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Novel imidazo[2,1-*b*][1,3,4]thiadiazole carrying rhodanine-3-acetic acid as potential antitubercular agents

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ABSTRACT

The increase in the prevalence of multi drug-resistant and extensively drug-resistant strains of *Mycobacterium tuberculosis* case demonstrates the urgent need of discovering new promising compounds with antimycobacterial activity. As part of our research program and with a aim of identifying new antitubercular drug candidates, a new class of 2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole derivatives has been synthesized by both conventional as well as microwave assisted method and evaluated for their in vitro antitubercular activity against *M. tuberculosis* H_{37}Rv. Moreover, various drug-likeness properties of new compounds were predicted. Seven compounds from the series exhibited good activity with MIC in range 3.12–1.56 μg/ml. The present study suggests that compounds **6b, 6c, 6d, 6e** and **6f** may serve as promising lead scaffolds for further generation of new anti-TB agents.

The prevalence of tuberculosis (TB) has steadily risen in the last decade. TB is a disease of poverty affecting mostly young adults in their most productive years. The vast majority of TB deaths are in the developing countries. The estimated death from TB was 1.7 million in 2009, including 380,000 people with HIV, equal to 4700 deaths a day.[1] TB is considered to be a major public health problem in India. India accounts for one-fifth of the global TB incident cases. Each year nearly 2 million people in India are infected by TB, of which around 0.87 million are infectious cases. It is estimated that annually around 330,000 Indians die due to TB.[2] Furthermore, the increase in TB cases caused by multi drug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis* (Mtb), which are insensitive to one or more of the first line drugs, has further worsened the situation.[3] Moreover, the association of TB and HIV infections has caused an urgent need in search of alternative chemotherapeutics for *M. tuberculosis* infections.

The diverse biological activities of imidazo[2,1-*b*][1,3,4]-thiadiazole and their derivatives have been known from early 1950s and since then, the research work on this heterocyclic system has led to significant developments in their chemistry and biology. Kolavi et al.[4] in 2006 reported some2-(2-furyl)-6-phenylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehyde and (2-cyclohexyl-6-phenylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl)methanol as antitubercular agents against *M. tuberculosis*. Subsequently, a large number of imidazo[2,1-*b*][1,3,4]-thiadiazole derivatives have been reported to possess diverse pharmacological activities, viz., antibacterial,[5,6] antifungal,[7] anticancer,[8,9] anticonvulsant and analgesic,[10] anthelmintic,[11] Carbonic anhydrase inhibitors,[12] calcium channel blocker,[13] diuretic activity.[14]

Thiazolidine-2,4-diones, rhodanines and their derivatives have attracted interest in medicinal chemistry, exhibiting pharmacological and therapeutic properties, since the introduction of various glitazones and epalrestat into clinical use for the treatment of type II diabetes mellitus and diabetic complications, respectively. Chemical modifications of these heterocycles constantly result in compounds with a wide spectrum of biological activities. Singh et al.[15] in 2008 reported the antitubercular effects of rhodanines. Bryk et al.[16] in 2008 have reported some of furan derivatives of rhodanines as irreversible, substrate-dependent and time-dependent inhibitor of Mtb dihydrolipoamide acylatransferase (DlaT). Tomasic et al.[17] in 2009 have reported some thiazolidine-2,4-diones and rhodanines are active inhibitors of Mur ligases. Rhodanine-based molecules have been shown to be small molecule inhibitors of numerous targets such as hepatitis C virus (HVC) NS3 protease,[18] β-lactamase,[19] UDP-*N*-acetylmuramate/L-alanine ligase,[20] penicillin binding protein (PBP),[21] and histidine decarboxylase.[22] In addition, Talele et al.[23] in 2010 have reported that rhodanine analogs are inhibitors of the HCV enzyme NS5B polymerase.

In view of the high degree of bioactivity shown by the above two heterocyclic system, and continuation of our search for biological active heterocyclic compounds, it was envisaged to construct a

