Asian J. Exp. Sci., Vol. 22, No. 3, 2008; 00-00

Antimutagenic Activity of Few Nitrogen and Sulphur Heterocyclics Synthesized via Microwave Irradiation

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Abstract : Sulphur and nitrogen containing heterocycles represent an important group of compounds that are promising for use in practical applications. Thieno quinolines form a class of hetero aromatics with several pharmaceutical and biological activities. Hence this paper is aimed at synthesizing dihydrothienoquinolines and the precursors required for its synthesis - quinolone, chloro quinolines and thione. The foresaid compounds are required for the synthesis of thieno quinolines. Microwave synthesis was adopted owing to its user-friendly nature. The antimutagenic activity of the compounds has been assessed by Ames Salmonella Microsome Assay. Microwave reactions of the compounds resulted in drastic reduction in the time of synthesis and improved yields. Several compounds showed good antimutagenicity. The results were found to be statistically significant (P=0).

Key words : Antimutagenic Activity , Heterocyclics , Microwave synthesis, Ames.

Introduction

Sulphur and nitrogen containing heterocycles represent an important group of compounds that are promising for use in practical applications. The synthesis of quinolines and their derivatives has been of considerable interest because a large number of natural products and drugs contain this heterocyclic unit (Morimoto *et al*, 1991; Isobe *et al*, 1992; Markees *et al*, 1970; Alhaider *et al*, 1985; Campbell *et al*, 1988). Thieno quinolines form a class of hetero aromatics in which the thiophene ring is fused to the quinoline nucleus. There are several reports (Makitsuno, 1973, Makisumi, 1969; 1970; 1974, Makikado, 1973, Sarithadevi *et al*, 1993) on the pharmaceutical and biological activity of these compounds. Dihydrothieno quinolines are heterocyclic ring systems of considerable interest due to several biological and pharmaceutical activities associated with this scaffold: Some analogues have been found to act as effective pharmaceutical and biological agents. *Consequently, it was decided to try to corner the interest to dihydrothienoquinolines and the precursors required for its synthesis - quinolone, chloroquinolines and thione. Microwave synthesis was adopted owing to its user-friendly nature*. (Gedye *et al* , 1988; Varma,1999, 2000, 2001). QSAR studies have proved the pharmaceutical and biological importance of many quinoline compounds. (Hayes *et al*, 2002). The broad application spectrum and *in vivo* efficiency of quinolone antibacterials (Wise *et al*, 1983), thiadiazoles (Ashour *et al*, 1990) and oxadiazoles (Dort and Counsel, 1987) have generated much enthusiasm in the medical community and prompted extensive research in the pharmaceutical industry as well. *Owing to the*

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significant biological and pharmacological activity of the organic compounds as seen from literature hunt, it was felt essential to explore the importance of dihydrothieno quinolines, vinyl-2-quinolones, vinyl-2-chloro quinolines and vinyl-2-thiones. The antimutagenic activity of the compounds has hence been studied.

Materials and Methods

Melting points were determined in open-end capillaries using a Joshibha Model melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrometer model 599 and the absorption frequencies are quoted in cm^{-1}. The compounds were characterized from their Co-IR and comparison with literature melting points. All microwave reactions were carried out in domestic microwave ovens - IFB model 179 MIS of output power 750W. Laminar Airflow Cabit (Kemi), autoclave (Osworld "Autoclave Steam Sterilizer"JRIC-39) and incubator (Genuine) were used for antimutagenic activity studies.

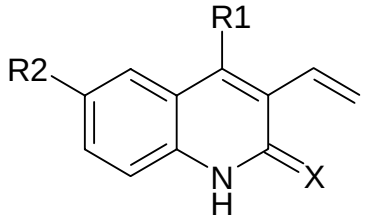
Preparation of 4-alkyl -3- vinyl quinoline-2(1H) ones (1a-d)

The procedure of Senthil et al., (1993) for adopted for the preparation of 3-vinyl-quinoline-2(1H)-ones.

