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SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL ACTIVITY OF SOME THIAZOLE HYDRAZINES

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Abstract: The present work reports the synthesis and characterization of some thiazole hydrazine derivatives of vanillin, and 5-iodovanillin by condensation with thiosemicarbazide followed by cyclization with phenacyl bromide in ethanol under reflux condition. The synthesized compounds were screened against S. aureus, E. coli, P. aeruginosa, S. pyogenus bacteria, and C. albicans, A. clavatus, and A. niger fungal strains. Most of the compounds possessed good to moderate antimicrobial activity against the used microbes. Antimalarial screening of the synthesized compounds showed a good antimalarial activity against Plasmodium falciparum; but less than the standard quinine. One of the synthesized compounds (**4d**) exhibited promising antimalarial activity against Plasmodium falciparum as compared to the standard quinine.

Keywords: Thiazole hydrazines, Antimicrobial, Antimalarial

Introduction

Thiazole-based heterocyclic compounds possess several biological activities, such as antimicrobial, antifungal, anti-inflammatory, analgesic, antitubercular, antitumor, and antiprotozoal properties [1-2]. Thiazole-derived compounds have proven their efficiency by stimulating apoptosis in cell lines [3].

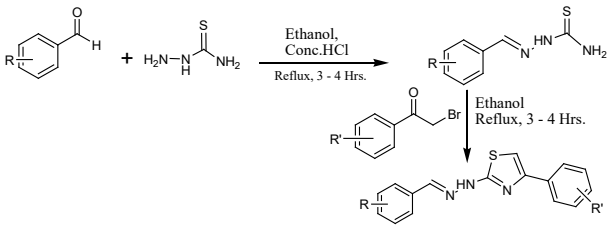
Besides, thiazoles possess a broad array of commendable biological properties, such as anthelmintic, anti-diabetic, antimalarial, antiviral, antischizophrenic, antiallergic, anticonvulsant, antioxidant, and anti-cholinesterase potential [4-5].

Malaria is a common challenge all over the world, mainly in Africa and Sub-Sahara which can be very easily transmitted through international travelers as well [6].

According to the report of WHO in 2017, around 219 million cases of malaria were observed worldwide along with an increase of 2 million cases per year [7].

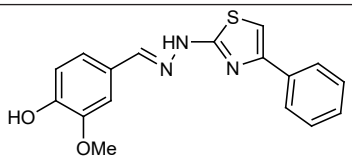
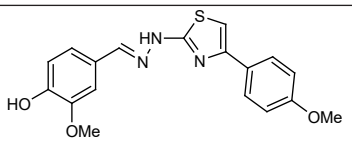
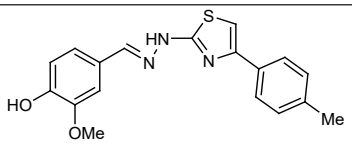
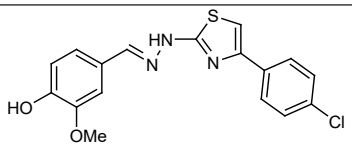
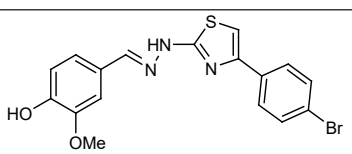
The antimicrobial activity of thiazole derivatives has been extensively studied by various researchers as documented in the literature [8-9]. Compounds containing thiazole ring systems are used as antiviral agents and some are used as pesticides [10-11]. Herein, in the present work we report synthesis, characterization, antimicrobial and antimalarial activity of thiazoles containing vanillin, and 5-iodovanillin moieties

