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Design and Synthesis of Some Pyrazole, Isoxazole, Benzoxazepine and Benzothiazepine Derivatives as Anti-Inflammatory and Antimicrobial Agents

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ABSTRACT

An efficient and rapid synthesis of some new pyrazoles, isoxazole, benzoxazepine and benzothiazepine derivatives is described. The synthesized compounds were investigated for their anti-inflammatory and antimicrobial activities and some of them showed potent anti-inflammatory and anti-microbial activities.

Keywords: Anti-inflammatory activity**,** Prostaglandin, Pyrazole, Isoxazole, Benzoxazepine, Benzothiazepine, Antimicrobial activity

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INTRODUCTION

Infectious diseases are a major cause of morbidity and mortality around worldwide[1]. Inflammation caused by invading pathogens and prostaglandins has also become a serious public concern around the world[2-3]. Anti-inflammatory drugs are the valuable addition in medicine to control inflammation related pain and discomfort. Pyrazole and isoxazole derivatives have received enormous attention in the last two decades as versatile bioactive molecules, as they were found to exhibit especially, anti-inflammatory activity by inhibiting COX enzymes such as COX-1 and COX-2[4-7]. In addition, some pyrazole derivatives exhibited important biological properties such as antitumor cyclin-dependent kinase (CDK) inhibitors[8] and monoamine oxidase-B (MAO-B) inhibitors[9]. Furthermore, some isoxazole derivatives have been associated with anti-HIV[10] and antioxidant and anti-inflammatory[11] activity. 1, 5-Benzoxazepine derivatives have been identified as novel microtubule-depolymerising agents[12], antipsychotic and central nervous system depressant activity[13]. Several benzothiazepine derivatives have been reported to have potential calcium channel blocker[14] activity. On the other hand, the compounds containing aryl sulfonate moiety have dominated the surfactant industry and have been received considerable attention during last two decades as they are endowed with variety of biological activities like papillomavirus microbicidal[15], anti-human immunodeficiency virus-1[16], antineoplastic[17], and anticancer activity[18].

Thus, our interest in the synthesis of some novel bioactive heterocyclic molecules containing aryl sulfonate moiety and basic pyrazole, isoxazole, thiazepine, oxazepine nucleus using microwave irradiation technique under solvent-free conditions.

MATERIALS AND METHODS

All the used chemicals were of analytical grade. Melting points were performed in open capillary tubes and were uncorrected. IR spectra were recorded on Avance 650 Spectrometer by using KBr pellets and frequencies are expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra are recorded in $CDCl_3$ on Perkin Elmar 200 MHz and 50 MHz Spectrometers. Anti-inflammatory activity of all compounds was tested at National Toxicology Centre, Pune.

Procedure for the synthesis of 2-acetylphenyl benzoate (2)

A mixture of 2-hydroxy acetophenone (0.01mol), benzoyl chloride (0.01mol) and anhydrous K_2CO_3 (0.012 mol) was grinded well in mortar for 6-7 minutes. The reaction mixture was left aside for one hour at room temperature and poured into ice cold water with constant stirring for 10 minutes. The solid obtained was filtered, washed with water and purified by column

chromatography using chloroform / n-hexane mixture.

Procedure for the synthesis of 1-(2-hydroxyphenyl)-3-phenylpropane-1, 3-dione (3)

A mixture of 2-acetylphenyl benzoate (0.01 mol) and KOH (0.02 mol) in 10 ml dry pyridine was grinded well in mortar for 10 minutes. The crude yellow solid obtained was poured into 10 ml ice cold water containing 5% acetic acid and stirred for 5 min. The solid thus separated was filtered, washed several times by water containing little amount of acetic acid. The crude product was purified by column chromatography using chloroform / ethanol mixture.

Procedure for the synthesis of 1-phenyl-3-(2-(tosyloxy) phenyl) propane-1, 3-dione (4)

A mixture of 1-(2-hydroxyphenyl)-3-phenylpropane-1, 3-dione (0.01mol), *p*-toluene sulfonyl chloride (0.01mol) and anhydrous K_2CO_3 (0.012mol) was grinded well in mortar for 6-7 minutes. The reaction mixture was left aside for one hour at room temperature and poured into ice cold water with constant stirring for 10 minutes. The solid obtained was filtered, washed with water, dried and crystallized from ethanol to enhance purity.

