PSM Journals

PSM
Biological Research

Research Article 2024 | Volume 9 | Issue 1 | 30-40

Open Access

Article Information

Received: October 28, 2023

Accepted: November 8, 2023

Published: November 20, 2023

Keywords
Synthesis,
Characterization,
New pyrimidine derivatives,
Spectroscopy analysis,
Biological activity.

Authors' Contribution
AKAAH conceived and designed the study; AKAAH and MAA wrote and revised the paper.

How to cite
Almakhzoum, K.A.A.H., Almaqtari, M.A., 2024. Synthesis and Characterization of Some Novel 6-(Heteroatom-substituted) Pyrimidine Derivatives and Study the Biological Activity. PSM Biol. Res., 9(1): 30-40.

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Synthesis and Characterization of Some Novel 6-(Heteroatom-substituted) Pyrimidine Derivatives and Study the Biological Activity

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Abstract:
The series of new pyrimidine derivatives 6- substituted - 5 - cyano - 4 -(P- phenyl - 4H) Pyrimidine and Substituted thieno [2, 3- d] Pyrimidine were synthesized by the reaction between some substituted compounds of benzaldehydes (P- methoxy benzaldehyde, P- methyl benzaldehyde, P- hydroxyl benzaldehyde, P- ethyl benzaldehyde) with ethyl cyanoacetate in the presence of ethanol as a solvent. All the synthesized compounds of new pyrimidine derivatives were characterized by ^{1}HNMR and Mass Spectrum analysis that proved the newly synthesized compounds. The antimicrobial activity against the tested bacteria *Staphylococcus aureus, Escherichia coli*, and the fungi *Aspergillus flavus* and *Aspergillus niger* was investigated, which showed activity between strong, moderate, and slight for the newly synthesized compounds.

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INTRODUCTION

The pyrimidine derivatives are those compounds that possess an acyclic structure with two Nitrogen atoms in the ring most of the sugar, vitamins, and alkaloids, which are Nitrogenous bases occurring in many antibiotics such as penicillin are the Pyrimidine derivatives (Sondhi *et al.*, 2001) phosphorous oxy chloride pyrimidine derivatives have been found to possess interesting antibacterial (Araki *et al.*, 1993), antipsychotic (Yerich *et al.*, 1992), anticancer (Shishoo *et al.*, 2000; Tylińska *et al.*, 2021) anti-schizophrenia (Singh *et al.*, 2021) and antihypertensive (Irshad *et al.*, 2021) antiviral (Farghaly *et al.*, 2023), antitumor (Mahapatra *et al.*, 2021) anti-inflammatory (Rashid *et al.*, 2021), antimicrobial (Zhuang and Ma, 2020) and anti-fungal (Sun *et al.*, 2011), antihistaminic (Fatima *et al.*, 2023), analgesic (Nofal *et al.*, 2011) and anti-oxidant properties (Nair *et al.*, 2022). Aromatic and heteroaromatic compounds bearing an O-aminoester group are useful substrates for the preparation of various condensed pyrimidines heterocyclic system (Bhuiyan *et al.*, 2006; Chowdhury and Shibata, 2001; Rateb *et al.*, 2011).

In this study, newly synthesized pyrimidine derivatives were identified and characterized by spectra analyses (^{1}HNMR, Mass Spectra). The biological activity of the new pyrimidine derivatives was then investigated.

MATERIAL AND METHODS

Materials Preparation

All chemical materials including substituted benzaldehyde, thiourea, potassium carbonate, Ethyl aceto acetate, activated charcoal, and solvents were obtained from BDH.

Synthesis of Compounds

In this study new series of pyrimidine derivatives 2-and 6- substituted of 5-cyano -4-(p- phenyl) pyrimidine and substituted thieno [2,3-d] pyrimidine was synthesized through reactions between some benzaldehydes substituted and cyano aceto acetate in the presence of ethanol as a solvent and by subsequent steps (Kassium and Hussein, 2019).

