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Synthesis of some new aryl sulfonyl derivatives and study of their biological activity

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This work focuses on the synthesis of some N-aryl sulfonyl derivatives (H_1-H_9) through the reaction of benzene sulfonyl chloride or P-toluene sulfonyl chloride with aromatic amines containing a pyrimidine ring in their structures (I-VI) in the presence of pyridine as catalyst at room temperature. The spectral data of infrared and nuclear magnetic resonance besides the C, H, N, and S analyses confirmed the validity of the synthesized derivatives. Likewise, the biological activity of the prepared derivatives (H_1 - H_9) was estimated, including antitumor and antibacterial activity. These activities were determined *in vitro* using the cytotoxicity assay (MTT cell viability assay) in MCF7 cells to detect the anticancer activity and Kirby-Bauer disc diffusion method used for antibiotic sensitivity test against different pathogenic strains of bacteria. In this study, the **MCF-7** cell line was used to assay the anti-proliferative activity of compounds (H_1-H_9), compound H_4 was the most potent in this group with **IC_{50}** value of 8.66 µg/mL and compound H_8 was the lowest in potency with **IC_{50}** value of 52.29 µg/mL. In addition, the synthesized compounds have been screened for antibacterial against six multidrug resistant Gram-positive and Gram-negative bacteria and the results showed effectiveness against tested bacteria.

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KEYWORDS

Oxopyrimidine; thiopyrimidine; chalcone; benzene sulfonyl chloride; antitumor; antibacterial; MCF-7 cells; IC_{50}.

Introduction

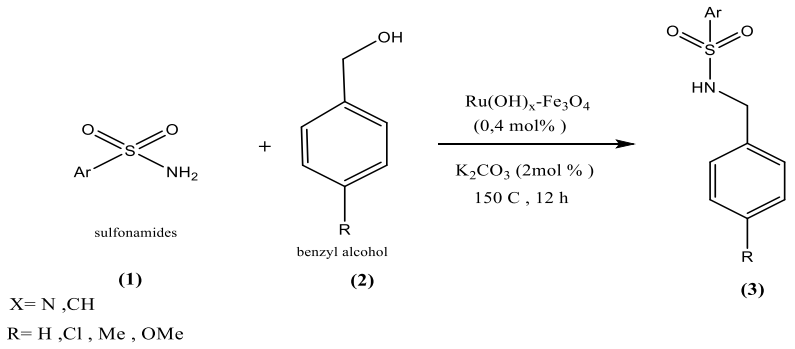
The term "heterocyclic compounds" refers to cyclic organic compounds that contain at least one heteroatom. The most frequent heteroatoms are nitrogen, oxygen, and sulfur though heterocyclic rings with other hetero atoms are also well-known. A carbocyclic compound is an organic compound with rings made entirely of carbon atoms [1]. More than half of all known organic compounds are heterocycles, which are an incredibly significant and distinctive family of compounds with a wide range of physical, chemical, and biological properties spanning a broad spectrum of reactivity and stability [2]. Because their structural subunits are present in a variety of natural products, such as vitamins, hormones, antibiotics, and alkaloids, as well as in pharmaceuticals, agrochemicals, dyes, and many other substances, heterocycles are widely distributed in nature and play a significant role in metabolism [3]. Many synthetic heterocyclic compounds with significant physiological and pharmacological effects are also known in addition to naturally occurring molecules [4]. In a huge variety of pharmacological and commercial uses, heterocyclic derivatives a significant group of organic compounds are used. They are renowned for their biological and pharmacological qualities, which include anti-inflammatory, antibacterial, anticancer, antitumor, and antiviral activity [5]. The majority of heterocycles have significant uses in materials science, such as analytical

reagents, fluorescence sensors, brightening agents, information storage, and dyes. They also have uses in polymer and supramolecular chemistry, particularly with conjugated polymers. Besides, they work as liquid crystalline compounds, organic conductors, semiconductors, molecular wires, photovoltaic cells, organic light-emitting diodes (OLEDs), light harvesting devices, optical data carriers, and chemically programmable switches. Due to their synthetic value as organic catalysts, protecting groups, chiral auxiliaries, synthetic intermediates, and metal ligands in asymmetric catalysts in organic synthesis, heterocycles are also of great interest. Therefore, there has been a lot of focus on creating new, effective ways to create heterocycles [6]. In addition to be widely presented in both natural and synthetic chemicals, heterocyclic systems are used as building blocks in the synthesis of organic compounds. A heterocyclic fragment is presented in the structures of more than 90% of novel medicines [7]. Early studies of chemistry made extensive use of nitrogen-containing heterocyclic

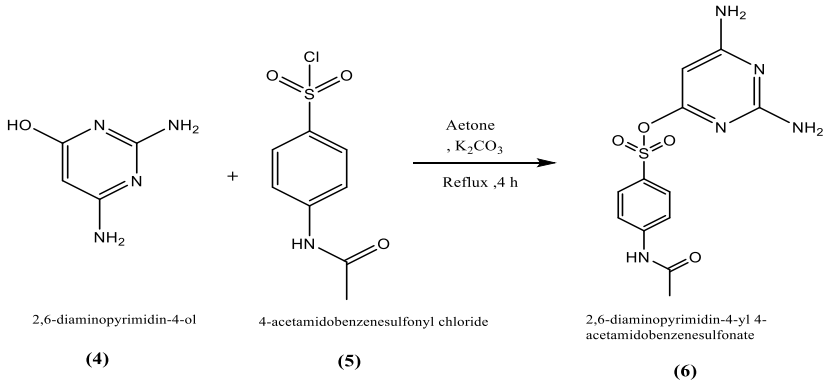
compounds and these compounds were closely related to the development of organic chemistry which dealt with the study of materials isolated from living sources, while inorganic chemistry dealt with the study of inanimate materials [8]. Nitrogen-containing heterocyclic compounds can be found in pharmaceuticals, dyes and high-performance materials [9]. The bridge-head nitrogens in pyridines, fused pyridines and other heterocyclic scaffolds are significant components found in a variety of biologically active compounds and natural products [10]. There is a demand for novel, effective, and general methods for the synthesis of these families of compounds due to their wide-ranging and emerging uses [11].

