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Alexandra Fillion, Sophie Vichier-Guerre, Paola Barbara Arimondo. Adenine, a Key Player in Biology and Medicinal Chemistry. *Comptes Rendus. Chimie*, 2024, 27 (S2), pp.1-18. 10.5802/crchim.279 . pasteur-04561306v1

HAL Id: pasteur-04561306

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Submitted on 26 Apr 2024 (v1), last revised 29 Apr 2024 (v2)

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Adenine, a Key Player in Biology and Medicinal Chemistry

L'adénine, un acteur majeur en biologie et en chimie médicinale

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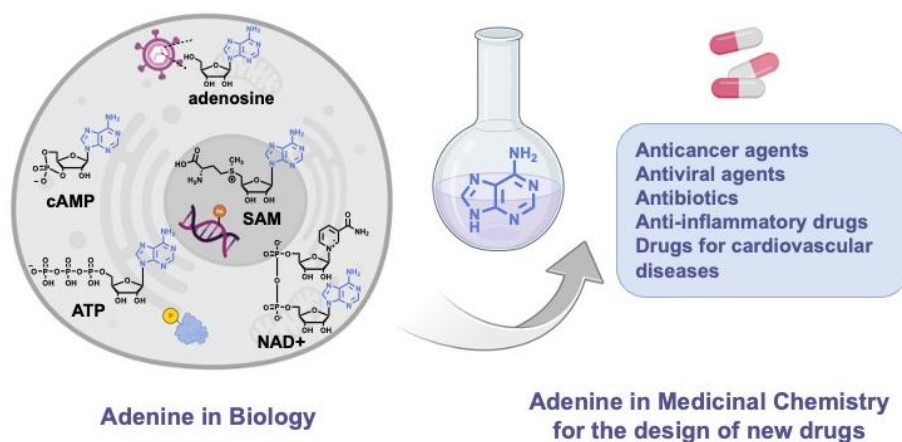
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25 **Abstract:**

26



27

28

29 Adenine is one of the most ubiquitous heterocycles in life. In addition of being one of the four
30 nucleobases constituting DNA and RNA, adenine is also contained in many biological
31 molecules (ATP, SAM, NAD, cAMP, coA...) that have fundamental roles in the functioning
32 of living systems, *e.g.* energy source, cofactors of enzymes and proteins. As such, the adenine
33 has naturally become a privileged scaffold explored in medicinal chemistry for biomedical
34 applications. Many chemical modifications and Structure-Activity Relationships studies have
35 been carried out on the adenine scaffold to result in potent analogues with various biological
36 activities. Today, numerous adenine-based inhibitors are used to treat a wide range of diseases
37 including cancer, viral and bacterial diseases. This review aims to introduce the adenine and
38 discuss adenine-based inhibitors, their design and use for different therapeutic targets through
39 examples of drugs and compounds that reached clinical and preclinical trials.

40

41 **Key words:** Adenine; medicinal chemistry; inhibitors; anticancer; antiviral and antibacterial
42 agents.

43

44 **Résumé :**

45

46 L'adénine est l'un des hétérocycles les plus représentés dans la nature. En plus d'être l'une des
47 quatre bases constituant l'ADN et l'ARN, elle est également présente dans de nombreuses
48 molécules biologiques (ATP, SAM, NAD, cAMP, coA...) qui jouent un rôle fondamental dans
49 le fonctionnement des systèmes vivants, comme source d'énergie, cofacteurs d'enzymes ou de
50 protéines. L'adénine est ainsi devenue un hétérocycle largement exploré en chimie médicinale
51 pour de nombreuses applications biomédicales. De multiples modifications chimiques
52 associées à l'étude de Relations Structure-Activité ont été réalisées sur le squelette de l'adénine
53 pour aboutir à des analogues puissants aux activités biologiques variées. Aujourd'hui, de
54 nombreux inhibiteurs analogues d'adénine sont utilisés pour traiter un large éventail de
55 maladies, comme le cancer et les maladies infectieuses. Cette revue a pour but de présenter
56 l'adénine dans son contexte biologique et de discuter d'exemples d'inhibiteurs constitués d'une
57 adénine (ou de l'un de ses analogues) en décrivant leur conception et utilisation pour différentes
58 cibles thérapeutiques.

59

60 **Mots clés :** adénine ; chimie médicinale ; inhibiteurs ; agents anticancéreux ; antiviraux et
61 antibiotiques.

62

63 **Introduction**

64

65 The purine ring system, and especially *adenine*, is one of the most ubiquitous natural
66 heterocyclic compounds and plays major roles in various biological processes. In addition of
67 being a nucleobase and building block of the genetic material and its transcription and
68 translation in proteins, adenine stores energy in the form of Adenosine TriPhosphate (ATP)
69 and is found in the structure of cofactors of many enzymes such as ATP, *S*-Adenosyl-*L*-
70 Methionine (SAM or AdoMet), Nicotinamide Adenine Dinucleotide (NAD), Flavin Adenine
71 Dinucleotide (FAD) and in substrates of metabolic pathways, as acetyl-Coenzyme A (acetyl-
72 CoA) (Fig. 1). ATP is both the source of energy at the cellular level, a precursor to DNA and
73 RNA synthesis and a cofactor of protein kinases to phosphorylate their substrates.[1] SAM is
74 used as methyl donor by MethylTransferases (MTases) to methylate histones, DNA, lipids and
75 small biological molecules.[2] NAD⁺ is a cofactor for redox reactions and has a central role in
76 energy metabolism. It is also a coenzyme for non-redox NAD⁺-dependent enzymes [CD38,
77 sirtuins and poly(ADP-ribose)] and is a substrate for Nicotinamide Adenine Dinucleotide
78 Kinases (NADK).[3] Some signaling molecules such as cyclic Adenosine MonoPhosphate
79 (cAMP) contain also an adenine scaffold. cAMP is an ubiquitous second messenger that
80 regulates various biological processes, interacting with protein effectors such as Protein Kinase
81 A (PKA), Exchange Proteins Activated by cAMP (EPACs) and Cyclic Nucleotide-Gated
82 (CNG) channels.[4]

83 Importantly, these biological pathways are deregulated in diseases and the
84 aforementioned protein families represent major therapeutic targets. Thus, the adenine scaffold
85 has been exploited to design and develop therapeutic agents.[5–7] Chemical modifications of
86 the adenine scaffold - giving *adenine analogues* – have been carried out to identify inhibitors
87 of these pathways deregulated in diseases. Kinases and MTases inhibitors, based on the adenine

88 scaffold are used for cancer treatment.[8,9] Adenosine analogues inhibiting DNA/RNA
 89 synthesis are widely utilized as anticancer and antiviral agents.[10,11] NAD Analogues are
 90 investigated to target NADK in the context of bacterial infection.[12] Finally, cAMP analogues
 91 are emerging as modulators of EPACs, playing a role in inflammation, diabetes and
 92 cardiovascular diseases.[13] Another example is the use of adenosine receptor agonists as
 93 anticancer agents.[14]

94

95 Herein, we review the highlights of the use of the adenine scaffold for the design of
 96 versatile therapeutic agents and its role in biological processes. This review is not meant to be
 97 exhaustive and presents its chemical modulation in Medicinal Chemistry through chosen
 98 examples of approved drugs and inhibitors in clinical trials and preclinical studies for each
 99 selected therapeutic target.

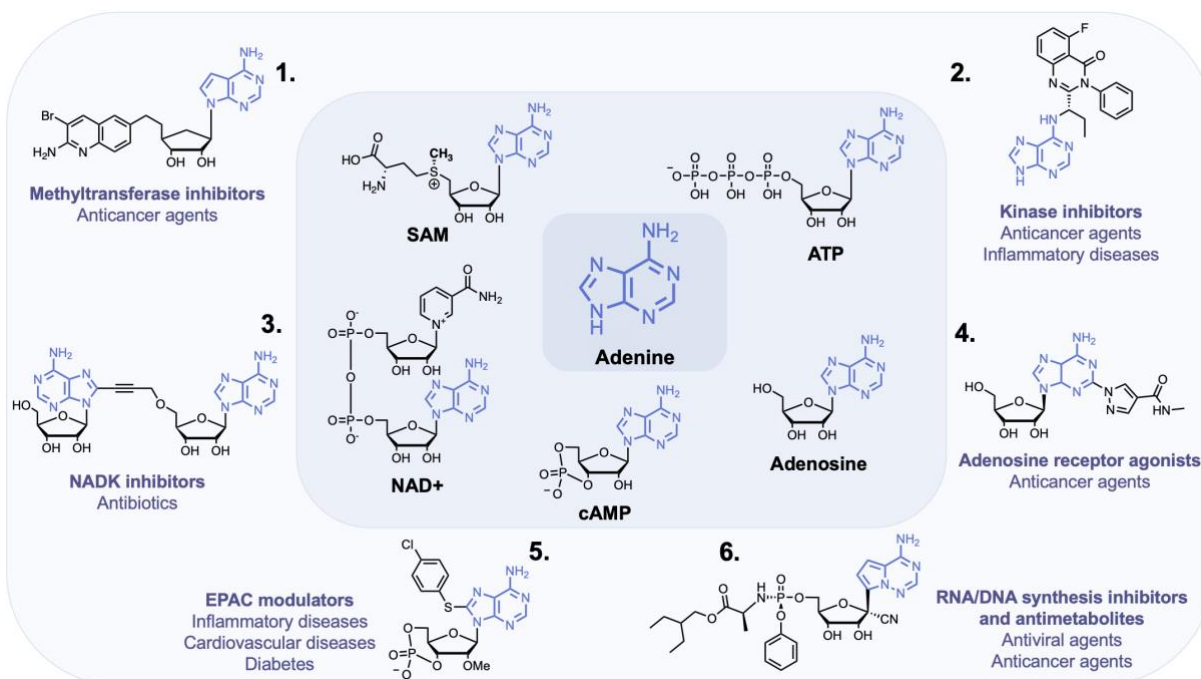


Figure 1. The adenine scaffold (in blue) in biological molecules and therapeutic agents.

