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An updated review of fatty acid residue-tethered heterocyclic compounds: synthetic strategies and biological significance

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Heterocyclic compounds have been featured as the key building blocks for the development of biologically active molecules. In addition to being derived from renewable raw materials, fatty acids possess a variety of biological properties. The two bioactive ingredients are being combined by many researchers to produce hybrid molecules that have a number of desirable properties. Biological activities and significance of heterocyclic derivatives of fatty acids have been demonstrated in a new class of heterocyclic compounds called heterocyclic fatty acid hybrid derivatives. The significance of heterocyclic-fatty acid hybrid derivatives has been emphasized in numerous research articles over the past few years. In this review, we emphasize the development of synthetic methods and their biological evaluation for heterocyclic fatty acid derivatives. These reports, combined with the upcoming compilation, are expected to serve as comprehensive foundations and references for synthetic, preparative, and applicable methods in medicinal chemistry.

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1. Introduction

Among the monocarboxylic acids, fatty acids (FA) contain long hydrocarbon chains. Saturated or unsaturated oils are generally formed from the cleavage of fats and oils that come from natural sources, like triglycerides or phospholipids.[1] The length of the aliphatic tails of the FAs determines the classification: short chain fatty acids (SCFA) have aliphatic tails of five or less carbon atoms, medium chain fatty acids (MCFA) begin with six carbon atoms or more, and long chain fatty acids (LCFA) begin with 14 or more carbon atoms.[2,3] In addition to their involvement in membrane function, fatty acids are believed to play a significant role in brain and retinal function.[4] Since each fatty acid involves non-physiological conditions, it is hard to evaluate their function in relation to protein function. Nonetheless, many review articles argue that a diet low in saturated fat may decrease the risk of diabetes, heart disease, and death.[5,6] Their applications are quite wide in industrial uses such as fuels, surfactants and catalysts.[7–9] Furthermore, they can be used as precursors for biologically active compounds through simple transformations; such as the reaction of the carboxylic moiety to produce a stable ester or amide bond.[10] These bioactive compounds, branched and cyclic chain FAs, have a variety of biological effects[11] such as antiinflammatory,[12] antibacterial,[13] antioxidant capabilities,[14] and have recently been used for cancer treatment.[15]

On the other hand, heterocyclic rings serve as a primary scaffold for the synthesis of bioactive compounds,[16,17] and have a high proclivity for forming complexes with various metals. Some of these complexes have been utilized as antibiotics[18] and catalysts in a variety of processes, including the Tsuji–Trost and Mizoroki–Heck reactions.[19] Hybridization of fatty acids with heterocyclic rings yields the heterocyclic-fatty acid hybrid derivatives, which results in novel hybrid molecules to broaden the scope of applications compared to the applications of each group separately.[12,20]

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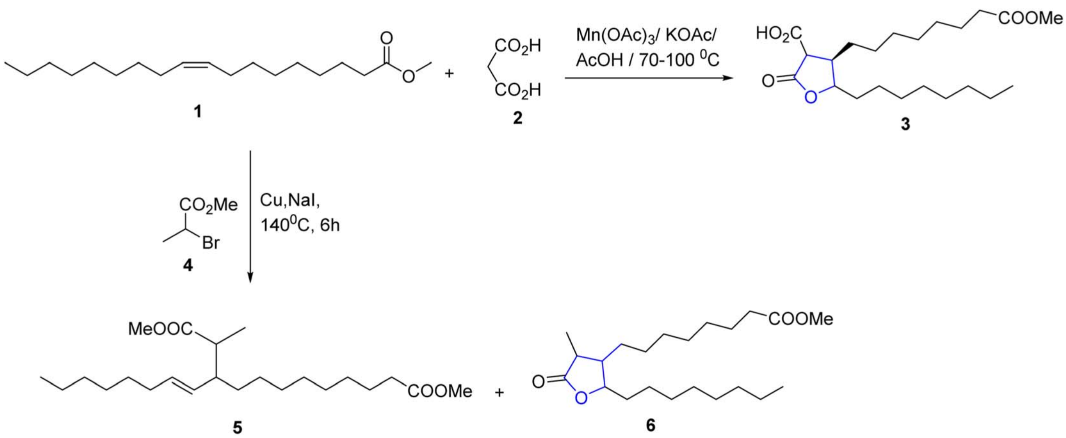
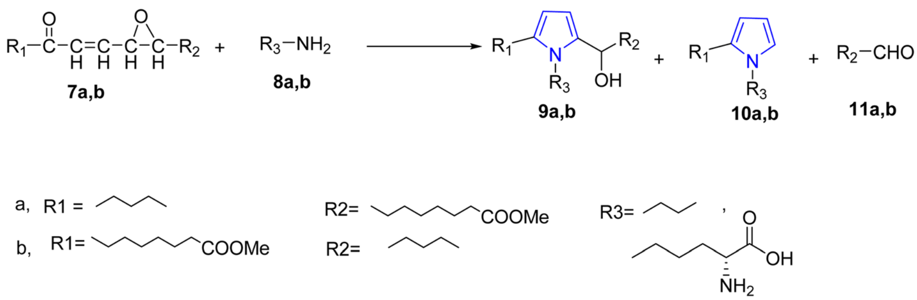
2. Synthesis of five membered heterocycles with one heteroatom

Unsaturated fatty substances were utilized to produce a new C–C bond through radical additions reaction initiated *via*



Scheme 1 Synthesis of 2-oxotetrahydrofuran derivative (**3**) and γ-lactone **6**.

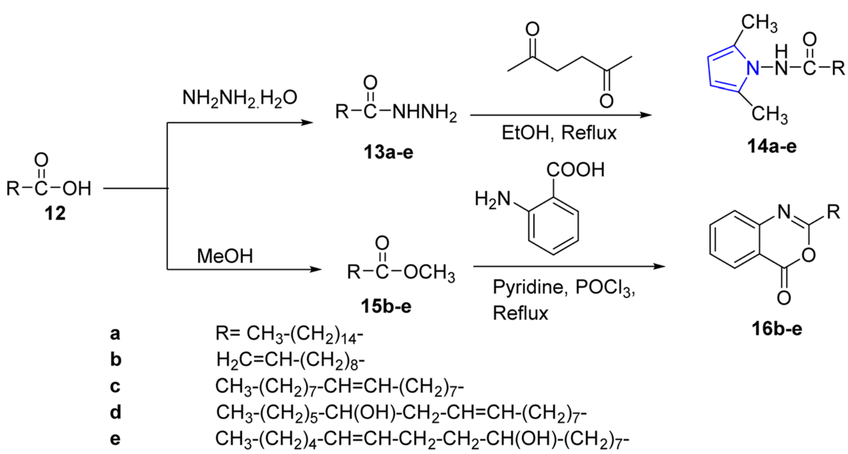


Scheme 2 Preparation of di- and tri-substituted pyrroles.

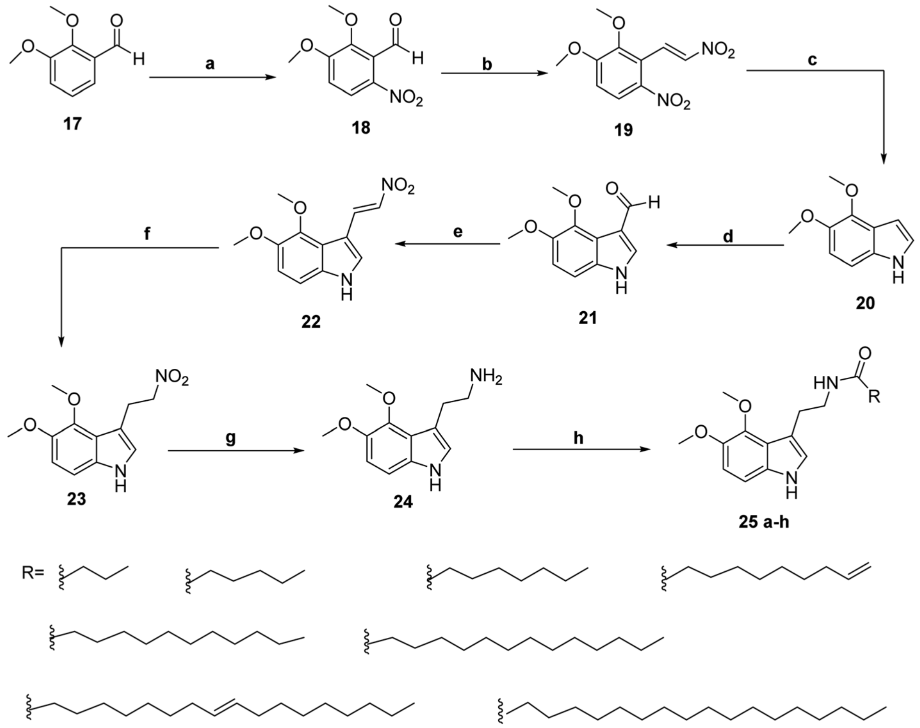
a metal as catalyst. The methyl oleate **1** was used as the precursor to produce the 2-oxotetrahydrofuran derivative (**3**) through the reaction with malonic acid and manganese(III) acetate as catalyst under acid condition.[21] On the other hand, the reaction of 2-bromopropane methyl ester with **1**, using copper as an initiator gave the γ-lactone **6** in 58% yield, in addition to compound **5** that forms as a side product *via* an addition–elimination reaction[22] (Scheme 1).

Hidalgo *et al.*, reported the synthesis of certain novel *N*-substituted long-chain pyrrole fatty acids *via* reaction of epoxyoxoene fatty acids **7a** and **7b** with butylamine and lysine **8a** and **8b**. Two types of pyrroles were isolated and characterized. 1,2,5-Trisubstituted pyrroles **9a** and **9b** were the major product while 1,2-disubstituted pyrrole **10a** and **10b** and short chain aldehydes **11a** and **11b** were formed in minor[23] (Scheme 2).

In 2017, a series of 2,5-dimethyl pyrrole **14a–e** derivatives were synthesized by Ahmad and co-workers *via* the reaction of



Scheme 3 Synthesis of 2,5-dimethyl pyrroles **14a–e**, and synthesis of benzoxazine-4-one derivatives **16a–e**.



Reagents and conditions: **(a)** fuming HNO_3, glacial AcOH, RT for 4 h; **(b)** N-methyl morpholine, CH_3NO_2, KF, 18-crown-6-ether, 12 h, NaOAc, acetic anhydride, 60°C, 1 h; **(c)** Fe-powder, SiO_2, CH_3COOH, toluene, 90°C, 1 h; **(d)** $POCl_3$, DMF at 0°C, RT for 4 h; **(e)** CH_3COONH_4, CH_3NO_2, 90°C, 6 h; **(f)** $NaBH_4$, MeOH: DMF (1:1) at RT for 4 h; **(g)** Fe, NH_4Cl, MeOH: H_2O (5:1), reflux for 2 h; **(h)** Acid chloride, Et_3N, DCM, RT for 2 h.

Scheme 4 Synthesis of 4,5-dimethoxy tryptamine derivatives **25a–h** with long chain fatty acids from 2,3-dimethoxybenzaldehyde **17**.

fatty acid **12** with hydrazine hydrate to form fatty acid hydrazides **13a–e** which cyclized with acetonyl acetone in presence of ethyl alcohol to afford pyrrole compounds **14a–e**. Then, **12** was reacted with methanol to yield the fatty acid esters **15b–e**, which later through the reaction with anthranilic acid in the presence of $POCl_3$ furnished the 1,3-benzoxazin-4-one derivatives **16a–e** (ref. 24) (Scheme 3).

Furthermore, a series of 4,5-dimethoxy tryptamine derivatives with long chain fatty acids were synthesized by Venepally *et al.*[25] The target compounds were obtained *via* synthetic routes with eight steps sequence. The nitration of 2,3-dimethoxy benzaldehyde **17** as the starting material with fuming nitric acid and glacial acetic acid yielded a mixture of 5-nitro and 6-nitro derivatives. The beseeched compound **19** was obtained *via* the conversation of **18** by using nitromethane in the presence of 18-crown ether and n-methyl morpholine. Then compound **19** was subjected to cyclization to give 4,5-dimethoxy-1*H*-indole **20** in the presence of iron and acetic acid. Vilsmeier–Haack reaction was used to yield compound **21** *via* the introduction of aldehyde moiety to compound **20** (Scheme 4).

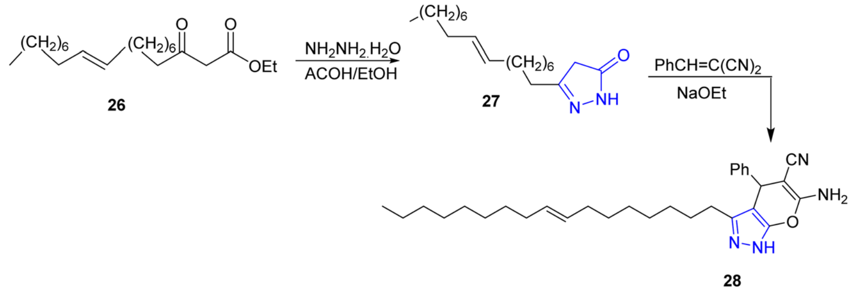
Compound **21** was condensed with nitromethane and ammonium acetate based on the Henry reaction to form the corresponding 4,5-dimethoxy-3-(2-nitrovinyl)-1*H*-indole **22**. The latter compound was reduced to yield 4,5-dimethoxy-3-(2-nitroethyl)-1*H*-indole **23**. Furthermore, compound **23** was refluxed in methanol and water in presence of Fe powder and ammonium chloride to give 2-(4,5-dimethoxy-1*H*-indol-3-yl) ethylamine **24**, which was reacted with fatty acid chlorides in dichloromethane and triethylamine as catalyst giving the corresponding amide derivatives **25a–h** (Scheme 4).

3. Synthesis of five membered heterocycles with two heteroatoms

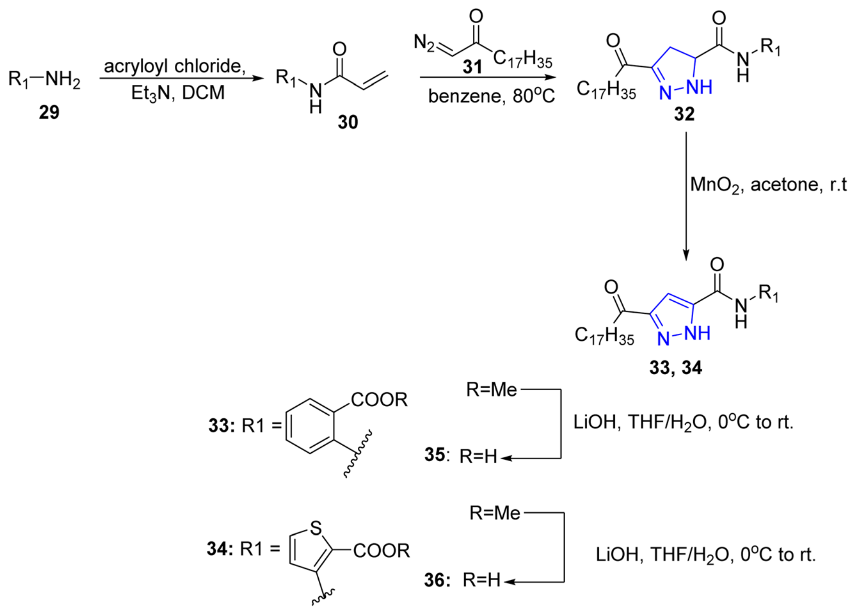
3.1. Synthesis of pyrazole derivative

Compound **26** was treated with hydrazine hydrate in acetic acid/ethanol mixture to yield the pyrazol-5-one **27** bearing the long chain oleyl residue at 3-position. The later compound was subjected to reaction with benzylidene malononitrile in the presence of sodium ethoxide offering the pyrazole derivative **28** (ref. 26) (Scheme 5).

