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# Synthesis and structure–activity relationship of a novel sulfone series of TNF-α converting enzyme inhibitors

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**Abstract**—Replacement of the amide functionality in IM491 (*N*-hydroxy-(5*S*,6*S*)-1-methyl-6-{[4-(2-methyl-4-quinolinylmethoxy)anilinyl]carbonyl}-5-piperidinecarboxamide) with a sulfonyl group led to a new series of α,β-cyclic and β,β-cyclic γ-sulfonyl hydroxamic acids, which were potent TNF-α converting enzyme (TACE) inhibitors. Among them, inhibitor **4b** (*N*-hydroxy-(4*S*,5*S*)-1-methyl-5-{[4-(2-methyl-4-quinolinylmethoxy)phenyl]sulfonylmethyl}-4-pyrrolidinecarboxamide) exhibited $IC_{50}$ values of <1 nM and 180 nM in porcine TACE (pTACE) and cell assays, respectively, with excellent selectivity over MMP−1, −2, −9 and −13 and was orally bioavailable with an F value of 46% in mice.


In our previous communication,[1a] we disclosed the rational design of a novel series of cyclic succinate TACE (TNF-α converting enzyme)[2] inhibitors based on a broad spectrum MMP (matrix metalloproteinase) inhibitor. Extensive SAR studies from this series led to the identification of IM491[1b] (Fig. 1), one of the most effective TACE inhibitors reported so far in the literature[3] inhibiting TNF-α release in a LPS-stimulated human whole blood assay (WBA, $IC_{50}$ = 20 nM) with excellent selectivity (over MMPs) and pharmacokinetics profiles. Since an aniline moiety (A, Fig. 1) was present in IM491 through an amide linkage to the piperidine core (B, Fig. 1), we were concerned about the break-down of this amide bond and the potential toxicity of the released aniline residue (A). We therefore investigated the stability of the amide bond under physiological conditions. In a simulated gastric fluid at pH = 7.5, about 0.5% of A was generated from IM491 over a

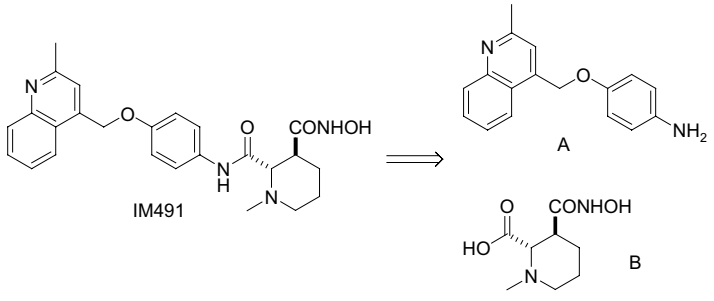


**Figure 1.**

*Keywords*: TNF-α production; TNF-α converting enzyme inhibitors; Sulfone derivatives.
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period of 24 h at 37 °C. Subsequently compound A was subjected to AMES test and positive result was obtained, revealing its mutagenic liability. For these reasons, IM491 was discontinued for further development.

Given the attractive profile of IM491 in cellular activity, TACE selectivity over MMPs and in vivo property, we set out to address the mutagenic issue associated with the aniline residue A by exploring the possibility of replacing the amide bond with other hydrogen-bond acceptors. Modeling studies suggested that the amide functionality could be replaced with a sulfonyl group (Fig. 2) to provide either β-sulfonyl hydroxamic acids (I) or γ-sulfonyl hydroxamic acids (II). Structure I was ruled out based on the consideration that β-elimination could occur under strong basic conditions to produce α,β-unsaturated hydroxamic acid and sulfinic acid. Structure II (*cis* configuration preferred based on modeling) was considered to be stable to base and as such, a series of piperidine or pyrrolidine hydroxamic acids with a sulfonyl γ to the hydroxamic acid group were prepared as shown in Table 1. All compounds prepared contain a basic piperidine or pyrrolidine nitrogen in order to maintain the good water solubility and low protein binding of IM491.

