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Synthesis and characterization of imidazo[1,2-b]pyridazine linked thiazolidin amides

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ABSTRACT

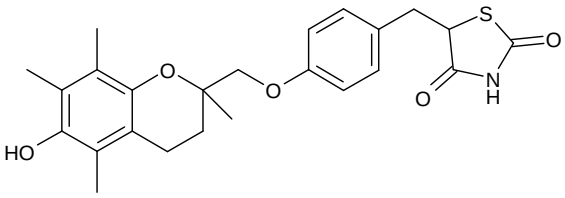
Introducing thiazolidin moiety into the imidazo[1,2-b]pyridazine ring which leads to the presence of three active pharmacophores in a single molecular frame work for the intensified biological activity. A variety of novel imidazo[1,2-b]pyridazine-2-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amides have been synthesized in good to excellent yields. The title compounds were obtained from commercially available imidazo[1,2-b]pyridazine-2-carboxylic acid as starting compound and imidazo[1,2-b]pyridazine-2-carbonyl chloride, imidazo[1,2-b]pyridazine-2-carboxylic acid hydrazide and imidazo[1,2-b]pyridazine-2-carboxylic acid benzylidene-hydrazide as integral part of the synthesis.

Keywords: Thiazolidin, Pyridazine and heterocyclic compounds.

INTRODUCTION

Thiazole is used for manufacturing biocides, fungicides, pharmaceuticals, and dyes. Thiazoles are a class of organic compounds related to azoles with a common thiazole functional group. The thiazole moiety is a crucial part of vitamin-B1 (thiamine) and epothilone. Other important thiazoles are benzothiazoles, for example, the firefly chemical luciferin. The thiazole nucleus appears frequently in the structure of various natural products and biologically active compounds, notably thiamine, penicillin, antibiotics such as micrococcin [1], troglitazone [2] and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)thiazole-4-carboxylic acids [3]. Numerous thiazolidinone derivatives have shown significant pharmacological and biological activities [4] like sedative [5], anti-inflammatory [6], antibacterial [7], antifungal [8], antitubercular [9], anticancer [10], antitumor [11], analgesic and hypothermic [12], local and spinal anesthetic [13], CNS stimulant [14], hypnotic [15], anti-HIV [16] and nematicidal [17].

Many biologically active products having thiazolidinones are used in medicine for the treatment of various diseases, *e.g*. Troglitazone **1** and Rosiglitazone **2** used as insulin sensitizing drugs for the treatment of type-2 diabetes. 2-Imino-4-thiazolidinones, **3** and **4**, proved to have interesting anti-inflammatory activity [18-20].



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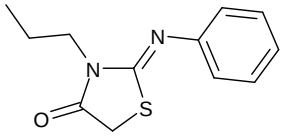

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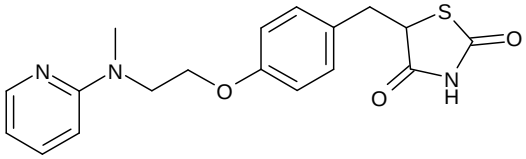

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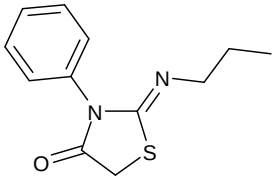

