Ultrasound-promoted One-Pot, Three Component Synthesis Of Novel 5-Amino-2-(4-Chlorophenyl)-7- Substituted Phenyl-8,8a-Dihydro-7H-[1,3,4]Thiadiazolo[3,2-a]Pyrimidine-6-Carbonitrile Derivatives

Presented By

Dr. Anna Pratima G. Nikalje[1]*, Shailee Tiwari[1], Zahid Zaheer[1] Julio Seijas Vázquez [2].

*annapratimanikalje@gmail.com

[1] Department of Pharmaceutical Chemistry,
Dr. Rafiq Zakaria Campus,
Y. B. Chavan College of Pharmacy,
Aurangabad. MS. India

[2] **Universidad De Santiago De Compostela-Lugo (Spain)**

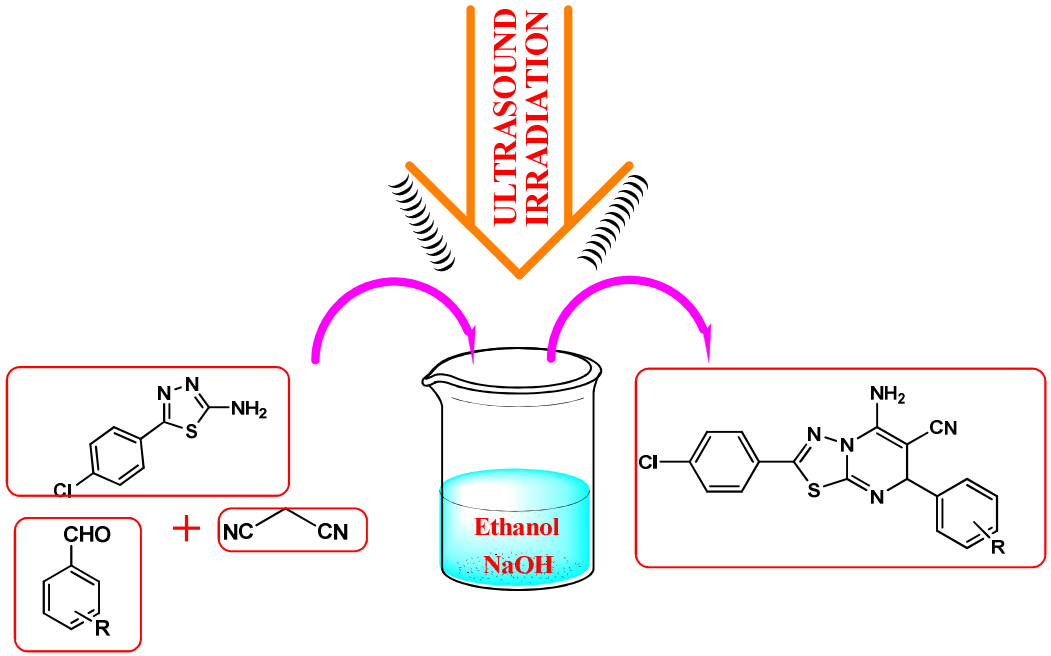
Abstract:

Here is the report of an environment friendly, rapid, and convenient one-pot ultrasound-promoted synthesis of 5-amino-2-(4-chlorophenyl)-7- substituted phenyl-8,8a-dihydro-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile derivatives. Multi-component reactions are useful for the creation of chemical libraries of drug-like compounds with levels of molecular complexity and diversity. 1,3,4-Thiadiazolo[3,2-a]pyrimidine skeleton belongs to a well-known and important class of fused heterocycles prevalent in a number of natural products of biological activities including antitumor, fungicidal, antibacterial, and herbicidal, hence, prompted us to synthesis 1,3,4-Thiadiazolo[3,2-a]pyrimidines. The final ten derivatives were obtained in excellent yield through a one-pot, three component condensation reaction of aldehyde, 4-chlorophenyl-2-aminothiadiazole, and malononitrile in 10-12 ml of ethanol as solvent and sodium hydroxide as a catalyst. (VCX 500-220, Ultrasound Solid probe, irradiation at 80^0C and 20% amplitude).

We have carried out the same reaction by conventional method, which requires 9-10 hrs of refluxing and yield is lesser. Because of the advantage of faster reaction rates and better yields, use of Ultrasound solid probe, was found to be more suitable for this reaction. Structure of the synthesized derivatives was confirmed by IR, NMR and Mass spectral study.

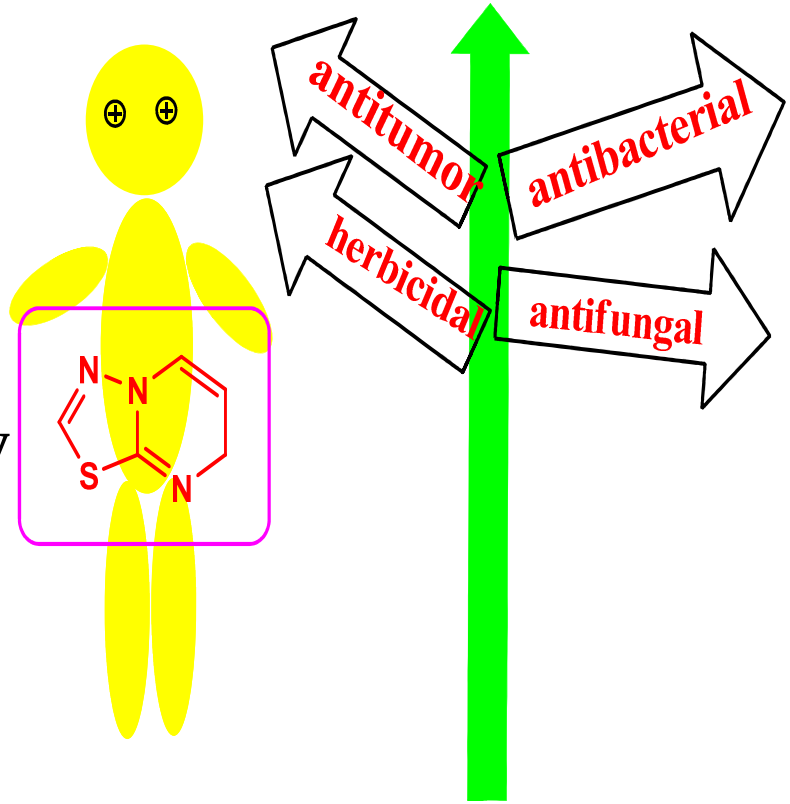
Keywords: 1,3,4-Thiadiazolo[3,2-a]pyrimidine, multi-component reaction, ultrasound-promoted synthesis.

Graphical abstract



Contents

- Introduction
- Objective & Need of Study
- Materials and methods
- Scheme for synthesis
- Experimental
- Result & Discussion
- Spectral characterization
- Conclusion



Introduction

Heterocyclic compounds have drawn special attention in organic chemistry because of their abundance in
natural products and their diverse biological properties [1]. During recent years there have been intense investigations on fused thiadiazole and pyrimidine systems. Literature survey revealed that [1,3,4] thiadiazolo[3,2-a]pyrimidine nucleus is associated with diverse pharmacodynamic and chemotherapeutic activities [2,3], including antimicrobial [4,5,6] and antitumor activities [4, 6], herbicidal, antifungal, neuramidase inhibitors. 1,3,4-thiadiazolo[3,2-a]pyrimidines have been used as key building blocks for the preparation of a variety of novel bioactive agents.[7]

The conventional multistep methods for the preparation of complex molecules involve large synthetic operations, including extraction and purification processes for each individual step, that lead to synthetic inefficiency and the generation of large amounts of waste. So designing multicomponent reactions (MCRs) in one pot and creation of several bonds in a single operation are the major challenge for modern organic chemistry. Multicomponent reactions (MCRs) are chemical transformations in which three or more different starting materials combine together via a one-pot procedure to give a final complex product.

