1. Introduction

The pyridine skeleton is a structural part of numerous natural alkaloids, metal complexes, and organic compounds, including drug molecules. 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. Previously, these reactions were considered in the context of classical multicomponent transformations and were included as single examples in some relevant reviews.

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-sulfanylpyridines. 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-arylidemalononitrile and thiols (3CR). Analysis of published data on the synthesis of 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile derivatives was performed using the SciFinder® database demonstrating 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. 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 $11 \pm 2$ nM; LUF5834, a partial adenosine A2B receptor agonist (EC$_{50}$ hA2B of $12 \pm 2$ nM); P453, a strong hA2B receptor agonist (EC$_{50}$ hA2B of $9.5 \pm 0.9$ nM); BAY60-6583, an adenosine A2B receptor agonist (EC$_{50}$ = 3 nM); and LUF-5831, an adenosine A1 receptor agonist ($K_i$ = 144 nM). 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), 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%. 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.

2-Amino-6-sulfanylpyridine-3,5-dicarbonitrile Cp-60 inhibits accumulation of PrPSc in scrapie-infected mouse neuroblastoma cells ScN2a (IC$_{50}$ 18.0 ± 1.5 mM). The molecule of II exhibits inhibitory activity in vitro against HIV-1 integrase (IC$_{50}$ = 4 μM). 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-...
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-arylidemalononitrile 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\(_3\)N,\(^{19}\) diazabicycloundecene (DBU),\(^{20}\) 1,4-diazabicyclo[2.2.2]octane (DABCO),\(^{21}\) 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) ionic liquid,\(^{22}\) KF·Al\(_2\)O\(_3\),\(^{23}\) tetrabutylammonium hydroxide (TBAH) or piperidine,\(^{24}\) nano-SiO\(_2\),\(^{25}\) piperidine/MW,\(^{26}\) ZnCl\(_2\)/MW,\(^{27}\) and KF·Al\(_2\)O\(_3\)/MW.\(^{28}\) Highly functionalized bis-pyridines 8 were...
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 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 \((\text{ZrOCl}_2\cdot8\text{H}_2\text{O}/\text{NaNH}_2, \text{ultrasonic irradiation )})\), \([\text{bmim}]\text{BF}_4\) 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) \((\text{choline chloride : urea (1 : 2)})\) 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 \((\text{CH}_3\text{S})_2\) in the pseudo-4CR 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 \textit{in situ} formation of arylmethyleneomalononitriles 1.\(^{90}\)
| No. | Catalyst [M], mol% or mol eq. | Solvent | Temperature, °C | Reaction time, min | Yield 4, % | Activity | Substitutes R or Ar/Alk | Reference |
|-----|-------------------------------|---------|----------------|-------------------|------------|----------|------------------------|-----------|
| 1   | Et$_3$N 3 drops on 1 mmol 5, nano-sized MgO 50 mg on 1 mmol 5 | C$_2$H$_5$OH | rt | 180–420 | 44–50 | — | R = Ph | 3 |
|     |                               |         |                |                   |            |          | Ar = Ph; 4-Cl-C$_6$H$_5$; 4-OMe-C$_6$H$_4$; 4-Me-C$_6$H$_4$ | |
| 2   | Et$_3$N 6 drops on 1 mmol 5  | C$_2$H$_5$OH | Reflux | 300 | 45–72 | Inhibitor | R = Ph | 30 |
