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Note

Synthesis of some new 2-(4-alkylthiophenoxy)-4-substituted-1, 3-thiazoles as possible anti-inflammatory and antimicrobial agents

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A series of new 2-{[4-(alkylthio)phenoxy]methyl}-4-substituted-1,3-thiazoles **4a-q, 6a-j** have been synthesized from ethyl [4-(alkylthio)phenoxy]acetates **1a,b** through multi-step reaction sequence. The structures of new compounds have been established on the basis of their elemental analysis and IR, ^{1}H and ^{13}C NMR and mass spectral data. Selected title compounds have been evaluated for anti-inflammatory activity and *in vitro* antibacterial testing against two pathogenic strains and antifungal screening against two fungi.

Keywords: 2-{[4-(Alkylthio)phenoxy]methyl}-4-aryl-1,3-thiazoles, 4-(substitutedmethyl)-2-{[4-(alkylthio)phenoxy]meth-yl}-1,3 thiazoles, anti-inflammatory activity, antibacterial, antifungal screening

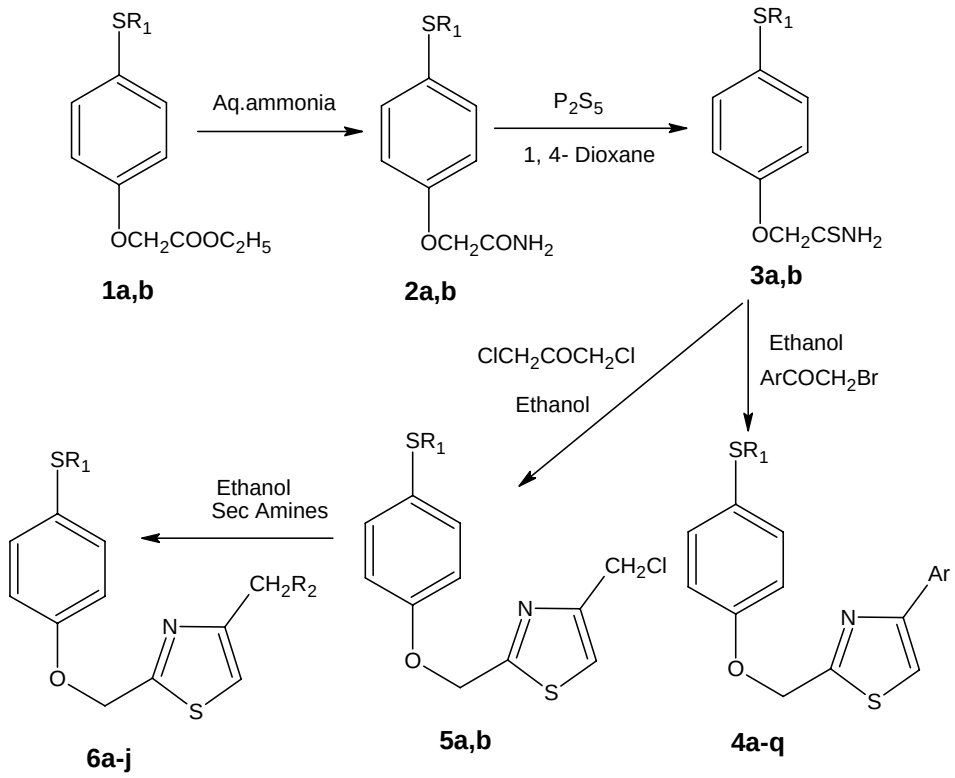
Thiazole derivatives have attracted a great deal of interest owing to their antibacterial[1], antifungal[2] anti-inflammatory[3,4], CNS depressant[5], antitubercular[6], anti-tumor[7], anthelmintic[8], sedative hypnotic[9] and anti-retroviral properties[10]. In addition to being used in the pharmaceutical industry, thiazoles also find wide application in the dye and photographic industries. A survey of the literature reveals that introduction of 4-alkylthiophenyl group into different heterocycles has yielded many biologically active compounds endowed with a wide spectrum of pharmacological activity[11,12]. It has been well established that the presence of 4-alkylthiophenoxy moieties is an important structural feature of wide variety of synthetic drugs[13-15]. Encouraged by the above reports, it was planned to synthesize new 1,3-thiazole derivatives containing 4-alkylthiophenoxy moiety at position 2 and substituted methyl/aryl group at position 4 of the thiazole ring, with the hope that the resulting molecules would exhibit promising biological properties. The present study describes the synthesis of hitherto unreported 2-{[4-(alkylthio)-phenoxy]methyl}-4-substitutedmethyl / aryl-1,3-thiazoles **4a-q, 6a-j** and evaluation of their *in vivo* anti-inflammatory properties and *in vitro* antibacterial and antifungal activity against pathogenic strains.

