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NEW ANTIOXIDANT DRUG DEVELOPMENT STUDIES ON NEUROHORMONE MELATONIN AND SYNTHETIC ANALOGUES

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Antioxidants scavenge and prevent the formation of free radicals so they are exceedingly important for the treatment and management of these kinds of diseases. Therefore, in recent years, there has been an increasing interest in finding new antioxidant compounds. Oxidant molecules can cause extensive damage to DNA, protein, and lipids. This is a major reason of aging and many degenerative diseases of aging such as cancer, cardiovascular disease, immune-system decline and brain dysfunction. Melatonin (*MLT*) synthesized mainly in the pineal gland, has a number of physiological functions. Main functions include regulating circadian rhythms, reimbursement of free radicals, help to improve immunity and generally inhibiting the oxidation of biomolecules directly or indirectly. With this study based on MLT, series of new indole imines were developed. Three parts of the MLT molecule were modified in order to find out better antioxidant behavior and structure activity relationship of the new indole analogue compounds. In this ongoing study, the synthesized new MLT analogues are indole hydrazide/hydrazones derivatives that have 5-bromo, 5-chloro and N-methyl substitutions. These studies showed that most of the compounds showed significant antioxidant activity at concentrations comparable with or much higher than that of MLT in the antioxidant experiments of ROS-induced DCFH-DA oxidation, lipid peroxidation and DPPH assay.

Keywords: Melatonin, Indole, Antioxidant activity.

Introduction

Overproduction of the free radicals can be responsible for tissue injuries that cause many health problems which include cancer, aging, heart diseases, neurological disorders, Alzheimer's disease, Huntington disease etc[1]. Melatonin (MLT), the main secretory product of the pineal gland is a well-known antioxidant and free radical scavenger. Synthesis of MLT-related compounds such as MLT metabolites and synthetic analogues are under investigation to determine which exhibit the highest activity with the lowest side effects[2,3].

Results and Discussion

Since the modifications on the MLT (**Fig 1**) molecule resulted in a set of compounds having different physical property and different substitution at the indole nucleus, it was hoped to have better SAR discussion in view of the effect of substituents with different electronic properties on the antioxidant activity.

5-chloroindole hydrazide/hydrazone derivatives were synthesized (**Scheme 1**) from 5-chloroindole-3-carboxaldehyde and phenyl hydrazine derivatives[1]. All the compounds characterized and in vitro antioxidant activity was investigated against MLT and BHT. Most of the compounds showed strong inhibitory effect on the superoxide radical scavenging assay at 1 mM concentration (79 to 95%). Almost all the tested compounds possessed strong scavenging activity against the DPPH radical scavenging activity with IC50 values (2 to 60 μM). Lastly, compound 1j revealed stronger inhibitory activity against MLT in the LP inhibitory assay at 0.1mM concentration (51%) while the rest of the compounds showed moderate inhibition.

With another study sixteen MLT analogue bromo indole hydrazide/hydrazone derivatives (**Scheme 2**) were synthesized and *in vitro* antioxidant activity was investigated[4]. All the tested compounds possessed strong scavenging activity against the DPPH radical scavenging activity with IC_{50} values (19.22-40.51μM). Compounds, that have anisic acid hydrazide **1k**, **1m** and izonicotinic acid hydrazide **1n** in the 3rd position of indole ring showed no free radical scavenging effect. Rest of the compounds showed very strong antioxidant activity (approximately 20 times higher) compare to MLT in DPPH assay. Almost all tested compounds revealed potent inhibitory activity against the LP inhibitory assay at 0.1mM concentration (74-91 %) , with the exception of **1l** and **1n** that showed 24 and 37 % inhibition at the same concentration. At a concentration of 0.05 mM almost all compounds exhibited 47-81 % inhibition, with the exception of **1k-1n.**