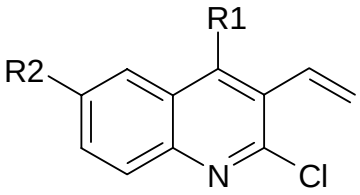
Microwave enhanced synthesis of 2-chloro-3-vinyl quinolines (2a-d)

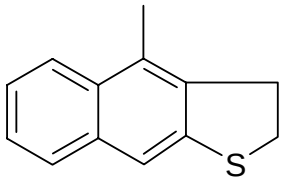
The vinyl quinolone (1mole) was microwaved at 350W with phosphorous oxychloride (few drops to wet the reaction mixture) in an IFB Model 17PMIS domestic microwave. The completion of the reaction was monitored every 30seconds by recording TLC of the reaction mixture. After completion of the reaction as noted by the disappearance of the starting compound, the reaction mixture was cooled and poured into ice water. It was then macerated well and carefully neutralized with ammonia solution. The neutralized reaction mixture was extracted with chloroform and the chloroform extract was washed with water, dried and evaporated. The residue obtained was chromatographed over alumina (neutral) and eluted with petroleum ether as the case may be.

2-Chloro-4- methyl -3-vinyl quinolines	
4-Methyl -3- vinyl quinoline-2(1H)-one	: 100mg
$POCl_3$	: 0.3 ml
Solvent for chromatography	: benzene – pet-ether mixture
2-Chloro-4- phenyl-3-vinyl quinolines	
4-Phenyl -3- vinyl quinoline-2(1H- one	: 100 mg
$POCl_3$	: 0.4 ml
Solvent for chromatography	: benzene – pet-ether mixture
2,6-Dichloro -4- phenyl -3-vinyl quinolines	
6-Chloro-4- phenyl -3-vinyl quinoline-2(1H)-one	: 100 mg
$POCl_3$	: 0.4 ml
Solvent for chromatography	: benzene – pet-ether mixture
6- Nitro -2-chloro -4- phenyl -3-vinyl quinolines	
6-Nitro-4- phenyl -3-vinyl quinoline-2(1H)-one	: 100 mg
$POCl_3$	: 0.5 ml
Solvent for chromatography	: benzene – pet-ether mixture



1a	$R1=CH_3$	R2=H	X=O;	**1b**	$R1=C_6H_5$	R2=H	X=O
1c	$R1=C_6H_5$	R2=Cl	X=O;	**1d**	$R1=C_6H_5$	$R2=NO_2$	X=O
3a	$R1=CH_3$	R2=H	X=S;	**3b**	$R1=C_6H_5$	R2=H	X=S
3c	$R1=C_6H_5$	R2=Cl	X=S;	**3d**	$R1=C_6H_5$	$R2=NO_2$	X=S





2a	$R1=CH_3$	R2=H	;	**2b**	$R1=C_6H_5$	R2=H
2c	$R1=C_6H_5$	R2=Cl	;	**2d**	$R1=C_6H_5$	$R2=NO_2$

Microwave enhanced conversion of 2-chloro-3-vinyl quinolines (2a-d) into the corresponding 3-vinyl quinoline-2(1H)-thiones(3a-d)

A mixture of chloroquinoline (0.005mole), thiourea (0.007mole) and anhydrous ethanol (just to wet the reaction mixture) was microwaved at 750W. The completion of reaction was monitored by thin layer chromatography after which the reaction mixture was cooled, poured into ice-water and macerated to get a yellow solid. The thiouronium salt that precipitated was collected and washed with little ethanol and then digested with 10% aqueous sodium hydroxide on a steam bath for 30min.The thione was recovered from the alkaline extract by acidification, as yellow powder. The residue after evaporation of the alcoholic filtrate (from which the thiouronium salt was separated) was digested with 10% aqueous sodium hydroxide on a steam-bath for 30min and acidified after cooling. The product was collected, dried and purified to give a further crop of the thione. The actual quantities of the reagent and the solvent employed are:

4-Methyl -3-vinyl quinoline-2(1H)-thiones		
2-Chloro-4- methyl -3-vinyl quinolines	:	100 mg
Thiourea	:	50mg
Absolute ethanol	:	0.5ml

