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Discovery of BMS-986251: A Clinically Viable, Potent, and Selective RORγt Inverse Agonist

Robert J. Cherney,* Lyndon A. M. Cornelius, Anurag Srivastava, Carolyn A. Weigelt, David Marcoux, James J.-W. Duan, Qing Shi, Douglas G. Batt, Qingjie Liu, Shiuhang Yip, Dauh-Rurng Wu, Max Ruzanov, John Sack, Javed Khan, Jinhong Wang, Melissa Yarde, Mary Ellen Cvijic, Arvind Mathur, Sha Li, David Shuster, Purnima Khandelwal, Virna Borowski, Jenny Xie, Mary Obermeier, Aberra Fura, Kevin Stefanski, Georgia Cornelius, Joseph A. Tino, John E. Macor, Luisa Salter-Cid, Rex Denton, Qihong Zhao, Percy H. Carter, and T. G. Murali Dhar

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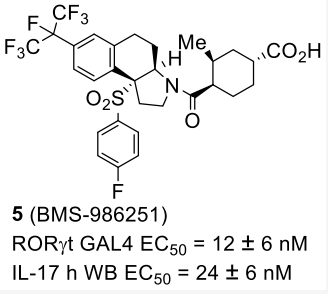
ABSTRACT: Novel tricyclic analogues were designed, synthesized, and evaluated as RORγt inverse agonists. Several of these compounds were potent in an IL-17 human whole blood assay and exhibited excellent oral bioavailability in mouse pharmacokinetic studies. This led to the identification of compound **5**, which displayed dose-dependent inhibition of IL-17F production in a mouse IL-2/IL-23 stimulated pharmacodynamic model. In addition, compound **5** was studied in mouse acanthosis and imiquimod-induced models of skin inflammation, where it demonstrated robust efficacy comparable to a positive control. As a result of this excellent overall profile, compound **5** (BMS-986251) was selected as a clinically viable developmental candidate.



KEYWORDS: *RORγt, RORc, inverse agonist, IL-17, IL-23R, psoriasis*

Retinoic acid-related orphan receptor γt (RORγt) is a nuclear hormone receptor (NHR) and a member of the RORγ subfamily.[1,2] RORγt is expressed in the thymus and is responsible for the differentiation of $CD4^+T$ cells into Th17 cells.[3] Hence, RORγt plays a significant role in the production of the pro-inflammatory cytokine IL-17 as well as other cytokines (GM-CSF, IL-21, and IL-22).[4] Recently, anti-IL-17 biologics have been shown to be clinically effective against autoimmune diseases such as psoriasis.[5−8] As these clinical agents are monoclonal antibodies, there is still a need for small molecule oral therapies modulating IL-17. As a result, there has been much interest in small molecule inhibitors of RORγt, including inverse agonists, as a strategy to suppress IL-17.[9−18] Herein, we report our continued optimization of tricyclic[19] inverse agonists of RORγt, which culminated in the identification of a viable clinical candidate.

As shown in Figure 1, we recently[19] reported the synthesis and evaluation of the potent tricyclic RORγt inverse agonists **1** and **2**. In an effort to optimize the potency and overall profile of these RORγt inverse agonists, we examined the X-ray crystal structure of **2**[19] in RORγt and observed that the cyclohexane ring of **2** came in close proximity to helix 5 of the receptor (Figure 2). This region of helix 5 contains some lipophilic amino acids, including Ala368. We reasoned that a moiety substituted off the C2 or C3 position of the cyclohexane ring (or cyclic sulfone ring of **1**) might bring about a favorable interaction with residues of

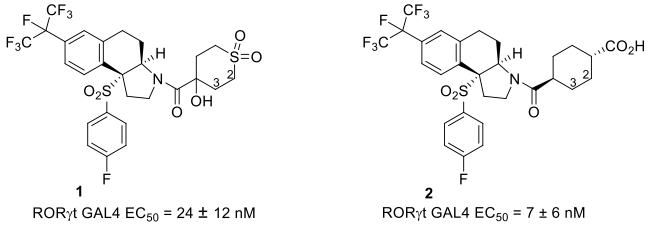


Figure 1. Our previously reported RORγt inverse agonists.

helix 5 and thereby provide an opportunity to improve affinity for RORγt. From this model, the new C2 or C3 vectors did not appear to disrupt the key carboxylate (or sulfone of compound **1**) interactions with Arg367 and Arg364. Likewise, the amide carbonyl of **1** or **2** was still able to engage the backbone NH of Phe377.

