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Research Article

SYNTHESIS, DOCKING AND ANTITUBERCULAR ACTIVITY OF SOME NEWER THIAZOLIDINONES

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ABSTRACT

Thiazolidinones are important class of heterocyclic compounds due to their versatile biological activity. A novel series of 2-phenyl-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one(VIa-n) derivatives were synthesized in good yield by the cycloaddition of *N*-[(1*E*)-phenyl methylene]-5-pyridin-3-yl-1,3,4-thiadiazol-2-amine with thioglycollic acid in presence of dimethylformamide. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, MASS data and elemental analysis. Docking studies has been carried out by using Hex software for all the newly synthesized compounds. All the synthesized compounds were tested against *Mycobacterium tuberculosis* using Microplate Alamar Blue Assay method. Preliminary results indicated that most of the compounds tested in this study demonstrated comparable activity against *Mycobacterium tuberculosis* as compared with standard Streptomycin, Pyrazinamide and Ciprofloxacin. Among the series, compounds VI l and VI n showed better antitubercular activity compared to all the standards pyrazinamide, streptomycin and ciprofloxacin and compounds VI e, VI g, VI j, VI k and VI m showed similar activity compared to standard streptomycin. The structure and biological activity relationship of titled compounds showed that the presence of pharmacophoric moieties like 1,3,4-thiadiazole nucleus and the substituent's like 2-methoxy benzaldehyde, 4-methoxy benzaldehyde, 2-hydroxy benzaldehyde and 4-hydroxy benzaldehyde attached to it will increases the activity.

Keywords: Antituberculosis, Thiazolidinones, 1,3,4-thiadiazole, Thioglycollic acid, Docking.

INTRODUCTION

It is well established that slight alterations in the structure of certain compounds are able to bring drastic changes to yield better drug with less toxicity to the host. It is observed that chemical modification not only alters physicochemical properties but also pharmacological activities[1]. Discovery of newer and more potent analogs of molecules with already established activities form a key part of research in the pharmaceutical field. Bringing about slight modifications in the parent compound often serves to enhance the activity of the compound and also in most cases eliminates adverse effects or toxicity associated with the parent drug[2]. The historical importance of thiazole derivatives was emphasized during the period 1941-45, when work on the structure of penicillin's showed the thiazolidine ring in it. The occurrence of thiazole derivative in nature was reported 1952 when actithiazic acid, an antibiotic was found to be a 4-thiazolidinone derivative. Biological activity of these heterocycles has helped the medicinal chemist to plan, organize and implement newer approaches towards the discovery of new drugs. In view of the general observation that pharmacological activity is invariably associated with a large variety of heterocyclic compounds, the investigation of some heterocycles such as thiazolidinone derivatives has been undertaken. Derivatives of these compounds are reported to possess a wide spectrum of biological activities which include anti-inflammatory, analgesic, antitumour, antihypertensive, anticonvulsant and antimicrobial activity. Owing to the importance and established physiological activity of these thiazolidinones it was thought to synthesize and investigate compounds with comparable structures[3-8]. Owing to the importance and established pharmacological activity of these compounds we are directed our attention towards synthesis of some new 4-thiazolidinone derivatives with object of screening them for antitubercular activity.

MATERIALS AND METHODS

Chemistry:

All Chemicals used in the synthesis of the compounds

described were purchased from Loba chemicals, Ozone chemicals, S.D. fine chemicals Ltd. and Spectrochem Ltd. They were nicotinic acid, isonicotinic acid, thiosemicarbazide, phosphoryl oxy trichloride, chloroacetyl chloride, ethanol, dimethyl formamide, thioglycollic acid and various aromatic aldehydes, sulphuric acid, potassium hydroxide etc. These are either AR/LR grade or the best possible pharma grade available were used here. Melting points were determined in open capillaries in electrical melting point apparatus and are uncorrected. FT-IR spectra in KBr disk were recorded from 4000 to 400 cm^{-1} on Avatar 330 FT-IR spectrometer equipped with DTGS detector. ^1H NMR spectra were recorded on 400-MHz and 500-MHz Bruker spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. Mass spectra were recorded using Agilent 1100 MSD spectrometer in electro spray mode. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by exposing to UV light and iodine vapours. The following materials that were either AR/LR grade or the best possible pharma grade available were used as supplied by the manufacturer.