MCRs advantages [8-9].

- high atom economy,
- low cost,
- reduction in overall reaction time
- operational simplicity
- Less or no generation of waste
- No individual step extraction and purification processes
- less amount of solvents required

Green chemistry has become a major inspiration for organic chemists to develop environmentally benign routes for synthesis of organic compounds of biological values. For instance, performing reactions under ultrasonic irradiation due to the formation of high energy intermediates to enhance the reaction efficiency from both economical and ecological points has significant synthetic value and received great attention.

In recent years, ultrasound has been extensively applied as a fantastic tool for different types of chemical reactions [8]

Ultrasound-promoted synthesis has various advantages over conventional synthesis techniques

- highly accelerated reaction rate,
- reasonable good yields,
- simple open systems,
- very less amount of solvents required ,
- eco friendly method ,
- clean heating system, neat and clean synthetic protocol,
- cheaper reagents and
- less extreme physical conditions ,
- control on reaction parameters,
- milder reaction conditions.

Mechanism of ulrasound irradiation in synthesis:

The waves of ultrasound can be transmitted through any substance containing elastic property. The motion of these sounds is transferred to the particles of the environment, which vibrate in the route of the ultrasound wave. As the molecules oscillate, the molecular distance decreases in the compaction cycle and increases during rarefaction. When the molecular distance exceeds the critical amount necessary to hold the liquid perfect, the liquid collapse; bubbles and cavities are generated. This procedure (cavitation), refers to the generation and the energetic life of bubbles in liquids. The bubbles absorb energy from the waves of ultrasound and grow. Then bubble collapse consequences in pressure changes and high temperature. The solvent vapor suffers fragmentation to produce reactive particles, such as carbenes or free radicals. These high-energy particles are concentrated and lead to intermolecular reactions. In general, the yield of product increases, reactions occur faster, with lower temperatures and minor percentage of by-products achieved [10].

NEED of study

The existing synthetic methodologies for [1,3,4] thiadiazolo[3,2-a]pyrimidine nucleus in a modular fashion are not straightforward and the synthetic routes involve multiple steps.

For example, 1,3,4-thiadiazolo[3,2-a]pyrimidine-7-sulfonamide derivatives were synthesized from 5-aminol,3,4-thiadiazole-2-sulfonamide via a two step approach.[11] Salimov et al. prepared 2-bromo-7-methyl-5-oxo-5H-1,3,4-thiadiazolo[3,2-a]pyrimidine by two steps involving the addition of 2-aminothiadiazole derivatives to ethyl acetoacetate, tandem hydrolysis of the ester to the acid, and cyclization to give the ring-fused thiadiazolo[3,2-a]pyrimidines in PPA.

Most of these are multistep protocols, which suffer from generation of by-products, low yields, and use of metal-containing reagents.

Therefore, it is quite significant to develop the direct, efficient, and green alternative approaches to get the functionalized thiadiazolo[3,2-a]pyrimidine derivatives from the viewpoint of green chemistry.

OBJECTIVE OF STUDY

1. To design and synthesize the novel, coupled 4-Methyl-7-(3-(4-methylpiperazin-1-yl)-3-oxo-1-substituted phenyl prop-1-en-2-yloxy)-2H-chromen-2-one derivatives, by fragment joining using ultrasonic processor.

2. To conduct physicochemical characterization of intermediates and synthesized compounds**.**

3. To confirm the structures of synthesized compounds by analytical and spectral techniques such as TLC, FT-IR, MS, ^{1}H NMR and ^{13}C NMR .

MATERIALS AND METHODS

General

All the reactions were performed in oven-dried glassware's. All reagents and solvents were used as obtained from the supplier or recrystallized /redistilled unless otherwise noted. The ultrasound sonicator (Sonics Vibra-cell, Modelno. VCX 500) equipped with solid synthetic probe, 13 mm in tip diameter, operating at 20 kHz with a maximum power output of 500 W, was used for synthesis of final title compounds. The purity of the synthesized compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G (Merck) coated aluminium plates, visualized by iodine vapour and melting points were determined in open capillary tubes. The homogeneity of the compounds was monitored by ascending thin layer chromatography(TLC) on silica gel-G (Merck) coated aluminium plates, visualized by iodine vapour**.**

The ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds were recorded on Bruker Avance II 400 NMR Spectrometer at 400 MHz Frequency in deuterated DMSO and $CDCl_3$ and using TMS as internal standard (chemical shift δ in ppm). Mass spectra of some compounds were scanned on FTMS+p ESI full mass (100.00-1500.00).

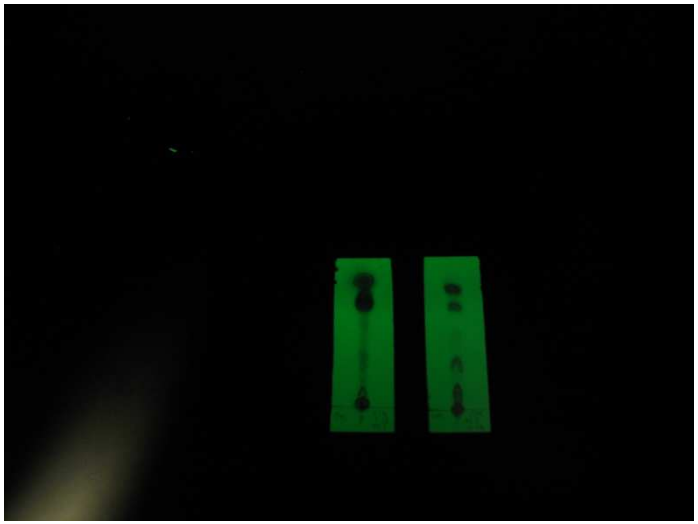
General Procedure for the Synthesis of 5-Amino-2-(4-Chlorophenyl)-7- Substituted Phenyl-8,8a-Dihydro-7H-[1,3,4]Thiadiazolo[3,2-A]Pyrimidine-6-Carbonitrile Derivatives

***Method A*:** A 25 mL round bottom flask was charged with a mixture of an 5-(4-chlorophenyl)-1,3,4-thiadiazol-2 amine (0.01mol) , aromatic aldehyde (0.01mol) in ethanol (10-12 ml) and the catalyst NaOH (20% mmol) and the reaction mixture was refluxed for 1.30-2 h. After completion of the reaction (i.e formation of Schiff base) as indicated by TLC, malononitrile (0.01mol) was added to the reaction mixture and again it was refluxed. . After completion of the reaction (monitored by TLC), the mixture was poured into ice cold water. The product obtained, was filtered and dried. The corresponding product was obtained in high purity after recrystallization of the crude product from ethanol. The authenticity of compounds was established by 1H NMR, 13C NMR, IR and HRMS.

