Structure-based Discovery of Phenyl (3-Phenylpyrrolidin-3-yl)sulfones as Selective, Orally Active ROR γ t Inverse Agonists

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Supporting Information

ABSTRACT: A new phenyl (3-phenylpyrrolidin-3-yl)sulfone series of ROR γ t inverse agonists was discovered utilizing the binding conformation of previously reported bicyclic sulfonamide **1**. Through a combination of structure-based design and structure–activity relationship studies, a polar set of amides at N1-position of the pyrrolidine ring and perfluoroisopropyl group at *para*-position of the 3-phenyl group were identified as critical structural elements to achieve high selectivity against PXR, LXR α , and LXR β . Further optimization led to the discovery of (1*R*,4*r*)-4-((*R*)-3-((4-fluorophenyl)sulfonyl)-3-(4-(perfluoropropan-2-yl)phenyl)pyrrolidine-1-carbonyl)cyclohexane-1-carboxylic acid (**26**), which displayed excellent selectivity, desirable liability and pharmacokinetic properties *in vitro*, and a good pharmacokinetic profile in mouse. Oral administration of **26** demonstrated dose-dependent inhibition of IL-17 production in a mouse IL-2/IL-23-induced pharmacodynamic model and biologic-like efficacy in an IL-23-induced mouse acanthosis model.

KEYWORDS: ROR γ t, inverse agonist, structure-based design, pyrrolidin-3-ylsulfone, X-ray crystallography

ROR γ t belongs to the ROR (Retinoic acid-related Orphan Receptor) family of nuclear receptors that consists of ROR α , ROR β , and ROR γ (ROR γ t being a splice variant of ROR γ). As a key transcription factor for T helper 17 (Th17) cells, $\gamma\delta$ T cells, and innate lymphoid cells, ROR γ t regulates production of multiple pro-inflammatory mediators including IL-17 (interleukin 17) and IL-22.^{1,2} Genetic deletion of ROR γ t was shown to ameliorate diseases in animal models of psoriasis, inflammatory bowel diseases (IBD), and multiple sclerosis (MS). Small molecule inverse agonists of ROR γ t also demonstrated efficacy in animal models of psoriasis, IBD, and MS. Clinically, anti-IL-17 antibodies were found to be effective in treating patients with psoriasis, ankylosing spondylitis, and psoriatic arthritis, further validating the IL-17/Th17 pathway for treating inflammatory diseases.^{3,4} As a result, inverse agonists of ROR γ t have been widely pursued in the pharmaceutical industry.^{5–8}

We previously reported a bicyclic sulfonamide series of ROR γ t inverse agonists⁹ as exemplified by the tetrahydroquinoline (THQ) analogue **1** (Figure 1). While demonstrating promising activity, compound **1** could not be advanced because it was found to have agonist activity against the pregnane X receptor (PXR) *in vitro* (EC₅₀ = 2000 nM, Y_{max} = 100%) and induce cytochrome P450 *in vivo* in mice. To address these issues, we explored alternative templates employing the binding mode of **1** as the starting point for structure-based design. Early in the design process, the perfluoroisopropyl alcohol and the *para*-fluorophenyl group in **1** were kept constant because the former group was engaged in a hydrogen bond with ROR γ t and the latter moiety fit nicely in a hydrophobic pocket.⁹ One remarkable feature of **1**, when

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Figure 1. Previously reported sulfonamide **1** and newly designed benzylsulfone **2**, (1-phenylcyclopentyl)sulfone **3**, and (3-phenylpyrrolidin-3-yl)sulfone **4**.

bound to RORyt, was that the sulfonyl group adopted a pseudoaxial orientation with respect to the THQ core, and the *para*-fluorophenyl group was stacked against the phenyl ring of the THQ in a face-to-face fashion, resulting in an overall near U-shaped conformation (3-D picture in Figure 1). While searching for alternative scaffolds, we noticed that phenyl benzylsulfones have been reported to prefer a conformation reminiscent of the binding mode of **1**.^{10,11} Therefore, we set out to explore a series of phenyl benzylsulfones as alternatives to the THQ sulfonamide core.^{12,13}

