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Synthesis, characterization and antifungal activity of substituted Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-*5H*-[1,3]-thiazolo[3,2-a]pyrimidie-6-carboxylate derivatives

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ABSTRACT

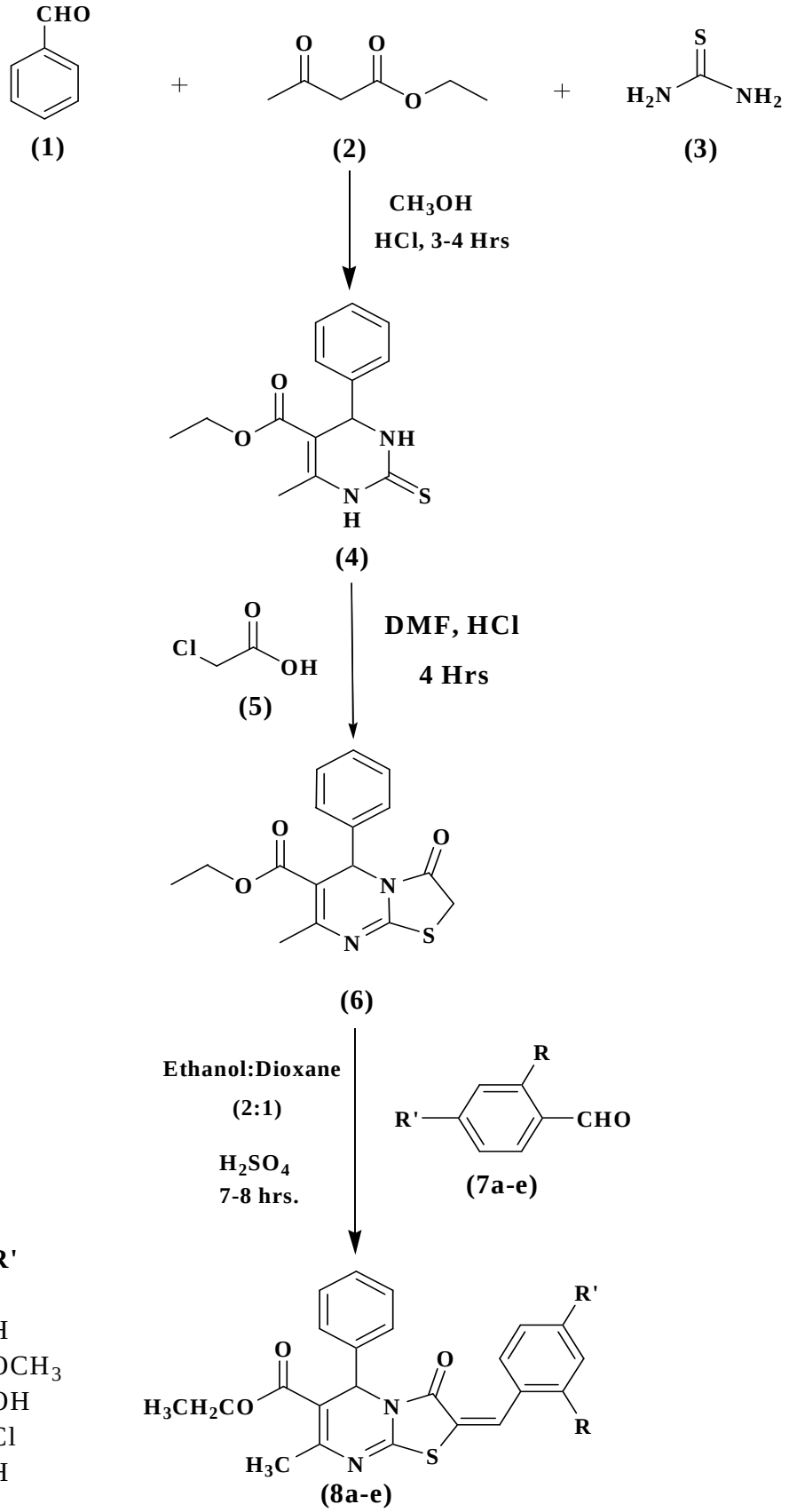
The title compounds were synthesized by reaction of Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-a]pyrimidine-6-carboxylate ***(6)*** *with different aromatic aldehydes****(7a-e)*** *in ethanol:dioxane (2:1) medium. Compound* ***(6)*** *were obtained by the cyclization reaction between 3,4-dihydropyrimidin-2(1H)-ones* ***(4)*** *and chloroacetic acid* ***(5)*** *in dimethylformamide (DMF). The newly synthesized compounds were characterized by* ^{1}*H NMR and IR spectral data. Further all the compounds were screened for antifungal activity against Aspergillus niger, Candida albicans and Aspergillus flavus. Evaluation of antifungal activity showed that almost all the compounds exhibited promising activity and thus could be promising novel drug candidates.*

