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Design, synthesis, molecular docking and biological evaluation of new dithiocarbamates substituted benzimidazole and chalcones as possible chemotherapeutic agents

Keerthana Bacharaju [a], Swathi Reddy Jambula [a], Sreekanth Sivan [b], Saritha JyostnaTangeda [a], Vijjulatha Manga [b,*]

[a] Sarojini Naidu Vanitha Pharmacy Maha Vidyalaya, Osmania University, Hyderabad 500001, Andhra Pradesh, India
[b] Molecular Modeling and Medicinal Chemistry Group, Department of Chemistry, Nizam College, Osmania University, Hyderabad 500001, Andhra Pradesh, India

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ABSTRACT

A series of novel dithiocarbamates with benzimidazole and chalcone scaffold have been designed synthesised and evaluated for their antimitotic activity. Compounds **4c** and **9d** display the most promising antimitotic activity with IC_{50} of 1.66 μM and 1.52 μM respectively.

Benzimidazoles are one of the most extensively studied classes of heterocyclic compounds known for their wide range of biological activities.[1,2] Extensive studies have been carried out on benzimidazoles and their chemotherapeutic activity.[3,4] On the other side, dithiocarbamates are a common class of organic molecules, that form mono and bidentate coordination with transition metals. Transition metal complexes of dithiocarbamate present a wide range of biological activities[5] and are recently applied in the treatment of cancer.[6,7] Since brassinin (Fig. 1), a phytoalexin first isolated from cabbage had cancer preventive activity, structural modification on this compound led to the synthesis of isobrassinin (Fig. 1)[8] and a series of dithiocarbamates, some of these were found to have antitumor activity.[9]

Beside the compounds mentioned above chalcones are the biogenetic precursors of all known flavonoids and isoflavanoids and are abundant in edible plants.[10] They exhibit a broad spectrum of pharmacological activities such as anticancer,[11] antiinflammatary,[12] antimalarial,[13] antifungal,[14] antilipidemic,[15] antiviral,[16] antileshmanial,[17] antiulcer[18] and antioxidant activities.[19] Recently Yong Qian and coworkers reported a series of chalcone derivatives (Fig. 1), with dithiocarbamate moieties which possessed potential antiproliferative and anti-tubulin properties.[20] Microtubules are among the most important molecular targets for cancer chemotherapeutic agents. These small molecules bind to the tubulin, interfering with the polymerisation or depolymerisation of microtubules and there by inducing cell cycle arrest, resulting in cell death or apoptosis.

Although many new chalcone derivatives have been synthesized as potential antitumor agents, there is very scarce recent literature data on antitumor potentials of dithiocarbamate-substituted chalcones. This combination should provide favourable structural properties of both dithiocarbamate and chalcone moieties.

It improves their binding affinities with the protein via hydrogen bonding, hydrophobic contact and to further explore their chemotherapeutic properties. New molecules were designed in which indole moiety, is isosterically replaced with benzimidazole. A series of novel derivatives containing both benzimidazole nucleus and dithiocarbamate as side chain possessing different substituents on nitrogen linked through methylene group at second position of benzimidazole were synthesized.

Route applied for the synthesis of a various dithiocarbamate analogues is summarized in Schemes 1 and 2. Key intermediate 2-chloromethylbenzimidazole (**2**) (Scheme 1) was prepared by the addition of chloroaceticacid to *o*-phenylenediamine in 4 N hydrochloric acid as reported earlier.[21] Dithiocarbamates were synthesized from various amines and carbon disulfide, using dimethylformamide as solvent and anhydrous potassium phosphate as base, followed by treatment with 2-chloromethylbenzimidazoles.[22] Chalconedithiocarbamates were obtained by

* Corresponding author. Tel.: +91 040 23234321; fax: +91 040 23240806.
E-mail address: vijjulathamanga@gmail.com (V. Manga).

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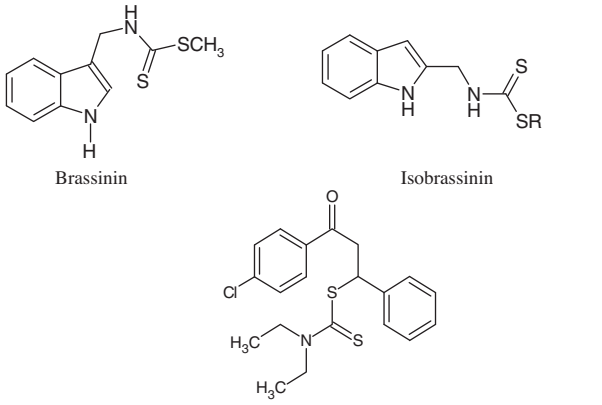