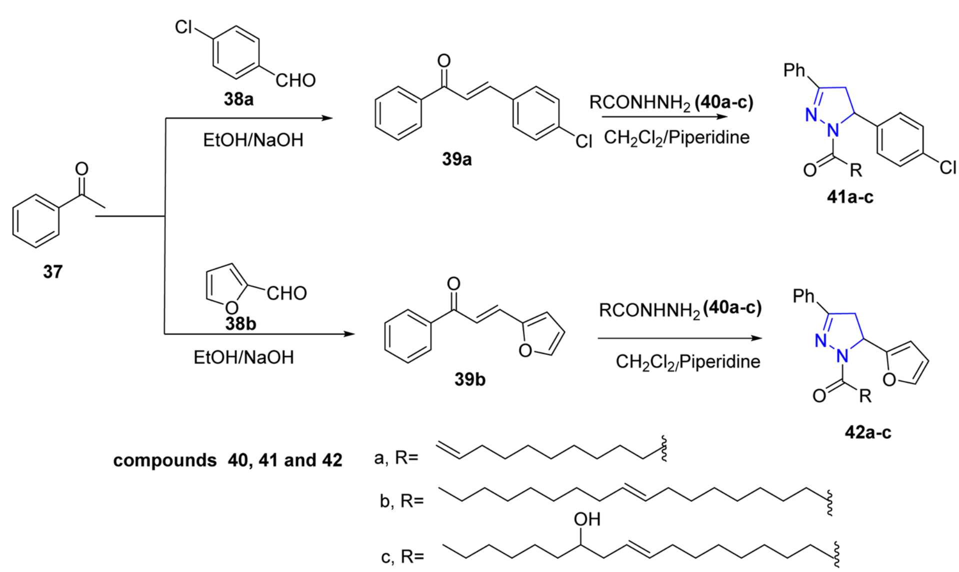
Preliminary structural optimization of the series provided compounds **35** and **36** which may lead to the discovery of new inhibitory agents against the cell division cycle 25 (CDC25) phosphatases. Starting from primary amines **29**, acylation with acryloyl chloride yielded *N*-substituted compound **30**, which was used as dipolarophile to carry out 1,3-dipolar cycloaddition reaction with α-diazo carbonyl compounds **31** (ref. 27 and 28) in benzene, yielding pyrazoline derivatives **32**. The treatment of these derivatives with MnO_2 in acetone provided the desired products **33** and **34** which were hydrolyzed by LiOH in THF to



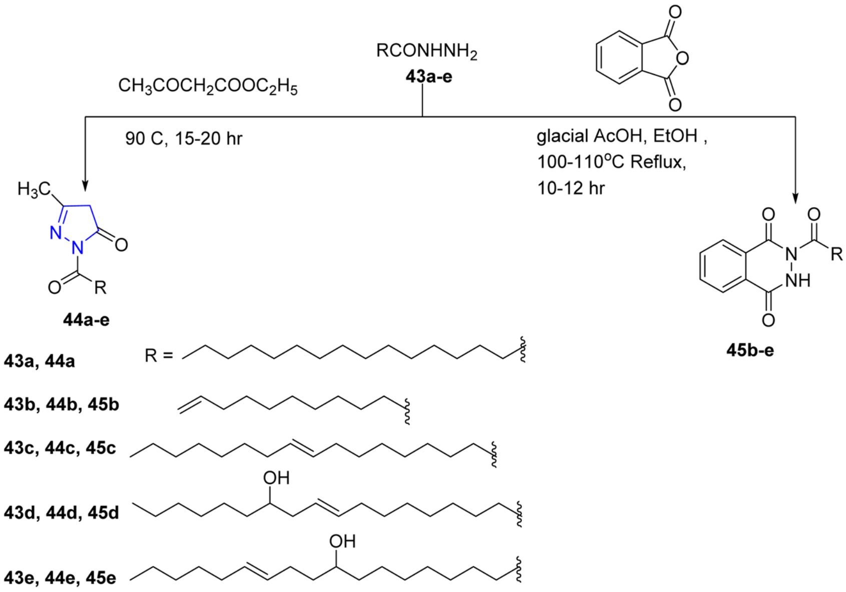
Scheme 5 Synthesis of a pyrazole core containing a pyrano system.



Scheme 6 Preparation of pyrazolo amide derivatives 35 and 36.



Scheme 7 Synthesis of pyrazoline derivatives bearing fatty acid chain *via* Claisen–Schmidt condensation.



Scheme 8 Synthesis of 1*H*-pyrazol-5(4*H*)-one derivatives **44a–e**.

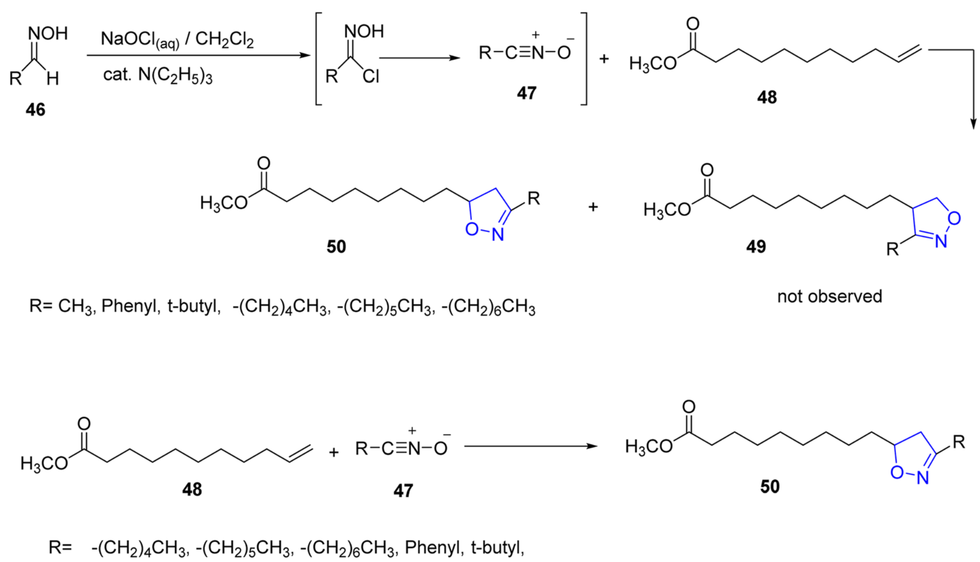
introduce free carboxylic group in compounds **35** and **36**, respectively[29] (Scheme 6).

A series of novel pyrazoline derivatives bearing fatty acid chain were synthesized by Laskar *et al.* Claisen–Schmidt condensation was used to react the acetophenone **37** with *p*-chlorobenzaldehyde **38a** and furfural **38b** in ethanol in presence of sodium hydroxide yielding the products **39a** and **39b**, respectively. These chalcone compounds were cyclized by various fatty acid hydrazides **40a–c** to give the pyrazoline derivatives **41a–c** and **42a–c** (ref. 30) (Scheme 7).

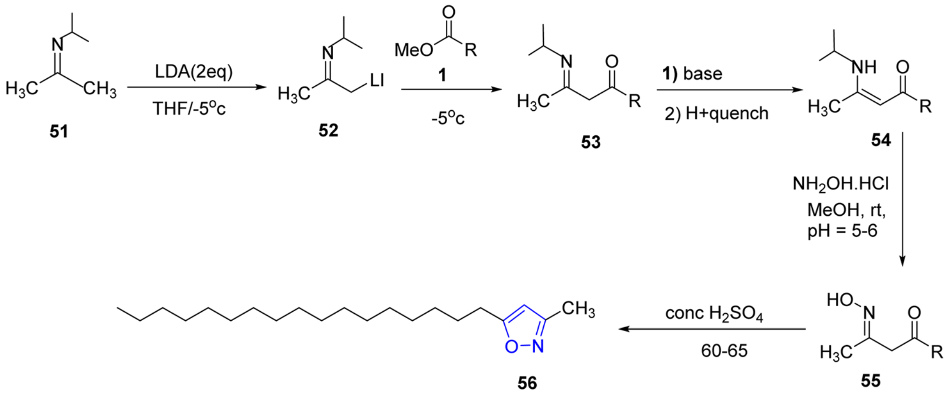
In 2014, Ahmed and coworkers utilized the fatty acid hydrazides **43a–e** as the starting material to prepare new long chain fatty acid derivatives of 1,3-disubstituted-1*H*-pyrazol-5(4*H*)-one **44a–e** and 2-substituted-3*H*-1,4-phthalazin-1,4-dione **45b–e**, through the condensation of hydrazide compound **43a–e** with ethylacetoacetate, followed by cyclization to afford pyrazole derivatives **44a–e**. Meanwhile, the fatty acid hydrazide **43a–e** reacted with phthalic anhydride in ethanol and glacial acetic acid as a catalyst to give phthalazine derivatives **45b–e** (ref. 31) (Scheme 8).

3.2. Synthesis of 3,5-disubstituted isoxazoles

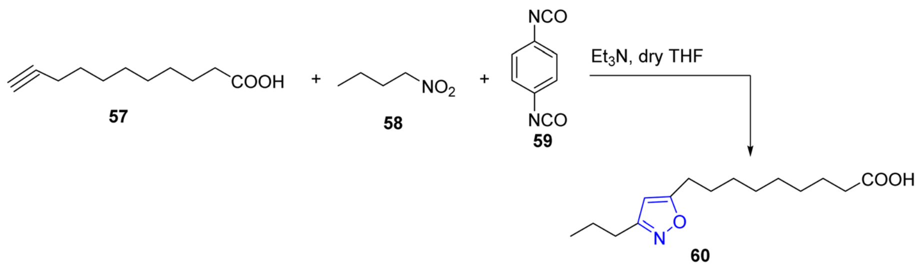
Kenar *et al.*, synthesized fatty acid esters of disubstituted isoxazoles in two steps starting from aldoximes. Firstly, aldoximes **46** reacted with aqueous sodium hypochlorite and a catalytic amount of triethylamine to form the reactive intermediate **47**



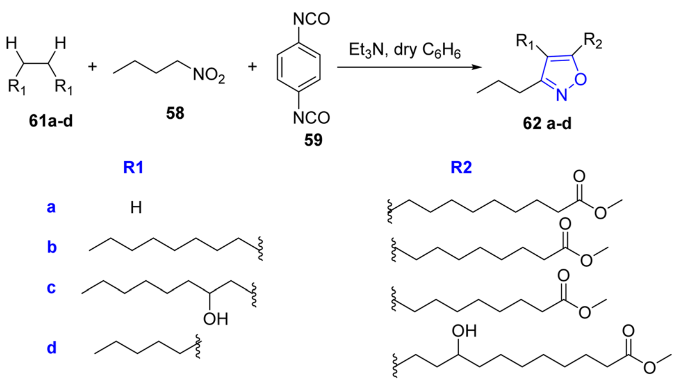
Scheme 9 Synthesis of fatty ester isoxazoline derivatives **50**.



Scheme 10 Preparation of 5-heptadecyl-3-methylisoxazole **56** by using lithium diisopropyl amide.



Scheme 11 Synthesis of carboxy isoxazol **60**.



Scheme 12 Synthesis of isoxazole derivatives **62a–d**.

which was trapped with methyl 10-undecenoate **48** leading to yield the target compound of the fatty ester isoxazoline derivatives **50** (ref. 32 and 33) (Scheme 9).

In addition, the same research group synthesized new isoxazole bearing long chain fatty acid through many steps. It is found that the treatment of *N*-(propan-2-ylidine) propan-2-amine **51** with an excess of lithium diisopropyl amide (LDA) in THF below −5 °C, gives its corresponding lithiated imine anion **52.** Subsequent reaction of the lithiated anion with fatty ester **1** (methyl oleate) which was deprotonated by a second equivalent of LDA to yield the keto enamine **53** which undergoes rearrangement to produce **54.** Enamine **54** was then converted into its corresponding ketoxime derivative **55** through the reaction of hydroxylamine hydrochloride at pH 5–6. The latter compound was heated in concentrated sulfuric acid to afford the fatty isoxazole **56** as final product with fairly good yield[34] (Scheme 10).

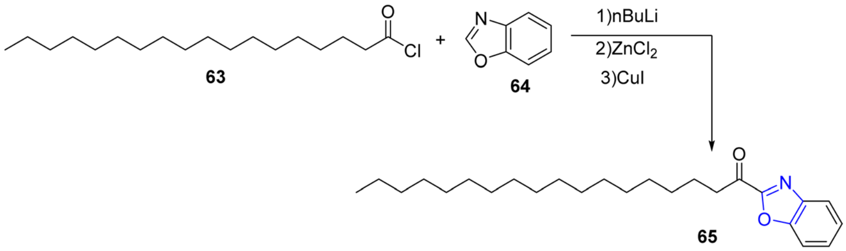
In an attempt to prepare isoxazole with fatty acid, a reaction between three-components; the long chain alkynoic acid **57**, Nitrobutane **58** and 1,4-phenylene diisocyanate **59** occurred in tetrahydrofuran (THF) and catalytic amount of Triethylamine to afford 5-(carboxyoctyl)-3-propylisoxazole **60** (Scheme 11).

With the same previous method, the esters of fatty acids **61a–d** reacted with nitrobutane **58** and 1,4-phenylene diisocyanate **59** in dry benzene yielded derivatives from fatty acid isoxazole **62a–d** (ref. 35) (Scheme 12).

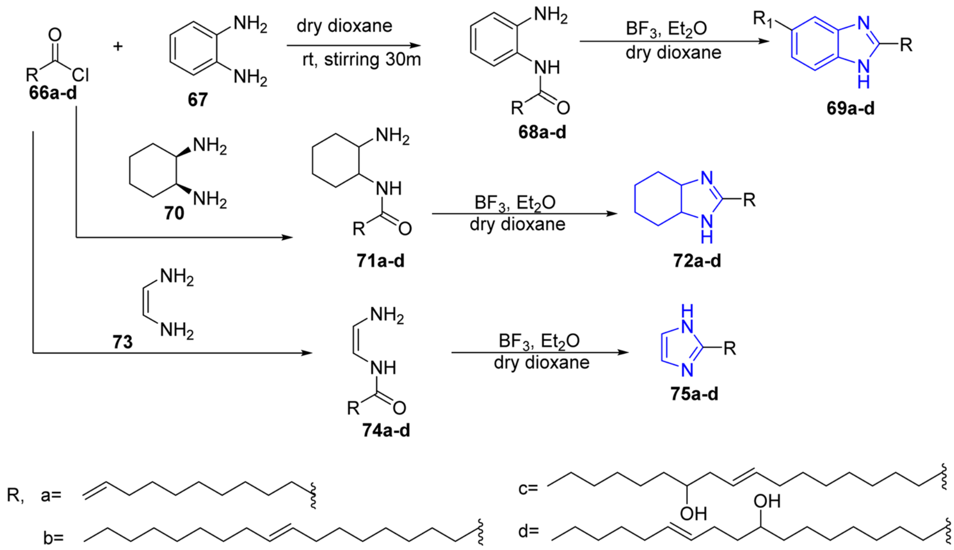
Anderson *et al.* have described the preparation of α-keto benzoxazole **65** *via* acylation of oleoyl chloride **63** with Zn/Cu metalated benzoxazole **64** according to the following scheme[36] (Scheme 13).