Results and Discussion

The reaction sequences employed for synthesis of title compounds are shown in **Scheme I**. The key intermediates, ethyl[4-(alkylthio)phenoxy]acetates **1a,b** were prepared[16] by treating ethyl chloroacetate with 4-(methylthio)phenol or 4-(ethylthio)phenol in boiling acetone in presence of potassium carbonate**.** Further, the compounds **1a,b** were readily converted to [4-(alkylthio)phenoxy]acetamides **2a,b** by treating them with liquor ammonia. The acetamides **2a,b** on reaction with phosphorous pentasulfide in dioxane at 40°C yielded 2-[4-(alkylthio)phenoxy]ethanethio-amides **3a,b** which on condensation with various phenacyl bromides in alcoholic medium at reflux temperature afforded 2-{[4-(alkylthio)phenoxy]-methyl}-4-aryl-1,3-thiazoles **4a-q** in good yield. On the other hand, **3a,b** on refluxing with alcoholic 1,3-dichloroacetone gave 4-(chloromethyl)-2-{[4-(alkyl-thio)phenoxy]methyl}-1,3-thiazoles **5a-b**. They were finally converted to the title compounds 4-(substi-tutedmethyl)-2-{[4-(alkylthio)phenoxy]methyl}-1,3-thiazoles **6a-j** by refluxing them with various heterocyclic secondary amines in alcoholic medium.

The structural assignments of the new compounds were based on their elemental analysis and spectral (IR, ^{1}H and ^{13}C NMR and MS) data. The characterization data of all the new compounds have been given in the experimental part.

The formation of [4-(methylthio)phenoxy]aceta-mide **2a** from methyl[4-(methylthio)phenoxy]acetate **1a** was confirmed from its IR, ^{1}H NMR data and elemental analysis. IR spectrum of **2a** showed absorption bands at 3431, 2971, 1664, 1605 and 826 cm^{-1} due to NH_2, CH_3, C=O, and C=C and SCH_3 groups respectively, while ^{1}H NMR showed sharp singlets at δ 2.4 and 4.4, which correspond to SCH_3



where R_1: CH_3, C_2H_5; R_2: Piperidine, N-methylpiperazine, pyrrolidine, piperazine and morpholine

Scheme I

and CH_2 protons respectively. Two doublets appeared at δ 6.85 and 7.3 indicating the presence of four aromatic protons and one broad peak at δ 5.8 shows $CONH_2$. Further, conversion of **2a** to 2-[4-(alkylthio)phenoxy]ethanethioamide was confirmed from its IR spectrum which showed peaks at 3319, 2971, 1493 and 814 cm^{-1} indicating the presence of NH_2, CH_3, C=S, and C=C and SCH_3 groups respectively. Disappearance of characteristic peak due to C=O group further confirmed the formation of **3a**. In its ^1H NMR spectrum, peaks due to SCH_3 and CH_2 protons appeared at δ 2.4 and 4.9 respectively. Two doublets appeared at δ 6.9 and 7.3 indicating the presence of four aromatic protons.

Further, cyclization of **3a** to title compound, 2-{[4-(methylthio)phenoxy]methyl}-4-phenyl-1,3-thiazole **4a** was confirmed from its IR spectrum which showed absorption bands at 2918, 1493, 1175, 1088 and 814 cm^{-1} indicating the presence of CH_3, C=C, C=N, C-S-C and SCH_3 groups respectively and the disappearance of characteristic peak due to NH_2 group of **3a** clearly indicated the smooth cyclization. In its ^1H NMR spectrum, peaks due to SCH_3 and CH_2 protons appeared at δ 2.45 and 5.41 respectively as singlets. Peaks due to phenoxy group appeared at δ 6.97 and 7.26 as doublets and peaks due to 4-phenyl moiety appeared at δ 7.3-7.4 as multiplet and δ 7.9 as a doublet. Appearance of one singlet at δ 7.5 is due to thiazole proton. ^{13}C NMR (DEPT experimentation) spectrum of **4a** showed peaks at δ 17.83, 67.82, 115.71, 126.32, 128.24, 128.8 and 129.67 which are due to SCH_3, CH_2, C_3 and C_5 of phenoxy moiety, C_2 and C_6 of phenoxy moiety, C_3, C_4, C_5 of 4-phenyl moiety, C_4 of thiazole, and C_2 and C_6 of 4-phenyl moiety respectively. The peaks due to quaternary carbon atoms disappeared in the spectrum. Further, LC-MS of **4a** showed the molecular ion peak at *m/z* 313.9 $[M]^+$ which is in agreement with the molecular formula, $C_{17}H_{15}NOS_2$.

The structural elucidation of the intermediate compound, 4-(chloromethyl)-2-{[4-(methylthio) phenoxy]methyl}-1,3-thiazole **5a** is based on its IR, ^1H and ^{13}C NMR spectral data. IR spectrum of **5a** showed absorption bands at 3110, 1522, 1494, 1256 and 813 cm^{-1} indicating the presence of CH_3, C=C, C=N, C-S-C and SCH_3 groups respectively and the

disappearance of characteristic peak due to NH_2 group of **3a** which clearly indicated the smooth cyclization. In the ^1H NMR spectrum of **5a** the appearance of singlets at δ 2.4, 4.8 and 5.0 correspond to the presence of SCH_3, CH_2 and OCH_2 protons respectively and also two doublets at δ 7.0 and 7.25 which are due to four aromatic protons. The lone thiazole proton appeared at δ 7.78. ^{13}C NMR (75 MHz) spectrum of **5a** showed signals at δ 16.21 due to SCH_3 while peaks at δ 40.75, 66.71, 115.81, 120.14, 128.71, 129.74 151.6, 155.64 and 167.18 are due to CH_2, OCH_2, C_2 and C_6 of phenoxy group, C_3 and C_5 of phenoxy moiety, C_5 of thiazole moiety, C_4 of phenoxy moiety, C_1 of phenoxy moiety, C_2 of thiazole and C_4 of thiazole, respectively. The peaks due to quaternary carbon atoms disappeared on DEPT experimentation.

