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ARTICLE

Synthesis and in vitro antimicrobial studies of thiodihydropyrimidine derivatives

Mani Pasupathi[1] | **Namasivayam Santhi**[1] | **Kasi Venkatesan**[2]

[1]PG & Research, Department of Chemistry, Government Arts College, C. Mutlur, Chidambaram, Tamil Nadu, India

[2]Department of Humanities and Sciences, CVR College of Engineering, Vastunagar, Telangana, India

Correspondence
Kasi Venkatesn, Department of Humanities and Sciences, CVR College of Engineering, Vastunagar, Telangana, India.
Email: venkippk@gmail.com

Namasivayam Santhi, PG & Research, Department of Chemistry, Government Arts College, C. Mutlur, Chidambaram, Tamil Nadu, India.
Email: nsanthi@gmail.com

Abstract

In the present study, a series of thiodihydropyrimidine derivatives were synthesized from different substituted aromatic aldehydes, ethyl acetoacetate, and urea/thiourea using a bimetallic TUD-1 catalyst. The structures of all the synthesized compounds were characterized by melting point determination, thin layer chromatography (TLC), infrared (IR), ^{1}HNMR, and ^{13}C-NMR values. All the synthesized compounds were screened for their antimicrobial activities against two gram positive bacteria, two-gram negative bacteria, and two fungal strains.

KEYWORDS

antibacterial, antifungal, thiodihydropyrimidine

1 | INTRODUCTION

The survival of pathogens against the accessible medications is quickly turning into a noteworthy issue in the field of medicinal chemistry. Presently, most of the infections, organisms, and microbes display the multiple drug resistant, and this phenomenon is progressively dominant among human, creature, and plant pathogens. Diseases caused by bacterial biofilms cause high health costs and in addition economic loss in farming. Death from intense respiratory problems, diarrheal illnesses, measles, AIDS, malaria, and tuberculosis, causes excess of the mortality due to the infections by pathogens around the world. The resistance toward the firstline drugs of majority of the pathogens causing these infections is very drastically increased from zero to almost 100%. Henceforth, the need to plan new drugs to manage this obstruction has turned out to be a standout among the most critical zones of research today. Pyrimidine and their derivatives assumed to have the dynamic role in the field of drug discovery and agriculture. Pyrimidine could be a fundamental core in DNA and RNA; it is related with different organic activities.[1] Pyrimidine derivatives are found to exhibit exceedingly potent biological activity. Pyrimidine derivatives have been found to show cytostatic,[2–4] immunomodulating,[5,6] and antibacterial properties.[7–13] Pyrimidines and related fused heterocycles are vital classes of heterocyclic compounds that display a wide range of biological activities, for example, anticancerous,[14–16] antiviral,[17,18] antibacterial,[19] antioxidant,[20] and anti-inflammatory.[21] The partly hydrogenated pyrimidine derivatives, for example, dihydropyrimidones and thiodihydropyrimidones, have been utilized as key substrates to create compounds as new drugs or powerful lead compounds in the field of medicinal chemistry.[22]

The synthesis of substituted Pyrimidine and many more review have been reported.[23,24] "Pyrimidine" and their derivatives are predominant in inorganic synthetic chemistry. Pyrimidine does not exist in nature anyway with as its various derivatives, they are broadly distributed. Pyrimidine compounds are of high attraction because of their pharmacological properties such as anticancer,[25] analgesic,[26]

antagonist,[27,28] antifolate,[29] antimicrobial,[30] anti-HIV,[31] antiproliferative,[32] antiplatelet,[33] antithrombotic,[34] antifilarial[35] activities, and so on. Motivated by these perceptions, we synthesized a series of pyrimidine derivatives by fusing the diketoester, aldehyde, and urea/thiourea with the expectation of getting better antimicrobial action. All these synthesized compounds have been screened for their antimicrobial activities.

2 | EXPERIMENTAL

All the chemicals were purchased from Sigma Aldrich. M.p.s is uncorrected and was determined by open capillary method. IR spectra recorded on KBr, cm^{-1} was recorded on an FT IR/5300 spectrometer. ^1H NMR spectra (ppm) were taken on Bruker AVIII (500 MHz) spectrometer and ^{13}C NMR spectra were taken in the 200 MHz range.

