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Synthesis, characterization and anti-bacterial screening of Piroxicam based sulfonates

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ABSTRACT

A series of sulfonate esters derived from piroxicam was synthesized via simple convenient synthetic route which involves the sulfonation of the enolic OH of piroxicam in one pot. The structures of the newly synthesized compounds were established on the basis of modern analytical techniques. These were evaluated for their antibacterial activities. All the compounds were found to be potent when tested against gram positive and gram negative bacteria.

Keywords: Piroxicam, sulfonation, antibacterial activity.

INTRODUCTION

The anti-inflammatory, analgesic, and anti-pyretic properties of NSAIDs are particularly useful in treating rheumatic and other musculoskeletal disorders. During the last fifty years a plethora of NSAIDs have been introduced on the market indicative of the commercial potential for such compounds and attesting to their utility in the treatment of pain and inflammation of varying origin from the head to the big toe. NSADs also show antibacterial activity.[1] Two common NSAIDs ibuprofen (1, FIG. 1) and aspirin (2, FIG. 1) which were attached to a nitrogen mustard ester or a tripeptide showed antibacterial activity against penicillin susceptible or resistant E. Coli.[2] Diclofenac (3, FIG. 1), indomethacin (4, FIG. 1) and mefenamic acid (5, FIG. 1) were also screened for antibacterial activity by using disc diffusion assay and spectrophotometric technique.[3] Mefenamic acid (5) showed potential ability to prevent growth of dermatophytes.[4] Piroxicam (1,2-benzothiazine-3-caboxamide-4-hydroxy-2-methyl-N-(2-pyridyl)-1, 1-dioxide, 6, FIG. 1),[5] a nonsteroidal anti-inflammatory drug (NSAID) belongs to oxicam class of NSAID, widely used for

the treatment of inflammatory conditions in patients suffering from rheumatism and was developed prior to the discovery of cyclooxygenase-2 (COX-2, the second inducible isoform of cyclooxygenase responsible for inflammation). Several piroxicam derivatives[6-9] were prepared in order to reduce the gastrointestinal side effects, which leaded to many produgs[10] which are now marketed like ampiroxicam (ether carbonate derivative, 7, FIG. 2),[7,8]droxicam (proxicampivalic ester, 8, FIG. 2) [8] or cinnoxicam (piroxicamcinnamate, 9, FIG. 2).[9] These derivatives were found to be stable under gastric conditions.

There are conditions when an inflammation occurs in response to a microbial infection, and a combination of the anti-inflammatory drug with antimicrobial agent is prescribed in such conditions. These combinations often cause side effects because of high doses of drugs. Searching for new compounds, which would combine two activities seem to be promising way to overcome that problem. In view of these points and in continuation of our work on novel hybrid molecules, it was considered worthwhile to study various derivatives of piroxicam in order to improve their efficacy and to decrease side effects. Only few studies were reported on acyl derivatives and only one has reported sulfonyl derivatives[11] which were chemically stable and found to be moderately selective COX-2 inhibitors over COX-1, with lower gastrointestinal side effects than piroxicam. Here in we report our one pot synthesis of sulfonate molecules related to piroxicam using simple convenient synthetic route which are stable and studied their biological activity.