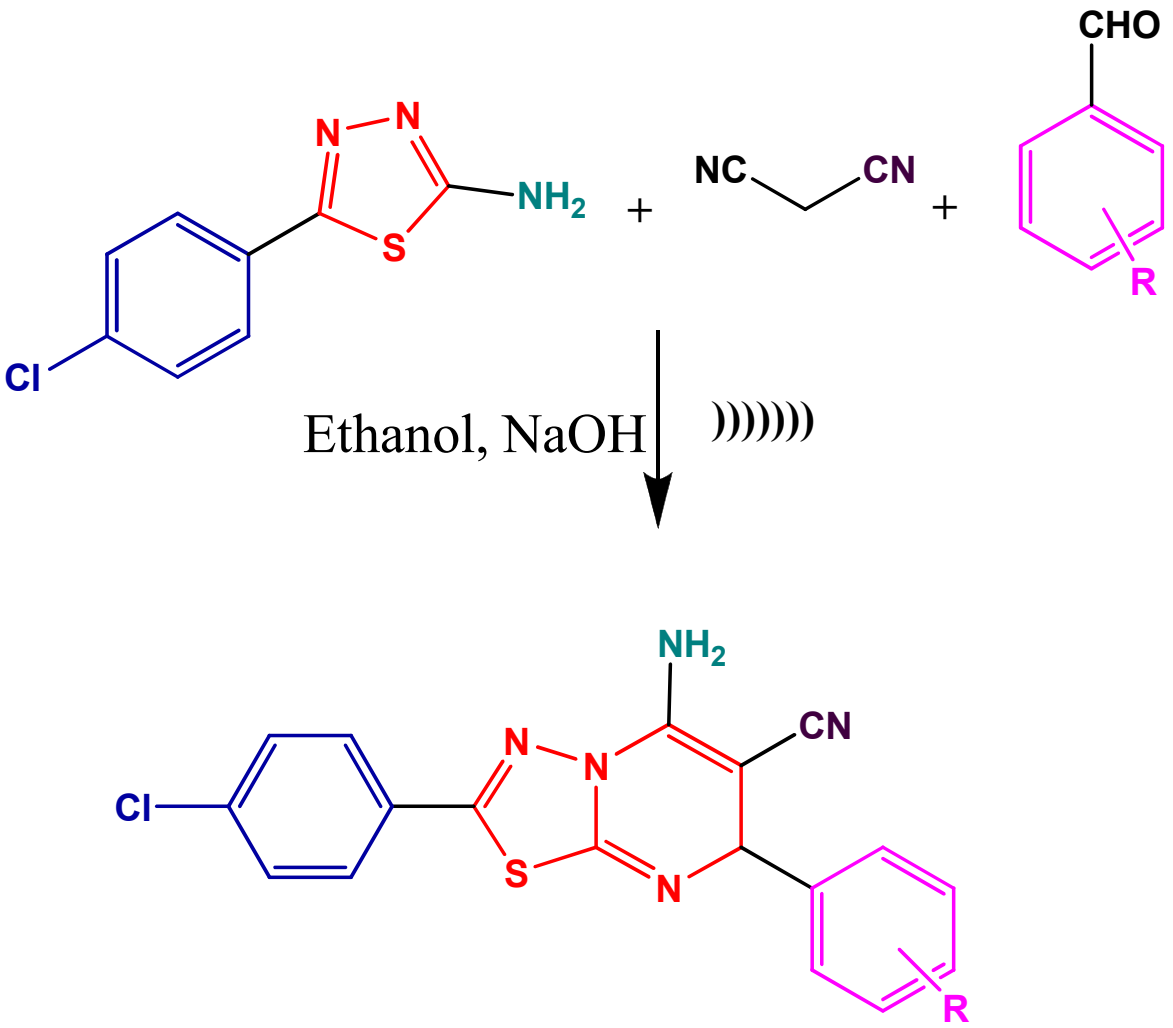
***Method B*:** A 25 mL a beaker was charged with a mixture of an 5-(4-chlorophenyl)-1,3,4-thiadiazol-2 amine (0.01mol) , aromatic aldehyde (0.01mol) in ethanol (10-12 ml) and the catalyst NaOH (20% mmol)) and the reaction mixture was kept inside an Ultrasonicator acoustic chamber at 80^0C at 20% amplitude for 10-15min. After completion of the reaction (i.e formation of Schiff base) as indicated by TLC, malononitrile (0.01mol) was added to the reaction mixture and again was kept inside an Ultrasonicator acoustic chamber at 80^0C at 20% amplitude for 1-1.30 hrs. After completion of the reaction (monitored by TLC), the mixture was poured into ice cold water. The product obtained, was filtered and dried. The corresponding product was obtained in high purity after recrystallization of the crude product from ethanol.

Identification

- Silica gel thin-layer chromatography (TLC)
- ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy
- Infrared (IR) spectroscopy

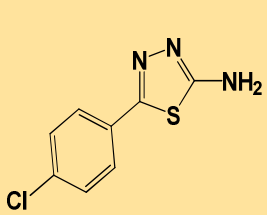
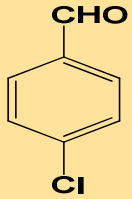
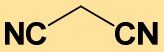
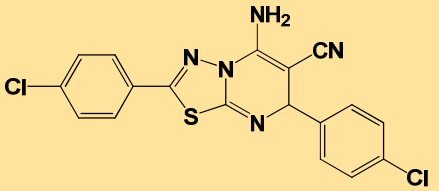
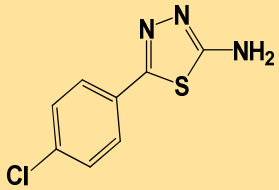
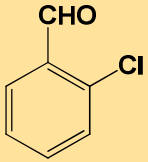
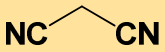
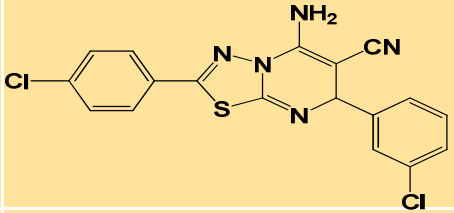
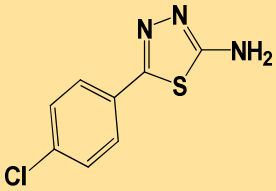
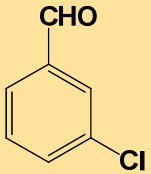
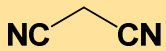
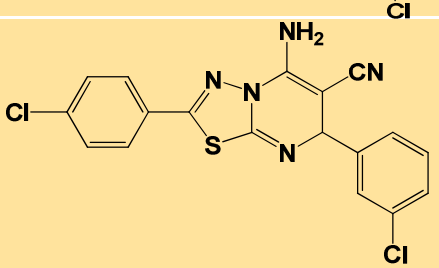
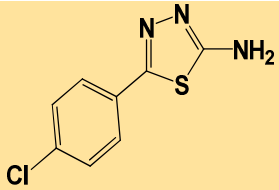
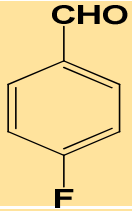
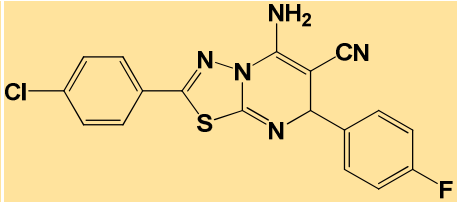
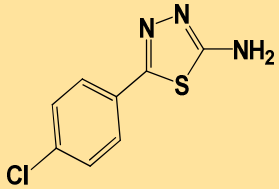
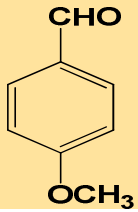
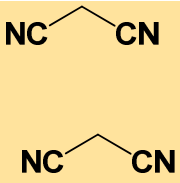
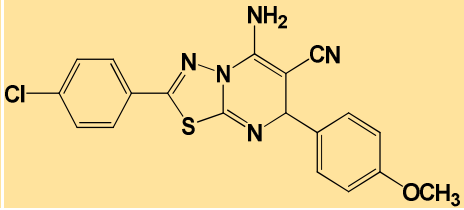