To quickly assess the impact on activity, the parent phenyl benzylsulfone **2** (Figure 1) was selected as the initial target. In a RORyt inverse agonist assay (a Gal-4 reporter assay using the Jurkat cell line),⁹ compound **2** exhibited an EC₅₀ of 2980 nM. We envisioned that α,α -disubstitution at the benzyl position would enhance the population of the U-shaped conformation, through the Thorpe–Ingold effect, and in turn improve potency. After exploring different substituents *in silico*, phenyl (1-phenylcyclopentyl)sulfone **3** (the predicted lowest energy conformation shown in Figure 1) was selected as the target to synthesize. To our delight, this benzylic methylene-to-cyclopentane transformation increased RORyt potency by more than 10-fold (232 nM for **3** vs 2980 nM for **2**). Unfortunately, compound **3** displayed significant cross reactivity against PXR and liver X receptor α and β (LXR α and LXR β). We had reported earlier that in the THQ series, the C2 acetamide group of **1** played an important role in significantly right shifting PXR, LXR α , and LXR β potency,⁹ so it was logical to explore the acetamide binding site in order to improve selectivity of the sulfone series (**3**). With this in mind, phenyl (3-phenylpyrrolidin-3-yl)sulfone **4** was designed. Molecular modeling studies of **4** with the ligand-binding domain (LBD)

of RORyt suggested that the acyl substituents off the pyrrolidine nitrogen (–COR in **4**) could provide a suitable vector toward the C2 acetamide site. An added benefit of the cyclopentane-to-pyrrolidine switch was that the pyrrolidine ring would allow rapid structure–activity relationship (SAR) study through simple acylation reactions.

The free NH pyrrolidine **5** (*R*-enantiomer, Table 1) was 2.5-fold less potent against RORyt than the cyclopentane **3**. Small

Table 1. Initial Pyrrolidinylsulfone Analogues

<i>R</i> -enantiomers:				
5 : R = H	10 : R =	11 : R =	12 : R =	13 : R =
6 : R = Ac (<i>rac</i>)				
7 : R = COOMe (<i>rac</i>)				
8 : R = CONHEt (<i>rac</i>)				
9 : R =				
<i>S</i> -enantiomers:				
14 : R = H	15 : R =			

#	RORyt EC ₅₀ nM ^a	PXR EC ₅₀ nM ^b (% max) ^c	LXRα ^d EC ₅₀ nM ^b (% max)	LXRβ ^d EC ₅₀ nM ^b (% max)
5	595 ± 237	434 (110)	2920 (58)	>7500
6	2650 ± 1280	480 (100)	>7500	>7500
7	1040 ^b	ND	408 (62)	1900 (39)
8	1260 ^b	ND	>7500	>7500
9	378 ± 224	794 (99)	>7500	>7500
10	224 ± 78	7810 (81)	>7500	>7500
11	88 ± 35	>2470 (89)	>7500	>7500
12	55 ± 25	4930 (86)	>7500	>7500
13	4340 ± 847	>50000 (11)	>3750	>7500
14	4500 ± 1750	520 (110)	>7500	>7500
15	4200 ^b	>5140 (72)	>7500	>7500

^aRORyt reporter assay using a Jurkat cell line; values from two or more experiments performed in duplicate unless otherwise noted; % max typically close to 100%. ^bValue from a single experiment performed in duplicate. ^c% max relative to rifampicin. ^dLXR assays (agonist mode) were performed using a CV-1 cell line; % max relative to T0901317. ND = not determined.

amide, carbamate, and urea analogues **6–8** (all racemic mixtures) resulted in slightly weaker activity than **5**, while the larger cyclopentylcarboxamide **9** (racemic mixture) restored potency to the level of **3**. Noteworthy here is that pyrrolidines **5–9** displayed weaker activities against PXR, LXR α , and LXR β compared to **3**.

Examination of the RORyt cocrystal structure with an analogue of **1** (compound **33** in ref ⁹) revealed that the *tert*-alcohol of the C2 acetamide group is surrounded by polar side chains comprising Arg364, Arg367, and Tyr281 as well as the carbonyl group of Cys285. To engage these amino acids, a biased SAR effort to incorporate polar amide groups was carried out (analogues **10–13**, *R* enantiomer, Table 1). Compared to the cyclopentane **3**, compounds **10–12** showed comparable or better potency against RORyt. Importantly, **10–12** completely dialed out LXR α and LXR β activities (>7.5 μ M). Their PXR EC₅₀ values were also significantly right-shifted (greater than 100-fold) compared to **3**, although *Y*_{max} values were still high. Carboxylic acid **13** was less active. Analogues incorporating the *S*-pyrrolidine enantiomer were also evaluated. Compounds **14** and **15**, the corresponding *S*-

enantiomers of **5** and **12** respectively, were considerably weaker against ROR γ t.

