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REVIEW ARTICLE

Synthesis of the inosine 5′-monophosphate dehydrogenase (IMPDH) inhibitors

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Abstract

Inosine 5′-monophosphate dehydrogenase (IMPDH) is important molecular target for potential anticancer, antiviral, antibacterial and immunosuppressive agents. A lot of compounds were obtained to establish their activity toward this enzyme, and to improve therapeutic properties of IMPDH inhibitors used as the drugs. Some of the recently reported analogs exhibited promising results during *in vitro* and *in vivo* examinations in comparison to substances applied in clinic. In this review, we describe synthesis and biological activity evaluations of the newly designed IMPDH inhibitors.

Keywords

Anticancer activity, antiviral activity, IMPDH inhibitors, mycophenolic acid, organic synthesis

History

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Introduction

Inosine 5′-monophosphate dehydrogenase [IMPDH; IMP-NAD oxidoreductase, Enzyme Classification (EC) 1.2.1.14] catalyzes a metabolic branch point reaction in purine synthesis and has been an area of intellectual convergence in biological and medicinal chemistry[1]. This enzyme is responsible for the catalysis of NAD-dependent oxidation of inosine monophosphate (IMP) as a substrate to xanthosine 5′-monophosphate (XMP), which is used in the *de novo* biosynthesis of guanine. XMP is converted to guanosine monophosphate (GMP) with glutamine as an amino donor. The *de novo* pathway of purine synthesis is considered as a more significant source of nucleotides for B and T cells than the salvage pathway, in order that IMPDH inhibitors are potential immunosuppressive agents[2,3]. In this review, we focus mainly on synthesis and biological activity of human IMPDH inhibitors.

The inhibition of IMPDH induces a reduction in guanine nucleotide pools that produce an interruption of DNA and RNA synthesis[4], a decline in intracellular signaling[5], and down-regulation of c-myc and K_i-ras oncogenes *in vitro*[6–8] and in leukemic cells of patients treated with inhibitors[8]. IMPDH inhibition results in apoptosis in both neoplastic cell lines and activated T-lymphocytes[6,9].

The role of IMPDH as a chemotherapeutic target was further advanced by the discovery, in 1990 by Natsumeda et al.[10], that the enzyme exists as two isoforms: labeled type I and type II[10]. These isoforms are of identical size and share 84% sequence identity. However, the type I ''housekeeping'' isoform is constitutively expressed in both normal and neoplastic cells[11], while type II expression is preferentially up-regulated in human neoplastic cell lines[10,12].

The type II isoform is also a target for immunosuppression. The role of this isoform in immunosuppression has been elucidated by a series of mice knockout models described by Gu et al.[13]. While the type II enzyme is the major isoform in normal human T-lymphocytes, these cells appear to induce both type I and type II enzymes when stimulated by mitogen[13]. Recently, hIMPDH-I has been identified as anti-angiogenic drug target and mycophenolic acid (MPA) was found to block tumor-induced angiogenesis *in vivo*[14]. Therefore, in this review newly designed compounds are also discussed, which indicated interesting selectivity between both isofoms of hIMPDH.

Enzymes of purine nucleotide biosynthesis pathways are attractive targets for the design of potential anticancer, immunosuppressant, antiviral and antibacterial agents[14–20]. There were obtained many of the compounds that inhibit IMPDH activity, but only a few have been used in medicine.

IMPDH inhibitors used in clinic

IMPDH is recognized as a validated target for several major therapeutic areas[21]. A number of potent and selective inhibitors of IMPDH are used in clinic (Figure 1). Ribavirin (**1**) is a prodrug of corresponding 5′-monophosphate, which as a competitive inhibitor interacts with the IMP domain of IMPDH[22,23].

Ribavirin (**1**) (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, Virazole®, Valeant Pharmaceuticals, Laval, Quebec, Canada) is a broad spectrum antiviral agent inhibiting the replication of a wide range of DNA and RNA viruses *in vitro* and *in vivo*, the most sensitive being HSV-1, HSV-2, vaccinia, influenza, parainfluenza, measles, rhino, respiratory syncytial and some tumor viruses[24–26]. It is also active against various retroviruses including HIV and is used for treatment of AIDS

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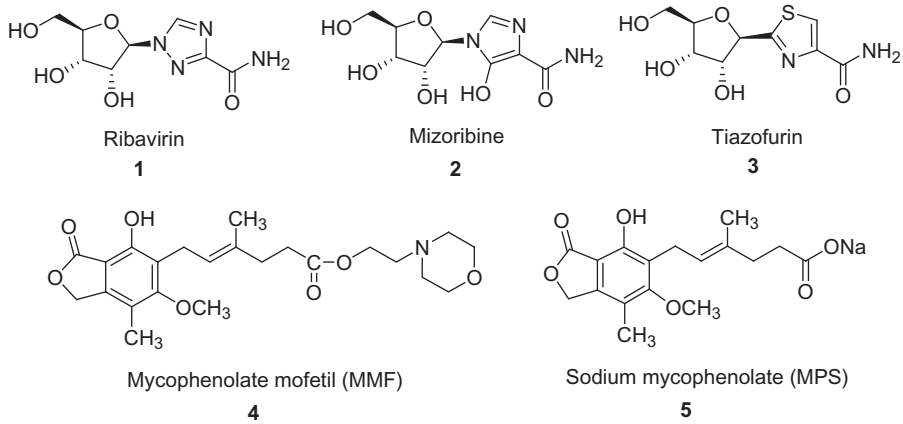

Figure 1. Currently used drugs that target IMPDH.

patients[27]. The combination of interferon-α and ribavirin was proved to be successful in therapy for patients with chronic hepatitis C infection[28].

Mizoribine (**2**) (MZB) is an imidazole nucleoside and an immunosuppressive agent. The immunosuppressive effect of MZB has been reported to be due to the inhibition of DNA synthesis in the S-phase of the cell cycle. After phosphorylation, mizoribine-5′-monophosphate (MZB-P) inhibits GMP synthesis by antagonistic blocking of IMPDH and GMP synthetase in the pathway from IMP to GMP in the purine synthesis system. MZB was found to suppress both humoral and cellular immunity by selective inhibition of lymphocyte proliferation, which led to its development as an immunosuppressive agent[29]. MZB (Bredinin®, Asahi Kasei Pharma Corporation, Tokyo, Japan) is used in Japan as an immunosuppressant similarly to mycophenolate mofetil (MMF). Noteworthy, MZB-P (K_i value of 10 nM) inhibits stronger IMPDH than ribavirin monophosphate (K_i value of 250 nM), which can be due to additional hydrogen bond from hydroxyl group in imidazole ring[30].

The third, tiazofurin (**3**) (TR) is metabolically converted into thiazole-4-carboxamide adenine dinucleotide (TAD) and interacts with NAD site of enzyme. Noteworthy, TR is the only IMPDH inhibitor applied clinically in cancer treatment. It was approved as an orphan drug in case of patients in blast crisis of chronic myelogenous leukemia (CML)[31].

The last ones: mycophenolate mofetil (**4**) (2-morfolinoethyl, MMF, CellCept, F. Hoffmann-La Roche Ltd, Basel, Switzerland) and sodium mycophenolate (**5**) (MPS, Myfortic, Novartis Pharmaceuticals Corporation) are used in clinic as immunosuppressants in prophylaxis of organ transplant rejection. The former is a prodrug of MPA **6** (Figure 2), which binds to the *N* sub-site of IMPDH (an uncompetitive inhibitor) and is one of the most potent inhibitors of human IMPDH (*h*IMPDH), with a slight higher potency against isoform II (K_i in the range of 7–14 nM) over isoform I of the enzyme (K_i in the range of 11–33 nM)[32]. The both proteins consist of 514 amino acids and possess molecular mass 56 kDa[1,30,32–34]. According to molecular modeling studies, functional groups in MPA interact in binding site with adequate amino acids in IMPDH: carboxylic group—Ser 276, phenol group—Gln 441, Thr 333, lactone—Thr 333 and Gly 326. *Trans* configuration of the double bond in side chain is important for the proper arrangement of the interacting with Ser 276 carboxylic group and maintenance of biological activity. In van der Waals contacts are involved: Asn 303, Arg 322, Asp 274, Gly 415 and Met 414[30,32]. However, none of the mentioned agents shows significant selectivity against IMPDH type II isoform.

Despite of the progress in development of clinically applied IMPDH inhibitors, new drugs with improved therapeutic properties are still desired. As a result, new compounds are designed to evaluate their potential activity. It includes structural modifications of known IMPDH inhibitors and investigations of new substances, which were synthetically obtained or isolated from natural sources[30–32,35,36].

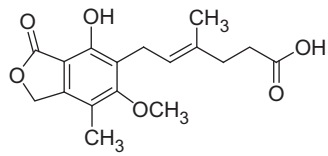

Figure 2. Structure of MPA **6**.