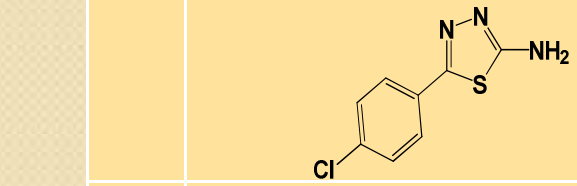
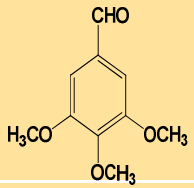
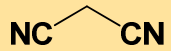
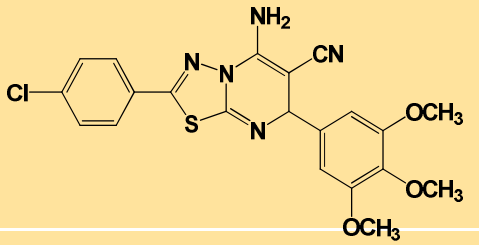
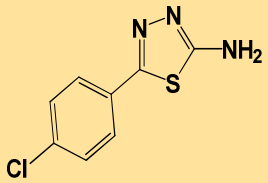
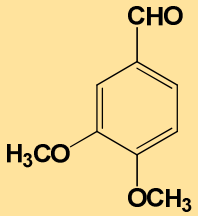
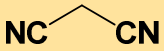
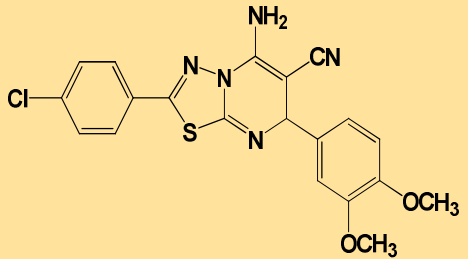
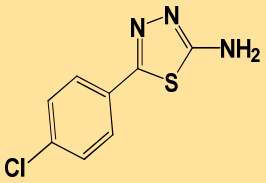
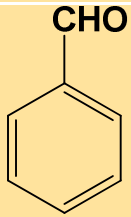
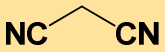
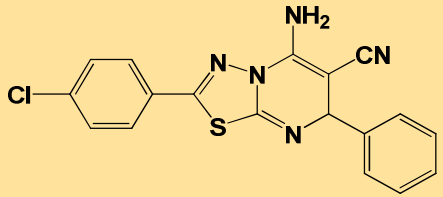
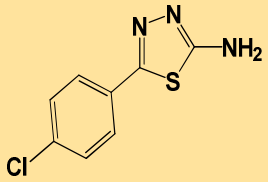
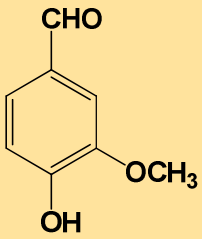
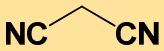
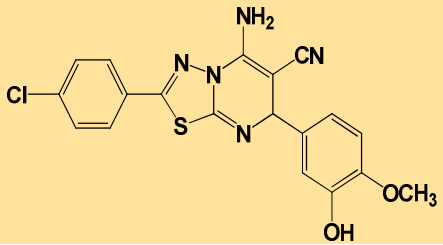
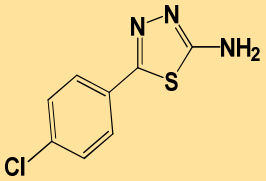
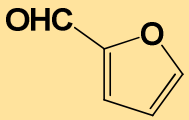
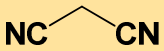
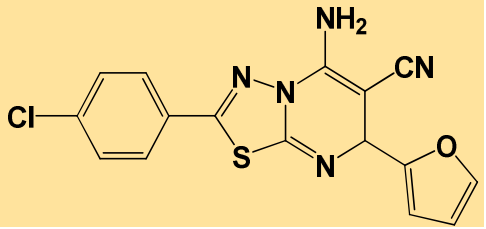
SCHEME OF SYNTHESIS



5-Amino-2-(4-Chlorophenyl)-7- Substituted Phenyl-8,8a-Dihydro-7H-[1,3,4]Thiadiazolo [3,2-A]Pyrimidine-6-Carbonitrile Derivatives.

Table 1: Final 10 synthezised derivatives:

Sr. no	Amine	Aldehyde	Malononitrile	Product
1.				
2.				
3.				
4.				
5.				

Sr. no	Amine	Aldehyde	Malononitrile	Product
6.				
7.				
8.				
9.				
10.				

Results and discussion

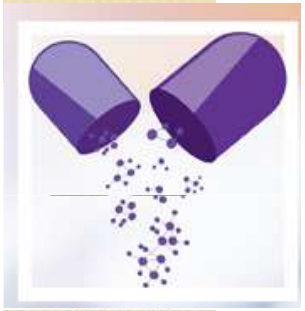
Chemistry:

Herein we report the one-pot synthesis of novel 5-Amino-2-(4-Chlorophenyl)-7- Substituted Phenyl-8,8a-Dihydro-7H-[1,3,4]Thiadiazolo[3,2-A]Pyrimidine-6-Carbonitrile Derivatives from three component reactions of an 5-(4-chlorophenyl)-1,3,4-thiadiazol-2 amine, aromatic aldehydes and malononitrile in the presence of NaOH under reflux and ultrasonic irradiation as shown in **scheme 1.** To determine the optimal reaction conditions, the one pot reactions between 5-(4-chlorophenyl)-1,3,4-thiadiazol-2 amine, aromatic aldehyde, malononitrile was carried out using different solvents in the presence of NaOH as a catalyst at different mole percentage as shown in Table 1, the desired product was not formed when H2O was chosen as solvent and when acetonitrile, methanol and dimethylformaide was chosen as solvent , the desired product was formed in low yield under reflux and ultrasonic irradiation as shown in Table 1. Proposed mechanism for the formation of 1,3,4-thiadiazolo[3,2-a]pyrimidine skeleton is as shown in figure 1. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectroscopy and IR. Physical characterization data of synthesized compound is as shown in table 2.

Table 2: Optimization of reaction conditions for Novel 5-Amino-2-(4-Chlorophenyl)-7- Substituted Phenyl-8,8a-Dihydro-7H-[1,3,4]Thiadiazolo[3,2-A]Pyrimidine-6-Carbonitrile Derivatives using various solvent and different mole percentage of NaOH

Entry	Catalyst	Amount (% mol)	Solvent	Method a Conventional		Method b Ultrasound	
				Time (hrs)	yield%	Time (hrs)	yield%
1.	NO catalyst	-	EtOH	9	-	2	-
2.	NaOH	30	EtOH	9	70	2	89
3.	NaOH	20	EtOH	9	70	2	89
4.	NaOH	20	H_2O	9	-	2	-
5.	NaOH	20	MeOH	11	55	2.30	60
6.	NaOH	20	CH_3CN	11	40	2.30	50
7.	NaOH	20	DMF	12	40	2.30	55
8.	NaOH	10	EtOH	13	60	2.45	65
9.	NaOH	5	EtOH	15	50	3.30	60

Table 3: Optimization of reaction conditions for 1,3,4-thiadiazolo[3,2-a]pyrimidine skeleton



Entry	R	Conventional		Ultrasound	
		Time (hrs)	Yield%	Time (hrs)	Yield%
a	4-chlorophenyl	7	70	1	89
b	2-chlorophenyl	7.30	68	1.30	85
c	3-chlorophenyl	7.30	65	1.30	85
d	4-flurophenyl	7	62	1.30	80
e	4-methoxyphenyl	8	58	2	75
f	3,4,5-methoxyphenyl	9	58	2	78
g	3,4-methoxyphenyl	9	55	2	75
h	phenyl	7	60	1	80
i	3-hydroxy-4-methoxyphenyl	9	60	2	82
j	2-furfuraldehyde	8	45	1.30	65