We first prepared compounds **1a**–**b**, which are the closest analogs to IM491. With no substitution on the piperidine nitrogen, compound **1a** was more potent than IM491 in porcine TACE (pTACE) assay with similar

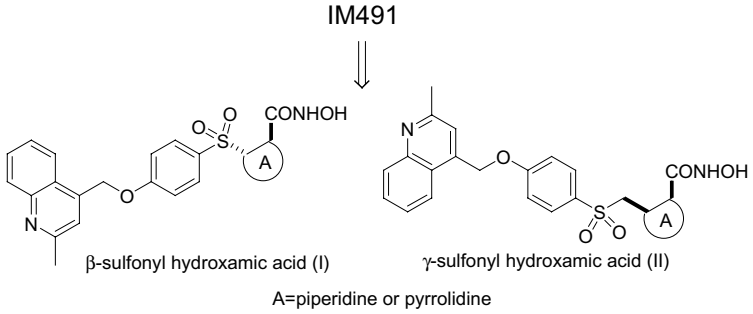
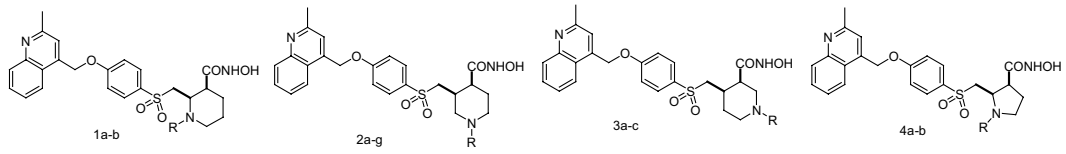



**Figure 2.**

**Table 1.** In vitro and in vivo profile of α,β-cyclic γ-sulfonyl hydroxamic acid inhibitors[a–d]




| Compd | R | pTACE $IC_{50}$ (nM) | WBA $IC_{50}$ (nM) | MMP-1 $K_i$ (nM) | MMP-2 $K_i$ (nM) | MMP-9 $K_i$ (nM) | MMP-13 $K_i$ (nM) | Caco-2 *P*app ($\times 10^{-6}$ cm/s) | LPS-Mouse[e] Inhibition @10 mg/kg (po) |
|---|---|---|---|---|---|---|---|---|---|
| IM491 | | 6.2 | 20 | >4900 | >3300 | >2100 | | 2.1 | >50% ($ED_{50}$ = 3–5 mg/kg) |
| **1a** | H | <1 | 240 | >4900 | >3300 | >2100 | 754 | 0.1 | |
| **1b** | Me | 1.1 | >3000 | >4900 | >3300 | >2100 | >5000 | | |
| **2a** | H | 1 | 250 | >4900 | >3300 | >2100 | >5000 | 0.1 | |
| **2b** | Me | 1.9 | 190 | >4900 | >3300 | >2100 | >5000 | 0.1 | |
| **2c** | Isopropyl | 1.5 | 230 | >4900 | >3300 | >2100 | >5000 | 0.1 | 38% |
| **2d** | Allyl | 1.8 | 160 | >4900 | >3300 | >2100 | 503 | 0.97 | 25% |
| **2e** | Propargyl | 1.0 | 180 | >4900 | >3300 | >2100 | 377 | 1.3 | 24% |
| **2f** | *n*-Butyl | <1 | 900 | >4900 | >3300 | >2100 | >5000 | 1.6 | 35% |
| **2g** | Isobutyl | <1 | 1070 | >4900 | >3300 | >2100 | >5000 | 1.8 | 33% |
| **3a** | H | 1.5 | 250 | >4900 | >3300 | >2100 | >5000 | 0.1 | |
| **3b** | Me | 6.5 | 510 | >4900 | >3300 | >2100 | >5000 | 0.2 | |
| **3c** | Isopropyl | 11 | >1000 | >4900 | >3300 | >2100 | >5000 | 0.65 | |
| **4a** | H | <1 | 83 | >4900 | >3300 | >2100 | 955 | 0.1 | 20% |
| **4b** | Me | <1 | 180 | >4900 | >3300 | >2100 | 1708 | 1.0 | >50% ($ED_{50}$ = 2.5 mg/kg) |

[a] Compounds **1a**–**b** and **4a**–**b** are single enantiomers. Compounds **2a**–**g** and **3a**–**c** are racemates.
[b] See Ref. 4 for pTACE, WBA and MMP assay protocols.
[c] pTACE $IC_{50}$ and MMP $K_i$ values are from single determination.
[d] Inhibition of TNF-α release in whole blood assay (WBA) was determined with three donors.
[e] See Ref. 5 for LPS-mouse model studies.

selectivity profile over MMPs (Table 1). However it exhibited 12-fold loss of cellular activity in WBA and much lower Caco-2 permeability compared with IM491. While the lower Caco-2 permeability of **1a** was disappointing, the weaker WBA activity was not a surprise since the NH analog of IM491 was six-fold less active than IM491 in WBA.[1b] We expected the cellular activity of **1a** to be improved by methylation at the piperidine nitrogen. Unfortunately the SAR in the IM491 series did not translate into this series. *N*-Methylation of **1a** resulted in a dramatic loss in WBA potency. Analog **1b** was inactive at a concentration of 3 μM in WBA despite its potent pTACE activity.