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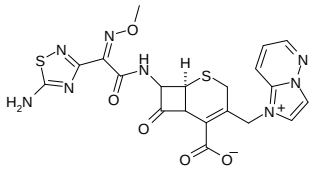
3-Methyl-5[(4-nitrophenyl)azo]rhodanin was reported as a potent anthelmintic compound [21] which was effective when administered in feed against *Hymenolepsis nana* and *Syphacia obvelata* infections in mice, *Asceridia galli* infections in chickens and *Toxocera canis*, *Ancylostoma caninum* and *Uncinaria stenocephala* infections in dogs, pigs and horses. A new series of 2-aryl-4-oxo-thiazolidin-3-yl amide was synthesized and evaluated for their ability to inhibit the growth of prostate cancer cells [22]. Thiazolidinones are known to show their action on histamine receptors [23]. Ottana *et al*. investigated 4-thiazolidinone derivatives showed interesting stereoselective anti-inflammatory activities together with better gastrointestinal safety profile than known NSAIDs [24]. Albanese *et al*. reported that thiazolidinone derivative possessed moderate activities as an agonist of Follicle Stimulating Hormone (FSH) receptor [25]. A series of 2,3-disubstituted-4-thiazolidinones was prepared by different groups of scientists and evaluated for their anticonvulsant activity [26,27]. Rout and Mahapatra [28] reported an improved method for the synthesis of thiazolidiononones and screened for their fungicidal action. It is well known that thiazole and thiazolidinone derivatives owe their antitubercular action because of the N-C-S linkage [29]. Desai [30] reported the synthesis and antimicrobial activity of some 2-arylamino-4-oxothiazolidinones. Desai *et al* [31] reported the synthesis of some 4-oxothiazolidines, 2-imino-4-oxothiazolidines as possible anti-HIV, anticancer and antitubercular agents. Kumar *et al* [32] reported the synthesis of a series of 3-[5-(3''-indolo-methylene)-1',3',4'-thiodiazol-2'-yl]-2-substituted aryl-4-thiazolidinones as potential anticonvulsant agents. Goes *et al* [33] reported the synthesis and Toxoplasma gondii activity of thiosemicarbazone and 4-thiazolidinone derivatives in one step and two steps respectively from thiosemicarbazide. Pyridazine is mainly used in research and industry as building block for more complex compounds. The pyridazine structure is found within a number of herbicides such as credazine, pyridafol and pyridate [56]. It is also found within the structure of several pharmaceutical drugs such as cefozopran **(5)**, cadralazine **(6)**, minaprine **(7)**, pipofezine **(8)**, hydralazine **(9)** and cilazapril **(10)**.



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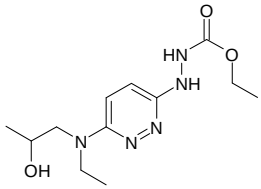

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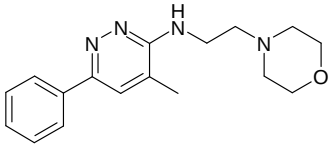

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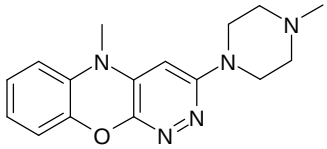

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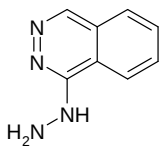

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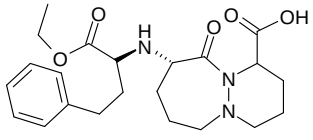

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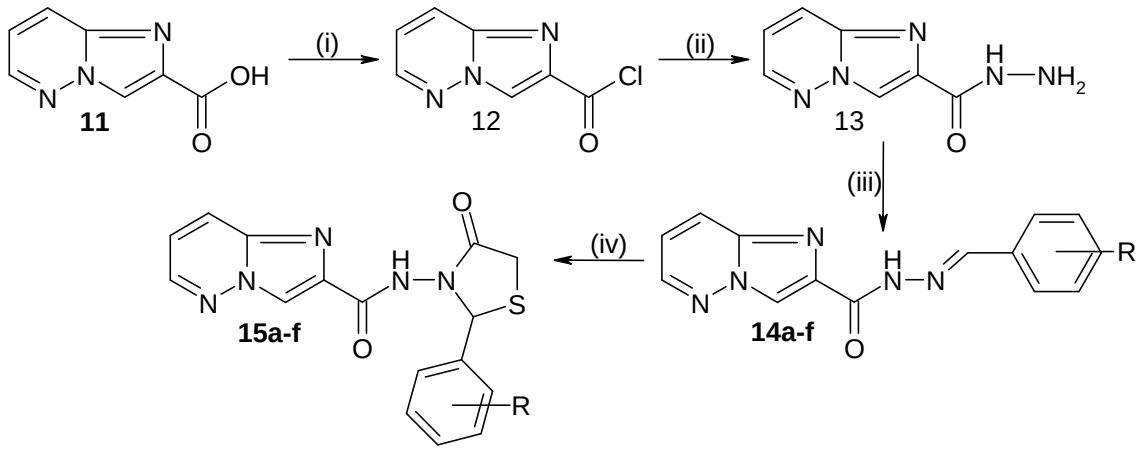
Pyridazines and fused pyridazines are an important class of heterocycles of considerable interest, which have been the subject of extensive research, particularly in the pharmaceutical and agrochemical areas, so their synthesis and applications have been comprehensively reviewed [34-39].

