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Novel Thiazole Derived Sulfonamide-Schiff Bases: Green Synthesis and Biological Evaluation

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ABSTRACT
An environmentally benign method of synthesis of Schiff bases through condensation of sulfonamides bearing pyranothiazole with different para-substituted aromatic aldehydes in presence of PPA-SiO_2 solid acid catalyst in neat and solvent-free conditions under microwave irradiation has been developed. The synthesized compounds were characterized by microanalyses, IR and ^1H & ^{13}C NMR spectral studies. These compounds were evaluated for their antimicrobial activity against certain bacteria and fungi and found that all have shown moderate antimicrobial activity.

KEY WORDS: *Pyranothiazoles, Schiff bases, antimicrobial activity, microwave-assisted synthesis*

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I. INTRODUCTION

Azoles are the very interesting and perspective class of five-membered heterocycles having one and up to five N atom(s) and can also have at least one S or O atom as a part of the azole conjugated ring [1]. Thiazole and related heterocycles are commonly known as 1, 3-azoles which are isomeric with 1, 2-azoles being called isothiazoles. Thiazole derivatives are of great interest due to their high potential in the design and synthesis of biologically active chemical compounds for medicines and agriculture [2-3]. Sulfonamides constitute an important class of drugs, with several types of pharmacological activities [4-5]. Schiff bases are a type of molecule that has biological and pharmacological properties such as antibacterial, antifungal, antitubercular properties [6-7]. However, no work on this specific type of Schiff base has been envisaged.

Green methods or environmentally benign methods of synthesis of organic compounds are the non-traditional synthetic approaches. Microwave-assisted synthetic approach of organic compounds is now a key, universally used and versatile preferred technique / method of synthesis of organic compounds at laboratory and industrial level [8-9]. This method offers easy workup, quick, safe, accelerating organic synthetic reactions in the solvent-free or in green solvents or in the presence of solid support vis. clays, alumina & silica, environmental benignity and sustainability by reducing chemical wastes. Microwave-assisted organic synthesis of heterocycles has proven to be a successful approach for synthesizing new heterocyclic scaffolds promptly and efficaciously but has been seen little application in the synthesis of thiazoles [10-14].

As a part of our research projects to synthesize new bioactive compounds [15], we intended in this research article, the microwave-assisted synthesis of designed Schiff bases through condensation of sulfonamides bearing pyranothiazole with different aromatic aldehydes and subsequently purified and characterized by different spectroscopic techniques. The molecules were *in vitro* screened for antifungal and antibacterial potential by agar cup-plate method [16-17].

II. EXPERIMENTAL

Materials & Methods:

All the chemicals and solvents used in this research project were of analytical grade and were obtained from Sigma Aldrich, Spectrochem Pvt Ltd. and Alfa Aesar. All the investigated compounds were analysed satisfactorily for C, H and N using Carl-Ebra 1106 Elemental Analyser in the micro-analytical laboratory. The Shimadzu UV-Vis-160A spectrophotometer (wavelength 200-1100 nm) was used for obtaining the electronic spectra of the investigated compounds (in DMSO at 10^{-3} M). The infrared spectra of the investigated compounds were recorded (using KBr or $CHCl_3$) on Shimadzu 8400-S FT-IR spectrophotometer in the wavelength range of 4000-400 cm^{-1}. The NMR Varian-Mercury 400 MHz spectrometer was used for recording the ^1H NMR & ^{13}C NMR spectra of the compounds in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. The chemical shift was measured in ppm on the δ scale and the coupling constants were measured in Hertz. The