During these reactions, the intermediate products (3a-e) react with alkyl or aryl halide in ethanol and get new pyrimidine derivatives (4a-e), that were heated with phosphorous oxy chloride in dioxin to form (5a-e). Next in ethanol solvent, the (5a-e) react with thiourea and produce (6a-e). Finally, the last compounds (6a-e) react with chloro acetic acid and form new substituted thieno [2,3-d] pyrimidine (8a-e) (Kassium and Hussein, 2019).

Characterization of Compounds

The new pyrimidine derivatives were identified and characterized by physical properties (melting points, yields, colors) and their structural formulas were confirmed by spectra analyses (^{1}HNMR, Mass Spectra) that coincide with its molecular formulas.

Biological Screening

The synthesized compounds were tested for their antibacterial and antifungal activity against two species of bacteria (*Staphylococcus aureus*, *Escherichia coli*) and two species of fungi (*Aspergillus flavus*, and *Aspergillus niger*), using filter paper disc method, antibacterial (Hussain *et al.*, 2016; Iqbal *et al.*, 2016; Iqbal and Ashraf, 2020; Saleem *et al.*, 2018; Saleem *et al.*, 2020) and antifungal activity (Kalim *et al.*, 2016) was determined by measuring the diameter of zone inhibition after incubation for 48h at 37°C for bacteria and 28°C for fungi, activity of each compound were compared with Ciprofloxacin and Ampicillin drug as a positive control.

RESULTS AND DISCUSSION

The prepared pyrimidine derivatives were confirmed based on their spectral analyses (Tables 1).

Pyrimidine ring is present in a large number of biologically important compounds as nucleic acids, alkaloids, antimicrobial agents or drugs, and

numerous studies on the synthesis and structure activity relationships of Pyrimidine derivatives have been reported (Chowdhury and Shibata, 2001). Therefore, preparation of some highly substituted pyrimidine giving a possibility for further transformation can be of substantial interest.

^{1}H- NMR spectrums of Compounds (3a, 3b, 3c, 4a)

The ^{1}H NMR spectrum of compound (3a; DMSO - d6) showed signals: at δ 3.36 (s, 3H, CH_3 of OCH_3 ether); 8.45 (s, H, NH); 2.52 (s, H, SH); 7.04-8.85 (s, 4H of Ar-H) in (Figure 1) and (Table 1). The 1HNMR spectrum of compound (3b; DMSO - d6) showed signals: at δ 7.61 (s, H, NH); 2.52 (s, H, SH); 7.12 - 7.45(s, 4H of Ar-H) in figure (2) and (Table 1). The ^{1}HNMR spectrum of compound (3c; DMSO - d6) showed signals: at δ 1.92 (s, 3H, CH_3); 8.13 - 8.19 (s, H, NH); 2.51 (s, H, SH); 8.19 - 8.35 (s, 4H of Ar-H) (Figure 3) and (Table 1). The ^{1}HNMR spectrum of compound (4a; DMSO - d6) showed signals: at δ 3.22 (s, 3H, CH_3 of OCH_3ether); 8.40(s, H, NH); 2.52(s, H, SH); 7.26- 7.34 (s, 4H of Ar-H) (Figure 4) and (Table 1). Several studies have documented the characterization of pyrimidine derivatives using ^{1}H NMR spectrum analysis (More, 2018; Sayed and Abdelrehim, 2022).

Table 1. Characterization ^{1}H -NMR spectra of some prepared compounds (3a, 3b, 3c, 4a).

Compound No	δ H ,CH_3(ether) δ H, CH_2 at ppm	δ H, NH at ppm	δ H, SH thiol at ppm	δ H, H (aromatic) at ppm
3a	3.36 s for OCH_3 -	8.45 s -	2.52 s -	7.04- 8.85 d.d -
3b	- -	7.61 s -	2.52 s -	7.12 - 7.45 t -
3c	1.92 s -	8.13-8.19 s -	2.51 s -	8.19-8.35 q -
4a	3.22 s for OCH_3 -	8.40 s -	2.52 s -	7.26-7.34 m -

s =singlet, d= doublet, m= multiplet, d.d = double doublet.