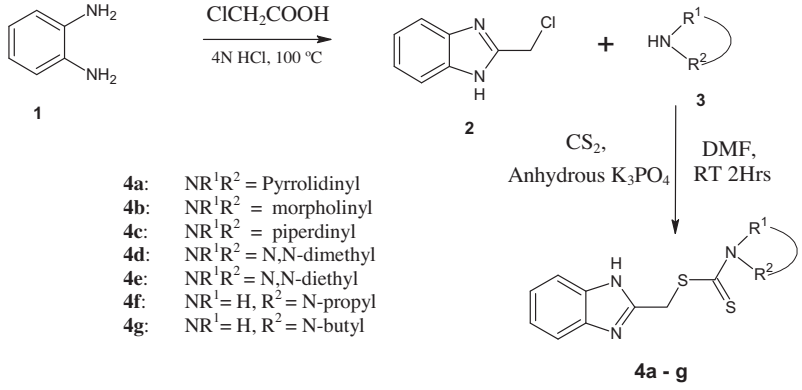
Figure 1. Structure of known chalcone derivatives.

one pot reaction of various amines, carbondisulfide and intermediate chalcone[23] (Scheme 2).

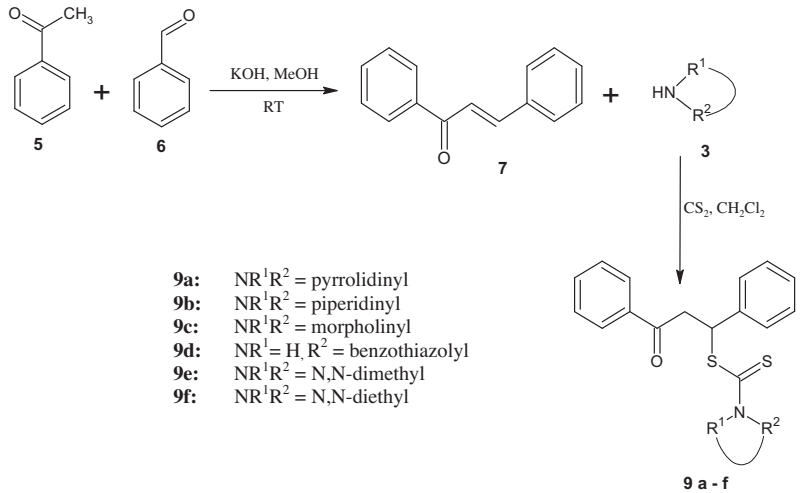
Synthesized compounds were evaluated for their biological activity using chick pea seeds (Cicer arietinum)[24] for their potential antimitotic activity, it is a rapid and inexpensive cytotoxicity test for the preliminary screening of new drugs.[25,26] Synthesized compounds were found to inhibit the growth of the germinating roots from the seeds. Inhibitory activity values (IC_{50}) are listed in Table 1. Among the series compound **4c** (piperidine) showed highest potency with IC_{50} of 1.66 μM. Compounds **4a** (pyrrolidine) and **4b** (morpholine) were found to be equipotent with IC_{50} 1.8 μM and 1.89 μM respectively. In case of the compounds with alkyl substituted aminodithiocarbamates, compound with diethyl (**4e**) substitution showed greater potency than the corresponding dimethyl amine (**4d**) with IC_{50} values 1.86 and 2.12 μM respectively. However compound **4f** and **4g** with propyl amine and butyl amine exhibited similar activity like **4d** as evidenced from the IC_{50} values 2.29 and 2.11 μM respectively. Overall results indicate that the cyclic amines have higher activity when compared to aliphatic amines.

Antimitotic activity of **9a–9f** series, compound **9d** (2-amino benzothiazole side chain) showed highest potency of 1.52 μM. Compound **9a** (pyrrolidine) and **9c** (morpholine) were equipotent with IC_{50} 1.67 and 1.65 μM respectively. On the contrary compound **9b** (piperidine) showed slight decrease in potency (1.85 μM). In case of the compounds with dialkyl amine side chain the compound **9f** (diethyl amine) showed greater potency than the corresponding compound **9e** (dimethyl amine) with IC_{50} 1.84 μM and 2.43 μM, respectively.

In order to gain more insight into the interaction between these new series of dithiocarbamate derivatives and β-tubulin that is involved in assembly of microtubules. Crystal structure of β-tubulin of bovine (pdb id: 1SA0) was download from the protein data bank (Since the plant β-tubulin experimental structure is not available and it has 94% sequence similarity with bovine). GLIDE 5.6 was



Scheme 1. Synthetic route to the benzimidazole dithiocarbamates (**4a–4g**).



Scheme 2. Synthetic route to the chalcone dithiocarbamates (**9a–9f**).