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# SYNTHESIS AND IN VITRO ANTI-INFLAMMATORY ACTIVITY OF NEW 2-METHYLSULPHONYL AMINO)-4- ARYLOXY METHYL THIAZOLES

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**ABSTRACT:**
New2-methylsulphonyl amino-4-aryloxy methyl thiazoles**(6a-f)**have been synthesized by novel route starting from readily available reactants namely 1, 3-dichlroacetone **(1)** and thiourea**(2)** using successive steps like Hantzsch synthesis to give 2-amino 4-chloromethyl thiazole hydrochloride (3), mesylation to yield 2-methylsulphonylamino 4-chloromethyl thiazole (4) and etherification with phenols.Synthesized intermediates and final compounds were characterized by I.R, $^1$H NMR, MASS spectroscopic techniques and C, H, N & S analysis. Synthesized final compounds were evaluated for in vitro anti-inflammatory activity by HRBC membrane stabilization method. Most of the synthesized compound exhibited good anti-inflammatory activity as compared to standard Diclofenac sodium.

**KEY WORDS:**Hantzshthiazolesynthesis, 2-methylsulphonyl amino-4-chloromethyl thiazole, phenols, In vitro anti-inflammatory activity.

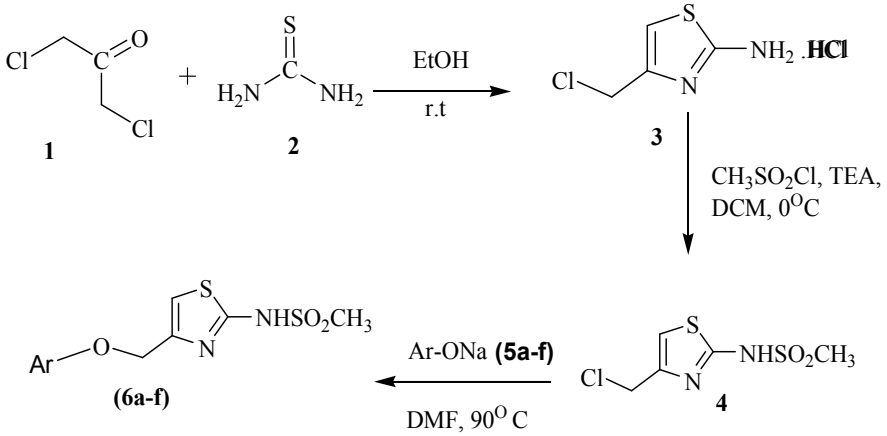
## INTRODUCTION:

Thiazole is an important core of various bioactive molecules. Organic compounds bearing thiazoles with different pharmacodynamic nuclei have been found to possess potent anti-inflammatory activity.[1-3] Amino thiazoles have wide range of biological activities viz.antimicrobial, anti- tubercular, anti-cancer, cyclooxygenase inhibitor, antiviral, antifungal and antipsycotic,[4]antiinflammatory.[5] Literature survey revealed that 2-amino 4-substitued thiazoles[6] and their various derivatives such as 2-(2, 4-disubstituted-thiazole-5-yl)-3-aryl-3*H*quinazoline-4-ones,[7]3-[4'(*p*-chlorophenyl)thiazol-2'-yl]-2-[(substitutedazetidinone/ thiazolidinone)-aminomethy]-6-bromoquinazolin-4-ones,[8]4-oxothiazolidine and its 5-arylidenes,[9] (Z)-4-((2,4-dioxothiazolidin-5-ylidene) methyl)-*N*-(4-substituted phenylthiazol-2-yl) benzene sulfonamides and 2-substituted-N-(4-Substituted-phenylthiazol-2yl) acetamides,[10]thiazolyl-N-Ph piperazines,[11]2-(4-arylthiazol-2-yl-amino)-n-aryl acetamides[12]have displayed considerable anti-inflammatory activity. Aryloxythiazole

