Journal of Applied Pharmaceutical Science Vol. 6 (06), pp. 073-078, June, 2016
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2016.60613
ISSN 2231-3354

Pyrimidinethione derivatives with tosyl substitution: Synthesis, and antimicrobial property investigation

Shubhalaxmi[a], B. S. Manjunatha[a], K. Ananda[b], K. Subrahmanya Bhat[a*]

[a]Department of Chemistry, Manipal Institute of Technology, Manipal University, Manipal-576 104, India. [b]Biological Sciences Division, Poornaprajna Institute of Scientific Research, Devanahalli, Bangalore-562 164, India.

ARTICLE INFO

Article history:
Received on: 05/04/2016
Revised on: 05/05/2016
Accepted on: 24/05/2016
Available online: 28/06/2016

Key words:
Chalcones; Pyrimidine derivatives; Antimicrobial property; Spectral characterization.

ABSTRACT

Substitution of tosyl group on hydroxyacetophenones orhydroxybenzaldehyde and their subsequent condensation yielded several tosyloxy substituted chalcones which were derivatized to obtain the corresponding pyrimidinethione derivatives. The synthesized compounds were characterized by spectroscopic techniques like FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. These compounds were subjected to initial screening for their bioactivity using zone of inhibition method and were found moderately active against the tested microorganisms, viz. *Mycobacterium smegmatis*, *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*.

INTRODUCTION

Pyrimidines are an interesting scaffold for biological targets as they are building blocks of nucleosides. They are widely spread in many natural products hence are extensively studied for several chemotherapeutic properties (Ali *et al.*, 2001). Pyrimidines in general are present in many marketed drugs with assorted chemotherapeutic capacity, in addition to the fact that they are being exhaustively evaluated for their potential bio-activities. Pyrimidines possess impeccable potential of showing antimicrobial, antiviral, anti-inflammatory and anticancer activity to name a few (Behbehani *et al.*, 2011; Rashad *et al.*, 2006; Yewale *et al.*, 2012; Pierozz *et al.*, 2012). Some compounds which are of practical interest and has pyrimidine unit in it are listed in Figure-1 (Sharma *et al.*, 2014).

Sulfa drugs are well-known for their antimicrobial property, and thus structural analogs could be made by introduction of tosyl group into the hydroxyl substituted groups at positions 4, and 6 of pyrimidine moiety (Mandloi *et al.*, 2015).

This also renders novelty to the synthesized molecules, and allows us to study the effect of such derivatization on the antimicrobial potential of the molecules.

Moreover, tosyl group can be replaced by other nucleophiles to generate novel structures. In view of these, we considered it worthwhile to synthesize some novel pyrimidinethiones and evaluate their antimicrobial potential.

** Corresponding Author*
K. Subrahmanya Bhat, Department of Chemistry, Manipal Institute of Technology, Manipal University, Manipal-576 104, India.
Email: sbkjrf@yahoo.co.in

