SYNTHESIS OF THIENOPYRIMIDINE DERIVATIVES STARTING FROM THIOPHENE AND PYRIMIDINE RINGS

Abdelreheem A. Saddik,[a][b]* Adel M. Kamal El-Dean,[a] Khairy M. Hassan,[a] and Mohamed S. Abbady[a]

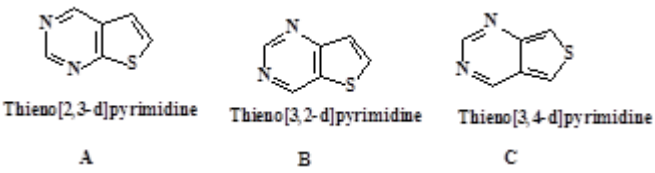
Keywords: thieno[3,4-*d*]pyrimidines; thieno[3,2-*d*]pyrimidines; thieno[2,3-*d*]pyrimidines.

Thienopyrimidines derivatives continue to attract great interest due to the wide variety of interesting biological activities observed for compounds characterized by this heterocyclic system. This review results from the literature survey containing the synthesis of thieno[2,3-*d*]pyrimidines, thieno[3,2-*d*]pyrimidines and thieno[3,4-*d*]pyrimidines from thiophene ring then build pyrimidine ring and from pyrimidine ring then build thiophene ring.

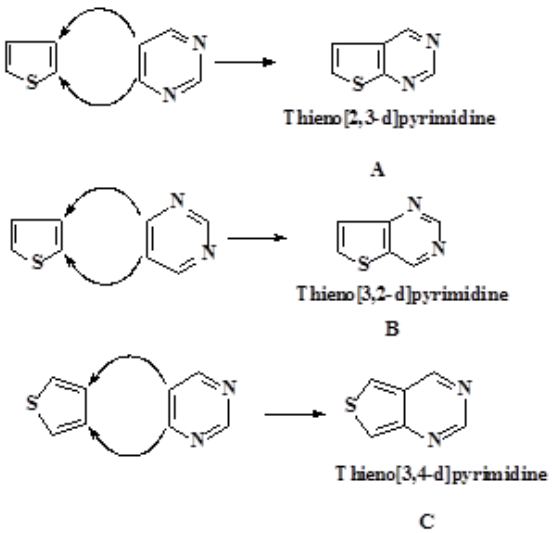
* Corresponding Authors
E-Mail: *abdelraheemseddik*@gmail.com
[a] Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt
[b] Department of Materials Science and Engineering National Chiao Tung University Hsinchu, 300, Taiwan (Republic of China)

Introduction

Thienopyrimidine can be represented in three structures as shown below.[1]



Synthesis of thienopyrimidines was accomplished either starting with thiophene moiety followed by construction of pyrimidine moiety on it or starting with pyrimidine nucleus followed by construction of thiophene block on it.



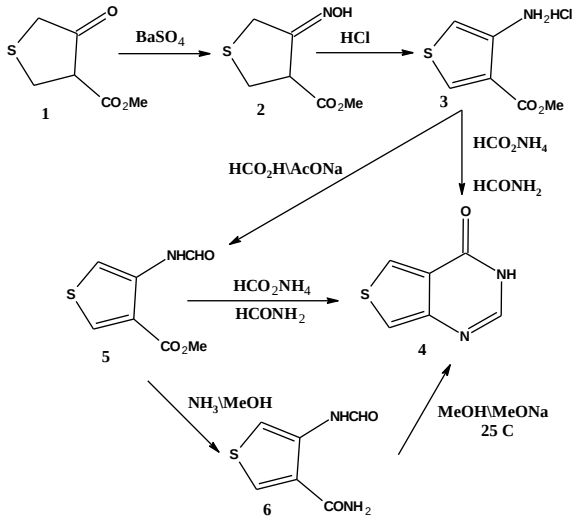
Synthesis

Preparation of thieno[3,4-*d*]pyrimidine

a) From 4-oxo-tetrahydrothiophene-3-carboxylate

3-Methyl 4-oxo-tetrahydrothiophene-3-carboxylate (**1**)[2] was converted to the oxime (**2**) by reacting with hydroxylamine hydrochloride in methanol and barium carbonate. The produced oxime was rearranged with hydrogen chloride in methanol at room temperature[3] into 3-amino-4-carbomethoxythiophene (**3**). Methyl 4-amino thiophene-3-carboxylate (**4**) was converted into thieno[3,4-*d*]pyrimidin-4(3H)-one (**3**) by reacting with formamide at 175 ^{0}C in the presence of ammonium formate in 71 % yield.[4]

Application of these conditions in the case of the free base, compound (**3**) gave only traces of the desired (**4**) along with large amounts of tar. Since aminothiophene bases are notoriously unstable, the molecule was stabilized by formylation with formic acid in the presence of sodium acetate to give (**5**) in 59 % yield, which when treated with ammonium formate and formamide at 145 ^{0}C gave a 50 % yield of the thienopyrimidine (**4**).

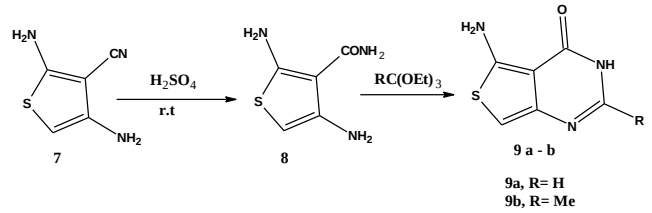


Scheme 1.

On the other hand, methyl 4-formamidothiophene-3-carboxylate (**5**) was converted into the corresponding 4-formamidothiophene-3-carboxamide (**6**) using methanolic ammonia solution which easily gave thienopyrimidine (**4)** with methanolic sodium methoxide in 93 % yield (Scheme 1).

b) From 4-amino-thiophene-3-carboxylic acid amide

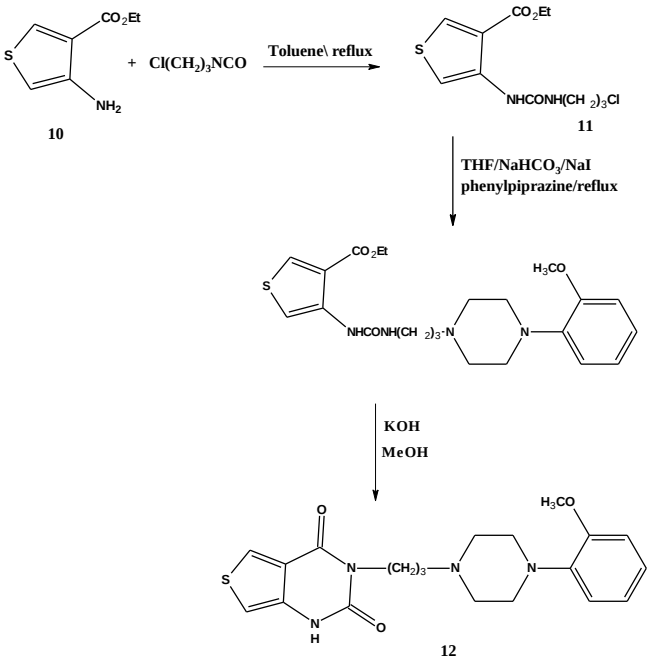
2,4-Diaminothiophene-3-carbonitrile (**7**) was converted to amide (**8**) by using sulfuric acid at room temperature cyclization by using triethyl orthoformate or triethyl orthoacetate gave thieno[3,4-*d*]pyrimidine (**9**) in 65 % yield (Scheme 2).[5]



Scheme 2.

c) From 3-aminothiophene-4-carboxylic ester

Thiophene amino esters (**10**) were reacted with 2-chloroethyl isocyanate in toluene and gave the 4-(2-chloroethyl)thiophene derivatives (**11**). Compounds (**11**) were then reacted with 2-methoxyphenylpiperazines in THF, 2-propanol or DMF to afford the thienopyrimidine-2,4-dione derivatives in 56 % yield (**12**) (Scheme 3).[6]

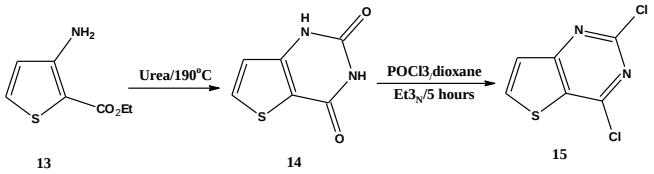


Scheme 3.

Thieno[3,2-*d*]pyrimidine

From rthyl or mMethyl 3-aminothiophene carboxylate derivatives

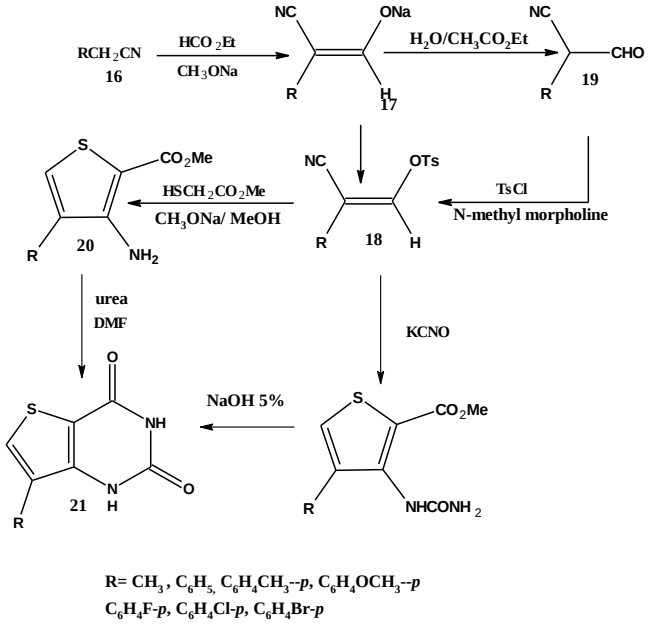
Ethyl 3-aminothiophene-2-carboxylate (**13**) was heated up to 190 °C with urea under neat condition followed by treatment with sodium hydroxide then acidified with sulfuric acid gave thieno[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (**14**) in 84 % yield. The latest compound was converted into 2,4-dichlorothieno[3,2-*d*]pyrimidine (**15**) by the reaction with phosphorus oxychloride in dioxane in the presence of triethylamine in 81.4 % yield (Scheme 4).[7]



Scheme 4.