New potent IMPDH inhibitors derived from MPA

During last years derivatives of MPA are one of the most interesting group of IMPDH inhibitors. In literature we can find a lot of new analogs, unfortunately only a few of them exhibit interesting activity[3,35,36]. Moreover, immunosuppressive agents cause side effect like dose-limiting gastrointestinal (GI) toxicity upon MMF or MPA oral administration. Yang et al.[37] synthesized 35 isobenzofuran derivatives and assessed their structure–activity relationship within T-cell proliferation and IMPDH type II inhibition. The synthesis of the three series of isobenzofuran analogs **8**, **10** and **11** is depicted in Scheme 1. The starting material for all target compounds **8**, **10** and **11** was 5-aminoisobenzofuran-1(3*H*)-one **7**.

Treatment of **7** with generated *in situ* derivative of cinnamic acid chloride provided α,β-unsaturated amides **8**. Among these compounds, the highest activity toward T-cells (the proliferative response of mouse splenocytes to concanavalin A) revealed analogs possessing fluor, methoxyl and acetoxyl as R_1 substituent at position 3 (in case of methoxyl also disubstituted in 3 and 4 and **8a**; Figure 3) of phenyl ring of cinnamic acid moiety. T-cells proliferation test gave results IC_{50} *ca.* 0.03 μM, whereas MPA occurred to be less active (IC_{50} value of 0.28 μM). In contrast to that, electron-withdrawing CN group at 4th position, similarly to bulky substituents at 2nd position, decreased observed activity.

The first stage of urea analogs **10** synthesis involved reaction of (**7**) with 2,2,2-trichloroethylchloroformate. Then, carbamate **9** underwent nuclephilic substitution at acyl carbon atom with appropriate amine. In general, urea analogs **10** were less active than α,β-unsaturated amides **8**, and secondary amine derivative of **10** (R_2 = phenyl, R_3 = methyl) showed loss of activity

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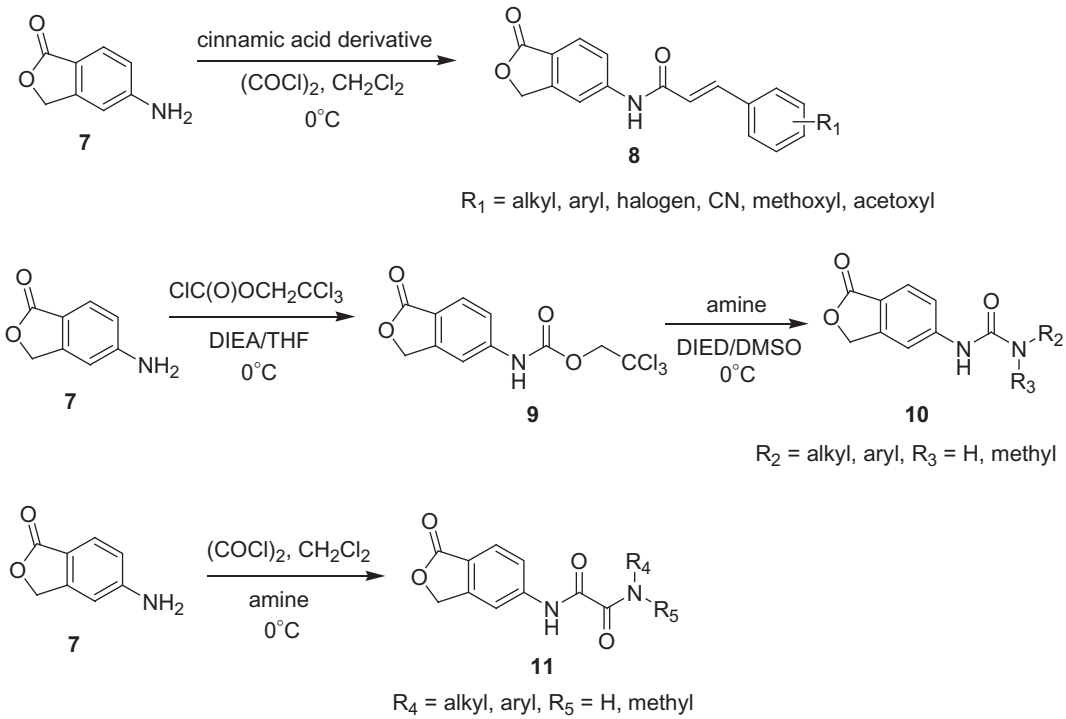

Scheme 1. The synthesis of isobenzofuran analogs **8**, **10** and **11**[37].

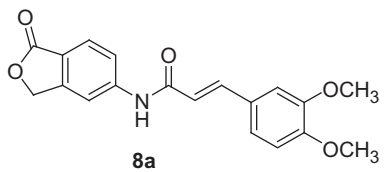

Figure 3. Isobenzofuran derivative **8a** active *in vitro* toward both T-cells proliferation and IMPDH type inhibition[37].

($IC_{50} > 100\,\mu M$) probably due to hydrogen bonding donor role of amide group. On the other hand, primary amine derivatives, especially bearing substituted phenyl ring ($R_2 = 2$-methylphenyl, $R_3 = H$) exhibited considerable activity (IC_{50} value of $0.90\,\mu M$). Interestingly, size of the halogen substituent at *para* position improved inhibitory properties too ($R_2 = 4$-fluorophenyl, $R_3 = H$, IC_{50} value of $4.19\,\mu M$ and $R_2 = 4$-iodophenyl, $R_3 = H$, IC_{50} value of $1.37\,\mu M$). Furthermore, aromatic amine derivatives ($R_2 =$ aryl, $R_3 = H$) indicated better activity if compared with alkyl ones ($R_2 =$ cyclohexyl or *n*-propyl, $R_3 = H$). On the basis of these results it was concluded, that benzene-ring conjugated system is crucial for retain or increase activity of urea analogs **10**.

Different structure–activity relationship was observed in case of diamide analogs **10**. These compounds were obtained in the reaction of **7** with oxalyl chloride and adequate amine. Analog hold aliphatic amine ($R_4 =$ *tert*-butyl, $R_5 = H$, IC_{50} value of $3.40\,\mu M$) occurred to be more active like derivative having aromatic amine ($R_4 =$ phenyl, $R_5 = H$, IC_{50} value of $36.07\,\mu M$). However, presence of substituent being hydrogen bond donor in aromatic ring enhanced potency significantly ($R_4 = 4$-hydroxyphenyl, $R_5 = H$, IC_{50} value of $5.03\,\mu M$, $R_4 = 4$-methoxyphenyl, $R_5 = H$, IC_{50} value of $153.33\,\mu M$). The highest activity was observed in case *p*-fluorophenyl derivative ($R_4 = 4$-fluorophenyl, $R_5 = H$, IC_{50} value of $0.57\,\mu M$).

Subsequently, isobenzofuran analogs **8**, **10** and **11** were evaluated as IMPDH type II inhibitors. The highest potency was observed in case of 3,4-dimethoxyphenyl cinnamic acid derivative **8a** (Figure 3). Its inhibition toward IMPDH type II (IC_{50} value of $2.1\,\mu M$) was slightly lower than MPA (IC_{50} value of $1.5\,\mu M$).

Among IMPDH inhibitors can be found also acridone derivatives[31]. Nitroacridines are known as a high cytotoxic compounds and in search of potent MPA derivatives, Malachowska-Ugarte et al.[38] designed conjugates of MPA and nitroacridine/acridone **13** and **15** (Scheme 2). The amide bond was formed between free carboxylic group of MPA **6** and primary amine group of 9-(ω-aminoalkyl)amino-1-nitroacridines 12, and 1-[(ω-aminoalkyl)-4-nitro-9(10*H*)]acridones 14 in the presence of optimized coupling reagent.

Conjugates **13** and **15** were evaluated as inhibitors of leukemia cell lines (Jurkat, Molt-4, HL-60, CCRF and L1210) and human peripheral blood mononuclear cells (PBMC). These compounds occurred to be IMPDH inhibitors in the experiments based on addition of GMP to Jurkat cell line[2]. Their activity depend both on length of the diamine linker and type of heterocycle. Basically, acridine analogs **13** indicated higher potency than acridones **15** and parent MPA **6**. However, Yurkat cells were surprisingly more sensitive toward acridones **15** (IC_{50} in MTT test value of $<0.0008\,\mu M$), than acridines **13** (IC_{50} in the range of 0.17–$0.86\,\mu M$) or MPA **6** (IC_{50} value of $0.193\,\mu M$). Conjugates **13** and **15** exhibited intermediate activities between respective starting acridine **12** or acridone **14** and MPA **6**, so that the observed effects were rather additive, not synergistic. On the other hand, it could be advantageous for optimization cytotoxic properties for *in vivo* investigations.

In literature are reported some structural modifications of MPA based on polar groups at the end of its side chain. They provided some derivatives indicating significant activity if comparison with parent MPA, which is in good agreement with molecular modeling studies[30,32,35].