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process and analysis of drugs in late development or on the market shows that 68% of them are heterocycles [40]. Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received special attention. Of these heterocycles, pyridazine derivatives which are a rare in nature have been reported [41] to possess a wide range of biological activities; these include antiviral and anticancer [42], antituberculosis [43], antihypertensive [44], anti-inflammatory [45] and antimicrobial [46] activities. Pyridazine derivatives have also been the subject of extensive research in the agrochemical areas[47-50]. Moreover, pyridazines are useful intermediates in the construction of several other heterocycles [51] and in physical organic chemistry [52] and recently have been explored as new R-helix mimetics [53].

PRESENT WORK

Inspired by the biological profile of imidazole, pyridazine and thiazolidines and their increasing importance in pharmaceutical and biological fields and in continuation of our research on biologically active heterocycles, we have incorporated thiazolidin moiety into the imidazo[1,2-*b*]pyridazine ring which leads to the presence of three active pharmacophores in a single molecular frame work for the intensified biological activity. Thus we have designed and synthesized a variety of novel imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amides **(15a-f)** in good to excellent yields. The title compounds were obtained from commercially available imidazo[1,2-*b*]pyridazine-2-carboxylic acid **(11)** as starting compound and imidazo[1,2-*b*]pyridazine-2-carbonyl chloride **(12)**, imidazo[1,2-*b*]pyridazine-2-carboxylic acid hydrazide **(13)** and imidazo[1,2-*b*]pyridazine-2-carboxylic acid benzylidene-hydrazide **(14a-f)** as integral part of the synthesis. The synthetic route leading to the title compounds is summarized in **scheme 1**.



Scheme 1: *(i) $SOCl_2$, EtOH, RT, 3 h, (ii) $NH_2NH_2.H_2O$, EtOH, Reflux, 7 h, (iii) Aromatic aldehyde, MeOH, reflux, 2-4 h, (iv) SH-CH_2-COOH, THF, $ZnCl_2$, reflux, 12-14 h.*

14/15 R = (a) C_6H_5, (b) 2-OH-C_6H_4, (c) 4-OH-C_6H_4, (d) 4-CH_3-C_6H_4, (e) 4-OCH_3-C_6H_4, (f) 4-OH, 3-OCH_3-C_6H_3.

Thus the initial intermediate, imidazo[1,2-*b*]pyridazine-2-carbonyl chloride **(12)** has been prepared from the raw material, imidazo[1,2-*b*]pyridazine-2-carboxylic acid **(11)** on reaction with thionyl chloride in ethanol solvent at ambient temperature on constant stirring for 3 h.

