(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2012 (05.01.2012)

PCT

(10) International Publication Number
WO 2012/002680 A2

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 13/12* (2006.01)
C07D 401/14 (2006.01) *A61P 11/00* (2006.01)
C07D 413/14 (2006.01) *A61P 19/10* (2006.01)
A61K 31/437 (2006.01) *A61P 25/28* (2006.01)

(21) International Application Number:
PCT/KR2011/004631

(22) International Filing Date:
24 June 2011 (24.06.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/826,338 29 June 2010 (29.06.2010) US

(71) Applicant *(for all designated States except US)*: **EWHA UNIVERSITY-INDUSTRY COLLABORATION FOUNDATION** [KR/KR]; 11-1, Daehyun-dong, Seodaemun-gu, Seoul 120-750 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KIM, Dae Kee** [KR/KR]; 101-1403 Parkpalace, Naesu-dong, Jongno-gu, Seoul 110-901 (KR). **SHEEN, Yhun Yhong** [KR/KR]; 122-1401 Raemian Firstige Apt., Banpo 2(i)-dong, Seocho-gu, Seoul 137-764 (KR). **JIN, Cheng Hua** [KR/KR]; Pharmaceutical Science Building A #200, Ewha Womans Univ., Daehyeon-dong, Seodaemun-gu, Seoul 120-750 (KR). **PARK, Chul-Yong** [KR/KR]; Eungam-2-dong, 376-32 (#301), Eunpyeong-gu, Seoul 122-919 (KR). **SREENU, Domalapally** [IN/KR]; Pharmaceutical Science Building A #200, Ewha Womans Univ., Daehyeon-dong, Seodaemun-gu, Seoul 120-750 (KR). **RAO, Kota Sudhakar** [IN/KR]; Pharmaceutical Science Building A #200, Ewha Womans Univ., Daehyeon-dong, Seodaemun-gu, Seoul 120-750 (KR). **KRISHNAIAH, Maddeboina** [IN/KR]; Pharmaceutical Science Building A #200, Ewha Womans Univ., Daehyeon-dong, Seodaemun-gu, Seoul 120-750 (KR). **SUBRAHMANYAM, Vura Bala** [IN/KR]; 101 Geumhwa House, Sinchon-dong 1-8, Seodaemun-gu, Seoul 120-140 (KR).

(74) Agent: **HALLA PATENT & LAW FIRM**; 9F KAMCO Yangjae Tower, 949-3 Dogok-dong, Gangnam-gu, Seoul 135-270 (KR).

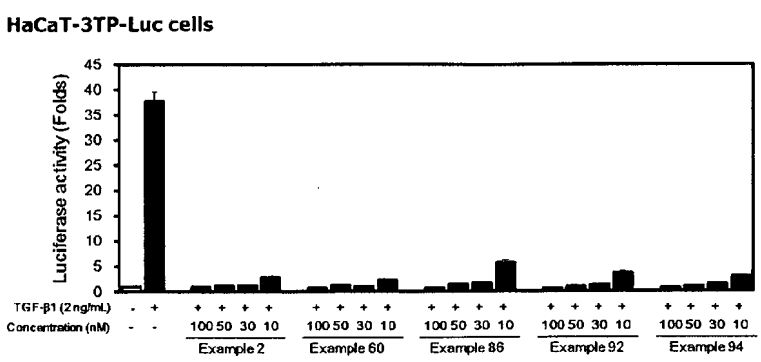
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: 2-PYRIDYL SUBSTITUTED IMIDAZOLES AS THERAPEUTIC ALK5 AND/OR ALK4 INHIBITORS

[Fig. 1]



(57) Abstract: This invention relates to 2-pyridyl substituted imidazoles which are inhibitors of the transforming growth factor-β (TGF-β) type I receptor (ALK5) and/or the activin type I receptor (ALK4), methods for their preparation, and their use in medicine, specifically in the treatment and prevention of a disease state mediated by these receptors.

WO 2012/002680 A2

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

Description

Title of Invention: 2-PYRIDYL SUBSTITUTED IMIDAZOLES AS THERAPEUTIC ALK5 AND/OR ALK4 INHIBITORS

Technical Field

[0001] This invention relates to 2-pyridyl substituted imidazoles which are inhibitors of the transforming growth factor-β (TGF-β) type I receptor (ALK5) and/or the activin type I receptor (ALK4), methods for their preparation, and their use in medicine, specifically in the treatment and prevention of a disease state mediated by these receptors.

[0002]

Background Art

[0003] TGF-β denotes a family of proteins, TGF-β1, TGF-β2 and TGF-β3, which are pleiotropic modulators of cell proliferation and differentiation, wound healing, extracellular matrix production, and immunosuppression. Other members of this superfamily include activins, inhibins, bone morphogenetic proteins, growth and differentiation factors, and Mullerian inhibiting substance.

[0004] TGF-β1 transduces signals through two highly conserved single transmembrane serine/threonine kinases, the type I (ALK5) and type II TGF-β receptors. Upon ligand induced oligomerization, the type II receptor hyperphosphorylates serine/threonine residues in the GS region of the ALK5, which leads to activation of the ALK5 by creating a binding site for Smad proteins. The activated ALK5 in turn phosphorylates Smad2 and Smad3 proteins at the C-terminal SSXS-motif thereby causing their dissociation from the receptor and heteromeric complex formation with Smad4. Smad complexes translocate to the nucleus, assemble with specific DNA-binding co-factors and co-modulators to finally activate transcription of extracellular matrix components and inhibitors of matrix-degrading proteases.

[0005] Activins transduce signals in a manner similar to TGF-β. Activins bind to serine/thereonine kinase, the activin type II receptor (ActRIIB), and the activated type II receptor hyperphosphorylates serine/threonine residues in the GS region of the ALK4. The activated ALK4 in turn phosphorylates Smad2 and Smad3. The consequent formation of a hetero-Smad complex with Smad4 results in the activin-induced regulation of gene transcription.

[0006] Numerous experimental animal studies demonstrate an association between glomerular expression of TGF-β and fibrosis, including the Thy-1 rat model of proliferative glomerulonephritis, anti-GBM glomerulonephritis in rabbits, and the 5/6 nephrectomy rat model of focal segmental glomerulosclerosis, as has been reviewed recently (e.g., Bitzer, M. et al., *Kidney Blood Press. Res.* 21: 1-12 (1998)). Neutralizing

antibody to TGF-β improves glomerular histology in the Thy-1 nephritis model (e.g., Border, W. A. et al., *Nature* 346: 371-374 (1990)).

[0007] Hyperglycemic conditions increase TGF-β mRNA and protein synthesis in both murine proximal tubule cells and human mesangial cells (e.g., Wahab, N. A. et al., *Biochem. J.* 316: 985-992 (1996); Rocco, M. V. et al., *Kidney Int.* 41: 107-114 (1992)). Diabetic patients with early kidney disease show increased accumulation of TGF-β mRNA and protein within the glomerulus (e.g., Yoshioka, K. et al., *Lab. Invest.* 68: 154-163 (1993)). In kidneys with chronic renal interstitial fibrosis, the hallmarks are thickened tubular basement membranes and an expanded interstitial compartment, with interstitial fibrosis characterized by an increase in collagens I, III, V, VII, and fibronectin (e.g., Eddy, A. A., *J. Am. Soc. Nephrol.* 7: 2495-2508 (1996)).

[0008] TGF-β gene expression and protein production are increased in a variety of animal models of pulmonary fibrosis including bleomycin, silica, asbestos, and radiation (e.g., Phan, S. H. and Kunkel, S. L., *Exp. Lung Res.* 18: 29-43 (1992); Williams, A. O. et al., *Am. J. Pathol.* 142: 1831-1840 (1993); Rube, C. E. et al., *Int. J. Radiat. Oncol. Biol. Phys.* 47: 1033-1042 (2000)). Coincident increase in TGF-β1 protein and collagen gene expression in adjacent tissue slices from idiopathic pulmonary fibrosis is observed in human pulmonary fibrotic disease (e.g., Broekelmann, T. J. et al., *Proc. Natl. Acad. Sci. USA* 88: 6642-6646 (1991)). Increased TGF-β production has been documented in patients with sarcoidosis, pneumoconiosis, asbestosis, and radiation-induced fibrosis (e.g., Khalil, N. et al., *Am. J. Respir. Cell. Mol. Biol.* 14: 131-138 (1996); Jagirdar, J. et al., *Environ. Health Perspect.* 105: 1197-1203 (1997)). Anti-TGF-β antibodies and TGF-β-soluble receptors could partially inhibit fibrosis in bleomycin-induced lung fibrosis rodent models (e.g., Giri, S. N. et al., *Thorax* 48: 959-966 (1993); Wang, Q. et al., *Thorax* 54: 805-812 (1999)). Tobacco smoke has been implicated as one of the most important factors that can cause small airway disease followed by chronicobstructive pulmonary disease (COPD) (e.g., Wright, J. M. et al., *Am. Rev. Respir. Dis.* 146: 240-262 (1992)). COPD is a slowly progressiveand irreversible disorder characterized by the functional abnormalityof airway obstruction. TGF-β has been hypothesized to be involved in airway remodeling found in chronic airway inflammatory disorders such as COPD (e.g., Takizawa, H. *Int. J. Mol. Med.* 1: 367-378 (1998); Ning, W. et al., *Proc. Natl. Acad. Sci. USA* 101: 14895-14900 (2004)).

[0009] Hepatic stellate cells (HSC) are the major source of extracellular matrix proteins in hepatic fibrosis. Extracellular matrix production by activated hepatic stellate cells is markedly increased through the action of TGF-β1 (e.g., Friedman, S. L., *Prog. Liver Dis.* 14: 101-130 (1996); Pietrangelo, A., *Semin. Liver Dis.* 16: 13-30 (1996)). Transgenic mice that overexpress TGF-β1 in the liver develop hepatic fibrosis as well

as extrahepatic pathologies such as renal fibrosis (e.g., Sanderson, N. et al., *Proc. Natl. Acad. Sci. USA* 92: 2572-2576 (1995)).

[0010] TGF-β1 and its receptors are overexpressed in injured blood vessels and in fibroproliferative vascular lesions leading to overproduction of extracellular matrix (e.g., Saltis, J. et al., *Clin. Exp. Pharmacol. Physiol.* 23: 193-200 (1996); McCaffrey, T. A. et al., *J. Clin. Invest.* 96: 2667-2675 (1995)).

[0011] Anti-TGF-β antibodies reduce scar formation and improve the cytoarchitecture of the neodermis in rats (e.g., Shah, M., *J. Cell. Sci.* 108: 985-1002 (1995)), improve healing of corneal wounds in rabbits (e.g., Moller-Pedersen, T., *Curr. Eye Res.* 17: 736-747 (1998)), and accelerate wound healing of gastric ulcers in rats (e.g., Ernst, H., *Gut* 39: 172-175 (1996)).

[0012] Radiation fibrosis is a frequent sequel of therapeutic or accidental radiation overexposure in normal human tissues. TGF-β1 plays a central role in the initiation, development, and persistence of radiation fibrosis, as has been reviewed recently (e.g., Martin, M. et al., *Int. J. Radiat. Oncol. Biol. Phys.* 47: 277-290 (2000)).

[0013] Organ transplantation is complicated in many instances by chronic rejection and for some organs such as the kidney, it is the major forms of graft loss. In human patients, chronic rejection of lung and kidney transplants is associated with increased expression of TGF-β within the tissue (e.g., El-Gamel, A. et al., *Eur. J. Cardiothorac. Surg.* 13: 424-430 (1998); Shihab, F. S. et al., *J. Am. Soc. Nephrol.* 6: 286-294 (1995)).

[0014] TGF-β is implicated in peritoneal adhesions (e.g., Saed, G. M. et al., *Wound Repair Regen.* 7: 504-510 (1999)). The peritoneal and sub-dermal fibrotic adhesions could be prevented by inhibitors of ALK5 and/or ALK4.

[0015]

[0016] TGF-β2 levels are increased in nearly half of the eyes with primary open-angle glaucoma (POAG) and in most of the eyes with juvenile glaucoma in the aqueous humor of eyes (e.g., Picht, G. et al., *Graefes Arch. Clin. Exp. Ophthalmol.* 239: 199-207 (2001)). Both TGF-β1 and TGF-β2 isoforms are reported to increase extracellular matrix production in cultured human Tenon's capsule fibroblasts derived from patients with pseudoexfoliation glaucoma and POAG (e.g., Kottler, U. B. et al., *Exp. Eye Res.* 80: 121-134 (2005)). US 2007/0142376 A1 discloses treatment of glaucoma and control of intraocular pressure using ALK5 modulating agents, and an ALK5 inhibitor reduces the level of fibronectin in TGF-β2-treated perfused human anterior segments and the levels of fibronectin, plasminogen activator inhibitor-1 (PAI-1), and pro-collagen type I C-peptide in TGF-β2-treated trabecular meshwork cell cultures.

[0017] The tumor cells and the stromal cells within the tumors in late stages of various cancers generally overexpress TGF-β. This leads to stimulation of angiogenesis and cell motility, suppression of the immune system, and increased interaction of tumor

cells with the extracellular matrix (e.g., Hojo, M. et al., *Nature* 397: 530-534 (1999)). Consequently, the tumor cells become more invasive and metastasize to distant organs (e.g., Maehara, Y. et al., *J. Clin. Oncol.* 17: 607-614 (1999); Picon, A. et al., *Cancer Epidemiol. Biomarkers Prev.* 7: 497-504 (1998)).

[0018] PAI-1 is the major physiological inhibitor of both tissue-type plasminogen activator and urokinase-type plasminogen activator. Elevated levels of PAI-1 are associated with thrombosis and vascular disease, suggesting that high plasma PAI-1 may promote a hypercoagulable state by disrupting the natural balance between fibrinolysis and coagulation (e.g., Vaughan, D. E., *J. Invest. Med.* 46: 370-376 (1998)). It is known that TGF-β stimulates the expressionof PAI-1 (e.g., Dennler, S. et al., *EMBO J.* 17: 3091-3100 (1998)). Accordingly, inhibition of the production of PAI-1 with an inhibitor of the TGF-β signaling pathway could produce a novel fibrinolytic therapy.

[0019] Activin signaling and overexpression of activin is linked to pathological disorders that involve extracellular matrix accumulation and fibrosis (e.g., Matsuse, T. et al., *Am. J. Respir. Cell Mol. Biol.* 13: 17-24 (1995); Inoue, S. et al., *Biochem. Biophys. Res. Comm.* 205: 441-448 (1994); Matsuse, T. et al., *Am. J. Pathol.* 148: 707-713 (1996); De Bleser et al., *Hepatology* 26: 905-912 (1997); Pawlowski, J. E., et al., *J. Clin. Invest.* 100: 639-648 (1997); Sugiyama, M. et al., *Gastroenterology* 114: 550-558 (1998); Munz, B. et al., *EMBO J.* 18: 5205-5215 (1999)), inflammatory responses (e.g., Rosendahl, A. et al., *Am. J. Respir. Cell Mol. Biol.* 25: 60-68 (2001), cachexia or wasting (Matzuk, M. M. et al., *Proc. Natl. Acd. Sci. USA* 91: 8817-8821 (1994); Coerver, K. A. et al., *Mol. Endocrinol.* 10: 534-543 (1996); Cipriano, S. C. et al., *Endocrinology* 141: 2319-2327 (2000)), diseases or pathological responses in the central nervous system (e.g., Logan, A. et al., *Eur. J. Neurosci.* 11: 2367-2374 (1999); Logan, A. et al., *Exp. Neurol.* 159: 504-510 (1999); Masliah, E. et al., *Neurochem. Int.* 39: 393-400 (2001); De Groot, C. J. A. et al., *J. Neuropathol. Exp. Neurol.* 58: 174-187 (1999); John, G. R. et al., *Nat. Med.* 8: 1115-1121 (2002)) and hypertension (e.g., Dahly, A. J. et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283: R757-767 (2002)). Studies have shown that TGF-β and activin can act synergistically to induce extracellular matrix production (e.g., Sugiyama, M. et al., *Gastroenterology* 114; 550-558 (1998)).

[0020] Therefore, it becomes evident that inhibition of ALK5 and/or ALK4 phosphorylation of Smad2 and Smad3 by the preferred compounds of this invention could treat and prevent disorders involving these signaling pathways.

[0021] WO 00/61576 and US 2003/0149277 A1 disclose triarylimidazole derivatives and their use as ALK5 inhibitors. WO 01/62756 A1 discloses pyridinylimidazole derivatives and their use as ALK5 inhibitors. WO 02/055077 A1 discloses use of imidazolyl cyclic acetal derivatives as ALK5 inhibitors. WO 03/087304 A2 discloses tri-

substituted heteroaryls and their use as ALK5 and/or ALK4 inhibitors. WO 2005/103028 A1 and US 7,407,958 B2 disclose 2-pyridyl substituted imidazoles as ALK5 and/or ALK4 inhibitors. Especially, one of the representative compounds claimed in WO 2005/103028 A1 and US 7,407,958 B2 , IN-1130, demonstrates its use in several animal models as ALK5 and/or ALK4 inhibitors. IN-1130 effectively suppresses renal fibrosis induced by unilateral ureteral obstruction (UUO) in rats (Moon, J.-A. et al., *Kidney Int.* 70: 1234-1243 (2006)), ameliorates experimental autoimmune encephalomyelitis (EAE) in SBE-luc and GFAP-luc mice immunized with MOG_{35-55} (Luo, J. et al., *J. Clin. Invest.* 117: 3306-3315 (2007)), lessens tunical fibrosis and corrects penile curvature in rats (Ryu, J.-K. et al., *J. Sex. Med.* 6: 1284-1296 (2009)), and dramatically reduces tumor volume with an enhanced immune response in mice treated with murine prostate cancer cell line Tramp C2 (Lee, G. T. et al., *J. Urol.* 180: 2660-2667 (2008)). And, also, US 2008/0319012 A1 discloses 2-pyridyl substituted imidazoles as ALK5 and/or ALK4 inhibitors. Especially, one of the representative compounds claimed in US 2008/0319012 A1, IN-1233, demonstrates its use in several animal models as ALK5 and/or ALK4 inhibitors. IN-1233 effectively prevents the development and progression of pulmonary arterial hypertension in the monocrotaline rat model through the inhibition of TGF-β signaling (Long, L. et al., *Circulation* 119: 566-576 (2009)) and also prevents granulation tissue formation after bare metallic stent placement in a rat urethral model (Kim, J. H. et al., *Radiology* 255: 75-82 (2010)).

[0022]

Summary of Invention

Solution to Problem

[0023] Surprisingly, it has now been discovered that a class of 2-pyridyl substituted imidazoles function as potent and selective inhibitors of ALK5 and/or ALK4 and, therefore, have utility in the treatment, prevention, and reduction of various disease states mediated by ALK5 and/or ALK4, such as glomerulonephritis, diabetic nephropathy, lupus nephritis, hypertension-induced nephropathy, renal interstitial fibrosis, renal fibrosis resulting from complications of drug exposure, HIV-associated nephropathy, transplant nephropathy, liver fibrosis due to all etiologies, hepatic dysfunction attributable to infections, alcohol-induced hepatitis, disorders of the biliary tree, cystic fibrosis, pulmonary fibrosis, interstitial lung disease, acute lung injury, adult respiratory distress syndrome, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary disease due to infectious or toxic agents, post-infarction cardiac fibrosis, congestive heart failure, dilated cardiomyopathy, myocarditis, intimal thickening, vascular stenosis, hypertension-induced vascular remodeling, pulmonary

arterial hypertension, coronary restenosis, peripheral restenosis, carotid restenosis, stent-induced restenosis, atherosclerosis, ocular scarring, corneal scarring, proliferative vitreoretinopathy, glaucoma, intraocular pressure, excessive or hypertrophic scar or keloid formation in the dermis occurring during wound healing resulting from trauma or surgical wounds, peritoneal and sub-dermal adhesion, scleroderma, fibrosclerosis, progressive systemic sclerosis, dermatomyositis, polymyositis, arthritis, osteoporosis, ulcers, impaired neurological function, male erectile dysfunction, Peyronie's disease, Dupuytren's contracture, Alzheimer's disease, Raynaud's syndrome, radiation-induced fibrosis, thrombosis, tumor metastasis growth, multiple myeloma, melanoma, glioma, glioblastomas, leukemia, sarcomas, leiomyomas, mesothelioma, and carcinomas of lung, breast, colon, kidney, ovary, cervix, liver, biliary tract, gastrointestinal tract, pancreas, prostate, head, and neck.

[0024]

Brief Description of Drawings

[0025] The aforementioned aspects and other features of the present invention will be explained in the following description, taken in conjunction with the accompanying drawings, wherein:

[0026] FIG. 1 shows effect of Examples 2, 60, 86, 92, and 94 on the TGF-β1-induced 3TP-Luc reporter activity in HaCaT-3TP-Luc cells,

[0027] FIG. 2 shows effect of Examples 2, 60, 86, 92, and 94 on the TGF-β1-induced 3TP-Luc reporter activity in 4T1-3TP-Luc cells,

[0028] FIG. 3 shows effect of Example 2 on the TGF-β1-induced Smad2/3 nuclear translocation in MCF10A cells,

[0029] FIG. 4 shows effect of Example 2 on the TGF-β1-induced cell migration in MCF10A cells,

[0030] FIGS. 5a and 5b show effect of Example 2 on the TGF-β1-induced cell invasion in 4T1 cells.

[0031] (5a). DAPI-stained cells remaining on the bottom surface. (5b). Average cell number per view field obtained from 5 random fields,

[0032] FIG. 6 shows effect of Example 2 on the cell growth of 4T1 cells,

[0033] FIG. 7 shows effect of Example 2 on the cell growth of MCF10A cells,

[0034] FIGS. 8a and 8b show effect of Example 3 on the breast tumor metastasis to the lung in BALB/c 4T1 xenografted mice. Example 3 (13.6 or 27.3 mg/kg) dissolved in water (vehicle) was given to mice orally BID five consecutive days per week for four weeks. (8a). White spots on the lung surface indicate metastastic nodules (white arrows). (8b). Number of metastastic nodules on whole lung surface,

[0035] FIGS. 9a and 9b show effect of Example 2 on the breast tumor metastasis to the lung

in BALB/c 4T1 xenografted mice. Example 2 (5, 10, 20, or 40 mg/kg) dissolved in artificial gastric fluid formulation (vehicle) was given to mice orally five consecutive days per week for three weeks. (9a). White spots on the lung surface indicate metastastic nodules. (9b). Number of metastastic nodules on surface of left lobe of lung,

[0036] FIGS. 10a, 10b, and 10c show effect of Example 2 on the breast tumor metastasis to the lung in BALB/c 4T1 xenografted mice. Example 2 (5, 10, 20, or 40 mg/kg) dissolved in artificial gastric fluid formulation (vehicle) was given to mice orally every other day (three times per week) for 24 days. (10a). White spots on the lung surface indicate metastastic nodules. (10b). Number of metastastic nodules on surface of left lobe of lung. (10c). Effect on the TGF-β1-induced Smad2 phosphorylation in tumor tissues,

[0037] FIGS. 11a, 11b, and 11c show effect of Example 61 on the breast tumor metastasis to the lung in BALB/c 4T1 xenografted mice. Example 61 (43.6 mg/kg) dissolved in saline (vehicle) was given to mice intraperitoneally every other day (three times per week) for 2.5 weeks. (11a). White spots on the lung surface indicate metastastic nodules. (11b). Number of metastastic nodules on surface of left lobe of lung. (11c). Volume of primary tumor,

[0038] FIGS. 12a, 12b, 12c, and 12d show effect of Example 61 on the breast tumor metastasis to the lung in MMTV/c-Neu mice. Tumor-bearing MMTV/c-Neu mice were treated intraperitoneally with Example 61 (43.6 mg/kg) every other day for three weeks. (12a). Hematoxylin and eosin (H&E) staining of mammary tumor and lung tissues. (12b). Number of histologically detectable metastastic lesions in the lung. (12c). Volume of mammary tumor. (12d). β-Casein mRNA level,

[0039] FIGS. 13a and 13b show effect of Example 3 on the breast tumor metastasis to the lung in MMTV/c-Neu mice. Tumor-bearing MMTV/c-Neu mice were treated intraperitoneally with Example 3 (43.6 mg/kg) every other day for ten weeks. (13a). β-Casein mRNA level. (13b). Activity of MMP-9 and MMP-2 in the primary mammary tumor,

[0040] FIGS. 14a, 14b, 14c, and 14d show effect of Example 3 on the bile duct-ligated liver fibrosis in rats. Example 3 (21.8 or 43.6 mg/kg) dissolved in saline (vehicle) was given to rats orally three times per week for four weeks starting from BDL surgery. (14a). Activity of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). (14b). Level of pSmad3 protein in the liver. (14c). Level of α-SMA, fibronectin, and vimentin proteins in the liver. (14d). Hematoxylin and eosin (H&E) staining of liver tissues,

[0041] FIGS. 15a, 15b, and 15c show effect of Example 2 on the bile duct-ligated liver fibrosis in rats. Example 2 (5, 10, or 20 mg/kg) dissolved in artificial gastric fluid for-

mulation (vehicle) was given to rats orally three times per week for four weeks starting from BDL surgery. (15a). Activity of ALT and AST. (15b). Level of α-SMA and fibronectin proteins in the liver. (15c). Hematoxylin and eosin (H&E) staining of liver tissues,

[0042] FIGS. 16a and 16b show effect of Example 2 on the bleomycin-induced lung fibrosis in mice. Example 2 (5, 10, or 20 mg/kg) dissolved in artificial gastric fluid formulation (vehicle) was given to mice orally five times per week for two weeks starting from day 7. (16a). Level of α-SMA and fibronectin proteins in the lung. (16b). Hematoxylin and eosin (H&E) staining of lung tissues.

[0043] Table 1 shows structures and ^{1}H NMR and MS spectral data of Examples 1-139,

[0044] Table 2 shows structures and ^{1}H NMR and MS spectral data of Examples 140-153,

[0045] Table 3 shows IC_{50} values of selected Examples on ALK5 kinase phosphorylation,

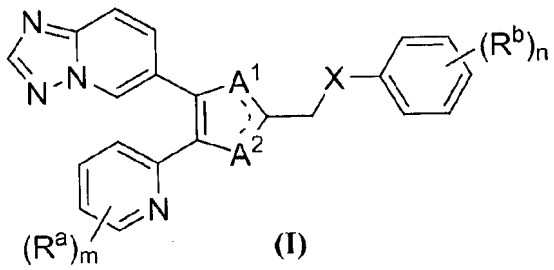
[0046] Table 4 shows either IC_{50} values or % inhibition of Example 2 on various kinases phosphorylation,

[0047] Table 5 shows effect of Example 3 on the body and organ weight changes in BDL rats, and

[0048] Table 6 shows effect of Example 2 on the body and organ weight changes in BDL rats.

Best Mode for Carrying out the Invention

[0049] In an embodiment of the present invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:

[0050] 

(I)

[0051] wherein each R^a is independently H, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, OH, —O—C_{1-6}alkyl, —O—C_{1-6}haloalkyl, —O—C_{3-6}cycloalkyl, NH_2, —NH—C_{1-6}alkyl, —NH—C_{1-6}haloalkyl, —NH—C_{3-6}cycloalkyl, —S—C_{1-6}alkyl, —S—C_{1-6}haloalkyl, —S—C_{3-6}cycloalkyl, CN, or NO_2;

[0052] m is 0, 1, 2, 3, or 4;

[0053] one of A^1 and A^2 is N and the other is NR^1, wherein R^1 is H, OH, C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{3-6}cycloalkyl;

[0054] X is a bond, —$(CH_2)_p$—, —NR^2—, —O—, or —S—, wherein p is 0 or 1, and R^2 is H or C_{1-3}alkyl;

[0055] each R^b is independently H, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl,

C_{2-6}alkynyl, —$(CH_2)_q$—OR^3, —$(CH_2)_q$—NR^3R^4, —$(CH_2)_q$—SR^3, —$(CH_2)_q$—NO_2, —$(CH_2)_q$—CONHOH, —$(CH_2)_q$—CN, —$(CH_2)_q$—COR^3, —$(CH_2)_q$—CO_2R^3, —$(CH_2)_q$—$CONR^3R^4$, —$(CH_2)_q$—tetrazole, —$(CH_2)_q$—CH=CH-CN, —$(CH_2)_q$—CH=CH—CO_2R^3, —$(CH_2)_q$—CH=CH—$CONR^3R^4$, —$(CH_2)_q$—CH=CH-tetrazole, —$(CH_2)_q$—$NHCOR^3$, —$(CH_2)_q$—$NHCO_2R^3$, —$(CH_2)_q$—$CONHSO_2R^3$, —$(CH_2)_q$—$NHSO_2R^3$, —$(CH_2)_q$—C≡C—CN, —$(CH_2)_q$—C≡C—CO_2R^3, —$(CH_2)_q$-C≡C—$CONR^3R^4$, —$(CH_2)_q$—C≡C-tetrazole, —$(CH_2)_q$—SOR^5, —$(CH_2)_q$—SO_2R^5, or —$(CH_2)_r$— $(OR^3)_2$, wherein R^3 and R^4 are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{3-6}cycloalkyl; or taken together with the nitrogen atom to which they are attached form a mono-cyclic ring such as imidazole, pyrrolidine, piperidine, morpholine, piperazine and homopiperazine; R^5 is C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{3-6}cycloalkyl; q is 0, 1, 2, 3, or 4; and r is 1, 2, 3, or 4;

[0056] n is 0, 1, 2, 3, 4, or 5.

[0057] As used herein, the double bond indicated by the dotted lines of formula (I), represent the possible tautomeric ring forms of the compounds falling within the scope of this invention, the double bond being to the unsubstituted nitrogen.

[0058] Preferably, R^a is C_{1-3}alkyl or halo.

[0059] Preferably, m is 1 or 2.

[0060] Preferably, one of A^1 and A^2 is N and the other is NR^1, wherein R^1 is H.

[0061] Preferably, X is —$(CH_2)_p$— or —NR^2—, wherein p is 0 and R^2 is H.

[0062] Preferably, R^b is halo, C_{1-3}alkyl, C_{1-3}haloalkyl, C_{3-4}cycloalkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, —$(CH_2)_q$—OR^3, —$(CH_2)_q$—NR^3R^4, —$(CH_2)_q$—SR^3, —$(CH_2)_q$—CN, —$(CH_2)_q$—COR^3, —$(CH_2)_q$—CO_2R^3, —$(CH_2)_q$—$CONR^3R^4$, —$(CH_2)_q$—$NHCOR^3$, —$(CH_2)_q$—$NHSO_2R^3$, —$(CH_2)_q$—SOR^5, or —$(CH_2)_q$—SO_2R^5, wherein R^3 and R^4 are independently H, C_{1-3}alkyl,

[0063] C_{1-3}haloalkyl, or C_{3-4}cycloalkyl; or taken together with the nitrogen atom to which they are attached form a mono-cyclic ring such as imidazole, pyrrolidine, piperidine, morpholine, piperazine and homopiperazine; R^5 is methyl; and q is 0, 1, or 2.

[0064] Preferably, n is 1, 2, or 3.

[0065] Specific compounds of the invention which may be mentioned include the following and pharmaceutically acceptable salts thereof:

[0066] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)aniline;

[0067] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoroaniline;

[0068] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-fluoroaniline;

[0069] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl

)methyl)-4-fluoroaniline;

[0070] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2,3-difluoroaniline;

[0071] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,4-difluoroaniline;

[0072] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,5-difluoroaniline;

[0073] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-chloroaniline;

[0074] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-chloroaniline;

[0075] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-chloroaniline;

[0076] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2,3-dichloroaniline;

[0077] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,4-dichloroaniline;

[0078] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,5-dichloroaniline;

[0079] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-bromoaniline;

[0080] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-bromoaniline;

[0081] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-bromoaniline;

[0082] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-methylaniline;

[0083] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-methylaniline;

[0084] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-methylaniline;

[0085] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2,3-dimethylaniline;

[0086] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,4-dimethylaniline;

[0087] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,5-dimethylaniline;

[0088] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl

)methyl)-2-ethylaniline;

[0089] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-ethylaniline;

[0090] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-isopropylaniline;

[0091] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-isopropylaniline;

[0092] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-isopropylaniline;

[0093] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-vinylaniline;

[0094] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-vinylaniline;

[0095] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-vinylaniline;

[0096] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-ethynylaniline;

[0097] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-methoxyaniline;

[0098] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-methoxyaniline;

[0099] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-methoxyaniline;

[0100] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2,3-dimethoxyaniline;

[0101] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,4-dimethoxyaniline;

[0102] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,5-dimethoxyaniline;

[0103] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(methoxymethyl)aniline;

[0104] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(methoxymethyl)aniline;

[0105] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-(methoxymethyl)aniline;

[0106] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(trifluoromethoxy)aniline;

[0107] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl

)methyl)-3-(trifluoromethoxy)aniline;

[0108] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-(trifluoromethoxy)aniline;

[0109] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(methylthio)aniline;

[0110] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(methylthio)aniline;

[0111] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-(methylthio)aniline;

[0112] 2-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)benzonitrile;

[0113] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)benzonitrile;

[0114] 4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)benzonitrile;

[0115] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)phthalonitrile;

[0116] 2-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)benzamide;

[0117] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)benzamide;

[0118] 4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)benzamide;

[0119] 2-(3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetonitrile;

[0120] 2-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetonitrile;

[0121] 1-(3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)ethanone;

[0122] 1-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)ethanone;

[0123] Methyl 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H* -imidazol-

[0124] 2-yl)methylamino)benzoate;

[0125] Methyl 4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H* -imidazol-

[0126] 2-yl)methylamino)benzoate;

[0127] *N*-(2-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2

-yl)methylamino)phenyl)acetamide;

[0128] *N*-(3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetamide;

[0129] *N*-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetamide;

[0130] *N*-(2-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)methanesulfonamide;

[0131] *N*-(3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)methanesulfonamide;

[0132] *N*-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)methanesulfonamide;

[0133] N^1-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-N^2,N^2-dimethylbenzene-1,2-diamine;

[0134] N^1-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-N^3,N^3-dimethylbenzene-1,3-diamine;

[0135] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(pyrrolidin-1-yl)aniline;

[0136] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-morpholinoaniline;

[0137] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-morpholinoaniline;

[0138] N^3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-fluoro-N^1,N^1-dimethylbenzene-1,3-diamine;

[0139] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-5-(dimethylamino)benzonitrile;

[0140] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-4-(dimethylamino)benzonitrile;

[0141] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-((dimethylamino)methyl)aniline;

[0142] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-((dimethylamino)methyl)aniline;

[0143] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(pyrrolidin-1-ylmethyl)aniline;

[0144] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(pyrrolidin-1-ylmethyl)aniline;

[0145] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(morpholinomethyl)aniline;

[0146] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl

)methyl)-3-(morpholinomethyl)aniline;

[0147] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-5-((dimethylamino)methyl)-2-fluoroaniline;

[0148] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-((dimethylamino)methyl)-2-fluoroaniline;

[0149] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoro-3-(pyrrolidin-1-ylmethyl)aniline;

[0150] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoro-3-(morpholinomethyl)aniline;

[0151] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-4-((dimethylamino)methyl)benzonitrile;

[0152] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-2-((dimethylamino)methyl)benzonitrile;

[0153] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-5-((dimethylamino)methyl)benzonitrile;

[0154] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-4-(pyrrolidin-1-ylmethyl)benzonitrile;

[0155] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-2-(pyrrolidin-1-ylmethyl)benzonitrile;

[0156] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-5-(pyrrolidin-1-ylmethyl)benzonitrile;

[0157] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-4-(morpholinomethyl)benzonitrile;

[0158] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-2-(morpholinomethyl)benzonitrile;

[0159] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methylamino)-5-(morpholinomethyl)benzonitrile;

[0160] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(2-(dimethylamino)ethylaniline;

[0161] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(2-(dimethylamino)ethylaniline;

[0162] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-ethylpyridin-2-yl)-1*H*-imidazol-2-yl)m ethylamino)benzonitrile;

[0163] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-ethylpyridin-2-yl)-1*H*-imidazol-2-yl) methyl)-2-fluoroaniline;

[0164] *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoro-*N*-methylaniline;

[0165] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)

methyl)(methyl)amino)benzonitrile;

[0166] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methyl)(methyl)amino)benzamide;

[0167] 6-(2-benzyl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin e;

[0168] 6-(2-(2-fluorobenzyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5 -*a*]pyridine;

[0169] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methyl)benzonitrile;

[0170] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methyl)benzamide;

[0171] 6-(5-(6-methylpyridin-2-yl)-2-(phenoxymethyl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1, 5-*a*]pyridine;

[0172] 6-(2-((2-fluorophenoxy)methyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]t riazolo[1,5-*a*]pyridine;

[0173] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methoxy)benzonitrile;

[0174] 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl) methoxy)benzamide;

[0175] 6-(5-(6-methylpyridin-2-yl)-2-(phenylthiomethyl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine;

[0176] 6-(2-((2-fluorophenylthio)methyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine.

[0177] The compounds of the present invention typically are small organic molecules (non-peptide small molecules), generally less than about 1,000 daltons in size. Preferred non-peptide small molecules have molecular weights of less than about 750 daltons, more preferably less than about 500 daltons.

[0178] Compounds of formula (I) may also be supplied in the form of a "prodrug" which is designed to release compound of formula (I) when administered to a subject. Prodrug formed designs are well known in the art, and depend on the substituents contained in compound of formula (I). For example, a substituent containing hydroxyl could be coupled to a carrier which renders the compound biologically inactive until it is removed by endogenous enzymes or, for example, by enzymes targeted to a particular receptor or location in the subject.

[0179] A compound of formula (I) that is acidic in nature (e.g., having a carboxyl or phenolic hydroxyl group) can form a pharmaceutically acceptable salt such as a sodium, potassium, calcium, or gold salt. Also within the scope of the invention are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines,

hydroxyalkylamines, and *N*-methylglycamine. A compound of formula (I) can be treated with an acid to form acid addition salts. Examples of such acids include hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, methanesulfonic acid, phosphoric acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, oxalic acid, malonic acid, salicyclic acid, malic acid, fumaric acid, ascorbic acid, maleic acid, acetic acid, and other mineral and organic acids well known to those skilled in the art. The acid addition salts can be prepared by treating a compound of formula (I) in its free base form with a sufficient amount of an acid (e.g., hydrochloric acid) to produce an acid addition salt (e.g., a hydrochloride salt). The acid addition salt can be converted back to its free base form by treating the salt with a suitable dilute aqueous basic solution (e.g., sodium hydroxide, sodium bicarbonate, potassium carbonate, or ammonia).

[0180] Some of the compounds of this invention may be crystallized or recrystallized from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilization.

[0181] Compounds of formula (I) may contain one or more asymmetric centers and thus can exist as enantiomers or diastereomers. It is to be understood that the invention includes both mixtures and separate individual isomers of compounds of the formula (I). Furthermore, certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

[0182] Compounds of formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers thereof.

[0183] Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

[0184] As used herein, the term "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-6 carbon atoms. An alkyl group can be straight or branched. Examples of an alkyl group include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, and *n*-hexyl. An alkyl group can be optionally substituted with one or more substituents such as alkoxy, cycloalkoxy, amino, nitro, carboxy, cyano, halo, hydroxyl, sulfo, or mercapto.

[0185] As used herein, the term "cycloalkyl" group refers to an aliphatic carbocyclic ring of 3-6 carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0186] As used herein, the term "haloalkyl" group refers to an alkyl group containing one or more halogen atoms. Examples of haloalkyl groups include fluoromethyl,

chloromethyl, bromomethyl, and trifluoromethyl.

[0187] As used herein, the term "halo" group refers to fluorine, chlorine, bromine, or iodine.

[0188] As used herein, the term "alkenyl" group refers to an aliphatic carbon group that contains 2-6 carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to, vinyl, allyl, isoprenyl, 2-butenyl, and 2-hexenyl. An alkenyl group can be optionally substituted with one or more substituents such as alkoxy, cycloalkoxy, amino, nitro, carboxy, cyano, halo, hydroxyl, sulfo, or mercapto.

[0189] As used herein, the term "alkynyl" group refers to an aliphatic carbon group that contains 2-6 carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, ethynyl, propargyl, and butynyl. An alkynyl group can be optionally substituted with one or more substituents such as alkoxy, cycloalkoxy, amino, nitro, carboxy, cyano, halo, hydroxyl, sulfo, or mercapto.

[0190] As used herein, the term "ALK5 and/or ALK4 inhibitor" refers to a compound, other than inhibitory Smads, e.g. Smad6 and Smad7, which selectively inhibits the ALK5 and/or ALK4 receptors preferentially over p38 or type II receptors.

[0191] As used herein, the term "ALK5 and/or ALK4-mediated diease state" refers to any disease state which is mediated (or modulated) by ALK5 and/or ALK4, for example, a disease which is modulated by the inhibition of the phosphorylation of Smad2 and Smad3 in the TGF-β and/or activin signaling pathways.

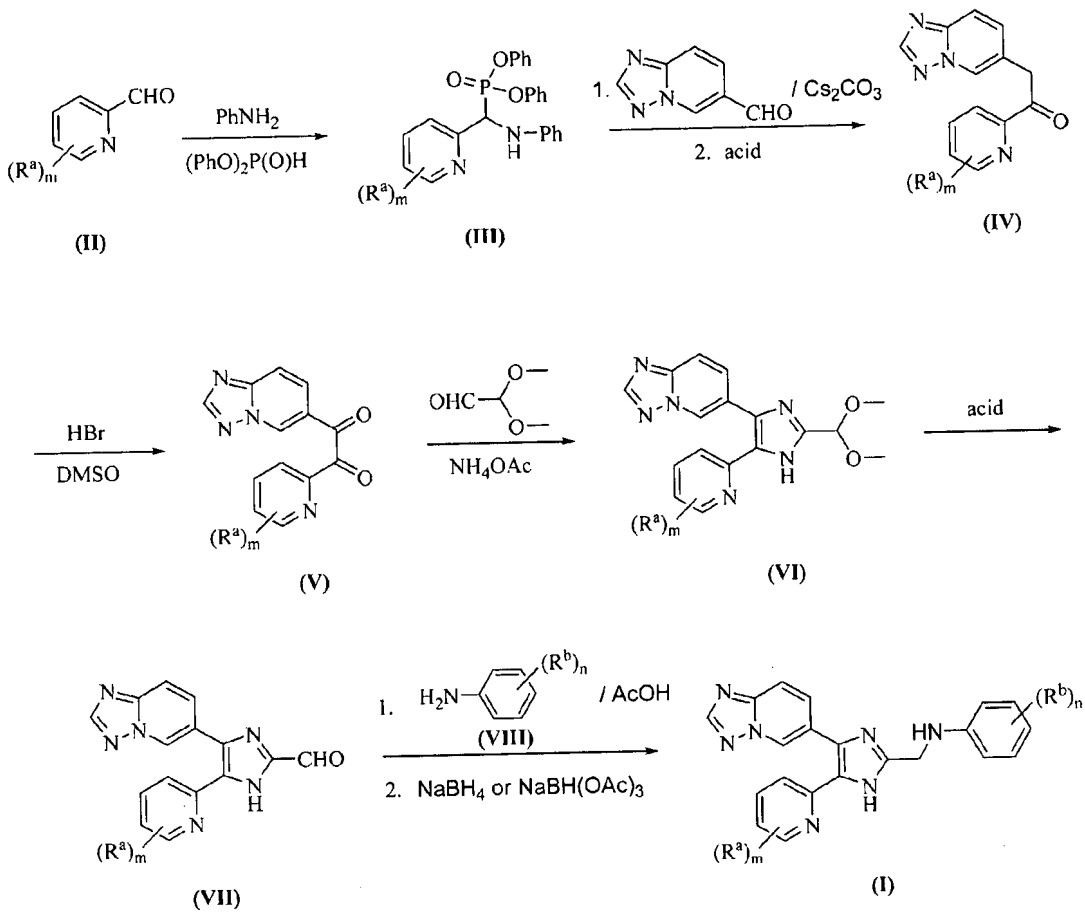
[0192] As used herein, the term "ulcers" is used to include, but not to be limited to, diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers.

[0193] Compounds of formula (I) may be prepared by a number of known methods from commercially available or known starting materials. If the starting materials are unavailable from a commercial source, they can be prepared by procedures known in the art.

[0194]

[0195] Scheme 1

[0196]



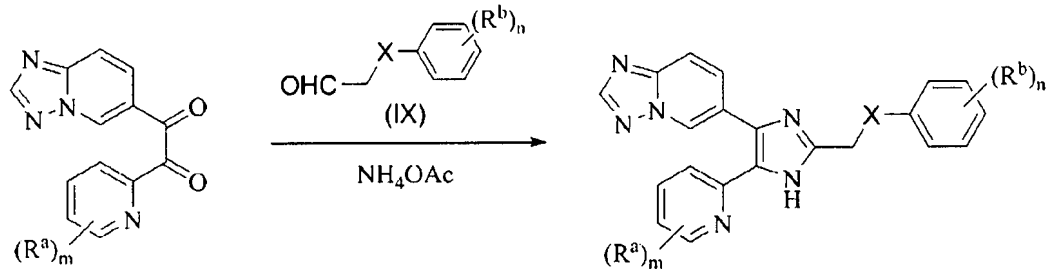
(II) (III) (IV) (V) (VI) (VII) (VIII) (I)

[0197] In one method, compounds of formula (I) wherein A^1 is N and A^2 is NH, or A^1 is NH and A^2 is N, and X is —NH— are prepared according to Scheme 1. Specifically, R^a-substituted pyridine-2-carbaldehyde (II) is reacted with aniline and diphenyl phosphite to give *N,P*-acetal (III), which can be further coupled with [1,2,4]triazolo[1,5-*a*]pyridine-6-carbaldehyde followed by hydrolysis in acidic condition to produce a monoketone (IV). The monoketone (IV) may be oxidized to a diketone (V) with HBr in DMSO. This diketone (V) can then be condensed with 2,2-dimethoxyacetaldehyde in the presence of ammonium acetate to yield an acetal-protected imidazole (VI), which can be hydrolyzed in acidic condition to produce an imidazole-2-carbaldehyde (VII). The imidazole-2-carbaldehyde (VII) can be coupled with R^b-substituted aniline (VIII) in the presence of an acid such as acetic acid to generate an immine, which can be further reduced with a reducing agent such as sodium borohydride or sodium triacetoxyborohydride to yield a compound of formula (I). R^a, R^b, m, and n have been defined as above.

[0198]

[0199] Scheme 2

[0200]



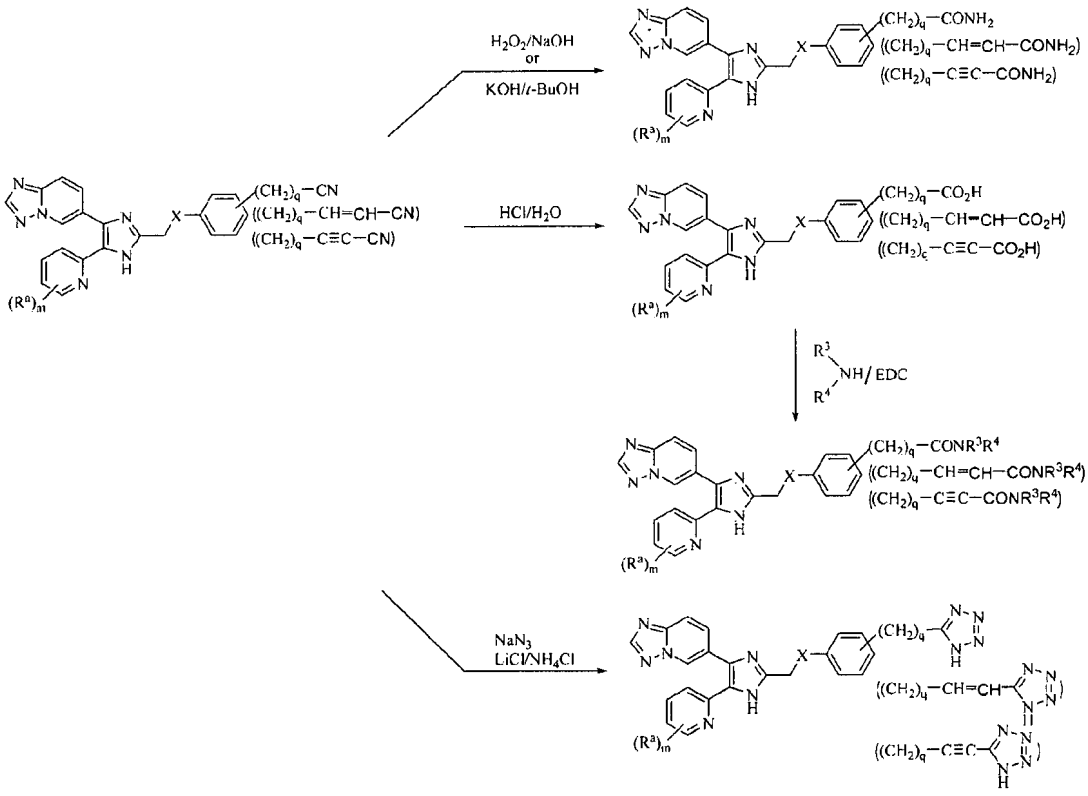
[0201] In another method, compounds of formula (I) wherein A^1 is N and A^2 is NH, or A^1 is NH and A^2 is N, and X is $—(CH_2)_p—$, —NR²—, —O—, or —S—, wherein p is 0 or 1, and R^2 is

[0202] C_{1-3}alkyl, are prepared according to Scheme 2. The diketone (V) can be condensed with an appropriate R^b-substituted aldehyde (IX) in the presence of ammonium acetate to yield a compound of formula (I). R^a, R^b, m, and n have been defined as above.

[0203]

[0204] Scheme 3

[0205]



[0206] Alternatively, when R^b compounds of formula (I) is $—(CH_2)_q—CN$, $—(CH_2)_q—CH=CH-CN$, or $—(CH_2)_q—C\equiv C—CN$, it can be further functionalized to form a compound of formula (I) as depicted in Scheme 3. R^a, R^3, R^4, X, m, and q have been

defined as above.

[0207] The resulting compounds of this invention represented by the formula (I)-(IX) can be separated and purified by appropriate conventional methods such as column chromatography and recrystallization.

[0208] Compounds of the invention may be administered by any suitable route, for example by oral, buccal, sub-lingual, rectal, vaginal, nasal, topical or parenteral (including intravenous, intramuscular, subcutaneous and intracoronary) administration.

[0209] The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

[0210] The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually, they will form up to about 80% of the formulation.

[0211] For administration to man in the curative or prophylactic treatment of the disorders identified above, oral, buccal or sub-lingual dosages of a compound of formula (I) will generally be in the range of from 50-5000 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 25-500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for parenteral administration will typically be within the range of from 25-250 mg per single dose as required. In practice the physician will determine the actual dosing regimen which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can be individual instances in which higher or lower dosage ranges may be merited, and such are within the scope of this invention.

[0212] For human use, a compound of formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound may be administered orally, buccally or sublingually, in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations may be prepared with pharmaceutically acceptable additives such as suspending agent (e.g. methylcellulose, a semi-synthetic glyceride such as witepsol or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters or mixtures of PEG-8 and

caprylic/capric glycerides). A compound may also be injected parenterally, for example intravenously, intramuscularly, subcutaneously or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which may contain other substances, for example, salts, or monosaccharides such as mannitol or glucose, to make the solution isotonic with blood.

[0213] Thus, the invention provides in a further aspect a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, together with a pharmaceutically acceptable diluent or carrier therefor.

[0214] The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing either entity, for use in therapy.

[0215] The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition containing either entity, for the manufacture of a medicament for the treatment of a disease, mediated by the ALK5 and/or ALK4 receptors in mammals.

[0216] ALK5- and/or ALK4-mediated disease states include, but are not limited to glomerulonephritis, diabetic nephropathy, lupus nephritis, hypertension-induced nephropathy, renal interstitial fibrosis, renal fibrosis resulting from complications of drug exposure, HIV-associated nephropathy, transplant nephropathy, liver fibrosis due to all etiologies, hepatic dysfunction attributable to infections, alcohol-induced hepatitis, disorders of the biliary tree, cystic fibrosis, pulmonary fibrosis, interstitial lung disease, acute lung injury, adult respiratory distress syndrome, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary disease due to infectious or toxic agents, post-infarction cardiac fibrosis, congestive heart failure, dilated cardiomyopathy, myocarditis, intimal thickening, vascular stenosis, hypertension-induced vascular remodeling, pulmonary arterial hypertension, coronary restenosis, peripheral restenosis, carotid restenosis, stent-induced restenosis, atherosclerosis, ocular scarring, corneal scarring, proliferative vitreoretinopathy, glaucoma, intraocular pressure, excessive or hypertrophic scar or keloid formation in the dermis occurring during wound healing resulting from trauma or surgical wounds, peritoneal and sub-dermal adhesion, scleroderma, fibrosclerosis, progressive systemic sclerosis, dermatomyositis, polymyositis, arthritis, osteoporosis, ulcers, impaired neurological function, male erectile dysfunction, Peyronie's disease, Dupuytren's contracture, Alzheimer's disease, Raynaud's syndrome, radiation-induced fibrosis, thrombosis, tumor metastasis growth, multiple myeloma, melanoma, glioma, glioblastomas, leukemia, sarcomas, leiomyomas, mesothelioma, and carcinomas of lung, breast, colon, kidney, ovary, cervix, liver, biliary tract, gastrointestinal tract, pancreas, prostate, head, and neck.

[0217] The invention further provides a method of inhibiting the TGF-β and/or activin

signaling pathways in human, for example, inhibiting the phosphorylation of Smad2 or Smad3 by ALK5 and/or ALK4.

[0218] The invention further provides a method of reducing the accumulation of excess extracellular matrix in human by inhibiting the TGF-β and/or activin signaling pathways, for example, inhibiting the phosphorylation of Smad2 or Smad3 by ALK5 and/or ALK4.

[0219] The invention further provides a method of treating, preventing, or reducing metastasis of tumor cells in human by inhibiting the TGF-β signaling pathway.

[0220] The invention further provides a method of treating, preventing, or reducing carcinomas mediated by an overexpression of TGF-β in human by inhibiting the TGF-β signaling pathway.

[0221] The invention further provides a method of treating, preventing, or reducing vascular injuries in human by inhibiting the TGF-β signaling pathway.

[0222]

[0223] The present invention is further illustrated in the following Examples, which should not be taken to limit the scope of the invention described in the claims. In the Examples, electrospray ionization mass spectra (ESI-MS) were obtained on a Q-Tof2 mass spectrometer (Micromass, Manchester, UK).

[0224]

[0225] EXAMPLES

[0226]

[0227] Preparative Example 1

[0228]

[0229] Preparation of diphenyl (6-methylpyridin-2-yl)(phenylamino)methylphosphonate (a compound of the formula **(III)** wherein $R^a = CH_3$)

[0230] A mixture of 6-methylpyridine-2-carboxaldehyde (2.12 g, 17.50 mmol), aniline (1.63 g, 17.50 mmol), diphenyl phosphite (4.92 g, 21.00 mmol), and zirconyl chloride octahydrate (0.56 g, 1.75 mmol) was stirred at room temperature 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the CH_2Cl_2 solution was washed with water (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give the titled compound (6.96 g, 92%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (t, 1 H, J = 7.8 Hz), 7.38 (dd, 1 H, J = 7.6, 2.0 Hz), 7.27-7.22 (m, 4 H), 7.19-7.15 (m, 2 H), 7.14-7.07 (m, 4 H), 7.05-7.02 (m, 3 H), 6.80-6.74 (m, 3 H), 5.53 (pseudo t, 1 H, J = 7.4 Hz), 5.36 (dd, 1 H, J = 21.0, 8.2 Hz), 2.54 (s, 3 H).

[0231]

[0232] Preparative Example 2

[0233]

[0234] Preparation of diphenyl (6-ethylpyridin-2-yl)(phenylamino)methylphosphonate (a compound of the formula (**III**) wherein $R^a = CH_2CH_3$)

[0235] The titled compound was prepared as described in Preparative Example 1 by using 6-ethylpyridine-2- carboxaldehyde in place of 6-methylpyridine-2-carboxaldehyde. Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (t, 1 H, J = 7.6 Hz), 7.38 (dd, 1 H, J = 7.6, 2.0 Hz), 7.26-7.09 (m, 8 H), 7.07-7.00 (m, 5 H), 5.59 (pseudo t, 1 H, J = 7.0 Hz), 5.34 (dd, 1 H, J = 20.8, 8.0 Hz), 2.82 (q, 2 H, J = 7.6 Hz), 1.28 (t, 3 H, J = 7.6 Hz).

[0236]

[0237] Preparative Example 3

[0238]

[0239] Preparation of 2-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-1-(6-methylpyridin-2-yl)ethanone (a compound of the formula (**IV**) wherein $R^a = CH_3$)

[0240] To a stirred solution of [1,2,4]triazolo[1,5-*a*]pyridine-6-carbaldehyde (2.50 g, 17.01 mmol) (prepared according to the method described in WO 03/087304 A2) and diphenyl (6-methylpyridin-2-yl)(phenylamino)methylphosphonate (7.32 g, 17.01 mmol) in a mixture of THF (40 mL) and *i*-PrOH (10 mL) was added Cs_2CO_3 (7.20 g, 22.11 mmol), and the mixture was stirred at room temperature overnight. A solution of 3 N HCl (25 mL) was added dropwise to the reaction mixture, and the mixture was stirred for 1 h. It was then diluted with *tert*-butyl methyl ether (40 mL) and extracted with 1 N HCl (2 × 35 mL). The aqueous extracts were neutralized with 50% KOH until pH 7-8 was reached. The precipitates were collected by filtration, washed with water, and dried over P_2O_5*in vacuo* to give the titled compound (3.41 g, 80%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, 1 H, J = 0.8 Hz), 8.31 (s, 1 H), 7.88 (dd, 1 H, J = 7.6, 1.6 Hz), 7.73 (t, 1 H, overlapped, J = 7.6 Hz), 7.71 (dd, 1 H, overlapped, J = 9.2, 0.8 Hz), 7.54 (dd, 1 H, J = 9.2, 1.6 Hz), 7.37 (dd, 1 H, J = 7.6, 1.6 Hz), 4.62 (s, 2 H), 2.67 (s, 3 H).

[0241]

[0242] Preparative Example 4

[0243]

[0244] Preparation of 2-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-1-(6-ethylpyridin-2-yl)ethanone (a compound of the formula (**IV**) wherein $R^a = CH_2CH_3$)

[0245] The titled compound was prepared as described in Preparative Example 3 by using diphenyl (6-ethylpyridin-2-yl)(phenylamino)methylphosphonate in place of diphenyl (6-methylpyridin-2-yl)(phenylamino)methylphosphonate. Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (dd, 1 H, J = 1.6, 0.8 Hz), 8.29 (s, 1 H), 7.88 (br d, 1 H, J = 7.6 Hz), 7.74 (t, 1 H, J = 7.6 Hz), 7.70 (dd, 1 H, J = 9.2, 0.8 Hz), 7.54 (dd, 1 H, J = 9.2, 1.6

Hz), 7.37 (dd, 1 H, J = 7.6, 0.8 Hz), 4.62 (s, 2 H), 2.93 (q, 2 H, J = 7.6 Hz), 1.39 (t, 3 H, J = 7.6 Hz).

[0246]

[0247] Preparative Example 5

[0248]

[0249] Preparation of 1-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione (a compound of the formula (**V**) wherein $R^a = CH_3$)

[0250] To a stirred suspension of 2-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-1-(6-methylpyridin-2-yl)ethanone (6.20 g, 24.57 mmol) in DMSO (48 mL) was added dropwise HBr (48 wt. % in water, 5.96 g, 12.4 mL) at 0°C, and the mixture was heated at 60-70°C. After 2 h, the reaction mixture was cooled to 0°C, poured onto ice water (20 mL), and basified to pH 10 with solid K_2CO_3.The mixture was extracted with $CHCl_3$ (2 × 250 mL), and the organic phase was washed with water (2 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of MeOH and CH_2Cl_2 as eluent to give the titled compound (6.02 g, 92%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (dd, 1 H, J = 1.6, 1.2 Hz), 8.47 (s, 1 H), 8.14 (dd, 1 H, J = 9.2, 1.6 Hz), 8.04 (br d, 1 H, J = 7.6 Hz), 7.88 (dd, 1 H, J = 9.2, 1.2 Hz), 7.84 (t, 1 H, J = 7.8 Hz), 7.42 (br d, 1 H, J = 8.0 Hz), 2.49 (s, 3 H).

[0251]

[0252] Preparative Example 6

[0253]

[0254] Preparation of 1-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-2-(6-ethylpyridin-2-yl)ethane-1,2-dione (a compound the of formula (**V**) wherein $R^a = CH_2CH_3$)

[0255] The titled compound was prepared as described in Preparative Example 5 by using 2-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-1-(6-ethylpyridin-2-yl)ethanone in place of 2-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-1-(6-methylpyridin-2-yl)ethanone. Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (dd, 1 H, J = 1.6, 0.8 Hz), 8.42 (s, 1 H), 8.08 (dd, 1 H, J = 9.2, 1.6 Hz), 7.98 (br d, 1 H, J = 7.6 Hz), 7.83 (dd, 1 H, overlapped, J = 9.2, 0.8 Hz), 7.82 (t, 1 H, overlapped, J = 7.6 Hz), 7.38 (br d, 1 H, J = 7.6 Hz), 2.71 (q, 2 H, J = 7.6 Hz), 1.08 (t, 3 H, J = 7.6 Hz).

[0256]

[0257] Preparative Example 7

[0258]

[0259] Preparation of 6-(2-(dimethoxymethyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (a compound of the formula (**VI**) wherein

$R^a = CH_3$)

[0260] A stirred solution of 1-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione (6.00 g, 22.49 mmol) in *tert*-butyl methyl ether (120 mL) was treated with glyoxal dimethyl acetal (60 wt. % solution in water, 7.8 mL, 44.98 mmol). NH_4OAc (4.33 g, 56.2 mmol) in MeOH (60 mL) was added to it, and the resulting mixture was stirred at room temperature for 3 h. The pH of the reaction was adjusted to 8 with saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with $CHCl_3$ (2 × 150 mL), and the $CHCl_3$ solution was washed with water (100 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of MeOH and CH_2Cl_2 as eluent to give the titled compound (6.13 g, 78%) as a light yellow foam. ^1H NMR (400 MHz, $CDCl_3$): δ 10.54 (br s, 1 H), 8.96 (s, 1 H), 8.36 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.77 (dd, 1 H, J = 9.2, 0.8 Hz), 7.47 (t, 1 H, J = 7.8 Hz), 7.23 (d, 1 H, J = 7.6 Hz), 7.04 (d, 1 H, J = 8. 0 Hz), 5.57 (s, 1 H), 3.48 (s, 6 H), 2.58 (s, 3 H).

[0261]

[0262] Preparative Example 8

[0263]

[0264] Preparation of 6-(2-(dimethoxymethyl)-5-(6-ethylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (a compound of the formula (**VI**) wherein $R^a = CH_2CH_3$)

[0265] The titled compound was prepared as described in Preparative Example 7 by using 1-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-2-(6-ethylpyridin-2-yl)ethane-1,2-dione in place of 1-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione. Yield: 68%; ^1H NMR (400 MHz, $CDCl_3$): δ 10.67 (br s, 1 H), 8.97 (br s, 1 H), 8.35 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.76 (dd, 1 H, J = 9.2, 0.8 Hz), 7.50 (t, 1 H, J = 7.8 Hz), 7.25 (br d, 1 H, J = 7.6 Hz), 7.05 (d, 1 H, J = 8.0 Hz), 5.56 (s, 1 H), 3.46 (s, 6 H), 2.83 (q, 2 H, J = 7.6 Hz), 1.31 (t, 3 H, J = 7.6 Hz).

[0266]

[0267] Preparative Example 9

[0268]

[0269] Preparation of 4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazole-2-carbaldehyde (a compound of the formula (**VII**) wherein $R^a = CH_3$)

[0270] 6-(2-(Dimethoxymethyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (6.00 g, 17.12 mmol) was dissolved in 1 N HCl (120 mL), and the mixture was heated at 70°C for 3 h. The reaction mixture was allowed to cool to 0°C, and then it was neutralized with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with 10% MeOH in $CHCl_3$ (3 × 200 mL), and the organic phase was dried

over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure to give the titled compound (4.69 g, 90%) as a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1 H), 9.01 (br s, 1 H), 8.41 (s, 1 H), 7.85 (dd, 1 H, J = 9.2, 0.8 Hz), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.55 (t, 1 H, J = 7.8 Hz), 7.33 (br s, 1 H), 7.16 (d, 1 H, J = 8. 0 Hz), 2.60 (s, 3 H).

[0271]

[0272] Preparative Example 10

[0273]

[0274] Preparation of 4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-ethylpyridin-2-yl)-1*H* -imidazole-2-carbaldehyde (a compound of the formula (**VII**) wherein $R^a = CH_2CH_3$)

[0275] The titled compound was prepared as described in Preparative Example 9 by using 6-(2-(dimethoxymethyl)-5-(6-ethylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine in place of 6-(2-(dimethoxymethyl)-5-(6-methylpyridin-2-yl)-1*H* -imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. Yield: 99%; ^1H NMR (400 MHz, DMSO-d_6) δ 9.86 (t, 1 H, J = 1.2 Hz), 9.59 (s, 1 H), 8.43 (s, 1 H), 8.21 (dd, 1 H, J = 9.2, 1.6 Hz), 7.82 (br d, 1 H, J = 8.0 Hz), 7.73 (dd, 1 H, J = 9.2, 0.8 Hz), 7.69 (t, 1 H, J = 7.8 Hz), 7.08 (br d, 1 H, J = 7.6 Hz), 2.71 (q, 2 H, J = 7.6 Hz), 1.16 (t, 3 H, J = 7.6 Hz).

[0276]

[0277] Preparative Example 11

[0278]

[0279] Preparation of 3-amino-5-(dimethylamino)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 3-cyano-5-dimethylamino). This compound was prepared by the following 2 steps.

[0280] 3-Bromo-*N,N*-dimethyl-5-nitroaniline (1.73 g, 7.06 mmol) (prepared according to the method described in *J. Org. Chem.* 60: 5091-5103 (2003)), pyridine (24 mL), and CuCN (1.26 g, 2.14 mmol) were added to a dry sealed tube. The mixture was heated at 220°C with stirring for 3.5 h. The reaction mixture was allowed to cool to 100°C, poured into a flask containing a mixture of aqueous ammonia (100 mL) and water (100 mL), and extracted with EtOAc (2 × 100 mL). The EtOAc solution was washed with diluted ammonia solution (100 mL), water (100 mL) and brine (100 mL) successively, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 3-(dimethylamino)-5-nitrobenzonitrile (0.44 g, 33%) as an orange solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, 1 H, J = 2.0, 1.2 Hz), 7.65 (t, 1 H, J = 2.2 Hz), 7.11 (dd, 1 H, J = 2.4, 1.2 Hz), 3.10 (s, 6 H).

[0281] The above nitro compound, 3-(dimethylamino)-5-nitrobenzonitrile (0.42 g, 2.22 mmol) in methanol (80 mL) was hydrogenated in the presence of 10% Pd/C (0.04 g)

under a hydrogen gas atmosphere overnight. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give the titled compound (0.29 g, 80%) as a brown viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (dd, 1 H, J = 2.4, 1.6 Hz), 6.28 (dd, 1 H, J = 2.0, 1.6 Hz), 6.14 (t, 1 H, J = 2.2 Hz), 3.76 (br s, 2 H), 2.92 (s, 6 H).

[0282]

[0283] Preparative Example 12

[0284]

[0285] Preparation of 3-((dimethylamino)methyl)-2-fluroaniline (a compound of the formula (**VIII**) wherein R^b = 3-(dimethylamino)methyl-2-fluoro). This compound was prepared by the following 3 steps started with commercially available 2-fluoro-1-methyl-3-nitrobenzene.

[0286] A stirred solution of 2-fluoro-1-methyl-3-nitrobenzene (15.80 g, 101.94 mmol) and *N*-bromosuccinimide (18.14 g, 101.94 mmol) in CCl_4 (400 mL) was treated with benzoyl peroxide (0.37 g, 1.52 mmol). The mixture was heated at reflux temperature overnight and then cooled to room temperature. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL) and filtered again. The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 1-(bromomethyl)-2-fluoro-3-nitrobenzene (8.11 g, 34%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (m, 1 H), 7.71 (m, 1 H), 7.30 (td, 1 H, J = 8.4, 1.6 Hz), 4.55 (d, 2 H, J = 1.6 Hz).

[0287] To a stirred mixture of 1-(bromomethyl)-2-fluoro-3-nitrobenzene (0.70 g, 2.99 mmol) and dimethylamine hydrochloride (0.48 g, 5.98 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.91 g, 8.97 mmol) dropwise. The mixture was stirred at room temperature for 3 h and evaporated to dryness under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (2 × 25 mL). The EtOAc solution was washed with water (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 1-(2-fluoro-3-nitrophenyl)-*N*,*N*-dimethylmethanamine (0.45 g, 76%) as a yellow viscous liquid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.04-7.99 (m, 1 H), 7.78-7.73 (m, 1 H), 7.37 (td, 1 H, J = 8.0, 1.0 Hz), 3.64 (d, 2 H, J = 2.0 Hz), 2.29 (d, 6 H, J = 0.8 Hz).

[0288] A mixture of the above nitro compound, 1-(2-fluoro-3-nitrophenyl)-*N*,*N*-dimethylmethanamine (0.45 g, 1.93 mmol), iron powder (1.35 g, 2.41 mmol), 2 N HCl (1 mL), and ethanol (5 mL) was heated at reflux temperature with stirring for 2 h. After cooling to room temperature, the mixture was filtered through a Celite pad. The filtrate

was evaporated to dryness under reduced pressure, and the residue was diluted with water (10 mL) and basified with solid K_2CO_3 to pH 10. The aqueous mixture was extracted with EtOAc (2 × 25 mL), and the EtOAc solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give the titled compound (0.35 g, 91%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (td, 1 H, J = 7.8, 1.0 Hz), 6.72-6.67 (m, 2 H), 3.71 (br s, 2 H), 3.47 (d, 2 H, J = 1.6 Hz), 2.27 (s, 6 H).

[0289]

[0290] Preparative Example 13

[0291]

[0292] Preparation of 2-fluoro-3-(pyrrolidin-1-ylmethyl)aniline (a compound of the formula (**VIII**) wherein R^b = 2-fluoro-3-(pyrrolidin-1-ylmethyl))

[0293] To a stirred solution of 1-(bromomethyl)-2-fluoro-3-nitrobenzene (2.00 g, 8.54 mmol) and pyrrolidine (0.91 g, 12.82 mmol) in CH_2Cl_2 (15 mL) was added tri-ethylamine (1.72 g, 17.08 mmol) dropwise at 0°C. The mixture was stirred at room temperature overnight and then evaporated to dryness under reduced pressure. The residue was diluted with water (15 mL) and extracted with EtOAc (2 × 30 mL). The EtOAc solution was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 1-(2-fluoro-3-nitrobenzyl)pyrrolidine (1.20 g, 63%) as a viscous oil. ^{1}H NMR (400 MHz, CD_3OD): δ 8.02-7.97 (m, 1 H), 7.81-7.76 (m, 1 H), 7.36 (td, 1 H, J = 8.0, 1.2 Hz), 3.81 (d, 1 H, J = 2.0 Hz), 2.62-2.58 (m, 4 H), 1.84-1.80 (m, 4 H).

[0294] The titled compound was prepared as described in Preparative Example 12 by using 1-(2-fluoro-3-nitrobenzyl)pyrrolidine in place of 1-(2-fluoro-3-nitrophenyl)-*N*,*N*-dimethylmethanamine. Yield: 80%; ^{1}H NMR (400 MHz, CD_3OD): δ 6.87 (td, 1 H, J = 8.0, 0.8 Hz), 6.77 (td, 1 H, J = 8.0, 2.0 Hz), 6.68-6.64 (m, 1 H), 3.67 (d, 2 H, J = 1.6 Hz), 2.60-2.57 (m, 4 H), 1.82-1.78 (m, 4 H).

[0295]

[0296] Preparative Example 14

[0297]

[0298] Preparation of 2-fluoro-3-(morpholinomethyl)aniline (a compound of the formula (**VIII**) wherein R^b = 2-fluoro-3-(morpholinomethyl))

[0299] A stirred solution of 1-(bromomethyl)-2-fluoro-3-nitrobenzene (2.50 g, 10.6 mmol) and morpholine (2.78 g, 32.0 mmol) in toluene (24 mL) was heated at reflux tem-perature for 2.5 h. The reaction mixture was allowed to cool to room temperature and then washed with 1 N NaOH (2 × 20 mL). The aqueous layer was extracted with

EtOAc (2 x 25 mL), and the combined toluene solution and EtOAc extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 4-(2-fluoro-3-nitrobenzyl)morpholine (1.95 g, 89%) as a light yellow solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.02-7.97 (m, 1 H), 7.83-7.78 (m, 1 H), 7.36 (td, 1 H, J = 8.0, 1.0 Hz), 3.70-3.67 (m, 6 H), 2.51 (br t, 4 H, J = 4.6 Hz).

[0300] The titled compound was prepared as described in Preparative Example 12 by using (4-(2-fluoro-3-nitrobenzyl)morpholine) in place of 1-(2-fluoro-3-nitrophenyl)-*N*,*N*-dimethylmethanamine. Yield: 90%; ^{1}H NMR (400 MHz, CD_3OD): δ 6.87 (td, 1 H, J = 8.0, 0.8 Hz), 6.77 (td, 1 H, J = 8.0, 2.0 Hz), 6.68-6.64 (m, 1 H), 3.68 (br t, 4 H, J = 4.8 Hz), 3.55 (d, 2 H, J = 1.6 Hz), 2.49 (br t, 4 H, J = 4.8 Hz).

[0301]

[0302] Preparative Example 15

[0303]

[0304] Preparation of 3-amino-4-((dimethylamino)methyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 5-cyano-2-(dimethylamino)methyl)

[0305] To a stirred mixture of 4-(bromomethyl)-3-nitrobenzonitrile (5.00 g, 20.74 mmol) (prepared according to the method described in WO 07/024945 A1) and dimethylamine hydrochloride (2.03 g, 24.89 mmol) in CH_2Cl_2 (70 mL) was added tri-ethylamine (6.30 g, 62.23 mmol) dropwise at 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 4-((dimethylamino)methyl)-3-nitrobenzene (3.58 g, 84%) as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (br s, 1 H), 7.92 (br s, 1 H), 7.85 (br d, 1 H, J = 7.2 Hz), 3.80 (s, 2 H), 2.27 (s, 6 H).

[0306] The titled compound was prepared as described in Preparative Example 11 by using 4-((dimethylamino)methyl)-3-nitrobenzonitrile in place of 3-(dimethylamino)-5-nitrobenzonitrile. Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (dd, 1 H, J = 7.6, 0.4 Hz), 6.91 (dd, 1 H, J = 7.6, 1.6 Hz), 6.84 (d, 1 H, J = 1.6 Hz), 5.05 (br s, 2 H), 3.43 (s, 2 H), 2.18 (s, 6 H).

[0307]

[0308] Preparative Example 16

[0309]

[0310] Preparation of 3-amino-2-((dimethylamino)methyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 3-cyano-2-(dimethyamino)methyl)

[0311] To a stirred mixture of 2-(bromomethyl)-3-nitrobenzonitrile (1.10 g, 4.56 mmol) (prepared according to the method described in *Tetrahedron* 40: 1863-1868 (1984)) and dimethylamine hydrochloride (0.74 g, 9.13 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (1.85 g, 18.25 mmol) dropwise at 0°C. The resulting mixture was stirred at room temperature for 2 h and evaporated to dryness under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (3 × 50 mL). The EtOAc solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 2-((dimethylamino)methyl)-3-nitrobenzonitrile (0.75 g, 80%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (br d, 1 H, J = 8.0 Hz), 7.85 (dd, 1 H, J = 8.0, 1.4 Hz), 7.55 (t, 1 H, J = 8.0 Hz), 3.94 (s, 2 H), 2.24 (s, 6 H).

[0312] The titled compound was prepared as described in Preparative Example 11 by using 2-((dimethylamino)methyl)-3-nitrobenzonitrile in place of 3-(dimethylamino)-5-nitrobenzonitrile. Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (t, 1 H, J = 7.6 Hz), 7.00 (dd, 1 H, J = 7.6, 0.8 Hz), 6.83 (d, 1 H, J = 7.6 Hz), 5.06 (br s, 2 H), 3.73 (s, 2 H), 2.29 (s, 6 H).

[0313]

[0314] Preparative Example 17

[0315]

[0316] Preparation of 3-amino-5-((dimethylamino)methyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 3-cyano-5-(dimethylamino)methyl)

[0317] To a stirred mixture of 3-(bromomethyl)-5-nitrobenzonitrile (1.50 g, 6.22 mmol) (prepared according to the method described in *J. Org. Chem.* 55: 1040-1043 (1990)) and dimethylamine hydrochloride (1.01 g, 12.44 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (1.88 g, 18.66 mmol) dropwise at 0°C. The resulting mixture was stirred at room temperature for 3 h and evaporated to dryness under reduced pressure. The residue was diluted with water (15 mL) and extracted with EtOAc (3 × 50 mL). The EtOAc solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 3-((dimethylamino)methyl)-5-nitrobenzonitrile (1.10 g, 87%) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1 H), 8.40 (d, 1 H, J = 1.6 Hz), 8.01 (s, 1 H), 3.59 (s, 2 H), 2.30 (s, 6 H).

[0318] The titled compound was prepared as described in Preparative Example 11 by using 3-((dimethylamino)methyl)-5-nitrobenzonitrile in place of 3-(dimethylamino)-5-nitrobenzonitrile. Yield: 98%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (m, 1 H), 6.88 (br d, 1 H, J = 0.8 Hz), 6.80 (dd, 1 H, J = 2.4, 1.6 Hz), 3.86 (br s, 2

H), 3.34 (s, 2 H), 2.24 (s, 6 H).

[0319]

[0320] Preparative Example 18

[0321]

[0322] Preparation of 3-amino-4-(pyrrolidin-1-ylmethyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 5-cyano-2-(pyrrolidin-1-ylmethyl))

[0323] To a stirred solution of 4-(bromomethyl)-3-nitrobenzonitrile (5.12 g, 21.57 mmol) and pyrrolidine (1.84 g, 25.88 mmol) in CH_2Cl_2 (72 mL) was added triethylamine (6.54 g, 64.71 mmol) dropwise at 0°C. The mixture was stirred at room temperature for 1.5 h and evaporated to dryness under reduced pressure. The residue was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 3-nitro-4-(pyrrolidin-1-ylmethyl)benzonitrile (2.24 g, 45%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, 1 H, J = 1.6 Hz), 7.94 (br d, 1 H, J = 8.0 Hz), 7.83 (dd, 1 H, J = 8.0, 1.6 Hz), 3.99 (s, 2 H), 2.54 (br s, 4 H), 1.79 (m, 4 H).

[0324] The titled compound was prepared as described in Preparative Example 11 by using 3-nitro-4-(pyrrolidin-1-ylmethyl)benzonitrile in place of 3-(dimethylamino)-5-nitrobenzonitrile. Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, 1 H, J = 7.6 Hz), 6.91 (dd, 1 H, J = 7.6, 1.6 Hz), 6.84 (d, 1 H, J = 1.6 Hz), 5.08 (br s, 2 H), 3.64 (s, 2 H), 2.47 (br s, 4 H), 1.78 (br s, 4 H).

[0325]

[0326] Preparative Example 19

[0327]

[0328] Preparation of 3-amino-2-(pyrrolidin-1-ylmethyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 3-cyano-2-(pyrrolidin-1-ylmethyl))

[0329] To a stirred solution of 2-(bromomethyl)-3-nitrobenzonitrile (1.10 g, 4.56 mmol) and pyrrolidine (0.65 g, 9.13 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (1.85 g, 18.25 mmol) dropwise at 0°C. The mixture was stirred at room temperature for 2 h and evaporated to dryness under reduced pressure. The residue was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 3-nitro-2-(pyrrolidin-1-ylmethyl)benzonitrile (0.96 g, 91%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 1 H, J = 7.6 Hz), 7.83 (dd, 1 H, J = 7.6, 0.8 Hz), 7.52 (t, 1 H, J = 7.6 Hz), 4.14 (s, 2 H), 2.52 (br s, 4 H), 1.72 (br s, 4 H).

[0330] The titled compound was prepared as described in Preparative Example 11 by using 3-nitro-2-(pyrrolidin-1-ylmethyl)benzonitrile in place of

3-(dimethylamino)-5-nitrobenzonitrile. Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (t, 1 H, J = 7.8 Hz), 6.99 (dd, 1 H, J = 7.8, 1.2 Hz), 6.82 (d, 1 H, J = 8.0 Hz), 5.11 (br s, 2 H), 3.91 (s, 2 H), 2.58 (br s, 4 H), 1.81 (br s, 4 H).

[0331]

[0332] Preparative Example 20

[0333]

[0334] Preparation of 3-amino-5-(pyrrolidin-1-ylmethyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 3-cyano-5-(pyrrolidin-1-ylmethyl))

[0335] To a stirred solution of 3-(bromomethyl)-5-nitrobenzonitrile (1.50 g, 6.22 mmol) and pyrrolidine (0.53 g, 7.46 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (1.88 g, 18.68 mmol) dropwise at 0°C, and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was diluted with water (15 mL) and extracted with EtOAc (3 × 50 mL). The EtOAc solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 3-nitro-5-(pyrrolidin-1-ylmethyl)benzonitrile (1.30 g, 90%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br s, 1 H), 8.39 (br t, 1 H, J = 1.6 Hz), 8.02 (br s, 1 H), 3.78 (s, 2 H), 2.56 (br s, 4 H), 1.84 (br s, 4 H).

[0336] The titled compound was prepared as described in Preparative Example 11 by using 3-nitro-5-(pyrrolidin-1-ylmethyl)benzonitrile in place of 3-(dimethylamino)-5-nitrobenzonitrile. Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (pseudo t, 1 H, J = 1.6 Hz), 6.94 (pseudo t, 1 H, J = 1.6 Hz), 6.79 (dd, 1 H, J = 2.4, 1.6 Hz), 3.87 (br s, 2 H), 3.56 (s, 2 H), 2.54 (m, 4 H), 1.81 (m, 4 H).

[0337]

[0338] Preparative Example 21

[0339]

[0340] Preparation of 3-amino-4-(morpholinomethyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 5-cyano-2-(morpholinomethyl))

[0341] To a stirred solution of 4-(bromomethyl)-3-nitrobenzonitrile (7.12 g, 29.55 mmol) and morpholine (3.09 g, 35.45 mmol) in CH_2Cl_2 (98 mL) was added triethylamine (8.97 g, 88.64 mmol) dropwise at 0°C. The mixture was stirred at room temperature for 1.5 h and evaporated to dryness under reduced pressure. The residue was diluted with water (40 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The CH_2Cl_2 solution was washed with water (50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 4-(morpholinomethyl)-3-nitrobenzonitrile (5.84 g, 80%) as a yellow solid. ^{1}H NMR

(400 MHz, $CDCl_3$): δ 8.12 (s, 1 H), 7.83 (br s, 2 H), 3.84 (s, 2 H), 3.67 (t, 4 H, J = 4.6 Hz), 2.45 (t, 4 H, J = 4.6 Hz).

[0342] The titled compound was prepared as described in Preparative Example 11 by using 4-(morpholinomethyl)-3-nitrobenzonitrile in place of 3-(dimethylamino)-5-nitrobenzonitrile. Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, 1 H, J = 8.0 Hz), 6.92 (dd, 1 H, J = 8.0, 1.6 Hz), 6.86 (d, 1 H, J = 1.6 Hz), 5.02 (br s, 2 H), 3.68 (br t, 4 H, J = 4.0 Hz), 3.53 (s, 2 H), 2.41 (br s, 4 H).

[0343]

[0344] Preparative Example 22

[0345]

[0346] Preparation of 3-amino-2-(morpholinomethyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 3-cyano-2-(morpholinomethyl))

[0347] To a stirred solution of 2-(bromomethyl)-3-nitrobenzonitrile (1.10 g, 4.56 mmol) and morpholine (0.80 g, 9.13 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (1.85 g, 18.25 mmol) dropwise at 0°C. The mixture was stirred at room temperature for 1.5 h and evaporated to dryness under reduced pressure. The residue was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 2-(morpholinomethyl)-3-nitrobenzonitrile (1.02 g, 90%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (br d, 1 H, J = 8.0 Hz), 7.84 (dd, 1 H, J = 8.0, 1.2 Hz), 7.56 (t, 1 H, J = 8.0 Hz), 3.99 (s, 2 H), 3.60 (br t, 4 H, J = 4.4 Hz), 2.46 (br s, 4 H).

[0348] The titled compound was prepared as described in Preparative Example 11 by using 2-(morpholinomethyl)-3-nitrobenzonitrile in place of 3-(dimethylamino)-5-nitrobenzonitrile. Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (t, 1 H, J = 7.6 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.83 (d, 1 H, J = 7.6 Hz), 5.00 (br s, 2 H), 3.78 (s, 2 H), 3.69 (br s, 4 H), 2.50 (br s, 4 H).

[0349]

[0350] Preparative Example 23

[0351]

[0352] Preparation of 3-amino-5-(morpholinomethyl)benzonitrile (a compound of the formula (**VIII**) wherein R^b = 3-cyano-5-(morpholinomethyl))

[0353] To a stirred solution of 3-(bromomethyl)-5-nitrobenzonitrile (1.50 g, 6.22 mmol) and morpholine (0.65 g, 7.46 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (1.88 g, 18.66 mmol) dropwise at 0°C. The mixture was stirred at room temperature overnight and then evaporated to dryness under reduced pressure. The residue was diluted with water (15 mL) and extracted with EtOAc (3 × 50 mL). The EtOAc solution was dried

over anhydrous Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 3-(morpholinomethyl)-5-nitrobenzonitrile (0.87 g, 85%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (br s, 1 H), 8.41 (br s, 1 H), 8.01 (br s, 1 H), 3.74 (br t, 4 H, J = 4.4 Hz), 3.64 (s, 2 H), 2.48 (br t, 4 H, J = 4.4 Hz).

[0354] The titled compound was prepared as described in Preparative Example 11 by using 3-(morpholinomethyl)-5-nitrobenzonitrile in place of 3-(dimethylamino)-5-nitrobenzonitrile. Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (br t, 1 H, J = 1.6 Hz), 6.93 (br s, 1 H), 6.81 (dd, 1 H, J = 2.4, 1.6 Hz), 3.88 (br s, 2 H), 3.74 (br t, 4 H, J = 4.6 Hz), 3.44 (s, 2 H), 2.47 (br s, 4 H).

