New 1, 2, 3-triazole-Furan Scaffold Schiff bases: Design, Synthesis, Characterization and biological studies

Somanatha T.M.[1], Krishnaswamy G.[2], Nayana R.[2], Nayana J.[2], Bhavana R.[1,3], Shivaraj G.[2], Sreenivasa S.[1,4] and Shet Prakash M.[1*]

1. Department of Studies and Research in Chemistry, University College of Science, Tumkur University, Tumakuru-572103, Karnataka, INDIA
2. Department of Studies and Research in Organic Chemistry, Tumkur University, Tumakuru-572103, Karnataka, INDIA
3. Department of Chemistry, Indian Institute of Technology Gandhinagar, Palaj, Gandhinagar-382055, Gujarat, INDIA
4. National Assessment and Accreditation Council, Nagarbhavi, Bengaluru-560072, Karnataka, INDIA

*shirsatpm@gmail.com

Abstract

In the present investigation, Schiff bases (SBs) bearing 1, 2, 3-triazole and furan motif were synthesized through condensation reaction via conventional approach (Route-A) and solvent free approach (Route-B). It has been found that route-B is efficient since it is eco friendly with short reaction time and satisfactory yield than route-A.

The structure and formation of targeted Schiff bases (SBs) were confirmed by different spectroscopic techniques (^{1}H NMR, ^{13}C NMR and Mass). Finally, in vitro antimicrobial screening result revealed that the synthesised SBs derivatives may act as moderate antimicrobial agents.

Keywords: 1, 2, 3-Triazole, Schiff base, aromatic azides, substituted furaldehyde, biological profile.

Introduction

In new drug development, hydrazones having an azomethine linkage (-NHN=CH-) play a crucial role since they possess a wide variety of biological profile such as antimicrobial[12], anticonvulsant[10], anti-inflammatory[24], anticancer[22], antitubercular[2] and anti-platelet activities[5]. These linkages have been extensively used in drug discovery due to its tenability. Millions of Schiff bases clubbed with heterocyclic rings have been developed in order to get better chemotherapeutic results[4,16,19].

Among the five membered heterocycles, 1, 2, 3-triazoles and its derivatives find variety of applications in the field of organic as well as medicinal chemistry[16]. These nitrogen heterocycles are stable towards biological transformations like oxidation, reduction and hydrolysis (acidic and basic) and possess particular interest due to their biological profile such as antimicrobial, analgesic, anti-inflammatory, anticancer, antiviral, antioxidant and anti-HIV activities[3,6,7,9,14,17,20].

On the other hand, furan, another five membered oxygen containing heterocycle with variety of pharmacological importance provides medicinal chemist a distinguishable difference in their biological profile by substituent modification[1,11,13].

**** Author for Correspondence***

We have synthesized new 1, 2, 3-triazole-Furan Scaffold Schiff bases adopting molecular hybridization approach[23]. Following steps were performed in order to accomplish the present work: (i) collection of resources and synthetic protocol, (ii) structure identification via different spectroscopic techniques and (iii) *in vitro* antimicrobial evaluation.

Material and Methods

All solvents, reagents and chemicals were procured from standard commercial sources and were used without further purification. Hot stage apparatus was used to determine the melting point ranges of solid compounds in open capillary tubes. Purity of the compounds and monitoring of reactions were checked by using Merck silica gel 60 F_{254} TLC plates and visualized in UV cabinet or by staining wherever necessary. The ^{1}H and ^{13}CNMR spectra were recorded on Agilent/Jeol (400 MHz, ^{1}H NMR) and (100 MHz, ^{13}C NMR) spectrometers using deuteriated solvents ($CDCl_3$ or DMSO-d_6) and tetramethylsilane (TMS) as an internal standard. The chemical shift values were expressed in δ ppm and coupling constants (J) were reported in Hertz (Hz). The Mass spectra were recorded in Waters Alliance 2795 separation module with Waters Micromass LCT mass detector.

Reagents: (i) $NaNO_2$, HCl, NaN_3, 0^{o}C-rt, 1 hr. **(ii)** Ethylacetoacetate, Et_3N, DMF, rt, 24 hr. **(iii)** Hydrazine hydrate, EtOH:DMF, reflux, 4-5 hr. **(iv)** Substituted furaldehyde, DMF;EtOH, Con.H_2SO_4, 100^{o}C, 5-6 hr. **(v)** Substituted furaldehyde, I_2, Grind, 30-40 mins.

