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Synthesis, Antimicrobial of N-[4-(4-Arylidene)-2-(4-X-Phenyl)-5-Oxo-4, 5-Dihydro-Imidazol-1-Yl] - Benzenesulfonamides

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Abstract
A novel series of (1a-e and 2a-e) were synthesized and characterized using IR, ^{1}HNMR and C^{13}NMR. These compounds were in vitro screened against several bacterial species as well as Candida albicans, the common fungi species and found exhibiting moderate to potent activity. The newly synthesized sulfonamide derivatives were evaluated. Sulfonamide derivatives have been prepared by added *p*-toluenesulfonyl chloride or benzenesulfonyl chloride to the mixure of N-aminoimidazoline in pyridine was added drop wise at 0 ◦C. The resulting solution was stirred at room temperature for 7 hr. the reaction monitored by TLC. At the end of this period, the reaction solution was poured into mixture of ice and concentrated hydrochloride acid and water; the yellow colored precipitate was recovered. Washed with dilute hydrochloric acid and water, and recrystallized from the ethanol: water.

Keywords: N-amino-imidazoline, benzenesulfonamides antibacterial and fungal agent, Synthesis.

1. Introduction
Sulfonamides are very important compounds due to their wide range of biological activities, being also the first synthetic compounds to have had utility in human therapy as antimicrobial drugs, thus opening the route for the antibiotic revolution in medicine. (V, Mihali, PhD, 2012) [17]. According to the World Health Organization (WHO), the antimicrobial resistance and the limited number of efficacious antimicrobial drugs represent the main hurdle to the treatment of infectious diseases worldwide. Thus, the synthesis and discovery of new efficient antimicrobial agents is intensively considered during the last decade (None, 2012) [10]. In recent years, significant attention has been drawn to imidazole derivatives due to their diversified therapeutic activities like antibacterial (Kathiravan *et al*., 2012), antifungal (Hussain *et al*., 2009) [3], antiviral (Tonelli *et al*., 2010) [16], anti-inflammatory (Kahlon, D.K., 2009) [6], antitubercular (Shingalapur *et al*., 2009) [13], antidepressant (Gentili, F. 2006) [2] analgesics (Li, J.-X. 2011) [5], and antitumor (Refaat, 2010) [12]. These facts encouraged us to explore the synthesis of novel imidazoline derivatives and illustrate their activities against some gram positive and gram negative bacteria as well as Candida albicans, the most common fungi species. To explain the promising activity of these derivatives,

2. Experimental part
2.1. Synthesis
All starting materials and solvents were purchased from Aldrich and Fluka and used without further purification. Melting points were determined on an electro-thermal capillary apparatus and are uncorrected; FT-IR measurements were recorded on a Shimadzu model FTIR-8400S. ^{1}HNMR, C^{13}NMR spectra were obtained with a Bruker spectrometer model ultra-shield at 400 MHz in DMSO-d TMS as internal standard. Note: in16 solution with the ^{1}H NMR spectra, the peaks at d 2.5 and 3.35 are for solvent (DMSO-d) and dissolved water in (DMSO-d6), respectively.

2.2. General Procedure for the synthesis of compounds (1a-e and 2a-e)
Synthesis 4-Nitro-hippuric acid or hippuric acid Glycine (10mmol) in 10ml of 1N sodium hydroxide was cooled at 0-5 ℃ and the cold solution was added dropwise to a solution of 10 mmol of an appropriate acid chlorides or in 15ml of chloroform. The reaction mixture was continued under stirring for an additional one hour. The aqueous layer was separated and acidified with 2N hydrochloric acid. The products were collected by filtration and recrystallized from 80% ethanol. To a stirring mixture of hippuric acid or 4-Nitro-hippuric acid (0.01 mol)

