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Therapeutic Potencies of Dithiocarbamates – A Review

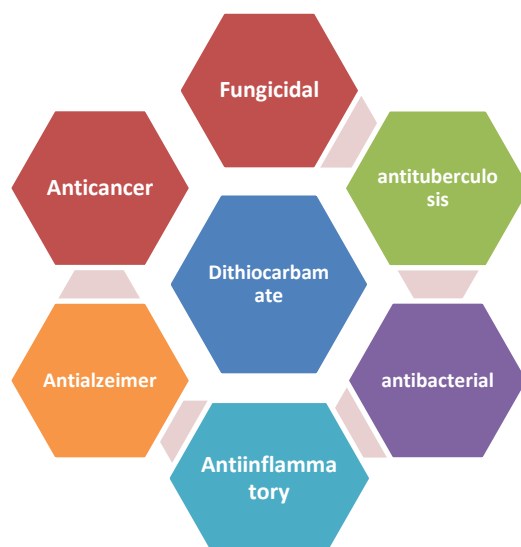
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ABSTRACT: Dithiocarbamate is a novel compound which has numerous applications and due to which it has more demand in pharmaceutical Industry. They were vastly utilized as hardening agents in rubber industry before discovering their potential therapeutic properties. The Pharmaceutical applications are increased due to its high efficient binding property to metal and high reactivity with thiols. Because of its enormous pharmacological scope, DTCs has been an evolving subject of interest for many researchers around the world. In this review article we focus on advancement in new discoveries of dithiocarbamates derivatives (DTCs), which shows potential biological activities.

Graphical Abstract



KEYWORDS: Dithiocarbamate, Thiols, Fungicides, Apoptosis and Anticancer.

I. INTRODUCTION

Pharmaceutical industry is a big ocean with discoveries of new novel drugs which have significant applications. It is a need of an hour to discover the drugs which are less toxic, have minimal side effects and more potential activity. Cancer is one such disease where treatment of which causes huge side effects to the body. Chemotherapy is complicated procedure which leaves severe side effects on patient, so researchers are working to get the drugs which are less harmful and more bioactive on malignancy. Dithiocarbamate is getting popular as potential anticancer drug because, DTCs exhibited enormous pharmacological activities. As DTCs can form complex with metal and are very

reactive towards thiols, they possess several applications in the field of pharmaceuticals, agrochemicals, as intermediates in chemical synthesis, as an amino protecting group in peptide chemistry [1-2].

DTCs journey was as interesting as their applications, in spite of having pharmaceutical properties they used as hardening agents in rubber industry in early 1880's. In 1943, researchers discovered first DTC derivative, nabam (a) [3], as fungicide for agricultural use. Zineb (b) [4] was the first DTC to be coupled with a metal. Disulfiram (DSF) (c) is first used as anti-alcoholic drug which later showed significant effects on cancer and is used as potent anticancer drug [5]. The popular DTC derivative, diethyldithiocarbamate (DDC) (d) is the active metabolite of DSF, (Bala et al., 2014) [6]. Strong nucleophilic and redox properties of dithiocarbamate is because of sulfur present in it, and that's why it has accumulated more significance among medicinal chemists. mainly, this element presents in natural product called brassinin (e) [7] which have anti-tumour activity. There are marketed drugs like sulbentine (f), epalrestat (g), and sulforamate (h), which have various biological activities that hold dithiocarbamate as potential pharmacophore. [8-10].

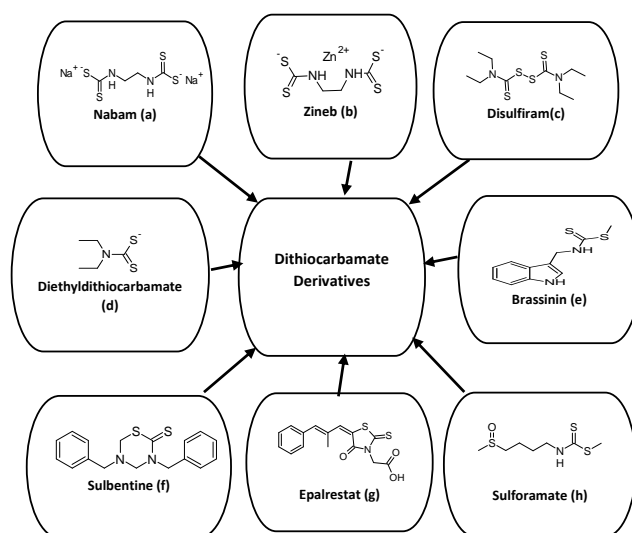


Figure 1. Examples of some DTC derivatives with their structures.