104 **1. S-Adenosyl-L-Methionine/S-Adenosyl-L-Homocystein (SAM/SAH)**
105 **analogues to target SAM-dependent methyltransferases**

106

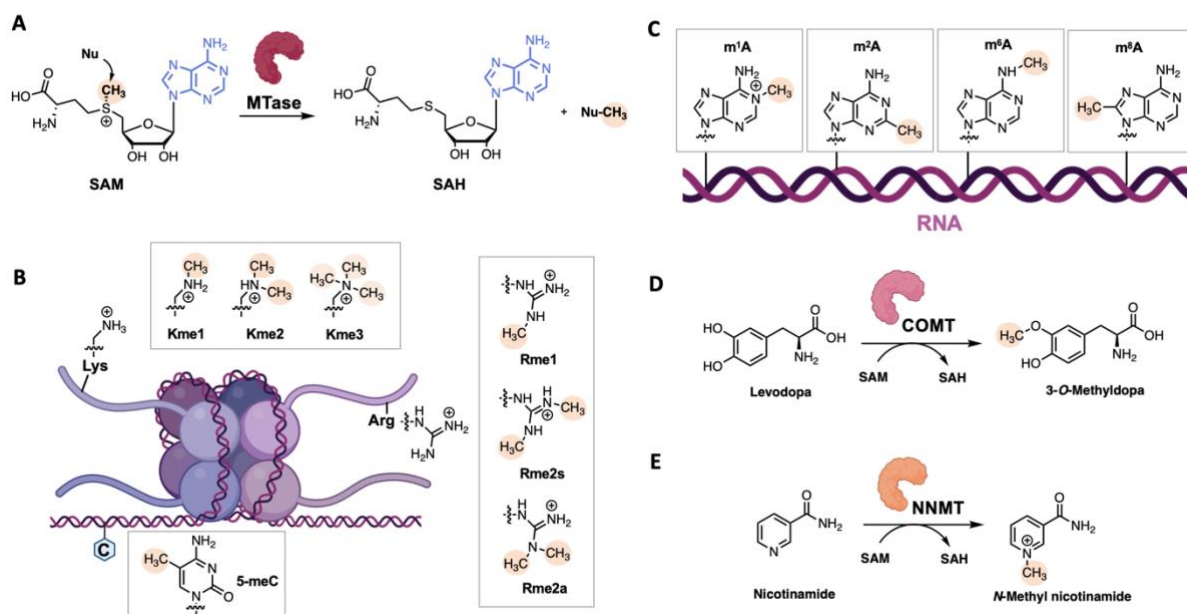
107 *S*-Adenosyl-*L*-Methionine is one of the most ubiquitous cofactors. It is mainly used by
108 the SAM-dependent MethylTransferases (MTases) as methyl donor to methylate their
109 substrates (DNA, RNA, proteins, carbohydrates and metabolites). These methylated substrates
110 contribute for example to the epigenetic regulation, protein function modulation, metabolites
111 synthesis and degradation etc...[15–19]

112 SAM is a hybrid compound of adenosine bonded to the sulfur atom of methionine. The
113 sulfonium group that bears the methyl group confers the SAM's reactivity. Under the catalytic
114 reaction, the nucleophilic substrate (N-, C-, O- or S-nucleophiles) attacks the electrophilic
115 methyl group through an S_N2-type mechanism generating *S*-Adenosyl-*L*-Homocystein (SAH)
116 as by product (Fig. 2A).[20,21] The methyl group transfer happens in the catalytic site of
117 MTases that is composed of two pockets: a SAM binding site and a substrate binding site.[15]

118 SAM-Dependent MTases are a wide and diversified class of enzymes. They can be
119 classified according to their type of substrate. First, Histone MethylTransferases (HMTs)
120 catalyze the transfer of methyl group on lysine and arginine residues of histones and are
121 partitioned into Protein Arginine MethylTransferases (PRMTs) and Lysine
122 MethylTransferases (KMTs) (Fig. 2B).[22,23] Other protein methyltransferases methylate side
123 chains of non-histone proteins,[24] especially *N*-Terminal MethylTransferases (NTMTs) have
124 raised interest recently.[25,26] Among the DNA MTases, C5 DNA MethylTransferases
125 (DNMTs) catalyze the methylation of C5-position of cytosines (5mC) in DNA (Fig. 2B), which
126 plays a major role in human diseases, and for which we and other have developed several
127 inhibitors.[27] Additional MTases are responsible for the methylation of small molecules such

128 as Catechol *O*-MethylTransferases (COMT) that methylate catecholamines for
 129 neurotransmitter degradation.[28]

130 Due to the plethora of biological functions of MTases but also to their involvement in
 131 various diseases, SAM and SAH analogues have been developed and exploited either as
 132 MTases inhibitors or as tools to study the functions of MTases.[29]



133
 134 **Figure 2.** A) SAM-dependent MTase-catalyzed methylation reaction; B) Examples of methylation products:
 135 mammalian histone and DNA methylation by HMTs and DNMTs; C) Examples of adenine methylation on RNA;
 136 D) COMT-catalyzed methylation of Levodopa; E) NNMT-catalyzed methylation of nicotinamide.
 137 (Biorender.com was used to prepare part of the Figure.)

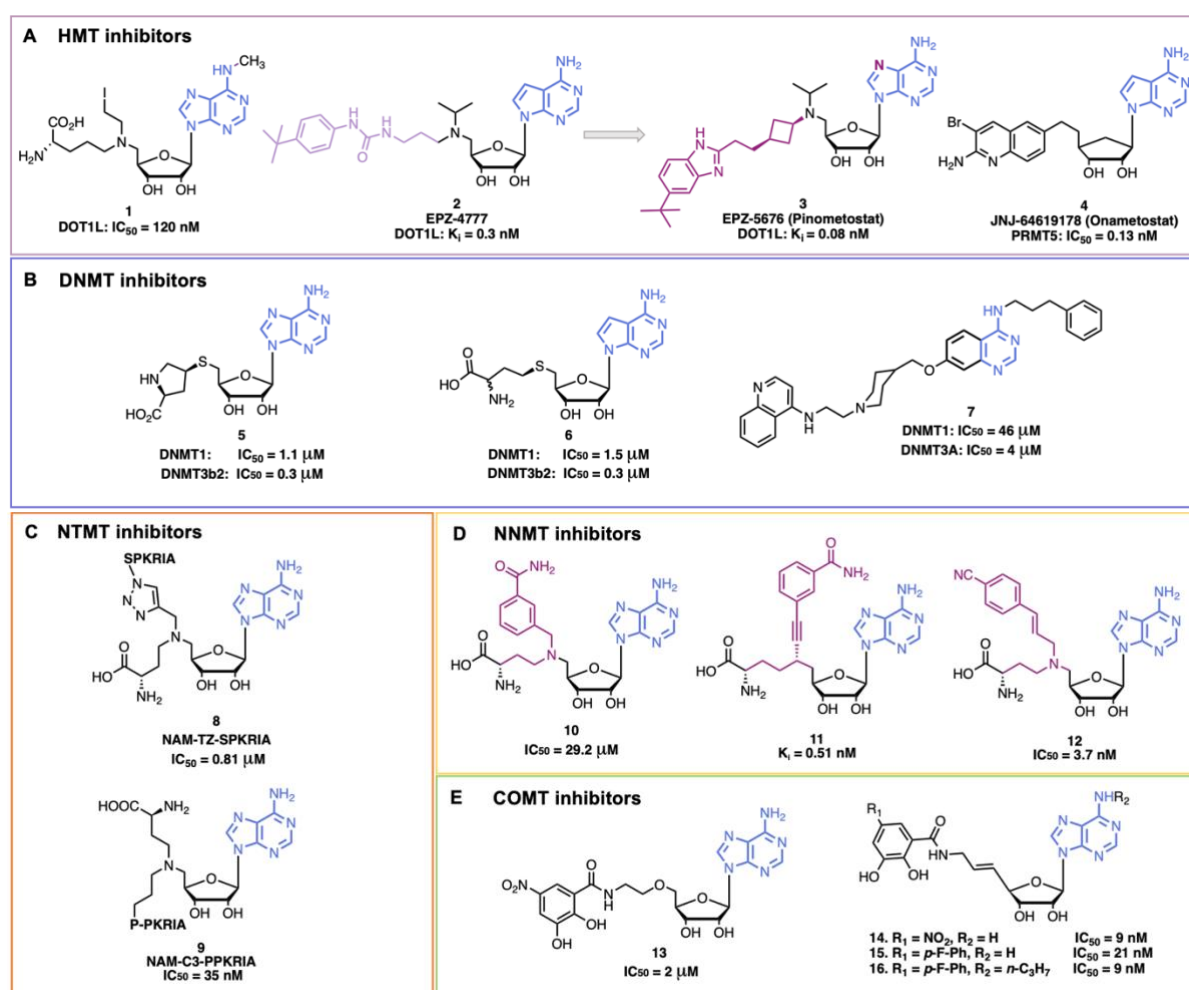
138
 139

140 **1.1 Histone MethylTransferases (HMT) inhibitors**

141

142 HMTs are a broad class of enzymes with more than 50 members of KMTs and 9
 143 PRMTs.[30] KMTs catalyze mono- (Kme1), di- (Kme2) or tri- (Kme3) methylation of lysine
 144 residues, whereas PRMTs catalyze monomethylation of arginines (Rme1) or dimethylation of
 145 arginines (in a symmetrical (Rme2s) or asymmetrical (Rme2a) manner) (Fig. 2B). HMTs are