The chemistry of amines, amides, and other nitrogen-containing substances is crucial to the process of creating organic molecules. Urine was actually the first organic substance to be produced [12].The significance of this type of nitrogen-containing molecule stems from a number of elements. The first is that various nitrogen derivatives, including amino acids and nucleotides have been selected by nature as their characteristic building blocks for the creation of life [13].This category should also contain other significant minor compounds, such as neurotransmitters, naturally occurring toxins, alkaloids, and other active biomolecules, in addition to the main components of nature [14]. An essential step in organic synthesis is the N-alkylation of aniline derivatives which is frequently used to make dyes, fluorescent probes, agrochemicals and medicines [15]. The difficulty with this reaction is getting good selectivity for mono- or dialkylation products while avoiding the production of matching quaternary ammonium salts from N, N-dialkylaryl amines. A wide range of techniques have been examined for the synthesis of substituted amines [16,17]. There still have certain issues, namely the employment of hazardous chemicals [18] and the management of the selectivity of mono and dialkylation-aniline derivatives [19]. An attempt to solve these issues, numerous homogeneous phase reports on noble metal complexes and salts using alcohols as alkylating agents and Ru [20], Ir [21,22], Pt [23], Au [24,25] and Pd [26,27] as catalysts have been published. Development of methods for preparing amines is of great importance due to the wide spread of amine cracks inside natural products, medicines and fine chemicals [28].

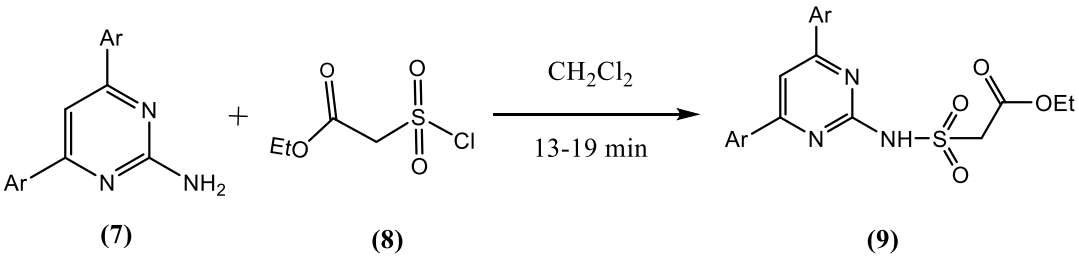
Gabriela Guillena *et al.* has synthesized (3) from the alkylation of sulfonamides (1), the reaction using an excess of benzyl alcohol (2), substoichiometric amounts of Ru(OH)x-Fe_3O_4, and K_2CO_3 at 150 °C without solvent [29].



Preparation of 2,6-diaminopyrimidin-4-yl 4-acetamidobenzenesulfonate (6) from the reaction of 4-acetamidobenzenesulfonyl chloride (5) with 2,6-diaminopyrimidin-4-ol (4) in acetone [30].



[31] reported the synthesis of 4,6 - diaryl- 2 - ethylacetate sulfony amino pyrimidine (9) from the reaction of 4,6 - diaryl- 2 - amino pyrimidine (7) and ethyl acetate sulfony chloride (8) in the presence of methylene chloride.



Ar =4-Me.Ph , 4-Cl.Ph

Materials and methods

Chemistry

General Information

Uncorrected melting points were determined using Hot -stage, Gallen Kamp melting point apparatus. They are measured in the Department of Chemistry, College of Science, University of Misan, Iraq. FTIR spectra were recorded using potassium bromide discs on a 8400s Shimadzu spectrophotometer and FTIR spectrophotometer, Shimadzo (IR prestige-21).These spectra are achieved in Medicine College, Misan University, Iraq. ^{1}H-NMR and ^{13}C-NMR spectra were carried out

by: Bruker, model: Ultra shield 300 MHz, origin: Switzerland and are reported in ppm (δ). DMSO was used as a solvent with TMS as an internal standard were made at Chemistry Department, Al-Basra University, Iraq. Elemental analysis was performed at the Micro Analytical at Cairo University by Euro Vector 3000 A Elemental Analysis (Italy). Thin layer chromatography (TLC) is performed using TLC grade silica gel 'G' (Acme Synthetic Chemicals). The spots are made visible by exposing plates to UV, and eluted with petroleum ether: ethyl acetate 3:2 mixtures unless otherwise stated.

Preparation of 4[6- (4-substituted phenyl) -2 – oxo or thioxo-1, 2,-dihydropyrimidine- 4-yl] aniline (I-VII)

A mixture of 4-aminoacetophenone (2 mol), 4-substituted benzaldehyde (chloro, bromo, and nitro) (2 mol), and urea or thiourea (3 mol), were added in a mortar. The mixture was blended together, and then shifted into a round flask and mix it with NaOH 50ml (0.20 g in 50%ml water). The mixture was heated about 70 °C under atmospheric conditions, and the reaction could be finished within 3-4 hours. The reaction mixture was poured into water, filtered, dried, and recrystallized from ethanol.

Preparation of N-(4-(6-(4-substituted phenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-4-methyl-N-tosylbenzenesulfonamide (H_1-H_3)

A mixture of (I), (II), or (III) (0.01 mol) and 4-toluene sulfonyl chloride (0.01 mol) in pyridine (20 mL) was refluxed on water bath for 3 hrs. and T.L.C was monitored to check the completion of reaction. After completion of reaction, the reaction mixture was cooled to room temperature, and then poured into ice cold water. The obtained precipitate was filtered, washed with water, and dried. The product was recrystallized from ethanol.

Preparation of N-(4-(6-(4-substituted phenyl)-2-thioxo or oxo-1,2-dihydropyrimidin-4-yl)phenyl)-N-(phenylsulfonyl)benzenesulfonamide (H_4-H_9)

A mixture of (I , II , III , IV , V, or VI) (0.01 mol) and benzene sulfonyl chloride (0.01 mol) in pyridine (20 mL) was refluxed on water bath for 3 hrs. until the T.L.C showed no further reaction. After completion of reaction, the reaction mixture was cooled to room temperature, and then poured into ice cold water. The precipitate obtained was filtered, washed with water, and dried. The product was recrystallized from ethanol.

