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ANTI INFLAMMATORY ACTIVITY OF SOME NEW THIO-ETHER DERIVATIVES OF QUINOXALINE

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ABSTRACT

A series of thioether derivatives of 2-Chloro-3-methylquinoxaline have been synthesized by reacting 3-methylquinoxalin-2-thiosodium with 2-chloro-N-(substituted aryl/alkyl)-acetamides. The synthesis was initiated with the reaction of o-phenylenediamine ***(1)*** *with ethyl pyruvate in n-butanol to yield 2-hydroxy-3-methyl quinoxaline* ***(2),*** *which on treatment with $POCl_3$,yielded 2-chloro-3-methylquinoxaline* ***(3).*** *A mixture of the compound* ***(3)*** *and sodium sulphide in DMF was refluxed to yield 3-methylquinoxalin-2-thiosodium* ***(4),*** *which on treatment with different N-substituted chloroacetamides afforded the one pot synthesis of 2-(2-methylquinoxalin-3-ylthio)-N-substituted-aryl/alkyl)-acetamides* ***(5a-k).*** *2-chloro-N-substituted acetamides were prepared by treating substituted anilines in glacial acetic acid with chloroacetylchloride, warming on the water bath for half an hour and then precipitating, 2-chloro-N-substituted acetamides by addition of saturated aqueous solution of anhydrous sodium acetate. A compound 2-(benzylthio)-3-methylquinoxaline* ***5l*** *was also prepared. The newly synthesized compounds have been characterized by IR, and ^{1}HNMR spectra, analysis. All compounds* ***(5a-l)*** *were screened for their in vivo anti inflammatory activity by carrageenan induced rat paw edema method. Compounds* ***5a, 5b, 5d, 5e, 5g*** *and* ***5k*** *have been found to possess good anti inflammatory activity.*

Keywords: *Quinoxalines, 2-Chloro-N-(substituted- aryl/alkyl)-acetamides, 2-(2-methylquinoxalin-3-ylthio)-N-substituted- aryl/alkyl)-acetamides, anti-inflammatory activity.*

Introduction

Quinoxaline is commonly called 1, 4-diazanaphthalene or, bezopyrazine. Quinoxaline and its derivatives are mostly of synthetic origin. They have been described as a part of bicyclic desipeptide antibiotic having activity against gram positive bacteria and certain tumors by acting through inhibition of RNA synthesis. Quinoxaline ring structure is also found in the antibiotic such as Echinomycin, Levomycin and actinoleutin. It has been used in the synthesis of dyes, azo dyes, fluorescein dyes and pigments. Compounds containing the quinoxaline nucleus exhibit a broad spectrum of biological activity such as antibacterial [1-3], antifungal [4, 5], antiviral [6], anticancer [7], antituberculosis [8], antimalarial [9] and anti-inflammatory [10]. Thioethers have also been reported for their bactericidal, fungicidal, anti-inflammatory anticholestemic, hypolipidemic and neurotropic activities [11, 12], therefore in continuation of our previous work on 2-chloro-3-methylquinoxaline,"Synthesis and antimicrobial activity of some thioether derivatives of quinoxaline," it was thought worthwhile to evaluate their anti-inflammatory activity too.

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Material and Methods

The chemical synthesis (**scheme I**) was initiated with the reaction of o-phenylenediamine **(1)** with ethyl pyruvate in n-butanol to yield 2-hydroxy-3-methyl quinoxaline **(2),** which on treatment with $POCl_3$,yielded 2-chloro-3-methylquinoxaline**(3).**A mixture of the compound**(3)** and sodium sulphide in DMF was refluxed to yield 3-methylquinoxalin-2-thiosodium**(4),**which on treatment with different N-substituted aryl and cyclohexyl chloroacetamides afforded the one pot synthesis of 2-(2-methylquinoxalin-3-ylthio)-N-substituted-aryl) and cyclohexyl -acetamides**(5a-k).** 2-chloro-N-substituted acetamides (the list of these compounds is shown in the **Table 1**) were prepared by treating substituted anilines in glacial acetic acid with chloroacetylchloride, warming on the water bath for half an hour and then precipitating, 2-chloro-N-substituted acetamides by addition of saturated aqueous solution of anhydrous sodium acetate. A compound 2-(benzylthio)-3-methylquinoxaline **5l** was also prepared. All these compounds **(5a-l)** are depicted in **Table 2.** The compounds were purified by recrystallization from appropriate solvents**.** Purity of the compounds was checked by thin layer chromatography using silica gel-G on micro slide glass plates and spots were detected under iodine vapor.