Keywords: Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-*a*]pyrimidine-6-carboxylate, 3,4-dihydropyrimidin-2(*1H*)-ones, thiazolo[3,2-*a*]pyrimidine, antifungal activity.

INTRODUCTION

Molecules containing heterocyclic substructures continue to be attractive targets for synthesis since they often exhibit diverse biological properties and serves as a key template for the development of various therapeutic agents [1]. Literature review revels that a number of heterocyclic are endowed with a large number of biological and pharmacological activities, such as antimicrobia, antifungal [2], insecticidal [3], virucidal [4], acaricidal [5], anti-inflammatory and central nervous system [6,7]. Large number of heterocyclic compounds carrying pyrimidine, thiazole, imidazole, triazole, phthalimide, morpholine and tetrahydrocarbazole moeity are found to be associated with diverse biological activity such as insecticidal, antimicrobial, antiviral, analgesic and antiflammatory activity [8-13]. In this context, Pyrimidine derivatives have played an important role in the medicinal chemistry [14-16].Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS [17]. In addition substituted thiazoles and their biheterocycles have received considerable attention during last two decades as they are endowed with wide range of therapeutic properties [18]. Thiazole nucleus possess different biological activities such as anti hypertensive, anti-inflammatory, anti-schizophrenic, antibacterial, anti-HIV, hypnotic, anti-allergic and more recently analgesic, fibrinogen receptor antagonists with antithrombotic activity, inhibitors of bacterial DNA gyrase B and antitumor and cytotoxic activities [19].

The widespread properties of pyrimidines and thiazoles have prompted us to synthesize them in single molecular framework in order to study their pharmacological activity. Hence, the present investigation was undertaken to study the *In Vitro* antifungal activity of pyrimidine derivatives containing substituted thiazole.



Compd.	R	R'
8a	H	H
8b	H	OCH_3
8c	H	OH
8d	H	Cl
8e	NO_2	H

Scheme I: Synthetic routs for the compounds (8a-e)

MATERIALS AND METHODS

All the solvents and reagents were obtained from commercial sources and were used without further purification. Melting points were determined in open capillaries and were uncorrected. TLC was used to monitor the progress of all reactions and to check the purity of compounds. The IR spectra (KBr pellets) were recorded on Perkin-Elmer spectrum BX series FT-IR spectrometer. ^{1}H NMR spectra was recorded on a Bruker 400 MHz spectrometer with TMS as an internal standard.

Methods:
Benzaldehyde **(1)** reacts with ethylacetoacetate **(2)** and thiourea **(3)** via Biginelli reaction to give 3,4-dihydropyrimidine-2(*1H*)-thione **(4)** followed by the cyclization reaction with chloroacetic acid **(5)** gives Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo [3,2-*a*]pyrimidine-6-carboxylate **(6)** which upon reaction with different aromatic aldehydes **(7a-e)** gives substituted thiazole derivatives **(8a-e)**. **Scheme I** shows the synthetic protocol of the final compounds **(8a-e)**.

Procedure for the synthesis of 3,4-dihydropyrimidine-2(*1H*)-thione (4):
A mixture of benzaldehyde **(1)** (0.05 mol), Ethylacetoacetate **(2)** (0.05 mol), and thiourea **(3)** (0.05 mol) and a few drops of HCl as catalyst was refluxed in ethanol for about 1.5 hr. The progress of the reaction was monitored continuously by TLC. After completion of reaction, the resulting mixture was cooled and poured into crushed ice. The solid separated was filtered off and washed several times with water to remove unreacted thiourea [20]. The product was further washed with ether, and purified by recrystallization from methanol.