Biological part

Bacterial isolates

The bacteriological unit at Al-Saddar Teaching Hospital in Maysan, Iraq provided all of the isolates, which were subsequently re-identified [32] in the bacteriological laboratory at the Pharmacy College at Maysan University. Following identification, one collection was placed in a test tube with 5 ml of nutritional broth and cultured for 24 hours at 37 °C. To acquire pure and isolated collections from each bacterium for the sensitivity test, the tested bacteria were strict on blood or chocolate agar and likewise incubated at 37 °C for 24 hours.

Preparation of bacterial suspension

The cell density of the bacteria suspension, which was made by taking [33]-[35] isolated collections from each microbe and transferring them to a test tube with 5 ml of normal saline after shaking, was 1.5 x 108 cells per milliliter.

Antibiotic sensitivity test

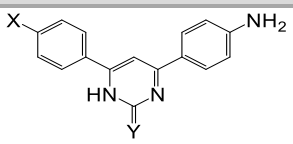
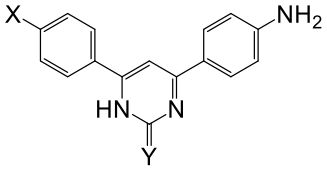
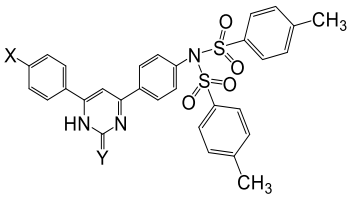
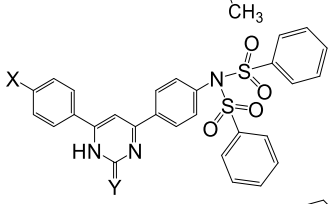
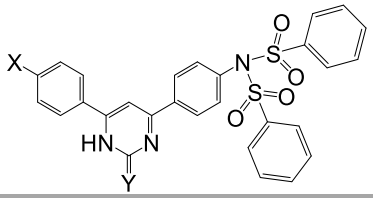
Antibiotic sensitivity testing is done using the Kirby-Bauer disc diffusion method [35]. After evenly swabbing a Muller-Hinton agar plate

with a sterile cotton swab dipped in bacterial solution, the plates were incubated at 37 °C for 30 minutes. The antibiotic discs (used as a control) are placed on the agar with a forceps firmly pressed to ensure contact with the agar, and then the plate is inverted and incubated. After incubation for 24 hours at 37 °C, the inhibition zone around the disc is read. According to NCCLS criteria, isolates were classified as either sensitive or resistant [34].

Biological activity evaluation by agar diffusion well assay

Agar diffusion well experiment [35] was used to assess the chemical compounds' biological activity *in vitro* against 10 microorganisms, including eight bacterial isolates (four of them were Gram-negative, and four of them were Gram-positive). A Muller-Hinton agar plate's surface is equally covered with a sterile cotton swab soaked in the prepared suspension, with seven 7 mm-diameter holes spaced 20 mm apart in the agar gel. The resulting diluted concentrations (12.5, 25, 50, 100, 150, and 200 mg/mL) were then applied to each well at a volume of 100 L. One of these holes was filled with either DMSO or ethanol (20% each) to observe the effect of the solvent. The plates that weren't converted were incubated at 37 °C for 24 hours. After incubation, growth was seen, and the amount by which it was inhibited was measured in millimeters.

TABLE 1 Chemical structure of the prepared compounds

Compound Symbol	Structural formula	Y	X
I-III		O	Cl, Br, NO_2
IV-VI		S	Cl, Br, NO_2
H_1-H_3		O	Cl, Br, NO_2
H_4-H_6		S	Cl, Br, NO_2
H_7-H_9		O	Cl, Br, NO_2

Characterization of the prepared compounds

Characterization of compounds (I-VI) (starting materials)

The starting materials (**I-VI**) were characterized by some physical measurement, such as melting points besides the spectroscopic techniques, IR, ^{1}H-NMR, and ^{13} C-NMR.

The IR spectra of the starting materials are studied as KBr disc, as shown in Table 2. These compounds are characterized by eight bands corresponding to the stretching vibrations of the NH-, aromatic C - H, C = O, C = N, C = C, C = N, C-S, and C-X groups, which occur within the ranges (3487.3-3342.64), (3107.32-3037.77), (1647.21-1629.85), (1647.21-1583.59), (1629.85-1487.12), (1400.32-1340.53), (1182.36-1178.51), (1344.46-617.22) cm^{-1}, respectively. Likewise, the starting materials were identified by ^{1}H-NMR spectra which appeared four signals shown in Table 3. The range of the signals are δ (4.24-6.21), (6.23-8.64), (9.97-11.43), and (8.64 -10.17) ppm which are represented the -NH-, Ar-H, O=C-NH, and S=C-NH, respectively, whereas the ^{13}C-NMR spectra of starting materials showed seven signals ascribed to the C-N, C = C, C = N, C=O, C=S, and C-X, as clarified in Table 4.

Characterization of the compounds (H_1-H_9) (products)

Infrared spectra (IR) of aryl sulfonyl derivatives (H_1-H_9)

Infrared spectra of the synthesized compounds (H_1-H_9) showed a similarity in the stretching absorption bands.

These spectra of derivatives (H_1-H_9) showed the disappearance of the stretching vibration bands into a group (NH_2) which appeared within the range (3118.90-3487.30) cm^{-1}, as presented in Table 2. On the other hand, new medium bands appeared within the range (1400.32-1485.19) cm^{-1} , which belongs to the stretching vibration of the S=O of sulfonyl group, which confirmed the occurrence of a di-substitution reaction between the amino groups of the compounds (**I-VI**) and benzenesulfonyl chloride or P-toluene sulfonyl chloride. The other stretching vibrations of the prepared derivatives (H_1-H_9) are occur within the ranges (3219.19-3369.64), (3037.99-3128.54), (2840.61-2972.01), (1653.00-1660.71), (1595.18-1616.35), (1487.17-1598.99), (1328.95-1344.38), (1157.33-1222.87), and (663.51-1344.38) cm^{-1} which are corresponding with -NH , Ar-H, Aliph-H, C=O, C=N, C=C, C-N, C=S, and C-X groups, respectively, as illustrated in Table 5 and Figure 2.

