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Role of Organic Dithiocarbamates in Drug Discovery Research

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Editorial

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Organic dithiocarbamates are the stable class of compounds derived from the unstable dithiocarbamic acid (NH_2CSSH) having S-CS-NH- linkage [1,2], which holds unique applications in the field of pharmaceuticals, agrochemicals (pesticides, herbicides, insecticides, fungicides, etc.), intermediates in organic synthesis, in the forms of drugs and prodrugs, for the protection of amino groups in peptide chemistry, as a useful synthons, as linkers in combinatorial chemistry and also have interesting medicinal and biological properties [3]. In recent years, several reports have indicated that by incorporating dithiocarbamate linkage in between the active pharmacophores of various structurally diverse molecules increases manifold biological activities of semisynthetic/synthetic natural/synthetic molecules and proved to be a boon against various disease such as anti-cancer, anti-bacterial, anti-fungal, anti-malarial, anti-viral, anti-HIV, anti-estrogenic, anti-progestational, anti-osteoporosis, antinflammatory, anti-filarial, anti-tubercular, anti-diabetic, anti-obesity, anti-convulsant, anti-helminthes, anti-alzheimer, CNS and CVS active etc. [4,5]. Keeping in view the importance of dithiocarbamates, our group has been working since more than a decade upon the synthesis and evaluations of these compounds [6-8].

In recent years, several workers from the different part of the world have incorporated dithiocarbamates in between the active pharmacophores of structurally diverse natural products and realized that dithiocarbamates play a crucial role in increasing the biological activity of these molecules. We have found that several derivatives of natural/synthetic dithiocarbamates have emerged as potent anticancer drugs and prodrugs [9]. In the present letter, we will focus some of the potential molecules in which by incorporating dithiocarbamate linkage may led to increase manifold biological activity.

Butenolide 1 are lactones bearing chemical moieties derived from large number of natural products like seeds of the tropical plant *Annona muricata* [10] are known to be associated with large number biological activities like anticancer, bactericides, fungicides etc. [11]. A new family of butenolide containing dithiocarbamate was synthesized and tested for their *in-vitro* anti-tumor activity. Among them compound 2 (EC-9706=34.26 ± 1.4 μM, MCF 7=31.93 ± 1.3 μM) bearing benzylamine at C-3 position with dithiocarbamate side chain was found to be more potent than standard drug flourocil (EC-9706=20.30 ± 1.3 μM, MCF 7=7.54 ± 0.7 μM) **(Figure 1)** [12].

Classical antifolates such as compound 3 containing a benzylamine moiety in the dithiocarbamate side chain was found active against human myelogenous leukaemia K_{562} with IC_{50} value of 4.0 μM [13]. Depending upon these results a series of 4-(3H)-quinazolinone derivatives were prepared to enhance the anti-tumor activity of classical antifolates and study structure activity relationship. These compounds were screened using the colorimetric MTT assay to test *in-vitro* cytotoxicity against A-549 (human non-small cell lung cancer), HCT-8 (human colon cancer), and Bel-7402 (human liver cancer) cell lines. Compound 4 (A549=81.8 μM, HCT8=88.6 μM, Bel-7402=86.6 μM) obtained by replacing phenyl in compound 3 by 3-pyridinyl showed comparable cytotoxicity to 3 (A549=81.7 μM, HCT8=89.4 μM, Bel-7402=88.0 μM) but higher than the standard drug 5-fluorouracil (A549=76.7 μM, HCT8=76.3 μM, Bel-7402=84.4 μM) **(Figure 2)** [14].

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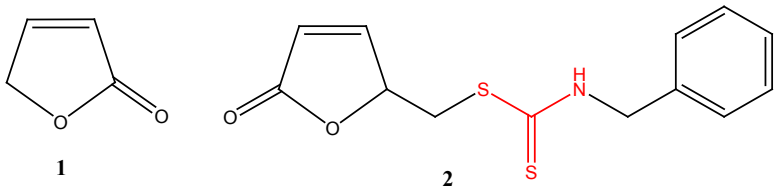

Figure 1. Butenolide 1 and its dithiocarbamates derivative 2.