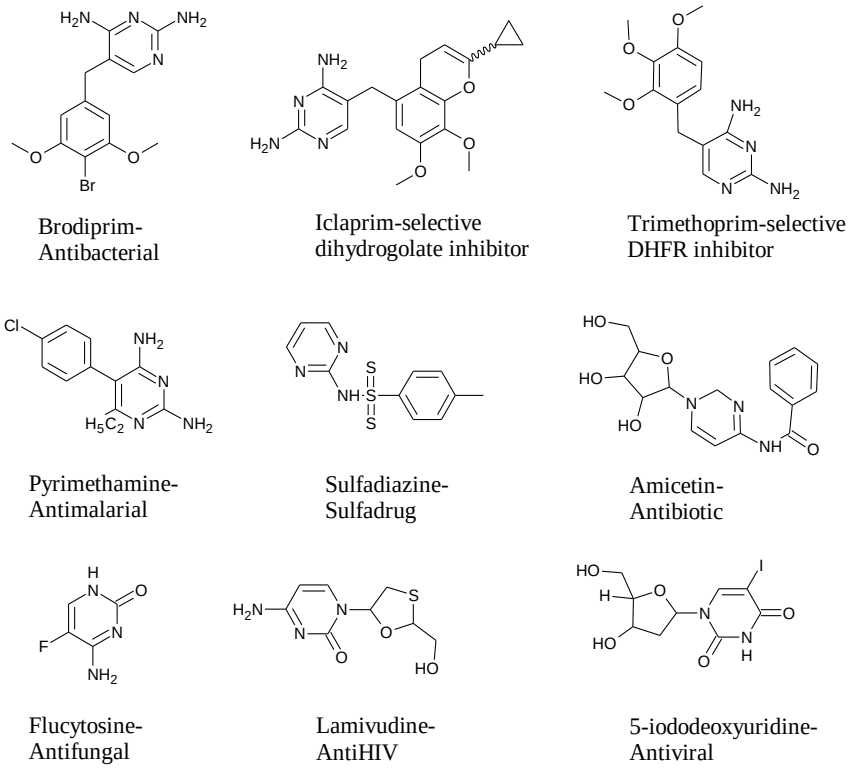


Fig. 1: Drugs with pyrimidine moiety as a pharmacophore.

MATERIALS AND METHODS

Reagents, and reactantsare used as procured from commercial suppliers without further purification. Solvents were purified before use. The purity of compounds, and course of reaction were monitored using thin layer chromatography on silica gel-G (Merck grade), with ethyl acetate and hexane mixture as mobile phase, and plates were viewed under UV light. The melting points were measured in open capillaries, with the help of Thomas Hoover melting point apparatus, are expressed in °C and are uncorrected. Infrared spectra (IR) were recorded on Shimadzu 8400S Infrared Spectrophotometer using potassium bromide (KBr) pellets and the values are expressed in cm^{-1}, ^{1}H and ^{13}C NMR spectra of the compounds were recorded on Bruker Ascend 400 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm; LC-MS using Mass spectrometer, ABSciex-API4000; and elemental analyses were performed on a Flash EA1112 CHN analyzer (Thermo Electron Corporation).

Experimental

Procedure for the synthesis of compounds, 4-formylphenyl 4-methylbenzenesulfonate and 4-acetylphenyl 4-methylbenzenesulfonate, 3 and 4.

A mixture of 4-hydroxybenzaldehyde (0.02 mol)/4-hydroxyacetophenone, 4-toluenesulfonylchloride (0.03 mol) and K_2CO_3 (0.03 mol) in THF (10 mL) were refluxed at 70 ºC for 7 h. The reaction mixture was cooled, and solvent was evaporated. The product was precipitated from ice-cold water. The solid product obtained was filtered, dried, and recrystallized from ethanol to obtain compounds **3**, and **4** (Furniss *et al.*, 2005; Maiya *et al.*, 2015; Shubhalaxmi *et al.*, 2016).

Procedure for the synthesis of compounds, 4-[(1E)-3-oxo-3-phenylprop-1-en-1-yl]phenyl-4-methylbenzenesulfonate and 4-[(2E)-3-phenylprop-2- enoyl]phenyl-4-methylbenzenesulfonate(7a-h)

A mixture of 4-tosyloxybenzaldehyde (0.06 mol), substituted acetophenones (0.06mol) and 10% aqueous sodium hydroxide (5mL) in ethanol (10mL) was stirred at room temperature for about 6 h. The resulting solid was washed, dried and crystallized from ethanol for obtaining compounds **7 a-h**. A mixture of 4-tosyloxyacetophenone (0.06 mol), aromatic aldehydes (0.06mol) and 10% aqueous sodium hydroxide (5mL) in ethanol (10mL) was stirred at room temperature for about 6 h. The resulting solid was filtered, washed, dried and recrystallized from ethanol.

The physicochemical characterization data for compound **7 a-h** are given in Table-1.We have carried out FTIR, ^{1}H NMR and single crystal XRD analysis for representative compound **7g**in the series and reported earlier (Shubhalaxmi *et al.*, 2015).

General procedure for the synthesis of compounds, 4-(6-phenyl-2-thioxo-2,3-dihydropyrimidin-4-yl)phenyl4 -methyl benzenesulfonate and 4-(6-phenyl-2-thioxo-1,2-dihydro pyrimidin-4-yl)phenyl 4-methylbenzenesulfonate (8 a-h).

Chalcone obtained from step 2 (0.03 mol) are dissolved in Ethanol (5 mL) and was refluxed with thiourea (0.06 mol) in 1 mL of 30 % KOH solution. The reaction was continued for 7-8 hours, under constant monitoring by TLC. The solvent was evaporated, and the precipitate was obtained after pouring into the crushed ice; filtered, washed with cold solution of 5% ethanol and dried. The products were purified by recrystallization from ethanol, or acetone-water mixture as required.