II. METHODOLOGY AND DISCUSSION

Anti-cancer agents

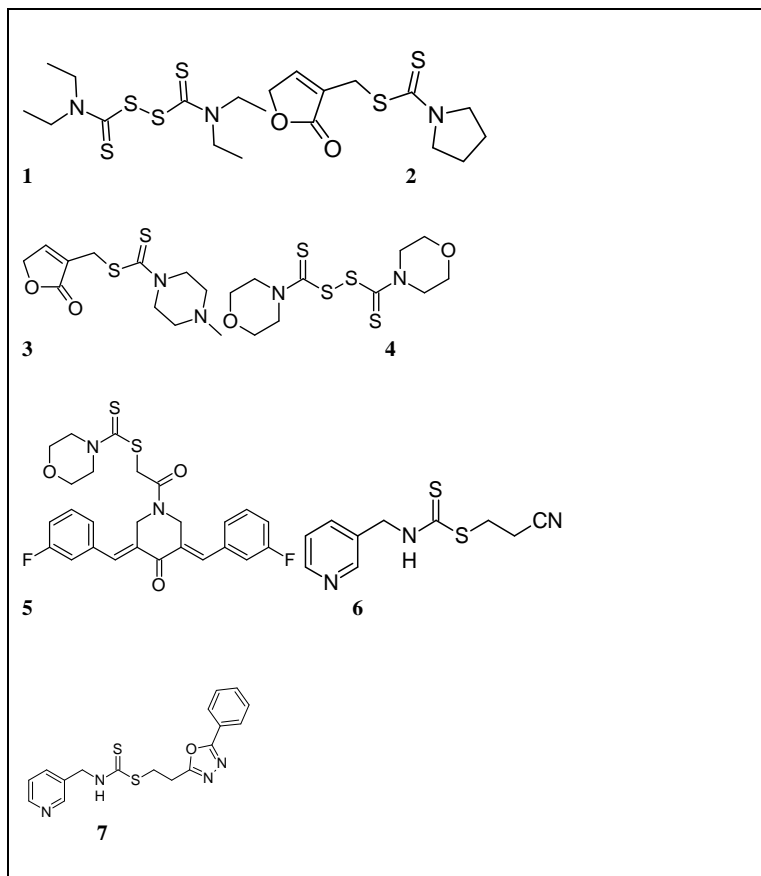


Figure 2. structures of Some anticancer agents.

As per report published by the World Health Organization (WHO), in 2018, one in six deaths was caused by cancer worldwide. Cancer is a disease which shows abnormal and uncontrolled growth in body cells. Chemotherapy is one of the treatments for cancer but it shows toxic side effects and limited therapeutic activity due to the development of drug resistances in a huge number of patients [11]. Therefore, Cancer is a subject of interest in researchers and vast research is going on to discover anticancer drugs that are less toxic and more therapeutically active.

Disulfiram (DSF) (1) was first given to alcoholic patient as anti-alcoholic drug but it completely cured metastatic breast cancer in 1977 [12-13]. According to clinicaltrials.gov, due to DSFS anti-cancer properties they have seen DSF as the subject of 21 clinical trials with the focus on metastatic breast, prostate, and pancreatic cancer, glioblastoma, and melanoma. In these trials, DSF was trialed alone, with copper (Cu_{2+}) salts or as subsidiary to standard chemotherapy. Yang et al. (2019) reviewed these clinical trials involving treatment with DSF against cancer. Previously, the outcome of a phase IIb clinical trial indicated that combining DSF with cisplatin and vinorelbine delayed progression-free and overall survival of patients diagnosed with phase IV non-small cell lung cancer [14]. Depending on these results, the National Cancer Institute in Slovakia initiated a phase II study, rating the effectiveness of DSF-Cu with vinorelbine and cisplatin for the treatment of metastatic breast cancer. The enrolment of DSF-Cu was hypothesized to increase the objective response rate in patients with refractory metastatic breast cancer by withdrawing drug resistance in cancer cells and by inhibiting cancer stem cells through inactivation of aldehyde dehydrogenase (ALDH) [14].