Chemical synthesis:

General method for the synthesis of 5-(substituted) phenyl-*N*-[(1*E*)-(substituted) phenyl methylene]-1,3,4-thiadiazol-2-amine (V a-n)[9-10]

2-amino-5-substituted acid-1,3,4-thiadiazole (IV a-b) required as the starting material was prepared by the reaction of thiosemicarbazide with substituted acids. 2-amino-5-substituted acid-1,3,4-thiadiazole (IV a-b) on condensation with various selected aromatic aldehydes furnished schiff bases, 5-(substituted) phenyl-*N*-[(1*E*)-(substituted) phenyl methylene]-1,3,4-thiadiazol-2-amine (**V a-n**) as shown in scheme.

General method for the synthesis of 2-(substituted) phenyl-3-[5-(substituted) phenyl [1,3,4] thiadiazol-2-yl]-1,3-thiazolidin-4-one (VI a-n)[11-12]

The five membered thiazolidine ring in compound was introduced by the cycloaddition of 5-(substituted) phenyl-*N*-[(1*E*)-(substituted) phenyl methylene]-1,3,4-thiadiazol-2-amine (**V a-n**) with thioglycollic acid in presence of dimethylformamide to give 2-(substituted) phenyl-3-[5-(substituted) phenyl [1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one **(VI a-n)** as shown in scheme 1. The physicochemical parameters of the synthesized compounds are depicted in Table 1.

DOCKING STUDIES

Docking study was done with *HEX*-software for the newly synthesized compounds to dock with the antitubercular protein (2YES) from Protein Data Base (PDB). *Hex* is an interactive molecular graphics program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. *Hex* can also calculate protein-ligand docking, assuming the ligand is rigid, and it can superpose pairs of molecules using only knowledge of their 3D shapes. In *Hex*'s docking calculations, each molecule is modeled using 3D expansions of real orthogonal spherical polar basis functions to encode both surface shape and electrostatic charge and potential distributions. *Hex* is also very easy to use. However, to use *Hex* most effectively, sometimes require some thought when setting up the calculation, especially when setting up the starting orientations of the proteins to be docked.

Molecular docking involves the following steps using *Hex* 5.1 software:

Identified a target protein 2YES from the Protein data Bank. Downloaded PDB FILE (text) and saved it in Example Folder of *Hex* 5.1.Drawn all the ligands using chemsketch. Generated 3-D view (SDF format), convert it into MOL file. Converted into PDB format by using Swiss PDB viewer and saved it.Open Hex 5.1 software, selected appropriate protein and ligand and performed docking. The docking results of the synthesized compounds VIIa-n are depicted in Table 2.

ANTITUBERCULAR ACTIVITY

Method: Microplate Alamar Blue Assay[13] (MABA)

Preparation of Inoculum: 100 µl of the Middle brook 7H9 broth

Requirements: 96 wells plate, Para film (all are sterilized by dry heat).

Nutrient Medium: 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80

Working procedure Stock solutions of the synthesized compounds and standard drug used were prepared in sterile deionized water and taken in the concentration of 0.1 to 100 µl/ml.