We next investigated the regio-effect of the piperidine nitrogen by moving the nitrogen one atom away from the P1′ group while keeping the 4-(2-methyl-4-quinolinylmethoxy)phenyl P1′ residue constant. Without substitution on the piperidine nitrogen, analog **2a** (racemate) was equipotent to **1a** in WBA with same low Caco-2 permeability. Methylation (**2b**) or isopropylation (**2c**) at the piperidine nitrogen maintained the WBA activity but did not improve Caco-2 permeability. The low Caco-2 permeability of **2c** is consistent with the low in vivo anti-TNF-α activity in an LPS-mouse model in which an oral dose of 10 mg/kg achieved only 38% inhibition of TNF-α release. Lowering the basicity of the piperidine nitrogen by replacing the methyl in **2b** with allyl (**2d**) or propargyl (**2e**) significantly improved the Caco-2 permeability while retaining the cellular activity of **2b**. In spite of the improvement in Caco-2 permeability, both analogs were inactive in the LPS-mouse model at an oral dose of 10 mg/kg, indicating that they were not orally bioavailable. Further improvement in Caco-2 permeability was achieved by increasing the size of the substituent to *n*-butyl (**2f**) and isobutyl (**2g**). However, these larger alkyl analogs suffered a considerable loss in cellular activity despite their better pTACE potency, probably due to increased protein binding caused by the larger alkyl groups.

Moving the basic piperidine nitrogen one atom further away from the P1′ residue in **2a** provided analog **3a** (racemate), which was comparable to **2a** in pTACE activity, WBA potency, selectivity over MMPs and Caco-2 permeability. Methylation (**3b**) or isopropylation (**3c**) on the piperidine nitrogen in **3a** attenuated the pTACE and WBA activities.

We next turned our SAR studies to smaller nitrogen-containing heterocycles. Shrinking the six-membered piperidine ring in **1a** to five-membered pyrrolidine ring provided analog **4a**, which was three-fold more potent than **1a** in cellular activity, with an $IC_{50}$ value of 80 nM in WBA and highly selective over MMPs. Unfortunately the Caco-2 permeability of **4a** remained low and it was not orally active in the LPS-mouse model. Methylation at the pyrrolidine nitrogen in **4a** reduced the WBA potency by two-fold but improved the Caco-2 *P*app value to $1.0\times10^{-6}$ cm/s. Accompanied by the enhancement in cell permeation was the good oral anti-TNF-α activity in the LPS-mouse model, with an $ED_{50}$ value of 2.5 mg/kg, which is slightly more active

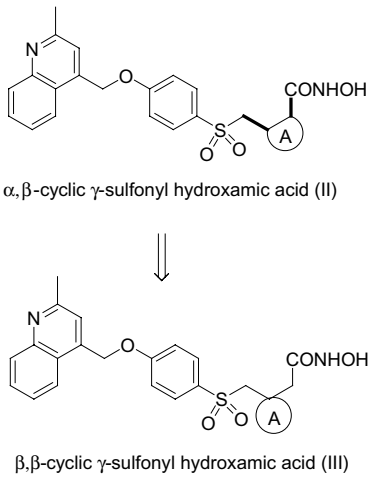



**Figure 3.**

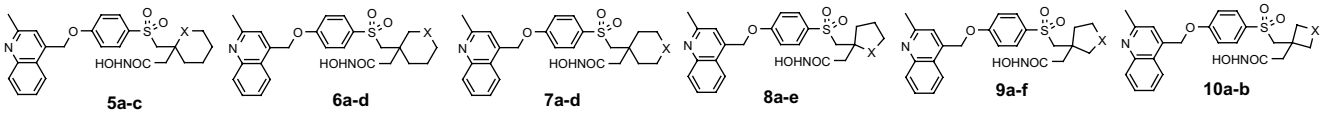
than IM491, indicating that analog **4b** is orally bioavailable in mice.