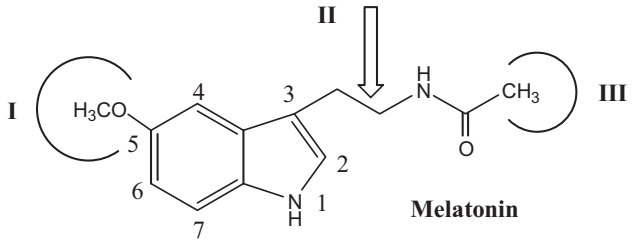
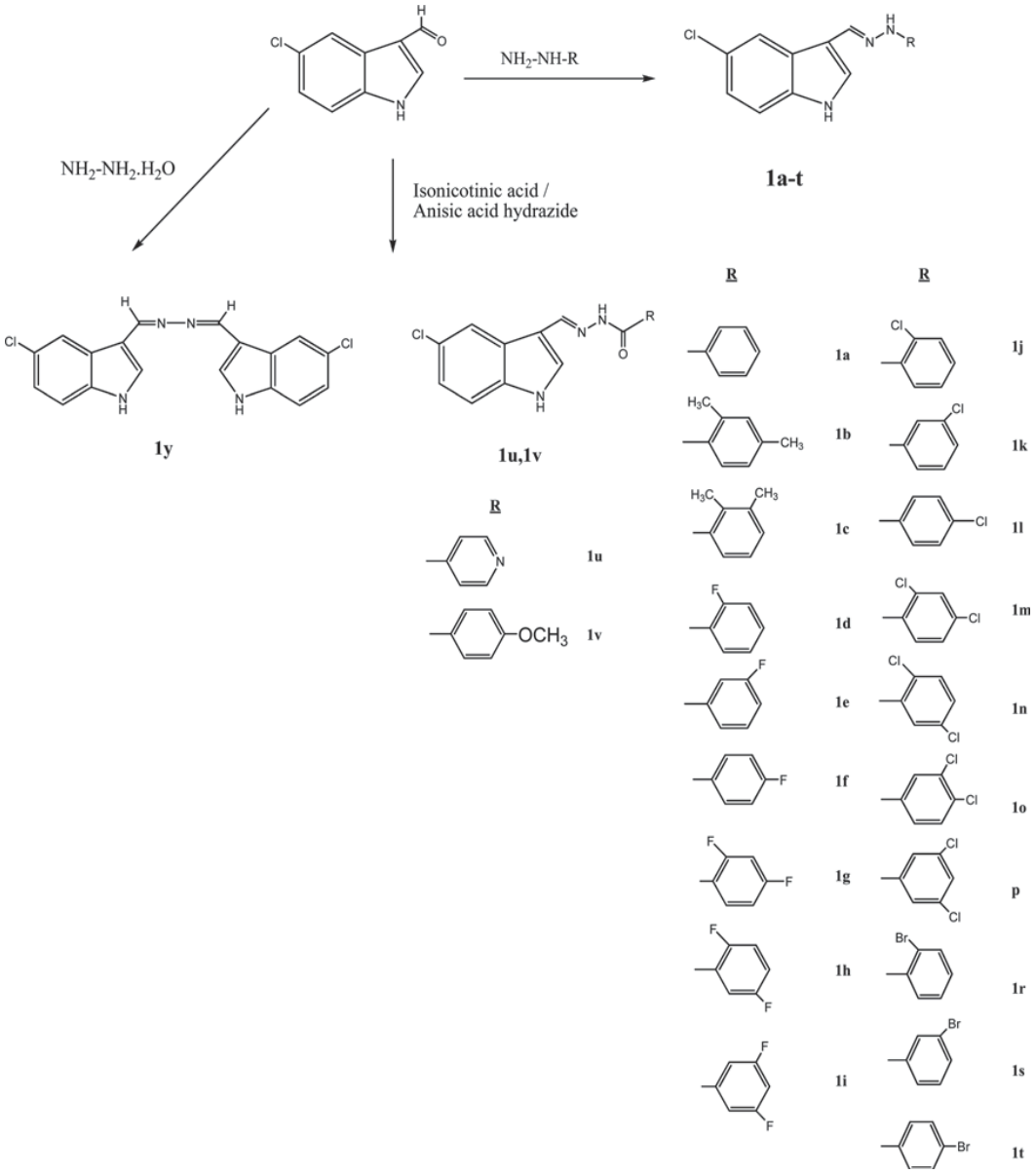