Further the compound **12** is turned into the next intermediate, imidazo[1,2-*b*]pyridazine-2-carboxylic acid hydrazide **(13)** when reacts with hydrazine hydrate in refluxing ethanol on stable stirring for 7 h. Formation of the compound **13** is confirmed by IR, ^1H & ^{13}C NMR and mass spectral data analysis. The IR spectrum showed the bands at 3342 (N-H), 3245 (N-H, NH_2), 3041 (C-H, Ar), 1675 (C=O), 1642 (C=N) and 1610 (C=C) cm^{-1}. The proton NMR spectrum of this compound showed a signal between δ 7.72-7.45 ppm as multiplet for three protons corresponding

to the aromatic ring. The signal at δ 7.65 ppm as singlet for one proton related to the CONH group. The δ-chemical shift at 7.32 ppm as singlet for one proton is associated with CH group. The NH_2 signal for two protons is appeared at resonance frequency δ 5.54 ppm as singlet. The ^{13}C NMR spectrum of this compound exhibited the signals at different δ-chemical shifts like 164.3, 135.3, 132.7, 131.8, 129.4, 126.7 and 124.9 ppm. The mass spectrum of the compound **13** showed a peak at m/z 177 (M^+).

The final intermediate, imidazo[1,2-*b*]pyridazine-2-carboxylic acid benzylidene-hydrazide **(14a-f)** has been achieved from condensation on steady reflux of a mixture consisting compound **13** and an aromatic aldehyde in methanol solvent for 2-4 h. Emergence of the compound **14a** is established by its different spectral study. The IR spectrum showed of **14a** exhibited the bands at 3358 (N-H), 3062 (C-H, Ar), 1670 (C=O), 1612 (C=C, Ar) and 1458 (C=N) cm^{-1}. The proton NMR spectrum showed a signal at δ 7.78-7.25 ppm as multiplet for eight protons corresponding to the benzene rings. The signal at δ-chemical shift 7.62 ppm as singlet for one proton corresponding to the CH group. The signal at δ 7.31 ppm as singlet for one proton related to another CH group. The signal at lowest δ-chemical shift 7.25 ppm as singlet for one proton is related to NH group. The ^{13}C NMR spectrum of this compound showed the signals at different δ-chemical shifts such as 168.2, 154.3, 151.4, 145.0, 138.9, 136.2, 132.5, 130.7, 128.1, 126.5, 124.1 and 123.9 ppm. The mass spectrum of the compound **14a** showed a peak at m/z 265 (M^+).

Finally the title compounds, imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amide **(15a-f)** were obtained through cyclization on reaction with mercapto acetic acid and anhydrous $ZnCl_2$ in presence of refluxing THF on uniform stirring for 12-14 h. Development of the compound **15a** is identified by IR, NMR and mass spectral examination. Evolution of the compound **15a** is confirmed by IR, NMR and mass spectral investigation. The IR spectrum of **15a** showed the absorption bands at 3344 (N-H), 3052 (C-H, Ar), 2958 (C-H, CH_2), 1668 (C=O), 1645 (C=C, Ar) and 1468 (C=N) cm^{-1}. The proton NMR spectrum of compound **15a** showed a signal in the range of δ 7.70-7.25 ppm as multiplet integrating for eight protons is assigned to aromatic rings. One proton of CH group is appeared as singlet at δ 7.70 ppm. The signal at δ 7.39 ppm as singlet for one proton is indicates the NH group. The δ-chemical shift at 4.10 ppm as singlet for two protons is assigned to CH_2 group. The lowest resonance frequency at δ 3.89 ppm for one proton as singlet is assigned to the other CH group. The ^{13}C NMR spectrum of this compound exhibited the signals at various δ-chemical shifts such as 167.5, 164.8, 153.2, 144.6, 137.4, 135.2, 131.8, 129.7, 127.6, 126.3, 125.3, 124.7, 123.4 and 121.7 ppm. The mass spectrum of this compound showed molecular ion peak at m/z 339. The chemical structures of the all newly synthesized compounds were established by their IR, ^1H & ^{13}C NMR, mass spectral data and elemental analysis. Further, the target compounds were used to find their antimicrobial activity against various microorganisms.

