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Synthesis and in vitro evaluation of 2-amino-4-*N*-piperazinyl-6-(3,4-dimethoxyphenyl)-pteridines as dual immunosuppressive and anti-inflammatory agents

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ABSTRACT

Screening of a pteridine-based compound library led to the identification of compounds exhibiting immunosuppressive as well as anti-inflammatory activity. Optimization afforded a series of 2-amino-4-*N*-piperazinyl-6-(3,4-dimethoxyphenyl)pteridine analogues. The most potent congeners in this series displayed low nM IC_{50} values in the Mixed Lymphocyte Reaction (MLR) assay. In addition, these compounds also have potent anti-inflammatory activity as measured in the Tumor Necrosis Factor (TNF) assay.

Autoimmune diseases represent a major cause of morbidity and mortality. More than 70 autoimmune diseases have been described, and, although many of these diseases are quite rare, the collective prevalence of autoimmune diseases is high. The major autoimmune diseases include psoriasis, rheumatoid arthritis, Crohn's disease, multiple sclerosis, and systemic lupus erythematosus. During the past decade, the largest advances in the treatment of these diseases have arisen from highly potent and selective macromolecule-based therapies.[1] Three biological agents targeting Tumor Necrosis Factor α (TNF-α) are currently licensed for the treatment of rheumatoid arthritis. Infliximab (Remicade®) is a mouse-human chimeric anti-TNF monoclonal antibody, whereas adalimumab (Humira®) is a fully human TNF-α monoclonal antibody. Etanercept (Enbrel®) is a TNF-α receptor-Fc fusion protein. These agents validated the TNF-α pathway as a target for anti-inflammatory therapy, and, although they do show impressive efficacy, their main drawback is their parenteral administration. Therefore, pharmaceutical industry is actively looking for orally bioavailable, small molecule TNF inhibitors. A wide variety of compounds, with different molecular targets, have been discovered and are in various stages of development. Examples include the p38 mitogen-activated protein (MAP) kinase inhibitors,[2] the Nuclear Factor (NF)-κB inhibitors,[3] and inhibitors of the TNF-α converting enzyme (TACE).[4]

There is a close link between anti-inflammatory drugs and compounds used to prevent graft rejection after organ transplantation.[5] A mainstay in immunosuppressive therapy has been the use of cyclosporine and tacrolimus. These drugs target signal transduction in T-lymphocytes by inhibiting the phosphatase calcineurin. Rapamycin is another immunosuppressant in clinical use to inhibit rejection of transplanted organs; it is targeting the protein mammalian target of rapamycin (mTOR). Rapamycin has shown efficacy in animal models of autoimmunity, including adjuvant arthritis. Two rapamycin analogues, everolimus and temsirolimus are undergoing clinical trials for autoimmune diseases such as rheumatoid arthritis and multiple sclerosis.[6] Another, T-cell target therapy is FTY720. FTY720 is converted to its active form in vivo by sphingosine kinase 2, and the product of this reaction acts as an agonist of the sphingosine-1-phosphate receptor. This has been shown to prevent lymphocyte egress from the thymus and secondary lymphoid tissues.[6] FTY720 reached phase 3 clinical trials in the organ transplantation and is currently evaluated in the clinic for the treatment of multiple sclerosis.

As part of an ongoing research program towards the identification of novel immunomodulatory agents, a dual screening system has been set up in order to discover compounds with an unique

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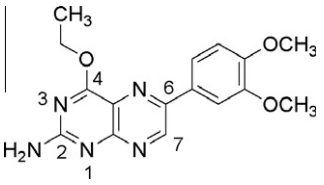


Figure 1. Structure of hit **1**.