^{1}H-NMR of aryl sulfonyl derivatives (H_1-H_9)

The most important characteristic of the ^{1}H-NMR spectra of the aryl sulfonyl derivatives was disappearance of the singlet signal of the amino group (-NH-), belonging to the starting materials (**I - VI**) at the range δ (4.24-6.21) ppm, as listed in Table 3, which is consistent with the data we obtained from the spectra of IR. These data (IR and ^{1}H-NMR) confirmed that the reaction has taken place and that is di-substitution. The rest of the resonance signals are for aryl sulfonyl derivative (H_1-H_9) as appear in a Table (6) and Figure (3) are δ (1.07-2.34), (6.59-8.50), (10.92-11.04), (10.98-11.01), (10.14-10.41) ppm which are attributed to CH_3, Ar-H, O=C-NH, S=C-NH, and NH-S=O, respectively.

^{13}C-NMR of the synthesized derivatives (H_1 - H_9)

The ^{13}C-NMR spectral data of aryl sulfonyl derivatives (H_1-H_9) are illustrated in Table 7 and Figure 4. The resonance signals shown by these spectra of the derivatives synthesized above are: δ (21.4-21.4), (118.2-144.2), (136.6-143.2), (144.2-148.4), (187.7-187.8), (187.8-187.8), and (124.3-141.6) ppm which ascribes to -CH_3, aromatic ring, C-N, C=N, C=O, C=S, and C-X, respectively.

Elemental Analysis

The practical values of the precise elemental analysis for C, H, N, and S of the prepared compounds showed that the difference with calculated values falls within the range, which confirms the correctance of the suggested structures of the prepared samples Table (8).

TABLE 2 FT-IR spectra of the stretching vibrations of starting materials (I-VI) (cm^{-1})

Compound No.	Symbol	-NH_2	C-H Aromatic	C=N	C=C	C=O	C=S	C-N	C-X
1	**(I)**	3460.30 3344.57 (m)	3066.82 (w)	1604.77 (m)	1573.91 (m)	1629.85 (m)		1346.31 (s)	(C-Cl) 840.96 (w)
2	**(II)**	3462.22 3342.64 (m)	3049.46 (w)	1606.7 (m)	1487.12 (m)	1647.21 (s)	.....	1340.53 (m)	(C-Br) 642.30 (s)
3	**(III)**	3482.37 3390.88 (s)	3037.77 (w)	1583.59 (s)	1506.41 (s)	1637.58 (s)	.....	1342.46 (m)	(C-NO_2) 1317.35 1344.46 (s)
4	**(IV)**	3460.3 3342.64 (s)	3051.39 (w)	1647.21 (m)	1629.85 (m)	.....	1178.51 (m)	1346.31 (m)	(C-Cl) 813.96 (s)
5	**(V)**	3462.22 3342.64 (m)	3047.53 (w)	1647.21 (m)	1627.92 (m)	.....	1180.44 (m)	1340.53 (m)	(C-Br) 671.23 (m)
6	**(VI)**	3487.3 3388.93 (s)	3107.32 (w)	1610.56 (s)	1610.56 (m)	.....	1182.36 (m)	1342.46 (s)	(C-NO_2) 1317.38 1342.46 (s)

TABLE 3 ^{1}H-NMR spectra data of the starting materials (I-VI) (ppm)

Compound No.	Symbol	-NH_2 (s)	Aromatic Protons (m)	NH (C=O) (s)	NH (C=S) (s)
1	**(I)**	4.24	6.70-8.08	9.97	.....
2	**(II)**	5.19	6.23-8.03	10.00	.....
3	**(III)**	5.19	6.75-8.08	11.43	.....
4	**(IV)**	6.20	6.65-7.94	.....	8.66
5	**(V)**	6.21	6.67-8.64	.....	8.64
6	**(VI)**	5.33	6.30-8.31	.....	10.17

TABLE 4 ^{13}C-NMR spectra data of the starting materials (I-VI) (ppm)

Compound No.	Symbol	C-NH_2	Aromatic	C-N (Heterocycle)	C=N	C=O	C=S	C-X
1	**(I)**	141.6	113.9-151.3	155.9	160.3	187.7	.....	C-Cl 135.8
2	**(II)**	140.4	113.2-140.4	154.4	161.8	186.1	.....	C-Br 125.7
3	**(III)**	140.7	111.2-134.9	152.3	167.3	186.3	.....	C-NO_2 134.9
4	**(IV)**	140.3	113.2-134.8	154.4	166.8	.....	186.1	C-Cl 134.8
5	**(V)**	140.4	113.2-140.4	154.4	161.8	.....	186.1	C-Br 125.7
6	**(VI)**	142.2	113.2-139.1	154.7	166.3	.....	185.8	C-NO_2 139.1

TABLE 5 Infrared spectra (IR) of the aryl sulfonyl derivatives (H_1-H_9) (cm^{-1})