MATERIALS AND METHODS

All the reagents and solvents were used as purchased without further purification. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Crude products were purified by column chromatography on silica gel of 60-120 mesh. IR spectra were obtained on a Perkin-Elmer BX serried FTIR 5000 spectrometer using KBr pellet. NMR spectra were recorded on a Varian 300 MHz spectrometer for ^1H-NMR and 100 MHz for ^{13}C-NMR. The chemical shifts were reported as ppm down field using TMS as an internal standard. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Synthesis of imidazo[1,2-*b*]pyridazine-2-carboxylic acid hydrazide (13)

A mixture of imidazo[1,2-*b*]pyridazine-2-carbonyl chloride **(12)** (0.01 mol) and hydrazine hydrate (0.04 mol) in ethanol solvent (20 ml) was refluxed with constantly stirring for 7 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature, the solid thus separated was filtered, washed thoroughly with water. The crude product was purified by column chromatography on silica gel with hexane-ethyl acetate as an eluent to get the pure imidazo[1,2-*b*]pyridazine-2-carboxylic acid hydrazide **(13)**.

Synthesis of imidazo[1,2-*b*]pyridazine-2-carboxylic acid benzylidene-hydrazide (14a-f)

An equimolar mixture of imidazo[1,2-*b*]pyridazine-2-carboxylic acid hydrazide **(13)** (0.01mol) and the aromatic aldehydes in methanol (5 ml) were refluxed on a water bath for 2-4 h with constant stirring. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the obtained solid was separated by filtration, dried and purified by recrystallization from ethanol to yield corresponding **14a-f** in pure form.

Synthesis of imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amide (15a-f)
A mixture of imidazo[1,2-*b*]pyridazine-2-carboxylic acid benzylidene-hydrazide **(14a-f)** (0.01 mol), mercapto acetic acid (0.01 mol) with anhydrous $ZnCl_2$ (0.05gm) in THF (15 ml) was refluxed for 12-14 h on uniform stirring. After completion of the reaction (monitored by TLC), the solvent was removed to get a residue, which was dissolved in pet-ether and passed through a column of silica gel using pet-ether: chloroform (6:4; v/v) mixture as eluent. The eluate was concentrated and the product recrystallized from alcohol to give pure **15a-f**.