biological profile: compounds should be able to inhibit T-cell proliferation (immunosuppressive properties) and they should be inhibitory towards TNF production (anti-inflammatory activity). The screening assays that have been implemented are the Mixed Lymphocyte Reaction (MLR) assay and the lipopolysaccharide (LPS)-induced TNF-α production assay. The MLR assay measures the degree of T-cell proliferation that occurs in response to mixing of allogeneic lymphocytes. When lymphocytes mismatched at major histocompatibility loci are combined under normal conditions, a robust proliferative response is observed. This proliferative response is attenuated in the presence of immunosuppressive compounds.[7] The TNF-α assay was used to determine the suppression of production of human TNF-α by LPS-stimulated human peripheral blood mononuclear cells.[8] Both are non-target, cellular based assays having the advantage of being not biased towards any particular target. Some of the currently widely used immunosuppressive agents have been discovered using the MLR assay. In addition, anti-TNF activity of the well-known pyridinyl imidazoles have been discovered through screening in LPS-stimulated human monocytes, after which a biochemical tour de force revealed the molecular target to be p38 MAPK.[9] It validates both cellular assays as being appropriate for drug discovery. The combined use of both assays allows us to identify a novel class of drugs with a unique combination in the field of immunomodulation.

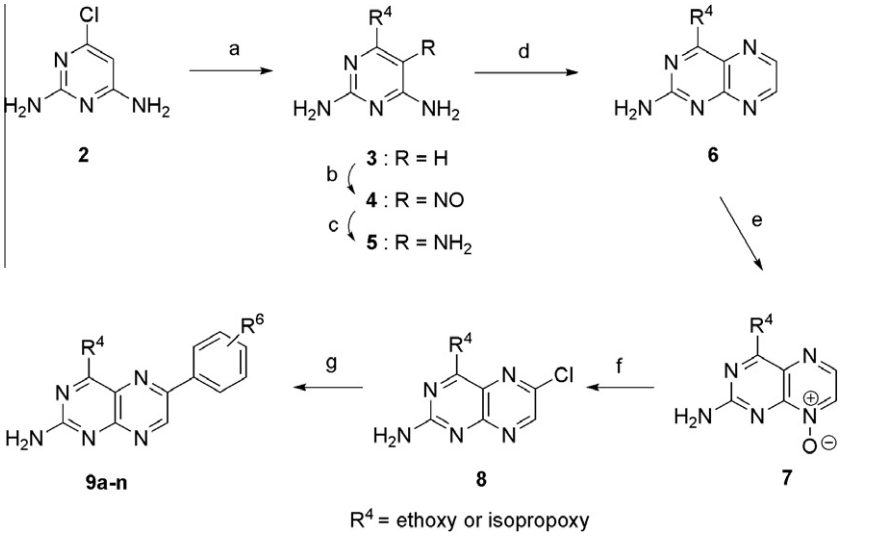
In previous publications, we disclosed the activity of representative lead compounds that arose from this optimization process in preclinical animal models of Crohn's disease.[8,10] In this Letter, we present the medicinal chemistry strategy that gave access to these compounds.

In order to start a medicinal chemistry program, a screening campaign of the corporate compound library was initiated. This library is mainly built around the pteridine scaffold with a wide range of analogues (approximately 4000 compounds), bearing structural variety of substituents. In sharp contrast with closely related heterocycles such as purines and quinazolines, the pteridine scaffold has not been very well explored in medicinal chemistry programs. The only marketed drugs based on pteridine core structure are triamterene (a diuretic drug) and methotrexate (originally developed as an anti-cancer drug, but also used for the treatment of rheumatoid arthritis).

