ARTICLE

Synthesis and *in vitro* Anti-inflammatory Activity of Some 2-(Methylsulphonyl Amino)-4-(Arylthio)methyl Thiazoles

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ABSTRACT

New 2-methylsulphonyl amino-4-arythio methyl thiazoles (**6a-f**) have been synthesized by novel route starting from 1,3-dichlroacetone (**1**) and thiourea (**2**), by multistep synthesis which involves cyclocondensation, mesylation and thioetherification. Synthesized intermediates and final compounds were characterized by IR, ^{1}H NMR, mass spectroscopic techniques and elemental analysis. Synthesized titled compounds were evaluated for *in vitro* anti-inflammatory activity by the human red blood cell membrane stabilization method. The compounds **6c**, **6d**, **6e** and **6f** displayed good anti-inflammatory activity as compared with standard diclofenac sodium.

KEYWORDS

2-Amino-4-chloromethylthiazole hydrochloride, Mesylation, Arythiols, Anti-inflammatory activity.

INTRODUCTION

Among the different aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process, and this ring structure is found in several marketed drugs. Organic compounds bearing thiazoles with different pharmacodynamic nuclei have been found to possess potent anti-inflammatory activity [1-3]. Therien *et al.* [4] and Roy *et al.* [5] reported thiazole derivatives as selective COX-2 inhibitors.

Literature survey revealed that 2-amino-4-substitued thiazoles [2] and their various derivatives such as 2-(2,4-disubstituted thiazole-5-yl)-3-aryl-3*H*-quinazoline-4-ones [6], 3-[4′-(*p*-chlorophenyl)thiazol-2′-yl]-2-[(substituted azetidinone/thiazolidinone)aminomethy]-6-bromoquinazolin-4-ones [7], 4-oxothiazolidine and its 5-arylidenes [8], (*Z*)-4-((2,4-dioxothiazolidin-5-ylidene)methyl)-N-(4-substituted phenylthiazol-2-yl)-benzene sulphonamides and 2-substituted-N-(4-substituted phenylthiazol-2-yl)acetamides [9], thiazolyl-N-Ph piperazines [10], 2-(4-arylthiazol-2-yl-amino)-*n*-aryl acetamides [11] and 2-(4-alkylthiophenoxy)-4-substituted-1,3-thiazoles have displayed considerable anti-inflammatory activity. A survey of the literature revealed that the introduction of 4-alkylthiophenyl group into different heterocycles has produced many compounds endowed with a broad spectrum pharmacological activity. It has been well established that the presence of 4-alkylthiophenoxy moieties is an important structural feature of many synthetic

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drugs [12]. Arythio thiazole 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 diaryl or aryl/heteroarylthioethers are also known to be selective inhibitors of COX-2 [15]. From the literature survey, it was revealed that little attention has been paid towards the synthesis and anti-inflammatory evaluation of 2,4-disubstituted thiazoles having methylsulphonyl amino moiety at 2-position and thioether at 4-position. Considering, the anti-inflammatory activity associated with 2,4-disubstituted thiazoles, methanesulphonamides and thioether linkages, it was thought worthwhile to synthesize new compounds such as 2-methylsulphonyl amino-4-arythio methylthiazoles with the hope to generate the new therapeutic agents with better anti-inflammatory activity.

EXPERIMENTAL

Reactions were monitored by thin-layer chromatography (TLC), which was performed with Merk precoated TLC plates and silica gel 60 F_{254} with thickness of 0.25 mm and spots were visualized by irradiation with ultraviolet light (254 nm). Melting points were determined by the open capillary method and are uncorrected. IR spectra were recorded on Bruker alpha ATR spectrophotometer. ^{1}H NMR spectra were carried out on Bruker apparatus at DRX-300 MHz, using TMS as an 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 JMS 100LC, AccuTOF spectrometers. The elemental analysis was performed on Perkin-Elmer 2400 CHNS Elemental analyzer at SAIF, CDRI, Lucknow, India.

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 ºC for further 12 h. The crystalline mass appeared was filtered and crystallized from ethanol. Yield: 70 %, m.p. 144-145 ºC (lit. m.p. 144-145 ºC [16]).

