American Journal of Organic Chemistry 2019, 9(1): 1-8
DOI: 10.5923/j.ajoc.20190901.01

Synthesis, Reactions and Biological Importance of α, β-Unsaturated Carbodithioate Esters: A Review

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Abstract Carbodithioate esters are important functional organosulfur compounds widely used in different fields such as pharmaceuticals, agrochemicals and material sciences. *α, β*-unsaturated dithioesters, carbodithioates are the type of organosulfur chemical compounds that attract the special interest of organic chemists. *α, β*-unsaturated dithioester type compounds have various applications in medicinal chemistry and provided numerous potent *α, β*-unsaturated dithioester derivatives for different therapeutic targets. *α, β*-unsaturated dithioesters are widely used as solvents, polymers, and biopharmaceutical agents. For the treatment of tuberculosis, leprosy and dermatitis herpetiformis diseases, several drug molecules containing *α, β*-unsaturated dithioester groups are used. Based on these applications, researchers have engaged in the preparation and study of many types of *α, β*-unsaturated dithioester derivatives for their medicinal activities e.g. biological, antimalarial, antimicrobial, anti-inflammatory, anticancer, anti-HIV, and anti-inflammatory properties. The present article provides a targeted review of recent synthetic strategies, pertinent reactions and applications of *α, β*-unsaturated dithioester type compounds to facilitate future research efforts so that the medicinal and industrial applications of this important class of compounds continue to be beneficial to society.

Keywords *α, β*-unsaturated carbodithioates, Synthesis, Anticancer activity, Biological importance, Medicinal chemistry

1. Introduction

Carbon-sulfur bond formation is a fundamental approach to introduce sulfur into organic compounds. Carbon-sulfur bond formation has received considerable attention due to the prominence of the C-S bond in various molecules that are of biological, pharmaceutical and material interest [1].

α, β-unsaturated thioesters have attracted much attention as active esters for the syntheses of different compounds. Synthetic methods for *α, β*-unsaturated dithioesters have received considerable interest in view of their increased reactivity, compared to their carboxylic analogues, as potential dienes or dienophiles in hetero Diels–Alder cycloadditions [2]. Moreover, the cycloaddition products, thiochromenes, are potential precursors of a wide range of thioheterocycles with interesting biological properties. There are very few general methods available for the synthesis of *α, β*-unsaturated dithioesters and those known are mostly specific to certain substrate classes. The methods available in the literature include (i) alkylation of thiolate anions obtained by the addition of vinyl cuprates to carbon disulfide [3], (ii) isomerization of *α, β*-unsaturated dithioesters [4], (iii) base catalyzed elimination of *β*-hydroxy dithioesters [5], and (iv) Wittig–Horner, Peterson or Mukaiyama type condensation reactions of aldehydes and ketones [6]. Hartke *et al.* have also shown that *α, β*-unsaturated amides can be transformed into the corresponding dithioesters by a sequence of reactions involving thionation, alkylation and sulfhydrolysis [7]. Although dithioesters have been known for many years [8], it is only recently that *α, β*-unsaturated dithioesters have attracted attention. We were interested in that *α, β*-unsaturated dithioesters as potential heterodienes or in cycloaddition reactions [9].

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Published online at http://journal.sapub.org/ajoc

2. Synthesis and Reactions

In 1978, the preparation of the β-hydroxydithioester **1** was described [10] involving the treatment of ethyl dithioacetate with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) followed by isobutyraldehyde at - 78°C. It is recently that *α, β*-unsaturated dithioesters have attracted attention. Preparative approaches to these compounds **2** which have been investigated include: *(a)* reaction of a vinyl cuprate with carbon disulphide followed by methyl iodide [11]; this

is successful for compounds **(2a-c),** but attempts to make the dithioester **(2d)** in this way gave its dimer; ***(b)*** sulphydrolysis at -75°C of the immonium salt derived by S-methylation of the thioamide gave the phenyl derivative **(2e)** [12] which dimerized above -30°C; (c) base-catalysed isomerisation of β,γ-unsaturated dithioesters [13], in turn prepared from N-phenyliminothioesters, gave **(2a)** and, at -40°C, **(2f)** which dimerized at room temperature; and flash pyrolysis of the bridged anthracene and trapping of the product in a matrix at -196°C gave the parent dithioacrylate **(2g).** K. R. Lawson *et al.* were interested in *α, β*-unsaturated dithioesters as potential heterodienes or heterodienophiles in cycloaddition reactions [14], and they describe their preparation from *β*-hydroxydithioesters and some cycloadditions in which they are involved. Subsequent to the completion of their work it was reported that addition of Grignard reagents to *β*-ketodithioesters gave 3,3-disubstituted *β*-hydroxydithioesters, and the latter were dehydrated to 3,3-disubstituted *α, β*-unsaturated dithioesters on treatment with toluene-*p*-sulphonic acid in benzene at reflux [15].