Based on this rationale, we synthesized and evaluated analogues of compound **1** and **2** as outlined in Table 1. These

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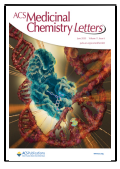

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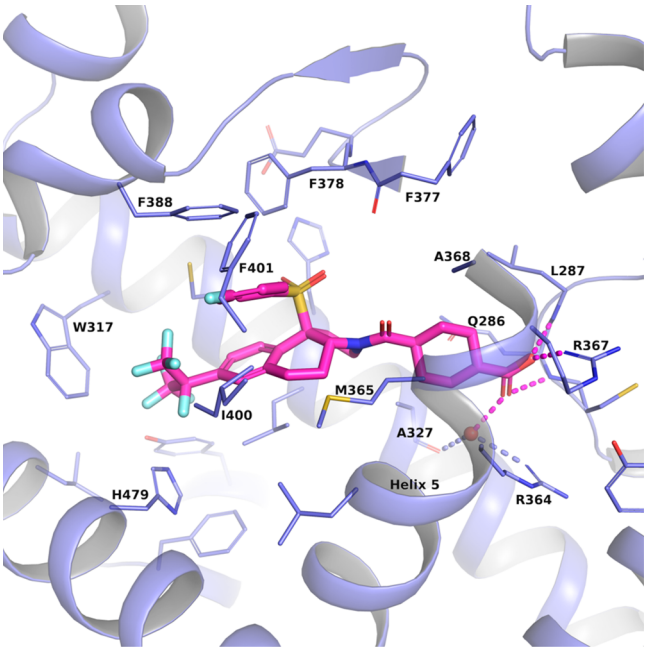


Figure 2. Crystal structure of compound **2** in RORγt (pdb id: 6U25).

compounds were assessed in our RORγt inverse agonist assay (RORγt GAL4 EC_{50}, GAL-4 reporter assay in Jurkat cell line),[19] in an IL-17 human whole blood assay (IL-17 hWB EC_{50}),[19] and in liver microsomes (LM $t_{1/2}$) to assess stability. As shown previously,[19] compound **1** was active in both the GAL-4 assay and the whole blood assay with excellent liver microsome stability. Starting with compounds substituted at the C2 of the cyclic sulfone, the first diastereomer **3** was almost 3-fold more active in the GAL-4 assay than compound **1**, indicating that a new interaction with the receptor was possible. The second diastereomer **4** also had excellent GAL-4 activity similar to that of compound **3**, but neither compound offered a real advantage over compound **1** as far as whole blood activity or liver microsome stability. For this reason, we shifted focus to our

Table 2. Mouse PK Data for Select Compounds[a]

#	Cmax (μM)	AUC_{24h} (μM*h)	C24h (μM)
5	11 ± 8	68 ± 5	0.52 ± 0.13
8	12 ± 2	72 ± 18	0.78 ± 0.65
10	9 ± 1	134 ± 10	2.2 ± 0.47