2.1 | General procedure

In typical reaction condition, the solution of benzaldehyde (2 mmol), ethyl acetoacetic ester (2 mmol), and urea/thiourea (3 mmol) were transferred into 50 ml round base flask, which contains pre-dried AlTiTUD-1 (100 mg) catalyst and acetonitrile (5 ml) as solvent. The solution was mixed well and warmed at 80°C under reflux condition for 6 hr. The progress of the reaction was checked by thin layer chromatography (TLC). After completion of the reaction, the mixture was poured into crushed ice with constant stirring. The crude compound obtained was filtered and washed with 95% hot ethanol. At last, the catalyst was separated and the obtained product was recrystallized with hot ethanol to give pure dihydropyrimidines (DHPMs). Spectral data of products are given in the following.

2.1.1 | Ethyl-1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylate (4a)

IR (KBr, cm^{-1}): 3,321 and 3,167 (N–H str.), 1,662 (C=O str.), 1,456 (C–N str.), 1,324 (C–N–C str, sym.), 2,918 (C–H aliphatic), and 3,099 (C–H phenyl ring); ^1H NMR (500 MHz, DMSO-d_6) δ: 1.093–1.119 (t, 3H, J = 6.5 Hz, OCH_2CH_3), 2.307 (s, 3H, CH_3), 3.985–4.030 (q, 2H, J = 7.5 Hz, CH_2), 5.191 (s, 1H, CH), 7.234–7.365 (m, 5H, Ar-H), and 9.668 and 10.347 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.2, 17.6, 54.5, 60.1, 101.2, 126.9, 128.1, 129.0, 155.0, 165.6, and 174.7 ppm.

2.1.2 | Ethyl-1,2,3,4-tetrahydro-6-methyl-4-(3-trifluorophenyl)-2-thioxopyrimidine-5-carboxylate (4b)

IR (KBr, cm^{-1}): 3,296 and 3,180 (N–H str.), 1,653 (C=O str.), 1,448 (C–N str.), 1,373 (C–N–C str, sym.), 2,982 (C–H aliphatic), and 3,102 (C–H phenyl ring); 1H NMR (500 MHz, DMSO-d_6) δ: 1.064–1.092 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 2.307 (s, 3H, CH_3), 4.023–4.044 (q, 2H, J = 3.5 Hz, CH_2), 5.283–5.289 (d, 1H, J = 3.0 Hz, CH), 7.60–7.666 (m, 4H, Ar-H), and 9.721 and 10.458 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.3, 17.6, 54.2, 60.1, 100.5, 123.6, 124.9, 145.3, 146.2, 165.4, and 174.9 ppm.

2.1.3 | Ethyl-1,2,3,4-tetrahydro-6-methyl-4-(2,4-dimethoxyphenyl)-2-thioxopyrimidine-5-carboxylate (4c)

IR (KBr, cm^{-1}): 3,301 and 3,172 (N–H str.), 1,701 (C=O str.), 1,446 (C–N str.), 1,384 (C–N–C str, sym.), 2,934 (C–H aliphatic), and 3,098 (C–H phenyl ring); ^1H NMR (500 MHz, DMSO-d_6) δ: 1.042–1.070 (t, 3H, J = 7 Hz, OCH_2CH_3), 2.282 (s, 3H, CH_3), 3.733 (s, 3H, OCH_3), 3.774 (s, 3H, OCH_3), 3.929–3.952 (q, 2H, J = 3.8 Hz, CH_2), 5.409–5.414 (d, 1H, J = 2.5 Hz, CH), 6.452–6.540 (m, 3H, Ar-H), and 9.180 and 10.181 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.4, 17.5, 49.5, 55.7, 56.0, 98.0, 100.1, 105.0, 158.1, 160.7, 165.7, and 174.4 ppm.