In order to validate the hypothesis regarding the binding conformation of phenyl (3-phenylpyrrolidin-3-yl)sulfones and the proposed engagement of key amino acid residues in the polar pocket, an X-ray structure of **12** with the ROR γ t LBD was obtained (Figure 2). As predicted from modeling, the

Figure 2. X-ray crystal structure of compound **12** and the LBD of ROR γ t (PDB ID 6NXH). The carbons of the protein are colored in pink and those of **12** in green. Sulfurs are colored in yellow, N in blue, O in red and F in cyan. A hydrogen bond of **12** with Arg367 of ROR γ t is indicated by a dashed line.

benzyl phenyl sulfone backbone of **12** adopted a near U-shaped conformation and interacts with ROR γ t in a fashion reminiscent of the bicyclic sulfonamide series (**1**). Specifically, the *p*-fluorophenyl group occupies a hydrophobic pocket formed by the side chains of Met365, Val376, Phe378, Phe388, Ile400, and Phe401 (not shown for clarity except Phe388 and Met365) and forms a face-to-face π stacking interaction with the side chain of Phe388. The two CF₃ substituents of the hexafluoroisopropanol group also occupy a hydrophobic pocket, formed by the side chains of residues Trp317, Met358, Leu391, Ile397, Ile400, and His479 (some not shown in Figure 2 for clarity). Although the hydroxy group is in the vicinity of His479 on helix 11, it does not appear to have the desired orientation to form a hydrogen bond. The implications of this will become apparent in subsequent SAR studies (*vide infra*). In the center of the ROR γ t pocket, the pyrrolidine ring makes hydrophobic contacts with the side chains of Leu324, Met365, and Val361. The pyrrolidine moiety also provides a vector for the 4-acylpiperazinylcarbonyl substituent to bind in the polar acetamide binding pocket. Consistent with our hypothesis, the 4-acyl group forms a hydrogen bond with the side chain of Arg367.

A crystal structure of **3** in the PXR LBD was also solved. Interestingly, **3** binds to PXR in two binding modes that differ in the orientation of the *p*-fluorophenylsulfonyl group and the benzene linker between the cyclopentane and the hexafluoroisopropyl alcohol (Figure 3). The hexafluoroisopropyl alcohol group is positioned in the same fashion in both binding modes: with the hydroxy group forming a hydrogen bond to the side

Figure 3. X-ray crystal structure of compound **3** and the LBD of PXR (PDB ID 6NX1). Compound **3** binds to PXR in alternate conformations with 70%/30% occupancy, as depicted by thicker sticks (orange) and skinnier sticks (magenta), respectively. The carbons of the protein are colored in green. Sulfurs are colored in yellow, N in blue, O in red, and F in cyan. Hydrogen bonds of **3** with PXR are indicated by dashed lines.

chain of His407 and the trifluoromethyl groups fill a small hydrophobic pocket. In both binding modes, the cyclopentane ring projects into an enclosed hydrophobic pocket formed by the side chains of Leu209, Val211, Trp299, Leu308, Met323, and Leu324. This structure could explain the reduced PXR potency of **10–12**. The substituted pyrrolidines in **10–12** would be too polar and sterically encumbered to fit in the small hydrophobic pocket. As a result, analogues **10–12** exhibited improved selectivity against PXR compared to **3**.

Using the cyclopentyl sulfone **3** as a starting point, SAR around the hexafluoroisopropyl alcohol moiety was investigated (Table 2). Incorporating a methyl group in place of one of the CF₃ resulted in 6-fold loss of ROR γ t potency (**16**, racemic mixture). The corresponding ethyl analogue **17** (racemic mixture) partially restored activity. Attempts to