4-(6-phenyl-2-thioxo-2,3-dihydropyrimidin-4-yl)phenyl 4-methylbenzenesulfonate (8a)

66%, 128-130 ºC; IR (KBr, cm^{-1}): 3220 (N-H str), 3066 (Ar-H str), 2945 (C-H str), 1596 (ArC=C), 1554(Ar C=N), 1350 (S=O asym), 1168 (S=O sym), 1041 (C=S str); ^{1}H NMR (400 MHz, DMSO-d_6, δ-ppm): 2.33 (3H, s, CH_3), 6.55 (1H, s, pyrimidine CH), 7.34-8.33 (13 H, m, Ar-H), 10.66 (1H, s, NH);^{13}C NMR (100 MHz, DMSO-d_6, δ-ppm): 179.42, 156.80, 150.62, 149.82, 145.38, 138.63, 134.53, 132.32,130.26, 129.95, 129.43, 128.50, 128.26, 128.00, 122.84, 106.26, 37.86; MS (API) $[M]^+$: m/z 434; ANAL. Calcd. for $C_{23}H_{18}N_2O_3S_2$; calcd: C, 63.57; H, 4.18; N, 6.45. found: C, 63.82; H, 4.19;N, 6.47.

4-[6-(2,4-dichlorophenyl)-2-thioxo-2,3 -dihydropyrimidin-4-yl]phenyl 4-methylbenzenesulfonate (8b)

66%, 163-165 ºC;IR (KBr, cm^{-1}): 3210 (N-H str), 3054 (Ar-H str), 2895 (C-H str), 1600 (Ar C=C), 1556 (Ar C=N), 1353 (S=O asym), 1164 (S=O sym), 1049 (C=S str); ^{1}H NMR (400 MHz, DMSO-d_6, δ-ppm): 2.34 (3H, s, CH_3), 6.52 (1H, s, pyrimidine CH), 7.09-7.82 (11 H, m, Ar-H), 10.42 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ-ppm): 179.08,157.25, 151.34, 149.62, 139.23, 136.26, 134.89, 134.27,132.11, 129.55, 129.15, 128.26, 127.84,105.98, 38.57;MS (API) $[M-1]^+$: m/z 502; ANAL. Calcd. for $C_{23}H_{16}Cl_2N_2O_3S_2$,; calcd: C, 54.87; H, 3.20; N, 5.56. found: C, 55.03; H, 3.20; N, 5.57.

4-[6-(4-bromophenyl)-2-thioxo -2,3-dihydropyrimidin-4-yl]phenyl 4-methylbenzenesulfonate (8c)

60%, 158-160 ºC;IR (KBr, cm^{-1}): 3270 (N-H str), 3054 (Ar-H str), 2980 (C-H str), 1598 (Ar C=C), 1546 (Ar C=N), 1320 (S=O asym), 1164 (S=O sym), 1049 (C=S str);^{1}H NMR (400 MHz, DMSO-d_6, δ-ppm): 2.33 (3H, s, CH_3), 6.53 (1H, s, pyrimidine CH), 7.24-7.98 (12 H, m, Ar-H), 10.63 (1H, s, NH);ANAL. Calcd. for $C_{23}H_{17}BrN_2O_3S_2$; calcd: C, 53.80; H, 3.34; N, 5.46. found: C, 53.96; H, 3.35; N, 5.47.

4-[6-(4-methoxyphenyl)-2-thioxo-2,3 -dihydropyrimidin-4-yl]phenyl 4-methylbenzenesulfonate (8d)

51%, 134-136 ºC; IR (KBr, cm^{-1}): 3265 (N-H str), 3046 (Ar-H str), 2947 (C-H str), 1600 (Ar C=C), 1556 (Ar C=N), 1338 (S=O asym), 1162 (S=O sym), 1118 (C-O str), 1070 (C=S str); ^{1}H NMR (400 MHz, DMSO-d_6, δ-ppm): 2.33 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 6.64 (1H, s, pyrimidine CH), 7.02-7.90(12 H, m, Ar-H), 10.53 (1H, s, NH); ANAL. Calcd. for$C_{24}H_{20}N_2O_4S_2$; calcd: C, 62.05; H, 4.34; N, 6.03. found: C, 62.17; H, 4.34; N, 6.04.