3.3. Synthesis of imidazole, benzoimidazole and thioimidazoline derivatives

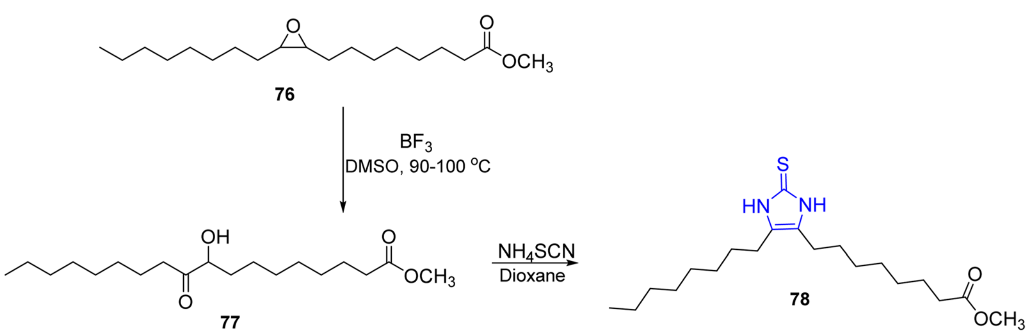
Abdul Rauf and co-worker have synthesized imidazole, benzoimidazole and tetrahydrobenzimidazoles bearing long chain fatty acid *via* a one-pot manner. This reaction started by the formation of the acid chlorides of **66a–d**, which then reacted with 1,2-phenylenediamine derivatives **67** in dry dioxane to yield *N*-acyl-1,2-phenylenediamine derivatives **68a–d.** The latter compounds were cyclized by using borontrifluoride and diethylether to afford the target compounds **69a–d.** The same method



Scheme 13 Synthesis of α-keto benzoxazole **65** *via* acylation of oleoyl chloride **63**.



Scheme 14 Formation of imidazole, benzoimidazole and tetrahydrobenzimidazoles bearing long chain fatty acid.

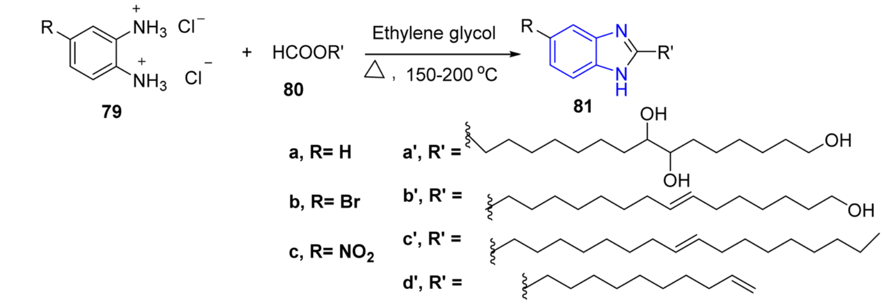


Scheme 15 Synthesis of thioimidazoline derivative **78**.

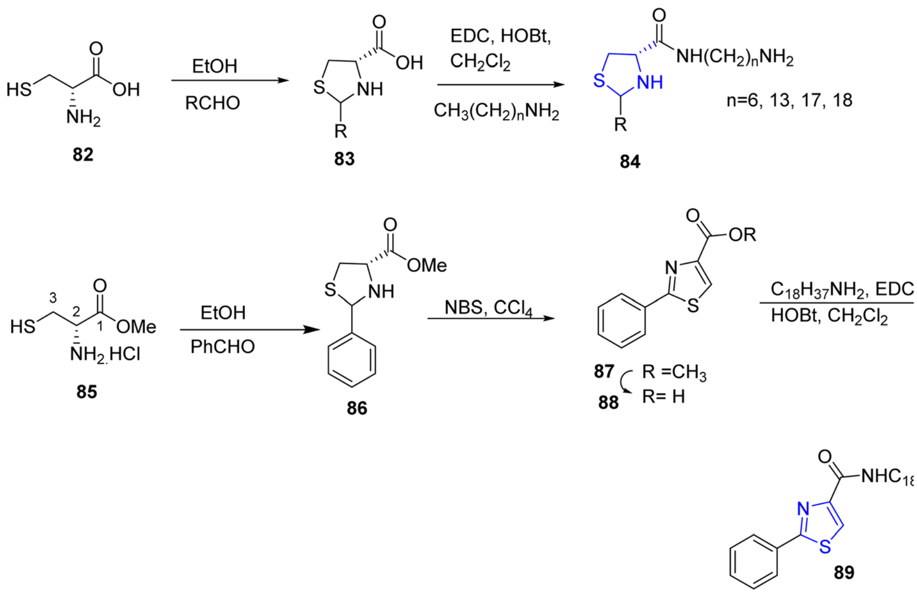
was applied to prepare tetrahydrobenzimidazole **72a–d** and imidazole **75a–d** using tetrahydrodiamine **70** and ethylenediamine **73**, respectively[37] (Scheme 14).

The α-hydroxy ketone of oleic acid **77** was achieved in accordance with the method published by Brous and Lefort[38] *via* the oxidation of methyl *cis*-9,10-epoxyoctadecanoate **76** with dimethyl sulfoxide at 90–100 °C in the presence of boron trifluoride, which was cyclized to obtain the thioimidazoline derivative **78** through the method published by Vandenberghe and Willems procedure[39,40] (Scheme 15).

On the other hand, Hosamani *et al.*, described a convenient method for the preparation of 2-alkyl substituted benzimidazole derivatives. These target compounds were synthesized from the reaction of derivatives of *o*-phenylenediamine dihydrochloride **79** and fatty acid derivatives **80** using ethylene glycol as reaction media to furnish the 2-alkyl substituted benzimidazole derivatives **81** (ref. 41) (Scheme 16).



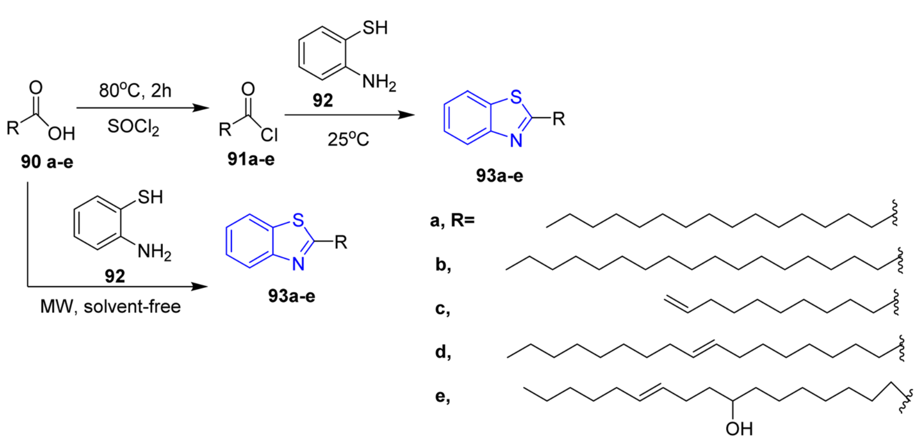
Scheme 16 Synthesis of 2-alkyl substituted benzimidazole derivatives **81**.



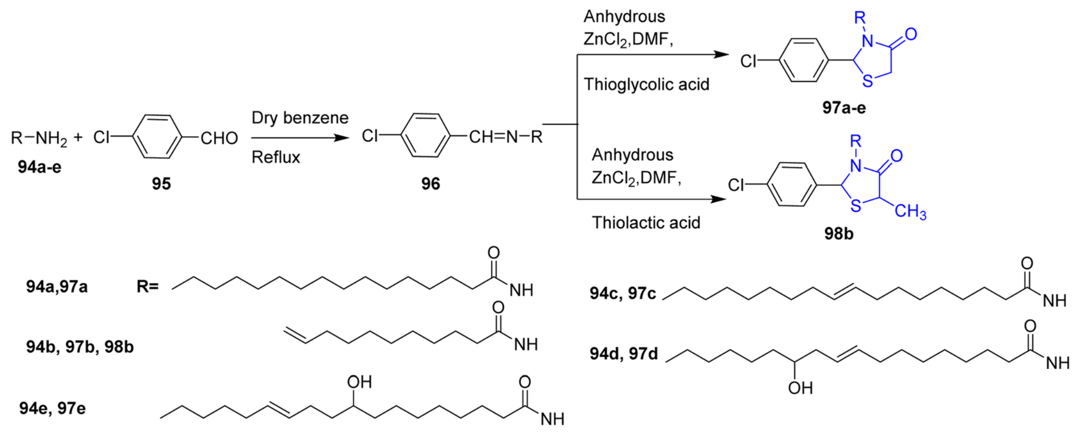
Scheme 17 Synthesis of *N*-octadecyl-2-phenylthiazole-4-carboxamide **89**.

3.4. Synthesis of thiazole, benzothiazole and thiazolidinone derivatives

Many scientific researchers have reported the preparation of thiazolidine derivatives with fatty acid,[42–44] therefore, a series of thiazolidine and thiazole appended fatty acid derivatives were synthesized *via* Gududuru *et al.* reaction of L-cysteine **82** with numerous aldehydes in ethanol which led to the corresponding acids **83** as diastereomeric mixtures. These mixtures reacted with alkylamines in presence of methylene chloride and EDC/HOBt to afford the corresponding alkylamide thiazolidine **84**.



Scheme 18 Synthesis of benzothiazoles bearing long chain fatty acid **93a–e**.



Scheme 19 Synthesis of 2,3-disubstituted-4-thiazolidinones derivatives.

Similarly, thiazole fatty acid **89** was prepared *via* reaction of the methyl D-cysteinate hydrochloride **85** with benzaldehyde to give compound **86** which was converted to the thiazole **87** by NBS, CCl_4, then the acidic compound **88** was reacted with alkylamine to afford the target compound of thiazole **89** (ref. 45) (Scheme 17).

In 2008, Abdul Rauf *et al.* designed and synthesized benzothiazoles bearing long chain fatty acid **93a–e** in two steps. First, fatty acid derivatives **90a–e** reacted with thionyl chloride to afford the corresponding acid chlorides **91a–e**, which reacted with 2-aminothiophenol **92** in toluene to yield the 2-substituted benzothiazoles **93a–e.** Alternatively, these target compounds are obtained using microwave by the reaction of fatty acid **90a–e** directly with 2-aminothiophenol **92** (ref. 46) (Scheme 18).

A novel series of 2,3-disubstituted-4-thiazolidinones was synthesized by Varshney *et al.*[47] This was accomplished by the condensation of fatty acid hydrazides **94a–e** with *p*-chlorobenzaldehyde **95** in dry benzene to afford the key intermediate compounds **96.** These intermediates; **96** were conducted on thioglycolic acid (mercapto acetic acid) and thiolactic acid in presence of DMF and catalytic amount of $ZnCl_2$ yielding the thiazolidinones **97a–e** and **98b**, respectively (Scheme 19).

4. Synthesis of five membered heterocycles with three heteroatoms

4.1. Synthesis of oxadiazole and thiadiazole derivatives

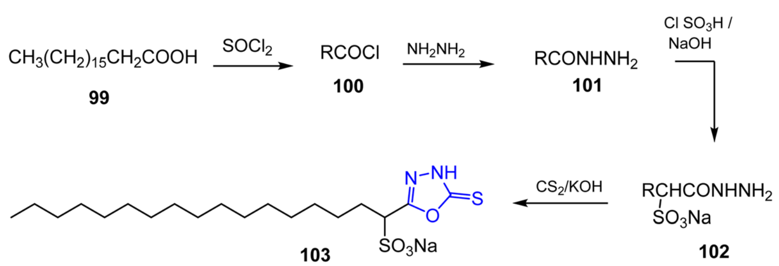
The fatty acid hydrazide **101** was reacted with chlorosulphonic acid in carbon tetrachloride and neutralized by sodium hydroxide to give sodium salt of α-sulphonated fatty acid hydrazide **102**. The later compound has been reacted with carbon disulphide in the presence of potassium hydroxide as a catalyst to give the oxadiazole derivative **103** (ref. 48) (Scheme 20).

In another study, Abdul Rauf and collaborators synthesized a series of new 2,5-disubstituted-1,3,4-oxadiazoles by using long-chain alkanoic and alkenoic acids. Fatty acids **104a–f** reacted with thionylchloride to afford acid chloride of fatty acids **105a–f**, then reacted with hydrazine hydrate in dry dioxane furnishing the corresponding 1,2-diacylhydrazine **106a–f.** These derivatives underwent cyclodehydration *via* using BF_3–OEt_2 yielding fatty acid of 1,3,4-oxadiazoles **107a–f** (ref. 49) (Scheme 21).

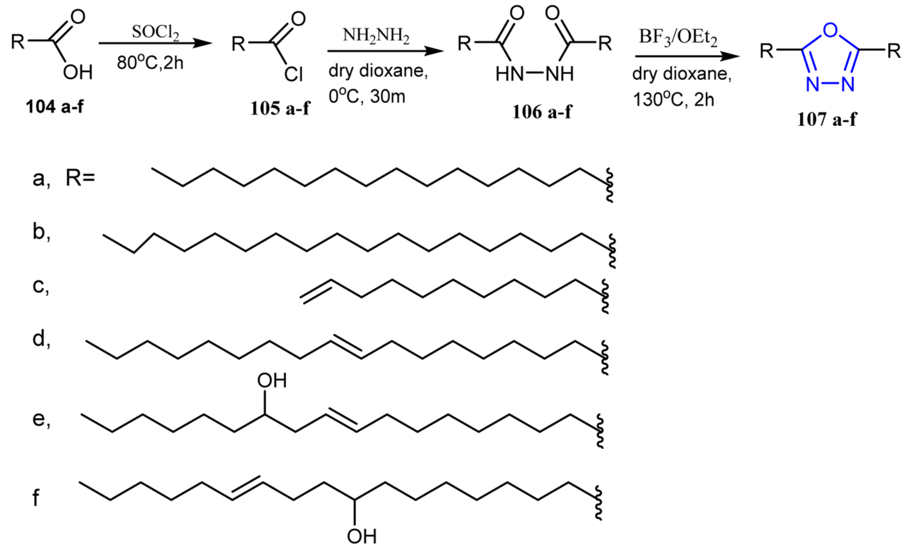
Farshori and co-workers[50] reported the synthesis of thiadiazole **110a–c** and oxadiazole **112a–c** derivatives from long chain fatty acid hydrazides. In this reaction fatty acid hydrazides **108a–c** reacted with phenyl isothiocyanate in dry benzene to afford the corresponding thiosemicarbazide derivatives **109a–c** which were cyclized using acetic anhydride to give thiadiazoles **110a–c** (Scheme 22).