Synthesis of 2-methylsulphonyl amino-4-chloromethyl thiazole (4): A mixture of triethylamine (55 mmol) and 2-amino-(4-chloromethyl)thiazole hydrochloride (50 mmol) was stirred in DCM (40 mL) for 30 min, till pink colour was observed which indicated the generation of free 2-amino-4-chloromethyl thiazole. The reaction mass was then cooled to 0-5 ºC followed by the addition of mesyl chloride (50 mmol) in one lot. Triethylamine (55 mmol) was then added dropwise to this reaction mass, maintaining reaction temperature at 0-5 ºC. After completely adding the base, the reaction mass was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC, using *n*-hexane/ethyl acetate as a solvent system. On completion, 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 vacuum distillation. The residual solid was then crystalized from ethanol-DMF. Yield: 62 %, m.p. 178-180 ºC. IR (cm^{-1}): 3256 (-NH str.), 3246 (arom. C-H), 3110 (arom. C-H), 2927 (aliph. C-H), 2857 (aliph. C-H), 1717 (C=N str.), 1606 (C=C), 1552 (N-H bend), 1293 (S=O assym.) 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, thiozolyl) and 12.50 (s, 1H, -NH, exchangeable with D_2O). MS (ESI$^+$ mode): *m/z* (% intensity): 226.96 (M$^+$, 100), 228.96 (M+2, 30). Elemental analysis: $C_5H_7N_2O_2S_2Cl$: Found (calcd.) %: 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-arylthio)-methyl thiazoles (6a-f): A mixture of 2-methylsulphonyl amino-4-chloromethyl thiazole (**4**, 10 mmol), thiophenol (10 mmol) and sodium ethoxide (10 mmol) was refluxed in methanol (25 mL). The progress of the reaction was monitored by TLC, using petroleum ether/ethyl acetate (7:3) as a solvent system. After 2 h, the reaction mass was concentrated under vacuum and poured in ice-cold water. Thus, the obtained solid product was filtered, dried and crystallized from ethanol. Similarly, other compounds of the series were prepared and their characteristic physical data are recorded.

2-(Methylsulphonyl amino)-4-(phenylthio)methyl thiazole (6a): Yield: 93 %, m.p. 139-141 ºC; IR (cm^{-1}): 3252 (-NH str.), 3160 (Ar-H str.), 2925 (C-H aliph. str. assym.), 2856 (C-H aliph. str. symm.), 1699 (C=N), 1604 (C=C), 1550 (N-H bend.), 1294 (S=O asymm.) and 1122 (S=O symm.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.27 (s, 3H, Ar-CH_3), 2.89 (s, 3H, -SO_2CH_3), 3.98 (s, 2H, CH_2), 6.42 (s, 1H, thiozolyl), 7.13 (d, 2H, *J* = 8 Hz), 7.25 (d, 2H, *J* = 7.9 Hz) and 12.56 (s, 1H, -NH, exchangeable with D_2O). MS (ESI$^+$ mode): 315 (M$^+$). Elemental analysis: $C_{12}H_{14}N_2O_2S_3$: Found (calcd.) %: C 45.80 (45.84); H 4.42 (4.49); N 8.83 (8.91); S 30.52 (30.59).

2-(Methylsulphonylamino)-4-(4-amino phenylthio)-methyl thiazole (6b): Yield: 85 %, m.p. 115-117 ºC; IR (cm^{-1}): 3520 and 3340 (Ar-NH_2) str., 3254 ((-NH-SO_2CH_3) str.), 3163 (Ar-H str.), 2927(C-H aliphatic str. assym.), 2859 (C-H aliph. str. symm.), 1700 (C=N), 1608 (C=C), 1552 (N-H bend.), 1290 (S=O asymm.) and 1122 (S=O symm.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.32 (s, 3H, Ar-CH_3), 2.92 (s, 3H, -SO_2CH_3), 4.01 (s, 2H, CH_2), 5.12 (s, 2H, -NH_2, exchangeable with D_2O), 6.47 (s, 1H, thiozolyl), 7.16-7.82 (m, 4H) and 12.62 (s, 1H, -NH, exchangeable with D_2O). MS (ESI$^+$ mode): 316.02 (M$^+$). Elemental analysis: $C_{12}H_{14}N_2O_2S_3$: Found (calcd.) %: C 41.85 (41.88); H 4.11 (4.15); N 13.30 (13.32); O 10.12 (10.14); S 30.52 (30.50).

