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BENZAMINE DERIVATIVES: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY STUDY

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Abstract: *Our study is included the synthesis of a number of benzamide drivatives through two chemical processes. The first is the benzoylation of some aromatic amines containing a pyrimidine or a pyrazoline ring in their structures (A-G) using benzoyl chloride or p-chloronbenzoyl chloride in the presence of 1,4-dioxan as solvent productive (N1-N6, N13-N16) derivatives. The second is the tosylation of (N2-N6, N15) by p-toluene sulfonyl chloride in the presence of pyridine as catalyst and base at room temperature to produce (B1-B6) derivatives . The products have been characterized by IR, ^{1}H-NMR ,^{13} C-NMR and mass spectroscpies and the physical properties of the products are recorded . The spectral data confirmed the validity of the benzamide derivatives. Also the work is included the study of antimicrobial activity of the synthesized compounds represented by determining the inhibition diameter zone (IZ), minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) given by these compounds against the test organisms Staphylococcus aureas (Gr^{+}positive) and Escherichia coli (Gr^{-} negative). Furthermore, the results of MIC and MBC were compared with those of some common antibiotics such as tetracycline, ampicillin and streptomycin. This comparison showed that it is possible to use the synthesized derivatives as antimicrobials.*

Keywords: *oxopyrimidine, pyrazoline, p-toluene sulfonyl chloride, tosylation, benzoylation*

1. Introduction

Heterocyclic compounds constitute the largest and most diverse group of organic compounds. Today, there are many heterocyclic compounds, and the number is increasing rapidly due to tremendous research in addition to their synthetic usefulness [1-3]. Research interest in heterogeneous compounds is increasing due to their applications. These compounds have gained a lot of interest due to many important medical and biological uses, covering the majority of recently synthesized bioactive heterocyclic compounds from antifungal, anti-inflammatory, antibacterial, antiviral, anti-allergic, anti-histamine, herbicide and in the pharmaceutical industry [4]. Most heterocyclic organic compounds are extracted from animal or plant sources [5]. In general, knowledge of the chemistry of heterogeneous compounds is of great importance in the field of studying natural products, biological preparations, and drug metabolism processes [6, 7]. Derivatives of the amine group have great biological importance, as they play a major role in biological activities, such as in enzymatic transfer reactions of the amine group of amino acids, and they have great importance in medicine and pharmaceuticals [8]. Foods contain many amines, many of which are called biogenic amines due to their biological activity and their ability to cause poisoning when present in high concentrations. Some biogenic amines, such as serotonin, histamine, and tyramine, play an important role in many physiological functions in humans and animals. The diamines putrecine and the polyamines oligoamines such as spermidine and cermin are also involved in some physiological processes such as cell division. Biogenic amines are important in foods, as the process of measuring biogenic amines is used as evidence of food spoilage [9].

Benzoylation is a chemical reaction in which a benzoyl group is catalyzed by the removal of an H attached to an O or N of aromatic ring. There are many well-known benzoyl compounds, such as benzoyl esters and amides, and are commonly used in organic chemistry. Benzoyl esters can act

as protecting agents in organic synthesis and can be easily removed by hydrolysis [10]. Benzoyl chloride is the commonly used chemical and is the source of the benzoyl group, which can be used in the preparation of benzoyl ketones and benzoyl esters. The natural source of the benzoyl group is thio ester benzoyl-CoA. For the purposes of new drug planning, a number of researchers use the strategy of combining molecules by performing the benzoyl process, as this combination gives a more responsive and metabolically relevant drug benefit [11]. There are many applications for the benzoylation process, as it is an effective and inexpensive method despite the toxicity of benzoyl chloride, including the decomposition of amino acids [12], and the production of peroxides, in addition to its importance in the production of perfumes, medicines, and resins. It also plays a role in determining most of the neurotransmitters in the organism's body and common low-molecular-weight metabolites [13]. The benzoyl process is also used in the preparation of a number of therapeutic ointments, including benzoyl peroxide. It is used for sterilization against germs, mainly against bacterial acne [14]. It also helps reduce the percentage of fat secreted in the epidermis [15].

Tosylation is an organic reaction that occurs on aromatic compounds in which the sulfonic acid functional group replaces a hydrogen atom on the aromatic ring. This reaction is widely used in the manufacture of dyes and pharmaceutical drugs [16]. The p-toluene sulfonyl chloride reagent is used in the pharmaceutical field in the manufacture of the sulfa drug and the drug metsulfuron. It is also used as an analytical reagent in molecular rearrangement reactions in organic synthesis [17]. Biological activity of sulfonamide compounds have been widely used as antibacterial, both types of Gram positive (Gr +) and Gram negative (Gr-), antifungal, and antiviral. They have been used to protect plants in agriculture, and as pesticides for harmful insects and weeds [18]. They have also been used in the medical field as an antipyretic and treatment of Joints inflammation, tuberculosis treatment, and an antiseptic and sterilizer of odors and germs. However, sulfonamide compounds have side effects such as hypersensitivity, jaundice, nausea, and an effect on the kidney. They have also been used in treating some nervous system diseases such as forgetfulness (Alzheimer's) and in treating cancer [19]. This study led to the successful synthesis of a series of novel heterocyclic compounds derived from Benzamine Derivatives. The starting materials containing a thioxo group give a greater yield than starting materials containing an oxo group and It was noted that benzamide derivatives containing a pyrimidine ring give a greater yield than those containing a pyrazoline ring.

2. Experimental part

2.1 General

Uncorrected melting points were determined by 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 taken on (prestige-21) at Medicine College, Misan University-Iraq. All the spectra were recorded as KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra were carried out by (Bruker, model: Ultra shield 300 MHz) at Chemistry Department, Education College for pure Sciences, Al-Basrah University-Iraq using DMSO as a solvent and TMS as an interral standard. Mass spectra are achieved in University of Tehran - Faculty of Science in the Islamic Republic of Iran carried out by (Agilent Tenchnology (HP)Model 5973).

2.2 Preparation of starting materials

2.2.1 Preparation 4(6-(4-substituted phenyl)-2-substituted-1,2,dihydropyrimidine-4-yl) aniline (A-F) [20].

A mixture of 4-amino acteophenome (2 mmol) and 4-substituted benzaldehyde (chloro, bromo, and nitro) (2 mmol), and urea or thiourea (3 mmol), were added in a mortar. The mixture was blended together and shifted into a round flask and mixed with 50 ml of NaOH (0.2g in 50% water). The mixture was heated at 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.

2.2.2 Preparation 4-(5-(4-substituted phenyl)-1H-pyrazol-3-yl)aniline (G) [21].

In a mortar, a combination of 2 mmol of amino acteophenome, 2 mmol of 4-substituted benzaldehyde (nitro, bromo, and chloro), and 3 mmol of aquenous hydrazine were added. After blending, the mixture was transferred to a round flask and combined with 50 milliliters of NaOH (0.2 grams in 50% aqueous solution). The mixture was heated to 70°C in an atmospheric setting, allowing the reaction to be completed in three to four hours. After being added to water, the reaction mixture was filtered, dried, and recrystallized from the ethanol.

