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Pyrimidine-5-carbonitriles: A review of available synthetic approaches and biological evaluation for promising compounds over the last decade.

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Abstract

The structural diversity and biological significance of pyrimidine core attracted the attention of many researchers and scientists in the past years owing to their inclusion in the composition of most nucleotides, including DNA and RNA. One unique scaffold was pyrimidine-5-carbonitrile and its importance is largely related to a wide range of biological activities of pyrimidine-5-carbonitrile derivatives such as anticancer, antimicrobial, anti-inflammatory, antifungal, antitubercular, antiviral, antihypertensive, anthelmintic, anticonvulsant, and antimalarial. The key point of this review is to collect and review the most recent and available synthetic pathways for pyrimidine-5-carbonitrile derivatives from different starting materials and focus on the promising derivatives with valuable pharmacological activities.

Key words: Pyrimidine-5-carbonitriles, biological activity

Contents:

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1. Introduction

In medicinal chemistry, many heterocyclic scaffolds have a fundamental trend in the discovery of novel drugs. With all heterocyclic compounds, pyrimidines have received considerable attention because they are essential constituents of nucleic acids and are involved in all living cells. Pyrimidine nucleus is one of the three isomeric diazines, containing two nitrogen atoms at positions 1 and 3 of the six-membered ring. It is a much weaker base than pyridine and soluble in water. Due to its prominence, it has versatile biological properties and applications in drug discovery.[1–3] Different substituents of pyrimidine-5-carbonitrile possess antitubercular [4] antibacterial [5,6], anticonvulsant [7], anti-inflammatory [8], anticancer [9–11] and other medicinal activities.The present review is an attempt to give plentiful information about the synthesis and several biological activities of pyrimidine-5-carbonitriles and their derivatives [12,13]. Various synthetic routes for the synthesis of different derivatives of pyrimidine-5-carbonitrile from diverse starting materials have been illustrated in this collective chart (Figure 1) and discussed in detail in this review.

2. Synthetic Approaches for the Preparation of various Derivatives of Pyrimidine-5-carbonitriles:

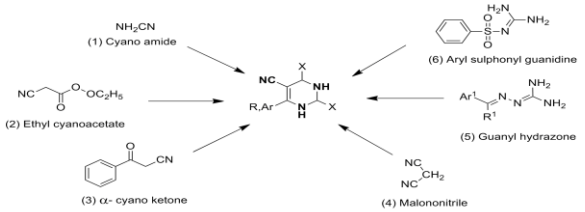
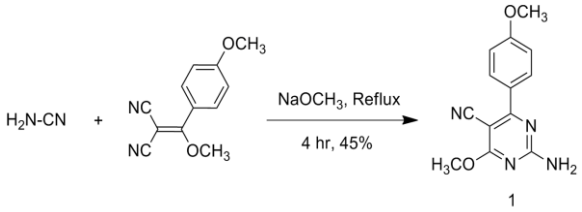


Figure 1: Certain synthetic pathways for preparation of pyrimidine-5-carbonitriles

The synthetic approaches adopted for the preparation of Pyrimidine-5-carbonitrile derivatives can be classified according to the starting material as follows:

2.1. From cyanoamide:

By solvent-free protocol, Al-Ghulikah *et al*.,[14] described the synthesis of 2-amino-4-methoxy-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile **(1)** from cyanamide and 2-(methoxy (4-methoxyphenyl) methylene) malononitrile in the presence of sodium methoxide as catalyst with 49% under reflux for 4 hr. (Scheme 1)

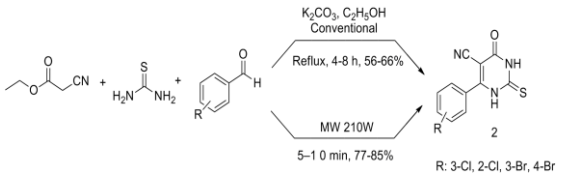


Scheme 1: Synthesis of pyrimidine-5-carbonitrile **1** using cyanoamide

2.2. From ethyl cyanoacetate:

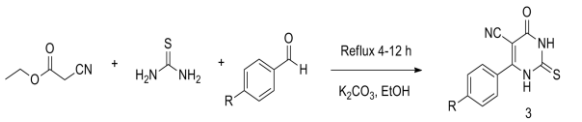
Different substituents of pyrimidine-5-carbonitrile were obtained from ethyl cyanoacetate via various methods and catalysts:

Cyclocondensation of ethyl cyanoacetate, thiourea, and substituted aromatic aldehyde in ethanol was refluxed for 4–8 hours by the use of potassium carbonate as a catalyst in a water bath to afford pyrimidine-5-carbonitrile derivatives **2** by Sahoo and his colleagues .[15] While using microwave irradiation for 5–10 min at (210W), the yield increased from 55 to 85% (Scheme 2).



Scheme 2: Synthesis of pyrimidine-5-carbonitrile derivatives **2** using ethyl cyanoacetate in comparison with conventional and microwave irradiation method

It was reported in many publications [16–26] starting in 2014, using the conventional method, one pot reaction of ethyl cyanoacetate, thiourea and an appropriate aldehyde in absolute ethanol for 4-12 h afforded 5-cyanopyrimidine derivatives **3**. (Scheme 3).

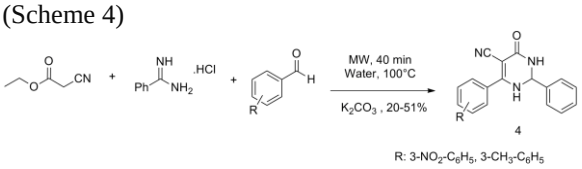


R: isovaleraldehyde, 4-Cl-C_6H_5, 4-OCH_3-C_6H_5, 4-NO_2-C_6H_5, pyrazole aldehyde, 4-F-C_6H_5, propane-aldehyde, 4-N,N-dimethylamino benzaldehyde

Scheme 3: Synthesis of pyrimidine-5-carbonitrile derivatives **3** by conventional method

On the other hand, Xavier and co-workers [27] synthesized pyrimidine 5-carbonitrile derivatives **4** from the cyclization of ethyl cyanoacetate, benzamidine hydrochloride, and aromatic aldehydes. The reaction was performed in water with potassium carbonate as the base under microwave irradiation for 40 min, obtaining a yield of 22 to 70%. Microwave synthesis provides a higher yield, a shorter reaction

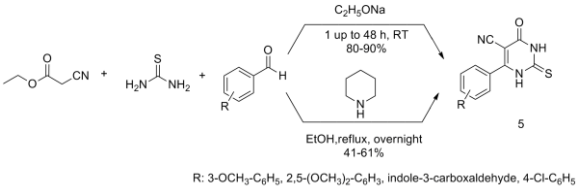
time, a simple procedure, mild conditions, and easy workup as compared to the conventional method. (Scheme 4)



Scheme 4: Cyclization of pyrimidine-5-carbonitrile **4** using ethyl cyanoacetate and aryl amidine

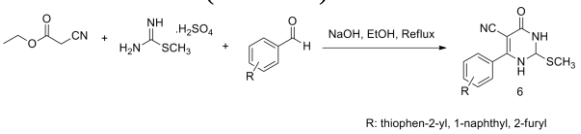
Second, by using sodium hydroxide, sodium ethoxide, sodium carbonate or pipridine as an alkaline catalyst in different conditions, synthesis was performed by a group of researchers.

In 2014, pyrimidine-5-carbonitrile derivatives were synthesized by scientists [28,29] by adding sodium ethoxide to ethyl cyanoacetate, thiourea, and appropriate aldehydes with a yield of 90%.While, Stella and his colleague [30] used piperidine as a catalyst for the same reaction, which refluxed over night with a yield of 41-61%. (Scheme 5).



Scheme 5: Synthesis of pyrimidine-5-carbonitriles **5** using sod.ethoxide or pipridine as catalysts

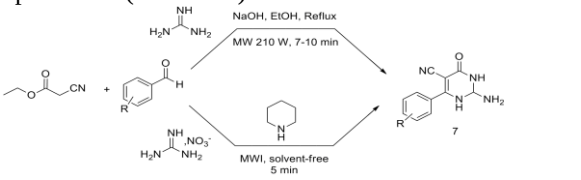
Also, 1,6-dihydro-2-methylthio-6-oxo-4-arylpyrimidine-5-carbonitriles **6** were reported by Abdel-Aziz and co-authors [31], who prepared **6** with the multicomponent reaction of ethyl cyanoacetate, S-methyl isothiourea sulfate, and aryl aldehyde that refluxed in the presence of sodium hydroxide and ethanol as solvent. (Scheme 6)



Scheme 6: Multicomponents reaction for pyrimidine-5-carbonitriles **6** formation using sod.hydroxide as base catalyst

Recently, Majee *et al*. [32] reviewed microwave-assisted convenient synthesis of pyrimidine-5-carbonitrile **7** as potential antitubercular agents. The synthesis was carried out by the condensation of ethyl cyanoacetate, guanidine, and aryl aldehyde in the presence of ethanolic sodium hydroxide under microwave irradiation for 7–12 min with a yield of 84%.

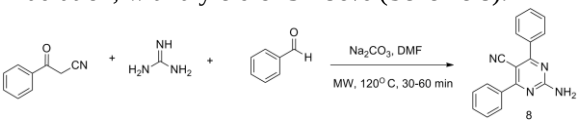
Whereas, using piperidine as a catalyst, Bhatewara and co-authors [33] synthesize pyrimidine-5-carbonitrile derivatives **7** by cyclization of ethyl cyanoacetate, guanidine nitrate, and appropriate aldehydes with varying microwave power from 150 watts to 750 watts. It was observed that there was an increase in yield and a shortened reaction time when power was increased up to 600 watts with a yield of up to 90%. (Scheme 7)



Scheme 7: Synthesis of pyrimidine-5-carbonitriles **7** using sod.hydroxide or pipridine

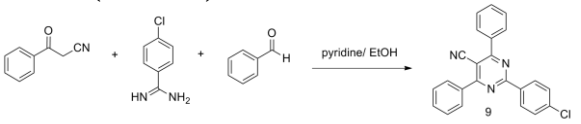
2.3. From α-cyano ketone

The reaction of α-cyano ketone as benzoyl acetonitrile, guanidine, and aryl aldehyde in DMF using sodium carbonate at 120 °C for 30-60 min furnished the corresponding 2-Amino-4,6-diphenylpyrimidine-5-carbonitrile **(8)** by Val and co-workers [34]. In comparison with the conventional method and microwave method for this reaction, the best results were obtained by using microwave irradiation, with a yield of 34-86% (Scheme 8).



Scheme 8: Synthesis of pyrimidine-5-carbonitrile **8** using α-cyano ketone and sod.carbonate as catalyst

By using pyridine as a base catalyst, Jang *et al*.[35] designed the synthesis of 2-(4-chlorophenyl)-4,6-diphenylpyrimidine-5-carbonitrile **(9)** by condensation of benzoyl acetonitrile with aryl aldehyde and 4-chlorobenzimidamide in the presence of ethanol as a solvent. (Scheme 9)



Scheme 9: Synthesis of 2-(4-chlorophenyl)-4,6-diphenylpyrimidine-5-carbonitrile **9** using α-cyano ketone and pyridine as catalyst

2.4. From malononitrile:

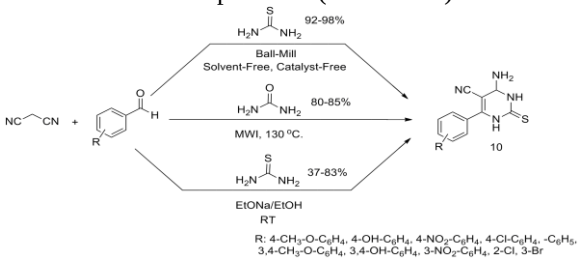
Many reactions have been done by malononitrile and its substituents with various reagents and catalysts to afford derivatives of pyrimidine-5-carbonitrile.

Mohamed and his partner [36] showed that condensation of an equimolar amount of malononitrile, thiourea, and appropriate aldehyde by using Ball-Mill solvent-free and catalyst-free conditions afforded pyrimidine-5-carbonitrile **10**.

