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# The Discovery of 3,3'-spiro[azetidine]-2-oxo-indoline Derivatives as Fusion Inhibitors for Treatment of RSV Infection

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*KEYWORDS RSV, Fusion inhibitor, Benzimidazole*

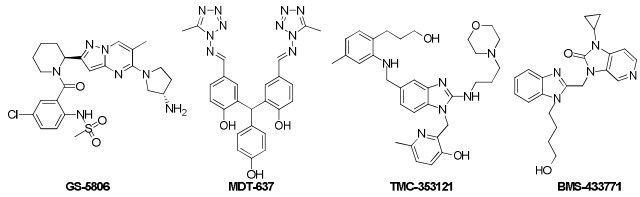
**ABSTRACT:** A new series of 3,3'-spirocyclic-2-oxo-indoline derivatives were synthesized and evaluated against Respiratory Syncytial Virus (RSV) in the cell-based assay and animal model. Extensive structure-activity relationship study led to a lead compound **14h**, which exhibited excellent *in vitro* potency with an EC50 value of 0.8 nM and demonstrated 71% oral bioavailability in mice. In a mouse challenge model of RVS infection, **14h** demonstrated superior efficacy with a 3.9log RSV virus load reduction in the lung following an oral dose of 50 mg/kg.

## Introduction

Respiratory syncytial virus (RSV) is a major cause of pneumonia and bronchiolitis in young children, immunocompromised adults and the elderly, resulting in ~125,000 hospitalizations annually in the United States[1,2]. However, the treatment of RSV lower respiratory tract infection (LRTI) is limited[3]. Synagis (Palivizumab), a marketed humanized monoclonal antibody targeting fusion glycoprotein (F protein) of RSV, was licensed for passive prophylaxis intervention in high-risk infants. However, its high cost of treatment and relatively low protection to high-risk children limit its usage. An aerosol formulation of Ribavirin (Virazole) is the only chemotherapeutic agent on the market. Virazole is not a specific protection for young children and is rarely used due to its variable efficacy and toxicity.

Clearly, there is an unmet need for a new drug to prevent and treat RSV infection. In the past two decades, several chemical series of RSV fusion protein inhibitors have been reported, including the most advanced compound GS-5806 which is currently in Phase 2 study[4,5]. Another Phase 2 compound is MDT-637 (formerly VP-14637) and is being developed as a dry powder inhaled product due to its low oral bioavailability. Both BMS-433771[6] and TMC-353121[7] were progressed into late preclinical / early clinical development but discontinued, mainly due to the unfavorable pharmaceutical properties or early safety findings. The two RSV F protein inhibitors contain the same benzimidazole heterocycle. Therefore, we intend to address the drug-like properties of benzimidazole RSV fusion inhibitors especially improving activity *in vitro*, pharmacokinetics, and pharmacodynamics. Herein we describe the identification of a promising candidate isopropyl 1'-((5-bromo-1-(4-hydroxybutyl)-1H-benzo[d]imidazol-2-yl)methyl)-2'-oxospiro[azetidine-3,3'-indoline]-1-carboxylate (**14h**) that was effective in a mouse challenge model of RSV infection. Meanwhile, the extensive structure-activity relationship (SAR) of this 3,3'-spirocyclic-2-oxo-indoline derivatives was revealed herein.

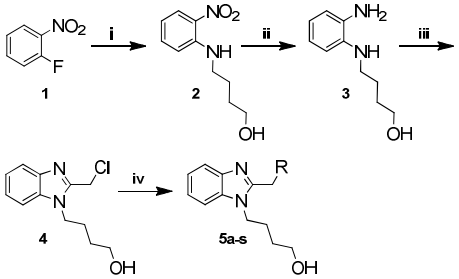
**Figure 1. RSV inhibitors explored in early stage clinical studies**




## Results and Discussion

In order to investigate a strategy of pyridinoimidazolone replacements on BMS-433771, a small library containing nineteen scaffold hopping derivatives were designed and synthesized (**Scheme 1**). The key intermediate **4** was prepared from starting material **1** via displacement reaction, hydrogenation reaction followed by cyclization reaction with excellent overall yields (68.4%). The target compounds **5a-s** were obtained by alkylation reaction of intermediate **4** in the presence of $K_2CO_3$ in $CH_3CN$ or NaH in DMF.