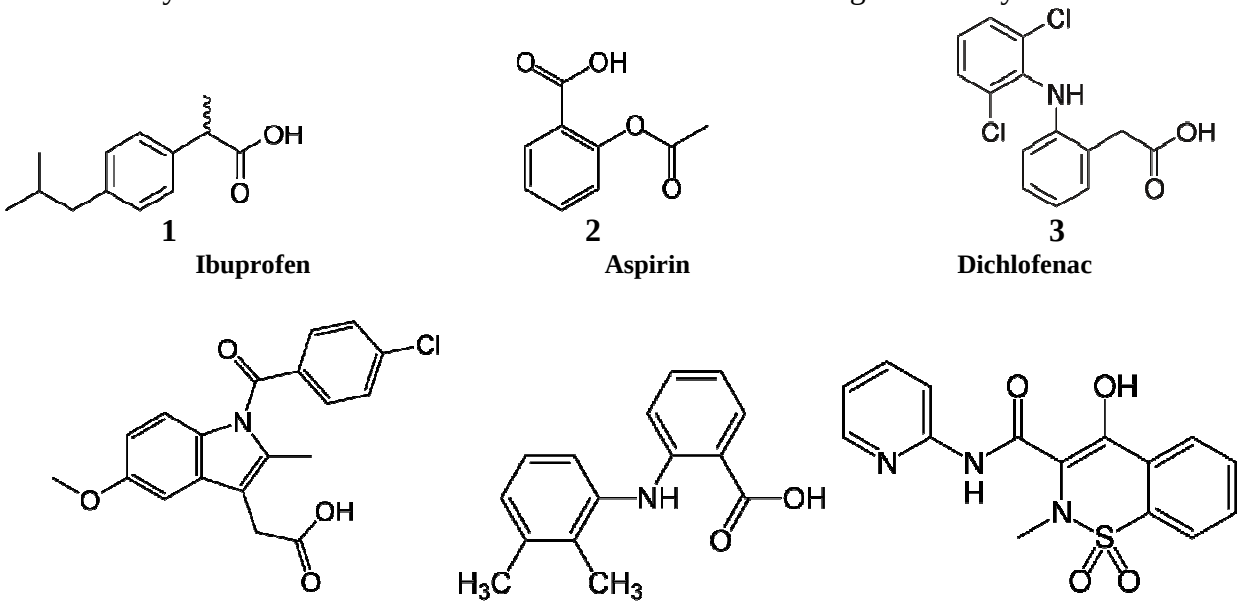


FIG. 1. NSAIDs having antibacterial activity

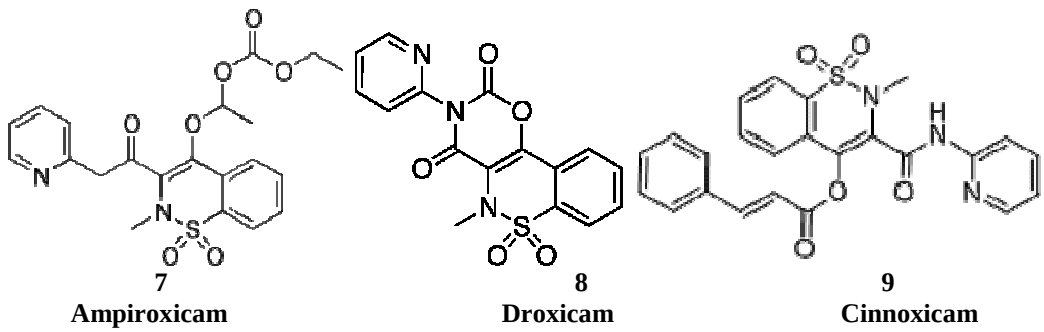


FIG. 2. Derivatives of piroxicam having medicinal importance

EXPERIMENTAL SECTION

General methods: Melting points were all determined by open glass capillary method on a Cintex melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer spectrometer in KBr pellets. ^{1}HNMR spectra were recorded on a Bruker ACF-300 machine or a Varian 300 or 400 MHz spectrometer using either DMSO-d_6 or $CDCl_3$ as a solvent with tetramethylsilane as internal reference (TMS, δ =0.00). Chemical shift (δ) values of rotameric hydrogens whenever identified are presented within the parenthesis by assigning asterisk (*) mark along with that of other form. Elemental analyses were performed by Varian 3LV analyzer series CHN analyzer. Mass spectra were recorded on a Jeol JMCD-300 instrument. All solvents used were commercially available and distilled before use. All reactions were monitored by TLC on pre-coated silica gel plates (60 F 254; Merck). Column chromatography was performed on 100-200 mesh silica gel (SRL, India) using 10-20 fold excess (by weight) of the crude product. The organic extracts were dried over anhydrous Na_2SO_4. Piroxicam and few aryl sulfonyl chlorides used are commercially available.

