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Original article

Synthesis, antitumor activity and molecular docking study of novel Sulfonamide-Schiff's bases, thiazolidinones, benzothiazinones and their C-nucleoside derivatives

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ABSTRACT

A series of sulfapyridine-polyhydroxyalkylidene (or arylidene)-imino derivatives (Schiff's bases) **2a–c** and **4a–e** were prepared by condensation of 4-amino-*N*-pyridin-2-ylbenzenesulfonamide (**1**) with different monosaccharides or with aromatic aldehydes. Treatment of **2a–c** with thioglycolic acid led to the formation of the C-nucleosides (**3a–c**), while treatment of **4a–e** with thioglycolic and/or thiosalicylic acids afforded the corresponding 2-arylthiazolidin-4-one or 2-arylbenzothiazin-4-one derivatives **5a–e** and/or **6a–e**, respectively. Some representative examples of the newly prepared compounds showed considerable cytotoxic effect against breast carcinoma cell line **MCF7** and cervix carcinoma cell line **HELA** in comparison with 5-flurouracil and doxorubicin. AutoDock molecular docking into PTK has been done for lead optimization of the compounds in study as potential PTK inhibitors.

1. Introduction

The chemistry of sulfanilamides [1,2], thiazolidinones [3] and benzothiazines [4] have been of increasing interest since many of these derivatives produce useful applications as chemotherapeutic agents especially against pathogenic bacteria and tumor cells. On the other hand, it has been reported that a wide range of Schiff's bases with their reactive azomethine linkage shows interesting inhibitory activity against experimental tumor cells [5–8]. It is also suggested that the Schiff's bases could be hydrolyzed selectively by the tumor cells to act as alkylating agents at the same time as the active amine becomes free to act as antimetabolite [9]. Besides, the Schiff's bases represent active intermediates to develop various heterocyclic systems of biological importance as the above mentioned pyridines, thiazolidines, benzothiazines and their C-nucleoside analogues. Based on all of these findings, it was of interest to synthesize some new sulfapyridine-Schiff's bases and their cyclic products and/or their C-nucleoside analogues to be evaluated for their cytotoxic activity.

The role of tyrosine kinase in the control of cellular growth and differentiation is central to all organisms and the tyrosine kinase has been found to participate in human neoplastic diseases. Tyrosine kinase inhibitors and their potentials in the clinical applications are well documented by dramatic examples such as Gleevec, Iressa and Herceptin. Several tyrosine kinase inhibitors are undergoing human trials and several are in the pipeline of drug discovery [10]. Molecular docking has been a focus of attention for many years. Generally speaking, today's flexible docking programs such as AutoDock are able to predict protein–ligand complex structures with reasonable accuracy and speed [11]. One of the most reliable, robust and popular energy-based docking packages is AutoGrid/AutoDock (Morris et al., 1998) because it allows a very efficient docking of flexible ligands (*e.g.* substrates, drug candidates, inhibitors, peptides, *etc.*) onto receptors (*e.g.* enzymes, antibodies, nucleic acids, *etc.*) [12].

2. Chemistry

The discovery of C-nucleosides and continuous study of their biological activities [13,14] led us to construct compounds containing sulfapyridine Schiff's bases incorporated into different aldoses, thiazolidinones, benzothiazines and/ or their C-nucleoside analogues which might be of potential anticancer properties against experimental tumor cell lines. Thus the reaction of

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sulfapyridine **1** dissolved in DMF containing few drops of acetic acid with various monosaccharide (aldoses) namely, D-arabinose, D-xylose and/ or D-mannose dissolved in water, gave the corresponding Schiff's bases: *N*-[1- (1,2,3,4-tetrahydroxypentylidene)]-imino 4-[(pyridinylamino)sulfonyl]benzenes (**2a**, **b**) and/ or *N*-[1-(1,2,3,4,5- pentahydroxyhexyl idene)- imino-4-[(pyridin-2-ylamino)sulfonyl]benzene (**2c**), respectively. Cyclocondensation of Schiff's bases **2a**–**c** with thioglycolic acid in dry dioxane, afforded the corresponding thiazolidinones, namely; 2-[1-(1,2,3,4- tetrahydroxybutyl)]-3-[4-[(pyridin-2-yl amino) sulfonyl]phenyl] thiazolidin-4-one (**3a**,**b**) and/ or 2-[1-(1,2,3,4,5-penta- hydroxyl- pentyl)]-3-[4-[(pyridin-2-ylamino)]sulfonyl]-phenyl]thiazolidin-4-one (**3c**), respectively (Scheme 1).

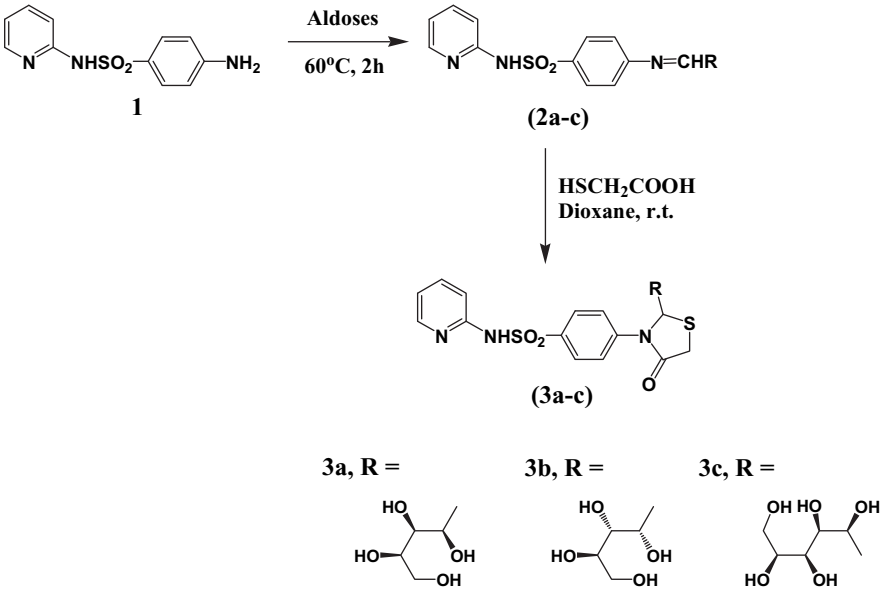
Also, reaction of sulfapyridine **1** with different aromatic aldehydes, namely; *p*-anisaldehyde, 3,4-dimethoxybenzaldehyde, 2-hydroxy-4-methoxybenzaldehyde, 3,4,5-trimethoxybenzal- dehyde and/ or indol-3-carboxaldehyde in the presence of few drops of acetic acid, afforded Schiff's bases, namely; *N*-(substituted arylidene)-imino-4-[(pyridin-2-ylamino)sulfonyl]benzenes (**4a**–**e**), respectively. Compounds **4a**–**e** were reacted with thioglycolic acid and/ or thiosalicylic acid to give the corresponding 2-aryl- 3-[4-[(pyridin-2-ylamino)sulfonyl]phenyl] thiazolidin-4-ones (**5a**–**e**) and/or 2-aryl-3-[4-[(pyridin-2-ylamino)sulfonyl]phenyl]-2,4-dihydr- obenzo[e][1,3]thiazin-4-ones (**6a**–**e**), respectively (Scheme 2).