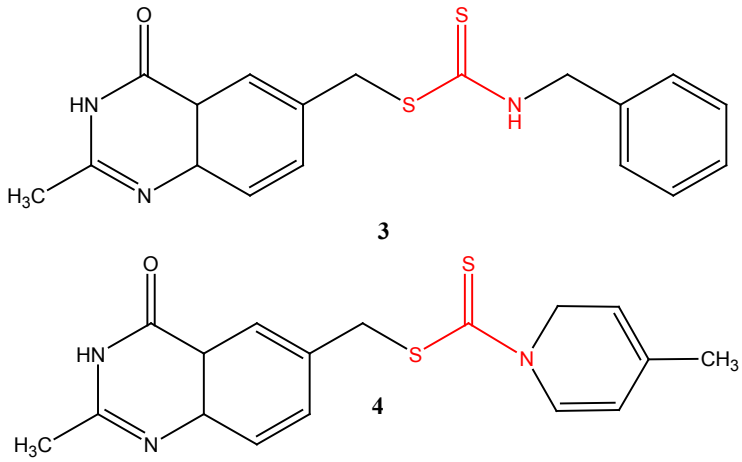

Figure 2. Anticancer dithiocarbamate drrivatives 3 and 4.

Pyrrolo [2,1-c] [1,4] benzodiazepines (PBD) are potent naturally occurring antitumor antibiotic derived from *streptomyces* species, possess a unique DNA interaction with the formation of a covalent aminal bond between the C11-position of the central B-ring and N2-amino group of a guanine base [15]. A new series of PBD bearing dithiocarbamate at C-8 position was synthesized and evaluated for cytotoxicity against selected cancer cell lines displaying melanoma, leukemia, CNS, ovarian, breast and renal cancer phenotypes. Among them compound 5 has shown promising cytotoxic potency (GI_{50}) against leukemia (MOLT-4=0.63 μM, RPMI-2286=0.79 μM, SR=0.99 μM), colon cancer (HCT 116=0.36 μM), CNS cancer (SF 268=0.53 μM), melanoma (LOX IMVI=0.86 μM, M14=0.90 μM), ovarian cancer (IGROV1=0.47 μM, OVCAR3=0.83 μM), renal cancer (786-0=0.23 μM, ACHN=0.81 μM), Breast cancer (MCF7/NCI=0.54 μM) and prostate cancer (DU 145=0.82) **(Figure 3)** [16].

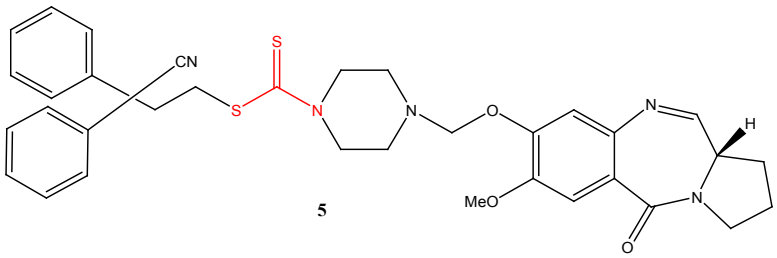

Figure 3. Anticancer dithiocarbamates of pyrrolo-[2,1-c] [1,4]-benzodiazepines 5.

A novel dual dithiocarbamates compound 6 exhibited potent anticancer activity when tested against selected cancer lines with high inhibitory rates (H460=92.3%, HepG 2=42.9%, BCG 823=87.8%, Hela=88.2%, HCT116=88.7%, MDA-MB-231=88.8% and HL-60=95.8%) at 10 μM *in-vitro*. Considering the high activity of compound 6, it was selected as the lead for the further modification by replacing methyl group by various benzene, pyridine, thiazole, coumarin, benzo(p)thiophene and quinoline ring. Among all, compound 7 (Hep G2=54 nM, MCF7=23 nM) possessing quinoline ring proved to be drug like scaffold showing more potency than the lead compound 6 **(Figure 4)** [17].

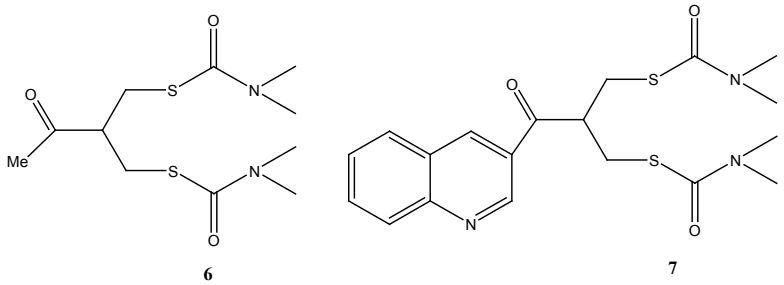

Figure 4. Anticancer dithiocarbamate drrivatives 6 and 7.

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