HETEROCYCLES, Vol. 94, No. 8, 2017, pp. 1389 - 1426. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 27th April, 2017, Accepted, 15th June, 2017, Published online, 5th July, 2017
DOI: 10.3987/REV-17-862

UPDATE ON THE REACTIVITY OF SACCHARIN: AN EXCELLENT PRECURSOR FOR THE SYNTHESIS OF BIOLOGICALLY IMPORTANT MOLECULES

Rabia Akhtar,[1] Ameer Fawad Zahoor,[1*] Sajjad Ahmad,[2] Syed Ali Raza Naqvi,[1] Samreen Gul Khan,[1] and Muhammad Suleman[3]

[1]Department of Chemistry, Government College University Faisalabad, Faisalabad-38000, Pakistan

[2] Department of Chemistry, University of Engineering and Technology Lahore, Faisalabad Campus, Faisalabad-38000, Pakistan

[3] Department of Chemistry, Women University of Azad Jammu and Kashmir, Bagh, Pakistan

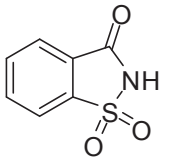
*Corresponding Author: fawad.zahoor@gcuf.edu.pk; fawad.zahoor@gmail.com

Abstract – Saccharin is a versatile starting material for the synthesis of different biologically active molecules. Its derivatives play an important role in medicinal chemistry as they act as analgesic, anti-inflammatory, antimicrobial, antirheumatic, antipyretic, anticancer and antioxidant agents. This review article describes the recent advances in the synthesis of saccharin derivatives reported from 2010 to 2017. This article critically summarizes the methodologies and pathways adopted by various research groups for the synthesis of these important molecules.

CONTENTS

1. INTRODUCTION

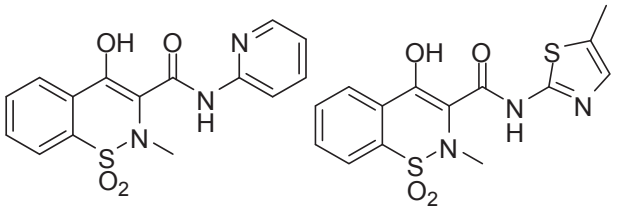
Saccharin, 1,2-benzisothiazole-3(2*H*)-one 1,1-dioxide (**1**), was first discovered by Fahlberg in 1879 and has been used as an artificial sweetener since 1885 (Figure 1). It is an inexpensive and versatile starting material for the synthesis of different heterocyclic compounds. Saccharin derivatives have attained great importance in the pharmaceutical industry because they act as serine protease inhibitors, cathepsin grandproteinase 3 inhibitors, human leukocyte elastase inhibitors, analgesics, aldehyde dehydrogenase inhibitors, β-carbonic anhydrase inhibitors and antiproliferative agents. Saccharin and amino acid bearing derivatives have also been investigated to determine their utility as potential peptidomimetic building blocks.[1,2]



1

Figure 1. Structure of saccharin **1**

1,2-Benzothiazine 1,1-dioxide derivatives that can be derived from commercially available saccharin, have found numerous applications in the pharmaceutical industry because they can act as anticancer, analgesic, antileukemic, antimicrobial, antirheumatic and antipyretic agents. Among these, piroxicam **2** and meloxicam **3** which are non-steroidal anti-inflammatory drugs, have considerable importance (Figure. 2).[3]

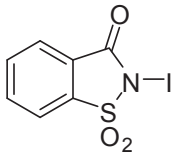


2 **3**

Figure 2. Structures of biologically active piroxicam **2** and meloxicam **3**

Saccharin has also been useful in ionic liquids in which it forms complexes with metals like ruthenium as reported by Thai et al. which synthesized arene ruthenium bis-saccharinato complexes [(η^6-arene)Ru(sacc)$_2$(OH)$_2$], that can be used for the oxidation of secondary alcohols to give the corresponding ketones.[4]

Saccharin derivatives are also used as catalysts in the synthesis of various bioactive molecules. For example, Rai and Yadav described the use of *N*-iodosaccharin **4** as a catalyst in the formation of 1, 3-oxazines via [2+4] cycloadditions of imines and enones (Figure 3).[5] Similarly, pyridinium saccharinate salts act as competent recyclable acylation catalysts including 4-*N*,*N*-dimethylaminopyridinium saccharinate, 4-(1-pyrrolidinyl)pyridinium saccharinate, 2-*N*,*N*-dimethylaminopyridinium saccharinate, and pyridinium saccharinate.[6]



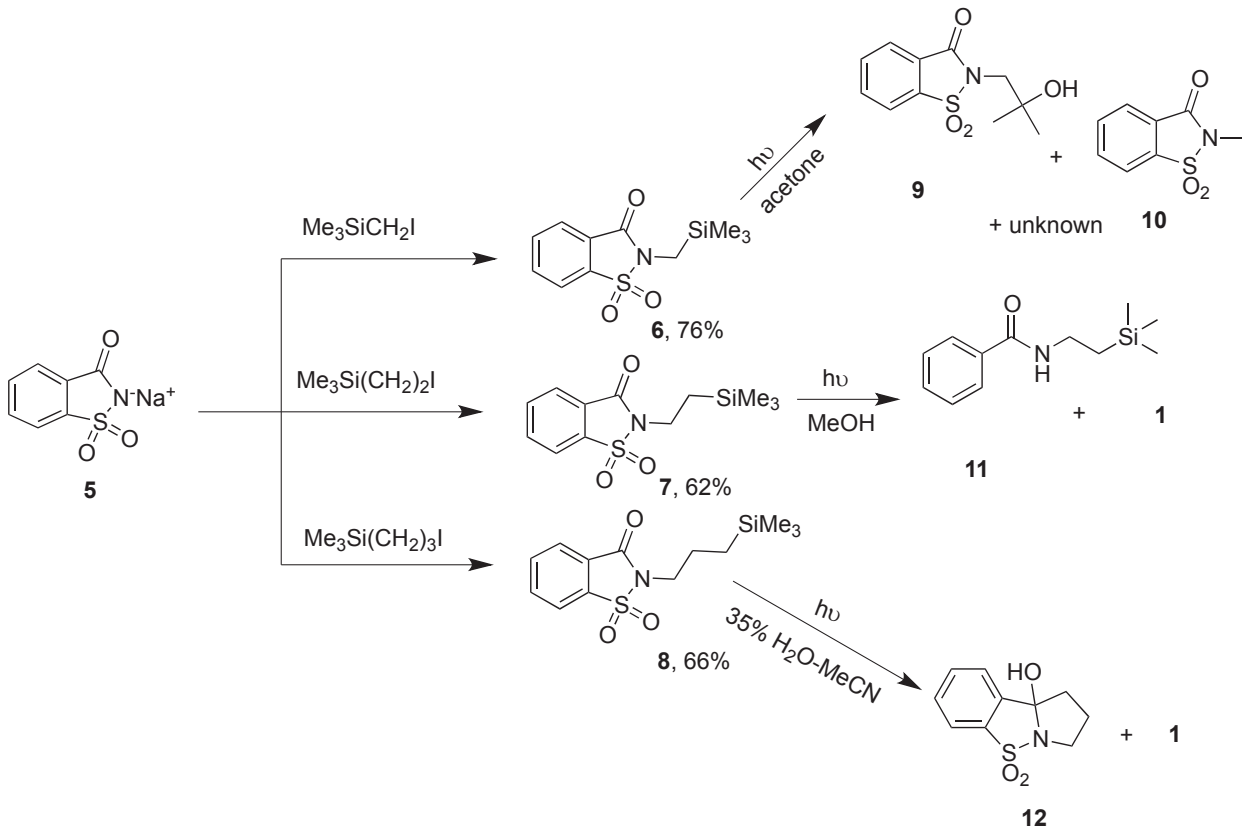
4

Figure 3. Structure of *N*-iodosaccharin **4**

2. REVIEW OF LITERATURE

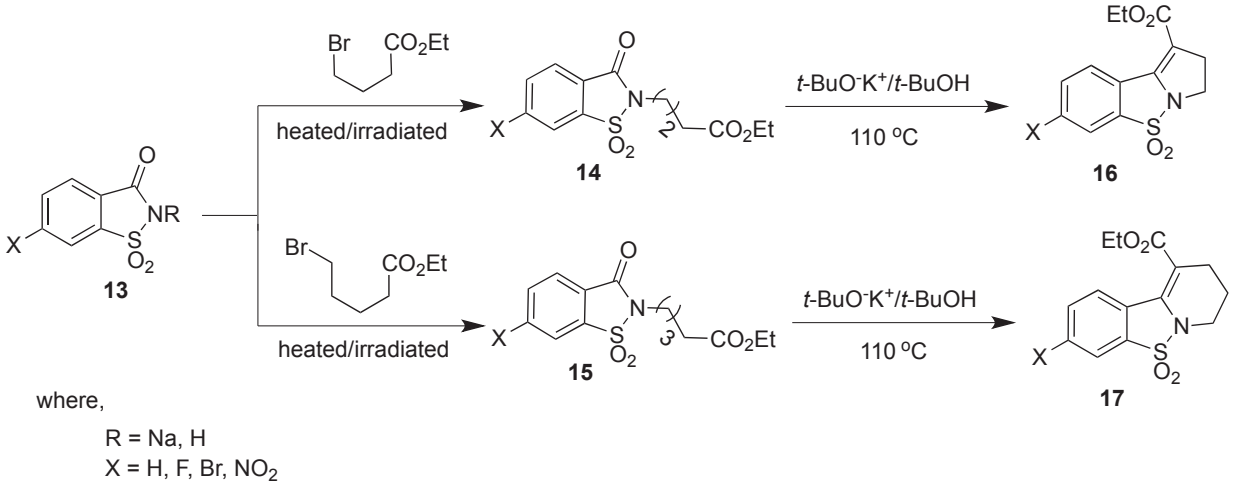
2-1. Synthesis of saccharin derivatives via N/O-alkylation reactions

Imides that contain α-silyl terminated electron donor/polydonor moieties can undergo various single electron transfer (SET) photochemical reactions that provide an effective and efficient strategy for the regioselective construction of highly functional heteromacrocyclic systems. This was demonstrated during a study of the photochemistry of *N*-[(trimethylsilyl)alkyl]saccharins by Cho et al. in 2010.[7] In their study, the photo-induced silyl-transfer reactions of *N*-[(trimethylsilyl)alkyl]saccharins were examined and various saccharin-based products were obtained. First, sodium saccharin **5** was alkylated in the presence of different trimethylsilylalkyl iodides to give the *N*-[(trimethylsilyl)alkyl]saccharin derivatives **6-8** in 76, 62 and 66% yield respectively. *N*-[(Trimethylsilyl)methyl]saccharin **6** was then irradiated in different types of solvents and in the presence of various additives such as methyl acrylate or acrylonitrile. However, using acetone as solvent, compound **6** upon irradiation afforded the solvent-incorporating tertiary alcohol **9**, *N*-methylsaccharin **10**, and an unidentified compound. When *N*-[(trimethylsilyl)ethyl]saccharin **7** was subjected to a photoreaction in the presence of methanol, it gave a mixture of benzamide **11** and saccharin **1**. Afterwards, the irradiation of *N*-[(trimethylsilyl)propyl]saccharin **8** using 35% H_2O-MeCN produced pyrrolizidine **12** and saccharin **1** (Scheme 1).



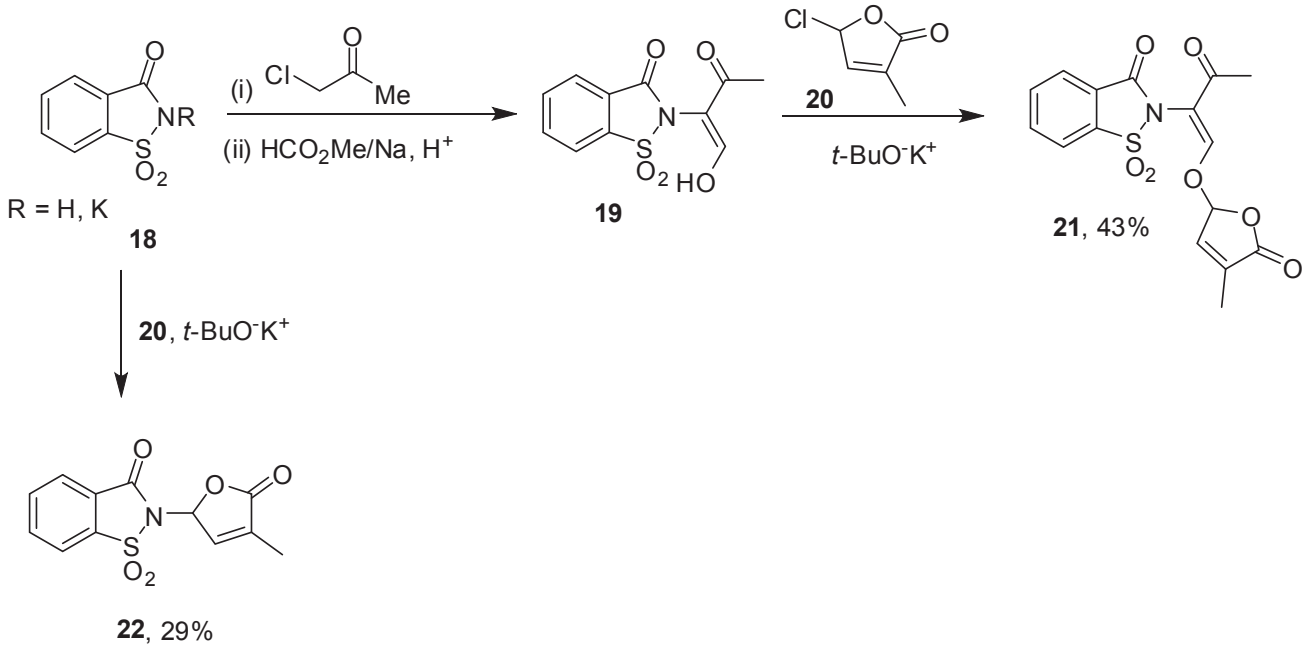
Scheme 1. Photochemical reaction of *N*-[(trimethylsilyl)alkyl]saccharins **6-8**

The saccharin anion is ambifunctional (i.e., in a nucleophilic reaction, it can react either via nitrogen or oxygen) based on the parameters employed, such as the temperature, solvent, type of cation and electrophile. Kinetic or thermodynamic conditions control the mode of action of ambident anions. The S_N1 character of the reaction facilitates the alkylation at the more electronegative atom of the ambident ion. However, with alkyl halides, saccharin anions undergo the reaction at the less electronegative nitrogen atom, resulting in different *N*-alkylated saccharin derivatives. With these considerations in mind, Jakopin and Dolenc performed *N*-alkylation of 6-substituted saccharins using heating or microwave irradiation.[8] Saccharin derivatives bearing electron withdrawing and electron donating substituents were alkylated to test that either the electronic properties of these functionalities altered the yield of the alkylation reaction or not. For this purpose, saccharin derivative **13** was treated with the bromoalkanoic acid ester either by heating for 3 h at 140 ºC or by irradiating in a microwave reactor for 15 minutes at 100 ºC, yielding the *N*-alkylated products, **14** and **15**, followed by further treatment with potassium *tert*-butoxide produced the fused polycyclic sultams, **16** (11-60%) and **17** (13-53%). These are useful in medicinal chemistry due to their hydrophilic nature (Scheme 2). Generally, the synthesis of the saccharin derivatives, **14** (13-87%) and **15** (19-89%), was achieved in excellent yields via microwave irradiation; however, with a fluorine substituted saccharin derivative, the reaction gave a high yield via the conventional heating process.



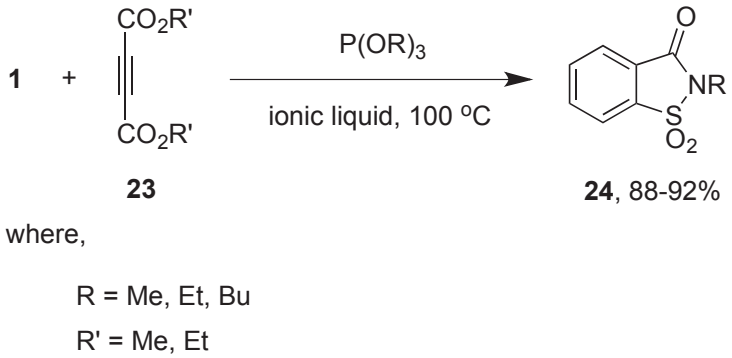
Scheme 2. *N*-Alkylation of saccharin derivative **13**

Strigolactones (SLs) are important due to their recent employment as plant hormones. Although these hormones have been isolated from the root sheddings of different plants, these can also be synthesized from simple starting materials. Considering their vital role in plant growth stimulation and in seed germination, Zwanenburg and Mwakaboko reported the concise synthesis of strigolactone SL analogues and mimics that were derived from saccharin.[9] The synthesis of the saccharin SL analogue was achieved via the reaction of potassium saccharinate **18** with chloroacetone followed by hydroxymethylidenation using methyl formate and metallic sodium, yielded enol **19**. Then, the coupling of enol **19** with chlorobutenolide **20** afforded saccharin SL analogue **21** in 43% yield. However, the direct coupling of saccharin **18** with chlorobutenolide **20** produced SL mimic **22** in 29% yield (Scheme 3).



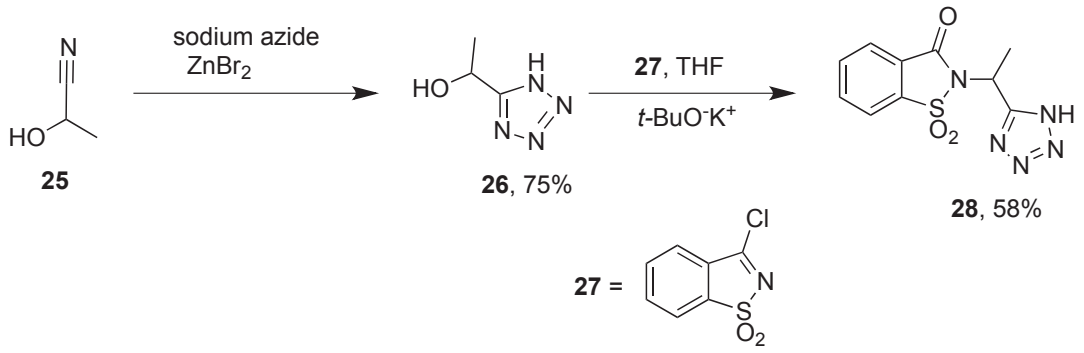
Scheme 3. Synthesis of SL analogue **21** and SL mimic **22** from saccharin **18**

N-Alkylation of heterocyclic compounds can be influenced by a variety of factors such as the temperature, solvent, reaction time and the nature of the electrophile used. Preliminary studies of the *N*-alkylation of heterocyclic compounds were preceded by industrially impracticable protocols such as microwave irradiation and heating. These protocols were accompanied with problems such as a long reaction time, poor reaction yields and the utilization of hazardous solvents. To overcome these difficulties, a new three-component, environmentally friendly and convenient one-pot procedure was developed by Hassanabadi and co-workers for the synthesis of *N*-alkylated saccharin.[10] In their study, saccharin **1** was treated with dialkyl acetylenedicarboxylate **23**, trialkyl phosphate and an ionic liquid, such as 1,3-dialkylimidazolium, at 100 °C for 8 h. As a result, the *N*-alkylated saccharin **24** was obtained in excellent yield (88-92%) (Scheme 4).



