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Synthesis and antimicrobial activities of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine

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- ✓ amines,
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- ✓ anti-microbial activity.

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Abstract

The study presented a two-step sequence of 4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-thione and subsequently *S*-alkylated with amines. The purity of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydopyrimidine were tested by thin-layer chromatography (TLC) and characterized by Fourier transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (NMR), ^{13}C nuclear magnetic resonance (^{13}C-NMR), and DEPT 135 to confirm the presence and nature of CH_2. All the synthesized compounds (**1-3**) were screened against *Pseudomonas aeruginosa, Escherichia coli, Bacillus subtilis, methicillin-susceptible Staphylococcus aureus, methicillin-resistant Staphylococcus aureus,* and *Candida albicans* using the standard microbiological method. Compound **3** exhibited moderate activities when compared with the standard drug ciprofloxacin and itraconazole.

1. Introduction

Pyrimidine is an aromatic six-membered organic compound with four carbon and two nitrogen atoms at positions one and three. It is the most imperative member of the three diazines known as an *m*-diazine or 1,3-diazine.

Pyrimidine moiety is abundant in nature, present in various natural drugs, and synthetic pharmaceutical agents with unique anti-cancer [1-2], anticonvulsant [3], adenosine receptor (AR) antagonist [4], anti-platelet aggregations [5], anti-tubercular [6-7], insecticidal [8], anti-microbial [9-14], congestive heart failure [15].

2-Thiopyrimidine (2-TP) or 2-mercaptopyrimidine is a significant class of pyrimidine, exists in tautomeric equilibria with thione forms. Several thiopyrimidines are developed as drugs and found widespread in clinical applications and agrochemicals like 2-alkylthiopyrimidines. Pyrimidinethione has three possible structures, resulting from the position of the thione group (Figure 1).

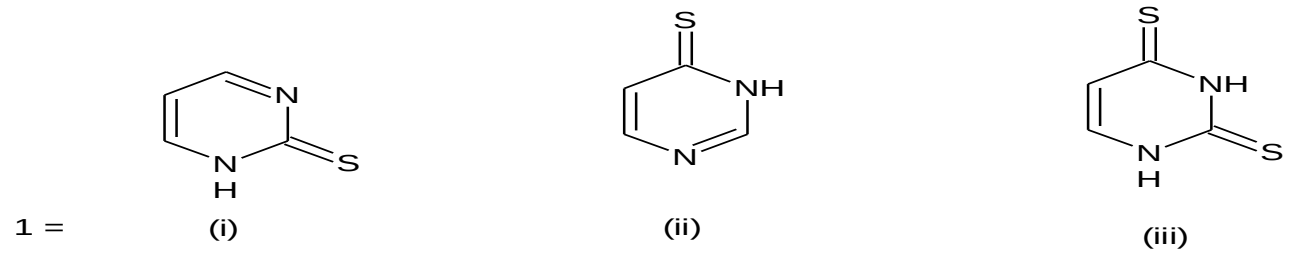


Figure 1: Compound: 2-Pyrimidinethione (i), 4-Pyrimidinethione (ii), 2,4-Pyrimidinethione (iii)

Research has shown that heterocyclic compounds are versatile as pharmaceuticals and industrial compounds with marked biological activities and industrial values. Hence the need to search for new compounds to solve the challenges in pharmaceutical, agrochemical and other industries. Therefore, the study aims at the synthesis of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine and screened for microbial activities.

2. Material and Methods

2.1. Materials

Acetophenone, benzaldehyde, 1-(2-chloroethyl)pyrrolidine hydrochloride, 1-(2-chloroethyl) dimethylamine hydrochloride, 1-(2-chloroethyl)piperidine hydrochloride, potassium carbonate, potassium hydroxide, sodium hydroxide, acetone, hydrochloric acid, thiourea, and ethanol were purchased from Hopkin and William Ltd, Chadwell Heath, Essex England, UK, BDH Chemicals Ltd, Poole, England UK, Sigma Aldrich and from JHD and were of Analar grade.

