Utility of 2-Thiohydantoin Derivatives in the Synthesis of Some Condensed Heterocyclic Compounds with Expected Biological Activity

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Abstract: On the pharmaceutical account of the reported anticancer activity of imidazole and condensed imidazole, new imidazo [2,1-b][1,3,5]thiadiazines **3a-d ,** pyrrolo[1,2-e]imidazole **5**, imidazo[2,1-b][1,3]thiazines **6a,b, 6\a**, imidazo[2,1-b][1,3]benzothiazines **7a,b, 9a,b** imidazo[2,1-b][1,3]thiazoles **11a,b, 12a,b, 18a,b, 19a,b, 20a,b, 24**; thieno[3\,2\,:4,5]pyrimido[1,2-a]imidazoles **14a,b, 15a,b,** pyrido[3',2':4,5]thieno[3,2-d]imidazo[1,2-a]pyrimidines **17a,b ,** imidazole derivatives **8a,b**, **10a,b, 21, 22**, **23** and imidazo[2\,1\:2,3]thiazolo[4,5-c]pyrazole **25** were synthesized through different chemical reactions. Structures of all synthesized compounds were supported by spectral and elemental analyses. The selected compounds by NCI were evaluated for their *in vitro* antitumor activity against 60 human tumour cell lines.

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1. Introduction:

2-Thiohydantoin derivatives represent an important class of biologically active molecules having broad pharmacological activities, anticancer [1], anticonvulsant [2], antidiabetic [3], antimicrobial [4], antiarrythmic [6], hypolipidemic [6] and hypotensive [7] activities, as well as herbicidal and fungicidal [8] applications. Furthermore, many thiohydantions are responsible for inhibition of fatty acid hydrolase [9], glycogen phosphorylase [10], amylase [11] and serine protease [12] enzymes.

The aforementioned biological activities together with the industrial importance of these compounds stimulated our interest for the synthesis of several new condensed heterocyclic compounds containing thiohydantoin moiety condensed with each of thiadiazine, thiazine, benzothiazine, pyrimidine, thiazole and pyrrole.

The new condensed heterocyclic derivatives possessing latent functional substituents appear promising to fulfill the objectives of our biological activity studies and the desired chemical transformations. However, 2-thiohydantoin and 5-arylidene-2-thiohydantoin seemed to be excellent candidates for these synthesis.

2.Discussion:

1,3,5-Thiadiazine derivatives belong to a promising class of heterocyclic compounds [13] with a broad spectrum of biological activities. In particular, some functionalized thiadiazines have been found to exhibit antibacterial [14,15], fungicial, herbicidal [16,17] and insecticidal [18] activities. Fused derivatives of 1,3,5-thiadiazine are most suitably synthesized by the "Mannich condensation" of mercaptoazoles with formaline and primary amines [15,19-23]. The reaction of 5-arylidene-2-thiohydantoins **2a,b** with formaline and primary aromatic amine was readily accomplished in boiling DMF without any catalyst [24] to yield the novel imidazo[2,1-b][1,3,5]thiadiazine derivatives **3a-d .**

It should be noted that the aminomethylation of thiohydantoin derivatives **2a,b** has been repeatedly studied earlier [25,26]. It has been shown with a number of examples that the aminomethylation of 2-thiohydantoins exclusively involves the N(3) atom [25]. Based on these findings, we assumed that the reaction intermediate is the aminomethylthiohydantoin **2\,** whose structure permits subsequent cyclocondensation with formaline along the only possible pathway leading to imidazo[2,1-b][1,3,5] thiadiazines **3a-d**. It is worth noting that, documented examples of the synthesis of compounds containing the imidazo[2,1-b][1,3,5]thiadiazine fragment are few [17,23,27-32]. The structures of compounds **3a-d** were confirmed by spectroscopic data and elemental analyses. For instance, the IR spectra of compounds **3a-d** were devoid of absorption bands at 3400-3100 cm^{-1} characteristic for NH fragment, instead they showed

bands characteristic to stretching vibrations of the conjugated amide C=O group and the C=N fragments at 1739-1720 and 1658-1596 cm^{-1}. ^{1}H-NMR spectra of compounds **3a & 3c** showed, apart from the characteristic signals of the aromatic protons, singlets attributed to the methine protons at δ 6.74, 6.76 ppm, two peaks for the methylene protons of the 1,3,5-thiadiazine rings at δ 5.44, 5.96 and 4.90, 5.42 ppm, respectively. The mass spectrum of compound **3a** revealed the molecular ion peak at m/z 380 (0.02) and the base peak at m/z 61(100).

2-Thiohydantoin **1** was converted with N,N-dimethylformamide / dimethylacetal (DMF/DMA) into the corresponding 5-[(N,N-dimethylamino)methylene]-2-thioxoimidazolidine-4-one **4** by fusion, in 57% yield. The IR spectrum of compound **4** exhibited bands in the region 3398, 3300, 1680 and 1398 cm^{-1} corresponding to (two NH), (C=O) and (C=S) groups respectively. Furthermore, treatment of compound **4** with malononitrile by refluxing in ethanol and in the presence of a catalytic amount of piperidine, yielded 5-amino-2,3-dihydro-1-oxo-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carbonitrile **5**. The structure of the latter product was established on the basis of its elemental analysis and spectral data. The IR spectrum of **5** showed absorption bands at 3305, 3117, 2207, 1694 cm^{-1} due to NH_2, NH, CN and amide carbonyl functions respectively. The mass spectrum of compound **5** revealed the molecular ion peak at m/z 192 (M^+, 5.99) and the base peak at 56(100). **(Scheme 1)**.

Since, the thiazine moiety of imidazo[2,1-b][1,3]thiazines is an important pharmacophoric group for the benzodiazepine receptor binding activity [23,33]. Bicyclic compounds of imidazo[2,1-b][1,3]thiazines **6-9** were synthesized and screened for their anticancer activities. This was accomplished through the reaction of 5-arylidene-2-thiohydantoin **2a,b**, with 1,3-dichloropropane in acetone in the presence of triethylamine [34]. Earlier, it was found by our research group [35,36], that during the reaction of 5-arylidene-2-thiohydantoins with 1,2-dibromoethane two isomeric products were obtained. In an analogous reaction, upon reacting 1,3-dichloropropane with 5-(4-chlorobenzylidne)-2-thiohydantoin **2a**, the two isomeric products **6a, 6\a** were obtained in a 1:4 ratio. On the contrary, when 5-(4-methoxybenzylidene)-2-thiohydantoin **2b** was reacted with 1,3-dichloropropane, only one product **6b** was obtained in a yield 65%. The structures of the products were supported by ^{1}H-NMR, IR spectroscopy and elemental analysis. The ^{1}H-NMR spectrum of **6a** showed resonance signals at δ 2.20-2.38, 3.10-3.20 and 3.70-3.80 ppm attributed to three CH_2 functions of the thiazine ring and a singlet at δ 6.89 ppm due to olefinic proton.

Cyclocondensation of o-chlorobenzaldehyde and 5-arylidene-2-thiohydantoins **2a,b** proceeds by fusion of equimolar amounts of these compounds affording 2-(4-substitutedbenzylidene)-5-hydroxy-2H-imidazo[2,1-b][1,3]benzothiazin-3-(5H)-ones **7a,b**. The structures of **7a,b** were supported by ^{1}H-NMR and IR spectroscopy and elemental analyses.

The mass spectrum of compound **7a** showed peaks at m/z 344 due to M+2 (0.04), molecular ion peak at 342 (0.06) in addition to the base peak at 139 (100). The ^{1}H-NMR spectrum of **7b** revealed characteristic signals at δ 3.20-3.40 ppm corresponding to methoxy protons and C5 proton [37]. The IR spectra of compounds **7a,b** showed broad bands due to OH group at 3494-3394cm^{-1}.

Acylation of 5-arylidene-2-thiohydantoin **2a,b** with different substituted benzoyl chloride in dry toluene and in presence of piperidene as catalyst afforded 4-(4-chlorobenzylidene)-1-(4-substitutedphenylcarbonyl)-2-thioxo-5-oxo-2,3,4,5-tetrahydro-1H-imidazoles **8a,b** and 2-(4-substitutedbenzylidene)-8-chloro-2H-benzo[e]imidazo[2,1-b][1,3]thiazine-3,5-diones **9a,b**. Actually the heating of 4-nitro or 4-bromobenzoyl chloride with the thiones **2a,b** under experimental conditions, we assumed to yield N-acyl derivatives **8a,b** which were isolated. However, further trials to cyclize **8a,b** to yield fused systems all failed under the same experimental conditions. While, upon the reaction of 2,4-dichlorobenzoyl chloride with thiones **2a,b** under experimental conditions, the intermediate N-acylated derivative **8** could not be isolated and it was capable of intramolecular cyclization to provide compounds **9a,b**.

The structures of the N-acyl derivatives **8a,b** have been established on the basis of their elemental analyses and spectral data. The IR spectra of compounds **8a,b** showed characteristic absorption bands at 3433-3305, 1712 and 1650 cm^{-1} attributed to NH and two C=O groups. The IR spectra of compounds **9a,b** lacked the absorption bands at 3400-3100 cm^{-1} characteristic of the NH group and showed absorption bands at 1712- 1652 cm^{-1} corresponding to carbonyl groups of imidazole and thiazine rings. The mass spectrum of **9a** revealed a peak at m/z 376 corresponding to (M+2, 8.47) and the base peak at m/z 50(100). While the mass spectrum of **9b** showed the molecular ion peak at m/z 370 (M^+, 6.01) and the base peak at 52(100). **(Scheme 2).**

As a part of our aim towards the development of simple new procedures for the synthesis of fused heterocyclic compounds, the reaction of 5-arylidene-2-thiohydantoins **2a,b** with monohalogenated

compounds such as ethyl iodide, chloro acetonitrile and methyl bromoacetate was accomplished under the influence of alkali metal alkoxides to give ethyl mercapto derivatives **10a,b**. However, further cyclization of alkylthio derivatives via the Thorpe reaction yielded 3-amino-6-(4-substitutedbenzylidene)imidazo[2,1-b][1,3]thiazol-5-(6H)-ones **11a,b** and 6-(4-substitutedbenzylidene)imidazo[2,1-b]thiazole-3,5(2H,6H)diones **12a,b** was observed in the case of electron acceptor substituents in the thioalkyl group (R=CN, $COOCH_3$) under the influence of alkali metal alkoxides. It should be noted that the non cyclic alkyl derivatives of compounds **11a,b** and **12a,b** intermediates were not isolated in such reaction . The structures of compounds **(10-12) a,b** were supported by elemental analyses and spectral data. The IR spectra of compounds **10a,b** showed the presence of absorption bands at 3303-3131 and 1711-1700 cm^{-1} could be attributed to NH and carbonyl groups respectively, while the spectra of compounds **11a,b** revealed the disappearance of bands due to cyano group and the presence of absorption bands at 3224-3130 and 1724-1697 cm^{-1} due to amino and carbonyl groups respectively. However, the IR spectra of compounds **12a,b** showed absorption bands at 1742-1735 cm^{-1} due to two carbonyl groups of imidazole and thiazole rings.

The ^{1}H-NMR spectrum of **10a** showed a triplet at δ1.37ppm, a quartet at δ 3.22 ppm assigned to ethyl group protons, in addition to a deuterium oxide exchangeable singlet at δ 11.81 ppm assigned to the NH function. The ^{1}H-NMR spectrum of **11a** revealed no signals of –S-CH_2– protons but revealed signals for thiazole and NH_2 protons at δ 6.40 and 10.61 ppm respectively. Also, the structure of compound **11b** was supported by its mass spectrum, which showed molecular ion peak at m/z 273 (7.19) and the base peak m/z 53(100), which is in agreement with its molecular formula ($C_{13}H_{11}N_3O_2S$). The ^{1}H-NMR spectrum of **12a** showed a signal for –S-CH_2– protons of the thiazole ring at δ 4.49 ppm and the disappearance of signals due to the two NH functions of the starting compounds, while the mass spectrum of compound **12b** showed the molecular ion peak at m/z 274(0.05) and the base peak at 156(100). **(Scheme 3).**

Compounds containing a fused pyrimidine ring represent a broad class of compounds which have received considerable attention over the past years due to their wide range of biological activity. With the development of clinically useful anticancer, antihypertensive agents, antiviral, antibacterial, antiallergic, antimalarial, analgesic and anti-inflammatory drugs [38, 39], there has been recently remarkable interest in the synthesis of annulated pyrimidines.

Reaction of o-aminoester (ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate) **13** [40] or o-aminonitrile (3-amino-4,6-diphenylthieno[2,3-b]pyridine-2-carbonitrile) **16** [41] with 2-ethylthiohydantoin derivatives **10a,b** in glacial acetic acid or by fusion leading to condensed systems **(14, 15 &17)a,b**. The postulated mechanism for the reaction of the o-aminoester with **10a,b** involves an initial nucleophilic addition of the amino group of the o-aminoester to the electron deficient imidazole C2 cation to form the intermediates **14'** by elimination of ethyl mercaptane which carry out subsequent nucleophilic attack of the nitrogen atom of imidazole moiety on the sp^2 carbon of the carboxylate group followed by elimination of an ethanol moiety to give two products **14a,b** and **15a,b.**

The structure of the new compounds **(14, 15 & 17)a,b** were established on the basis of elemental analyses and spectral data. The IR spectra of compounds **14a,b** and **15a,b** showed absorption bands at 3410-3208, 3380-3213cm^{-1} corresponding to NH functions, respectively. In addition to bands at 1710-1666, 1720-1710 cm^{-1} for imidazole carbonyl group and 1666-1662, 1658-1656 cm^{-1} for thiazine carbonyl group, respectively. The mass spectrum of compound **14a** showed peaks at m/z 359 due to (M+2, 20.02), m/z 357 attributed to (M^+, 8.3) and the base peak at m/z 49 (100). ^{1}H-NMR spectrum of compound **15b** showed a deuterium oxide exchangeable singlet at δ 4.98 ppm assigned to the NH_2 protons. In addition to two doublets at δ 7.73, 8.15 ppm corresponding to aromatic protons. Furthermore, the electron impact mass spectrum of compound **15a** showed a peak corresponding to M+2 at m/z 359(6.7) and the molecular ion peak at m/z 357(9.72) and the base peak at m/z 59 (100) which are in agreement with its molecular formula $C_{17}H_{12}ClN_3O_2S$. Moreover, the spectra of compounds **17a,b** showed absorption band at 3417-3209 cm^{-1} characteristic to amino group and another absorption bands at 1712-1710 cm^{-1} assigned for carbonyl group respectively. While, the ^{1}H-NMR spectra of the compounds **18a,b** apart from the characteristic signals attributed to the aromatic protons, they revealed deuterium oxide exchangeable singlets attributed to the amino protons at δ 8.14 ppm and another singlets due to pyridine C3 proton at δ 7.41 and 7.88 ppm, respectively. **(Scheme 4).**

The work was extended to shed more light on the activity and synthetic potential of the (NH_2) group in each of compounds **11a & 11b.** Thus, compounds **11a,b** were reacted with phenyl isothiocyanate to yield the corresponding 1-[6(4-substitutedbenzylidene)-5,6-dihydro-5-

oxoimidazo[2,1-b][1,3]thiazol-3-yl]-3-phenylthioureas **18a,b**. The IR and ^{1}H-NMR spectral data of **18a,b** were found to be in agreement with the assigned structure. The IR spectra of compounds **18a,b** showed bands at 3467-3193 cm^{-1} characteristic to two NH groups. In addition to four bands corresponding to N-C=S functions at 1597-1590, 1258-1253, 1180-1096 and 1027-1014 cm^{-1}, respectively.