Iwaszkiewicz-Grzes et al.[39] synthesized amino acids derivatives of MPA **17** and **18** (Scheme 3). First, MPA **6** produced with amino acid methyl esters **16** in the presence of EDCI as coupling reagent analogs **17**. Subsequently, esters **17** were hydrolyzed to

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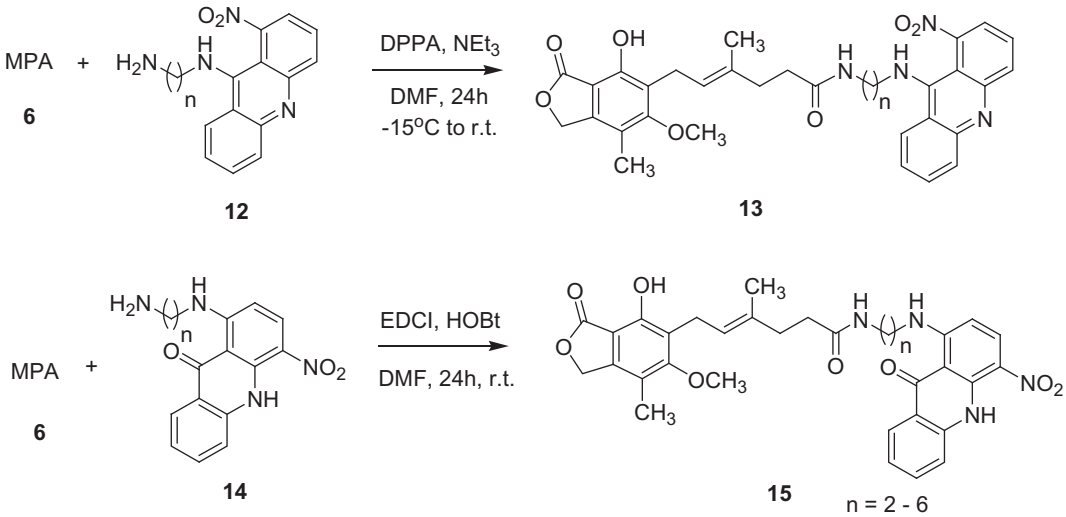
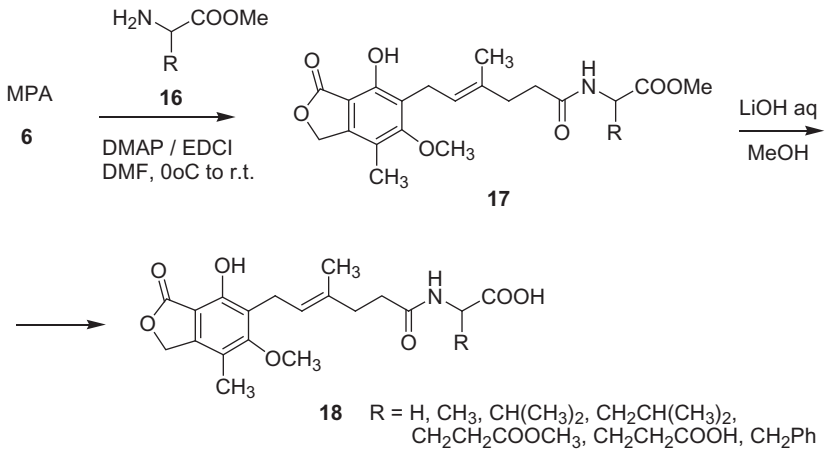


Scheme 2. The synthesis of analogs **16** and **18**[38].

Scheme 3. Synthesis of amino acid MPA derivative **17** and **18**[39].



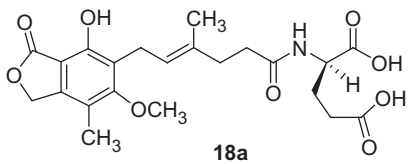


Figure 4. *N*-mycophenoyl-D-glutamic acid **18a**[39].

amino acid derivatives **18** possessing free carboxylic groups. Compounds **17** and **18** occurred to be IMPDH inhibitors and their activity was evaluated against lymphoid cell line Jurkat and activated PBMC as *in vitro* model of immunosuppression.

According to obtained results, recovering of free carboxylic group-enhanced activity. Furthermore, inhibitory properties depended on amino acid attached (R substituent) and configuration at chiral center. The most promising outcome in this series of compounds was received in case of D-glutamic acid analog **18a** (Figure 4). Antiproliferation activity toward Jurkat cell line of **18a** expressed as EC_{50} (antiproliferation test based on incorporation [^{3}H]thymidine) was 0.45 μM and selectivity index SI defined as $SI = EC_{50}/IC_{50}$ (MTT test) value of 47.1, whereas MPA **6** gave EC_{50} value of 9.45 μM, and SI value of 2.99.

Taking the fact, that IMPDH is a nicotinamide adenine dinucleotide (NAD)-dependent enzyme, Pankiewicz et al.[40] designed several classes of NAD-based IMPDH inhibitors. For instance, MPA amino acid derivatives **18b** were coupled with 5′-aminoadenosine **19** to respective diamides **20** (Scheme 4). In this series D-valine derivative of 20 revealed nanomolar potency toward IMPDH-I (K_i value of 3 nM) and IMPDH-II (K_i value of 88 nM). In the same communicate were reported also new mycophenolic adenine dinucleotide (MAD) analogs **21** being substituted at position 2. High activities, both toward IMPDH-I (K_i value of 0.6 nM), IMPDH-II (K_i value of 14 nM), and several cancer cell lines were observed in case of 2-(4-pyridyl) MAD derivative of 21. The authors also modified linker between adenosine and MPA derived units. For instance, 2-ethyl substituted difluoromethylene MAD analog **22** gave K_i value of 0.6 nM with IMPDH-I, K_i value of 24 nM with IMPDH-II and IC_{50} value of 0.4 nM against K562. In search of selective IMPDH-II inhibitor, the same scientific group designed 4-aminobenzimidazole analog **23**. This compound was prepared *via* coupling of *bis*(phosponate) 24 with *O*-isopropylidene-4-nitrobenzimidazole **25**, followed by deprotection of 2′and 3′-hydroxyl groups and hydrogenolysis. The inhibitory toward IMPDH-I reached $K_i = 491$ nM, and was considerably better in case of IMPDH-II: $K_i = 165$ nM. These results are coincident with analysis of the crystal structure of IMPDH-II–NAD complex, whereas adenine ring interacts with two amino acids: His 253 and Phe 282 possessing aromatic systems. In contrast to that, IMPDH-I provides only Tyr 282. As a result, replacement of adenine

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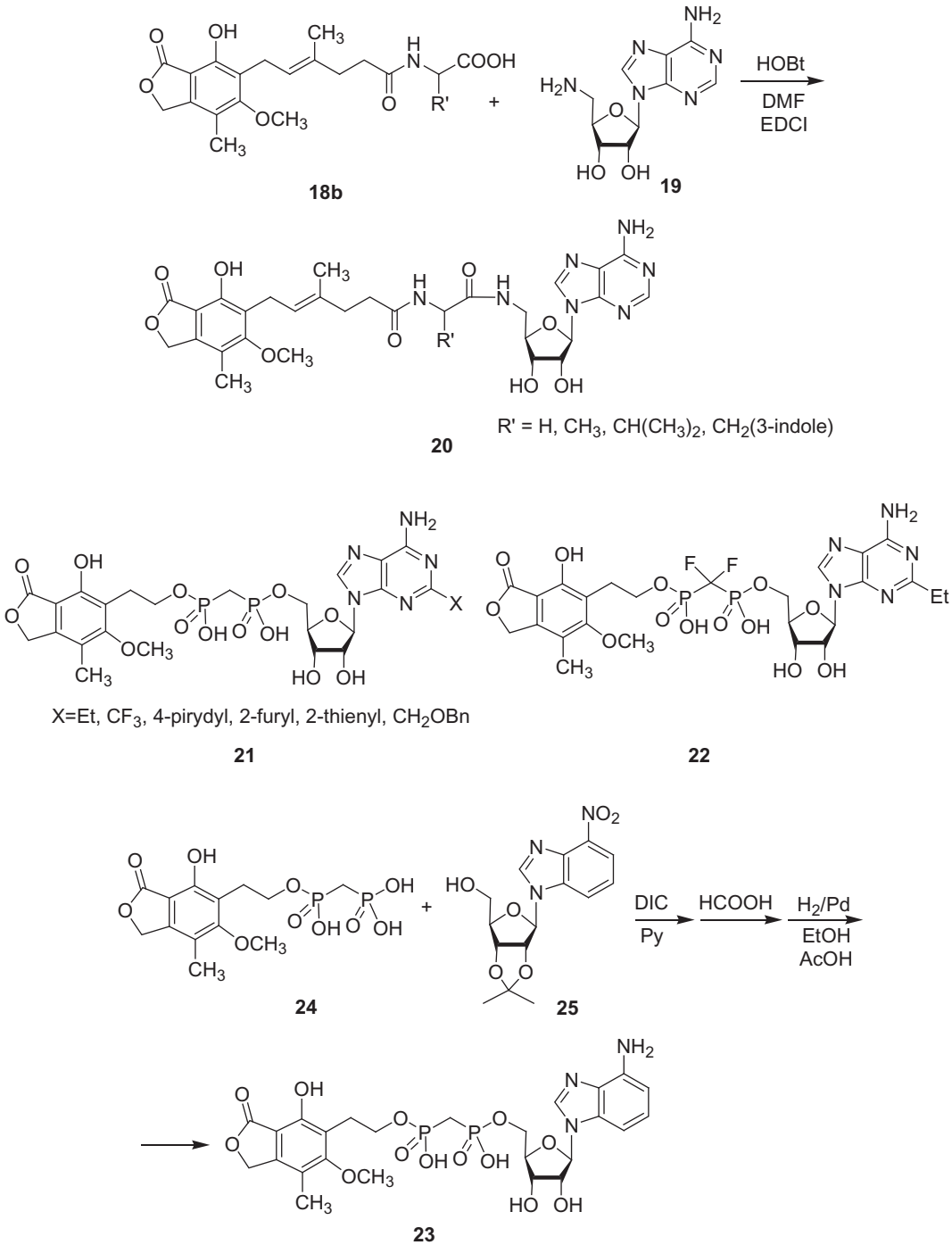

Scheme 4. NAD-based IMPDH inhibitors[40].

moiety by 4-aminobenzimidazole enables stronger stacking interactions and better selectivity to IMPDH-II.