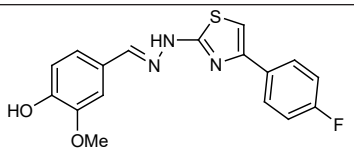
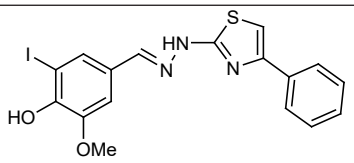
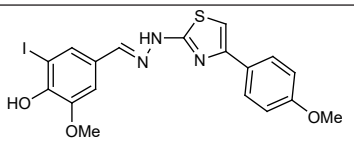
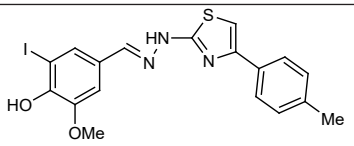
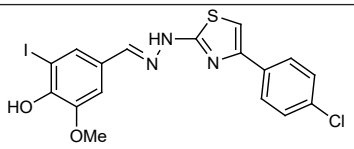
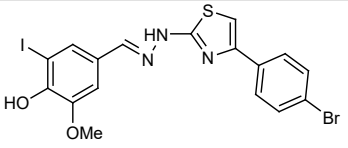
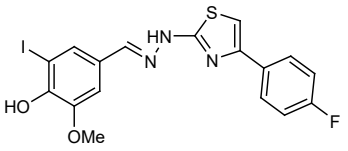
(**Scheme 1**):



Scheme 1: General scheme for the synthesis of thiazoles

Table 1: Yields and melting points of the synthesized thiazoles incorporated with vanillin and 5-iodovanillin moieties

Entry	R	R^1	Product	Code	Yield@ (%)	M. P. (°C)
1	3-OMe, 4-OH	H		4a	83	110-112
2	3-OMe, 4-OH	4-OMe		4b	88	178-180
3	3-OMe, 4-OH	4-Me		4c	82	205-207
4	3-OMe, 4-OH	4-Cl		4d	89	120-122
5	3-OMe, 4-OH	4-Br		4e	87	130-132

6	3-OMe, 4-OH	4-F		4f	78	139-141
7	3-OMe, 4-OH, 5-I	H		4g	84	204-206
8	3-OMe, 4-OH, 5-I	4-OMe		4h	87	150-152
9	3-OMe, 4-OH, 5-I	4-Me		4i	83	163-165
10	3-OMe, 4-OH, 5-I	4-Cl		4j	92	134-136
11	3-OMe, 4-OH, 5-I	4-Br		4k	88	216-218
12	3-OMe, 4-OH, 5-I	4-F		4l	76	184-186

@Yields isolated for the reaction of vanillin, and 5-iodovanillin (3 mmol), thiosemicarbazide (3 mmol), and cyclization with phenacyl bromide (3 mmol) in EtOH (5 mL) under reflux.

Materials and Methods:

The chemicals used were SD fine or Sigma Aldrich made. Reactions were monitored on Merck-made TLC plates precoated with silica gel on aluminum. Melting points of the purified compounds were recorded in capillaries open at one end on a digital melting point apparatus and were uncorrected. ^{1}H NMR spectra

of the synthesized compounds were recorded on a 400-MHz Bruker Advance NMR spectrometer and chemical shifts were measured in δppm using tetramethylsilane as an internal standard.

General procedure for the synthesis of thiazole hydrazines (4a-4l):

Aldehyde (3 mmol) was refluxed with thiosemicarbazide (3 mmol) in the presence of a few drops of concentrated HCl in ethanol (3 mL) for 3 h and the obtained solid was filtered off as pure thiosemicarbazone. The resulting thiosemicarbazone was refluxed with an equimolar quantity of variously substituted phenacyl bromides in ethanol (3 mL) for further 4h. Progress of the reaction was monitored on TLC in 30% ethyl acetate: n-hexane. After completion of the reaction, the reaction mixture was cooled, basified with an ice-cold aqueous saturated solution of sodium bicarbonate, and filtered off the resulting yellow to orange solid as the pure thiazole hydrazines which were characterized by ^{1}H NMR and mass spectral data.