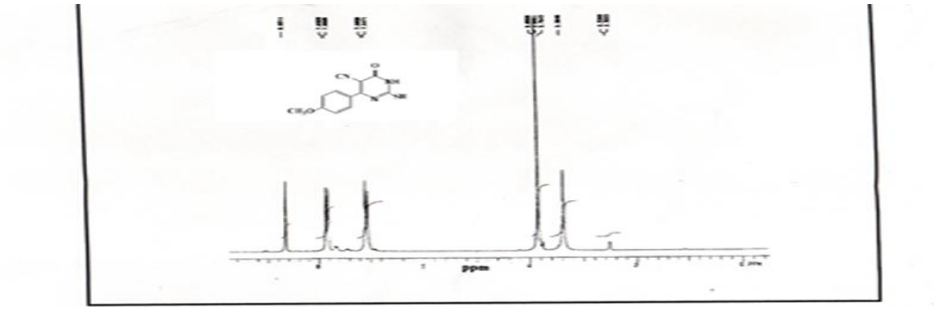


Fig. 1. ^{1}HNMR spectrum of compound (3a) in DMSO.

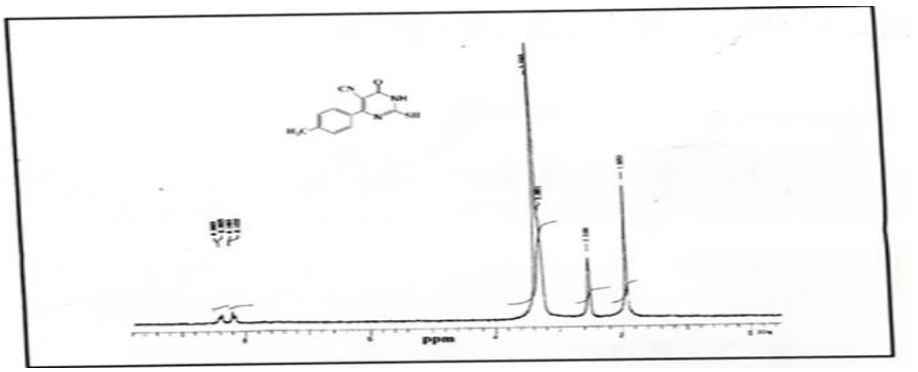


Fig.2. [1]HNMR spectrum of compound (3b) in DMSO DMSO.

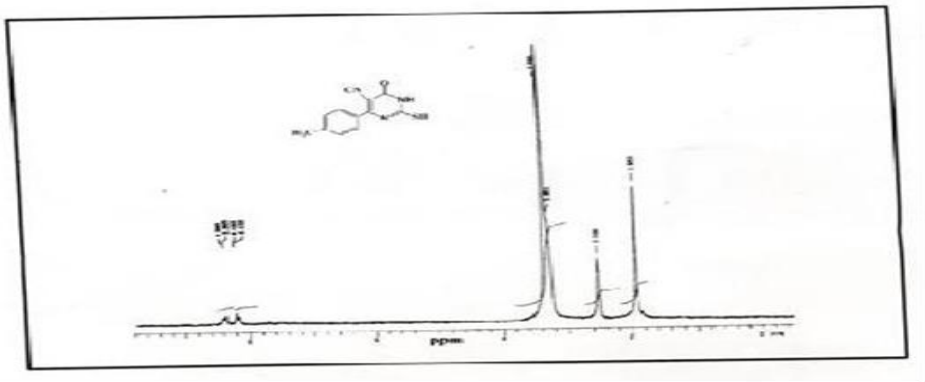


Fig.3. [1]HNMR spectrum of compound (3c) in DMSO.