**Scheme 1. General synthesis of pyridinoimidazolone replacements analogs**

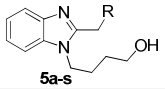



**Reagents and conditions:** (i) 4-aminobutan-1-ol, $Et_3N$, dioxane, 90%; (ii) Pd/C, $H_2$, MeOH, 95%; (iii) 2-chloroacetic acid, 4N HCl, 80°C, ~60%; (iv) for 5a-g, 5j-p, $K_2CO_3$, MeCN, 70°C or NaH, DMF, 20°C; for 5h/i, $K_2CO_3$, then Pd(OH)2; for 5q-s, $K_2CO_3$, then TFA

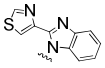
Cyclopropyl indolin-2-one **5a** was first recorded in ReViral ltd's patent for RSV treatment, but no antiviral activity was reported[8]. Hoffmann-La Roche discolsed spiro azain-

dolin-2-one analogs, however only spirocylicpropanes were introduced[9-11]. In order to perform pyridinoimidazolone replacement strategy, **5a-c** were synthesized and evaluated by the CPE assay. The antiviral activities were listed in **Table 1**. The importance of carbonyl group for the activities against RSV was demonstrated when its replacement with a hydrogen (**5e** and **5f**, with $EC_{50}$ of 0.20 and 0.18 μM, respectively) resulted in a moderate activity in comparison to BMS-433771. The presence of small aliphatic substituent at ortho-position of carbonyl was also found to be desirable (**5g-j**). Attempt to replace the fused phenyl ring with saturated ring resulted in a 100-fold less active compound **5k** with an $EC_{50}$ of 12 μM versus **5f**. Other pyridinoimidazolone replacements (**5m-s**) showed negative impact on activities. In summary, though the SAR for pyridinoimidazolone replacement strategy is kind of rigid, the ring system 3,3'-spiro[cyclopropane]-2-oxo-indoline (**5a-c**) was identified to gain a superior level of activity.

**Table 1 Antiviral activity of a small library of pyridinoimidazolone replacements**



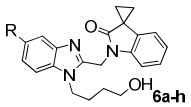
**5a-s**

| cpd. | R | $EC_{50}$(uM)[a] | $CC_{50}$(uM)[b] | cpd. | R | $EC_{50}$(uM) | $CC_{50}$(uM) |
|---|---|---|---|---|---|---|---|
| BMS-433771 |  | 0.020 | >100 | **5j** |  | 1.8 | >100 |
| **5a** |  | 0.015 | >100 | **5k** |  | 12 | >100 |
| **5b** |  | 0.016 | >100 | **5l** |  | 26 | >100 |
| **5c** |  | 0.037 | >100 | **5m** |  | 1.7 | >100 |
| **5d** |  | 0.13 | >100 | **5n** |  | 0.47 | >100 |
| **5e** |  | 0.20 | >100 | **5o** |  | 0.11 | >100 |
| **5f** |  | 0.18 | >100 | **5p** |  | 0.11 | >100 |
| **5g** |  | 0.35 | >100 | **5q** |  | 5.0 | >100 |
| **5h** |  | 1.0 | >100 | **5r** |  | 0.48 | >100 |
| **5i** |  | 2.2 | >100 | **5s** |  | >50 | >100 |

[a]RSV CPE assay in Hep-2 cells, data was generated from two or more determinations. [b]$CC_{50}$ was performed on the same cells and method.

As a new chemical starting point, chloride (**6a**) and methyl group (**6b**) were introduced at 5-position of the corresponding benzimidazole moiety following Feng's work on imidazolepyrimidines[12,13]. Unfortunately, both of these two compounds did not boost the antiviral activities, demonstrating 10 nM and 16 nM respectively versus 15 nM of **5a**. In the meantime, an entire attrition was observed on 5-cyclohexyl substituent (**6c**) possibly due to increased steric bulk, electronic withdrawing groups 5-CN (**6e**) and 5-$CF_3$ (**6f**) attenuated the activities by more than 10-fold. Single-digital nanomolar activity was obtained when bromine was introduced and **6h** demonstrated 7-fold potency improvement in comparison to **5a**. Given that the introduction of 5-bromo had a significant impact on anti-RSV activity, we decided to pursue 5-bromobenzimidazole moiety for further SAR optimizations.