2. 3 Preparation of the products

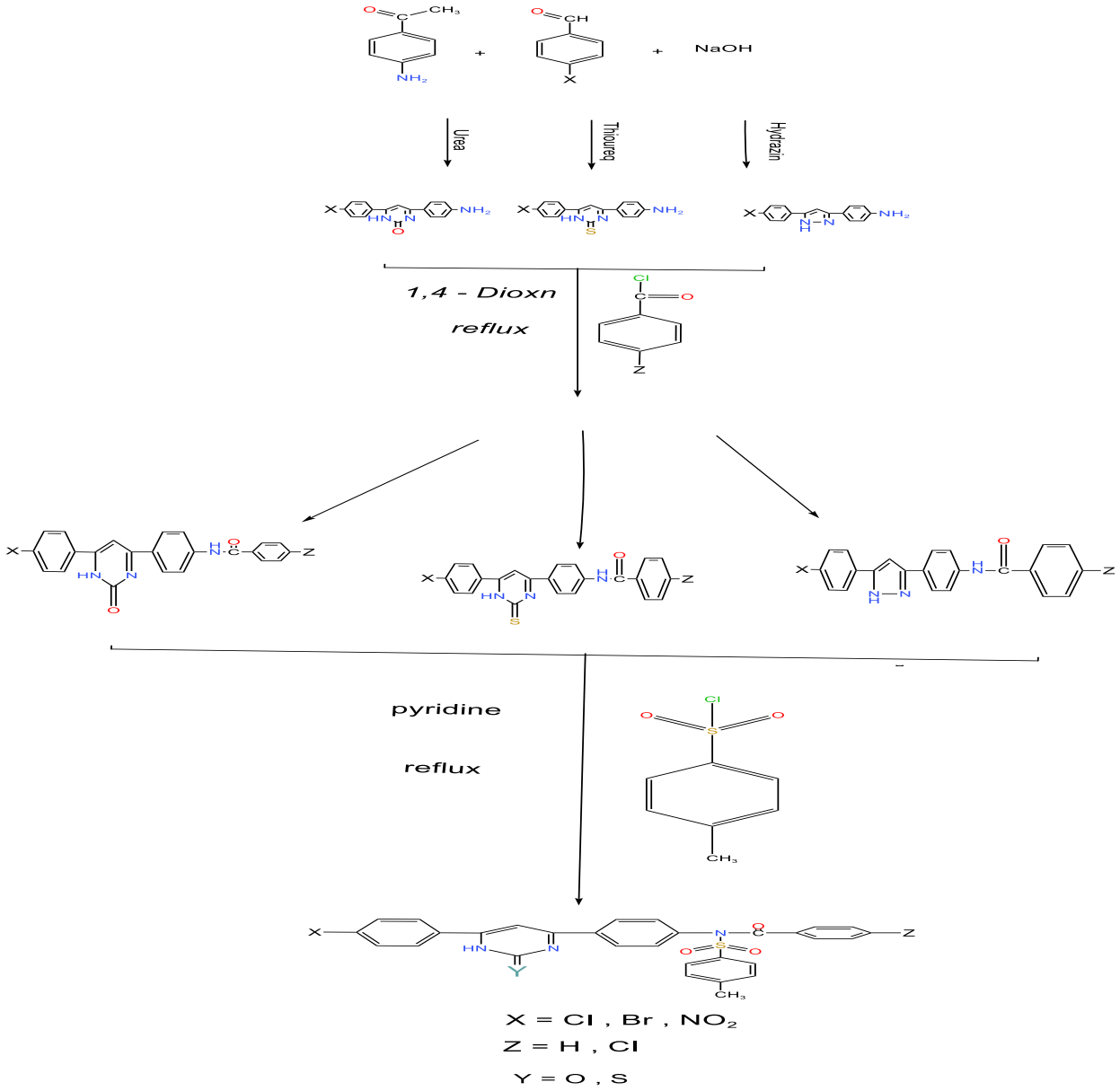


Diagram 1. The flow of reaction

2.3.1 Synthesis of 4-substituted-N-(4-(6-(4-substitutedphenyl)-2-substituted-1,2-dihydropyrimidin-4-yl)phenyl)benzamide (N1-N6 , N13-N15) [22].

Equimolar of (A-F) (1mmol) and benzoyl chloride or p-chloro benzoyl chloride (1mmol) were dissolved in 1,4-Dioxan (6 ml). This mixture was refluxed for 24 hours. The reaction was followed by placing litmus paper on the nozzle of the condenser, where the appearance of the red color indicates that the reaction has occurred. When the red color turns to yellow besides the T.L.C (pertolum ether 6:1 ethyl acetate) showed no further reaction, this means that the reaction is complete. When the mixture was poured on ice and the precipitate was formed. The precipitate was filtered, washed with cold distilled water, left to dry and finally recrystallized from ethanol.

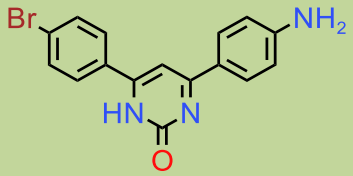
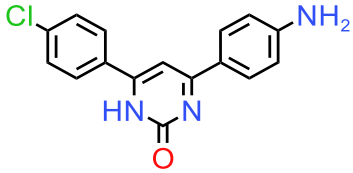
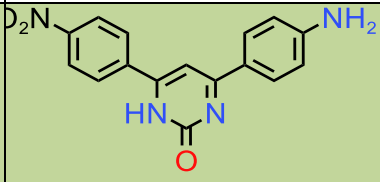
2.3.2 Synthesis of 4-substituted –N-(4-(5-(4-substitutedphenyl)-1H-pyrazol-3-yl phenyl) benzamide (N16) [23].

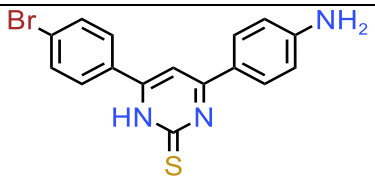
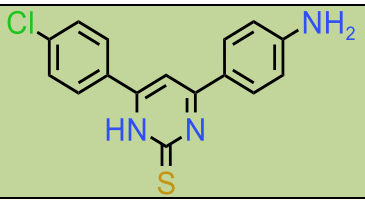
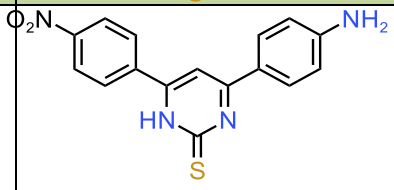
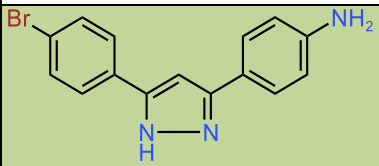
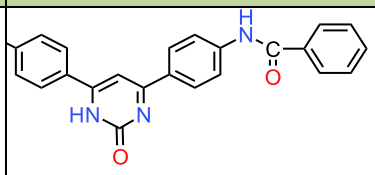
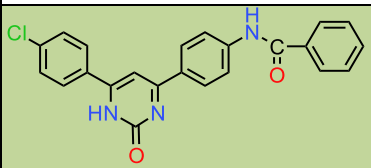
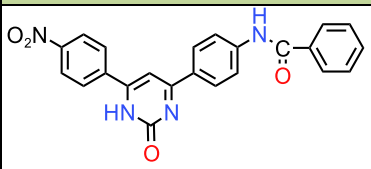
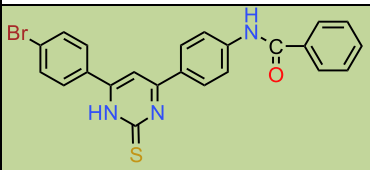
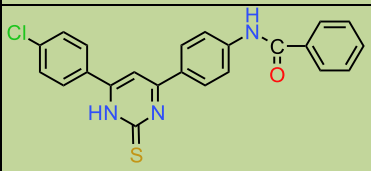
1,4-Dioxan (6 ml) was used to dissolve an equimolar amount (G) (0.01 mol) and either benzoyl chloride or p-chloro benzoyl chloride (0.01 mol). For a full day, this mixture was refluxed. After the reaction, litmus paper was placed on the condenser nozzle; the paper turned red, signifying that the reaction had taken place. The reaction is finished when the red color changes to yellow and there is no longer any reaction visible in the T.L.C. (pertolum ether 6:1 ethyl acetate) solution. When the precipitate developed after the mixture was put over ice. After filtering and washing with cold distilled water, the precipitate was allowed to dry before recrystallizing from the ethanol.

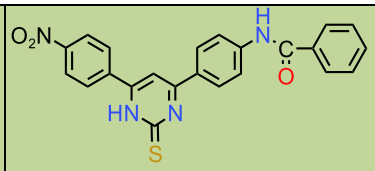
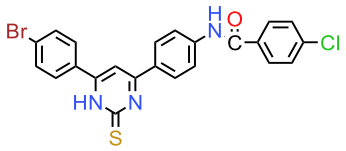
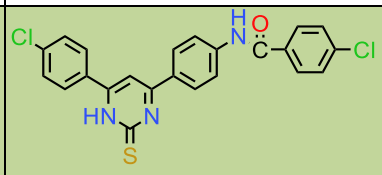
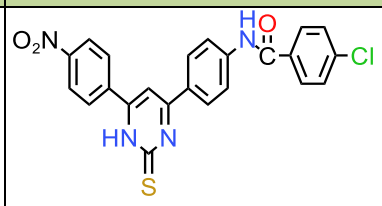
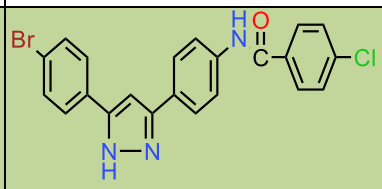
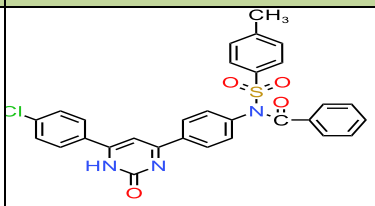
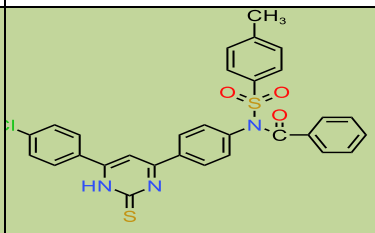
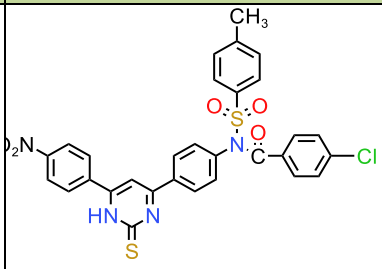
2.3.3 Synthesis of (4-substituted -N-(4-(6-(4-substituted phenyl)-2-substituted -1,2-dihydropyrimidin-4-yl)phenyl)-N-tosylbenzamide (B1-B6) [24].