derivatives have been proved to be anti-inflammatory.[13]When methane sulphonamido moiety was incorporated in the heteocycles the modified products are found to have appreciable anti-inflammatory activity with COX-2 selectivity.[14]The di-aryl or aryl/heteroaryl-ethers are also known to be selective inhibitors of COX-2.[15] These pharmacophores collectively responsible for anti-inflammatory activity associated with nimesulide, flosulide and their analogs.From the above literature survey it was revealed that little attention has been found to be paid towards the synthesis and anti-inflammatory evaluation of 2,4-disubstituted thiazoles having methylsulphonyl amino moiety at 2-position and ether at 4-position. Considering the anti-inflammatory activity associated with 2,4-disubstituted thiazoles, methanesulphonamides and ether linkages it was thought worthwhile to construct/synthesize new compounds such as 2-methylsulphonyl amino-4-aryloxy methylthiazoles with hope to generate the new therapeutic agents with better anti-inflammatory activity.

## MATERIALS AND METHODS:

Reactions were monitored by thin layer chromatography. TLC was performed with Merkprecoated TLC plates, silica gel 60F254 with thickness of 0.25mm and spots were visualized by irradiation with ultraviolet light (254 nm). Melting points were determined by open capillary method and are uncorrected. IR spectra were recorded on Bruker alpha ATR spectrophotometer. $^{1}$H NMR and $^{15}$C NMR spectra were carried out on Bruker apparatus at DRX-300 MHz, using TMS as internal reference and DMSO-$d_6$ as medium. Chemical shifts (δ values) are expressed in parts per million (ppm). Mass spectra have been scanned on DART-MS ($ESI^+$) and on JMS 100LC, AccuTOF spectrometers. Elemental analysis was performed on Perkin–Elmer 2400 CHNS Elemental analyzer at SAIF CDRI Luckhnow, India.




**Scheme 1.Synthesis of 2-(methylsulphonyl amino)-4-aryloxy methyl thiazole**

## SYNTHESIS:

**Synthesis of 2-Amino-4-(chloromethyl) thiazole hydrochloride (3).**

Thiourea (100 mmol) was added to a solution of 1, 3-dichloropropanone (100 mmol) in absolute ethanol 40 ml. The solution was then stirred at room temperature for 24 h and allowed to stand at 5$^{o}$C for further 12 h. The crystalline mass appeared was filtered and crystallized from ethanol. Yield: 12.98 g (70 %), m. p.: 144–145$^{o}$C (Lit.[16]144–145$^{o}$C).

**Synthesis 2-methylsulphonyl amino -4-chloromethyl thiazole(4).**

A mixture of triethyl amine (55 mmol) 2-amino-(4-chloromethyl) thiazole hydrochloride (50 mmol) was stirred in DCM (40 mL) for 30 minutes, till pink color was observed which indicated the generation of free 2-amino-4-chloromethyl thiazole. Then the reaction mass was

cooled to 0-5$^{o}$C and to this then mesyl chloride (50 mmol) was added in one lot. To this reaction mass then triethyl amine (55 mmol) was added drop wise, maintaining reaction temp 0-5$^{o}$C. After complete addition of the base the reaction mass was stirred at r.t. for 6 Hours.The progress of the reaction was monitored by thin layer chromatography, using n-hexane/ethyl acetate as a solvent system. On completion of the reaction the reaction content was poured in ice water (40 mL). The separated organic layer was dried with anhydrous sodium sulphate. DCM from the dried organic solution was removed by vacuumdistillation. The residual solid was then crystalized from ethanol-DMF.