[0355]

[0356] Preparative Example 24

[0357]

[0358] Preparation of 2-(2-fluorophenoxy)acetaldehyde (a compound of the formula (**IX**) wherein R^b = 2-fluoro, X = O). This compound was prepared by the following 2 steps.

[0359] A stirred mixture of 2-fluorophenol (1.00 g, 8.92 mmol), 2-bromo-1,1-diethoxyethane (1.75 g, 8.92 mmol), and K_2CO_3 (1.47 g, 10.7 mmol) in anhydrous DMF (10 mL) was heated at 110°C overnight. The reaction mixture was poured into ice cold water (15 mL) and extracted with EtOAc (2 × 100 mL). The EtOAc solution was washed with water (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 1-(2,2-diethoxyethoxy)-2-fluorobenzene (1.65 g, 81%) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09-6.96 (m, 3 H), 6.93-6.87 (m, 1 H), 4.85 (t, 1 H, J = 5.2 Hz), 4.07 (d, 2 H, J = 5.2 Hz), 3.82-3.74 (m, 2 H), 3.69-3.61 (m, 2 H), 1.24 (t, 6 H, J = 7.0 Hz).

[0360] To a stirred solution of 1-(2,2-diethoxyethoxy)-2-fluorobenzene (1.65 g, 7.23 mmol) in a mixture of 1,4-dioxane (50 mL) and water (40 mL) at 0°C was added conc. HCl (17.6 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0°C, neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc (2 × 200 mL). The EtOAc solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give the titled compound (0.78 g, 71%) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1 H), 7.12 (ddd, 1 H, J = 11.4, 8.2, 1.6 Hz), 7.08-7.04 (m, 1 H), 7.01-6.95 (m, 1 H), 6.91 (td. 1 H, J = 8.2, 1.6 Hz), 4.63 (s, 2 H).

[0361]

[0362] Preparative Example 25

[0363]

[0364] Preparation of 2-(2-fluorophenylthio)acetaldehyde (a compound of the formula (**IX**) wherein R^b = 2-fluoro, X = S). This compound was prepared by the following 2 steps.

[0365] A mixture of 2-fluorothiophenol (1.00 g, 7.80 mmol), bromoacetaldehyde diethyl acetal (1.41 mL, 9.36 mmol), and Cs_2CO_3 (3.05 g, 9.36 mmol) in anhydrous DMF (20 mL) was stirred under N_2 at room temperature overnight. The reaction mixture was filtered through a sintered funnel, and the filtrate was diluted with water (20 mL). The aqueous mixture was extracted with Et_2O (3 × 100 mL), and the organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give (2,2-diethoxyethyl)(2-fluorophenyl)sulfane (1.81 g, 95%) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.41 (m, 1 H), 7.24-7.18 (m, 1 H), 7.09-7.02 (m, 1 H), 4.64 (t, 1 H, *J*= 5.6 Hz), 3.69-3.61 (m, 2 H), 3.56-3.49 (m, 2 H), 3.10 (d, 2 H, *J*= 5.6 Hz), 1.17 (t, 6 H, *J*= 7.2 Hz).

[0366] To a stirred solution of (2,2-diethoxyethyl)(2-fluorophenyl)sulfane (1.00 g, 4.09 mmol) in a mixture of 1,4-dioxane (30 mL) and water (25 mL) at 0°C was added conc. HCl (9 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0°C, neutralized with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was washed with water (50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure to give the titled compound (0.59 g, 85%) as a viscous liquid, which was immediately used for the next step without further purification. ^{1}H NMR (400MHz, $CDCl_3$): δ 9.56 (td, 1 H, *J* = 3.2, 1.2 Hz), 7.42-7.38 (m, 1 H), 7.31-7.25 (m, 1 H), 7.12-7.06 (m, 2 H), 3.58 (d, 2 H, *J*= 3.2 Hz).

[0367]

[0368] Preparative Example 26

[0369]

[0370] Preparation of 3-(methyl(2-oxoethyl)amino)benzonitrile (a compound of the formula (**IX**) wherein R^b = 3-cyano, X = NMe). This compound was prepared by the following 3 steps started with commercially available 3-aminobenzonitrile.

[0371] To a stirred solution of 3-aminobenzonitrile (2.50 g, 21.10 mmol) in anhydrous DMSO (30 mL) at 0°C was added NaH (0.61 g, 25.39 mmol) portionwise, and the mixture was stirred at room temperature for 20 min and then treated with bromoacetaldehyde diethyl acetal (4.20 g, 21.10 mmol). After 2 h, to it, saturated aqueous NH_4Cl (20 mL) was added slowly at 0°C, and the reaction mixture was extracted with EtOAc (2 × 50 mL). The EtOAc solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using EtOAc and hexane as eluent to give

3-(2,2-diethoxyethylamino)benzonitrile (0.86 g, 17%) as a light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (td, 1 H, J = 7.8, 0.6 Hz), 6.97 (m, 1 H), 6.84-6.81 (m, 2 H), 4.67 (t, 1 H, J = 5.4 Hz), 3.77-3.69 (m, 2 H), 3.61-3.53 (m, 2 H), 3.24 (d, 2 H, J = 5.6 Hz), 1.24 (t, 6 H, J = 7.0 Hz).

[0372] To a stirred solution of 3-(2,2-diethoxyethylamino)benzonitrile (0.84 g, 3.59 mmol) in anhydrous DMF (5 mL) at 0°C was added NaH (0.10 g, 4.30 mmol) portionwise. After 20 min, MeI (0.61 g, 4.30 mmol) was added, and the mixture was stirred at room temperature for 6 h. The reaction mixture was cooled to 0°C, and to it, aqueous NH_4Cl (10 mL) solution was added dropwise. The aqueous mixture was extracted with $CHCl_3$ (2 × 30 mL), and the organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give 3-((2,2-diethoxyethyl)(methyl)amino)benzonitrile (0.65 g, 73%) as a viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 1 H), 6.96-6.93 (m, 3 H), 4.60(t, 1 H, J = 5.2 Hz), 3.76-3.69 (m, 2 H), 3.55-3.47 (m, 2 H), 3.46 (d, 2 H, J = 5.2 Hz), 3.02 (s, 3 H), 1.20 (t, 6 H, J = 7.0 Hz).

[0373] To a stirred solution of 3-((2,2-diethoxyethyl)(methyl)amino)benzonitrile (0.65 g, 2.61 mmol) in anhydrous dioxane (6 mL) at 0°C was added 1 N HCl (4.30 mmol) dropwise, and the mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0°C, neutralized with aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (2 × 30 mL). The $CHCl_3$ solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure to give the titled compound (0.24 g, 52%) as a viscous liquid, which was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (t, 1 H, J = 0.8 Hz), 7.29 (ddd, 1 H, J = 8.8, 7.4, 0.8 HZ), 7.02 (ddd, 1 H, J = 7.4, 0.8, 1.2 Hz), 6.86 (dd, 1 H, J = 2.4, 1.2 Hz), 6.82 (ddd, 1 H, J = 8.8, 2.4, 1.2 Hz) 4.14 (d, 2 H, J = 0.8 Hz), 3.10 (s, 3 H).

[0374]

[0375] Preparative Example 27

[0376]

[0377] Preparation of 2-((2-fluorophenyl)(methyl)amino)acetaldehyde (a compound of the formula (**IX**) wherein R^b = 2-fluoro, X = NMe). This compound was prepared by the following 3 steps started with commercially available 2-fluoroaniline.

[0378] A stirred mixture of 2-fluoroaniline (2.00 g, 17.90 mmol), bromoacetaldehyde dimethyl acetal (3.25 mL, 21.40 mmol), and Cs_2CO_3 (11.70 g, 35.80 mmol) in anhydrous DMF (10 mL) was heated to 120°Covernight. The reaction mixture was evaporated to dryness under reduced pressure, and the residue was extracted with Et_2O (2 × 150 mL). The Et_2O solution was washed with water (4 × 50 mL) and brine (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under reduced

pressure. The residue was purified by MPLC on silica gel using a mixture of EtOAc and hexane as eluent to give *N*-(2,2-diethoxyethyl)-2-fluoroaniline(2.00 g, 49%) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$): δ 7.03-6.95 (m, 2 H), 6.82-6.77 (m, 1 H), 6.71-6.65 (m, 1 H), 4.72 (t, 1 H, *J*= 5.6 Hz), 3.78-3.71 (m, 2 H), 3.62-3.54 (m, 2 H), 3.29 (d, 2 H, *J*= 5.6 Hz), 1.26-1.22 (m, 6 H).

[0379] To a stirred solution of *N*-(2,2-diethoxyethyl)-2-fluoroaniline (1.00 g, 4.40 mmol) in anhydrous DMF (10 mL) at 0°C was added NaH (0.16 g, 6.60 mmol) portionwise. After 30 min, MeI (0.5 mL, 8.80 mmol) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (2 × 100 mL), and the EtOAc solution was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure to give *N*-(2,2-diethoxyethyl)-2-fluoro-*N*-methylaniline (0.41 g, 38%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05-6.96 (m, 3 H), 6.83-6.81 (m, 1 H), 4.69 (t, 1 H, *J*= 5.2 Hz), 3.72-3.64 (m, 2 H), 3.55-3.49 (m, 2 H), 3.33 (dd, 2 H, *J*= 5.2, 1.2 Hz), 2.97 (s, 3 H), 1.19-1.53 (m, 6 H).

[0380] To a stirred solution of *N*-(2,2-diethoxyethyl)-2-fluoro-*N*-methylaniline (0.40 g, 1.60 mmol) in 1,4-dioxane (5 mL) at 0°C was added 2.5 N HCl (5 mL) dropwise, and the mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0°C, neutralized with saturated $NaHCO_3$ solution, and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ solution was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure to give the titled compound (0.27 g, 98%) as a colorless oil, which was used for next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (dd, 1 H, *J* = 2.4, 1.2 Hz), 7.07-6.89 (m, 4 H), 3.91 (dd, 2 H, *J*= 1.8, 0.8 Hz), 2.97 (s, 3 H).

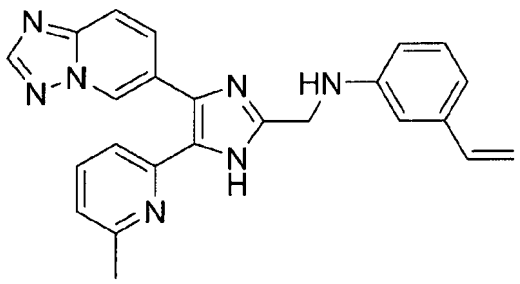
[0381]

[0382] Practice Example 1

[0383]

[0384] Preparation of *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-vinylaniline (Example 37)

[0385]

[0386] 

[0387] To a stirred solution of 4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazole-2-carbaldehyde (4.00 g, 13.14 mmol) in 1,2-dichloroethane (240 mL) were added 3-vinylaniline (2.36 g, 19.71 mmol) and AcOH (0.79 g, 13.14 mmol), and the mixture was heated at 80°C for 2 h. The reaction mixture was cooled to 0°C and, to it, was added $NaBH(OAc)_3$ (5.56 g, 26.20 mmol). The mixture was stirred at 40°C overnight, and then the pH of the reaction mixture was adjusted to 7-8 at 0°C with 10% K_2CO_3 solution. The reaction mixture was extracted with 5% MeOH in $CHCl_3$ (2 × 200 mL), and the organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of MeOH and CH_2Cl_2 (1:19 (v/v)) as eluent to give the titled compound (2.89 g, 63%) as a solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.59 (br s, 1 H), 8.94 (s, 1 H), 8.37 (s, 1 H), 7.81 (d, 1 H, J = 9.2 Hz), 7.77 (d, 1 H, J = 9.2 Hz), 7.45 (t, 1 H, J = 7.8 Hz), 7.20 (br d, 1 H, overlapped, J = 7.6 Hz), 7.15 (t, 1 H, overlapped, J = 7.8 Hz), 7.00 (d, 1 H, J = 8.0 Hz), 6.86 (d, 1 H, J = 7.6 Hz), 6.75 (t, 1 H, J = 2.0 Hz), 6.63 (dd, 1 H, overlapped, J = 17.6, 10.8 Hz), 6.61 (dd, 1 H, overlapped, J = 8.0, 2.0 Hz), 5.69 (dd, 1 H, J = 17.6, 0.8 Hz), 5.21 (dd, 1 H, J = 10.8, 0.8 Hz), 4.55 (s, 2 H), 4.39 (br s, 1 H), 2.51 (s, 3 H); MS (ESI) *m/z* 408.21 (MH^+).

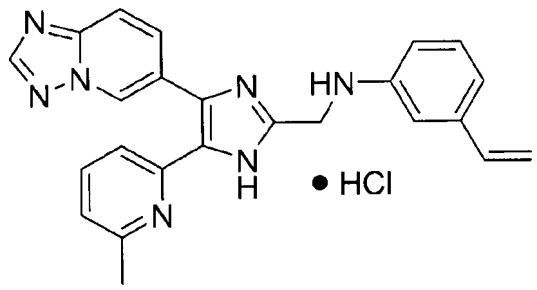
[0388]

[0389] Practice Example 2

[0390]

[0391] Preparation of *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-vinylaniline hydrochloride (Example 38)

[0392]



[0393]

[0394] A stirred suspension of *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-vinylaniline (1.00 g, 2.45 mmol) in anhydrous $CHCl_3$ (12 mL) was heated at 50°C to give a clear solution. The $CHCl_3$ solution was cooled to 0°C and, to it, was added 1.0 M HCl in Et_2O (7.36 mL, 7.36 mmol). After 5 min, the precipitates were filtered under N_2 and dried thoroughly over P_2O_5 *in vacuo* to give the titled compound (1.07 g, 98%) as a yellow

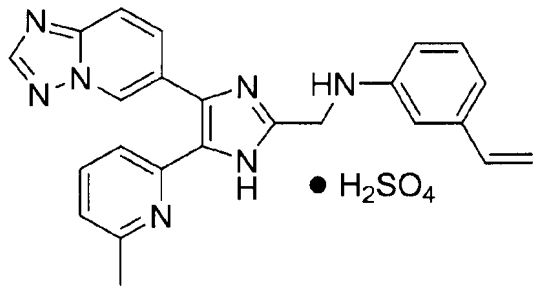
powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (dd, 1 H, J = 1.6, 0.8 Hz), 8.65 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.86 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.85 (t, 1 H, overlapped, J = 7.8 Hz), 7.65 (d, 1 H, J = 8.0 Hz), 7.38 (d, 1 H, J = 7.6 Hz), 7.12 (t, 1 H, J = 7.8 Hz), 6.91 (t, 1 H, J = 1.6 Hz), 6.79 (d, 1 H, J = 7.6 Hz), 6.71 (dd, 1 H, J = 8.0, 1.6 Hz), 6.64 (dd, 1 H, J = 17.6, 11.2 Hz), 5.80 (dd, 1 H, J = 17.6, 0.8 Hz), 5.20 (dd, 1 H, J = 11.2, 0.8 Hz), 4.79 (s, 2 H), 2.51 (s, 3 H).

[0395]

[0396] Practice Example 3

[0397]

[0398] Preparation of *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-vinylaniline sulfate (Example 39)

[0399] 

[0400] To a stirred suspension of *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-vinylaniline (100 mg, 0.25 mmol) in anhydrous EtOH (2 mL) at 0°C was added 10% H_2SO_4 in anhydrous EtOH (0.20 mL, 0.37 mmol). The mixture was allowed to warm to room temperature and stirred for 10 min. The reaction mixture was diluted with anhydrous Et_2O (8 mL) and stirred for an additional 10 min. The precipitates were filtered under N_2, washed with anhydrous Et_2O (4 × 4 mL), and then dried thoroughly over P_2O_5*in vacuo* to give the titled compound (79 mg, 64%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.98 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, J = 8.0 Hz), 7.76 (dd, 1 H, J = 9.2, 1.6 Hz), 7.43 (d, 1 H, J = 7.6 Hz), 7.40 (d, 1 H, J = 8.0 Hz), 7.13 (t, 1 H, J = 7.8 Hz), 6.80 (br s, 1 H), 6.79 (d, 1 H, overlapped, J = 7.6 Hz), 6.64 (dd, 1 H, overlapped, J = 17.6, 11.2 Hz), 6.63 (dd, 1 H, overlapped, J = 7.6, 2.0 Hz), 5.74 (dd, 1 H, J = 17.6, 0.8 Hz), 5.21 (dd, 1 H, J = 11.2, 0.8 Hz), 4.68 (s, 2 H), 2.58 (s, 3 H).

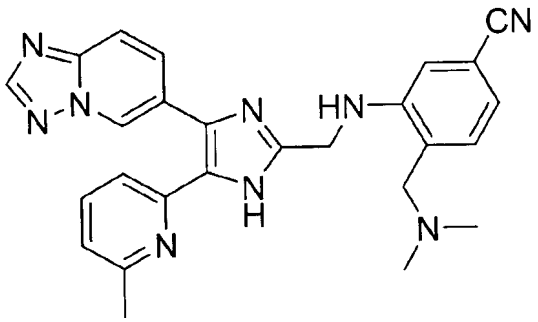
[0401]

[0402] Practice Example 4

[0403]

[0404] Preparation of 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-4-((dimethylamino)methyl)benzonitrile (Example 116)

[0405]



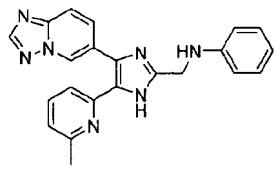
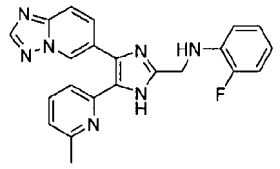
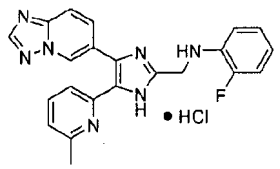
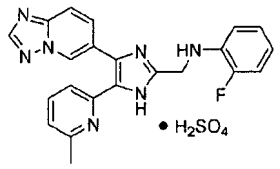
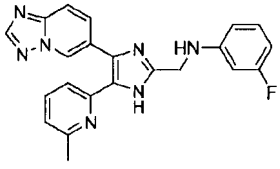
[0406] To a stirred solution of 4-((1,2,4)triazolo(1,5-*a*)pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazole-2-carbaldehyde (0.50 g, 1.64 mmol) in 1,2-dichloroethane (30 mL) were added 3-amino-4-((dimethylamino)methyl)benzonitrile (0.43 g, 2.46 mmol) and AcOH (0.20 g, 3.29 mmol), and the mixture was heated at 80°C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in anhydrous MeOH (30 mL). To a methanolic solution at 0°C was added $NaBH_4$ (0.25 g, 6.57 mmol), and then the mixture was allowed to warm to room temperature and stirred for an additional 3 h. The pH of the reaction mixture was adjusted to 7-8 at 0°C with 1 N HCl, and then MeOH was removed under reduced pressure. The aqueous mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the CH_2Cl_2 solution was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of MeOH and CH_2Cl_2 (1:19 (v/v)) as eluent to give the titled compound (0.60 g, 79%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.36 (s, 1 H), 7.86 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.47 (t, 1 H, J = 7.6 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.09 (d, 1 H, J = 7.6 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.98 (dd, 1 H, J = 7.6, 1.6 Hz), 6.93 (br s, 1 H), 4.59 (s, 2 H), 3.63 (s, 2 H), 2.53 (s, 3 H), 2.33 (s, 6 H); MS (ESI) *m/z* 464.23 (MH^+).

[0407] The compounds listed in the following Table 1 were prepared in an analogous manner to those described in the Practice Examples 1-4 above. The mass spectroscopy data of these compounds are included in the Table 1.

[0408]

[0409]

[Table 1]

Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
1		(400 MHz, $CDCl_3$) δ 10.43 (br s, 1 H), 8.96 (s, 1 H), 8.37 (s, 1 H), 7.82 (dd. 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.25–7.19 (m, 3 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.80 (tt, 1 H, *J* = 8.0, 1.2 Hz), 6.74–6.72 (m, 2 H), 4.55 (s, 2 H), 2.53 (s, 3 H)	382.19
2		(400 MHz, $CDCl_3$) δ 11.34 (br s, 1 H), 8.96 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.35 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.74 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.23 (d, 1 H, *J* = 7.6 Hz), 6.97–6.90 (m, 2 H), 6.94 (dd, 1 H, *J* = 8.0, 1.2 Hz), 6.72 (td, 1 H, *J* = 8.4, 1.6 Hz), 6.69–6.63 (m, 1 H), 4.51 (s, 2 H), 2.35 (s, 3 H).	400.18
3		(400 MHz, DMSO-d_6) δ 9.44 (d, 1 H, *J* = 0.8 Hz), 8.62 (s, 1 H), 7.96 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.83 (t, 1 H, *J* = 8.0 Hz), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.53 (d, 1 H, *J* = 8.0 Hz), 7.38 (d, 1 H, *J* = 7.6 Hz), 7.10 (ddd, 1 H, *J* = 12.0, 8.0, 1.2 Hz), 7.01 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.88 (br t, 1 H, *J* = 8.6 Hz), 6.70–6.64 (m, 1 H), 4.75 (s, 2 H), 2.54 (s, 3 H)	
4		(400 MHz, DMSO-d_6) δ 9.40 (dd, 1 H, *J* = 2.0, 0.8 Hz), 8.64 (s, 1 H), 7.99 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.85 (t, 1 H, *J* = 8.0 Hz), 7.77 (dd, 1 H, *J* = 9.2, 2.0 Hz), 7.42 (pseudo t, 2 H, *J* = 7.4 Hz), 7.11 (ddd, 1 H, *J* = 12.0, 8.0, 1.2 Hz), 7.02 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.82 (td, 1 H, *J* = 8.0, 1.2 Hz), 6.71–6.65 (m, 1 H), 4.73 (s, 2 H), 2.59 (s, 3 H)	
5		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.4 Hz), 8.36 (s, 1 H), 7.79 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.75 (dd, 1H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.13–7.07 (m, 1 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.47–6.41 (m, 2 H), 6.37 (dt, 1 H, *J* = 8.8, 2.4 Hz), 4.49 (s, 2 H), 2.49 (s, 3 H)	400.19
TABLE 1-continued			

[0410]

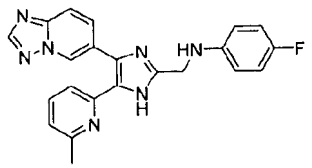
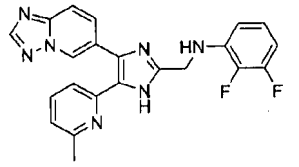
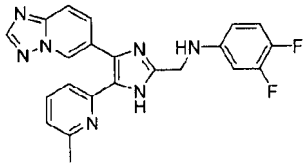
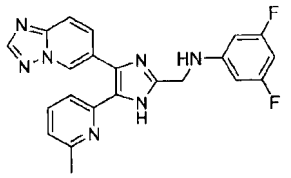
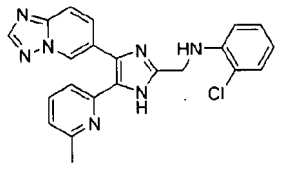
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
6		(400 MHz, $CDCl_3$) δ 8.95 (dd, 1 H, *J* = 1.6, 1.2 Hz), 8.37 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.23 (d, 1 H, *J* = 7.6 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.92–6.88 (m, 2 H), 6.65–6.62 (m, 2 H), 4.49 (s, 2 H), 2.51 (s, 3 H)	400.19
7		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.38 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.47 (t, 1 H, *J* = 7.6 Hz), 7.24 (d, 1 H, *J* = 7.6 Hz), 7.02 (dd, 1 H, *J* = 7.6, 0.4 Hz), 6.94–6.88 (m, 1 H), 6.60–6.51 (m, 2 H), 4.71 (br s, 1 H), 4.58 (d, 2 H, *J* = 3.6 Hz), 2.51 (s, 3 H)	418.18
8		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.4 Hz), 8.38 (s, 1 H), 7.81 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, overlapped, *J* = 9.2, 1.2 Hz), 7.47 (t, 1 H, *J* = 7.8 Hz), 7.24 (d, 1 H, *J* = 8.0 Hz), 7.03 (d, 1 H, *J* = 7.6 Hz), 7.04–6.95 (m, 1 H), 6.52 (ddd, 1 H, *J* = 12.4, 6.8, 2.8 Hz), 6.42–6.37 (m, 1 H), 4.48 (s, 2 H), 2.55 (s, 3 H)	418.18
9		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.2 Hz), 8.38 (s, 1 H), 7.81 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.79 (dd, 1 H, overlapped, *J* = 9.2, 1.2 Hz), 7.47 (t, 1 H, *J* = 7.8 Hz), 7.24 (d, 1 H, *J* = 8.0 Hz), 7.03 (d, 1 H, *J* = 7.6 Hz), 6.24–6.19 (m, 3 H), 4.71 (br s, 1 H), 4.50 (s, 2 H), 2.55 (s, 3 H)	418.18
10		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 1.0 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.29 (dd, 1 H, *J* = 7.6, 1.6 Hz), 7.23 (br d, 1 H, *J* = 7.6 Hz), 7.14 (td, 1 H, *J* = 8.4, 1.6 Hz), 7.01 (dd, 1 H, *J* = 7.6, 0.4 Hz), 6.75 (dd, 1 H, *J* = 8.8, 1.4 Hz), 6.72 (td, 1 H, *J* = 8.4, 1.6 Hz), 5.01 (br s, 1 H), 4.60 (br s, 2 H), 2.50 (s, 3 H)	416.16

TABLE 1-continued

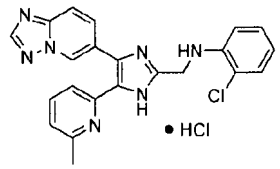
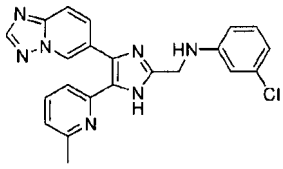
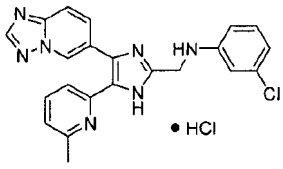
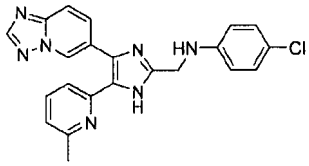
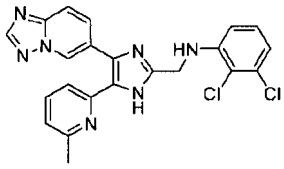
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
11		(400 MHz, DMSO-d_6) δ 9.43 (s, 1 H), 8.61 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.8 Hz), 7.82 (t, 1 H, overlapped, J = 7.8 Hz), 7.81 (dd, 1 H, overlapped, J = 9.2, 2.0 Hz), 7.49 (d, 1 H, J = 8.0 Hz), 7.36 (d, 1 H, J = 7.6 Hz), 7.32 (dd, 1 H, J = 7.8, 1.4 Hz), 7.17 (td, 1 H, J = 8.4, 1.2 Hz), 6.87 (dd, 1 H, J = 8.4, 1.2 Hz), 6.69 (td, 1 H, J = 7.8, 1.4 Hz), 6.15 (br s, 1 H), 4.76 (s, 2 H), 2.55 (s, 3 H)	
12		(400 MHz, $CDCl_3$) δ 8.95 (t, 1 H, J = 1.6 Hz), 8.37 (s, 1 H), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.77 (dd, 1 H, J = 9.2, 1.2 Hz), 7.47 (t, 1 H, J = 7.8 Hz), 7.24 (d, 1 H, J = 8.0 Hz), 7.10 (t, 1 H, J = 8.0 Hz), 7.02 (d, 1 H, J = 7.6 Hz), 6.75 (ddd, 1 H, J = 8.0, 2.0, 0.8 Hz), 6.69 (t, 1 H, J = 2.0 Hz), 6.57 (ddd, 1 H, J = 8.0, 2.4, 0.8 Hz), 4.51 (s, 2 H), 2.52 (s, 3 H)	416.16
13		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, J = 8.0 Hz), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.56 (d, 1 H, J = 8.4 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.15 (t, 1 H, J = 8.0 Hz), 6.80 (t, 1 H, J = 2.2 Hz), 6.71–6.65 (m, 2 H), 4.71 (s, 2 H), 2.54 (s, 3 H)	
14		(400 MHz, $CDCl_3$) δ 8.95 (t, 1 H, J = 1.4 Hz), 8.38 (s, 1 H), 7.81 (dd, 1 H, overlapped, J = 9.2, 1.4 Hz), 7.78 (dd, 1 H, overlapped, J = 9.2, 1.2 Hz), 7.47 (t, 1 H, J = 7.6 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.16 (m, 2 H), 7.02 (br d, 1 H, J = 7.6 Hz), 6.65 (m, 2 H), 4.51 (s, 2 H), 2.54 (s, 3 H)	416.16
15		(400 MHz, $CDCl_3$) δ 11.02 (br s, 1 H), 8.97 (s, 1 H), 8.36 (s, 1 H), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.75 (dd, 1 H, J = 9.2, 0.8 Hz), 7.46 (t, 1 H, J = 8.0 Hz), 7.24 (d, 1 H, J = 8.0 Hz), 7.03 (t, 1 H, overlapped, J = 8.0 Hz), 7.00 (d, 1 H, overlapped, J = 8.0 Hz), 6.85 (dd, 1 H, J = 8.0, 1.6 Hz), 6.63 (dd, 1 H, J = 8.0, 1.6 Hz), 5.15 (t, 1 H, J = 5.6 Hz), 4.57 (d, 2 H, J = 5.6 Hz), 2.43 (s, 3 H)	450.12

TABLE 1-continued

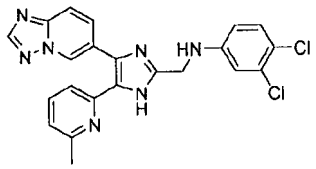
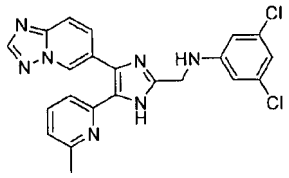
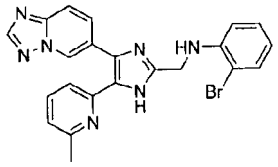
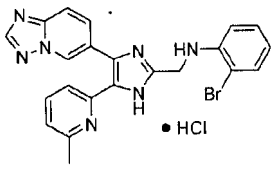
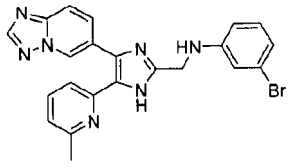
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
16		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, J = 1.2 Hz), 8.37 (s, 1 H), 7.80 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.77 (dd, 1 H, overlapped, J = 9.2, 1.2 Hz), 7.47 (t, 1 H, J = 8.0 Hz), 7.24 (br d, 1 H, J = 8.0 Hz), 7.20 (d, 1 H, J = 8.8 Hz), 7.03 (d, 1 H, J = 8.0 Hz), 6.77 (d, 1 H, J = 2.8 Hz), 6.53 (dd, 1 H, J = 8.8, 2.8 Hz), 4.47 (s, 2 H), 2.51 (s, 3 H)	450.12
17		(400 MHz, $CDCl_3/CD_3OD$) δ 8.90 (s, 1 H), 8.24 (s, 1 H), 7.71 (dd, 1 H, J = 9.2, 1.6 Hz), 7.64 (dd, 1 H, J = 9.2, 0.8 Hz), 7.45 (t, 1 H, J = 7.6 Hz), 7.16 (br d, 1 H, J = 7.6 Hz), 6.99 (d, 1 H, J = 7.6 Hz), 6.57 (t, 1 H, J = 1.6 Hz), 6.51 (d, 2 H, J = 1.6 Hz), 4.36 (s, 2 H), 2.45 (s, 3 H)	450.12
18		(400 MHz, $CDCl_3$) δ 10.94 (br s, 1 H), 8.97 (br s, 1 H), 8.36 (s, 1 H), 7.82 (d, 1 H, J = 9.2 Hz), 7.75 (d, 1 H, J = 9.2 Hz), 7.45 (t, 1 H, overlapped, J = 7.8 Hz), 7.43 (dd, 1 H, J = 8.0, 1.6 Hz), 7.21 (d, 1 H, J = 8.0 Hz), 7.16 (td, 1 H, J = 8.4, 1.2 Hz), 6.99 (d, 1 H, J = 7.6 Hz), 6.71 (dd, 1 H, J = 8.4, 1.2 Hz), 6.63 (td, 1 H, J = 8.0, 1.6 Hz), 4.99 (t, 1 H, J = 5.6 Hz), 4.57 (d, 2 H, J = 5.6 Hz), 2.44 (s, 3 H)	460.11
19		(400 MHz, DMSO-d_6) δ 9.43 (dd, 1 H, J = 1.6, 0.8 Hz), 8.62 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.83 (t, 1 H, J = 7.6 Hz), 7.80 (dd, 1 H, J = 9.2, 1.6 Hz), 7.50 (d, 1 H, J = 7.6 Hz), 7.48 (dd, 1 H, J = 8.0, 1.6 Hz), 7.37 (d, 1 H, J = 7.6 Hz), 7.21 (td, 1 H, J = 7.6, 1.6 Hz), 6.87 (dd, 1 H, J = 8.0, 1.2 Hz), 6.63 (td, 1 H, J = 7.6, 1.2 Hz), 6.04 (br s 1 H), 4.78 (s, 2 H), 2.55 (s, 3 H)	
20		(400 MHz, $CDCl_3$) δ 8.89 (br s, 1 H), 8.30 (s, 1 H), 7.75 (dd, 1 H, J = 9.2, 1.6 Hz), 7.69 (d, 1 H, J = 9.2 Hz), 7.44 (br t, 1 H, J = 7.6 Hz), 7.12 (br d, 1 H, J = 7.6 Hz), 7.00 (d, 1 H, J = 8.0 Hz), 6.97 (t, 1 H, overlapped, J = 8.0 Hz), 6.82–6.78 (m, 2 H), 6.58 (ddd, 1 H, J = 8.2, 2.4, 0.8 Hz), 4.41 (s, 2 H), 2.49 (s, 3 H)	460.11

TABLE 1-continued

[0411]

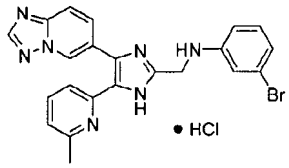
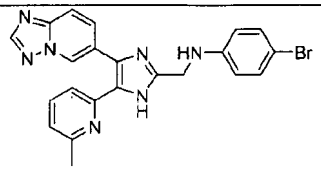
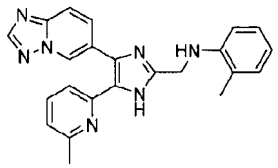
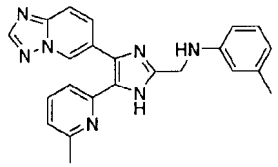
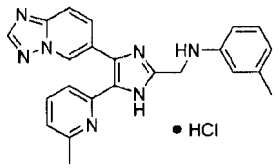
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
21		(400 MHz, DMSO-d_6) δ 9.44 (d, 1 H, J = 0.8 Hz), 8.61 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.8 Hz), 7.83 (t, 1 H, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.50 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 7.6 Hz), 7.08 (t, 1 H, J = 8.0 Hz), 6.94 (t, 1 H, J = 2.0 Hz), 6.79 (ddd, 1 H, J = 7.6, 2.0, 0.8 Hz), 6.71 (ddd, 1 H, J = 8.4, 2.0, 0.8 Hz), 4.63 (s, 2 H), 2.55 (s, 3 H)	
22		(400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 8.38 (s, 1 H), 7.82–7.77 (m, 2 H), 7.46 (t, 1 H, J = 7.6 Hz), 7.29 (m, 2 H), 7.21 (d, 1 H, J = 7.6 Hz), 7.02 (d, 1 H, J = 7.6 Hz), 6.61 (m, 2 H), 4.51 (s, 2 H), 4.44 (br s, 1 H), 2.54 (s, 3 H)	460.11
23		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.46 (t, 1 H, J = 7.8 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.14 (t, 1 H, overlapped, J = 8.0 Hz), 7.12 (d, 1 H, overlapped, J = 7.6 Hz), 7.01 (d, 1 H, J = 8.0 Hz), 6.76 (td, 1 H, J =7.6, 0.8 Hz), 6.69 (d, 1 H, J = 7.6 Hz), 4.61 (s, 2 H), 2.54 (s, 3 H), 2.26 (s, 3 H)	396.21
24		(400 MHz, $CDCl_3$) δ 8.96 (dd, 1 H, J = 1.6, 1.2 Hz), 8.37 (s,1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 1.2 Hz), 7.46 (t, 1 H, J = 7.8 Hz), 7.22 (br d, 1 H, J = 8.0 Hz), 7.11 (t, 1 H, J = 7.8 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.63 (dt, 1 H, J = 7.6, 0.8 Hz), 6.57–6.53 (m, 2 H), 4.55 (s, 2 H), 2.54 (s, 3 H), 2.29 (s, 3 H)	396.21
25		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.83 (t, 1 H, J = 8.0 Hz), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.56 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.02 (t, 1 H, J = 7.8 Hz), 6.60 (s, 1 H), 6.54 (dd, 1 H, J = 8.0, 2.0 Hz), 6.49 (d, 1 H, J = 7.6 Hz), 4.69 (s, 2 H), 2.52 (s, 3 H), 2.21 (s, 3 H)	

TABLE 1-continued

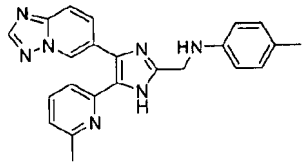
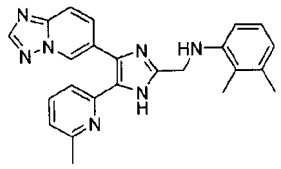
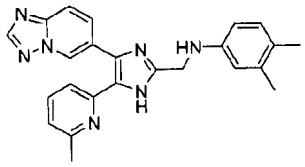
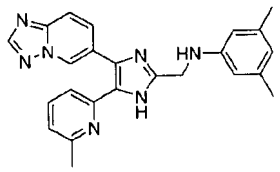
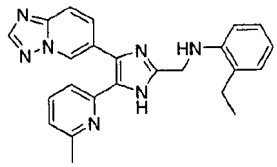
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
26		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.82 (d d, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.03 (m, 2 H), 7.02 (d, 1 H, overlapped, *J* = 7.6 Hz), 6.65 (m, 2 H), 4.53 (s, 2 H), 2.53 (s, 3 H), 2.25 (s, 3 H)	396.21
27		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 7.6 Hz), 7.03 (t, 1 H, overlapped, *J* = 7.8 Hz), 7.02 (d, 1 H, overlapped, *J* = 8.0 Hz), 6.69 (d, 1 H, *J* = 7.6 Hz), 6.58 (d, 1 H, *J* = 8.0 Hz), 4.59 (s, 2 H), 2.54 (s, 3 H), 2.31 (s, 3 H), 2.17 (s, 3 H)	410.23
28		(400 MHz, $CDCl_3$) δ 8.96 (d, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.98 (d, 1 H, *J* = 8.0 Hz), 6.57 (d, 1 H, *J* = 2.4 Hz), 6.50 (dd, 1 H, *J* = 8.0, 2.4 Hz), 4.53 (s, 2 H), 2.54 (s, 3 H), 2.20 (s, 3 H), 2.16 (s, 3 H)	410.23
29		(400 MHz, $CDCl_3$) δ 8.95 (dd, 1 H, *J* = 1.6, 1.2 Hz), 8.36 (s, 1 H), 7.79 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.74 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (d, 1 H, *J* = 8.0 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.44 (br s, 1 H), 6.31 (s, 2 H), 4.49 (s, 2 H), 2.48 (s, 3 H), 2.21 (s, 6 H)	410.23
30		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.23 (br d, 1 H, *J* = 7.6 Hz), 7.16–7.11 (m, 2 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.80 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.71 (dd, 1 H, *J* = 8.4, 1.2 Hz), 4.60 (s, 2 H), 2.60 (q, 2 H, *J* = 7.6 Hz), 2.52 (s, 3 H), 1.32 (t, 3 H, *J* = 7.6 Hz)	410.23

TABLE 1-continued

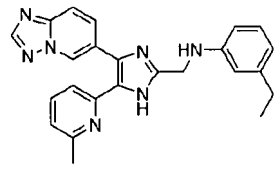
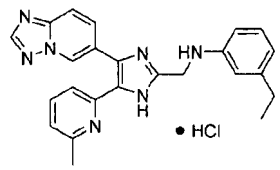
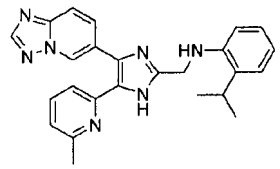
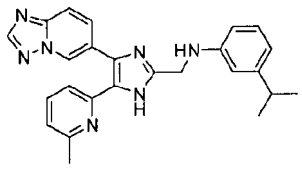
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
31		(400 MHz, $CDCl_3$) δ 8.96 (d, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.14 (t, 1 H, *J* = 7.8 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.66 (dd, 1 H, *J* = 7.6, 0.8 Hz), 6.58 (d, 1 H, *J* = 2.0 Hz), 6.55 (dd, 1 H, *J* = 7.6, 2.0 Hz), 4.55 (s, 2 H), 2.58 (q, 2 H, *J* = 7.6 Hz), 2.53 (s, 3 H), 1.21 (t, 3 H, *J* = 7.6 Hz)	410.23
32		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.83 (t, 1 H, *J* = 8.0 Hz), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.57 (d, 1 H, *J* = 8.0 Hz), 7.37 (d, 1 H, *J* = 8.0 Hz), 7.05 (t, 1 H, *J* = 7.6 Hz), 6.64 (d, 1 H, *J* = 1.6 Hz), 6.57–6.52 (m, 2 H), 4.71 (s, 2 H), 2.53 (s, 3 H), 2.50 (q, 2 H, *J* = 7.6 Hz), 1.14 (t, 3 H, *J* = 7.6 Hz)	
33		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.23 (br d, 1 H, overlapped, *J* = 8.0 Hz), 7.21 (dd, 1 H, overlapped, *J* = 7.6, 1.6 Hz), 7.12 (td, 1 H, *J* = 7.6, 1.6 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.83 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.71 (dd, 1 H, *J* = 8.0, 1.2 Hz), 4.58 (s, 2 H), 3.00 (heptet, 1 H, *J* = 6.8 Hz), 2.50 (s, 3 H), 1.31 (d, 6 H, *J* = 6.8 Hz)	424.24
34		(400 MHz, $CDCl_3$) δ 8.96 (dd, 1 H, *J* = 1.4, 0.8 Hz), 8.35 (s, 1 H), 7.79 (dd, 1 H, *J* = 9.2, 1.4 Hz), 7.73 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.21 (d, 1 H, *J* = 7.6 Hz), 7.11 (t, 1 H, *J* = 7.8 Hz), 6.99 (dd, 1 H, *J* = 7.8, 0.4 Hz), 6.67 (d, 1 H, *J* = 7.6 Hz), 6.57 (t, 1 H, *J* = 2.4 Hz), 6.50 (ddd, 1 H, *J* = 8.0, 2.4, 0.8 Hz), 4.51 (s, 2 H), 2.80 (heptet, 1 H, *J* = 6.8 Hz), 2.47 (s, 3 H), 1.20 (d, 6 H, *J* = 6.8 Hz)	424.24

TABLE 1-continued

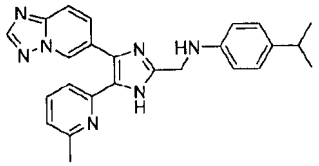
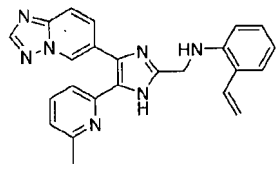
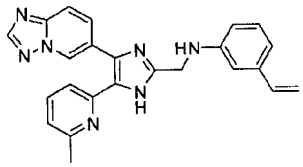
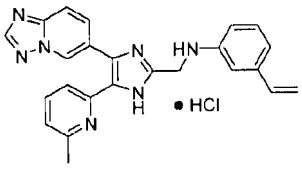
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
35		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, *J* = 1.2 Hz), 8.36 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.75 (d, 1 H, *J* = 9.2 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.21 (d, 1 H, *J* = 8.0 Hz), 7.06 (m, 2 H), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.64 (m, 2 H), 4.50 (s, 2 H), 2.80 (heptet, 1 H, *J* = 6.8 Hz), 2.48 (s, 3 H), 1.19 (d, 6 H, *J* = 6.8 Hz)	424.24
36		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.35 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.28 (dd, 1 H, *J* = 7.6, 1.2 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.15 (td, 1 H, *J* = 7.8, 1.2 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.79 (dd, 1H, overlapped, *J* = 17.2, 11.2 Hz), 6.78 (td, 1 H, overlapped, *J* = 7.6, 0.8 Hz), 6.68 (dd, 1 H, *J* = 8.2, 1.0 Hz), 5.62 (dd, 1 H, *J* = 17.2, 1.4 Hz), 5.34 (dd, 1 H, *J* = 11.2, 1.4 Hz), 4.53 (s, 2 H), 2.45 (s, 3 H)	408.21
37		(400 MHz, $CDCl_3$) δ 10.59 (br s, 1 H), 8.94 (s, 1 H), 8.37 (s, 1 H), 7.81 (d, 1 H, *J* = 9.2 Hz), 7.77 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.20 (br d, 1 H, overlapped, *J* = 7.6 Hz), 7.15 (t, 1 H, overlapped, *J* = 7.8 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.86 (d, 1 H, *J* = 7.6 Hz), 6.75 (t, 1 H, *J* = 2.0 Hz). 6.63 (dd, 1 H, overlapped, *J* = 17.6, 10.8 Hz), 6.61 (dd, 1 H, overlapped, *J* = 8.0, 2.0 Hz), 5.69 (dd, 1 H, *J* = 17.6, 0.8 Hz), 5.21 (dd, 1 H, *J* = 10.8, 0.8 Hz), 4.55 (s, 2 H), 4.39 (br s, 1 H), 2.51 (s, 3 H)	408.21
38		(400 MHz, DMSO-d_6) δ 9.49 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.65 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.86 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.85 (t, 1 H, overlapped, *J* = 7.8 Hz), 7.65 (d, 1 H, *J* = 8.0 Hz), 7.38 (d, 1 H, *J* = 7.6 Hz), 7.12 (t, 1 H, *J* = 7.8 Hz), 6.91 (t, 1 H, *J* = 1.6 Hz), 6.79 (d, 1 H, *J* = 7.6 Hz), 6.71 (dd, 1 H, *J* = 8.0, 1.6 Hz), 6.64 (dd, 1 H, *J* = 17.6, 11.2 Hz), 5.80 (dd, 1 H, *J* = 17.6, 0.8 Hz), 5.20 (dd, 1 H, *J* = 11.2, 0.8 Hz), 4.79 (s, 2 H), 2.51 (s, 3 H)	

TABLE 1-continued

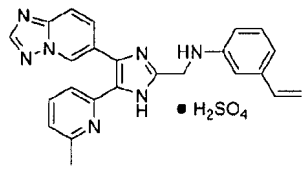
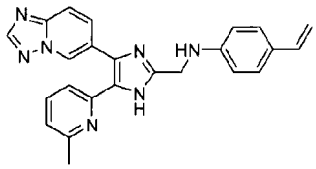
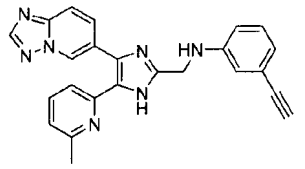
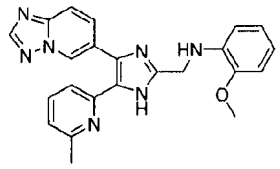
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
39		(400 MHz, DMSO-d_6) δ 9.40 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.98 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, J = 8.0 Hz), 7.76 (dd, 1 H, J = 9.2, 1.6 Hz), 7.43 (d, 1 H, J = 7.6 Hz), 7.40 (d, 1 H, J = 8.0 Hz), 7.13 (t, 1 H, J = 7.8 Hz), 6.80 (br s, 1 H), 6.79 (d, 1 H, overlapped, J = 7.6 Hz), 6.64 (dd, 1 H, overlapped, J = 17.6, 11.2 Hz), 6.63 (dd, 1 H, overlapped, J = 7.6, 2.0 Hz), 5.74 (dd, 1 H, J = 17.6, 0.8 Hz), 5.21 (dd, 1 H, J = 11.2, 0.8 Hz), 4.68 (s, 2 H), 2.58 (s, 3 H)	
40		(400 MHz, $CDCl_3$) δ 10.39 (br s, 1 H), 8.96 (s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.45 (t, 1 H, J = 7.6 Hz), 7.28 (m, 2 H), 7.22 (br d, 1 H, J = 7.6 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.69 (m, 2 H), 6.61 (dd, 1 H, J = 17.6, 10.8 Hz), 5.55 (dd, 1 H, J = 17.6, 0.8 Hz), 5.05 (dd, 1 H, J = 10.8, 0.8 Hz), 4.56, (s, 2 H), 2.53 (s, 3 H)	408.21
41		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, J = 1.2 Hz), 8.35 (s, 1 H), 7.77 (dd, 1 H, J = 9.2, 1.2 Hz), 7.72 (d, 1 H, J = 9.2 Hz), 7.46 (t, 1 H, J = 7.8 Hz), 7.23 (d, 1 H, J = 8.0 Hz), 7.07 (t, 1 H, J = 7.8 Hz), 6.99 (d, 1 H, J = 7.6 Hz), 6.86 (d, 1 H, J = 7.6 Hz), 6.73 (br s, 1 H), 6.61 (br d, 1 H, J = 8.0 Hz), 4.45 (s, 2 H), 2.98 (s, 1 H), 2.42 (s, 3 H)	406.18
42		(400 MHz, $CDCl_3$) δ 8.98 (br s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.45 (t, 1 H, J = 7.6 Hz), 7.22 (br d, 1 H, J = 7.6 Hz), 7.00 (d, 1 H, J = 7.6 Hz), 6.87 (td, 1 H, J = 7.6, 1.6 Hz), 6.84 (dd, 1 H, J = 8.0, 1.6 Hz), 6.77 (td, 1 H, J = 7.8, 1.6 Hz), 6.69 (dd, 1 H, J = 7.8, 1.6 Hz), 4.58 (s, 2 H), 3.91 (s, 3 H), 2.53 (s, 3 H)	412.21

TABLE 1-continued

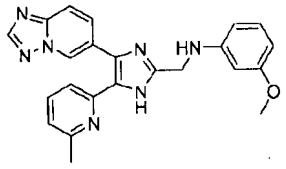
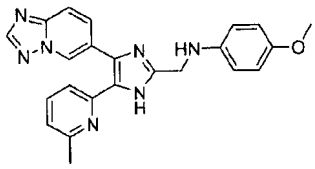
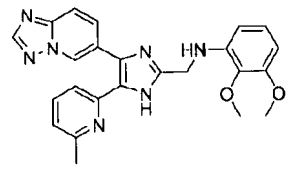
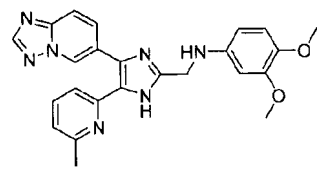
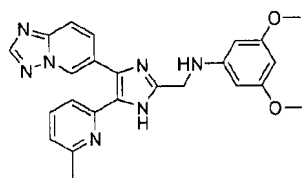
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
43		(400 MHz, $CDCl_3$) δ 8.95 (br s, 1 H), 8.37 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.22 (d, 1 H, *J* = 7.6 Hz), 7.11 (t, 1 H, *J* = 8.0 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.36–6.31 (m, 2 H), 6.27 (t, 1 H, *J* = 2.4 Hz), 4.52 (s, 2 H), 3.75 (s, 3 H), 2.51 (s, 3 H)	412.21
44		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 7.6 Hz), 7.01 (br d, 1 H, *J* = 8.0 Hz), 6.80 (m, 2 H), 6.70 (m, 2 H), 4.50 (s, 2 H), 3.74 (s, 3 H), 2.53 (s, 3 H)	412.21
45		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.34 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.72 (d, 1 H, *J* = 9.2 Hz), 7.42 (t, 1 H, *J* = 7.6 Hz), 7.20 (br d, 1 H, *J* = 7.6 Hz), 6.96 (d, 1 H, *J* = 7.6 Hz), 6.88 (td, 1 H, *J* = 8.2, 0.4 Hz), 6.36 (d, 1 H, overlapped, *J* = 8.0 Hz), 6.34 (d, 1 H, overlapped, *J* = 8.2 Hz), 4.52 (s, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 2.43 (s, 3 H)	442.22
46		(400 MHz, $CDCl_3$) δ 8.94 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.34 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.72 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 8.0 Hz), 7.21 (br d, 1 H, *J* = 8.0 Hz), 6.99 (d, 1 H, *J* = 8.0 Hz), 6.71 (d, 1 H, *J* = 8.4 Hz), 6.30 (d, 1 H, *J* = 2.4 Hz), 6.19 (dd, 1 H, *J* = 8.4, 2.4 Hz), 4.46 (s, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.47 (s, 3 H)	442.22
47		(400 MHz, $CDCl_3$) δ 10.43 (br s, 1 H), 8.94 (s, 1 H), 8.37 (s, 1 H), 7.81 (d, 1 H, *J* = 9.2 Hz), 7.77 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.20 (d, 1 H, *J* = 7.6 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 5.96 (t, 1 H, *J* = 2.0 Hz), 5.92 (d, 2 H, *J* = 2.0 Hz), 4.52 (d, 2 H, *J* = 2.8 Hz), 4.41 (br s, 1 H), 3.75 (s, 6 H), 2.54 (s, 3 H)	442.22

TABLE 1-continued

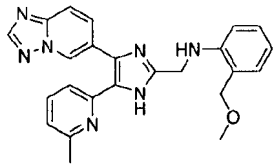
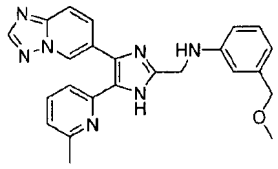
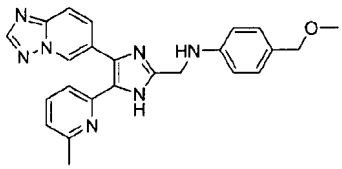
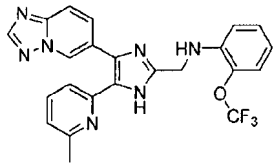
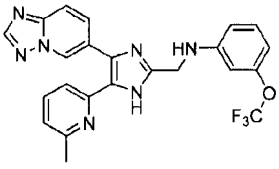
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
48		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.23 (td, 1 H, overlapped, *J* = 7.6, 1.6 Hz), 7.22 (br d, 1 H, overlapped, *J* = 7.6 Hz) 7.12 (dd, 1 H, *J* = 7.6, 1.6 Hz), 7.01 (d, 1 H, *J* = 8.0 Hz), 6.77–6.73 (m, 2 H), 4.63 (s, 2 H), 4.60 (s, 2 H), 3.42 (s, 3 H), 2.53 (s, 3 H)	426.22
49		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.21 (t, 1 H, overlapped, *J* = 8.0 Hz), 7.20 (br d, 1 H, overlapped, *J* = 7.6 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.76 (d, 1 H, overlapped, *J* = 8.0 Hz), 6.75 (d, 1 H, overlapped, *J* = 1.6 Hz), 6.67–6.64 (m, 1 H), 4.56 (s. 2 H), 4.40 (s, 2 H), 3.38 (s, 3 H), 2.54 (s, 3 H)	426.22
50		(400 MHz, $CDCl_3$) δ 10.36 (br s, 1 H), 8.95 (s, 1 H), 8.37 (s, 1 H), 7.82 (br d, 1 H, *J* = 9.2 Hz), 7.78 (br d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.20 (br d, 1 H, overlapped, *J* = 7.6 Hz), 7.19 (d, 2 H, overlapped, *J* = 8.4 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.71 (d, 2 H, *J* = 8.4 Hz), 4.55 (s, 2 H), 4.40 (br s, 1 H), 4.34 (s, 2 H), 3.34 (s, 3 H), 2.53 (s, 3 H)	426.22
51		(400 MHz, $CDCl_3$) δ 10.42 (br s, 1 H), 8.96 (br s, 1 H), 8.37 (s, 1 H), 7.82 (d, 1 H, *J* = 9.2 Hz), 7.78 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.25–7.18 (m, 2 H), 7.15 (td, 1 H, *J* = 7.8, 1.2 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.81 (dd, 1 H, *J* = 8.0, 1.2 Hz), 6.76 (td, 1 H, *J* = 7.8, 1.6 Hz), 4.85 (t, 1 H, *J* = 5.6 Hz), 4.61 (d, 2 H, *J* = 5.6 Hz), 2.52 (s, 3 H)	466.18
52		(400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 8.37 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.23 (br d, 1 H, *J* = 8.0 Hz), 7.19 (t, 1 H, *J* = 8.2 Hz), 7.02 (d, 1 H, *J* = 7.6 Hz), 6.64–6.60 (m, 2 H), 6.55 (br s, 1 H), 4.62 (br s, 1 H), 4.52 (s, 2 H), 2.52 (s, 3 H)	466.18

TABLE 1-continued

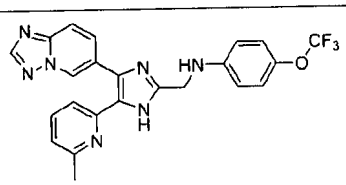
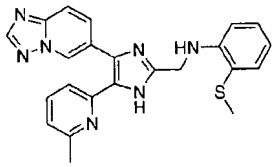
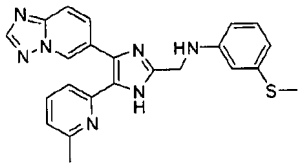
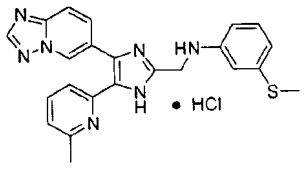
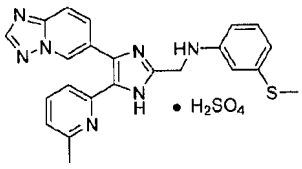
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
53		(400 MHz, $CDCl_3$) δ 8.95 (s, 1 H), 8.38 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.08 (m, 2 H), 7.02 (d, 1 H, *J* = 7.6 Hz), 6.70 (m, 2 H), 4.53 (s, 2 H), 2.54 (s, 3 H)	466.18
54		(400 MHz, $CDCl_3$) δ 11.34 (br s, 1 H), 8.99 (s, 1 H), 8.34 (s, 1 H), 7.83 (br d, 1 H, *J* = 9.2 Hz), 7.72 (br d, 1 H, *J* = 9.2 Hz), 7.43 (t, 1 H, *J* = 7.8 Hz), 7.35 (dd, 1 H, *J* = 7.6, 1.6 Hz), 7.21 (br d, 1 H, *J* = 7.6 Hz), 7.12 (td, 1 H, *J* = 7.8, 1.6 Hz), 6.95 (d, 1 H, *J* = 8.0 Hz), 6.70 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.65 (dd, 1 H, *J* = 8.0, 1.2 Hz), 5.49 (br t, 1 H, *J* = 4.8 Hz), 4.55 (d, 2 H, *J* = 4.8 Hz), 2.33 (s, 3 H), 2.32 (s, 3 H)	428.18
55		(400 MHz, $CDCl_3$) δ 11.06 (br s, 1 H), 8.94 (s, 1 H), 8.35 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.74 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.21 (br d, 1 H, *J* = 8.0 Hz), 7.07 (t, 1 H, *J* = 7.8 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.64 (dd, 1 H, *J* = 7.6, 2.0 Hz), 6.54 (t, 1 H, *J* = 1.6 Hz), 6.42 (dd, 1 H, *J* = 8.0, 1.6 Hz), 4.47 (s, 2 H) 4.42 (br s, 1 H), 2.45 (s, 3 H), 2.40 (s, 3 H)	428.19
56		(400 MHz, DMSO-d_6) δ 9.43 (br s, 1 H), 8.62 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.84 (t, 1 H, *J* = 7.6 Hz), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.51 (d, 1 H, *J* = 7.6 Hz), 7.38 (d, 1 H, *J* = 7.6 Hz), 7.08 (t, 1 H, *J* = 7.8 Hz), 6.62 (t, 1 H, *J* = 2.0 Hz), 6.55 (d, 1 H, *J* = 7.6 Hz), 6.51 (dd, 1 H, *J* = 8.0, 2.0 Hz), 4.68 (s, 2 H), 2.55 (s, 3 H), 2.41 (s, 3 H)	
57		(400 MHz, DMSO-d_6) δ 9.40 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.98 (d, 1 H, *J* = 9.6 Hz), 7.84 (t, 1 H, *J* = 7.6 Hz), 7.77 (dd, 1 H, *J* = 9.6, 1.6 Hz), 7.43 (d, 1 H, *J* = 7.6 Hz), 7.40 (d, 1 H, *J* = 7.6 Hz), 7.08 (t, 1 H, *J* = 8.0 Hz), 6.60 (t, 1 H, *J* = 2.0 Hz), 6.56 (d, 1 H, *J* = 8.0 Hz), 6.48 (dd, 1 H, *J* = 8.0, 2.0 Hz), 4.65 (s, 2 H), 2.58 (s, 3 H), 2.40 (s, 3 H)	

TABLE 1-continued

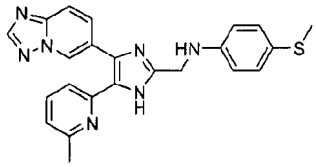
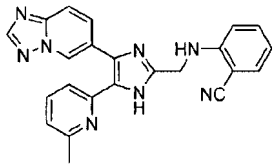
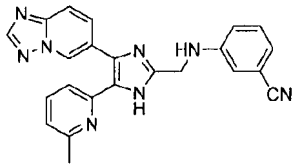
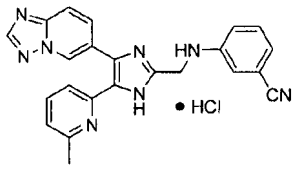
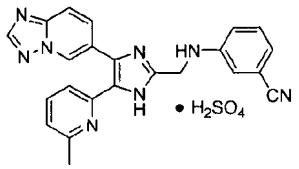
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
58		(400 MHz, $CDCl_3$) δ 11.08 (br s, 1 H), 8.94 (s, 1 H), 8.35 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.21 (br d, 1 H, *J* = 8.0 Hz), 7.17 (m, 2 H), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.60 (m, 2 H), 4.46 (s, 2 H), 2.45 (s, 3 H), 2.37 (s, 3 H)	428.18
59		(400 MHz, $CDCl_3$) δ 8.98 (br s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.47 (t, 1 H, *J* = 7.8 Hz), 7.40 (br d, 1 H, overlapped, *J* = 7.6 Hz), 7.38 (t, 1 H, *J* = 7.8 Hz), 7.25 (br d, 1 H, *J* = 8.0 Hz), 7.00 (d, 1 H, *J* = 7.6), 6.80 (d, 1 H, *J* = 8.4 Hz), 6.75 (td, 1 H, *J* = 8.0, 0.8 Hz), 5.32 (br t, 1 H, *J* = 5.6 Hz), 4.62 (d, 2 H, *J* = 5.6 Hz), 2.41 (s, 3 H)	407.19
60		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.2 Hz), 8.38 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.77 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.55 (t, 1 H, *J* = 8.0 Hz), 7.31 (d, 1 H, *J* = 8.0 Hz), 7.25 (t, 1 H, *J* = 8.0 Hz), 7.08 (d, 1 H, *J* = 8.0 Hz), 7.02 (dt, 1 H, *J* = 7.6, 1.2 Hz), 6.96–6.92 (m, 2 H), 4.56 (s, 2 H), 2.62 (s, 3 H)	407.19
61		(400 MHz, DMSO-d_6) δ 9.47 (d, 1 H, *J* = 0.8 Hz), 8.66 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.87 (t, 1 H, overlapped, *J* = 7.8 Hz), 7.85 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.63 (d, 1 H, *J* = 7.6 Hz), 7.40 (d, 1 H, *J* = 8.0 Hz), 7.33 (t, 1 H, *J* = 7.8 Hz), 7.16 (t, 1 H, *J* = 1.6 Hz), 7.11 (dd, 1 H, *J* = 8.4, 1.6 Hz), 7.06 (br d, 1 H, *J* = 7.6 Hz), 4.79 (s, 2 H), 2.53 (s, 3 H)	
62		(400 MHz, DMSO-d_6) δ 9.39 (br s, 1 H), 8.64 (s, 1 H), 7.99 (d, 1 H, *J* = 9.2 Hz), 7.87 (t, 1 H, *J* = 7.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.45 (d, 1 H, overlapped, *J* = 7.6 Hz), 7.44 (d, 1 H, overlapped, *J* = 7.6 Hz), 7.34 (t, 1 H, *J* = 8.0 Hz), 7.10 (d, 1 H, *J* = 2.0 Hz), 7.07 (d, 1 H, overlapped, *J* = 7.6 Hz), 7.04 (dd, 1 H, overlapped, *J* = 8.0, 2.0 Hz), 4.70 (s, 2 H), 2.60 (s, 3 H)	

TABLE 1-continued

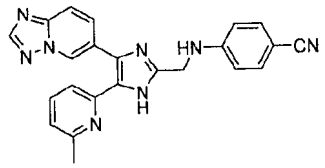
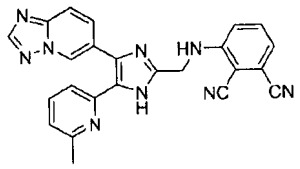
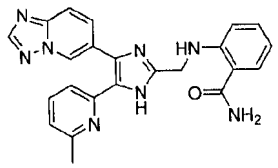
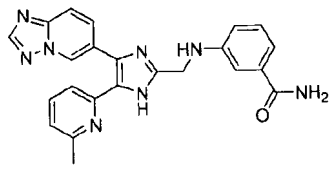
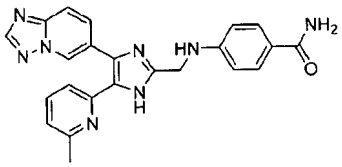
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
63		(400 MHz, $CDCl_3$) δ 8.93 (t, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.79 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, overlapped, *J* = 9.2, 0.8 Hz), 7.48 (t, 1 H, *J* = 7.8 Hz), 7.43 (m, 2 H), 7.24 (d, 1H, *J* = 8.0 Hz), 7.03 (d, 1 H, *J* = 7.6 Hz), 6.68 (m, 2 H), 5.12 (br s, 1 H), 4.54 (d, 2 H, *J* = 4.0 Hz), 2.51 (s, 3 H)	407.19
64		(400 MHz, $CDCl_3$) δ 8.99 (br s, 1 H), 8.35 (s, 1 H), 7.84 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.74 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.50 (t, 1 H, *J* = 7.8 Hz), 7.37 (t, 1 H, *J* = 8.2 Hz), 7.27 (br d, 1 H, *J* = 7.6 Hz), 7.05 (d, 1 H, *J* = 8.8 Hz), 7.01 (d, 1 H, overlapped, *J* = 8.0 Hz), 6.98 (d, 1 H, overlapped, *J* = 7.6 Hz), 5.94 (br t, 1 H, *J* = 5.6 Hz), 4.66 (d, 2 H, *J* = 5.6 Hz), 2.30 (s, 3 H)	432.19
65		(400 MHz, $CDCl_3$) δ 9.04 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.48 (br s, 1 H), 8.33 (s, 1 H), 7.84 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.72 (d, 1 H, *J* = 9.2 Hz), 7.41 (t, 1 H, *J* = 7.8 Hz), 7.37 (dd, 1 H, *J* = 7.6, 1.2 Hz), 7.29 (td, 1 H, *J* = 8.4, 1.2 Hz), 7.21 (br d, 1 H, *J* = 8.0 Hz), 6.92 (d, 1 H, *J* = 7.6 Hz), 6.83 (d, 1 H, *J* = 8.4 Hz), 6.62 (td, 1 H, *J* = 8.0, 1.0 Hz), 6.25 (br s, 2 H), 4.59 (d, 2 H, *J* = 5.2 Hz), 2.32 (s, 3 H)	425.20
66		(400 MHz, CD_3OD) δ 9.06 (br s, 1 H), 8.34 (s, 1 H), 7.83 (br d, 1 H, *J* = 9.2 Hz), 7.71 (d, 1 H, *J* = 9.2 Hz), 7.59–7.55 (m, 2 H), 7.22–7.18 (m, 2 H), 7.15 (dt, 1 H, *J* = 7.6, 2.0 Hz), 7.10 (dd, 1 H, *J* = 8.4, 0.8 Hz), 6.86 (ddd, 1 H, *J* = 7.6, 2.0, 0.8 Hz), 4.51 (s, 2 H), 2.50 (s, 3 H)	425.20
67		(400 MHz, $CDCl_3/CD_3OD$) δ 9.03 (br s, 1 H), 8.32 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.70 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.67 (m, 2 H), 7.55 (t, 1 H, *J* = 7.6 Hz), 7.26 (br d, 1 H, *J* = 7.6 Hz), 7.09 (d, 1 H, *J* = 7.6 Hz), 6.71 (m, 2 H), 4.52 (s, 2 H), 2.51 (s, 3 H)	425.20

TABLE 1-continued

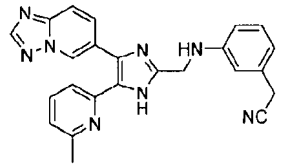
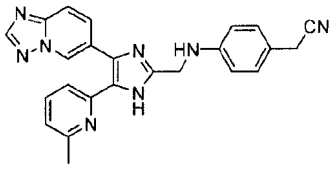
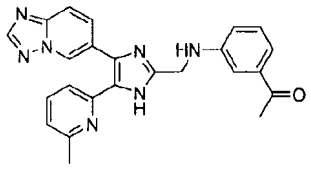
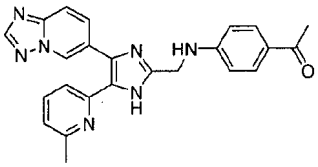
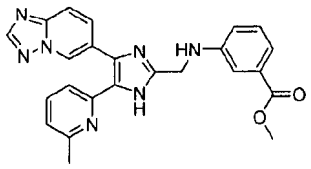
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
68		(400 MHz, $CDCl_3$) δ 10.76 (br s, 1 H), 8.94 (br s, 1 H), 8.37 (s, 1 H), 7.81 (br d, 1 H, *J* = 9.2 Hz), 7.76 (br d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.21 (br d, 1 H, *J* = 7.6 Hz), 7.20–7.15 (m, 1 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.69 (dd, 1 H, *J* = 7.6, 0.8 Hz), 6.62–6.40 (m, 2 H), 4.53 (br s, 1 H, overlapped), 4.52 (br s, 2 H, overlapped), 3.65 (s, 2 H), 2.50 (s, 3 H)	421.21
69		(400 MHz, $CDCl_3$) δ 10.78 (br s, 1 H), 8.94 (br s, 1 H), 8.36 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.76 (d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 7.6 Hz), 7.11 (d, 2 H, *J* = 8.4 Hz), 7.01 (d, 1 H, *J* = 8.0 Hz), 6.67 (d, 2 H, *J* = 8.4 Hz), 4.50 (br s, 3 H), 3.61 (s, 2 H), 2.49 (s, 3 H)	421.21
70		(400 MHz, $CDCl_3$) δ 11.09 (br s, 1 H), 8.92 (s, 1 H), 8.35 (s, 1 H), 7.79 (d, 1 H, *J* = 9.2 Hz), 7.74 (d, 1 H, *J* = 9.2 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.30 (d, 1 H, *J* = 7.6 Hz), 7.26–7.24 (m, 1 H), 7.23 (t, 1 H, overlapped, *J* = 7.8 Hz), 7.19 (br d, 1 H, *J* = 8.0 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.86 (dd, 1 H, *J* = 8.0, 1.8 Hz), 4.68 (br s, 1 H), 4.52 (d, 2 H, *J* = 5.2 Hz), 2.53 (s, 3 H), 2.47 (s, 3 H)	424.21
71		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, *J* = 1.4 Hz), 8.37 (s, 1 H), 7.81 (d, 2 H, *J* = 8.8 Hz), 7.79–7.76 (m, 2 H), 7.54 (t, 1 H, *J* = 7.8 Hz), 7.30 (d, 1 H, *J* = 8.0 Hz), 7.07 (d, 1 H, *J* = 7.6 Hz), 6.70 (d, 2 H, *J* = 8.8 Hz), 4.63 (s, 2 H), 2.59 (s, 3 H), 2.48 (s, 3 H)	424.21
72		(400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 8.34 (s, 1 H), 7.77 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.72 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.39 (dt, 1 H, *J* = 7.6, 1.2 Hz), 7.32 (dd, 1 H, *J* = 2.4, 1.6 Hz), 7.22 (d, 1 H, overlapped, *J* = 8.0 Hz), 7.19 (t, 1 H, overlapped, *J* = 8.0 Hz), 6.98 (d, 1 H, *J* = 7.6 Hz), 6.81 (ddd, 1 H, *J* = 8.0, 2.4, 0.8 Hz), 4.49 (s, 2 H), 3.84 (s, 3 H), 2.43 (s, 3 H)	440.20

TABLE 1-continued

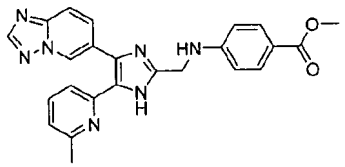
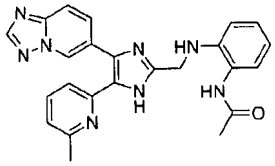
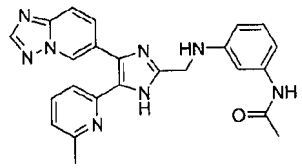
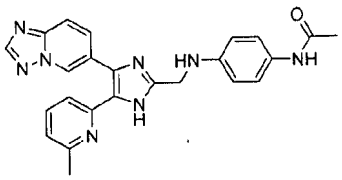
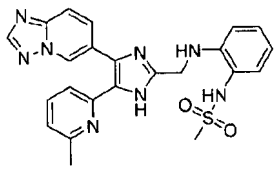
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
73		(400 MHz, $CDCl_3$) δ 10.52 (br s, 1 H), 8.94 (s, 1 H), 8.37 (s, 1 H), 7.89 (m, 2 H), 7.81 (br d, 1 H, *J* = 9.6 Hz), 7.78 (br d, 1 H, *J* = 9.6 Hz), 7.46 (t, 1 H, *J* = 8.0 Hz), 7.21 (d, 1 H, *J* = 8.0 Hz), 7.02 (d, 1 H, *J* = 8.0 Hz), 6.68 (m, 2 H), 4.90 (t, 1 H, *J* = 5.6 Hz), 4.58 (d, 2 H, *J* = 5.6 Hz), 3.85 (s, 3 H), 2.51 (s, 3 H)	440.20
74		(400 MHz, DMSO-d_6) δ 12.56 (br s, 1 H), 9.58 (s, 1 H), 9.36 (s, 1 H), 8.50 (s, 1 H), 8.00 (br d, 1 H, *J* = 9.2 Hz), 7.82 (d, 1 H, *J* = 9.2 Hz), 7.71 (t, 1 H, *J* = 7.8 Hz), 7.44 (br s, 1 H), 7.16 (d, 1 H, overlapped, *J* = 8.0 Hz), 7.15 (d, 1 H, overlapped, *J* = 7.6 Hz), 7.03 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.81 (d, 1 H, *J* = 7.6 Hz), 6.61 (td, 1 H, *J* = 7.6, 1.2 Hz), 5.65 (t, 1 H, *J* = 6.0 Hz), 4.45 (d, 2 H, *J* = 6.0 Hz), 2.47 (br s, 3 H), 2.09 (s, 3 H)	439.22
75		(400 MHz, DMSO-d_6) δ 8.97 (br s, 1 H), 8.35 (s, 1 H), 7.79 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.38 (br s, 1 H), 7.24 (d, 1 H, *J* = 8.0 Hz), 7.15 (br s, 1 H), 7.09 (t, 1 H, *J* = 8.0 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.69 (br d, 1 H, *J* = 8.0 Hz), 6.41 (dd, 1 H, *J* = 8.0, 1.6 Hz), 4.50 (s, 2 H), 2.51 (s, 3 H), 2.13 (s, 3 H)	439.22
76		(400 MHz, DMSO-d_6) δ 8.96 (br s, 1 H), 8.37 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.27 (m, 2 H), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.10 (br s, 1 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.66 (m, 2 H), 4.50 (s, 2 H), 2.53 (s, 3 H), 2.13 (s, 3 H)	439.22
77		(400 MHz, CD_3OD) δ 9.18 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.41 (s, 1 H), 7.87 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.75 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.66 (t, 1 H, *J* = 7.8 Hz), 7.38 (br d, 1 H, *J* = 7.6 Hz), 7.20 (dd, 1 H, *J* = 7.8, 1.4 Hz), 7.16 (d, 1 H, overlapped, *J* = 7.6 Hz), 7.15 (td, 1 H, overlapped, *J* = 8.0, 1.6 Hz), 6.82 (dd, 1 H, *J* = 8.0, 1.2 Hz), 6.71 (td, 1 H, *J* = 8.0, 1.4 Hz), 4.59 (s, 2 H), 3.05 (s, 3 H), 2.48 (s, 3 H)	475.19

TABLE 1-continued

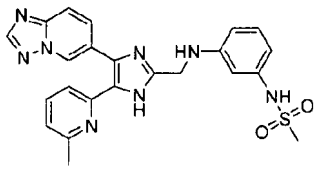
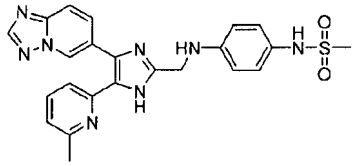
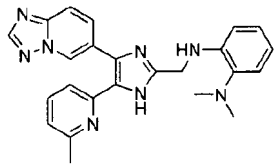
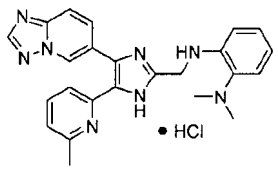
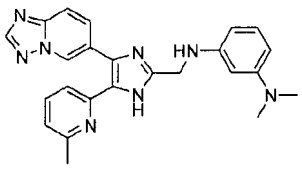
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
78		(400 MHz, $CDCl_3$) δ 8.92 (br s, 1 H), 8.35 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.21 (br d, 1 H, *J* = 7.6 Hz), 7.11 (t, 1 H, overlapped, *J* = 8.2 Hz), 7.10 (br s, 1 H, overlapped), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.58 (t, 1 H, *J* = 2.0 Hz), 6.54 (ddd, 1 H, *J* = 8.2, 2.0, 0.8 Hz), 6.49 (ddd, 1 H, *J* = 8.2, 2.0, 0.8 Hz), 4.50 (s, 2 H), 2.94 (s, 3 H), 2.51 (s, 3 H)	475.19
79		(400 MHz, $CDCl_3$) δ 8.93 (br s, 1 H), 8.38 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.09 (d, 2 H, *J* = 8.8 Hz), 7.02 (d, 1 H, *J* = 7.6 Hz), 6.67 (d, 2 H, *J* = 8.8 Hz), 6.34 (br s, 1 H), 4.52 (br s, 3 H), 2.93 (s, 3 H), 2.54 (s, 3 H)	475.19
80		(400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.23 (br d, 1 H, *J* = 7.6 Hz), 7.10 (dd, 1 H, *J* = 8.0, 1.2 Hz), 7.02 (td, 1 H, overlapped, *J* = 7.6, 1.2 Hz), 7.00 (d, 1 H, overlapped, *J* = 8.0 Hz), 6.78 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.72 (dd, 1 H, *J* = 8.0, 1.2 Hz), 4.58 (s, 2 H), 2.73 (s, 6 H), 2.50 (s, 3 H)	425.20
81		(400 MHz, DMSO-d_6) δ 9.47 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.87 (t, 1 H, *J* = 7.8 Hz), 7.84 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.59 (br d, 1 H, overlapped, *J* = 8.0 Hz), 7.58 (d, 1 H, *J* = 7.6 Hz), 7.41 (d, 1 H, *J* = 7.6 Hz), 7.29 (t, 1 H, *J* = 7.4 Hz), 6.99 (dd, 1 H, *J* = 7.6, 0.8 Hz), 6.89 (t, 1 H, *J* = 7.4 Hz), 4.81 (s, 2 H), 3.10 (s, 6 H), 2.56 (s, 3 H)	
82		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.36 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.75 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.07 (t, 1 H, *J* = 8.2 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.24 (d, 1 H, *J* = 8.0 Hz), 6.14 (br s, 2 H), 4.55 (s, 2 H), 2.90 (s, 6 H), 2.52 (s, 3 H)	425.21

TABLE 1-continued

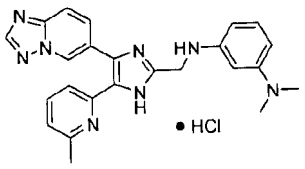
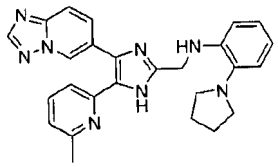
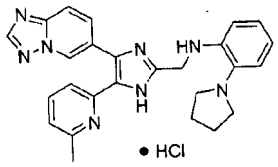
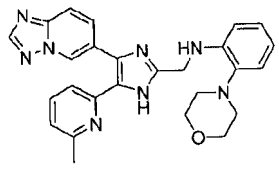
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
83		(400 MHz, DMSO-d_6) δ 9.48 (dd, 1 H, J = 1.6, 0.8 Hz), 8.64 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.86 (t, 1 H, overlapped, J = 7.8 Hz), 7.85 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.62 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.28 (t, 1 H, J = 8.2 Hz), 7.17 (br s, 1 H), 6.98 (br d, 1 H, J = 8.0 Hz), 6.81 (br d, 1 H, J = 8.4 Hz), 4.78 (s, 2 H), 3.09 (s, 6 H), 2.52 (s, 3 H)	
84		(400 MHz, $CDCl_3$) δ 10.41 (br s, 1 H), 8.99 (s, 1 H), 8.36 (s, 1 H), 7.84 (dd, 1 H, J = 9.2, 1.2 Hz), 7.76 (d, 1 H, J = 9.2 Hz), 7.45 (t, 1 H, J = 7.8 Hz), 7.23 (br s, 1 H), 7.10 (dd, 1 H, J = 7.6, 1.2 Hz), 7.00 (td, 1 H, overlapped, J = 7.6, 1.2 Hz), 6.99 (d, 1 H, overlapped, J = 7.6 Hz), 6.77 (td, 1 H, J = 7.6, 1.2 Hz), 6.72 (d, 1 H, J = 8.0 Hz), 4.58 (s, 2 H), 3.12 (br s, 4 H), 2.51 (s, 3 H), 1.98 (br s, 4 H)	451.22
85		(400 MHz, DMSO-d_6) δ 9.47 (dd, 1 H, J = 2.0, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.87 (t, 1 H, J = 7.8 Hz), 7.84 (dd, 1 H, J = 9.2, 2.0 Hz), 7.60 (d, 1 H, J = 8.0 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.41 (d, 1 H, J = 7.6 Hz), 7.30 (td, 1 H, J = 7.8, 0.8 Hz), 7.02 (dd, 1 H, J = 7.8, 1.2 Hz), 6.88 (td, 1 H, J = 8.0, 1.2 Hz), 4.82 (s, 2 H), 3.72 (br s, 4 H), 2.55 (s, 3 H), 2.17 (m, 4 H)	
86		(400 MHz, $CDCl_3$) δ 8.96 (s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 1.2 Hz), 7.48 (t, 1 H, J = 7.6 Hz), 7.25 (br d, 1 H, J = 7.6 Hz), 7.09 (dd, 1 H, J = 8.0, 1.6 Hz), 7.05 (td, 1 H, overlapped, J = 7.6, 1.6 Hz), 7.02 (d, 1 H, overlapped, J = 7.6 Hz), 6.80 (td, 1 H, J = 7.6, 1.2 Hz), 6.71 (dd, 1 H, J = 8.0, 1.2 Hz), 4.57 (s, 2 H), 3.90 (br t, 4 H, J = 4.6 Hz), 2.96 (br t, 4 H, J = 4.6 Hz), 2.54 (s, 3 H)	467.22

TABLE 1-continued

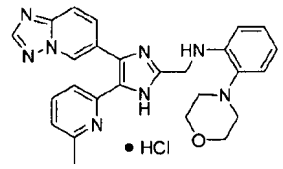
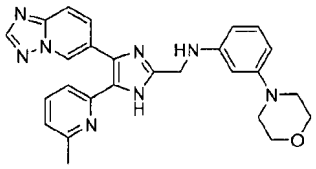
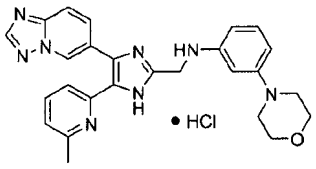
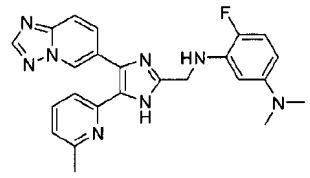
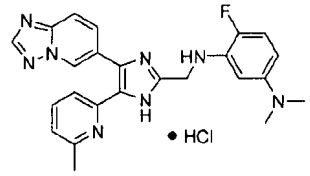
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
87		(400 MHz, DMSO-d_6) δ 9.46 (dd, 1 H, J = 1.6, 0.8 Hz), 8.64 (s, 1 H), 7.98 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.38 (d, 1 H, J = 7.6 Hz), 7.06 (dd, 1 H, J = 7.6, 1.2 Hz), 6.98 (td, 1 H, J = 7.8, 1.2 Hz), 6.82 (dd, 1 H, J = 7.8, 1.2 Hz), 6.70 (td, 1 H, J = 7.6, 1.2 Hz), 4.80 (s, 2 H), 3.84 (br t, 4 H, J = 4.4 Hz), 2.89 (br t, 4 H, J = 4.4 Hz), 2.53 (s, 3 H)	
88		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, J = 1.2 Hz), 8.37 (s, 1 H), 7.82–7.76 (m, 2 H), 7.48 (t, 1 H, J = 7.6 Hz), 7.24 (br d, 1 H, J = 7.6 Hz), 7.12 (t, 1 H, J = 8.0 Hz), 7.03 (d, 1 H, J = 7.6 Hz), 6.39 (dd, 1 H, J = 8.0, 1.6 Hz), 6.34 (t, 1 H, J = 2.0 Hz), 6.29 (dd, 1 H, J = 8.0, 2.0 Hz), 4.56 (s, 2 H), 3.85–3.82 (m, 4 H), 3.15–3.12 (m, 4 H), 2.56 (s, 3 H)	467.23
89		(400 MHz, DMSO-d_6) δ 9.47 (dd, 1 H, J = 1.6, 0.8 Hz), 8.64 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, J = 8.0 Hz), 7.84 (dd, 1 H, J = 9.2, 1.6 Hz), 7.60 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 8.0 Hz), 7.17 (t, 1 H, J = 8.0 Hz), 6.86 (br s, 1 H), 6.76 (br s, 1 H), 6.59 (br d, 1 H, J = 7.6 Hz), 4.76 (s, 2 H), 3.92 (br s, 4 H), 3.34 (br s, 4 H), 2.52 (s, 3 H)	
90		(400 MHz, $CDCl_3$) δ 8.95 (t, 1 H, J = 1.2 Hz), 8.35 (s, 1 H), 7.78 (dd, 1 H, J = 9.2, 1.6 Hz), 7.70 (dd, 1 H, J = 9.2, 1.2 Hz), 7.43 (t, 1 H, J = 7.8 Hz), 7.21 (d, 1 H, J = 8.0 Hz), 6.94 (d, 1 H, J = 7.6 Hz), 6.80–6.73 (m, 1 H), 6.14 (br d, 1 H, J = 7.6 Hz), 6.00–5.95 (m, 1 H), 4.49 (s, 2 H), 2.79 (s, 6 H), 2.31 (s, 3 H)	443.21
91		(400 MHz, DMSO-d_6) δ 9.49 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.84 (t, 1 H, overlapped, J = 8.0 Hz), 7.60 (d, 1 H, J = 8.0 Hz), 7.39 (br s, 1 H, overlapped), 7.38 (d, 1 H, overlapped, J = 8.0 Hz), 7.24 (pseudo t, 1 H, J = 9.8 Hz), 6.97 (br s, 1 H), 4.86 (s, 2 H), 3.10 (s, 6 H), 2.52 (s, 3 H)	