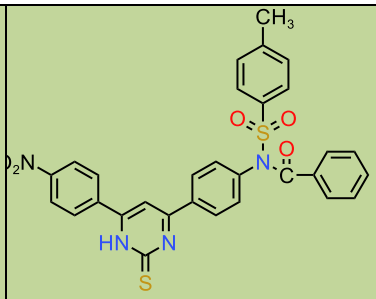
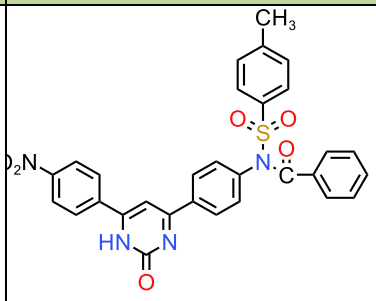
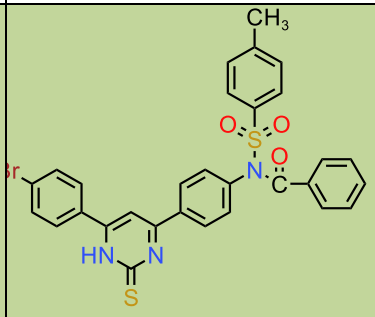
Equimolar amounts of (N2-N6, N16) (0.01 mol) and 4-toluene sulfonyl chloride (0.01 mol) were dissolved in dry pyridine (20 ml). The mixture was reflux on water bath for four hours and the T.L.C (petroleum ether 2:1 ethyl acetate) showed no further reaction. After ensuring that the reaction had finished the reaction mixture was cooled to room temperature. After that, when the mixture was poured into ice cold water, and a precipitate was formed. The precipitate was filtered, washed with distilled water, dried and recrystallized from ethanol.

Table 1. Some physical properties of the prepared compounds

Comp Symbol	Nomenclature	Structural formula	Molecular formula	M.P	Yield %	Color
A	4-(4-aminophenyl)-6-(4-bromophenyl) pyrimidin-2(1H)-one		$C_{16}H_{12}OBrN_3$	156-159	82	Yellow
B	4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidin-2(1H)-one		$C_{16}H_{12}OClN_3$	158-160	72	Yelow
C	4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidin-2(1H)-one		$C_{16}H_{12}O_3N_4$	206-208	90	Dark orange

D	4-(4-aminophenyl)-6-(4-bromophenyl)pyrimidine-2(1H)-thione		$C_{16}H_{12}BrN_3S$	147-149	80	Pale yellow
E	4-(4-aminophenyl)-6-(4-chlorophenyl)pyrimidine-2(1H)-thione		$C_{16}H_{12}ClN_3S$	148-150	88	Pale yellow
F	4-(4-aminophenyl)-6-(4-nitrophenyl)pyrimidine-2(1H)-thione		$C_{16}H_{12}O_2N_4S$	200-202	96	Pale brown
G	4-(5-(4-bromophenyl)-1H-pyrazol-3-yl)aniline		$C_{15}H_{12}BrN_3$	208-210	66	Pale yellow
N1	N-(4-(6-(4-bromophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamide		$C_{23}H_{16}O_2BrN_3$	233-230	76	Yellow
N2	N-(4-(6-(4-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamide		$C_{23}H_{16}O_2ClN_3$	227-225	89	Yellow
N3	N-(4-(6-(4-nitrophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamide		$C_{23}H_{16}O_4N_4$	242-240	94	Orange
N4	N-(4-(6-(4-bromophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamid		$C_{23}H_{16}OBrN_3S$	241-230	88	Yellow
N5	N-(4-(6-(4-bromophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamide		$C_{23}H_{16}OClN_3S$	228-225	59	Yellow

N6	N-(4-(6-(4-nitrophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamide		$C_{23}H_{16}O_3N_4S$	241-239	80	Orange
N13	N-(4-(6-(4-bromophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)-4-chlorobenzamide		$C_{23}H_{15}OBrClN_3S$	223-220	85	Yellow
N14	4-chloro-N-(4-(6-(4-chlorophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamide		$C_{23}H_{15}OCl_2N_3S$	214-210	73	Yellow
N15	4-chloro-N-(4-(6-(4-nitrophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamide		$C_{23}H_{15}O_3ClN_4S$	238-236	76	Yellow
N16	N-(4-(5-(4-bromophenyl)-1H-pyrazol-3-yl)phenyl)-4-chlorobenzamide		$C_{22}H_{15}OBrClN_3$	246-242	84	White
B1	N-(4-(6-(4-chlorophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)benzamide		$C_{30}H_{21}O_6ClN_4S$	320-323	80	White
B2	N-(4-(6-(4-chlorophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)-N-tosylbenzamide		$C_{30}H_{22}O_3ClN_3S_2$	337-334	79	Pale yellow
B3	4-chloro-N-(4-(6-(4-nitrophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)-N-tosylbenzamide		$C_{30}H_{21}O_5ClN_4S_2$	360-363	86	White

B4	N-(4-(6-(4-nitrophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)-N-tosylbenzamide		$C_{30}H_{22}O_5N_4S_2$	390-392	50	Pale brown
B5	N-(4-(6-(4-nitrophenyl)-2-oxo-1,2-dihydropyrimidin-4-yl)phenyl)-N-tosylbenzamide		$C_{30}H_{22}O_6N_4S$	387-389	68	Pale yellow
B6	N-(4-(6-(4-bromophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl)-N-tosylbenzamide		$C_{30}H_{22}O_3BrN_3S_2$	344-346	55	Yellow

2.4 Biological Activity

2.4.1 Determining the inhibition diameters (Inhibition Zones)

The agricultural medium used (nutrient agar) was sterilized using an autoclave device, and after the completion of the sterilization process, the medium was cooled and poured into plastic dishes with a size of 18-20 ml for each dish, and the dishes were left until they dried completely. The bacterial suspension was prepared using isolates identified at the Food Research Center in Baghdad, Iraq. Bacterial isolates were activated to a cell concentration of 10^8 µg/L according to the McFarland method [25]. The bacterial suspension was transferred to the agricultural medium and mat spreads were made using a swab for each type of bacteria. After that, holes were made using a cork drill with a diameter of 0.6 cm, and then a volume of ml (0.1) of each concentration of the prepared compounds was added. In the hole designated for it and the same is true with the other concentrations of each of the two types of bacteria used (*E. coli* and *Staphylococcus aure*) . The cultured dishes were transferred to the incubator at 37 °C for 24 hours, after which the diameters of inhibition were measured.

2.4.2 Estimation the minimum inhibitory concentration and bactericidal concentration [26].

The examination was performed using a concave microtiter plate containing 96 holes according to the following steps: ***a***. Add 100 µL of Muller-Hinton broth medium at double concentration from hole No. 1 to hole No. 12, ***b*** It had been put 100 µL of (N2, N4, N6, N14, N15, B2) solution (10 µg/ml) in hole No. 1 and mixed well with the medium, ***c***. 100 µL from the first hole mixture was transferred to the second hole using a sterile micropipette and mixed well. Then 100 µL of the mixture was transferred from the second hole to the third hole and mixed well. This serial dilution continued until the tenth hole. Finally, 100 µL from the tenth hole was removed and

discarded. The final concentration (N2, N4, N6, N15, N14, B2) solution became half of the original concentration in each hole , Hole No. 11 was left without adding a negative control substance, ***d***. Hole No. 11 was left without adding any materiall(control negative), ***e***. Hole No. 12 was left without adding any amount of solution of the prepared derivatives (N2, N4, N14, N15, B2) (control positive), ***f***. 10 microliters (0.5µg/L) of diluted bacterial suspension (McFarland) at a concentration of was added (hole 1-12), then 30 microliters (0.015 µg/L) of Resazurin solution was added to all the holes and incubated at 37°C for another 4 hours, ***g***. The changes in color from blue to pink are recorded. The concentration before the color change is represented the minimum inhibitory concentration as shown in the following Figure :

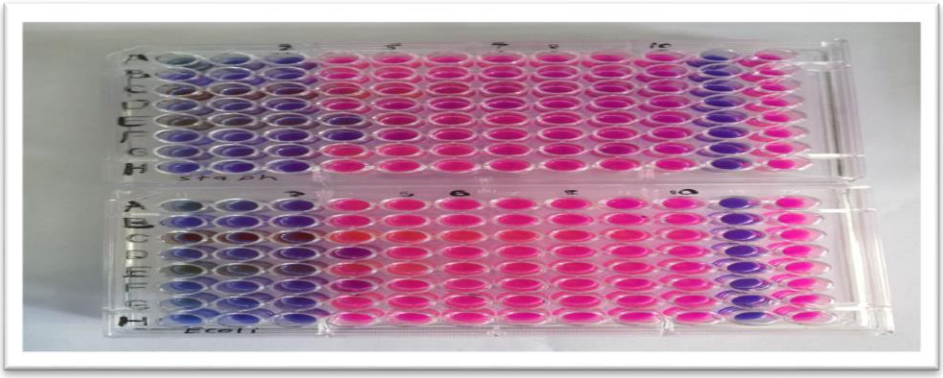


Fig.1. Estimation the minimum inhibitory concentration and bactericidal concentration

3. Characterization of the prepared compound

3.1 Infrared spectra (IR) [27-34]:

The starting materials (A-G) as shown in Table 2 and Figures 2 and 5. Infrared spectra of the Benzoylated derivatives (N1-N6, N13-N16) are appeared eight bands as shown in Table 5 and Fig. 8. The ranges of these bands are (3267.41-3417.86), (3055.24-3109.26) ,(1651.07-1654.92), (1516.05-1651.07), (1597.06-1674.21), (1010.70-1219.01), (1404.18-1485.19) and (621.08-1334.74) cm^{-1} which are as ascribed to the (NH, Ar-H, C=O, C=C, C=N, C=S, C-N, and C-X(X = CI, Br, NO) groups respectively . The lnfrared spectra tosylated Derivatives (B1-B6) as shown in Table 8 and Fig. 11 showed the disappearance the stretching band of the –NH group of the benzoylated derivatives (N1-N6, N15) and appeorance of a band in the rang (2839.22-2924.09) cm^{-1} representing aliphatic-H. The confirms replacing a hydrogen atom with an –NH group by a tosyl group . The range of the t stretching bands for the tosylated derivatives are: (3055.24-3105.39), (1654.92-1674.21), (1593.20-1670.35), (1512.19-1597.06), (1010.70-1107.14), (1404.18-1489.05), (1334.74-1338.60), (6994.37-829.39) cm^{-1} which represent the (Ar-H, C=O, C=N, C=C, S=O, C=S, and C-X) groups respectively.

