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Original Article

The Antifungal Effect of some 4-Chloro-6-Methoxy-*N*, *N*-Dimethylpyrimidin-2-Amine Derivatives Containing a Heterocyclic Compound on the Important types of Fungi

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ABSTRACT

Objective: 4-methoxy-*N, N*-dimethyl-6-(phenylthio) pyrimidin-2-amine, 4-(benzo[d]thiazol-2-ylthio)-6-methoxy-*N,N*-dimethylpyrimidin-2-amine, 4-(4-(1,2,3-selenadiazol-4-yl)phenoxy)-6-methoxy-*N,N*-dimethylpyrimidin-2-amine and 4-(4-(1,2,3-thiadiazol-4-yl)phenoxy)-6-methoxy-*N,N*-dimethylpyrimidin-2-amine have been synthesized. **Method**: The prepared compounds were synthesized by nucleophilic displacement of chloride substituted in pyrimidine heterocyclic ring. **Results**: The synthesized compounds were being identified by different methods included TLC technique, IR, 1H-NMR and 13C-NMR spectrophotometers. All compounds confirmed by elemental analysis. The biological activity of these new compounds investigated against some fungi like *Aspergillus terreus* and *Aspergillus niger*, the results was *Aspergillus terreus* more effected by antifungal compare with *Aspergillus niger,* the effect ration 0.98, 1.32 with 200μM respectively and the compound number (2) has more effect than other compounds. **Conclusion**: It is concluded that synthesized dimethylpyrimidin-derivatives are biologically active and developed into useful Antifungal agents.

Key words: Pyrimidine, Dimethylpyrimidin-derivatives, Heterocyclic compound, *Aspergillus terreus, Aspergillus niger*.

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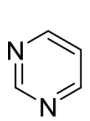
INTRODUCTION

Pyrimidines are important member in the heterocyclic compounds. Pyrimidines exist in nature as a component of nuclear acid and isolated for the first time by Gabriel in 1899 Gabriel and Colman in 1899.[1] The name pyrimidine was approved by the International Union of Pure and Applied Chemistry (IUPAC) for this heterocyclic ring system. Several hydro and oxo derivatives of the pyrimidine which are particularly important in biological systems are normally referred to by their nonsystematic names such as 2,4-(1H,3H)-pyrimidinedione[2] (Uracil), 5-methyluracil[3] (Thymine) and 4-aminopyrimidine-2-(1H)-one[4] (Cytosine).[2,3]



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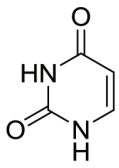

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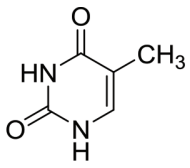

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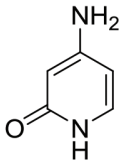

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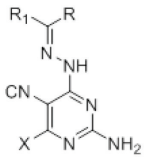
The pyrimidine nucleus also establishes the major part of vital molecules including vitamins such as thiamine,[4] riboflavin,[5] and folic acid.[6] Derivatives of pyrimidine have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of acquired immunodeficiency syndrome (AIDS).

Several pyrimidine derivatives exhibited significant antitumor activity e.g. hydrazine-pyrimidine-5-carbonitrile derivatives[5] with inhibitory effects on the growth of a wide range of cancer cell lines generally at some cases at 10^{-7} M concentrations.[7] 2,4-Diamino-N_4-6-diarylpyrimidnes[6] were identified as blocked proliferation of tumor cell lines *in vivo,* especially duodenum cancer (DU145, IC_{50} = 0.23



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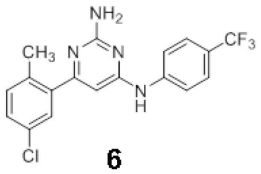

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Azam *et al.*[8] have synthesized pyrimidine bridged thiadiazole derivatives 5- {(4,6-disubstituted pyrimidine-2-yl) thio methyl}-*N*-phenyl-1,3,4, thiadiazol-2-amines which exhibited significant antitumor activity against human breast cancer MCF 7 cell line. However, moderate antioxidant activity was observed. Analogously, Amin and *et al.*[9] synthesized three tetralin-6-yl pyrimidines found that they were active against liver cancer cell (Hep G_2) with IC_{50}=8.66 and 7.11 μg/ml respectively.