acetic acid (5 ml) acetic anhydride (20 ml), aromatic aldehyde (0.01 mol) was added. Refluxed with temperature of reaction was reached to 80 °C for 4hr, The mixture become almost solid, and then as the temperature rises, it gradually liquefies and turns deep yellow in color. After completion of the reaction monitored by TLC [Methanol: Ether: n-hexane (1: 3: 2)] the reaction is allowed to cool, then the mixture was poured in to crushed ice and stirred for 30 min. the product was collected and recrystallized from suitable solvent to yield the desired compound**.** To a mixture of oxazolones derivatives compounds (0.01 mol) in dry pyridine (5ml) hydrazine hydrate (99%) (10ml) was added. The reaction mixture was refluxed for 30 hr the reaction monitored by TLC. Then, the mixture was allowed to cool to room temperature and pyridine was removed. The product was recrystallized from ethanol to afford the desired compounds (N-amino imidazoline) which prepared previously. In these paper we prepare sulfonamide derivatives to the mixure of N-aminoimidazoline (0.004 mol) in pyridine (10 mL) *p*- toluenesulfonyl chloride or benzenesulfonyl chloride (0.004mol) was added drop wise at 0 ◦C. The resulting solution was stirred at room temperature for 7 hr. the reaction monitored by TLC. At the end of this period, the reaction solution was poured into mixture of ice and concentrated hydrochloride acid and water; the yellow colored precipitate was recovered. Washed with dilute hydrochloric acid and water, and recrystallized from the ethanol: water.

2.2.1. Synthesisof N-[4-(4-Arylidene)-2-(4-X-phenyl)-5-oxo-4, 5-dihydro-imidazol-1-yl]-4-methyl-benzenesulfonamides (1a-e)

To the mixure of N-aminoimidazoline (0.004 mol) in pyridine (10 mL) *p*- toluenesulfonyl chloride (0.76g, 0.004mol) was added drop wise at 0 ◦C. The resulting solution was stirred at room temperature for 5 h. At the end of this period, the reaction solution was poured into mixture of ice and concentrated hydrochloride acid and water; the yellow colored precipitate was recovered. Washed with dilute hydrochloric acid and water, and recrystallized from the ethanol: water.

- **N-[4-(4-Bromo-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-4-methyl-benzenesulfonamide** (yield 80%), (m.p, 162-164 °C), (FTIR (KBr) υ: 3423.65-3250 (NH), 3174.83,3030 (C-H ar.=CH olf.),2926.01 $_{assym}$,2862.36 $_{sym}$ (C-H al.) 1651.07 (-C=O imidazole.), 1630 (-C=N, C=C olf.), 1595..13,1520 (C=C ar.), (1332.81 $_{asy}$, 1161.15$_{sy}$ S=O Str.), 798.53 cm-1 (C-Br str.), (798.53,686.66 CH_{ar} out of plane).). ^{1}HNMR (DMSO-d 6) ς (p p m),2.88(-CH3,s,3H), 6.58 – 8.88 (m, Aromatic protons and s, C=CH- proton) 9.53(s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (163.90, C=O**), (**158.21**,** C=N**), (**157.11, 152.76**,** C=C**),** (115.51-142.95Ar. Carbon), 20.73(-CH3)

- **N-[4-(4-Chloro-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-4-methyl-enzenesulfonamide.** (yield 75%), (m.p, 173-176 °C,), (FTIR (KBr) υ: 3425.58-3201.83 (NH), 3043.67 (C-H ar.=CH olf.), 2950$_{assym}$,2870.2 $_{sym}$, C-$H_{alif.}$ 1666.5 (-C=O imidazole.), 1635.64 (-C=N, C=C olf.), 1589.34, 1411.89(C=C ar.), (1342.46$_{asy}$,1161.15 $_{sy}$ S=O Str.), 775.38 cm-1 (C-Cl str.), (798.12, 624.94 CH_{ar} out of plane).). ^{1}HNMR (DMSO-d 6) ς (p p m),2.32(-CH3,s,3H), 7.03 – 8.94 (m, Aromatic protons and s, C=CH- proton) 9.46(s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (164.01, C=O**), (**163.97**,** C=N**), (**158.24, 145.95**,** C=C**),** (117.89-145.37Ar. Carbon), 21.00 (-CH3)