The electron impact mass spectrum of compound **18a** showed peaks at m/z 414(1.25), 412(1.1) due to M+2 and M$^+$, respectively. In addition to the base peak at 60 (100). However, ^{1}H-NMR spectrum of **18b** showed a deuterium oxide exchangeable singlet at δ 10.57 ppm attributed to two NH protons, in addition to other signals corresponding to other protons. Compounds **18a,b** were further reacted with both phenacyl bromide and chloroacetic acid to yield compounds **19a,b** and **20a,b** respectively. The reaction with phenacyl bromide was applied in ethanol as solvent and in the presence of a catalytic amount of triethylamine. While the reaction with chloroacetic acid was performed in acetic acid as solvent and by using sodium acetate as a catalyst. Both reactions were accomplished via dehydrobromination or dehydrochlorination followed by cyclization through water elimination. IR spectral analyses for compounds **19a** and **20a** revealed the disappearance of bands corresponding to NH and C=S functions. ^{1}H-NMR spectrum of compound **19b** showed two singlets at δ 7.49 and 7.52 ppm corresponding to thiazole and imidazothiazole protons, respectively. In addition to signals corresponding to aromatic protons. Also, ^{1}H-NMR spectrum of compound **20b** showed two singlets at δ 5.07 and 9.38 ppm attributed to S-CH_2 protons and thiazole CH proton, respectively. **(Scheme 5).**

The synthesis of new compounds outlined in **(Scheme 6)** was accomplished by hydrazinolysis of 6-(4-chlorobenzylidene)imidazo[2,1-b][1,3]thiazole-3,5-(2H,6H) dione **12a** by boiling with hydrazine hydrate in ethanol to furnish 2-[4-(4-chlorobenzylidene)-4,5-dihydro-5-oxo-1H-imidazol-2-ylthio]acetohydrazide **21.** This reaction has proceeded via the rupture of the endocyclic C-N bond. Compound **21** was further reacted with phenyl isothiocyanate in ethanol to give the thiosemicarbazide derivative **22**. The latter compound was cyclized with ethyl bromoacetate in the presence of anhydrous sodium acetate to yield the corresponding 2-[4-(4-chlorobenzylidene)-4,5-dihydro-5-oxo-1H-imidazol-2-ylthio]-N-[4-oxo-3-phenyl-thiazolidin-2-ylidne)acetohydrazide **23.**

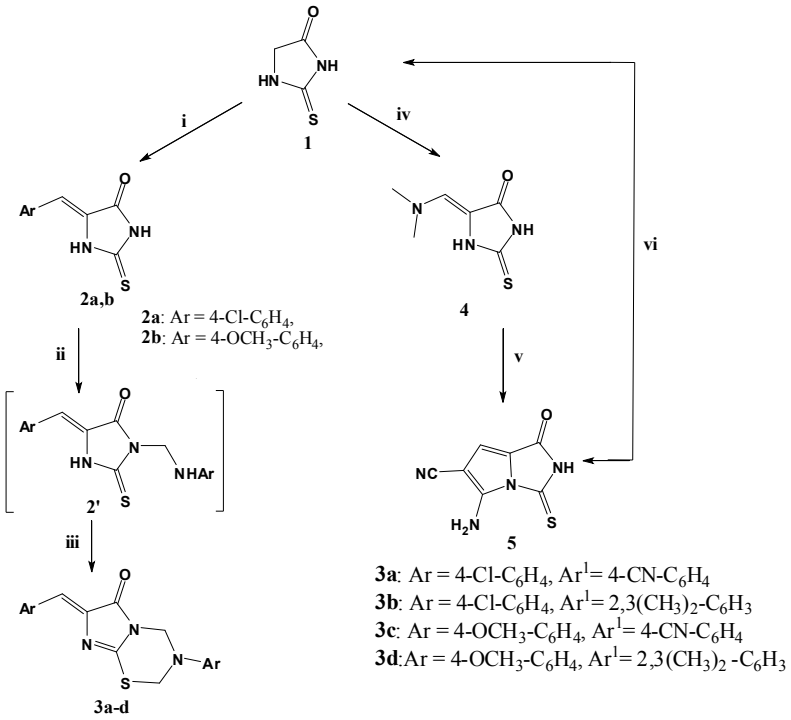
The IR spectrum of compound **21** displayed bands corresponding to imidazole and acidhydrazide NH functions at 3300, 3186 cm^{-1}, while that of compound **22** showed additional bands due to thioamidic functions at 1593, 1203, 1097 and 1033 cm^{-1}. However, the IR spectrum of compound **23** lacked the thioamidic absorption bands and displayed additional bands at 1658 cm^{-1} due to thiazolidin-C_4–carbonyl group. The ^{1}H-NMR spectrum of compound **21** revealed the presence of three deuterium oxide exchangeable singlets at δ 7.68, 7.70 and 10.44 ppm attributed to NH_2, acid hydrazide-NH and imidazole NH, respectively. In addition to a singlet at δ 4.20 ppm due to S-CH_2–CO protons. While the ^{1}H-NMR spectrum of compound **22** displayed signals at δ 7.30-7.35 ppm attributed to three NH protons and aromatic protons, in addition to the deuterium oxide exchangeable singlet at δ 11.02 ppm due to imidazole –NH. Besides to a singlet at δ 4.50 ppm corresponding to S-CH_2–CO- protons.

Moreover, the ^{1}H-NMR spectrum of **23** showed two deuterium oxide exchangeable singlets at δ 7.32 and 10.42 ppm attributed to CO-NH and imidazole NH, respectively. In addition to two singlets at δ 2.08 and 3.70 ppm corresponding to exocyclic –S-CH_2 and thiazolidin-S-$\underline{CH_2}$ protons, respectively.

Moreover, compound **12a** was condensed with 4-chlorobenzaldehyde in presence of anhydrous sodium acetate in glacial acetic acid to give the corresponding 2,6-bis(4-chlorobenzylidene)imidazo[2,1-b][1,3]thiazol-3,5-(2H, 6H)dione **24** which was further treated with hydrazine hydrate to afford 6-(4-chlorobenzylidene)-3-(4-chlorophenyl)-3,3a-dihydro-2H-imidazo[2',1':2,3][1,3]thiazolo[4,5-c]pyrazol-7(6H)-one **25** through cyclocondensation reaction.

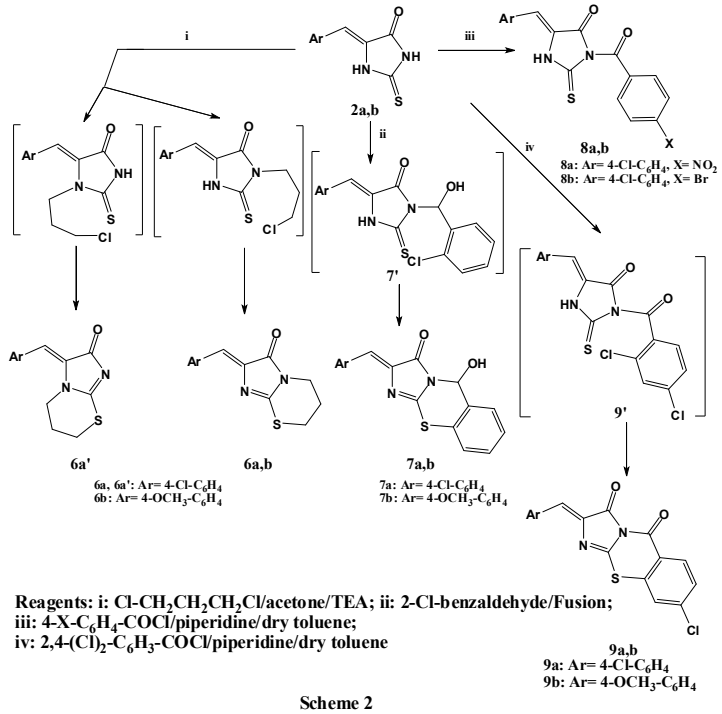
The electron impact mass spectrum of compound **24** revealed peaks at m/z 402(0.8) due to M+2 and the molecular ion peak at m/z 400(0.29), in addition to the base peak at m/z 90(100).

However, the IR spectrum of compound **25** showed absorption bands at 3421, 3224 cm^{-1} attributed to NH function. Moreover, the electron impact mass spectrum of compound **25** showed a peak at m/z 418(0.37) corresponding to (M+4) that complies with the molecular formula of the compound $C_{19}H_{12}Cl_2N_4OS$ and a base peak at m/z 57 (100).



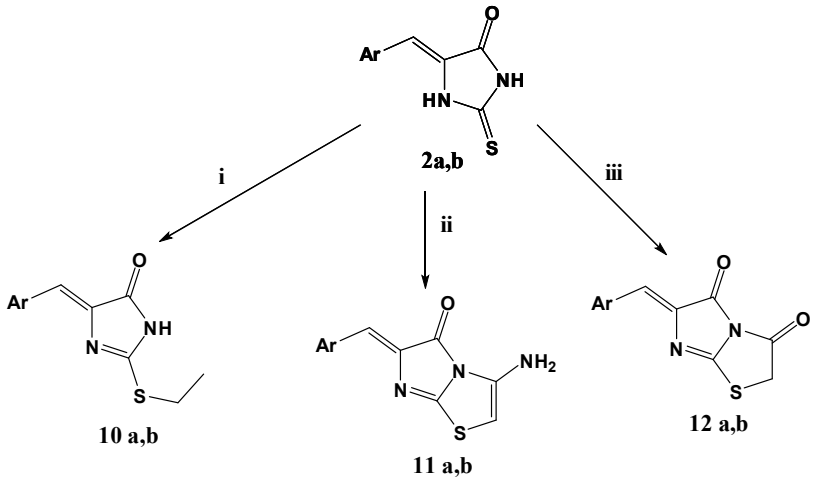
Reagents: i: Ar-CHO/CH_3COOH/CH_3COONa; ii: Ar_1NH_2/HCHO/DMF; iii: excess HCHO; v: DMF/DMA/Fusion; v: $CH_2(CN)_2$/Piperidine/CH_3CH_2OH; vi: DMF/DMA/$CH_2(CN)_2$/Piperidine/CH_3CH_2OH.

Scheme 1



Reagents: i: Cl-$CH_2CH_2CH_2Cl$/acetone/TEA; ii: 2-Cl-benzaldehyde/Fusion; iii: 4-X-C_6H_4-COCl/piperidine/dry toluene; iv: 2,4-$(Cl)_2$-C_6H_3-COCl/piperidine/dry toluene

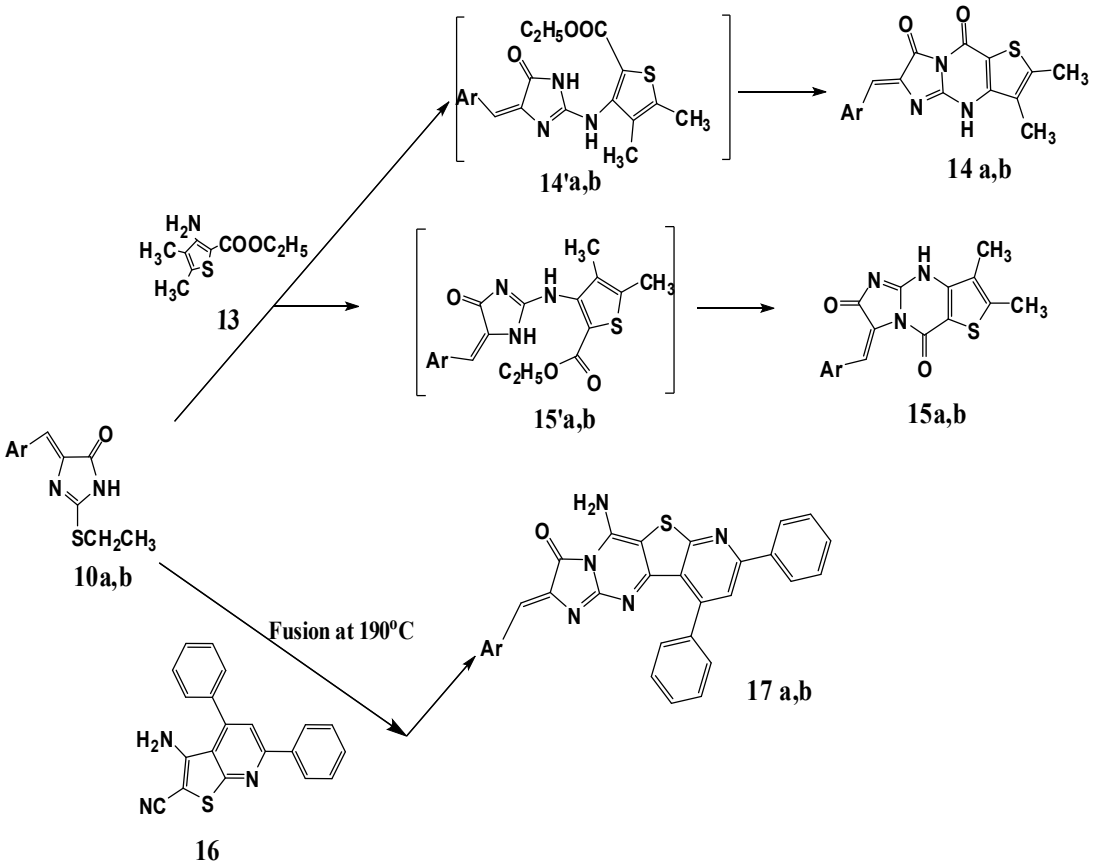
Scheme 2



a: Ar= 4- Cl-C_6H_4; b: Ar= 4-OCH_3-C_6H_4

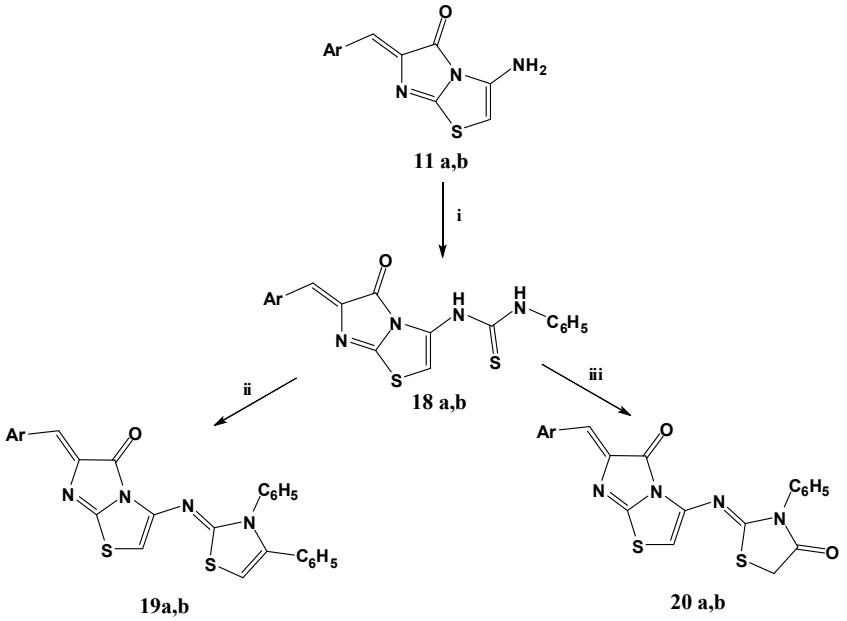
Reagents: i: CH_3CH_2I/ Na^+ $O^-C_2H_5$; ii: $ClCH_2CN$/ Na OC_2H_5 iii: $BrCH_2COOCH_3$/ $Na^+O^-C_2H_5$

