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New Imidazothiazine-containing Scaffolds as Promising Anticancer Agents: Design, Synthesis, and Antiproliferative Estimation

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Abstract: One of the main reasons of death worldwide is cancer. There is a growing interest in the study of imidazolidinone derivatives where their synthesis and characteristics have been thoroughly discussed as appropriate precursors in pharmaceutical industry. Employing some drug design approaches such as divergence of substituents and hybridization of pharmacophores, a new set of imidazothiazines **5a-d** have been designed and constructed. The structure of the prepared hybrids was asserted through spectral data. All synthesized conjugates were assayed for their seven dose anticancer assay against three carcinomas namely hepatic HepG2, mammary gland MCF-7, and prostate PC-3 carcinomas. The tested entities exerted promising anticancer activity toward the chosen carcinomas. Noticeably, compounds bearing 4-methoxy **5a** or 4-hydroxy **5b** groups with positive mesomeric action at phenyl ring on C-5 of imidazothiazine scaffold showed a more potent anticancer effect than compounds containing chloro group with a negative inductive effect **5c** and **5d**. Besides, the presence of carbonitrile functionality at C-6 of imidazothiazine ring as in **5c** has a positive impact on the anticancer activity compared with the carboxamide moiety in **5d**.

Keywords: Anticancer; Imidazole; Imidazothiazine; Synthesis; Thiazine.

1. INTRODUCTION

One of the main reasons of death worldwide is cancer that is predicted to cause about 10 million deaths globally by the year 2050 [1,2]. There is a growing interest in the study of 2-thiohydantoin derivatives where their synthesis and characteristics have been thoroughly discussed as appropriate precursors in pharmaceutical industry [3,4]. A lot of hydantoin and thiohydantoin hybrids have been synthesized and illustrated promising biological activities including anticancer [5,6], hypolipidemic [7], anticonvulsant [8], antiviral [9], antibacterial [10], fungicidal [11] and antileishmanial effect [12]. Some imidazole-bearing anticancer drugs have been approved by FDA and become usable drugs in the market such as Nazartinib. Nazartinib is one of the most effective antitumor medications in the third generation of EGFR suppressors [13]. Besides, Enzulutamide is thiohydantoin-containing drug that has been confirmed *via* FDA in the management of prostate cancer (**Figure 1**) [14].

Entity **I** has exhibited a significant anticancer effect toward MCF-7 and HepG2 tumor cells with very low IC_{50} [15]. Also, imidazole bearing derivative **II** has exerted powerful antiproliferative action against three mammary gland carcinomas, MCF-7, MDA-MB-231, and T47D as well as colon HT-29 and lung A549 cells [16]. It has been reported that 1,3-disubstitutedphenyl-2-thiohdantoin **III** displayed potent cytotoxicity and selectivity toward HepG2, HCT116, and MCF-7 carcinomas with IC_{50} at the micromolar level (**Figure 2**) [17].

Furthermore, thiazine moiety is nitrogen containing heterocyclic pharmacophore incorporated in some antitumor drugs. Benzylidene thiazinediones **IV** showed an eclectic anticancer effect toward leukemia cell lines [18]. Meanwhile, imidazole thiazine hybrid **V** has been discussed to present considerable cytotoxic action against colon HCT-116 with IC_{50} of 3.6 µM [19]. Bis-1,3-thiazine analog **VI** has displayed significant anticancer impact toward hepatocellular HepG2 and breast MCF-7 cells with IC_{50} of 4.5 and

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3.8 µM, respectively showing non-remarkable cytotoxicity against normal cells (**Figure 3**) [20].

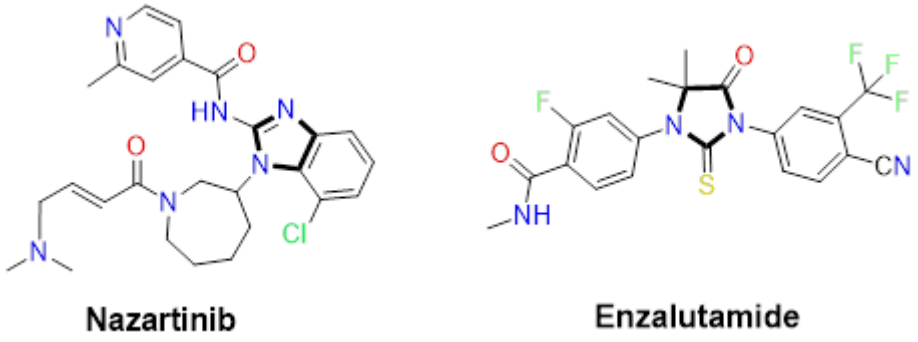


Figure 1. FDA approved imidazole-containing drugs.