Also, Divate and co-workers [37] obtained the 5-cyanopyrimidine derivative **10** by the reaction of malononitrile, urea, and aromatic aldehyde, which was irradiated by microwave at a maximum power of 200 watts at 130 °C.

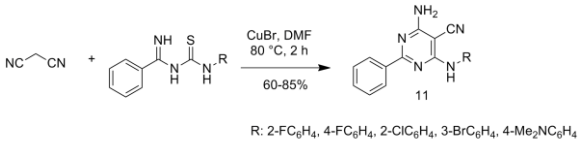
In 2016, Atapour and her partners [38] presented substituted pyrimidine-5-carbonitrile **10** by a one-pot reaction of malononitrile, thiourea, and suitable aryl

aldehyde in the presence of sodium ethoxide in ethanol at room temperature. (Scheme 10)



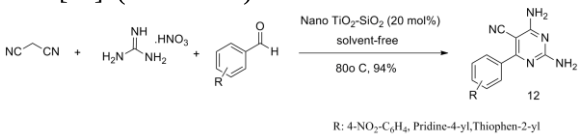
Scheme 10: Synthesis of pyrimidine-5-carbonitrile derivatives **10** using different reagents and catalysts

On the other hand, Mahdavi et al. [39] synthesized pyrimidine-5-carbonitriles 11 from the condensation of malononitrile and N-(substituted carbamothioyl)benzimidamide. The reaction occurred in the presence of copper bromide and dimethyl formamide and was heated at 80 °C. (Scheme 11).



Scheme 11: Synthesis of pyrimidine-5-carbonitriles **11** using copper bromide

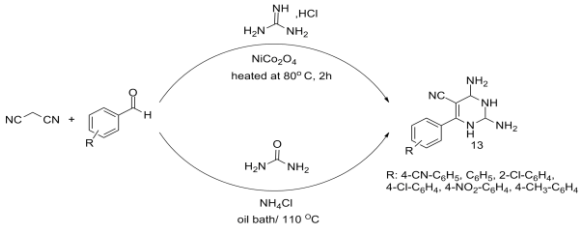
In addition, some researchers synthesized pyrimidine-5-carbonitrile derivatives **12** by a multicomponent reaction of malononitrile, guanidine nitrate, and appropriate aldehyde using 20 mol% TiO2/SiO2 (silicon dioxide and titanium dioxide) nanocomposite as a catalyst with a yield of up to 94%.[40]. (Scheme 12)



Scheme 12: Using Silicon dioxide/ titanium dioxide nanoparticles in synthesis of pyrimidine-5-carbonitriles **12**

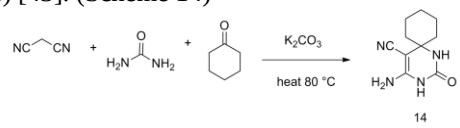
Also, by reacting malononitrile, guanidine hydrochloride, and aryl aldehyde in the presence of $NiCo_2O_4$ (nickel cobaltite), which was heated in the oil bath under reflux conditions at 80° C for 2 h, Ghasemzadeh and co-authors [41] obtained pyrimidine-5-carbonitriles **13**.

Moreover, with the simple, quick, and eco-friendly method, Aher and his prosaists [42] synthesized pyrimidine-5-carbonitrile derivatives **13** with malononitrile, urea, and appropriate aldehyde in the presence of NH_4Cl (ammonium chloride) as a catalyst in the oil bath for 4 h. (Scheme 13)



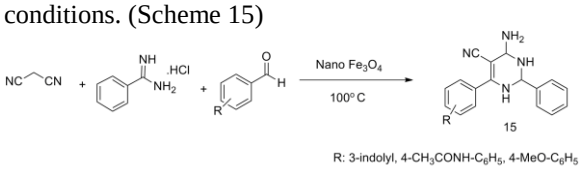
Scheme 13: Synthesis of pyrimidine-5-carbonitriles **13**

Furthermore, with malononitrile, urea, and by replacing aryl aldehyde with ketone as cyclohexanone in the presence of potassium carbonate, the reaction mixture was allowed to heat up to 90°C to form 4-Amino-2-oxo-1,3-diazaspiro [5.5]. undec-4-ene-5-carbonitrile (**14**) [43]. (Scheme 14)



Scheme 14: Synthesis of 4-Amino-2-oxo-1,3-diazaspiro[5.5]undec-4-ene-5-Carbonitrile **14** using by malononitrile using pot.carbonate as catalyst

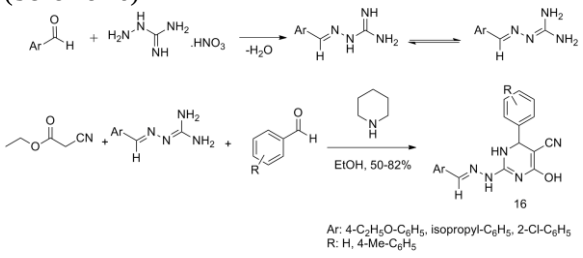
Finally, scientists [44,45] reviewed the synthesis of 4-amino-6-substitutedphenyl-2-phenylpyrimidine-5-carbonitrile **15** via a reaction of malononitrile, benzamide hydrochloride, and aryl aldehyde in the presence of Fe_3O_4 (magnetite) nanoparticles, which obtained a high yield in 1–1.5 h in solvent-free conditions. (Scheme 15)



Scheme 15: Using magnetite nanoparticles in synthesis of pyrimidine-5-carbonitriles **15**

2.5. From guanyl hydrazone:

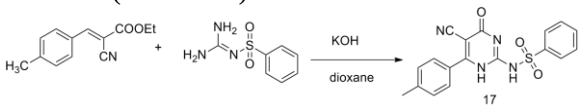
Compound **16** was synthesized from a ring closure reaction of ethyl cyanoacetate, guanyl hydrazone derivatives, and aryl aldehyde in the presence of piperidine at room temperature or reflux. Guanyl hydrazone derivatives obtained from the reaction of aryl aldehyde with aminoguanidine nitrate [46]. (Scheme 16)



Scheme 16: Synthesis of pyrimidine-5-carbonitriles **16** using guanyl hydrazone and pipridine as catalyst

2.6. Aryl sulphonyl guanidine

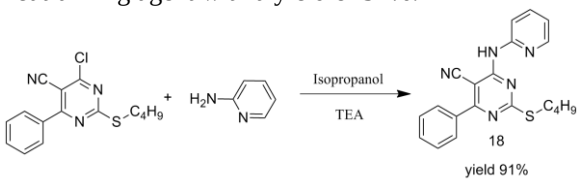
N-[5-Cyano-4-(4-methylphenyl)-6-oxo-1,6-dihydropyrimidin-2-yl]benzene sulfonamide **(17)** was investigated by Azzam and her prosaists [47,48] via a Michael addition of *N*-(diaminomethylidene)benzenesulfonamide with ethyl (2*E*)-2-cyano-3-(4-methylphenyl)prop-2-enoate, in the presence of potassium hydroxide with dioxane as a solvent. (Scheme 17)



Scheme 17: Using aryl sulphonyl guanidine in synthesis **17**

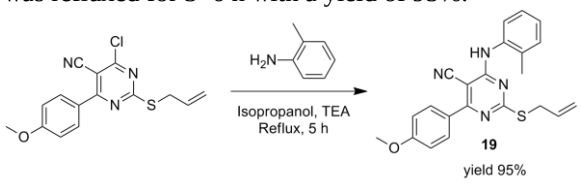
3. Synthesis of biologically active pyrimidine-5-carbonitrile derivatives:

Nasser *et al*.,[49] were designed and synthesized pyrimidine-5-carbonitrile derivative **18** by reacting 2-(butylthio)-4-chloro-6-phenylpyrimidine-5-carbonitrile with the appropriate hetero aromatic amine in isopropyl alcohol containing TEA as a neutralizing agent with a yield of 91%.



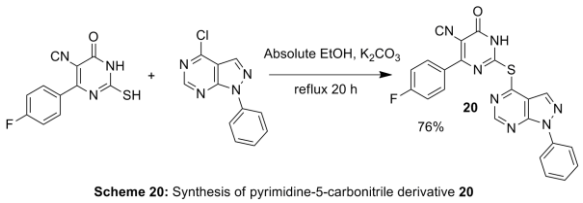
Scheme 18: Synthesis of pyrimidine-5-carbonitrile derivative **18**

Pyrimidine-5-carbonitrile **19** was synthesized by the nucleophilic attack of aromatic amines on chloro derivatives in isopropyl alcohol in the presence of the acid binder triethylamine. [50] The reaction mixture was refluxed for 3–6 h with a yield of 95%.



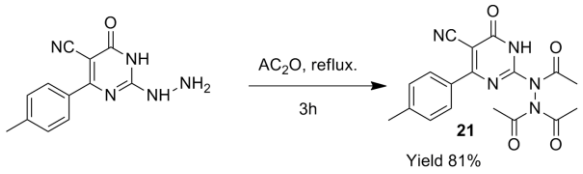
Scheme 19: Synthesis of pyrimidine-5-carbonitrile derivative **19**

Also, the derivative **20** was obtained with a yield of 76% via the reaction of 4-chloro-pyrazolopyrimidine and 4-(4-fluorophenyl)-2-mercapto-6-oxo-1,6-dihydropyrimidine-5-carbonitrile for 20 h in absolute ethanol in the presence of potassium carbonate as a catalyst.[51]



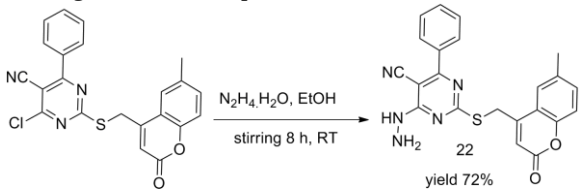
Scheme 20: Synthesis of pyrimidine-5-carbonitrile derivative **20**

Amin and co-workers [52] were afforded *N′*,*N′*-diacetyl-*N*-(5-cyano-1,6-dihydro-6-oxo-4-p-tolylpyrimidin-2-yl)acetohydrazide **(21)** by electrophilic attack of acetic anhydride with 2-hydrazinyl-1,6-dihydro-6-oxo-4-p-tolyl pyrimidine, which refluxed for 3 h.



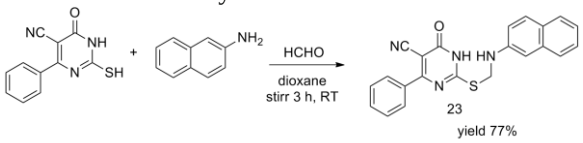
Scheme 21: Synthesis of pyrimidine-5-carbonitrile derivative **21**

Morsy and co-workers [53] were synthesized the most active coumarin-containing compound, **22**. The solution of 4-chloro-2-6-methyl-2-oxo-2H-chromen-4-yl-methyl-thio-6-phenylpyrimidine-5-carbonitrile was stirred for 8 hours with hydrazine hydrate in absolute ethanol and triethyl amine, then left to stand overnight at room temperature.



Scheme 22: Synthesis of pyrimidine-5-carbonitrile derivative **22**

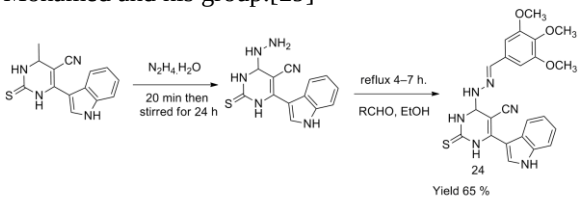
El-Naggar *et al*.,[20] were used the Mannich reaction as a convenient process for the introduction of an amino methylene fragment in compounds bearing an acidic proton by stirring 2-mercapto-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile with *β*-naphthylamine for 3 h at room temperature to obtain 2-naphthalen-2-ylamino-methyl-thio-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile **(23)** with an excess of formaldehyde in dioxane.