TABLE 1-continued

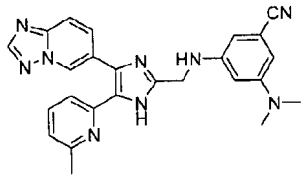
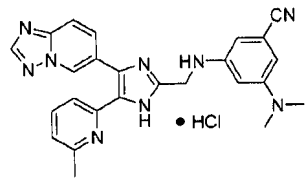
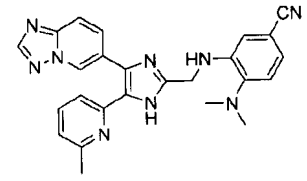
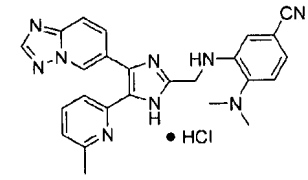
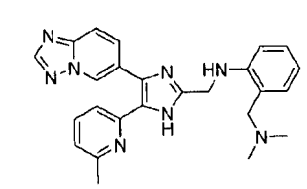
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
92		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.2 Hz), 8.38 (s, 1 H), 7.80 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, overlapped, *J* = 9.2, 1.2 Hz), 7.49 (t, 1 H, *J* = 7.6 Hz), 7.25 (d, 1 H, *J* = 7.6 Hz), 7.04 (d, 1 H, *J* = 7.6 Hz), 6.38 (dd, 1 H, *J* = 2.4, 1.2 Hz), 6.30 (t, 1 H, *J* = 1.6 Hz), 6.18 (t, 1 H, *J* = 2.2 Hz), 4.53 (s, 2 H), 2.92 (s, 6 H), 2.56 (s, 3 H)	450.21
93		(400 MHz, DMSO-d_6) δ 9.44 (dd, 1 H, *J* = 2.0, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.85 (t, 1 H, *J* = 7.8 Hz), 7.81 (dd, 1 H, *J* = 9.2, 2.0 Hz), 7.55 (d, 1 H, *J* = 8.0 Hz), 7.40 (d, 1 H, *J* = 7.6 Hz), 6.47 (s, 2 H), 6.37 (br s, 1 H), 4.73 (s, 2 H), 2.90 (s, 6 H), 2.55 (s, 3 H)	
94		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, *J* = 1.6 Hz), 8.38 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.79 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.53 (t, 1 H, *J* = 7.8 Hz), 7.31 (d, 1 H, *J* = 8.0 Hz), 7.08–7.03 (m, 3 H), 6.87 (d, 1 H, *J* = 1.6 Hz), 5.44 (br s, 1 H), 4.55 (s, 2 H), 2.74 (s, 6 H), 2.58 (s, 3 H)	450.21
95		(400 MHz, DMSO-d_6) δ 9.44 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.64 (s, 1 H), 7.99 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.84 (t, 1 H, overlapped, *J* = 7.8 Hz), 7.82 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.51 (d, 1 H, *J* = 8.0 Hz), 7.39 (d, 1 H, *J* = 7.6 Hz), 7.15 (dd, 2 H, overlapped, *J* = 7.6, 0.8 Hz), 7.14 (d, 1 H, overlapped, *J* = 1.2 Hz), 4.79 (s, 2 H), 2.71 (s, 6 H), 2.56 (s, 3 H)	
96		(400 MHz, $CDCl_3$) δ 10.57 (br s, 1 H), 8.97 (s, 1 H), 8.34 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.74 (d, 1 H, *J* = 9.2 Hz), 7.43 (t, 1 H, *J* = 7.8 Hz), 7.21 (br s, 1 H, overlapped), 7.17 (td, 1 H, *J* = 8.0, 1.6 Hz), 7.01 (dd, 1 H, *J* = 7.6, 1.6 Hz), 6.98 (d, 1 H, *J* = 7.6 Hz), 6.72–6.66 (m, 2 H), 4.61 (s, 2 H), 3.54 (s, 2 H), 2.51 (s, 3 H), 2.28 (s, 6 H)	439.23

TABLE 1-continued

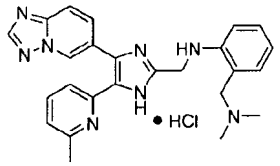
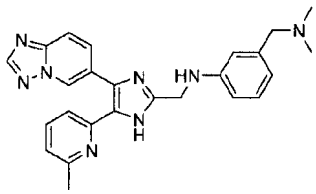
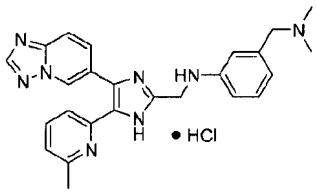
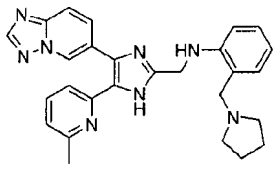
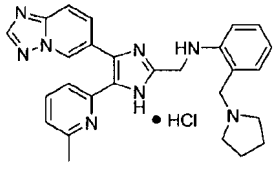
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
97		(400 MHz, DMSO-d_6) δ 10.03 (br s, 1 H), 9.48 (dd, 1 H, J = 1.6, 0.8 Hz), 8.62 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.8 Hz), 7.87–7.82 (m, 2 H), 7.64 (d, 1 H, J = 7.6 Hz), 7.38 (d, 1 H, J = 7.6 Hz), 7.33–7.27 (m, 2 H), 6.95 (br s, 1 H), 6.78–6.74 (m, 2 H), 4.81 (s, 2 H), 4.43 (s, 2 H), 2.77 (s, 6 H), 2.52 (s, 3 H)	
98		(400 MHz, $CDCl_3$) δ 9.02 (br s, 1 H), 8.35 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.74 (dd, 1 H, J = 9.2, 0.8 Hz), 7.46 (t, 1 H, J = 7.6 Hz), 7.27 (br d, 1 H, J = 7.6 Hz), 7.13 (t, 1 H, J = 7.8 Hz), 7.00 (d, 1 H, J = 7.6 Hz), 6.90 (br s, 1 H), 6.67 (d, 1 H, J = 7.6 Hz), 6.61 (dd, 1 H, J = 8.0, 2.0 Hz), 4.54 (s, 2 H), 3.48 (s, 2 H), 2.51 (s, 3 H), 2.30 (s, 6 H)	439.23
99		(400 MHz, DMSO-d_6) δ 10.69 (br s, 1 H), 9.48 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, J = 8.0 Hz), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.61 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.21 (t, 1 H, J = 8.2 Hz), 7.09 (br s, 1 H), 6.85 (dd, 1 H, overlapped, J = 8.4, 2.2 Hz), 6.82 (d, 1 H, J = 8.0 Hz), 4.76 (s, 2 H), 4.16 (d, 1 H, J = 4.8 Hz), 2.66 (d, 6 H, J = 4.4 Hz), 2.51 (s, 3 H)	
100		(400 MHz, $CDCl_3$) δ 10.40 (br s, 1 H), 8.98 (s, 1 H), 8.35 (s, 1 H), 7.83 (d, 1 H, J = 9.2 Hz), 7.75 (d, 1 H, J = 9.2 Hz), 7.43 (t, 1 H, J = 7.6 Hz), 7.20 (br s, 1 H, overlapped), 7.15 (td, 1 H, J = 8.0, 1.6 Hz), 7.04 (d, 1 H, J = 8.0 Hz), 6.98 (d, 1 H, J = 7.6 Hz), 6.69 (pseudo t, 2 H, J = 7.2 Hz), 4.58 (s, 2 H), 3.72 (s, 2 H), 2.56 (br s, 4 H), 2.50 (s, 3 H), 1.80 (br s, 4 H)	465.25
101		(400 MHz, DMSO-d_6) δ 10.29 (br s, 1 H), 9.47 (t, 1 H, J = 0.8 Hz), 8.62 (s, 1 H), 7.95 (d, 1 H, J = 9.2 Hz), 7.87–7.83 (m, 2 H), 7.65 (d, 1 H, J = 8.0 Hz), 7.38 (br d, 2 H, J = 7.6 Hz), 7.27 (td, 1 H, J = 8.0, 1.2 Hz), 6.75 (t, 1 H, overlapped, J = 7.6 Hz), 6.72 (d, 1 H, overlapped, J = 7.6 Hz), 4.82 (s, 2 H), 4.47 (s, 2 H), 3.44 (br s, 2 H), 3.17 (br s, 2 H), 2.52 (s, 3 H), 2.04 (br s, 2 H), 1.94 (br s, 2 H)	

TABLE 1-continued

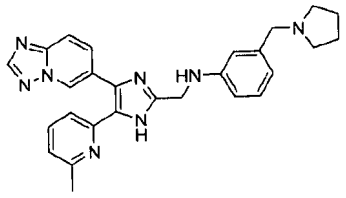
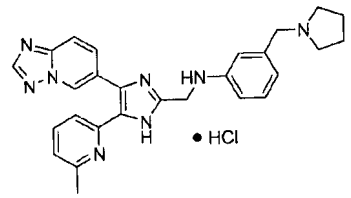
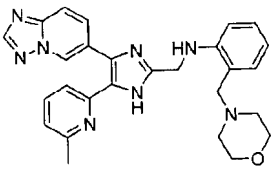
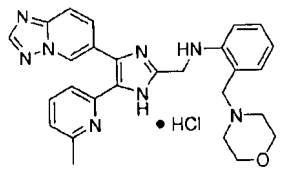
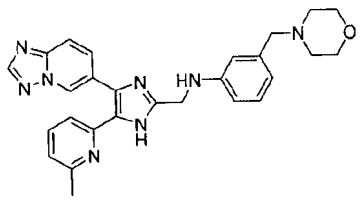
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
102		(400 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 8.35 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (d, 1 H, *J* = 9.2 Hz), 7.47 (t, 1 H, *J* = 7.8 Hz), 7.28 (br d, 1 H, *J* = 7.6 Hz), 7.11 (t, 1 H, *J* = 7.8 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.95 (br s, 1 H), 6.68 (d, 1 H, *J* = 7.6 Hz), 6.60 (dd, 1 H, *J* = 8.0, 2.0 Hz), 4.54 (s, 2 H), 3.65 (s, 2 H), 2.61 (br s, 4 H), 2.51 (s, 3 H), 1.78–1.75 (m, 4 H)	465.25
103		(400 MHz, DMSO-d_6) δ 10.93 (br s, 1 H), 9.48 (dd, 1 H, *J* = 1.2, 1.6 Hz), 8.63 (s, 1 H), 7.96 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.86–7.81 (m, 2 H), 7.61 (d, 1 H, *J* = 8.0 Hz), 7.37 (d, 1 H, *J* = 7.6 Hz), 7.19 (t, 1 H, *J* = 7.8 Hz), 7.15 (br s, 1 H), 6.86–6.81 (m, 2 H), 4.76 (s, 2 H), 4.22 (d, 2 H, *J* = 5.6 Hz), 3.29 (m, 2 H), 3.00 (m, 2 H), 2.51 (s, 3 H), 1.92 (m, 2 H), 1.82 (m, 2 H)	
104		(400 MHz, $CDCl_3$) δ 10.35 (br s, 1 H), 8.97 (s, 1 H), 8.36 (s, 1 H), 7.83 (d, 1 H, *J* = 9.2 Hz), 7.76 (d, 1 H, *J* = 9.2 Hz), 7.44 (t, 1 H, *J* = 7.6 Hz), 7.21 (br s, 1 H, overlapped), 7.19 (td, 1 H, *J* = 7.6, 1.6 Hz), 7.04 (dd, 1 H, *J* = 7.6, 1.6 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.73–6.68 (m, 2 H), 4.57 (s, 2 H), 3.71 (br s, 4 H), 3.63 (s, 2 H), 2.50 (br s, 7 H)	481.25
105		(400 MHz, DMSO-d_6) δ 9.46 (s, 1 H), 8.62 (s, 1 H), 7.96 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.85 (t, 1 H, overlapped, *J* = 8.0 Hz), 7.83 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.60 (d, 1 H, *J* = 8.0 Hz), 7.38 (br d, 2 H, *J* = 8.0 Hz), 7.29 (td, 1 H, *J* = 8.0, 1.2 Hz), 6.75 (t, 1 H, overlapped, *J* = 8.0 Hz), 6.74 (d, 1 H, overlapped, *J* = 8.0 Hz), 4.82 (s, 2 H), 4.45 (s, 2 H), 3.93 (br s, 4 H), 3.34 (br s, 4 H), 2.53 (s, 3 H)	
106		(400 MHz, $CDCl_3$) δ 10.78 (br s, 1 H), 8.97 (s, 1 H), 8.35 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.74 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.23 (br s, 1 H), 7.13 (t, 1 H, *J* = 7.8 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.79 (br s, 1 H), 6.71 (d, 1 H, *J* = 7.6 Hz), 6.59 (dd, 1 H, *J* = 8.0, 1.6 Hz), 4.53 (s, 2 H), 4.44 (br s, 1 H), 3.66 (m, 4 H), 3.45 (s, 2 H), 2.49 (s, 3 H), 2.44 (br s, 4 H)	481.25

TABLE 1-continued

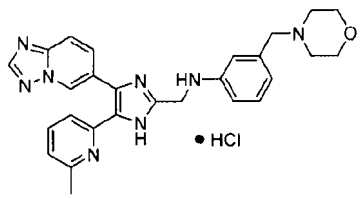
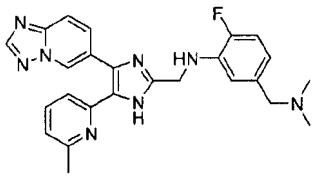
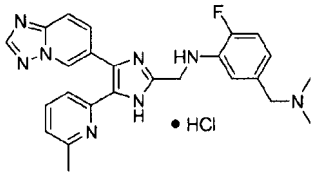
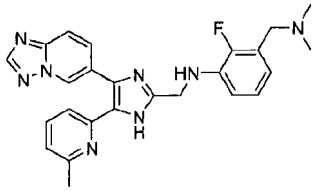
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
107		(400 MHz, DMSO-d_6/D_2O) δ 9.36 (dd, 1 H, J = 1.8, 1.0 Hz), 8.62 (s, 1 H), 7.95 (dd, 1 H, J = 9.4, 1.0 Hz), 7.87 (t, 1 H, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.4, 1.8 Hz), 7.48 (d, 1 H, J = 8.0 Hz), 7.42 (d, 1 H, J = 7.6 Hz), 7.28 (t, 1 H, J = 7.8 Hz), 6.90 (br s, 1 H), 6.86–6.82 (m, 2 H), 4.68 (s, 2 H Hz), 4.23 (s, 2 H), 3.70 (br s, 4 H), 3.22 (br s, 2 H), 3.14 (br s, 2 H), 2.58 (s, 3 H)	
108		(400 MHz, $CDCl_3$) δ 9.06 (s, 1 H), 8.34 (s, 1 H), 7.84 (dd, 1 H, J = 9.2, 1.6 Hz), 7.72 (d, 1 H, J = 9.2 Hz), 7.48 (t, 1 H, J = 7.6 Hz), 7.32 (br s, 1 H), 7.18 (br s, 1 H), 7.00 (d, 1 H, J = 7.6 Hz), 6.90 (dd, 1 H, J = 11.2, 8.0 Hz), 6.55–6.51 (m, 1 H), 4.78 (br s, 1 H), 4.59 (d, 2 H, J = 6.4 Hz), 3.54 (s, 2 H), 2.50 (s, 3 H), 2.34 (s, 6 H)	457.22
109		(400 MHz, DMSO-d_6) δ 10.73 (br s, 1 H), 9.46 (t, 1 H, J = 1.2 Hz), 8.62 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.82 (t, 1 H, overlapped, J = 7.8 Hz), 7.55 (d, 1 H, J = 8.0 Hz), 7.37 (dd, 1 H, overlapped, J = 8.2, 2.0 Hz), 7.36 (d, 1 H, J = 7.6 Hz), 7.18 (dd, 1 H, J = 11.8, 8.2 Hz), 6.82–6.78 (m, 1 H), 4.79 (s, 2 H), 4.17 (br s, 2 H), 2.64 (d, 6 H, J = 1.6 Hz), 2.52 (s, 3 H)	
110		(400 MHz, $CDCl_3$) δ 8.99 (br s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.76 (d, 1 H, J = 9.2 Hz), 7.46 (t, 1 H, J = 7.8 Hz), 7.24 (br s, 1 H), 6.99 (d, 1 H, overlapped, J = 8.0 Hz), 6.95 (t, 1 H, overlapped, J = 8.0 Hz), 6.76–6.70 (m, 2 H), 4.73 (br s, 1 H), 4.56 (d, 2 H, J = 5.6 Hz), 3.60 (s, 2 H), 2.50 (s, 3 H), 2.36 (s, 6 H)	457.23

TABLE 1-continued

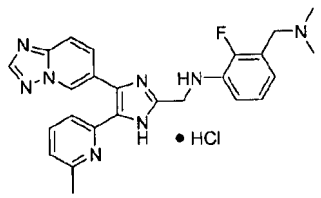
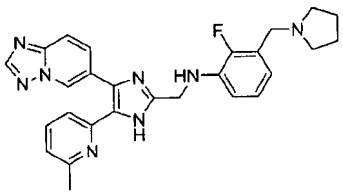
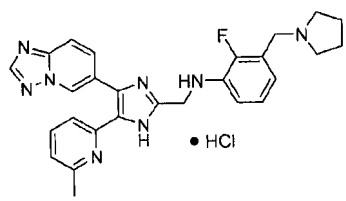
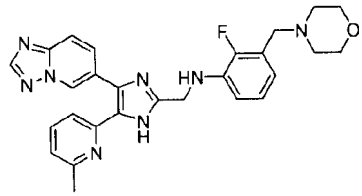
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
111		(400 MHz, DMSO-d_6) δ 10.62 (br s, 1 H), 9.46 (s, 1 H), 8.62 (s, 1 H), 7.96 (d, 1 H, J = 9.2 Hz), 7.84 (t, 1 H, overlapped, J = 8.0 Hz), 7.83 (d, 1 H, overlapped, J = 9.2 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.10 (t, 1 H, J = 7.6 Hz), 7.02 (t, 1 H, J = 7.6 Hz), 6.93 (pseudo t, 1 H, J = 6.6 Hz), 4.78 (s, 2 H), 4.30 (d, 2 H, J = 4.8 Hz), 2.72 (d, 6 H, J = 4.4 Hz), 2.53 (s, 3 H)	
112		(400 MHz, $CDCl_3$) δ 11.11 (br s, 1 H), 8.98 (s, 1 H), 8.35 (s, 1 H), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.73 (d, 1 H, J = 9.2 Hz), 7.44 (t, 1 H, J = 7.8 Hz), 7.23 (br s, 1 H), 6.97 (d, 1 H, J = 8.0 Hz), 6.91 (t, 1 H, J = 8.0 Hz), 6.75 (td, 1 H, J = 8.0, 1.2 Hz), 6.65 (td, 1 H, J = 8.0, 1.2 Hz), 4.66 (br s, 1 H), 4.51 (d, 2 H, J = 5.6 Hz), 3.66 (s, 2 H), 2.59 (br s, 4 H), 2.42 (s, 3 H), 1.81–1.75 (m, 4 H)	483.24
113		(400 MHz, DMSO-d_6) δ 10.84 (br s, 1 H), 9.46 (s, 1 H), 8.62 (s, 1 H), 7.95 (d, 1 H, J = 9.2 Hz), 7.84 (t, 1 H, J = 7.8 Hz), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.36 (d, 1 H, J = 7.6 Hz), 7.08 (t, 1 H, J = 7.8 Hz), 7.03–6.96 (m, 2 H), 4.77 (s, 2 H), 4.36 (d, 2 H, J = 5.2 Hz), 3.39 (m, 2 H), 3.07 (m, 2 H), 2.53 (s, 3 H), 2.03–1.87 (m, 4 H)	
114		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.36 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 2.0 Hz), 7.76 (dd, 1 H, J = 9.2, 0.8 Hz), 7.46 (t, 1 H, J = 7.6 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.00 (d, 1 H, J = 7.6 Hz), 6.95 (t, 1 H, J = 8.0 Hz), 6.76 (t, 1 H, J = 7.6 Hz), 6.70 (td, 1 H, J = 8.0, 1.6 Hz), 4.67 (br s, 1 H), 4.54 (d, 2 H, J = 4.8 Hz), 3.73 (m, 4 H), 3.59 (s, 2 H), 2.53 (br s, 4 H), 2.47 (s, 3 H)	499.24

TABLE 1-continued

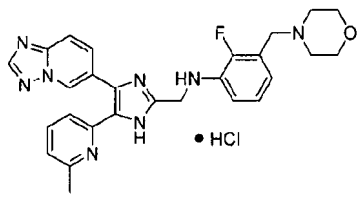
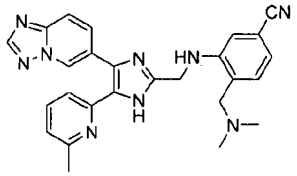
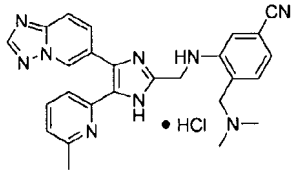
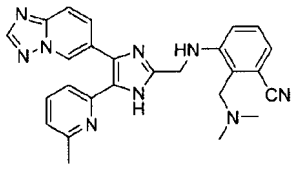
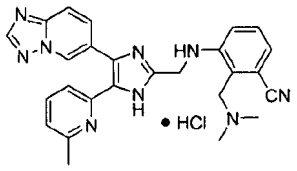
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
115		(400 MHz, DMSO-d_6) δ 11.18 (br s, 1 H), 9.46 (dd, 1 H, J = 1.6, 1.2 Hz), 8.62 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, overlapped, J = 7.8 Hz), 7.83 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.57 (d, 1 H, J = 7.6 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.10 (t, 1 H, J = 7.8 Hz), 7.05–6.99 (m, 2 H), 4.78 (s, 2 H), 4.34 (s, 2 H), 3.93 (br s, 2 H), 3.81 (br t, 2 H, J = 11.8 Hz) 3.29 (br s, 2 H), 3.13 (br s, 2 H), 2.53 (s, 3 H)	
116		(400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.36 (s, 1 H), 7.86 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.47 (t, 1 H, J = 7.6 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.09 (d, 1 H, J = 7.6 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.98 (dd, 1 H, J = 7.6, 1.6 Hz), 6.93 (br s, 1 H), 4.59 (s, 2 H), 3.63 (s, 2 H), 2.53 (s, 3 H), 2.33 (s, 6 H)	464.23
117		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.60 (s, 1 H), 7.94 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, overlapped, J = 7.6 Hz), 7.84 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.57 (d, 1 H, J = 7.6 Hz), 7.52 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.30 (br s, 1 H), 7.19–7.17 (m, 2 H), 4.79 (s, 2 H), 4.48 (s, 2 H), 2.78 (s, 6 H), 2.55 (s, 3 H)	
118		(400 MHz, DMSO-d_6) δ 12.70 (br s, 1 H), 9.54 (s, 1 H), 8.50 (s, 1 H), 7.99 (dd, 1 H, J = 9.2, 2.0 Hz), 7.83 (dd, 1 H, J = 9.2, 0.8 Hz), 7.72 (t, 1 H, J = 7.8 Hz), 7.52 (br s, 1 H), 7.32 (t, 1 H, J = 7.6 Hz), 7.17–7.13 (m, 2 H), 7.07 (d, 1 H, J = 8.0 Hz), 7.02 (dd, 1 H, J = 7.6, 0.8 Hz), 4.48 (d, 2 H, J = 5.6 Hz), 3.68 (s, 2 H), 2.47 (s, 3 H), 2.23 (s, 6 H)	464.23
119		(400 MHz, DMSO-d_6) δ 9.48 (t, 1 H, J = 1.2 Hz), 8.60 (s, 1 H), 7.92 (dd, 1 H, J = 9.2, 1.2 Hz), 7.86 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.85 (t, 1 H, overlapped, J = 8.0 Hz), 7.64 (d, 1 H, J = 8.0 Hz), 7.49 (t, 1 H, J = 7.8 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.24 (dd, 1 H, J = 7.6, 0.8 Hz), 7.10 (dd, 1 H, J = 8.0, 0.8 Hz), 4.81 (s, 2 H), 4.61 (s, 2 H), 2.89 (s, 6 H), 2.52 (s, 3 H)	

TABLE 1-continued

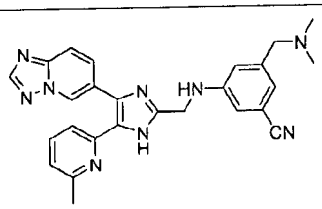
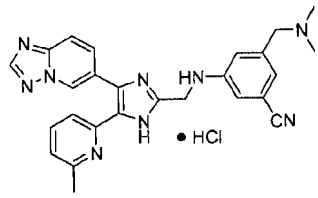
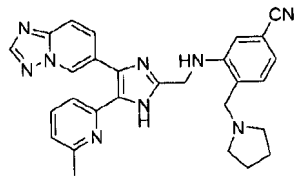
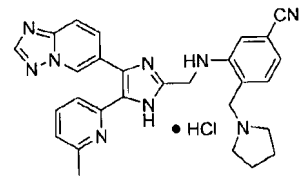
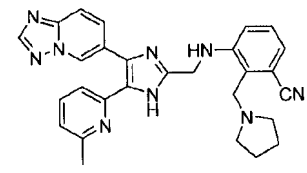
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
120		(400 MHz, $CDCl_3$) δ 9.01 (s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.49 (t, 1 H, *J* = 7.6 Hz), 7.28 (br d, 1 H, *J* = 7.6 Hz), 7.15 (br s, 1 H), 7.03 (d, 1 H, *J* = 7.6 Hz), 6.94 (s, 1 H), 6.82 (dd, 1 H, *J* = 2.0, 1.2 Hz), 4.86 (br s, 1 H), 4.55 (d, 2 H, *J* = 5.6 Hz), 3.48 (s, 2 H), 2.54 (s, 3 H), 2.32 (s, 6 H)	464.23
121		(400 MHz, DMSO-d_6) δ 10.77 (br s, 1 H), 9.46 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.60 (s, 1 H), 7.94 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.85 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.84 (t, 1 H, overlapped, *J* = 7.8 Hz), 7.55 (d, 1 H, *J* = 7.6 Hz), 7.36 (d, 1 H, overlapped, *J* = 8.0 Hz), 7.35 (s, 1 H, overlapped), 7.23 (br s, 2 H), 4.71 (s, 2 H), 4.22 (s, 2 H), 2.67 (s, 6 H), 2.53 (s, 3 H)	
122		(400 MHz, $CDCl_3$) δ 10.40 (br s, 1 H), 8.96 (s, 1 H), 8.36 (s, 1 H), 7.84 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.24 (br d, 1 H, *J* = 7.6 Hz), 7.09 (d, 1 H, *J* = 7.6 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.96 (dd, 1 H, *J* = 7.6, 1.6 Hz), 6.86 (br s, 1 H), 4.55 (s, 2 H), 3.74 (s, 2 H), 2.54 (br s, 4 H), 2.51 (s, 3 H), 1.81 (br s, 4 H)	490.25
123		(400 MHz, DMSO-d_6) δ 10.47 (br s, 2 H), 9.46 (s, 1 H), 8.61 (s, 1 H), 7.95 (dd, 1 H, *J* = 9.2, 0.4 Hz), 7.86 (t, 1 H, overlapped, *J* = 7.6 Hz), 7.85 (dd, 1 H, overlapped, *J* = 9.2, 1.2 Hz), 7.60 (d, 1 H, *J* = 7.6 Hz), 7.59 (d, 1 H, *J* = 8.0 Hz), 7.39 (d, 1 H, *J* = 7.6 Hz), 7.32 (br s, 1 H), 7.18 (dd, 1 H, *J* = 7.6, 1.6 Hz), 7.14 (d, 1 H, *J* = 1.6 Hz), 4.82 (s, 2 H), 4.53 (s, 2 H), 3.23 (br s, 4 H), 2.55 (s, 3 H), 1.99 (br s, 4 H)	
124		(400 MHz, DMSO-d_6) δ 12.71 (br s, 1 H), 9.52 (s, 1 H), 8.50 (s, 1 H), 7.98 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.83 (d, 1 H, *J* = 9.2 Hz), 7.71 (t, 1 H, *J* = 7.8 Hz), 7.51 (br s, 1 H), 7.37 (t, 1 H, *J* = 5.2 Hz), 7.31 (t, 1 H, *J* = 8.0 Hz), 7.16 (d, 1 H, *J* = 7.6 Hz), 7.05 (d, 1 H, *J* = 8.0 Hz), 7.00 (dd, 1 H, *J* = 8.0, 1.2 Hz), 4.47 (d, 2 H, *J* = 5.2 Hz), 3.87 (s, 2 H), 2.51 (br s, 4 H), 2.47 (s, 3 H), 1.74 (br s, 4 H)	490.25

TABLE 1-continued

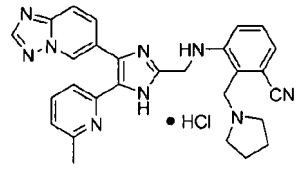
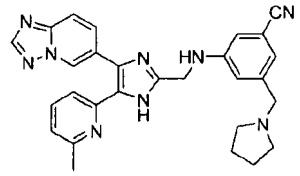
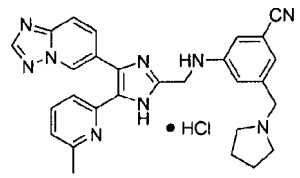
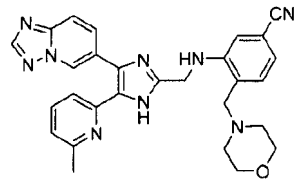
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
125		(400 MHz, DMSO-d_6/D_2O) δ 9.41 (dd, 1 H, J = 1.6, 0.8 Hz), 8.61 (s, 1 H), 7.94 (dd, 1 H, J = 9.2, 0.8 Hz), 7.89 (t, 1 H, J = 7.8 Hz), 7.84 (dd, 1 H, J = 9.2, 1.6 Hz), 7.55 (d, 1 H, J = 8.0 Hz), 7.50 (t, 1 H, J = 7.6 Hz), 7.42 (d, 1 H, J = 7.6 Hz), 7.25 (dd, 1 H, J = 7.6, 0.8 Hz), 7.09 (d, 1 H, J = 7.6 Hz), 4.78 (s, 2 H), 4.64 (s, 2 H), 3.45 (br s, 4 H), 2.58 (s, 3 H), 2.06 (br s, 4 H)	
126		(400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.36 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.77 (d, 1 H, J = 9.2 Hz), 7.48 (t, 1 H, J = 7.6 Hz), 7.27 (br d, 1 H, J = 7.6 Hz), 7.13 (br s, 1 H), 7.03 (d, 1 H, J = 7.6 Hz), 6.97 (br s, 1 H), 6.81 (dd, 1 H, J = 2.4, 1.2 Hz), 4.81 (br s, 1 H), 4.54 (d, 2 H, J = 5.6 Hz), 3.62 (s, 2 H), 2.57 (br s, 4 H), 2.54 (s, 3 H), 1.79 (br s, 4 H)	490.25
127		(400 MHz, DMSO-d_6) δ 10.96 (br s 1 H), 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.60 (s, 1 H), 7.94 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.83 (t, 1 H, overlapped, J = 7.8 Hz), 7.54 (d, 1 H, J = 8.0 Hz), 7.39 (br s, 1 H), 7.36 (d, 1 H, J = 7.6 Hz), 7.26 (s, 1 H), 7.21 (dd, 1 H, J = 2.0, 1.6 Hz), 4.72 (s, 2 H), 4.29 (s, 2 H), 3.02 (br s, 4 H), 2.53 (s, 3 H), 1.95 (br s, 2 H), 1.84 (br s, 2 H)	
128		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.37 (s, 1 H), 7.84 (dd, 1 H, J = 9.2, 1.6 Hz), 7.79 (dd, 1 H, J = 9.2, 1.2 Hz), 7.49 (t, 1 H, J = 7.8 Hz), 7.29 (br d, 1 H, J = 8.0 Hz), 7.12 (d, 1 H, J = 7.6 Hz), 7.03 (d, 1 H, J = 7.6 Hz), 6.99 (dd, 1 H, J = 7.6, 1.6 Hz), 6.93 (br s, 1 H), 4.57 (s, 2 H), 3.75 (br s, 4 H, overlapped), 3.72 (s, 2 H, overlapped), 2.55 (br s, 7 H)	506.25

TABLE 1-continued

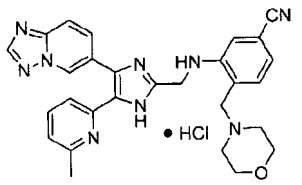
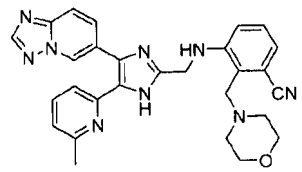
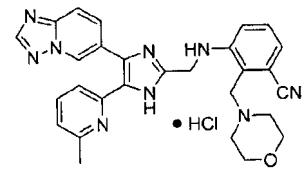
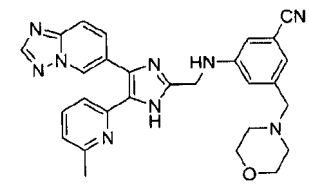
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
129		(400 MHz, DMSO-d_6) δ 9.45 (d, 1 H, J = 0.4 Hz), 8.61 (s, 1 H), 7.96 (d, 1 H, J = 9.2 Hz), 7.86 (t, 1 H, overlapped, J = 8.0 Hz), 7.85 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.60 (d, 1 H, J = 8.0 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 8.0 Hz), 7.19 (s, 1 H), 7.17 (dd, 1 H, overlapped, J = 8.0, 1.2 Hz), 4.82 (s, 2 H), 4.52 (s, 2 H), 3.91 (br s, 4 H), 3.32 (br s, 4 H), 2.55 (s, 3 H)	
130		(400 MHz, DMSO-d_6) δ 12.70 (br s, 1 H), 9.48 (br s, 1 H), 8.50 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 1.6 Hz), 7.84 (d, 1 H, J = 9.2 Hz), 7.71 (t, 1 H, J = 7.6 Hz), 7.44 (br s, 1 H), 7.34 (t, 1 H, J = 8.0 Hz), 7.28 (t, 1 H, J = 5.6 Hz), 7.16 (d, 1 H, J = 7.6 Hz), 7.07 (d, 1 H, J = 8.4 Hz), 7.03 (dd, 1 H, J = 7.6, 1.2 Hz), 4.49 (d, 2 H, J = 5.6 Hz), 3.76 (s, 2 H), 3.58 (m, 4 H), 2.48 (s, 3 H), 2.41 (br s, 4 H)	506.24
131		(400 MHz, DMSO-d_6) δ 9.46 (d, 1 H, J = 0.8 Hz), 8.60 (s, 1 H), 7.94 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, overlapped, J = 7.6 Hz), 7.84 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.60 (d, 1 H, J = 7.6 Hz), 7.47 (t, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.22 (dd, 1 H, J = 7.6, 0.8 Hz), 7.08 (d, 1 H, J = 8.0 Hz), 4.82 (s, 2 H), 4.57 (s, 2 H), 3.95 (br t, 4 H, J = 4.4 Hz), 3.40 (br s, 4 H), 2.53 (s, 3 H)	
132		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.38 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.48 (t, 1 H, J = 7.6 Hz), 7.28 (br d, 1 H, J = 7.6 Hz), 7.06 (br s, 1 H, overlapped), 7.04 (d, 1 H, J = 7.6 Hz), 7.01 (s, 1 H), 6.84 (dd, 1 H, J = 2.0, 1.2 Hz), 4.79 (br s, 1 H), 4.54 (d, 2 H, J = 7.6 Hz), 3.70 (m, 4 H), 3.48 (s, 2 H), 2.55 (s, 3 H), 2.47 (br s, 4 H)	506.24

TABLE 1-continued

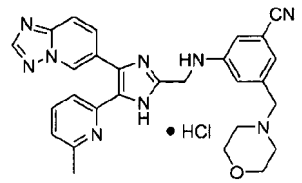
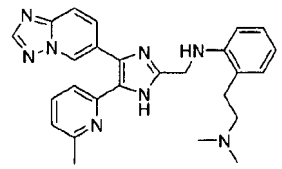
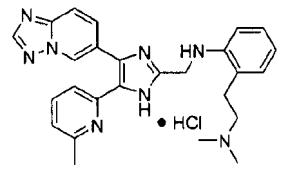
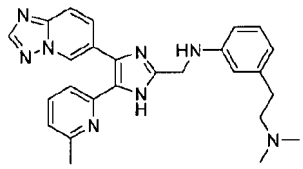
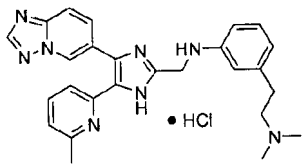
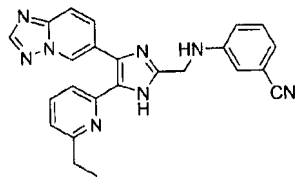
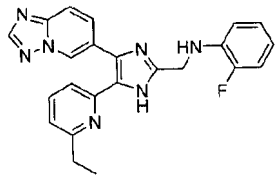
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
133		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.61 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, overlapped, J = 7.6 Hz), 7.84 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.54 (d, 1 H, J = 7.6 Hz), 7.43 (br s, 1 H), 7.37 (d, 1 H, J = 7.6 Hz), 7.28 (s, 1 H), 7.23 (dd, 1 H, J = 2.2, 1.4 Hz), 4.74 (s, 2 H), 4.28 (s, 2 H), 3.83 (br s, 4 H), 3.81 (br s, 2 H), 3.08 (br s, 2 H), 2.54 (s, 3 H)	
134		(400 MHz, $CDCl_3$) δ 8.98 (s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.76 (dd, 1 H, J = 9.2, 0.8 Hz), 7.45 (t, 1 H, J = 7.8 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.13 (td, 1 H, J = 8.0, 1.2 Hz), 7.04 (dd, 1 H, J = 8.0, 1.2 Hz), 6.99 (d, 1 H, J = 8.0 Hz), 6.72 (d, 1 H, overlapped, J = 7.6 Hz), 6.71 (td, 1 H, overlapped, J = 8.0, 1.2 Hz), 4.56 (s, 2 H), 2.81 (t, 2 H, J = 6.4 Hz), 2.63 (t, 2 H, J = 6.4 Hz), 2.52 (s, 3 H), 2.36 (s, 6 H)	453.25
135		(400 MHz, DMSO-d_6/D_2O) δ 9.40 (dd, 1 H, J = 1.8, 0.8 Hz), 8.63 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.86 (t, 1 H, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.2, 1.8 Hz), 7.48 (d, 1 H, J = 8.0 Hz), 7.41 (d, 1 H, J = 7.6 Hz), 7.17–7.12 (m, 2 H), 6.75–671 (m, 2 H), 4.73 (s, 2 H), 3.32 (br t, 2 H, J = 8.4 Hz), 3.02 (br t, 2 H, J = 8.4 Hz), 2.90 (s, 6 H), 2.58 (s, 3 H)	
136		(400 MHz, $CDCl_3$) δ 9.08 (s, 1 H), 8.32 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.68 (d, 1 H, J = 9.2 Hz), 7.47 (t, 1 H, J = 7.6 Hz), 7.34 (br d, 1 H, J = 7.6 Hz), 7.04 (t, 1 H, J = 7.6 Hz), 6.99 (dd, 1 H, J = 7.6, 0.4 Hz), 6.66 (br s, 1 H), 6.53–6.49 (m, 2 H), 4.48 (s, 2 H), 2.89–2.83 (m 4 H), 2.56 (s, 6 H), 2.48 (s, 3 H)	453.25

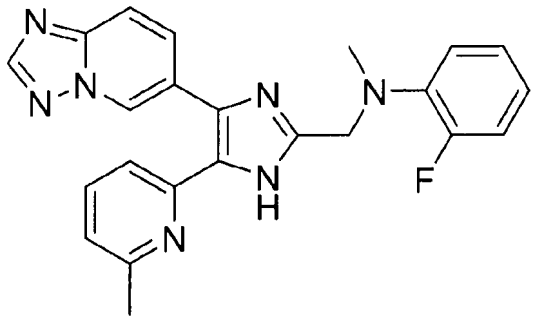
TABLE 1-continued

Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
137		(400 MHz, DMSO-d_6) δ 10.47 (br s, 1 H), 9.49 (t, 1 H, J = 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (dd, 1 H, overlapped, J = 9.2, 1.2 Hz), 7.84 (t, 1 H, overlapped, J = 7.8 Hz), 7.64 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 7.6 Hz), 7.10 (t, 1 H, J = 8.0 Hz), 6.81 (br s, 1 H), 6.66 (dd, 1 H, J = 8.0, 1.6 Hz), 6.58 (d, 1 H, J = 8.0 Hz), 4.75 (s, 2 H), 3.30–3.25 (m, 2 H), 2.94–2.89 (m, 2 H), 2.77 (d, 6 H, J = 4.8 Hz), 2.51 (s, 3 H)	
138		(400 MHz, $CDCl_3$) δ 10.40 (br s, 1 H), 8.94 (s, 1 H), 8.38 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.2 Hz), 7.80 (dd, 1 H, J = 9.2, 0.8 Hz), 7.49 (t, 1 H, J = 7.8 Hz), 7.30–7.27 (m, 1 H), 7.24 (d, 1 H, J = 8.0 Hz), 7.06 (dt, 1 H, overlapped, J = 7.6, 1.2 Hz), 7.05 (d, 1 H, overlapped, J = 7.6 Hz), 6.94–6.93 (m, 2 H), 4.72 (t, 1 H, J = 5.2 Hz), 4.54 (d, 2 H, J = 5.2 Hz), 2.82 (q, 2 H, J = 7.6 Hz), 1.31 (t, 3 H, J = 7.6 Hz)	421.21
139		(400 MHz, $CDCl_3$) δ 10.37 (br s, 1 H), 8.96 (s, 1 H), 8.38 (s, 1 H), 7.84 (dd, 1 H, J = 9.2, 1.2 Hz), 7.79 (dd, 1 H, J = 9.2, 0.8 Hz), 7.48 (t, 1 H, J = 7.8 Hz), 7.22 (d, 1 H, J = 8.0 Hz), 7.06–7.00 (m, 3 H), 6.80 (td, 1 H, J = 8.0, 1.2 Hz), 6.76–6.70 (m, 1 H), 4.62 (br s, 1 H, overlapped), 4.60 (s, 2 H), 2.80 (q, 2 H, J = 7.6 Hz), 1.29 (t, 3 H, J = 7.6 Hz)	414.20

[0412] Practice Example 5

[0413]

[0414] Preparation of *N*-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoro-*N*-methylaniline (Example 140)

[0415] 

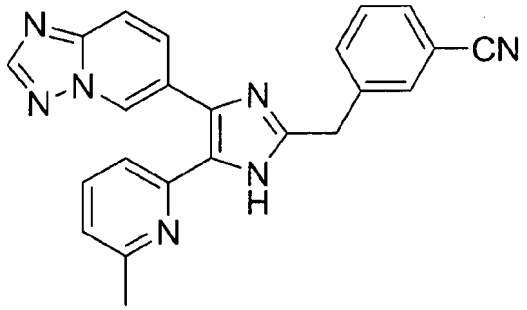
[0416] To a stirred solution of 1-((1,2,4)triazolo(1,5-*a*)pyridin-6-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione (0.20 g, 0.75 mmol) in a mixture of *tert*-butyl methyl ether (10 mL) and MeOH (8 mL) were added 2-((2-fluorophenyl)(methyl)amino)acetaldehyde (190 mg, 1.13 mmol) and NH_4OAc (0.15 g, 1.88 mmol), and the mixture was stirred at room temperature for 2 h. The pH of the mixture was adjusted to 8 with saturated aqueous $NaHCO_3$ solution. After removal of the solvent, the reaction mixture was extracted with $CHCl_3$ (2 × 100 mL), and the $CHCl_3$ solution was washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of MeOH and CH_2Cl_2 (1:19 (v/v)) as eluent to give the titled compound (90 mg, 32%) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 1.2 Hz), 7.49 (t, 1 H, J = 7.8 Hz), 7.25 (br d, 1 H, J = 7.6 Hz), 7.14—7.06 (m, 3 H), 7.04 (d, 1 H, J = 7.6 Hz), 7.00—6.94 (m, 1 H), 4.44 (s, 2 H), 2.91 (s, 3 H), 2.58 (s, 3 H); MS (ESI) *m/z* 414.20 (MH^+).

[0417]

[0418] Practice Example 6

[0419]

[0420] Preparation of 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)benzonitrile (Example 145)

[0421] 

[0422] To a stirred solution of 1-((1,2,4)triazolo(1,5-*a*)pyridin-6-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione (4.00 g, 15.02 mmol) in a

mixture of *tert*-butyl methyl ether (30 mL) and MeOH (30 mL) were added 3-(fomylmethyl)benzonitrile (prepared according to the method described in WO 02/096875 A1) (6.54 g, 45.07 mmol) and NH_4OAc (11.58 g, 150.24 mmol), and the mixture was stirred at room temperature for 90 min. The pH of the mixture was adjusted to 8 with saturated aqueous $NaHCO_3$ solution. After removal of solvent, the mixture was extracted with EtOAc (2 × 150 mL), and the EtOAc solution was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of MeOH and CH_2Cl_2 (1:19 (v/v)) as eluent to give the titled compound (1.92 g, 33%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.70 (br s, 1 H), 9.53 (br s, 1 H), 8.49 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 1.8 Hz), 7.84 (d, 1 H, J = 2.0 Hz), 7.82 (d, 1 H, J = 9.2 Hz), 7.74—7.71 (m, 2 H), 7.69 (t, 1 H, overlapped, J = 7.6 Hz), 7.56 (t, 1 H, J = 7.8 Hz), 7.47 (br s, 1 H), 7.15 (d, 1 H, J = 7.6 Hz), 4.18 (s, 2 H), 2.47 (s, 3 H); MS (ESI) *m/z* 392.18 (MH^+).

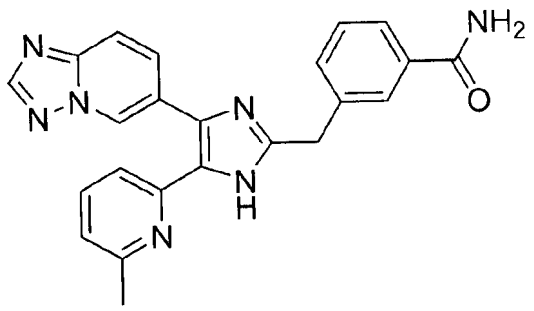
[0423]

[0424] Practice Example 7

[0425]

[0426] Preparation of 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)benzamide (Example 147)

[0427]



[0428] To a stirred solution of 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)benzonitrile(41 mg, 0.10 mmol) in EtOH (2 mL) were added 28% H_2O_2 (13.9 mL, 0.11 mmol) and 1N NaOH (0.39 mL, 0.39 mmol) at room temperature. The mixture was heated to at 60°C for 1 h and then, to it, was added 1 N HCl at 0°C to adjust pH 7-8. After removal of the solvent, the residue was extracted with CH_2Cl_2 (2 × 15 mL). The CH_2Cl_2 solution was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by MPLC on silica gel using a mixture of MeOH and CH_2Cl_2 (1:9 (v/v)) as eluent to give the titled compound (15 mg, 35%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 8.32 (s, 1 H), 7.77 (s, 1 H), 7.76 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.69

(d, 1 H, J = 9.2 Hz), 7.56 (d, 1 H, J = 8.0 Hz), 7.44 (t, 1 H, J = 7.6 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.26 (t, 1 H, J = 8.0 Hz), 7.21 (d, 1 H, J = 7.6 Hz), 6.98 (d, 1 H, J = 7.6 Hz), 6.60 (br s, 1 H), 6.27 (br s, 1 H), 4.15 (s, 2 H), 2.44 (s, 3 H); MS (ESI) m/z 410.19 (MH^+).

[0429] The compounds listed in the following Table 2 were prepared in an analogous manner to those described in the Practice Examples 5-7 above. The mass spectroscopy data of these compounds are included in the Table 2.

[0430]

[Table 2]

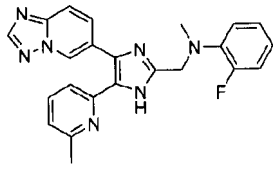
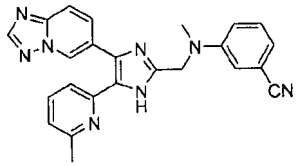
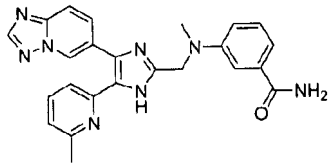
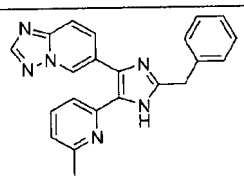
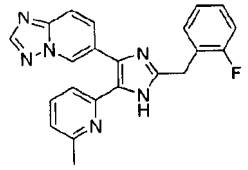
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
140		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.49 (t, 1 H, *J* = 7.8 Hz), 7.25 (br d, 1 H, *J* = 7.6 Hz), 7.14–7.06 (m, 3 H), 7.04 (d, 1 H, *J* = 7.6 Hz), 7.00–6.94 (m, 1 H), 4.44 (s, 2 H), 2.91 (s, 3 H), 2.58 (s, 3 H)	414.20
141		(400 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 8.37 (s, 1 H), 7.80–7.78 (m, 2 H), 7.48 (t, 1 H, *J* = 7.6 Hz), 7.35–7.30 (m, 1 H), 7.24 (br d, 1 H, *J* = 8.0 Hz), 7.08–7.05 (m, 3 H), 7.02 (d, 1 H, *J* = 7.6 Hz), 4.67 (s, 2 H), 3.14 (s, 3 H), 2.50 (s, 3 H)	421.20
142		(400 MHz, $CDCl_3/CD_3OD$) δ 8.86 (dd, 1 H, *J* = 1.6, 1.2 Hz), 8.18 (s, 1 H), 7.62 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.57 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.43 (t, 1 H, *J* = 8.0 Hz), 7.24 (dd, 1 H, *J* = 2.4, 1.6 Hz), 7.14 (t, 1 H, overlapped, *J* = 8.0 Hz), 7.13 (d, 1 H, overlapped, *J* = 8.0 Hz), 7.04 (ddd, 1 H, *J* = 8.0, 1.2, 0.8 Hz), 6.97 (d, 1 H, *J* = 7.6 Hz), 6.83 (ddd, 1 H, *J* = 8.0, 2.4, 0.8 Hz), 4.54 (s, 2 H), 2.99 (s, 3 H), 2.38 (s, 3 H)	439.22
143		(400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 8.36 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.40–7.28 (m, 5 H), 7.20 (br d, 1 H, *J* = 8.0 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 4.21 (s, 2 H), 2.51 (s, 3 H)	367.18
144		(400 MHz, $CDCl_3$) δ 8.93 (t, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.80 (dd, 1 H, overlapped, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, overlapped, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.39 (td, 1 H, *J* = 7.6, 1.6 Hz), 7.31–7.25 (m, 1 H), 7.21 (br d, 1 H, *J* = 8.0 Hz), 7.14 (td, 1 H, overlapped, *J* = 7.6, 1.2 Hz), 7.10 (dd, 1 H, *J* = 8.4, 1.2 Hz), 7.02 (br d, 1 H, *J* = 7.6 Hz), 4.24 (s, 2 H), 2.55 (s, 3 H)	385.17

TABLE 2-continued

[0431]

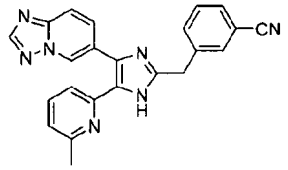
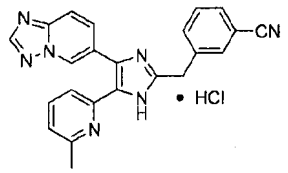
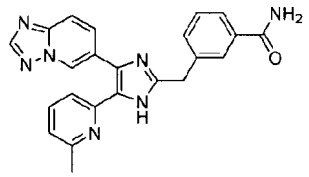
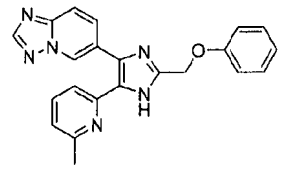
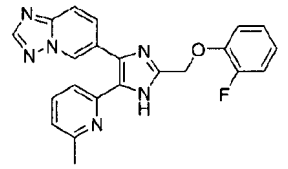
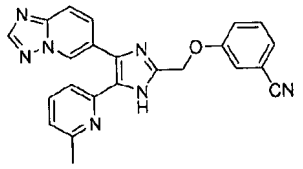
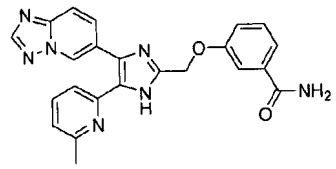
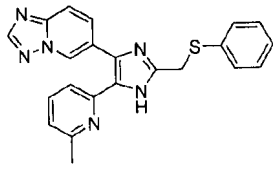
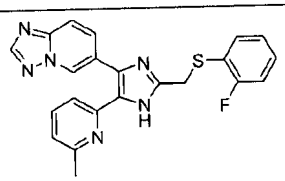
Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
145		(400 MHz, DMSO-d_6) δ 12.70 (br s, 1 H), 9.53 (br s, 1 H), 8.49 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 1.8 Hz), 7.84 (d, 1 H, J = 2.0 Hz), 7.82 (d, 1 H, J = 9.2 Hz), 7.74–7.71 (m, 2 H), 7.69 (t, 1 H, overlapped, J = 7.6 Hz), 7.56 (t, 1 H, J = 7.8 Hz), 7.47 (br s, 1 H), 7.15 (d, 1 H, J = 7.6 Hz), 4.18 (s, 2 H), 2.47 (s, 3 H)	392.18
146		(400 MHz, DMSO-d_6) δ 9.51 (dd, 1 H, J = 1.6, 0.8 Hz), 8.65 (s, 1 H), 8.08 (br s, 1 H), 7.97 (dd, 1 H, overlapped, J = 9.2, 0.8 Hz), 7.95 (br d, overlapped, 1 H, J = 8.0 Hz), 7.87 (dd, 1 H, J = 9.2, 1.6 Hz), 7.85–7.79 (m, 2 H), 7.63 (dd, 1 H, overlapped, J = 7.6, 1.2 Hz), 7.61 (t, 1 H, overlapped, J = 7.6 Hz), 7.36 (d, 1 H, J = 7.6 Hz), 4.55 (s, 2 H), 2.50 (s, 3 H)	
147		(400 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 8.32 (s, 1 H), 7.77 (s, 1 H), 7.76 (dd, 1 H, overlapped, J = 9.2, 1.6 Hz), 7.69 (d, 1 H, J = 9.2 Hz), 7.56 (d, 1 H, J = 8.0 Hz), 7.44 (t, 1 H, J = 7.6 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.26 (t, 1 H, J = 8.0 Hz), 7.21 (d, 1 H, J = 7.6 Hz), 6.98 (d, 1 H, J = 7.6 Hz), 6.60 (br s, 1 H), 6.27 (br s, 1 H), 4.15 (s, 2 H), 2.44 (s, 3 H)	410.19
148		(400 MHz, $CDCl_3$) δ 8.94 (s, 1 H), 8.37 (s, 1 H), 7.77–7.72 (m, 2 H), 7.51 (t, 1 H, J = 7.6 Hz), 7.32–7.25 (m, 3 H), 7.06 (d, 1 H, J = 7.6 Hz), 7.00 (t, 1 H, overlapped, J = 7.6 Hz), 6.97 (d, 2 H, overlapped, J = 8.0 Hz), 5.22 (s, 2 H), 2.54 (s, 3 H)	383.17
149		(400 MHz, $CDCl_3$) δ 8.95 (t, 1 H, J = 1.2 Hz), 8.38 (s, 1 H), 7.80 (dd, 1 H, J = 9.2, 0.8 Hz), 7.77 (dd, 1 H, J = 9.2, 1.2 Hz), 7.56 (t, 1 H, J = 8.0 Hz), 7.31 (d, 1 H, J = 7.6 Hz), 7.19 (td, 1 H, J = 8.0, 1.6 Hz), 7.14–7.06 (m, 3 H), 7.01–6.95 (m, 1 H), 5.34 (s, 2 H), 2.64 (s, 3 H)	401.17

TABLE 2-continued

Example	Structure	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
150		(400 MHz, $CDCl_3/CD_3OD$) δ 8.94 (dd, 1 H, *J* = 1.6, 1.2 Hz), 8.32 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.52 (t, 1 H, *J* = 7.8 Hz), 7.42–7.37 (m, 1 H), 7.31–7.26 (m, 3 H), 7.25 (br d, 1 H, overlapped, *J* = 8.0 Hz), 7.07 (d, 1 H, *J* = 7.6 Hz), 5.23 (s, 2 H), 2.55 (s, 3 H)	408.17
151		(400 MHz, $CDCl_3/CD_3OD$) δ 8.94 (t, 1 H, *J* = 1.6 Hz), 8.31 (s, 1 H), 7.76 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.70 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.51–7.47 (m, 2 H), 7.42 (ddd, 1 H, *J* = 8.0, 2.4, 1.2 Hz), 7.31 (t, 1 H, *J* = 8.0 Hz), 7.23 (d, 1 H, *J* = 7.6 Hz), 7.12 (ddd, 1 H, *J* = 8.0, 2.4, 0.8 Hz), 7.04 (d, 1 H, *J* = 7.6 Hz), 5.22 (s, 2 H), 2.51 (s, 3 H)	426.18
152		(400 MHz, $CDCl_3$) δ 8.89 (t, 1 H, *J* = 1.4 Hz), 8.35 (s, 1 H), 7.76–7.19 (m, 2 H), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.39–7.36 (m, 2 H), 7.30–7.26 (m, 2 H), 7.23–7.19 (m, 2 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 4.26 (s, 2 H), 2.49 (s, 3 H)	399.15
153		(400 MHz, $CDCl_3$) δ 8.86 (br s, 1 H), 8.37 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.72 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.54–7.48 (m, 2 H), 7.31–7.27 (m, 1 H), 7.25 (br d, 1 H, *J* = 8.0 Hz), 7.13–7.08 (m, 2 H), 7.06 (d, 1 H, *J* = 8.0 Hz), 4.30 (s, 2 H), 2.64 (s, 3 H)	417.15

[0432] Biological Data

[0433] The biological activity of the compounds of the invention may be assessed using the following assays:

[0434] Cell-Free Assay for Evaluating Inhibition of ALK5 Kinase Phosphorylation

[0435] ALK5 protein was expressed in Sf9 insect cells as human recombinant GST-fusion protein using the baculovirus expression system. Expressed protein was purified by affinity chromatography using GSH-agarose (Sigma-Aldrich). Kinase assay was performed in 96-well FlashPlates™ from Perkin Elmer (Boston, MA, USA) in a 50 μL reaction volume. The reaction cocktail was pipetted in four steps in the following order: 20 μL of assay buffer (standard buffer), 5 μL of ATP solution in H_2O, 5 μL of each test compounds of formula (I) in 10% DMSO, 10 μL of GSK3 (14-27) (200 ng)/10 μL of ALK5 solution (1 ng) (premixed). The reaction cocktail contained 60 mM HEPES-NaOH, pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 μM Na_3VO_4, 1.2 mM DTT, 50 μg/mL PEG_{20000}, 1 μM [γ-^{33}P]-ATP (approximately 2.5×10^5cpm per well), 200 ng/10 μL GSK3 (14-27), and 1 ng/10 μL ALK5. The reaction cocktail was incubated at 30°C for 60 min. The reaction was stopped with 50 μL of 2% (v/v) H_3PO_4, and plates were

aspirated and washed two times with 200 μL 0.9% (w/v) NaCl. Assay was performed with a BeckmanCoulter Biomek 2000 robotic system. Incorporation of $^{33}P_i$ (counting of "cpm") was determined with a microplate scintillation counter (Microbeta, Wallac).

[0436] Compounds of formula (I) typically exhibited IC_{50} values of less than 1 μM; some exhibited IC_{50} values of less than 0.1 μM; and some even exhibited IC_{50} values less than 10 nM, which is shown in the table 3.

[0437]

[0438]

[Table 3]

Example	IC_{50} (nM)	Example	IC_{50} (nM)
1	13.10	**51**	12.30
2	6.68	**52**	23.40
5	9.41	**53**	60.10
6	17.40	**54**	9.93
7	8.96	**55**	6.70
8	9.84	**58**	39.60
9	6.39	**59**	19.50
10	9.41	**60**	4.83
12	6.16	**63**	32.10
14	10.70	**64**	20.60
15	12.30	**65**	29.70
16	7.54	**66**	9.14
17	14.60	**67**	54.60
18	6.54	**68**	11.00
20	4.53	**69**	24.50
22	17.10	**70**	12.80
23	13.90	**71**	59.10
24	9.07	**72**	16.60
26	15.60	**73**	78.00
27	18.00	**74**	39.50
28	17.40	**75**	15.40
29	14.30	**76**	39.00
30	10.60	**77**	15.30
31	8.01	**78**	15.10
33	14.20	**79**	46.60
34	16.20	**138**	9.40
35	46.00	**139**	23.20
36	14.20	**140**	49.80
37	11.90	**141**	118.00

40	29.60	**142**	153.00
42	14.40	**143**	19.80
43	14.30	**144**	25.10
44	48.10	**145**	12.40
45	57.50	**147**	40.00
46	44.20	**148**	13.10
47	14.40	**149**	25.40
48	24.10	**150**	23.90
49	15.30	**151**	22.50
50	50.70	**152**	20.70

[0439]

[0440] Cell-Free Assay for Evaluating Inhibition of ALK4 Kinase Phosphorylation

[0441] Inhibition of the ALK4 kinase phosphorylation by test compounds of formula (I) can be determined in a similar manner to that described above for ALK5 inhibition except that GST-tagged ALK4 (Invitrogen Corporation) and RBER-CHKtide are used in place of the GST-tagged ALK5 and GSK3 (14-27).

[0442] Compounds of formula (I) typically exhibited IC_{50} values of less than 1 μM; some exhibited IC_{50} values of less than 0.1 μM; and some even exhibited IC_{50} values less than 10 nM.

[0443]

[0444] Kinase Selectivity Profiling

[0445] Kinase assays were performed in 96-well FlashPlates™ from Perkin Elmer in a 50 μL reaction volume. The reaction cocktail was pipetted in four steps in the following order: 15 μL of ATP solution in H_2O, 20 μL of assay buffer (standard buffer), 5 μL of Example 2 in 10% DMSO, 10 μL of enzyme/substrate mixture in H_2O. The reaction cocktail contained 70 mM HEPES-NaOH, pH 7.5, 3 mM $MnCl_2$, 3 μM Na_3VO_4, 1.2 mM DTT, 1 μM [γ-^{33}P]-ATP (approximately 6×10^5cpm per well), protein kinase (variable amounts), and substrate (variable amounts). The reaction cocktails were incubated at 30°C for 60 min. The reaction was stopped with 50 μL of 2% (v/v) H_3PO_4, and plates were aspirated and washed two times with 200 μL 0.9% (w/v) NaCl. ALL assays were performed with a BeckmanCoulter Biomek 2000/SL robotic system. Incorporation of $^{33}P_i$ (counting of "cpm") was determined with a microplate scintillation counter.

[0446]

[0447]

[Table 4]

protein kinase	IC_{50} (μM)	% inhibition at 10 μM	% inhibition at 1 μM
ALK5	0.00668		
ALK4	0.0173		
P38α	1.720		
VEGF-R1	0.391		
VEGF-R2	0.097		
VEGF-R3	0.257		
ALK1		66	20
ALK2		71	17
ALK3		27	-6
AKT1		3	0
CDK1/CycA		2	5
CHK1		5	-2
DAPK1		11	5
EGF-R wt		43	-8
ERK1		66	17
GSK3α		15	10
MEK1 wt		47	14
MET wt		12	-5
MST1		3	-7
PAK1		-3	-7
PDGFRα wt		91	53
PDGFRβ		87	47
PKA		18	-7
PKCα		4	-9
ROCK1		9	3
RPS6KA1		14	6
STK23		-1	-4

[0448]

[0449] Assay for Evaluating Cellular Inhibition of TGF-β Signaling

[0450] HaCaT-3TP-Luc stable cells or 4T1-3TP-Luc stable cells that have p3TP-Luc (neo) expression plasmid were seeded at 2.5×10^4 cells/well or 5×10^5 cells/well in 96-well plate, respectively. Cells were concomitantly treated with TGF-β1 (2 ng/mL) in 0.2% FBS in the presence or absence of each test compounds of formula (I) at approximately 60-70% confluence for 24 h at 37°C in 5% CO_2. Cell lysates were prepared using Luciferase Assay System (Promega) according to the manufacturer's instruction, and luminescence was measured by a luminometer, Micro Lumat Plus (Berthold, Germany).

[0451] Compounds of formula (I) typically exhibited IC_{50} values of less than 1 μM; some exhibited IC_{50} values of less than 0.1 μM; and some even exhibited IC_{50} values of less than 10 nM.

[0452]

[0453] Immunofluorescence Assay

[0454] MCF10A cells were plated on the cover glass in 6-well plate at 2×10^5 cells/well. After 12 h, when cells were attached, 10% FBS medium was changed to 0.5% FBS medium. Twenty-four hours later, cells were treated with TGF-β1 (2 ng/mL) with or without Example 2 (1 μM) for 2 h. Then, cells were fixed with 4% formaldehyde solution for 30 min at room temperature and quenched with quenching solution (50 mM NH_4Cl in PBS) for 15 min. After being washed three times with PBS, cells were incubated with blocking/permeabilization solution (1% BSA and 0.1% Triton X-100 in PBS) for 1 h at room temperature and incubated with anti-Smad2/3 antibody (BD Biosciences, Franklin Lakes, NJ, USA) overnight at 4°C. Fluorescence was visualized by Cy3-conjugated goat anti-mouse IgG (Jackson ImmunoResearch Laboratories, Bar Harbor, ME, USA). Nuclei of the same cells were stained with DAPI solution. Cells were analyzed using the LSM 510 META laser confocal microscopy system (Carl Zeiss, Germany).

[0455] Example 2 suppressed TGF-β1-induced Smad2/3 nuclear translocation in MCF10A cells.

[0456]

[0457] Wound Healing Assay

[0458] MCF10A cells were seeded at 2×10^5 cells/well in 6-well plate. When each well was occupied by cells over 80% of the area, 10% FBS was changed to 0.2% FBS. After 24 h, wound was made by a plastic pipette tip, and then cells were treated with TGF-β1 (2 ng/mL) with or without Example 2 (1 μM) for 16 h. Wound area change from 0 to 16 h was calculated based on Image J program (National Institutes of Health, MD, USA) based on phase-contrast images of cells taken by microscope.

[0459] Example 2 suppressed TGF-β1-induced cell migration in MCF10A cells.

[0460]

[0461] Matrigel Invasion Assay

[0462] The upper surface of Transwells (6.5 mm diameter, 8 μm pore size; Corning, Lowell, MA, USA) were coated with 20 μL diluted Matrigel (BD Biosciences). 4T1 cells were seeded at 4×10^4 cells/well on the upper chamber of transwell in serum free medium with or without TGF-β1 (2 ng/mL) in the presence or absence of Example 2. The lower chamber was filled with 10% FBS with TGF-β1 (2 ng/mL) in the presence or absence of Example 2. After incubation for 20 h at 37°C in 5% CO_2, the cells remaining on the upper surface of the membrane were removed with a cotton swab, and DAPI-stained cells remaining on the bottom surface were observed using fluorescence microscopy. Average cell number per view field was obtained from 5 random fields.

[0463] Example 2 suppressed TGF-β1-induced cell invasion in matrigel invasion assay.

[0464]

[0465] Cell Growth Study

[0466] Either 4T1 cells or MCF10A cells were seeded in 96-well plate at 5×10^3 cells per well. After cells were attached, cells were treated with Example 2 dissolved in DMSO in 0.2% serum medium. After incubation for four days, cell viability was determined by SRB assay.

[0467] Example 2 showed no effect on 4T1 cell growth and slightly increased MCF10A cell growth without significance, thus, suggesting that the anti-metastatic effect of Example 2 were not due to the primary tumor growth inhibition

[0468]

[0469] Anti-metastatic Effect on BALB/c 4T1 xenografted mice model

[0470] Female BALB/c mice were purchased from Orient Bio Inc. (Seoul, Korea). Animals were maintained in a temperature-controlled room (22°C) and supplied with food and water ad libitum. 4T1 cells (1.2×10^4 cells) were suspended in PBS and implanted into the left #4 mammary fat pad of five to six-week-old female BALB/c mice (day 0). In Experiment 1, treatment was started after tumor implantation (day 0). Example 3 (13.6 or 27.3 mg/kg) dissolved in water was given to mice orally BID five consecutive days per week for four weeks. In Experiment 2, treatment was started on day 4. Example 2 (5, 10, 20, or 40 mg/kg) dissolved in artificial gastric fluid formulation was given to mice orally five consecutive days per week for three weeks. In Experiment 3, treatment was started on day 4. Example 2 (5, 10, 20, or 40 mg/kg) dissolved in artificial gastric fluid formulation was given to mice orally every other day (three times per week) for 24 days. In Experiment 4, 4T1 cells (1×10^4 cells) were suspended in PBS and implanted into the left #4 mammary fat pad of ten-week-old female BALB/c mice (day 0). Treatment was started on day 10. Example 61 (43.6 mg/kg) dissolved in saline was given to mice intraperitoneally every other day for 2.5 weeks. In all Experiments, mice were sacrificed at 24 to 72 h after the last dosing, and 15% India ink solution (Hardy

Diagnostics) in PBS was immediately injected into the trachea. The India ink-stained lungs were isolated and destained with Feket's solution (60% ethanol, 3% formaldehyde, and 4% acetic acid in PBS) for at least 20 min. Number of metastatic nodule was counted on the surface of left lobe of lung, and picture of lung was taken with digital camera. The tumor size was measured using calipers, and the tumor volume was calculated by using the following equation:

[0471] Tumor volume = $(0.5236) \times (\text{width})^2 \times (\text{length})$

[0472] Examples 2, 3, and 61 significantly reduced the number of metastastic nodules on the lung.

[0473] In Experiment 3, Western blot analysis was performed to examine the effect of Example 2 on the Smad2 phosphorylation in tumor tissues. Either vehicle buffer (4 mM HCl, 1 mg/mL BSA) or TGF-β1 (50 ng/mouse) in vehicle buffer was given to mice intravenously at 2 h before mice were sacrificed. Tumor tissues from mice were lysed in RIPA buffer [50 mM Tris, pH 7.5, 150 mM NaCl, 0.1% sodium dodecyl sulfate, 0.5% sodium deoxycholate, 1% NP-40, 1 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF, a protease inhibitor cocktail (1 tablet of Roche Diagnostics GmbH protease inhibitor cocktail/10 mL) (Roche)] for 20 min on ice. Lysates were cleared by centrifugation at 13000 rpm at 4°C for 20 min. Protein content of supernatants was determined using Micro-BCA (bicinchoninic acid) protein assay kit (Thermo Scientific). Lysates containing 20—50 μg total protein were separated by electrophoresis on polyacrylamide gel and then electrophoretically transferred to polyvinylidene difluoride transfer membranes (Millipore, Billerica, MA, USA). Membranes were blocked with 5% BSA (Sigma-Aldrich) in PBS containing 0.5% Tween-20 (PBST) for 1 h and incubated overnight at 4°C with one of following antibodies: anti-phospho-Smad2 (Millipore), anti-Smad2/3 (BD Transduction Laboratories, NJ, USA), or anti-β-actin (Sigma-Aldrich) in PBST containing 1% BSA. Membranes were washed three times with PBST and incubated with either horseradish peroxidase (HRP)-conjugated goat anti-mouse antibody or HRP-conjugated goat anti-rabbit antibody (SantaCruz Biotechnology, Santa Cruz, CA, USA) at room temperature for 1 h. Bound antibodies were detected using Western Blotting Luminol Reagent (SantaCruz Biotechnology). Band intensities were analyzed using a densitometer LAS-3000 imager (FUJIFILM, Tokyo, Japan).

[0474] Example 2 suppressed TGF-β1-induced Smad2 phosphorylation in tumor tissues.

[0475]

[0476] Anti-metastatic Effect on MMTV/c-Neu mice breast cancer model

[0477] MMTV/c-Neu female transgenic mice were purchased from Jackson Laboratory (Bar Harbor, ME, USA). Animals were maintained in a temperature-controlled SPF room (22°C) and supplied with food and water ad libitum. In Experiment 1, Example

61(43.6 mg/kg) dissolved in saline was given to thirty two-week-old MMTV/c-Neu mice intraperitoneally every other day for three weeks. In Experiment 2, Example 3 (43.6 mg/kg) dissolved in saline was given to thirty two-week-old MMTV/c-Neu mice intraperitoneally every other day for ten weeks. Mice were sacrificed at 24 h after the last dosing, and tissues of mammary tumor and lung were analyzed by hematoxylin and eosin (H&E) staining. To analyse β-casein mRNA level in tissues of mammary tumor and lung, total RNAs were isolated from these tissues using TRIzol reagent (Invitrogen Corporation) and RNeasy Mini kit (Qiagen) according to the manufacturer's instruction. The cDNAs were synthesized from 2 μg of total RNAs using random primer (Invitrogen Corporation) by MMLV RTase (Invitrogen Corporation) for 1 h at 37°C and subjected to PCR amplification using Taq polymerase (Promega) and following gene-specific primers: mouse GAPDH (forward) 5'-ATG TGT CCG TCG TGG ATC TGA-3' and (reverse) 5'-TTG AAG TCG CAG GAG ACA ACC-3', mouse β-casein (forward) 5'-TCC CAC AAA ACA TCC AGC C-3' and (reverse) 5'-ACG GAA TGT TGT GGA GTG G-3'. Amplified DNA was analyzed by agarose gel electrophoresis.

[0478] Example 61 significantly reduced the number of metastastic lesions in the lung. Significant level of β-casein (a mammary differentiation marker) mRNA was detected in the lung of MMTV/c-Neu mice. Examples 3 and 61 significantly inhibited β-casein mRNA expression level in the lung, demonstrating their anti-metastatic effect.

[0479] Activity of MMP-9 and MMP-2 in the primary mammary tumor was measured by gelatin zymography. Tumor tissues from mice (30 mg) was lysed in 500 μL RIPA buffer (50 mM Tris, 150 mM NaCl, 0.1% sodium dodecyl sulfate, 0.5% sodium deoxycholate, 1% NP-40, protease inhibitor without EDTA) for 10-20 min on ice. Lysates were cleared by centrifugation at 13000 rpm at 4°C for 10 min. Protein content of supernatants was determined using Micro-BCA protein assay kit (Thermo Scientific). Loading samples were prepared by adding loading buffer (0.5 M Tris, pH 6.8, 50% glycerol, 10% SDS, and 1% bromophenol blue solution) into lysates containing 15 μg of total protein. Loading samples were heated at 60°C for 5 min and separated by electrophoresis on 10% polyacrylamide gel containing 0.2% gelatin. Gel was washed twice with washing buffer [2.5% Triton-X100, 0.05 M Tris-HCl, pH 7.5, and 0.1 M NaCl] for 30 min at room temperature. Then, the gel was incubated in incubation buffer [0.05 M Tris-HCl, pH 7.5, 0.15 M NaCl, 0.01 M $CaCl_2$, 0.02% NaN_3, and 1 μM $ZnCl_2$] at 37°C for 16-18 h with shaking. Gel was stained by 0.5% Coomassie blue R250 solution containing 5% methanol and 10% acetic acid for 2-4 h at room temperature and destained twice by destaining solution (5% methanol and 10% acetic acid) for 30 min at room temperature. Gel image was obtained using a densitometer LAS-3000 imager (FUJIFILM) in cybergreen mode.

[0480] Example 3 significantly inhibited activity of MMP-9 and MMP-2 in the primary mammary tumor.

[0481]

[0482] Anti-fibrotic Effect on Bile Duct-ligated Liver Fibrosis Model

[0483] Six-week-old male Sprague—Dawley (SD) rats were purchased from Orient Bio Inc.. In Experiment 1, SD rats weighing 180—200 g were randomly divided into five experimental groups: sham-operated control rats (n = 5), sham-operated rats treated with Example 3 (43.6 mg/kg, n = 5), bile duct-ligated (BDL) rats (n = 10), BDL rats treated with either 21.8 or 43.6 mg/kg of Example 3 (n = 10). In Experiment 2, SD rats weighing 180—200 g were randomly divided into five experimental groups: sham-operated control rats (n = 5), BDL rats (n = 10), BDL rats treated with either 5, 10, or 20 mg/kg of Example 2 (n = 10). For BDL, the animals were anesthetized with zoletil (20 mg/kg) and xylazine (10 mg/kg), and the common bile duct was exposed and double-ligated using 3-0 silk. The first ligature was placed below the junction of the hepatic duct, and the second was placed above the entrance of the pancreatic duct. The common bile duct was then cut between the double ligatures. In sham-operated rats, an incision was made in the abdomen and then closed without any treatment. Treatment was started within 2 h after surgical procedure. Either Example 3 dissolved in saline (Experiment 1) or Example 2 dissolved in artificial gastric fluid formulation (Experiment 2) was given to rats orally three times per week for four weeks starting from BDL surgery. Animals were maintained in a temperature controlled room (at 21°C) and supplied with autoclaved food and water. At 48 h after the last dosing, animals were killed, and the serum, spleens and livers were removed. The livers were sagittally sliced into several parts, snap frozen in liquid nitrogen, and kept at —70°C. A part of livers was immersed into 10% neutral buffered-formalin for histopathological examinations. All experimental procedures were conducted in accordance with our institutional guidelines.The activity of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was determined using a spectrophotometric enzyme assay kit (Asan Pharm. Co., Ltd., Hwaseong-si, Korea) according to the manufacturer's instruction. Automated instrument was also used to assay general serum biochemistry. Liver specimens were fixed in 10% neutral buffered-formalin prior to routine processing in paraffin-embedded blocks. Sections (5 μm thick) were cut and stained using hematoxylin and eosin (H&E), and examined by light microscopy. Liver tissues were lysed in RIPA buffer [50 mM Tris, pH 7.5, 150 mM NaCl, 1 mM EDTA, 0.1% sodium dodecyl sulfate, 0.5% sodium deoxycholate, 1% NP-40, 50 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF, a protease inhibitor cocktail (1 tablet of Roche Diagnostics GmbH protease inhibitor cocktail/10 mL) (Roche)] for 20 min on ice. Lysates were cleared by centrifugation at 13000 rpm at 4°C for 20 min. Protein content of su-

pernatants was determined using Micro-BCA protein assay kit (Thermo Scientific). Lysates containing 20—60 μg total protein were separated by electrophoresis on 6—10% sodium dodecyl sulfate—polyacrylamide gel and then transferred to nitrocellulose (Whatman®, Germany) or polyvinylidene difluoride membranes (Millipore). Membranes were blocked with 5% BSA (Sigma-Aldrich) or 5% nonfat dry milk solution for 1 h and incubated overnight at 4°C with one of following antibodies: rabbit antiphospho-Smad3 (Cell Signaling Technology, Beverly, MA, USA), rabbit anti-α-SMA (Millipore), mouse anti-fibronectin, mouse anti-vimentin (BD Biosciences), or mouse anti-β-actin (Sigma-Aldrich). Membranes were washed three times with Tris-buffered saline and incubated with either HRP-conjugated goat anti-rabbit antibody or HRP-conjugated goat anti-mouse antibody (SantaCruz Biotechnology) at room temperature for 1 h. Bound antibodies were detected using an ECL kit (GE Healthcare, Princeton, NJ, USA). Band intensities were analyzed using a densitometer LAS-3000 imager (FUJIFILM).

[0484] BDL rats showed body weight loss and organ (liver and spleen) weight increase compared with sham-operated control rats. Examples 2 and 3 recovered body weight loss and decreased organ (liver and spleen) weight in BDL rats. A significant increase in serum ALT and AST was observed in BDL rats as compared with sham-operated animals. Examples 2 and 3improved serum ALT and AST in BDL rats. Examples 3 inhibited Smad signaling and suppressed α-SMA, fibronectin, and vimentin in BDL rat liver. Examples 2 suppressed α-SMA and fibronectin in BDL rat liver. BDL rat livers showed typical histological changes characterized by central ± central architecture disruption and bridge fibrosis formation compared with that of normal rat livers. Examples 2 and 3 greatly abolished BDL-induced histological change.

[0485]

[0486] [Table 5]

Groups (mg/kg)		Body weight (g)	Organ weight			
			Liver (g)	Spleen (g)	Liver/Body (%)	Spleen/Body(%)
Sham	vehicle	357 ± 5.2	11.7 ± 0.36	0.78 ± 0.06	3.28 ± 0.07	0.22 ± 0.02
	Example 3 (43.6)	354 ± 12.2$^{\#\#}$	11.8 ± 0.71	0.81 ± 0.04	3.34 ± 0.12	0.23 ± 0.01
BDL	vehicle	308 ± 6.1**	22.8 ± 1.30**	2.01 ± 0.14**	7.43 ± 0.44**	0.65 ± 0.04**
	Example 3 (21.8)	340 ± 9.6$^{\#}$	16.4 ± 0.72$^{**,\#\#}$	1.30 ± 0.07**	4.85 ± 0.26$^{**,\#\#}$	0.39 ± 0.03$^{**,\#\#}$
	Example 3 (43.6)	335 ±8.4	16.1 ± 0.57$^{**,\#\#}$	1.19 ± 0.09**	4.84 ± 0.26$^{**,\#\#}$	0.36 ± 0.03$^{**,\#\#}$

Data represents the mean ± S.E. (n = 5−8).
**: $p < 0.01$ vs. sham. #: $p < 0.05$ vs. BDL. ##: $p < 0.01$ vs. BDL.

[0487]

[Table 6]

Groups (mg/kg)		Body weight(g)	Organ weight			
			Liver(g)	Spleen(g)	Liver/Body(%)	Spleen/Body(%)
Sham	vehicle	345 ± 6.3	12.1 ± 0.77	0.83 ± 0.05	3.51 ± 0.21	0.24 ± 0.02
BDL	vehicle	315 ± 16.1*	20.3 ± 2.45**	2.54 ± 0.29**	6.39 ± 0.51**	0.80 ± 0.05**
	Example 2(5)	324 ± 7.3	17.5 ± 1.82	2.00 ± 0.28**	5.46 ± 0.62	0.63 ± 0.09**
	Example 2(10)	312 ± 10.4	15.8 ± 1.88	1.57 ± 0.12#	5.08 ± 0.60	0.51 ± 0.05#
	Example 2(20)	312 ± 8.4*	15.2 ± 1.80	1.50 ± 0.16#	4.88 ± 0.63	0.48 ± 0.05#

Data represents the mean ± S.E. (n = 5–8).
*: $p < 0.05$ vs. sham. **: $p < 0.01$ vs. sham. #: $p < 0.05$ vs. BDL.

[0488] Anti-fibrotic Effect on Bleomycin-induced Lung Fibrosis Model

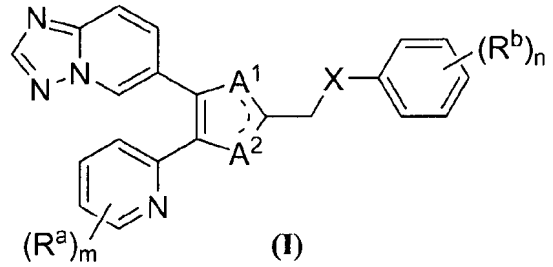
[0489] Six-week-old male ICR mice were purchased from Orient Bio Inc.. Mice weighing 31—35 g were randomly divided into five experimental groups: sham-operated control mice (saline, n = 6), bleomycin (BLM)-treated mice (n = 10), BLM-treated mice treated with either 5, 10, or 20 mg/kg of Example 2 (n = 10). For the induction of lung fibrosis, mice were anesthetized with zoletil (10 mg/kg) and xylazine (5 mg/kg) and were given BLM (given as BLM sulfate, 1 mg/kg) (MBcell, Los Angeles, CA, USA) dissolved in 60 μL of saline once on day 0 through intratracheal instillation. Example 2 dissolved in artificial gastric fluid formulation was given to mice orally five times per week for two weeks starting from day 7. Animals were maintained in a temperature controlled room (at 21°C) and supplied with autoclaved food and water. At three weeks post-surgery, animals were killed, and the lungs were removed. The lungs were sagittally sliced into several parts, snap frozen in liquid nitrogen, and kept at —70°C. A part of lungs was immersed into 10% neutral buffered-formalin for histopathological examinations. All experimental procedures were conducted in accordance with our institutional guidelines. Lung specimens were fixed in 10% neutral buffered-formalin prior to routine processing in paraffin-embedded blocks. Sections (5 μm thick) were cut, stained using hematoxylin and eosin (H&E), and examined by light microscopy. Lung tissues were lysed in RIPA buffer [50 mM Tris, pH 7.5, 150 mM NaCl, 1 mM EDTA, 0.1% sodium dodecyl sulfate, 0.5% sodium deoxycholate, 1% NP-40, 50 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF, a protease inhibitor cocktail (1 tablet of Roche Diagnostics GmbH protease inhibitor cocktail/10 mL) (Roche)] for 20 min on ice. Lysates were cleared by centrifugation at 13000 rpm at 4°C for 20 min. Protein content of supernatants was determined using Micro-BCA protein assay kit (Thermo Scientific). Lysates containing 20—50 μg total protein were separated by electrophoresis on 6—10% sodium dodecyl sulfate—polyacrylamide gel and then transferred to nitrocellulose (Whatman®). Membranes were blocked with 5% nonfat

dry milk solution for 1 h and incubated overnight at 4°C with either rabbit anti-α-SMA (Millipore) or mouse anti-fibronectin (BD Biosciences). Membranes were washed three times with Tris-buffered saline and incubated with either HRP-conjugated goat anti-rabbit antibody or HRP-conjugated goat anti-mouse antibody (SantaCruz Biotechnology) at room temperature for 1 h. Bound antibodies were detected using an ECL kit (GE Healthcare). Band intensities were analyzed using a densitometer LAS-3000 imager (FUJIFILM).