Several methods have been reported for the synthesis of various pyrimidines. One method was classic Biginelli reaction,[10] many papers have been reported for the synthesis of pyrimidine derivatives.[11-14] Monastrol, ethyl 4-(3-hydroxyphenyl)-6-methyl-2-sulfanylidene-3,4-dihydro-1H-pyrimidine-5-carboxylate was discovered by Prof. Mayer of Konstanz University, Germany,[15] shown to inhibit the Kinesin Eg 5, a motor protein important for spindle bipolarity. Drugs that inhibit kinesins are being developed as anti-cancer agents with the hope that they will inhibit proliferation of tumor cells. Many substituted pyrimidine derivatives synthesized and evaluated against cancer and HIV showed different

significant activity toward cancer cell *in vitro*.[16-18] In continuous of our works to synthesized and evaluated some derivative of pyrimidine towards HIV, HCV, many type of bacteria, cyclin-dependent kinase 2 (CDK2) inhibitory activities and monastrol analogues,[19-21] so we herein aim to study the activity of some heterocyclic rings like [1,2,3-thiadiazole, 1,2,3-selenadiazole, benzo[*d*]thiazol-2-ylthio)] and thiophenyl compounds against some fungi such as *Aspergillus terreus* and *Aspergillus niger*.

Aspergillus terreus was described as a filamentous fungus that linked with organic detritus decay in the soil rhizosphere,[22] Additionally, *A. terreus* has been described as a human pathogen and can initiate cutaneous, and subcutaneous mycoses that disturb the nail bed,[23] outer ear canal,[24] and skin.[25] Newly, *A. terreus* has been documented to be accompanying with postoperative osteomyelitis,[26] endophthalmitis and peritonitis.[27] In addition to *Aspergillus niger* which Genome sequencing of *A. niger* is significant because of its participation in formation citric acid as well as industrial enzymes, such as proteases and lipases. Additional properties of this species involve pathogens that initiate the decomposition of food and formation of secondary metabolites, such as aflatoxin.[28,29]

Experimental Section

General

Melting points are uncorrected and were measured on a strut melting point apparatus (England). NMR data were obtained on 500 MHz (1H) and (150.91 MHz (13C spectrometers (Bruker, Tehran Medical University) with DMSO-d6 solvent, with tetramethylsilane (TMS) as an internal standard, was used to record 1H-NMR spectra and 13C-NMR. Chemical shifts were reported in (δ ppm.) spectrometers. Elemental analyses were performed on a PE-2400 elemental analyzer; the C, H and N analysis were repeated duplicate. Microwave oven LG MOD MH7947S 1450-1150 W. All solvents and reagents were obtained commercially from Aldrich, Fluka. Silica gel (0.040 – 0.063 mm) used for analytical silica gel TLC plates 60 F254 were purchased from Merck, compounds were detected by their absorption under UV light.

Experiment Chemistry

General procedure of O-nucleophilic displacement of chloride substituted in the pyrimidine heterocyclic ring.

A mixture of different nucleophilic compounds[6,7] potassium carbonate (2.71 g, 19.65 mmol), potassium iodide (5.21 g, 19.6 mmol) and 4-chloro-6-methoxy-*N, N*-dimethylpyrimidin-2-amine **1** (0.5 g, 0.0026 mol) in (40 ml) of dry acetone and 2-3 drops of Aliquate 336 was refluxed for under microwave irradiation. The reaction was followed by TLC in chloroform until completion (40-45 min). Then the reaction mixture was cooled to room temperature, the precipitated salt was removed by filtration. The organic solvent was dried in vacuo together with the excess of compound **1** After that the product was separated from the traces of compound **1** on a Silica gel column (40 cm) with petroleum ether. Then, the product which was remained at upper the part of the column was eluted by chloroform.

