New Analogues of Mycophenolic Acid

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Abstract: Mycophenolic acid (MPA) possesses antibacterial, antifungal, antiviral, immunosuppressive and anticancer properties. It is a non-competitive and reversible inhibitor of dehydrogenase inosine-5'-monophosphate (IMPDH) [1,2]. This compound belongs to the immunosuppressive drugs used for the prevention of both acute and chronic transplant rejection [3]. Until now, two derivatives of MPA have been used clinically: mycophenolate mofetil (MMF, CellCept) and mycophenolate sodium (MPS, Myfortic). They cause, similar to MPA, although at lower degree, the side effects such as vomiting, abdominal pain, diarrhea, nausea, gastrointestinal, urogenital tract, blood or nervous system disorders. These drawbacks and glucuronidation of MPA *in vivo* limit the use of these compounds as pharmaceuticals [4]. Therefore, research is still going on for more effective analogs that are less toxic to the organism and could improve the quality of life of patients. In this review article, the authors present the synthesis of novel derivatives of mycophenolic acid, together with their initial biological investigations.

Keywords: Anticancer agents, antiproliferative activity, conjugates, immunosuppressants, IMPDH, Mycophenolic acid.

INTRODUCTION

Over the past 40 years, there has been tremendous growth of transplantation. It is a new field of medicine that saves and improves the quality of life of many patients suffering from end-stage heart failure, liver, kidneys and respiratory system failures. The success of organ transplantation is dependent on many factors, including the use of immunosuppressive therapy [1].

Immunosuppressive therapy is aimed at inhibiting of immune response, and as a further consequence, the reduction of graft rejection and prolongation of the survival of the recipient, which determines the success of transplantation. The reported immunosuppressants should be selective in order to reduce the risk of over-immunosuppression, which can lead to bacterial, viral, and fungal infections and an increased risk of malignancy [2]. In the immunosuppressive therapy, drugs with different mechanisms of action, are administered simultaneously. Used regimens of treatment depend on many factors such as the transplanted organ, the degree of risk of the immune response as well as the side effects or other associated disease [3].

Until the mid-90s primary immunosuppressive agent, used in Poland was azathioprine (AZA) **1** (Fig. (**1**)). AZA **1** found application in the treatment of kidney transplantation. However, now actual participation of AZA **1** in the treatment of transplant is reduced, because it has a lot of adverse effects. AZA possesses mutagenic properties, probably due to the presence of the nitro group which in the organism is metabolised and leads to an abnormal increase of the number of free radicals causing oxidative stress. Moreover, this drug is hepatotoxic, impairs bone marrow, pancreas inflammation, hair loss, fever, cardiac arrhythmias and many others. It is also observed that patients receiving AZA more often suffer from cancer. On the field appeared drugs that act more efficiently - mycophenolate mofetil (MMF) - prodrug of MPA **2** [4, 5] (Fig. (**2**)). MMF **3** and MPS (mycophenolate sodium) **4** (Fig. (**3**)) are currently the most widely used antiproliferative immunosuppressants. However, the basic problem of their use are diseases of the digestive, blood, urogenital, nervous system and cancers [6,7]. Therefore, research is still conducted on better tolerated potential drugs based on the structure of mycophenolic acid.

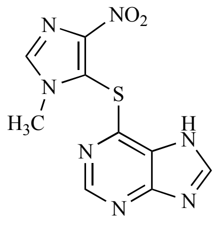

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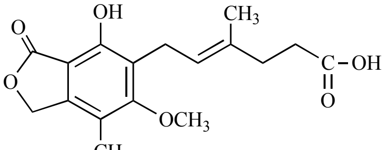
Fig. (1). Structure of azathioprine (AZA).

Mycophenolic acid (MPA) **2** (Fig. (**2**)) was isolated in 1896 from culture *Penicillium* as a natural product of mold fermentation by the italian physicist Gosio [8-10], and its structure was determined in 1957 [11]. This compound was approved by FDA for the transplantation in 1995. Since then, his popularity increased significantly [10]. MPA **2** comprises a phthalide, wherein the aromatic ring is six-substituted with hydroxy, methyl, methoxy and six carbon chain with double bond in the *trans* configuration and the free carboxyl group.



2

Fig. (2). Structure of MPA [12].

MPA exhibits antibacterial, antifungal, antiviral, immunosuppressive and anticancer properties [12]. This compound is used as an immunosuppressive drug in transplantation for the prevention of acute and chronic transplant rejection [13-15]. MPA is characterized by a very poor absorption from the gastrointestinal tract, and in case of MMF the esterification significantly improves the bioavailability [16]. So far, there are clinically applied two derivatives of MPA: mycophenolate mofetil **3** (MMF) under the trade name CellCept produced by Roche and mycophenolic acid **4** (MPS) (Fig. (**3**)) known as Myfortic manufactured by Novartis.

MPA **2** is a competitive and reversible inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH), predominantly isoforms II, which is present in tumor cells and in activated lymphocytes [17]. IMPDH is required for the *de novo* purine synthesis, is involved in the conversion of IMP to GMP. It is concluded that the MPA **2** is connected to a previously created complex enzyme-IMP-NAD [18].

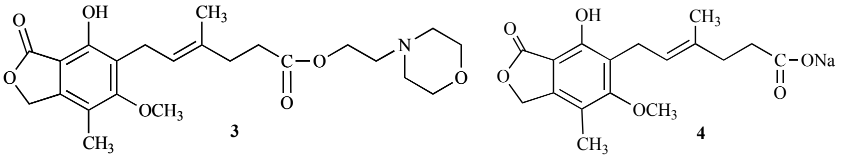
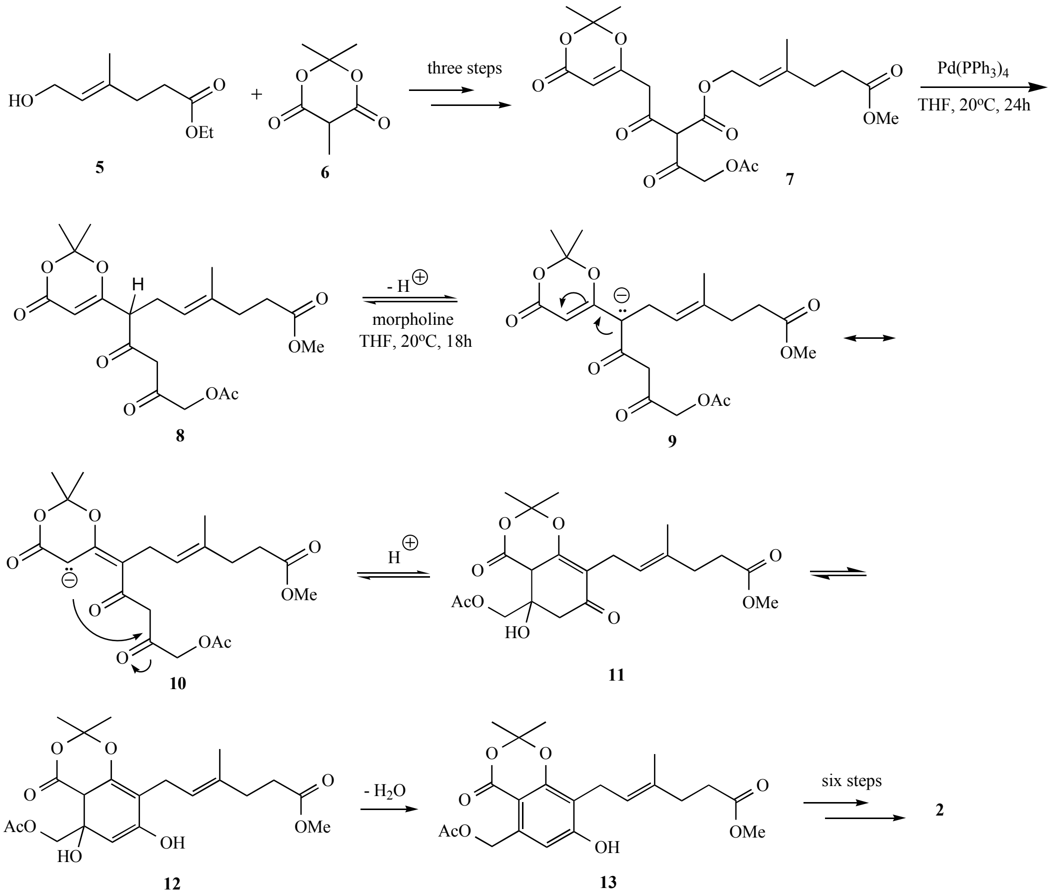


Fig. (3). Structures of MMF **3** and MPS **4** [12].



Scheme (1). Synthesis of mycophenolic acid reported by Brookes *et al.* [23].