Procedure for the synthesis of Ethyl-5-methyl-1-(4-nitrophenyl)-1H-1, 2, 3-triazole-4-carboxylate [2a]: To a round bottom flask of 50 mL containing 2 mL of DMF, compound [1a] (1.0 mmol), ethylacetoacetate (2.0 mmol) and tri ethylamine (2.0 mmol) were added and the resulting mixture was stirred at lab temperature for 24 hrs. The reaction was followed by thin layer chromatography. After completion of reaction, dilute the reaction mixture with 10 mL of water resulting in formation of precipitate. The precipitated product was collected through filtration, washed with water and dried. Following the above procedure, [2b-d] derivatives were prepared.

Procedure for the synthesis of Ethyl-5-methyl-1-(4-nitrophenyl)-1H-1, 2, 3-triazole-4-carbohydrazide [3a]: To a round bottom flask of 50 mL containing 4 mL of DMF:EtOH (1:1), compound [2a] (1.0 mmol) and hydrazine

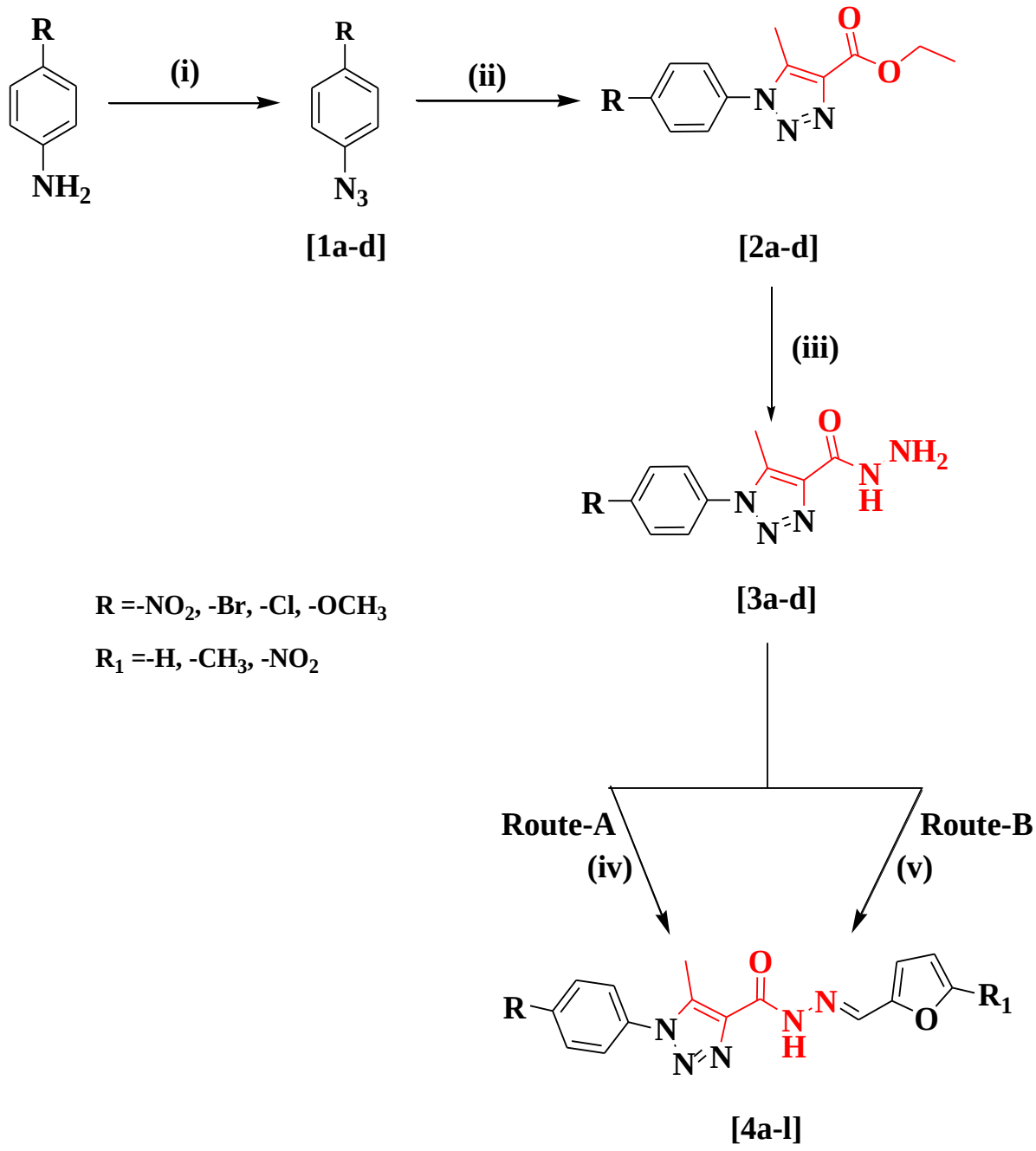
hydrate (2.0 mmol) were added and the resulting mixture was stirred at 100°C for 4-5 hrs.