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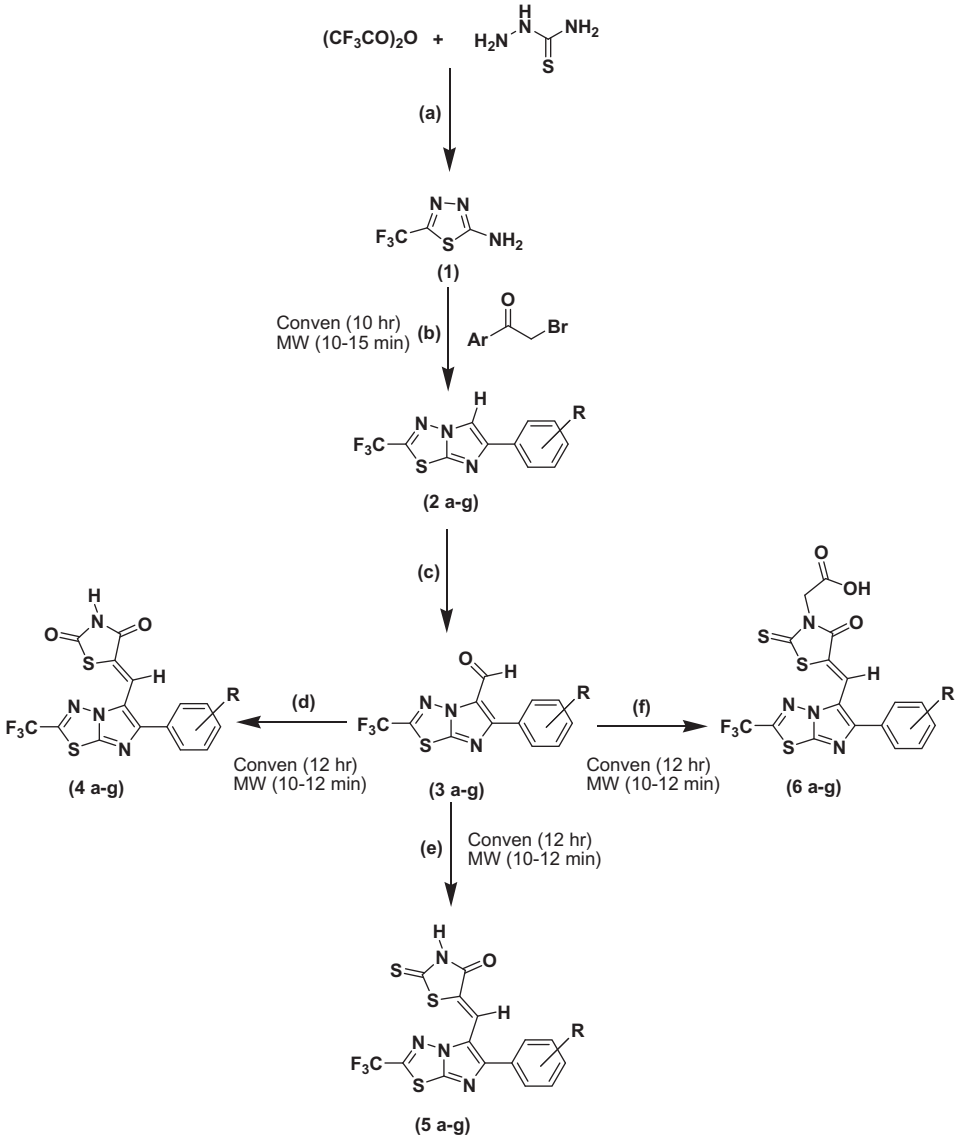
system, which combines both these systems in a single molecular frame and to explore the additive effects towards their antitubercular activities. Hence we have synthesized and evaluated new series of 2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazole derivatives.

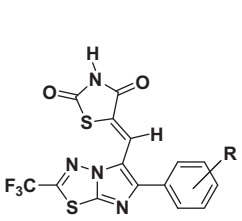
The 21 new 2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazole derivatives presented in this work were prepared through the synthetic route illustrated in Scheme 1. The route adapted for the synthesis of 2-(trifluoromethyl)-6-arylimidazo-[2,1-*b*][1,3,4]-thiadiazole compounds using a modified literature method.[24] The starting compounds 2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazoles (**2a–g**) were synthesised by microwave assisted reaction between 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine (**1**) and various substituted α-haloaryl ketone. In the next step, imidazo[2,1-*b*][1,3,4]-thiadiazoles **(2a–g)** were subjected in to Vilsmeier–Haack reaction to afford 2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehydes **(3a–g)**. Then, obtained imidazo[2,1-*b*][1,3,4]thiadiazoles-5-carbaldehydes **(3a–g)** were subjected to Knoevenagel condensation[25,26] with thiazolidine-2,4-dione, 2-thioxothiazolidin-4-one (rhodanine) and 2-(4-oxo-2-thioxothiazolidin-3-yl)acetic acid (rhodanine acetic acid) in the presence of catalytic amount of piperidineacetate to afford 5-{[2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl]methylene}thiazolidine-2,4-dione **(4a–g)**, 5-{[2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl]methylene}-2-thioxothiazolidin-4-one **(5a–g)** and 2-[(5*Z*)-5-{[2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl]methylene}-4-oxo-2-thioxothiazolidin-3-yl]acetic acid **(6a–g)** respectively. Purity of the compounds was checked on TLC plates (silica gel G) which were visualized by exposing to iodine vapours. All the reactions under microwave irradiation were completed within 10–15 min whereas similar reactions under conventional heating (oil bath) at reflux gave poor yields after much longer reaction time. The comparison study data are given in Table 1. The structures of these compounds were confirmed by IR, NMR, mass spectra and also by elemental analysis.