General procedure for the preparation of2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl esters: Piroxicam (1 g, 0.003 mol) dissolved in chloroform (15 mL), was taken in a 100 mL round bottommed flask, arylsulfonylchloride (0.003 mol) was added at 0^0C, followed by triethylamine (1.0 mL, 0.007 mol). The reaction mixture was stirred at room temp for 5hrs. After completion of the reaction (monitored by TLC), the mixture was poured into ice and extracted with chloroform (3 x 25 mL). The organic layers were collected, washed with 5% NaOH (20 mL) solution followed by 5% HCl (20 mL) and finally with brine (2 x 30 mL). The combined chloroform extract was dried over anhydrous Na_2SO_4, filtered and concentrated. The solid crude residue was purified by recrystallation from chloroform and ethyl acetate.

Synthesis of 4-Acetylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester (11a).

Off white solid; Yield: 38%; mp: 172-174^{0}C; R_f: 0.57 (Chloroform / Ethylacetate 9:1); IR (KBr cm^{-1}): 3386.5, 1692.1, 1590.0, ; MS (ES): m/z 528 (M^+, 100%); ^{1}HNMR (400MHz, DMSO-d_6): δ 10.88 (s, 1H, NH, D_2O exchangeable), 10.35 (s, 1H, NH, D_2O exchangeable), 8.35 (s, ArH, 1H), 7.89 -7.50 (m, ArH, 10H), 7.20 (t, ArH , 1H, *J* 4.9 Hz), 3.03 (s, >NCH_3, 3H), 2.10 (s, 3H, -$NHCOCH_3$) .

Synthesis of 4-Acetylamino-2-chloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridine-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester (11b).

White solid; Yield: 36%; mp: 182-184^{0}C; R_f: 0.57 (Chloroform / Ethylacetate 9:1); IR (KBr cm^{-1}): 3402.55, 3385.64, 2922.69, 1697.18 ; MS (ES): m/z 563 (M^+, 100%); ^{1}HNMR (300MHz, DMSO-d_6): δ 11.12 (s, 1H, NH, D_2O exchangeable), 10.53 (s, 1H, NH, D_2O exchangeable), 8.34 (s, ArH, 1H), 7.91 – 7.79 (m, ArH, 7H), 7.65 (d, ArH, 1H, *J* 8.7 Hz), 7.41 (d, ArH, 1H, , *J* 8.3 Hz), 7.19(s, 1H), 3.17 (s, >NCH_3, 1H), 2.13 (s, -$NHCOCH_3$,3H) .

Synthesis of 4-Acetylamino-2-methyl-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester(11c).

White solid; Yield: 37%; mp: 188-190^{0}C; R_f: 0.61 (Chloroform / Ethylacetate 9:1); MS (ES): m/z 543 (M^+, 100%); ^{1}HNMR (300MHz, DMSO-d_6): δ 11.04 (s, 1H, NH, D_2O exchangeable), 10.93 (s, 1H, NH, D_2O exchangeable), 8.35 (d, ArH, 1H, *J* 3.9Hz), 7.92-7.75 (m, ArH, 6H), 7.52 (d, ArH, 1H, *J* 8.4Hz), 7.40 (d, ArH, 2H, *J* 11.7Hz), 7.20 (s, ArH, 1H), 2.99 (s, >NCH_3, 3H), 2.25 (s, $ArCH_3$, 3H), 2.11 (s, -$NHCOCH_3$, 3H).

Synthesis of 4-Propionylamino-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester (11d).