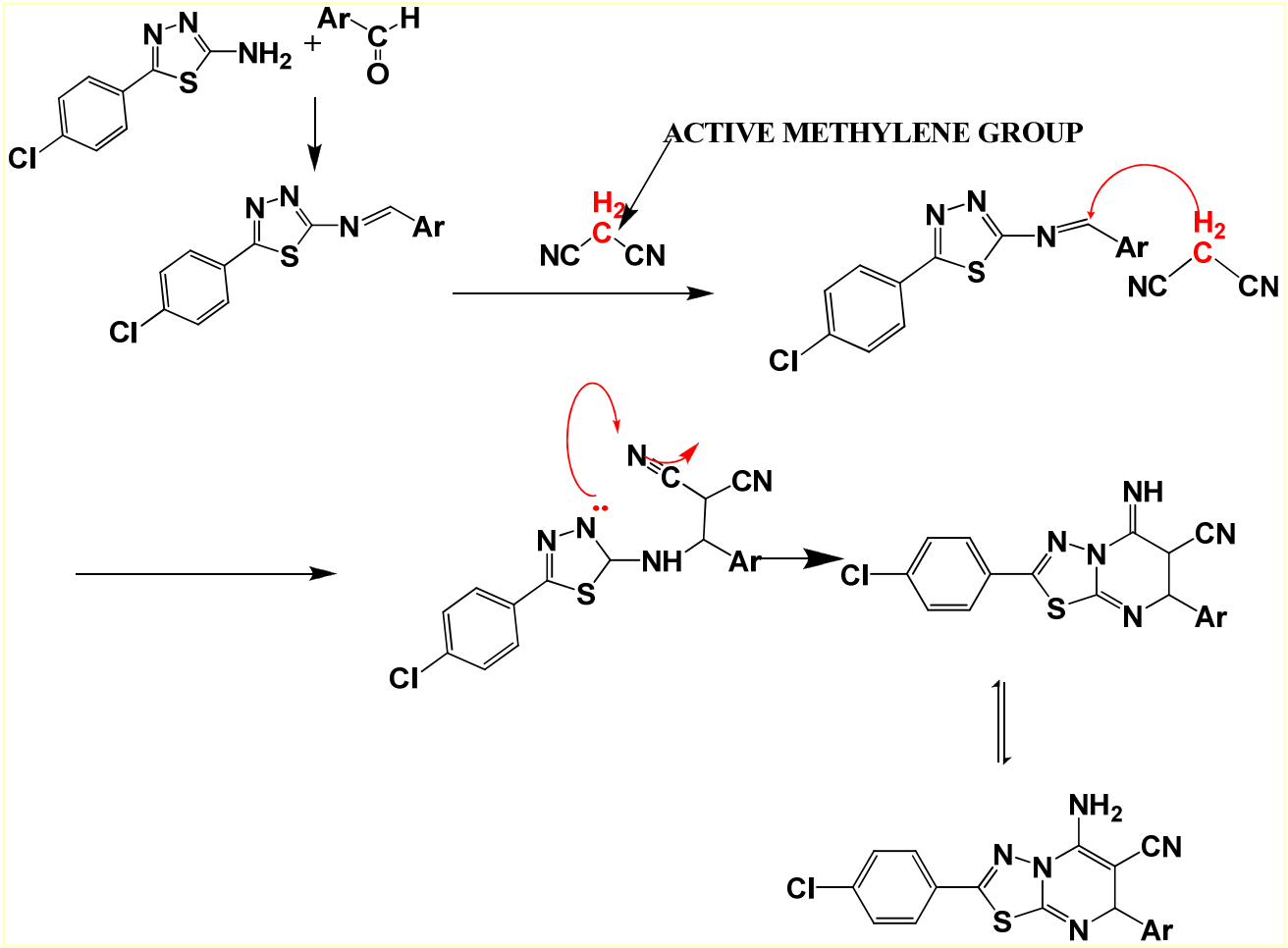


Figure.1. Proposed mechanism for the formation of 1,3,4-thiadiazolo[3,2-a]pyrimidine skeleton

Table 4: Physical Characterization data of compounds

Entry	R	Molecular formula	Molecular Weight	Melting point	R_f value
a	4-chlorophenyl	$C_{18}H_{11}Cl_2N_5S$	400	237-240	0.28
b	2-chlorophenyl	$C_{18}H_{11}Cl_2N_5S$	400	240-242	0.24
c	3-chlorophenyl	$C_{18}H_{11}Cl_2N_5S$	400	235-238	0.20
d	4-flurophenyl	$C_{18}H_{11}ClFN_5S$	383	239-242	0.37
e	4methoxyphenyl	$C_{19}H_{14}ClN_5OS$	395	210-212	0.37
f	3,4,5-methoxyphenyl	$C_{21}H_{18}ClN_5O_3S$	455	220-222	0.26
g	3,4-methoxyphenyl	$C_{20}H_{16}ClN_5O_2S$	425	225-228	0.50
h	phenyl	$C_{18}H_{12}ClN_5S$	365	218-220	0.43
i	3-hydroxy-4-methoxyphenyl	$C_{19}H_{14}ClN_5O_2S$	411	240-245	0.50
j	2-furfuraldehyde	$C_{16}H_{10}ClN_5OS$	355	200-210	0.49

1. 5-amino-2,7-bis(4-chlorophenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 237-240. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 H^1NMR δ: 8.00 (d,2H,ArH), 7.51 (d, 2H, ArH), 3.3 (s, 1H, ArCH), 6.79 (d, 2H, ArH), 7.06 (d, 2H, ArH), 10 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 172 (CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 143.2(C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 139.5 (C of Aromatic ring), 136.5 (C of Aromatic ring), 131 (C of Aromatic ring), 130.5 (C of Aromatic ring), 129.8 (C of Aromatic ring), 128.5 (C of Aromatic ring), 127.9 (C of Aromatic ring), 118.2 (C of carbonitrile group), 60.2 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 54.5 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine)

2. 5-amino-7-(2-chlorophenyl)-2-(4-chlorophenyl)7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 240-242. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 H^1NMR δ: 8.00 (d,2H,ArH), 7.50 (d, 2H, ArH), 3.3 (s, 1H, ArCH), 7.80 (d, 2H, ArH), 7.02, 7.27 (m, 2H, ArH), 10 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 170 (CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158.3 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 143.7 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 138.1 (C of Aromatic ring), 134.2 (C of Aromatic ring), 129.5 (C of Aromatic ring), 129 (C of Aromatic ring), 128.5 (C of Aromatic ring), 127 (C of Aromatic ring), 126 (C of Aromatic ring), 117.5 (C of carbonitrile group), 60 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 55 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine).

3. 5-amino-7-(3-chlorophenyl)-2-(4-chlorophenyl)7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 235-238. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 H^1NMR δ: 8.00 (d, 2H, ArH), 7.51 (d, 2H, ArH), 3.2 (s, 1H, ArCH), 7.06, 7.27, 7.38 (t, 3H, ArH), 7.49 (s, 1H, ArH), 10 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 172.2 (CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 143.5 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 142.5 (C of Aromatic ring), 136.6 (C of Aromatic ring), 134 (C of Aromatic ring), 129 (C of Aromatic ring), 128.5 (C of Aromatic ring),128 (C of Aromatic ring), 127 (C of Aromatic ring), 125.5 (C of Aromatic ring), 117 (C of carbonitrile group), 59 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 53 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine). MS; m/z 400.

