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One-pot multicomponent synthesis of novel thiazol-2-imines *via* microwave irradiation and their antifungal evaluation

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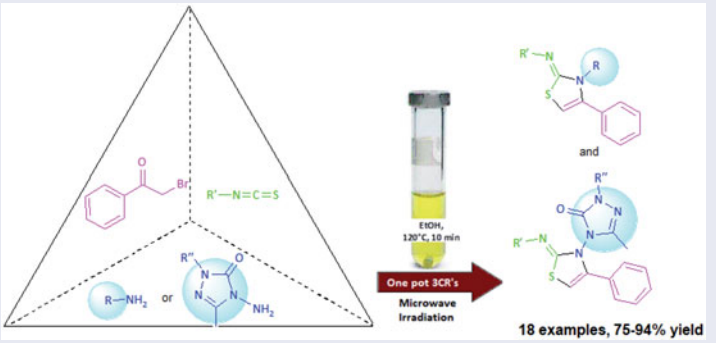
ABSTRACT

Microwave-assisted green approach is developed for an efficient synthesis of thiazol-2-imines under catalyst-free conditions. The desired products are formed by one-pot three-component reaction which is an improvised method for Hantzsch thiazole synthesis. The microwave-assisted protocol gives excellent yields with high purity in just 10–15 min. All the synthesized compounds have been screened for antifungal activity and some of the derivatives show a broad spectrum against fungal pathogens.

GRAPHICAL ABSTRACT



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KEYWORDS
1,2,4-Triazolone; antifungal activity; green synthesis; multicomponent reaction; thiazol-2-imines

Introduction

Green synthesis is one of the trending and effective forms of artwork which has revolutionized the research perspective for a synthetic organic chemist. In quest of these, microwave-assisted organic synthesis (MAOS) has successfully accomplished the synthesis of a structurally diverse collection of complex molecules as well as a small library of compounds under short intervals of time. This method is also known for its spectacular accelerations in most of the reactions with improved yields, reduced cost, reduced

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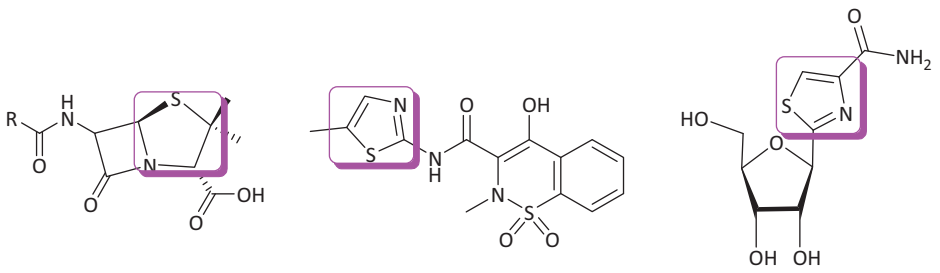


Figure 1. Clinically available drugs with thiazole moieties.

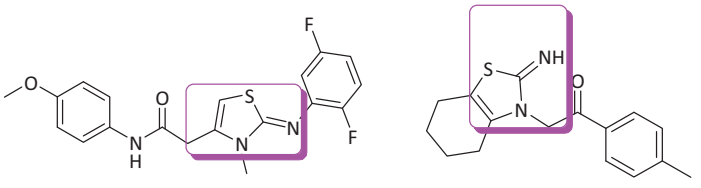


Figure 2. Examples of biological active thiazol-2-imine derivatives.

energy, higher atom economy, low-waste, short reaction time, and use of environmentally greener solvents which implies to be labeled as one of the pioneers in "green chemistry".[1] The MAOS has been found to be an effective synthetic strategy which increases the reaction rates of multicomponent reactions.[2]