Yield: 82%; m.p: 189-191°C; Anal. cacld for $C_{13}H_{14}N_2OS$ M.W.: 246 Calc. C, 63.39; H, 5.73; N, 11.37; found: C, 63.61; H, 5.70; N, 11.43. IR (υ cm-1): benzene ring: 1650, 1510 and 1485 (skeletal vibration), 3075 (C-H stretching), 765 and 700 (C-H and C-C bending for mono-substituted ring); aliphatic methyl group (-CH_3): 2990 (asymm. and symm. stretching), 1405 (C-H bending); carbonyl of acetyl group (CH_3-C=O): 1325 (C-C-C stretching and C-C=O-C bending), 1695 (C=O stretching); sec. thioamide (NH-C=S-NH): 1240 (C=S stretching), 3125 (N-H asymm. and symm. stretching), 1550 (N-H bending), 1305 (C-N stretching). 1H NMR: δ 2.1 (3H,s,CH_3 of pyrimidine ring), 2.3 (3H,s,CH_3 of acetyl group), 5.3 (1H,s, H on pyrimidine ring), 7.8 (1H,s,NH of pyrimidine ring), 9.2 (1H,s,NH of pyrimidine ring), 7.2-7.3 (5H,m, aromatic proton).

Procedure for the synthesis of Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (6):
Cyclization of 3,4-dihydropyrimidine-2(1*H*)-thione **(4)** in to fused thiazolo[3,2-*a*]pyrimidines has been carried out by using chloroacetic acid in dimethylformamide (DMF) [21]. A mixture of 3,4-dihydropyrimidine-2(1*H*)-thione **(4)** (0.01 mol) and chloroacetic acid **(5)** (0.011 mol) in DMF was refluxed for 4 hrs. The resulting solution was allowed to stand at room temperature for an hour and cooled to 0°C. The solid separated was filtered off, washed with chilled water and recrystallized from ethanol to yield Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **(6)**.

White solid, mp 189-191^{0}C, Yield 71%; Anal. cacld for $C_{16}H_{16}N_2O_3S$ M.W.: 316 Calc. C, 60.74; H, 5.10; N, 8.85; found: C, 60.45; H, 5.45; N, 8.67; IR (υ cm^{-1}): benzene ring: 1610, 1580 and 1520 (skeletal vibration), 3180 (C-H stretching), 830 and 700 (C-H and C-C bending for mono substituted ring); aliphatic methyl group (-CH_3): 3000 and 2900 (asymm. and symm. stretching), 1440 (C-H bending); carbonyl of ester group (-C=O): 1240 and 1160 (C-O-C asymm. and symm. stretching), 1725 (C=O stretching), thiazole ring: 1700 (C=O stretching), 1375(ring stretching), 870, 830 and 725 (-CH out of plane bending), 1320 (C-N stretching), 600 (out of plane bending of S-C-N); ^{1}H NMR (δ ppm): δ 1.1 (3H,t,CH_3 of -OCH_2CH_3), 2.2 (3H,s,CH_3 of pyrimidine ring), 4.0 (2H,q,CH_2 of -OCH_2CH_3), 3.9 (2H,s,CH_2 of thiazole ring), 5.9 (1H,s,H on pyrimidine ring), 7.2-7.5 (5H,m,one aromatic rings).

Procedure for the synthesis of substituted Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-a]pyrimidie-6-carboxylate derivatives (8a-e):
A mixture of Ethyl-5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **(6)** (0.002 mol) and benzaldehyde **(7a)** (0.002 mol) was refluxed in ethanol:1,4-dioxan medium (2:1) in the presence of concentrate HCl on sand bath for about 7 to 8 hrs. The progress of the reaction was monitored continuously by TLC. After completion of reaction, the resulting mixture was cooled and poured into crushed ice. The solid obtained was filtered off, washed thoroughly with hot water, air-dried and recrystallized from appropriate solvent to yield Ethyl-2-benzylidene-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **(8a)**.

In a similar manner the other substituted Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-a]pyrimidie-6-carboxylate derivatives **(8b-e)** were prepared by using other aromatic aldehyde namely anisaldehyde, 4-

hydroxybenzaldehyde, 4-chloroxybenzaldehyde and 2-nitrobenzaldehyde respectively. **Scheme I** shows the general reaction protocol for the synthesis of substituted Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo [3,2-a]pyrimidie-6-carboxylate derivatives **(8a-e)**.