Similarly, refluxing the key compounds **108a–c** with phenyl isocyanate in presence of dry benzene afforded the semicarbazides **111a–c**, then, the treatment of **111a–c** with $POCl_3$ furnished oxadiazoles **112a–c** (Scheme 23).

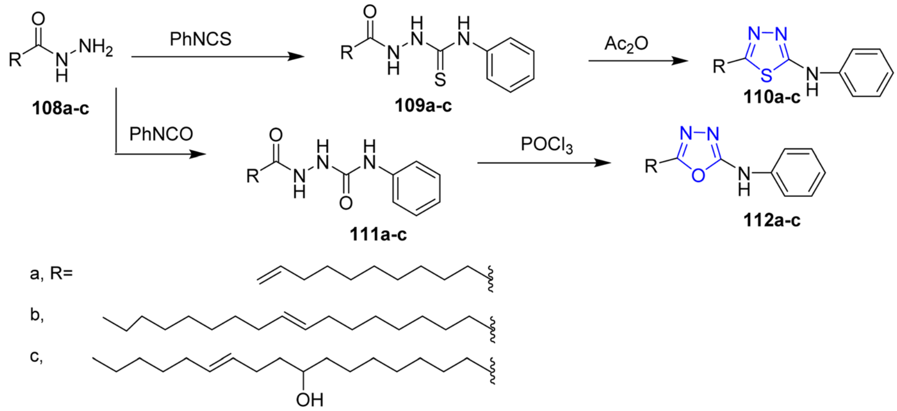
In 2010, Banda and co-workers developed an efficient and facile route for the preparation of disubstituted 1,3,4-oxadiazoles. Fatty acid hydrazides **13a–d** were treated with benzoyl chloride under inert atmospheric conditions to afford the intermediates of diacylhydrazide which were cyclized by using dehydrating agent and phosphorus oxychloride to yield the 2-



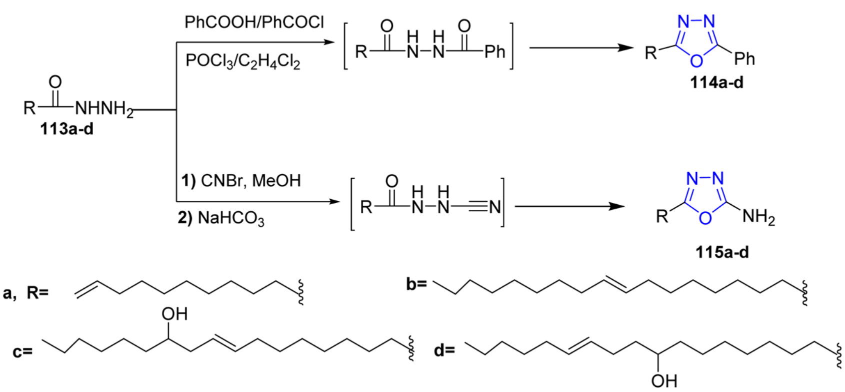
Scheme 20 Synthesis of oxadiazole **103**.



Scheme 21 Synthesis of fatty acid of 1,3,4-oxadiazoles **107a–f**.



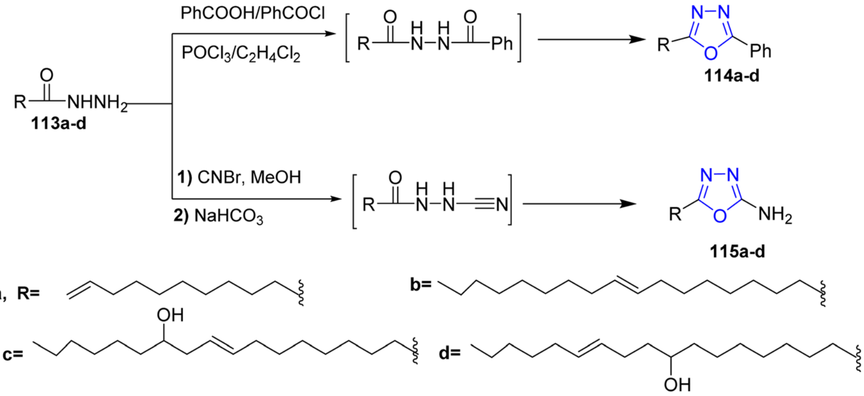
Scheme 22 Synthesis of thiadiazole **110a–c** and oxadiazole **112a–c** derivatives.



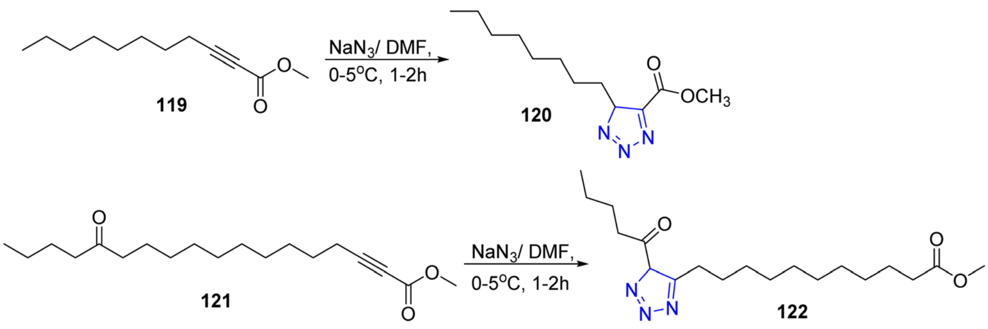
Scheme 23 Preparation of di-substituted 1,3,4-oxadiazoles derivatives.

(alkenyl)-5-phenyl-1,3,4-oxadiazoles **114a–d**. Alternatively, the 5-(alkenyl)-2-amino-1,3,4-oxadiazoles **115a–d** were prepared *via* treatment of fatty acid hydrazides **113a–d** with cyanogen bromide in dry methanol then cyclized to form the target aminoxadiazoles **115a–d** (ref. 51) (Scheme 23).

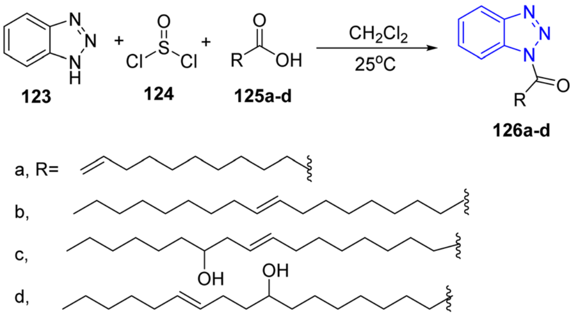
In 2017, Soliman *et al.*,[52] described an efficient and facile route for the preparation of thiadiazole derivatives. This



Scheme 24 Synthesis of thiadiazole derivatives **118a** and **118b**.



Scheme 25 Synthesis of ester of 1,2,3-triazole derivatives **120** and **122**.



Scheme 26 Preparation of benzotriazole derivatives **126a–d**.

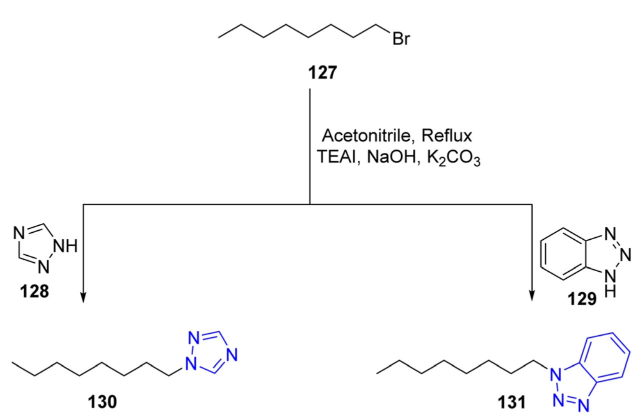
occurred through the reaction of palmitic thiosemicarbazide **116** (prepared *via* reaction of palmitic acid hydrazide with phenyl isothiocyanate in dry dioxane) and ethyl ester of hydrozonylhalides **117a** and **117b** in dimethylformamide and catalytic amount of triethylamine which afforded the substituted thiadiazole derivatives **118a** and **118b** (Scheme 24).

4.2. Synthesis of triazole and benzotriazole derivatives

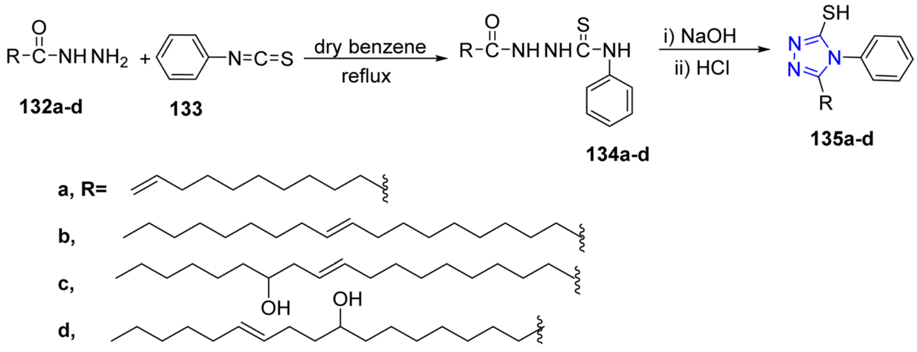
In 1998, a series of 1,2,3-triazole derivatives was synthesized *via* the reaction of acetylenic fatty acid esters such as methyl 2-undecynoate **119**, 14-oxo-12-octadecynoates **121** with sodium azide in presence of dimethylformamide to afford the corresponding triazoles **120** and **122**, respectively[53] (Scheme 25).

Furthermore, Abdul Rauf and co-workers reported one pot synthesis of fatty –N-acyl-1*H*-1,2,3 benzotriazoles **126a–d** by stirring benzotriazoles **123**, thionylchloride **124** and fatty acids **125a–d** in methylene chloride at room temperature[54] (Scheme 26).

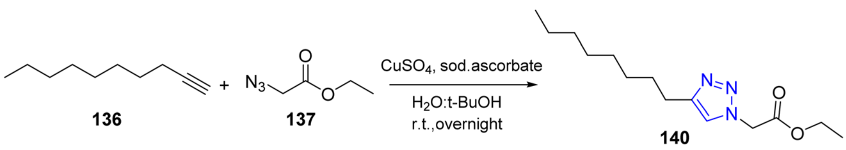
Similarly in 2009, Rezaei *et al.*, described the synthesis of triazole and benzotriazoles bearing fatty acids from refluxing triazole **128** and benzotriazoles **129** with alkylbromide **127a** in acetonitrile added to catalytic amount of tetra ethyl ammonium iodide (TEAI), sodium hydroxide (NaOH) and anhydrous



Scheme 27 Synthesis of triazole **130** and benzotriazole **131**.



Scheme 28 Synthesis of triazole derivatives **135a–d** from fatty acid hydrazides.



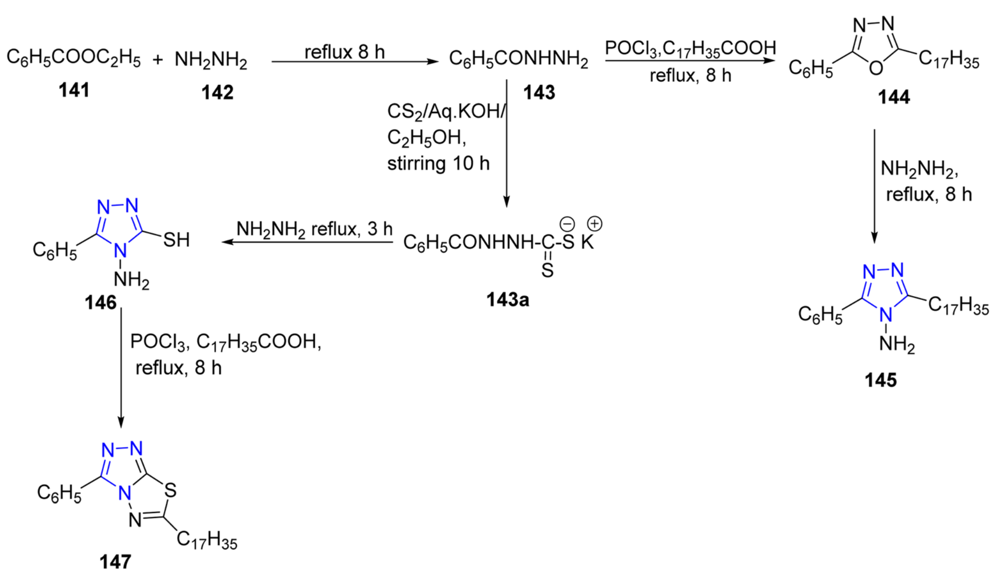
Scheme 29 Synthesis of triazole **140** *via* click reaction.

potassium carbonate (K_2CO_3) to furnish the target compounds **130** and **131**, respectively[55] (Scheme 27).

In addition, the refluxing of fatty acid hydrazides **132a–d** with phenyl isothiocyanate **133** in dry benzene gave thiosemicarbazides **134a–d.** The later compounds were subjected to intermolecular cyclization in alkaline medium (2 M, NaOH) followed by acidification with HCl to yield 1,2,3-triazoles **135a–d** (ref. 56) (Scheme 28).

Moreover, click chemistry was considered as an interesting method for triazole preparation.[57–60] Therefore, Labadie and coworkers utilized click chemistry to obtain triazole compounds. Therefore, the azide compound reacted with alkynes by using sodium ascorbate as reductant in the mixture of water and *t*-BuOH, under catalytic activity of copper(II) sulphate to afford 1,2,3-triazole[61] (Scheme 29).

In 2012, another important work for the synthesis of stearic fatty acid of triazoles by Jubie *et al.* was described. The key intermediate of benzoic hydrazide **143** was obtained by refluxing ethyl benzoate **141** and hydrazine hydrate **142** in ethyl alcohol. Compound **143** reacted with stearic acid in presence of phosphorous oxychloride and neutralized with NaOH to furnish 1,3,4-oxadiazole **144**. The treatment of **144** with excess hydrazine yielded the 2-(heptadecyl)-5-phenyl-1,2,4-triazole **145**. In addition, the reaction of acid hydrazide **143** with



Scheme 30 Synthesis of 3-heptadecyl-5-phenyl-4*H*-1,2,4-triazol-4-amine **145** and 6-heptadecyl-3-phenyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **147**.

carbondisulfide in ethanol using potassium hydroxide led to the formation of the corresponding potassium dithiocarbazinate **143a** which was refluxed with hydrazine hydrate to give 4-amino-5-phenyl-4*H*-1,2,4 triazole-3-thiol **146**. The later compound was subjected to cyclization using stearic acid and $POCl_3$ as a solvent to get 6(-heptadecyl)-3-phenyl-[1,2,4] triazolo [3,4-*b*]1,3,4-thiadiazole **147** (ref. 62) (Scheme 30).