|     |                               |         |                |                   |            |          | Ar = Ph; 3-NO$_2$-C$_6$H$_4$; 4-C$_6$H$_2$-C$_6$H$_5$; 2-Me-C$_6$H$_4$; 3-Py; 2-Cl-C$_6$H$_4$; 2-F-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 3-OMe-4-OMe-C$_6$H$_4$; 2-Cl-3-OMe-C$_6$H$_4$; 3-OMe-4-OMe-C$_6$H$_4$; 3-OMe-4-Cl-C$_6$H$_4$; 3-OMe-4-OMe-C$_6$H$_4$; 2-Br-4-OMe-5-OMe-C$_6$H$_4$; 3-Br-4-OMe-5-OMe-C$_6$H$_4$; 2-OMe-3-OMe-4-OMe-C$_6$H$_4$; 2-OMe-3-OMe-4-OMe-C$_6$H$_4$; 3,4,5-((OMe)$_3$)-C$_6$H$_3$; 3,5-((OMe)$_2$)-C$_6$H$_5$; f-NH; 2-NH; C$_6$H$_3$-CH$_2$-O-4-OMe-C$_6$H$_4$; 4-C$_6$H$_5$-CH$_2$-O-C$_6$H$_4$ | |
| 3   | Diethyamine 20 mol%           | C$_2$H$_5$OH | rt | 240–360 | 67–82 | Glucosidase | R = C$_6$H$_5$OH; Ph; Bn; 2-NH$_2$-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-Me-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-OMe-CH$_2$-C$_6$H$_4$ | 31 |
|     |                               |         |                |                   |            |          | Ar = Ph; 3,4-((OMe)$_2$)-C$_6$H$_5$; 4-Br-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 3-NO$_2$-C$_6$H$_4$; 4-Me-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 2-thienyl; 4-CN-C$_6$H$_4$; 4-CH$_2$-CH$_2$-C$_6$H$_4$; cyclo-3,4-(OCH$_2$O)-C$_6$H$_3$; 2-furyl; 2,6-(CH$_3$)$_2$-C$_6$H$_5$; 2,6-(Cl)$_2$-C$_6$H$_5$ | |
| 4   | Deep eutectic solvent (DES)   | DES     | 60            | 80–240           | 60–82     | —         | R = Ph; 4-Me-C$_6$H$_4$; 4-Br-C$_6$H$_4$ | 32 |
|     | (choline chloride : urea (1 : 2)), 0.5 mL on 1 mmol 5 |         |                |                   |            |          | Alk/Ar = n-C$_4$H$_9$; Ph; 4-Cl-C$_6$H$_4$; 3-NO$_2$-C$_6$H$_4$; 3-Br-C$_6$H$_4$; 2-thienyl; 2-furyl; 4-Me-C$_6$H$_4$; 4-Br-C$_6$H$_4$; 3-OMe-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 1-NH | |
| 5   | —                             | Water-choline hydroxide (1 : 4) | Reflux | 15–50 | 85–94 | —         | R = Ph | 33 |
|     |                               |         |                |                   |            |          | Ar = Ph; 4-OMe-C$_6$H$_4$; 4-NO$_2$-C$_6$H$_4$; 2-furyl; 4-Cl-C$_6$H$_4$; 4-Br-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-Me-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 2-thienyl; 3-NO$_2$-C$_6$H$_4$; 2-NO$_2$-C$_6$H$_4$; 2-NH | |
| 6   | Baker's yeast, 1 g on 9.4 mmol 5 | C$_2$H$_5$OH | rt | 40 | 82–93 | —         | R = Ph | 34 |
|     |                               |         |                |                   |            |          | Ar = Ph; 4-Br-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 2-NO$_2$-C$_6$H$_4$; 4-N(Me)$_2$-C$_6$H$_4$; 3,4-(OMe)$_2$-C$_6$H$_4$; 7-Me-C$_6$H$_4$ | |
| 7   | Water extract of banana       | C$_2$H$_5$OH | 65            | 10–45            | 80–90     | —         | R = Ph | 35 |
|     |                               |         |                |                   |            |          | Ar = Ph; 4-Cl-C$_6$H$_4$; n-C$_6$H$_4$; n-C$_6$H$_4$ | |
|     |                               |         |                |                   |            |          | Alk/Ar = Ph; 3-0H-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-Me-C$_6$H$_4$; 3-Br-C$_6$H$_4$; 2-Cl-C$_6$H$_4$; 4-F-C$_6$H$_4$; 4-NO$_2$-C$_6$H$_4$; 4-Py; 2-thienyl; 2-NH | |
| 8   | Tetra-n-butylammonium fluoride (1.0 mol L$^{-1}$ in THF), 10 mol% | H$_2$O | 80            | 45–630           | 62–96     | —         | R = Ph; 2-NH$_2$-C$_6$H$_4$ | 36 |