The formation of title compound 4-[(2-{[4-(methylthio)phenoxy]methyl}-1,3-thiazol-5-yl) methyl]morpholine **6a** from **5a** is evidenced by its IR, ^1H and ^{13}C NMR and mass spectral data. IR spectrum of **6a** reveals the presence of CH_3, C=C, C=N, C-S-C and SCH_3 groups due to peaks at 2948, 1524, 1495, 1253 and 806 cm^{-1} respectively. Its ^1H NMR spectrum showed singlets at δ 2.49 and 5.36, which correspond to SCH_3, OCH_2 protons respectively and two multiplets at δ 2.40 and 3.56 that correspond to eight protons of morpholine and CH_2 protons respectively and also two doublets at δ 6.99 and 7.24 which are due to four aromatic protons. A sharp peak which appeared at δ 7.50 corresponds to thiazole proton. ^{13}C NMR (75 MHz) spectrum of **6a** showed signal at δ 16.21 due to SCH_3 while peaks at δ 53.04, 57.61, 66.17, 66.76, 115.84, 117.98, 128.69, 129.61, 152.81, 155.72 and 165.62 are due to CH_2, C_2 and C_6 of morpholine, C_3 and C_5 of morpholine, OCH_2, C_2 and C_6 of phenoxy group, C_5 of thiazole moiety, C_3 and C_5 of phenoxy moiety, C_4 of phenoxy moiety, C_4 of thiazole, C_1 of phenoxy moiety and C_2 of thiazole respectively. The quaternary carbon atom peaks disappeared on DEPT experimentation. Further, FAB-MS of **6a** showed the molecular ion peak at *m/z* 337 $[M+H]^+$ and 336 $[M]^+$ which is in agreement with their molecular formula, $C_{16}H_{20}N_2O_2S_2$.

Biological activity

Anti-inflammatory activity

Anti-inflammatory activity was evaluated for selected title compounds **4a-q** by carrageenan paw oedema test in rats[17]**.** Acute inflammation was produced by sub plantar injection of 0.1 mL of 1% suspension of carrageenan in 1% Tween-80, in the right hind paw of the rats. Diclofenac sodium 25 mg/kg, b.w. suspended in 1% Tween-80 was used as the standard drug for comparison and test compounds having dose level of 25 mg/kg, b.w. suspended in 1% tween-80 were administered orally. The paw volume was measured using the mercury displacement technique with the help of plethysmograph (Ugo Basile, Italy) immediately before and 0.5, 1.0, 2.0, 3.0 and 4.0 hr after the carrageenan injection. The results are summarized in **Table I**.

Table I — Anti-inflammatory activity of thiazole derivatives

Compd	0 hr	0.5 hr	1.0 hr	2.0 hr	3.0 hr	4.0 hr
Control	1.29(±0.026)	1.35(±0.0464)	1.36(±0.023)	1.36(±0.069)	1.39(±0.069)	1.35(±0.029)
Diclofenac sodium	1.18(±0.027)	1.37**(±0.033)	1.23**(±0.045	1.18**(±0.029)	1.01***(±0.058)	1.005***(±0.037)
4a	1.29(±0.026)	1.25(±0.018)	1.11**(±0.042)	1.15**(±0.024)	1.12**(±0.022)	1.12**(±0.02)
4b	1.32(±0.044)	1.33(±0.045)	1.30(±0.038)	1.26(±0.029)	1.24(±0.022)	1.25(±0.023)
4c	1.25(±0.022)	1.32(±0.012)	1.28*(±0.014)	1.14**(±0.020)	1.11**(±0.011)	1.09***(±0.001)
4d	1.29(±0.026)	1.115**(±0.039)	1.17**(±0.045)	1.13**(±0.044)	1.10**(±0.014)	1.11**(±0.07)
4g	1.32(±0.015)	1.29(±0.020)	1.24(±0.016)	1.22(±0.013)	1.21(±0.034)	1.22(±0.028)
4j	1.29(±0.019)	1.28(±0.018)	1.25*(±0.019)	1.23*(±0.023)	1.25*(±0.024)	1.26*(±0.027)
4l	1.27(±0.04)	1.25(±0.036)	1.21*(±0.038)	1.18*(±0.046)	1.18*(±0.045)	1.21*(±0.024)
4m	1.28(±0.024)	1.26(±0.022)	1.25(±0.022)	1.2(±0.041)	1.21(±0.041)	1.21(±0.017)
4p	1.30(±0.023)	1.30(±0.015)	1.26*(±0.010)	1.22*(±0.011)	1.11**(±0.015)	1.14**(±0.026)
4q	1.29(±0.026)	1.25(±0.055)	1.22(±0.033)	1.21(±0.031)	1.19(±0.029)	1.23(±0.024)