Scheme 3



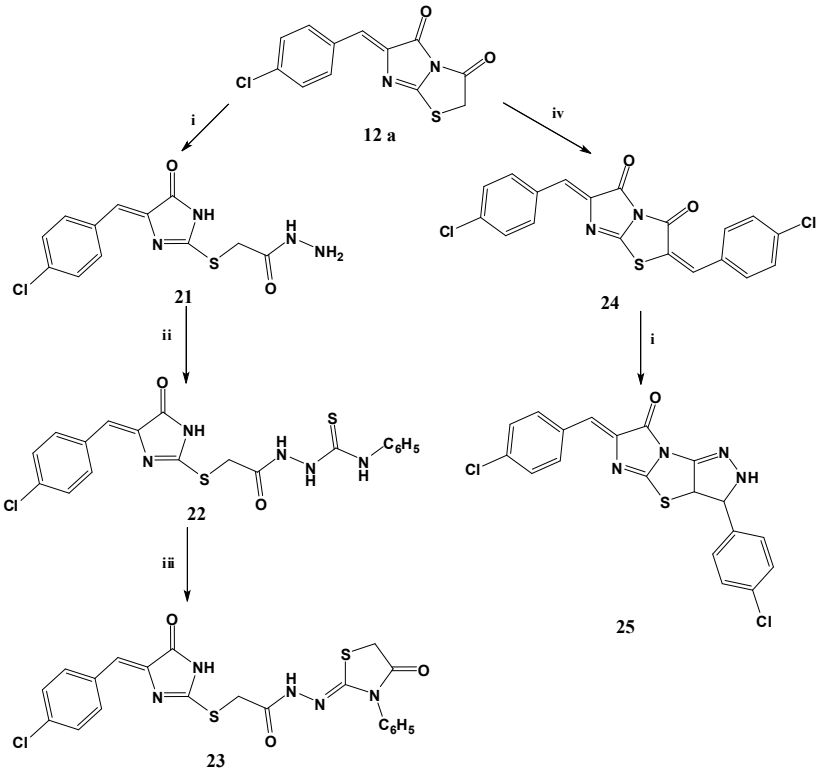
a : Ar = 4-Cl-C_6H_4 , b : Ar = 4-OCH_3-C_6H_4

Scheme 4



Reagents: i: C_6H_5NCS/ Benzene; ii: $C_6H_5COCH_2Br$/ TEA/ C_2H_5OH; iii: $ClCH_2COOH$/ CH_3COO Na/ CH_3COOH

Scheme 5



Reagents: i: NH_2NH_2/C_2H_5OH; ii: C_6H_5NCS/ pyridine; iii: $BrCH_2COOC_2H_5$/ C_2H_5OH;
iv: 4-Cl-C_6H_4-CHO/ CH_3COOH/ CH_3COO Na

Scheme 6

3.Experimental:

All melting points were measured on Electro thermal LA 9000 SERIS, Digital Melting point Apparatus and are uncorrected. IR spectra (KBr) were recorded on FT-IR 5300 spectrophotometer and Perkin Elmer spectrum RXIFT-IR system (ν, cm^{-1}). ^{1}H-NMR spectra were recorded in (DMSO-d_6) at 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were recorded on GC Ms-QP 1000 EX mass spectrometer at 70 eV. Microanalytical data were performed in Micro analytical Research Center, Cairo University. Thin layer chromatography was performed on pre-coated (0.25mm) silica gel GF_{254} plates (E. Merck, Germany). Compounds were detected with 254 nm UV lamp.

*General procedure for the synthesis of compounds **3a-d:***

To an equimolar mixture of compound **2a,b** (2.9 mmol) and the appropriate aromatic amine (2.9 mmol) in DMF (5 ml) an excess amount of 37% formaline solution (3ml) was added. The reaction mixture was refluxed for 30 min with vigorous stirring and then stirred at 20°C for 22h. Compounds **(3a-d)** were obtained as crystals which were filtered off and recrystallized from the suitable solvent.

*7-(4-Chlorobenzylidene)-3-(4-cyanophenyl)-3,4-dihydro-2H-imidazo[2,1-b][1,3,5] thiadiazin-6(7H)-one; **3a**.*

Red powder; recrystallized from EtOH; m.p. 215-217°C, yield 80%. **IR** (KBr, cm^{-1}): 3070 (CH–Ar); 2869 (CH-aliph.); 2210 (C≡N); 1735 (C=O); 1654 (C=N). **MS**: m/z(%): 381(M+1,0.01); 380($M^{+\cdot}$,0.02); 365(0.03); 358(0.02); 347(0.03); 345(0.03); 320(0.07); 318(0.03); 308(0.09); 307(0.09); 287(0.1); 285(0.08); 269(0.1); 268(0.13); 267(0.13); 266(0.14) ;265(0.11); 258(0.12); 256(0.12); 241(0.28); 240(0.27); 239(0.33); 238(0.18); 236(0.11); 229(0.24); 228(0.23); 227(0.21); 216(0.18); 215(0.27); 214(0.27); 213(0.26); 206(0.13); 204(0.43); 203(0.49); 201(0.41); 192(0.16); 190(0.27); 175(0.3); 167(0.23); 157(0.3); 155(0.68); 153(0.78); 152(0.98); 150(0.82); 148(0.31); 130(3.1); 129(3.32); 128(1.75); 120(0.98); 119(3.03); 114(0.96); 103(4.70); 102(5.98); 101(3.55); 100(1.53); 91(2.96); 89(3.35); 88(4.24); 87(9.06); 86(7.14); 78(2.19); 77(4.62); 76(5.66); 64(11.28); 63(13.52); 61(100); 53(71.84).**Anal. Form** : $C_{19}H_{13}ClN_4OS$. **Calcd.** (%): C, 59.92; H, 3.44; N, 14.71 **Found:** (%) C, 59.98; H, 3.47; N, 14.83.

*7-(4-Chlorobenzylidene)-3-(2,3-dimethylphenyl)-3,4-dihydro-2H-imidazo[2,1-b] [1,3,5]thiadiazin-6(7H)-one; **3b***

Yellow powder; recrystallized from EtOH; m.p. 213-215; yield 87%. **IR** (KBr, cm^{-1}): 3074 (CH–Ar); 2931, 2869 (CH-aliph.); 1739 (C=O); 1658 (C=N). **Anal. form**: $C_{20}H_{18}ClN_3OS$ **Calcd.** (%): C, 62.57; H, 4.73; N, 10.95. **Found** (%): C, 62.63; H, 4.78; N, 11.04.

*3-(4-Cyanophenyl)-7-(4-methoxybenzylidene)-3,4-dihydro-2H-imidazo[2,1-b][1,3,5] thiadiazin-6(7H)-one; **3c.***

Red powder; recrystallized from EtOH; m.p. 201-203; yield, 85%. **IR** (KBr, cm^{-1}): 3043 (CH–Ar); 2927, 2854 (CH–aliph.); 2218(C≡N); 1728 (C=O); 1596 (C=N); 1249, 1018 (C–O–C). **^{1}H-NMR** (DMSO-d_6-δppm): 3.87 (s, 3H, OCH_3); 5.44 (s, 2H, N–CH_2–N); 5.96 (s, 2H, S–CH_2–N); 6.74 (s, 1H, =CH); 6.99–7.01 (m, 4H, 4–OCH_3–C_6H_4); 7.38 (d, 2H, J= 8.9 Hz, 4–CN–C_6H_4–$C_{2,6}$–H); 7.47(d, 2H, J= 8.9 Hz, 4–CN-C_6H_4–$C_{3,5}$–H). **Anal. form**: $C_{20}H_{16}N_4O_2S$ **Calcd.** (%): C, 63.81; H, 4.28; N, 14.88. **Found** (%): C, 63.89; H, 4.32; N, 15.02.

*7-(4-Methoxybenzylidene)-3,4-dihydro-3-(2,3-dimethylphenyl)-2H-imidazo[2,1-b] [1,3,5]thiadiazin-6(7H)-one; **3d***

Yellow powder; recrystallized from EtOH; m.p. 223-225°C; yield 90%. **IR** (KBr, cm^{-1}): 3080 (CH–Ar); 2926, 2858 (CH–aliph.); 1720 (C=O); 1642 (C=N); 1290, 1000 (C–O–C). **^{1}H-NMR** (DMSO-d_6–δppm): 2.89 (s, 3H, phenyl–C_3-CH_3); 2.96 (s, 3H, phenyl–C_2–CH_3); 3.87 (s, 3H, OCH_3); 4.90 (s, 2H, N–CH_2–N); 5.42 (s,2H, S–CH_2-N); 6.76 (s, 1H, =CH); 6.94-6.96 (m, 3H, 2,3-$(CH_3)_2C_6H_4$–$C_{4,5,6,}$–H); 7.38 (d, 2H, J= 8.7Hz, 4-OCH_3-C_6H_4–$C_{3,5}$–H); 7.43 (d, 2H, J = 8.7Hz, 4–OCH_3–C_6H_4–$C_{2,6}$–H). **MS**: m/z(%): 379($M^{\cdot+}$, 50.31); 351(45.71); 345(46.75); 334(41.09); 308(41.33); 301(48.32); 285(74.72); 273(77.06); 248(88.82); 231 (67.14); 203(49.76); 173(66.78); 170(55.77); 131(47.17); 128(51.84); 108(44.43); 85(53.32); 69(44.97); 63(46.78); 54(40.24); 51(60.85); 50(100). **Anal. form**: $C_{21}H_{21}N_3O_2S$ **Calcd.** (%): N, 11.08. **Found** (%): N, 11.21.

*Synthesis of 5-[N,N-dimethylaminomethylene]-2-thioxoimidazolidin-4-one; **4** and 5-amino-2,3-dihyro-1-oxo-3-thioxo-1H-pyrrolo[1,2-e]imidazole-6-carbonitrile; **5.***

Method A:

Step 1:

An equimolar mixture of compound **1** (10 mmol) and DMF/DMA (1.06g, 1.48 mL, 10 mmol) was fused at 180°C for 6h. Then the solid product was collected, washed with EtOH and recrystallized from DMF to yield black crystals of compound **4** in 80% yield.

Step 2:

A mixture of compound **4** (10 mmol) and malononitrile (0.66g, 10 mmol) was refluxed in EtOH (20 mL) in the presence of pipridine (0.5 mL) as catalyst for 12h. The solvent was then evaporated

under reduced pressure and the solid product was collected and recrystallized from EtOH. Yield, 60%.

Method B:

A one pot reaction was carried out by refluxing an equimolar mixture of compound **1** and malononitrile (0.66g, 10 mmol) in (30 mL) of DMF/DMA (2:1) and in presence of a catalytic amount of piperidine. Reflux was allowed for 12hrs. and then the reaction was cooled, the solid product was collected and recrystallized from EtOH. Yield, 40%.

5-[N,N-Dimethylaminomethylene]-2-thioxoimidazolidin-4-one; ***4***.

Black powders; recrystallized from DMF; m.p.>360°C [42]; yield 80%. **IR** (KBr, cm^{-1}): 3398, 3300 (NH); 2928 (CH–aliph.); 1680 (C=O); 1398 (C=S).

5-Amino-2,3-dihydro-1-oxo-3-thioxo-1H-pyrrolo[1,2-e] imidazole-6-carbonitrile; ***5***.

Brownish black, crystals; recrystallized from EtOH; m.p. 358-360°C; yield 60%. **IR** (KBr, cm^{-1}): 3305, 3117 (NH, NH_2); 2207 (C≡N); 1694 (C=O); 1583 (C=N); 1359 (C=S). **MS:** m/z(%): 192(M^{+}, 5.99); 150(14.68); 149(10.88); 139(9.25); 128(10.09); 98(10.2); 91(10.24); 85(11.98); 84(17.81), 78(15.83); 77(14.93); 71 (20.97); 69(23.76), 68(35.14); 65(18.09); 57(44.44); 56 (100); 55(89.49); 53(32); 50(50.92). **Anal.form**: $C_7H_4N_4OS$ **Calcd**. (%): C, 43.74; H, 2.10; N, 29.15. **Found** (%): C, 43.75; H, 2.13; N, 29.23.

General procedure for the synthesis of compounds ***6a,b*** *and* ***6a'****:*

Compound **2a,b** (10 mmol) was refluxed with 1,3-dichloropropane (1.12 g, 0.94 mL, 10 mmol) in dry acetone (20 mL) as solvent and in presence of few drops of triethylamine (2 drops). Reflux was carried out for 50hrs., then the reaction mixture was cooled and the solid precipitate was collected and recrystallized from EtOH.