4-(4-(1,2,3-selenadiazol-4-yl) phenoxy)-6-methoxy-N, N-dimethylpyrimidin-2-amine (2)

From 4-(1,2,3–seleniadiazol-4-yl) phenol compound 6 (0.87 g, 0.0039 mole)Yield 94%, color red, m.p = 87-88 °C IR spectrum υ = cm^{-1} 1591 (C=N), 1382 (C-N), 1030 (C-O-C), 1535 (N=N), 1490, 1450 (C=C) aromatic, 621 (C-Se): 1H-NMR (DMSO-d_6) δ (ppm) 9.01 (s, 1H, $H_{seleniadiazole}$), 8.11-7.39 (m, 4H, $H_{phenoxy}$), 6.95 (s, 1H, $H_{primidine}$), 3.78 (s, 3H, OMe), 3.08 (s, 6H, NMe_2); 13C-NMR (DMSO-d_6) δ (ppm) 171.63 (C4), 163.787 (C6), 162.06 (C2), 156.00 (C7), 130.03 (C10), 128.17 (C3'+C4'), 125.50 (C9), 122.84 (C11), 114.94 (C1'+C2'), 92.73 (C5), 52.45 (C-OMe), 36.41 (C-NMe_2). Anal. calc. for $C_{15}H_{15}N_5O_2Se$ (376.28 C, 47.88; H, 4.02; N, 18.61; Found: C, 47.48; H, 4.00; N, 18.01.

4-(4-(1,2,3-thiadiazol-4-yl) phenoxy)-6-methoxy-N, N-dimethylpyrimidin-2-amine (3)

From 4-(1,2,3–thiazol-4-yl) phenol compound 7 (0.69 g, 0.0039 mole). Yield 92%, color Pale yellow, m.p = 90-91 °C IR spectrum υ = cm^{-1} 1591 (C=N), 1380 (C-N), 1035 (C-O-C), 1537 (N=N), 1494, 1452 (C=C), 667 (C-S): 1H-NMR (DMSO-d_6) δ (ppm) 9.02 (s, 1H, $H_{thiadiazole}$), 8.29-8.02 (m, 4H, $H_{phenoxy}$), 6.62 (s, 1H, $H_{primidine}$), 3.90 (s, 3H, OMe), 3.20 (s, 6H, NMe_2); 13C-NMR (DMSO-d_6) δ (ppm) 171.22 (C4), 163.33 (C6), 162.28 (C2), 138.64 (C7), 136.98 (C10), 133.17 (C3'+C4'), 132.94 (C9), 128.54 (C11), 115.75 (C1'+C2'), 91.25 (C5), 53.43 (C-OMe), 36.95 (C-NMe_2). Anal. calc. for $C_{15}H_{15}N_5O_2S$ (329.38): C, 54.70; H, 4.59; N, 9.71; S, 9.73 Found: C, 54.40; H, 4.29; N, 9.56; S, 9.13.

General procedure of *S*-nucleophilic displacement of chloride substituted in the pyrimidine heterocyclic ring.

A mixture of different nucleophilic compounds[8,9] and 4-chloro-6-methoxy-*N, N*-dimethylpyrimidin-2-amine **1** (0.5 g, 0.0026 mol) in (30 ml) of dry DMF and few drops of conc. NaOH was refluxed for under microwave irradiation. The reaction was followed by TLC in chloroform until completion (30 min). Then the reaction mixture was cooled to room temperature, the precipitated salt was removed by filtration. The organic solvent was dried in vacuo together with the excess of compound **1**, after that the product was separated from the traces of compound **1** on a Silica gel column (30 cm) with petroleum ether. Then, the product which was remained at upper the part of the column was eluted by chloroform.

4-methoxy-N, N-dimethyl-6-(phenylthio) pyrimidin-2-amine (4)

From sodium benzene thiolate compound **8** (0.51 g, 0.0039 mol). Yield 96%, color Pale yellow, m.p = 67-68 °C IR spectrum υ = cm^{-1} 1597 (C=N), 1382 (C-N), 1037 (C-O-C), 1450, 1419 (C=C), 621 (C-S): 1H-NMR (DMSO-d_6) δ (ppm) 7.63-7.07 (m, 5H, H_{phenyl}), 6.82 (s, 1H, $H_{primidine}$), 3.87 (s, 6H, NMe_2), 3.16 (s, 3H, OMe); 13C-NMR (DMSO-d_6) δ (ppm) 171.53 (C4), 163.70 (C6), 162.06 (C2), 137.26 (C1'), 132.88-124.19 ($C_{aromatic}$), 92.22 (C5), 53.04 (C-OMe), 36.43 (C-NMe_2). Anal. calc. for $C_{13}H_{15}N_3OS$ (261.34): C, 59.75; H, 5.79; N, 16.08; O, 6.12; S, 12.27 Found: C, 59.55; H, 5.09; N, 16.01; O, S, 12.07.

