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DOI: 10.2478/auoc-2024-0005

Ovidius University Annals of Chemistry Volume 35, Number 1, pp. 36 - 42, 2024

Synthesis, spectral study and evaluation of antibacterial activity of some novel 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)pyrimidine-2(1*H*)-thiones

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Abstract. The objective of this study was to synthesize some novel substituted 4-(2-methoxynaphthalen-6-yl) pyrimidine-2(1*H*)-thione compounds using sodium hydroxide catalyzed three component condensation and cyclization reaction of substituted 6-methoxy-2-acetonapthone, various substituted benzaldehydes and thiourea. These thione derivatives were characterized by their analytical, physical, and spectroscopic data. In addition, the *in vitro* antibacterial activities of these pyrimidine derivatives were evaluated using Bauer-Kirby disc diffusion method.

***Keywords*:** pyrimidinethiones; acetonaphthones; thiourea; NMR spectra; antibacterial activity.

1. Introduction

Brugnatelli's oxidation of uric acid with nitric acid resulted in the isolation of the first pyrimidine derivative, alloxan (5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione). Because they are a fundamental component of all cells and consequently, of all living things, pyrimidines are one of the most significant heterocycles among all heterocyclic compounds and display exceptional pharmacological effects [1-5]. Two nitrogen atoms are included in the six-membered heterocyclic ring known as pyrimidine. At positions 1 and 3 of the six-membered ring, it has two nitrogen atoms [6]. Pyrimidinethiones were first studied in the nineteenth century. Although it might be claimed that thiol groups are a less well-known type of chemical modification, they also provide the object with more functionalization opportunities and the ability to influence the oxidative processes in the cell [7]. In earlier using multi-step synthesis, the derivative of 1-(1-biphenyl) pyrimidine-2(1*H*)-thione was synthesized and reported. Biginelli described first for the single-step synthesis of 3,4-dihydropyrimidin-2(1H)-one utilizing the three-component condensation of aldehydes, ethyl acetoacetate, and urea in alcohol. These items, often referred to as Biginelli compounds, have a variety of medicinal effects, including antibacterial, antiviral, anti-inflammatory, antihypertensive, and antitumor agents [8-15]. At present, various synthetic methods and biological properties of pyrimidine derivatives are reported including the condensed pyrimidine analogues with an exocyclic sulfur atom in the 2nd position of pyrimidine ring [16-18]. In practice, pyrimidinethiones are converted into pyrimidiones by S-alkylation, subsequent hydrolysis, and oxidation to a sulfinic or sulfonic acid with subsequent hydrolysis [19, 20]. The novel pyrimidinethiones molecules were created by base catalyzed reaction of 2-pyrimidinethiones and benzyl halides or 2-(chloromethyl)-1H-benzimidazole. The first 2-pyrimidinethiones were created by a stereochemical reaction involving ethyl acetoacetate, thiourea, and *p*-alkyl benzaldehydes with acidic catalyst under conventional heating in ethanol medium [20-25]. Pyrimidine has a long history of usage as a treatment for pain-related thrombotic disease, stomach and gastric cancer, parasite infections, and as an intermediary in the creation of several pharmaceutical substances. These compounds have received substantial research owed to their well-known synthetic value in the creation of pyrimidinethiones as well as their biological actions, which include analgesics [26] anti-inflammatory [26], antimitotic [27], antituberculoid [28], antifungal [28], antimalarial [28], antiprotozoal [28], antioxidant [29], antitumor [29] and anticancer qualities [30]. Recently, a simple approach for the production of a novel class of spiro-thiolane hybrids based on 2-iminothiazolidin-4-one, 2-thioxothiazolidin-4-one (rhodamine) and thiazolidine-2,4-dione were reported. The adducts from Knoevenagel reaction of 2-thioxothiazolidin-4-one, thiazolidine-2,4-dione, 2-iminothiazolidin-4-ones, and mercapto acetaldehyde were reacted at room temperature with DABCO (1,4-diazabicyclo[2.2.2]octane) (20 mol%) to produce the compounds. The reaction occurs through 1,4-sulfa-Michael and then forms spiro-thiolane by an intramolecular aldol reaction [31]. Following up on a previous work on heterocyclic chemistry, synthetic organic chemists and scientists synthesized a variety of pyrimidinethione derivatives and assessed their antibacterial qualities in light of these findings. In chemical synthesis, substituted arylpyrimidine-2(1H)-thiones are important precursors