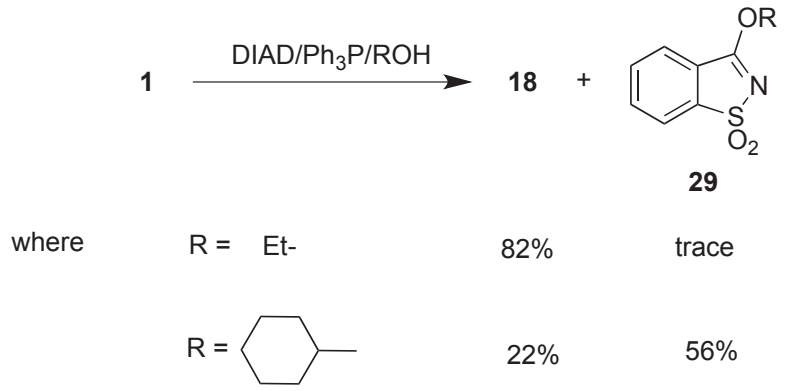
Scheme 4. Synthesis of *N*-alkylated saccharin derivative **24** from saccharin **1**

Tetrazoles and benzisothiazoles are important heterocyclic systems that are used in many medical, food industry and agricultural fields. With tetrazoles, most of these applications are due to the acidic fragment of tetrazole (i.e., -CN_4H, which can act as a ligand in the coordination chemistry through its four electron donor nitrogen atoms and forms different types of metal-organic structural frameworks). Similarly, the 1,2-benzisothiazol-3-one 1,1-dioxide anion can also coordinate with metal anions through hydrogen bonding. Considering the wide applications of tetrazoles and benzisothiazoles as multidentate ligands, great interest was focused on the synthesis of the tetrazole-saccharyl conjugate, 2-[1-(1*H*-tetrazol-5-yl)ethyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide, by Ismael et al. in 2012.[11] The methodology that they adopted to synthesize these compounds started from 2-hydroxypropanenitrile **25**, which was treated with sodium azide in the presence of zinc bromide under reflux to produce the tetrazole-based compound, **26** in 75% yield. Compound **26** was further treated with chlorinated compound **27** using potassium *tert*-butoxide to afford the required tetrazole-saccharyl compound, **28** in 58% yield (Scheme 5).



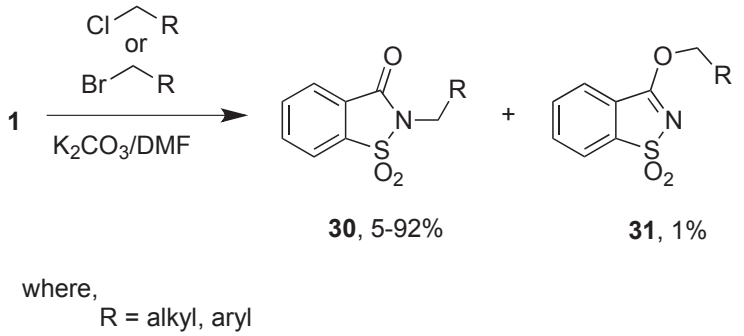
Scheme 5. Synthetic route leading to tetrazole-saccharyl conjugate **28**

The alkylation of saccharin can also be achieved by using alcohols rather than alkyl halides. In 2013, Wang and co-workers examined the alkylation reaction of saccharin under Mitsunobu conditions using various types of alcohols.[12] They found that the regioselectivity of the product depends upon the nature of the alcohol (i.e., less sterically hindered alcohols preferably produce *N*-alkylated saccharins in the highest yield and alcohols with a significant steric hindrance result in *O*-alkylated saccharins in the highest yield) (Scheme 6).



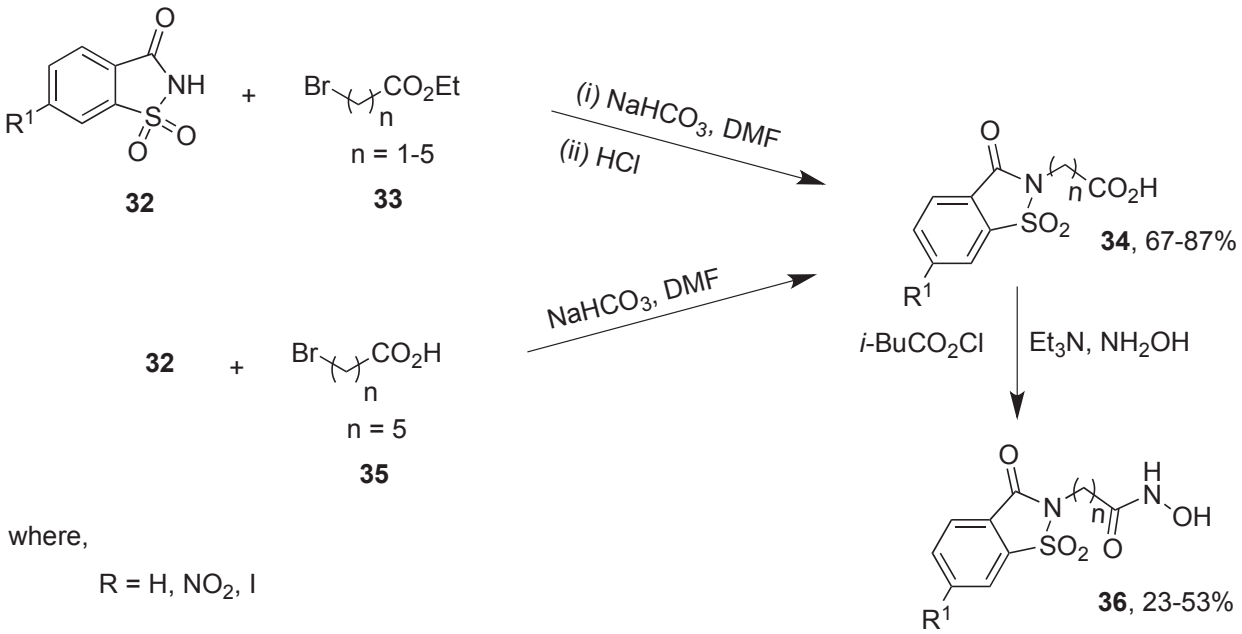
Scheme 6. Regioselective alkylation of saccharin **1**

In another approach, D'Ascenzio et al. and Carradori et al. reported a competent method for the synthesis of *N*-alkylated saccharin derivatives.[13,14] In their methodology, deprotonation of saccharin **1** was achieved by using anhydrous potassium carbonate, followed by the successive treatment of the generated saccharin anions with an alkyl halide in the presence of *N*,*N*-dimethylformamide at 80 ºC to produce *N*-alkylated compounds **30** (5-89%) (Along with a minor *O*-alkylated product **31** (1%)) (Scheme 7). These compounds were also tested for the inhibition of tumour-associated human carbonic anhydrase XII.



Scheme 7. Synthesis of *N*-alkylated saccharin derivatives, **30** and *O*-alkylated compound **31**, from saccharin **1**

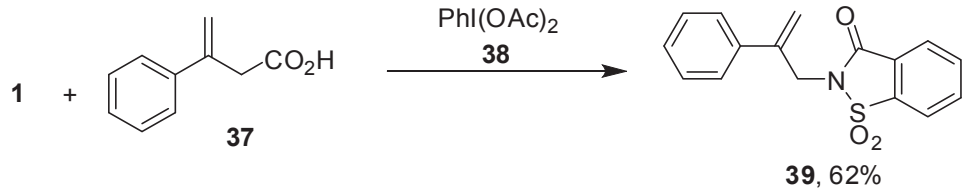
A variety of novel histone deacetylase (HDAC) inhibitors have already been designed such as *N*-hydroxybenzamide, tetrahydroisoquinoline and 1,3,4-thiadiazole. Among these three derivatives, tetrahydroisoquinoline exhibited the most significant antiproliferative activities. Because of the structural similarity with tetrahydroisoquinoline, saccharin was selected by Fang and co-workers as a cap group for HDAC inhibitors.[15] The coupling of saccharin **32** with ester **33** or the corresponding acid, **35**, followed by the addition of Et_3N, isobutyl chloroformate and hydroxylamine yielded saccharin-based hydroxamic acid **36** in 23-53% yield, which can be used as a histone deacetylase inhibitor (Scheme 8).



Scheme 8. Synthesis of compound **36** from saccharin **32**

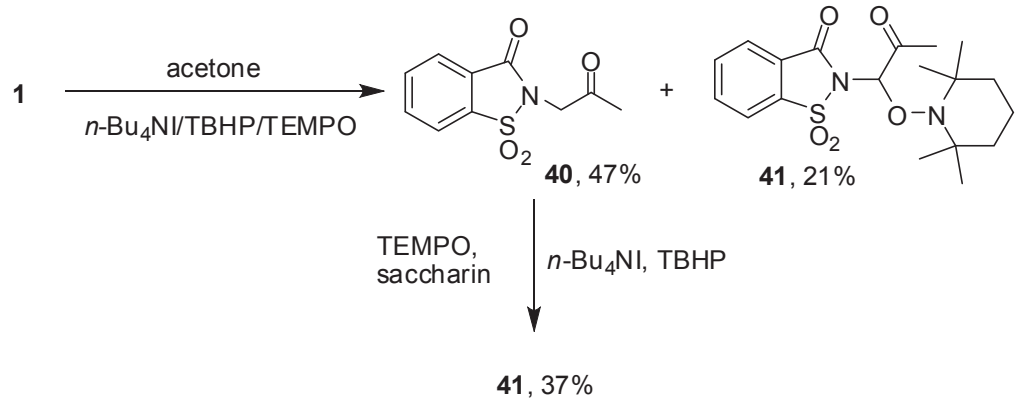
The decarboxylative functionalization of carboxylic acids is an important reaction in organic synthesis but has gained considerably less attention. This transformation involves the construction of a *C*-heteroatom bond, i.e., the *C*-*O* and *C*-*N* bonds. Thus, based on this consideration, a novel approach was developed by

Minakata and colleagues for the synthesis of *N*-alkylated saccharin derivatives **39**.[16] For this purpose, the oxidative decarboxylation of β,γ-unsaturated carboxylic acid **37** was performed using a hypervalent iodine(III) reagent **38** and saccharin **1**. This reaction resulted in the formation of unsaturated saccharin derivative **39** in 62% yield (Scheme 9).



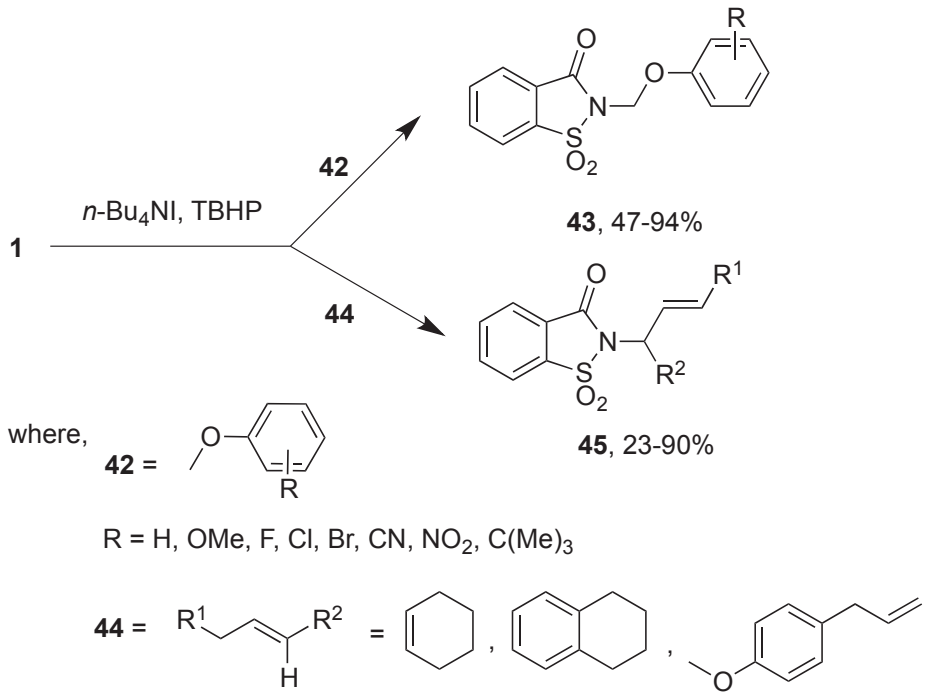
Scheme 9. Synthesis of saccharin derivative **37** using a hypervalent iodine(III) reagent **38**

In another study, the facile synthesis of *N*-alkylated saccharin derivatives was accomplished by Zhang and co-workers during their exploration of the scope and generalization of acetone α-imidation.[17] In their approach, different imides were used as a nitrogen source for the preparation of α-aminoketones. The imidation of ketones was performed by treating saccharin **1** with acetone in the presence of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), *n*-Bu_4NI as the catalyst and TBHP as the oxidant to obtain the desired saccharin derivatives, **40** (47%) and **41** (21 and 37%) (Scheme 10).



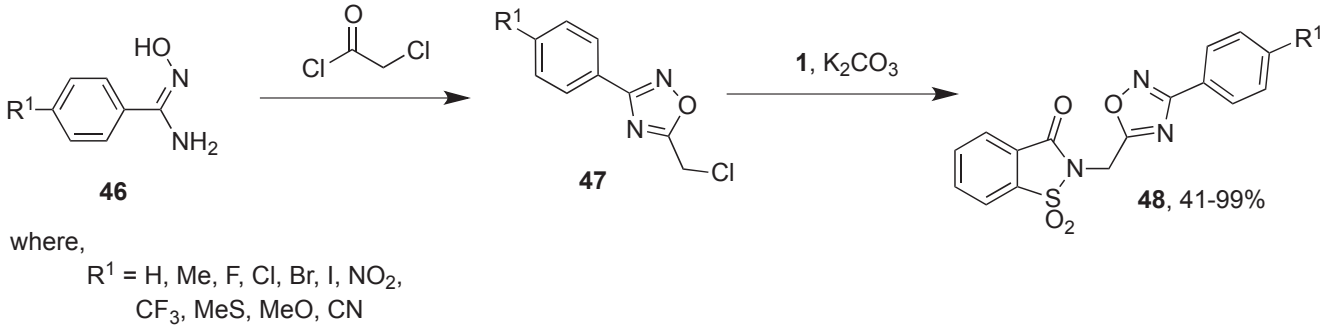
Scheme 10. Synthesis of α-amino ketones using saccharin **1** and *n*-Bu_4NI

For a long time, no examples of the oxidative amidation of C(sp^3)-H bonds adjacent to oxygen atoms of methyl aryl ethers were found until a highly regioselective layout was proposed by Sun and co-workers.[18] They described the imidation of different types of aryl ethers, **42**, by coupling with saccharin **1** under metal free conditions. In their protocol, *n*-Bu_4NI was used as the catalyst and TBHP was used as the oxidant, which yielded a new class of saccharin derivatives, **43** in 47-94% yield. In 2016, Lv and co-workers designed *N*-allylic saccharin **45** (unsaturated carbocyclic nucleoside) (23-90% yield) employing the same reaction conditions on saccharin **1** and alkene **44**.[19] These nucleosides can be used to generate important therapeutic agents (Scheme 11).



Scheme 11. Synthesis of saccharin derivative **43** and *N*-allylic saccharin **45** from saccharin **1** using TBHP and *n*-Bu_4NI

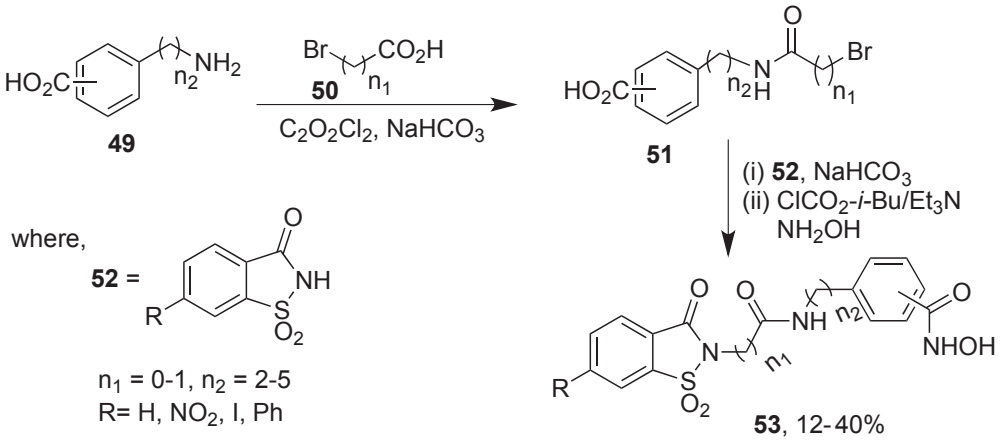
To synthesize a variety of heterocyclic compounds that are related to amidoximes, a concise preparation of new saccharin-based heterocyclic compounds was reported by Durust et al. in 2015.[20] For this purpose, monoamidoxime **46** was first treated with chloroacetyl chloride to give oxadiazole **47**, which was then reacted with saccharin **1** to produce the oxadiazolylmethyl substituted compound, **48** in 41-99% yield (Scheme 12). After synthesizing different saccharin derivatives, they evaluated the anti-tumour, anti-protozoal and antimicrobial activities of these compounds.