Heterocycles are chemically flexible framework as they respond to various demands of biological systems which invariably make them demonstrate interesting biological activities.[3] In particular, thiazole and their derivatives have found to be a core unit in drug designing and development of various therapeutic agents (Fig. 1).[4] Thiazole ring has been found to play a crucial role in the lead identification and optimization, as pharmacophoric and bioisosteric elements, and also as a spacer.[5] Organic compounds containing the thiazole ring are used as antitumor, cytotoxic,[6] antifungal,[7] antibacterial,[8] antiparasitic,[9] antitubercular,[10] anticancer,[11] and anti-inflammatory agents.[12]

Then comes into action is the thiazol-2-imine ring system which is present in several drug motifs, which is found to be of considerable interest due to its significant biological activities[13]. The structural fragment thiazol-2-imine is found in muscarinic agonists as well as in anti-inflammatory, analgesic, and kinase (CDK1, CDK5, and GSK3) inhibition,[14] antifungal,[15] melanin-reducing activity (skin whitening agent) KHG22394 (Fig. 2),[16] and as platelet GPIIb/IIIa receptor antagonist.[17] Also, the scaffold of thiazol-2-imine, Pifithrin (Pft-α) (Fig. 2) has been predicted as a possible lead for the diagnosis of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, stroke, cancer therapy.[18]

The synthesis of 2-aminothiazole was first reported by Hantzsch basically employing the thiourea and α-haloketones.[19] Many of the reaction conditions also unveiled that could possibly synthesize thiazol-2-imines in basic medium or neutral medium or with ammonium thiocyanate and also in aqueous media catalyzed by diammonium hydrogen phosphate or DABCO.[20] Also, the condensation reaction of α-haloketones with

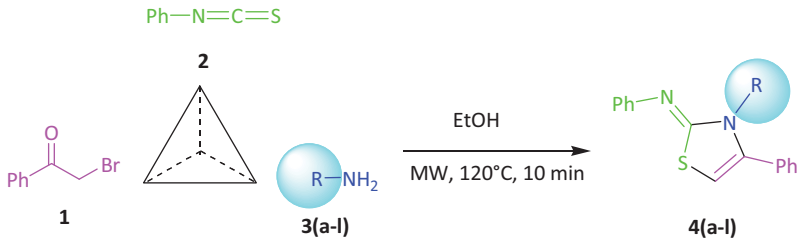
thiourea under acidic conditions gave rise to various quantity of aminothiazoles as side products. The same method was embraced for the synthesis of the *N*-alkylated iminothiazolines that could be obtained by replacing thioureas with mono and *N*, *N*-disubstituted thioureas under different reaction conditions.[21] Various other strategies include potassium thiocyanate treatment of α-bromoketimines,[22] reaction of *N*-monoalkylated thioureas with 3-bromomethyl-2-cyanocinnamonitrile,[23] cycloadditions followed by elimination of 5-imino-1,2,4-thiazolidin-3-ones with enamines and ester enolate,[24] ring transformation of 1-arylmethyl-2-(thiocyanomethyl)aziridines in the presence of $TiCl_4$ and acylchloride,[25] reaction of *N*-propargylaniline with acylisothiocyanates,[26] and phenylamino acetonitrile with alkyl isothiocyanates.[27] In addition to this, the synthesis of thiazol-2-imines was also carried out by the reaction of substituted amines with isothiocyanates.[28] Lately, the three component reaction of phenacyl bromide or 2-chloro-1,3-dicarbonyl compound, amine and phenyl isothiocyanate has been developed to give subsequent thiazol-2-imines.[29] The one-pot reaction of 1,1-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT), as a brominating agent, enolizable ketones and disubstituted thioureas was reported by Murru et al.[30]

Although there are reports of the one-pot three-component[31] reaction of thiazol-2-imines in basic alumina under MW irradiation[32] or the trypsin-catalyzed reactions[33] which are effective, but the drawbacks associated with many reported methods are unavoidable and hazardous with malicious workups. Therefore, there is an urgent need to develop efficient, easily available and green approach which can be easily pursued for the synthesis of thiazol-2-imines. Our attempt to synthesize thiazol-2-imines without the use of catalyst or reagent of that sort, towards directing a greener approach instigated us to explore the microwave irradiation method. We could overcome many drawbacks with respect to the existing methodologies such as easy workup, higher yields, atom economy, short reaction time, and low wastage during the course of the reaction.

