Heterocyclic Letters
Vol. 10| No.2|299-307|Feb–April | 2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL SCREENING OF SOME NOVEL IMIDAZOL ASSOCIATED 1,2,4-TRIAZOLO LINKED 1,3,4-THIADIAZINE

M. SOMESWARA RAO[1], B. PULLA RAO[2], Ch. PURNA KOTESWARA RAO[1] and T. BHASKARA RAO[*1]

[1]Department of Chemistry, Koneru Lakshmaiah Education Foundation, Green fields, Vaddeswaram, Guntur- 522502, India
[2]Department of Chemistry, Acharya Nagajuna University, Nagarjuna Nagar, Guntur-522 510, India, E-mail: tbhaskararao208@gmail.com

ABSTRACT: Several novel imidazole associated 3-(1-methyl-1*H*-imidazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **(6a-f)** have been synthesized by using 1-methyl-1*H*-imidazole-5-carboxylic acid **(1)** as starting material and by participating four corresponding intermediates through different type of reactions like substitution, condensation and cyclization. The chemical structures of all the newly synthesized intermediates and products were confirmed by IR, ^{1}H NMR, mass spectral studies and elemental analysis. Further, the synthesized target compounds were used to screen for their antibacterial activity.

KEYWORDS: Imidazole, 1,2,4-Triazole, 1,3,4-Thiadiazine, Antibacterial activity

INTRODUCTION

Literature survey revealed that the history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry. After World War II, there was an enormous explosion research in the field of heterocycles. About one half of over six million compounds recorded in Chemical Abstracts are heterocyclic. Heterocyclic chemistry is one of the most complex and intriguing branch of organic chemistry and heterocyclic compounds constitute the largest and most varied family of organic compounds. Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry and biochemistry. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents.

Heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. Since in heterocycles non-carbons usually are considered to replace carbon atoms, they are called heteroatoms e.g. different from carbon and hydrogen. A ring with only heteroatoms is called homocyclic compound and heterocycles are the counterparts of

homocyclic compounds. Thus incorporation of oxygen, nitrogen, sulfur or an atom of a related element into an organic ring structure in place of a carbon atom gives rise to a heterocyclic compound. These structures may comprise either simple aromatic rings or non-aromatic rings. The heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyzed or depolymerized. Heterocycles with three atoms in the ring are more reactive because of ring strain. Those containing one heteroatom are in general, stable. Those with two hetero atoms are more likely to occur as reactive intermediates. Heterocyclic compounds played a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthocyanins and flavones as well as in haem and chlorophyll. Additionally some vitamins, proteins, hormones contain aromatic heterocyclic system. Synthetically produced heterocycles designed by organic chemists are used for instance as agrochemicals and pharmaceuticals and play an important role in human life. Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs. In short, heterocyclic chemistry is the branch of chemistry dealing with synthesis, properties and applications of heterocycles. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, while countless additives and modifiers used in industrial application ranging for cosmetics, reprography, information storage and plastics are heterocyclic in nature.

The therapeutic effect of 1,2,4-triazoles have been well studied for a number of pathological conditions including inflammation, cancer, pain, tuberculosis and hypertension [i-ix]. In addition, it was reported that 1,3,4-thiadiazine exhibits various biological activities possibly due to the presence of the N-C-S moiety. Moreover, synthesis of triazoles fused to another heterocyclic ring has attracted wide spread attention due to their diverse applications as antibacterial, antidepressant, antiviral, antitumor, anti-inflammatory agents, pesticides, herbicides, dyes, lubricant and analytical reagents [x,xi].

It is known that many 1,3,4-thiadiazole and derivatives have biological activity, with their antibacterial [xii], antimycobacterial [xiii], antimycotic [xiv], antifungal [xv], antidepression [xvi] and cardiotonic [xvii] action being notable. Recent research has also established for these heterocycles as analgesic [xviii] and anti-inflammatory [xix] activity. The literature for heterocyclic pharmaceutical agents includes sulphur containing compounds particularly those incorporating the N-C-S linkage in their skeleton exhibit a broad spectrum of pharmacological activities such as antimalarial [xx], HIV-1 inhibitors [xxi] and antimicrobial [xxii].

Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level [xxiii]. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures [xxiv]. In that connection, the high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Medicinal properties of imidazole include anticancer, synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial [xxv-xxxix].