Scheme 12. Synthesis of 2-[(3-(*p*-substituted phenyl)-1,2,4-oxadiazol-5-yl)methyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide **48**

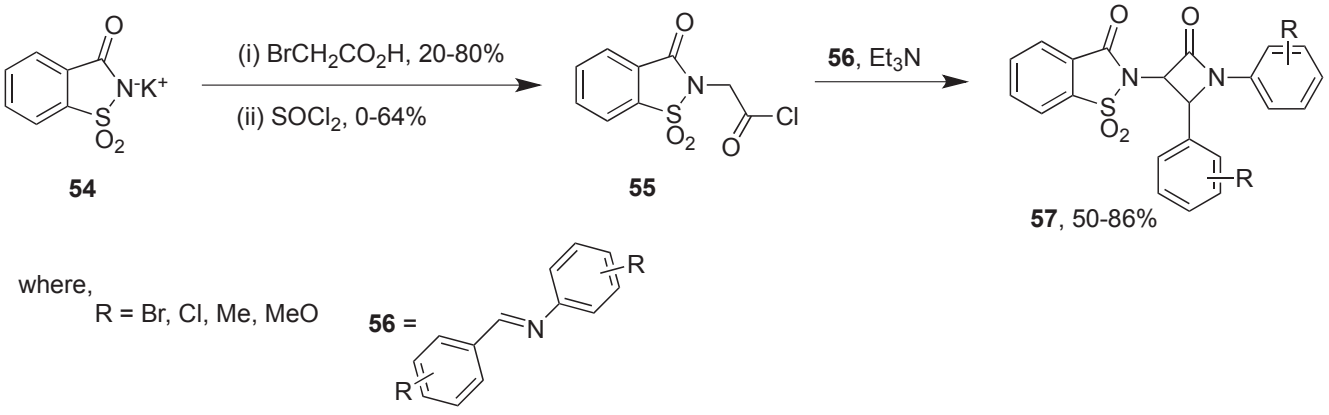
Saccharin-based *N*-hydroxybenzamides were synthesized as histone deacetylases inhibitors by Fang and colleagues in 2015.[21] The methodology began from the reaction of amino substituted benzoic acid **49** with bromocarboxylic acid **50** in the presence of oxalyl chloride, lead to the formation of compound **51**.

Compound **51** was further treated with substituted saccharin **52** and then reacted with isobutyl chloroformate in the presence of hydroxylamine to form the saccharin-based *N*-hydroxybenzamide, **53** in 12-40% yield (Scheme 13).



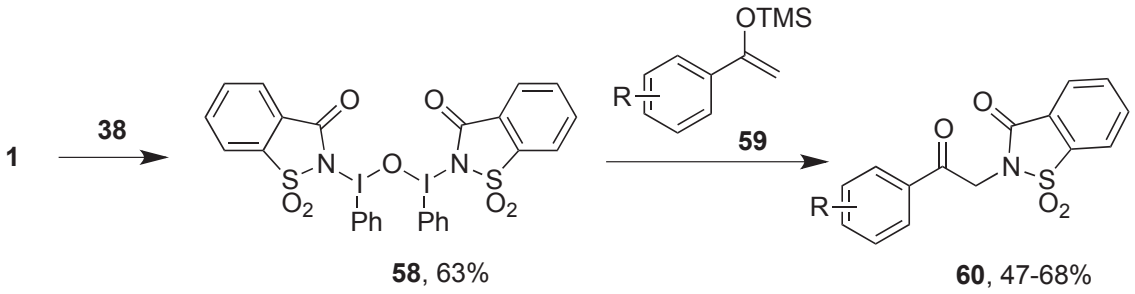
Scheme 13. Synthesis of *N*-hydroxybenzamide **53** from saccharin **52**

Synthesis of saccharin derivatives that have the *β*-lactam ring, which is the central motif of their antibacterial properties, was first reported by Islami and co-workers.[22] Their methodology involved the reaction of (*N*-saccharinyl)acetic acid with the Mukaiyama reagent and aromatic imine **56** in the presence of Et_3N, which yielded azetidinone **57** in 50-86% yield. This reaction was explained by two separate mechanisms involving important intermediates, a zwitterion and the saccharinyl ketene (Scheme 14).



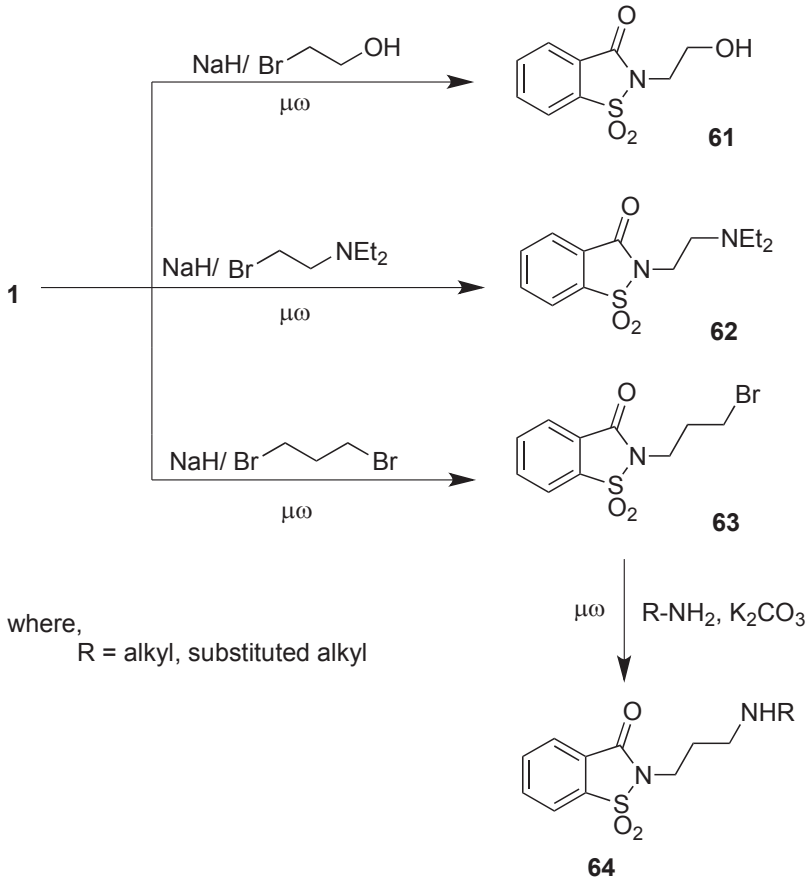
Scheme 14. Synthesis of the *β*-lactam substituted saccharin derivative **57**

In an effort to search for highly reactive electrophilic aminating reagents, Yoshimura et al. investigated the synthesis of saccharin-based μ-oxoimidoiodane.[23] In their protocol, the saccharin-based hypervalent iodine compound, **58** (63%), was prepared by the reaction of saccharin **1** with diacetoxyiodoarene **38**. Compound **58** was further treated with silyl enol ether **59** to produce α-aminated carbonyl compound **60** in 47-68% yield (Scheme 15).



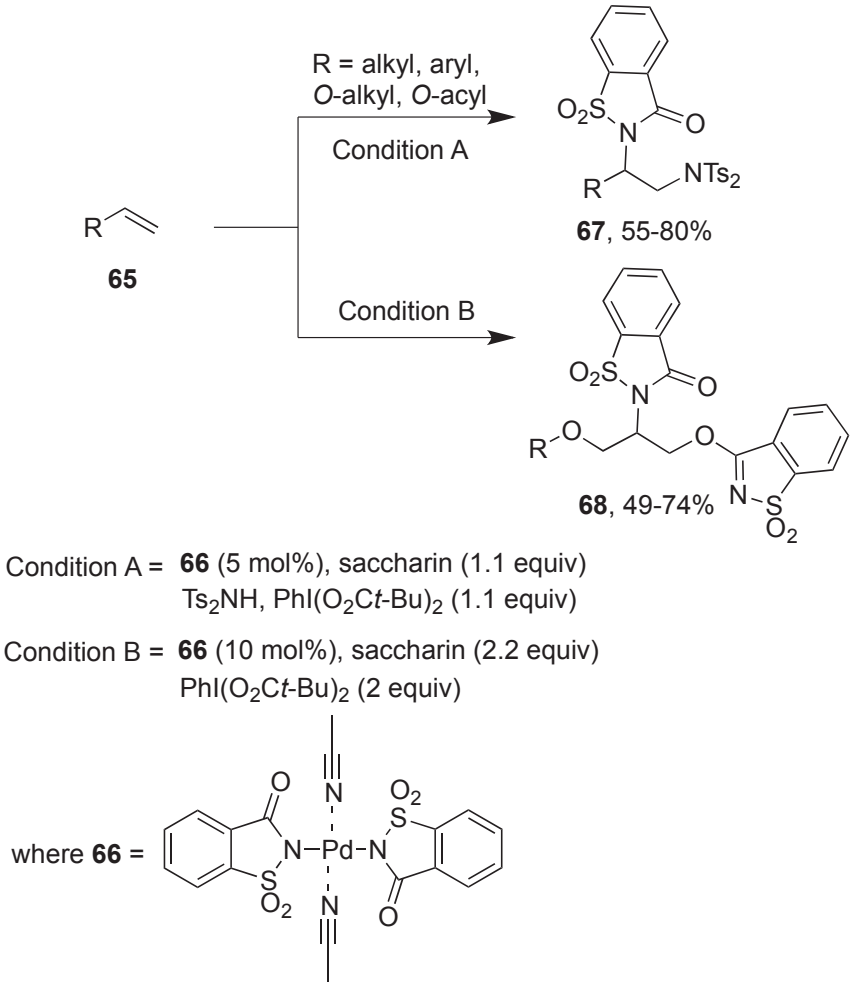
Scheme 15. Synthesis of the saccahrin-based hypervalent iodine compound, **58**, leading to the α-aminated product, **60**

To develop anti-amyloidogenic compounds, in 2015, Bag et al. proposed a method for synthesis, biological evaluation and numerous multifunctional approaches for different sulfonamide-based small molecules such as saccharin and other equivalents.[24] Their methodology involved the reaction of saccharin **1** with different alkyl halides under microwave irradiation to form the respective sulfonamides, **61-64** (Scheme 16). These compounds were found to be effective for treating Alzheimer's disease.



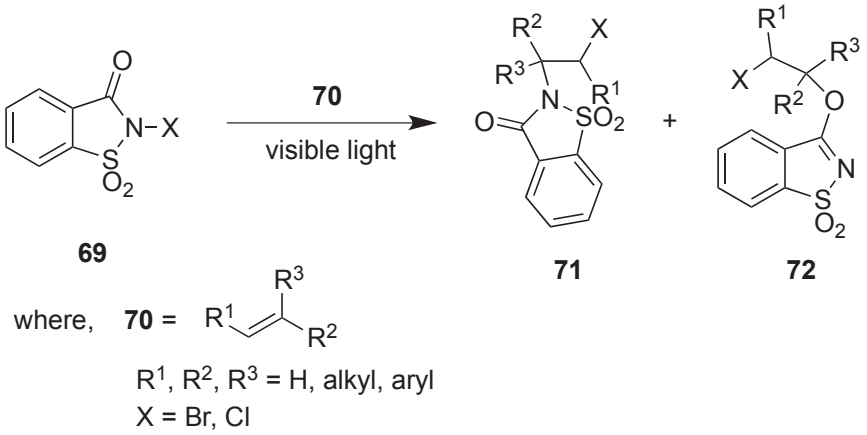
Scheme 16. Synthesis of different derivatives, **61-64**, from saccharin **1**

To modify, simple hydrocarbons by inducing 1,2-heteroatom in organic molecules, oxidative difunctionalization of alkenes is an important phenomenon. To achieve such difunctionalization, palladium catalyzed reactions play a significant role. For searching such reaction conditions that are appropriate for intermolecular reactions is particularly important. In this regard, limited number of methods have been adopted up till now comprising dihalogenation, dioxygenation, aminooxygenation, aminofluorination, and diamination reactions. Keeping this view in mind, Muniz and colleagues developed a method for the diamination and aminooxygenation of alkenes with saccharin.[25] For this purpose, a variety of alkenes including allylic ethers and esters **65** were treated with saccharin by employing condition A (saccharin (1.1 equiv), bissaccharido palladium (II) complex **66** (5 mol%) and $PhI(O_2C\textit{t}\text{-}Bu)_2$ (1.1 equiv)) and condition B (saccharin (2.2 equiv), bissaccharido palladium (II) complex **66** (10 mol%) and $PhI(O_2C\textit{t}\text{-}Bu)_2$ (2 equiv)) to yield diaminated product **67** (55-80%) and aminooxygenated product **68** (49-74%) respectively. It was observed that complex **66** is only stabilized in the environment of hypervalent iodine reagents, so, $PhI(O_2C\textit{t}\text{-}Bu)_2$ was used for this purpose along with complex **66** (Scheme 17).

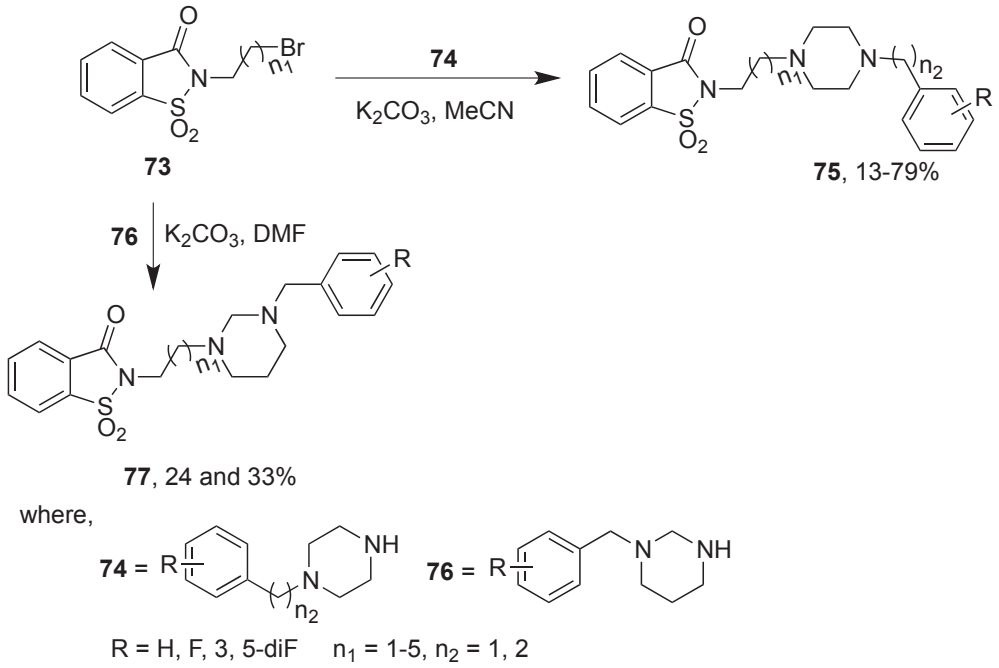


Scheme 17. Palladium catalyzed diamination and aminooxygenation of alkene **65**

Halogenated compounds which act as versatile synthons in organic chemistry can be produced by halofunctionalization of alkenes. By employing different reaction conditions including Lewis acids, bases and photolysis, first the halogenium ion or aziridium ion intermediates are formed which can then be converted into desired halogenated skeletons. Among these conditions, photolytic process has limited applications as it requires severe conditions and gives intense reactivity and low selectivity. Focusing on this, Luo and coworkers designed a technique for the synthesis of haloamines and haloethers by using visible-light.[26] They treated *N*-halosaccharin **69** with a variety of alkenes **70** in the presence of visible-light to afford bromoamidation **71** and bromoetherification products **72** in high yields (75-95%) (Scheme 18).



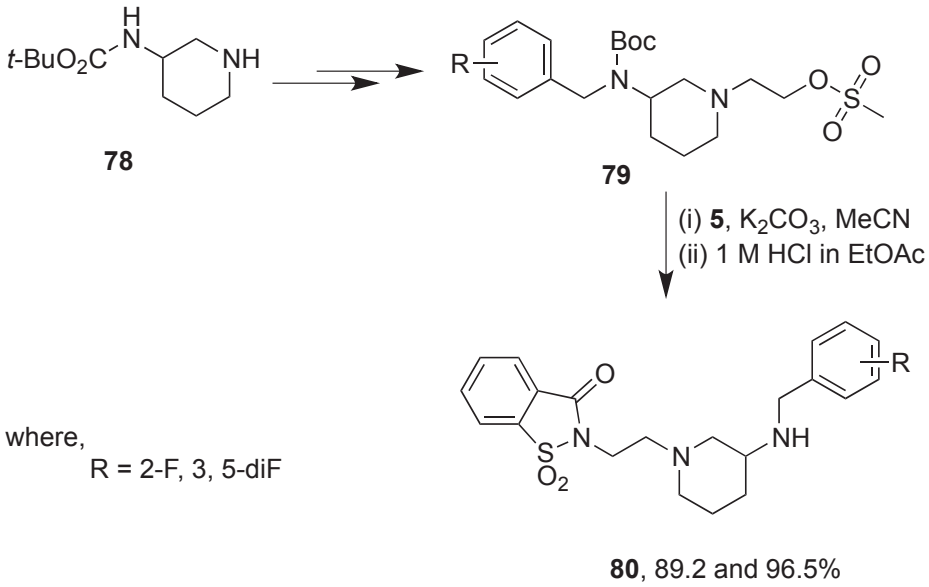
Scheme 18. Synthesis of haloamines **71** and haloethers **72** in the presence of visible-light



Scheme 19. Synthesis of piperazine **75** and hexahydropyrimidine derivatives **77** by the alkylation of saccharin **73** with *N*-phenylalkylheterocyclic derivatives, **74** and **76**, respectively

Alzheimer's disease (AD) is a chronic form of dementia affecting elderly people which are above 74 years old. 40 Million people are involved in this disease world widely which are expected to increase three fold upto 2050. So there is a dire need of search for such effective agents which can control AD competently. Focusing on this, the research group of Malawska reported the synthesis of a new class of saccharin derivatives which act as anti-AD agents with cholinesterase, β-secretase and β-amyloid inhibitory activities.[27] Their work started from the synthesis of piperazine **75** and hexahydropyrimidine derivatives **77** which were obtained by the alkylation reaction of *N*-phenylalkylpiperazine derivatives **74** or hexahydropyrimidine **76** with saccharin **73** respectively (Scheme 19).

Afterwards, the synthesis of 3-aminopiperidine derivatives **80** was started from the (*tert*-butylpiperidin-3-yl)carbamate **78** which under different reaction conditions converted into mesylates **79**. Sodium saccharin **5** and mesylate **79** through alkylation reaction and after Boc-deprotection was converted into required derivatives (Scheme 20).