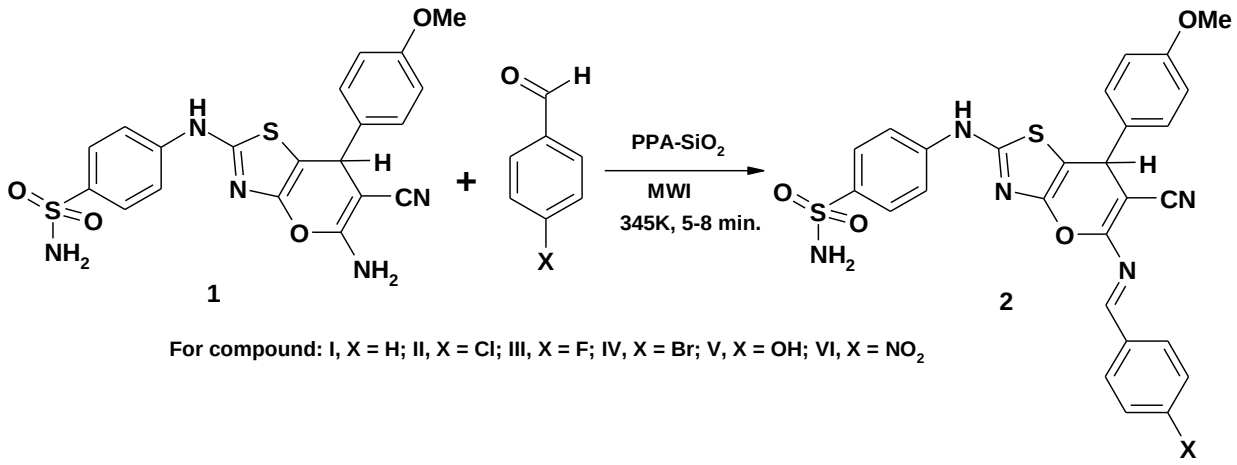
mass spectra were run on Hewlett Packard Model MS-5988 spectrometer. A modified microwave oven model 2001 ETB with rotating tray and a power source 230V, microwave energy output 800 W and microwave frequency 2450 MHz was used for the microwave assisted syntheses of the investigated compounds. The progress of the synthetic reactions was monitored by performing TLC where TLC sheets precoated with UV fluorescent silica gel, Merck 60 F254 that was visualized by UV lamp.

Microwave-Assisted Synthesis of Sulfonamide-Schiff Bases

A mixture of pyrano-thiazole (**1**), required aromatic aldehyde and PPA-SiO_2 was ground thoroughly using mortar and pestle. The triturated reaction mixture was placed in the microwave oven and was exposed to microwave irradiation (MWI) (360W) at 345 K for about 5-8 minutes and reaction was monitored by TLC (scheme-1). Then, the reaction mixture was filtered and the solid product recovered by recrystallization with ethanol and identification was confirmed by IR, NMR spectra and the melting point. All the synthesized products (**2**) are listed in table-1 and the spectral characterization data for synthesized compounds were presented in table-2. The IUPAC names of the synthesized compounds (**2**) are as follows:

I. 4-{[5-[(E)-[(4-phenyl)methylidene]amino]-6-cyano-7-(4-methoxyphenyl)-7H-pyrano[2,3-d][1,3]thiazol-2-yl]amino}benzene-1-sulfonamide
II. 4-({5-[(E)-[(4-chlorophenyl)methylidene]amino]-6-cyano-7-(4-methoxyphenyl)-7H-pyrano[2,3-d][1,3]thiazol-2-yl}amino) benzene-1-sulfonamide
III. 4-({5-[(E)-[(4-fluorophenyl)methylidene]amino]-6-cyano-7-(4-methoxyphenyl)-7H-pyrano[2,3-d][1,3]thiazol-2-yl}amino) benzene-1-sulfonamide
IV. 4-({5-[(E)-[(4-bromophenyl)methylidene]amino]-6-cyano-7-(4-methoxyphenyl)-7H-pyrano[2,3-d][1,3]thiazol-2-yl}amino) benzene-1-sulfonamide
V. 4-({5-[(E)-[(4-hydroxyphenyl)methylidene]amino]-6-cyano-7-(4-methoxyphenyl)-7H-pyrano[2,3-d][1,3]thiazol-2-yl}amino) benzene-1-sulfonamide
VI. 4-({5-[(E)-[(4-nitrophenyl)methylidene]amino]-6-cyano-7-(4-methoxyphenyl)-7H-pyrano[2,3-d][1,3]thiazol-2-yl}amino) benzene-1-sulfonamide

Scheme-1: *Green synthesis of Pyranothiazole Sulfonamide-Schiff Bases*



For compound: I, X = H; II, X = Cl; III, X = F; IV, X = Br; V, X = OH; VI, X = NO_2

Table-1: *Physical and analytical data of the synthesized compounds with comparison in CM & GM*
CM =Conventional Method; GM = Green Method