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for pharmaceutical compounds. Aldol condensation of carbonyl condensation cum cyclisation with thiourea processes have been used to synthesize therapeutically active substituted aryl pyrimidine-2(1H)-thione derivatives [32, 33]. Aside from substituted aryl pyrimidine-2(1H)-thione's biological relevance, numerous of its scaffolds were created as chemotherapeutic drugs and have found broad clinical application [32-34] including threptic and chemotherapic relevance's [34, 35]. According to literature survey, there is no report availed for the synthesis and evaluation of biological activities of 6-methoxy-2-naphthyl based pyrimidine thiones in earlier and present. Hence, the authors have taken the effort to synthesize some new 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl) pyrimidine-2(1*H*)-thione derivatives employing one pot three component condensation cum cyclization method, established their structures by spectroscopic technique and evaluation of their biological activity.

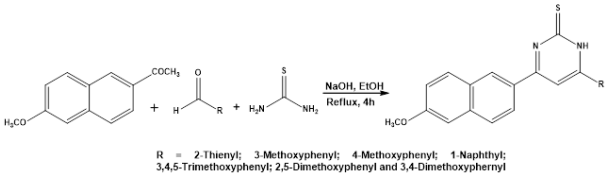
2. Experimental

2.1. Materials and methods

The chemicals and solvents utilized in this work were precured from Sigma-Aldrich and Merck chemical companies. Melting points of all 4-(6-methoxynaphthalen-2-yl) -6-(substituted aryl) pyrimidine-2(1*H*)-thione derivatives were determined on Mettler FP51 melting point apparatus in open glass capillaries. The Shimadzu-2010 Fourier transform spectrophotometer has captured IR spectra (KBr, 4000-400 cm^{-1}). The NMR spectra were recorded using a Bruker 400 spectrometer running at 400 MHz for ^{1}H-NMR spectra and 100 MHz for ^{13}C-NMR spectra in a $CDCl_3$ solvent using TMS as an internal standard.

2.2. General procedure for synthesizing 4-(6-methoxynaphthalen-2-yl) -6-(substituted aryl)pyrimidine-2-(1H)-thione compounds by crossed-aldol condensation cum cyclization reaction

Equimolar concentrations of 6-methoxy-2-acetonapthone (1 mmol) and several aryl aldehydes (1 mmol), thiourea (1 mmol), 20 mL of ethanol and sodium hydroxide (1 N, 0.5 mL) were taken in a 50 mL round-bottom flask. The reaction mixture was refluxed on a water bath for 4 h to produce 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl) pyrimidine-2(1*H*)-thiones (Scheme 1), while TLC was adopted continuously monitored to ensure that the reaction had fully completed.



Scheme 1. Synthesis of 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)pyrimidine-2-(1*H*)-thiones.

After the reaction was feasible, the 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl) pyrimidine-2(1*H*)-thiones were poured into crushed ice. It was then filtered, cleaned with water, dried in an air oven, and recrystallized from ethanol to produce a yellow solid.

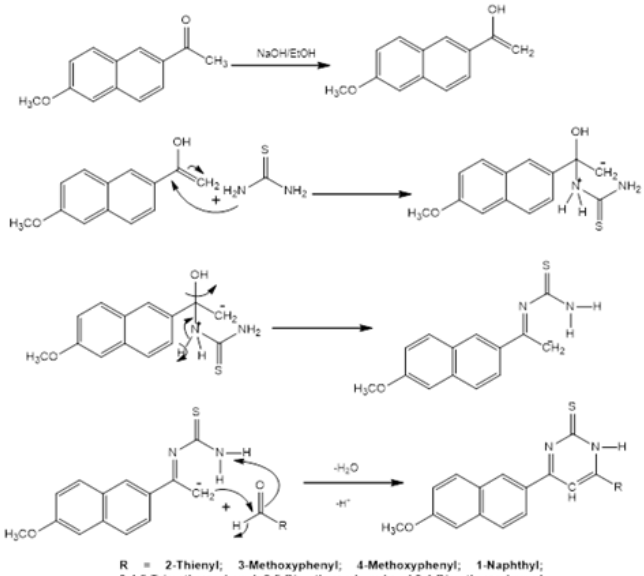
2.3. Measurement of antibacterial activity