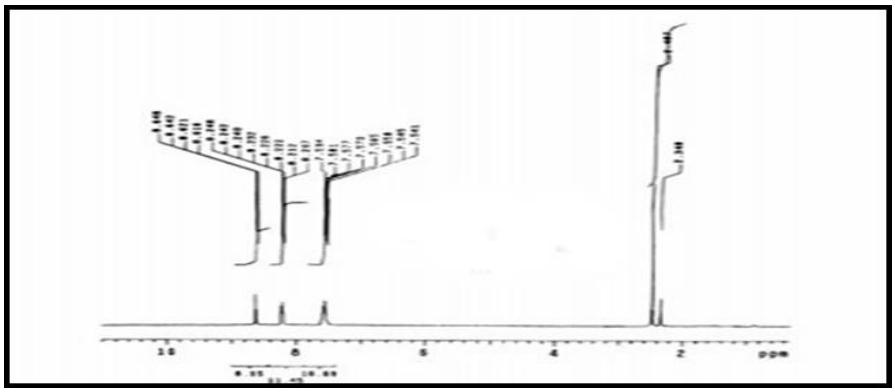


Fig. 4. [1]HNMR spectrum of compound (4a) in DMSO.

[1]H- NMR spectrums of Compounds (8b, 8c, 8e)

The [1]H NMR spectrum of compound (8b; DMSO - d6) showed signals: at δ1.13-1.20 (s, 3H, CH_3), δ 9.054 (s, 2H, NH_2); δ 7.1-7.52 (m, 4H of Ar-H) in figure (5) and (Table 2). The [1]H NMR spectrum of compound (8c; DMSO-d6) showed signals: at δ 1.303- 1.355 (t, 3H, CH_3), 4.318 – 4.347 (q, 2H, CH_2), 1.3 (s, 3H CH3), 2.50 (s, H, SCH_2); 9.009-9.013 (s, 2H, NH_2), 7.60-7. 56 (m, Ar-H) in figure (6) and (Table 2). The [1]H NMR

spectrum of compound (8e; DMSO - d6) showed signals: at δ 1.20 (t, 3H, CH_3), 4.318 – 4.347 (q, 2H, CH_2), 1.33 (s, 3H CH_3), 9.15 (s, 2H, NH_2), 7.562 - 7.872 (m, Ar-H) in figure (7) and (Table 2).

Table 2. Characterization ^{1}H -NMR spectra of some prepared compounds (8b, 8c, 8e).

Compound No	δ H ,CH_3(ether) δ H, CH_2 at ppm	δ H, $SHCH_2$ thiol at ppm	δ H, NH_2 at ppm	δ H, H (aromatic) at ppm
8b	1.13-1.20 s -	- -	9.054 -	7.1-7.52 m -
8c	1.303- 1.355 t 4.318 – 4.347 q	- 2.50 s	9.009-9.013 -	7.60- 7. 56 m -
8e	1.20 t 4.318 – 4.347 q	- -	9.150 -	7.562 - 7.872 -

s =singlet, d= doublet, m= multiplet, d.d = double doublet.

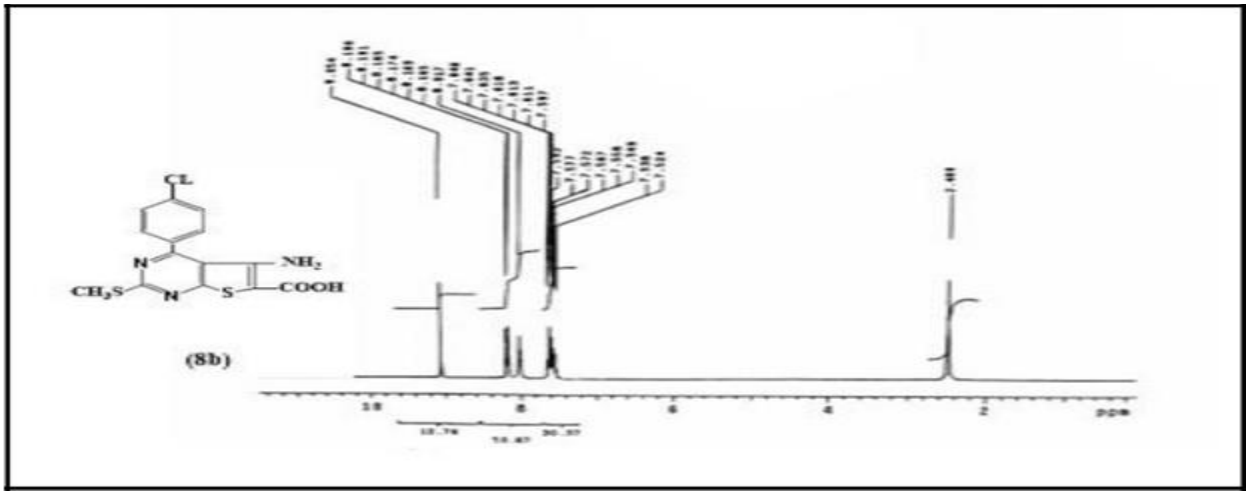


Fig.5. ^{1}HNMR spectrum of compound (8b) in DMSO.