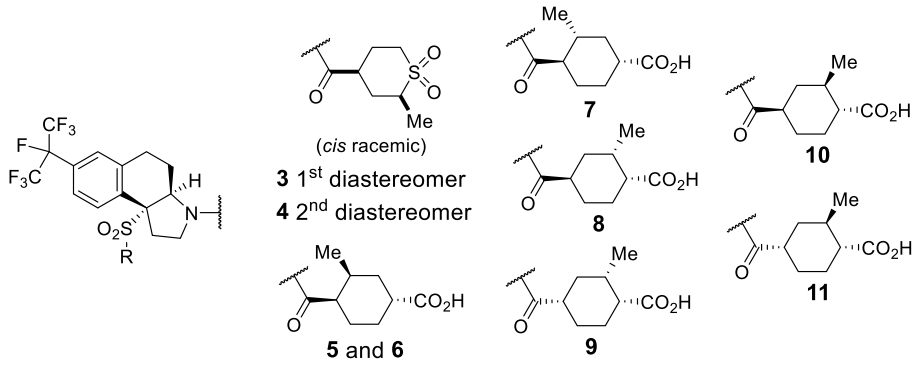
[a]Balb/c mice dosed at 10 mg/kg *PO*. Values are means from three mice. Vehicle: 5% NMP; 76% PEG 400; 19% TPGS.

Table 3. Compound 5 Profile[a]

Assay	Result
RORγt GAL4 EC_{50}	12 ± 6 nM
RORα GAL4 EC_{50}	>10000 nM
RORβ GAL4 EC_{50}	>10000 nM
IL-17 hWB EC_{50}	24 ± 6 nM
mouse Th17 EC_{50}	11 ± 2 nM
PXR/LXRα/LXRβ EC_{50}[b]	>5000/>7500/>7500 nM
rCYP 1A2/2C8/2C9/2C19 IC_{50}[c]	>20/16/>20/>20 μM
rCYP 2D6/3A4 BFC IC_{50}	>20/>20 μM
Caco-2 A-B (nm/s)	240 nm/s
Caco-2 efflux ratio	0.5
Protein binding % free h/m/r	1.2/1.6/2.1

[a]Protein binding: human (h), mouse (m), rat (r). [b]PXR, pregnane X receptor; LXR, liver X receptor. [c]rCyP, recombinant cytochrome P450.

Table 1. Evaluation of Methyl Substituted Analogues[a]



#	R	RORγt GAL4 EC_{50} (nM)	IL-17 hWB[b] EC_{50} (nM)	LM $t_{1/2}$: h, m, r[c] (min)
1	Figure 1	24 ± 12	43 ± 17	>120, >120, >120
2	Figure 1	7 ± 6	19 ± 8	>120, >120, >120
3	4-F-Ph	9 ± 6 (2)	37 ± 19 (6)	>120, >120, >120
4	4-F-Ph	9 ± 3 (2)	44 ± 17 (4)	>120, 98, 33
5	4-F-Ph	12 ± 6 (3)	24 ± 6 (8)	>120, >120, >120
6	3-F-Ph	11 ± 3 (2)	38 ± 9 (6)	>120, >120, 107
7	4-F-Ph	39 (1)	44 ± 25 (2)	>120, >120, >120
8	3-F-Ph	7 (1)	27 ± 9 (4)	>120, >120, >120
9	3-F-Ph	85 (1)	ND[d]	ND
10	4-F-Ph	7 ± 1 (2)	40 ± 15 (3)	>120, >120, 73
11	4-F-Ph	106 (1)	ND	ND

[a]EC_{50} values (*n*) are displayed as ± standard deviation. [b]Human whole blood assay (hWB). [c]Liver microsomes (LM) incubation: human (h), mouse (m), and rat (r). [d]ND = not determined.

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Table 4. Pharmacokinetic Data for Compound 5 in Preclinical Species[a]

		iv			*po*		
species	dose (mg/kg) *iv*/*po*	CL (mL min^{-1} kg^{-1})	Vss (L/kg)	$t_{1/2}$ (h)	Cmax (μM)	AUC_{24h} (μM h)	F (%)
mouse	2/4	2.7	1.9	7.7	4.8 ± 0.3	37	~100
rat	2/4	1.3 ± 0.3	1.2 ± 0.3	11 ± 0.8	4.7 ± 0.5	64 ± 3.4	94
dog	1/1	0.18 ± 0.04	0.5 ± 0.1	36 ± 3	6.4 ± 1.0	120 ± 21	~100
cyno	1/1	1.1 ± 0.2	2.0 ± 0.4	33 ± 4	3.1 ± 0.3	35 ± 3.1	~100

[a]Values are means obtained from three or more animals.