3. Results and discussion

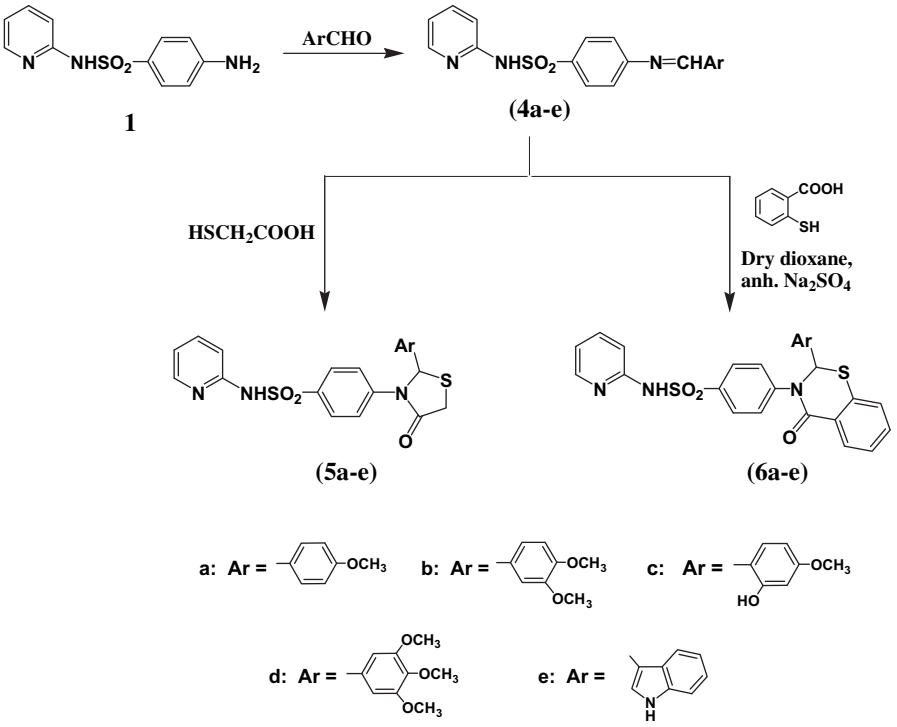
3.1. Biological evaluation

Chemotherapy is a major therapeutic approach for the both localized and metastasized cancers. In the present work, six of the newly synthesized compounds **2b**, **3b**, **4a**, **4e**, **5e**, **6a** were selected to evaluate their in vitro growth inhibitory activities against two human cultured cell lines, which are cervix carcinoma cell line (**HELA**) and breast carcinoma cell lines (**MCF7**) in comparison to the known anticancer drugs: 5-flurouracil and doxorubicin as reference drugs. The six compounds selected being, **2a**, **3b**, **4a**, **4e**, **5e**, and **6a** were carefully selected to be representatives for all the newly synthesized 21 derivatives. And covering all structural variations in these analogs, being of sulfapyridine attached to xylose (**2a**), thiazolidinone (**3b**), sulfapyridine attached to *p*-methoxyphenyl (**4a**), sulfapyridine attached to indole (**4e**), thiazolidinone attached to indole (**5e**), and benzothiazine analogue (**6a**). It has been noticed from Table 1 that all of the tested compounds showed significant antitumor activities and this might be explained that the presence of the phenyl ring of sulfapyridine moiety provided good affinity towards the enzyme on account of the force of electrostatic attraction between the planar phenyl and the target site pocket of the tumor cells. In comparison to 5-flurouracil, the attachment of xylose nucleus to sulfapyridine via azomethine linkage in compound **2b** gave antitumor activity against HELA (IC_{50}: 3.56 μg/mL); about one third that of 5-flurouracil (IC_{50}:1.01 μg/mL), but the activity against MCF7 (IC_{50}: 1.68 μg/mL) was one half that of the reference compound (IC_{50}: 0.67 μg/mL). The antitumor activity of thiazolidinone analogue **3b** against HELA increased (IC_{50}: 2.01 μg/mL), while the activity against MCF7 decreased to be about one fourth of the activity of the comparing drug (IC_{50}: 2.68 μg/mL). Also, combining sulfapyridine moiety with *p*-methoxyphenyl via azomethine linkage in derivative **4a** enhances the antitumor activity against both types of carcinoma cell lines HELA and MCF7 to be very close to that gained by the comparing drug (IC_{50}: 1.88 and 0.74 μ/mL, respectively). The benzothiazine analogue **6a** showed more slight increase in the activity against HELA (IC_{50}: 1.48 μg/mL), but the activity against MCF7 decreased (IC_{50}: 1.61 μg/mL). The derivative **4e** containing indole moiety attached to sulfapyridine through azomethine linkage induced antitumor activity against HELA of about one half that of 5-flurouracil (IC_{50}: 2.82 μg/mL) and against MCF7 of about one third that of the comparing drug (IC_{50}: 2.28 μg/mL). The cyclized analogue bearing thiazolidinone ring **5e** exhibited increase in the antitumor activity against both HELA (IC_{50}:1.95 μg/mL) and MCF7 (IC_{50}: 1.07 μg/mL). It is noteworthy that, comparing to doxorubicin (IC_{50}: 8.72 and 7.71 μg/mL against HELA and MCF7, respectively), all of the tested derivatives showed much higher antitumor activity against both types of carcinoma cell lines (IC_{50}: 0.74–3.56 μg/mL).

Considering the structure activity relationship (SAR) of the aforementioned selected compounds, they exhibited narrow range of variation of IC_{50}, being [0.74–3.56] μg/ml. This indicate that SAR of



Scheme 1.



Scheme 2.

these compounds mainly depends on their main structural feature of: 4-[(pyridin-2-ylamino) sulfonyl]benzene which is considered as the pharmacophoric moiety. Whereas, the attached fragment being alkylidene imino (**2a**–**c**), thiazolidin-4-one (**3a**–**c**) and (**5a**–**e**), arylidene imino (**4a**–**e**), and benzo[e][1,3]thiazin-4-ones (**6a**–**e**) play a minor role in structure activity relationship, namely as auxiliary group for the antitumor activity.

3.2. Molecular docking study

Both pharmaceutical companies and university laboratories have been active to develop compounds which can inhibit tyrosine kinase activity in the expectation that the potent and selective inhibitors would represent a new class of therapeutics for cancers as well as other proliferative diseases. Therefore, PTK inhibitors can be applied aptly as a new mode of cancer therapy. Depending on the above mentioned idea, herein we investigated the AutoDock binding affinities of the synthesized sulfonylbenzenes, sulfonylphenylthiazolidinones, and sulf- onylphenylbenzo[e] [1,3]thiazinones into PTK. Towards optimization of the aforementioned lead compounds of the promising antitumor activities, the advanced docking program AutoDock 3.0.5 [15] was used to evaluate the binding free energies as potential inhibitors into the target PTK macromolecule.

Table 1
Effect of some selected sulfapyridine derivatives on **MCF7** and **HELA** tumor cell lines.

Compound	IC50 [μg/ml]	
	MCF7	**HELA**
5-Fluorouracil (5-FU)	0.67	1.01
Doxorubicin (Dox)	6.71	8.72
2b	1.68	3.56
3b	2.68	2.01
4a	0.74	1.88
4e	2.28	2.82
5e	1.07	1.95
6a	1.61	1.48

3.2.1. Validation of the accuracy of AutoDock

As cited in literature [10] if the RMSD (root mean square deviation) of the best docked conformation is $\leq$2.0 Å from the bound ligand in the experimental crystal, the used scoring function is successful. Therefore, the docked results were compared to the crystal structure of the bound ligand–protein complex. The obtained success rates of AutoDock (Morris et al., 1998) were highly excellent as cited in Table 2. The STI-571 ligand (Imatinib or Gleevec), 4-(4-methylpiperazin-1-ylmethyl)-*N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)phenyl]ben-zamide, was docked into its c-Kit receptor PTK (pdb code:1t46). The RMSD of the docked ligand was 0.25 Å as it seems exactly superimposed on the native bound one. Moreover, the obtained binding free energy (ΔG_b) was quite low being −18.43 kcal/mol. The docked ligand (yellow stick) exhibited hydrogen bonds with almost same atoms of amino acids involved with the native ligand (ball and stick, colored by element). These results indicated the high accuracy of the AutoDock simulation in comparison with the biological methods [16].

