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ORIGINAL ARTICLE

Synthesis and reducing power assay of methyl semicarbazone derivatives

Manmohan Singhal [a,*], **Arindam Paul** [b], **Hemendra P. Singh** [c]

[a] *School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India*
[b] *G.D. Memorial College of Pharmacy, Jodhpur, Rajasthan, India*
[c] *B.N. College of Pharmacy, Udaipur, Rajasthan, India*

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Abstract In the present study we have designed a new pharmacophore 'Chalconesemicarbazone' by pharmacophore hybridization approach of drug design. A series of novel chalconesemicarbazones was synthesized and evaluated for their antioxidant activity by reducing power assay. Most of the compounds were found to be potent antioxidants. Free radicals play an important role in various pathological and xenotoxic effects so antioxidant may have protective role in these pathological conditions. Based on the results of reducing power assay 1-[1-(2,4-dihydroxyphenyl)-3-(2-hydroxyphenyl)allylidene]-4-(4-methylphenyl)semicarbazide (compound **18**) and 1-[1-(2,5-dihydroxyphenyl)-3-(6-hydroxyphenyl)allylidene]-4-(4-methylphenyl)semicarbazide (compound **21**) were the most active lead compounds. It was found that methoxy and hydroxyl substituted chalconesemicarbazones exhibited potent reducing power and unsubstituted compound showed less reducing potential.

1. Introduction

Free radical is an atom or molecule that bears an unpaired electron and is extremely reactive, capable of engaging in rapid change reaction that destabilize other molecules and generate many more free radicals. In plants and animals these free radicals are deactivated by antioxidants. These antioxidants act as an inhibitor of the process of oxidation, even at relatively small concentration and thus have diverse physiological role in the body. The body is constantly exposed to the negative and sometimes lethal effects of oxidants during normal physiological processes. The harmful free radicals such as hydroxyl, peroxyl and the superoxide anion are constantly being produced as a result of metabolic reactions in living systems. On a daily basis, up to 5% of inhaled oxygen may be converted to reactive oxygen species (ROS). These ROS have the ability to bind to cellular structures, and have been implicated in a number of pathological processes such as aging, inflammation, re-oxygenation of ischemic tissues, atherosclerosis, cancer and even Parkinson's disease in men (Setiadi et al., 2003). Two

* Corresponding author. Tel.: +91 9829153193.
E-mail address: manu.research2@gmail.com (M. Singhal).

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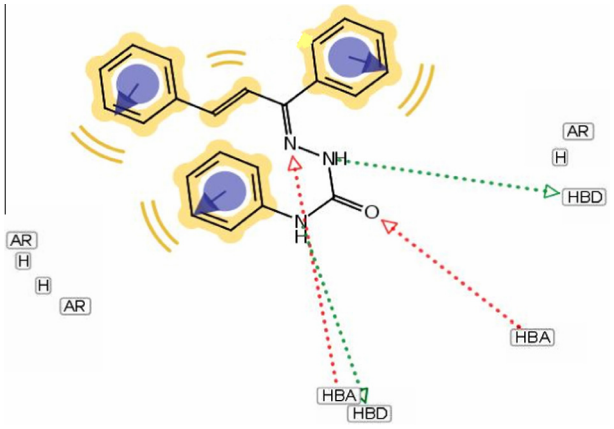

Figure 1 Pharmacophore of the designed chalconesemicarbaz-one.

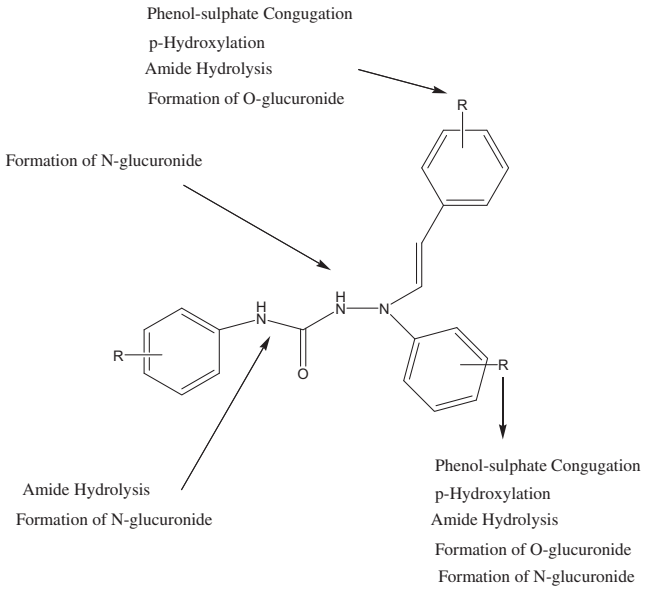

Figure 2 In Silico metabolism of the chalconesemicarbazone.