**Table 2 Antiviral activity of compound 6a-i**



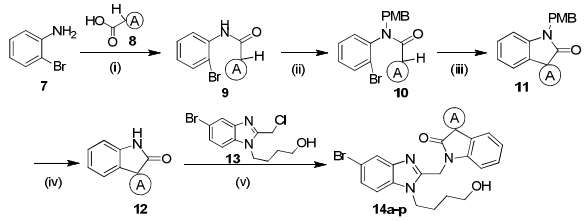
**6a-h**

| cpd. | R | $EC_{50}$(nM)[a] | $CC_{50}$(uM)[b] | cpd. | R | $EC_{50}$(nM) | $CC_{50}$(uM) |
|---|---|---|---|---|---|---|---|
| **5a** | 5-H | 15 | >100 | **6e** | 5-CN | 190 | >100 |
| **6a** | 5-Cl | 10 | >100 | **6f** | 5-$CF_3$ | 210 | >100 |
| **6b** | 5-Me | 16 | >100 | **6g** | 5-$CH_2NH_2$ | 7.0 | >100 |
| **6c** | 5-cyclohexyl | >10 000 | >100 | **6h** | 5-Br | 2.3 | >100 |
| **6d** | 5-F | 13 | >100 | **6i** | 5-I | 21 | >100 |

[a]RSV CPE assay in Hep-2 cells, data was generated from two or more determinations. [b]$CC_{50}$ was performed on the same cells and method.

Furthermore, 3,3'-spirocylic-2-oxo-indolines are found in compounds that exert a range of pharmacological activities. Analog 3,3'-spiro[succinimide]-2-oxo-indoline antagonized chemoattractant receptor-homologous expressed on Th2 lymphocytes (CRTH2 or DP2)[14], and 3,3'-spiro[piperidine]-2-oxo-indolines were in development for cathepsin K inhibitors[15]. Therefore, the following study focused on optimizing 3,3'-spirocylic-2-oxo-indoline moiety of **6h**.

**Scheme 2. Synthetic route to produce key intermediate 12**



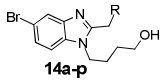
A represents cyclio ring

Reagents and conditions: (i) $T_3P$, ethyl acetate, 30°C, 90%; (ii) PMBCl, DMF, NaH 30°C, or $Cs_2CO_3$, 90°C, 85%; (iii) i-Pr-PEPPSI, tBuONa, 1,4-dioxane, 90°C, 65%; (iv) CAN, acetonitrile, 0°C, 30% or $CF_3SO_3H$, TFA, 30°C, 75%; (v) $K_2CO_3$, MeCN, 70°C or NaH, DMF, 20°C, 70%~90%

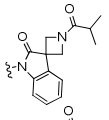
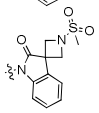
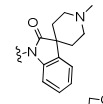
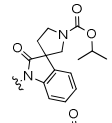
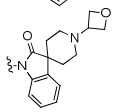
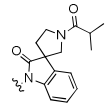
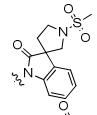
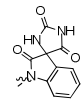
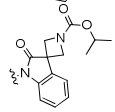
In order to explore more potent 3,3-spirocylic-2-oxo-indoline derivatives, a small library of spiro hetero cyclic analogs were successfully designed and synthesized. The synthesis of intermediate **12**, as shown in **Scheme 2**, was generally commenced with commercially available 2-bromo aniline, which was condensed with the acid **8** via $T_3P$ to generate the amide **9**, followed by alkylation with PBMCl to yield intermediates **10**. This intermediate was then subjected to an intramolecular palladium-catalyzed

α -arylation reaction[16]. After removal of PMB via in CAN or TfOH acid conditions, intermediate **12** was generated in moderate to good yield (30-75%). As shown in **Table 3**, **14a** and **14b** displayed good potency, with $EC_{50}$ of 6 nM and 8 nM. Sulfide **14c**, sulfone **14d** exhibited 5 nM and 21 nM antiviral activities, respectively. Encouraged by the tolerances of hetero atoms, nitrogen was introduced. 5-Membered analogs **14e**, **14f** and **14g** attenuated 4-5 fold anti-RSV activities compared with **6h**. However, 4- membered azetidine spiro analogs, isopropyl carbamate **14h**, improved the antiviral activity into subnanomolar level of 0.8 nM, 3 fold more potent compared to that of **6h**, and isobutyl amide **14i** and methanesulfonyl amide **14j** exhibited comparable activities of 3 nM. Other approaches of aliphatic amine (**14k-l**) and steric bulky 6 membered spiro rings (**14m-p**) attenuated the activities.