3.2.2. AutoDock binding affinities of the synthesized compounds into PTK

The binding affinity was evaluated by the binding free energies (ΔG_b, kcal/mol), inhibition constants (K_i), hydrogen bonding, and RMSD values. The compounds which revealed the highest binding affinities, *i.e.*, lowest binding free energies, within PTK and the hydrogen bond interactions into the target macromolecule are represented in Table 2. These compounds include: (**2a**–**c**), (**3a**–**3c**), (**4a**–**e**), (**5a**–**e**) and (**6a**–**e**). As shown in Table 2, the compounds exhibiting the lowest binding free energy are compound **2a** (ΔG_b: −8.84 kcal/mol) which exhibited four hydrogen bonds with Glu640, Asp810, and Cys673 and RMSD: 3.80 Å, compound **4a**, (ΔG_b: −9.07 kcal/mol) which exhibited one hydrogen bonds with Thr670, and RMSD: 0.99 Å, compound **4c** (ΔG_b: −8.99 kcal/mol)

Table 2
The best docking results based on the binding free energies (ΔG_b) and inhibition constants (K_i) of compounds docked into PTK, the distances and angles of hydrogen bonds between compounds and amino acids in PTK, and RMSD from the co-crystallized STI ligand.

Compound	ΔG_b (kcal/mol)	K_i	Hydrogen bonds between atoms of compounds and amino acids				RMSD (Å)
			Atom of compound	Amino acid	Distance (Å)	Angle (°)	
1	−7.43	3.59E-06	SO_2NH	OH of Thr670	1.92	127.0	5.34
2a	−7.88	1.67E-06	Arabinose-OH	O=C of Val668	2.34	140.8	1.78
2b	−6.80	1.03E-05	SO_2NH	O=C of Glu640	1.97	128.4	3.20
2c	−8.84	3.31E-07	SO_2NH	O=C of Glu640	193	109.9	3.80
			SO_2NH	O=C of Asp810	2.39	138.5	
			Mannose-OH	O=C of Cys673	2.16	134.0	
			Mannose-O	HN of Cys673	1.65	145.8	
3a	−5.43	1.04E-04	(Arabinose)-4-OH	O=C of Ile789	2.07	121.1	9.05
3b	−5.90	4.77E-05	(Xylose)-2-OH	O=C of 810	2.08	136.1	6.87
3c	−7.68	2.35E-06	Thiazole-S	HO of Thr670	2.39	123.8	0.80
4a	−9.07	7.40E-07	$HNSO_2$	HO of Thr670	2.45	112.5	0.993
4b	−8.36	2.58E-07	SO_2NH	O=C of Asp810	2.35	131.7	4.91
			SO_2NH	O=C of Glu640	2.21	123.8	
			Pyridine-N	HN of Asp810	1.94	171.7	
4c	−8.99	2.58E-07	HNSO2	HN of Lys623	2.247	106.0	3.74
4d	−8.57	5.26E-07	SO_2NH	O=C of His790	1.907	148.3	4.10
4e	−10.81	1.19E-08	Pyrrole-NH	O=C of Cys673	2.17	123.7	3.70
			SO_2NH	O=C of Asp810	1.96	149.6	
			Pyridine-N	HN of Asp810	2.40	110.9	
5a	−8.39	7.05E-07		–	–	–	0.80
5b	−8.16	1.05E-06	SO_2NH	O=C of Glu640	2.33	107.3	4.23
			$HNSO_2$	HN of Asp810	2.08	153.8	
5c	−6.57	1.54E-05	OH	O=C of Asp810 1.91	1.91	134.3	7.24
5d	−7.20	5.32E-06	SO_2NH	O=C of Glu640	2.05	112.6	5.55
			SO_2NH	O=C of Asp810	1.81	123.4	
5e	−8.65	4.57E-07	SO_2NH	O=C of Asp810	1.86	153.1	5.87
6a	−8.07	1.22E-06	$HNSO_2$	HN of Asp810	2.256	108.9	6.82
6b	−7.64	2.51E-06	–	–	–	–	8.27
6c	−7.27	4.72E-06	*o*-aryl-OH	O=C of Asp810	2.06	146.3	7.96
6d	−5.88	4.87E-05					6.59
6e	−8.54	5.53E-07	Pyrrole-NH	O=C of Ile789	1.78	142.6	8.20
STI	−18.43	3.08E-14	N3N	HN of Cys673	1.66	161.0	0.25
			NH(H79)	OF of Thr670	1.86	147.2	
			O(O29)	HN of Asp810	2.01	133.3	

which exhibited one hydrogen bonds with Lys623 and RMSD: 3.74 Å, compound **4e** (ΔG_b: −10.81 kcal/mol) which exhibited three hydrogen bonds with Cys 673 and Asp810, and RMSD: 3.70 Å, and compound **5e** (ΔG_b: −8.65 kcal/mol) which exhibited one hydrogen bond with Asp810 and RMSD: 5.87 Å.

As shown in Fig. 1, the molecular docking study revealed the binding affinities of the synthesized 2-[(2S,3R,4R)1-(1,2,3,4-tetrahydroxy butyl)]-3-[4- [(pyridin-2-ylamino)sulfonyl] phenyl]thiazolidin-4-one (**3a**), N-(*o*-hydroxy-*p*-methoxy phenyl-arylidene)-imino-4-[(pyridin-2-ylamino)sulfonyl]benzenes (**4c**),N-(indol-3-ylarylidene)-imino-4-[(pyridin-2-ylamino)sulfonyl]benzenes (**4e**), and 2-(indol-3-yl)-3-[4-[(pyridin-2-ylamino)-sulfonyl]phenyl]thiazolidin-4-ones (**5e**); into PTK. Where compounds **4c,e** exhibited the highest binding free energies being (ΔG_b: −8.99 and −10.81 kcal/mol, respectively) with 1–3 hydrogen bonds with Lys623, Cys673, and Asp810 mainly via their sulfamoyl moiety. Whereas compound **3a** revealed the poor binding affinity with binding free energy being (ΔG_b: −5.43 kcal/mol) which predict its weak biological antitumor activity (not measured yet), but it may be similar to its analog namely sulfonylphenylthiazolidin-4-one (**3b**) of IC_{50} against HELA cells (Cervix carcinoma) and MCF7 cells (breast carcinoma) being 2.01 and 2.68 μg/ml, respectively.

Fig. 2 illustrates differential binding affinities on docking of compound **3b**; (ΔG_b: −5.90 kcal/mol) which docked shifted from the main binding pocket of PTK in another region of the binding site along with STI-ligand and compound **4a**; exhibited one hydrogen bond, docked in almost superimposed manner with the native ligand STI. This different binding mode of these compounds may explain their good correlation with their antiproliferative activity against HELA cells and MCF7 cells as cited in biology results.

