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Chemistry and Biological Activities of Ethyl-2-benzothiazolyl Acetate and its Corresponding Hydrazides

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ABSTRACT

This review article explores the synthesis and diverse reactions of ethyl-2-benzothiazolyl acetate and its corresponding hydrazide derivatives. The study presents a comprehensive investigation into various synthetic methodologies, demonstrating the versatility of these compounds in generating diverse chemical entities. The synthesis of ethyl-2-benzothiazolyl acetate involves several methods, including reactions with 2-aminothiophenol, ethyl cyanoacetate, ethyl ethoxycarbonylacetimidate hydrochloride, and diethyl malonate. Additionally, cyanomethylene benzothiazole can be converted to ethyl-2-benzothiazolyl acetate. These methods offer various pathways to achieve the desired compound with notable yields. Furthermore, detailed synthesis of 2-benzothiazolyl acetohydrazide from ethyl-2-benzothiazolyl acetate through reactions with hydrazine hydrate or by reacting 2-aminothiophenol with cyanoacetohydrazide was also descried. The subsequent derivatization of 2-benzothiazolyl acetohydrazide and its derivatives through various reactions highlights the potential for creating diverse chemical scaffolds. The study explores the reactions of these compounds with various reagents, including aromatic aldehydes, 1,2,4-triazole, cinnamyl alcohol, hydroxybenzaldehyde, and more. The resulting compounds exhibit a range of structural and functional diversity. Moreover, the review systematically examines the diverse biological activities demonstrated by these compounds. The exploration of these activities extends to their potential applications in various fields, such as pharmaceuticals, and materials science. Additionally, the synthesis of fluorescent sensors and potential inhibitors for enzymes is discussed.

1. Introduction

Benzothiazoles are a class of heterocyclic compounds categorized within the realm of organic chemistry. Specifically, 2-substituted benzothiazoles manifest a diverse

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spectrum of activities encompassing biological effects [1-22], interactions involving dyes [23-25], and chemical reactivity [26]. The archetype of this group, benzothiazole A, assumes a pivotal role as a fungicidal agent [27]. Methabenzthiazuron (MBTU), designated as compound B, demonstrates utility as an herbicidal entity in the cultivation of winter corn crops, serving as a key constituent in two commercially available preparations: Tribunil and Ormet [28]. The domain of 2-substituted BTA (Benzothiazole) derivatives constitutes a substantial cohort of xenobiotic entities, fabricated on a global scale to serve a multitude of applications [29], encompassing deployment as slimicides in the context of the paper and pulp industry [30]. Certain disperse azo dyes, represented as C, find their genesis through the synthetic utilization of 2-aminobenzothiazole [31]. Rhone-Poulenc (Rilutek) markets riluzole (2-amino-6-trifluoromethoxy-benzothiazole) to address the treatment of amyotrophic lateral sclerosis [32], whereas 2-(4-aminophenyl)benzothiazole, denoted as D, exhibits noteworthy antitumor properties [33]. The repertoire of BTA derivatives serves as catalysts for the formation of sulfide linkages (reticulation) within unsaturated elastomeric polymers, resulting in the generation of a cross-linked material distinguished by its dual attributes of flexibility and elasticity. Among these derivatives, 2-mercaptobenzothiazole (MBT/BTSH), herein referred to as E, emerges as the preeminent rubber accelerator extensively employed across a spectrum of specialized products, including the domain of tire manufacturing [34].

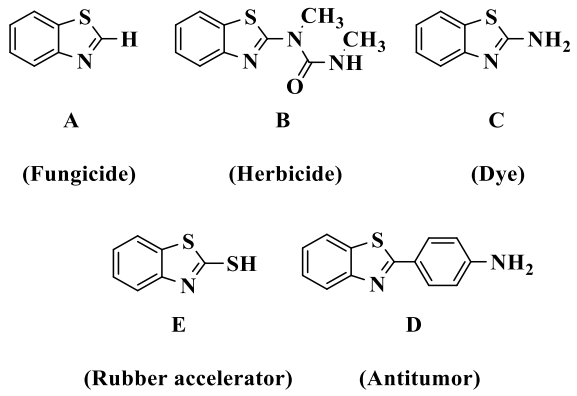


Fig. 1: Utilities of different benzothiazole compounds.

In recent years, benzothiazole esters and hydrazides have emerged as constituents in numerous chemical compounds, unveiling their versatile applications across various domains, including industries [35, 36] and the medical field [37-39]. Ethyl 2-(6-substituted benzo[*d*]thiazol-2-ylamino)-2-oxoacetate derivatives denoted as **E** were subjected to *in vitro* testing against protein tyrosine phosphatase-1B (PTP-1B). Through *in vivo* assessments, these compounds exhibited significant reductions in plasma glucose concentrations in an acute normoglycemic model and an oral glucose tolerance test, mirroring the effects of the hypoglycemic drug glibenclamide [37]. The strategic substitution of heterocyclic systems at position-2 of benzothiazole has led to the development of potent anthelmintic compounds. Compound **F** displayed remarkable *in vitro* anthelmintic activity, comparable to the standard drug albendazole [39]. Exploring the anti-inflammatory potential of novel derivatives of 4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylates unveiled significant activity among several compounds within this series. Notably, among these, the compound ethyl-(4*R*)-2-amino-6-chloro-4-(3,4,5-trimethoxyphenyl)-4*H*-pyrimido[2,1-*b*][1,3]-benzothiazole-3-carboxylate, referred to as **G**, exhibited the most promising anti-inflammatory activity [39].

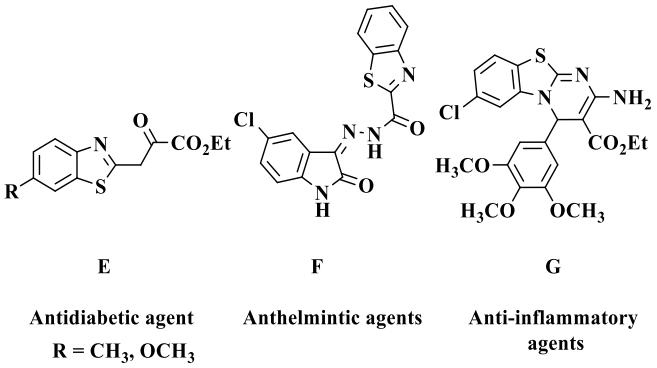
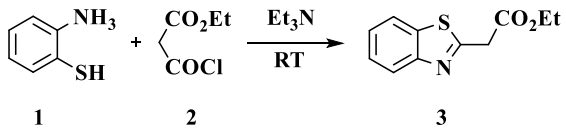


Fig. 2: Biological activity of different benzothiazole ester and hydrazide compounds.

2. Synthesis of ethyl-2-benzothiazolyl acetate and its corresponding hydrazide

2.1 Synthesis of ethyl-2-benzothiazolyl acetate

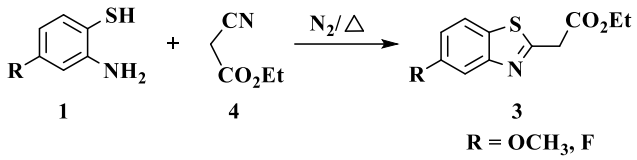
Benzothiazole acetate has been synthesized employing diverse methodologies. A primary and direct approach involves the reaction of 2-aminothiophenol **1** with ethyl 3-chloro-3-oxopropanoate **2** in the presence of trimethylamine. This reaction culminates in the formation of the desired benzothiazole acetate **3** with favorable yield, as depicted in Scheme 1 [40].



