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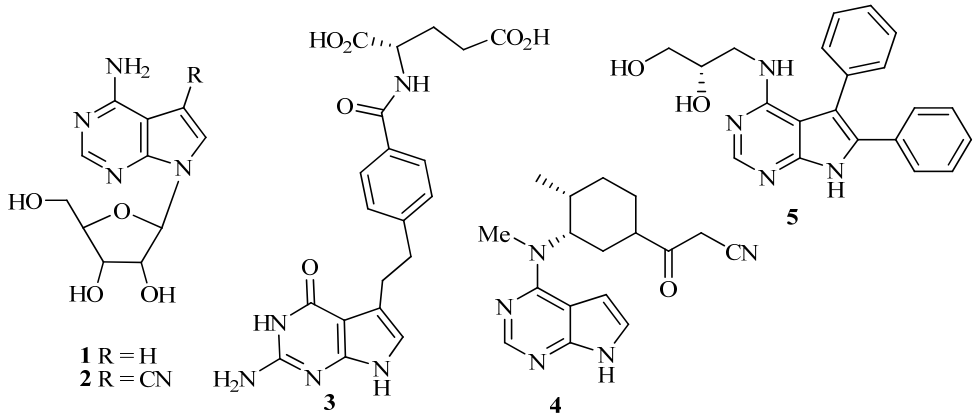
MULTICOMPONENT SYNTHESIS OF THE MEDICINALLY IMPORTANT PYRROLO[2,3-*d*]PYRIMIDINE SCAFFOLD

(MINIREVIEW)

Multicomponent reactions are emerging as a powerful tool in the synthesis of heterocyclic privileged medicinal scaffolds. This highlight describes a recently developed approach to the construction of the medicinally important pyrrolo[2,3-*d*]pyrimidine scaffold using a one-pot synthesis from commercially available starting materials via novel multicomponent reactions.

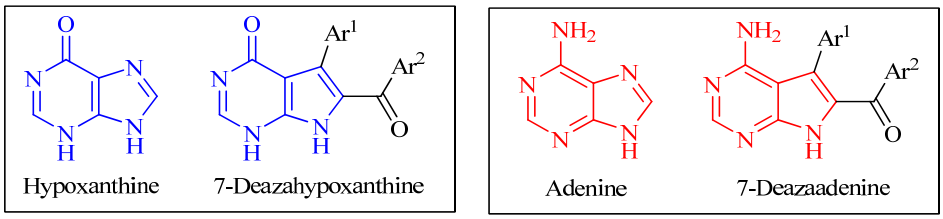
Keywords: 7-deazapurines, drug discovery, heterocycle, multicomponent reactions, privileged scaffold.

7-Deazapurine (pyrrolo[2,3-*d*]pyrimidine) is an important structural motif occurring naturally in nucleic acids [1] or as part of monomeric ribonucleosides, such as tubercidin (**1**) or toyocamycin **2** [2]. Heterocycles containing pyrrolo-[2,3-*d*]pyrimidine moiety are also found in approved (e. g., folate antimetabolite pemetrexed (**3**) [3] and Janus kinase JAK3 inhibitor tofacitinib (**4**) [4]) or experimental drugs (e. g., checkpoint kinase Chk1 inhibitor DF2 (**5**) [5]). In addition, numerous literature reports describe diverse biological activities associated with compounds based on this privileged purine-mimetic scaffold, including anti-inflammatory [6, 7], anticancer [8–13], antiviral [14–15], adenosine A1 and A3 receptor modulatory [16], adenosine kinase [17, 18], and dihydrofolate reductase inhibitory [19], among many others.

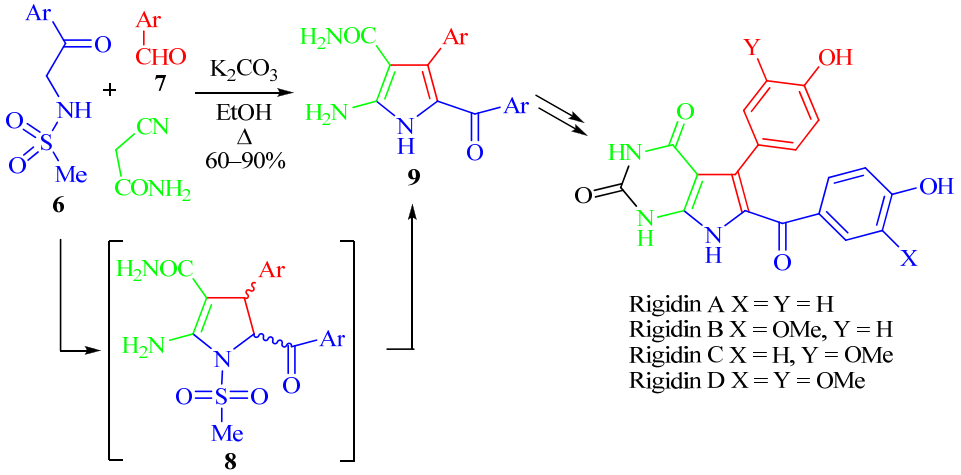


Commonly, pyrrolo[2,3-*d*]pyrimidines are synthesized by preparing a properly functionalized pyrrole [20–23] or pyrimidine [24–29] moiety and then carrying out a necessary ring-closure to construct the remaining ring [20–29]. Such transformations generally involve multistep synthetic sequences and are not easily adaptable to analog preparation for biological studies. Although multicomponent reactions leading to the construction of both pyrrole [30] and pyrimidine [31] rings