Table 2. Hexafluoroisopropyl Alcohol SAR

#			ROR γ t EC ₅₀ nM ^a	PXR EC ₅₀ nM ^b (% max) ^c
	R ₁	R ₂		
3	CF ₃	OH	232 ± 28	10 (110)
16 ^d	Me	OH	1400 ± 390	239 (110)
17 ^d	Et	OH	643 ^b	48 (110)
18	CF ₃	NH ₂	888 ± 573	275 (120)
19	CF ₃	OMe	1130 ± 65	920 (110)
20	CF ₃	Me	3650 ^b	752 (140)
21	CF ₃	F	494 ^b	1010 (130)
22	CF ₃	Cl	271 ± 337	229 (110)

^aROR γ t reporter assay using a Jurkat cell line; values from two or more experiments performed in duplicate unless otherwise noted; % max typically close to 100%. ^bValue from a single experiment performed in duplicate. ^c% max relative to rifampicin. ^dTested as racemic mixture.

Table 3. *In Vitro* Profile of Perfluoroisopropyl Analogues^a

#	R ₁	R ₂	R ₃	RORγt EC ₅₀ nM ^b	PXR EC ₅₀ nM ^c (% max.) ^d	MLM (% remaining) ^e	hPB, mPB (% unbound)
23		F	H	269 ± 6	>50000 (7)	ND	ND
24		F	H	161 ± 51	>50000 (2)	69	ND
25		F	H	48 ± 38	>50000 (10)	68	ND
26		F	H	119 ± 28	>50000 (18)	86	3.7, 10.5
27		F	H	4230 ^c	ND	ND	ND
28		F	H	383 ± 102	>46100 (23)	88	ND
29		H	H	396 ± 61	>50000 (10)	96	ND
30		Me	H	64 ± 5	12600 (29)	85	1.3, 2.6
31		Et	H	84 ± 61	>50000 (3)	100	ND
32		Cl	H	106 ± 39	6440 (22)	100	ND
33		OMe	H	686 ^c	>50000 (12)	98	ND
34		F	Me	61 ± 20	>22800 (40)	84	1.7, 2.9
35		F	Et	54 ± 7	>50000 (9)	73	ND
36		F	<i>c</i> -Pr	149 ^c	>50000 (9)	74	ND

^aAll compounds showed EC₅₀ values greater than 7500 nM in LXRα and LXRβ assays. ^bRORγt reporter assay using a Jurkat cell line; values from two or more experiments performed in duplicate unless otherwise noted; % max typically close to 100%. ^cValue from a single experiment performed in duplicate. ^d% max relative to rifampicin. ^eMetabolic stability in mouse liver microsome; percentage remaining after 10 min of incubation. ND = not determined.

replace the hydroxyl group with an amino, methoxy, methyl, fluoro, or chloro group all led to weaker RORγt inverse agonists (18–22). Among them, 21 and 22 were found to have potency closest to 3. The perfluoroisopropyl analogue 21 was especially interesting because it had dramatically right-shifted PXR activity compared to 3 (100-fold), while being only 2-fold less potent at RORγt. The right shift in PXR EC₅₀ for analogue 21 can potentially be explained by the X-ray cocrystal structures of compounds 12 and 3 (Figures 2 and 3, respectively). Assuming that 3 binds like 12 in RORγt, the hydroxy group would not be involved in hydrogen bonding and, therefore, can be replaced with a fluoro group (21) without significant loss of activity. In PXR, the hydroxy group of 3 serves as a hydrogen bond donor. The fluoro replacement cannot maintain this hydrogen bond. As a result, 21 displayed a dramatic loss of PXR potency.

In order to further improve RORγt potency and selectivity of compound 21 for PXR, SAR of the perfluoroisopropyl moiety in combination with the pyrrolidinesulfone scaffold was carried out (Table 3). Compounds 23 and 25 showed

similar RORγt potency to the corresponding alcohols 10 and 12 (Table 1), while 24 was 2-fold weaker than 11. Surprisingly, the cyclohexanecarboxylic acid 26 was quite active with an EC₅₀ of 119 nM, 35-fold more potent than the corresponding alcohol 13. The *trans*-cyclohexane stereochemistry in 26 is important as the *cis* isomer 27 was significantly less potent for RORγt. Replacing the cyclohexane with a piperidine moiety also resulted in a less potent compound (28).