**Table 3 Antiviral activity of 3,3-spirocyclic-2-oxo-indoline derivatives 14a-p**



**14a-p**

| cpd. | R | $EC_{50}$(nM)[a] | $CC_{50}$(uM)[b] | cpd. | R | $EC_{50}$(nM) | $CC_{50}$(uM) |
|---|---|---|---|---|---|---|---|
| **6h** |  | 2.3 | >100 | **14i** |  | 3 | >100 |
| **14a** |  | 6 | >100 | **14j** |  | 3 | >100 |
| **14b** |  | 8 | >100 | **14k** |  | 19 | >100 |
| **14c** |  | 5 | >100 | **14l** |  | 43 | >100 |
| **14d** |  | 21 | >100 | **14m** |  | 307 | >100 |
| **14e** |  | 11 | >100 | **14n** |  | 42 | >100 |
| **14f** |  | 10 | >100 | **14o** |  | 55 | >100 |
| **14g** |  | 8 | >100 | **14p** |  | 76 | >100 |
| **14h** |  | 0.8 | >100 | | | | |

[a]RSV CPE assay in Hep-2 cells, data was generated from two or more determinations. [b]$CC_{50}$ was performed on the same cells and method.

## PK Results and Discussion

Plasma pharmacokinetics after 1 mg/kg intravenous and 10 mg/kg oral administration of compound **14h** and BMS433771[6] to female balb/c mice were characterized. PK parameters were listed in **table 4**, indicating that compound **14h** showed lower clearance and volume of distribution (Vd), but higher AUC with similar half-life (T1/2). However, compound **14h** had much better oral profile than that of BMS433771, as evidenced by oral exposure (8076 nM*h versus 1170 nM*h) and absolute oral bioavailability (71% versus 13%).

**Table 4 Pharmacokinetic parameters after single intravenous and oral administration of 14h and BMS433771 to female Balb/c mice.**

| cpd. | 14h | BMS-433771 |
|---|---|---|
| ***i.v.* @1mpk** | | |
| CL (mL/min/kg) | 28 | 67 |
| $T_{1/2}$ (h) | 1.4 | 1.7 |
| $V_d$ (L/kg) | 1.6 | 2.4 |
| $AUC_{0\text{-}inf}$ (nM*h) | 1130 | 920 |
| ***p.o.* @10mpk** | | |
| $C_{max}$ (nM) | 3319 | 2098 |
| $T_{max}$ (h) | 0.25 | 0.25 |
| $AUC_{0\text{-}inf}$ (nM*h) | 8076 | 1170 |
| %F | 71 | 13 |

(A) Data reported are mean values from the dosing cohorts (Female Balb/c-Mouse, fasted, n = 3/dose). (B) Dosages are 1 mg/kg *i.v.* (1 mg/mL in DMSO: PEG400: water = 5:40:55, clear solution) and 10 mg/kg *p.o.* (2 mg/mL in DMSO: PEG400: water = 5:40:55, clear solution). (C) CL stands for plasma clearance. $T_{1/2}$ is the plasma half-life of the compounds. $V_d$ means volume of distribution. $C_{max}$ represents the highest observed plasma concentration and $T_{max}$ is time to reach $C_{max}$. AUC is the area under the plasma concentration-time curve. %F represents absolute oral bioavailability.

## Pharmacology Results and Discussion

The *in vivo* efficacy was evaluated in the Balb/c mouse RSV infection model. As shown in **table 5**, compound **14h** showed a clear dose-dependent effect on virus load reduction from 5 mg/kg to 50 mg/kg. In addition, the 5 mg/kg group of **14h** reduced the lung tissue virus load Δlog10 to 1.6 which was superior to BMS-433771 1.2 Δlog10 at 50 mg/kg dose. Moreover, the 50 mg/kg group of **14h** reduced virus load of all the experimental animals to below the detection limit, which demonstrated that compound **14h** exhibited excellent anti-RSV efficacy and significantly superior to BMS433771 in this RSV mouse challenge model.

