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2-Amino-3,5-dicarbonitrile-6-sulfanylpyridines: synthesis and multiple biological activity – a review

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This review integrates the published data of the last decade (from 2010 to 2020) on the synthesis of the 2-amino-3,5-dicarbonitrile-6-sulfanylpyridine scaffold, the derivatives of which are widely used in the synthesis of biologically active compounds. Currently, no systematic accounts of synthetic routes towards this class of heterocyclic compounds can be found in the literature. The present-day trends in the catalytic synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines are considered using pseudo-four-component reaction (pseudo-4CR) by condensation of malononitrile molecules with thiols and aldehydes, and alternative three-component (3CR) condensations of malononitrile with 2-arylidenemalononitrile and S-nucleophiles.

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1. Introduction

The pyridine skeleton is a structural part of numerous natural alkaloids, metal complexes, and organic compounds,[1] including drug molecules.[2] A method for the design of highly functionalized pyridine compounds is based on the condensation involving malononitrile, aldehydes, and thiols. The attraction of this method is the simple introduction of accessible reagents giving a pyridine ring with various functional groups, which can be used to perform further transformations.[3] Previously, these reactions were considered in the context of classical multicomponent transformations and were included as single examples in some relevant reviews.[4]

Therefore, in this review we give a systematic account of original approaches developed in the last decade to the synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridine scaffold, derivatives of which are highly functionalized heterocyclic compounds with a potential biological activity. The synthesis is based on two approaches to the target products, first, cyclocondensation of two malononitrile molecules with aromatic aldehydes and thiols (pseudo-4CR) and, second, three-component cyclocondensation of malononitrile with 2-arylidenemalononitrile and thiols (3CR). Analysis of published data on the synthesis of 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile derivatives **I** performed using the SciFinder®[5] database demonstrated that the year of 2012 was the most effective period for this subject (Fig. 1).

The library of synthesized 2-amino-6-sulfanylpyridine-3,5-dicarbonitriles with various substituents at the C-2, C-4, or C-6 positions of the pyridine scaffold shows unique therapeutic properties. For example, non-nucleoside agonists for the treatment of cardiovascular diseases were proposed on the basis of substituted pyridines. There are quite a few non-ribose compounds possessing low nanomolar activity and improved selectivity towards adenosine receptors (ARs) of A1, A2A, and A2B subtypes; this subject is addressed in a number of reviews.[6] Fig. 2 depicts the structural diversity of such molecules, in particular, LUF5853, a partial hA1AR agonist, with the ligand – receptor binding affinity K_i hA1 of 11 ± 2 nM;[7] LUF5834, a partial adenosine A2B receptor agonist (EC_{50} hA2B of 12 ± 2 nM);[8] P453, a strong hA2B receptor agonist (EC_{50} hA2B of 9.5 ± 0.9 nM);[9] BAY60-6583, an adenosine A2B receptor agonist (EC_{50} = 3 nM);[6] and LUF-5831, an adenosine A1 receptor agonist (K_i = 144 nM).[10] Also, noteworthy is the therapeutic agent capadenoson (completed Phase II clinical trials), which is a highly efficient selective partial adenosine A1 receptor agonist (A1AR) (EC_{50} of 0.1 nM), and adenosine A2B receptor agonist (EC_{50} of 8.94 ± 0.33 nM),[11] developed by Bayer pharmaceutical company for the use in atrial fibrillation and stable angina patients. Previously, capadenoson was shown to decrease the electrically induced tachycardia in rats by 45%.[12] Neladenoson bialanate hydrochloride (phase II clinical trials) was used as a water-soluble partial A1 receptor agonist for oral administration in patients with chronic cardiac insufficiency.[11,13]

2-Amino-6-sulfanylpyridine-3,5-dicarbonitrile Cp-60 inhibits accumulation of PrP^{Sc} in scrapie-infected mouse neuroblastoma cells ScN2a (IC_{50} 18.0 ± 1.5 mM).[14] The molecule of **II** exhibits inhibitory activity *in vitro* against HIV-1 integrase (IC_{50} = 4 μM).[15]

In addition, polyfunctional pyridines with structure **I** exhibit anticorrosion properties. According to electrochemical impedance spectroscopy, potentiodynamic polarization, and weight loss measurements, the studied pyridines (the substituent Ar contains –H, -OMe, or $–NO_2$ in the C-4 position) behave as mixed-type corrosion inhibitors in 1 M HCl; the lead compound is 2-amino-4-(4-methoxyphenyl)-6-(phenylsulfanyl)pyridine-3,5-

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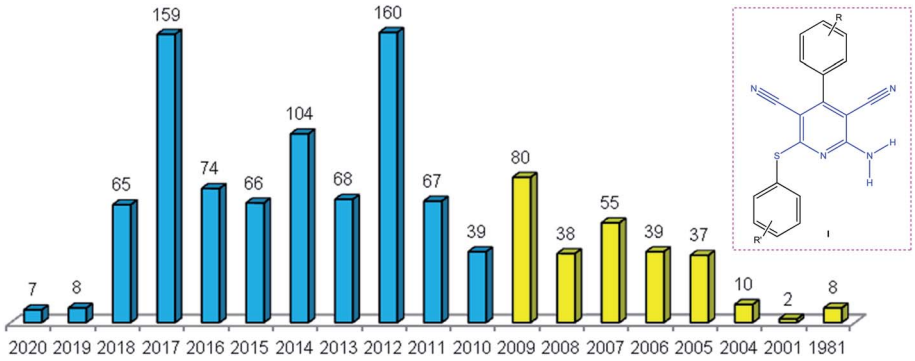


Fig. 1 Number of results from SciFinder® concerning the synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridine derivatives I, depending on the year of publication (altogether 1086 results). The blue color marks the publications discussed in this review.

dicarbonitrile **III** with inhibition efficiency of 97.6% when present in 1.22 mmol L^{-1} concentration.[16]

Antimicrobial activity was found for a series of new penta-substituted pyridine derivatives bearing a quinoline moiety in the C-4 position of the pyridine ring. Among them, compound **IV** exhibited activities against *Escherichia coli* (MIC = 62.5 μg mL^{-1}), *Bacillus subtilis* (MIC = 200 μg mL^{-1}), *Clostridium tetani* (MIC = 250 μg mL^{-1}), and *Salmonella typhi* (MIC = 100 μg mL^{-1}), the activities being higher than or equal to those of ampicillin used as the reference substance.[17]

2. One-pot synthesis of 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile scaffold

The catalytic synthesis of 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile **4** with spectroscopic evidence for the structures of products was performed for the first time in 1981 by S. Kambe and co-workers according to one-pot 3CR protocol (Scheme 1). The target product **4** was prepared in two ways: by the reaction of 2-arylidenemalononitrile **1** with thiol **2** (pathway I) and by the reaction of thiol **2** with malononitrile **3** (pathway II), which resulted in the formation of intermediate imines **A** and **B**. Triethylamine was used as the catalyst; reaction proceeded in ethanol and gave pyridines in 17% to 49% yields depending on the nature of Ar substituents in the starting compound **1**.[18]

The following catalysts were proposed earlier for the synthesis of pyridines **4** and their analogues using the pseudo-four-component reaction (pseudo-4CR) of malononitrile, aldehydes, and thiols: Et_3N,[19] diazabicycloundecene (DBU),[20] 1,4-diazabicyclo[2.2.2]octane (DABCO),[21] 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) ionic liquid,[22] $KF \cdot Al_2O_3$,[23] tetrabutylammonium hydroxide (TBAH) or piperidine,[24] nano-SiO_2,[25] piperidine/MW,[26] $ZnCl_2$/MW,[27] and KF–Al_2O_3/MW.[28] Highly functionalized bis-pyridines **8** were

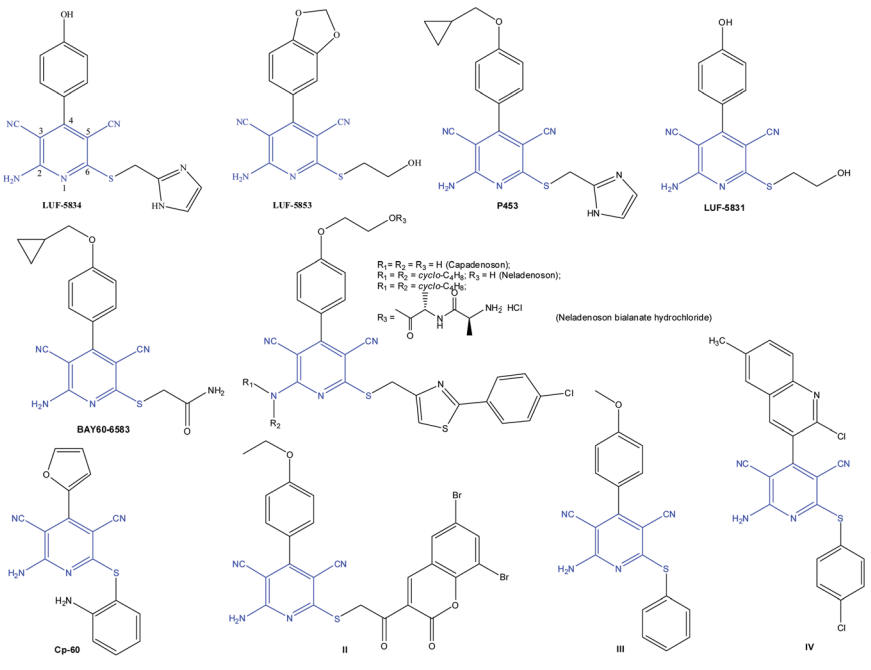
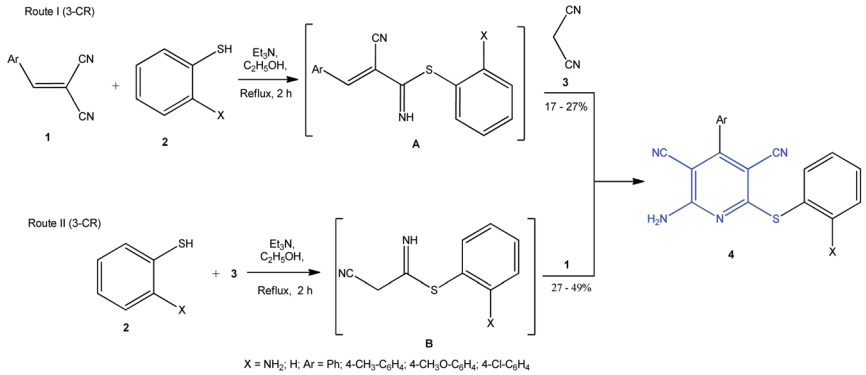
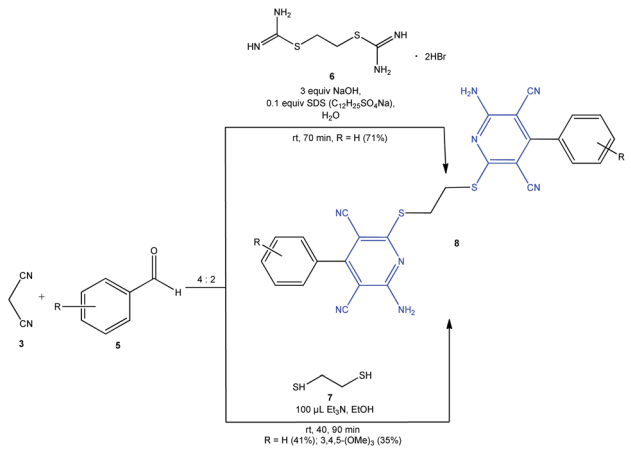