4- Phenyl -3-vinyl quinoline-2(1H)-thiones		
2-Chloro-4- phenyl -3-vinyl quinolines	:	130 mg
Thiourea	:	53 mg
Absolute ethanol	:	0.5 ml
6-Chloro-4- phenyl -3-vinyl quinoline-2(1H)-thiones		
2,6-Dichloro-4- phenyl -3-vinyl quinolines	:	150 mg
Thiourea	:	53mg
Absolute ethanol	:	0.5 ml
6-Nitro-4- phenyl -3-vinyl quinoline-2(1H)-thiones		
6-Nitro-2-chloro-4- phenyl -3-vinyl quinolines	:	110 mg
Thiourea	:	56mg
Absolute ethanol	:	0.5 ml

Microwave enhanced synthesis of 2, 3 – dihydro-4-methyl-thieno (2, 3-b)

Quinolines (4)

Method I

4-methyl -3- vinyl quinoline-2(1H) thione (120 mg) was irradiated under microwave at 300W with sodium acetate (100 mg) and glacial acetic acid (10 drops) just to wet the reaction mixture. The product was noticed in 25seconds. The reaction was prolonged further for 1 minute. After the disappearance of the starting compound in 2 minutes, the reaction mixture was cooled, poured into ice-water and extracted with chloroform. Evaporation of the dried extract furnished a residue. Chromatography of the residue over alumina in benzene gave dihydrothieno quinoline as colourless needles. **Yield: 96 mg (80%); m.p: 158-159^{O}C.**

Method II

The 3-vinyl quinoline-2(1H)-thione (100 mg) was treated with 0.5 ml of ortho phosphoric acid and microwaved at 300W till the completion of reaction in 3 minutes as seen from TLC. Then the reaction mixture was cooled, poured into ice-water and neutralized with sodium bicarbonate. The neutralized solution was extracted with chloroform and the chloroform layer was separated, dried, and evaporated under reduced pressure to yield white crystals of dihydrothienoquinoline. **Yield: 80 mg (80%); m.p: 158-159^{O}C.**

Method III

The 3-vinyl quinoline-2(1H)-thione (70 mg) was treated with PPA (50mg P_2O_5 and 0.3ml ortho phosphoric acid) and microwaved at 300W for 2 minutes. Reaction showed the absence of thione after 5 minutes. The reaction mixture was then poured into ice – water and neutralized with ammonium hydroxide. The yellow solid obtained was filtered and the filtrate extracted with methylene chloride. The organic layer was separated, dried and evaporated under reduced pressure to yield a yellow solid. Both solids showed three spots. Preparatory TLC of the compound gave dihydrothienoquinoline as white crystals and thiato quinoline as minor product. One of the base spots was identified as the disulphide. On developing the preparatory plate several bands started to appear in contrast to the anticipated three bands. **Yield: 60 mg (86%); m.p: 158-159^{O}C.**

Method IV

The 3-vinyl quinoline-2(1H)-thione (100 mg) was treated with 2ml methylene dichloride and 1 ml 5% sulphuric acid and micro-waved cautiously under low power (75 W). The

reaction was complete in 2 sec at 75W. The reaction mixture was poured into ice-water, neutralized and shaken with ether. The ether layer was dried and evaporated to give 2,3 – dihydro-4-methylthieno(2,3-b)quinoline. **Yield: 89 mg (89%); m.p: 158-159^{O}C.**

Method V

The 3-vinyl quinoline-2(1H)-thione (100 mg) was treated with 1ml acetonitrile and 0.3ml perchloric acid and micro waved very cautiously under low power (75 W). The reaction was complete in 2 sec at 75W. The reaction mixture was poured into ice, neutralized and then shaken with ether. The ether layer was dried and evaporated to give 2,3 – dihydro-4-methylthieno(2,3-b)quinoline. **Yield: 90 mg (90%); m.p: 158-159^{O}C.**

Antimutagenic Activity of Compounds

Of the 13 compounds synthesized 9 compounds – 1a-1d,2a,2b,3a,3b and 4 were taken up for antimutagenic studies.