|     |                               |         |                |                   |            |          | Alk/Ar = Me; Et; Ph; 4-Cl-C$_6$H$_4$; 4-F-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 3,4-(OMe)$_2$-C$_6$H$_5$; 2-furyl; 2-thienyl; piperonyl | |
| 9   | o-iodosybenzoic acid, 10 mol% | H$_2$O | 70            | 90–150           | 69–83     | —         | R = Ph; 2-Br-C$_6$H$_4$; 2,4,6-Me$_3$-C$_6$H$_2$; 2-Me-C$_6$H$_4$; 4-Cl-C$_6$H$_4$ | 37 |
| No. | Catalyst [M], mol% or mol eq. | Solvent | Temperature, °C | Reaction time, min | Yield, % | Activity | Substitutes R or Ar/Alk | Reference |
|-----|--------------------------------|---------|----------------|-------------------|----------|----------|-------------------------|----------|
| 10  | Diethylamine, 20 mol% → Dess− | C₂H₅OH → DMF | rt              | 1.5–2.5           | 90–96    |          | Ar = Ph; 4-Me-C₆H₄; 4-OMe-C₆H₄; 3,4-(OMe)₂-C₆H₄; | [38]     |
|     | Martin periodinane (DMP) (1 |        |                 |                   |          |          | 4-NO₂-C₆H₄; 4-Br-C₆H₄; 4-Cl-C₆H₄; 2,6-(Cl)₂-C₆H₄; |          |
|     | mmol)                          |         |                 |                   |          |          | 3,4-Me₂-C₆H₃               |          |
| 11  | Piperidine                     | C₂H₅OH, CH₃CN | Reflux         | 180–1440          | 5–86     |          | Ar = 2,6-(Me)₂-C₆H₃; 2,6-(OMe)₂-C₆H₃; 2,6-Cl₂-C₆H₄; | [39]     |
|     | MW²                            |         |                 |                   |          |          | 2,6-F₂-C₆H₃              |          |
| 12  | Piperidine, 0.03 mL on 5 mmol 5 | C₂H₅OH | Reflux          | 180               | 57–86    |          | R = Ph; 4-Me-C₆H₄; 4-Cl-C₆H₄; 4-OMe- | [17]     |
|     |                                |         |                 |                   |          |          | C₆H₄                  |          |
| 13  | Imidazole, 0.2 mmol on 1 mmol 5 | C₂H₅OH | Reflux          | 30–120            | 81–92    |          | R = C₆H₄₃; Ph; 2-Me-C₆H₄ | [40]     |
|     |                                |         |                 |                   |          |          | 2-NH₂-C₆H₄; 2-CH₃-C₆H₄; 4-Cl-C₆H₄ |          |
| 14  | 1-Arginine, 20 mol%            | H₂O     | Reflux          | 30–90             | 81–96    |          | 2-NH₂-C₆H₄; 2-CH₃-C₆H₄; 4-Cl-C₆H₄ | [41]     |
|     |                                |         |                 |                   |          |          | 2-NH₂-C₆H₄; 2-CH₃-C₆H₄; 4-Cl-C₆H₄ |          |
| 15  | N₂N’-Di(1H-tetrazol-5-yl)-6H,12H- | EtOH   | Reflux          | 30–120            | 81–92    |          | Ar = Ph; 4-Me-C₆H₄; 4-Cl-C₆H₄; 4-OMe- | [42]     |
|     | ethanedibenzol [b,f][1,5]diazocine-3,9- |        |                 |                   |          |          | C₆H₄; 3,4-(OMe)₂-C₆H₄; 2,6-(Cl)₂-C₆H₄ |          |
|     | dicarboxamide, 5 mol%           |         |                 |                   |          |          | R = Ph; C₂H₅OH; 4-Me-C₆H₄; 4-Cl-C₆H₄; 4-OMe- |          |
| 16  | Choline methoxide, 5-10 mol%    | H₂O-C₂H₅OH (7 : 3) | Reflux     | 50–60             | 20–40    |          | R = Ph; 4-Me-C₆H₄; 4-Cl-C₆H₄; 4-OMe- | [43]     |
|     |                                |         |                 |                   |          |          | C₆H₄; 4-OMe-C₆H₄; 4-Br-C₆H₄ |          |
|     | Nanomaterial-based catalysts    |         |                 |                   |          |          |                                  |          |
| 17  | Nano-CaO, 0.01 g on 1 mmol 5   | H₂O-C₂H₅OH (1 : 1) | 50              | 80–150            | 70–92    |          | R = Ph; 4-Me-C₆H₄; 4-Br-C₆H₄; 4-OMe-C₆H₄; | [44]     |
