating the presence of a *E*-configuration for the exocyclic double bond, in agreement with the ^{13}C-NMR spectra of 3-substituted (*E*)-5-(arylidene)-1-methyl-2-thiohydantoin derivatives whose vinyl, carbonyl and thiocarbonyl groups appear at δ 115-125, 160-162 and 175-177 ppm, respectively [54]. Furthermore, structures of novel compounds were confirmed by spectroscopic methods and by elemental analyses for C, H, and N. The (*E*)-configuration around the exocyclic C=C double bond in compound **5d** was determined by NMR (HMBC technique) based on the magnitude of long-range heteronuclear coupling constant, $^3J_{C-H}$. The magnitude of the coupling constant, $^3J_{C-H}$ = 10.80 Hz, indicates the *trans*-relationship between the methylidene proton at the 6–position and the carbonyl carbon atom at the 4-position and is also in agreement with the literature data [62,63]. The (*E*)-configuration, around the exocyclic double bond C=C in compounds **5b** was additionally confirmed by NOESY spectroscopy. A small value of NOE between the protons at the positions 1 (CH_3–*N*) and CH_{ortho} indicates the *trans*-relationship between these two protons. On the other hand, NOE was observed between the following protons: a) H_3C–*N*(1)···H(6) of Ph (11%) and H_{ortho} of Ph···H_3C–*N*(1) (3%) in the case of compound **5b** (Fig. 2). The structural assignment of these compounds was fully supported by the physical data.

The synthetic pathway for the described compounds is illustrated in Scheme 2. The synthesis started with the preparation of (*E*)-5-(arylidene)-3-ethyl-1-methyl-2-thioxo-4-imidazolidinones **6a-d** and ethyl (*E*)-2-(5-(arylidene)-1-methyl-4-oxo-2-thioxoimidazolidin-3-yl)acetates **7a-d** from (*E/Z*)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-ones **5a-d** and ethyl iodide in the presence of anhydrous acetonitrile and sodium hydride. Compounds **6a-d** were prepared from the reaction of **5a-d** with ethyl iodide the presence of anhydrous acetonitrile and sodium hydride. On the other hand, Compounds **6a-d** were prepared from the reaction of **1** with ethyl isothiocyanate in refluxing ethanol, followed by condensation with aryl carboxaldehyde derivatives **4a-d** in the presence of morpholine. Compounds **7a-d** were prepared from the reaction of **5a-d** with ethyl bromoacetate in anhydrous acetonitrile and sodium hydride. The structural assignment of these compounds was fully supported by the physical data.

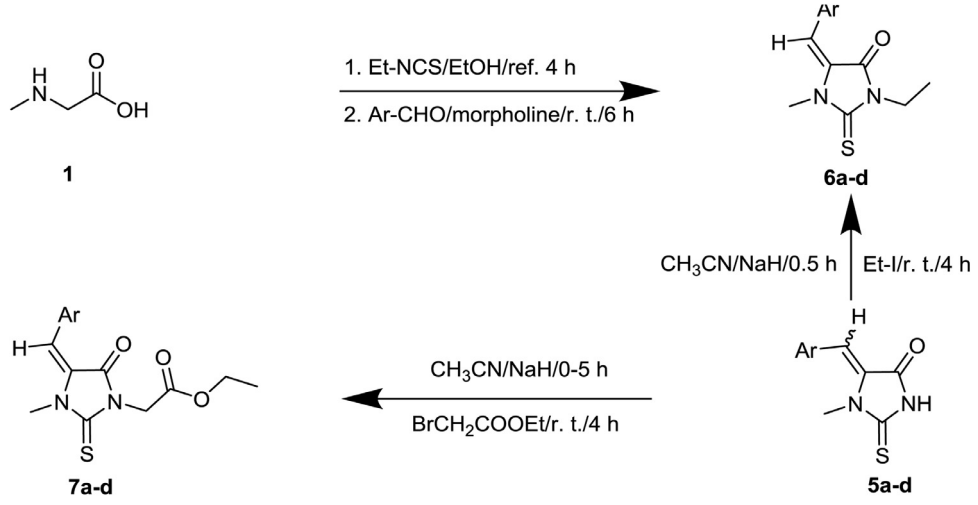
The synthetic pathway for the described compounds is illustrated in Scheme 3. The key intermediates for the synthesis of cyclic *N*-glycosides are shown in Scheme 3. Analogously, treatment of **5a-d** with 1.1 equivalents of NaH in anhydrous acetonitrile furnished the sodium salts of 2-thioxothiazolidin-4-ones **8a-d**, which in turn were treated with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**9a**) or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**9b**) to afford the *N*-glycosylated nucleosides **10a–h** in between medium and good yields (40–90%), (Scheme 3). Thin layer chromatography (CH_2Cl_2/MeOH, 98:2) indicated the formation of pure compounds. The structures of the *N*-glycoside **10a–h** was confirmed by elemental analysis and spectral data (IR, ^{1}H–NMR, ^{13}C–NMR). The ^{1}H–NMR (500 MHz, $CDCl_3$) spectrum of compound **10a** as an example, showed the anomeric proton of the glucose moiety as a doublet at δ 6.17 ppm with a coupling constant $^2J_{1',2'}$ = 10.50 Hz indicating β-configuration of the anomeric center. The other protons of the glucopyranose ring resonated at δ 4.21–6.11 ppm, while the four acetoxy groups appeared as four singlets at δ 1.98–2.09 ppm. The ^{13}C–NMR (125 MHz, $CDCl_3$) revealed the presence of the thione carbon atom at about 174.58 ppm (Fig. 3). The signals at δ, 169.69, 170.16, 170.72 ppm were due to the four acetoxy carbonyl atoms (4C=O), and the six signals at δ 61.84, 67.90, 68.13, 73.44, 74.54, 81.98 ppm were assigned to C-6',C-2', C-3', C-4', C-5', and C-1', respectively. Moreover, the IR spectra of compounds **10a-h** revealed the presence of the stretching signal of a thione group. These data are also in agreement with the ^{13}C–NMR (125 MHz, DMSO-d_6) spectrum of (*E*)-5-(benzylidene)-3-[2-(4-morpholino)ethyl]-1-methyl-2-thiohydantoin [64] since the vinylic carbon atom appears at δ_c 120.39 ppm, indicating the presence of (*E*)-configuration around the exocyclic C=C double bond, the carbonyl at C-4 appears at δ_c 161.44 ppm and –N_1-CS–N_3– carbon atom (C-2) appears at δ_C 176.72 ppm, indicating the presence of *N*-glycosylation (Fig. 3). The structural assignment of these compounds was fully supported by the physical data.

The synthetic pathway for the described *N*-glycosidic compounds is illustrated in Scheme 3. Removal of the acetyl groups from the glycopyranose moiety of **10a-h** with a solution of conc. HCl/MeOH at 40-50 °C for 2h furnished (*E*)-5-(arylidene)-1-methyl-3-(β-D-glycopyranosyl)-2-thioxoimidazolidin-4-ones (**11a-h**), indicating the presence of *N*-glycosylation (Scheme 3). The structures of **11a-h** were confirmed by their spectroscopic and mass spec-



4-5	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-$CH_3OC_6H_4$
d	4-ClC_6H_4

Scheme 1. Synthesis of the target compounds **3** and **5a-d**.



5-7	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-$CH_3OC_6H_4$
d	4-ClC_6H_4

Scheme 2. Synthesis of the target compounds **6a-d** and **7a-d**.

tral data. The mass spectrum of **10a** showed a molecular ion peak at m/z = 380 ($M^{+\cdot}$, 5%), while the ^{1}H-NMR (500 MHz, $CDCl_3$) spectrum showed a doublet at δ_H 5.51 with $J_{1',2'}$ = 10.00 Hz, corresponding to the 1′-H and indicating a β-configuration. Vinylic carbon (=CH) of **10a** resonated at δ_C 121.28 ppm, indicating (*E*)-configuration. Carbon 2 of **10a** resonated at δ_C 180.00 ppm, establishing the *N*-glycosylation. Furthermore, the heteronuclear spectra (HMQC, DFQ-COSY) of **10a-h** no such correlation was shown between N_1-CH_3 and 1′-H, which is an indication of the *N*-glycosylation. The nucleoside bases **5a-d** can be utilized as starting materials for the synthesis of other carbohydrate derivatives as deoxy, amino and azido nucleosides. The structural assignment of these compounds was fully supported by the physical data.

2.2. Computational Method

The molecular structures of the investigated compounds were optimized using DFT (density functional theory) in combination with the Beck's three parameter exchange functional along with

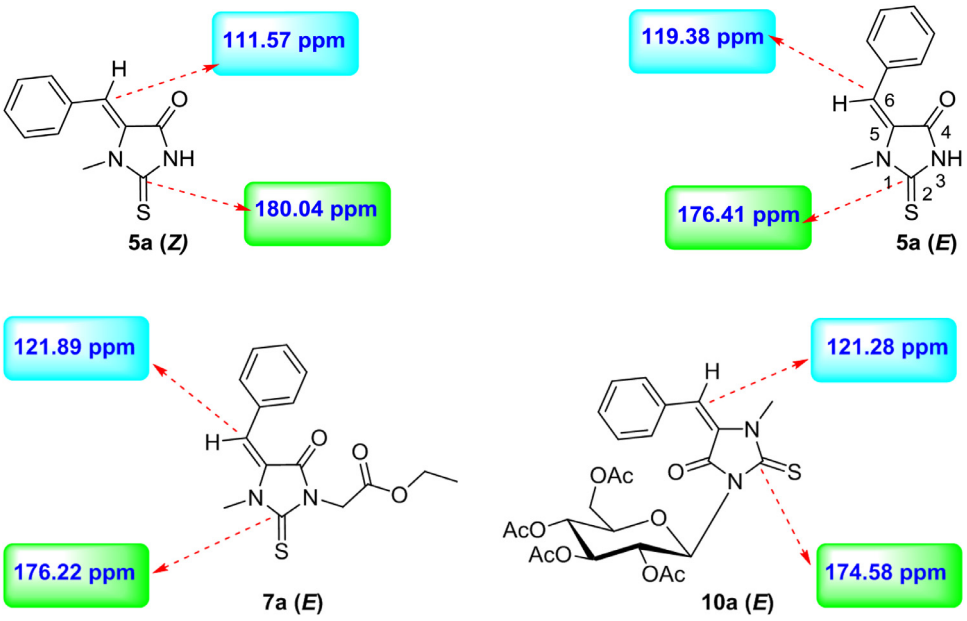
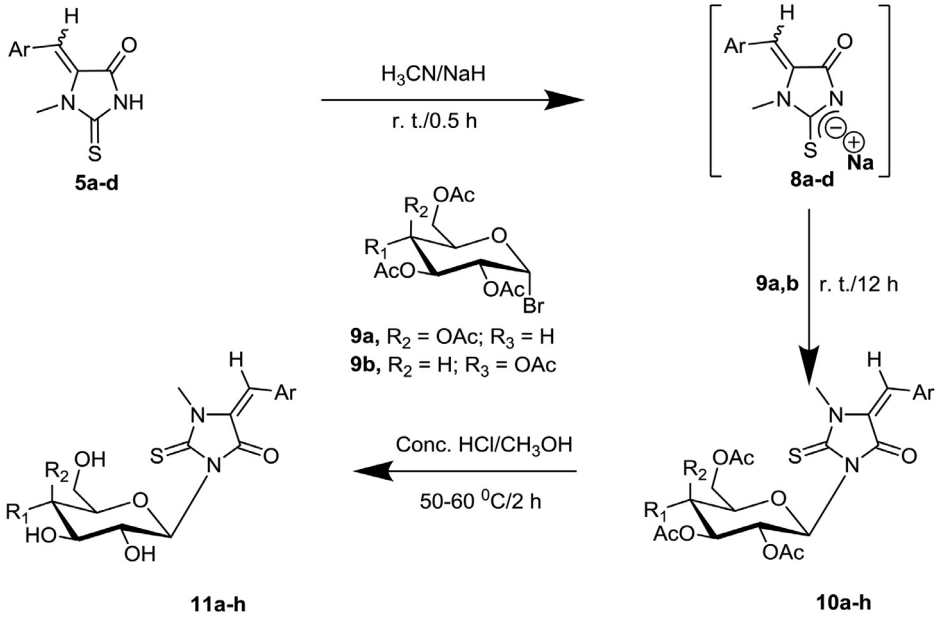