2.1.4 | Ethyl-1,2,3,4-tetrahydro-6-methyl-4-(2,4-dichlorophenyl)-2-thioxopyrimidine-5-carboxylate (4d)

IR (KBr, cm^{-1}): 3,400 and 3,177 (N–H str.), 1,707 (C=O str.), 1,461 (C–N str.), 1,380 (C–N–C str, sym.), 2,977 (C–H aliphatic), and 3,095 (C–H phenyl ring); 1H NMR (500 MHz, DMSO-d_6) δ: 1.000–1.029 (t, 3H, J = 7.25 Hz, OCH_2CH_3), 2.290 (s, 3H, CH_3), 3.897–3.939 (q, 2H, J = 7.0 Hz, CH_2), 5.600–5.606 (d, 1H, J = 3.0 Hz, CH), 7.533–7.630 (m, 3H, Ar-H), and 9.628 and 10.407 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.3, 17.5, 51.2, 60.0, 99.8, 128.5, 133.6, 140.29, 146.3, 165.1, and 175.3 ppm.

2.1.5 | Ethyl-1,2,3,4-tetrahydro-6-methyl-4-(2,6-dichlorophenyl)-2-thioxopyrimidine-5-carboxylate (4e)

IR (KBr, cm^{-1}): 3,282 and 3,179 (N–H str.), 1,691 (C=O str.), 1,466 (C–N str.), 1,371 (C–N–C str, sym.), 2,924 (C–H aliphatic), and 2,980 (C–H phenyl ring); ^1H NMR

(500 MHz, DMSO-d_6) δ: 0.889–0.917 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 2.172 (s, 3H, CH_3), 3.818–3.864 (q, 2H, J = 7.6 Hz, CH_2), 6.145 (s, 1H, CH), 7.291–7.609 (m, 3H, Ar-H), and 9.440 and 10.272 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.1, 17.6, 52.6, 59.6, 96.7, 128.5, 130.3, 146.5, 165.2, 174.2, and 184.3 ppm.

2.1.6 | Ethyl-1,2,3,4-tetrahydro-6-methyl-4-(2,3-dimethoxyphenyl)-2-thioxopyrimidine-5-carboxylate (4f)

IR (KBr, cm^{-1}): 3,339 and 3,212 (N–H str.), 1,703 (C=O str.), 1,459 (C–N str.), 1,385 (C–N–C str, sym.), 2,976 (C–H aliphatic), and 3,106 (C–H phenyl ring); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.064 (t, 3H, J = 7 Hz, OCH_2CH_3), 2.289 (s, 3H, CH_3), 3.774 (s, 3H, OCH_3), 3.808 (s, 3H. OCH_3), 3.915–3.950 (q, 2H, J = 6 Hz, CH_2), 5.455–5.461 (d, 1H, J = 2.5 Hz, CH), 6.690–7.017 (m, 3H, Ar-H), and 9.307 and 10.236 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.4, 17.6, 50.4, 56.2, 56.5, 59.9, 100.4, 113.0, 146.7, 152.9, 165.6, and 174.4 ppm.

2.1.7 | Ethyl4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (4g)

IR (KBr, cm^{-1}): 3,382 and 3,220 (N–H str.), 1,701 (C=O str.), 1,453 (C–N str.), 1,397 (C–N–C str, sym.), 2,973 (C–H aliphatic), and 3,088 (C–H phenyl ring); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.237–1.265 (t, 3H, J = 7 Hz, OCH_2CH_3), 2.322 (s, 3H, CH_3), 4.316–4.346 (q, 2H, J = 4 Hz, CH_2), 5.370 (s, 1H, CH), 6.180–7.017 (m, 2H, Ar-H), 6.080–6.097 (m, 2H, Ar-H), and 7.307 and 8.541 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.1, 18.5, 55.0, 60.1, 101.3, 115.4, 128.2, 128.4, 139.7, 146.4, 153.6, 163.3, and 165.5 ppm.

2.1.8 | Ethyl4-(2,4-dihydroxyphenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (4h)