[0490] BLM-induced fibrotic lungs showed the elevated levels of α-SMA and fibronectin compared with those of sham-operated animals. Example 2suppressed α-SMA and fibronectin in BLM-induced fibrotic lung. Lung tissues from the BLM-treated mice showed typical histology that pulmonary interalveolar septa became thickened and infiltrated by inflammatory cells with collagen depositions in the interstitium disclosed. Example 2 greatly reduced BLM-induced histological changes at all dose levels tested.

Claims

[Claim 1] A compound of the formula (I):



(I)

Wherein:

each R^a is independently H, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6} cycloalkyl, OH,

—O—C_{1-6}alkyl, —O—C_{1-6}haloalkyl, —O—C_{3-6}cycloalkyl, NH_2,

—NH—C_{1-6}alkyl,

—NH—C_{1-6}haloalkyl, —NH—C_{3-6}cycloalkyl, —S—C_{1-6}alkyl,

—S—C_{1-6}haloalkyl,

—S—C_{3-6}cycloalkyl, CN, or NO_2;

m is 0, 1, 2, 3, or 4;

one of A^1 and A^2 is N and the other is NR^1, wherein R^1 is H, OH, C_{1-6} alkyl, C_{1-6} haloalkyl,

or C_{3-6}cycloalkyl;

X is a bond, —$(CH_2)_p$—, —NR^2—, —O—, or —S—, wherein p is 0 or 1, and R^2 is H or

C_{1-3}alkyl;

each R^b is independently H, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6} cycloalkyl, C_{2-6}alkenyl,

C_{2-6}alkynyl, —$(CH_2)_q$—OR^3, —$(CH_2)_q$—NR^3R^4, —$(CH_2)_q$—SR^3, —$(CH_2)_q$—NO_2,

—$(CH_2)_q$—CONHOH, —$(CH_2)_q$—CN, —$(CH_2)_q$—COR^3, —$(CH_2)_q$—CO_2R^3,

—$(CH_2)_q$—$CONR^3R^4$, —$(CH_2)_q$—tetrazole, —$(CH_2)_q$—CH=CH-CN,

—$(CH_2)_q$—CH=CH—CO_2R^3, —$(CH_2)_q$—CH=CH—$CONR^3R^4$,

—$(CH_2)_q$—CH=CH-tetrazole, —$(CH_2)_q$—$NHCOR^3$, —$(CH_2)_q$—$NHCO_2R^3$,

—$(CH_2)_q$—$CONHSO_2R^3$, —$(CH_2)_q$—$NHSO_2R^3$, —$(CH_2)_q$—C≡C—CN,

—$(CH_2)_q$—C≡C—CO_2R^3, —$(CH_2)_q$-C≡C—$CONR^3R^4$, —$(CH_2)_q$—C≡C-tetrazole,
—$(CH_2)_q$—SOR^5, —$(CH_2)_q$—SO_2R^5, or —$(CH_2)_r$— $(OR^3)_2$,
wherein R^3 and R^4 are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{3-6} cycloalkyl; or taken together with the nitrogen atom to which they are attached form a mono-cyclic ring such as imidazole, pyrrolidine, piperidine, morpholine, piperazine and homopiperazine; R^5 is C_{1-6}alkyl, C_{1-6}haloalkyl, or C_{3-6}cycloalkyl; q is 0, 1, 2, 3, or 4; and r is 1, 2, 3, or 4; n is 0, 1, 2, 3, 4, or 5; or a pharmaceutically acceptable salt or hydrate thereof.

[Claim 2] The compound of claim 1, which is selected from the group consisting of:
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-fluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-fluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2,3-difluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,4-difluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,5-difluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-chloroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-chloroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-chloroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2,3-dichloroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,4-dichloroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,5-dichloroaniline;

N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-bromoaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-bromoaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-bromoaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-methylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-methylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-methylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2,3-dimethylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,4-dimethylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,5-dimethylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-ethylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-ethylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-isopropylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-isopropylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-isopropylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-vinylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-vinylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-vinylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-ethynylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-methoxyaniline;

N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-methoxyaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-methoxyaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2,3-dimethoxyaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,4-dimethoxyaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3,5-dimethoxyaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(methoxymethyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(methoxymethyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-(methoxymethyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(trifluoromethoxy)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(trifluoromethoxy)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-(trifluoromethoxy)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(methylthio)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(methylthio)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-(methylthio)aniline;
2-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)benzonitrile;
4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phthalonitrile;
2-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-n yl)methylamino)benzamide;

3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)benzamide;
4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)benzamide;
2-(3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetonitrile;
2-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetonitrile;
1-(3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)ethanone;
1-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)ethanone;
Methyl 3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)benzoate;
Methyl 4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)benzoate;
N-(2-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetamide;
N-(3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetamide;
N-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)acetamide;
N-(2-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)methanesulfonamide;
N-(3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)methanesulfonamide;
N-(4-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)phenyl)methanesulfonamide;
N^1-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-N^2,N^2-dimethylbenzene-1,2-diamine;
N^1-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-N^3,N^3-dimethylbenzene-1,3-diamine;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(pyrrolidin-1-yl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-morpholinoaniline;

N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-morpholinoaniline;
N^3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-4-fluoro-N^1,N^1-dimethylbenzene-1,3-diamine;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-5-(dimethylamino)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-4-(dimethylamino)benzonitrile;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-((dimethylamino)methyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-((dimethylamino)methyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(pyrrolidin-1-ylmethyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(pyrrolidin-1-ylmethyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(morpholinomethyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(morpholinomethyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-5-((dimethylamino)methyl)-2-fluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-((dimethylamino)methyl)-2-fluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoro-3-(pyrrolidin-1-ylmethyl)aniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoro-3-(morpholinomethyl)aniline;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-4-((dimethylamino)methyl)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-2-((dimethylamino)methyl)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-5-((dimethylamino)methyl)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-4-(pyrrolidin-1-ylmethyl)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-2-(pyrrolidin-1-ylmethyl)benzonitrile;

3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-5-(pyrrolidin-1-ylmethyl)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-4-(morpholinomethyl)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-2-(morpholinomethyl)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)-5-(morpholinomethyl)benzonitrile;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-(2-(dimethylamino)ethylaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-3-(2-(dimethylamino)ethylaniline;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-ethylpyridin-2-yl)-1*H*-imidazol-2-yl)methylamino)benzonitrile;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-ethylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoroaniline;
N-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)-2-fluoro-*N*-methylaniline;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)(methyl)amino)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2- yl)methyl)(methyl)amino)benzamide;
6-(2-benzyl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine;
6-(2-(2-fluorobenzyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methyl)benzamide;
6-(5-(6-methylpyridin-2-yl)-2-(phenoxymethyl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine;
6-(2-((2-fluorophenoxy)methyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methoxy)benzonitrile;
3-((4-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl)methoxy)benzamide;

6-(5-(6-methylpyridin-2-yl)-2-(phenylthiomethyl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine;
6-(2-((2-fluorophenylthio)methyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridine, and pharmaceutically acceptable salts or hydrates thereof.

[Claim 3] A pharmaceutical composition comprising one or more compounds of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable diluent or carrier.

[Claim 4] A method of inhibiting the TGF-β or activin signaling pathways or both in human, comprising administering to a human in need of said treatment, a therapeutically effective amount of the one or more compounds of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

[Claim 5] A method of treating, preventing, or reducing metastasis of tumor cells in human, comprising administering to a human in need of said treatment, a therapeutically effective amount of the one or more compounds of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

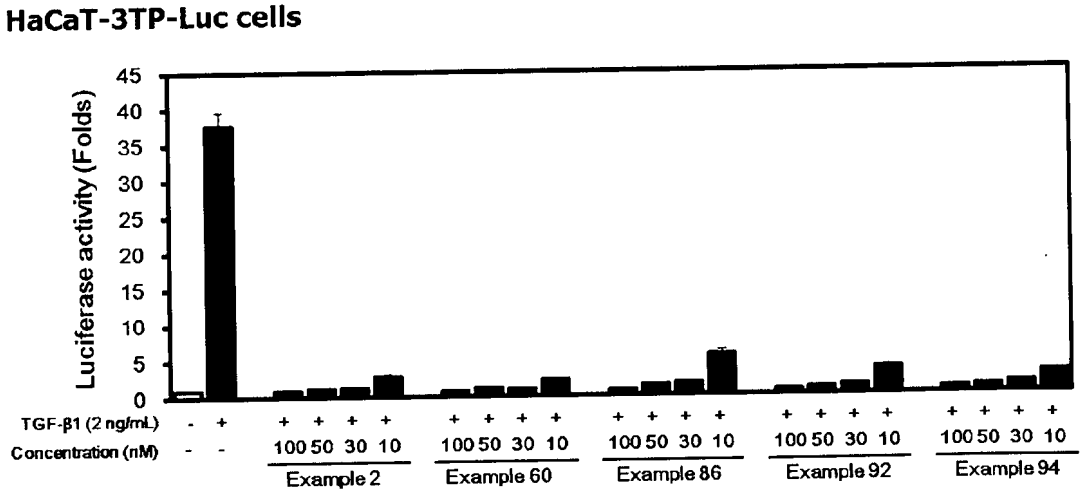
[Claim 6] A method of treating, preventing, or reducing carcinomas mediated by an overexpression of TGF-β by inhibiting a TGF-β signaling pathway in human, comprising administering to a human in need of said treatment, a therapeutically effective amount of the one or more compounds of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

[Claim 7] A method of treating, preventing, or reducing vascular injuries in human, comprising administering to a human in need of said treatment, a therapeutically effective amount of the one or more compounds of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

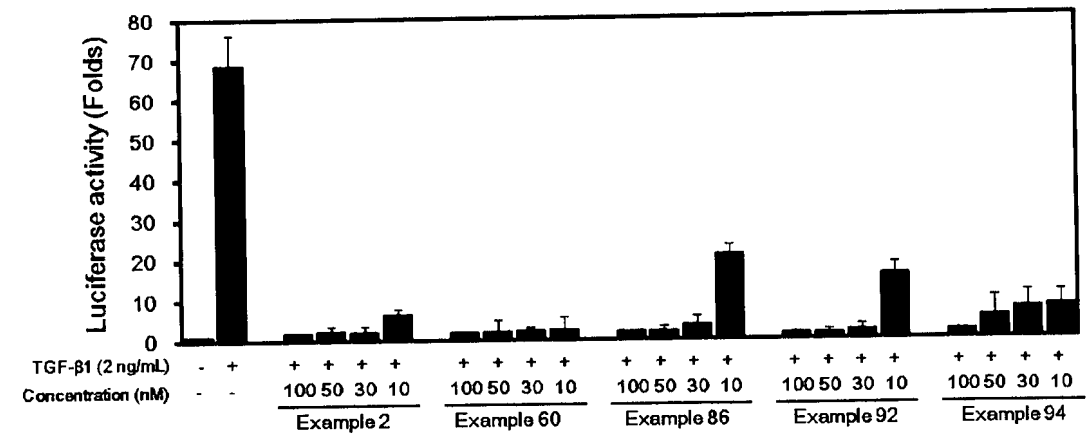
[Claim 8] A method for treating, preventing, or reducing a disease in human selected from the group consisting of glomerulonephritis, diabetic nephropathy, lupus nephritis, hypertension-induced nephropathy, renal interstitial fibrosis, renal fibrosis resulting from complications of drug exposure, HIV-associated nephropathy, transplant nephropathy, liver fibrosis due to all etiologies, hepatic dysfunction attributable to infections, alcohol-induced hepatitis, disorders of the biliary tree, cystic fibrosis, pulmonary fibrosis, interstitial lung disease, acute lung injury, adult respiratory distress syndrome, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary disease due to in-

fectious or toxic agents, post-infarction cardiac fibrosis, congestive heart failure, dilated cardiomyopathy, myocarditis, intimal thickening, vascular stenosis, hypertension-induced vascular remodeling, pulmonary arterial hypertension, coronary restenosis, peripheral restenosis, carotid restenosis, stent-induced restenosis, atherosclerosis, ocular scarring, corneal scarring, proliferative vitreoretinopathy, glaucoma, intraocular pressure, excessive or hypertrophic scar or keloid formation in the dermis occurring during wound healing resulting from trauma or surgical wounds, peritoneal and sub-dermal adhesion, scleroderma, fibrosclerosis, progressive systemic sclerosis, dermatomyositis, polymyositis, arthritis, osteoporosis, ulcers, impaired neurological function, male erectile dysfunction, Peyronie's disease, Dupuytren's contracture, Alzheimer's disease, Raynaud's syndrome, radiation-induced fibrosis, thrombosis, tumor metastasis growth, multiple myeloma, melanoma, glioma, glioblastomas, leukemia, sarcomas, leiomyomas, mesothelioma, and carcinomas of lung, breast, colon, kidney, ovary, cervix, liver, biliary tract, gastrointestinal tract, pancreas, prostate, head, and neck, comprising administering to a human in need of said treatment, a therapeutically effective amount of the one or more compounds of claim 1, or a pharmaceutically acceptable salt or hydrate thereof.

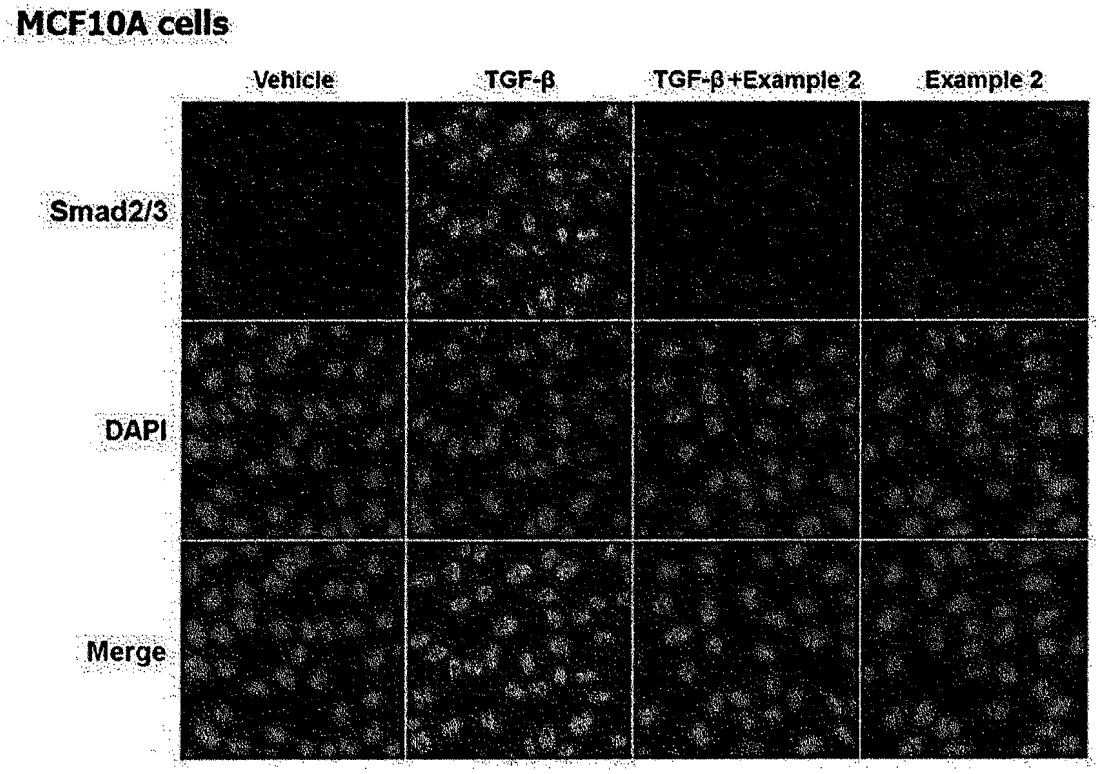
[Fig. 1]


HaCaT-3TP-Luc cells
Luciferase activity (Folds)
45
40
35
30
25
20
15
10
5
0
TGF-β1 (2 ng/mL) - + + + + + + + + + + + + + + +
Concentration (nM) - - 100 50 30 10 100 50 30 10 100 50 30 10 100 50 30 10 100 50 30 10
Example 2
Example 60
Example 86
Example 92
Example 94

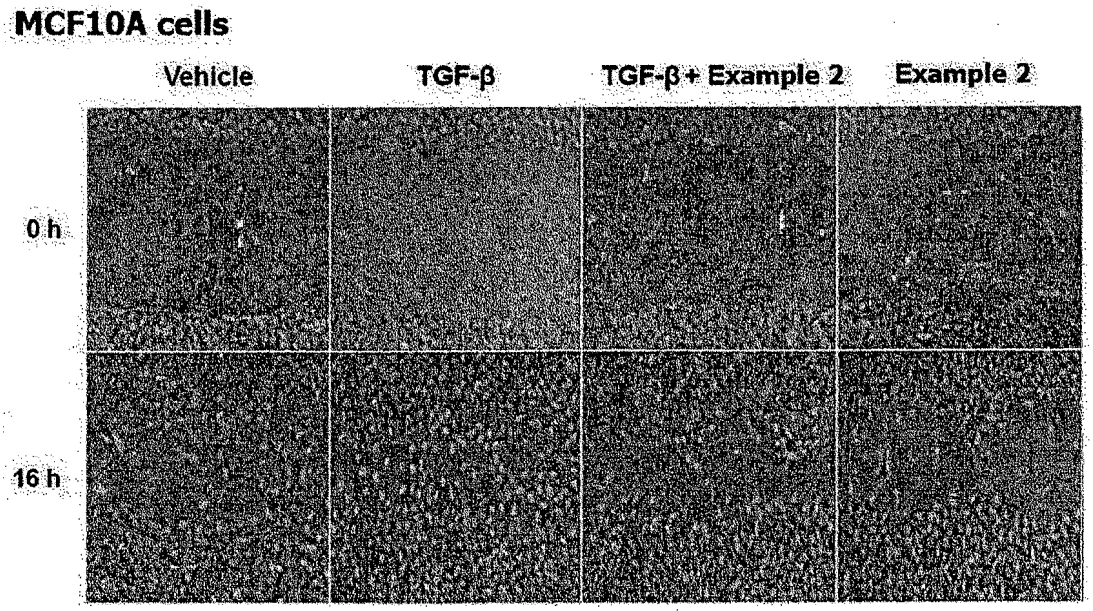
[Fig. 2]


4T1-3PT-Luc cells
Luciferase activity (Folds)
80
70
60
50
40
30
20
10
0
TGF-β1 (2 ng/mL) - + + + + + + + + + + + + + + +
Concentration (nM) - - 100 50 30 10 100 50 30 10 100 50 30 10 100 50 30 10 100 50 30 10
Example 2
Example 60
Example 86
Example 92
Example 94

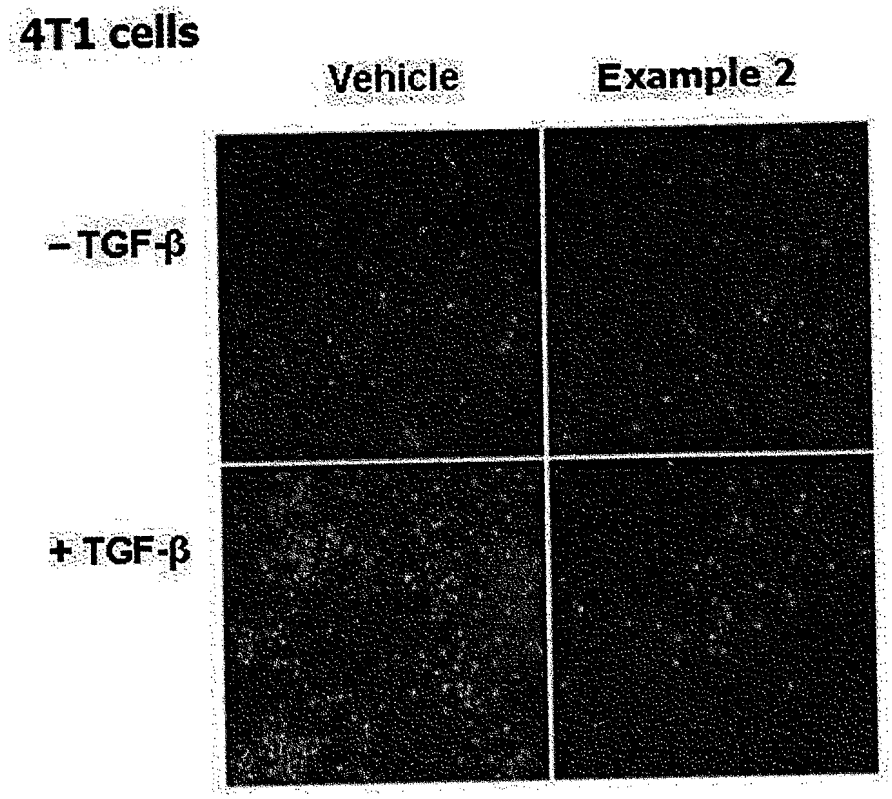
[Fig. 3]


MCF10A cells
Vehicle
TGF-β
TGF-β +Example 2
Example 2
Smad2/3
DAPI
Merge

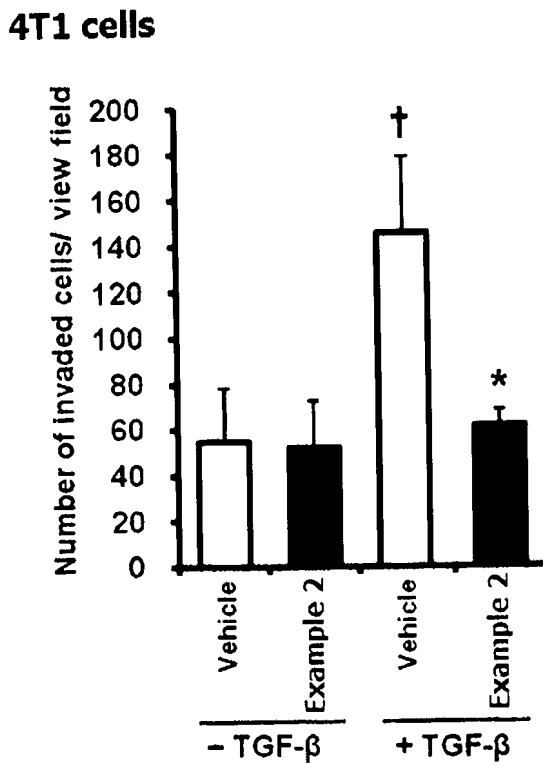
[Fig. 4]


MCF10A cells
Vehicle
TGF-β
TGF-β + Example 2
Example 2
0 h
16 h

[Fig. 5a]

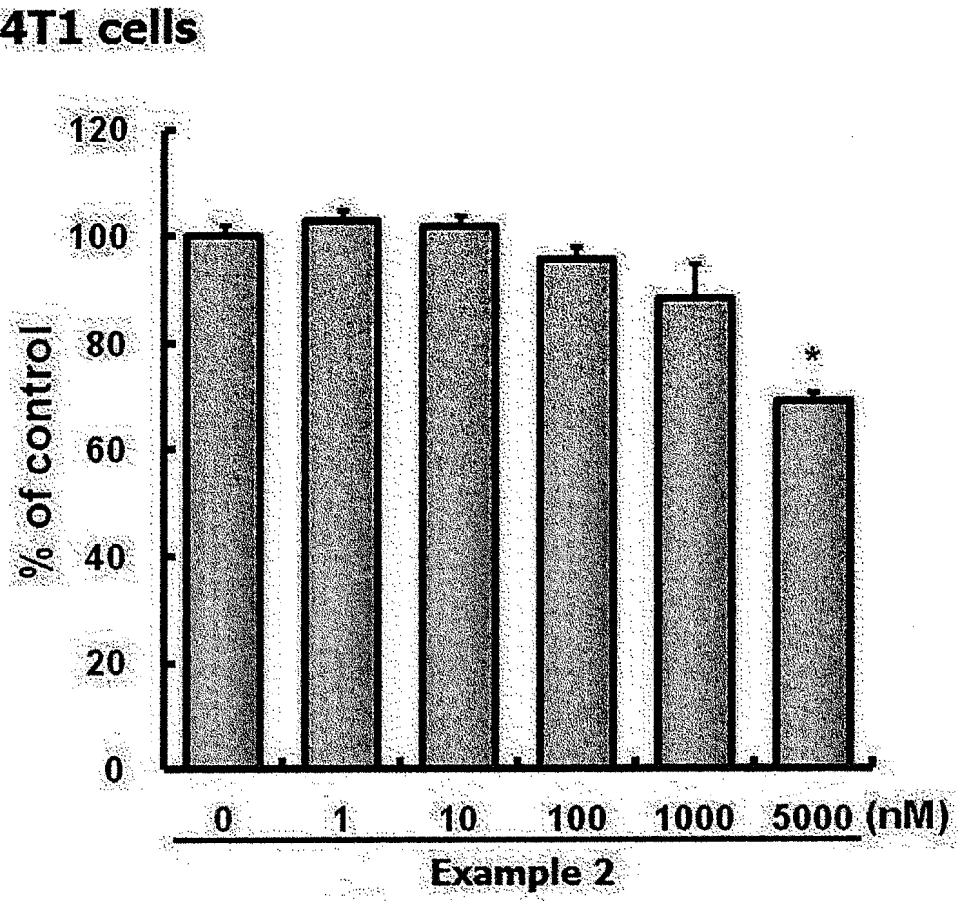


[Fig. 5b]



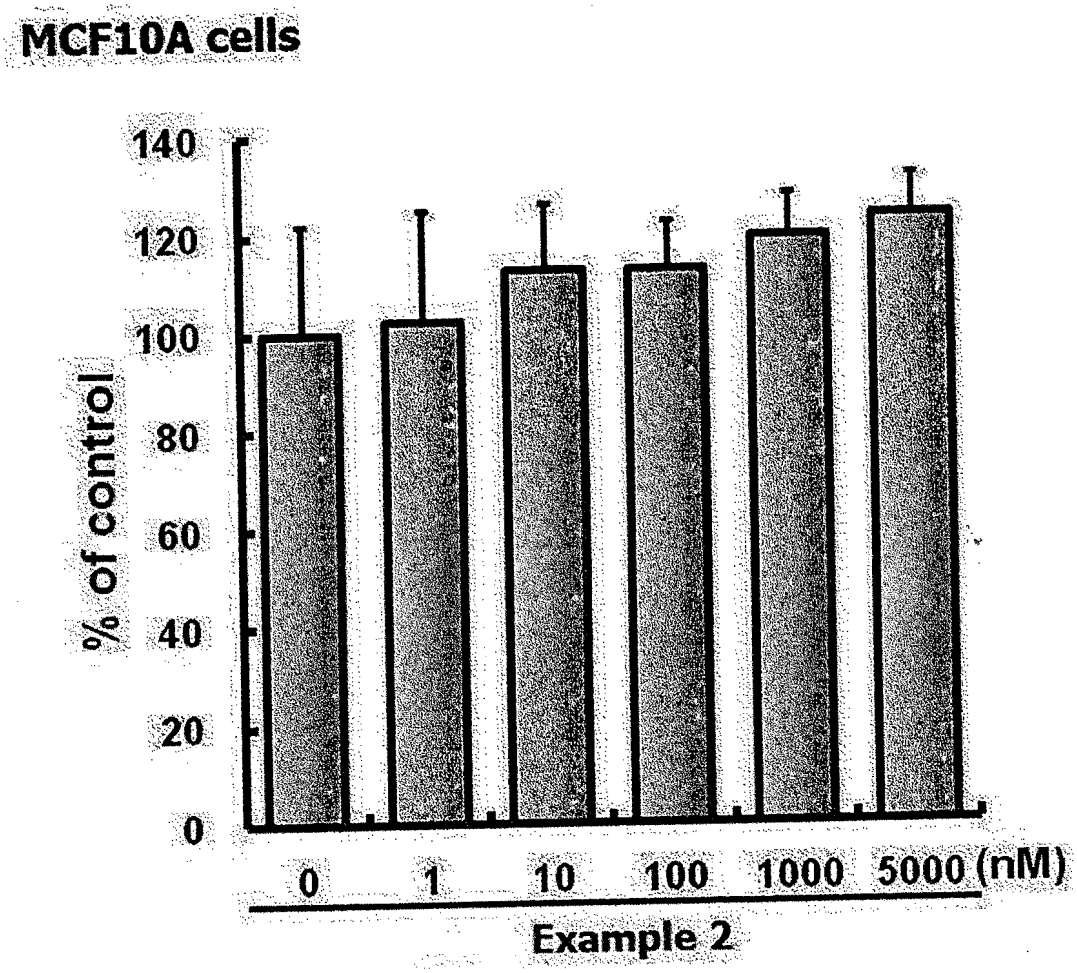
Data represents the mean number of invaded cells per view field ± S.D. (n = 3).
†: significantly different from vehicle group ($P < 0.05$).
*: significantly different from TGF-β- treated group ($P < 0.05$).

[Fig. 6]



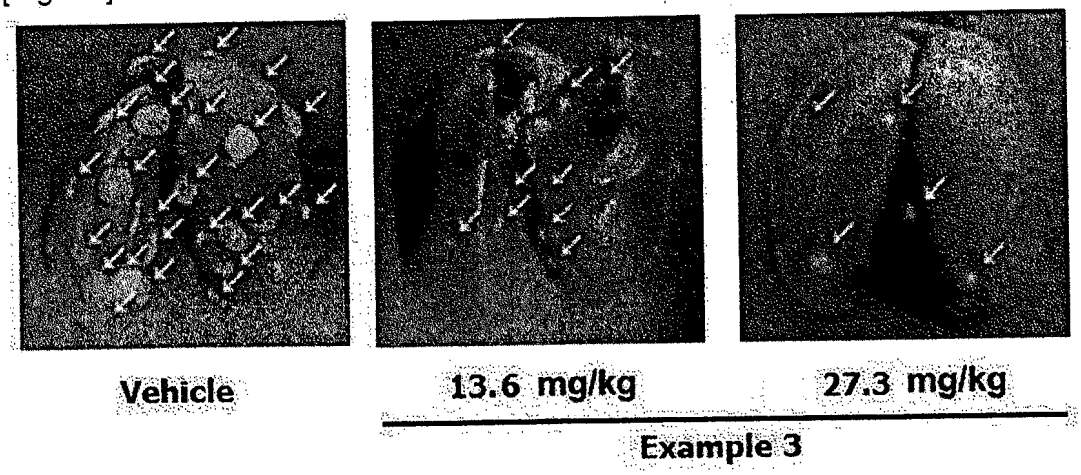
Data represents the mean ± S.D. (n = 4).
*: significantly different from control group ($p < 0.05$).

[Fig. 7]

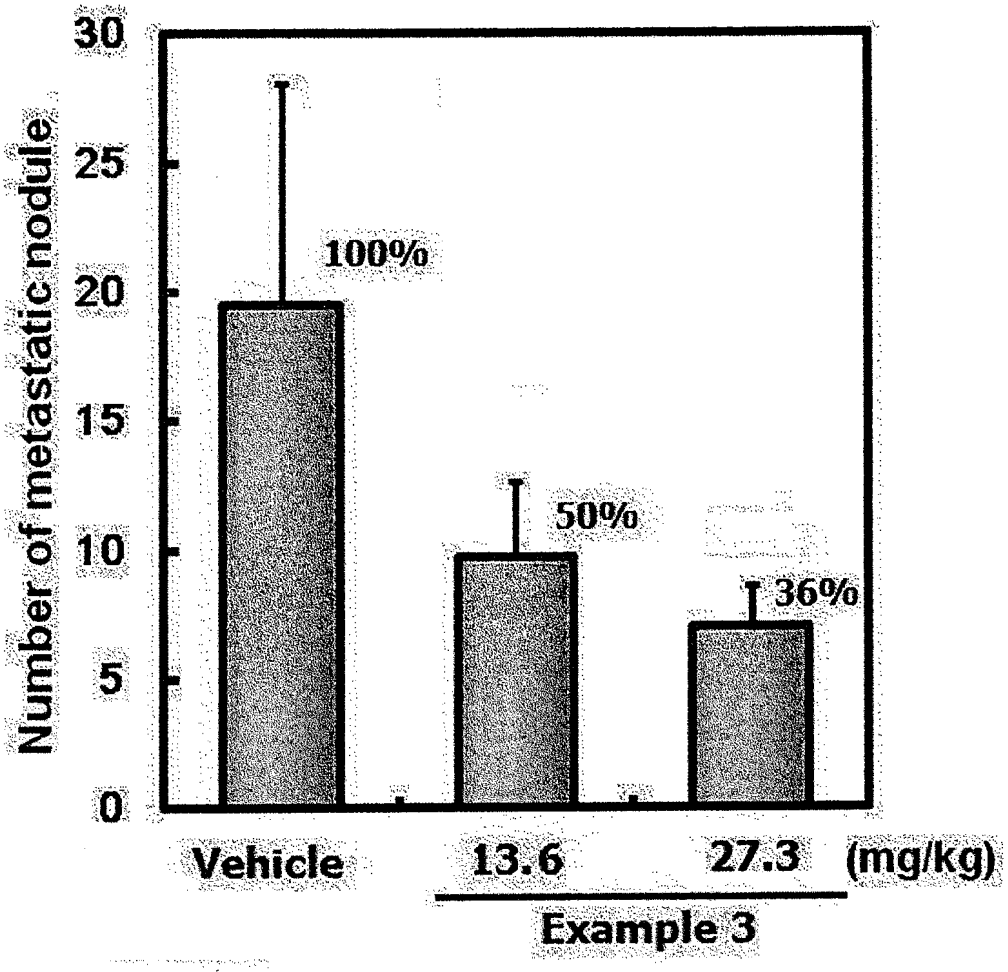


Data represents the mean ± S.D. (n = 4).

[Fig. 8a]

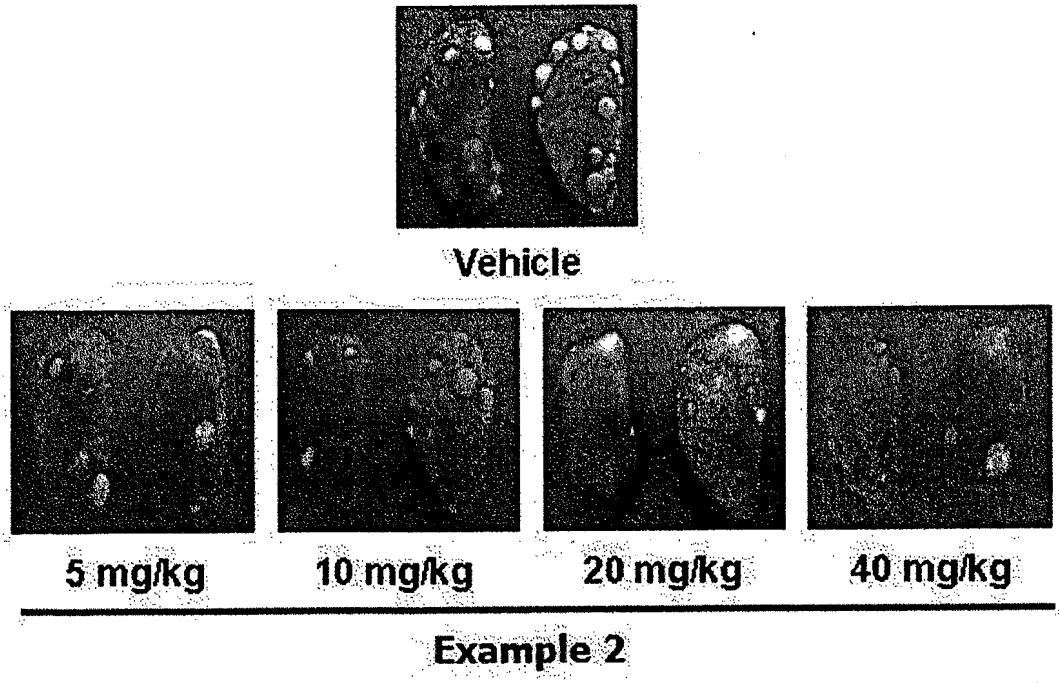


[Fig. 8b]

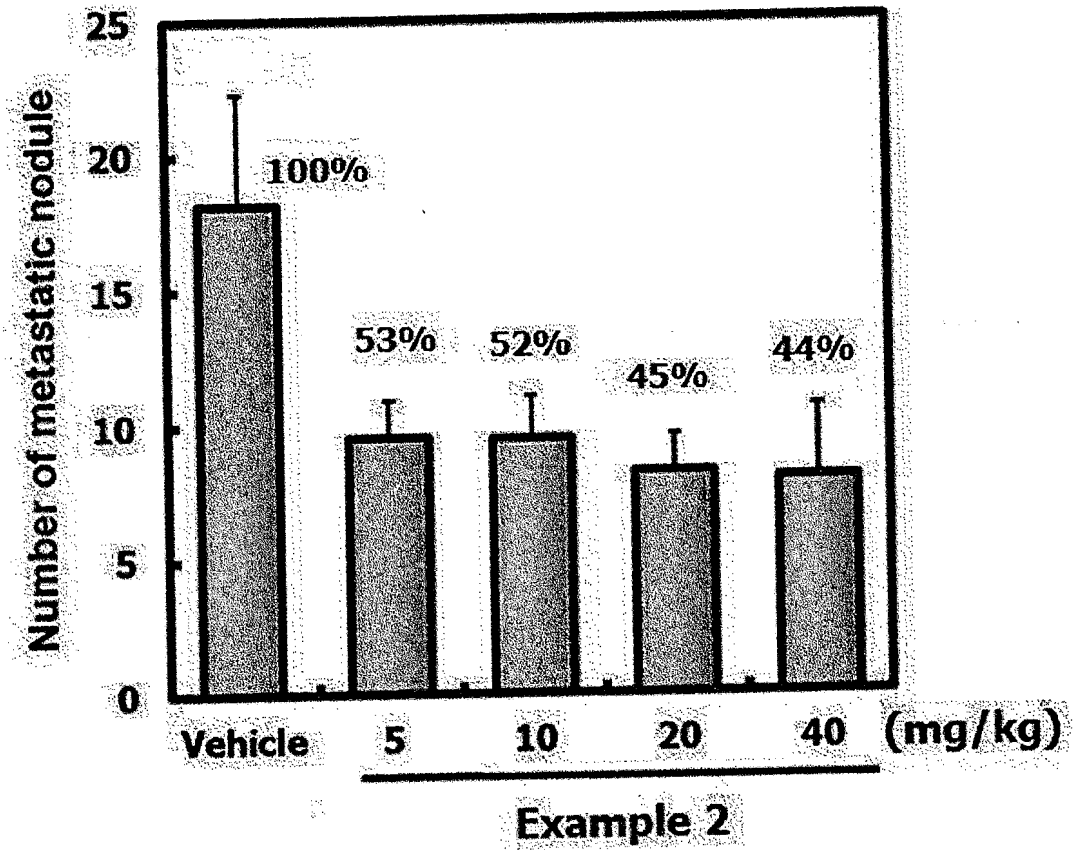


Data represents the mean ± S.E. (n = 8).

[Fig. 9a]

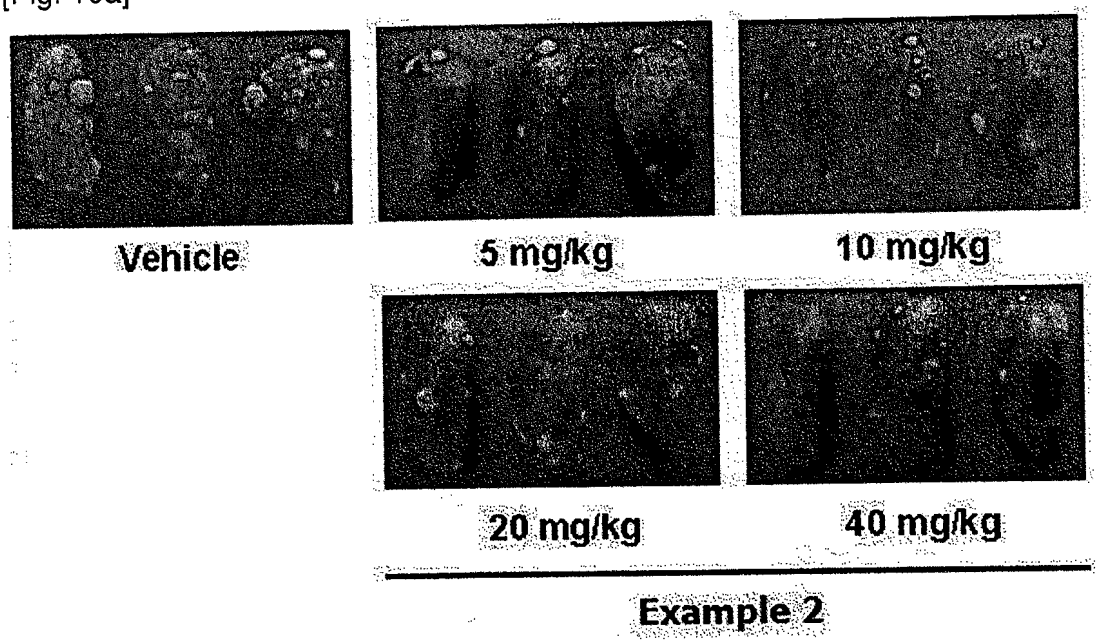


[Fig. 9b]

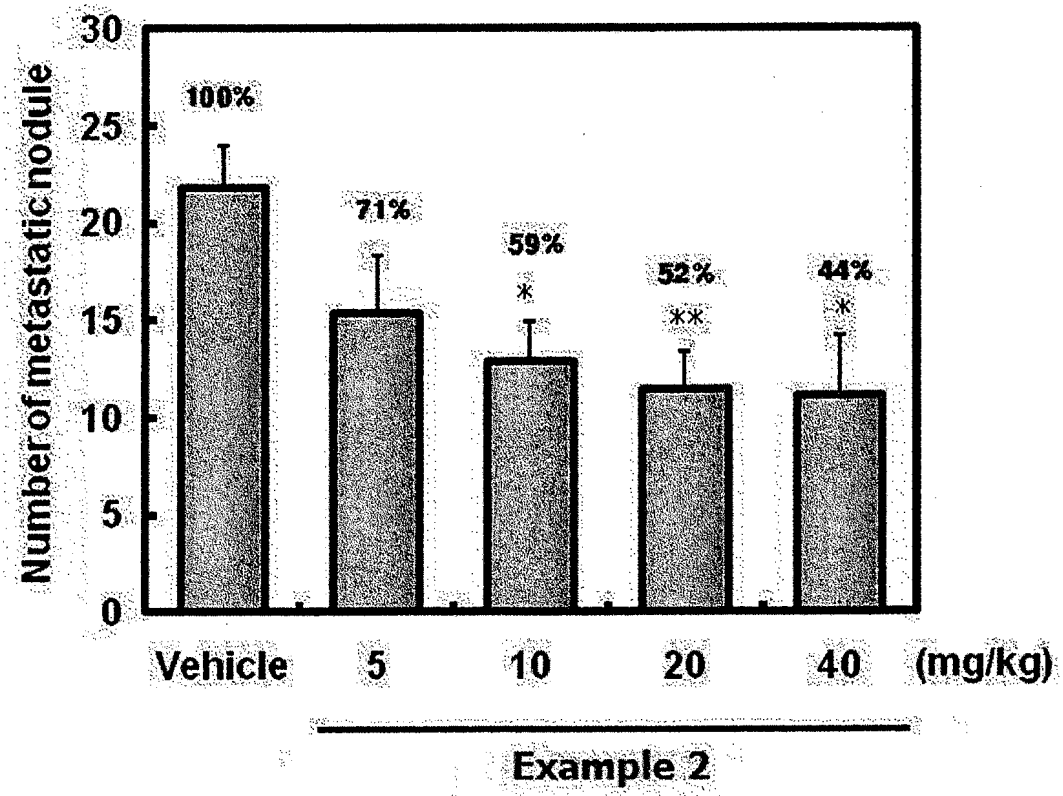


Data represents the mean ± S.E. (n = 7–10).

[Fig. 10a]

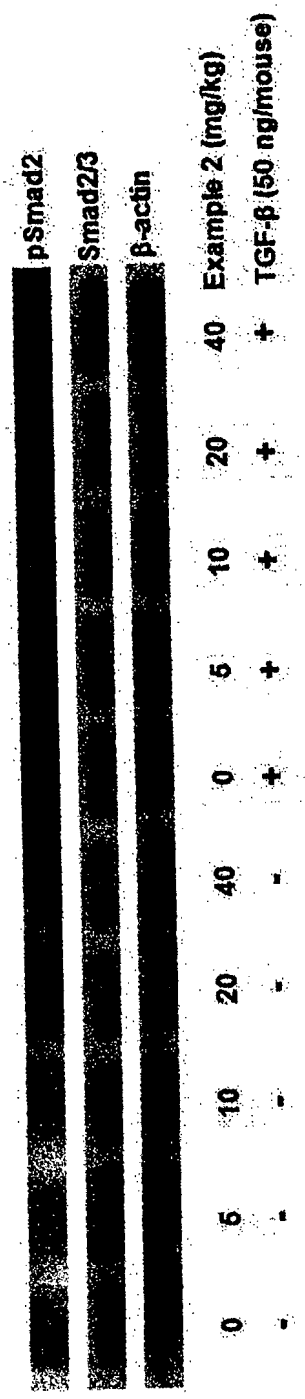


[Fig. 10b]

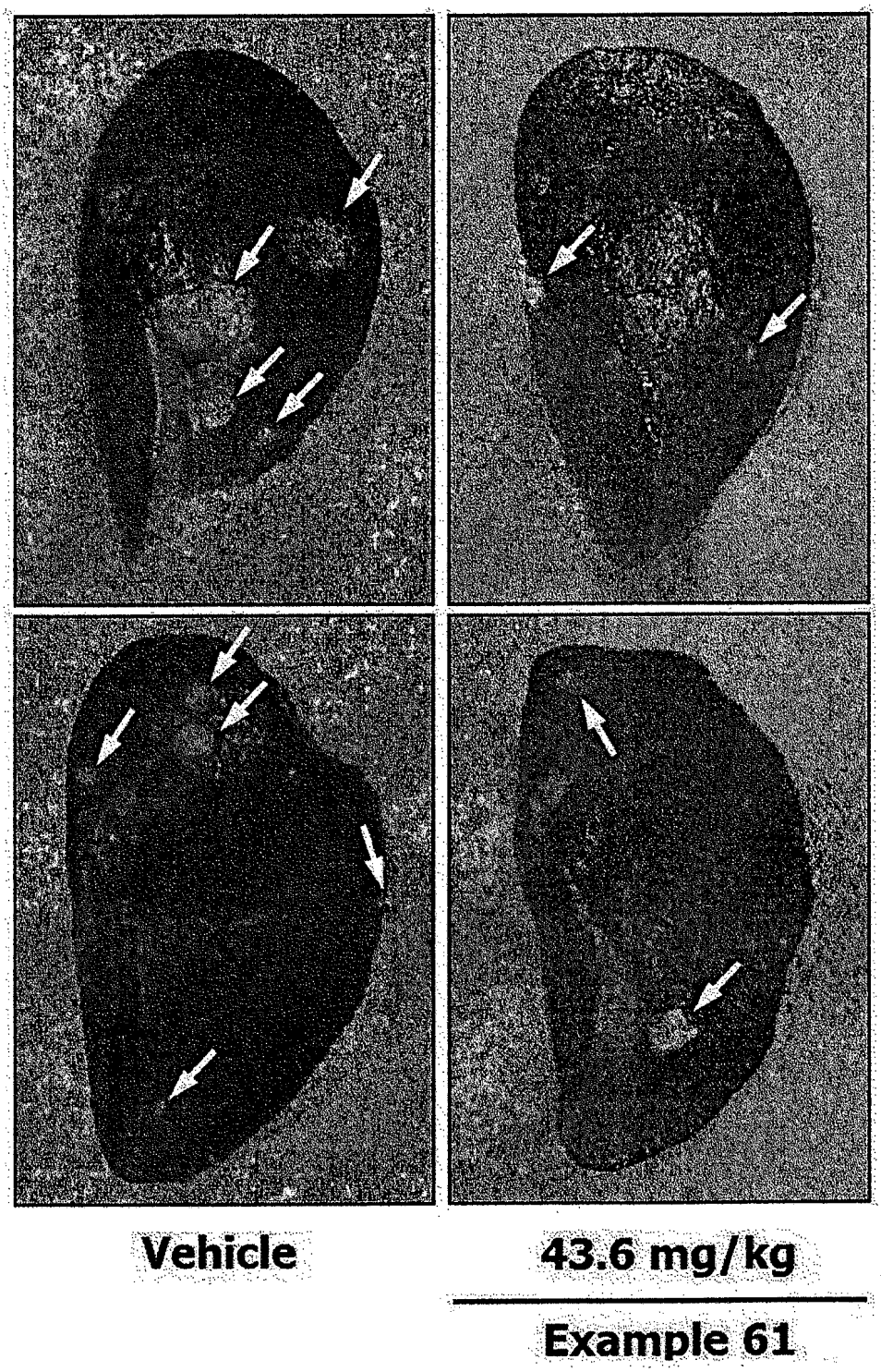


Data represents the mean ± S.E. (n = 9–10).
*: significantly different from vehicle group ($p < 0.05$).
**: significantly different from vehicle group ($p < 0.01$).

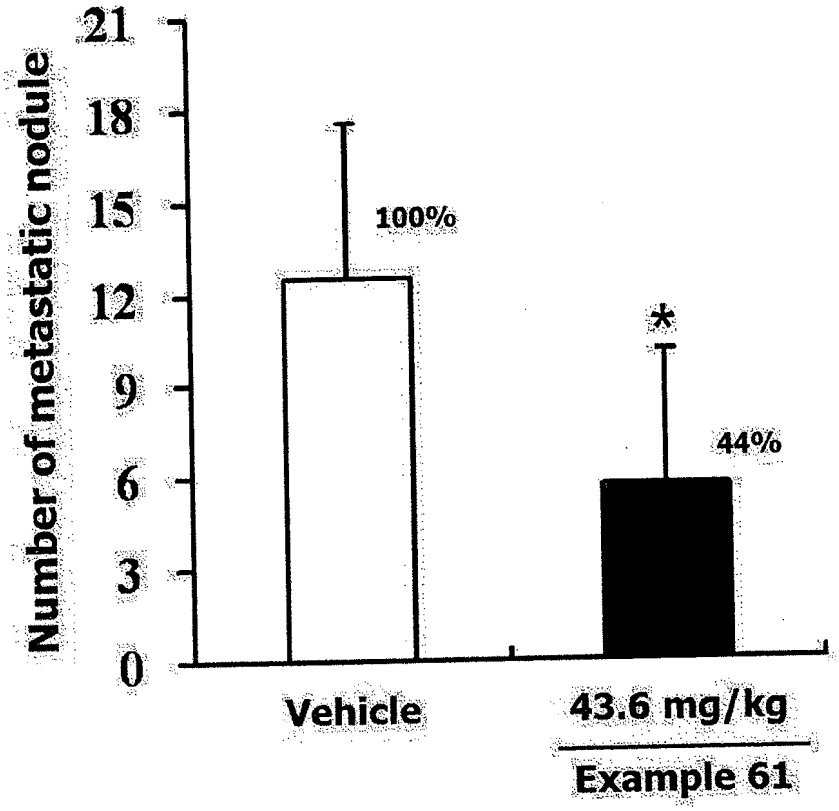
[Fig. 10c]


pSmad2
Smad2/3
β-actin
Example 2 (mg/kg)
TGF-β (50 ng/mouse)
0 5 10 20 40 0 5 10 20 40
- - - - - + + + + +

[Fig. 11a]

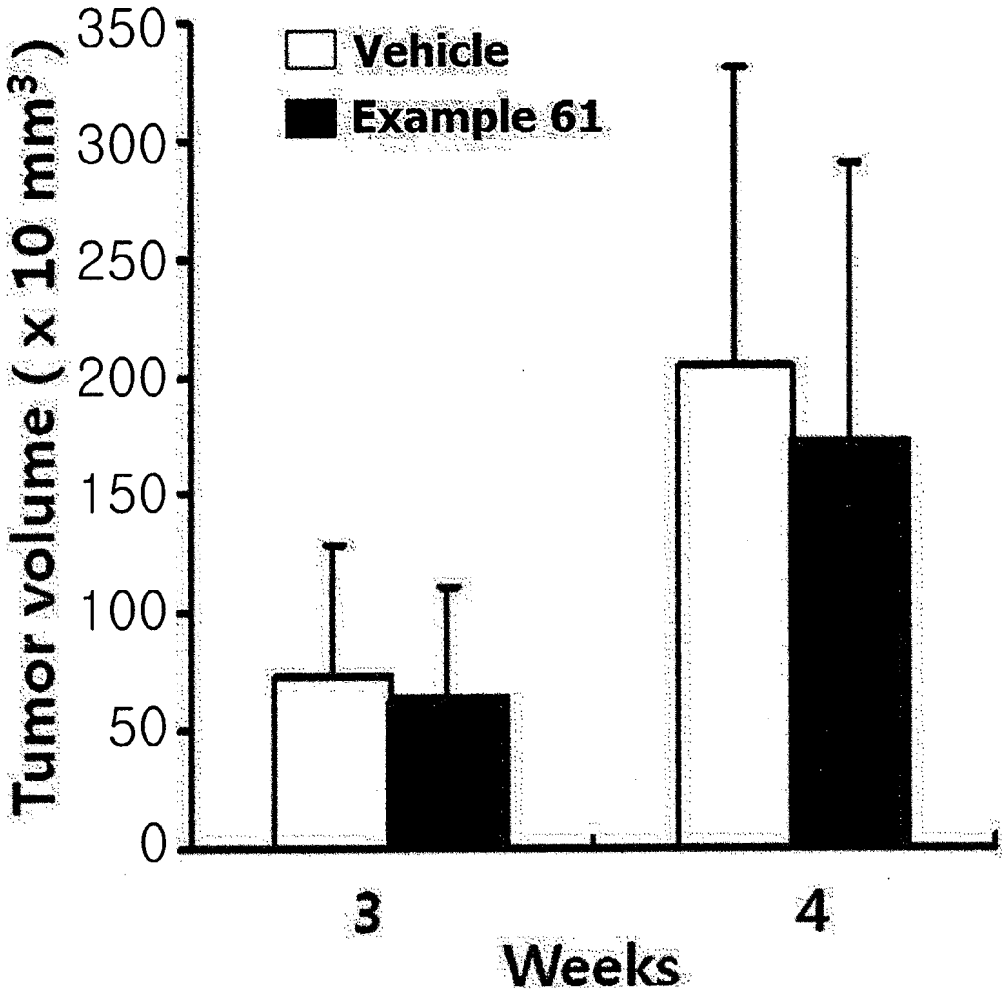


[Fig. 11b]



Data represents the mean ± S.D. (n = 8).
*: significantly different from vehicle group ($p < 0.05$).

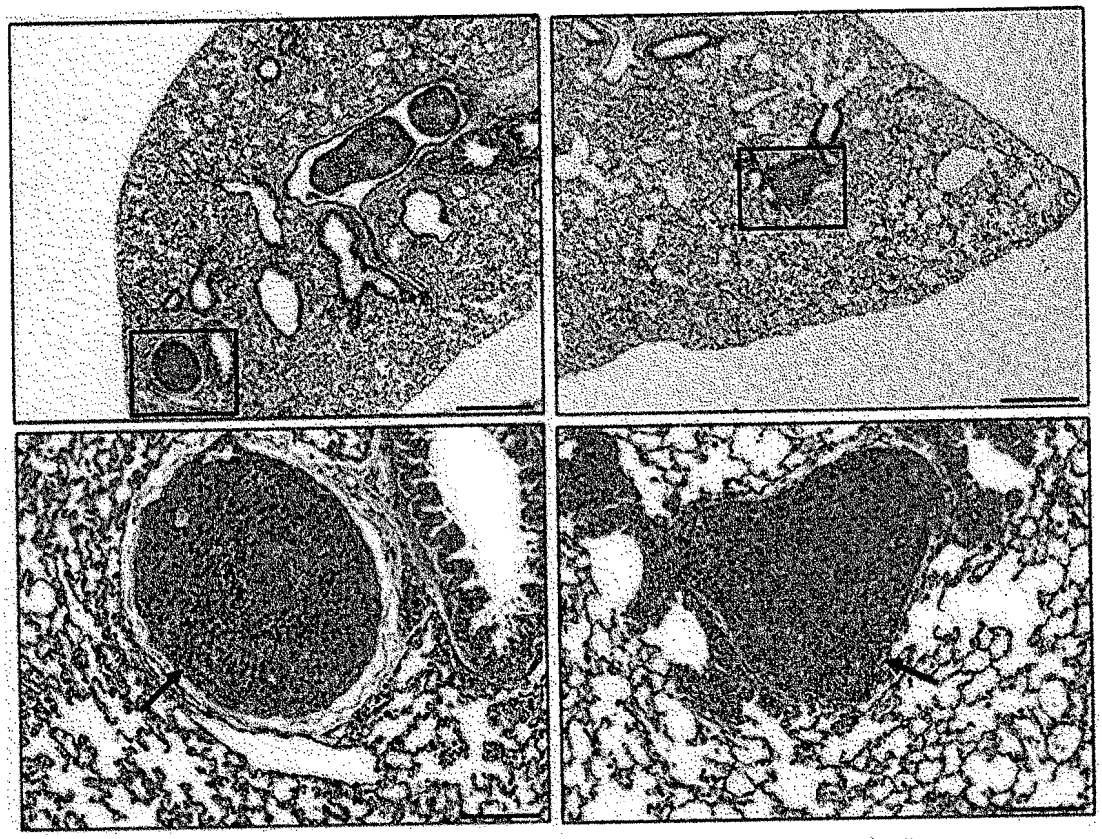
[Fig. 11c]



Data represents the mean ± S.D. (n = 6).

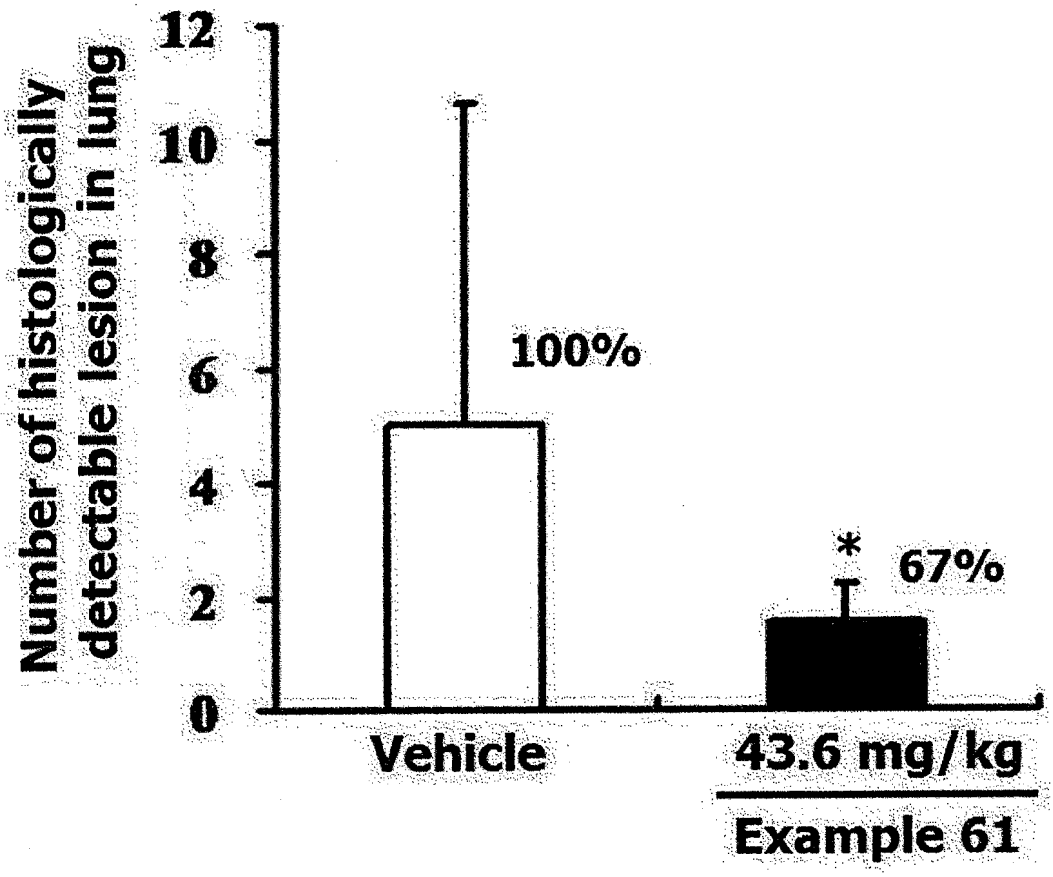
[Fig. 12a]

H&E staining



Arrows indicate metastatic lesions in the lung.

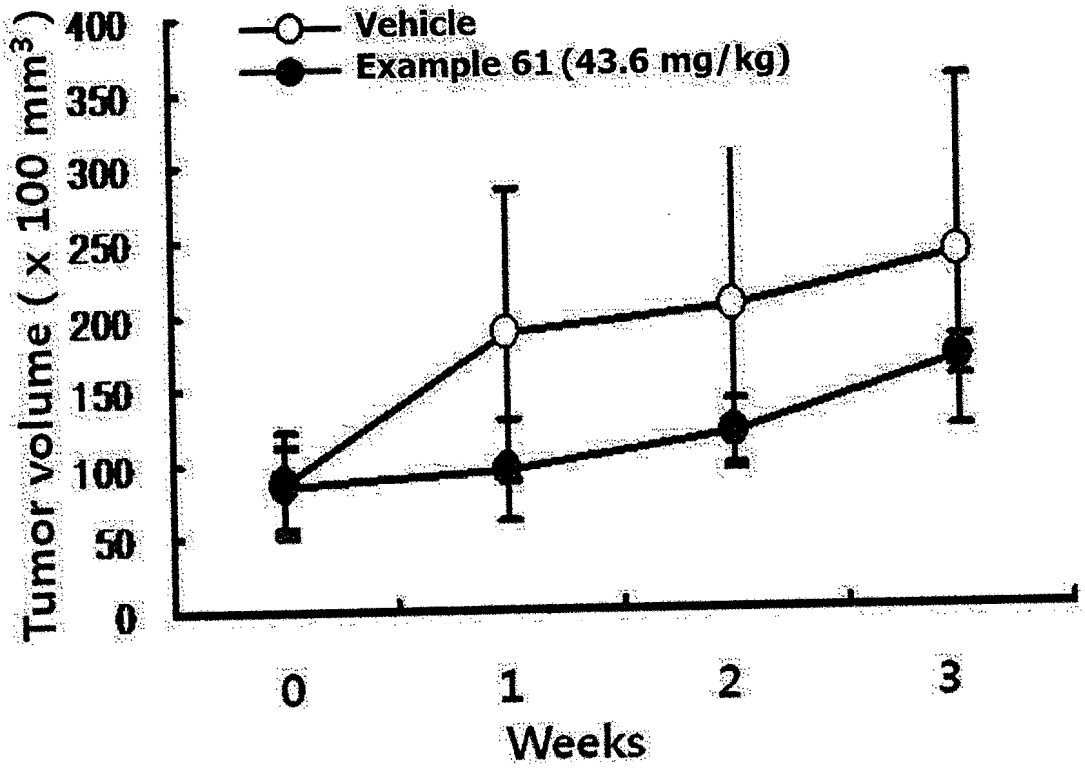
[Fig. 12b]



Data represents the mean ± S.D. (n = 3).

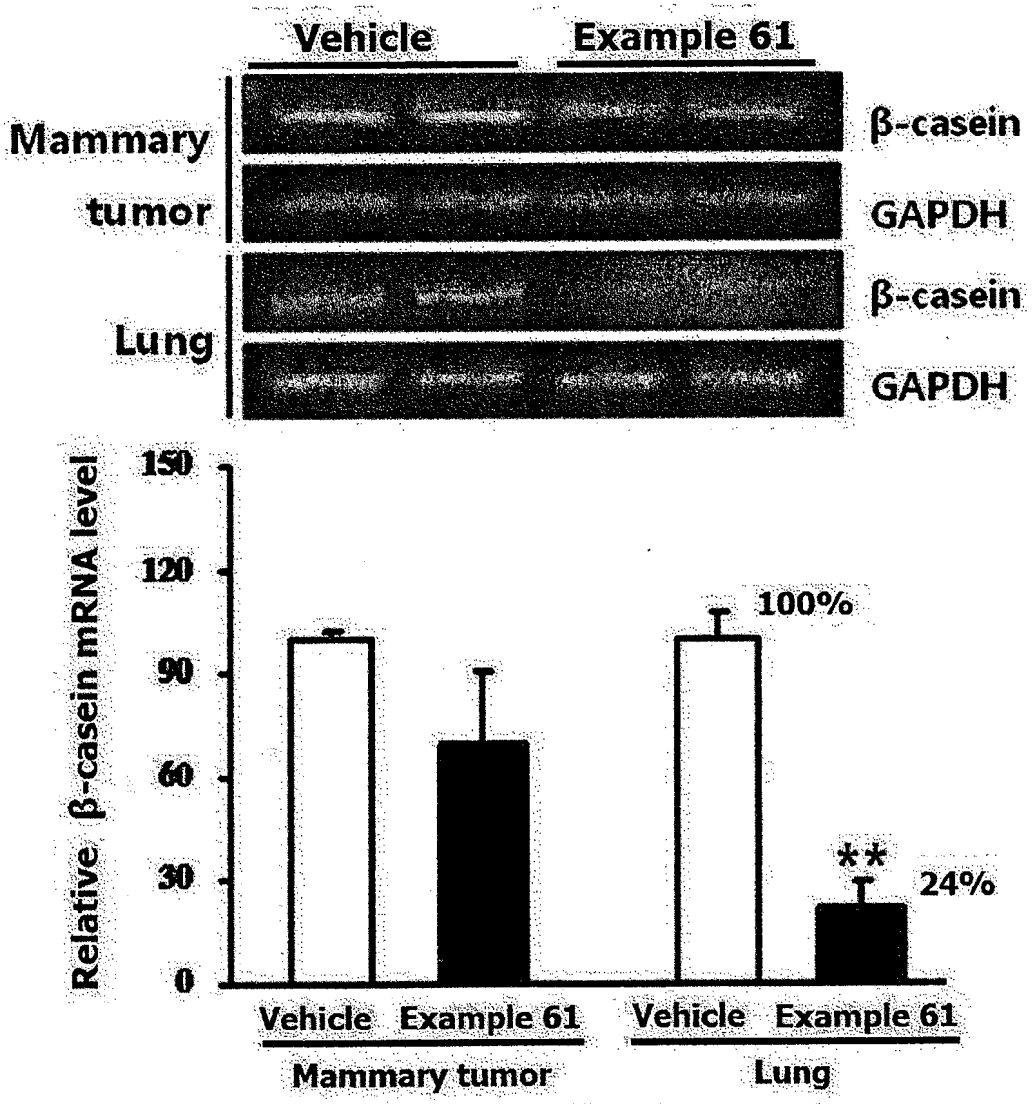
*: significantly different from vehicle group ($p < 0.05$).

[Fig. 12c]



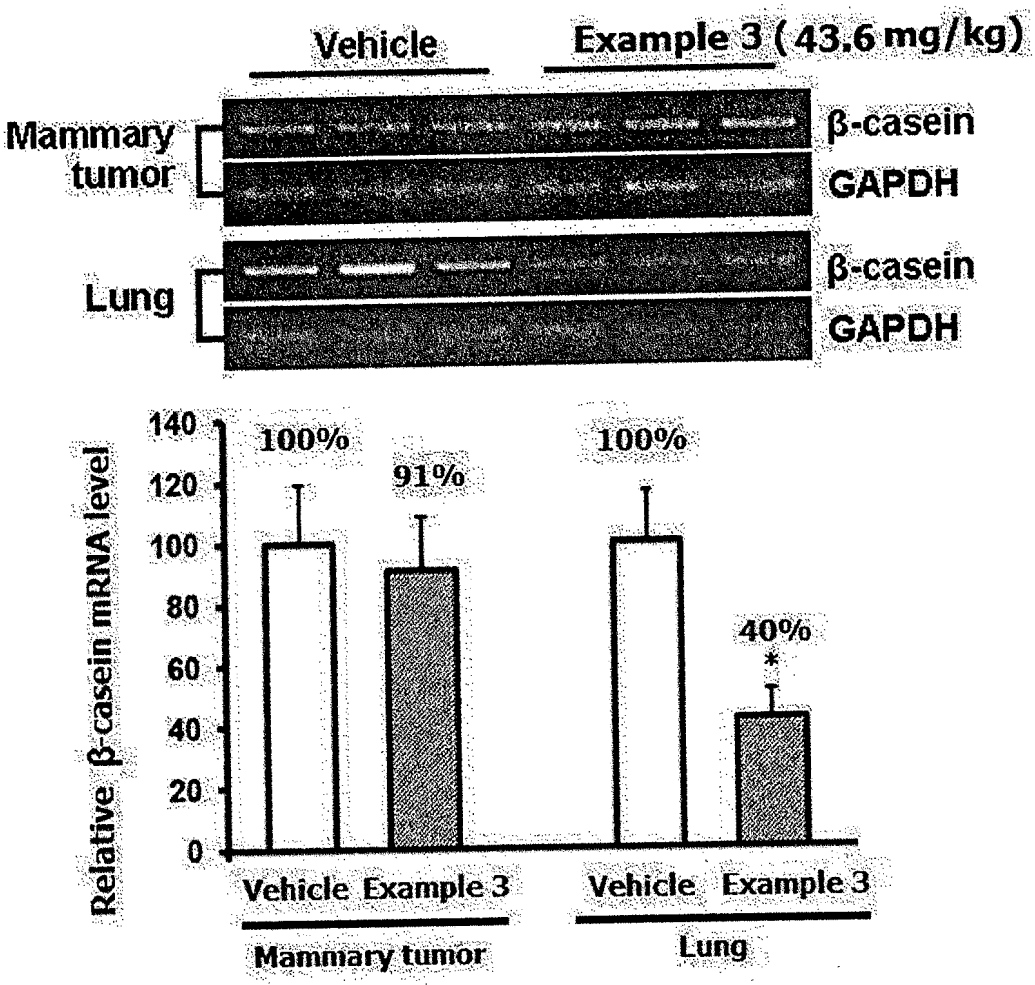
Data represents the mean ± S.D. (n = 3).

[Fig. 12d]



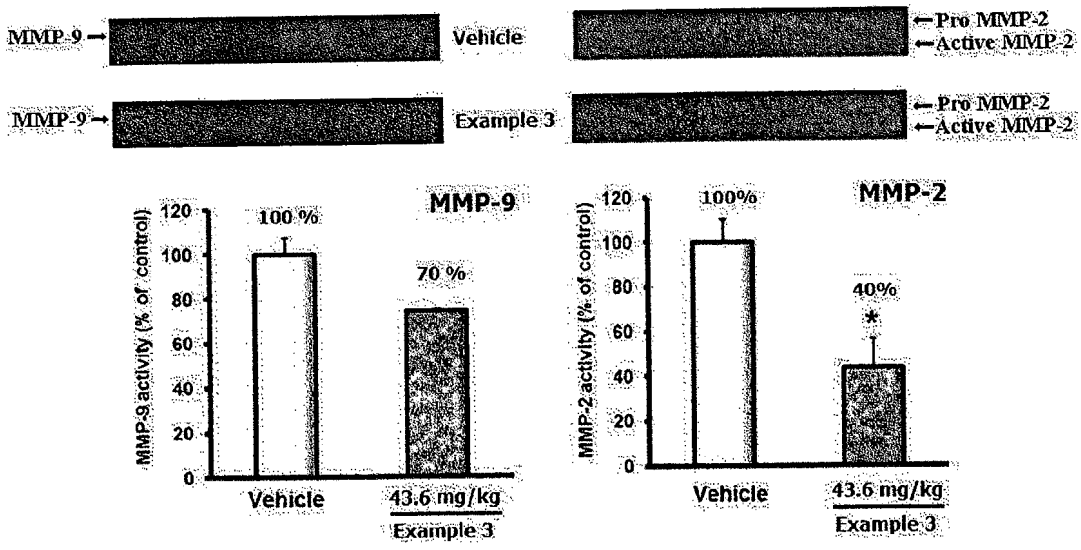
Data represents the mean ± S.D. (n = 6).
**: significantly different from vehicle group in lung ($p < 0.01$).

[Fig. 13a]



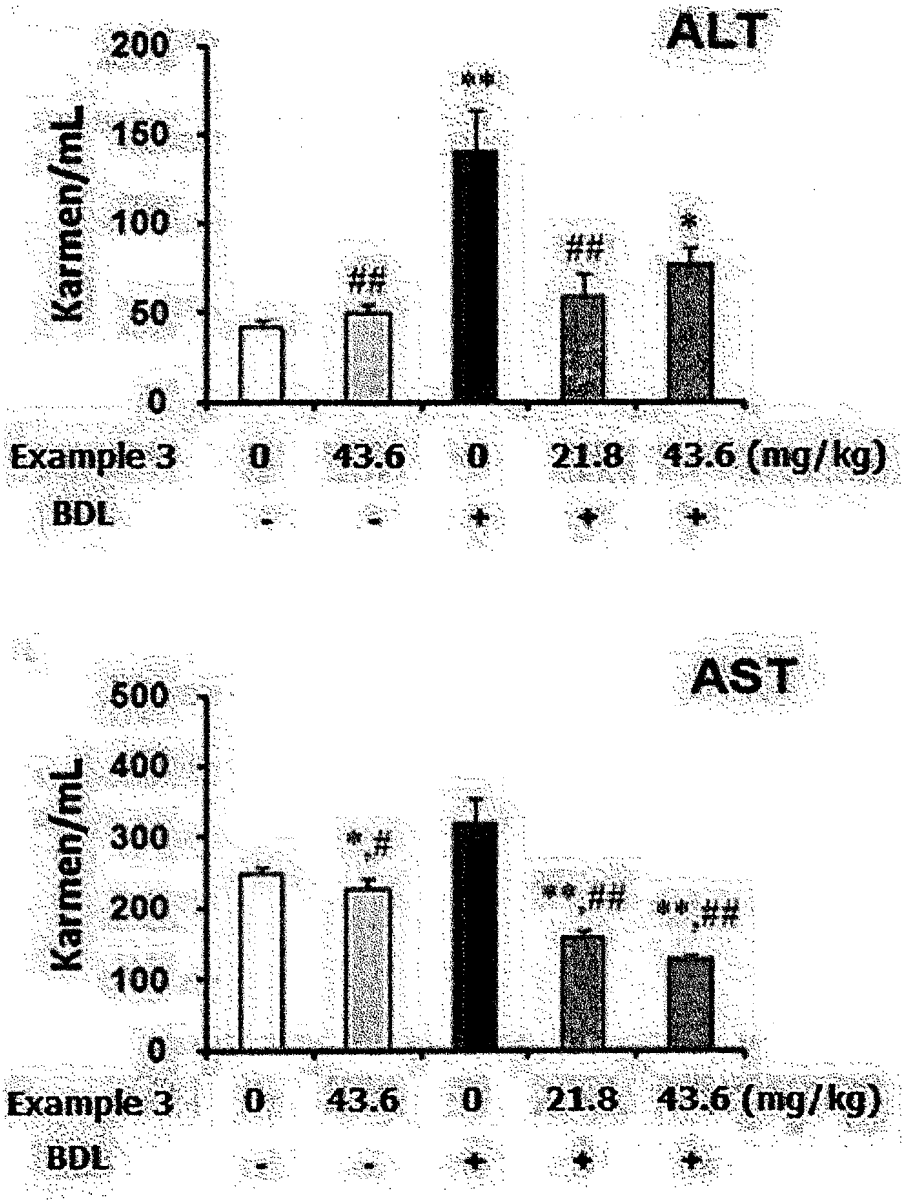
Data represents the mean ± S.E. (n = 7–10).
* : significantly different from vehicle group in lung ($p < 0.05$).

[Fig. 13b]



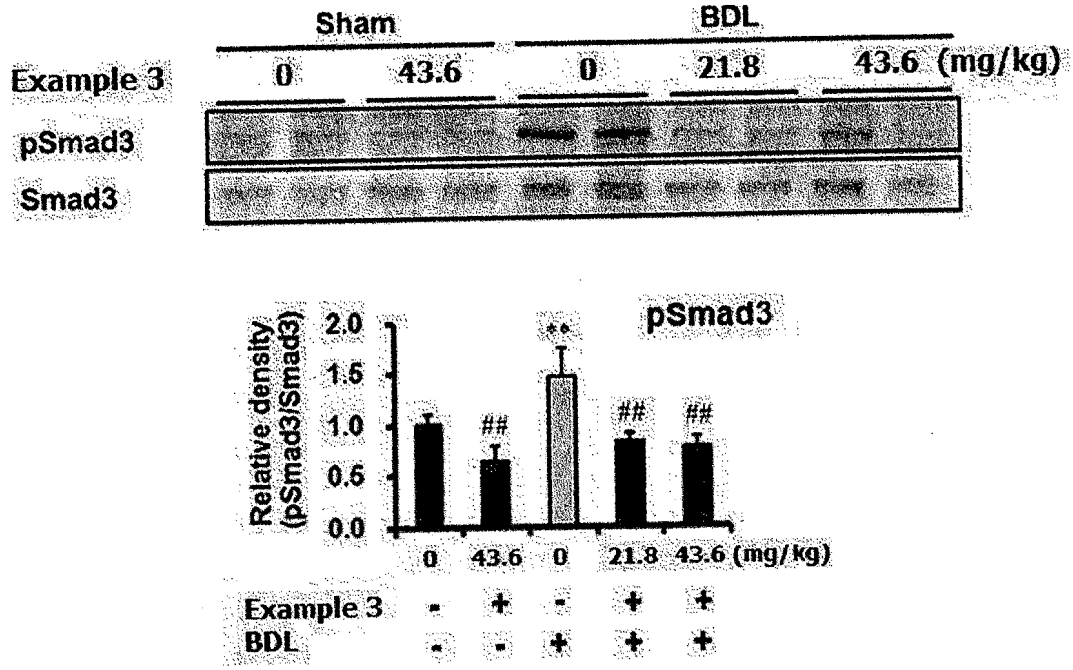
Data represents the mean ± S.E. (n = 5–10).
*: significantly different from vehicle group ($p < 0.05$).

[Fig. 14a]



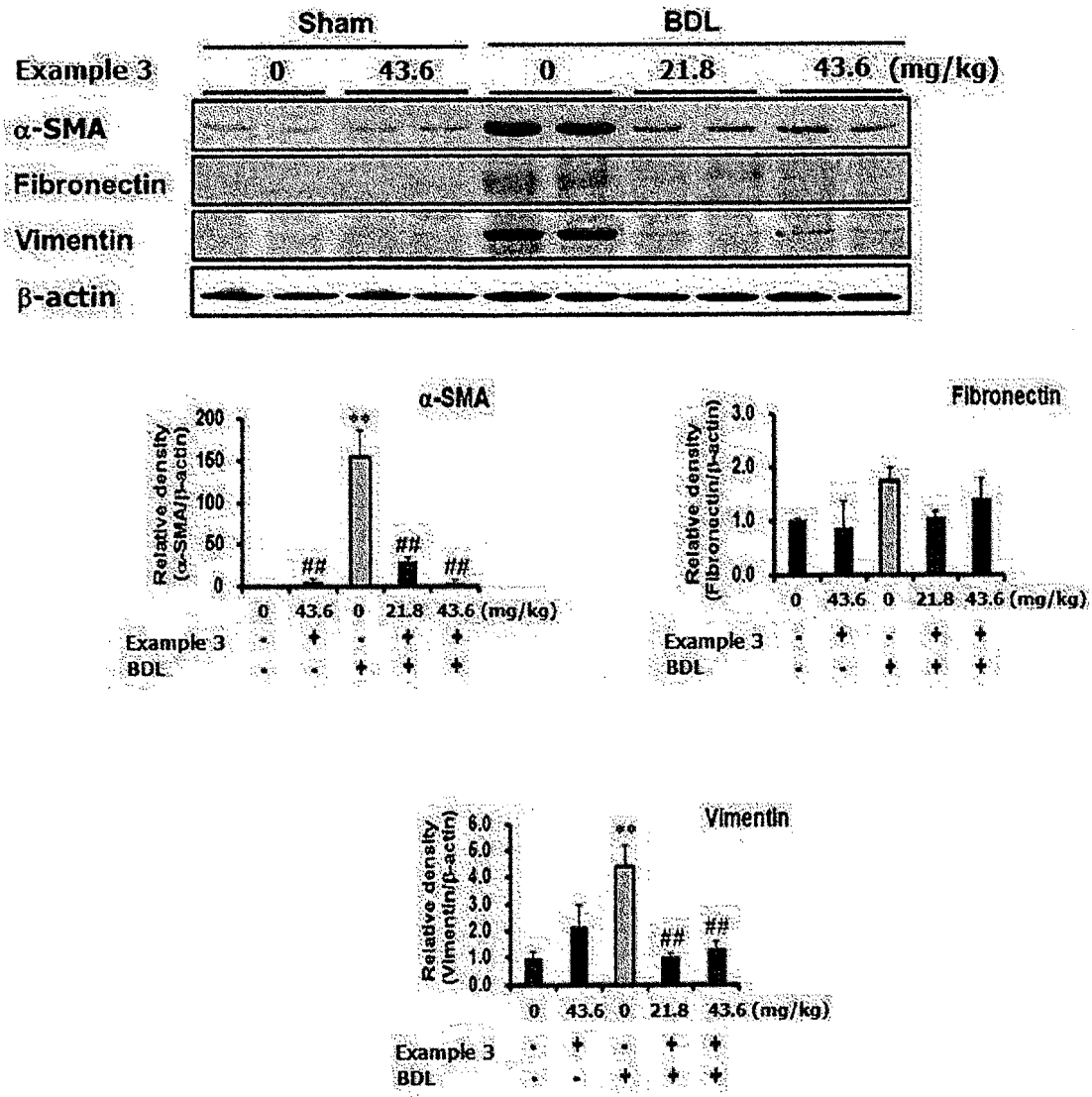
Data represents the mean ± S.E. (n = 5–8).
*: $p < 0.05$ vs. sham. **: $p < 0.01$ vs. sham.
#: $p < 0.05$ vs. BDL. ##: $p < 0.01$ vs. BDL.

[Fig. 14b]



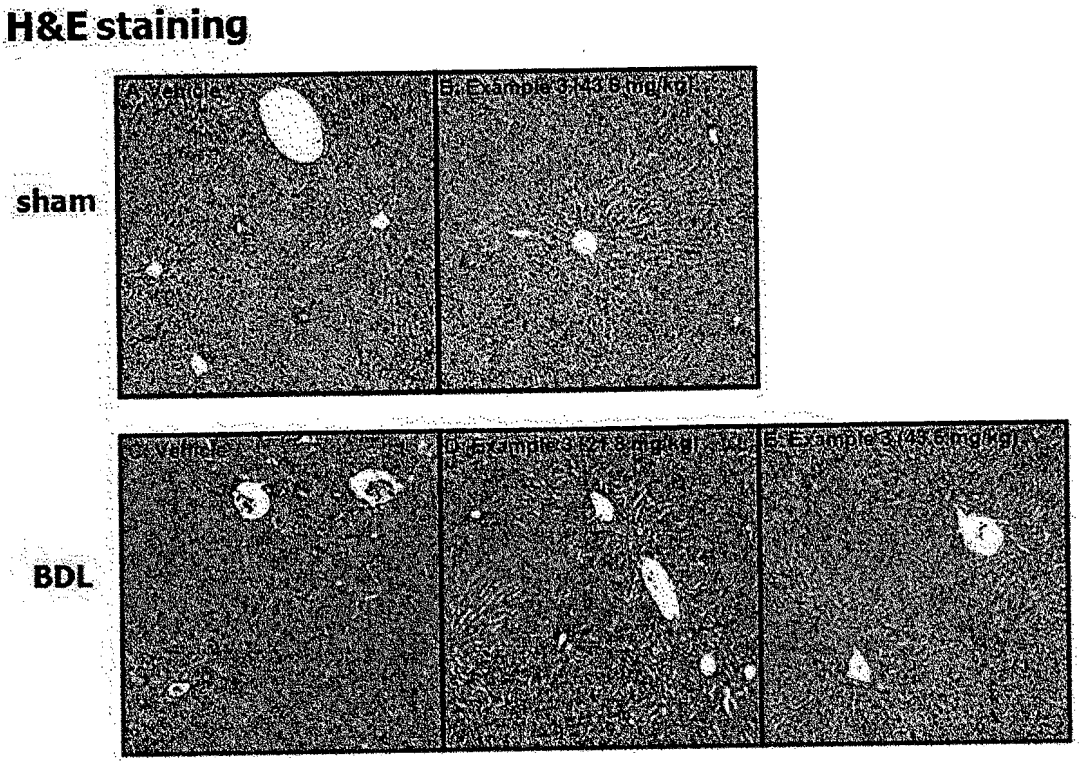
Data represents the mean ± S.E. (n = 5).
**: $p < 0.01$ vs. sham. ##: $p < 0.01$ vs. BDL.