separately abound, until recently such processes constructing the entire 7-deazapurine system simultaneously were unknown. In a recent advance, Magedov and co-workers described a novel four-component process optimized for the preparation of 7-deazahypoxanthine and 7-deazaadenine skeletons [32]. Furthermore, the initial biological evaluation of these series of compounds revealed significant anticancer activity associated with the 7-deazahypoxanthine-based heterocycles [32].



This discovery originated from the previous synthetic work by Magedov's group aimed at a general total synthesis of marine alkaloid rigidins A, B, C, and D, in which a three-component reaction to construct the pyrrole fragment of these natural products was discovered [33]. This reaction involved a cyclocondensation of sulfonamides **6** with aldehydes **7** and cyanoacetamide to form intermediate pyrrolines **8**, which after a base-promoted elimination of the methanesulfonyl group afforded pyrroles **9**.

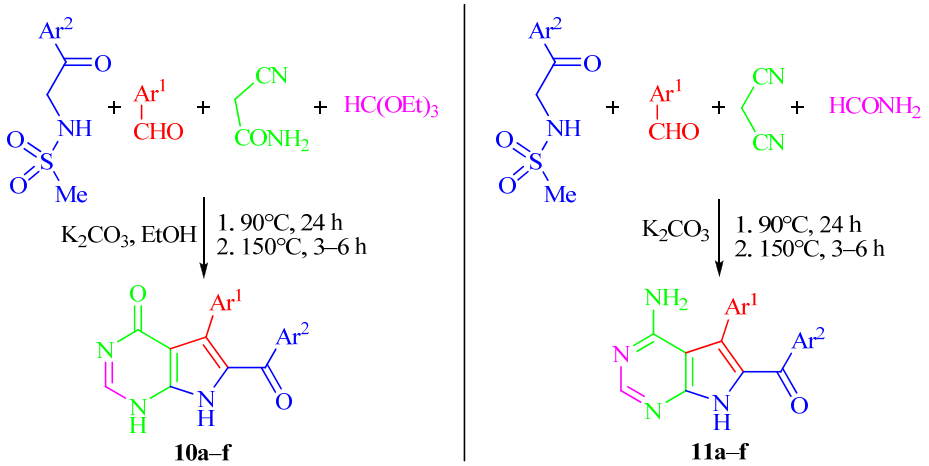


In a further development, Magedov and co-workers found that the use of a 1:1 mixture of EtOH and triethyl orthoformate solvents and specific temperature regime (heating at 90°C and then at 150°C leading to slow evaporation of ethanol) results in the formation of 7-deazahypoxanthines **10a–f** (Table 1, left). Furthermore, when the reaction is performed in formamide as a solvent, and cyanoacetamide is replaced with malononitrile, 7-deazaadenines **11a–f** are obtained (Table 1, right) [32].

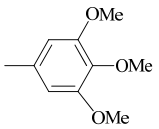
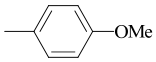
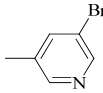
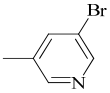
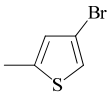
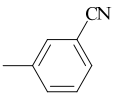
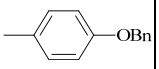
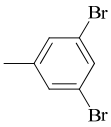
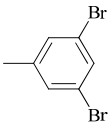
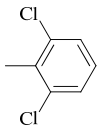
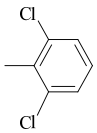
Electron-neutral (e. g., **10a** and **11a**), electron-rich (e. g., **10b** and **11b**), and electron-poor (e. g., **10c**, **10e**, **11c**, and **11e**) substrates react equally well. In addition, the reaction tolerates both heterocyclic (e. g., **10c**, **10d**, **11b**, and **11c**) and *o*,*o*-disubstituted (e. g., **10f** and **11f**) aromatic substituents. At present, the reaction involves the use of aromatic aldehydes and acylsulfonamides and has not been optimized for the utilization of aliphatic substrates prone to undergoing competing aldol processes.