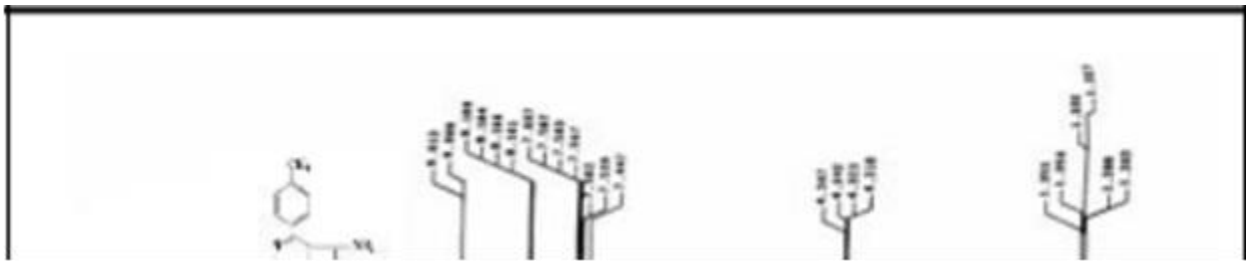


Fig.6. ^{1}HNMR spectrum of compound (8c) in DMSO.

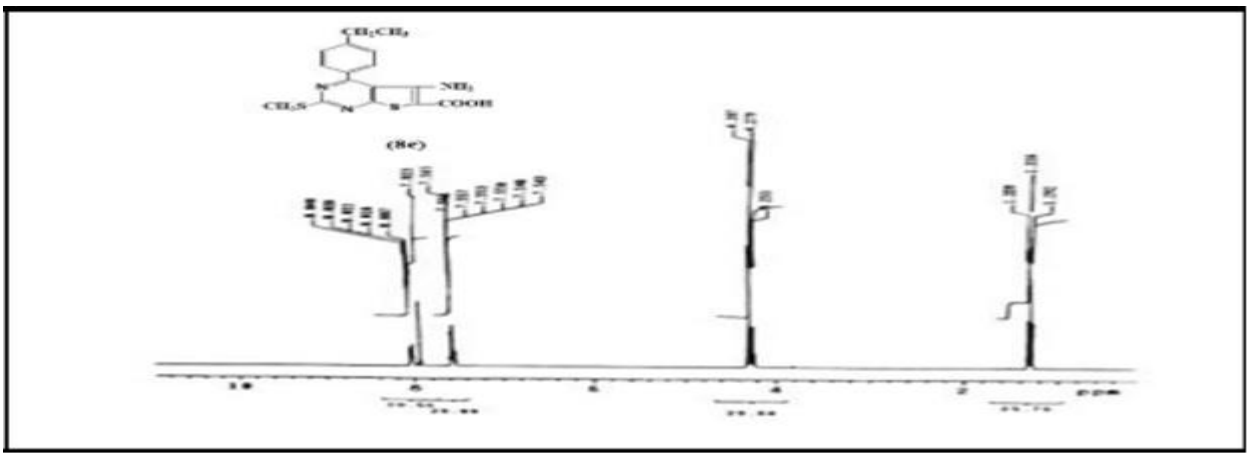


Fig.7. ^{1}HNMR spectrum of compound (8e) in DMSO.