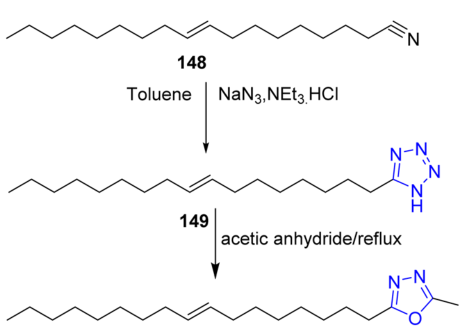
5. Synthesis of five membered heterocycles with four heteroatoms

5.1. Synthesis of 5-alkyl-1*H*-tetrazoles

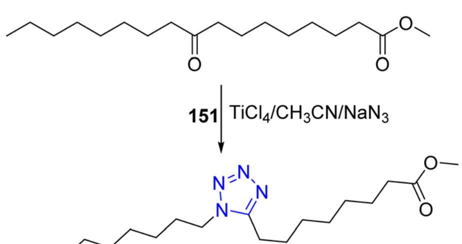
Various fatty nitriles[63] were converted to the corresponding 5-alkyl-1*H*-tetrazoles by using 3 equivalents of sodium azide and triethylamine hydrochloride in dry toluene such as oleyl nitrile **148** which could be converted to 5-oleyl-1*H*-tetrazole **149** (ref. 33). It is worthy to mention that, the 5-oleyl-1*H*-tetrazole **149** could be converted to the corresponding 1,3,4-oxadiazole **150** in a satisfactory yield *via* Huisgen reaction[64] (Scheme 31).

Further, Suzuki *et al.*[65] reported that the 1,5-disubstituted tetrazoles may be synthesized from ketones. Therefore, a mixture of methyl 9-oxoheptadecanoate **151**, sodium azide and titanium(IV) chloride were refluxed in acetonitrile, to produce methyl 8-(1-octyl-1*H*-tetrazol-5-yl)octanoate **152** in a good yield (Scheme 32).

Moreover, the alkyl branched tetrazole could be achieved by the reaction of methyl oleate **1** with iodoacetonitrile in the presence of copper powder.[66] Then, the resulting cyanomethyl-iodo derivative **153** was reduced under hydrogenation in the presence of palladium on charcoal to afford the intermediate **154** which was reacted with sodium azide to give the alkyl branched tetrazole derivative **155** as a final product[33] (Scheme 33).



Scheme 31 Synthesis of tetrazole **149** and oxadiazole **150**.



Scheme 32 Synthesis of methyl 8-(1-octyl-1*H*-tetrazol-5-yl)octanoate **152**.

6. Synthesis of six membered heterocycles with one heteroatom

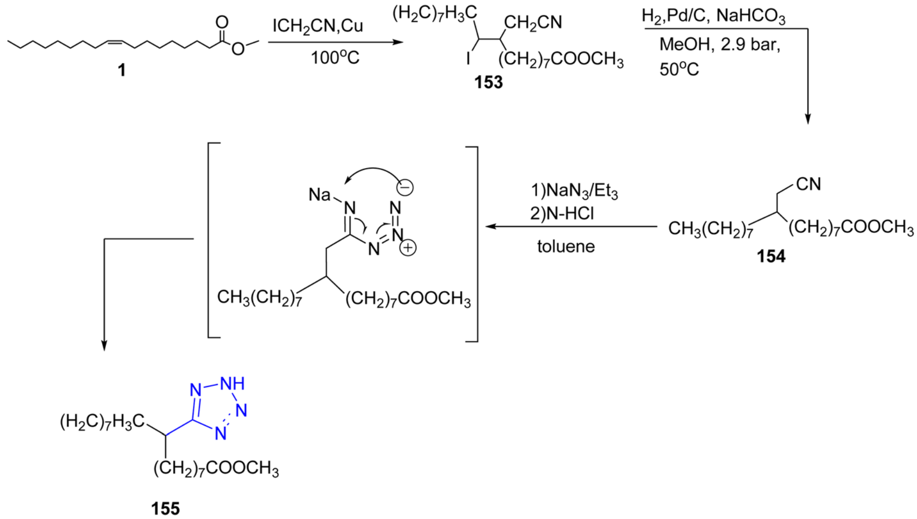
6.1. Synthesis of quinolone and isoquinoline derivatives

In 2016, Venepally *et al.*, performed the synthesis of dihydro-4-oxoquinoline linked to fatty acids. Starting from the reduction of 3,4-difluoro nitrobenzene **156** with iron and ammonium chloride in methanol to afford 3,4-difluorobenzenamine **157**. The latter compound was treated with diethyl ethoxymethylene malonate to give diethyl-2-((3,4-difluorophenylamino) methylene) malonate **158**. Then compound **158** was cyclized under reflux in presence of diphenyl ether yielding ethyl 6,7-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate **159**. Furthermore, ethyl-1-ethyl-6,7-difluoro-1,4-dihydro4-oxoquinoline-3-carboxylate **160** was obtained by the treatment of compound **159** with iodoethane in the presence of potassium carbonate. The next step aimed at the formation of azide group at C-7 position by reacting compound **160** with sodium azide in dimethyl formamide to give compound **161**. This compound was reduced using zinc and ammonium chloride to yield compound **162**. Finally, the fatty acyl chlorides reacted with compound **162** in the presence of triethylamine in dichloromethane to form the corresponding target compounds **163a–h** (ref. 67) (Scheme 34).

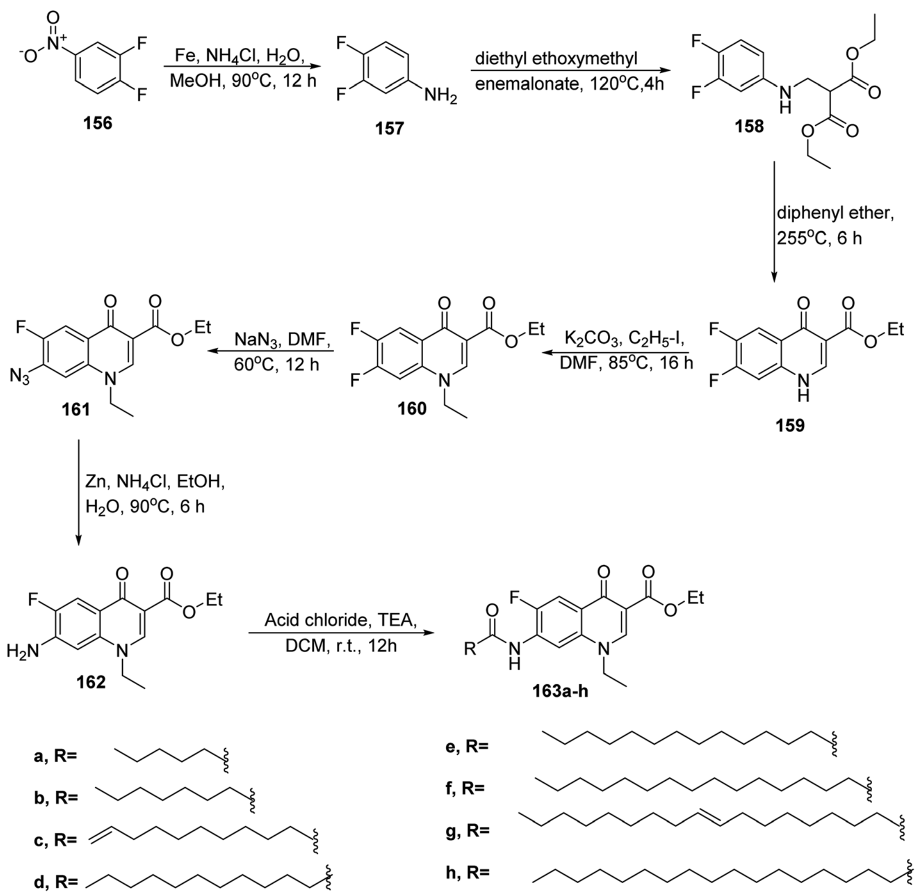
In addition, Malinak and co-workers published the reflux reaction of 6-hydroxyquinoline **164** with alkylbromide in acetonitrile to afford 6-hydroxyquinolinium salts bearing long chain side chain **165a–d** (ref. 68) (Scheme 35).

Moreover, the Pictet–Spengler reaction[69,70] for the synthesis of isoquinolines was used to afford 1-substituted-1,2,3,4-tetrahydroisoquinolines **168a–d** through the reaction of dopamine **166** with aldehyde derivatives **167a–d** in *n*-propanol. The treatment of **168a–d** with an excess of methyl chloroformate in the presence of pyridine gave the peracyl derivatives **169a–d.** The deprotection of carbonate groups was performed *via* ammonolysis under very mild conditions to afford amides **170a–d** which directly were di-*o*-methylated with methyl iodide to give the 1-substituted-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **171a–d** in fair yields[71,72] (Scheme 36).

Also, there was another method for preparation of isoquinoline skeleton named Bischler–Napieralski cyclization.[69,70] In that case, it has been started by homoveratrylamine (3,4-dimethoxyphenethylamine) **172** and the appropriate fatty acid **173a–d** to form amides **174a–d** in mild condition reaction.[73] This method afforded optimal yield of the product, in addition to the chemical and stereochemical stability of the acid used. Then, treatment of the amides **174a–d** with phosphorous pentachloride in dichloromethane at 0 °C gave relatively unstable imines **175a–d** in fair yields, which were pure without any contamination of chlorinated products. The later compounds **175a–d** were reduced with sodium borohydride to afford the



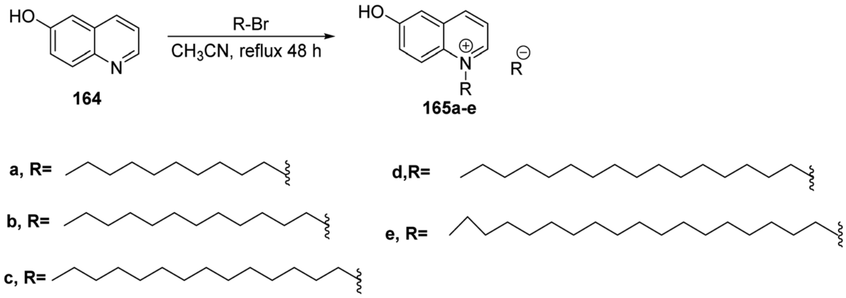
Scheme 33 Synthesis of tetrazole **155** from methyl oleate **1**.



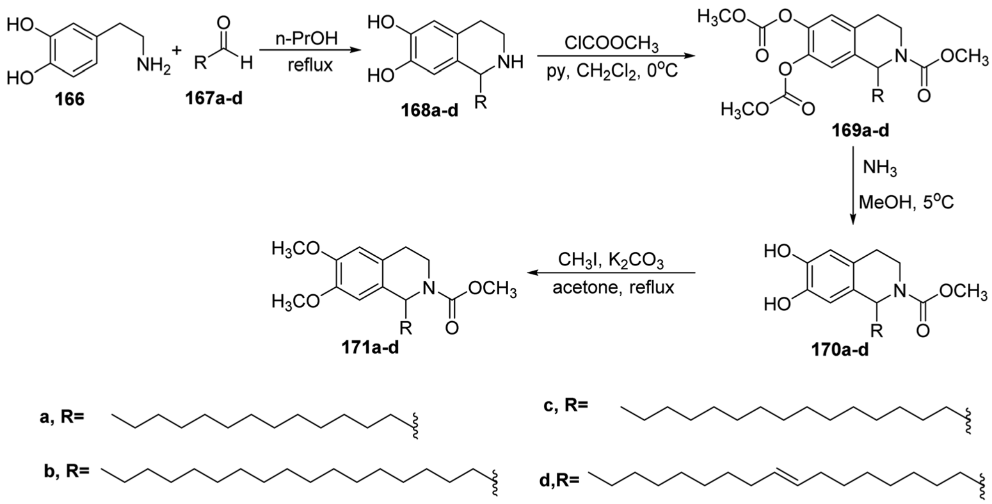
Scheme 34 Preparation of dihydro-4-oxoquinoline derivatives **163a–h**.

secondary amines **176a–d** in high yields (around 80%), which were quite stable without observable decomposition at room temperature[74] (Scheme 37).

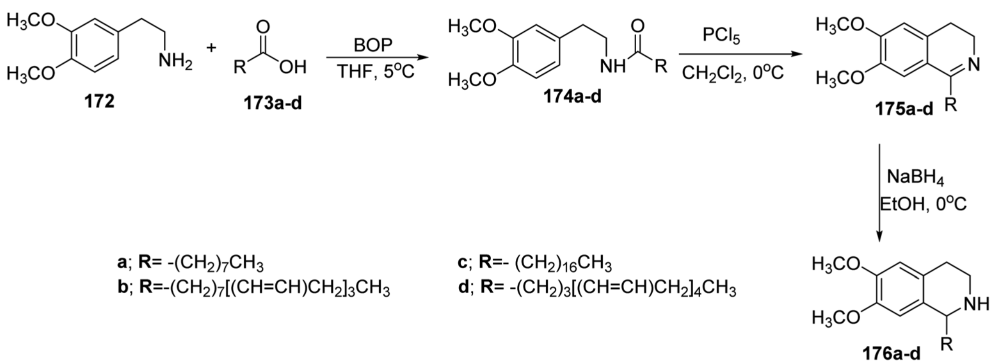
In 2016, Diego da Costa Cabrera *et al.* utilized a multi-component reaction to prepare polyhydroquinoline with fatty acid in the presence of catalyst. In this reaction, a mixture of four-component reaction including fatty β-ketoesters **177a–c** with the appropriate aromatic aldehydes **178a–e**, dimedone **179** and ammonium acetate **180** were boiled in acetonitrile in presence of sulfamic acid (H_2NSO_3H) or indium chloride ($InCl_3$)



Scheme 35 Synthesis of 6-hydroxyquinolinium salts bearing fatty acids derivatives **165a–e**.



Scheme 36 Synthesis of 1-substituted-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **171a–d** by using Pictet–Spengler reaction.

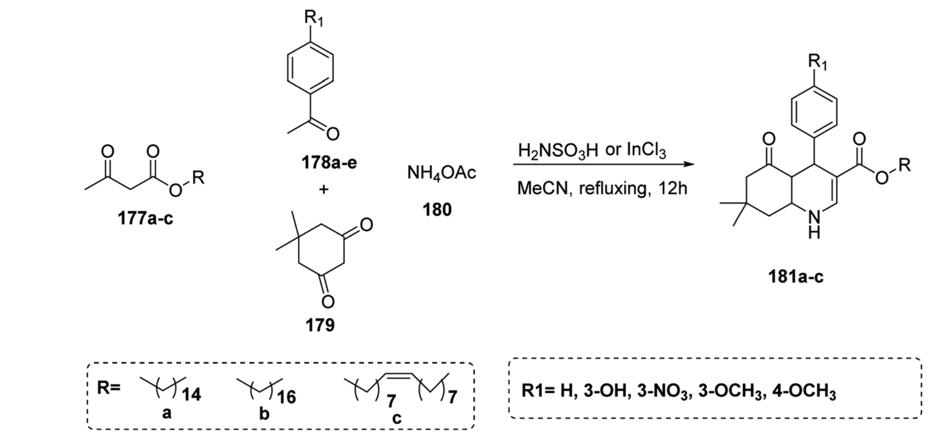


Scheme 37 Synthesis of isoquinoline derivatives **176a–d**.

