



SYNTHESIS OF SOME TETRAZOLE AND THIAZOLIDINE-4-ONE DERIVATIVES OF SCHIFF BASE BY USING IONIC LIQUIDS AS CATALYST AND EVALUATION OF THEIR ANTIFUNGAL AND ANTIBACTERIAL ACTIVITY

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Abstract

Compound (1a) (1-amino-4-methyl-6-phenyl pyrimidine- 2-(1H)-thione) was synthesized in the current study. By using a tetrabutylammonium iodide (TBAI) as a catalyst to react with various aromatic aldehydes in distilled water to give a new series of Schiff's bases (2a-2h). New tetrazole derivatives (3a-3h) were made by reacting Schiff's bases (2a-2h) with sodium azide in H₂O. New thiazolidine-4-one was prepared from reactions of Schiff's bases (2a-2h) with thioglycolic acid in distilled water-giving compounds (4a-4h). Finally, The structure of the synthesized compounds is confirmed by, ¹H NMR, IR, and ¹³C-NMR spectra as well as some physical data.

Keywords: tetrazole, thiazolidinone, Schiff bases, Ionic Liquids.

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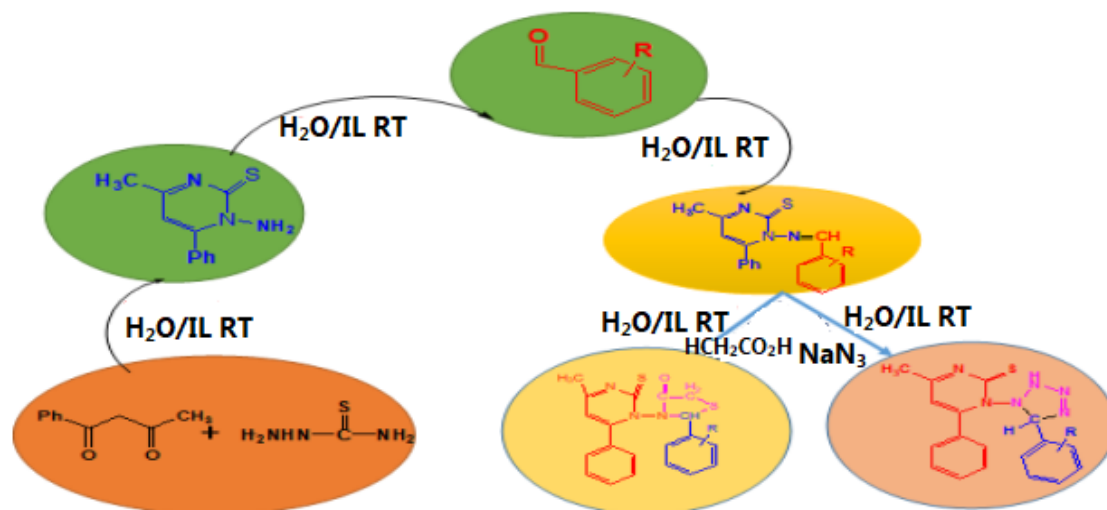
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Introduction

Schiff's bases are a significant group of organic compounds (1a). Hugo Schiff first reported them in 1864 [1]. Schiff's bases are formed by the condensation of primary amines with carbonyl compounds. Azomethine is a structural feature shared by these compounds, and R^1 can be alkyl, aryl, cycloalkyl, or heterocyclic [2]. A Schiff's base (also known as imine or azomethine) is the nitrogen analog of an aldehyde or ketone in which the carbonyl group ($>C=O$) has been replaced by an imine or azomethine group. Schiff's bases have also been shown to have antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties [3,4]. Imine or azomethine groups can be found in a wide range of natural, naturally derived, and nonnatural compounds. The presence of an imine group in such compounds is essential for their biological activities [5-7]. Because of their wide range of industrial applications, Schiff's bases are important compounds [8]. Schiff's bases are used to photostabilize poly (vinyl chloride) polymers against photodegradation by ultraviolet radiation [9-11], as well as to improve poly(methyl methacrylate) degradation [12] and to prevent photodegradation of polystyrene by adding them to polymer films [13,14]. Thiazolidinones, which are important heterocyclic compounds with sulfur and nitrogen in a five-member ring, are the derivatives of thiazolidine. It is regarded as a magical moiety that is capable of almost all biological functions. Due to their intriguing and varied pharmacological activities, which include, antifungal, antibacterial, antiproliferative, anti-inflammatory, and anti convulsant properties, compounds from the thiazolidinone series are synthesized, and this represents an important research area. Tetrazole is