Analyzing crystal structures found that the MPA **2** binds to subdomain N and P subdomain part [17] and causes a reduction of guanine nucleotide pools, especially GTP. This results in disruption of DNA and RNA, leading to apoptosis [10]. MPA **2** reduces the amount of guanosine triphosphate in cells which results in cell cycle arrest in the G1 phase, inhibition of dendritic cell maturation, proliferation of T cells and their migration to the graft and production of antibodies stimulated by mitogen and antigens [19-21]. The exhaustion of the nucleotide guanosine leads to reduced possibility of organ rejection after transplantation.

In this review we present recent synthetic approach to mycophenolic acid, newly isolated MPA derivatives from natural sources, and novel MPA derivatives including their synthetic aspects and biological properties.

NEW TOTAL SYNTHESIS OF MYCOPHENOLIC ACID

Mycophenolic acid can be obtained by fermentation techniques or chemical synthesis. Although MPA structure seems to be not so complicated at first sight (no asymmetric centers or fused rings), its six-substituted aromatic ring is quite synthetically challenging. Since Birch first developed synthesis of MPA in 1969, there were many attempts to improve method of MPA obtaining [22]. However, they suffer from poor performance or consist of to many stages. Recently Brookes *et al.* [23] created a new approach based on the palladium-catalyzed allylation, biomimetic cyclization and aromatization as shown in Scheme **1**. In this method, mycophenolic acid was received in twelve stages with a final yield of 6%. The starting materials were ester **5** and Meldrum's acid derivative **6**, converted to diketo ester dioxinone **7**. In the next stage, **7** underwent palladium-catalyzed decarboxylation and alkenylation to **8**, and treatment with morpholine provided carbanion **9**. Its mesomeric form **10** was cyclized to **11** (in tautomeric equilibrium with **12**), followed by dehydration to benzene derivative **13**.

MPA DERIVATIVES ISOLATED FROM NATURAL SOURCES

In 2012 Chen and co-workers reported the novel derivatives of MPA that were isolated from fungi *Panicillium* Sp. SOF07 of marine sediments [24]. It turned out that these fungi produce biologically active compounds exhibiting cytotoxicity against human tumor cell lines: HCT15, A549 and HEP3B. Analogs **14-17** (Fig. (**4**)) were isolated from strain Sp. SOF07 upon fermentation in medium rice with sea salt. The collected fractions were extracted and analyzed by HPLC.

According to the assessment of biological activity, each of the isolated analogues inhibited IMPDH, although at lower level than MPA. The most active compound within **14-17** was analogue **14** and the weakest occurred to be **17**.

Qiong-Ying *et al.* [25] isolated three new mycophenolic acid derivatives **18-20** (Fig. (**4**)) from cultures of the mushroom *Laetiporus sulphureu*. Compounds were isolated and purified by various chromatographic techniques and also evaluated for cytotoxic activities.

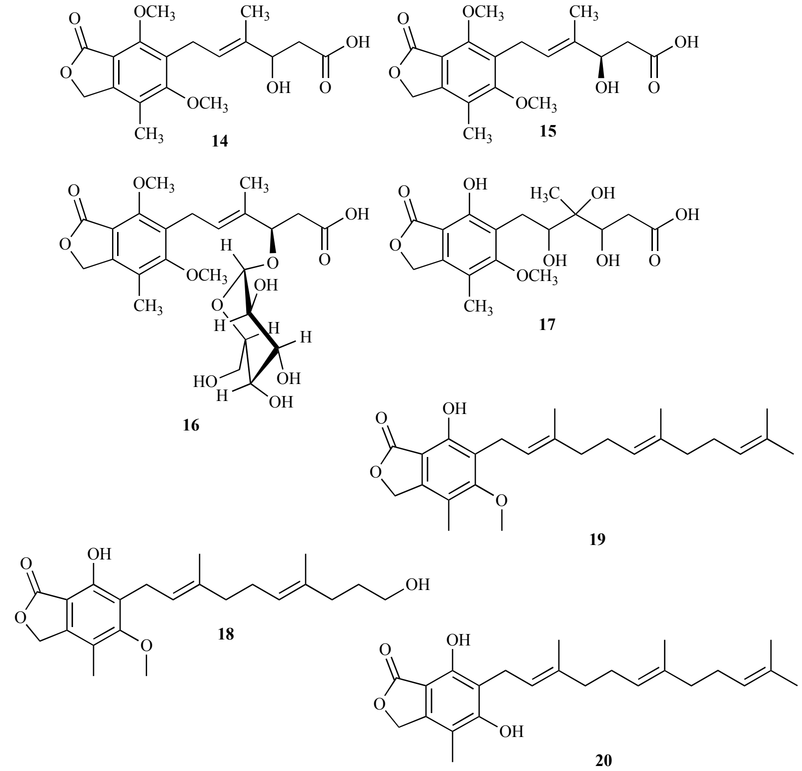


Fig. (4). Structures of isolated analogue MPA: 4'-hydroxymycophenolic **14** Penicacid A **15**, Penicacid B **16** and Penicacid C **17** [24], and **18-20** from cultures of the mushroom *Laetiporus sulphureu* [25].

Cytotoxicity assay was based on human myeloid leukemia HL-60, hepatocellular carcinoma SMMC-7721, lung cancer A-549 cells, breast cancer MCF-7, and colon cancer SW480 cell lines. Only compound **20** exhibited moderate inhibitory effects against five human cancer cell lines.

NOVEL SYNTHETIC ANALOGS OF MPA

Most of the recently reported structural alterations of MPA analogs concern hex-4-enoate side chain, whereas phthalide ring moiety remained unspoiled. Hydrogen bond between carboxylic group of MPA and Ser276 of IMPDH is one of the important interactions in MPA-IMPDH complex [17], and the modifications of the polar group at the end of the side chain of MPA consisted significant studies in design of its novel derivatives [22]. Iwaszkiewicz-Grześ *et al.* [10] described amino acid analogs MPA in the form of methyl esters **21a-k**, and with the free carboxyl group of **22a-k**. The most preferred method for forming an amide bond between the carboxyl group of MPA and amino acids ester **21a-k** found the use of a condensing reagent EDCI in the presence of DMAP. Hydrolysis of the methyl ester with lithium hydroxide in methanol gave analogs with a free carboxyl group of **22a-k** (Fig. (**5**)).

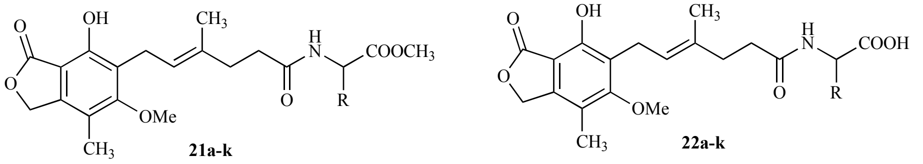
The cytotoxicity of the obtained derivatives was evaluated *in vitro* against Jurkat cell line and PBMCs. MPA analogs with a free carboxyl group were more cytotoxic. Both series of compounds **21a-k** and **22a-k** showed comparable antiproliferative activity to MPA and also act as inhibitors of IMPDH. Their biological activity depended both on the configuration at the chiral center in the molecule, and the amino acid substituents. Methyl ester of *N*-mykofenoilo-L-phenylalanine **21j**, *N*-mykofenoilo-D-glutamic acid **22e** and *N*-mykofenoilo-L-leucine **22h** are characterized by high antiproliferative activity in comparison to MPA together with the lowest toxicity. Therefore they were selected for *in vivo* studies as a new potential immunosuppressants.

Małachowska-Ugarte *et al.* [26] synthesized conjugates 1-nitroacridine/4-nitroacridone of MPA **23a-e** and **24a-e** ((Fig. (**6**)). Derivatives differed with the length of the diamine linker between MPA moiety and heterocyclic unit. The best yields were achieved with DPPA/Et$_3$N for coupling of MPA with diaminie derivatives of acridine and EDCI/HOBt in case of acridones.

The antiproliferative activity of the received compounds was investigated against PBMC and lymphoid cell lines (CCRF-CEM, JURKAT T, MOLT-4, HL-60, L1210). The more active ones occurred to be conjugates of MPA and 1-nitroacridines **23a-e** than **24a-e**, as derivatives of high cytotoxic acridines. In general, both types of conjugates revealed intermediate activity between MPA and relevant heterocyclic part and acted as IMPDH inhibitors [25].