|     |                                |         |                 |                   |          |          | 3,4-(OMe)₂-C₆H₄; 4-NO₂-C₆H₄; 3-Me-C₆H₄; 4-Me-C₆H₄; 4-CN-C₆H₄; 3-OMe-C₆H₄; 4-OMe-C₆H₄; |          |
| 18  | SnO nanoparticles, 6 mol%       | C₂H₅OH (abs.) | 60              | 54–142            | 79–92    |          | R = Ph; 4-Me-C₆H₄; 4-OMe-C₆H₄; 4-NO₂-C₆H₄; | [45]     |
|     |                                |         |                 |                   |          |          | 3-Me-C₆H₄; 4-OMe-C₆H₄; 4-NO₂-C₆H₄; 4-CI-C₆H₄; 3-CH₂-C₆H₄; 4-OMe-C₆H₄; 4-Br-C₆H₄ |          |
| 19  | Cul nanoparticles, 10 mol%      | C₂H₅OH | 60              | 85–200            | 70–94    |          | R = C₂H₅OH; Ph; 4-Me-C₆H₄; 4-OMe-C₆H₄ | [46]     |
| No. | Catalyst [M], mol% or mol eq. | Solvent | Temperature, °C | Reaction time, min | Yield, % | Activity | Substitutes R or Ar/Alk | Reference |
|-----|-------------------------------|---------|----------------|-------------------|----------|----------|------------------------|-----------|
| 20  | ZnO nanoparticles, 0.015 g on 1 mmol 5, 20 mol% | C₂H₅OH | 50 | 80-150 | 75-94 | | | 47 |
| 21  | Nanocrystalline MgO (NAP-MgO), 0.1 g on 1 mmol 5 | C₂H₅OH | 50 | 120-540 | 41-69 | | | 48 |
| 22  | Heterogeneous nanocatalyst Cu[n]/l-His@Fe₃O₄ | H₂O | 80 | 60 | 86-95 | | | 49 |
| 23  | Nano-TiO₂, 5 mol% 0.06 g on 1 mmol 5 | C₂H₅OH | Reflux | 14-27 | 89-97 | | | 50 |
| 24  | | | | | | | | |
| 25  | | | | | | | | |
| 26  | Co⁴⁺[macrocyclic Schiff base ligand containing 1,4-diazepane] immobilized on Fe₃O₄ nanoparticles (Fe₃O₄@Co⁴⁺), 0.02 g on 1 mmol 5 | | | | | | | |
| No. | Catalyst [M], mol% or mol eq. | Solvent | Temperature, °C | Reaction time, min | Yield, % | Activity | Substitutes R or Ar/Alk | Reference |
|-----|--------------------------------|---------|-----------------|-------------------|----------|----------|------------------------|-----------|
| 27  | NH₄OH, 12 mol%                | MeOH (abs.) | rt              | 360              | 75–90    | —        | R = Ph                 | 55        |
|     |                                |          |                 |                   |          |          | Ar = Ph; 4-Cl-C₆H₄; 2-Cl-C₆H₄; 4-OMe-C₆H₄; 2-NO₂-C₆H₄ |          |
| 28  | NH₄OH, 12 mol%                | MeOH (abs.) | rt              | 360              | 60–90    | —        | R = Ph                 | 56        |
|     |                                |          |                 |                   |          |          | Ar = Ph; 4-Cl-C₆H₄; 2-Cl-C₆H₄; 4-OMe-C₆H₄; 2-NO₂-C₆H₄; 3,4-(OMe)₂-C₆H₄; 2-NO₂-C₆H₄ |          |
| 29  | H₂BO₃, 15 mol%, CTAB, 10 mol% | H₂O     | 80              | 25–50            | 79–92    | Adsorption and anti-corrosion activity | R = Ph; 4-NO₂-C₆H₄; 4-OMe-C₆H₄ | 58        |
|     |                                |          |                 |                   |          |          | Ar = Ph; 4-Cl-C₆H₄; 4-F-C₆H₄; 4-OMe-C₆H₄; 4-HO-C₆H₄; 4-NO₂-C₆H₄; 4-Me-C₆H₄; 4-HO-3-OMe-C₆H₄; 3,4-(OMe)₂-C₆H₄; piperonyl; 2-furyl; 2-thienyl |          |
| 30  | H₂BO₃, 15 mol%, CTAB, 10 mol% | H₂O     | 80              | —                | —        |          | R = Ph                 | 59        |
|     |                                |          |                 |                   |          |          | Ar = Ph; 4-Cl-C₆H₄; 4-F-C₆H₄; 4-OMe-C₆H₄; 4-HO-C₆H₄; 4-NO₂-C₆H₄; 4-Me-C₆H₄; 4-HO-3-OMe-C₆H₄; 3,4-(OMe)₂-C₆H₄; piperonyl; 2-furyl; 2-thienyl |          |