**Spectral data of intermediate, 2-methylsulphonyl amino -4-chloromethyl thiazole(4):**

**Yield-**62%**, mp-**178-180**°C IR (cm $^{-1}$):** 3256 (-NH stretch), 3246 (aromatic C-H), 3110 (aromatic C-H), 2927 (aliphatic C-H), 2857 (aliphatic C-H), 1717(C=N strech) 1606 (C=C), 1552 (N-H bend), 1293 (S=O assy.) and 1119 (S=O symm.). **$^{1}$H NMR** (DMSO-$d_6$, 300 MHz), δ(ppm) **:** 3.87 (s, 3H,-$SO_2CH_3$), 4.61(s, 2H,-$CH_2Cl$) and 6.91(s, 1H,thizolyl) and12.50 (s,1H,-NH, exchangable with D2O). **$^{13}$C NMR** (DMSO-$d_6$, 75 MHz) δ(ppm) **:** 43.07**,** 56.24, 107.93, 124.81 and 168.05. **MS** (ESI$^{+}$ mode): m/ z (% intensity) **:** 226. 96 (M$^{+}$,100), 228.96 (M+2,30). **Elemental Analysis : M.F-**$C_5H_7ClN_2O_2S_2$: Found% ( Calculated %) **:** C, 26.23 (26.49); H, 3.09 (3.11); N, 12.31 (12.36); S, 28.25 (28.29).

**Synthesis of 2-methylsulphonyl amino-4-aryloxy methyl thiazoles.(6a-f).**

A mixture of a 2-methylsulphonyl amiono-4-chloromethyl thiazole (**4**). (10 mmol), and sodium phenoxide (10 mmol), was heated at 90$^{o}$C in DMF for 2 h. The progress of the reaction was monitored by thin layer chromatography, using petroleum ether/ethyl acetate (7:3) as a solvent system. After two hours, reaction mass was poured on crushed ice. Thus obtained solid product was filtered, dried and, crystallized from ethanol to afford the pure (**6a**). Similarly other compounds of the series were prepared and their characteristics physical data is recorded.

**2-methylsulphonyl amino-4-phenoxy methyl thiazole (6a)**

**Yield-**92%,**mp-** 197-198°C**IR (cm $^{-1}$):** 3397 (N-H stretch), 3252 (Ar-H asymm. stretch), 2977(C-H stretch aliphatic assym), 2879 (C-H stretch aliphatic symm.), 1674 (C=N), 1596 (C=C) 1531 (N-H bend) 1290 (S=O asym.), 1234 (C-O-C).and 1122 (S=O symm.) **$^{1}$H NMR** (DMSO-$d_6$, 300MHz) δ (ppm) **:** 2.89(s, 3H, -$SO_2CH_3$), 4.89 (s, 2H, -CH2), 6.8(s,1H, thiozolyl), 6.88-7.3 (m, 5H, Ar-H) and 12.75 (s,1H,-NH, exchangable with $D_2O$). **MS** (ESI$^{+}$ mode): 285.03.**Elemental Analysis : M.F-** $C_{11}H_{12}N_2O_3S_2$ **:**Found% ( Calculated %) **:** C, 46.42 (46.46); H, 4.20 (4.25); N, 9.84 (9.85); S, 22.52 (22.55).

**2-methylsulphonyl amino-4-(4-chloro) phenoxy methyl thiazole (6b)**

**Yield-8**7%,**mp-** 239-241**°CIR (cm $^{-1}$):** 3402 (N-H stretch), 3258 (Ar-H asymm. stretch), 2982(C-H stretch aliphatic assym), 2883 (C-H stretch aliphatic symm.), 1681(C=N), 1602 (C=C) 1537 (N-H bend) 1295(S=O assym.), 1240 (C-O-C).and 1130 (S=O symm.) **$^{1}$H NMR** (DMSO-$d_6$, 300MHz) δ (ppm) **:** 2.96(s, 3H, -$SO_2CH_3$), 4.97 (s, 2H, -CH2), 6.9(s,1H, thiozolyl), 6.90-7.62 (m, 5H, Ar-H) and 12.81 (s,1H,-NH, exchangable with $D_2O$). **MS** (ESI$^{+}$ mode):318.99 (M+),320.99 (M+2). **Elemental Analysis : M.F-** $C_{11}H_{11}ClN_2O_3S_2$**:**Found% ( Calculated %) **:** C,41.40(41.44); H, 3.49 (3.48); Cl, 11.10 (11.12); N, 8.74 (8.79); O, 15.02(15.06); S, 20.09 (20.12).