2-(4-Chlorobenzylidene)-6,7-dihydro-2H-imidazo[2,1-b][1,3]thiazin-3(5H)-one; ***6a***.

Yellow crystals; recrystallized by EtOH; m.p. 200-201 [43]; yield 77%. **IR**(KBr, cm^{-1}): 3058 (CH-Ar); 2916, 2828 (CH-aliph.); 1710 (C=O); 1632 (C=N). **^{1}H-NMR** (DMSO-d_6-δppm): 2.20–2.38 (m, 2H, perhydrothiazine–C_3–H); 3.10–3.20 (m, 2H, Perhydrothiazine-C_4–H); 3.70–3.80 (m, 2H, perhydrothiazine-C_2–H); 6.89 (s, 1H, =CH); 7.36 (d, 2H, J= 8.4 Hz, 4-Cl–C_6H_4–$C_{2,6}$–H); 8.04 (d, 2H, J = 8.4Hz, 4–Cl–C_6H_4–$C_{3,5}$–H). **MS:** m/z (%): 280(M+2 ,3.57); 278(M^{+},12.5); 237(10.71); 178(7.74); 152(10.12); 150(100); 123(39.29); 115(7.14); 114(22.02); 99(20.83); 87(26.79); 85(22.02); 76(4.17); 75(18.45); 73(15.48); 63(67.86); 62(79.76). **Anal. form**: $C_{13}H_{11}ClN_2OS$ **Calcd.** (%): C, 56.01; H, 3.98; N, 10.05. **Found** (%): C, 56.04; H, 4.02; N, 10.13.

2-(4-Methoxybenzylidene)-6,7-dihydro-2H-imidazo[2,1-b][1,3]thiazin-3(5H)-one; ***6b***

Yellowish orange crystals; recrystallized from EtOH; m.p. 243-245°C [43]; yield 65%. **IR**(KBr, cm^{-1}): 3020 (CH-Ar); 2927 (CH–aliph); 1701 (C=O); 1589 (C=N); 1245, 1018 (C–O–C). H). **Anal. Form**: $C_{14}H_{14}N_2O_2S$ **Calcd**. (%): C, 61.29; H, 5.14. **Found** (%): C, 61.38; H, 5.14.

3-(4-Chlorobenzylidene)-3,5,6,7-tetrahydro-2H-imidazo[2,1-b][1,3]thiazin-2-one; ***6'a***

Yellow crystals; insoluble in EtOH; m.p. 240-242 °C; yield 12%. **IR**(KBr, cm^{-1}): 3080 (CH–Ar); 2920 (CH–aliph.); 1710 (C=O); 1632 (C=N). **MS:** m/z (%): 280(M+2,1.62); 278(M^{+},2.6); 276(2.6) 271(2.6); 243(3.9); 219(2.6); 216(2.92); 214(3.57); 210(4.55); 199(4.87); 190(3.57); 175(2.6); 161(4.55); 154(3.57); 153(3.25); 150(4.55); 145(3.57); 140(3.9); 134(3.9); 120(5.19); 110(6.49); 104(6.17); 102(3.57); 94(4.22); 93(5.84); 89(7.47); 87(5.52); 83(5.52); 79(9.42); 77(15.58); 75(11.04); 70(30.19); 69(34.42); 66(24.35); 52(100). **Anal. form:** $C_{13}H_{11}ClN_2OS$ **Calcd**. (%): C, 56.01; H, 3.98; N, 10.05 **Found**(%): C, 56.05; H, 3.99; N, 10.12.

Synthesis of 2-(4-substitutedbenzylidene)-5-hydroxy-2H-imidazo[2,1-b][1,3] benzothiazin-3(5H)-ones; ***7a,b****:*

An equimolar mixture of compound **2a,b** (2 mmol) and o-chlorobenzaldehyde (0.28 g, 0.22 mL, 2 mmol) was fused at 180°C for 15-30hrs. The solid product was collected, washed with EtOH and recrystalized from EtOH.

2-(4-Chlorobenzylidene)-5-hydroxy-2H-imidazo[2,1-b][1,3]benzothiazin-3(5H)-one; ***7a.***

White crystals; recrystallized from EtOH; m.p. 158-160°C; yield 97%**.** **IR** (KBr, cm^{-1}): 3494, 3394 (OH broad band); 3075 (CH–Ar); 2900, 2869 (CH–aliph.); 1681 (C=O); 1604 (C=N). **MS:** m/z (%): 344**(**M+2, 0.04); 342(M^{+},0.06**)**; 333(14.56); 331(0.57); 317(16.5); 316(5.5); 315(0.05); 313(4.2); 311(0.02); 305(2.36); 293(3.85); 291(0.19); 287(14.31); 274(7.69); 265(10.4); 258(14.32) 251(2.27); 237(6.51); 216(2.18); 204(15.1); 202(5.02); 201(22.66); 190(14.85); 189(3.84); 177(6.42); 163(4.25); 159(4.64); 156(47.94); 155(9.99); 141(30.05); 139(100); 138(3.09); 113(11.7); 112(9.35); 111(6.98); 99(3.55); 89(4.9); 87(15.38); 76(33.48); 66(52.86); 63(5.74); 62(6.02); 55(3.97); 51(56.39). **Anal.form**: $C_{17}H_{11}ClN_2O_2S$ **Calcd.** (%): C, 59.56; H, 3.23; N, 8.17. **Found** (%): C, 59.62; H, 3.21; N, 8.29.

5-Hydroxy-2(4-methoxybenzylidene)-2H-imidazo[2,1-b][1,3]-benzothiazin-3(5H)-one; ***7b***

White crystals; recrystallized from EtOH; m.p. 142-144°C; yield 92%. **IR** (KBr, cm^{-1}): 3475, 3402 (OH broad band); 3060 (CH–Ar); 2890 (CH–aliph.); 1688 (C=O); 1590 (C=N); 1250, 1044 (C-O-C). **^{1}H-NMR** (DMSO-d_6-δppm): 3.20–3.40 (m, 4H, OCH_3, CH-OH); 7.34 (s, 1H, =CH); 7.35–7.43 (m, 4H, C_6H_4–H); 7.44–7.53 (m, 2H, 4-OCH_3-C_6H_4–$C_{3,5}$–H); 7.77 (d, 2H, J = 7.8Hz, 4–OCH_3–C_6H_4–$C_{2,6}$–H); 13.38 (s, 1H, OH, D_2O exchangeable). **Anal.form**: $C_{18}H_{14}N_2O_3S$ **Calcd**. (%): C, 63.89; H, 4.17; N, 8.28 **Found** (%): C, 63.92; H, 4.18; N, 8.36.

*General procedure for the synthesis of compounds **8a,b** and **9a,b**:*

Compound **2a, b** (8 mmol) was refluxed with the appropriate benzoyl chloride (12 mmol) in 15 mL of anhydrous toluene for 48 h. The reaction mixture was then cooled and the obtained product was collected and recrystallized from the suitable solvent.

*4-(4-Chlorobenzylidene)-1-(4-nitrophenylcarbonyl)-2-thioxo-5-oxo-2,3,4,5-tetrahydro -1H-imidazole; **8a.***

Greenish grey crystals; recrystallized from EtOH; m.p. 205-207; yield 90%. **IR** (KBr, cm^{-1}): 3363, 3305 (NH); 3075 (CH-Ar); 2939 (CH–aliph.); 1712, 1650 (two C=O); 1589, 1353 (NO_2); 1450, 1261, 1172, 1022 (I, II, III, IV bands of N–C=S). **Anal form**: $C_{17}H_{10}ClN_3O_4S$ **Calcd**. (%): C, 52.65; H, 2.60; N, 10.84. **Found** (%): C, 52.66; H, 2.58; N, 10.91.

*1-(4-Bromophenylcarbonyl)-4-(4-chlorobenzylidene)-2-thioxo-5-oxo-2,3,4,5-tetrahydro-1H-imidazole; **8b***

Yellow powder; recrystallized from ethyl acetate; m.p. 235-237°C; yield 76%. **IR** (KBr, cm^{-1}): 3433, 3363 (NH); 3136 (CH-Ar); 2927 (CH–aliph.); 1712 (C=O); 1647 (C=N); 1589, 1261, 1190, 1099 (I, II, III, IV bands of N–C=S). **Anal form**: $C_{17}H_{10}ClBrN_2O_2S$ **Calcd**. (%): C, 48.42; H, 2.39; N, 6.64. **Found** (%): C, 48.47; H, 2.41; N, 6.71.

*8-Chloro-2-(4-chlorobenzylidene)-2H-benzo[e]imidazo[2,1-b][1,3]thiazine-3,5-dione; **9a***

Yellowish orange crystals; recrystallized from EtOH; m.p. 234-235°C; yield 85%**. IR** (KBr, cm^{-1}): 3126, 3048 (CH-Ar), 1712, 1652 (two C=O); 1590 (C=N). **MS:** m/z (%): 376(M+2, 8.47); 374(M^+, 1.83); 360(5.06); 325(7.2); 323(5.47); 307(5.72) 295(7.83) 294(12.08); 271(8.23); 266(7.83); 264(6.92); 244(5.76); 241(6.61); 217(5.73); 215(6.87); 201(10.92); 187(10.89); 177(10.77); 171(8.55); 159(7.17); 158(11.41); 152(12.65); 151(14.74); 140(15.32); 137(5.92); 131(9.84); 123(6.6); 122(8.59); 114(7.34); 113(6.41); 92(18.23); 91(17.03); 79(8.85); 77(98.86); 76 (25.28); 75(23); 74(32.87); 73(32.64); 65(44.77); 63(55.53); 62(61.34); 61(34.09); 55(34.08); 54(25.1); 52(56.58); 51(44.8); 50(100); 49(85.63). **Anal. form**: $C_{17}H_8Cl_2N_2O_2S$ **Calcd.**: C, 54.42; H, 2.15. **Found** (%): C, 54.62; H, 2.11.

*8-Chloro-2-(4-methoxybenzylidene)-2H-benzo[e]imidazo[2,1-b][1,3]thiazine-3,5-dione; **9b***

Yellowish brown powder; recrystallized from acetone; m.p. 155-157°C; yield 56%. **IR** (KBr, cm^{-1}): 3010 (CH-Ar.); 1693 (C=O); 1589 (C=N); 1257, 1045 (C–O–C). **MS**: m/z (%): 370(M^+, 6.01); 327(4.77); 192(5.44); 191(4.69); 177(4.67); 176(18.03); 175(12.24); 174(28.18); 173(42.29); 147(4.22); 145(4.83); 138(5.21); 135(5.44); 133(5.67); 132(6.87); 111(4.79); 110(8.4); 100(5.45); 98(9.18); 96(5.69); 85(8.43); 83(11.18); 78(5.33); 76(8.69); 75(14.12); 74(17); 73(27.56); 72(20.05); 66(8.04); 65(21.37); 64(19.06); 63(34.65); 62(66.16); 61(20.55); 55(40.87); 54(37.25); 52(100); 51(98.24). **Anal. form :** $C_{18}H_{11}ClN_2O_3S$ **Calcd.** (%): C, 58.30; H, 2.99; N, 7.55 **Found** (%)**:** C, 58.32; H, 3.04; N, 7.63.

*Synthesis of 4-(4-substitutedbenzylidene)-2-ethylthio-1H-imidazol-5(4H)–ones **10a,b**:*

A solution of compound **2a,b** (10 mmol) in absolute ethanol (50 mL) confining sodium ethoxide [prepared from 0.23 g, 10 mmol atom sodium] were treated with ethyl iodide (1.56 g, 0.8 mL, 10 mmol). The reaction mixture was stirred for 3h. and left overnight at room temperature, the solid obtained was filtered off, washed with water and recrystallized from EtOH to give the target compounds.

*4-(4-Chlorobenzylidene)-2-ethylthio-1H-imidazol-5(4H)–one; **10a***

Yellow crystals; recrystallized from EtOH; m.p. 218-220°C; yield 85%. **IR:** (KBr, cm^{-1}): 3131 (NH); 3050 (CH-Ar); 2882, 2820 (CH-aliph.); 1711 (C=O); 1643 (C=N). **^{1}H-NMR** (DMSO-d_6-δppm): 1.37 (t, 3H, J=7.2Hz, SCH_2CH_3); 3.22 (q, 2H, J=7.2Hz, SCH_2CH_3); 6.61 (s, 1H, =CH); 7.44 (d, 2H, J= 8.5Hz, 4-Cl–C_6H_4–$C_{2,6}$-H); 8.12 (d, 2H, J= 8.5Hz, 4-Cl–C_6H_4–$C_{3,5}$–H); 11.81 (s, 1H, imidazole NH, D_2O exchangeable). **Anal. Form:** $C_{12}H_{11}ClN_2OS$ **Calcd.** (%): C, 54.03; H, 4.16; N, 10.50. **Found** (%): C, 54.09; H, 4.15 ; N, 10.61 .

*2-Ethylthio-4-(4-methoxy benzylidene)-1H-imidazol-5(4H)-one; **10b***

Yellow crystals; recrystallized from EtOH; m.p. 163-165°C [44]; yield 93%. **IR:** (KBr, cm^{-1}): 3303, 3143 (NH); 3068 (CH-Ar); 2907,2802 (CH-aliph.); 1700 (C=O); 1605 (C=N) ; 1256,1031 (C–O–C) .

*General procedure for the synthesis of compounds **11a,b** & **12a,b**:*

Compound **2a,b** (5 mmol) was dissolved in 10 mL 8.5% Na ethoxide, this solution was added to (2.25 g, 1.88 mL, 30 mmol) of chloroacetonitrile or (4.59 g, 2.284 mL, 30 mmol) methyl bromoacetate and refluxed for 12h. The reaction mixture was then poured onto crushed ice to yield crystalline precipitate

which was filtered off, washed with a large amount of water and recrystalized from the appropriate solvent.

3-Amino-6-(4-chlorobenzylidene)imidazo[2,1-b]thiazol-5(6H)-one; ***11a.***

Yellowish grey powder; recrystallized from EtOH; m.p. 232-234°C; yield 80%. **IR**(KBr, cm^{-1}): 3224 (NH_2); 1724 (C=O); 1646 (C=N); 1589 (C=C). **^{1}H-NMR** (DMSO-d_6-δppm): 6.40 (s, 1H, thiazole-CH); 6.87 (s,1H, =CH); 7.63 (d, 2H, J = 8.5 Hz, 4-Cl–C_6H_4–$C_{2,6}$–H); 7.76 (d, 2H, J=8.5 Hz, 4-Cl-C_6H_4–$C_{3,5}$–H); 10.61 (s, 2H, NH_2, D_2O exchangeable). **Anal.form**: $C_{12}H_8ClN_3OS$ **Calcd**. (%): C, 51.90; H, 2.90; N, 15.13**.** **Found**(%): C,51.88; H, 2.93; N, 15.21.