Butenolides are pervasive chemical moieties found in several natural products and have been associated with numerous biological activities [15]. Furthermore, Wang et al., revealed a new family of butenolides-containing dithiocarbamates with their in vitro cytotoxic activity. SAR-analysis revealed that the inclusion of dithiocarbamate side chain at C-3 position of butenolide notably improved anti-cancer activity. Particularly, dithiocarbamates with pyrrolidine (2) and

piperazine (**3**) as a secondary amine exhibited selective and remarkable cytotoxicity on HeLa cancer cell line, with an IC_{50} of 2.63 ± 0.2 and $0.77 \pm 0.3 \mu\text{M}$, respectively [16].

Sun et al., described JX06 (**4**) as a selective covalent inhibitor of PDK1. A dose dependent inhibitory study showed that, JX06 hindered PDK1, PDK2 and PDK3, with an IC_{50} of $0.049 \pm 0.003 \mu\text{M}$, $0.101 \pm 0.028 \mu\text{M}$ and $0.313 \pm 0.006 \mu\text{M}$, respectively. According to SAR analysis structural features such as disulfide bond, thioamides and N-methyl substituents were basis for activity. Alteration of disulfide bond showed complete loss of activity. Inclusion of amide/ketones instead of thioamides also reduced the activity. However, keeping one thioamide was enough to show PDK1 inhibition. In contrast, changing the N-substitutions with other alkyl groups resulted in minimal change in the potency of the inhibitor signifying flexible binding pocket [17].

Curcumin, a yellow tincture present in the dried rhizome of herb *Curcuma longa* L family Zingiberaceae. is widely used for multiple pharmacological activities. In spite of displaying notable biological and safety profile approval of curcumin as a therapeutic agent is hindered due to poor bioavailability. Anthwal et al., invented a cyclic curcumin analogue with 5 carbon enone spacer and dithiocarbamate linker. later, in vitro cytotoxicity screening of these hybrids on chronic myeloid leukemia (KBM5) cell line displayed most active compound (**5**) with $87.43 \pm 0.73\%$ growth inhibition. Besides, Compared to Curcumin all other synthesized hybrids suppressed the TNF- α -mediated NF- κ B activation at $5 \mu\text{M}$ on KBM5 cells. The authors also exhibited theoretical physico-chemical properties of the dithiocarbamate derivatives by applying Molinspiration computational tool. Several parameters, such as logP and total polar surface area (TPSA) were calculated to show the pharmacokinetic properties. All the reported hybrids showed logP value <5 and TPSA <140 suggesting outstanding bioactivity [18-20].

Li et al., reported a new series of heteroaryl methyl carbamodithioates derived from the lead compound (**6**) and rated for their in vitro anticancer activity. 1,3,4- Oxadiazole derivative (**7**) strong activity on SK-BR-3 cancer cell with IC_{50} value of $0.58 \mu\text{M}$. Apoptosis and cell cycle arrest via disordering of spindle assembly in mitotic advancement are basis of anticancer activity. SAR study revealed that alteration of pyridine heterocycle in first part of structure was ideal for anti-cancer activity; while second part of structure, 5-phenyl 1,3,4-oxadiazole was most powerful. Nature of substitution on phenyl ring of 1,3,4-oxadiazole moiety has critical influence on cytotoxicity. Cytotoxic activity against Bel-7402 boosted by Inclusion of methoxy, trifluoromethyl, chloro substitutions at para-position. Furthermore, adding of heteroaromatic ring instead of phenyl ring with heterocycles increased the activity against Bel-7402 and MDA-MB-468 cells. [21-22].