The reaction was followed by thin layer chromatography. After completion of reaction, dilute the reaction mixture with 10 mL of water resulting in formation of precipitate. The precipitated product was collected through filtration, washed with water and dried. Adopting the above procedure, [3b-d] derivatives were prepared.

Procedure for the synthesis of 1, 2, 3-triazole-Furan Scaffold Schiff base [4a]

Route A: To a round bottom flask of 50 mL containing 4 mL of DMF:EtOH (1:1), compound [3a] (1.0 mmol) and furaldehyde (1.0 mmol) were added with catalytic amount of conc.H_2SO_4 and the resulting mixture was stirred at 100°C for 5-6 hrs. The reaction was followed by thin layer chromatography. After completion of reaction, dilute the reaction mixture with 10 mL of water resulting in formation of precipitate. The precipitated product was collected through filtration, washed with water and dried. The obtained product was recrystallized using ethanol to get Schiff Base [3a]. Adopting the above procedure remaining [4b-l] derivatives were prepared.

Route B: A mixture of compound [3a] (1.0 mmol), furaldehyde (1.0 mmol) and catalytic resublimed iodine (0.5 mmol) were ground with a pestle for 30-40 mins at lab temperature in a clean and dry mortar till a paste/semi-solid mass is obtained.



Scheme 1: Synthetic route for the preparation of 1, 2, 3-triazole-Furan Scaffold Schiff bases (SBs) [4a-l]

Progress of the reaction was monitored by thin layer chromatography. After completion of reaction, the mixture is washed successively with an ice-cold solution of sodium thiosulfate (5 mL) to remove residual iodine. The solid separated out was filtered, washed with cold water and dried. The obtained mass was recrystallized using ethanol to get Schiff Base [3a]. Adopting the above procedure, remaining [4b-l] derivatives were prepared.

Biological evaluation

Antimicrobial activity: Newly synthesized SBs [4a-l] were screened to investigate their antibacterial activity against two Gram positive, two gram negative bacterial strains and antifungal activity against two fungal strains by cup-plate method[8,16]. Sterile Petri dish with solidified agar nutrient media having 6 mm diameter bore was used and 1mL of respective SBs dissolved in DMSO was dispensed into each well. Ciprofloxacin (antibacterial) and ketoconazole (antifungal) were used as positive controls and DMSO solvent as negative control. The inoculated plates were incubated for 24-36 hr at 37 °C for bacterial and 48-72 hr at 28± 2 °C for fungal strains. The results were recorded for each tested compound as average diameter of zone of inhibition (in mm) around the well and repeated in triplicate.

Spectral Interpretation

Ethyl-5-methyl-1-(4-nitrophenyl)-1H-1, 2, 3-triazole-4-carboxylate [2a]:

^{1}H NMR (400MHz, δ ppm, DMSO-d_6): 8.50-8.47 (m, 2H, Ar-H), 8.00-7.96 (m, 2H, Ar-H), 4.39-4.34 (q, 2H, CH_2), 2.59 (s, 3H, CH_3), 1.36-1.32 (t, 3H, CH_3); **^{13}C NMR (DMSO-d_6, δ ppm):** 163.58 (COO), 140.55, 138.82, 135.99, 133.72, 128.27, 125.24, 64.25 (CH_2COO), 15.34, 9.98.

Table 1
Comparative table for the synthesise of SBs [4a-l]

Code	Route-A			Route-B		
	Reaction condition	Time	Yield (%)	Reaction condition	Time	Yield (%)
4a	DMF;EtOH, Con.H_2SO_4, 100°C	5-6 hrs	45	I_2, Grind, Lab temperature	30-40 mins	55
4b			40			70
4c			35			60
4d			50			75
4e			45			80
4f			40			55
4g			34			76
4h			50			55
4i			45			60
4j			45			80
4k			40			65
4l			50			55
4m			35			73
4n			37			66
4o			40			58

Table 2
Physical Characterization data of SBs [4a-l]