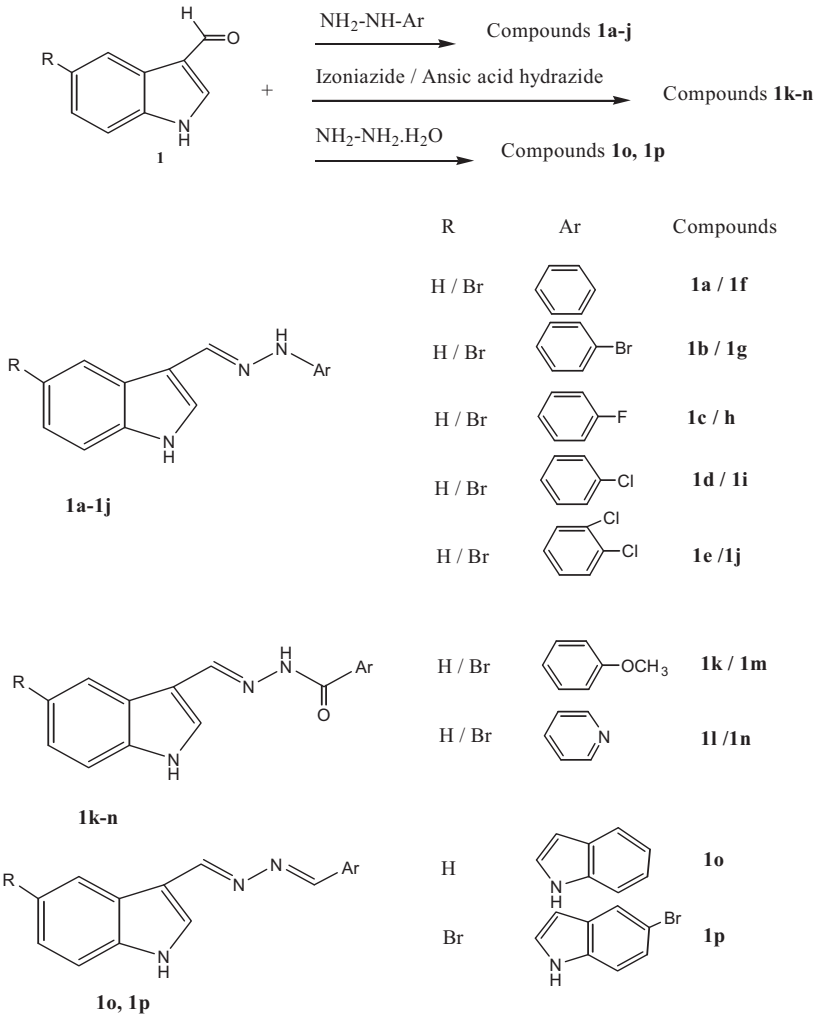
Figure 1. Modifications made on MLT molecule.