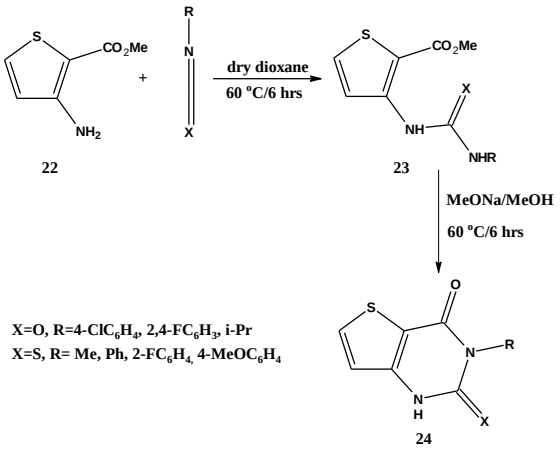
Aryl acetonitrile (**16**) reacted with ethyl formate in the presence of sodium methoxide to afford the corresponding sodium 2-cyano-2-arylethenolate (**17**) which was reacted with p-toluenesulfonyl chloride in DMF affording 2-aryl-3-(p-toluenesulfonato) acylonitriles (**18**).

The latter compound underwent acidic hydrolysis to give 2-formyl-2-arylacylonitriles (**19**) which reacted with p-toluenesulfonyl chloride in the presence of excess 4-methylmorpholine in dichloromethane to give 2-cyano-2-arylylvinyl toluenesulfonate (**18**). The obtained compound, when treated with methyl thioglycolate, gave the thiophene (**20**). The thiophene **20** was cyclized either by potassium cyanate or urea to thieno[3,2-*d*]pyrimidine in 80 % yield (**21**) (Scheme 5).[8]



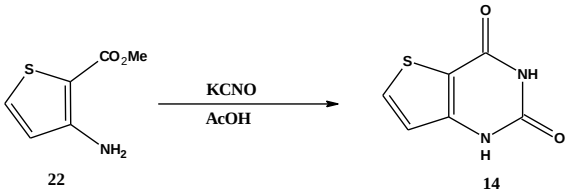
Scheme 5.

Shestakov A. S. *et al.*[9] reported synthesis of thieno[3,2-*d*]pyrimidine by the reaction of methyl 3-aminothiophene-2-carboxylate (**22**) with isocyanates and isothiocyanates. Initially, carbamides or thiocarbamides (**23**) were formed, alkaline treatment of (**23**) led to the formation of pyrimidinediones or 2-thioxopyrimidin-4-ones in 95 % yield (**24**) (Scheme 6).



Scheme 6.

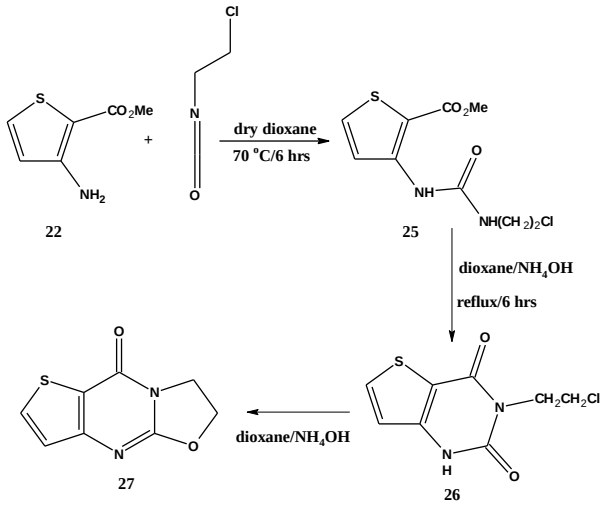
Thieno[3,2-*d*]pyrimidin-2,4(1H,3H)-dione (**14**) was prepared by Temburnikar *et al*.[10] in the reaction of methyl-3-amino-2-thiophene carboxylate (**22**) with potassium cyanate in the presence of acetic acid as white solid in yield (71 %) (Scheme 7).



Scheme 7.

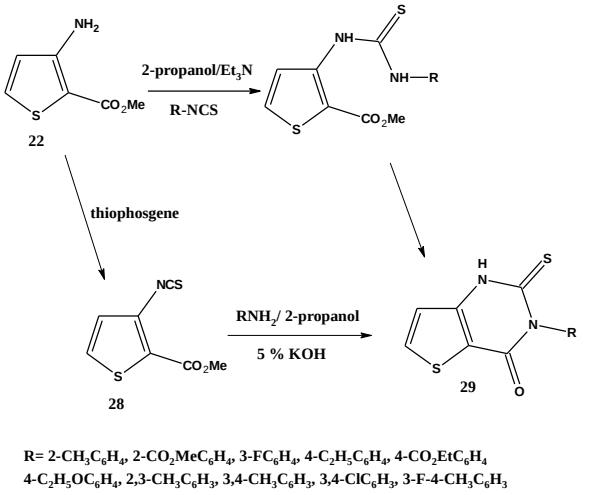
The interaction of methyl 3-aminothiophene-2-carboxylate (**22**) and 2-chloroethylisocyanates gave methyl 3-(3-(2-chloroethyl)ureido)thiophene-2-carboxylate (**25**) with potential antihypertensive activity.[11] The attempts to obtain 3-(2-chloroethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (**26**) led to a very slow reaction. In more complicated conditions (two-days boiling ammonia-dioxane solution) led to a tricyclic compound in 78 % yield (**27**) (Scheme 8).

A. Ivachtchenko *et al*.[11] reported that the amino-thiophene ester (**22**) was reacted with thiophosgene to generate isothiocyanate (**28**).



Scheme 8.

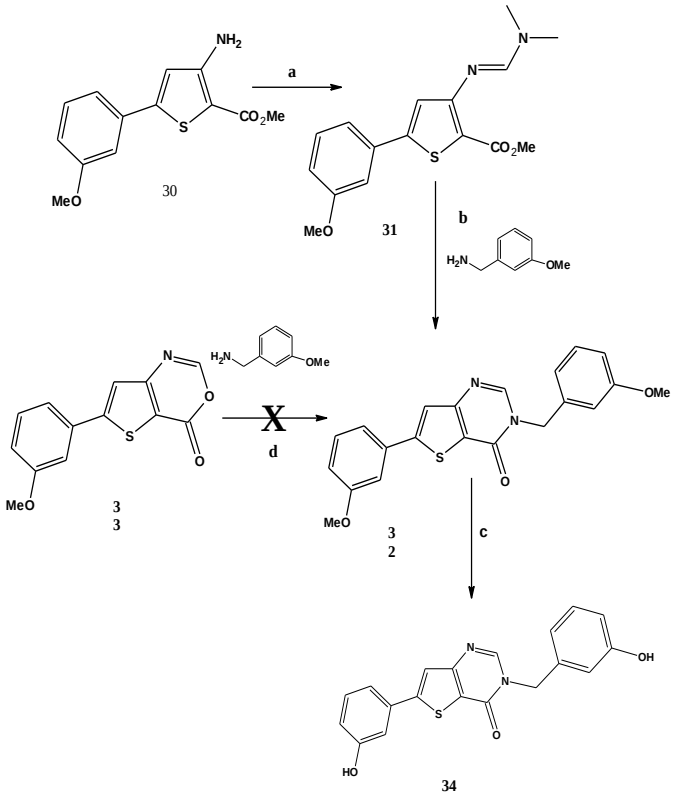
Further condensation of this reactive isothiocyanate intermediate with various primary amines in a mixture of 2-propanol and 5 % aqueous KOH under reflux smoothly afford thieno[3,2-*d*]pyrimidines (**29**). On the other hand compound (**29**) was prepared directly by reacting of aminothiophene ester (**22**) with isothiocyanate derivatives in the presence of 2-propanol and triethylamine in 75 % yield (Scheme 9).



Scheme 9.

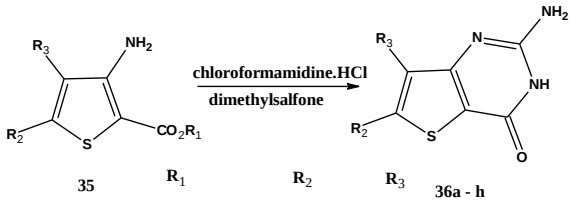
Thieno[3,2-*d*]pyrimidines were synthesized by E. Perspicace *et al*.[12] in a two- or a three-step procedure, respectively, as depicted in the following Scheme, starting from compound (**30**). The starting materials methyl 3-amino-5-(3-methoxyphenyl)-thiophene-2-carboxylate (**30**) was synthesized using the multi-step procedure well described in the literature.[13] The condensation of molecule (**30**) with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) gave methyl 3-dimethylaminomethylideneamino-5-(3-methoxy-phenyl)thiophene-2-carboxylate (**31**) in very good yield[14] which were used directly in the next step without purification to afford compound (**32**). The condensation of 6-(3-methoxyphenyl)-4*H*-thieno[3,2-*d*][1,3]oxazin-4-one (**33**) with 3-methoxybenzyl amine as an alternative route to produce (**32**) was failed.