[Fig. 14c]

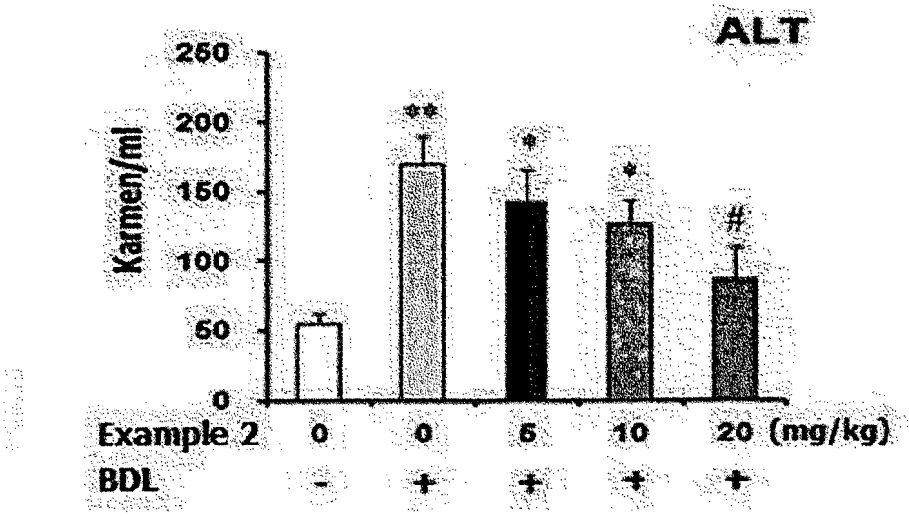


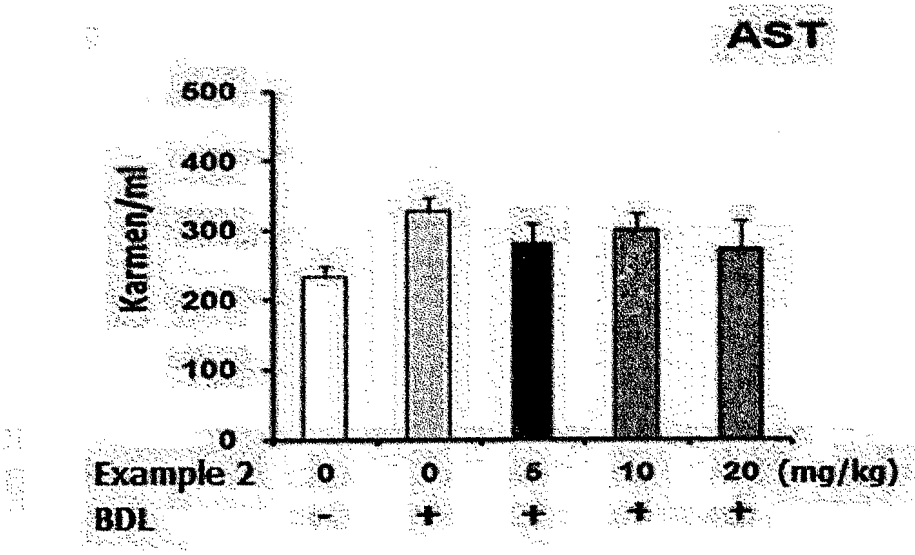
Data represents the mean ± S.E. (n = 5).
**: $p < 0.01$ vs. sham. ##: $p < 0.01$ vs. BDL.

[Fig. 14d]


H&E staining
sham
BDL
A. Vehicle
B. Example 3-143 6 mg/kg
C. Vehicle
D. Example 3-127 6 mg/kg
E. Example 3-143 6 mg/kg

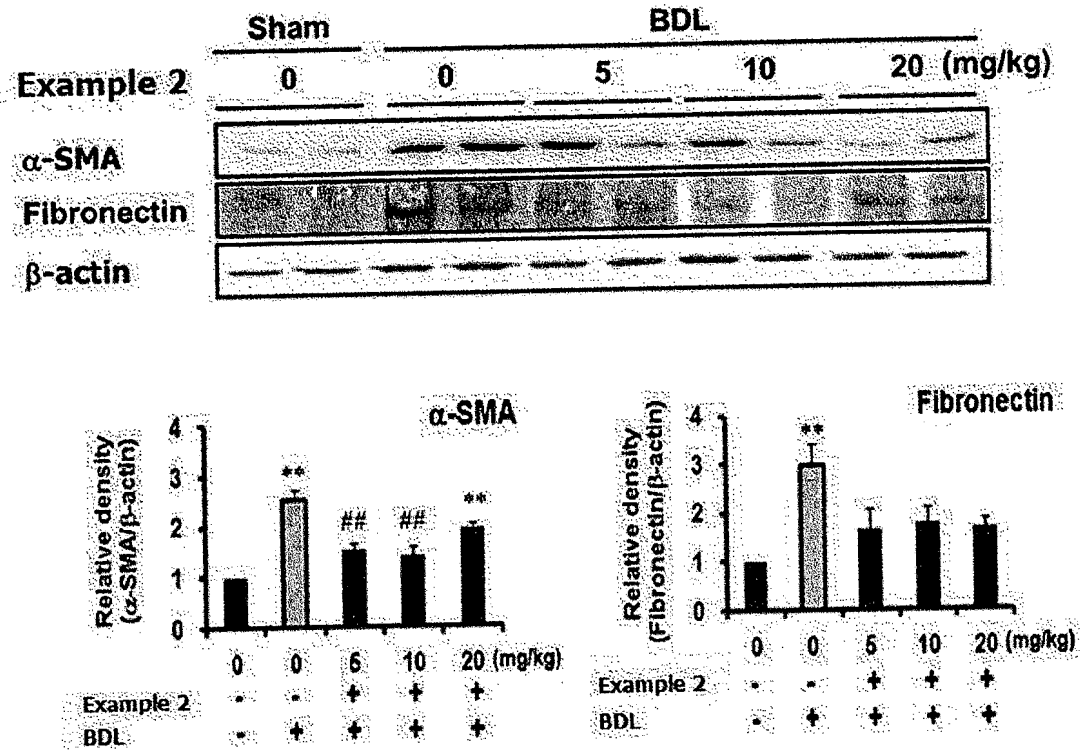
[Fig. 15a]





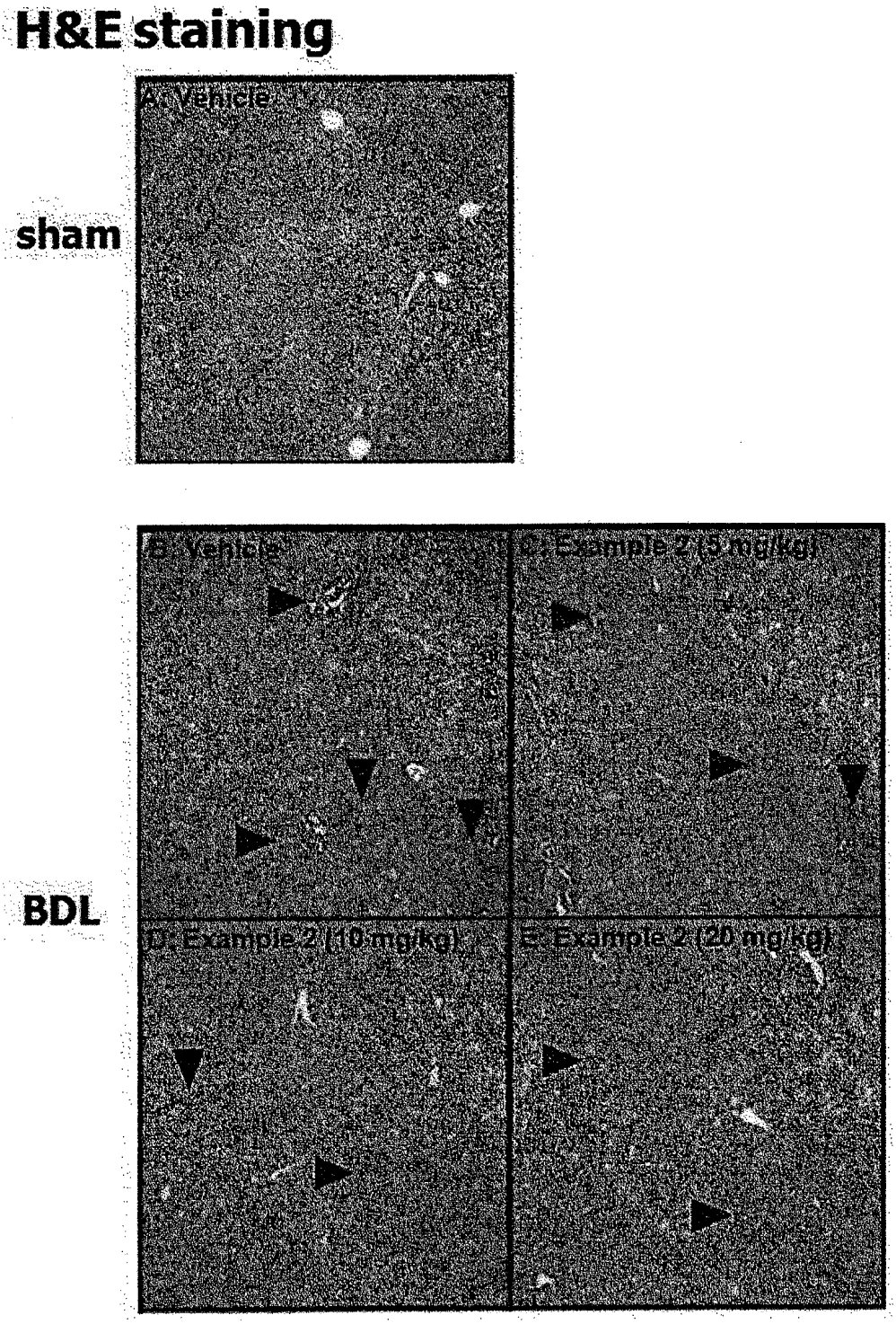
Data represents the mean ± S.E. (n = 5–8).
*: $p < 0.05$ vs. sham. **: $p < 0.01$ vs. sham.
#: $p < 0.05$ vs. BDL.

[Fig. 15b]

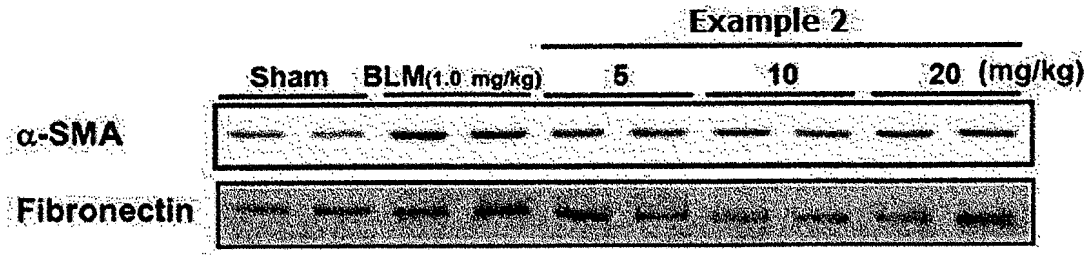


Data represents the mean ± S.E. (n = 5).
**: $p < 0.01$ vs. sham. ##: $p < 0.01$ vs. BDL.

[Fig. 15c]

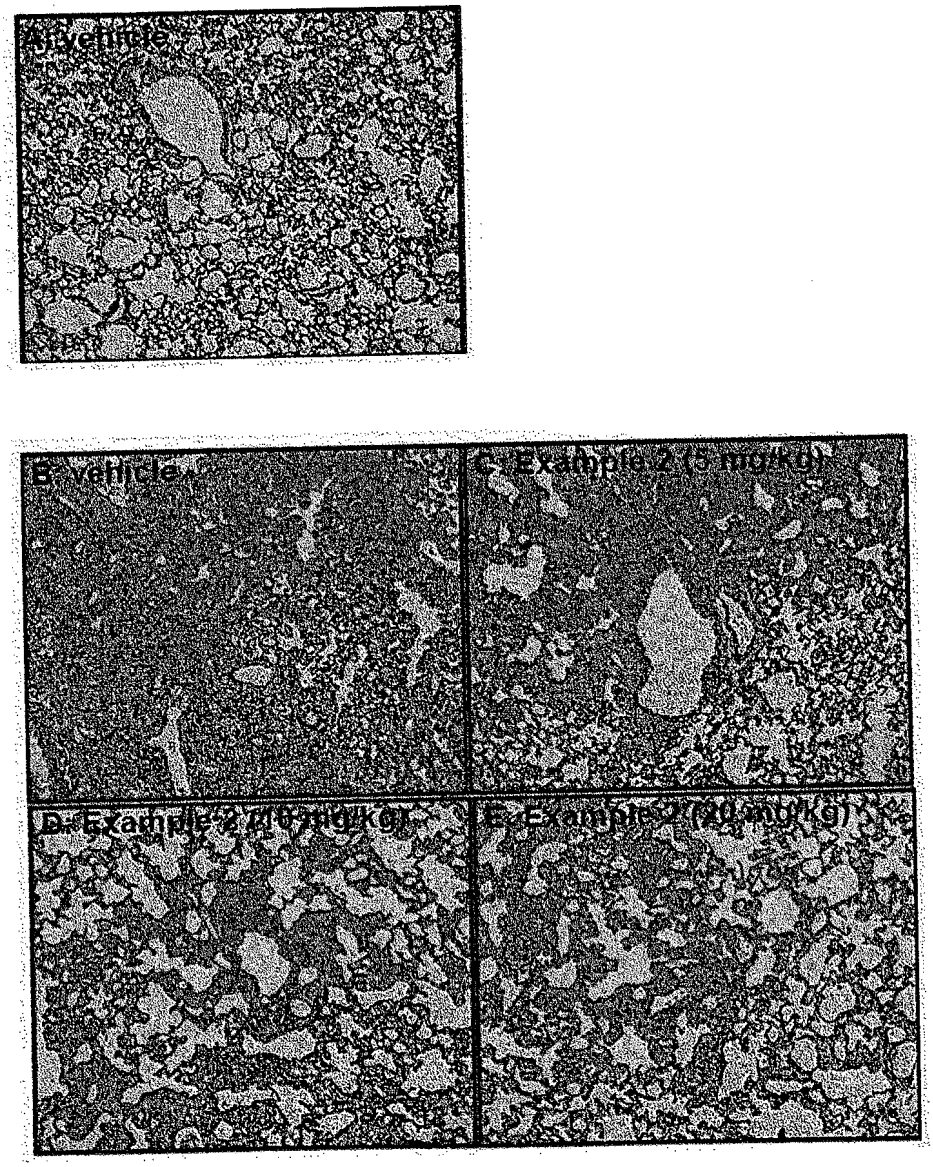


[Fig. 16a]



[Fig. 16b]

H&E staining



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2012 (05.01.2012)

PCT

(10) International Publication Number
WO 2012/002680 A3

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61P 13/12* (2006.01)
C07D 401/14 (2006.01) *A61P 11/00* (2006.01)
C07D 413/14 (2006.01) *A61P 19/10* (2006.01)
A61K 31/437 (2006.01) *A61P 25/28* (2006.01)

(21) International Application Number:
PCT/KR2011/004631

(22) International Filing Date:
24 June 2011 (24.06.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/826,338 29 June 2010 (29.06.2010) US

(71) Applicant *(for all designated States except US)*: **EWHA UNIVERSITY-INDUSTRY COLLABORATION FOUNDATION** [KR/KR]; 11-1, Daehyun-dong, Seodaemun-gu, Seoul 120-750 (KR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KIM, Dae Kee** [KR/KR]; 101-1403 Parkpalace, Naesu-dong, Jongno-gu, Seoul 110-901 (KR). **SHEEN, Yhun Yhong** [KR/KR]; 122-1401 Raemian Firstige Apt., Banpo 2(i)-dong, Seocho-gu, Seoul 137-764 (KR). **JIN, Cheng Hua** [KR/KR]; Pharmaceutical Science Building A #200, Ewha Womans Univ., Daehyeon-dong, Seodaemun-gu, Seoul 120-750 (KR). **PARK, Chul-Yong** [KR/KR]; Eungam-2-dong, 376-32 (#301), Eunpyeong-gu, Seoul 122-919 (KR). **SREENU, Domalapally** [IN/KR]; Pharmaceutical Science Building A #200, Ewha Womans Univ., Daehyeon-dong, Seodaemun-gu, Seoul 120-750 (KR). **RAO, Kota Sudhakar** [IN/KR]; Pharmaceutical Science Building A #200, Ewha Womans Univ., Daehyeon-dong, Seodaemun-gu, Seoul 120-750 (KR). **KRISHNAIAH, Maddeboina** [IN/KR]; Pharmaceutical Science Building A #200, Ewha Womans Univ., Daehyeon-dong, Seodaemun-gu, Seoul 120-750 (KR). **SUBRAHMANYAM, Vura Bala** [IN/KR]; 101 Geumhwa House, Sinchon-dong 1-8, Seodaemun-gu, Seoul 120-140 (KR).

(74) Agent: **HALLA PATENT & LAW FIRM**; 9F KAMCO Yangjae Tower, 949-3 Dogok-dong, Gangnam-gu, Seoul 135-270 (KR).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

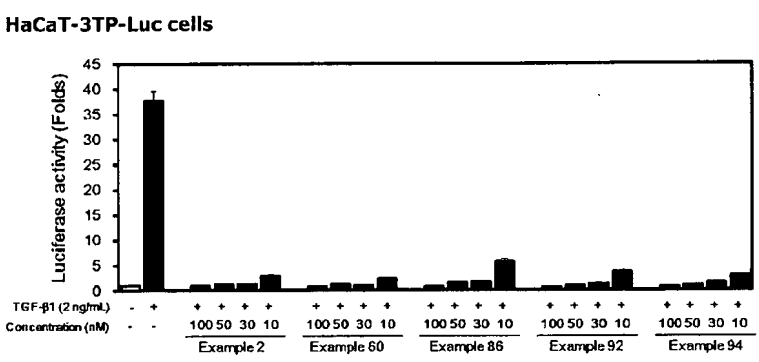
Published:

— *with international search report (Art. 21(3))*

[Continued on next page]

(54) Title: 2-PYRIDYL SUBSTITUTED IMIDAZOLES AS THERAPEUTIC ALK5 AND/OR ALK4 INHIBITORS

[Fig. 1]



(57) Abstract: This invention relates to 2-pyridyl substituted imidazoles which are inhibitors of the transforming growth factor-β (TGF-β) type I receptor (ALK5) and/or the activin type I receptor (ALK4), methods for their preparation, and their use in medicine, specifically in the treatment and prevention of a disease state mediated by these receptors.

WO 2012/002680 A3

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
26 April 2012

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2011/004631

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04(2006.01)i, C07D 401/14(2006.01)i, C07D 413/14(2006.01)i, A61K 31/437(2006.01)i, A61P 13/12(2006.01)i, A61P 11/00(2006.01)i, A61P 19/10(2006.01)i, A61P 25/28(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 471/04; C07D 403/14; A61K 31/444; A61K 31/4525; A61P 25/14; C07D 401/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), CAplus, Google, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008-0227824 A1 (MINIDIS, A. et al.) 18 September 2008 See the entire document.	1-3
A	US 2007-0078166 A1 (BORGHESE, A. et al.) 05 April 2007 See the entire document.	1-3
A	US 4775762 A (KNOX, I. L. et al.) 04 October 1988 See the entire document.	1-3

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 FEBRUARY 2012 (14.02.2012)	**16 FEBRUARY 2012 (16.02.2012)**

Name and mailing address of the ISA/KR

Korean Intellectual Property Office
Government Complex-Daejeon, 189 Cheongsa-ro,
Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

LEE, Dong Wook

Telephone No. 82-42-481-8163

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2011/004631

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 4-8
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 4-8 pertain to a method for treatment of the human by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2011/004631

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008-0227824 A1	18.09.2008	CA 2623009 A1	12.04.2007
		CN 101273037 A0	24.09.2008
		EP 1934209 A1	25.06.2008
		JP 2009-510064 A	12.03.2009
		JP 2010-013476 A	21.01.2010
		KR 10-2008-0050421 A	05.06.2008
		RU 2008108219 A	10.11.2009
		TW 200800976 A	01.01.2008
		US 2007-129408 A1	07.06.2007
		US 7476684 B2	13.01.2009
		WO 2007-040982 A1	12.04.2007
US 2007-0078166 A1	05.04.2007	CA 2542140 A1	12.05.2005
		CN 1863791 A	15.11.2006
		DE 602004026333 D1	12.05.2010
		EP 1675846 A1	05.07.2006
		EP 1675846 B1	31.03.2010
		ES 2340772 T3	09.06.2010
		JP 2007-509143 A	12.04.2007
		KR 10-0848407 B1	28.07.2008
		US 7381826 B2	03.06.2008
		WO 2005-042515 A1	12.05.2005
US 4775762 A	04.10.1988	None	

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 103025731 A
(43)申请公布日 2013.04.03

(21)申请号 201180031417.9

(22)申请日 2011.06.24

(30)优先权数据
12/826,338 2010.06.29 US

(85)PCT申请进入国家阶段日
2012.12.25

(86)PCT申请的申请数据
PCT/KR2011/004631 2011.06.24

(87)PCT申请的公布数据
WO2012/002680 EN 2012.01.05

(71)申请人 梨花女子大学校产学协力团
地址 韩国首尔

(72)发明人 金大起 申尹容 金成华 朴哲龙
D·斯雷努 K·S·劳
M·克里斯奈哈
V·B·苏布拉曼雅姆

(74)专利代理机构 中国国际贸易促进委员会专利商标事务所 11038
代理人 李华英

(51)Int.Cl.
C07D 471/04(2006.01)
C07D 401/14(2006.01)
C07D 413/14(2006.01)
A61K 31/437(2006.01)
A61P 13/12(2006.01)
A61P 11/00(2006.01)
A61P 19/10(2006.01)
A61P 25/28(2006.01)

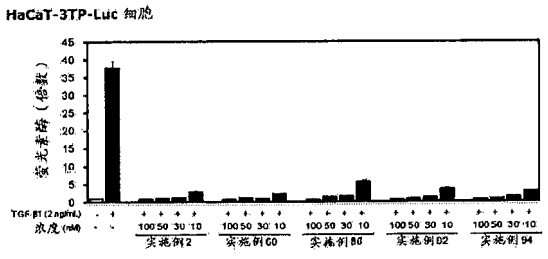
权利要求书 8 页 说明书 72 页 附图 29 页

(54)发明名称

作为ALK5和/或ALK4抑制剂的2-吡啶基取代的咪唑

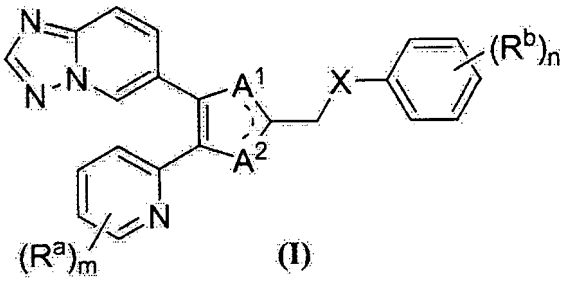
(57)摘要

本发明涉及2-吡啶基取代的咪唑，它们是转化生长因子-β(TGF-β)I型受体(ALK5)和/或活化素I型受体(ALK4)的抑制剂，还涉及它们的制备方法和它们在医药中的用途，具体用于治疗和预防由这些受体介导的疾病状态。



CN 103025731 A

1. 式 (I) 化合物：



(I)

其中：

每个 R^a 独立地是 H、卤素、C_{1-6} 烷基、C_{1-6} 卤代烷基、C_{3-6} 环烷基、OH、－O－C_{1-6} 烷基、－O－C_{1-6} 卤代烷基、－O－C_{3-6} 环烷基、NH_2、－NH－C_{1-6} 烷基、－NH－C_{1-6} 卤代烷基、－NH－C_{3-6} 环烷基、－S－C_{1-6} 烷基、－S－C_{1-6} 卤代烷基、－S－C_{3-6} 环烷基、CN 或 NO_2；

m 是 0、1、2、3 或 4；

A^1 和 A^2 之一是 N，另一个是 NR^1，其中 R^1 是 H、OH、C_{1-6} 烷基、C_{1-6} 卤代烷基、或 C_{3-6} 环烷基；

X 是一条键、－$(CH_2)_p$－、－NR^2－ 、－O－或－S－，其中 p 是 0 或 1，R^2 是 H 或 C_{1-3} 烷基；

每个 R^b 独立地是 H、卤素、C_{1-6} 烷基、C_{1-6} 卤代烷基、C_{3-6} 环烷基、C_{2-6} 烯基、C_{2-6} 炔基、－$(CH_2)_q$－OR^3、－$(CH_2)_q$－NR^3R^4、－$(CH_2)_q$－SR^3、－$(CH_2)_q$－NO_2、－$(CH_2)_q$－CONHOH、－$(CH_2)_q$－CN、－$(CH_2)_q$－COR^3、－$(CH_2)_q$－CO_2R^3、－$(CH_2)_q$－$CONR^3R^4$、－$(CH_2)_q$－四唑、－$(CH_2)_q$－CH=CH－CN、－$(CH_2)_q$－CH=CH－CO_2R^3、－$(CH_2)_q$－CH=CH－$CONR^3R^4$、－$(CH_2)_q$－CH=CH－四唑、－$(CH_2)_q$－$NHCOR^3$、－$(CH_2)_q$－$NHCO_2R^3$、－$(CH_2)_q$－$CONHSO_2R^3$、－$(CH_2)_q$－$NHSO_2R^3$、－$(CH_2)_q$－C≡C－CN、－$(CH_2)_q$－C≡C－CO_2R^3、－$(CH_2)_q$－C≡C－$CONR^3R^4$、－$(CH_2)_q$－C≡C－四唑、－$(CH_2)_q$－SOR^5、－$(CH_2)_q$－SO_2R^5 或－$(CH_2)_r$－$(OR^3)_2$，其中 R^3 和 R^4 独立地是 H、C_{1-6} 烷基、C_{1-6} 卤代烷基或 C_{3-6} 环烷基；或者与它们所连接的氮原子一起构成单环，例如咪唑、吡咯烷、哌啶、吗啉、哌嗪和高哌嗪；R^5 是 C_{1-6} 烷基、C_{1-6} 卤代烷基或 C_{3-6} 环烷基；q 是 0、1、2、3 或 4；r 是 1、2、3 或 4；

n 是 0、1、2、3、4 或 5；或者其药学上可接受的盐或水合物。

2. 权利要求 1 的化合物，选自下组：

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基) 苯胺；

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟苯胺；

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 氟苯胺；

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 氟苯胺；

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2,3- 二氟苯胺；

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3,4- 二氟苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3,5- 二氟苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-2- 氯苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3- 氯苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-4- 氯苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-2,3- 二氯苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3,4- 二氯苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3,5- 二氯苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-2- 溴苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3- 溴苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-4- 溴苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-2- 甲基苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3- 甲基苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-4- 甲基苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-2,3- 二甲基苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3,4- 二甲基苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3,5- 二甲基苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-2- 乙基苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪 唑 -2- 基) 甲基)-3- 乙基苯胺 ;

N-((4-([1,2,4] 三 唑 并 [1,5-a] 吡 啶 -6- 基)-5-(6- 甲 基 吡 啶 -2- 基)-1H- 咪

唑 -2- 基) 甲基)-2- 异丙基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 异丙基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 异丙基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 乙烯基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 乙烯基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 乙烯基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 乙炔基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 甲氧基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 甲氧基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 甲氧基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2,3- 二甲氧基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3,4- 二甲氧基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3,5- 二甲氧基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(甲氧基甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(甲氧基甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4-(甲氧基甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(三氟甲氧基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(三氟甲氧基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4-(三氟甲氧基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(甲硫基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(甲硫基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4-(甲硫基) 苯胺 ;

2-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲腈 ;

4-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 邻苯二甲腈 ;

2-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲酰胺 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲酰胺 ;

4-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲酰胺 ;

2-(3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 乙腈 ;

2-(4-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 乙腈 ;

1-(3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 乙酮 ;

1-(4-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 乙酮 ;

甲基 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲酸酯 ;

甲基 4-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲酸酯 ;

N-(2-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 乙酰胺 ;

N-(3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 乙酰胺 ;

N-(4-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 乙酰胺 ;

N-(2-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 甲磺酰胺 ;

N-(3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪

唑 -2- 基) 甲基氨基) 苯基) 甲磺酰胺 ;

N-(4-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯基) 甲磺酰胺 ;

N^1-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-N^2,N^2- 二甲基苯 -1,2- 二胺 ;

N^1-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-N^3,N^3- 二甲基苯 -1,3- 二胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(吡咯烷 -1- 基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 吗啉代苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 吗啉代苯胺 ;

N^3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 氟 -N^1,N^1- 二甲基苯 -1,3- 二胺 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-5-(二甲基氨基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-4-(二甲基氨基) 苯甲腈 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-((二甲基氨基) 甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-((二甲基氨基) 甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(吡咯烷 -1- 基甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(吡咯烷 -1- 基甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(吗啉代甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(吗啉代甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-5-((二甲基氨基) 甲基)-2- 氟苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-((二甲基氨基) 甲基)-2- 氟苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟 -3-(吡咯烷 -1- 基甲基) 苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟 -3-(吗啉代甲基) 苯胺 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-4-((二甲基氨基) 甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-2-((二甲基氨基) 甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-5-((二甲基氨基) 甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-4-(吡咯烷 -1- 基甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-2-(吡咯烷 -1- 基甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-5-(吡咯烷 -1- 基甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-4-(吗啉代甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-2-(吗啉代甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-5-(吗啉代甲基) 苯甲腈 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(2-(二甲基氨基) 乙基苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(2-(二甲基氨基) 乙基苯胺 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 乙基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲腈 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 乙基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟苯胺 ;

N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟 -N- 甲基苯胺 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)(甲基) 氨基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)(甲基) 氨基) 苯甲酰胺 ;

6-(2- 苄基 -5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -4- 基)-[1,2,4] 三唑并 [1,5-a] 吡啶 ;

6-(2-(2- 氟苄基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -4- 基)-[1,2,4] 三唑并 [1,5-a] 吡啶 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基) 苯甲腈 ;

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪

唑 -2- 基）甲基）苯甲酰胺；

6-(5-(6- 甲基吡啶 -2- 基）-2-（苯氧基甲基）-1H- 咪唑 -4- 基）-[1,2,4] 三唑并 [1,5-a] 吡啶；

6-(2-((2- 氟苯氧基）甲基）-5-(6- 甲基吡啶 -2- 基）-1H- 咪唑 -4- 基）-[1,2,4] 三唑并 [1,5-a] 吡啶；

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基）-5-(6- 甲基吡啶 -2- 基）-1H- 咪唑 -2- 基）甲氧基）苯甲腈；

3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基）-5-(6- 甲基吡啶 -2- 基）-1H- 咪唑 -2- 基）甲氧基）苯甲酰胺；

6-(5-(6- 甲基吡啶 -2- 基）-2-（苯硫基甲基）-1H- 咪唑 -4- 基）-[1,2,4] 三唑并 [1,5-a] 吡啶；

6-(2-((2- 氟苯硫基）甲基）-5-(6- 甲基吡啶 -2- 基）-1H- 咪唑 -4- 基）-[1,2,4] 三唑并 [1,5-a] 吡啶，

及其药学上可接受的盐或水合物。

3. 药物组合物，包含一种或多种权利要求 1 的化合物或者其药学上可接受的盐或水合物，和药学上可接受的稀释剂或载体。

4. 抑制人类 TGF-β 或活化素信号传导途径或此二者的方法，包括对需要所述治疗的人给予治疗有效量的一种或多种权利要求 1 的化合物或者其药学上可接受的盐或水合物。

5. 治疗、预防或减少人类肿瘤细胞转移的方法，包括对需要所述治疗的人给予治疗有效量的一种或多种权利要求 1 的化合物或者其药学上可接受的盐或水合物。

6. 通过抑制人类 TGF-β 信号传导途径来治疗、预防或减少由 TGF-β 过度表达介导的癌的方法，包括对需要所述治疗的人给予治疗有效量的一种或多种权利要求 1 的化合物或者其药学上可接受的盐或水合物。

7. 治疗、预防或减少人类血管损伤的方法，包括对需要所述治疗的人给予治疗有效量的一种或多种权利要求 1 的化合物或者其药学上可接受的盐或水合物。

8. 治疗、预防或减轻人类选自下组的疾病的方法：肾小球性肾炎、糖尿病性肾病、狼疮性肾炎、高血压 - 诱发的肾病、肾间质性纤维化、由药物暴露并发症所致肾纤维化、与 HIV 有关的肾病、移植物肾病、各种病因的肝纤维化、可归因于感染的肝功能障碍、酒精 - 诱发的肝炎、胆系疾患、囊性纤维化病、肺纤维化、间质性肺病、急性肺损伤、成人呼吸窘迫综合征、特发性肺纤维化、慢性阻塞性肺病、由感染性或毒性因子引起的肺病、梗塞后心纤维化、充血性心力衰竭、扩张型心肌病、心肌炎、内膜增厚、血管狭窄、高血压引起的血管重构、肺动脉高压、冠状动脉再狭窄、周围动脉再狭窄、颈动脉再狭窄、支架诱导的再狭窄、动脉粥样硬化、眼部瘢痕形成、角膜瘢痕形成、增生性玻璃体视网膜病变、青光眼、眼内压高、发生在由创伤或手术伤口所致伤口愈合期间的过度性或肥厚性真皮瘢痕或瘢痕疙瘩形成、腹膜与皮下粘连、硬皮病、纤维硬化、进行性系统性硬化病、皮肌炎、多肌炎、关节炎、骨质疏松、溃疡、神经系统功能减低、男性勃起功能障碍、佩罗尼氏病、杜普伊特伦氏挛缩、阿尔茨海默氏病、雷诺氏综合征、辐射 - 诱发的纤维化、血栓形成、肿瘤转移性生长、多发性骨髓瘤、黑素瘤、神经胶质瘤、胶质母细胞瘤、白血病、肉瘤、平滑肌瘤、间皮瘤，以及肺、乳腺、结肠、肾、卵巢、宫颈、肝、胆管、胃肠道、胰腺、前列腺、头和颈的癌，所述方法包括对需要所述治疗的人给予

治疗有效量的一种或多种权利要求 1 的化合物或者其药学上可接受的盐或水合物。

作为 ALK5 和 / 或 ALK4 抑制剂的 2- 吡啶基取代的咪唑

技术领域

[0001] 本发明涉及 2- 吡啶基取代的咪唑，它们是转化生长因子 -β (TGF-β) I 型受体 (ALK5) 和 / 或活化素 (activin) I 型受体 (ALK4) 的抑制剂，本发明还涉及它们的制备方法和它们在医药中的用途，具体用于治疗和预防由这些受体介导的疾病状态。

背景技术

[0002] TGF-β 表示蛋白质家族 TGF-β 1、TGF-β 2 和 TGF-β 3，它们是细胞增殖与分化、伤口愈合、细胞外基质产生和免疫抑制的多效调控剂。这种超家族的其他成员包括活化素、抑制素、骨形态发生蛋白、生长与分化因子和米勒 (Mullerian) 抑制物。

[0003] TGF-β 1 通过两种高保守性单跨膜丝氨酸 / 苏氨酸激酶转导信号，即 I 型 (ALK5) 和 II 型 TGF-β 受体。一旦配体诱发低聚化，II 型受体过度磷酸化 ALK5GS 区中的丝氨酸 / 苏氨酸残基，通过创建 Smad 蛋白的结合位点引起 ALK5 的活化。活化的 ALK5 继而磷酸化 C- 末端 SSXS- 基序处的 Smad2 和 Smad3 蛋白，从而导致它们从受体中离解，并且与 Smad4 生成异质复合体 (heteromeric complex)。Smad 复合体易位于核，与特异性 DNA- 结合性辅因子和辅调控剂装配，最终活化细胞外基质组分和基质 - 降解性蛋白酶抑制剂的转录。

[0004] 活化素转导信号的方式与 TGF-β 相似。活化素与丝氨酸 / 苏氨酸激酶、活化素 II 型受体 (ActRIIB) 结合，活化的 II 型受体过度磷酸化 ALK4GS 区中的丝氨酸 / 苏氨酸残基。活化的 ALK4 继而磷酸化 Smad2 和 Smad3。随后与 Smad4 生成异 -Smad 复合体，导致活化素 - 诱导的基因转录调节。

[0005] 大量实验性动物研究证明了 TGF-β 的肾小球表达与纤维化之间 的关联，包括增殖性肾小球性肾炎的 Thy-1 大鼠模型、兔抗 -GBM 肾小球性肾炎和局灶性节段性肾小球硬化的 5/6 肾切除大鼠模型，最近已有评述 (例如，Bitzer, M. 等人，Kidney Blood Press. Res. 21:1-12(1998))。TGF-β 的中和抗体改进 Thy-1 肾炎模型中的肾小球组织学 (例如，Border, W. A. 等人，Nature 346:371-374(1990))。

[0006] 高血糖条件增加鼠近侧小管细胞和人肾小球系膜细胞中的 TGF-β mRNA 和蛋白质合成 (例如，Wahab, N. A. 等人，Biochem. J. 316:985-992(1996)；Rocco, M. V. 等人，Kidney Int. 41:107-114(1992))。伴有早期肾疾病的糖尿病患者显示 TGF-β mRNA 和蛋白质在肾小球内的蓄积增加 (例如，Yoshioka, K. 等人，Lab. Invest. 68:154-163(1993))。在患有慢性肾间质性纤维化的肾脏中，标志是小管基底膜增厚和间质腔扩大，伴有以胶原 I、III、V、VII 和纤连蛋白增加为特征的间质性纤维化 (例如，Eddy, A. A., J. Am. Soc. Nephrol. 7:2495-2508(1996))。

[0007] TGF-β 基因表达和蛋白质产生在多种肺纤维化动物模型中都增加了，包括博莱霉素、二氧化硅、石棉和辐射 (例如，Phan, S. H. and Kunkel, S. L., Exp. Lung Res. 18:29-43(1992)；Williams, A. O. 等人，Am. J. Pathol. 142:1831-1840(1993)；Rube, C. E. 等人，Int. J. Radiat. Oncol. Biol. Phys. 47:1033-1042(2000))。在人肺纤维化疾病中观察到来自自发性肺纤维化的相邻组织切片中 TGF-β 1 蛋白和胶原基因表达有一致性

增加（例如，Broekelmann, T. J. 等人，Proc. Natl. Acad. Sci. USA 88:6642-6646(1991)）。已有文献记载肉样瘤病、尘肺病、石棉沉着病和辐射-诱发的纤维化患者中的TGF-β产生增加（例如，Khalil, N. 等人，Am. J. Respir. Cell. Mol. Biol. 14:131-138(1996)；Jagirdar, J. 等人，Environ. Health Perspect. 105:1197-1203(1997)）。抗-TGF-β抗体和TGF-β-可溶性受体能够部分地抑制博莱霉素-诱发的肺纤维化啮齿动物模型中的纤维化（例如，Giri, S. N. 等人，Thorax 48:959-966(1993)；Wang, Q. 等人，Thorax 54:805-812(1999)）。烟草烟雾已经成为能够导致小气道疾病继之以慢性阻塞性肺疾病（COPD）的最重要因素之一（例如，Wright, J. M. 等人，Am. Rev. Respir. Dis. 146:240-262(1992)）。COPD是一种缓慢进展的和不可逆的疾患，以气道阻塞的功能性异常为特征。TGF-β已被假设参与在慢性气道炎性疾患、例如COPD中见到的气道再造（例如，Takizawa, H. Int. J. Mol. Med. 1:367-378(1998)；Ning, W. 等人，Proc. Natl. Acad. Sci. USA 101:14895-14900(2004)）。

[0008] 肝星形细胞（HSC）是肝纤维化中细胞外基质蛋白的主要来源。通过TGF-β1的作用，活化的肝星形细胞产生细胞外基质明显增加（例如，Friedman, S. L., Prog. Liver Dis. 14:101-130(1996)；Pietrangelo, A., Semin. Liver Dis. 16:13-30(1996)）。过度表达肝中TGF-β1的转基因小鼠形成肝纤维化以及肝外病变，例如肾纤维化（例如，Sanderson, N. 等人，Proc. Natl. Acad. Sci. USA 92:2572-2576(1995)）。

[0009] TGF-β1及其受体在受损血管和纤维增殖性血管损伤中被过度表达，引起细胞外基质的过度产生（例如，Saltis, J. 等人，Clin. Exp. Pharmacol. Physiol. 23:193-200(1996)；McCaffrey, T. A. 等人，J. Clin. Invest. 96:2667-2675(1995)）。

[0010] 抗-TGF-β抗体在大鼠中减少瘢痕形成，改进新生真皮的细胞体系结构（例如，Shah, M., J. Cell. Sci. 108:985-1002(1995)），在兔中促进角膜伤口的愈合（例如，Moller-Pedersen, T., Curr. Eye Res. 17:736-747(1998)），并且在大鼠中加速胃溃疡的伤口愈合（例如，Ernst, H., Gut 39:172-175(1996)）。

[0011] 辐射性纤维化是正常人体组织中治疗性或意外过度暴露于辐射的常见后果。TGF-β1在辐射性纤维化的引发、发展和持续中扮演核心角色，最近已有评述（例如，Martin, M. 等人，Int. J. Radiat. Oncol. Biol. Phys. 47:277-290(2000)）。

[0012] 器官移植在很多情形中并发有慢性排斥，就有些器官而言，例如肾脏，它是移植物损失的主要方式。在人类患者中，肺和肾移植的慢性排斥与TGF-β在组织内表达增加有关（例如，El-Gamel, A. 等人，Eur. J. Cardiothorac. Surg. 13:424-430(1998)；Shihab, F. S. 等人，J. Am. Soc. Nephrol. 6:286-294(1995)）。

[0013] TGF-β在腹膜粘连中有牵连（例如，Saed, G. M. 等人，Wound Repair Regeneration 7:504-510(1999)）。ALK5和/或ALK4抑制剂能够预防腹膜和皮下纤维化粘连。

[0014] TGF-β2水平在大多数患有少年青光眼的眼房水肿瘤眼中和几乎一半患有原发性开放角度青光眼（POAG）的眼中都有增加（例如，Picht, G. 等人，Graefes Arch. Clin. Exp. Ophthalmol. 239:199-207(2001)）。TGF-β1和TGF-β2亚型据报道都增加培养的来自假性剥脱性青光眼和POAG患者的人特农氏囊成纤维细胞的细胞外基质产生（例如，Kottler, U. B. 等人，Exp. Eye Res. 80:121-134(2005)）。US 2007/0142376 A1公开了使用ALK5调控

剂治疗青光眼和控制眼内压，ALK5 抑制剂减少经 TGF-β 2 处理的灌注人前段中的纤连蛋白水平以及经 TGF-β 2 处理的小梁网状细胞培养物中的纤连蛋白、纤溶酶原激活物抑制剂 -1(PAI-1) 和前胶原 I 型 C- 肽的水平。

[0015] 在各种癌症的晚期，肿瘤细胞和肿瘤内基质细胞一般过度表达 TGF-β。这引起血管生成与细胞运动的刺激、免疫系统的抑制和肿瘤细胞与细胞外基质的相互作用增加（例如，Hojo, M. 等人，Nature 397:530-534(1999)）。所以，肿瘤细胞变得更有侵袭性，转移至远侧器官（例如，Maehara, Y. 等人，J. Clin. Oncol. 17:607-614(1999)；Picon, A. 等人，Cancer Epidemiol. Biomarkers Prev. 7:497-504(1998)）。

[0016] PAI-1 是组织型纤溶酶原激活物和尿激酶型纤溶酶原激活物的主要生理抑制剂。PAI-1 水平升高与血栓形成和血管疾病有关，提示了高血浆 PAI-1 可能通过破坏纤维蛋白溶解与凝固之间的天然平衡而促进过高凝固性状态（例如，Vaughan, D. E., J. Invest. Med. 46:370-376(1998)）。已知 TGF-β 刺激 PAI-1 的表达（例如，Dennler, S. 等人，EMBO J. 17:3091-3100(1998)）。因此，用 TGF-β 信号传递途径抑制剂抑制 PAI-1 的产生能够提供一种新颖的纤维蛋白溶解疗法。

[0017] 活化素信号传递和活化素的过度表达与下列疾病有联系：牵涉细胞外基质蓄积与纤维化的病理疾患（例如，Matsuse, T. 等人，Am. J. Respir. Cell Mol. Biol. 13:17-24(1995)；Inoue, S. 等人，Biochem. Biophys. Res. Comm. 205:441-448(1994)；Matsuse, T. 等人，Am. J. Pathol. 148:707-713(1996)；De Bleser 等人，Hepatology 26:905-912(1997)；Pawlowski, J. E., 等人，J. Clin. Invest. 100:639-648(1997)；Sugiyama, M. 等人，Gastroenterology 114:550-558(1998)；Munz, B. 等人，EMBO J. 18:5205-5215(1999))、炎性反应（例如，Rosendahl, A. 等人，Am. J. Respir. Cell Mol. Biol. 25:60-68(2001)、恶病质或消瘦 (Matzuk, M. M. 等人，Proc. Natl. Acd. Sci. USA 91:8817-8821(1994)；Coerver, K. A. 等人，Mol. Endocrinol. 10:534-543(1996)；Cipriano, S. C. 等人，Endocrinology 141:2319-2327(2000))、中枢神经系统疾病或病理反应（例如，Logan, A. 等人，Eur. J. Neurosci. 11:2367-2374(1999)；Logan, A. 等人，Exp. Neurol. 159:504-510(1999)；Masliah, E. 等人，Neurochem. Int. 39:393-400(2001)；De Groot, C. J. A. 等人，J. Neuropathol. Exp. Neurol. 58:174-187(1999)；John, G. R. 等人，Nat. Med. 8:1115-1121(2002)) 和高血压（例如，Dahly, A. J. 等人，Am. J. Physiol. Regul. Integr. Comp. Physiol. 283:R757-767(2002)）。研究显示，TGF-β 和活化素能够协同作用，诱导细胞外基质产生（例如，Sugiyama, M. 等人，Gastroenterology 114;550-558(1998)）。

[0018] 因此，显然用本发明优选的化合物抑制 Smad2 和 Smad3 的 ALK5 和 / 或 ALK4 磷酸化能够治疗和预防牵涉这些信号传递途径的疾患。

[0019] WO 00/61576 和 US 2003/0149277 A1 公开了三芳基咪唑衍生物和它们作为 ALK5 抑制剂的用途。WO 01/62756 A1 公开了吡啶基咪唑衍生物和它们作为 ALK5 抑制剂的用途。WO 02/055077 A1 公开了咪唑基环状缩醛衍生物作为 ALK5 抑制剂的用途。WO 03/087304 A2 公开了三取代的杂芳基和它们作为 ALK5 和 / 或 ALK4 抑制剂的用途。WO 2005/103028 A1 和 US 7,407,958 B2 公开了作为 ALK5 和 / 或 ALK4 抑制剂的 2- 吡啶基取代的咪唑。尤其是在 WO 2005/103028 A1 和 US 7,407,958 B2 中要求保护的代表性化合物之一 IN-1130 证实了其在若干动物模型中作为 ALK5 和 / 或 ALK4 抑制剂的用途。IN-1130 有效地 抑制大鼠由单侧输

尿管阻塞 (UUO) 诱发的肾纤维化 (Moon, J.-A. 等人, Kidney Int. 70:1234-1243(2006)), 改善用 MOG_{35-55} 致免疫化的 SBE-luc 和 GFAP-luc 小鼠实验性自体免疫性脑脊髓炎 (EAE) (Luo, J. 等人, J. Clin. Invest. 117:3306-3315(2007)), 减少大鼠的被膜纤维化和纠正其阴茎弯曲 (Ryu, J.-K. 等人, J. Sex. Med. 6:1284-1296(2009)), 并且显著地缩小用鼠前列腺癌细胞系 Tramp C2 处理过的小鼠肿瘤体积, 同时增强免疫应答 (Lee, G. T. 等人, J. Urol. 180:2660-2667(2008))。而且, US 2008/0319012 A1 公开了作为 ALK5 和 / 或 ALK4 抑制剂的 2- 吡啶基取代的咪唑。尤其是在 US 2008/0319012 A1 中要求保护的代表性化合物之一 IN-1233 证实了其在若干动物模型中作为 ALK5 和 / 或 ALK4 抑制剂的用途。IN-1233 通过抑制 TGF-β 信号传递, 有效地预防野百合碱大鼠模型肺动脉高血压的形成与进展 (Long, L. 等人, Circulation 119:566-576(2009)), 还预防大鼠尿道模型放置裸金属支架后的肉芽组织生成 (Kim, J. H. 等人, Radiology 255:75-82(2010))。

发明内容

[0020] 现已惊人地发现, 一类 2- 吡啶基取代的咪唑作为有效的和选择性的 ALK5 和 / 或 ALK4 抑制剂, 因此可用于治疗、预防和减轻由 ALK5 和 / 或 ALK4 介导的各种疾病状态, 例如肾小球性肾炎、糖尿病性肾病、狼疮性肾炎、高血压 - 诱发的肾病、肾间质性纤维化、由药物暴露并发症所致肾纤维化、与 HIV 有关的肾病、移植物肾病、各种病因的肝纤维化、可归因于感染的肝功能障碍、酒精 - 诱发的肝炎、胆系疾患、囊性纤维化病、肺纤维化、间质性肺病、急性肺损伤、成人呼吸窘迫综合征、特发性肺纤维化、慢性阻塞性肺病、由感染性或毒性因子引起的肺病、梗塞后心纤维化、充血性心力衰竭、扩张型心肌病、心肌炎、内膜增厚、血管狭窄、高血压引起的血管重构、肺动脉高压、冠状动脉再狭窄、周围动脉再狭窄、颈动脉再狭窄、支架诱导的再狭窄、动脉粥样硬化、眼部瘢痕形成、角膜瘢痕形成、增生性玻璃体视网膜病 变、青光眼、眼内压高、发生在由创伤或手术伤口所致伤口愈合期间的过度性或肥厚性真皮瘢痕或瘢痕疙瘩形成、腹膜与皮下粘连、硬皮病、纤维硬化、进行性系统性硬化病、皮肌炎、多肌炎、关节炎、骨质疏松、溃疡、神经系统功能减低、男性勃起功能障碍、佩罗尼氏病、杜普伊特伦氏挛缩、阿尔茨海默氏病、雷诺氏综合征、辐射 - 诱发的纤维化、血栓形成、肿瘤转移性生长、多发性骨髓瘤、黑素瘤、神经胶质瘤、胶质母细胞瘤、白血病、肉瘤、平滑肌瘤、间皮瘤, 以及肺、乳腺、结肠、肾、卵巢、宫颈、肝、胆管、胃肠道、胰腺、前列腺、头和颈的癌症。

附图说明

[0021] 本发明的上述方面和其他特征将在下列说明中加以解释, 并且结合附图, 其中 :

[0022] 图 1 显示实施例 2、60、86、92 和 94 对 HaCaT-3TP-Luc 细胞中 TGF-β1- 诱导的 3TP-Luc 受体活性的影响。

[0023] 图 2 显示实施例 2、60、86、92 和 94 对 4T1-3TP-Luc 细胞中 TGF-β1- 诱导的 3TP-Luc 受体活性的影响。

[0024] 图 3 显示实施例 2 对 MCF10A 细胞中 TGF-β1- 诱导的 Smad2/3 核易位的影响。

[0025] 图 4 显示实施例 2 对 MCF10A 细胞中 TGF-β1- 诱导的细胞迁移的影响。

[0026] 图 5a 和 5b 显示实施例 2 对 4T1 细胞中 TGF-β1- 诱导的细胞侵袭的影响。

[0027] (5a). DAPI- 染色的细胞停留在底表面上。(5b). 5 个随机视野所得每视野平均细胞数。

[0028] 图 6 显示实施例 2 对 4T1 细胞的细胞生长的影响。

[0029] 图 7 显示实施例 2 对 MCF10A 细胞的细胞生长的影响。

[0030] 图 8a 和图 8b 显示实施例 3 对 BALB/c 4T1 异种移植小鼠乳腺肿瘤转移至肺的影响。将实施例 3 (13.6 或 27.3mg/kg)溶于水(载体), 口服给予小鼠 BID,每周连续五天,持续四周。

[0031] (8a). 肺表面上的白点指示了转移的结节(白箭头)。(8b). 全肺表面上转移结节的数量。

[0032] 图 9a 和 9b 显示实施例 2 对 BALB/c 4T1 异种移植小鼠乳腺肿瘤转移至肺的影响。将实施例 2(5、10、20 或 40mg/kg)溶于人工胃液制剂(载体),口服给予小鼠,每周连续五天,持续三周。

[0033] (9a). 肺表面上的白点指示了转移的结节。(9b). 左侧肺叶表面上转移结节的数量。

[0034] 图 10a、10b 和 10c 显示实施例 2 对 BALB/c 4T1 异种移植小鼠乳腺肿瘤转移至肺的影响。将实施例 2 (5、10、20 或 40mg/kg)溶于人工胃液制剂(载体),口服给予小鼠,每隔一天一次(每周三次),持续 24 天。

[0035] (10a). 肺表面上的白点指示了转移的结节。(10b). 左侧肺叶表面上转移结节的数量。(10c). 对肿瘤组织中 TGF-β1- 诱导的 Smad2 磷酸化的影响。

[0036] 图 11a、11b 和 11c 显示实施例 61 对 BALB/c 4T1 异种移植小鼠乳腺肿瘤转移至肺的影响。将实施例 61 (43.6mg/kg)溶于盐水(载体),腹膜内给予小鼠,每隔一天一次(每周三次),持续 2.5 周。

[0037] (11a). 肺表面上的白点指示了转移的结节。(11b). 左侧肺叶表面上转移结节的数量。(11c). 原始肿瘤的体积。

[0038] 图 12a、12b、12c 和 12d 显示实施例 61 对 MMTV/c-Neu 小鼠乳腺肿瘤转移至肺的影响。将携带肿瘤的 MMTV/c-Neu 小鼠用实施例 61 (43.6mg/kg)腹膜内处理,每隔一天一次,持续三周。

[0039] (12a). 乳腺肿瘤和肺组织的苏木精与曙红 (H&E) 染色。(12b). 肺中组织学上可检测的转移性损伤的数量。(12c). 乳腺肿瘤的体积。(12d). β-酪蛋白 mRNA 水平。

[0040] 图 13a 和 13b 显示实施例 3 对 MMTV/c-Neu 小鼠乳腺肿瘤转移至肺的影响。将携带肿瘤的 MMTV/c-Neu 小鼠用实施例 3 (43.6mg/kg) 腹膜内处理,每隔一天一次,持续十周。

[0041] (13a). β-酪蛋白 mRNA 水平。(13b). 原始乳腺肿瘤中 MMP-9 和 MMP-2 活性。

[0042] 图 14a、14b、14c 和 14d 显示实施例 3 对大鼠胆管-结扎的肝纤维化的影响。将实施例 3 (21.8 或 43.6mg/kg)溶于盐水(载体),口服给予大鼠,每周三次,持续四周,始于 BDL 手术之后。

[0043] (14a). 血清丙氨酸氨基转移酶 (ALT) 和天冬氨酸氨基转移酶 (AST) 的活性。(14b). 肝中 pSmad3 蛋白水平。(14c). 肝中 α-SMA、纤连蛋白和波形蛋白的水平。(14d). 肝组织的苏木精与曙红 (H&E) 染色。

[0044] 图 15a、15b 和 15c 显示实施例 2 对大鼠胆管-结扎的肝纤维化的影响。将实施例

2（5、10 或 20mg/kg）溶于人工胃液制剂(载体)，口服给予大鼠，每周三次，持续四周，始于 BDL 手术之后。

[0045] (15a). ALT 和 AST 的活性。(15b). 肝中 α-SMA 和纤连蛋白的水平。(15c). 肝组织的苏木精与曙红 (H&E) 染色。

[0046] 图 16a 和 16b 显示实施例 2 对博莱霉素 - 诱发的小鼠肺纤维化的影响。将实施例 2（5、10 或 20mg/kg)溶于人工胃液制剂(载体)，口服给予小鼠，每周五次，持续两周，始于第 7 天。

[0047] (16a). 肺中 α-SMA 和纤连蛋白的水平。(16b). 肺组织的苏木精与曙红 (H&E) 染色。

[0048] 表 1 显示实施例 1-139 的结构和 ^{1}H NMR 与 MS 光谱数据。

[0049] 表 2 显示实施例 140-153 的结构和 ^{1}H NMR 与 MS 光谱数据。

[0050] 表 3 显示所选实施例对 ALK5 激酶磷酸化的 IC_{50} 值。

[0051] 表 4 显示实施例 2 对各种激酶磷酸化的 IC_{50} 值或抑制 %。

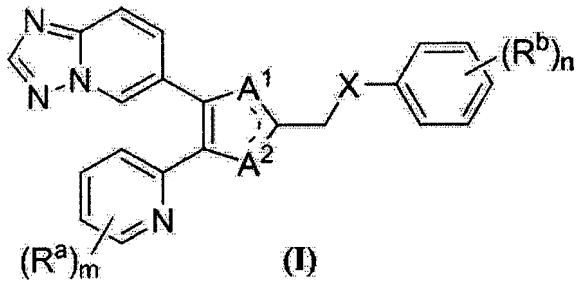
[0052] 表 5 显示实施例 3 对 BDL 大鼠体重和器官重量变化的影响。

[0053] 表 6 显示实施例 2 对 BDL 大鼠体重和器官重量变化的影响。

[0054] 本发明最佳实施方式

[0055] 在本发明的一种实施方式中，提供式 (I) 化合物或其药学上可接受的盐：

[0056]



(I)

[0057] 其中每个 R^a 独立地是 H、卤素、C_{1-6} 烷基、C_{1-6} 卤代烷基、C_{3-6} 环烷基、OH、-O-C_{1-6} 烷基、-O-C_{1-6} 卤代烷基、-O-C_{3-6} 环烷基、NH_2、-NH-C_{1-6} 烷基、-NH-C_{1-6} 卤代烷基、-NH-C_{3-6} 环烷基、-S-C_{1-6} 烷基、-S-C_{1-6} 卤代烷基、-S-C_{3-6} 环烷基、CN 或 NO_2；

[0058] m 是 0、1、2、3 或 4；

[0059] A^1 和 A^2 之一是 N，另一个是 NR^1，其中 R^1 是 H、OH、C_{1-6} 烷基、C_{1-6} 卤代烷基或 C_{3-6} 环烷基；

[0060] X 是一条键、$-(CH_2)_p-$、$-NR^2-$、-O- 或 -S-，其中 p 是 0 或 1，R^2 是 H 或 C_{1-3} 烷基；

[0061] 每个 R^b 独立地是 H、卤素、C_{1-6} 烷基、C_{1-6} 卤代烷基、C_{3-6} 环烷基、C_{2-6} 烯基、C_{2-6} 炔基、$-(CH_2)_q-OR^3$、$-(CH_2)_q-NR^3R^4$、$-(CH_2)_q-SR^3$、$-(CH_2)_q-NO_2$、$-(CH_2)_q-CONHOH$、$-(CH_2)_q-CN$、$-(CH_2)_q-COR^3$、$-(CH_2)_q-CO_2R^3$、$-(CH_2)_q-CONR^3R^4$、$-(CH_2)_q-$ 四唑、$-(CH_2)_q-CH=CH-CN$、$-(CH_2)_q-CH=CH-CO_2R^3$、$-(CH_2)_q-CH=CH-CONR^3R^4$、$-(CH_2)_q-CH=CH-$ 四唑、$-(CH_2)_q-NHCOR^3$、$-(CH_2)_q-NHCO_2R^3$、$-(CH_2)_q-CONHSO_2R^3$、$-(CH_2)_q-NHSO_2R^3$、$-(CH_2)_q-C\equiv C-CN$、$-(CH_2)_q-C\equiv C-CO_2R^3$、$-(CH_2)_q-C\equiv C-CONR^3R^4$、$-(CH_2)_q-C\equiv C-$ 四唑、$-(CH_2)_q-SOR^5$、$-(CH_2)_q-SO_2R^5$ 或 $-(CH_2)_r-(OR^3)_2$，其中 R^3 和 R^4 独立地是 H、C_{1-6} 烷基、C_{1-6} 卤代烷基或 C_{3-6} 环烷基；或者与它们所连接的氮原子一起构成单环的环，例如咪唑、吡咯烷、哌啶、吗啉、哌嗪和高哌嗪；R^5 是

C_{1-6} 烷基、C_{1-6} 卤代烷基或 C_{3-6} 环烷基；q 是 0、1、2、3 或 4；r 是 1、2、3 或 4；

[0062] n 是 0、1、2、3、4 或 5。

[0063] 正如本文所使用的，由式 (I) 虚线所示双键代表落入本发明范围内的化合物可能的互变异构环形式，双键连接于未取代的氮。

[0064] 优选地，R^a 是 C_{1-3} 烷基或卤素。

[0065] 优选地，m 是 1 或 2。

[0066] 优选地，A^1 和 A^2 之一是 N，另一个是 NR^1，其中 R^1 是 H。

[0067] 优选地，X 是 $-(CH_2)_p-$ 或 $-NR^2-$，其中 p 是 0，R^2 是 H。

[0068] 优选地，R^b 是卤素、C_{1-3} 烷基、C_{1-3} 卤代烷基、C_{3-4} 环烷基、C_{2-4} 烯基、C_{2-4} 炔基、$-(CH_2)_q-OR^3$、$-(CH_2)_q-NR^3R^4$、$-(CH_2)_q-SR^3$、$-(CH_2)_q-CN$、$-(CH_2)_q-COR^3$、$-(CH_2)_q-CO_2R^3$、$-(CH_2)_q-CONR^3R^4$、$-(CH_2)_q-NHCOR^3$、$-(CH_2)_q-NHSO_2R^3$、$-(CH_2)_q-SOR^5$ 或 $-(CH_2)_q-SO_2R^5$，其中 R^3 和 R^4 独立地是 H、C_{1-3} 烷基、C_{1-3} 卤代烷基或 C_{3-4} 环烷基；或者与它们所连接的氮原子一起构成单环的环，例如咪唑、吡咯烷、哌啶、吗啉、哌嗪和高哌嗪；R^5 是甲基；q 是 0、1 或 2。

[0069] 优选地，n 是 1、2 或 3。

[0070] 可以提到的具体本发明化合物包括如下及其药学上可接受的盐：

[0071] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基) 苯胺；

[0072] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟苯胺；

[0073] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 氟苯胺；

[0074] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 氟苯胺；

[0075] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2,3- 二氟苯胺；

[0076] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3,4- 二氟苯胺；

[0077] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3,5- 二氟苯胺；

[0078] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氯苯胺；

[0079] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 氯苯胺；

[0080] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 氯苯胺；

[0081] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2,3- 二氯苯胺；

[0082] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3,4- 二氯苯胺；

[0083] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3,5-二氯苯胺；

[0084] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-溴苯胺；

[0085] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-溴苯胺；

[0086] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-4-溴苯胺；

[0087] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-甲基苯胺；

[0088] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-甲基苯胺；

[0089] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-4-甲基苯胺；

[0090] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2,3-二甲基苯胺；

[0091] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3,4-二甲基苯胺；

[0092] N((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3,5-二甲基苯胺；

[0093] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-乙基苯胺；

[0094] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-乙基苯胺；

[0095] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-异丙基苯胺；

[0096] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-异丙基苯胺；

[0097] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-4-异丙基苯胺；

[0098] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-乙烯基苯胺；

[0099] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-乙烯基苯胺；

[0100] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-4-乙烯基苯胺；

[0101] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-乙炔基苯胺；

[0102] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪

唑 -2- 基) 甲基)-2- 甲氧基苯胺 ;

[0103] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 甲氧基苯胺 ;

[0104] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 甲氧基苯胺 ;

[0105] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2,3- 二甲氧基苯胺 ;

[0106] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3,4- 二甲氧基苯胺 ;

[0107] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3,5- 二甲氧基苯胺 ;

[0108] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(甲氧基甲基) 苯胺 ;

[0109] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(甲氧基甲基) 苯胺 ;

[0110] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4-(甲氧基甲基) 苯胺 ;

[0111] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(三氟甲氧基) 苯胺 ;

[0112] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(三氟甲氧基) 苯胺 ;

[0113] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4-(三氟甲氧基) 苯胺 ;

[0114] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(甲硫基) 苯胺 ;

[0115] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(甲硫基) 苯胺 ;

[0116] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4-(甲硫基) 苯胺 ;

[0117] 2-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲腈 ;

[0118] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲腈 ;

[0119] 4-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲腈 ;

[0120] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 邻苯二甲腈 ;

[0121] 2-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基) 苯甲酰胺 ;

[0122] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯甲酰胺；

[0123] 4-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯甲酰胺；

[0124] 2-(3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)乙腈；

[0125] 2-(4-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)乙腈；

[0126] 1-(3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)乙酮；

[0127] 1-(4-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)乙酮；

[0128] 甲基3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-

[0129] 2-基)甲基氨基)苯甲酸酯；

[0130] 甲基4-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-

[0131] 2-基)甲基氨基)苯甲酸酯；

[0132] N-(2-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)乙酰胺；

[0133] N-(3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)乙酰胺；

[0134] N-(4-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)乙酰胺；

[0135] N-(2-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)甲磺酰胺；

[0136] N-(3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)甲磺酰胺；

[0137] N-(4-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯基)甲磺酰胺；

[0138] N1-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-N^2,N^2-二甲基苯-1,2-二胺；

[0139] N1-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-N^3,N^3-二甲基苯-1,3-二胺；

[0140] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-(吡咯烷-1-基)苯胺；

[0141] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-吗啉代苯胺；

[0142] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪

唑 -2- 基) 甲基)-3- 吗啉代苯胺 ;

[0143] N3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-4- 氟 -N^1,N^1- 二甲基苯 -1,3- 二胺 ;

[0144] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-5-(二甲基氨基) 苯甲腈 ;

[0145] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-4-(二甲基氨基) 苯甲腈 ;

[0146] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-((二甲基氨基) 甲基) 苯胺 ;

[0147] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-((二甲基氨基) 甲基) 苯胺 ;

[0148] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(吡咯烷 -1- 基甲基) 苯胺 ;

[0149] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(吡咯烷 -1- 基甲基) 苯胺 ;

[0150] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2-(吗啉代甲基) 苯胺 ;

[0151] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-(吗啉代甲基) 苯胺 ;

[0152] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-5-((二甲基氨基) 甲基)-2- 氟苯胺 ;

[0153] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3-((二甲基氨基) 甲基)-2- 氟苯胺 ;

[0154] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟 -3-(吡咯烷 -1- 基甲基) 苯胺 ;

[0155] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟 -3-(吗啉代甲基) 苯胺 ;

[0156] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-4-((二甲基氨基) 甲基) 苯甲腈 ;

[0157] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-2-((二甲基氨基) 甲基) 苯甲腈 ;

[0158] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-5-((二甲基氨基) 甲基) 苯甲腈 ;

[0159] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-4-(吡咯烷 -1- 基甲基) 苯甲腈 ;

[0160] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-2-(吡咯烷 -1- 基甲基) 苯甲腈 ;

[0161] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基氨基)-5-(吡咯烷 -1- 基甲基) 苯甲腈 ;

[0162] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)-4-(吗啉代甲基)苯甲腈；

[0163] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)-2-(吗啉代甲基)苯甲腈；

[0164] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)-5-(吗啉代甲基)苯甲腈；

[0165] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-(2-(二甲基氨基)乙基苯胺；

[0166] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-(2-(二甲基氨基)乙基苯胺；

[0167] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-乙基吡啶-2-基)-1H-咪唑-2-基)甲基氨基)苯甲腈；

[0168] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-乙基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-氟苯胺；

[0169] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-2-氟-N-甲基苯胺；

[0170] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)(甲基)氨基)苯甲腈；

[0171] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)(甲基)氨基)苯甲酰胺；

[0172] 6-(2-苄基-5-(6-甲基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶；

[0173] 6-(2-(2-氟苄基)-5-(6-甲基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶；

[0174] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)苯甲腈；

[0175] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)苯甲酰胺；

[0176] 6-(5-(6-甲基吡啶-2-基)-2-(苯氧基甲基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶；

[0177] 6-(2-((2-氟苯氧基)甲基)-5-(6-甲基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶；

[0178] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲氧基)苯甲腈；

[0179] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲氧基)苯甲酰胺；

[0180] 6-(5-(6-甲基吡啶-2-基)-2-(苯硫基甲基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶；

[0181] 6-(2-((2-氟苯硫基)甲基)-5-(6-甲基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]

三唑并 [1,5-a] 吡啶。

[0182] 本发明化合物通常是小的有机分子(非肽小分子),大小一般小于约 1,000 道尔顿。优选的非肽小分子的分子量小于约 750 道尔顿,更优选小于约 500 道尔顿。

[0183] 式 (I) 化合物也可以以"前体药物"形式应用,它被设计成在对受治疗者给药时释放式 (I) 化合物。前体药物设计是本领域熟知的,依赖于式 (I) 化合物所含有的取代基。例如,含有羟基的取代基能够与载体偶联,所述载体使该化合物在生物学上无活性,直至被内源性酶除去,或者例如被靶向于受治疗者中特定受体或位置的酶所除去。

[0184] 在属性上为酸性的式 (I) 化合物(例如具有羧基或酚羟基)能够生成药学上可接受的盐,例如钠、钾、钙或金盐。在本发明的范围内还有与药学上可接受的胺生成的盐,例如氨、烷基胺、羟基烷基胺和 N- 甲基葡糖胺。式 (I) 化合物可以用酸处理,生成酸加成盐。这类酸的实施例包括盐酸、氢溴酸、氢碘酸、硫酸、甲磺酸、磷酸、对 - 溴苯磺酸、碳酸、琥珀酸、柠檬酸、苯甲酸、草酸、丙二酸、水杨酸、苹果酸、富马酸、抗坏血酸、马来酸、乙酸和本领域技术人员熟知的其他无机和有机酸。酸加成盐可以制备如下,将式 (I) 化合物的游离碱形式用足量酸(例如盐酸)处理,生成酸加成盐(例如氢氯化物)。酸加成盐可以通过下列方式转化回其游离碱形式:将盐用适合的稀碱水溶液(例如氢氧化钠、碳酸氢钠、碳酸钾、或氨)处理。

[0185] 有些本发明化合物可以从溶剂中结晶或重结晶,例如水性和有机溶剂。在这类情况下可以生成溶剂化物。本发明在其范围内包括化学计量的溶剂化物,包括水合物以及含有可变量水的化合物,可以借助冷冻干燥等过程生成。

[0186] 式 (I) 化合物可以含有一个或多个不对称中心,因而可能存在对映体或非对映体。所要理解的是,本发明包括式 (I) 化合物的混合物和分开的单个异构体。此外,含有烯基的某些式 (I) 化合物可以存在顺式 - 或反式 - 异构体。在每种情形中,本发明包括混合物和分开的单个异构体。

[0187] 式 (I) 化合物也可以存在互变异构形式,本发明包括混合物和其分开的单个互变体。

[0188] 在本发明中还包括适合于生物研究的式 (I) 化合物的放射性标记衍生物。

[0189] 本文所用的术语"烷基"表示含有 1-6 个碳原子的饱和脂族烃基团。烷基可以是直链或支链的。烷基的实例包括但不限于甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基、叔丁基、正戊基和正己基。烷基可以可选地被一个或多个取代基取代,例如烷氧基、环烷氧基、氨基、硝基、羧基、氰基、卤素、羟基、磺基或巯基。

[0190] 本文所用的术语"环烷基"表示 3-6 个碳原子的脂族碳环。环烷基的实例包括环丙基、环丁基、环戊基和环己基。

[0191] 本文所用的术语"卤代烷基"表示含有一个或多个卤原子的烷基。卤代烷基的实例包括氟甲基、氯甲基、溴甲基和三氟甲基。

[0192] 本文所用的术语"卤素"或"卤代基"表示氟、氯、溴或碘。

[0193] 本文所用的术语"烯基"表示含有 2-6 个碳原子和至少一条双键的脂族碳基团。象烷基一样,烯基可以是直链或支链的。烯基的实例包括但不限于乙烯基、烯丙基、异丙烯基、2- 丁烯基和 2- 己烯基。烯基可以可选地被一个或多个取代基取代,例如烷氧基、环烷氧基、氨基、硝基、羧基、氰基、卤素、羟基、磺基或巯基。

[0194] 本文所用的术语“炔基”表示含有 2-6 个碳原子和至少一条叁键的脂族碳基团。炔基可以是直链或支链的。炔基的实例包括但不限于乙炔基、炔丙基和丁炔基。炔基可以可选地被一个或多个取代基取代，例如烷氧基、环烷氧基、氨基、硝基、羧基、氰基、卤素、羟基、磺基或巯基。

[0195] 本文所用的术语“ALK5 和 / 或 ALK4 抑制剂”表示这样的化合物，除了抑制 Smad、例如 Smad6 和 Smad7 以外，它选择性抑制 ALK5 和 / 或 ALK4 受体，优先于 p38 或 II 型受体。

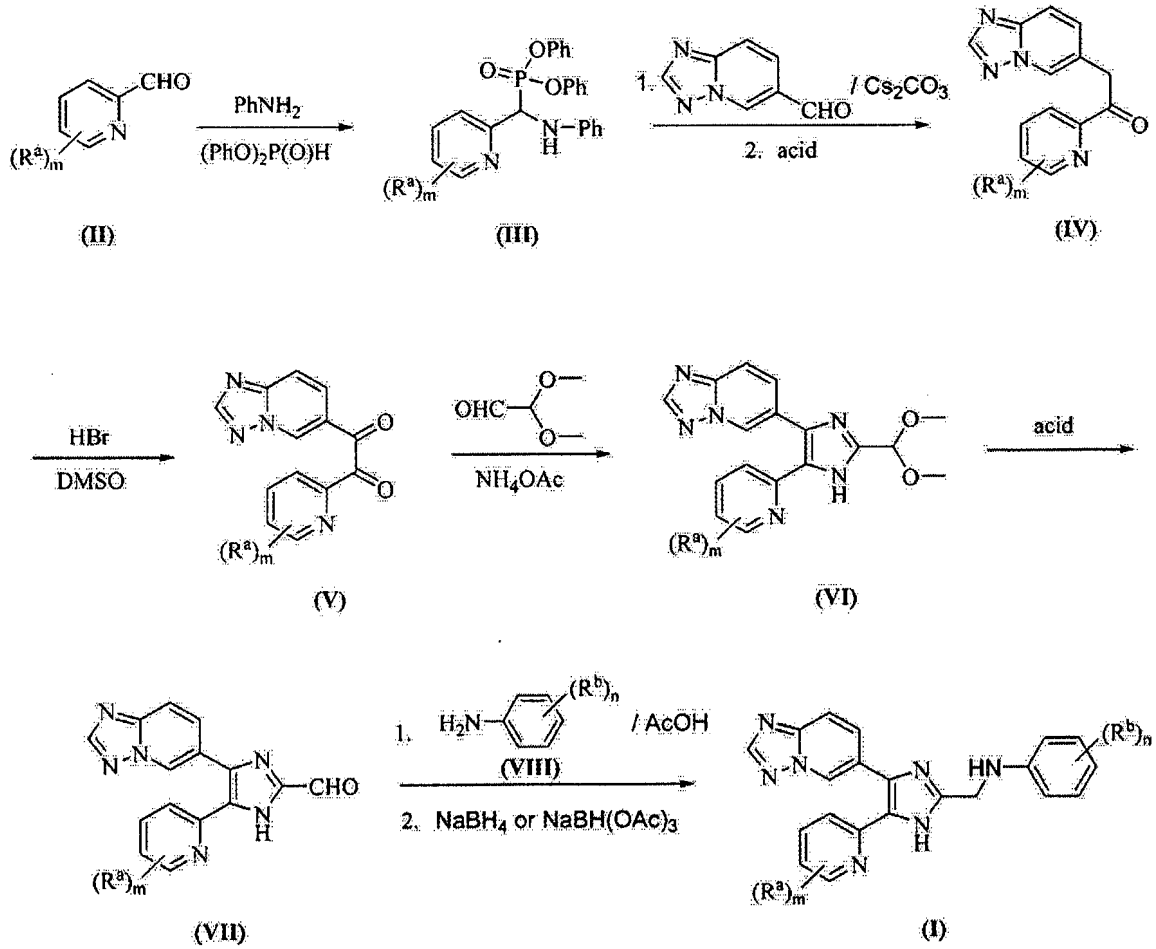
[0196] 本文所用的术语“ALK5- 和 / 或 ALK4- 介导的疾病状态”表示任何受 ALK5 和 / 或 ALK4 介导（或调控）的疾病状态，例如受 TGF-β 和 / 或活化素信号传递途径中 Smad2 和 Smad3 磷酸化的抑制所调控的疾病。

[0197] 本文所用的术语“溃疡”用于包括但不限于糖尿病性溃疡、慢性溃疡、胃溃疡和十二指肠溃疡。

[0198] 式 (I) 化合物可以借助大量已知方法从商业上可获得或已知的原料制备。如果原料不可从商业来源获得，可以借助本领域已知的工艺制备它们。

[0199] 流程 1

[0200]

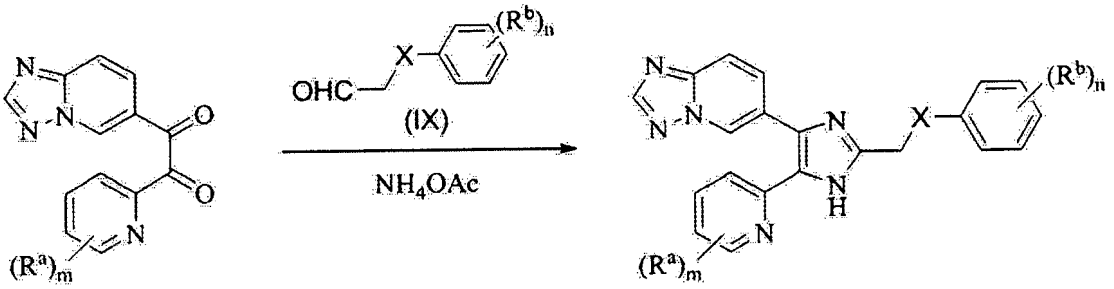


[0201] 在一种方法中，按照流程 1 制备式 (I) 化合物，其中 A^1 是 N，A^2 是 NH，或者 A^1 是 NH，A^2 是 N，X 是 -NH-。具体而言，使 R^a- 取代的吡啶 -2- 甲醛 (II) 与苯胺和二苯基亚磷酸酯反应，得到 N,P- 缩醛 (III)，它可以进一步与 [1,2,4] 三唑并 [1,5-a] 吡啶 -6- 甲醛偶联，随

后在酸性条件中水解，生成一元酮 (IV)。一元酮 (IV) 可以用 HBr 的 DMSO 溶液氧化为二酮 (V)。这种二酮 (V) 然后可以在乙酸氨的存在下与 2,2- 二甲氧基乙醛缩合，得到缩醛 - 被保护的咪唑 (VI)，它可以在酸性条件中水解，生成咪唑 -2- 甲醛 (VII)。该咪唑 -2- 甲醛 (VII) 可以在酸的存在下，例如乙酸，与 R^b- 取代的苯胺 (VIII) 偶联，生成亚胺，它可以进一步用还原剂还原，例如硼氢化钠或三乙酰氧基硼氢化钠，得到式 (I) 化合物。R^a、R^b、m 和 n 定义同上。

[0202] 流程 2

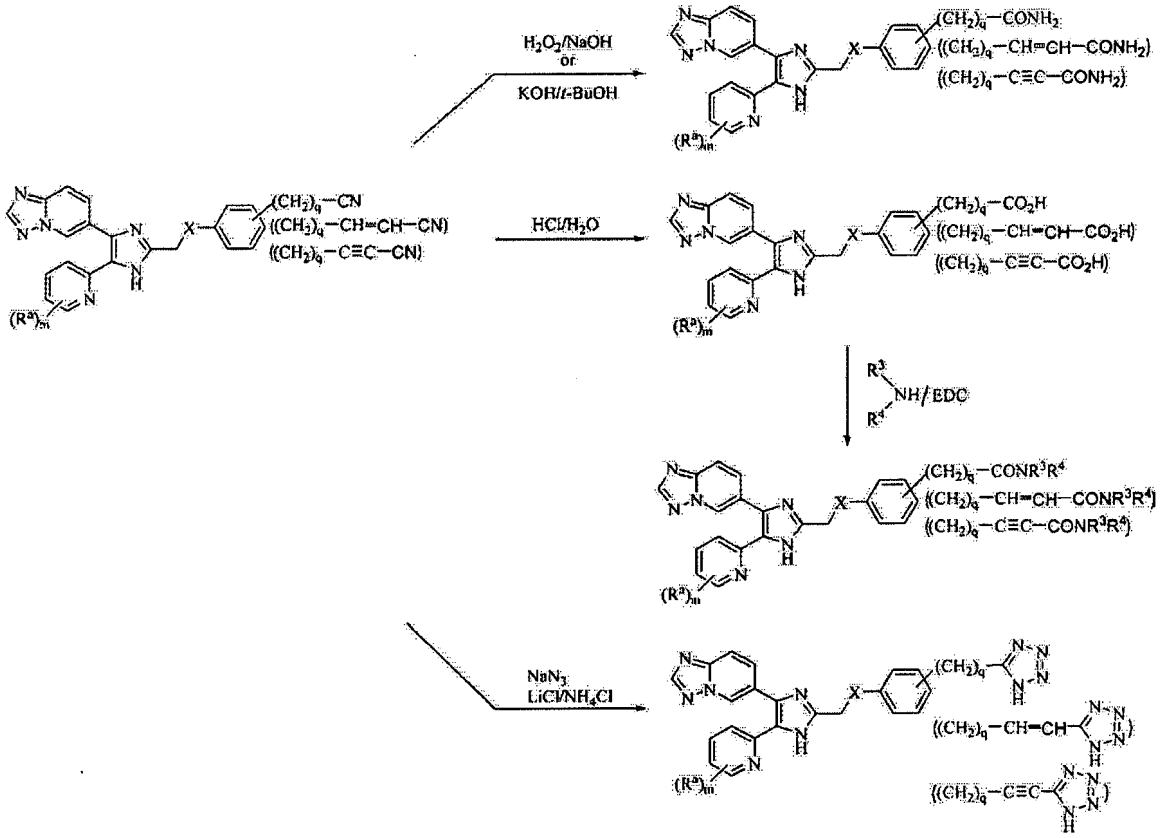
[0203]



[0204] 在另一种方法中，按照流程 2 制备式 (I) 化合物，其中 A^1 是 N，A^2 是 NH，或者 A^1 是 NH，A^2 是 N，X 是 $-(CH_2)_p-$、$-NR^2-$、-O- 或 -S-，其中 p 是 0 或 1，R^2 是 C_{1-3} 烷基。二酮 (V) 可以在乙酸氨的存在下与适当的 R^b- 取代的醛 (IX) 缩合，得到式 (I) 化合物。R^a、R^b、m 和 n 定义同上。

[0205]

流程 3



[0206] 作为替代选择，正如流程 3 所描绘的，当式 (I) 化合物中的 R^b 是 $-(CH_2)_q-CN$、$-(CH_2)_q-CH=CH-CN$ 或 $-(CH_2)_q-C\equiv C-CN$ 时，它可以进一步被官能化生成式 (I) 化合物。R^a、R^3、R^4、X、m 和 q 定义同上。

[0207] 所得由式 (I)-(IX) 代表的本发明化合物可以借助适当的常规方法分离和纯化，例如柱色谱和重结晶。

[0208] 本发明化合物可以借助任意适合的途径给药，例如口服、口腔、舌下、直肠、阴道、鼻、局部或肠胃外 (包括静脉内、肌内、皮下和冠状动脉内) 给药。

[0209] 本发明的外用制剂可以为例如软膏、霜剂或洗剂、眼用软膏和眼用或耳用滴剂、浸渗敷料和气雾剂，并且可以含有适当的常规添加剂，例如防腐剂、帮助药物渗透的溶剂以及软膏和霜剂中的软化剂。

[0210] 制剂也可以含有可相容的常规载体，例如霜剂或软膏基质和用于洗剂的乙醇或油醇。这类载体可以占制剂的约 1% 直至约 98%。更通常地，它们将构成制剂的多达约 80%。

[0211] 关于在上述疾患的治疗或预防性处置中对人给药，式 (I) 化合物的口服、口腔或舌下剂量一般将在 50-5000mg 每天的范围内，就普通成年患者 (70kg) 而言。因而就典型的成年患者而言，单个药片或胶囊在适合的药学上可接受的介质或载体中含有 25-500mg 活性化合物，每天一次或多次以单一或多重剂量给药。根据需要，肠胃外给药剂量通常将在 25-250mg 每单一剂量的范围内。在实践中，医师将确定实际的服药方案，它将最适合于个体患者，并且将因特定患者的年龄、体重和反应而异。上述剂量是平均情况的示例，但是也能存在个别情形，其中可能适用更高或更低的剂量范围，这也在本发明的范围内。

[0212] 就人类用途而言，式（I）化合物可以被单独给药，但是一般与药物载体混合给药，根据预定给药途径和标准药学实践选择载体。例如，化合物可以被口服、口腔或舌下给药，剂型为片剂，含有赋形剂，例如淀粉或乳糖，或者剂型为胶囊或扁囊，单独或与赋形剂混合，或者剂型为酏剂或混悬液，含有矫味剂或着色剂。这类液体制剂可以用药学上可接受的添加剂制备，例如悬浮剂（例如甲基纤维素，半合成甘 油酯，例如 witepsol，或甘油酯混合物，例如杏仁油与 PEG-6 酯的混合物或 PEG-8 与辛酸 / 癸酸甘油酯的混合物）。化合物也可以被肠胃外注射，例如静脉内、肌内、皮下或冠状动脉内。就肠胃外给药而言，化合物最好采用无菌水溶液的形式，其中可以含有其他物质，例如盐，或者单糖，例如甘露糖醇或葡萄糖，使溶液与血液等渗。

[0213] 因而，本发明在另一方面提供药物组合物，包含式（I）化合物或其药学上可接受的盐或溶剂化物，以及药学上可接受的稀释剂或载体。

[0214] 本发明也提供用于治疗的式（I）化合物或其药学上可接受的盐或溶剂化物或者含有任一实体的药物组合物。

[0215] 本发明进一步提供式（I）化合物或其药学上可接受的盐或溶剂化物或者含有任一实体的药物组合物用于制备药物的用途，该药物用于治疗哺乳动物由 ALK5 和 / 或 ALK4 受体介导的疾病。

[0216] ALK5- 和 / 或 ALK4- 介导的疾病状态包括但不限于肾小球性肾炎、糖尿病性肾病、狼疮性肾炎、高血压 - 诱发的肾病、肾间质性纤维化、由药物暴露并发症所致肾纤维化、与 HIV 有关的肾病、移植物肾病、各种病因的肝纤维化、可归因于感染的肝功能障碍、酒精 - 诱发的肝炎、胆系疾患、囊性纤维化病、肺纤维化、间质性肺病、急性肺损伤、成人呼吸窘迫综合征、特发性肺纤维化、慢性阻塞性肺病、由感染性或毒性因子引起的肺病、梗塞后心纤维化、充血性心力衰竭、扩张型心肌病、心肌炎、内膜增厚、血管狭窄、高血压引起的血管重构、肺动脉高压、冠状动脉再狭窄、周围动脉再狭窄、颈动脉再狭窄、支架诱导的再狭窄、动脉粥样硬化、眼部瘢痕形成、角膜瘢痕形成、增生性玻璃体视网膜病变、青光眼、眼内压高、发生在由创伤或手术伤口所致伤口愈合期间的过度性或肥厚性真皮瘢痕或瘢痕疙瘩形成、腹膜与皮下粘连、硬皮病、纤维硬化、进行性系统性硬化病、皮肌炎、多肌炎、关节炎、骨质疏松、溃疡、神经系统功能减低、男性勃起功能障碍、佩罗尼氏病、杜普伊特伦氏挛缩、阿尔茨海默氏病、雷诺氏综合征、辐射 - 诱发的纤维化、血栓形成、肿瘤转移性生长、多发性骨髓瘤、黑素瘤、神经胶质瘤、胶质母细胞瘤、白血病、肉瘤、平滑肌瘤、间 皮瘤，以及肺、乳腺、结肠、肾、卵巢、宫颈、肝、胆管、胃肠道、胰腺、前列腺、头和颈的癌症。