146 involved in various diseases, in particular cancers and infectious diseases, and are thus very
 147 interesting therapeutic targets.[31–35] SAM and SAH scaffolds were exploited to develop
 148 numerous HMT inhibitors.[36] We chose few examples among the large literature to show the
 149 design and application of adenine-based inhibitors (Fig. 3).



150
 151 **Figure 3.** Examples of some SAM/SAH inhibitors. A) HMT inhibitors; B) DNMT inhibitors; C) NTMT
 152 inhibitors; D) NNMT inhibitors; E) COMT inhibitors.

153
 154 SAH is an endogenous inhibitor of many MTases and shows, for example, a similar
 155 inhibitory potency for PRMT4, G9a and DOT1L (IC₅₀ ≈ 1.5 μM). Hence, co-crystal structures
 156 of SAH complexed with different HMTs were exploited to develop HMT inhibitors. DOT1L,
 157 the only HMT that catalyzes H3K79 methylation, attracted the interest notably because it is a

158 major target for acute leukemia with Mix Lineage Leukemia (MLL) translocations.
159 Interestingly, DOT1L is a KMT that does not bear the catalytic SET domain but rather shows
160 a similarity in the 3D structure of the catalytic pocket with the PRMT's one, and exhibits a
161 unique hydrophobic subpocket in the adenosine binding site.[37] Following this rationale, Yao
162 *et al.* designed a potent and selective compound, **1** (Fig. 3A), with a methyl substitution on the
163 N6 position of SAH (to protrude interactions in the hydrophobic pocket specific of DOT1L)
164 and the C-S bond of SAH was replaced by a C-N bond (DOT1L, IC₅₀ = 120 nM) (Fig. 3A).[38]
165 In 2011, Epizyme Inc. developed a new potent DOT1L inhibitor EPZ-4777, **2**, where the 7-
166 deaza SAM mimics is linked to a bulky 4-*tert*-butylphenyl group to occupy also the substrate
167 pocket (DOT1L, IC₅₀ = 0.4 nM ± 0.1).[39,40] This compound is a SAM competitive inhibitor
168 and the 4-*tert*-butylphenyl group occupies a newly opened hydrophobic subpocket. EPZ-4777
169 efficiently inhibits the proliferation of MLL-rearranged leukemia cell lines but the poor
170 pharmacokinetic properties of the compound blocked its progress. To improve the
171 pharmacokinetic parameters, a new compound EPZ-5676, **3** (Pinometostat), was developed. In
172 EPZ-5676 the propyl chain of EPZ-4777 is replaced by a *cis*-cyclobutyl ring and the
173 benzimidazole moiety replaces the aryl-substituted urea group. Moreover, the adenosine part
174 of SAM is conserved in EPZ-5676.[41] The compound is very potent (DOT1L, K_i = 0.08 nM
175 ± 0.03) and is selective towards DOT1L. In addition, EPZ-5676 shows better residence time
176 (>24 h vs 1 h) and entered clinical trials (NCT03701295). Interestingly, since EPZ-4777 weakly
177 inhibits PRMT5 (at 30 μM), it served as starting point for the development of new PRMT5
178 SAM-competitive inhibitors. After extensive SAR exploration, compound JNJ-64619178, **4**
179 (by Johnson and Johnson), was developed (Fig. 3A). It is a bisubstrate inhibitor composed of
180 a 7-deaza SAM mimics and a substituted quinoline moiety, occupying the second substrate
181 binding pocket. JNJ-64619178 is potent (PRMT5, IC₅₀ = 0.13 nM) and selective towards

182 PRMT5; it displays favorable pharmacokinetic properties[42] and entered clinical trial notably
183 for the treatment of advanced solid tumors (NCT03573310).[9]

184

185 ***1.2. DNA MethylTransferases (DNMT) inhibitors***

186

187 DNA methylation, mediated by DNMTs, contributes to maintain normal cell function and
188 to embryonic development. DNMT1 catalyzes methylation of newly synthesized DNA strands,
189 while DNMT3A/B are responsible for *de novo* DNA methylation.[43] In humans, DNA
190 methylation mainly takes place on position 5 of cytosine in a CpG dinucleotide context and is
191 generally associated with gene repression when in promoters. Abnormal DNA methylation
192 patterns and alterations in DNMTs activity can induce tumor development and maintenance.
193 DNMTs are thus interesting anticancer targets.[27] Azacitidine (VidazaTM) and Decitabine
194 (Dacogen®), are two DNMT inhibitors approved by the FDA (US Food and Drug
195 Administration).[44,45] These drugs are cytosine analogues that replace cytosine in DNA, and
196 in RNA for the former. However, they lack selectivity towards CpGs and show poor stability.
197 More recently, a new class of reversible DNMT1-selective inhibitors has been developed by
198 GlaxoSmithKline (GSK), targeting allosteric sites. The compound GSK-3484862 that contains
199 a dicyanopyridine moiety is promising with its low cytotoxicity and great specificity.[46,47]
200 In addition, adenine analogues have been investigated to mimic SAH. MethylGene Inc.
201 performed structural modifications of SAH and showed that substituting the homocystein with
202 a proline mimics confers potent activity (compound **5** in Fig. 3B), [48] while the 7-deaza SAH,
203 **6**, showed similar activity as SAH.[49] Finally, DNMT bisubstrate inhibitors with a
204 quinazoline moiety as adenine mimic were developed by our laboratory and others.[50–53]
205 Compound **7** inhibited DNMT3A and DNMT1 at 4 μ M and 46 μ M respectively (Fig. 3B).[54]

206

207 **1.3. N-Terminal MethylTransferase (NTMT) inhibitors**

208

209 Protein N-Terminal MethylTransferase 1 (NTMT1) methylates the N-terminal amine of
210 proteins and recognizes the canonical motif X-P-K (with X= A, P or S).[55] Dysregulation of
211 NTMT1 is associated with several cancers and aging processes.[56] NTMT inhibitors have
212 been developed notably to study the biological functions of N α methylation. A first NMT1
213 bisubstrate inhibitor NAM-TZ-SPKRIA, **8**, has been developed by Zhang *et al.* (Fig. 3C).[57]
214 It is composed of 5'-N SAM analogue coupled to an hexapeptide (SPKRIA) *via* a triazole
215 linker. The compound is very potent (IC₅₀= 0.81 \pm 0.13 μ M) and shows a 60-fold selectivity
216 over other representative MTases. Later, Chen *et al.*, developed a new series of NTMT1
217 bisubstrate inhibitors.[58] With a new synthetic route, they replaced the first serine residue of
218 the SPKRIA peptide by a proline residue giving the NAM-C3-PPKRIA, **9** (Fig. 3C), exhibiting
219 an improved potency (IC₅₀ = 35 \pm 2 nM) and more than 100-fold selectivity over NTMT1
220 against a panel of MTases. However, the compound showed a poor cell permeability preventing
221 cell-based studies. Nonetheless, this work enabled to obtain the first co-crystal structure of
222 inhibitors with NTMT1 that would help for the development of novel NTMT1 inhibitors.