Mycophenolic adenine *bis*(sulfonoamides)[41] (MABSs) (Figure 5) **26** possess isosteric linker to the methylene*bis* (phosphonates) **21**. The tetrahedral sulfur atoms provide similar geometry and charge delocalization if compared with the naturally occurring pyrophosphate linkage. These series of compounds revealed comparable to MAD analogs **21** IMPDH inhibition, together with an observable selectivity to isoform II of the enzyme.

Dual inhibitor of histone deacetylase (HDAC, zinc-dependent enzyme) and IMPDH, e.g. hydroxamic acid derivative of MPA **27** (Figure 6), are considered as potential anticancer agents, which could provide also the selectivity toward IMPDH-II over IMPDH-

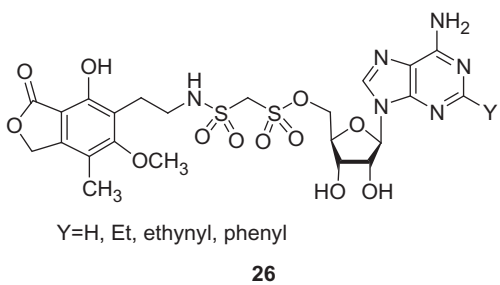

Figure 5. Methylene*bis*(sulfonamide) analogs **21** of mycophenolic adenine methylene*bis*(phosphonate)s **26**[41].

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I[29,40]. Sunohara et al.[42] focused on synthesis of 10 new derivatives of MPA **28**, **29** possessing efficient zinc-binding moieties, as potential dual inhibitors for HDAC and IMPDH-II that would improve transplantation therapy and chemotherapy.

Authors proposed to combine MPA at C-6′ position with groups of heterocyclic amide, thiols, and investigate their structure–activity relationships for inhibitory activity against human IMPDH (*in vitro*), inductive activity on erythroid differentiation (K562 cells), and inhibitory effect on K562 cell proliferation. Base assumption in modeling of the new structure of derivatives was that zinc-dependent enzyme can be molecular target in cancer treatment. Another designed zinc-binding moiety was epoxide similarly to potential anticancer agent Trapoxin.

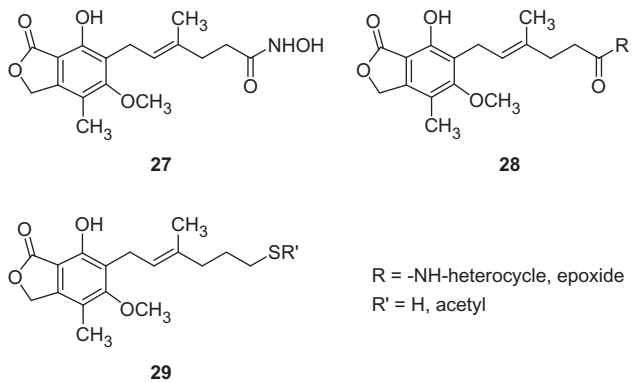
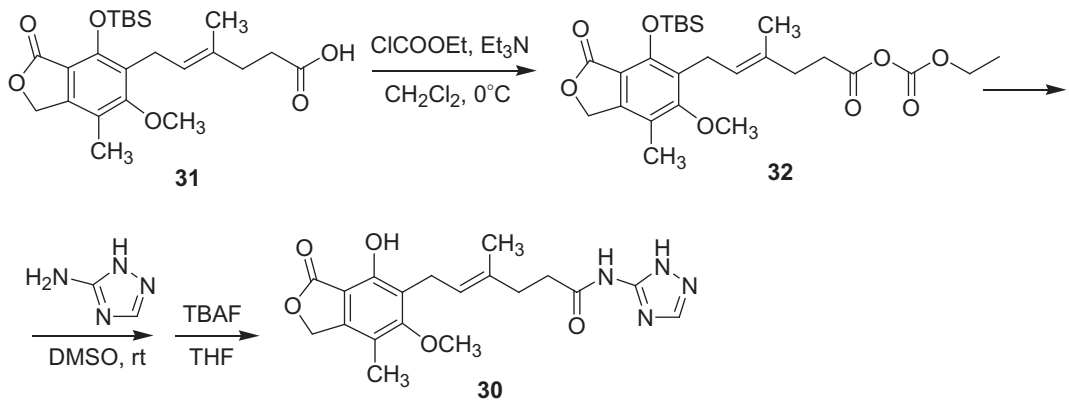


Figure 6. MPA derivatives as dual IMPDH and HDAC inhibitors.

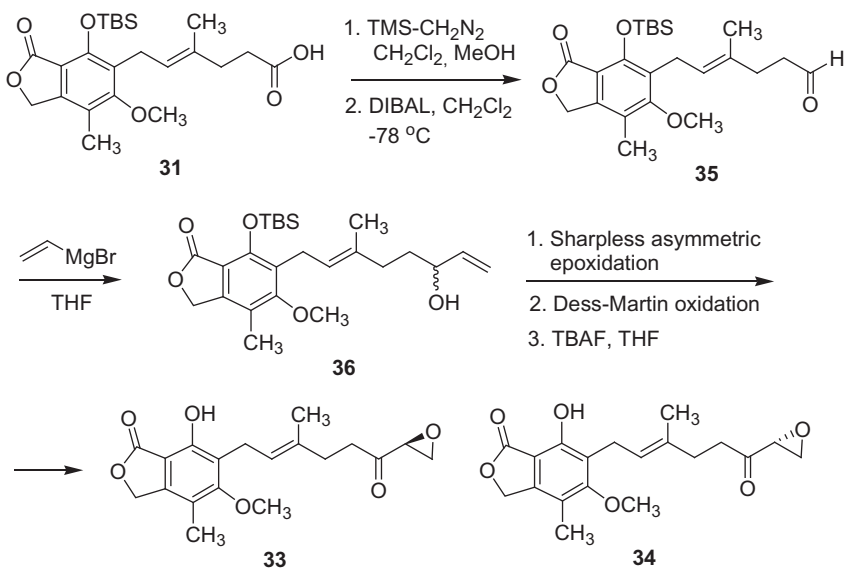
The most potent compound against K562 cells occurred to be *N*-(2,3,5-triazoyl)mycophenolic amide **30** ($IC_{50} = 0.48\,\mu M$, Scheme 5), and was comparable to MPA **6** ($IC_{50} = 0.19\,\mu M$). Its inhibitory activities were $IC_{50} = 0.105\,\mu M$ toward IMPDH-I, $IC_{50} = 0.098\,\mu M$ against IMPDH-II, which gave selectivity index IMPDH-I/IMPDH-II value of 1.1. To compare, MPA 6 indicated $IC_{50} = 0.019\,\mu M$ toward IMPDH-I, $IC_{50} = 0.012\,\mu M$ against IMPDH-II and selectivity index IMPDH-I/IMPDH-II was 1.6. Since amine group of 3-amino-1,2,4-triazole is a poor nucleophile, synthesis of *N*-(2,3,5-triazoyl)mycophenolic amide **30** required use of MPA possessing protected phenol group. *Tert*-butyldimethylsilyl ether of MPA **31** was treated with ethyl chloroformate to produce mixed anhydride **32**, followed by reaction with 3-amino-1,2,4-triazole. Finally, deprotection of phenol group with tetrabutylamonium fluoride yielded amide **30**.

Tert-butyldimethylsilyl ether of MPA **31** was also used in synthetic pathway of epoxyketones **33** and **34** (Scheme 6). Carboxylic group of **30** was methylated, subsequently respective methyl ester underwent reduction by DIBAL to aldehyde **35**. Then, nucleophilic addition of vinyl magnesium bromide to **35** produced racemic alcohol **36**. Alcohol (*R*)-**36** provided epoxyketone **33** and (*S*)-**36** led to epoxyketone **34**. The both products **33**



Scheme 5. Synthesis of *N*-(2,3,5-triazoyl)mycophenolic amide **30**[42].

Scheme 6. Synthesis of enantiomeric mycophenolic epoxyketones **33** and **34**[42].