- **4-Methyl-N-[4-(4-nitro-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-benzenesulfonamide**. (yield 79%), (m.p, 163-166 °C,), (FTIR (KBr) υ: 3375.43-3201.83(NH),3078.39, 3030(C-Har.,=CHolf.), 2939.52$_{asy}$, 2839.22$_{sy}$, C-$H_{aliph.}$ 1666.5(-C=O,imidazole.), 1635.64 (-C=N, C=C olf.), 1589.34,1508.33 (C=C ar.), 1489.05, $_{assy}$. 1330.88 $_{sy}$. of (Ar-NO2) (1346.31 $_{asy}$, 1161.15 $_{sy}$ S=O Str.), 771.53 cm-1 (C-Cl str.), (813.96, 648..08 CH_{Ar} out of plane).). ^{1}HNMR (DMSO-d 6) ς (p p m),2.29(-CH3,s,3H), 6.573 – 8.87 (m, Aromatic protons and s, C=CH- proton) 9.46(s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (163.93, C=O**), (**163.89**,** C=N**), (**158.21, 157.17**,** C=C**),** (112.17-152.77Ar. Carbon), 20.04 (-CH3)

- **N-[4-(4-Bromo-benzylidene)-2-(4-nitro-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-4-methyl-benzenesulfonamide**. (yield 75%), (m.p, 135-137 °C,), (FTIR (KBr) υ: 3250.05 (NH), 3061.03 (C-H ar.=CH olif.), 2924.09,2854.65(C-H al.) 1699.29, 1680 (-C=O imidazole.), 1639.49 (-C=N, C=C olf.), 1608.63.1539.20 (C=C ar.), 1502.55asy.,1336.67 $_{sy}$. of (Ar-NO2), (1336.67$_{asy}$, 1161.15$_{sy}$ S=O Str.), 769.6 cm-1 (C-Br str.), (765.74,663.51 CH_{Ar} out of plane).). ^{1}HNMR (DMSO-d 6) ς (p p m), 2.29(-CH3,s,3H), 7.04 – 8.62 (m, Aromatic protons and s, C=CH- proton) 9.76(s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (167.99, C=O**), (**165.69**,** C=N**), (**158.22,145.89**,** C=C**),** (112.17-145.74Ar. Carbon), 20.91 (-CH3).

- **4-Methyl-N-[4-(4-nitro-benzylidene)-2-(4-nitro-phenyl)-5-oxo-4, 5-dihydro-imidazol-1-yl]-benzenesulfonamide.** (Yield 85%), (m.p, 212-215 °C,), (FTIR (KBr) υ :).3373.5-3248.13 (NH), 3043.67 (C-H ar. =CH olf.), 2926.01 $_{assym}$, 2866.22 $_{sym}$ (C-H al.) 1653 (-C=O imidazole.), 1630 (-C=N, C=C olf.), 1604.77,1510.26 (C=C ar.), 1438.9 $_{assy}$.,1332.81 $_{sy}$. of (Ar-NO2), (1332.81 $_{assy}$, 1159.22$_{sy}$ S=O Str.), 815..89 cm-1 (C-Cl str.), (763.81,663.51 CH_{ar} out of plane). ^{1}HNMR (DMSO-d 6) ς (p p m),2.37 (-CH3,s,3H), 6.51-8.48 (m, Aromatic protons and s, C=CH- proton) 9.90(s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (167.65, C=O**), (**165.62**,** C=N**), (**158.21, 157.139**,** C=C**),** (112.03-151.45 Ar. Carbon), 20.91 (-CH3).

2.2.2. Synthesis of N-[4-(4-Arylidene)-2-(4-X-phenyl)-5-oxo-4, 5-dihydro-imidazol-1-yl]-benzenesulfonamide (2a-e)

To the mixure of compound (3) (0.004 mol) in pyridine (10 mL) benzenesulfonyl chloride (0.7g, 0.004mol) was added drop wise at 0 ◦C. The resulting solution was stirred at room temperature for 5 h. At the end of this period, the reaction solution was poured into ice water. The precipitate was filtered, dried, and recrystallized from the ethanol: water. The physical appearance, percent yield and melting point are

- **N-[4-(4-Nitro-benzylidene)-2-(4-nitro-phenyl)-5-oxo-4, 5-dihydro-imidazol-1-yl]-benzenesulfonamide**. (yield 65%), (m.p, 195-187 °C,), (FTIR (KBr) υ: 3356.15, 3251.98 (NH), 3190.26, 3080 (C-H ar.=CH olf.), 2939.52 $_{asy}$ – 2870.08 $_{sy}$ (C-H al.),1678.07, 1651.07 (-C=O

imidazole.), 1620 (-C=N, C=C olf.), 1581.63 (C=C ar.), 1489.05, $_{asy}$. 1330.88 $_{sy}$. of (Ar-NO2),). ^{1}HNMR (DMSO-d 6) ς (p p m), 6.56-8.62 (m, Aromatic protons, s,1H,-C=CH- proton) 9.46(s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (164.06, C=O**), (**161.70**,** C=N**), (**157.11,155.36**,** C=C**),** (119.58-148.47Ar. Carbon).