In the next stage of the study Cholewiński *et al.* [27] developed the synthesis of ester conjugates MPA with *N*-(ω-hydroxyalkyl)-9-acridone-4-carboxamides or *N*-(ω-hydroxyalkyl)acridine-4-carboxamides of the linker length n = 1-5 carbon atoms between the MPA and the heterocyclic moiety **31a-e**, **32a-e** (Scheme **2**). These compounds hold acridine/acridone without nitro group, which might cause reduction of toxicity. The target esters **31a-e**, **32a-e** were prepared using the method of Yamaguchi. Mycophenolic acid bearing protected phenol group **25** or **26** reacted with the respective acridone **27a-e** or acridine **28a-e** to produce **29a-e**, **30a-e**, followed by deprotection. Noteworthy, acridines **32a-e** formation needed more stable *tert*-butyldiphenylsilyl ether, because undesired deprotection during esterification diminished yield of the reaction [27].

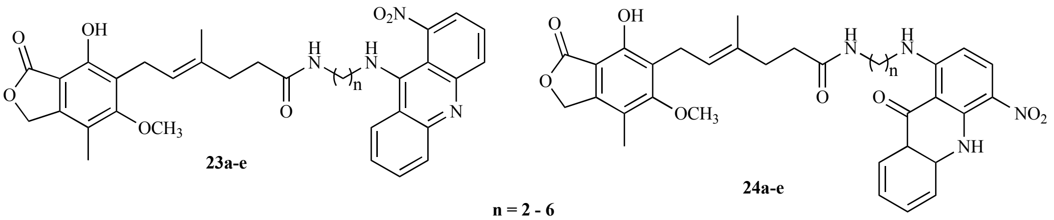
Antiproliferative activity study was performed on Jurkat cell lines and PBMCs. Acridine conjugates **32a-e** were more active than acridone derivatives **31a-e**. The observed activity was also influenced by the length of the chain between MPA and heterocyclic moieties. The most promising compounds



21a-k **22a-k**

21,22 a: D-CH$_3$
21,22b: L-CH$_3$
21,22c: H
21,22d: L-CH$_2$CH$_2$COOR'
21,22e: D-CH$_2$CH$_2$COOR'
21,22f: L-CH(CH$_3$)$_2$
21,22g: D-CH(CH$_3$)$_2$
21,22h: L-CH$_2$CH(CH$_3$)
21,22i: D-CH$_2$CH(CH$_3$)$_2$
21,22j: L-CH$_2$Ph
21,22k: D-CH$_2$Ph

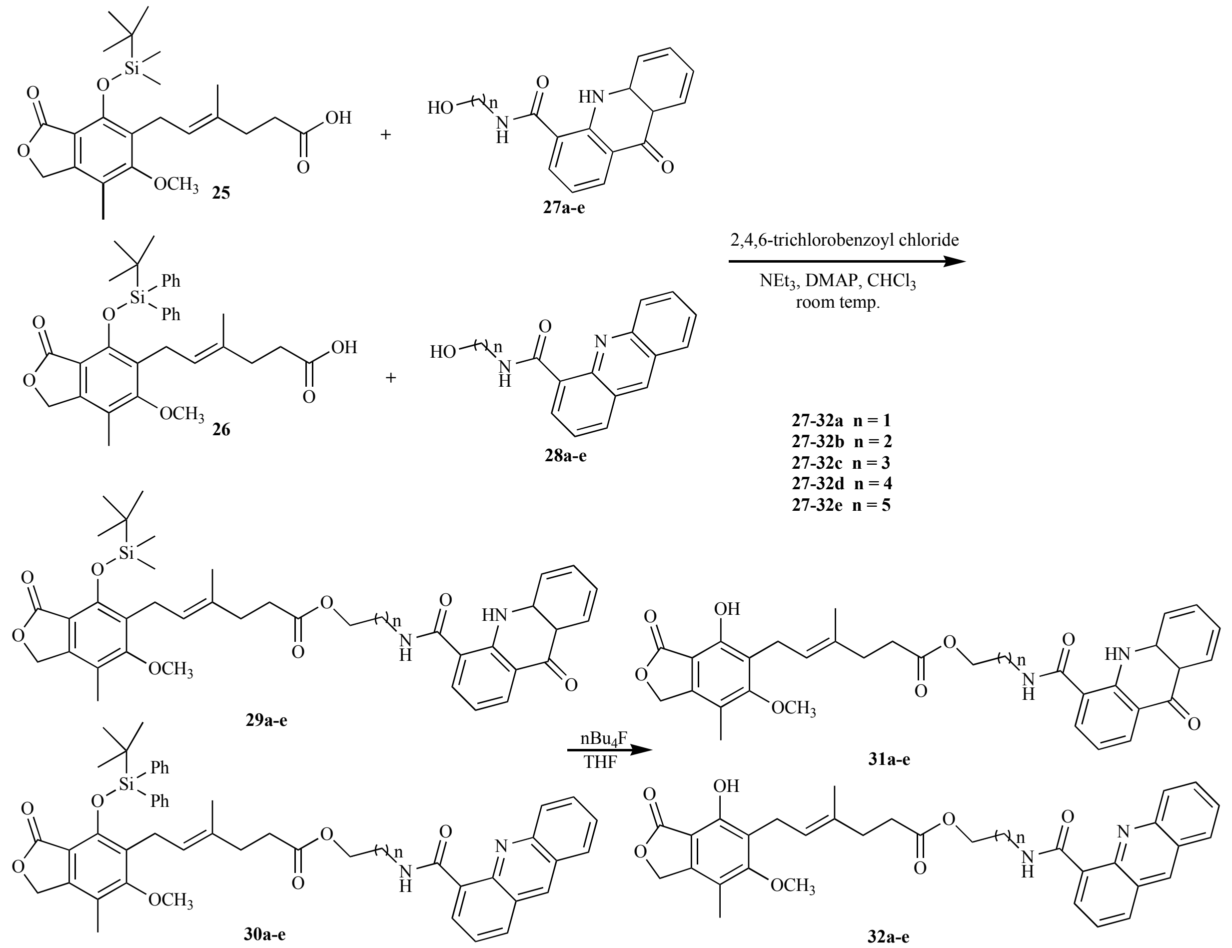
Fig. (5). Structures of amino acid MPA analogs methyl ester **21a-k** and their derivatives with free carboxyl group **22a-k** [10].



23a-e **24a-e**

n = 2 - 6

Fig. (6). Synthesis of conjugates 1-nitroacridine/4-nitroacridone MPA **23a-e** and **24a-e** [26].



Scheme (2). Synthesis of conjugates of MPA with acridones **31a-e** and conjugates of MPA with acridines **32a-e** [27].

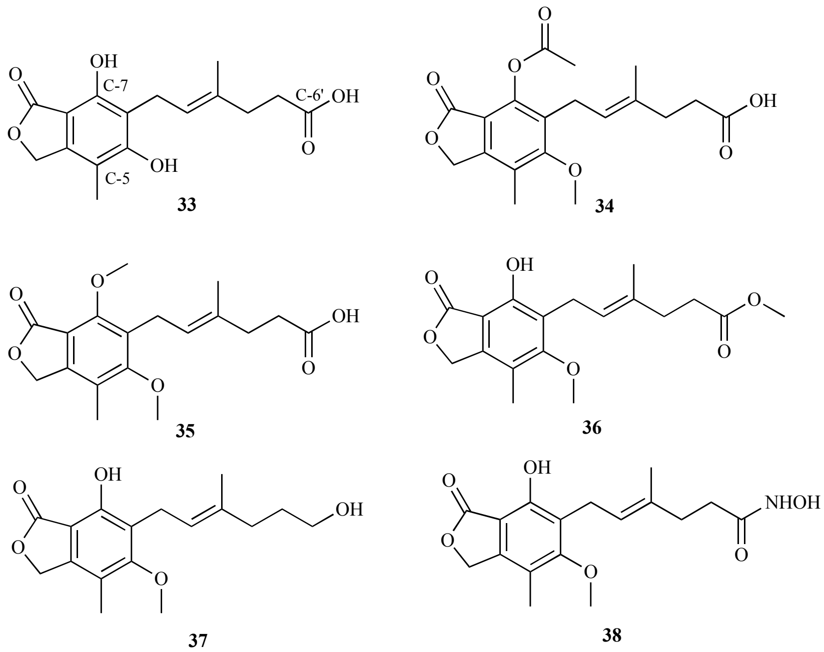


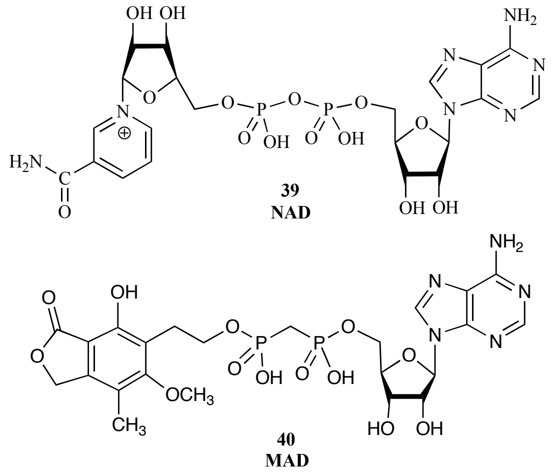
Fig. (7). Structures of derivatives **33-38** with modification at C-5, C-7 and C-6’ position [28].

proved to be **31b**, **31d**, **32a** and **32b** and were proposed to be studied further as potential novel immunosuppressive compounds.