In parallel to the above SAR studies, we tried to modify the core structure of II by moving the α,β-cyclic ring to the β,β-position to form a new series of β,β-cyclic γ-sulfonyl hydroxamic acids (III, Fig. 3). This modification not only retains the relative orientation of the hydroxamate with respect to the sulfonyl (two key components required for binding interaction with TACE) as suggested by modeling studies but also eliminates at least the stereogenic center α to the hydroxamate in II. We first investigated a piperidine heterocycle (Table 2). Without substituent on the piperidine nitrogen, compound **5a** exhibited potent pTACE activity ($IC_{50}<1$ nM) with high selectivity over MMP−1, −2, −9 and −13 but weak WBA potency ($IC_{50}=632$ nM). Substitution on the piperidine nitrogen with an alkyl is detrimental to the pTACE activity; the larger the alkyl group, the weaker the pTACE activity, suggesting that a substituent at this position may interfere with the orientation of the hydroxamate relative to the sulfonyl group.

In contrast to the 2,2-disubstituted piperidine series, substitution on the piperidine nitrogen with different size of alkyl groups in the 3,3- and 4,4-disubstituted piperidine series had little effect on pTACE potency. However, larger alkyl groups such as isopropyl and isobutyl provided analogs with much weaker WBA potency, probably due to higher protein binding. While the NH analog **6a** in the 3,3-disubstituted series and the *N*-methyl analog **7b** in the 4,4-disubstituted series displayed desired WBA activity ($IC_{50}=102$ and 123 nM, respectively), they exhibited low Caco-2 permeability, consistent with their low oral activity in the LPS-mouse model.

We next investigated a pyrrolidine heterocycle (Table 2). All pyrrolidine analogs prepared manifested same SAR trend as observed in the piperidine series. Increment in the size of a substituent on the pyrrolidine nitrogen in the 2,2-disubstituted pyrrolidine series gradually decreased the pTACE potency (**8a**–**d**) whereas any size of

**Table 2.** In vitro and in vivo profile of β,β-cyclic γ-sulfonyl hydroxamic acid inhibitors[a,b]




| Compd | X | p-TACE $IC_{50}$ (nM) | WBA $IC_{50}$ (nM) | MMP-1 $K_i$ (nM) | MMP-2 $K_i$ (nM) | MMP-9 $K_i$ (nM) | MMP-13 $K_i$ (nM) | Caco-2 *P*app ($\times 10^{-6}$ cm/s) | LPS-Mouse % inhibition @ 5 mg/kg (po) |
|---|---|---|---|---|---|---|---|---|---|
| **5a** | N–H | <1 | 632 | >4900 | >3300 | >2100 | 753 | 1.7 | 50 |
| **5b** | N–Me | 5.1 | >3000 | >4900 | >3300 | >2100 | >5000 | 5.1 | |
| **5c** | N-*i*-Bu | 48 | | >4900 | >3300 | >2100 | >5000 | | |
| **6a** | N–H | 2.8 | 123 | >4900 | >3300 | >2100 | >5000 | 0.1 | 31 |
| **6b** | N–Me | 3.6 | 208 | >4900 | >3300 | >2100 | 3869 | 0.2 | 49 |
| **6c** | N-*i*-Pr | 2.7 | 506 | >4900 | >3300 | >2100 | >5000 | 0.2 | |
| **6d** | N-*i*-Bu | 3.3 | 2503 | >4900 | >3300 | >2100 | >5000 | 0.7 | 25 |
| **7a** | N–H | 14 | | >4900 | >3300 | >2100 | >5000 | 0.1 | 57 |
| **7b** | N–Me | 2 | 102 | >4900 | >3300 | >2100 | 2613 | 0.2 | |
| **7c** | O | 1 | 258 | >4900 | >3300 | >2100 | >5000 | | |
| **7d** | $CH_2$ | <1 | 867 | >4900 | 1400 | >2100 | 1206 | 22 | 59 |
| **8a** | N–H | 1 | 403 | >4900 | >3300 | >2100 | >5000 | 0.4 | 19 |
| **8b** | N–Me | 2.9 | >3000 | >4900 | >3300 | >2100 | 3266 | 1.6 | |
| **8c** | N-*i*-Bu | 20 | | >4900 | 1333 | >2100 | >5000 | 0.7 | |
| **8d** | N-Ac | 660 | | >4900 | >3300 | >2100 | >5000 | 0.6 | |
| **8e** | O | 1 | 913 | >4900 | >3300 | >2100 | >5000 | 5.0 | 57 |
| **9a** | N–H | 1.5 | 76 | >4900 | >3300 | >2100 | 3266 | 0.1 | 34 |
| **9b** | N–Me | 3.2 | 109 | >4900 | >3300 | >2100 | >5000 | 0.3 | 28 |
| **9c** | N-*i*-Pr | 1.6 | 77 | >4900 | 1333 | 2100 | 653 | 0.2 | 37 |
| **9d** | N-*i*-Bu | 2.6 | 161 | >4900 | 2167 | >2100 | 603 | 0.8 | 22 |
| **9e** | N-neo-Pent | 3.4 | 418 | >4900 | >3300 | >2100 | 1758 | | 22 |
| **9f** | $CH_2$ | 0.8 | 420 | >4900 | 1566 | 1511 | 804 | 18 | |
| **10a** | O | 1 | 595 | >4900 | >3300 | >2100 | >5000 | | |
| **10b** | $CH_2$ | <1 | 223 | >4900 | 2566 | >2100 | 753 | 4.9 | 86 |