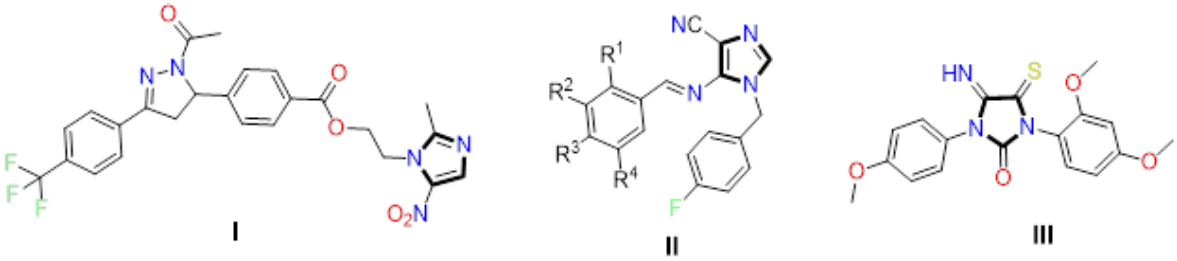


Figure 2. Imidazole-bearing anticancer agents.

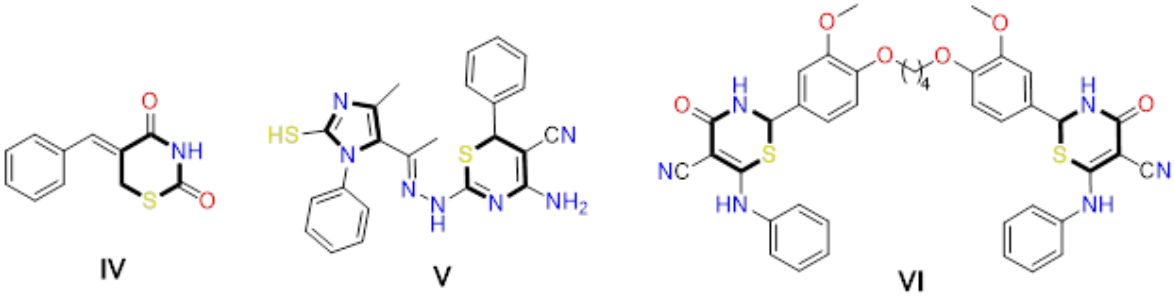


Figure 3. Thiazine-containing anticancer agents.

Hybridization of two or more pharmacophores in a single novel candidate is an effective approach in drug discovery [21–25]. The attained hybrids are proposed to display enhanced biological activity and selectivity toward the active sites. Herein, in keeping with our current research on the synthesis of novel potential antitumor drugs [26–28], we aimed to synthesize a novel set of imidazothiazine-bearing compounds as promising anticancer drugs. All novel hybrids were investigated by MTT assay for their antiproliferative effect against hepatic HepG2, mammary gland MCF-7, as well as prostate PC-3 tumors.

2. METHODS

2.1. Chemistry

All data specifications of devices utilized in the characterization of novel prepared analogs were attached in the supplementary material. The reagents **4a-d** were constructed following the recorded methods [29,30].

2.1.1. Overall proceedings of the preparation of 7-amino-5-(4-substitutedphenyl)-3-oxo-2-(arylidene/heteroarylidene)-2,3-dihydro-5H-imidazo[2,1-b][1,3]thiazine-6-carbonitrile/ carboxamide derivatives 5a–d.

An equimolar mixture of **3a** or **3b** (0.002 mol) and suitable arylidenes of either malononitrilecarbonit or cyanoacetamide **4a-d** (0.002 mol) were refluxed in 30 mL ethanol together with triethylamine (3 drops) for 7-12 hours. Cooling the solution helps the products of imidazo[2,1-*b*][1,3]thiazines **5a-d** to precipitate where they were recrystallized from methanol. All characterization data of novel entities are presented in **Table 1**.

2.2. Anticancer evaluation

The examined carcinomas comprising hepatic HepG2, mammary gland MCF-7 as well as prostate PC-3 were purchased from the ATCC, USA. The antitumor estimation of constructed conjugates was performed at concentrations 100, 50, 25, 12.5, 6.25, 3.125, and 1.56 µM utilizing MTT assay where Doxorubicin was employed as a standard based on the recorded approach [31].