processes, which produce free radicals in vivo, have been identified and named the Fenton reaction and the Haber–Weiss reaction.

Antioxidants play an important role in animal health. Conventional antioxidants have been shown to improve animal performance during conditions characterized by increased tissue oxidant levels such as stress, injury and infections (Nickels, 2003). The semicarbazone is an electron withdrawing group and exhibited antioxidant activity. Favorable substitution may increase their free radical scavenging effect (Dutta et al., 2005).

In the present study we have used pharmacophore hybridization technique of drug design and designed a pharmacophore model 'chalconesemicarbazone', which is having hydrogen acceptor site, hydrogen donor site, lipophilic site etc. (Fig. 1), which may help in binding with receptors and plays an important role in pharmacological activities. On these observations, we have designed a synthetic scheme to synthesize this pharmacophore, and also synthesize some lead compounds. We have also done the pharmacological screening as antioxidant activity by reducing power assay. No exact mechanism study were done on molecular level but further studies were in process in our lab for searching the exact mechanism of action of these compounds, which may support the showing activities of the synthesized compounds.

In-Silico metabolism prediction of the synthesized compounds is given in Fig. 2. The major pathway of metabolism was found to be p-hydroxylation and amide hydrolysis however in some compounds glucuronide and sulfate conjugation may also occur.

2. Materials and methods

2.1. Chemistry

Chalconesemicarbazones were synthesized according to synthetic scheme as shown in Fig. 3. Melting points were measured in open capillary tubes on a Buchi 530 melting point apparatus and were uncorrected. Infrared (IR) and proton nuclear magnetic resonance (1H NMR) spectra were recorded for the compounds on Jasco IR Report 100 (KBr) and Brucker Advance (300 MHz) instruments, respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. All exchangeable protons were confirmed by addition of D_2O. Mass spectra were measured with a Shimadzu GC–MS–QP5000 spectrophotometer. Only molecular ions (M+) and base peaks are given. Elemental analysis (C, H and N) were undertaken with a Perkin-Elmer model 240C analyzer, and all analyses were consistent with theoretical values (within 0.4%) unless indicated. The homogeneity of the compounds was monitored by ascending thin-layer chromatography (TLC) on silica gel G (Merck) coated aluminum plates, visualized by iodine vapor.

2.1.1. Synthesis of substituted chalcone derivatives

Substituted benzaldehydes (0.012 mol) were added to a mixture of substituted acetophenones (0.01 mol) in 25 ml of ethanol in a 200 ml beaker. The content of the beaker was mixed well and to that 10 ml of 10% potassium hydroxide solution was added and stirred vigorously at 25 °C until the mixture was so thick that stirring was no longer effective (3–4 h).

After the completion of the stirring, the reaction mixture was kept in a refrigerator overnight. The reaction mixture was then diluted with ice-cold water (50 ml), acidified with 10% aqueous hydrochloric acid to precipitate the chalcones. The product was filtered with suction on a Buchner funnel, washed with cold water until the washings were neutral to litmus and then washed with 10 ml of ice-cold rectified spirit. The dried product was recrystallized from chloroform. The physicochemical properties of the synthesized chalcone derivatives are given in Table 1.

*2.1.2. Synthesis of methyl phenyl urea (**2**)*

Substituted aniline (0.1 mol) was dissolved in 20 ml of glacial acetic acid and 10 ml of water. To this, 0.1 mol of sodium cyanate (6.5 g) in 80 ml of warm water was added with continuous stirring. The reaction mixture was allowed to stand for 30 min and then cooled in ice. The crude solid, thus obtained was filtered, dried and recrystallized with boiling water to yield methyl phenyl urea.