[a] All compounds were synthesized in racemic form if a stereogenic center was involved.
[b] See footnotes b–e in Table 1.

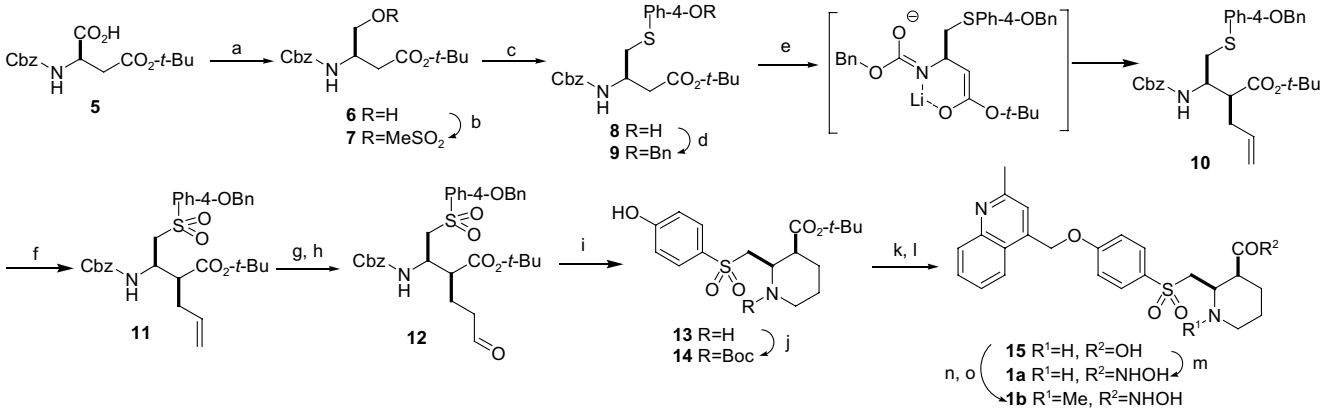
substituent on the pyrrolidine nitrogen in the 3,3-disubstituted pyrrolidine series was tolerated for binding (**9a**–**e**). Of particular note in the 3,3-disubstituted pyrrolidine series are compounds **9a**–**c**, which were very potent in the cellular assay, with $IC_{50}$ values at or below 100 nM. Unfortunately these analogs exhibited low Caco-2 permeability and low oral bioavailability in the LPS-mouse model.

To improve the Caco-2 permeability of this series, we shifted our SAR studies to replacement of the piperidine and pyrrolidine heterocycles with less polar oxygen-containing heterocycles (**7c**, **8e**, and **10a**) or carbocycles (**7d**, **9f**, and **10b**). While significant improvement in Caco-2 permeability was achieved, all analogs exhibited weak to moderate WBA potency albeit potent pTACE activity (IC50's $\leqslant$ 1 nM). Of particular interest is the cyclobutane derivative **10b**, which showed decent WBA activity ($IC_{50}$ = 223 nM), high selectivity over MMPs and high Caco-2 permeability. Consistent with its Caco-2 permeability, **10b** is orally active in the LPS-mouse model, with 86% inhibition at an oral dose of 5 mg/kg.

The good in vitro and in vivo profiles of **4b** and **10b** prompted us to evaluate their pharmacokinetics in mice in a discrete manner for **4b** and in rats in *n*-in-1 for **10b** (Table 3). After iv administration, **4b** exhibited high systemic clearance (4.5 L/h/kg), short half-life (0.5 h) and moderate volume of distribution (2.6 L/kg). Despite the high clearance, oral absorption was impressive, with AUC value at 4612 nM h at a dose of 20 mg/kg and an oral bioavailability of 46%, consistent with the observed good oral anti-TNF-α activity in the LPS-mouse model. In contrast to **4b**, **10b** exhibited much longer half life