Table 1. The physical properties and characterization data of the prepared entities.

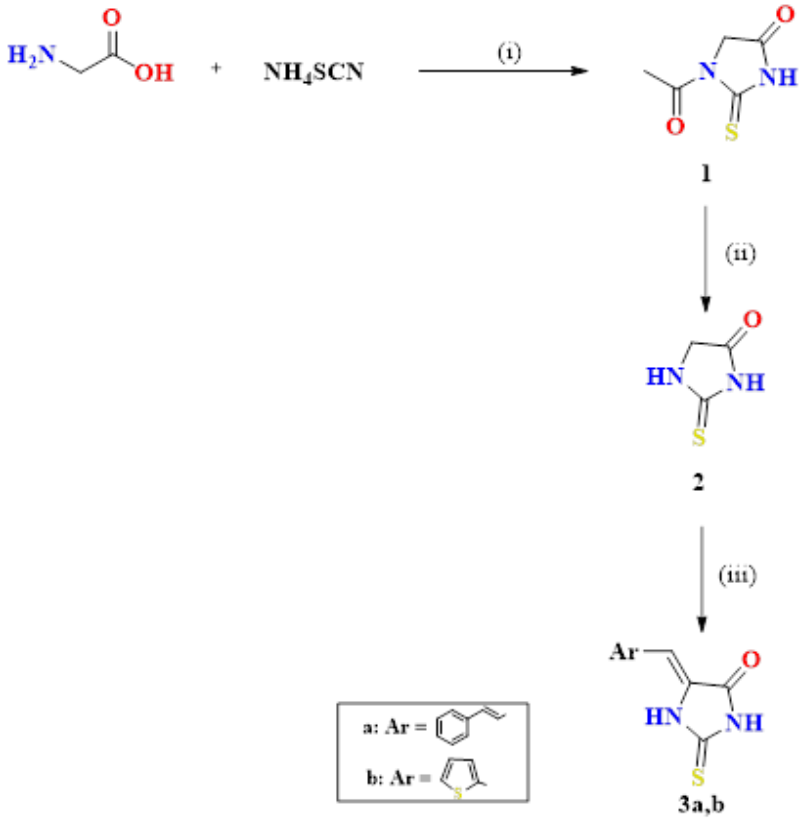
Item / compound number	**5a**	**5b**	**5c**	**5d**
Name	*7-Amino-5-(4-methoxyphenyl)-3-oxo-2-(3-phenylallylidene)-2,3-dihydro-5H-imidazo[2,1-b][1,3]thiazine-6-carbonitrile*	*7-Amino-5-(4-hydroxyphenyl)-3-oxo-2-(thiophen-2-ylmethylene)-2,3-dihydro-5H-imidazo[2,1-b][1,3]thiazine-6-carbonitrile*	*7-Amino-5-(4-chlorophenyl)-3-oxo-2-(thiophen-2-ylmethylene)-2,3-dihydro-5H-imidazo[2,1-b][1,3]thiazine-6-carbonitrile*	*7-Amino-5-(4-chlorophenyl)-3-oxo-2-(thiophen-2-ylmethylene)-2,3-dihydro-5H-imidazo[2,1-b][1,3]thiazine-6-carboxamide*
Yield	70 %	80 %	75 %	78 %
Melting point	190-192 °C	140-142 °C	200-202 °C	183-185 °C
IR (KBr, cm^{-1})	3295, 3183 (NH_2), 3090 (CH-arom.); 2941 (CH-aliph.); 2222 (CN); 1712 (C=O); 1620 (C=N); 1594 (C=C)	3478 (OH); 3300, 3194 (NH_2), 3020 (CH-arom.); 2944 (CH-aliph.); 2230 (CN); 1716 (C=O); 1640 (C=N); 1570 (C=C)	3294, 3188 (NH_2), 3015 (CH-arom.); 2916 (CH-aliph.); 2218 (CN); 1709 (C=O); 1618 (C=N); 1604 (C=C)	3206, 3191 (NH_2), 3005 (CH-arom.); 2900 (CH-aliph.); 2209 (CN); 1702, 1665 (2C=O); 1622 (C=N) 1614 (C=C)
^{1}H NMR (400M Hz, DMSO-d_6, δ ppm)	3.56 (s, 3H, OCH_3); 4.35 (s, 1H, imidazothiazine-C_5-H); 6.38 (d, 1H, *J*= 15.6 Hz, C_6H_5-CH=CH-CH=); 6.44 (d, 1H, *J*= 15.6 Hz, C_6H_5-CH=CH-CH=); 7.08 (t, 1H, *J*= 15.6 Hz, C_6H_5-CH=CH-CH=); 7.35 (t, 1H, *J* =7.2 