No.	Symbol	-NH-	Ar-H	Aliph-H	C=O	C=N	C=C	C=S	S=O	C-N	C-X
1	H_1	3356.14 (w)	3126.91 (m)	$-CH_3$ 2972.01(w)	1653.00 (s)	1597.95 (s)	1490.97 (m)	.....	1409.97 (m)	1328.95 (s)	812.03 (s) X=Cl
2	H_2	3369.64 (w)	3128.54 (m)	$-CH_3$ 2970.08(w)	1653.00 (s)	1608663 (s)	1597.06 (m)	.....	1402.25 (m)	1328.95 (s)	663.51(s) X=Br
3	H_3	3313.71 (s)	3078.39, 3043.67(w)	$-CH_3$ 2930.05(w)	1660.71 (s)	1604.77 (s)	1519.91 (s)	.....	1406.11 (m)	1342.46 (s)	1342.46(s) 1316.34(m) X=NO_2
4	H_4	3265.49 (m)	3080.32, 3035.96(w)	.....	.....	1604.77 (s)	1595.13 (s)	1219.01 (m)	1402.25 (s)	1344.38 (m)	813.96 (s) X=Cl
5	H_5	3277.06 (m)	3101.54 (w)	.....	.....	1606.70 (s)	1510.26 (s)	1219.01 (m)	1400.32 (s)	1344.38 (s)	688.59(m) X=Br
6	H_6	3273.20 (m)	3113.11 (w)	.....	.....	1604.77 (m)	1514.12 (s)	1222.87 (s)	1400.32 (w)	1342.46 (s)	1342.46(m) 1317.32(m) X=NO_2
7	H_7	3365.78 (m)	3082.25 (w)	.....	1654.92 (s)	1604.77 (s)	1595.13 (s)	.....	1402.25 (m)	1344.38 (s)	719.45(m) X=Cl
8	H_8	3277.06 (s)	3082.25 (w)	.....	1656.85 (s)	1606.70 (s)	1598.99 (s)	.....	1400.32 (s)	1344.38 (s)	688.54(m) X=Br
9	H_9	3219.19 (s)	3066.82 (w)	.....	1656.85 (s)	1616.35 (m)	1597.06 (m)	.....	1411.89 (m)	1344.38 (s)	1344.38(s) 1318.13(m) X=NO_2

TABLE 6 ^{1}H-NMR Spectral data of aryl sulfonyl derivatives (H_1-H_9) (ppm)

Compound No.	Symbol	CH_3 (s)	AromaticProtons (m)	O=C-NH (s)	S=C-NH (s)
1	H_1	2.33	7.72-8.09	10.92	.....
2	H_2	2.34	7.30-8.41	10.93	.....
3	H_3	1.07	7.21-8.50	10.95	.....
4	H_4	.....	7.30-8.10	.....	11.00
5	H_5	.....	6.64-8.08	.....	10.98
6	H_6	.....	6.59-8.28	.....	11.01
7	H_7	.....	7.27-8.09	10.99	.....
8	H_8	.....	7.30-8.09	10.99	.....
9	H_9	.....	7.31-8.27	11.04	.....

TABLE 7 ^{13}C-NMR Spectral data of aryl sulfonyl derivatives (ppm)

Compound No.	Symbol	-CH_3	Aromatic	C-N	C=N	C=O	C=S	C-X
1	**H_1**	21.4	118.3-142.5	142.9	144.2	187.8	.....	C-Cl 136.8
2	**H_2**	21.4	118.3-136.8	142.5	144.2	187.8	.....	C-Br 124.3
3	**H_3**	21.4	118.2-144.2	143.2	148.4	187.7	.....	C-NO_2 141.6
4	**H_4**	.....	118.4-135.4	139.7	142.8	.....	187.8	C-Cl 134.1
5	**H_5**	.....	118.4-134.4	139.7	142.8	.....	187.8	C-Br 124.3
6	**H_6**	.....	118.4-113.1	143.1	148.4	.....	187.8	C-NO_2 141.0
7	**H_7**	.....	118.4-135.4	139.7	142.8	187.8	.....	C-Cl 134.1
8	**H_8**	.....	118.4-139.7	142.5	142.8	187.8	.....	C-Br 124.3
9	**H_9**	.....	118.4-141.6	143.1	148.4	187.7	.....	C-NO_2 139.7

TABLE 8 Elemental analysis of the products(H_1-H_9)

Compound No.	Symbol	Molecular formula	Mol. Wt g/mole	C %		H %		N %		S %	
				Cal.	**Fou.**	**Cal.**	**Fou.**	**Cal.**	**Fou.**	**Cal.**	**Fou.**
1	**H_1**	$C_{30}H_{24}ClN_3O_5S_2$	605.82	59.47	60.00	3.96	4.20	6.93	7.44	10.58	10.95
2	**H_2**	$C_{30}H_{24}BrN_3O_5S_2$	650.27	55.40	54.86	3.69	3.45	6.45	6.74	9.86	9.70
3	**H_3**	$C_{30}H_{24}N_4O_7S_2$	616.53	58.45	58.95	3.89	3.64	9.08	9.37	10.40	10.74
4	**H_4**	$C_{28}H_{20}ClN_3O_4S_3$	593.87	56.62	56.13	3.36	3.25	7.07	6.61	16.19	15.75
5	**H_5**	$C_{28}H_{20}BrN_3O_4S_3$	638.14	52.69	53.20	3.13	3.36	6.58	6.87	15.07	15.45
6	**H_6**	$C_{28}H_{20}N_4O_6S_3$	604.40	55.63	56.11	3.30	3.57	9.26	8.96	15.91	16.41
7	**H_7**	$C_{28}H_{20}ClN_3O_5S_2$	577.80	58.20	57.72	3.46	3.75	7.26	7.03	11.09	11.40
8	**H_8**	$C_{28}H_{20}BrN_3O_5S_2$	622.25	54.04	54.53	3.21	2.93	6.74	7.07	10.30	10.61
9	**H_9**	$C_{28}H_{20}N_4O_7S_2$	588.33	57.15	57.58	3.39	3.60	9.51	9.92	10.89	11.38

Biological activity

The cytotoxic activity for synthesized compounds against human breast cancer cells line (MCF-7)