Scheme 23: Synthesis of pyrimidine-5-carbonitrile derivetive **23**

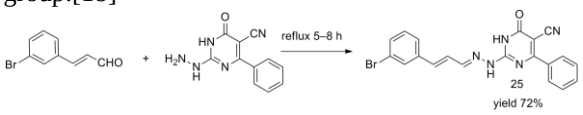
A mixture of 4-chloropyrimidine and hydrazine hydrate was refluxed in methanol for 20 min and stirred for 24 h to afford a hydrazine derivative. Then, the hydrazine derivative and appropriate aldehyde in ethanol were heated under reflux for 4–7 h to

synthesize pyrimidine-5-carbonitrile **24**. According to Mohamed and his group.[29]



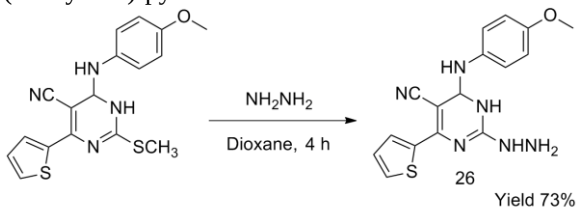
Scheme 24: Synthesis of pyrimidine-5-carbonitrile derivative **24**

Via a hydrazine linker, (*E*)-3-(3-bromophenyl)acrylaldehyde reacted with the hydrazino derivative for 5-8 h to furnish pyrimidine-5-carbonitrile **25**. According to El-Atawy and his group.[18]



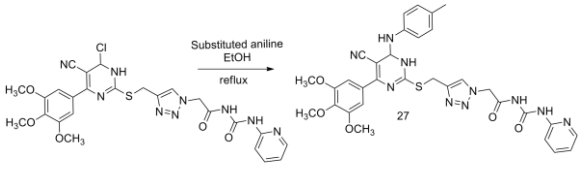
Scheme 25: Synthesis of pyrimidine-5-carbonitrile derivative **25**

AboulWafa *et al*.,[54] were designed and synthesized pyrimidine-5-carbonitrile derivative **26** via nucleophilic attack of hydrazine hydrate on 2-(methylthio)-pyrimidine-5-carbonitrile.



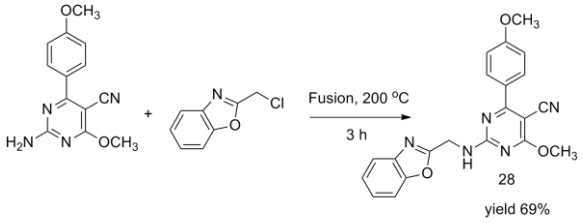
Scheme 26: Synthesis of pyrimidine-5-carbonitrile derivative **26**

Group of researchers [17,55] synthesized triazole-pyrimidine hybrid derivative **27** by reaction chloro derivative with substituted aniline via nucleophilic attack.



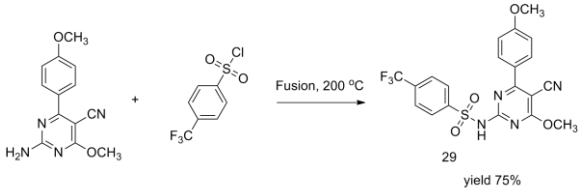
Scheme 27: Synthesis of pyrimidine-5-carbonitrile derivative **27**

AL-Ghulikah and co-workers [14] were presented the 2-(Benzo[d]oxazol-2-Ylmethylamino)-4-methoxy-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile **(28)** by reaction of 2-amino derivative with benzo[d]oxazolo derivative by fusion at 200 ºC for 3 h.



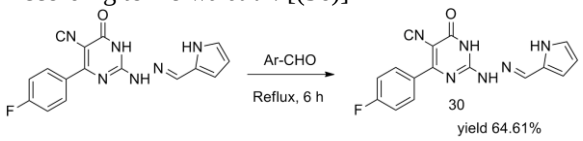
Scheme 28: Synthesis of pyrimidine-5-carbonitrile derivative **28**

2-Aminopyrimidine was fused with an equimolar quantity of various sulfonyl chloride derivative 4-(trifluoromethyl)benzene-1-sulfonyl chloride at ~200 ºC for 2 h to furnish pyrimidine-5-carbonitrile derivative **29**.[14]



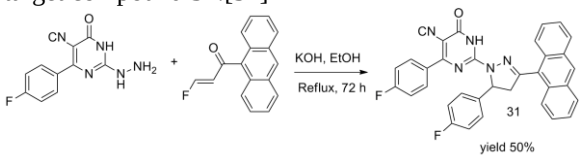
Scheme 29: Synthesis of pyrimidine-5-carbonitrile derivative **29**

Hydrazone derivative **30** was obtained by reaction a mixture of 5-cyano pyrimidine derivative, the appropriate aldehyde and glacial acetic acid in absolute ethanol was heated under reflux for 6 h. According to Helwa *et al.* [(56)]



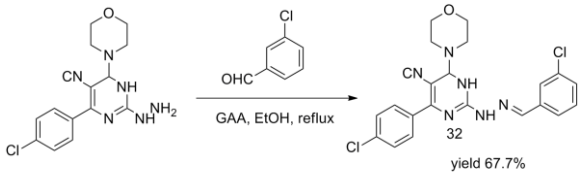
Scheme 30: Synthesis of pyrimidine-5-carbonitrle dertivative **30**

Cyclocondensation reaction of the corresponding 2-hydrazinopyrimdine derivatives and the appropriate propenones in absolute ethanol in the presence of potassium hydroxide with reflux for 72 h afforded the target compound **31**.[57]



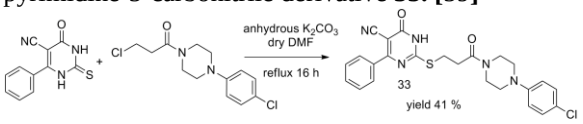
Scheme 31: Synthesis of pyrimidine-5-carbonitrile derivative **31**

Rady and co-workers [58] were synthesized pyrimidine-5-carbonitrile (schiff's base) **32** by refluxing hydrazine derivative with 3-cl-benzaldehyde for 5-6 h in presence of glacial acetic acid as catalyst.



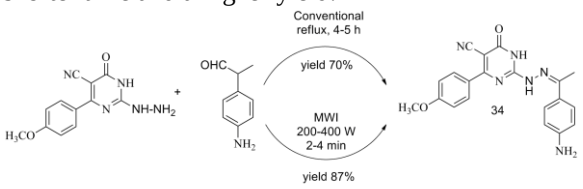
Scheme 32: Synthesis of pyrimidine-5-carbonitrile derivative **32**

A mixture of pyrimidine-2-thione and chloro derivative in presence of anhydrous K_2CO_3 in dry DMF was heated under reflux for 16 h to afford pyrimidine-5-carbonitrile derivative **33. [**59**]**



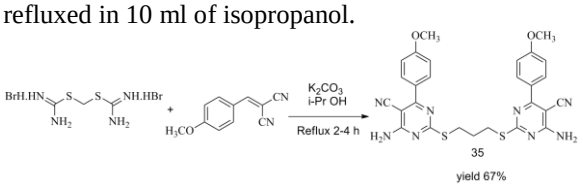
Scheme 33: Synthesis of pyrimidine-5-carbonitrile derivative **33**

By using various conditions for the synthesis of the Schiff's base pyrimidine-5-carbonitrile derivative **34**, Abbas and co-workers [60] were reacted hydrazinopyrimidine with acetyl compounds as 4-amino-acetophenone by conventional method in the presence of glacial acetic acid and ethanol and refluxed for 4-5 hours. Also, with microwave irradiation at 200–400 W power and 120 ºC for several minutes (4-6 minutes), By comparison between both methods, microwave irradiation afforded the product a shorter time and a higher yield.



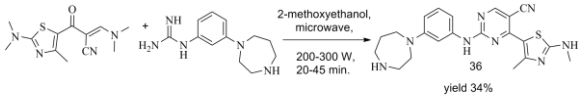
Scheme 34: Synthesis of pyrimidie-5-carbonitrle derivative **34**

Boualia *et al*.,[61] were synthesized bis(4-amino-5-cyano-pyrimidines) **35** by introduced 2-alkylthiouronium and 2-(arylidene)malononitrile derivative in the presence of K_2CO_3. The mixture was refluxed in 10 ml of isopropanol.



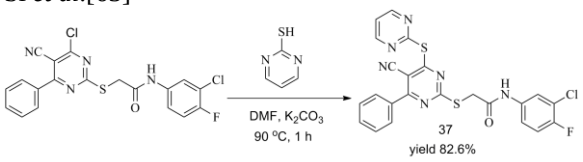
Scheme 35: Synthesis of bis(4-amino-5-cyano-pyrimidines **35**

A mixture of the appropriate 3-(dimethylamino)-1-(4-methyl-2-(methylamino)thiazol-5-yl)prop-2-en-1-one and 1-phenylguanidine in 2-methoxyethanol was heated in a microwave at 100−140 °C for 20−45 min furnished the synthesis of pyrimidine-5-carbonitrile **36**.[62]



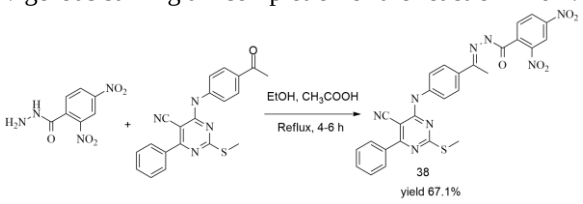
Scheme 36: Synthesis of pyrimidine-5-carbonitrile derivative **36**

In presence of DMF as solvent, chloro derivative reacted with heterocyclic compound to obtain pyrimidine-5-carbonitrile derivative **37**. According to Si *et al*.[63]



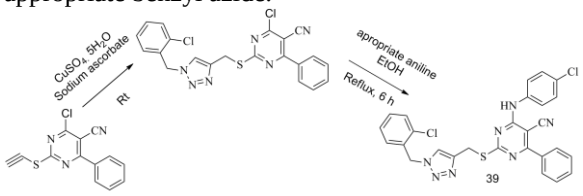
Scheme 37: synthesis of pyrimidine-5-carbonitrile derivative **37**

Hydrazono derivative **38** was synthesized by Saleh and his group [19] by neucleuphilic attack of 2,4-dinitrobenzohydrazide to 5-cyano pyrimidine derivative. The reaction mixture was refluxed with vigorous stirring till completion of the reaction 4–6 h.



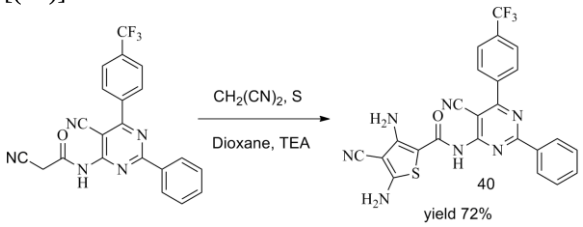
Scheme 38: synthesis of pyrimidine-5-carbonitrile derivative **38**

Jubeen *et al*.,[64] were reviewed the synthesis of pyrimidine-5-carbonitrile **39** by reflux chloro derivative with aniline. Chloro derivative was obtained by reaction of propargyl bromide with 2-thioxo pyrimidine in dioxane and then reaction with phosphorous oxychloride, then treatment with appropriate benzyl azide.