Hz, C_6H_5-C_4-H); 7.36-7.48 (m, 4H, C_6H_5-$C_{2,3,5,6}$-H); 7.51 (d, 2H, *J*= 7 Hz, 4-OCH_3-C_6H_4-$C_{3,5}$-H); 7.57 (d, 2H, *J*= 7 Hz, 4-OCH_3-C_6H_4-$C_{2,6}$-H); 12.33 (s, 2H, NH_2, interchangeable with D_2O)	5.25 (s, 1H, imidazothiazine-C_5-H); 6.63-7.87 (m, 7H, Ar-H); 9.44 (s, 1H, OH, interchangeable with D_2O); 12.26 (s, 2H, NH_2, interchangeable with D_2O)	4.30 (s, 1H, imidazothiazine-C_5-H); 6.63 (s, 1H, =CH); 6.86-7.87 (m, 7H, Ar-H); 11.99 (s, 2H, NH_2, interchangeable with D_2O)	5.34 (s, 1H, imidazothiazine-C_5-H); 6.63 (s, 1H, =CH); 6.86-7.87 (m, 7H, Ar-H); 11.98 (s, 2H, NH_2, interchangeable with D_2O). 12.26 (s, 2H, $CONH_2$, interchangeable with D_2O)
MS (*m/z* %)	414 (M^+, 15.58)	380 (M^+, 28.39)	401 (M+2, 6.20); 399 (M^+, 20.16)	418 (M+2, 9.10); 416 (M^+, 32.80)
Elemental analyses	Analysis % for $C_{23}H_{18}N_4O_2S$ (414.48). **Calcd.** (%): C, 66.65; H, 4.38; N, 13.52; S, 7.73. **Found** (%): C, 66.69; H, 4.35; N, 13.50; S, 7.76	Analysis % for $C_{18}H_{12}N_4O_2S_2$ (380.44). **Calcd.** (%): C, 56.83; H, 3.18; N, 14.73; S, 16.85. **Found** (%):C, 56.78; H, 3.11; N, 14.70; S, 16.87	Analysis % for $C_{18}H_{11}ClN_4OS_2$ (398.88). **Calcd.** (%): C, 54.20; H, 2.78; N, 14.05; S, 16.07. **Found** (%): C, 54.24; H, 2.81; N, 14.02; S, 16.05	Analysis % for $C_{18}H_{13}ClN_4O_2S_2$ (416.90). **Calcd.** (%): C, 51.86; H, 3.14; N, 13.44; S, 15.38. **Found** (%): C, 51.89; H, 3.17; N, 13.41; S, 15.40