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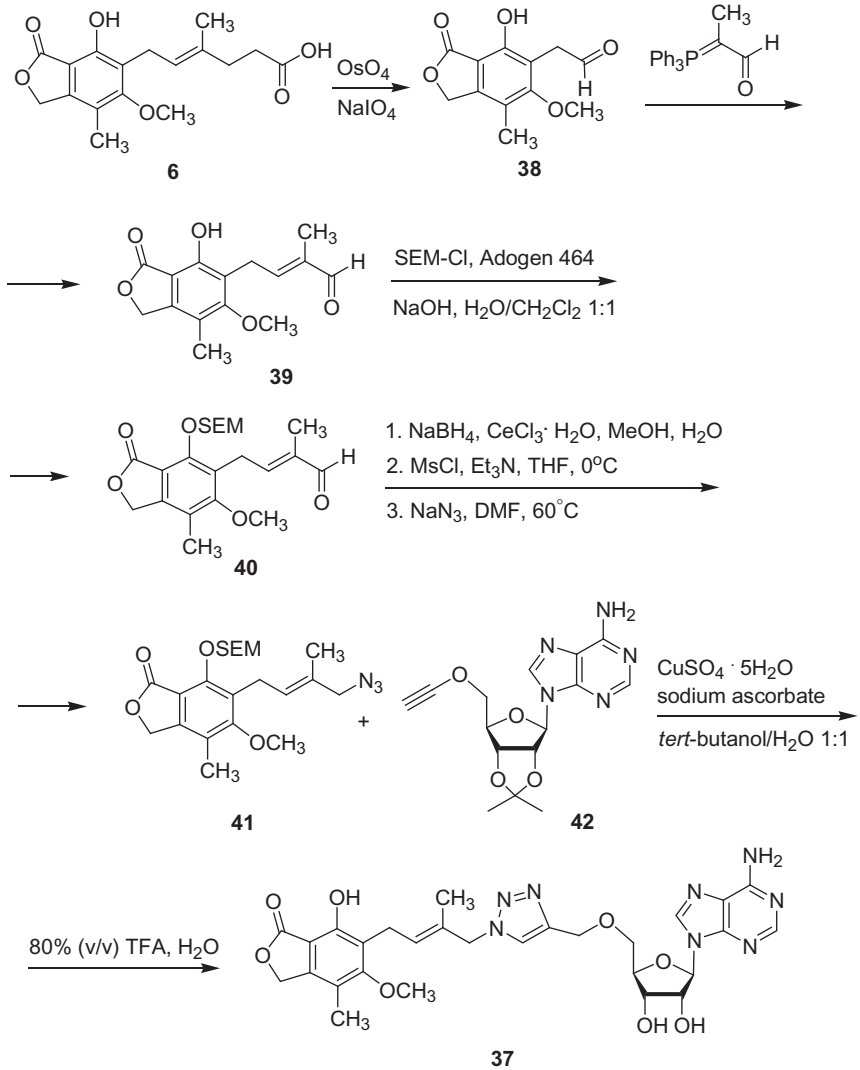

Scheme 7. Synthesis of triazole-linked IMPDH inhibitor **37**[43].

and **34** revealed similar to MPA selectivity index IMPDH-I/IMPDH-II, 1.7 and 1.8, respectively[42].

Chen et al.[43] designed triazole-linked MPA derivatives, which revealed high activity *in vitro* toward IMPDH. Moreover, compound **37** (Scheme 7) occurred to be not only IMPDH inhibitor (K_i value of 0.070 μM against type I and K_i value of 0.044 μM against type II), but also toward *Mycobacterium tuberculosis* IMPDH (K_i value of 1.5–2.2 μM) whereas MPA **6** gave 0.033 μM (Type I), 0.007 μM (Type II) and 62 μM (*mt*IMPDH), respectively. The target compound **37** was obtained from MPA **6**. First, MPA **6** was oxidized to aldehyde **38**, which reacted with 2-(triphenylphosphoranylidene)propionaldehyde to produce **39**. In the next step, phenol group was protected under phase transfer catalysis with 2-(trimethylsilyl)etoxymethyl chloride (SEM-Cl). Subsequently, aldehyde **40** underwent reduction followed by mesylation and convertion to adequate azide **41**. Then, terminal alkyne **42** participated in catalyzed by Cu(I) 1,3-dipolar cycloaddition to azide **41**. Both 2-(trimethylsilyl)etoxymethyl (SEM) ether and isopropylidene protecting groups were removed with aqueous TFA to yield **37**.

The other types of conjugates were developed by Wu H. and co-workers[44]. In search of less toxic immunosuppressant to prevent rejection in human islet transplantation, MPA was coupled with quinic acid derivative **43** (KZ41) as anti-inflammatory component (Scheme 8). The obtained ester **44** (JP-3-110) revealed similar immunosuppressive activity *in vitro* to MPA **6**; however, it can provide safer drug for human islet transplantation due to diminishing of pro-apoptotic effect of **6**. The synthesis of conjugate **45** required use of MPA with protected phenol group (**45**). Quinic acid (**46**) was converted to 3,4-*O*-isopropylidene-1,5-quinic lactone (**47**) in the reaction with 2,2-dimethoxypropane (2,2-DMP), *p*-toluenesulfonic acid in boiling acetone. Then, lactone (**47**) provided amide **43** upon treatment with *n*-propyl amine in acetic acid. Subsequently, MPA derivative **45** was coupled with quinic acid analog **43** (KZ41) in the presence of *N*,*N*′-diisopropylcarbodiimide (DIC) to ester **48**, followed by removing of protecting acetonide group. The structure of the obtained conjugate **44** (JP-3-110) will be optimized toward better solubility and stability to improve its pharmacological properties.

Three new derivatives of MPA were isolated and identified from marine-derived *Penilillium fungus* (sp. SOF07, from South China Sea) by Chen et al.[45]. These compounds exhibited moderate activity in the range IC_{50} value of 6.43–73.24 μM toward IMPDH-II and IC_{50} value of 2.46 μM to >30 μM against mouse splenocyte proliferation. MPA **6** and 4′-hydroxymycophenolic acid (**49**) (Figure 7) were also isolated from mentioned sample. Their inhibitions were IC_{50} value of 0.63 μM, 1.79 μM toward IMPDH-II, and IC_{50} value of 0.32 μM, 1.10 μM against mouse splenocyte proliferation, respectively.

IMPDH inhibitors including oxazol moiety

According to molecular modeling studies, the C7 phenol group in MPA **6** provides very significant interaction between MPA **6**

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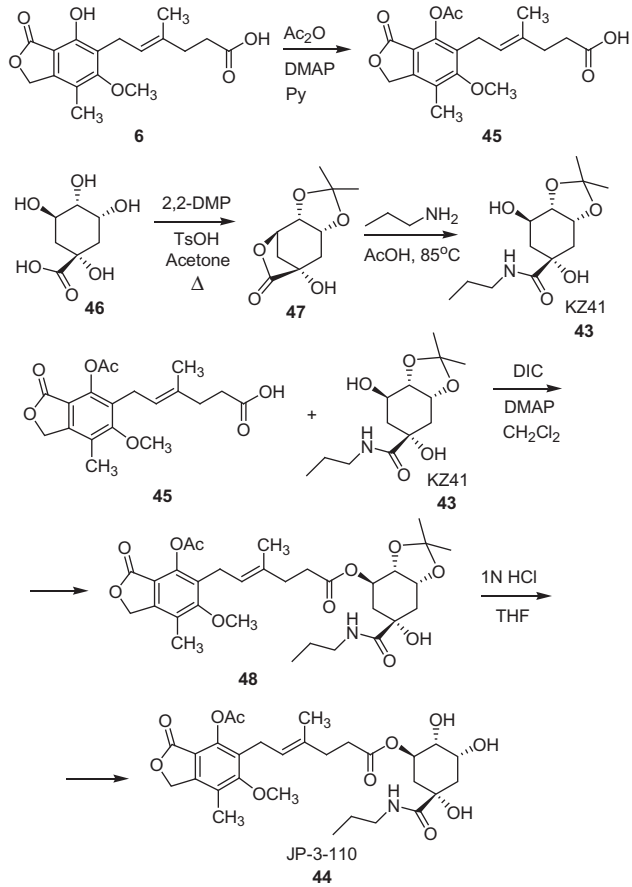
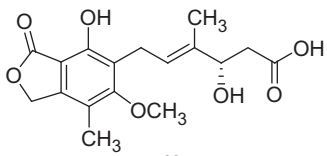


Scheme 8. Synthesis of conjugate of MPA and quinic acid derivative **44**[44].



49

Figure 7. Structure of 4′-hydroxymycophenolic acid 49 isolated from *Penilillium fungus* (sp. SOF07)[45].

molecule and IMPDH and is crucial for drug activity[30]. On the other hand, the C7 phenol group undergoes glucuronidation *in vivo*, which considerably limits therapeutic properties. To overcome this metabolic drawback, derivatives possessing other polar group or heterocyclic moieties were designed[35,46,47]. Chen et al.[48] developed suberoylanilide hydroxamic acid (**50**) (SAHA, potent HDACs inhibitor) derivative **51** (Scheme 9), as dual HDAC and IMPDH inhibitor. Apart from zinc-binding hydroxamic acid group, compound **51** hold also phenyloxazol moiety possessing *ortho* methoxy substituent as a part interacting with IMPDH.

