

Discovery of Clinical Candidate BMS-906024: A Potent Pan-Notch Inhibitor for the Treatment of Leukemia and Solid Tumors

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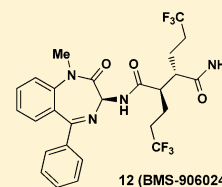
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S Supporting Information

ABSTRACT: Structure–activity relationships in a series of (2-oxo-1,4-benzodiazepin-3-yl)-succinamides identified highly potent inhibitors of γ -secretase mediated signaling of Notch1/2/3/4 receptors. On the basis of its robust in vivo efficacy at tolerated doses in Notch driven leukemia and solid tumor xenograft models, **12** (BMS-906024) was selected as a candidate for clinical evaluation.



KEYWORDS: Notch inhibitor, γ -secretase inhibitor, SAR, triple-negative breast cancer, T-acute lymphoblastic leukemia

Notch signaling is an evolutionally conserved cell signaling pathway involved in cell fate control and multiple cell differentiation processes during embryonic and adult life. Recent literature reports provide a strong rationale for pursuing Notch signaling inhibition as a cancer treatment strategy.^{1–4} Deregulation of the Notch pathway has been shown to be oncogenic in many human solid tumors and hematologic malignancies. Inappropriate activation of the Notch pathway produces many of the hallmarks of cancer, including uncontrolled proliferation, restricted differentiation leading to increased self-renewal capacity, evasion of apoptosis, and enhancement of angiogenesis and metastasis. In addition, there is strong evidence that Notch signaling plays a role in the maintenance and survival of cancer stem cells.⁴ Drug resistance during chemotherapy has also been attributed to activation of the Notch pathway.² Finally, targeting the Notch–ligand interaction in endothelial cells can produce antitumor effects through inhibition of tumor angiogenesis that is distinct from the VEGF pathway.

The mammalian Notch receptor family has four homologues (Notch1–4). Signaling is normally activated by contact of a Notch receptor-bearing cell with a cell carrying one of the five transmembrane ligands (Jagged 1 and 2, and Delta-like ligand 1, 3, and 4). Binding of ligand promotes two successive proteolytic processing events, the second of which is catalyzed by γ -secretase. As a result of proteolysis, the Notch intracellular domain (NICD) is liberated and can enter the nucleus to engage DNA-binding proteins and regulate gene expression.

The involvement of each of the four Notch receptors in cancer development has been well established.² Notch1 is the most commonly activated oncogene in T-acute lymphoblastic leukemia (TALL). Notch1 and Notch4 are coexpressed in breast cancer, but not in normal breast tissue. There is increasing evidence supporting the role of Notch3-mediated signaling in solid tumors. These data support our central hypothesis that pan-Notch inhibition will provide the broadest spectrum of antitumor efficacy in humans.

γ -Secretase is a membrane bound protease with presenilin-1 or presenilin-2 as the catalytic core and three accessory proteins, Aph-1, Pen-2, and nicastrin.⁵ It is also involved in the sequential cleavage of amyloid precursor proteins to release β -amyloid ($A\beta$) peptides that are thought to play a causative role in Alzheimer's disease (AD). Several APP-selective γ -secretase inhibitors (GSIs) were developed for the treatment of AD but demonstrated side effects attributed to the inhibition of Notch1. Some of these GSIs that were developed as $A\beta$ inhibitors are now being repositioned in the clinic as Notch inhibitors for the treatment of cancer (Figure 1).⁵

Chronic inhibition of Notch1 signaling has been associated with development of severe gastrointestinal (GI) toxicity due to conversion of proliferative cells in intestinal crypts to goblet

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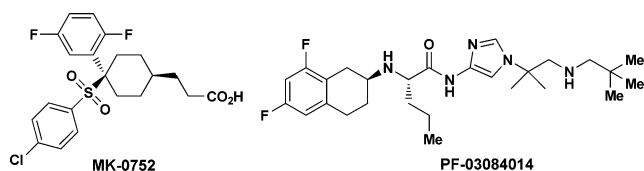


Figure 1. Examples of Notch inhibitors undergoing clinical evaluation in cancer.

cells.⁶ However, intermittent dosing with GSIs or combination with glucocorticoids have been shown to mitigate GI toxicity without affecting antitumor effects.⁷ With these strategies, Notch1 inhibition can be tolerated, but inhibition of this receptor subtype is still likely to be the source of dose-limiting toxicity. Therefore, a balanced inhibitor that provides roughly equally potent inhibition of the important Notch2/3/4 receptors as well as the critical but dose-limiting Notch1 receptor should produce the optimal efficacy/tolerability spectrum. In addition, the relatively short half-life of small molecule Notch inhibitors should offer an advantage over antibody-based therapies by enabling regimens that allow for target recovery in key cell types which mediate toxicity. This Letter describes structure–activity relationships (SARs) in a series of (2-oxo-1,4-benzodiazepin-3-yl)-succinamides as inhibitors of γ -secretase mediated signaling of Notch1/2/3/4 receptors leading up to the identification of **12** (BMS-906024), which has advanced into clinical development.⁸