**Table 5 *In vivo* antiviral activity in a mouse model of RSV infection**

| Group (n=7) | Viral load in lung (Log10 pfu/g lung) | Vial load reduction in lung (△log10) |
|---|---|---|
| **Vehicle** | 3.91±0.10 | – |
| **BMS433771**-50mpk | 2.75±0.20 | 1.16±0.24 |
| **14h**-5mpk | 2.27±0.24 | 1.64±0.26 |
| **14h**-15mpk | 1.86±0.31 | 2.05±0.31 |
| **14h**-50mpk | 0.00±0.00 | 3.91 |

## Conclusion

In summary, we have explored a series of 3,3'-spiro[azetidine]-2-oxo-indoline derivatives proved to be potent inhibitors of RSV in the CPE assay. The investiga-

tion led to the identification of **14h** as a compound demonstrating additional efficacy in the Balb/c mouse model of RSV infection after oral dosing. Further safety assessment will be conducted in due course.

## ASSOCIATED CONTENT

### Supporting Information

Synthetic procedures, analytical data, assay protocol are available free of charge on the ACS Publications website.

## AUTHOR INFORMATION

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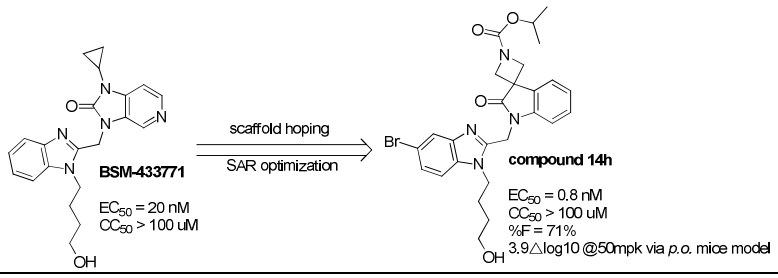
## ABBREVIATIONS

PK, pharmacokinetics; PO, per oral; Cmax, peak concentration; Tmax, time to peak; CL, clearance; T1/2, half-life; Vd, volume of distribution; AUC, area under curve; mpk, mg/kg;; %F, oral bioavailability.