Spectral data:

Spectral data of the synthesized compounds are mentioned below:

Thiazole hydrazine (4a): Yellow solid, Yield = 83%; Melting point: 110-112^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.91 (s, 3H), 6.68 (s, 1H), 6.82 (s, 1H), 6.91 (s, 1H), 7.25 (d, 1H), 7.28 (d, 1H), 7.29 (s, 1H) 7.3 (t, 1H), 7.4 (t, 2H), 7.80 (d, 2H); IR (KBr) cm^{-1}: 3406, 3188, 2935, 1595, 1510, 1431, 1271.

Thiazole hydrazine (4b): Yellow solid, Yield = 88%; Melting point: 178-180^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.74 (s, 3H), 3.91 (s, 3H), 6.68 (s, 1H), 6.82 (s, 1H), 6.91 (s, 1H), 7.25 (d, 1H), 7.27 (d, 1H), 7.29 (s, 1H), 7.4 (t, 2H), 7.80 (d, 2H); IR (KBr) cm^{-1}: 3496, 3388, 2937, 1585, 1512, 1273, 1240, 1026.

Thiazole hydrazine (4c): Yellow solid, Yield = 82%; Melting point: 105-107^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.44 (s, 3H), 3.91 (s, 3H), 6.64 (s, 1H), 6.80 (s, 1H), 6.83 (s, 1H), 7.18 (d,1H), 7.20 (d, 1H), 7.25 (s, 1H), 7.70 (t, 2H), 7.72 (d, 2H); IR (KBr) cm^{-1}: 3371, 3064, 2939, 1564, 1510, 1267.

Thiazole hydrazine (4d): Yellow solid, Yield = 89%; Melting point: 120-122^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.93 (s, 3H), 6.79 (s, 1H), 6.81 (s, 1H), 6.82 (s, 1H), 7.0 (s, 1H), 7.25 (s, 2H), 7.34 (d, 2H), 7.73 (d, 2H), 7.76 (d, 2H); IR (KBr) cm^{-1}: 3495, 3147, 1593, 1564, 1508, 1267, 1159.

Thiazole hydrazine (4e): Yellow solid, Yield = 87%; Melting point: 130-132 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.94 (s, 3H), 6.82 (s, 1H), 6.89 (s, 1H), 7.11 (s, 1H), 7.26 (d, 1H), 7.50 (d, 1H), 7.53 (s, 1H), 7.65 (d), 7.67 (d, 2H); IR (KBr) cm^{-1}: 3490, 2939, 1622, 1510, 1271, 1031.

Thiazole hydrazine (4f): Yellow solid, Yield = 78%; Melting point: 139-141^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.84 (s, 3H), 5.70 (s, 1H), 6.72 (s, 1H), 6.76 (s, 1H), 6.90 (d, 1H), 7.12 (d, 1H), 7.25 (s, 1H), 7.75 (d, 2H), 7.78 (d, 2H); IR (KBr) cm^{-1}: 3512, 3070, 2966, 1591, 1508, 1271, 1157.

Thiazole hydrazine (4g): Yellow solid, Yield = 84%; Melting point: 204-206^{o}C;

^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.83 (s, 3H), 6.80 (s, 1H), 7.07 (s, 1H), 7.08 (s, 1H), 7.22 (s, 1H), 7.26 (s, 1H), 7.34 (t, 1H),7.36 (t, 2H), 7.70 (d, 2H); IR (KBr) cm^{-1}: 3487, 3055, 2935, 1618, 1487, 1278, 1041.

Thiazole hydrazine (4h): Yellow solid, Yield = 87%; Melting point: 150-152 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.73 (s, 3H), 3.91 (s, 3H), 6.59 (s, 1H), 6.96 (s, 1H), 6.98 (s, 1H), 7.00 (s, 1H), 7.57 (s, 1H), 7.68 (d, 2H), 7.98 (d, 2H); IR (KBr) cm^{-1}: 3365, 2835, 1614, 1593, 1247, 1166, 1035.