General procedure for the synthesis of pyrazoles and isoxazoles (5a-b & 6)

A mixture of 1-phenyl-3-(2-(tosyloxy) phenyl) propane-1, 3-dione (0.01 mol) and hydrazine hydrate or phenyl hydrazine or hydroxylamine hydrochloride in 1 gm SiO_2 was grinded well in mortar with pestle for 5 min. The uniform mixture was then subjected to microwave oven for 3-4 minutes at low-medium power (40%, 100 °C temperature). The mixture was cooled and analyzed by TLC which has showed the complete disappearance of starting material. The precipitate was extracted with ethyl acetate and evaporated the solvent under vacuum gave solid product. The crude product was purified by column chromatography using ethyl acetate / n-hexane mixture.

General procedure for the synthesis of benzoxazepines and benzothiazepines (7a-b)

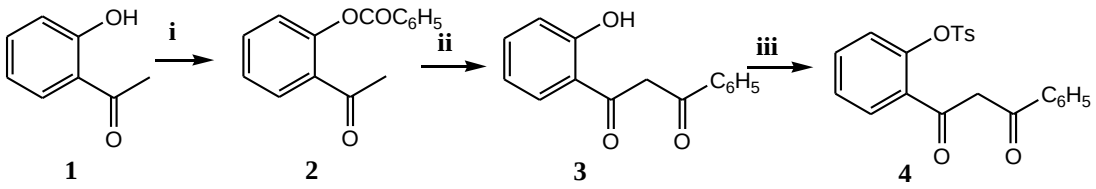
A mixture of 1-phenyl-3-(2-(tosyloxy) phenyl) propane-1, 3-dione (0.01 mol) and 2-aminophenol or 2-aminothiophenol in 1 gm SiO_2 was grinded well in mortar with pestle for 5 minutes. The uniform mixture was subjected to microwave irradiation for 5-6 minutes at medium-high power (40-60%, 110-115 °C temperature). The mixture was cooled and analyzed by TLC which has showed the complete disappearance of starting material. The solid product was extracted with acetone. The obtained product was purified by column chromatography using chloroform/ethanol mixture.

RESULTS AND DISCUSSION

The synthesis of designed compounds was carried out using convenient and versatile synthetic route outlined in **Scheme 1** and **2**. The condensation of 2-hydroxy acetophenone with benzoyl

chloride in the presence of catalytic amount of mild base K_2CO_3 under solvent free conditions using grindstone technique gave intermediate (**2**). The formation of product was confirms by the ferric chloride functional group test for phenolic OH which was found negative. The resulting compound was purified by crystallization using ethanol. This compound on treatment with pyridine and KOH mixture gave rearranged 1, 3-diketone derivative 1-phenyl-3-(2-(tosyloxy) phenyl) propane-1, 3-dione (**3**). The reaction of 1, 3-diketone with *p*-toluene sulfonyl chloride in the presence of K_2CO_3 using grindstone technique under solvent free conditions gave 1-phenyl-3-(2-(tosyloxy) phenyl) propane-1, 3-dione in good yield (**4**) (**Scheme 1**).

The synthesis of **5a-b** were achieved by the reaction of **4** with either hydrazine hydrate or phenyl hydrazine under solvent free conditions using microwaves in the presence of silica gel (SiO_2) as catalyst. The disappearance of bands in IR spectrum for C=O and OH functional groups and appearance of a band for NH group clearly indicate the formation of **5a**. In ^{1}H NMR, the appearance of singlet D_2O exchangeable signal corresponding to NH at chemical shift 10.36 and the appearance of deshielded singlet signal at δ 6.89 for CH=C confirms the formation of pyrazole molecule. Similarly compound **6** were also synthesized by the reaction of **4** and hydroxyl amine hydrochloride under microwaves in the presence of SiO_2.