Synthesis of **51** included coupling of 3-methoxy-4-(5-oxazolyl)phenylamine (**52**) with suberic acid monomethyl ester (**53**), followed by selective nucleophilic substitution at acyl carbon atom of methyl ester with hydroxylamine. The product **51** revealed promising activity. Its inhibition toward IMPDH was K_i value of 5.0 μM (Type I) and 1.7 μM (Type II) in comparison to MPA: 0.04 μM (Type I) and 0.01 μM (Type II), respectively. Noteworthy, potency of **51** against HDAC (IC_{50} value of 0.06 μM) was higher than in case of MAHA (**19**), SAHA (**50**): 5.0 and 0.41 μM, respectively. Additionally, activity of compound **50** toward K562 (IC_{50} value of 0.29 μM) occurred to be better like of MPA **6**, MAHA (**27**) and SAHA (**50**): 7.7, 4.8 and 0.75 μM, respectively.

Merimepodib (**54**) (Scheme 10) is a potent IMPDH inhibitor (K_i in the range of 6–10 nM for the both *h*IMPDHs) and drug candidate for hepatitis C developed by Vertex Pharmaceuticals (South Boston, MA)[31,49,50]. There was completed a Phase 2b clinical trial and synthesis of **54** optimized to commercial route. The final step depicted in Scheme 10 was coupling of 3-methoxy-4-(5-oxazolyl)aniline **52** with carbamate **55** in the presence of diisopropylethylamine as a base.

Several synthetic pathways toward 3-methoxy-4-(5-oxazolyl)aniline **52** were reported in the chemical literature[51,52]. The starting material, 2-methoxy-4-nitrotoluene **56** was oxidized to respective 1,1-diacetate **57**, followed by hydrolysis to aldehyde **58** (Scheme 11). Then, **58** was converted with TosMIC (toluenesulfonylmethyl isocyanide) to oxazolyl derivative **59**. Subsequently, hydrogenolysis[52] of **59** provided amine **52**.

Carbamate **55** was obtained from (*S*)-3-hydroxytetrahydrofuran (**60**) (Scheme 12). The reaction of the alcohol **60** with phosgene (or triphosgene) gave crude chloroformate **61**, which underwent nucleophilic substitution at acyl carbon atom with amine generated from hydrochloride **62**. Next, hydrogenolysis of nitro compound **63** to amine **64**, followed by treatment with phenyl chloroformate[53] led to carbamate **55**.

Research group from Bristol–Myers Squibb developed IMPDH inhibitors, in which urea linker in VX-497 (**54**) was replaced by heterocycles[53,54]. In the series of 2-aminooxazoles, BMS-337197 (**65**) (Scheme 13) revealed excellent immunosuppressive activity in mouse model of arthritis. In the key synthetic stage isothiocyanate (**66**) reacts with β-keto azide (**67**) in the presence to triphenylphosphine to form 2-(*N*-aryl)-1,3-oxazole (**68**). Then, acetate in **68** was hydrolyzed, and obtained hydroxyl group was converted to adequate methanesulfonate. Next, nucleophilic substitution with morpholine provided desired product **65**.

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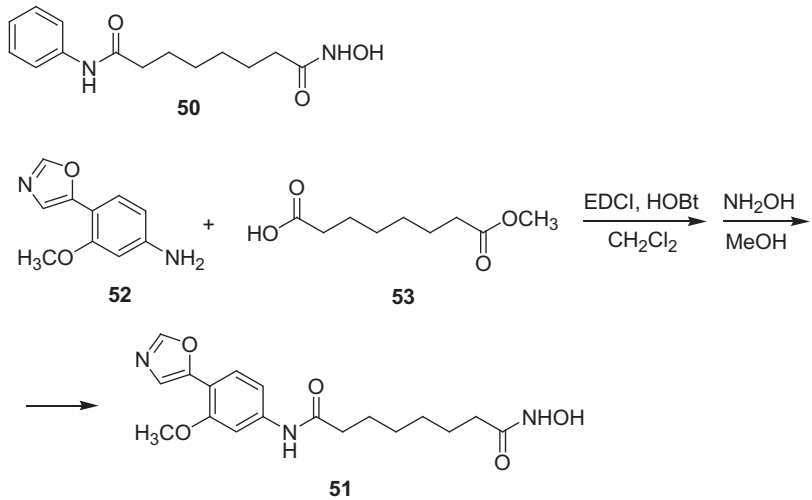
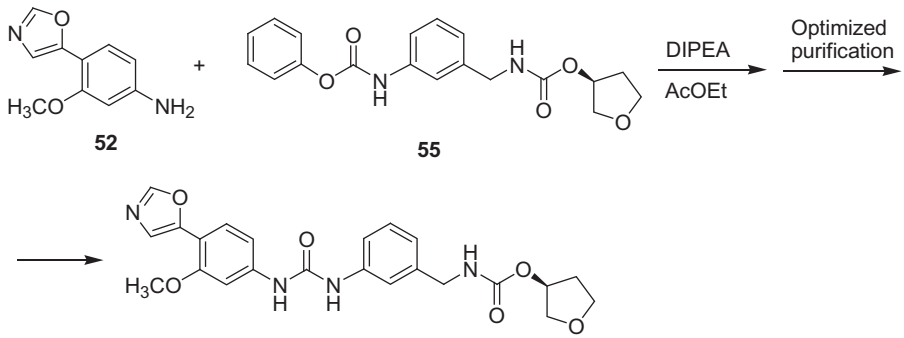
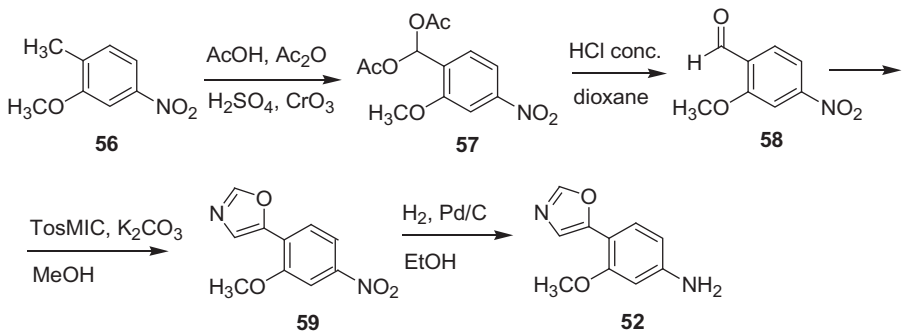
Scheme 9. Synthesis of dual HDAC and IMPDH inhibitor **51**[48].



Scheme 10. Synthesis of merimepodib **54**[49].



Scheme 11. Synthesis of 3-methoxy-4-(5-oxazolyl)aniline **52**[52].



In search of new chemotherapeutics against drug resistance, Pankiewicz et al. developed dual inhibitors of IMPDH (isoform I and II), and HDAC based on cinnamic hydroxamic acid (CHA) and *N*-(3-metoxy-4-(5-oxazolyl)phenyl]amino (MOA) scaffold possessing urea (**69**) or diamide (**70**) linker[55] (Figure 8). MOA structural unit was derived from potent IMPDH inhibitors [VX-497 (**54**), BMS-337197], whereas CHA moieties are known as zinc-dependent HDAC inhibitors. To compare with VX-148 [IMPDH inhibitor derived from *N*-(4-cyano-3-methoxyphenyl)amine (CMA)], Pankiewicz et al. reported also urea analogs, in which 5-oxazolyl ring was replaced by –CN substituent.

One of the most potent compounds occurred to be urea derivative **69a** (Scheme 14). This compound was active toward both isofoms IMPDH (K_i value of 0.30 μM against Type I and K_i value of 0.25 μM against Type II), HDAC (IC_{50} value of 0.55 μM) and also K562 cell line.

The synthetic pathway includes reaction of 3-methoxy-4-(5-oxazolyl)aniline (**52**) with ethyl 4-aminocinnamate (**71**) in the presence of triphosgene to form urea (**72**). Then, ethyl ester in **72** underwent alkaline hydrolysis, followed by coupling of respective carboxylic acid with *O*-tritylhydroxylamine. Subsequently, deprotection with triethylsilane gave the product **69a**.