Mass spectrum of some selected Compounds (3a, 3b)

The mass spectrum of compound (3a) showed m/z 259 (M+) as the molecular ion peak which is in agreement with its molecular formula $C_{12}H_9N_3SO_2$ and the base peak in 244 (100%) the other peaks at 258, 77, 51 (Table 3 and Figure 8). The mass spectrum of compound (3c) showed m/z 243 (M+) as the molecular ion peak which is in agreement with its molecular formula $C_{12}H_9N_3SO$ and the base peak is 210 (100%) the other peaks at 242, 74, 51 (Table 3 and Figure 9). Several studies have documented the characterization of pyrimidine derivatives using Mass spectrum analysis (Bhesaniya and Baluja, 2014; Sureja *et al.*, 2016).

Table 3. Characterization mass spectra of some selected compounds (3a, 3c).

Compound No	Fragment 1 M^+	Frag 2 M^+ -1	Frag 3 Base Peak	Frag 4	Frag 5
3a	259	258	244	77	51
3c	243	242	210	74	51

Fragment 1(M^+) = the molecular ion; Frag 4 and Frag 5= the other fragmentation; Frag 3 base peak = the fragmentation of high peak.

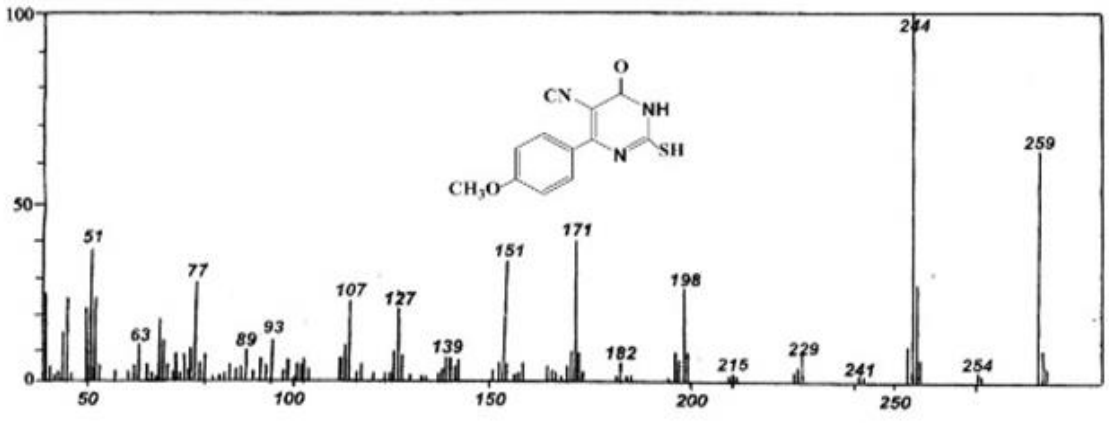


Fig. 8. Mass Spectrum of Compound (3a).

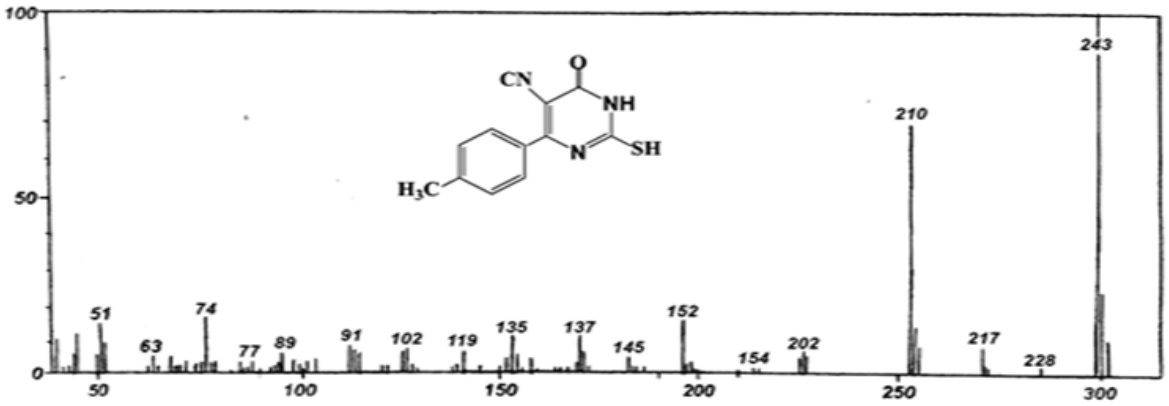


Fig. 9. Mass Spectrum of Compound (3b).