4-(6-phenyl-2-thioxo-1 ,2-dihydropyrimidin-4-yl)phenyl 4-methylbenzenesulfonate (8e)

77%, 126-128 ºC;IR (KBr, cm^{-1}): 3151 (N-H str), 3062 (Ar-H str), 2984 (C-H str), 1604 (Ar C=C), 1566 (Ar C=N), 1373 (S=O asym), 1172 (S=O sym), 1091 (C=S str); ^{1}H NMR (400 MHz, DMSO-d_6, δ-ppm): 2.34 (3H, s, CH_3), 6.50 (1H, s, pyrimidine CH), 7.20-7.98 (13 H, m, Ar-H), 10.42 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ-ppm): 179.43, 160.16, 151.23, 150.24, 145.28, 138.68, 134.46, 131.62, 130.26, 129.54, 128.98, 128.27, 128.10, 127.28, 123.62, 106.43, 33.17; MS (API) $[M]^+$: m/z 434; ANAL. Calcd. for $C_{23}H_{18}N_2O_3S_2$; calcd: C, 63.57; H, 4.18; N, 6.45. found: C, 63.76; H, 4.19; N, 6.46.

4-[6-(4- chlorophenyl)-2-thioxo-1,2-dihydropyrimidin-4-yl]phenyl 4-methylbenzenesulfonate(8f)

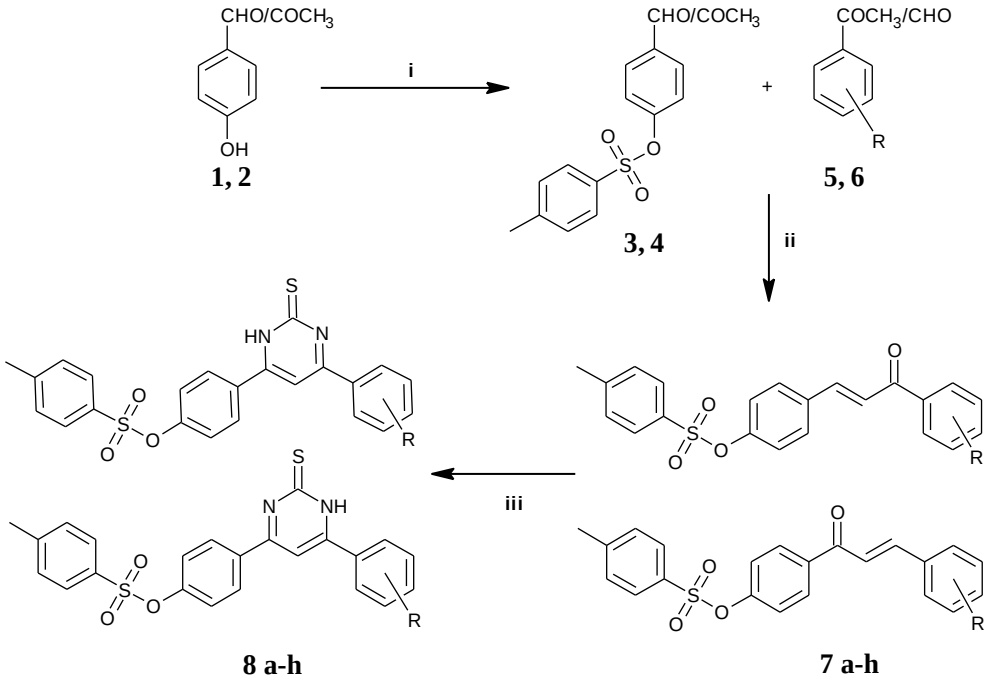
63%, 149-151 ºC; IR (KBr, cm^{-1}): 3155 (N-H str), 3070 (Ar-H str), 2981 (C-H str), 1596 (Ar C=C), 1542 (Ar C=N), 1342 (S=O asym), 1164 (S=O sym), 1057 (C=S str);^{1}H NMR (400 MHz, DMSO-d_6, δ-ppm): 2.42 (3H, s, CH_3), 6.53 (1H, s, pyrimidine CH), 6.98-7.96 (12 H, m, Ar-H), 10.63 (1H, s, NH);^{13}C NMR (100 MHz, DMSO-d_6, δ-ppm): 179.67, 160.26, 154.60, 150.68, 146.62,139.35, 136.86, 134.44, 132.82, 130.32, 129.94, 128.80, 128.64, 128.48, 124.38, 108.62, 36.08, MS (API) $[M-1]^+$: m/z 468; ANAL. Calcd. for $C_{23}H_{17}ClN_2O_3S_2$; calcd: C, 58.90; H, 3.65; N, 5.97. found: C, 59.01; H, 3.65; N, 5.98.