Mitsuhashi *et al.* [28] synthesized 6 mycophenolic acid derivatives to evaluate structure-activity relationships (SAR) for inhibition of inosine monophosphate dehydrogenase (type I and type II) and differentiation induction of K562 cells. The modifications were performed on functional groups at C-5, C-7, and C-6` positions in MPA (Fig. (**7**)).

Studies showed that none of these modifications provided any better inhibitor than MPA **2**. However, SAR results presented important conclusions: (i) functional groups (C-5, C-7, C-6`) in MPA were important for inhibitory activity against IMPDH (ii) modification of 5-, 7-, and 6`-groups did not improve specificity for IMPDH II against IMPDH I (iii) modification in compound **33** (demethylation of 5-OMe) increased hydrophilicity and diminished cell permeability (iv) esters at C-7' and C-6 were hydrolyzed in cells (v) HDACs inhibitor **38** caused significantly lower proliferation and differentiation, whereas its IMPDH inhibition was less decreased.

Since MPA **2** binds at NAD binding pocket of IMPDH, Pankiewicz research group developed MPA analogs of NAD **39** (Fig. (**8**)). The novel inhibitors based on NAD **39** exhibited both antitumor activity against various cell lines and inhibitory activity towards IMPDH. Previously obtained compounds, e.g. MAD **40** proved to be interesting analogs for further modifications as active, selective and non-toxic inhibitors of IMPDH, resistant to glucuronidation, although their activities were slightly lower than in case of MPA **2** [29-35]. MAD analogs **40** hold methylenebis(phosphonate) linker instead of pyrophosphate one to decrease their susceptibility to hydrolysis.



39
NAD

40
MAD

Fig. (8). Structures of NAD **39** and MAD **40** [29].

Potency of MAD analogues was improved by linker modifications and substitution at 2 position of adenosine moiety. Difluoromethylenebis(phosphonate) derivative **41** (Fig. (**9**)) possesses isosteric P-CF$_2$-P to P-O-P linker and ethyl group at 2 position of adenosine. High inhibitory towards IMPDH I (K$_i$= 0.6 nM), IMPDH II (K$_i$ = 14 nM) and antiproliferative activity were established in case of 4-pyridyl MAD **42**. Tetrazole-linked conjugate **43** revealed significant activity towards Mycobacterium tuberculosis IMPDH (*K*i value of 1.5-2.2 μM). The authors investigated also the structure of complex of IMPDH with MAD, where *anti* conformation of adenosine moiety was observed. In contrast to that, 8-bromoadenosine derivative **44** although existing in *syn* conformation, gave higher activity against both IMPDH I and II than MAD **40**.

The direct bromination of MAD **40** did not work in the synthesis of compound **44**. The synthetic route (Scheme **3**) included reaction of adenosine derivative **45** with bromine, then **46** was coupled with alcohol **47**, followed by deprotection to **44**.

It was established, that mycophenolate mofetil **3** (MMF) undergoes hydrolysis by cellular esterases to MPA **2** and is rapidly glucuronidated. This susceptibility is pharmacologically important and is investigated in case of novel MPA derivatives. For instance, unexpectedly D-adenosine ester analogue **49** (Fig. (**10**)) was more stable and exhibited higher activity towards IMPDH I, II, K562 than unnatural L-enantiomer **50**. Amide **51** showed similar inhibitory properties to ester **49** towards both IMPDHs and less antiproliferative potency than **49** and **50**. The compound should be resistant to esterases, but can be cleaved by cellular peptidases. In search of compounds possessing modified metabolic profile, amino acids were introduced between MPA and adenosine units. Among these diamides, both valine derivatives **52** (D or L) revealed nanomolar IMPDH inhibition, even better than in case of MPA **2**. In contrast to that, antiproliferative activities of **52** against cancer cell lines were not observed and authors concluded that diamides like **52** were probably not transported into the cell. Noteworthy, diamide **52** (D or L) occurred to be more potent towards IMPDH than respective amino acid MPA derivatives **21f**, **22f**, **21g**, **22g** (Fig. (**5**)). Amino acid methyl esters **21f**, **21g** inhibited IMPDH weaker than carboxylic analogues **22f**, **22g**. On the other hand, methyl esters **21f**, **21g** provided higher antiproliferative activity towards cancer lines in comparison to free acids **22f**, **22g**, which suggested better cell membrane penetration [29].

The next example of MPA – derived conjugates are derivatives of quinic acid. Previously, Wu and co-workers described ester **53** (JP-3-110) (Fig. (**11**)) [36,37], which gave similar to MPA **2** immunosuppressive activity together with less toxicity as immunosuppressive agent to prevent rejection in human islet transplantation. However, poor stability caused by susceptibility to hydrolysis was a serious metabolic drawback. The structure was modified to amide **54** (MQ4). As expected, the authors observed improved stability and according to less toxicity compound **54** was subjected to *in vivo* examinations as promising immunosuppressive agent.

Synthesis of amide **54** (Scheme **4**) included conversion of MPA **2** to active ester with *N*-hydroxysuccinimide (HOSu) **55**, and upon ethylenediamine treatment amine **56** was produced. The target compound **54** was received in the reaction of **56** with quinic acid tetraacetate active ester **57** [37].

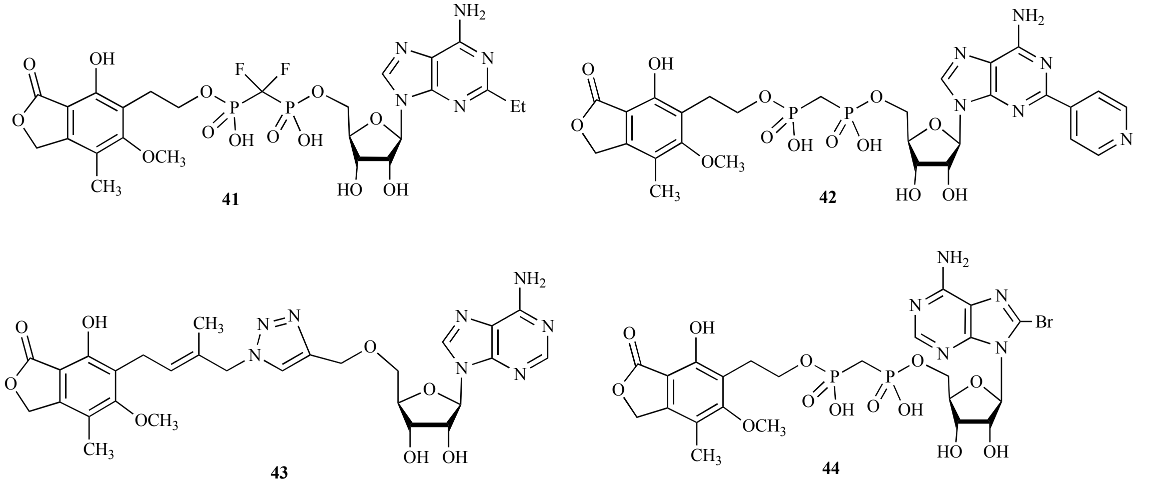
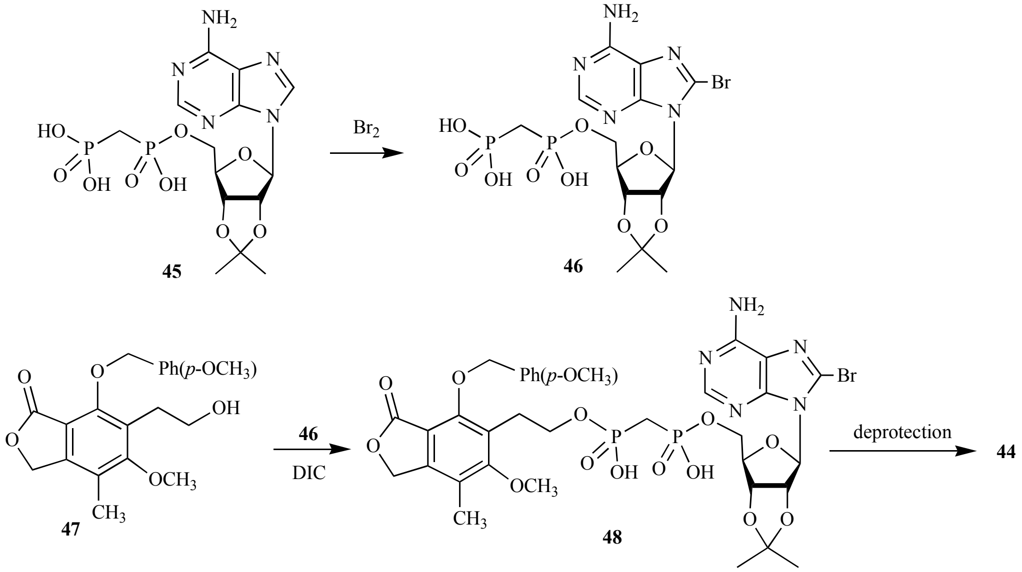


Fig. (9). Structures o MPA conjugates with difluoromethylenebis(phosphonate) group **41**, 4-pyridyl MAD **42**, tetrazole-linked analog **43** and 8-bromoadenosine derivative **44** [29].