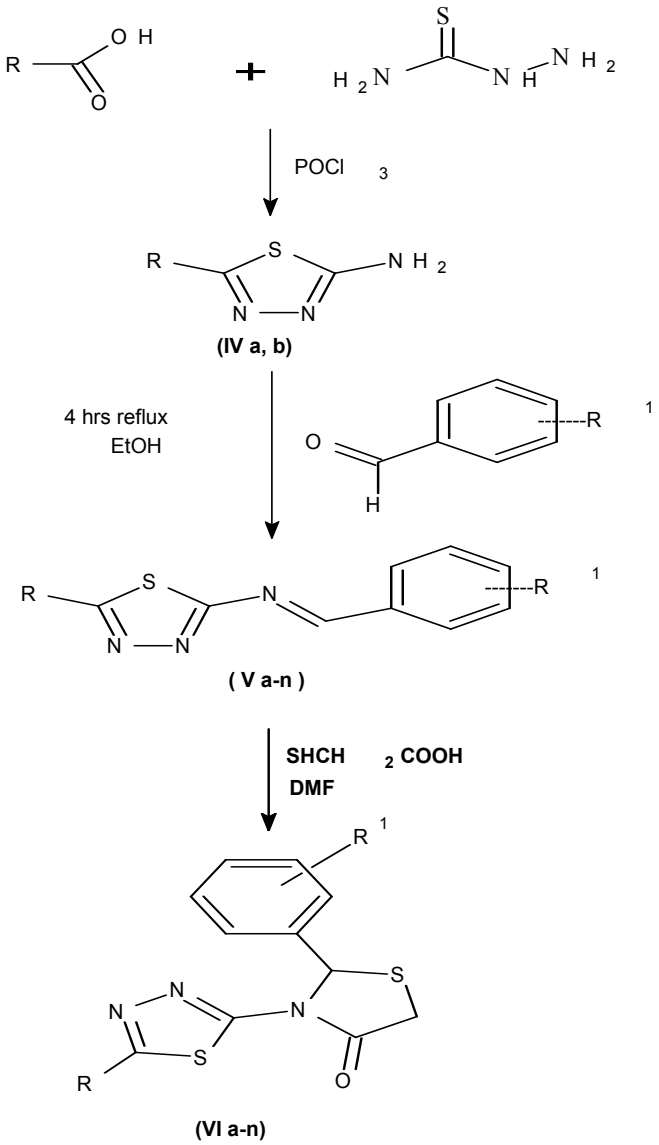
The anti-mycobacterial activities of compounds III a-n were assessed against M. tuberculosis using Microplate Alamar Blue Assay[14] (MABA). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method[15-16].Briefly, 200µl of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middle brook 7H9 broth and serial dilutions of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. Plates were covered and sealed with Para film and incubated at 37ºC for five days. After this time, 25µl of freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink. The antitubercular activities of the synthesized compounds are depicted in Table 3.

RESULTS AND DISCUSSION

A new series of 2-phenyl-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one (VI a-n) were synthesized in good yield synthesized according to reaction scheme 1. All the newly synthesized compounds were screened for the antitubercular activity by MABA (Microplate Alamar Blue Assay) method. Pyrazinamide, Streptomycin and Ciprofloxacin drugs are used as standards and activity of all newly synthesized compounds were measured against it. Docking studies has been carried out by using Hex software for all the compounds. All the derivatives were docked with target protein for tuberculosis (2YES) to predict the antitubercular activity. The result of the docking studies

clearly confirms that compounds VI e, VI g, VI j and VI k are active against the tuberculosis and VI l and VI n compound showed potent antitubercular activity. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, FABMS data and elemental analysis. The antimycobacterial activities of compounds VI a-n were assessed against *M. tuberculosis*H_{37}Rv (ATCC 27294) using Microplate Alamar Blue Assay (MABA). This methodology is nontoxic, uses a thermally-stable reagent and shows good correlation with BACTEC radiometric methods and the activity expressed as the minimum inhibitory concentration (MIC) in µg/ml. The MICs of the compounds were carried out and showed good antitubercular activity compared to standards pyrazinamide, streptomycin and ciprofloxacin. In this series, VI a-n, compounds VI l and VI n showed better antitubercular activity compared to all the standards pyrazinamide, streptomycin and ciprofloxacin and compounds VI e, VI g, VI j, VI k and VI m showed similar activity compared to standard streptomycin. The structure and biological activity relationship of title compounds showed that the presence of 1,3,4-thiadiazole nucleus and the substituent's like 2-methoxy benzaldehyde, 4-methoxy benzaldehyde, 2-hydroxy benzaldehyde and 4-hydroxy benzaldehyde attached to it will increases the activity.