Compound	X	MP (in K)	Mol. Formula (Mol. wt.)	Period of synthesis		Percentage yield (%)		Analytical results % Found (calc.)			
				CM	GM	CM	GM	H	C	N	S
I	H	463	$C_{27}H_{21}N_5O_4S_2$ (543,6 amu)	5 hrs.	8 min.	51	70	3.9 (4.1)	59.6 (60.0)	12.9 (13.1)	11.8 (12.1)
II	Cl	480	$C_{27}H_{20}ClN_5O_4S_2$ (578,1 amu)	5 hrs.	7 min.	64	82	3.49 (3.51)	56.1 (56.2)	12.12 (12.2)	11.09 (11.2)
III	F	382	$C_{27}H_{20}FN_5O_4S_2$ (561,6 amu)	5 hrs	7 min.	60	75	3.59 (3.60)	57.7 (58.0)	12.47 (12.5)	11.42 (11.5)
IV	Br	458	$C_{27}H_{20}BrN_5O_4S_2$ (622,5 amu)	5 hrs.	7 min.	62	78	3.24 (3.3)	52.09 (52.2)	11.25 (11.3)	10.3 (10.5)
V	OH	445	$C_{27}H_{21}N_5O_5S_2$ (559,6 amu)	5 hrs.	8 min.	46	65	3.78 (3.8)	57.95 (58.0)	12.51 (12.5)	11.46 (11.5)
VI	NO_2	472	$C_{27}H_{20}N_6O_6S_2$ (581,6 amu)	4 hrs.	5 min.	75	89	3.43 (3.5)	55.1 (55.2)	14.28 (14.3)	10.89 (10.9)

CM =Conventional Method; GM = Green Method

Table-2: Spectral characterization data of synthesized compounds

Compound	X	IR Bands {KBr, cm^{-1}}	^{1}H-NMR (DMSO-d_6) {δ-ppm}	^{13}C-NMR {δ-ppm}	MS (m/z): Relative abundance
I	H	3252, 3205, 3151 (NH, NH_2); 3063 (Ar-CH); 2935, 2850 (CH, R); 2205 (C≡N), 1600 (C=N); 1325, 1160 (SO_2)	3.76 (s,3H,OCH_3) 5.56(t, 1H, CH pyran) 14.38(s, 1H, NH) 8.25 (s, 1H, N=CH) 6.75-7.79 (m, 15H, Ar-H & SO_2NH_2)	C_1-C_6: 119-139; C_9 :162; C_{12} :126; C_{13} :164; C_{14} :35; C_{16} :172; C_{17} :79; C_{21} :167; C_{22} :134; C_{23}-C_{27}: 128; **C_{26}: 131**; C_{32}: 134; C_{33}: 158; C_{34-37}: 113; C_{35-36}: 127; C_{39}: 55	543: 1.00 544: 0.33 545: 0.15 546: 0.04 547: 0.01
II	Cl	3330, 3270, 3225 (NH, NH_2); 3040 (Ar-CH); 2935, 2850 (CH, R); 2202 (C≡N), 1605 (C=N); 1330, 1165 (SO_2)	3.76 (s,3H,OCH_3) 5.59(t, 1H, CH pyran) 14.42(s, 1H, NH) 8.29 (s, 1H, N=CH) 6.75-7.79 (m, 14H, Ar-H & SO_2NH_2)	C_1-C_6: 119-139; C_9 :162; C_{12} :126; C_{13} :164; C_{14} :35; C_{16} :172; C_{17} :79; C_{21} :167; C_{22} :134; C_{23}-C_{27}: 128; **C_{26}: 137**; C_{32}: 134; C_{33}: 158; C_{34-37}: 113; C_{35-36}: 127; C_{39}: 55	577: 1.00 578: 0.33 579: 0.47 580: 0.14 581: 0.06 582: 0.01
III	F	3335, 3207, 3180 (NH, NH_2); 3033 (Ar-CH); 2935, 2848 (CH, R); 2200 (C≡N), 1602 (C=N); 1328, 1170 (SO_2)	3.76 (s,3H,OCH_3) 5.58(t, 1H, CH pyran) 14.42(s, 1H, NH) 8.29 (s, 1H, N=CH) 6.75-7.76 (m, 14H, Ar-H & SO_2NH_2)	C_1-C_6: 119-139; C_9 :162; C_{12} :126; C_{13} :164; C_{14} :35; C_{16} :172; C_{17} :79; C_{21} :167; C_{22} :134; C_{23}-C_{27}: 128; **C_{26}: 163**; C_{32}: 134; C_{33}: 158; C_{34-37}: 113; C_{35-36}: 127; C_{39}: 55	561: 1.00 562: 0.33 563: 0.15 564: 0.04 565: 0.01
IV	Br	3332, 3204, 3152 (NH, NH_2); 3061 (Ar-CH); 2934, 2852 (CH, R); 2203 (C≡N), 1602 (C=N); 1327, 1162 (SO_2)	3.76 (s,3H,OCH_3) 5.58(t, 1H, CH pyran) 14.41(s, 1H, NH) 8.29 (s, 1H, N=CH) 6.75-8.02 (m, 14H, Ar-H & SO_2NH_2)	C_1-C_6: 119-139; C_9 :162; C_{12} :126; C_{13} :164; C_{14} :35; C_{16} :172; C_{17} :79; C_{21} :167; C_{22} :134; C_{23}-C_{27}: 128; **C_{26}: 126**; C_{32}: 134; C_{33}: 158; C_{34-37}: 113; C_{35-36}: 127; C_{39}: 55	621: 0.89 622: 0.29 623: 1.00 624: 0.32 625: 0.14 626: 0.03 627: 0.01
V	OH	3335, 3265, 3225 (NH, NH_2); 3069 (Ar-CH); 2933, 2845 (CH, R); 2203 (C≡N), 1601 (C=N); 1332, 1165 (SO_2)	3.76 (s,3H,OCH_3) 5.56(t, 1H, CH pyran) 14.80(s, 1H, NH) 8.32 (s, 1H, N=CH) 8.19 (s, 1H, OH) 6.74-7.76 (m, 14H, Ar-H & SO_2NH_2)	C_1-C_6: 119-139; C_9 :162; C_{12} :126; C_{13} :164; C_{14} :35; C_{16} :172; C_{17} :79; C_{21} :167; C_{22} :134; C_{23}-C_{27}: 128; **C_{26}: 158**; C_{32}: 134; C_{33}: 158; C_{34-37}: 113; C_{35-36}: 127; C_{39}: 55	559: 1.00 560: 0.33 561: 0.15 562: 0.04 563: 0.01