[0217] 本发明进一步提供抑制哺乳动物 TGF-β 和 / 或活化素信号传递途径的方法，例如抑制 Smad2 或 Smad3 被 ALK5 和 / 或 ALK4 磷酸化。

[0218] 本发明进一步提供减少人过量细胞外基质蓄积的方法，该方法通过抑制 TGF-β 和 / 或活化素信号传递途径，例如抑制 Smad2 或 Smad3 被 ALK5 和 / 或 ALK4 磷酸化。

[0219] 本发明进一步提供治疗、预防或减少人类肿瘤细胞转移的方法，该方法通过抑制 TGF-β 信号传递途径。

[0220] 本发明进一步提供治疗、预防或减少人类由 TGF-β 过度表达介导的癌症的方法，该方法通过抑制 TGF-β 信号传递途径。

[0221] 本发明进一步提供治疗、预防或减少人类血管损伤的方法，该方法通过抑制

TGF-β 信号传递途径。

具体实施方式

[0222] 下列实施例进一步阐述本发明，它们不应被视为限制权利要求所述发明的范围。在实施例中，电子喷雾电离质谱 (ESI-MS) 是在 Q-Tof2 质谱仪 (Micromass, Manchester, UK) 上获得的。

[0223] 实施例

[0224] 制备例 1

[0225] 二苯基 (6- 甲基吡啶 -2- 基)(苯基氨基) 甲基膦酸酯 (式 (III) 化合物，其中 R^a=CH_3) 的制备

[0226] 将 6- 甲基吡啶 -2- 甲醛 (2.12g, 17.50mmol)、苯胺 (1.63g, 17.50mmol)、二苯基亚磷酸酯 (4.92g, 21.00mmol) 与氯化氧锆八水合物 (0.56g, 1.75mmol) 的混合物在室温下搅拌 1h (h, 小时，下同)。将反应混合物用 CH_2Cl_2 萃取 (3×50mL)，CH_2Cl_2 溶液用水洗涤 (2×20mL)，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到标题化合物 (6.96g, 92%)，为白色固体。^{1}H NMR (400MHz, $CDCl_3$) : δ 7.51 (t, 1H, J=7.8Hz), 7.38 (dd, 1H, J=7.6, 2.0Hz), 7.27-7.22 (m, 4H), 7.19-7.15 (m, 2H), 7.14-7.07 (m, 4H), 7.05-7.02 (m, 3H), 6.80-6.74 (m, 3H), 5.53 (pseudo t, 1H, J=7.4Hz), 5.36 (dd, 1H, J=21.0, 8.2Hz), 2.54 (s, 3H)。

[0227] 制备例 2

[0228] 二苯基 (6- 乙基吡啶 -2- 基)(苯基氨基) 甲基膦酸酯 (式 (III) 化合物，其中 R^a=CH_2CH_3) 的制备

[0229] 如制备例 1 所述制备标题化合物，使用 6- 乙基吡啶 -2- 甲醛代替 6- 甲基吡啶 -2- 甲醛。收率 :81%; ^{1}H NMR (400MHz, $CDCl_3$) : δ 7.55 (t, 1H, J=7.6Hz), 7.38 (dd, 1H, J=7.6, 2.0Hz), 7.26-7.09 (m, 8H), 7.07-7.00 (m, 5H), 5.59 (pseudo t(假三重峰，下同), 1H, J=7.0Hz), 5.34 (dd, 1H, J=20.8, 8.0Hz), 2.82 (q, 2H, J=7.6Hz), 1.28 (t, 3H, J=7.6Hz)。

[0230] 制备例 3

[0231] 2-([1, 2, 4] 三唑并 [1, 5-a] 吡啶 -6- 基)-1-(6- 甲基吡啶 -2- 基) 乙酮 (式 (IV) 化合物，其中 R^a=CH_3) 的制备

[0232] 向所搅拌的 [1, 2, 4] 三唑并 [1, 5-a] 吡啶 -6- 甲醛 (2.50g, 17.01mmol) (按照 WO 03/087304 A2 所述方法制备) 与二苯基 (6- 甲基吡啶 -2- 基)(苯基氨基) 甲基膦酸酯 (7.32g, 17.01mmol) 在 THF (40mL) 与 i-PrOH (10mL) 混合物中的溶液加入 Cs_2CO_3 (7.20g, 22.11mmol)，将混合物在室温下搅拌过夜。向反应混合物滴加 3N HCl 溶液 (25mL)，将混合物搅拌 1h。然后用叔丁基甲基醚 (40mL) 稀释，用 1N HCl 萃取 (2×35mL)。含水萃取液用 50%KOH 中和，直至达到 pH 7-8。过滤收集沉淀，用水洗涤，在真空中经 P_2O_5 干燥，得到标题化合物 (3.41g, 80%)，为灰白色固体。^{1}H NMR (400MHz, $CDCl_3$) : δ 8.61 (d, 1H, J=0.8Hz), 8.31 (s, 1H), 7.88 (dd, 1H, J=7.6, 1.6Hz), 7.73 (t, 1H, 重叠 , J=7.6Hz), 7.71 (dd, 1H, 重叠 , J=9.2, 0.8Hz), 7.54 (dd, 1H, J=9.2, 1.6Hz), 7.37 (dd, 1H, J=7.6, 1.6Hz), 4.62 (s, 2H), 2.67 (s, 3H)。

[0233] 制备例 4

[0234] 2-([1,2,4]三唑并[1,5-a]吡啶-6-基)-1-(6-乙基吡啶-2-基)乙酮(式(IV)化合物,其中 R^a=CH_2CH_3)的制备

[0235] 如制备例3所述制备标题化合物,使用二苯基(6-乙基吡啶-2-基)(苯基氨基)甲基膦酸酯代替二苯基(6-甲基吡啶-2-基)(苯基氨基)甲基膦酸酯。收率:78%;^{1}H NMR(400MHz, $CDCl_3$):δ 8.61(dd, 1H, J=1.6, 0.8Hz), 8.29(s, 1H), 7.88(br d, 1H, J=7.6Hz), 7.74(t, 1H, J=7.6Hz), 7.70(dd, 1H, J=9.2, 0.8Hz), 7.54(dd, 1H, J=9.2, 1.6Hz), 7.37(dd, 1H, J=7.6, 0.8Hz), 4.62(s, 2H), 2.93(q, 2H, J=7.6Hz), 1.39(t, 3H, J=7.6Hz)。

[0236] 制备例5

[0237] 1-([1,2,4]三唑并[1,5-a]吡啶-6-基)-2-(6-甲基吡啶-2-基)乙烷-1,2-二酮(式(V)化合物,其中 R^a=CH_3)的制备

[0238] 在0℃下,向所搅拌的2-([1,2,4]三唑并[1,5-a]吡啶-6-基)-1-(6-甲基吡啶-2-基)乙酮(6.20g, 24.57mmol)的DMSO(48mL)混悬液滴加HBr(48wt.%水溶液,5.96g, 12.4mL),在60-70℃下加热混合物。2h后,将反应混合物冷却至0℃,倒在冰水(20mL)上,用固体 K_2CO_3 碱化至pH 10。将混合物用 $CHCl_3$ 萃取(2×250mL),有机相用水洗涤(2×100mL),经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶MPLC纯化,使用MeOH与 CH_2Cl_2 的混合物作为洗脱剂,得到标题化合物(6.02g, 92%),为浅黄色固体。^{1}H NMR(400MHz, $CDCl_3$):δ 9.11(dd, 1H, J=1.6, 1.2Hz), 8.47(s, 1H), 8.14(dd, 1H, J=9.2, 1.6Hz), 8.04(br d, 1H, J=7.6Hz), 7.88(dd, 1H, J=9.2, 1.2Hz), 7.84(t, 1H, J=7.8Hz), 7.42(br d, 1H, J=8.0Hz), 2.49(s, 3H)。

[0239] 制备例6

[0240] 1-([1,2,4]三唑并[1,5-a]吡啶-6-基)-2-(6-乙基吡啶-2-基)乙烷-1,2-二酮(式(V)化合物,其中 R^a=CH_2CH_3)的制备

[0241] 如制备例5所述制备标题化合物,使用2-([1,2,4]三唑并[1,5-a]吡啶-6-基)-1-(6-乙基吡啶-2-基)乙酮代替2-([1,2,4]三唑并[1,5-a]吡啶-6-基)-1-(6-甲基吡啶-2-基)乙酮。收率:79%;^{1}H NMR(400MHz, $CDCl_3$):δ 9.11(dd, 1H, J=1.6, 0.8Hz), 8.42(s, 1H), 8.08(dd, 1H, J=9.2, 1.6Hz), 7.98(br d, 1H, J=7.6Hz), 7.83(dd, 1H, 重叠, J=9.2, 0.8Hz), 7.82(t, 1H, 重叠, J=7.6Hz), 7.38(br d, 1H, J=7.6Hz), 2.71(q, 2H, J=7.6Hz), 1.08(t, 3H, J=7.6Hz)。

[0242] 制备例7

[0243] 6-(2-(二甲氧基甲基)-5-(6-甲基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶(式(VI)化合物,其中 R^a=CH_3)的制备

[0244] 将所搅拌的1-([1,2,4]三唑并[1,5-a]吡啶-6-基)-2-(6-甲基吡啶-2-基)乙烷-1,2-二酮(6.00g, 22.49mmol)的叔丁基甲基醚(120mL)溶液用乙二醛二甲缩醛(60wt.%水溶液,7.8mL, 44.98mmol)处理。向其中加入 NH_4OAc(4.33g, 56.2mmol)的MeOH(60mL)溶液,将所得混合物在室温下搅拌3h。用饱和 $NaHCO_3$ 水溶液调节反应的pH至8。将反应混合物用 $CHCl_3$ 萃取(2×150mL), $CHCl_3$ 溶液用水(100mL)洗涤,经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶MPLC纯化,使用MeOH与 CH_2Cl_2 的混合物作为洗脱剂,得到标题化合物(6.13g, 78%),为浅黄色泡沫。^{1}H NMR(400MHz, $CDCl_3$):δ 10.54(brs, 1H), 8.96(s, 1H), 8.36(s, 1H), 7.82(dd, 1H, J=9.2, 1.6Hz), 7.77(dd, 1H, J=9.2, 0.8H

z), 7.47(t, 1H, J=7.8Hz), 7.23(d, 1H, J=7.6Hz), 7.04(d, 1H, J=8.0Hz), 5.57(s, 1H), 3.48(s, 6H), 2.58(s, 3H)。

[0245] 制备例 8

[0246] 6-(2-(二甲氧基甲基)-5-(6-乙基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶(式(VI)化合物,其中 R^a=CH_2CH_3)的制备

[0247] 如制备例 7 所述制备标题化合物,使用 1-([1,2,4]三唑并[1,5-a]吡啶-6-基)-2-(6-乙基吡啶-2-基)乙烷-1,2-二酮代替 1-([1,2,4]三唑并[1,5-a]吡啶-6-基)-2-(6-甲基吡啶-2-基)乙烷-1,2-二酮。收率:68%;^{1}H NMR(400MHz, $CDCl_3$): δ 10.67(br s, 1H), 8.97(br s, 1H), 8.35(s, 1H), 7.83(dd, 1H, J=9.2, 1.6Hz), 7.76(dd, 1H, J=9.2, 0.8Hz), 7.50(t, 1H, J=7.8Hz), 7.25(br d, 1H, J=7.6Hz), 7.05(d, 1H, J=8.0Hz), 5.56(s, 1H), 3.46(s, 6H), 2.83(q, 2H, J=7.6Hz), 1.31(t, 3H, J=7.6Hz)。

[0248] 制备例 9

[0249] 4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-甲醛(式(VII)化合物,其中 R^a=CH_3)的制备

[0250] 将 6-(2-(二甲氧基甲基)-5-(6-甲基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶(6.00g, 17.12mmol)溶于 1N HCl(120mL),将混合物在 70℃下加热 3h。使反应混合物冷却至 0℃,然后用饱和 $NaHCO_3$ 水溶液中和。将混合物用 10%MeOH 的 $CHCl_3$ 溶液萃取(3×200mL),有机相经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干,得到标题化合物(4.69g, 90%),为浅黄色固体。^{1}H NMR(400MHz, $CDCl_3$): δ 9.82(s, 1H), 9.01(br s, 1H), 8.41(s, 1H), 7.85(dd, 1H, J=9.2, 0.8Hz), 7.82(dd, 1H, J=9.2, 1.6Hz), 7.55(t, 1H, J=7.8Hz), 7.33(br s, 1H), 7.16(d, 1H, J=8.0Hz), 2.60(s, 3H)。

[0251] 制备例 10

[0252] 4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-乙基吡啶-2-基)-1H-咪唑-2-甲醛(式(VII)化合物,其中 R^a=CH_2CH_3)的制备

[0253] 如制备例 9 所述制备标题化合物,使用 6-(2-(二甲氧基甲基)-5-(6-乙基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶代替 6-(2-(二甲氧基甲基)-5-(6-甲基吡啶-2-基)-1H-咪唑-4-基)-[1,2,4]三唑并[1,5-a]吡啶。收率:99%;^{1}H NMR(400MHz, DMSO-d_6) δ 9.86(t, 1H, J=1.2Hz), 9.59(s, 1H), 8.43(s, 1H), 8.21(dd, 1H, J=9.2, 1.6Hz), 7.82(brd, 1H, J=8.0Hz), 7.73(dd, 1H, J=9.2, 0.8Hz), 7.69(t, 1H, J=7.8Hz), 7.08(br d, 1H, J=7.6Hz), 2.71(q, 2H, J=7.6Hz), 1.16(t, 3H, J=7.6Hz)。

[0254] 制备例 11

[0255] 3-氨基-5-(二甲基氨基)苯甲腈(式(VIII)化合物,其中 R^b=3-氰基-5-二甲基氨基)的制备。该化合物按下列 2 步制备。

[0256] 向干燥的密封试管加入 3-溴-N,N-二甲基-5-硝基苯胺(1.73g, 7.06mmol)(按照 J. Org. Chem. 60:5091-5103(2003)所述方法制备)、吡啶(24mL)和 CuCN(1.26g, 2.14mmol)。在 220℃下加热混合物,同时搅拌 3.5h。使反应混合物冷却至 100℃,倒入含有氨水(100mL)与水(100mL)的混合物的烧瓶,用 EtOAc 萃取(2×100mL)。将 EtOAc 溶液连续用稀氨溶液(100mL)、水(100mL)和盐水(100mL)洗涤,经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶 MPLC 纯化,使用 EtOAc 与己烷的混合物作为洗脱剂,得到 3-(二甲基氨

基)-5-硝基苯甲腈 (0.44g, 33%),为橙色固体。^{1}H NMR(400MHz, $CDCl_3$): δ 7.74(dd, 1H, J=2.0, 1.2Hz), 7.65(t, 1H, J=2.2Hz), 7.11(dd, 1H, J=2.4, 1.2Hz), 3.10(s, 6H)。

[0257] 在 10%Pd/C(0.04g) 的存在下,使上述硝基化合物 3-(二甲基氨基)-5-硝基苯甲腈 (0.42g, 2.22mmol) 在甲醇 (80mL) 中、在氢气氛下氢化过夜。通过 C 盐 (Celite) 垫过滤反应混合物,在减压下蒸发滤液至干。残余物经过硅胶 MPLC 纯化,使用 EtOAc 与己烷的混合物作为洗脱剂,得到标题化合物 (0.29g, 80%),为褐色粘性液体。^{1}H NMR(400MHz, $CDCl_3$): δ 6.35(dd, 1H, J=2.4, 1.6Hz), 6.28(dd, 1H, J=2.0, 1.6Hz), 6.14(t, 1H, J=2.2Hz), 3.76(br s, 2H), 2.92(s, 6H)。

[0258] 制备例 12

[0259] 3-((二甲基氨基)甲基)-2-氟苯胺(式 (VIII) 化合物,其中 R^b=3-(二甲基氨基)甲基-2-氟)的制备。该化合物按下列 3 步制备,始于可商购的 2-氟-1-甲基-3-硝基苯。

[0260] 将所搅拌的 2-氟-1-甲基-3-硝基苯 (15.80g, 101.94mmol) 与 N-溴琥珀酰亚胺 (18.14g, 101.94mmol) 的 CCl_4(400mL) 溶液用过氧化苯甲酰 (0.37g, 1.52mmol) 处理。将混合物在回流温度下加热过夜,然后冷却至室温。过滤反应混合物,在减压下蒸发滤液至干。将残余物溶于溶于 CH_2Cl_2(100mL),再次过滤。在减压下蒸发滤液至干,残余物经过硅胶 MPLC 纯化,使用 EtOAc 与己烷的混合物作为洗脱剂,得到 1-(溴甲基)-2-氟-3-硝基苯 (8.11g, 34%),为灰白色固体。^{1}H NMR(400MHz, $CDCl_3$): δ 8.02(m, 1H), 7.71(m, 1H), 7.30(td, 1H, J=8.4, 1.6Hz), 4.55(d, 2H, J=1.6Hz)。

[0261] 向所搅拌的 1-(溴甲基)-2-氟-3-硝基苯 (0.70g, 2.99mmol) 与盐酸二甲胺 (0.48g, 5.98mmol) 在 CH_2Cl_2(10mL) 中的混合物滴加三乙胺 (0.91g, 8.97mmol)。将混合物在室温下搅拌 3h,在减压下蒸发至干。将残余物用水 (10mL) 稀释,用 EtOAc 萃取 (2×25mL)。将 EtOAc 溶液用水 (20mL) 洗涤,经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶 MPLC 纯化,使用 EtOAc 与己烷的混合物作为洗脱剂,得到 1-(2-氟-3-硝基苯基)-N, N-二甲基甲烷胺 (0.45g, 76%),为黄色粘性液体。^{1}H NMR(400MHz, CD_3OD): δ 8.04-7.99(m, 1H), 7.78-7.73(m, 1H), 7.37(td, 1H, J=8.0, 1.0Hz), 3.64(d, 2H, J=2.0Hz), 2.29(d, 6H, J=0.8Hz)。

[0262] 将上述硝基化合物 1-(2-氟-3-硝基苯基)-N, N-二甲基甲烷胺 (0.45g, 1.93mmol)、铁粉 (1.35g, 2.41mmol)、2N HCl(1mL) 与乙醇 (5mL) 的混合物在回流温度下加热并搅拌 2h。冷却至室温后,通过 C 盐垫过滤混合物。在减压下蒸发滤液至干,残余物用水 (10mL) 稀释,用固体 K_2CO_3 碱化至 pH 10。将含水混合物用 EtOAc 萃取 (2×25mL), EtOAc 溶液经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶 MPLC 纯化,使用 EtOAc 与己烷的混合物作为洗脱剂,得到标题化合物 (0.35g, 91%),为白色固体。^{1}H NMR(400MHz, $CDCl_3$): δ 6.88(td, 1H, J=7.8, 1.0Hz), 6.72-6.67(m, 2H), 3.71(br s, 2H), 3.47(d, 2H, J=1.6Hz), 2.27(s, 6H)。

[0263] 制备例 13

[0264] 2-氟-3-(吡咯烷-1-基甲基)苯胺(式 (VIII) 化合物,其中 R^b=2-氟-3-(吡咯烷-1-基甲基))的制备

[0265] 在 0℃下,向所搅拌的 1-(溴甲基)-2-氟-3-硝基苯 (2.00g, 8.54mmol) 与吡咯烷

(0.91g, 12.82mmol) 的 CH_2Cl_2 (15mL) 溶液滴加三乙胺 (1.72g, 17.08mmol)。将混合物在室温下搅拌过夜，然后在减压下蒸发至干。残余物用水 (15mL) 稀释，用 EtOAc 萃取 (2×30mL)。将 EtOAc 溶液用盐水 (20mL) 洗涤，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 1-(2- 氟 -3- 硝基苄基) 吡咯烷 (1.20g, 63%)，为粘 性的油。^1H NMR(400MHz, CD_3OD): δ 8.02-7.97(m, 1H), 7.81-7.76(m, 1H), 7.36(td, 1H, J=8.0, 1.2Hz), 3.81(d, 1H, J=2.0Hz), 2.62-2.58(m, 4H), 1.84-1.80(m, 4H)。

[0266] 如制备例 12 所述制备标题化合物，使用 1-(2- 氟 -3- 硝基苄基) 吡咯烷代替 1-(2- 氟 -3- 硝基苯基)-N, N- 二甲基甲烷胺。收率 :80%; ^1H NMR(400MHz, CD_3OD): δ 6.87(td, 1H, J=8.0, 0.8Hz), 6.77(td, 1H, J=8.0, 2.0Hz), 6.68-6.64(m, 1H), 3.67(d, 2H, J=1.6Hz), 2.60-2.57(m, 4H), 1.82-1.78(m, 4H)。

[0267] 制备例 14

[0268] 2- 氟 -3-(吗啉代甲基) 苯胺 (式 (VIII) 化合物，其中 R^b=2- 氟 -3-(吗啉代甲基)) 的制备

[0269] 将所搅拌的 1-(溴甲基)-2- 氟 -3- 硝基苯 (2.50g, 10.6mmol) 与吗啉 (2.78g, 32.0mmol) 的甲苯 (24mL) 溶液在回流温度下加热 2.5h。使反应混合物冷却至室温，然后用 1N NaOH 洗涤 (2×20mL)。含水层用 EtOAc 萃取 (2×25mL)，合并甲苯溶液和 EtOAc 萃取液，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 4-(2- 氟 -3- 硝基苄基) 吗啉 (1.95g, 89%)，为浅黄色固体。^1H NMR(400MHz, CD_3OD): δ 8.02-7.97(m, 1H), 7.83-7.78(m, 1H), 7.36(td, 1H, J=8.0, 1.0Hz), 3.70-3.67(m, 6H), 2.51(br t, 4H, J=4.6Hz)。

[0270] 如制备例 12 所述制备标题化合物，使用 (4-(2- 氟 -3- 硝基苄基) 吗啉) 代替 1-(2- 氟 -3- 硝基苯基)-N, N- 二甲基甲烷胺。收率 :90%; ^1H NMR(400MHz, CD_3OD): δ 6.87(td, 1H, J=8.0, 0.8Hz), 6.77(td, 1H, J=8.0, 2.0Hz), 6.68-6.64(m, 1H), 3.68(br t, 4H, J=4.8Hz), 3.55(d, 2H, J=1.6Hz), 2.49(br t, 4H, J=4.8Hz)。

[0271] 制备例 15

[0272] 3- 氨基 -4-((二甲基氨基) 甲基) 苯甲腈 (式 (VIII) 化合物，其中 R^b=5- 氰基 -2-(二甲基氨基) 甲基) 的制备

[0273] 在 0℃下，向所搅拌的 4-(溴甲基)-3- 硝基苯甲腈 (5.00g, 20.74mmol) (按照 WO 07/024945 A1 所述方法制备) 与盐酸二甲胺 (2.03g, 24.89mmol) 在 CH_2Cl_2 (70mL) 中的混合物滴加三乙胺 (6.30g, 62.23mmol)，将混合物在室温下搅拌过夜。在减压下蒸发反应混合物至干，残余物用水 (20mL) 稀释，用 CH_2Cl_2 萃取 (3×100mL)。CH_2Cl_2 溶液经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 4-((二甲基氨基) 甲基)-3- 硝基苯 (3.58g, 84%)，为橙色固体。^1H NMR(400MHz, $CDCl_3$): δ 8.15(br s, 1H), 7.92(br s, 1H), 7.85(br d, 1H, J=7.2Hz), 3.80(s, 2H), 2.27(s, 6H)。

[0274] 如制备例 11 所述制备标题化合物，使用 4-((二甲基氨基) 甲基)-3- 硝基苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率 :91%; ^1H NMR(400MHz, $CDCl_3$): δ 7.02(dd, 1H, J=7.6, 0.4Hz), 6.91(dd, 1H, J=7.6, 1.6Hz), 6.84(d, 1H, J=1.6Hz), 5.05(br

s, 2H), 3.43(s, 2H), 2.18(s, 6H)。

[0275] 制备例 16

[0276] 3- 氨基 -2-((二甲基氨基)甲基)苯甲腈(式(VIII)化合物,其中 R^b=3- 氰基 -2-(二甲基氨基)甲基)的制备

[0277] 在 0℃下,向所搅拌的 2-(溴甲基)-3- 硝基苯甲腈(1.10g, 4.56mmol)(按照 Tetrahedron 40:1863-1868(1984) 所述方法制备)与盐酸二甲胺(0.74g, 9.13mmol)在 CH_2Cl_2(15mL)中的混合物滴加三乙胺(1.85g, 18.25mmol)。将所得混合物在室温下搅拌 2h,在减压下蒸发至干。残余物用水(10mL)稀释,用 EtOAc 萃取(3×50mL)。EtOAc 溶液经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶 MPLC 纯化,使用 EtOAc 与己烷的混合物作为洗脱剂,得到 2-((二甲基氨基)甲基)-3- 硝基苯甲腈(0.75g, 80%)为黄色油状物。^1H NMR(400MHz, $CDCl_3$): δ 7.93(br d, 1H, J=8.0Hz), 7.85(dd, 1H, J=8.0, 1.4Hz), 7.55(t, 1H, J=8.0Hz), 3.94(s, 2H), 2.24(s, 6H)。

[0278] 如制备例 11 所述制备标题化合物,使用 2-((二甲基氨基)甲基)-3- 硝基苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率:93%;^1H NMR(400MHz, $CDCl_3$): δ 7.15(t, 1H, J=7.6Hz), 7.00(dd, 1H, J=7.6, 0.8Hz), 6.83(d, 1H, J=7.6Hz), 5.06(br s, 2H), 3.73(s, 2H), 2.29(s, 6H)。

[0279] 制备例 17

[0280] 3- 氨基 -5-((二甲基氨基)甲基)苯甲腈(式(VIII)化合物,其中 R^b=3- 氰基 -5-(二甲基氨基)甲基)的制备

[0281] 在 0℃下,向所搅拌的 3-(溴甲基)-5- 硝基苯甲腈(1.50g, 6.22mmol)(按照 J. Org. Chem. 55:1040-1043(1990) 所述方法制备)与盐酸二甲胺(1.01g, 12.44mmol)在 CH_2Cl_2(15mL)中的混合物滴加三乙胺(1.88g, 18.66mmol)。将所得混合物在室温下搅拌 3h,在减压下蒸发至干。残余物用水(15mL)稀释,用 EtOAc 萃取(3×50mL)。EtOAc 溶液经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶 MPLC 纯化,使用 EtOAc 与己烷的混合物作为洗脱剂,得到 3-((二甲基氨基)甲基)-5- 硝基苯甲腈(1.10g, 87%),为粘性液体。^1H NMR(400MHz, $CDCl_3$): δ 8.45(s, 1H), 8.40(d, 1H, J=1.6Hz), 8.01(s, 1H), 3.59(s, 2H), 2.30(s, 6H)。

[0282] 如制备例 11 所述制备标题化合物,使用 3-((二甲基氨基)甲基)-5- 硝基苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率:98%;^1H NMR(400MHz, $CDCl_3$): δ 6.96(m, 1H), 6.88(br d, 1H, J=0.8Hz), 6.80(dd, 1H, J=2.4, 1.6Hz), 3.86(br s, 2H), 3.34(s, 2H), 2.24(s, 6H)。

[0283] 制备例 18

[0284] 3- 氨基 -4-(吡咯烷 -1- 基甲基)苯甲腈(式(VIII)化合物,其中 R^b=5- 氰基 -2-(吡咯烷 -1- 基甲基))的制备

[0285] 在 0℃下,向所搅拌的 4-(溴甲基)-3- 硝基苯甲腈(5.12g, 21.57mmol)与吡咯烷(1.84g, 25.88mmol)的 CH_2Cl_2(72mL)溶液滴加三乙胺(6.54g, 64.71mmol)。将混合物在室温下搅拌 1.5h,在减压下蒸发至干。残余物用水(30mL)稀释,用 CH_2Cl_2 萃取(3×100mL)。CH_2Cl_2 溶液经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶 MPLC 纯化,使用 EtOAc 与己烷的混合物作为洗脱剂,得到 3- 硝基 -4-(吡咯烷 -1- 基甲基)苯甲腈

(2.24g, 45%)，为黄色固体。^{1}H NMR(400MHz, $CDCl_3$)：δ 8.16(d, 1H, J=1.6Hz), 7.94(br d, 1H, J=8.0Hz), 7.83(dd, 1H, J=8.0, 1.6Hz), 3.99(s, 2H), 2.54(br s, 4H), 1.79(m, 4H)。

[0286] 如制备例 11 所述制备标题化合物，使用 3- 硝基 -4-(吡咯烷 -1- 基甲基) 苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率 :91%;^{1}H NMR(400MHz, $CDCl_3$)：δ 7.06(d, 1H, J=7.6Hz), 6.91(dd, 1H, J=7.6, 1.6Hz), 6.84(d, 1H, J=1.6Hz), 5.08(br s, 2H), 3.64(s, 2H), 2.47(brs, 4H), 1.78(br s, 4H)。

[0287] 制备例 19

[0288] 3- 氨基 -2-(吡咯烷 -1- 基甲基) 苯甲腈 (式 (VIII) 化合物，其中 R^b=3- 氰基 -2-(吡咯烷 -1- 基甲基)) 的制备

[0289] 在 0℃下，向所搅拌的 2-(溴甲基)-3- 硝基苯甲腈 (1.10g, 4.56mmol) 与吡咯烷 (0.65g, 9.13mmol) 的 CH_2Cl_2(15mL) 溶液滴加三乙胺 (1.85g, 18.25mmol)。将混合物在室温下搅拌 2h，在减压下蒸发至干。残余物用水 (10mL) 稀释，用 CH_2Cl_2 萃取 (3×50mL)。CH_2Cl_2 溶液经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯 化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 3- 硝基 -2-(吡咯烷 -1- 基甲基) 苯甲腈 (0.96g, 91%)，为黄色固体。^{1}H NMR(400MHz, $CDCl_3$)：δ 7.90(d, 1H, J=7.6Hz), 7.83(dd, 1H, J=7.6, 0.8Hz), 7.52(t, 1H, J=7.6Hz), 4.14(s, 2H), 2.52(br s, 4H), 1.72(br s, 4H)。

[0290] 如制备例 11 所述制备标题化合物，使用 3- 硝基 -2-(吡咯烷 -1- 基甲基) 苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率 :93%;^{1}H NMR(400MHz, $CDCl_3$)：δ 7.13(t, 1H, J=7.8Hz), 6.99(dd, 1H, J=7.8, 1.2Hz), 6.82(d, 1H, J=8.0Hz), 5.11(br s, 2H), 3.91(s, 2H), 2.58(br s, 4H), 1.81(br s, 4H)。

[0291] 制备例 20

[0292] 3- 氨基 -5-(吡咯烷 -1- 基甲基) 苯甲腈 (式 (VIII) 化合物，其中 R^b=3- 氰基 -5-(吡咯烷 -1- 基甲基)) 的制备

[0293] 在 0℃下，向所搅拌的 3-(溴甲基)-5- 硝基苯甲腈 (1.50g, 6.22mmol) 与吡咯烷 (0.53g, 7.46mmol) 的 CH_2Cl_2(15mL) 溶液滴加三乙胺 (1.88g, 18.68mmol)，将混合物在室温下搅拌过夜。在减压下蒸发反应混合物至干，残余物用水 (15mL) 稀释，用 EtOAc 萃取 (3×50mL)。EtOAc 溶液经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 3- 硝基 -5-(吡咯烷 -1- 基甲基) 苯甲腈 (1.30g, 90%)，为黄色固体。^{1}H NMR(400MHz, $CDCl_3$)：δ 8.45(br s, 1H), 8.39(br t, 1H, J=1.6Hz), 8.02(br s, 1H), 3.78(s, 2H), 2.56(br s, 4H), 1.84(br s, 4H)。

[0294] 如制备例 11 所述制备标题化合物，使用 3- 硝基 -5-(吡咯烷 -1- 基甲基) 苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率 :85%;^{1}H NMR(400MHz, $CDCl_3$)：δ 6.99(pseudo t, 1H, J=1.6Hz), 6.94(pseudo t, 1H, J=1.6Hz), 6.79(dd, 1H, J=2.4, 1.6Hz), 3.87(br s, 2H), 3.56(s, 2H), 2.54(m, 4H), 1.81(m, 4H)。

[0295] 制备例 21

[0296] 3- 氨基 -4-(吗啉代甲基) 苯甲腈 (式 (VIII) 化合物，其中 R^b=5- 氰基 -2-(吗啉代甲基)) 的制备

[0297] 在 0℃下，向所搅拌的 4-(溴甲基)-3- 硝基苯甲腈 (7.12g, 29.55mmol) 与吗啉 (3.09g, 35.45mmol) 的 CH_2Cl_2(98mL) 溶液滴加三乙胺 (8.97g, 88.64mmol)。将混合物在室

温下搅拌 1.5h，在减压下蒸发至干。残余物用水 (40mL) 稀释，用 CH_2Cl_2 萃取 (3×100mL)。CH_2Cl_2 溶液用水 (50mL) 洗涤，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 4-(吗啉代甲基)-3- 硝基苯甲腈 (5.84g, 80%)，为黄色固体。^1H NMR(400MHz, $CDCl_3$)：δ 8.12(s, 1H), 7.83(br s, 2H), 3.84(s, 2H), 3.67(t, 4H, J=4.6Hz), 2.45(t, 4H, J=4.6Hz)。

[0298] 如制备例 11 所述制备标题化合物，使用 4-(吗啉代甲基)-3- 硝基苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率：78%；^1H NMR(400MHz, $CDCl_3$)：δ 7.05(d, 1H, J=8.0Hz), 6.92(dd, 1H, J=8.0, 1.6Hz), 6.86(d, 1H, J=1.6Hz), 5.02(br s, 2H), 3.68(br t, 4H, J=4.0Hz), 3.53(s, 2H), 2.41(br s, 4H)。

[0299] 制备例 22

[0300] 3- 氨基 -2-(吗啉代甲基) 苯甲腈 (式 (VIII) 化合物，其中 R^b=3- 氰基 -2-(吗啉代甲基)) 的制备

[0301] 在 0℃下，向所搅拌的 2-(溴甲基)-3- 硝基苯甲腈 (1.10g, 4.56mmol) 与吗啉 (0.80g, 9.13mmol) 的 CH_2Cl_2(15mL) 溶液滴加三乙胺 (1.85g, 18.25mmol)。将混合物在室温下搅拌 1.5h，在减压下蒸发至干。残余物用水 (10mL) 稀释，用 CH_2Cl_2 萃取 (3×50mL)。CH_2Cl_2 溶液经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 2-(吗啉代甲基)-3- 硝基苯甲腈 (1.02g, 90%)，为黄色固体。^1H NMR(400MHz, $CDCl_3$)：δ 7.90(br d, 1H, J=8.0Hz), 7.84(dd, 1H, J=8.0, 1.2Hz), 7.56(t, 1H, J=8.0Hz), 3.99(s, 2H), 3.60(br t, 4H, J=4.4Hz), 2.46(br s, 4H)。

[0302] 如制备例 11 所述制备标题化合物，使用 2-(吗啉代甲基)-3- 硝基苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率：82%；^1H NMR(400MHz, $CDCl_3$)：δ 7.15(t, 1H, J=7.6Hz), 7.01(d, 1H, J=7.6Hz), 6.83(d, 1H, J=7.6Hz), 5.00(br s, 2H), 3.78(s, 2H), 3.69(br s, 4H), 2.50(br s, 4H)。

[0303] 制备例 23

[0304] 3- 氨基 -5-(吗啉代甲基) 苯甲腈 (式 (VIII) 化合物，其中 R^b=3- 氰基 -5-(吗啉代甲基)) 的制备

[0305] 在 0℃下，向所搅拌的 3-(溴甲基)-5- 硝基苯甲腈 (1.50g, 6.22mmol) 与吗啉 (0.65g, 7.46mmol) 的 CH_2Cl_2(15mL) 溶液滴加三乙胺 (1.88g, 18.66mmol)。将混合物在室温下搅拌过夜，然后在减压下蒸发至干。残余物用水 (15mL) 稀释，用 EtOAc 萃取 (3×50mL)。EtOAc 溶液经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 3-(吗啉代甲基)-5- 硝基苯甲腈 (0.87g, 85%)，为灰白色固体。^1H NMR(400MHz, $CDCl_3$)：δ 8.45(br s, 1H), 8.41(br s, 1H), 8.01(br s, 1H), 3.74(br t, 4H, J=4.4Hz), 3.64(s, 2H), 2.48(br t, 4H, J=4.4Hz)。

[0306] 如制备例 11 所述制备标题化合物，使用 3-(吗啉代甲基)-5- 硝基苯甲腈代替 3-(二甲基氨基)-5- 硝基苯甲腈。收率：85%；^1H NMR(400MHz, $CDCl_3$)：δ 7.00(br t, 1H, J=1.6Hz), 6.93(br s, 1H), 6.81(dd, 1H, J=2.4, 1.6Hz), 3.88(br s, 2H), 3.74(br t, 4H, J=4.6Hz), 3.44(s, 2H), 2.47(br s, 4H)。

[0307] 制备例 24

[0308] 2-(2- 氟苯氧基) 乙醛 (式 (IX) 化合物，其中 R^b=2- 氟，X=O) 的制备。该化合物

按下列 2 步制备。

[0309] 将所搅拌的 2- 氟苯酚 (1.00g, 8.92mmol)、2- 溴 -1, 1- 二乙氧基乙烷 (1.75g, 8.92mmol) 与 K_2CO_3 (1.47g, 10.7mmol) 在无水 DMF (10mL) 中的混合物在 110℃下加热过夜。将反应混合物倒入冰冷的水 (15mL) 中，用 EtOAc 萃取 (2×100mL)。EtOAc 溶液用水 (25mL) 和盐水 (25mL) 萃取，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 1-(2, 2- 二乙氧基乙氧基)-2- 氟苯 (1.65g, 81%)，为粘性液体。^1H NMR (400MHz, $CDCl_3$)：δ 7.09-6.96 (m, 3H), 6.93-6.87 (m, 1H), 4.85 (t, 1H, J=5.2Hz), 4.07 (d, 2H, J=5.2Hz), 3.82-3.74 (m, 2H), 3.69-3.61 (m, 2H), 1.24 (t, 6H, J=7.0Hz)。

[0310] 在 0℃下，向所搅拌的 1-(2, 2- 二乙氧基乙氧基)-2- 氟苯 (1.65g, 7.23mmol) 在 1, 4- 二噁烷 (50mL) 与水 (40mL) 混合物中的溶液加入浓 HCl (17.6mL)，将混合物在室温下搅拌过夜。将反应混合物冷却至 0℃，用饱和 $NaHCO_3$ 溶液中和，用 EtOAc 萃取 (2×200mL)。EtOAC 溶液经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到标题化合物 (0.78g, 71%)，为粘性液体。^1H NMR (400MHz, $CDCl_3$)：δ 9.87 (s, 1H), 7.12 (ddd, 1H, J=11.4, 8.2, 1.6Hz), 7.08-7.04 (m, 1H), 7.01-6.95 (m, 1H), 6.91 (td. 1H, J=8.2, 1.6Hz), 4.63 (s, 2H)。

[0311] 制备例 25

[0312] 2-(2- 氟苯硫基) 乙醛 (式 (IX) 化合物，其中 R^b=2- 氟，X=S) 的制备。该化合物按下列 2 步制备。

[0313] 将 2- 氟苯硫酚 (1.00g, 7.80mmol)、溴乙醛二乙缩醛 (1.41mL, 9.36mmol) 与 Cs_2CO_3 (3.05g, 9.36mmol) 在无水 DMF (20mL) 中的混合物 在 N_2 和室温下搅拌过夜。使反应混合物通过烧结漏斗过滤，滤液用水 (20mL) 稀释。含水混合物用 Et_2O 萃取 (3×100mL)，有机相经无水 $MgSO_4$ 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 (2, 2- 二乙氧基乙基)(2- 氟苯基) 硫烷 (1.81g, 95%)，为粘性液体。^1H NMR (400MHz, $CDCl_3$)：δ 7.46-7.41 (m, 1H), 7.24-7.18 (m, 1H), 7.09-7.02 (m, 1H), 4.64 (t, 1H, J=5.6Hz), 3.69-3.61 (m, 2H), 3.56-3.49 (m, 2H), 3.10 (d, 2H, J=5.6Hz), 1.17 (t, 6H, J=7.2Hz)。

[0314] 在 0℃下，向所搅拌的 (2, 2- 二乙氧基乙基)(2- 氟苯基) 硫烷 (1.00g, 4.09mmol) 在 1, 4- 二噁烷 (30mL) 与水 (25mL) 混合物中的溶液加入浓 HCl (9mL)，将混合物在室温下搅拌 2h。将反应混合物冷却至 0℃，用饱和 $NaHCO_3$ 溶液中和，用 CH_2Cl_2 萃取 (3×50mL)。有机相用水 (50mL) 洗涤，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干，得到标题化合物 (0.59g, 85%)，为粘性液体，立即用于下一步，无需进一步纯化。^1H NMR (400MHz, $CDCl_3$)：δ 9.56 (td, 1H, J=3.2, 1.2Hz), 7.42-7.38 (m, 1H), 7.31-7.25 (m, 1H), 7.12-7.06 (m, 2H), 3.58 (d, 2H, J=3.2Hz)。

[0315] 制备例 26

[0316] 3-(甲基 (2- 氧代乙基) 氨基) 苯甲腈 (式 (IX) 化合物，其中 R^b=3- 氰基、X=NMe) 的制备。该化合物按下列 3 步制备，始于可商购的 3- 氨基苯甲腈。

[0317] 在 0℃下，向所搅拌的 3- 氨基苯甲腈 (2.50g, 21.10mmol) 的无水 DMSO (30mL) 溶液逐份加入 NaH (0.61g, 25.39mmol)，将混合物在室温下搅拌 20min，然后用溴乙醛二乙缩醛

(4.20g, 21.10mmol) 处理。2h 后，在 0℃下向其中缓慢加入饱和 NH_4Cl 水溶液 (20mL)，反应混合物用 EtOAc 萃取 (2×50mL)。EtOAc 溶液经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 3-(2,2- 二乙氧基乙基氨基) 苯甲腈 (0.86g, 17%)，为浅橙色油。^1H NMR(400MHz, $CDCl_3$)：δ 7.22(td, 1H, J=7.8, 0.6Hz), 6.97(m, 1H), 6.84-6.81(m, 2H), 4.67(t, 1H, J=5.4Hz), 3.77-3.69(m, 2H), 3.61-3.53(m, 2H), 3.24(d, 2H, J=5.6Hz), 1.24(t, 6H, J=7.0Hz)。

[0318] 在 0℃下，向所搅拌的 3-(2,2- 二乙氧基乙基氨基) 苯甲腈 (0.84g, 3.59mmol) 的无水 DMF(5mL) 溶液逐份加入 NaH(0.10g, 4.30mmol)。20min 后，加入 MeI(0.61g, 4.30mmol)，将混合物在室温下搅拌 6h。将反应混合物冷却至 0℃，向其中滴加 NH_4Cl(10mL) 溶液。含水混合物用 $CHCl_3$ 萃取 (2×30mL)，有机相经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 3-((2,2- 二乙氧基乙基)(甲基) 氨基) 苯甲腈 (0.65g, 73%)，为粘性液体。^1H NMR(400MHz, $CDCl_3$)：δ 7.28-7.24(m, 1H), 6.96-6.93(m, 3H), 4.60(t, 1H, J=5.2Hz), 3.76-3.69(m, 2H), 3.55-3.47(m, 2H), 3.46(d, 2H, J=5.2Hz), 3.02(s, 3H), 1.20(t, 6H, J=7.0Hz)。

[0319] 在 0℃下，向所搅拌的 3-((2,2- 二乙氧基乙基)(甲基) 氨基) 苯甲腈 (0.65g, 2.61mmol) 的无水二噁烷 (6mL) 溶液滴加 1N HCl(4.30mmol)，将混合物在室温下搅拌 1h。将反应混合物冷却至 0℃，用 $NaHCO_3$ 水溶液中和，用 $CHCl_3$ 萃取 (2×30mL)。$CHCl_3$ 溶液经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干，得到标题化合物 (0.24g, 52%)，为粘性液体，无需进一步纯化即可用于下一步。^1H NMR(400MHz, $CDCl_3$)：δ 9.74(t, 1H, J=0.8Hz), 7.29(ddd, 1H, J=8.8, 7.4, 0.8HZ), 7.02(ddd, 1H, J=7.4, 0.8, 1.2Hz), 6.86(dd, 1H, J=2.4, 1.2Hz), 6.82(ddd, 1H, J=8.8, 2.4, 1.2Hz) 4.14(d, 2H, J=0.8Hz), 3.10(s, 3H)。

[0320] 制备例 27

[0321] 2-((2- 氟苯基)(甲基) 氨基) 乙醛 (式 (IX) 化合物，其中 R^b=2- 氟，X= NMe) 的制备。该化合物按下列 3 步制备，始于可商购的 2- 氟苯胺。

[0322] 将所搅拌的 2- 氟苯胺 (2.00g, 17.90mmol)、溴乙醛二甲缩醛 (3.25mL, 21.40mmol) 与 Cs_2CO_3(11.70g, 35.80mmol) 在无水 DMF(10mL) 中的混合物加热至 120℃过夜。在减压下蒸发反应混合物至干，残余物用 Et_2O 萃取 (2×150mL)。Et_2O 溶液用水 (4×50mL) 和盐水 (2×50mL) 洗涤，经无水 $MgSO_4$ 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 EtOAc 与己烷的混合物作为洗脱剂，得到 N-(2,2- 二乙氧基乙基)-2- 氟苯胺 (2.00g, 49%)，为无色的油。^1H NMR(400MHz, $CDCl_3$)：δ 7.03-6.95(m, 2H), 6.82-6.77(m, 1H), 6.71-6.65(m, 1H), 4.72(t, 1H, J=5.6Hz), 3.78-3.71(m, 2H), 3.62-3.54(m, 2H), 3.29(d, 2H, J=5.6Hz), 1.26-1.22(m, 6H)。

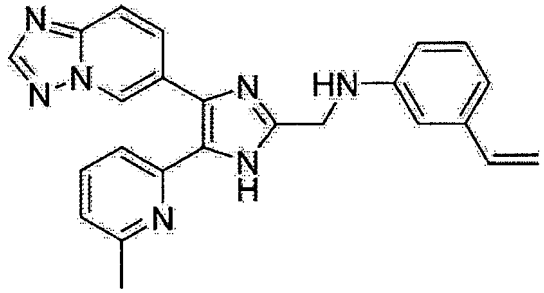
[0323] 在 0℃下，向所搅拌的 N-(2,2- 二乙氧基乙基)-2- 氟苯胺 (1.00g, 4.40mmol) 的无水 DMF(10mL) 溶液逐份加入 NaH(0.16g, 6.60mmol)。30min 后，加入 MeI(0.5mL, 8.80mmol)，将混合物在室温下搅拌过夜。将反应混合物用 EtOAc 萃取 (2×100mL)，EtOAc 溶液用水 (50mL) 和盐水 (50mL) 洗涤，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干，得到 N-(2,2- 二乙氧基乙基)-2- 氟 -N- 甲基苯胺 (0.41g, 38%)，为无色的油。^1H NMR(400MHz, $CDCl_3$)：δ 7.05-6.96(m, 3H), 6.83-6.81(m, 1H), 4.69(t, 1H, J=5.2Hz), 3.72-3.64(m, 2H), 3.55-3.49(m, 2H), 3.33(dd, 2H, J=5.2, 1.2Hz), 2.97(s, 3H), 1.19-1.53(m, 6H)。

[0324] 在 0 ℃ 下，向所搅拌的 N-(2,2- 二乙氧基乙基)-2- 氟 -N- 甲基苯胺 (0.40g,1.60mmol) 的 1,4- 二噁烷 (5mL) 溶液滴加 2.5N HCl(5mL)，将混合物在室温下搅拌过夜。将反应混合物冷却至 0℃，用饱和 $NaHCO_3$ 溶液中和，用 $CHCl_3$ 萃取 (2×50mL)。$CHCl_3$ 溶液用水 (20mL) 和盐水 (20mL) 洗涤，经 Na_2SO_4 干燥，过滤，在减压下蒸发至干，得到标题化合物 (0.27g,98%)，为无色的油，无需进一步纯化即可用于下一步。^1H NMR(400MHz,$CDCl_3$)：δ 9.80(dd,1H,J=2.4,1.2Hz),7.07-6.89(m,4H),3.91(dd,2H,J=1.8,0.8Hz),2.97(s,3H)。

[0325] 实践例 1

[0326] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 乙烯基苯胺 (实施例 37) 的制备

[0327]

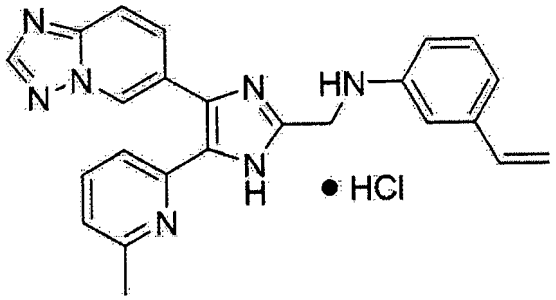


[0328] 向所搅拌的 4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 甲醛 (4.00g,13.14mmol) 的 1,2- 二氯乙烷 (240mL) 溶液加入 3- 乙烯基苯胺 (2.36g,19.71mmol) 和 AcOH(0.79g,13.14mmol)，将混合物在 80℃ 下加热 2h。将反应混合物冷却至 0℃，向其中加入 $NaBH(OAc)_3$(5.56g,26.20mmol)。将混合物在 40℃ 下搅拌过夜，然后在 0℃ 下用 10%K_2CO_3 溶液调节反应混合物的 pH 至 7-8。将反应混合物用 5%MeOH 的 $CHCl_3$ 溶液萃取 (2×200mL)，有机相经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 MeOH 与 CH_2Cl_2(1:19(v/v)) 的混合物作为洗脱剂，得到标题化合物 (2.89g,63%)，为固体。^1H NMR(400MHz,$CDCl_3$) δ 10.59(br s,1H),8.94(s,1H),8.37(s,1H),7.81(d,1H,J=9.2Hz),7.77(d,1H,J=9.2Hz),7.45(t,1H,J=7.8Hz),7.20(br d,1H, 重叠,J=7.6Hz),7.15(t,1H, 重叠,J=7.8Hz),7.00(d,1H,J=8.0Hz),6.86(d,1H,J=7.6Hz),6.75(t,1H,J=2.0Hz),6.63(dd,1H, 重叠,J=17.6,10.8Hz),6.61(dd,1H, 重叠,J=8.0,2.0Hz),5.69(dd,1H,J=17.6,0.8Hz),5.21(dd,1H,J=10.8,0.8Hz),4.55(s,2H),4.39(br s,1H),2.51(s,3H);MS(ESI)m/z 408.21(MH^+).

[0329] 实践例 2

[0330] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-3- 乙烯基苯胺氢氯化物 (实施例 38) 的制备

[0331]

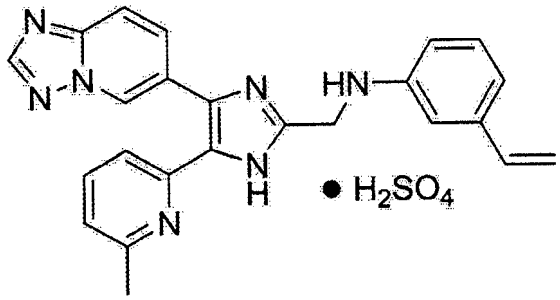


[0332] 在50℃下加热所搅拌的N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-乙烯基苯胺(1.00g,2.45mmol)在无水$CHCl_3$(12mL)中的混悬液,得到澄清的溶液。将$CHCl_3$溶液冷却至0℃,向其中加入1.0M HCl的Et_2O溶液(7.36mL,7.36mmol)。5min后,在N_2下过滤沉淀,在真空中经P_2O_5充分干燥,得到标题化合物(1.07g,98%),为黄色粉末。^1H NMR(400MHz,DMSO-d_6)δ9.49(dd,1H,J=1.6,0.8Hz),8.65(s,1H),7.97(dd,1H,J=9.2,0.8Hz),7.86(dd,1H,重叠,J=9.2,1.6Hz),7.85(t,1H,重叠,J=7.8Hz),7.65(d,1H,J=8.0Hz),7.38(d,1H,J=7.6Hz),7.12(t,1H,J=7.8Hz),6.91(t,1H,J=1.6Hz),6.79(d,1H,J=7.6Hz),6.71(dd,1H,J=8.0,1.6Hz),6.64(dd,1H,J=17.6,11.2Hz),5.80(dd,1H,J=17.6,0.8Hz),5.20(dd,1H,J=11.2,0.8Hz),4.79(s,2H),2.51(s,3H)。

[0333] 实践例3

[0334] N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-乙烯基苯胺硫酸盐(实施例39)的制备

[0335]



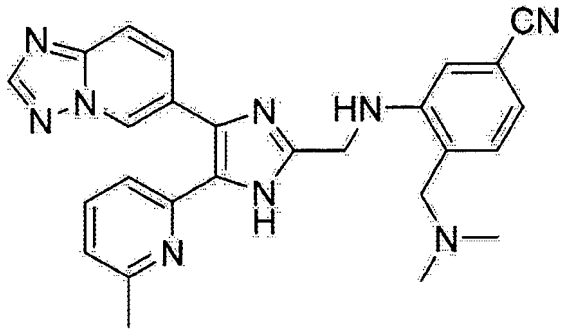
[0336] 在0C下,向所搅拌的N-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪唑-2-基)甲基)-3-乙烯基苯胺(100mg,0.25mmol)在无水EtOH(2mL)中的混悬液加入10%H_2SO_4的无水EtOH溶液(0.20mL,0.37mmol)。使混合物升温至室温,搅拌10min。将反应混合物用无水Et_2O(8mL)稀释,搅拌另外10min。在N_2下过滤沉淀,用无水Et_2O洗涤(4×4mL),然后在真空中经P_2O_5充分干燥,得到标题化合物(79mg,64%),为黄色固体。^1H NMR(400MHz,DMSO-d_6)δ9.40(dd,1H,J=1.6,0.8Hz),8.63(s,1H),7.98(dd,1H,J=9.2,0.8Hz),7.84(t,1H,J=8.0Hz),7.76(dd,1H,J=9.2,1.6Hz),7.43(d,1H,J=7.6Hz),7.40(d,1H,J=8.0Hz),7.13(t,1H,J=7.8Hz),6.80(br s,1H),6.79(d,1H,重叠,J=7.6Hz),6.64(dd,1H,重叠,J=17.6,11.2Hz),6.63(dd,1H,重叠,J=7.6,2.0Hz),5.74(dd,1H,J=17.6,0.8Hz),5.21(dd,1H,J=11.2,0.8Hz),4.68(s,2H),2.58(s,3H)。

[0337] 实践例4

[0338] 3-((4-([1,2,4]三唑并[1,5-a]吡啶-6-基)-5-(6-甲基吡啶-2-基)-1H-咪

唑 -2- 基) 甲基氨基)-4-((二甲基氨基) 甲基) 苯甲腈 (实施例 116) 的制备

[0339]



[0340] 向所搅拌的 4-((1,2,4) 三唑并 (1,5-a) 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 甲醛 (0.50g, 1.64mmol) 的 1,2- 二氯乙烷 (30mL) 溶液加入 3- 氨基 -4-((二甲基氨基) 甲基) 苯甲腈 (0.43g, 2.46mmol) 和 AcOH(0.20g, 3.29mmol), 将混合物在 80℃下加热过夜。在减压下浓缩反应混合物, 将残余物溶于无水 MeOH(30mL)。在 0℃下, 向该甲醇溶液加入 $NaBH_4$(0.25g, 6.57mmol), 然后使混合物升温至室温, 搅拌另外 3h。在 0℃下用 1N HCl 调节反应混合物的 pH 至 7-8, 然后在减压下除去 MeOH。含水混合物用 CH_2Cl_2 萃取 (2×50mL), CH_2Cl_2 溶液经无水 Na_2SO_4 干燥, 过滤, 在减压下蒸发至干。残余物经过硅胶 MPLC 纯化, 使用 MeOH 与 CH_2Cl_2(1:19(v/v)) 的混合物作为洗脱剂, 得到标题化合物 (0.60g, 79%), 为白色固体。^1H NMR(400MHz, $CDCl_3$) δ 8.99(s, 1H), 8.36(s, 1H), 7.86(dd, 1H, J=9.2, 1.6Hz), 7.78(dd, 1H, J=9.2, 0.8Hz), 7.47(t, 1H, J=7.6Hz), 7.23(br d, 1H, J=7.6Hz), 7.09(d, 1H, J=7.6Hz), 7.01(d, 1H, J=7.6Hz), 6.98(dd, 1H, J=7.6, 1.6Hz), 6.93(br s, 1H), 4.59(s, 2H), 3.63(s, 2H), 2.53(s, 3H), 2.33(s, 6H); MS(ESI) m/z 464.23(MH^+).

[0341] 按照类似于上述实践例 1-4 所述方式制备下表 1 所列化合物。在表 1 中包括这些化合物的质谱数据。

[0342] 【表 1】

[0343]

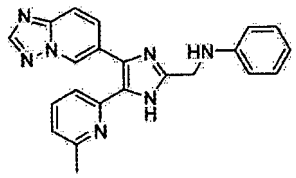
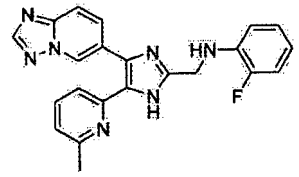
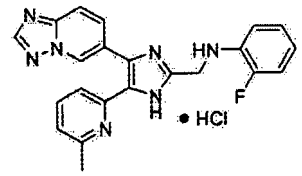
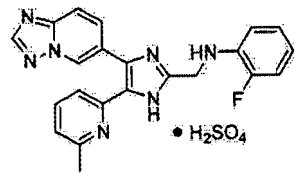
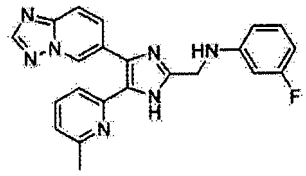
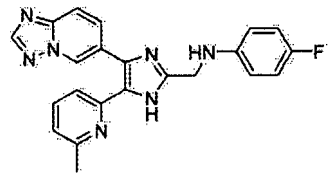
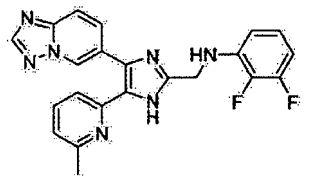
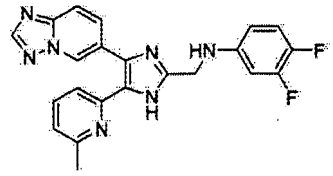
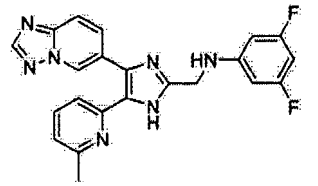
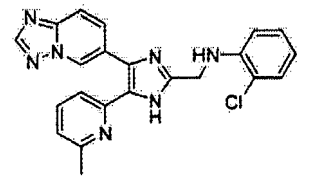
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
1		(400 MHz, $CDCl_3$) δ 10.43 (br s, 1 H), 8.96 (s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.25–7.19 (m, 3 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.80 (tt, 1 H, *J* = 8.0, 1.2 Hz), 6.74–6.72 (m, 2 H), 4.55 (s, 2 H), 2.53 (s, 3 H)	382.19
2		(400 MHz, $CDCl_3$) δ 11.34 (br s, 1 H), 8.96 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.35 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.74 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.23 (d, 1 H, *J* = 7.6 Hz), 6.97–6.90 (m, 2 H), 6.94 (dd, 1 H, *J* = 8.0, 1.2 Hz), 6.72 (td, 1 H, *J* = 8.4, 1.6 Hz), 6.69–6.63 (m, 1 H), 4.51 (s, 2 H), 2.35 (s, 3 H).	400.18
3		(400 MHz, DMSO-d_6) δ 9.44 (d, 1 H, *J* = 0.8 Hz), 8.62 (s, 1 H), 7.96 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.83 (t, 1 H, *J* = 8.0 Hz), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.53 (d, 1 H, *J* = 8.0 Hz), 7.38 (d, 1 H, *J* = 7.6 Hz), 7.10 (ddd, 1 H, *J* = 12.0, 8.0, 1.2 Hz), 7.01 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.88 (br t, 1 H, *J* = 8.6 Hz), 6.70–6.64 (m, 1 H), 4.75 (s, 2 H), 2.54 (s, 3 H)	
4		(400 MHz, DMSO-d_6) δ 9.40 (dd, 1 H, *J* = 2.0, 0.8 Hz), 8.64 (s, 1 H), 7.99 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.85 (t, 1 H, *J* = 8.0 Hz), 7.77 (dd, 1 H, *J* = 9.2, 2.0 Hz), 7.42 (假三重峰, 2 H, *J* = 7.4 Hz), 7.11 (ddd, 1 H, *J* = 12.0, 8.0, 1.2 Hz), 7.02 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.82 (td, 1 H, *J* = 8.0, 1.2 Hz), 6.71–6.65 (m, 1 H), 4.73 (s, 2 H), 2.59 (s, 3 H)	
5		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.4 Hz), 8.36 (s, 1 H), 7.79 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.75 (dd, 1H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.13–7.07 (m, 1 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.47–6.41 (m, 2 H), 6.37 (dt, 1 H, *J* = 8.8, 2.4 Hz), 4.49 (s, 2 H), 2.49 (s, 3 H)	400.19

表 1-续

[0344]

实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
6		(400 MHz, $CDCl_3$) δ 8.95 (dd, 1 H, *J* = 1.6, 1.2 Hz), 8.37 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.23 (d, 1 H, *J* = 7.6 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.92–6.88 (m, 2 H), 6.65–6.62 (m, 2 H), 4.49 (s, 2 H), 2.51 (s, 3 H)	400.19
7		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.38 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.47 (t, 1 H, *J* = 7.6 Hz), 7.24 (d, 1 H, *J* = 7.6 Hz), 7.02 (dd, 1 H, *J* = 7.6, 0.4 Hz), 6.94–6.88 (m, 1 H), 6.60–6.51 (m, 2 H), 4.71 (br s, 1 H), 4.58 (d, 2 H, *J* = 3.6 Hz), 2.51 (s, 3 H)	418.18
8		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.4 Hz), 8.38 (s, 1 H), 7.81 (dd, 1 H, 重叠, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, 重叠, *J* = 9.2, 1.2 Hz), 7.47 (t, 1 H, *J* = 7.8 Hz), 7.24 (d, 1 H, *J* = 8.0 Hz), 7.03 (d, 1 H, *J* = 7.6 Hz), 7.04–6.95 (m, 1 H), 6.52 (ddd, 1 H, *J* = 12.4, 6.8, 2.8 Hz), 6.42–6.37 (m, 1 H), 4.48 (s, 2 H), 2.55 (s, 3 H)	418.18
9		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.2 Hz), 8.38 (s, 1 H), 7.81 (dd, 1 H, 重叠, *J* = 9.2, 1.6 Hz), 7.79 (dd, 1 H, 重叠, *J* = 9.2, 1.2 Hz), 7.47 (t, 1 H, *J* = 7.8 Hz), 7.24 (d, 1 H, *J* = 8.0 Hz), 7.03 (d, 1 H, *J* = 7.6 Hz), 6.24–6.19 (m, 3 H), 4.71 (br s, 1 H), 4.50 (s, 2 H), 2.55 (s, 3 H)	418.18
10		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 1.0 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.29 (dd, 1 H, *J* = 7.6, 1.6 Hz), 7.23 (br d, 1 H, *J* = 7.6 Hz), 7.14 (td, 1 H, *J* = 8.4, 1.6 Hz), 7.01 (dd, 1 H, *J* = 7.6, 0.4 Hz), 6.75 (dd, 1 H, *J* = 8.8, 1.4 Hz), 6.72 (td, 1 H, *J* = 8.4, 1.6 Hz), 5.01 (br s, 1 H), 4.60 (br s, 2 H), 2.50 (s, 3 H)	416.16
表 1-续			

[0345]

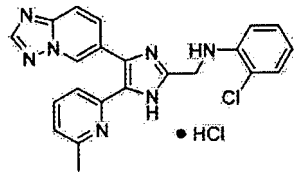
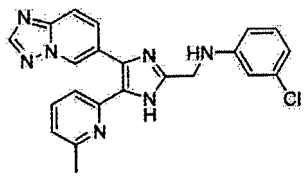
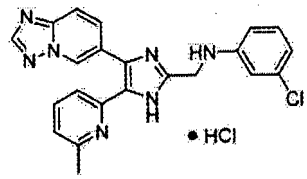
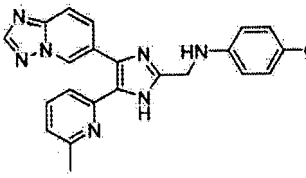
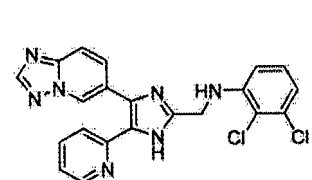
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
11		(400 MHz, DMSO-d_6) δ 9.43 (s, 1 H), 8.61 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.8 Hz), 7.82 (t, 1 H, 重叠, J = 7.8 Hz), 7.81 (dd, 1 H, 重叠, J = 9.2, 2.0 Hz), 7.49 (d, 1 H, J = 8.0 Hz), 7.36 (d, 1 H, J = 7.6 Hz), 7.32 (dd, 1 H, J = 7.8, 1.4 Hz), 7.17 (td, 1 H, J = 8.4, 1.2 Hz), 6.87 (dd, 1 H, J = 8.4, 1.2 Hz), 6.69 (td, 1 H, J = 7.8, 1.4 Hz), 6.15 (br s, 1 H), 4.76 (s, 2 H), 2.55 (s, 3 H)	
12		(400 MHz, $CDCl_3$) δ 8.95 (t, 1 H, J = 1.6 Hz), 8.37 (s, 1 H), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.77 (dd, 1 H, J = 9.2, 1.2 Hz), 7.47 (t, 1 H, J = 7.8 Hz), 7.24 (d, 1 H, J = 8.0 Hz), 7.10 (t, 1 H, J = 8.0 Hz), 7.02 (d, 1 H, J = 7.6 Hz), 6.75 (ddd, 1 H, J = 8.0, 2.0, 0.8 Hz), 6.69 (t, 1 H, J = 2.0 Hz), 6.57 (ddd, 1 H, J = 8.0, 2.4, 0.8 Hz), 4.51 (s, 2 H), 2.52 (s, 3 H)	416.16
13		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, J = 8.0 Hz), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.56 (d, 1 H, J = 8.4 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.15 (t, 1 H, J = 8.0 Hz), 6.80 (t, 1 H, J = 2.2 Hz), 6.71–6.65 (m, 2 H), 4.71 (s, 2 H), 2.54 (s, 3 H)	
14		(400 MHz, $CDCl_3$) δ 8.95 (t, 1 H, J = 1.4 Hz), 8.38 (s, 1 H), 7.81 (dd, 1 H, 重叠, J = 9.2, 1.4 Hz), 7.78 (dd, 1 H, 重叠, J = 9.2, 1.2 Hz), 7.47 (t, 1 H, J = 7.6 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.16 (m, 2 H), 7.02 (br d, 1 H, J = 7.6 Hz), 6.65 (m, 2 H), 4.51 (s, 2 H), 2.54 (s, 3 H)	416.16
15		(400 MHz, $CDCl_3$) δ 11.02 (br s, 1 H), 8.97 (s, 1 H), 8.36 (s, 1 H), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.75 (dd, 1 H, J = 9.2, 0.8 Hz), 7.46 (t, 1 H, J = 8.0 Hz), 7.24 (d, 1 H, J = 8.0 Hz), 7.03 (t, 1 H, 重叠, J = 8.0 Hz), 7.00 (d, 1 H, 重叠, J = 8.0 Hz), 6.85 (dd, 1 H, J = 8.0, 1.6 Hz), 6.63 (dd, 1 H, J = 8.0, 1.6 Hz), 5.15 (t, 1 H, J = 5.6 Hz), 4.57 (d, 2 H, J = 5.6 Hz), 2.43 (s, 3 H)	450.12

表 1-续

[0346]

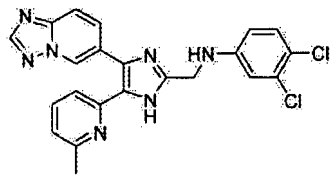
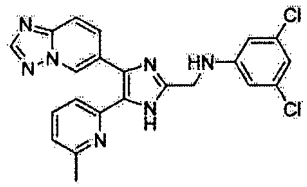
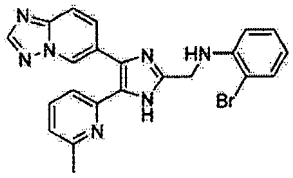
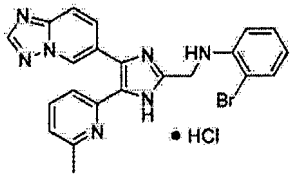
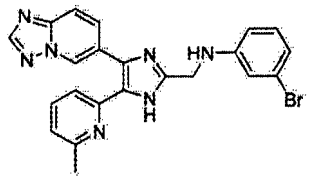
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
16		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.80 (dd, 1 H, 重叠, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, 重叠, *J* = 9.2, 1.2 Hz), 7.47 (t, 1 H, *J* = 8.0 Hz), 7.24 (br d, 1 H, *J* = 8.0 Hz), 7.20 (d, 1 H, *J* = 8.8 Hz), 7.03 (d, 1 H, *J* = 8.0 Hz), 6.77 (d, 1 H, *J* = 2.8 Hz), 6.53 (dd, 1 H, *J* = 8.8, 2.8 Hz), 4.47 (s, 2 H), 2.51 (s, 3 H)	450.12
17		(400 MHz, $CDCl_3$/CD_3OD) δ 8.90 (s, 1 H), 8.24 (s, 1 H), 7.71 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.64 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.16 (br d, 1 H, *J* = 7.6 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.57 (t, 1 H, *J* = 1.6 Hz), 6.51 (d, 2 H, *J* = 1.6 Hz), 4.36 (s, 2 H), 2.45 (s, 3 H)	450.12
18		(400 MHz, $CDCl_3$) δ 10.94 (br s, 1 H), 8.97 (br s, 1 H), 8.36 (s, 1 H), 7.82 (d, 1 H, *J* = 9.2 Hz), 7.75 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, 重叠, *J* = 7.8 Hz), 7.43 (dd, 1 H, *J* = 8.0, 1.6 Hz), 7.21 (d, 1 H, *J* = 8.0 Hz), 7.16 (td, 1 H, *J* = 8.4, 1.2 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.71 (dd, 1 H, *J* = 8.4, 1.2 Hz), 6.63 (td, 1 H, *J* = 8.0, 1.6 Hz), 4.99 (t, 1 H, *J* = 5.6 Hz), 4.57 (d, 2 H, *J* = 5.6 Hz), 2.44 (s, 3 H)	460.11
19		(400 MHz, DMSO-d_6) δ 9.43 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.62 (s, 1 H), 7.96 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.83 (t, 1 H, *J* = 7.6 Hz), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.50 (d, 1 H, *J* = 7.6 Hz), 7.48 (dd, 1 H, *J* = 8.0, 1.6 Hz), 7.37 (d, 1 H, *J* = 7.6 Hz), 7.21 (td, 1 H, *J* = 7.6, 1.6 Hz), 6.87 (dd, 1 H, *J* = 8.0, 1.2 Hz), 6.63 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.04 (br s 1 H), 4.78 (s, 2 H), 2.55 (s, 3 H)	
20		(400 MHz, $CDCl_3$) δ 8.89 (br s, 1 H), 8.30 (s, 1 H), 7.75 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.69 (d, 1 H, *J* = 9.2 Hz), 7.44 (br t, 1 H, *J* = 7.6 Hz), 7.12 (br d, 1 H, *J* = 7.6 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.97 (t, 1 H, 重叠, *J* = 8.0 Hz), 6.82–6.78 (m, 2 H), 6.58 (ddd, 1 H, *J* = 8.2, 2.4, 0.8 Hz), 4.41 (s, 2 H), 2.49 (s, 3 H)	460.11

表 1-续

[0347]

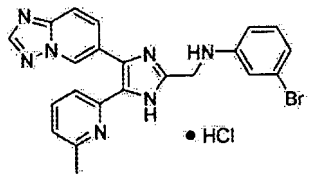
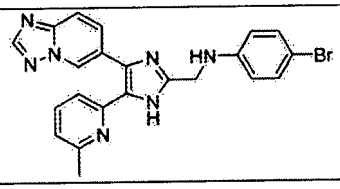
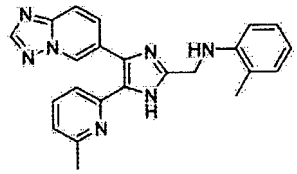
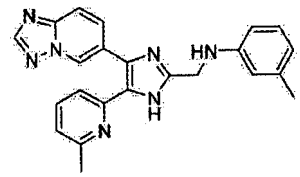
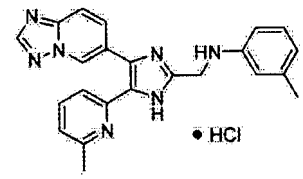
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
21		(400 MHz, DMSO-d_6) δ 9.44 (d, 1 H, J = 0.8 Hz), 8.61 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.8 Hz), 7.83 (t, 1 H, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.50 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 7.6 Hz), 7.08 (t, 1 H, J = 8.0 Hz), 6.94 (t, 1 H, J = 2.0 Hz), 6.79 (ddd, 1 H, J = 7.6, 2.0, 0.8 Hz), 6.71 (ddd, 1 H, J = 8.4, 2.0, 0.8 Hz), 4.63 (s, 2 H), 2.55 (s, 3 H)	
22		(400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 8.38 (s, 1 H), 7.82–7.77 (m, 2 H), 7.46 (t, 1 H, J = 7.6 Hz), 7.29 (m, 2 H), 7.21 (d, 1 H, J = 7.6 Hz), 7.02 (d, 1 H, J = 7.6 Hz), 6.61 (m, 2 H), 4.51 (s, 2 H), 4.44 (br s, 1 H), 2.54 (s, 3 H)	460.11
23		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.46 (t, 1 H, J = 7.8 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.14 (t, 1 H, 重叠, J = 8.0 Hz), 7.12 (d, 1 H, overlapped, J = 7.6 Hz), 7.01 (d, 1 H, J = 8.0 Hz), 6.76 (td, 1 H, J =7.6, 0.8 Hz), 6.69 (d, 1 H, J = 7.6 Hz), 4.61 (s, 2 H), 2.54 (s, 3 H), 2.26 (s, 3 H)	396.21
24		(400 MHz, $CDCl_3$) δ 8.96 (dd, 1 H, J = 1.6, 1.2 Hz), 8.37 (s,1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 1.2 Hz), 7.46 (t, 1 H, J = 7.8 Hz), 7.22 (br d, 1 H, J = 8.0 Hz), 7.11 (t, 1 H, J = 7.8 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.63 (dt, 1 H, J = 7.6, 0.8 Hz), 6.57–6.53 (m, 2 H), 4.55 (s, 2 H), 2.54 (s, 3 H), 2.29 (s, 3 H)	396.21
25		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.83 (t, 1 H, J = 8.0 Hz), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.56 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.02 (t, 1 H, J = 7.8 Hz), 6.60 (s, 1 H), 6.54 (dd, 1 H, J = 8.0, 2.0 Hz), 6.49 (d, 1 H, J = 7.6 Hz), 4.69 (s, 2 H), 2.52 (s, 3 H), 2.21 (s, 3 H)	

表 1-续

[0348]

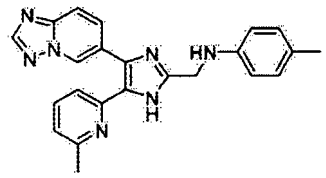
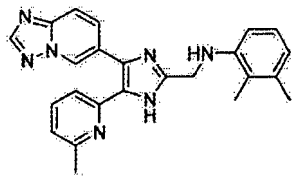
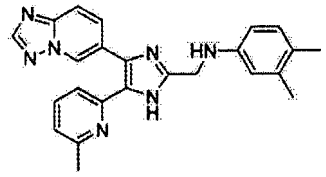
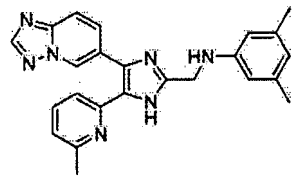
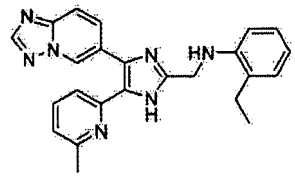
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
26		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.82 (d d, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.03 (m, 2 H), 7.02 (d, 1 H, 重叠, *J* = 7.6 Hz), 6.65 (m, 2 H), 4.53 (s, 2 H), 2.53 (s, 3 H), 2.25 (s, 3 H)	396.21
27		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 7.6 Hz), 7.03 (t, 1 H, 重叠, *J* = 7.8 Hz), 7.02 (d, 1 H, 重叠, *J* = 8.0 Hz), 6.69 (d, 1 H, *J* = 7.6 Hz), 6.58 (d, 1 H, *J* = 8.0 Hz), 4.59 (s, 2 H), 2.54 (s, 3 H), 2.31 (s, 3 H), 2.17 (s, 3 H)	410.23
28		(400 MHz, $CDCl_3$) δ 8.96 (d, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.98 (d, 1 H, *J* = 8.0 Hz), 6.57 (d, 1 H, *J* = 2.4 Hz), 6.50 (dd, 1 H, *J* = 8.0, 2.4 Hz), 4.53 (s, 2 H), 2.54 (s, 3 H), 2.20 (s, 3 H), 2.16 (s, 3 H)	410.23
29		(400 MHz, $CDCl_3$) δ 8.95 (dd, 1 H, *J* = 1.6, 1.2 Hz), 8.36 (s, 1 H), 7.79 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.74 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (d, 1 H, *J* = 8.0 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.44 (br s, 1 H), 6.31 (s, 2 H), 4.49 (s, 2 H), 2.48 (s, 3 H), 2.21 (s, 6 H)	410.23
30		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.23 (br d, 1 H, *J* = 7.6 Hz), 7.16–7.11 (m, 2 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.80 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.71 (dd, 1 H, *J* = 8.4, 1.2 Hz), 4.60 (s, 2 H), 2.60 (q, 2 H, *J* = 7.6 Hz), 2.52 (s, 3 H), 1.32 (t, 3 H, *J* = 7.6 Hz)	410.23

表 1-续

[0349]

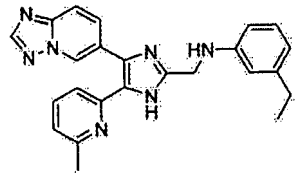
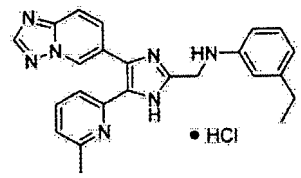
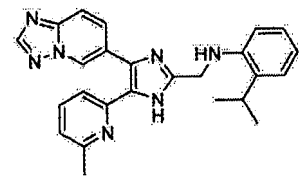
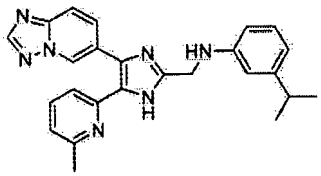
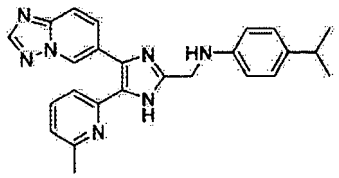
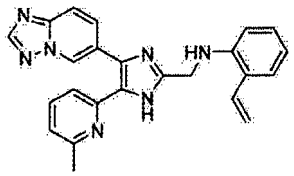
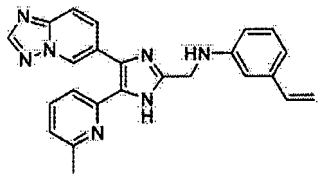
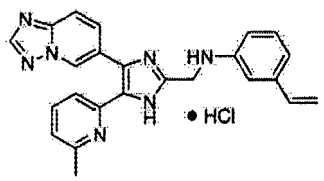
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
31		(400 MHz, $CDCl_3$) δ 8.96 (d, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.14 (t, 1 H, *J* = 7.8 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.66 (dd, 1 H, *J* = 7.6, 0.8 Hz), 6.58 (d, 1 H, *J* = 2.0 Hz), 6.55 (dd, 1 H, *J* = 7.6, 2.0 Hz), 4.55 (s, 2 H), 2.58 (q, 2 H, *J* = 7.6 Hz), 2.53 (s, 3 H), 1.21 (t, 3 H, *J* = 7.6 Hz)	410.23
32		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.83 (t, 1 H, *J* = 8.0 Hz), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.57 (d, 1 H, *J* = 8.0 Hz), 7.37 (d, 1 H, *J* = 8.0 Hz), 7.05 (t, 1 H, *J* = 7.6 Hz), 6.64 (d, 1 H, *J* = 1.6 Hz), 6.57–6.52 (m, 2 H), 4.71 (s, 2 H), 2.53 (s, 3 H), 2.50 (q, 2 H, *J* = 7.6 Hz), 1.14 (t, 3 H, *J* = 7.6 Hz)	
33		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.23 (br d, 1 H, 重叠, *J* = 8.0 Hz), 7.21 (dd, 1 H, 重叠, *J* = 7.6, 1.6 Hz), 7.12 (td, 1 H, *J* = 7.6, 1.6 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.83 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.71 (dd, 1 H, *J* = 8.0, 1.2 Hz), 4.58 (s, 2 H), 3.00 (七重峰, 1 H, *J* = 6.8 Hz), 2.50 (s, 3 H), 1.31 (d, 6 H, *J* = 6.8 Hz)	424.24
34		(400 MHz, $CDCl_3$) δ 8.96 (dd, 1 H, *J* = 1.4, 0.8 Hz), 8.35 (s, 1 H), 7.79 (dd, 1 H, *J* = 9.2, 1.4 Hz), 7.73 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.21 (d, 1 H, *J* = 7.6 Hz), 7.11 (t, 1 H, *J* = 7.8 Hz), 6.99 (dd, 1 H, *J* = 7.8, 0.4 Hz), 6.67 (d, 1 H, *J* = 7.6 Hz), 6.57 (t, 1 H, *J* = 2.4 Hz), 6.50 (ddd, 1 H, *J* = 8.0, 2.4, 0.8 Hz), 4.51 (s, 2 H), 2.80 (七重峰, 1 H, *J* = 6.8 Hz), 2.47 (s, 3 H), 1.20 (d, 6 H, *J* = 6.8 Hz)	424.24

表 1-续

[0350]

实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
35		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, *J* = 1.2 Hz), 8.36 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.75 (d, 1 H, *J* = 9.2 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.21 (d, 1 H, *J* = 8.0 Hz), 7.06 (m, 2 H), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.64 (m, 2 H), 4.50 (s, 2 H), 2.80 (七重峰, 1 H, *J* = 6.8 Hz), 2.48 (s, 3 H), 1.19 (d, 6 H, *J* = 6.8 Hz)	424.24
36		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.35 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.28 (dd, 1 H, *J* = 7.6, 1.2 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.15 (td, 1 H, *J* = 7.8, 1.2 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.79 (dd, 1H, 重叠, *J* = 17.2, 11.2 Hz), 6.78 (td, 1 H, 重叠, *J* = 7.6, 0.8 Hz), 6.68 (dd, 1 H, *J* = 8.2, 1.0 Hz), 5.62 (dd, 1 H, *J* = 17.2, 1.4 Hz), 5.34 (dd, 1 H, *J* = 11.2, 1.4 Hz), 4.53 (s, 2 H), 2.45 (s, 3 H)	408.21
37		(400 MHz, $CDCl_3$) δ 10.59 (br s, 1 H), 8.94 (s, 1 H), 8.37 (s, 1 H), 7.81 (d, 1 H, *J* = 9.2 Hz), 7.77 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.20 (br d, 1 H, 重叠, *J* = 7.6 Hz), 7.15 (t, 1 H, 重叠, *J* = 7.8 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.86 (d, 1 H, *J* = 7.6 Hz), 6.75 (t, 1 H, *J* = 2.0 Hz), 6.63 (dd, 1 H, 重叠, *J* = 17.6, 10.8 Hz), 6.61 (dd, 1 H, 重叠, *J* = 8.0, 2.0 Hz), 5.69 (dd, 1 H, *J* = 17.6, 0.8 Hz), 5.21 (dd, 1 H, *J* = 10.8, 0.8 Hz), 4.55 (s, 2 H), 4.39 (br s, 1 H), 2.51 (s, 3 H)	408.21
38		(400 MHz, DMSO-d_6) δ 9.49 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.65 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.86 (dd, 1 H, 重叠, *J* = 9.2, 1.6 Hz), 7.85 (t, 1 H, 重叠, *J* = 7.8 Hz), 7.65 (d, 1 H, *J* = 8.0 Hz), 7.38 (d, 1 H, *J* = 7.6 Hz), 7.12 (t, 1 H, *J* = 7.8 Hz), 6.91 (t, 1 H, *J* = 1.6 Hz), 6.79 (d, 1 H, *J* = 7.6 Hz), 6.71 (dd, 1 H, *J* = 8.0, 1.6 Hz), 6.64 (dd, 1 H, *J* = 17.6, 11.2 Hz), 5.80 (dd, 1 H, *J* = 17.6, 0.8 Hz), 5.20 (dd, 1 H, *J* = 11.2, 0.8 Hz), 4.79 (s, 2 H), 2.51 (s, 3 H)	
表 1-续			

[0351]