223

224 **1.4. Nicotinamide N-MethylTransferase (NNMT) inhibitors**

225

226 NNMT catalyzes methylation of nicotinamide using the SAM cofactor (Fig. 2E). NNMT
227 has a major role in cell detoxification and metabolism. Indeed, NNMT can recognize a broad
228 range of substrates (pyridines, quinolines, diverse heterocyclic metabolites) and catalyzes their
229 methylation, which is followed by their excretion.[59] Nicotinamide is also the precursor of
230 NAD⁺. Moreover, NNMT balances SAM/SAH ratio that impacts indirectly gene
231 expression.[60] Indeed, it has been reported that NNMT is also involved in the development

232 and progression of cancers, neurodegenerative diseases, diabetes and obesity.[61–63] To better
233 understand the role of NNMT in these diseases, several NNMT inhibitors have been developed,
234 as potent bisubstrate compounds composed of SAM and nicotinamide mimics covalently
235 bound through a linker. In 2017, Van Haren *et al.* developed the first bisubstrate compound **10**
236 targeting NNMT ($IC_{50} = 29.2 \pm 4.0 \mu M$),[64] followed by other derivatives.[65,66] In
237 particular, Policarpo *et al.* synthesized a new potent bisubstrate compound **11** with an increased
238 potency in the nanomolar range ($K_i = 0.51 \pm 0.08 nM$).[67] They figured out that an alkyne
239 linker between the NAM-like and SAM-like fragments was optimal to mimic the transition
240 state geometry. Recently, Gao *et al.* developed a novel potent bisubstrate compound **12** (IC_{50}
241 $= 3.7 \pm 0.2 nM$) with a *para*-cyano substituted styrene scaffold in the nicotinamide mimic that
242 replaces the common benzamide moiety.[68] However, the compound was not potent in cell-
243 based assays probably due to a poor cell permeability. All these findings help the further design
244 and development of new NNMT inhibitors.

245

246 **1.5. Catechol O-Methyltransferases (COMT) inhibitors**

247

248 COMT catalyzes methylation of catecholamines (*e.g.* dopamine and epinephrine) but also
249 of Levodopa (L-dopa) producing 3-*O*-Methyldopa (Fig. 2D). L-Dopa is the precursor of
250 dopamine and is used to treat the symptoms of Parkinson Disease (PD).[69] Administering
251 COMT inhibitors avoids L-dopa deactivation and prolongs the effects of PD treatment.[70]
252 COMT bisubstrate inhibitors were developed. Based on the crystal structure of COMT with
253 Mg^{2+} , SAM and 3,5-dinitrocatechol, the bisubstrate compound **13** was designed.[71]
254 Compound **13** is a competitive inhibitor of SAM and a noncompetitive inhibitor of catechol.
255 The potency was increased by rigidifying the linker with a double bond giving compound **14**
256 ($IC_{50} = 9 nM$).[72] To avoid hepatotoxicity, the nitro group was replaced by fluoro-substituted

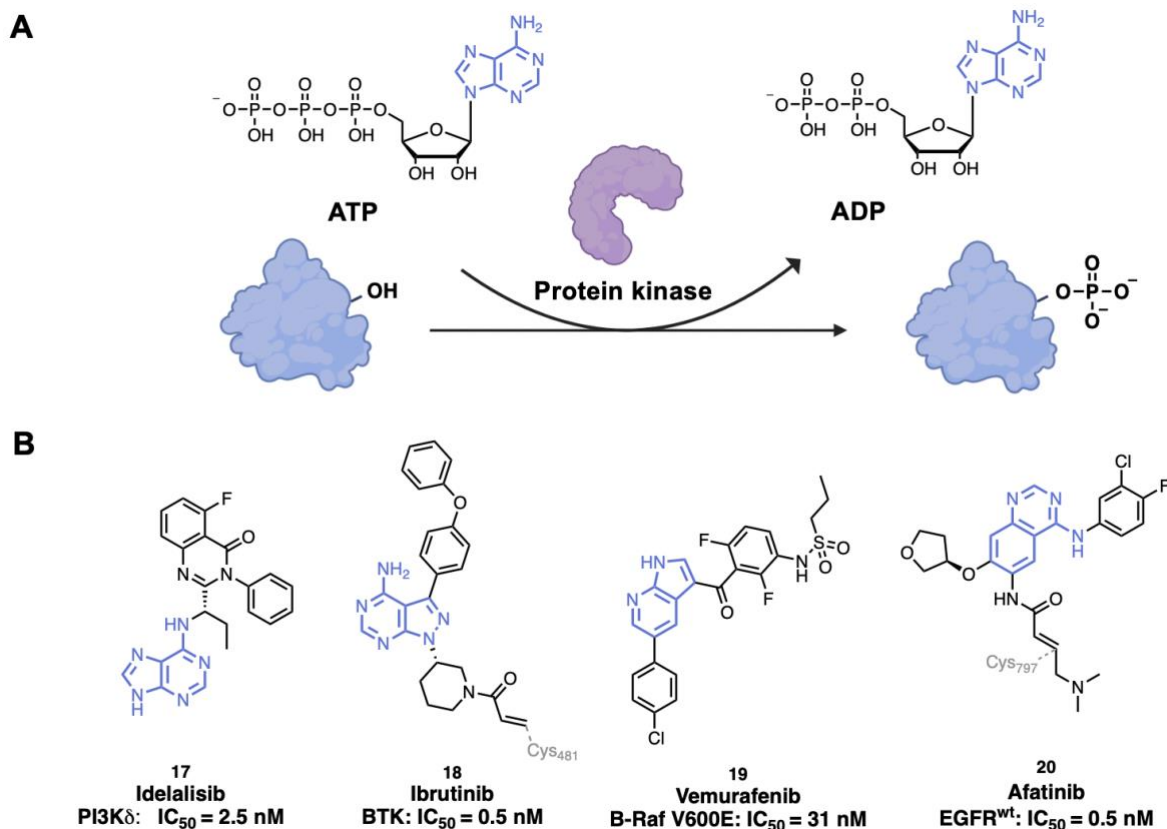
257 phenyl moiety giving the potent compound **15** ($IC_{50} = 21$ nM).[73] Substitution of the OH at
258 position 3 of ribose gave compound **16** ($IC_{50} = 9$ nM).[74]

259

260 **2. Adenine scaffold in kinase inhibitors**

261

262 Protein kinases catalyze the transfer of a γ -phosphate group from ATP to a substrate as for
263 example tyrosine, serine or threonine residues of proteins (Fig. 4A). Approximately 538
264 kinases have been identified in the human genome so far.[75] Kinases play major roles in
265 numerous cellular processes such as cell proliferation, transcription, apoptosis and cell
266 survival. However, they are also involved in the development and progression of numerous
267 diseases, especially cancers but also inflammatory, neurological and cardiovascular
268 diseases.[1] Kinases are thus validated drug targets. Over 70 kinase inhibitors targeting more
269 than 20 different protein kinases have been approved with most of them used for cancer
270 treatment.[76] Kinase inhibitors can be classified according to their binding mode: *Type I*
271 *inhibitors* are ATP-competitive inhibitors and bind to the active conformation of kinases, *Type*
272 *II inhibitors* bind to the inactive conformation of kinases, *Type III inhibitors* bind to an
273 allosteric pocket adjacent to the ATP-binding pocket and *Type IV inhibitors* bind to an
274 allosteric pocket distant to the ATP-binding pocket.[77]



275

276 **Figure 4.** A) Protein phosphorylation-catalyzed reaction by protein kinases; B) Examples of kinase inhibitors
 277 with an adenine analogue scaffold. (Biorender.com was used to prepare part of the Figure.)

278

279 Most of the kinase inhibitors bind to the ATP-binding site. ATP mimics bind making
 280 hydrogen bonds to the kinase hinge backbone similarly to the ATP adenine ring.[77] Different
 281 chemical scaffolds of adenine analogues are used (Fig. 4B). Some of them present the *purine*
 282 *scaffold* that occupies the adenine pocket such as Idelalisib, **17**, (Zydelig®, by Gilead
 283 Sciences), a PhosphoInositide 3-Kinase δ (PI3K δ) inhibitor approved to treat relapsed Chronic
 284 Lymphocytic Leukemia (CLL).[78] Idelalisib establishes a type II binding.[79] The 5-
 285 fluoroquinazolinone part binds to an induced hydrophobic specificity pocket and the purine
 286 moiety occupies the adenine pocket by forming a key hydrogen bond between the N6 position
 287 of the adenine ring and Val828.[80,81] The *pyrazolo aminopyrimidine scaffold* is also used as
 288 adenine mimic in inhibitors such as in Ibrutinib, **18**, (Imbruvica®, by Pharmacyclics Inc.), a
 289 Non-Receptor protein Tyrosine Kinase (NRTK) targeting Burton's Tyrosine Kinase (BTK)

290 that was approved to treat mantle cell lymphoma and CLL.[82] Crystallography studies showed
291 that Ibrutinib is an irreversible BTK inhibitor, which covalently binds through Michael addition
292 with Cys481 of BTK.[83] However, some insights on the mechanism of action remain to be
293 understand, as more recently, the determination of the structure of Ibrutinib with SRC (a non-
294 receptor protein tyrosine kinase, PDB ID: 6L8L) showed that Ibrutinib binds *via* a non-covalent
295 manner to the protein.[84] Pyrrolo pyridine scaffolds are also used, as in Vemurafenib, **19**,
296 (Zelboraf®, licensed to Roche), an inhibitor of the serine/threonine B-Raf enzyme (member
297 of the Raf kinase family) approved for late-stage melanoma.[85] The structure of Vemurafenib
298 complexed with V600E B-Raf, determined by X-ray crystallography (PDB ID: 3OG7), showed
299 a type I inhibition mechanism. The pyrrolo pyridine core of Vemurafenib mimics the adenine
300 core of ATP by forming hydrogen bonds with hinge residue Cys532 and Gln530. Moreover,
301 the sulfonamide moiety interacts through hydrogen bonds to the DFG residues and the 4-
302 chlorophenyl moiety is exposed to the solvent.[86] Since resistance has appeared with
303 mutations in the protein, new inhibitors have been designed (Belvarafenib by Hanmi
304 Pharmaceutical/Genetech and Lifirafenib by Novartis for example).[87] Kinase inhibitors with
305 a fused six-membered ring system such as a quinazoline, quinoline or isoquinoline moiety are
306 the most used ATP mimics (18 FDA approved inhibitors).[77] For instance, Afatinib, **20**,
307 (Gilotrif®, by Boehringer Ingelheim), composed of a quinazoline moiety, is an irreversible
308 inhibitor of Human epidermal growth factor receptor 2 (Her2) and Epidermal Growth Factor
309 Receptor (EGFR) kinase. It was the first irreversible kinase inhibitor clinically approved for
310 treatment of Non-Small Cell Lung Carcinoma (NSCLC).[88] A type I binding mode was
311 shown with co-crystal structures of EGFR-Afatinib (PDB ID: 4G5J) and mutant T790M
312 EGFR-Afatinib (PDB ID: 4G5P). The quinazoline core binds with a conserved hydrogen bond
313 to the hinge residue Met793.[89]