**Table 3.** Pharmacokinetics parameters of inhibitor **4b** in mice and inhibitor **10b** in rats

| Compd | Dose (mg/kg) | CL (L/h/kg) | $T_{1/2}$ (h) | Vss (L/kg) | $T_{max}$ (h) | $C_{max}$ (nM) | AUC (nM h) | *F* (%) |
|---|---|---|---|---|---|---|---|---|
| **4b** | iv 6.7 | 4.5 | 0.5 | 2.6 | | | 3367 | |
| | po 20 | | 1.0 | | 1 | 3511 | 4612 | 46 |
| **10b** | iv 5 | 6.6 | 7.2 | 6.9 | | | 1322 | |
| | po 5 | | | | 0.25 | | 217 | 16 |

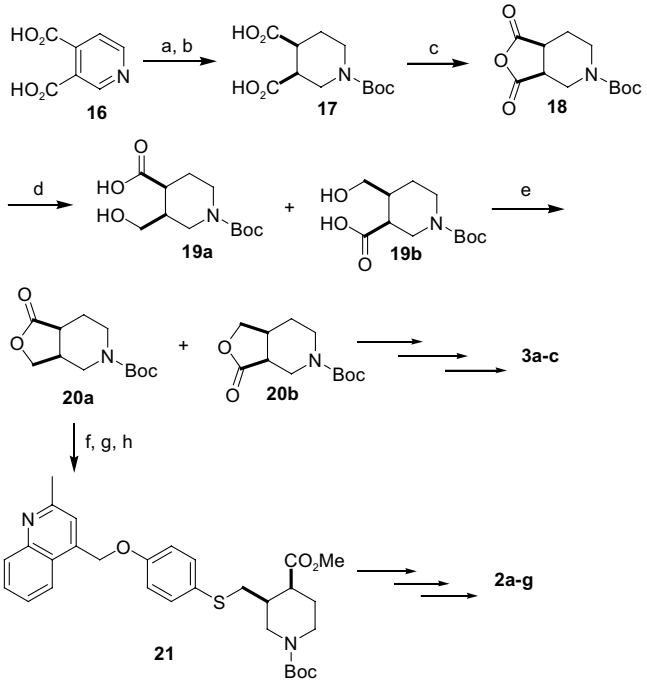


**Scheme 1.** Reagents and conditions: (a) $BH_3$, THF, 60%; (b) $MeSO_2Cl$, TEA, $CH_2Cl_2$, 97%; (c) 4-mercaptophenol, NaH, DMF, rt, 60%; (d) BnBr, $K_2CO_3$, DMF, 95%; (e) LDA, allyl bromide, THF, 90%; (f) Oxone, MeOH, $H_2O$, 90%; (g) 9-BBN, THF, 67%; (h) PDC, $CH_2Cl_2$, 71%; (i) $H_2$, Pd–C, MeOH, 95%; (j) $(Boc)_2O$, THF, $H_2O$, 90%; (k) 4-chloromethyl-2-methylquinoline, $K_2CO_3$, DMF, 65%; (l) TFA, $CH_2Cl_2$, 100%; (m) $HONH_2$, BOP, NMM, DMF, 75%; (n) HCHO, $Na(OAc)_3BH$, NMM, THF, 100%; (o) $HONH_2 \cdot HCl$, BOP, NMM, DMF, 75%.

(7.2 h) and higher volume of distribution (6.9 L/kg) but lower oral exposure, with an *F* value of 16%.

Compounds **1a**–**b** were asymmetrically synthesized using the protocol described in Scheme 1. Reduction of *N*-Cbz-D-aspartic acid (**5**) using borane provided the alcohol **6** in 60% yield. The reaction was sluggish when 2 equiv of borane were used and over 4 equiv of borane were required to complete the reaction. Following conversion of the alcohol to a mesylate, displacement of mesylate **7** with 2 equiv of 4-mercaptophenol using NaH (4 equiv) produced the thioether **8** in 60% yield. The phenol in **8** was alkylated by treating with benzyl bromide in the presence of potassium carbonate. The resulting benzyl ether **9** was subjected to an LDA alkylation with allyl bromide. Formation of the Li-coordinated enolate intermediate followed by attack of allyl bromide from the less hindered face gave rise to the desired diastereomer **10** as the exclusive product, which was isolated in 90% yield. Following oxidation of the sulfide **10** to sulfone **11** using Oxone, the olefin in **11** was converted to an alcohol using 9-BBN and the resulting alcohol was oxidized to an aldehyde using pyridinium dichromate (PDC). Upon cyclization by hydrogenation using palladium on carbon as a catalyst, the resulting piperidine nitrogen in **13** was blocked with Boc by treating with di-*tert*-butyl dicarbonate. Alkylation of phenol **14** with 4-chloromethyl-2-methylquinoline followed by acid treatment afforded **15** from which optically pure **1a** was obtained by BOP coupling with hydroxylamine. Reductive amination of **15** with formaldehyde using sodium triacetoxyborohydride followed by BOP coupling with hydroxylamine completed the synthesis of **1b**.