Fig. 2 Skeletal diversity of biologically significant 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile structures.



Scheme 1 Two approaches to one-pot of the synthesis of 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile derivatives **4** *via* 3-CR.



Scheme 2 One-pot synthesis of highly functionalized bis-pyridines **8** by using different thiolating agents **6** and **7**.

prepared using bis-isothiuronium salt **6** or 1,2-ethanedithiol **7** as thiolating agents (Scheme 2).[19,29]

Meanwhile, most of the cited methods suffer from number of drawbacks such as low yields of target products, long time and drastic conditions of the synthesis, and high catalyst toxicity or complex catalyst preparation procedure.

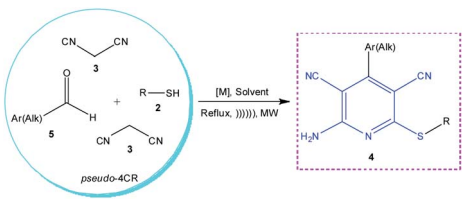
Over recent years, considerable progress has been made in the catalysis of this reaction, which increases the product yields or allows conducting the reactions under mild conditions. The most recent achievements in the synthesis of 2-amino-6-sulfanylpyridine-3,5-dicarbonitriles **4** by condensation of two moles of malononitrile **3**, thiols **2**, and aldehydes **5** (pseudo-4CR, Scheme 3) are summarized in Table 1, which gives 60 examples of target compounds of type **4** with indicated conditions of synthesis, yields of products, and practical applications of the products.

Analysis of the results of the last decade presented in the Table 1 indicates that methods for the synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines are developing towards green chemistry principles: the use and regeneration of catalysts, including nanocomposites (examples 17–26), Bronsted and Lewis acids and bases (examples 27–46), and heterogeneous catalysts (examples 47–56, Table 1); the use of green solvents (altogether 14 examples of using water), in particular, together with ionic liquids (examples 57–60); physicochemical treatment (microwave and ultrasonic irradiation) together with catalysts (altogether 8 examples). The catalytic activation is still the major trend (60 examples, Table 1). A particular place belongs to organocatalysts taken in minor quantities, which illustrates a metal-free strategy (examples 1–16, Table 1).

In most of the synthesized 2-amino-6-sulfanylpyridine-3,5-dicarbonitriles, ethanol, water, or their mixtures are proposed as solvents. The use of an ionic liquid together with a catalyst and ultrasonic irradiation ($ZrOCl_2 \cdot 8H_2O/NaNH_2$, ultrasonic irradiation))))))), [bmim]BF_4) at room temperature induces a synergistic effect, giving substituted pyridines in more than 90% yields within 5 minutes (example 46, Table 1).[74] A fairly promising is the use of a deep eutectic solvent (DES) (choline chloride : urea (1 : 2)) as a green reaction medium and a catalyst (example 4, Table 1).[32] An additional advantage of using DES is the possibility of reuse (three cycles without the loss of activity) with a simple recovery procedure.

Bayat and co-workers used nitroketene dithioacetal **9** as the S-nucleophile (CH_3S^-) in the pseudo-4-CR to prepare the desired pyridines **4** in 55%–76% yields (Scheme 4). A drawback of the method is the formation of an equimolar amount of 2-(nitromethylene)imidazolidine **10** by-product formed in the condensation.[89]

2-(Phenylseleno)pyridines **12**, selenium analogues of sulfanylpyridines **4**, were synthesized from malonodinitrile **3**, aldehydes **5**, and PhSeH **11** in polyethylene glycol (PEG-400) as the solvent under ultrasonic irradiation (Scheme 5). The authors assumed that PEG-400 is favorable for *in situ* formation of arylmethylenemalononitriles **1**.[90]



Scheme 3 Construction of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridine scaffold **4** by pseudo-4CR with the participation of 2 moles of malononitrile, 1 mol of aldehydes and 1 mol of thiols.

Table 1 Conditions of one-pot condensation involving malononitrile, aldehydes, and thiols

No.	Catalyst [M], mol% or mol eq.	Solvent	Temperature, °C	Reaction time, min	Yield **4**, %	Activity	Substitutes R or Ar/Alk	Reference
Organocatalysts								
1	Et_3N 3 drops on 1 mmol **5**, nano-sized MgO 50 mg on 1 mmol **5**	C_2H_5OH	rt 50	180–420 60–300	44–50 65–75	—	R = Ph Ar = Ph; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 4-Me-C_6H_4	3
2	Et_3N 6 drops on 1 mmol **5**	C_2H_5OH	Reflux	300	45–72	Inhibitor α-Glucosidase	R = Ph Ar = Ph; 3-NO_2-C_6H_4; 4-C_6H_5-C_6H_4; 2-Me-C_6H_4; 3-Py; 2-Cl-C_6H_4; 2-F-C_6H_4; 4-Cl-C_6H_4; 4-OH-C_6H_4; 3-OH-C_6H_4; 3-OH-4-OMe-C_6H_3; 2-Cl-3-OMe-C_6H_3; 3-OMe-4-OH-C_6H_3; 3-OMe-4-F-C_6H_3; 3-OMe-4-OH-5-I-C_6H_2; 3-OMe-4-Br-5-OMe-C_6H_2; 2-Br-4-OMe-5-OMe-C_6H_2; 3-Br-4-OMe-5-OMe-C_6H_2; 2-OMe-3-OMe-4-OMe-C_6H_2; 2-OMe-3-OMe-4-OMe-C_6H_2; 3,4,5-$(OMe)_3$-C_6H_2; 2-OMe-4-OMe-C_6H_3; 4,5-$(OMe)_2$-C_6H_3; 3,5-$(OMe)_2$-C_6H_3; 1-Nh; 2-Nh; 3-$C_6H_5CH_2O$-4-OMe-C_6H_4; 4-$C_6H_5CH_2O$-C_6H_4	30
3	Diethylamine 20 mol%	C_2H_5OH	rt	240–360	67–82		R = C_2H_4OH; Ph; Bn; 2-NH_2-C_6H_4; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4; 4-OMe-$CH_2C_6H_4$ Ar = Ph; 3,4-$(OMe)_2$-C_6H_3; 4-Br-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 3-NO_2-C_6H_4; 4-Me-C_6H_4; 4-OH-C_6H_4; 2-thienyl; 4-CN-C_6H_4; 4-$(CH_3)_2CH$-C_6H_4; *cyclo*-3,4-(OCH_2O)-C_6H_3; 2-furyl; 2,6-$(CH_3)_2$-C_6H_3; 2,6-$(Cl)_2$-C_6H_3	31
4	Deep eutectic solvent (DES) (choline chloride : urea (1 : 2)), 0.5 mL on 1 mmol **5**	DES	60	80–240	60–82		R = Ph; 4-Me-C_6H_4; 4-Br-C_6H_4 Alk/Ar = *n*-C_7H_{15}; Ph; 4-Cl-C_6H_4; 3-NO_2-C_6H_4; 3-Br-C_6H_4; 2-thienyl; 2-furyl; 4-Me-C_6H_4; 4-Br-C_6H_4; 3-OMe-C_6H_4; 4-OMe-C_6H_4; 1-Nh	32
5	—	Water–choline hydroxide (1 : 4)	Reflux	15–50	85–94		R = Ph Ar = Ph; 4-OMe-C_6H_4; 4-NO_2-C_6H_4; 2-furyl; 4-Cl-C_6H_4; 4-Br-C_6H_4; 4-Me-C_6H_4; 4-OH-C_6H_4; 2-thienyl; 3-NO_2-C_6H_4; 2-NO_2-C_6H_4; 2-Nh	33
6	Baker's yeast, 1 g on 9.4 mmol **5**	C_2H_5OH	rt	40	82–93	—	R = Ph Ar = Ph; 4-Br-C_6H_4; 4-F-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 4-OH-C_6H_4; 2-NO_2-C_6H_4; 4-$N(Me)_2$-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 4-Me-C_6H_4	34
7	Water extract of banana	C_2H_5OH	65	10–45	80–90	—	R = Ph; 4-Cl-C_6H_4; *n*-C_4H_9; *n*-C_8H_{17} Alk/Ar = Ph; 3-OH-C_6H_4; 4-OH-C_6H_4; 4-OMe-C_6H_4; 4-Me-C_6H_4; 3-Br-C_6H_4; 4-Cl-C_6H_4; 2-Cl-C_6H_4; 4-F-C_6H_4; 4-NO_2-C_6H_4; 4-Py; 2-thienyl; 2-Nh	35
8	Tetra-*n*-butylammonium fluoride (1.0 mol L^{-1} in THF), 10 mol%	H_2O	80	45–630	62–96		R = Ph; 2-NH_2-C_6H_4 Alk/Ar = Me; Et; Ph; 4-Cl-C_6H_4; 4-F-C_6H_4; 4-OMe-C_6H_4; 4-OH-C_6H_4; 4-NO_2-C_6H_4; 4-Me-C_6H_4; 4-OH-3-Me-C_6H_3; 3,4-$(OMe)_2$-C_6H_3; 2-furyl; 2-thienyl; piperonyl	36
9	*o*-Iodoxybenzoic acid, 10 mol%	H_2O	70	90–150	69–83		R = Ph; 2-Br-C_6H_4; 2,4,6-Me_3-C_6H_2; 2-Me-C_6H_4; 4-Cl-C_6H_4	37

