Enzymatic Activity of Selected Nucleoside 5′-Triphosphates and Their Analogs

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Nucleoside 5'-triphosphate derivatives and their analogs (NTPDA) have been extremely helpful in explaining many important details of the mechanism of reactions catalyzed by a family of NTP dependent enzymes. Different versions of NTPDAs represent various modifications of the bases, sugars, triphosphate chain and the combinations of those. Many of the modifications result in changes in the essential properties of the nucleoside 5'-triphosphates, and most importantly their behavior in the enzymatic reactions.

1. Substrate activity of NTPDAs often changes compared to that of the parent NTPs (usually reduced).

2. NTPDAs may become inhibitors of the enzymatic reactions through various mechanisms. For example:

    a. NTPDAs (depending on the type of modification) may physically block the binding, catalytic or allosteric sites of the enzyme thus competing with the substrate, the reaction product or an allosteric regulator(s).
    b. NTPDAs may cause a termination of the enzymatic chain reaction by producing a modified product lacking the chemical function required for continuation of the enzymatic process.
    c. NTPDAs possessing a reactive group(s) may also cause a chemical modification of the crucial enzyme functions responsible for substrate recognition, catalytic action, or conformation stability of the peptide structure (or disrupt the association forces keeping the functional multiunit enzymes).

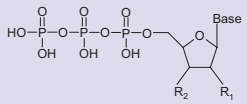
The tables on the following pages are examples of different enzymatic activities of the selected nucleoside 5'-triphosphate derivatives and their analogs. Where it is known, the mode of NTPDA action and the research or practical application(s) is briefly indicated with a reference to a primary source of information.

The data presented in the tables should not be considered as a complete compilation by any means. Rather, it is an overview of the main classes of NTPDAs and illustration of their ability to serve as tools for the different biochemical applications.

Abbreviations used in Tables:

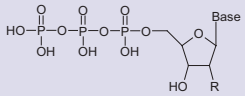
AMV RT	Avian Myeloblastosis Virus Reverse Transcriptase
ATPase	Adenosine 5'-triphosphatase
ASS	Adenylylsuccinate Synthesase
ATP/CTP tRNA NT	ATP/CTP Dependent tRNA Nucleotidyl Transferase
DD DP	DNA Dependant DNA Polymerase
DD RP	DNA Dependant RNA Polymerase
RD DP	RNA Dependant DNA Polymerase
RD RP	RNA Dependant DNA Polymerase
RNR	Ribonucleotide Reductase
PNP	Polynucleotide Phosphorylase
Poly(A) Pol	Polyadenylate Polymerase
PRPPS	Phosphoribosylpyrophosphate Synthesase
TNDT	Terminal Nucleotidyl Transferase
tRNA NT	tRNA Nucleotidyl Transferase
aa tRNA S	Aminoacyl tRNA Synthesase
2',5'-OAS	2',3'-Oligoadenylate Synthesase
HIV RT	Human Immunodeficiency Virus Reverse Transcriptase
AC	Adenylate Cyclase
GC	Guanylate Cyclase
CK	Creatine Kinase
HK	Hexokinase
PK	Pyruvate Kinase
PFK	Phosphofructose Kinase

Table 1: Sugar modified nucleoside 5'-triphosphate analogs



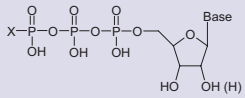
Application	Mode of Action	R_2	R_1	Base	Enzyme class	References
DNA Sequencing	Chain Termination	H	H	A,C,G,T,I	DD DP	1,2
		H	OH	A,C,G,U	DD RP	3-6
		F	OH	A,C,G,U	DD RP	14
		NH_2	OH	A,C,G,U	DD RP	15-18
		Me	OH	A,C,G,U	DD RP	15, 25-27
	Substrate	OH	F	A,C,G,U	DD DP	13
RNA Sequencing	Chain Terminator	H	OH	A,C,G,U	RD RP	3,9
		OMe	OH	A,C,G,U	DD RP	25
		Me	OH	A,C,G,U	DD RP	15, 25-27
		N_3	OH	A,C,G,U	DD RP	15
Synthesis Of Modified DNA	Substrate	OH	F	A,C,G,U	DD DP	13
Synthesis Of Modified RNA	Substrate	OH	OMe	A	DD RP	11
		NH_2	OH	A,C,G,U	DD RP	15-18
		NH_2	OH	A	tRNA-NT	19-21
Ribosomal Research	Substrate	NH_2	OH	A	tRNA-NT	19-21
Enzymatic Research	Inhibition	H	OH	A,C,G,U	DD RP	7
		H	OH	A,C,G,U	aa tRNA S	8
		OH	OMe	A	aa tRNA S	8
		OH	Ara-OH	A,C	RNR	10
		NH_2	OH	A,G	RD RP, DD RP	22,23
		H	OH	A	Poly(A) Pol	24
		NH_2	Ara-OH	G	RD RP DD RP	22
		N_3	OH	A,G	RD RP DD RP	22,23
		OMe	OH	A	aa tRNA S	8
		CHO	CHO	A,C,G,U	DD RP	30,31
		H	OH	U,T	DD RP	64
		Xylo-OH	OH	U,T	DD RP	67
	Activation	OH	OMe	A	RNR	10
		OMe	OH	A	RNR	10
	Chain Termination	NCS	H	A	DD RP	17
		$NHC(O)CH_2Br$	OH	A	DD RP	17
		2',3'-Epoxide	2',3'-Epoxide	A	DD DP	28
	Modification of Enzyme	OH	Arylazido	A	ATP-ase	12
		NCS	H	A	DD RP	17
		$NHC(O)CH_2Br$	OH	A	DD RP	17
		CHO	CHO	A	ATP-ase	29
		CHO	CHO	A	aa tRNA S	32-34