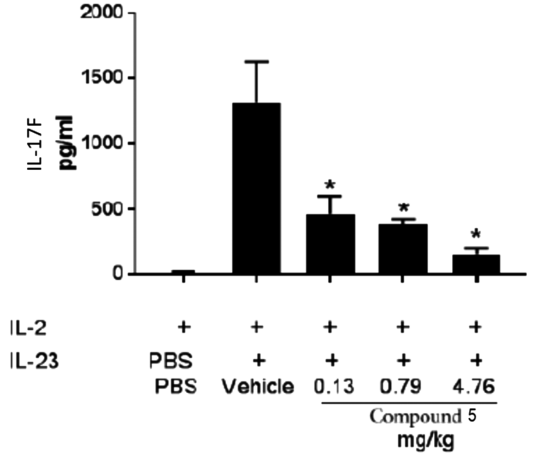

Figure 3. Oral dosing of compound **5** inhibits IL-17F production in a mouse PD model. *: $P < 0.05$ (one-way ANOVA) versus vehicle group.

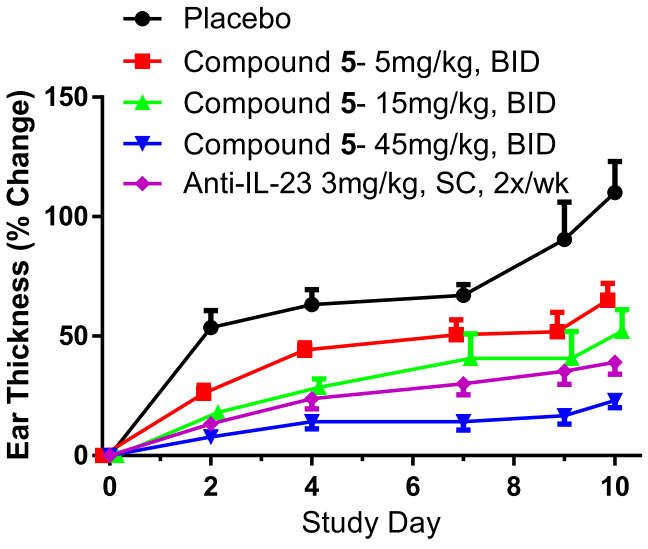

Figure 4. Oral efficacy of compound **5** in mouse acanthosis model.

previously described carboxylate-based inverse agonists. Carboxylate **5** was 2-fold more active in both the GAL-4 assay and the whole blood assay than compound **1** and equipotent with compound **2**. In addition, carboxylate **5** showed excellent microsomal stability. Switching to the 3-fluoro-phenylsulfone of compound **6** did not provide any additional advantage over compound **5**. The methyl diastereomer **7** was at least 2-fold less potent in the GAL4/hWB assays as compared to compound **5**. Moving the methyl to the C2 position was advantageous, as compound **8** retained the same excellent GAL-4 and whole blood activity as compound **5**. As anticipated, based on previous structure−activity relationships (SAR),[19] the 1,4-*cis*-cyclohexane analogues **9** and **11** were less active. Diastereomer **10**