Scheme-1 Reaction Conditions and reagents: i) Anhydrous K_2CO_3, benzoyl chloride, grind, solvent free, 7-8 min.; ii) Pyridine / KOH, grind, 10 min.; iii) P-TsCl, anhydrous K_2CO_3, grind, solvent free, 7-8 min

The compound **4** on cyclic condensation with 2-amino phenol or 2-amino thiophenol gave **7a-b** in good to excellent yield. The IR spectrum of **7a** shows the disappearance of C=O bands and appearance of bands for SO_3, C=N, and C=C at1373, 1462 and 1608-1469 cm^{-1}. In ^{1}H NMR, the appearance of singlet at δ 4.604 clearly indicated the presence of CH=C functionality in oxazepine ring. The appearance of distinct peaks at δ 81.8, 143.0, 165.3 and 167.6 ppm in ^{13}C NMR spectra was attributed due to the carbons in oxazepine ring.

1-Phenyl-3-(2-(tosyloxy) phenyl) propane-1, 3-dione (1, 3-diketone) (4).

Yield: 82%, M. p.: 112-115 °C; IR (KBr, cm^{-1}): ν_{max} 3065-3050 (Ar C-H), 1602-1483 (Ar C=C), 1345 (SO_3), 1640 (C=O), 3436 (O-H); ^{1}H NMR (200 MHz, $CDCl_3$) (δ ppm): 2.29 (3H, s, -CH_3), 7.10-7.90 (13H, *J* = 8.72 Hz, m, Ar-H), 6.61 (1H, s, CH=C-), 16.15 (1H, s, enolic-OH).

2-(3-Phenyl-1H-pyrazol-5-yl) phenyl-4-methylbenzene sulphonate (5a)

Yield: 88%, M. p.: 177-180 °C; IR (KBr, cm^{-1}): v_{max} 3034 (Ar C-H), 2924 (C-H, CH_3), 1590-1471 (Ar C=C), 1391 (SO_3), 3264 (NH); ^{1}H NMR (200 MHz, $CDCl_3$), (δ ppm): 2.34 (3H, s, CH_3), 6.92-7.64 (13H, *J* = 7.54 Hz, m, Ar-H), 6.89 (1H, s, CH=C), 10.36 (1H, s, pyrazole, NH, D_2O exchangeable); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7, 99.5, 116.6, 117.2, 119.6, 125.7, 126.7, 128.0, 128.2, 128.8, 129.2, 129.5, 144.1, 152.9, 155.9; Anal. Calcd for $C_{22}H_{18}N_2O_3S$ (392.45): C, 67.67; H, 4.65; N, 7.17; S, 8.20. Found: C, 67.84; H, 4.72; N, 7.27; S, 8.60.

2-(1, 3-Diphenyl-1*H*-pyrazol-5-yl) phenyl-4-methylbenzene sulphonate (5b)

Yield: 80%, M. p.: 142-45 °C; IR (KBr, cm^{-1}): v_{max} 3036 (Ar C-H), 2927 (C-H, CH_3), 1608-1460 (Ar C=C), 1394 (SO_3); ^{1}H NMR (200 MHz, $CDCl_3$), (δ ppm): 2.35 (3H, s, -CH_3), 6.94-7.70 (13H, *J* = 7.54 Hz, m, Ar-H), 7.82- 7.96 (5H, *J* = 7.54 Hz, m, Ar-H), 6.90 (1H, s, CH=C); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7, 99.5, 116.6, 117.2, 119.6, 125.7, 126.7, 128.0, 128.2, 128.8, 129.2, 129.5, 131.3, 132.0, 132.2, 133.2, 133.2, 140.5, 144.7, 153.2, 156.6; Anal. Calcd for $C_{28}H_{22}N_2O_3S$ (392.45): C, 72.08; H, 4.75; N, 6.00; S, 6.87. Found: C, 71.80; H, 4.55; N, 6.17; S, 7.05.

2-(3-Phenylisoxazol-5-yl) phenyl-4-methylbenzene sulphonate (6)

Yield: 85%, M. p.: 76-78 °C; IR (KBr, cm^{-1}): v_{max} 3055 (Ar C-H), 2922 (C-H, CH_3), 1603-1464 (Ar C=C), 1376 (SO_3); ^{1}H NMR (200 MHz, $CDCl_3$), (δ ppm): 2.35 (3H, s, CH_3), 6.94-7.70 (13H, *J* = 8.32 Hz, m, Ar-H), 6.84 (1H, s, CH=C); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.7, 107.7, 118.2, 124.1, 125.3, 125.8, 126.4, 129.1, 131.7, 131.9, 133.9, 146.2, 150.0, 156.4, 163.5, 178.6; Anal. Calcd for $C_{22}H_{17}NO_4S$ (391.44): C, 67.50; H, 4.38; N, 3.58; S, 8.30. Found: C, 67.31; H, 4.42; N, 3.52; S, 8.25.