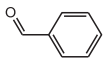
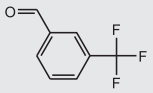
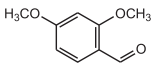
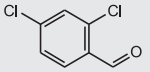
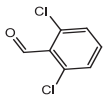
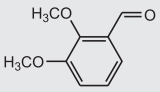
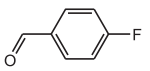
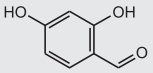
IR (KBr, cm^{-1}): 3,381 and 3,222 (N–H str.), 1,700 (C=O str. of ester), 1,650 (C=O str. of pyrimidine ring), 1,453 (C–N str.), 1,397 (C–N–C str, sym.), 2,975 (C–H aliphatic), and 3,091 (C–H phenyl ring); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.266–1.302 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.366 (s, 3H, CH_3), 4.316–4.346 (q, 2H, J = 4 Hz, CH_2), 5.234 (s, 1H, OH), 5.437 (s, 1H. OH), 5.710 (s, 1H, CH), 6.909–7.105 (m, 3H, Ar-H), and 7.658 and 7.698 (s, 1H, NH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ: 14.3, 17.6, 50.4, 60.0, 99.2, 106.2, 108.4, 117.5, 146.7, 152.9, 155.5, 162.6, and 164.1 ppm.

3 | ANTIMICROBIAL ACTIVITY

3.1 | Test microorganisms

Totally four bacterial strains and two fungal strains were used for antimicrobial studies. All the bacterial and fungal cultures were obtained from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, and Chandigarh, India. The bacterial strains such as *Escherichia coli* (MTCC 1302), *Bacillus subtillis* (MTCC 1305), *Enterococcus*

TABLE 1 Different groups substituted benzaldehyde with its product and percentage yields

Compound	Various benzaldehydes	Yield (%)	Melting point (°C)
4a		80	183–185
4b		70	201–203
4c		72	186–188
4d		69	210–212
4e		75	223–225
4f		71	181–183
4g		72	177–179
4h		68	204–206

faecalis (MTCC 439), and *Serratia marcescens* (MTCC 2645) were used for antibacterial activity. The fungal strains used were *Aspergillus terreus* (MTCC 1782) and *Candida albicans* (MTCC 183). The young bacterial broth cultures were prepared before the screening procedure.

3.2 | Antimicrobial assay

3.2.1 | Preparation of inoculums

Stock cultures were maintained at 4°C on slopes of nutrient agar. Active cultures of experiment were prepared by transferring a loopful of cells from the stock cultures to test tube of Muller–Hinton broth (MHB) for bacteria that were incubated without agitation for 24 hr at 37°C. The cultures were diluted with fresh MHB to achieve optical densities corresponding to 2.0×10^6 colony forming units (CFU/ml) for bacteria.

3.3 | Antibacterial assay

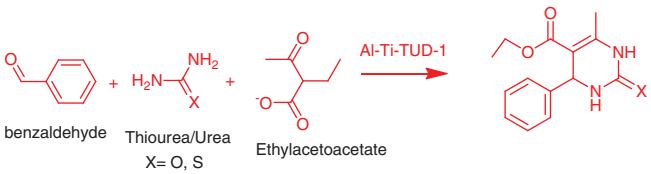
The well diffusion method was used to screen the antimicrobial activity. in vitro antimicrobial activity was screened by using Muller–Hinton Agar (MHA) obtained from Himedia (Mumbai). The MHA plates were prepared by pouring 15 ml of molten media into sterile petriplates. The plates were allowed to solidify for 5 min and 0.1% inoculums suspension was swabbed uniformly and the inoculums were allowed to dry for 5 min. Wells were cut and different concentrations of test drug were added. The plates were then incubated at 37°C for 24 hr. The antibacterial activity was assayed by measuring the diameter of the inhibition zone formed around the well (NCCLS, 1993). Chloramphenicol disc was used as a positive control.

3.4 | Antifungal assay

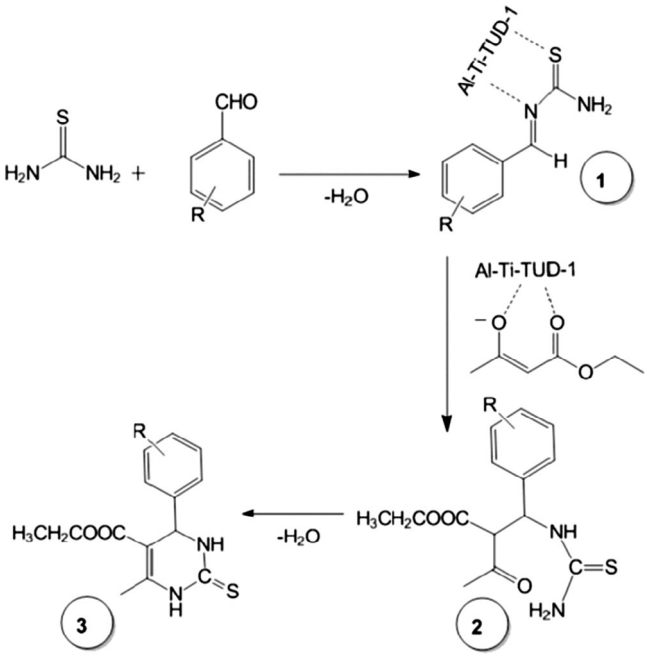
Totally two fungal strains were used throughout investigation. All the fungal cultures were obtained from MTCC, Institute of Microbial Technology, Chandigarh, India.