Table 1 (*Contd.*)

No.	Catalyst [M], mol% or mol eq.	Solvent	Temperature, °C	Reaction time, min	Yield **4**, %	Activity	Substitutes R or Ar/Alk	Reference
							Ar = Ph; 4-Me-C_6H_4; 4-OMe-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 4-NO_2-C_6H_4; 4-Br-C_6H_4; 4-Cl-C_6H_4; 2,6-$(Cl)_2$-C_6H_4; 3,4-Me_2-C_6H_3	
10	Diethylamine, 20 mol% → Dess–Martin periodinane (DMP) (1 mmol)	C_2H_5OH → DMF	rt 5–10	1.5–2.5 5–10	90–96		R = Et; *n*-Bu; C_6H_{11}; Ph; 4-Br-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 4-Me-C_6H_4 Ar = 2,6-$(Me)_2$-C_6H_3; 2,6-$(OMe)_2$-C_6H_3; 2,6-Cl_2-C_6H_3; 2,6-F_2-C_6H_3	38
11	Piperidine MW[a]	C_2H_5OH, CH_3CN	Reflux 90	180–1440 0.5–60	5–86 6–97		R = Ph; 4-Cl-C_6H_4 Alk/Ar = *t*-Bu; Ph; 4-F-C_6H_4; 4-Cl-C_6H_4; 2-thienyl; 2,6-$(Cl)_2$-C_6H_3; 2,6-$(F)_2$-C_6H_3; 2-Cl-6-F-C_6H_3; 2-F-6-CF_3- C_6H_3	39
12	Piperidine, 0.03 mL on 5 mmol **5**	C_2H_5OH	Reflux	180	57–86	Anti-microbial activity[b]	R = Ph; 4-Me-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4 Ar =  R_1 = R_2 = H; R_1 = Me, R_2= H; R_1 = OMe, R_2= H; R_1 = Cl, R_2= H; R_1 = H, R_2= Me;	17
13	Imidazole, 0.2 mmol on 1 mmol **5**	C_2H_5OH	Reflux	30–120	81–92	—	R = C_6H_{11}; Ph; 2-Me-C_6H_4 Alk/Ar = C_6H_{11}; Ph; 4-OMe-C_6H_4; 4-CN-C_6H_4; 2-Nh; 4-Cl-C_6H_4	40
14	L-Arginine, 20 mol%	H_2O	Reflux	30–90	81–96		R = C_6H_{11}; Ph; Bn; 2-NH_2-C_6H_4; 2-CH_3-C_6H_4 Alk/Ar = C_6H_{11}; Ph; 2-Nh; 4-Br-C_6H_4; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4; 3-NO_2-C_6H_4; 2,6-$(OMe)_2$-C_6H_3; 3,4-$(OMe)_2$-C_6H_3; 2,6-$(Cl)_2$-C_6H_3	41
15	*N*,*N*′-Di(1*H*-tetraazol-5-yl)-6H,12*H*-5,11-ethanedibenzo [*b*,*f*][1,5]diazocine-3,9-dicarboxamide, 5 mol%	EtOH	Reflux			Antitumor activity[c]	R = Ph; C_2H_4OH; 4-Me-C_6H_4; 4-Cl-C_6H_4 Ar = Ph; 4-Me-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 4-NO_2-C_6H_4; Pr; quinoline; 4-CN-C_6H_4; 4-Br-C_6H_4; 2-Me-2-furil; 2-Me-2-thienyl; 2-CH_3-Pr; 2-Br-Pr	42
16	Choline methoxide, 5–10 mol%	H_2O–C_2H_5OH (7 : 3)	50–60	20–40	—	—	R = Ph Ar = Ph; 4-NO_2-C_6H_4; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4; 4-OH-C_6H_4; 4-Br-C_6H_4	43
Nanomaterial-based catalysts								
17	Nano-CaO, 0.01 g on 1 mmol **5**	H_2O–C_2H_5OH (1 : 1)	50	80–150	70–92	—	R = Ph; 4-Me-C_6H_4 Ar = Ph; 4-Br-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 3-Me-C_6H_4; 4-Me-C_6H_4; 4-CN-C_6H_4; 3-OH-C_6H_4; 4-OH-C_6H_4	44
18	SnO nanoparticles, 6 mol%	C_2H_5OH (abs.)	60	54–142	79–92	—	R = Ph, 4-Me-C_6H_4; 4-OMe-$CH_2C_6H_4$ Ar = Ph, 4-OMe-$CH_2C_6H_4$; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-Cl-C_6H_4; 3-CH_3-C_6H_4; 4-OH-C_6H_4; 4-Br-C_6H_4	45
19	CuI nanoparticles, 10 mol%	C_2H_5OH	60	85–200	70–94	—	R = C_2H_4OH; Ph; 4-Me-C_6H_4; 4-OMe-C_6H_4	46

Table 1 (*Contd.*)

No.	Catalyst [M], mol% or mol eq.	Solvent	Temperature, °C	Reaction time, min	Yield **4**, %	Activity	Substitutes R or Ar/Alk	Reference
							Alk/Ar = CH_3; *n*-C_4H_9; Ph, 3-Me-C_6H_4; 4-Me-C_6H_4; 3-OH-C_6H_4; 4-OH-C_6H_4; 4-OMe-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-Br-C_6H_4; 4-Cl-C_6H_4; 4-SMe-C_6H_4; 4-CN-C_6H_4	
20	ZnO nanoparticles, 0.015 g on 1 mmol **5**, 20 mol%	C_2H_5OH	50	80–150	75–94		R = Ph; 4-Me-C_6H_4 Ar = Ph; 3-Me-C_6H_4; 4-Me-C_6H_4; 3-OH-C_6H_4; 4-OH-C_6H_4; 4-OMe-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-Cl-C_6H_4; 4-Br-C_6H_4; 4-CN-C_6H_4	47
21	Nanocrystalline MgO (NAP-MgO), 0.1 g on 1 mmol **5**	C_2H_5OH	50	120–540	41–69		R = C_6H_{11}; Ph; Bn; 4-Me-C_6H_4; 4-Cl-C_6H_4; 2-furyl Ar = Ph; 4-OMe-C_6H_4; 4-Me-C_6H_4; 4-NO_2-C_6H_4; 4-OH-C_6H_4; 4-Cl-C_6H_4; 4-HOOC-C_6H_4; 2-furyl; *cyclo*-3,4-(OCH_2O)-C_6H_3	48
22	Heterogeneous nanocatalyst Cu(II)/L-His@Fe_3O_4	H_2O	80	60	86–95		R = Ph Ar = Ph; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-Br-C_6H_4; 4-OMe-C_6H_4; 4-OH-C_6H_4; 4-F-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 4-NO_2-C_6H_4	49
23	Nano-TiO_2, 5 mol% 0.06 g on 1 mmol **5**	C_2H_5OH	Reflux	14–27	89–97		R = 4-Me-C_6H_4 Ar = Ph; 3-Cl-C_6H_4; 4-Cl-C_6H_4; 3-Br-C_6H_4; 4-Br-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-OMe-C_6H_4	50
	Nano-TiO_2, 5 mol%	C_2H_5OH	rt	60	81–87		R = 4-Me-C_6H_4 Ar = Ph; 3-Cl-C_6H_4; 4-Cl-C_6H_4; 3-Br-C_6H_4; 4-Br-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-OMe-C_6H_4	51
24	1,4-Dinitropyrazine-1,4-diium trinitromethanide {[1,4-pyrazine-NO_2][$C(NO_2)_3$]$_2$} nanostructured molten salt (NMS), 2 mol%	Solvent free reaction conditions	rt	20–40	83–93		R = Bn Ar = 4-NO_2-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 2,4-Cl_2-C_6H_3; 3,4-$(OMe)_2$-C_6H_3; 3-NO_2-C_6H_4; 2,5-$(OMe)_2$-C_6H_3; 4-N$(Me)_2$-C_6H_4; 1-Nh; C_6H_5-C_6H_4; 2-Furyl; 2-Thienyl; 4-Py; 4-  ; OH-C_6H_4; -C_6H_4-;	52
25	Covalently bonded sulfonic acid nano magnetic graphene oxide (Fe_3O_4@GO-Pr-SO_3H), 0.06 g on 1 mmol **5**	EtOH	Reflux	19–27	89–95		R = Ph; 4-Me-C_6H_4 Ar = Ph; 3-Cl-C_6H_4; 3-Br-C_6H_4; 4-Br-C_6H_4; 4-Cl-C_6H_4; 4-NO_2-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-OMe-C_6H_4; 2-furil; 2-thienyl	53
26	Co^{II}(macrocyclic Schiff base ligand containing 1,4-diazepane) immobilized on Fe_3O_4 nanoparticles (Fe_3O_4@Co^{II}), 0.02 g on 1 mmol **5**	—	100	11–25	90–98	—	R = Ph Ar = Ph; 3-Py; 4-N$(Me)_2$-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-OH-C_6H_4; 2-thienyl; 4-F-C_6H_4	54

Table 1 (*Contd.*)