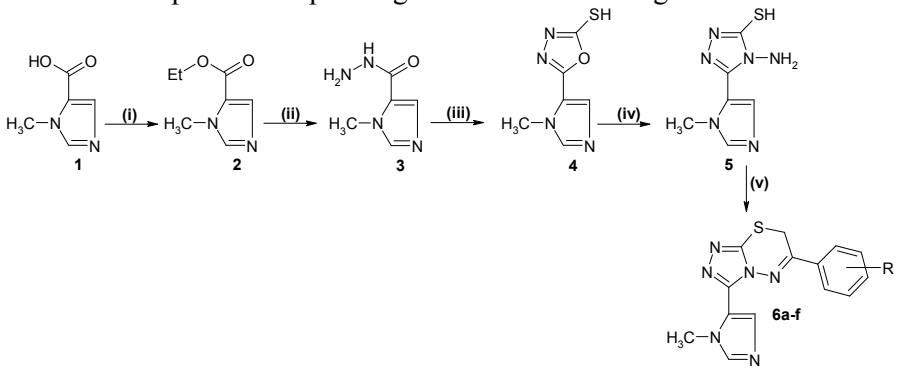
RESULTS AND DISCUSSION

These initial reports stimulated us to synthesize biologically active heterocycles, we integrated 3-imidazole and 1,2,4-triazole moieties into 1,3,4-thiadiazine, since these systems possess well documented activity. Accordingly, in this paper, we reported the synthesis of 3-(1-methyl-1*H*-imidazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo [3,4-b][1,3,4]-thiadia-zine and its derivatives **(6a-f)**. The syntheses of the target compounds **6a-f** commenced from

commercially available 1-methyl-1*H*-imidazole-5-carboxylic acid **(1)**. The chemical structures of all the newly synthesized intermediates and products were confirmed by IR, ^{1}H NMR, mass spectral studies and elemental analysis. The synthetic route leading to the title compounds is summarized in scheme 1.

Thus, the initial intermediate, ethyl-1-methyl-1*H*-imidazole-5-carboxylate **(2)**, has been prepared in excellent yield by boiling of a mixture of compound **1** and absolute ethyl alcohol in the presence of catalytic amount of conc. H_2SO_4 for 5 h with constant stirring. . The structure of this intermediate was characterized by IR, ^{1}H-NMR, Mass spectra and elemental analysis. Its IR spectrum showed strong absorption bands at 1742 and 1640 cm^{-1} due to (C=O) and (C=N) groups respectively. In addition, the appearance of the absorption band at 1145 cm^{-1} corresponding to the C-O stretching vibration. In the ^{1}H-NMR spectrum, the characteristic CH_3 and CH_2 of ethyl group resonated as triplet and quartet at δ 1.29 ppm and δ 4.12 ppm respectively by disappearing OH group. Final proof for the structure was obtained by recording its mass spectrum, which exhibited a molecular ion peak at m/z 154 corresponding to its molecular weight.

Then the intermediate **2** is turned into next intermediate, 1-methyl-1*H*-imidazole-5-carbohydrazide **(3)**, when reacts with hydrazine hydrate in ethyl alcohol at reflux for 4 h with uniform stirring. The success of the oxidation reaction was confirmed by IR, ^{1}H-NMR and Mass spectral analysis of compound **3**. In the IR spectrum, the characteristic N-H and C=O groups were observed at 3240 and 1640 cm^{-1}. Its ^{1}H-NMR spectrum not showed signals of CH_3 and CH_2 groups which are present in its precursor **2**. The mass spectrum of the prepared compound contains the peak corresponding to its molecular weight at 140.



Scheme 1: (i) H_2SO_4, EtOH, reflux, 5 h; **(ii)** NH_2NH_2, EtOH, reflux, 4 h; **(iii)** CS_2, KOH, EtOH, reflux, 8 h; **(iv)** NH_2NH_2, EtOH, reflux, 6 h; **(v)** PhCOCHBr**,** EtOH, reflux, 7-9 h; **6(a)** R = H, **(b)** R = 2-CH_3, **(c)** R = 2-OCH_3, **(d)** R = 2-Cl, **(e)** R = 2-Br, **(f)** R = 2-NO_2