Fig. 3. The chemical shift of the corresponding carbon atom at positions 2 and 6 in **5a** (*Z*), **5a** (*E*), **7a** (*E*), and **10a** (*E*).



5-10	Ar	R_1	R_2	11	Ar	R_1	R_2
a	C_6H_5	OAc	H	**a**	C_6H_5	OH	H
b	4-$CH_3C_6H_4$	OAc	H	**b**	4-$CH_3C_6H_4$	OH	H
c	4-$CH_3OC_6H_4$	OAc	H	**c**	4-$CH_3OC_6H_4$	OH	H
d	4-ClC_6H_4	OAc	H	**d**	4-ClC_6H_4	OH	H
e	C_6H_5	H	OAc	**e**	C_6H_5	H	OH
f	4-$CH_3C_6H_4$	H	OAc	**f**	4-$CH_3C_6H_4$	H	OH
g	4-$CH_3OC_6H_4$	H	OAc	**g**	4-$CH_3OC_6H_4$	H	OH
h	4-ClC_6H_4	H	OAc	**h**	4-ClC_6H_4	H	OH

Scheme 3. Synthesis of the target compounds **10a-h** and **11a-h**.

Table 1
The calculated quantum chemical parameters obtained from DFT/B3LYP/6-31+G (d,p) of the investigated compounds.

Compound	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	DM (D)	IP (eV)	EA (eV)	η (eV)	σ (eV^{-1})	μ (eV)	χ (eV)	ω	E a. u.	IC_{50} MC7
6b	-6.280	-2.170	4.111	3.764	6.280	2.170	2.056	0.486	4.225	-4.225	4.341	-1126.089	ND
6d	-6.536	-2.114	4.421	4.631	6.536	2.114	2.211	0.452	4.325	-4.325	4.230	-1546.335	12.4
7d	-6.509	-2.328	4.181	0.329	6.509	2.328	2.091	0.478	4.416	-4.416	4.663	-1774.245	10.43
10a	-4.887	-2.006	2.884	3.198	4.887	2.006	1.442	0.693	3.447	-3.447	4.120	-2229.492	6.63
10g	-4.853	-1.979	2.874	3.200	4.853	1.979	1.437	0.696	3.416	-3.416	4.060	-2268.810	5.76
11b	-6.046	-2.427	3.618	5.991	6.046	2.427	1.809	0.553	4.237	-4.237	4.962	-1658.132	4.3

the Lee-Yang-Parr non local correlation functional (B3LYP) [65-67] with 6-31+G (d,p) basis set which is implemented in Gaussian 09 program package [68]. An estimate of molecular properties related to molecular reactivity was calculated with DFT/B3LYP combination [69]. The molecular properties include the highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), global hardness and softness, electronegativity, electron affinity, ionization potential, etc. [60,70–72].

2.3. Quantum Chemical Study

The quantum chemical methods and molecular modelling techniques can define a large number of molecular quantities characterizing the reactivity, shape, and binding properties of a complete molecule as well as of molecular fragments and substituents. Quantum chemical calculations were performed to investigate the effect of structural parameters on the biological activity of some investigated compounds. The optimized molecular structures with minimum energies obtained from the calculations of the investigated compounds are shown in Fig. 4.

We started our calculations to make a comparison between the stability of the investigated compounds in *Z*- and *E*-forms and the calculations showed that they are more stable in the *E*-form than *Z*-form, by about 0.081 au, which is in a good agreement with the experimental observations. So, we performed DFT calculations on the stable structures of *E*-form for all molecules.

The experimental data showed that the presence of sugar moiety at *N*-atom of five membered ring increases the biological activity as in the case of (compounds **10a, 10g** and **11b**) with respect to the other compounds without sugar moiety (compounds **7d, 6d** and **6b**), which was confirmed by the calculation. The calculations showed that the insertion of sugar moiety increases the energy of HOMO to be (-4.887, -4.853 and -6.046 eV) for compounds (**10a, 10g** and **11b**), respectively, which is the donor part of the molecule, and increases the softness to be (0.693, 0.696 and 0.553 eV^{-1}), respectively, with respect to lower softness for compounds (**6b, 6d** and **7d**) (0.486, 0.452 and 0.478 eV^{-1}), respectively. It was shown from the calculations that decreasing the energy gap between HOMO-LUMO for compounds (**10a, 10g** and **11b**) (2.884, 2.874and 3.618 eV), respectively, more than in the case of compounds (**6b, 6d** and **7d**) (4.111, 4.421 and 4.181 eV), restively, which is probably more favourable for the reactivity of compounds 2, 5 and 7 towards the enzyme. The decreasing of the chemical potential, electronegativity and electrophilicity mean increasing the reactivity of the molecules (**11b, 10a** and **10g**) and accordingly increase the biological activity, which agrees well with the experimental observations, Table 1.

Comparing the reactivity between compounds (**10a**) and (**10g**), we noticed that the replacing of H-atom on phenyl moiety (compound **10a**) by CH_3O-group (compound **10g**) increases its reactivity. This was confirmed from the increasing the energy of HOMO of molecule (**10g**) by 0.034 eV, and decreasing its energy gap by 0.01 eV. Also, the increasing the values of dipole moment and softness of compound (**10g**) by 0.002 D and 0.003 eV^{-1}, respectively, increases its reactivity. Moreover, the decreasing of the chemical potential, electronegativity and electrophilicity mean increasing the reactivity of the molecule (**10g**) and accordingly increases its biological activity, which agrees well with the experimental observations, Table 1.

Experimentally, it was shown that the replacing the acetate moiety on sugar (compounds **10a** and **10g**) by a hydroxyl moiety (compound **11b**) increases the reactivity. This was confirmed from the decreasing the energy of LUMO and increasing the dipole moment of compound (**11b**), which means that molecule (**11b**) acts as an acceptor (electrophile) from the enzyme with high lipophobic character which is in a good agreement with experimental observations. The electrophilicity is the descriptor of reactivity and is sufficient to describe the toxicity of the molecules. It also provides the direct relationship between the rates of reactions and the ability to identify the function or capacity of an electrophile and the electrophilic power of the compounds. It was shown from the calculations that the compound (**11b**) has higher electrophilicity index (4.962 eV), than those of compounds (**10a** and **10g**), which probably enhance its biological activities and agrees well with the experimental observations, Table 1.

Comparing the reactivity of compound (**7d**), with substitution at N-atom, and compound (**6d**), where the substitution at *S*-atom, it was shown experimentally that the biological activity increases with the substitution on *N*-atom more than that at S-atom. This was confirmed theoretically, by increasing the energy of HOMO level by 0.025 eV which means increasing the donation ability to the active sites of enzyme, Table 1. On the other side, the ability of compound (**7d**) to accept charge from the surrounding is higher than that of compound (**6d**), which means that this compound could react as electrophiles. The electrophilicity is the descriptor of reactivity and is sufficient to describe the toxicity of the molecules. It also provides the direct relationship between the rates of reactions and the ability to identify the function or capacity of an electrophile and the electrophilic power of the compounds. It was shown from the calculations that the compound (**7d**) has higher electrophilicity (4.663) than that of compound (**6d**), (4.230) which probably enhances its biological activity and agree well with the experimental observations. Also, the calculations showed that the substituent at *N*-atom increases the softness, chemical potential and electronegativity which means increasing the reactivity of compound (**7d**), with substituent at *S*-atom, and accordingly increases its biological activity, Table 1. This is in a good agreement with the experimental data.

2.4. Frontier Molecular Orbitals (FMO)

The HOMO and LUMO levels are very common quantum chemical parameters which play a role in determining the way the molecule interacts with another molecule. The HOMO and the LUMO levels charge density distribution for the studied molecules are shown in Fig. 4. It was shown from the investigated compounds that the HOMO levels, which could be reacted as a nucleophile (hydrogen bond acceptor) with the biological target, is mainly localized on the lone-pair of *S, N* and keto-oxygen atoms except phenyl, ethyl acetate and ethyl moieties in the case of com-