After *O*-demethylation using boron trifluoride methyl sulfide complex $BF_3.SMe_2$, the thieno[3,2-*d*]pyrimidin-4(3H)-one (**34**) was obtained in 82 % yield (Scheme 10).



Scheme 10. Reagents and conditions: (**a**) DMF-DMA, EtOH, microwave irradiation (100 °C, 80 W, 15 min), 98%; (**b**) DMF, microwave irradiation (100 °C, 80 W, 15 min), 31%; (**c**) $BF_3.SMe_2$, CH_2Cl_2, rt, 82 %; (**d**) MeOH, reflux.

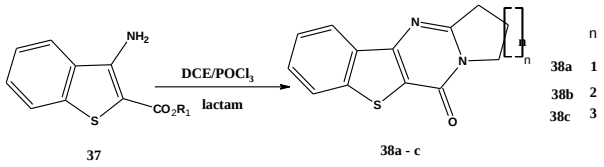
The reaction of 3-aminothiophene derivatives with chloroform amidine hydrochloride in dimethylsulfone gave thieno[3,2-*d*]pyrimidine derivatives in yield from 40 to 90 % according to the Scheme 11.[15]



	R_1	R_2	R_3
36a	Ph	H	Et
36b	Ph-Me-*p*	H_2	Et
36c	Ph-Cl-*p*	H_2	Et
36d	Ph-OMe-*p*	H_2	Me
36e	*t*-Bu	H_2	Et
36f	C-Hex		Me
36g	1,2-dihydronaphthalene		Et
36h	H_2	H_2	H_2

Scheme 11.

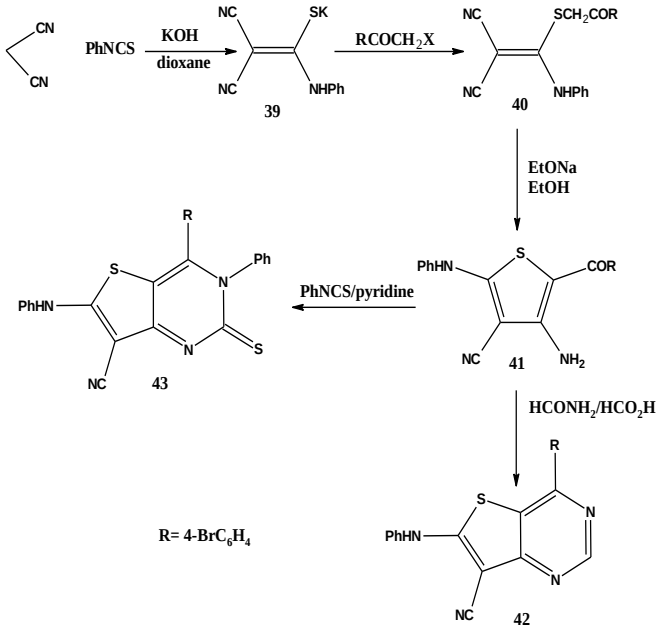
Reaction of methyl 3-aminobenzothiophene-2-carboxylate (**37**) with lactams in the presence of dichloroethane and $POCl_3$ gave benzothieno[3,2-*d*]pyrimidinone derivatives (**38a-c**) in yield 88, 60 and 93 %, respectively (Scheme 12).[16]



Scheme 12.

From o-ketoaminothiophene

The reaction of malononitrile with phenyl isothiocyanate in the presence of potassium hydroxide afford the potassium salt of ketene N,S-acetal (**39**). Compound (**39**) was allowed to react with *p*-bromophenacyl bromide or chloroacetone to afford the *S*-alkylated derivatives (**40**) which underwent cyclization in the presence of sodium ethoxide into compound (**41**). The reaction of (**41**) with formamide and formic acid under refluxing temperature gave 4-(4-bromophenyl)-6-(phenylamino)thieno[3,2-*d*]pyrimidine-7-carbonitrile (**42**) in 60 % yield. Also, compound (**41**) was allowed to react with phenyl isothiocyanate in pyridine when the corresponding 4-(4-bromophenyl)-3-phenyl-6-(phenylamino)-2-thioxo-2,3-dihydrothieno[3,2-*d*]pyrimidine-7-carbonitrile (**43**) was formed in 74 % yield (Scheme 13).[17]



Scheme 13.

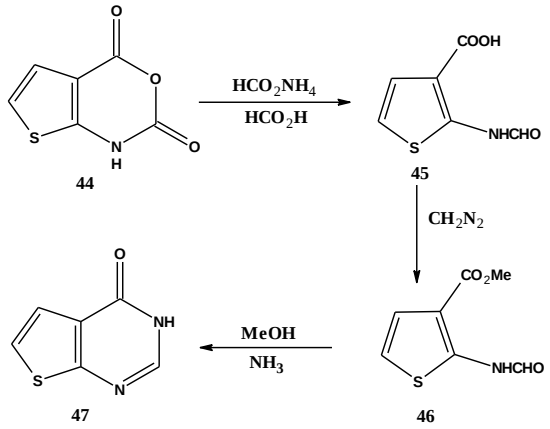
Thieno[2,3-*d*]pyrimidines

A-Starting from thiophene ring and building pyrimidine ring on it

1H-Thieno[2,3-*d*][1,3]oxazin-2,4-dione

Thieno[2,3-*d*]pyrimidine was first synthesized by Baker *et al.*..[18] when thieno[2,3-*d*][1,3]oxazine-2,4-dione (**44**) was treated with ammonium formate in 89 % formic acid at 100 ^{0}C to initiate ring opening and formylation with formation of 2-formylamino-thiophene-3-carboxylic acid (**45**).

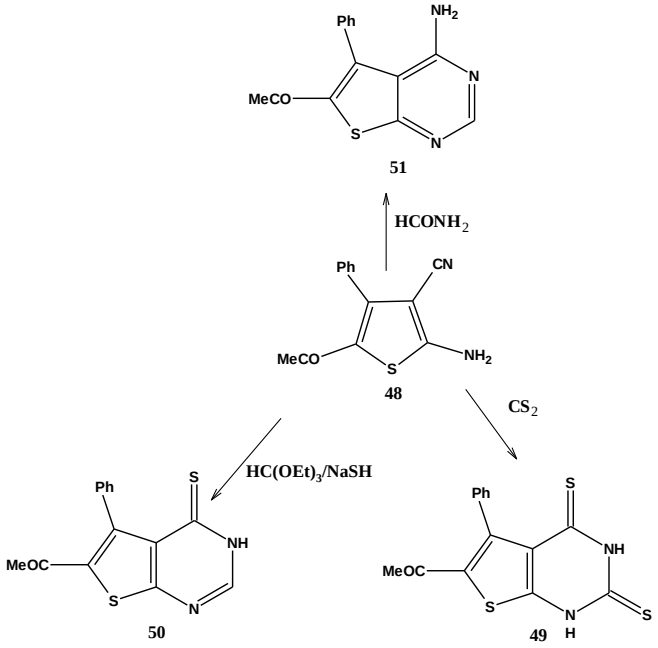
The compound (**45**) then was reacted with diazomethane to give methyl ester (**46**), the methyl ester (**46**) was treated with methanolic ammonia to give 3H-thieno[2,3-*d*] pyrimidin-4-one (**47**) in 4 % yield (Scheme 14).



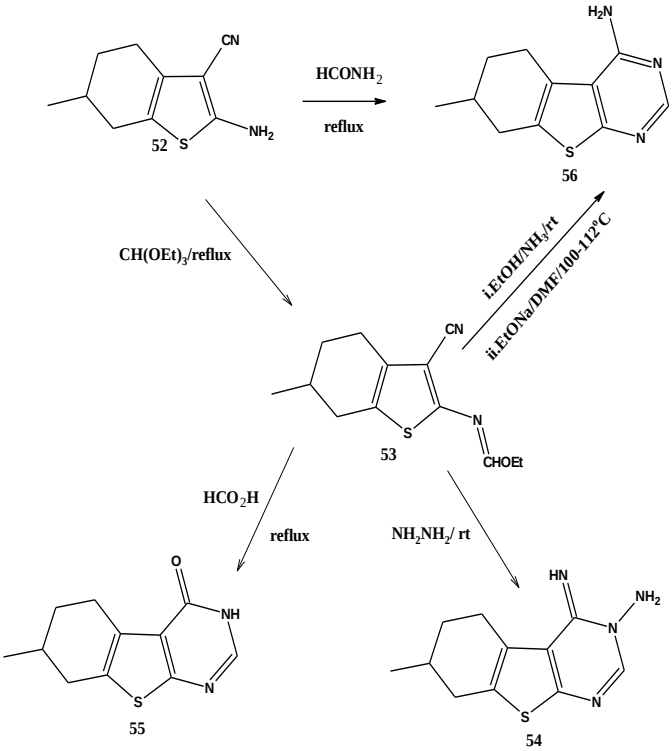
Scheme 14.