Significance levels * P< 0.05, ** P< 0.01, *** P< 0.001 compared with respective control (ANOVA followed by Dunnett's test). Each value represents ±SE (n=6)

Table II — Antibacterial activity of thiazoles

Compd	*Staphylococcus aureus*	*Bacillus subtilis*
4a	7	5
4b	9	6
4c	5	4
4d	8	5
4g	11	3
4j	7	5
4l	5	5
4m	6	5
4p	9	6
4q	14	10
6a	9	8
6b	11	10
6c	9	9
6d	6	7
6f	12	9
Standard (Gentamycin)	7	12

Table III — Antifungal activity of thiazoles

Compd	*Penicillium sp*	*A.niger*
4a	9	8
4b	10	8
4c	8	7
4d	6	8
4g	10	9
4j	7	9
4l	5	7
4m	9	6
4p	7	6
4q	12	10
6a	15	14
6b	13	16
6c	13	15
6d	14	11
6f	12	10
Standard (Gentamycin)	15	12

Antibacterial activity

Selected title compounds **4a-q, 6a-j** were evaluated for their *in vitro* antibacterial activity against two gram positive bacteria *viz*., *Bacillus subtilis* and *Staphylococcus aureus* using cup-plate method[18] after dissolving them in N,N-dimethylformamide (DMF) to obtain a 1mg/mL solution (1000 ppm). The inhibition zones of microbial growth were measured in millimetres at the end of an incubation period of 24 hr at 37°C for both types of bacteria. The solvent DMF showed no zone inhibition. The activity was compared with known standard drug Gentamycin, used at a concentration of 1000 ppm. The results are given in **Table II**.

Antifungal activity

Selected compounds **4a-q** and **6a-j** were evaluated for their *in vitro* antifungal activity against *A. niger* and *Penicillium sp* using Cup-plate method[18] after dissolving them in DMF to obtain a 1 mg/mL solution (1000 ppm). The inhibition zones of microbial growth were measured in millimetres at the end of an incubation period of 48 hr at 28°C. The solvent DMF showed no zone of inhibition. The activity was compared with known standard drug Gentamycin, used at a concentration of 1000 ppm. The results are summarized in **Table III**.

Experimental Section

Melting points are uncorrected and were determined in open capillaries using Serwell Instruments Inc, India melting point apparatus. Homogeneity of the compounds was checked by thin layer chromatography (TLC) on a silica coated aluminum sheet (silica gel $60F_{254}$) using chloroform and methanol (9:1, v/v). IR spectra were recorded on Nicolet Avatar 330-FTIR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz NMR spectrometer using TMS as an internal standard. Chemical shifts are reported in ppm (δ) and signals are described as singlet (s), doublet (d), triplet (t), quartet (q), broad (br,) and multiplet (m). The FAB mass spectra were recorded on a Jeol SX 102/DA-6000 spectrometer/Data system using Argon/Xenon (6 KV, 10 mA) FAB gas, at 70 eV. Elemental analysis was carried out using FlashEA 1112 Series, CHNSO Analyzer (Thermo). Solvents and reagents were purchased from the commercial vendors in the appropriate grade and were used as received.

General procedure for the preparation of 2-[4-(alkylthio) phenoxy] acetamides, 2a,b

A mixture of [4-(alkylthio)phenoxy] acetates **1a,b** (1 mmol) and 20 mL aqueous ammonia (20%) was stirred for 12-14 hrs at RT with purging of ammonia

gas. The progress of the reaction was monitored by TLC. The white solid product obtained was filtered, dried and purified by recrystallization from ethanol.

2-[4-(Methylthio) phenoxy] acetamide, 2a m.p. 142-45°C; IR: 3431 (NH_2), 2923 (CH_3), 1664 (C=O), 1605(C=C), 826 cm^{-1} (SCH_3); ^1H NMR ($CDCl_3$): δ 2.4 (s, 3H, SCH_3), 4.4 (s, 2H, CH_2), 5.8 (b, 1H, $CONH_2$), 6.85 (d, 2H, C_2, C_6-H of 4-methylthiophenoxy moiety *J*=8.72 Hz), 7.24 (d, 2H, C_3, C_5-H of 4-methylthiophenoxy moiety *J*=7.8 Hz). Anal. Calcd. for $C_9H_{11}NO_2S$: C, 54.8; H, 5.62; N, 7.1. Found: C, 54.82; H, 5.64; N, 7.12%.

2-[4-Ethylthio)phenoxy]acetamide, 2b m.p. 138-40°C; IR: 3437 (NH_2), 2971 (C_2H_5), 1644 (C=O), 1495 (C=C), 815 cm^{-1} (SCH_3); Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.2; N, 6.63. Found: C, 56.82; H, 6.2; N, 6.61%.

General procedure for the preparation of 2-[4-(alkylthio)phenoxy]ethanethioamides, 3a,b

To a solution of 2-[4-(alkylthio)phenoxy]acetamides **2a,b** (1 mmol) in 25 mL of dioxane, phosphorous pentasulfide (2 mmol) was added slowly at 10-12°C over a period of 2 hr with stirring. The reaction mixture was heated to 40°C for 2-2.5 hr. It was then plunged into ice cold water. The precipitated yellow solid was filtered, washed with water, dried and purified by recrystallization from ethyl acetate.