4-(benzo[d]thiazol-2-ylthio)-6-methoxy-N, N-dimethylpyrimidin-2-amine (5)

From benzo[d]thiazole-2-thiol compound **9** (0.65 g, 0.0039 mole). The yellow oil that was obtained is crystallized very slowly in ice bath. Yield 90%, color yellow, m.p = 112-113 °C IR spectrum υ = cm^{-1} 1593 (C=N), 1380 (C-N), 1033 (C-O-C), 1490, 1448 (C=C), 620 (C-S): 1H-NMR (DMSO-d_6) δ (ppm) 8.02-8.31 (m, 4H, H_{Benzo}), 6.62 (s, 1H, $H_{primidine}$), 3.20 (s, 6H, NMe_2), 3.09 (s, 3H, OMe); 13C-NMR (DMSO-d_6) δ (ppm) 171.78 (C7), 164.55 (C6), 161.07 (C4), 185.89 (C2), 155.22 (C2'), 129.17 (C1'), 125.38 (C4'+C5'), 122.64 (C3'+C6'), 95.02 (C5), 35.54 (C-OMe), 36.85 (C-NMe_2). Anal. calc. for $C_{14}H_{14}N_4OS_2$ (318.06): C, 52.75; H, 4.33; N, 17.44; S, 20.10 Found: C, 52.81; H, 4.43; N, 17.60; S, 20.14.

Antifungal activity

Potato dextrose agar (PDA)

The culture was prepared by dissolving 40 gm. from (PDF) powder in amount of distilled water and completes the volume to 1000 ml, then it sterilized in autoclave at 121C° and 15 pound /in^2 pressure for 20 min.

This medium was used for determination of optimum culture media for inhibition process.

The source of fungi isolates

The fungi which include *Aspergillus terreus*, *Aspergillus niger* were obtained from the unit of isolation and classification of fungi isolates / Department of Biology /College of Science /University of Babylon.

Method of holes

Antifungal bioassays were performed on petri dish plates contain 20 ml of standard PDA agar. After the mycelia colonies were developed, 3 wells of 0.5 cm in diameter were made 1cm from the rim. The antibiotic was (1 ml) to add to the wells and the plates were incubated at 25C° for 5d. Growth inhibition zone were observed. The percentage inhibition of radial mycelia growth of the test fungus was calculated. Stability.

The stability of antibiotic compounds was monitored by using FT-IR spectrum for each compound (one measure every one week). The spectrum was obtained for compounds that stored at refrigerator (2-8C°). Any change in the FT-IR spectrum is interpreted as a change in the structure of the corresponding compound.

Solubility

The solvents listed in Table 3 and synthesized compounds were used without further purification. The water used was distilled, deionized, and filtered (0.2µm). The temperature was kept with 25 ± 0.02°C.

Toxicity

The toxicity of synthesized compounds was studied via determination the lethal dose (LD_{50}). Lethal dose (LD_{50}) is represents the quantity of an ingested material that kills fifty percent of a test sample in the study. It is expressed in milligrams of material per kilogram of body weight. A suitable method of Miller and Tainter[30] is used; as described by Agina *et al*.[31]

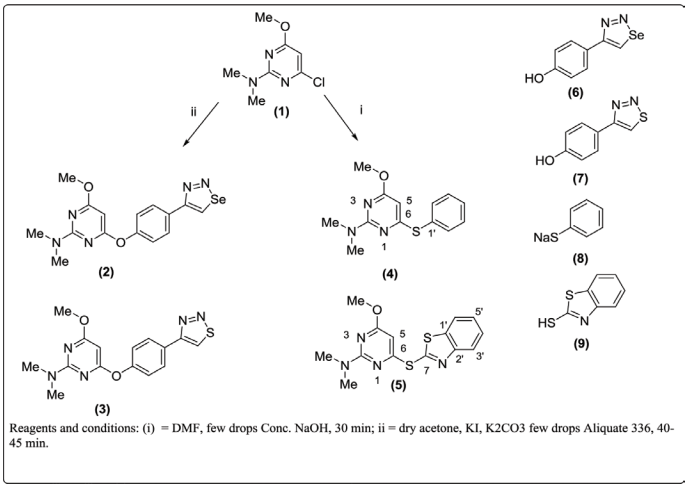
Statistical analysis

Data analysis was established using SPSS 21 for Windows (SPSS Inc., Chicago, IL, USA). Data were evaluated by one-way analysis of variance (ANOVA) followed by LSD test.

