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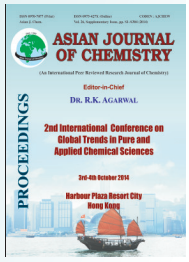

Synthesis of Novel 2,4-Disubstituted Bioactive Thiazoles

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A series of 2,4-disubstituted thiazoles was synthesized by iodine mediated method in good to excellent yield. All the novel compounds were evaluated for *in vitro* anti-mutagenic activity, revealing synergistic results. The structures of all new fabricated compounds were characterized by FTIR, UV and MS techniques.

Keywords: Thiazole, Iodine mediated, Synthesis, Anti-mutagenic activity.

INTRODUCTION

Recently in the scenario of drug design and synthesis, the urge to discover new motifs with synergistic effects has endorsed the researchers to explore new horizons of research in medicinal and synthetic chemistry. Therefore, an extensive variety of heterocyclic systems has been explored to develop novel bioactive moieties as chief molecule in the field of drug discovery[1]. Mutations caused by carcinogens not only led to cancer but may also provide grounds for pathogenesis of some chronic degenerative ailments involving hepatic disorders, diabetes, arthritis, chronic inflammation, cardiovascular disorders and in the process of aging[2]. To prevent the mutagenic disorders natural antimutagens, available in plants and human diet resources including flavonoids, coumarins, phenolics and also from eatable and the rapeutic plants are of particular significance since these might be beneficial to prevent from human cancer[3]. Studies on antimutagens from natural resources, to protect human beings from mutagenic disorders, is an interesting area of research[4]. While among synthetic compounds the thiazole ring is a useful structural motif in numerous pharmacologically active molecules[5]. This ring system is involved in the synthesis of diverse significant medications, essential to treat inflammatory[6], cancerous[7], bacterial[8] HIV infections[9] and hypertension[10]. Few of the thiazole derivatives are employed as fungicides, herbicides or as anthelmintic drugs[11]. Due to the pharmacological importance thiazoles and their derivatives have engrossed great interest and have been integrated into a wide range of therapeutically active drugs[12]. Up till now, the antimutagenic activity of thiazoles has not been reported. So owing to its privileged importance a variety of thiazoles have been afforded *via* Pd catalyzed methods[13], Cu mediated[14], I_2 promoted reactions[15] or metal free synthesis[16]. In present study we aimed to design and synthesize some novel, bioactive thiazoles and focused on their evaluation as antimutagenic activity.

EXPERIMENTAL

All the reagents and solvents used were of analytical grade and used as received without purification. The reaction was monitored by Merck silica gel plates visualized under U.V light at 254 and 365 nm. The FTIR spectra were obtained and recorded on MIDAC M 2000 spectrophotometer using KBr discs. The absorption spectra of all the compounds were recorded on HITACHI U-2800 spectrophotometer. Mass spectroscopic analysis was done and recorded at an ionizing voltage of 70 ev on SHIMADZU QP 2010 spectrophotometer.

Synthesis of 1*H*-indole-1-carbothioamide (3): The mixture of indole (1 mmol, 11.7 g), thiourea (1 mmol, 7.2 g) and sodium acetate (1 mmol, 8.2 g) were taken in ethanol and stirred for 3 h at 78 °C. The reaction was monitored by TLC. After reflux poured the reaction mixture on crushed ice that furnished off-white precipitates (81 % yield). Then collected the solid by filteration, dried and recrystallized from ethyl acetate; m.p. 98 °C, IR. 1646, 1149, 1104, 616, UV-visible 310 nm, M.S *m/z* 176 (M^+).

General procedure for preparation of thiazoles (5a-f): Compound **3** (1 mmol), ketone (**4a-f**) and I_2 (1 mmol) each in DMSO was refluxed. The reaction progress was monitored

by thin layer chromatography (10 % *n*-hexane:ethyl acetate), for 2.5- 4 h. After cooling the reaction mixture was poured on crushed ice, in it added liquid ammonia. The product was then extracted from ethyl acetate. The organic layer was washed with 5 % sodium thiosulphate solution to remove excess iodine. Drying over Na_2SO_4 tracked by filtration along with concentration under vacuum gave the final product which was recrystallized from ethanol.