4-[6-(4-methylphenyl)-2-thioxo-1, 2-dihydropyrimidin-4-yl]phenyl 4-methylbenzenesulfonate (8g)

38%, 80-82ºC;IR (KBr, cm^{-1}): 3224 (N-H str), 3066 (Ar-H str), 2965 (C-H str), 1596 (Ar C=C), 1554 (Ar C=N), 1350 (S=O asym), 1168 (S=O sym), 1041 (C=S str); ^{1}H NMR (400 MHz, DMSO-d_6, δ-ppm): 2.22 (3H, s, CH_3), 2.34 (3H, s, CH_3), 6.56 (1H, s, pyrimidine CH), 6.98-7.85 (12 H, m, Ar-H), 10.56 (1H, s, NH); ANAL. Calcd. for $C_{24}H_{20}N_2O_3S_2$; calcd: C, 64.26; H, 4.49; N, 6.25. found: C, 64.51; H, 4.50; N, 6.27.

4-[6-(4-methoxyphenyl)- 2-thioxo-1,2-dihydropyrimidin-4-yl]phenyl 4-methylbenzenesulfonate (8h)

53%, 138-140 ºC;IR (KBr, cm^{-1}): 3155 (N-H str), 3049 (Ar-H str), 2964 (C-H str), 1600 (Ar C=C), 1562 (Ar C=N), 1346 (S=O asym), 1164 (S=O sym), 1110 (C-O str), 1077 (C=S str); ^{1}H NMR (400 MHz, DMSO-d_6, δ-ppm): 2.38 (3H, s, CH_3), 4.32 (3H, s, OCH_3), 6.52 (1H, s, pyrimidine CH), 6.94-7.80 (12 H, m, Ar-H), 10.48 (1H, s, NH); ANAL Calcd. for $C_{24}H_{20}N_2O_4S_2$; calcd: C, 62.05; H, 4.34; N, 6.03. found: C, 62.17; H, 4.34; N, 6.04.



i: CH_3-C_6H_5-SO_2Cl/ K_2CO_3/ THF, 70-80^{0}C; **ii**: NaOH, EtOH; **iii**: thiourea, KOH, EtOH, 80-85^{0}C.

Scheme 1: Synthetic protocol for preparation of pyrimidinethione derivatives.

Antimicrobial Activity

The antimicrobial screening of compounds **7a-h** and **8a–h** was evaluated using well diffusion method in nutrient agar media by measuring the inhibition zones of the test compounds against microorganisms considered (Sathish *et al.*, 2012; Palomino *et al.*, 2002).

The bacterial cultures which were 12 h old of a tuberculosis variant bacteria *Mycobacterium smegmatis* (MTCC 944), gram positive bacteria *Staphylococcus aureus* (MTCC 3160), and gram negative bacteria *Escherichia coli* (MTCC 1687) were taken for the i*n vitro* antibacterial evaluation of compounds. Antifungal activity of the compounds were tested against pathogenic fungi *Candida albicans* (MTCC 7253). All the bacterial and fungal cultures were purchased from IMTECH, Chandigarh, India and maintained as per the standard protocol. About 15-20 mL of nutrient agar media was poured into each petri plate and allowed to solidify for 15 minutes inside laminar air flow chamber. 100µL of 0.5 McFarland standard of bacterial/fungal suspension was inoculated on the agar media and spread on the whole surface by swabbing with sterile cotton buds. 5 mm wells were dig on the seeded agar plates with a sterile cork borer. Working solutions of the test compounds were prepared in DMSO at 10 mg/mL as stock and were poured at different concentrations (25 and 50 µg mL^{-1}) in to the wells and the experiments were done in triplicates. The test plates were incubated at 37 °C for 12 h before observing for the zone of inhibition, which is measured in millimeter. DMSO was used as a negative control. Ciprofloxacin was used as antibacterial standard and fluconozole as antifungal standard (10 mcg discs).