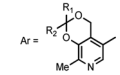
No.	Catalyst [M], mol% or mol eq.	Solvent	Temperature, °C	Reaction time, min	Yield **4**, %	Activity	Substitutes R or Ar/Alk	Reference
Bronsted and Lewis acids and basic catalysis								
27	NH_4OH, 12 mol%	MeOH (abs.)	rt	360	75–90	—	R = Ph Ar = Ph; 4-Cl-C_6H_4; 2-Cl-C_6H_4; 4-OMe-C_6H_4; 2-NO_2-C_6H_4	55
28	NH_4OH, 12 mol%	MeOH (abs.)	rt	360	60–90		R = Ph Ar = Ph; 4-OH-C_6H_4; 4-OMe-C_6H_4; 2-OMe-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 2-NO_2-C_6H_4	56
29	H_3BO_3, 15 mol%, CTAB, 10 mol% H_3BO_3, 15 mol%, CTAB, 10 mol%,))))))) (35 kHz, 200 W)	H_2O	80	25–50 8–15	79–92 83–74		R = Ph; 2-NH_2-C_6H_4 Ar = Ph; 4-Cl-C_6H_4; 4-F-C_6H_4; 4-OMe-C_6H_4; 4-HO-C_6H_4; 4-NO_2-C_6H_4; 4-Me-C_6H_4; 4-HO-3-OMe-C_6H_3; 3,4-$(OMe)_2$-C_6H_3; piperonyl; 2-furyl; 2-thienyl	57
30	H_3BO_3, 15 mol%, CTAB, 10 mol%,))))))[a]	H_2O	80	—	—	Adsorption and anti-corrosion activity	 Ar = Ph; 4-NO_2-C_6H_4; 4-OMe-C_6H_4	58
31	Phosphotungstic acid, 2 mol%, cetrimonium bromide, 10 mol%	H_2O	80	30–50	70–93		R = Ph, 4-NH_2-C_6H_4 Ar = Ph, 4-Cl-C_6H_4; 4-OH-C_6H_4; 4-NO_2-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4; 4-CHO-C_6H_4; 4-OH-3-OMe-C_6H_3	59
32	KOH, 10 mol%	C_2H_5OH	rt	60	25–40	Anti-bacterial and anti-neoplastic activities[d]	R_3 = Ph; 4-Me-C_6H_4; 4-Cl-C_6H_4  R_1 and R_2 see scheme 7	60
33	KOH, 10 mol%	C_2H_5OH	rt	30–90	71–90		R = C_6H_{11}; Ph; Bn; 2-NH_2-C_6H_4; 2-Me-C_6H_4 Alk/Ar = C_6H_{11}; Ph; Bn; 4-OMe-C_6H_4; 3-Cl-C_6H_4; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-Br-C_6H_4; 4-SMe-C_6H_4; 3-NO_2-C_6H_4; β-$C_{10}H_7$; 4-CN-C_6H_4	61
34	NaOH, 1 mol eq.,))))))) (40 kHz, 250 W)	C_2H_5OH	rt	90–120	90–96		R = Bn Ar = Ph; 4-OMe-C_6H_4; 4-Br-C_6H_4; 4-OH-C_6H_4; 4-$N(Me)_2$-C_6H_4	62
35	NaCl, 15 mol% NaCl, 15 mol%,))))))[a]	H_2O	Reflux Reflux	2–180 20–35	18–90 22–92		R = Ph Alk/Ar = CH_3; *n*-Pr; Ph, 4-Cl-C_6H_4; 4-NO_2-C_6H_4; 4-OMe-C_6H_4; piperonyl; 4-OH-3-OMe-C_6H_3; 3,4-$(OMe)_2$-C_6H_3; 2-thienyl; 2-furyl; 4-OH-C_6H_4; 4-Me-C_6H_4	63
36	K_2CO_3, 20 mol%, $KMnO_4$ 1.1 mol eq.	H_2O–C_2H_5OH (1 : 1)	Reflux	45–180	60–90		R = C_2H_4OH; Ph; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-NH_2-C_6H_4 Alk/Ar = $CH_3(CH_2)_6$; 4-OMe-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 3,4,5-$(OMe)_3$-C_6H_2; 3-OH-C_6H_4; 4-OH-C_6H_4; 2,6-$(Cl)_2$-C_6H_4; 4-Cl-C_6H_4; 4-Br-C_6H_4; 4-F-C_6H_4; 4-CN-C_6H_4; 3-NO_2-C_6H_4; 2-thienyl; 3-Py	64
37	K_2CO_3, 10 mol%,	PEG-400	40	1–60	82–92		R = Ph; 4-Br-C_6H_4; 4-OMe-C_6H_4; 2-NH_2-C_6H_4	65

Table 1 (*Contd.*)

No.	Catalyst [M], mol% or mol eq.	Solvent	Temperature, °C	Reaction time, min	Yield **4**, %	Activity	Substitutes R or Ar/Alk	Reference
							Alk/Ar = Ph; 4-Me-C_6H_4; 4-OMe-C_6H_4; 4-Cl-C_6H_4; 4-Br-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 2-thienyl; 2-furyl; 3-HO-C_6H_4; 4-OH-C_6H_4	
38	K_2CO_3, 1 mol eq., grinding in a pestle	Solvent free reaction conditions	rt	20–35	82–92	Antibacterial activity[e]	R = 2-mercaptopyridine Ar = Ph; 3,4-F_2-C_6H_3; 4-F-C_6H_4; 4-Br-C_6H_4; 4-OMe-C_6H_4; 3-OH-C_6H_4; 4-NO_2-C_6H_4; 3,4,5-$(OMe)_3$-C_6H_2; 4-Py	66
39	$NaHCO_3$, 10 mol%	H_2O–C_2H_5OH (1 : 1)	110	8	87–93		R = 2-NH_2-C_6H_4 Ar = Ph; 4-Me-C_6H_4; 4-F-C_6H_4; 4-OMe-C_6H_4; 4-Cl-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 2,4-Cl_2-C_6H_4; 3-Cl-C_6H_4; 2-Cl-C_6H_4; 4-COOH-C_6H_4; 2-HO-C_6H_4; 4-HO-C_6H_4; 2,5-$(OMe)_2$-C_6H_3; 1-Nh; 4-$N(Me)_2$-C_6H_4; 3-indolyl; hydrocinnamyl; 4-Br-C_6H_4; cinnamamyl; 9-anthracyl	67
40	10% aqueous suspension of aluminum oxide	H_2O	rt	50–100	79–90		R = Ph; 2-NH_2-C_6H_4 Ar = Ph; 4-Cl-C_6H_4; 4-F-C_6H_4; 4-OMe-C_6H_4; 4-OH-C_6H_4; 2-NO_2-C_6H_4; 4-NO_2-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; piperonyl; 2-furyl; 2-thieny; 4-OH-3-OMe-C_6H_3	68
41	$Sc(OTf)_2$, 5 mol%	C_2H_5OH	Reflux	120	65–85		R = Ph; 4-NH_2-C_6H_4; 4-Br-C_6H_4 Ar = Ph; 3-Br-C_6H_4; 4-F-C_6H_4; 4-Br-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 2-Cl-6-F-C_6H_3; 2-OMe-3-Br-C_6H_3; 2-Cl-6-Cl-C_6H_3; 2-F-6-F-C_6H_3	69
42	CH_3COONa, 12 mol%, MW (280 W)	MeOH (abs.)	—	3–12	62–92		R = Ph; C_2H_4OH Ar = Ph; 4-Cl-C_6H_4; 2-OMe-C_6H_4; 4-OMe-C_6H_4; 2-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-OH-C_6H_4; 4-OH-3-OMe-C_6H_3; 3-OH-4-OMe-C_6H_3; CH_2-CH_2-C_6H_3; 3,4-$(OMe)_2$-C_6H_3; 3,4,5-$(OMe)_3$-C_6H_2; 2-furyl	70
43	C_6H_5COONa, 10 mol%	PEG-400 : H_2O (1 : 1)	50 → 70	90–110	82–88		R = Ph Ar = Ph; 4-OMe-C_6H_4; 4-Cl-C_6H_4; 3-NO_2-C_6H_4; 3-OH-C_6H_4; 4-OH-C_6H_4; 4-Me-C_6H_4; 4-Br-C_6H_4	71
44	Cs_2CO_3, 5 mol% and tetra-*n*-butylammonium bromide, 5 mol %	CH_3OH	rt	180	85–92		R = Ph; 4-Me-C_6H_4; 4-OMe-C_6H_4 Ar = Ph; 4-Me-C_6H_4; 4-F-C_6H_4; 4-Cl-C_6H_4; 4-NO_2-C_6H_4; 3-OMe-4-OH-C_6H_3; 3,4-$(OMe)_2$-C_6H_3; 4-OMe-C_6H_4; 2-furyl; 2-thienyl; 4-OH-C_6H_4	72
45	Zn(II) or Cd(II) metal–organic frameworks, 2 mol%	Solvent free reaction conditions	100	30–60	61–88	—	R = Ph; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4; Ar = Ph, 4-F-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 2-NO_2-C_6H_4; 4-Me-C_6H_4; 2-thienyl; *n*-C_5H_{11}	73
46		$[Bmim]BF_4$	rt	5–20	90–98		R = Ph; C_6F_5; 4-Br-C_6H_4; 2-Nh	74

Table 1 (*Contd.*)