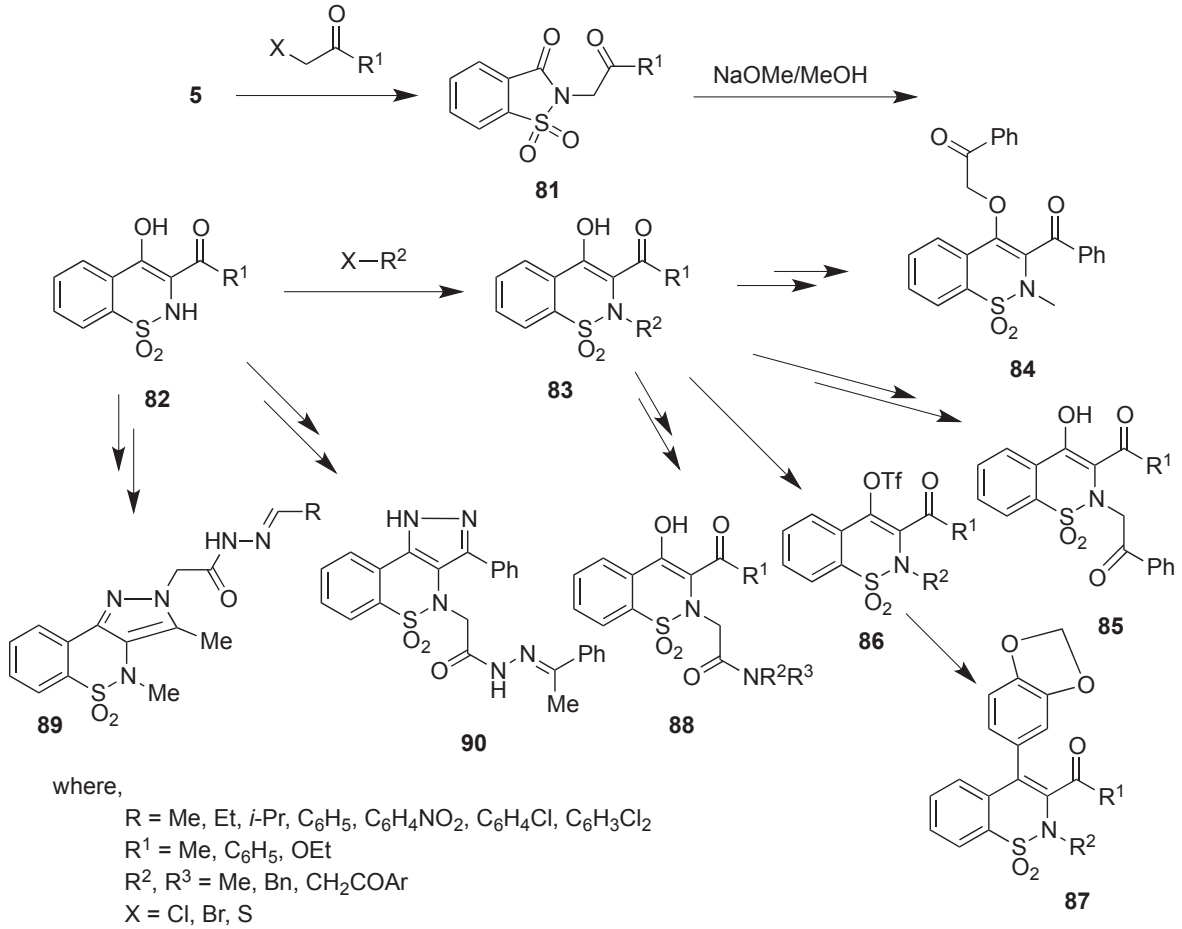


Scheme 20. Synthesis of 3-aminopiperidine derivatives **80** by the alkylation of sodium saccharin **5** with mesylates **79**

2-2. Benzothiazine derivatives

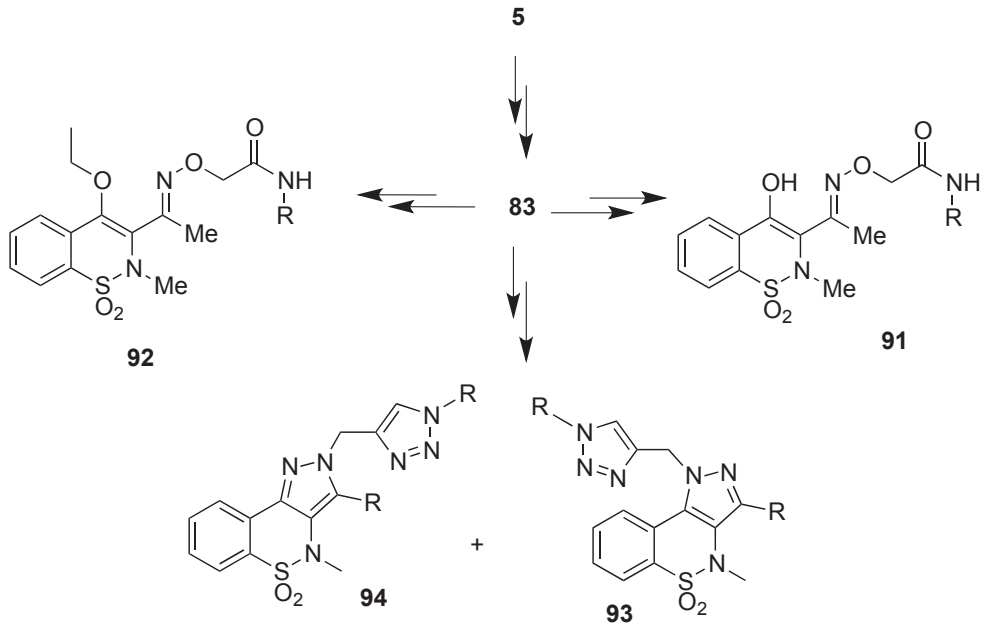
Benzothiazine derivatives are of great importance in the pharmaceutical industry and in organic synthesis because they show significant biological activities. A minor change in the structure of benzothiazine derivatives significantly affects their biological activities. A diverse range of benzothiazine derivatives can be synthesized from a simple precursor such as sodium saccharin. All of these derivatives can be obtained by following a similar protocol. In general, the reaction of sodium saccharin **5** with α-haloketone or α-haloester resulted in the saccharin-based ketone or ester **81**, respectively. Next, sodium methoxide

was added to methanol, which resulted in a Gabriel-Colman rearrangement to yield the benzothiazine derivatives, **82**. The benzothaizine derivatives, **82**, were further alkylated to give compound **83**. Compounds **82** and **83** produced different benzothiazine derivatives under suitable conditions. Kim et al. reported different *O*- and *N*-alkylated benzothiazines, **84-88**, in 2010 and in 2011 which could be used as 11β-hydroxysteroid dehydrogenase 1 inhibitors.[28,29] Ahmad et al. and Aslam et al. reported different pyrazole-based benzothiazine derivatives, **89** and **90**, using compound **82**.[30,31] In 2013, Shahwar et al. also described the synthesis of the simple 1,2-benzothiazine derivative, **83**, using compound **82**, and the resulting compound **83** was evaluated for antioxidant activities (Scheme 21).[32]

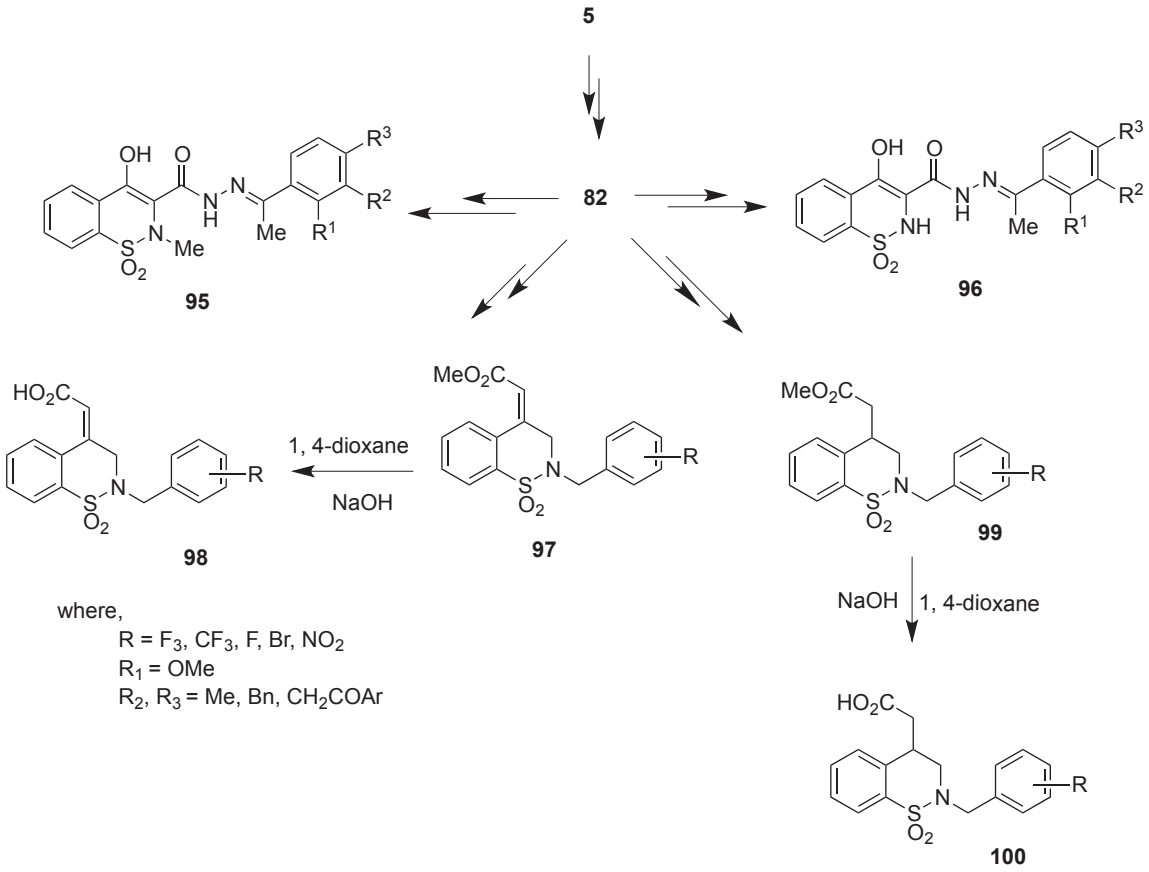


Scheme 21. Synthesis of cyclic sulfonamides **84-88** and the pyrazole-based benzothiazines, **89** and **90**, using sodium saccharin **5**

Similarly, Gannarapu et al. constructed 1,2-benzothiazine 1,1-dioxide-3-ethanone oxime *N*-aryl acetamide ether derivatives, **91** and **92**, which are anti-inflammatory agents.[33] In 2014, Narsaiah and co-workers synthesized the pyrazole based benzothiazines, **93** and **94**, using compound **83**. Biological evaluation of the compounds **93** and **94** reveals that they exhibit antimicrobial and antioxidant activities (Scheme 22).[34]



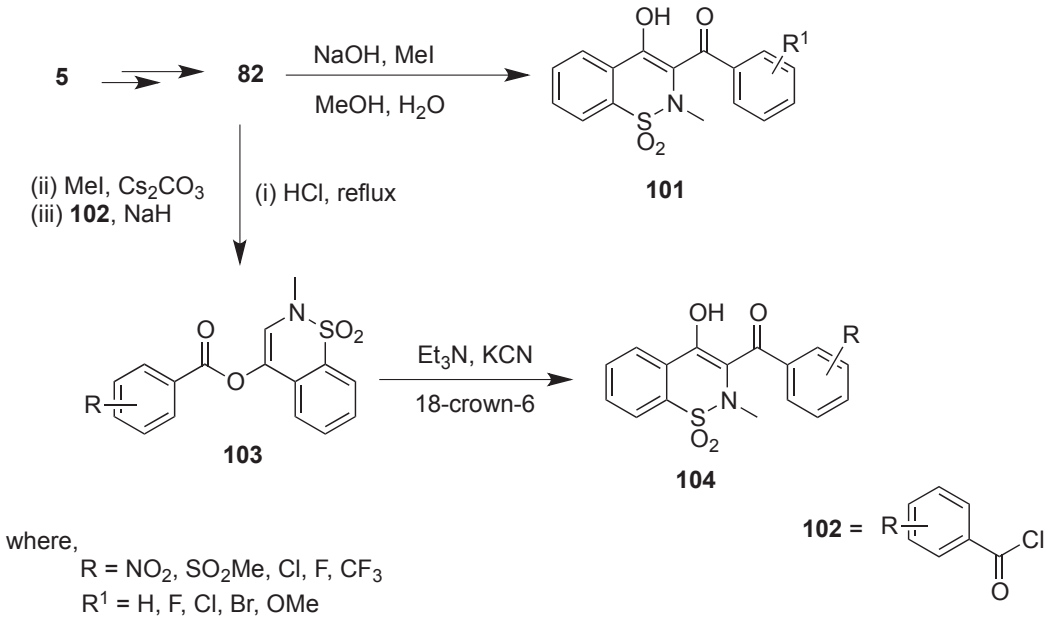
Scheme 22. Synthesis of the benzothiazineacetamide ether derivatives, **91** and **92**, and the pyrazole-based benzothiazines, **93** and **94**, from sodium saccharin **5**



Scheme 23. Synthesis of the benzothiazinecarbohydrazide derivatives, **95** and **96**, and the benzothiazine-carboxylate derivatives (**97-100**)

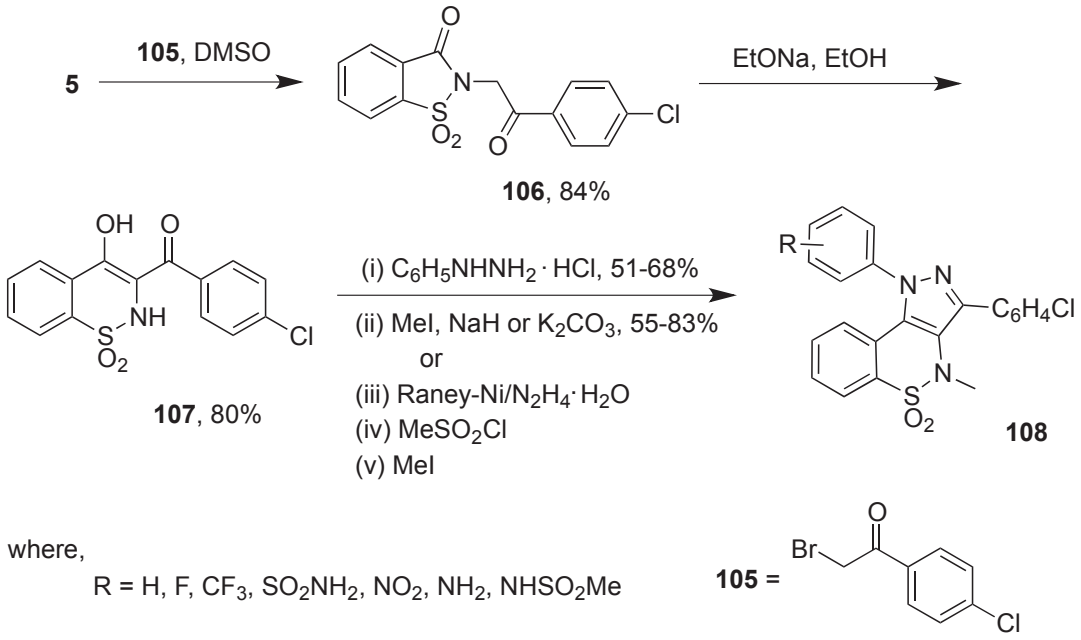
In 2011, Zia-ur-Rehman and co-workers reported the synthesis of the benzothiazinecarbohydrazide derivatives, **95** and **96**, which possess good antimicrobial activities.[35] In the same year, Chen et al. reported the preparation of the benzothiazinecarboxylate derivatives (**97-100**) from compound **82** which were evaluated for their inhibition of aldose reductase (Scheme 23).[36]

As an extention of their work on the determination of herbicidal activities, Xu and co-workers synthesized the (2-benzoylethen-1-ol)-based benzothiazine derivatives, **101** and **104**, from benzothiazine **82** which firstly when treated with methyl iodide converted into respective benzothiazine derivative **101**.[37] The target compound, **104**, was synthesized via another highly developed method in which compound **82** was reacted with conc. HCl followed by the treatment of caesium carbonate, methyl iodide and benzoyl chloride **102** under refluxing conditions afforded compound **103**, which was further reacted with potassium cyanide and 18-crown-6 ethers to form the desired product **104** (Scheme 24).

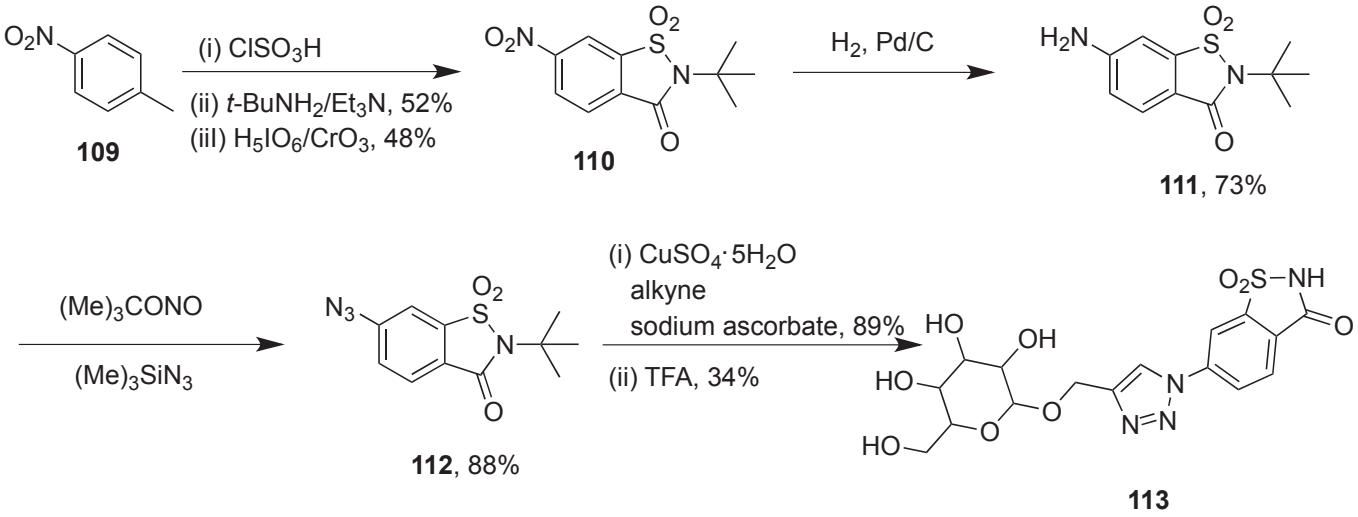


Scheme 24. Synthesis of the benzothiazine-based compounds, **101** and **104**

The pyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxides, which have been used as inhibitors against a bacterium (*Staphylococcus aureus*), were synthesized by Sabatini and co-workers.[38] The strategy involved the reaction of sodium saccharin **5** with 2-bromo-1-(4-chlorophenyl)ethanone **105**, which afforded *N*-alkylated saccharin **106** in 84% yield. After Gabriel-Colman ring expansion, **106** was converted into benzothiazine **107** in 80% yield. Then, the conversion of **107** into pyrazole-substituted benzothiazine **108** (55-83%) was successfully achieved either by using phenylhydrazine hydrochloride and methyl iodide or adopting an alternative pathway that used Raney-Ni, hydrazine, methanesulfonyl chloride and methyl iodide (Scheme 25).