To gain insight into the potency disconnect, 13 and 26 were tested in a RORγt binding assay. While the binding IC₅₀ of 26 (55 nM) correlated reasonably well with its Jurkat activity, 13 displayed considerably more potent binding (146 nM) than its Jurkat IC₅₀. We hypothesized that cell membrane permeability was probably responsible for the poor functional activity of 13 in the Jurkat assay. Consistent with this hypothesis, compound 13 showed low permeability in Caco-2 assay (permeation coefficient less than 15 nm/s). In contrast, analogue 26 showed significantly improved permeability (120 nm/s).

The effect of substituents on the phenylsulfone moiety was also studied (29–36, Table 3). Replacing the *para*-fluoro

group (R_2) in **26** with a methyl, ethyl, or chloro group (**30–32**) maintained or slightly improved ROR γ t activity vs **26**, whereas the hydrogen and methoxy analogues (**29** and **33**) led to reduced activity. Additional analogues of **26** with *meta*-substituents (R_3) were also synthesized. Methyl and ethyl analogues (**34** and **35**) improved activity by approximately 2-fold vs **26**. A larger cyclopropyl analogue **36** was slightly less active.

The SAR outlined in Table 3 clearly shows that the perfluoroisopropyl moiety consistently improved selectivity against PXR for the pyrrolidinylsulfone series. All compounds in Table 3 showed PXR $Y_{\max}$ under 40%, with most of them having EC_{50} values greater than the assay limit. These compounds also exhibited excellent selectivity against LXR α and LXR β , typically with EC_{50} values greater than 7.5 μ M.

To identify a tool compound for *in vivo* studies, majority of the compounds in Table 3 were first tested in a 10 min mouse liver microsome (MLM) assay to get a rough estimation of microsomal stability. Compounds **24** and **25** were found to have moderate stability (69% and 68% remaining after 10 min incubation). In general, compounds with carboxylic acid moieties showed improved stability in the MLM assay (for example, **26**, **30**, and **34**). Compounds **26**, **30**, and **34** were also tested for protein binding, and **26** was found to have the highest free fraction (3.7% and 10.5% unbound in human and mouse proteins, respectively). Based on its overall profile in terms of ROR γ t potency, selectivity, metabolic stability, and protein binding, analogue **26** was selected for further evaluation.

Compound **26** was inactive against ROR α and ROR β in either inverse agonist or agonist mode ($>40 \mu$ M). In addition to its selectivity against PXR, LXR α , and LXR β (*vide supra*), **26** displayed IC_{50} values greater than 150 μ M against the broader family of nuclear receptors including androgen receptor, estrogen receptor α , glucocorticoid receptor, and progesterone receptor. Compound **26** was also tested in a panel of 38 additional assays ranging from GPCRs, transporters, enzymes, and ion channels and was found to be inactive within the concentration limit of the assays (typically 30 μ M).

In the Caco-2 assay, **26** demonstrated good permeability (P_c of 120 nm/s) with a modest efflux ratio of 2.6. It showed no significant *in vitro* inhibition against a panel of cytochrome P450 isozymes ($IC_{50} > 20 \mu$ M for 1A2, 1B2, 2C9, 2C19, 2D6, and 3A4), except 2C8 (IC_{50} of 0.68 μ M). In a more accurate $t_{1/2}$ MLM assay, **26** displayed a stability half-life of greater than 120 min, which translated into low clearance (7.2 mL/min/kg) and a long half-life (7.2 h) after intravenous administration of 2 mg/kg in mice (Table 4). An oral dose of 10 mg/kg of **26** led to an excellent overall profile with $C_{\max}$ of 6.6 μ M, AUC (area under the curve) of 36.6 μ M·h, and an oral bioavailability of 99%.

Having identified compound **26** as a highly selective ROR γ t inverse agonist with an excellent mouse PK profile, we tested the compound in an IL-2/IL-23-stimulated mouse pharmacodynamic (PD) model (Figure 4).⁹ In the study, naive mice were challenged three times with IL-2 and IL-23 (at 0, 7, and 23 h) after IL-2 alone priming (–24 h), and **26** was dosed orally 30 min prior to each IL-2/IL-23 challenge. Serum was analyzed 7 h after the last IL-2/IL-23 administration. As shown in Figure 4, at oral bid doses of 5, 15, and 50 mg/kg, **26** achieved 47%, 77%, and 98% inhibition of IL-17F production, respectively. In addition, dose-dependent inhibition of IL-17A,