Scheme 1

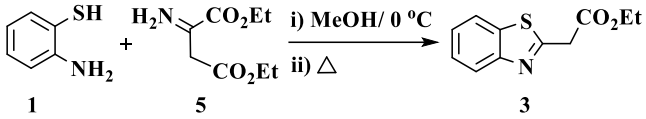
An alternative method for the synthesis of benzothiazole acetate 3 entails the reaction between 2-aminothiophenol **1** and ethyl cyanoacetate **4**, conducted at an elevated temperature of 120 °C through a fusion process under a protective nitrogen atmosphere. This synthetic route, illustrated in Scheme 2, has been documented in the literature

and is supported by studies from references [41, 42].



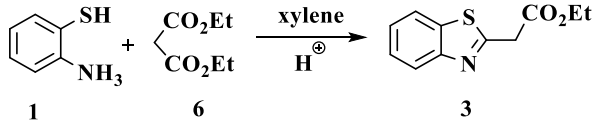
Scheme 2

The synthesis of benzothiazole acetate **3** can also be achieved through the reaction between 2-aminobenzenethiol **1** and ethyl ethoxycarbonylacetimidate hydrochloride **5**. This chemical transformation results in the production of benzothiazole acetate **3** with a notable high yield, as elaborated in detail within Scheme 3 [43].



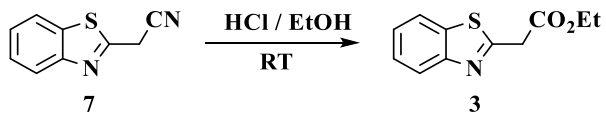
Scheme 3

Furthermore, an alternative synthetic pathway for synthesizing benzothiazole acetate **3** involves the reaction of 2-aminobenzenethiol **1** with diethyl malonate **6**, which is conducted under reflux conditions in a xylene solvent system enriched with catalytic quantities of *p*-toluene sulfonic acid. This transformation, meticulously depicted in Scheme 4, has been documented in reference [44].



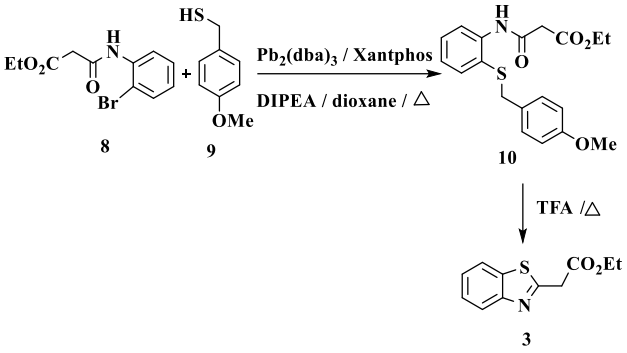
Scheme 4

Ethyl 2-benzothiazolyl acetate **3** can be alternatively synthesized through the conversion of cyanomethylene benzothiazole **7**. This process involves subjecting cyanomethylene benzothiazole **7** to a reaction mixture composed of concentrated hydrochloric acid (HCl) and ethanol (EtOH), maintained at ambient temperature for a duration of 2 days. The intricacies of this synthetic transformation are depicted in a detailed schematic representation, namely Scheme 5, as elucidated in reference [45]. This strategy underscores the significance of manipulating the chemical reactivity of cyanomethylene benzothiazole **7** under controlled conditions, leading to the targeted synthesis of ethyl 2-benzothiazolyl acetate **3** within the designated timeframe.



Scheme 5

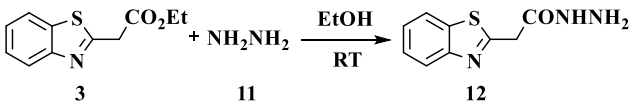
Ethyl 2-benzothiazolylacetate **3** was also synthesized utilizing a distinct approach involving the reaction between 2-bromobenzanilide **8** and (4-methoxyphenyl)methanethiol **9**. This chemical transformation was facilitated in the presence of tris(dibenzylideneacetone)dipalladium (0) [$Pd_2(dba)_3$] and Xantphos, (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene), as catalysts, within a reaction medium composed of *N*,*N*-diisopropylethylamine (DIPEA) and dioxane. The outcome of this reaction was the formation of the corresponding sulphide **10**. Subsequently, the introduction of Trifluoroacetic acid (TFA) directly to compound **10** yielded ethyl 2-benzothiazolyl acetate **3** with a remarkable yield, as intricately depicted in Scheme 6 as outlined in reference [46].



Scheme 6

2.2 Synthesis of 2-benzothiazolyl acetohydrazide

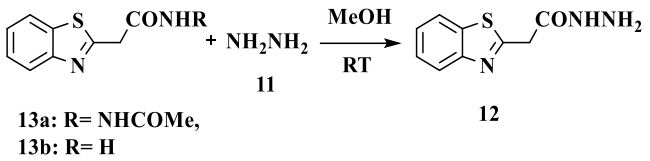
The synthesis of 2-benzothiazolyl acetohydrazide **12** was realized through a specific chemical route involving the reaction of ethyl 2-benzothiazolyl acetate **3** with hydrazine hydrate **11**. This transformation was orchestrated at ambient room temperature, with ethanol serving as the chosen solvent to facilitate the reaction milieu. The procedural steps, as illustrated in Scheme 7, were meticulously followed to ensure successful conversion, as outlined in reference [47]. This strategic synthesis underscores the significance of employing hydrazine hydrate **11** to react with ethyl 2-benzothiazolyl acetate **3** under the influence of ethanol, ultimately leading to the targeted formation of 2-benzothiazolyl acetohydrazide **12** in accordance with the outlined protocol in Scheme 7.



Scheme 7

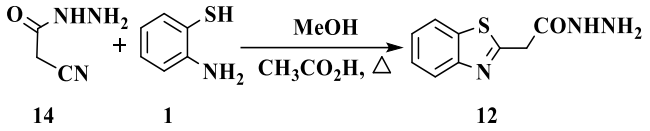
The synthesis of 2-benzothiazolyl acetohydrazide **12** was also achieved through a distinct synthetic pathway, involving the reaction between *N*-acetylbenzothiazol-2-ylacetohydrazide **13a** or benzothiazol-2-ylacetamide **13b** and hydrazine hydrate **11**.

The chemical transformation was effectively conducted utilizing methanol as the chosen solvent, as depicted in the comprehensive schematic representation, Scheme 8, as detailed in reference [48].



Scheme 8

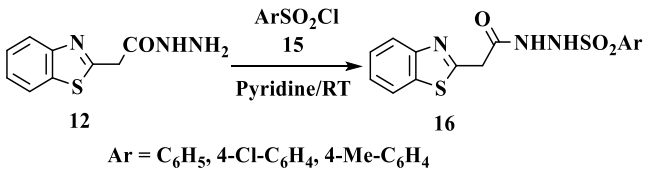
Another way for the synthesis of 2-benzothiazolyl acetohydrazide **12** is by the reaction of 2-aminothiophenol **1** and cyanoacetohydrazide **14** in methanol–acetic acid solution, Scheme 9 [49].