3.2 ^{1}H-NMR spectra [28, 32, 34]:

The starting materials (A-G) as shown in Table 3 and Figures 3 and 6. The most important characteristic of the ^{1}H-NMR spectra of the benzyolated derivatives (N1-N6, N15) is the disappearance of the resonance signal in the range (5.33-6.65) ppm which is attributed to the amino group of the starting materials and the appearance of a new single resonance signal in the range (10.55-11.57) ppm which is represent the NH-C=Oph . The ranges of the other resonance signals are: (7.22-8.89), (10.01-10. 76), (10.03-10.76) and (13.23) ppm which belong to the (Ar-H, O=C-NH, S=C-NH and Py=NH) group respectively. As shown in Table 6 and Fig. 9. The disappearance of the singlet resonance signal in the range (10.32-11.50) ppm in the ^{1}H-NMR spectra of the derivatives (B1-B6), which belong to the NH-C=Oph group , and the appearance of a singlet resonance signal in the range (1.02-1.50) ppm , which return to the CH_3 group , confirming the replacement of the tosyl group with a proton of -NH-C=Oph. As for the rest of the signals, they fall within the ranges (1.02-1.50), (7.43-8.67), (10.51-10.54), and (10.24-10.73) which belong to the (CH_3, aromatic C-H, NH-C=O and NH-C=S) group respectively as shown in Table 9 and Fig. 12.

3.3 ^{13}C-NMR spectral [28]:

The starting materials (A-G) as shown in Table 4 and Figures 4 and 7. The ^{13}C-NMR spectra of the benzyolated derivatives(N1-N6, N15) are appeared six resonance signals as shown in table 7 and Fig. 10. The ranges of these signals are (140.62-147.96), (100.01-149.42), (139.25-149.74), (165.38-190.12), (184.82-198.86) and (130.91-135.73) ppm which belong to the (C-N, Ar-H, C=N, C=O, C=S and C-X (X= Br, CI, NO_2) group respectively. ^{13}C-NMR spectra of the prepared derivatives (B1-B6) as shown in Table 10 and Fig. 13 are showed a new resonance signal in the range (18.23-25.02) return to the CH_3 group, which confirms the correctness of the structure of B1-B6 derivtive. The remaining ranges of the resonant singnals for the prepared derivatives are (112.21 -166.25), (132.58-137.34), (134.36-145.65), (188.68-189.98), (187.31-189.99) and (135.35-144.94) ppm, which refers to the (Ar-H, C-N, C=N, C =O, C=S, and C-X) group respectively.

3.4 Biological Activity

3.4.1 Inhibition Zones (IZ.mm)

The derivative (N1-N6, B2) were showed varying biological effectiveness inspite of they have a similar general structural formula so that we believe that this difference is due to the difference in the type of groups (X = CI, Br, NO_2) group which substituted in the benzene ring.

As these derivatives were subjected to preliminary screening against the two types of bacteria (*S.aureas* (Gr +) and (*E.coli*). Gr $^-$) and gave biological effectiveness based on the diameters of inhibition (IZ. Mm). Through the values of the diameters of inhibition, it appears that (B2) is the most biologically effective compound against both positive and negative bacteria. This is due to the fact that this derivative is a tosylate compound containing a sulfonyl group (SO^{2-}), which has known biological activity in a number of drugs and medicines, including sulfonamides [34].

3.4.2 Minimum inhibitory concentration of the prepared derivatives (MIC) [35]

Table 12 shows that the values of the minimum inhibitory concentration (MIC) of the prepared derivatives confirm that these derivatives have ranges that allow them to be used as therapeutic antibacterial substances when compared with the minimum inhibitory concentrations of some common antibiotics, tetracycline, ampicillin, and streptomycin. We notice from the given values that the minimum inhibitory concentration for the prepared derivatives gave values that were lower or higher than those for the antibiotics. It was found that the MIC values for the prepared derivatives against the two types of bacteria used were higher than those given for the antibiotic tetracycline [36], while in the case of ampicillin, it was found that the MIC of these derivatives is higher in the case of bacteria (*St. aurea*) except for compound N14 and less in the case of bacteria (*E. coli*). While the opposite was observed with the antibiotic streptomycin, since the minimum inhibitory concentrations of the prepared derivatives were less than those of the antibiotic against bacteria (*St. aurea*) and higher values compared to the values of the antibiotic against bacteria (*E. coli*) [37].

3.4.3.Minimum Bactericidal concentration of prepared derivatives (MBC)

Regarding the MBC values, it was observed that, with the exception of N14, which produced lower MBC values, the values of the derivatives made against the bacteria S. aurea coincide with the MBC values of the antibiotic tetracycline. In contrast to the tetracycline antibiotic, the MBC values of the produced derivatives against the E. coli bacterium are greater. Regarding the antibiotic ampicillin, it provided fatal concentration values for both positive and negative types of bacteria that were significantly greater than those provided by the produced compounds. It is observed that, with respect to the two types of bacteria employed, the MBC values for the antibiotic streptomycin displayed greater values than those for the produced derivatives. We conclude from the above values that there is a discrepancy in the values of the minimum lethal concentrations of the prepared derivatives when compared with the MBC of some common antibiotics. This discrepancy may sometimes be due to the type of bacteria or to the type and composition of the antibiotic used for comparison [38].

Table 2. FT-IR spectra of the stretching vibrations of staring materials (cm^{-1})

Symbol	$-NH_2$ (m)	-NH-C=O	C-H Aromatic	C=O	C=N	C=C	S=O	C-N
A	3375.43 3338.53	3247.87 s	3105.39 w	1670.35 m	1593.20 s	1516.05 s		1338.60 **s**
B	3456.44 3336.85	3213.41 m	3043.67 w	1627.92 m	1573.91 m	1546.91 m		1342.46 **s**
C	3456.44 3336.85	3213.41 m	3047.53 w	1627.92 s	1600.92 s	1570.06 s		1342.46 s
D	3456.44 3336.85	3213.41 m	3043.67 m		1600.92 m	1573.91 159691 m	1130.29 s	1392.46 m
E	3483.44 3383.14	.32370 m	3059.10 m		1635.64 1585.49 m	1562.34 1504.48 s	1107.14 s	1338.60 m
F	3468.10 3379.29	3221.65 m	3109.25 m		1593.20 s	1519.91 s	1010.70 m	1288.45 m
G	3468.01 3379.29	3277.53 m	3109.25 w		1593.20 m	1519.91 m		1342.46 m

Table 3. ^{1}H-NMR spectral data of starting materials (ppm)

Symbol	$-NH_2$ (s)	C-H Heterocycle (s)	Aromatic proton (m)
A	6.34	7.53	7.45 -8.09
B	6.22	7.64	6.98 -8.08
C	6.21	7.21	7.31 -8.02
D	6.65	6.56	6.53 -8.02
E	6.15	6.67	7.08 -8.32
F	6.35	7.23	7.03-8.37
G	5.33	7.43	7.23-8.32

Table 4. ^{13}C-NMR spectral data of starting materials (ppm)

Symbol	NH_2	Aromatic	C-N (Heterocycle)	C=O	C=S	C=N	C-X
A	132.03	114.65-158.97	157.43	189.75		157.89	C-Br 146.32
B	140.51	113.94 - 155.25	150.55	186.17		160.85	C-CI 132.50
C	140.01	110.43 - 155.22	158.28	187.87		164.50	C-NO_2 130.02

D	140.39	110.19-156.81	154.46		188.99	162.22	C-Br 133.89
E	142.20	112.54 - 155.97	148.87		189.94	148.15	C-CI 132.01
F	143.52	113.52-154.23	149.32		187.7	154.98	C-NO_2 135.76
G	142.02	113.21-154.25	154.96			161.59	C-Br 139.98

Table 5. FT- IRspectra of the stretching vibrations of benzylated derivatives (cm^{-1})

Symbol	**-NH**	**Ar-H**	**C=O**	**C=C**	**C=N**	**C=S**	C-N	**C-X**
N1	3267.41 (m)	3055.24 3109.26 (w)	1651.07 (s)	1527.62 (s)	1600.92 (s)		1404.18 (m)	C-Br (636.51) (m)
N2	3278.99 (s)	3101.54 3055.24 (w)	1654.92 (s)	1527.62 (s)	1600.92 (s)		1404.18 (s)	(C-CI) (837.11) (s)
N3	3417.86 (m)	3078.39 (w)	1654.92 (s)	1516.05 (s)	1597.06 (s)		1408.04 S 1485.19 W	(C-NO_2) (1334.11) (s)
N4	3271.27 (s)	3055.24 (w)		1527.62 1651.07 (s)	1600.92 (s)	1180.44 1107.14 1068.56 (m)	1481.33 (m)	(C-Br) (690.52) (m)
N5	3282.84 (s) 3356.14 (w)	3055.24 3105.39 (w)		1527.62 (s)	1600.92 1651.07 (s)	1091.71 1029.99 1010.70 (m)	1485.19 1404.18 (s)	(C-CI) (813.96) (m)
N6	3417.86 (m)	3101.54 (m)		1516.05 (s)	1597.06 1654 (s)	1180.44 (m) 1103.28 (m)	1404.18 (s) 1485.19 (w)	(C-NO_2) (1334.74) (s)
N13	3340.71 (m)	3059.10 (m)		1523.76 (s)	1593.20 (s)	1176.58 1095.57 (m)	1485.19 1404.18 (m)	(C-Br) (621.08) (m)
N14	3356.14 (s)	3055.24 (w)		1519.91 (s)	1597.06 1674.21 (s)	1180.44 1095.57 1010.70 (m)	1404.18 1485.19 (s)	C-C)(31 (894.97) (m)
N15	3344.57 (s)	3097.68 (w)		1519.91 (s)	1597.06 1674.21 (s)	1219.01 (m)	1408.04 (s)	(C-NO_2) (1338) (s)