The overall correlation between the growth inhibitory activities (IC_{50}, μg/mL) of the synthesized sulfonylbenzenes, sulfonylphenylthiazolidinones and sulfonyl- phenylbenzo[e] [1,3]thiazinone against tumor cells and the binding affinities predicted by AutoDock was fairly good for some compounds.

Considering the growth inhibition against HELA cells, it was noticed that the correlation between IC_{50} of **2b**, **4a**, **5e** and **6a** and their AutoDock binding free energies revealed a reasonable correlation coefficient (R^2) of 0.652 (not represented). Whereas, the growth inhibition against MCF7 cells revealed an excellent correlation with AutoDock binding free energies for compounds **2b**, **3b**, **4a**, **5e**, and **6a** of correlation coefficient (R^2) value of 0.897 as shown in Fig. 3.

4. Conclusion

In this study, eight novel sulfapyridine-polyhydroxyalkylidene (arylidine)-imino derivatives (Schiff's bases) **2a–c** and **4a–e** were synthesized by reacting the key starting sulfapyridine with different monosacharides and/or aromatic aldehydes. Further condensation of **4a–e** and **2a–c** with thioglycolic acid afforded the corresponding thiazolidin-4-one derivatives **5a–e** and their C-nucleoside analogues **3a–c**, respectively. Additionally, treatment of the hydrazone derivatives **4a–e** with thiosalicylic acid gave the corresponding benzothiazine-4-one derivatives **6a–e**. In vitro growth inhibitory activities of compounds **2b**, **3b**, **4a**, **4e**, **5e**, **6a** against (**HELA**) and (**MCF7**) cell lines revealed significant potential antitumor activity. Best results were gained by compound **4a** since it showed approximately similar potency against HELA and MCF7 (IC_{50}: 1.88 and 0.74 μ/mL, respectively) to that of 5-flurouracil

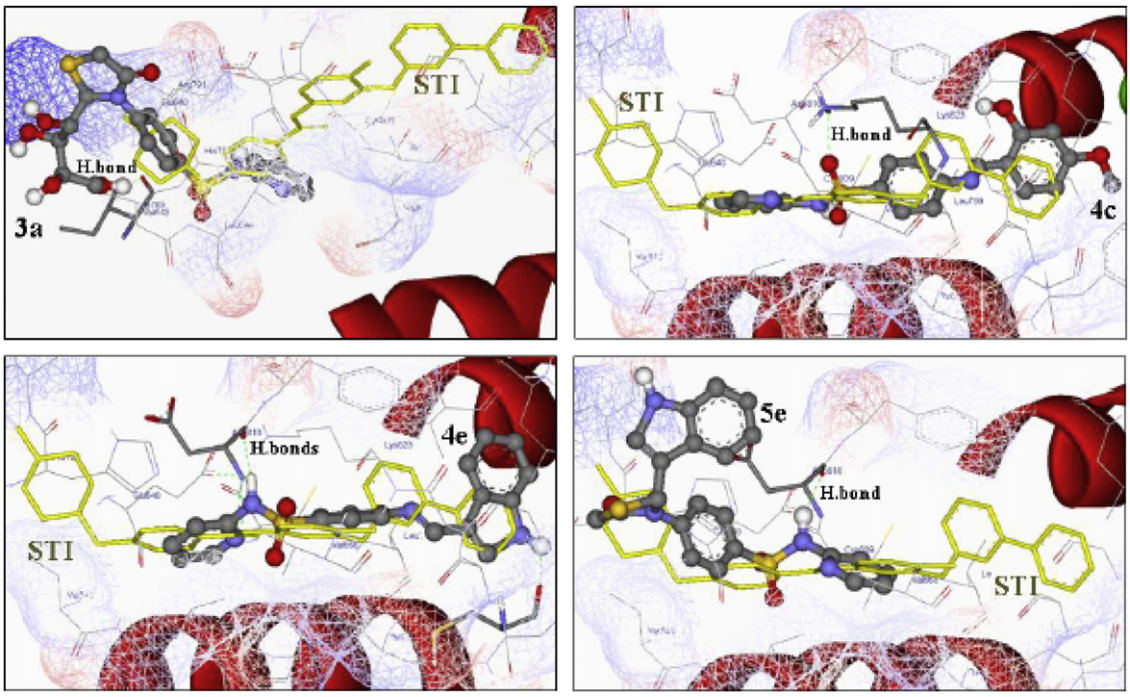


Fig. 1. Comparative binding affinities of compounds (**3a**, **4c**, **4e**, and **5e**; colored by element, ball and stick) into PTK. Where compounds **4c**, **e** exhibited the highest binding energy with 1–3 hydrogen bonds. The binding pocket of PTK is shown in transparent solid surface with labeled amino acids and the STI ligand is shown as yellow line. The settled hydrogen bonds are shown as green dotted lines.

(IC_{50}:1.01 μg/mL and 0.67 μg/mL, respectively). Also its benzothiazine analogue **6a** exhibited significant potency against **HELA** (IC_{50}: 1.48 μg/mL). Fortunately, all of the tested compounds showed higher antitumor activity against both types of carcinoma cell lines (IC_{50}: 0.74–3.56 μg/mL) than that obtained by doxorubicin IC_{50}: 8.72 and 7.71 μg/mL against HELA and MCF7, respectively.

The AutoDock investigation of the synthesized analogs, (**2a–c**), (**3a–c**), (**4a–e**), (**5a–e**) and (**6a–e**) was carried out for molecular modeling study. Thus, they were docked within c-kit protein tyrosine kinase. The overall correlation between the growth inhibitory activities (IC_{50}, μg/mL) of the synthesized compounds against tumor cells and the binding affinities predicted by

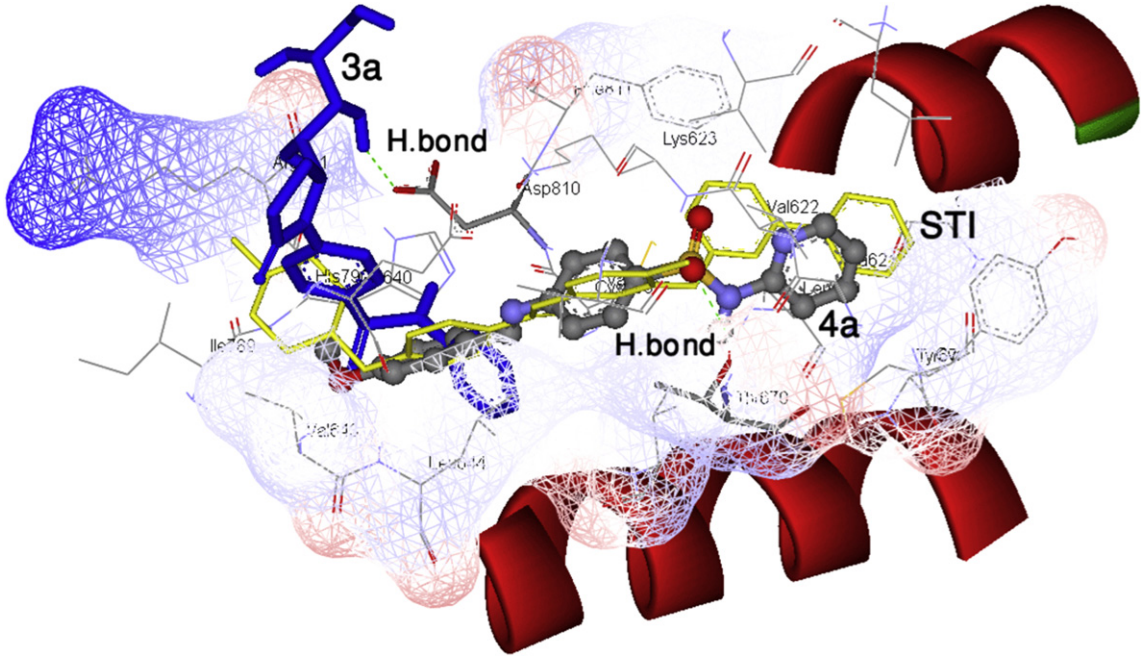


Fig. 2. Differential binding affinities of compounds (**3b**; blue, stick) and (**4a**; ball and stick) into PTK. Where compounds **4a** exhibited the higher binding energy being (ΔG_b: −9.07 kcal/mol). Whereas compound **3b** exhibited (ΔG_b: −5.90 kcal/mol). The binding pocket of PTK is shown in wire mesh view with labeled amino acids and the STI ligand as yellow line. The settled hydrogen bonds are shown as green dotted lines.