2-[4-(Methylthio)phenoxy]ethanethioamide, 3a m.p. 136-38°C; IR: 3385 (NH_2), 2971 (CH_3), 1619 (C=S), 1493(C=C), 814 cm^{-1} (SCH_3); ^1H NMR ($CDCl_3$): δ 2.4 (s, 3H, SCH_3), 4.9 (s, 2H, CH_2), 6.9 (d, 2H, C_2, C_6-H of 4-methylthio phenoxy moiety), 7.3 (d, 2H, C_3, C_5-H of 4-methylthio phenoxy moiety). Anal. Calcd. for $C_9H_{11}NOS_2$: C, 50.67; H, 5.2; N, 6.57. Found: C, 50.65; H, 5.18; N, 6.54%.

2-[4-(Ethylthio)phenoxy]ethanethioamide, 3b m.p. 130-32°C; IR: 3399 (NH_2), 2971 (CH_3), 1494(C=C), 1180, 1041, 821 cm^{-1} (SCH_3). Anal. Calcd. for $C_{10}H_{13}NOS_2$: C, 52.83; H, 5.76; N, 6.16. Found: C, 52.85; H, 5.78; N, 6.14%.

General procedure for the preparation of 2-{[4-(alkylthio) phenoxy] methyl}-4-phenyl-1,3-thiazoles, 4a-r

An equimolar mixture of 2-[4-(alkylthio)phenoxy]-ethanethioamides **3a,b** (1 mmol) and phenacyl bromide (1 mmol) in 20 mL of absolute ethanol was refluxed for 8 hr and left over-night at RT. The solid obtained was filtered, washed with ethanol and purified by recrystallisation from ethanol.

The characterization data are shown in **Table IV**.

2-{[4-(Methylthio)phenoxy]methyl}-4-phenyl-1,3-thiazole, 4a

IR: 2918 (CH_3), 1493 (C=C), 1175 (C=N), 1088 (C-S-C), 814 cm^{-1} (SCH_3); ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, SCH_3), 5.41 (s, 2H, CH_2), 6.97 (d, 2H, C_2, C_6-H of 4-methylthio phenoxy moiety *J*=8.72 Hz), 7.26 (d, 2H, C_3, C_5-H of 4-methylthio phenoxy moiety *J*=7.8 Hz), 7.3-7.4 (m, 3H, C_3 C_4, C_5-H of 4-phenyl moiety *J*=8.0), 7.5 (s, 1H, C_5-H, of thiazole), 7.9 (d, 2H, C_2-H, C_6-H of 4-phenyl moiety *J*=7.5); ^{13}C NMR : DEPT: CH and CH_3 δ: 17.83 (SCH_3), 115.71 (C_3H and C_5H), 126.32 (C_2H and C_6H), 128.24 (C_3, C_4, C_5-H of 4-phenyl moiety), 128.8 (C_4-H, of thiazole), 129.67 (C_2, C_6-H of 4-phenyl moiety), 67.82 (CH_2); LC-MS: *m/z* (%) 313.9 (100) $[M]^+$, 174.1 (50) [M-methyl thiophenol].

4-(2,4-Dichlorophenyl)-2-{[4-(methylthio) phenoxy]methyl}-1,3-thiazole, 4b

IR: 2913 (CH_3), 1494 (C=C), 1181 (C=N), 1057 (C=S), 811 cm^{-1} (SCH_3); ^1H NMR ($CDCl_3$): δ 2.45(s, 3H, SCH_3), 5.39 (s, 2H, CH_2), 6.92 (d, 2H, C_2, C_6H of 4-methylthio phenoxy moiety *J*=8.0), 7.26 (d, 2H, C_3, C_5-H of 4-methylthio phenoxy moiety *J*=8.1), 7.3 (d, 1H, C_5-H of 4-phenyl moiety *J*=7.5), 7.5 (s, 1H, C_3-H of thiazole), 7.9 (d, 2H, C_3, C_6-H of 4-phenyl moiety *J*=7.6); FAB-MS $^+$: *m/z* (%) 382(100) $[M]^+$, 381 (100), 242(80) [M-methyl thiophenol].

2-{[4-Ethylthio)phenoxy]methyl}-4-phenyl-1,3-thiazole, 4j

IR: 2921 (CH_2CH_3), 1490 (C=C), 1172 (C=N), 1066 (C=S), 811 cm^{-1} (SC_2H_5); ^1H NMR ($CDCl_3$): δ 1.3 (t, 3H, CH_3 of SCH_2CH_3), 2.8 (q, 2H, SCH_2), 5.42 (s, 2H, CH_2), 6.95 (d, 2H, C_2, C_6-H of 4-methylthio phenoxy moiety *J*=8.72 Hz), 7.2 (d, 2H, C_3, C_5-H of 4-methylthio phenoxy moiety *J*=7.8 Hz), 7.3-7.4 (m, 3H, C_3 C_4, C_5-H of 4-phenyl moiety *J*=8.0), 7.5 (s, 1H, C_5-H, of thiazole), 7.9 (d, 2H, C_2-H, C_6-H of 4-phenyl moiety *J*=7.5); LC-MS: *m/z* (%) 328 (100) $[M]^+$ 174.1 (50) [M-ethyl thiophenol].