At Bristol-Myers Squibb (BMS), the Notch program was initiated with the development of high-throughput cell-based transcriptional reporter assays for Notch1–4 receptors.⁹ Initial screening of the collection of GSIs was carried out in Notch1 and -3 assays and selected hits were subsequently evaluated in all the four Notch signaling assays. The caprolactam **1** screening hit was preferred since it provided a similar level of inhibitory potency for Notch1 and -3 receptors (Figure 2). Early SAR

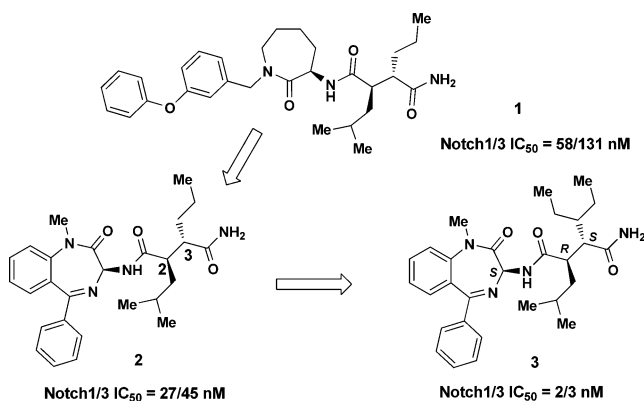
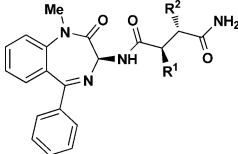


Figure 2. Notch inhibitors: Hit to Lead.

investigation suggested that the caprolactam can be replaced with a 1,4-benzodiazepin-2-one moiety without any loss of potency (compound **2**). This change was preferred since it improved pharmacokinetic properties in the lead series (data not shown). Further SAR exploration established that the primary amide was essential for potency, lipophilic groups were preferred on the succinamide moiety, and the *S,R,S* configuration was optimal for this series of pan-Notch inhibitors. These efforts led to the discovery of compound **3** as a highly potent pan-Notch inhibitor (Notch1/2/3/4 IC_{50} = 2/1/3/2 nM) with a commensurate level of potency in the

TALL-1 cell proliferation assay (Table 1).⁹ TALL-1 is a T-cell acute lymphoblastic leukemia cell line sensitive to Notch inhibition,¹⁰ which was recently reported to have an activating mutation in Notch3.¹¹

Table 1. Effects of Succinamide Modifications on Notch1/3 Inhibitory Potency and in Vitro Metabolic Stability



compd #	R ¹	R ²	Notch1/3 IC_{50} (nM) ^a	TALL-1 IC_{50} (nM)	HLM/MsLM (%) ^b
3			2/3	3	2/2
4			3/3	ND ^c	1/6
5			13/24	158	45/51
6			10/11	72	100/100
7			9/16	16	36/47
8			59/68	ND ^c	100/98
9			41/23	ND ^c	99/100
10			7/15	7	61/62
11			3/5	1	67/74
12			2/3	4	100/100

^aData reported as average of three test results. See ref 9 for description of assay conditions. ^bPercentage of the parent compound (0.5 μ M) remaining after a 10 min incubation with 1 mg/mL of HLM or MsLM. ^cNot determined.

Compound **3** exhibited very poor metabolic stability in isolated human or mouse liver microsomes (Table 1). Therefore, biotransformation studies were conducted to identify the metabolic soft spots (Figure 3). Abundance of the metabolites (Met1–5) was estimated based on their liquid chromatography–ultraviolet (LC–UV) peak heights compared to that of **3** at the start of incubation. Structural analysis of the