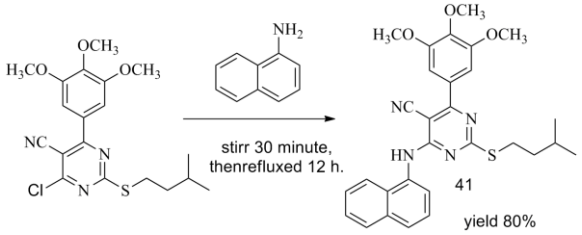
Scheme 39: Synthesis of pyrimidine-5-carbonitrile derivative **39**

Compound **40** was synthesized by refluxing 5-cyano pyrimidine with malononitrile and elemental sulfur in dioxane containing few drops of triethylamine for 3 h. [(65)]



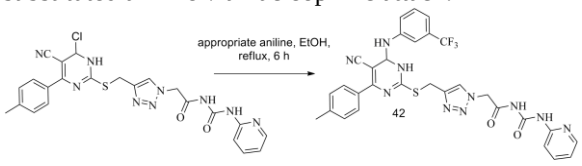
Scheme 40: Synthesis of pyrimidine-5-carbonitrile derivative **40**

Derivative of trimethoxy phenyl bearing naphthyl substitution of 5-cyano pyrimidine **41** was synthesized by reaction of the chloropyrimidine derivative with slowly added alcoholic solution of aromatic amines at room temperature. After 30 minute of stirring, the mixture was refluxed at 90 ºC for 12 h. [66]



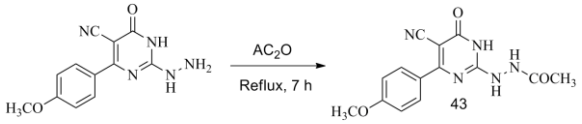
Scheme 41: Synthesis of pyrimidine-5-carbonittrile derivative **41**

Ma *et al*.,[67] were synthesized triazole-pyrimidine hybrid derivative **42** by reaction chloro derivative with substituted aniline via nucleophilic attack.



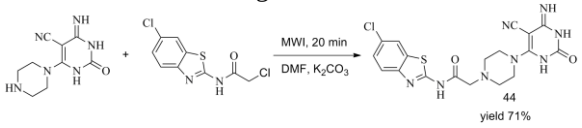
Scheme 42: Synthesis of pyrimidine-5-carbonitrile derivative **42**

Refluxing of hydrazino derivative with acetic anhydride for 7 h afforded the mono acetyl pyrimidine-5-carbonitrile derivative **43. [**68**]**



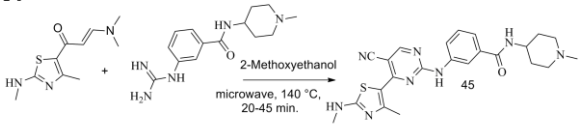
Scheme 43: Synthesis of pyrimidine-5-carbonitrile derivative **43**

Piperazin-1-ylpyrimidine-5-carbonitrile and benzothiazole derivative was refluxed for 20 min in microwave oven on 520 W in presence of potassium carbonate to obtain pyrimidine-5-carbonitrile derivative **44.** According to Ghule *et al*. [69]



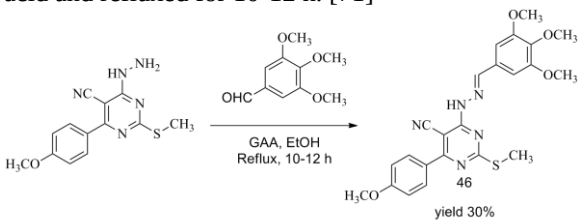
Scheme 44: Synthesis of pyrimidine-5-carbonitrile derivative **44**

By mixture of the appropriate enaminones and 1-phenylguanidine in 2-methoxyethanol was heated in a Discovery Microwave at 100-140 °C for 30-45 minutes, Shao and his associates [70] synthesized pyrimidine-5-carbonitrle derivative **45.**



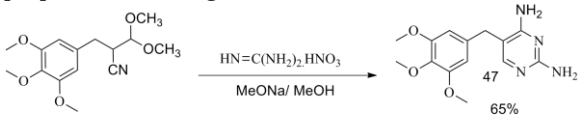
Scheme 45: Synthesis of pyrimidine-5-carbonitrile **45**

Schiff's base derivative **46** was obtained by reaction of 5-cyano pyrimidine with 3,4,5-trimethoxy benzaldehyde with catalytic amount of glacial acetic acid and refluxed for 10-12 h. [71]



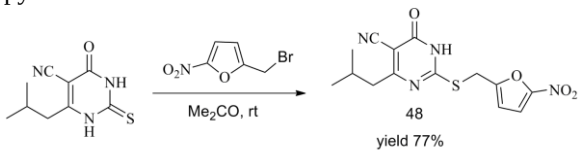
Scheme 46: Synthesis of pyrimidine-5-cabonitrile **46**

Synthesis of **47** was carried out using a powerful cyclization of 3-anilino-2-(3,4,5- trimethoxybenzyl)-propenenitrile and guanidine. [72]



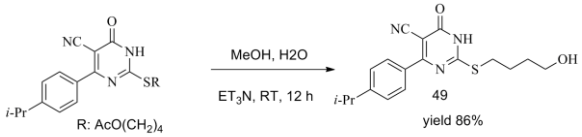
Scheme 47: Synthesis of pyrimidine-5-carbonitrile **47**

To a solution of the appropriate 2-thiouracil-5-carbonitrile in acetone and 2-bromomethyl-5-nitrofuran in presence of anhydrous potassium carbonate, the mixture was stirred at room temperature for 12 h, El-Deeb *et al*.,[73] were synthesized pyrimidine-5-carbonitrile derivative **48**.



Scheme 48: Synthesis of pyrimidine-5-carbonitrile **48**

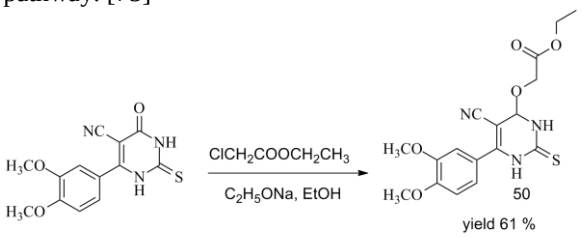
A mixture of pyrimidine-5-carbonitrile and potassium carbonate in anhydrous acetone was stirred at room temperature for 1 h. Then, 4-Bromobutyl acetate was added, the mixture was stirred for 8–12 h at room temperature to synthesis pyrimidine-5-carbonitrile derivative **49.** [74]



Scheme 49: Synthesis of pyrimidine-5-carbonitrle derivative **49**

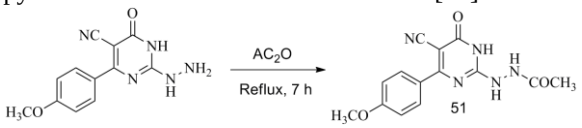
Refluxing 2-thioxo- pyrimidine and with ethyl chloroacetate in ethanol and sodium ethoxide gave the corresponding *O*-alkylated pyrimidine-5-carbonitrie product **50.** The presence of electron withdrawing group (C≡N) in the *α*-position to the carbonyl of the

amide also acts as an effective factor in the reaction pathway. [75]



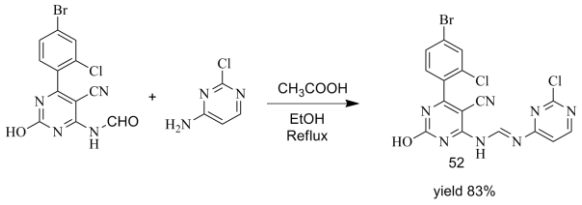
Scheme 50: Synthesis of pyrimidine-5-carbonitrile drivative **50**

Refluxing of hydrazine derivative with acetic anhydride for 7 h afforded the mono acetyl pyrimidine-5-carbonitrile derivative **51.** [68]



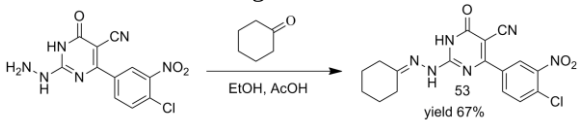
Scheme 51: Synthesis of pyrimidine-5-carbonitrile derivative **51**

The Schiff's base **52** was prepared by reaction of formamidine derivative and 2-chloropyrimidin-4-amine. Each reactant was dissolved in a minimum amount of ethanol, then added glacial acetic acid. The solution was refluxed for 8 h. [76]



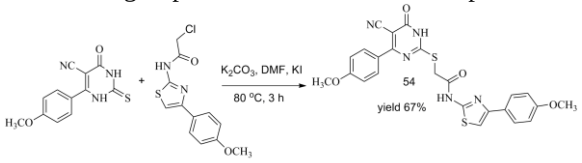
Scheme 52: Synthesis of pyrimidine-5-carbonitrle derivative **52**

By changing aldehyde to ketone as cyclohexanone, hydrazine derivative refluxed for 4–5 h with ketone to afford pyrimidine-5-carbonitrile derivative **53** in a mixture of ethanol and glacial acetic acid. [77]



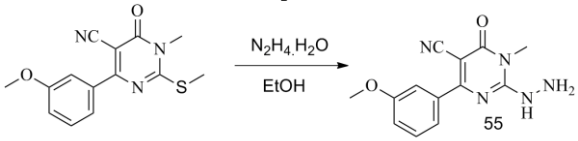
Scheme 53: Synthesis of pyrimidine-5-carbonitrile derivative **53**

S-alkylation of 2-thioxo-pyrimidine in the presence of anhydrous potassium carbonate with 2-chloro-N-(4-methoxy-phenyl-thiazol-2- yl)-acetamide, Abdel-Aziz [8] and his group furnished the desired compound **54**.



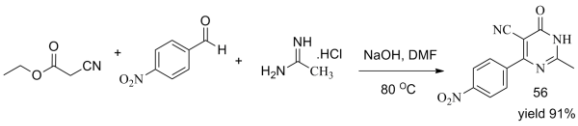
Scheme 54: Synthesis of pyrimidine-5-carbonitrile derivative **54**

2-hydrazino derivative **55** was obtained by heating 2-methylsulphanyl derivative with hydrazine hydrate in ethanol until reaction completion. [78]



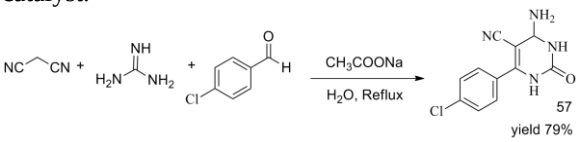
Scheme 55: Synthesis of pyrimidine-5-carbonitrile derivative **55**

With multicomponent reaction ethyl cyanoacetate, 4-nitrobenzaldehyde using quantitative
amount of sodium hydroxide in ethanol was stirred at room temperature for 10 min followed by addition of acetamidine hydrochloride and heated at 80 °C, Undare *et al.*, [79] was obtained pyrimidine-5-carbonitrle derivative **56.**



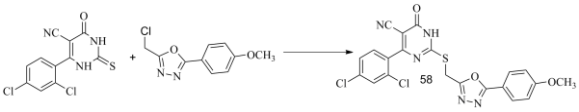
Scheme 56: Synthesis of pyrimidine-5-carbonitrile derivative **56**

In addition, some researchers [80] synthesized pyrimidine-5-carbonitrile derivative **57** by multicomponent reaction of malononitrile, guanidine, and p-cl-benzaldehyde using sodium acetate as a catalyst.



Scheme 57: Synthesis of pyrimidine-5-carbonitrile derivative **57**

S-alkylation of 2-thioxo-pyrimidine with 2-chloro-*N*-(4-methoxy-phenyl-thiazol-2-yl)-acetamide, Alfyomy and his group [81] furnished the desired compounds **58**.

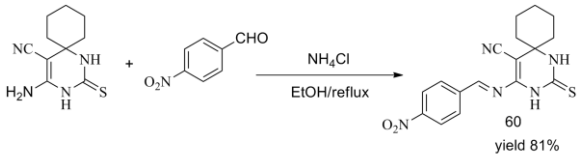


Scheme 58: Synthesis of pyrimidine-5-carbonitrile derivative **58**

4-imino-6-methylthio-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile and heteryl amines was refluxed for 5 h in the presence of DMF and anhydrous potassium carbonate to obtaine pyrimidine-5-carbonitrile derivative **59**. [82]

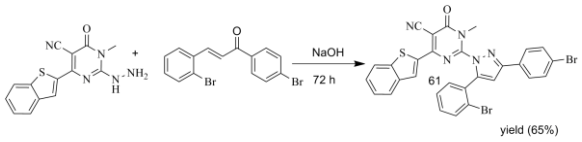
Scheme 59: Synthesis of pyrimidine-5-carbonitrile dertivative **59**

The reaction of 2-sulphanyl pyrimidine-5-carbonitrle derivative and p-nitro-benzaldehyde afforded 4-(4-Nitrobenzylideneamino)-2-thioxo-1,3-diaza-spiro[5.5]undec-4-ene-5-carbonitrile **(60).** The catalytic behavior of ammonium chloride through a mechanistic pathway for the synthesis of 4-arylideneamino derivatives Ammonium chloride may activate the carbonyl compounds by hydrogen bonding to promote the reaction via the nucleophilic attack of amines. [83]



Scheme 60: Synthesis of pyrimidine-5-carbonitrile **60**

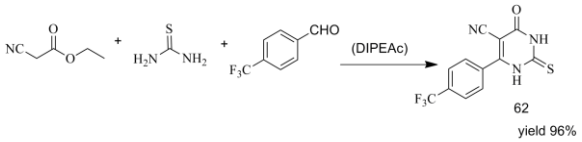
Hamouda and co-worker [84] was synthesized 4-(benzo[b]thiophen-2-yl)-2-(3-(4-bromophenyl)-5-(2-bromophenyl)-1H-pyrazol-1-yl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **(61)** by reaction of hydrazine derivative with the appropriate 1-propenone and sodium hydroxide in absolute ethanol which refluxed for 72 h.