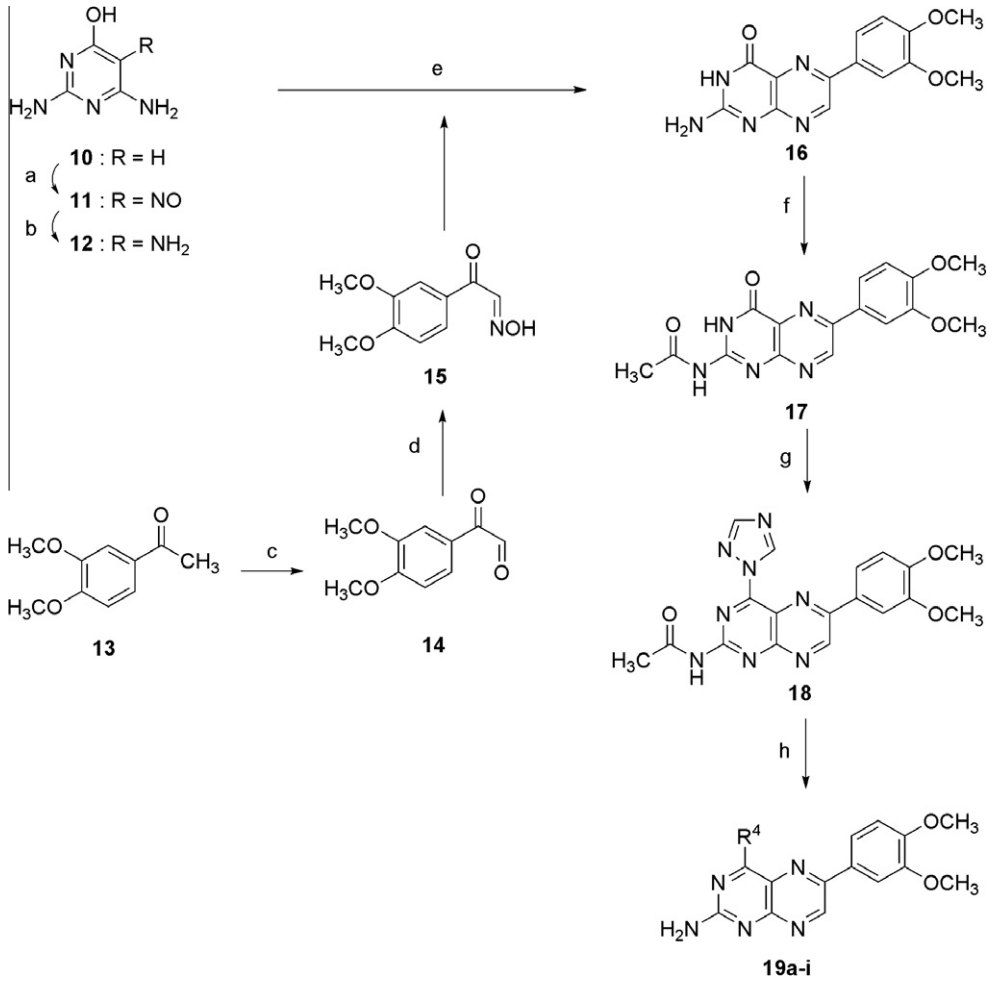
Screening of this pteridine-based compound library, yielded a number of hits, including compound **1** (Fig. 1), displaying an IC_{50} of 1.2 μM and 6.6 μM in the MLR and TNF assay, respectively. Based on this lead compound, a medicinal chemistry program was initiated to evaluate the structure–activity relationship (SAR) around the pteridine scaffold. In this respect, we focused at positions 4 and 6 of the pteridine core structure and kept the exocyclic amino group at position 2 intact.

The chemistry started off with the synthesis of a focused library of 6-aryl substituted pteridine analogues (Scheme 1). Starting from commercially available 2,6-diamino-4-chloro-pyrimidine, sodium ethoxide or sodium isopropoxide was used to introduce an alkoxy substituent. Nitrosation of the pyrimidine ring, followed by reduction of the nitroso group (using sodium dithionite in water) yielded a 5,6-diamino-pyrimidine derivative **5**, which was used for a ring closure reaction with glyoxal, affording 2-amino-4-alkoxy-pteridine **6**.[11] Oxidation of **6** in trifluoroacetic acid with 30% H_2O_2 afforded the *N*-(8)-oxide derivative **7**. The chlorine was regioselectively introduced at position 6 of the scaffold via a Katada type of rearrangement using acetyl chloride and trifluoroacetic acid, yielding 2-amino-4-alkoxy-6-chloro-pteridine **8**.[12] This was used as a key building block to carry out Suzuki couplings with a range of boronic acids, affording a small library of compounds **9a**–**n**.