- **N-[4-(4-Bromo-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-benzenesulfonamide**.
(yield 70%), (m.p, 181-183°C,), (FTIR (KBr) υ: 3371.57-3224.98 (NH), 3086.11,3010 (C-H ar.=CH olf.), 2893.22$_{asy}$,2808.36$_{sy}$,C-H$_{aliph.}$ 1712.79,1651.07 (-C=O imidazole.), 1610 (-C=N, C=C olf.), 158163,1516.05(C=C ar.), (1334.74$_{asy}$, 1157.29$_{sy}$ S=O Str.), 798.53 cm-1 (C-Br str.), (798.53,686.66 CH$_{ar}$ out of plane).).). ^{1}HNMR (DMSO-d 6) ς (p p m), 6.57-8.49 (m, Aromatic protons, s, 1H, - C=CH- proton) 8.85 (s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (172.48, C=O**), (**166.54**,** C=N**), (**158.25, 15665**,** C=C**),** (115.52-156.65 Ar. Carbon).

- **N-[4-(4-Chloro-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-enzenesulfonamide**.
(yield 80%), (m.p, 196-199 °C,), (FTIR (KBr) υ: 3302.13(NH),3078.39,3030(C-H ar.,=CH olf.), 2930$_{assy}$,2835.36 $_{sy}$, C-H$_{alif.,}$ 1651.07 (-C=O,imidazole.), 1651.07(-C=N,C=Colf.),1590, 1577.77, (C=C ar.), 1489.05, $_{assy}$. 1330.88 $_{sy}$. of (Ar-NO2) (1346.31 $_{asy}$,1161.15 $_{sy}$ S=O Str.), (771.53, 648..08 cm-1 CH$_{ar}$ out of plane).). ^{1}HNMR (DMSO-d 6) ς (p p m), 6.56 -8.49 (m, Aromatic protons, s,1H,- C=CH- proton) 9.55 (s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (164.07, C=O**), (**158.22, C=N**), (**152.79, 144.12**,** C=C**),** (112.13-143.56 Ar. Carbon).

- **N-[4-(4-Chloro-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-benzenesulfonamide**.
(yield 80%), (m.p, 141-143 °C,), (FTIR (KBr) υ: 3356.14-3302.13 (NH), 3078.39.3020(C-HAr.,=CH olf.), 2943.37$_{asy}$, 2870.08$_{sy}$, C-H$_{aliph.}$ 1651.07 (-C=O imidazole.), 1651.07(-C=N, C=C olf.), 1593.2,1577.77 (C=C ar.), (1342.75 $_{asy}$,1161.15 $_{sy}$ S=O Str.), 756..1 cm-1 (C-Cl str.), (798.53, 628.79 CH$_{Ar}$ out of plane). ^{1}HNMR (DMSO-d 6) ς (p p m), 6.59 -8.88 (m, Aromatic protons, s,1H,- C=CH- proton) 9.53 (s,1H,-NH). C^{13}NMR (DMSO-d 6) ς (p p m), (164.11, C=O**), (**164.06, C=N**), (**158.21, 157.09**,** C=C**),** (115.52-152.75 Ar. Carbon).

- **N-[4-(4-Bromo-benzylidene)-2-(4-nitro-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-benzenesulfonamide**.
(yield 81%), (m.p, 198-200 C°,), (FTIR (KBr) υ:). 3377.36,3219.19 (NH), 3062.96 (C-H ar.=CH olf.), 1683.86 (-C=O imidazole.), 1625.99 (-C=N, C=C olf.), 1604.77,1541.12 (C=C ar.), 1502.55 $_{asy}$.,1336.67 $_{sy}$. of (Ar-NO2), (1330.88$_{asy}$, 1163.08$_{sy}$ S=O Str.), 752.24 cm-1 (C-Br str.) (752.24, 686.66 CH$_{Ar}$ out of plane). ^{1}HNMR (DMSO-d 6) ς (p p m), 9.3 (s, 1H,-NH) 6.6 -8.8 (m, Aromatic protons, s, 1H,- C=CH- proton). C^{13}NMR (DMSO-d 6) ς (p p m), (168, C=O**), (**166, C=N**), (**158,156**,** C=C**),** (112-152 Ar. Carbon).