Table 2: Base modified nucleoside 5'-triphosphate analogs



Application	Mode of Action	R	Base	Enzyme class	References
DNA Sequencing	Substrate	H	7-Deaza (A,G,I)	DD DP	38-41
		H	N^4-Me-C	DD DP	46
Synthesis Of Modified DNA	Substrate	H	Benzimidazole	DD DP	35
		H	5-Me-C	DD DP	42-44
		H	7-Deaza (A,G)	Hum. telomerase	45
		H	N^6,N^6-Etheno-2,6-DAP	DD DP	47
		H	Dihydrothymidine	DD DP	48
Synthesis Of Modified RNA	Substrate	OH	5-Br-U	DD RP	49
		OH	5-I-U	DD RP	49
		OH	5-I-C	tRNA NT	50
		OH	5-Formyl U (β anomer)	DD RP	53-56
		OH	2-Thio U	DD RP	59
		OH	5-Br-C	DD DP	59
		OH	Formycin A	DD RP	60
PCR	Substrate	H	N^4-Me-C	DD DP	46
Enzymatic Research	Substrate	H	Benzimidazole	RNR	10
		H	5-Br-U	DD RP	36,37
		OH	8-Azido-A	DD RP	51
		OH	5-Formyl U (α anomer)	DD RP	53-56
		OH	4-Thio-U	DD RP	57-59
		OH	Xanthine	ASS	61
	Inhibition	H	7-Deaza (A,G)	Hum. telomerase	45
		OH	8-Azido-A	aa tRNA S	8
		OH	8-Br-A	aa tRNA S	8
		OH	8-Cl-A	aa tRNA S	8
		OH	9-Purinyl	aa tRNA S	8
	Modification of Enzyme	H	5-I-U	DD RP	49
Ribosomal Research	Photomodification of Ribosomal protiens	OH	3-(Azidooxymethylphenyl)-G	DD DP	52

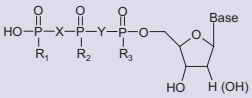
Table 3: Nucleoside 5'-triphosphate analogs with modified γ-phosphate



Application	Mode of Action	X	Nucleoside	Enzyme class	References
Enzymatic Research	Substrate	Anilide	rA	DD RP	141
		4-Azidoanilide	r(A, C, G)	DD RP	142 - 144
		4-Azidoanilide	rA	aa tRNA S	145-150
		1-(5-sulfonatenapthyl)-amide	rA	DD RP	160, 161
		1-(5-sulfonatenapthyl)-amide	r(A,C,G,U)	SVPD	162
		1-(5-sulfonatenapthyl)-amide	d(C, T)	SVPD	162
	Inhibition	Anilide	rA	aa tRNA S	138-140
		4-Azidoanilide	rA	aa tRNA S	145-150
		4-Azidoanilide	rA, Etheno-rA	CK	151-153
		2,4,6-$(Me)_3$-C_6H_4-C(O)O-	rA	aa tRNA S	155, 156
		$BrCH_2C(O)NH$-C_6H_4O-	rG	Ribosome	159
		4-(N-2-Chloroethyl, N-methylamino)-benzylamide	dA, dT	RD DP, DD DP, HK	163-165
		N-Methyl,N-(4-azidobenzyl)-amide	rA	aa tRNA S	124, 148
	Enzyme Modification	N_3	rG	DD RP	154
		2,4,6-$(Me)_3$-C_6H_4-C(O)O-	rA	ATP-ase	157
		FSO_2-C_6H_4-C(O)O-	rA	PK	158
		4-(N-2-Chloroethyl, N-methylamino)-benzylamide	dA, dT	RD DP, DD DP, HK	163-165
		N-Methyl,N-(4-azidobenzyl)-amide	rA	aa tRNA S	124, 148
		Cyclic trimetaphosphate*	rA, Etheno-rA	aa tRNA S	166
		Cyclic trimetaphosphate*	rA	DD RP	167, 168
	Enzyme Photo- Modification	4-Azidoaniline	r(A, C, G)	DD RP	142 - 144
		4-Azidoaniline	rA	aa tRNA S	145-150
		4-Azidoaniline	rA, Etheno-rA	CK	151-153
		4-Azidobenzylamide	rG	DD RP	154