Further intermediate, 5-(1-methyl-1*H*-imidazol-5-yl)-1,3,4-oxadiazole-2-thiol **(4)** has been achieved in good yield from the reaction occurred between compound **3** and carbon disulfide in presence of potassium hydroxide in ethanol at reflux for 8 h on steady stirring followed by acidification. The structure of compound **4a** was established through by spectroscopic (IR, ^{1}H-NMR, MS) as well as elemental analyses data. The IR spectrum showed characteristic absorption peak at 2836 cm^{-1} assigned to S-H group along with other expected bands. From the ^{1}H-NMR spectrum, the appearance of signal related to the S-H group as singlet at δ 10.85 ppm was a clear evidence for the formation of this compound and the MS spectrum of showed M^+ ion peak at m/z 182 consistent with its molecular formula.
Then this intermediate **4** is converted into final intermediate, 4-amino-5-(1-methyl-1*H*-imidazol-5-yl)-4*H*-[1,2,4]-triazole-2-thiol **(5)** in excellent yield when reacts with hydrazine

hydrate in ethanol at reflux for 6 h with consistent stirring. The chemical structure of the final intermediate **5** has been established on the basis IR, ^{1}H NMR, MS spectra and elemental analysis. The IR spectra of this series of compounds disclosed the appearance broad absorption band corresponding to the N-H of NH_2 group at 3365 cm^{-1}. In the ^{1}H-NMR spectrum, one S-H group was recorded at the related δ-chemical shift value due to the formation of triazole ring. The MS spectrum of this compound **5** contained the peaks corresponding to their molecular weights.

Finally, the target compounds, 3-(1-methyl-1*H*-imidazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo [3,4-b][1,3,4]-thiadiazine and its derivatives **(6a-f)** have been synthesized in good to excellent yields successfully from the condensation reaction performed between compound **5** and a variety of phenacyl-bromides in ethanol under reflux for 7-9 h on uniform stirring. The IR spectrum of compound **6a** clearly showed the presence of two characteristic bands at 1264 and 1148 cm^{-1} are assigned to C-S and C-O groups. The formation of the thiadiazine ring in the proposed structure of compound **6a** was also established on the basis of its ^{1}H-NMR spectrum in which the existence of a characteristic singlet at δ 3.90 ppm assigned to the S-CH_2 group confirming the completion of the reaction. The mass spectrum of compound **6a** showed M^+ peak at m/z 296 in agreement with its molecular formula. The chemical structures of the rest of compounds of this series **6b-f** were identified with their different spectra. Further, the target compounds were used to find their antimicrobial ability against different microorganisms.

ANTIMICROBIAL ACTIVITY

The antibacterial and antifungal activities of the target compounds, 3-(1-methyl-1*H*-imidazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo [3,4-b][1,3,4] thiadiazines **(6a-f)** have been performed with cup plate method [40] using nutrient agar medium against four bacterial stains such as *Stapylococcus aureous*, *Streptococcus pyogenes*, *Escherichia coli* and *Pseudomonas aureginosa* and towards one fungal organism like *Candida albicans*. Ampicilline and Fluoconazole were used as reference drugs for antibacterial and antifungal study respectively. The DMSO was used as sample solution and the size of sample of all compounds was fixed at 0.1 mL and the concentration is restricted at 100 μg/mL. The test compound solution (0.1 mL) was added in the cups and the petri dishes were subsequently incubated at 37 ^{o}C for 48 hrs. Zone of inhibition produced by each compound was measured in mm and the results are listed in Table 1. According to the results, compounds **6c**, **6e** and **6f** are highly active against all types of tested bacteria. Compounds like **6c** and **6f** are also highly active against *S. aureus*. Compounds **6a** and **6d** are highly active against *P. aureginosa* and *C. albicans* while compound **6b** is highly active against *P. aureginosa* and *E. coli*. The rest of products were found to be moderately active against the tested organisms. It is interesting to note that, none of the compound is inactive towards any microorganism this property may be obtained to the target compound by incorporating imidazole and triazole rings into thiadiazine moiety. The outstanding properties of this new class of antibacterial substances deserve further investigation in order to clarify the mode of action at molecular level, responsible for the activity observed. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure-activity relationship (SAR) and to optimize the effectiveness of this series of molecules.