SCHEME 1



R = Nicotinic acid, Isonicotinic acid

R^{1}= H, 2-Cl, 4-Cl, 2-OCH_3, 4-OCH_3, 2-OH, 4-OH

Reaction sequence for the synthesis of 2-phenyl-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one (VI a-n)

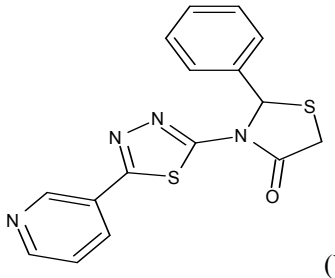
Table 1: Physico-chemical data of 2-(substituted)phenyl-3-[5-(substituted)phenyl [1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one(VI a-n)

Compound	R	R^1	Yield (%)	M. P. (^{0}C)	Rf*	Molecular Formula
VI a	Nicotinic acid	H	59	175	0.75	$C_{16}H_{12}N_4OS_2$
VI b	Nicotinic acid	2-Cl	61	171	0.83	$C_{16}H_{11}ClN_4OS_2$
VI c	Nicotinic acid	4-Cl	58	180	0.66	$C_{16}H_{11}ClN_4OS_2$
VI d	Nicotinic acid	2-OCH_3	53	178	0.69	$C_{17}H_{14}N_4O_2S_2$
VI e	Nicotinic acid	4-OCH_3	49	190	0.73	$C_{17}H_{14}N_4O_2S_2$
VI f	Nicotinic acid	2-OH	55	198	0.77	$C_{16}H_{12}N_4O_2S_2$
VI g	Nicotinic acid	4-OH	63	170	0.67	$C_{16}H_{12}N_4O_2S_2$
VI h	Isonicotinic acid	H	68	179	0.61	$C_{16}H_{12}N_4OS_2$
VI i	Isonicotinic acid	2-Cl	60	164	0.68	$C_{16}H_{11}ClN_4OS_2$
VI j	Isonicotinic acid	4-Cl	49	190	0.83	$C_{16}H_{11}ClN_4OS_2$
VI k	Isonicotinic acid	2-OCH_3	45	198	0.70	$C_{17}H_{14}N_4O_2S_2$
VI l	Isonicotinic acid	4-OCH_3	55	188	0.68	$C_{17}H_{14}N_4O_2S_2$
VI m	Isonicotinic acid	2-OH	56	169	0.72	$C_{16}H_{12}N_4O_2S_2$
VI n	Isonicotinic acid	4-OH	60	193	0.75	$C_{16}H_{12}N_4O_2S_2$

*** Benzene:Methanol:Ammonia (75:25:0.25) as a mobile phase and iodine vapours as visualizing agent.**

SPECTRAL DATA

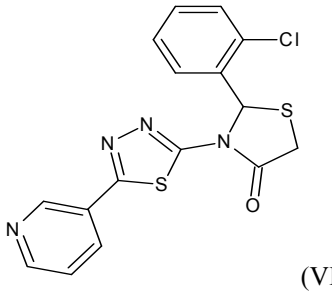
- **2-phenyl-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIa)

The following spectral data were recorded for compound VI a: FTIR (KBr) cm^{-1}: 3121 (Ar C-H); 2972 (C-H); 2877 (C-H thiazole); 1692 (-C=O), 705 (C-S-C). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.21 (s, 1H, CH); 7.82 (s, 1H, CH); 7.28-7.58 (m, 10H, Ar-H); 4.11 (s, 1H, -N-CH), 4.08 (s, 2H, SCH_2); MS spectrum, *m/z*: 341[M+1]$^+$; Anal. Calcd. for $C_{16}H_{12}N_4OS_2$: C (57.40), H (3.80), N (10.57). Found: C (57.35), H (3.74) and N (10.49).

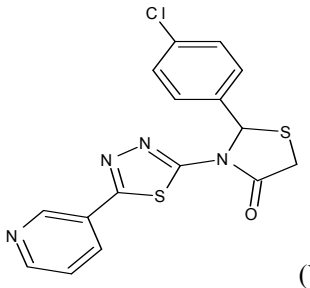
- **2-(2-chlorophenyl)-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIb)

The following spectral data were recorded for compound VI b: FTIR (KBr) cm^{-1}: 3112 (Ar C-H); 2950 (C-H); 2870 (C-H thiazole); 1685 (-C=O), 703 (C-S-C), 761 (-C-Cl). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.11(s, 1H, CH); 7.92 (s, 1H, CH); 7.35-7.75 (m, 9H, Ar-H) 4.12 (s, 1H, -N-CH), 4.17 (s, 2H, SCH_2); MS spectrum, *m/z*: 375[M+1]$^+$.