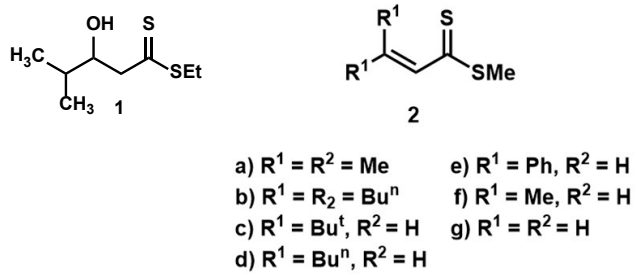
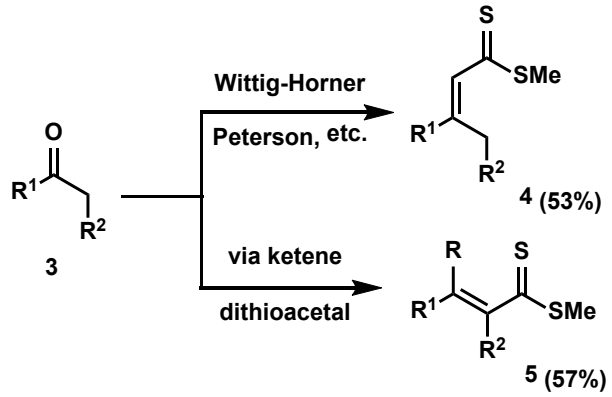


Figure 1. *β*-hydroxydithioester and *α, β*-unsaturated dithioesters

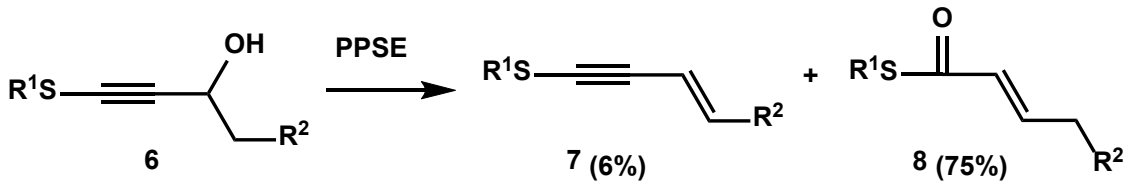
In most of the known methods [6] of preparation of a *α, β*-unsaturated dithioesters starting from carbonyl compound **3**, the dithioester functionality is introduced along with the *α*-methylene group to form **4**. The present method provides an opportunity to introduce dithioester functionality at the *α*-position of the carbonyl group of the starting ketone to afford **5** (Scheme 1).



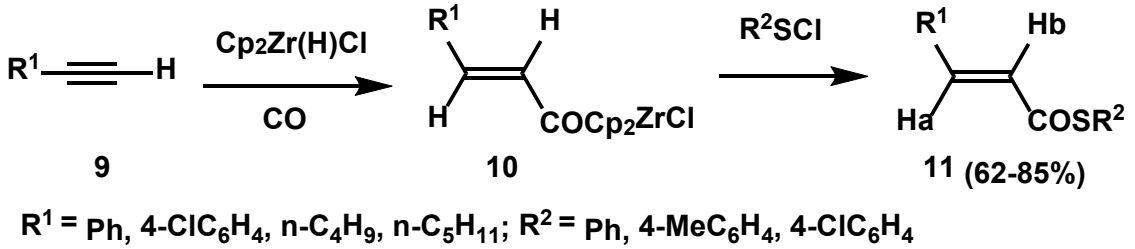
Scheme 1. Synthesis of *α, β*-unsaturated dithioesters through Wittig-Horner method and via ketene dithiacetal process

There are many ways to synthesize *α, β*-unsaturated thioesters and dithioesters. The treatment of y-chalcogen-substituted propargyl alcohols with polyphosphoric acid trimethylsilyl ester (PPSE) gave *α, β*-unsaturated thioesters via the Meyer-Schuster type rearrangement [16] instead of y-chalcogen-substituted enynes (Scheme 2). γ-Sulfur-substituted propargyl alcohols **6** reacted with PPSE **7** to give the *α, β*-unsaturated thioesters **8** in good yields. However, the reactions also gave the enyne sulfides [17].