RESULT AND DISCUSSION

The pyrimidine derivative compounds are widely used in different application fields It is anti-HIV drugs that some substituted pyrimidine derivatives exhibited a potent activity against the fatal disease AIDS such as Riplivirin and Etravrin.[32-35] These molecules prompted us to synthesize new models of substituted pyrimidines having potential substituents, aiming to optimize the antibiotic activity as well as evaluation their activity against other harmful diseases, so 4-chloro-6-methoxy-*N*,*N*-dimethylpyrimidin-2-amine **1** has been selected as a precursor for the synthesis of new pyrimidine derivatives. Herein the reaction occurs is nucleophilic substitution with *O*- and *S*-nucleophiles (phenoxides and thiophens ions), bearing some heterocyclic rings like 1,2,3-seleniadiazole, 1,2,3-thiadiazole and benzothiazole, which are formed *in situ* in the reactions of phenols and thiophenyl in bases with chlorinated pyrimidine derivative **1**, has been reported in (scheme 1).

Treatment of **1** with 4-(1,2,3-selenadiazol-4-yl) phenol or 4-(1,2,3-thiadiazol-4-yl) phenol in refluxing DMF with few drops of conc. NaOH afforded, *via* nucleophilic displacements of the chlorine group, **2** and **3** in 94 and 92% yield, respectively. Similarly, reaction of **1** with sodium benzenethiolate and benzo[d]thiazole-2-thiol afforded compound **4** and **5** in 96 and 90% yield in refluxing dry acetone and Aliquite 336 as catalyst working as surfactants (Scheme 1).



Scheme 1: Schematic representation of synthetic procedure for compounds 1-9.

The structures of **2**-**5** were determined from the ^{1}H, and ^{13}C NMR spectra. The methyl protons (NMe_2) (6H) appeared as singlets at the range *d* = 3.20-2.08 ppm, while H-5 of the pyrimidine ring resonated at the range *d* = 6.62-6.95 ppm. The ^{1}H NMR spectrum of all compounds showed a doublet of doublets of doublets (ddd) at *d* = 7.07-8.31 ppm with *J* constant between for all of them (*J* = 7.1-7.5 Hz). The ^{1}H NMR spectrum of **2** showed a singlet at *d* = 9.01 ppm assigned to the proton in 1,2,3-sleniadiazole heterocyclic ring, whereas the singlet at *d* = 9.02 ppm attributed to the proton in 1,2,3-thiadiazole heterocyclic ring for compound **3**.

The ^{13}C NMR spectra of **2**-**5** contained similar resonance signals of the pyrimidine carbons ring C2 - C6, as well as the methoxy and NMe_2 carbons. Carbon atoms of methoxy and NMe_2 pyrimidine ring of compounds **2**-**5** resonated at the ranges δ = 62.4 -53.8 ppm and δ = 36.9-36.4 ppm, respectively. In the ^{13}C NMR spectrum of **2**, *d* = C-2, C-4, C-5 and C-6 resonated at *d* = 162.0, 171.0, 92.7 and 163.7 ppm, respectively. The ^{13}C NMR of compounds **2** and **3** characterized by the presence of the down-field signals at *d* = 130.0 and 122.6 and 136.9 and 128.5 ppm were assigned to two carbons atoms in heterocyclic rings, respectively.

The structure of compound **3** was confirmed in ^{13}C NMR were all similar carbons atom apereas at same regions (C-NMe, C-OMe, C5 and C6) as in the above, multiplet signals resonated at *d* = 137.2-124.1 for aromatic carbons. Similarly, the carbon atoms of compound **4** characterized by the presence of C1', C2', (C4'-C5'), (C3'-C6') = 129.1, 155.2, 125.3 and 122.6 ppm, respectively. The IR spectrum of compound **2** showed υ = cm^{-1} 1591 (C=N), 1382 (C-N), 1030 (C-O-C), 1535 (N=N), 1490-1450 ($C=C_{aromatic}$) and 621 ($C\text{-}Se_{Heterocyclic}$). The IR spectrum of compound **3** showed υ = cm^{-1} 1591 (C=N), 1380 (C-N), 1033 (C-O-C), 1537 (N=N), 1494-1452 ($C=C_{aromatic}$) and 667 ($C\text{-}S_{Heterocyclic}$). But IR spectrum of compound **4** showed υ = cm^{-1} 1597 (C=N), 1382 (C-N), 1037 (C-O-C), 1537 (N=N), 1450-1419 ($C=C_{aromatic}$) and 621 (C-S). Furthermore compound **5** exhibited absorption bands at υ = cm^{-1} 1593 (C=N), 1380 (C-N), 1033 (C-O-C), 1537 (N=N), 1490-1448 ($C=C_{aromatic}$) and 620 ($C\text{-}S_{Heterocyclic}$) all these dates were confirmed the functional groups that make up the overall structure of the molecules.