314

315 It is worth mentioning that kinase inhibitors are also used to treat non-oncologic
316 diseases such as inflammatory diseases, autoimmune diseases, cardiovascular diseases,
317 diabetes and some neurodegenerative disorders.[90] Noteworthy, some promising kinase
318 inhibitors with as adenine scaffold are currently in preclinical trials for Amyotrophic Lateral
319 Sclerosis (ALS).[91]

320

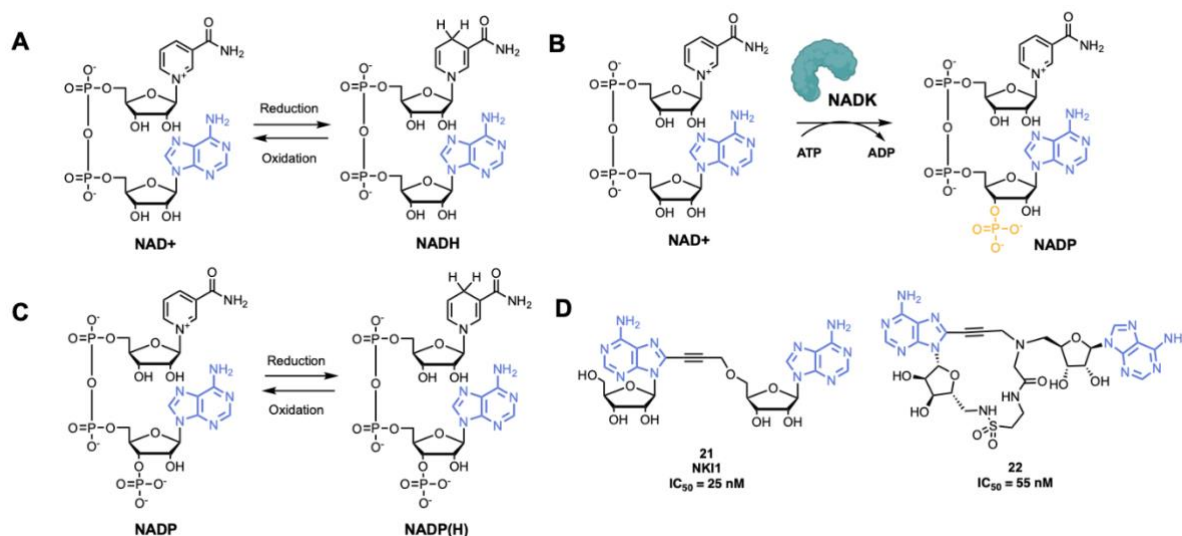
321 **3. Nicotinamide Adenine Dinucleotide (NAD) analogues to target**

322 **Nicotinamide Adenine Dinucleotide Kinases (NADK)**

323

324 Nicotinamide adenine dinucleotide is an essential cofactor in energy metabolism. NAD is a
325 dinucleotide containing an adenine and nicotinamide linked together through a ribose-
326 phosphodiester backbone (Fig. 5A). NAD can be in two forms: in an oxidized form (NAD⁺)
327 or in a reduced form (NADH). NADK catalyze the phosphorylation of NAD on the 3'OH of
328 the adenosine to NADP, which is further reduced to NADP(H) (Fig. 5B-C).[92,93] NADK is
329 the unique enzyme producing NADP *de novo* and is essential to control the balance of NADH
330 and NADP(H) in various metabolic pathways. NADK has crucial roles in pathogenic bacteria
331 such as *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Bacillus subtilis* and *Listeria*
332 *monocytogenes*. [12, 94–98] Thus, NADK is a very promising therapeutic target for the
333 development of novel antibiotics.[99,100]

334



335

336 **Figure 5.** A) Reduction-oxidation reaction of NAD⁺/NADH; B) NAD⁺ phosphorylation-catalyzed reaction by
337 NADK; C) Reduction-oxidation reaction of NADP/NADP(H); D) Examples of NADK inhibitors. (Biorender.com
338 was used to prepare part of the Figure.)

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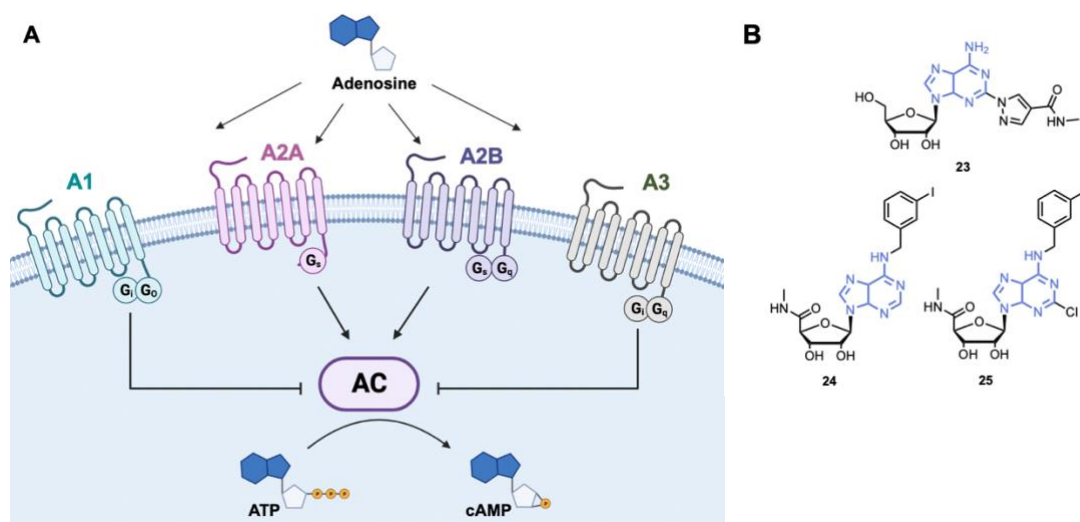
340 A series of adenosine derivatives targeting recombinant *L. monocytogenes* and *S.*
341 *aureus* NADKs has been recently developed by the group of Pochet.[12,101–103] This work
342 led to the synthesis of the first NADK inhibitor NKI1, **21** (Fig. 5D), showing activity in mice
343 infected with *S. aureus*. [12] NKI1 is a dinucleoside of adenosine coupled through a propargyl
344 linker. This linker confers a restricted conformation that is essential for the binding to the NAD-
345 binding site of bacterial NADK. It was suggested that even more constrained compounds would
346 have better affinity and specificity for NADKs.[104,105] Thus, macrocycle compounds were
347 investigated. The potent compound **22** was developed and the macrocyclization was performed
348 by intramolecular amide bond (Fig. 5D). Compound **22** is active at 55 nM on recombinant
349 NADK from *L. monocytogenes* (*LmNADK1*) and represents the best NADK-binder described
350 to date.[106]

351

352 4. Adenosine analogues as adenosine receptor agonists

353 Adenosine is a major cell regulator that is involved in numerous physiological processes
354 such as the nervous system, vascular function, immune system, and platelet aggregation. More
355 precisely, adenosine interacts with four G Protein-Coupled Receptors (GPCR) Adenosine
356 Receptors (ARs): A1, A2A, A2B and A3 (Fig. 6A).[107,108] ARs exhibit seven-passed
357 transmembrane α -helix structures, the amino terminus being extracellular and the carboxyl
358 terminus intracellular. Receptors A1 and A3 activate G_i proteins that inhibit the activity of the
359 Adenylyl Cyclase (AC) and consequently reduce the intracellular level of cAMP. On the
360 contrary, receptors A2A and A2B are coupled to G_s proteins that activate AC and induce an
361 increase in the cAMP level. ARs are distributed throughout the body, for example receptors
362 A1 are distributed in the brain, the spinal cord, heart muscles, kidney. Receptors A2A are
363 mainly found in the immune system and the stratum, while receptors A2B are at high
364 concentration in the respiratory pathway. Receptors A3 are located into hippocampus,
365 thalamus, astrocytes, epithelial cells, inflammatory cells etc...[109]

366



367

368 **Figure 6.** A) Schematic representation of adenosine signaling; B) Examples of adenosine receptor agonists. AC:

369 Adenylyl Cyclase, (Biorender.com was used to prepare panel A.)

370 By their role, ARs are involved in various pathological functions in several human diseases
371 as for example in central nervous system disorders, cardiovascular diseases, asthma, and
372 cancer. ARs are thus interesting therapeutic targets and several drugs including agonists,
373 antagonists and allosteric enhancers have been developed and approved. The drugs targeting
374 adenosine signaling pathways are described in a recent review by Kutryb-Zajac *et al.*[14] A
375 major strategy for the design of agonists of ARs consists in modifying the *N*-6 position of
376 adenine and the 5'-position of ribose.