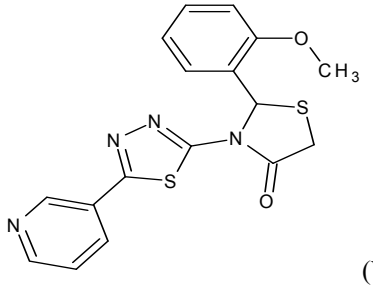
- **2-(4-chlorophenyl)-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIc)

The following spectral data were recorded for compound VI c: FTIR (KBr) cm^{-1}: 3115 (Ar C-H); 2972 (C-H); 2869 (C-H thiazole); 1674 (-C=O), 710 (C-S-C), 755 (-C-Cl). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 11.09 (s, 1H, CH); 7.76 (s, 1H, CH); 7.30-7.70 (m, 9H, Ar-H); 4.10 (s, 1H, -N-CH), 4.18 (s, 2H, SCH_2); MS spectrum, *m/z*: 375[M+1]$^+$.

- **2-(2-methoxyphenyl)-3-(5-pyridin-3-yl-1,3,4-thiadiazol -2-yl)-1,3-thiazolidin-4-one**

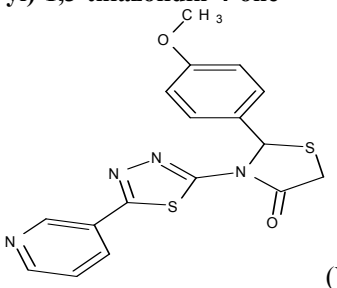


(VId)

The following spectral data were recorded for compound VI d: FTIR (KBr) cm^{-1}: 3153 (Ar C-H); 2928 (C-H); 2358 (C-H thiazole); 1693 (-C=O), 723 (C-S-C). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.05 (s, 1H, CH); 7.87 (s, 1H, CH); 7.21-7.24 (m, 9H, Ar-H); 2.84 (s, 3H, CH_3); 4.44 (s, 1H, -N-CH), 4.72 (s, 2H, SCH_2); ^{13}C NMR (75 MHz, DMSO-d_6):

δ 28.02, 28.27, 28.32, 32.87, 37.26, 128.93, 130.60, 132.44, 137.26, 140.97, 144.65, 153.55, 160.17, 160.68, 163.33, 164.43, 177.97;MS spectrum, MS spectrum, *m/z*: 371 $[M+1]^+$; Anal. Calcd.for $C_{17}H_{14}N_4O_2S_2$: C (58.37), H (4.16), N (10.21). Found: C (58.31), H (4.14) and N (10.14).

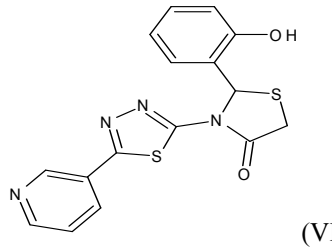
- **2-(4-methoxyphenyl)-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIe)

The following spectral data were recorded for compound VI e: FTIR (KBr) cm^{-1}: 3110 (Ar C-H); 2960 (C-H); 2880 (C-H thiazole); 1685 (-C=O), 669 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.16 (s, 1H, CH); 7.86 (s, 1H, CH); 7.32-7.63 (m, 8H, Ar-H); 2.74 (s, 6H, CH_3); 4.06 (s, 1H, -N-CH), 4.19 (s, 2H, SCH_2); MS spectrum, MS spectrum, *m/z*: 371 $[M+1]^+$.

