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Synthesis and Biological Activity of Novel Mycophenolic Acid Conjugates Containing Nitro-acridine/acridone Derivatives

Magdalena Malachowska-Ugarte[a*], Grzegorz Cholewinski*, Krystyna Dzierzbicka*, Piotr Trzonkowski**

* Department of Organic Chemistry, Gdansk University of Technology, ul. Narutowicza 11/12, 80-233 Gdansk, Poland
** Department of Clinical Immunology and Transplantology, Medical University of Gdansk, ul. Debinki 7, 80-211 Gdansk, Poland

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Abstract

Hybrid pharmacophore antiproliferative compounds, comprised of mycophenolic acid (MPA) and 1-nitroacridine/4-nitroacridone derivative have been synthesized and evaluated as inhibitors of five different leukemia cell lines (Jurkat, Molt-4, HL60, CCRF-CEM, L1210) and human peripheral blood mononuclear cells from healthy donors. These conjugates possess different length of the linker between MPA and heterocyclic units. The type of heterocyclic part influenced their cytotoxic and anti-proliferative properties. Coupling of MPA **1** with 9-(ω-aminoalkyl)amino-1-nitroacridines **2** and 1-[(ω-aminoalkyl)-4-nitro-9(10*H*)]-acridones **3** was tested. Although all tested conjugates were active, compounds **4a-e** exhibited the highest potency. Preliminary experiments with GMP suggested that the tested compounds acted as IMPDH inhibitors.

1. Introduction

Mycophenolic acid **1** (Figure 1) is an antibiotic possessing wide spectrum of biological activity. Its antifungal, antibacterial, antiviral, as well as immunosuppressive properties are well known [1,2]. MPA is uncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), the crucial enzyme in *de novo* biosynthesis of purine nucleotides. There are two isoforms of IMPDH-type I and II. Type I is expressed constitutively, while the level of type II is increased radically in activated lymphocytes and tumor cells [3]. Mycophenolic acid is used (as mycophenolate mofetil MMF or mycophenolate sodium MPS) as immunosuppressive drug in solid organ transplant patients.

Although it has proved beneficial biological activity, MPA exhibits severe metabolic drawbacks. Its C-4 hydroxyl group is highly susceptible to glucuronidation *in vivo.* Moreover, MPA metabolites undergo subsequent cleavage, which causes many adverse effect in immunosuppressive therapy [1]. For this reason numerous MPA derivatives were obtained and for most of them biological activity has been tested [4]. For instance, Pankiewicz and co-workers developed MPA conjugates with adenosine as promising compounds in human leukemia [5].

Anderson and colleagues designed indole analogs of MPA which exhibited interesting properties in prostate cancer [6,7].
Natural and synthetic acridine derivatives possess fungicidal, antimicrobial, anti-parasitic, anti-inflammatory, anticancer and antiviral activity, widely described in the literature [8-15]. Their antiproliferative properties are known as well. Some of acridine derivatives can bind DNA through intercalation, which leads to cell apoptosis. Series of 1-nitroacridine derivatives was developed as potential anticancer agents, among which nitracrine appeared to be very potent cytotoxin. It is known that 1-nitro-9-acridine derivatives exhibit high cytotoxic activity. These compounds during metabolic activation are transformed to more active products, which bind covalently DNA and other cellular macromolecules [9]. Class of 9-(ω-aminoalkyl)-amino-1-nitroacridines consist of the most potent cytotoxic agents in the acridines family.

In this paper we would like to report the synthesis of new MPA conjugates containing 1-nitroacridine **4a-e** or 4-nitroacridone **5a-e** derivatives, which antiproliferative and immunosuppressive activity were evaluated. We hypothesize that a conjugate comprised two compounds with different mechanisms of antiproliferative action can result in enhanced activity *in vivo.* The concept of hybridization of two bioactive molecules often leads to increased activity due to synergistic effects [15-17]. For example, dual inhibitor of IMPDH and histone deacetylases (HDACs) MAHA (mycophenolic hydroxamic acid) which comprises of MPA and SAHA (suberoylanilide hydroxamic acid), inhibits both these enzymes [18]. SAHA (Vorinostat) is known as one of the most potent HDACs inhibitors, and it is used in the therapy of resistant form of cutaneous T cell lymphoma.