Bacterial Tester Strains and Chemicals

Salmonella typhimurium TA98 tester strains were generously donated by Professor B.N. Ames (University of California, Berkeley, U.S.A). All the chemicals used are of analytical grade from Himedia and Qualigens Fine Chemicals, India.

Ames Salmonella Microsome Assay **(Maron and Ames, 1983**) was carried out for the test compounds for determining mutagenicity / antimutagenicity.

Determination of Number of Bacteria

The bacterial culture was diluted 1: 200,000 times. 100ìl of this diluted culture and 500ìl of histidine enriched KCl were added to 2 ml molten top agar, mixed and poured onto minimal basal agar. It was incubated at 37^{o}C overnight and the colonies were counted.

Preparation of solutions for mutagenesis/ antimutagenesis assay-

Minimal glucose (basal agar) plates

For the mutagenesis/antimutagenesis assay the minimal glucose agar medium was prepared as follows.

Solution A

Chemical required	**Quantity**
Water	2.625 litres
Citric acid	190.48 g/l
K_2HPO_4	1247.62 g/l
$NaNH_4PO_4$	333.3 g/l

Solution **A** was prepared by dissolving the above substances in the order given making sure that one is completely dissolved before adding the next. The prepared solution was filled in screw-capped bottles in 400 ml portions and autoclaved. Risk of contamination by opening of bottles was minimal, since bacteria cannot grow well in concentrated salt solution.

Solution B

Dissolved 20g $MgSO_4.7H_2O$ in 1000 ml water, filled in 200ml portions and autoclaved.

Solution C

In a 2-litre flask, 30g of Bactoagar in 1500 ml water was autoclaved.

Solution D

Autoclaved 40g glucose in 500 ml water. The solution was allowed to cool for 20-40 minutes.

Basal agar: Solutions C and D were combined and 40 ml of solution A and 10 ml of solution B were then added to it. The mixture was poured into sterile petriplates @ 25 ml/ plate.

Nutrient Broth for Culturing Bacteria

The nutrient broth (25g) was mixed in one litre water, filled in 20-40ml portions and autoclaved immediately. This broth can be stored for any length of time.

- **Histidine-Biotin solution**

Chemical required	Quantity
Histidin.HCl	350mg/l
D-Biotin	625 mg
Sodium phosphate buffer (pH 7.4.)	250 mM

450ìl Histidine hydrochloride and 512ìl biotin were dissolved in about 3 litres of 250 mM sodium phosphate buffer.

- **Histidine-Tryptophan enriched KCl**

Dissolved 2.8 mg histidine, 2.8 mg tryptophan per ml KCl solution and filtered sterile.

- **Top Agar**

Chemical required	Quantity
Bacto agar 0.6%	30g
NaCl 0.6%	30g
Water	5 litres

The top agar solution was autoclaved

- **HB-TopAgar**

To 10 volumes of cooled top agar, 1 volume of Histidine-Biotin solution was added and mixed well. It was then distributed in 2 ml portions in sterile tubes and maintained at 45°C to 50°C.

Effect of Samples on the Mutagenicity/ Antimutagenicity of *Salmonella Typhimurium* TA98

The antimutagenicity of the samples was carried out in the absence of metabolic mixture. The Standard Mutagen Daunomycin was used for TA 98.

The concentration of Standard Mutagen used was as follows: Daunomycin: 6ìg/plate. The results of the Ames test are expressed as number of revertants / plate.

Summary of the Assay

HB-top agar was distributed into 2 ml portions and held at 45°C. To the top agar, depending on the test group, the following were added in succession.

A 100 ìl of overnight grown culture

B 10 ìl of sample

C 10 ìl Standard Mutagen

Spontaneous Revertants (SR) : A alone

Mutagenicity / antimutagenicity of compounds : A and B

Standard Mutagen (SM) : A and C

Mutagenicity / antimutagenicity of the sample : A, B and C

Culturing Bacteria

Prior to carrying out the experiment, the nutrient broth was inoculated with the cells scrapped from the master plates and incubated overnight in a shaker incubator at 37°C.

Statistical Analysis

The data observed with respect to different studies were scrutinized and subjected to student‘t’ test.