Scheme (3). Synthesis of 8-bromoadenosine derivative **44** [29].

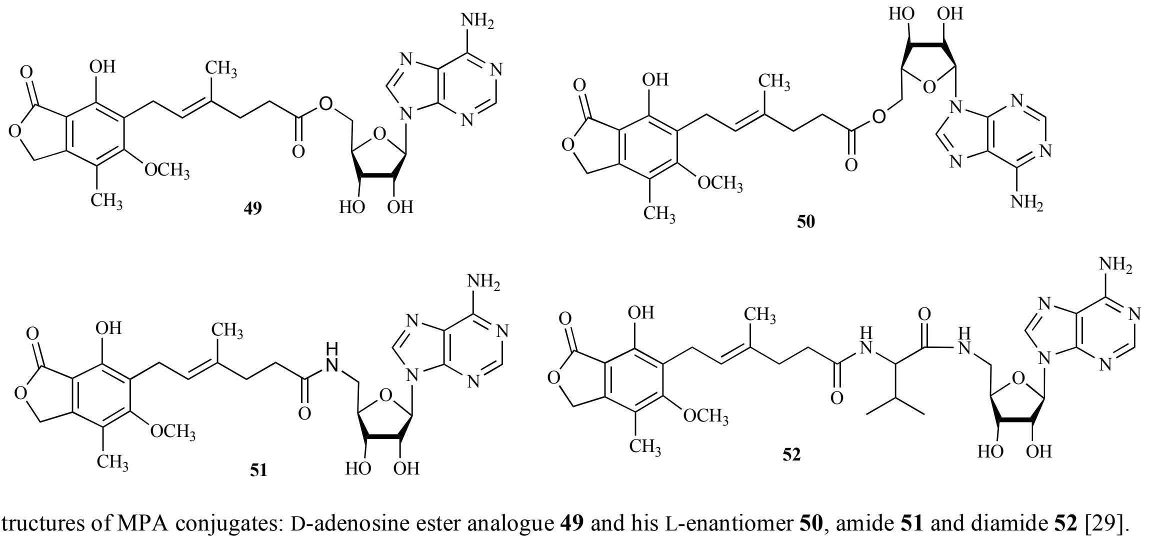


Fig. (10). Structures of MPA conjugates: D-adenosine ester analogue **49** and his L-enantiomer **50**, amide **51** and diamide **52** [29].

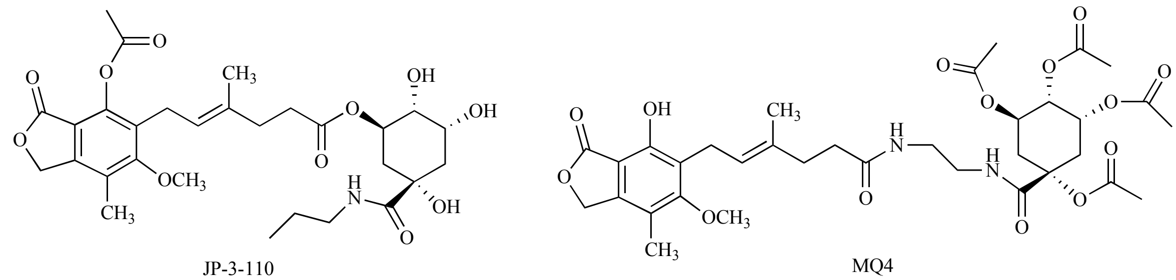
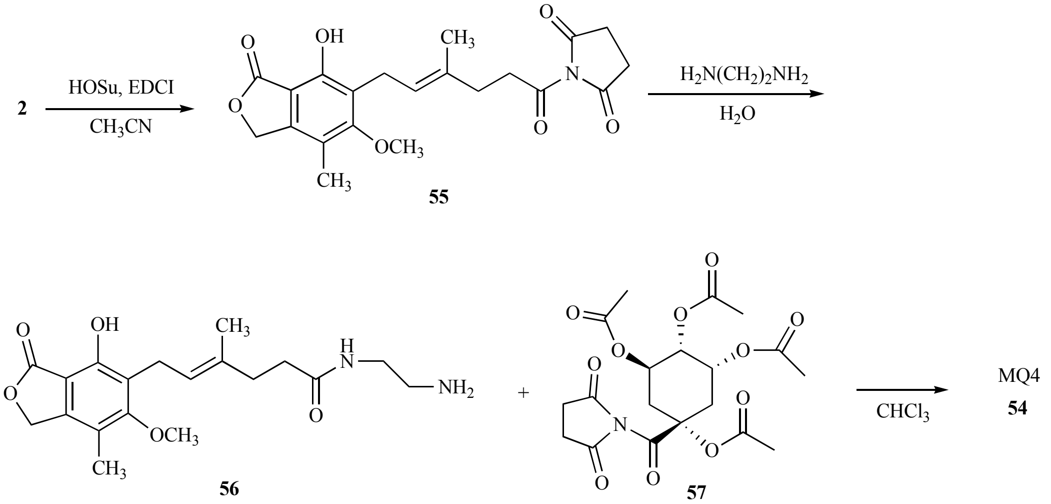

JP-3-110
53
MQ4
54

Fig. (11). MPA conjugates with quinic acid JP-3-110 **53**, MQ4 **54** [36, 37].



Scheme (4). Synthesis of amide conjugate of MPA and quinic acid MQ4 **54** [37].

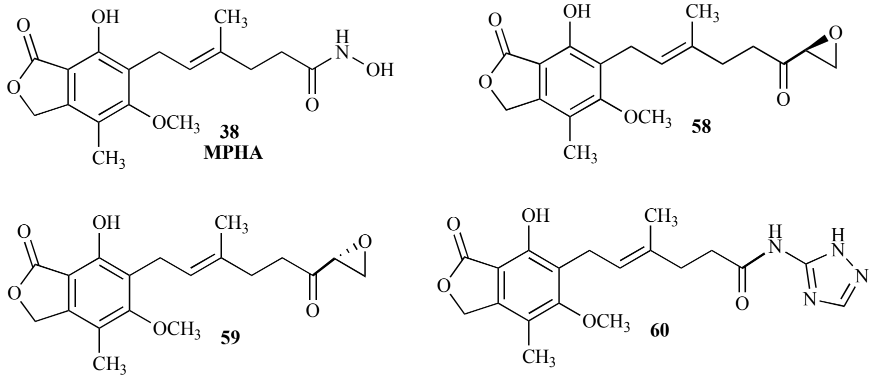
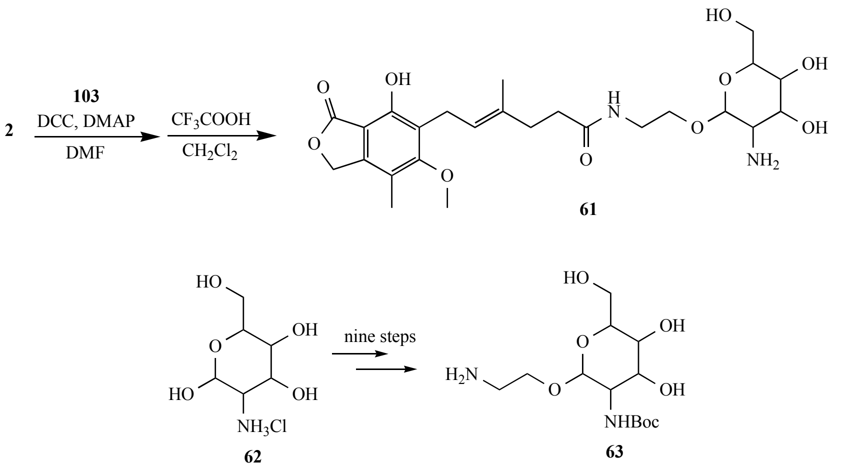

38
MPHA
58
59
60

Fig. (12). The structure MPHA **38** and new derivatives including epoxides **58**, **59** and hetorocycles like 2,3,5-triazoyl group **60** [38].