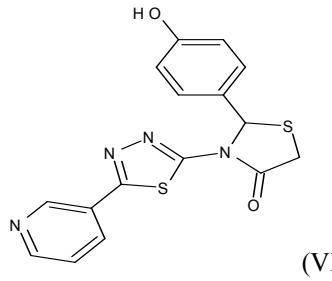
- **2-(2-hydroxyphenyl)-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIf)

The following spectral data were recorded for compound VI f: FTIR (KBr) cm^{-1}: 3543 (O-H), 3153 (Ar C-H); 2980 (C-H); 2895 (C-H thiazole); 1748 (-C=O), 713 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 10.15 (s, 1H, CH), 7.81 (s, 1H, CH), 7.32-7.48 (m, 8H, Ar-H), 5.23 (s, 1H, OH), 2.24 (s, 6H, CH_3), 4.12 (s, 1H, -N-CH), 4.30 (s, 2H, SCH_2); MS spectrum, MS spectrum, *m/z*: 357 $[M+1]^+$.

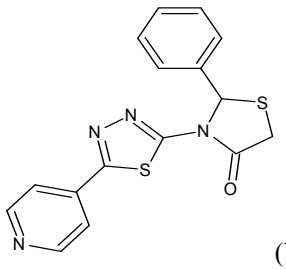
- **2-(4-hydroxyphenyl)-3-(5-pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIg)

The following spectral data were recorded for compound VII g: FTIR (KBr) cm^{-1}: 3545 (O-H); 3005 (Ar C-H); 2955 (C-H); 2875 (C-H thiazole); 1738 (-C=O), 675 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.63 (s, 1H, CH); 7.83 (s, 1H, CH); 7.18-7.34 (m, 9H, Ar-H); 5.28 (s, 1H, OH); 4.15 (s, 1H, -N-CH), 4.19 (s, 2H, SCH_2); MS spectrum, *m/z*: 357 $[M+1]^+$.

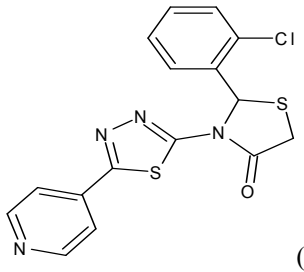
- **2-phenyl-3-(5-pyridin-4-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIh)

The following spectral data were recorded for compound VI h: FTIR (KBr) cm^{-1}: 3005 (ArC-H); 2955 (C-H); 2875 (C-H thiazole); 1750 (-C=O), 705 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.63 (s, 1H, CH); 7.83 (s, 1H, CH); 7.28-7.44 (m, 8H, Ar-H); 4.10 (s, 1H, -N-CH), 4.17 (s, 2H, SCH_2); MS spectrum, *m/z*: 341 $[M+1]^+$.

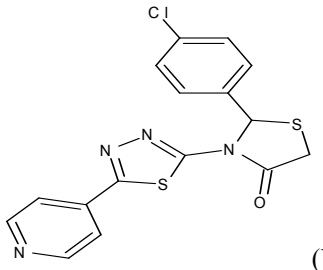
- **2-(2-chlorophenyl)-3-(5-pyridin-4-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIi)

The following spectral data were recorded for compound VI i: FTIR (KBr) cm^{-1}: 3005 (ArC-H); 2955 (C-H); 2875 (C-H thiazole); 1738 (-C=O), 715 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.63 (s, 1H, CH); 7.83 (s, 1H, CH); 7.32-7.54 (m, 8H, Ar-H); 4.11 (s, 1H, -N-CH), 4.23 (s, 2H, SCH_2); MS spectrum, *m/z*: 375 $[M+1]^+$.

- **2-(4-chlorophenyl)-3-(5-pyridin-4-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**

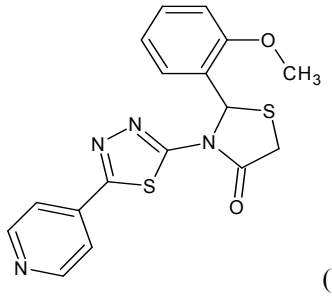


(VIj)

The following spectral data were recorded for compound VI j: FTIR (KBr) cm^{-1}: 3105 (Ar C-H); 2945 (C-H); 2785 (C-H thiazole); 1695 (-C=O), 703 (C-S-C). ^1H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.84 (s, 1H, CH); 6.36 (s, 1H, CH); 7.39-7.72 (m, 9H, Ar-H); 1.42-1.47(s, 6H, CH_3); 4.18 (s, 1H, -N-CH), 4.25 (s, 2H, SCH_2);MS spectrum, *m/z*: 375 $[M+1]^+$.