Scheme 9

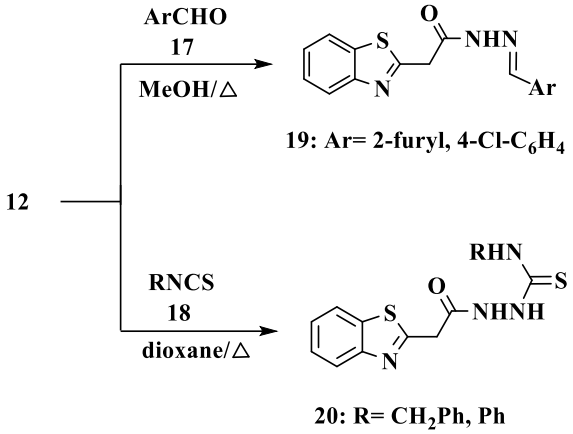
2.3 Synthesis of 2-benzothiazolyl acetohydrazide derivatives

Elgemeie and his research team extensively investigated the intricate reactions involving esters and hydrazides in conjunction with the benzothiazole moiety, an exploration detailed across various publications. Notably, the interaction of benzothiazole acetohydrazide **12** with arylsulfonyl chloride **15** was scrutinized as part of their investigations. This reaction was meticulously conducted under ambient room temperature conditions, utilizing pyridine as a vital reagent. As a result, a series of compounds designated as **16** were proficiently synthesized, yielding remarkable high yields, thereby highlighting the effectiveness of this process [47].



Scheme 10

Hydrazide derivatives of methylene benzothiazole were successfully synthesized through distinct synthetic routes. One approach involved the reaction of the hydrazide with furan-2-aldehyde or 4-chlorobenzaldehyde **17**, which took place in a methanol medium. Alternatively, the hydrazide was subjected to a reaction with either benzyl isothiocyanate or phenyl isothiocyanate **18** within a solvent system of dry dioxane, catalyzed by trimethylamine. These intricate transformations, as meticulously orchestrated and elucidated, are elegantly depicted in Scheme 11, as expounded upon in reference [48].

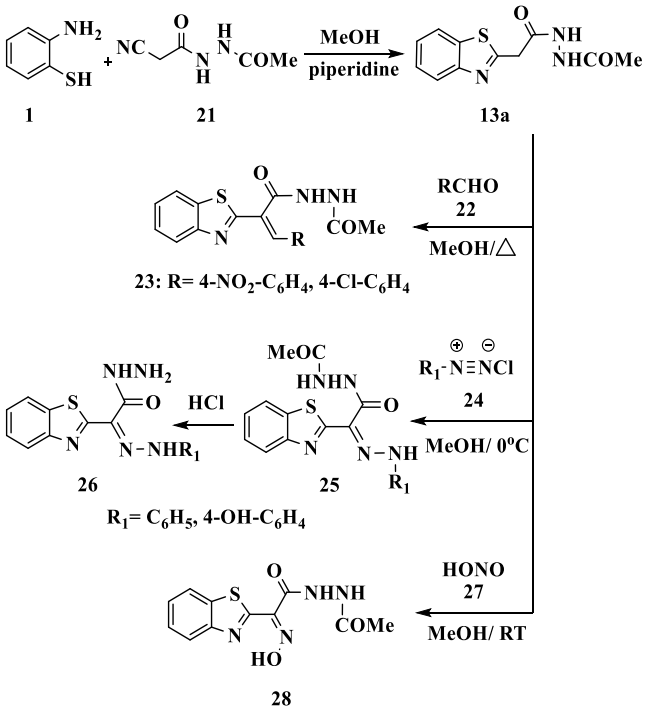


Scheme 11

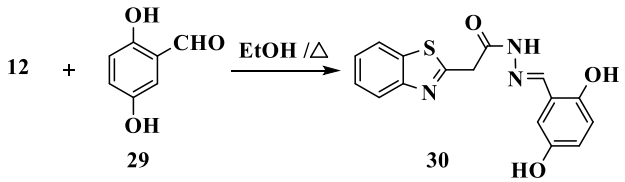
Multiple hydrazide derivatives of methylene benzothiazole have been successfully synthesized, employing diverse reaction conditions. Initially, compound **22** was meticulously prepared through the reflux of a mixture comprising 2-aminothiophenol **1** and *N*-acetylcyanoacetohydrazide **21** in methanol, under the influence of piperidine, over a period of 3 hours. Subsequently, compound **14** served as the pivotal starting material for a series of three distinct reactions. In the first scenario, compound **13** was subjected to reflux conditions with the corresponding aldehyde **22**, employing methanol and piperidine as reaction components, culminating in the formation of product **23**. Conversely, compound **13a** was stirred alongside diazonium salts of aniline **24** in a methanol solution under cooling conditions within an ice bath, leading to the creation of compound **25**. Compound **25**, in turn, underwent a transformative reaction with HCl, resulting in the synthesis of compound **26**. Furthermore, compound **13a** was subjected to stirring in the presence of acetic acid and methanol, in conjunction with sodium nitrite **27**, a process meticulously illustrated in Scheme 12, as elaborated upon within reference [49]. This systematic exploration underscores the versatility and adaptability underpinning the generation of a myriad of hydrazide derivatives of methylene benzothiazole, each requiring tailored reaction conditions and meticulously orchestrated sequences, as intricately depicted within Scheme 12.

The Schiff base ligand **30** was synthesized through a sequential process. Initially, a solution of 2-(benzothiazol-2-yl)acetohydrazide **12** in hot ethanoic solvent was combined with a hot ethanoic solution of 2,5-dihydroxybenzaldehyde **29**. The resultant mixture was subsequently refluxed for a duration of two hours. Following the reaction, the volume of the mixture was reduced by half, and the resulting yellow precipitate was isolated through filtration in high yield, as meticulously illustrated in Scheme 13, as detailed within reference [50].

By using ligands **30** and their metal complexes (Co, Cu, Ni, Mn, and Zn) to examine antifungal efficacy against fungi (*Aspergillus nigar* and *Fusarium oxysporium*), antifungal activity of copper(II) complexes were higher than that of the ligands and their aqueous counterparts.

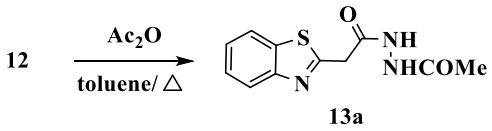


Scheme 12



Scheme 13

Moreover, the acylation reaction of 2-benzothiazolyl acetohydrazide **12** led to the formation of compound **13a** (Scheme 14) [51].



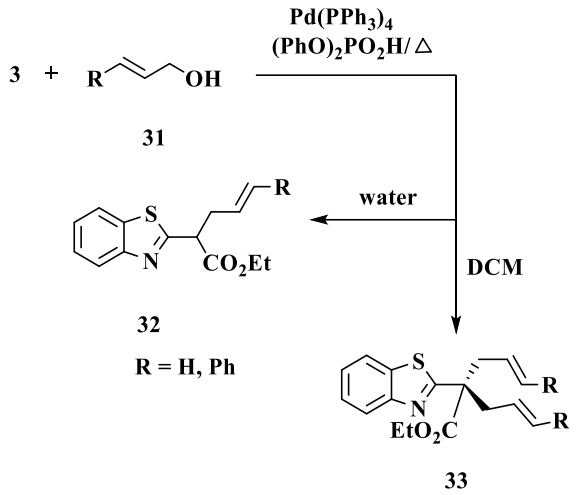
Scheme 14

3. Reactions of ethyl-2-benzothiazolyl acetate and its corresponding hydrazide

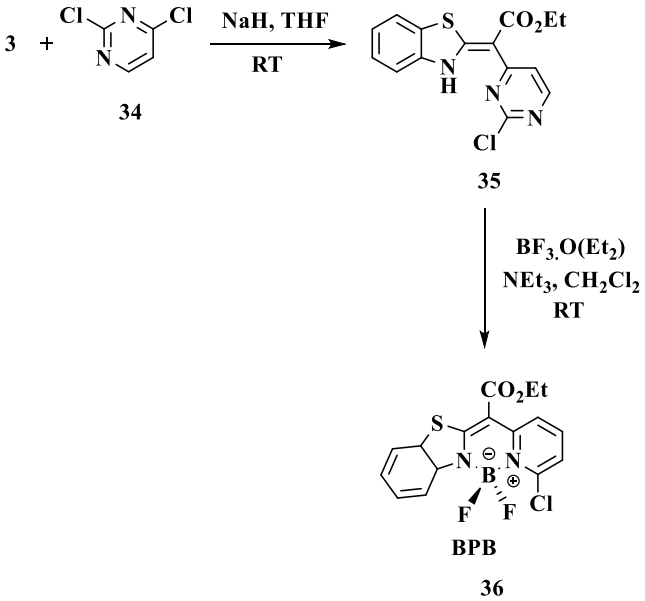
3.1. Reactions of ethyl-2-benzothiazolyl acetate