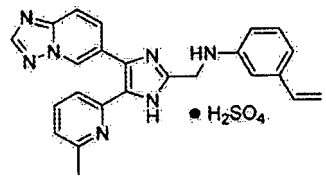
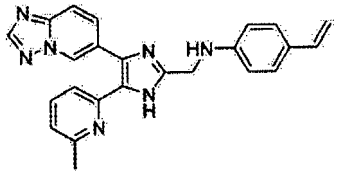
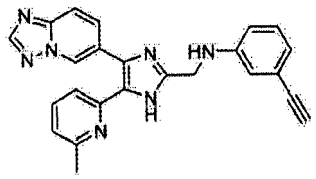
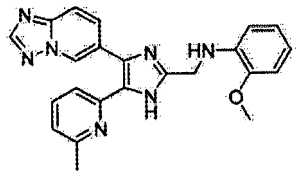
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
39		(400 MHz, DMSO-d_6) δ 9.40 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.98 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, J = 8.0 Hz), 7.76 (dd, 1 H, J = 9.2, 1.6 Hz), 7.43 (d, 1 H, J = 7.6 Hz), 7.40 (d, 1 H, J = 8.0 Hz), 7.13 (t, 1 H, J = 7.8 Hz), 6.80 (br s, 1 H), 6.79 (d, 1 H, 重叠, J = 7.6 Hz), 6.64 (dd, 1 H, 重叠, J = 17.6, 11.2 Hz), 6.63 (dd, 1 H, 重叠, J = 7.6, 2.0 Hz), 5.74 (dd, 1 H, J = 17.6, 0.8 Hz), 5.21 (dd, 1 H, J = 11.2, 0.8 Hz), 4.68 (s, 2 H), 2.58 (s, 3 H)	
40		(400 MHz, $CDCl_3$) δ 10.39 (br s, 1 H), 8.96 (s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.45 (t, 1 H, J = 7.6 Hz), 7.28 (m, 2 H), 7.22 (br d, 1 H, J = 7.6 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.69 (m, 2 H), 6.61 (dd, 1 H, J = 17.6, 10.8 Hz), 5.55 (dd, 1 H, J = 17.6, 0.8 Hz), 5.05 (dd, 1 H, J = 10.8, 0.8 Hz), 4.56, (s, 2 H), 2.53 (s, 3 H)	408.21
41		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, J = 1.2 Hz), 8.35 (s, 1 H), 7.77 (dd, 1 H, J = 9.2, 1.2 Hz), 7.72 (d, 1 H, J = 9.2 Hz), 7.46 (t, 1 H, J = 7.8 Hz), 7.23 (d, 1 H, J = 8.0 Hz), 7.07 (t, 1 H, J = 7.8 Hz), 6.99 (d, 1 H, J = 7.6 Hz), 6.86 (d, 1 H, J = 7.6 Hz), 6.73 (br s, 1 H), 6.61 (br d, 1 H, J = 8.0 Hz), 4.45 (s, 2 H), 2.98 (s, 1 H), 2.42 (s, 3 H)	406.18
42		(400 MHz, $CDCl_3$) δ 8.98 (br s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.45 (t, 1 H, J = 7.6 Hz), 7.22 (br d, 1 H, J = 7.6 Hz), 7.00 (d, 1 H, J = 7.6 Hz), 6.87 (td, 1 H, J = 7.6, 1.6 Hz), 6.84 (dd, 1 H, J = 8.0, 1.6 Hz), 6.77 (td, 1 H, J = 7.8, 1.6 Hz), 6.69 (dd, 1 H, J = 7.8, 1.6 Hz), 4.58 (s, 2 H), 3.91 (s, 3 H), 2.53 (s, 3 H)	412.21

表 1-续

[0352]

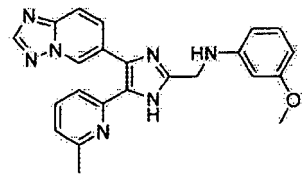
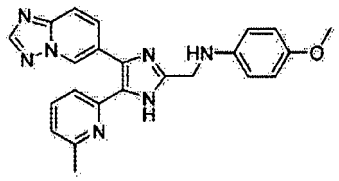
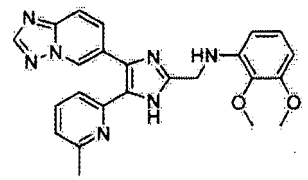
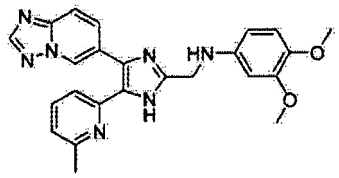
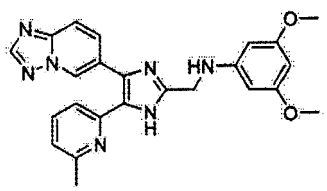
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
43		(400 MHz, $CDCl_3$) δ 8.95 (br s, 1 H), 8.37 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.22 (d, 1 H, *J* = 7.6 Hz), 7.11 (t, 1 H, *J* = 8.0 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.36–6.31 (m, 2 H), 6.27 (t, 1 H, *J* = 2.4 Hz), 4.52 (s, 2 H), 3.75 (s, 3 H), 2.51 (s, 3 H)	412.21
44		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 7.6 Hz), 7.01 (br d, 1 H, *J* = 8.0 Hz), 6.80 (m, 2 H), 6.70 (m, 2 H), 4.50 (s, 2 H), 3.74 (s, 3 H), 2.53 (s, 3 H)	412.21
45		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.34 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.72 (d, 1 H, *J* = 9.2 Hz), 7.42 (t, 1 H, *J* = 7.6 Hz), 7.20 (br d, 1 H, *J* = 7.6 Hz), 6.96 (d, 1 H, *J* = 7.6 Hz), 6.88 (td, 1 H, *J* = 8.2, 0.4 Hz), 6.36 (d, 1 H, 重叠, *J* = 8.0 Hz), 6.34 (d, 1 H, 重叠, *J* = 8.2 Hz), 4.52 (s, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 2.43 (s, 3 H)	442.22
46		(400 MHz, $CDCl_3$) δ 8.94 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.34 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.72 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 8.0 Hz), 7.21 (br d, 1 H, *J* = 8.0 Hz), 6.99 (d, 1 H, *J* = 8.0 Hz), 6.71 (d, 1 H, *J* = 8.4 Hz), 6.30 (d, 1 H, *J* = 2.4 Hz), 6.19 (dd, 1 H, *J* = 8.4, 2.4 Hz), 4.46 (s, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.47 (s, 3 H)	442.22
47		(400 MHz, $CDCl_3$) δ 10.43 (br s, 1 H), 8.94 (s, 1 H), 8.37 (s, 1 H), 7.81 (d, 1 H, *J* = 9.2 Hz), 7.77 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.20 (d, 1 H, *J* = 7.6 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 5.96 (t, 1 H, *J* = 2.0 Hz), 5.92 (d, 2 H, *J* = 2.0 Hz), 4.52 (d, 2 H, *J* = 2.8 Hz), 4.41 (br s, 1 H), 3.75 (s, 6 H), 2.54 (s, 3 H)	442.22

表 1-续

[0353]

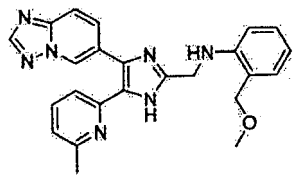
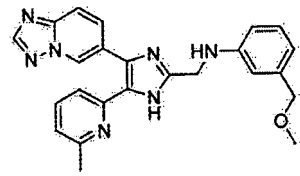
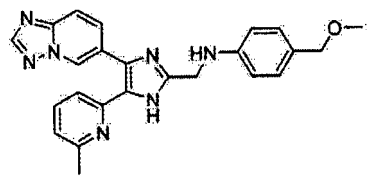
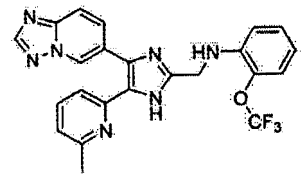
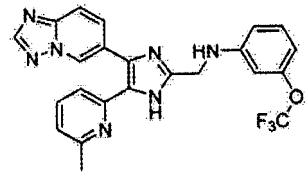
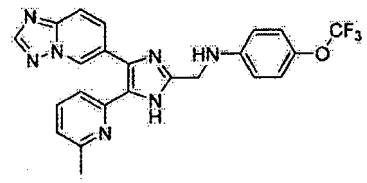
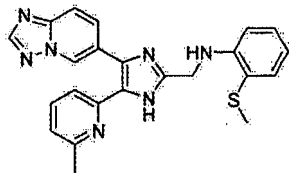
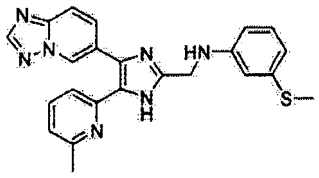
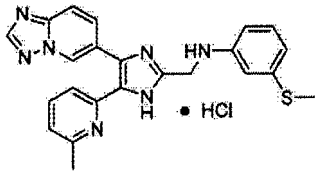
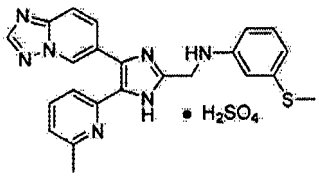
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
48		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.23 (td, 1 H, 重叠, *J* = 7.6, 1.6 Hz), 7.22 (br d, 1 H, 重叠, *J* = 7.6 Hz) 7.12 (dd, 1 H, *J* = 7.6, 1.6 Hz), 7.01 (d, 1 H, *J* = 8.0 Hz), 6.77–6.73 (m, 2 H), 4.63 (s, 2 H), 4.60 (s, 2 H), 3.42 (s, 3 H), 2.53 (s, 3 H)	426.22
49		(400 MHz, $CDCl_3$) δ 8.96 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.21 (t, 1 H, 重叠, *J* = 8.0 Hz), 7.20 (br d, 1 H, 重叠, *J* = 7.6 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.76 (d, 1 H, 重叠, *J* = 8.0 Hz), 6.75 (d, 1 H, 重叠, *J* = 1.6 Hz), 6.67–6.64 (m, 1 H), 4.56 (s, 2 H), 4.40 (s, 2 H), 3.38 (s, 3 H), 2.54 (s, 3 H)	426.22
50		(400 MHz, $CDCl_3$) δ 10.36 (br s, 1 H), 8.95 (s, 1 H), 8.37 (s, 1 H), 7.82 (br d, 1 H, *J* = 9.2 Hz), 7.78 (br d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.6 Hz), 7.20 (br d, 1 H, 重叠, *J* = 7.6 Hz), 7.19 (d, 2 H, 重叠, *J* = 8.4 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.71 (d, 2 H, *J* = 8.4 Hz), 4.55 (s, 2 H), 4.40 (br s, 1 H), 4.34 (s, 2 H), 3.34 (s, 3 H), 2.53 (s, 3 H)	426.22
51		(400 MHz, $CDCl_3$) δ 10.42 (br s, 1 H), 8.96 (br s, 1 H), 8.37 (s, 1 H), 7.82 (d, 1 H, *J* = 9.2 Hz), 7.78 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.25–7.18 (m, 2 H), 7.15 (td, 1 H, *J* = 7.8, 1.2 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.81 (dd, 1 H, *J* = 8.0, 1.2 Hz), 6.76 (td, 1 H, *J* = 7.8, 1.6 Hz), 4.85 (t, 1 H, *J* = 5.6 Hz), 4.61 (d, 2 H, *J* = 5.6 Hz), 2.52 (s, 3 H)	466.18
52		(400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 8.37 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.23 (br d, 1 H, *J* = 8.0 Hz), 7.19 (t, 1 H, *J* = 8.2 Hz), 7.02 (d, 1 H, *J* = 7.6 Hz), 6.64–6.60 (m, 2 H), 6.55 (br s, 1 H), 4.62 (br s, 1 H), 4.52 (s, 2 H), 2.52 (s, 3 H)	466.18

表 1-续

[0354]

实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
53		(400 MHz, $CDCl_3$) δ 8.95 (s, 1 H), 8.38 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.08 (m, 2 H), 7.02 (d, 1 H, *J* = 7.6 Hz), 6.70 (m, 2 H), 4.53 (s, 2 H), 2.54 (s, 3 H)	466.18
54		(400 MHz, $CDCl_3$) δ 11.34 (br s, 1 H), 8.99 (s, 1 H), 8.34 (s, 1 H), 7.83 (br d, 1 H, *J* = 9.2 Hz), 7.72 (br d, 1 H, *J* = 9.2 Hz), 7.43 (t, 1 H, *J* = 7.8 Hz), 7.35 (dd, 1 H, *J* = 7.6, 1.6 Hz), 7.21 (br d, 1 H, *J* = 7.6 Hz), 7.12 (td, 1 H, *J* = 7.8, 1.6 Hz), 6.95 (d, 1 H, *J* = 8.0 Hz), 6.70 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.65 (dd, 1 H, *J* = 8.0, 1.2 Hz), 5.49 (br t, 1 H, *J* = 4.8 Hz), 4.55 (d, 2 H, *J* = 4.8 Hz), 2.33 (s, 3 H), 2.32 (s, 3 H)	428.18
55		(400 MHz, $CDCl_3$) δ 11.06 (br s, 1 H), 8.94 (s, 1 H), 8.35 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.74 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.21 (br d, 1 H, *J* = 8.0 Hz), 7.07 (t, 1 H, *J* = 7.8 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.64 (dd, 1 H, *J* = 7.6, 2.0 Hz), 6.54 (t, 1 H, *J* = 1.6 Hz), 6.42 (dd, 1 H, *J* = 8.0, 1.6 Hz), 4.47 (s, 2 H) 4.42 (br s, 1 H), 2.45 (s, 3 H), 2.40 (s, 3 H)	428.19
56		(400 MHz, DMSO-d_6) δ 9.43 (br s, 1 H), 8.62 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.84 (t, 1 H, *J* = 7.6 Hz), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.51 (d, 1 H, *J* = 7.6 Hz), 7.38 (d, 1 H, *J* = 7.6 Hz), 7.08 (t, 1 H, *J* = 7.8 Hz), 6.62 (t, 1 H, *J* = 2.0 Hz), 6.55 (d, 1 H, *J* = 7.6 Hz), 6.51 (dd, 1 H, *J* = 8.0, 2.0 Hz), 4.68 (s, 2 H), 2.55 (s, 3 H), 2.41 (s, 3 H)	
57		(400 MHz, DMSO-d_6) δ 9.40 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.98 (d, 1 H, *J* = 9.6 Hz), 7.84 (t, 1 H, *J* = 7.6 Hz), 7.77 (dd, 1 H, *J* = 9.6, 1.6 Hz), 7.43 (d, 1 H, *J* = 7.6 Hz), 7.40 (d, 1 H, *J* = 7.6 Hz), 7.08 (t, 1 H, *J* = 8.0 Hz), 6.60 (t, 1 H, *J* = 2.0 Hz), 6.56 (d, 1 H, *J* = 8.0 Hz), 6.48 (dd, 1 H, *J* = 8.0, 2.0 Hz), 4.65 (s, 2 H), 2.58 (s, 3 H), 2.40 (s, 3 H)	
表 1-续			

[0355]

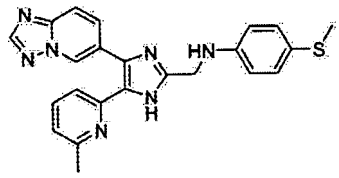
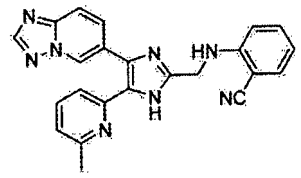
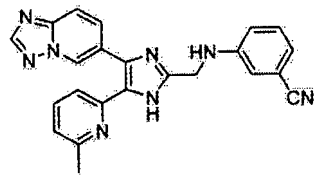
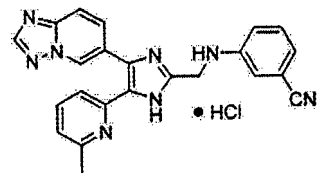
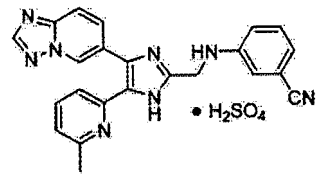
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
58		(400 MHz, $CDCl_3$) δ 11.08 (br s, 1 H), 8.94 (s, 1 H), 8.35 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.21 (br d, 1 H, *J* = 8.0 Hz), 7.17 (m, 2 H), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.60 (m, 2 H), 4.46 (s, 2 H), 2.45 (s, 3 H), 2.37 (s, 3 H)	428.18
59		(400 MHz, $CDCl_3$) δ 8.98 (br s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.47 (t, 1 H, *J* = 7.8 Hz), 7.40 (br d, 1 H, 重叠, *J* = 7.6 Hz), 7.38 (t, 1 H, *J* = 7.8 Hz), 7.25 (br d, 1 H, *J* = 8.0 Hz), 7.00 (d, 1 H, *J* = 7.6), 6.80 (d, 1 H, *J* = 8.4 Hz), 6.75 (td, 1 H, *J* = 8.0, 0.8 Hz), 5.32 (br t, 1 H, *J* = 5.6 Hz), 4.62 (d, 2 H, *J* = 5.6 Hz), 2.41 (s, 3 H)	407.19
60		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, *J* = 1.2 Hz), 8.38 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.77 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.55 (t, 1 H, *J* = 8.0 Hz), 7.31 (d, 1 H, *J* = 8.0 Hz), 7.25 (t, 1 H, *J* = 8.0 Hz), 7.08 (d, 1 H, *J* = 8.0 Hz), 7.02 (dt, 1 H, *J* = 7.6, 1.2 Hz), 6.96–6.92 (m, 2 H), 4.56 (s, 2 H), 2.62 (s, 3 H)	407.19
61		(400 MHz, DMSO-d_6) δ 9.47 (d, 1 H, *J* = 0.8 Hz), 8.66 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.87 (t, 1 H, 重叠, *J* = 7.8 Hz), 7.85 (dd, 1 H, 重叠, *J* = 9.2, 1.6 Hz), 7.63 (d, 1 H, *J* = 7.6 Hz), 7.40 (d, 1 H, *J* = 8.0 Hz), 7.33 (t, 1 H, *J* = 7.8 Hz), 7.16 (t, 1 H, *J* = 1.6 Hz), 7.11 (dd, 1 H, *J* = 8.4, 1.6 Hz), 7.06 (br d, 1 H, *J* = 7.6 Hz), 4.79 (s, 2 H), 2.53 (s, 3 H)	
62		(400 MHz, DMSO-d_6) δ 9.39 (br s, 1 H), 8.64 (s, 1 H), 7.99 (d, 1 H, *J* = 9.2 Hz), 7.87 (t, 1 H, *J* = 7.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.45 (d, 1 H, 重叠, *J* = 7.6 Hz), 7.44 (d, 1 H, 重叠, *J* = 7.6 Hz), 7.34 (t, 1 H, *J* = 8.0 Hz), 7.10 (d, 1 H, *J* = 2.0 Hz), 7.07 (d, 1 H, 重叠, *J* = 7.6 Hz), 7.04 (dd, 1 H, 重叠, *J* = 8.0, 2.0 Hz), 4.70 (s, 2 H), 2.60 (s, 3 H)	

表 1-续

[0356]

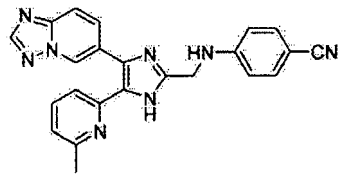
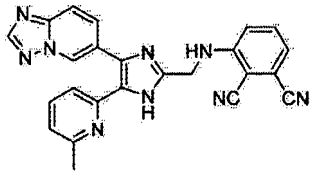
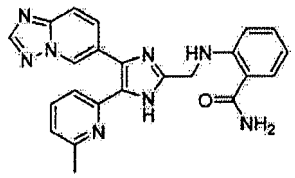
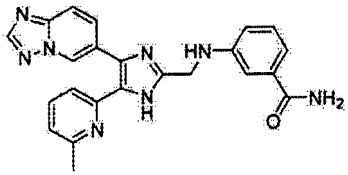
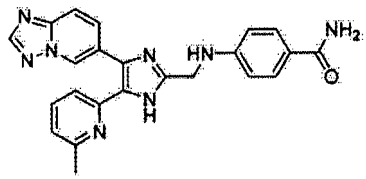
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
63		(400 MHz, $CDCl_3$) δ 8.93 (t, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.79 (dd, 1 H, 重叠, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, 重叠, *J* = 9.2, 0.8 Hz), 7.48 (t, 1 H, *J* = 7.8 Hz), 7.43 (m, 2 H), 7.24 (d, 1H, *J* = 8.0 Hz), 7.03 (d, 1 H, *J* = 7.6 Hz), 6.68 (m, 2 H), 5.12 (br s, 1 H), 4.54 (d, 2 H, *J* = 4.0 Hz), 2.51 (s, 3 H)	407.19
64		(400 MHz, $CDCl_3$) δ 8.99 (br s, 1 H), 8.35 (s, 1 H), 7.84 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.74 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.50 (t, 1 H, *J* = 7.8 Hz), 7.37 (t, 1 H, *J* = 8.2 Hz), 7.27 (br d, 1 H, *J* = 7.6 Hz), 7.05 (d, 1 H, *J* = 8.8 Hz), 7.01 (d, 1 H, 重叠, *J* = 8.0 Hz), 6.98 (d, 1 H, 重叠, *J* = 7.6 Hz), 5.94 (br t, 1 H, *J* = 5.6 Hz), 4.66 (d, 2 H, *J* = 5.6 Hz), 2.30 (s, 3 H)	432.19
65		(400 MHz, $CDCl_3$) δ 9.04 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.48 (br s, 1 H), 8.33 (s, 1 H), 7.84 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.72 (d, 1 H, *J* = 9.2 Hz), 7.41 (t, 1 H, *J* = 7.8 Hz), 7.37 (dd, 1 H, *J* = 7.6, 1.2 Hz), 7.29 (td, 1 H, *J* = 8.4, 1.2 Hz), 7.21 (br d, 1 H, *J* = 8.0 Hz), 6.92 (d, 1 H, *J* = 7.6 Hz), 6.83 (d, 1 H, *J* = 8.4 Hz), 6.62 (td, 1 H, *J* = 8.0, 1.0 Hz), 6.25 (br s, 2 H), 4.59 (d, 2 H, *J* = 5.2 Hz), 2.32 (s, 3 H)	425.20
66		(400 MHz, CD_3OD) δ 9.06 (br s, 1 H), 8.34 (s, 1 H), 7.83 (br d, 1 H, *J* = 9.2 Hz), 7.71 (d, 1 H, *J* = 9.2 Hz), 7.59–7.55 (m, 2 H), 7.22–7.18 (m, 2 H), 7.15 (dt, 1 H, *J* = 7.6, 2.0 Hz), 7.10 (dd, 1 H, *J* = 8.4, 0.8 Hz), 6.86 (ddd, 1 H, *J* = 7.6, 2.0, 0.8 Hz), 4.51 (s, 2 H), 2.50 (s, 3 H)	425.20
67		(400 MHz, $CDCl_3$/CD_3OD) δ 9.03 (br s, 1 H), 8.32 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.70 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.67 (m, 2 H), 7.55 (t, 1 H, *J* = 7.6 Hz), 7.26 (br d, 1 H, *J* = 7.6 Hz), 7.09 (d, 1 H, *J* = 7.6 Hz), 6.71 (m, 2 H), 4.52 (s, 2 H), 2.51 (s, 3 H)	425.20

表 1-续

[0357]

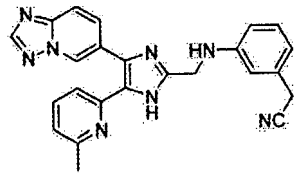
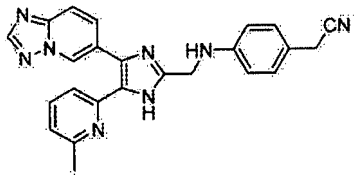
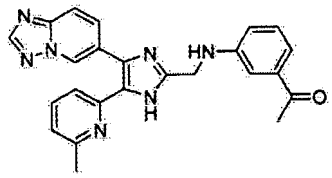
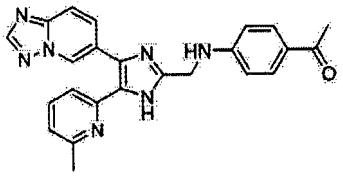
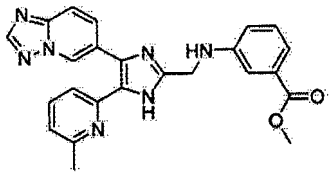
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
68		(400 MHz, $CDCl_3$) δ 10.76 (br s, 1 H), 8.94 (br s, 1 H), 8.37 (s, 1 H), 7.81 (br d, 1 H, *J* = 9.2 Hz), 7.76 (br d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.21 (br d, 1 H, *J* = 7.6 Hz), 7.20–7.15 (m, 1 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.69 (dd, 1 H, *J* = 7.6, 0.8 Hz), 6.62–6.40 (m, 2 H), 4.53 (br s, 1 H, 重叠), 4.52 (br s, 2 H, 重叠), 3.65 (s, 2 H), 2.50 (s, 3 H)	421.21
69		(400 MHz, $CDCl_3$) δ 10.78 (br s, 1 H), 8.94 (br s, 1 H), 8.36 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.76 (d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 7.6 Hz), 7.11 (d, 2 H, *J* = 8.4 Hz), 7.01 (d, 1 H, *J* = 8.0 Hz), 6.67 (d, 2 H, *J* = 8.4 Hz), 4.50 (br s, 3 H), 3.61 (s, 2 H), 2.49 (s, 3 H)	421.21
70		(400 MHz, $CDCl_3$) δ 11.09 (br s, 1 H), 8.92 (s, 1 H), 8.35 (s, 1 H), 7.79 (d, 1 H, *J* = 9.2 Hz), 7.74 (d, 1 H, *J* = 9.2 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.30 (d, 1 H, *J* = 7.6 Hz), 7.26–7.24 (m, 1 H), 7.23 (t, 1 H, 重叠 , *J* = 7.8 Hz), 7.19 (br d, 1 H, *J* = 8.0 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.86 (dd, 1 H, *J* = 8.0, 1.8 Hz), 4.68 (br s, 1 H), 4.52 (d, 2 H, *J* = 5.2 Hz), 2.53 (s, 3 H), 2.47 (s, 3 H)	424.21
71		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, *J* = 1.4 Hz), 8.37 (s, 1 H), 7.81 (d, 2 H, *J* = 8.8 Hz), 7.79–7.76 (m, 2 H), 7.54 (t, 1 H, *J* = 7.8 Hz), 7.30 (d, 1 H, *J* = 8.0 Hz), 7.07 (d, 1 H, *J* = 7.6 Hz), 6.70 (d, 2 H, *J* = 8.8 Hz), 4.63 (s, 2 H), 2.59 (s, 3 H), 2.48 (s, 3 H)	424.21
72		(400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 8.34 (s, 1 H), 7.77 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.72 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.39 (dt, 1 H, *J* = 7.6, 1.2 Hz), 7.32 (dd, 1 H, *J* = 2.4, 1.6 Hz), 7.22 (d, 1 H, 重叠 , *J* = 8.0 Hz), 7.19 (t, 1 H, 重叠 , *J* = 8.0 Hz), 6.98 (d, 1 H, *J* = 7.6 Hz), 6.81 (ddd, 1 H, *J* = 8.0, 2.4, 0.8 Hz), 4.49 (s, 2 H), 3.84 (s, 3 H), 2.43 (s, 3 H)	440.20

表 1-续

[0358]

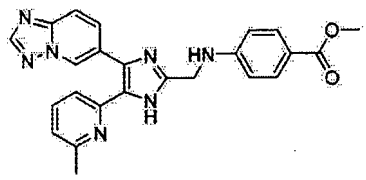
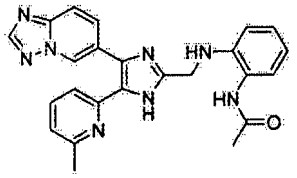
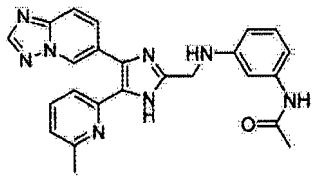
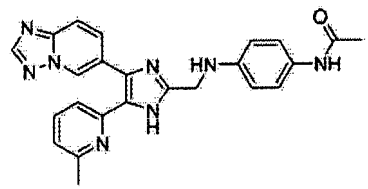
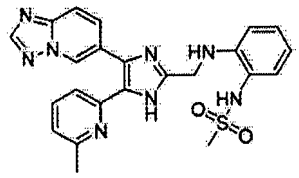
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH$^+$)
73		(400 MHz, $CDCl_3$) δ 10.52 (br s, 1 H), 8.94 (s, 1 H), 8.37 (s, 1 H), 7.89 (m, 2 H), 7.81 (br d, 1 H, *J* = 9.6 Hz), 7.78 (br d, 1 H, *J* = 9.6 Hz), 7.46 (t, 1 H, *J* = 8.0 Hz), 7.21 (d, 1 H, *J* = 8.0 Hz), 7.02 (d, 1 H, *J* = 8.0 Hz), 6.68 (m, 2 H), 4.90 (t, 1 H, *J* = 5.6 Hz), 4.58 (d, 2 H, *J* = 5.6 Hz), 3.85 (s, 3 H), 2.51 (s, 3 H)	440.20
74		(400 MHz, DMSO-d_6) δ 12.56 (br s, 1 H), 9.58 (s, 1 H), 9.36 (s, 1 H), 8.50 (s, 1 H), 8.00 (br d, 1 H, *J* = 9.2 Hz), 7.82 (d, 1 H, *J* = 9.2 Hz), 7.71 (t, 1 H, *J* = 7.8 Hz), 7.44 (br s, 1 H), 7.16 (d, 1 H, 重叠, *J* = 8.0 Hz), 7.15 (d, 1 H, 重叠, *J* = 7.6 Hz), 7.03 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.81 (d, 1 H, *J* = 7.6 Hz), 6.61 (td, 1 H, *J* = 7.6, 1.2 Hz), 5.65 (t, 1 H, *J* = 6.0 Hz), 4.45 (d, 2 H, *J* = 6.0 Hz), 2.47 (br s, 3 H), 2.09 (s, 3 H)	439.22
75		(400 MHz, DMSO-d_6) δ 8.97 (br s, 1 H), 8.35 (s, 1 H), 7.79 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.38 (br s, 1 H), 7.24 (d, 1 H, *J* = 8.0 Hz), 7.15 (br s, 1 H), 7.09 (t, 1 H, *J* = 8.0 Hz), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.69 (br d, 1 H, *J* = 8.0 Hz), 6.41 (dd, 1 H, *J* = 8.0, 1.6 Hz), 4.50 (s, 2 H), 2.51 (s, 3 H), 2.13 (s, 3 H)	439.22
76		(400 MHz, DMSO-d_6) δ 8.96 (br s, 1 H), 8.37 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.27 (m, 2 H), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.10 (br s, 1 H), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.66 (m, 2 H), 4.50 (s, 2 H), 2.53 (s, 3 H), 2.13 (s, 3 H)	439.22
77		(400 MHz, CD_3OD) δ 9.18 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.41 (s, 1 H), 7.87 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.75 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.66 (t, 1 H, *J* = 7.8 Hz), 7.38 (br d, 1 H, *J* = 7.6 Hz), 7.20 (dd, 1 H, *J* = 7.8, 1.4 Hz), 7.16 (d, 1 H, 重叠, *J* = 7.6 Hz), 7.15 (td, 1 H, 重叠, *J* = 8.0, 1.6 Hz), 6.82 (dd, 1 H, *J* = 8.0, 1.2 Hz), 6.71 (td, 1 H, *J* = 8.0, 1.4 Hz), 4.59 (s, 2 H), 3.05 (s, 3 H), 2.48 (s, 3 H)	475.19

表 1-续

[0359]

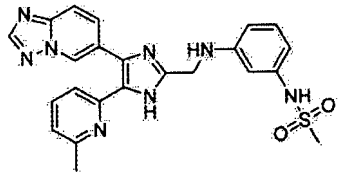
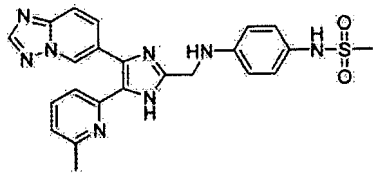
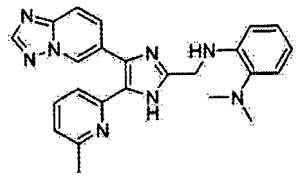
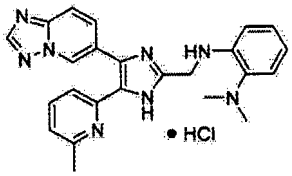
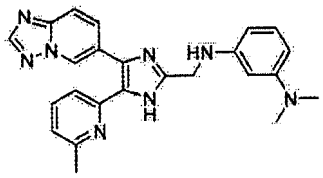
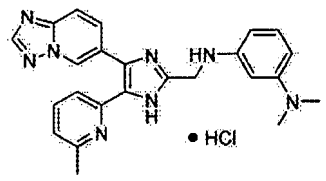
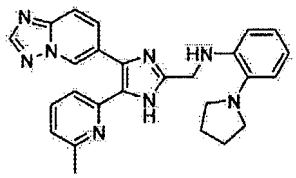
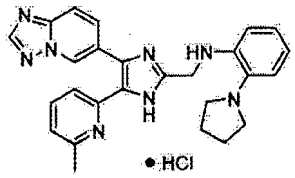
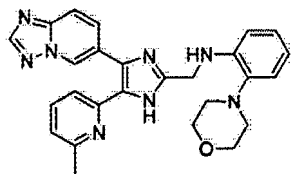
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
78		(400 MHz, $CDCl_3$) δ 8.92 (br s, 1 H), 8.35 (s, 1 H), 7.78 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.21 (br d, 1 H, *J* = 7.6 Hz), 7.11 (t, 1 H, 重叠, *J* = 8.2 Hz), 7.10 (br s, 1 H, 重叠), 7.01 (d, 1 H, *J* = 7.6 Hz), 6.58 (t, 1 H, *J* = 2.0 Hz), 6.54 (ddd, 1 H, *J* = 8.2, 2.0, 0.8 Hz), 6.49 (ddd, 1 H, *J* = 8.2, 2.0, 0.8 Hz), 4.50 (s, 2 H), 2.94 (s, 3 H), 2.51 (s, 3 H)	475.19
79		(400 MHz, $CDCl_3$) δ 8.93 (br s, 1 H), 8.38 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.22 (br d, 1 H, *J* = 8.0 Hz), 7.09 (d, 2 H, *J* = 8.8 Hz), 7.02 (d, 1 H, *J* = 7.6 Hz), 6.67 (d, 2 H, *J* = 8.8 Hz), 6.34 (br s, 1 H), 4.52 (br s, 3 H), 2.93 (s, 3 H), 2.54 (s, 3 H)	475.19
80		(400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.23 (br d, 1 H, *J* = 7.6 Hz), 7.10 (dd, 1 H, *J* = 8.0, 1.2 Hz), 7.02 (td, 1 H, 重叠, *J* = 7.6, 1.2 Hz), 7.00 (d, 1 H, 重叠, *J* = 8.0 Hz), 6.78 (td, 1 H, *J* = 7.6, 1.2 Hz), 6.72 (dd, 1 H, *J* = 8.0, 1.2 Hz), 4.58 (s, 2 H), 2.73 (s, 6 H), 2.50 (s, 3 H)	425.20
81		(400 MHz, DMSO-d_6) δ 9.47 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.87 (t, 1 H, *J* = 7.8 Hz), 7.84 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.59 (br d, 1 H, 重叠, *J* = 8.0 Hz), 7.58 (d, 1 H, *J* = 7.6 Hz), 7.41 (d, 1 H, *J* = 7.6 Hz), 7.29 (t, 1 H, *J* = 7.4 Hz), 6.99 (dd, 1 H, *J* = 7.6, 0.8 Hz), 6.89 (t, 1 H, *J* = 7.4 Hz), 4.81 (s, 2 H), 3.10 (s, 6 H), 2.56 (s, 3 H)	
82		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.36 (s, 1 H), 7.80 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.75 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.23 (d, 1 H, *J* = 8.0 Hz), 7.07 (t, 1 H, *J* = 8.2 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.24 (d, 1 H, *J* = 8.0 Hz), 6.14 (br s, 2 H), 4.55 (s, 2 H), 2.90 (s, 6 H), 2.52 (s, 3 H)	425.21

表 1-续

[0360]

实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
83		(400 MHz, DMSO-d_6) δ 9.48 (dd, 1 H, J = 1.6, 0.8 Hz), 8.64 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.86 (t, 1 H, 重叠, J = 7.8 Hz), 7.85 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.62 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.28 (t, 1 H, J = 8.2 Hz), 7.17 (br s, 1 H), 6.98 (br d, 1 H, J = 8.0 Hz), 6.81 (br d, 1 H, J = 8.4 Hz), 4.78 (s, 2 H), 3.09 (s, 6 H), 2.52 (s, 3 H)	
84		(400 MHz, $CDCl_3$) δ 10.41 (br s, 1 H), 8.99 (s, 1 H), 8.36 (s, 1 H), 7.84 (dd, 1 H, J = 9.2, 1.2 Hz), 7.76 (d, 1 H, J = 9.2 Hz), 7.45 (t, 1 H, J = 7.8 Hz), 7.23 (br s, 1 H), 7.10 (dd, 1 H, J = 7.6, 1.2 Hz), 7.00 (td, 1 H, 重叠, J = 7.6, 1.2 Hz), 6.99 (d, 1 H, 重叠, J = 7.6 Hz), 6.77 (td, 1 H, J = 7.6, 1.2 Hz), 6.72 (d, 1 H, J = 8.0 Hz), 4.58 (s, 2 H), 3.12 (br s, 4 H), 2.51 (s, 3 H), 1.98 (br s, 4 H)	451.22
85		(400 MHz, DMSO-d_6) δ 9.47 (dd, 1 H, J = 2.0, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.87 (t, 1 H, J = 7.8 Hz), 7.84 (dd, 1 H, J = 9.2, 2.0 Hz), 7.60 (d, 1 H, J = 8.0 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.41 (d, 1 H, J = 7.6 Hz), 7.30 (td, 1 H, J = 7.8, 0.8 Hz), 7.02 (dd, 1 H, J = 7.8, 1.2 Hz), 6.88 (td, 1 H, J = 8.0, 1.2 Hz), 4.82 (s, 2 H), 3.72 (br s, 4 H), 2.55 (s, 3 H), 2.17 (m, 4 H)	
86		(400 MHz, $CDCl_3$) δ 8.96 (s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 1.2 Hz), 7.48 (t, 1 H, J = 7.6 Hz), 7.25 (br d, 1 H, J = 7.6 Hz), 7.09 (dd, 1 H, J = 8.0, 1.6 Hz), 7.05 (td, 1 H, 重叠, J = 7.6, 1.6 Hz), 7.02 (d, 1 H, 重叠, J = 7.6 Hz), 6.80 (td, 1 H, J = 7.6, 1.2 Hz), 6.71 (dd, 1 H, J = 8.0, 1.2 Hz), 4.57 (s, 2 H), 3.90 (br t, 4 H, J = 4.6 Hz), 2.96 (br t, 4 H, J = 4.6 Hz), 2.54 (s, 3 H)	467.22
表 1-续			

[0361]

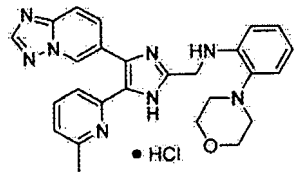
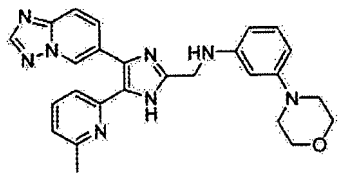
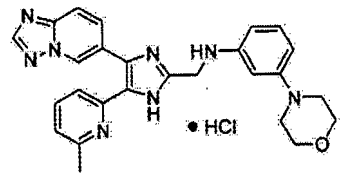
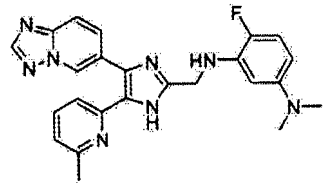
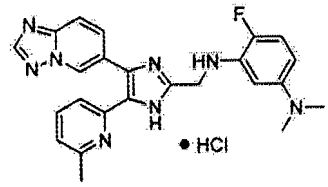
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
87		(400 MHz, DMSO-d_6) δ 9.46 (dd, 1 H, J = 1.6, 0.8 Hz), 8.64 (s, 1 H), 7.98 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.38 (d, 1 H, J = 7.6 Hz), 7.06 (dd, 1 H, J = 7.6, 1.2 Hz), 6.98 (td, 1 H, J = 7.8, 1.2 Hz), 6.82 (dd, 1 H, J = 7.8, 1.2 Hz), 6.70 (td, 1 H, J = 7.6, 1.2 Hz), 4.80 (s, 2 H), 3.84 (br t, 4 H, J = 4.4 Hz), 2.89 (br t, 4 H, J = 4.4 Hz), 2.53 (s, 3 H)	
88		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, J = 1.2 Hz), 8.37 (s, 1 H), 7.82–7.76 (m, 2 H), 7.48 (t, 1 H, J = 7.6 Hz), 7.24 (br d, 1 H, J = 7.6 Hz), 7.12 (t, 1 H, J = 8.0 Hz), 7.03 (d, 1 H, J = 7.6 Hz), 6.39 (dd, 1 H, J = 8.0, 1.6 Hz), 6.34 (t, 1 H, J = 2.0 Hz), 6.29 (dd, 1 H, J = 8.0, 2.0 Hz), 4.56 (s, 2 H), 3.85–3.82 (m, 4 H), 3.15–3.12 (m, 4 H), 2.56 (s, 3 H)	467.23
89		(400 MHz, DMSO-d_6) δ 9.47 (dd, 1 H, J = 1.6, 0.8 Hz), 8.64 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, J = 8.0 Hz), 7.84 (dd, 1 H, J = 9.2, 1.6 Hz), 7.60 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 8.0 Hz), 7.17 (t, 1 H, J = 8.0 Hz), 6.86 (br s, 1 H), 6.76 (br s, 1 H), 6.59 (br d, 1 H, J = 7.6 Hz), 4.76 (s, 2 H), 3.92 (br s, 4 H), 3.34 (br s, 4 H), 2.52 (s, 3 H)	
90		(400 MHz, $CDCl_3$) δ 8.95 (t, 1 H, J = 1.2 Hz), 8.35 (s, 1 H), 7.78 (dd, 1 H, J = 9.2, 1.6 Hz), 7.70 (dd, 1 H, J = 9.2, 1.2 Hz), 7.43 (t, 1 H, J = 7.8 Hz), 7.21 (d, 1 H, J = 8.0 Hz), 6.94 (d, 1 H, J = 7.6 Hz), 6.80–6.73 (m, 1 H), 6.14 (br d, 1 H, J = 7.6 Hz), 6.00–5.95 (m, 1 H), 4.49 (s, 2 H), 2.79 (s, 6 H), 2.31 (s, 3 H)	443.21
91		(400 MHz, DMSO-d_6) δ 9.49 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.84 (t, 1 H, 重叠, J = 8.0 Hz), 7.60 (d, 1 H, J = 8.0 Hz), 7.39 (br s, 1 H, 重叠), 7.38 (d, 1 H, 重叠, J = 8.0 Hz), 7.24 (假三重峰, 1 H, J = 9.8 Hz), 6.97 (br s, 1 H), 4.86 (s, 2 H), 3.10 (s, 6 H), 2.52 (s, 3 H)	

表 1-续

[0362]

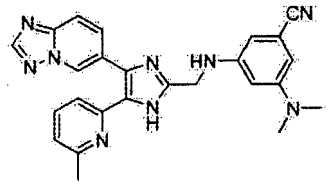
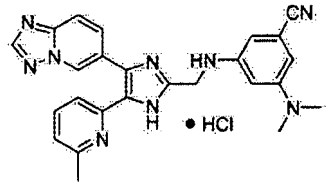
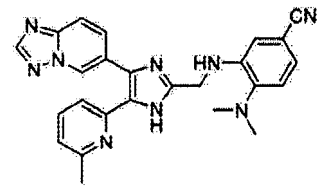
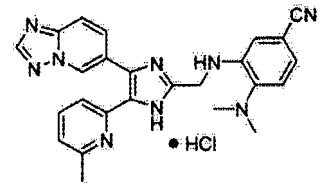
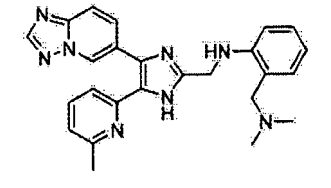
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
92		(400 MHz, $CDCl_3$) δ 8.94 (t, 1 H, J = 1.2 Hz), 8.38 (s, 1 H), 7.80 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, 重叠, J = 9.2, 1.2 Hz), 7.49 (t, 1 H, J = 7.6 Hz), 7.25 (d, 1 H, J = 7.6 Hz), 7.04 (d, 1 H, J = 7.6 Hz), 6.38 (dd, 1 H, J = 2.4, 1.2 Hz), 6.30 (t, 1 H, J = 1.6 Hz), 6.18 (t, 1 H, J = 2.2 Hz), 4.53 (s, 2 H), 2.92 (s, 6 H), 2.56 (s, 3 H)	450.21
93		(400 MHz, DMSO-d_6) δ 9.44 (dd, 1 H, J = 2.0, 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, J = 7.8 Hz), 7.81 (dd, 1 H, J = 9.2, 2.0 Hz), 7.55 (d, 1 H, J = 8.0 Hz), 7.40 (d, 1 H, J = 7.6 Hz), 6.47 (s, 2 H), 6.37 (br s, 1 H), 4.73 (s, 2 H), 2.90 (s, 6 H), 2.55 (s, 3 H)	
94		(400 MHz, $CDCl_3$) δ 8.96 (t, 1 H, J = 1.6 Hz), 8.38 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.79 (dd, 1 H, J = 9.2, 0.8 Hz), 7.53 (t, 1 H, J = 7.8 Hz), 7.31 (d, 1 H, J = 8.0 Hz), 7.08–7.03 (m, 3 H), 6.87 (d, 1 H, J = 1.6 Hz), 5.44 (br s, 1 H), 4.55 (s, 2 H), 2.74 (s, 6 H), 2.58 (s, 3 H)	450.21
95		(400 MHz, DMSO-d_6) δ 9.44 (dd, 1 H, J = 1.6, 0.8 Hz), 8.64 (s, 1 H), 7.99 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, 重叠, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.2, 0.8 Hz), 7.51 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.15 (dd, 2 H, 重叠, J = 7.6, 0.8 Hz), 7.14 (d, 1 H, 重叠, J = 1.2 Hz), 4.79 (s, 2 H), 2.71 (s, 6 H), 2.56 (s, 3 H)	
96		(400 MHz, $CDCl_3$) δ 10.57 (br s, 1 H), 8.97 (s, 1 H), 8.34 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.2 Hz), 7.74 (d, 1 H, J = 9.2 Hz), 7.43 (t, 1 H, J = 7.8 Hz), 7.21 (br s, 1 H, 重叠), 7.17 (td, 1 H, J = 8.0, 1.6 Hz), 7.01 (dd, 1 H, J = 7.6, 1.6 Hz), 6.98 (d, 1 H, J = 7.6 Hz), 6.72–6.66 (m, 2 H), 4.61 (s, 2 H), 3.54 (s, 2 H), 2.51 (s, 3 H), 2.28 (s, 6 H)	439.23

表 1-续

[0363]

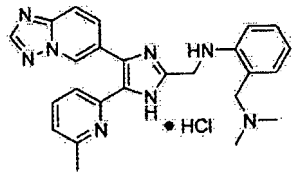
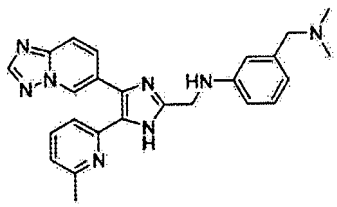
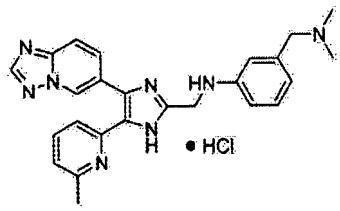
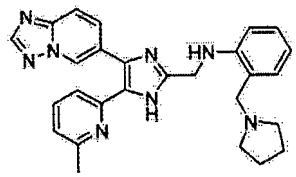
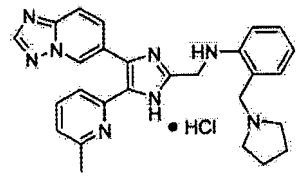
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
97		(400 MHz, DMSO-d_6) δ 10.03 (br s, 1 H), 9.48 (dd, 1 H, J = 1.6, 0.8 Hz), 8.62 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.8 Hz), 7.87–7.82 (m, 2 H), 7.64 (d, 1 H, J = 7.6 Hz), 7.38 (d, 1 H, J = 7.6 Hz), 7.33–7.27 (m, 2 H), 6.95 (br s, 1 H), 6.78–6.74 (m, 2 H), 4.81 (s, 2 H), 4.43 (s, 2 H), 2.77 (s, 6 H), 2.52 (s, 3 H)	
98		(400 MHz, $CDCl_3$) δ 9.02 (br s, 1 H), 8.35 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.74 (dd, 1 H, J = 9.2, 0.8 Hz), 7.46 (t, 1 H, J = 7.6 Hz), 7.27 (br d, 1 H, J = 7.6 Hz), 7.13 (t, 1 H, J = 7.8 Hz), 7.00 (d, 1 H, J = 7.6 Hz), 6.90 (br s, 1 H), 6.67 (d, 1 H, J = 7.6 Hz), 6.61 (dd, 1 H, J = 8.0, 2.0 Hz), 4.54 (s, 2 H), 3.48 (s, 2 H), 2.51 (s, 3 H), 2.30 (s, 6 H)	439.23
99		(400 MHz, DMSO-d_6) δ 10.69 (br s, 1 H), 9.48 (dd, 1 H, J = 1.6, 0.8 Hz), 8.63 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, J = 8.0 Hz), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.61 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.21 (t, 1 H, J = 8.2 Hz), 7.09 (br s, 1 H), 6.85 (dd, 1 H, 重叠, J = 8.4, 2.2 Hz), 6.82 (d, 1 H, J = 8.0 Hz), 4.76 (s, 2 H), 4.16 (d, 1 H, J = 4.8 Hz), 2.66 (d, 6 H, J = 4.4 Hz), 2.51 (s, 3 H)	
100		(400 MHz, $CDCl_3$) δ 10.40 (br s, 1 H), 8.98 (s, 1 H), 8.35 (s, 1 H), 7.83 (d, 1 H, J = 9.2 Hz), 7.75 (d, 1 H, J = 9.2 Hz), 7.43 (t, 1 H, J = 7.6 Hz), 7.20 (br s, 1 H, 重叠), 7.15 (td, 1 H, J = 8.0, 1.6 Hz), 7.04 (d, 1 H, J = 8.0 Hz), 6.98 (d, 1 H, J = 7.6 Hz), 6.69 (假三重峰, 2 H, J = 7.2 Hz), 4.58 (s, 2 H), 3.72 (s, 2 H), 2.56 (br s, 4 H), 2.50 (s, 3 H), 1.80 (br s, 4 H)	465.25
101		(400 MHz, DMSO-d_6) δ 10.29 (br s, 1 H), 9.47 (t, 1 H, J = 0.8 Hz), 8.62 (s, 1 H), 7.95 (d, 1 H, J = 9.2 Hz), 7.87–7.83 (m, 2 H), 7.65 (d, 1 H, J = 8.0 Hz), 7.38 (br d, 2 H, J = 7.6 Hz), 7.27 (td, 1 H, J = 8.0, 1.2 Hz), 6.75 (t, 1 H, 重叠, J = 7.6 Hz), 6.72 (d, 1 H, 重叠, J = 7.6 Hz), 4.82 (s, 2 H), 4.47 (s, 2 H), 3.44 (br s, 2 H), 3.17 (br s, 2 H), 2.52 (s, 3 H), 2.04 (br s, 2 H), 1.94 (br s, 2 H)	

表 1-续

[0364]

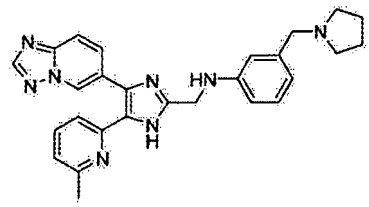
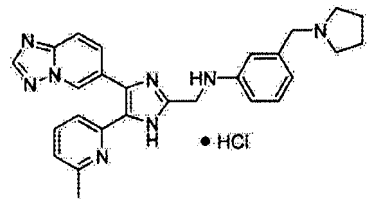
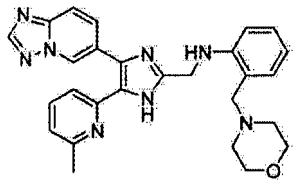
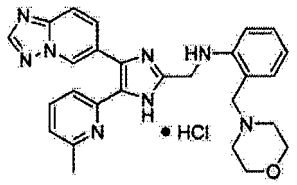
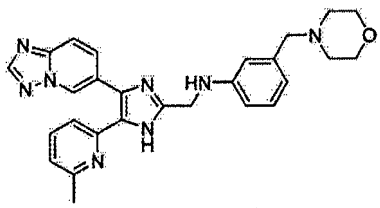
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
102		(400 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 8.35 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.73 (d, 1 H, *J* = 9.2 Hz), 7.47 (t, 1 H, *J* = 7.8 Hz), 7.28 (br d, 1 H, *J* = 7.6 Hz), 7.11 (t, 1 H, *J* = 7.8 Hz), 7.00 (d, 1 H, *J* = 8.0 Hz), 6.95 (br s, 1 H), 6.68 (d, 1 H, *J* = 7.6 Hz), 6.60 (dd, 1 H, *J* = 8.0, 2.0 Hz), 4.54 (s, 2 H), 3.65 (s, 2 H), 2.61 (br s, 4 H), 2.51 (s, 3 H), 1.78–1.75 (m, 4 H)	465.25
103		(400 MHz, DMSO-d_6) δ 10.93 (br s, 1 H), 9.48 (dd, 1 H, *J* = 1.2, 1.6 Hz), 8.63 (s, 1 H), 7.96 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.86–7.81 (m, 2 H), 7.61 (d, 1 H, *J* = 8.0 Hz), 7.37 (d, 1 H, *J* = 7.6 Hz), 7.19 (t, 1 H, *J* = 7.8 Hz), 7.15 (br s, 1 H), 6.86–6.81 (m, 2 H), 4.76 (s, 2 H), 4.22 (d, 2 H, *J* = 5.6 Hz), 3.29 (m, 2 H), 3.00 (m, 2 H), 2.51 (s, 3 H), 1.92 (m, 2 H), 1.82 (m, 2 H)	
104		(400 MHz, $CDCl_3$) δ 10.35 (br s, 1 H), 8.97 (s, 1 H), 8.36 (s, 1 H), 7.83 (d, 1 H, *J* = 9.2 Hz), 7.76 (d, 1 H, *J* = 9.2 Hz), 7.44 (t, 1 H, *J* = 7.6 Hz), 7.21 (br s, 1 H, 重叠), 7.19 (td, 1 H, *J* = 7.6, 1.6 Hz), 7.04 (dd, 1 H, *J* = 7.6, 1.6 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 6.73–6.68 (m, 2 H), 4.57 (s, 2 H), 3.71 (br s, 4 H), 3.63 (s, 2 H), 2.50 (br s, 7 H)	481.25
105		(400 MHz, DMSO-d_6) δ 9.46 (s, 1 H), 8.62 (s, 1 H), 7.96 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.85 (t, 1 H, 重叠 , *J* = 8.0 Hz), 7.83 (dd, 1 H, 重叠 , *J* = 9.2, 1.6 Hz), 7.60 (d, 1 H, *J* = 8.0 Hz), 7.38 (br d, 2 H, *J* = 8.0 Hz), 7.29 (td, 1 H, *J* = 8.0, 1.2 Hz), 6.75 (t, 1 H, 重叠 , *J* = 8.0 Hz), 6.74 (d, 1 H, 重叠 , *J* = 8.0 Hz), 4.82 (s, 2 H), 4.45 (s, 2 H), 3.93 (br s, 4 H), 3.34 (br s, 4 H), 2.53 (s, 3 H)	
106		(400 MHz, $CDCl_3$) δ 10.78 (br s, 1 H), 8.97 (s, 1 H), 8.35 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.74 (d, 1 H, *J* = 9.2 Hz), 7.45 (t, 1 H, *J* = 7.8 Hz), 7.23 (br s, 1 H), 7.13 (t, 1 H, *J* = 7.8 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.79 (br s, 1 H), 6.71 (d, 1 H, *J* = 7.6 Hz), 6.59 (dd, 1 H, *J* = 8.0, 1.6 Hz), 4.53 (s, 2 H), 4.44 (br s, 1 H), 3.66 (m, 4 H), 3.45 (s, 2 H), 2.49 (s, 3 H), 2.44 (br s, 4 H)	481.25

表 1-续

[0365]

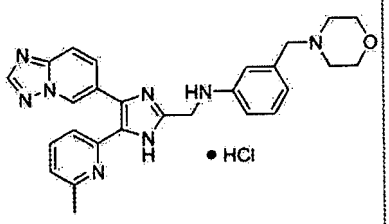
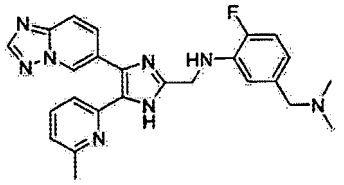
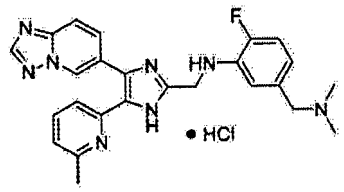
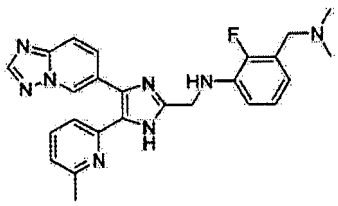
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
107		(400 MHz, DMSO-d_6/D_2O) δ 9.36 (dd, 1 H, J = 1.8, 1.0 Hz), 8.62 (s, 1 H), 7.95 (dd, 1 H, J = 9.4, 1.0 Hz), 7.87 (t, 1 H, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.4, 1.8 Hz), 7.48 (d, 1 H, J = 8.0 Hz), 7.42 (d, 1 H, J = 7.6 Hz), 7.28 (t, 1 H, J = 7.8 Hz), 6.90 (br s, 1 H), 6.86–6.82 (m, 2 H), 4.68 (s, 2 H Hz), 4.23 (s, 2 H), 3.70 (br s, 4 H), 3.22 (br s, 2 H), 3.14 (br s, 2 H), 2.58 (s, 3 H)	
108		(400 MHz, $CDCl_3$) δ 9.06 (s, 1 H), 8.34 (s, 1 H), 7.84 (dd, 1 H, J = 9.2, 1.6 Hz), 7.72 (d, 1 H, J = 9.2 Hz), 7.48 (t, 1 H, J = 7.6 Hz), 7.32 (br s, 1 H), 7.18 (br s, 1 H), 7.00 (d, 1 H, J = 7.6 Hz), 6.90 (dd, 1 H, J = 11.2, 8.0 Hz), 6.55–6.51 (m, 1 H), 4.78 (br s, 1 H), 4.59 (d, 2 H, J = 6.4 Hz), 3.54 (s, 2 H), 2.50 (s, 3 H), 2.34 (s, 6 H)	457.22
109		(400 MHz, DMSO-d_6) δ 10.73 (br s, 1 H), 9.46 (t, 1 H, J = 1.2 Hz), 8.62 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.82 (t, 1 H, 重叠, J = 7.8 Hz), 7.55 (d, 1 H, J = 8.0 Hz), 7.37 (dd, 1 H, 重叠, J = 8.2, 2.0 Hz), 7.36 (d, 1 H, J = 7.6 Hz), 7.18 (dd, 1 H, J = 11.8, 8.2 Hz), 6.82–6.78 (m, 1 H), 4.79 (s, 2 H), 4.17 (br s, 2 H), 2.64 (d, 6 H, J = 1.6 Hz), 2.52 (s, 3 H)	
110		(400 MHz, $CDCl_3$) δ 8.99 (br s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.76 (d, 1 H, J = 9.2 Hz), 7.46 (t, 1 H, J = 7.8 Hz), 7.24 (br s, 1 H), 6.99 (d, 1 H, 重叠, J = 8.0 Hz), 6.95 (t, 1 H, 重叠, J = 8.0 Hz), 6.76–6.70 (m, 2 H), 4.73 (br s, 1 H), 4.56 (d, 2 H, J = 5.6 Hz), 3.60 (s, 2 H), 2.50 (s, 3 H), 2.36 (s, 6 H)	457.23

表 1-续

[0366]

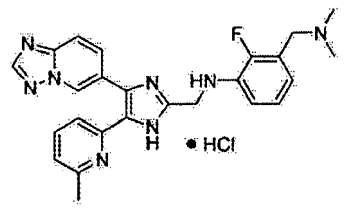
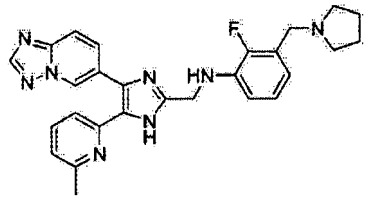
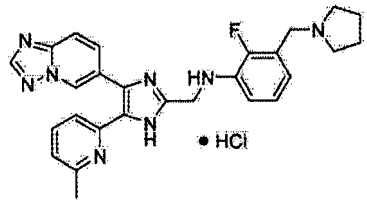
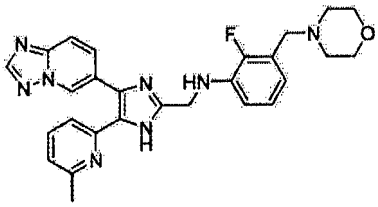
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH$^+$)
111		(400 MHz, DMSO-d_6) δ 10.62 (br s, 1 H), 9.46 (s, 1 H), 8.62 (s, 1 H), 7.96 (d, 1 H, J = 9.2 Hz), 7.84 (t, 1 H, 重叠, J = 8.0 Hz), 7.83 (d, 1 H, 重叠, J = 9.2 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.10 (t, 1 H, J = 7.6 Hz), 7.02 (t, 1 H, J = 7.6 Hz), 6.93 (假三重峰, 1 H, J = 6.6 Hz), 4.78 (s, 2 H), 4.30 (d, 2 H, J = 4.8 Hz), 2.72 (d, 6 H, J = 4.4 Hz), 2.53 (s, 3 H)	
112		(400 MHz, $CDCl_3$) δ 11.11 (br s, 1 H), 8.98 (s, 1 H), 8.35 (s, 1 H), 7.81 (dd, 1 H, J = 9.2, 1.6 Hz), 7.73 (d, 1 H, J = 9.2 Hz), 7.44 (t, 1 H, J = 7.8 Hz), 7.23 (br s, 1 H), 6.97 (d, 1 H, J = 8.0 Hz), 6.91 (t, 1 H, J = 8.0 Hz), 6.75 (td, 1 H, J = 8.0, 1.2 Hz), 6.65 (td, 1 H, J = 8.0, 1.2 Hz), 4.66 (br s, 1 H), 4.51 (d, 2 H, J = 5.6 Hz), 3.66 (s, 2 H), 2.59 (br s, 4 H), 2.42 (s, 3 H), 1.81–1.75 (m, 4 H)	483.24
113		(400 MHz, DMSO-d_6) δ 10.84 (br s, 1 H), 9.46 (s, 1 H), 8.62 (s, 1 H), 7.95 (d, 1 H, J = 9.2 Hz), 7.84 (t, 1 H, J = 7.8 Hz), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.36 (d, 1 H, J = 7.6 Hz), 7.08 (t, 1 H, J = 7.8 Hz), 7.03–6.96 (m, 2 H), 4.77 (s, 2 H), 4.36 (d, 2 H, J = 5.2 Hz), 3.39 (m, 2 H), 3.07 (m, 2 H), 2.53 (s, 3 H), 2.03–1.87 (m, 4 H)	
114		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.36 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 2.0 Hz), 7.76 (dd, 1 H, J = 9.2, 0.8 Hz), 7.46 (t, 1 H, J = 7.6 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.00 (d, 1 H, J = 7.6 Hz), 6.95 (t, 1 H, J = 8.0 Hz), 6.76 (t, 1 H, J = 7.6 Hz), 6.70 (td, 1 H, J = 8.0, 1.6 Hz), 4.67 (br s, 1 H), 4.54 (d, 2 H, J = 4.8 Hz), 3.73 (m, 4 H), 3.59 (s, 2 H), 2.53 (br s, 4 H), 2.47 (s, 3 H)	499.24

表 1-续

[0367]

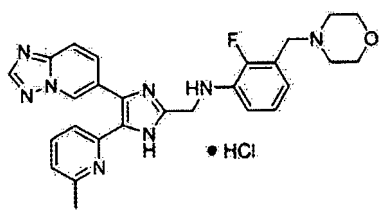
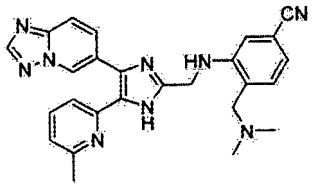
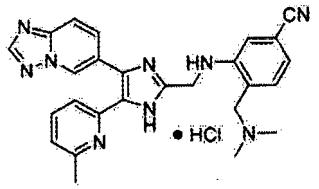
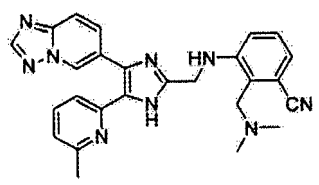
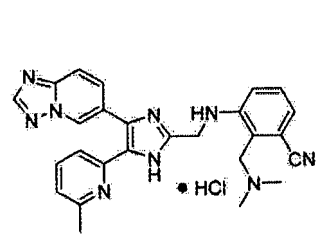
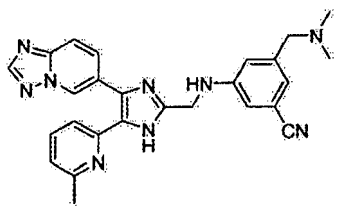
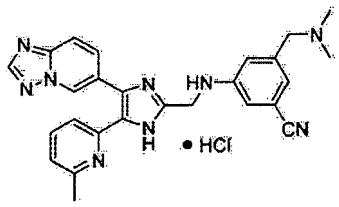
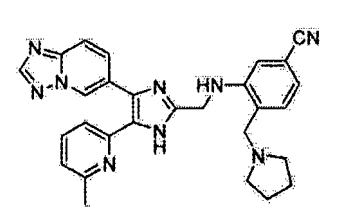
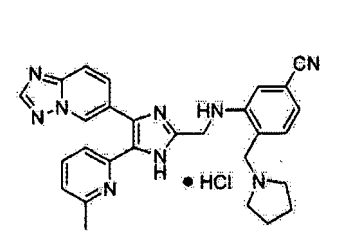
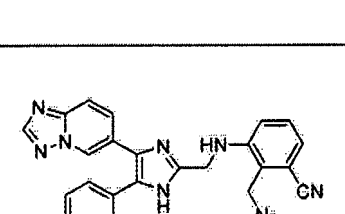
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
115		(400 MHz, DMSO-d_6) δ 11.18 (br s, 1 H), 9.46 (dd, 1 H, J = 1.6, 1.2 Hz), 8.62 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (t, 1 H, 重叠, J = 7.8 Hz), 7.83 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.57 (d, 1 H, J = 7.6 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.10 (t, 1 H, J = 7.8 Hz), 7.05–6.99 (m, 2 H), 4.78 (s, 2 H), 4.34 (s, 2 H), 3.93 (br s, 2 H), 3.81 (br t, 2 H, J = 11.6 Hz) 3.29 (br s, 2 H), 3.13 (br s, 2 H), 2.53 (s, 3 H)	
116		(400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.36 (s, 1 H), 7.86 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.47 (t, 1 H, J = 7.6 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.09 (d, 1 H, J = 7.6 Hz), 7.01 (d, 1 H, J = 7.6 Hz), 6.98 (dd, 1 H, J = 7.6, 1.6 Hz), 6.93 (br s, 1 H), 4.59 (s, 2 H), 3.63 (s, 2 H), 2.53 (s, 3 H), 2.33 (s, 6 H)	464.23
117		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.60 (s, 1 H), 7.94 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, 重叠, J = 7.6 Hz), 7.84 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.57 (d, 1 H, J = 7.6 Hz), 7.52 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.30 (br s, 1 H), 7.19–7.17 (m, 2 H), 4.79 (s, 2 H), 4.48 (s, 2 H), 2.78 (s, 6 H), 2.55 (s, 3 H)	
118		(400 MHz, DMSO-d_6) δ 12.70 (br s, 1 H), 9.54 (s, 1 H), 8.50 (s, 1 H), 7.99 (dd, 1 H, J = 9.2, 2.0 Hz), 7.83 (dd, 1 H, J = 9.2, 0.8 Hz), 7.72 (t, 1 H, J = 7.8 Hz), 7.52 (br s, 1 H), 7.32 (t, 1 H, J = 7.6 Hz), 7.17–7.13 (m, 2 H), 7.07 (d, 1 H, J = 8.0 Hz), 7.02 (dd, 1 H, J = 7.6, 0.8 Hz), 4.48 (d, 2 H, J = 5.6 Hz), 3.68 (s, 2 H), 2.47 (s, 3 H), 2.23 (s, 6 H)	464.23
119		(400 MHz, DMSO-d_6) δ 9.48 (t, 1 H, J = 1.2 Hz), 8.60 (s, 1 H), 7.92 (dd, 1 H, J = 9.2, 1.2 Hz), 7.86 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.85 (t, 1 H, 重叠, J = 8.0 Hz), 7.64 (d, 1 H, J = 8.0 Hz), 7.49 (t, 1 H, J = 7.8 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.24 (dd, 1 H, J = 7.6, 0.8 Hz), 7.10 (dd, 1 H, J = 8.0, 0.8 Hz), 4.81 (s, 2 H), 4.61 (s, 2 H), 2.89 (s, 6 H), 2.52 (s, 3 H)	

表 1-续

[0368]

实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
120		(400 MHz, $CDCl_3$) δ 9.01 (s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.76 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.49 (t, 1 H, *J* = 7.6 Hz), 7.28 (br d, 1 H, *J* = 7.6 Hz), 7.15 (br s, 1 H), 7.03 (d, 1 H, *J* = 7.6 Hz), 6.94 (s, 1 H), 6.82 (dd, 1 H, *J* = 2.0, 1.2 Hz), 4.86 (br s, 1 H), 4.55 (d, 2 H, *J* = 5.6 Hz), 3.48 (s, 2 H), 2.54 (s, 3 H), 2.32 (s, 6 H)	464.23
121		(400 MHz, DMSO-d_6) δ 10.77 (br s, 1 H), 9.46 (dd, 1 H, *J* = 1.6, 0.8 Hz), 8.60 (s, 1 H), 7.94 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.85 (dd, 1 H, 重叠, *J* = 9.2, 1.6 Hz), 7.84 (t, 1 H, 重叠, *J* = 7.8 Hz), 7.55 (d, 1 H, *J* = 7.6 Hz), 7.36 (d, 1 H, 重叠, *J* = 8.0 Hz), 7.35 (s, 1 H, 重叠), 7.23 (br s, 2 H), 4.71 (s, 2 H), 4.22 (s, 2 H), 2.67 (s, 6 H), 2.53 (s, 3 H)	
122		(400 MHz, $CDCl_3$) δ 10.40 (br s, 1 H), 8.96 (s, 1 H), 8.36 (s, 1 H), 7.84 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (d, 1 H, *J* = 9.2 Hz), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.24 (br d, 1 H, *J* = 7.6 Hz), 7.09 (d, 1 H, *J* = 7.6 Hz), 7.00 (d, 1 H, *J* = 7.6 Hz), 6.96 (dd, 1 H, *J* = 7.6, 1.6 Hz), 6.86 (br s, 1 H), 4.55 (s, 2 H), 3.74 (s, 2 H), 2.54 (br s, 4 H), 2.51 (s, 3 H), 1.81 (br s, 4 H)	490.25
123		(400 MHz, DMSO-d_6) δ 10.47 (br s, 2 H), 9.46 (s, 1 H), 8.61 (s, 1 H), 7.95 (dd, 1 H, *J* = 9.2, 0.4 Hz), 7.86 (t, 1 H, 重叠, *J* = 7.6 Hz), 7.85 (dd, 1 H, 重叠, *J* = 9.2, 1.2 Hz), 7.60 (d, 1 H, *J* = 7.6 Hz), 7.59 (d, 1 H, *J* = 8.0 Hz), 7.39 (d, 1 H, *J* = 7.6 Hz), 7.32 (br s, 1 H), 7.18 (dd, 1 H, *J* = 7.6, 1.6 Hz), 7.14 (d, 1 H, *J* = 1.6 Hz), 4.82 (s, 2 H), 4.53 (s, 2 H), 3.23 (br s, 4 H), 2.55 (s, 3 H), 1.99 (br s, 4 H)	
124		(400 MHz, DMSO-d_6) δ 12.71 (br s, 1 H), 9.52 (s, 1 H), 8.50 (s, 1 H), 7.98 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.83 (d, 1 H, *J* = 9.2 Hz), 7.71 (t, 1 H, *J* = 7.8 Hz), 7.51 (br s, 1 H), 7.37 (t, 1 H, *J* = 5.2 Hz), 7.31 (t, 1 H, *J* = 8.0 Hz), 7.16 (d, 1 H, *J* = 7.6 Hz), 7.05 (d, 1 H, *J* = 8.0 Hz), 7.00 (dd, 1 H, *J* = 8.0, 1.2 Hz), 4.47 (d, 2 H, *J* = 5.2 Hz), 3.87 (s, 2 H), 2.51 (br s, 4 H), 2.47 (s, 3 H), 1.74 (br s, 4 H)	490.25
表 1-续			

[0369]

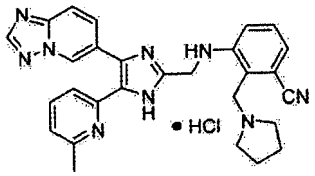
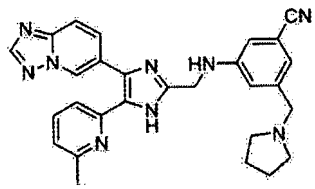
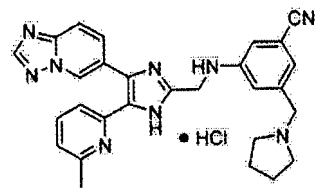
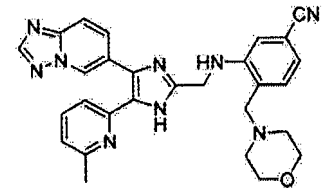
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
125		(400 MHz, DMSO-d_6/D_2O) δ 9.41 (dd, 1 H, J = 1.6, 0.8 Hz), 8.61 (s, 1 H), 7.94 (dd, 1 H, J = 9.2, 0.8 Hz), 7.89 (t, 1 H, J = 7.8 Hz), 7.84 (dd, 1 H, J = 9.2, 1.6 Hz), 7.55 (d, 1 H, J = 8.0 Hz), 7.50 (t, 1 H, J = 7.6 Hz), 7.42 (d, 1 H, J = 7.6 Hz), 7.25 (dd, 1 H, J = 7.6, 0.8 Hz), 7.09 (d, 1 H, J = 7.6 Hz), 4.78 (s, 2 H), 4.64 (s, 2 H), 3.45 (br s, 4 H), 2.58 (s, 3 H), 2.06 (br s, 4 H)	
126		(400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 8.36 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.77 (d, 1 H, J = 9.2 Hz), 7.48 (t, 1 H, J = 7.6 Hz), 7.27 (br d, 1 H, J = 7.6 Hz), 7.13 (br s, 1 H), 7.03 (d, 1 H, J = 7.6 Hz), 6.97 (br s, 1 H), 6.81 (dd, 1 H, J = 2.4, 1.2 Hz), 4.81 (br s, 1 H), 4.54 (d, 2 H, J = 5.6 Hz), 3.62 (s, 2 H), 2.57 (br s, 4 H), 2.54 (s, 3 H), 1.79 (br s, 4 H)	490.25
127		(400 MHz, DMSO-d_6) δ 10.96 (br s 1 H), 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.60 (s, 1 H), 7.94 (dd, 1 H, J = 9.2, 0.8 Hz), 7.84 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.83 (t, 1 H, 重叠, J = 7.8 Hz), 7.54 (d, 1 H, J = 8.0 Hz), 7.39 (br s, 1 H), 7.36 (d, 1 H, J = 7.6 Hz), 7.26 (s, 1 H), 7.21 (dd, 1 H, J = 2.0, 1.6 Hz), 4.72 (s, 2 H), 4.29 (s, 2 H), 3.02 (br s, 4 H), 2.53 (s, 3 H), 1.95 (br s, 2 H), 1.84 (br s, 2 H)	
128		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.37 (s, 1 H), 7.84 (dd, 1 H, J = 9.2, 1.6 Hz), 7.79 (dd, 1 H, J = 9.2, 1.2 Hz), 7.49 (t, 1 H, J = 7.8 Hz), 7.29 (br d, 1 H, J = 8.0 Hz), 7.12 (d, 1 H, J = 7.6 Hz), 7.03 (d, 1 H, J = 7.6 Hz), 6.99 (dd, 1 H, J = 7.6, 1.6 Hz), 6.93 (br s, 1 H), 4.57 (s, 2 H), 3.75 (br s, 4 H, 重叠), 3.72 (s, 2 H, 重叠), 2.55 (br s, 7 H)	506.25

表 1-续

[0370]

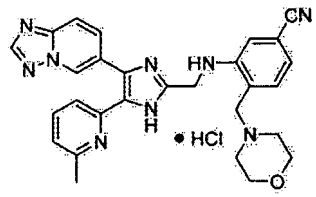
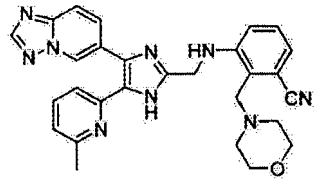
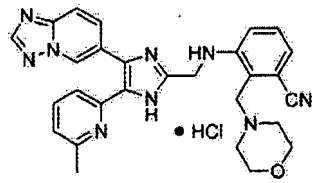
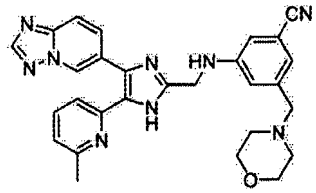
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
129		(400 MHz, DMSO-d_6) δ 9.45 (d, 1 H, J = 0.4 Hz), 8.61 (s, 1 H), 7.96 (d, 1 H, J = 9.2 Hz), 7.86 (t, 1 H, 重叠, J = 8.0 Hz), 7.85 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.60 (d, 1 H, J = 8.0 Hz), 7.57 (d, 1 H, J = 8.0 Hz), 7.39 (d, 1 H, J = 8.0 Hz), 7.19 (s, 1 H), 7.17 (dd, 1 H, 重叠, J = 8.0, 1.2 Hz), 4.82 (s, 2 H), 4.52 (s, 2 H), 3.91 (br s, 4 H), 3.32 (br s, 4 H), 2.55 (s, 3 H)	
130		(400 MHz, DMSO-d_6) δ 12.70 (br s, 1 H), 9.48 (br s, 1 H), 8.50 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 1.6 Hz), 7.84 (d, 1 H, J = 9.2 Hz), 7.71 (t, 1 H, J = 7.6 Hz), 7.44 (br s, 1 H), 7.34 (t, 1 H, J = 8.0 Hz), 7.28 (t, 1 H, J = 5.6 Hz), 7.16 (d, 1 H, J = 7.6 Hz), 7.07 (d, 1 H, J = 8.4 Hz), 7.03 (dd, 1 H, J = 7.6, 1.2 Hz), 4.49 (d, 2 H, J = 5.6 Hz), 3.76 (s, 2 H), 3.58 (m, 4 H), 2.48 (s, 3 H), 2.41 (br s, 4 H)	506.24
131		(400 MHz, DMSO-d_6) δ 9.46 (d, 1 H, J = 0.8 Hz), 8.60 (s, 1 H), 7.94 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, 重叠, J = 7.6 Hz), 7.84 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.60 (d, 1 H, J = 7.6 Hz), 7.47 (t, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.22 (dd, 1 H, J = 7.6, 0.8 Hz), 7.08 (d, 1 H, J = 8.0 Hz), 4.82 (s, 2 H), 4.57 (s, 2 H), 3.95 (br t, 4 H, J = 4.4 Hz), 3.40 (br s, 4 H), 2.53 (s, 3 H)	
132		(400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.38 (s, 1 H), 7.82 (dd, 1 H, J = 9.2, 1.6 Hz), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.48 (t, 1 H, J = 7.6 Hz), 7.28 (br d, 1 H, J = 7.6 Hz), 7.06 (br s, 1 H, + 重叠), 7.04 (d, 1 H, J = 7.6 Hz), 7.01 (s, 1 H), 6.84 (dd, 1 H, J = 2.0, 1.2 Hz), 4.79 (br s, 1 H), 4.54 (d, 2 H, J = 7.6 Hz), 3.70 (m, 4 H), 3.48 (s, 2 H), 2.55 (s, 3 H), 2.47 (br s, 4 H)	506.24

表 1-续

[0371]

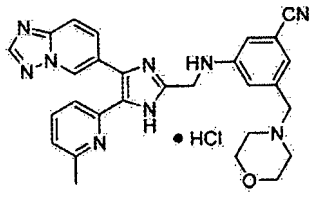
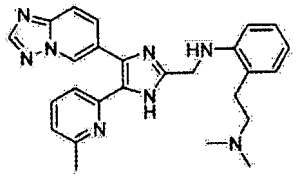
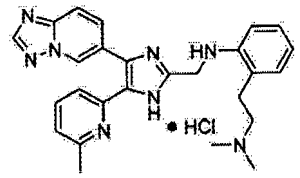
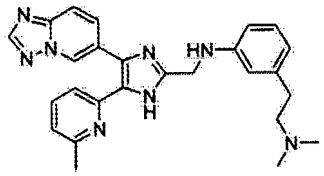
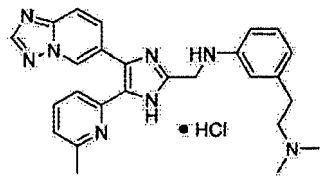
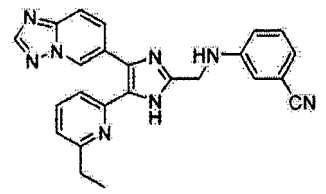
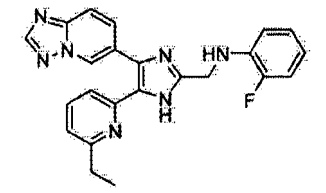
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
133		(400 MHz, DMSO-d_6) δ 9.45 (dd, 1 H, J = 1.6, 0.8 Hz), 8.61 (s, 1 H), 7.95 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (t, 1 H, 重叠, J = 7.6 Hz), 7.84 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.54 (d, 1 H, J = 7.6 Hz), 7.43 (br s, 1 H), 7.37 (d, 1 H, J = 7.6 Hz), 7.28 (s, 1 H), 7.23 (dd, 1 H, J = 2.2, 1.4 Hz), 4.74 (s, 2 H), 4.28 (s, 2 H), 3.83 (br s, 4 H), 3.81 (br s, 2 H), 3.08 (br s, 2 H), 2.54 (s, 3 H)	
134		(400 MHz, $CDCl_3$) δ 8.98 (s, 1 H), 8.36 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.76 (dd, 1 H, J = 9.2, 0.8 Hz), 7.45 (t, 1 H, J = 7.8 Hz), 7.23 (br d, 1 H, J = 7.6 Hz), 7.13 (td, 1 H, J = 8.0, 1.2 Hz), 7.04 (dd, 1 H, J = 8.0, 1.2 Hz), 6.99 (d, 1 H, J = 8.0 Hz), 6.72 (d, 1 H, 重叠, J = 7.6 Hz), 6.71 (td, 1 H, 重叠, J = 8.0, 1.2 Hz), 4.56 (s, 2 H), 2.81 (t, 2 H, J = 6.4 Hz), 2.63 (t, 2 H, J = 6.4 Hz), 2.52 (s, 3 H), 2.36 (s, 6 H)	453.25
135		(400 MHz, DMSO-d_6/D_2O) δ 9.40 (dd, 1 H, J = 1.8, 0.8 Hz), 8.63 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 0.8 Hz), 7.86 (t, 1 H, J = 7.8 Hz), 7.82 (dd, 1 H, J = 9.2, 1.8 Hz), 7.48 (d, 1 H, J = 8.0 Hz), 7.41 (d, 1 H, J = 7.6 Hz), 7.17–7.12 (m, 2 H), 6.75–671 (m, 2 H), 4.73 (s, 2 H), 3.32 (br t, 2 H, J = 8.4 Hz), 3.02 (br t, 2 H, J = 8.4 Hz), 2.90 (s, 6 H), 2.58 (s, 3 H)	
136		(400 MHz, $CDCl_3$) δ 9.08 (s, 1 H), 8.32 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.6 Hz), 7.68 (d, 1 H, J = 9.2 Hz), 7.47 (t, 1 H, J = 7.6 Hz), 7.34 (br d, 1 H, J = 7.6 Hz), 7.04 (t, 1 H, J = 7.6 Hz), 6.99 (dd, 1 H, J = 7.6, 0.4 Hz), 6.66 (br s, 1 H), 6.53–6.49 (m, 2 H), 4.48 (s, 2 H), 2.89–2.83 (m 4 H), 2.56 (s, 6 H), 2.48 (s, 3 H)	453.25

表 1-续

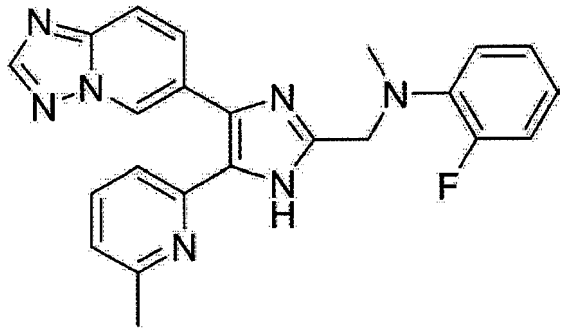
[0372]

实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
137		(400 MHz, DMSO-d_6) δ 10.47 (br s, 1 H), 9.49 (t, 1 H, J = 0.8 Hz), 8.63 (s, 1 H), 7.97 (dd, 1 H, J = 9.2, 0.8 Hz), 7.85 (dd, 1 H, 重叠, J = 9.2, 1.2 Hz), 7.84 (t, 1 H, 重叠, J = 7.8 Hz), 7.64 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 7.6 Hz), 7.10 (t, 1 H, J = 8.0 Hz), 6.81 (br s, 1 H), 6.66 (dd, 1 H, J = 8.0, 1.6 Hz), 6.58 (d, 1 H, J = 8.0 Hz), 4.75 (s, 2 H), 3.30–3.25 (m, 2 H), 2.94–2.89 (m, 2 H), 2.77 (d, 6 H, J = 4.8 Hz), 2.51 (s, 3 H)	
138		(400 MHz, $CDCl_3$) δ 10.40 (br s, 1 H), 8.94 (s, 1 H), 8.38 (s, 1 H), 7.83 (dd, 1 H, J = 9.2, 1.2 Hz), 7.80 (dd, 1 H, J = 9.2, 0.8 Hz), 7.49 (t, 1 H, J = 7.8 Hz), 7.30–7.27 (m, 1 H), 7.24 (d, 1 H, J = 8.0 Hz), 7.06 (dt, 1 H, 重叠, J = 7.6, 1.2 Hz), 7.05 (d, 1 H, 重叠, J = 7.6 Hz), 6.94–6.93 (m, 2 H), 4.72 (t, 1 H, J = 5.2 Hz), 4.54 (d, 2 H, J = 5.2 Hz), 2.82 (q, 2 H, J = 7.6 Hz), 1.31 (t, 3 H, J = 7.6 Hz)	421.21
139		(400 MHz, $CDCl_3$) δ 10.37 (br s, 1 H), 8.96 (s, 1 H), 8.38 (s, 1 H), 7.84 (dd, 1 H, J = 9.2, 1.2 Hz), 7.79 (dd, 1 H, J = 9.2, 0.8 Hz), 7.48 (t, 1 H, J = 7.8 Hz), 7.22 (d, 1 H, J = 8.0 Hz), 7.06–7.00 (m, 3 H), 6.80 (td, 1 H, J = 8.0, 1.2 Hz), 6.76–6.70 (m, 1 H), 4.62 (br s, 1 H, 重叠), 4.60 (s, 2 H), 2.80 (q, 2 H, J = 7.6 Hz), 1.29 (t, 3 H, J = 7.6 Hz)	414.20

[0373] 实践例 5

[0374] N-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基)-2- 氟 -N- 甲基苯胺 (实施例 140) 的制备

[0375]



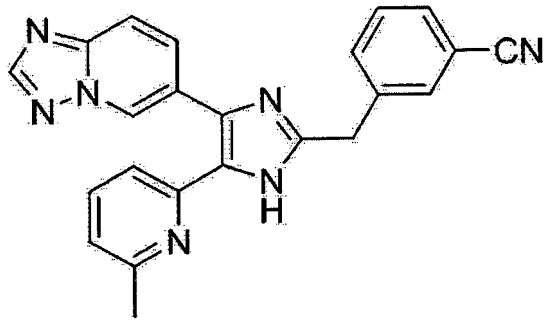
[0376] 向所搅拌的 1-((1,2,4) 三唑并 (1,5-a) 吡啶 -6- 基)-2-(6- 甲基吡啶 -2- 基) 乙烷 -1,2- 二酮 (0.20g,0.75mmol) 在叔丁基甲基醚 (10mL) 与 MeOH(8mL) 混合物中的溶液加入 2-((2- 氟苯基)(甲基) 氨基) 乙醛 (190mg,1.13mmol) 和 NH_4OAc(0.15g,1.88mmol),将混合物在室温下搅拌 2h。用饱和 $NaHCO_3$ 水溶液调节混合物的 pH 至 8。除去溶剂后,将反应混合物用 $CHCl_3$ 萃取 (2×100mL),$CHCl_3$ 溶液用水 (20mL) 和盐水 (20mL) 洗涤,经无水 Na_2SO_4 干燥,过滤,在减压下蒸发至干。残余物经过硅胶 MPLC 纯化,使用 MeOH 与 CH_2Cl_2(1:19(v/v))

的混合物作为洗脱剂，得到标题化合物 (90mg, 32%)，为淡黄色固体。^{1}H NMR(400MHz, $CDCl_3$) δ 8.97(br s, 1H), 8.37(s, 1H), 7.82(dd, 1H, J=9.2, 1.6Hz), 7.78(dd, 1H, J=9.2, 1.2Hz), 7.49(t, 1H, J=7.8Hz), 7.25(br d, 1H, J=7.6Hz), 7.14-7.06(m, 3H), 7.04(d, 1H, J=7.6Hz), 7.00-6.94(m, 1H), 4.44(s, 2H), 2.91(s, 3H), 2.58(s, 3H); MS(ESI)m/z 414.20(MH^+).