**2-methylsulphonyl amino-4-(4-Bromo-phenoxy) methyl thiazole (6c)**

**Yield-**82**%, mp-** 271-272°**C IR (cm $^{-1}$):** 3406 (N-H stretch), 3262 (Ar-H asymm. stretch), 2985(C-H stretch aliphatic assym), 2889 (C-H stretch aliphatic symm.), 1684 (C=N), 1606 (C=C) 1540 (N-H bend) 1299 (S=O asym.), 1243 (C-O-C).and 1132 (S=O symm.) **$^{1}$H NMR** (DMSO-$d_6$, 300MHz) δ (ppm) **:** 2.98(s, 3H, -$SO_2CH_3$), 4.99 (s, 2H, -$CH_2$), 6.92(s,1H, thiozolyl), 7.09-8.10 (m, 5H, Ar-H) and 12.87 (s,1H,-NH, exchangable with $D_2O$). **MS** (ESI$^{+}$ mode)**:**362.94 (M+), 36.94 (M+2).**Elemental Analysis : M.F-** $C_{11}H_{11}BrN_2O_3S_2$**:**Found% (

Calculated %) **:**C, 36.33(36.37); H, 3.01(3.05); Br, 22.10(22.00); N,7.70 (7.71); O, 13.19(13.21); S, 17.63(17.65).

**2-methylsulphonyl amino-4-(4-Methyl-phenoxy) methyl thiazole (6d)**

**Yield-**88%,**mp-** 221-222°C**IR (cm $^{-1}$):** 3394 (N-H stretch), 3248 (Ar-H asymm. stretch), 2975 (C-H stretch aliphatic assym), 2877 (C-H stretch aliphatic symm.), 1671(C=N), 1593 (C=C) 1529 (N-H bend) 1289 (S=O asym.), 1232 (C-O-C).and 1119 (S=O symm.) **$^1$H NMR** (DMSO-$d_6$, 300MHz) δ (ppm) **:**2.29 (s,3H, -$CH_3$) 2.86 (s, 3H, -$SO_2CH_3$), 4.87 (s, 2H, -CH2), 6.77(s,1H, thiozolyl), 6.82-7.32 (m, 5H, Ar-H) and 12.70 (s,1H,-NH, exchangable with $D_2O$). **MS** ($ESI^+$ mode)**:**299.04 (M+).**Elemental Analysis : M.F-** $C_{12}H_{14}N_2O_3S_2$**:**Found% ( Calculated %) **:**C, 48.28(48.30); H,4.70( 4.73); N, 9.36(9.39); O,16.06( 16.09); S,21.46( 21.49).

**2-methylsulphonyl amino-4-(2-Chlorol-phenoxy) methyl thiazole (6e)**

**Yield-**85**%, mp-** 235-236**°C IR (cm $^{-1}$):** 3401 (N-H stretch), 3257 (Ar-H asymm. stretch), 2983 (C-H stretch aliphatic assym), 2884 (C-H stretch aliphatic symm.), 1680 (C=N), 1601 (C=C) 1536 (N-H bend) 1294 (S=O asym.), 1239 (C-O-C).and 1128 (S=O symm.) **$^1$H NMR** (DMSO-$d_6$, 300MHz) δ (ppm) **:** 2.94(s, 3H, -$SO_2CH_3$), 4.96 (s, 2H, -CH2), 6.88(s,1H, thiozolyl), 6.90-7.60 (m, 5H, Ar-H) and 12.80 (s,1H,-NH, exchangable with $D_2O$). **MS** ($ESI^+$ mode): 318.99(M+), 319.99(M+2).**Elemental Analysis : M.F-** $C_{11}H_{11}ClN_2O_3S_2$**:**Found% ( Calculated %) **:**C, 41.40 (41.44); H,3.45 ( 3.480; Cl,11.10 ( 11.12); N,8.74 ( 8.79); O, 15.03 (15.06); S,20.09 (20.12).