4. 5-amino-2-(4-chlorophenyl)-7-(4-fluorophenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 239-242. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 (C-F) 1053 H^1NMR δ: 8.00 (d,2H,ArH), 7.50 (d, 2H, ArH), 3.3 (s, 1H, ArCH), 7.06 (d, 2H, ArH), 7.27 (d, 2H, ArH), 9.7 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 172 (CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 159 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 143.2 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 136.6 (C of Aromatic ring), 136 (C of Aromatic ring), 130.6 (C of Aromatic ring), 129.5 (C of Aromatic ring), 128.9 (C of Aromatic ring), 128.7 (C of Aromatic ring),117 (C of carbonitrile group), 60 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 52 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine). MS; m/z 383.

5. 5-amino-2-(4-chlorophenyl)-7-(4-methoxyphenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 210-212. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400; (C-Cl) 740.55; (C=N) 1623; (C-OCH_3) 1055. H^1NMR δ: 8.00 (d, 2H, ArH), 7.50 (d, 2H, ArH), 3.3 (s, 1H, ArCH), 7.06 (d, 2H, ArH),6.79 (d, 2H, ArH), 10 (s, 2H, amino attached to pyrimidine ring), 3.56 (s, 3H, methoxy group) C^{13} NMR δ: 172 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158(C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 157.5 (C of Aromatic ring), 143.5 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 136 (C of Aromatic ring), 133 (C of Aromatic ring), 130 (C of Aromatic ring), 129.5 (C of Aromatic ring), 128.5 (C of Aromatic ring), 128 (C of Aromatic ring), 117.3 (C of carbonitrile group), 60 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 55 (C of methoxy group) 53 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine). MS; m/z 383

6. 5-amino-2-(4-chlorophenyl)-7-(3,4,5-trimethoxyphenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 220-222. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 (C-OCH_3) 1059. H^1NMR δ: 8.00 (d, 2H, ArH), 7.50 (d, 2H, ArH), 3.3 (s, 1H, ArCH), 6.79 (d, 2H, ArH), 3.56 (s, 9H, methoxy group), 10 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 172(CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 152.8 (C of Aromatic ring), 143(C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 136.5(C of Aromatic ring), 136 (C of Aromatic ring), 135 (C of Aromatic ring), 129.5 (C of Aromatic ring), 128.5 (C of Aromatic ring), 128 (C of Aromatic ring), 117.5(C of carbonitrile group), 106.5 (C of Aromatic ring), 61 (C of methoxy group), 60(C of 1,3,4-thiadiazolo[3,2-a]pyrimidine) , 56(C of methoxy group), 53 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine). MS; m/z 455

7. 5-amino-2-(4-chlorophenyl)-7-(3,4-dimethoxyphenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 225-228. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 (C-OCH_3) 1052. H^1NMR δ: 8.00 (d, 2H, ArH), 7.50 (d, 2H, ArH), 3.3 (s, 1H, ArCH), 7.27 (s, 1H, ArH), 7.02- 6.79 (d, 2H, ArH),3.56 (s, 6H, methoxy group), 10 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 172(CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 149 (C of Aromatic ring), 146 (C of Aromatic ring), 143(C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 136.5(C of Aromatic ring), 134.5 (C of Aromatic ring), 129.5 (C of Aromatic ring), 128.5 (C of Aromatic ring), 128 (C of Aromatic ring), 122 (C of Aromatic ring), 117.5(C of carbonitrile group), 114 (C of Aromatic ring), 112.5 (C of Aromatic ring), 60(C of 1,3,4-thiadiazolo[3,2-a]pyrimidine) , 56(C of methoxy group), 53 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine). MS; m/z 425

8. 5-amino-2-(4-chlorophenyl)-7-phenyl-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

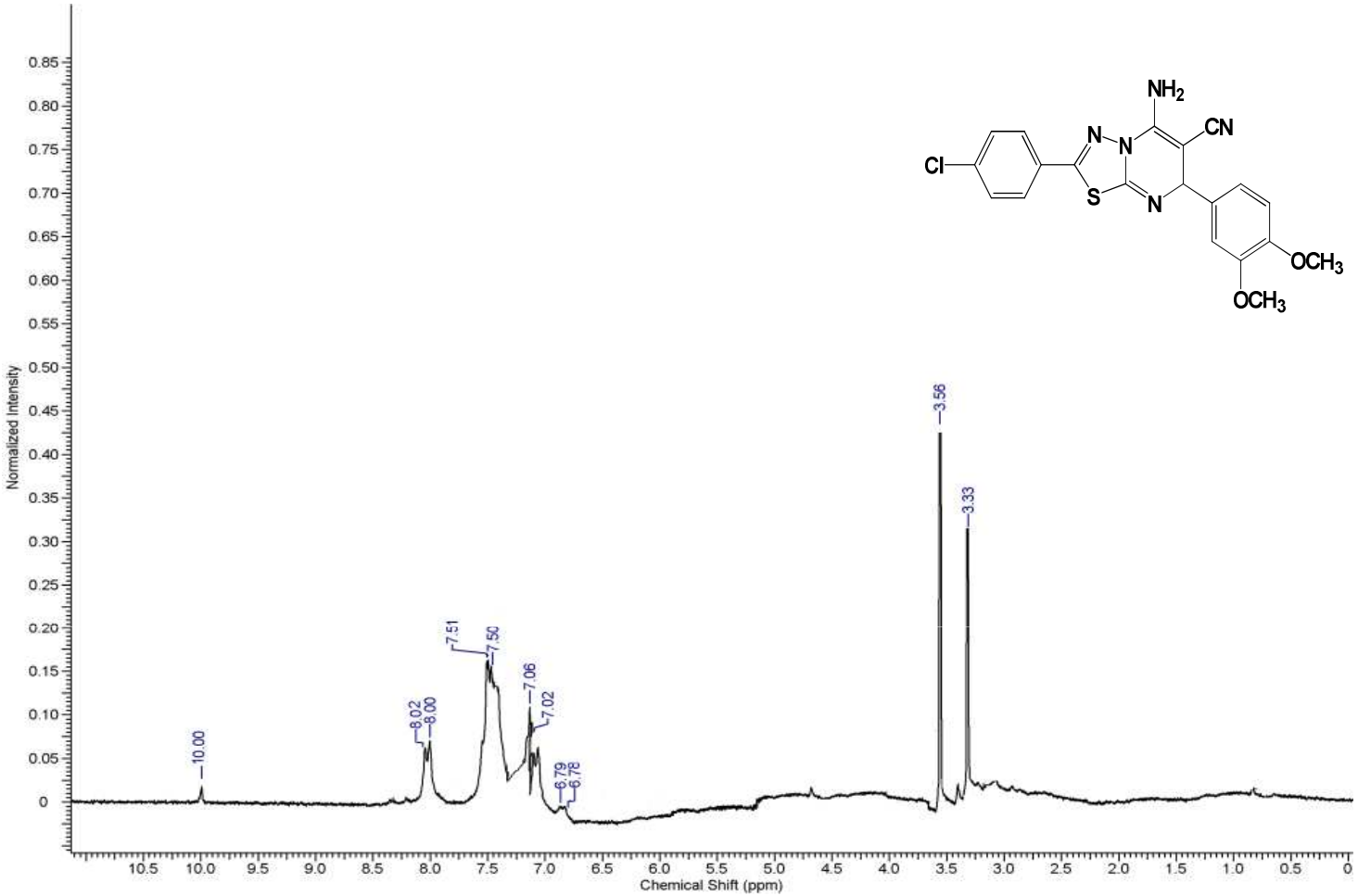
M.P: 218-220. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 H^1NMR δ: 8.00 (d, 2H, ArH), 7.51 (d, 2H, ArH), 3.2 (s, 1H, ArCH), 7.23 (d, 2H, ArH), 7.33 (d, 2H, ArH), 7.26 (m, 1H, ArH), 10 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 172(CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine) 143.7 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 141 (C of Aromatic ring), 136.5 (C of Aromatic ring), 129.5 (C of Aromatic ring), 129 (C of Aromatic ring), 128.6 (C of Aromatic ring), 128.5 (C of Aromatic ring), 125.7 (C of Aromatic ring), 125.6 (C of Aromatic ring), 117.5(C of carbonitrile group), 60 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 53 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine). MS; m/z 365