As the 6-(3,4-dimethoxyphenyl) substituent turned out to be optimal for immunosuppressive and anti-inflammatory activity, a novel series of compounds was synthesized by introducing nitrogen nucleophiles at position 4 of the pteridine scaffold (Scheme 2). Introduction of a nitroso group at position 5 of 2,6-diamino-4-hydroxy-pyrimidine **10** and its subsequent reduction yielded the 5,6-diamino-pyrimidine derivative **12**. The 6-(3,4-dimethoxyphenyl)-pteridine scaffold was constructed by a regioselective condensation reaction between pyrimidine **12** and α-ketoaldoxime **15** (which was prepared from the corresponding acetophenone derivative **13** by oxidation with SeO_2, followed by



Scheme 1. Reagents and conditions: (a) R_4H, Na, 160 °C, 6 h, 72%; (b) $NaNO_2$, CH_3COOH, H_2O, 80 °C, 68%; (c) $Na_2S_2O_4$, H_2O, 60 °C, 61%; (d) glyoxal, ethanol or isopropanol, reflux, 4 h, 62%; (e) TFA, H_2O_2, 4 °C, 2 d, 32%; (f) AcCl, TFA, −40–0 °C, 72%; (g) $ArB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, dioxane, reflux, 4 h, 20–70%.



Scheme 2. Reagents and conditions: (a) $NaNO_2$, CH_3COOH, H_2O, 97%; (b) $Na_2S_2O_4$, H_2O, rt, 83%; (c) SeO_2, dioxane, H_2O, 50 °C; (d) acetonoxime, CH_3OH, H_2O, 50 °C, 2 h, 71% (over 2 steps); (e) **15**, CH_3OH, reflux, 3 h, 85%; (f) Ac_2O, CH_3COOH, reflux, 1 h, 77%; (g) $POCl_3$, 1,2,4-triazole, pyridine, rt, 4 h, 80%; (h) amine, dioxane, rt, o/n and then K_2CO_3, H_2O, CH_3OH, rt, o/n, 30–65%.

oxime formation).[13] The 6-substituted pterine analogue **16** precipitates out of the reaction mixture in high purity. The exocyclic amino group was protected as an acetyl group and the tautomeric hydroxyl group was activated for a nucleophilic displacement reaction by preparing the corresponding 4-(1,2,4-triazolyl)-pteridine derivative **18** using $POCl_3$ and 1,2,4-triazole.[14] This key intermediate was sufficiently stable to be kept on the bench for several months. Reaction of this 4-*N*-triazolyl-pteridine derivative **18** with a number of nucleophiles, followed by alkaline deprotection of the acetyl group, afforded a series of 4-N-substituted pteridine analogues **19a–i** (Table 2). This synthetic sequence works very well, but has the disadvantage of additional protection/deprotection steps which lengthens the synthesis. Therefore, in order to have easy access to 4-N-substituted pteridine analogues, a short sequence using a one step silylation–amination approach has been established using hexamethyldisilazane (HMDS) using *p*-toluenesulfonic acid and ammonium sulfate as catalysts (Scheme 3). This transformation is well known in nucleoside chemistry, where it has been explored to convert uracil into cytosine analogues.[15] Two series of compounds have been prepared by this methodology (Table 3). A number of commercially available N-substituted-