White solid; Yield: 56%; mp: 192-194^{0}C; R_f: 0.57 (Chloroform / Ethylacetate 9:1); IR (KBr, cm^{-1}): 3381.01, 3300.30, 1670.20; MS (ES): m/z 543 (M^+, 100%); ^{1}HNMR (300MHz, $CDCl_3$): δ 8.29 (bs, ArH, 2H), 7.98 (t, ArH, 2H, *J* 7.7Hz), 7.86 (d, 1H, *J* 1.3Hz), 7.77-7.67, (m, ArH, 5H), 7.476 (d, ArH, 2H, *J* 8.8Hz), 7.12 (t, 2H, ArH, *J* 4.0Hz), 3.02 (s, >NCH_3, 3H), 2.33 (q, CH_2, 2H, *J* 7.4Hz), 1.22 (t, , -NHCOCH_3, 3H, *J* 7.4Hz).

Synthesis of 4-Chloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester (11e).

Light yellow solid; Yield: 62%; mp: 184-186^{0}C ; R_f: 0.59 (Chloroform/Ethylacetate 9:1); IR (KBr cm^{-1}): 3341.01, 2899.12, 1569.02 ; MS (ES): m/z 508.1 (M^+ M^++2, 3:1 ratio); ^{1}HNMR (400MHz, DMSO-d_6): δ 11.02 (s, 1H, NH, D_2O exchangeable), δ 8.38 (s, ArH, 1H), 7.96-7.76 (m, ArH, 6H), 7.66 (d, 2H, *J* 6.4 Hz), 7.47 (d, 2H, *J* 4Hz), 7.24 (t, 1H, *J* 8Hz), 3.15 (m, >NCH_3, 3H).

Synthesis of 4-Bromo-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester (11f).

White solid; Yield: 67%; mp: 184-186^{0}C ; R_f: 0.62 (Chloroform/Ethylacetate 9:1); IR (KBr cm^{-1}): 3372.09, 3102.37, 1681.00, ; MS (ES): m/z 552 (M^+ : M+2, 1:1 ratio);^{1}HNMR (300MHz, DMSO-d_6): δ 11.00 (s, 1H, NH, D_2O exchangeable), 8.37 (d, ArH , 1H, *J* 3.9Hz), 7.92-7.78 (m, ArH, 6H), 7.75-7.56 (m, ArH, 4H), 7.22 (t, 1H, ArH, *J* 5.6Hz), 3.04 (s, >NCH_3, 3H).

Synthesis of Benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][(1,2]thiazin-4-yl ester (11g).

Yellow solid; Yield: 68%; mp: 256-258^{0}C ; R_f: 0.58 (Chloroform / Ethylacetate 9:1); IR (KBr cm^{-1}): 3086.21, 2850.88, 1705.13 ; MS (ES): m/z 471 (M^+, 100%); ^{1}HNMR (300MHz, DMSO-d_6): δ 11.00 (s, 1H, NH, D_2O exchangeable), 9.12 (t, 1H, *J* 8Hz), 8.32-7.95 (m, ArH, 5H), 7.72-7.46 (m, ArH, 4H), 7.30 (m, ArH, 3H), 3.16 (s, >NCH_3, 3H).

Synthesis of 5-Acetylamino-napthalene-1-sulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester (11h).

Off white solid; Yield: 38%; mp: 194-196^{0}C; R_f: 0.63 (Chloroform / Ethylacetate 9:1); IR (KBr cm^{-1}): 3332.02, 2892.01, 1651.01, ; MS (ES): m/z 579.2 (M^+, 100%); ^{1}HNMR (400MHz, DMSO-d_6): δ 11.02 (s, 1H, NH, D_2O exchangeable), 10.05 (s, 1H, NH, D_2O exchangeable), 8.47 (d, ArH , 1H, *J* 12Hz), 8.26 -7.05(m, ArH , 13H), 3.00 (s, >NCH_3, 3H), 2.20 (s, -NHCOCH_3, 3H).