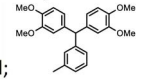
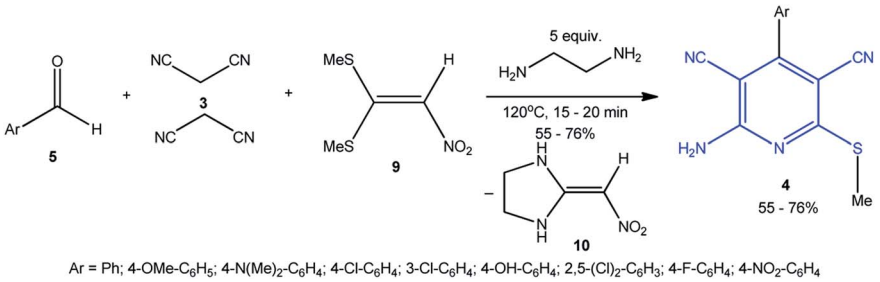
No.	Catalyst [M], mol% or mol eq.	Solvent	Temperature, °C	Reaction time, min	Yield **4**, %	Activity	Substitutes R or Ar/Alk	Reference
	$ZrOCl_2 \cdot 8H_2O/NaNH_2$, 20 mol%,))))))[a]						Ar = Ph; 2-NO_2-C_6H_4; 2,4-$(NO_2)_2$-C_6H_3; 4-Me-C_6H_4; 4-Br-C_6H_4; 4-F-C_6H_4; 4-CF_3-C_6H_4; 2-Nh; 2-furyl	
Heterogeneous catalysts								
47	Functionalized organosilane with spherical mesoporous silica nanoparticles with grafted piperidine, 20 mg on 1 mmol **5**	H_2O	Reflux	180–360	76–95		R = Ph, 3-Cl-C_6H_4; 2-Nh; 4-Me-C_6H_4 Ar = 4-OMe-C_6H_4; 4-Cl-C_6H_4; 4-Br-C_6H_4; 4-CN-C_6H_4; 4-Py; 4-$N(Me)_2$-C_6H_4	75
48	Propylphosphonium hydrogen carbonate ionic liquid supported on nano-silica (PPHC–nSiO_2) (0.7 mol%)	Solvent free reaction conditions	50	20–33	80–95	—	R = Ph, 4-Me-C_6H_4; 3-OMe-$CH_2C_6H_4$; 2-Nh Ar = Ph, 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 3-Br-C_6H_4; 4-$(CH_3)_2CH$-C_6H_4; 3-OMe-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 2-Cl-C_6H_4; 3-Br-C_6H_4; 2,4-$(Cl)_2$–C_6H_3; 2-Nh; Anthracene; 3-Py; 2-  CH_3-Furfural;	76
49	Silica-bonded *N*-propyldiethylenetriamine, 0.1 g on 1 mmol **5**	C_2H_5OH	rt	30–45	75–90	—	R = 2-NH_2-C_6H_4; 4-Me-C_6H_4 Ar = Ph; 4-Br-C_6H_4; 3-Cl-C_6H_4; 4-Cl-C_6H_4; 4-OMe-C_6H_4; 4-Me-C_6H_4; 4-OEt-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-CN-C_6H_4	77
50	2-Hydroxyethylammonium sulphonate immobilized on γ-Fe_2O_3 nanoparticles (γ-Fe_2O_3-2-HEAS), 0.08 g on 1 mmol **5**	Solvent free reaction conditions	50	5–20	79–91		R = *n*-Bu Ph; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4 Alk/Ar = Me; Ph; 4-Me-C_6H_4; 4-Cl-C_6H_4; 2-Nh; 3-Py; 3-$C_6H_4(CH_2)_2$	78
51	2-Hydroxyethylammonium acetate immobilized on Fe_2O_3 nanoparticles (Fe_3O_4-2-HEAA), 1 mol%, 0.016 g on 1 mmol **5**	Solvent free reaction conditions	70	5–15	80–90		R = *n*-Bu; Ph; 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4 Alk/Ar = Me; Ph; 4-Cl-C_6H_4; 4-Me-C_6H_4; 2-Nh; 3-Py; 3-$C_6H_4(CH_2)_2$	79
52	Molecular sieves (MS 4A), 200 mg on 1 mmol **5**,))))))) (35 kHz, 200 W)	H_2O	Reflux	40–120 30–60	78–91 81–90		R = Ph; 2-NH_2-C_6H_4 Ar = Ph; 4-Cl-C_6H_4; 4-F-C_6H_4; 4-NO_2-C_6H_4; 4-OH-C_6H_4; 4-Me-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; piperonyl; 2-furyl; 2-thienyl; 4-OMe-C_6H_4; 3-OMe-4-OH-C_6H_3	80
53	Na_2SiO_2 5 mol%	C_2H_5OH	rt	60	78–82		R = 4-Me-C_6H_4 Ar = Ph; 3-Cl-C_6H_4; 4-Cl-C_6H_4; 4-Br-C_6H_4; 3-NO_2-C_6H_4; 4-NO_2-C_6H_4; 4-OMe-C_6H_4	81
54	Graphene oxide–TiO_2 (GO–TiO_2), 20 mg on 1 mmol **5**	H_2O	rt	60–120	81–89		R = Ph	82

Table 1 (*Contd.*)

No.	Catalyst [M], mol% or mol eq.	Solvent	Temperature, °C	Reaction time, min	Yield **4**, %	Activity	Substitutes R or Ar/Alk	Reference
							Ar = Ph; 4-Br-C_6H_4; 2-OH-C_6H_4; 4-OMe-C_6H_4; 4-CHO-C_6H_4; 2-NO_2-C_6H_4; 2-OH-5-Br-C_6H_3; 2,3-$(OH)_2$-C_6H_3; 4-CF_3-C_6H_4	
55	Ceramic glass, 20 mg on 1 mmol **5**	H_2O	Reflux	120	76–95		R = Ph; 3-Cl-C_6H_4; 4-Cl-C_6H_4; 4-Br-C_6H_4; 2-Nh Ar = Ph; 4-OMe-C_6H_4; 2-Br-C_6H_4; 3-Br-C_6H_4; 4-Br-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4; 4-Cl-C_6H_4; 3,4-$(OMe)_2$-C_6H_3; 4-Py	83
56	Dolomite limestone, 5.0 mass%,))))))) (35 kHz, 160/640 W)	H_2O–C_2H_5OH (1 : 1)	45–50	30–45	90–98		R = 2-Py; Ph Ar = Ph; 3-OH-C_6H_4; 4-OMe-C_6H_4; 3,4,5-$(OMe)_3$-C_6H_2; 4-NO_2-C_6H_4; 4-F-C_6H_4; 3-Br-C_6H_4; 4-Br-C_6H_4; 3,4-$(F)_2$-C_6H_3; 2-Py; 4-Me-C_6H_4; 4-Cl-C_6H_4	84
Ionic liquids								
57	[Bmim]Br, 1.2 mmol	—	120	4–12	75–86		R = Ph Ar = Ph; 3-Br-C_6H_4; 4-Br-C_6H_4; 4-Cl-C_6H_4; 4-OH-C_6H_4; 4-OMe-C_6H_4; 4-Me-C_6H_4	85
58	1-(2-Aminoethyl)pyridinium hydroxide, 1.0 mmol	H_2O–C_2H_5OH (1 : 1)	rt	30–60	76–89		R = Ph; 2-NH_2-C_6H_4 Ar = Ph; 4-OMe-C_6H_4; 4-Me-C_6H_4; 4-OH-C_6H_4; 4-Cl-C_6H_4; 4-F-C_6H_4; 3-Br-C_6H_4; 3-OMe-4-OH-C_6H_3; 4-NO_2-C_6H_4	86
59	—	$[Bmim]BF_4$	50	20–30	78–89		R = Ph; 2-NH_2-C_6H_4 Ar = Ph; 3-Br-C_6H_4; 4-Cl-C_6H_4; 4-F-C_6H_4; 4-NO_2-C_6H_4; 4-OH-C_6H_4; 4-Me-C_6H_4; 4-OMe-C_6H_4	87
60	2-Hydroxyethylammonium acetate, 0.5 mL on 1 mmol **5**	H_2O	rt	5	70–96	—	R = Ph; *n*-Bu, 4-OMe-C_6H_4; 4-Me-C_6H_4; 4-Cl-C_6H_4 Ar = Me, Ph, Bn, 2-Nh, 3-Py, 4-Cl-C_6H_4; 4-Me-C_6H_4; 4-CHO-C_6H_4	88

[a] No information about the frequency and power of the device. [b] *Bacillus subtilis*, *Clostridium tetani*, *Streptococcus Pneumonia*, *Escherichia coli*, *Salmonella typhi*, *Vibrio cholera*, *Aspergillus Fumigates*, *Candida albicans*. [c] A549 (adenocarcinomic human), MCF-7 (breast cancer cell), MDA-MB-231 (human breast cancer), HBE (human bronchial epithelial). [d] *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*; MCF-7 (adenocarcinoma), SNB-19 (glioblastoma), HCT-116 (colon colorectal carcinoma), HSF (human foreskin fibroblast). [e] *Micrococcus luteus*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*.



Scheme 4 Synthesis of 2-amino-6-(methylsulfanyl)pyridine-3,5-dicarbonitriles **4** using nitroketenedithioacetal **9** as S-nucleophile.

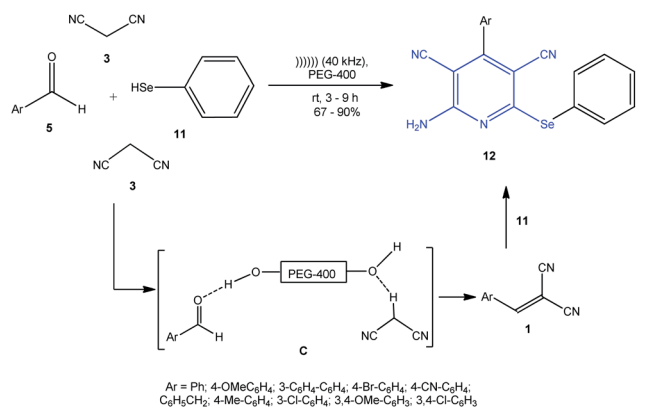
3. Design, synthesis of biologically active compounds with 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile scaffold

Grigor'ev and co-workers[91] developed an original approach for the synthesis of privileged scaffolds, 4-acyl-2-amino-3,5-dicarbonitrile-6-sulfanylpyridines **14**, by heterocyclization of potassium 2-acyl-1,1,3,3-tetracyanopropenides **13** with thiols **2** in superbasic medium, DMSO-Na or DMSO-NaH,[92] in which the target products were formed in more than 60% yields (Scheme 6).