an aromatic azapyrrazole. It is a five-membered ring compound with one carbon, four nitrogen, two hydrogen, and two double bonds. Tetrazoles do not exist in the natural world. CN_4H_2 is the most fundamental tetrazole. It has a faint, distinguishing odour and is a white to pale yellow crystalline solid. It is soluble in both alcohol and water. It is acidic in nature as a result of the four nitrogens that are present. The lone pair of one nitrogen provides two of the six Huckel-required electrons for tetrazoles, while the other four electrons are supplied by the other four ring atoms [15]. Since the weak mesomeric effect (+M) is outweighed by the strong electron-withdrawing inductive effect (-I) of the tetrazole ring, Tetrazole rings are deactivating groups because they have strong electron-withdrawing inductive effects (-I) compared to weak mesomeric effects (+M) [16]. Tetrazoles can be used as isosteric substitutes for different functional groups in the creation of biologically active substances because of this property. Tetrazole has experienced a renaissance in recent years, particularly as a substitute for carboxylic acids. Tetrazoles' biological characteristics result from their higher metabolic stability than the acid function [17]. As a result, there is an ongoing endeavour to develop a cost-effective and practical method for the synthesis of tetrazole and Thiazolidinone derivatives from Schiff bases. Thus, the use of an ionic liquid as a catalyst is from an environmentally sustainable and healthy point of view in the presence of a free solvent at room temperature and good results are obtained in a short time. The acquired findings were compared regarding reaction time and yield to the other reported methods for the synthesis of tetrazole and thiazolidin-4-ones.



EXPERIMENTAL

BDH and Fluka are the sources of all chemicals and reagents. The type of melting point apparatus used to measure melting points were electrothermal. Shimadzu's FT-IR-8400 infrared spectrophotometer was used to record the FT-IR spectra. NMR spectra for ^1H and ^{13}C . Acetone- d_6 and CDCl_3 have used the solvents at 1400 (400 MHz).

Synthesis of 1-amino-4-methyl-6-phenyl pyrimidine-2-(1H) thion (1a).

A mixture of (0.02 mole) of benzoyl acetone and (0.02 mole) of thiosemicarbazide in (15 ml) distilled water containing a few quantities of ionic liquid then reflux for 50 min. the product filtered, the solid recrystallized from ethanol to give the pale-yellow product (Yield: 97 %; m.p.161-163°C).

Synthesis of Schiff bases (2a-2h)

A mixture of compound (1a) (0.02 mole) and different aromatic aldehyde (0.02 mole) in distilled water (15 ml) containing a few quantities of ionic liquid was stirred for 37 min. the solvent was evaporated under a vacuum, and the solid yield crystallized by methanol. Table 1 involved physical properties.

Synthesis of Tetrazole derivatives(3a-3h)

For 77 min, reflux a mixture of compound (2a-c) (0.008 mole) dissolved in (15 ml) distilled water and (0.012 mole) sodium azide. Absolute ethanol was used to filter and recrystallize the product. Table 3 dealt with physical properties.

Synthesis of Thiazolidinones derivatives (4a-4h)

Schiff bases (0.002 mole) and mercapto acetic acid (0.004 mole) were combined in 10 ml of distilled water (2a-c). Refluxed the mixture for 72 min, then produced the compound by treating it with potassium bicarbonate. ethanol filtered and crystallised the final product. Table 5 featured physical characteristics.

Results and Discussion

The new Schiff bases were created by combining 1-amino-4-methyl-6-phenyl pyrimidine-2- (1H)-thione (1a) with a different aromatic aldehyde in distilled water with a catalytic amount of ionic liquids. The FT-IR spectra of Schiff's bases (2a-2h) revealed the absence of a carbonyl group peak and the appearance of new peaks at 1580-1606 cm^{-1} , which are attributed to the new azomethine (C=N) group. **Table. 1.** contains some spectral data. Schiff's bases (2a-2h) were combined with sodium azide in THF to produce tetrazole compounds (3a-