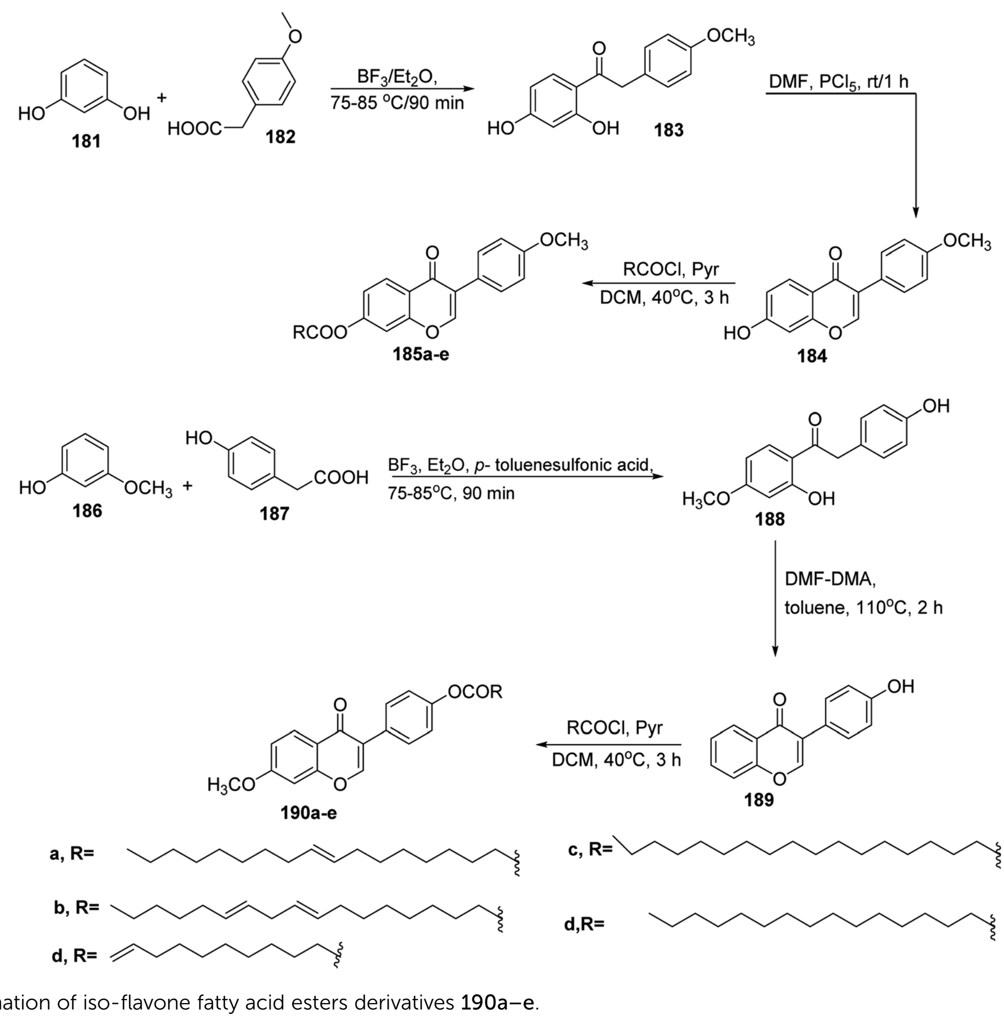
as a catalyst to afford the polyhydroquinoline derivatives bearing long chain fatty acid **181a–c** as target compounds[75] (Scheme 38).

6.2. Synthesis of iso flavone and pseudopyronine fatty acid derivatives

The Iso flavone fatty acid esters were obtained by refluxing the derivatives of daidzein **184** and fatty acid chloride in pyridine as a catalyst and methylene chloride. In this reaction, 2,4-dihydroxy-4′-methoxydeoxybenzoin **183** was prepared from reaction of resorcinol **181** and 4-methoxy phenyl acetic acid **182** by Friedel–Crafts acylation using boron trifluoride etherate as a solvent. Then, compound **183** was treated with Vilsmeier reagent to afford 4′-methoxy daidzein **184** (7-hydroxy-3-(4-methoxyphenyl)-4*H*-chromen-4-one) under mild conditions.[76] The later compound reacted with fatty acid chloride derivatives yielding daidzein derivatives **185a–e**. Furthermore, 7-methoxy daidzein with fatty acid derivatives **190a–e** were obtained with a similar strategy using 3-methoxyphenol **186** as starting material[77,78] (Scheme 39).

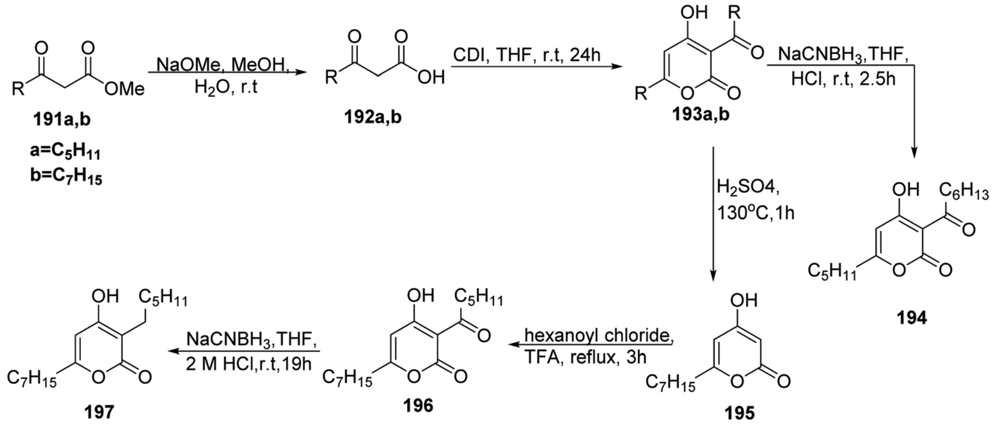


Scheme 38 Synthesis of polyhydroquinoline derivatives bearing long chain fatty acid **181a–c** through one-pot four-component reaction.



Scheme 39 Formation of iso-flavone fatty acid esters derivatives **190a–e**.

On the other hand, the preparation of pseudo pyronine **194** (ref. 79 and 80) started from the known methyl β-oxo esters **191a** and **191b**, which were deesterified to the corresponding carboxylic acids **192a** and **192b** *via* saponification.[81] Then, cyclization of **192** using carbonyl diimidazole afforded the target acylpyrone skeleton **193a** & **193b.** Then the deviation started, the pseudo pyronine **194** was achieved by reducing **193a.**[82] Alternatively, the achievement of pseudopyrone B **197** began with the deacylation of **193b** to yield 6-heptyl-4-hydroxy-2-



Scheme 40 Synthesis of pseudo pyronine **194** and pseudopyrone B **197**.

pyrone **195** followed by acylation to furnish **196**, which was reduced giving **197** (ref. 83) (Scheme 40).

7. Synthesis of six membered heterocycles with two heteroatoms

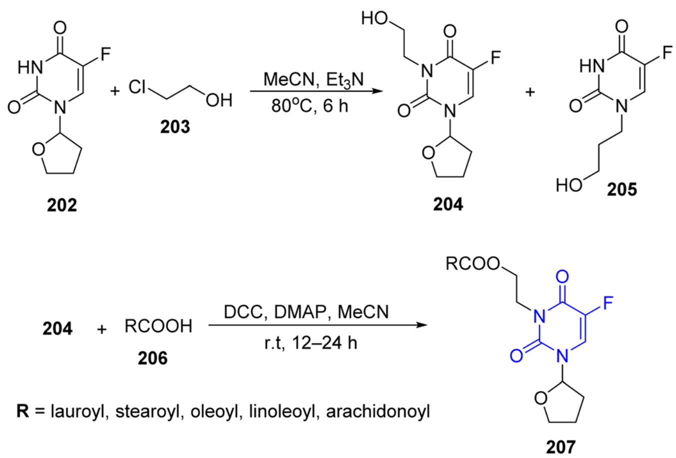
7.1. Synthesis of uracil bearing fatty residues

In this study, uracil derivative **198** was subjected to silylation process using hexamethyldisilazine (HMDS) to afford bis (trimethylsilyl) derivative **199**, then reacted with fatty acid of stearoyl chloride **200** to give uracil having N-fatty residue **201** (ref. 84) (Scheme 41).

Xu and co-workers[85] have reported the reaction of fluorouracil **202** with 2-chloroethanol **203** in acetonitrile and $NaHCO_3$ affording a mixture of two compounds **204** and **205** in 1 : 6 molar ratio. Then, novel fatty acid nucleoside conjugates **207** were synthesized *via* the reaction of **204** with the appropriate fatty acid **206** (Scheme 42).

Furthermore, The β-keto ester **208** was reacted with thiourea in the presence of sodium ethoxide to afford **209** having the fatty residue at position 6 (ref. 86) (Scheme 43).

Moreover, it has been mentioned that the syntheses of 1,6-heptadienes with uracil and/or thymine was achieved starting from the 2-allyl-pent-4-enoic acid **210**.[87] Reduction of compound **210** to the corresponding primary alcohol, 2-allyl-pent-4-en-1-ol **211**, was achieved with lithium aluminum hydride (LAH) in 98% yield.[88,89] The ^{3}N-protected uracil and thymine bases have been prepared following the reported procedures.[90] The Mitsunobu reaction was then employed to couple the ^{3}N-protected nucleic bases to 2-allyl-pent-4-en-1-ol utilizing triphenylphosphine and diisopropyl azodicarboxylate

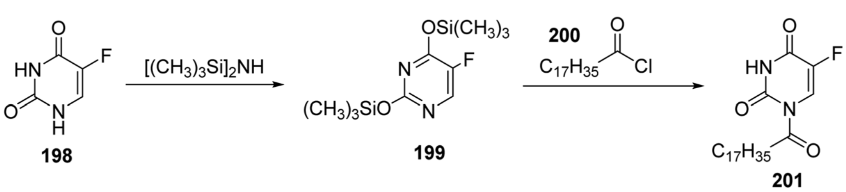


Scheme 42 Synthesis of fluorouracil bearing ester of fatty acids derivatives **207**.

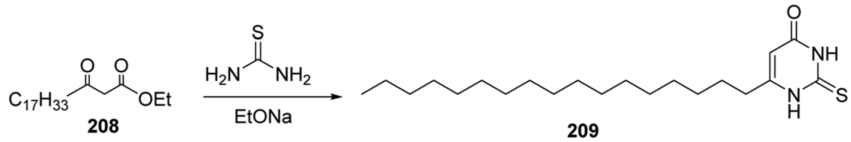
(DIAD) in dry dioxane to yield the heptadiene derivatives **212** and **213** in 69% and 77% yield, respectively.[91–93] The ^{3}N-benzoyl groups of intermediates **212** and **214** were then hydrolyzed in a methanolic solution of sodium methoxide to yield the target compounds 1-(2-allyl-pent-4-enyl)-1*H*-pyrimidine-2,4-dione **213** and 1-(2-allyl-pent-4-enyl)-5-methyl-1*H*-pyrimidine-2,4-dione **215** in 85% and 78% yield, respectively[94] (Scheme 44).

7.2. Synthesis of tetrahydropyrimidine and hydropyrimidinone derivatives

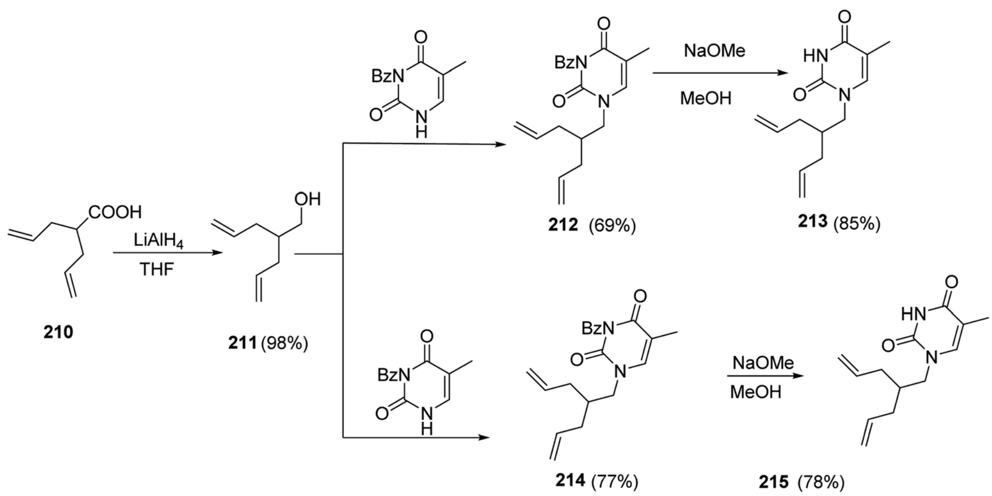
Recently, a synthetic approach to new glycolipids has been developed using Staudinger reaction. Starting from the reaction of lactose octaacetate **216** with commercially available 1,3-



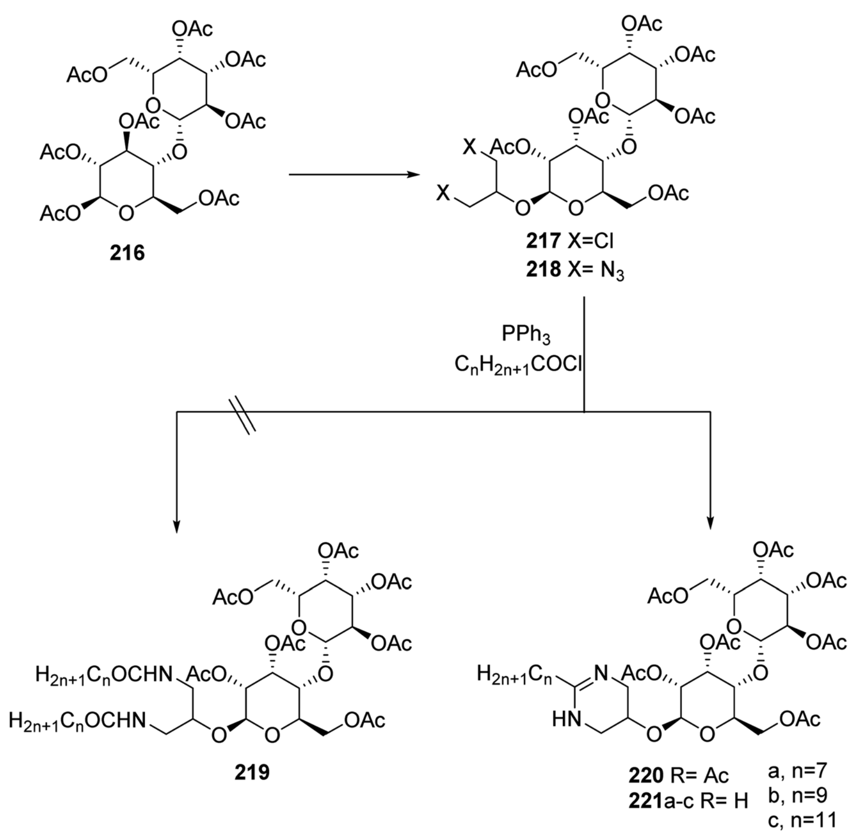
Scheme 41 Synthesis of 5-fluoro-1-stearoylpyrimidine-2,4(1*H*,3*H*)-dione **201**.