The formation of 5-(trifluoromethyl)-1,3,4-thiadiazol-2-amine **(1)** by IR and ^{1}H NMR spectra, which showed the presence of amine (–NH_2) band at 3468 cm^{-1} in the IR spectra and appearance of amine proton at δ 7.96 ppm in the ^{1}H NMR spectra. Structures of imidazothiadiazole derivatives (**2a–g**) were established by the absence of amine (–NH_2) band in IR spectra, and the ^{1}H NMR spectra

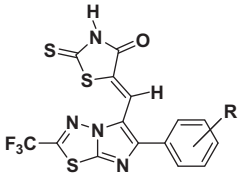


Scheme 1. Reagents and conditions: (a) −5 to 0 °C, 2 h, 81%; (b) M.W. (600 watts) 10–15 min; 65–71%; (c) Vilsmeiere–Haack reagent, 8 h, 50–66%; (d) thiazolidine-2,4-dione, M.W. (600 watts) 10 min; 69–72%; (e) rhodanine, M.W. (600 watts) 12 min; 69–75%; (f) rhodanine acetic acid, M.W. (600 watts) 12 min 68–76%.

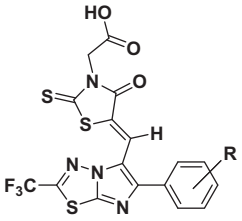
Table 1
Physical constant and antimycobacterial activity of 2-(trifluoromethyl)-6-arylimidazo [2,1-*b*][1,3,4]-thiadiazole derivatives



(4 a-g)



(5 a-g)



(6 a-g)

Compound	R	Mol. formula	Mol. wt	Mp[a] (°C)	Conventional method		Microwave method		MIC (μg/ml)
					Yield (%)	Period (h)	Yield (%)	Period (min)	
4a	H	$C_{15}H_7F_3N_4O_2S_2$	396	211–212	57	15	69	10	25
4b	Cl	$C_{15}H_6ClF_3N_4O_2S_2$	430	220–222	53	15	71	10	3.12
4c	Br	$C_{15}H_6BrF_3N_4O_2S_2$	475	150–151	45	15	72	10	25
4d	F	$C_{15}H_6F_4N_4O_2S_2$	414	194–195	52	15	71	10	25
4e	CH_3	$C_{16}H_9F_3N_4O_2S_2$	410	270–271	44	15	70	10	25
4f	OCH_3	$C_{16}H_9F_3N_4O_3S_2$	426	270–272	48	15	69	10	25
4g	NO_2	$C_{15}H_6F_3N_5O_4S_2$	441	266–267	50	15	72	10	50
5a	H	$C_{15}H_7F_3N_4OS_3$	412	250–251	57	15	70	10	6.25
5b	Cl	$C_{15}H_6ClF_3N_4OS_3$	446	210–211	55	15	69	10	50
5c	Br	$C_{15}H_6BrF_3N_4OS_3$	491	195–197	52	15	71	10	3.12
5d	F	$C_{15}H_6F_4N_4OS_3$	430	190–192	53	15	72	10	6.25
5e	CH_3	$C_{16}H_9F_3N_4OS_3$	426	270–272	54	15	71	10	6.25
5f	OCH_3	$C_{16}H_9F_3N_4O_2S_3$	442	228–230	56	15	75	10	25
5g	NO_2	$C_{15}H_6F_3N_5O_3S_3$	457	270–271	51	15	70	12	50
6a	H	$C_{17}H_9F_3N_4O_3S_3$	470	246–247	55	15	69	10	6.25
6b	Cl	$C_{17}H_8ClF_3N_4O_3S_3$	504	180–182	51	15	69	10	3.12
6c	Br	$C_{17}H_8BrF_3N_4O_3S_3$	549	158–159	54	15	67	10	3.12
6d	F	$C_{17}H_8F_4N_4O_3S_3$	488	210–211	58	15	76	10	3.12
6e	CH_3	$C_{18}H_{11}F_3N_4O_3S_3$	484	237–238	56	15	73	11	3.12
6f	OCH_3	$C_{18}H_{11}F_3N_4O_4S_3$	500	216–217	58	15	74	10	1.56
6g	NO_2	$C_{17}H_8F_3N_5O_5S_3$	515	255–256	50	15	68	13	25
Rifampicin	—	—	—	—	—	—	—	—	0.78
Isoniazid	—	—	—	—	—	—	—	—	1.56