| 31  | Phosphotungstic acid, 2 mol%, | H₂O     | 80              | 30–50            | 70–93    | Anti-bacterial and anti-neoplastic activities | R = Ph; 4-Cl-C₆H₄; 4-F-C₆H₄; 4-OMe-C₆H₄; 4-HO-C₆H₄; 4-NO₂-C₆H₄; 4-Me-C₆H₄; 4-HO-3-OMe-C₆H₄ | 60        |
|     | cetrimonium bromide, 10 mol%  |          |                 |                   |          |          | Ar = Ph; 4-Cl-C₆H₄; 4-F-C₆H₄; 4-OMe-C₆H₄; 4-HO-C₆H₄; 4-NO₂-C₆H₄; 4-Me-C₆H₄; 4-HO-3-OMe-C₆H₄; 3,4-(OMe)₂-C₆H₄; piperonyl; 2-furyl; 2-thienyl |          |
| 32  | KOH, 10 mol%                  | C₂H₅OH  | rt              | 60               | 25–40    |          | R = C₆H₄; Ph; Bn; 2-NH₂-C₆H₄; 2-Me-C₆H₄ | 61        |
| 33  | KOH, 10 mol%                  | C₂H₅OH  | rt              | 30–90            | 71–90    |          | R = C₆H₄; Ph; Bn; 2-NH₂-C₆H₄; 2-Me-C₆H₄ | 61        |
| 34  | NaOH, 1 mol eq., )))))) (40 kHz, 250 W) | C₂H₅OH  | rt              | 90–120           | 90–96    |          | Ar = Ph; 4-OMe-C₆H₄; 4-Br-C₆H₄; 4-CH₃-C₆H₄; 4-C₆H₄; 4-CH₃-C₆H₄; 3-NO₂-C₆H₄; C₆H₄; β-C₆H₄; C₆H₄; C₆H₄ | 62        |
| 35  | NaCl, 15 mol%                 | H₂O     | Reflux          | 2–180            | 18–90    |          | R = Ph                 | 63        |
|     | NaCl, 15 mol%, )))))) f       |          | Reflux          | 20–35           | 22–92    |          | Ar = Ph; 4-OMe-C₆H₄; 4-Br-C₆H₄; 4-CH₃-C₆H₄; 3-NO₂-C₆H₄; C₆H₄; β-C₆H₄; C₆H₄; C₆H₄ | 63        |
| 36  | K₂CO₃, 20 mol%, KMnO₄ 1.1 mol eq. | H₂O-C₂H₅OH (1 : 1) | Reflux          | 45–180         | 60–90    |          | Ar = Ph; 4-OMe-C₆H₄; C₆H₄ | 64        |
|     |                                |          |                 |                   |          |          | Ar = Ph; 4-OMe-C₆H₄; C₆H₄ | 64        |
| 37  | K₂CO₃, 10 mol%                | PEG-400 | 40              | 1–60             | 82–92    |          | R = Ph; 4-Br-C₆H₄; 4-OMe-C₆H₄; 2-NH₂-C₆H₄ | 65        |
| No. | Catalyst [M], mol% or mol eq. | Solvent | Temperature, °C | Reaction time, min | Yield, % | Activity | Substitutes R or Ar/Alk | Reference |
|-----|-------------------------------|---------|-----------------|-------------------|----------|----------|-------------------------|-----------|
| 38  | K$_2$CO$_3$, 1 mol eq., grinding in a pestle | Solvent free reaction conditions | rt | 20–35 | 82–92 | Antibacterial activity* | Alk/Ar = Ph; 4-Me-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-Br-C$_6$H$_4$; 3-NO$_2$-C$_6$H$_4$; 4-NO$_2$-C$_6$H$_4$; 2-thienyl; 2-furyl; 3-HO-C$_6$H$_4$; 4-HO-C$_6$H$_4$ | R = 2-mercaptoprydine |
| 39  | NaHCO$_3$, 10 mol% | H$_2$O-C$_2$H$_5$OH (1 : 1) | 110 | 8 | 87–93 | | | |
| 40  | 10% aqueous suspension of aluminum oxide | H$_2$O | rt | 50–100 | 79–90 | | | |
| 41  | Sc(OTf)$_3$, 5 mol% | C$_2$H$_5$OH | Reflux | 120 | 65–85 | | | |
| 42  | CH$_3$COONa, 12 mol%, MW [280 W] | MeOH (abs.) | — | 3–12 | 62–92 | | | |
| 43  | C$_6$H$_5$COONa, 10 mol% | PEG-400 : H$_2$O (1 : 1) | 50 → 70 | 90–110 | 82–88 | | | |
| 44  | Cs$_2$CO$_3$, 5 mol% and tetra-n-butylammonium bromide, 5 mol% | CH$_3$OH | rt | 180 | 85–92 | | | |
| 45  | Zn(n) or Cd(n) metal–organic frameworks, 2 mol% | Solvent free reaction conditions [Bmim][BF$_4$] | rt | 5–20 | 90–98 | | | |
| 46  | | | | | | | |
| No. | Catalyst [M], mol% or mol eq. | Solvent | Temperature, °C | Reaction time, min | Yield, % | Activity | Substitutes R or Ar/Alk | Reference |
|-----|-------------------------------|---------|----------------|-------------------|---------|----------|--------------------------|-----------|