Scientists from Bristol–Myers Squibb developed series of quinolone-based IMPDH inhibitors **73** (Scheme 15) to establish their structure–activity relationship (SAR). In case of derivatives **73**, urea or diamide linkage is replaced by bicyclic quinolone scaffold[56]. The authors rationalized, that quinoline NH group would provide hydrogen bond with the carboxylate of Asp 274 of IMPDH. Additionally, quinolone carbonyl could be involved as hydrogen bond acceptor in interaction with Gln 441 of IMPDH. Some of the developed compounds revealed comparable or better activity *in vitro* than MPA **6**. For instance, analog **73a** gave

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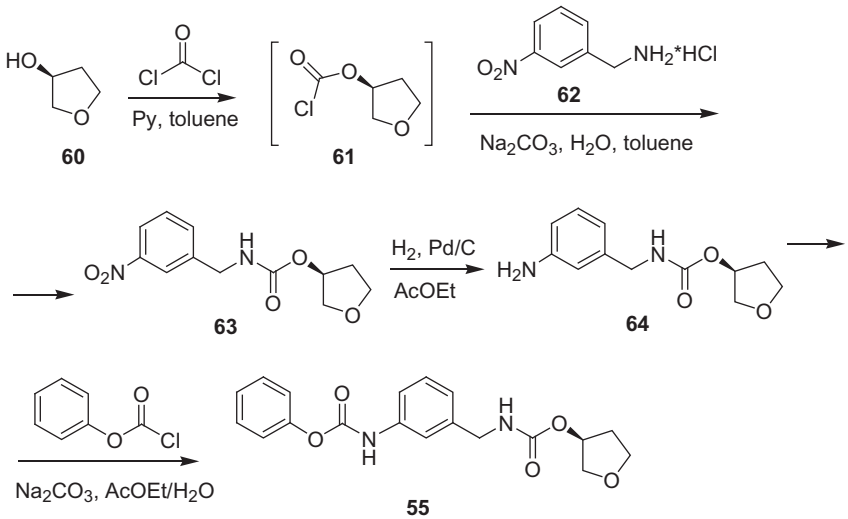
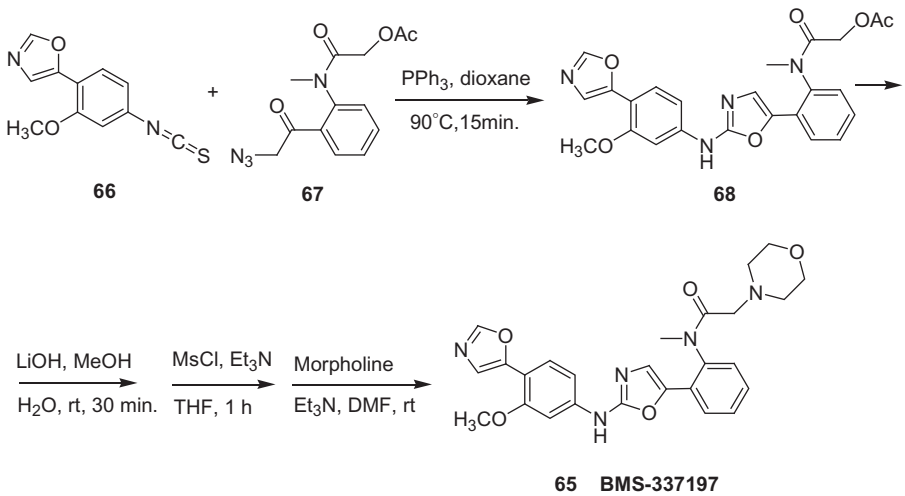
Scheme 12. Synthesis of carbamate **55**[53].



Scheme 13. Synthesis of BMS-337197 **65**[51,52].



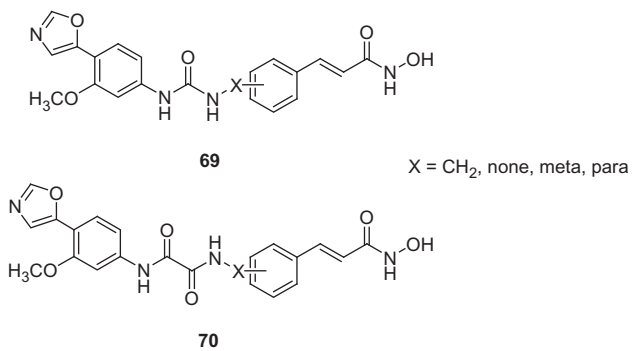


Figure 8. Urea and diamide derivatives of cinnamic hydroxamic acid and *N*-(3-metoxy-4-(5-oxazolyl)phenyl]amine **69** and **70**[55].

$IC_{50} = 0.099\,\mu M$ toward IMPDH-I and $IC_{50} = 0.008\,\mu M$ against IMPDH-II, (selectivity IMPDH-I/IMPDH-II value of 12), where MPA **6** exhibited 0.055, 0.014 and 3.9, respectively. The synthesis of **73a** included reaction of amine **52** with β-ketoester (**74**) in the presence of *p*-toluenesulfonic acid. In the next stage, ethyl ester **75** underwent cyclization under heating to product **73a**. The best selectivity IMPDH-I/IMPDH-II (value of 30) was obtained in case 3-methyl derivative **73b**, which showed $IC_{50} = 0.15\,\mu M$ toward IMPDH-I and $IC_{50} = 0.005\,\mu M$ against IMPDH-II[54]. However, this high selectivity was neither explained nor confirmed at higher concentrations of the enzyme[32].

Zhong et al.[57] obtained and characterized novel (5-oxazolyl)-phenyl amines (**76**) (Scheme 16) as potential antiviral agents for HCV and CVB. Since, there is currently no vaccine against hepatitis C virus compounds being active toward HCV are highly desired. One of the most active derivative occurred to be *N*-[3-methoxy-4-(5-oxazolyl)phenyl]-(2-thienylmethyl) amine (**76a**), which gave CC_{50} (50% cytotoxic concentration) 51.32 μM, $IC_{50} = 0.28\,\mu M$ (SI = 183.3) against HCV. The product **76a** was received in the reaction of amine **52** with 2-thiophenecarboxaldehyde (**77**), followed by reduction of imine **78**.

Miscellaneous

Wittine et al.[58] developed 1,2,4-triazole and imidazole derivatives of L-ascorbic acid as potential agents toward tumor and hepatitis C virus. The synthesis of target compounds was based on Vorbrüggen condensation and biological results were referred to ribavirin (**1**) (Figure 1). The most promising derivative occurred to be imidazole analog **81** (Scheme 17), which was obtained from 4,5-dimethylimidazole carboxylate (**79**) and 2,3-di-*O*-benzyl-5,6-di-*O*-acetyl-L-ascorbic acid (**80**) in the presence of 1,8-diazobicyclo[5.4.0]undec-7-en (DBU) and trimethylsilyl trifluoromethanesulfonate (TMSOTf). The product **81** revealed the highest activity against hepatitis C virus replication in the Huh 5-2

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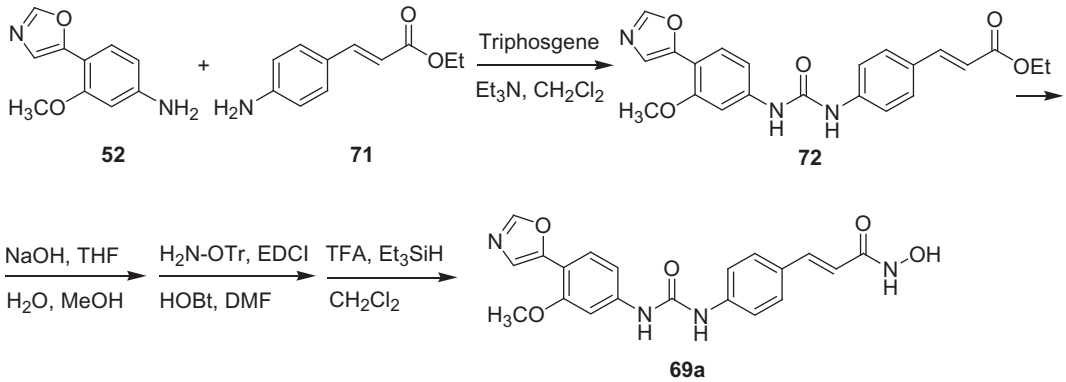
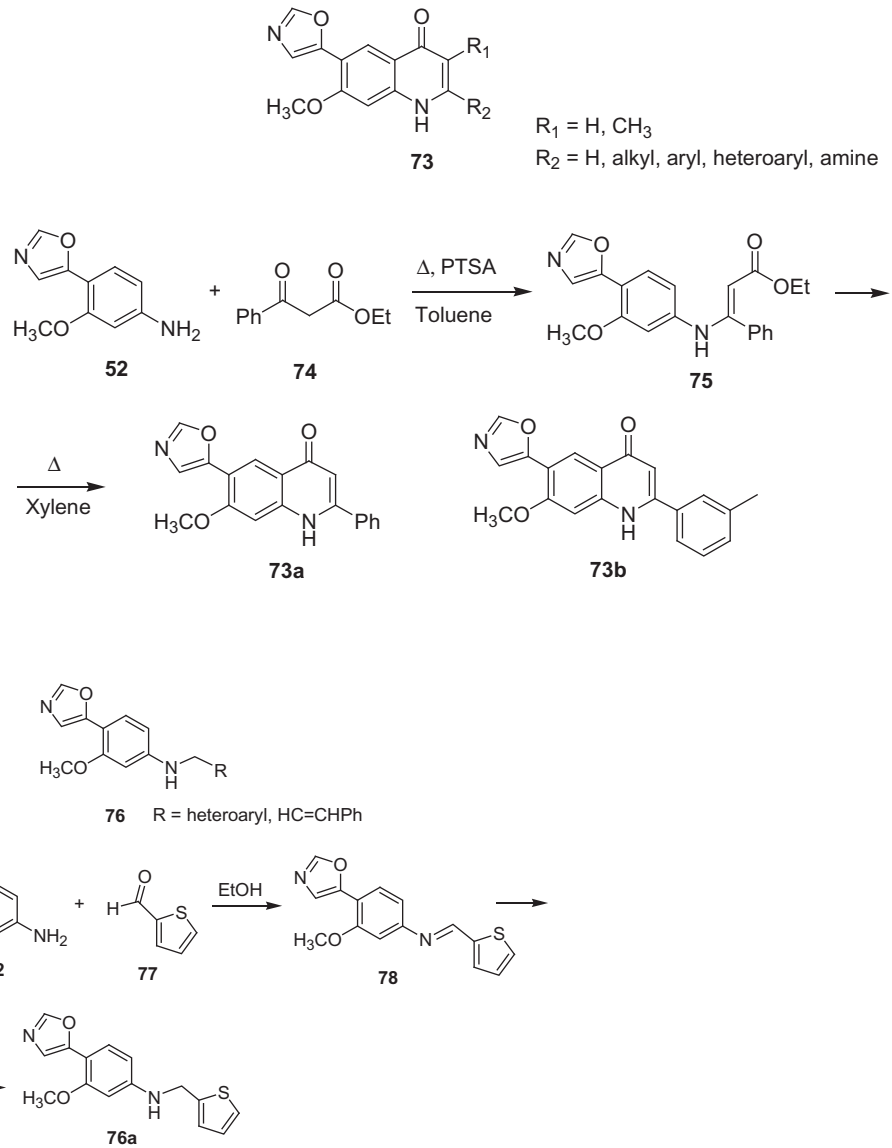


Scheme 14. Synthesis of urea derivative **69a**[53].