The standard procedure of Bauer-Kirby [35] disc diffusion method was used to carry out the antibacterial sensitivity test. Using a sterile glass spreader, 0.5 mL of the bacterial test sample was evenly distributed over solidified Mueller-Hinton agar on Petri plates individually. The possible inhibitor solution was then applied to 5 mm Whatman No. 1 filter paper discs, which were then positioned on the filter paper by sterile forceps. For a full day at 37 ºC, plates were incubated upside down to prevent the accumulation of water droplets.

After a day, the plates were examined and the zone of inhibition span values was evaluated [35-41]. The synthesized pyrimidinethiones were mixed with dimethyl sulfoxide (DMSO) separately at a concentration of 1 mg/mL for the antibacterial assay. The antibacterial actions of eight synthesized 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1*H*)-thiones were investigated using the Kirby-Bauer technique against two gram-positive pathogenic strains *Bacillus subtilis*, *Staphylococcus aureus* and two gram-negative strains *Escherichia coli* and *Pseudomonas aeruginosa*. The standard was Ampicillin.

3. Results and discussion

In our research laboratory, authors attempt to synthesize some higher 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1*H*)-thiones by sodium hydroxide catalyzed single step one pot three constituents' condensation cum cyclization of 6-methoxy-2-acetonaphthone, aryl aldehydes under reflux condition.



Scheme 2. The proposed mechanism of 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)pyrimidine-2-(1*H*)-thione derivatives synthesis.

All reactions gave greater than 80% yields. The electron donating group in the aldehydes gave better

yields than other aldehydes. This reaction consists of addition of thiourea to the ketone then cyclization with aldehydes. A feasible reaction mechanistic pathway of this condensation cum cyclization was illustrated in Scheme 2. The microanalysis, physical constants, and yields of the 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)pyrimidine-2-(1*H*)-thione were performed, as given in Table 1.

Table 1. Physical constants, yield, analytical and microanalysis of 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)pyrimidine-2-(1*H*)-thione compounds.

Cpd.	M. F.	M. W.	Yield (%)	M. P. (ºC)	Micro analysis (%) (Calcd.)		
					C	H	N
1	$C_{19}H_{14}N_2OS_2$	350	89	75-76	65.18 (65.12)	4.09 (4.03)	7.93 (7.99)
2	$C_{22}H_{18}N_2O_2S$	374	84	78-79	70.62 (70.57)	4.79 (4.85)	7.40 (7.48)
3	$C_{22}H_{18}N_2O_2S$	374	94	78-79	65.18 (65.12)	4.09 (4.03)	7.93 (7.99)
4	$C_{25}H_{18}N_2OS$	394	94	83-84	65.20 (65.12)	3.98 (4.03)	7.96 (7.99)
5	$C_{29}H_{20}N_2OS$	445	87	107-108	78.28 (78.35)	4.48 (4.53)	6.28 (6.30)
6	$C_{24}H_{22}N_2O_4S$	435	90	103-104	66.40 (66.34)	5.06 (5.10)	6.38 (6.45)
7	$C_{23}H_{20}N_2O_3S$	404	88	98-99	68.37 (68.30)	4.92 (4.98)	6.98 (6.93)
8	$C_{23}H_{20}N_2O_3S$	404	92	98-7-98	68.32 (68.30)	4.94 (4.98)	6.95 (6.93)

The complete spectroscopic data of the synthesized 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)pyrimidine-2-(1*H*)-thione derivatives are given below.

4-(6-methoxynaphthalen-2-yl)-6-(thiophen-2-yl)pyrimidine-2-(1*H*)-thione (1): FT-IR (KBr, cm^{-1}): ῡ =1620.21 (C=C), 1672.28 (C=N), 2968.45 (C-H), 3652 (N-H), 1018.41 (C=S). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (s,1H, -NH), 5.26 (s,1H, -CH, Py ring), 7.65-7.93 (m, 6H, Ar-H). ^{13}CNMR (100MHz, $CDCl_3$) δ = 159.77 (C=N),197.90 (C=S), 55.43 (OCH_3), 120.81, 125.16, 127.15, 128.63, 132.63, 137.34 (Ar-C). Mass (m/z): 351[M^+]; Calcd.: 350.