2-Amino-thiophene-3-carbonitrile from 5-acetyl-2-amino-4-phenyl-thiophene-3-carbonitrile

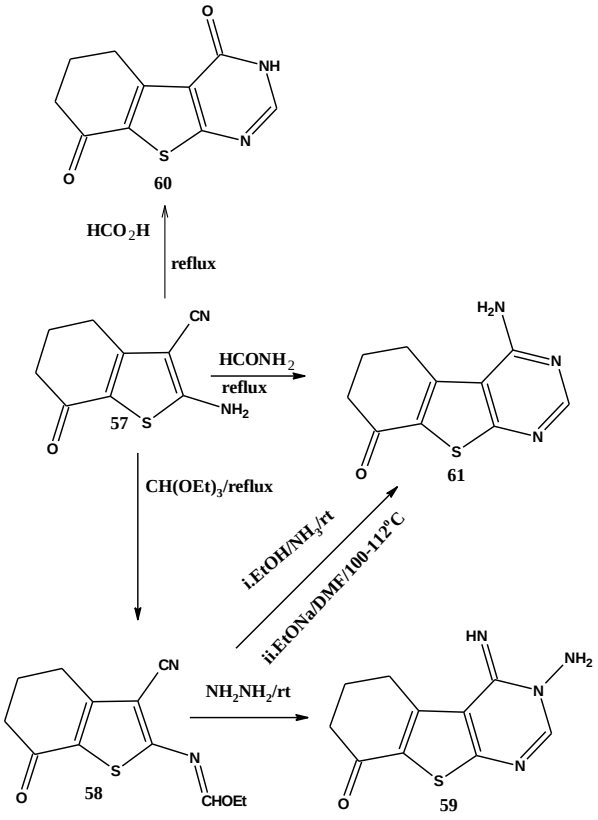
5-Acetyl-2-amino-4-phenyl-thiophene-3-carbonitrile (**48**)[19] was reacted with carbon disulfide in pyridine to afford the thieno[2,3-*d*]pyrimidine dithione derivative (**49**) in 45 % yield.[20] When compound (**48**) was reacted with triethyl orthoformate followed by sodium hydrogen sulfide treatment according to Taylor *et al*.[21], the thieno[2,3-*d*]pyrimidine thione derivative (**50**)[20] was formed in 67% yield. Compound (**48**) was underwent cyclocondensation during refluxing in formamide[22] to afford the aminothieno[2,3-*d*]pyrimidine derivatives (**51**) in 78 % yield (Scheme 15).[20]



Scheme 15.



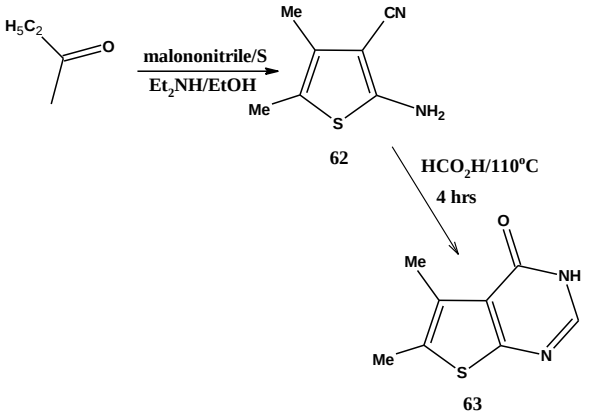
Scheme 16.



Scheme 17.

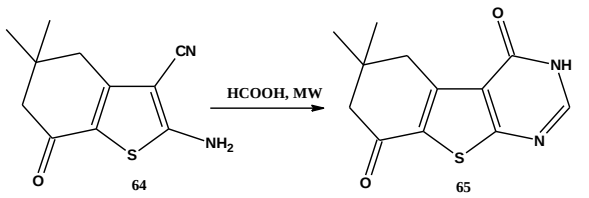
Imidoformates (**53, 58**) were prepared in excellent yield by treatment of 2-amino-6-methyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (**52**) prepared by Gewald reaction as reported in the literature[23] and 2-amino-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (**57**) prepared from 1,3-cyclohexanedione[24] with triethyl orthoformate at reflux temperature. Reactions of imidoformates (**53, 58**) with hydrazine hydrate afford the thienopyrimidines (**54, 59**) in 77 % and 64 % yields, respectively. Similarly, the reaction of imidoformates (**53, 58**) with ethanolic ammonia followed by the cyclization of intermediates with sodium ethoxide in refluxed dimethylformamide, the formation of aminothienopyrimidines (**56, 61**) in 80 % and 75 % yields, respectively. The reaction of compounds (**52, 57**) with formic acid gave thienopyrimidinone derivatives (**55, 60**) in 80 % yield (Scheme16 and Scheme 17).

The compounds (**56, 61**) were prepared by refluxing 2-amino-3-cyanothiophenes (**52, 57**) with formamide. Also, M. I. Hossain *et al*.[25] used the 2-aminothiophene-3-carbonitrile (**62**) which prepared by Gewald method from 2-butanone with sulfur and malononitrile to synthesize thieno[2,3-*d*]pyrimidine (**63**) in 85 % yield (Scheme 18).



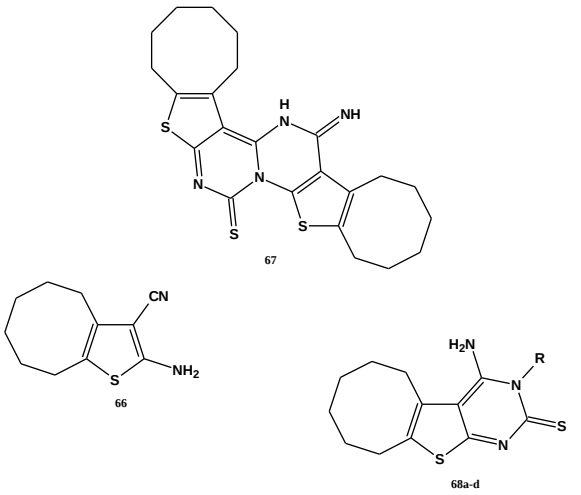
Scheme 18.

Nitinkumar S. Shetty *et al.*[26] used microwave irradiation to synthesize thieno[2,3-*d*]pyrimidine from α-aminothiophene carbonitriles.[23,27] The precursor 2-amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (**64**) was prepared by the reaction of 1,3-dimedone under conditions reported by K. Gewald.[22,24] Thienopyrimidin-4-one (**65**) was prepared by the microwave irradiation of 2-amino-3-cyanothiophene (**64**) in the presence of formic acid in 80 % yield (Scheme 19).



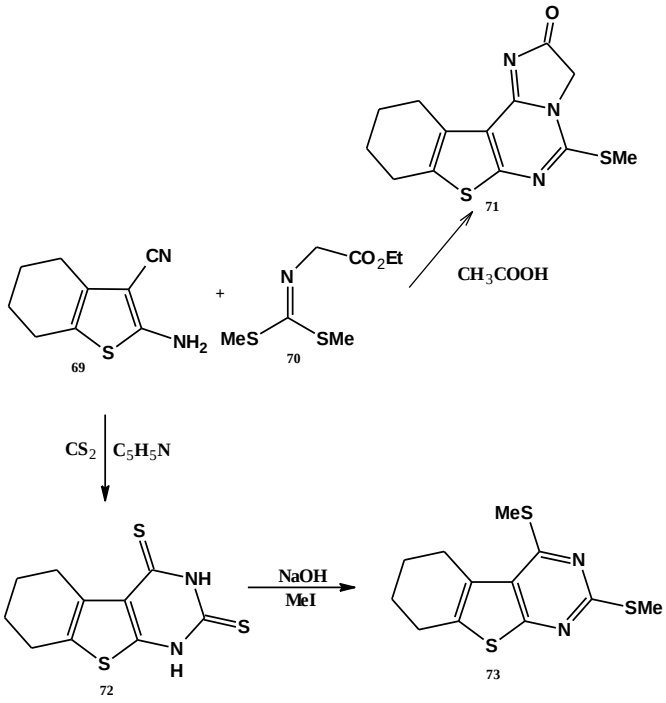
Scheme 19.

Compounds (**68a-d**) were obtained by reacting the aminocyano derivative (**66**) with the aromatic isothiocyanates in ethanol in the presence of a catalytic amount of triethylamine. Using phenyl isothiocyanate, hexacyclothienopyrimidine (**76**) was produced in 50 % yield (Scheme 20).[28]



Scheme 20.

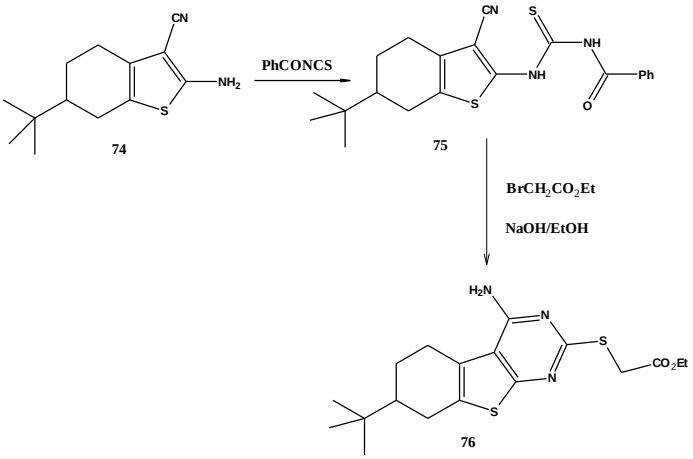
Reaction of heteroaromatic 2-aminothiophene-3-carbonitrile (**69**) with ethyl *N-bis*(methylthio)methylene-amino acetate (**70**) gave thieno[2,3-*d*]pyrimidine (**71**) in a one-step process in 75 % yield.[29] Compound (**69**) reacted with carbon disulfide in pyridine to afford thieno[2,3-*d*]pyrimidin-2,4-dithione (**72**) which could be alkylated with methyl iodide in the presence of sodium hydroxide and gave compound (**73**) in 81 % yield (Scheme 21).