2.2. Characterization

Melting points (MP) were measured uncorrected using R000103248 Stuart SMP-10 (Barloworld Scientific Limited apparatus). Fourier-transform infrared spectra (ATR, FT-IR) were recorded using CARY 630 product (Agilent Technologies, USA). ^{1}H, ^{13}C NMR and DEPT 135 (confirm the nature of CH_2) spectra were recorded by Bruker 500 spectrometer with $CDCl_3$ as a solvent. Column chromatography was carried with flash silica gel 40-63 µm (230-400 mesh) with respective eluents to give desired products. Thin-layer chromatography was performed on 0.25 mm Kieselgel 60, Merck DC pre-coated aluminum plates, and viewed with 254 nm UV lamp.

2.3. Methodology

2.3.1. Synthesis of Chalcone

A mixture of NaOH (5.5 g, 0.14 mol) in 50 mL water and 25 g of ethanol was added to a 250-mL conical flask and stirred for 15 min in an ice-water bath. An equimolar of freshly distilled acetophenone (13.0 g, 0.11 mol), then benzaldehyde (11.5 g, 0.11 mol) was added at once, stirred at 25-28 ^{o}C until the thick mixture was formed, and kept in the refrigerator overnight. The chalcone was filtered, washed with cold water until neutral to litmus, washed with ethanol, dried, and later recrystallized from ethanol to give pale yellow crystals 15.2 g, 67.49% and MP 56 ^{o}C (Scheme 1) [16].

2.3.2. Synthesis of 4,6-diphenylpyrimidin-2-thiol

Equimolar of 0.01 mol of chalcone (2.08 g) and thiourea (0.76 g) were dissolved in 1.00 g potassium hydroxide in 20-mL ethanol in a 250-mL flask, stirred (300 rpm), heated at reflux for 6 h, and concentrated to remove excess solvent. The cooled mixture was poured into cold water and stirred. The yellow solid residue obtained was filtered, triturated with ice-water, dried, and recrystallized from ethanol to give yellowish crystals MP, 182-184 ^{o}C (1.88g, 70.7%) [17].

2.3.3. Synthesis of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine

4,6-Diphenylpyrimidin-2-thiol (2.66 g, 0.010 mol), an appropriate amine (0.015 mol), and K_2CO_3 (3.45 g, 0.025 mol) were mixed in acetone (30 ml) in a 250-mL flat-bottom flask and heated at ~70 ^{o}C for 8-10 h. The mixture was concentrated to remove excess solvent. The cool mixture was poured into ice-water, acidified with 1 M HCl, the viscous oil was collected, and run through flash column chromatography to achieve a spot on TLC, the R_f, and yield presented (Table 1).

Table 1: Physical data of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine

Compound	Molecular formula	Appearance	Yield	R_f
1	$C_{23}H_{27}N_3S$	Viscous reddish brown oil	71.07	0.75 (7Ethyl: 3Pet ether)
2	$C_{22}H_{25}N_3S$	Viscous pale brown oil	69.57	0.50 (8Ethyl: 2Pet ether)
3	$C_{20}H_{23}N_3S$	Viscous yellowish oil	63.03	0.62 (9Ethyl: 1Hex)

4,6-diphenyl-2-{[2-(piperidin-1-yl)ethyl]thiol}-1,6-dihydropyrimidine (1)