Table 1
SAR of 2-amino-4-alkoxy-6-aryl-pteridines

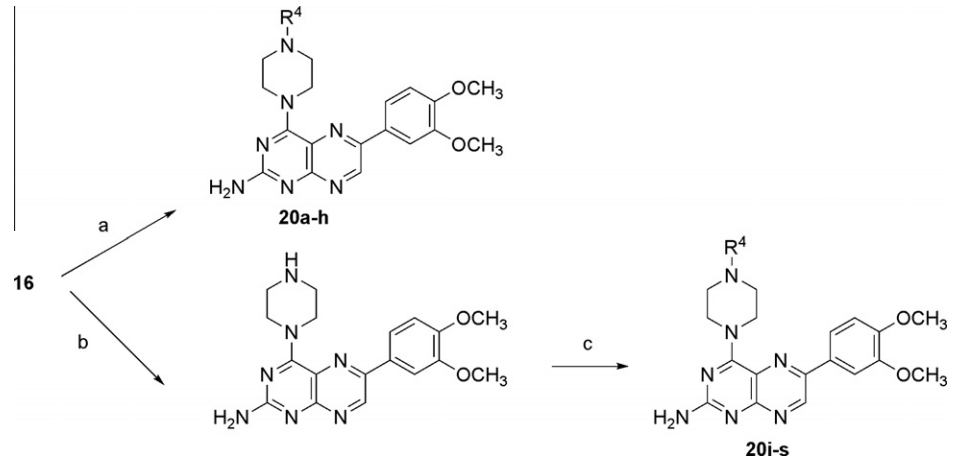
Compd	R^4	R^6	MLR IC_{50}[a] (μM)	TNF IC_{50}[a] (μM)
9a	Ethoxy	4-CF_3	10	>10
9b	Ethoxy	3,4-DiF	>10	>10
9c	Ethoxy	3-OCH_3	8.3	10
9d	Ethoxy	4-CN	>10	>10
9e	Ethoxy	4-Et	8.2	8.5
9f	Ethoxy	3,4-di-Cl	>10	>10
9g	Ethoxy	4-OMe	>10	4.5
9h	Isopropoxy	4-CF_3	>10	9.1
9i	Isopropoxy	3,4-Di-F	10	6.6
9j	Isopropoxy	4-OCH_3	>10	6.2
9k	Isopropoxy	4-OEt	10	10
9l	Isopropoxy	3,4-DiMe	10	6.7
9m	Isopropoxy	3,4-Di-OCH_3	0.4	2.3
9n	Isopropoxy	4-CN	>10	6.3

[a] Values are means of two independent experiments and variations are less than 15%.

Table 2
SAR of 2-amino-4-substituted-6-(3,4-dimethoxyphenyl)-pteridines

Compd	R^4	MLR IC_{50}[a] (μM)	TNF IC_{50}[a] (μM)
19a	Benzylamino	13	6.5
19b	Phenethylamino	6	7.1
19c	Cyclopentylamino	0.8	0.6
19d	Isopropylamino	0.6	0.3
19e	4-Methyl-*N*-piperidino	0.8	0.3
19f	2-Thienylmethylamino	4.1	7.2
19g	Morpholino	0.1	0.4
19h	Thiomorpholino	0.4	0.5

[a] Values are means of two independent experiments and variations are less than 15%.



Scheme 3. Reagents and conditions: (a) and (b) 1,1,1,3,3,3-hexamethyldisilazane, (N-substituted)-piperazine, ammonium sulfate, *p*-TsOH, toluene, 120 °C, 1 d, 35–85%; (c) isocyanate, DMF, rt, 2 h, 60–80% or acid chloride, NEt_3, CH_2Cl_2, rt, 2 h, 40–85%.

Table 3
SAR of 2-amino-4-*N*-piperazinyl-6-(3,4-dimethoxyphenyl)-pteridines

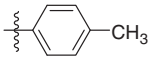
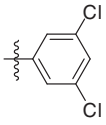
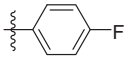
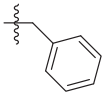
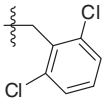
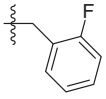
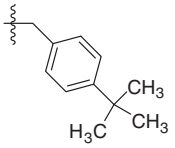
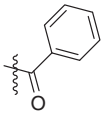
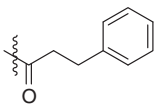
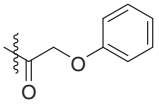
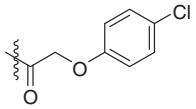
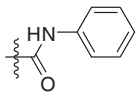
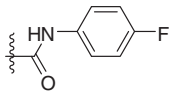
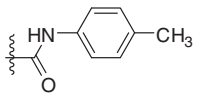
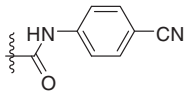
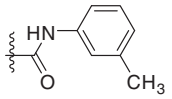
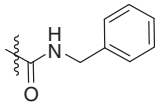
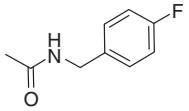
Compd	R^4	MLR IC_{50}[a] (μM)	TNF IC_{50}[a] (μM)
20a		0.4	0.05
20b		0.3	0.01
20c		3.4	0.5
20d		0.1	0.05
20e		0.9	0.09
20f		7.6	0.7
20g		0.7	0.2
20h		4.3	0.7
20i		0.4	0.4
20j		0.1	0.01
20k		0.004	0.08