Experimental

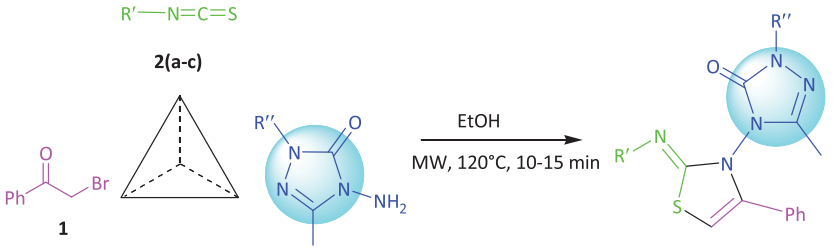
General procedure for the synthesis of (5Z)-N-(3-(aryl)-4-phenylthiazol-2(3H)-ylidene)benzenamine 4(a–l) and 5-methyl-2-aryl-4-((2Z)-4-phenyl-2-(arylimino)thiazol-3(2H)-yl)-2H-1,2,4-triazol-3(4H)-one 4(o–t)

The reaction was performed in a single mode Discover SP (CEM Corporation, Matthews, North Carolina, United States) microwave synthesizer with controlled irradiation up to 300 W having a magnetic stirrer. An equimolar ratio of compounds **1**, **2a**, and **3(a–l)** were taken in a sealed glass tube vial (30.0 mL) in ethanol (10.0 mL). The sealed vessel with reaction mixture was pre-stirred for 60 s at room temperature. Further, the reaction mixture was irradiated by 100 W microwave radiation at 120 °C for 10–15 min at medium stirring. The reaction temperatures were monitored with an IR sensor equipped outside of the reactor. After completion of the reaction (TLC), the reaction mixture was cooled and quenched in ice. The resulting precipitate was filtered and recyrstallized from ethanol (Scheme 1). Similarly, compounds **4(o–t)** were prepared by employing equimolar ratio of compounds **1**, **2(a--c)**, and **3(m–n)** in a sealed glass tube vial (30.0 mL) in ethanol (10.0 mL), which was further irradiated by 100 W microwave radiation at 120 °C for 10–15 min, followed by similar workup (Scheme 2).



a) R = -C_6H_5, **b**) R = -C_6H_4-2-Cl, c) R = -C_6H_4-3-Cl, **d**) R = -C_6H_4-4-Cl, **e**) R = -C_6H_4-4-Br, **f**) R = -C_6H_4-4-F, **g**) R = -C_6H_4-4-OCH_3, **h**) R = -C_6H_4-4-CH_3, **i**) R = -C_6H_4-4-CF_3, **j**) R = -C_6H_4-3-NO_2, **k**) R = -NH-C_6H_5, **l**) R = -$(CH_2)_2$

Scheme 1. One-pot three-component synthesis of thiazol-2-imines **4(a–l)**.



a) R′ = -C_6H_5, **b**) R′ = -C_6H_4-4-Cl, **c**) R′ = -C_6H_4-4-OCH_3, **m**) R″ = -C_6H_5, **n**) R″ = -C_6H_4-4-CH_3, **o**) R′ = -C_6H_5; R″ = -C_6H_5, **p**) R′ = -C_6H_4-4-Cl; R″ = -C_6H_5, **q**) R′ = -C_6H_4-4-OCH_3; R″ = -C_6H_5, **r**) R′ = -C_6H_5; R″ = -C_6H_4-4-CH_3, **s**) R′ = -C_6H_4-4-Cl; R″ = -C_6H_4-4-CH_3, **t**) R′ = -C_6H_4-4-OCH_3; R″ = -C_6H_4-4-CH_3

Scheme 2. One-pot three-component synthesis of thiazol-2-imines **4(o–t)**.