Analytical and spectral data of synthesized compounds (8a-e):

Ethyl-2-benzylidene-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate ***(8a):***

White solid, mp 221-223^{0}C, Yield 64%; Anal. cacld for $C_{23}H_{20}N_2O_3S$ M.W.: 404 Calc. C, 68.30; H, 4.98; N, 6.93; found: C, 68.34; H, 4.95; N, 6.90; IR (υ cm^{-1}): benzene ring: 1649 and 1465 (skeletal vibration), 3245 (C-H stretching), 824 and 699 (C-H and C-C bending for mono substituted ring), 1599 (C=N stretching); aliphatic methyl group (-CH_3): 3116 and 2979 (asymm. and symm. stretching), 1421 (C-H bending); carbonyl of ester group (-C=O): 1222 and 1146 (C-O-C asymm. and symm. stretching), 1725 (C=O stretching), thiazole ring: 1700 (C=O stretching), 1368 (ring stretching), 920, 878 and 782 (-CH out of plane bending), 1313 (C-N stretching), 515 (out of plane bending of S-C-N); ^{1}H NMR (δ ppm): δ 1.1 (3H,t,CH_3 of -OCH_2CH_3), 2.2 (3H,s,CH_3 of pyrimidine ring), 4.0 (2H,q,CH_2 of -OCH_2CH_3), 5.0 (1H,d,H of -C=CH), 5.9 (1H,s,H on pyrimidine ring), 7.2-7.5 (10H,m,two aromatic rings).

Ethyl-2-(4-methoxybenzylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate ***(8b):***

Cream white solid, mp 175-177^{0}C, Yield 61%; Anal. cacld for $C_{24}H_{22}N_2O_4S$ M.W.: 434 Calc. C, 66.34; H, 5.10; N, 6.45; found: C, 66.30; H, 5.14; N, 6.48; IR (υ cm^{-1}): benzene ring: 1649 and 1465 (skeletal vibration), 3245 (C-H stretching), 824 and 699 (C-H and C-C bending for mono substituted ring), 1599 (C=N stretching); aliphatic methyl group (-CH_3): 3116 and 2979 (asymm. and symm. stretching), 1421 (C-H bending); carbonyl of ester group (-C=O): 1222 and 1146 (C-O-C asymm. and symm. stretching), 1725 (C=O stretching), thiazole ring: 1700 (C=O stretching), 1368 (ring stretching), 920, 878 and 782 (-CH out of plane bending), 1313 (C-N stretching), 515 (out of plane bending of S-C-N); ^{1}H NMR (δ ppm): δ 1.1 (3H,t,CH_3 of -OCH_2CH_3), 2.2 (3H,s,CH_3 of pyrimidine ring), 3.7 (3H,s,CH3 of -OCH3), 4.0 (2H,q,CH_2 of -OCH_2CH_3), 5.0 (1H,d,H of -C=CH), 5.9 (1H,s,H on pyrimidine ring), 7.2-7.5 (9H,m,two aromatic rings).

Ethyl-2-(4-hydroxybenzylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate **(8c):**

White solid, mp 241-243^{0}C, Yield 66%; Anal. cacld for $C_{23}H_{20}N_2O_4S$ M.W.: 420 Calc. C, 65.70; H, 4.79; N, 6.66; found: C, 65.68; H, 4.82; N, 6.67; IR (υ cm^{-1}): benzene ring: 1648, 1599 and 1465 (skeletal vibration), 3245 (C-H stretching), 824 and 700 (C-H and C-C bending for mono substituted ring), 1599 (C=N stretching); aliphatic methyl group (-CH_3): 3117 and 2979 (asymm. and symm. stretching), 1420 (C-H bending); carbonyl of ester group (-C=O): 1223 and 1181 (C-O-C asymm. and symm. stretching), 1726 (C=O stretching), thiazole ring: 1701 (C=O stretching), 1368 (ring stretching), 921, 878 and 782 (-CH out of plane bending), 1313 (C-N stretching); hydroxyl group (-OH): 3510 (-OH stretching), 515 (out of plane bending of S-C-N); ^{1}H NMR (δ ppm): δ 1.8 (3H,t,CH_3 of -OCH_2CH_3), 2.3 (3H,s,CH_3 of pyrimidine ring), 4.1 (2H,q,CH_2 of -OCH_2CH_3), 5.6 (1H,d,H of -C=CH), 6.1 (1H,s,H on pyrimidine ring), 7.0-7.7 (9H,m,two aromatic rings), 9.1 (1H,s,H of -OH).