3h). The disappearance of the FT-IR absorption bands at (1580-1599) cm^{-1} provides strong evidence for the reaction's success. These absorption bands are caused by the stretching frequency of the (C=N) imine group. Furthermore, the FT-IR spectra of tetrazole revealed distinct absorption bands at (1441-1499) cm^{-1} due to (N=N). Aside from that, the FT-IR spectra appeared in the band at (2077-2360) cm^{-1} , which was attributed to the azide group's stretching frequency. **Table. 3.** Contains some spectral data and showed a good yield (3a-3h). **Table. 5.** contains some spectral data. Thiazolidinone compounds (4a-4h) were synthesised in distilled water by reacting Schiff's bases (2a-2h) with thioglycolic acid. Due to the (C=O) imide stretching frequency, the FT-IR spectrum showed sharp peaks at (1724-1700) cm^{-1} . good evidence for the reaction's success at this stage.

1-Amino-4-methyl-6-phenyl pyrimidine-2-(1H)-thione Compound (1a).

M.p.161-163 °C; FT-IR (KBr, cm^{-1}): 3198 (=C-H), 2998 (R-CH), 1598 Endo (C=N Exo), 1081 (C=S), 936 (N-N), 3267-3401(NH_2); ^1H NMR (CDCl_3 400 MHz): d = 7.30-7.37 (m, 5H, Ar-H), 5.96 (s, 1 H, H-C=C), 3.45-3.40 (dd, 2H, NH_2), 2.04 (s, 3H, CH_3). ^{13}C NMR (CDCl_3 , 400 MHz): d = 175.5 (C=S), 155.4 (C=N), 144.1, 128.7, 128.0, 124.0, 95.3 (Ar-H), 55.2 (C=C-H), 16.1 (CH_3) calculated for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$ + 217 found.

4-methyl-1-{[1E].(2-nitrophenyl) methylene}amino}-6-phenyl pyrimidine-2(1H)-thione Compound (2a).

M.p. 227-229 °C; FT-IR (KBr, cm^{-1}): 3145 (=C-H), 2981 (R-CH), 1596 (C=N Exo), 1227 (C=S), 1026 (N-N), 1521-1342 NO_2 (asy/sym); ^1H NMR (acetone- d_6 , 400 MHz): d = 8.61 (s, 1H, H-C=N), 8.5-8.1 (m, 4H, Ar-H), 7.5-7.7 (m, 5H, Ar-H), 6.4 (s, 1H, H-C=C). 2.8 (s, 3H, CH_3). ^{13}C NMR (acetone - d_6 , 400 MHz): d = 180.2 (C=S), 148.9 (C=N), 140.0, 136.4, 133.2, 130.1, 121.3 (Ar-H), 28.4 (CH_3) calculated for $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_2\text{S}$ + 350 found

4-methyl-1-{[1E].(4-nitrophenyl)methylene}amino}-6-phenyl pyrimidine-2(1H)-thione compound (2d)

M.p. 97-99 °C; FT-IR (KBr, cm^{-1}): 3089 (=C-H), 2986 (R-CH), 1580 (C=N Exo), 1270 (C=S), 1085 (N-N), 1513-1330 NO_2 (asy/sym); ^1H NMR (DMSO- d_6 , 400 MHz): d = 8.4 (s, 1H, H-C=N), 8.2-8.1 (m, 4H, Ar-H), 7.4-7.3 (m, 4H, Ar-H), 6.4 (s, 1H, H-C=C). 3.3 (s, 3H, CH_3). ^{13}C NMR (DMSO- d_6 , 400 MHz): d = 179.9 (C=S), 148.1 (C=N), 142.1, 140.0, 129.8, 125.5, (phenyl ring),

39.5 (CH₃) calculated for C₁₈H₁₄N₄O₂S + 350 found.

4-methyl-1-[(1E). (4-amino phenyl)methylene] amino}-6-phenyl pyrimidine-2(1H)-thione Compound (2e).