Yield 71.07%. FT-IR (neat, *v*max, cm^{-1}): 3329 (NH wk); 3060, 3027 (=C−H str, aromatic); 2933, 2855, 2799 (CH_2, piperidine); 2371, 1241 (C-S); 1678 (C=N str, pyrimidine); 1566, 1446 (C=C str, aromatic); 1178 (C-N str, pyrimidine). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 1.47 - 1.49 (m, 1H), 1.66 - 1.68 (m, 3H), 2.60 (brd, NH), 2.86 - 2.88 (m, 4H, 2 × CH_2), 3.08 - 3.10 (t, *J* = 5 Hz, CH_2), 3.29 - 3.32 (t, *J* = 7.5 Hz, CH_2), 3.34 - 3.36 (d, *J* = 5 Hz, 5-CH), 3.48 - 3.52 (t, *J* = 10 Hz, CH_2), 5.50 - 5.54 (d, *J* = 10 Hz, 6-CH), 7.28 - 7.32 (m, 2H) 7.43 - 7.47 (m, 2H), 7.51 - 7.54, (m, 3H), 7.95 - 7.98 (m, H), 8.05 - 8.06 (d, *J* = 5 Hz, H), 8.16 - 8.18 (m, H). ^{13}C NMR ($CDCl_3$, ppm): 24.18, 27.74, 44.92, 54.42, 58.51, 60.41 (C-6), 108.07 (C-5), 126.15, 127.28 (2C), 128.04, 128.14, 128.44, 128.54, 128.62, 128.88 (2C), 131.01, 133.08, 144.86 (C-4), 171.15 (C-2).

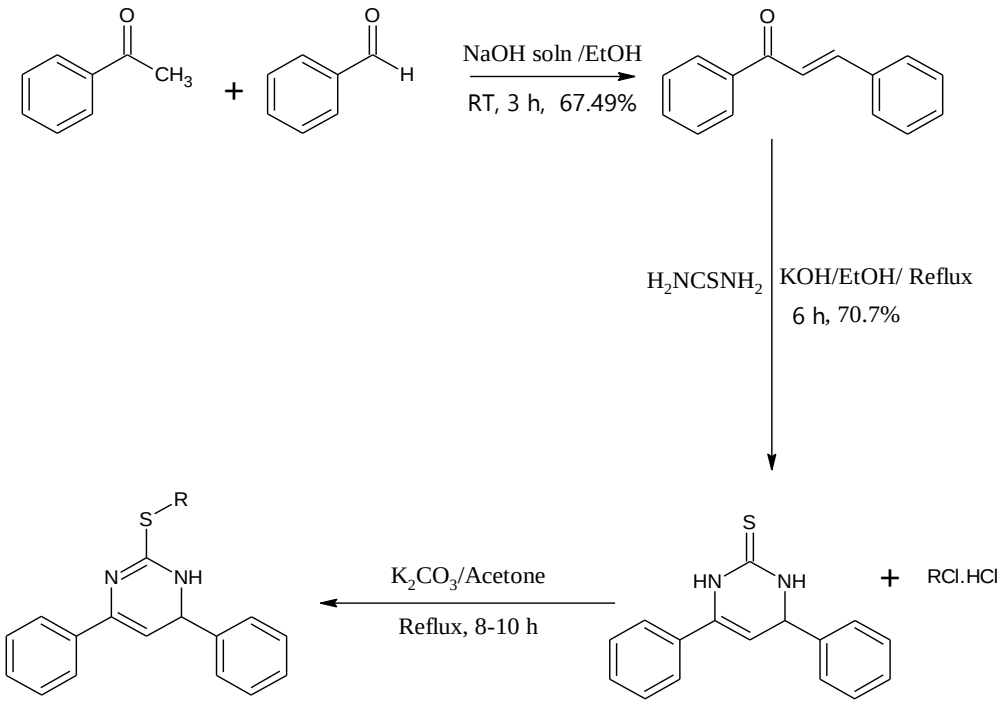
4,6-diphenyl-2-((2-pyrrolidin-1yl)ethylthio-1,6-dihydropyrimidine (2)

Yield 69.57%. FT-IR (neat, *v*max, cm^{-1}): 3313 (NH wk); 3060, 3027 (=C−H str, aromatic); 2922, 2855 (CH_2, pyrrolidine); 2371, 1228 (C-S); 1682 (C=N str, pyrimidine); 1566, 1446 (C=C str, aromatic). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 1.57 - 1.59 (t, 4H, *J* = 5 Hz, 2 × CH_2), 2.61 (s, NH), 3.09 - 3.12 (t, 4H, *J* = 7.5 Hz, 2 × CH_2), 3.30 - 3.33 (t, *J* = 7.5 Hz, CH_2), 3.36 - 3.38 (t, *J* = 5 Hz, CH_2), 3.48 - 3.50 (d, *J* = 5 Hz, 5-CH), 5.19 - 5.23 (d, *J* = 10 Hz, 6-CH), 7.30 - 7.35 (m, 2H) 7.43 - 7.47 (m, 2H), 7.49 - 7.56