Figure 1 Structure of mycophenolic acid (MPA) **1**

2. Chemistry

Synthesis of heterocyclic components for MPA conjugates: 9-(ω-aminoalkyl)amino-1-nitroacridines **2a-e,** 1-[(ω-aminoalkyl)-4-nitro-9(10*H*)]acridones **3a-e**, was performed according to the method described in literature [19-22].
In the next stage of our study mycophenolic acid was coupled with 9-(ω-aminoalkyl)amino-1-nitroacridines **2a-e** and 1-[(ω-aminoalkyl)-4-nitro-9(10*H*)]-acridones **3a-e** (Scheme 1). MPA **1** molecule possesses electrophilic center at acyl carbon atom in lactone ring and free phenol group. To form an amide bond between carboxyl group of **1** and primary amine of **2a-e/3a-e** selectively, few coupling agents: diphenyl phosphoroazidate (DPPA), 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide with 1-hydroxybenzotriazole (EDCI/HOBt), *N,N'*-dicyclohexylcarbodiimide (DCC), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), mixed anhydrides method (isobutyl chloroformate) were tested. The optimization was elaborated with acridine derivative **4a** and acridone component **5a** (Table 1). Then, the best coupling reagent was used for preparation of the other analogues **4b-e** and **5b-e**, respectively.
The syntheses of conjugates of mycophenolic acid **1** and 1-nitroacridine/4-nitroacridone derivatives **4a-e** and **5a-e** were accomplished as shown in Scheme 1. According to data presented in Table 1, DPPA/Et_3N allowed to obtain conjugates **4a-e** containing 1-nitroacridine derivatives in moderate yields (50-72 %) and EDCI/HOBt gave 4-nitroacridone derivatives **5a-e** in yields 27-32 %. The lower yields in case of conjugates **5a-e** is probably due to poor solubility of acridones **3a-e**

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in the reaction medium.

Scheme 1. Synthesis of conjugates of mycophenolic acid **1** and 1-nitroacridine derivatives **4a-e** and 4-nitroacridone derivatives **5a-e**

Compound no	n	DPPA	EDCI	DCC	EEDQ	Isobutyl chloroformate
4a	2	72	35	31	41	53
4b	3	59	-	-	-	-
4c	4	55	-	-	-	-
4d	5	52	-	-	-	-
4e	6	50	-	-	-	-
5a	2	25	32	30	21.5	27
5b	3	-	33	-	-	-
5c	4	-	32	-	-	-
5d	5	-	29	-	-	-
5e	6	-	27	-	-	-

Table 1. Yields of conjugates **4a-e** and **5a-e** obtained with various coupling reagents.

3. Pharmacology

Cytotoxic activity of compounds **4a-e**, **5a-e** was evaluated against five lymphoid cell lines and activated peripheral blood mononuclear cells (PBMC) as *in vitro* model of immunosuppression. IC_{50} values were calculated with colorimetric MTT test and reported as the compound dose required to reduce the viability of the tested cells by 50% in regard to control sample (48 h incubation in the presence of the tested compounds).

Compounds **2a-e** and **3a-e** were tested in order to evaluate their influence on total biological activity of **4a-e** and **5a-e** and **1** as a reference. To screen antiproliferative activity of tested compounds, five cell lines were selected. Human acute leukemias (ALL): Jurkat, CCFR-CEM, Molt-4, mouse murine leukemia L1210 are derived from lymphocytes, while HL-60 (human acute myelocytic leukemia) from monocytes.

The problem of strong cytotoxic antitumor agents, exemplified in 1-nitroacridine derivatives, is their nonselectivity and, related to this, acute toxicity. The solution is to couple them with a bioactive molecule that exhibits high selectivity. We speculate that selective targeting *in vivo*, due to the MPA part, can result in enhanced activity of the conjugates against leukemias and PBMC cells.

In general, all conjugates **4a-e** and **5a-e** were active against tested cell lines and activated PBMC. MPA derivatives containing acridine moieties **4a-e** were more active than acridone analogues **5a-e**. It is not surprising since 1-nitroacridines have been known to be much more cytotoxic agents than their acridone counterparts. However, **5a-e** are expected to exhibit lower general toxicity *in vivo* in comparison to **4a-e**.

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Data in Table 2 shows *in vitro* inhibition of viability of the cell lines and PBMC by the conjugates **4a-e** and their parent compounds: acridines **2a-e** and MPA **1**. The observed general tendency is that the conjugates exhibit additive, rather than synergistic, cytotoxic activity.

Conjugates **4a-e** are basically more active against tested cell lines than parent MPA, with IC_{50} values depending on the tested cell line. The most susceptible cell line appeared to be mouse leukemia L1210, with IC_{50} values in the range 0.042-0.087 μM. In two cell lines (Molt-4, L1210) and PBMC, conjugate **4c** was the most active among all tested compounds (0.124, 0.02, 0.108 μM, respectively). For Jurkat and CCRF-CEM cell lines conjugate **4e** was the most potent (0.17, 0.53 μM, respectively). For human leukemia HL-60, the least susceptible to tested compounds, conjugate **4b** was the most potent – 2.67 μM.