Antifungal agents

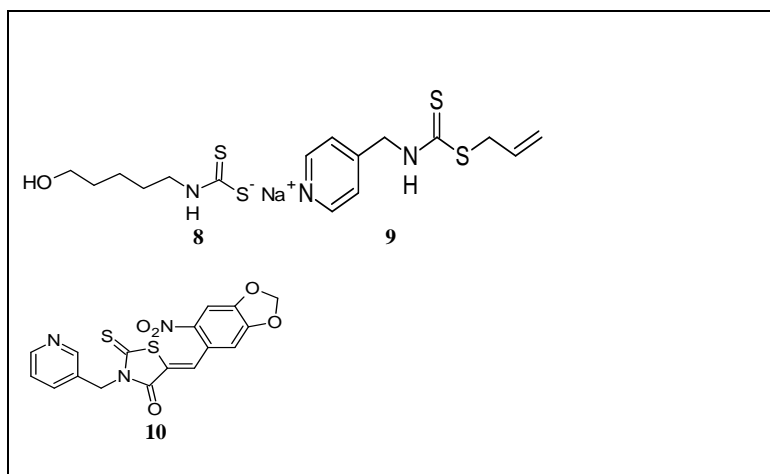


Figure 3. Antifungal agents.

Who doesn't like healthy and shiny hairs? but maintaining hairs is a big task. Dandruff is one of the common and serious issue worldwide, which occurs in more than 50% of the population. There are various reasons for dandruff, but it mainly occurs by fungi from the genus *Malassezia*. Vullo et al., reveal use of dithiocarbamates as β -class carbonic anhydrase inhibitor (CAs, EC 4.2.1.1) from the fungal parasite *Malassezia globosa*, MgCA. Compound (**8**) is effective with K_i value of 66.5 ± 3.7 , 17.3 ± 1.0 and 383 ± 12 against hCA I, hCA II and MgCA respectively which was better with contrast to the standard sulfonamide (K_i of $74 \mu\text{M}$) [23].

Chauhan et al., reported antifungal agents (**9**) and (**10**) containing pyridine and rhodanine moiety which show MIC value of 1.56 and 0.75 $\mu\text{g/mL}$ against *Candida albicans* MTCC183, respectively. Furthermore, these compounds are potentially active against *Sporothrixschenckii* with MIC value of 0.39 and 1.56 $\mu\text{g/mL}$. As per Docking study, these active compounds targeted lanosterol 14a-demethylase (CYP-51). According to the SAR study of these compounds' substitution on sulphur of dithiocarbamate was responsible for their activity. S-allyl group exerted potent antifungal action when compared to the -ethyl, -propyl and -butyl substitutions. In case of rhodanine, substitutions of electron withdrawing groups on arylidine ring displayed high potency showed in fig.3 [24].

Anti- Alzheimer agents

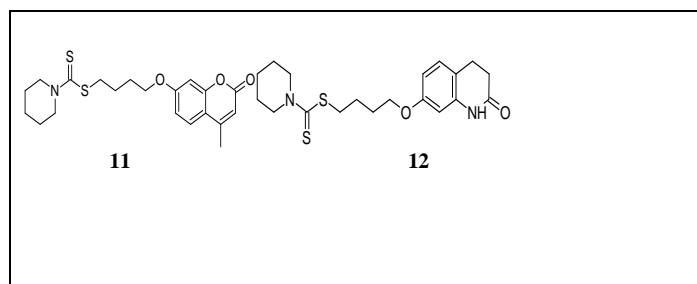


Figure 4. Anti-Alzheimer agents.

Alzheimer's disease is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. Her symptoms included memory loss, language problems, and unpredictable behavior. After she died, he examined her brain and found many abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary, or tau, tangles).