In Scheme 15, Benzothiazole ester **3** underwent a reaction with allyl alcohol and cinnamyl alcohol **31**. This transformation was facilitated by the utilization of $Pd(PPh_3)_4$, also known as palladium-tetrakis(triphenylphosphine), and $(PhO)_2PO_2H$, which stands for dibenzyl phosphate. The reaction took place in the presence of either water forming compound **32** or dichloromethane (DCM) forming compound **33** [52].

A novel fluorescent sensor targeting Cys was synthesized using a benzothiazole-pyrimidine-based boron difluoride complex (BPB) **36**. This complex was derived from the reaction of ethyl-2-benzothiazolyl acetate **3** with dichloropyrimidine **34**, leading to the formation of the initial compound **35**. Notably, BPB **36** exhibited a distinct preference for reacting with Cys in comparison to Hcy, GSH, and various other amino acids (Scheme 16) [53].

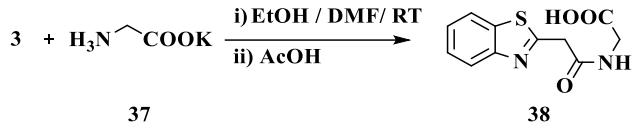


Scheme 15



Scheme 16

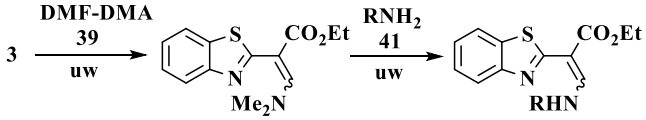
In Scheme 17, a reaction was carried out by stirring potassium glycinate **37** and ethyl benzothiazol-2–acetate **3** for a duration of 24 hours in the presence of an ethanol / DMF mixture. Subsequently, the reaction mixture was neutralized using acetic acid, resulting in the formation of compound **38** [54].



37 38

Scheme 17

Novel *α*-hetero *β*-enamino esters **42** are successfully synthesized with high yields through transamination reactions [55]. These reactions involve ethyl 3-dimethylamino acrylate **40** and a range of readily volatile amines **41**, all conducted under solvent-free conditions with the aid of focused microwave irradiation, Scheme 18. The majority of the resulting *α*-hetero *β*-enamino ester derivatives **3** exhibit a (*E*)-*s*-*cis*/*trans* conformation.

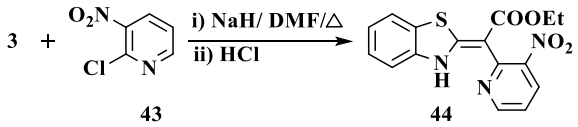


40 42

R= Me_2CH; Me_3C, Et(Me)CH, propyl, $(EtO)_2CHCH_2$

Scheme 18

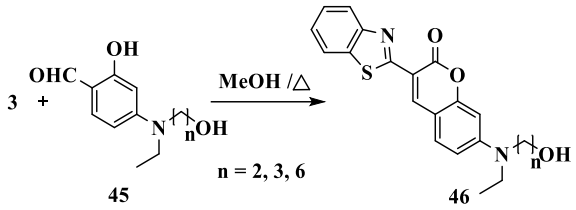
Benzothiazole ester **3** is first dissolved in DMF (dimethylformamide) in the presence of sodium hydride, Scheme 19 [43]. This mixture is then reacted with chloronitropyridine **43**. The resulting intermediate is subsequently hydrolyzed using HCl. This series of steps leads to the formation of compound **44** as the final product.



43 44

Scheme 19

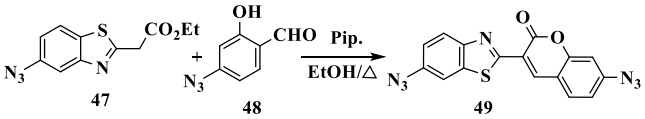
The procedure involved in the synthesis of coumarin compound **46** (Scheme 20) [56] begins with the ester of methylene benzothiazole **3** undergoing an aldol condensation reaction. This condensation takes place through the reaction of methylene benzothiazole **3** with a suitably substituted salicylaldehyde. The reaction mixture is then subjected to reflux conditions under an atmosphere of nitrogen (N_2), utilizing methanol as the solvent along with the addition of small amounts of piperidine.



45 46

Scheme 20

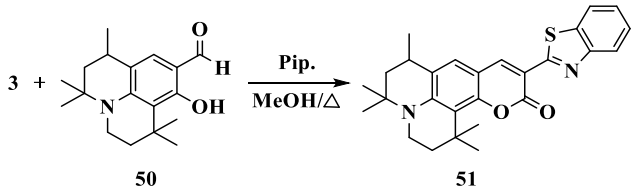
The synthesis of coumarin **49** was accomplished through a successful reaction between azido-building blocks benzothiazole ester **47** and hydroxybenzaldehyde **48**. This transformation took place in the presence of ethanol and piperidine as reaction catalysts, leading to the formation of coumarin **49** in a highly favorable yield. This synthetic procedure is depicted in Scheme 21, and the details of this reaction can be found in reference [57].



47 48 49

Scheme 21

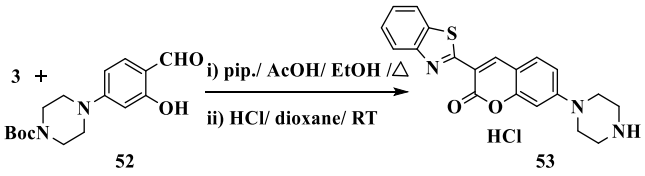
The synthesis of coumarin compound **51** was achieved by subjecting ester **3** to a reaction with hydroxyaldehyde compound **50**. This reaction was carried out in the presence of methanol and piperidine, serving as essential components for the successful transformation. The chemical process leading to the formation of coumarin **51** is visually represented in Scheme 22 [58- 65].



50 51

Scheme 22

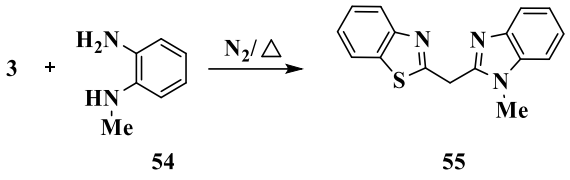
To create 3,7-disubstituted coumarins **53**, ethyl 2-benzothazole acetate **3** can engage in an aldol condensation reaction with a properly modified salicylaldehyde **52**. The transient intermediate formed during this condensation process then undergoes a ring-closing transesterification reaction, ultimately yielding coumarin **53** after the Boc protecting group is eliminated by treatment with hydrogen chloride in 1,4-dioxane, as depicted in Scheme 23 [66].