The melting points were determined in laboratory melting point apparatus using capillary method and are uncorrected. IR spectra were recorded in KBr disk on a Simadzu FTIR- 8400 spectrophotometer and ^{1}HNMR spectra on JEOL FTNMR Spectrometer (300 MHz) using TMS as an internal standard. All chemical shift values were recorded as δ (ppm).

Scheme I

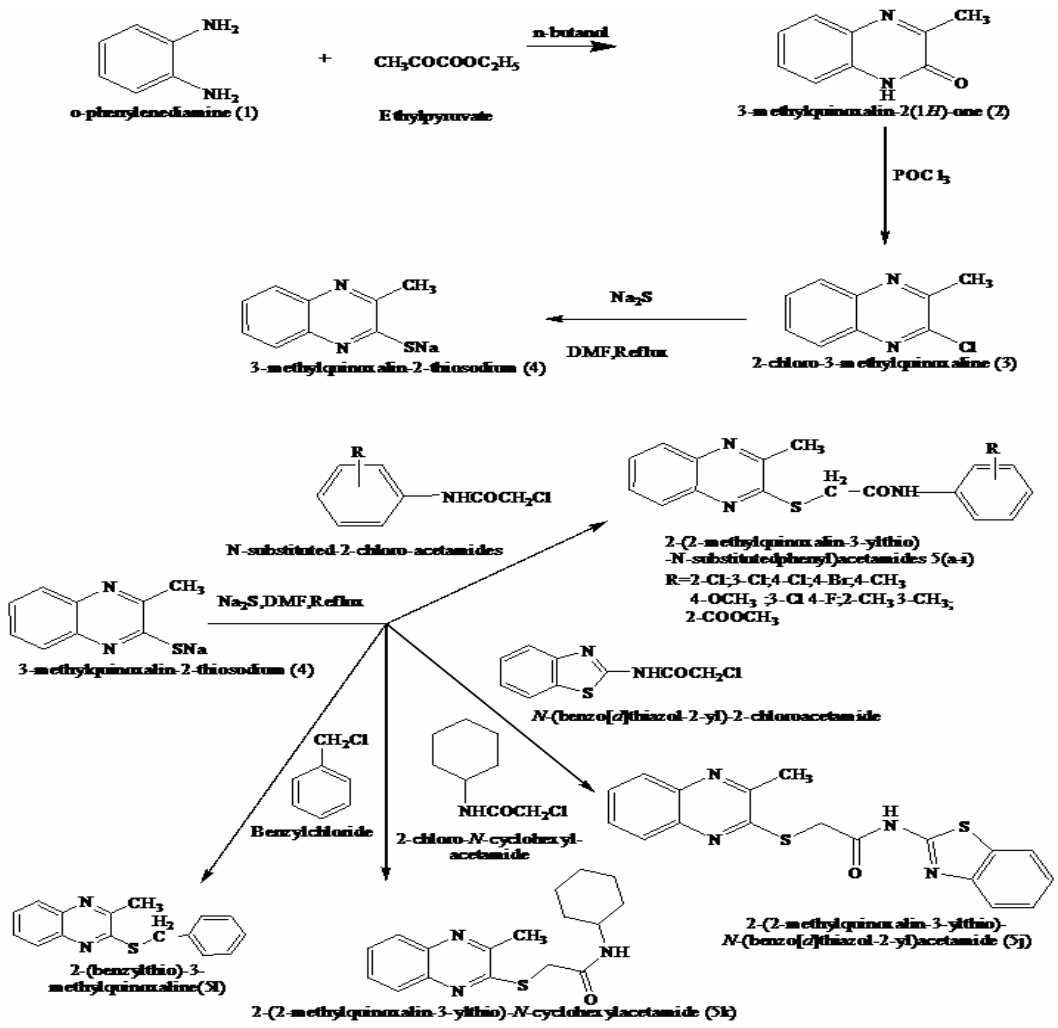
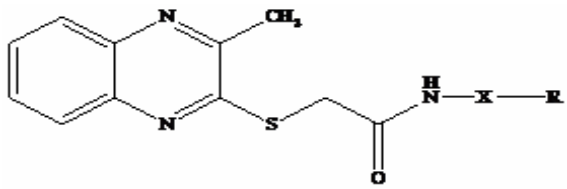