The other modification of the side chain of MPA reported Sunohara *et al.* as potential inhibitors of IMPDH and histone deacetylase (HDECs) (Fig. (**12**)) [38]. These enzymes are the molecular target for anti-cancer drugs, since catalyze the removal of acetyl group of lysine in histones [39]. Similarly to mycophenolate hydroxamic acid (MPHA) **38**, the developed compounds hold zinc binding group including thiol, epoxides **58**,**59**, and hetorocycles like 2,3,5-triazoyl **60**. Both epoxides **58**,**59** and triazoyl analogue **60** revealed high potency towards IMPDH and K562.

Wang *et al.* [40] focused on the synthesis of mycophenolic acid-glucosamine conjugate **61** to improve drug efficacy with a lower dosage and better kidney targeting in patients after renal transplantation. According to recent authors' studies, 2-glucosamine due to low toxicity was ideal as a therapeutic carrier. Conjugate **61** occurred to be less cytotoxic *in vitro*, and investigations *in vivo* confirmed higher bioavailability of **61** than in case of MPA. The synthetic route started from 2-glucosamine **62** which was converted to amine **63**. Then compound **63** was coupled with



Scheme (5). Synthesis of a conjugate of mycophenolic acid with glucosamine **61** [40].

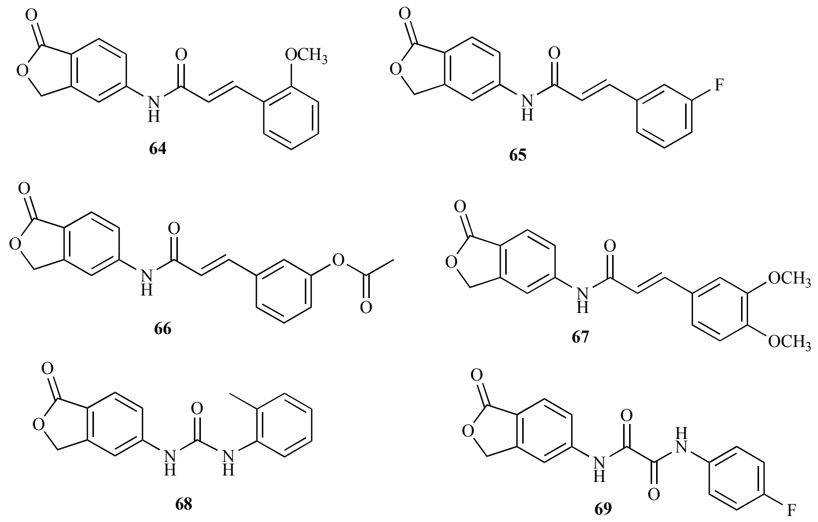


Fig. (13). Structures of isobenzofurans with *o*-methoxy **64**, *m*-fluoro 65, *m*-acetoxy **66**, 3,4-dimethoxy **67** groups, urea derivative **68** and analogue **69** possessing *p*-fluorophenyl ring [41].

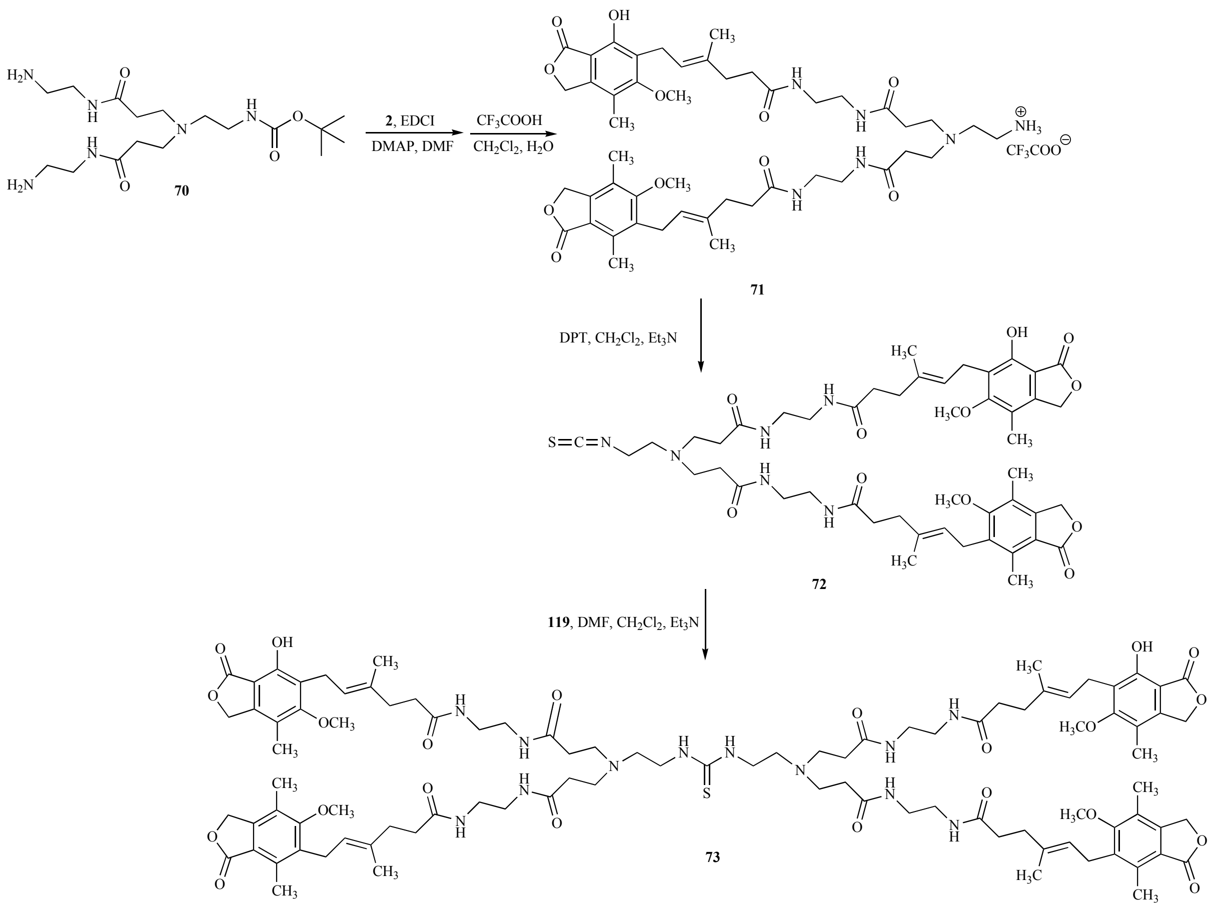
mycophenolic acid **2** using reagent DCC in the presence of DMAP, followed by deprotection provided conjugate **61** according to Scheme **5**.

Yang group [41] synthesized isobenzofuran IMPDH II inhibitors (**64-69**) (Fig. (**13**)) to assess their structure-activity relationship on the basis of T-cells proliferation activity. Among α,β-unsaturated amides the highest antiproliferative activity, better than MPA **2**, gave *o*-methoxy **64**, *m*-fluoro **65**, *m*-acetoxy **66**, 3,4-dimethoxy **67** analogues. On the other hand, a strong electron-withdrawing CN group at 4 position and bulky substituent at 2 position diminished the observed activity. In case of ureas, compound **68** exhibited the highest potency. Hydrogen bond formation was clearly important, since *N*,*N*-disubsituted urea derivative gave no activity. Analogue **69** possessing *p*-fluorophenyl ring occurred to be the most potent diamide. Additionally, respective *p*-hydroxyphenyl derivative was significantly more active in comparison to *p*-methoxyphenyl one, probably due to hydrogen bond formation.

Guazelli and co-workers [42] received a new family of MPA dendrimers, where MPA units were connected by scaffolding between carboxyl groups. They decided on the dendrimers as drug delivery system and used one of the most known poly (amidoamine) (PAMAM) structures (Scheme **6**).

In order to obtain a symmetrical dendrimer **73**, diamine **70** was coupled with two moles of MPA **2** to produce, after deprotection, trifluoroacetate **71**. Subsequently, the resulting compound **7** reacted with di-2-pyridyl thionocarbonate (DPT) in the presence of triethylamine to give isothiocyanate **72**, which yielded product **73** (Scheme **6**). Immunosuppressive properties of the resulting compound **73** are currently investigated.