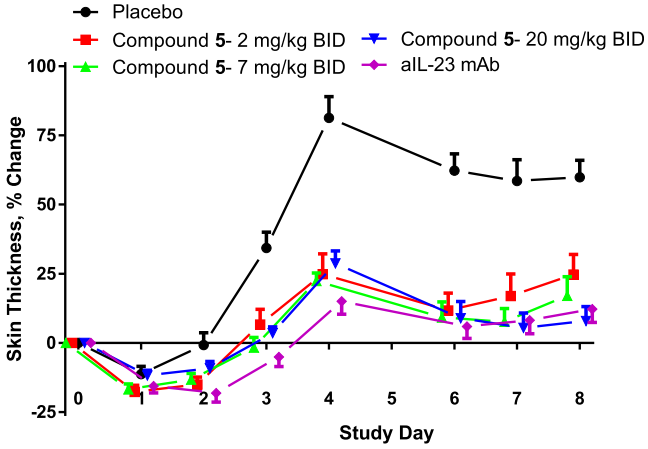

Figure 5. Efficacy of compound **5** dosed orally in IMQ mouse model.

was one of the more active GAL-4 compounds with reasonable human whole blood activity.

With this activity information in hand, we selected three compounds for oral pharmacokinetic (PK) studies in mice. As shown in Table 2, all three compounds showed good oral exposure. Compound **10** had the best 24-h AUC, whereas compounds **5** and **8** were very similar and still promising. Even though compound **10** displayed the best mouse PK of the three compounds tested, it was about 2-fold less active in our human whole blood assay as compared to compound **5**. Therefore, based on its overall profile, compound **5** was selected for further evaluation.

Table 3 outlines the full *in vitro* profile of compound **5**. Compound **5** was selective not only against ROR family members (RORα and RORβ) but also against other nuclear receptors (PXR, LXRα, and LXRβ). Compound **5** was tested in a mouse reporter assay, and this correlated very well with the human values. The Caco-2 data confirms that compound **5** has good permeability with a low efflux ratio, which is consistent with the mouse PK study shown above. Compound **5** did not inhibit any of the CYP's tested. With this promising profile in hand, compound **5** was selected for additional PK studies in other species (Table 4).

As shown in Table 4, compound **5** displayed excellent oral bioavailability across all the four species in addition to exhibiting low clearance. The half-life in rodent was excellent (7.7 h to 11 h); however, the half-life in dog and cyno did trend high (33 h to 36 h). Given these favorable PK results, compound **5** was selected for mouse *in vivo* efficacy studies.

Compound **5** was first assessed in an IL-2/IL-23 stimulated mouse pharmacodynamic (PD) model.[19] In this model, naïve C57BL/6 female mice (7−9 weeks of age from Charles River) were injected intraperitoneally with 5 μg/ms of IL-2 at −24, 0, and 23 h and 10 μg/ms at 7 h. In addition, IL-23 (dose of 1 μg/ms) was injected intraperitoneally at 0, 7, and 23 h. Compound **5**

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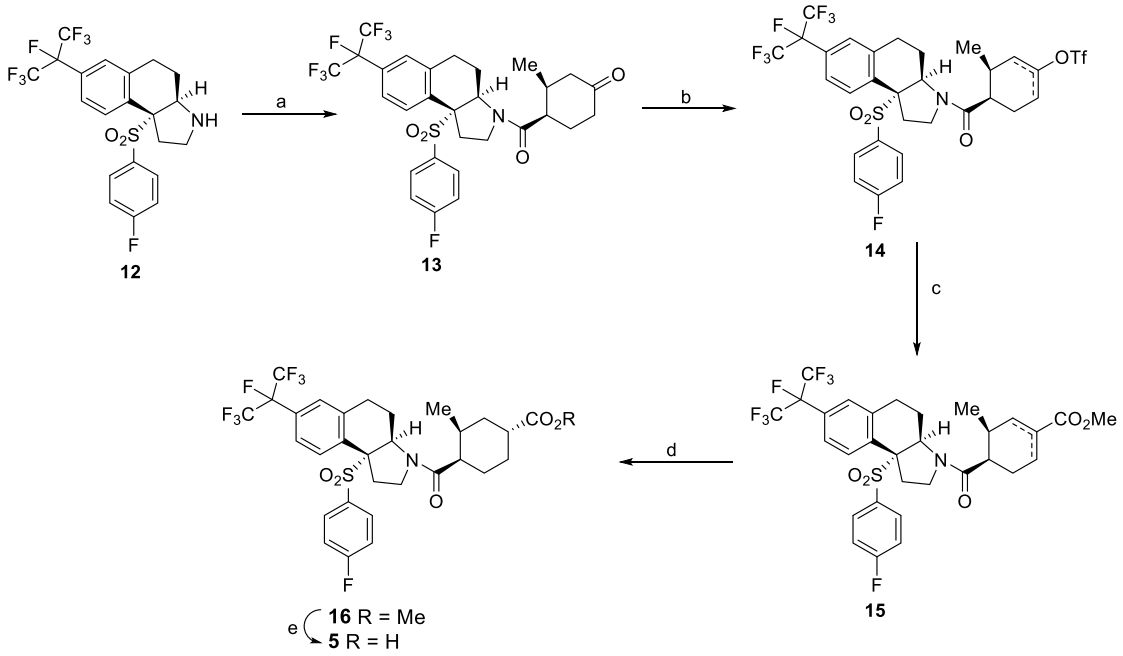
Scheme 1. Synthesis of Compound 5[a]