**2-methylsulphonyl amino-4-(1-Napthyl) methyl thiazole (6f)**

**Yield-82%, mp-** 285-287**°C IR (cm $^{-1}$):** 3399 (N-H stretch), 3254 (Ar-H asymm. stretch), 2980 (C-H stretch aliphatic assym), 2881 (C-H stretch aliphatic symm.), 1677 (C=N), 1598 (C=C) 1533 (N-H bend) 1292 (S=O asym.), 1237 (C-O-C).and 1125 (S=O symm.) **$^1$H NMR** (DMSO-$d_6$, 300MHz) δ (ppm) **:** 2.91(s, 3H, -$SO_2CH_3$), 4.92 (s, 2H, -CH2), 6.84(s,1H, thiozolyl), 6.91-7.42 (m, 7H, Ar-H) and 12.78 (s,1H,-NH, exchangable with $D_2O$). **MS** ($ESI^+$ mode): 335.04. **Elemental Analysis : M.F-** $C_{15}H_{14}N_2O_3S_2$**:**Found% ( Calculated %) **:**C, 53.87; H, 4.22; N, 8.38; O, 14.35; S, 19.18

**In vitro anti-inflammatory activity by HRBC membrane stabilization method.**

Fresh whole human blood was collected and it was mixed with equal volumes of sterilized Alsever's solution (D-glucose 2.05 g, sodium citrate 0.8 g, citric acid 0.055 g, sodium chloride 0.42 g dissolved in100 mLdistilled water). This blood solution was centrifuged at 3000 rpm for 10min and was washed three times with equal volume of normal saline. The volume of the blood is measured and reconstituted as 10% v/v suspension with normal saline. The reaction mixture consists of 1.0mL of test sample of different concentrations in normal saline and 0.5mL of 10% HRBC suspension, 1mL of 0.2M phosphate buffer, 1mlhypo saline were incubated at 37°C for 30 min and centrifuged at 3,000 rpm for 30 minutes. The hemoglobin content of the supernatant solution was estimated spectrophotometrically at 560nm wavelength. Each experiment was performed in triplicate. Diclofenac sodium was used as standard and distilled water as control in this study.[17] Where the blood control represents 100% lysis or zero percent stability, the percentage of HRBC hemolysis calculated by formula,

% Hemolysis = (O.D of Test Sample / O.D of Control) × 100.

The concentration of a compound, where 50% of its maximal effect is observed ($EC_{50}$) using graph pad prism was measured.

## RESULTS AND DISCUSSION:

### Chemistry:

2-Amino-(4-chloromethyl)thiazole was obtained in the form of crystalline hydrochloride (**3**, 70%) by a simple stirring the equimolar amount of thiourea **(2)** and 1,3-dichloropropanone**(1)** in ethanol at room temperature and then keeping the reaction mixture at $5^0$c for 12 h. Solid formed was filtered washes and recrystallized with absolute alcohol, white crystalline solid obtained with yield 70%.When the literature procedure[18] was used the yield of the thiazoles was less than 50%. Mesylation of 2-amino-(4-chloromethyl) thiazole was carried by using methyl sulphonyl chloride and triethyl amine in dichloromethane as solvent at 0-5$^o$C. It was observed that when the condensation was run in DCM by allowing the interaction of equimolar quantities of amineHCl and triethylamine at 0-5$^o$C for 15 minutes and then to this adding equimolar amount of mesyl chloride and successively in portions one more equimolar amount of triethyl amine under stirring for further 2 h at 0-5 °C gave better yield of the expected 2-methylsulphonyl amino-4-chloromethyl thiazole without any byproduct.2-(Methylsulphonyl amino)-4-phenoxy methyl thiazole has been synthesized byreactingequimolar amount of 2-methylsulphonyl amino -4-chloromethyl thiazole and sodium phenoxides in DMF at 90$^o$C for 2-hours. Reaction was monitored by TLC and on completion of the reaction, resulting reaction mass was poured on ice cold water and then filtered dried and recrystallized from ethanol.