Scheme 25. Synthesis of pyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide **108** from sodium saccharin **5**



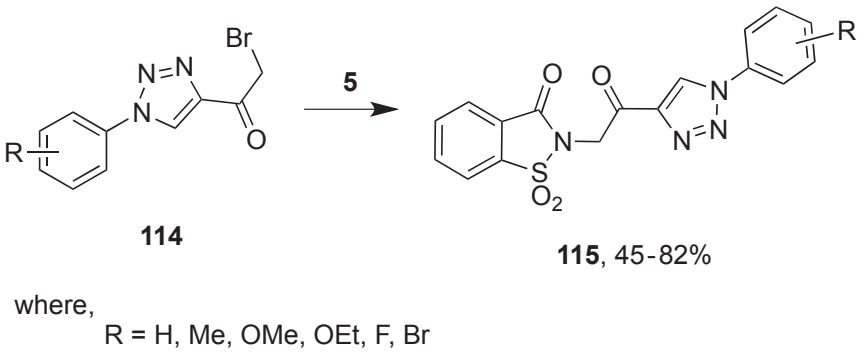
Scheme 26. Synthesis of cyclic secondary sulfonamide **113**

2-3. Triazole-based saccharin derivatives

1,2,3-Triazole is an important aromatic heterocyclic moiety that displays diverse biological activities. By introducing this moiety into various organic molecules, compounds show moderate dipole character, hydrogen bonding capability, rigidity and stability. Keeping these considerations in mind, the synthesis of cyclic secondary sulfonamides that have the triazole ring system via saccharin and its derivatives was reported by Moeker et al. in 2014.[39] These derivatives were found to be good inhibitors of cancer-related carbonic anhydrase enzymes (CA IX). In their study, the selectivity and affinity of saccharin for CA IX enzymes was also demonstrated. 6-Nitrosaccharin **110** was obtained by using nitrotoluene **109**,

chlorosulfuric acid and *tert*-butylamine, followed by subsequent oxidation. After that, compound **110** was transformed into 6-aminosaccharin **111** via catalytic reduction, followed by subsequent treatment with *t*-butyl nitrite and azidomethylsilane to obtain 6-azidosaccharin **112** which was derivatized into the triazole-based compound, **113**, in the presence of an alkyne, sodium ascorbate and copper sulfate (Scheme 26).

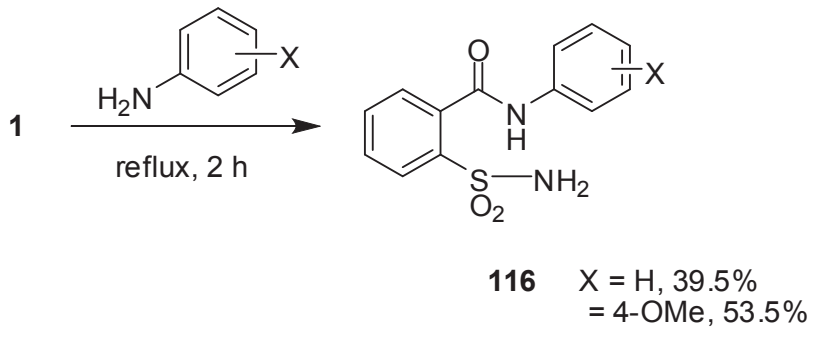
To evaluate the agricultural chemical activities of saccharin, synthesis of a series of saccharin derivatives that bear the triazole moiety was reported by the research group of Wei.[40] Their methodology involved the coupling of the triazole-based compound, **114**, with sodium saccharin, which resulted in the synthesis of the target compounds **115** in 45-82% yield that exhibited herbicidal activity (Scheme 27).



Scheme 27. Synthesis of triazole-based compound **115** using sodium saccharin

2-4. Ring opening/ ring expansion reactions

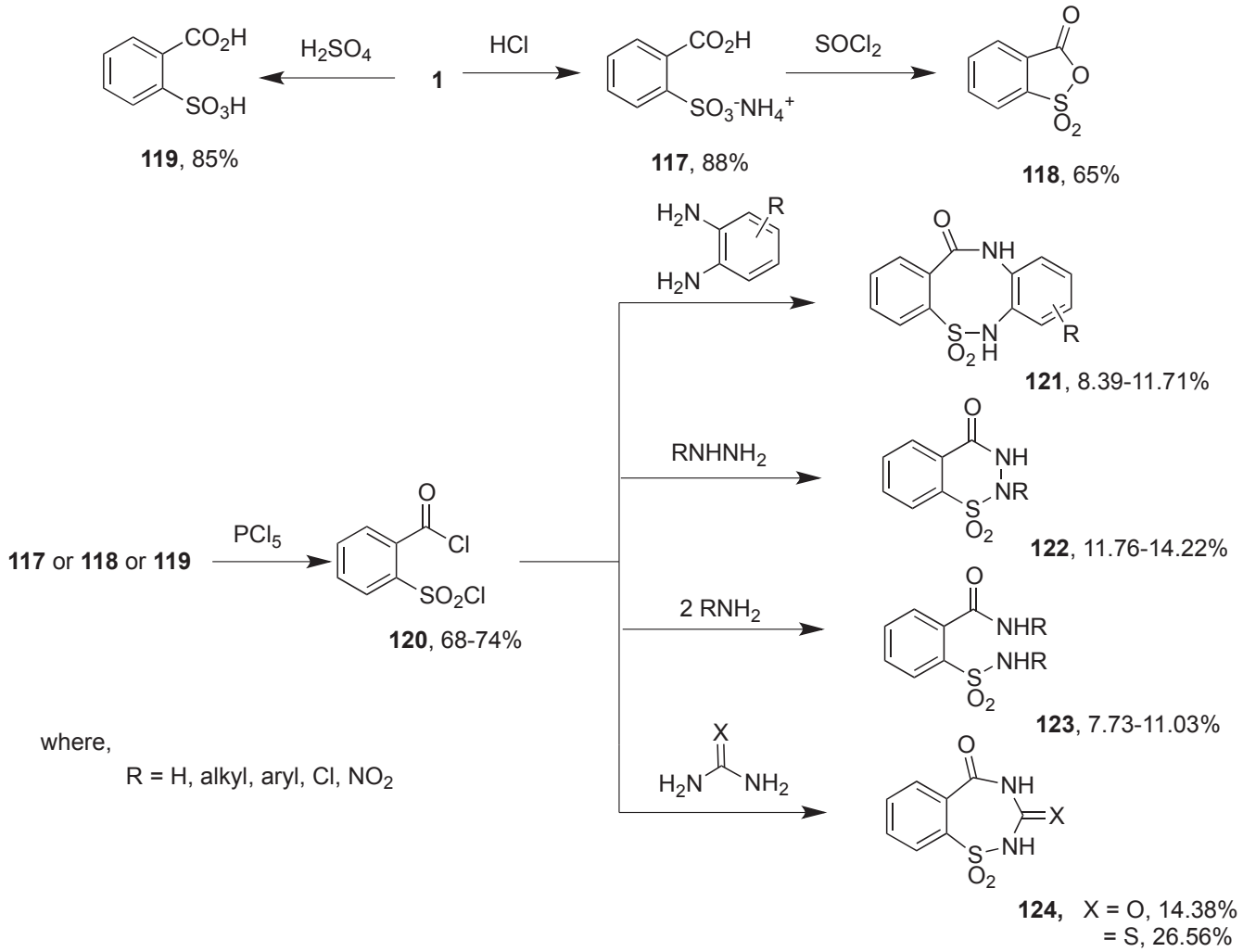
A simple and straightforward synthesis of the *o*-[(phenyl/*p*-methoxyphenyl)carbamoyl]benzene-sulfonamide derivative, **116**, was proposed by Siddiqui et al. in 2010.[41] The synthesis of **116** involved the reaction of saccharin **1** and an excess of aniline under refluxing conditions for 2 h (Scheme 28).



Scheme 28. Synthesis of *o*-[(phenyl/*p*-methoxyphenyl)carbamoyl]benzenesulfonamides (**116**) from saccharin **1**

In another approach, the synthesis of cyclothiadiazanones and aminosulfonylbenzamides from saccharin was reported by Ramana and Reddy.[42] First, the hydrolysis of saccharin **1** with HCl and H_2SO_4 yielded

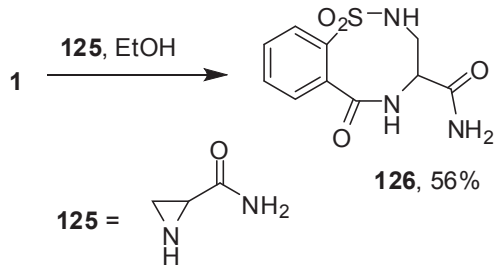
1,2-diacids **117** (88%) and **119** (85%), respectively. The reaction of **117** with thionyl chloride produced 2-sulfobenzoic anhydride **118** in 65% yield. Then, chlorination (of **117**, **118** or **119**) with PCl_5 afforded 2-chlorosulfonylbenzoyl chloride **120** (68-74%), which was condensed with various amines to produce the required products i.e., when it was treated with *o*-phenylenediamine, dibenzothiadiazocinones **121** (8.39-11.71%) was obtained. However, upon treatment with hydrazine or phenylhydrazine, benzothiadiazinetrione **122** was produced in 14.22 and 11.76% respectively. The reaction of **120** with aniline or aliphatic diamines afforded the acyclic aminosulfonylcarboxybenzamides, **123** (7.73-11.03%), and the condensation of **120** with urea and thiourea gave benzothiadiazepinone **124** in 14.38 and 26.56% yield respectively (Scheme 29).



Scheme 29. Synthesis of cyclothiadiazanones and aminosulfonylbenzamides from saccharin **1**

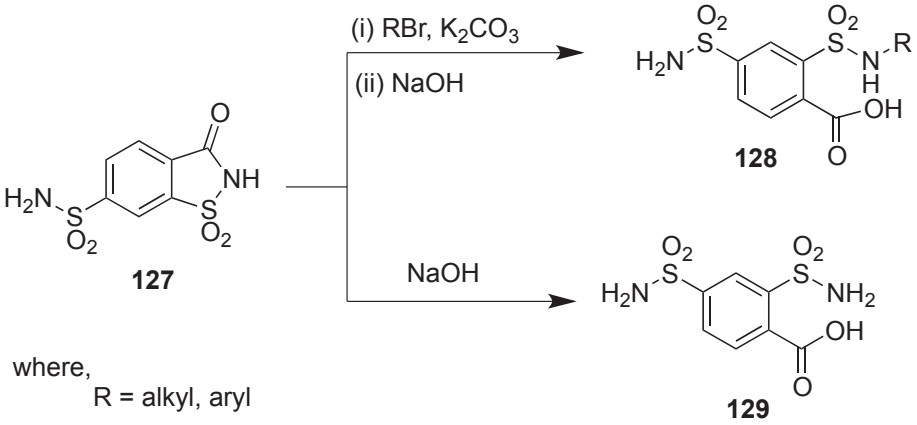
The concise synthesis of the 8-membered heterocyclic compound (6-oxo-3,4,5,6-tetrahydro-2*H*-1,2,5-benzothiadiazocine-4-carboxamide 1,1-dioxide **126**) was proposed by Žalubovskis and co-workers.[43] Their domino process utilized simple starting precursors such as saccharin

1 and leakadine **125**. In their strategy, an intermediate was formed by *N*-alkylation of aziridine **125** with saccharin **1**, which underwent intramolecular nucleophilic substitution via the expansion of the ring to produce the targeted compound, **126** in 56% yield (Scheme 30).



Scheme 30. Synthesis of the 8-membered heterocyclic compound **126** from saccharin **1** and leakadine **125**

In 2015, Ivanova et al. prepared *N*-alkylated 6-sulfamoylsaccharin derivatives and assayed their activities as carbonic anhydrase inhibitors.[44] 6-Sulfamoylsaccharin **127** and its alkylated product, which was produced under alkaline hydrolytic conditions, yielded the bissulfamoylbenzoic acids, **128** and **129** (Scheme 31).

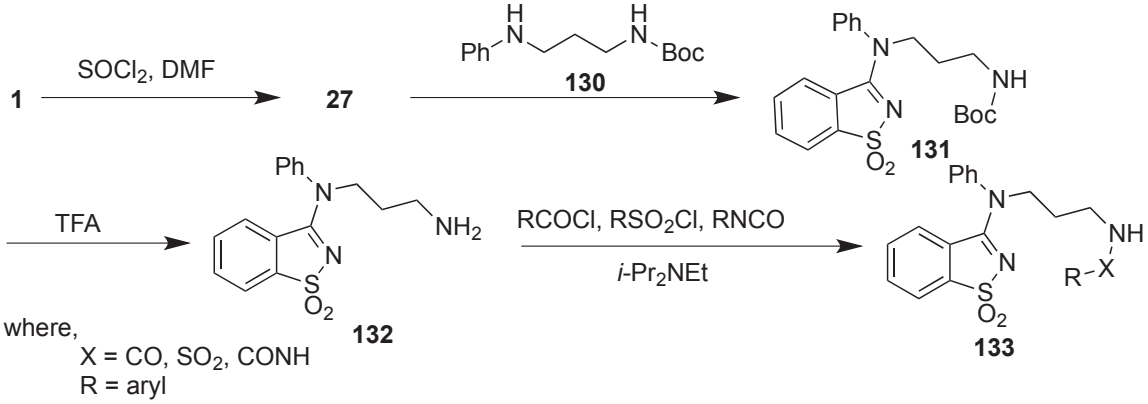


Scheme 31. Synthesis of bissulfamoylbenzoic acids **128** and **129** from 6-sulfamoylsaccharin **127**

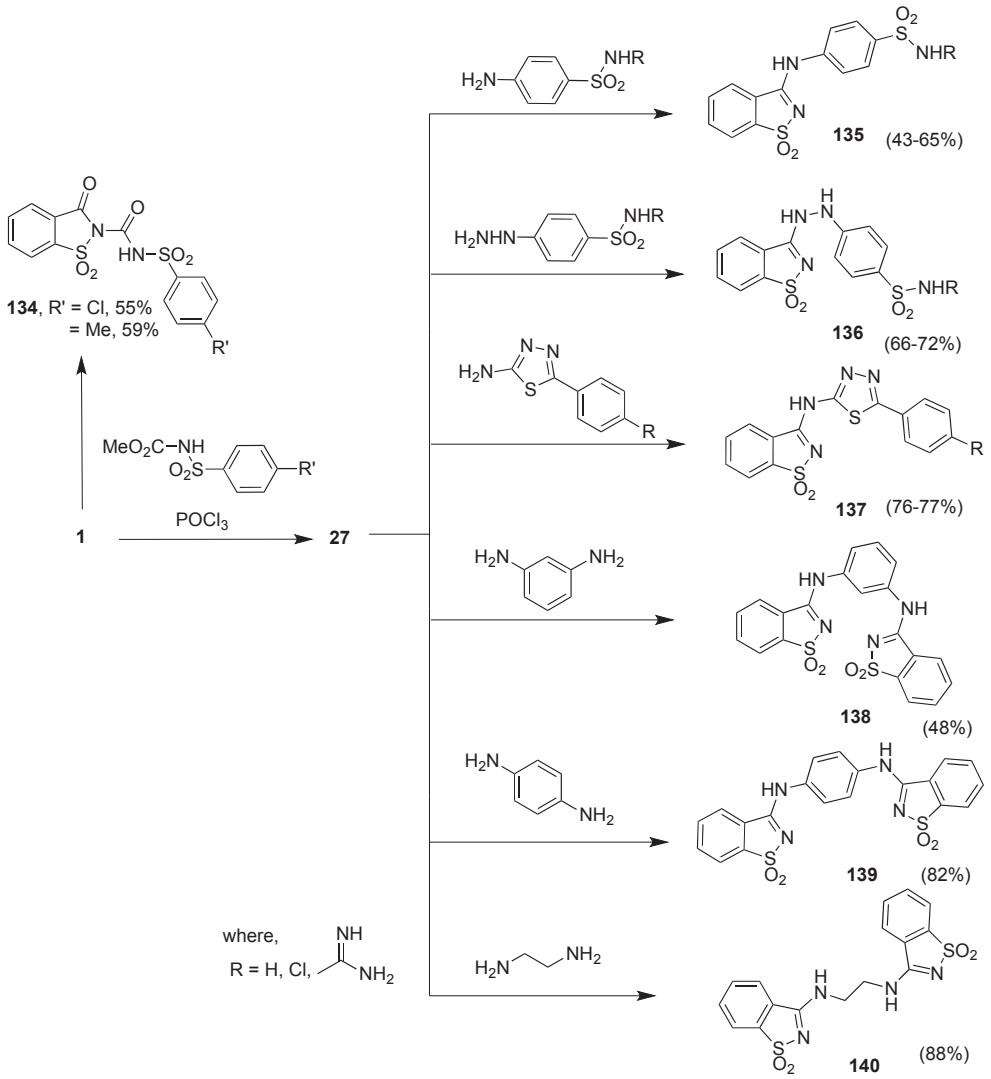
2-5. Reactions with amines/hydrazides

An efficient synthesis of different saccharin derivatives, such as *N*-{3-[1,1-dioxido-1,2-benzothiazol-3-yl)(phenyl)amino]propyl}benzamide, was reported by Haffner and colleagues and these derivatives exhibited inhibitory activities against Kv 1.3 (voltage gated potassium channels).[45] It has been suggested that the inhibition of Kv 1.3 may improve insulin activity and regulate body weight via increased energy expenditure. The preparation of these compounds began from the reaction of saccharin **1** with thionyl chloride to generate the chlorinated compound, **27**, which was reacted with the Boc-protected diamine, **130**, to produce the coupled product, **131**. After removing the

Boc-protection, amine **132** was treated with acid chloride, sulfonyl chloride or isocyanate to give the respective amides, sulfonamides or urea derivatives (Scheme 32).



Scheme 32. Synthesis of saccharin-based benzamides **133** from saccharin **1**

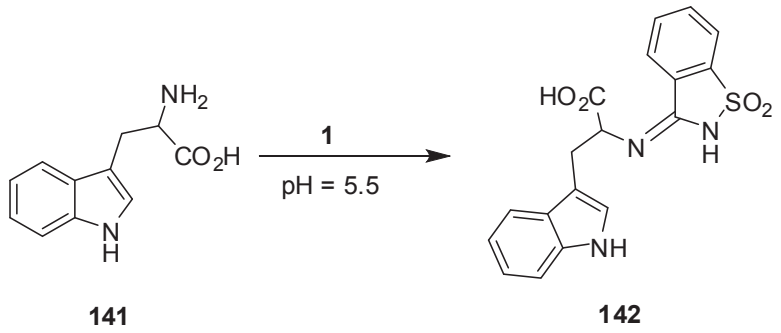


Scheme 33. Synthesis of the benzo[*d*]isothiazole derivatives, **134-140**, from saccharin **1**

A series of substituted quinazoline and 1,1-dioxobenxo[*d*]isothiazole derivatives were synthesized by Amin et al. in 2011.[46] In their approach, saccharin **1** was reacted with *N*-[(4-methylphenyl)sulfonyl]carbamic acid methyl ester and was converted into *N*-substituted saccharin **134** (55 and 59%). Saccharin **1** was also reacted with phosphoryl chloride and produced the chlorinated compound, **27**, which further yielded benzisothiazole derivatives **135-140** upon reaction with sulfonamide, 4-hydrazinosulfonamide, 2-amino-5-(4-chlorophenyl/phenyl)-1,3,4-thiadiazole, 1,3-phenylenediamine, 1,4-phenylenediamine, and 1,2-ethylenediamine, respectively (Scheme 33).