Table 3 (*continued*)

Compd	R^4	MLR IC_{50}[a] (μM)	TNF IC_{50}[a] (μM)
20l		0.0005	0.077
20m		0.0034	0.09
20n		0.007	0.51
20o		0.0008	0.43
20p		0.074	0.63
20q		0.007	0.1
20r		0.018	0.6
20s		0.037	0.7

[a] Values are means of two independent experiments and variations are less than 15%.

piperazines was coupled to the pteridine scaffold, affording compounds **20a–h** (Table 3). On the other hand, in a two-step procedure, in which first the free piperazine moiety is introduced, the second nitrogen was further derivatized as an amide group (by reaction with acid chlorides) furnishing compounds **20i–l**, or as an urea (by coupling with isocyanates) yielding derivatives **20m–s**.

All compounds were evaluated for their biological activity in the MLR and TNF assay. The initial SAR focused on modifications of the

6-aryl substituent of hit **1**, without modifications of the rest of the molecule (Table 1). Both methoxy groups of compound **1** seem to be essential for activity, as the 4-methoxyphenyl (compound **9g**), as well as the 3-methoxyphenyl (compound **9c**) derivative, are much less active. Other types of substituent on the phenyl ring, such as halogens (compounds **9b** and **9f**), electron withdrawing groups such as trifluoromethyl and cyano (compounds **9a** and **9d**) or electron-donating substituents (compound **9e**) do not show biological activity in any of the two assays. In order to prove that the presence of a dimethoxyphenyl substituent is mandatory for immunosuppressive and anti-inflammatory activity, the closely related 4-isopropoxy-pteridine series (compounds **9h–n**) was synthesized. The same trend was observed here as the dimethoxyphenyl containing analogue (compound **9m**) resulted in superior IC_{50} values in the MLR and TNF assay (IC_{50} values of 0.4 and 2.3 μM, respectively), when compared to other types of substitutions on the phenyl ring. In addition, this isopropoxy derivative **9m** is threefold more potent than the corresponding ethoxy analogue **1** in both assays.

In a second round of optimization, a series of 6-(3,4-dimethoxyphenyl)-pteridine derivatives (compounds **19a**–**h**) were made in which a number of nitrogen nucleophiles is introduced at position 4 of the scaffold. As can be derived from Table 2, it seems that aromatic rings (e.g. compounds **19a–b** and **19f**) do not exhibit potent immunosuppressive or anti-inflammatory activity. On the other hand, a number of aliphatic and cycloaliphatic substituents are tolerated for activity (compounds **19c**–**e** and **19g**–**h**) and give rise to dual acting compounds with IC_{50} around 0.5 μM in the MLR, as well as in the TNF assay.