Scheme 61: Synthesis of pyrimidine-5-carbonitrile derivative **61**

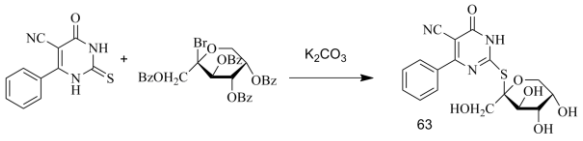
By using Diisopropylethylammonium Acetate (DIPEAc) as catalyst, Jadhave *et al*.,[85] were synthesized a pyrimidine-5-carbonitrile derivative **62** by reaction of ethylcyanoacetate, thiourea and aldehyde in DIPEAc, mixture was stirred at room temperature for 45 min.

*Synthesis of DIPEAc: A mixture of N,N-diisopropylethylamine (3 mmol) and acetic acid (3 mmol) was stirred at 0−10 °C for 20 min. The viscous liquid, diisopropylethylammonium acetate, was achieved.



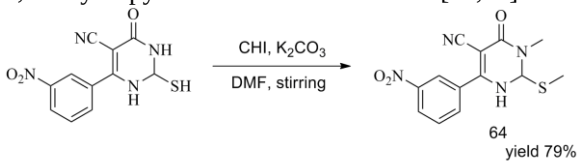
Scheme 62: synthesis of pyrimidin-4-carbonitrile **62**

When the thiouracil derivative was stirred with bromo sugar (L-sorbose) in present of anhydrous potassium carbonate in DMF for 24 h, the corresponding S-glycosides analouge **63** was obtained [86]. Also, to a mixture of Anhydrous L-Sorbose (2g) and dry pyridine (5mL) in dry $CHCl_3$ (20 mL) mixture benzoyl chloride (7mL) was added in (0- 5 ^oC), then reflux with continuous stirring for 5h, at (55-60 ^oCo) to afford protected 1,3,4,6-Tetra-O-benzoyl–L-Sorbo pyranosyl bromide.



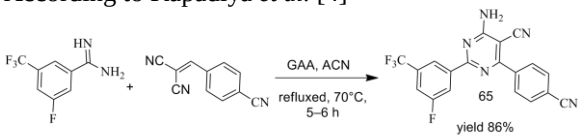
Scheme 63: Synthesis of s-glycoside containing pyrimidine-5-carbonitrile unit **63**

Stirring of 2-thioxo-pyrimidine-5-carbonitrile and methyl iodide in DMF in the presence of potassium carbonate yielded dimethylated adduct, 4-(3-nitrophenyl)-1-methyl-2-(methylsulphanyl)-6- oxo-1,6-dihydropyrimidine-5-carbonitrile **64**.[87,88]



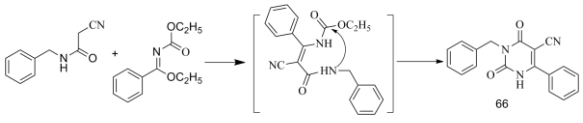
Scheme 64: Synthesis of pyrimidine-5-carbonitrile derivative **64**

Benzimidamide derivative and 2-benzylidenemalononitrile were used to carry out final novel pyrimidine-5-carbonitrile derivative **65**. The mixture was refluxed in ACN for 5–6 h in the presence of the catalytic amount of glacial acetic acid. According to Kapadiya *et al.* [4]



Scheme 65: Synthesis of pyrimidine-5-carbonitrile derivative **65**

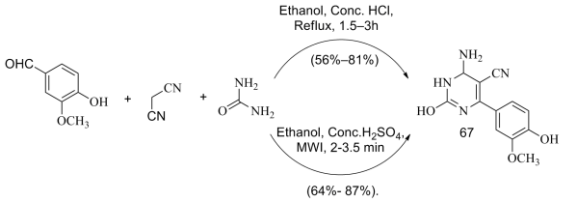
Condensation of the cyanoacetanilide salt and ethyl *N*-ethoxycarbonylbenzimidate then, followed by nucleophilic attack (by the NH group) on the ester group with the loss of an ethanol molecule were obtained the corresponding pyrimidine-5-carbonitrile derivative **66.** [89]



Scheme 66: Synthesis of pyrimidine-5-carbonitrile derivative **66**

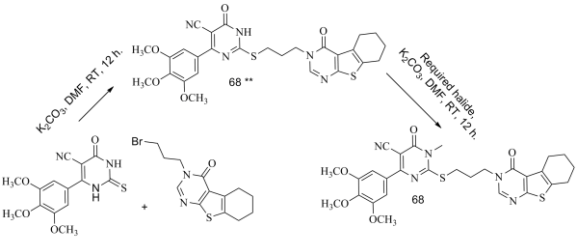
A simple and efficient approach toward single-step synthesis of pyrimidine-5-carbonitrile derivative **67** was developed by three-component condensation of

aromatic aldehydes, malononitrile and urea using conventional heating and microwave irradiation technique. The microwave-assisted synthesis was advantageous in simple reaction conditions and easy workup procedures, less time consuming and eco-friendly which result in better yields over the conventional method. [90]



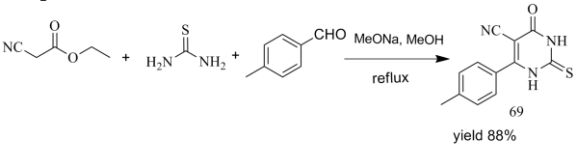
Scheme 67: Synthesis of pyrimidine-5-carbonitrile derivative **67** with convenient and MWI methods

Condensation of 2-thioxo-pyrimidine derivative and thienopyrimidine derivative were obtained the corresponding propyl thienopyrimidine derivative **68****. Iodomethane was added to the reaction mixture and stirred at RT for 12 h to obtain pyrimidine-5-carbonitrile derivative **68**.[91]

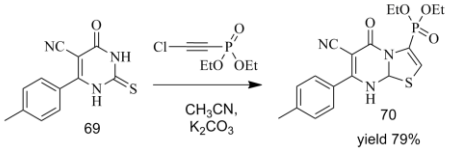


Scheme 68: Synthesis of pyrimidine-5-carbonitrile derivative **68**

By Cyclocondesation reaction, refluxing of ethyl cyanoacetate, thiourea and 4-methyl-benzaldehyde in sodium methoxide for 12-18 h afforded pyrimidine-5-carbonitrile derivative **69**. Then, the reaction of **69** with diethylchloroethynylphosphonates proceeds leading to the formation of diethyl (6-cyano-5-oxo-7-(*p*-tolyl)-5*H*-thiazolo[3,2-*a*]-pyrimidin-3-yl)phosphonate (**70**) in presence of potassium carbonate and anhydrous acetonitrile at room temperature for 2–3 h. [92,93]

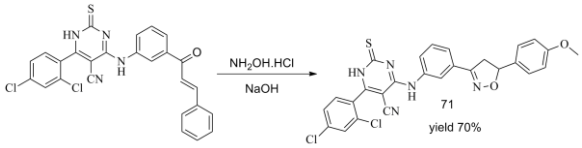


Scheme 69: Synthesis of pyrimidine-5-carbonitrile derivatives **69**



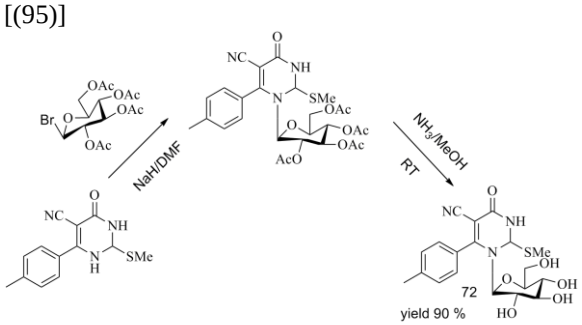
Scheme 70: Synthesis of pyrimidine-5-carbonitrile derivatives **70**

Mohamed and his group [94] were designed and synthesized pyrimidine-5-cabonitrile derivative **71** by refluxed of chalcone derivative with hydroxylamine hydrochloride and sodium hydroxide in 80% ethanol was for 4h.



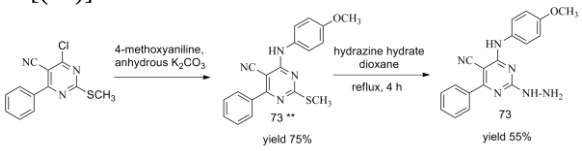
Scheme 71: Synthesis of pyrimidine-5-carbonitrile derivative **71**

Reaction of 1-*O*-acetyl-β-D-glycolpyranosyl)-5-cyanopyrimidin with conc. Ammonia and methanol and stirred at room temperature for 2 h furnished glycosidic pyrimidine-5-carbonitrile derivative **72**. [(95)]



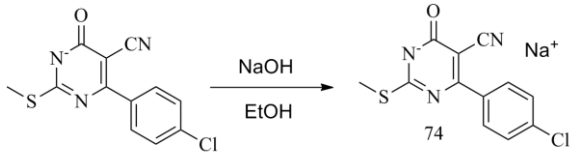
Scheme 72: Synthesis of glycosidic pyrimidine-5-carbonitrile derivative **72**

Reaction of chloro derivative with 4-methoxyaniline and anhydrous K_2CO_3 under reflux for 5 h afforded 2-methylthiopyrimidine-5-carbonitrile **73.** Then, compound **73** was obtained by neuleophilic attack of hydrazine hydrate to **73** in dioxane under reflux for 4 h. [(96)]



Scheme 73: Synthesis of pyrimidine-5-carbonitrile derivative **73**

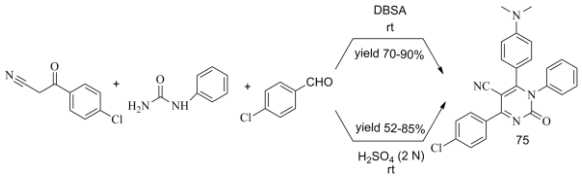
Andrade and co-workers [97] were synthesized pyrimidine 5-carbonitrile sodium salt **74**, by adding pyrimidinone derivative to 1 mmol of NaOH dissolved in ethanol. The reaction mixture was sonicated at a frequency of 40 kHz for 30 minutes.



Scheme 74: Synthesis of pyrimidine-5-carbonitrile derivative 74

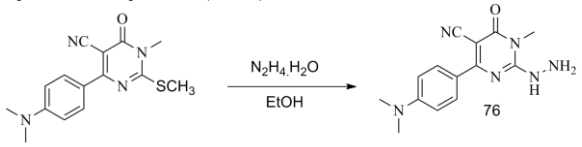
By using different reagent and conditions Sapkal and coworker [98] were furnished pyrimidine-5-carbonitrile derivative **75** by these affordable methods.

Method A: A mixture of p-chloro-benzoylacetonitrile, aldehyde and substituted urea in presence of DBSA (Dodecylbenzenesulfonic acid) in water (20 ml) were stirred at room temperature.
Method B: A mixture of p-chloro-benzoylacetonitrile, aldehyde and substituted urea and conc H_2SO_4 (2N) in ethanol (20 ml) were stirred at room temperature.
Reaction proceed through DBSA was produced a rapid Knoevenagel condensation of p-chlorobenzoyle acetonitrile with the aromatic aldehyde, followed by Michael addition, cycloaddition, isomerization, aromatization to afford the pyrimidine-5-carbonitrile derivative **75**.