Coupling reactions of acylzirconocene chlorides with organic halides afforded the corresponding ketones [18]. Considering the high electrophilicity of arylsulfenyl chlorides, P. Zhong and his coworkers [19] attempted to react them with the *α, β*-unsaturated acylzirconocene chlorides **10.** Experimental results show that, $Cp_2Zr(H)Cl$ [20] adds to terminal alkynes **9** in CH_2C1_2 at room temperature stereospecifically with high regioselectivity to yield vinylic Zr^{IV} complex, which was stirred under CO atmosphere to give the *α, β*-unsaturated acylzirconocene chlorides the adducts **10. 10** react with arylsulfenyl chlorides [21] rapidly at O°C to afford *α, β*-unsaturated thioesters **11** with good to excellent yields (Scheme 3).



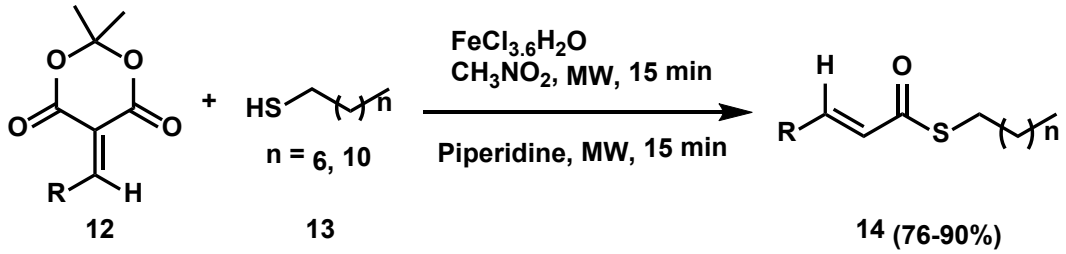
Scheme 2. Meyer-Schuster rearrangement of γ-sulfur-substituted propargyl alcohols to synthesis of *α, β*-unsaturated thioesters in 1995



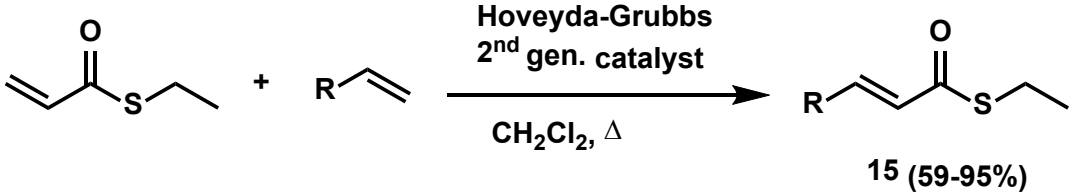
Scheme 3. A stereoselective synthetic route to (E)-*α, β*-unsaturated thioesters

Interestingly, *α, β*-unsaturated thioesters have marked reactivity as Michael acceptors and they are proved to be excellent substrates in the synthesis of several natural products [22]. Although, it is a very useful intermediate, traditional syntheses of thioesters are encountered with the occasional difficulties such as 1,4-addition of thiolate and subsequent separation from the main product [23]. Olefin cross-metathesis has been elegantly explored to construct *α, β*-unsaturated thioesters using thioacrylate [24]. Encouraged by the success of synthesis of *α, β*-unsaturated esters, A.R. Mohite *et al* [25]. planned to extend the protocol for the straightforward synthesis of *α, β*-unsaturated thioesters using the optimized reaction conditions for esters. To compare the reactivity and to extend the application, thiols **13** (1 eq.) were treated with few benzylidene derivative of MA **12** under optimized reaction conditions (Scheme 4). The corresponding *α, β*-unsaturated thioesters **14** were obtained in good to excellent yields (76–90%) in just 30 min (Scheme 4).