3-Amino-6-(4-methoxybenzylidene)imidazo[2,1-b]thiazol-5(6H)-one; ***11b.***

Orange powder; recrystallized from ethyl acetate; m.p. 205-207°C; yield 70%. **IR**(KBr, cm^{-1}): 3130 (NH_2); 3064 (CH-Ar); 1697 (C=O); 1595 (C=N); 1516 (C=C); 1260, 1030 (C–O–C)**. MS**: m/z (%): 273(M^+,7.19); 271(6.51); 257(6.11); 242(8.28); 239(12.21); 229(8.96); 228(8.14); 219(8.41); 215(7.46); 213(6.24); 211(7.19); 208(7.33); 207(6.51); 205(6.24); 204(8.41); 194(6.65); 191(7.33); 190(9.36); 188(7.46); 186(9.77); 180(6.11); 178(8.41); 176(13.57); 173(18.32); 172(16.55); 171(11.94); 149(13.16); 137(10.72); 133(15.2); 131(30.94); 130(26.32); 117(26.32); 116(21.3); 104(16.01); 101(18.32); 87(28.9); 78(30.12); 76(28.49); 72(45.05); 64(24.05); 62(45.86); 61(54.14); 56(69.47); 55(73.54); 53(100). **Anal.form:** $C_{13}H_{11}N_3O_2S$ **Calcd.** (%)**:** C, 57.13; H, 4.06; N, 15.37 **Found**(%): C, 57.17; H, 4.11; N, 15.42.

6-(4-Chlorobenzylidene)imidazo[2,1-b]thiazole-3,5-(2H, 6H)-dione; ***12a.***

Yellowish white powder; recrystallized from EtOH; m.p. 129-130°C [45]; yield 92%. **IR** (KBr, cm^{-1}): 3055 (CH-Ar); 2986, 2940 (CH-aliph.); 1742 (two C=O); 1640 (C=N). **^{1}H-NMR** (DMSO-d_6-δppm): 4.49 (s, 2H, thiazole–CH_2); 6.96 (s, 1H, =CH); 7.48 (d, 2H, J=8.8Hz, 4-Cl-C_6H_4–$C_{2,6}$–H); 8.19 (d, 2H, J = 8.8Hz, 4-Cl-C_6H_4–$C_{3,5}$–H)**.** **Anal. Form:** $C_{12}H_7ClN_2O_2S$ **Calcd.** (%): C, 51.71; H, 2.53; N, 10.05 **Found** (%). C, 51.73; H, 2.57; N, 10.18.

6-(4-Methoxybenzylidene)imidazo[2,1-b]thiazole-3,5(2H, 6H)-dione; ***12b.***

Yellow crystals; recrystallized from EtOH; m.p. 116-118°C; yield 80%. **IR** (KBr, cm^{-1}): 3078 (CH-Ar); 2981, 2927 (CH-aliph.); 1735 (C=O); 1693 (C=N); 1242, 1029 (C–O–C). **MS**: m/z (%): 274(M^+,0.05); 273(0.02); 260(0.02); 258(0.01); 243(0.02); 239(0.03); 227(0.05); 225(0.02); 213(0.02); 211(0.02); 205(0.04); 200(0.05); 195(0.02); 192(0.13); 182(0.03); 180(0.05); 171(0.01); 167(0.11); 156(100); 147(2.09); 146(1.7); 145(0.38); 140(0.13); 116(3.38); 105(0.9); 103(12.15); 93(0.8); 89(67.79); 86(1.88); 78(3.08); 76(1.77); 64(11.8); 59(13.54); 55(4.11). **Anal. form**: $C_{13}H_{10}N_2O_3S$ **Calcd.**(%): C, 56.92; H, 3.67; N, 10.21. **Found** (%): C, 57.01; H, 3.72; N, 10.29.

General procedure for the synthesis of compounds ***14a,b*** *&* ***15a,b****:*

Equimolar amounts of compound **10a,b** (5 mmol) and compound **13** [40] (0.99 g, 5 mmol) were refluxed in glacial acetic acid (6 mL) for 12h. The reaction mixture was allowed to cool and the obtained precipitate was filtered off to yield compounds **14a,b.** While the filtrate was poured onto crushed ice, filtered, washed with water to give compounds **15 a,b.**

2-(4-Chlorobenzylidene)-6,7-dimethylthieno[3',2':4,5]pyrimido[1,2-a]imidazole-3,5(2H, 9H)-dione*;* ***14a.***

Orange powder; recrystallized from EtOH; m.p.>300°C; yield 35%. **IR**(KBr, cm^{-1}): 3410, 3208 (NH); 3050 (CH–Ar); 1710 (C=O imidazole); 1662 (C=O thiazine); 1598 (C=N). **MS:** m/z(%): 359(M+2, 20.02); 357($M^{\cdot+}$, 8.3); 344(33.31); 335(33); 324(31.21); 322(36.8); 286(40.94); 247(22.4); 221(19.88); 216(34.46); 209(26.92); 179(20.82); 166(30.91); 160(26.04); 154(22.02); 153(33.18); 152(21.54); 151(21.71); 150(36.45); 148(96.88); 139(63.79); 128(44.88); 118(23.12); 112(52.38); 102(31.57); 100(57.36); 89(25.24); 86(62.82); 83(20.83); 79(28.39); 75(54.13); 74(60.99); 72(43.13); 70(49.97); 59(91.15); 54(72.73); 52(73.41); 49(100%); 48(42.16). **Anal.form**: $C_{17}H_{12}ClN_3O_2S$ **Calcd.** (%):N, 11.74; S, 8.96**.** **Found**(%): N, 11.83; S, 9.04.

6,7-Dimethyl-2-(4-methoxybenzylidene)thieno[3',2':4,5] pyrimido[1,2-a]imidazole-3,5(2H, 9H)-dione*;* ***14b.***

Yellowish brown powder; recrystallized form EtOH; m.p.> 300°C; yield 33%**. IR** (KBr, cm^{-1}): 3375, 3298 (NH); 3080 (CH–Ar); 2947 (CH–aliph.); 1666(C=O); 1593 (C=N); 1249, 1022 (C–O–C). **Anal.form**: $C_{18}H_{15}N_3O_3S$ **Calcd.**(%): N, 11.89; S, 9.07. **Found** (%): N, 12.04; S, 9.14.

3-(4-Chlorobenzylidene)-6,7-dimethylthieno[3',2':4,5]pyrimido [1,2-a] imidazole-2,5(3H, 9H)-dione*;* ***15a***

Greyish brown powder; recrystallized from EtOH; m.p. 278-280°C; yield 45%**.** **IR**(KBr, cm^{-1}): 3220 (NH); 3100 (CH–Ar); 2974 (CH-aliph.); 1720 (C=O imidazole); 1656 (C=O thiazine); 1560 (C=N). **MS:** m/z(%): 359(M+2, 6.7); 357($M^{\cdot+}$, 9.72); 344(9.29); 328(8.42); 321(5.18); 319(5.83); 304(9.07); 301(2.81); 299(5.4); 275(4.75); 273(4.1); 272(3.89); 270(4.75); 263(5.83); 261(2.81); 257(5.18); 255(3.02); 247(5.62); 245(5.62); 242(7.34); 240(6.7); 237(8.64); 236(5.62); 235(7.99);

230(10.37); 222(10.58); 218(3.46); 216(4.1); 204(9.5); 198(3.67); 197(13.39); 196(9.29); 193(8.42); 189(4.75); 187(4.32); 180(6.91); 176(3.46); 174(9.72); 169(10.8); 153(12.31); 144(5.62); 130(8.42); 127(11.88); 121(5.18); 115(15.77); 112(6.48); 110(7.34); 101(10.8); 90(11.02); 84(12.74); 77(4.97); 76(13.17); 75(12.1); 72(12.53); 70(19.22); 67(17.93); 63(20.73); 60(22.46); 59(100); 58(80.99); 57(37.37); 53(23.97); 50(29.59).**Anal.Form:** $C_{17}H_{12}ClN_3O_2S$ **Calcd**.(%): C, 57.06; H, 3.36; N, 11.74; S, 8.96. **Found**(%): C,57.11; H, 3.42; N, 11.81; S, 9.04.

6,7-Dimethyl-3-(4-methoxybenzylidene)thieno[3',2':4,5]pyrimido[1,2-a]imidazole-2,5(3H, 9H)-dione*; **15b.***

Pale brownish powder; recrystallized from EtOH; m.p. 268-270°C; yield 47%**. IR**(KBr, cm^{-1}): 3380, 3213 (NH); 3082 (CH–Ar); 2931 (CH–aliph.); 1710, 1658 (C=O); 1596 (C=N); 1245, 1014 (C–O–C)*.* **^{1}H-NMR** (DMSO-d_6–δppm): 2.28 (s, 3H, thienyl - C_3–H); 2.32 (s, 3H, thienyl–C_2–H); 3.82 (s, 1H, OCH_3); 4.98 (s, 1H, NH_2, D_2O exchangeable); 6.72 (s, 1H, =CH); 7.73 (d, 2H, J= 8.7Hz, 4–OCH_3–C_6H_4–$C_{3,5}$–H); 8.15 (d, 2H, J=8.7Hz, 4-OCH_3–C_6H_4–$C_{2,6}$–H). **Anal.form**: $C_{18}H_{15}N_3O_3S$ **Calcd.**(%): C, 61.18; H, 4.28; N, 11.89; S, 9.05. **Found** (%): C, 61.24; H, 4.23; N, 12.02; S, 9.12.

*Synthesis of 5-amino-8,10-diphenyl-2-(4-substitutedbenzylidene)pyrido[3',2':4,5] thieno[3,2-d]imidazo[1,2-a]pyrimidin-3(2H)–ones; **17 a,b***

An equimolar mixture of compound **10 a,b** (5 mmol) and compound **16** (1.63 g , 5 mmol) [41] was fused at 190°C for 6h. The formed precipitate was triturated with EtOH to yield compounds **17a,b** .

*5-Amino-2-(4-chlorobenzylidene)-8,10-diphenylpyrido[3',2':4,5]thieno[3,2-d] imidazo[1,2-a]pyrimidin-3(2H)–one ; **17a***

Black crystals; recrystallized from dioxane; m.p. 280-282°C; yield 60%. **IR**(KBr, cm^{-1}): 3359, 3301 (NH_2); 3070 (CH–Ar); 2927, 2858 (CH-aliph.); 1710 (C=O) ; 1608 (C=N)**. ^{1}H-NMR**(DMSO-d_6-δppm): 7.38 (s, 1H, =CH); 7.41 (s, 1H, pyridine-C_3-H); 7.56-7.72 (m, 10H, two C_6H_5-H); 7.76-7.80 (m, 2H, 4-Cl-C_6H_4–$C_{2,6}$–H); 8.14 (s, 2H, NH_2, D_2O exchangeable); 8.36-8.42 (m, 2H, 4-Cl- C_6H_4–$C_{3,5}$-H). **Anal. form**: $C_{30}H_{18}ClN_5OS$ **Calcd.** (%): C, 67.73; H, 3.41; N, 13.16; S, 6.03. **Found** (%): C, 67.75; H, 3.45; N, 13.27; S, 6.09.

*5-Amino-8,10-diphenyl-2-(4-methoxybenzylidene)pyrido[3',2':4,5]thieno[3,2-d] imidazo[1,2-a]pyrimidin-3(2H)–one ; **17b.***

Black crystals; recrystallized from dioxane; m.p. 265-267°C; yield 54%. **IR**(KBr, cm^{-1}): 3417, 3209 (NH_2); 2900 (CH–aliph.); 1712 (C=O); 1643, 1616 (C=N); 1245, 1041 (C-O-C). **^{1}H-NMR** (DMSO-d_6-δppm): 3.79 (s, 3H, OCH_3); 6.78 (s, 1H, =CH); 6.93 (d, 2H, J=8.4 Hz, 4-OCH_3- C_6H_4 – $C_{3,5}$ – H); 7.02-7.14 (m, 4H, two C_6H_4- $C_{3,5}$-H); 7.57-7.70 (m, 2H, two C_6H_4- C_4-H); 7.75-7.87 (m, 4H, two C_6H_4-$C_{2,6}$-H); 7.88 (s, 1H, pyridine-C_3-H); 8.14 (s, 2H, NH_2, D_2O exchangeable); 8.38 (d, 2H, J=8.4Hz, 4-OCH_3-C_6H_4 - $C_{2,6}$-H). **Anal. form**: $C_{31}H_{21}N_5O_2S$ **Calcd.** (%): C, 70.57; H, 4.01; N, 13.27; S, 6.08. **Found** (%): C, 70.61; H, 4.03; N, 13.35; S, 6.13.

*Synthesis of 1-[6-(4-substitutedbenzylidene)-5,6-dihydro-5-oxoimidazo[2,1-b] [1,3]thiazol-3-yl]-3-phenylthioureas; **18a,b**:*

1 mmol of compound **12a,b** was refluxed with phenyl isothiocyanate (0.14 g, 0.12 mL,1 mmol) in dry benzene (10 mL) for 12h. The reaction mixture was allowed to cool and the obtained product was collected, filtered off and recrystallized from the appropriate solvent.

*1-[6-(4-Chlorobenzylidene)-5,6-dihydro-5-oxoimidazo[2,1-b][1,3]thiazol-3-yl]-3-phenylthiourea; **18a.***

Brown powder; recrystallized from EtOH; m.p. 250-251°C; yield 75%. **IR** (KBr, cm^{-1}): 3467, 3236 (Two NH); 3050 (CH–Ar); 2854 (CH-aliph.); 1732 (C=O); 1647 (C=N); 1590, 1253, 1180, 1014 (I, II, III, IV bands of N–C=S). **MS:** m/z(%): 414(M+2, 1.25); 412(M^+, 1.1); 402(1.58); 400(1.29); 383(1.05); 381(1.25); 377(1.25); 375(2.06); 370(2.2); 341(1.63); 339(2.25); 260(2.3); 258(2.68); 215(4.07); 213(3.93); 175(4.98); 161(4.12); 160(6.61); 159(4.17); 152(15.09); 146(5.6); 136(5.41); 131(5.94); 116(10.2); 103(14.46); 101(1.15); 88(14.37); 80(11.06); 78(10.87); 62(26.68); 60(100); 59(35.97). **Anal form**: $C_{19}H_{13}ClN_4OS_2$ **Calcd**. (%): C, 55.27; H, 3.17; N, 13.57, S, 15.53. **Found** (%): C, 55.32; H, 3.19; N, 13.68; S, 15.59.