Code	R	R_1	Molecular Formula	Molecular Weight	M.P. (°C)
4a	4-NO_2	-H	$C_{15}H_{12}N_6O_4$	340.29	142-144
4b	4-NO_2	-CH_3	$C_{16}H_{14}N_6O_4$	354.32	173-175
4c	4-NO_2	-NO_2	$C_{15}H_{11}N_7O_6$	385.29	>300
4d	4-Br	-H	$C_{15}H_{12}BrN_5O_2$	374.19	165-167
4e	4-Br	-CH_3	$C_{16}H_{14}BrN_5O_2$	388.21	184-186
4f	4-Br	-NO_2	$C_{15}H_{11}BrN_6O_4$	419.18	>300
4g	4-Cl	-H	$C_{15}H_{12}ClN_5O_2$	329.74	145-147
4h	4-Cl	-CH_3	$C_{16}H_{14}ClN_5O_2$	343.76	156-158
4i	4-Cl	-NO_2	$C_{15}H_{11}ClN_6O_4$	374.73	>300
4j	4-OMe	-H	$C_{16}H_{15}N_5O_3$	325.32	155-157
4k	4-OMe	-CH_3	$C_{17}H_{17}N_5O_3$	339.34	168-170
4l	4-OMe	-NO_2	$C_{16}H_{14}N_6O_5$	370.31	>300

Ethyl-5-methyl-1-(4-bromophenyl)-1H-1, 2, 3-triazole-4-carboxylate [2b]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 7.87-7.85 (m, 2H, Ar-H), 7.63-7.61 (m, 2H, Ar-H), 4.37-4.33 (q, 2H, CH_2), 2.52 (s, 3H, CH_3), 1.34-1.32 (t, 3H, CH_3); **^{13}C NMR (DMSO-d$_6$, δ ppm):** 161.58 (COO), 138.75, 136.92, 134.39, 132.92, 126.77, 124.24, 61.15 (CH_2COO), 14.34, 9.96.

Ethyl-5-methyl-1-(4-chlorophenyl)-1H-1, 2, 3-triazole-4-carboxylate [2c]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 7.57-7.54 (m, 2H, Ar-H), 7.43-7.40 (m, 2H, Ar-H), 4.49-4.45 (q, 2H, CH_2), 2.59 (s, 3H, CH_3), 1.46-1.43 (t, 3H, CH_3); **^{13}C NMR (DMSO-d$_6$, δ ppm):** 160.98 (COO), 139.48, 135.84, 134.78, 133.96, 129.75, 127.32, 60.46 (CH_2COO), 14.15, 9.66.

Ethyl-5-methyl-1-(4-methoxyphenyl)-1H-1, 2, 3-triazole-4-carboxylate [2d]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 7.37-7.33 (m, 2H, Ar-H), 7.07-7.03 (m, 2H, Ar-H), 4.48-4.44 (q, 2H, CH_2), 3.88 (s, 3H, OCH_3), 2.55 (s, 3H, CH_3), 1.46-1.43 (t, 3H, CH_3); **^{13}C NMR (DMSO-d$_6$, δ ppm):** 161.12 (COO), 160.22, 139.32, 135.55, 127.92, 127.00, 114.73, 60.37 (CH_2COO), 55.60 (OCH_3), 14.16, 9.66.

Ethyl-5-methyl-1-(4-nitrophenyl)-1H-1, 2, 3-triazole-4-carbohydrazide [3a]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 9.80 (s, 1H, NH), 8.55-8.17 (m, 2H, Ar-H), 7.97-7.86 (m, 2H, Ar-H), 4.50 (s, 2H, NH_2), 2.62 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 159.96, 147.77, 140.21, 136.94, 126.33, 125.14, 9.41.

Ethyl-5-methyl-1-(4-bromophenyl)-1H-1, 2, 3-triazole-4-carbohydrazide [3b]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 9.75 (s, 1H, NH), 7.86-7.53 (m, 2H, Ar-H), 7.63-7.61 (m, 2H, Ar-H), 4.48 (s, 2H, NH_2), 2.52 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 161.63, 137.32, 136.58, 134.28, 132.79, 126.49, 124.02, 9.51.

Ethyl-5-methyl-1-(4-chlorophenyl)-1H-1, 2, 3-triazole-4-carbohydrazide [3c]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 9.76 (s, 1H, NH), 7.73-7.67 (m, 4H, Ar-H), 4.48 (s, 2H, NH_2), 2.53 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 160.13, 137.61, 136.40, 134.54, 134.21, 129.72, 127.13, 9.18.

Ethyl-5-methyl-1-(4-methoxyphenyl)-1H-1, 2, 3-triazole-4-carbohydrazide [3d]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 9.70 (s, 1H, NH), 7.55-7.51 (m, 2H, Ar-H), 7.17-7.14 (m, 2H, Ar-H), 4.46 (s, 2H, NH_2), 3.85 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 160.31, 160.06, 137.30, 136.21, 128.15, 126.82, 114.70, 55.59, 9.13.