52 53

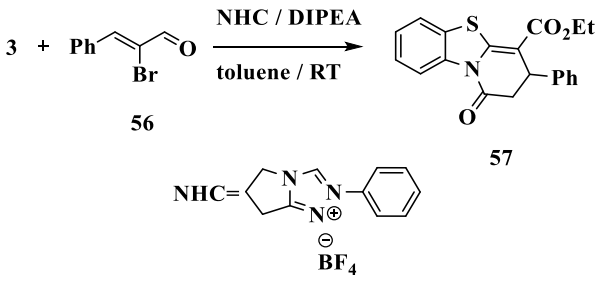
Scheme 23

The synthesis of Imidazole cycle **55** was successfully achieved through a series of chemical transformations starting from benzothiazole ester **3**. This transformation was accomplished by subjecting benzothiazole ester **3** to a treatment with diamine compound **54**, as outlined in Scheme 24 [67]. This strategic approach led to the formation of the desired imidazole cycle **55**, representing a significant advancement in the field of synthetic organic chemistry. In this synthetic pathway, benzothiazole ester **3** serves as a crucial starting material, providing the necessary structural framework for the subsequent transformations. The utilization of diamine compound **54** as the reactive partner facilitates the key step in the synthesis, where the desired imidazole ring is forged. This step not only involves the formation of the imidazole ring but also introduces structural complexity and diversity into the molecule, enhancing its potential utility in various applications.



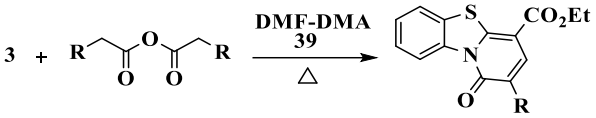
Scheme 24

The model reaction of benzothiazole ester **3** with 2-bromocinnamaldehyde **56** at room temperature in the presence of the triazolium precatalyst A (NHC) gave the product **57** with toluene as solvents and *N*,*N*-diisopropyl ethylamine (DIPEA) as bases (Scheme 25) [68].



Scheme 25

A novel and environmentally friendly three-component reaction (3CR) were innovated for the synthesis of pyridobenzothiazoles **59**. This innovative approach allows for the integration of a basic hydrolysis step within a single reaction vessel, streamlining the process and minimizing the need for multiple synthetic steps. By employing a benzothiazole acetate **3**, *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA), and an anhydride **58** (as outlined in Scheme 26), this reaction not only enhances yields but also significantly reduces the overall reaction time, presenting a more efficient and sustainable route to the pyridobenzothiazole scaffold [69].

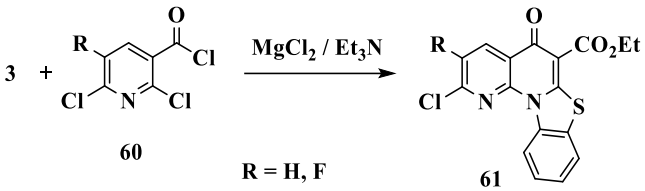


R = H, $CH_2C_6H_5$, 4-Cl-C_6H_4, 4-MeO-C_6H_4, 2-F-C_6H_4, 3-F-C_6H_4, 2-Me-C_6H_4, 3-Me-C_6H_4

Scheme 26

Scheme 27 depicts the overarching synthetic pathway employed for the creation of quinolone **61**. The initiation of analogue synthesis involves a reaction between ethyl 2-benzothiazolyl acetate **3** and substituted 2,6-dichloronicotinic acid chloride **60**, catalyzed by magnesium chloride [70].

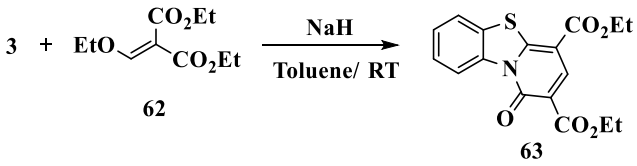
In HCT-116 cancer cells, compound **61** had a moderate (IC_{50} = 0.66 M) level of cellular activity, but completely lost its ability to inhibit the Pol I (rRNA synthesis) and Pol II (c-myc mRNA synthesis) enzymes.



R = H, F

Scheme 27

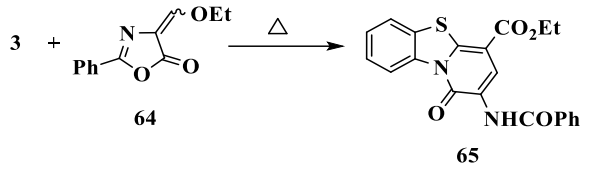
Through a meticulously orchestrated chemical process, the transformation of ethyl 2-benzothiazolyl acetate **3** was seamlessly accomplished. This remarkable achievement was realized by subjecting compound **3** to a reaction with diethyl (ethoxymethylene) malonate **62**, catalyzed by the presence of NaH. The culmination of these reactions culminated in the formation of the intriguing pyridobenzothiazole compound **63**, as elegantly depicted in Scheme 28 [44]. Central to this synthetic endeavor, ethyl 2-benzothiazolyl acetate **3** serves as the foundational building block, providing the essential chemical framework for subsequent transformations. The interaction between compound **3** and diethyl (ethoxymethylene) malonate **62**, under the influence of NaH, stands as a pivotal step in this transformative journey.



Scheme 28

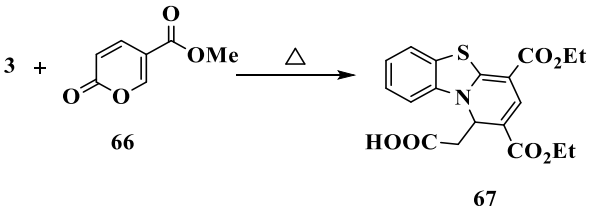
Pyridobenzothiazole **65** was prepared from the reaction of benzothiazole ester **3** with oxazolone compound **64** by heating (Scheme 29) [71]. The reaction proceeds via the addition of active methylene to ethoxymethylene of

oxazolone followed by intramolecular acylation of the nitrogen atom of benzothiazole with cleavage of the oxazolone ring.



Scheme 29

In a sustainable stride towards harnessing biorenewable resources, the compound methyl coumalate **66** was strategically engaged in a transformative chemical reaction. This ingenious process involved the judicious fusion of methyl coumalate **66** with benzothiazole ester **3**, orchestrated without the need for additional solvents or catalysts. This innovative approach resulted in the formation of compound **67**, ushering in a new paradigm of eco-friendly synthesis, as elegantly depicted in Scheme 30 [72]. This compound serves as a sustainable starting point for the synthesis, aligning with the principles of green chemistry by minimizing environmental impact. Through a strategic coupling with benzothiazole ester **3**, devoid of solvent and catalyst, this reaction showcases the potential for streamlined and environmentally conscious chemical processes.

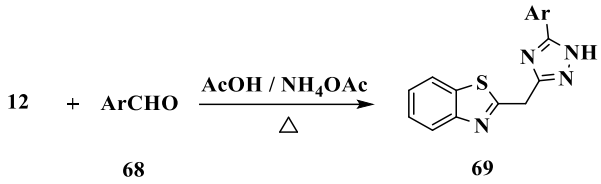


Scheme 30

3.2. Reactions of 2-benzothiazolyl acetohydrazide

Reaction of benzothiazole methylene hydrazide **12** with aromatic aldehydes **68** in the presence of AcOH and ammonium acetate under reflux yielded the target compound 2-((5-phenyl-1*H*-1,2,4-triazol-3-yl)methyl)benzo[*d*]thiazole **69** in good yield (Scheme 31) [73].