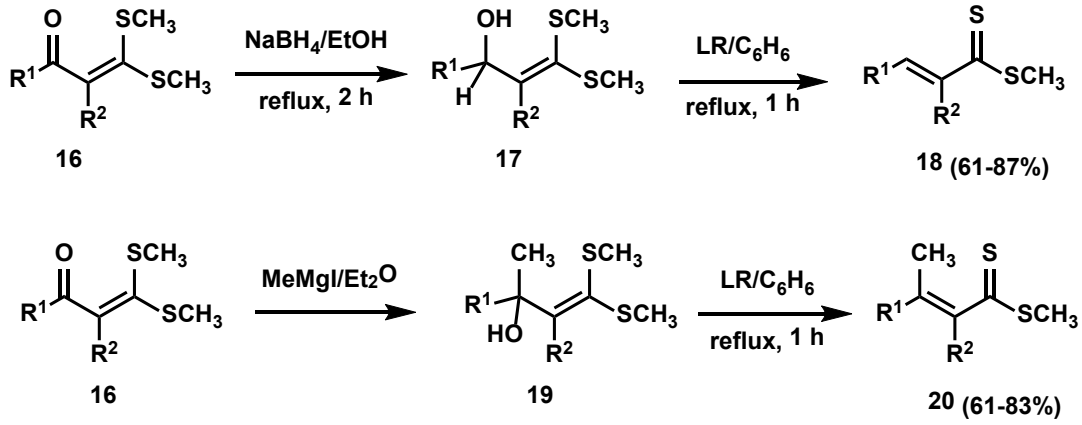
Thioesters are highly relevant compounds due to their distinctive chemical properties: the reduced electron delocalization provides for enhanced reactivity compared to oxoesters [26]. The importance of thioesters in the cell is well established: biological systems use their relative reactivity in many enzymatic reactions by employing, for example, acetyl coenzyme A, cysteine proteases, or polyketide and fatty acid synthases [27]. Their enhanced reactivity compared to that of oxoesters has been employed successfully in a wide range of synthetic organic transformations, some inspired directly by related biosynthetic pathways. Stereoselective aldol reactions often depend on the distinctive reactivity of thioesters [28] and their synthetic versatility is further illustrated by many other well-known transformations including *α*-alkylations, [29] selective reductions [29, 30], and Pd-catalyzed coupling reactions [31] among others [32]. Considering these importance, A. W. van Zijl and his coworkers [33] found a mild and scalable new route to *S*-ethyl thioacrylate **15** (Scheme 5). The feasibility of the use of this olefin in cross-metathesis reactions with the Hoveyda-Grubbs second generation catalyst is demonstrated. The high functional group tolerance of the reaction allows the preparation of a broad range of versatile functionalized *α, β*-unsaturated thioesters.



Scheme 4. One-pot direct synthesis of *α, β*-unsaturated thioesters

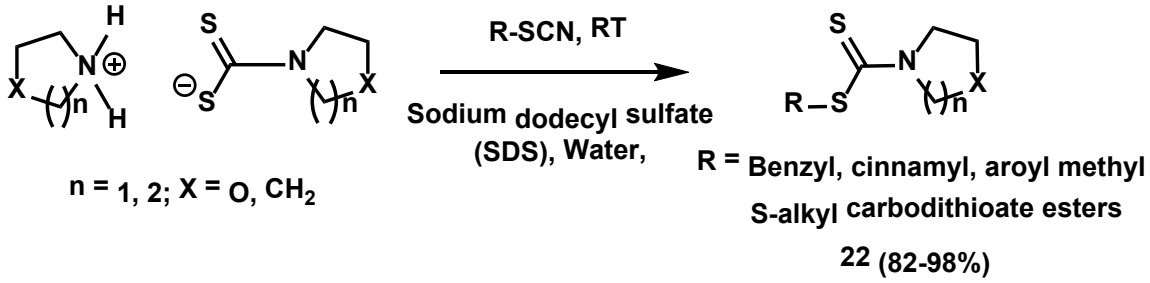


Scheme 5. Cross-metathesis reaction of *S*-ethyl thioacrylate with a variety of olefins to give substituted *α, β*-unsaturated thioesters



Scheme 6. Synthesis of *α, β*-unsaturated dithioesters from the reactions of *α*-hydroxyketene dithioacetals with Lawesson's reagent

Scheme 7. Synthesis of functionalized O, S-dialkyldithiocarbonates



Scheme 8. Synthesis of carbodithioate esters from organyl thiocyanates

S. K. Nair and his coworkers have developed a facile two-step process for the conversion of a *α*-oxoketene dithioacetals to *α, β*-unsaturated dithioesters, which are valuable intermediates in organic synthesis and the method described here provides a valuable alternative to the previous methods for the synthesis of these compounds. The *α*-hydroxyketene dithioacetals **17** and **19**, obtained from *α*-oxoketene dithioacetals **16** by 1,2-reduction or 1,2-addition of carbon nucleophiles, on treatment with Lawesson's reagent afforded *α, β*-unsaturated dithioesters **18** and **20** in good yields (Scheme 6) [34].