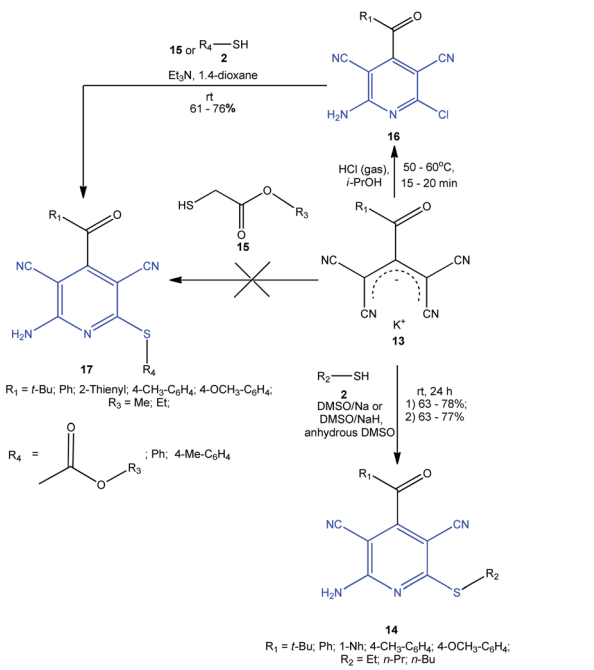
In the case where thioglycolic acid esters **15** were used as the starting reactants, it was impossible to isolate the target pyridines **17**. However, the synthesis of compounds **17** from 2-chloropyridines **16** follows the S_NAr mechanism and proceeds under milder conditions, involving thioglycolates **15** and arylthiols **2**.[93]

The mentioned research group continued these studied by the synthesis of a combinatorial series of functionalized 2-amino-6-sulfanylpyridine-3,5-dicarbonitriles with a pyridoxine moiety **21** (Scheme 7).[60] The proposed one-pot synthesis is based on the pseudo-4CR of pyridoxine derivative **20**, two moles of malononitrile **3**, and thiols **2** in the presence of 10 mol% KOH, giving the target pyridine-3,5-dicarbonitriles **21** in more than 25% yield. For increasing the solubility and enhancing the antimicrobial activity, the resulting sulfanylpyridines were regioselectively converted to quaternary salts **22** and **23**. The compounds exhibited pronounced antimicrobial activity against *Staphylococcus aureus* (MIC = 2 μg mL^{-1}), *Staphylococcus epidermidis* (MIC = 1 μg mL^{-1}), and *Bacillus subtilis* (MIC = 1 μg mL^{-1}), which exceeded the activity of reference samples (myramistin, benzalkonium chloride). The activity of compounds depends on their lipophilicity and decreases in the series R^1, R^2 = octyl > pentyl > ethyl.

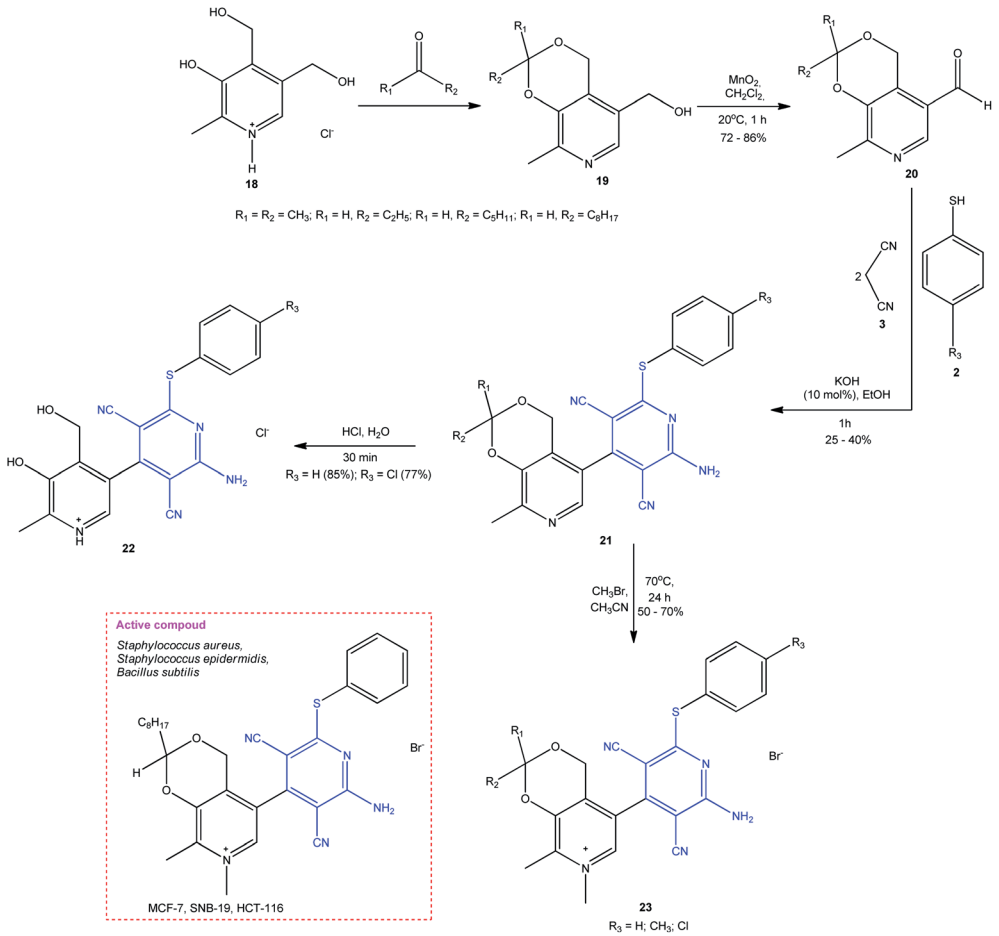
Some of compounds **19** had a cytotoxic activity against some types of tumor cells: MCF-7 (IC_{50} = 2.8 μM) (human breast cancer cell line), SNB-19 (IC_{50} = 5.1 μM) (glioblastoma cell line), and HCT-116 (IC_{50} = 2.8 μM) (human colon cancer cell line), being inferior to the activity of doxorubicin used as the ref. 60 The authors also noted that these compounds do not show selectivity to the HSF normal cells (human foreskin fibroblasts), *e.g.*, for the lead compound, IC_{50} = 2.8 μM, which indirectly attests to poor selectivity of their action and toxicity in experiments *in vivo*.



Scheme 5 Ultrasonic synthesis of 2-(phenylseleno)pyridines **12** in PEG-400 as the solvent.

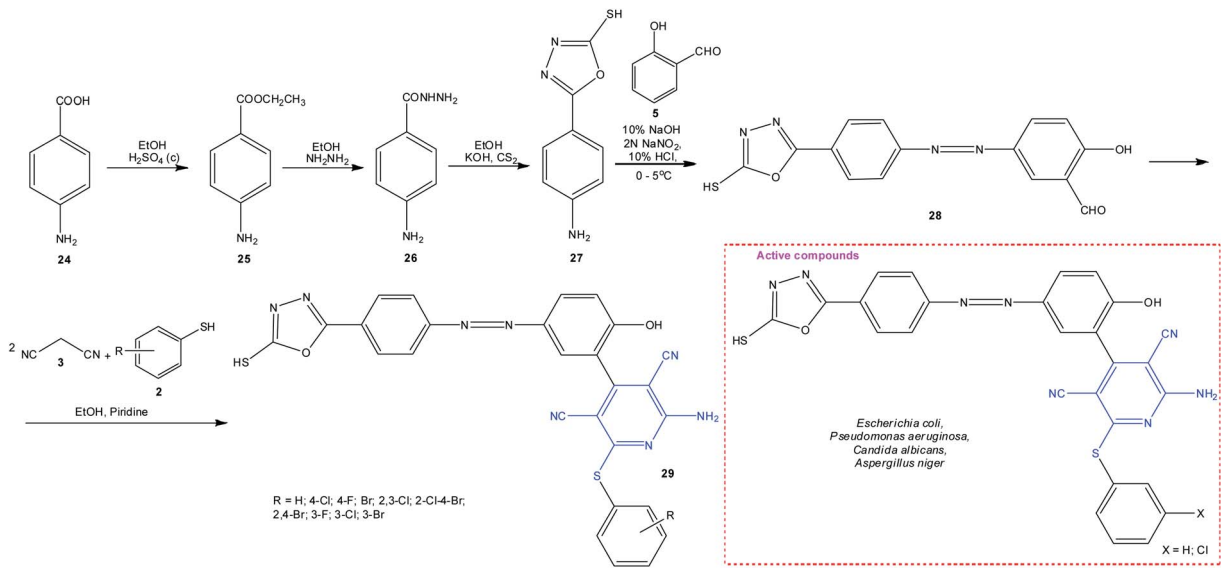


Scheme 6 Synthesis of 4-acyl-2-amino-3,5-dicarbonitrile-6-sulfanylpyridines **14**, **17** based on potassium 2-acyl-1,1,3,3-tetracyanopropenides **13**.

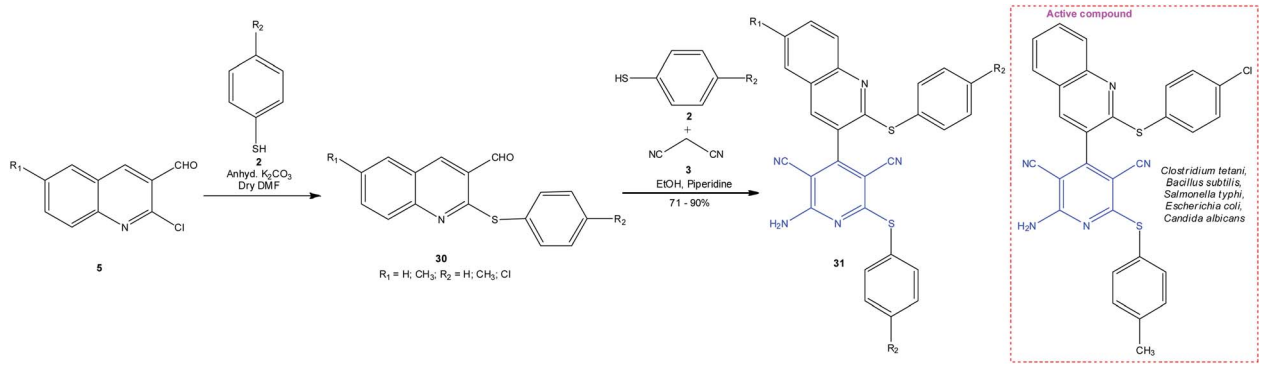


Scheme 7 Design of 2-amino-6-sulfanylpyridine-3,5-dicarbonitriles **23** with pyridoxine moiety exhibiting antimicrobial and antineoplastic activity.