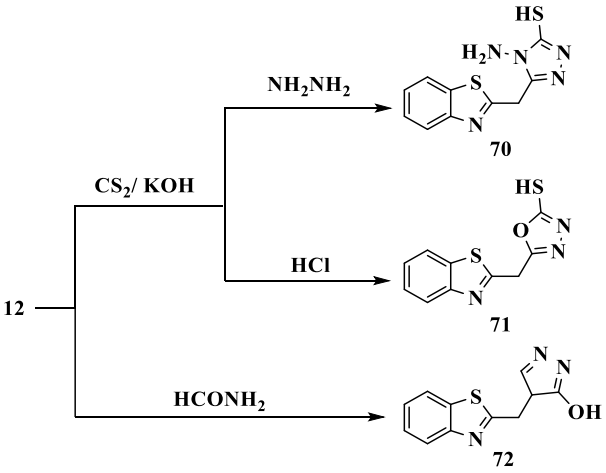
The assessment of biological activities has illuminated a remarkable facet of compound **69**, revealing its notable effectiveness as an antibacterial agent. Notably, in the context of its activity against *Klebsiella pneumonia*, compounds featuring ortho bromo and meta hydroxyl functional groups emerged as the most potent contenders. These specific structural motifs demonstrated impressive efficacy against *Salmonella paratyphi* A and B, further underscoring their significance as bioactive entities. The investigation into compound **69**'s antibacterial activity offers a glimpse into its potential as a therapeutic agent against bacterial infections. The presence of certain structural features, such as ortho bromo and meta hydroxyl groups, appears to confer enhanced antibacterial potency. This correlation between structural attributes and biological activity showcases the intricate relationship between molecular architecture and functional effects within a biological context.



Ar = C_6H_5, 4-MeO-C_6H_4, 3-MeO-C_6H_4, 4-Cl-C_6H_4, 2-Cl-C_6H_4, 4-Br-C_6H_4, 2-Br-C_6H_4, 3-OH-C_6H_4

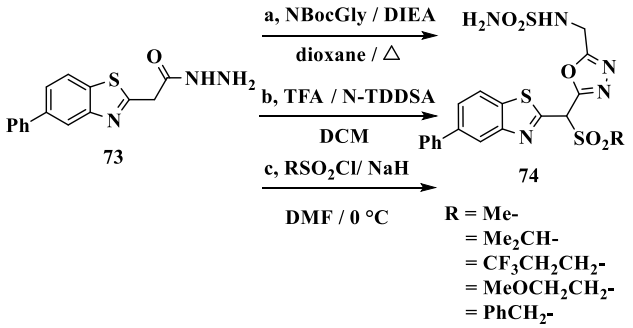
Scheme 31

In a sequence of carefully orchestrated chemical transformations, hydrazide compound **12** underwent diverse reactions to yield a collection of distinct compounds. Initially, the treatment of compound **12** with carbon disulfide resulted in the formation of a salt. This intermediate was then subjected to two different reaction pathways: one involving hydrazine hydrate in methanol under reflux conditions for 3 hours, leading to the creation of triazole **70**, and the other involving HCl, which yielded oxadiazole **71**. In a separate trajectory, compound **12** was subjected to reflux conditions in formamide for a duration of 6 hours, culminating in the production of pyrazole **72**. The intricate series of reactions is elegantly represented in Scheme 32 [48, 74].



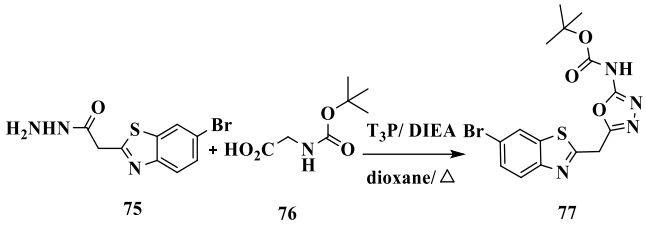
Scheme 32

Benzothiazole hydrazide **73** was entered to series of reactions started with NBocGly (*N*-(tert-butoxycarbonyl) glycine) and finished with regioselective sulfonylation to give oxadiazole **74** (Scheme 33) [75]. Compound **74** was considered as an inhibitor for endothelial lipase (EL).



Scheme 33

In a meticulously orchestrated chemical transformation, the benzothiazolyl hydrazide derivative **75** and 2-((tert-butoxycarbonyl)amino)acetic acid **76** were thoughtfully brought together. These compounds were dissolved in dioxane and subjected to a reaction milieu where ethyl acetate, DIEA (diisopropylethylamine), and 1-propanephosphonic acid cyclic anhydride (T_3P) coalesced. This strategic combination, operating at a controlled temperature of 70°C, catalyzed the metamorphosis of the initial components into the desired oxadiazole derivative **77**. Scheme 34 offers a visual narrative, delineating the sequential steps that underpin the conversion of starting materials into the final product, oxadiazole derivative **77**. This schematic encapsulates the strategic bond-forming events and the orchestrated interaction between the reagents and catalysts.

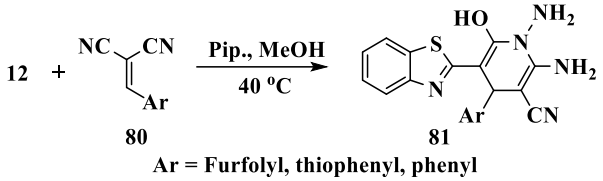


Scheme 34

Under the conditions outlined in Scheme 35, compound **12** underwent reflux for a duration of 3 hours in the presence of acetyl acetone **78** and methanolic potassium hydroxide. This reaction culminated in the formation of pyridone benzothiazole **79** [49].

Scheme 35

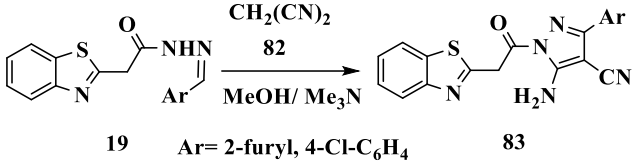
The expansion of the molecular diversity of pyridone benzothiazole **81** was deftly achieved through a subsequent derivatization process. This transformative step involved a reaction that engaged benzothiazole hydrazide **12** and benzyldene malononitriles **80**. Orchestrated in the presence of piperidine as a foundational base and utilizing methanol as the solvent, this reaction emerged as an artful maneuver to introduce new functional groups. The intricacies of this process are vividly depicted in Scheme 36 [77].



Scheme 36

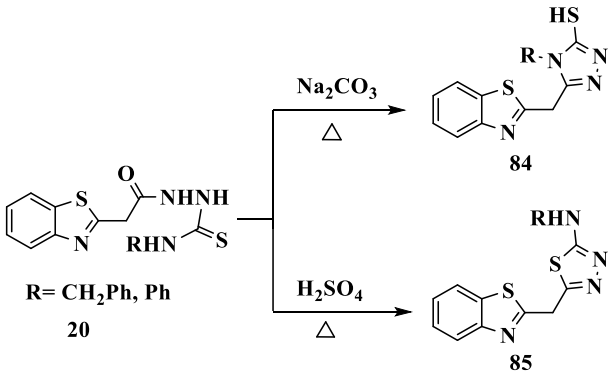
3.3. Reactions of 2-benzothiazolyl acetohydrazide derivatives

Nucleophilic addition of malononitrile **82** to the C=N group of Schiff base **19** resulting in the formation of a 1:1 adduct. This adduct then undergoes cyclization to create a pyrazoline intermediate, which is subsequently dehydrogenated to yield the final product, compound **83** (Scheme 37) [48].