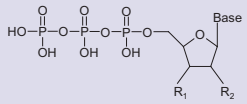
* Nucleoside 5'-Trimetaphosphate

Table 4: Nucleoside 5'-triphosphate analogs with modified triphosphate chain



Application	Mode of Action	X	Y	R_1	R_2	R_3	Nucleoside	Enzyme class	References
DNA Sequencing	Substrate	O	O	O^-	O^-	S^-	dA, dT	DD DP	110-117
		O	O	O^-	O^-	S^-	d(A,C,G,T)	DD DP	118
		O	O	O^-	O^-	BH_3	5-(Me,Et,Br,or I) C	DD DP	137
Synthesis Of Modified DNA	Substrate	O	O	O^-	O^-	S^-	dA, dT	DD DP	110-117
		O	O	O^-	O^-	Me	dT	DD DP, TDNT, HIV-RT, AMV-RT	133,134
Enzymatic Research	Inhibition	CF_2	O	O^-	O^-	O^-	rG	DD DR	66
		CH_2	O	O^-	O^-	O^-	rA	Various enzymes	67-70
		CH_2	O	O^-	O^-	O^-	rA	PFK	72
		O	CH_2	O^-	O^-	O^-	rA	AC	73
		NH	O	O^-	O^-	O^-	rA, rG	Various enzymes	74-82
		O	NH	O^-	O^-	O^-	rA	Various enzymes	67-69
	Substrate	CH_2	O	O^-	O^-	O^-	rA	CK	71
		CH_2	O	O^-	O^-	O^-	rA	DD DP	66
		O	CH_2	O^-	O^-	O^-	rA	CK	71
		O	NH	O^-	O^-	O^-	rA	DD RP, CK	83
		O	O	O^-	O^-	S^-	r(A,C,G,U)	Myosine	84, 85
		O	O	O^-	O^-	S^-	rA	Kinases	86-92
		O	O	O^-	O^-	S^-	rA	PRPPS	93
		O	O	O^-	O^-	S^-	rA, rG	DD RP	94-99
		O	O	O^-	O^-	S^-	rA	2',5' OAS	100, 101
		O	O	O^-	O^-	S^-	rA	PNP	102, 103
		O	O	O^-	O^-	S^-	rA	tRNA NT	104
		O	O	O^-	O^-	S^-	rA	RNA ligase	105
		O	O	O^-	O^-	S^-	rA	GS	106
		O	O	O^-	O^-	S^-	rA	AS	107, 108
		O	O	O^-	O^-	S^-	rA	UDP GPP, GP UT	109
		O	O	O^-	O^-	S^-	dA, dT	DD DP	110-117
		O	O	O^-	O^-	S^-	dA	AMV RT	119
		O	O	O^-	S^-	O^-	rA	Kinases	86-92, 120-122
		O	O	O^-	S^-	O^-	rA	aa tRNA S	123, 124
		O	O	O^-	S^-	O^-	rA	ATP-ase	125
		O	O	O^-	S^-	O^-	dA	DD DP	110-111
		O	O	S^-	O^-	O^-	rA	Kinases	126-129
		O	O	S^-	O^-	O^-	rA, rG	ATP and GTP-ases	125, 130-132
		O	O	O^-	O^-	Me	dT	DD DP, TDNT, HIV-RT, AMV-RT	133,134
		O	O	O^-	O^-	BH_3	d(A,C,G,T)	DD DP	135, 136

Table 5: Sugar and Base modified nucleoside 5'-triphosphate analogs



Application	Mode of Action	R_1	R_2	Base	Enzyme class	References
DNA Sequencing	Chain Terminator	NH_2	H	5-(2-Br-vinyl)-U	DD DP	35
		NH_2	H	5-(2-Br-vinyl)-U	AMV RT	35
		N_3	H	5-(2-Br-vinyl)-U	DD DP	35
		N_3	H	5-(2-Br-vinyl)-U	AMV RT	35
RNA Sequencing	Inhibition of DNA synthesis	H	OH	5-F-C	DNA Primase	7
	Inhibition of DNA synthesis	H	OH	5-F-U	DNA Primase	7
Enzymatic Research	Inhibition	N_3	H	Ribavirin	RD RP	22
		Xylo-OH	OH	5-F-U	DD RP	64
		Xylo-OH	OH	5-Cl-U	DD RP	64
		Xylo-OH	OH	5-Br-U	DD RP	64
		Xylo-OH	OH	5-I-U	DD RP	64
		Xylo-OH	OH	5-Ethyl-U	DD RP	64
		Xylo-OH	OH	5-Propyl-U	DD RP	64
		Xylo-OH	OH	5-Butyl-U	DD RP	64
	Modification of Enzyme	CHO	CHO	Etheno-A	Nitrogenase	65
	Photo-Modification of Enzyme	OH	OH	8-Azido-A	DD RP	62
		Arylazido	OH	8-Azido-A	ATP-ase	63

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