4-(4-Chlorophenyl)-2-{[4-(ethylthio)phenoxy]methyl}-1,3-thiazole, 4l

IR: 2973 (CH_2CH_3), 1509[1] (C=C), 1173 (C=N), 1042 (C=S), 834 cm^{-1} (SC_2H_5); ^1H NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 2.8 (q, 2H, SCH_2), 5.5 (s, 2H, CH_2),

Table IV — Characterization data of compounds **4a-q**

Compd	Ar	R_1	Mol.formula	m.p. (°C)	Yield (%)	Mol. wt.	Found (%) (calcd) C	H	N
4a	Phenyl	SCH_3	$C_{17}H_{15}NOS_2$	120-33	60	313	65.1 (65.14	4.80 4.82	4.45 4.47)
4b	2,4-Di-Chloro phenyl	SCH_3	$C_{17}H_{13}Cl_2NOS_2$	138-40	65	382	53.42 (53.40	3.44 3.43	3.68 3.66)
4c	4-Chloro phenyl	SCH_3	$C_{17}H_{14}ClNOS_2$	170-73	68	347.5	58.65 (58.69	4.04 4.06	4.06 4.03)
4d	4-Nitrophenyl	SCH_3	$C_{17}H_{14}N_2O_3S_2$:	142-45	66	358	56.95 (56.96	3.96 3.94	7.86 7.82)
4e	4-Methyl phenyl	SCH_3	$C_{18}H_{17}NOS_2$	150-52	64	327	66.04 (66.02	5.25 5.23	4.3 4.28)
4f	4-Methoxy phenyl	SCH_3	$C_{18}H_{17}NO_2S_2$	160-63	68	343	66.96 (66.94	4.96 4.99	4.06 4.08)
4g	4-Pyridyl	SCH_3	$C_{16}H_{14}N_2OS_2$	210-13	73	314	61.14 (61.12	4.46 4.49	8.94 8.91)
4h	4-Aminophenyl	SCH_3	$C_{17}H_{16}N_2OS_2$	116-18	67	328	62.14 (62.16	4.94 4.91	8.55 8.53)
4i	2-Hydroxy Benzamide	SCH_3	$C_{18}H_{16}N_2O_3S_2$	171-73	65	372	58.06 (58.04	4.36 4.33	7.55 7.52)
4j	Phenyl	SC_2H_5	$C_{18}H_{17}NOS_2$	122-25	60	327	66.04 (66.02	5.24 5.23	4.26 4.28)
4k	2,4-Di-Chloro phenyl	SC_2H_5	$C_{18}H_{15}Cl_2NOS_2$	120-22	65	396.5	54.58 (54.55	3.81 3.81	3.55 3.53)
4l	4-Chloro phenyl	SC_2H_5	$C_{18}H_{16}ClNOS_2$	139-41	68	361	59.76 (59.74	4.48 4.46	3.85 4.87)
4m	4-Nitrophenyl	SC_2H_5	$C_{18}H_{16}N_2O_3S_2$:	119-22	66	372	58.07 (58.04	4.36 4.33	7.55 7.52)
4n	4-Methyl phenyl	SC_2H_5	$C_{19}H_{19}NOS_2$	125-27	64	341	66.86 (66.83	5.63 5.61	4.13 4.1)
4o	4-Methoxy phenyl	SC_2H_5	$C_{19}H_{19}NO_2S_2$	150-53	68	357	63.85 (63.83	5.38 5.36	3.96 3.92)
4p	4-Pyridyl	SC_2H_5	$C_{17}H_{16}N_2OS_2$	176-78	73	328	62.14 (62.16	4.96 4.91	8.54 8.53)
4q	2-Hydroxy Benzamide	SC_2H_5	$C_{19}H_{18}N_2O_3S_2$	160-62	65	386	59.06 (59.05	4.66 4.69	7.22 7.25)

7.0 (d, 2H, C_3, C_5-H of ethylthio phenoxy moiety *J*=8.3), 7.26 (d, 2H, C_2, C_6-H of ethylthio phenoxy moiety *J*=7.5), 7.4 (d, 2H, C_3, C_5-H of 4-phenyl moiety *J*=7.5), 7.5 (s, 1H, C_5-H of thiazole,), 7.82 (d, 2H, C_2, C_6-H of 4-phenyl moiety *J*=8.2); FAB-MS $^+$: *m/z* (%) 363(70) $[M+2]^+$, 362 (60) $[M+1]^+$, 361(60) $[M]^+$, 208(30) [M-ethyl thiophenol], 120 (30), 107 (20).

General procedure for the preparation of 2-{[4-(alkylthio)phenoxy]methyl}-4-phenyl-1,3-thiazoles, 5a,b

To a clear solution of 2-[4-(methyl/ethylthio) phenoxy] ethanethioamides **(3a,b**, 1 mmol) in ethanol (15 mL) 1,3-dichloroacetone (1.2 mmol) was added slowly over a period of 1 hr with stirring. The mixture was then refluxed for 3 hr and left overnight at RT. The solid obtained was filtered, washed with ethanol and purified by recrystallization from ethanol.