Scheme 21.

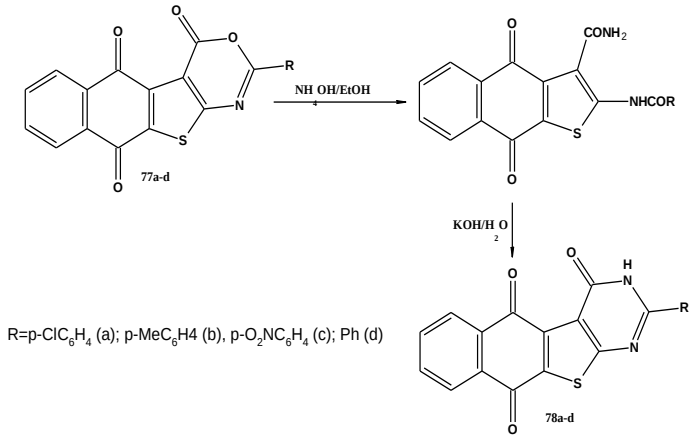
From ethyl 2-aminothiophene-3-carboxylate

Li *et al.*[30] prepared thieno[2,3-*d*]pyrimidine derivative (**74**) by reaction of 2-aminobenzo[b]thiophene-3-carbonitrile (**75**) with benzoyl isothiocyanate to give N-((6-(tert-butyl)-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)carbamoyl)benzamide (**76**) which reacted with ethyl bromoacetate in ethanol in the presence of sodium hydroxide as white crystal in yield 57 % (Scheme 22).



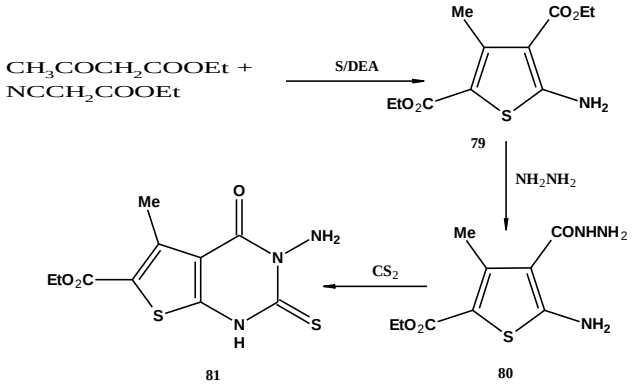
Scheme 22.

2-Aryl-4H-naphtho[2',3':4,5]thieno[2,3-*d*][1,3]oxazine-4,5,10-triones (**77a-d**) allowed to get 2-aryl-naphtho[2',3',4,5]thieno[2,3-*d*][1,3]pyrimidine-4,5,10(*3H*)-triones (**78a-d**) easily. Pyrimidine triones were obtained in 78 % yield in the reaction of oxazinetriones with ammonium hydroxide in ethanol without the isolation of intermediate compounds which were transformed by 5 % solution KOH during 1 h (Scheme 23).



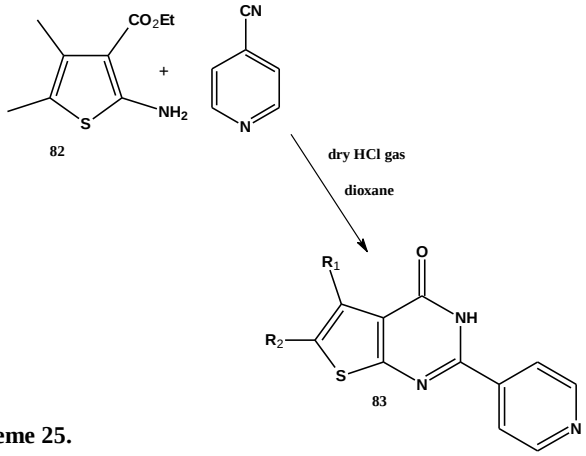
Scheme 23.

The interaction of ethyl acetoacetate with ethyl cyanoacetate and elementary sulfur in ethanol medium and in the presence of diethylamine led to diethyl 5-amino-3-methylthiophene-2,4-dicarboxylate.[29] The hydrazide (**80**) obtained by refluxing of ethyl carboxylate (**79**) with hydrazine hydrate in ethanol compound (**80**) was treated with carbon disulfide to afford the 3-amino-6-carboxyethyl-5-methyl-2-thioxothieno[2,3-*d*]pyrimidin-4-one (**81**) in 68 %yield (Scheme 24).[31]



Scheme 24.

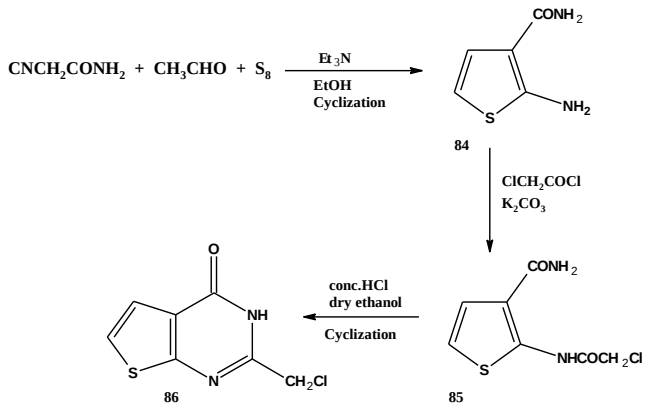
Nitin G. Haswani *et al.*[32] reported the synthesis of 2-aminothiophene-3-carboxylate (**82**) according to Gewald method and the product was subjected to react with nitriles in the presence of HCl gas to afford thienopyrimidine (**83**) in 98 % yield (Scheme 25).



Scheme 25.

From 2-aminoindeno[2,1-b]thiophene-3-carboxylic amide

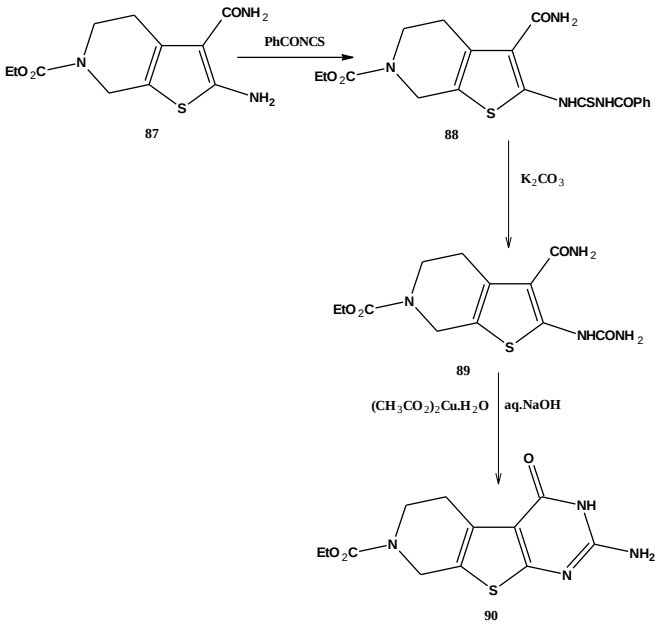
Cyano acetamide was reacted with acetaldehyde in the presence of sulfur and triethylamine according to Gewald method in ethanol to give 2-aminothiophene-3-carboxamide (**84**) which reacted with chloroacetyl chloride to give the intermediate chloroacetyl derivative (**85**).



Scheme 26.

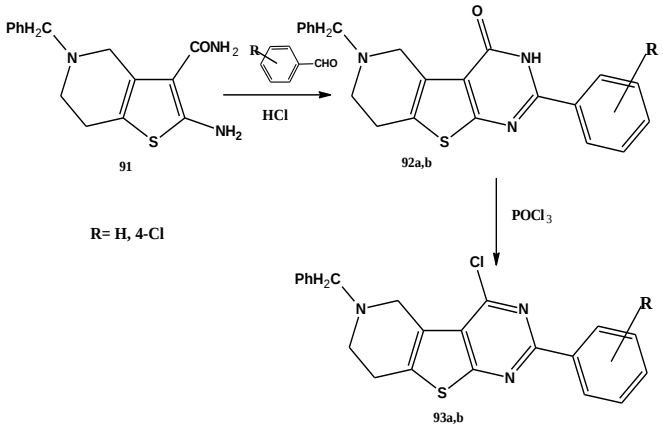
The chloroacetyl derivative was cyclized with concd. HCl in ethanol producing thieno[2,3-*d*]pyrimidine (**86**) in 78 % yield (Scheme 26).[33]

The reaction of 2-aminothiophene-3-carboxamide (**87**) with benzoyl isothiocyanate in acetone afforded the corresponding [*N*-benzoyl(thiocarbamoyl)]-aminothiophene derivative (**88**) in 67 % yield. The isolated compound (**88**) was hydrolyzed to yield the corresponding thiourea (**89**). In the accomplishment of the cyclodesulfurization by use of a heavy metal salt, compound (**89**) was added to a suspension of a slight excess of the metal salt in aqueous sodium hydroxide to give thieno[2,3-*d*]pyrimidine (**90**) in 97 % yield (Scheme 27).[34]



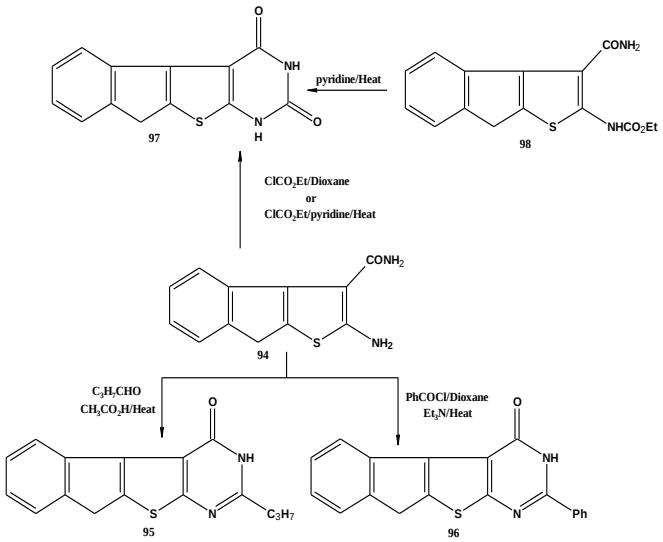
Scheme 27.