When for CCRF-CEM**,** L1210 and PBMC cell lines conjugates based on acridine structure **4a-e** were more active than MPA itself. For acute lymphoblastic leukemia MOLT-4 conjugates **4c** and **4d** exhibited higher activity than MPA. Noteworthy, leukemia CCRF-CEM was resistant to MPA, with IC_{50} higher than 156 μM.

Compound no	JURKAT	MOLT-4	CCRF-CEM	HL-60	L1210	PBMC
4a	0.86±0.05	5.44±1.42	2.27±0.162	8.96±0.125	0.046±0.0094	0.21±0.029
4b	0.8±0.058	3.36±1.12	1.90±0.152	2.67±0.20	0.057±0.0142	0.33±0.098
4c	0.41±0.152	0.124±0.0093	0.68±0.0155	3.29±0.18	0.02±0.006	0.108±0.046
4d	0.48±0.0136	0.104±0.019	1.86±0.19	4.86±0.29	0.27±0.0122	0.19±0.114
4e	0.17±0.03	0.3±0.05	0.53±0.126	45.07±2.71	0.087±0.0153	0.37±0.23
2a	<0.0018	9.13±0.166	1.27±0.117	5.27±0.53	0.042±0.003	0.152±0.0287
2b	<0.0017	4.45±0.47	0.206±0.028	2.43±0.243	<0.0017	0.061±0.0162
2c	<0.0016	0.19±0.296	0.151±0.00242	2.22±0.052	<0.0016	0.061±0.0212
2d	<0.0015	<0.0015	0.293±0.00243	0.74±0.086	0.197±0.020	0.043±0.0148
2e	0.0162±0.0010	0.0215±0.00230	0.35±0.038	3.01±0.251	0.0041±0.00047	0.068±0.0180
1	0.193±0.069	0.075±0.0165	156>	9.77±0.94	2.18±0.47	1.28±0.237

Table 2. IC_{50} (μM) values of **4a-e**, **2a-e**, **1** (Values are the mean of triplicates of two independent experiments for cell lines and six independent experiments, each with different donors, for PBMC)

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Table 3 summarizes IC50 values for acridone-MPA conjugates **5a-e** and their parent compounds. Cell lines CCRF-CEM and HL-60 were resistant to acridone-MPA conjugates with IC_{50} values more than 76 μM. In MOLT-4 and PBMC conjugate **5c** was the most potent inhibitor (0.027 and 0.60 μM, respectively) and **5e** was the most potent inhibitor for L1210 cells (0.03 μM). As compared to MPA **1,** all conjugates exhibited weaker activity in MOLT-4 (besides **5c, 5d**) and HL-60 cell lines. On the other hand, JURKAT T cells were surprisingly sensitive to compounds **5a-e** with IC_{50} values below 0.0008 μM.

IC_{50} values for activated PBMC revealed that conjugates **4a-e** were more active (0.108-0.37 μM) than MPA **1** (1.28 μM). The conjugates **5a-e** with IC_{50} values between 0.60 and 2.75 μM were in the same magnitude of activity as **1**.

Noteworthy, IC_{50} values of compounds **4a-e** calculated for CCRF-CEM and HL-60 (Table 2, 3) were the most similar to values estimated for human activated lymphocytes. Both of these cell lines were originally derived from the peripheral blood, CCRF-CEM cells were isolated from buffy coat of a child with acute lymphoblastic leukemia.

Compound no	Jurkat	MOLT-4	CCRF-CEM	HL-60	L1210	PBMC
5a	<0.0008	0.60±0.105	>83.8	>83.5	0.102±0.0135	0.87±0.073
5b	<0.0008	0.34±0.085	>81.5	>81.5	0.73±0.150	0.88±0.122
5c	<0.0008	0.027±0.002	>79.5	>79.5	0.83±0.049	0.60±0.060
5d	<0.0008	0.20±0.126	>78	>78	1.03±0.028	0.97±0.17
5e	<0.0008	0.138±0.0071	>76	>76	0.03±0.00097	1.06±0.50
3a	<0.0017	0.0114±0.00111	0.258±0.0060	22.41±1.41	0.03±0.01	2.75±1.17
3b	<0.0016	0.0096±0.00131	1.12±0.054	25.89±0.45	0.074±0.0109	1.09±0.22
3c	<0.0015	0.034±0.0202	2.39±0.187	477.54±19.31	1.59±0.095	1.65±0.03
3d	0.0109±0.0823	0.238±0.0038	1.59±0.273	40.51±3.00	0.126±0.0262	2.59±0.38
3e	0.54±0.39	0.13±0.0271	2.34±0.186	180.99±3.50	0.090±0.0164	3.41±0.51
1	0.193±0.069	0.075±0.0165	>156	9.76±0.94	2.18±0.47	1.28±0.237

Table 3. IC_{50} (μM) values of **4a-e**, **2a-e**, **1** (Values are the mean of triplicates of two independent experiments for cell lines and four for PBMC)

Subsequently, we investigated the mechanism of action of conjugates **4a-e** and **5a-e**.