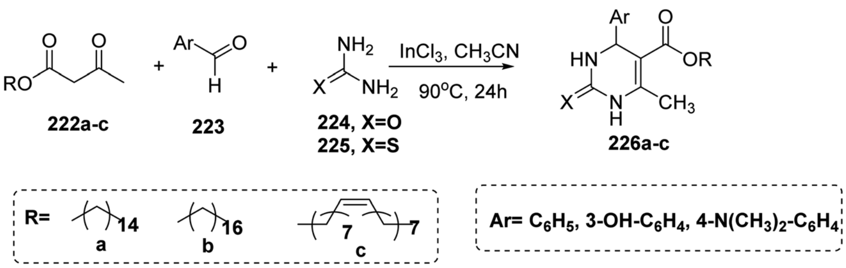
Scheme 43 Synthesis of 6-heptadecyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one **209**.



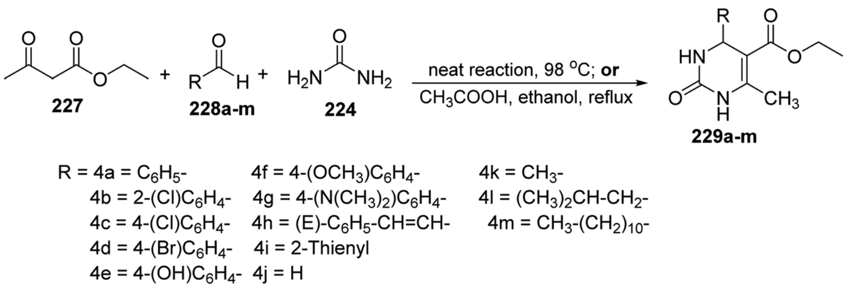
Scheme 44 Synthesis of 1-(2-allyl-pent-4-enyl)-1*H*-pyrimidine-2,4-dione **213** and 1-(2-allyl-pent-4-enyl)-5-methyl-1*H*-pyrimidine-2,4-dione **215**.



Scheme 45 Synthesis of tetrahydropyrimidine derivatives **220** and **221a–c**.



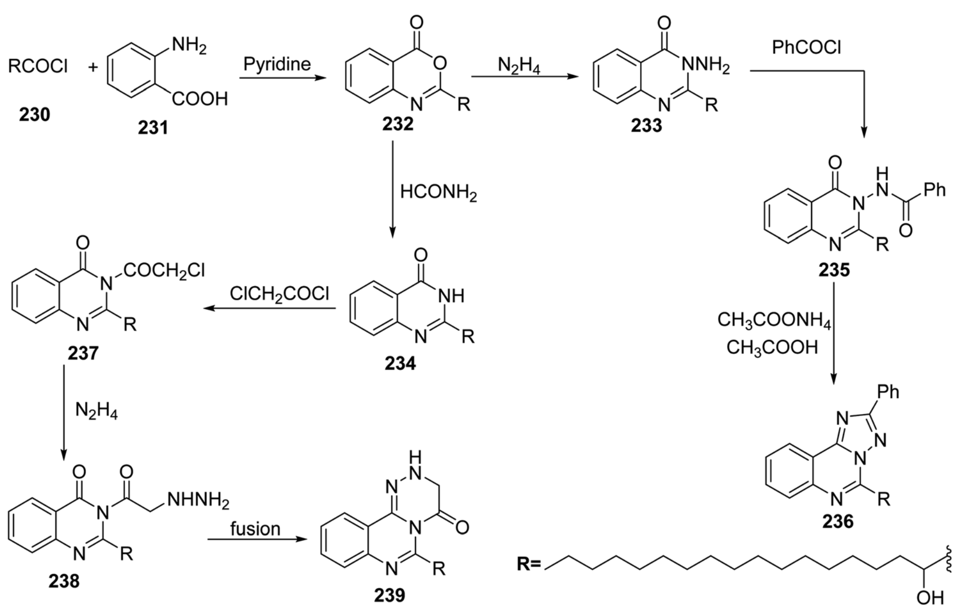
Scheme 46 Preparation of dihydropyrimidinone bearing fatty acids **226a–c** *via* one-pot three-component reaction.



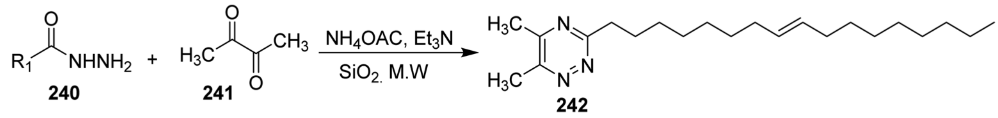
Scheme 47 Synthesis of dihydropyrimidinone **229a–m**.

dichloro-2-propanol followed by a subsequent substitution of the halide **217** (ref. 95) provided diazide **218** (ref. 96) in 48% yield. Staudinger reactions with various fatty acid chlorides ranging from C_8 to C_{12}, however, failed to provide the expected diamide **219**. Instead, the cyclic coupling products **220** were obtained in reproducible yields of 70%, which provided the corresponding surfactants **221a–c** upon deacetylation. Although phosphine mediated cyclizations of azido-amides have been reported previously,[97–99] the reaction product is rather unexpected. This does not only refer to the formation of tetrahydopyrimidines, which so far have been accessed by different strategies,[100–102] but particularly relates to the different behavior of glucose and lactose, despite identical stereochemistry at the reducing sugar[103] (Scheme 45).

Moreover, in 2015 Treptow *et al.*[104] synthesized new series of fatty acid 3,4-dihydropyrimidinones as a result of utilization of Biginelli multicomponent reaction. This reaction occurred by boiling a mixture of fatty acid of β-ketoester **222a–c**, with aromatic aldehydes **223** and urea **224** or thiourea **225** in acetonitrile in the presence of indium chloride as catalytic amount to



Scheme 48 Synthesis of quinazoline derivatives **234–239**.



Scheme 49 Preparation of 3,5,6-trisubstituted-1,2,4-triazines **242**.

afford the target compounds of dihydropyrimidinone bearing fatty acids **226a–c** (Scheme 46).

In 2017, Kumarasamy and co-workers described an efficient strategy for the preparation of derivatives of dihydropyrimidinone **229a–m** *via* the reaction of ethyl acetoacetate **227**, with different aldehydes **228a–m** and urea **224**. This reaction was conducted under two different conditions: first condition was solvent free heating and the other was reflux in acetic acid and ethanol[105] (Scheme 47).

7.3. Synthesis of quinazoline derivatives

It has been reported that 2-hydroxyheptadecanoic acid chloride **230** reacted with anthranilic acid **231** in pyridine to produce 2-(1-hydroxyheptadecyl)-1,3-benzoxazin-4-one **232**, which was used as starting material to synthesize some condensed and non-condensed heterocyclic compounds by the reaction with nitrogen nucleophiles such as hydrazine hydrate and formamide to give 3-amino-2-(hydroxyheptadecyl)-3*H*-quinazolin-4-one **233** and 2-(1-hydroxy heptadecyl)-3*H*-quinazolin-4-one **234**, respectively. Later, compound **233** was reacted with benzoyl chloride to afford **236.** Also, the treatment of **234** with chloroacetyl chloride in dimethyl formamide as a solvent gave **237** which was converted to the corresponding hydrazine derivative **238** *via* the heating of hydrazine hydrate in butanol. The hydrazine-derivative **238** was cyclized by fusion above its melting point to **239** (ref. 106) (Scheme 48).

8. Synthesis of six-membered heterocyclic compounds with three heteroatoms

8.1. Synthesis of triazines

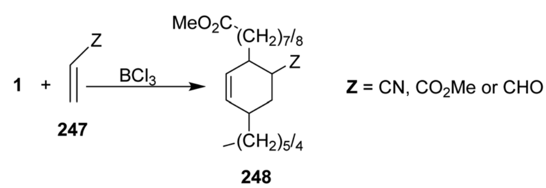
Synthesis of 3,5,6-trisubstituted-1,2,4-triazines **242** has been achieved by condensation of 1,2-diketones **241** with various saturated and olefinic fatty acid hydrazides **240** (*e.g.* oleoyl hydrazide) under Microwave (MW) and solvent-free conditions in short times[107] (Scheme 49).

9. Synthesis of other heterocycles

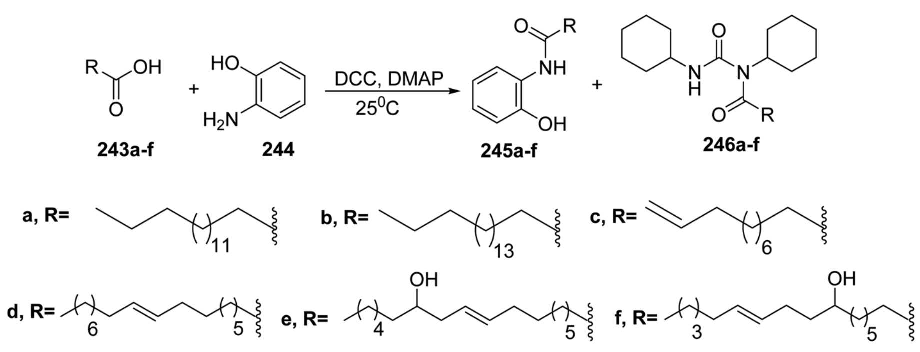
The reaction of carboxylic acids **243a–f** with 2-aminophenol **244** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane to afford several *o*-hydroxy anilide derivatives **245a–f** and 1-substituted-1,3-dicyclohexylurea analogues of carboxylic acids **246a–f** was conducted. During the DCC mediated reaction for the amide synthesis, the1,3-dicyclohexylurea analogues are formed as a side product[108] (Scheme 50).

Pericyclic reaction such as the reaction of fatty esters as diene (*e.g.* methyl *cis*-9,10-epiminooctadecanoate **1**) with dienophile **247** in the presence of Lewis acid (*e.g.*: BCl_3 or $SnCl_4$) as a catalyst, to give the cyclic adduct (Scheme 51). Moreover, cyclo addition of fatty acids with dimethyl acetylene dicarboxylate **249** gave Diels–Alder cyclo adduct **250** which was oxidized with DDQ to give the cycloarenes **251** which has a fatty acid residue[109] (Scheme 52). Furthermore, it has been found that the reaction of glucose **252** with oleic acid **253** in the presence of pyridine afforded *O*-oleoylglucose **254** in fairly yield[110] (Scheme 53).

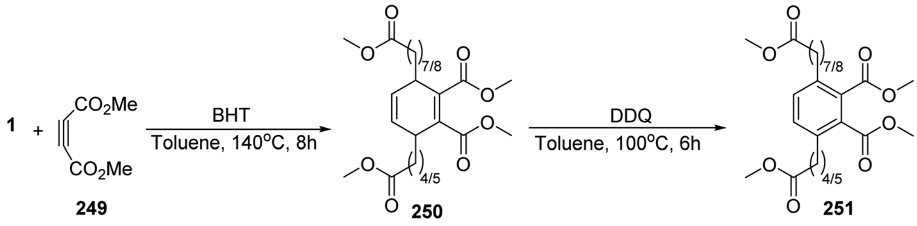
The target aminoacyl **263** was prepared in 7 steps, where, the 5′ position of **255** was protected with the TBDMS group to yield compound **256**, which was reacted with oleic acid to obtain 2′-



Scheme 51 One-pot synthesis of **248**.

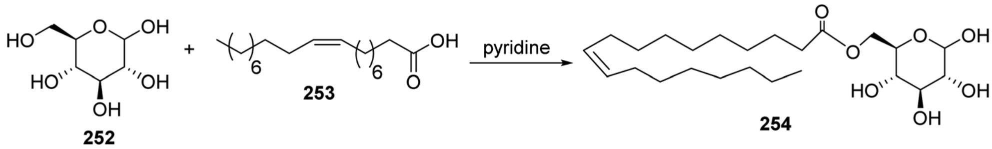


Scheme 50 Synthesis of *o*-hydroxy anilide derivatives **245a–f** and 1-substituted-1,3-dicyclohexylurea analogues of carboxylic acids **246a–f**.

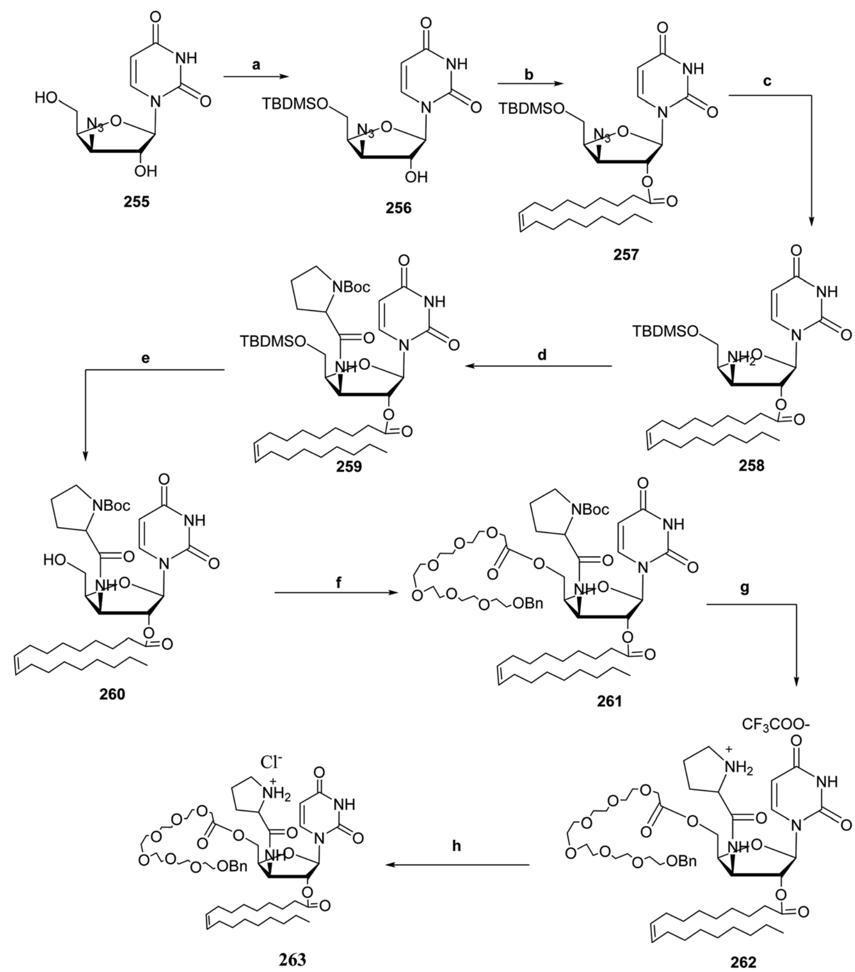


BHT = 2,6-di-*tert*-butylphenol
DDQ = 2,3-dichloro-5,6-dicyan-1,4-benzoquinon

Scheme 52 Synthesis of cycloarenes 251 *via* Diels–Alder reaction.