(m, 2H), 7.97 - 8.01 (d, *J* = 5 Hz, H), 8.06 - 8.07 (d, *J* = 5 Hz, H), 8.13 - 8.15 (m, H), 8.18 - 8.22 (m, H). ^{13}C NMR ($CDCl_3$, ppm): 26.58, 44.95, 53.42, 57.03, 63.48 (C-6), 108.02 (C-5), 126.20, 127.37, 128.09 (2C), 128.20, 128.50, 128.59, 128.68 (2C), 129.00, 129.14, 133.14, 144.92 (C-4), 175.20 (C-2).

2-[(4,6-diphenyl-1,6-dihydropyrimidin-2-yl)thiol]-*N*,*N*-dimethylethanamine (3)

Yield 63.03%. FT-IR (neat, *v*max, cm^{-1}): 3324 (NH wk); 3060, 3027 (=C−H str, aromatic); 2933, 2851 (CH_2); 2371, 1238 (C-S); 1681 (C=N str, pyrimidine); 1566, 1446 (C=C str, aromatic); 1178 (C-N str, pyrimidine). ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 2.61 (brd, NH), 2.80 - 2.82 (s, 6H, 2 × CH_3), 3.30 - 3.33 (t, *J* = 10 Hz, CH_2), 3.40 - 3.42 (t, *J* = 5 Hz, CH_2), 3.50 - 3.52 (d, *J* = 5 Hz, 5-CH), 5.26 - 5.30 (d, *J* = 5 Hz, 6-CH), 7.28 - 7.30 (m, 2H) 7.43 - 7.47 (m, 2H), 7.50 - 7.53, (m, 3H), 7.96 - 7.99 (m, H), 8.05 - 8.07 (d, *J* = 5 Hz, H), 8.14 - 8.15 (m, H). ^{13}C NMR ($CDCl_3$, ppm): ^{13}C NMR ($CDCl_3$, ppm): 39.68, 44.90, 57.76, 63.17 (C-6), 108.16 (C-5), 126.55, 127.30, 127.72 (2C), 128.02, 128.16, 128.18, 128.59 (2C), 128.86, 129.16, 133.00, 142.31 (C-4), 175.03 (C-2).



Compound	R	Yield
1	$(CH_2)_2N(CH_2)_5$	71.07%
2	$(CH_2)_2N(CH_2)_4$	69.57%
3	$(CH_2)_2N(CH_3)_2$	63.03%

Scheme 1: Synthesis of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine

2.4. Antimicrobial Activity

P. aeruginosa, E. coli, K. pneumoniae, B. subtilis, and *C. albicans* investigated in this study were procured from the University of Benin Teaching Hospital while methicillin-susceptible *S. aureus,*

methicillin-resistant *S. aureus,* and *B. subtilis* NCTC 8236 gotten from Pharmaceutical Microbiology, University of Benin. All bacterial strains were cultured and subcultured from the stock into sterile nutrient agar, *C. albicans* on Sabouraud dextrose agar plate at 37 °C for 48 h and standardized to 10^6CFU/mL in 12 h sterile broth before use. Synthesized 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine (15, 35, 58 mg/mL of **1, 2, 3** respectively) was dissolved in dichloromethane and distilled water 1:1 as diluent (solvent control). Ciprofloxacin and itraconazole (30 and 50 mg/mL respectively) were used as the standard for antibacterial and antifungal activities respectively.