M.p. 145-147 °C; FT-IR (KBr ,cm⁻¹): 3076 (=C-H), 2963 (R-CH), 1606 (C=N Exo),1214 (C=S), 1103 (N-N), 3215-3473 (NH₂); ¹H NMR (DMSO-d 6 , 400 MHz): d = 10.7 (s, 2H, 2NH₂), 7.8 (s, 1H, H-C=N), 6.8-7.31 (m, 4H, Ar-H), 7.38-7.46 (m, 5H, Ar- H), 1.67 (s, 3H, CH₃). ¹³C NMR (DMSO-d 6 , 400 MHz): d = 179.7 (C=S), 148.9 (C=N), 140.0, 136.5, 134.1, 131.2, 123.0, 121.0 (phenyl ring) calculated for C₁₈H₁₆N₄S +350 found

4-methyl- 1- {(1E)-1- (4-methoxyphenyl) methylene] amino} -6-phenyl pyrimidine-2(1H)-thione Compound (2f).

M.p. 133-135 °C; FT-IR (KBr ,cm⁻¹): 3113 (=C-H), 2986 (R-CH), 1585 (C=N Exo), 1284 (C=S), 1084 (N-N), 1118-1224 (C-O-C) ¹H NMR (DMSO-d 6 , 400 MHz): d = 8.9 (s, 1H, H-C=N), 8.7 (s, 1H, H-C=C), 8.3-8.0 (m, 5H, Ar-H), 7.1-7.7 (m, 5H, Ar-H), 3.8 (s,3H,OCH₃). ¹³C NMR (DMSO-d 6 ,400 MHz): d = 160.1 (C=S), 150.3 (C=N), 131, 130, 128, 124, 117, 115 (phenyl ring), 59 (OCH₃ , 55 (C=C-H). (Dhanya et al ., 2014).2CH₃). ¹³C NMR (acetone -d 6 , 400 MHz): d = 141.2, 134.6, 133.1, 130.3, 128.8, 128.6, 124.8, 124.5,122.0 (phenyl ring), 29.5 (CH₃) calculated for C₁₉H₁₇N₃OS +335 found.

1,1'- ((1,4- phenylenebis (methaneylylidene)) bis (azaneylylidene))bis(4-methyl-6-phenylpyrimidine -2(1H)-thione) Compound (2g).

M.p. 142-144-326⁰C; FT-IR (KBr ,cm⁻¹): 3195 (=C-H), 2988 (R-CH), 1590 (C=N Exo), 1225 (C=S), 1097 (N-N); ¹H NMR (acetone-d 6 , 400 MHz): d = 8.68 (s,1H, H-C=N), 8.08-8.20 (m, 4H, Ar-H), 7.55- 7.88 (m, 10H, Ar-H), 5.3 (s, 1H, C=C-H), 2.85 (br, 6H, 2CH₃). ¹³C NMR (acetone -d 6 , 400 MHz): d = 141.2, 134.6, 133.1, 130.3, 128.8, 128.6, 124.8, 124.5,122.0 (phenyl ring), 29.5 (CH 3) calculated for C₃₀H₂₄N₆S +533 found.

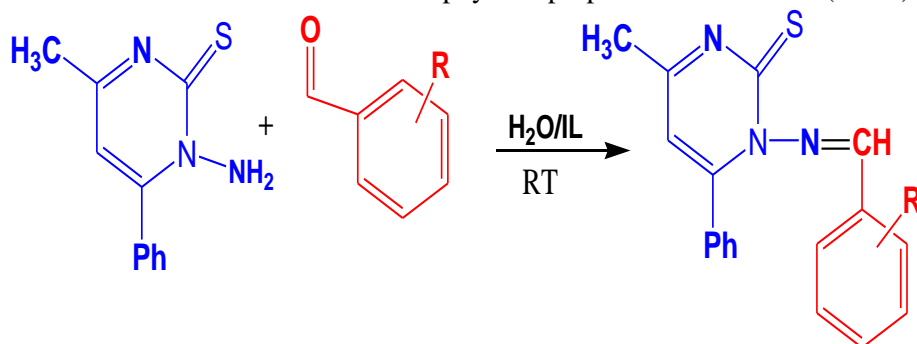
4-methyl-1-[5-(2-nitro phenyl)-2,5-dihydro-1H-tetrazol-1-yl]-6-phenyl pyrimidine-2(1H)-thione Compound (3d).