RESULTS AND DISCUSSION

Chemistry

The title compounds were synthesized starting from hydroxy acetophenones and hydroxy aldehydes by introducing tosyl substitution, 4-formylphenyl 4-methylbenzenesulfonate and 4-acetylphenyl 4-methylbenzenesulfonate, viz., **3** and **4**. The tosyloxy substituted aldehyde/ and acetophenones were made to react with different aryl acetophenones and aldehydes respectively to yield respective chalcones, viz., 4-[(1E)-3-oxo-3-phenylprop-1-en-1-yl]phenyl 4-methylbenzenesulfonate, and 4-[(2E)-3-phenylprop-2-enoyl]phenyl 4-methylbenzenesulfonate,**7 a-h** in good yields, in continuation of what we reported in our previous paper, using the similar procedure. The chalcones were condensed with thiourea in basic condition inorder to give the corresponding pyrimidinethione derivatives, namely, 4-(6-phenyl-2-thioxo-2,3-dihydropyrimidin-4-yl)phenyl 4-methylbenzenesulfonate and 4-(6-phenyl-2-thioxo-1,2-dihydropyrimidin-4-yl)phenyl4-methylbenzenesulfonate, **8 a-h**. The structures of all the compounds were confirmed using FT-IR, ^{1}H NMR, and elemental analysis. The representative compounds were analyzed by^{13}C NMR and mass spectral techniques, and confirmed the predicted structures.IR spectra of the tosyl substituted aldehyde and acetophenone showed characteristic peaks of S=O asymmetric stretching at region around 1350 cm^{-1} and S=O symmetric stretching around 1180 cm^{-1}. Also the absence of OH group of parent hydroxy group confirms the formation of corresponding

tosyloxy derivative. The IR spectra for tosyloxy substituted chalcones show strong band around 1650 cm^{-1}, indicating the presence of C=O, which is shifted to lower frequencies due to conjugation with C=C bonds. The spectra also shows characteristic peaks around 1180 cm^{-1} for S=O asymmetric, 1340 cm^{-1} for S=O symmetric stretch implying that the tosyl group has remained intact during the course of reaction. Absence of the carbonyl peak around 1650 cm^{-1}suggests the formation of pyrimidinethione derivative in corresponding IR spectra, the additional peaks due to NH stretch at around 3200 cm^{-1}, C=S at around 1050cm^{-1}, and C=N, around 1550 cm^{-1} confirms the assumption. The presence of S=O asymmetric and symmetric stretching bands in FTIR spectra of the compounds also proves that tosyl substitution is stable under the experimental conditions.

The PMR spectra for compound **4**, shows a singlet at 2.4 ppm corresponding to 3H of methyl group on the tosyl substitution, in addition to the absence of OH peak of parent hydroxyl acetophenone, confirms the formation of product. The PMR spectra for representative chalcone, **7g**, shows the following peaks, 1.6 ppm for aryl CH_3 (s), 2.4 ppm tosyloxy aryl CH_3 (s), 7.64-7.78 ppm CH=CH (dd), and 8aromatic protons (m). The PMR spectra of compound **8g** shows, 1.6 ppm for aryl CH_3 (s), 2.4 ppm tosyloxy aryl CH_3 (s), 6.8 ppm CH of pyrimidine ring (s), and 8aromatic protons (m), and 10.48 ppm for NH proton (s). The ^{13}C NMR spectra of representative compounds show peaks corresponding to number of carbons present. The mass spectra of representative compounds show $[M]^+$ or $[M+1]^+$ as base peaks.

Biological Evaluation

The initial screening by measuring zones of inhibition showed that many compounds are moderately active against all the tested gram positive microorganisms. The compounds showed no zones of inhibition against the tested gram negative bacteria, *E. coli*, suggesting that these class of compounds are inactive against similar bacteria. Many of the compounds showed significant zones of inhibition against the fungi considered for the study, *C. albicans*.

The isomer with no substitution on the benzene ring, **8a** showed considerably bigger zone of diameter 16mm, 19mm, and 21.33 mm against *M. smegmatis*, *S. aureus*, and *C. albicans* respectively at 50 µL concentration. Compounds **8b**, and **8f** with 2,4-dichloro, and 4-chloro substitution also showed higher zone diameters ranging from 15 mm to 18 mm against all the tested compounds at 50 µL concentration. In comparison to the parent chalcones, the pyrimidinethione derivatives showed enhanced activity against the tested microbes, as can be seen from Table-2.