VI	NO_2	3340, 3225, 3152 (NH, NH_2); 3065 (Ar-CH); 2935, 2845 (CH, R); 2200 (C≡N), 1597 (C=N); 1335, 1166 (SO_2)	3.76 (s,3H,OCH_3) 5.61(t, 1H, CH pyran) 14.85(s, 1H, NH) 8.31 (s, 1H, N=CH) 6.75-8.36 (m, 14H, Ar-H & SO_2NH_2)	C_1-C_6: 119-139; C_9 :162; C_{12} :126; C_{13} :164; C_{14} :35; C_{16} :172; C_{17} :79; C_{21} :167; C_{22} :134; C_{23}-C_{27}: 128; **C_{26}: 150**; C_{32}: 134; C_{33}: 158; C_{34-37}: 113; C_{35-36}: 127; C_{39}: 55	588: 1.00 589: 0.33 590: 0.16 591: 0.04 592: 0.01

Antimicrobial activity: Zone of Inhibition & Minimum Inhibitory Concentration (MIC)

The antimicrobial activity of the compounds synthesized through green methodology was investigated using the agar cup-plate method. The antibacterial screening was performed for two gram-positive bacteria (*S. aureus* & *S. epidermis*) and two gram-negative bacteria (*E. coli* & *S. typhi*) using nutrient agar broth as test media and antifungal screening was done against two fungi (*A. niger* & *C. albicans*) using the potato dextrose agar as test media. Chloramphenicol and Nystatin were used as references for antibacterial and antifungal activities respectively. The experimental observations/results are presented in table-3.

The minimum inhibitory concentration (MIC) against the studied bacteria was determined by broth dilution method [18] and the results are presented in table -4.

Table-3: Average z*one of inhibition against studied microorganisms*

Compound	**Concentration (µg/10µl)**	**Zone of inhibition in mm (SEM)**					
		Gram-positive bacteria		**Gram-negative bacteria**		**Fungi**	
		S. aureus	***S. epidermis***	***E. coli***	***S. typhi***	***A. niger***	***C. albicans***
Chloramphenicol	30	10	12	12	16	-	-
Nystatin	30	-	-	-	-	18	21
I	50	11	12	8	12	13	14
	100	14	16	10	15	17	20
II	50	10	12	6	8	12	13
	100	12	16	9	10	16	18
III	50	10	9	7	9	13	14
	100	14	15	10	15	17	19
IV	50	11	12	8	10	12	13
	100	15	16	12	15	17	19
V	50	8	10	7	9	11	12
	100	11	13	12	16	19	19
VI	50	9	11	8	10	12	14
	100	10	16	13	15	16	18