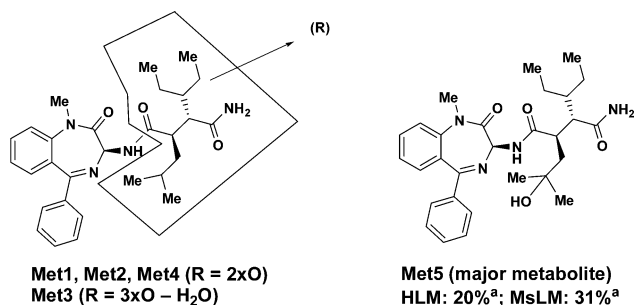
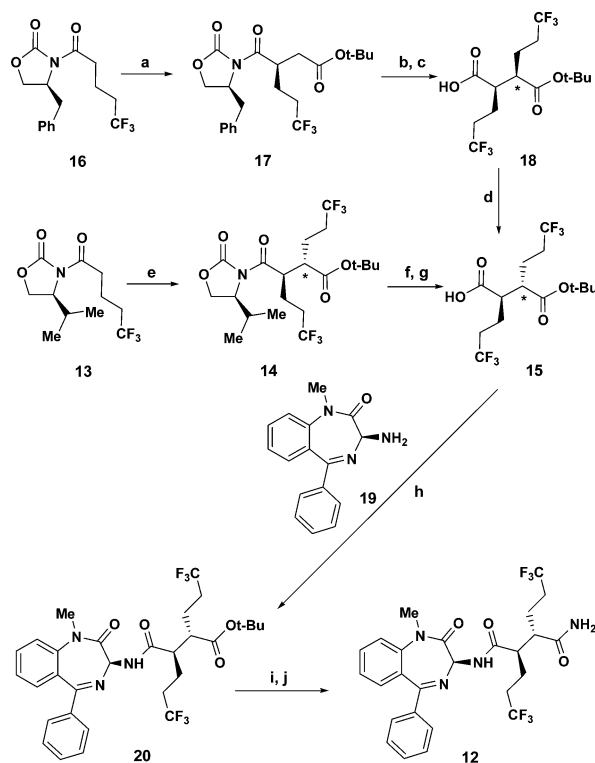


Figure 3. Oxidative metabolites of **3** in human liver microsomes (HLM) and mouse liver microsomes (MSLM). ^aYield of microsomal transformation.

metabolites by mass spectroscopy and ¹H NMR indicated that alkyl groups on the succinamide moiety were the preferred sites for oxidative metabolism. Met1, Met2, and Met4 incorporated two additional oxygen atoms in the succinamide side chain, whereas the structure of Met3 represented a net gain of three oxygen atoms followed by the loss of a water molecule. The methine functionality on the isobutyl group appeared to be the most susceptible to enzymatic oxidation since the corresponding hydroxylated compound (Met5) was isolated as the most abundant metabolite. This information was utilized to initiate succinamide SAR with the objective to improve metabolic stability (Table 1). Incorporation of an additional methyl group (compound **4**) in place of the metabolically labile methine proton in the isobutyl moiety in **3** maintained potency but did not improve oxidative stability, suggesting that oxidation of the 3-pentyl group was also likely. Indeed, successive replacement of the 3-pentyl moiety with propyl (compound **5**) and trifluoropropyl (compound **6**) groups provided dramatic improvement in metabolic stability. However, these changes were accompanied by reduction in potency in the Notch1/3 signaling and the TALL-1 cell proliferation assays. Further optimization was attempted by varying the R¹ alkyl group on the succinamide. A comparison of **6** with **4** and **7** indicates that both alkyl groups on the succinamide contribute to the overall metabolic stability in this series. Surprisingly, even small structural variations at the R¹ position led to significant changes in potency in the Notch1/3 signaling assays (e.g., compare **7** to **8**). The profile of succinamide **10** represented an encouraging combination of Notch1/3 and TALL-1 potency along with oxidative stability in the liver microsomes. The corresponding regioisomeric compound **11** exhibited an improvement in TALL-1 potency while retaining a similar level of metabolic stability. When these two changes were incorporated together, the resulting bis(trifluoropropyl) succinamide **12** provided a very high level of in vitro potency together with complete oxidative stability when incubated with human or mouse liver microsomes.

New compounds were prepared according to the sequence illustrated in Scheme 1 for the synthesis of **12**. An oxidative intermolecular enolate heterocoupling reaction was employed to prepare the 2,3-disubstituted succinate **15**.¹² Thus, reaction of the lithium enolate of *t*-butyl trifluoropentanoate with the lithium enolate of trifluoropentanoyl oxazolidinone **13** in the presence of copper(II) 2-ethylhexanoate afforded the adduct **14** in 66% yield as a 1.6:1 mixture in favor of the depicted diastereomer. Chemoselective removal of the chiral auxiliary with lithium peroxide provided the corresponding carboxylic acid, which was subjected to epimerization¹³ with LDA and