Mass spectrum of some selected Compounds (8a, 8d)

Mass spectrum of compound (8a) (Table 4) showed m/z437 (M+) the molecular ion peak which is in agreement with its molecular formula $C_{21}H_{15}N_3S_2O_4$ and the base peak in 77 (100%) the other peaks at 436, 105, 51 (Table 4 and Figure 10).

The mass spectrum of compound (8d) showed m/z 347 (M+) the molecular ion peak which is in agreement with its molecular formula and the base peak is 253 (100%) the other peaks at 346, 196, 77 (Table 4 and Figure 10).

Table 4. Characterization ^{1}H -NMR spectra of some prepared compounds (8a, 8d).

Compound No	Fragment 1 M^+	Frag 2 M^+ -1	Frag 3 Base Peak	Frag 4	Frag 5
8a	437	436	77	105	51
8d	347	346	253	196	77

Fragment 1(M^+) = the molecular ion; Frag 4 and Frag 5= the other fragmentation; Frag 3 base peak = the fragmentation of high peak.

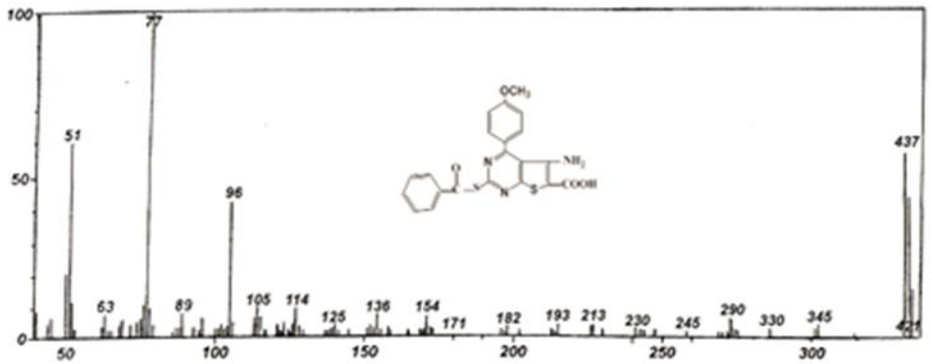


Fig. 10. Mass spectrum of compound (8a).

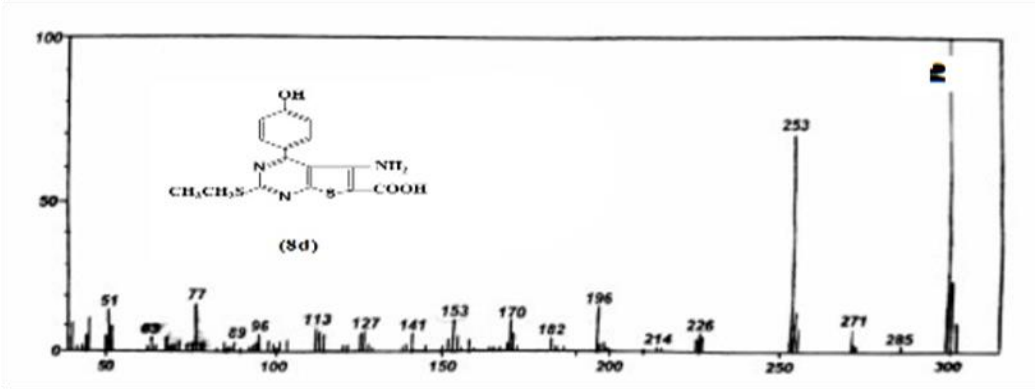
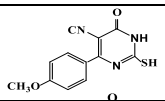
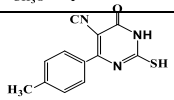
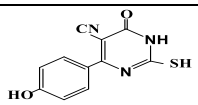
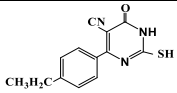
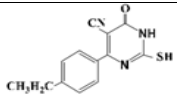


Fig. 11. Mass spectrum of compound (8d).