2-(4-Phenylbenzo[b] [1, 4] oxazepin-2-yl) phenyl 4-methylbenzene sulfonate (7a)

Yield: 82%, M. p.: 168-71 °C; IR (KBr, cm^{-1}): v_{max} 3063 (Ar C-H), 2921 (C-H), 1608-1469 (Ar C=C), 1373 (SO_3); ^{1}H NMR (200 MHz, $CDCl_3$), (δ ppm): 2.29 (3H, s, CH_3), 6.48-8.40 (17H, *J* = 7.86 Hz, m, Ar-H), 4.60 (1H, s, -CH=C-); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.7, 81.8, 108.9, 112.6, 115.3, 119.7, 121.0, 122.0, 125.5, 125.6, 126.1, 126.3, 126.3, 126.4, 127.3, 127.9, 135.9, 139.8, 143.0, 149.5, 165.3, 167.6; Anal. Calcd for $C_{28}H_{21}NO_4S$ (467.54): C, 71.92; H, 4.53; N, 3.10; S, 6.84. Found: C, 71.82; H, 4.64; N, 2.88; S, 6.94.

2-(4-phenylbenzo[b] [1, 4] thiazepin-2-yl) phenyl-4-methylbenzene sulfonate (7b)

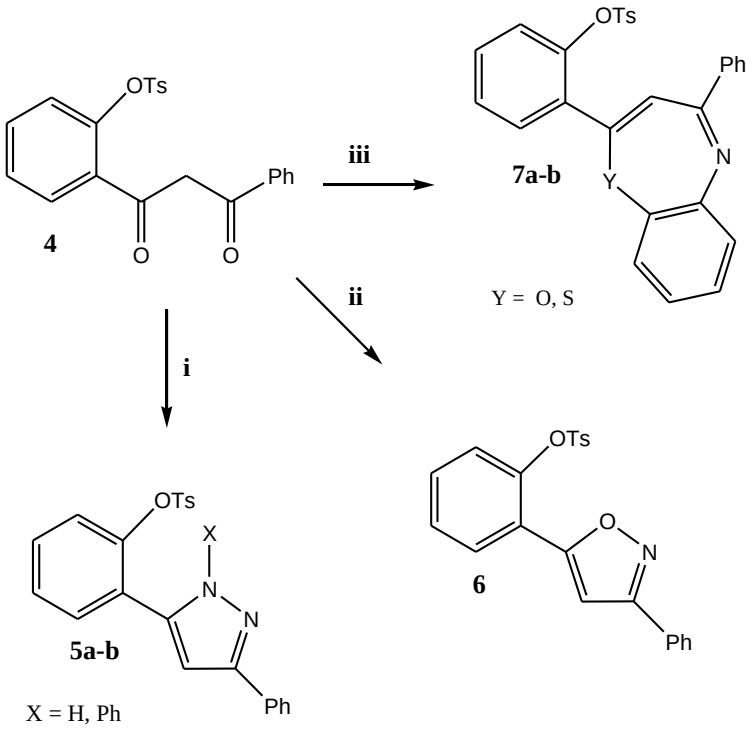
Yield: 86%, M. p.: 120-22 °C; IR (KBr, cm^{-1}): v_{max} 3061 (Ar C-H), 2919 (C-H), 1610-1472 (Ar C=C), 1369 (SO_3). ^{1}H NMR (200 MHz, $CDCl_3$), (δ ppm): 2.29 (3H, s, -CH_3), 6.55-7.90 (17H, *J* = 7.85 Hz, m, Ar-H), 4.33 (1H, s, CH=C-); ^{13}CNMR (50 MHz, $CDCl_3$): δ 21.7, 98.0, 112.8,

119.7, 120.1, 122.3, 124.6, 125.3, 125.3, 125.7, 125.7, 126.4, 127.3, 127.8, 127.8, 127.9, 128.4, 128.8, 129.8, 129.9, 130.2, 138.7, 144.4, 148.8, 149.3, 161.5; Anal. Calcd for $C_{28}H_{21}NO_3S_2$ (483.58): C, 69.54; H, 4.38; N, 2.93; S, 13.25. Found: C, 69.50; H, 4.48; N, 2.71; S, 13.45.