## REFERENCES

1. Shane, S. Respiratory syncytial virus market. *Nat. Rev. Drug. Discov.* **2010**, 9(1), 15-16.
2. Hall, C. B.; Weinberg, G. A.; Iwane, M. K.; Blumkin, A. K.; Edwards, K. M.; Staat, M. A.; Auinger, P.; Griffin, M. R.; Poehling, K. A.; Erdman, D.; Grijalva, C. G.; Zhu, Y.; Szilagyi, P. The Burden of Respiratory Syncytial Virus Infection in Young Children. New. Engl. J. Med. 2009, 360(6), 588-598.
3. Nair, H.; Nokes, D. J. Gessner, B. D.; Dherani, M.; Madhi, S. A.; Singleton, R. J.; O'Brien, K. L.; Roca, A.; Wright, P. F.; Bruce, N.; Chandran, A.; Theodoratou, E.; Sutanto, A.; Sedyaningsih, E. R.; Ngama, M.; Munywoki, P. K.; Kartasasmita, C.; Simões, E. A.; Rudan, I.; Weber, M. W.; Campbell, H. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010, 375(9725), 1545-1555.
4. Mackman, R. L.; Sangi, M.; Sperandio, D.; Parrish, J. P.; Eisenberg, E.; Perron, M.; Hui. H.; Zhang, L.; Siegel, D.; Yang, H.; Saunders, O.; Boojamra, C.; Lee, G.; Samuel, D.; Babaoglu, K.; Carey, A.; Gilbert, B. E.; Piedra, P. A.; Strickley, R.; Iwata, Q.; Hayes, J.; Stray, K.; Kinkade, A.; Theodore, D.; Jordan, R.; Desai, M.; Cihlar, T. Discovery of an oral respiratory syncytial virus (RSV) fusion inhibitor (GS-5806) and clinical proof of concept in a human RSV challenge study. J. Med. Chem. 2015, 58(4), 1630-1643.
5. DeVincenzo, J. P.; Whitley, R. J.; Machman, R. L.; Weinlich, C. S.; Harrison, L.; Farrell, E.; McBride, S.; Williams, R. L.; Jordan, R.; Xin, Y.; Ramanathan, S.; O'Riordan, T.; Lewis, S. A.; Li, X.; Toback, S. L.; Lin, S. L.; Chien, J. W. Oral GS-5806 activity in a respiratory syncytial virus challenge study. New. Engl. J. Med. 2014, 371(8), 711-722.
6. Yu, K. L.; Sin, N.; Civiello, R. L.; Wang, X. A.; Combrink, K. D.; Gulgeze, H. B.; Venables, B. L.; Wright, J. J.; Dalterio, R. A.; Zadjura, L.; Marino, A.; Dando, S.; D'Arienzo, C.; Kadow, K. F.; Cianci, C. W.; Li, Z.; Clarke, J.; Genovesi, E. V.; Medina, I.; Lamb, L.; Colonno, R. J.; Yang, Z.; Krystal, M.; Meanwell, N. A. Respiratory syncytial virus fusion inhibitors. Part 4: optimization for oral bioavailability. Bioorg. Med. Chem. Lett. 2007, 17(4), 895-901.
7. Bonfanti, J. F.; Meyer, C.; Doublet, F.; Fortin, J.; Muller, P.; Queguiner, L.; Gevers, T.; Janssens, P.; Szel, H.; Willebrords, R.; Timmerman, P.; Wuyts, K.; Remoortere, P. V.; Janssens, F.; Wigerinck, P.; Andries, K. Selection of a respiratory syncytial virus fusion inhibitor clinical candidate. 2. Discovery of a morpholinopropylaminobenzimidazole derivative (TMC353121). J. Med. Chem. 2008, 51(4), 875-896.
8. Cockerill, S; Pilkington, C; Lumley, J; Angell, R; Mathews, N. Pharmaceutical compounds. WO2013/68769;
9. Feng, S; Gao, L; Guo, L; Huang, M; Liang, C; Wang, B; Wang, L; Wu, G; Yun, H; Zhang, W; Zheng, X; Zhu, W. Aza-oxo-indoles for the treatment and prophylaxis of respiratory syncytial virus infection. WO2014/184163;
10. Gao, L; Guo, L; Liang, C; Wang, B; Wang, L; Yun, H; Zhang, W; Zheng, X. Novel aza-oxo-indoles for the treatment and prophylaxis of respiratory syncytial virus infection. WO2015/22263
11. Wang, L; Yun, H; Zhang, W; Zheng, X. Novel aza-oxo-indoles for the treatment and prophylaxis of respiratory syncytial virus infection. WO2015/22301;
12. Feng, S; Hong, D; Wang, B; Zheng, X; Miao, K; Wang, L; Yun, H; Gao, L; Zhao, S; Shen, H. C. Discovery of imidazopyridine derivatives as highly potent respiratory syncytial virus fusion inhibitors. ACS Med Chem Lett. 2015, 6(3), 359-362.
13. Feng, S; Li, C; Chen, D; Zheng, X; Yun, H; Gao, L; Shen, H. C. Discovery of methylsulfonyl indazoles as potent and orally active respiratory syncytial Virus(RSV) fusion inhibitors. Eur J Med Chem. 2017, 138, 1147-1157.
14. Crosignani, S.; Page, P.; Missotten, M.; Colovray, V.; Cleva, C.; Arrighi, J. F.; Atherall, J.; Macritchie, J.; Martin, T.; Humbert, Y.; Gaudet, M.; Pupowicz, D.; Maio, M.; Pittet, P. A.; Golzio, L.; Giachetti, C.; Rocha, C.; Bernardinelli, G.; Filinchuk, Y.; Scheer, A.; Schwarz, M. K.; Chollet, A. Discovery of a New Class of Potent, Selective, and Orally Bioavailable CRTH2 (DP2) Receptor Antagonists for the Treatment of Allergic Inflammatory Diseases. J. Med. Chem. 2008, 51(7), 2227-2243.
15. Teno, N.; Masuya, K.; Ehara, T.; Kosaka, T.; Miyake, T.; Irie, O.; Hitomi, Y.; Matsuura, N.; Umemura, I.; Iwasaki, G.; Fukaya, H.; Toriyama, K.; Uchiyama, N.; Nonomura, K.; Sugiyama, I.; Kometani, M. Effect of Cathepsin K Inhibitors on Bone Resorption. J. Med. Chem. 2008, 51(17), 5459-5462.
16. Pfefferkorn, J. A; Choi, C. Convenient synthesis of 1,1'-H-spiro[indoline-3,3o-piperidine]. *Tetrahedron Lett.* **2008**, 49(28), 4372-4373.

## Table of Contents


scaffold hoping
SAR optimization
BSM-433771
EC50 = 20 nM
CC50 > 100 uM
compound 14h
EC50 = 0.8 nM
CC50 > 100 uM
%F = 71%
3.9△log10 @50mpk via p.o. mice model