Results And Discussion

The compounds synthesized were characterized from their Co-IR with authentic samples (Shanmugam et al, 1976) and comparison with literature melting points.

The results obtained in microwave-accelerated synthesis are expressed in Table 1. It is understandable from the yield of products obtained that there is an increase in the percentage yield compared to conventional synthesis. It can be seen that there is drastic reduction in the time of synthesis as anticipated. The time required for the completion of synthesis is approximately 20-60 times lesser than that required in classic

Table 1 : Microwave Enhanced Synthesis

Compound	Yield (%)	Time (min.)
2-chloro-4- methyl -3-vinyl quinoline	90	21/2
2–chloro– 4 –phenyl-3 vinyl quinoline	90.4	61/2
2,6 -dichloro-4- phenyl -3-vinyl quinoline	94.3	6
6-nitro-2-chloro-4-phenyl -3-vinyl quinoline	84.3	9
4- methyl -3-vinyl quinoline-2(1H)-thione	88	3
4–phenyl–3 vinyl quinoline–2(IH)–thione	86.8	4/5
6-chloro-4- phenyl -3-vinyl quinoline-2(1H)-thione	95	6
6-nitro-4- phenyl -3-vinyl quinoline-2(1H)-thione	88	8

Table 2 : Microwave Enhanced Synthesis Of 2, 3 - Dihydro-4-Alkyl Thieno (2, 3-B) Quinolines (4)

Entry	Reaction	Yield (%)	Time
1	Method I	80	2
2	Method II	80	3
3	Method III	86	2
4	Method IV	89	0.033(2s)
5	Method V	90	0.033(2s)

reactions. The results of microwave enhanced synthesis of 2,3-dihydro-4-alkyl-thieno(2,3-b)quinolines are given in Table 2. Undoubtedly microwave heating offers clean and quick methodology than the previously reported conventional methods (Shanmugam et al,1971;1976).

Assessment of Antimutagenic Effects of Compounds in Salmonella Microsome Assay

The S*almonella typhimurium* reverse mutation assay is the most commonly used method to assess the mutagenic potential of test chemicals which may cause base-pair and form shift mutation in the genome of this organism (Maron and Ames,1983). Daunomycin and sodium azide are the known genotoxicants in mammalian and microbial test systems. Addition of daunomycin to the test plate resulted in the significant induction of histidine revertant colonies. SR represents spontaneous revertant (stock culture), which is equivalent to negative control. SM represents standard mutagen, which is equivalent to control. SR+ X represents the effect of X as mutagen/antimutagen in the standard mutagen induced plates (X is the selected sample).The present study is a reverse mutation assay where the reduction in histidine^{+} revertant colonies in the Standard Mutagen induced plates by the addition of sample indicates the antimutagenicity of the sample.

The data pertaining to mutagenic/ antimutagenic test carried out for the test compounds are presented in Tables 3, 4 and 5. The number of Spontaneous Revertants was found to be 262 ± 9.7 and by the addition of Standard Mutagen there was increase in revertant frequency by 456 ± 14.7.

The addition of compounds 1a,1b,4 and 3b to Spontaneous Revertant did not show any statistical result whereas the addition of the foresaid compounds to Standard Mutagen (Daunomycin) induced plate resulted in

Table 3 : Antimutagenic Effect of Compounds in Salmonella Typhimurium (Ta 98) Strain

Compound	SR	SM	SR+X	SM+X
1a	262±9.7	456±14.7**	371±14.3 NS	176±5.8**
1b	262±9.7	456±14.7**	189±19.7 NS	181±5.0**
1c	262±9.7	456±14.7**	400±11.46**	219±2.89**
1d	262±9.7	456±14.7**	153±10.22**	153±6.8**
2a	262±9.7	456±14.7**	160±6.3**	243±6.6 N.S
2b	262±9.7	456±14.7**	456±13.3**	375±14.12 NS
3b	262±9.7	456±14.7**	260±16.1 NS	173±5.8**
3a	262±9.7	456±14.7**	175±5.5**	253±9.6 N.S
4	262±9.7	456±14.7**	225±19.6 N.S	231±5.7**