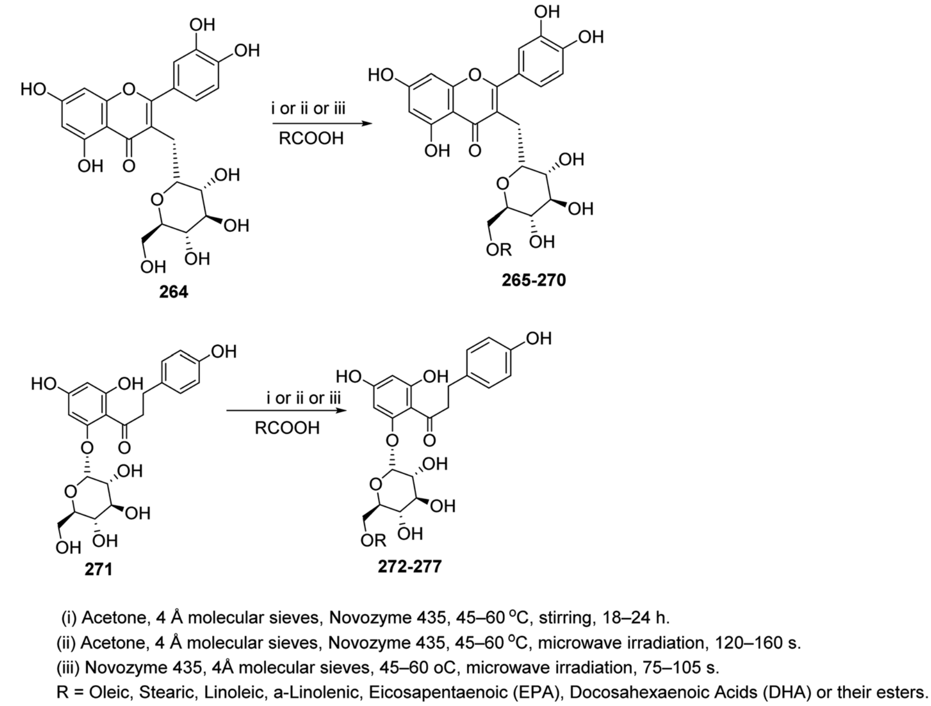


Scheme 53 Synthesis of *O*-oleoylglucose 254 from oleic acid.



a) TBDMSCl, imidazole, DMF, 1 h, r.t., 80% yield; **b)** Oleic acid, DCC, DMAP, CH_2Cl_2, 2 h, r.t.,74% yield;
c) H_2, (P ¼ 1 atm), Pd/C 10% p.p., AcOEt, 12 h, r.t., 99% yield;
d) N-Boc L-Proline, DCC, DMAP, CH_2Cl_2, 12 h, r.t., 98% yield; **e)** Et_3N 3xHF, THF, 12 h, r.t., 93% yield;
f) $BnO(CH_2CH_2O)_6CH_2COOH$, DCC, DMAP, CH_2Cl_2, 2 h, r.t., 87% yield;
g) 10% TFA/TIS, CH_2Cl_2, 1 h, r.t., 99% yield,**h)** $NH_4^+Cl^-$, H_2O

Scheme 54 Synthesis of compound 263.



Scheme 55 Acylate isoquercitrin **264** and phloridzin **271** with fatty acids.

oleyl derivative **257** in high yield. The 3′-azido group was reduced to 3′-amine **258** through catalytic hydrogenation. The next step involved the condensation of **258** with the protected L-proline to give the aminoacyl nucleolipid **259**, which was deprotected at the 5′ position to give **260**. At this stage a hydrophilic residue previously synthesized[111] was attached at the 5′ position through an ester linkage giving nucleoside **261**, followed by mild acidic treatment to provide the aminoacyl nucleolipid **262** as trifluoroacetate salt. Finally, the trifluoroacetate counterion was then replaced with chloride to receive the target compound **263** in biocompatible form[112] (Scheme 54).

Finally, the enzymatic reactions are used to provide hybrid compounds of flavonoids and fatty acids using lipase to create esters. Ziaullah *et al.*, used such technique to acylate isoquercitrin **264** and phloridzin **271** with fatty acids (C_{18}–C_{22}) using lipase novozyme under several reaction conditions[113] (Scheme 55).

10. Application and pharmacological uses of fatty substances

10.1. Application of fatty substances

10.1.1. Their usage as surface active agents. It was noticed that when the fatty acids are present in the surfactant range (C_8–C_{16}) the highly surface-active compounds are formed,[7,9] so that there is a family of novel mono-alkyl glycerol ether surfactants with different hydrophobic length (C_9–C_{16}) and tryptophan were synthesized. Based on the number and polarity of groups present, the amphiphile is going from hydrophilic to lipophilic with the increase of carbon atoms in the alkyl chains (*e.g.* phthalazine derivative **278** as a good anionic surfactant)[51] (Fig. 1).

Moreover, the surface-active properties of fatty acid–dihydroxazole hybrids **279** were reported. Also, their respective salts are good cationic surfactants[114] (Fig. 1).

In addition, a novel group of nonionic surface-active agents were synthesized, which consist of a hybrid from α-hydroxyl

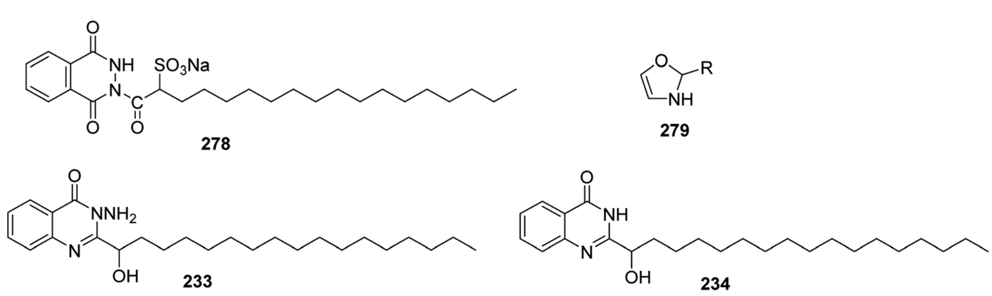
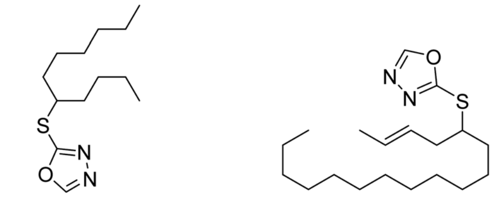


Fig. 1 Compounds as surface active agents.



280 281

Fig. 2 Heterocyclic compounds having fatty residue with anticorrosion effect.

fatty acid and quinazolines **233** and **234.** The active hydrogen at position 2 of quinazoline was subjected to reaction with ethylene oxide or propylene oxide[115,116] to produce these hybrids having a double functions as antimicrobials and surface active agents which can be useful in the manufacture of drugs and cosmetics[106] (Fig. 1).

10.1.2. As corrosion inhibitor. Heterocyclic compounds having fatty residue possess anticorrosion effect.[117] Compounds **280** (UMOD) and **281** (HMOD) were prepared and their anticorrosive effect mild steel was investigated by weight-loss and potentiodynamic polarization techniques. Their inhibitory effect varied depending on concentration, temperature and immersion time. Their adsorption on the steel surface obeys Temkin's adsorption isotherm. The potentiodynamic polarization data showed that the inhibitory type of the synthesized compounds is mixed[118] (Fig. 2).

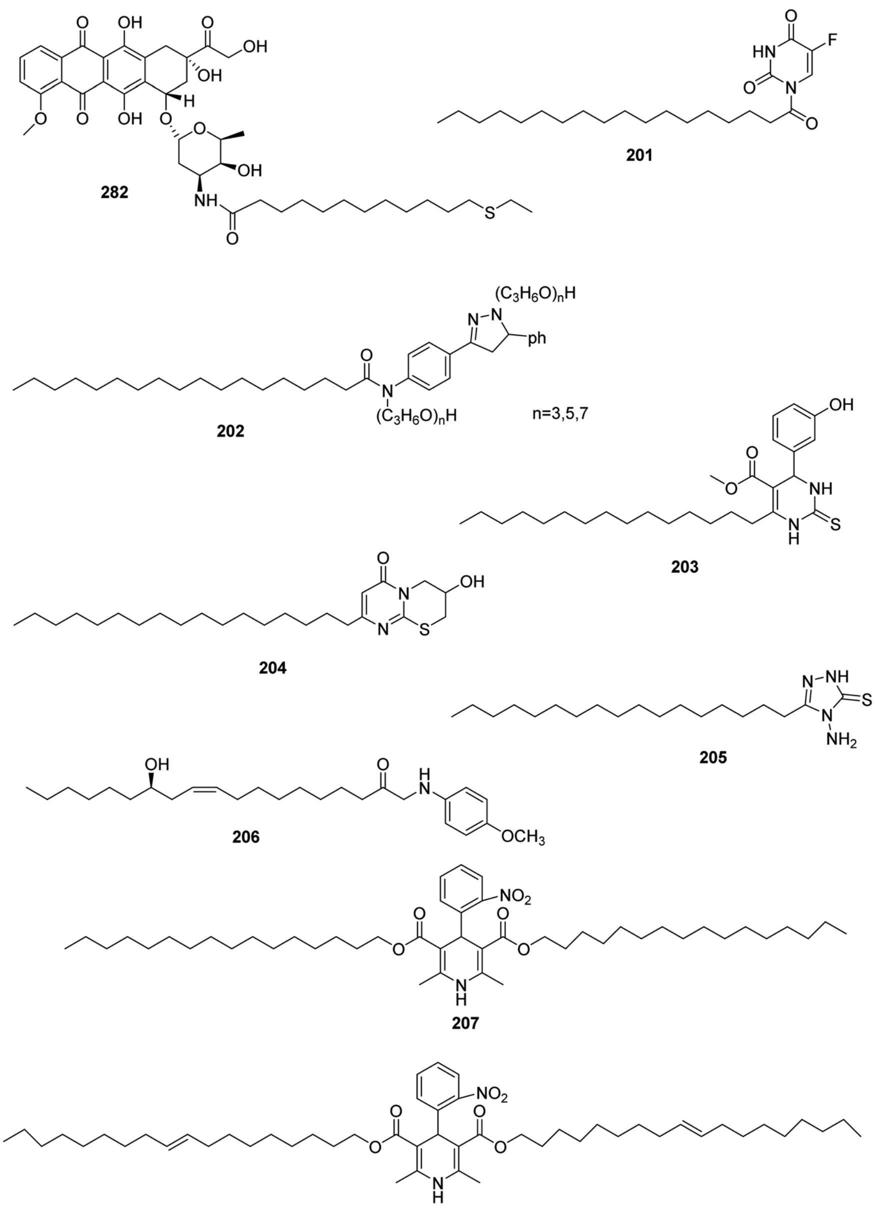


Fig. 3 Compounds have pharmacological activity.

10.2. Pharmaceutical uses

It was reported that the anti-proliferative profile of fatty acyl amide derivatives was higher in ovarian and colon cell lines than leukemia and breast cancer cells. Moreover, the dodecanoyl derivative was the most effective concerning *in vitro* test of all the examined cell lines, which indicates its potential application for slow delivery of doxorubicin. Therefore, doxorubicin bearing fatty acyl amide moiety (**282**) was prepared which showed higher lipophilicity than doxorubicin[119] (Fig. 3).

In addition, **201** was obtained by the acylation of 5-fluorouracil, then was incorporated into solid lipid nanoparticles (SLN) to produce the mean dimer 5-FUS-SLN. This dimer has better profile concerning liver targeting properties by enhancing drug liposoluble properties[120] (Fig. 3).

Abdelmajeid *et al.* synthesized new series of pyrazole, isoxazole, pyrimidine and pyridine derivatives with heptadecyl fatty acids and screened them for their antioxidant and anticancer activity. The biological evaluations showed that the most effective compound concerning antioxidant and cytotoxic activities was **202** (ref. 121) (Fig. 3).

In 2018, De Oliveira *et al.* prepared novel derivatives of long-chain monastrol analogues as antitumor agents against rat glioblastoma cells.[122] The series was synthesized *via* the multicomponent reaction then tested for their *in vitro* antitumor activity. Compound **203** showed the strongest antitumor effect (IC_{50} = 5.11 μM), higher than 13-fold of the reference; monastrol (IC_{50} = 87.83 μM) (Fig. 3).

In addition, new pyrimidine derivatives having fatty acids residue were synthesized by alkylation of 6-oleyl-2-thiouracil and evaluated for their anticancer potency. The thiazinopyrimidine derivative **204** showed the highest anticancer activity against both cancer cell lines HEPG-2 and MCF-7 with IC_{50} value of 20.4 and 12.5 μg mL^{-1}, respectively,[123] (Fig. 3).

The antimicrobial activity of 4-amino-1,2,4-triazole and 1,3,4-oxadiazole derivatives were synthesized by Chehrouri *et al.* the results revealed that compound **205** had potent effect against Gram-positive (*S. aureus*, and *E. faecalis*), Gram-negative (*E. coli*, and *P. aeruginosa*) bacteria, and one fungus (*Candida albicans*)[124] (Fig. 3).

Costa Cabrera and coworker obtained new dihydropyridine derivatives with potential antioxidant properties. They performed the synthesis using Hantzsch multicomponent reactions including ketoester of fatty acids, aldehydes and ammonium acetate in the presence of sulfamic acid. Their antioxidant activity was evaluated using three different methods: ABTS, DPPH, and FRAP assays. Compound **207** and **208** were the most active derivatives as antioxidant activity similar to reference drug (vitamin E, and BHT)[125] (Fig. 3).

In 2021, Nengroo *et al.* synthesized new series of fatty acids linked with 4-methoxybenzylamides *via* the reaction of fatty acids with 4-methoxybenzylamine (PMBA). Compound **206** with hydroxyl group on fatty acid showed the highest antifungal activity as well as antibacterial activity[126] (Fig. 3).

11. Conclusions and future perspective

The purpose of this review is to include various methods of synthesizing hybrid heterocyclic molecules with fatty acids, as well as their biological applications and evaluations. Clearly, the literature review indicates that these molecules are highly promising medicinal agents with diverse applications in industry. In addition, the presence of substituents on the heterocyclic system has a great impact on the results obtained. Hence, the incorporation of heterocyclic scaffolds with fatty acids is crucial to improving the biological and application properties. It is anticipated that the present review paper will support the development of more potent, safer, and selective candidates for potential therapeutic applications in various industries.

Conflicts of interest

The authors declare no conflict of interest.

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