Table 1: Antimicrobial activity of compounds 6a-f (Zones of inhibition in mm)

Compound	**Antibacterial activity**				**Antifungal activity**
	S. aureus	*S. pyogenes*	*P. aureginosa*	*E. coli*	*C. albicans*

6a	10.5	13.6	11.2	10.4	15.4
6b	12.7	12.4	12.8	12.7	11.5
6c	17.8	16.6	13.6	13.5	15.3
6d	12.5	14.2	13.7	10.3	14.5
6e	11.7	17.8	13.3	13.2	12.7
6f	17.3	16.3	12.3	13.5	15.6
Ampicilline	18	14	14	16	—
Fluoconazole	—	—	—	—	18

EXPERIMENTAL

All 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. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer. The chemical shifts were reported as ppm down field using TMS as an internal standard. Electrospray ionization (ESI) mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV.

Preparation of ethyl-1-methyl-1*H*-imidazole-5-carboxylate (2)

To the solution of 1-methyl-1*H*-imidazole-5-carboxylic acid **(1)** (0.01 mol) in absolute ethyl alcohol (10 ml), conc. H_2SO_4 (2 ml) was added. The mixture was refluxed for 5 h with constant stirring. After completion of the reaction (monitored by the TLC), the mixture was poured into ice-cold water. Crude product was collected by filtration, washed with 10% $NaHCO_3$ solution, dried and recrystallized from ethyl alcohol to get pure ethyl-1-methyl-1*H*-imidazole-5-carboxylate **(2)**.

Preparation of 1-methyl-1*H*-imidazole-5-carbohydrazide (3)

A mixture of ethyl-1-methyl-1*H*-imidazole-5-carboxylate **(2)** (0.01 mol) and hydrazine hydrate (0.02 mol) in ethyl alcohol (20 ml) was refluxed for 4 h with consistent stirring. After realization of the reaction (examined by the TLC), the reaction mixture is cooled to room temperature and filtered. The crude product was recrystallized from ethanol to offer pure 1-methyl-1*H*-imidazole-5-carbohydrazide **(3)**.

Preparation of 5-(1-methyl-1*H*-imidazol-5-yl)-1,3,4-oxadiazole-2-thiol (4)

A mixture of 1-methyl-1*H*-imidazole-5-carbohydrazide **(3)** (0.01 mol), potassium hydroxide (0.02 mol) and carbon disulfide (0.01 mol) in ethanol (25 ml) was heated under reflux with steady stirring for 8 h. After accomplishment of the reaction (scanned by the TLC), the solvent was distilled *in vacuo*, the residual mass was poured over crushed ice and neutralized the alkaline solution with 10% hydrochloric acid. The precipitated crude product was filtered, washed with water, dried and recrystallized from ethanol to achieve pure 5-(1-methyl-1*H*-imidazol-5-yl)-1,3,4-oxadiazole-2-thiol **(4)**.

Preparation of 4-amino-5-(1-methyl-1*H*-imidazol-5-yl)-4*H*-[1,2,4]-triazole-2-thiol (5)

To a warm solution of 5-(1-methyl-1*H*-imidazol-5-yl)-1,3,4-oxadiazole-2-thiol **(4)** (0.01 mol) in ethanol (15 ml), 80% hydrazine hydrate (0.02 mol) was added drop wise and the reaction mixture was heated under reflux for 6 h with stable stirring. After fulfilment of the reaction (scrutinized by the TLC), the solvent was distilled off *in vacuo,* cooled and the crystals separated were filtered, washed with cold ethanol and recrystallized from chloroform to give pure 5-(1-methyl-1*H*-imidazol-5-yl)-4*H*-[1,2,4]-triazole-2-thiol **(5)**.

Preparation of 3-(1-methyl-1*H*-imidazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-es (6a-f)

A mixture of 5-(1-methyl-1*H*-imidazol-5-yl)-4*H*-[1,2,4]-triazole-2-thiol **(5)** (0.01 mol) and corresponding phenacylbromide (0.01 mol) in absolute ethanol (15 ml), was refluxed for 7-9 h with sustained stirring. After achievement of the reaction (inspected by the TLC), the reaction mixture was concentrated and cooled to room temperature, and the remaining solvent was removed under reduced pressure, then diethyl ether (10 ml) was added and the reaction mixture was left at 0 ^{o}C for overnight. The precipitated solid was filtered off; the crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to afford pure 3-(1-methyl-1*H*-imidazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazines **(6a-f)**.