2-(Methylsulphonylamino)-4-(4-methyl phenylthio)-methyl thiazole (6c): Yield: 89 %, m.p. 184-186 ºC; IR (cm^{-1}): 3153 (-NH str.), 3246 (Ar-H str.), 2922 (C-H aliph. str. assym.), 2851 (C-H aliph. str. symm.), 1695 (C=N), 1600 (C=C), 1542 (N-H bend.), 1290 (S=O asymm.) and 1120 (S=O symm.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.25 (s, 3H, Ar-CH_3), 2.86 (s, 3H, -SO_2CH_3), 3.94 (s, 2H, CH_2), 6.38 (s, 1H, thiozolyl), 7.12 (d, 2H, *J* = 8 Hz), 7.26 (d, 2H, *J* = Hz) and 12.50 (s, 1H, -NH, exchangeable with D_2O). MS (ESI$^+$ mode): 315.03 (M$^+$, 100). Elemental analysis: $C_{12}H_{14}N_2O_2S_3$: Found (calcd.) %: C 45.80 (45.84); H 4.42 (4.49); N 8.83 (8.91); S 30.52 (30.59).

2-(Methylsulphonylamino)-4-(4-chloro phenylthio)-methyl thiazole (6d): Yield: 86 %, m.p. 202-203 ºC; IR (cm^{-1}): 3171 (-NH str.), 3263 (Ar-H str.), 2936 (C-H aliph. str. assym.), 2867 (C-H aliph. str. symm.), 1709 (C=N), 1617 (C=C), 1561 (N-H bend.), 1299 (S=O asymm.) and 1127 (S=O symm.); ^{1}H

NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.40 (s, 3H, Ar-CH_3), 2.96 (s, 3H, -SO_2CH_3), 3.99 (s, 2H, CH_2), 6.56 (s, 1H, thiozolyl), 7.20 (d, 2H, J = 8 Hz,), 7.41 (d, 2H, J = 7.9 Hz) and 12.76 (s, 1H, -NH, exchangeable with D_2O). MS (ESI$^+$ mode): 334.97 (M^+), 336.97 (M+2). Elemental analysis: $C_{11}H_{11}N_2O_2S_3Cl$: Found (calcd.) %: C 39.46 (39.45); H 3.29 (3.31); N 8.38 (8.37); O 9.57 (9.56); S, 28.74 (28.73); Cl, 10.55 (10.59).

2-(Methylsulphonylamino)-4-(4-methoxy phenylthio)-methyl thiazole (6e): Yield: 84 %; m.p. 210-211 ºC; IR (cm^{-1}): 3176 (-NH str.), 3263 (Ar-H str.), 2936 (C-H aliph. str. assym.), 2867 (C-H aliph. str. symm.), 1709 (C=N), 1617 (C=C), 1561 (N-H bend.), 1299 (S=O asymm.) and 1127 (S=O symm.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.44 (s, 3H, Ar-CH_3), 2.98 (s, 3H, -SO_2CH_3), 3.78 (s, 3H, -OCH_3), 3.99 (s, 2H, CH_2), 6.60 (s, 1H, thiozolyl), 7.13 (d, 2H, J = 8.1 Hz), 7.25 (d, 2H, J = 7.9 Hz) and 12.81 (s, 1H, -NH, exchangeable with D_2O). MS (ESI$^+$ mode): 315 (M^+, 100). Elemental analysis: $C_{12}H_{14}N_2O_3S_3$: Found (calcd.) %: C 43.60 (43.62); H 4.29 (4.27); N 8.46 (8.48); O 14.55 (14.53); S 29.13 (29.11).