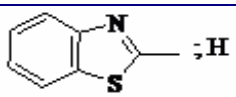
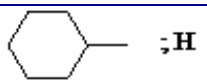
Table 1: Physical data of 2-chloro-N-(substituted aryl/alkyl)-acetamides

Sl. No.	Name	Melting point°c	Rf value
1.	2-chloro-N-(2-chlorophenyl)acetamide	70-72	0.82
2.	2-chloro-N-(3-chlorophenyl)acetamide	78	0.80
3.	2-chloro-N(4-chlorophenyl)acetamide	164-166	0.75
4.	2-chloro-N-(4-bromophenyl)acetamide	170-172	0.77
5.	2-chloro-N-(p-tolyl)acetamide	160-162	0.70
6.	2-chloro-N-(4-methoxyphenyl)acetamide	104	0.86
7.	2-chloro-N-(3-chloro,4-fluorophenyl)acetamide	75-77	0.64
8	2-chloro-N-(2,3dimethylphenyl)acetamide	122-124	0.72
9.	methyl 2-(2-chloroacetamido)benzoate	78	0.90
10.	N-(benzo[d]thiazol-2-yl)-2-chloroacetamide.	141-142	0.68
11.	2-chloro-N-cyclohexylacetamide	98	0.88

Table 2: Physical data of compounds **(5a-l)** and structures



General structure of the synthesized compounds

Compounds	X ; R	Reaction Time	M.P. (^{0}C)	R_f value
5a.	C_6H_4 ; 2-Cl	6 Hr	138	0.90
5b.	C_6H_4 ; 3-Cl	6 Hr	109	0.83
5c.	C_6H_4 ; 4-Cl	6 Hr	144-145	0.84
5d.	C_6H_4 ; 4-Br	6 Hr	166-167	0.80
5e.	C_6H_4 ; 4-CH_3	5 Hr	176	0.66
5f.	C_6H_4 ; 4-OCH_3	7 Hr	160	0.79
5g.	C_6H_3 ; 3-Cl, 4-F	9 Hr	159-160	0.81
5h.	C_6H_3 ; 2- CH_3 , 3-CH_3	6 Hr	182-183	0.78
5i	C_6H_4 ; 2-$COOCH_3$	6 Hr	130	0.86
5j.		6 Hr	180	0.57
5k.		6 Hr	168-169	0.60
5l.	R-X-NHCO = C_6H_5	2 Hr	170-171	0.80

Physical data of compounds **(5a-l)** and structures are shown in the **Table 2.**

Anti inflammatory activity

Carrageenan induced rat paw edema method [13] was employed for screening of the anti inflammatory activity of the synthesized compounds.

Wistar rats of albino rats of either sex weighing 180-250g were used for the experiments. They were housed in clean polypropylene cages and kept under room temperature (25± 2ºC) relative humidity 60-70% in a 12:12 hr natural light-dark cycle. The animals were given standard laboratory food and water. Food was withdrawn 12 hr before and during experimental hour.

The animals were divided in to several groups of six each. The control group received 2% gum acacia suspension orally, while the other groups received different drug treatment as detailed bellow. One hr after oral administration of the drug, acute inflammation was produced by sub plantar injection of 0.1 mL of 1% suspension of carrageenan with 2% gum acacia in normal saline, in the right hind paw of the rats. A mark was applied on the leg at the malleolus to facilitate subsequent readings. The paw volume was measured plythysmometrically at 30min, 1, 2, 3 and 4 hr after the injection of carrageenan. The % inhibition was calculated by applying Newbould formula [14] - %Inhibition = (1-Vt/Vc) x100 Where Vt and Vc are the mean change in paw volume of treated and control rats respectively.

Statistical analysis

The results were expressed as mean ± SEM and were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's t-test .The probability of 0.05 or less was considered statistically significant.

The results of inflammatory activity are shown in the **table1**.