PHYSICAL AND SPECTRAL DATA

Ethyl-1-methyl-1*H*-imidazole-5-carboxylate (2)

Yellow solid; Yield 80%; Mp 112-114 ^{0}C; IR (KBr) 3024 (=C-H), 2945 (C-H, CH_3), 1742 (C=O), 1640 (C=N) 1560 (C=C), 1145 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 5.4 Hz, CH_3), 2.42 (s, 3H, CH_3), 4.12 (q, 2H, J = 5.4 Hz, CH_2), 7.12 (s, 1H, CH), 7.45 (s, 1H, CH); MS *m/z* 154 (M^+); Elemental analysis: Calculated for $C_7H_{10}N_2O_2$: C-54.54, H-6.54, N-18.17, O-20.76. Found: C-54.41, H-6.53, N-18.15, O-20.74.

1-Methyl-1*H*-imidazole-5-carbohydrazide (3)

Pale yellow solid; Yield 75%; Mp 120-122 ^{0}C; IR (KBr) 3240 (N-H), 3035 (=C-H), 2954 (C-H, CH_3), 1640 (C=O), 1630 (C=N), 1568 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H, CH_3), 5.28 (s, 2H, NH_2), 7.21 (s, 1H, CH), 7.45 (s, 1H, CH), 7.58 (s, 1H, NH); MS *m/z* 140 (M^+); Elemental analysis: Calculated for $C_5H_8N_4O$: C-42.85, H-5.75, N-39.98, O-11.42. Found: C-42.78, H-5.74, N-39.95, O-11.41.

5-(1-Methyl-1*H*-imidazol-5-yl)-1,3,4-oxadiazole-2-thiol (4)

White solid; Yield 70%; Mp 136-138 ^{0}C; IR (KBr) 3041 (=C-H), 2936 (C-H, CH_3), 2836 (S-H), 1642 (C=N), 1610 (C=C), 1128 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 7.32 (s, 1H, =C-H), 7.52 (s, 1H, =C-H), 10.85 (s, 1H, S-H); MS *m/z* 182 (M^+); Elemental analysis: Calculated for $C_6H_6N_4OS$: C-39.55, H-3.32, N-30.75, O-8.78, S-17.60. Found: C-39.52, H-3.31, N-30.73, O-8.77, S-17.59.

4-Amino-5-(1-methyl-1*H*-imidazol-5-yl)-4*H*-[1,2,4]-triazole-2-thiol (5)

Brown solid; Yield 69%; Mp 105-107 ^{0}C; IR (KBr) 3365 (N-H, NH_2), 3038 ((=C-H), 2928 (C-H, CH_3), 2848 (S-H), 1635 (C=N), 1575 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 2H, NH_2), 2.66 (s, 3H, CH_3), 7.33 (s, 1H, =CH), 7.59 (s, 1H, =CH), 10.21 (s, 1H, S-H); MS *m/z* 196 (M^+); Elemental analysis: Calculated for $C_6H_8N_6S$: C-36.72, H-4.11, N-42.83, S-16.34. Found: C-36.69, H-4.10, N-42.80, S-16.33.

3-(1-Methyl-1*H*-imidazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (6a)

Yellow solid; Yield 74%; Mp 108-110 ^{0}C; IR (KBr) 3057 (C-H, Ar), 2959 (C-H, CH_3), 1652 (C=N), 1632 (C=C, Ar), 1264 (C-S), 1148 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69 (s, 3H, CH_3), 3.57 (s, 3H, O-CH_3), 3.90 (s, 2H, S-CH_2), 7.35 (s, 1H, =CH), 7.39-7.55 (m, 4H, Ar-H), 7.55 (s, 1H, =CH); MS *m/z* 296 (M^+); Elemental analysis: Calculated for $C_{14}H_{12}N_6OS$: C-56.74, H-4.08, N-28.36, S-10.82. Found: C-56.74, H-4.08, N-28.36, S-10.82.