3.5 | Antifungal activity

Antifungal activity was measured using methods of well diffusion plates on agar. In order to test the antifungal activity, the fractions of different concentrations of the synthesized compounds were dissolved in 70% ethanol. Twenty milliliters of Sabouraud Dextrose Agar was poured into each 15 cm Petri dish. *C. albicans* and *A. terreus* were grown in Sabouraud Dextrose Broth at 27°C for 48 hr. Growth was adjusted to OD (600 nm) of 0.1 by dilution with Sabouraud Dextrose Broth. Then, Wells were cut and different concentrations of test drug were placed on agar to load 50 and 100 µL of each sample (1 mg/mL). Hundred units of Fluconazole, obtained from a local pharmacy, were used as a positive control. Zone of inhibition was measured after incubation at 27°C for 48 hr.



SCHEME 1 Preparation of thio/oxodihydropyrimidine



SCHEME 2 Mechanism of AlTiTUD-1-catalyzed Biginelli reaction

4 | RESULTS AND DISCUSSION

The mesoporous AlTiTUD-1 catalyst is used for the Biginelli reactions of aromatic aldehydes with acetoacetate ester and urea/thiourea (Scheme 1). The reaction conditions, for example, catalytic quantity, time, and solubility were streamlined by screening. The reaction was conducted in 80°C refluxing conditions and acetonitrile as solvent. The various groups substituted benzaldehydes with

its product percentage yields are recorded in Table 1. Previously, the progress of the reaction is checked with the assistance of TLC. As the reaction continues, white to yellow precipitate appears, because of the formation of DHPMs. After the reaction is finished, catalyst is isolated by filtration and recrystallization and the filtrate contained the pure DHPM compounds. The separated and purified catalyst was reused for the further reaction cycle. Amazingly, 65–86% of product yields are gotten by utilizing the acidic catalyst for various substituted aldehydes. While without catalyst, there is no transformation of reactant is observed. This perception simply shows the significance of catalyst for the progress of the reaction.

The mostly acknowledged mechanism of Biginelli reaction was proposed by numerous researchers.[36–38] By following the mechanism reported by Kumar et al., AlTiTUD-1-catalyzed reaction mechanism is proposed in Scheme 2.[38] It incorporates the Bronsted acid site-catalyzed development of an iminium intermediate (1), from the parent aldehyde and thiourea, and on the assistance of its nucleophilic attack by coordinated acetoacetic ester to yield the dihydropyrimidinones (3). Another plausible mechanism involves the AlTiTUD-1 acidic-catalyzed development of acyl imine intermediate formed by reaction of the aldehyde with thiourea. Furthermore, the interference of iminium intermediate by diketoester enolate produces an open chain uride, which, in this manner, cyclizes to dihydropyrimidinones. Remarkably, for the condensation steps, B/L acidic sites are required in the reaction. The B/L acidic site-established homogeneous and heterogeneous catalysts have been used for the Biginelli reaction.

In the AlTiTUD-1 catalyst, the presence of Bronsted and Lewis sites is in charge of the formation of the product. The interaction between B and L acidic sites in the AlTiTUD-1 is hard to discover for the Biginelli reaction. In the AlZrTUD-1 catalyst, B and L acidity impacts are clearly discussed on the Prins cyclisation and meerwein–ponndorf–verley reduction individually.[37] However, the impacts of nature of acidity (B/L), strength of acidity, and multicomponent reaction mechanism are still under examination.