O, S-dialkyldithiocarbonates are a class of organo-sulfur compounds which are frequently used as versatile source of radicals [35] and useful intermediates in the synthesis of thiols [36], thiocarbonates [37] alkenes [38], alkanes [39], α, β-unsaturated esters through S-activated carbanions [40] and as photosensitizer [41] of vinyl monomers. Besides, these are used as vulcanization accelerators [42] and in the syntheses of ionic liquids [43]. These are also used to prepare S-containing natural products [44] and find use in Claisen rearrangements leading to interesting derivatives [45].

Normally these (*viz*. dithiocarbonates) are prepared from a three-step process from alcohol, alkyl halide and CS_2 using a strong base [46]. Recently efficient one-pot processes of their preparation have been reported using basic resin (Amberlite IRA) [47] or Trion B [48]. But in those communications only a non-functional alkyl group was used for alkylation of the sulfur center, and the syntheses are stepwise processes.

Multicomponent reactions (MCRs) [49] involve combination of three or more starting materials in a single operation and are gaining popularity in the synthesis of complex compounds due to their high atom economy [50], synthetic convergence and reduced effort in preparation and workup [51]. The early MCRs were mostly discovered by chance or serendipity. But rational design strategies for these reactions are currently being devised [52]. G. C. Patra *et al.* [53] has developed an easy and effective preparation of dithiocarbonates **21** in which the S-alkyl part is functionalized with an ester or nitrile group employing a three-component single step procedure (Scheme 7).

An efficient and practical method for the preparation of carbodithioate esters **22** from organyl thiocyanates reported by Biswas, K. *et al.* through the reaction with cyclic amine-based dithiocarbamic acid salts in water [54] (Scheme 8). This type of protocol is found to be applicable in general to various thiocyanates such as benzyl or aroyl methyl or cinnamyl and so on. Some other notable features that there are no by-products such as disulfides, metal- and alkali-free, aqueous conditions, and finally easy and near-quantitative formation of cyclic amine-based dithiocarbamic acid salt which acts as a stable alternative reagent.

3. Biological Importance of *α, β*-Unsaturated Carbodithioate Esters

There is a malignant disease named acute myelogenous leukemia (AML) which is characterized by an aberrant accumulation of immature myeloid haematopoietic cells [55]. This AML is the most common form of acute leukemia in adults and constitutes approximately 80% of cases [56]. Though the treatments of AML significantly improved the rate of remission, still more than 50% relapse with to a resistant form of the disease. So still there is challenge for this AML chemotherapy [57]. Another group of leukemic cells, (Leukemia stem cells (LSCs)) have shown self-renewal ability as well as the capability to produce heterogeneous leukemia cell populations [58, 59]. It has been considered to play significant role in the initiation and relapse of acute leukemia [60]. LSCs are also considered to be an effective strategy for the treatment and possible cure of AML [61-640]. Also, LSCs are refractory to clinical used chemotherapy drugs, such as nucleoside analogues like cytosine arabinoside and anthracyclines like idarubicin and daunorubicin [65, 66]. So, the effective agents that can selectively eradicate LSCs are urgently needed for the development of new therapies for treatment of leukemia.

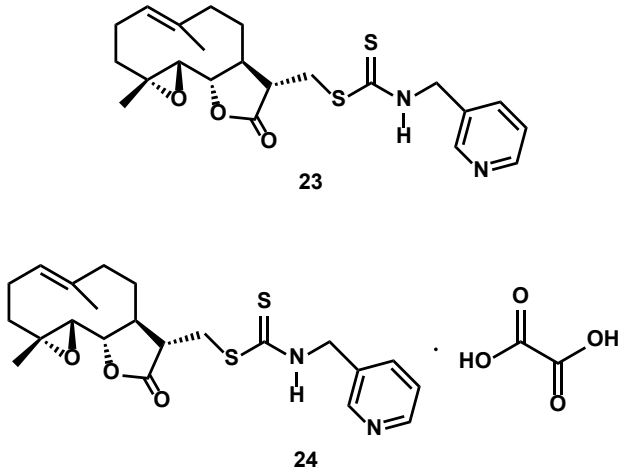
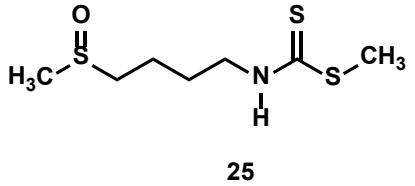