Anti-inflammatory activity[19]

The normal control, indomethacin and test compounds were administered to the rats 30 minutes before the injection of 0.1ml of 1% carrageenan suspension in normal saline. The test drugs 50 mg/kg and the standard drug 10 mg/kg were dosed to the animals. The animals were divided into eight groups containing six animals in each group. Male and female adult Wistar albino rats marked H, B, and T having weight 25-50 gm were used for the study. The animals were kept overnight on fasting. The anti-inflammatory activity study was carried by using Winter *et al.* method. The experimental procedures were carried out under the guidelines of Institutional Animal Ethics Committee (IAEC) at National Toxicology Centre, Pune. A no. 26 gauge needle was used to inject the carrageenan suspension into the sub planar region of the right hind paw. Immediately thereafter the edema volume of the injected paws was measured plethysmographically by water displacement method. For comparison purpose the volume of edema at various prefixed time intervals 1h, 2h, 4h and 6h was measured. The difference between paw volumes of the treated animals was measured and the mean edema volume was calculated. Percentage reduction in edema volume was calculated by using the formula, % reduction = 100 x V_0-Vt/V_0. Where, V_0 = Volume of the paw of control at time‘t’. Vt = Volume of the paw of drug treated at time‘t’. From the obtained data, the mean edema volume and percentage reduction in edema was calculated. The results are presented in **Table 1**. The SD and SEM were calculated by using ANOVA, Dunnet’s‘t’ test.

In the series of derivatives **5a-7b**, the compound **5a** showed highest value of reduction in edema volume after 6h. The replacement of H atom by phenyl from NH group of pyrazole ring resulted in decrease of activity. Among the series, isoxazole derivative **6** showed lowest value of reduction in edema volume. The benzoxazepine and benzothiazepine derivatives showed decreased value of reduction in edema volume in comparison with pyrazoles. All synthesized compounds showed significant anti-inflammatory activity in comparison with standard drug indomethacin.



Scheme-2 Reaction conditions and reagents i) SiO_2, MW 3-4 min. $NH_2.NH_2.H_2O$ or $PhNHNH_2$, solvent free; ii) SiO_2, MW 3-4 min, $NH_2OH.HCl$; iii) SiO_2, MW 5-6 min, 2-amino phenol or 2-amino thiophenol, solvent free.

Table 1: Anti-inflammatory activity of synthesized compounds (5a-7b)

Group (n)	Substance	Dose mg / kg	Difference in paw edema value after 1 h Mean ± SEM	% REV	2h Mean ± SEM	% REV	4h Mean ± SEM	% REV	6h Mean ± SEM	% REV
1.	Control	0.1 ml	4.94 0.219	-	4.63[a] 0.210	-	4.93 0.446	-	4.73 0.262	-
2.	Standard	10	4.56[a] 0.256	7.69	4.16 0.171	10.15	4.29 0.231	12.98	3.96[a] 0.182	16.27
3.	5a	50	4.67 0.154	5.46	4.30[b] 0.062	7.12	4.39 0.131	10.95	4.08 0.245	13.74
4.	5b	50	4.76[b] 0.314	3.64	4.36[b] 0.215	5.83	4.43[b] 0.413	10.14	4.11[a] 0.230	13.10
5.	6	50	4.77[b] 0.312	3.44	4.42[b] 0.221	4.53	4.60[b] 0.412	6.69	4.26[a] 0.232	9.93
6.	7a	50	4.79[b] 0.201	3.03	4.37[a] 0.214	5.61	4.54[c] 0.412	7.91	4.23[b] 0.236	10.57
7.	7b	50	4.78[b] 0.203	3.23	4.44[b] 0.134	4.10	4.59[c] 0.451	6.89	4.20[b] 0.154	11.20

n: Six albino rats in each group; REV: Reduction in edema volume; ± SEM: The standard error of the mean; Standard: Indomethacin drug; Significance level: [a]$p<0.05$, [b]$p<0.01$, [c]$p< 0.001$ compared with respective control.