M.p. 270-272 °C; FT-IR (KBr ,cm⁻¹): 3356 (N-H) 3159 (=C-H), 2962 (R-CH), 1207 (C=S), 911 (N-N), 1447 (N=N) ¹H NMR (DMSO-d 6 , 400 MHz): d = 11.6 (s,1H, NH), 8.7 (s, 1H, C=C-H), 8.1-8.4 (m, 4H, Ar-H), 7.2- 7.7 (m, 5H, Aar-H), 4.1 (s, 1H, H-C-N). 3.4 (s, 3H, CH 3). ¹³C NMR (DMSO-d 6 , 400MHz): d = 179.1 (C=S), 155 (C=N), 149, 140, 135, 134, 131, 129, 128, 129, 124, 122, (phenyl ring), 95 (C=C-H), 55 (HC-N), 16 (CH₃) calculated for C₁₈H₁₅N₇O₂S +393 found.

3-(4-methyl-6-phenyl-2-thioxo pyrimidin-1(2H)-yl)-2-(4-nitrophenyl)-1,3-thiazolidin-4-one Compound (4b).

M.p.186-188 °C; FT-IR (KBr ,cm⁻¹): 3024 (=C-H), 2982 (R-CH), 1207 (C=S), 933 (N-N), 1704 (c=o) imide, 809 (C-S-C); ¹H NMR (CDCl₃ , 400 MHz): d = 8.20 – 8.26 (m,4H, Ar-H), 7.52-7.87 (m, 5H, Ar-H), 6.98, (S, 1H, H-C-N), 5.77 (s, 1H, H-C=C), 4.40 (br, 2H, CH₂), 2.34 (s, 3H, CH₃) calculated for C₂₀H₁₆N₄O₃S₂ +533 found.

Table. 1. Some physical properties of shiff base (2a-2h)



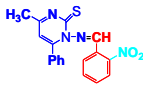

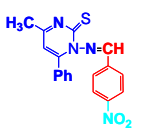

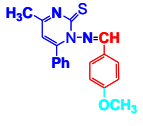

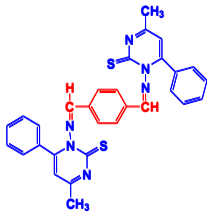
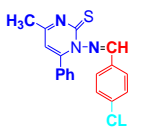
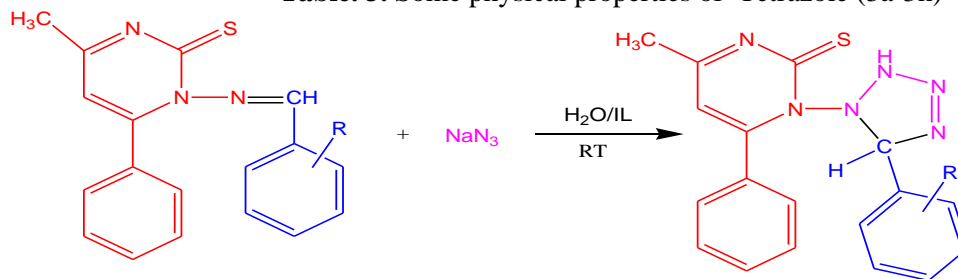
Comp.No	Structure	M.P. °C	Colour	Time(min)	Yield 100%	Cryst. Solvent
2a		227-229	White	15	94	Ethanol
2b		187-189	White	17	89	Ethanol
2c		235-237	Yellow	16	91	Ethanol
2d		97-99	Light Yellow	23	93	Methanol
2e		145-147	Pale yellow	27	87	Ethanol
2f		133-135	White	19	91	Methanol
2g		324-326	Brown	33	85	Ethanol
2h		177-199	White	37	93	Methanol

Table. 2. Comparative study of various catalysts as well as a solvent in recent work and TBAI for maximum yield of Schiff base

Entry	Catalyst	Solvent	Temperature (C ⁰)	Time	Yield(%)	Ref
1	amino acid	H ₂ O	35	6(h)	39	18
2	amino acid	EtOH	80	6(h)	60	19
3	[BMIM][NTf ₂]	decane	55	271(min)	62	20
4	PIL-SB-Mn(III)	EtOH	100	6(h)	60	21
5	PIL-SB-Mn(III)	H ₂ O	RT	12(h)	55	21
6	SYSU-Zn@IL2	DMF	12(h)	12(h)	88	22
7	TBAI	THF	RT	10(h)	77	presnt work
8	TBAI	EtOH	80	8(h)	79	presnt work
9	TBAI	H ₂ O	RT	30(min)	94	presnt work

Table 3. Some physical properties of Tetrazole (3a-3h)