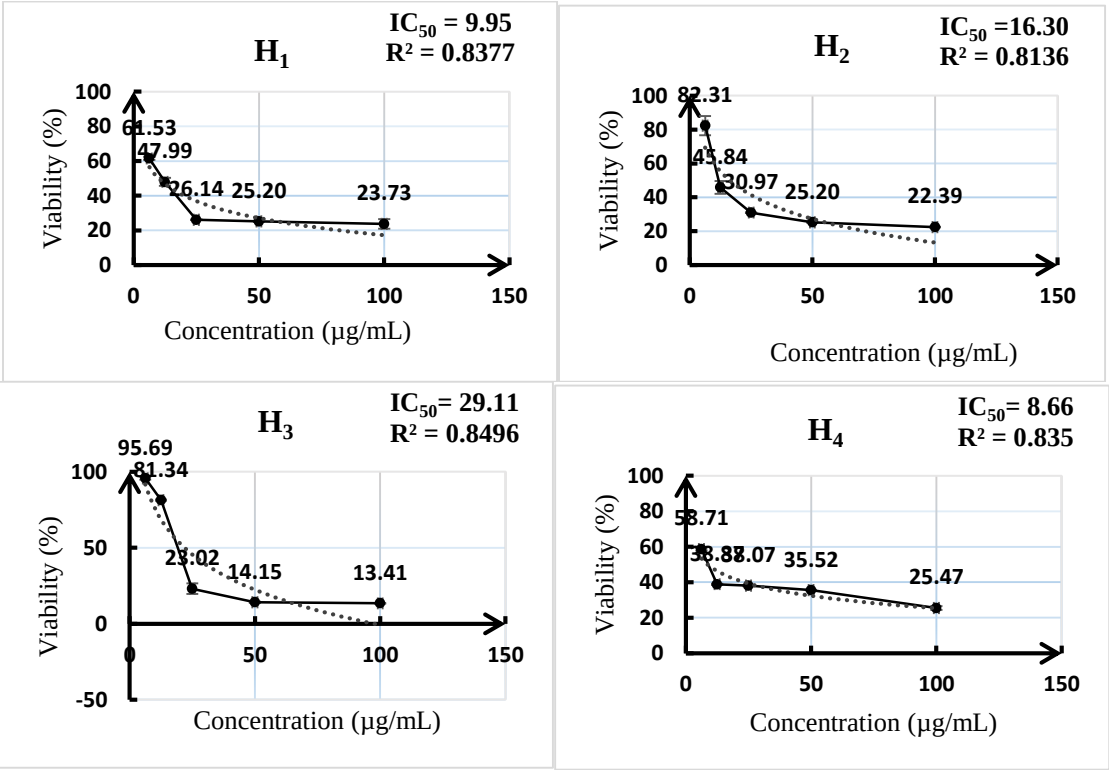
The concept of **IC_{50}** is widely used in the pharmaceutical field as an inhibition efficiency indicator of a biological and biochemical material, and its value shows the inhibitory concentration that is required to halve a specific biological substance or biochemical function. The high **IC_{50}** values indicate low inhibitory activity with the material in contrast to the materials with low **IC_{50}** values. In this study, the **MCF-7** cell line was used to assay the anti-proliferative activity of compounds (H_1-H_9), compound H_4 was the most potent in this group with **IC_{50}** value of 8.66 µg/mL and compound H_8 was the lowest in potency with **IC_{50}** value of 52.29 µg/mL, as displayed in Figure 1. Microscopic examination of the tested compounds in the cell line at 100 µg/mL used to confirm the calculation of the **IC_{50}**.

Antibacterial activity of the compounds

Due to their extensive spectrum of biological functions, organic molecules with heterocyclic ring structures continue to attract a lot of attention. In this work, six gram-positive and gram-negative bacteria with multidrug resistance were examined using heterocyclic compounds and their treatments, as listed in Table 9. The findings in Table 10 revealed varying levels of efficacy against the tested microorganisms.

1. The **IV** compound at concentration 5, 10, 15, 20, and 30 mg/mL inhibited the growth of *Escherichia coli* 1 and *Escherichia coli* 2 with zone (10 and 12) mm, respectively, in *Staphylococcus aureus* 1 only the (20 and 30) mg/mL displayed inhibition zone (15 and 18) mm respectively, While *Streptococcus agalactiae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* 2 showed less sensitivity against this compound.
2. The **VI** compound at concentration 10, 15, 20, and 30 mg/mL inhibited the growth of *Escherichia coli* 1with zone (12, 15, and 20) mm, respectively, although showed the inhibited (12,13, 15,15) mm of the growth of this compound at 30 mg/mL concentration for *Pseudomonas aeruginosa, Escherichia coli* 2, *Staphylococcus aureus* 1, and *Staphylococcus aureus* 2, respectively. No effect of *Streptococcus agalactiae* was observed against this compound.
3. The H_1, H_2, H_3, and H_5 compounds at concentration 5 mg/mL inhibited only the growth of *Streptococcus agalactiae* and *Pseudomonas aeruginosa* (20 and 47) mm, correspondingly. Although the H_1 at (20 and 30 mg/mL) increased the inhibition zone to (15 and 18) mm of *Staphylococcus aureus,* respectively.
4. The H_4 and H_7 compounds at concentration 5 mg/mL inhibited only the growth of *Staphylococcus aureus* 1 (15 mm) for each one.
5. The H_3 compound at concentration 5 mg/mL inhibited only the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* (20 mm) for each one.

The H_8 compound at concentration 5, 10, 20, and 30 mg/mL inhibited only the growth of *Escherichia coli* 1 (12, 15, 15, and 20) mm, respectively