(E)-1-(4-Nitrophenyl)-5-methyl-N'-((furan-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4a]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 12.23 (s, 1H, NH), 8.50-8.48 (m, 3H, N=CH & Ar-H), 8.03-8.01 (m, 3H, Ar-H), 6.92-6.91 (d, 1H, Ar-H), 6.65-6.64 (q, 1H, Ar-H), 2.66 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 157.55, 155.68, 153.90, 147.37, 136.47, 137.99, 135.08, 130.23, 127.76, 127.53, 115.50, 109.07, 9.83; **Mass**: m/z: Calculated: 340.29; Found: 341.1251.

(E)-1-(4-Nitrophenyl)-5-methyl-N'-((5-methylfuran-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4b]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 12.13 (s, 1H, NH), 8.50-8.47 (m, 2H, Ar-H), 8.38 (d, 1H, N=CH), 8.02-7.99 (m, 2H, Ar-H), 6.799-6.7990 (d, 1H, Ar-H), 6.278-6.270 (t, 2H, Ar-H), 2.65 (s, 3H, CH_3), 2.36 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 156.82, 154.55, 147.98, 147.84, 140.03, 138.36, 137.77, 137.45, 126.45, 125.06, 115.20, 108.58, 13.46, 9.53; **Mass**: m/z: Calculated:354.32; Found: 355.1211.

(E)-1-(4-Nitrophenyl)-5-methyl-N'-((5-nitrofuran-2-yl) methylene)-1H-1,2,3-triazole-4-carbohydrazone [4c]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 12.72 (s, 1H, NH), 8.55-8.48 (m, 3H, N=CH & Ar-H), 8.04-8.00 (m, 2H, Ar-H), 7.81-7.80 (d, 1H, Ar-H), 7.27-7.26 (d, 1H, Ar-H), 2.66 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 157.24, 151.80, 147.93, 139.91, 139.15, 137.22, 135.87, 126.52, 125.09, 115.15, 114.66, 9.60; **Mass**: m/z: Calculated: 385.29; Found: 386.2145.

(E)-1-(4-Bromophenyl)-5-methyl-N'-((furan-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4d]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 12.17 (s, 1H, NH), 8.47 (s, 1H, N=CH), 7.89-7.86 (m, 4H, Ar-H), 7.66-7.62 (m, 2H, Ar-H), 6.91-6.90 (d, 1H, Ar-H), 6.65-6.63 (d, 1H, Ar-H), 2.57 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 156.25, 155.88, 152.80, 144.37, 136.47, 135.08, 130.23, 130.02, 127.76, 127.53, 118.88, 115.61, 115.50, 9.23; **Mass**: m/z: Calculated: 374.19; Found: 375.1120; 376.2100 .

(E)-1-(4-Bromophenyl)-5-methyl-N'-((5-methylfuran-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4e]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 12.10 (s, 1H, NH), 8.37 (s, 1H, N=CH), 7.89-7.86 (m, 3H, Ar-H), 7.67-7.64 (m, 3H, Ar-H), 6.789-6.783 (d, 1H, Ar-H), 6.274-6.270 (d, 1H, Ar-H), 2.57 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 157.35, 155.78, 154.90, 148.37, 137.68, 135.08, 130.12, 127.53, 115.61, 13.83, 9.33; **Mass**: m/z: Calculated: 388.21; Found: 389.1103; 390.2891.

(E)-1-(4-Bromophenyl)-5-methyl-N'-((5-nitrofuran-2-yl) methylene)-1H-1,2,3-triazole-4-carbohydrazone [4f]
^{1}H NMR (400MHz, δ ppm, DMSO-*d*$_6$): 12.68 (s, 1H, NH), 8.53 (s, 1H, N=CH), 7.88-7.86 (m, 2H, Ar-H), 7.67-7.65 (s, 2H, Ar-H), 7.26-7.25 (d, 1H, Ar-H), 7.06-6.73 (dd, 1H, Ar-H), 2.58 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-*d*$_6$):** 157.25, 155.78, 153.90, 148.37, 138.47, 136.89, 136.68,

135.08, 130.23, 126.26, 119.78, 108.07, 9.53; **Mass**: m/z: Calculated: 419.18; Found: 420.1121; 421.0988.

(E)-1-(4-chlorophenyl)-5-methyl-N'-((furan-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4g]
^{1}H NMR (400MHz, δ ppm, DMSO-d_6): 12.08 (s, 1H, NH), 8.37 (d, 1H, N=CH), 7.74-7.70 (m, 4H, Ar-H), 6.78-6.77 (d, 1H, Ar-H), 6.269-6.265 (d, 1H, Ar-H), 2.59-2.56 (d, 3H, CH_3), 2.35 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-d_6):** 156.25, 154.28, 153.70, 147.37, 137.08, 136.09, 135.18, 130.03, 126.76, 125.44, 116.48, 108.17, 9.23; **Mass**: m/z: Calculated: 329.74; Found: 330.4511; 331.6601.