The 4,5-disubstituted piperidine derivatives **2a**–**g** were prepared as racemates using the procedures outlined in Scheme 2. Reduction of 3,4-pyridinedicarboxylic acid (**16**) by hydrogenation using platinum oxide as a catalyst followed by treatment with di-*tert*-butyl dicarbonate provided *N*-Boc-*cis*-3,4-piperidinedicarboxylic acid **17** in 74% yield. This dicarboxylic acid was subjected to a



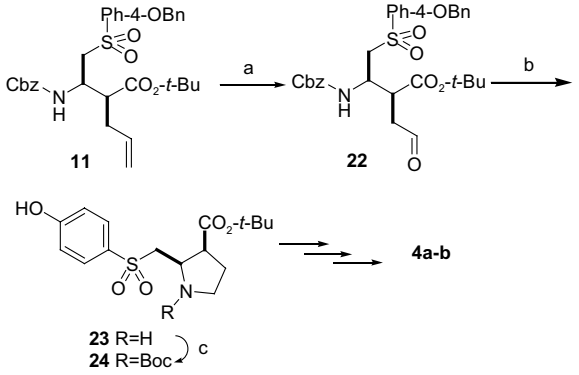
**Scheme 2.** Reagents and conditions: (a) $H_2$, $PtO_2$, 1 N HCl; (b) $(Boc)_2O$, NaOH, 74% for two steps; (c) $Ac_2O$, THF, 100%; (d) $NaBH_4$, THF; (e) MeI, $K_2CO_3$, DMF, rt, 44% for **20a**, 46% for **20b**; (f) 4-mercaptophenol (2 equiv), NaH (4 equiv), DMF, 80 °C, 3 h, 76%; (g) MeI, $K_2CO_3$, DMF; (h) 4-chloromethyl-2-methylquinoline, $K_2CO_3$, DMF, 80 °C, 59% for two steps.

treatment with acetic anhydride to form the cyclic anhydride **18**, which was reduced with sodium borohydride to yield two regio-isomers of γ-hydroxycarboxylic acid **19a** and **19b**. Without separation, the mixture was subjected to treatment with iodomethane in the presence of potassium carbonate to generate two lactones, which were separated by column chromatography to give **20a** (racemate) in 44% yield and **20b** (racemate) in 46% yield. Both structures were characterized using 2 D NMR. Ring opening of **20a** with 4-mercaptophenol (2 equiv)

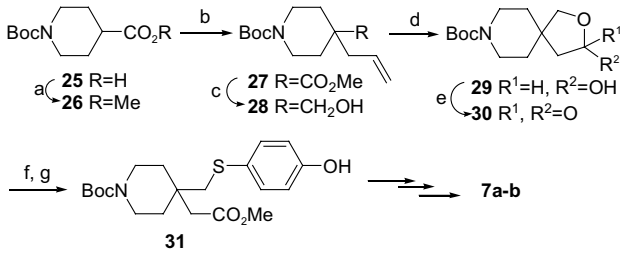
in the presence of NaH (4 equiv), esterification of the resulting carboxylic acid with iodomethane and alkylation of the phenol with 4-chloromethyl-2-methylquinoline yielded the intermediate **21**, which was converted to the final products **2a**–**g** following the procedures described in Scheme 1. Starting from intermediate **20b**, compounds **3a**–**c** were obtained in a similar manner (Scheme 2).

Syntheses of compounds **4a**–**b** were shown in Scheme 3. Intermediate **11** was subjected to an ozonolysis to provide the aldehyde **22** in 36% yield. The low yield of the ozonolysis was probably caused by the interference of the Cbz-protected amino group that, among other things, could attack the generated aldehyde to form a semiaminal. Ring closure to form a pyrrolidine from aldehyde **22** was effected by hydrogenation using palladium on carbon as catalyst. After protection of the resulting pyrrolidine **23** with Boc, the intermediate **24** was converted to the final products **4a**–**b** following the procedures depicted in Scheme 1.