| 47  | Functionalized organosilane with spherical mesoporous silica nanoparticles with grafted piperidine, 20 mg on 1 mmol 5 | H₂O | Reflux | 180–360 | 76–95 | — | Ar = Ph; 2-NO₂-C₆H₄; 4-Me-C₆H₄; 4-Br-C₆H₄; 2-furyl | 75 |
| 48  | Propylphosphonium hydrogen carbonate ionic liquid supported on nano-silica (PPHC_nSiO₂) (0.7 mol%) | Solvent free reaction conditions | 50 | 20–33 | 80–95 | — | R = Ph, 3-Cl-C₆H₄; 2-NH₂-C₆H₄; 4-Me-C₆H₄ | 76 |
| 49  | Silica-bonded N-propyldiethylenetriamine, 0.1 g on 1 mmol 5 | C₂H₅OH | rt | 30–45 | 75–90 | — | R = 2-NH₂-C₆H₄; 4-Me-C₆H₄; Ph | 77 |
| 50  | 2-Hydroxyethylammonium sulphonate immobilized on γ-Fe₂O₃ nanoparticles (γ-Fe₂O₃-2-HEAS), 0.08 g on 1 mmol 5 | Solvent free reaction conditions | 50 | 5–20 | 79–91 | — | R = n-BuPh; 4-Cl-C₆H₄; 4-Me-C₆H₄; 4-OMe-C₆H₄; 4-C₆H₄(CH₂)₂ | 78 |
| 51  | 2-Hydroxyethylammonium acetate immobilized on Fe₂O₃ nanoparticles (Fe₂O₃-2-HEAS), 1 mol%, 0.016 g on 1 mmol 5 | Solvent free reaction conditions | 70 | 5–15 | 80–90 | — | R = n-Bu; Ph; 4-Cl-C₆H₄; 4-Me-C₆H₄; 4-OMe-C₆H₄ | 79 |
| 52  | Molecular sieves (MS 4A), 200 mg on 1 mmol 5, (35 kHz, 200 W) | H₂O | Reflux | 40–120 | 78–91 | — | R = Ph; 2-NH₂-C₆H₄; 4-Me-C₆H₄ | 80 |
| 53  | Na₂SiO₃ 5 mol% | C₂H₅OH | rt | 60 | 78–82 | — | R = Ph; 3-Cl-C₆H₄; 4-Cl-C₆H₄; 4-OMe-C₆H₄; 4-C₆H₄(CH₂)₂ | 81 |
| 54  | Graphene oxide-TiO₂ (GO-TiO₂), 20 mg on 1 mmol 5 | H₂O | rt | 60–120 | 81–89 | — | R = Ph | 82 |
| No. | Catalyst [M], mol% or mol eq. | Solvent | Temperature, °C | Reaction time, min | Yield, % | Activity | Substitutes R or Ar/Alk | Reference |
|-----|-----------------------------|---------|-----------------|-------------------|----------|----------|-------------------------|-----------|
| 55  | Ceramic glass, 20 mg on 1 mmol | H$_2$O  | Reflux          | 120               | 76-95    |          | Ar = Ph; 4-Br-C$_6$H$_4$; 2-OH-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-CHO-C$_6$H$_4$; 2-NO$_2$-C$_6$H$_4$; 2-OH-5-Br-C$_6$H$_4$; 2,3-{OH}$_2$-C$_6$H$_4$; 4-CF$_3$-C$_6$H$_4$ | 83        |
| 56  | Dolomite limestone, 5.0 mass%, (3.5 kHz, 160/640 W) | H$_2$O-C$_2$H$_5$OH (1 : 1) | 45-50            | 30-45            | 90-98    |          | Ar = Ph; 3-Cl-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-Br-C$_6$H$_4$; 2-NH$_2$          | 84        |
|     | Ionic liquids              |         |                 |                   |          |          | R = 2-Py; Ph | Ar = Ph; 3-OMe-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 3,4,5-(OMe)$_3$-C$_6$H$_4$ |           |
| 57  | [Bmim]Br, 1.2 mmol         | —       | 120             | 4-12              | 75-86    |          | R = Ph | Ar = Ph; 3-Br-C$_6$H$_4$; 4-Br-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-Me-C$_6$H$_4$ | 85        |
| 58  | 1-(2-Aminoethyl)pyridinium hydroxide, 1.0 mmol | H$_2$O-C$_2$H$_5$OH (1 : 1) | rt               | 30-60            | 76-89    |          | Ar = Ph; 4-OMe-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-NO$_2$-C$_6$H$_4$ | 86        |
| 59  | —                           | [Bmim]BF$_4$ | 50              | 20-30            | 78-89    |          | R = Ph; 2-NH$_2$-C$_6$H$_4$ | Ar = Ph; 3-Br-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-NO$_2$-C$_6$H$_4$; 4-OMe-C$_6$H$_4$ | 87        |
| 60  | 2-Hydroxyethylammonium acetate, 0.5 mL on 1 mmol | H$_2$O  | rt              | 5                | 70-96    |          | R = Ph; n-Bu, 4-OMe-C$_6$H$_4$; 4-Cl-C$_6$H$_4$ | Ar = Me; Ph; Bn, 2-NH$_2$; 3-Py; 4-Cl-C$_6$H$_4$; 4-OMe-C$_6$H$_4$; 4-CHO-C$_6$H$_4$ | 88        |