[a] Melting points are uncorrected.

revealed that singlet at the region of δ 7.91–8.12 ppm was assigned to the imidazole proton (H-5). IR spectra of imidazo[2,1-*b*][1,3,4]thiadiazoles-5-carbaldehydes **(3a–g)** displayed a sharp band for carbonyl stretching frequency around 1695 cm^{-1} and the signal for imidazole proton (H-5) in ^1H NMR spectrum was absent. A new signal for aldehyde proton was observed around δ 10 ppm in the ^1H NMR spectra, thus substantiating the formation of imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes.

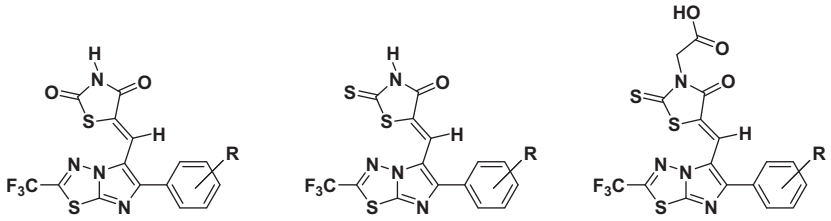
The formation of title compounds **(4a–g), (5a–g)** and **(6a–g)** was confirmed by the absence of signal for aldehyde proton in ^1H NMR spectra, the appearance of 5-methylidene proton was observed around δ 7.8 ppm. In the ^1H NMR spectra of 5-{[2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl]methylene} thiazolidine-2,4-dione (**4a–g**) and 5-{[2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl]methylene}-2-thioxothiazolidin-4-one **(5a–g)** a signal attributable to NH resonance was diagnostic: in particular ^1H NMR spectra showed singlet at δ 11.56–12.45 ppm for thiazolidinedione compounds and δ 12.65–12.87 ppm for rhodanine compounds. The structure of rhodanine acetic acid compounds **(6a–g)** were also confirmed by means of their characteristic N–CH_2 resonance at δ 4.68–4.87 ppm. The elemental analysis results were within ±0.4% of the theoretical values.

The antitubercular activities of newly synthesized compounds **(4a–g), (5a–g)** and **(6a–g)** have been assessed against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) using the Micro plate Alamar Blue assay (MABA) method.[27] The activity is expressed as minimum inhibitory concentration (MIC), that is the lowest concentration of compound which prevented the colour change from blue to pink, the MIC of the synthesized compounds determined in duplicate along with that of standard drug are reported in Table 1 with standard drug Isoniazid and rifampicin for the comparison.

The data of the antitubercular activity screening reveal that the compounds (**4a–g)** having a thiazolidinedione moiety did not show any considerable activity except compound **4b** (MIC at 3.12 μg/ml), in spite of the changes at position-6 of imidazo[2,1-*b*][1,3,4]thiadiazole system. However, when a rhodanine moiety was introduced in place of thiazolidinedione (**5a–g**), it resulted in some molecules having enhanced antimycobacterial activity. Compounds **5a**, **5d**, and **5e** exhibited antitubercular activity at MIC value 6.25 μg/ml, and **5c** at MIC value 3.12 μg/ml. Promising antimycobacterial activity profile was also found when rhodanine-3-acetic acid replaced by rhodanine (**6a–g**). Among seven compounds in this series, five compounds (**6b, 6c, 6d, 6e** and **6f**) were found to be active with minimum inhibitory concentration of 1.56–3.12 μg/ml. The compound **6f** was found to be active against MTB at a MIC 1.56 μg/ml comparable to that of Isoniazid. Finally, these studies suggests that imidazo[2,1-*b*][1,3,4]thiadiazole carrying rhodanine-3-acetic acid as potential antitubercular agents.

The computed molecular properties are shown in Table 2. The degree of absorption is expressed by the percentage of absorption. Absorption percent (%ABS) was calculated by using %ABS = 109 − (0.345 × TPSA).[28,29] Molecular polar surface area (PSA), Log *P*, number of rotatable bonds, number of hydrogen bond donor and accepter atoms of Lipinski's rule of five[30] were calculated using Molinspiration online property calculation toolkit.[31] Drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft[32] software.