*1-[6-(4-Methoxybenzylidene)-5,6-dihydro-5-oxoimidazo[2,1-b]thiazol-3-yl]-3-phenyl-thiourea; **18b.***

Brown crystals; recrystalized from ethyl acetate; m.p. 249-251°C; yield 77%. **IR** (KBr, cm^{-1}): 3273, 3193 (NH); 3118 (CH-Ar), 2839 (CH-aliph.); 1719 (C=O); 1649 (C=N); 1597, 1258, 1096, 1027 (I,II,III,IV bands of N–C=S and C–O–C). **^{1}H-NMR** (DMSO-d_6-δppm): 3.86 (s, 3H, OCH_3); 6.70 (s, 1H, =CH); 6.90-7.02 (m, 2H, C_6H_5- $C_{3,5}$–H); 7.30 (t, 1H, J = 7.8Hz, C_6H_4–C_4–H); 7.45 (s, 1H, CH-thiazole); 7.55 (d, 2H, J = 7.8Hz, C_6H_4–$C_{2,6}$-H); 7.74 (d, 2H, J= 9.3Hz , 4-OCH_3-C_6H_4–$C_{3,5}$–H); 7.83 (d, 2H, J= 9.3 Hz, 4-OCH_3–C_6H_4–$C_{2,6}$-H); 10.57 (s, 2H, two NH, D_2O exchangeable). **Anal form**: $C_{20}H_{16}N_4O_2S_2$ **Calcd.** (%): C, 58.80; H, 3.95; N, 13.72; S, 15.68. **Found** (%): C, 58.81; H, 3.98; N, 13.79; S, 15.72.

*Synthesis of 6-(4-substitutedbenzylidene)3-(3,4-diphenylthiazol-2-(3H) ylideneamino) imidazo[2,1-b][1,3]thiazol-5(6H)-ones; **19a,b**:*

An equimolar mixture of compound **18a,b** (10 mmol) and phenacylbromide (1.99 g, 10 mmol.) in absolute EtOH (20 mL) and catalytic amount of triethylamine (1 mL) were refluxed for 6h. The reaction mixture was allowed to cool and the solid separated after neutralization with 10% HCl was recrystallized from acetone.

6-(4-Chlorobenzylidene)3-(3,4-diphenylthiazol-2-(3H)ylideneamino)imidazo[2,1-b] [1,3]thiazol-5(6H)-one; ***19a***

Brownish orange powder; recrystallized from acetone; m.p. 117-119°C; yield 50%**. IR**(KBr, cm^{-1}): 2820 (CH–aliph.); 1731 (C=O); 1639 (C=N). **MS**: m/z(%): 514(M+2, 0.01); 512(M^{+}, 0.01); 503(0.02); 500(0.23); 487(0.02); 485(0.03); 476(0.02); 474(0.09); 469(0.03); 467(0.02); 455(0.02); 452(0.09); 446(0.05); 439(0.17); 429(0.07); 427(0.08); 415(0.04); 413(0.12); 395(1.05); 369(6.88); 340(1.91); 313(0.62); 279(0.91); 263(2.89); 248(2.52); 238(11.11); 222(37.76); 207(1.01); 191(1.33); 167(2.21); 154(6.31); 152(17.07); 117(5.58); 105(19.22); 86(100). **Anal form:** $C_{27}H_{17}N_4OS_2$ **Calcd.** (%): N, 10.92; S, 12.50. **Found** (%): N, 11.09; S, 12.62.

6-(4-Methoxybenzylidene)-3-(3,4-diphenylthiazol-2(3H)-ylideneamino)imidazo[2,1-b] [1,3]thiazol-5(6H)-one; ***19b.***

Brownish red powder; recrystallized from acetone; m.p. 103-105°C; yield 55%. **IR**(KBr, cm^{-1}): 3090 (CH–Ar); 2923, 2852 (CH-aliph.); 1704 (C=O); 1643, 1596 (C=N); 1249, 1018 (C-O-C). **^{1}H-NMR** (DMSO-d_6–δppm): 3.61 (s, 3H, OCH_3); 5.15 (s, 1H, =CH); 7.49 (s, 1H, thiazole–C_5-H); 7.52 (s, 1H, imidazothiazole-C_2–H); 7.63 (d, 2H, J=7.6 Hz, 4-OCH_3-C_6H_4–$C_{3,5}$-H,); 7.67-7.74 (m, 10H, two C_6H_5); 8.05 (d, 2H, J=7.6 Hz, 4-OCH_3-C_6H_4–$C_{2,6}$–H**). Anal. form:** $C_{28}H_{20}N_4O_2S_2$ **Calcd.**(%): C, 66.12; H, 3.96; N, 11.02; S, 12.61. **Found**(%): C, 66.09; H, 3.98; N, 11.09; S, 12.64.

Synthesis of 6-(4-substitutedbenzylidene)-3-(4-oxo-3-phenylthiazolidin-2-ylidene amino)imidazo[2,1-b][1,3]thiazol-5(6H)-one; ***20a,b.***

A mixture of compound **18a,b** (5 mmol), chloroacetic acid (0.47 g, 5 mmol) and sodium acetate (0.25 g, 3 mmol) was refluxed in glacial acetic acid (20 mL) for 6h. The reaction mixture was then cooled, and poured on crushed ice. The yellow coloured solid separated was filtered; dried and recrystallized from the suitable solvent.

6-(4-Chlorobenzylidene)-3-(4-oxo-3-phenylthiazolidin-2-ylideneamino)imidazo[2,1-b][1,3]thiazol-5(6H)-one; ***20a.***

Yellowish powder; recrystallized from ethyl acetate ; m.p.>300°C; yield 70%. **IR**(KBr, cm^{-1}): 3078 (CH-Ar); 2920 (CH-aliph.); 1710 (C=O); 1608 (C=N). **Anal. form**: $C_{21}H_{13}N_4O_2S_2$ **Calcd**. (%): C, 55.69; H, 2.89; N, 12.37; S, 14.16 **Found** (%): C, 55.73; H, 2.93; N, 12.45; S, 14.21.

6-(4-Methoxybenzylidene)-3-(4-oxo-3-phenylthiazolidin-2-ylideneamino)imidazo [2,1-b][1,3]thiazol-5(6H)-one; ***20b.***

Pale yellowish powder; recrystallized from EtOH; m.p. 199-201°C; yield 70%. **IR** (KBr, cm^{-1}): 3025 (CH-Ar); 1700 (C=O); 1601 (C=N); 1251, 1074 (C-O-C). **^{1}H-NMR** (DMSO-d_6-δppm): 3.77 (s, 3H, OCH_3); 5.07 (s, 2H, S-CH_2); 7.67-7.69 (m, 10H, Ar-H & = CH); 9.38 (s, 1H, CH-thiazole). **MS:** m/z(%): 435(M- CH_3,1.52); 309(2.07); 290(2.2); 289(3.54); 280(3.54); 278(3.57); 276(3.14); 268(3.62); 267(3.11); 262(6.78); 249(4.43); 236(6.6); 219(4.09); 204(4.02); 197(6.07);185(3.65); 178(6.32); 174(5.81); 167(5.86); 159(3.77); 157(6.83); 152(5.89); 151(9.72); 150(15.69); 149(10.77); 141(9.84); 137(9.99); 136(10.86); 135(11.6); 125(9.16); 122(13.19); 109(18.43); 105(40.84); 97(10.77); 95(14.27); 91(16.35); 83(37.14); 81(52.34); 79(42.42); 76(42.52); 69(39.63); 68(32.92); 57(98.57); 55(100); 50(35.07). **Anal form**: $C_{22}H_{16}N_4O_3S_2$ **Calcd.** (%): N, 12.49; S, 14.30 **Found** (%): N, 12.63; S, 14.19.

Synthesis of 2-[4-(4-chlorobenzylidene)-4,5-dihydro-5-oxo-1H-imidazol-2-yl thio]acetohydrazide; ***21.***

Compound **12a** (2.78 g, 10 mmol) was refluxed in absolute EtOH (20 mL) in presence of hydrazine hydrate 99% (0.32 g, 0.31 mL, 10 mmol) for 6 h. The reaction mixture was cooled and the solid precipitate obtained was collected, dried and recrystallized from THF.

Yellow crystals; m.p.> 300°C; yield 65%. **IR**(KBr,cm^{-1}): 3300, 3186 (NH_2,NH); 3000 (CH-Ar); 2920 (CH-aliph.); 1700, 1671 (two C=O); 1500 (C=N). **^{1}H-NMR** (DMSO-d_6–δppm): 4.20 (s, 2H,S–CH_2-CO); 6.25 (s, 1H, =CH); 7.43 (d, 2H, J = 8.8Hz ,4–Cl–C_6H_4–$C_{2,6}$-H,); 7.63 (d, 2H, J=8.8Hz, 4–Cl-C_6H_4–$C_{3,5}$–H); 7.68 (s, 2H, NH_2, D_2O exchangeable); 7.70 (s, 1H, NH-NH_2, D_2O exchangeable); 10.44 (s, 1H, imidazole-NH; D_2O exchangeable). **Anal. Form:** $C_{12}H_{11}ClN_4O_2S$ **Calcd.** (%): C, 46.38; H, 3.57; N, 18.03. **Found** (%): C, 46.42; H, 3.59; N, 18.14.

Synthesis of 1-[2-(4-(4-Chlorobenzylidene)-4,5-dihydro-5-oxo-1H-imidazol-2-yl)thioacetyl]-4-phenylthiosemicarbazide; ***22.***

Compound **21** (3.1 g, 10 mmol) in pyridine (10 mL) was added to (1.35 g, 1.2 mL, 10 mmol) of phenyl isothiocyanate and heated under reflux for 8h. The resulted solution was allowed to cool at room temperature and light yellow crystals were collected, filtered off and recrystallized from EtOH.

Yellow crystals; m.p. 54-56°C; yield 95%. **IR**(KBr, cm^{-1}): 3210, 3119 (NH); 3045 (CH–Ar); 2988 (CH-aliph.); 1720,1692 (two C=O); 1593, 1203, 1097, 1033 (I, II, III, IV bands of N-C=S);

1544 (C=N). **^{1}H-NMR** (DMSO-d_6-δppm): 4.50 (s, 2H, S-CH_2); 6.14 (s, 1H, =CH); 7.30-7.35 (m, 8H, 3NH & C_6H_5); 7.40-7.80 (m, 4H, 4-Cl-C_6H_4); 11.02 (s, 1H, imidazole-NH, D_2O exchangeable). **Anal.form:** $C_{19}H_{16}ClN_5O_2S_2$ **Calcd**.(%): C, 51.17; H, 3.62; N, 15.70; S, 14.38. **Found.** (%): C, 51.22; H, 3.65; N, 15.79; S, 14.42.

Synthesis of 2-[4-(4-chlorobenzylidene)-4,5-dihydro-5-oxo-1H-imidazol-2-yl thio]-N-(4-oxo-3-phenylthiazolidin-2-ylidene)acetohydrazide; ***23.***

To a solution of compound **22** (4.45 g, 10 mmol) in EtOH (20 mL), an equimolar amount of ethyl bromoacetate (1.67 g, 1.1 mL, 10 mmol) was added and the reaction was refluxed for 8h. The reaction mixture was then cooled, poured onto crushed ice and the resulted precipitate was filtered, dried and recrystallized from acetone.

Pale yellow crystals; m.p. 142-144°C; yield 80%. **IR**(KBr, cm^1): 3282 (NH); 3020 (CH–Ar.); 2927 (CH–aliph.); 1712, 1658 (C=O); 1600 (C=N). **^{1}H-NMR**(DMSO-d_6-δppm): 2.08 (s, 2H, S-CH_2-CO); 3.70 (s, 2H, thiazolidine-CH_2); 7.03 (s, 1H, =CH); 7.06-7.08 (m, 5H, C_6H_5); 7.28 (d, 2H , J= 8.1Hz, 4–Cl–C_6H_4–$C_{2,6}$–H); 7.32 (s, 1H, NH, N-NH-CO, D_2O exchangeable); 7.44 (d, 2H, J = 8.1Hz, 4-Cl-C_6H_4-$C_{3,5}$–H); 10.42 (s, 1H, imidazole NH, D_2O exchangeable). **Anal.form:** $C_{21}H_{16}ClN_5O_3S_2$ **Calcd.**:(%): N, 14.41; S, 13.20. **Found**(%):N, 14.49; S, 13.26**.**

Synthesis of 2,6-bis (4-chlorobenzylidene)imidazo[2,1-b][1,3]thiazole–3,5-(2H, 6H)dione; ***24***

An equimolar mixture of compound **12a** (2.78 g, 10 mmol) and 4-chlorobenzaldehyde (1.4 g, 10 mmol) in glacial acetic acid (10 mL) was refluxed for 8 h. in presence of anhydrous sodium acetate (1.64 g, 20 mmol). The reaction mixture was allowed to cool and solid precipitate was filtered, dried and recrystallized from EtOH.

Brown powder; m.p. 220-222°C; yield 80%. **IR**(KBr, cm^{-1}): 3074 (CH–Ar.); 2927 (CH–aliph.); 1650 (C=O); 1566 (C=N). **MS:** m/z: 402(M+2,0.8); 400(M^+, 0.29); 392(0.61); 390(0.4); 386(0.36); 384(0.51); 382(0.36); 372(0.29); 370(0.69); 367(0.4); 365(0.58); 359(0.58); 349(0.83); 337(0.87); 325(1.01); 310(2.17); 308(0.98); 303(0.61); 295(0.61); 294(1.16); 289(1.08); 279(0.87); 277(0.9); 268(0.87); 266(0.98); 255(1.23); 250(1.3); 238(1.73); 195(2.1); 183(1.92); 181(2.6); 174(1.63); 172(2.39); 160(5.2); 159(6.11); 155(3.83); 143(4.26); 140(8.85); 133(9.07); 132(14.56); 131(17.28); 130(14.56); 126(11.82); 124(11.42); 118(20.46); 117(24.79); 106(13.05); 104(31.59); 91(5.75); 90(100); 89(90.64); 83(31.88); 80(50.34); 78(83.95); 77(75.82); 75(21.97); 65(46.98); 64(93.86); 60(57.14); 54(52.37). **Anal. form**: $C_{19}H_{10}Cl_2N_2O_2S$ **Calcd**. (%): C, 56.87; H, 2.51; N, 6.98. **Found** (%): C, 57.08; H, 2.49; N, 7.14.