2-6. Synthesis of saccharin-based Schiff bases

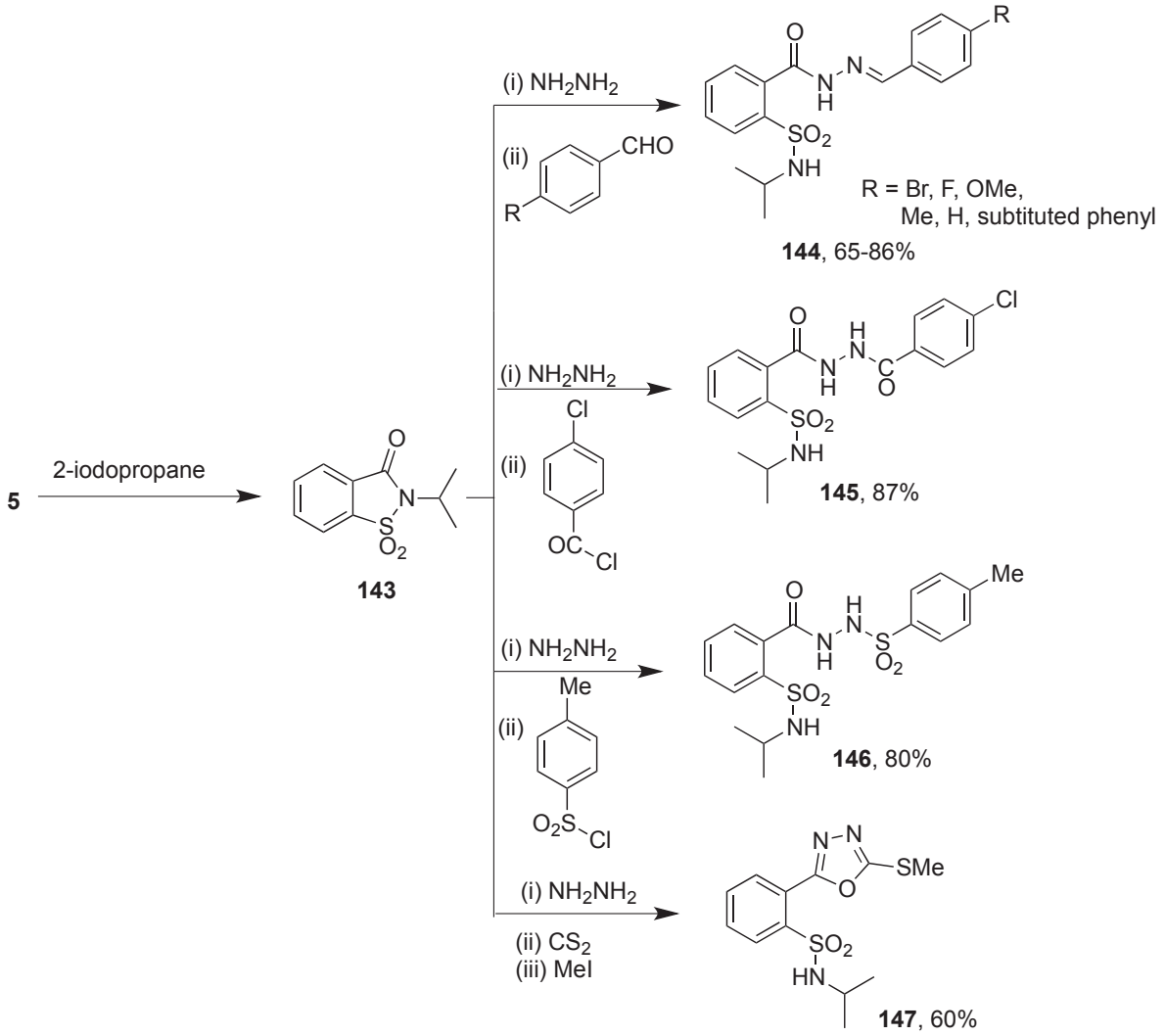
Tryptophan is an amino acid and an important starting material for the synthesis of various drugs. In 2010, Cakir and Bicer reported a new method for the synthesis of a novel Schiff base from saccharin **1** and tryptophan **141**.[47] An aqueous solution of tryptophan **141** was added to saccharin **1** and the pH of the mixture was set to *ca*. 5.5 using NaOH. The reaction proceeded at approximately 45 ºC for 4 h, and the Schiff base, **142**, was obtained (Scheme 34).



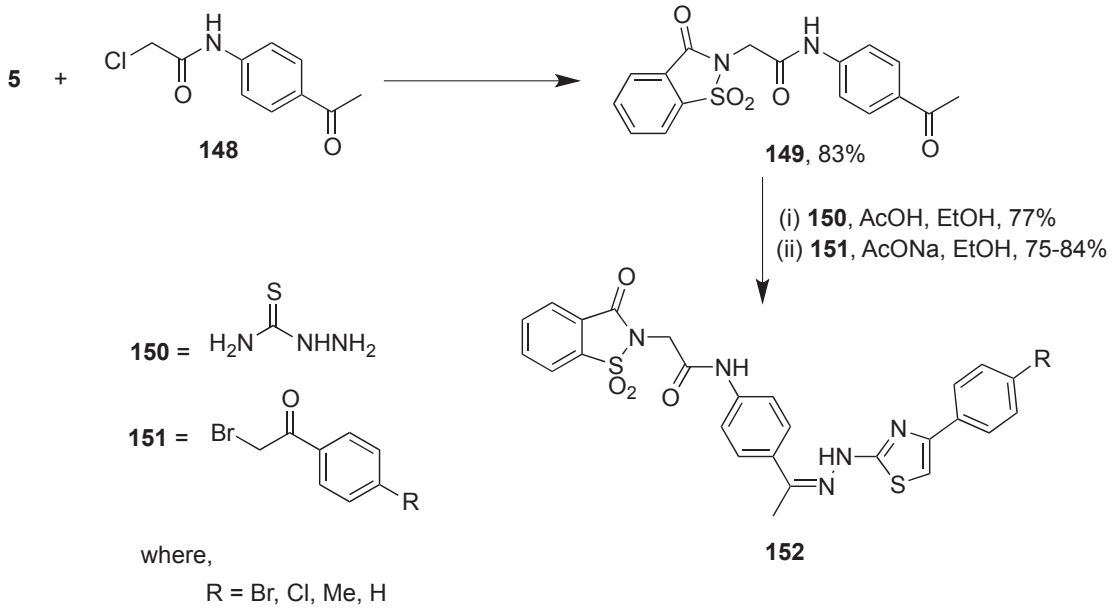
141 **142**

Scheme 34. Synthesis of the novel Schiff base **142** from tryptophan **141** and saccharin **1**

In another study, different new derivatives of saccharin, such as benzenesulfonamide and benzisothiazolone, were prepared by El-Sabbagh in 2013, and they evaluated the antiviral activities of the synthesized derivatives.[48] They converted sodium saccharin **5** into *N*-isopropyl-saccharin **143** using 2-iodopropane, which yielded hydrazide when it was allowed to react with hydrazine hydrate. Hydrazide was further derivatized into benzenesulfonamide **144** (65-86%) using aromatic aldehydes or converted into benzenesulfonamides **145** (87%) and **146** (80%) using *p*-chlorobenzoyl or *p*-toluenesulfonyl chlorides, respectively, or it afforded benzenesulfonamide **147** (60%) using carbon disulfide and methyl iodide (Scheme 35).



Scheme 35. Synthesis of a new series of benzenesulfonamides, **144**-**147**, using sodium saccharin **5**

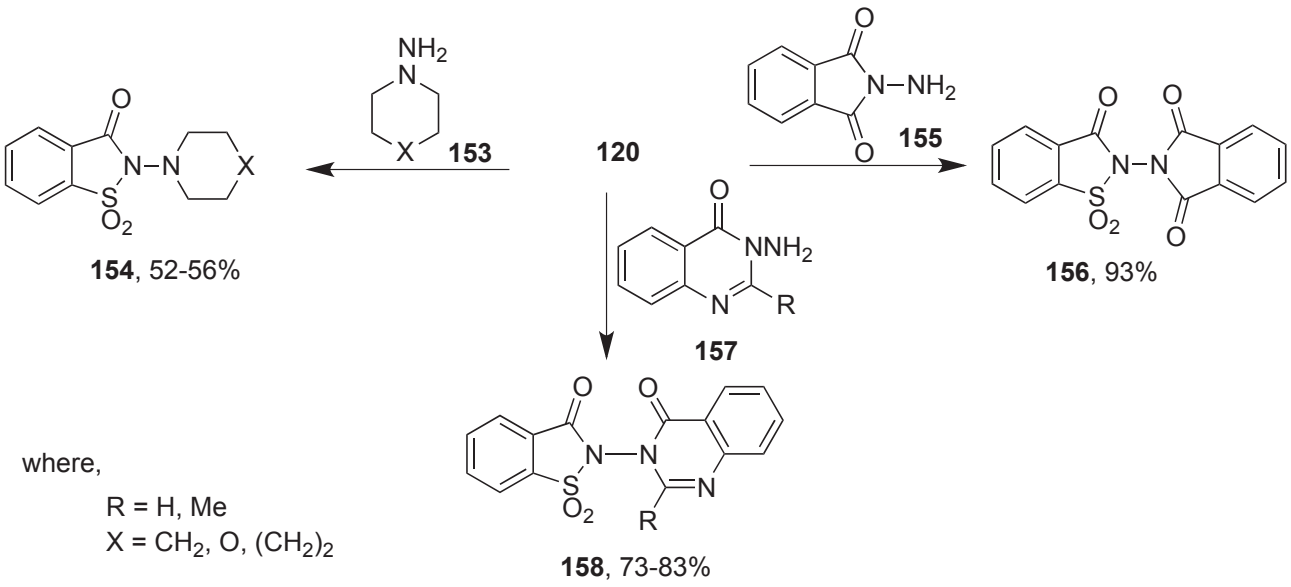


Scheme 36. Synthesis of a new series of benzisothiazolone **152** from sodium saccharin **5**

Furthermore, when sodium saccharin **5** was refluxed with acetamide **148**, acetamide derivative **149** (83%) was formed. Afterwards, the condensation of compound **149** with thiosemicarbazide **150**, followed by the addition of phenacyl bromide **151**, afforded the benzisothiazolone derivative, **152** in a good yield range (Scheme 36).

2-7. *N*-*N*'-Linked benzothiazoles

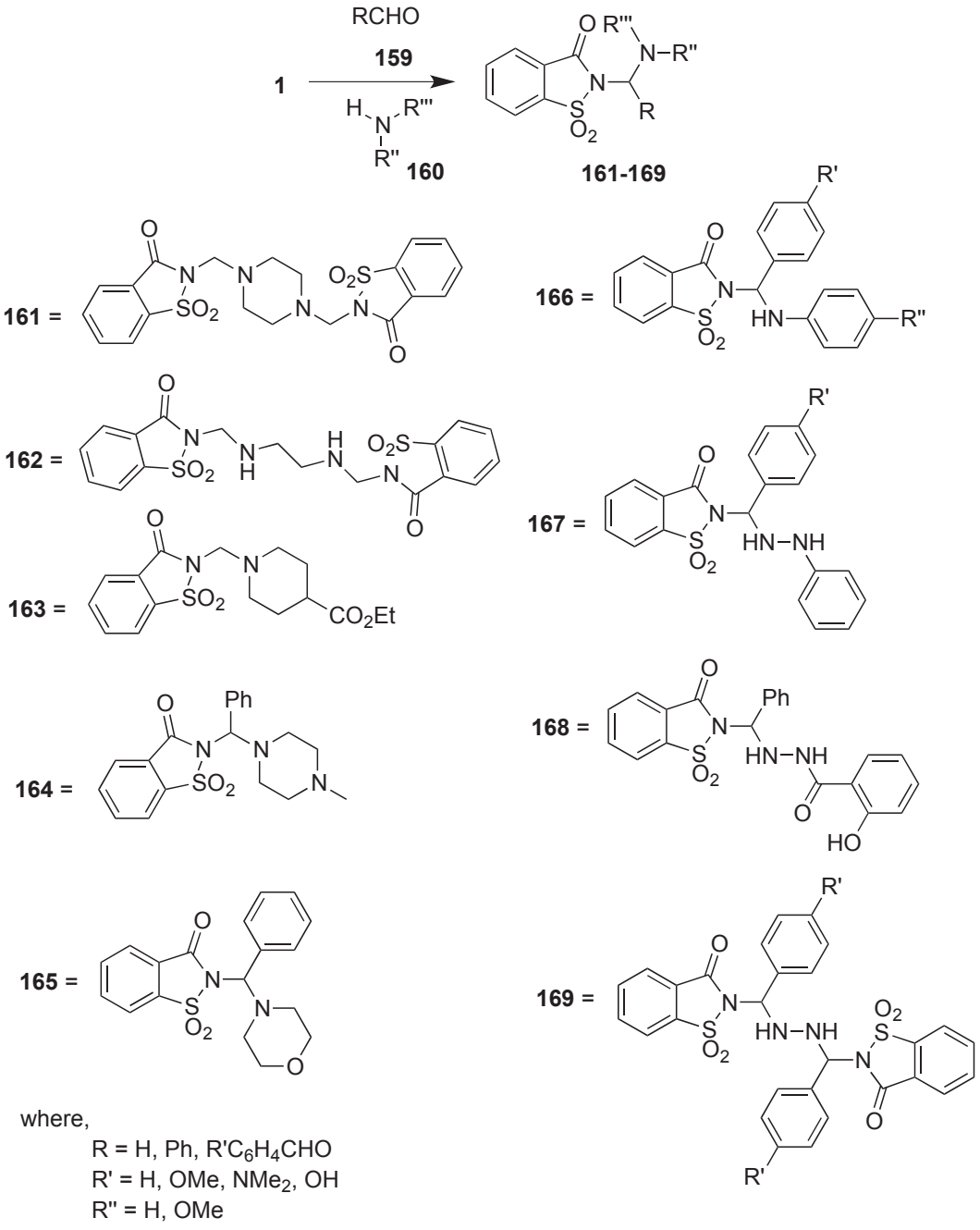
In practice, *N*-alkylation of saccharin has been confined to only *N*-alkyl or *N*-aryl derivatives, and no heterocyclic derivative was synthesized having the *N*,*N*′ connection until Zakharova et al. in 2010 described the synthesis of *N*,*N*′-linked 1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides, which showed inhibitory activity toward human leukocyte elastase (HLE) and acetylcholinesterase (AChE).[49] The reaction of the *N*-amino heterocycles, **153**, **155** and **157**, with 2-chlorosulfonylbenzoyl chloride **120** yielded different *N*-substituted benzisothiazol-3(2*H*)-one 1,1-dioxides, **154**, **156** and **158**, respectively, in good yields (Scheme 37).



Scheme 37. Synthesis of the *N*, *N*'-linked 1, 2-benzisothiazol-3(2*H*)-one 1,1-dioxides, **154**, **156** and **158**

2-8. Applications towards the synthesis of Mannich bases

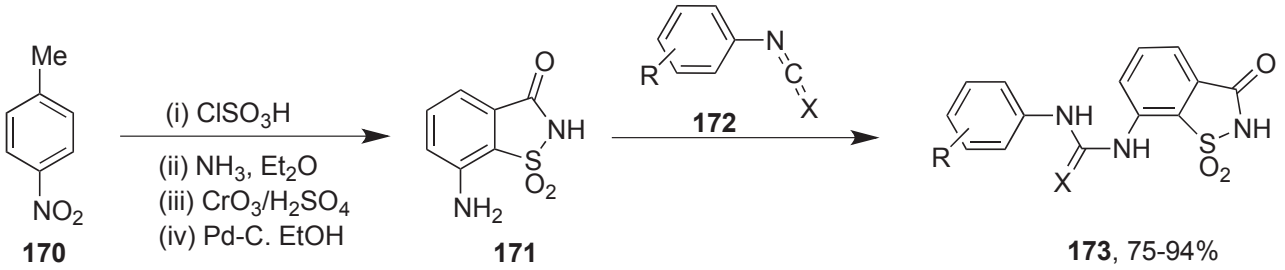
Saccharin derivatives with *N*-basic side chains exhibit important antimicrobial and antioxidant activities. In 2011, Hamama et al. reported the synthesis of saccharin-bearing Mannich bases.[50] Their synthetic protocol was comprised of a Mannich reaction in which saccharin **1** was allowed to react with various aliphatic or aromatic aldehydes, **159**, and primary or secondary amines, **160**, to form the respective Mannich bases, **161-169** (Scheme 38).



Scheme 38. Synthesis of Mannich bases **161-169** using saccharin **1**

2-9. Urea derivatives

A new class of saccharin derivatives, such as the 6-(phenylurenyl/thiourenyl)saccharin compound, **173**, was synthesized by Gencer et al. in 2012.[51] Additionally, they determined their biological activities as tyrosinase inhibitors. The synthetic scheme started from 4-nitrotoluene **170**, which was converted into 6-aminosaccharin **171** by passing through four steps. These steps involved the treatment of compound **170** with chlorosulfonic acid and ammonia solution with subsequent oxidation and reduction reactions. As a result, 6-aminosaccharin **171** was obtained which further reacted with phenylisocyanate or phenylisthiocyanate **172** to achieve the target compound, **173**, in a high yield (Scheme 39).



where,

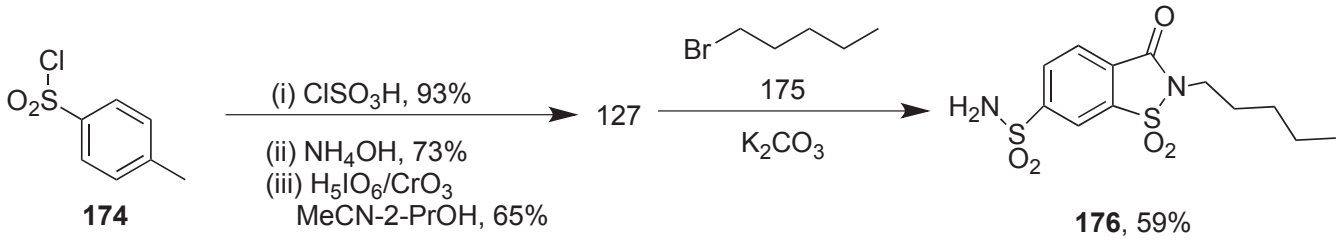
R = H, alkyl, halogen

X = O, S

Scheme 39. Synthesis of the 6-phenylurenyl/thiourenylsaccharin compounds **173**

2-10. Sulfonamide derivatives of saccharin

Sulfonamide-bearing molecules exhibit a wide range of pharmacological activities such as antibacterial, antifungal, antitumor, diuretic and hypoglycemic activities. Considering the importance of sulfonamides, Ivanova et al. in 2012 reported the formation of 6-sulfamoylsaccharin and their derivatives.[52] The methodology started from the synthesis of 6-sulfamoylsaccharin **127** from tosyl chloride **174** using chlorosulfonic acid and aqueous ammonia followed by an oxidation reaction. Then, compound **127** was subjected to an alkylation reaction, which resulted in the *N*-alkylated compound, **176** in 59% yield (Scheme 40).