Thiazole hydrazine (4i): Yellow solid, Yield = 90%; Melting point: 163-165 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 2.42 (s, 3H), 3.94 (s, 1H), 6.69 (s, 1H), 7.06 (s, 1H), 7.24 (s, 1H), 8.0 (d, 1H), 7.32 (s, 1H), 7.46 (s, 1H), 7.63 d, 2H), 7.81 (d, 2H); IR (KBr) cm^{-1}: 3402, 3294, 2935, 1614, 1566, 1487, 1409, 1273, 1174, 1039.

Thiazole hydrazine (4j): Yellow solid, Yield = 92%; Melting point: 134-136°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.90 (s, 3H), 6.78 (s, 1H), 7.13 (s, 1H), 7.26 (s, 1H), 7.39 (s, 1H), 7.42 (s, 1H), 7.50 (d, 2H), 7.70 (d, 2H); IR (KBr) cm^{-1}: 3485, 3232, 2941, 1624, 1487, 1273, 1091, 819, 750.

Thiazole hydrazine (4k): Yellow solid, Yield = 88%; Melting point: 216-218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.96 (s, 3H), 6.79 (s, 1H), 7.16 (s, 1H), 7.26 (s, 1H), 7.59 (s, 1H), 7.56 (s, 1H), 7.62 (d, 2H), 7.91 (d, 2H); IR (KBr) cm^{-1}: 3479, 3051, 2937, 1620, 1487, 1273, 1039, 817.

Thiazole hydrazine (4l): Yellow solid, Yield = 76%; Melting point: 184-186°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.85 (s, 3H), 6.76 (s, 1H), 7.10 (s, 1H), 7.21 (s, 1H), 7.26 (s, 1H), 7.34 (s, 1H), 7.46 (d, 2H), 7.78 (d, 2H); IR (KBr) cm^{-1}: 3487, 3267, 3074, 2941, 1564, 1489, 1409, 1276, 1039, 839.

Biological activity of the synthesized thiazole hydrazines:

The synthesized thiazole hydrazines were studied for antimicrobial activity against four bacteria - *E. coli* (MTCC 443), *S. aureus* (MTCC 96), *P. aeruginosa* (MTCC 1688), and *S. pyogenus* (MTCC 442) and three fungi - namely*C. albicans* (MTCC 227), *A. niger*(MTCC 282)*,A. clavatus* (MTCC 1323) by using broth dilution method [12].

For the antibacterial screening, chloramphenicol and ciprofloxacin were used as the standard drugs whereas for antifungal activity; greseofulvin and nystatin were used as the standard drug. The Minimum Inhibitory Concentration (MIC) of a drug is the least concentration of the sample that inhibits visible growth of the microbe. MIC values of the products were measured and are expressed in **Tables 2** and **3**.

The antimalarial efficiency of the synthesized thiazole hydrazines was studied *in-vitro* against *Plasmodium falciparum* in a 96-well microtitre plate using Rieckmann and co-workers' protocol [13] using quinine as the standard and the results were expressed in IC_{50} values.

Results and discussion

For the synthesis of thiazole hydrazines, initially, a mixture of vanillin, and 5-iodovanillin (3 mmol) was treated with thiosemicarbazide (3 mmol) in the presence of 2-3 drops of concentrated HCl in ethanol (3 mL) under reflux at 80 ^{o}C. Afterwards, the obtained thiosemicarbazone was filtered off, washed with ethanol, and then cyclized with phenacyl bromide (3 mmol) in ethanol (3 mL) for further 4 h. The reaction was monitored by Thin Layer Chromatography (TLC) in 30% ethyl acetate: n-hexane.

Upon completion of the reaction, the reaction mass was cooled, basified with a saturated solution of sodium bicarbonate, and the resulting solid was filtered off to get thiazole hydrazine product which was further crystallized with ethanol and characterized by analysis of ^{1}H NMR and mass spectral data.

The thiazole hydrazines can also be synthesized by using a one-pot three-component strategy as in our previous work [14-15]; however, with the present strategy, we found a more clean reaction profile and reduced reaction time for the cyclization step. Under these optimized reaction conditions, we used vanillin, and 5-iodovanillin (3 mmol), thiosemicarbazide (3 mmol), and various substituted phenacyl bromides (3 mmol) for the synthesis of thiazole derivatives as indicated **Table 1**. The purified compounds were further subjected to the screening of antimicrobial and antimalarial potential.