Scheme 15. Structure and synthesis of quinolone derivatives **73**[56].



Scheme 16. Synthesis of (5-oxazolyl)phenyl amines **76**[57].

replication system and comparable to ribavirin (**1**) *in vitro* antitumor activity. For example, cytostatic activity of **81** against human T-cell acute lymphoblastic leukemia (CEM) reached IC_{50} value of 10 μM, whereas ribavirin (**1**) gave IC_{50} value of 63 μM. Moreover, imidazole derivative (**81**) exhibited non-toxic effect on human diploid fibroblasts and initial experiments with L1210 and CEM cell lines proved, which its mechanism of action includes IMPDH inhibition.

Nakanishi et al.[59] optimized lead compound from Astellas library to novel and highly potent IMPDH inhibitor (Figure 9) named *N*-((4-fluorophenyl)(1-methyl-1*H*-imidazol-2-yl)methyl)-2-methyl-3-(1,2,4-thiadiazol-5-yl)-1*H*-indole-6-carboxamide,

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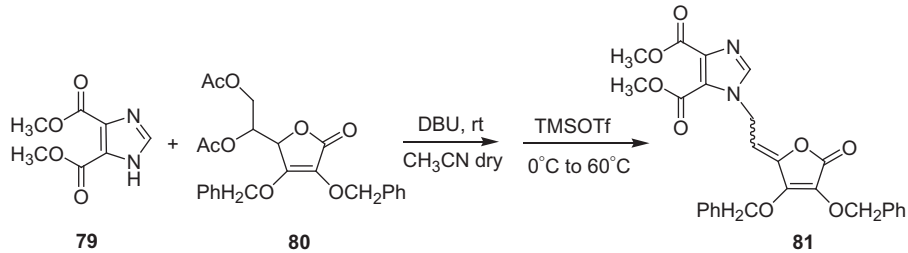
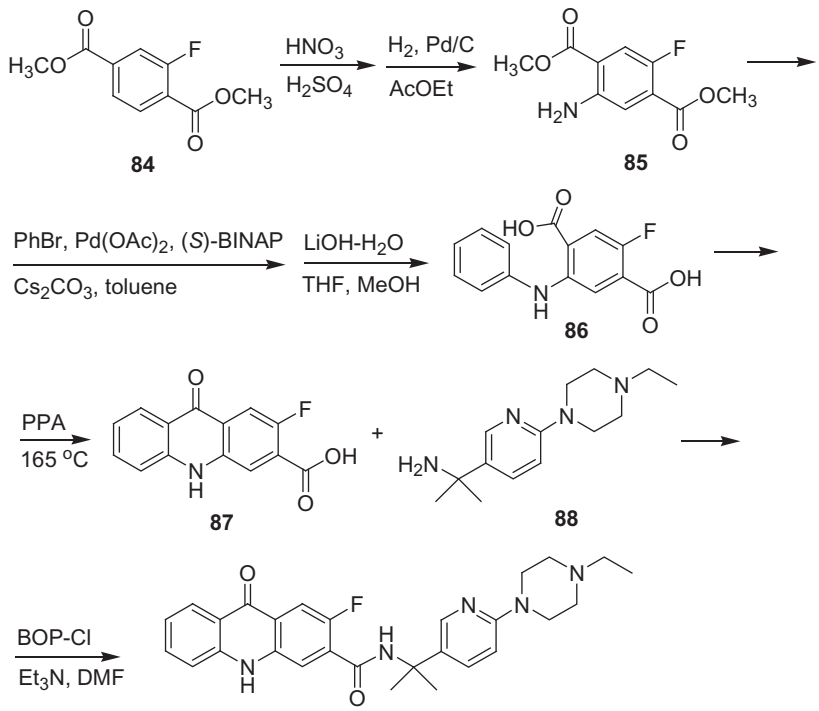
Scheme 17. Synthesis of imidazole derivative of L-ascorbic acid **81**[58].



Scheme 18. Synthesis of BMS-566419 **84**[60].



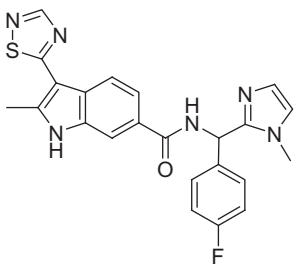


Figure 9. Chemical structure of AS2643361 **82**[58].

AS2643361 (**82**). Inhibitory *in vitro* activities of **82** and MPA **6** against two types of human IMPDH were similar. However, IC_{50} received in case of **82** was 71 nM toward IMPDH-II in the presence of 50% human serum and was eight times better than for MPA **6** (540 nM). These results suggested, that AS2643361 (**82**) binds weaker than MPA **6** to serum proteins.

Further tests concentrated on cellular activity and included concanavalin A-stimulated T cell proliferation, lipopolysaccharide-stimulated B cell proliferation, mixed lymphocyte reaction and *in vitro* IgM production. On this field AS2643361 showed five- to six-fold higher potency over MPA **6**. Evaluations *in vivo* were performed on rats' models of cardiac transplantation. Important fact is that AS2643361 (**82**) shows four- to eight-fold lower GI toxicity than MMF **4** and is promising candidate for acute and chronic rejection in transplant medicine.

In the course of SAR of acridone derivatives, Watterson et al.[60] discovered potent IMPDH-II inhibitor BMS-566419 (**83**) (Scheme 18). Compound **83** gave *ca*. three-fold better result than MMF **4** (Figure 1) in its therapeutic index with respect to GI toxicity in rat adjuvant arthritis model. The synthesis started from dimethyl 2-fluoroterephtalate **84**, which underwent nitration followed by reduction to amine **85**. Then, amine **85** was used in Buchwald–Hartwig condensation with phenyl bromide in the presence of palladium(II) acetate, (*S*)-(-)-2,2′-*bis*(diphenylphosphino)-1,1′-binaphtyl, cesium carbonate. Subsequently, ester groups in 2-fluoro-5-phenylaminoterephtalic acid dimethyl ester were hydrolized to 2-fluoro-5-phenylaminoterephtalic acid (**86**). In the next stage, cyclization of **86** under heating with polyphosphoric acid provided 2-fluoro-9-oxo-9,10-dihydroacridine-3-carboxylic acid (**87**), which was coupled in the presence of *N*,*N*-*bis*[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOP-Cl) as a coupling reagent with 2-(6-(4-ethylpiperazin-1-yl)pyridine-3-yl)propan-2-amine (**87**) to produce BMS-566419 (**83**).

The amine **88** was obtained via nucleophilic aromatic substitution of 2-chloropyridine-5-carbonitrile (**89**) by *N*-ethylpiperazine (**90**) (Scheme 19). Next, 6-(4-ethylpiperazin-1-yl)

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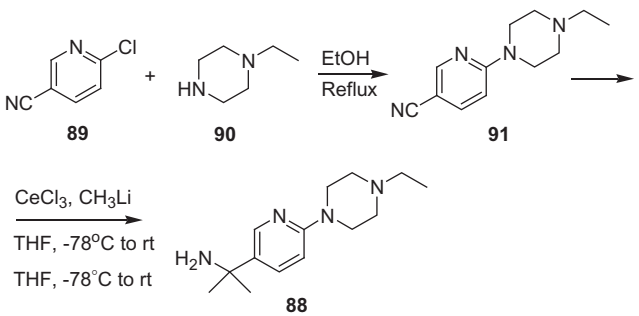

Scheme 19. Synthesis of amine **88**[60].

nicotinonitrile (**91**) was converted to amine **88** upon dimethylation with generated *in situ* CH_3CeCl_2[60].

Conclusions

The important progress was made recently in the development of new IMPDH inhibitors. Considerable part of designed structures included isobenzofuran moiety, which were derived from MPA as conjugates or analogs possessing modified functional groups. However, data received from molecular modeling studies enabled also to develop other classes of compounds giving interesting results in the course of *in vitro* or *in vivo* biological activity evaluations. Selectiveness toward IMPDH-II over IMPDH-I remains still challenging, but among the recently reported compounds can be found drug candidates having promising antiviral, anticancer, immunosuppressive and antibacterial properties.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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