The results are in agreement with the previous work by our group wherein presence of free OH group is essential for antimicrobial activity as against tosyloxy substituted chalcones (Shubhalaxmi *et al.*, 2015; Maiya *et al.*, 2015).Now we conclude that cyclization to form pyrimidine derivative improves the inhibition zones. We are at present working on nucleophilic substitution of tosyloxy group with novel nucleophiles to obtain newer molecules for developing novel structures for antimicrobial testing.

Table 1: Physicochemical data of tosyloxy chalcones.

Compound	Mol. formulae	R	Mol. weight	Yield (in %)	MP (in °C)
7a	$C_{22}H_{18}O_4S$	H	378	70	148-50
7b	$C_{22}H_{16}Cl_2O_4S$	2,4-Cl_2	447	82	142-44
7c	$C_{22}H_{17}BrO_4S$	4- Br	457	56	98-101
7d	$C_{23}H_{20}O_5S$	4-OCH_3	408	72	157-59
7e	$C_{22}H_{18}O_4S$	H	378	74	160-62
7f	$C_{22}H_{17}ClO_4S$	4-Cl	413	86	158-60
7g	$C_{23}H_{20}O_4S$	4-CH_3	392	73	118-20
7h	$C_{23}H_{20}O_5S$	4-OCH_3	408	72	150-53

Table 2: Antimicrobial activity of tosyloxy chalcones & pyrimidinethione derivatives by well diffusion assay.

Compounds	Inhibition Zone in mm; Mean ± SD					
	M.smegmatis		*S.aureus*		*C.albicans*	
	50 µL	25 µL	50 µL	25 µL	50 µL	25 µL
7a	20.00 ± 0	16.33 ± 0.57	17.00 ± 1.00	15.33 ± 0.57	22.00 ± 0	20.00 ± 0
7d	-	-	-	-	12.00 ± 0	9.33 ± 0.57
8a	16.00 ± 1.00	14.00 ± 1.00	19.00 ± 1.00	15.33 ± 0.57	21.33 ± 0.57	19.00 ± 0
8b	16.33 ± 0.57	13.33 ± 0.57	15.66 ± 1.52	13.66 ± 0.57	17.33 ± 0.57	14.33 ± 0.57
8c	16.66 ± 0.57	12.66 ± 0.57	15.00 ± 1.00	14.00 ± 1.00	19.00 ± 1.00	16.33 ± 0.57
8d	13.33 ± 0.57	10.66 ± 0.57	17.00 ± 0	13.33 ± 0.57	17.33 ± 0.57	16.33 ± 0.57
8e	14.33 ± 0.57	13.00 ± 0	13.66 ± 0.57	11.33 ±0.57	17.33 ± 1.15	15.00 ± 0
8f	17.00 ± 0	13.66 ± 0.57	15.00 ± 1.00	12.33 ± 0.57	17.66 ± 0.57	16.00 ± 0
8g	10.66 ± 0.57	10.33 ± 0.57	16.33 ± 0.57	10.66 ± 0.57	15.33 ± 0.57	9.33 ± 0.57
8h	13.00 ± 1	-	13.00 ± 1.00	10.66 ± 0.57	15.66 ± 0.57	12.66 ± 1.15
ABS/AFS	46.67±0.58		33.33±0.58		30.27±1.55	

ABS; antibacterial standard Ciprofloxacin; AFS; anti-fungal standard Fluconazole; both standards used are 10 µg discs; - not detected inhibition; control: dimethylsulfoxide; *E.coli* did not show any sensitivity to tested compounds. Chalcones **7b**, **7c**, **7e**, **7f**, **7g**, **7h** showed no inhibition zones against tested microbes.

CONCLUSION

A series of pyrimidinethione derivatives of different tosyloxy substituted chalcones were synthesized using simple synthetic strategy. Some of these compounds are positional isomers of one another. These compounds were characterized by spectral techniques. The compounds are subjected to qualitative screening for their antimicrobial action using well diffusion assay and compared with the standard drug ciprofloxacin, and fluconazole for antibacterial and antifungal action respectively. The antimicrobial studies indicate that the compounds show better inhibition zones as compared to the corresponding chalcones, as well as some of the compounds showed considerably biggerzones of inhibition at 50 µL concentrations.