4-(6-methoxynaphthalen-2-yl)-6-(3-methoxyphenyl)pyrimidine-2-(1*H*)-thione (2): FT-IR (KBr, cm^{-1}): ῡ = 1620.22 (C=C), 1672.20 (C=N), 2964.59 (C-H), 3649.12 (N-H), 1018.40 (C=S). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (s, 1H, -NH), 5.29 (s, 1H, -CH Py-ring), 7.66-7.92 (m, 10H, Ar-H). ^{13}CNMR (100 MHz, $CDCl_3$) δ = 159.96 (C=N), 197.94 (C=S), 55.33 (OCH_3), 119.73, 124.30, 124.67, 127.83, 128.07, 128.63, 129.84, 132.63, 136.76, 137.34 (Ar-C). Mass (m/z): 375[M^+]; Calcd.: 374.

4-(6-methoxynaphthalen-2-yl)-6-(4-methoxyphenyl)pyrimidine-2-(1*H*)-thione (3): FT-IR (KBr, cm^{-1}): ῡ = 1620.21 (C=C), 1672.28 (C=N), 2931.80 (C-H), 3650.16 (N-H), 1020.34 (C=S).^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59 (s,1H,-NH), 5.23 (s, 1H, -CH Py ring),7.86-8.08(m, 10H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.84 (C=N), 197.93 (C=S), 55.89 (OCH_3), 119.95, 124.68, 127.46, 127.92, 130.70, 131.19, 131.68, 132.65, 135.3, 137.36 (Ar-C). Mass(m/z): 375[M^+]; Calcd.: 374.

4-(6-methoxynaphthalen-2-yl)-6-(naphthalene-1-yl)pyrimidine-2(1*H*)-thione (4): FT-IR (KBr, cm^{-1}): ῡ= 1620.21 (C=C), 1672.28 (C=N), 2966.52 (C-H), 3652.32 (N-H), 1018.41 (C=S).^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58 (s, 1H, -NH), 5.28 (s, 1H, -CH Py ring), 7.87-8.04 (m, 10H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.84 (C=N), 197.92 (C=S), 55.88(OCH_3), 119.94, 124.68, 125.9, 126.17, 127.46, 127.92, 130.69, 131.68, 132.65, 137.36 (Ar-C). Mass(m/z): 393.8[M^+]; Calcd.: 394.

4-(6-methoxynaphthalen-2-yl)-6-(anthracen-10-yl)pyrimidine-2(1*H*)-thione (5): FT-IR (KBr, cm^{-1}): ῡ = 1598.99 (C=C), 1672.28 (C=N), 2937.59 (C-H), 3651.23 (N-H), 1018.41 (C=S). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.29 (s, 1H, -NH), 5.39 (s, 1H, -CH Py ring), 7.65-7.92 (m, 10H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.77 (C=N), 197.94 (C=S), 55.42 (OCH_3), 119.73, 124.66, 125.9, 127.10, 127.82, 130.08, 131.13, 132.61 133.6, 137.30 (Ar-C). Mass(m/z): 445[M^+]; Calcd.: 445.

4-(6-methoxynaphthalen-2-yl)-6-(3,4,5-trimethoxyphenyl)pyrimidine-2(1*H*)-thione (6): FT-IR (KBr, cm^{-1}): ῡ = 1622.13 (C=C), 1674.21 (C=N), 2968.45 (C-H), 3651.35 (N-H), 1020.34 (C=S).^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (s, 1H, -NH), 5.31 (s, 1H, -CH Py ring), 7.69-7.95 (m, 10H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.06 (C=N), 197.94 (C=S), 57.82(OCH_3), 119.22, 124.67, 126.31, 127.32, 127.82, 128.5, 129.17, 132.36, 134.11, 137.30 (Ar-C). Mass(m/z): 436[M^+]; Calcd.: 435.