2.3. Antimicrobial studies
The sulfonamide and N-amino imidazoline derivatives (1a-e and 2a–e) were tested for their antimicrobial activity against Escherichia coli, Pseudomonas aeruginosa, (gram -ve), Staphylococcus aureus, Bacillus SPP (gram +ve) as well as C. albicans using the well diffusion method (Tomi *et al*., 2010). DMSO was run as a control and the test was performed at 1 mg/mL concentration using DMSO solvent. Sulfamethoxazole and miconozole were used as standard drugs. Each experiment was made in triplicate and the average reading was taken.

2. 4.Antimicrobial activity
This research included the in vitro assay of the synthesized compounds (1a-e and 2a–e) against several microbial species (Table 1). The in vitro assay achieved using concentrations of synthesized derivatives 1 mg/mL. The compounds were active against all bacterial and fungi strains. The tested derivatives exhibited promising activity at the 1mg/mL concentration against E. coli, P. aeruginosa, (gram negative species) moderate activity against and moderate activity against S. aureus (gram positive).When we compared the microbial activity of the compounds with the standard drug, compound 2b shows highest inhibition activity against. All the tested compounds showed no activity against S. aureus. The all derivatives were screened against C. albicans, the common fungi species and evaluated as potent antifungal.

3. Results and Discussion
Sulfonamides derivatives were synthesized and identify on the basis of melting point range, Rf values, solubility, FTIR, ^{1}HNMR, C13 NMR., All the compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, Bacilluse Spp and S aureus, using disc diffusion method. Selected of some newly synthesized Sulfonamides derivatives were screened *in vitro* for their antibacterial activity against four types of pathogenic bacterial isolates and for antifungal activity against one type of Candida albicans. DMSO as a blank exhibited no antimicrobial activity against any of the tested microorganisms used. The bacterial isolates were more susceptible to the synthesized compounds than isolated fungal. The recorded inhibition zones are summarized in Table (1). We observed some important results from the data of inhibition zone: Most of the synthesized compounds showed antibacterial and/or antifungal activities. All compounds at concentration (1 mg/ml) were highly active against *Staphylococcus aureus* except (1b, 2a, 2c) showed resistance. Most compounds at concentration (1 mg/ml) were highly active against Bacillus *subtilis* whereas (3c) showed moderate activity against this microorganism. All compounds at concentration (1 mg/ml) except (1a) showed highly active against *E. Coli*. Gram (-ve) type *Pseudomonas aeuroginosa* showed resistance to compound (1a) all Compounds acts highly activity as antifungal agents towards *Candida Albicans*. While Compounds *(2c)* show moderate activity as antifungal agents towards *Candida Albicans*. Therefore sulfonamide derivatives compounds (1a-b and 2a-c) can be recommended for further studies.

4. Conclusion
The sulfonamide and N-amino imidazoline derivatives have been discovered and reflected significant biological activities with appreciably wider spectrum. The versatile synthetic applicability & biological activity of these heterocycles will help the medicinal chemists to plan, organize & implement new approaches towards discovery of novel drugs. Further combinatorial libraries of these compounds can be generated which can be screened optimal pharmacological activities by optimization techniques using QSAR investigation