Mycophenolic acid analogues can be combined with other immunosuppressive agents in order to achieve synergy effects. Unfortunately, there is a possibility of increased risk of infection or neoplasia [43]. In the case of a combination mycophenolate mofetil with rapamycin (RPM), it is possible



Scheme (6). Synthesis of dendrimer **73** [42].

to increase the inhibition of T cell proliferation as compared to cyclosporine [44], and can also interfere with early immune response by targeting the important functions of dendritic cells [45]. Therefore, the combination of the MMF with RPM appears to be safer and more complementary immunosuppressive effects of reducing the side effects compared to the use of these drugs alone. In addition to the immunosuppressive properties of these drugs they are used in dermatology, as glucocorticoid sparing agents for autoimmune and inflammatory disorders as atopic dermatitis (AD).

Jung *et al.* [46] investigated the therapeutic effect of applied rapamycin (RPM) and MPA on atopic dermatitis which is a chronic inflammatory skin disorder. Scientists administrated topically RPM and MPA at various ratios with 2-chloro-1,3,5-trinitrobenzene on mice skin. Results of therapeutic effects were assessed by measuring skin severity scores, ear thickness and histological changes (mast cell count, total serum levels). Expression of interleukin and interferon was also examined. Results showed that RPM with MPA significantly improved clinical signs (erythema, edema, excoriation and dryness), also decreased epidermal thickening, dermal edema and cellular infiltration. This combination of drugs also suppresses expression of Th-1/Th-2-related cytokines. This concludes that RMP with MPA may be promising candidates for the treatment of atopic dermatitis.

Cheng *et al.* [47] focused on developing inhibitor for Middle East respiratory syndrome coronavirus (MERS-CoV) which is highly pathogenic human coronaviruses. In 2014, there were over 938 people infected with a fatality rate of about 36% globally. To overcome this issue, there were combined previous research of two SARS-CoV inhibitors: 6-mercaptopurine (6MP) **74**, 6-thioguanine (6TG) **75** (Fig. (**14**)) with immunosuppressive drug, mycophenolic acid, which led to promising activity against MERS-CoV. Further studies on this synergistic effect and antiviral properties can be anticipated.

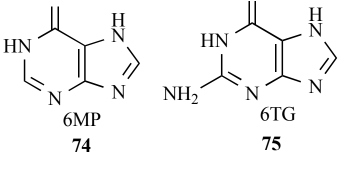


Fig. (14). Structures of 6-Mercaptopurine (6MP) **74**, 6-Thioguanine (6TG) **75** [47].

CONCLUSION

Since 1893 when Bartolomeo Gosio isolated mycophenolic acid from culture *Penicilium*, a few decades ahead were discovered his broad-spectrum acting drug having antiviral, antibacterial, anticancer, properties. Nowadays, MPA is most commonly used immunosuppressant, and its biological activity is widely used in the treatment of many of today's disease. In recent years, a lot of new derivatives of MPA have been received, *inter alia* there are analogues based on combined structures NAD and MPA, isobenzofurans, epoxy, thiol derivatives of MPA, MPHA and its modifications, amino acid and heterocyclic analogues, conjugates of MPA derivatives with 1-nitroacridine/4-nitroacridone, quinic acid, glucosoamine. Some compounds showed inhibitory action, not only to the IMPDH but also for HDAC. Some of the compounds of the preliminary tests *in vitro* have been qualified for *in vivo* assessments. Studies concerning mycophenolic acid and its derivatives are still in progress and can provide new promising chemotherapeutics.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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REFERENCES

[1] Gołąb, J.; Jakóbisiak, M.; Lasek, W., Stokłosa, T. *Immunologia*, PWN: Warszawa, **2011**.

[2] Sereno, J.; Parada, B.; Rodrigues-Santos, P.; Lopes, P.C.; Carvalho, E.; Vala, H.; Teixeira-Lemos, E.; Alves, R.; Figueiredo, A.; Mota, A.; Teixeira, F.; Reis, F. Serum and rental tissue markers of nephropathy in rats under immunosuppressive therapy: cyclosporine versus sirolimus. *Transplant. Proc.*, **2013**, *45*, 1149-1156.

[3] Rowiński, W.; Duplik, M. *Zalecenia dotyczące leczenia immunosupresyjnego po przeszczepach narządów unaczynionych.*; Fundacja Zjednoczeni dla Transplantacji: Warszawa, **2006**.

[4] Satoh, S.; Tada, H.; Murakami, M.; Tsuchiya, N.; Inoue, T.; Togashi, H.; Matsuura, S.; Hayase, Y.; Suzuki, T.; Habuchi, T. The influence of mycophenolate mofetil versus azathioprine and mycophenolic acid pharmacokinetics on the incidence of acute rejection and infectious complications after renal transplantation. *Transplant. Proc.*, **2005**, *37*, 1751-1753.

[5] David, K.M.; Morris, J.A.; Steffen, B.J.; Chi-Burris, K.S.; Gotz, V.P.; Gordon, R.D. Mycophenolate mofetil vs. azathioprine is associated with decreased acute rejection, late acute rejection, and risk for cardiovascular death in renal transplant recipients with pretransplant diabetes. *Clin. Transplant.*, **2005**, *19*, 279-285.

[6] Pareja-Ciuro, F.; Diez-Canedo, J.S.; Gomez-Bravo, M.A.; Garcia-Gonzalez, I.; Tamayo-López, M.J.; Sousa-Martin, J.M.; Pascasio-Acevedo, J.M.; Porras-Lopez, M.F.; Gavilan-Carrasco, F.; Bernardos-Rodriguez, A. Efficacy and safety of mycophenolate mofetil as part of induction therapy in liver transplantation. *Transplant. Proc.*, **2005**, *37*, 3926-3929.

[7] Jimenez-Perez, M.; Lozano-Rey, J.M.; Marin-Garcia, D.; Olmendo Martin, R.; de la Cruz Lombardo, J.; Rodrigo Lopez, J.M. Efficacy and safety of monotherapy with mycophenolate mofetil in liver transplantation. *Transplant. Proc.*, **2006**, *38*, 2480-2481.

[8] Gosio, B.; *Rivista d'Igiene e Sabita publica Ann*., **1896**, *7*, 825.

[9] Ardestani, F.; Fatemi, SS.; Yakhchali, B.; Hosseyni, SM.; Najafpour, G. Evaluation of Mycophenolic Acid Production by Penicillium bervicompactum MUCL 19011 in Batch and Continuous Submerged Cultures. *Biochem. Engineer. J.*, **2010**, *50*, 99-103.

[10] Iwaszkiewicz-Grześ, D.; Cholewiński, G.; Kot-Wasik, A.; Trzonkowski, P.; Dzierzbicka, K. Synthesis and biological activity of mycophenolic acid-amino acid derivatives. *Eur. J. Med. Chem.*, **2013**, *69*, 863-871.

[11] Clutterbuck, P.W.; Raistick, H. Studies in the biochemistry of micro-organisms: The molecular constitution of the metabolic products of *Penicillium* brevi-compactum Dierckx and releated species. II. Mycophenolic acid. *J. Biochem.*, **1933**, *27*, 654-667.

[12] Covarrubias-Zúniga, A.; Gonzalez-Lucas, A.; Dominguez, M.M. Total synthesis of mycophenolic acid. *Tetrahedron*, **2003**, *59*, 1989-1994.

[13] Kaplan, B. Mycophenolic acid trough level monitoring in solid organ transplant recipients treated with mycophenolate mofetil: Association with clinical outcomes. *Curr. Med. Res. Opin.*, **2006**, *22*, 2355-2364.

[14] Ghio, L.; Ferraresso, M.; Zacchelloc, G.; Murere, L.; Ginevrid, F.; Belingheria, M.; Peruzzie, L.; Zanonf, F.; Perfumod, F.; Berardinellib, L.; Tirelling, S.; Strologoh, LD.; Fontanai, I.; Valentei, U.; Carilloj, M.; Edefontia, A. Longitudinal evaluation of mycophenolic acid pharmacokinetics in pediatric kidney transplant recipients. The role of post-transplant clinical and therapeutic variables. *Clin. Transplant.*, **2009**, *23*, 264-270.

[15] Jablecki, J.; Kaczmarzyk, L.; Patrzałek, D.; Domanasiewicz, A.; Boratyńska, Z. First Polish forearm transplantation: report after 17 months. *Transplant. Proc.*, **2009**, *41*, 549-553.

[16] Rowiński, W.; Wałaszewski, J.; Pączek, L. *Transplantologia kliniczna*.; PZWL: Warszawa, **2004**.

[17] Sintchak, M.D.; Nimmesgern, E. The structure of inosine 5'-monophosphate dehydrogenase and the disgn of novel inhibitors. *Immunopharmocol.*, **2000**, *47*, 163-184.

[18] Digits. J.A.; Hedstrom, L. Species-Specific Inhibition of Inosine 5'-Monophosphate Dehydrogenase by Mycophenolic Acid. *Biochem.*, **1999**, *38*, 15388.