Synthesis of 2-(4-chlorobenzylidene)-5-(4-chlorophenyl)-5,6-dihydro-4aH-imidazo[2',1':2,3][1,3]thiazolo[4,5-c]pyrazol-1(2H)-one*;* ***25***

Compound **24** (4 g, 10 mmol) and hydrazine hydrate (0.64 g, 0.62 mL, 20 mmol) were refluxed in absolute alcohol (20 mL) and in presence of a catalytic amount of glacial acetic acid (2 mL) for 8h. The reaction was cooled then poured onto crushed ice. The product obtained was filtered, washed with water, dried and recrystallized from methanol.

White crystals; m.p. 102-104°C; yield 88%. **IR**(KBr, cm^{-1}): 3421, 3224 (NH); 3050 (CH–Ar); 1660 (C=O); 1612 (C=N)**. MS:** m/z(%): 418(M+4,0.37); 403(0.52); 394(0.65); 365(0.55); 363(0.60); 362(0.49); 352(0.56); 307(0.58); 280(0.66); 279(0.95); 269(0.64); 268(1.64); 257(0.89); 256(1.4); 234(1.08); 226(1.61); 214(2.49); 211(1.24); 207(1.34); 203(1.4); 196(0.85); 195(1.86); 187(2.33); 184(2.33); 183(1.16); 180(1.06); 178(2.22); 177(1.29); 174(1.36); 173(1.84); 171(1.62); 170(3.04); 167(6.3); 154(7.08); 149(23.11); 141(4.31); 140(3.06); 139(6.46); 138(4.88); 136(3.84); 133(3.51); 129(3.94); 128(3.84); 127(10.31); 125(8.37); 123(4.05); 122(4.03); 119(4.99); 118(3.91); 113(7.17); 111(14); 105(6.28); 101(3.08); 97(17.51); 91(6.19); 85(10.67); 83(12.63); 82(36.86); 79(34.32); 76(12.91); 71(52.02); 69(44.53); 67(18.9); 63(12.69); 59(18.99); 58(16.1); 57(100); 54(89.92); 50(31.99); 46(23.34). **Anal. Form**: $C_{19}H_{12}Cl_2N_4OS$ **Calcd.** (%): N, 13.49. **Found**(%): N, 13.61.

Anticancer screening:

Developmental Therapeutic Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), Bethesda, Maryland, USA has adopted an in-vitro model consisting of 60 human tumor cell lines for primary anticancer screening. Nineteen of the newly synthesized compounds were selected by the NCI for screening in a two stage process, beginning with evaluation of all compounds against 60 human tumor cell lines in a one dose (10 μmol) screening panel. The output from the single 60 cell panel screen is reported as a mean graph and is available for analysis by the COMPARE program. Compounds which inhibit growth by more than 50% in a threshold number of cell lines was determined by comparison with historical NCl 60 cell and in-vivo data (COMPARE program), were selected for 5-dose assay [46,47]. However, one compound **11b** of which was selected for 5-dose assay. The one dose screening results of the selected compounds are presented in tables **1-5**.

Table (1): The mean growth percent, delta values and the percent growth inhibition against some subpanel cell lines of the selected compounds of scheme 1.

Comp. No.	NSC-number	Mean growth percent	Delta	Panel	Subpanel cell lines (Growth inhibition percent)
3a	767500	94.70	20.81	Leukemia	MOLT-4(24.11), RPMI-8226 (25.77).
				Non-Small Cell Lung Cancer	HOP-92(26.11), NCI-H522 (19.38).
				Colon Cancer	HCT-116 (13.23).
				CNS Cancer	SNB-19 (11.38), SNB-75(20.95).
				Melanoma	SK-MEL-5(23.83), UACC-62 (13.63).
				Renal Cancer	786-0(14.70), SN12C(10.41),UO-31 (19.71).
				Prostate Cancer	PC-3(22).
				Breast Cancer	MCF7(10.51), MDA-MB-231/ATCC(21.01), BT-549(12.91).
3c	767501	98.82	24.80	Leukemia	MOLT-4(11.93), RPMI-8226 (17.52), SR(22.94).
				Non-Small Cell Lung Cancer	NCI-H522 (25.98).
				CNS Cancer	SNB-75 (23.54).
				Melanoma	LOX IMVI (11.61), UACC-62 (12.56).
				Breast Cancer	MCF7 (10.40).

Table (2): The mean growth percent, delta values and the percent growth inhibition against some subpanel cell lines of the selected compounds of scheme 2.

Comp. No.	NSC-number	Mean growth percent	Delta	Panel	Subpanel cell lines (Growth inhibition percent)
6a	767504	97.97	21.52	Leukemia	K-562(13.58), MOLT-4 (13.54).
				Non-Small Cell Lung Cancer	NCI-H522(23.55)
				Ovarian Cancer	OVCAR-4(10.09).
				Renal Cancer	CAKI-1(20.04), UO-31(13.33).
				Prostate Cancer	PC-3(10.67).
6b	767505	96.25	16.11	Leukemia	CCRF–CEM(17.52), MOLT-4(11.46), RPMI-8226(15.50), SR(19.86).
				Non-Small Cell Lung Cancer	A549/ATCC(11.07), NCI-H522 (18.24).
				Colon Cancer	HCT-15(11.01), HT29(12.34).
				Renal Cancer	786-0(13.13). A498(12.81), CAKI-1 (16.25), TK-10 (11.89), UO-31 (12).
9a	767502	100.51	24.72	Leukemia	HL-60(TB)(10.90). MOLT-4(10.91), SR(24.21)
				Non-Small Cell Lung Cancer	A549/ATCC (13.42), NCI-H522 (21.09)
				Renal Cancer	CAKI-1 (21.48)
9b	767503	98.18	33.16	Leukemia	SR(11.56)
				Non-Small Cell Lung Cancer	HOP-92(17.38), NCI-H226 (17.03), NCI-H522(12.51)
				CNS Cancer	SNB-75(23.25)
				Renal Cancer	CAKI-1(26.17),UO-31 (34.98).
				Prostate Cancer	PC-3 (14.51).

Table (3): The mean growth percent, delta values and the percent growth inhibition against some subpanel cell lines of the selected compounds of scheme 3.

Comp. No.	NSC-number	Mean growth percent	Delta	Panel	Subpanel cell lines (Growth inhibition percent)	Lethality
11a	767512	69.98	83.51	Leukemia	HL-60(TB) (60.08), K-562(59.93), MOLT-4 (91.88), RPMI-8226(60.08)	CCRF-CEM (13.53), SR(2.29)
				Non-Small Cell Lung Cancer	A549/ATCC (25.79), HOP-62(16.50), HOP-92 (30.45), NCI-H226(19.75), NCI-H23(27.41), NCI-H460(37.85), NCI-H522(66 .20)	
				Colon Cancer	HCT-116(33.93), HCT-15(33.25), HT29(37.38), KM12 (10.84), SW-620 (28.70).	
				CNS Cancer	SNB-19(13), SNB-75(12.64).	
				Melanoma	LOX IMVI (49.40), MALME-3M (35.11), M14 (23.22), MDA-MB-435(31.97), SK-MEL-5 (27.38).	
				Ovarian Cancer	IGROV1(20.79), OVCAR-3(28.38), OVCAR-4(15.87), OVCAR-8(27.70), NCI/ADR-RES(23.95), SK-OV-3 (10.68).	

				Renal Cancer	786-0(18.61), A498(34.44), ACHN(11.67), CAKI-1 (61.18), RXF393 (34.31), SN12C(23.15), TK-10(27.20), UO-31(41.79).	
				Prostate Cancer	PC-3(19.37), DU-145(22.09)	
				Breast Cancer	MCF7(32.78), MDA-MB-231/ ATCC(16.82), BT-549(24.68), T-47D(21.04), MDA-MB-468 (35.50).	
11b	767513	14.10	68.60	Leukemia	K-562(94.71).	CCRF-CEM (40.21), HL-60(TB) (39.98). MOLT-4 (15.92), RPMI-8226 (28.76), SR (21.30).
				Non-Small Cell Lung Cancer	A549/ATCC (67.23), HOP-62(59.77), NCI-H226(48.39), NCI-H23(76.38), NCI-H322M(53.36), NCI-H460(82.75).	HOP-92 (8.02), NCI-H522 (54.50).
				Colon Cancer	Colo 205 (87.49), HCC-2998(59.08), HCT-15 (79.26), HT29 (90.88), KM12(53.11), SW-620(78.06).	HCT-116(6.91).
				CNS Cancer	SF-268(62.65), SF-539(73.30), SNB-19(46.23), SNB-75(74.79).	
				Melanoma	M14(75.16), MDA-MB- 435(90.41), SK-MEL-28 (56.26), SK-MEL-5 (95.35), UACC-62 (77.02).	LOXIMVI (47.54), MALME-3M (15.30).
				Ovarian Cancer	IGROV1(90.19), OVCAR-3(75.76), OVCAR-4(78.50), OVCAR-5(40.11), OVCAR-8(64.26), NCI/ADR-RES (57.74), SK-OV-3(54.37).	
				Renal Cancer	786-0(66.83), A498(94.33), ACHN (67.04), SN12C (79.57), TK-10 (80.46).	CAKI-1(32.99), RXF 393 (21.24), UO-31(4.09).
				Prostate Cancer	PC-3(79.38), DU-145 (73.53).	
				Breast Cancer	MCF7(86.60), MDA-MB-231/ ATCC (57.53), HS 578T (49.64), BT-549 (88.25), T-47D (90.25).	MDA-MB-468 (31.93).
12a	767510	99.24	29.66	Leukemia	CCRF-CEM (12.99),HL-60(TB) (24.48), K-562 (14.06), MOLT-4 (18.86), RPMI-8226(15.92), SR(30.42).	
				Non-Small Cell Lung Cancer	HOP-92(14.81), NCI-H522(25.69).	
				Melanoma	MALME-3M (15.06).	
				Renal Cancer	CAKI-1 (12.07), UO-31(11.33).	
12b	767511	98.21	27.44	Leukemia	CCRF-CEM (10.73), HL-60(TB) (27.68), K-562 (14.07), MOLT-4 (20.86), SR(29.23).	
				Non-Small Cell Lung Cancer	HOP-92(13.69), NCI-H522 (24.00)	
				Ovarian Cancer	OVCAR-4 (10.29).	
				Renal Cancer	CAKI-1(14.14), UO-31(21.73).	

Table (4): The mean growth percent, delta values and the percent growth inhibition against some subpanel cell lines of the selected compounds of scheme 4.

Comp. No.	NSC-number	Mean growth percent	Delta	Panel	Subpanel cell lines (Growth inhibition percent)
14a	767507	100.66	18.94	Leukemia	SR(13.45).
				Non-Small Cell Lung Cancer	NCI-H522(11.94).
				CNS Cancer	SNB-75 (10.43).
				Ovarian Cancer	OVCAR-5(18.28).
14b	767508	98.03	17.75	Leukemia	CCRF-CEM(10.13), HL-60 (TB) (10.65), MOLT-4(12.67), SR (19.72).

				Non-Small Cell Lung Cancer	NCI-H522(16.22).
				Ovarian Cancer	OVCAR-4(10.52).
				Renal Cancer	CAKI-1(16.26), UO-31(11.97).
15a	767506	94.31	28.74	Leukemia	CCRF-CEM (25.81), K-562 (11.74), MOLT-4(31.87), SR (32.31).
				Non-Small Cell Lung Cancer	A549/ATCC (15.24), HOP-92(34.43).
				Lung Cancer	NCI-H23(13.07), NCI H522 (25.21).
				Colon Cancer	HCT-15(18.58).
				CNS Cancer	SF-268(15.82), SNB-19(16.13).
				Renal Cancer	786-0(19.59), A498(12.47), RXF 393 (12.19), SN12C (10.11), UO-31(22.81).
				Prostate Cancer	PC-3(16.61).
				Breast Cancer	BT-549(17.72).
15b	767509	89.26	35.31	Leukemia	CCRF-CEM (33.12), HL-60 (TB) (28.19), K-562(18.38), MOLT-4(37.66), RPMI-8226 (17.14), SR (46.05).
				Non-Small Cell Lung Cancer	A549/ATCC(20.30), NCI-H460 (11.68), NCI-H522(25.56).
				Colon Cancer	HCT-15(26.79), HT29(11.85).
				CNS Cancer	SF-268(11.52), SNB-19 (11.60).
				Melanoma	MDA-MB-435(13.17), UACC-62(19.56).
				Ovarian Cancer	OVCAR-4(18.21), OVCAR-8 (22.25), NCI/ADR-RES(20.70).
				Renal Cancer	786-0 (11.87), CAKI-1(25.76), SN12C(15.96), UO-31(27.04).
				Breast Cancer	BT-549(14.86), MDA-MB-468(16.89).
				Breast Cancer	MDA-MB-231/ATCC(11.31).

Table (5): The mean growth percent, delta values and the percent growth inhibition against some subpanel cell lines of the selected compounds of schemes 5 and 6.

Comp. No.	NSC-number	Mean growth percent	Delta	Panel	Subpanel cell lines (Growth inhibition percent)
19a	767514	102.82	23.52	Leukemia	MOLT-4(13.12), SR(14.06).
				Non-Small Cell Lung Cancer	HOP-92(20.37), NCI-H522 (12.76).
				CNS Cancer	SNB-75(10.85).
				Renal Cancer	UO-31(20.70).
				Prostate Cancer	PC-3(10.93).
19b	767515	101.11	23.27	Leukemia	MOLT-4(10.06), SR (13.91).
				Non-Small Cell Lung Cancer	NCI-H522 (12).
				CNS Cancer	SNB-75 (12.03).
				Renal Cancer	UO-31(22.16).
20a	767519	99.74	20.83	Leukemia	HL-60(TB)(20.74), MOLT-4 (17.33), SR(20.71).
				CNS Cancer	SNB-75(15.70).
				Renal Cancer	CAKI-1(19.18), UO-31(21.09).
20b	767520	99.52	18.96	Leukemia	K-562(10.30), MOLT-4(11.22), SR (19.44).
				CNS Cancer	SNB-75 (11.91).
				Renal Cancer	CAKI-1(16.17), UO-31(19.03).
				Breast Cancer	T-47D (11.18).
25	767516	74.10	60.67	Leukemia	CCRF-CEM(85.07), HL-60 (TB) (51.62), K-562(86.57), MOLT-4 (67.30), SR (73.34).
				Non-Small Cell Lung Cancer	A549/ATCC(52.32), HOP-62 (36.16), HOP-92 (17.06), NCI-H23(14.46), NCI-H460 (43.99), NCI-H522(56.20).
				Colon Cancer	COLO 205 (29.44), HCT-116 (52.74), HT29(77.18), KM12(15.93), SW-620(42.23).
				CNS Cancer	SF-268(29.75).
				Melanoma	LOX IMVI(79.38), M14(31.42), MDA-MR-435 (23.41), UACC-62(17.39).
				Ovarian Cancer	IGROV1(58.26), OVCAR-5 (22.16), OVCAR-8(21.24), SK-OV-3(15.90).
				Renal Cancer	786-0(58), A498(26.60), ACHN (13.84), CAKI-1 (22.42), RXF 393(23.55), SN12C (15.14). TK-10(14.28), UO-31(47.88).
				Breast Cancer	MCF7 (23.19), MDA-MB-231 /ATCC(63.62), MDA-MB-468 (10.87).