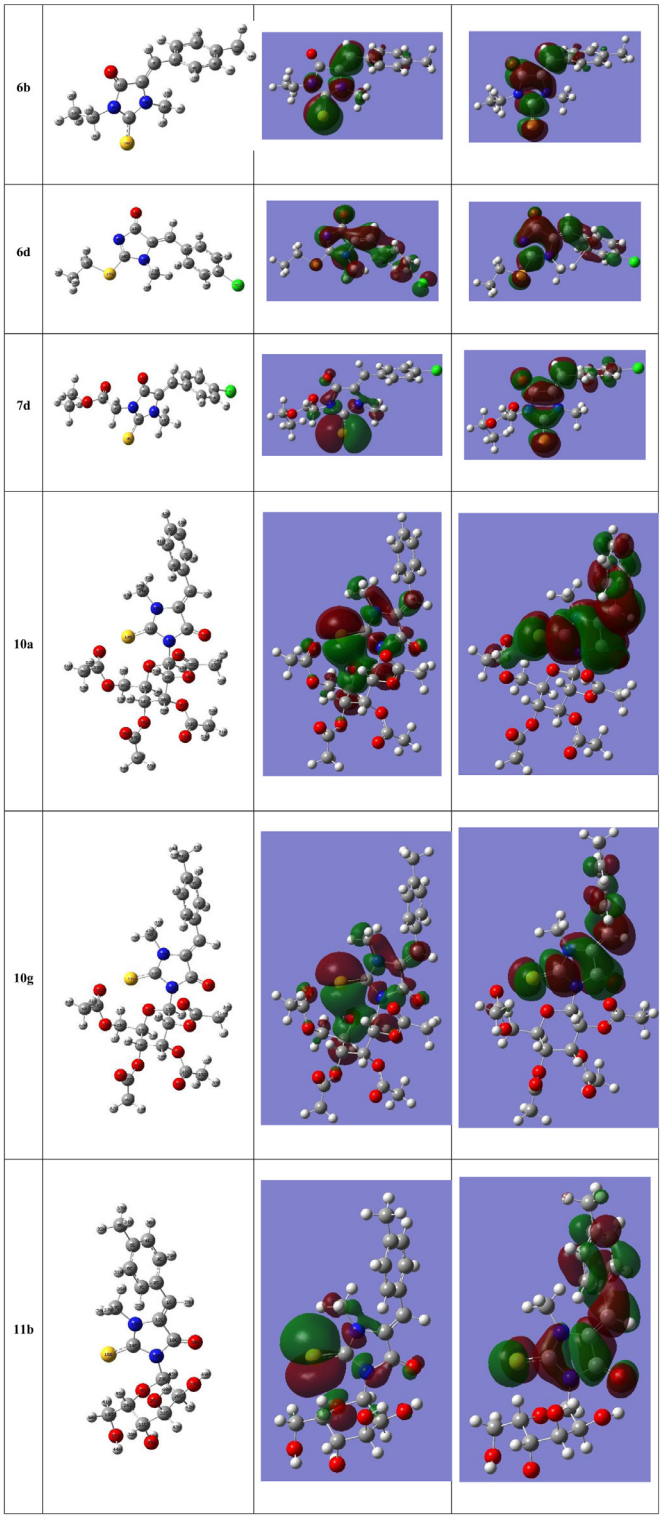


Fig. 4. The optimized molecular structures, charge density distributions (HOMO and LUMO) for the investigated compounds.

pounds **6b, 6d** and **7d**, respectively. But in the case of compounds **10a, 10g** and **11b**, the sugar and phenyl moieties will not contribute to the HOMO level. The LUMO, which could be reacted as a nucleophile (hydrogen bond donor) with the biological target, is mainly delocalized over the whole molecule with π^* character except for phenyl, ethyl acetate and ethyl moieties in the case of compounds **6b, 6d** and **7d**, but for compounds **10a, 10g** and **11b**, the sugar moiety will not contribute in the LUMO level. The calculations showed that charge transfer may occur from the nucleophilic sites to the electrophilic part of the same molecules. It was concluded from FMOs that the effect of substituents on the **diazole moiety** plays an important role to enhance the affinity of the tested compounds towards the target enzymes.

2.5. Molecular Docking Studies

Table 2 Summarizes the ligand-receptor interactions inside the **2a4l** binding site to compare the overall interactions of the docked compounds with that made by the co-crystallized ligand. From this comparison, we concluded that compounds might have human cyclin-dependent kinase activity as the co-crystallized ligand where they form the same interactions with **Leu 83** and **Lys 89** which are the key amino acid interactions. So, these promising derivatives were worthy of being further tested against cancer cell lines to collect an overview of their biological activity.

2.6. In Vitro *Cytotoxic Results*

In vitro cytotoxic activity of the tested derivatives was tested against liver (HepG2) cell line by measuring the percentage of cell survival against their serial dilutions (1, 10, 100, and 1000 µM). *In vitro* cytotoxic activity illustrated the percentage of cell survival relative to control decreases with increasing concentrations proving their cytotoxic activities. It decreased in a dose-response curve that means with increasing concentrations percentage of cell survival decreased. Moreover, some of the analyzed compounds exhibited a substantial decrease in the percentage of cell survival than the standard drug itself. As seen in Table 3, **11b** was cytotoxic nearly as the 5-FU by having non-significant IC_{50} values of 4.3 µM and 4.34 µM, respectively against MCF-7 cells. Additionally, it had slightly weaker cytotoxic against HepG2, and A549 with IC_{50} values of 5.53 and 9.43 µM, respectively than the 5-FU with IC_{50} values of 4.43 and 5.54 µM against the corresponding cells.

3. Conclusions

In the present study, we have carried out the successful synthesis of hitherto unreported (*Z*/*E*)-5-(arylidene)-1-methyl-2-thioxo-4-imidazolidinones **5a-d**, (*E*)-5-(arylidene)-3-ethyl-1-methyl-2-thioxoimidazolidin-4-ones **6a-d**, ethyl (*E*)-5-(arylidene)-1-methyl-4-oxo-2-thioxoimidazolidin-3-yl)acetate **7a-d**, (*E*)-**5**-(arylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-glycopyranosyl)-1-methyl-2-thioxoimidazoliden-4-ones **10a-h** and (*E*)-5-(arylidene)-3-(β-D-glycopyranosyl)-1-methyl-2-thioxoimidazoliden-4-ones **11a-h**. The conformational analyses of their most stable configurations were established by NMR spectroscopy. The antiviral and the further antitumor activities of the new prepared compounds are under investigation and will be reported in the due time. The nucleobase **5** can be utilized as starting materials for the synthesis of other carbohydrate derivatives as deoxy, amino and azido nucleosides. The electronic and geometric structures were deduced from DFT calculations with B3LYP/6-31+G (d) level to analyze the stable structure of the compounds. The quantum chemical parameters obtained from the calculations showed a good correlation with the experimental observations. The synthesized derivatives exhibited good binding interactions towards the cyclin-dependent kinase 2, especially compound **11b**, which have better key interactions than the co-crystallized ligand. Additionally, it had potent cytotoxic activities with IC_{50} = 4.30, 5.53, 9.43 µM against MCF-7, HepG2, and A549, respectively. Finally, we recommend further *in vivo* cancer model for this compound so that it can be developed as chemotherapeutic anti-cancer agent.

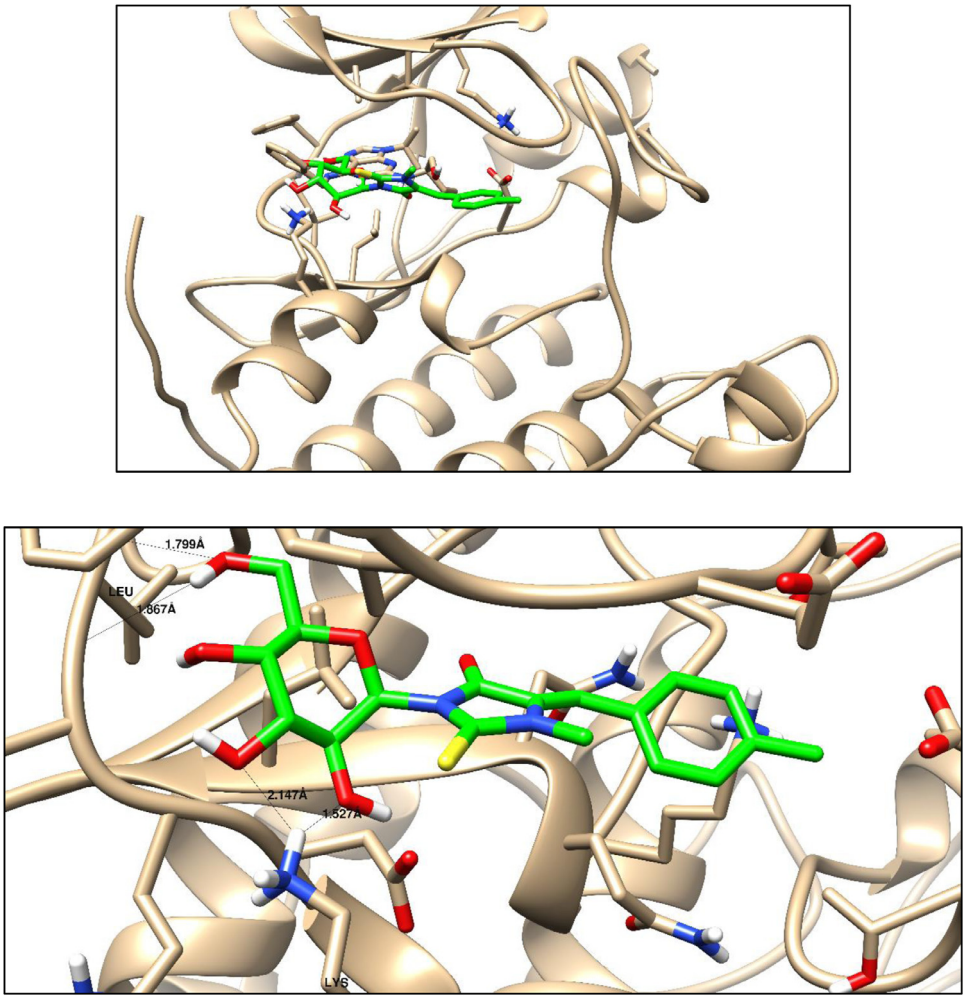


Fig. 5. A. Superimposed pose of the docked tested compounds **11b** (green) and the co-crystallized ligand (buff) and **B.** Binding mode of the docked compound **11b** and its molecular interactions inside the binding site of **2a4l** receptor.

4. Experimental Section

4.1. General procedures

All melting points were taken on Electrothermal IA 9100 series digital melting point apparatus. Microanalytical data (in accord with the calculated values) were performed by Vario, Elementary apparatus (Shimadzu). The IR spectra (KBr) were recorded on a Perkin Elmer 1650 spectrometer (USA). ^{1}H–NMR and ^{13}C–NMR spectra were determined on a JEOL ECA-500. Chemical shifts were expressed in ppm relative to $SiMe_4$ as internal standards and DMSO-d_6 or $CDCl_3$ or CD_3OD as solvent. Mass spectra were recorded on 70 eV EI Ms-QP 1000 EX (Shimadzu).