2-[(2-Methysulphonylaminolthiazol-4-yl)methylthio]-benzo[*d*]thiazole (6f): Yield: 82 %; m.p. 105-107 ºC; IR (cm^{-1}): 3167 (-NH str.), 3256 (Ar-H str.), 2929 (C-H aliph. str. assym.), 2861 (C-H aliph. str. symm.), 1700 (C=N), 1610 (C=C), 1554 (N-H bend.), 1296 (S=O asymm.) and 1126 (S=O symm.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.32 (s, 3H, Ar-CH_3), 2.92 (s, 3H, -SO_2CH_3), 4.01 (s, 2H, CH_2), 6.51 (s, 1H, thiozolyl), 7.4 (t, J = 7.5 Hz, 1H), 7.6 (t, J = 8 Hz, 1H), 8.0 (d, J = 8.1 Hz, 1H), 8.1 (d, J = 7.6 Hz, 1H), 12.56 (s, 1H, -NH, exchangeable with D_2O). MS (ESI$^+$ mode): 357.98 (M^+); Elemental analysis: $C_{12}H_{11}N_3O_2S_4$: Found (calcd.) %: C 40.29 (40.32); H 3.10 (3.10); N 11.74 (11.75); O 8.93(8.95); S 35.86 (35.88).

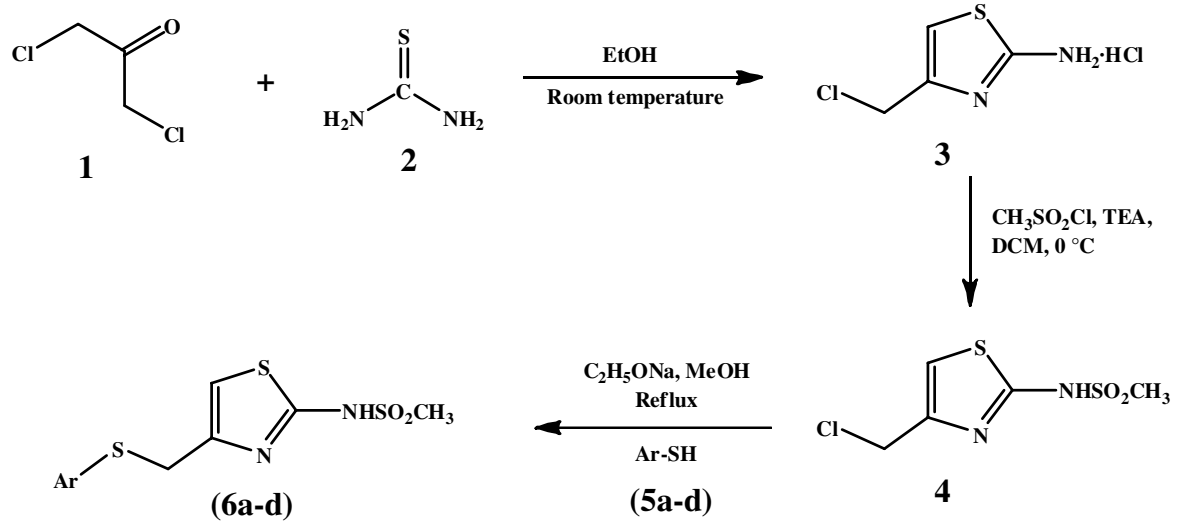
***in vitro* Anti-inflammatory activity by HRBC membrane stabilization method:** Fresh whole human blood was collected and mixed with equal volumes of sterilized Alsever's solution (dextrose 2 %, sodium citrate 0.8 %, citric acid 0.05 %, sodium chloride 0.42 % and 100 mL of distilled water). This blood solution was centrifuged at 3000 rpm for 10 min and 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 mL of test sample of different concentrations in normal saline, and 0.5 mL of 10 % human red blood cell (HRBC) suspension, 1 mL of 0.2 M phosphate buffer and 1 mL hyposaline were incubated at 37 ºC for 30 min and centrifuged at 3000 rpm for 30 min. The haemoglobin content of supernatant solution was estimated spectrophotometrically at 560 nm. Each experiment was performed in triplicate. Diclofenac sodium was used as standard and distilled water as control in this study [17], where blood control represents 100 % lysis or zero per cent stability, the percentage of HRBC hemolysis is calculated by the following formula:

$$\text{Hemolysis (\%)} = \frac{\text{OD of test sample}}{\text{OD of control}} \times 100$$