5-(Chloromethyl)-2-{[4-(methylthio)phenoxy]methyl}-1,3-thiazole, 5a

IR: 3110 (CH_3), 1522 (C=C), 1494 (C=N), 1256 (C-S-C), 813 cm^{-1} (SCH_3); ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, SCH_3), 4.8 (s, 2H, CH_2), 5.39 (s, 2H, OCH_2), 7.0 (d, 2H, C_2, C_6-H of 4-methylthio phenoxy moiety), 7.25 (d, 2H, C_3, C_5-H of 4-methylthio phenoxy moiety), 7.76 (s, 1H, C4-H of thiazole); ^{13}C NMR:

Table V — Characterization data of compounds **6a-j**

Compd	R_2	R_1	Mol. formula	m.p. (°C)	Yield (%)	Mol.wt.	Found % (calcd)		
							C	H	N
6a	Morpholine	SCH_3	$C_{16}H_{20}N_2O_2S_2$	120-23	64	336	57.13 (57.11	5.96 5.99	8.35 8.33)
6b	Piperazine	SCH_3	$C_{16}H_{21}N_3OS_2$	129-32	65	335	57.25 (57.28	6.33 6.31	12.55 12.53)
6c	N-Methyl Piperazine	SCH_3	$C_{17}H_{23}N_3OS_2$	111-13	67	349	58.45 (58.42	6.67 6.63	12.05 12.02)
6d	Piperidine	SCH_3	$C_{17}H_{22}N_2OS_2$	120-23	60	334	61.06 (61.04	6.66 6.63	8.40 8.37)
6e	Pyrrolidine	SCH_3	$C_{16}H_{20}N_2OS_2$	90-93	58	320	59.98 (59.96	6.31 6.29	8.76 8.74)
6f	Piperazine	SC_2H_5	$C_{17}H_{23}N_3OS_2$	92-95	65	349	58.45 (58.42	6.64 6.63	12.05 12.02)
6g	N-Methyl Piperazine	SC_2H_5	$C_{18}H_{25}N_3OS_2$	45-47	75	363	59.49 (59.47	6.96 6.93	11.56 11.55)
6h	Piperidine	SC_2H_5	$C_{18}H_{24}N_2OS_2$	40-43	67	348	62.06 (62.03	6.97 6.94	8.06 8.04)
6i	Pyrrolidine	SC_2H_5	$C_{17}H_{22}N_2OS_2$	38-40	63	334	61.06 (61.04	6.67 6.63	8.36 8.37)
6j	Morpholine	SC_2H_5	$C_{17}H_{22}N_2O_2S_2$	48-50	64	350	58.21 (58.25	6.36 6.33	7.96 7.99)

δ 16.21 (SCH_3), 40.75 (CH_2), 66.71 (OCH_2), 115.81 (C_2 and C_6 of phenoxy group), 120.14 (C_5 of thiazole moiety), 128.71 (C_3 and C_5 of phenoxy moiety), 129.74 (C_4 of phenoxy moiety) 151.6 (C_1 of phenoxy moiety), 155.64 (C_2 of thiazole) and 167.18 (C_4 of thiazole, respectively). The peaks due to quaternary carbon atoms disappeared on DEPT experimentation, the peaks due to CH_2 and OCH_2 showed downwards, CH and CH_3 showed upwards.

5-(Chloromethyl)-2-{[4-(ethylthio)phenoxy]methyl}-1,3-thiazole, 5b

IR: 2972 (CH_2CH_3), 1495 (C=C), 1286 (C=N), 1134 (C-S-C), 830 cm^{-1} (SC_2H_5): Anal. Calcd. for $C_{13}H_{14}ClNOS_2$: C,52.07; H,4.71; N, 4.67. Found: C,52.05; H,4.74; N,4.68%.

General procedure for the preparation of 4-[(2-{[4-(Alkylthio) phenoxy] methyl}-1,3-thiazol-5-yl) methyl] substituted amines, 6a-j

A mixture of 2-{[4-(alkylthio) phenoxy] methyl}-4-phenyl-1,3-thiazole (**5a,b**, 1 mmol), secondary amines (1.2 mmol) and super dry ethanol **(**20 mL) was heated under reflux for 3-4 hr. The reaction mass was left overnight at RT and the solid obtained was filtered, washed with cold ethanol, dried and purified by recrystallization from ethanol. The characterization data are shown in **Table V**.

4-[(2-{[4-(Methylthio)phenoxy methyl}-1,3-thiazol-4-yl) methyl]morpholine, 6a

IR: 2948 (CH_3), 1524 (C=C), 1495 (C=N), 1253 (C-S-C), 806 cm^{-1} (SCH_3); ^1H NMR (DMSO-d_6): δ 2.4 (m, 4H, C_2 H and C_6H morpholine), 2.49 (s, 3H, SCH_3), 3.56 (t, 6H, C_3, C_5-H of morpholine and CH_2), 5.36 (s, 2H, OCH_2), 6.99 (d, 2H, C_2, C_6-H of 4-methylthio phenoxy moiety), 7.24 (d, 2H, C_3, C_5-H of 4-methylthio phenoxy moiety), 7.48 (s, 1H, C_4-H of thiazole); ^{13}C NMR : δ 16.21 (SCH_3), 53.04 (CH_2), 57.61 (CH_2 of piperazine), 66.17 (CH_2 of piperazine), 66.76 (OCH_2), 115.84 (C_2 and C_6 of phenoxy group), 117.98 (C_5 of thiazole moiety), 128.69 (C_3 and C_5 of phenoxy moiety), 129.61 (C_4 of phenoxy moiety) 152.81 (C_4 of thiazole moiety), 155.72 (C_1 of phenoxy moiety) and 165.62 (C_2 of thiazole, respectively). The peaks due to quaternary carbon atoms disappeared on DEPT experimentation, the peaks due to CH_2 and OCH_2 showed downwards, CH and CH_3 showed upwards; FAB-MS $^+$: *m/z* (%) 337 (100) $[M+1]^+$, 336 (40) $[M]^+$, 293(40), 250 (50) [M-morpholine], 198(90) [M- methyl thiophenol], 196 (80).