Synthesis of Toulene-4-sulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benz[e][1,2]thiazin-4-yl ester (11i).

Off white solid; Yield: 65%; mp: 146-148^{0}C ; R_f: 0.57 (Chloroform/Ethylacetate 9:1); IR (KBr cm^{-1}): 3352, 1738, 1688; MS (ES): m/z 486 (M^+, 100%); ^{1}HNMR (300MHz, $CDCl_3$): δ 8.33 (d, ArH,1H *J* 3.8Hz) δ 8.25 (s, 1H, NH, D_2O exchangeable), 8.01-7.67 (m, ArH, 8H), 7.13-7.11 (m, ArH , 1H), 7.04 (d, ArH, 2H, *J* 9Hz), 3.01 (s, >NCH_3, 3H), 2.10 (s, CH_3, 3H).

Synthesis of 3,4-Dichloro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester (11j).

Off white solid; Yield: 62%; R_f: 0.58 (Chloroform / Ethylacetate 9:1); mp: 170-172^{0}C; R_f: 0.58 (chloroform/Ethylacetate 9:1); IR (KBr cm^{-1}): 3384.0, 2993.7, 1555.8 ; MS (ES): m/z 542 (M^+ M+2, 3:1ratio, 100%); ^{1}HNMR (400MHz, DMSO-d_6): δ 11.10 (s, 1H, NH, D_2O exchangeable), 8.41 (s, ArH, 1H), 7.90-7.22 (m, ArH, 10H), 3.02 (s, >NCH_3, 3H).

Synthesis of 4-Ethyl-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^{6}benzo[e][1,2]thiazin-4-yl ester (11k).

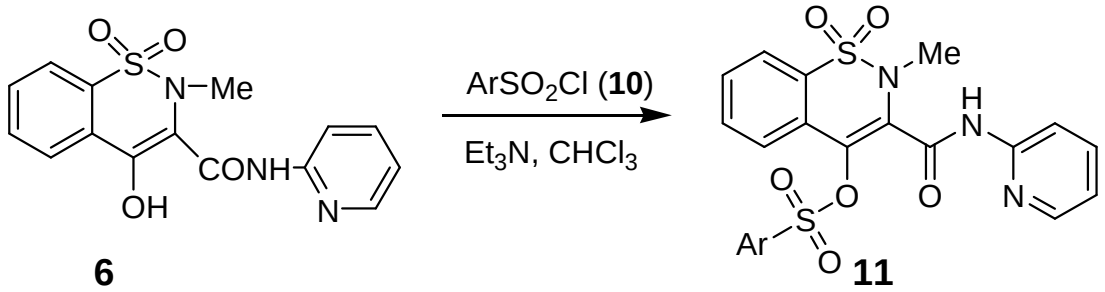
Off white solid; Yield: 61%; mp: 160-162^{0}C; R_f: 0.62 (Chloroform / Ethylacetate 9:1); IR (KBr cm^{-1}): 3317.9, 2930.9, 1687.8 ; MS (ES): m/z 500 (M^+, 100%);^{1}HNMR (300MHz, $CDCl_3$): δ 10.58 (s, 1H, NH, D_2O exchangeable), 8.38 (s, ArH, 1H), 7.90-7.73 (m, ArH , 6H), 7.59 (d, 2H, *J*=8.8Hz), 7.24 (d, 2H, *J*=7.8Hz), 3.2 (s, , >NCH_3, 3H), 2.57 (m, 2H), 1.15 (m, 6H).

Synthesis of 4-Fluoro-benzenesulfonicacid 2-methyl-1,1-dioxo-3-(pyridin-2-ylcarbamoyl)-1,2-dihydro-1λ^6-benzo[e][1,2]thiazin-4-yl ester (11l).