4.2. General procedure for the preparation of 1-methyl-2-thioxoimidazoliden-4-one (3)

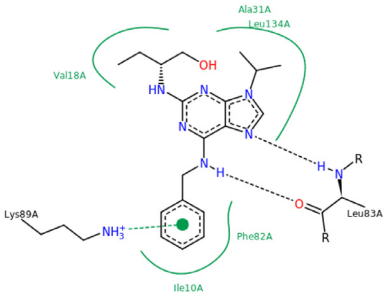
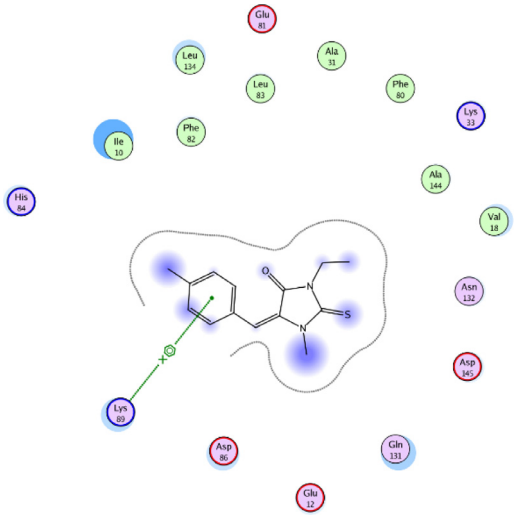
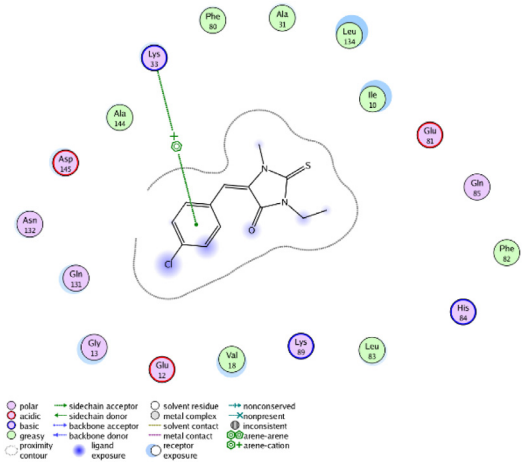
A mixture of *N*-methyl glycine (**1**) (0.89 g, 10 mmol) and ammonium thiocyanate (1.52 g, 20 mmol) was stirred for 4 h at 140-150 °C in an oil bath until the starting material was consumed (TLC). The solid residue was washed with methanol and collected by filtration and recrystallized from ethanol to give 1.45 g (55%) of **3** as a white solid. Mp 198-200 °C (lit. [63], 90%, 230-232 °C; lit. [73], 44%, 221-224 °C). IR (KBr): ν 3387 (NH), 1647 (CO), 1319 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.10 (3H, s, N_1-CH_3), 4.20 (2H, s, CH_2), 11.60 (1H, s, NH). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 33.32 (*N*-CH_3), 55.70 (CH_2), 172.68 (CO), 182.16 (CS).

4.3. General procedure for the preparation of (Z/E)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-ones 5a-d

To a mixture of **3** (1.30 g, 10 mmol), morpholine (0.09 g, 10 mmol) and ethanol (30 ml) was added the appropriate aryl carboxaldehydes namely benzaldehyde (**4a**) (1.27 g, 11 mmol), 4-methylbenzaldehyde (**4b**) (1.32 g, 11 mmol), 4-methoxybenzaldehyde (**4c**) (1.50 g, 11 mmol), and finally 4-chlorobenzaldehyde (**4d**) (1.56 g, 11 mmol). The mixture was stirred at 40-50 °C for 12 h until the starting material was consumed (TLC), cooled to room temperature, deposited with distilled water (30 ml) and the neutralized with 1 N HCl with stirring for 5 min. The yellow solid separated was filtered off and recrystallized from ethanol to give the products **5a-d**..

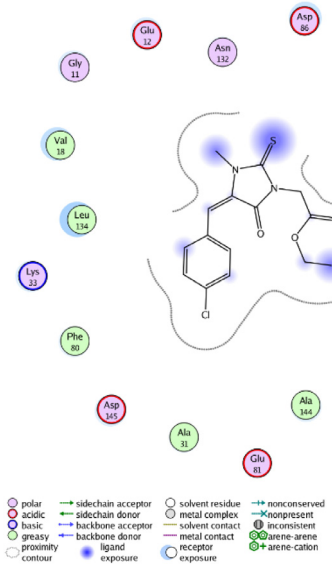
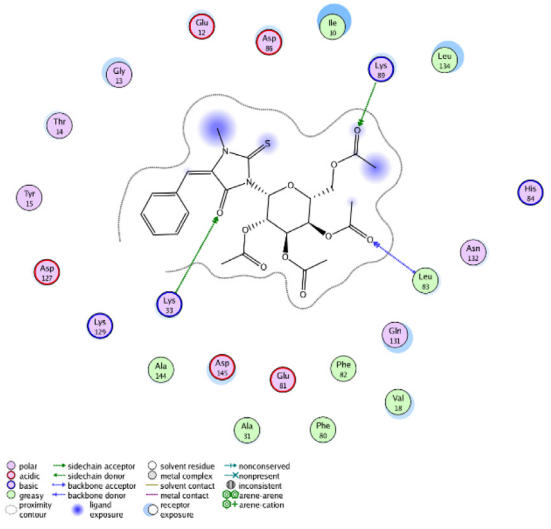
(*Z*/*E*)-5-(Benzylidene)-1-methyl-2-thioxoimidazolidin-4-one (5a): Yield: 1.20 g (55%) (*E*/*Z* ratio, 1.3:1.0). Mp: 202-204 °C. IR (KBr): ν = 3094 (NH), 1714 (C=O), 1364 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.20 (3H, s, N_1-CH_3, *Z*-form), 3.47 (3H, s, N_1-CH_3, *E*-form), 6.63 (1H, s, =CH, *E*-form), 6.66 (1H, s, =CH, *Z*-form), 7.36-8.02 (10H, m, H-Ar, *E*-form, *Z*-form), 12.13 ppm (2H, br. s, NH, *E*-form, *Z*-form). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 30.18 (N_1-CH_3, *E*-form), 34.11 (N_1-CH_3, *Z*-form), 111.57 (=CH, *Z*-form), 119.38 (=CH, *E*-form), 128.56, 128.64, 129.58,130.15, 131.08, 131.80, 133.24 (C-5, C-Ar, *Z*-form, *E*-form), 162.68 (C-4, *E*-form), 164.43 (C-4, *Z*-form), 176.41 (C-2, *E*-form), 180.04 (C-2, *Z*-form). MS: $C_{11}H_{10}N_2OS$: *m/z*: 218 ($M^{+\cdot}$, 64.80%).

Table 2
Ligand-receptor interactions for the tested derivatives as inhibitors for Human cyclin-dependent kinase 2.

Ligands	Binding affinity (Kcal/mol)	Hydrogen bonds			Van der Waals interactions
		No.	With amino acid residues	Bond length (A°)	
Co-crystallized ligand (PDB**2a4l**)	**-18.73**	**2**	**Leu 83**	**1.98, 1.23**	1 arene-cation interaction with Lys 89
					
Docked derivatives					
6b	**-10.55**	-	-	-	1 arene-cation interaction with Lys 89
					
6d	**-7.95**	NO binding interactions			-
					

(*continued on next page*)

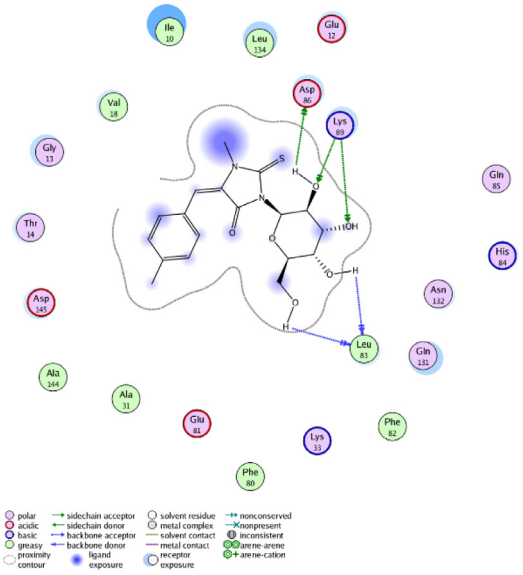
Table 2 (*continued*)

Ligands	Binding affinity (Kcal/mol)	Hydrogen bonds			Van der Waals interactions
		No.	With amino acid residues	Bond length (A°)	
7d	**-13.63**	**1**	**Lys 89**	**1.68**	**-**
					
10a	**-18.44**	**2HB**	**Lys 89**	**1.87**	-
			Leu 83	**2.01**	
		fx			
10g	**-19.56**	**2**	**Lys 89**	**1.98, 1,76**	-
					
11b	**-21.34**	**2**	**Leu 83**	**1.60, 1.77**	-
		2	**Lys 89**	**1.65, 1.60**	

(*continued on next page*)

Table 2 (*continued*)

Ligands	Binding affinity (Kcal/mol)	No.	With amino acid residues	Hydrogen bonds	Bond length (A°)	Van der Waals interactions



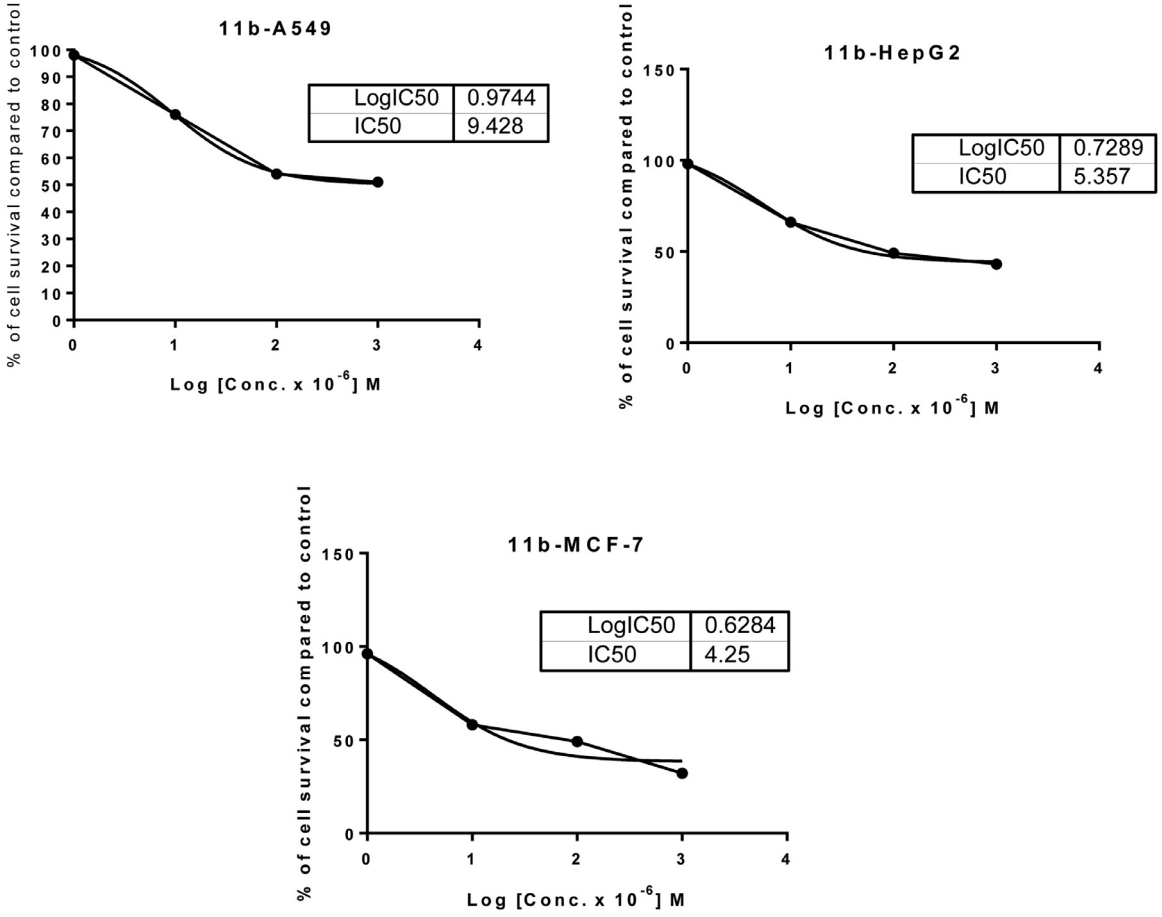


Fig. 6. Sigmoidal dose-response curve for the IC_{50} of **11b** against A549, HepG2, and MCF-7 cancer cell lines.