In order to enhance the biological activity of target sulfanylpyridines, the aldehyde or thiol component was modified by introducing the pharmacophore groups. As an example, consider the synthesis of pyridine **29** from amino acid **24** (Scheme 8).[94] Primary screening for the *in vitro* antimicrobial activity revealed the highest activity (MIC = 15.625 μg mL^{-1})



Scheme 8 Synthesis of 2-amino-3,5-dicarbonitrile-6-sulfanylpyridines **29** containing 1,3,4-oxadiazole moiety exhibiting antimicrobial activity.

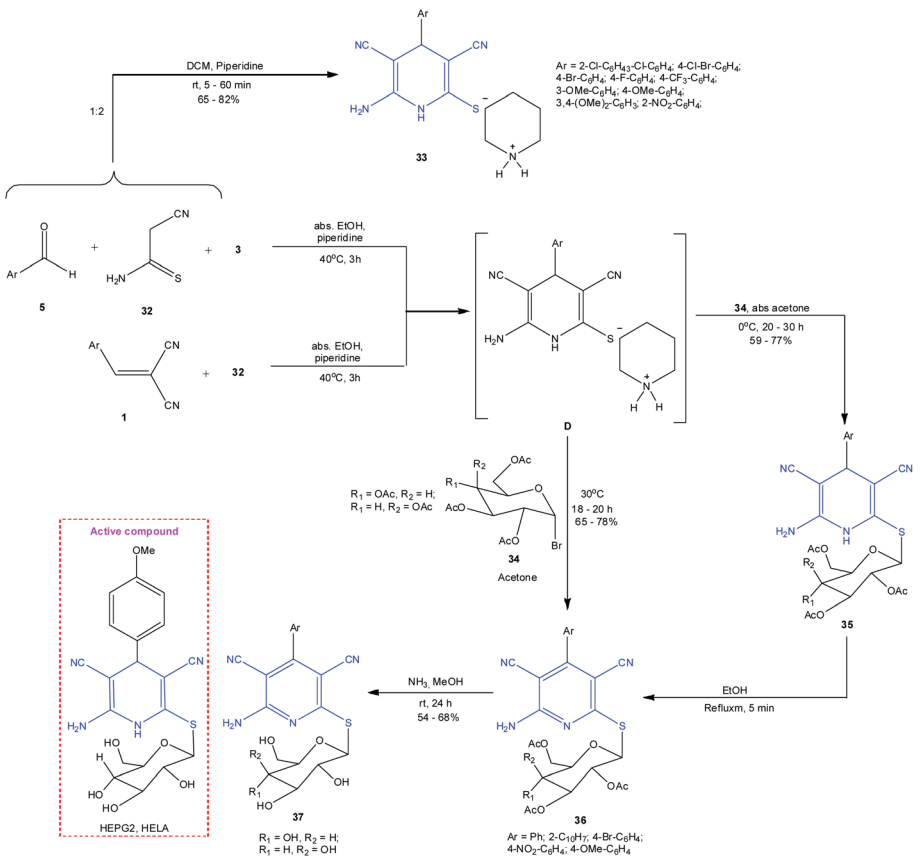


Scheme 9 Synthesis of sulfanylpyridines **31** containing 2-(ArS)-quinoline moieties.

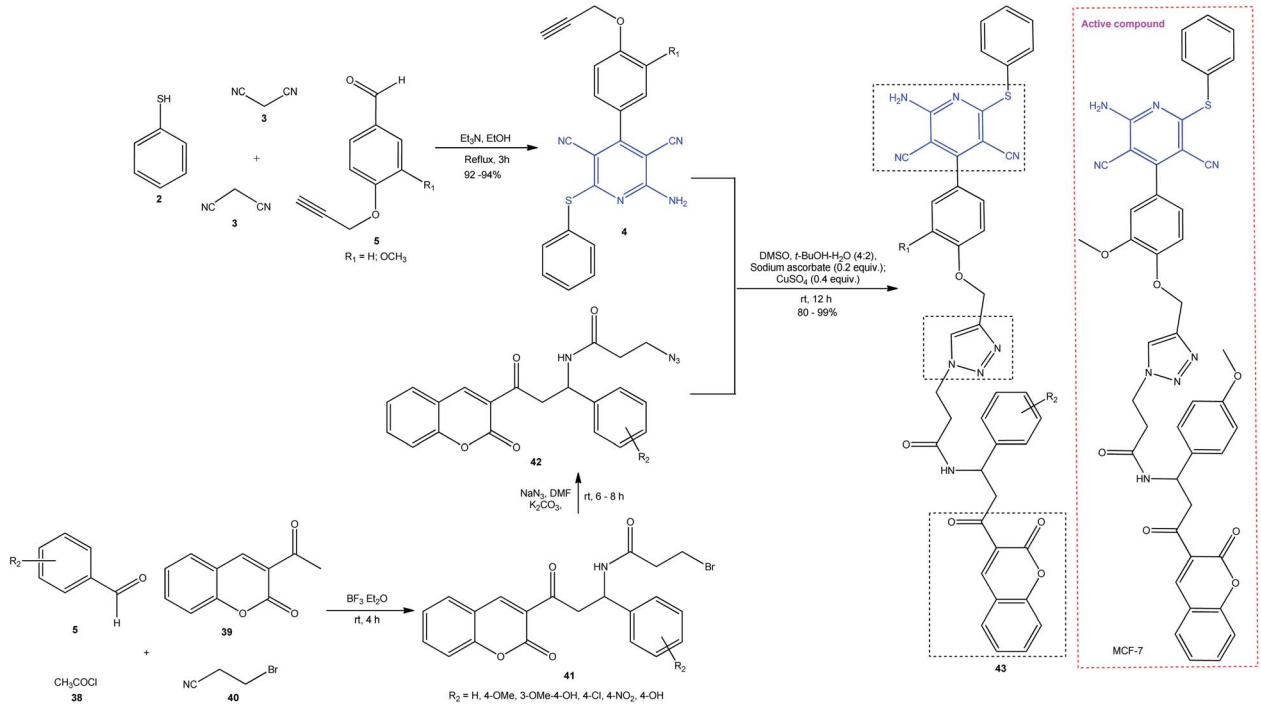
against *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger* for compounds with phenyl and 3-chlorophenyl substituents at the sulfur atom in pyridine **29**.

A proposed route towards antimicrobial agents includes the synthesis of hybrid structures **31** containing 2-(ArS)-amino-3,5-dicyanopyridine and 2-(ArS)-quinoline moieties (Scheme 9).[95] For this purpose, 3-formyl-2-phenylsulfanylquinoline **30**, obtained by the reaction of 2-chloro-3-formylquinoline **5** with thiols **2**, was used as the aldehyde component in pseudo-4-CR. The resulting compounds **31** possessed clear-cut antibacterial and fungicidal activities *in vitro* against the *Streptococcus pneumoniae*, *Bacillus subtilis*, *Clostridium tetani*, *Escherichia coli*, *Salmonella typhimurium*, *Vibrio cholera*, *Aspergillus fumigatus*, and *Candida albicans* strains.

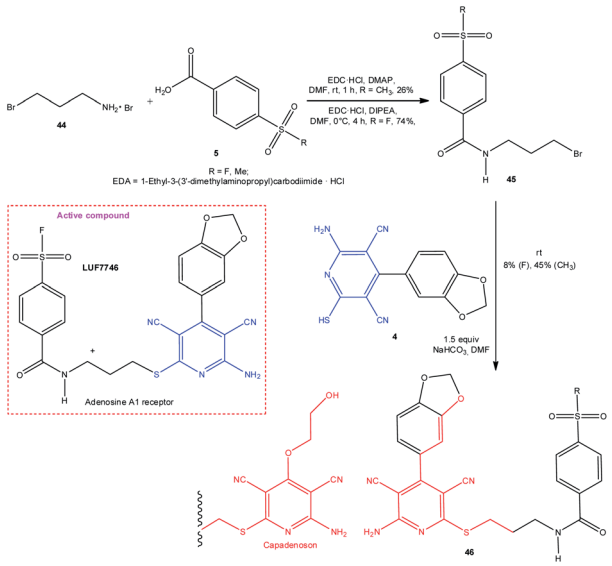
A recently proposed method[96] for the synthesis of piperidinium salts **33** is based on the 3-CR of cyanothioacetamide **32** with malononitrile **3** and aromatic aldehydes **5** in the presence of piperidine. With the goal to prepare pyridine cytostatic agents, Abbas and co-workers performed a four-step synthesis of a number of new 3,5-dicyanopyridine thioglycosides **37**.[97] The obtained piperidinium salts of dihydropyridinethiones **D** were treated, without isolation, with 2,3,4,6-tetra-*O*-acetyl-α-*D*-gluco-



Scheme 10 Synthesis of thioglycosides 3,5-dicyanopyridines **37** exhibiting antitumor activity.



Scheme 11 Synthesis of polycyclic hybrid peptidomimetics **43** with pyridine, coumarin, and triazole pharmacophore moieties.