Spectral data for synthesized compounds (5a-f)

1-(4-Phenyl-1,3-thiazol-2-yl)-1*H*-indole (5a): Light brown solid, m.p.: 230 °C IR (KBr, ν_{max}, cm^{-1}): 3218, 1630, 1564, 1444, 1391, 666, MS *m/z* 276 (M^+)

1-(4-Methyl-1,3-thiazol-2-yl)-1*H*-indole (5b): White solid, m.p.: 198 °C IR (KBr, ν_{max}, cm^{-1}): 3296, 1638, 1512, 1457, 1397, 750, MS *m/z* 214 (M^+)

1-[2-(1*H*-Indol-1-yl)-1,3-thiazol-4-yl]-2,3,4,9-tetrahydro-1*H*-carbazole (5c): Dark brown gummy solid, IR (KBr, ν_{max}, cm^{-1}): 3410, 1638, 1560, 1416, 1370, 640, MS *m/z* 369 (M^+)

1-[2-(1*H*-indol-1-yl)-1,3-thiazol-4-yl]-6,8-dinitro-2,3,4,9-tetrahydro-1*H*-carbazole (5d): Orange brown sticky product, IR (KBr, ν_{max}, cm^{-1}): 3400, 1637, 1580, 1438, 1108, 765, MS *m/z* 459 (M^+)

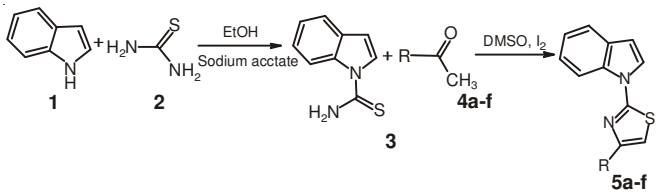
1-[2-(1*H*-indol-1-yl)-1,3-thiazol-4-yl]-6-nitro-2,3,4,9-tetrahydro-1*H*-carbazole (5e): Dark orange semi solid, IR (KBr, ν_{max}, cm^{-1}): 3395, 1633, 1556, 1401, 1365, 780, MS *m/z* 414 (M^+)

3-[2-(1*H*-indol-1-yl)-1,3-thiazol-4-yl]-2*H*-chromen-2-one (5f): Brown semi solid, IR (KBr, ν_{max}, cm^{-1}): 3420, 1708, 1631, 1433, 1108, 745, MS *m/z* 344 (M^+)

Antimutagenic assay: In order to screen all the synthesized thiazoles **5(a-f)** for their antimutagenic activity, potato disc antitumor assay was carried out. The method reported by Ferrigni *et al.*[17] was used with minor modifications. The wild type *Agrobacterium tumefaciens* (At 10) was inoculated to nutrient broth medium for 24 h at room temperature (28 °C) in shaking incubator at 100 rpm. The 1000 ppm stock solutions of the compounds **5(a-f)** were prepared in DMSO. Further dilutions were made to get final concentrations of 100 and 10 ppm from the stock solutions. The inocculum was prepared by centrifuging the *A. tumefaciens* culture, just to concentrate the cells in a minimum volume of nutrient broth. The cells were diluted in 1 mL of each three dilutions (1000, 100 and 10 ppm) of all six compounds **5(a-f)** in individual autoclaved eppendorf tubes. Fresh potatoes were surface sterilized by using diluted bleach solution and were washed with autoclaved distilled water. A cork borer was used to make cylinders of potato and 5 mm slices were made. These potato discs were placed on solidified nutrient agar plates (five discs per plate) and 40 µL of inoculums was poured over each disc of the respective concentration. The anticancerous drug vincristine (100 ppm) was used as a positive control while DMSO without any compound was used as a negative control. The plates were incubated at 28 °C for three weeks and the discs were stained with Lugol's solution *i.e.* 10 % KI and 5 % iodine in water and number of tumors were counted under dissecting microscope. In order to avoid the false positive results the antibacterial assay was peroformed with *A. tumefaciens*. The experiment was carried out in triplicate and the data obtained was statistically analysed by applying one way ANOVA on SPSS 17.0.

RESULTS AND DISCUSSION

The exciting biological profile of thiazole encouraged us to design thiazole moiety by establishing the synthesis of 2,4 disubstituted thiazoles from indolylthioamide (**3**) in good yield by refluxing (**1**) and (**2**) in ethanol where sodium acetate facilitated the reaction as the base (**Scheme-I**). To explore the conditions for 2,4-disubstituted thiazoles, compound **3** was treated with acetophenone as a model substrate in 2 propanol in the presence of iodine as a catalyst[18]. The corresponding thiazole **5a** was obtained in 60 % yield in 5 h. In order to increase the yield and reduce reaction time we attempted this reaction in two other solvents. In ethanol the reaction had not proceeded at all even after 24 h (Table-1). Replacing the solvent with DMSO proved better results with 78 % yield of **5a** in only 2.5 h reflux time (**Scheme-II**). With these established conditions in hand we synthesized iodine promoted series of 2,4-disubstituted thiazoles using various substituted ketones with moderate to good yields (Table-2).