(*E*)-5-(4-Methylbenzylidene)-1-methyl-2-thioxoimidazolidin-4-one (5b): Yield: 1.90 g (82%). Mp: 210-212 °C. IR (KBr): ν = 3125 (NH), 1734 (CO), 1373 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 2.33 (3H, s, $CH_3C_6H_4$), 3.47 (3H, s, N_1-CH_3), 6.65 (1H, s, =CH), 7.22 (2H, d, J = 7.5, Hz, H-3', H-5'), 8.02 (2H, d, J = 8.0 Hz, H-2', H-6'), 12.50 ppm (1H, s, NH). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 21.22 ($CH_3C_6H_4$), 30.17 (N_1-CH_3), 120.15 (=CH), 129.25, 130.32, 130.41, 131.23, 139.71 (C-Ar and C-5), 164.27 (C-4), 177.56 (C-2). MS: $C_{12}H_{12}N_2OS$: *m/z*: 232 ($M^{+\cdot}$, 78.50%).

(*E*)-5-(4-Methoxylbenzylidene)-1-methyl-2-thioxoimidazolidin-4-one (5c): Yield: 1.40 g (57%). Mp: 182-184 °C. IR (KBr): ν = 3230 (NH), 1718 (CO), 1386 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.46 (3H, s, N_1-CH_3), 3.79 (3H, s, OCH_3), 6.66 (1H, s, =CH), 6.96 (2H, d, J = 8.0 Hz, H-2', H-6') 8.13 (2H, d, J = 7.5 Hz, H3',5'), 12.45 ppm (1H, s, NH). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 30.18 (N_1-CH_3), 55.76 (OCH_3), 114.21, 121.07, 125.68, 128.87, 133.3, 160.91 (=CH, C-5 and C-Ar), 163.06 (C-4), 176.07 (C-2).

(*E*)-5-(4-Chlorobenzylidene)-1-methyl-2-thioxoimidazolidin-4-one (5d): Yield: 1.33 g (53%). Mp: 204-206 °C. IR (KBr): ν = 3116 (NH), 1733 (CO), 1314 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.46 (3H, s, N_1-CH_3), 6.71 (1H, s, =CH), 7.46 (2H, d, J = 8.0 Hz, H-2', H-6'), 8.07 (2H, d, J = 8.5, H-3', H-5'), 12.50 (1H, br. s, NH). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 30.20 (N_1-CH_3), 118.62 (=CH), 128.64, 131.03, 131.98, 132.81,134.24 (C-Ar and C-5), 163.55 (C-4), 177.15 (C-2). MS: $C_{11}H_9ClN_2OS$: *m/z*: 252($M^{+\cdot}$, 69.23%).

4.4. General procedure for the preparation of (E)-5-(arylidene)-3-ethyl-1-methyl-2-thioxoimidazolidin-4-ones 6a-d

Method A: A mixture of 5-((*E*)-arylidene)-1-methyl-2-thioxo-4-imidazolidinones **5a-d** (1 mmol), anhydrous acetonitrile (10 mL) and sodium hydride (45 mg, 80%) was stirred at room temperature for ½ hour. Ethyl bromide (0.22 g, 2 mmol) was added to the mixture with stirring at 40-50 °C until the starting material was consumed (4 h; TLC, ethyl acetate/chloroform, 95:5) and cooled at room temperature. Then solvent was removed under reduced pressure and the residue was treated with cold water. The solid separated was collected by filtration and recrystallized from ethanol to give the products **6a-d** in quantitative yields.

(*E*)-5-(Benzylidene)-3-ethyl-1-methyl-2-thioxoimidazolidin-4-one (6a): Yield: 0.23 g (89%). Mp: 140-142 °C. IR (KBr): ν = 1720 (CO), 1396 (CS) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.28 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.59 (3H, s, N_1-CH_3), 4.26 (2H, q, J = 7.0 Hz, CH_2CH_3), 6.46 (1H, s, =CH), 7.41 (3H, m, H-Ar), 8.01 (2H, d, J = 6.5 Hz, H-Ar). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 13.09 (CH_3CH_2), 30.45 (N_1-CH_3), 37.01 (CH_3CH_2), 120.45 (=CH), 128.40, 129.51, 129.92, 130.76, 132.04 (C-Ar and C-5), 161.35 (C-4), 176.60 (C-2). MS: $C_{13}H_{14}N_2OS$: *m/z*: 246 ($M^{+\cdot}$, 100%). Calculated for $C_{13}H_{14}N_2OS$ (246.33): C, 63.39; H, 5.73; N, 11.37. Found: C, 63.41; H, 5.14; N, 11.10.

(*E*)-5-(Methylbenzylidene)-3-ethyl-1-methyl-2-thioxoimidazolidin-4-one (6b): Yield: 0.17 g (61%). Mp: 114-116 °C. IR (KBr): ν = 1720 (CO), 1374 (CS) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.20 (3H, t, J =7.0 Hz, CH_2CH_3), 2.55 (3H, s, $CH_3C_6H_4$), 3.54 (3H, s, N_1-CH_3), 3.93 (2H, q, J =7.0 Hz, CH_2CH_3), 6.39 (1H, s, =CH), 7.15 (2H, d, J = 8.0 Hz, H-3', H-5'), 7.86 (2H, d, J = 8.0 Hz, H-2', H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 13.06 (CH_3CH_2), 21.62 ($CH_3C_6H_4$), 30.47 (N_1-CH_3), 36.99 (CH_3CH_2), 120.94 (=CH), 128.40, 129.22, 130.87, 140.61 (C-Ar and C-5), 161.42 (C-4), 176.36 (C-2). MS: $C_{14}H_{16}N_2OS$: *m/z*: 260 ($M^{+\cdot}$, 100%). Calculated for $C_{14}H_{16}N_2OS$ (260.36): C, 64.58; H, 6.19; N, 10.76. Found: C, 65.03; H, 5.80; N, 10.96.

(*E*)-5-(Methoxylbenzylidene)-3-ethyl-1-methyl-2-thioxoimidazolidin-4-one (6c): Yield: 0.14 g (50%). Mp: 96-100 °C. IR (KBr): ν = 1710 (CO), 1384 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.29 (3H, t, J =7.0 Hz, CH_2CH_3), 3.62 (3H, s, N_1-CH_3), 3.87 (3H, s, OCH_3), 4.04 (2H, q, J = 7.0 Hz, CH_2CH_3), 6.48 (1H, s, =CH), 6.95 (2H, d, J = 9.0 Hz, H-2', H-6'), 8.09 (2H, d, J = 9.0, H-2', H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 13.09 (CH_3CH_2), 30.48 (N_1-CH_3), 36.98 (CH_3CH_2), 55.42 (OCH_3), 121.14 (=CH), 113.95, 124.89, 127.63, 132.71, 133.17, 161.17 (C-Ar and C-5), 161.51 (C-4), 175.86 (C-2). MS: $C_{14}H_{16}N_2O_2S$: *m/z*: 276 ($M^{+\cdot}$, 79%). Calculated for $C_{14}H_{16}N_2OS$ (276.36): C, 60.85; H, 5.84; N, 10.14. Found: C, 61.27; H, 5.76; N, 10.22.

(*E*)-5-(Chlorobenzylidene)-3-ethyl-1-methyl-2-thioxoimidazolidin-4-one (6d): Yield: 0.15 g (54%). Mp: 118-120 °C. IR (KBr): ν = 1718 (CO), 1384 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.29 (3H, t, J =7.0 Hz, CH_2CH_3), 3.63 (3H, s, N_1-CH_3), 4.03 (2H, q, J = 7.0 Hz, CH_2CH_3), 6.42 (1H, s, =CH), 7.39 (2H, d, J = 9.0 Hz, H-2', H-6'), 8.09 (2H, d, J = 9.0 Hz, H-2', H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 13.04 (CH_3CH_2), 30.45 (N_1-CH_3), 37.07 (CH_3CH_2), 118.73 (=CH), 128.76, 129.60, 130.56, 132.02, 135.76 (C-Ar and C-5), 161.40 (C-4), 176.74 (C-2). MS: $C_{13}H_{13}ClN_2OS$: *m/z*: 280 ($M^{+\cdot}$, 92%). Calculated for $C_{13}H_{13}ClN_2OS$ (280.77): C, 55.61; H, 4.67; N, 9.98. Found: C, 55.78; H, 4.58; N, 9.96.

Method B: A mixture of *N*-methyl glycine (**1**) (0.89 g, 10 mmol) and ethyl isothiocyanate (0.96 g, 11 mmol) and anhydrous ethanol (30 ml) was stirred with refluxing for 4 h until the starting material was consumed (TLC). Then morpholine (0.09 g, 10 mmol) and the appropriate aryl carboxaldehydes namely benzaldehyde (**4a**) (1.27 g, 11 mmol), 4-methylbenzaldehyde (**4b**) (1.32 g, 11 mmol), 4-methoxybenzaldehyde (**4c**) (1.50 g, 11 mmol), and finally 4-chlorobenzaldehyde (**4d**) (1.56 g, 11 mmol) were added to the reaction mixture. The mixture was stirred at 40-50 °C for 12 h until the starting material was consumed (TLC), cooled to room temperature, deposited with distilled water (30 ml) and the neutralized with 1 N HCl with stirring for 5 min. The yellow solid separated was filtered off and recrystallized from ethanol to give the products **6a** (30%), **6b** (35%), **6c** (16%), **6d** (35%), respectively. They were identical with authentic samples, which were prepared

Table 3
IC_{50} for the *in vitro* cytotoxic activity of the tested compounds against MCF-7, HepG2, A549, and HCT116 cell lines.

Compounds	IC_{50} (μM)*			
	Breast MCF-7	Liver HepG2	Lung A549	Colon HCT116
6b	ND	17.8	26.7	ND
6d	12.4	>50	ND	16.7
7d	10.43	ND	12.4	>50
10a	6.63	ND	18.54	7.98
10g	5.76	>50	ND	8.76
11b	4.30	5.53	9.43	>50
5-FU	4.23	4.43	5.54	ND

* values are expressed as Mean of three independent replicates.

in method A, by melting points, mixed melting points and TLC determinations.