3. RESULTS & DISCUSSION

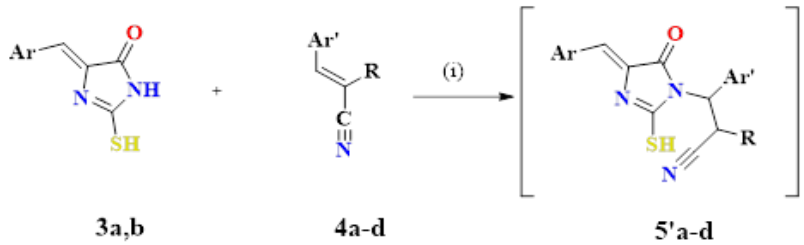
3.1. Chemistry

Glycine and ammonium thiocyanate were reacted in acetic anhydride to produce 1-acetyl-2-thioxoimidazolidin-4-one (**1**), which was then hydrolyzed in 10% HCl to provide 2-thioxoimidazolidin-4-one (**2**) [32,33]. Applying Knoevenagel condensation with appropriate aromatic or heterocyclic aldehydes to entity **2**, the starting analogs **3a–b** were created employing the previously described techniques [34,35] (**Scheme I**).

About the crucial part that arylidenes of malononitrile \ cyanoacetamide play in the synthesis of many beneficial and potent medicinal ingredients [36–40], it was significant to employ such chemical reagents in the preparation of imidazothiazine containing scaffold. The construction of imidazothiazines were discuused to be carried out *via* the reaction of 2-mercaptoimidazole with arylidenes of activated nitriles in basic media [41,42]. However, the proposed imidazothiazines may not be attained in some cases where the open chain imidazolylimidothioates were formed [43]. Hence, compounds **5a-d** were synthesized from the cyclization of the starting analogs **3a,b** with arylidene of malononitrile / cyanoacetamide **4a-d** in basic medium (trimethylamine) **(Scheme 2)**. The dinucleophilic cycloaddition of 2-thiohydantoins **3a,b** with arylidenes of malononitrile \ cyanoacetamide **4a-d** have been accomplished through Michael nucleophilic addition of secondary amino function of **3a,b** on the olefinic bond of the arylidenes **4a-d** to furnish the non-isolable intermediate **5'a-d**. The nucleophilic addition of thiol group on the cyano moiety with concomitant aromatization yielded the targeted imidazothiazines **5a-d** (**Chart 1**). Relying on spectral data, the structural criteria of the novel entities **5a-d** were emphasized. IR spectra of **5a-d** presented absorptions at 3300-3183 cm^{-1} corresponding to amino group and bands at 2230-2209 cm^{-1} assigned for nitrile functionality in entities **5a-c**. Besides, **5d** showed broad band at 3478 cm^{-1} assigned for hydroxyl functionality. ^1H NMR spectra of **5a-d** illustrated a singlet at δ 4.30-5.34 ppm due to imidazothiazine C_5 protons as well as D_2O interchangeable singlet at δ 11.98-12.33 ppm attributed to primary amino protons. Additionally, there are two D_2O exchangeable singlets at δ 9.44 and 12.26 ppm in entities **5b** and **5d** corresponding to hydroxyl and carboxamide protons, respectively.



Scheme 1. Synthesis of the starting compounds 3a, b.

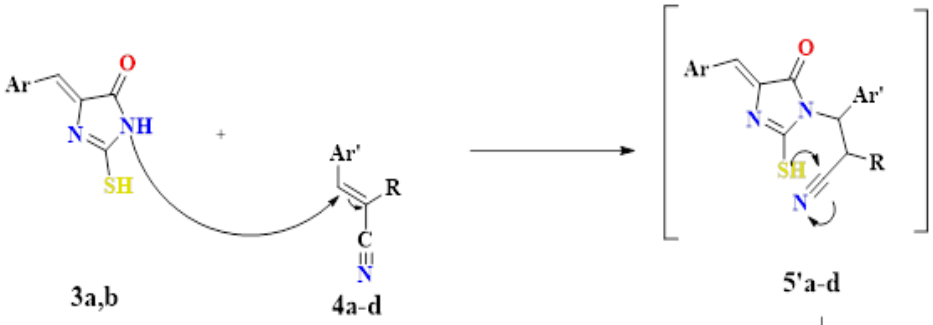


Comp. no.	Ar	Ar'	R
5a			-CN
5b			-CN
5c			-CN
5d			$-CONH_2$

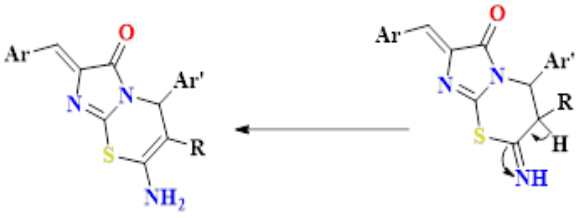
5a-d

Reagents and conditions: (i) $(CH_3CH_2)_3N$, C_2H_5OH, reflux.

Scheme 2. Synthesis of the target derivatives 5a- d.



Comp. no.	Ar	Ar'	R
5a			-CN
5b			-CN
5c			-CN
5d			$-CONH_2$



5a-d

Chart 1. Suggested mechanism for the formation of compounds 5a-d.

3.2. Biological assay

3.2.1. In vitro anticancer estimation

The prepared hybrids were estimated for their anticancer effect by MTT colorimetric assay against hepatic HepG2, mammary gland MCF-7 together with prostate PC-3 carcinomas employing Doxorubicin as a standard drug. These carcinomas were selected based on their sensitivity toward imidazole and imidazothiazine bearing candidates [44–47]. The tabulated anticancer findings illustrated the superior anticancer activity of the synthesized imidazothiazines **5a-d** with IC_{50} range of 1.02-26.87 µM **(Table 2)**.

Table 2. Cytotoxicity of the novel analogs.