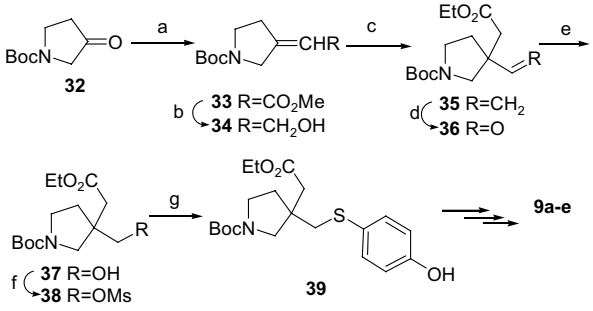
Most of the β,β-cyclic γ-sulfonyl hydroxamic acids were synthesized using a sequence as exemplified in Scheme 4. The commercially available carboxylic acid **25** was converted to a methyl ester **26** under $K_2CO_3$ and MeI conditions. Treatment of **26** with LDA in THF at −78 °C, followed by addition of allyl bromide, furnished the




**Scheme 3.** Reagents and conditions: (a) $O_3$, $P(OMe)_3$, $CH_2Cl_2$, 36%; (b) $H_2$, Pd–C, MeOH, 99%; (c) $(Boc)_2O$, $NaHCO_3$, $H_2O$, THF, 97%.




**Scheme 4.** Reagents and conditions: (a) $K_2CO_3$, MeI, rt; (b) LDA, THF, −78 °C, then allyl bromide; (c) DIBAL, $CH_2Cl_2$, −78 °C; (d) $O_3$, $CH_2Cl_2$, −78 °C, then $P(OMe)_3$, rt; (e) PDC, $CH_2Cl_2$, rt; (f) NaH, 4-mercaptophenol, DMF, 140 °C; (g) $TMSCHN_2$, MeOH, rt.




**Scheme 5.** Reagents and conditions: (a) Methyl (triphenylphosphoranylidene)acetate, toluene, 110 °C; (b) DIBAL, THF, −78 °C; (c) $CH_3C(OEt)_3$, propionic acid, 180 °C; (d) $O_3$, $CH_2Cl_2$, −78 °C, then $P(OMe)_3$, rt; (e) $NaBH_4$, EtOH, rt; (f) MsCl, DIEA, $CH_2Cl_2$, 0 °C; (g) NaH, 4-mercaptophenol, DMF, 0 °C.

allylation product **27**. DIBAL reduction of **27** gave rise to the alcohol **28**, which was converted to the hemiacetal **29** upon ozonolysis. Following oxidation of the hemiacetal to a lactone under PDC conditions, the lactone ring in **30** was selectively opened with 4-mercaptophenol and the resulting carboxylic acid was esterified using $TMSCHN_2$. Conversion of ester **31** to the final product **7a**–**b** was accomplished following the procedures described in Scheme 1.

A different synthetic route to compounds **9a**–**e** was developed due to the commercial unavailability of the required carboxylic acid. As illustrated in Scheme 5, commercially available ketone **32** was reacted with methyl (triphenylphosphoranylidene)acetate, to provide the unsaturated esters **33** as a mixture of *cis* and *trans* isomers (1:1 ratio). DIBAL reduction of this mixture led to a mixture of allylic alcohol **34**, which set the stage for the crucial Claisen rearrangement. A mixture of **34** and ethyl orthoacetate was heated up in the presence of propionic acid in a sealed tube overnight and only one γ,δ-unsaturated ester **35** was obtained. Ozonolysis of **35**, followed by reduction with $NaBH_4$, gave rise to the alcohol **37**, which was mesylated and displaced with 4-mercaptophenol to afford **39**. Following the similar steps as illustrated in Scheme 1, **39** was transformed to the final products **9a**–**e**.

In summary, replacement of the amide functionality in IM491 with a sulfonyl group led to a new series of α,β-cyclic and β,β-cyclic γ-sulfonyl hydroxamic acids. While most of the sulfone analogs prepared had higher affinity for pTACE than IM491, they were less potent in the inhibition of TNF-α production in WBA probably due to higher protein binding and/or poorer cell penetration of the sulfone molecules. The best analog identified from this series is the five-membered pyrrolidine analog **4b** that exhibited $IC_{50}$ values of <1 and 180 nM in the pTACE and cell assays, respectively, high selectivity over MMP−1, −2, −9 and −13, decent Caco-2 permeability and good oral anti-TNF-α activity in the LPS-mouse model. Pharmacokinetics study demonstrated that **4b** was orally bioavailable, with an *F* value of 46% in mice.

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