- **2-(2-methoxyphenyl)-3-(5-pyridin-4-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**

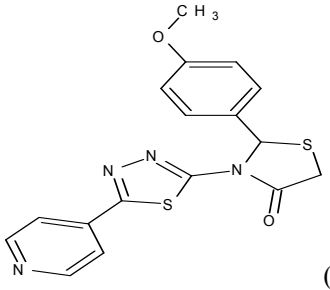
The following spectral data were recorded for compound VI k: FTIR (KBr) cm^{-1}: 3095 (Ar C-H); 2895 (C-H); 2760 (C-H thiazole); 1675 (-C=O), 675 (C-S-C).



(VIk)

^{1}H NMRchemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.77 (s, 1H, CH); 6.45 (s, 1H, CH); 7.80-7.95 (m, 8H, Ar-H); 3.15 (s, 3H, $-OCH_3$); 1.42-1.47(s, 6H, CH_3); 4.13 (s, 1H, -N-CH), 4.21 (s, 2H, SCH_2); MS spectrum, *m/z*: 371 $[M+1]^+$.

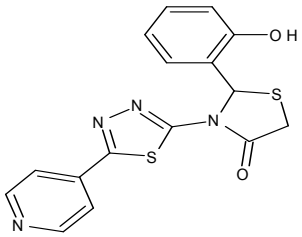
- **2-(4-methoxyphenyl)-3-(5-pyridin-4-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIl)

The following spectral data were recorded for compound VI l: FTIR (KBr) cm^{-1}: 3105 (Ar C-H); 2925 (C-H); 2880 (C-H thiazole); 1666 (-C=O), 708 (C-S-C). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.67 (s, 1H, CH); 6.49 (s, 1H, CH); 7.66-7.89 (m, 8H, Ar-H); 3.55 (s, 3H, $-OCH_3$); .1.40-1.49(s, 6H, CH_3); 4.05 (s, 1H, -N-CH), 4.19 (s, 2H, SCH_2); MS spectrum, *m/z*: 371 $[M+1]^+$.

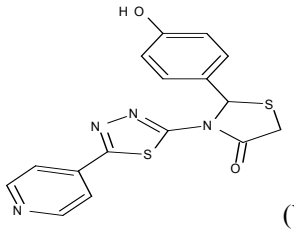
- **2-(2-hydroxyphenyl)-3-(5-pyridin-4-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIm)

The following spectral data were recorded for compound VIm: FTIR (KBr) cm^{-1}: 3548 (O-H); 3007 (Ar C-H); 2953 (C-H); 2875 (C-H thiazole); 1739 (-C=O), 675 (C-S-C). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.62 (s, 1H, CH); 7.81 (s, 1H, CH); 7.17-7.37 (m, 9H, Ar-H); 5.25 (s, 1H, OH); 4.16 (s, 1H, -N-CH), 4.17 (s, 2H, SCH_2); MS spectrum, *m/z*: 357 $[M+1]^+$.

- **2-(4-hydroxyphenyl)-3-(5-pyridin-4-yl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one**



(VIn)

The following spectral data were recorded for compound VI n: FTIR (KBr) cm^{-1}: 3545 (O-H); 3003 (Ar C-H); 2957 (C-H); 2876 (C-H thiazole); 1735 (-C=O), 677 (C-S-C). ^{1}H NMR chemical shifts at (400 MHz, $CDCl_3$, δ ppm): 9.63 (s, 1H, CH); 7.84 (s, 1H, CH); 7.16-7.34 (m, 9H, Ar-H); 5.24 (s, 1H, OH); 4.13 (s, 1H, -N-CH), 4.15 (s, 2H, SCH_2); MS spectrum, *m/z*: 357 $[M+1]^+$.