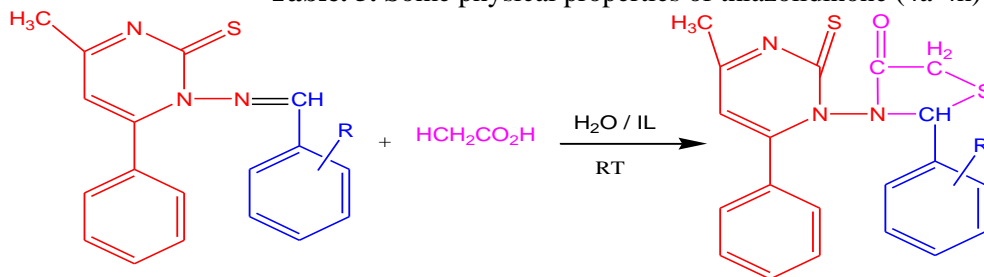


Comp.No	Structure	M.P. °C	Colour	Time(min)	Yield 100%	Cryst. Solvent
3a		202-204	Brown	51	88	Ethanol
3b		230-232	Light Brown	63	90	Ethanol
3c		252-245	Yellow	47	84	Ethanol
3d		270-272	Yellow	51	89	Methanol
3e		195-197	Llight Brown	63	91	Methanol
3f		188-190	Dark Brawn	71	87	Methanol
3g		268-270	Yellow	77	90	Ethanol
3h		222-224	yellow	52	88	Ethanol

Table 4. Comparative study of various catalysts as well as a solvent in recent work and TBAI for maximum yield of Tetrazole

Entry	Catalyst	Solvent	Temperature (C ^o)	Yield(%)	Time	Ref
1	[Bmim]BF ₄	Ethanol	100	75	7(h)	23
2	[bmim][CF ₃ SO ₃	Ethanol	100	79	5(h)	24
3	{BiPy}(SO ₃ H) ₂ Cl ₂	EG	80	89	1.5(h)	25
4	Amberlyst-15	DMSO	85	82	12(h)	26
5	ZnBr ₂	H ₂ O	Reflux	76	24(h)	27
6	TBAI	THF	100	84	8(h)	present work
7	TBAI	Ethanol	100	87	10(h)	present work
8	TBAI	H ₂ O	RT	92	66(min)	present work

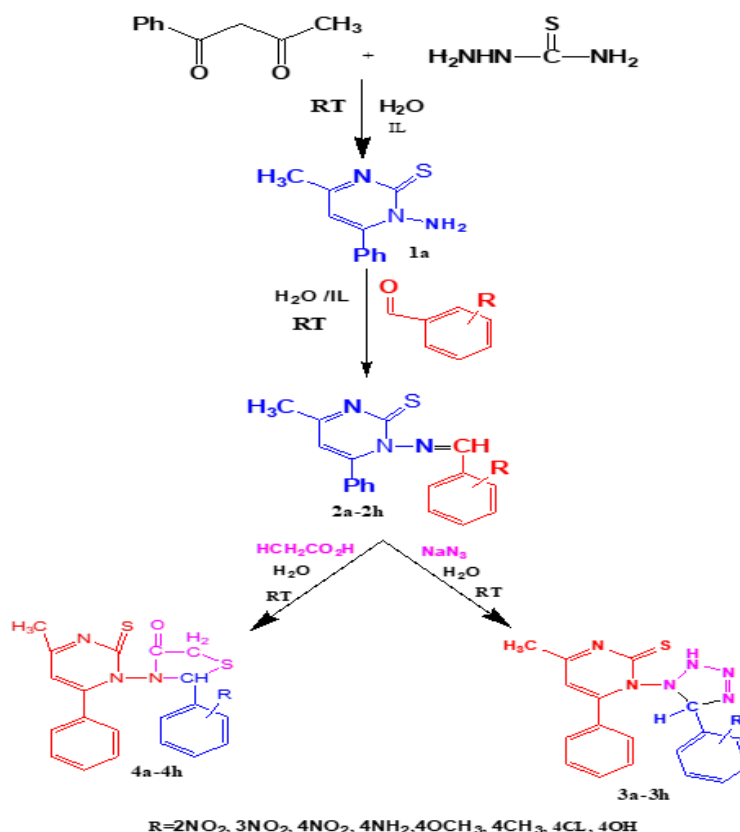
Table 5. Some physical properties of thiazolidinone (4a-4h)