3-(1-Methyl-1*H*-imidazol-5-yl)-6-*o*-tolyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (6b)
Pale yellow solid; Yield 71%; Mp 139-141 ^{0}C; IR (KBr) 3048 (C-H, Ar), 2968 (C-H, CH_3), 1660 (C=N), 1625 (C=C, Ar), 1275 (C-S), 1158 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 3H, CH_3), 3.51 (s, 3H, CH_3), 3.74 (s, 2H, S-CH_2), 7.25 (s, 1H, =CH), 7.39-7.68 (m, 4H, Ar-H), 7.49 (s, 1H, =CH); MS *m/z* 310 (M^+); Elemental analysis: Calculated for $C_{15}H_{14}N_6S$: C-58.05, H-4.55, N-27.08, S-10.33. Found: C-58.00, H-4.54, N-27.06, S-10.32.

6-(2-Methoxyphenyl)-3-(1-methyl-1*H*-imidazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (6c)
Yellow solid; Yield 67%; Mp 120-122 ^{0}C; IR (KBr) 3051 (C-H, Ar), 2964 (C-H, CH_3), 1648 (C=N), 1623 (C=C, Ar), 1270 (C-S), 1148 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (s, 3H, CH_3), 3.54 (s, 3H, O-CH_3), 3.87 (s, 2H, S-CH_2), 7.32 (s, 1H, =CH), 7.34-7.59 (m, 4H, Ar-H), 7.52 (s, 1H, =CH); MS *m/z* 326 (M^+); Elemental analysis: Calculated for $C_{15}H_{14}N_6OS$: C-55.20, H-4.32, N-25.75, O-4.90, S-9.82. Found: C-55.12, H-4.31, N-25.72, O-4.89, S-9.81.

6-(2-Chlorophenyl)-3-(1-methyl-1*H*-imidazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (6d)
Yellow solid; Yield 74%; Mp 112-114 ^{0}C; IR (KBr) 3064 (C-H, Ar), 2976 (C-H, CH_3), 1655 (C=N), 1637 (C=C, Ar), 1287 (C-S), 1159 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (s, 3H, CH_3), 3.80 (s, 2H, S-CH_2), 7.37 (s, 1H, =CH), 7.39-7.58 (m, 4H, Ar-H), 7.51 (s, 1H, =CH); MS *m/z* 331 (M^+); Elemental analysis: Calculated for $C_{14}H_{11}ClN_6S$: C-50.83, H-3.35, Cl-10.72, N-25.41, S-9.69. Found: C-50.78, H-3.34, Cl-10.71, N-25.39, S-9.68.

6-(2-Bromophenyl)-3-(1-methyl-1*H*-imidazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (6e)
Brown solid; Yield 77%; Mp 144-146 ^{0}C; IR (KBr) 3071 (C-H, Ar), 2968 (C-H, CH_3), 1651 (C=N), 1631 (C=C, Ar), 1292 (C-S), 1162 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (s, 3H, CH_3), 3.86 (s, 2H, S-CH_2), 7.35 (s, 1H, =CH), 7.36-7.61 (m, 4H, Ar-H), 7.48 (s, 1H, =CH); MS *m/z* 374 (M^+); Elemental analysis: Calculated for $C_{14}H_{11}BrN_6S$: C-44.81, H-2.95, Br-21.29, N-22.40, S-8.55. Found: C-44.76, H-2.94, Br-21.27, N-22.38, S-8.54.

6-(2-Nitrophenyl)-3-(1-methyl-1*H*-imidazol-5-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine (6f)
Yellow solid; Yield 72%; Mp 103-105 ^{0}C; IR (KBr) 3066 (C-H, Ar), 2975 (C-H, CH_3), 1655 (C=N), 1625 (C=C, Ar), 1284 (C-S), 1174 (C-O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 3H, CH_3), 3.89 (s, 2H, S-CH_2), 7.32 (s, 1H, =CH), 7.35-7.58 (m, 4H, Ar-H), 7.52 (s, 1H, =CH); MS *m/z* 341 (M^+); Elemental analysis: Calculated for $C_{14}H_{11}N_7O_2S$: C-49.26, H-3.25, N-28.72, O-9.37, S-9.39. Found: C-49.08, H-3.24, N-28.70, O-9.36, S-9.38.

CONCLUSION

A novel series of 3-(1-methyl-1*H*-imidazol-5-yl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazine and its derivatives **(6a-f)** has been achieved from different steps in good to excellent yields. The title compounds were also used to evaluate for their antibacterial activity against different bacterial strains

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Received on December 26, 2019.