Symbol	-NH	Ar-H	C=O	C=C	C=N	C=S	C-N	C-X
N16	3348.42 (s)	3055.24 (w)		1519.91 (s)	1651.07 1604.77 (s)		1481.33 1404.18 (s)	(C-Br) (651.94) (s)

Table 6. ^{1}H-NMR spectra data of benzyolated derivatives (ppm)

Symbol	Aromatic Protons (m)	O=C-NH (s)	S=C-NH (s)	Py=NH (s)	NH-C=Oph (s)
N1	7.50-8.89	10.01			11.02
N2	7.99-8.02	10.21			10.32
N3	7.54-8.59	10.57			12.52
N4	7.52-8.44		10.03		10.55
N5	7.41-8.44		10.33		10.59
N6	7.22-8.03		10.01		10.88
N13	7.69-8.25		10.09		10.98
N14	7.43-8.24		10.76		11.57
N15	7.65-8.67		10.32		11.31
N16	7.24-8.26			13.23	11.43

Table 7. ^{13}C-NMR spectra data of the benzoylated derivatives (ppm)

Symbol	C-N	Aromatic	C=N	C=O	C=S	C-X
N1	145.62	118.21-135.86	146.75	187.76		C-Br 132.89
N2	147.64	112.23-136.21	148.97	190.12		C-CI 135.73
N3	146.32	-135.65 112.32	147.73	190.15		C-NO_2 130.76
N4	143.64	110.34-136.51	142.45	165.38	189.58	C-Br 137.75
N5	147.96	100.01-132.31	142.35		187.98	C-CI 131.53
N6	140.57	98.79-132.69	149.74		184.82	C-NO_2 130.91
N13	143.32	104.76-144.35	145.56		187.97	C-Br 133.03
N14	142.54	125.32 - 145.87	147.98		198.86	C-CI 134.52
N15	147.32	100.41 - 149.42	148.76		190.76	C-Br 134.89
N16	144.87	11 3.96 - 145.32	139.25			C-Br 132.25

Table 8. FT-IR spectral of tosylated derivatives(B1-B6) cm^{-1}

Symbol	Ar-H	Aliph-H	C=O	C=N (s)	C=C (s)	C=S	S=O	C-N	C-X
B1	3105.39 w	2924.09 w	1674.21 s	1593.20	1519.91		1481.33 1408.04 s	1338.60 s	c-no_2 756.10 825.53 m
B2	3055.24 w	2920.23 2850.79 w		1651.07 1600.92	1527.62	1091.71 1026.13 m	1489.05 w 1404.18 m	1334.74 m	c-ci 813.96 694.37 m
B3	31105 3074.53 w	2920.23 2846.93 w		1670.35	1593.20 1516.05	1099.43 1010.70	1481,33 w 1408.04 m	1338.60 s	c-no_2 829.39 c-ci 756.10 m
B4	3078.39 m	2916.37 2846.93 w		1670.35 1654.92	1597.06 1512.19	1107.14 m	1485.19 1404.18 m	1338.60 s	c-no_2 829.39 702.09 s
B5	3078.39 s	2924.09 2839.22 s	1654.92 s	1597.06	1516.05		1485.19 1408.04 s	1334.74 s	c-no_2 829.39 702.09 s
B6	3105.39 3055.24 s	2920.24 2850.79 s		1651.07 1600.92	1527.62	1072.42 1006.84 s	1485.19 1404.18 s	1334.74 s	c-br 813.96 s

Table 9. ^{1}H-NMR spectra data of tosylated derivatives (ppm)

Symbol	-CH_3 (s)	Aromatic Protons (m)	O=C-NH (s)	S=C-NH (s)
B1	1.07	7.43-8.43	10.54	
B2	1.45	7.65-8.23		10.36
B3	1.52	7.67-8.64		10.24
B4	1.21	7.6-8.67		10.63
B5	1.02	7.51-8.57	10.51	
B6	1.50	7.64-8.21		10.73

Table 10. ^{13}C-NMR spectra data of tosylated derivatives (ppm)

Symbol	-CH_3	Aromatic	C-N	C=N	C=S	C=O	C-X
B1	19.89	113.22-148.54	137.34	141.88	189.87		C-NO_2 144.5
B2	18.23	112.21-166.25	133.58	141.01	188.68		C-CI 142.32
B3	19.59	115.23-147.85	132.68	134.65	189.98		C-NO_2 142.23

B4	25.02	113.21-156.65	133.98	145.65		189.99	C-NO_2 142.65
B5	20.31	120.54-149.34	133,89	139.45	188.78		C-NO_2 144.95
B6	24.54	119.43-144.86	134.79	134.63		187.31	C-Br 135.35

Table 12. Inhibition diameters (IZ.mm) for derivatives (N6-N1, B2)

Derivative	*Escherichia coli (E.coli)*			*Staplylococcous aureas (S. aureas)*		
	Concn of derivative, µg/ml			*Concn of derivative µg/ml*		
	25	50	100	25	50	100
N_1	8	8	9	13	15	17
N_2	8	9	10	11	15	18
N_3	15	16	17	11	14	16
N_4	13	14	17	10	15	18
N_5	15	16	18	9	12	16
N6	10.4	22.4	23.4	13.4	28.4	32.4
B_2	13.3	15.2	31.4	16.4	31.4	34.4

Table 14. Minimum inhibitory concentration (MIC) and Bactericidal concentration (MBC) of synthetic derivatives and some antibiotics

Derivative/antibiotics	**Concentration (µg/ml)against *E.coli***		**Concentration (µg/ml)against *S .aureas***	
	MBC	MIC	MBC	**MIC**
N2	2500	1250	2500	1250
N4	2500	1250	2500	1250
N6	2500	1250	2500	1250
N14	2500	1250	1250	625
N15	2500	1250	2500	1250
B2	2500	1250	2500	1250
Ampicillin	>5	2500	5	1000
Tetracycline	<=1.56	315	2.5	250

Streptomycin	5.0	500	5	5

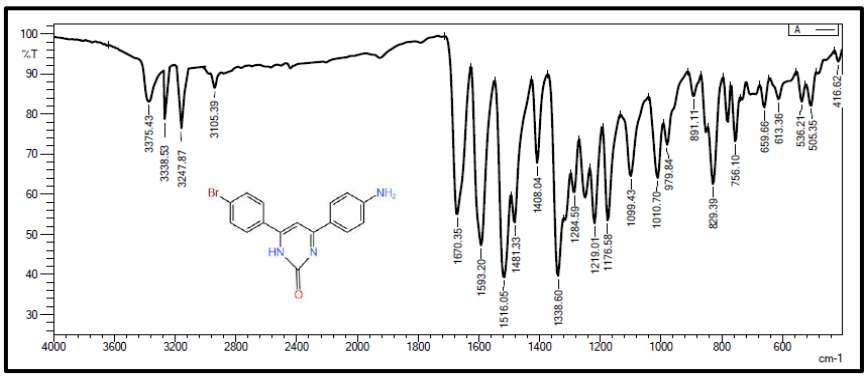


Fig. 2. IR spectrum of compound (A)

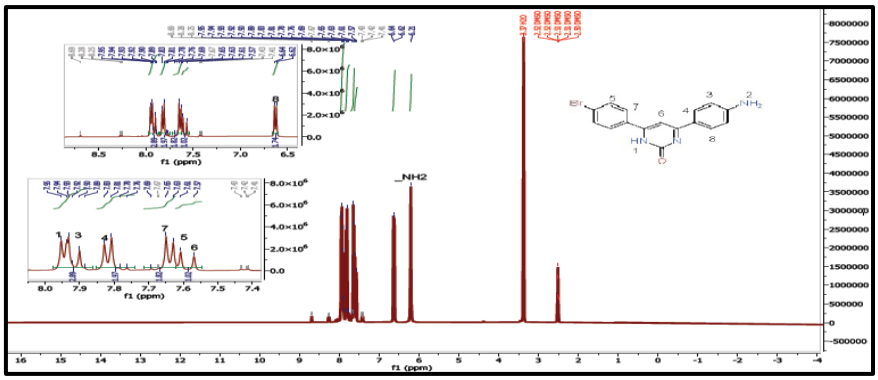


Fig. 3. ^{1}H-NMR spectrum of compound (A)