In addition to all these compounds were confirmed by micro elemental analysis that proved compounds formation.

Table 1: Effect of antibiotic compound (μM) on fungus growth (cm) inhibition zone rate.

Compound type / Fungal type	1			2			3			4			Fluconazole		
	50	100	200	50	100	200	50	100	200	50	100	200	50	100	200
Aspergillus niger	6.37*	5.55*	4.89*	2.93	2.67	1.32	4.61*	4.61*	3.98*	3.08	3.60	2.98	3.23	3.14	3.00
Aspergillus terreus	4.52*	4.09*	3.56*	1.60	1.32	0.98	3.36	3.12	2.54	2.96	2.84	1.65	2.33	2.45	2.77

*The mean difference is significant at the 0.05 level compared to Fluconazole.

Table 2: Stability and toxicity of the antibiotic compound.

Compound type / Parameter	1	2	3	4
Stability (month)	More than six month	More than five month	More than six month	More than six month
Toxicity (LD_{50})	220 mg/kg	220 mg/kg	210 mg/kg	190 mg/kg

Table 3: Solubility of the compounds (g of antibiotic/kg of solvent) in different solvents at 25°C temperature.

Compound type / Solvent	1	2	3	4
2-propanol	117	119	105	115
Water	23	25	25	27

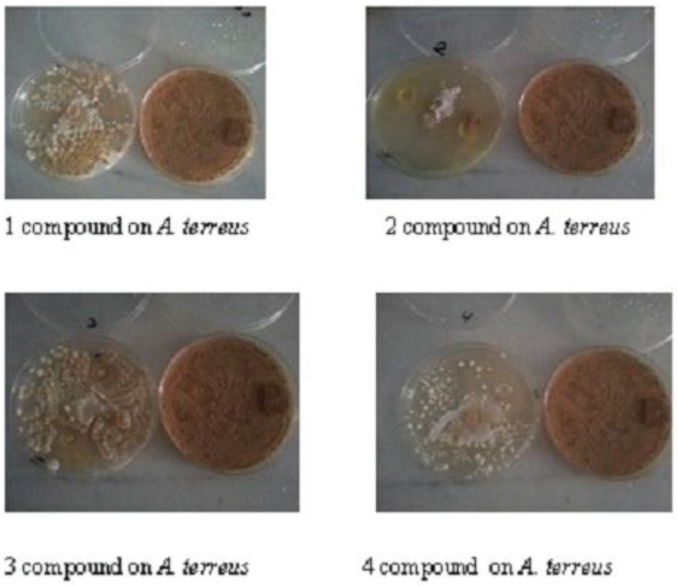


Figure 1: The inhibition zone with most significant results.

Antifungal activity

The results were based upon the scale developed by Arora and Bhardwaj.[36] The zone of inhibition and the result of drug sensitivity were described as below.

The results showed activity against *A. terreus* with different zone of inhibition, respectively, with the three concentrations of 50 μM, 100 μM and 200 μM respectively. 2 compound showed activity against with *A. terreus* 0.98 cm of zone of inhibition with the concentration of 200 Mm Table 1. We also tested these compounds against *A. niger* the antimicrobial activity 2.96, 2.84 and 1.65 with 50 μM, 100 μM and 200 μM respectively. The results of Table 2 show the stability and toxicity of antibiotic compound; while the results of Table 3 elucidate the solubility of compounds (g of antibiotic/kg of solvent) in different solvents at 25°C temperature. Figure 1 shows the inhibition zone with most significant results.