ACKNOWLEDGEMENTS

Shubhalaxmi is grateful to Manipal University for fellowship under MU structured PhD program, and also thanks the laboratory facilities of Biological Sciences Division, Poornaprajna Institute of Scientific Research, Bangalore for carrying out the necessary antimicrobial evaluation. The central instrumentation facility of Manipal Institute of Technology, Manipal is acknowledged for carrying out ^{1}H and ^{13}C NMR characterization.

REFERENCES

Ali A, Aster SD, Graham DW, Patel GF, Taylor GE, Tolman RL *et al.* Design and synthesis of novel antibacterial agents with inhibitory activity against DNA polymerase III. Bioorg. Med. Chem. Lett., 2001, 11(16), 2185-88.

Behbehani H, Ibrahim HM, Makhseed S, Mahmoud H. Applications of 2-arylhydrazononitriles in synthesis: Preparation of new indole containing 1,2,3-triazole, pyrazole and pyrazolo[1,5-a]pyrimidine derivatives and evaluation of their antimicrobial activities. Eur Jour Med Chem., 2011, 46(5), 1813-20.

Furniss BS, Hannaford AJ, Smith PWG, Tatchell AR. 2005. Vogel's textbook of practical organic chemistry. Pearson Education, New Delhi.

Maiya M, Akshatha SJ, Shobha KL, Shenoy V, Bhat KS. Effect of novel chalcone derivatives on clinical isolates of multidrug resistant bacterial strains, Res. J. Pharm. Biol. Chem. Sci., 2015, 6, 466-470.

Mandloi D, Joshi S, Khadikar PV, Khosla N, QSAR study on the antibacterial activity of some sulfa drugs: building blockers of Mannich bases, Bioorg. Med. Chem. Lett., 2015, 15, 405-411.

Palomino JC, Martin A, Camacho M, Guerra H, Swings J, Portaels F, Resazur in microtiter assay plate: simple and inexpensive method for detection of drug resistance in Mycobacterium tuberculosis. Antimicrob Agents Chemother., 2002; 46(8): 2720-22

Pierroz V, Joshi T, Leonidova A, Mari C, Schur J, Ott I. Molecular and cellular characterization of the biological effects of ruthenium(II) complexes incorporating 2 – pyridyl-2-pyrimidine-4-carboxylic acid, J. Am. Chem. Soc., 2012, 134(50), 20376-87.

Rashad AE, Ali MA. Synthesis and antiviral screening of some thieno[2,3-*d*]pyrimidine nucleosides. Nucleosides Nucleotides Nucleic Acids., 2006, 25(1), 17-28.

Sathish L, Pavithra N, Ananda K, Antimicrobial activity and biodegrading enzymes of endophytic fungi from eucalyptus. Int J. Pharm. Sci. Res, 2012, 3(8), 2574-84.

Sharma V, Chitranshi N, Agarwal AK. Significance and biological importance of pyrimidine in the microbial world. Int. J. Med. Chem. 2014, 2014, Article id 202784.

Shubhalaxmi, Geidner B, Kumar CS, Fun HK, Bhat KS. Synthesis and crystal structure studies of novel 4-tosyloxychalcone derivative. Mol. Cryst. Liq. Cryst., 2015, 623, 365-371.

Shubhalaxmi, Pathak L, Ananda K and Bhat KS, Synthesis of focused library of novel aryloxyacids and pyrazoline derivatives: Molecular docking studies and antimicrobial investigation, Cogent Chemistry., 2016, 2, 1141388.

Yewale SB, Ganorkar SB, Baheti KG, Shelke RU. Novel 3-substituted-1-aryl-5-phenyl-6-anilinopyrazolo[3,4-d]pyrimidin-4-ones: Docking, synthesis and pharmacological evaluation as a potential anti-inflammatory agents. Bioorg. Med. Chem. Lett., 2012, 22(21), 6616-6620.

How to cite this article:

Shubhalaxmi, Manjunatha BS, Ananda K, Subrahmanya Bhat K. Pyrimidinethione derivatives with tosyl substitution: Synthesis, and antimicrobial property investigation. J App Pharm Sci, 2016; 6 (06): 073-078.