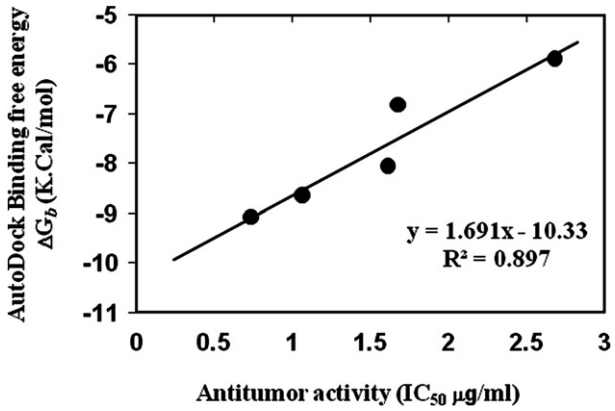


Fig. 3. Correlation between the binding free energy (ΔG_b) and IC_{50} of **2b**, **3b**, **4a**, **5e** and **6a** against MCF7 tumor cell lines.

AutoDock was fairly good for some compounds, namely; **2b**, **4a**, **5e** and **6a** against HELA tumor cell lines, with the correlation coefficient (R^2) of 0.652. While the correlation between IC_{50} of compounds **2b**, **3b**, **4a**, **5e** and **6a** against MCF7 tumor cell lines was excellent correlation being with correlation coefficient (R^2) value of 0.897. These computationally studied compounds may be promising candidates for further investigation.

5. Experimental

5.1. Chemistry

All melting points are uncorrected and were recorded on an open glass capillaries using an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Analytical data were obtained from the Microanalytical Unit, Cairo University, Egypt. IR spectra (KBr discs) were recorded on a Perkin Elmer 1430 spectrophotometer. ^{1}H NMR spectra were measured with Joel 270 MHz in DMSO-d6 and the chemical shifts were recorded in ppm relative to TMS. The mass spectra were recorded on GCMC-QP 1000 EX Shimadzo Gas Chromatography MS spectrometer, Japan E.I.70 ev. Follow-up of the reactions and checking the purity of the compounds were made by TLC on silica gel pre-coated aluminum sheets (Type 60F254, Merck, Darmstadt, Germany) and the spots were detected by exposure to UV lamp at λ_{254} nanometer for few seconds.

5.1.1. *N-[1-(E)-Polyhydroxyalkylidene]-imino-4-[(pyridin-2-ylamino) sulfonyl] benzenes (**2a–c**)*

General procedure: A mixture of sulfapyridine **1** (2.5 g; 10 mmol) dissolved in ethanol (5 mL) and DMF (5 mL) and the respective monosacaride, namely; arabinose, xylose and/ or mannose (D-series) (10 mmol) dissolved in water (1.0 mL) containing few drops of acetic acid, was heated on a water bath at 60 °C for 2 h. The solid that separated after cooling was filtered off, washed with water followed with cold ethanol and dried to give compounds **2a–c**, respectively.

N-[1-(*E*)-1,2,3,4-Tetrahydroxypentylidene]-imino-4-[(pyridin-2-ylamino)sulfonyl] benzenes (2a,b)

5.1.1.1. ***2a*** *(From arabinose).* Yield 80%, mp 156 °C (C_2H_5OH/H_2O). Anal. calcd. for $C_{16}H_{19}N_3O_6S$ (381.42): C, 50.38; H, 5.02; N, 11.01; S, 8.40. Found: C, 50.49; H, 5.30; N, 11.43; S, 8.00. IR (KBr, cm^{-1}): 3435–3210 (broad, OH, NH), 1617 (C═N) and 1336 &1140 (SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.30–3.60 (m, 4H, 5′-H, 5″-H, 4′-H, 5′-OH), 4.25 (m, 1H, 2′H), 4.35–4.65 (m, 3H, 3′-H, 3′-OH, 4′-OH), 4.95 (d, J = 6.4 Hz, 1H, 2′-OH) and 7.10–8.43 (m, 10H, aromatic, 1′H and NH protons). MS, *m*/*z* (%): *M* at 381(5).

5.1.1.2. ***2b*** *(From xylose).* Yield 75%, mp 144 °C (C_2H_5OH/H_2O). Anal. calcd. for $C_{16}H_{19}N_3O_6S$ (381.42): C, 50.38; H, 5.02; N, 11.01; S, 8.40. Found: C, 50.00; H, 4.89; N, 11.50; S, 8.21. IR (KBr, cm^{-1}): 3343–3295 (broad, OH, NH), 1620 (C═N) and 1330 & 1140 (SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.35–3.65 (m, 4H, 5′-H, 5′-H, 4′-H, 5′-OH), 4.2 (m, 1H, 2′-H), 4.35–4.58 (m, 3H, 3′-H, 3′-OH, 4′-OH), 4.97 (d, J = 6.4 Hz, 1H, 2′-OH) and 7.10–8.43 (m, 10H, aromatic, 1′H and NH protons).

N-[1-(*E*)-(1,2,3,4,5-Pentahydroxyhexylidene)]-imino-4-[(pyridin-2-yl amino) sulfonyl]benzenes **2c**

5.1.1.3. ***2c*** *(From mannose).* Yield 70%, mp 150 (C_2H_5OH/H_2O). Anal. calcd. for $C_{17}H_{21}N_3O_7S$ (411.45): C, 49.62; H, 5.14; N, 10.21; S, 7.79. Found: C, 49.33; H, 4.81; N, 10.01; S, 7.52. IR (KBr, cm^{-1}): 34389–3213 (broad, OH, NH), 1619 (C═N) and 1320 & 1140 (SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.24–3.44 (m, 2H, 6′-H, 6″-H), 3.56 (m, 3H, 5′-H, 4′-H, 6′-OH), 4.13 (d, 1H, J = 6.2 Hz, 5′-OH), 4.35 (d, 1H, J = 6.5 Hz, 4′-OH), 4.40 (m, 3H, 2′-H, 3′-H, 3′-OH), 4.73 (d, J = 6.7 Hz, 1H, 2′-OH), and 7.10–8.42 (m, 10H, aromatic, 1′H and NH protons). MS, *m*/*z* (%): (M + 1) at 411 (0.7).