377

378 ***4.1 Specific A2A receptor agonist***

379 Regadenoson, **23** (Lexiscan®), is the only A2A receptor agonist that has been approved by
380 the FDA (Fig. 6B). Regadenoson is a pyrazole derivative of adenosine that induces coronaries
381 dilatation by binding to A2A receptors of the coronary arteries.[110,111] Regadenoson is more
382 than 100 times more potent than adenosine as an agonist of A2A receptor. It is used as a stress
383 agent in conjunction with Myocardial Potential Imaging (MPI) for diagnosis of Coronary
384 Artery Disease (CAD). Regarding its therapeutic use, Regadenoson is currently in phase I/II
385 study for the treatment of COVID-19. Indeed, by inhibiting hyperinflammation, Regadenoson
386 could reduce COVID-19 induced lung injury and ameliorate recovery of patients.[112]

387

388 ***4.2 Specific A3 receptor agonists***

389 The A3 receptor is a promising therapeutic target because it is highly expressed in the skin
390 of psoriasis patients, in inflamed tissues of arthritic patients and in several solid tumor cells
391 (breast, pancreatic, melanoma...).[113–115] Importantly, A3 agonists inhibit cytokine
392 production and downregulate the NF-κB pathway in cancer and inflamed tissues. Piclidenoson,
393 **24** (Fig. 6B), is an adenosine A3 agonist showing anti-inflammatory effects in arthritis and
394 inflammatory bowel disease.[116,117] A phase II study showed that the drug was safe and

395 well-tolerated for patients with rheumatoid arthritis.[118] Piclidenoson was tested in phase III
396 to treat patients with moderate to severe plaque psoriasis (NCT03168256).[119]

397 The A3 receptor is also overexpressed in HepatoCellular Carcinoma (HCC) tissues and it
398 has been shown that the A3 agonist Namodenoson, **25** (Fig. 6B), inhibits tumor cell growth *in*
399 *vitro* and *in vivo*.[120,121] Namodenoson is currently in phase III to treat advanced HCC
400 (NCT05201404).[119]

401

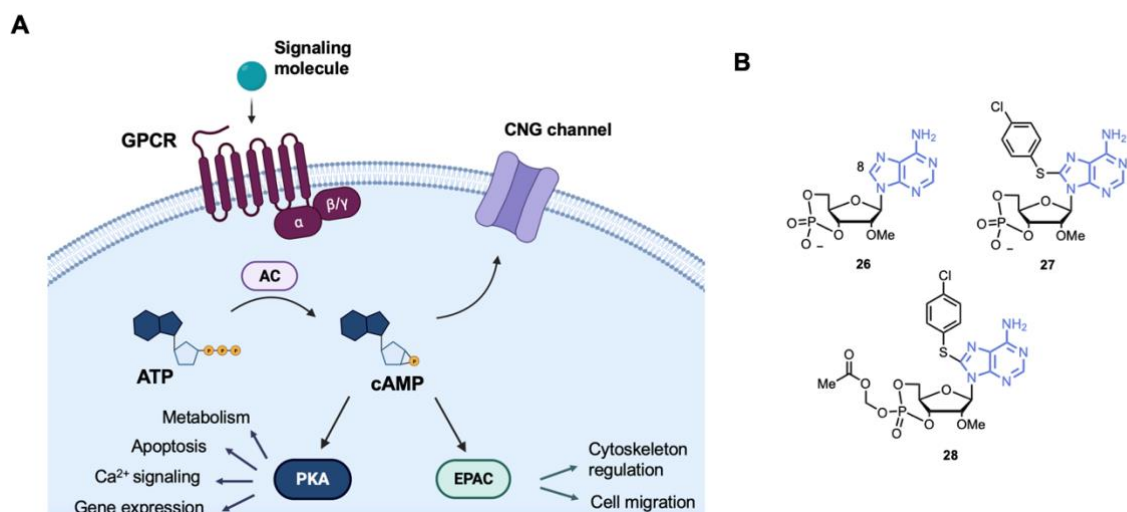
402 Targeting adenosine receptors has shown promising results, however due to the complexity
403 of the AR signaling and the wide distribution in the body of ARs, only a small amount of
404 adenosinergic drugs have been approved. Development of new drugs is currently explored.

405

406 **5. cyclic Adenosine MonoPhosphate (cAMP) analogues as Exchange** 407 **Proteins Activated by cAMP (EPAC) agonist modulators**

408

409 cAMP is a versatile chemical second messenger that mediates extracellular signals to
410 intracellular responses in most types of cells. Many biological processes are regulated by
411 cAMP such as cell activation, proliferation, migration or apoptosis regulation.[122] The cAMP
412 response is first initiated by primary signaling molecules (hormones, neurotransmitters or
413 prostaglandins) that activate mainly G-Protein-Coupled Receptors (GPCR), which in turn
414 activate adenylyl cyclases (Fig. 7A). ACs catalyze ATP cyclization to produce cAMP.[123]
415 There are several intracellular receptors for cAMP, as the Protein Kinase A (PKA) family,
416 EPACs and CNG channels.[124–126] Deregulations in local cAMP signaling has been
417 correlated to various pathophysiological disorders such as cancer, diabetes, cardiac dysfunction
418 and immunological diseases.[127–129]



421

422 **Figure 7.** A) Schematic representation of the intracellular cAMP signaling cascade; B) Examples of cAMP
 423 analogues used to target EPACs (Exchange Proteins Activated by cAMP). AC= Adenylyl Cyclase; CNG= Cyclic
 424 Nucleotide Gated; PKA= Protein Kinase A. (Biorender.com was used to prepare panel A.)

425

426 EPACs activate Ras-like small GTPases (Rap1 and Rap2) that are involved in cell-cell
 427 adhesion. [122, 125, 130] EPAC1 and EPAC2 have been identified as potent targets for several
 428 human diseases, as in cancer and cardiovascular diseases, thus small molecules modulating
 429 EPAC have been developed. EPAC modulators can be classified into cAMP analogues and
 430 non-cyclic nucleotide molecules (for a specific review see Wang *et al.*).[13] Here we focused
 431 on the cAMP analogues (Fig. 7B). cAMP analogues display EPAC agonist activity. Bos *et al.*
 432 first showed that 2'-OH modification increases selectivity EPAC/PKA selectivity. For
 433 example, substitution of the 2'-OH by a methoxy group led to compound **26** with about 10- to
 434 60- fold selectivity EPAC/PKA.[131] Then, bulky substitution on adenine at the C8-position
 435 gave EPAC agonist **27** with an half-maximal EPAC1 activation at 2.2 μM and about 100-fold
 436 EPAC/PKA selectivity.[132] However, compound **27** showed poor membrane penetrating
 437 capability. Then, a prodrug, compound **28** (Fig. 7B) was developed with esterification of the

438 4-phosphate group. Compound **28** was over 100-fold more potent than compound **27** and did
439 not affect EPAC/PKA selectivity but acted also as a PhosphoDiEsterases (PDE) inhibitor.[133]