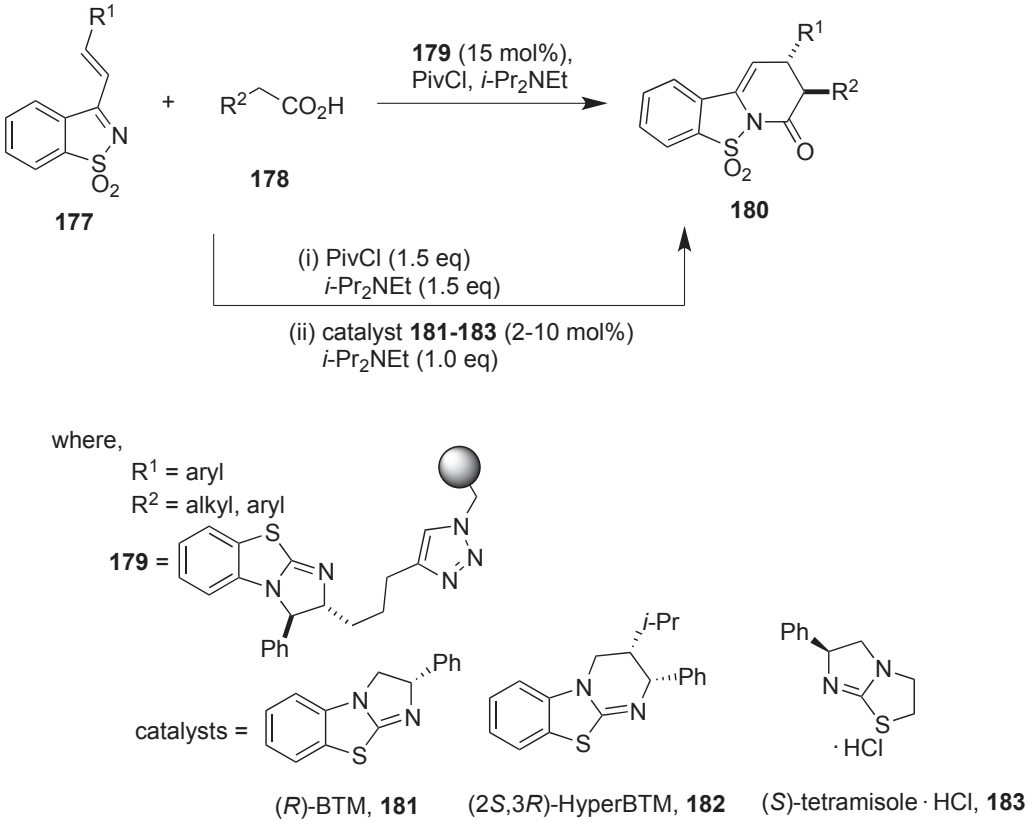


Scheme 40. Synthesis of 6-sulfamoylsaccharin **175** from **174**

2-11. Synthesis of saccharin derivatives via Michael addition/cyclization reactions

Organocatalysts perform a key role in industrial and pharmaceutical chemistry due to little effect of moisture or oxygen on them, low toxicity and easy availability. Moreover, they are helpful for such transformations which are rarely accomplished by other techniques. Consequently the increasing demand of such catalysts encouraged Izquierdo and Pericàs and they synthesized polystyrene-supported, enantiopure benzotetramisole (BTM) analogue **179** from (2*S*,3*S*)-phenylglycidol which serves as recyclable catalyst and shows outstanding performance in Michael addition/cyclization reaction.[53] For achieving Michael adducts, arylacetic acid **178** was treated with saccharin based Michael acceptors **177** in the presence of catalyst **179**, pivaloyl chloride and *i*-Pr$_2$NEt. As a result, tricyclic derivatives **180** were

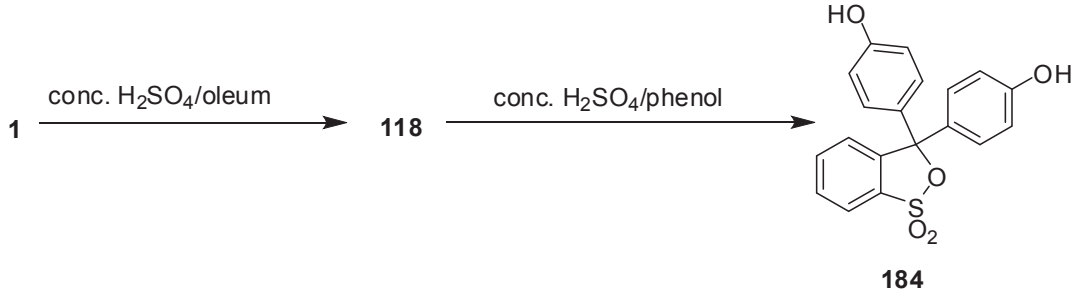
obtained in 72-96% yield. On the other hand, Smith reported that by using catalysts **181**, **182** and **183**, dihydropyridinone **180** was achieved in 16-99% yield.[54] However, HyperBTM proved to be an excellent catalyst which afforded required product at -78 ºC with greater diastereo- and enantioselectivity (Scheme 41).



Scheme 41. Formation of tricyclic derivatives **180** by employing Michael addition/cyclization reaction

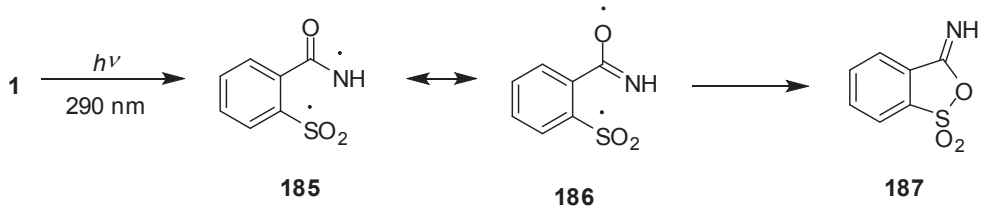
2-12. Miscellaneous derivatives

Considering the importance of phenolsulfonephthalein as an indicator and its applications in the clinical field, Tillu et al. described the solvent-free synthesis of sulfonephthaleins.[55] For this purpose, 2-sulfobenzoic anhydride **118** was reacted with phenol in the presence of H_2SO_4 to form sulfonephthalein **184** (Scheme 42).



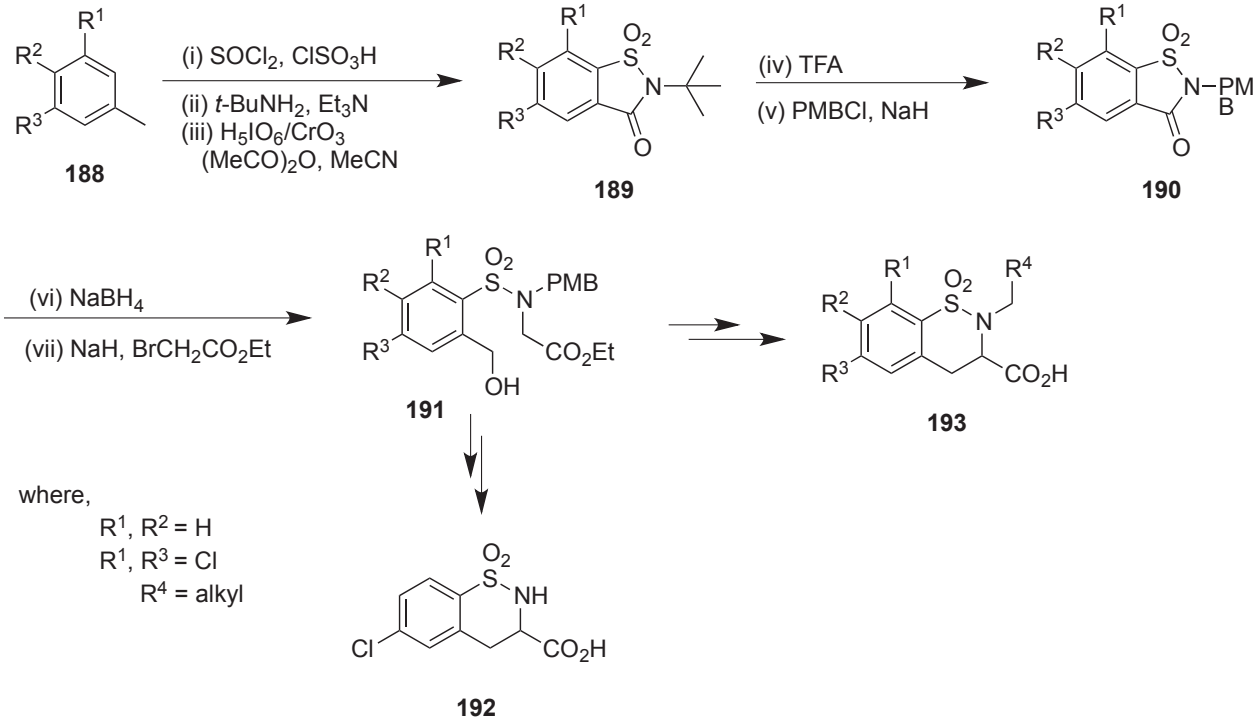
Scheme 42. Synthesis of phenolsulfonephthalein **184** from saccharin **1**

In another approach, Duarte et al. reported the photoisomerization of saccharin and its derivatives to determine that either these compounds were photochemically stable when subjected to UV radiation or not.[56] They concluded that when saccharin was subjected to narrow-band UV irradiation, structural rearrangements took place, and saccharin **1** was converted into iso-saccharin **187** (Scheme 43).



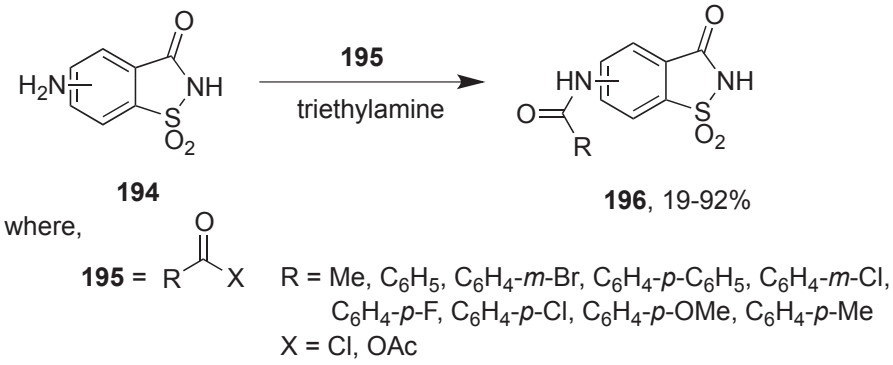
Scheme 43. Photoisomerization of saccharin **1**

As a novel and less polar ligand for the *N*-methyl-D-aspartate (NMDA) ligand receptor glycine binding site, the synthesis of 2-substituted 3,4-dihydro-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxides was performed by Bluke et al.[57] Their synthetic scheme started from the chlorosulfonation of the toluene derivative, **188**, followed by its reaction with *tert*-butylamine. Then, upon oxidation, it was converted into saccharin **189**, whose reaction with ethyl bromoacetate after reduction yielded sulfonamide **191**, which under different conditions produced the desired compounds, **192** and **193** (Scheme 44).



Scheme 44. Synthetic route for the synthesis of benzothiazine-3-carboxylic acid-based derivatives **192** and **193**

Solid tumors are creating major health problems world widely. 21.4 Million new cases and 13.2 million deaths due to cancer are expected by 2030. Along with preventive measures and early screenings, effective anticancer agents may be helpful for the proper treatment of cancer patients. Keeping this view in mind, Coviello et al. designed a technique for the synthesis of 1,2-benzisothiazole derivatives which act as inhibitors of carbonic anhydrase isoform IX.[58] For attaining these compounds, aminobenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide derivative **194** was treated with acyl chlorides/acetic anhydride **195** in the presence of triethylamine yielded 19-92% saccharin derivatives **196** (Scheme 45).



Scheme 45. Synthesis of saccharin derivatives **196** from aminobenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide derivative **194**

In supramolecular chemistry, heteracalixaromatics play a significant role as they used in fabrication of metal organic frameworks liquid crystals, CO_2-absorbents, anion responsive vesicles, stationary phase, and organic catalysts. By seeing their importance, the research group of Wang discovered a reliable method for the synthesis of functionalized heteracalixaromatics.[59] In their methodology, arylcopper (III) compounds **197** (Figure 4) coupled with saccharin in the presence of tripotassium phosphate under reflux conditions, as a result required macrocycles were obtained in a reasonable amount of yield.

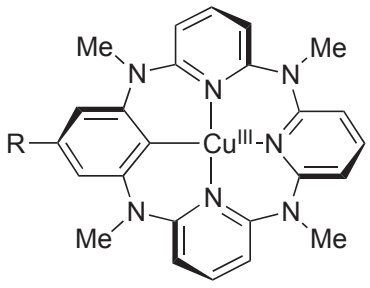
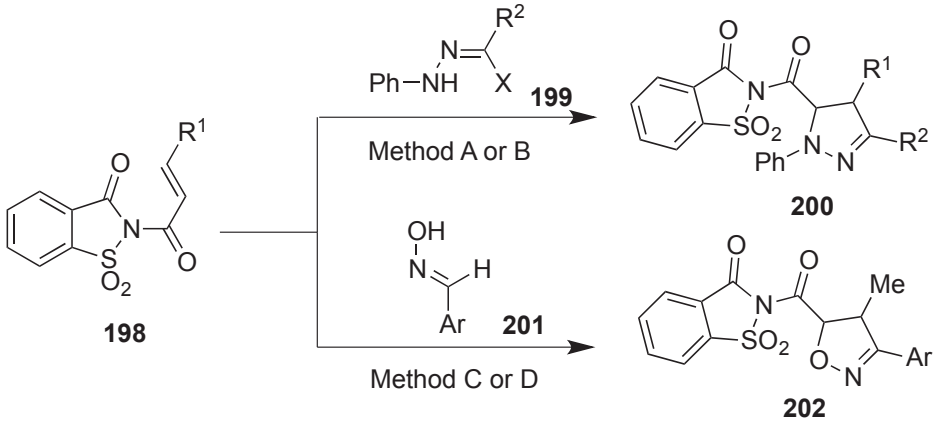


Figure 4. Arylcopper (III) compound **197**

Studies reveal that isoxazoline and pyrazoline containing molecules play a significant role in pharmaceutical industry as they display antituberculosis, anti-inflammatory, antiviral, antifungal, antihepatotoxic and pesticidal properties. By considering their importance, Bougrin and colleagues

reported isoxazoline and pyrazoline *N*-substituted saccharin derivatives by employing classical and solvent free microwave conditions.[60] For achieving pyrazoline derivatives **200**, *N*-substituted saccharin **198** was treated with nitrile imine **199** either in the presence of Et_3N using THF solvent (Method A) or expending *p*-HAP300 as catalyst under solvent free microwave condition (Method B). Similarly, to obtain isoxazoline derivatives **202**, saccharin **198** was reacted with arylnitrile oxide **201** either in the presence of sodium hypochlorite using DCM solvent (Method C) or by employing solvent free microwave condition which possessed *p*-HAP300 and NCS (Method D). It is a remarkable point that required derivatives were obtained in excellent yields by retaining solvent free microwave conditions (Scheme 46).



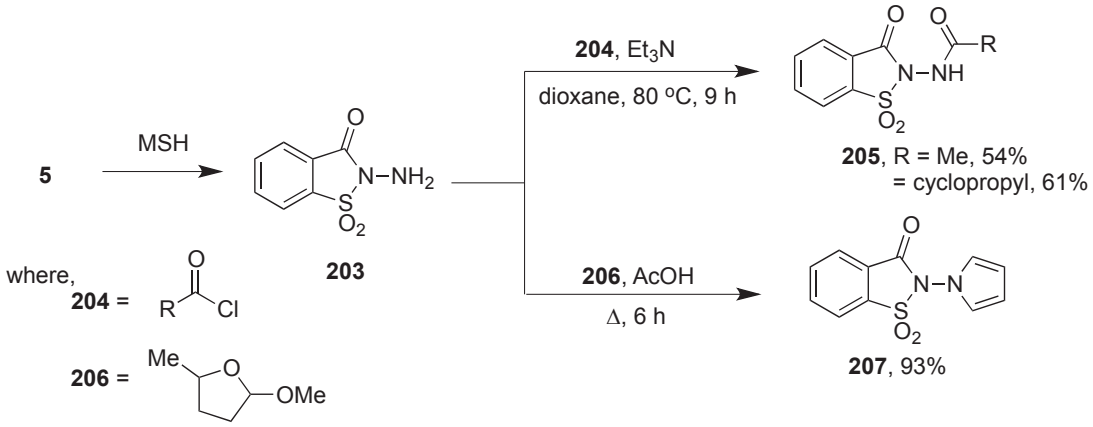
where,

Method A = Et_3N, THF, Δ, 8-24 h (70-88%)
Method B = MW, *p*-HAP300, 6-10 min (80-90%)
Method C = NaOCl aq, DCM, 0-5 ºC, 18-24 h (37-48%)
Method D = NCS, MW, *p*-HAP300, 3 min (80-98%)
R_1 = Me, Ph
R_2 = Ph, CO_2Me
Ar = C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 4-$Me_2NC_6H_4$

Scheme 46. Synthesis of pyrazoline **200** and isoxazoline *N*-substituted saccharin derivatives **202** from saccharin **198**

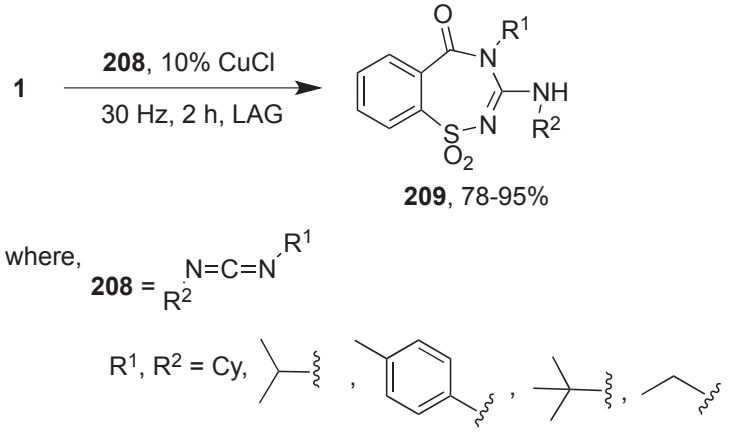
It was investigated that *N*-aminosaccharin act as building block for the synthesis of biologically active molecules via derivatization of the free hydrazine nitrogen atom but in the literature limited examples are reported related to these derivatives. Focusing on this, in 2017 Kuznetsov and co-workers declared that *N*-aminosaccharin **203** was obtained in good to excellent yield (51-82%) by the treatment of sodium saccharin **5** with hydroxylamine-*O*-mesitylenesulfonic acid (MSH).[61] The variation in the yield range depends upon the reaction conditions. However, the best yield was attained by using aqueous THF at ambient temperature with no base additive. Result declared that *N*-aminosaccharin proved to be an excellent inhibitor of human carbonic anhydrase I than the parent molecule. After that, by using different

acyl chlorides **204**, *N*-aminosaccharin **203** was derivatized into respective hydrazide **205** in moderate yield range. However, when **203** was treated with 2,5-dimethoxytetrahydrofuran **206** in acetic acid medium, *N*-pyrrol-1-ylsaccharin **207** was obtained in excellent yield (Scheme 47).