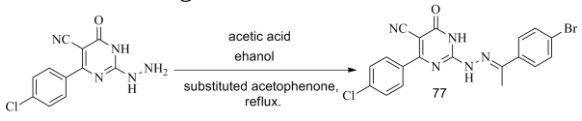
Scheme 75: Synthesis of pyrimidine-5-carbonitrile derivative **75**

Bhavsar *et al*., [(99,100)] were reviewed that 2-hydrazino-1-methyl-5-cyano-6-oxo-4-*N*,*N*-dimethyl-phenyl-1,6-dihydropyrimidine **76** was obtained by refluxing 2-methylthiopyrimidine derivative with hydrazine hydrate (80%) in ethanol For 6 h.



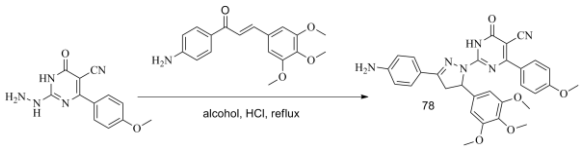
Scheme 76: synthesis of pyrimidine-5-carbonitrile derivative **76**

The synthesis of 6-oxo-4-cl-phenyl-1,6-dihydropyrimidine-5-carbonitrile **77** was conducted by refluxing hydrazine derivative with different substituted acetophenone in a mixture of acetic acid and absolute ethanol. The formation of Schiff bases involved the attack of nitrogen as a nucleophile on the carbonyl group, followed by deprotonation of nitrogen, and finally displacement of a water molecule, leaving a C=N bond. [7]



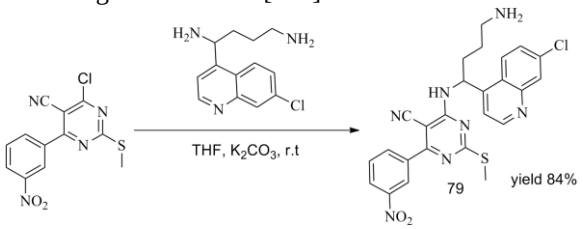
Scheme 77: Synthesis of pyrimdine-5-carbonitrile derivative **77**

Equimolar amount of hydrazinyl-dihydropyrimidine, appropriate chalcone and hydrochloric acid (3–4drops) was refluxed in absolute ethanol for 48–96 h for synthesis of pyrimidine-5-carbonitrile derivative **78**. [(101)]



Scheme 78: Synthesis of pyrimidine-5-carbonitrile derivative **78**

The solution of appropriate 4-aminoquinoline in dry THF was added to the stirred solution of 2-thiomethyl pyrimidine derivative and potassium carbonate. The reaction mixture was stirred at room temperature for 48 h to obtain pyrimidine-5-carbonitrile derivative **79** according to Kaur *et al.* [102]



Scheme 79: Synthesis of pyrimidine-5-carbonitrile derivative **79**

4. Biological activity of pyrimidine-5-carbonitriles

Over the past decade, promising compounds containing pyrimidine-5-carbonitriles have been intensively studied for their biological application such as anticancer, antimicrobial, anti-inflammatory, antifungal, antitubercular, antiviral, antihypertensive, anthelmintic, anticonvulsant, and antimalarial.

4.1. Anticancer activity:

Nasser *et al*. [49] reported that compound 2-(Butylthio)-4-phenyl-6-(pyridine-2-ylamino)pyrimidine-5-carbonitrile **(18)** displayed potent cytotoxicity with IC_{50} = 3.37, 3.04, 4.14, and 2.40 µM more than erlotinib with IC_{50} = 17.32, 13.76, 23.70, and 20.11 µM against HCT-116, HepG-2, MCF-7, and A549 cells, respectively.
Also, Osman and co-workers [50] reported that 2-(Allylthio)-4-(4-methoxyphenyl)-6-(o-tolylamino)pyrimidine-5-carbonitrile **(19)** presented cytotoxicity value IC_{50}= 11.58 µM against normal human lung cells (WI-38) compared to erlotinib IC_{50}= 6.72 µM and arrested the cell growth in Hep-G2 cells at the G2/M phase which induced a significant increase in apoptotic cells.
Compound **20** was the most active compound of pyrazolo[3,4-d]pyrimidine-5-carbonitrile series and reported by Abbas and co-authors [51] which showed 91% inhibition of EGFR tyrosine kinase enzyme. A good correlation between the docking study and

EGFR-TK inhibition presented compound **25** as a promising and attractive antitumor agent.

While, Amin and her scholars [52] afforded *N′*,*N′*-diacetyl-*N*-(5-cyano-1,6-dihydro-6-oxo-4-p-tolylpyrimidin-2-yl)acetohydrazide **(21)** which evaluated as a potent anticancer activity with high thymidylate synthase (TS) inhibitory activity with IC_{50} value 3.89 nM.

Furthermore, from a new series of coumarin-containing compounds, 4-Hydrazinyl-2-{[(6-methyl-2-oxo-2H-chromen-4-yl)methyl]sulfanyl}-6-phenyl pyrimidine-5-carbonitrile **(22)** was synthesized by Morsy and co-workers [53] and was exhibited strong activity against both MCF-7 and HepG-2 cell lines with IC_{50} values of 5.5 and 6.9 µ/ml, compared with 5-FU with IC_{50}= 7.9 and 5.4 µ/ml, respectively. (illustrated in Figure 2).

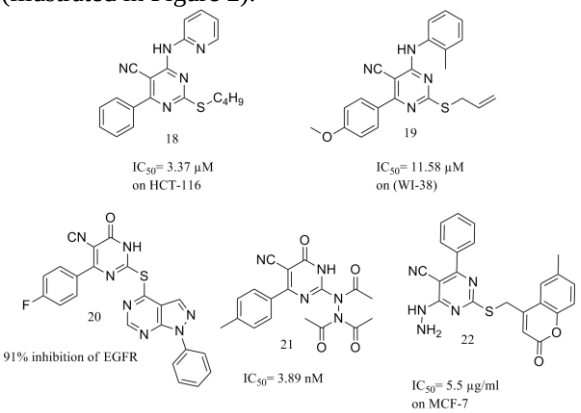


Figure 2: Some compounds showing anticancer activity

Additionally, El-Naggar and her colleagues [19] were found that compound **23** was a potent anticancer product with IC_{50} values between 3.89 ± 0.42 and 7.9 ± 0.14 µM against HepG-2, MCF-7, HCT-116, and PC-3 cell lines as well as their thymidylate synthase inhibitory activities.

Mohamed *et al*.,[29] prepared Compound (*E*)-6-(1H-indol-3-yl)-2-thioxo-4-(2-(3,4,5 trimethoxybenzylidene) hydrazinyl)-1,2,3,4-tetra hydropyrimidine-5-carbonitrile **(24)** and screened as the highly active compound against colon carcinoma (CaCo-2) cell line with IC_{50} = 8.84 ± 0.11 µg/mL compared to the reference drug doxorubicin by using Sulforhodamine-B (SRB) assay and showed that anticancer activity is due to presence of phenyl hydrazone moieties.

El-Atawy and co-workers [26] prepared compound **25** which exhibited two-fold more potent than the reference vinblastine sulfate with an IC_{50} value of 21 µM against the PC3 cell line.

Also, AboulWafa and her researchers [54] investigated that the most active compound **26** was endowed with remarkable antiproliferative activity with IC_{50} of 3.27 and 3.86 µM in comparison to 5-FU with IC_{50} = 10.80 and 11.41 µM against MCF-7 and MDA-MB-231 cell lines, respectively.

One more, Roopan and his partners [17,55] reviewed that compound **27** one of 1,2,3-triazole–pyrimidine–urea hybrids series, was manifested as anticancer activity against four cancer cell lines: MGC-803, EC-109, MCF-7, and B16-F10 with IC_{50}= 21.34±1.15, 20.97±1.14, 7.03±0.84, 0.032±0.003 µM, respectively, with compared with 5-FU. (illustrated in Figure 3)

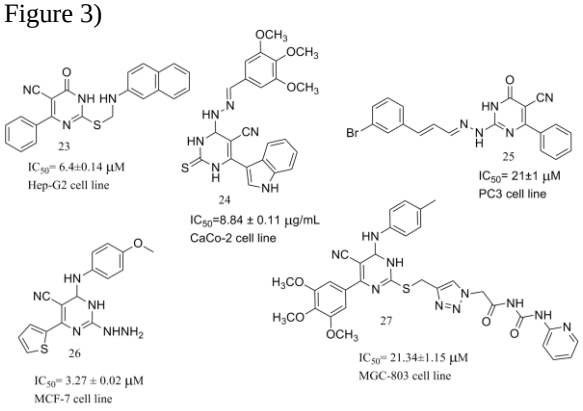


Figure 3: Some compounds showing anticancer activity

Al-Ghulikah *et al*.,[14] reported a series of pyrimidine-5-carbonitriles **28**, **29** which displayed the most potent agents. Further assessed for their anticancer activity showed potent cytotoxic activity against four cell lines MCF-7, A549, A498, and Hep-G2 with IC_{50} values ranging from 1± 0.03 nM to 22 ± 0.62 nM for both compounds and the activity was higher than doxorubicin with low cytotoxicity on the normal WI-38 cell line.

Furthermore, compound 2(2-((1H-pyrrol-2-yl)methylene) hydrazinyl)-4(4-fluorophenyl)-6-oxo-1,6-dihydropyr imidine-5-carbonitrile **(30)** prepared and evaluated by Helwa and her researchers [56] as the most potent on the MCF-7, A549 and Caco-2 cell lines with IC_{50}= 1.42, 1.98 and 9.50 µM, respectively, as compared with 5-FU IC_{50}= 1.71, 10.32 and 20.22 µM, respectively.

While, Ahmed and co-workers [57] have afforded novel series of pyrimidine pyrazoline-anthracene derivatives, one of them was compound **31** which investigated as anti -liver cancer activity against two hepatocellular carcinoma cell lines Hep-G2 and Huh-7 with IC_{50}= 5.34 ± 0.21, 6.13 ± 1.01 µg/mL, respectively due to electronegative effect of the fluorine atom among all promising anticancer agents of pyrimidine pyrazoline-anthracene derivatives.

Compound **32** exhibited excellent antitumor activity against the leukemia SR cell line, which is the most sensitive cell line, with IC_{50} 0.10 ± 0.01 µM. According to Rady *et al*.(58)

Also, Said and co-authors [59] reported that compound **33** displayed potency on the MCF-7 cell line with IC_{50}= 18.3 nM/mL, with high cytotoxicity

on the normal cell line MRC-5 (human lung fibroblast cell line with IC_{50} of 64.38 nM/mL. (illustrated in Figure 4)

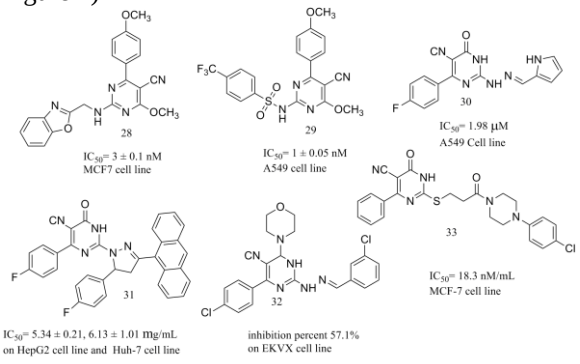


Figure 4: Some compounds showing anticancer activity

Abbass *et al*.,[60] were synthesized (*Z*)-2-(3-(4-aminophenyl)but-2-en-1-yl)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **(34)** and exhibited a potent anticancer activity against two types of human cancer cells Hep-G2 and HCT-116 with IC_{50}= 8.76 ± 0.9 and 10.46 ± 1.6 µM, respectively, compared to doxorubicinas as positive control.