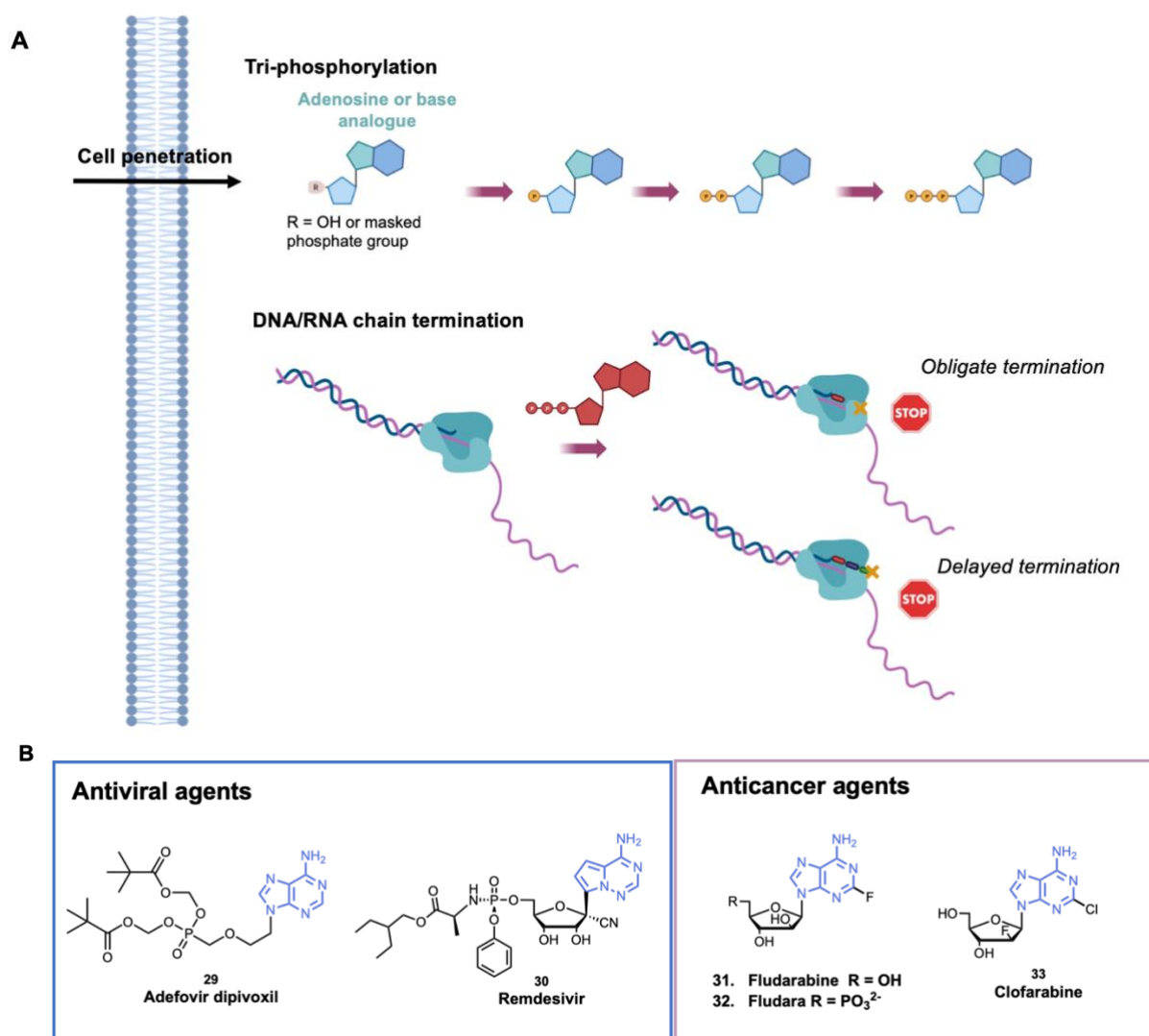
440

441 **6. Adenosine analogues as antiviral and anticancer agents**

442

443 Nucleoside analogues are widely used for antiviral and anticancer therapy by targeting DNA
444 or RNA replication of the virus or the rapidly replicating cancer cells. Nucleoside analogues
445 are mainly “*chain terminators*” and belong to the inhibitors described as anti-metabolites (Fig.
446 [8A](#)). After penetration in the cell, the nucleoside analogues are tri-phosphorylated by viral or
447 human cells. The triphosphorylated compounds are then recognized by polymerases and
448 incorporated into the growing DNA/RNA chain. During DNA/RNA chain elongation, the
449 ($n+1$) nucleoside triphosphate is attached to the 3'-OH of the n terminal nucleotide of the
450 growing chain. The 3'-OH group is thus essential for chain elongation and “*obligate chain*
451 *terminators*” nucleoside analogues lack the 3'-OH group so that their incorporation
452 consequently results in chain termination.[134] Either the 3'-OH group is substituted with a
453 non-reactive group (-H, -Cl, -F, -Br and -N₃ for example) or the deoxyribose is replaced by
454 arabinose derivatives. In general, only few modifications are performed on the nucleobase in
455 order to facilitate the incorporation of the nucleoside analogues as its natural counterpart.[135]

456 Several adenosine analogues are used as “*chain terminators*” for the treatment of cancer or
 457 viral infection.



458
 459 **Figure 8.** A) Schematic representation of the main mechanisms of nucleoside analogues to inhibit DNA/RNA
 460 synthesis; B) Examples of adenosine analogues as antiviral and anticancer agents. (Biorender.com was used to
 461 prepare panel A)

6.1. Antiviral agents

464 One example of chain terminator antiviral agent is Adefovir dipivoxil, **29** (Hepsera®),
 465 that was approved by the FDA in 2002 for the treatment of Hepatis B Virus (HBV) (Fig.
 466 **8B**).[136] It is a ester prodrug of a viral replication terminator Adefovir that blocks the HBV

467 reverse transcriptase and is the prototype of acyclic adenosine phosphonate analogues. The
468 phosphonate bond (-PC-) mimics the 5'-monophosphate of natural nucleotides and enables
469 Adefovir to be phosphorylated by kinases to phosphono-diphosphate form. Adefovir
470 diphosphate competes with the natural substrate dATP and its incorporation results in blockage
471 of the viral polymerase causing chain termination. The phosphonate bond is more stable than
472 the phosphate bond and cannot be cleaved by phosphodiesterases.[137] Based on this efficient
473 strategy, several similar acyclic nucleoside phosphonate compounds have been optimized. In
474 parallel, some nucleoside analogues display a “*delayed chain termination*” mechanism.[138]
475 These compounds exhibit a locked sugar conformation, and after their incorporation in the
476 growing chain, two or three other nucleotides can be further incorporated. Then, due to steric
477 hindrance and displacement of the growing chain in the catalytic site, strand elongation is
478 impeded.[134] This mechanism was developed to avoid exonucleolytic removal of nucleoside
479 analogues. For example, Remdesivir, **30** (Veklury®), is a delayed chain terminator that has
480 been recently approved by the FDA for the treatment of COVID-19.[139, 140] More precisely,
481 Remdesivir is a prodrug of adenosine, the 1'-cyano group avoids the translocation of
482 coronavirus polymerases. According to molecular modeling data, repulsion between the cyano
483 group and S861 in the protein pocket would inhibit the polymerase translocation to position
484 ($n+4$).[141]

485

486 **6.2. Anticancer agents**

487 Fludarabine, **31** (F-ara-A), was approved by the FDA for the treatment of B-cell chronic
488 lymphocytic leukemia (Fig. 8B). After cell penetration in its nucleoside form, Fludarabine is
489 triphosphorylated (forming F-ara-ATP) and competes with the natural substrate. Incorporation
490 of F-ara-ATP into DNA by DNA polymerase triggers chain termination.[142] Then, to improve
491 solubility, the 5'-monophosphate derivative, **32** (Fludara®), was designed. Fludara® is then

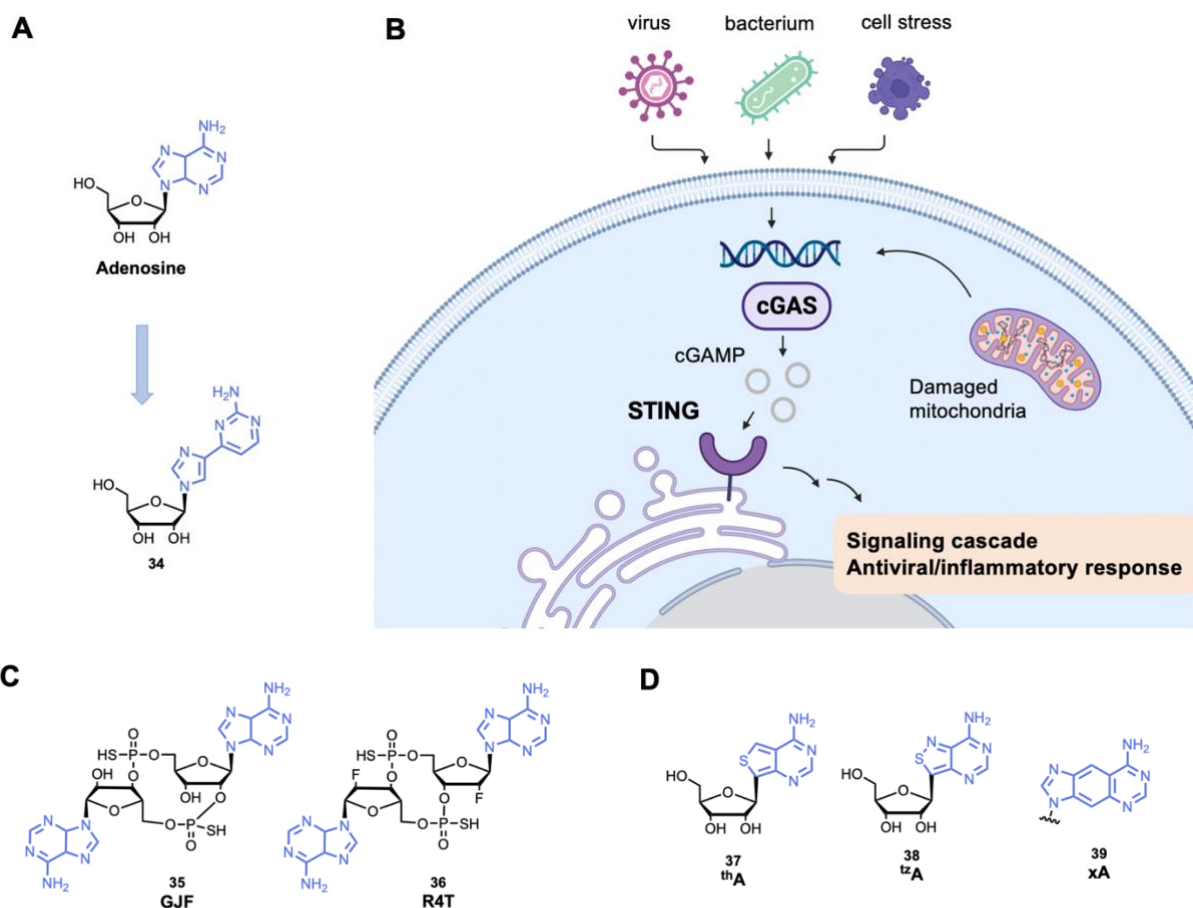
492 converted into fludarabine by phosphatase (Fig. 8B). Clofarabine, **33** (ClolarTM, Genzyme), a
493 next-generation deoxyadenosine analogue, was approved by the FDA in 2004 to treat relapsed
494 or refractory Acute Lymphoblastic Leukemia (ALL) (Fig. 8B). Clofarabine showed an
495 improved stability in the acidic gastric environment and in plasma, notably thanks to the
496 fluorine group at the 2'-position that increases its stability at acidic pH. After its
497 triphosphorylation by kinases, Clofarabine competes with the natural dATP for binding to
498 DNA polymerase α and ϵ . At high ratios of Clofarabine/dATP, Clofarabine is inserted into
499 internal and terminal sites of DNA and inhibits DNA elongation.[143] The anticancer activity
500 of Clofarabine is also due to the inhibition of ribonucleotide reductase and induction of
501 apoptosis.[144] These compounds belong to the antimetabolites that are used in the treatment
502 of cancer based on the higher proliferation of the cancer cells, however they target all
503 proliferating cells showing the well-known side effects (*e.g.* hair loss).