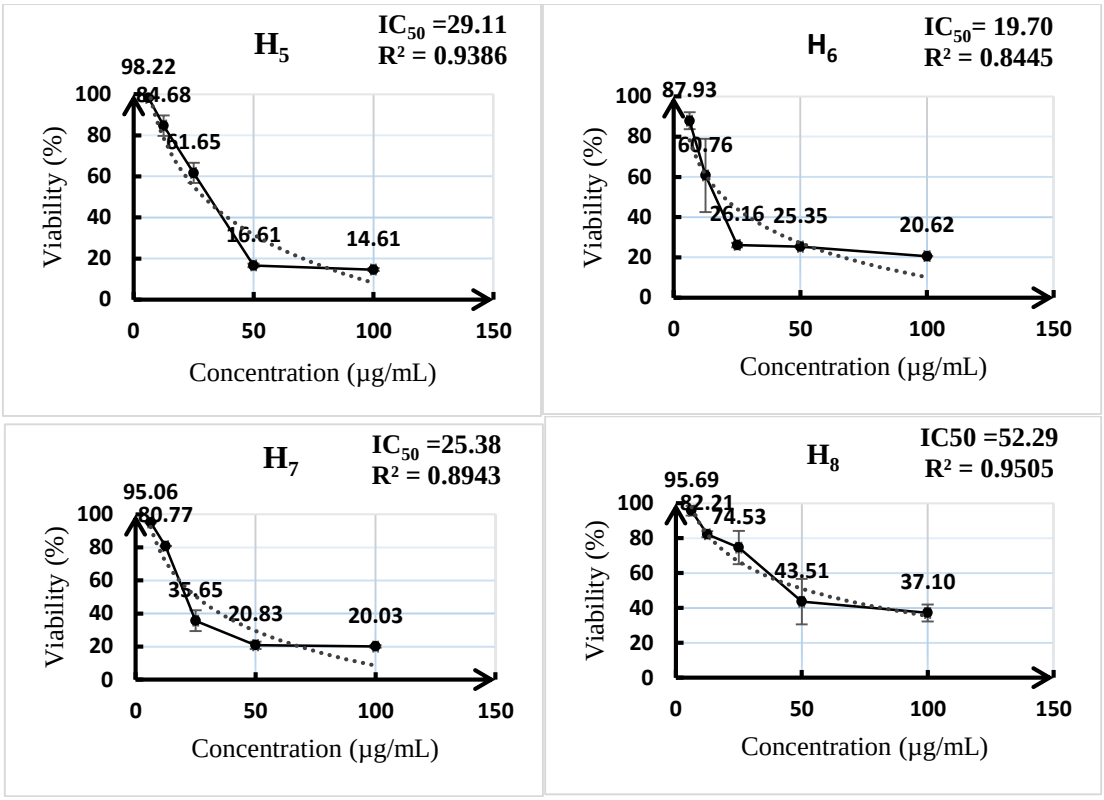


FIGURE 1 The IC_{50} Values of compounds against MCF-7 Cell line

TABLE 9 Biological activity of the compound on tested bacteria (the starting materials)

Sample	Conc. mg/ml	Diameter of inhibition zone (mm)					
		E.coli 1	*Phsed.*	*Staph.1*	*Psd.monous*	*E.coli 2*	*Staph.2*
IV	30	10	0.00	18	0.00	12	0.00
IV	20	10	0.00	15	0.00	12	0.00
IV	5,10,15	10	0.00	0.00	0.00	12	0.00
VI	30	20	0.00	15	12	13	15
VI	20,10	15	0.00	0.00	0.00	0.00	0.00
VI	15	12	0.00	0.00	0.00	0.00	0.00

TABLE 10 Biological activity of synthesis compound on tested bacteria (the products)

Sample	Conc. mg/ml	Diameter of inhibition zone (mm)					
		E.coli 1	*Phsed.*	*Staph.1*	*Psuelo.1*	*E.coli 2*	*Staph.2*
H_1,H_2,H_3,H_5	5	0.00	20	0.00	45-47	0.00	0.00
H_1,H_5	5	0.00	20	20	0.00	0.00	0.00
H_1	30	0.00	0.00	18	0.00	0.00	0.00
H_1	20	0.00	0.00	15	0.00	0.00	0.00
H_4	5	0.00	0.00	15	0.00	0.00	0.00
H_7	5	0.00	0.00	15	0.00	0.00	0.00
H_8	20,10	15	0.00	0.00	0.00	0.00	0.00
H_8	5	12	0.00	0.00	0.00	0.00	0.00
H_8	30	20	0.00	0.00	0.00	0.00	0.00

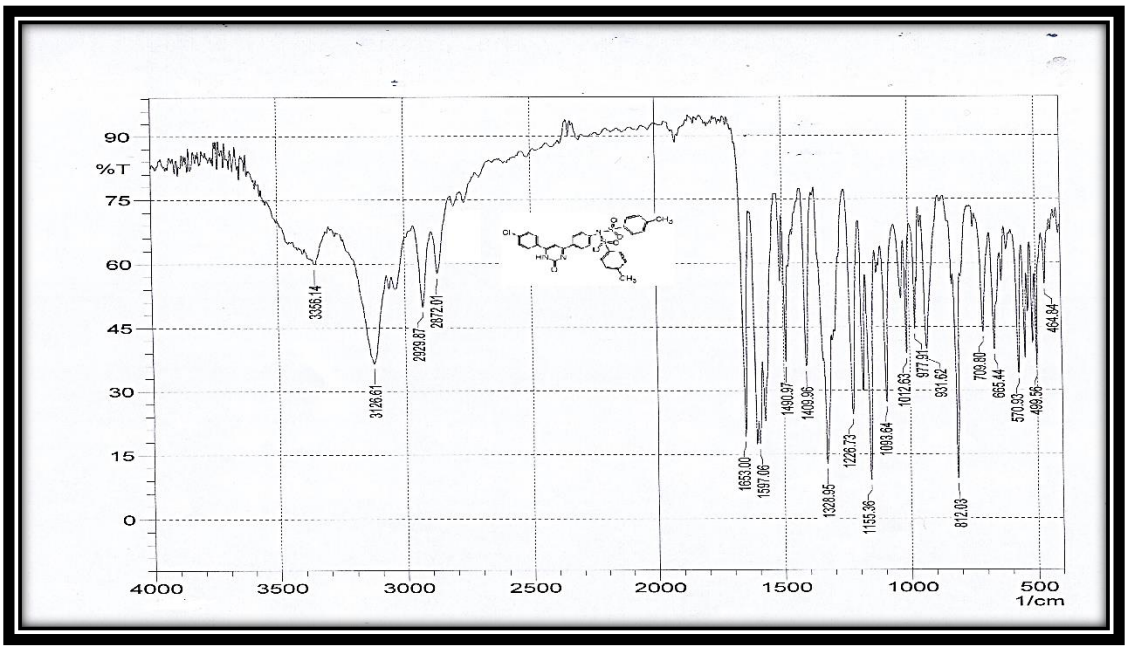


FIGURE 2 IR spectrum of compound (H_1)