Table-4: *Average minimum inhibitory concentration (MIC) for the tested bacteria*

Compound	**MIC (in µg/mL)**			
	Gram-positive bacteria		**Gram-negative bacteria**	
	S. aureus	***S. epidermis***	***E. coli***	***S. typhi***
I	23	24	16	18
II	20	21	15	16
III	21	22	16	18
IV	22	23	16	19
V	22	23	16	20
VI	21	22	16	19

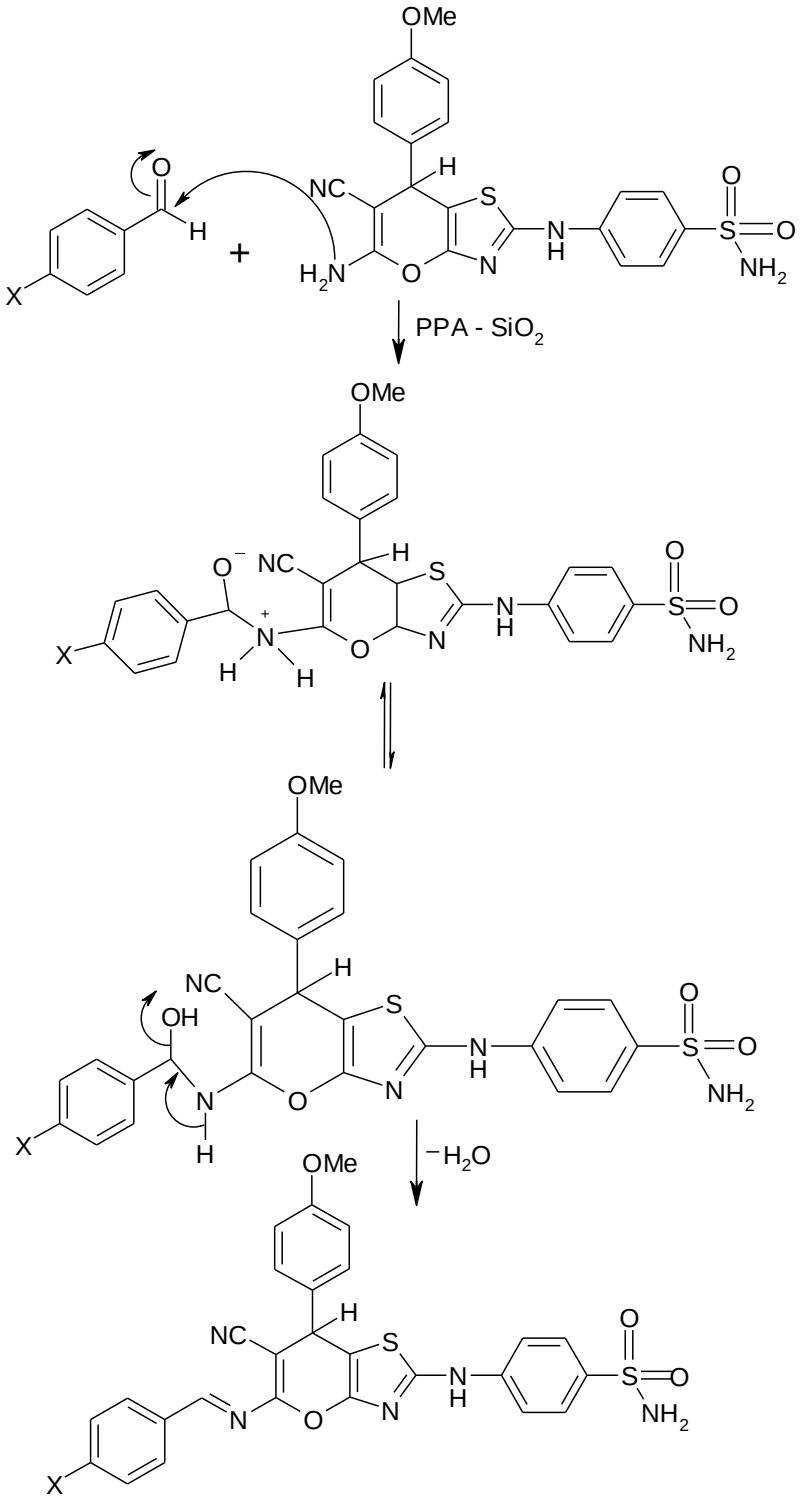
III. RESULTS & DISCUSSION

A series of new novel thiazole derived sulfonamide-Schiff Bases of pharmaceutical interest were synthesized by applying eco-friendly microwave-assisted synthetic approach by condensation of sulfonamides bearing pyranothiazole with different aromatic aldehydes in presence of PPA-SiO_2 as solid acid catalyst [19] in clean and green conditions. This procedure accomplished with excellent yield in the shortest period in compare to the conventional methods (table-1).