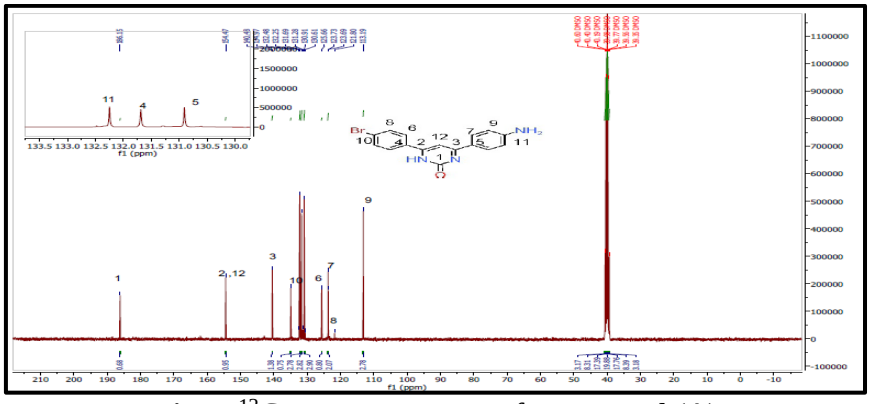


Fig.4. ^{13}C-NMR spectrum of compound (A)

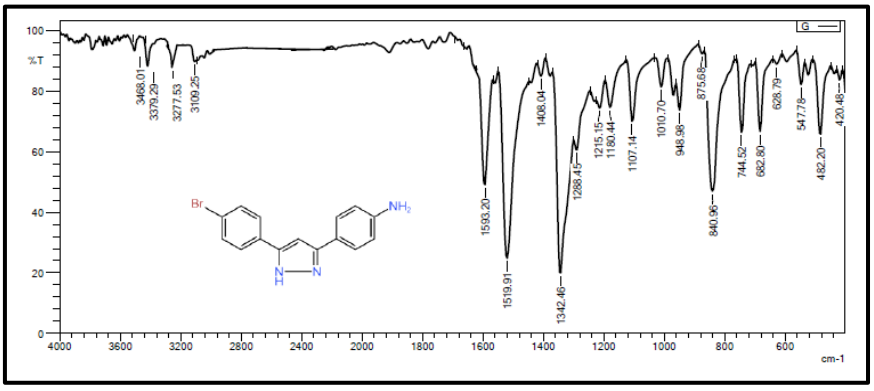


Fig. 5. IR spectrum of compound (G)

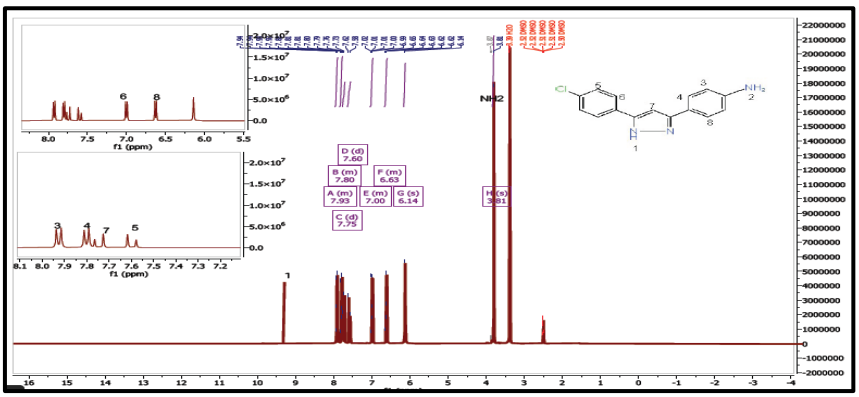


Fig.6. ^{1}H-NMR spectrum of compound (G)

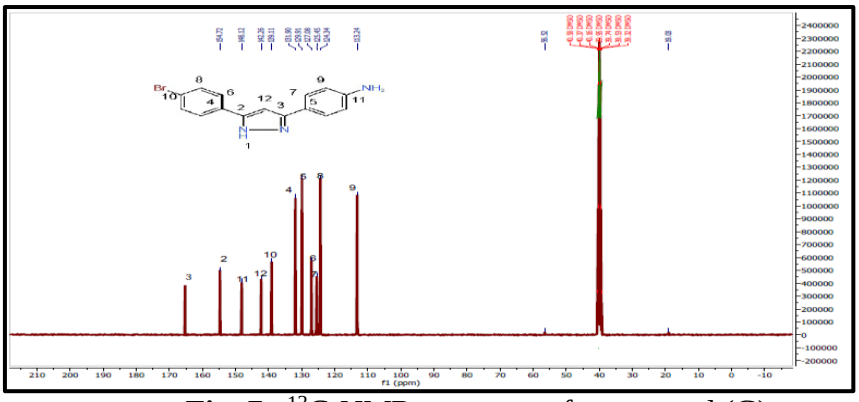


Fig. 7. ^{13}C-NMR spectrum of compound (G)

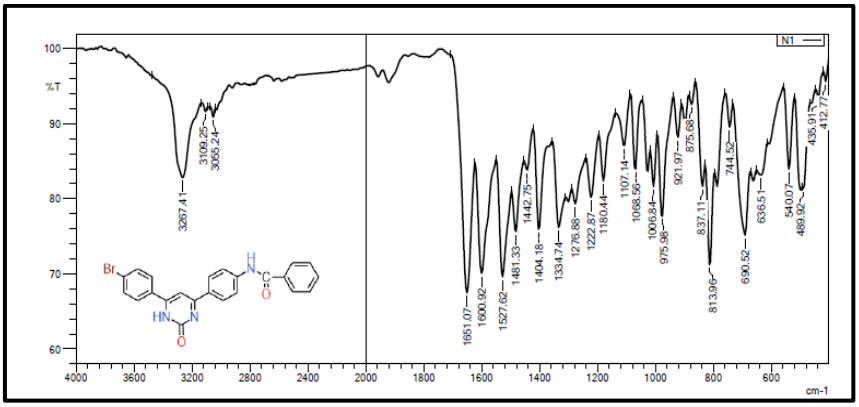


Fig. 8. IR spectrum of compound (N1)

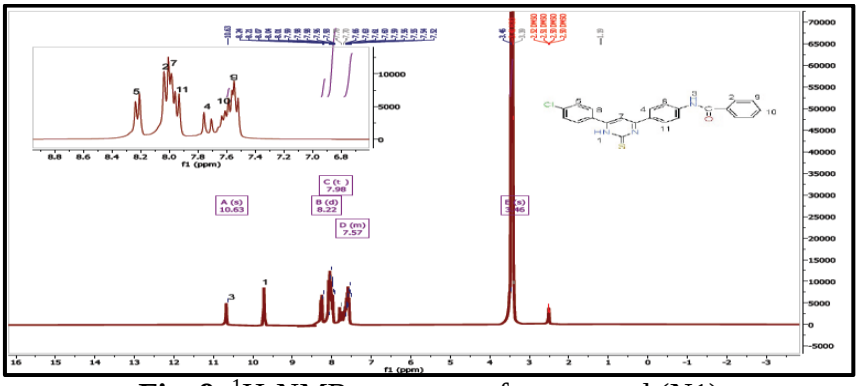


Fig. 9. ^{1}H-NMR spectrum of compound (N1)

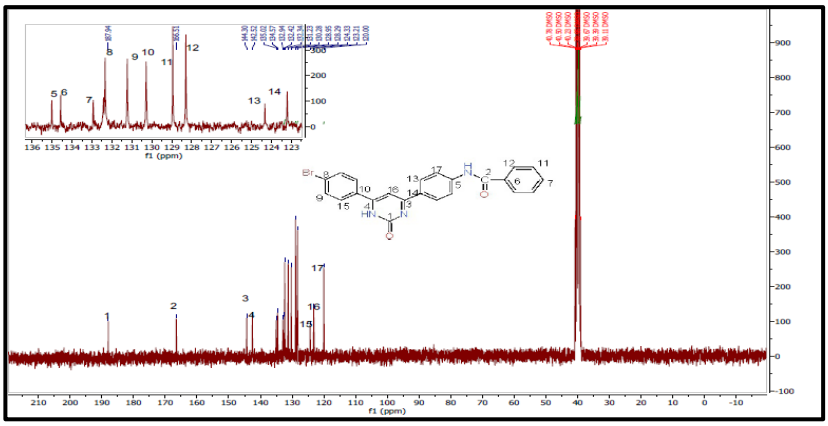


Fig. 10. ^{13}C-NMR spectrum of compound (N1)

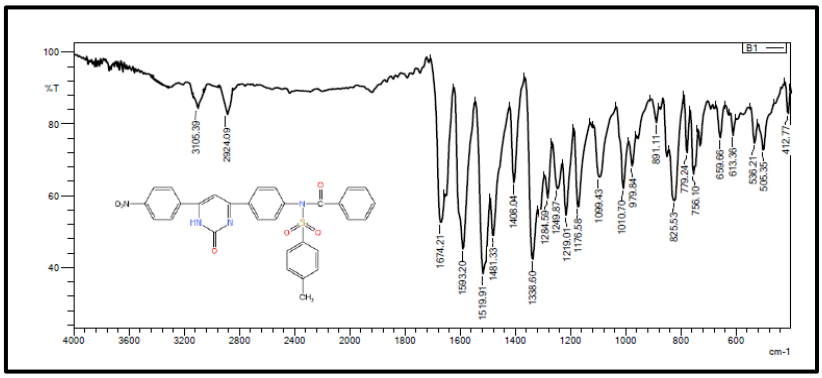


Fig. 11. IR spectrum of compound (B1)