[a]Reagents and conditions: (a) (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylic acid, HATU, NMM, DMF, 78%; (b) $KN(TMS)_2$, *N*-phenyl-*bis*(trifluoromethanesulfonimide), THF, −78 °C; (c) $Pd(PPh_3)_2Cl_2$, CO (1 atm), MeOH, DMF, 75%; (d) Crabtree's catalyst, H_2 (1 atm), DCM, 89%; (e) LiOH, MeOH, H_2O, THF, 65%.

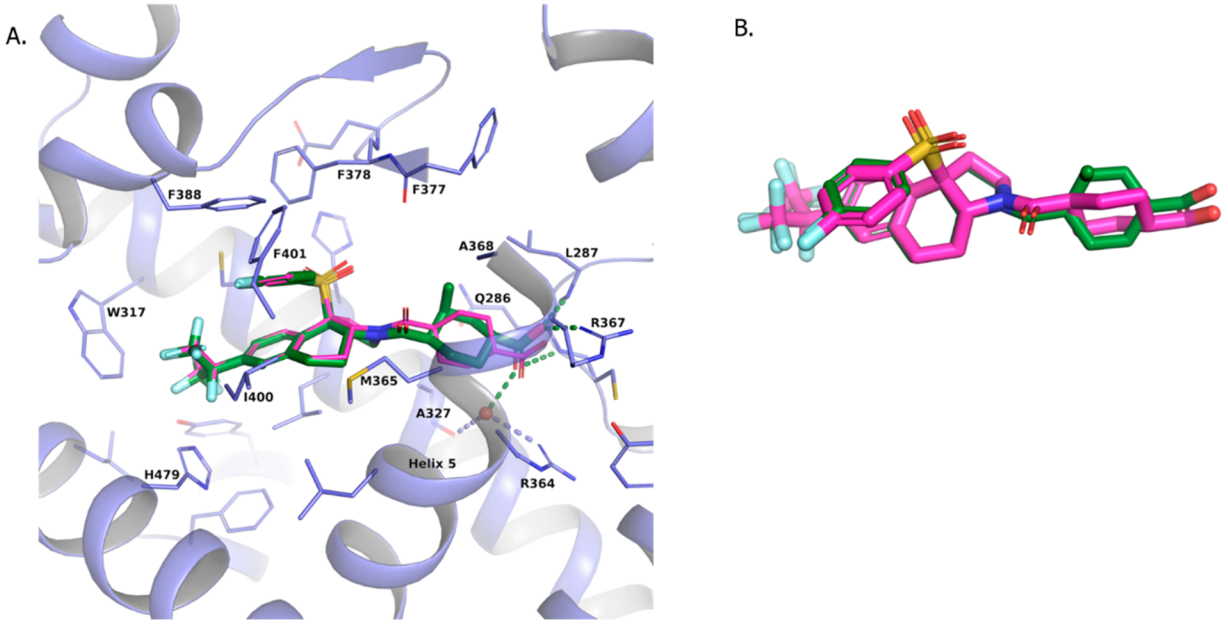


Figure 6. (A) Overlay of two crystal structures in RORγt: compound **5** (green; pdb id: 6VQF) and compound **2** (compound in purple and protein excluded). (B) Overlay of the crystal structure ligands of compounds **5** and **2**.