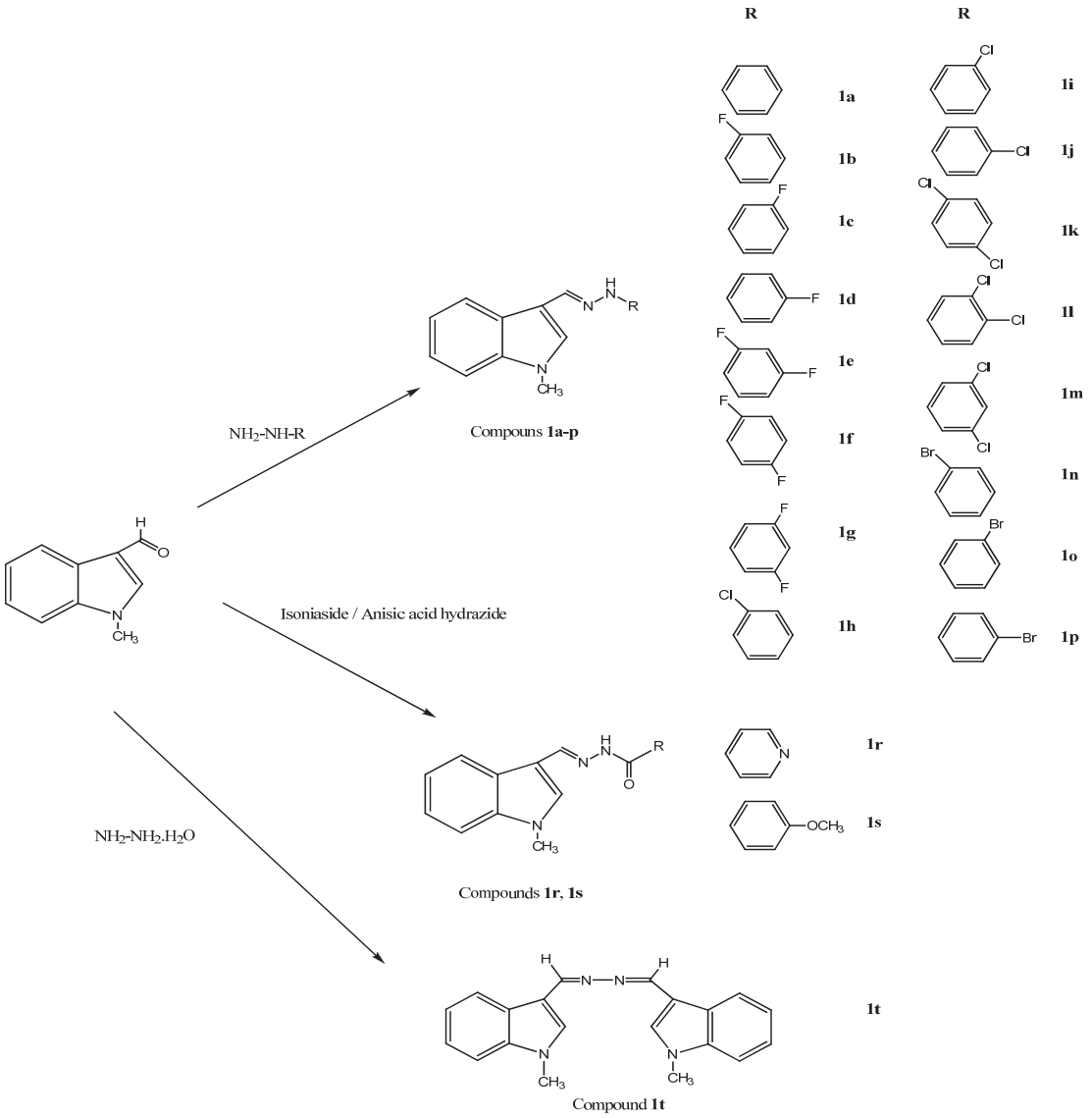
Scheme 1. 5-Chloroindole hydrazide/hydrazone derivatives[1]

As a part of our ongoing study nineteen indole hydrazide/hydrazone derivatives were synthesized[5] (Scheme 3), characterized and their in vitro antioxidant activity was investigated by three different assays: by evaluating their reducing effect against oxidation of a redox sensitive fluorescent probe, by examining their protective effect against H_2O_2-induced membrane lipid peroxidation and by determining their inhibitory effect on AAPH–induced hemolysis of human erythrocytes. In general all the synthesized indole derivatives were found to have potent antioxidant activity, even higher than MLT itself, according to the results of three *in vitro* antioxidant experiments. No significant antioxidant activity was observed in two compounds

isonicotinic (**1r**) and anisic acid (**1s**) hydrazides of indole 3-aldehydes and they have no halogen atoms in their structure that makes them different from the rest of the synthesized compounds. Structural investigation of the rest of the active compounds showed that having o- and m-halogenated aromatic side chain increase the antioxidant activity (such as compounds **1b**, **1c**, **1m**, **1k** and **1l**).



Scheme 2. 5-Bromoindole hydrazide/hydrazone derivatives[4]



Scheme 3. N-methylindole hydrazide/hydrazone derivatives[5]

Conclusions

In conclusion, majority of synthesized indole derivatives related to MLT showed significant antioxidant activity in three in vitro assays. In general, lack of methoxy group and introduction of Cl or Br in the 5-position did not effect the antioxidant capacity of the new indole derivatives infect the in vitro assays showed that many of the compounds were much more active than MLT itself. Introduction of hydrazide or hydrazone side chain containing aromatic halogenated ring increased the antioxidant activity of indoles comparing to MLT.

This may be due to increased stability of the indole ring and delocalization of the electrons to help to scavenge free radicals. For the antioxidant activity of melatonin analogue indole derivatives, not only the indole ring is important, but so is the side chain containing the amide group.

Acknowledgements

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