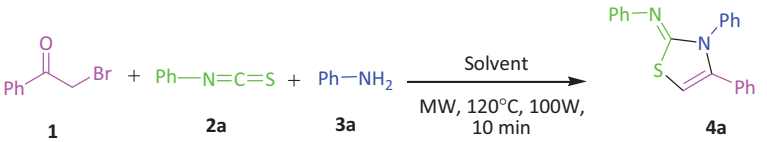
(5Z)-N-(3,4-Diphenylthiazol-2(3H)-ylidene)benzenamine (4a)

Yield: 94%; chrome yellow solid, m.p.: 189–192 °C; IR (KBr, cm^{-1}): 3443, 1617, 1578. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.98 (1H, s, CH), 7.05 (2H, dd, $J = 8$ Hz, Ar-H), 7.13 (2H, dd, $J = 8$ Hz, Ar-H), 7.18–7.21 (4H, m, Ar-H), 7.27–7.30 (3H, m, Ar-H), 7.31–7.36 (4H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 97.2, 121.57, 123.16, 127.47, 128.15, 128.23, 128.79, 129.10, 129.35, 131.62, 137.40, 137.94, 139.90, 151.84, 160.08. GC-MS *m/z* Calcd Mass: 328.43; Found: 328. CHN analysis for $C_{21}H_{16}N_2S$ Calcd: C, 76.80; H, 4.91; N, 8.53. Found: C, 76.82; H, 4.90; N, 8.55.

Results and discussion

The present methodology proposes the multicomponent strategy for the synthesis of substituted thiazol-2-imines through a green approach (Schemes 1 and 2). Our investigation started when 2-bromoacetophenone **1**, phenylisothiocyanate **2a** and aniline **3a** were taken in a one-pot three-component (3CR's) condition in absolute ethanol under microwave (MW) irradiation at 100 W maximum power for 10 min at the temperature of 120 °C. To our surprise, the neat reaction occurred affording the desired product **4a** in 89% in just 10 min. To understand the efficiency of the above methodology, the reaction was also performed under conventional heating at 150 °C for about 1.5–2 h and yield of the reaction was 65% (Table 1, entry **2**).

Table 1. Optimization of the reaction conditions for the synthesis of **4a**.[a]



1 **2a** **3a** **4a**

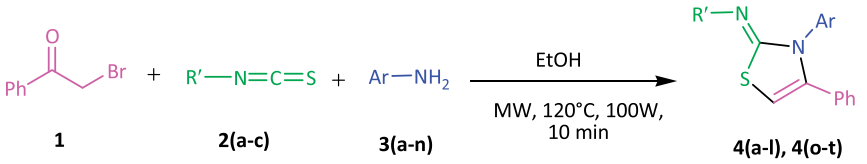
Entry No.	Solvent	Time (min)	**Yield** (%)[b]
1	EtOH	10	89
2	EtOH	1.5–2 h	68[c]
3	MeOH	10	75
4	AcOH	10	72
5	1:1(H_2O:EtOH)	10	68
6	DMF	10	72
7	CH_3CN	10	67
8	THF	10	65[d]
9	PEG	1–2 h	55
10	Ethyl-L-lactate	1–2 h	53
11	Neat	1 h	No reaction

[a]Reaction conditions: a mixture of 2-bromoacetophenone **1** (1.0 mmol), phenylisothiocyanate **2a** (1.0 mmol) and aniline **3a** (1.0 mmol) in EtOH (5 mL) was irradiated at 100 W maximum power, at the temperature of 120 °C; [b]isolated yield; [c]reaction was performed under conventional heating at 150 °C; [d]incomplete reaction even after the 30–45 min of microwave irradiation.