On the other hand, 2-amino-5-benzyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-3-carboxamide (**91**) was condensed with aromatic aldehydes in ethanol in the presence of concd. HCl affording 6-benzyl-2-phenyl(or 4-chlorophenyl)-5,6,7,8-tetrahydropyridothieno[2,3-*d*]pyrimidine-4(4H)-ones (**92a-b**) in 70 % and 78 % yield, respectively.[35] Compounds **92a-b** were reacted with phosphorus oxychloride to give 4-chloro derivatives (**93a-b**) in 90 % and 70 % yields, respectively (Scheme 28).



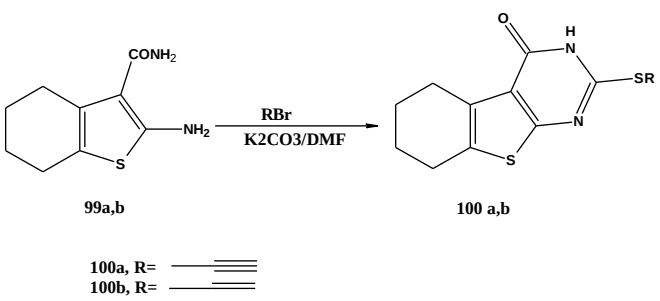
Scheme 28.

2-Aminoindeno[2,1-*b*]thiophene-3-carboxylic acid amide (**94**)[36] was cyclized with butyraldehyde and benzoyl chloride to afford 2-propyl-3,9-dihydroindeno[1',2':4,5]thieno[2,3-*d*]pyrimidin-4-one (**95**) and 2-phenyl-3,9-dihydroindeno[1',2':4,5]thieno[2,3-*d*] pyrimidin-4-one (**96**) in 85 % yield and 62 % yields, respectively. Moreover, treatment of compound **94** with ethyl chloroformate in dry dioxane under reflux afforded not only to the cyclized thieno[2,3-*d*]pyrimidindione derivative (**97**) but also gave (3-carbamoyl-8H-indeno[2,1-*b*]thiophen-2-yl)carbamic acid ethyl ester (**98**) as well. Refluxing compound **98** in dry pyridine or compound **94** with ethyl chloroformate in dry pyridine gave in both cases the same product, 1,3,9-trihydroindeno[1',2':4,5]thieno[2,3-*d*] pyrimidine-2,4-dione (**97**) in 69 % yield. The pyrimidinedione (**97**) could be formed *via* the formation of compound **98**, which was isolated and cyclized by refluxing that in pyridine to thieno[2,3-*d*]pyrimidinedione (**97**) (Scheme 29).



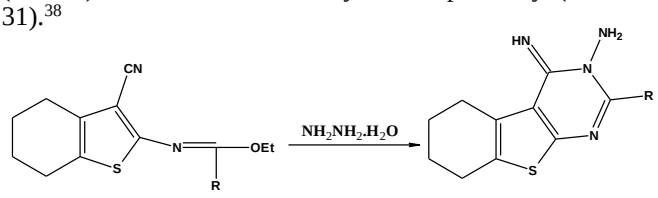
Scheme 29.

2-Aminobenzo[*b*]thiophene-3-carboxamide (**99a-b**) reacted with propargyl bromide or with allyl bromide in DMF in the presence of K_2CO_3 to give 2-(prop-2-yn-1-ylthio)benzothieno[2,3-*d*]pyrimidinone (**100a**) or 2-(allylthio)benzothieno[2,3-*d*] pyrimidinone derivatives (**100b**) in yield 60 % and 64 %, respectively (Scheme 30).[37]



Scheme 30.

N-(3-Cyano-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)-acetimidic acid ethyl ester and (Z)-ethyl N-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylpropionimidate (**101a,b**) were reacted with hydrazine hydrate in ethanol to give 4-iminobenzothieno[2,3-*d*]pyrimidin-3[4H]-amine and 2-ethyl-4-iminobenzothieno[2,3-*d*] pyrimidin-3[4H]-amine (**102a,b**) in 77 % and 65 % yield, respectively (Scheme 31).[38]



101 a,b **102a,b**

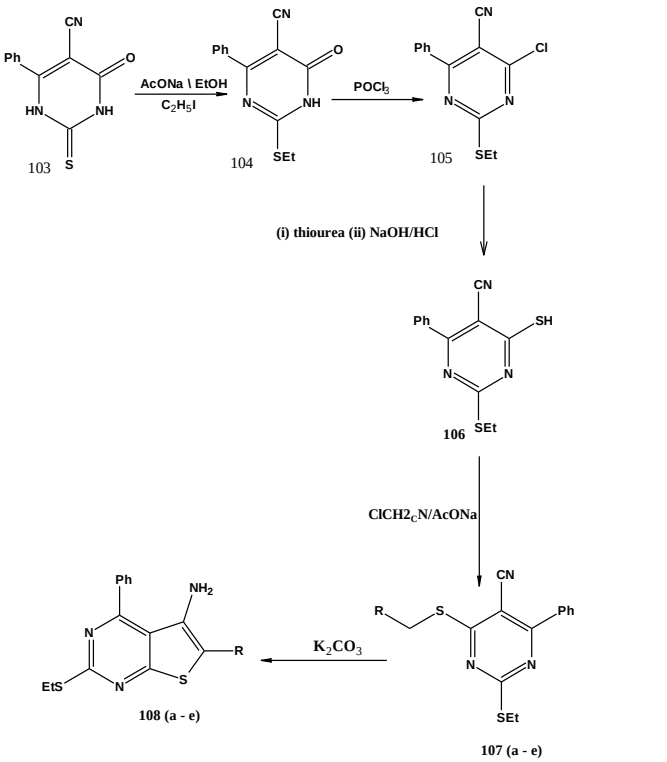
a= CH3
b= $C2_H5$

Scheme 31.

B) Starting from pyrimidine ring and building thiophene ring on it

From 4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carbonitrile

4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbo-nitrile (**103**)[39] was alkylated and gave 2-ethylmercapto-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitrile (**104**). Compound **104** was converted into 2-ethylmercapto-4-chloro-6-phenyl-3,4-dihydropyrimidine-5-carbonitrile (**105**) using phosphorus oxychloride.



103 104 105 106 107 (a - e) 108 (a - e)

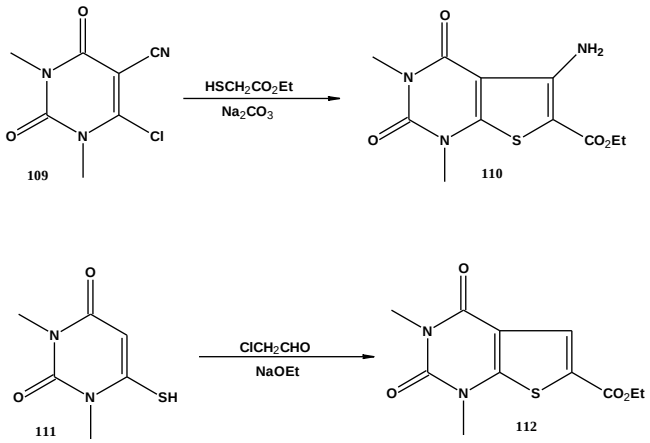
108a: R= $CONH_2$, 108b: R= CN, 108c: R= CO_2Et, 108d: R= CONHPh-Cl-*p*, 108e: R= CONHPh-OMe-*p*

Scheme 32.