Ethyl-2-(4-chlorobenzylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate **(8d):**

Brown solid, mp 208-210^{0}C, Yield 69%; Anal. cacld for $C_{23}H_{19}ClN_2O_3S$ M.W.: 438 Calc. C, 62.94; H, 4.36; Cl, 8.08; N, 6.38; found: C, 62.91; H, 4.39; N, 8.07; IR (υ cm^{-1}): benzene ring: 1647 and 1465 (skeletal vibration), 3245 (C-H stretching), 824 and 700 (C-H and C-C bending for mono substituted ring); aliphatic methyl group (-CH_3): 3116 and 2978 (asymm. and symm. stretching), 1420 (C-H bending); carbonyl of ester group (-C=O): 1222 and 1181 (C-O-C asymm. and symm. stretching),1724 (C=O stretching), 1599 (C=N stretching); thiazole ring: 1702 (C=O stretching), 1368 (ring stretching), 920, 878 and 783 (-CH out of plane bending), 1313 (C-N stretching), 515 (out of plane bending of S-C-N); chlorine group (-Cl): 662 (-Cl stretching). ^{1}H NMR (δ ppm): δ 1.0 (3H,t,CH_3 of -OCH_2CH_3), 2.4 (3H,s,CH_3 of pyrimidine ring), 4.0 (2H,q,CH_2 of -OCH_2CH_3), 4.9 (1H,d,H of -C=CH), 5.7 (1H,s,H on pyrimidine ring), 7.0-7.5 (9H,m,two aromatic rings).

Ethyl-2-(2-nitrobenzylidene)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate ***(8e):***

Light green solid, mp 289-291^{0}C, Yield 60%; Anal. cacld for $C_{23}H_{19}N_3O_5S$ M.W.: 449 Calc. C, 61.46; H, 4.26; N, 9.35; found: C, 61.45; H, 4.23; N, 9.34; IR (υ cm^{-1}): benzene ring: 1649 and 1465 (skeletal vibration), 3245 (C-H stretching), 824 and 699 (C-H and C-C bending for mono substituted ring), 1599 (C=N stretching); aliphatic methyl group (-CH_3): 3116 and 2979 (asymm. and symm. stretching), 1421 (C-H bending); carbonyl of ester group (-C=O): 1222 and 1146 (C-O-C asymm. and symm. stretching), 1725 (C=O stretching), thiazole ring: 1700 (C=O stretching), 1368 (ring stretching), 920, 878 and 782 (-CH out of plane bending), 1313 (C-N stretching), 515 (out of plane

bending of S-C-N); ^{1}H NMR (δ ppm): δ 1.1 (3H,t,CH_3 of -OCH_2CH_3), 2.2 (3H,s,CH_3 of pyrimidine ring), 4.0 (2H,q,CH_2 of -OCH_2CH_3), 5.0 (1H,d,H of -C=CH), 5.9 (1H,s,H on pyrimidine ring), 7.2-7.5 (10H,m,two aromatic rings).

Biological Evaluation

Antifungal activity

The antifungal activity of newly synthesized compounds was determined using agar cup disc method [22,23]. Antifungal activity was carried out against *Aspergillus niger*, *Aspergillus flavus* and *Candida albicans* using sabouraud's dextrose agar medium **(Table 2)**. Imidil was used as standard drugs for antifungal activity. DMSO was used as solvent control. The compounds were tested at a 500 µg/ml concentration against fungal strains.

Procedure for *Antifungal activity:*

A test tube containing sterilized melted soft agar (2% in distilled Water, 6.0 ml) was cooled to 40°C and inoculated with 0.2 mL suspension of the test culture, mixed thoroughly and poured in the Petri dish containing sterilized sabouraud's dextrose agar medium and allowed to solidify. The cup-borer was sterilized by dipping into absolute ethanol and flaming it and then allowed to cool it down. With the help of sterilized cup-borer, four cups in the agar were made. Three cups were filled with 0.1 ml of test compound solutions of 500 ppm concentrations of three different test compounds and one was filled with 0.1 ml of DMF solvent as control. Then test sample was allowed to diffuse for 1 hour in refrigerator at 4-5°C. The plates were incubated in upright position at 37°C for 48 hrs and after two day the zone of inhibition of surrounding each cup was observed. Same experiment was performed using standard antibiotics for fungi.