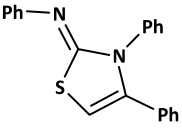
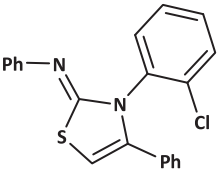
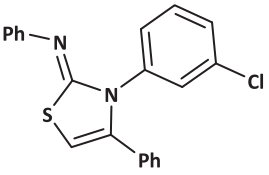
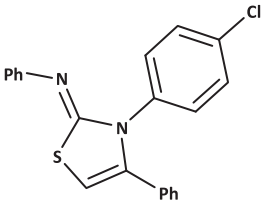
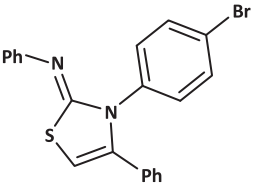
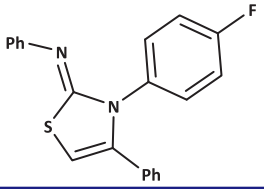
By earlier literature reports it was observed that the synthesis of substituted thiazol-2-imines occurs with the use of enzyme-catalyzed reactions and also under basic conditions.[32,33] But we could isolate the desired product in good yields without the use of any catalyst but just by performing the protocol under microwave irradiation. Encouraged by these results we thought to optimize the reaction conditions by varying the solvent systems and also to accord their resulting yields. We screened various solvents like methanol, acetic acid, dimethylformamide, acetonitrile, tetrahydrofuran, and aqueous EtOH (1:1) under microwave conditions. Through the investigation, we could observe that the polar protic solvents yielded better than aprotic solvents. Also the solvents such as PEG and ethyl-L-lactate were investigated under microwave conditions but the yields were observed to be moderate percentage with an incomplete reaction. Out of these screened solvents, an equimolar ratio of water and ethanol yielded the product in 68% (Table 1, entry **5**). All the other solvents yielded the desired product **4a** in moderate to excellent yields. It was also observed that the reaction was incomplete when it was irradiated in THF for about 30–45 min (Table 1, entry **8**). The model reaction was also carried out under neat condition and through our investigation, we found out that the reaction gave a mixture of products (no trace of desired product) along with unreacted starting materials even after 48 h (Table 1, entry **11**).

The substrate scope of this methodology was explored by a wide range of aromatic and heterocyclic amines with aryl isothiocyanate and 2-bromoacetophenone. All the substituted amines readily reacted with aryl isothiocyanate and 2-bromoacetophenone to furnish the products in excellent yields (Table 2). The percentage yield of the desired product was affected by the electronic nature as well as the positions of the substituents on the aromatic ring of the amines, respectively. Higher yield was observed when electron-donating groups were present at the *para* position of the amine analogs (Table 2, entries **7** and **8**). The significant decrease in the yields was observed when electron-withdrawing groups were present at the *para* position (Table 2, entries **4–6**) compared to the

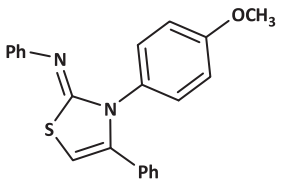
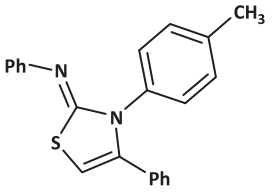
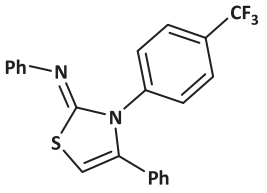
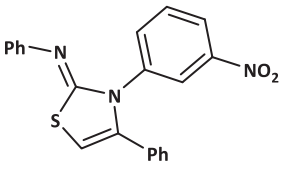
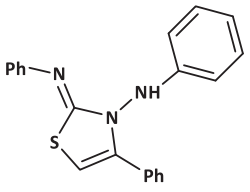
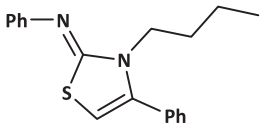
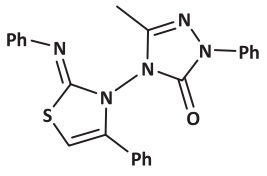
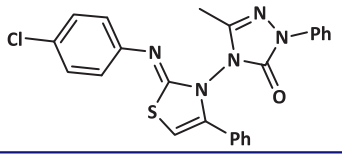
Table 2. Optimization of substrate scope of amines.[a]