The structures of intermediate and all new 2-Mehylsulphonyl amino 4-aryloxymethyl thiazoles**(6a-f)** have been elucidated by elemental analyses, I.R., $^1$H NMR, $^{13}$C NMR and Mass spectroscopic measurements. FT I.R. spectra of Intermediate 2-methylsulphonyl amino -4-chloromethyl thiazole**(4)**displayeddiagnostic3256 (-NH stretch)&1552 (N-H bend) secondary amino i.e methyl sulphonyl amino, 1717(C=N stretch) 1606 (C=C)thiazolyl, 1293 (S=O assy.) and 1119 (S=O symm.)sulphonyl.$^1$H NMR spectra of (4) supports structure proposed 3.87 (s, 3H,-$SO_2\underline{CH_3}$), 4.61(s, 2H,-$CH_2$Cl) and 6.91(s, 1H, thizolyl)12.56 (s, 1H,-NH, exchangeable with $D_2O$).$^{13}$C NMR spectra showed peaks at 43.07(-$\underline{CH_2}$-Cl), 56.24(-$SO_2\underline{CH_3}$), 107.93(C=C), 124.81(C=C) and 168.05 ($\underline{C}$=N). Mass spectral data in good agreement with molecular weight calculated 226. 96 (M+,100),228.96 (M+2, 30).In the IRspectra of compounds **(3a-g)** along with other diagnostic peak ether –C-O-C-stretching band (1132-1125 cm$^{-1}$) is recorded. $^1$H NMR spectra all final compounds prove 2-methylsulphonyl amino 4-aryloxy methyl thiazole structure.Mass spectra of titled compounds are in good agreement with molecular weight calculated and structures proposed for **6a-f**.

### Anti-inflammatory activity:

Anti-inflammatory agents inhibit the cyclooxygenase enzymes which are responsible for the conversion of arachidonic acid to prostaglandins. Because human red blood cell (HRBC) membranes are similar to these lysosomal membrane components, the prevention of hypotonicity induced HRBC membrane lysis was taken as a measure in estimating anti-inflammatory activity.[17] Anti-inflammatory activity done by Human Red Blood Cell (HRBC), DFS stabilizes the membrane, thereby reducing the hemolysis. Thus with the increase in the component are prevented from leaking, thus as the concentration of DFS increases, the O.D decreases thereby decreasing the effect of the tonicity caused by hypo saline. Thus, HRBC membrane stabilization method[19] was used to estimate anti-inflammatory activity. The result of the in vitro membrane stabilization activity of synthesized thiazoles**(6a-f)** is presented in **Table 1**, **Fig.1** and **Fig.2.** According to these results all the compounds showed dose dependent inhibition of hemolysis. Compound **6b**($EC_{50}$ = 4.47± 0.06), **6c** ($EC_{50}$ = 4.57± 0.07) and **6f** ($EC_{50}$ =6.22 ± 0.10) displayed very good activity among the series as compared to standard Diclofenac sodium ($EC_{50}$ = 13.24). Other compound **6d**

($EC_{50}$ = 8.02 ± 0.07) showed moderate activity and **5f**($EC_{50}$ = 15.51 ± 0.14), **5a**($EC_{50}$= 19.68 ± 0.11) had exhibitedlower anti-inflammatory activity as compared to standard DCS.