Table 1

Four-component reactions leading to the formation of substituted 7-deazahypoxanthines 10a–f and 7-deazaadenines 11a–f



10a–f **11a–f**

Compound	Ar^1	Ar^2	Yield, %	Compound	Ar^1	Ar^2	Yield, %
10a	Ph	Ph	71	**11a**	Ph	Ph	48
10b			56	**11b**		Ph	85
10c		Ph	88	**11c**		Ph	66
10d		Ph	71	**11d**			54
10e		Ph	77	**11e**		Ph	58
10f		Ph	74	**11f**		Ph	72

Representative general procedure for the synthesis of 1*H*-pyrrolo[2,3-*d*]pyrimidin-4(7*H*)-ones (7-deazahypoxanthines) 10 [32]. To a solution of *N*-(2-oxo-2-arylethyl)-methanesulfonamide (0.676 mmol), selected aldehyde (0.879 mmol), and cyanoacetamide (0.072 g, 0.879 mmol) in a mixture of EtOH (2.5 ml) and $HC(OEt)_3$ (2.5 ml) was added anhydrous granulated K_2CO_3 (0.052 g, 0.372 mmol) in one portion. The mixture was purged with nitrogen for 5 min, and then heated at 90°C for 24 h under the nitrogen atmosphere. The formation of the intermediate pyrrole was monitored by TLC. After that the reaction temperature was increased to 150°C and the reaction mixture was heated for 3–6 h. The mixture was cooled to room temperature and the formed precipitate was collected by filtration and washed with EtOH (2 ml) and diethyl ether (2 ml) to give the desired 7-deazahypoxanthine **10**. An additional amount of the product was obtained by the evaporation of the mother liquor and purification of the residue by column chromatography with MeOH–CH_2Cl_2 from 1:40 to 1:20 gradient.

Table 2

Antiproliferative properties of rigidins* and synthetic 7-deazahypoxanthines [32] against cell lines representing cancers with dismal prognoses

7-Deazapurine	GI_{50} *in vitro* values, μM			
	Glioma		Carcinoma	Melanoma
	U373	Hs683	A549	SKMEL-28
Rigidin A	>100	>100	>100	>100
Rigidin C	39	44	53	43
10a	< 0.01	0.01	0.02	< 0.01
10c	0.03	0.02	0.03	0.02
10e	0.03	0.02	0.02	0.02

* Unpublished data.

Representative general procedure for the synthesis of 4-amino-7*H*-pyrrolo[2,3-*d*]-pyrimidines (7-deazaadenines) 11 [32]. To a solution of *N*-(2-oxo-2-arylethyl)methane-sulfonamide (2.0 mmol), selected aldehyde (2.6 mmol), and malononitrile (2.6 mmol) in formamide (2 ml) anhydrous granulated K_2CO_3 (0.167 g, 1.2 mmol) was added in one portion. The mixture was purged with nitrogen for 5 min, and then heated at 90°C for 24 h under the nitrogen atmosphere. The formation of the intermediate pyrrole was monitored by TLC. After that the reaction temperature was increased to 150°C and the reaction mixture was heated for 3–6 h. The mixture was cooled to room temperature and poured in water (30 ml). The formed precipitate was collected by filtration and washed with EtOH (2 ml) and diethyl ether (2 ml) to give the desired 7-deazaadenine **11**.

Due to the structural similarity of the deazapurines **10** and **11** with the marine alkaloids rigidins, which were reported to have antiproliferative and calmodulin-antagonistic activities [34, 35], the synthesized compounds were tested for these and other biological properties. Since rigidins exhibited only weak antiproliferative effects (double-digit micromolar or higher, Table 2), it was a thrilling discovery that the novel 7-deazahypoxanthines harbor a potent antiproliferative pharmaco-phore. Thus, selected compounds from this series **10a**,**c**,**e** exhibited nanomolar potencies when challenged with a minipanel of human cancer cell lines consisting of U373 glioblastoma, Hs683 anaplastic oligodendroglioma, A549 non-small-cell lung cancer and SKMEL-28 melanoma. It should be noted that these cell lines represent cancers known to be associated with dismal prognoses due to their intrinsic resistance to pro-apoptotic stimuli [36]. Thus, the rise in incidence of gliomas and melanomas has not been paralleled by improved therapeutic options over the years [37] and, therefore, the discovery of a novel 7-deazahypoxanthine-based pharmacophore capable of providing compounds with potency against these cell lines is significant. Noteworthily, compound **10a** exhibits single-digit nanomolar potencies against glioma and melanoma cells, and it is available using the discovered multicomponent process in one-pot from commercially available materials ($Ar^1 = Ar^2 = Ph$, Table 1).

In conclusion, the four-component synthesis developed by Magedov and co-workers represents the first construction of the entire privileged pyrrolo[2,3-*d*]-pyrimidine framework in one-pot and utilizes all commercially available starting materials. At present, two modifications of this process can be used to produce 7-deazahypoxanthine and 7-deazaadenine skeletons. Furthermore, the compounds based on the 7-deazahypoxanthine skeleton were found to possess nanomolar

antiproliferative effects against human cell lines serving as models for cancers with dismal prognoses. The advancement of these compounds as anticancer lead agents is underway in a number of collaborating laboratories.

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