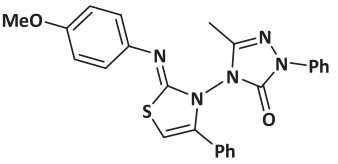
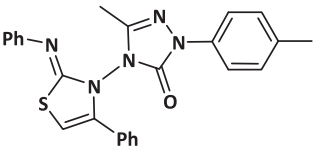
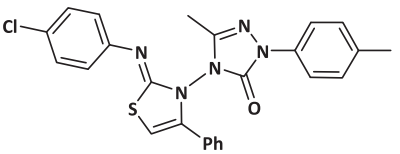
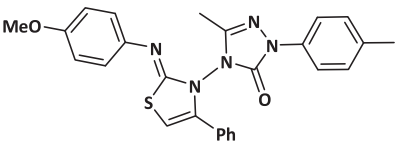
1 **2(a-c)** **3(a-n)** **4(a-l), 4(o-t)**

Entry No.	Compound	Structure	Yield (%)[b]
1	**4a**		89
2	**4b**		84
3	**4c**		83
4	**4d**		78
5	**4e**		76
6	**4f**		71

(*continued*)

7	**4g**		**94**
8	**4h**		89
9	**4i**		82
10	**4j**		67
11	**4k**		79
12	**4l**		85
13	**4o**		88
14	**4p**		72

(*continued*)

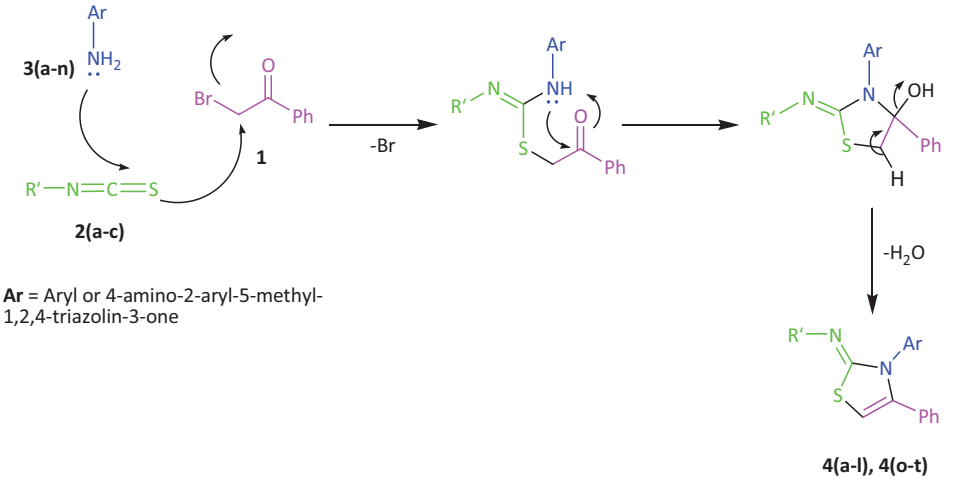
15	**4q**		84
16	**4r**		92
17	**4s**		75
18	**4t**		89

[a]Reaction conditions: a mixture of 2-bromoacetophenone 1 (1.0 mmol), **2**(**a**–**c**) (1.0 mmol), and **3**(**a**–**n**) (1.0 mmol) in EtOH (5 mL) was irradiated at 100 W maximum power, at the temperature of 120 °C; [b]isolated yield.