Before starting in vivo work with this type of compounds, we felt it necessary to further improve the potency of the compounds. Given the low molecular weight of the lead compounds, adding additional groups in order to exploit additional interactions was still justified. Position 4 of the pteridine scaffold was the preferred site to do so, as it tolerated quite some structural variety. As heterocyclic aliphatic substituents such as morpholino, piperidine, thiomorpholino were found to be active in both assays, we focused on piperazine as the 4-substituent as it represents an easy handle for further derivatization. A number of commercially available *N*-aryl (compounds **20a–d**) and *N*-benzyl (compounds **20e**–**h**) piperazine derivatives were incorporated onto the pteridine core structure. The *N*-phenyl-piperazine derivative **20a** was the first compound in this optimization campaign with very potent activity in the TNF assay (IC_{50} = 50 nM). On the other hand, the MLR IC_{50} of compound **20a** did not improve when compared to smaller substituents such as morpholine. The nature of the substitution pattern on the phenyl ring determines the biological activity: the unsubstituted phenyl ring (compound **20a**) and its 4-methyl (compound **20b**) and 4-fluoro (compound **20d**) congeners show comparable activity in the MLR assay (IC_{50} values ranging from 0.1 to 0.4 μM) and the TNF assay (IC_{50} values ranging from 10 to 50 nM), whereas the 3,5-dichlorophenyl analogue **20c** is approximately 10-fold less active in the MLR as well as in the TNF assay (IC_{50} of 3.4 and 0.5 μM, respectively). Similarly, *N*-benzyl derivatives (compounds **20e**–**h**) have been prepared, from which the unsubstituted benzyl ring (compound **20e**) seems to be most potent (MLR IC_{50} = 0.9 μM and TNF IC_{50} = 0.09 μM). The 2-fluoro analogue (compound **20g**) has a very similar profile (MLR IC_{50} and TNF IC_{50} values of 0.7 and 0.2 μM, respectively). The 2,6-dichloro-benzyl (compound **20f**) and the 4-*tert*-butyl derivative (compound **20h**) are clearly less potent in both assays.

A series of amides was also prepared. The benzoyl derivative (compound **20i**) is a pure dual acting compound with equipotent activity in the MLR and TNF assay (IC_{50} of 0.4 μM in both assays). A big step forward in the immunosuppressive activity was achieved by introduction of appropriate linkers between the carbonyl group and the phenyl moiety. A two carbon linker yielded compound **20j**, displaying a TNF IC_{50} value of 10 nM and a MLR IC_{50} of 100 nM. A phenoxyacetyl side chain on the piperazine group (compound **20k**) led to an extremely potent immunosuppressive agent with an IC_{50} value of 4 nM. The corresponding 4-chloro analogue (compound **20l**) displayed even more pronounced immunosuppressive activity (MLR IC_{50} = 0.5 nM). In order to further probe into the SAR, we expanded the synthesis towards urea derivatised analogues. The phenyl substituted analogues (compounds **20m–q**) all show impressive activity in the MLR assay, with IC_{50} values in the low nanomolar range. Especially, the 4-methyl analogue (compound **20o**) was extremely potent (MLR IC_{50} = 0.8 nM), whereas the 4-cyano derivative (compound **20p**) was somewhat less active (MLR IC_{50} = 74 nM). The benzyl substituted urea derivatives (compounds **20r-s**) are approximately 10-fold less potent in the MLR assay than their phenyl counterparts (compounds **20m**–**n**). These *N*-acyl and *N*-carbamoyl-piperazine-pteridine derivatives represent the most powerful immunosuppressive drugs known up to now. For comparison, marketed immunosuppressive drugs were also evaluated in this MLR assay. The pteridine analogues display more pronounced immunosuppressive activity than cyclosporine (IC_{50} = 65 nM), while their potency is similar to that of tacrolimus (IC_{50} = 1 nM) and rapamycin (IC_{50} = 1 nM).

With respect to the anti-inflammatory activity of the amides and urea, it is clear that the most potent anti-inflammatory compounds (analogues **20j**–**m**) within this series have TNF IC_{50} values which are similar to the *N*-aryl-piperazine congeners. It demonstrates that a carbonyl function is an indispensable structural element to obtain potent immunosuppressive drugs, whereas this is not the case for the anti-inflammatory activity.

In conclusion, a novel series of 2-amino-4-*N*-piperazinyl-6-(3,4-dimethoxyphenyl)pteridine analogues have been prepared and evaluated for their immunosuppressive (using the MLR assay) and anti-inflammatory (using the TNF assay) properties. The herein described SAR study indicated that the 6-(3,4-dimethoxyphenyl) moiety is essential in obtaining immunosuppressive and anti-inflammatory activity. Further SAR studies revealed that derivatization of the piperazine moiety as amides or urea led to extremely potent immunosuppressives (sub nM IC_{50} values), while retaining good activity in the TNF assay. In vivo activity in preclinical animal models of Crohn's disease of some representative examples (compounds **20b** and **20k**) have been described by us before.[8,10]

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