5.1.2. *2-[1-(1,2,3,4-Tetrahydroxybutyl)]-[4-[(pyridin-2-ylamino)sulfonyl]phenyl]thiazo- lidin-4-ones (**3a**, **b**)*

General procedure: A solution of compounds **2a**, **b** (10 mmol) and mercaptoacetic acid (2 mL, 20 mmol) in dioxane (20 mL) was stirred at room temperature for two days. The solvent was evaporated under vacuum and the residue was washed with 4 N Na_2CO_3 solution then with water. The separated solid was filtered off, washed with water till carbonate free then with cold ethanol then ether and dried under vacuum at room temperature to give compounds **3a**, **b**.

5.1.2.1. ***3a*** *(From arabinose).* Yield 75%, mp 180 °C (C_6H_6). Anal. calcd. For $C_{18}H_{21}N_3O_7S_2$ (455.52): C, 47.46; H, 4.64; N, 9.22; S, 14.07. Found: C, 47.12; H, 4.32; N, 9.00; S, 14.00. IR (KBr, cm^{-1}): 3435–3210 (broad, OH, NH), 1705 (C═0) and 1617(C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.38 (s, 2H, CH2, thiazolidinone ring), 3.30–3.60 (m, 4H, 4′-H, 4″-H, 3′-H, 4′-OH), 4.25 (m, 1H, 1′H), 4.35–4.65 (m, 3H, 2′-H, 2′-OH, 3′-OH), 4.95 (d, , J = 6.4 Hz, 1H, 1′-OH), 5.91 (s, 1H, CH, thiazolidinone ring) and 7.09–8.43 (m, 8H, aromatic and NH protons). MS, *m*/*z* (%): (M + 1) at 456 (10).

5.1.2.2. ***3b*** *(From xylose).* Yield %70, mp 148 °C (C_6H_6). Anal. calcd. For $C_{18}H_{21}N_3O_7S_2$ (455.52): C, 47.46.00; H, 4.64; N, 9.22; S, 14.07. Found: C, 47.23; H, 4.43; N, 8.89; S, 14.34. IR (KBr, cm^{-1}): 3435–3210 (broad, OH and NH), 1705 (C═O) and 1617 (C═N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.30–3.61 (m, 4H, 3′-H, 4′-H, 4″-H, 4′-OH), 3.38 (s, 2H, CH_2, thiazolidinone ring), 4.25 (m, 1H, 1′H), 4.35–4.65 (m, 3H, 2′-H, 2′-OH, 3′-OH), 4.95 (d, J = 6.4 Hz, 1H, 1′-OH), 5.95 (s, 1H, CH, thiazolidinone ring) and 7.10–8.50 (m, 9H, aromatic and NH protons). MS, *m*/*z* (%): *M* at 455 (10).

*5.1.2.3. 2-[1-(1,2,3,4-Pentahydroxypentyl)]-[4-[(pyridin-2-ylamino)-sulfonyl]phenyl] thiazolidin-4-one (**3c**).* A solution of compound **2c** (2 g; 0.01 mol) and mercaptoacetic acid (2 mL; 0.02 mol) in dioxane (20 mL) was stirred at room temperature for two days. The solvent was evaporated under vacuum and the residue was washed with 4 N Na_2CO_3 solution, then with water. The separated solid was filtered off, washed with water till carbonate free, then with cold ethanol followed by ether and dried under vacuum at room temperature to give the compound **3c**.

5.1.2.3.1. ***3c*** *(From mannose).* Yield %75, mp 260 °C (C_6H_6). Anal. calcd. For $C_{19}H_{23}N_3O_8S_2$ (485.54): C, 47.00; H, 4.77; N, 8.65; S, 13.20. Found: C, 47.40; H, 4.79; N, 8.32; S, 13.00. IR (KBr, cm^{-1}): 3332 (OH), 3221 (NH), 1699 (C=O) and 1620 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 3.25–3.45 (m, 4H, 5′-H, 5″-H, 4′-H, 3′-H), 3.37 (s, 2H, CH2, thiazolidinone ring), 3.75 (t, 1H, 5′-OH), 4.25 (m, 2H, 4′-OH, 3′-OH), 4.50 (m, 3H, 1-H, 2′-H, 2′-OH), 4.73 (d, $J = 6.7$ Hz, 1H, 1′- OH), 5.9 (s, 1H, CH, thiazolidine ring) and 7.11–8.51(m, 8H, aromatic and NH protons).

*5.1.3. N-(Substituted arylidene)-imino-4-[(pyridin-2-ylamino)sulfonyl benzenes (**4a–e**)*

General procedure: A mixture of the aromatic aldehydes, namely; *p*-anisaldehyde, 3,4-dimethoxybenzaldehyde, 2-hydroxy-4-methoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde and/ or indole-3-carboxaldehyde (10 mmol) and sulfapyridine (2.5 g; 10 mmol) in ethanol (30 mL) containing few drops of glacial acetic acid was refluxed for 3 h. Then the hot mixture was filtered off. After cooling the filtrate was diluted with 50 mL of water and the resulting precipitate was filtered off and recrystallized from the appropriate solvent to give **4a–c**, respectively.

*5.1.3.1. N-(p-Methoxyphenylidene)-imino-4-[(pyridin-2-ylamino) sulfonyl] benzene (**4a**).* Yield 75%, mp 160 °C (CH_3COOH). Anal. calcd. for $C_{19}H_{17}N_3O_3S$ (367.43): C, 62.10; H, 4.66; N, 11.43; S, 8.72. Found: C, 62.22; H, 4.32; N, 11.75; S, 8.42. IR (KBr, cm^{-1}): 3220 (NH), 1627 (C=N), 1520 (C=N, pyridine) and 1330 & 1153 (SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.90 (s, 3H, OCH_3), 6.97–8.44 (m, 12H, aromatic and 1H (N=CH) protons) and 11.72 (S, 1H, NH, exchangeable with D_2O).

*5.1.3.2. N-(3,4-Dimethoxyphenylidene)-imino-4-[(pyridin-2-ylamino) sulfonyl] benzene (**4b**).* Yield 70%, mp 172 °C (CH_3COOH). Anal. calcd. For $C_{20}H_{19}N_3O_4S$ (397.46): C, 60.43; H, 4.81; N, 10.57; S, 8.06. Found: C, 60.10; H, 5.00; N, 10.72; S, 7.98. IR (KBr, cm^{-1}): 3220 (NH), 1628 (C=N), 1520 (C=N, pyridine) and 1333 & 1154 (SO_2). ^{1}H NMR (DMSO-δ ppm): 3.98 (s, 6H, 2(OCH_3)), 6.95–8.50 (m, 11H, aromatic and 1H (N=CH)) and 11.50 (s, 1H, NH, exchangeable with D_2O). MS, *m*/*z* (%): M at 379 (5).

*5.1.3.3. N-(2-Hydroxyl-4-methoxyphenylidene)-imino-4-[(pyridin-2-ylamino)sulfonyl] benzene (**4c**).* Yield 70%, mp 199 °C ($CH_3CH(OH)CH_3$/ pet. ether). Anal. calcd. for $C_{19}H_{17}N_3O_4S$, (383.43): C, 59.51; H, 4.46; N, 10.95; S, 8.36. Found: C, 59.65; H, 4.21; N, 10.75; S, 8.64. IR (KBr, cm^{-1}): 3435 (OH), 3210 (NH), 1617 (C=N), 1524 (C=N, pyridine) and 1335 & 1151 (SO_2). ^{1}H NMR (DMSO-d_6, δppm): 3.80 (s, 3H, OCH_3), 6.90–8.61 (m, 11H, aromatic and 1H (N=CH)), 11.70 (s, 1H, NH, exchangeable with D_2O) and 12.52 (s, 1H, OH, exchangeable with D_2O).