Antimicrobial activity

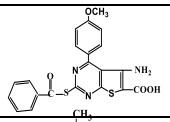
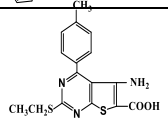
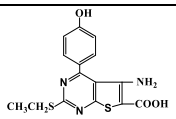
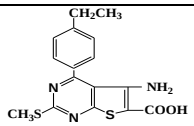
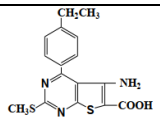
All the test compounds of (Tables 5 and 6) 3a, 3d, 8d have been strong activity against the two bacteria *Staphylococcus aureus, Escherichia coli* and the two fungi *Aspergillus flavus and Aspergillus niger* and the compounds (3b, 8a) moderately active for the types of fungi and bacteria but the compound (3c, 8c) showed slightly activity against the tested fungi and bacteria while the compound 8c showed strong activity against the *S. aureus*. The compounds (3b, 8b) were inactive for *A. niger* while the compound 8a was inactive for *A. flavus*. The biological activities of the synthesized compounds showed they play important roles in the biological systems, antimicrobial, and anti-fungal agents. Finding new and innovative antimicrobials is necessary since the development of resistance to various antimicrobial agents by microorganisms poses a serious threat to public health (Ashraf *et al.*, 2020; Iqbal *et al.*, 2019; Iqbal and Iqbal, 2020). The newly synthesized compounds could be employed as potential antibacterial agents (Kumar *et al.*, 2017; Sureja *et al.*, 2016).

Table 5. Effect of some new chemical compounds on the growth of bacteria and fungi (Zone of inhibition in mm) (3a, 3b, 3c, 3d, 3e).

Compounds	Structural formula	Antimicrobial activity against selected bacteria and fungi			
		S. aureus	*E. coli*	*A. flavus*	*A. niger*
3a		++	++	+++	+++
3b		++	+++	++	-
3c		+	+	+	+
3d		++	++	+++	+++
3e		++	++	+++	+++

Highly active = +++ (inhibition zone > 21.9 mm); Moderately active = ++ (inhibition zone 14.6- 21.9)l; Slightly active = + (inhibition zone 7.3- 14.6 mm); Inactive = - (inhibition zone < 7.3 mm).

Table 6. Effect of some new chemical compounds on the growth of bacteria and fungi (Zone of inhibition in mm) (8a, 8b, 8c, 8d, 8e).

Compounds	Structural formula	Antimicrobial activity against selected bacteria and fungi			
		S. aureus	***E. coli***	***A. flavus***	***A. niger***
8a		++	++	-	+
8b		++	+	+	-
8c		+++	+	+	+
8d		++	++	+++	+++
8e		+	+	+	+

Highly active = +++ (inhibition zone > 21.9 mm); Moderately active = ++ (inhibition zone 14.6- 21.9)l; Slightly active = + (inhibition zone 7.3- 14.6 mm); Inactive = - (inhibition zone < 7.3 mm).

CONCLUSION & RECOMMENDATION

The new synthesized pyrimidine derivatives were identified and characterized and the biological activities of the synthesized compounds were evaluated against some species of bacteria and fungi that show they play important roles in the biological systems, and have varied activities as antimicrobial agents or drugs, and anti-fungal agents, all the biological effects have many medical applications for the new derivatives of pyrimidine that are considered the base of nucleic acid.

Hetero cyclic compound chemistry required more concern and search as its derivatives had essential roles in the biological activities of the human body and important components in drugs such as antimicrobial, antifungal, analgesic, anti-malaria and aging disease dementia.

Pyrimidine derivatives are present in a large number of biologically important compounds as nucleic acids, alkaloids, antimicrobial agents, therefore the preparation of some highly substituted pyrimidine's maybe used in many medical applications for synthesis of some drugs which are considered the base of nucleic acids.

ACKNOWLEDGMENT

This work was supported by the Aden University Faculty of Sciences. The authors extend their thanks to the organic section for using their laboratory.

STATEMENT OF FUNDING

There are no sponsors for the research work carried out; rather whole work was funded by Dr. Khlood in Aden University Lab.

CONFLICT OF INTEREST

Authors hereby declare that they have no conflict of interest.

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