Boualia and co-workers [61] reported that compound **35** displayed the best AChE inhibitory activity with IC_{50} = 5.72 ± 1.53 µM

Compound **36** was reported by Shao and co-authors [62] which showed potency and selectivity effects on CDK9 with IC_{50} = 7 nM.

With different substituents of 5 cyanopyrimidine, compound **37** was showed good anti-proliferation activity against showed the most potent anti-proliferative activity against MGC-803, PC-3, A549, and H1975 cell lines with IC50 values of 2.98±0.47, 1.86±0.27, 8.33±0.92, and 2.25±0.35µM, respectively, which more potent than 5-Fluorouracil, also induced PC-3 cell cycle arrest in G0/G1 phase. [63]. (illustrated in Figure 5)

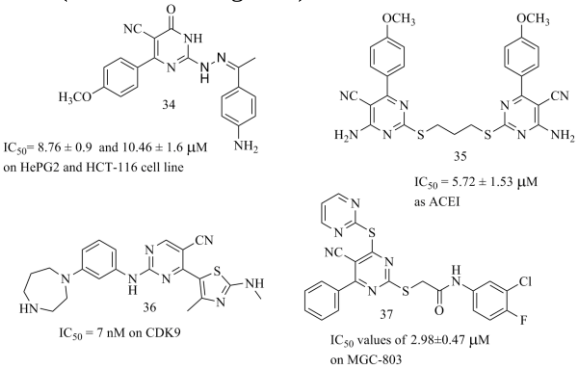


Figure 5: Some compounds showing anticancer activity

Saleh *et al*.,[18] synthesized compound (*E*)-*N*'-(1-(4-((5-cyano-2-(methylthio)-6-phenylpyrimidin-4-yl)amino)phenyl)ethylidene)-2,4-dinitrobenzohydrazide **(38)** and evaluated as anticancer agent with IC_{50}= 1.14, 1.54 µM on HCT-116 and MCF-7, respectively. Also, induced a significant increase in the apoptotic cells which arrested the HCT-116 cell growth at S and sub-G1phases.

Furthermore, Jubeen and co-workers [64] reviewed that fused 1,2,3-triazole-pyrimdine **(39)** was determined with its activity against MCF-7, EC-109, MGC-803 cancer cell lines, especially EC-109 cancer cells which inhibit the proliferation by inducing apoptosis and arresting the cell cycle at G2/M phase.

Compound **(40)** was presented by Masaret [65] and showed strong antitumor activity against HepG2, HCT-116, MCF-7 with IC50= 15.4 ± 2.5 12.2 ± 1.5 16.4 ± 2.5 µM respectively, compared to 5-flouro uracil. This activity is due to the intra-molecular hydrogen bonding of NH and NH_2 groups with one of the nucleobases of DNA and causes its damage.

Derivative of trimethoxy phenyl bearing naphthyl substitution of 5 cyano pyrimidine as compound **41** [66] was displayed the most promising broad-spectrum anticancer activity with high inhibition of growth of various 60 cancerous cell lines panel at the National Cancer Institute like SR leukemia and HCT-116 colon cancer cell lines with IC_{50}= 84.01 and 76.94 µM, respectively. (illustrated in Figure 6)

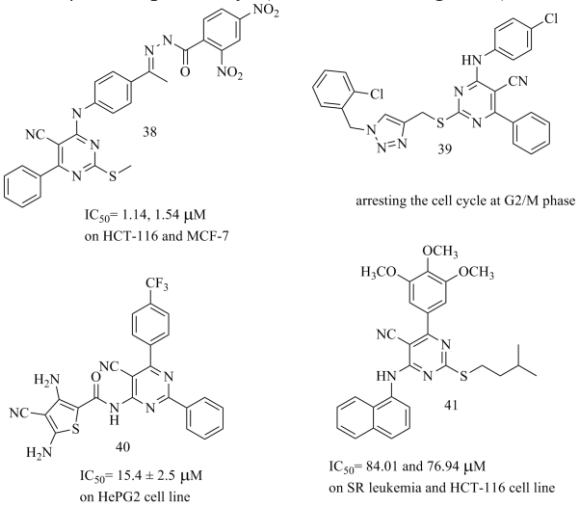


Figure 6: Some compounds showing anticancer activity

Ma *et al*.,[67] furnished compound **42** which contained a 1,2,3-triazole moiety and was evaluated as LSD1 inhibitors with IC_{50}= 183 nmol/L.

N'-(5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-2-yl)aceto hydrazide **(43)** was furnished by Mohamed and his researchers [68] and presented its potency toward Hep-G2 and MCF-7 with IC_{50}= 25.7 and 25.7 µM, respectively. Compared with 5-FU as a standard drug.

Ghule and his co-workers [69], reported that *N*-(6-chlorobenzo[d]thiazol-2-yl)-2-(4-(5-cyano-6-imino-

2-oxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl) acetamide **(44)** displayed antiproliferative activity toward non-small cell lung cancer, renal cancer and leukemia cancer cell lines with GI% 141.68, 54.68, 52.87 % respectively.

Shao and his partner [70] reviewed that compound **45** was a new derivative of 2,4,5-trisubstituted pyrimidine and screened as CDK inhibitors and capabled of activating caspase 3, reducing the level of Mcl-1 anti-apoptotic protein, inducing cancer cell apoptosis and exhibited IC_{50}= 0.79 ± 0.08 and 0.64 ± 0.08 µM, respectively against Colon carcinoma HCT-116 and Breast carcinoma MCF-7.

The derivative of 4-(4-methoxyphenyl)pyrimidine **46** reported by El-Dydamony *et al*.,[71] showed a strong effect in inhibiting PI3K and AKT enzymes and caused cell cycle arrest at the S phase leading to induction of apoptosis in leukemia k562 cells through caspase 3 activation with IC_{50}= 2.62 ± 0.12 µM. (illustrated in Figure 7)

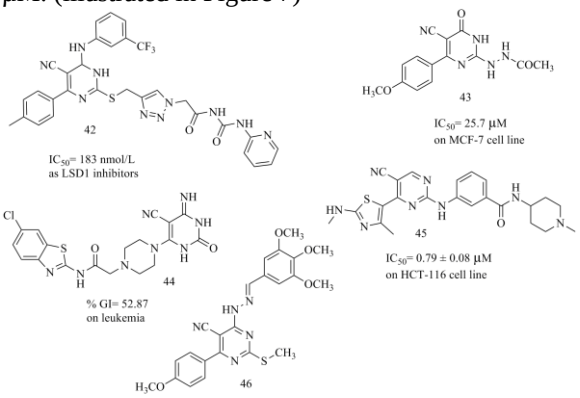


Figure 7: Some compounds showing anticaner activity

4.2. Antimicrobial activity:

2,4-Diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine (Trimethoprim) **(47)** was early discovered as a potent bacteriostatic drug mainly in the prophylaxis and treatment of urinary tract infections. [72]

Also, Al-Deeb *et al*.,[73] showed that pyrimidine-5-carbonitrile derivative **48** synthesized and tested for antimicrobial activity, result exhibited a potent antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive Bacteria), *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative bacteria) and *Candida albicans* strains with inhibition zones= 33, 28, 21, 19 and < 10 mm, with comparison with Gentamicin as standard drug.

Moreover, antimicrobial activity against Gram-positive *Bacillus cereus, Staphylococcus aureus,* and Gram-negative bacterial strains *Escherichia coli and Pseudomonas aeruginosa* were evaluated by Alkabli and his prosaists [74] with compound **49** and showed zones of inhibition= 27, 21, 29 and 26 mm, respectively with Ampicillin as standard by using a modified Kirby–Bauer disc diffusion method.

Salem and co-workers [75] observed that 5-cyano pyrimidine substituent **50** manifested good activity against Gram-positive and Gram-negative bacteria and the fungi *Candida albicans* and *Aspergillus niger* with a zone of inhibition= 19, 20 mm. Activity was increased due to the presence of the 3,4-dimethoxyphenyl group in compound **50**.

It has been observed that compound **51** was reported by Mohamed and co-authors [68] which incorporated in antimicrobial activity against *Staphylococcus aureus*, *Bacillus Subtilis*, *Escherichia coli*, *Candida albicans,* and *Aspergillus flavus* compared to the reference drugs Ampicillin and Colitrimazole,

Mallikarjunaswamy and co-workers [76] investigated that *E*-*N*-(6-(4-bromo-2-chlorophenyl)-5-cyano-2-hydroxyl pyrimidin-4-yl)-*N*'-(2 chloropyrimidin-4-yl)formamidine **(52)** showed promising antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus* with a zone of inhibition= 33, 26 mm, compared with Gentamycin with a zone of inhibition= 35, 30 mm, respectively.

Finally, 4-(4-Chloro-3-nitrophenyl)-2-(2-cyclohexylidenehydrazinyl)-6-oxo-1,6-di hydropyrimidine-5-carbonitrile **(53)** was evaluated by Nassar and co-authors [77] and displayed strong antimicrobial activity against Gram-positive *L. monocytogenes* and Gram-negative bacteria *E. coli* with Zone of inhibition= 14 and 13 mm, respectively, in comparison with Cefoperazone as standard. (illustrated in Figure 8)

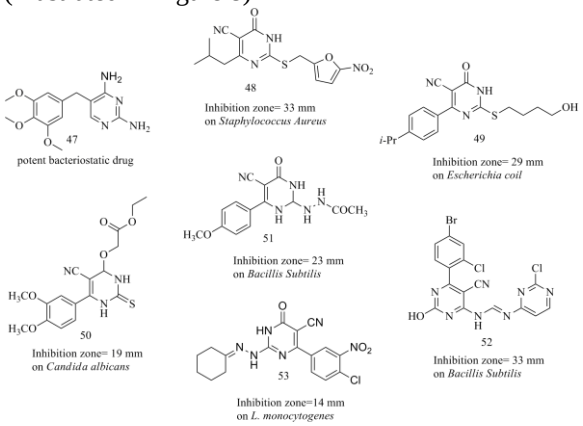


Figure 8: Some compounds showing antimicrobial activity

4.3. Anti-inflammatory:

The corresponding compound **54** was synthesized by Abdel-Aziz and co-workers [8] and showed the most potent COX-2 inhibitor with IC_{50}= 1.03 µM in comparison with celecoxib as standard.

Bhalgat *et al.*,[78] synthesized 2-Hydrazinyl-4-(3-methoxyphenyl)-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **(55)** which

displayed the most potent anti-inflammatory compound with inhibition percent 76 % due to presence of 3-OCH_3 group present in structure with comparison to the standard diclofenac sodium.

Also, Undare and his colleagues [79] reported that 5-cyano pyrimidine derivative **56** has promising anti-inflammatory activity due to the presence of a nitro group which increases the activity with inhibition percent 82 % in comparison with diclofenac sodium with inhibition percent 85 % by using the carrageenan-induced rat paw edema assay.

4-amino-6-(4-chlorophenyl)-2-hydroxypyrimidine-5-carbonitrile **(57)** afforded by Sureja and his researchers [80] which exhibited potent anti-inflammatory activity with inhibition percent 81% compared to the standard, diclofenac sodium.

Moreover, Al-fayomy and co-authors (81) reported that compound **58** screened as a potent anti-inflammatory activity with IC_{50}= 13.80 µM on COX-1 compared with celecoxib with IC_{50}= 14.7 µM and presented a lower ulcerogenic effect on gastric mucosa than the standard drug.

A new class of substituted 1, 2, 3, 4-tetrahydropyrimidine derivatives have the potential to design lead for anti-inflammatory activity, one of them was 4-Imino-2-oxo-6-piperazin-1-yl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile **(59)** that reported by Gondkar *et al*.,[82] and showed highly anti-inflammatory activity with inhibition of albumin denaturation= 98 % compared with Diclofenac as standard.