(E)-1-(4-chlorophenyl)-5-methyl-N'-((5-methylfuran-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4h]
^{1}H NMR (400MHz, δ ppm, DMSO-d_6): 12.08 (s, 1H, NH), 8.37 (d, 1H, N=CH), 7.74-7.70 (m, 4H, Ar-H), 6.78-6.77 (d, 1H, Ar-H), 6.269-6.265 (d, 1H, Ar-H), 2.59-2.56 (d, 3H, CH_3), 2.35 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-d_6):** 157.35, 155.78, 154.90, 148.37, 138.47, 137.68, 130.23, 130.02, 127.76, 118.88, 115.50, 13.93, 9.83; **Mass**: m/z: Calculated: 343.76; Found: 344.0014; 345.3891.

(E)-1-(4-chlorophenyl)-5-methyl-N'-((5-nitrofuran-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4i]
^{1}H NMR (400MHz, δ ppm, DMSO-d_6): 12.63 (s, 1H, NH), 8.47 (s, 1H, N=CH), 7.74-7.73 (m, 1H, Ar-H), 7.66 (s, 4H, Ar-H), 7.20 (s, 1H, Ar-H), 2.51 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-d_6):** 157.45, 156.18, 155.20, 148.47, 137.07, 135.08, 130.12, 130.02, 128.06, 127.53, 116.08, 115.61, 9.62; **Mass**: m/z: Calculated: 374.73; Found: 375.6021; 376.5238.

(E)-1-(4-methoxyphenyl)-5-methyl-N'-((furan-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4j]
^{1}H NMR (400MHz, δ ppm, DMSO-d_6): 12.05 (s, 1H, NH), 8.31 (d, 1H, N=CH), 7.66 (s, 6H, Ar-H), 6.72-6.71 (d, 1H, Ar-H), 6.21 (s, 1H, Ar-H), 2.50 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-d_6):** 155.78, 154.90, 148.37, 138.47, 137.99, 137.68, 135.08, 130.23, 130.02, 126.82, 114.70, 45.59, 9.03; **Mass**: m/z: Calculated: 325.32; Found: 326.2245.

(E)-1-(4-methoxyphenyl)-5-methyl-N'-((5-methylfuran-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4k]
^{1}H NMR (400MHz, δ ppm, DMSO-d_6): 12.06 (s, 1H, NH), 8.58 (d, 1H, N=CH), 7.57-7.56 (m, 2H, Ar-H), 7.18-7.16 (m, 2H, Ar-H), 6.77 (s, 1H, Ar-H), 6.26 (s, 1H, Ar-H), 3.85 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3), 2.35 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-d_6):** 155.08, 154.12, 148.27, 138.07, 136.85, 135.38, 134.18, 130.12, 129.92, 127.15, 125.02, 114.01, 56.13, 12.98, 9.14; **Mass**: m/z: Calculated: 339.34; Found: 340.2011.

(E)-1-(4-methoxyphenyl)-5-methyl-N'-((5-nitrofuran-2-yl)methylene)-1H-1,2,3-triazole-4-carbohydrazone [4l]
^{1}H NMR (400MHz, δ ppm, DMSO-d_6): 12.67 (s, 1H, NH), 8.54 (d, 1H, N=CH), 7.51 (s, 1H, Ar-H), 7.58 (d, 3H, Ar-H), 7.26 (s, 1H, Ar-H), 7.18 (d, 3H, Ar-H), 3.86 (s, 3H, OCH_3), 2.35 (s, 3H, CH_3); **^{13}C NMR (100MHz, δ ppm, DMSO-d_6):** 158.78, 157.90, 150.37, 148.47, 138.89, 137.68, 134.08, 130.33, 130.20, 130.02, 128.15, 119.70, 58.59, 9.43; **Mass**: m/z: Calculated: 370.31; Found: 371.3089.