Table 4. Pharmacokinetic Profile of **26** in balb/c Mice^a

	dose	
	2 mg/kg (iv)	10 mg/kg (po)
$C_{\max}$ (μ M)		6.6
$T_{\max}$ (h)		2
AUC (μ M·h)	7.4	36.6
$t_{1/2}$ (h)	7.2	
Cl (mL/min/kg)	7.2	
V_{ss} (L/kg)	3.4	
F (%)		99

^aDose vehicle: iv— 2.5% *N*-methyl-2-pyrrolidone, 67.5% polyethylene glycol 300, 4.5% pluronic F-68, 25.5% water; po— 5% *N*-methyl-2-pyrrolidone, 76% polyethylene glycol 300, 19% D- α -tocopheryl polyethylene glycol succinate (TPGS).

Figure 4. Inhibition of IL-17F production in an IL-2/IL-23 induced mouse PD model after oral administration of **26**.

IL-22, GM-CSF, KC (mouse IL-8), and IL-6 was also observed (data not shown). Collectively, these data demonstrated that **26** effectively blocked ROR γ t-dependent cytokine production in mice.

Compound **26** was also tested in an IL23-induced mouse model of acanthosis (see Supporting Information for description of this model).¹⁴ As illustrated in Figure 5, **26**

Figure 5. Efficacy of **26** in an IL-23-induced mouse acanthosis model.

significantly reduced ear swelling at both 10 and 50 mg/kg when dosed orally, bid. At the 50 mg/kg bid dose, **26** achieved efficacy nearly equivalent to an anti-IL-23 antibody, which was used as the positive control in this model.

Detailed protocols for the synthesis of compounds listed in Tables 1–3 are provided in Supporting Information. Schemes 1 and 2 highlight representative syntheses of cyclopentylsulfones and pyrrolidinylsulfone **26**. The methyl group of commercially available **37** was subjected to radical bromination conditions, and the product mixture (mostly monobromide) was reacted with sodium 4-fluorobenzenesulfonate to provide compound **2** (Scheme 1).¹⁵ After protection of the alcohol as a benzyl ether, the resulting intermediate **38** was treated with sodium hydride and (*Z*)-1,4-dichlorobut-2-ene to give the

Reaction scheme showing the synthesis of various sulfonamides from 37 and 3.

37 (4-methyl-2,2,2-trifluoro-1-phenylethan-1-ol) reacts with a benzoyl fluoride derivative (R=H or R=Bn) via steps a,b to form an ester intermediate, which is then converted to a sulfonamide (2 or 38) via steps d,e.

3 (4-(2,2,2-trifluoro-1-cyclopentyl-1-phenylethanesulfonyl)benzofluoride) reacts with an amine (H₂N-R) via steps f-h to form sulfonamides 18 or 19.

3 also reacts with a methoxy-substituted amine (MeO-R) via step i to form 19, or with a fluorinated amine (F-R) via step j to form 21.

3 is converted to 22 via step k, which is a 4-(2,2,2-trifluoro-1-cyclopentyl-1-(chloromethyl)phenylethanesulfonyl)benzofluoride.

Chemical reaction scheme showing the synthesis of compound 26:

- Compound **38** (a 4-(benzyloxycarbonyl)-4-(trifluoromethyl)phenyl 4-(4-fluorophenyl)benzenesulfonate derivative) is converted to compound **39** (a 4-(benzyloxycarbonyl)-4-(trifluoromethyl)phenyl 4-(4-fluorophenyl)benzenesulfonate derivative with a different stereochemistry) via steps *a, b*.
- Compound **39** is converted to compound **40** (a 4-(benzyloxycarbonyl)-4-(trifluoromethyl)phenyl 4-(4-fluorophenyl)benzenesulfonate derivative with a different stereochemistry) via steps *c, d*.
- Compound **40** is converted to compound **5** (a 4-(benzyloxycarbonyl)-4-(trifluoromethyl)phenyl 4-(4-fluorophenyl)benzenesulfonate derivative with a different stereochemistry) via steps *e, g*.
- Compound **5** is converted to compound **26** (a 4-(benzyloxycarbonyl)-4-(trifluoromethyl)phenyl 4-(4-fluorophenyl)benzenesulfonate derivative with a different stereochemistry) via steps *h, i*.

The structure of compound **26** is shown as a 3D ball-and-stick model, labeled "X-ray structure of 26".

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