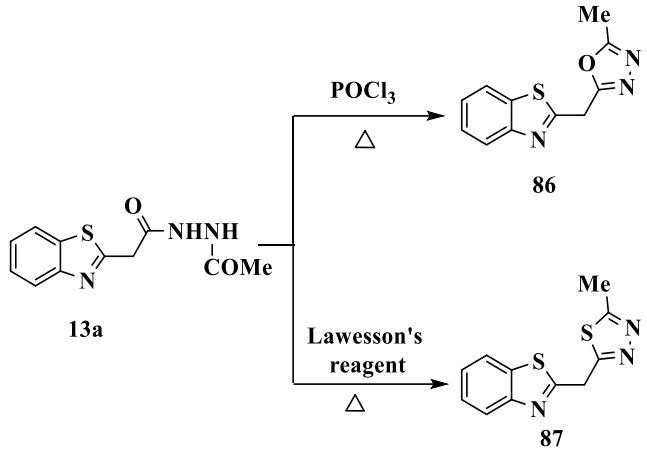
Scheme 37

In a sequence of well-calibrated reactions, compound **20** underwent transformative changes to yield two distinct compounds. The initial transformation involved the refluxing of compound **20** in a Na_2CO_3 solution for a duration of 4 hours, leading to the formation of compound **84**. Alternatively, when subjected to a different reaction pathway, compound **20** was heated for a brief 10-minute interval in concentrated H_2SO_4 at a temperature of 100ºC, resulting in the creation of compound **85**. These intricate reactions are visually captured in Scheme 38 [48].



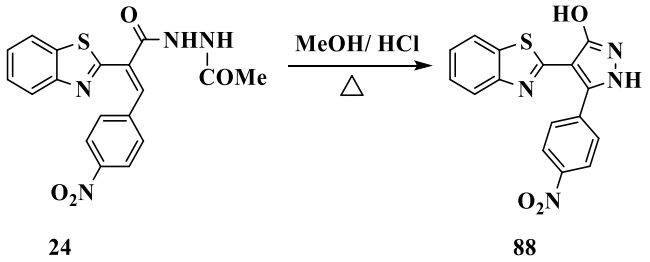
Scheme 38

The acylated hydrazide compound **22** was transformed into oxadiazole **86** by reacting it with $POCl_3$. Additionally, it can be converted to thiadiazoles **87** by reacting it with Lawesson's reagent (Scheme 39) [51].



Scheme 39

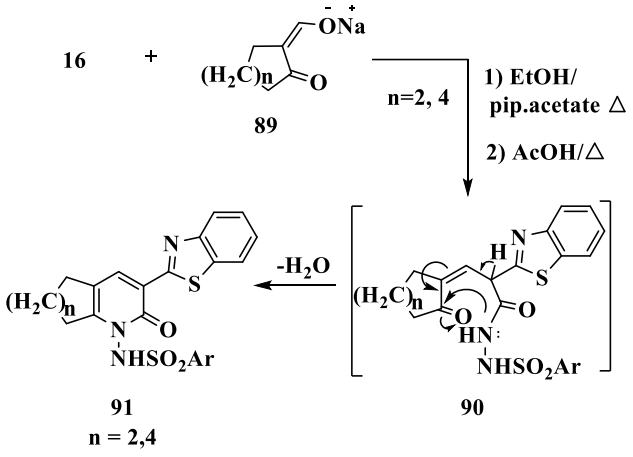
Through a controlled and strategic chemical process, compound 24 underwent a significant transformation. This compound was subjected to reflux conditions in a methanol solution containing HCl for 3 hours, resulting in the synthesis of pyrazole benzothiazole **88**. The intricate steps of this reaction are visually portrayed in Scheme 40 [49].



Scheme 40

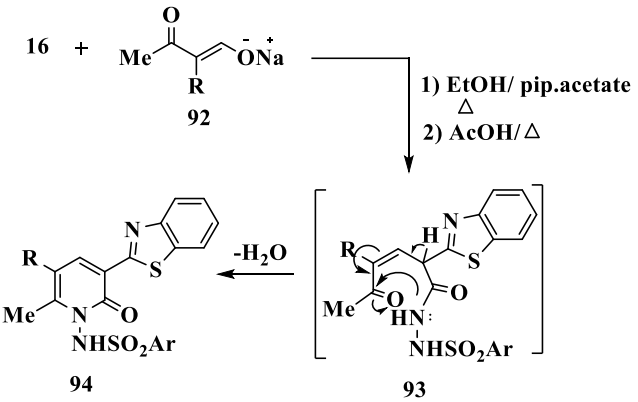
N-Arylsulfonohydrazides of benzothiazole **16** were reacted with 2-(hydroxymethylene)-1-cycloalcanones sodium salt **89** in piperidine acetate through intermediate formations, in a good yield, which led to composites formation of **91**. The reaction was proposed for the tolerance formyl group of cycloalkanones **89** forming intermediate **90** by a nucleophilic addition of the active methylene carbon-atom of benzothiazole hydrazides **16**, followed by the intramolecular cyclisation and removal of one water molecule to give the final product cycloalkane ring-fused *N*-sulfonyl aminated pyridones with benzothiazole moiety **91** (Scheme 41) [47].

N-Arylsulfonohydrazides of benzothiazole compounds **16** was reacted to sodium salts of the alkanone **92** in piperidine acetate through intermediate **93** formations. *N*-Arylsulfonylpyridones derivatives with benzothiazole moiety **94** were provided in reasonable yields by the intramolecular cyclisation of intermediate **93** (Scheme 42) [47].



Ar = C_6H_5, 4-Cl-C_6H_4, 4-Me-C_6H_4

Scheme 41



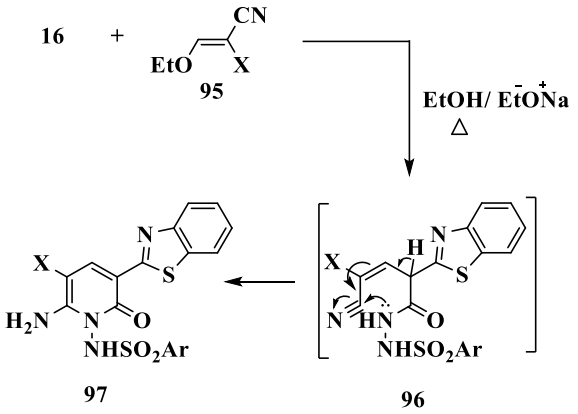
R = H, Me

Ar = C_6H_5, 4-Cl-C_6H_4, 4-Me-C_6H_4

Scheme 42

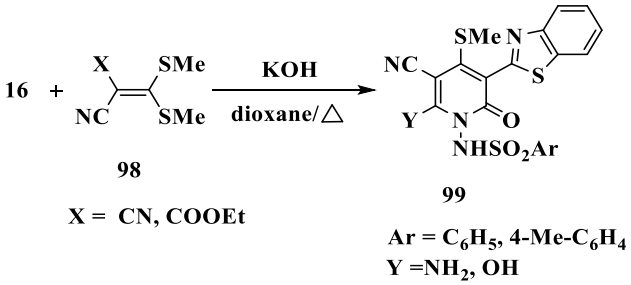
They expanded their research on the reactivity of *N*-arylsulfonohydrazides of benzothiazole **16** with ethoxymethylene compounds, 2-(ethoxymethylene) malononitrile **95**a and (*E*)-ethyl-2-cyano-3-ethoxyacrylate **95**b. *N*-Arylsulfonylpyridone **97** was prepared from this reaction in the presence of sodium ethoxide. All derivatives were shown to produce high yields. The reaction began with the Michael addition of *N*-arylsulfonohydrazide to the ethoxy methylene compounds, followed by the elimination of ethanol and the formation of intermediates **96**. Lastly, the addition of the NH group into the cyano group to provide *N*-arylsulfonylpyridone with benzothiazole moiety **97** products resulted in an intramolecular cyclization (Scheme 43) [47,78].