*5.1.3.4. N-(3,4,5-Trimethoxyphenylidene)-imino-4-[(pyridin-2-ylamino) sulfonyl]benzene (**4d**).* Yield 75%, mp 283.3 °C (CH3CH(OH)CH3/ pet. ether). Anal. calcd. for $C_{21}H_{21}N_3O_5S$, (427.49): C, 59.00; H, 4.95; N, 9.82; S, 7.50. Found: C, 59.32; H, 5.22; N, 9.52; S, 7.21. IR (KBr, cm^{-1}): 3212 (NH), 1620 (C=N), 1526 (C=N, pyridine) and 1335 & 1152(SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.85 (s, 9H, 3(OCH_3)), 7.10–8.57 (m, 10H, aromatic and 1H (N=CH) protons) and 11.8 (s, 1H, NH, exchangeable with D_2O).

*5.1.3.5. N-(3-Indolmethylidene)-imino-4-[(pyridin-2-ylamino)-sulfonyl] benzene (**4e**).* Yield 70%, mp 199 °C ($CH_3CH(OH)CH_3$/ pet. ether). Anal. calcd. for $C_{20}H_{16}N_4O_2S$ (376.45): C, 63.81, H; 4.28; N, 14.88; S, 8.51. Found: C, 63.52; H, 4.35; N, 14.54; S, 8.21. IR (KBr, cm^{-1}): 3212, 3190 (NH), 1620 (C=N), 1520 (C=N, pyridine) and 1335 & 1150 (SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 7.12–8.5 (m, 13H, aromatic and 1H (N=CH)) and 6.3,11.8 (2*s*,2H, 2NH, exchangeable with D_2O). MS, *m*/*z* (%): *M* at 376 (5).

*5.1.4. 2-Substituted aryl-3-[4-[(pyridin-2-ylamino)sulfonyl]phenyl] thiazolidin-4-ones (**5a–e**)*

General procedure: The foregoing method is the same as described for the preparation of C- nucleosides **3a–c**, using the Schiff's bases **4a–e** instead of **2a–c** derivatives.

*5.1.4.1. 2-(p-Methoxyphenyl)-3-[4-[(pryridin-2-ylamino)sulfonyl] phenyl]-thiazolidin-4-one (**5a**).* Yield 75%, mp 120 °C (C_2H_5OH). Anal. calcd. For $C_{21}H_{19}N_3O_4S_2$ (441.53): C, 57.12; H, 4.33; N, 9.51; S, 14.52. Found: C, 57.32; H, 4.01; N, 9.21; S, 14.23. IR (KBr, cm^{-1}): 3100 (NH), 1710 (C=O), 1620 (C=N) and 1322,1150(N–SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.32 (s, 2H, CH2, thizolidine), 3.95 (s, 3H, OCH3), 4.40 (s, 1H, CH, thiazolidine), 7.30–7.80 (m, 12H, aromatic) and 10.01 (s, 1H, NH, exchangeable with D2O). MS, *m*/*z* (%): *M* at 441(5).

*5.1.4.2. 2-(3,4-Dimethoxyphenyl)-3-[4-[(pyridin-2-ylamino)sulfonyl]-phenyl] thiazolidin-4-one (**5b**).* Yield 75%, mp 107 °C (C_2H_5OH). Anal. calcd. For $C_{22}H_{21}N_3O_5S_2$ (471.56): C, 56.03; H, 4.48; N, 8.91; S, 13.59. Found: C, 56.21; H, 4.51; N, 8.72; S, 13.32. IR (KBr, cm^{-1}): 3122 (NH), 1700 (C=O), 1620 (C=N) and 1322, 1153 (N–SO_2). MS, *m*/*z* (%): (M + 1) at 472 (1.5).

*5.1.4.3. 2-(2-Hydroxy-4-methoxyphenyl)-3-[4-(pyridin-2-ylamino)-sulfonyl] phenyl]thiazolidin-4-one (**5c**).* Yield 70%, mp 170 °C (CH_3OH). Anal. calcd. For $C_{21}H_{19}N_3O_5S_2$ (457.53): C, 55.12; H ,4.18; N, 9.18; S, 14.01. Found: C, 55.00; H, 4.00; N, 9.11; S, 14.32. ^{1}H NMR (DMSO-d_6, δ ppm): 3.35 (s, 2H, CH_2, thiazolidine), 3.90 (s, 3H, OCH3), 4.42 (s, 1H, CH, thiazolidine), 7.51–8.00 (m, 11H, aromatic) and 10.11 & 10.50 (2s, 2H, NH and OH, exchangeable with D_2O).

*5.1.4.4. 2-(3,4,5-Trimethoxyphenyl)-3-[4-(pyridin-2-ylamino)sulfonyl] phenyl]thiazolidin- 4-one (**5d**).* Yield 70%, mp 155 °C (C_2H_5OH). Anal. calcd. for $C_{23}H_{23}N_3O_6S_2$ (501.58): C, 55.07; H, 4.62; N, 8.37; S, 12.78. Found: C, 54.89; H, 4.43; N, 8.12; S, 12.42. IR (KBr, cm^{-1}): 3150 (NH), 1700 (C=O), 1625 (C=N) and 1320, 1153 (N–SO_2). ^{1}H NMR (DMSO-d_6, δppm): 3.32 (s, 2H, CH_2, thiazolidine), 3.85 (s, 9H, 3(OCH_3)), 4.42 (s, 1H, CH_2, thiazolidine), 7.22–8.53 (m, 10H, aromatic) and 10.02 (s, 1H, NH, exchangeable with D_2O).

*5.1.4.5. 2-(3-Indolyl)-3-[4-(pyridin-2-ylamino)sulfonyl]phenyl]thiazolidin-4-one (**5e**).* Yield 65%, mp 180 °C (C_2H_5OH). Anal. calcd. for $C_{22}H_{18}N_4O_3S_2$ (450.54): C, 58.64; H, 4.02; N, 12.43; S, 14.23. Found: C, 58.71; H, 4.21; N, 12.19; S, 14.43. IR (KBr, cm^{-1}): 3211, 3123 (2NH), 1698 (C=O), 1620(C=N) and 1325, 1151 (N–SO_2). MS, *m*/*z* (%): *M* at 450 (10).

*5.1.5. 2-(Substituted aryl)-3-[4-[(pyridin-2-ylamino)sulfonyl]-phenyl]-2,4-dihydrobenzo[e][1,3]thiazin-4-ones (**6a–e**)*

General procedure: The foregoing method for the preparation of the arylthiazolidinones **5a–e** was applied to prepare the benzothiazines **6a–e** except that thiosalicylic acid was used instead of thioglycolic acid.

*5.1.5.1. 2-(p-Methoxyphenyl)-3-[4-[(pyridin-2-ylamino)sulfonyl]-phenyl]-2,4dihydrobenzo [e][1,3]thiazin-4-one (**6a**).* Yield 72%, mp 283 °C (C2H5OH). Anal. calcd. for $C_{26}H_{21}N_3O_4S_2$ (503.61): C, 62.01; H, 4.20; N, 8.34; S, 12.73. Found: C, 62.17; H, 4.28; N, 8.05; S, 12.41. IR (KBr, cm^{-1}): 3394 (NH), 1675 (C=O), 1626 (C=N), 1529 (C=C) and 1322, 1157 (N–SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.51 (s, 1H, CH, benzothiazine), 3.85 (s, 3H, OCH_3), 7.3–8.3 (m, 16H, aromatic) and 10.11 (s, 1H, NH, exchangeable with D_2O).