PHYSICAL AND SPECTRAL DATA
Imidazo[1,2-*b*]pyridazine-2-carboxylic acid hydrazide (13)
Yield 73%; mp: 122-1234 ^{0}C; IR (KBr) 3342 (N-H), 3245 (N-H, NH_2), 3041 (C-H, Ar), 1675 (C=O), 1642 (C=N), 1610 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.45 (m, 3H, Ar-H), 7.65 (s, 1H, CONH), 7.32 (s, 1H, CH), 5.54 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 135.3, 132.7, 131.8, 129.4, 126.7, 124.9; MS *m/z* 177 (M^+); Elemental analysis: Calculated for $C_7H_7N_5O$: C-47.46, H-3.98, N-39.53, O-9.03. Found: C-46.56, H-3.52, N-38.41, O-8.87.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid benzylidene-hydrazide (14a)
Yield: 72%, mp: 120-122 °C; IR (KBr): 3358 (N-H), 3062 (C-H, Ar), 1670 (C=O), 1612 (C=C, Ar), 1458 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78-7.25 (m, 8H, Ar-H), 7.62 (s, 1H, CH), 7.31 (s, 1H, CH), 7.25 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.2, 154.3, 151.4, 145.0, 138.9, 136.2, 132.5, 130.7, 128.1, 126.5, 124.1, 123.9; MS: 265 m/z (M^+); Elemental analysis: Calculated for $C_{14}H_{11}N_5O$: C-63.39, H-4.18, N-26.40, O-6.03. Found: C-62.12, H-4.04, N-25.84, O-5.89.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid (2-hydroxy-benzylidene)-hydrazide (14b)
Yield: 70%, mp: 123-125 °C; IR (KBr): 3363 (N-H), 3245 (O-H), 3054 (C-H, Ar), 1668 (C=O), 1625 (C=C, Ar), 1463 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.81-7.26 (m, 7H, Ar-H), 7.58 (s, 1H, CH), 7.34 (s, 1H, CH), 7.28 (s, 1H, NH), 4.32 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.8, 154.3, 152.7, 144.6, 137.4, 135.6, 133.2, 132.6, 130.5, 129.7, 127.5, 126.4, 125.7, 120.7; MS: 281 m/z (M^+); Elemental analysis: Calculated for $C_{14}H_{11}N_5O_2$: C-59.78, H-3.94, N-24.90, O-11.38. Found: C-58.69, H-3.65, N-23.87, O-10.80.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4-hydroxy-benzylidene)-hydrazide (14c)
Yield: 73%, mp: 141-143 °C; IR (KBr): 3348 (N-H), 3262 (O-H), 3059 (C-H, Ar), 1672 (C=O), 1635 (C=C, Ar), 1462 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.79-7.42 (m, 3H, Ar-H), 7.58 (d, 2H, J = 7.0 Hz, Ar-H), 7.41 (d, 2H, J = 7.0 Hz, CH), 7.61 (s, 1H, CH), 7.38 (s, 1H, CH), 7.32 (s, 1H, NH), 4.38 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.3, 154.3, 151.2, 148.6, 137.5, 136.4, 128.6, 127.4, 125.6, 124.3, 123.5, 121.5; MS: 281 m/z (M^+); Elemental analysis: Calculated for $C_{14}H_{11}N_5O_2$: C-59.78, H-3.94, N-24.09, O-11.38. Found: C-58.74, H-3.56, N-23.12, O-10.84.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4-methyl-benzylidene)-hydrazide (14d) Yield: 74%, mp: 119.121 °C; IR (KBr): 3374 (N-H), 3068 (C-H, Ar), 2965 (C-H, CH_3),1662 (C=O), 1645 (C=C, Ar), 1474 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61-7.23 (m, 3H, Ar-H), 7.60 (s, 1H, CH), 7.55 (d, 2H, J = 7.2 Hz, Ar-H), 7.44 (d, 2H, J = 7.2 Hz, CH), 7.36 (s, 1H, CH), 7.30 (s, 1H, NH), 3.22 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 152.3, 150.4, 145.2, 136.8, 135.2, 131.2, 130.8, 128.6, 124.1, 121.1, 120.9, 42.5; MS: 279 m/z (M^+); Elemental analysis: Calculated for $C_{15}H_{13}N_5O$: C-64.51, H-4.69, N-25.07, O-5.73. Found: C-63.26, H-4.25, N-24.12, O-5.14.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4-methoxy-benzylidene)-hydrazide (14e)
Yield: 70%, mp: 138-140 °C; IR (KBr): 3341 (N-H), 3056 (C-H, Ar), 2973 (C-H, CH_3), 1674 (C=O), 1635 (C=C, Ar), 1462 (C=N), 1145 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65-7.32 (m, 3H, Ar-H), 7.66 (s, 1H, CH), 7.48 (d, 2H, J = 7.3 Hz, Ar-H), 7.41 (d, 2H, J = 7.3 Hz, CH), 7.40 (s, 1H, CH), 7.33 (s, 1H, NH), 3.36 (s, 3H, OCH_3-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.7, 156.3, 154.8, 145.6, 137.5, 133.6, 129.4, 128.4, 125.1, 125.1, 124.1, 122.7, 58.3; MS: 295 m/z (M^+); Elemental analysis: Calculated for $C_{15}H_{13}N_5O_2$: C-61.01, H-4.44, N-23.72, O-10.84. Found: C-59.84, H-4.02, N-22.12, O-9.98

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4-hydroxy-3-methoxy-benzylidene)-hydrazide (14f)
Yield: 71%, mp: 141-143 °C; IR (KBr): 3340 (N-H), 3258 (O-H), 3041 (C-H, Ar), 2962 (C-H, CH_3), 1664 (C=O), 1635 (C=C, Ar), 1470 (C=N), 1168 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78-7.20 (m, 3H, Ar-H), 7.67