Anti-microbial activity

The antibacterial activity of the test samples **5a-7b** was determined by agar cup plate method using ampicillin (100µg/ml) as standard drug and four pathogens such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. This method was based on diffusion of antibacterial component from reservoir bore to the surrounding inoculated nutrient agar medium so that the growth of microorganisms was inhibited as circular zone around the bore. The concentration of test compounds was 100µg/ml and was prepared in dimethyl sulfoxide (DMSO). The test samples and standard drug were placed in a bore made in Petri dishes, which contains different pathogens and were incubated at 37 ^{o}C for 24 hours. The zone of inhibitions around the bore was measured after 24 hours. The antibacterial and antifungal activity data is recorded in **Table 2**. Among the synthesized compounds, the pyrazole 5b and benzothiazepine 7b showed potent antibacterial activity.

The antifungal activity of synthesized compounds was determined by using *Aspergillus niger*, *Aspergillus flavus*, and *Fusarium oxysporium* pathogens. Dimethyl sulphoxide was used as control and dextrose agar as culture medium for antifungal activity. Norcadine (100µg/ml) was used as standard drug for the comparison and determination of their antifungal activities. In the series **5a-7b**, the compound **7b** showed highest antifungal activity while **7a** showed lowest activity.

The minimum inhibitory concentration (MIC) against the organisms was determined by the method of serial dilutions. Stock solutions of standard compound and synthesized compound having concentration 250 µg /ml was prepared by dissolving 25mg of synthesized compound in 2ml of DMSO and was made 100 ml with sterile distilled water. From this stock solution, the solutions of different concentrations such as 50 µg /ml, 25 µg /ml, 12.5 µg /ml, 6.25 µg /ml and 3.12 µg /ml were prepared. The results are presented in **Table 3**.

Table 2: Antibacterial and Antifungal activity of synthesized compounds (5a-7b)

Comp.	Bacteria (zone of inhibition in mm)				Fungi (zone of inhibition in mm)		
	B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*	*A. niger*	*A. flavus*	*F. oxysporium*
5a	10	12	12	14	08	10	12
5b	14	18	14	16	13	12	13
6	10	16	21	10	15	20	10
7a	15	12	10	19	19	-	10
7b	14	18	16	12	18	18	22
Std.	21	19	20	21	23	21	25

Concentration of the test compounds (5a-e) and standard drugs (Ampicillin & Norcadine): 100 µg/ml, Solvent Control: DMSO.

Table 3: Minimum Inhibitory Concentration (MIC µg /ml) of compounds

Compound	*B. subtilis*	*S. aureus*	*P. aeruginosa*	*E. coli*	*A. niger*	*A. flavus*	*F. oxysporium*
5a	25.0	25.0	25.0	25.0	50.0	50.0	50.0
5b	12.5	6.25	25.0	6.25	20.0	25.0	50.0
6	50.0	6.25	3.12	25.0	25.0	3.12	25.0
7a	6.25	12.5	25.0	3.12	3.12	50.0	25.0
7b	20.0	3.12	6.25	25.0	6.25	6.25	3.12
Std.	3.12	3.12	3.12	6.25	3.12	6.25	3.12

CONCLUSION

In conclusion, a simple, efficient and cost-effective procedure was developed for the synthesis of 1, 3-diketone and some new heterocyclic compounds (5-7) by using inexpensive and commercially available K_2CO_3 and SiO_2 as catalysts. The compounds were investigated for their anti-inflammatory and antimicrobial activities. All the tested compounds showed significant anti-inflammatory activity compared with standard Indomethacin. The compounds were also evaluated for their anti-microbial activity by cup-plate method against various gram positive, gram negative bacterial and fungal strains. Compound **6**, **7a**, **7b** were found to be more active compared with standard (Ampicillin and Norcadine). The minimum inhibitory concentration data also showed the lowest concentration of an antimicrobial (**6, 7a** and **7b**) that would inhibit the visible growth of a microorganism after overnight incubation.

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