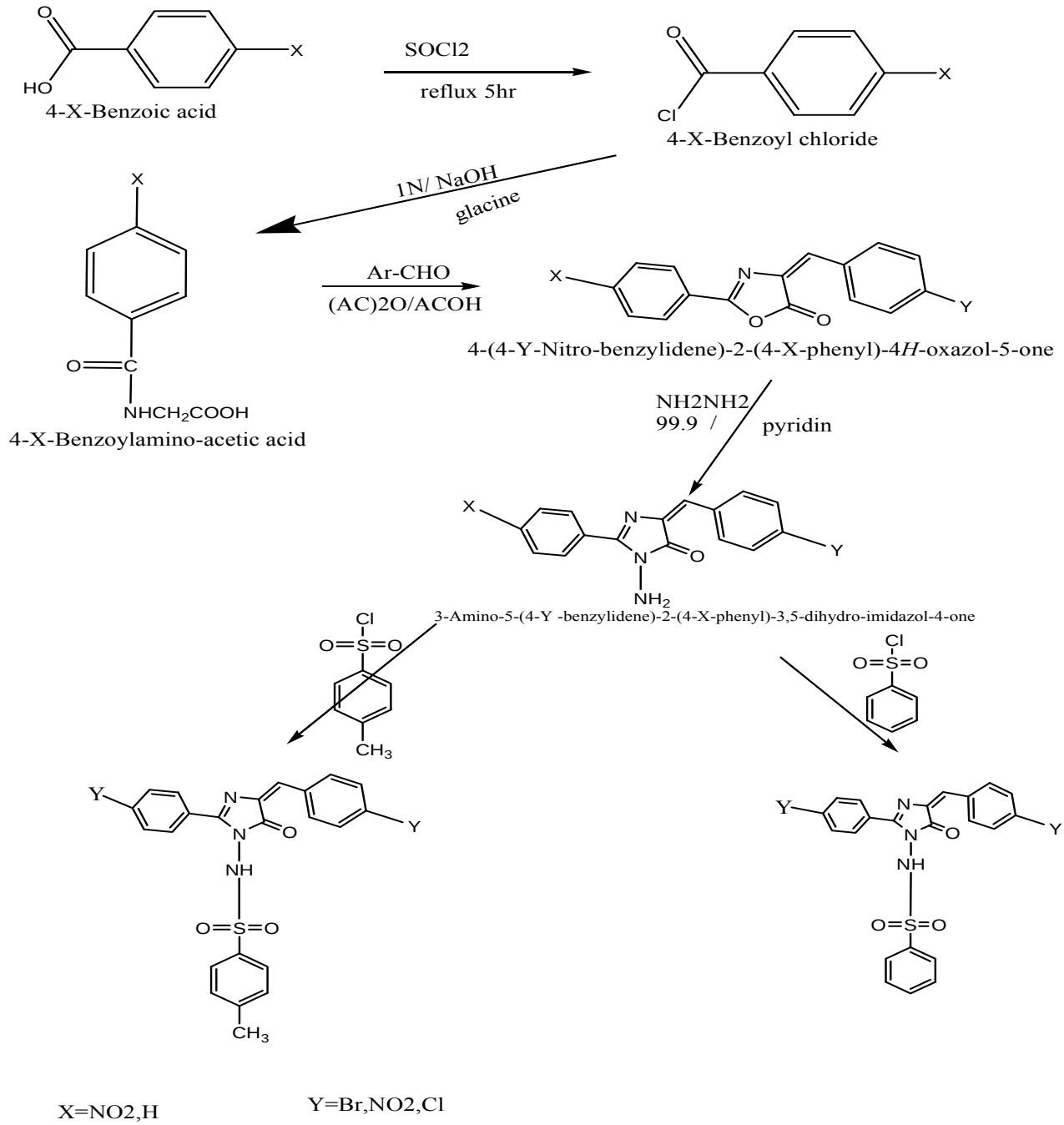

Fig 1: scheme for synthesis of targets compounds

Table 1: The antimicrobial activity of the tested compounds.

Compound		Zone of Inhibition in mm				
		Bacillus Spp.	**Staph. aureus**	**E.coli**	**Pseudo-monas aeruginosa**	**Candida albicans**
1a 22	1mg/ml	15	18	10	-	17
1b 24	1mg/ml	20	-	12	15	14
1c 26	1mg/ml	17	14	15	16	18
1d 16	1mg/ml	18	16	17	13	19
1e 20	1mg/ml	20	18	19	14	13
2a 21	1m 1mg/ml	19	-	13	18	15
2b 23	1mg/ml	17	20	11	10	16
2c 27	1mg/ml	11	-	12	15	12
2d 25	1mg/ml	14	17	18	21	14
2e 17	1mg/ml	15	15	20	17	17
sulfamethaxazole		34	32	31	29	
miconozole	-	-	-	-		16

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