4.5. General procedure for the preparation of ethyl (E)-5-(arylidene)-1-methyl-4-oxo-2-thioxoimidazolidin-3-yl)acetates 7a-d

A mixture of (*E*)-5-(arylidene)-1-methyl-2-thioxoimidazolidin-4-ones **5a-d** (1 mmol), anhydrous acetonitrile (10 mL) and sodium hydride (45 mg, 80%) was stirred at room temperature for ½ hour. ethyl bromoacetate (0.33 g, 2 mmol) was added to the mixture with stirring at 40-50 °C until the starting material was consumed (4 h; TLC, ethyl acetate/chloroform, 95:5) and cooled at room temperature. Then solvent was removed under reduced pressure and the residue was treated with cold water. The solid separated was collected by filtration and recrystallized from ethanol to give the products **7a-d** in quantitative yields.

Ethyl (*E*)-5-(benzylidene)-1-methyl-4-oxo-2-thioxoimidazolidin-3-yl)acetate (7a): Yield: 0.30 g (87%). Mp: 186-188 °C. IR (KBr): ν = 1733, 1689 (2CO), 1392 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.33 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.37 (3H, s, N_1-CH_3), 4.21 (2H, s, SCH_2), 4.28 (2H, q, J = 7.0 Hz, CH_2CH_3), 6.46 (1H, s, =CH), 7.34 (3H, m, H-Ar), 8.18 (2H, d, J = 6.5 Hz, H-Ar). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.11 (CH_3CH_2), 30.35 (N_1-CH_3), 34.17 (SCH_2), 62.50 (CH_3CH_2), 121.89 (=CH), 128.45, 129.39, 129.57, 130.11, 131.02 (C-Ar and C-5), 167.67 (C-4), 173.28 (CO_{ester}), 176.22 (C-2). Calculated for $C_{15}H_{16}N_2O_3S$ (304.37): C, 59.19; H, 5.30; N, 9.20. Found: C, 59.09; H, 4.80; N, 9.03.

Ethyl (*E*)-5-(methylbenzylidene)-1-methyl-4-oxo-2-thioxoimidazolidin-3-yl)acetate (7b): Yield: 0.32 g (99%); Mp: 164-166 °C. IR (KBr): ν = 1734, 1683 (2CO), 1394 (CS) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.32 (3H, t, J = 7.0 Hz, CH_2CH_3), 2.39 (3H, s, $CH_3C_6H_4$), 3.36 (3H, s, N_1-CH_3), 4.21 (2H, s, SCH_2), 4.28 (2H, q, J = 7.0 Hz, CH_2CH_3), 6.44 (1H, s, =CH), 7.23 (2H, d, J = 8.0 Hz, H-3', H-5'), 8.10 (2H, d, J = 8.0 Hz, H-2', H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.11 (CH_3CH_2), 21.64 (CH_3), 30.32 (N_1-CH_3), 34.49 (SCH_2), 62.47 (CH_3CH_2), 122.20 (=CH), 129.22, 129.55, 131.13, 133.48 (C-Ar and C-5), 167.73 (C-4), 173.40 (CO_{ester}), 175.56 (C-2). MS: $C_{16}H_{18}N_2O_3S$: *m/z*: 318 ($M^{+\cdot}$, 0.2%). Calculated for $C_{16}H_{18}N_2O_3S$ (318.39): C, 60.36; H, 5.70; N, 8.80. Found: C, 60.55; H, 5.72; N, 8.83.

Ethyl (*E*)-5-(methoxylbenzylidene)-1-methyl-4-oxo-2-thioxoimidazolidin-3-yl)acetate (7c): Yield: 0.32 g (98%). Mp: 176-178 °C. IR (KBr): ν = 1726, 1680 (2CO), 1390 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.31 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.34 (3H, s, N_1-CH_3), 3.86 (3H, s, OCH_3), 4.20 (2H, s, SCH_2), 4.27 (2H, q, J = J =7.0 Hz, CH_2CH_3), 6.41 (1H, s, =CH), 6.93 (2H, d, J = 8.5, H-2', H-6'), 8.24 (2H, d, J = 8.5, H-3', H-5'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.12 (CH_3CH_2), 30.32 (N_1-CH_3), 34.10 (SCH_2), 55.38 (OCH_3), 62.46 (CH_3CH_2), 114.04, 125.24, 131.39, 132.50, 133.24, 160.18 (=CH, C-Ar and C-5), 167.78 (C-4), 173.56 (CO_{ester}), 174.67 (C-2). MS: $C_{16}H_{18}N_2O_4S$: *m/z*: 334 ($M^{+\cdot}$, 5%). Calculated for $C_{16}H_{18}N_2O_4S$ (334.39): C, 57.47; H, 5.43; N, 8.38. Found: C, 57.45; H, 5.27; N, 8.32.

Ethyl (*E*)-5-(chlorobenzylidene)-1-methyl-4-oxo-2-thioxoimidazolidin-3-yl)acetate (7d): Yield: 0.30 g (92%). Mp: 160-162 °C. IR (KBr): ν = 1733, 1684 (2CO), 1395 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.33 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.38 (3H, s, N_1-CH_3), 4.21 (2H, s, SCH_2), 4.29 (2H, q, J = J =7.0 Hz, CH_2CH_3), 6.39 (1H, s, =CH), 7.39 (2H, d, J = 9.0 Hz, H-2', H-6'), 8.15 (2H, d, J = 8.5 Hz, H-3', H-5'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.12 (CH_3CH_2), 30.37 (N_1-CH_3), 34.24 (SCH_2), 62.50 (CH_3CH_2), 120.39 (=CH), 128.69, 130.84, 132.31, 134.25, 135.96 (C-Ar and C-5), 167.59 (C-4), 173.17 (CO_{ester}), 174.58 (C-2). Calculated for $C_{16}H_{18}N_2O_4S$ (338.81): C, 53.17; H, 4.46; N, 8.27. Found: C, 53.27; H, 4.15; N, 8.15.

4.6. General procedure for the preparation of (E)-5-(arylidene)-3-(2'.3'.4'.6'-tetra-O-acetyl-β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-ones 10a-h

The nucleobases **5a-d** (5mmol) were suspended in anhydrous acetonitrile (25 mL) at room temperature. To this suspension was added NaH (80% in mineral oil, 0.15 g, 5 mmol), and the mixture was stirred at room temperature for ½ hour. 2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-glycopyranosyl bromides (**8a,b**, 2.66 g, 5.50mmol) was added, and the mixture was stirred at room temperature for 12 hours until the starting material was consumed (TLC, CH_2Cl_2/MeOH, 98:2). The solvent was removed under reduced pressure and then treated with water. The solid separated was collected by filtration and recrystallized from ethanol to give the products **10a-h** in moderate and quantitative yields.

(*E*)-5-(Benzylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (10a): Yield: 0.80 g (64%). Mp: 186-188 °C. IR (KBr): ν = 1755 (CO), 1393 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.98 (3H, s, Ac), 2.04 (3H, s, Ac), 2.07 (3H, s, Ac), 2.09 (3H, s, Ac), 3.64 (3H, s, N_3-CH_3), 3.88 (1H, m, H-5′), 4.21 (2H, m, H-6′, H-6′'), 5.28 (1H, t, J = 9.50 Hz, 4′-H), 5.40 (1H, t, J = 10.0 Hz, 2′-H), 6.11 (1H, t, J = 9.0 Hz, 3′-H), 6.17 (1H, d, $^2J_{1',2'}$= 10.5 Hz, 1′-H), 6.55 (1H, s, =CH), 7.97 (3H, m, H-Ar), 7.29 (2H, d, J = 6.5 Hz, H-Ar). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.62, 20.79 (4Ac), 31.49 (N_3-CH_3), 61.84 (C-6′), 67.90 (C-2′), 68.13 (C-3′), 73.44 (C-4′), 74.54 (C-5′), 81.98 (C-1′), 121.28 (=CH), 128.28, 128.44, 130.21, 131.00, 131.57 (C-Ar and C-5), 159.90 (C-4), 169.38, 169.69, 170.16, 170.72 (4Ac), 174.58 (C-2). MS: $C_{25}H_{28}N_2O_{10}S$: *m/z*: 548 ($M^{+\cdot}$, 5%).

(*E*)-5-(Methylbenzylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (10b): Yield: 1.12 g (40%). Mp: 218-220 °C. IR (KBr): ν = 1750 (CO), 1388 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.97 (3H, s, Ac), 2.04 (3H, s, Ac), 2.06 (3H, s, Ac), 2.09 (3H, s, Ac), 2.80 (3H, s, $CH_3C_6H_4$), 3.61 (3H, s, N_3-CH_3), 3.87 (1H, m, H-5′), 4.92 (2H, m, H-6′, H-6′'), 5.26 (1H, t, J = 9.5 Hz, 4′-H), 5.37 (1H, t, J = 10.0 Hz, 2′-H), 6.10 (1H, t, J = 9.0 Hz, 3′-H), 6.12 (1H, d, $^2J_{1',2'}$= 10.5 Hz, 1′-H), 6.46 (1H, s, =CH), 7.38 (2H, d, J = 8.5 Hz, H-3', H-5'), 7.92 (2H, d, J = 8.0 Hz, H-2', H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.60, 20.78 (4Ac), 20.78 (CH_3), 31.44 (N_3CH_3), 61.80 (C-6′), 67.53 (C-2′), 67.87 (C-3′), 73.33 (C-4′), 74.55 (C-5′), 81.97 (C-1′), 120.04 (=CH), 128.59, 128.68, 130.11, 132.26, 136.06 (C-Ar and C-5), 159.96 (C-4), 169.37, 169.74, 170.11, 170.67 (4Ac), 175.96 (C-2). MS: $C_{25}H_{28}N_2O_{10}S$: *m/z*: 562 ($M^{+\cdot}$, 9%).

(*E*)-5-(Methoxylbenzylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (10c): Yield: 2.40 g (83%). Mp: 224-226 °C. IR (KBr): ν = 1742 (CO), 1384 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.99 (3H, s, Ac), 2.05 (3H, s, Ac), 2.07 (3H, s, Ac), 2.09 (3H, s, Ac), 3.64 (3H, s, N_3-CH_3), 3.88 (3H, s, OCH_3), 4.22 (1H, m, H-5′), 4.25 (2H, m, H-6′, H-6′'), 5.29 (1H, t, J = 9.5 Hz, 4′-H), 5.37 (1H, t, J = 10.0 Hz, 2′-H), 6.14 (1H, t, J = 9.0 Hz, 3′-H), 6.16 (1H, d, $^2J_{1',2'}$= 10.5 Hz, 1′-H), 6.52 (1H, s, =CH), 6.96 (2H, d, J = 8.5 Hz, H-2', H-6'), 8.05 (2H, d, J = 8.0 Hz, H-3', H-5'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.62, 20.79 (4Ac), 31.51 (N_3CH_3), 55.41 (OCH_3), 61.88 (C-6′), 67.94 (C-2′), 68.08 (C-3′), 73.53 (C-4′), 74.51 (C-5′), 81.95 (C-1′), 113.97, 122.35, 124.47, 126.59, 133.32, 158.96 (=CH, C-Ar and C-5), 161.42 (C-4), 169.39, 169.63, 170.14, 170.70 (4Ac), 175.19 (C-2). MS: $C_{26}H_{30}N_2O_{11}S$: *m/z*: 578 ($M^{+\cdot}$, 3%).