Scheme-I

TABLE-1
REACTION TIME AND YIELD IN DIFFERENT SOLVENT

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	I_2	IPA	5	61
2	I_2	EtOH	24	0
3	I_2	DMSO	2.5	78

The per cent tumor inhibition by six compounds **5(a-f)** was calculated and all the compounds tested were found to be antimutagenic (Fig. 1). However maximum inhibition was shown by compounds **5a** and **5d** and a non-significant effect of concentration ($p > 0.05$) was obtained when one way ANOVA was applied to the results. While other compounds (**5b**, **5c**, **5e**

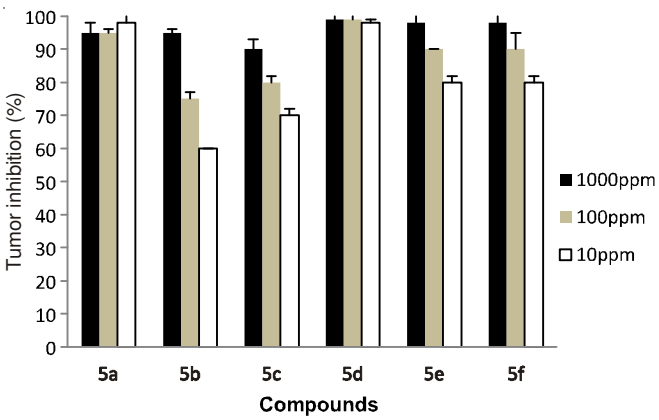
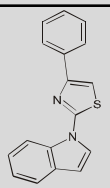
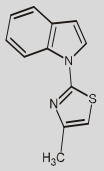
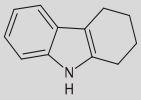
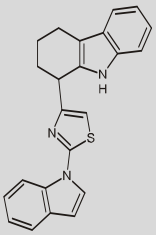
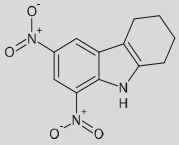
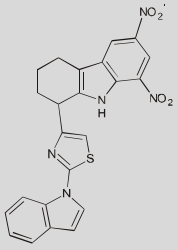
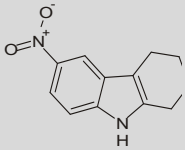
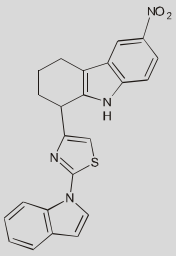
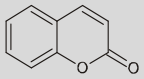
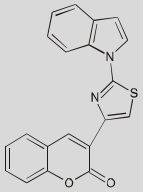


Fig. 1

TABLE-2
IODINE PROMOTED SYNTHESIS OF
2,4 DISUBSTITUTED THIAZOLES

Entry	R	Product	Time (h)	Yield (%)
5a			2.5	78
5b	CH_3		2.5	75
5c			3.0	78
5d			3.0	79
5e			3.0	75
5f			2.5	76

and **5f**) showed a concentration dependent inhibition and a significant effect of concentration was obtained ($p < 0.05$). The thaizole derivatives have been previously reported as potential anticancer agents when tested on human cancer cell lines[19,20]. In our work the activity of compound **5a** (having phenol as functional group) and **5d** (having dinitro tetra hydro carbazole) are found to have maximum tumor inhibition, the result is supported by the literature already published for both phenolic and carbazole moieties[21, 22].

No zone of inhibition was found when all the compounds were tested for their antibacterial activity against *A. tumefaciens*. It was concluded that the viability of the *A. tumefaciens* culture was not affected by the presence of synthetic compounds **5(a-f)**.

Conclusion

A novel I_2 mediated procedure for 2,4-disubstituted thiazoles **5(a-f)** was explored consisted in treating indolyl thioamide with different ketones in DMSO. Further these obtained 2,4-disubstituted thiazoles were subjected for antimutagenic activity of which **5a** and **5d** revealed excellent results.

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