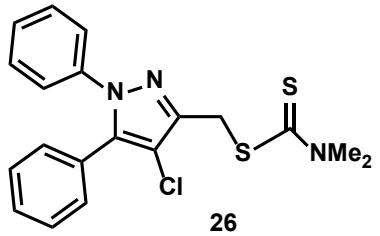
Figure 2. Dithiocarbamate esters **23,** showed potency against AML progenitor cell line KG1a and **24**, a promising drug candidate for the discovery of anti-LSCs drug

Using this information, Dinga, Y. *et al.* designed, synthesized, and evaluated a series of dithiocarbamate esters of parthenolide (PTL) for their anti-AML activities [67]. Among the most promising compound **23** showed greatly improved potency against AML progenitor cell line KG1a with IC_{50} value of 0.7 μM, and the efficacy found 8.7-folds comparing to that of PTL (IC_{50}= 6.1 μM). The compound **23** induced the apoptosis of total primary human AML cells and leukaemia stem cell (LSCs) of primary AML cells while sparing the normal cells. The compound **23** suppressed the colony formation of primary human leukaemia cells. The preliminary molecular mechanism study revealed that the compound **23**-mediated apoptosis is associated with mitogen-activated protein kinase signal pathway. After some of the research results, Dinga, Y. *et al.* proposed that the compound **24** also might be a promising drug candidate for ultimate discovery of anti-LSCs drug (Figure 2).

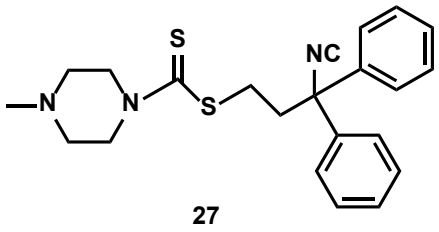
Dithiocarbamate (*S*-alkyl carbodithioate esters) are the functional organosulfur compounds which were first used as fungicides during World War II [68]. These types of compounds are also largely applied as important fungicides of crops, vegetables and plants [69-71]. Previous reports show that the *S*-alkyl carbodithioate esters and their derivatives show antibacterial [72-74], anticandidal activity and cytotoxicity [75], antihistaminic [76], anticancer properties [77, 78-80] and anthelmintic [77] properties. These types of compounds are very useful in the treatment of cardiovascular disorders and inflammatory diseases [81]. They show *in vitro* antitumor activity against human myelogenous leukemia K562 cells [82] and can be used as HIV-I NCp7 inhibitors [83], or non-vanilloid TRPV1 antagonists [84]. Examples of *S*-alkyl carbodithioate esters (compounds **25-28**) which have potential therapeutic value are shown in Figure 3. These carbodithioate esters are also broadly used as suitable ligands in the area of surface science and nanomaterial chemistry, for the assembly on metal nanoparticles [85, 86]. They are also used as sulfur vulcanization acceptors [87], and radical chain transfer agents in reversible addition fragmentation chain transfer polymerizations in the rubber industry [88-90]. Furthermore, they are also important synthetic intermediates [91-92]. As a result, many methods for the synthesis of these carbodithioate esters have been developed by researchers worldwide [93].



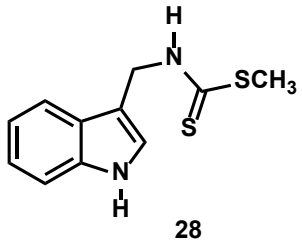
Sulforamate (M) used as cancer chemopreventive agent



RWJ-025856 (N) used as attenuating effects on tumor necrosis factor



990207 (O) used as inhibitor of the tumor growth of sarcoma-180, hepatocyte carcinoma-22



Brassinin (P) which is used as cancer chemopreventive agent

Figure 3. Carbodithioate esters which have the strong potential therapeutic values

4. Conclusions

This review has highlighted the synthesis, reactions and biological importance of *α, β*-unsaturated carbodithioesters type of compounds and their derivatives. *α, β*-unsaturated carbodithioesters and their derivatives have myriad applications in biological, pharmaceutical, medicinal and in many other fields. This class of sulfur-containing compounds will continue to be investigated in the future and new applications for these dithioesters will continue to be developed.

ACKNOWLEDGEMENTS

The authors are grateful to the Department of Chemistry and Biological Sciences, Faculty of Science and Engineering, Iwate University, Japan.

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