(*E*)-5-(Chlorobenzylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (10d): Yield: 1.40 g (47%). Mp: 233-235 °C. IR (KBr): ν = 1751 (CO), 1388 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.97 (3H, s, Ac), 2.04 (3H, s, Ac), 2.07 (3H, s, Ac), 2.09 (3H, s, Ac), 3.62 (3H, s, N_3-CH_3),

3.87 (1H, m, H-5′), 4.26 (2H, m, H-6′, H-6′′), 5.27 (1H, t, J = 9.5 Hz, 4′-H), 5.38 (1H, t, J = 10.0 Hz, 2′-H), 6.09 (1H, t, J = 9.0 Hz, 3′-H), 6.15 (1H, d, $^2J_{1',2'}$= 10.5 Hz, 1′-H), 6.52 (1H, s, =CH), 7.23 (2H, d, J = 8.5 Hz, H-2‘, H-6‘), 7.89 (2H, d, J = 8.0 Hz, H-3‘, H-5‘). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.62, 20.65 (4Ac), 31.49 (N_3CH_3), 61.86 (C-6′), 67.92 (C-2′), 68.11 (C-3′), 73.49 (C-4′), 74.52 (C-5′), 81.96 (C-1′), 121.24 (=CH), 127.65, 128.87, 129.22, 131.14, 140.94 (C-Ar and C-5), 161.38, 169.38, 169.63, 170.15, 170.71 (4Ac, C-4), 175.67 (C-2). MS: $C_{25}H_{27}ClN_2O_{10}S$: *m/z*: 582 ($M^{+\cdot}$, 4%).

(*E*)-5-(Benzylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (10e): Yield: 1.90 g (69%). Mp: 76-78 °C. IR (KBr): ν = 1751 (CO), 1373 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.05 (3H, s, Ac), 2.08 (3H, s, Ac), 2.26 (3H, s, Ac), 2.41 (3H, s, Ac), 3.36 (3H, s, N_3-CH_3), 4.10 (1H, m, H-5′), 4.30 (2H, m, H-6′, H-6′′), 5.25 (1H, t, J = 9.5 Hz, 4′-H), 5.50 (1H, t, J = 10.0 Hz, 2′-H), 6.02 (1H, t, J = 9.5 Hz, 3′-H), 6.20 (1H, d, $^2J_{1',2'}$ = 9.5 Hz, 1′-H), 7.00 (1H, s, =CH), 7.27 (3H, m, H-Ar), 7.29 (2H, d, J = 6.5 Hz, H-Ar). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.71(4Ac), 31.95 (N_3-CH_3), 63.43 (C-6′), 65.88 (C-2′), 66.87 (C-3′), 71.84 (C-4′), 73.20 (C-5′), 82.44 (C-1′), 116.00 (=CH), 128.00, 128.46, 129.58 130.52 131.20, (C-Ar and C-5), 165.00 (C-4), 168.00, 169.00, 170.00, 171.00 (4Ac), 173.00 (C-2). MS: $C_{25}H_{28}N_2O_{10}S$: *m/z*: 548 ($M^{+\cdot}$, 2%).

(*E*)-5-(Methylbenzylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (10f): Yield: 2.53 g (90%). Mp: 72-74 °C. IR (KBr): ν = 1751 (CO), 1376 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.91 (3H, s, Ac), 1.93 (3H, s, Ac), 1.95 (3H, s, Ac), 1.97 1.95 (3H, s, Ac), 2.18 (3H, s, $CH_3C_6H_4$), 3.25 (3H, s, N_3-CH_3), 3.90 (1H, m, H-5′), 4.20 (2H, m, H-6′, H-6′′), 5.10 (1H, t, J = 10.0 Hz, 4′-H), 5.40 (1H, t, J = 10.0 Hz, 2′-H), 5.90 (1H, t, J = 9.0 Hz, 3′-H), 6.29 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.90 (1H, s, =CH), 7.20 (2H, d, J = 8.5 Hz, H-3‘, H-5‘), 7.33 (2H, d, J = 8.0 Hz, H-2‘, H-6‘). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.74 (4Ac), 29.71 (CH_3), 31.45 (N_3CH_3), 61.43 (C-6′), 65.88 (C-2′), 66.86 (C-3′), 71.82 (C-4′), 73.22 (C-5′), 82.45 (C-1′), 116.14 (=CH). 128.45, 129.50, 131.05, 132.28, 136.04 (C-Ar and C-5), 160.98 (C-4), 168.00, 169.00, 170.00, 171.00 (4Ac), 173.00 (C-2). MS: $C_{25}H_{28}N_2O_{10}S$: *m/z*: 562 ($M^{+\cdot}$, 31%).

(*E*)-5-(Methoxybenzylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (10g): Yield: 2.50 g (87%). Mp: 58-60 °C. IR (KBr): ν = 1750(C O), 1394 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.03 (3H, s, Ac), 2.05 (3H, s, Ac), 2.08 (3H, s, Ac), 2.26 (3H, s, Ac), 3.39 (3H, s, N_3-CH_3), 3.88 (3H, s, OCH_3), 4.05 (1H, m, H-5′), 4.30 (2H, m, H-6′, H-6′′), 5.15 (1H, t, J = 10.0 Hz, 4′-H), 5.50 (1H, t, J = 10.0 Hz, 2′-H), 6.10 (1H, t, J = 9.0 Hz, 3′-H), 6.25 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.85 (1H, s, =CH), 7.00 (2H, d, J = 8.5 Hz, H-2‘, H-6‘), 7.30 (2H, d, J = 8.0 Hz, H-3‘, H-5‘). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.74 (4Ac), 29.38 (N_3CH_3), 55.52 (OCH_3), 61.88 (C-6′), 66.00 (C-2′), 67.00 (C-3′), 72.00 (C-4′), 74.00 (C-5′), 82.00 (C-1′), 114.03, 122.50, 128.00, 129.00, 131.36, 159.67 (=CH, C-Ar and C-5), 161.40 (C-4), 169.38, 169.61, 170.16, 170.75 (4Ac), 175.20 (C-2). MS: $C_{26}H_{30}N_2O_{11}S$: *m/z*: 578 ($M^{+\cdot}$, 2%).

(*E*)-5-(Chlorobenzylidene)-3-(2'.3'.4'.6'-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (10h): Yield: 2.26 g (76%). Mp: 84-86 °C. IR (KBr): ν = 1750 (CO), 1394 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.91 (3H, s, Ac), 1.95 (3H, s, Ac), 1.98 (3H, s, Ac), 2.17 (3H, s, Ac), 3.23 (3H, s, N_3-CH_3), 3.97 (1H, m, H-5′), 4.20 (2H, m, H-6′, H-6′′), 5.10 (1H, t, J = 10.0 Hz, 4′-H), 5.49 (1H, t, J = 10.0 Hz, 2′-H), 5.59 (1H, t, J = 9.00 Hz, 3′-H), 6.10 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.54 (1H, s, =CH), 7.19 (2H, d, J = 8.5 Hz, H-2‘, H-6‘), 7.50 (2H, d, J = 8.0 Hz, H-3‘, H-5‘). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.74 (4Ac), 29.72 (N_3CH_3), 61.42 (C-6′), 65.00 (C-2′), 67.00 (C-3′), 71.00 (C-4′), 74.00 (C-5′), 82.48 (C-1′), 122.24 (=CH), 127.56, 128.79, 130.79, 131.00, 140.54 (C-Ar and C-5), 161.36 (C-4), 165.32, 168.60, 169.12, 170.70 (4Ac), 175.76 (C-2). MS: $C_{25}H_{27}ClN_2O_{10}S$: *m/z*: 582 ($M^{+\cdot}$, 1%).

(*E*)-5-(Arylidene)-3-(β-D-glycopyranosyl)-1-methyl-2-thioxoimidazoliden-4-ones 11a-h

The protected nucleosides **10a-h** (1 mmol) were suspended in MeOH (15 mL), and concentrated HCl (0.5 mL) was added. The reaction mixture was stirred at 40-50°C for 2 h, then cooled to room temperature. To the resulting solution was added an ion-exchange resin (Amberlite IR-120, HO -form), previously washed with MeOH. After stirring for 5 min., the solution was filtered and evaporated in vacuum and the residue was purified by flash chromatography (eluent 0–5%, $CHCl_3$/MeOH) to afford **11a-h** as yellow solids.

(*E*)-5-(Benzylidene)-3-(β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (11a): Yield: 0.36 g (95%). Mp: 94-96 °C. IR (KBr): ν = 3500 (OH), 1734 (CO), 1390 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.13 (1H, m, H-5′), 3.15 (2H, m, H-6′, H-6′′), 3.21 (1H, t, J = 9.5 Hz, 4′-H), 3.28 (3H, s, N_3-CH_3), 3.70 (1H, t, J = 10.0 Hz, 3′-H), 4.32 (1H, t, J = 10.0 Hz, 2′-H), 4.61 (1H, s, 6'-OH), 5.07 (1H, s, 4'-OH), 5.16 (1H, s, 3'-OH), 5.30 (1H, s, 2'-OH), 5.51 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.91 (1H, s, =CH), 7.43 (3H, m, H-Ar), 7.51 (2H, d, J = 6.6 Hz, H-Ar). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 31.55 (N_3-CH_3), 62.88 (C-6′), 67.50 (C-2′), 70.72 (C-3′), 79.77 (C-4′), 80.64 (C-5′), 85.81 (C-1′), 115.00, 128.20, 128.50, 129.90, 131.00, 132.30 (=CH, C-Ar and C-5), 163.00 (C-4), 180.00 (C-2). MS: $C_{17}H_{20}N_2O_6S$: *m/z*: 380 ($M^{+\cdot}$, 5%).

(*E*)-5-(Methylbenzylidene)-3-(β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (11b): Yield: 0.36 g (92%). Mp: 234-238 °C. IR (KBr): ν = 3600 (OH), 1701 (CO), 1397 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.11 (1H, m, H-5′), 3.12 (2H, m, H-6′, H-6′′), 3.20 (1H, t, J = 9.5 Hz, 4′-H), 3.42 (3H, s, N_3-CH_3), 3.44 (3H, s, $CH_3C_6H_4$), 3.70 (1H, t, J = 10.0 Hz, 3′-H), 4.61 (1H, t, J = 10.0 Hz, 2′-H), 4.62 (1H, s, 6'-OH), 5.07 (1H, s, 4'-OH), 5.12 (1H, s, 3'-OH), 5.29 (1H, s, 2'-OH), 5.56 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.85 (1H, s, =CH), 7.26 (2H, d, J = 8.5 Hz, H-3‘, H-5‘), 7.99 (2H, d, J = 8.0 Hz, H-2', H-6‘). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 31.13 (CH_3), 31.60 (N_3-CH_3), 62.84 (C-6′), 67.52 (C-2′), 70.68 (C-3′), 79.76 (C-4′), 80.66 (C-5′), 85.86 (C-1′), 122.00 (=CH), 128.20, 128.90, 129.10, 129.90, 131.10 (C-Ar and C-5), 162.84 (C-4), 178.92 (C-2). MS: $C_{18}H_{22}N_2O_6S$: *m/z*: 394 ($M^{+\cdot}$, 42%).