Table 2
Calculated absorption (%ABS), polar surface area (PSA), Lipinski parameters and drug-likeness model score of title compounds **(4a–g)**, **(5a–g)** and **(6a–g)**



Compound	R	%ABS	Volume	PSA	NROTB	HBA	HBD	Log*p*, calcd	Formula weight	Drug-likeness model score
4a	H	81.35	283.58	80.13	3	6	1	2.78	396	−0.09
4b	Cl	81.35	297.11	80.13	3	6	1	3.46	430	0.01
4c	Br	81.35	301.46	80.13	3	6	1	3.59	475	−0.39
4d	F	81.35	288.51	80.13	3	6	1	2.94	414	−0.32
4e	CH_3	81.35	300.14	80.13	3	6	1	3.23	410	−0.24
4f	OCH_3	78.17	309.12	89.36	4	7	1	2.83	426	−0.03
4g	NO_2	65.54	306.91	125.95	4	9	1	2.74	441	−0.64
5a	H	87.24	292.45	63.06	3	5	1	3.12	412	−0.24
5b	Cl	87.24	305.99	63.06	3	5	1	3.80	446	−0.12
5c	Br	87.24	310.34	63.06	3	5	1	3.93	491	−0.50
5d	F	87.24	297.39	63.06	3	5	1	3.28	430	−0.42
5e	CH_3	87.24	309.01	63.06	3	5	1	3.57	426	−0.35
5f	OCH_3	84.05	318.00	72.29	4	6	1	3.18	442	−0.11
5g	NO_2	71.43	315.79	108.88	4	8	1	3.08	457	−0.72
6a	H	78.12	336.64	89.50	5	7	1	2.43	470	−0.09
6b	Cl	78.12	350.17	89.50	5	7	1	3.11	504	0.02
6c	Br	78.12	354.52	89.50	5	7	1	3.24	549	−0.31
6d	F	78.12	341.57	89.50	5	7	1	2.60	488	−0.24
6e	CH_3	78.12	353.20	89.50	5	7	1	2.88	484	−0.16
6f	OCH_3	74.93	362.18	98.73	6	8	1	2.49	500	0.15
6g	NO_2	62.42	359.97	135.32	6	10	1	2.39	515	−0.49

Pharmacokinetic property optimization is a rather complex undertaking that is likely to require changes in those molecular determinants that are responsible for binding affinity and specificity like hydrogen bonds. Hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) groups in the compound optimize the drug receptor interaction. Number of hydrogen bond acceptor ($\leqslant$10) and hydrogen bond donor ($\leqslant$5) in the proposed compounds obeys the Lipinski's rule of five, so it may have some of the compounds good absorption or permeability properties through the biological membrane. Dissolution is highly interdependent influences of aqueous solubility, ionizability (pK_a) and lipophilicity ($\log P$). Furthermore, $\log P$ is a crucial factor governing passive membrane partitioning, influencing permeability opposite to its effect on solubility. The $\log P$ values of the synthesized compounds lie in between 2.39 and 3.93. In addition, molecular weight of the compound is important in drug action, if the molecular weight is increased beyond a limit, the bulkiness of the compounds also increases, which will affect the drug action (affect the drug receptor/DNA interactions). Molecular weight of compounds like **4a–g, 5a–g** and **6a, 6d, 6e, and 6f** lies between 396 and 500 show that these compounds follows Lipinski's rule of five. So the bulkiness of the compounds is in optimum limit for the action. Molecular polar surface area (PSA) is a sum of surfaces of polar atoms (usually nitrogen and oxygen attached hydrogen) in a molecule. PSA is a very useful parameter for the prediction of drug transport property. PSA is inversely proportional to %ABS. Compounds like **5a, 5b, 5c, 5d** and **5e** have maximum absorption as their corresponding polar surface area was least among the series.

In conclusion, we have developed a simple, highly efficient, cost effective, and environmentally friendly method for the synthesis of 2-(trifluoromethyl)-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazole derivatives by using microwave irradiation technique. It has been demonstrated that the use of microwave heating can dramatically cut down reaction time, increase product purity and yields. The synthesized compounds were evaluated for their in vitro antitubercular activity against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294). Based on SAR studies suggests that compounds **6b, 6c, 6d, 6e** and **6f** may serve as promising lead scaffolds for further generation of new antitubercular agents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.052.

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