was dosed once a day orally at 0.13, 0.79, and 4.76 mg/kg (vehicle: 1-methyl-2-pyrrolidinone (NMP):PEG300:TPGS, 5:76:19 v/v) 30 min prior to the 0 h time point. Blood was collected for exposure and serum was collected for IL-17F luminex analysis at the 30 h time point. As shown in Figure 3, compound **5** displayed a dose-dependent reduction of the IL-17F produced. Compound **5** also performed better than compound **2** in this PD model (data not shown). These promising PD results prompted us to take compound **5** into the mouse acanthosis model (a preclinical model of psoriasis).

As shown in Figure 4, acanthosis[20,21] was induced with recombinant humanized IL-23 injected every other day into the right ear of C57BL/6 female mice until the last injection on day 9. A starting "baseline" measurement of the ear (before first injection) was made on day 0, and thereafter, ear thickness was measured every other day prior to the next ear injection. Compound **5** was dosed orally approximately 2 h before the first IL-23 injection and continued twice daily until day 9 (study ended on day 10). The placebo/control group was dosed with blank vehicle, and a human anti-IL-23 was administered SC as a

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positive control at doses of 3 mg/kg on days 0, 3, and 7 (human anti-IL-23 dosed at maximal efficacy). As shown in Figure 4, all doses of compound **5** resulted in reduced ear thickness, and the 15 mg/kg dose of **5** was comparable to the human anti-IL-23.

Compound **5** was also tested in the well-known imiquimod (IMQ)-induced model[22−24] of skin inflammation. In this model, IMQ cream was applied to the backs of C57BL/6 mice from day 0 to day 7. The percent change from baseline for skin thickness was measured daily (except for day 5) over 8 days. Compound **5** was dosed orally at 2, 7, and 20 mg/kg BID each day from day 0 to day 7 (Figure 5). Compound **5** significantly reduced IMQ-induced skin thickening at all dose levels compared to the placebo/control group, which was dosed with blank vehicle. An anti-mouse IL-23 antibody was dosed as a positive control at 10 mg/kg on day −1 and day 3. As shown in Figure 5, compound **5** dosed at 20 mg/kg BID was comparable in efficacy to the anti-mouse IL-23 antibody.

The synthesis of compound **5** is illustrated in Scheme 1, starting from the previously described tricyclic intermediate **12**.[19] Compound **12** was coupled to (1*R*,2*S*)-2-methyl-4-oxocyclohexane-1-carboxylic acid,[25] which was generated via a pig liver esterase (PLE)[26] cleavage of the corresponding ester. The resulting ketone **13** was converted to a mixture of regioisomeric enol triflates **14**.[27] A palladium-catalyzed carbonylation[28] of **14** in the presence of methanol gave a regioisomeric mixture of methyl esters **15**. This ester mixture **15** was hydrogenated with Crabtree's catalyst[29,30] to give a single diastereomer **16**. As a last step, ester **16** was saponified with LiOH to give the carboxylate **5**.

As shown in Figure 6, we were able to obtain a crystal structure of compound **5** in RORγt (pdb id: 6VQF), and it confirmed the normal interactions of the carboxylate to Arg364/Arg367 and amide carbonyl to Phe377 (Figure 6A). However, the structure of compound **5** was unique, as the cyclohexane of **5** was rotated approximately 75 degrees from that observed for the cyclohexane in the crystal structure of compound **2** (see Figure 6B). It appears that the C3 methyl of compound **5** forces the cyclohexane to rotate back away from helix 5 to make an interaction with Ala368 (distance of C3-methyl of **5** to Ala368 side chain methyl is 3.6 Å). This in turn brings the bottom portion of the cyclohexane of **5** in close proximity to helix 5 as it packs up against the helix. As mentioned, this is a unique orientation of the cyclohexane ring that we have not observed in other crystal structures.