Table 2. Antibacterial activity of thiazole hydrazines (MIC values) (4a-l)

Sr. No.	Code No.	E. coli	P. aureginosa	S. pyogenus	S. aureus
		MTCC 443	MTCC 1688	MTCC 442	MTCC 96
1	**4a**	125	250	100	250
2	**4b**	125	12.5	62.5	100
3	**4c**	250	250	100	125
4	**4d**	125	250	250	500
5	**4e**	250	100	500	250
6	**4f**	100	62.5	250	500
7	**4g**	12.5	50	250	500
8	**4h**	250	125	500	250
9	**4i**	125	250	12.5	50
10	**4j**	250	125	125	100
11	**4k**	100	100	250	125
12	**4l**	100	500	250	250
	Chloramphenicol	50	50	50	50
	Ciprofloxacin	25	25	50	50

The compound (**4g)** has lower MIC value (12.5 µg/mL) than the standard ciprofloxacin drug (25 µg/mL) against the *E. coli* bacteria. The compound (**4b)** (MIC = 12.5 µg/mL) was more potent than ciprofloxacin (MIC = 25 µg/mL) against the *P. aureginosa*bacteria; the compound (**4i)** had a lower MIC (12.5 µg/mL) than ciprofloxacin against *S. pyogenus*. The results of antibacterial activity against the *S. aureus* were found to be moderate, except the compound (**4i)** which was equipotent with ciprofloxacin and chloramphenicol in terms of their MIC values (**Table 2**).

Table 3. Antifungal activity of the synthesized compounds (MIC values) (4a-l)

Sr. No.	Code No.	C. albicans	A. clavatus	A. niger
		MTCC 227	MTCC 1323	MTCC 282
1	**4a**	>1000	500	500
2	**4b**	1000	500	500
3	**4c**	500	1000	500
4	**4d**	250	1000	1000

5	**4e**	250	500	250
6	**4f**	500	1000	1000
7	**4g**	250	500	500
8	**4h**	250	100	500
9	**4i**	500	500	>1000
10	**4j**	500	500	>1000
11	**4k**	250	500	500
12	**4l**	1000	500	1000
	Nystatin	100	100	100
	Greseoufulvin	500	100	100

From **Table 3**, the results of antifungal activity suggest that most of the synthesized compounds possess higher or equipotent antifungal activities against *C. albicans*. In particular, the compound **(4d), (4e), (4g), (4h)** and **(4k)** exhibited better antifungal activity against *C. albicans* as compared with the standard greseoufluvin. However, all the compounds were less potent against *A. Clavatus* and *A. Niger* as compared with both the standard drugs. The antimalarial activity was carried out against *Plasmodium falciparum;* one of the species, mainly responsible for malaria. The results of antimalarial activity were moderate to good as compared with the standard quinine (**Table 4).**

Table 4. Antimalarial activity of the synthesized compounds (4a-l)

MINIMAL INHIBITION CONCENTRATION		
Sr. No.	**Compound**	**MEANIC50 VALUES (μg/mL)**
1	4a	1.032
2	4b	2.87
3	4c	5.71
4	4d	0.76
5	4e	3.12
6	4f	1.35
7	4g	2.23
8	4h	1.04
9	4i	0.89
10	4j	2.30
11	4k	1.67
12	4l	0.87
	Quinine std.	0.26

Conclusions

In conclusion, the present work reports the synthesis, characterization, antibacterial, antifungal, and antimalarial activity of thiazole hydrazines derived from vanillin, and 5-iodovanillin. Thus, the results of antimicrobial and antimalarial activity reveal that the thiazole hydrazines incorporated with vanillin and iodovanillin possess good biological activity acting as promising antibacterial and antimalarial entities.

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