This neurodegenerative disorder is a global health problem. It occurs mainly due to deficiency in acetylcholine (ACh) and deposition of β -amyloid peptide ($A\beta$). Improving ACh level is the appropriate treatment for AD. Xie et al., reported coumarin-dithiocarbamate hybrid (**11**) as selective AChE inhibitor with an IC_{50} value of 0.027 μM for hAChE. It also inhibited $A\beta$ aggregation (40.19% at 25 mM). It also spontaneously interacted with catalytic active site (CAS) and peripheral anionic site (PAS) of AChE, and inhibit their activity. Anti-alzheimer drugs can efficiently cross blood brain barrier (BBB). The parallel artificial membrane permeation assay (PAMPA) was performed to measure permeability wherein, compound (**11**) showed a P_i value of 9.21×10^{-6} cm/s, indicating capability to cross BBB [25].

Compound (**12**) displayed significant eeAChE and hAChE inhibitory activity with IC_{50} of 0.22 and 0.16 μM , respectively. Derivative 12 with quinolinone ring effectively subdued AChE-induced $A\beta$ aggregation (29.02% at 100 μM) and self-induced $A\beta$ aggregation (30.67% at 25 μM). strangely, unsubstituted piperidine produced better AChE inhibition. Substitution with methyl or iso-propyl group resulted significant potent activity. However, adding of another piperidine to C-4 position enhanced BuChE inhibition [26].

Antibacterial agent

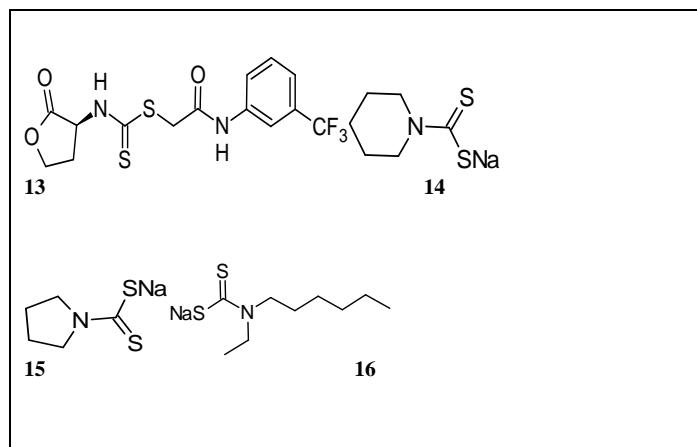


Figure 5. Antibacterial agents.

Ren et al., synthesized N-acyl-homoserine lactones (AHL) derivatives which are biologically active against Gram-positive bacteria. Especially, the most potentially active compound (**13**) which can inhibit *Bacillus subtilis* ($MIC_{50} = 1.443 \mu\text{g/ml}$). According to SAR study compounds with N-phenyl amide side chain were more active than those with hydrophobic alkyl chains. Substituting electron-releasing group ($-\text{CH}_3$) by electron-withdrawing functionalities like $-\text{CF}_3$ and $-\text{NO}_2$ at meta-position was beneficial for enhancing activity [27].

Wang et al., synthesized dithiocarbamate derivatives which show antibacterial activity and tested against several MBL in combination with MEM. Compounds (**14**) and (**15**) intensify the efficacy of MEM up to 2560 folds against blaIMP containing strains with MIC of $< 0.03125 \mu\text{g/mL}$. Whereas, compound **16** exerted enhanced activity against strains holding blaIMP-4 genes than those blaNDM-1 genes with MIC of $0.5 \mu\text{g/mL}$. Furthermore, these compounds were non-hemolytic and showed safe toxicity-profile for the normal human cells [28].

III. EXPERIMENTAL RESULT

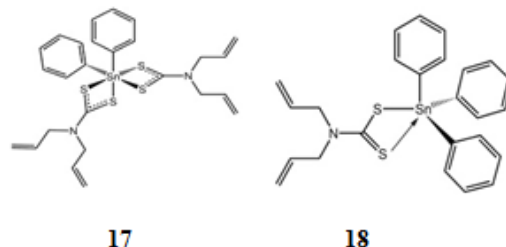
Table 1. Clinical trials of dithiocarbamates derivatives against cancer, viruses (from 2019 onwards), DSF= Disulfiram, DDC=Diethyldithiocarbamate