2.4.1. Preliminary Screening (Agar Spot Test)

The sterile molten 25 ml nutrient agar medium was emptied into a 90 mm flat bottom Petri dish, placed on the level surface to ensure uniform thickness of the medium, and dried at 40-50 ^oC for 15 min in hot air oven before usage. A rectangular cavity (rectangle: 4 × 30 mm^2) was bored with a small sterile surgical knife and sealed the base with sufficient warm nutrient agar. The wire loop (2 mm diameter) was used to streak six different standardized inoculums along the cavity and emptied 0.5 ml synthesized 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine into the cavity. The plate was left standing for 1 h at room temperature, incubated at 37 ^oC for 18 h and measured the zones of inhibition diameter. All experiments were carried out in triplicates.

2.4.2. Determination of Zone of Inhibition Using Agar-Well Method

Standardized inoculums of the test microorganisms were radially streaked with an individual cotton swab aseptically on their respective agar plates. A stainless steel sterile borer (8 mm) was used to bore six uniform sizes well, each was uniformly sealed, and filled with 100 µL of four different concentration ranges of the synthesized compound, one for standard, and sixth the control (diluent). The plate was left standing for 1 h at room temperature, incubated at 37 ^oC for 18 h, and measured the zones of inhibition diameter. All experiments were carried out in triplicates [18].

2.4.3. Determination of MIC Using Microdilution Broth Method

The minimum inhibitory concentration (MIC) values of synthesized 2-[(4,6-diphenyl-1,6-dihydropyrimidin-2-yl)thiol]-*N,N*-dimethylethanamine was determined using the microdilution broth method. Four different concentration range of 100 µL of synthesized pyrimidine diluted in double strength sterile Mueller Hinton broth in test tubes, 20 µL of standardized organisms was added and incubated at 37 ^oC overnight. The test compound was the positive control and diluent as the negative control against the microorganisms for the experiment. The MIC recorded as the lowest concentrations without any visible growth (turbidity) for each of the test organisms. All experiments were carried out in triplicates.

3. Results and Discussion

Some new series of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine were synthesized and screened for microbial activities. Chalcone was prepared using the Claisen-Schmidt condensation

reaction in ethanolic sodium hydroxide. 4,6-Diphenylpyrimidin-2-thiol was synthesized from an equimolar mixture of 1,3-diphenyl-2-propen-1-one and thiourea in ethanol catalyzed in the presence of potassium hydroxide heated at reflux temperature. 4,6-Diphenylpyrimidin-2-thiol was *S*-alkylated with appropriate amines in good yields, purified by flash silica gel column chromatography and achieved one isolable product from TLC. 4,6-Diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine were assigned structure based on spectroscopic data of FTIR, ^{1}H, ^{13}C NMR and DEPT 135. The FT-IR of the ring C-S had stretching vibrations at 2371, 1241-1238 (C-S), C=N stretching frequency appeared at 1681 - 1678, 1595 - 1569, C-N stretching vibrations appeared at 1178, 1074 and 3060 for C-H of aromatic ring (Table 2). The presence of stretching vibrations at 2933 - 2922, 2855 - 2851 (CH_2) confirmed the S-alkylation reaction. These stretching frequencies correlated with book of Pretsch *et al.* [19] and in line with related reported works of pyrimidine [3, 20]. ^{1}H NMR of the pyrimidine ring CH protons at 5 and 6 of pyrimidine ring resonated as a pair of doublets (d) at 3.34 – 3.52 ppm and 5.16 – 5.54 ppm which were due to vicinal coupling these correlated with the literature [3, 17, 21]. NH group at position N-1 of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine appeared as a broad singlet at 2.60 – 2.61 and the aromatic ring appeared at 7.28 – 8.22 (10H). The signals of the piperidine, pyrrolidine and dimethylamine were in line with some research works [22-23]. The most shielded signal of the pyrimidine C-6 appeared at 60.41 - 63.48, the C-5 appeared at 108.01 - 108.16 (C-5), the aromatic ring at 126.15 - 133.14, the C-4 at 142.31 - 144.92 and 171.15 - 175.20 (C-2) (Table 3).