Scheme 1. Synthesis of **12**^a



^aReagents and conditions: (a) sodium hexamethyldisilazane, THF, BrCH₂CO₂*t*-Bu, -78 °C, 68%; (b) lithium hydroxide, water, hydrogen peroxide, 0 °C, 83%; (c) LDA, THF, CF₃CH₂CH₂OTf, -78 to 0 °C, 80%; 5:1 ratio of diastereomers at *stereocenter; (d) LDA, THF, Et₂AlCl, hexane, -78 to 0 °C, 90%; 9:1 ratio of diastereomers at *stereocenter; (e) (1) LDA, toluene, THF, -78 °C; (2) LDA, toluene, THF, *t*-Bu 5,5,5-trifluoropentanoate, -78 °C; (3) Cu(2-ethylhexanoate)₂, -78 to 40 °C, 66%; 1.6:1 ratio of diastereomers at *stereocenter; (f) lithium hydroxide, water, hydrogen peroxide, 0 °C, 86%; (g) LDA, THF, Et₂AlCl, hexane, -78 to 0 °C, 99%; 9:1 ratio of diastereomers at *stereocenter; (h) **19**, TBUT, Et₃N, DMF, 89%; (i) TFA, CH₂Cl₂, 0 °C, 75%; (j) EDC, HOBT, iPr₂NEt, NH₄Cl, DMF, 79%.

diethylaluminum chloride to give **15** as a 9:1 mixture in favor of the desired diastereomer. An alternate synthetic route was developed for the large scale synthesis of **15**. Alkylation of **16** with *t*-butyl 2-bromoacetate afforded **17** in 68% yield.¹⁴ Removal of the chiral auxiliary and subsequent alkylation of the resulting succinate with trifluoropropyl trifluoromethanesulfonate provided **18**, which was epimerized with LDA and diethylaluminum chloride to give **15** as a 9:1 mixture in favor of the desired diastereomer. Coupling of acid **15** with (3*S*)-amino-1,4-benzodiazepin-2-one **19**¹⁵ in the presence of TBUT and triethylamine produced the amide **20** in 89% yield. Trifluoroacetic acid-mediated ester hydrolysis and subsequent coupling with ammonium chloride under standard conditions afforded **12** in 59% yield from intermediate **20**. The absolute configuration of **12** was further verified by X-ray diffraction studies.

Compound **12** inhibited Notch processing with IC₅₀ values of 1.6, 0.7, 3.4, and 2.9 nM for Notch1, -2, -3, and -4 receptors, respectively, and exhibited greater than 200-fold selectivity against a panel of diverse protein targets (receptors, ion channels, and enzymes). In cancer cell proliferation assays, **12** inhibited both leukemia (TALL-1) and triple-negative breast

cancer (MDA-MB-468) cells with IC_{50} of ~ 4 nM. In MDA-MB-468 cells, **12** elicited dose-dependent inhibition of Notch3 intracellular domain formation, and the potency of this inhibition was consistent with the potency observed for the inhibition of cell proliferation.¹⁶ Extensive in vitro and in vivo analysis identified several tumor cell lines that were sensitive (e.g., HCC70 and MDA-MB-157) and resistant (e.g., HCC1419 and SKBR3) to treatment with compound **12**.

The pharmacokinetic parameters obtained for **12** in four species are summarized in Table 2. The compound has good

Table 2. Pharmacokinetic Parameters for **12**

parameter	mouse ^a	rat ^a	dog ^a	cyno ^b
dose (mg kg ⁻¹) iv/po	1 ^c /1 ^d	1 ^c /1 ^f	0.05 ^g /0.05 ^f	0.2 ^h /0.2 ^d
C_{max} (μ M) iv/po	1.0/0.3	1.7/0.1	0.4/0.01	0.3/0.01
AUC _(0–24h) (μ M·h) iv/po	3.4/1.9	2.0/0.8	4.8 ⁱ /0.6 ^j	0.5/0.1
t_{max} (h) iv/po	0.4/0.8	0.2/1.2	0.2/5.3	0.2/2.0
$t_{1/2}$ (h) iv/po	4.6/5.3	6.6/4.2	51.1/32.1	6.7/13.0
MRT (h) iv	3.8	3.0	62.3	8.2
F_{po} (%)	57	46	29	30

^aData reported as average of three animals. ^bData reported as average of two animals. ^cVehicle: PEG400/water (70:30). ^dPEG300/TPGS/EtOH (80:10:10). ^ePEG400/water (75:25). ^fPEG300/TPGS/EtOH (60:20:20). ^gSaline/hydroxypropyl β -cyclodextrin/PEG300 (87:12:1). ^hPEG400 (100). ⁱAUC_(0–168h). ^jAUC_(0–72h).

intrinsic permeability in Caco-2 cells (104 nm/s) and was well absorbed following oral administration from solution formulations at the doses denoted in Table 2. Plasma half-life and mean residence time (MRT) were longer in dogs as compared to other species. Systemic clearance was less than 10% of the hepatic blood flow, and volume of distribution (V_{ss}) was larger than total body water, indicating extensive extravascular distribution. The measured oral bioavailability (F_{po}) ranged from 29% in dogs to 57% in mice. Compound **12** (10 μ M) was 88.7% bound to human serum proteins and 95.9%, 94.3%, 95.4%, and 87.6% bound to the serum proteins of mouse, rat, dog, and cynomolgus monkey, respectively.