The imidazothiadiazine analogues **3a** and **3c** showed moderate anticancer activity against some tumor cell lines namely, Leukemia, Non-Small Cell Lung Cancer, Melanoma and CNS cancer. Moreover, compounds containing imidazo[1,3]thiazine ring such as compounds **6a** and **6b** exhibited a slight increase in the growth inhibition activity against all cell lines. While, compounds **9a** and **9b** having benzo[e] imidazo[2,1-b]thiazine backbone showed a significant growth inhibition activity against Leukemia SR, Non-Small Cell Lung Cancer NCI-H522 and Renal Cancer CAKI-1 cell lines.

Furthermore, the one dose screening results as presented in table **(3)** of the 3-aminoimidazo[2,1-b]thiazole derivatives **11a** and **11b** revealed that these compounds exhibited promising growth inhibition activity against most cancer cell lines, even that compound **11b** was selected for further evaluation in the 5-dose screening assay. However, replacement of the chloro function in compound **11a** by methoxy moiety in compound **11b** resulted in enormous increase in the anticancer activity against almost all cell lines as it exerted a high lethal effect against Leukemia CCRF-CEM, HL-60(TB), MOLT-4, RPMI-8226 and SR cell lines by 40.21%, 39.98%, 15.92%, 21.3%, respectively. It also exhibited lethal effects towards Non-Small Cell Lung Cancer HOP-92 (8.02%) and NCI-H522 (54.5%) cell lines as well as Melanoma cell lines LOXIMVI (47.54%) and MALME-3M (15.3%). The cytotoxic effect of compound **11b** has extended also to Colon Cancer HCT-116 (6.91%), Renal Cancer CAKI-1 (32.99%), RXF393 (21.24%), UO-31 (4.09%) and Breast Cancer MDA-MB-468 (31.93%). Moreover, it also showed significant growth inhibition activity against various cell lines such as Leukemia K-562(94.71%), Non-Small Cell Lung Cancer NCI-H23 (76.38%) and NCI-H460 (82.75%), Colon Cancer Colo 205 by 87.49%, HCT-15 by 79.26%, HT 29 by 90.88% and SW-620 by 78.06% as well as Melanoma cell lines M14 (75.16%), MDA-MB-435(90.41%), SK-MEL-5 (95.35%) and UACC-62(77.02%). Furthermore, Ovarian Cancer cell lines were inhibited severely by the target compound showing growth inhibition activity by 90.19% and 78.5% against IGROV1 and OVCAR-4, respectively, Renal Cancer A498 (94.33%), SN12C(79.57%) and TK-10 (80.46%) cell lines. It also exerted potent activity against Breast Cancer MCF-7 (86.6%), BT-549 (88.25%) and T-47D (90.25%) cell lines. Replacement of 3-amino group in compound **11** by the 3-oxo function in compound **12** resulted in severe decrease in anticancer activity against all cell lines. The imidazo [2,1-b] pyrimidine compounds fused to thiophene ring **14a,b & 15a,b** showed moderate inhibitory activity against many cell lines.

The one dose screening results of compounds **19a, 19b, 20a, 20b** and **25** revealed that attachment of thiazole ring to 3-amino group of compound **11** strongly diminished the anticancer activity. Moreover, fusion of a pyrazole ring to the thiazole moiety as in compound **25** resulted in marked increase in the growth inhibitory activity against most of the cell lines especially, Leukemia CCRF-CEM (85.07%), K-562 (86.57%), Colon Cancer HT29 (77.18%) and Melanoma LOX IMVI (79.38%) cell lines as it showed much higher activity than compounds **19a** and **19b** as well as compounds **20a** and **20b** but it is still lower in activity than compound **11a** with free 3-amino thiazole moiety.

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References

1) Shih, R.U., Wu, J., Liu, Y., Liang, Y. C., Lin, S. Y., Sheu, M. T., Lee, W. S., 2004.. Biochem.Pharmacol. 67, 67-75.
2) Takashi, A., Matsuoka, H., Yamada, K., Uda, Y., 2005. Food Chem. Toxicol. 43, 521-528.
3) Al-Obaid, A. A., El-Subagh, H. I., Khodair, A. I. , Elmazar, M. M., 1996. Anticancer Drugs. 7, 873-880.
4) Chui, W. K., Wong, T. H. ,Thenomozhiyal, J. C. 2004.J. Med. Chem. 47, 1527-1535.
5) Poitout, L., Thurieau, C., Brault, V. 2001 Chem. Abstr. 134, 163050.
6) Szymanska, E., Kiec-Kononowicz, K., Bialecka, A. , Kasprowicz, A., 2002. Il Farmaco. 57, 39-44.
7) Gulati, D., Chauhan, P. M. S., Pratap, R., Bhakuni, D. S. 1994. Ind. J. Chem., 33B, 10-16.
8) Havera, H. J., Strycker, W. G. 1977. U.S. Patent 3994904: Chem. Abstr. 86, 106586m.
9) Tompkin, J. E. 1986. J. Med. Chem. 29, 855-859.
10) Gadwood, R. C., Kamdar, B. V., Dubray, L. A. C., Wolfe, M. L., Smith, M. P., Watt, W., Mizsak, S. A., Groppi, V. E. 1993. J. Med. Chem. 36, 1480-1487.
11) Mizuno, T., Kino, T., Ito, T., Miyata, T. 2000. Synth. Commun. 30, 1675-1688.
12) Mappes, C. J., pommer, E. H., Rentzea, C., Zeeh, B. 1980. U.S. Patent 4198423. 93, 71784.
13) Muccioli, G. C., Fazio, N., Scriba, G. K. E., Poppitz, W., Cannata, F., Poupaert, J. H., Wouters, J., Lambert, D. M. 2006. J. Med. Chem. 49, 417-425.
14) Agasimundin, Y. S., Mumper, M. W., Hasmane, R. S. 1998. Bioorg. Med. Chem. 6, 911-923.
15) Augstein, J., Green, S. M., Monro, A. M., Potter, G. W. H., Worthing, C. R., Wrigley, T. I. 1965. J. Med. Chem. 8, 446-456.
16) Gyemant, G., Kandra, L., Nagy, V., Somsak, L.2003. Biochem. Biophys. Res. Commun. 312, 334-339.

17) Kandra. L., Remenyik, J., Batta, G., Somsak, L., Gyemant, G., Park, K. H. 2005. Carbohydr. Res. 340, 1311-1317.
18) Kuang, R., Epp, J. B., Ruan, S., Chang, L. S., Venkataraman, R., Tu, J., He, S., Truong, T. M., Groutas, W. C. 2000.
19) Bioorg. Med. Chem. 8, 1005-1016. He, S., Kuang, R., Venkataraman, R., Tu, J., Truong, T. M., Chan, H. T., Groutas, W. C. 2000. Bioorg. Med. Chem. 8, 1713-1717.
20) Smalley, R. K. 1996. Six-Membered Rings with Two or More Heteroatoms and Fused Carbocyclic Derivatives. Comprehensive Heterocyclic Chemistry II. Vol.6. Ed. A. J. Boulton, Elsevier, Oxford, UK.
21) Wang, Z., Shi, H., Shi, H. 2001. Synth. Commun. 31, 2841. Wang, Z., You, T., Shi, H., Shi, H. 1996. Molecules. 1, 89.
22) Wang, Z., You, T., Shi, H., Shi, H. 1997. Gaodeng Xuexiao Huaxue Xuebao. 18(4), 550. Chem. Abstr. 1997, 127, 95265t.
23) Shi, H., Shi, H., Wang, Z., Huaxue,Y. 2000., 20 (3), 344. Chem. Abstr. 133, 120280c.
24) Ochoa, C., Perez, E., Perez, R., Suarez, M., Ochoa, E., Rodriguez, H., Barrio, A. G., Muelas, S., Nogal, J. J., Martinez, R. A. 1999. Arzneim. Forsch. 49, 746.
25) Song, Q., Zhang, Zh., Li, Zh., Mi, G., Ding, Y., 1997. Zhongguo Yaowu Huaxue Zazhi. 7, 93. 1999 Chem. Abstr. 130, 25042f. Ilhan, E., Capan, G., Ergenc, N., Uzun, M., Kiraz, M., Kaya, D., 1995. Farmaco. 50, 787.
26) Chande, M. S., Dravid, R. N., Shetgiri, N. P. 1988. Proc. Indian Acad. Sci. Chem. 100, 53.
27) Ertan, M., Bilgin, A. A., Palaska, E., Yulug, N. 1992. Arzeim. Forsch. 42, 160.
28) Ertan, M., Ayyildiz, H. G., Yulug, N. 1991. Arzeim. Forsch. 41, 1182. Yadav Lal Dhar, S., Vaish, A., Sharma, S. 1994. 42, 811.
29) Liu, S., Qian, X., Chen, J., Song, G., 2000. Monatsh. Chem. 131, 935.
30) Jpn. Pat. 0859643. 1996. Chem. Abstr. 125, 10860u. Jpn. Pat. 03215478. 1992. Chem. Abstr. 116, 59409g.
31) Shi, H., Wang, Zh., Shi, H. 1999. Synth. Commun. 29, 2027.
32) Hozein, Z. A., Abd El-Wareth, A. O. S., El-Sherief, H. A. H., Mahmoud, A. M., 1997. Z. Naturforsch., Tiel B. 52, 1401.
33) Shi, H., Shi, H., Wang, Zh. 2001. J. Heterocycl. Chem. 38, 929.
34) Shi, H., Wang, Zh., Shi, H. 1997. Chimia. 51.
35) Hozein, Z. A. 2000. J. Chem. Res. (S). 99.
36) Kiec-Kononowicz, K., Karolak-Wojciechowska, J., Muller, C. E., Schumacher, B., Pekala, E., Szymanska, E., 2001.Imidazo-thiazine, -diazinone and diazepinone derivatives. Synthesis, structure and benzodiazepine receptor binding. Eur. J. Med. Chem. 36, 407-419.
37) Aly, Y., El-Barbary, A., El-Shehawy, A. 2004. Phosphorus, Sulfur, Silicon, Relat. Elem. 179, 185.
38) Frolov, K. A., Dotsenko, V. V., Krivokolysko, S. G., Litvinov, V. P. 2005. Russian Chemical Bulletin, International Edition. 54, 2226-2228.
39) Griffiths, D., Hull, R., Seden, T. P. 1980. J. Chem. Soc., Perkin Trans.1, 1240.
40) Saczewski, F., Gdaniec, M. 1992. J. Chem. Soc., Perkin Trans.1, 47.
41) Hesek, D., Rybar, A., Alfoldi, J., Bella, J., Patoprsty, V. 1996. Collect. Czech. Chem. Commun. 61, 1642.
42) Vovk, M. V., Dorokhov, V. I., Samarai, L. I., 1993. Dokl. Akad. Nauk Ukr. 11, 140.
43) Fr. Pat. 2512450, 1983. Chem. Abstr. 99, 70775.
44) Johnson, T. B., Nicolet, B. H. 1911. J. Am. Chem. Soc. 33, 1973.
45) Broom, N. J. P., Harrington, F. P. 2003. 6-Substitutedmethylene penems and intermediates. US Patent 6600035 (B1).
46) Kiec-Kononowicz, K., Karolak-Wojciechowska, J., Muller, C. E.,Geis, U., Ksiazek, W., Szymanska, E., 1999. J. Heterocycl. Chem. 36, 257-263.
47) Kiec-Kononowicz, K., Karolak-Wojciechowska, J., 1992. Phosphorus, Sulfur, Silicon. 73, 235-248.
48) El Ashry, E. S. H., Rashed, N., Awad, L. F., Ramadan, E., Abdel-Maggeed, S. M., Rezki, N. 2007. Nucleosides, Nucleotides and Nucleic Acids. 26, 423-435.
49) Shvedov, V.I., Sycheva, T. P., Sakovich, T. V. 1979. Khim. Geterotsikl. Soedin. 10, 1331.
50) Shaifullah-Chowdhury, A.Z.M., Shibata, Y. 2001 J. Heterocyclic Chem., 38, 743.
51) Gursoy, A., Iyikosker, T., Terzioglu, N., Otuk, G. 2005 Turkish J. Pharm. Sci. 2(1), 1-10.
52) Gewald, K., Schinke, E., Boettcher, H., 1966. Chem.Ber., 99, 94.
53) (a) Attia, Abdel M., Elgemeie,Galal H. 2003 Synthetic Communications 33(13),2243-2255.
(b) Wagner,G., Leistner,S.,Vieweg,H., Krasselt,U., Prantz,J. 1993 Pharmazie 48(7),514-518.
54) Golovko, T.v., Parshin, V.A., Asnina, V.V., kuleshova, E.F., Anisimova, O.S., Bogdanova, G.A.m Granik, V.G. 1990 Khimiko Farmatsevticheskii Zhurnal, 24(4), 32-35.
55) Geis, U., Kiec-Kononowicz, K., MuellermChrista, E. 1996 Scientia Pharmaceutica ,64(3/4), 383-390.
56) Shirai, H., Yashiro, T. 1967 Yakugaku Zasshi, 87(2), 142-147.
57) Kiec-Kononowicz, K., Karolak-Wojcieckowska, J., Robak, J. 1997 Arch. der. Pharmazie, 330(4), 85-90.
58) Weislow, O.W., Kiser, R., Fine, D., Badr, J., Shoemaker, R.H., Boyed, M.R., 1989. J. National Cancer Inst., 81, 577.
59) Monks,A., Scdiero, D.A., Skehan, P., Shoemaker, R.H., Pall,K.D., Vistica, D.T., Hose, C., Langley, J., Cronice,P., Vaigro-Wolf, M., Gray-Goodrich, M., Campbell, H., Mayo, M.R., 1991 . J. National Cancer Inst., 83, 757.

2/20/2013