Table 3
Anti-microbial activity of SBs [4a-l]

Code	Zone of Inhibition (ZOI) in mm					
	Bacterial isolate				Fungal isolate	
	Gram Positive		Gram Negative			
	B. subtilis	*S. aureus*	*E. coli*	*Salmonella spp*	*A. niger*	*C. albicans*
4a	-	-	-	9	10	14
4b	-	2	-	4	10	12
4c	-	-	2	9	7	-
4d	2	2	-	8	9	6
4e	-	4	-	-	9	6
4f	4	-	2	-	8	-
4g	-	-	-	8	-	-
4h	2	4	-	-	9	8
4i	-	6	6	-	-	-
4j	-	-	9	2	-	9
4k	2	2	8	-	12	6
4l	-	-	9	-	6	6
CIP	**40**	**33**	**40**	**38**	**NA**	**NA**
KET	**NA**	**NA**	**NA**	**NA**	**10**	**7**
DMSO	-	-	-	-	-	-

CIP: Ciprofloxacin; **KET:** Ketaconazole

Results and Discussion

Chemistry: 1, 2, 3-triazole-Furan Scaffold Schiff bases (SBs) synthesis begins with the 1, 3-dipolar cycloaddition reaction of substituted azido benzene derivatives [1a-d] with ethyl acetoacetate in presence of base at lab temperature for 24 hours to produce ethyl-5-methyl-1-(4-substituted phenyl)-1H-1, 2, 3-triazole-4-carboxylate derivatives [2a-d]. Then obtained [2a-d] derivatives underwent hydrozinolysis reaction in presence of hydrazine hydrate to give desired ethyl-5-methyl-1-(4-substituted phenyl)-1H-1, 2, 3-triazole-4-carbohydrazide intermediate product [3a-d]. This intermediate product [3a-d] underwent condensation reaction with substituted furaldehyde via i) Route A conventional approach and ii) Route B solvent free approach.

In route A, condensation reaction was carried out in presence of DMF:EtOH solvent with catalytic amount of conc.H_2SO_4 as a catalyst at 100 ^oC to yield the final product [4a-l] with yield ranging from 30-50% (Scheme 1, table 1), whereas in route B, condensation was carried out in presence of catalytic amount of iodine under solvent free condition at lab temperature to produce the final product [4a-l] with yield ranging from 50-80% (Scheme 1, table 1). In comparison, route B is convenient than route A in terms of reaction condition, time and yield. Physical properties (table 2) and different spectroscopic evidences of the synthesized compounds established the proposed molecular structures of the compounds without any ambiguity.

Biological evaluation

Antimicrobial activity: Antibacterial screening results revealed that the newly synthesized SBs [4a-l] showed weak antibacterial activity against tested bacterial strains as tabulated in table 3 whereas antifungal screening of SBs [4a-l] showed weak to moderate activity compared to standard drug against *C. albicans* and *A. niger* as shown in table 3.

Conclusion

In the present study, synthesis of twelve new Schiff bases (SBs) bearing 1, 2, 3-triazole and furan motif has been reported by the condensation reaction between 1, 2, 3-triazole hydrazide and substituted furaldehyde via conventional approach (Route A) and solvent free approach (Route B). Route B synthetic strategy proved to be superior eco friendly with mild reaction condition and satisfactory yield than route A.

The structural identification of the Schiff bases (SBs) was established based on ^1H and ^{13}C NMR and Mass spectrometry. The synthesised molecular hybrids may act as moderate antimicrobial agents as revealed by their *in vitro* antimicrobial activities.

Acknowledgement

The authors are thankful to Tumkur University, Tumakuru for providing the laboratory facility to carry out this research work.

References

1. Arlindo Pascual Z., Carrera González S. and Francisco González Matilla J., Synthesis of Chalcones: Privilegial Structures in the Synthesis of Heterocycles with Biological Activity, *Psychol. Lat. Copyr*., 20–23, doi:10.1016/j.bmc.2007.04.047 **(2018)**

2. Bedia K.K., Elcin O., Seda U., Fatma K., Nathaly S., Sevim R. and Dimoglo A., Synthesis and Characterization of Novel Hydrazide-Hydrazones and the Study of Their Structure-Antituberculosis Activity, *Eur. J. Med. Chem*., **41**, 1253-1261 **(2006)**

3. Buckle D.R., Rockell C.J.M., Smith H. and Spicer B.A., Studies on 1,2,3-triazoles. 13. (Piperazinylalkoxy)-[1]benzopyrano[2,3-d]-1,2,3-triazol-9(1H)-ones with combined H1-antihistamine and mast cell stabilizing properties, *J. Med. Chem*., **29**, 2262 **(1986)**

4. Chaturvedi D. and Kamboj M., Role of Schiff Base in Drug Discovery Research, *Chem. Sci. J*, **7**, 2 **(2016)**

5. Cunha A.C., Figueiredo J.M., Tributino J.L.M., Miranda A.L.P., Castro H.C., Zingali R.B., Fraga C.A.M., de Souza M.C.B.V., Ferreira V.F. and Barreiro E.J., Antiplatelet properties of novel N-substituted-phenyl-1, 2, 3-triazole-4-acylhydrazone derivatives, *Bioorg. Med. Chem*., **11**, 2051 **(2003)**