9. 5-amino-2-(4-chlorophenyl)-7-(3-hydroxy-4-methoxyphenyl)-7H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 240-245. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 (C-OCH_3) 1055 (C-OH) 3333. H^1NMR δ: 8.00 (d, 2H, ArH), 7.51 (d, 2H, ArH), 3.2 (s, 1H, ArCH), 6.86 (s, 1H, ArCH), 6.68-6.70 (d, 2H, ArCH), 5.35 (s, 1H, hydroxyl group), 3.56 (s, 3H, methoxy group, 10 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 172(CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine) 147.1 (C of Aromatic ring), 147 (C of Aromatic ring), 143.7 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 136.6 (C of Aromatic ring), 134.9 (C of Aromatic ring), 129.5 (C of Aromatic ring), 128.5 (C of Aromatic ring), 128.5 (C of Aromatic ring), 122.6 (C of Aromatic ring), 117.5(C of carbonitrile group), 115 (C of Aromatic ring), 112.6 (C of Aromatic ring), 60 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 53 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine). MS; m/z 411

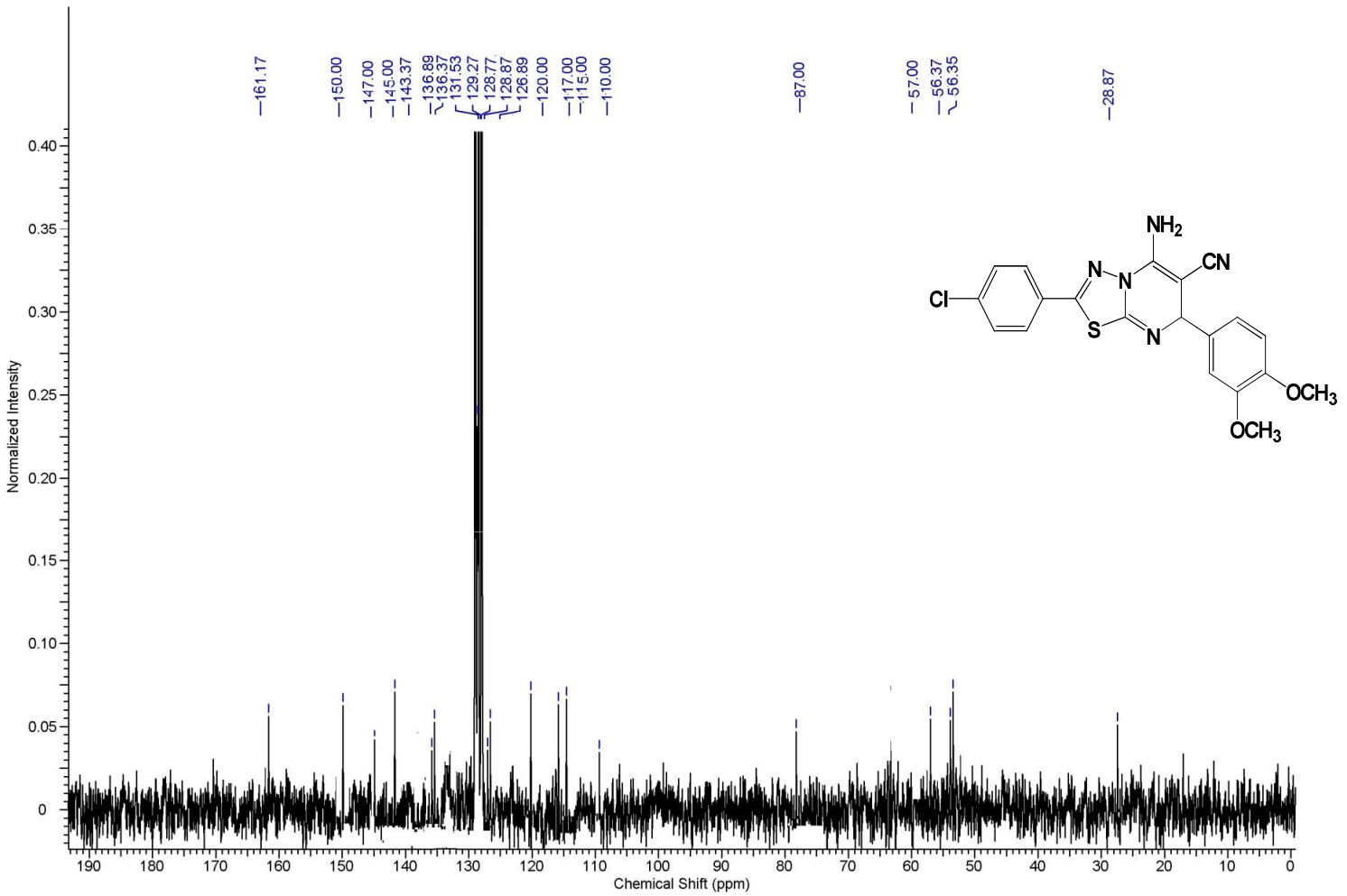
10. 5-amino-2-(4-chlorophenyl)-7-(furan-2-yl)-7H-[1,3,4] thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

M.P: 200-210. IR (KBr) cm^{-1}: (C-H Aromatic Stretch) 3000; (C-NH_2) 3400 (C-Cl) 740.55 (C=N) 1623 H^1NMR δ: 7.58 (d, 2H, furan ring), 7.36(d, 2H, ArH), 7.51 (d, 2H, ArH), 3.5 (s, 1H, ArCH), 6.40 (t, 3H, furan ring), 6.08 (d, 2H, furan ring), 10 (s, 2H, amino attached to pyrimidine ring) C^{13} NMR δ: 172(CH of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 158 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 152 (C of furan ring), 143.7 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 142 (C of furan ring), 136.6 (C of Aromatic ring), 129.5 (C of Aromatic ring), 128.7 (C of Aromatic ring), 128.5 (C of Aromatic ring), 117.5(C of cyno group), 110.6 (C of furan ring), 105 (C of furan ring),), 60 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine), 54 (C of 1,3,4-thiadiazolo[3,2-a]pyrimidine). MS; m/z 355.