**Table1. In vitro anti-inflammatory activity of synthesized compounds (6a-f).**

| Compound | % hemolysis at different concentrations | | | | ($EC_{50}$ ± SD) |
|---|---|---|---|---|---|
| | 1ug/ml | 5ug/ml | 25ug/ml | 50ug/ml | |
| **6a** | 64.41 | 69.32 | 74.23 | 82.82 | **19.68 ± 0.11** |
| **6b** | 76.68 | 80.36 | 85.88 | 91.41 | **3.80 ± 0.08** |
| **6c** | 66.87 | 73.61 | 90.79 | 95.09 | **5.43 ± 0.13** |
| **6d** | 70.55 | 74.23 | 80.98 | 90.18 | **8.02 ± 0.07** |
| **6e** | 63.80 | 73.61 | 78.52 | 85.27 | **15.51 ± 0.14** |
| **6f** | 72.39 | 77.91 | 81.59 | 91.41 | **6.22 ± 0.10** |
| **DCS** | 61.34 | 63.19 | 65.64 | 70.55 | **13.24 ± 0.09** |

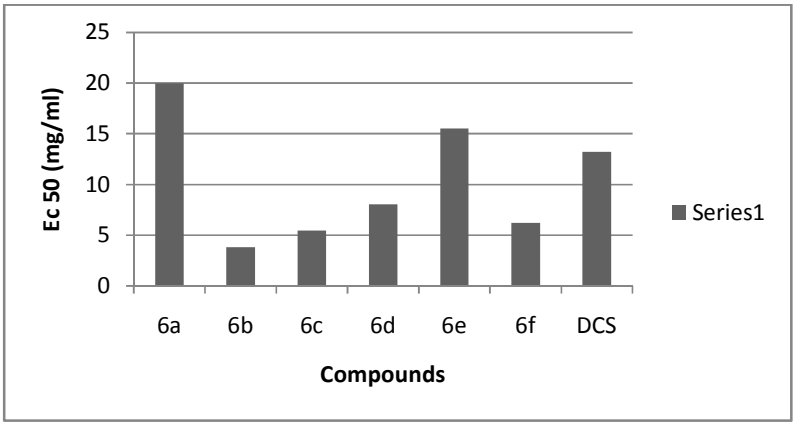



**Fig.1. $EC_{50}$ values of compounds (6a-f) and standard**

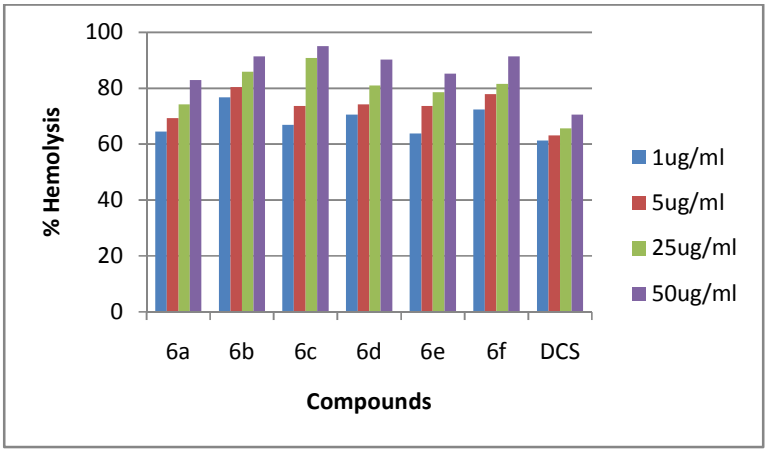



**Fig.2. % Hemolysisby compounds (6a-f) & standard at various concentrations.**

## CONCLUSION:

A new series of methylsulphonylamino and etherpharmacophorepossesing2, 4 disubstitutedthiazolederivatives has been synthesized by convenient synthetic protocols and characterized by different spectral and elemental analyses. The newly synthesized thiazoles**(6a-f)** showed anti-inflammatory activity compared with Diclofenacsodium. The compounds **6b**,**6c, 6d and 6f**exhibited most promising anti-inflammatory activity.

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