Date	Disease	Study	Compound	Status	NCT	Sponsor
2019/10-2021/07	Metastatic pancreatic cancer	Phase II	DSF-Cu	Recruiting	NCT03714555	HonorHealth Research Institute, United States
2019/05-2022/12	Germ cell tumors	Phase II	DSF	Recruiting	NCT03950830	National Cancer Institute, Slovakia
2020/01-2023/01	Metastatic breast cancer	Phase II	DSF-Cu	Recruiting	NCT04265274	National Cancer Institute, Slovakia
2020/12-2025/12	Multiple myeloma	Phase I	DSF-Cu	Not yet recruiting	NCT04521335	University of Utah, United States
2020/09-2021/09	COVID-19	Phase II	DSF	Not yet recruiting	NCT04485130	University of California, United States
2020/04-2023/04	Multiple myeloma	Observational	DDC-Zn	Recruiting	NCT04234022	The Royal Wolverhampton Hospitals NHS Trust, United Kingdom

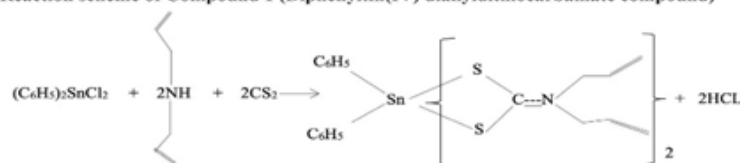
CURRENT STATUS ON NEW DISCOVERY OF DITHIOCARBAMATE DERIVATIVES

Diphenyltin(IV) diallyldithiocarbamate compound and triphenyltin(IV) diallyldithiocarbamate compound are two newly synthesised compounds of organotin(IV) with diallyldithiocarbamate ligands.

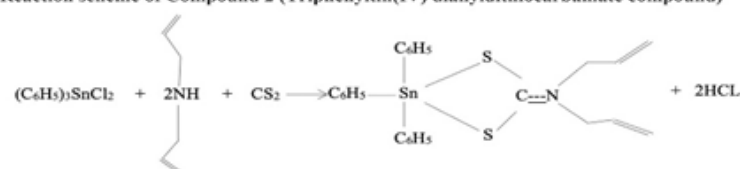
The cytotoxicity IC_{50} values for compounds **17** (diphenyltin(V) diallyldithiocarbamate) and **18** (triphenyltin(IV) diallyldithiocarbamate) evaluated. Both compounds showed potent cytotoxicity towards HT-29 cells. the IC_{50} value for compound **17** is $2.36 \mu\text{M}$, while the IC_{50} for compound **18** is lower than compound **17**, i.e., $0.39 \mu\text{M}$. Based on the IC_{50} value, compound **18** has higher toxicity compared to compound **17**. This showed that the HT-29 cells had higher sensitivity towards compound **18** compared to compound **17**. Compound **18** exhibits high cytotoxicity towards CCD-18Co cells, with an IC_{50} value of $3.52 \mu\text{M}$ upon 24 h of treatment. Meanwhile, the percentage of cell death modes between 60% and 75% for compound **17** and compound **18** were mainly due to apoptosis, suggesting that both compounds induced growth arrest [29].



Reaction scheme of Compound 1 (Diphenyltin(IV) diallyldithiocarbamate compound)



Reaction scheme of Compound 2 (Triphenyltin(IV) diallyldithiocarbamate compound)



IV.CONCLUSION

In conclusion, this review throws light on dithiocarbamate and its derivatives which exerted several biological activities. Dithiocarbamate with metal complex and thiols can show potent activity. Dithiocarbamates displayed diverse therapeutic profile such as anticancer, antifungal, antitubercular, antibacterial etc, yet in-depth study of their pharmacokinetic and toxicological characteristic is needed to be done. Moreover, DSF and DDC are currently being investigated in multiple clinical trials for applications in cancer, infectious diseases. Two new novel derivatives of dithiocarbamates, Diphenyltin(IV) diallyldithiocarbamate compound and triphenyltin(IV) diallyldithiocarbamate compound are synthesised by organotin(IV) with diallyldithiocarbamate ligands which showed significant anticancer activity. This piece of information can help to discover new novel dithiocarbamates derivatives for various diseases in further research.

V.CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

VI.ACKNOWLEDGEMENT

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