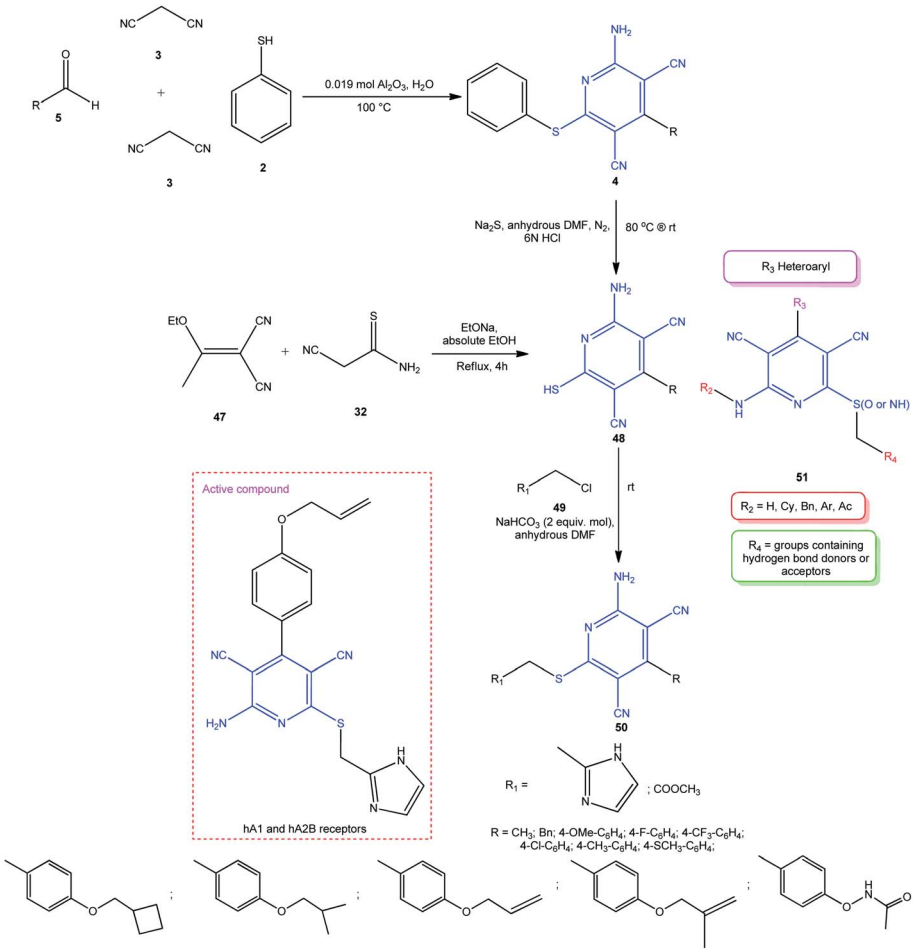
Scheme 12 Synthesis of functionalized pyridines **46** exhibiting adenosine A1 receptor agonist.

and galactopyranosyl bromides **34** to give the H-form of product **35** (Scheme 10). The subsequent aromatization and acetate deprotection resulted in the formation of 3,5-dicyanopyridine thioglycosides **37** in more than 50% yields. The *in vivo* anticancer activities against HEPG2 (human hepatocellular carcinoma cells) and HELA cell lines were an order of magnitude higher for the derivatives with glycopyranosyl moieties than for the corresponding acetyl derivatives.

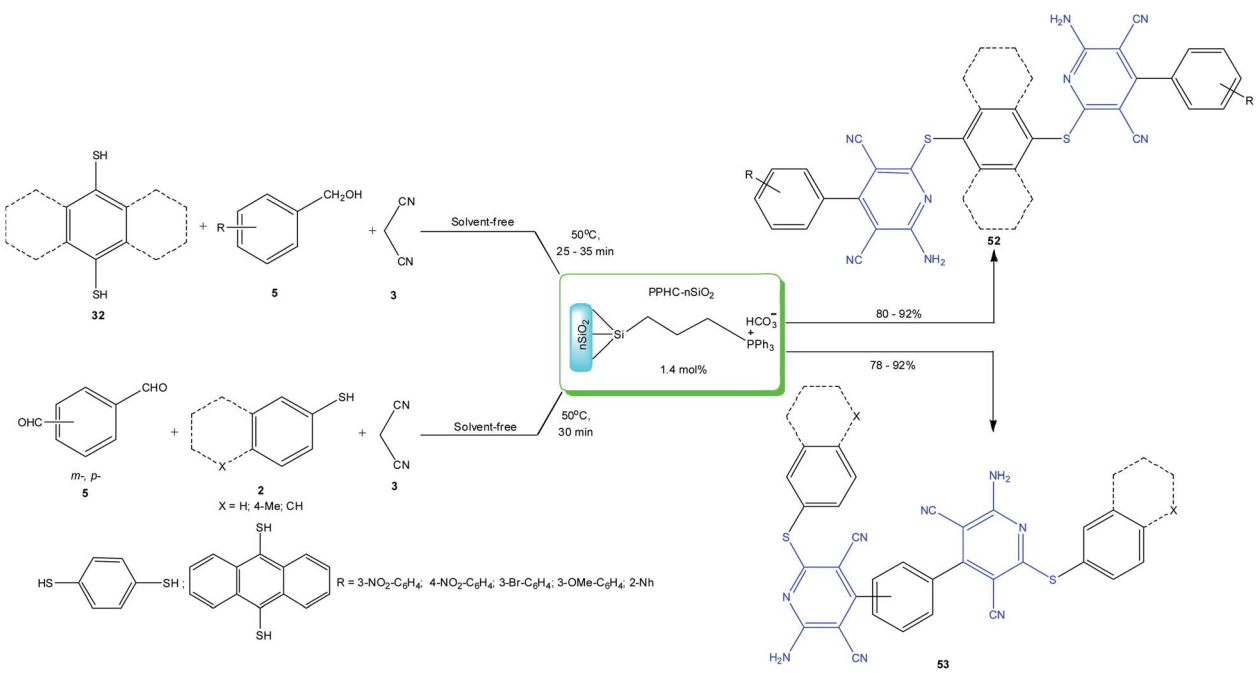
In 2016, Soumya and co-workers synthesized polycyclic hybrid peptidomimetic **43** (Scheme 11) bearing three pharmacophore moieties by linking the pyridine ring to the coumarin chromophore *via* a triazole linker. The authors implemented pseudo-4CR using 4- propynyloxybenzaldehyde **5**, acetyl chloride **38**, and 3-bromopropanenitrile **40** followed by copper(I)-catalyzed [3 + 2]azide–alkyne cycloaddition (CuAAC). Triazide **42** was prepared by a two-step procedure from coumarin **39**, benzaldehyde **6**, and 3-bromopropionic acid **40**. The intermediate brominated derivative **41** was easily transformed into triazide **42** on treatment with NaN_3. An additional screening of molecule **43** revealed the activity against the human breast carcinoma cells (MCF-7) with IC_{50} = 40 μM mL^{-1}.[98]

Recently, a method was proposed for the preparation of functionalized 3,5-dicyanopyridines **46**, a structural analogue of capadenoson (Scheme 12).[99] Fluorine-containing compound **46** (LUF7746) was fount to be a partial adenosine A1 receptor agonist with E_{50} = 61 ± 1% (hA1AR).

Catarzi and co-workers developed a method for the synthesis of a series of new pyridines **50**, which were studied for the structure–activity relationship with respect to adenosine receptors.[100] This approach is based on the transformation of the thiophenyl group in pyridines **4** into a mercapto group on treatment with Na_2S followed by hydrolysis to thiol **48**. The subsequent alkylation of 2-mercaptopyridine **48** with 2-(chloromethyl)-1*H*-imidazole or methyl chloroacetate **52** in the presence of sodium hydrogen carbonate at room temperature afforded target pyridine **51** (Scheme 13). It was shown that the sulfanyl-1*H*-imidazol-2-yl moiety in the C-6 position of the resulting molecule affects the activity of adenosine receptor agonists. The highest activity towards the hA2B receptor was found for 2-amino-6-[(1*H*-imidazol-2-ylmethyl)sulfanyl]-4-[4-



Scheme 13 Multistage synthesis of imidazolyl- and acetylpyridines **50** exhibiting the activity of adenosine receptor agonists.



Scheme 14 Heterogeneous catalyzed synthesis of polycyclic compounds **52** and **53** using ionic liquid.

(prop-2-en-1-yloxy)phenyl]pyridine-3,5-dicarbonitrile in a low nanomolar concentration range ($EC_{50} = 27 \pm 21$ nM).

The subsequent studies of this group aimed at the introduction of various substituents in the pyridine scaffold **51** demonstrated good possibilities for enhancing the biological effect (Scheme 13).[101]

A method was proposed for the synthesis of polycyclic compounds **52** and **53** (Scheme 14) in 80%–92% yields by the reaction of malononitrile with dialdehydes/dithiols and an ionic liquid, propylphosphonium hydrogen carbonate, supported on nanosilica (PPHC–nSiO_2), which served as a heterogeneous catalyst.[76] A drawback of the proposed method is the three-stage preparation procedure of the PPHC–nSiO_2 catalyst and that the ionic liquid contains phosphonium compounds, which is not quite consistent with green chemistry principles, as noted in the literature.[102]

4. Conclusions

The analysis of publications devoted to the chemistry and biological activity of 2-amino-6-sulfanylpyridine-3,5-dicarbonitriles indicates the continued interest of synthetic chemists in the last decade. Latest data summary in this review show the further development of the catalytic multicomponent reactions of malononitrile, aldehydes, and thiols (selenols) for the synthesis of new pharmaceutical agents based on the 2-amino-3,5-dicarbonitrile-6-sulfanylpyridine framework. Today, cluster of these compounds has been obtained with a yield of more than 70% using available and effective catalysts based on triethylamine, inorganic bases or boric acid, as well as Lewis acids, with most of which are realized in combination with ultrasonic irradiation. Attention is also drawn to innovative approaches using nanocatalysts, ionic liquids and catalysis with ceramic glass, eutectic mixture "choline chloride-urea", baker's yeast, allowing to obtain target pyridines in 80–98% yields. Another innovative segment is the expansion of the range of thiolating agents; in addition to thiols, dithioacetals and isothiuronium salts have been proposed. In our opinion, new discoveries await chemical researchers and pharmacists in the field of cyano-substituted seleno-pyridines.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgements

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