* No information about the frequency and power of the device.

** Bacillus subtilis, Clostridium tetani, Streptococcus Pneumonia, Escherichia coli, Salmonella typhi, Vibrio cholera, Aspergillus Fumigates, Candida albicans.**

A549 (adenocarcinomic human), MCF-7 (breast cancer cell), MDA-MB-231 (human breast cancer), HBE [human bronchial epithelium].

Staphyloccocus aureus, Staphylococcus epidermis, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa; MCF-7 (adenocarcinoma), SNB-19 (glioblastoma), HCT-116 (colon colorectal carcinoma), HSF (human foreskin fibroblast).

Micrococcus luteus, Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia.
3. Design, synthesis of biologically active compounds with 2-amino-6-sulfanylpyridine-3,5-dicarbonitrile scaffold

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

In the case where thioglycolic acid esters \(^\text{15}\) were used as the starting reactants, it was impossible to isolate the target pyridines \(^\text{17}\). However, the synthesis of compounds \(^\text{17}\) from 2-chloropyridines \(^\text{16}\) follows the \(S_N\text{Ar}\) mechanism and proceeds under milder conditions, involving thioglycolates \(^\text{15}\) and arylthiols \(^\text{2}\).\(^\text{93}\)

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

Some of compounds \(^\text{19}\) had a cytotoxic activity against some types of tumor cells: MCF-7 (IC\(_{50}\) = 2.8 \(\mu\)M) (human breast cancer cell line), SNB-19 (IC\(_{50}\) = 5.1 \(\mu\)M) (glioblastoma cell line), and HCT-116 (IC\(_{50}\) = 2.8 \(\mu\)M) (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 \(\mu\)M, which indirectly attests to poor selectivity of their action and toxicity in experiments \textit{in vivo}.
In order to enhance the biological activity of target sulfa-
nylpyridines, 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).\textsuperscript{24} Primary screening for the in vitro antimicrobial
activity revealed the highest activity (MIC = 15.625 \( \mu \text{g mL}^{-1} \))

Scheme 8  Synthesis of 2-amino-3,5-dicarbonitrile-6-sulfonylpyridines 29 containing 1,3,4-oxadiazole moiety exhibiting antimicrobial activity.
against *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger* for compounds with phenyl and 3-chlorophenyl substituents at the sulfur atom in pyridine. A proposed route towards antimicrobial agents includes the synthesis of hybrid structures containing 2-(ArS)-amino-3,5-dicyanopyridine and 2-(ArS)-quinoline moieties (Scheme 9). For this purpose, 3-formyl-2-phenylsulfanylquinoline, obtained by the reaction of 2-chloro-3-formylquinoline with thiols, was used as the aldehyde component in pseudo-4-CR. The resulting compounds 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 for the synthesis of piperidinium salts is based on the 3-CR of cyanothioacetamide with malononitrile and aromatic aldehydes 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. The obtained piperidinium salts of dihydropyridinethiones were treated, without isolation, with 2,3,4,6-tetra-O-acetyl-α-D-glucose.
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 anti-cancer 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-propynylbenzaldehyde 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 NaN₃. An additional screening of molecule 43 revealed the activity against the human breast carcinoma cells (MCF-7) with IC₅₀ = 40 μM mL⁻¹.

Recently, a method was proposed for the preparation of functionalized 3,5-dicyanopyridines 46, a structural analogue of capadenoson (Scheme 12). Fluorine-containing compound 46 (LUF7746) was found to be a partial adenosine A₁ receptor agonist with E₅₀ = 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. This approach is based on the transformation of the thiophenyl group in pyridines 4 into a mercapto group on treatment with Na₂S followed by hydrolysis to thiol 48. The subsequent alkylation of 2-mercaptopyridine 48 with 2-(chloromethyl)-1H-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-1H-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-{[1H-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 ± 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). 80

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–nSiO2), which served as a heterogeneous catalyst. 78 A drawback of the proposed method is the three-stage preparation procedure of the PPHC–nSiO2 catalyst and that the ionic liquid contains phosphonium compounds, which is not quite consistent with green chemistry principles, as noted in the literature. 80

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 multicompontent 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, ionic 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

This work was financially partly supported by the Russian Science Foundation (project no. 19-73-00070) and within the framework of the State Assignment AAAA-A19-11902290010-9.