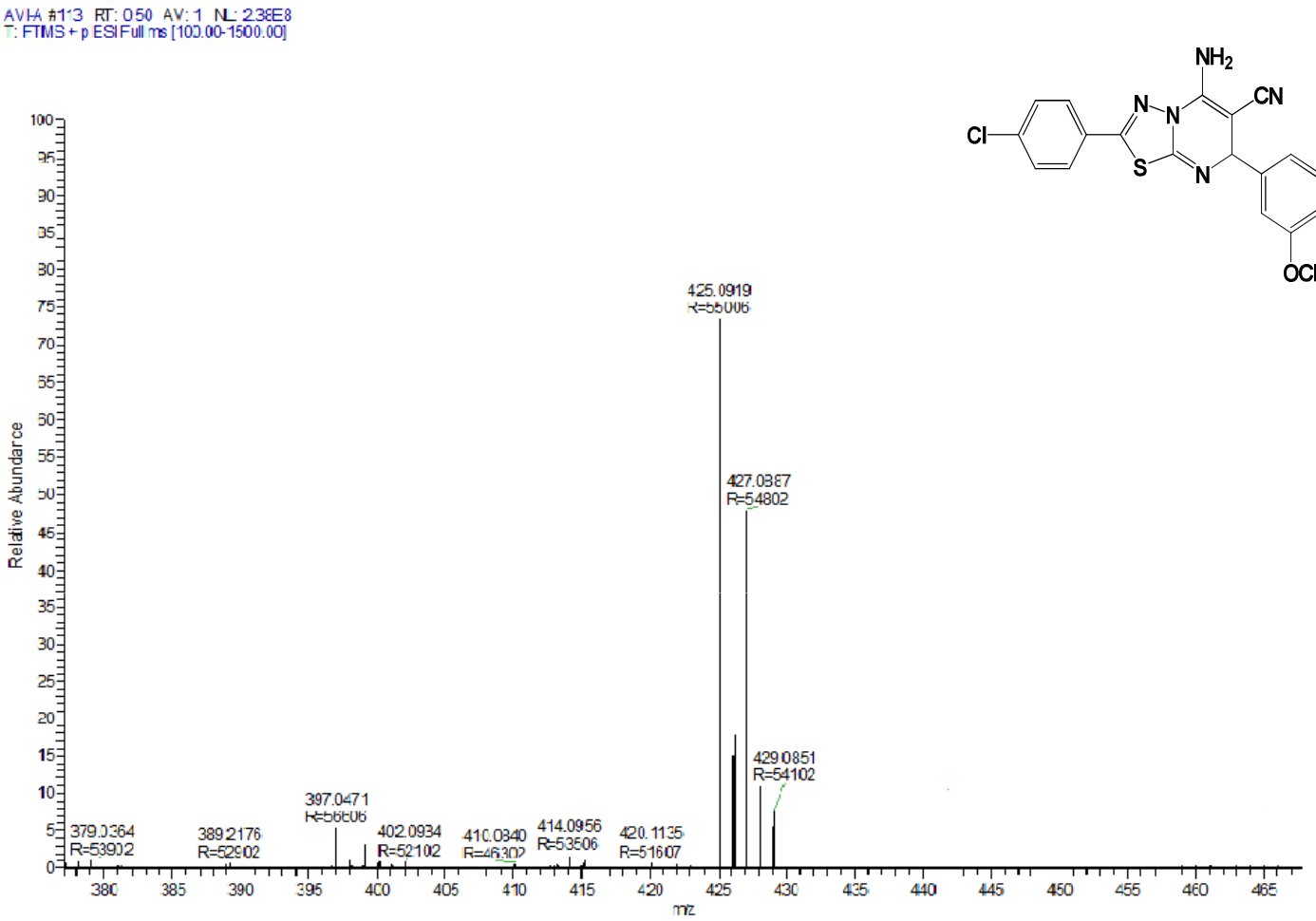
H[1]NMR

5-amino-2-(4-chlorophenyl)-7-(3,4-dimethoxyphenyl)7H[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile.



H^{13}NMR

5-amino-2-(4-chlorophenyl)-7-(3,4-dimethoxyphenyl)7H[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile.



Mass spectra of 5-amino-2-(4-chlorophenyl)-7-(3,4-dimethoxyphenyl)-7H[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile

Conclusion

We have developed an efficient one-pot method for the synthesis of 5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6-carbonitrile derivatives under ultrasound irradiation promopted multicomponent reaction of various aldehyde compounds, 5-(4-chlorophenyl)-1,3,4-thiadiazol-2 amine, and malononitrile in ethanol using sodium hydroxide as catalyst. The present protocol is also extendable to a wide variety of substrates. The advantages of this protocol are use of ecofriendly catalyst, easy work-up, ease of product isolation, and high yield. We believe that this method is a useful condensation reaction for the synthesis of 5H-[1,3,4]thiadiazolo[3,2-a]pyrimidine-6- carbonitrile derivatives.

Reference

1. Jha, M.; Guy, S.; Ting, Y.C. Microwave assisted synthesis of indole-annulated dihydropyrano[3,4-c]chromene derivatives via hetero-Diels–Alder reaction. Tetrahedron Lett. 2011, 52, 4337–4341
2. A.T. Taher, H.H. Georgey, H.I. El-Subbagh, Novel 1,3,4-heterodiazole analogues: synthesis and in vitro antitumor activity, Eur. J. Med. Chem. 47 (2012) 445e451.
3. R.A. Coburn, R.A. Glennon, Mesoionic purinone analogues. VI. Synthesis and in vitro antibacterial properties of mesoionic thiazolo[3,2-a]pyrimidine-5,7- diones and mesoionic 1,3,4-thiadiazolo[3,2-a]pyrimidine-5,7-diones, J. Pharm. Sci. 62 (1973) 1785e1789
4. M.A. Mahran, M.A. El-Sherbeny, A.M.A. El-Obaid, F.A. Badria, Heterocyclic systems containing pyrimidine nucleus as potential antimicrobial and antitumor agents, Alexandria J. Pharm. Sci. 12 (1998) 39e44.
5. Y. Tokunaga, S. Ito, Y. Kojima, S. Maeno, N. Sawai, Y. Sasao, Preparation of 2-phenylsulfinyl-5H-1,3,4-thiadiazolo[3,2-a]pyrimidin-5-one derivatives as agricultural and horticultural fungicides, Jpn. Kokai Tokkyo Koho JP Patent 01 (83) (1989) 084
6. R.A. Coburn, R.A. Glennon, Z.F. Chmielewicz, Mesoionic purinone analogues. 7. In vitro antibacterial activity of mesoionic 1,3,4-thiadiazolo[3,2-a]pyrimidine- 5,7-diones, J. Med. Chem. 17 (1974) 1025e1027
7. Bing Zhao , Yu Xu a , Qi-Gang Deng , Zhuo Liu a , Li-Yan Wang a , Yan Gao One-pot, three component synthesis of novel 5H-[1,3,4] thiadiazolo[3,2-a]pyrimidine-6-carboxylate derivatives by microwave irradiation, Tetrahedron Letters 55 (2014) 4521–4524.
8. D. Habibi, M. Nasrollahzadeh, L. Mehrabi, S. Mostafaee, P2O5–SiO2 as an efficient heterogeneous catalyst for the solvent-free synthesis of 1-substituted 1H-1,2,3,4-tetrazoles under conventional and ultrasound irradiation conditions, Monatsh. Chem. 144 (2013) 725–728
9. E. Mosaddegh, Ultrasonic-assisted preparation of nano eggshell powder: A novel catalyst in green and high efficient synthesis of 2-aminochromenes, Ultrason. Sonochem. 20 (2013) 1436-1441.
10.] M. Mirza-Aghayan, S. Zonoubi, M. Molaee Tavana, R. Boukherroub, Ultrasound assisted direct oxidative esterification of aldehydes and alcohols using graphite oxide and oxone, Ultrason. Sonochem. (2014)
11. Alan R. Katritzky, Kenneth C. Caster, Thomas H. Maren, Curtis W. Conroy, Amir Bar-Ilan synthesis and physicochemical properties of thiadiazole [3,2-a]pyrimidinesulfonamide and thiadiazole [3,2-a]triazinesulfonamides as canditate for topically effective carbonic anhydrase inhibitors, J. Med. Chem. 1987, 30, 2059–2062.

THANK YOU