Off white solid; Yield: 63%; mp: 190-192^{0}C; R_f: 0.58 (Chloroform/Ethylacetate 9:1); IR (KBr cm^{-1}): 3329.6, 3080.9, 2917.7, 1693.2; MS (ES): m/z 490 (M^+, 100%); ^{1}HNMR (400MHz, DMSO-d_6): δ 11.05 (s, 1H, NH, D_2O exchangeable), 8.38 (s, ArH, 1H), 7.90-7.68 (m, ArH, 8H), 7.25 (m, ArH, 3H), 3.05 (s, >NCH_3, 3H).

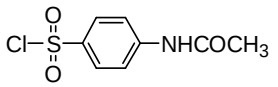
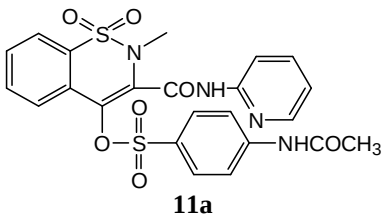
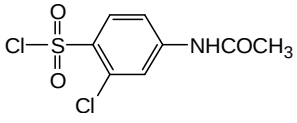
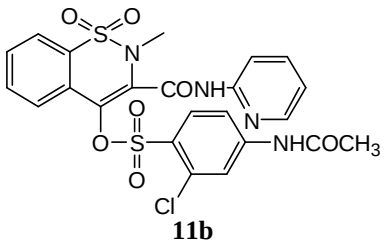
RESULTS AND DISCUSSION

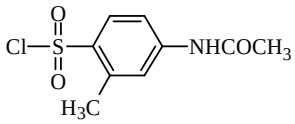
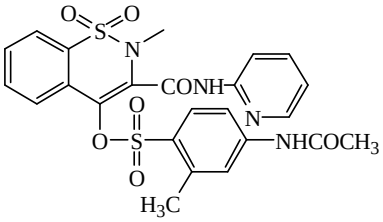
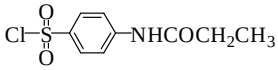
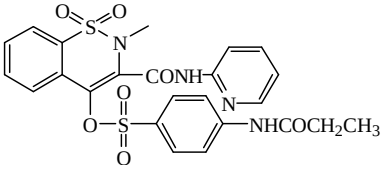
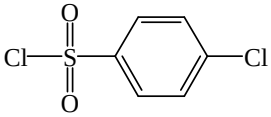
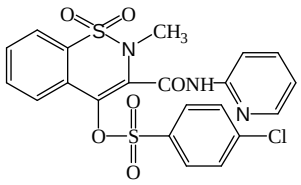
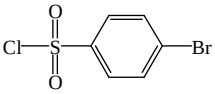
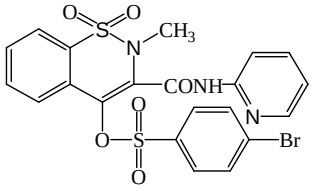
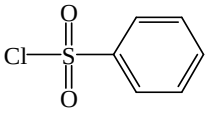
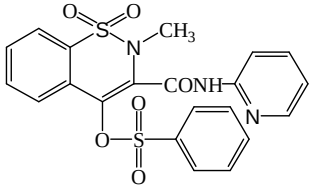
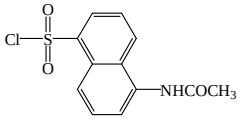
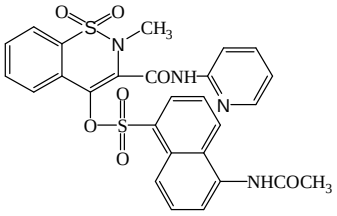
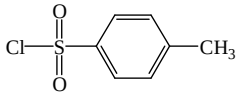
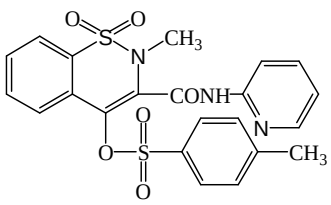
Chemistry: All target compounds were prepared via direct sulphonation of piroxicam (**6**) with a range of aryl sulfonyl chlorides (**10**, **Scheme 1**) respectively in moderate to good yield. The piroxicam was reacted with sulphonyl chloride in $CHCl_3$ in presence of Et_3N at room temperature for 5-7 h to give the desired compounds **11a-l.** Specific reaction condition for each reaction and yield are summarized in **Table 1**.