Scheme 47. Synthesis of *N*-aminosaccharin **203** and their derivatives, hydrazide **205** and *N*-pyrrol-1-ylsaccharin **207**

Due to the increasing significance of thiadiazepines, a number of methods have been reported for the synthesis of benzo[1,2,5]-, benzo[1,3,4]- and benzo[1,4,5]thiadiazepines which are used for the treatment of Alzheimer's disease, different types of cancer and diabetes mellitus. However, few cases are reported in which the synthesis of benzo[1,2,4]thiadiazepines is described. In 2017, Tan and Friscic described a method for the ring expansion of saccharin **1** to generate 7-membered benzo[1,2,4]thiadiazepines.[62] They declared that benzo[1,2,4]thiadiazepines **209** (78-95%) was achieved by the treatment of **1** with different carbodiimides **208** through liquid-assisted grinding (LAG) with 10 mol% CuCl. It was observed that CuCl not only accelerated the rate of the reaction but also accomplished it without bulk solvent (Scheme 48).



Scheme 48. Synthesis of benzo[1,2,4]thiadiazepines **209** from the ring expansion of saccharin **1** with carbodiimide **208**

3. CONCLUSION

Saccharin has been involved in the synthesis of a variety of biologically active products under suitable reaction conditions. This article provides a review of research articles published from 2010 to 2017, and the synthesis of various derivatives, such as *N*/*O*-alkylated saccharin derivatives, Mannich/Schiff bases bearing saccharin, benzothiazines, triazole/urea-based saccharin derivatives and *N*-*N*′-linked benisothiazoles, has been discussed.

ACKNOWLEDGEMENTS

The authors are thankful to GC University, Faisalabad for providing facilities to carry out this work.

REFERENCES

1. Z. Jakopin and M. S. Dolenc, *Synth. Commun*., 2008, **38**, 3422.
2. A. Eminoglu, D. Vullo, A. Asik, D. N. Colak, S. Canakci, A. O. Belduz, and C. Supuran, *Bioorg. Med. Chem. Lett*., 2016, **26**, 1821.
3. W. A. Siddiqui, S. Ahmad, I. U. Khan, H. L. Siddiqui, and G. W. Weaver, *Synth. Commun*., 2007, **37**, 767.
4. T.-T. Thai, B. Therrien, and G. J. Suss-Fink, *Organomet. Chem*., 2011, **696**, 3285.
5. A. Rai and L. D. S. Yadav, *Tetrahedron Lett*., 2010, **51**, 4045.
6. N. Lu, W.-H. Chang, R.-J. Wei, Y.-C. Fang, T.-W. Han, G.-Q. Wang, J.-Y. Chang, Y.-S. Wen, and L.-K. Liu, *Tetrahedron*, 2016, **72**, 3468.
7. D. W. Cho, S. W. Oh, D. U. Kim, H. J. Park, J. Y. Xue, U. C. Yoon, and P. S. Mariano, *Bull. Korean Chem. Soc.*, 2010, **31**, 2453.
8. Z. Jakopin and M. S. Dolenc, *Synth. Commun*., 2010, **40**, 2464.
9. B. Zwanenburg and A. S. Mwakaboko, *Bioorg. Med. Chem.*, 2011, **19**, 7394.
10. A. Hassanabadi, M. H. Mosslemin, M. Anary-Abbasinejad, A. Kalantarinejad, and M. J. Shirazi, *J. Chem*., 2012, **9**, 2074.
11. A. Ismael, A. Borba, L. Duarte, B. M. Giuliano, A. Gomez-Zavaglia, and M. L. S. Cristiano, *J. Mol. Struct*., 2012, **1025**, 105.
12. X. Wang, Y. Ma, and T. Ju, *J. Chem. Res.*, 2013, **37**, 417.
13. M. D'Ascenzio, S. Carradori, C. D. Monte, D. Secci, M. Ceruso, and C. T. Supuran, *Bioorg. Med. Chem*., 2014, **22**, 1821.
14. S. Carradori, D. Secci, C. D. Monte, A. Mollica, M. Ceruso, A. Akdemir, A. P. Sobolev, R. Codispoti, F. D. Cosmi, P. Guglielmi, and C. T. Supuran, *Bioorg. Med. Chem*., 2016, **24**, 1095.

15. L. Han, L. Wang, X. Hou, H. Fu, W. Song, W. Tang, and H. Fang, *Bioorg. Med. Chem*., 2014, **22**, 1529.
16. K. Kiyokawa, S. Yahata, T. Kojima, and S. Minakata, *Org. Lett*., 2014, **16**, 4646.
17. Y. Lv, Y. Li, T. Xiong, Y. Lu, Q. Liu, and Q. Zhang, *Chem. Commun*., 2014, **50**, 2367.
18. K. Sun, X. Wang, G. Li, Z. Zhu, Y. Jiang, and B. Xiao, *Chem. Commun*., 2014, **50**, 12880.
19. Y. Lv, K. Sun, T. Wang, Y. Wu, G. Li, W. Pu, and S. Mao, *Asian J. Org. Chem*., 2016, **5**, 325.
20. Y. Durust, B. Ozer, and B. M. Cariuki, *Mol. Divers*., 2015, **19**, 213.
21. H. Fu, L. Han, X. Hou, Y. Dun, L. Wang, X. Gong, and H. Fang, *Bioorg. Med. Chem*., 2015, **23**, 5774.
22. Z. F. A. Mortazavi, M. R. Islami, and M. Khaleghi, *Org. Lett*., 2015, **17**, 3034.
23. A. Yoshimura, S. R. Koski, J. M. Fuchs, A. Saito, V. N. Nemykin, and V. V. Zhdankin, *Chem. Eur. J*., 2015, **21**, 5328.
24. S. Bag, R. Tulsan, A. Sood, H. Cho, H. Redjeb, W. Zhou, III H. LeVine, B. Torok, and M. Torok, *Bioorg. Med. Chem*., 2015, **25**, 626.
25. C. Martinez, E. G. Perez, A. Iglesias, E. C. Escudero-Adan, and K. Muniz, *Org. Lett*., 2016, **18**, 2998.
26. L. Song, S. Luo, and J. -P. Cheng, *Org. Chem. Front*., 2016, **3**, 447.
27. D. Panek, A. Wieckowska, T. Wichur, M. Bajda, J. Godyn, J. Jonczyk, K. Mika, J. Janockova, O. Soukup, D. Kenz, J. Korabecny, S. Gobec, and B. Malawska, *Eur. J. Med. Chem*., 2017, **125**, 676.
28. S. H. Kim, R. Ramu, S. W. Kwon, S. H. Lee, C. H. Kim, S. K. Kang, S. D. Rhee, M. A. Bae, S. H. Ahn, D. C. Ha, H. G. Cheon, K. Y. Kim, and J. H. Ahn, *Bioorg. Med. Chem. Lett*., 2010, **20**, 1065.
29. S. H. Kim, S. W. Kwon, S. Y. Chu, J. H. Lee, B. Narsaiah, C. H. Kim, S. K. Kang, N. S. Kang, S. D. Rhee, M. A. Bae, S. H. Ahn, D. C. Ha, K. Y. Kim, and J. H. Ahn, *Chem. Pharm. Bull*., 2011, **59**, 46.
30. M. Ahmad, H. L. Siddiqui, M. Zia-ur-Rehman, and M. Parvez, *Eur. J. Med. Chem*., 2010, **45**, 698.
31. S. Aslam, M. Ahmad, M. Zia-Ur-Rehman, C. Montero, M. Detorio, M. Parvez, and R. F. Schinazi, *Arch. Pharm. Res*., 2013, **37**, 1380.
32. D. Shahwar, U. Sana, and N. Ahmad, *Turk. J. Chem*., 2013, **37**, 262.
33. M. R. Gannarapu, S. B. Vasamsetti, N. Punna, N. K. Royya, S. R. Pamulaparthy, J. B. Nanubolu, S. Kotamraju, and N. Banda, *Eur. J. Med. Chem*., 2014, **75**, 143.
34. G. M. Reddy, P. Nagender, R. N. Kumar, J. H. Ahn, K. P. Kumar, A. K. R. Kanugula, K. V. S. R. Krishna, S. Kotamraju, and B. Narsaiah, *J. Heterocycl. Chem*., 2014, **51**, 42.
35. N. Ahmad, M. Zia-ur-Rehman, H. L. Siddiqui, M. F. Ullah, and M. Parvez, *Eur. J. Med. Chem*., 2011, **46**, 2368.

36. X. Chen, S. Zhang, Y. Yang, S. Hussain, M. He, D. Gui, B. Ma, C. Jing, Z. Qiao, C. Zhu, and Q. Yu, *Bioorg. Med. Chem*., 2011, **19**, 7262.
37. K. Lei, X. -W. Hua, Y. -Y. Tao, Y. Liu, N. Liu, Y. Ma, Y. -H. Li, X. -H. Xu, and C. -H. Kong, *Bioorg. Med. Chem*., 2016, **24**, 92.
38. S. Sabatini, F. Gosetto, S. Serritella, G. Manfroni, O. Tabarrini, N. Iraci, J. P. Brincat, E. Carosati, M. Villarini, G. W. Kaatz, and V. Cecchetti, *J. Med. Chem*., 2012, **55**, 3568.
39. J. Moeker, T. S. Peat, L. F. Bornaghi, D. Vullo, C. T. Supuran, and S. -A. Poulsen, *J. Med. Chem*., 2014, **57**, 3522.
40. T. Xiaobin, L. Zhenghui, L. Yonghong, L. Wei, Y. Peng, L. Lixin, G. Yu, and Y. Cheng, *Chem. Res. Chin. Univ*., 2015, **31**, 71.
41. W. A. Siddiqui, S. Ahmad, H. L. Siddiqui, T. Hussain, and M. Parvez, *J. Chem. Crystallogr*., 2010, **40**, 116.
42. P. V. Ramana and A. R. Reddy, *J. Sulfur Chem*., 2010, **31**, 71.
43. G. Kiselev, A. F. Mishnev, E. M. Ivanova, I. V. Vozny, and R. Zalubovskis, *Chem. Heterocycl. Compd*., 2012, **48**, 1412.
44. J. Ivanova, J. Leitans, M. Tanc, A. Kazaks, R. Zalubovskis, C. T. Supuran, and K. Tars, *Chem. Commun*., 2015, **51**, 7108.
45. C. D. Haffner, S. A. Thomson, Y. Guo, L. T. Schaller, S. Boggs, S. Dickerson, J. Gobel, D. Gillie, and J. P. Condreay, *Bioorg. Med. Chem.*, 2010, **20**, 6983.
46. K. M. Amin, H. H. Georgey, and F. M. Awadallah, *Med. Chem. Res*., 2011, **20**, 1042.
47. S. Cakir and E. Bicer, *J. Iran. Chem. Soc*., 2010, **7**, 394.
48. O. I. El-Sabbagh, *Arch. Pharm. Chem*., 2013, **346**, 733.
49. V. M. Zakharova, O. Brede, M. Gutschow, M. A. Kuznetsov, M. Zibinsky, J. Sieler, and B. Schulze, *Tetrahedron*, 2010, **66**, 379.
50. W. S. Hamama, H. H. Zoorob, M. A. Gouda, and E. M. Afsah, *Pharm. Chem. J*., 2011, **45**, 118.
51. N. Gencer, D. Demir, F. Sonmez, and M. Kucukislamoglu, *Bioorg. Med. Chem.*, 2012, **20**, 2811.
52. E. M. Ivanova, E. Y. Simin, I. V. Vozny, P. Trapencieris, and R. Zalubovskis, *Chem. Heterocycl. Compd*., 2012, **47**, 1561.
53. J. Izquierdo and M. A. Pericas, *ACS Catal*., 2016, **6**, 348.
54. D. G. Stark, C. M. Young, T. J. C. O'Riordan, A. M. Z. Slawin, and A. D. Smith, *Org. Biomol. Chem*., 2016, **14**, 8068.
55. V. H. Tillu, D. K. Dumbre, H. B. Borate, R. D. Wakharkar, and V. R. Choudhary, *Synth. Commun*., 2012, **42**, 1101.
56. L. Duarte, I. Reva, M. L. S. Cristiano, and R. Fausto, *J. Org. Chem*., 2013, **78**, 3271.

57. Z. Bluke, E. Paass, M. Sladek, U. Abel, and V. Kauss, *J. Enzyme Inhib. Med. Chem.*, 2015, **30**, 1.
58. V. Coviello, B. Marchi, S. Sartini, L. Quattrini, A. M. Marini, F. Simorini, S. Taliani, S. Salerno, P. Orlandi, A. Fioravanti, T. D. Desidero, D. Vullo, F. D. Settimo, C. T. Supuran, G. Bocci, and C. L. Motta, *J. Med. Chem*., 2016, **59**, 6547.
59. Y. Liu, Q. Zhang, Q. -H. Guo, and M. -X. Wang, *J. Org. Chem*., 2016, **81**, 10404.
60. A. Saber, M. Driowya, S. Alaoui, H. Marzagi, L. Demange, E. Alvarez, R. Benhida, and K. Bougrin, *Chem. Heterocycl. Compd*., 2016, **52**, 31.
61. M. A. Kuznetsov, A. N. Shestakov, M. Zibinsky, M. Krasavin, C. T. Supuran, S. Kalinin, and M. Tanc, *Tetrahedron Lett*., 2017, **58**, 172.
62. D. Tan and T. Friscic, *Chem. Commun*., 2017, **53**, 901.

Dr. Ameer Fawad Zahoor is working as Assistant Professor in Government College Faisalabad, Pakistan. He is the recipient of Gold Medal and Academic Roll of Honor during his B.Sc. Hons in 2003 and Certificate of Distinction in M.Sc. in 2004 from GCU Lahore Pakistan. He was participant of 56th meeting of Nobel Laureates with young scholars held in Lindau, Germany in 2006. He joined Government College University Faisalabad as Lecturer in 2005. received PhD scholarship in 2006 funded by Higher Education Commission Pakistan-German Academic Exchange Service (DAAD), and joined research group of Prof. Dr. Uli Kazmaier (University of Saarland, Germany). He completed his PhD in 2011 and re-joined Government College University, Faisalabad. He was appointed as Assistant Professor in November, 2011. areas of interest include the synthesis of biologically active molecules (amino acids, etc) including radiopharmaceuticals as well as estimation of PAHs (polycyclic aromatic hydrocarbons) in raw food items.

Rabia Akhtar was born in 1990 in Faisalabad (Pakistan) and obtained her BS (Hons) degree in chemistry in 2014 and M.Phil (Organic Chemistry) in 2016 from Government College Faisalabad. Currently she is pursuing her PhD under the supervision of Dr. Ameer Fawad at Government College University Faisalabad, Pakistan.

Sajjad Ahmad was born in 1982 in Jhang (Pakistan). He obtained his B.Sc. Hons in Chemistry 2003 and M.Sc. in 2004 from GCU Lahore Pakistan. Before he joined the research group of Dr. Andrew Sutherland at university of Glasgow UK as a PhD student, he worked as R & D in a leading chemical manufacturing plant. In 2012 he received his PhD from university of Glasgow UK. Same year he was appointed as assistant professor of chemistry at UET Lahore. main focus is around organic synthesis and analytical estimations.

Syed Ali Raza Naqvi was born in 1980 in Sheikhupura (Pakistan) and obtained his B.Sc. in Chemistry from University of the Punjab, Lahore-Pakistan in 2000 and a M.Sc. in Analytical Chemistry from Government College University, Lahore-Pakistan in 2002. He received the Indigenous PhD Scholarship from Higher Education Commission (HEC), Islamabad-Pakistan in 2005 and joined the group of Prof. Dr. Saeed Ahmad Nagra in University of the Punjab, Lahore-Pakistan; while working on development of radiopharmaceuticals for diagnosis and therapy of malignant diseases in the group of Dr. Nagra he was selected for International Research Support Initiative Program (IRSIP) and he joined the cancer research group of Prof. Dr. Steve in London-UK. On return back from London he was awarded PhD degree in Chemistry in 2009. Then he joined Government College University, Faisalabad in 2010. Mainly he is working on the development of radiopharmaceuticals for diagnosis and therapy of malignancies. Up till now he has supervised more than 32 MPhil Students, 7 PhD student are working under his supervision, he won 2 competitive research grants from HEC and is an author and co-author of more than 50 international publications.

Dr. Samreen Gul Khan was born in Lahore (Pakistan). She obtained her M.Sc in Chemistry and M.Phil in Chemistry from Government College University in 2006 and 2009 respectively. During her M.Phil she worked on two industrial projects and also won a grant from RL Enterprise. In 2010 she obtained a Diploma in Forensic Chemistry from GC University, Lahore with distinction. In 2014 she completed her Ph.D in synthetic organic/medicinal chemistry from GC University, Lahore (Pakistan). Her doctoral work corresponded to the development of biologically active novel oxadiazole derivatives. She joined Department of Chemistry GC University, Faisalabad as Assistant Professor in 2015. Currently she is employing organic synthesis to prepare compounds for application in the areas of medicinal chemistry.

Muammad Suleman was born in 1978 in Faisalabad (Punjab) Pakistan and obtained his M.Sc in Chemistry from University of Punjab Lahore Pakistan. Muhammad Suleman received an Indigenous Fellowship from Higher Education Commission Islamabad Pakistan in 2007. Muhammad Suleman received his PhD from GC, University Faisalabad (Punjab) Pakistan in 2014. After that he joined Women University of AJ&K Bagh for Teaching and Research.