4-(6-methoxynaphthalen-2-yl)-6-(2,5-dimethoxyphenyl)pyrimidine-2(1*H*)-thione (7): FT-IR (KBr, cm^{-1}): ῡ = 1616.35 (C=C), 1670.35 (C=N), 2968.45 (C-H), 3652.07 (N-H), 1018.41 (C=S).^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (s, 1H, -NH), 5.27 (s, 1H, -CH Py ring), 7.68-7.94 (m, 10H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.78 (C=N), 197.90 (C=S), 55.44 (OCH_3), 119.74, 124.68, 127.10, 127.93, 130.08, 131.13.132.64, 137.30 (Ar-C). Mass(m/z): 405[M^+]; Calcd: 404.

4-(6-methoxynaphthalen-2-yl)-6-(3,4,-dimethoxyphenyl)pyrimidine-2(1*H*)-thione (8): FT-IR (KBr, cm^{-1}): ῡ = 1616.35 (C=C), 1670.35 (C=N), 2968.45 (C-H), 3651.43 (N-H), 1018.41 (C=S).^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (s, 1H, -NH), 5.28 (s, 1H, -CH Py ring), 7.66-7.93 (m, 10H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.78 (C=N), 197.89 (C=S), 55.48 (OCH_3), 119.73, 124.67, 127.10, 127.83, 130.06, 131.12, 132.64, 137.30(Ar-C). Mass(m/z): 404.5[M^+]; Calcd: 404.

These data are strongly supported for the obtaining of 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1*H*)-thiones.

3.1. Antibacterial activity

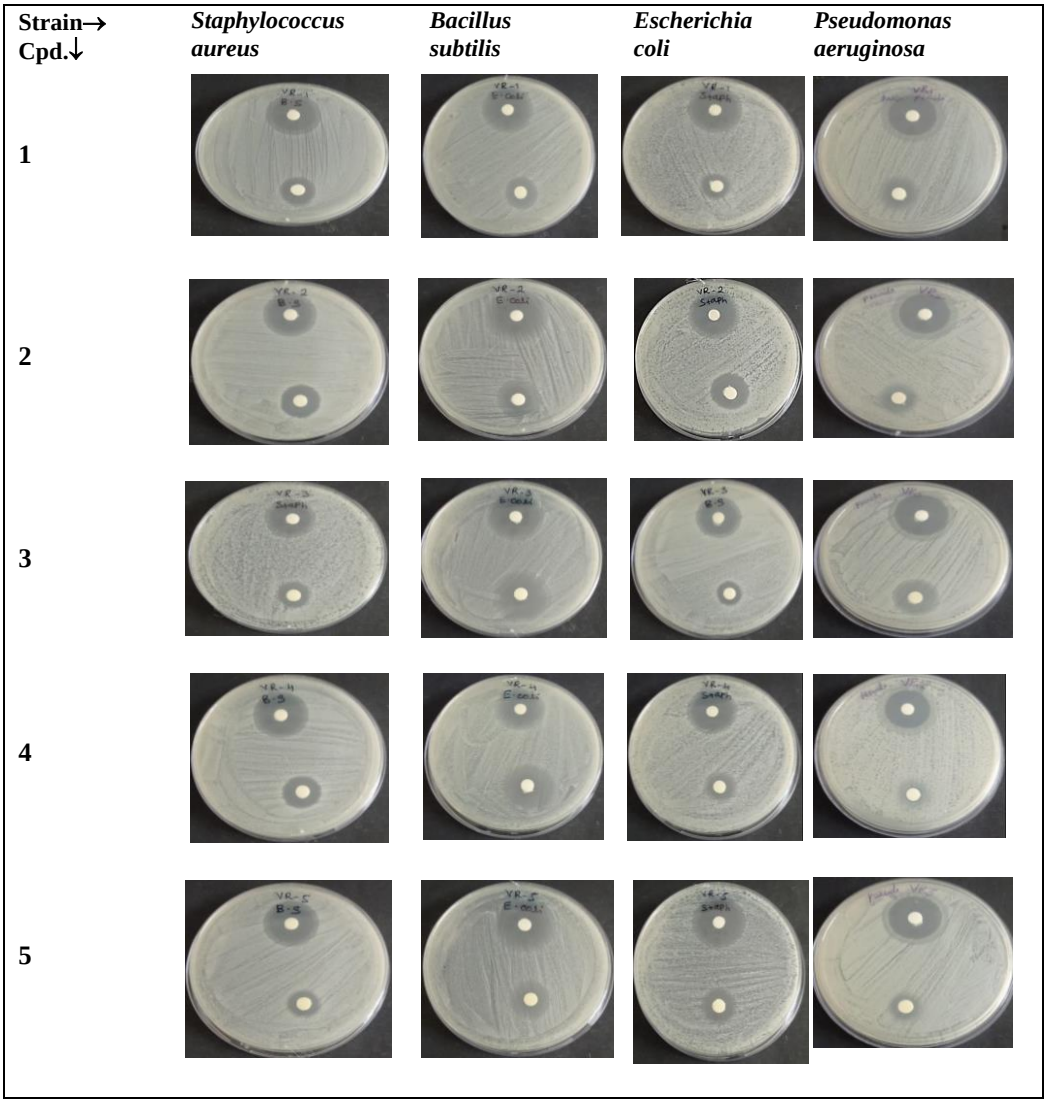
The measured values of inhibition zone (mm) for the antibacterial actions of synthesized 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1*H*)-thione compounds were displayed in Table 2. The width of the inhibition zone of all