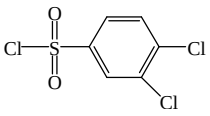
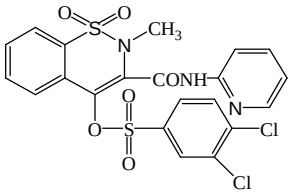
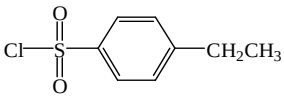
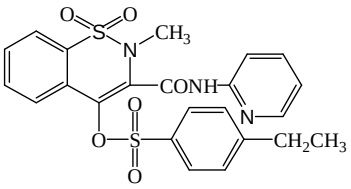
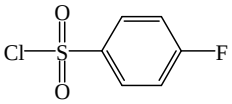
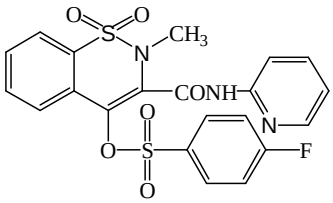


Scheme 1. Synthesis of **11.** Reaction conditions: $ArSO_2Cl$ (**2**) / Et_3N, $CHCl_3$, rt.

Table 1. Preparation of sulfonates (11) via the reaction of sulfonyl chloride (10) with piroxicam (6) respectively

Entry	RSO_2Cl (10)	Products (11)	Time/ Yield[a] (%) of the Reaction
1		 **11a**	4h / 38
2		 **11b**	6h / 36

3		 **11c**	5h / 37
4		 **11d**	4.5h / 56
5		 **11e**	4h / 66
6		 **11f**	5h / 65
7		 **11g**	6h / 63
8		 **11h**	5h / 64
9		 **11i**	5h / 66

10		 **11j**	4h / 58
11		 **11k**	6h / 63
12		 **11l**	7h / 62

Biological Activity

The antibacterial activities of the synthesized compounds were determined *in vitro* against various pathogenic bacteria such as Gram +ve and Gram –ve bacteria using Amikacin as standard and the concentration used was 1mg per mL.The results were summarized in **Table 2**.

Table 2. Antibacterial data of piroxicam sulfonate derivatives

Organisms	Type and nature	Control	**11c**	**11d**	**11e**	**11f**	**11g**	**11h**	**11i**	**11j**	**11k**
Staphylococcus aureus	Gram +ve, cocci	++++	++	-	+++	+++	+++	-	++	++	+
Bacillus subtillis	Gram +ve, rod shape	++++	+++	-	-	+++	++	-	-	++	+++
Eschirichia Coli	Gram _ve rod shape	++++	+++	+++	++	+++	-	++	-	++	++
Klebsiella pneumonia	Gram – ve, rod shape	++++	-	++	++	+++	+++	-	++	+++	++
Staphylococcus epidermis	Gram +ve, cocci	++++	+++	-	+++	+++	-	++	++	++	++

<6 = - , 7-9= +, 10-15 = ++, 16-22 = +++, 23-30 = ++++
Amikacin was used as a reference compound.

CONCLUSION

In conclusion, we have synthesized piroxicam based sulfonte esters in a convenient synthetic route. The synthesis of these compounds involves the sulfonation of piroxicam with different sulfonyl chlorides and was studied under conventional method. The approach showed significant

advantages. These results established the significance of searching of old drugs as a safer template to built new drug candidates. It can be concluded that this class of ester derivatives of piroxicam are expected to be safer and holds promise towards search to develop agents with improved pharmacological activity.

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