6. Deng L., Yang B., He Q. and Hu Y., Novel1,2,3-Triazole-linked norcanthradineanalogues:synthesis and evaluation of growth inhibition in a panel of selected tumo-cell lines, *Lett. Drug. Des. Discov*., **5**, 225 **(2008)**

7. Diana D.G. and Nitz J.J., Eur. Patent, 566199 **(1993)**

8. Indian Pharmacopoeia, Third Edition, Govt. of India, New Delhi **3**, 90 **(1985)**

9. Kalluraya B., Chimbalkar R. and Gunaga P., Synthesis and biological activities of some 1, 2, 4-triazole and 1, 3, 4-oxadiazoles, *Indian J. Het. Chem*., **6(2)**,103 **(1996)**

10. Kucukguzel Sx. G., Mazi A., Sahin F., Ozturk S. and Stables J., Synthesis and biological activities of diflunisal hydrazide–hydrazones, *Eur. J. Med. Chem*., **38**, 1005 **(2003)**

11. Loğoğlu E. et al, Synthesis and biological activity studies of furan derivatives, *Med Chem Res*., **19(5)**, 490–497 **(2010)**

12. Loncle C., Brunel J.M., Vidal N., Dherbomez M. and Letourneux Y., Synthesis and antifungal activity of cholesterol-hydrazone derivatives, *Eur. J. Med. Chem*., **39**, 1067 **(2004)**

13. Lukevits É. and Demicheva L., Biological activity of furan derivatives (review), *Chem Heterocycl Compd*., **29(3)**, 243–267 **(1993)**

14. Meier R., U.S. Patent, 4789680 **(1986)**

15. Musa Said A., Mohamed Reda Aouad, Daoud Khan J.O., Fawzia Al blewi F., Nadia Al-Kaff S., Adeeb Ali A., Nadjet Rezki and Mohamed Hagar, New 1, 2, 3-Triazole scaffold schiff bases as potential anti-COVID-19: Design, synthesis, DFT-molecular docking and cytotoxicity aspects, *Vaccines*, **9**, 1012 **(2021)**

16. Rose S.B. and Miller R.B., Studies with the Agar Cup Plate Method: I. A Standardized Agar Cup-Plate Technique, *J. Bacteriol*., **38**, 525-537 **(1939)**

17. Savini L., Massrelli P., Chiasserini L., Pellerano C. and Bruni G., Evaluation of antiinflammatory and analgesic properties, II, *Farmaco*, **49**, 633 **(1994)**

18. Schiff H., Mittheilungenaus dem Universitätslaboratorium in Pisa: Eine neue Reiheorganischer Basen, Justus Liebigs, *Ann. Chem*., **131**, 118–119 **(1864)**

19. Shetty S. and Kalluraya B., Design and synthesis of hydrazone incorporated pyrazoles and triazoles as possible antioxidants, *Der Pharma Chemica*., **7(12)**, 26-32 **(2015)**

20. Stefely J.A., Palchaudhuri R., Miller P.A., Peterson R.J., Moraski G.C., Hergenrother P.J. and Miller M.J., N-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)arylamide as a New Scaffold that Provides Rapid Access to Antimicrotubule Agents, *J. Med. Chem*., **53**, 3389 **(2010)**

21. Terzioglu N. and Gu¨rsoy A., Synthesis and anticancer evaluation of some new hydrazone derivatives of 2, 6-dimethylimidazo [2, 1-b][1, 3, 4] thiadiazole-5-carbohydrazide, *Eur. J. Med. Chem*., **38**, 781 **(2003)**

22. Todeschini A.R., de Miranda A.L.P., da Silva K.C.M., Parrini S.C. and Barreiro E.J., JSynthesis and Evaluation of Analgesic, Antiinflammatory and Antiplatelet Properties of New 2-Pyridylarylhydrazone Derivatives, *Eur. J. Med. Chem*., **33**,189 **(1998)**

23. Viegas-Junior C., Danuello A., da Silva Bolzani V., Barreiro E.J. and Fraga C.A.M., Molecular Hybridization: A Useful Tool in the Design of New Drug Prototypes, *Curr. Med. Chem*., **14**, 1829–1852 **(2007)**

24. Viola G. et al, Synthesis, cytotoxicity and apoptosis induction in human tumor cells by geiparvarin analogues, *Chem Biodivers*., **1(9)**, 1265–1280 **(2004)**.

(Received 29th November 2022, accepted 25th January 2023)