From the observation of the antimicrobial (AM) activity of the compounds the bioactivities of a series of pyrimidine derivatives are as follows and we can correlate a good structure function relationship amongst them.

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None.

CONFLICT OF INTEREST

All authors have none to declare.

REFERENCES

1. Jafar NN, Al-Dahmoshi HO, Jeburalmamoori AM, Al-Khafajii NS, Al-Masoudi N. Synthesis and biological activity of new derivatives of 6-chloro-5-((4-chlorophenyl) diazenyl) pyrimidine-2, 4-diamine and 4-chloro-6-methoxy-N, N-dimethylpyrimidin-2-amine. Biomed Pharmacol J . 2013;6(2).
2. Brown DJ. The Chemistry of Heterocyclic Compounds, The Pyrimidines. John Wiley and Sons; 2009.
3. Padwa A, Woolhouse AD, Katritzky AR, Rees CW. Comprehensive heterocyclic chemistry. Comprehensive heterocyclic chemistry. Oxford.1984;3:57.
4. Bettendorff L, Wirtzfeld B, Makarchikov AF, Mazzucchelli G, Frédérich M, Gigliobianco T, *et al.* Discovery of a natural thiamine adenine nucleotide. Nat Chem Biol. 2007;3(4):211-2.
5. Zempleni J, Galloway JR, McCormick DB. Pharmacokinetics of orally and intravenously administered riboflavin in healthy humans. Am J Clin Nutr. 1996;63(1):54-66.
6. Bailey SW, Ayling JE. The extremely slow and variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake. Proc Natl Acad Sci. 2009;106(36):15424-9.
7. Bailey SW, Ayling JE. The extremely slow and variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake. Proc Natl Acad Sci. 2009;106(36):15424-9.
8. Azam MA, Kumar BR, Shalini S, Suresh B, Reddy TK, Reddy CD. Synthesis and biological screening of 5-{[(4, 6-disubstituted pyrimidine-2-yl) thio] methyl}-N-phenyl-1, 3, 4-thiadiazol-2-amines. Indian J Pharm Sci. 2008;70(5):672.
9. Amin KM, El-Zahar MI, Anwar MM, Kamel MM, Mohamed MH. Synthesis and anticancer activity of novel tetralin-6-yl pyridine and tetralin-6-yl pyrimidine derivatives. Acta Pol Pharm. 2009;66:279-91.
10. Yadav JS, Kumar SP, Kondaji G, Rao RS, Nagaiah K. A Novel L-Proline Catalyzed Biginelli Reaction: One-Pot Synthesis of 3, 4-Dihydropyrimidin-2 (1H)-ones under Solvent-Free Conditions. Chem Let. 2004;33(9):1168-9.
11. Kappe CO. 100 years of the Biginelli dihydropyrimidine synthesis. Tetrahedron. 1993;49(32):6937-63.