Table 2: Docking results of 2-(substituted) phenyl-3-[5-(substituted)phenyl[1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one (VIIa-n)

Compound	R	R^1	PDB CODE	E SCORE (KJ/ Mol)
VI a	Nicotinic acid	H	2YES	-137.43
VI b	Nicotinic acid	2-Cl	2YES	-139.67
VI c	Nicotinic acid	4-Cl	2YES	-138.88
VI d	Nicotinic acid	2-OCH_3	2YES	-143.38
VI e	Nicotinic acid	4-OCH_3	2YES	-146.24
VI f	Nicotinic acid	2-OH	2YES	-142.46
VI g	Nicotinic acid	4-OH	2YES	-145.91
VI h	Isonicotinic acid	H	2YES	-142.72
VI i	Isonicotinic acid	2-Cl	2YES	-143.48
VI j	Isonicotinic acid	4-Cl	2YES	-146.48
VI k	Isonicotinic acid	2-OCH_3	2YES	-147.61
VI l	Isonicotinic acid	4-OCH_3	2YES	-149.45
VI m	Isonicotinic acid	2-OH	2YES	-146.71
VI n	Isonicotinic acid	4-OH	2YES	-148.61

The synthesized compounds were docked with target protein for tuberculosis (2YES) to predict the antitubercular activity. The result of the docking studies clearly confirms that the synthesized compounds VIe, VIg, VIj and VIk are active against the tuberculosis and VIl and VIn compound showed potent antitubercular activity.

Table 3: Antitubercular activity of 2-(substituted) phenyl-3-[5-(substituted) phenyl [1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one(VII a-n)

Compound	R	R^1	MIC (µg/mL) *M. tuberculosis* $H_{37}Rv$
VI a	Nicotinic acid	H	25
VI b	Nicotinic acid	2-Cl	25
VI c	Nicotinic acid	4-Cl	25
VI d	Nicotinic acid	2-OCH_3	12.5
VI e	Nicotinic acid	4-OCH_3	6.25
VI f	Nicotinic acid	2-OH	12.5
VI g	Nicotinic acid	4-OH	6.25
VI h	Isonicotinic acid	H	12.5
VI i	Isonicotinic acid	2-Cl	12.5
VI j	Isonicotinic acid	4-Cl	6.25
VI k	Isonicotinic acid	2-OCH_3	6.25
VI l	Isonicotinic acid	4-OCH_3	1.6
VI m	Isonicotinic acid	2-OH	6.25
VI n	Isonicotinic acid	4-OH	3.125
Pyrazinamide			3.125
Streptomycin			6.25
Ciprofloxacin			3.125

CONCLUSION

A new series of 2-(substituted)phenyl-3-[5-(substituted)phenyl [1,3,4]thiadiazol-2-yl]-1,3-thiazolidin-4-one VI a-n were synthesized in good yields as shown in table and were evaluated for antibacterial, antifungal and antitubercular activities. Docking studies has been carried out by using Hex software for all title compounds. The structures of the synthesized compounds were confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR, FABMS data and elemental analysis. All the derivatives of VI a-n were analyzed for their physicochemical properties as shown in table. All the derivatives of VI a-n were docked with target protein for tuberculosis (2YES) to predict the antitubercular activity. The results of the docking study for all the derivatives are shown in table. The result of the docking studies clearly confirms that compounds VI e, VI g, VI j and VI k are active against the tuberculosis and VI l and VI n compound showed potent antitubercular activity. The antimycobacterial activities of compounds VI a-n were assessed against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) using Microplate Alamar Blue Assay (MABA). This methodology is nontoxic, uses a thermally-stable reagent and shows good correlation with BACTEC radiometric methods and the activity expressed as the minimum inhibitory concentration (MIC) in µg/ml. The MICs of the compounds were carried out and showed good antitubercular activity compared to standards pyrazinamide streptomycin and ciprofloxacin. In the series VI a-n, compounds VI l and VI n showed better antitubercular activity compared to all the standards pyrazinamide, streptomycin and ciprofloxacin and compounds VI e, VI g, VI j, VI k and VI m showed similar activity compared to standard streptomycin. The structure and biological activity relationship of title compounds showed that the presence of 1,3,4-thiadiazole nucleus and the substituent's like 2-methoxy benzaldehyde, 4-methoxy benzaldehyde, 2-hydroxy benzaldehyde and 4-hydroxy benzaldehyde attached to it will increases the activity.

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