ortho and *meta* positions (Table 2, entries **2** and **3**). Subsequently, lower yields were observed in case of $-NO_2$ group at the *meta* positions due to its electron withdrawing nature (Table 2, entry **10**). In case of trifluoromethyl group at the *para* position (Table 2, entry **9**), the observed yield was moderate as compared to the unsubstituted aromatic amine (Table 2, entry **1**). When phenyl hydrazine was taken into account, moderate yield was observed (Table 2, entry **11**). Aliphatic amine also showed increase in the yields with good atom economy (Table 2, entry **12**). Substrate scope was further explored using 2-aryl-5-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-oxo-4-yl amines **3(m–n)**. To our delight all the substituted amines resulted into good yields (Table 2, entries **13–18**).

An attempt on synthesizing thiazol-2-imine with various aliphatic, aromatic, and heterocyclic amines under microwave condition at short interval of reaction time, with no catalysts, no acidic/basic reaction conditions and excellent yields proves to be a well-performed one. This methodology shows that there is more scope of exploration for the synthesis of various amines linked to thiazol-2-imine substrate which possesses potent pharmacological activities.

The plausible mechanism (multicomponent) for the formation of title compounds **4(a–l)**, **4(o–t)** has been outlined in Scheme 3. Initially, the addition of amine (s) to phenylisothiocyanate affords *in situ* thiourea intermediate, which undergoes *thia-Michael* addition of sulphur to the carbon of bromomethyl group of **1**. Further, it facilitates the abstraction of NH proton which undergoes cyclization by the loss of water to yield the product. The reaction proceeds to give the *syn* product because of the higher acidity of NH proton flanked by a phenyl group.



Scheme 3. Plausible mechanism for the formation of **4(a–l)** and **4(o–t)** under microwave conditions.

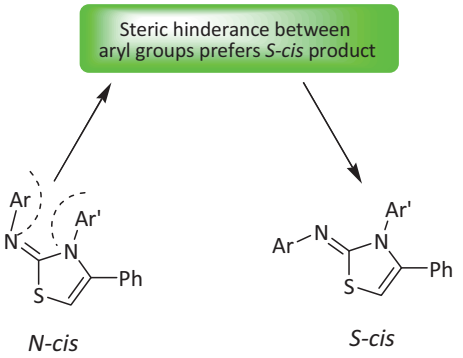


Figure 3. Schematic representation to show S-cis geometry of thiazol-2-imine **4(a–l), 4(o–t)**.

The synthesized compounds **4(a–l)** and **4(o–t)** were characterized by IR, ^{1}H, ^{13}C NMR, and GC-MS. The IR spectrum of all compounds showed a medium intense band appeared in the range of 1641–1685 cm^{-1} which corresponds to the C = N stretching. A strong adsorption band appears around 1708–1702 cm^{-1} due to the C = O stretching of the 1,2,4-triazolin-3-one group. In case of ^{1}H NMR, the C_5-H of the thiazole ring appeared as a singlet around 6.14–5.95 ppm. The signals which appeared around 6.96–8.01 ppm were attributed to the aromatic protons in all the compounds. In the case of ^{13}C NMR spectral analyses, the C_5 carbon of the thiazole ring and the imine carbon resonated around 97.16–98.87 ppm and 160.08–174.51 ppm, respectively. The other magnetically non-equivalent carbon atoms appeared as signals at their respective chemical shift values. The mass spectral analyses of titled compounds have shown the molecular ion peak corresponding to their molecular mass. The X-ray crystal structure of thiazol-2-imine by previously reported method also confirmed that they have *syn* (*S-cis*) stereochemistry due to the steric hindrance between the substituted phenyl and *N*-Phenyl groups (Fig. 3).[34]

Table 3. *In vitro* antifungal activities of **4(a–l)** and **4(o–t)** expressed in ZOI (mm) and MIC (μg/mL).