After incubation, the zone of inhibition was measured with the help of a scale to the nearest millimeter. All the experiments were conducted in duplicate for each test sample. The average zone of inhibition was noted.

Table I: Antifungal activity of the synthesized compounds (8a-e)

Compounds	Zone of inhibition(mm) at 500 µg/ml concentration		
	A. niger	*C. albicans*	*A. flavus*
8a	08	09	-
8b	10	12	10
8c	12	09	10
8d	19	15	18
8e	10	08	11
Imidil	18	20	16
Control (DMSO)	00	00	00

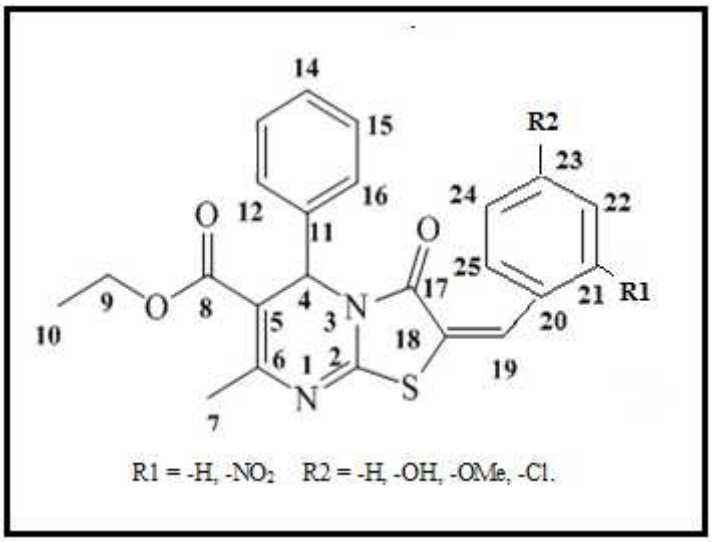
RESULTS AND DISCUSSION

Chemistry

Assignments of the products **(8a-e)** were based on elemental analysis, IR and ^{1}H NMR spectral studies.

The synthetic route followed for the preparation of substituted thiazole derivatives **(8a-e)** is outlined in **Scheme I**. For the synthesis of substituted thiazole derivatives **(8a-e)**, the optimum reaction conditions were established by changing molar ratio of solvent and acidity level. It was observed that the most suitable reaction medium was ethanol:dioxane (2:1) medium containing conc. HCl. The reaction time period was almost same (~7-8 hrs) for all the compounds. Thus the reaction of Ethyl 5,7-dimethyl-3-oxo-2,3-dihydro-5H-[1,3]-thiazolo[3,2-*a*]pyrimidine-6-carboxylate **(6)** with different aromatic aldehydes **(7a-e)** in ethanolic:dioxane medium containing few drops of conc. HCl gave substituted thiazole derivatives **(8a-e)** in the yields of 60% to 70%. The purity of compounds was checked by melting point and TLC. The structures of **(8a-e)** were established on the basis of analytical data and spectral data (FT-IR and ^{1}H NMR). Examination of analytical data of C, H and N content of final compounds are in good agreement with calculated values based on proposed structure **(Scheme I)**. Of these compounds synthesized, compound **(4)** and **(6)** have been previously reported [17,18]. The spectral and analytical data of **(4)** and **(6)** are in accordance with proposed chemical structure and literature [17,18].

The general structure of substituted thiazolo[3,2-*a*]pyrimidine **(8a-e)** is



Spectral characterization:

The spectral data of final compounds **(8a-e)** are in close agreement with that of **(6)**. However, the differences observed particularly due to aromatic aldehydes group are mentioned in the following.

8a	Benzaldehyde	1599and 1386 cm^{-1} (-C=C- aromatic ring stretching), 3116 cm^{-1} (-CH aromatic ring stretching), 758 cm^{-1} (-C=CH out of plane bending).
8b	Anisaldehyde	1594and 1380 cm^{-1} (-C=C- aromatic ring stretching), 3111 cm^{-1} (-CH aromatic ring stretching), 765 cm^{-1} (-C=CH out of plane bending), 1090, 1250 (-C-O-C- stretching of -OCH3).
8c	4-Hydroxy benzaldehyde	1599 and 1387 cm^{-1} (-C=C- aromatic ring stretching), 3117 cm^{-1} (-CH aromatic ring stretching), 759 cm^{-1} (-C=CH out of plane bending), 3510 cm^{-1} (-C-OH stretching).
8d	4-Chloro benzaldehyde	1647, 1599, 1465 cm^{-1} (-C=C- aromatic ring stretching), 3116 cm^{-1} (-CH aromatic ring stretching), 759 cm^{-1} (-C=CH out of plane bending), 662 cm^{-1} (-C-Cl stretching).
8e	2-Nitro benzaldehyde	1598and 1384 cm^{-1} (-C=C- aromatic ring stretching), 3121 cm^{-1} (-CH aromatic ring stretching), 758 cm^{-1} (-C=CH out of plane bending), 1360 (-NO2 symm. stretching), 1525 (-NO2) asymm. stretching), 855 (-CN stretching).