When the compounds **91** and **97** were tested against HSV-1, HAV HM175, HCVcc genotype 4a, CBV4 and HAdV7 in vitro, five of the newly synthesized compounds **91a, 91c, 91e, 91f** and **97a** showed a 50% reduction for antiviral activity. In addition, according to *in silico* physicochemical features they could have a high bioavailability when taken orally. Some inhibitory action has been observed against the USP7 enzyme in the two most powerful HSV-1 drugs, **91e** and **97a**.



Scheme 43

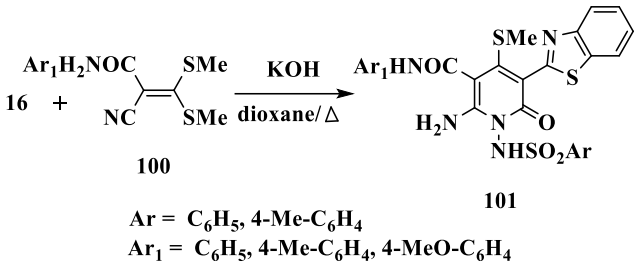
Similar studies were performed on benzothiazole hydrazide compound **16** with various S,S ketene dithioacetals and *N*-substituted bis (methylthiomethylene)(cyano)-acetamide derivatives. Benzothiazole aryl sulfonohydrazides **16** was reacted with either 2-(bis (methylthio)methylene)-malononitrile **98a** or ethyl 2-cyano-3,3-bis(methylthio)acrylate **98b** in presence of dry DMF containing pulver-potassium hydroxide. Compounds **99a,b** and **99c,d** were produced, respectively (Scheme 44) [79].



Scheme 44

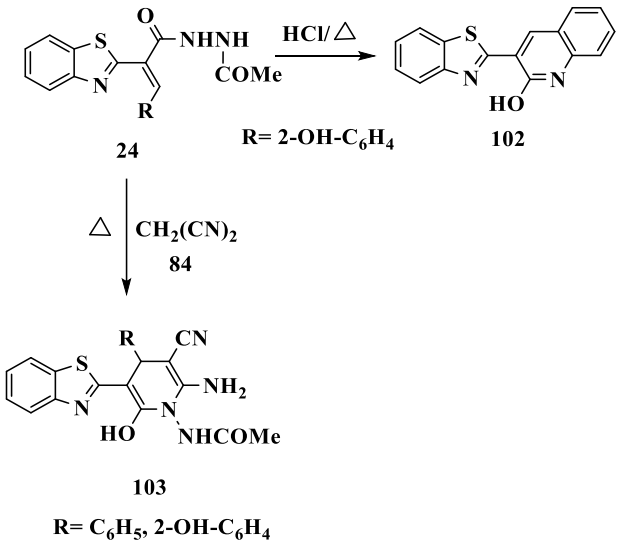
Reactions with alternative derivatives of *S,S* ketene dithioacetal compounds, i.e. *N*-substituted bis(methyl thiomethylene)(cyano)-acetamide derivatives **100**, were investigated in order to broaden the above evidence. The reaction of **100** with compound **16** produced *N*-(4-methylthio-6-oxopyridin-1-yl)arylsulfonamides with benzothiazole moiety **101** in the presence of dry 1,4-dioxane containing a catalytic amount of potassium hydroxide (Scheme 45) [79].

The biological study of compounds **16**, **99**, and **101** showed a significant antibacterial potency especially compounds **16b** and **99a,b**.



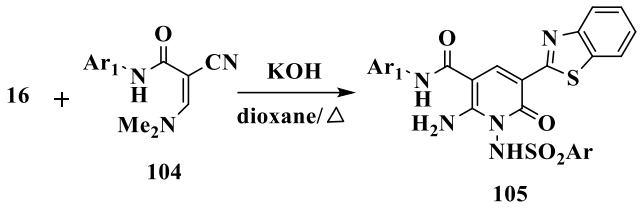
Scheme 45

Refluxing compounds **24a,b** with malononitrile **84** in the presence of dioxane and piperidine for 4 hours produced pyridine ring **103** while refluxing mechanic solution of **24**b in the presence of HCl for 3 hours produced pyridine ring **102** (Scheme 46) [49].



Scheme 46

N-Arylsulfonylpyridone derivatives bearing a benzothiazole moiety **105** were prepared through the reaction of *N*-arylsulfonylhydrazones **16** with *N*-aryl-2-cyano-3-(dimethylamino)acrylamide **104** in the presence of base medium, potassium hydroxide-containing, in dry dioxane [80]. Scheme 47 illustrates the synthetic pathway, which likely involved a Michael addition reaction first and elimination of $NH(CH_3)_2$ followed by the intramolecular cyclization to furniture with the desired product in high yield. The structure of the synthesized compounds was confirmed using spectral and elemental analysis.

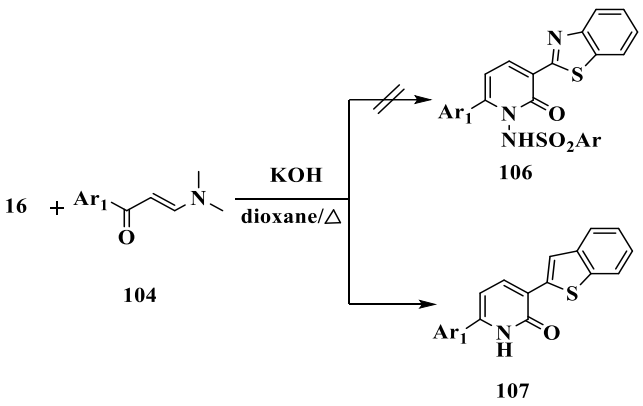


Ar = C_6H_5, 4-Me-C_6H_4
Ar_1 = C_6H_5, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4

Scheme 47

An endeavor was made to synthesize another set of derivatives involving benzothiazole substituted with *N*-arylsulfonylpyridones **106**. This synthesis involved the reaction of *N*-arylsulfonylhydrazones **16** with *N*-aryl-3-(dimethylamino)prop-2-en-1-one **105**. The outcome of the reaction yielded 2-pyridone derivatives **107** following the elimination of the NH-arylsulfonyl group (Scheme 48) [80].

The antimicrobial evaluation of compounds **105** and **107** have been resulted to moderate activities of such compounds against *S. aureus*.



Ar = C_6H_5, 4-Me-C_6H_4
Ar_1 = 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4

Scheme 48

Conclusions

In conclusion, the review presents an exhaustive exploration into the synthesis and reactivity of ethyl-2-benzothiazolyl acetate and its corresponding hydrazide derivatives. The comprehensive study showcases the diverse methodologies employed to synthesize these compounds and elucidates their transformation through a myriad of chemical reactions. The manuscript underscores the versatility of these compounds as building blocks for the creation of a wide range of structurally diverse molecules. The synthesis of ethyl-2-benzothiazolyl acetate is achieved through several distinct routes, each yielding the desired compound with favorable yields. These diverse synthetic pathways offer researchers a spectrum of options to tailor the synthesis according to specific needs, demonstrating the flexibility of these compounds in synthetic applications. Equally significant is the synthesis of 2-benzothiazolyl acetohydrazide and its subsequent derivatization. The reactions outlined in the manuscript exhibit the potential to introduce functional diversity, yielding compounds with varied structural motifs and potential biological activities. This work opens avenues for researchers to explore and harness the unique reactivity of these compounds for the creation of novel molecules with tailored properties. Furthermore, the manuscript provides glimpses into the potential biological significance of these compounds. Several derivatives exhibit promising antibacterial, antifungal, and enzyme inhibitory activities, hinting at their potential utility in therapeutic applications.

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