(*E*)-5-(Methoxybenzylidene)-3-(β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (11c): Yield: 0.38 g (93%). Mp: 222-224 °C. IR (KBr): ν = 3422 (OH), 1733 (CO), 1370 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.11 (1H, m, H-5′), 3.20 (2H, m, H-6′, H-6′′), 3.25 (1H, t, J = 10.0 Hz, 4′-H), 3.34 (3H, s, N_3-CH_3), 3.44 (3H, s, OCH_3), 4.32 (1H, t, J = 10.0 Hz, 3′-H), 5.19 (1H, t, J = 10.0 Hz, 2′-H), 4.68 (1H, s, 6'-OH), 5.12 (1H, s, 4'-OH), 5.24 (1H, s, 3'-OH), 5.30 (1H, s, 2'-OH), 5.52 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.85 (1H, s, =CH), 7.48 (2H, d, J = 8.5, H-2‘, H-6‘), 8.14 (2H, d, J = 8.5, H-3‘, H-5‘). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 30.98 (N_3CH_3), 55.25 (OCH_3), 62.68 (C-6′), 67.72 (C-2′), 70.68 (C-3′), 79.74 (C-4′), 80.60 (C-5′), 85.78 (C-1′), 114.35, 115.65, 121.12, 132.74, 133.82, 148.45 (=CH, C-Ar and C-5), 162.52 (C-4), 178.82 (C-2). MS: $C_{18}H_{22}N_2O_7S$: *m/z*: 410 ($M^{+\cdot}$, 5%).

(*E*)-5-(Chlorobenzylidene)-3-(β-D-glucopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (11d): Yield: 0.36 g (92%). Mp: 98-100 °C. IR (KBr): ν = 3400 (OH), 1734 (CO), 1389 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 3.12 (1H, m, H-5′), 3.20 (2H, m, H-6′, H-6′′), 3.24 (1H, t, J = 10.0 Hz, 4′-H), 3.30 (3H, s, N_3-CH_3), 3.70 (1H, t, J = 10.0 Hz, 3′-H), 4.32 (1H, t, J = 10.0 Hz, 2′-H), 4.52 (1H, s, 6'-OH), 5.05 (1H, s, 4'-OH), 5.15 (1H, s, 3'-OH), 5.30 (1H, s, 2'-OH), 5.52 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.88 (1H, s, =CH), 7.53 (2H, d, J = 8.5 Hz, H-2‘, H-6‘), 7.54 (2H, d, J = 9.0 Hz, H-3‘, H-5‘). ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 30.89 (N_3-CH_3), 62.80 (C-6′), 67.42 (C-2′), 70.62 (C-3′), 79.68 (C-4′), 80.74 (C-5′), 85.92 (C-1′),

122.00 (=CH), 123.16, 129.20, 130.08, 131.11, 132.12 (C-Ar and C-5), 162.46 (C-4), 178.78 (C-2). MS: $C_{17}H_{19}ClN_2O_6S$: *m/z*: 414 ($M^{+\cdot}$, 1%).

(*E*)-5-(Benzylidene)-3-(β-D-galactopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (11e): Yield: 0.37 g (97%). Mp: 138-140 °C. IR (KBr): ν = 3498 (OH), 1732 (CO), 1388 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, CD_3OD-d_4): δ = 3.67 (1H, m, H-5′), 3.69 (2H, m, H-6′, H-6′'), 3.76 (1H, t, J = 9.5 Hz, 4′-H), 3.95 (3H, s, N_3-CH_3), 3.97 (1H, t, J = 10.0 Hz, 3′-H), 4.32 (1H, t, J = 10.0 Hz, 2′-H), 5.74 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.94 (1H, s, =CH), 7.32 (3H, m, H-Ar), 8.00 (2H, d, J = 8.0, H-Ar). ^{13}C-NMR (125 MHz, CD_3OD-d_4): δ = 31.83 (N_3-CH_3), 62.35 (C-6′), 64.86 (C-2′), 70.66 (C-3′), 76.26 (C-4′), 79.74 (C-5′), 86.72 (C-1′), 122.25.00 (=CH), 129.19, 129.56, 130.74, 132.15, 134.08 (C-Ar and C-5), 164.98 (C-4), 182.00 (C-2).

(*E*)-5-(Methylbenzylidene)-3-(β-D-galactopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (11f): Yield: 0.29 g (74%). Mp: 140-142 °C. IR (KBr): ν = 3556 (OH), 1712 (CO), 1394 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, CD_3OD-d_4): δ = 2.46 (3H, s, $CH_3C_6H_4$), 3.47 (3H, s, N_3-CH_3), 3.50 (1H, m, 5'-H), 3.55 (2H, m, 6'-H, 6"-H), 3.59 (1H, t, J = 9.5 Hz, 4'-H), 3.62 (1H, t, J = 10.0 Hz, 3'-H), 3.99 (1H, t, J = 10.0 Hz, 2'-H), 5.74 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1'-H), 6.85 (1H, s, =CH), 7.26 (2H, d, J = 8.5 Hz, H-3′, H-5‘), 7.99 (2H, d, J = 8.0 Hz, H-2‘, H-6‘). ^{13}C-NMR (125 MHz, CD_3OD-d_4): δ = 30.78 (N_1CH_3), 36.12 (CH_3), 62.34 (C-6′), 64.54 (C-2′), 70.62 (C-3′), 76.27 (C-4′), 79.80 (C-5′), 87.00 (C-1′), 122.00 (=CH), 128.20, 128.90, 129.10, 129.90, 131.10 (C-Ar and C-5), 164.80 (C-4), 185.20 (C-2).

(*E*)-5-(Methoxybenzylidene)-3-(β-D-galactopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (11g): Yield: 0.40 g (97%). Mp: 92-94 °C. IR (KBr): ν = 3450 (OH), 1725 (CO), 1386 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, CD_3OD-d_4): δ = 3.41 (3H, s, N_3-CH_3), 3.58 (1H, m, 5'-H), 3.60 (2H, m, 6'-H, 6"-H), 3.76 (1H, t, J = 10.0 Hz, 4'-H), 3.87 (3H, s, OCH_3), 3.95 (1H, t, J = 10.0 Hz, 3'-H), 4.09 (1H, t, J = 10.0 Hz, 2'-H), 5.72 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1'-H), 6.93 (1H, s, =CH), 7.03 (2H, d, J = 8.5 Hz, H-2‘, H-6‘), 7.40 (2H, d, J = 8.5 Hz, H-3‘, H-5‘).

(*E*)-5-(Chlorobenzylidene)-3-(β-D-galactopyranosyl)-1-methyl-2-thioxoimidazoliden-4-one (11h): Yield: 0.32 g (82%). Mp: 120-122 °C. IR (KBr): ν = 3420 (OH), 1738 (CO), 1384 (CS) cm^{-1}. ^{1}H-NMR (500 MHz, CD_3OD-d_4): δ = 3.33 (3H, s, N_3-CH_3), 3.58 (1H, m, H-5′), 3.60 (2H, m, H-6′, H-6′'), 3.76 (1H, t, J = 10.0 Hz, 4′-H), 3.95 (1H, t, J = 10.0 Hz, 3′-H), 4.09 (1H, t, J = 10.0 Hz, 2′-H), 5.72 (1H, d, $^2J_{1',2'}$= 10.0 Hz, 1′-H), 6.93 (1H, s, =CH), 7.03 (2H, d, J = 9.0 Hz, H-2‘, H-6‘), 7.40 (2H, d, J = 9.0 Hz, H-3‘, H-5‘). ^{13}C-NMR (125 MHz, CD_3OD-d_4): δ = 31.82 (N_3-CH_3), 62.34 (C-6′), 67.53 (C-2′), 70.62 (C-3′), 72.94 (C-4′), 79.75 (C-5′), 86.74 (C-1′), 120.40 (=CH), 129.32, 129.74, 132.35, 133.72 (C-Ar and C-5), 162.42 (C-4), 182.27 (C-2).

4.7. Methodology

4.7.1. In Vitro *Cytotoxic Activity*

Cytotoxic efficacy of the synthesized derivatives against liver HepG2, lung A549, breast MCF-7, colon HCT116 cancer cell lines was tested using the MTT assay [74]. Cell lines; MCF-7 (ATCC® HTB-22™), HepG2 ((ATCC® HB-8065™), A549 (ATCC® CCL-185™), and the HCT-116 (ATCC® CCL-247™) were purchased from the National Research institute, Cairo, Egypt. Each cell line was propagated in a complete medium composed of DMEM (High Glucose w/ stable Glutamine w/ Sodium Pyruvate, Biowest) or RPMI-1640 (Lonza Verviers SPRL, Belgium) supplemented with 10% fetal bovine serum (Seralab, UK) and 1% Antibiotic (Antibiotic antimycotic, Biowest). Number of 10^4 cells/well were propagated in the corresponding media, incubated in 5% CO_2 and humidified at 37°C for growth according to the standard cell culture work [75]. Cells were treated for 48 h with serial concentrations of compounds (1, 10, 100, 1000 μM), and hence the percentages of cell survival and values of IC_{50} were determined using Graph Pad Prism 7.0.

4.7.2. *Molecular Docking Studies*

All the molecular modeling studies were carried out on Intel® Core™ i3 CPU, 2.40 GHZ processor, and 3 GB memory with Windows 7 operating system using Molecular Operating Environment (MOE 2008-10 Chemical Computing Group, Canada) as the computational software. For the docking studies, the crystal structure of human cyclin-dependent kinase 2 in complex with recovering was obtained from the freely accessible Protein data bank (PDB code: **2a4l**) [76], verification process was performed by re-docking of the co-crystallized ligand into the active site using the default settings. The steroidal derivatives were constructed 2D using ChemBio-office 2015, converted to 3D by builder interface of MOE program, and then were subjected to energy minimization with MMFF94X force and the partial charges were automatically calculated. Different conformers for each compound are imported by systematic conformational of the MOE and saved in an mdbdatabase file to be docked into the active site of the receptor. Visualization for ligand-receptor interactions was made by Chimera software.

Credit Author Statement

Ahmed I. Khodair: Design, introduction, interpretation of discussion, results, spectral data, expermental results, writing draft and English polishing; Safyah B. Bakare: Experimental results and interpretation of spectral data; Mohamed K. Awad: Computational calculations, interpretation of discussion and results of computational calculations data; Mohamed S. Nafie: Biological measurements, interpretation of discussion and results of biological measurements data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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