(s, 1H, CH), 7.54 (s, 1H, Ar-H), 7.50 (d, 1H, J = 7.5 Hz, Ar-H), 7.46 (d, 1H, J = 7.5 Hz, CH), 7.40 (s, 1H, CH), 7.37 (s, 1H, NH), 4.45 (s, 1H, OH), 3.74 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 153.6, 150.7, 148.8, 140.5, 138.7, 136.5, 129.6, 127.5, 125.4, 123.4, 122.0, 121.6, 120.1, 51.6; MS: 311 m/z (M^+); Elemental analysis: Calculated for $C_{15}H_{13}N_5O_3$: C-57.87, H-4.21, N-22.50, S-15.42. Found: C-56.6, H-4.02, N-21.24, S-14.87.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid (4-oxo-2-phenyl-thiazolidin-3-yl)-amide (15a)
Yield: 71%, mp: 150-152 °C; IR (KBr): 3344 (N-H), 3052 (C-H, Ar), 2958 (C-H, CH_2), 1668 (C=O), 1645 (C=C, Ar), 1468 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.70-7.25 (m, 8H, Ar-H), 7.70 (s, 1H, CH), 7.39 (s, 1H, NH), 4.10 (s, 2H, CH_2), 3.89 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 164.8, 153.2, 144.6, 137.4, 135.2, 131.8, 129.7, 127.6, 126.3, 125.3, 124.7, 123.4, 121.7; MS: 339 m/z (M^+); Elemental analysis: Calculated for $C_{16}H_{13}N_5O_2S$: C-56.63, H-3.86, N-20.64, O-9.43, S-9.45. Found: C-55.48, H-3.28, N-19.85, O-8.95, S-8.87.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid [2-(2-hydroxy-phenyl)-4-oxo-thiazolidin-3-yl]-amide (15b)
Yield: 69%, mp: 123-125 °C; IR (KBr): 3351 (N-H), 3268 (O-H), 3066 (C-H, Ar), 2962 (C-H, CH_2), 1659 (C=O), 1658 (C=C, Ar), 1474 (C=N), 1188 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.65-7.28 (m, 7H, Ar-H), 7.68 (s, 1H, CH), 7.35 (s, 1H, NH), 4.68 (s, 1H, OH), 4.14 (s, 2H, CH_2), 3.95 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 160.7, 151.8, 140.6, 138.9, 135.7, 132.8, 129.8, 128.6, 126.8, 125.4, 124.7, 122.0, 123.7, 120.1, 119.3; MS: 355 m/z (M^+); Elemental analysis: Calculated for $C_{16}H_{13}N_5O_3S$: C-54.08, H-3.69, N-19.71, O-13.51, S-9.02. Found: C-53.12, H-3.28, N-18.74, O-12.95, S-8.47.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid [2-(4-hydroxy-phenyl)-4-oxo-thiazolidin-3-yl]-amide (15c)
Yield: 74%, mp: 130-132 °C; IR (KBr): 3365 (N-H), 3278 (O-H), 3054 (C-H, Ar), 2970 (C-H, CH_2), 1654 (C=O), 1688 (C=C, Ar), 1470 (C=N), 1189 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.65-7.21 (m, 3H, Ar-H), 7.60 (s, 1H, CH), 7.55 (d, 2H, J = 7.0 Hz, Ar-H), 7.48 (d, 2H, J = 7.0 Hz, CH), 7.41 (s, 1H, NH), 4.52 (s, 1H, OH), 4.32 (s, 2H, CH_2), 3.84 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 163.2, 151.7, 142.8, 138.7, 135.4, 131.7, 129.6, 128.7, 127.2, 125.3, 124.3, 122.8, 119.8; MS: 355 m/z (M^+); Elemental analysis: Calculated for $C_{16}H_{13}N_5O_3S$: C-54.08, H-3.69, N-19.71, O-13.51, S-9.02. Found: C-53.21, H-3.28, N-18.47, O-12.98, S-8.49.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid [2-(4-methyl-phenyl)-4-oxo-thiazolidin-3-yl]-amide (15d)
Yield: 76%, mp: 151-153 °C; IR (KBr): 3368 (N-H), 3069 (C-H, Ar), 2974 (C-H, CH_2), 1682 (C=O), 1663 (C=C, Ar), 1472 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.72 (s, 1H, CH), 7.68-7.30 (m, 3H, Ar-H), 7.54 (d, 2H, J = 7.2 Hz, Ar-H), 7.50 (d, 2H, J = 7.2 Hz, CH), 7.42 (s, 1H, NH), 4.24 (s, 2H, CH_2), 3.75 (s, 1H, CH), 3.61 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 163.2, 154.8, 146.7, 143.7, 139.6, 136.7, 134.5, 132.7, 130.2, 128.7, 126.3, 124.7, 123.4, 48.6; MS: 353 m/z (M^+); Elemental analysis: Calculated for $C_{17}H_{15}N_5O_2S$: C-57.78, H-4.28, N-19.82, O-9.05, S-9.07. Found: C-56.58, H-3.95, N-18.92, O-8.74, S-8.88.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid [2-(4-methoxy-phenyl)-4-oxo-thiazolidin-3-yl]-amide (15e)
Yield: 70%, mp: 118-120 °C; IR (KBr): 3356 (N-H), 3049 (C-H, Ar), 2962 (C-H, CH_2), 1670 (C=O), 1689 (C=C, Ar), 1475 (C=N), 1164 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.61-7.34 (m, 3H, Ar-H), 7.58 (s, 1H, CH), 7.47 (d, 2H, J = 7.3 Hz, Ar-H), 7.36 (d, 2H, J = 7.3 Hz, CH), 7.31 (s, 1H, NH), 4.25 (s, 2H, CH_2), 3.78 (s, 1H, CH), 3.51 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 162.7, 155.4, 146.7, 143.0, 139.4, 134.2, 132.6, 130.2, 129.4, 127.6, 125.8, 123.2, 120.9, 74.8; MS: 369 m/z (M^+); Elemental analysis: Calculated for $C_{17}H_{15}N_5O_3S$: C-55.27, H-4.09, N-18.96, O-12.99, S-8.68. Found: C-54.26, H-3.84, N-17.85, O-12.12, S-8.06.