References

1 (a) S. X. Lin, M. A. Curtis and J. Sperry, Bioorg. Med. Chem., 2020, 28, 115820, DOI: 10.1016/j.bmc.2020.115820; (b) M. N. Zafar, A. H. Atif, M. F. Nazar, S. H. Sumrara, Gul-E-Saba and R. Paracha, Russ. J. Coord. Chem., 2016, 42, 1–18, DOI: 10.1134/S1070328416010097; (c) L. Yet, Six-membered ring systems: pyridine and benzo derivatives, in Progress in Heterocyclic Chemistry, ed. G. W. Gribble and J. A. Joule, Elsevier, 2020, vol. 31, p. 431.
2 M. Baumann and I. R. Baxendale, Beilstein J. Org. Chem., 2013, 9, 2265–2319, DOI: 10.3762/bjoc.9.265.
3 F. Alininghizadeh, M. Zahedifar, M. Seifi and H. Sheibani, J. Braz. Chem. Soc., 2016, 27, 663–669, DOI: 10.3935/0103-5053.20150309.
4 (a) G. M. Ziarani, Z. Khelkordi and P. Gholamzadeh, Mol. Diversity, 2020, 24, 771–820, DOI: 10.1007/s11030-019-00964-1; (b) M. Driowya, A. Saber, H. Marzag, L. Demange, R. Benhida and K. Bougrin, Molecules, 2016, 21, 492, DOI: 10.3390/molecules21040492; (c) Y. Gu, Green Chem., 2012, 14, 2091–2128, DOI: 10.1039/C2GC35635J; (d) C. Allais, J.-M. Grassot, J. Rodriguez and T. Constantieux, Chem. Rev., 2014, 114, 10829–10868, DOI: 10.1021/cr500099b.
5 SciFinder – chemical abstracts service, https://scifinder-n.cas.org, accessed on September 2020.
6 (a) D. D. Ben, C. Lambertucci, M. Buccioni, A. M. Nava, G. Marucci, A. Spinaci and R. Volpini, Pharmaceuticals, 2019, 12, 150, DOI: 10.3390/ph12040150; (b) K. A. Jacobson, D. K. Tosh, S. Jain and Z.-G. Gao, Front. Cell. Neurosci., 2019, 13, 124, DOI: 10.3389/fncel.2019.00124; (c) P. G. Baraldi, M. A. Tabrizi, F. Frutarolo, R. Romagnoli and D. Petti, Purinergic Signalling, 2008, 4, 287–303, DOI: 10.1007/s11302-008-0997-z.
7 L. C. W. Chang, J. K. von Frijtag Drabbe Künzel, T. Mulder-Krieger, R. F. Spanjersberg, S. F. Roerink, G. van den Hout, M. W. Beukers, J. Brussee and A. P. Ijzerman, J. Med. Chem., 2005, 48, 2045–2053, DOI: 10.1021/jm049597+.
8 M. W. Beukers, L. C. W. Chang, J. K. von Frijtag Drabbe Künzel, T. Mulder-Krieger, R. F. Spanjersberg, J. Brussee and A. P. Ijzerman, J. Med. Chem., 2004, 47, 3707–3709, DOI: 10.1021/jm049947s.
9 M. Betti, D. Catarzi, F. Varano, M. Falsini, K. Varani, F. Vincenzi, D. B. Diego, C. Lambertucci and V. Colotta, Eur. J. Med. Chem., 2018, 150, 127–139, DOI: 10.1016/j.ejmech.2018.02.081.
10 L. H. Heitman, T. Mulder-Krieger, R. F. Spanjersberg, J. K. von Frijtag Drabbe Künzel, A. Dalpiaz and A. P. Ijzerman, Br. J. Pharmacol., 2006, 147, 533–541, DOI: 10.1038/sj.bjp.0706655.
11 (a) D. Meibom, B. Albrecht-Küpper, N. Diedrichs, W. Hübsch, R. Kast, T. Krämer, U. Krenz, H.-G. Lerchen, J. Wittendorf, P. G. Nell, F. Süssemeier, A. Vakalopoulos and K. Zimmermann, ChemMedChem, 2017, 12, 728–737, DOI: 10.1002/cmdc.201700838; (b) J.-A. Baltos, E. A. Vecchio, M. A. Harris, C. X. Qin, R. H. Ritchie, A. Christopoulos, P. J. White and L. T. May, Front. Biosci. Eng., 2019, 11, 79–89, DOI: 10.1016/j.jbecp.2017.03.014.
12 E. A. Vecchio, M. A. Harris, C. X. Qin, R. H. Ritchie, A. Christopoulos, P. J. White and L. T. May, Biochem. Pharmacol., 2017, 135, 79–89, DOI: 10.1016/j.bcp.2017.03.014.
94 Y. O. Bhola and Y. T. Naliapara, World Sci. News, 2019, **117**, 221–227.
95 M. B. Kanani and M. P. Patel, Med. Chem. Res., 2013, **22**, 2912–2920, DOI: 10.1007/s00044-012-0292-7.
96 F. S. Hosseini, M. Bayat and M. Masoumi, J. Sulfur Chem., 2019, **40**, 65–74, DOI: 10.1080/17415993.2018.1523412.
97 H.-A. S. Abbas, W. A. El Sayed and N. M. Fathy, Eur. J. Med. Chem., 2010, **45**, 973–982, DOI: 10.1016/j.ejmech.2009.11.039.
98 T. V. Soumya, C. M. Ajmal and D. Bahulayan, Bioorg. Med. Chem. Lett., 2017, **27**, 450–455, DOI: 10.1016/j.bmcl.2016.12.044.
99 X. Yang, M. A. Dilweg, D. Osemwengie, L. Burggraaff, D. van der Es, L. H. Heitman and A. P. IJzerman, Biochem. Pharmacol., 2020, **180**, 114144, DOI: 10.1016/j.bcp.2020.114144.
100 D. Catarzi, F. Varano, K. Varani, F. Vincenzi, S. Pasquini, D. D. Ben, R. Volpini and V. Colotta, Pharmaceuticals, 2019, **12**, 159, DOI: 10.3390/ph12040159.
101 M. Betti, D. Catarzi, F. Varano, M. Falsini, K. Varani, F. Vincenzi, S. Pasquini, L. di Cesare Mannelli, C. Ghelardini, E. Lucarini, D. D. Ben, A. Spinaci, G. Bartolucci, M. Menicatti and V. Colotta, J. Med. Chem., 2019, **62**, 6894–6912, DOI: 10.1021/acs.jmedchem.9b00106.
102 G. Cevasco and C. Chiappe, Green Chem., 2014, **16**, 2375–2385, DOI: 10.1039/C3GC42096E.