The condensation of sulfonamide bearing pyranothiazole with different aromatic aldehydes involves the nucleophilic attack of NH_2 group on the electrophilic formyl group followed by dehydration to form corresponding Schiff bases (scheme-2). Thus, the reaction proceeds via nucleophilic substitution reaction. Since the used catalyst (PPA-SiO_2) was recycled by simple filtration and may be used over and over again. That is why this catalyst is known as green catalyst. Thus, the present syntheses comply with the principle of environmentally benign or sustainable or green chemistry.

In compare to conventional methods of synthesis of thiazole derived sulfonamide-Schiff bases, the microwave-assisted method under eco-friendly conditions in presence of PPA-SiO_2 as a recyclable solid catalyst

is the superior method since produces better yield in lesser time without use of any hazardous organic solvents. Further, the catalyst PPA-SiO_2 coordinates with carbonyl oxygen and enhances the electrophilicity of >C=O group and facilitates the nucleophilic attack of NH_2 on >C=O and also served as dehydrating agent to facilitate the removal of water.



Scheme-2: *Proposed* m*echanism for acid catalyzed Schiff base synthesis*

TLC was used to monitor the overall progress of the synthetic reaction and the synthesized compounds were characterized by their IR & NMR spectral analyses. The presence of bands in the range of 2200 - 2205 cm^-

^{1} corresponding to cyano-group, (-C≡N) confirmed their presence in the IR spectra of the synthesized compounds. Further, the IR spectra showed the presence of bands in the range of 1597-1605 cm^{-1} corresponding to -N=CH- (imine) group confirmed the synthesis of Schiff bases. The existence of bands corresponding to NH_2 group linked to SO_2 showed the non-involvement of sulfonamide NH_2 in the formation of imine compounds.

The formation of products, I-VI was confirmed using both ^{1}H NMR & ^{13}C NMR spectroscopy. The ^{1}H NMR spectra revealed singlets at 8.25 - 8.32 ppm corresponding to (-N=CH-), imine group in the synthesized compounds. The presence of imine group (-N=CH-) was confirmed by the ^{13}C NMR spectra (δ =167 ppm for C_{21}) of synthesized compounds [20].

It was observed that the electrophilicity of the carbonyl carbon of the aromatic aldehyde reduced due to the presence of electron-donating substituent groups through resonance which lead to the low yield of the reaction products and a comparatively more reaction time required for their completion (table-1).

All the investigated compounds performed moderate activity against all pathogens with exception of compound-V. In comparing the activity of compounds I to VI, the compound V was the most active with all the pathogens possibly due to its hydrogen bonding ability.

IV. CONCLUSIONS

The present article describes a new facile and microwave-assisted rapid synthetic protocol for the synthesis of Schiff bases of pyranothiazole sulfonamides by using highly active solid acid supported catalyst PPA-SiO_2 under solvent-free environment maintaining moderate to good yield. The synthesized products were purified by recrystallization using appropriate non-hazardous solvents. Further, this eco-friendly approach is more convenient, cleaner, safe, using simple workup, and involving mild reaction conditions without non-polluting and any toxic materials compared to traditional methods. Further, the catalyst was recovered over and over again without loss of catalytic activity so it is a cost-effective approach. All the synthesized compounds were evaluated for their antibacterial and antifungal activities and it was found that all were active and comparatively efficient.

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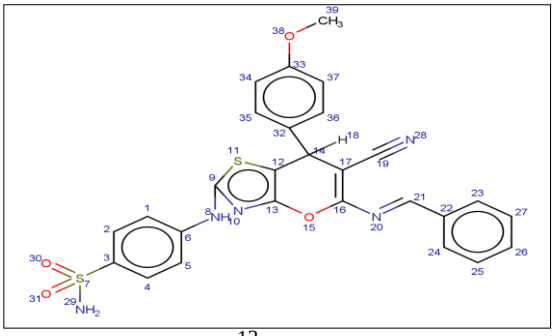

Notation for ^{13}C-NMR Spectrum

^{13}C-NMR Spectrum of compound-I (Measurement frequency: 500.0 MHz