SR – Spontaneous Revertant; ** *- Significant at P=0.01*; *SM – Standard Mutagen*; *NS – Not Significant*

Table 4 : SR + Compound

	SR	SM	1a	2a	3a	4	1b	2b	3b	1c	1d
	320	352	456	120	192	80	128	256	184	264	320
	144	440	296	168	128	160	168	416	200	336	184
	272	320	168	232	160	160	248	496	232	344	176
	176	400	472	304	160	200	288	600	304	496	208
	272	384	360	488	168	520	176	488	224	408	80
	256	448	400	240	256	440	192	568	304	480	56
	416	640	272	120	224	200	120	344	336	328	80
	240	664	544	192	112	40	192	480	296	544	120
Mean	262	456	371	233	175	225	189	456	260	400	153

Table 5 : SM + Compound

	SR	SM	1a	2a	3a	4	1b	2b	3b	1c	1d
	320	168	192	230	384	264	144	424	208	240	232
	144	128	208	256	408	240	168	288	168	256	240
	272	120	128	278	200	272	208	304	128	184	176
	176	112	272	389	256	192	248	304	272	240	128
	272	240	176	300	424	160	128	400	176	200	128
	256	120	112	222	392	176	232	632	112	216	80
	416	168	168	253	416	248	168	320	168	224	96
	240	120	152	204	344	296	152	328	152	192	144
Mean	262	147	176	266	353	231	189	375	173	219	153

Table 6 : t-Test Values

SM									
Compounds→	**1a**	**2a**	**3a**	**4**	**1b**	**2b**	**3b**	**1c**	**1d**
S.D	97.32	98.1	107.7	97.1	95.7	121.6	97.2	92.45	99.75
't' value	5.75	4.9	1.9	4.6	2.6	1.3	5.82	5.12	6
SR									
S.D	104.9	129.2	68.16	132.9	71.47	99.9	71.4	91.2	85.5
't' value	2	0.677	2.54	0.556	2.042	3.8	0.056	3	2.54

significant decrease in revertant frequency (Table 6) from the negative control, Standard Mutagen (456 ± 14.7). This shows that the foresaid compounds are highly antimutagenic. The data pretaining to antimutagenic activity of compounds 1a, 1b, 4 and 3b on Spontaneous Revertants turned to be non significant. The data showed a considerable decrease in the number of histidine^{+} revertant colonies when compared to the Standard Mutagen (456 ± 14.7).

The addition of compound 2b to Spontaneous Revertant resulted in the significant increase in the revertant frequency (456 ± 13.3) from (262 ± 9.7). This shows that compound 2b is mutagenic in nature.The addition of compound 2b to Standard Mutagen induced plate did not bring about any statistically significant reduction in the number of colonies, revealing that compound 2b is not antimutagenic.

The addition of compounds 2a and 3a to Spontaneous Revertant resulted in significant decrease in the revertant frequency. The addition of compounds 2a and 3a to Standard Mutagen induced plate did not bring about any statistically significant reduction in the number of colonies, revealing that compounds are not antimutagenic. The addition of compounds 1c and 1d to Spontaneous Revertant resulted in the significant increase in the revertant frequency. The addition of compounds 1c and 1d to Standard Mutagen induced plate was found to be statistically significant with reduction in the number of colonies, revealing that compounds are antimutagenic.The results were found to be statistically significant (P=0) (Table 6).

Conclusion

Microwave reactions of the compounds resulted in drastic reduction in the time of synthesis and improved yields. The microwave enhanced synthesis of 2,3-dihydro-4-methyl-thieno (2,3-b) quinolines the considerable increase (80-90%) in the yield. The addition of compounds 1a,1b,4 and 3b to Standard Mutagen (Daunomycin) induced plate resulted in significant decrease in revertant frequency from the negative control, Standard Mutagen indicating its high antimutagenicity. The addition of compounds 1c and 1d to Standard Mutagen induced plate was found to be statistically significant with reduction in the number of colonies, revealing that compounds are antimutagenic.The results were found to be statistically significant (P=0).

Acknowledgement

The authors thank the concerned authorities of the Avinashilingam University for Women, Coimbatore for providing facilities to carry out this work.

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