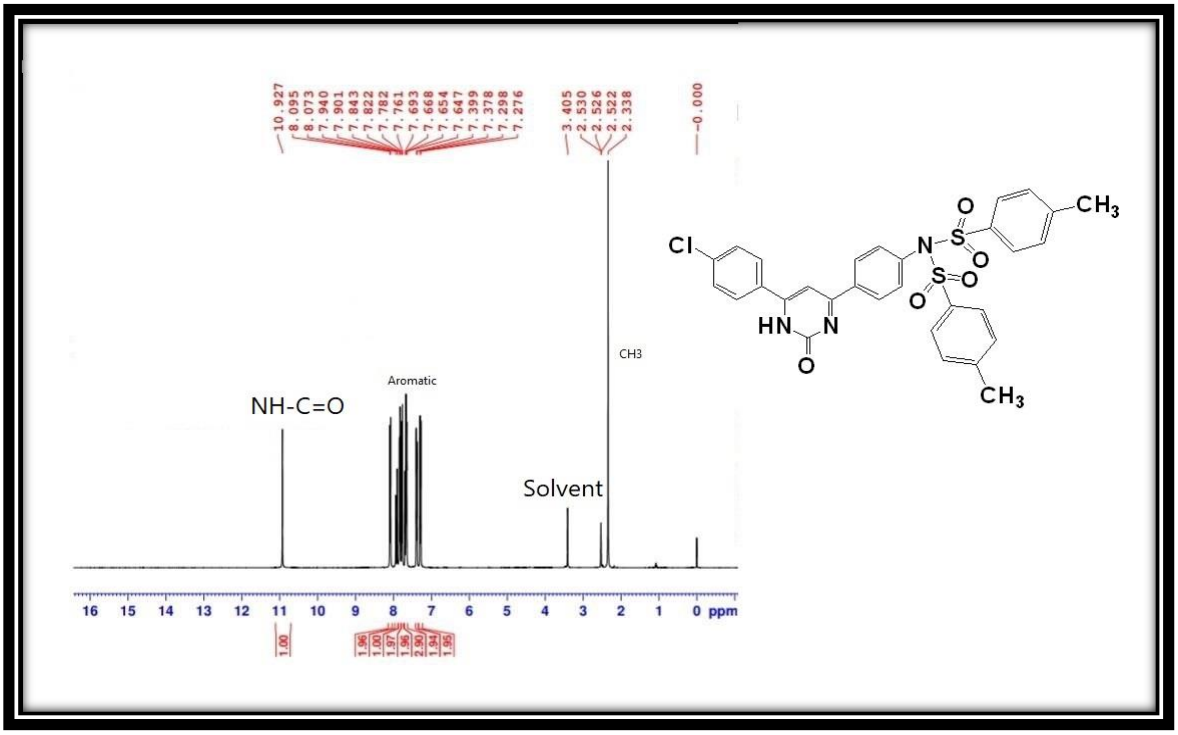


FIGURE 3 ^{1}H-NMR spectrum of compound (H_1)

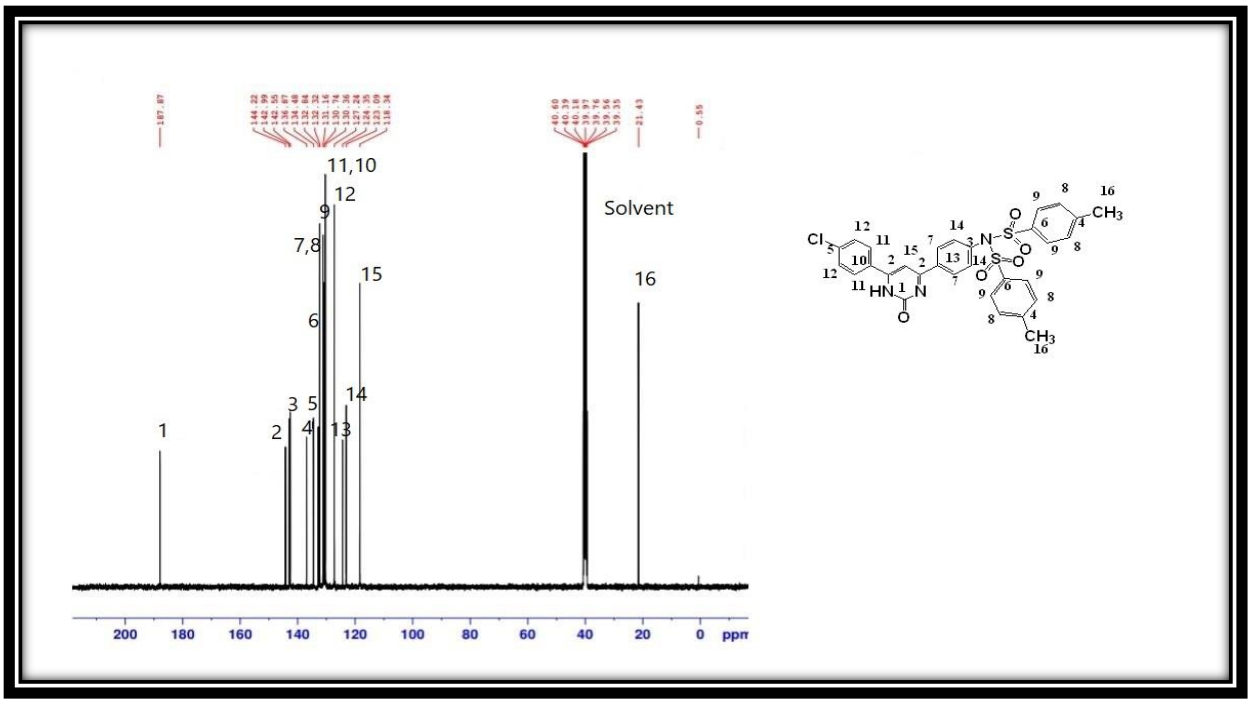


FIGURE 4 ^{13}C-NMR spectrum of compound (H_1)

Conclusion

1. The aryl sulfonyl derivatives gave higher yields compared to the yields given by the ally derivatives.
2. It was observed that the starting material containing a pyrimidine ring substituted with a thioxs group gave a greater amount of product compared to the one containing an oxo group.
3. The use of the yeagent benzene sulfonyl chloride leads to the production of products in a greater proportion than if the reagent p-toluene sulfonyl chloride was used in the preparation.
4. The biological activity of the prepared antibacterial compounds appeared to be much more than that one shown by the starting materials.

In general, the prepared compounds showed acceptable anti-breast cancer activity.

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Conflict of Interest

The authors declare no conflict of interest.

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