Table 2: FTIR of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine

Compound	NH	C-S	C=N	C=C	Ar C-H	C-N	CH_2
1	3329	2371, 1241	1678, 1595	1566, 1517	3060, 3027	1074	2933, 2855
2	3314	2371, 1238	1681, 1569	1539, 1517	3060, 3027	1074	2922
3	3325	2371, 1238	1681, 1595	1566, 1513	3060, 3027	1178, 1074	2922, 2851

Table 3: NMR of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine

Compound	d, 5-CH	d, 6-CH	Ar–H 10m	C-6	C-5	C-4	C-2	Ar–12C
1	3.34-3.36	5.50-5.54	7.28 -8.18	60.41	108.07	144.86	171.15	126.15-133.08
2	3.48-3.50	5.19-5.23	7.30 -8.22	63.48	108.02	144.92	175.20	126.20-133.14
3	3.50-3.52	5.26-5.30	7.28 -8.15	63.17	108.16	142.31	175.02	126.55-133.00

Multiplicity abbreviations: d – doublet, m – multiplet

Synthesized 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidines were screened against all tested microorganisms using a modified agar-well method for the preliminary screening for further

studies and **3** had activities except for *P. aeruginosa* and **1** had activities only against *B. subtilis (T)* (Table 4).

Table 4: Preliminary screening of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine for antimicrobial activities in mm

Compound	*P. aeruginosa*	*MSSA*	*E. coli*	*K. pneumoniae*	*B. subtilis (T)*	*B. subtilis*	*C. albicans*
1	-	-	-	-	12.50 ± 0.15	-	-
3	-	12.00 ± 0.17	9.00 ± 0.13	7.50 ± 0.10	12.00 ± 0.10	13.00 ± 0.23	20.00 ± 0.15

The zone of inhibition and MIC of 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidines of individual tested microorganisms were carried out using the cup-plate method and microbroth dilution method respectively. The zone of inhibition of 2-[(4,6-diphenyl-2*H*-5,6-pyrimidin-2-yl)thiol]-*N*,*N*-dimethylethanamine is presented (Table 5) in comparison with standard ciprofloxacin and itraconazole. Compound **3** inhibited moderately all bacteria and *C. albicans* except *K. pneumoniae* and *E. coli*. The MIC of **3** had a reasonable concentration range of 6.00 - 23.50 mg/ml (Table 6). The result above revealed that **3** containing dimethylamino exhibited moderate activities when compared with the standard ciprofloxacin and itraconazole.

Table 5: Zone of inhibition of 2-[(4,6-diphenyl-1,6-dihydropyrimidin-2-yl)thiol]-*N*,*N*-dimethylethanamine in mm

Compound	*P aureginosa*	*MSSA*	*B. subtilis(T)*	*B. subtilis*	*C. albicans*	*MRSA*
3	19.00 ± 0.33	12.00 ± 0.55	15.50 ± 0.20	10.00 ± 0.15	11.50 ± 0.35	16.00 ± 0.74
ciprofloxacin		26.00 ± 0.33	24.50 ± 0.30	26.00 ± 0.27	-	32.00 ± 0.40
itraconazole		-	-	-	26.50 ± 0.35	-

Table 6: MIC of 2-[(4,6-diphenyl-1,6-dihydropyrimidin-2-yl)thiol]-*N*,*N*-dimethylethanamine in mg/ml

Compound	*P. aureginosa*	*MSSA*	*B. subtilis(T)*	*B. subtilis*	*C. albicans*	MRSA
3	6.00 ± 0.33	8.00 ± 0.15	15.00 ± 0.20	7.00 ± 0.15	23.50 ± 0.25	8.00 ± 0.10

Conclusion

The study presented a two-step sequence of 4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-thione and *S*-alkylated with amines. The pure 4,6-diphenyl-2-((2-substitutedthio)-1,6-dihydropyrimidine were confirmed by (R_f values) and the spectral data (FT-IR, ^{1}H, ^{13}C –NMR, and DEPT 135 confirms the presence of nature of CH_2). All the synthesized compounds (**1-3**) were evaluated for antibacterial and antifungal activities. Compound **3** exhibited moderate activities when compared with the standard ciprofloxacin and itraconazole.

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