Imidazo[1,2-*b*]pyridazine-2-carboxylic acid [2-(4-hydroxy-3-methoxy-phenyl)-4-oxo-thiazolidin-3-yl]-amide (15f)
Yield: 73%, mp: 133-135 °C; IR (KBr): 3374 (N-H), 3270 (O-H), 3065 (C-H, Ar), 2949 (C-H, CH_2), 1674 (C=O), 1664 (C=C, Ar), 1479 (C=N), 1184 (C-O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.65-7.41 (m, 3H, Ar-H), 7.68 (s, 1H, CH), 7.59 (d, 1H, J = 7.6 Hz, Ar-H), 7.45 (d, 1H, J = 7.6 Hz, CH), 7.44 (s, 1H, NH), 7.32 (s, 1H, Ar-H), 4.69 (s, 1H, OH), 4.32 (s, 2H, CH_2), 3.70 (s, 1H, CH), 3.67 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 164.8, 153.2, 144.6, 141.6, 137.4, 135.4, 132.0, 131.8, 129.7, 127.6, 126.3, 125.2, 123.4, 121.7, 120.0, 76.4; MS: 385 m/z (M^+); Elemental analysis: Calculated for $C_{17}H_{15}N_5O_4S$: C-52.98, H-3.92, N-18.17, O-16.61, S-8.32. Found: C-51.23, H-3.36, N-17.41, O-15.85, S-7.96.

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