Among synthesized Schiff bases, Abdel-Mohsen *et al*.,[83] designed and evaluated 4-amino-2-thioxo-1,3-diazaspiro[5.5]undec-4-ene-5-carbonitrile derivatives and showed that compound **60** displayed anti-inflammatory activity with % inhibition of oedema= 0.416 ± 0.028 % compared to indomethacin as standard by using carrageenan_induced paw edema in rats. (illustrated in Figure 9)

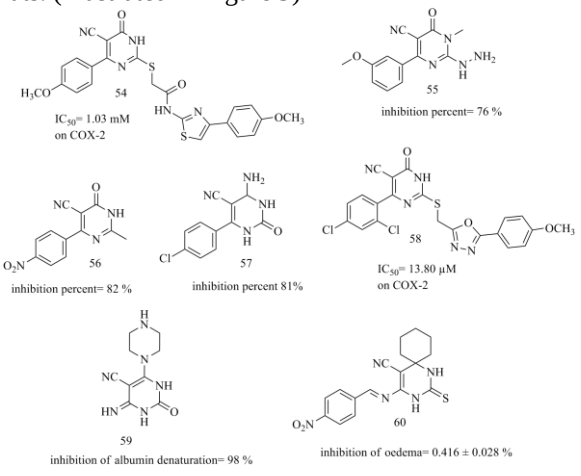


Figure 9: Some compounds showing anti-inflamatory activity

4.4. Antifungal activity:

By evaluating the efficacy of antifungal compounds, Hamouda *et al*.,[84] obtained 4-(benzo[b]thiophen-2-yl)-2-(3-(4-bromophenyl)-5-(2-bromophenyl)-1H-pyrazol-1-yl)-1-methyl-6-oxo-1,6-dihydro pyrimidine-5-carbonitrile **(61)** which displayed antifungal activity toward *C.albicans* and *A. niger* with MIC= 18.75, 18.75 µg / mL. respectively, with Amphotericin B as the standard.

Jadhav and co-workers [85] presented antifungal activity by using the micro dilution method against two fungal strains *Aspergellis. niger* and *Candida albicans* for promising compound **62** with MIC 12.5, 50 µg/mL, respectively, comparable with griseofulvin with MIC 500 µg/mL.

Also, S-glycosides analogs containing thiouracil unit as compound **63** prepared by Hussein *et al*.,[86] exhibited antifungal activity with an inhibition zone diameter of 14 mm on *macrosporium* compared to Luporal capsule with an inhibition zone diameter of 9 mm.

Additionally, compound 1-methyl-2-(methylsulphanyl)-4-(3-nitrophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **(64)** was furnished by Rani and his partners [(88)] and displayed potent activity against fungal strain *C. albicans* with inhibition zone diameter 12 mm when compared with amphotericin B. The antifungal potential of this compound was more due to the presence of a 3-nitrophenyl group on a benzene ring. (illustrated in Figure 10).

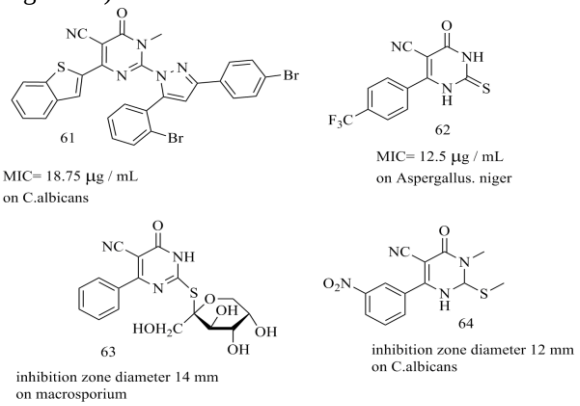


Figure 10: Some compounds showing antifungal activity

4.5. Antitubercular agents:

The antimycobacterial screening against M. tuberculosis H37Rv of **65** which was prepared by Kapadiya and co-authors [4] A pyrimidine-5-carbonitrile derivative that has nitrile functionality showed more potency than the other series of substituents with excellent MIC= 85 µM, IC_{50}= 53 µM and IC_{90}= 62 µM.

Boukthir *et al.*,[89] reported that pyrimidine-5-carbonitrile compound **66** presented as a potent antitubercular activity with MIC values ranging from 10-35 µg/ml.

Also, Mohan and co-workers [90] reviewed 6-amino-5-cyano-2-hydroxy-4-substituted pyrimidine **67** which displayed potent in vitro antitubercular activity with MIC > 100 µg/ml.

Compound **68** was prepared by Pisal *et al.*,[91] and manifested a very good antitubercular activity against dormant as well as active stages of M. tuberculosis H37Ra with MIC= 11 µg/ml, 17 µg/ml, respectively, compared with Rifampicin as reference drug. (illustrated in Figure 11)

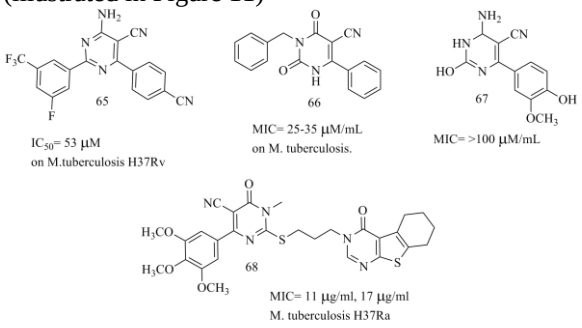


Figure 11: Some compounds showing Antitubercular activity

4.6. Antiviral activity:

Also, Fatahala and co-workers [92,93] reviewed the synthesis and anti-influenza A virus (H1N1) activity of 6-aryl-5-cyano-2-thiouracil **69**. By phosphonylation with diethyl chloroethynylphosphonate, compound **70** was obtained. These compounds showed promising antiviral activity with IC_{50} >300 µM.

Mohamed *et al.*,[(94)] reported that compound 6-(2,4-dichlorophenyl)-4-((3-(5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)amino)-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile **(71)** presented potent antiviral activity against bovine viral diarrhea virus (BVDV) compared with negative control with $4*10^{-4.6}$ PFU (plaque forming unit). Through BVDV plaque reduction assay.

In the case of (HBV), Hatawa and co-workers [95] synthesized promising substituted pyrimidine glycoside compound **72** which was found as a Hepatitis B virus inhibitor with IC_{50}= 0.66 µM, Lamivudine was used as a standard inhibitor of HBV. (illustrated in Figure 12).

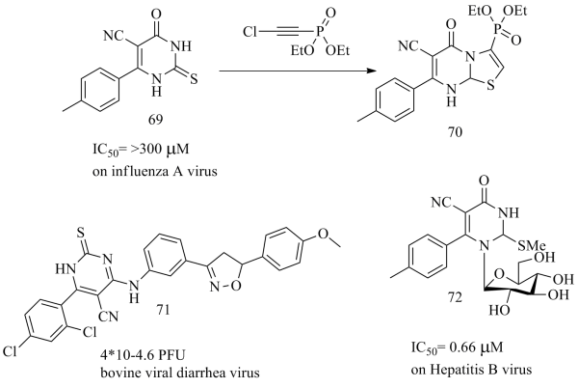


Figure 12: Some copounds showing antiviral activity

4.7. Antihypertensive:

Farghaly and co-workers [96] synthesized pyrimidine-5-carbonitrile analogue **73** which has a structural likeness to nifedipine. Compound **73** found as remarkable activity by decreasing mean arterial blood pressure (MABP) to 51.4 mmHg in rabbits compared with nifedipine 84.2 mmHg

To obtain water-soluble pyrimidinone derivatives as a sodium salt, Andrade *et al.*,[97] synthesized compound **74** and inhibited phenylephrine-induced contraction in isolated rat aorta and acted as the alpha-1 antagonist which candidated for anti-hypertensive drugs with contraction of phenylephrine= 0 g in comparison with prazocin as standard. (illustrated in Figure 13)

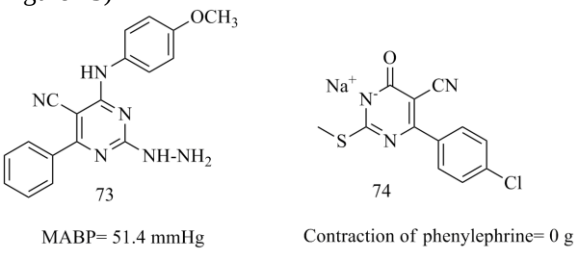


Figure 13: Some compounds showing Antihypertensive activity.

4.8. Anthelmintic activity:

Sapkal *et al.*,[98] were designed and synthesized 4-(4-chlorophenyl)-6-(4-(dimethylamino) phenyl)-2-oxo-1-phenyl-1,2-dihydropyrimidine-5-carbonitrile **(75)** and showed more potent paralyzing effect in 42 min in comparison with the standard albendazole in 50 min with concentration of 0.1 (m/v) using earthworms, *Pheretima posthuma.*

Bhavsar and co-authors [99] were reviewed that compound **76** was exhibited as potential anthelmintic activity 28.25 ± 0.14 and 54.22 ± 1.22 min at concentration 0.1% (w/v) for paralysis and death in

Pheretima posthuma, respectively, when compared with the standard drug Albendazole. (illustrated in Figure 14)

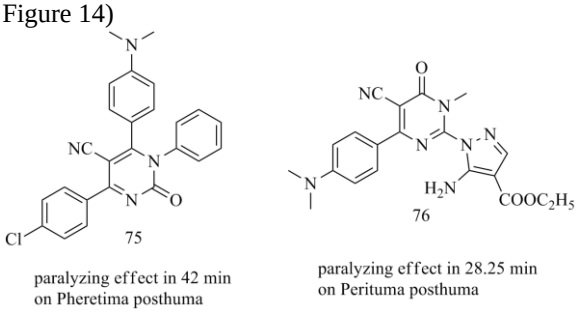


Figure 14: Some compounds showing Anthelmintic activity

4.9. Anticonvulsant:

Ali and his researchers [7] investigated that compound **77** showed anticonvulsant activity at a lower dose of 30 mg kg^{-1} at 0.5 to 4 h for maximal electroshock seizure. This activity of compound 82 was comparable to that of phenytoin and higher than that of carbamazepine which did not show any motor impairment. (illustrated in Figure 15)

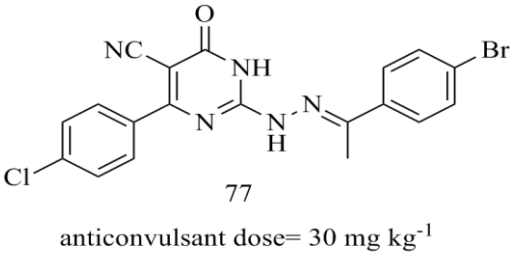


Figure15 Compound showing Anticonvulsant activity.

4.10. Antimalarial activity:

Compound **78** was afforded by Marella *et al*.,[101] and evaluated against the 3D7 strain of *Plasmodium falciparum* which was found to be the most potent with an IC_{50} value of 1.63 µM with lesser cytotoxicity. Chloroquine was used as the standard.
Kaur and co-workers [102] were reported that compound 2-Methylthio-4-(m-nitrophenyl)-6-[(7-chloroquinolin-4-yl)aminobutyl]aminopyrimidine-5-carbonitrile **(79)** displayed highest anti plasmodial activity IC_{50}= 55.8 nM (Dd2) against the CQR (chloroquine-resistant) strain. (illustrated in Figure 16).

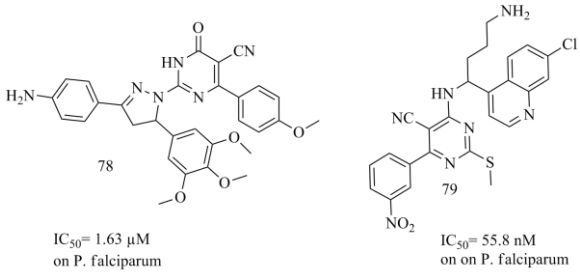


Figure 16: Some compound showing antimalarial activity

5. Conclusion

This study is a review article summarizing most of the published work about the available and obtainable approaches for design and synthesis of medicinally important pyrimidine-5-carbonitrile derivatives, one of the blossoming research fields, using various starting compounds with appropriate catalysts and different conditions over the past ten years. Also, the review presents various biological activities of compounds containing pyrimidine-5-carbonitrile derivatives that have pharmacological importance in medicinal chemistry fields.

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