Code	Cytotoxicity IC_{50} (µM)[a]		
	HepG2	**MCF-7**	**PC-3**
5a	3.36 ± 0.3	2.56 ± 0.4	5.11 ± 0.5
5b	1.84 ± 0.3	1.02 ± 0.2	2.72 ± 0.4
5c	9.48 ± 0.6	8.02 ± 0.6	17.02 ± 0.8
5d	14.35 ± 0.7	12.33 ± 0.7	26.87 ± 1.1
Doxorubicin	4.50 ± 0.2	4.17 ± 0.2	8.87 ± 0.6

[a] The data is calculated based on the average of 3 separated trials ± SD.

3.2.2. Structure activity relationship

The anticancer findings showed that **5a** possessing 4-methoxyphenyl ring with positive mesomeric effect at C-5 of imidazothiazine skeleton exerted significant anticancer action against HepG2, MCF-7 and PC-3 cells with IC_{50} of 3.36, 2.56, and 5.11 µM, respectively which exceed that of Doxorubicin. The replacement of 4-methoxy group in **5a** with hydroxyl group having a higher mesomeric action in **5b** elevated the anticancer activity towards all tested cells offering IC_{50} of 1.84, 1.02, and 2.72 µM, respectively which is approximately two to four fold higher than that of Doxorubicin. However, **5c** containing 4-chlorophenyl ring with a strong negative inductive effect and weak positive mesomeric effect showed moderate to potent cytotoxic activity against the examined carcinomas with IC_{50} range equal 8.02-17.02 µM. Additionally, the substitution of carbonitrile functionality at site 6 of imidazothiazine core in **5c** with carboxamide moiety in **5d** diminished the anticancer action against the three examined carcinomas. Collectively, compounds bearing 4-methoxy **5a** or 4-hydroxy **5b** groups with positive mesomeric action at phenyl ring on C-5 of imidazothiazine scaffold showed a more potent anticancer effect than compounds containing chloro group with a negative inductive effect **5c** and **5d**.

Besides, the presence of carbonitile functionality at C-6 of imidazothiazine ring has a positive impact on the anticancer activity compared with the carboxamide moiety (**Figure 4)**.

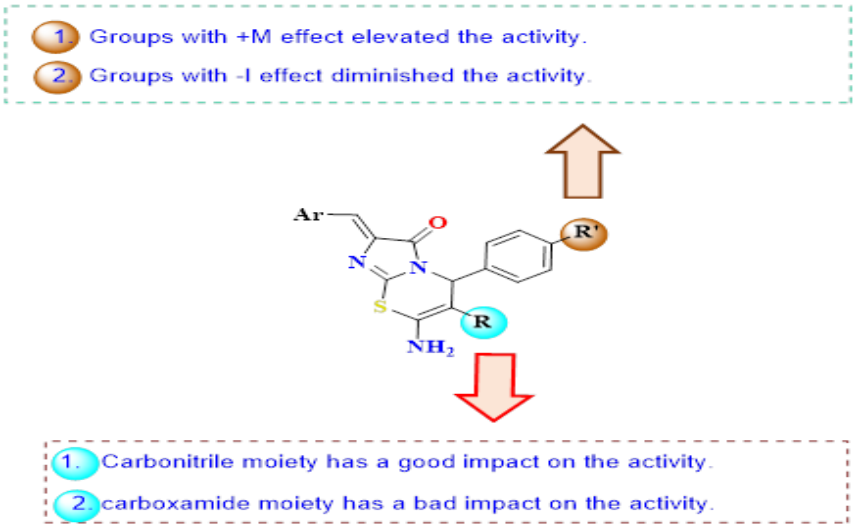


Figure 4. Graphical representation of SAR.

5. CONCLUSIONS

Deeming the development of novel anticancer heterocycles, a series of imidazothiazines **5a-d** have been designed and constructed. The structure of the prepared hybrids was asserted through spectral data. All synthesized conjugates were assayed for their seven dose anticancer assay against three carcinomas namely hepatic HepG2, mammary gland MCF-7, and prostate PC-3 carcinomas. The tested entities exerted promising anticancer activity toward the chosen carcinomas with IC_{50} range of 1.02-26.87 µM. Noticeably, compounds bearing 4-methoxy **5a** or 4-hydroxy **5b** groups with positive mesomeric action at phenyl ring on C-5 of imidazothiazine scaffold showed a more potent anticancer effect than compounds containing chloro group with a negative inductive effect **5c** and **5d**. Besides, the presence of carbonitile functionality at C-6 of imidazothiazine ring as in **5c** has a positive impact on the anticancer activity compared with the carboxamide moiety in **5d**.

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