Results of the in vivo activity of **12** in leukemia and solid tumor xenograft models are summarized in Table 3. As illustrated in Figure 4, once daily (10 days on; 2 days off; 5 days on) oral administration of **12** in mice bearing the TALL-1 tumors resulted in a dose-dependent inhibition of tumor growth with 1 mg/kg/day as the minimum efficacious dose

Table 3. In Vivo Antitumor Activity of **12** against MDA-MB-468 Triple-Negative Breast Cancer and TALL-1 Leukemia Xenografts (Schedule: qd $\times$ 10; 2 days off; qd $\times$ 5)

tumor model	dose ^a (mg kg ⁻¹)	LCK ^b	%TGI ^c
TALL-1	0.5	0.4	73
	1	1.1	100
	2	3.1	103
	5	6.1	107
	1	ND ^d	84
MDA-MB-468	4	ND ^d	92
	6	ND ^d	94

^aVehicle: PEG300/TPGS/EtOH (80:10:10). ^bLog Cell Kill (LCK) at the predetermined median tumor target size. ^cPercent tumor growth inhibition (TGI) at the end of the dosing period, $P < 0.05$. ^dNot determined.

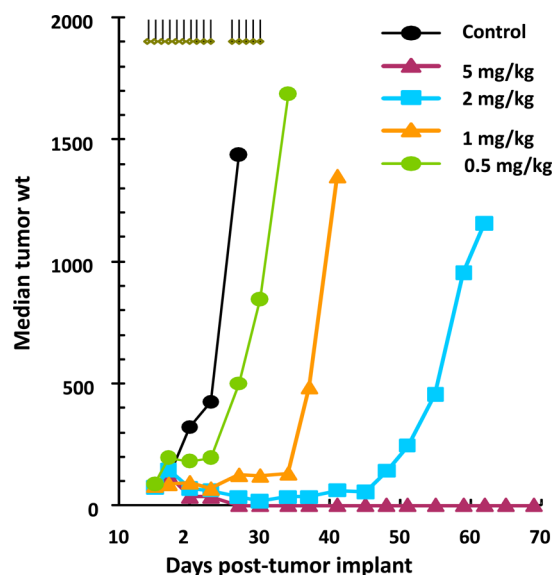


Figure 4. In vivo antitumor activity of **12** against TALL-1 leukemia xenografts (schedule: qd $\times$ 10; 2 days off; qd $\times$ 5).

(Log Cell Kill >1). Nearly complete tumor stasis was observed throughout the dosing regimen at this dose, but tumor growth resumed following the cessation of treatment. At higher doses, a significant delay in tumor growth was observed even after the dosing was completed. Dose-dependent antitumor activity was also demonstrated in the MDA-MB-468 triple negative breast cancer xenograft model. No overt toxicity as measured by morbidity or significant body weight loss was observed at the indicated doses in these experiments. Subsequently, **12** demonstrated broad-spectrum antineoplastic activity against a wide array of human cancer xenografts, including colon carcinoma, ovarian carcinoma, non-small cell lung carcinoma, HER2-positive breast carcinoma, pancreatic carcinoma, glioblastoma, and neuroblastoma.¹⁷

In conclusion, optimization of the in vitro potency and oxidative metabolic stability in a series of (2-oxo-1,4-benzodiazepin-3-yl)-succinamides led to the identification of **12**, a pan-Notch inhibitor that was orally efficacious in human tumor xenografts dependent on the Notch signaling pathway. On the basis of its favorable in vitro pharmacology, broad spectrum in vivo efficacy in multiple tumor models, and a satisfactory pharmacokinetic profile, **12** was advanced into clinical trials.¹⁸

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental details for synthetic procedures and associated chemical data for compounds 3–20. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

EDC, 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide; HLM, human liver microsomes; HOBt, 1-hydroxybenzotriazole; LDA, lithium diisopropylamide; MsLM, mouse liver microsomes; TBTU, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; TFA, trifluoroacetic acid; TPGS, *D*- α -tocopheryl polyethylene glycol 1000 succinate; VEGF, vascular endothelial growth factor

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