Compound **105** was converted into 2-ethylmercapto-4-mercapto-6-phenylpyrimidine-5-carbonitrile (**106**) *via* reaction with thiourea in refluxed ethanol followed by treatment with sodium hydroxide solution and then acidified with dilute HCl. When compound **106** reacted with α-halo carbonyl compounds in ethanol in the presence of sodium acetate, alkylation of mercapto group was occurred to afford compounds **107a-e**. Compounds **107a-e** were undergone *Thorpe-Ziegler* cyclization reaction in ethanol in the presence of potassium carbonate and afforded compounds **108a-e** in 62 %, 65 %, 70 %, 50 % and 40 % yield, respectively (Scheme 32).[40,41]

From 1,3-dimethyluracil derivatives

6-Chloro-5-cyano-1,3-dimethyluracil (**109**) prepared from the formyluracil in two steps,[42] was cyclized to 5-aminothieno[2,3-*d*]pyrimidine (**110**) on heating with ethyl 2-mercaptoacetate in the presence of sodium carbonate. 6-Mercaptouracil (**111**)[43] was allowed to react with chloroacetaldehyde in the presence of sodium acetate at room temperature to give the thieno[2,3-*d*] pyrimidine (**112**) (Scheme 33).[44]



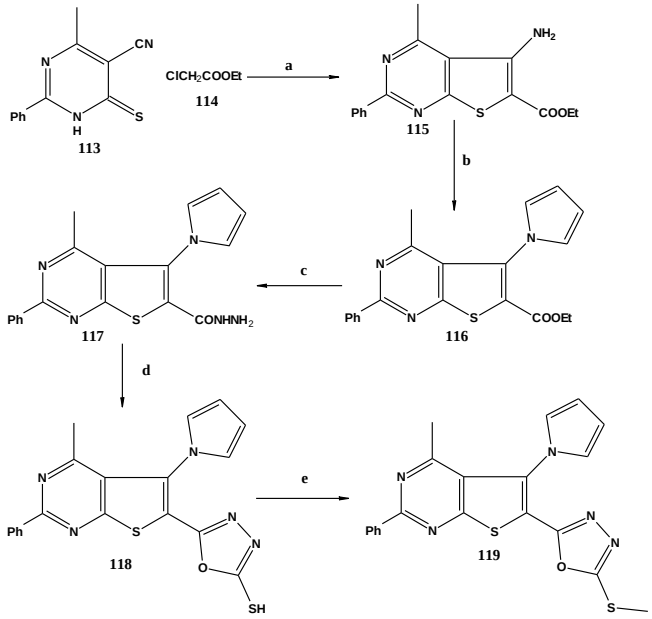
109 110 111 112

Scheme 33.

From 5-cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine

5-Cyano-1,6-dihydro-4-methyl-2-phenyl-6-thioxopyrimidine (**113**) was prepared by treating benzoyl isothiocyanate with 3-aminocrotononitrile in refluxing dioxane.[45,46] Cyclization of thioxopyrimidine (**113**) with ethyl chloroacetate (**114**) in DMF in the presence of excess anhydrous potassium carbonate at room temperature gave the ethyl 5-amino-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate (**115**) in 92 % yield (Scheme 34).

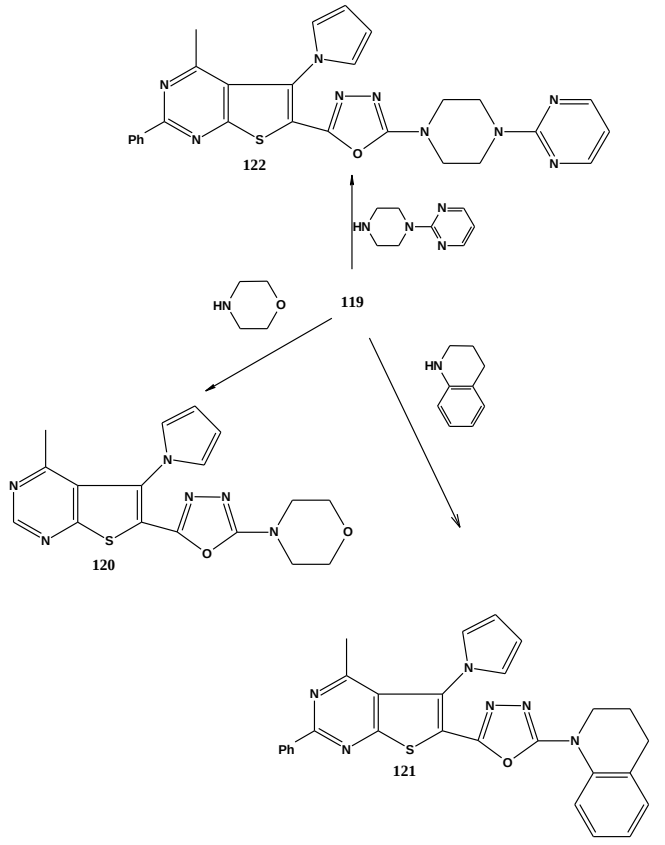
Treatment of compound **115** with 2,5-dimethoxytetrahydrofuran in glacial acetic acid produced the ethyl 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine-6-carboxylate (**116**), which reacted with an excess of 85 % hydrazine hydrate in refluxing ethanol to give the corresponding 5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-*d*]pyrimidine carbohydrazide (**117**).



Reagents: (a) DMF/K2CO3; (b) 2,5-(MeO)2-tetrahydrofuran, glacial acetic acid; (c) hydrazine hydrate; (d) CS2/pyridine; (e) MeI

Scheme 34.

The carbohydrazide (**117**) was used as a key intermediate for the synthesis of novel 1,3,4-oxadiazole-thieno[2,3-*d*]pyrimidine derivatives. Cyclization of carbohydrazide (**117**) with CS_2 in the presence of pyridine afforded the 6-(2,3-dihydro-2-mercapto-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyri-midine (**118**).

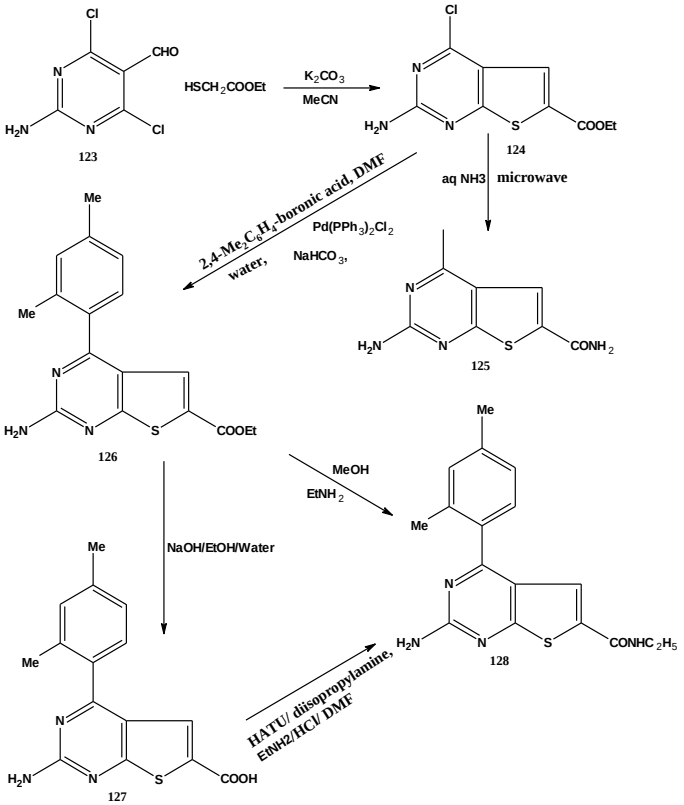


Scheme 35.

Its reaction with iodomethane in the presence of sodium methoxide yielded the 6-(2-methylthio-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-*d*]pyrimidine (**119**) (84 % yield) (Scheme 34). On the other hand, some novel 6-(2-substituted-1,3,4-oxadiazol-5-yl)-4-methyl-5-(1-pyrrolyl)-2-phe-nylthieno[2,3-*d*]pyrimidine derivatives (**120**, **121** and **122**) were also obtained by the condensation reaction of compound (**119**) with morpholine, 1,2,3,4-tetrahydro quinoline and 1-(2-pyrimidyl) piperazine in 90, 56 and 58 % yield, respectively (Scheme 35).[47]

From 4,6-dichloro-5-formyl pyrimidine

The reaction of ethyl-2-mercaptoacetate with 4,6-dichloro-5-formyl pyrimidine (**123**) gave the compound **124** in 22 % yield, which was reacted with aqueous ammonia at high temperature to afford 2,4-diaminothienopyrimidine (**125**) in 82 % yield.[48] The Suzuki cross-coupling reaction of compound **124** with commercially available boronic acid derivatives gave 4-aryl-2-aminopyrimidines.[49] Saponification of the ethyl ester (**126)** gave the corresponding acid **127**, which was coupled with ethylamine hydrochloride in the presence of HATU to give ethyl amide (**128)** in 72 % yield (Scheme 36).[50]



Scheme 36.

CONCLUSION

From the literature survey, thienopyrimidine derivatives were proved to be very important compounds with extensive biological activities which can use in treatment of many diseases.

On the other hand, thienopyrimidines derivatives have a lot of synthesis methods starting from thiophene ring but only several methods from pyrimidine ring containing compounds.

ACKNOWLEDGMENTS

I would like thanks to all authors worked in this review to can get it in this form.

REFERENCES

[1]Liuyu, D., Houying, G., Qiuming, Z., Xinming, H., Shaoyong, G., *Wuhan J. Nat. Sci.*, **2012**, *17(2)*, 177-184.

[2]Woodward, R. B., Eastman, R. H., *J. Am. Chem. Soc.*, **1946**, *68*, 2229-2234. https://doi.org/10.1021/ja01215a034

[3]Cheney, L. C., Piening, J. R., *J. Am. Chem Soc.*, **1945**, *67*, 731-735. https://doi.org/10.1021/ja01221a011

[4]Baker, B. R., Schaub, R. E., Joseph, J. P., McEroy, F. J., Wiims, J. H., *J. Org. Chem.*, **1953**, *18*, 138-152. https://doi.org/10.1021/jo01130a004

[5]El Azab, I. H., Kenzy, N. A., *Synth. Commun.*, **2014**, *44*, 2692-2714. https://doi.org/10.1080/00397911.2014.916301

[6]Russell, K. R., Press, J. B., Rampulla, R. A., McNally, J. J., Falotico, R., Keiser, J. A., Bright, D. A., Tobia, A., *J. Med. Chem.*, **1988**, *31*, 1786-1793. https://doi.org/10.1021/jm00117a019

[7]Ziegler, D., Brossmer, R., *Tetrahedron*, **1973**, *23*, 2055-2058. https://doi.org/10.1016/S0040-4039(01)86805-2

[8]Jourdan, F., Laaurèe, D., Robba, M., *J. Heterocycl. Chem.*, **1994**, *31*, 305-312. https://doi.org/10.1002/jhet.5570310208

[9]Shestakov, A. S., Prezent, M. A., Kartsev, V. G., Shikhaliev, K. S., *Eur. Chem. Bull.*, **2014**, *3(7)*, 713-718. DOI: 10.17628/ecb.2014.3.713-718.