Table1. The results of inflammatory activity

Treatment	Dose mg/Kg	Mean changes in paw edema (ml) (Mean ± SEM) (% Inhibition)				
		30min	1hr	2hr	3hr	4hr
Group-I, Control(5% Acacia solution)	-	0.611±0.031	0.698±0.033	0.732±0.028	0.621±0.037	0.654±0.040
Group-II, Standard (Indomethacin)p.o	25 mg/kg	0.264±0.012 (56.79)	0.266±0.016 (61.89)	0.267±0.017 (63.52)	0.267±0.016 (57.00)	0.268±0.017 (59.02)
Group-VII 5a	100 mg/kg	0.417±0.008 (31.75)	0.424±0.008 (39.26)	0.548±0.015 (25.14)	0.451±0.019 (27.37)	0.576±0.029 (11.93)
Group-VIII 5b	100 mg/kg	0.418±0.007 (31.59)	0.424±0.008 (39.26)	0.431±0.007 (41.12)	0.372 ±0.007 (40.09)	0.546±0.01 (16.51)
Group-IX 5c	100 mg/kg	0.469±0.012 (23.24)	0.564±0.016 (19.18)	0.568±0.012 (22.40)	0.612±0.034 (1.45)	0.602±0.037 (7.95)
Group-X 5d	100 mg/kg	0.465±0.008 (23.86)	0.482±0.009 (30.95)	0.579±0.008 (20.90)	0.473±0.015 (23.83)	0.418±0.024 (26.45)
Group-V 5e	100 mg/kg	0.430±0.014 (29.62)	0.469±0.014 (32.81)	0.541±0.023 (26.09)	0.446±0.019 (28.34)	0.701±0.017 (-)
Group-VI 5f	100 mg/kg	0.426±0.012 (30.28)	0.558±0.014 (20.06)	0.637±0.016 (12.99)	0.697±0.013 (-)	0.690±0.021 (-)
Group-XI 5g	100 mg/kg	0.483±0.006 (20.95)	0.599±0.011 (14.18)	0.593±0.021 (18.99)	0.633±0.023 (30.27)	0.680±0.024 (2.75)
Group-VI 5h	100mg/kg	0.555±0.019 (9.17)	0.571±0.025 (18.19)	0.659±0.024 (9.97)	0.709±0.023 (-)	0.744±0.025 (-)
Group-XII 5i	100 mg/kg	0.470±0.001 (23.08)	0.485±0.005 (30.52)	0.699±0.017 (4.51)	0.707±0.015 (-)	0.726±0.021 (-)
Group-XIII 5j	100 mg/kg	0.464±0.015 (24.06)	0.505±0.022 (27.65)	0.623±0.012 (14.89)	0.623±0.015 (-)	0.757±0.018 (-)
Group-XIV 5k	100 mg/kg	0.475±0.004 (22.26)	0.487±0.008 (30.23)	0.539±0.012 (26.37)	0.466±0.007 (24.96)	0.599±0.011 (. 8.41)
Group-III 5l	100 mg/kg	0.483±0.009 (20.95)	0.574±0.091 (17.77)	0.685±0.014 (6.42)	0.682±0.011 (-)	0.670±0.009 (-)

Result and Discussion

The attachment of various substituent groups in the synthesized compounds were also validated by their respective IR and ^{1}HNMR spectra. The structures of all newly synthesized compounds were elucidated on the basis of their spectral and analytical data.

The anti-inflammatory activity of the compounds **(5a-k)** was evaluated by carrageenan induced rat paw edema method. The compounds were tested at 100 mg/kg dose and the results were compared with that of Indomethacin as a reference drug. The results are summarized in the table1; suggest that the anti-

inflammatory activity screening are in the range of 23.34 to 40.09% inhibition, whereas the standard drug Indomethacin showed an activity of 57% inhibition after 3 hrs. Among the compounds, screened for anti-inflammatory activity, compounds 5a,5d,5e, and 5k are having moderate activity (23-28% inhibition) whereas the compound 5b,showed best anti-inflammatory activity (40.09% inhibition) and compound 5g showed good anti-inflammatory activity(30.27% inhibition).None of the compounds other than 5b(16.51) and 5d(26.47% inhibition) was found active after 4 hrs. It may be concluded that methyl (5e), chlorine (5a, 5b), bromine (5d), chlorine and fluorine (5g) substituted aromatic amines have enhancing effect on anti-inflammatory activity and in the case of compound(5k) the enhanced activity may be attributed due to presence of 2-aminobenzothiazole nucleus which is reported to have similar activity. Carrageenan-induced paw edema is believed to be biphasic and is commonly used to screen anti-inflammatory agents. The first phase is due to release of histamine or serotonin and the second phase is due to release of prostaglandin. Therefore, the anti-inflammatory activity of the synthesized compounds may be due to inhibition of histamine, serotonin or prostaglandin synthesis.

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