Comp.No	Structure	M.P. °C	Colour	Time(min)	Yield 100%	Cryst. Solvent
4a		180-182	Green	57	91	Ethanol
4b		186-188	Whait	63	89	Ethanol
4c		252-254	Yellow	47	84	Ethanol
4d		191-193	Green	51	88	Methanol
4e		195-197	Brown	61	90	Methanol
4f		185-187	Dark Brawn	71	87	Methanol
4g		318-320	Yellow	72	90	Ethanol
4h		212-214	yellow	51	89	Ethanol

Table 6. Comparative study of various catalysts as well as a solvent in recent work and TBAI for maximum yield of Thiazolidinones

Enty	Catalyst	Solvent	Temperature (C°)	Yield (%)	Time	compound	Ref
1	Co ₃ O ₄ @p[AVIM]Br	H ₂ O	25	79	2(h)	4v	28
2	[bmim][PF ₆]	Ethanol	80	59	4(h)	4h	29
3	[MOEMIM]TFA	Ethanol	80	78	3(h)	1d	30
4	MNP[pmim]HSO ₄	solvent-free	80	78	7(h)	8	31
5	[HDBU][HSO ₄]	solvent-free	80	80	2(h)	8	32
6	TBAI	H ₂ O	RT	91	81(min)	4a	present work



Antimicrobial activity

The products were examined for their antimicrobial activity by the method of spreading the cup plate by measuring the inhibition areas in milli metres at concentrations of 50 µg against *S. Paratyphi-A*, *E. coli*, *S. aureus* and then all the compounds were tested for their antimicrobial activity as in **Table 7**. During the examination in **Table 7**. The compounds 2C,3C and 4C are moderately active, while 2d, 3b and 4b are considered more active, and the remaining compounds are less active

compared to the standard drugs. Penicillin and Ampicillin are used as standard antibacterial drugs. Also, all the prepared compounds were examined against the fungal strains *A. niggers* and *F. molariform*. The compounds 2a, 2b, 3a and 4a showed us the maximum inhibition in the range 46.42% - 77.22% is the most active against all of the fungal species compared to the standard drugs. The remaining compounds showed moderate activity. Fungigural and Griseofulvin are used as standard anti-fungal medicines.

Table 7. Antimicrobial data of compounds 2,3,4(a-h)

Compound No	R	Antibacterial activity			Antifungal activity		
		Diameter of a zone of inhibition in mm			%Inhibition		
		<i>S. Paratyphi-A</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>B. subtilis</i>	<i>F. molariforme</i>	<i>A. niger</i>
2a	2NO ₂	05	11	07	08	57.55	45.35
2b	3NO ₂	05	08	07	09	63.33	69.21
2c	4NO ₂	13	12	10	15	77.22	67.45
2d	4NH ₂	17	19	16	15	46.78	62.30
3a	2NO ₂	07	09	11	06	54.25	59.34
3b	3NO ₂	13	16	18	18	59.79	69.40
3c	4NO ₂	11	12	11	14	46.42	43.42
4a	2NO ₂	09	05	07	05	57.32	55.87
4b	3NO ₂	16	15	15	17	46.55	40.57
4c	4NO ₂	12	15	11	13	57.45	56.44
Ampicillin	-----	31	33	35	35	-----	-----
Penicillin-G	-----	32	30	30	33	-----	-----
Griseofulvin	-----	-----	-----	-----	-----	86	81
Fungiguard	-----	-----	-----	-----	-----	78	77

Conclusion

From the experiment, it was concluded that the synthesis of tetrazole and Thiazolidine-4-One were prepared safe and simple with a good product yield, was prepared through this research by using a new tetrabutylammonium iodide (TBAI) to accelerate the synthesis of derivatives of both tetrazole and Thiazolidine-4-One from Schiff bases in an aqueous medium using an environmentally friendly material, which is not harmful to the environment. A non-toxic, reusable, and thermally stable catalyst that was used in an aqueous medium instead of organic solvents, making it a superior, environmentally friendly approach and alternative to previous methods. Using this catalyst, tetrazole and Thiazolidine-4-One derivatives were synthesized with good results and a high percentage and also yield, the antifungal and antibacterial activity was evaluated with good results as shown in **Table. 7**.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest

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