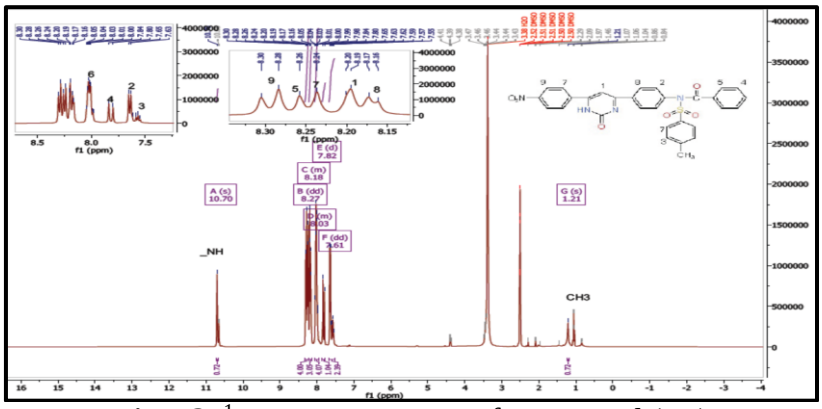


Fig. 12. ^{1}H-NMR spectrum of compound (B1)

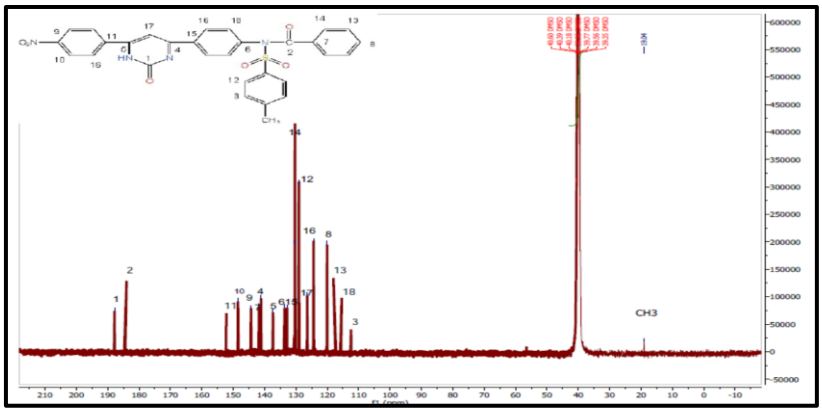


Fig.13. ^{13}C-NMR spectrum of compound (B1)

.35. Mass Spectra

Through the mass spectra recorded for the prepared derivatives (N1, N2, N4, N14, N16, B2, and B5), it was shown that the peak values of the molecular ion [M]+ agree with the resonance formulas proposed for these derivatives as shown in Table 11 and Figures 14 and 15.

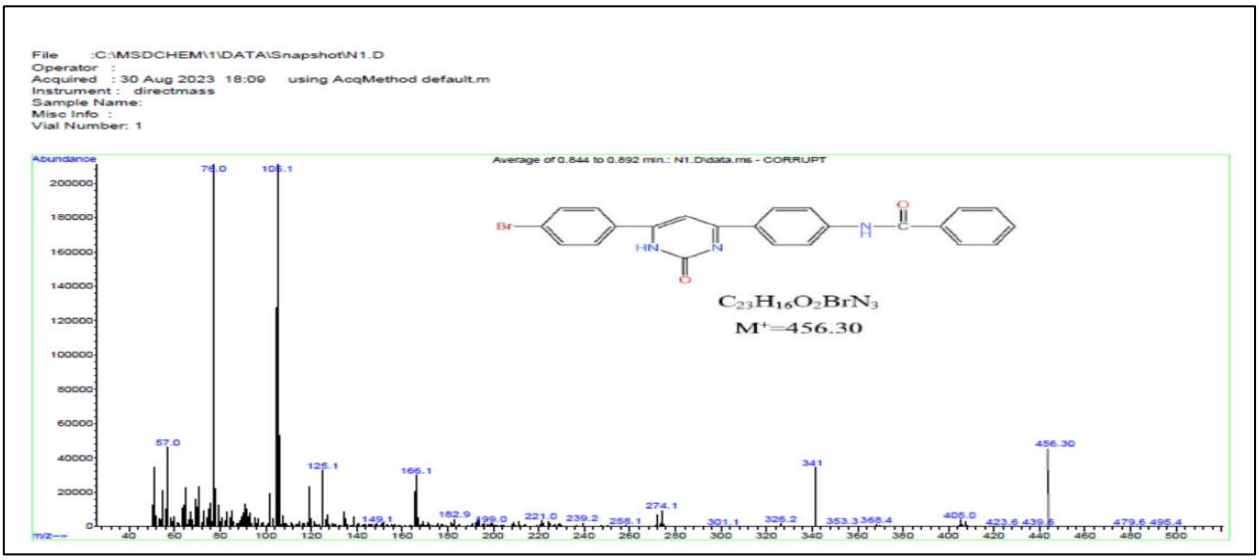


Fig. 14. Mass spectrum of the compound (N1)

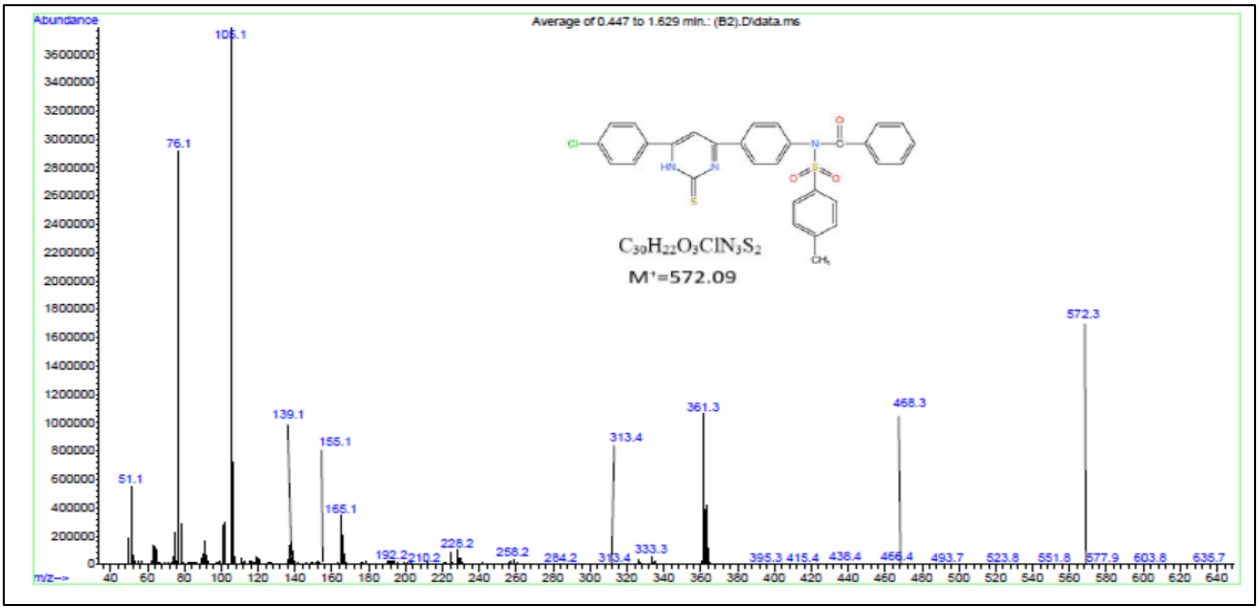


Fig.15. Mass spectrum of the compound (B1)