[10]Temburnikar, K. W., Zimmermann, S. C., Kim, N. T., Ross, C. R., Gelbmann, C., Salomon, C. E., Wilson, G. M., Balzarini, J., Seley-Radtke, K. L., *Bioorg. Med. Chem.*, **2014**, *22*, 2113-2122. https://doi.org/10.1016/j.bmc.2014.02.033

[11]Ivachtchenko, A., Kovalenko, S., Tkachenko, O. V., Parkhomenko, O., *J. Comb. Chem.*, **2004**, *6*, 573-583. https://doi.org/10.1021/cc049946l

[12]Perspicace, E., Oberwinkler, S. M., Hartmann, R. W., *Molecules*, **2013**, *18*, 4487-4509. https://doi.org/10.3390/molecules18044487

[13]Migianu E., Kirsch, G., *Synthesis*, **2002**, *8*, 1096-1100. https://doi.org/10.1055/s-2002-31963

[14]Hertzog, D. L., Al-Barazanji, K. A., Bigham, E. C., Bishop, M. J., Britt, C. S., Carlton, D. L., Cooper, J. P., Daniels, A. J., Garrido, D. M., Goetz, A. S., *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 4723-4727. https://doi.org/10.1016/j.bmcl.2006.07.008

[15]Kirsch, G., Abdillahi I., *Synthesis*, **2010**, *9*, 1428-1430. https://doi.org/10.1055/s-0029-1218697

[16]Kirsch, G., Abdillahi I., *Synthesis*, **2011**, *8*, 1314-1318. https://doi.org/10.1055/s-0030-1258469

[17]El-Saghier, A. M. M., Matough, F. S., Farhat, M. F., Saleh, N. A., Kreddan, K. M., El-Tier S. O., B. Hussien, H., *Jordan J. Chem.*, **2008**, *3(3)*, 223-232.

[18]Baker, B. R., Schaub, R. E., Joseph, J. P., McEroy F. J., Wiims, J. H., *J. Org. Chem.*, **1953**, *18*, 138-152. https://doi.org/10.1021/jo01130a004

[19]Gewald, K., *Chem. Ber.*, **1965**, *98*, 3571-3577. https://doi.org/10.1002/cber.19650981120

[20]Abdelrazek F. M., Ead, H., *J. Prakt. Chemie.*, **1988**, *8*, 585-589. https://doi.org/10.1002/prac.19883300412

[21]Taylor, E. C., McKillop A., Vromen, S., *Tetrahedron*, **1967**, *23*, 885-889. https://doi.org/10.1016/0040-4020(67)85037-3

[22]Ried W., Giesse, P., *Angew. Chem. Int. Ed.*, **1968**, *7*, 136. https://doi.org/10.1002/anie.196801361

[23]Sebnis, R. W., Ragnekar, D. W., Sonawane, N. D., *J. Heterocycl. Chem.*, **1999**, *36*, 333-345. https://doi.org/10.1002/jhet.5570360203

[24]Gewald, A. K., Schinke, E., Bottcher, H., *Chem. Ber.*, **1966**, *99*, 94-100. https://doi.org/10.1002/cber.19660990116

[25]Hossain M. I., Bhuiyan, M. M. H., *J. Sci. Res.*, **2009**, *1(1)*, 317-325.

[26]Shetty, N. S., *Int. J. Adv. Chem. Eng. Biol. Sci.*, **2014**, *1(1)*, 80-84.

[27]Dave, C. G., Shah, R. D., *J. Heterocycl. Chem.*, **1998**, *35*, 1295-1300. https://doi.org/10.1002/jhet.5570350609

[28]Kandeel, M. M., Mounir, A. A., Refaat, H. M., Kassab, A. E., *J. Chem. Res.*, **2012**, *2*, 105-110. https://doi.org/10.3184/174751912X13282020691270

[29]Bhuiyan, M. H., Rahman, K. M., Abdur Rahim, K. H., Abu Naser, M. I. H. M., *Acta Pharm.*, **2006**, *56*, 441-450.

[30]Li, S. G., Vilchèze, C., Chakraborty, S., Wang, X., Kim, H., Anisetti, M., Ekins, S., Rhee, K. Y., Jacobs, W. R., Freundlich, J. S., *Tetrahedron Lett.*, **2015**, *56*, 3246-3250. https://doi.org/10.1016/j.tetlet.2015.02.129

[31]Abu-Hashem, A. A., El-shehry, M. F., Badria, F. A., *Acta Pharm.*, **2010**, *60*, 311-323. https://doi.org/10.2478/v10007-010-0027-6

[32]Haswani, N. G., Bari, S. B., *Turk. J. Chem.*, **2011**, *35*, 915-924.

[33]Bhadane, M. R., Chandra, J. N. N. S., Nargund, L. V. G., *Der Pharma Chemica*, **2011**, *3(4)*, 238-244.

[34]Ameen, M. A., *Z. Naturforsch*, **2006**, *61b*, 1234-1238.

[35]Salahuddin, M., Singh, S., Shantakumar, S. M., *Rasayan J. Chem.*, **2009**, *2(1)*, 167-173.

[36]Hegab, M. I., Hassan, N. A., Rashad, A. E., Fahmy, A. A., Abdel-Megeid, F. M., *Phosphorus Sulfur Silicon Relat. Elem.*, **2007**, *182*, 1535-1556. https://doi.org/10.1080/10426500701247151

[37]Haggam, R. A., Moustafa, A. H., *AFINIDAD LXXI 565 Enero – Marzo*, **2014**, 68-73.

[38]Mulla, J. A. S., Khazi, M. I. A., Panchamukhi, S. I., Gong, Y. D., Khazi, I. A. M., *Med. Chem. Res.*, **2014**, *23*, 3235-3243. https://doi.org/10.1007/s00044-013-0900-1

[39]Kambe, S., Saito, K., Kishi, H., *Synthesis*, **1979**, *4*, 287-289. https://doi.org/10.1055/s-1979-28650

[40]Saddik, A. A., Hassan, Kh. M., Kamal El-Dean, A. M., Abbady, M. S., *Eur. Chem. Bull.*, **2015**, *4(9)*, 436-441. DOI: 10.17628/ecb.2015.4.436-441.

[41]Saddik, A. A., Kamal El-Dean, A. M., El-Sokary, G. H., Hassan, Kh. M., Abbady, M. S., Ismail, I. A., Saber, S. H., *J. Chin. Chem. Soc.*, **2017**, *64*, 87-93. https://doi.org/10.1002/jccs.201600279

[42]Senda, S., Hirota, K., Asso, T., *Chem. Pharm. Bull.*, **1978**, *26*, 3208-3211. https://doi.org/10.1248/cpb.26.3208

[43]Ogura, H., Sakaguchi, M., Takeda, K., *Chem. Pharm. Bull.*, **1972**, *20(2)*, 404-408. https://doi.org/10.1248/cpb.20.404

[44]Hirota, K., Shirahashi, M., Senda, S., Yogo, M., *J. Heterocycl. Chem.*, **1990**, *27*, 717-721. https://doi.org/10.1002/jhet.5570270345

[45]Ho, Y. W., Yao, C. T., *J. Chin. Chem. Soc.*, **2003**, *50*, 283-296. https://doi.org/10.1002/jccs.200300043

[46]Elnagdi, M. H., Abdelrazek, F. M., Ibrahim, N. S., Erian, A. W., *Tetrahedron*, **1989**, *45*, 3597-3604. https://doi.org/10.1016/S0040-4020(01)81038-3

[47]Ho Y.W., Suen, M.C., *J. Chin. Chem. Soc.*, **2009**, *56*, 408-415. https://doi.org/10.1002/jccs.200900060

[48]Clark, J., Shahhet, M. S., Korakas, D., Varvounis, G., *J. Heterocycl. Chem.*, **1993**, *30*, 1065-1072 .

[49]Zhu, L., Duquette, J., Zhang, M., *J. Org. Chem.*, **2003**, *68*, 3729-3732 .https://doi.org/10.1021/jo0269114

[50]Brough, P. A., Barril, X., Borgognoni, J., Chene, P., Davies, N. G. M., Davis, B., Drysdale, M. J., Dymock, B., Eccles, S. A., Echeverria, C. G., Fromont, C., Hayes, A., Hubbard, R. E., Jordan, A. M., Jensen, M. R., Massey, A., Merrett, A., Padfield, A., Parsons, R., Radimerski, T., Raynaud, F. I., Robertson, A., Roughley, S. D., Schoepfer, J., Simmonite, H., Sharp, S. Y., Surgenor, A., Valenti, M., Walls, S., Webb, P., Wood, M., Workman P., Wright, L., *J. Med. Chem.*, **2009**, *52*, 4794-4809.

Received: 25.05.2017.
Accepted: 02.07.2017.