The ^1H NMR spectra of final compounds **(8a-e)** showed the characteristic absorption bands of parent **(6)** and corresponding aromatic aldehyde moieties present in both of the compounds. They are as follows:

8a	Benzaldehyde	5.0 (1H,d,H of C_{19}), 7.2-7.5 (10H,m,two aromatic rings).
8b	Anisaldehyde	5.4 (1H,d,H of C_{19}), 3.7 (3H,s,CH3 of -OCH3 on C_{23}), 7.2-7.5 (9H,m,two aromatic rings).
8c	4-Hydroxy benzaldehyde	5.6 (1H,d,H of C_{19}), 7.0-7.7 (9H,m,two aromatic rings), 9.1 (1H,s,H of -OH on C_{23}).
8d	4-Chloro benzaldehyde	5.2 (1H,d,H of C_{19}), 7.2-7.5 (9H,m,two aromatic rings).
8e	2-Nitro benzaldehyde	5.4 (1H,d,H of C_{19}), 7.2-7.5 (9H,m,two aromatic rings).

Evidences for the formation substituted thiazolo[3,2-a]pyrimidines:

The IR spectra of **8c**, **8d** and **8e** showed the appearance of characteristic absorption band at 3510 cm^{-1} of -OH stretching of 4-hydroxybenzaldehyde, at 662 cm^{-1} of -C-Cl stretching of 4-chlorobenzaldehyde and 1360 cm^{-1} of -NO2 symm. stretching respectively which support the formation of substituted thiazole ring. Comparison of ^1H NMR spectra of the final compounds with its parent **(6)** have shown the absence of singlet at δ 3.9 ppm (2H, $-CH_2$ of thiazole ring) suggested that the 2H of carbon atom (C_{18}) of thiazolo[3,2-*a*]pyrimidine reacted with different aromatic aldehyde to yield the corresponding substituted thiazolo[3,2-a]pyrimidines. Besides this, the presence of doublet in the region δ 5.0 to 5.6 ppm due to 1H of C_{19} of **8a-e** confirm the formation of substituted thiazolo[3,2-a]pyrimidines. It is further supported by the appearance of additional aromatic protons in the region (i.e. 6.0-8.0 δ ppm) for the aromatic ring of corresponding aromatic aldehydes in all the final compounds **8a-e**.

Antifungal activity

Newly synthesized substituted thiazolo[3,2-*a*]pyrimidines derivatives **(8a-e)** were tested for the antifungal activity against three fungal microorganisms namely *Aspergillus Niger*, *Candida albicans* and *Aspergillus flavus* using

solution of 500 ppm of the test compounds. The antifungal data revealed that all the synthesized compounds were having promising antifungal activity against all the fungal species. Out of all the synthesize compounds, **(8d)** which have -Cl group as a substituent on the phenyl ring shows the excellent antifungal activity against *A. niger* and *A. flavus* as compared to the standard drug. The compounds which having -NO_2 **(8e)** substituent on phenyl ring were promising antifungal activity against *Aspergillus Niger* and *Aspergillus flavus* while compounds bearing methoxy **(8b)** and hydroxy **(8c)** substituent were displayed moderate activity against all the microorganisms.

CONCLUSION

This study reports the synthesis, characterization and antimicrobial activity of new series of pyrimidine derivatives containing thiazole moiety. All the compounds were tested for antifungal activity against *Aspergillus niger, Candida albicane* and *Aspergillus flavus* using imidil as standard drug. The screening results revealed that most of the compounds were found to exhibit significant antifungal activity. It should be noticed that some compounds tested exhibited better activity than commercial antifungal agents used as reference drugs and thus could be promising novel drug candidates.

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