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The question arose whether covalent amide bond acridine/acridone-MPA influenced cytotoxic activity in comparison to a mixture of parent compounds *in vitro*. We evaluated this using Jurkat and PBMC cells. According to results presented in Tables 4, 5, antiproliferative activities **4a-e**, **5a-e** were weaker or comparable to that of the units **2a-e + 1** tested separately, but mostly stronger than in case of mycophenolic acid **1**.
This intermediate activity can be advantageous for optimization of their cytotoxic properties *in vivo*.

	PBMC	2a-e + 1		JURKAT	2a-e + 1
4a	0.17±0.065	0.22±0.023	**4a**	0.00135±0.00017	0.0037±0.0019
4b	0.33±0.11	0.31±0.111	**4b**	0.0084±0.00022	<0.0008
4c	0.106±0.082	0.025±0.0036	**4c**	0.0143±0.00085	<0.0008
4d	0.26±0.037	0.032±0.014	**4d**	0.0125±0.0004	0.059±0.0093
4e	0.45±0.030	0.120±0.003	**4e**	0.010±0.007	0.014±0.0024
1	1.68±0.143		**1**	3.46±0.37	

Table 4. Comparison of IC_{50} (μM) values of conjugates **4a-e** and mixtures of their separate components: **2a-e** and **1**

	PBMC	3a-e + 1		JURKAT	3a-e + 1
5a	0.90±0.088	0.24±0.023	**5a**	0.055±0.0090	0.078±0.019
5b	0.86±0.0106	0.38±0.0058	**5b**	0.52±0.098	0.38±0.041
5c	0.49±0.029	0.99±0.39	**5c**	1.11±0.113	0.20±0.116
5d	0.97±0.26	0.27±0.114	**5d**	0.41±0.03	0.062±0.0092
5e	0.24±0.017	0.24±0.014	**5e**	0.065±0.0112	0.39±0.047
1	0.58±0.143		**1**	3.9±0.56	

Table 5. Comparison of IC_{50} (μM) values of conjugates **5a-e** and mixtures of their separate components: **3a-e** and **1**

In order to test whether conjugates **4a-e**, **5a-e** target IMPDH in the cells, we evaluated the effect of GMP (guanosine monophosphate) addition on the inhibition of cell proliferation. IMPDH

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inhibitors, including MPA, reduced GTP and deoxy-GTP pools and addition of guanine, guanosine, GMP (guanosine triphosphate) and deoxy-GMP reversed this effect [1, 23]. S. Mitsuhashi and co-workers reported that addition of guanosine to cell culture inhibited their growth by 50% [23].We observed the same effect in case of GMP addition (data not shown). Figures 2 and 3 provide data on inhibitory effect of compounds **1** (MPA) **4a**, **4e**, **5a**, **5e** on Molt-4 cell line in the absence or presence of GMP. Results collected in Figure 2 indicated that for acridine conjugates **4a** and **4e,** reversible effect of GMP could reach maximum of 50% increase of the proliferation (position 8 on the horizontal axis). In case of weak DNA intercalating agents conjugates **5a** and **5e** (see Figure 3), the observed effect was even stronger and the increase of the proliferation was around 70% in the highest concentration of GMP in the culture (position 7 on the horizontal axis). These results prove that conjugates **4a**, **4e**, **5a**, **5e** were IMPDH inhibitors.

Figure 2. Effect of GMP addition on inhibitory activity of compounds **1**, **4a**, **4e.** The data present the mean±SD of triplicate test (three separate experiments gave similar results)

Figure 3. Effect of GMP addition on inhibitory activity of compounds **1**, **5a**, **5e**. The data present the mean±SD of triplicate test (three separate experiments gave similar results)

Conclusions

In summary, the synthesis of the new derivatives of MPA **1** and 1-nitroacridine **2** or 4-nitroacridone **3** was optimized for the best yield and purity of the desired MPA analogues **4a-e**, **5a-e**. Antiproliferative activity of compounds **4a-e** and **5a-e** was evaluated on few lymphoid cell lines (CCRF-CEM, JURKAT T, MOLT4, HL60, L1210) using MTT colorimetric test.All compounds were active. Conjugates based on acridine structure **4a-e** exhibited much higher potency than **5a-e**. Tests on activated human lymphocytes confirmed results obtained on cell lines. According to our experiments, investigated conjugates occurred to be less active than mixtures of their components, but still they proved to be IMPDH inhibitors.
Derivatives **4a-e** will be examined *in vivo.*

Experimental

See electronic supplementary information.

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