12. Dondoni A, Massi A, Sabbatini S. Improved synthesis and preparative scale resolution of racemic monastrol. Tetrahedron Let. 2002;43(34):5913-6.
13. Movassaghi M, Hill MD. Single-step synthesis of pyrimidine derivatives. J Am Chem Soc. 2006;128(44):14254-5.
14. Ramalingan C, Kwak YW. Tetrachlorosilane catalyzed multicomponent one-step fusion of biopertinent pyrimidine heterocycles. Tetrahedron. 2008;64(22):5023-31.
15. Mayer TU, Kapoor TM, Haggarty SJ, King RW, Schreiber SL, Mitchison TJ. Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science. 1999;286(5441):971-4.
16. Baba M, Tanaka H, Clercq E, Pauwels R, Balzarini J, Schols D, *et al.* Highly specific inhibition of human immunodeficiency virus type 1 by a novel 6-substituted acyclouridine derivative. Biochem Biophys Res Commun. 1989;165(3):1375-81.
17. Tanaka H, Takashima H, Ubasawa M, Sekiya K, Nitta I, Baba M, *et al.* Structure-activity relationships of 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio) thymine analogues: effect of substitutions at the C-6 phenyl ring and at the C-5 position on anti-HIV-1 activity. J Med Chem. 1992;35(2):337-45.
18. Balzarini J, Baba M, Clercq E. Differential activities of 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio) thymine derivatives against different human immunodeficiency virus type 1 mutant strains. Antimicrob Agents Chemother. 1995;39(4):998-1002.
19. Jafar NN, Al-Masoudi NA, Baqir SJ, Leyssen P, Pannecouque C. Exploration of the *in vitro* antiviral activity of a series of new pyrimidine analogues on the replication of HIV and HCV. Antiviral Chemistry and Chemotherapy. 2013;23(3):103-12.
20. Jafar NN, Mohammed AN, Madlool AK. Synthesis of New Analogues of drug 'Monastrol' via Biginelli Reaction. Res J Pharm Biol Chem Sci. 2015;6(5):906-15.
21. Al-Masoudi NA, Jafar NN, Abbas LJ, Baqir SJ, Pannecouque C. Synthesis and anti-HIV Activity of New Benzimidazole, Benzothiazole and Carbohyrazide Derivatives of the anti-Inflammatory Drug Indomethacin. Z Naturforsch B J Chem Sci. 2011;66(9):953-60.
22. Wang H, Ng TB. Isolation of cicadin, a novel and potent antifungal peptide from dried juvenile cicadas. Peptides. 2002;23(1):7-11.
23. Hilmioglu-Polat S, Metin DY, Inci R, Dereli T, Kılınc I, Tümbay E. Non-dermatophytic molds as agents of onychomycosis in Izmir, Turkey–a prospective study. Mycopathologia. 2005;160(2):125-8.
24. Tiwari S, Singh SM, Jain S. Chronic bilateral suppurative otitis media caused by Aspergillus terreus. Mycoses. 1995;38(7-8):297-300.
25. Cheetham HD. Subcutaneous infection due to Aspergillus terreus. J Clin Path. 1964;17(3):251-3.
26. Natesan S, Abraham G, Mathew M, Lalitha MK, Srinivasan CN. Secondary sternal Aspergillus osteomyelitis in a diabetic hemodialysis patient with previous allograft rejection. Hemodial Int. 2007;11(4):403-5.
27. Garg P, Mahesh S, Bansal AK, Gopinathan U, Rao GN. Fungal infection of sutureless self-sealing incision for cataract surgery. Ophthalmology. 2003;110(11):2173-7.
28. May GS, Adams TH. The importance of fungi to man. Genome Res. 1997;7(11):1041-4.
29. Takahashi K, Inoue H, Sakai K, Kohama T, Kitahara S, Takishima K, *et al.* The primary structure of Aspergillus niger acid proteinase A. J Biol Chem. 1991;266(29):19480-3.
30. Miller LC, Tainter M. Estimation of the ED50 and Its Error by Means of Logarithmic-Probit Graph Paper. Proc Soc Exp Biol Med. 1944;57(2):261-4.
31. Agina OA, Omoja VU, Ekere SO, Odo S, Agina BC. A study on dichlorvos induced hematology, clinical biochemistry and reproductive abnormalities in male albino rats. J Mol Pathophysiol. 2017;6(1):5-11.
32. Janssen PA, Lewi PJ, Arnold E, Daeyaert F, Jonge M, Heeres J, *et al.* In search of a novel anti-HIV drug: multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1 E)-2-cyanoethenyl]-2, 6-dimethylphenyl] amino]-2-pyrimidinyl] amino] benzonitrile (R278474, rilpivirine). J Med Chem. 2005;48(6):1901-9.
33. Hargrave KD, Proudfoot JR, Grozinger KG, Cullen E, Kapadia SR, Patel UR, *et al.* Novel non-nucleoside inhibitors of HIV-1 reverse transcriptase. 1. Tricyclic pyridobenzo-and dipyridodiazepinones. J Med chem. 1991;34(7):2231-41.
34. Hargrave KD, Proudfoot JR, Grozinger KG, Cullen E, Kapadia SR, Patel UR, *et al.* Novel non-nucleoside inhibitors of HIV-1 reverse transcriptase. 1. Tricyclic pyridobenzo-and dipyridodiazepinones. J Med Chem. 1991;34(7):2231-41.
35. Dueweke TJ, Poppe SM, Romero DL, Swaney SM, So AG, Downey KM, *et al.* U-90152, a potent inhibitor of human immunodeficiency virus type 1 replication. Antimicrob Agents Chemother. 1993;37(5):1127-31.
36. Arora DS, Bhardwaj SK. Antimicrobial activity of tea (Camellia sinensis) against some plant pathogens. Geobios. 1997;24:127-31.

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