compounds against their microbes was illustrated in Figure 1. The statistical relative antibacterial actions of all pyrimidinethiones were illustrated in Figure 2.

According to Table 2, the majority of the 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1*H*)-thione compounds have demonstrated moderate, good, and satisfactory antibacterial activity. Pyrimidinethione compound (**1**) shows moderate antibacterial activity against all strains except *S. aures*. Good antibacterial action has been shown by the 4-(6-methoxynaphthalen-2-yl)-6-(3-methoxyphenyl) pyrimidine-2(1*H*)-thione compound (**2**) against all pathogens except *P. aeruginosa* microbes. The pyrimidinethione compound (**3**) exhibits good antibacterial activity against *E. coli* and *P. aeruginosa* strains. The antibacterial activity was low with other strains. The pyrimidinethione compound (**4**) exhibits good anti-bacterial activity against *B. subtilis* and *E. coli* strains. Pyrimidinethione compound (**5)** possessing the anthracene moiety shows moderate and less fair anti-bacterial activity against all strains. Pyrimidinethione compound (**6**) containing trimethoxy phenyl group shows good antibacterial action against *E. coli* and *P. aeruginosa* strains. Pyrimidinethione compound (**7**) shows good antibacterial activity against *B. subtilis* and *P. aeruginosa* strains. Pyrimidinethione compound (**8**) shows moderate antibacterial activity except *P. aeruginosa* strain. Here the electron donating -I effect of methoxy groups enhances the anti-bacterial activity than other aryl groups such as thienyl, naphthyl and anthryl.

Table 2. The zone of inhibition (mm) values of antibacterial activity of 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1*H*)-thiones.

Pathogens	**Diameter of zone of inhibition (mm)**							
	Concentration of compound (40 µg)							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Staphylococcus aureus	13	20	14	13	15	10	14	13
Bacillus subtilis	15	17	11	16	13	13	16	14
Escherichia coli	15	19	22	22	15	16	15	15
Pseudomonas aeruginosa	15	14	19	11	12	16	20	11
Ampicillin (standard)	26	24	24	24	23	22	22	23