In summary, we have investigated the optimization of our tricyclic RORγt inverse agonists via a potential interaction with the receptor's helix 5. Evaluation of these new analogues led to the identification of compound **5** as a potent and selective RORγt inverse agonist. Compound **5** demonstrated excellent oral bioavailability and metabolic stability across species. In addition, compound **5** was taken into a mouse PD model where it showed a dose-dependent reduction of the pro-inflammatory cytokine IL-17F. Compound **5** was also studied in mouse acanthosis and imiquimod-induced models (preclinical models of psoriasis), where it demonstrated robust efficacy comparable to that of a positive control. As a result of the above profile, compound **5** (BMS-986251) was selected as a viable clinical candidate (clinical trial ID: NCT03329885).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.0c00063.

Experimental details and compound characterization data for all target compounds are available. Details of the IMQ-induced model, the liver microsome $t_{1/2}$ assay, and the cocrystal structure method for compound **5** in RORγt (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Robert J. Cherney − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States;* orcid.org/0000-0002-6642-2834; Email: robert.cherney@bms.com

Authors

Lyndon A. M. Cornelius − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Anurag Srivastava − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Carolyn A. Weigelt − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

David Marcoux − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States;* orcid.org/0000-0002-0295-7717

James J.-W. Duan − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States;* orcid.org/0000-0003-2730-9924

Qing Shi − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States;* orcid.org/0000-0003-0125-729X

Douglas G. Batt − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Qingjie Liu − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Shiuhang Yip − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Dauh-Rurng Wu − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Max Ruzanov − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

John Sack − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Javed Khan − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Jinhong Wang − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Melissa Yarde − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Mary Ellen Cvijic − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

Arvind Mathur − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*

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Sha Li − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
David Shuster − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Purnima Khandelwal − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Virna Borowski − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Jenny Xie − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Mary Obermeier − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Aberra Fura − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Kevin Stefanski − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Georgia Cornelius − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Joseph A. Tino − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
John E. Macor − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Luisa Salter-Cid − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Rex Denton − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Qihong Zhao − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States*
Percy H. Carter − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States;* orcid.org/0000-0002-5880-1164
T. G. Murali Dhar − *Bristol Myers Squibb Company, Research and Early Development, Princeton, New Jersey 08540-4000, United States;* orcid.org/0000-0003-0738-1021

Complete contact information is available at:
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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

Ala, alanine; Arg, arginine; AUC, area under the curve; bid, twice a day; BMS, Bristol-Myers Squibb; Boc, butyloxycarbonyl; C, concentration; CL, clearance; DCM, dichloromethane; DMF, dimethylformamide; EC, efficacious concentration; F, bioavailability; Glu, glutamic acid; GM-CSF, granulocyte-macrophage colony-stimulating factor; HATU, hexafluorophosphate azabenotriazole tetramethyl uronium; hWB, human whole blood; IL, interleukin; IMQ, imiquimod; iv, intravenous; Leu, leucine; LM, liver microsome; LXR, liver X receptor; M, molar; ND, not determined; NMP, *N*-methylpyrrolidinone; NR, nuclear receptor; PD, pharmacodynamics; PEG, polyethylene glycol; PBS, phosphate-buffered saline; Phe, phenyl alanine; PK, pharmacokinetic; po, per os, oral dose; PXR, pregnane X receptor; qd, once a day; rCyP, recombinant cytochrome P450; ROR, receptor-related orphan receptor; SAR, structure activity relationship; SC, subcutaneous; SFC, supercritical fluid chromatography; Th17, T helper 17 cells; THF, tetrahydrofuran; TPGS, tocopheryl polyethylene glycol succinate; Vss, volume of distribution.

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