[19] Premaud, A.; Rousseau, A.; Johnson, G.; Canivet, C.; Gandia, P.; Muscari, F.; Peron, J.M.; Rostain, L.; Marquet, P.; Kamar, N. Inhibition of T-cell activation and proliferation by myphenolic acid in patients awaiting liver transplantation: PK/PD relationships. *Pharmacol. Res.*, **2011**, *63*, 432-438.

[20] Hea, X.; Smeets, R.L.; Koenen, H.J.P.M.; Vink, P.M.; Wagenaars, J.; Boots, A.M.H.; Joosten, I. Mycophenolic Acid-Mediated Suppression of Human CD4+ T Cells: More Than Mere Guanine Nucleotide Deprivation. *Am. J. Transplant.,* **2011**, *11*, 439-449.

[21] von Vietinghoff, S.; Ouyang, H.; Ley, K.; Mycophenolic acid suppresses granulopoiesis inhibition of interleukin-17 production. *Kidney International*, **2010**, *78*, 79-88.

[22] Cholewinski, G.; Malachowska-Ugarte M.; Dzierzbicka K. The chemistry of mycophenolic acid – synthesis and modifications towards desired biological activity. **2010**, *17*, 1926-1941.

[23] Brookes, P. A.; Cordes, J.; White, J. P. A.; Barrett, A. G. M.; Total synthesis of mycophenolic acid by a palladium-catalyzed decarboxylative allylation and biomimetic aromatization sequence. *Eur. J. Org. Chem*., **2013**, *32*, 7313-7319.

[24] Chen, Z.; Zheng, Z.; Huang, H.; Song, Y.; Zhang, X.; Ma, J.; Wang, B.; Zhang, C.; Ju, J. Penicacids A-C, three new mycophenolic acid derivatives and immunosuppressive activities from the marine-derived fungus Penicillium sp. SOF07. *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 3332-3335.

[25] Qiong-Ying, F.; Xia, Y.; Zheng-Hui, L.; Yan, L.; Ji-Kai, L.; Tao, F.; Bao-Hua, Z.; Mycophenolic acid derivatives from cultures of the mushroom Laetiporus sulphureu. *Chin. J. Nat. Med*., **2014**, *12*, 685-688

[26] Malachowska-Ugarte, M.; Cholewiński, G.; Dzierzbicka, K..; Trzonkowski, P. Synthesis and biological activity of novel mycophenolic acid conjugates containing nitro-acridine/acridone derivatives. *Eur. J. Med. Chem.*, **2012**, *54*, 197-201.

[27] Cholewiński, G.; Iwaszkiewicz-Grześ, Dorota.; Trzonkowski, P.; Dzierzbicka, K. Synthesis and biological activity of ester derivatives of mycophenolic aci and acridines/acridones as potential immunosuppressive agents. *J. Enzyme Inhib. Med. Chem.*, **2015**, DOI:10.3109/14756366.2015.1077821.

[28] Mitsuhashi, S.; Takenaka, J.; Iwamori, K.; Nakajima, N.; Ubukata, M.; Structure-activity relationships for inhibition of inosine monophosphate dehydrogenase and differentiation induction of K562 cells among the mycophenolic acid derivatives. *Bioorg. Med. Chem*., **2010**, 18, 8106-8111

[29] Felczak, K.; Vince, R.; Pankiewicz, K.W. NAD-based inhibitors with anticancer potential. *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 332-336.

[30] Pankiewicz, K.W.; Lesiak-Watanabe, K.B.; Watanabe, K.A.; Patterson, S.E.; Jayaram, H.N.; Yalowitz, J.A.; Miller, M.D.; Seidman, M.; Majumdar, A.; Prehna, G.; Goldstein, B.M. Novel mycophenolic adeninę bis(phosphonate) analogues as potential differentiation agents against human leukemia. *J. Med. Chem.*, **2002**, *45*, 703-712.

[31] Felczak, K.; Chen, L.; Wilson, D.; Williams, J.; Vince, R.; Petrelli, R.; Jayaram, H.N.; Kusumanchi, P.; Kumar, M.; Pankiewicz, K.W. Cofactor-type inhibitors of inosine monophosphate dehydrogenase via modular approach: targeting the pyrophosphate binding sub-domain. *Bioorg. Med. Chem.*, **2011**, *19*, 1594-1605.

[32] Felczak, K.; Pankiewicz, K.W. Rehab of NAD(P)-Dependent Enzymes with NAD(P)-Based Inhibitors. *Curr. Med. Chem.*, **2011**, *18*, 1891-1908.

[33] Pankiewicz, K.W.; Felczak, K. From ribavirin to NAD analogues and back to ribavirin in search for anticancer agents. *Heterocycl. Commun.*, **2015**, *21*, 249–257.

[34] Pankiewicz, K.W.; Petrelli, L.; Singh, R.; Felczak, K. Nicotinamide Adenine Dinucleotide Based Therapeutics, Update. *Curr. Med. Chem.*, **2015**, *22*, 3991-4028.

[35] Chen, L., Wilson, D.J.; Labello, N.P.; Jayaram, H.H.; Pankiewicz, K.W.; Mycophenolic acid analogs with a modified metabolic profile. *Bioorg. Med. Chem*., **2008**, 16, 9340-9345.

[36] Wu, H.; Pagadala, J.; Yates, C. R.; Miller, D.; Mahato, R. I. Synthesis and characterization of an anti-apoptotic immunosuppressive compound for improving the outcome of islet transplantation. *Bioconjugate Chem.*, **2013**, *24*, 2036-2044.

[37] Peng, Y.; Dong Y.; Mahato R.I. Synthesis and Characterization of a Novel Mycophenolic Acid−Quinic Acid Conjugate Serving as Immunosuppressant with Decreased Toxicity. *Mol. Pharmaceutics.*, **2015**, *12*, 4445−4453.

[38] Sunohara, K.; Mitsuhashi, S.; Shigetomi, K.; Nakata, M. Discovery of *N*-(2,3,5-triazoyl)mycophenolic amide and mycophenolic epoxyketone as novel inhibitors of human IMPDH. *Bioorg. Med. Chem. Lett.*, **2013**, *23*, 5140-5144.

[39] Chen, L.; Wilson, D.; Jayaram, H.N.; Pankiewicz, K.W. Dual inhibitors of IMP-dehydrogenase and histone deacetylases for cancer treatment. *J. Med. Chem.*, **2007**, *50*, 6685-6691.

[40] Wang, X.; Lin, Y.; Zeng, Y.; Sun, X.; Gong, T.; Zhang, Z.; Effects of mycophenolic acid-glucosamine conjugates on the base of kidney targeted drug delivery. *Inter. J. Pharma*., **2013**, *456*, 223-234.

[41] Yang, N.; Wang, Q.; Wang, W.; Wang, J.; Li, F.; Tan, S.; Cheng, M. The synthesis and *in vitro* immunosuppressive evaluation of novel isobenzofuran derivatives. *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 53-56.

[42] Guazelli, L.; D'Andrea, F.; Giorgelli, F.; Catelani, G.; Panattoni, A.; Luvisi, A. Synthesis of PAMAM Dendrimers Loaded with Mycophenolic Acid to Be Studied as New Potential Immunosuppressants. *J. Chem*., **2015**, http://dx.doi.org/10.1155/2015/263072.

[43] Callen, J.P.; Goldsmith, L.A.; Katz, S.I.; Gilchrest, B.A.; Paller, A.S.; Leffell, D.J.; Wolff, K. *Immunosuppressive and immunomodulatory drugs*, Fitzpatrick's Dermatology in General Medicine, 8th ed.; McGraw-Hill, **2012**, 223, 2807–2808.

[44] Nguyen, V.H.; Zeiser, R.; Negrin, R.S. Role of naturally arising regulatory T cells in hematopoietic cell transplantation, *Biol. Blood Marrow Transplant*., **2006**, 12, 995–1009.

[45] Hackstein, H.; Thomson, A.G. Dendritic cells: emerging pharmacological targets of immunosuppressive drugs, *Nat. Rev. Immunol*., **2004**, 4, 24–34.

[46] Jung, K. E.; Lee, Y. J.; Ryu, Y.H.; Kim, J. E.; Kim, H. S.; Kim, B. J.; Kang, H.; Park, Y. M.; Effects of topically applied rapamycin and mycophenolic acid od TNCB-induced atopic dermatitis-like lesions in NC/Nga mice. *Inter. Immunopharm*., **2015**, 26, 432-438.

[47] Cheng, K-W.; Cheng, S-Ch.; Chen, W-Y; Lin, M-H.; Chuang, S-J.; Cheng, I-H.; Sun, Ch-Y.; Chou, Ch-Y.; Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. *Antiviral Research*., **2015**, *115*, 9-16.