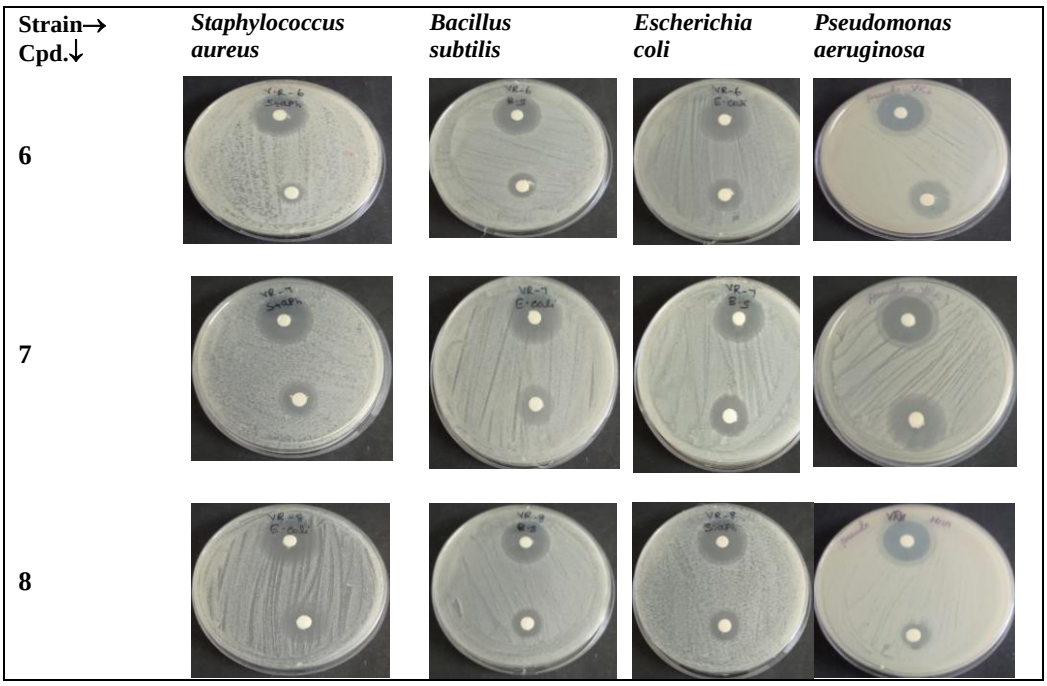


Figure 1. Anti-bacterial activity of 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1H)-thiones.

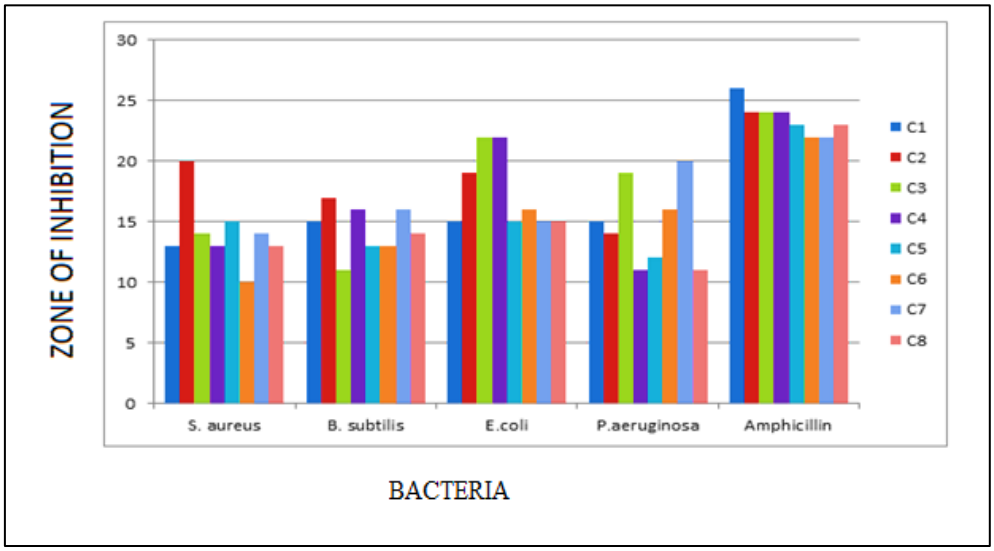


Figure 2. Antibacterial activity of 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1H)-thiones.

4. Conclusions

Herein, the authors developed an effective single pot three component synthesis of some novel 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl)-pyrimidine-2(1*H*)-thiones by condensation and cyclization of 6-methoxy-2-acetonapthone, several substituted arylaldehydes and thiourea with good yields. The prepared compounds were characterized by elemental analysis, mass, FT-IR and NMR spectral data. The antibacterial properties of the thiones were investigated using Kirby-Bauer method. All of the 4-(6-methoxynaphthalen-2-yl)-6-(substituted aryl) pyrimidine-2(1*H*)-thione derivatives were active against their antibacterial strains. All pyrimidinethiones showed good, moderate and satisfactory antibacterial activities owing to the -I effects of methoxy substituents in the aldehyde moieties.

Conflict of interest

Authors have no conflict of interest to declare.

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Received: 04.08.2023
Received in revised form: 02.04.2024
Accepted: 20.04.2024