The various Bronstead and Lewis acid active sites of the AlTiTUD-1 catalyst[39] are given in Figure 1

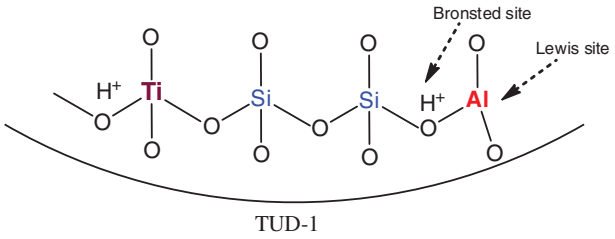


FIGURE 1 : Possible acid sites and incorporations developed in the AlTiTUD-1 catalyst

4.1 | Screening of antibacterial activity

The synthesized different substituted DHPM derivatives **4a–h** were screened for in vitro antibacterial activity using the standard procedure given in the Section 2. The synthesized compound **4b** exhibited highest activity against *E. coli*, *B. subtillis*, and *S. marcescens* and moderate activity against *E. faecalis*, while compounds **4e** and **4g** exhibited maximum activity against *E. faecalis* and moderate activity against other bacterial strains. The compounds **4f** and **4h** exhibited maximum activity against *E. coli* and moderate activity against other organisms. Compound **4c** exhibited highest activity against

TABLE 2 Antibacterial activities of the synthesized compounds **4a–h**

	Zone of inhibition (mm)							
	B. subtilis		*Enterococcus faecalis*		*Escherichia coli*		*Serratia marcescens*	
Compound	**50 µg/ml**	**100 µg/ml**	**50 µg/ml**	**100 µg/ml**	**50 µg/ml**	**100 µg/ml**	**50 µg/ml**	**100 µg/ml**
4a	12	16	11	15	11	17	12	16
4b	13	18	10	16	14	19	13	18
4c	13	18	12	17	14	17	13	19
4d	12	19	11	16	13	15	12	17
4e	11	16	13	19	14	17	12	16
4f	10	14	12	16	14	18	11	15
4g	12	16	14	19	11	15	13	17
4h	10	17	12	18	13	18	11	16
Chloramphenicol	26		27		25		27	

TABLE 3 Antifungal activities of the synthesized compounds **4a–h**

	Zone of inhibition (mm)			
	Aspergillus terreus		*Candida albicans*	
Compound	**50 μg/ml**	**100 μg/ml**	**50 μg/ml**	**100 μg/ml**
4a	12	16	13	18
4b	10	14	12	17
4c	11	16	10	14
4d	10	15	09	13
4e	08	14	10	15
4f	09	12	11	14
4g	08	12	10	16
4h	09	14	08	14
Fluconazole	22		25	

S. marcescens and the compound **4g** exhibited highest activity against *E. faecalis*. The antibacterial activity data of the synthesized compounds were given in Table 2.

4.2 | Screening of antifungal activity

All the synthesized DHPM derivatives **4a–h** were screened for in vitro antifungal activity using the standard procedure given in Section 2.

Compound **4a** exhibited maximum antifungal activity against *A. terreus* and *C. albicans* and compound **4c** exhibited highest activity against *A. terreus* and moderate activity against *C. albicans*, while compounds **4e**, **4f**, and **4g** exhibited least activity against *A. terreus* and medium activity against *C. albicans*. The compound **4d** exhibited least activity against *C. albicans* and moderate activity against *A. terreus*. The antifungal activity data of the synthesized compounds were displayed in Table 3.

5 | CONCLUSIONS

A simple and efficient method for the preparation of thiodihydropyrimidine derivatives via one-pot synthesis of various aldehydes, thiourea, and ethyl acetoacetate using mesoporous AlTiTUD-1 catalyst has been presented. The synthesized compounds **4a–h** were screened for their in vitro antimicrobial activity. The compound **4b** exhibited highest antibacterial activity against *E. coli, B. subtillis*, and *S. marcescens* and moderate activity against *E. faecalis*. Compound **4a** exhibited highest antifungal activity against *A. terreus* and *C. albicans* and compound **4c** exhibited moderate activity against *C. albicans* in comparison with standard drug.

ORCID

Kasi Venkatesan https://orcid.org/0000-0001-8010-0009

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