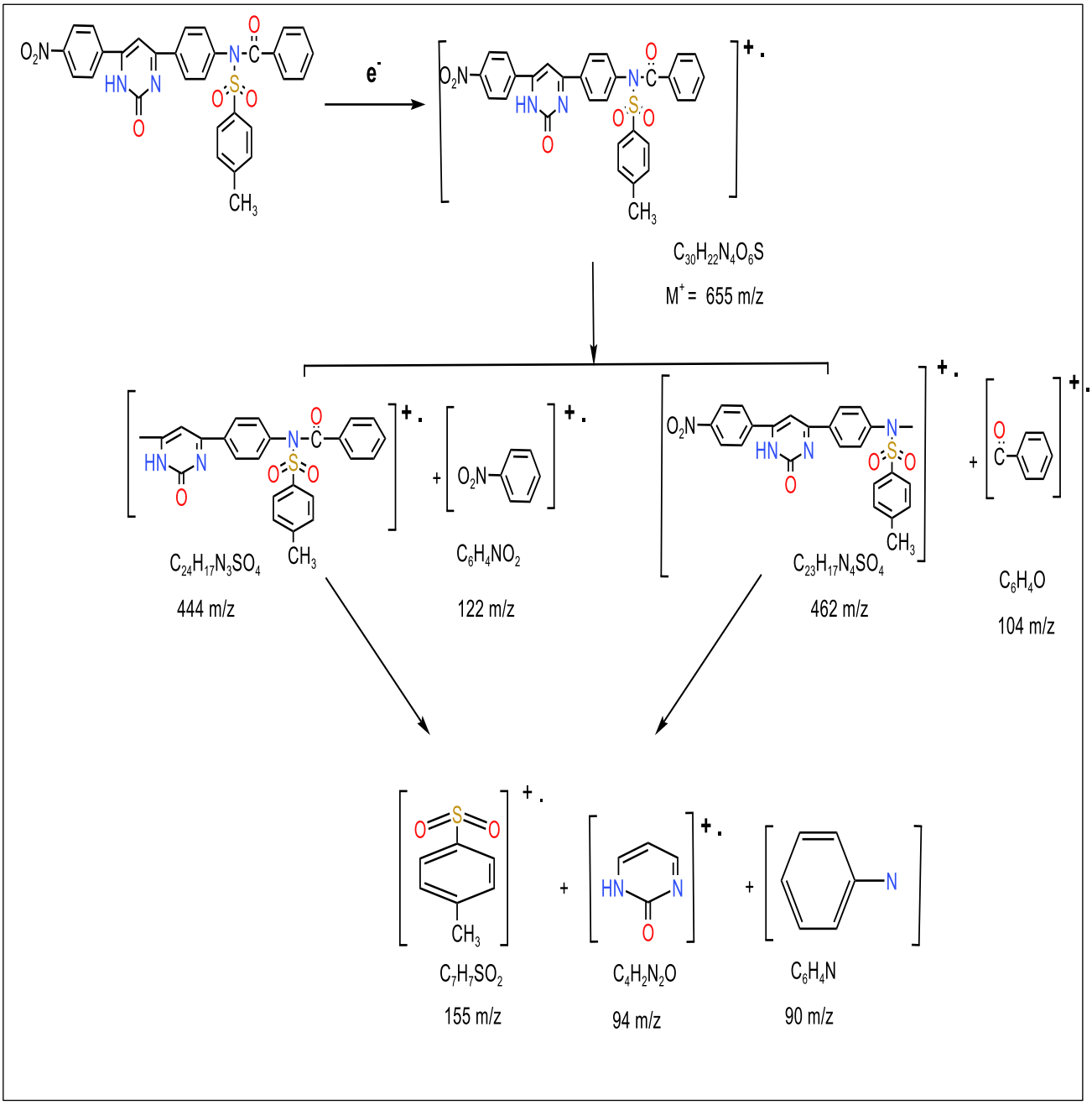


Diagram 2. The most important peaks produced for the compound (B5)

Table 11. The most important peaks and molecular ions in the mass spectra of the prepared compounds

Compound symbol	Molecular ion M+(m/z)	(m/z) Peaks
N1	456.30	$[C_{17}H_{12}OBrN_2]+\cdot$ =341 $[C_6H5]+\cdot$ =76 $[C_7H_5O\ ]+\cdot$ =105.1 $[C_{17}H_{12}O_2N_3\ ]+\cdot$ =276 $[C_9H_6N]+\cdot$ =128
N2	401	$[C_{16}H_{11}N_3OCI]+\cdot$ = 297 $[C_{11}H_8N_3O_2]+\cdot$ =290 $[C_7H_4O]+\cdot$ = 104 $[C_6H_4CI]+\cdot$ = 111

Compound symbol	Molecular ion M+(m/z)	(m/z) Peaks
		$[C_6H_5N]+\cdot$ = 91 $[C_4H_2N_2O]+\cdot$ = 94
N4	462.1	$[C_{16}H_{11}N_3OCI]+\cdot$ = 297 $[C_{11}H_8N_3O_2]+\cdot$ =290 $[C_7H_4O]+\cdot$ = 104 $[C_6H_4CI]+\cdot$ = 111 $[C_6H_5N\ ]+\cdot$ = 91 $[C_4H_2N_2O]+\cdot$ = 94
N14	452.35	$[C_{17}H_{11}CIN_3S]+\cdot$ =312 $[C_{17}H_{11}OCIN_3S]+\cdot$ =340 $[C_7H_4OCI]+\cdot$ = 139.1 $[C_6H_4CI]+\cdot$ =111 $[C_6H_5N]+\cdot$ =91 $[C_4H_2N_2S]+\cdot$ =110
N16	452.74	$[C_{15}H_{11}BrN_3\ ]+\cdot$ =313 $[C_7H_4CIO]+\cdot$ =139 $[C_6H_5CI]+\cdot$ =111.1 $[C_6H_5Br]+\cdot$ =156 $[C_9H_{11}OCIN_3]+\cdot$ =212 $[Br\ ]+\cdot$ =80
B2	572.09	$[C_7H_5O]+\cdot$ =105 $[C_{23}H_{17}O_2CIN_3S_2\ ]+\cdot$ =468.3 $[C_7H_7SO_2]+\cdot$ =155 $[C_{16}H_{10}CIN_3S]+\cdot$ =313 $[C_4H_2N_2S]+\cdot$ =110 $[C_7H_7O_2S]+\cdot$ =155 $[CN_2S]+\cdot$ =72
B5	566	$[C_{23}H_{17}N_4SO_5]+\cdot$ = 462 $[C_{24}H_{17}N_3SO_4]+\cdot$ =444 $[C_6H_4O]+\cdot$ =104 $[C_6H_4NO_2]+\cdot$ =122 $[C_7H_7SO_2]+\cdot$ =155 $[C_4H_2N_2O]+\cdot$ = 94 $[C_6H_4N]+\cdot$ = 90

Conclusions

The tosylation process was used to synthesize a new series of benzolated derivatives containing benzamide derivatives content apyrimidine ring and pyrazoline ring. These compounds were elucidated using techniques such as infrared spectroscopy, ^{1}H and ^{13}C-NMR, as well as mass spectrometry. Benzamide compounds substituted with a sulfonyl group (SO_2) give higher biological activity than those containing a carbonyl group (C=O) only. The prepared derivatives showed inhibitory concentration values lower than those of common antibiotics.

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BENZAMİN TÖRƏMƏLƏRİ: SİNTEZİ, XASSƏLƏRİ VƏ BİOLOJİ FƏALLIĞININ ÖYRƏNİLMƏSİ

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Xülasə: Tədqiqat işi iki kimyəvi üsulla bir sıra benzamid törəmələrinin sintezinə həsr olunmuşdur. Birinci üsul həlledici kimi 1,4-dioksanın iştirakı ilə tərkibində pirimidin və ya pirazolin halqası (A-G) olan bəzi aromatik aminlərin benzoil xlorid və ya p-xlorbenzoil xloriddən istifadə etməklə benzoillaşmasıdır (N1-N6, N13-N16). Törəmələri əldə etmək üçün ikinci üsul isə otaq temperaturunda katalizator və əsas kimi piridinin iştirakı ilə p-toluolsulfonilxlorid ilə (B1-B6) tozilasiyasıdır (N2-N6, N15). Alınan birləşmələr İQ spekroskopiya, ^{1}H-NMR, ^{13}C-NMR və kütlə spektroskopiyası ilə xarakterizə olunmuş, və onların fiziki xassələri öyrənilmişdir. Spektral məlumatlar benzamid törəmələrinin etibarlılığını təsdiqləyir. İşdə həmçinin sintez edilmiş maddələrin antimikrob xassələri öyrənilmişdir. Sınaq ilə əlaqədar olaraq bu birləşmələr tərəfindən verilən inhibitor zonasının diametri, minimum inhibitor qatılığının (MIQ) və minimum bakterisid qatılığının (MBQ) müəyyən edilməsi ilə təmsil olunan sintez edilmiş birləşmələrin antimikrob təsirin öyrənilmişdir. Test üçün *Staphylococcus aureas* (Gr+ müsbət) və *Escherichia coli* (Gr-mənfi) bakteriyalarından istifadə edilmişdir. Bundan əlavə, MİQ və MBQ nəticələri tetrasiklin, ampisilin və streptomisin kimi bəzi ümumi antibiotiklərin nəticələri ilə müqayisə edilmişdir. Müqayisə nəticəsində sintez edilmiş törəmələrin antimikrob preparatları kimi istifadə edilməsinin mümkünlüyü göstərilmişdir.
Açar sözlər: oksopirimidin, pirazolin, p-toluensülfonilxlorid, tosilləşmə, benzoilləşmə.

ПРОИЗВОДНЫЕ БЕНЗАМИНА: СИНТЕЗ, ХАРАКТЕРИСТИКА И ИЗУЧЕНИЕ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ

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Аннотация: Наше исследование включает синтез ряда производных бензамида посредством двух химических процессов. Первый - бензоилирование некоторых ароматических аминов, содержащих в своей структуре пиримидиновое или пиразолиновое кольцо (A-G), с использованием бензоилхлорида или п-хлорбензоилхлорида в присутствии 1,4-диоксана в качестве растворителя (N1-N6, N13-N16). Второй - тозилирование (N2-N6, N15) *n*-толуолсульфонилхлоридом в присутствии пиридина в качестве катализатора и основания при комнатной температуре с получением производных (B1-B6). Продукты были охарактеризованы методами ИК, ^{1}H-ЯМР, ^{13}C-ЯМР и масс-спектроскопии, а также записаны физические свойства продуктов. Спектральные данные подтвердили достоверность производных бензамида. Также в работе изучена антимикробная активность синтезированных соединений, представленной определением диаметра зоны ингибирования, минимальной ингибирующей концентрации (МИК) и минимальной бактерицидной концентрации (МБК), даваемых этими соединениями, в отношении тест-организмов Staphylococcus aureas (Gr^{+} положительный) и Escherichia coli (Gr^{-} отрицательный). Кроме того, результаты МИК и МБК сравнивались с результатами некоторых распространенных антибиотиков, таких как тетрациклин, ампициллин и стрептомицин. Проведенное сравнение показало возможность использования синтезированных производных в качестве противомикробных препаратов.
Ключевые слова: оксопиримидин, пиразолин, *n*-толуолсульфонилхлорид, тозилирование, бензоилирование.