Entry No.	ZOI (mm)	*C. albicans* MIC (μg/mL)	ZOI (mm)	*A. fumigatus* MIC (μg/mL)	ZOI (mm)	*niger* MIC (μg/mL)
4a	16	25	18	10	10	10
4b	12	50	14	25	16	25
4c	18	50	18	25	14	25
4d	15	25	12	10	12	5
4e	16	25	14	10	10	10
4f	10	10	10	10	10	2.5
4g	10	10	13	10	12	25
4h	14	50	16	25	14	25
4i	15	25	12	5	12	2.5
4j	16	50	12	25	16	25
4k	12	10	12	10	14	25
4l	18	25	12	25	16	25
4o	10	5	16	25	15	5
4p	16	5	15	10	14	5
4q	10	10	12	25	12	25
4r	12	10	14	10	10	5
4s	14	5	10	5	16	2.5
4t	18	25	10	10	12	10
Fluconazole	24	30	26	30	24	30

Antifungal activity

All the newly synthesized compounds were screened for their antifungal activity by the Disc Diffusion method. The antifungal activity of synthesized compounds **4(a–l)** and **4(o–t)** was screened against three (03) fungal strains *Candida albicans*, *Aspergillus fumigatus*, and *Aspergillus niger* using Fluconazole as a standard. All determinations were done in triplicate and the zones of inhibitions were recorded in mm. The preliminary investigations were conducted for all the compounds at a concentration of 100 μg/mL in DMSO, for the above-mentioned microorganisms. Series of dilutions of compounds were prepared (2.5, 5, 10, 25, 50, 75, 100 μg/mL) to determine the Minimum Inhibitory Concentrations (MIC) value. The Zone of Inhibition (ZOI) and MIC are summarized in Table 3. Antifungal activity with MIC$\leq$ 50 μg/mL was observed for all the synthesized derivatives. According to Table 3, the compounds **4(a–l)** and **4(o–t)** displayed moderate to excellent activity against three fungal strains.

Amongst compounds **4(a–l)**, **4f** (containing *p-fluro* substituent) and **4i** (containing *p-trifluoromethyl* substituent) exhibited highest activity against *A. niger* evidenced by the MIC of 2.5 μg/mL. Compound **4i** has also shown excellent activity against *A. fumigatus* with MIC of 5 μg/mL. All the other compounds have displayed good activity against *A. fumigatus* and *A. niger* in the MIC range of 5–25 μg/mL compared to the standard Fluconazole. Whereas, these compounds displayed moderate activity against *C. albicans*.

Among the series **4(o–t)**, the compound **4s** (containing *p-chloro* substituent) displayed remarkable activity against *A. niger* with MIC of 2.5 μg/mL whereas, compounds **4o**, **4p**, and **4r** have shown MIC of 5 μg/mL against fungal strain *A. niger*. Compounds **4o**, **4p**, and **4s** were found to be active against *C. albicans* with MIC of 5 μg/mL. All other compounds displayed good activity against all three fungal strains with the MIC range of 10–25 μg/mL when compared to the standard Fluconazole.

Conclusions

Microwave-assisted organic synthesis (MAOS) has become a remarkable tool that has initiated the need to explore the "chemistry space" and the diversity of the compounds,[35] which can also ease the drug discovery in the coming years.[36] In view of this, we have reported the synthesis of novel thiazol-2-imine by one-pot three-component method,[37] which is a greener approach under mild, catalyst-free conditions and to increase the atom economy starting from α-haloketones, isothiocyanates, and substituted amines. This methodology was found to execute the reaction into good to excellent yield when the electronic nature of the substituent came into action and thus, a wide variety of differently substituted derivatives could be synthesized. The synthesized compounds were screened for their *in vitro* antifungal activity against three fungal strains *C. albicans*, *A. fumigatus*, and *A.niger*. Amongst them compounds **4f**, **4i**, and **4s** displayed highest activity against *A. niger* whereas, most of the compounds have shown promising results.

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