*5.1.5.2. 2-(3,4-Dimethoxyphenyl)-3-[4-[(pyridin-2-ylamino)sulfonyl]phenyl]-2,4-dihydro- benzo[e][1,3]thiazin-4-one (**6b**).* Yield 70%, mp 295 °C (C_2H_5OH). Anal. calcd. for $C_{27}H_{23}N_3O_5S_2$ (533.63): C, 60.77; H, 4.34; N, 7.87; S, 12.01.Found: C, 60.59; H, 4.52; N, 7.65; S, 12.31. IR (KBr, cm^{-1}): 3325 (NH), 1670 (C═O), 1620 (C═N), 1529 (C═C) and 1359, 1153 (N–SO_2). MS, *m*/*z* (%): *M* at 533 (4.2).

*5.1.5.3. 2-(2-Hydroxy-4-methoxyphenyl)-3-[4-[(pyridin-2-ylamino) sulfonyl] phenyl]-2,4-dihydrobenzo[e][1,3]thiazin-4-one (**6c**).* Yield 75%, mp 300 °C (CH_3OH). Anal. calcd. for $C_{26}H_{21}N_3O_5S_2$ (519.61): C, 60.10; H, 4.07; N, 8.08; S, 12.34. Found: C, 59.85; H, 4.21; N, 7.92; S, 12.00. IR (KBr, cm1): 3415, 3233 (OH, NH), 1668 (C═O), 1620 (C═N), 1529 (C═C) and 1359, 1151 (N–SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.62 (s, 1H, CH, benzothiazine), 3.95 (s, 3H, OCH_3), 7.3–8.5 (m, 15H, aromatic) and 10.2 & 12.01 (2s,2H, NH and OH, exchangeable with D_2O).

*5.1.5.4. 2-(3,4,5-Trimethoxyphenyl)-3-[4-[(pyridin-2-ylamino)sulfonyl]phenyl]-2,4-dihyd- robenzo[e][1,3]thiazin-4-one (**6d**).* Yield 72%, mp > 300 °C (C_2H_5OH). Anal. calcd. for $C_{28}H_{25}N_3O_6S_2$ (563.66): C, 59.66; H, 4.47; N, 7.45; S, 11.37. Found: C, 59.42; H, 4.41; N, 7.22; S, 11.00. IR (KBr, cm^{-1}): 3313 (NH), 1675 (C═O), 1623 (C═N) and 1350, 1150 (N–SO_2). MS, *m*/*z* (%): M at 563 (5).

*5.1.5.5. 2-(3-Indolyl)-3-[4-[(pyridin-2-ylamino)sulfonyl]phenyl]-2,4-dihydrobenzo[e] [1,3 thiazin-4-one (**6e**).* Yield 70%, mp 299 °C (C_2H_5OH). Anal. calcd. for $C_{27}H_{20}N_4O_3S_2$ (512.62): C, 63.26; H, 3.93, N, 10.93; S, 12.51. Found: C, 63.49; H, 4.20; N, 10.65; S, 12.31. IR (KBr, cm^{-1}): 3320, 3211 (2NH), 1670 (C═O), 1620 (C═N) and 1359, 1151 (N–SO_2). ^{1}H NMR (DMSO-d_6, δ ppm): 3.56 (s, 1H, CH, benzothiazine), 7.5–8.4 (m, 17H, aromatic) and 10.82 & 11.10 (2s, 2H, 2NH). MS, *m*/*z* (%): *M* at 512 (6).

5.2. Biological screening

Preliminary experiments were done using the human cervix carcinoma cell tumor lines and breast carcinoma cell lines to identify the potential toxicity of six selected newly synthesized compounds (**2b**, **3b**, **4a**, **4e**, **5e** and **6a**) in comparison to the known anticancer drugs 5-Flurouracil and Doxorubicin by SRB using the method Skehan et al. (1990) [17] as follows: Cells were plated in 96-multiwell plate (104 cells/ well) for 24 h before treatment with compounds to allow attachment of cell to the wall of the plate. Different concentration of the compound under test (0.0, 1, 2.5, 5 and 10 g/ml) were added to the cell monolayer triplicate wells which were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained with Sulfo-Rhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line after the specified compound.

5.3. Molecular docking study

The advanced docking program AutoDock 3.0.5. [15] was used to evaluate the binding free energy of the inhibitors within the macromolecules. AutoDock performs the task of the docking. First, the ligand moves randomly in any one of six degrees of freedom, namely; 3 translation degrees and 3 rotation degrees, and the energy of the new ligand "state" is state, the new one is automatically accepted as the next step in docking.

5.3.1. Preparation of ligands and target protein tyrosine kinase

The compounds involved in this study as ligands include (**2a–c**), (**3a–c**), (**4a–e**), (**5a–e**) and (**6a–e**) were studied for their binding activities into PTK. The three dimensional structures of the aforementioned compounds were constructed using Chem3D ultra 8.0 software [Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2003)], then they were energetically minimized by using MOPAC with 100 iterations and minimum RMS gradient of 0.10. The crystal structure of c-Kit receptor protein-tyrosine kinase in complex with STI-571 (Imatinib or Gleevec) was extracted from the RCSB Protein Data Bank http://www.rcsb.org/pdb/Welcome.do. All bound waters, ligand were removed from the protein. For the target, the amino acids of the ligand binding site were defined using data in pdbsum http://www.ebi.ac.uk/thorntonsrv/databases/pdbsum/.

5.3.2. Grid generation and run of molecular docking

The grid maps representing the native ligand in the actual docking target site were calculated with AutoGrid. The grids were chosen to be sufficiently large to include not only the active site but also significant portions of the surrounding surface. The three dimensional grids, 60 Å grid size (*x*, *y*, *z*) with a spacing of 0.375 Å, were created. The cubic grid box was centered in the catalytic active region and encompassed the binding site where the ligands were embedded. Then automated docking studies were carried out using AutoDock version 3.0.5. [15] of the three different search algorithms offered by AutoDock, the GA-LS search algorithm (Genetic algorithm with local search) was chosen to search for the best conformers. The parameters were set using the software ADT (Autodock Tool Kit) on PC which is associated with Autodock 3.0.5. For all docking parameters, default values were used with 10 independent docking runs for each docking case.

5.3.3. Molecular modeling and analysis of the docked results

There are two kinds of free energies output by Autodock. One is the binding free energy that includes the intermolecular energy and torsional free energy, and the other the docking energy [15]. We used only the binding free energy of the first type as the criterion for ranking. Cluster analysis was performed on the docked results using a root mean square (RMS) tolerance of 0.5. Each of the clusters that exhibited significant negative interaction energies was examined by Accelrys, DS Visualizer v2.0. [Accelrys Inc., San Diego, CA (2007)] to determine their binding orientations, molecular modeling, evaluation of the hydrogen bonds and for measuring RMSD, which was measured as distance between the centroids of the docked inhibitor and the native ligand. The mode of interaction of the native ligand within PTK was used as a standard docked model as well as for RMSD calculation. The correct hydrogen bond interaction was considered according to Taylor et al., [18] who showed that C–H···O in crystals contacts occur within certain distance (3.0–4.0 Å) and angle (C–H···O, 90–180°) ranges. However, the more linear hydrogen bond is likely to be stronger [19]. Moreover, there is general agreement that for carbonyl acceptors, the H···O═C angle is distributed around 120°. Therefore, in our modeling results we consider the hydrogen bond angle $\geq$100° to be of a reasonable strength.

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