504

505 **Conclusion and Perspectives**

506

507 This review highlights the role of the adenine in the biology of cells and shows through
508 examples the design of adenine-based drugs and their use to treat human diseases, such as
509 cancer, neurological or infectious diseases. The adenine scaffold is involved in many essential
510 biological processes and participate to a broad range of mechanisms, as energy source,
511 cofactor, ... As these mechanisms are aberrant in diseases, they constitute potential targets for
512 treatment and thus the adenosine scaffold is a chemical starting point for the design of drugs in
513 medicinal chemistry. Many chemical modifications have been carried out on the heterocycle
514 moiety and on the side chain giving extensive chemical libraries of adenine derivatives with
515 comprehensive SAR studies. Moreover, it enabled to develop and investigate novel methods
516 in purine synthesis.[145–147]



517

518 **Figure 9.** A) Schematic representation of the STING pathway; B) Example of fleximer of adenosine; C)
 519 Examples of cGAMP analogues and D) Examples of adenosine derivatives used as fluorescent probes.
 520 (Biorender.com was used to prepare panel B.)

521

522 Importantly, membrane permeability and bioavailability remain an issue and many
 523 efforts are carried out to improve the pharmacological properties and extend the adenine
 524 analogues repertoire and explore adenine prodrugs. For example, adenosine fleximers, in which
 525 the purine base is split into two heterocycles connected by a bond allowing rotation, have been
 526 developed (Fig. 9A).[148] Thanks to their flexible structure, these derivatives have shown
 527 advantages compared to the corresponding purine-base nucleosides, as they can exert new
 528 interactions with the protein partner that are not possible with the corresponding nucleoside or
 529 their extended structure can give access to new space in the protein pocket.[149] Indeed, the

530 replacement of a guanine by fleximer in Acyclovir greatly improved its biological activity and
531 the ability of the fleximer analogue to adopt the *syn* conformation was able to inhibit efficiently
532 a SAH hydrolase.[150] These compounds have many promising applications in particular for
533 their antiviral activity but also as molecular probes and antitumor agents.[150]

534 Another emerging and promising topic consists of the development of new modified
535 cyclic dinucleotides targeting STimulator of INterferon Genes protein (STING). STING
536 recognizes 2'3' cyclic GMP-AMP (cGAMP), which is produced by the cyclic GMP-AMP
537 synthase (cGAS) after recognition of cytosolic endogenous or exogenous DNA (Fig. 9B).[151]
538 The STING activation induces a signaling cascade and transcription of antiviral and
539 proinflammatory genes.[152] Several cyclic dinucleotides with adenosine derivatives are
540 developed to activate STING (Fig. 9C), by mimicking cGAMP.[153] Such compounds should
541 be further explored and could be used to improve vaccination, control autoimmune disease or
542 treat cancer.

543 It is worth mentioning that the quinazoline core is also a common mimic of adenine and
544 used more broadly in the design of drugs as we can see in many kinase and DNA
545 methyltransferases inhibitors for example.

546 Finally, the adenine scaffold is also used to develop fluorescent probes. To confer and
547 modulate fluorescence properties, modifications are mainly carried out on the C8-position of
548 adenine (and few examples with modifications on C2-position) (Fig. 9D). By mimicking the
549 natural non-fluorescent adenine, these compounds have many biological applications such as
550 probing the structure of nucleic acids and their interactions with biological molecules.[154–
551 156] Finally, purine chemical libraries are extended with the guanine scaffold that is also used
552 in many biological applications including anticancer and antiviral therapy.[5,157]

553 The interest in the design of analogues of cofactors (SAM, NAD, ...) is increasing for
554 both anticancer, antiviral and antibiotics applications. Interesting, the advances in the

555 technologies to detect RNA modifications (epitranscriptomics) pointed out their role in
556 diseases, increasing the research on the design of analogues to target SAM-based enzymes,
557 ribozymes, deoxyribozymes.[158–162]

558 To conclude, adenine plays a major role in various biological processes but is also
559 involved in processes that are aberrant in diseases. Therefore, it is worth continuing to develop
560 new inhibitors based on this scaffold.

561

562 **Abbreviations**

563 AC=Adenylyl Cyclase

564 Acetyl-CoA= Acetyl-CoenzymeA

565 ALS=Amyotrophic Lateral Sclerosis

566 AR=Adenosine Receptors

567 ATP= Adenosine TriPhosphate

568 cAMP= cyclic Adenosine MonoPhosphate

569 5mC= 5-methylCytosine

570 BTK= Burton's Tyrosine Kinase

571 CAD= Coronary Artery Disease

572 CLL= Chronic Lymphocytic Leukemia

573 CNG= Cyclic Nucleotide-Gated channels

574 COMT= Catechol *O*-MethylTransferases

575 DNMT= C5 DNA MethylTransferases

576 EPAC= Exchange Protein Activated by cAMP

577 EGFR= Epidermal Growth Factor Receptor

578 FAD= Flavin Adenine Dinucleotide

579 FDA=U.S Food and Drug Administration

580 cGAS= cyclic GMP-AMP Synthase
581 cGMP= 2'3' cyclic GMP-AMP
582 GPCR= G-Protein-Coupled Receptors
583 HBV= Hepatis B Virus
584 HCC= HepatoCellular Carcinoma
585 Her2= Human epidermal growth factor receptor 2
586 HMT= Histone MethylTransferases
587 KMT= Lysine MethylTransferase
588 MLL= Mix Lineage Leukemia
589 MPI= Myocardial Potential Imaging
590 MTase= MethylTransferases
591 NAD= Nicotinamide Adenine Dinucleotide
592 NADK= Nicotinamide Adenine Dinucleotide Kinases
593 NNMT= Nicotinamide *N*-MethylTransferase
594 NRTK= Non-Receptor protein Tyrosine Kinase
595 NSCLC= Non-Small Cell Lung Carcinoma
596 NTMT= *N*-Terminal MethylTransferases
597 PDE= PhosphoDiEsterases
598 PI3K δ = PhosphoInositide 3-Kinase δ
599 PKA= Protein Kinase A
600 KMT= Lysine MethylTransferase
601 PRMT= Protein arginine MethylTransferases
602 SAH= *S*-Adenosyl-*L*-Homocystein
603 SAM= *S*-Adenosyl-*L*-Methionine (or AdoMet)
604 sSAR= Structure-Activity Relationships

605 STING= STimulator of INterferon Genes protein.

606

607

608

609 **Fundings and acknowledgements**

610 Authors acknowledge the French National Research Priority Plan PPR Antibioresistance for
611 grant AMI-AMR-2020_ANR-20-PAMR-0011 TheraEPI (to P.B.A) and The French Minister
612 of Higher Education, Research and Innovation for the ENS Paris Ulm CDSN PhD fellowship
613 to A.F.

614 Biorender.com was used to make parts of Figures graphical abstract, 2, 4, 5, 6, 7, 8 and 9.

615

616 **Note**

617 ~~This review was an invited contribution to the Special Issue “Women in Chemistry 2024”.~~

618

619

620

621 **Note about the authors**

622 ~~The authors are three women deeply involved in science. Mrs Alexandra Fillion is a PhD~~
623 ~~student of the Ecole Normale Supérieure de Paris; Dr Sophie Vichier Guerre is a senior~~
624 ~~scientist expert in the Chemistry of nucleobases, nucleotides and nucleic acids; Dr Paola B.~~
625 ~~Arimondo, director of research, leads research projects at the interface of Chemistry and~~
626 ~~Biology.~~

627

628

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630

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