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

RESULTS AND DISCUSSION

The synthetic strategies adopted to obtain the target compounds are given in **Scheme-I**. The intermediate 2-amino-(4-chloromethyl)thiazole (**3**) 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 ºC for 12 h. When the literature procedure [18] was used the yield of thiazoles was less than 50 %. Mesylation of 2-amino-(4-chloromethyl)thiazole (**3**) was carried by using methyl sulphonyl chloride and triethyl amine in dichloromethane as solvent at 0-5 ºC. It was observed that when the condensation was run in DCM by allowing the interaction of equimolar quantities of amine·HCl and triethylamine at 0-5 ºC for 15 min and then to this adding equimolar amount of mesyl chloride and successively in portions one more equimolar amount of triethylamine under stirring for further 2 h at 0-5 ºC gave better yield of expected 2-methylsulphonyl amino-4-chloromethyl thiazole (**4**) without any byproduct. 2-(Methylsulphonyl amino)-4-arylthiomethyl thiazole (**6a-f**) has been synthesized by reacting equimolar amount of intermediate **4**, arylthiols and sodium ethoxide in methanol under reflux condition.



Scheme-I: Synthesis of 2-(methylsulphonyl amino)-4-arylthio methyl thiazole

TABLE-1
in vitro ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS (**6a-d**)

Compound	Percentage hemolysis at different concentrations				EC_{50} ± SD
	1 µg/mL	5 µg/mL	25 µg/mL	50 µg/mL	
6a	63.19	68.09	70.07	80.98	19.67 ± 0.11
6b	65.64	76.07	80.36	84.04	11.61 ± 0.08
6c	64.41	73.71	80.36	87.77	5.43 ± 0.13
6d	73.61	81.59	87.11	89.57	3.82 ± 0.07
6e	67.48	75.46	85.27	91.41	9.97 ± 0.21
6f	67.53	77.91	82.20	85.88	6.97 ±0.33
DCS	61.34	63.19	65.64	70.55	13.24 ± 0.09

The structures of intermediate and all newly synthesized 2-methylsulphonylamino-4-arythiomethyl thiazoles (**6a-f**) have been elucidated by elemental analyses, IR, ^{1}H NMR and mass spectroscopic measurements. FT IR spectra of intermediate 2-methylsulphonylamino-4-chloromethyl thiazole (**4**) displayed diagnostic 3256 (-NH str.) and 1552 (N-H bend.) secondary amino *i.e*. methyl sulphonylamino, 1717 (C=N stretch) 1606 (C=C) thiazolyl, 1293 (S=O assym.) and 1119 (S=O symm.) sulphonyl. ^{1}H NMR spectra of intermediate **4** supports structure proposed 3.87 (s, 3H,-SO_2CH_3), 4.61 (s, 2H, -CH_2Cl) and 6.91 (s, 1H, thizolyl) 12.56 (s, 1H,-NH, exchangeable with D_2O). Mass spectral data in good agreement with molecular weight calculated 226. 96 (M^+, 100), 228.96 (M+2, 30). The IR, ^{1}H NMR spectral data of compounds (**3a-g**) proves 2-methylsulphonyl amino-4-arythiomethyl thiazole structure. Mass spectra of titled compounds are in good agreement with molecular weight calculated and structures proposed for synthesized compounds **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 [18]. 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 tonicity caused by hyposaline. Thus, HRBC membrane stabilization method [19] was used to estimate anti-inflammatory activity. The results of *in vitro* membrane stabilization activity of synthesized thiazoles (**6a-f**) are presented in Table-1. According to these results, all the compounds showed dose dependent inhibition of hemolysis. Compound **6c** (EC_{50} = 5.43 ± 0.13), **6d** (EC_{50} = 3.82 ± 0.07) and **6f** (EC_{50} = 6.97 ± 0.21) displayed very good activity among the series as compared to standard diclofenac sodium (EC_{50} = 13.24). Other compound **6b** (EC_{50} = 11.61 ± 0.08), **6e** (EC_{50} = 9.97 ± 0.21) exhibited moderate activity and, **6a** (EC_{50} = 19.67 ± 0.11) had exhibited lower anti-inflammatory activity as compared to standard diclofenac sodium.

Conclusion

A new series of methylsulphonylamino and thioether pharmacophore possesing 2,4-disubstituted thiazole derivatives 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 standard diclofenac sodium. The compounds **6c**, **6d**, **6e** and **6f** exhibited most promising anti-inflammatory activity.

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