4-[(2-{[4-(Methylthio)phenoxy]methyl}-1,3-thiazol-5-yl)methyl]pyrrolidine, 6e

IR: 2912 (CH_3), 1495 (C=C), 1285 (C=N), 1051 (C-S-C), 811 cm^{-1} (SCH_3); FAB-MS $^+$: *m/z* (%) 321 (80) $[M]^+$, 251(40) [M-pyrrolidine], 250 (30), 225 (25), 182(20) [M-methyl thiophenol], 111(20).

4-[(2-{[4-(Ethylthio) phenoxy]methyl}-1,3-thiazol-5-yl)methyl]piperazine,6f

IR: 2968 (CH_3), 1494(C=C), 1284 (C=N), 1045 (C-S-C), 823 cm^{-1} (SC_2H_5): ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3 of SCH_2CH_3), 2.6 (m, 8H, piperazine), 2.83 (q, 2H, CH_2 of SCH_2CH_3), 2.88 (NH of piperazine), 3.6 (2H, CH_2), 5.32 (s, 2H, OCH_2), 6.99 (d, 2H, C_2, C_6-H of 4-methylthio phenoxy moiety), 7.16 (s, 1H, C_4-H of thiazole), 7.34 (d, 2H, C_3, C_5-H of 4-methylthio phenoxy moiety) ; ^{13}C NMR : DEPT experimentation : δ 14.56 (CH_3 of SCH_2CH_3), 29.41 (CH_2 of SCH_2CH_3), 43.76 (CH_2 of piperazine), 52.8 (CH_2), 58 (CH_2 of piperazine), 67.48 (OCH_2), 115.84 (C_2 and C_6 of phenoxy group), 117.98 (C_5 of thiazole moiety), 132 (C_3 and C_5 of phenoxy moiety). The peaks due to quaternary carbon atoms disappeared, the peaks due to CH_2 and OCH_2 showed downwards, CH and CH_3 showed upwards; FAB-MS $^+$: *m/z* (%) 350(100) $[M+1]^+$, 333 (20), 197 (20) [M-ethyl thiophenol].

Conclusions

Preliminary anti-inflammatory studies of selected title compounds indicate that **4a, 4c, 4d,** and **4p** possess very good activity almost comparable with Diclofenac sodium. The compounds **4j** and **4l** possess moderate anti-inflammatory activity, while the compounds **4b, 4g, 4m** and **4q** possess low activity compared to the standard. However, further detailed studies on activity and long-term toxicity need to be carried out before any final conclusions can be drawn.

The enhanced activity is attributed to the presence of biologically active 4-(methylthio), 4-(ethylthio) phenoxy groups at position 2 and phenyl, 4-chlorophenyl, 4-nitrophenyl and pyridine groups at position 4 of thiazole moiety.

Antibacterial studies of selected title compounds reveal that **4b, 4d, 4g, 4p, 4q, 6a, 6b, 6c** and **6f** have shown higher activity than the standard Gentamycin against *Staphylococcus aureus* and **4j, 4m** and **6d** have shown good activity against *Staphylococcus aureus* which is comparable with standard, while the compounds **4q, 6b, 6c** and **6f** have shown moderate activity against *Bacillus subtilis*, compared to the standard. Antifungal screening results indicate that **6a, 6b** and **6c** have shown higher activity than standard Gentamycin against *Penicillium and A. niger* whereas compounds **4a, 4b**, **4d, 4g, 4j, 4q**, **6d** and **6f** have shown moderate activity which is comparable to the standard.

Increase in anti-bacterial activity of thiazoles is due to the presence of 4-(methylthio), 4-(ethylthio) phenoxy group at position-2 and phenyl, 2,4-dichlorophenyl, 4-nitrophenyl, pyridine and salicylamide, methylpiperidine, methylpiperazine, dimethylpiperazine, pyrrolidine, substituents at position 4 of thiazole. It has been observed that the thiazoles carrying 4-(methylthio)phenoxy substitution at position-2 and methylpiperidine, methylpiperazine, dimethylpiperazine, substituents at position 4 of thiazole moiety have shown very good anti-fungal activity.

From the results of antimicrobial screening it can be concluded that the compounds**, 6a, 6b,** and **6c** are found to be active agents; their enhanced activity may be attributed to the presence of biologically active 4-(methylthio)phenoxy substitution at position-2 and methylpiperidine, methylpiperazine, dimethylpiperazine groups at position 4 of thiazole ring.

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