[0377] 实践例 6

[0378] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基) 苯甲腈 (实施例 145) 的制备

[0379]

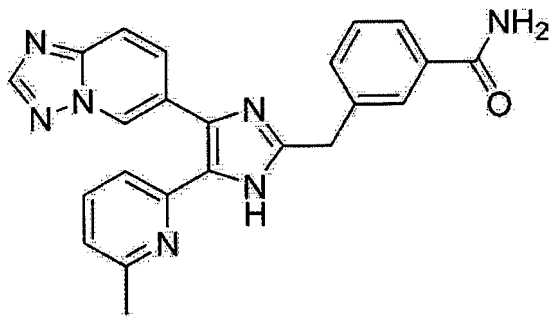


[0380] 向所搅拌的 1-((1,2,4) 三唑并 (1,5-a) 吡啶 -6- 基)-2-(6- 甲基吡啶 -2- 基) 乙烷 -1,2- 二酮 (4.00g, 15.02mmol) 在叔丁基甲基醚 (30mL) 与 MeOH(30mL) 混合物中的溶液加入 3-(甲酰基甲基) 苯甲腈 (按照 WO 02/096875 A1 所述方法制备)(6.54g, 45.07mmol) 和 NH_4OAc(11.58g, 150.24mmol)，将混合物在室温下搅拌 90min。用饱和 $NaHCO_3$ 水溶液调节混合物的 pH 至 8。除去溶剂后，将混合物用 EtOAc 萃取 (2×150 mL)，EtOAc 溶液用水 (50mL) 和盐水 (50mL) 洗涤，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 MeOH 与 CH_2Cl_2(1:19(v/v)) 的混合物作为洗脱剂，得到标题化合物 (1.92g, 33%)，为黄色固体。^{1}H NMR(400MHz, DMSO-d_6) δ 12.70(brs, 1H), 9.53(br s, 1H), 8.49(s, 1H), 7.96(dd, 1H, J=9.2, 1.8Hz), 7.84(d, 1H, J=2.0Hz), 7.82(d, 1H, J=9.2Hz), 7.74-7.71(m, 2H), 7.69(t, 1H, 重叠, J=7.6Hz), 7.56(t, 1H, J=7.8Hz), 7.47(br s, 1H), 7.15(d, 1H, J=7.6Hz), 4.18(s, 2H), 2.47(s, 3H); MS(ESI)m/z 392.18(MH^+).

[0381] 实践例 7

[0382] 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基) 苯甲酰胺 (实施例 147) 的制备

[0383]



[0384] 在室温下，向所搅拌的 3-((4-([1,2,4] 三唑并 [1,5-a] 吡啶 -6- 基)-5-(6- 甲基吡啶 -2- 基)-1H- 咪唑 -2- 基) 甲基) 苯甲腈 (41mg, 0.10mmol) 的 EtOH(2mL) 溶液加

入 28%H_2O_2(13.9mL, 0.11mmol) 和 1N NaOH(0.39mL, 0.39mmol)。将混合物加热至 60℃达 1h，然后在 0℃下向其中加入 1N HCl 以调节 pH 7-8。除去溶剂后，残余物用 CH_2Cl_2 萃取 (2×15mL)。CH_2Cl_2 溶液用水 (5mL) 和盐水 (5mL) 洗涤，经无水 Na_2SO_4 干燥，过滤，在减压下蒸发至干。残余物经过硅胶 MPLC 纯化，使用 MeOH 与 CH_2Cl_2(1:9(v/v)) 的混合物作为洗脱剂，得到标题化合物 (15mg, 35%)，为黄色固体。^1H NMR(400MHz, $CDCl_3$) δ 8.93(br s, 1H), 8.32(s, 1H), 7.77(s, 1H), 7.76(dd, 1H, 重叠, J=9.2, 1.6 Hz), 7.69(d, 1H, J=9.2Hz), 7.56(d, 1H, J=8.0Hz), 7.44(t, 1H, J=7.6Hz), 7.39(d, 1H, J=7.6Hz), 7.26(t, 1H, J=8.0Hz), 7.21(d, 1H, J=7.6Hz), 6.98(d, 1H, J=7.6Hz), 6.60(br s, 1H), 6.27(br s, 1H), 4.15(s, 2H), 2.44(s, 3H); MS(ESI)m/z 410.19(MH^+).

[0385] 按照类似于上述实践例 5-7 所述方式制备下表 2 所列化合物。在表 2 中包括这些化合物的质谱数据。

[0386] 【表 2】

[0387]

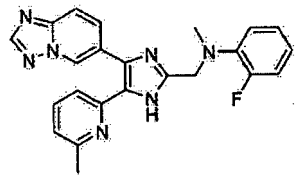
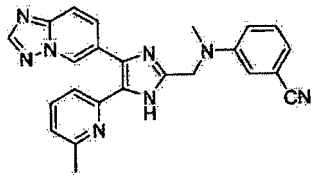
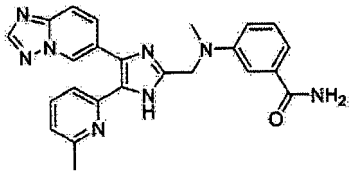
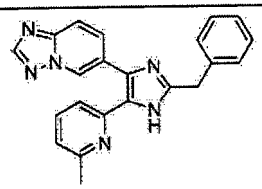
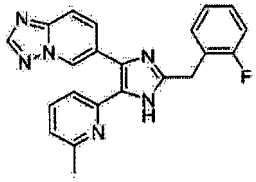
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
140		(400 MHz, $CDCl_3$) δ 8.97 (br s, 1 H), 8.37 (s, 1 H), 7.82 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.78 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.49 (t, 1 H, *J* = 7.8 Hz), 7.25 (br d, 1 H, *J* = 7.6 Hz), 7.14–7.08 (m, 3 H), 7.04 (d, 1 H, *J* = 7.6 Hz), 7.00–6.94 (m, 1 H), 4.44 (s, 2 H), 2.91 (s, 3 H), 2.58 (s, 3 H)	414.20
141		(400 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 8.37 (s, 1 H), 7.80–7.78 (m, 2 H), 7.48 (t, 1 H, *J* = 7.6 Hz), 7.35–7.30 (m, 1 H), 7.24 (br d, 1 H, *J* = 8.0 Hz), 7.08–7.05 (m, 3 H), 7.02 (d, 1 H, *J* = 7.6 Hz), 4.67 (s, 2 H), 3.14 (s, 3 H), 2.50 (s, 3 H)	421.20
142		(400 MHz, $CDCl_3$/CD_3OD) δ 8.86 (dd, 1 H, *J* = 1.6, 1.2 Hz), 8.18 (s, 1 H), 7.62 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.57 (dd, 1 H, *J* = 9.2, 1.2 Hz), 7.43 (t, 1 H, *J* = 8.0 Hz), 7.24 (dd, 1 H, *J* = 2.4, 1.6 Hz), 7.14 (t, 1 H, 重叠, *J* = 8.0 Hz), 7.13 (d, 1 H, 重叠, *J* = 8.0 Hz), 7.04 (ddd, 1 H, *J* = 8.0, 1.2, 0.8 Hz), 6.97 (d, 1 H, *J* = 7.6 Hz), 6.83 (ddd, 1 H, *J* = 8.0, 2.4, 0.8 Hz), 4.54 (s, 2 H), 2.99 (s, 3 H), 2.38 (s, 3 H)	439.22
143		(400 MHz, $CDCl_3$) δ 8.94 (br s, 1 H), 8.36 (s, 1 H), 7.81 (dd, 1 H, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, *J* = 9.2, 0.8 Hz), 7.44 (t, 1 H, *J* = 7.8 Hz), 7.40–7.28 (m, 5 H), 7.20 (br d, 1 H, *J* = 8.0 Hz), 6.99 (d, 1 H, *J* = 7.6 Hz), 4.21 (s, 2 H), 2.51 (s, 3 H)	367.18
144		(400 MHz, $CDCl_3$) δ 8.93 (t, 1 H, *J* = 1.2 Hz), 8.37 (s, 1 H), 7.80 (dd, 1 H, 重叠, *J* = 9.2, 1.6 Hz), 7.77 (dd, 1 H, 重叠, *J* = 9.2, 0.8 Hz), 7.46 (t, 1 H, *J* = 7.8 Hz), 7.39 (td, 1 H, *J* = 7.6, 1.6 Hz), 7.31–7.25 (m, 1 H), 7.21 (br d, 1 H, *J* = 8.0 Hz), 7.14 (td, 1 H, 重叠, *J* = 7.6, 1.2 Hz), 7.10 (dd, 1 H, *J* = 8.4, 1.2 Hz), 7.02 (br d, 1 H, *J* = 7.6 Hz), 4.24 (s, 2 H), 2.55 (s, 3 H)	385.17

表 2-续

[0388]

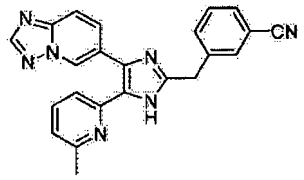
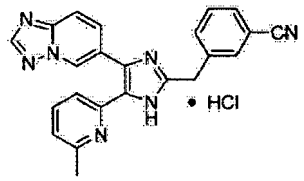
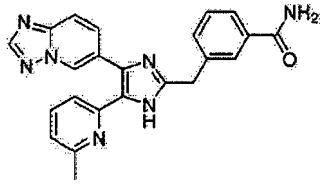
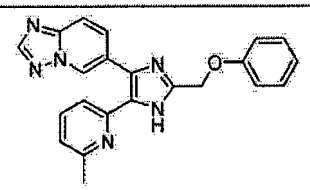
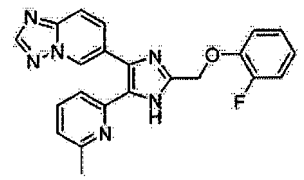
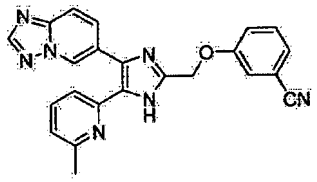
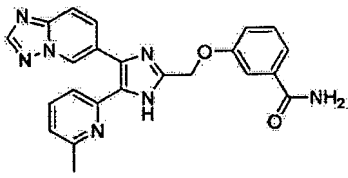
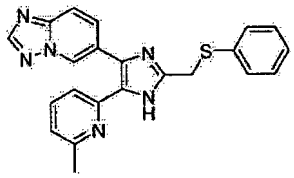
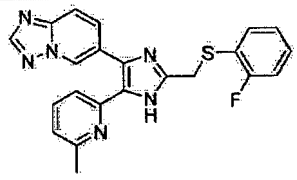
实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
145		(400 MHz, DMSO-d_6) δ 12.70 (br s, 1 H), 9.53 (br s, 1 H), 8.49 (s, 1 H), 7.96 (dd, 1 H, J = 9.2, 1.8 Hz), 7.84 (d, 1 H, J = 2.0 Hz), 7.82 (d, 1 H, J = 9.2 Hz), 7.74–7.71 (m, 2 H), 7.69 (t, 1 H, 重叠, J = 7.6 Hz), 7.56 (t, 1 H, J = 7.8 Hz), 7.47 (br s, 1 H), 7.15 (d, 1 H, J = 7.6 Hz), 4.18 (s, 2 H), 2.47 (s, 3 H)	392.18
146		(400 MHz, DMSO-d_6) δ 9.51 (dd, 1 H, J = 1.6, 0.8 Hz), 8.65 (s, 1 H), 8.08 (br s, 1 H), 7.97 (dd, 1 H, 重叠, J = 9.2, 0.8 Hz), 7.95 (br d, 重叠, 1 H, J = 8.0 Hz), 7.87 (dd, 1 H, J = 9.2, 1.6 Hz), 7.85–7.79 (m, 2 H), 7.63 (dd, 1 H, 重叠, J = 7.6, 1.2 Hz), 7.61 (t, 1 H, 重叠, J = 7.6 Hz), 7.36 (d, 1 H, J = 7.6 Hz), 4.55 (s, 2 H), 2.50 (s, 3 H)	
147		(400 MHz, $CDCl_3$) δ 8.93 (br s, 1H), 8.32 (s, 1 H), 7.77 (s, 1 H), 7.76 (dd, 1 H, 重叠, J = 9.2, 1.6 Hz), 7.69 (d, 1 H, J = 9.2 Hz), 7.56 (d, 1 H, J = 8.0 Hz), 7.44 (t, 1 H, J = 7.6 Hz), 7.39 (d, 1 H, J = 7.6 Hz), 7.26 (t, 1 H, J = 8.0 Hz), 7.21 (d, 1 H, J = 7.6 Hz), 6.98 (d, 1 H, J = 7.6 Hz), 6.60 (br s, 1 H), 6.27 (br s, 1 H), 4.15 (s, 2 H), 2.44 (s, 3 H)	410.19
148		(400 MHz, $CDCl_3$) δ 8.94 (s, 1 H), 8.37 (s, 1 H), 7.77–7.72 (m, 2 H), 7.51 (t, 1 H, J = 7.6 Hz), 7.32–7.25 (m, 3 H), 7.06 (d, 1 H, J = 7.6 Hz), 7.00 (t, 1 H, 重叠, J = 7.6 Hz), 6.97 (d, 2 H, 重叠, J = 8.0 Hz), 5.22 (s, 2 H), 2.54 (s, 3 H)	383.17
149		(400 MHz, $CDCl_3$) δ 8.95 (t, 1 H, J = 1.2 Hz), 8.38 (s, 1 H), 7.80 (dd, 1 H, J = 9.2, 0.8 Hz), 7.77 (dd, 1 H, J = 9.2, 1.2 Hz), 7.56 (t, 1 H, J = 8.0 Hz), 7.31 (d, 1 H, J = 7.6 Hz), 7.19 (td, 1 H, J = 8.0, 1.6 Hz), 7.14–7.06 (m, 3 H), 7.01–6.95 (m, 1 H), 5.34 (s, 2 H), 2.64 (s, 3 H)	401.17

表 2-续

[0389]

实施例	结构	^{1}H NMR (ppm)	MS (ESI) m/z (MH^+)
150		(400 MHz, $CDCl_3/CD_3OD$) δ 8.94 (dd, 1 H, J = 1.6, 1.2 Hz), 8.32 (s, 1 H), 7.78 (dd, 1 H, J = 9.2, 1.6 Hz), 7.73 (dd, 1 H, J = 9.2, 1.2 Hz), 7.52 (t, 1 H, J = 7.8 Hz), 7.42–7.37 (m, 1 H), 7.31–7.26 (m, 3 H), 7.25 (br d, 1 H, 重叠, J = 8.0 Hz), 7.07 (d, 1 H, J = 7.6 Hz), 5.23 (s, 2 H), 2.55 (s, 3 H)	408.17
151		(400 MHz, $CDCl_3/CD_3OD$) δ 8.94 (t, 1 H, J = 1.6 Hz), 8.31 (s, 1 H), 7.76 (dd, 1 H, J = 9.2, 1.6 Hz), 7.70 (dd, 1 H, J = 9.2, 0.8 Hz), 7.51–7.47 (m, 2 H), 7.42 (ddd, 1 H, J = 8.0, 2.4, 1.2 Hz), 7.31 (t, 1 H, J = 8.0 Hz), 7.23 (d, 1 H, J = 7.6 Hz), 7.12 (ddd, 1 H, J = 8.0, 2.4, 0.8 Hz), 7.04 (d, 1 H, J = 7.6 Hz), 5.22 (s, 2 H), 2.51 (s, 3 H)	426.18
152		(400 MHz, $CDCl_3$) δ 8.89 (t, 1 H, J = 1.4 Hz), 8.35 (s, 1 H), 7.76–7.19 (m, 2 H), 7.45 (t, 1 H, J = 7.8 Hz), 7.39–7.36 (m, 2 H), 7.30–7.26 (m, 2 H), 7.23–7.19 (m, 2 H), 7.01 (d, 1 H, J = 7.6 Hz), 4.26 (s, 2 H), 2.49 (s, 3 H)	399.15
153		(400 MHz, $CDCl_3$) δ 8.86 (br s, 1 H), 8.37 (s, 1 H), 7.78 (dd, 1 H, J = 9.2, 0.8 Hz), 7.72 (dd, 1 H, J = 9.2, 1.6 Hz), 7.54–7.48 (m, 2 H), 7.31–7.27 (m, 1 H), 7.25 (br d, 1 H, J = 8.0 Hz), 7.13–7.08 (m, 2 H), 7.06 (d, 1 H, J = 8.0 Hz), 4.30 (s, 2 H), 2.64 (s, 3 H)	417.15

[0390] 生物学数据

[0391] 利用下列测定法可以评估本发明化合物的生物学活性：

[0392] 评价 ALK5 激酶磷酸化的抑制作用的无细胞测定法

[0393] 使用杆状病毒表达系统，使 ALK5 蛋白在 Sr9 昆虫细胞中表达为人重组 GST- 融合蛋白。利用 GSH- 琼脂糖 (Sigma-Aldrich) 亲和色谱纯化所表达的蛋白质。在来自 Perkin Elmer(Boston, MA, USA) 的 96- 孔 FlashPlates™ 中进行激酶测定，反应体积为 50 μL。分四个步骤吸移反应鸡尾酒试剂，顺序如下：20 μL 测定缓冲液（标准缓冲液），5 μL ATP 水溶液，5 μL 含每种供试式 (I) 化合物的 10 % DMSO，10 μL GSK3(14-27)(200ng)/10 μL ALK5 溶液 (1ng)（预混合）。反应鸡尾酒试剂含有 60mM HEPES-NaOH, pH7.5、3mM $MgCl_2$、3mM $MnCl_2$、3 μM Na_3VO_4、1.2mM DTT、50 μg/mL PEG_{20000}、1 μM[γ-^{33}P]-ATP（大约 $2.5x10^5$cpm 每孔）、200ng/10 μL GSK3(14-27) 和 1ng/10 μL ALK5。使反应鸡尾酒试剂在 30℃下温育 60min。用 50 μL 2%(v/v)H_3PO_4 终止反应，将平板抽吸，用 200 μL 0.9%(w/v)NaCl 洗涤两次。用 BeckmanCoulter Biomek 2000 自动系统进行测定。用微量平板闪烁计数器 (Microbeta, Wallac) 测定 $^{33}P_i$ 的结合（以“cpm”计）。

[0394] 式 (I) 化合物通常表现小于 1 μM 的 IC_{50} 值；有些表现小于 0.1 μM 的 IC_{50} 值；有些甚至表现小于 10nM 的 IC_{50} 值，如表 3 所示。

[0395] 【表 3】

[0396]

实施例	IC_{50}(nM)	实施例	IC_{50}(nM)
1	13.10	51	12.30
2	6.68	52	23.40
5	9.41	53	60.10
6	17.40	54	9.93
7	8.96	55	6.70
8	9.84	58	39.60
9	6.39	59	19.50
10	9.41	60	4.83
12	6.16	63	32.10
14	10.70	64	20.60
15	12.30	65	29.70
16	7.54	66	9.14
17	14.60	67	54.60
18	6.54	68	11.00
20	4.53	69	24.50
22	17.10	70	12.80
23	13.90	71	59.10
24	9.07	72	16.60
26	15.60	73	78.00
27	18.00	74	39.50
28	17.40	75	15.40
29	14.30	76	39.00
30	10.60	77	15.30
31	8.01	78	15.10
33	14.20	79	46.60
34	16.20	138	9.40
35	46.00	139	23.20
36	14.20	140	49.80
37	11.90	141	118.00
40	29.60	142	153.00
42	14.40	143	19.80
43	14.30	144	25.10
44	48.10	145	12.40
45	57.50	147	40.00
46	44.20	148	13.10
47	14.40	149	25.40
48	24.10	150	23.90
49	15.30	151	22.50
50	50.70	152	20.70

[0397]

[0398] 评价 ALK4 激酶磷酸化的抑制作用的无细胞测定法

[0399] 可以按照与上述 ALK5 抑制作用所述相似的方式测定 ALK4 激酶磷酸化被供试式(I)化合物所抑制,除了使用 GST- 标记的 ALK4(Invitrogen Corporation) 和 RBER-CHK 肽代替 GST- 标记的 ALK5 和 GSK3(14-27) 以外。

[0400] 式(I)化合物通常表现小于 1μM 的 IC_{50} 值;有些表现小于 0.1μM 的 IC_{50} 值;有些甚至表现小于 10nM 的 IC_{50} 值。

[0401] 激酶选择性

[0402] 在来自 Perkin Elmer 的 96- 孔 FlashPlates™ 中进行激酶测定，反应体积为 50μL。分四个步骤吸移反应鸡尾酒试剂，顺序如下：15μL ATP 水溶液，20μL 测定缓冲液（标准缓冲液），5μL 含实施例 2 的 10%DMSO，10μL 酶 / 底物混合物的水溶液。反应鸡尾酒试剂含有 70mM HEPES-NaOH，pH 7.5、3mM $MnCl_2$、3μM Na_3VO_4、1.2mM DTT、1μM[γ-^{33}P]-ATP（大约 6x10^{5}cpm 每孔）、蛋白激酶（可变量）和底物（可变量）。使反应鸡尾酒试剂在 30℃下温育 60min。用 50μL 2%(v/v)H_3PO_4 终止反应，将平板抽吸，用 200μL 0.9%(w/v)NaCl 洗涤两次。全部测定都用 BeckmanCoulter Biomek 2000/SL 自动系统进行。用微量平板闪烁计数器测定 $^{33}P_i$ 的结合（以“cpm”计）。

[0403] 【表 4】

[0404]

蛋白激酶	IC_{50}(μM)	10μM 的抑制 %	1μM 的抑制 %
ALK5	0.00668		
ALK4	0.0173		
P38α	1.720		
VEGF-R1	0.391		
VEGF-R2	0.097		
VEGF-R3	0.257		
ALK1		66	20
ALK2		71	17
ALK3		27	-6
AKT1		3	0
CDK1/CycA		2	5
CHK1		5	-2
DAPK1		11	5
EGF-R wt		43	-8
ERK1		66	17
GSK3α		15	10
MEK1 wt		47	14
MET wt		12	-5
MST1		3	-7
PAK1		-3	-7
PDGFRα wt		91	53
PDGFRβ		87	47
PKA		18	-7
PKCα		4	-9
ROCK1		9	3
RPS6KA1		14	6
STK23		-1	-4

[0405]

[0406] 评价 TGF-β 信号传递的细胞抑制作用的测定法

[0407] 将具有 p3TP-Luc(neo) 表达质粒的 HaCaT-3TP-Luc 稳定细胞或 4T1-3TP-Luc 稳定细胞分别按照 2.5×10^4 细胞 / 孔或 5×10^5 细胞 / 孔的浓度接种在 96- 孔平板中。当融合率为大约 60-70% 时，在有或没有每种供试式 (I) 化合物的存在下，在 37℃和 5%CO_2 中用含 TGF-β1(2ng/mL) 的 0.2%FBS 处理细胞达 24h。按照厂商指导利用 Luciferase Assay System(Promega) 制备细胞溶解产物，借助发光计 Micro Lumat Plus(Berthold, Germany) 测量发光。

[0408] 式 (I) 化合物通常表现小于 1μM 的 IC_{50} 值；有些表现小于 0.1μM 的 IC_{50} 值；有些甚至表现小于 10nM 的 IC_{50} 值。

[0409] 免疫荧光测定法

[0410] 将 MCF10A 细胞按照 2×10^5 细胞 / 孔的浓度平板接种在 6- 孔平板的盖玻片上。12h 后，当细胞被附着时，改变 10%FBS 培养基为 0.5%FBS 培养基。二十四小时后，在有或没有实施例 2(1μM) 的存在下用 TGF-β1(2ng/mL) 处理细胞达 2h。然后，在室温下将细胞用 4% 甲醛溶液固定 30min，用淬灭溶液 (含 50mM NH_4Cl 的 PBS) 淬灭 15min。 用 PBS 洗涤三次后，使细胞与封闭 / 渗透溶液 (含 1%BSA 和 0.1% Triton X-100 的 PBS) 在室温下温育 1h，与抗 -Smad2/3 抗体 (BD Biosciences, Franklin Lakes, NJ, USA) 在 4℃下温育过夜。借助 Cy3- 缀合的山羊抗 - 小鼠 IgG(Jackson ImmunoResearch Laboratories, Bar Harbor, ME, USA) 使荧光可视化。用 DAPI 溶液染色相同细胞的核。利用 LSM 510META 激光同焦显微镜检系统 (Carl Zeiss, Germany) 分析细胞。

[0411] 实施例 2 抑制了 MCF10A 细胞中 TGF-β1- 诱导的 Smad2/3 核易位。

[0412] 伤口愈合测定法

[0413] 将 MCF10A 细胞按照 2×10^5 细胞 / 孔的浓度接种在 6- 孔平板中。当每孔被细胞占据超过 80% 的面积时，改变 10%FBS 为 0.2%FBS。24h 后，借助塑料吸移管尖制造伤口，然后在有或没有实施例 2(1μM) 的存在下用 TGF-β1(2ng/mL) 处理细胞达 16h。基于由显微镜采集的细胞相衬图象，根据 Image J 程序 (National Institutes of Health, MD, USA) 计算从 0 至 16h 的伤口面积变化。

[0414] 实施例 2 抑制了 MCF10A 细胞中 TGF-β1- 诱导的细胞迁移。

[0415] Matrigel 侵袭测定法

[0416] 将 Transwells(6.5mm 直径，8μm 孔径；Corning, Lowell, MA, USA) 的上表面涂以 20μL 经稀释的 Matrigel(BD Biosciences)。在有或没有实施例 2 的存在下，在含有或不含 TGF-β1(2ng/mL) 的无血清培养基中，将 4T1 细胞按照 4×10^4 细胞 / 孔的密度接种在 Transwell 的上部空间上。在有或没有实施例 2 的存在下，向下部空间填充含有 TGF-β1(2ng/mL) 的 10%FBS。在 37℃和 5%CO_2 中温育 20h 后，用棉签除去残留在膜的上表面上的细胞，利用荧光显微镜检观察残留在底表面上的 DAPI- 染色细胞。从 5 个随机视野得到每个视野的平均细胞数。

[0417] 实施例 2 在 matrigel 侵袭测定法中抑制了 TGF-β1- 诱导的细胞侵袭。

[0418] 细胞生长研究

[0419] 将 4T1 细胞或 MCF10A 细胞按照每孔 5×10^3 细胞的浓度接种在 96- 孔平板中。细胞被附着后，在 0.2% 血清培养基中用实施例 2 的 DMSO 溶液处理细胞。温育四天后，借助 SRB 测定法测定细胞生存能力。

[0420] 实施例 2 显示对 4T1 细胞生长没有影响，轻微增加 MCF10A 细胞生长且无显著性，从而提示了实施例 2 的抗 - 转移效应并非由于原有肿瘤的生长抑制。

[0421] 对 BALB/c 4T1 异种移植小鼠模型的抗 - 转移效应

[0422] 从 Orient Bio Inc. (Seoul, Korea) 购买雌性 BALB/c 小鼠。使动物供养在温控室内 (22℃)，自由供应食物和水。将 4T1 细胞 (1.2×10^4 细胞) 悬浮在 PBS 中，植入五至六周龄雌性 BALB/c 小鼠的左 #4 乳脂垫 (第 0 天)。在实验 1 中，处置始于肿瘤植入之后 (第 0

天)。将实施例 3(13.6 或 27.3mg/kg) 溶于水,口服给予小鼠 BID,每周连续五天,持续四周。在实验 2 中,处置始于第 4 天。将实施例 2(5、10、20 或 40mg/kg) 溶于人工胃液制剂,口服给予小鼠,每周连续五天,持续三周。在实验 3 中,处置始于第 4 天。将实施例 2(5、10、20 或 40mg/kg) 溶于人工胃液制剂,口服给予小鼠,每隔一天一次(每周三次),持续 24 天。在实验 4 中,将 4T1 细胞 (1×10^4 细胞) 悬浮在 PBS 中,植入十周龄雌性 BALB/c 小鼠的左 #4 乳脂垫(第 0 天)。处置始于第 10 天。将实施例 61(43.6mg/kg) 溶于盐水,腹膜内给予小鼠,每隔一天一次,持续 2.5 周。在全部实验中,在最后一次给药后 24 至 72h 处死小鼠,立即向气管内注射含 15% 印度墨汁溶液 (Hardy Diagnostics) 的 PBS。分离经印度墨汁染色的肺,用 Feket 氏溶液(含 60% 乙醇、3% 甲醛和 4% 乙酸的 PBS) 退色至少 20min。统计左肺叶 表面上转移结节的数量,用数码照相机拍摄肺的照片。利用测径规测量肿瘤尺寸,利用下列方程计算肿瘤体积 :

[0423] 肿瘤体积 =(0.5236)×(宽度)^2×(长度)

[0424] 实施例 2、3 和 61 显著减少了肺上转移结节的数量。

[0425] 在实验 3 中,进行蛋白质印迹分析,以检查实施例 2 对肿瘤组织中 Smad2 磷酸化的影响。在处死小鼠之前 2h,对小鼠静脉内给予载体缓冲液 (4mM HCl, 1mg/mL BSA) 或者含 TGF-β1(50ng/ 小鼠) 的载体缓冲液。在冰上,使来自小鼠的肿瘤组织在 RIPA 缓冲液 [50mM Tris, pH 7.5, 150mM NaCl, 0.1% 十二烷基硫酸钠 , 0.5% 脱氧胆酸钠 , 1%NP-40, 1mM NaF, 1mM Na_3VO_4, 1mM PMSF, 蛋白酶抑制剂鸡尾酒试剂 (1 片 Roche Diagnostics GmbH 蛋白酶抑制剂鸡尾酒试剂 /10mL)(Roche)] 中溶解 20min。在 4℃下,以 13000rpm 离心 20min,使溶解产物澄清。利用 Micro-BCA(bicinchoninic acid) 蛋白质测定试剂盒 (Thermo Scientific) 测定上清液的蛋白质含量。借助聚丙烯酰胺凝胶电泳分离含有 20-50μg 总蛋白质的溶解产物,然后电泳转移至聚偏二氟乙烯转移膜 (Millipore, Billerica, MA, USA)。将膜用含有 0.5% Tween-20(PBST) 的含 5%BSA(Sigma-Aldrich) 的 PBS 封闭 1h,与下列抗体之一在 4℃下温育过夜 :含抗 - 磷 -Smad2(Millipore)、抗 -Smad2/3(BD Transduction Laboratories, NJ, USA) 或抗 - β - 肌动蛋白 (Sigma-Aldrich) 的 PBST,其中含有 1%BSA。将膜用 PBST 洗涤三次,与辣根过氧化物酶 (HRP)- 缀合的山羊抗 - 小鼠抗体或 HRP- 缀合的山羊抗 - 兔抗体 (SantaCruz Biotechnology, Santa Cruz, CA, USA) 在室温下温育 1h。利用蛋白质印迹鲁米诺试剂 (SantaCruz Biotechnology) 检测所结合的抗体。利用密度计 LAS-3000 成像仪 (FUJIFILM, Tokyo, Japan) 分析谱带强度。

[0426] 实施例 2 抑制了肿瘤组织中 TGF-β1- 诱导的 Smad2 磷酸化。

[0427] 对 MMTV/c-Neu 小鼠乳腺癌模型的抗转移效应

[0428] 从 Jackson Laboratory(Bar Harbor, ME, USA) 购买 MMTV/c-Neu 雌性转基因小鼠。使动物供养在温控 SPF 房间内 (22℃),自由供应食物和水。在实验 1 中,将实施例 61(43.6mg/kg) 溶于盐水,腹膜内给予三十二周龄 MMTV/c-Neu 小鼠,每隔一天一次,持续三周。在实验 2 中,将实施例 3(43.6mg/kg) 溶于盐水,腹膜内给予三十二周龄 MMTV/c-Neu 小鼠,每隔一天一次,持续十周。最后一次给药后 24h 处死小鼠,借助苏木精与曙红 (H&E) 染色分析乳腺肿瘤和肺的组织。为了测定乳腺肿瘤和肺组织中的 β - 酪蛋白 mRNA 水平,按照厂商指导利用 TRIzol 试剂 (Invitrogen Corporation) 和 RNeasy Mini 试剂盒 (Qiagen) 从这些组织中分离总 RNA。在 37℃下,借助 MMLV RTase(Invitrogen Corporation),使用

随机引物 (Invitrogen Corporation) 从 2μg 总 RNA 合成 cDNA 达 1h，使用 Taq 聚合物酶 (Promega) 和下列基因特异性引物进行 PCR 扩增：小鼠 GAPDH（正向）5'-ATG TGT CCG TCG TGG ATC TGA-3' 与（反向）5'-TTG AAG TCG CAG GAG ACA ACC-3'，小鼠 β-酪蛋白（正向）5'-TCC CAC AAA ACA TCC AGC C-3' 与（反向）5'-ACG GAA TGT TGT GGA GTG G-3'。借助琼脂糖凝胶电泳分析所扩增的 DNA。

[0429] 实施例 61 显著减少肺中转移性损伤的数量。在 MMTV/c-Neu 小鼠的肺中检测到显著水平的 β-酪蛋白（一种乳腺分化标记物）mRNA。实施例 3 和 61 显著抑制肺中的 β-酪蛋白 mRNA 表达水平，证明了它们的抗转移效应。

[0430] 借助明胶酶谱学测量原始乳腺肿瘤中 MMP-9 和 MMP-2 的活性。在冰上，使来自小鼠的肿瘤组织 (30mg) 在 500μL RIPA 缓冲液（50mM Tris，150mM NaCl，0.1% 十二烷基硫酸钠，0.5% 脱氧胆酸钠，1%NP-40，不含 EDTA 的蛋白酶抑制剂）中溶解 10-20min。在 4℃下，以 13000rpm 离心 10min，使溶解产物澄清。利用 Micro-BCA 蛋白质测定试剂盒 (Thermo Scientific) 测定上清液的蛋白质含量。向含有 15μg 总蛋白质的溶解产物加入装载缓冲液（0.5M Tris，pH 6.8，50% 甘油，10%SDS 和 1% 溴酚蓝溶液），制备装载样本。将装载样本在 60℃下加热 5min，在含有 0.2% 明胶的 10% 聚丙烯酰胺凝胶上进行 电泳分离。在室温下，将凝胶用洗涤缓冲液 [2.5%Triton-X100，0.05M Tris-HCl，pH 7.5 和 0.1M NaCl] 洗涤 30min。然后，在 37℃下，使凝胶在温育缓冲液 [0.05M Tris-HCl，pH 7.5，0.15M NaCl，0.01M $CaCl_2$，0.02%NaN_3 和 1μM $ZnCl_2$] 中温育 16-18h，同时振摇。在室温下，将凝胶用含有 5% 甲醇与 10% 乙酸的 0.5% 库马斯蓝 R250 溶液染色 2-4h，再在室温下用退色溶液（5% 甲醇与 10% 乙酸）退色 30min。利用密度计 LAS-3000 成像仪 (FUJIFILM)，以 cybergreen 模式得到凝胶图象。

[0431] 实施例 3 显著抑制原始乳腺肿瘤中 MMP-9 和 MMP-2 的活性。

[0432] 对胆管 - 结扎的肝纤维化模型的抗纤维化效应

[0433] 从 Orient Bio Inc. 购买六周龄雄性 Sprague-Dawley(SD) 大鼠。在实验 1 中，将体重 180-200g 的 SD 大鼠随机分成五个实验组：假手术的对照大鼠 (n=5)，假手术的实施例 3 处置大鼠 (43.6mg/kg，n=5)，胆管 - 结扎的 (BDL) 大鼠 (n=10)，用 21.8 或 43.6mg/kg 实施例 3 处置的 BDL 大鼠 (n=10)。在实验 2 中，将体重 180-200g 的 SD 大鼠随机分成五个实验组：假手术的对照大鼠 (n=5)，BDL 大鼠 (n=10)，用 5、10 或 20mg/kg 实施例 2 处置的 BDL 大鼠 (n=10)。就 BDL 而言，将动物用 zoletil(20mg/kg) 和赛拉嗪 (10mg/kg) 麻醉，暴露共用胆管，利用 3-0 丝线双 - 结扎。将第一条结扎线置于肝管接合处下方，第二条置于胰管入口上方。然后切割双结扎线之间的共用胆管。在假手术的大鼠中，在腹部开一切口，然后缝合，无需任何处置。处置开始于手术操作后 2h 以内。对大鼠口服给予实施例 3 的盐水溶液（实验 1）或者实施例 2 的人工胃液制剂溶液（实验 2），每周三次，持续四周，BDL 始于手术。使动物供养在温控室 (21℃) 内，供应经过高压灭菌的食物和水。最后一次给药后 48h，杀死动物，除去血清、脾和肝。将肝脏矢状切成若干部分，在液氮中速冻，保存在 -70℃下。将一部分肝浸入 10% 中性缓冲的福尔马林，供组织病理学检查。全部实验操作都是按照我们的学会指南进行的。按照厂商指导，利用分光光度酶 测定试剂盒 (Asan Pharm. Co.，Ltd.，Hwaseong-si，Korea) 测定血清丙氨酸氨基转移酶 (ALT) 和天冬氨酸氨基转移酶 (AST) 的活性。也利用自动化仪器测定一般血清生化。将肝脏样品固定在 10% 中

性缓冲的福尔马林中，然后进行常规的石蜡包埋操作。切制切片（5μm厚），使用苏木精与曙红（H&E）染色，借助光学显微镜检查。在冰上，使肝组织在RIPA缓冲液[50mM Tris，pH 7.5，150mM NaCl，1mM EDTA，0.1%十二烷基硫酸钠，0.5%脱氧胆酸钠，1%NP-40，50mM NaF，1mM Na_3VO_4，1mM PMSF，蛋白酶抑制剂鸡尾酒试剂（1片RocheDiagnostics GmbH蛋白酶抑制剂鸡尾酒试剂/10mL）(Roche)]中溶解20min。在4℃下，以13000rpm离心20min，使溶解产物澄清。利用Micro-BCA蛋白质测定试剂盒（Thermo Scientific）测定上清液的蛋白质含量。借助6-10%十二烷基硫酸钠-聚丙烯酰胺凝胶电泳分离含有20-60μg总蛋白质的溶解产物，然后转移至硝基纤维素（Whatman ®，Germany）或聚偏二氟乙烯膜（Millipore）。将膜用5% BSA（Sigma-Aldrich）或5%脱脂脱水乳溶液封闭1h，与下列抗体之一在4℃下温育过夜：兔抗磷-Smad3（Cell Signaling Technology，Beverly，MA，USA），兔抗-α-SMA（Millipore），小鼠抗-纤连蛋白，小鼠抗-波形蛋白（BD Biosciences），或者小鼠抗-β-肌动蛋白（Sigma-Aldrich）。将膜用Tris-缓冲盐水洗涤三次，与HRP-缀合的山羊抗-兔抗体或HRP-缀合的山羊抗-小鼠抗体（SantaCruz Biotechnology）在室温下温育1h。利用ECL试剂盒（GE Healthcare，Princeton，NJ，USA）检测所结合的抗体。利用密度计LAS-3000成像仪（FUJIFILM）分析谱带强度。

[0434] 与假手术的对照大鼠相比，BDL大鼠显示有体重减轻和器官（肝和脾）重量增加。实施例2和3恢复了BDL大鼠的体重减轻，降低了器官（肝和脾）重量。与假手术的动物相比，在BDL大鼠中观察到血清ALT和AST有显著增加。实施例2和3提高了BDL大鼠的血清ALT和AST。实施例3抑制了Smad信号传递，并且抑制了BDL大鼠肝脏中的α-SMA、纤连蛋白和波形蛋白。实施例2抑制了BDL大 鼠肝脏中的α-SMA和纤连蛋白。与正常大鼠肝脏相比，BDL大鼠肝脏显示有典型的组织学改变，以中枢±中枢结构破坏和桥式纤维化形成为特征。实施例2和3明显消除了BDL-诱导的组织学改变。

[0435] 【表5】

[0436]

组别(mg/kg)		体重(g)	器官重量			
			肝(g)	脾(g)	肝/体(%)	脾/体(%)
假手术	载体	357±5.2	11.7±0.36	0.78±0.06	3.28±0.07	0.22±0.02
	实施例3 (43.6)	354±12.2$^{\#\#}$	11.8±0.71	0.81±0.04	3.34±0.12	0.23±0.01
BDL	载体	308±6.1**	22.8±1.30**	2.01±0.14**	7.43±0.44**	0.65±0.04**
	实施例3 (21.8)	340±9.6$^{\#}$	16.4±0.72$^{**,\#\#}$	1.30±0.07**	4.85±0.26$^{**,\#\#}$	0.39±0.03$^{**,\#\#}$
	实施例3 (43.6)	335±8.4	16.1±0.57$^{**,\#\#}$	1.19±0.09**	4.84±0.26$^{**,\#\#}$	0.36±0.03$^{**,\#\#}$

[0437] 数据代表平均±S.E.（n=5-8）。

[0438] **：p<0.01相对于假手术（sham）；#：p<0.05相对于BDL；##：p<0.01相对于BDL。

[0439] 【表6】

[0440]

组别(mg/kg)		体重(g)	器官重量			
			肝(g)	脾(g)	肝/体(%)	脾/体(%)
假手术	载体	345±6.3	12.1±0.77	0.83±0.05	3.51±0.21	0.24±0.02
BDL	载体	315±16.1**	20.3±2.45**	2.54±0.29**	6.39±0.51**	0.80±0.05**
	实施例 2 (5)	324±7.3	17.5±1.82	2.00±0.28**	5.46±0.62	0.63±0.09**
	实施例 2 (10)	312±10.4	15.8±1.88	1.57±0.12#	5.08±0.60	0.51±0.05#
	实施例 2 (20)	312±8.4*	15.2±1.80	1.50±0.16#	4.88±0.63	0.48±0.05#

[0441] 数据代表平均 ±S.E.(n=5-8)。

[0442] *:p<0.05 相对于假手术 (sham);**:p<0.01 相对于 sham;#:p<0.05 相对于 BDL。

[0443] 对博莱霉素 - 诱导的肺纤维化模型的抗纤维化效应

[0444] 从 Orient Bio Inc. 购买六周龄雄性 ICR 小鼠。将体重 31-35g 的小鼠随机分成五个实验组 :假手术的对照小鼠 (盐水 ,n=6),博莱霉素 (BLM)- 处置小鼠 (n=10),用 5、10 或 20mg/kg 实施例 2 处置的 BLM- 处置小鼠 (n=10)。就肺纤维化的诱导而言,将小鼠用 zoletil(10mg/kg) 和赛拉嗪 (5mg/kg) 麻醉,通过气管内滴注在第 0 天给予 BLM(BLM 硫酸盐 ,1mg/kg)(MBcell,Los Angeles,CA,USA) 的 60μL 盐水溶液。将实施例 2 溶于人工胃液制剂,口服给予小鼠,每周五次,持续两周,始于第 7 天。使动物供养在温控室 (21℃) 内,供应经过高压灭菌的食物和水。手术后三周,杀死动物,除去肺脏。将肺脏矢状切成若干部分,在液氮中速冻,保存在 -70℃下。将一部分肺浸入 10% 中性缓冲的福尔马林,供组织病理学检查。全部实验操作都是按照我们的学会指南进行的。将肺脏样品固定在 10% 中性缓冲的福尔马林中,然后进行常规的石蜡包埋操作。切制切片(5μm 厚),使用苏木精与曙红 (H&E) 染色,借助光学显微镜检查。在冰上,使肺组织在 RIPA 缓冲液 [50mM Tris,pH 7.5,150mM NaCl,1mM EDTA,0.1% 十二烷基硫酸钠 ,0.5% 脱氧胆酸钠 ,1%NP-40,50mM NaF,1mM Na_3VO_4,1mM PMSF, 蛋白酶抑制剂鸡尾酒试剂 (1 片 Roche Diagnostics GmbH 蛋白酶抑制剂鸡尾酒试剂 /10mL)(Roche)] 中溶解 20min。在 4℃下,以 13000rpm 离心 20min,使溶解产物澄清。利用 Micro-BCA 蛋白质测定试剂盒 (Thermo Scientific) 测定上清液的蛋白质含量。借助 6-10% 十二烷基硫酸钠 - 聚丙烯酰胺凝胶电泳分离含有 20-50μg 总蛋白质的溶解产物,然后转移至硝基纤维素膜 (Whatman ®)。将膜用 5% 脱脂脱水乳溶液封闭 1h,与兔抗 -α-SMA(Millipore) 或小鼠抗 - 纤连蛋白 (BD Biosciences) 在 4℃下温育过夜。将膜用 Tris- 缓冲盐水洗涤三次,与 HRP- 缀合的山羊抗 - 兔抗体或 HRP- 缀合的山羊抗 - 小鼠抗体 (SantaCruz Biotechnology) 在室温下温育 1h。利用 ECL 试剂盒 (GEHealthcare) 检测所结合的抗体。利用密度计 LAS-3000 成像仪 (FUJIFILM) 分析谱带强度。

[0445] 与假手术的动物相比,BLM- 诱导的纤维化肺显示有升高水平的 α-SMA 和纤连蛋白。实施例 2 抑制了 BLM- 诱导的纤维化肺中的 α-SMA 和纤连蛋白。来自 BLM- 处置小鼠的肺组织显示有典型的组织学特征,也就是肺泡间隔变厚,并且被炎性细胞浸润,还发现有胶原沉积在小间隙中。实施例 2 在全部供试剂量水平下都明显减少了 BLM- 诱导的组织学改变。

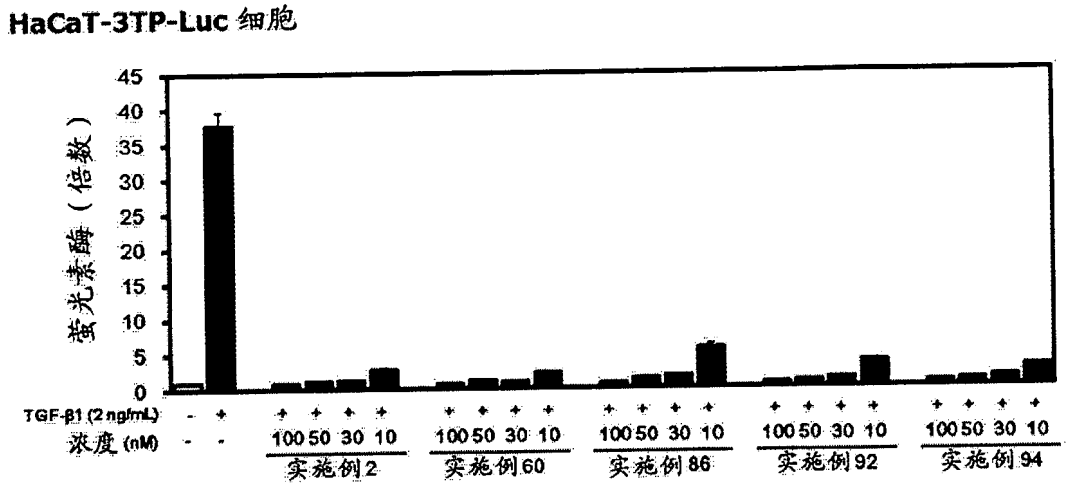

HaCaT-3TP-Luc 细胞
荧光素酶（倍数）
45
40
35
30
25
20
15
10
5
0
TGF-β1 (2 ng/mL) - +
浓度 (nM) - -
100 50 30 10
实施例 2
实施例 60
实施例 86
实施例 92
实施例 94

图 1

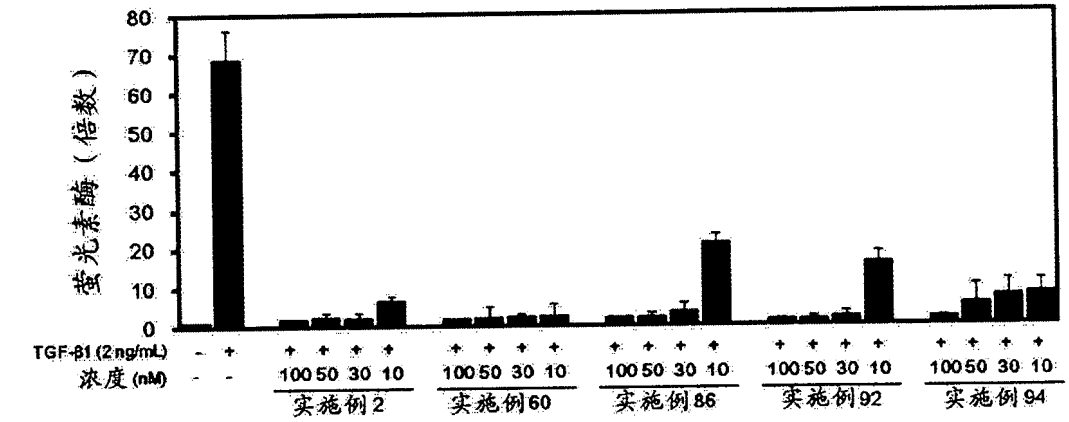

4T1-3PT-Luc 细胞
荧光素酶（倍数）
80
70
60
50
40
30
20
10
0
TGF-β1 (2 ng/mL) - +
浓度 (nM) - -
100 50 30 10
实施例 2
实施例 60
实施例 86
实施例 92
实施例 94

图 2

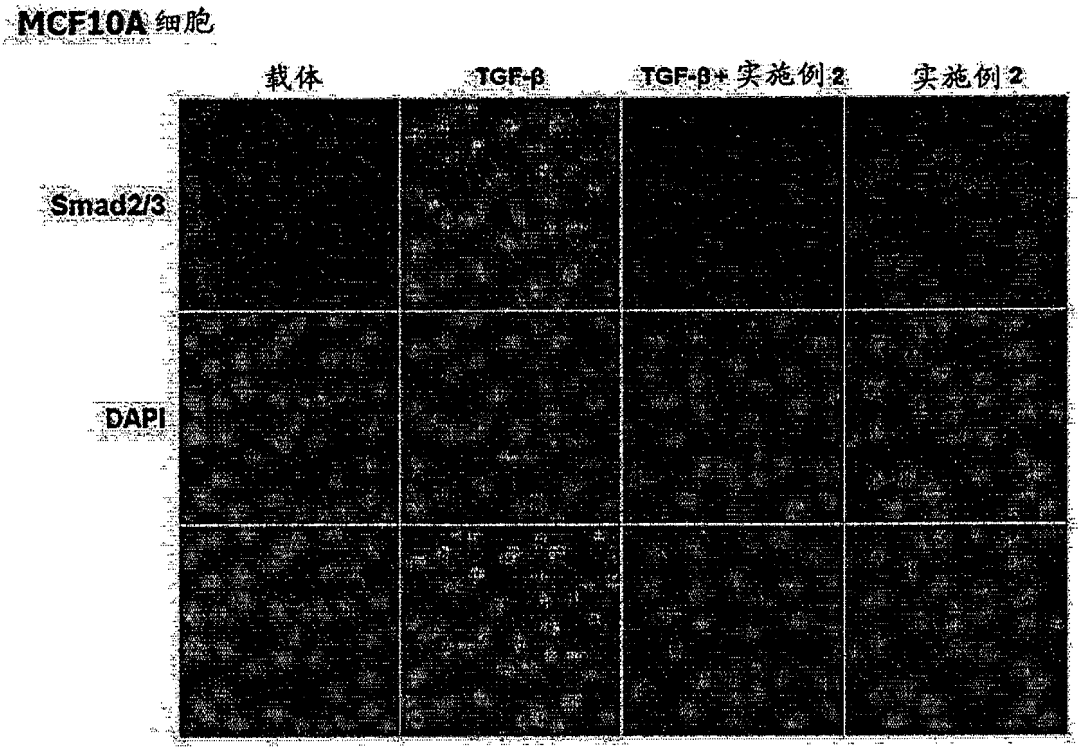

MCF10A 细胞
载体
TGF-β
TGF-β+ 实施例 2
实施例 2
Smad2/3
DAPI

图 3

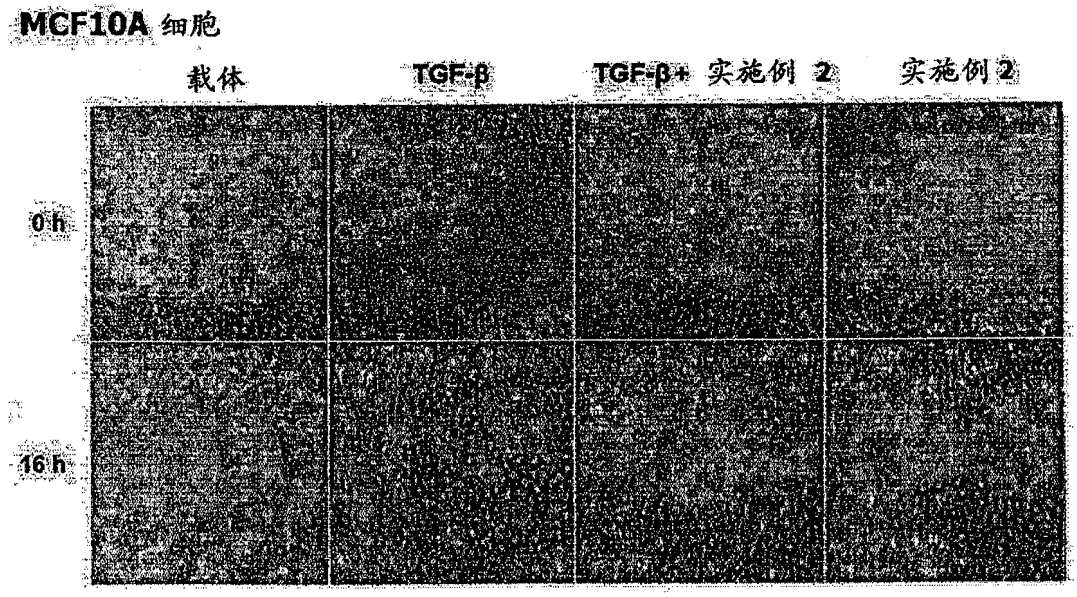

MCF10A 细胞
载体
TGF-β
TGF-β+ 实施例 2
实施例 2
0 h
16 h

图 4

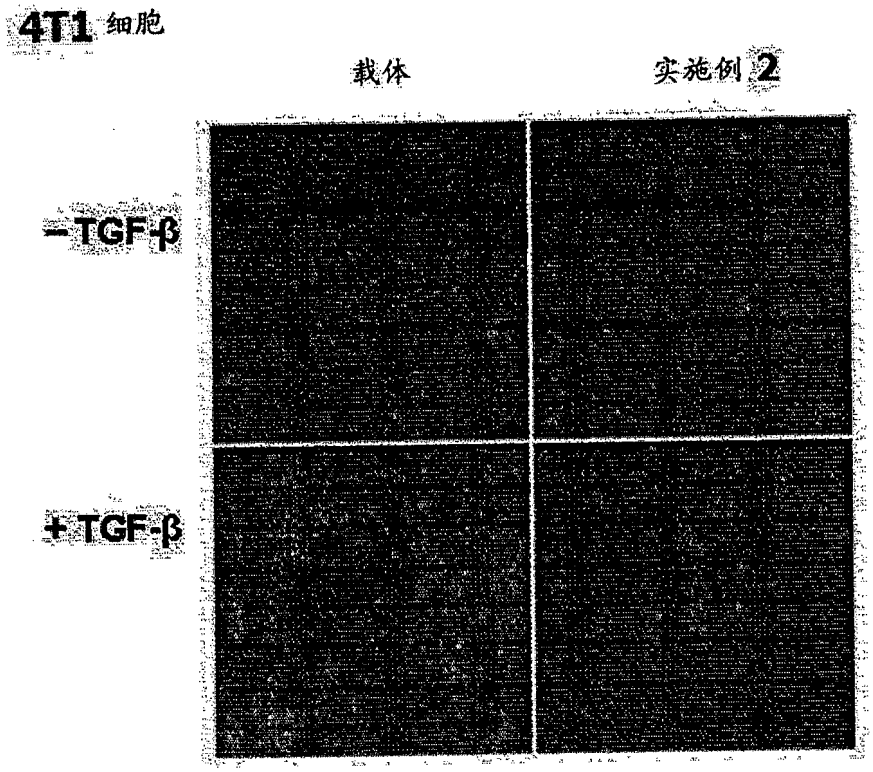
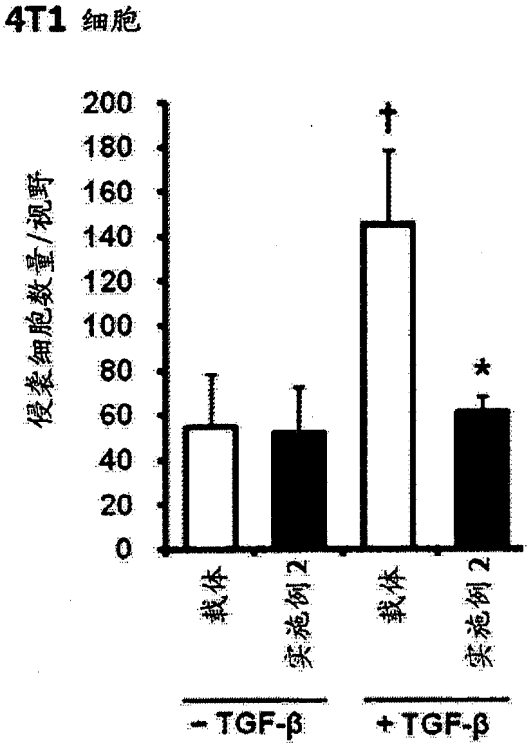


图 5a



数据代表每个视野的侵袭细胞数量 ± S.D. (n = 3).
†: 与载体组相比有显著性差异 ($P < 0.05$).
*: 与TGF-β-处理组相比有显著性差异($P < 0.05$).

图 5b

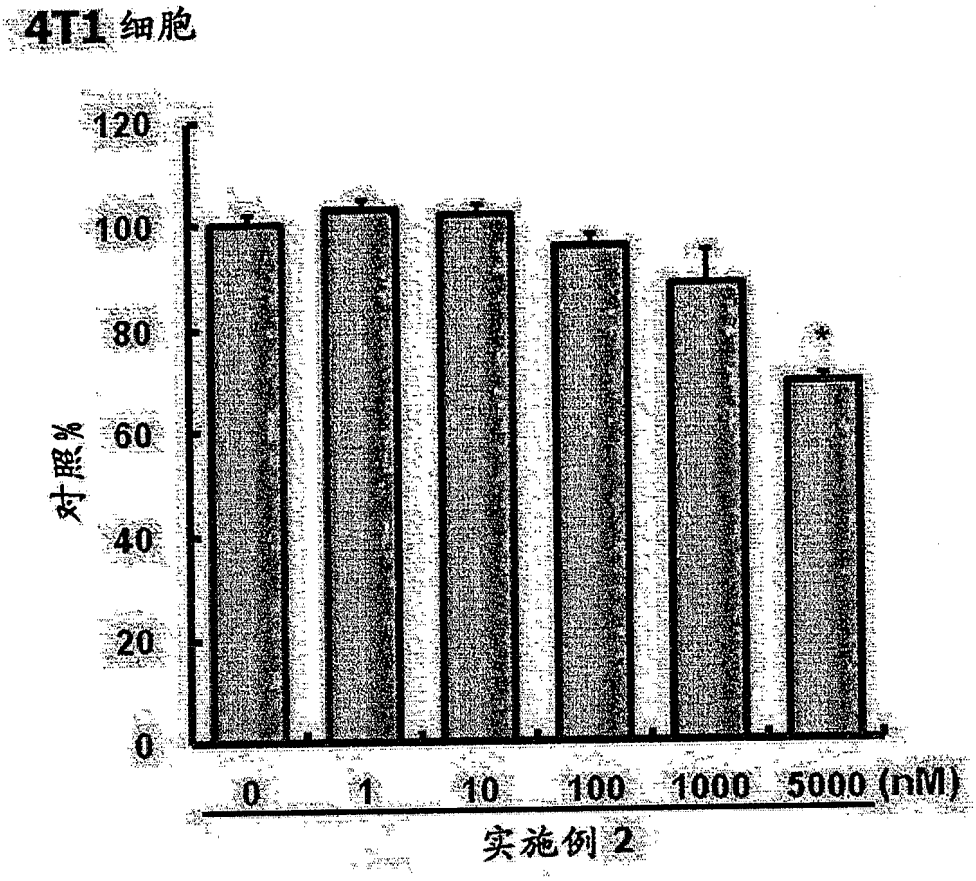

4T1 细胞
120
100
80
60
40
20
0
对照%
0
1
10
100
1000
5000 (nM)
实施例 2
数据代表平均值 ± S.D. (n = 4).
*: 与对照组相比有显著性差异 (P < 0.05).

图 6

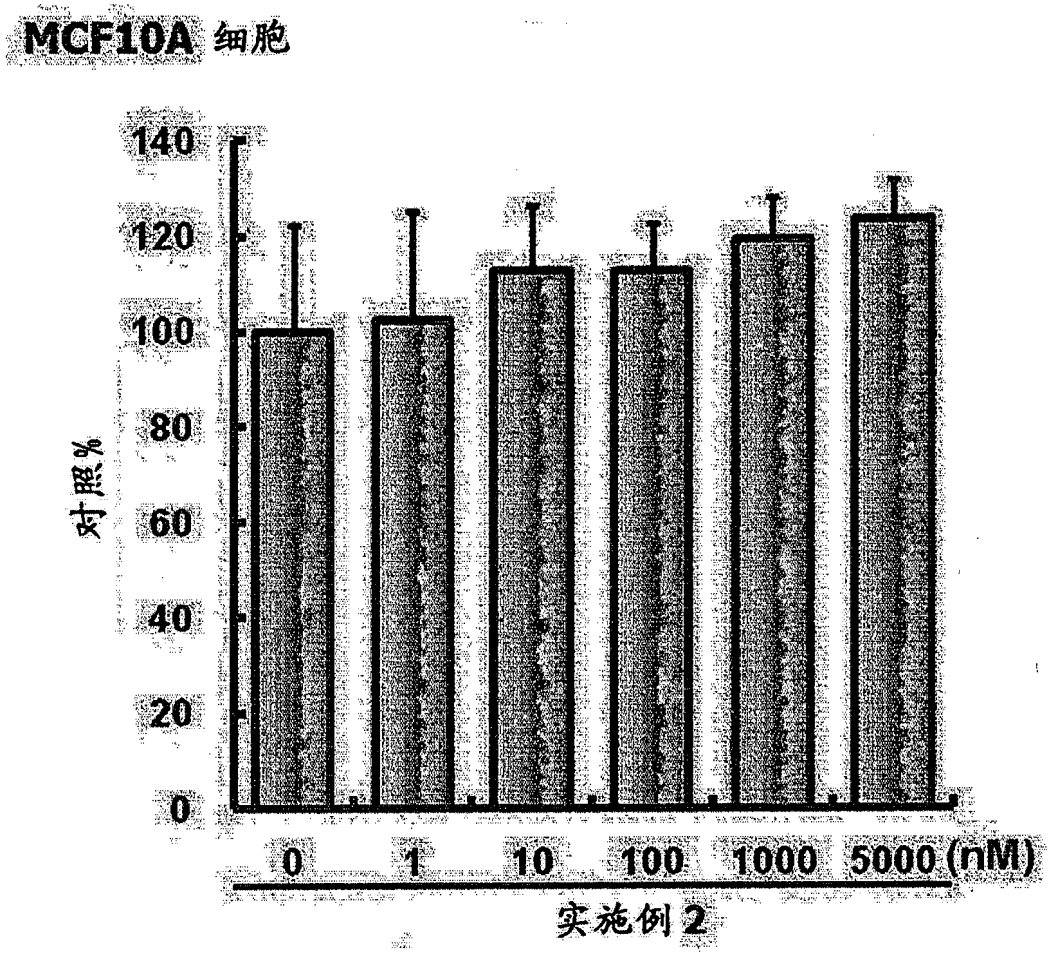

MCF10A 细胞
140
120
100
80
60
40
20
0
对照%
0
1
10
100
1000
5000 (nM)
实施例 2
数据代表平均值 ± S.D. (n = 4).

图 7

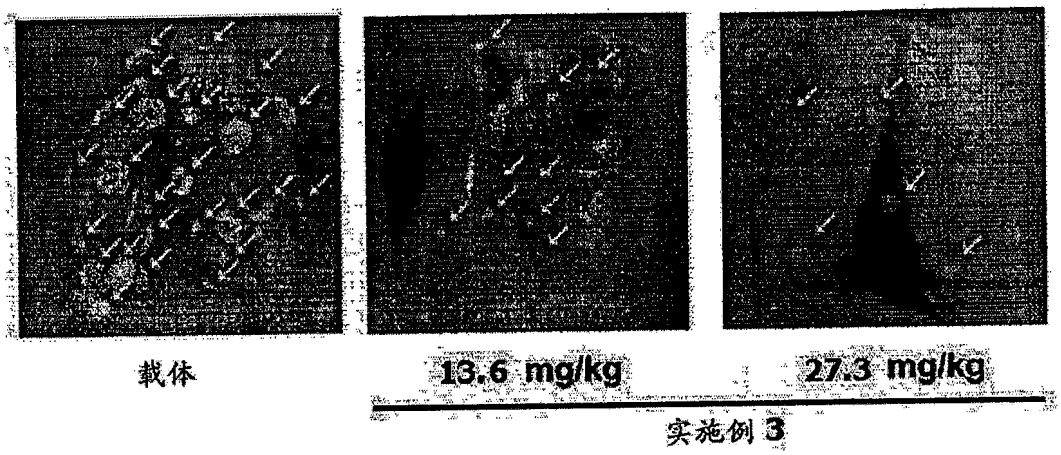
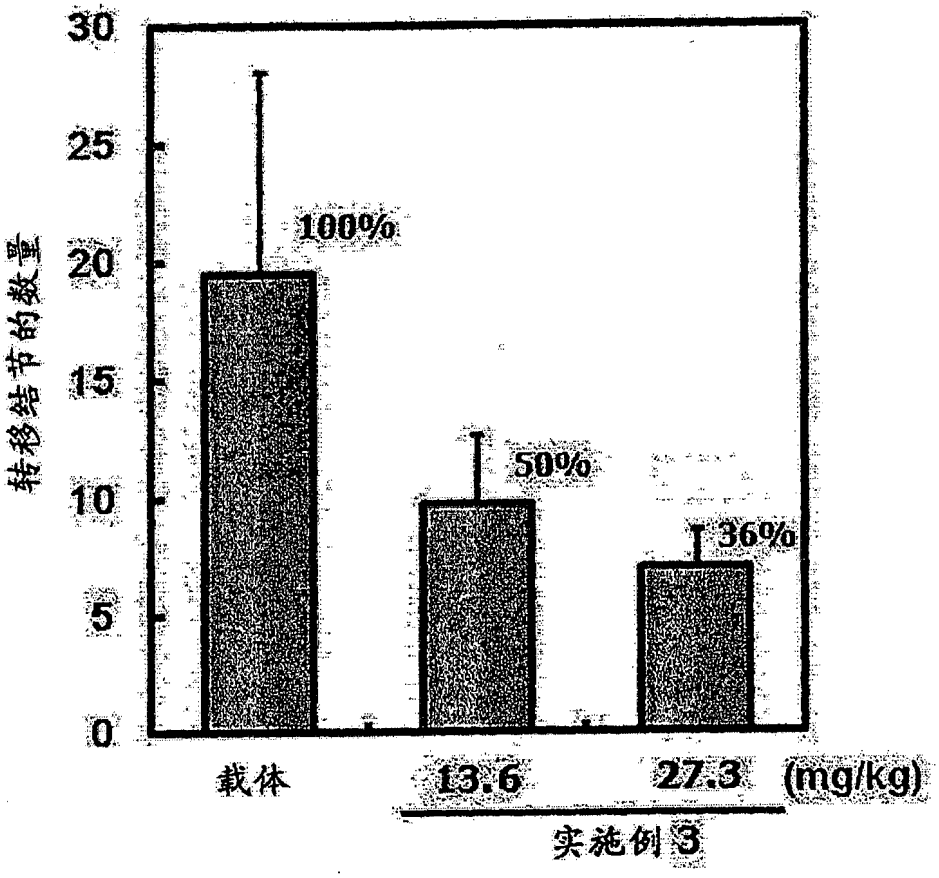


图 8a



数据代表平均值 ± S.E. (n = 8).

图 8b

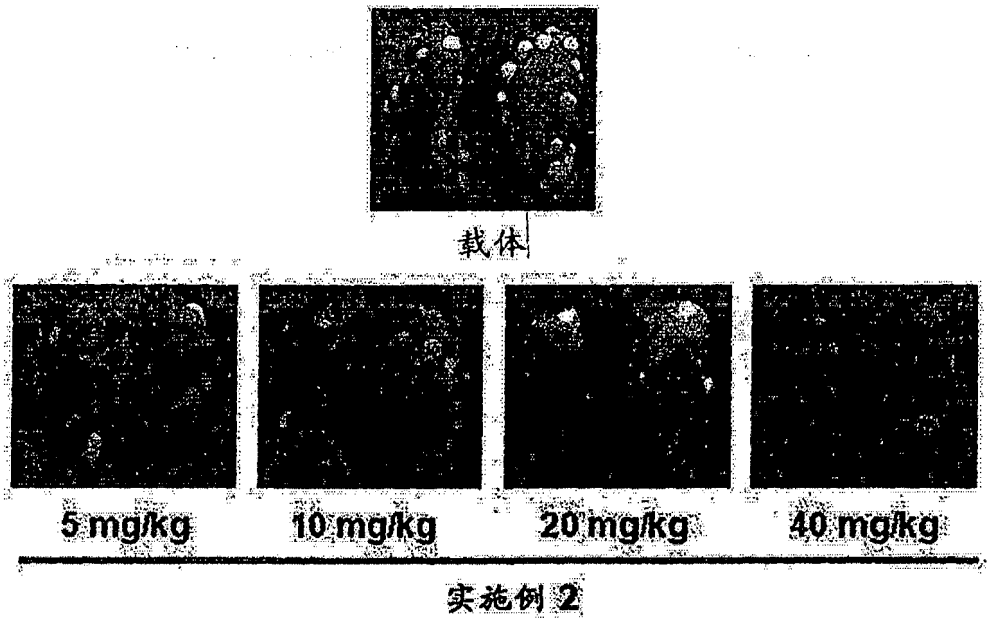


图 9a

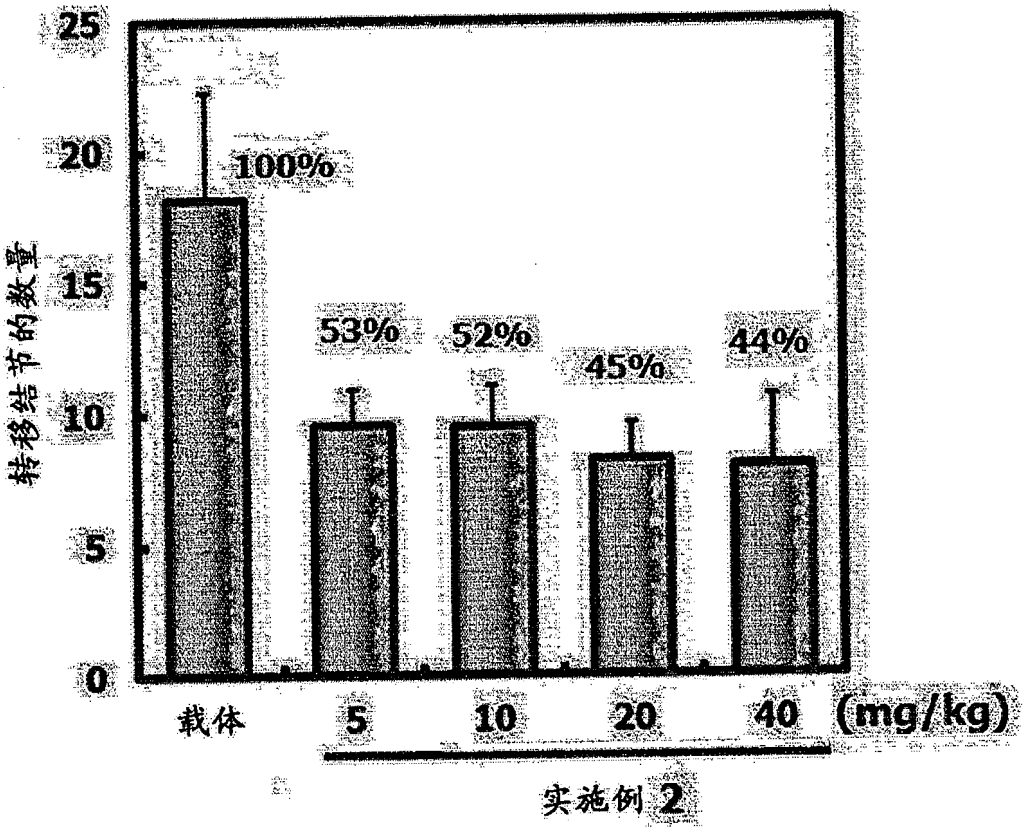

25
20
15
10
5
0
转移结节的数量
100%
53%
52%
45%
44%
载体
5
10
20
40
(mg/kg)
实施例 2
数据代表平均值 ± S.E. (n = 7–10).

图 9b

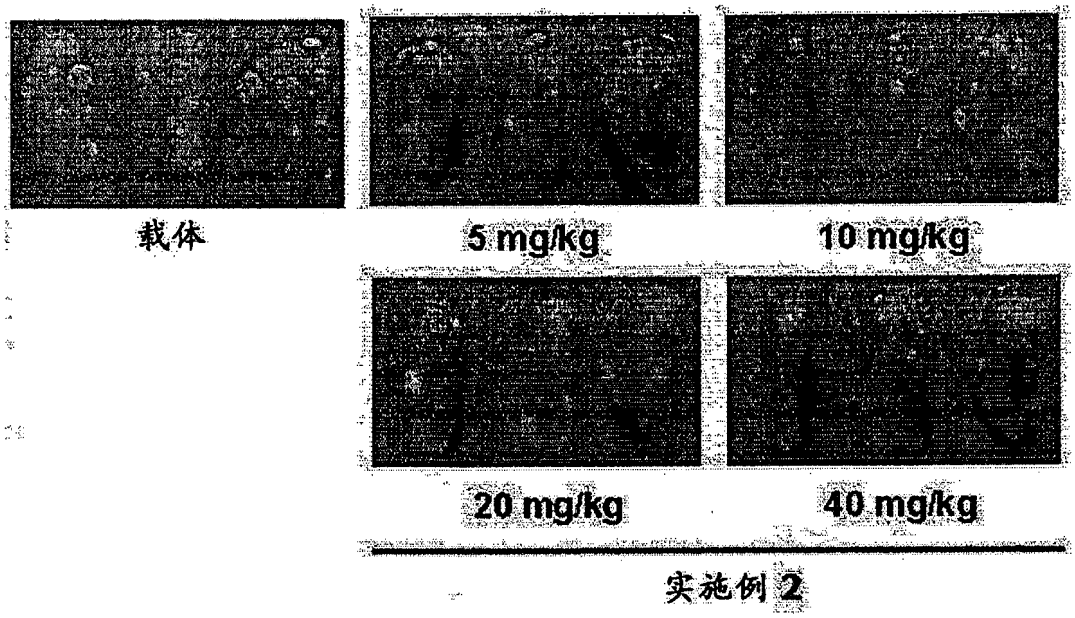


图 10a

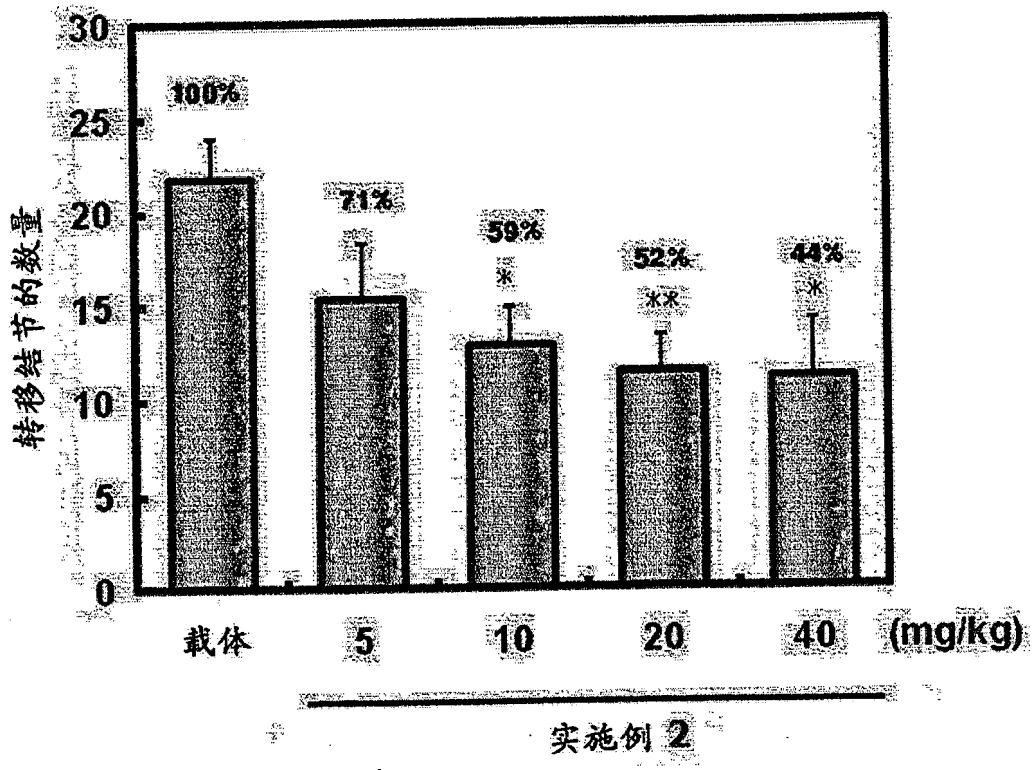

转移结节的数量
30
25
20
15
10
5
0
100%
71%
59%
52%
44%
*
**
*
载体
5
10
20
40
(mg/kg)
实施例 2
数据代表平均值 ± S.E. (n = 9–10).
*: 与载体组相比有显著性差异 ($p < 0.05$).
**: 与载体组相比有显著性差异 ($p < 0.01$).

图 10b

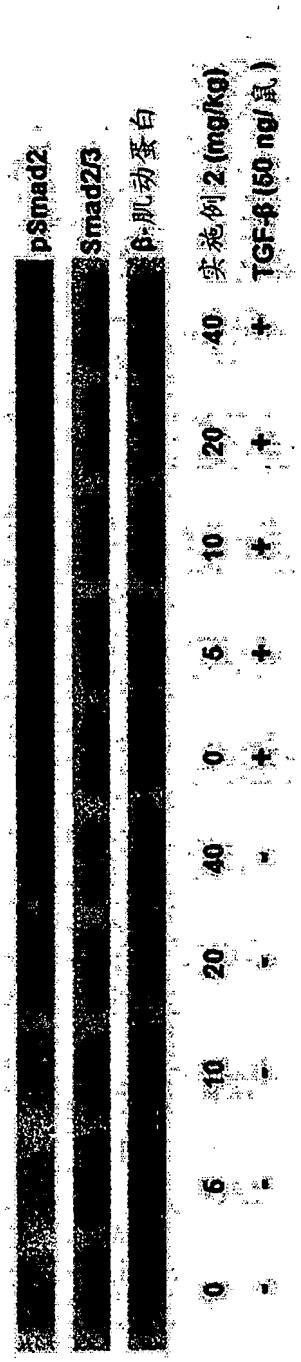

pSmad2
Smad2/3
β-肌动蛋白
实施例2 (mg/kg)
TGF-β (50 ng/鼠)
0
5
10
20
40
0
5
10
20
40
-
-
-
-
-
+
+
+
+
+

图 10c

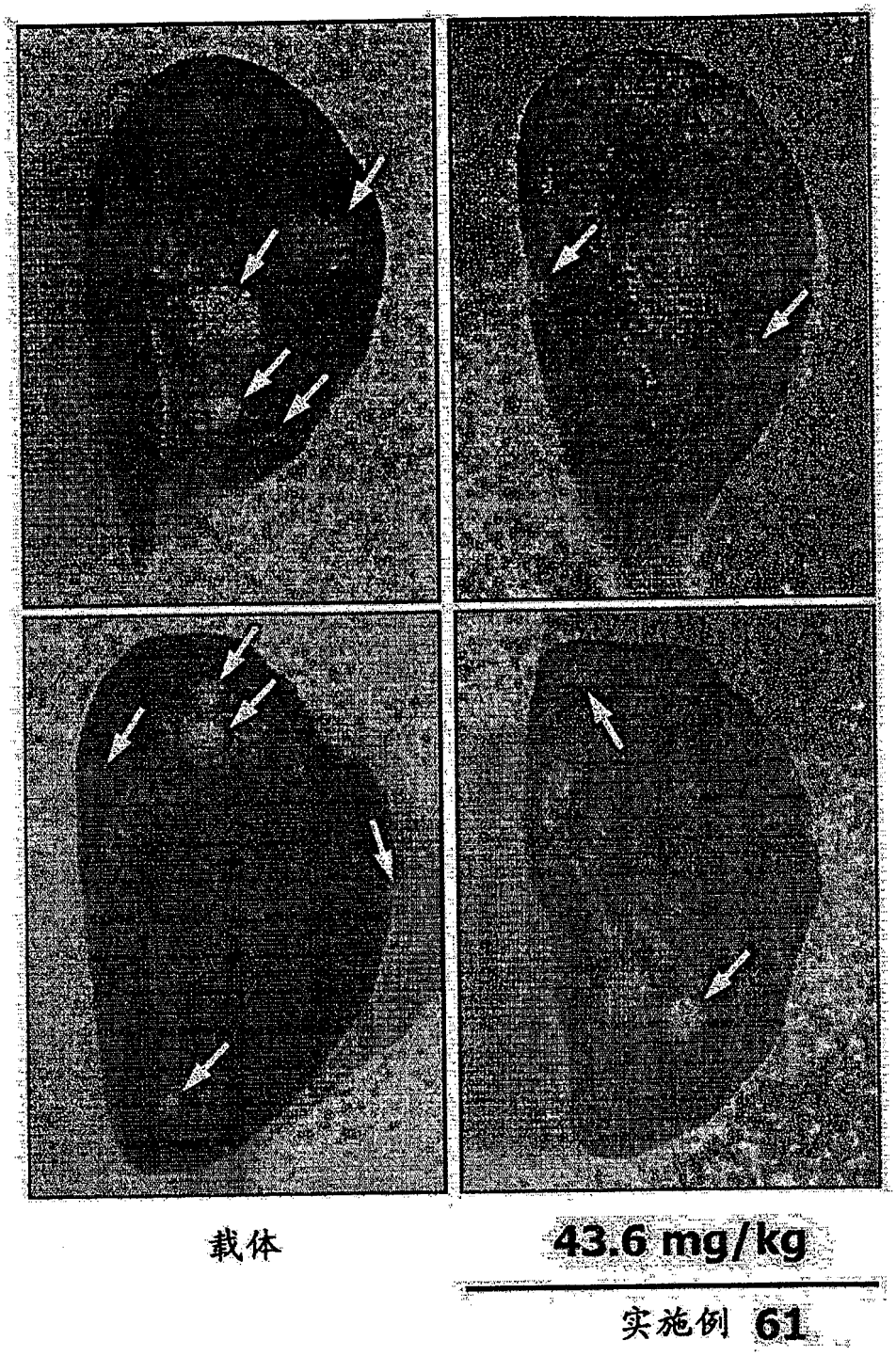
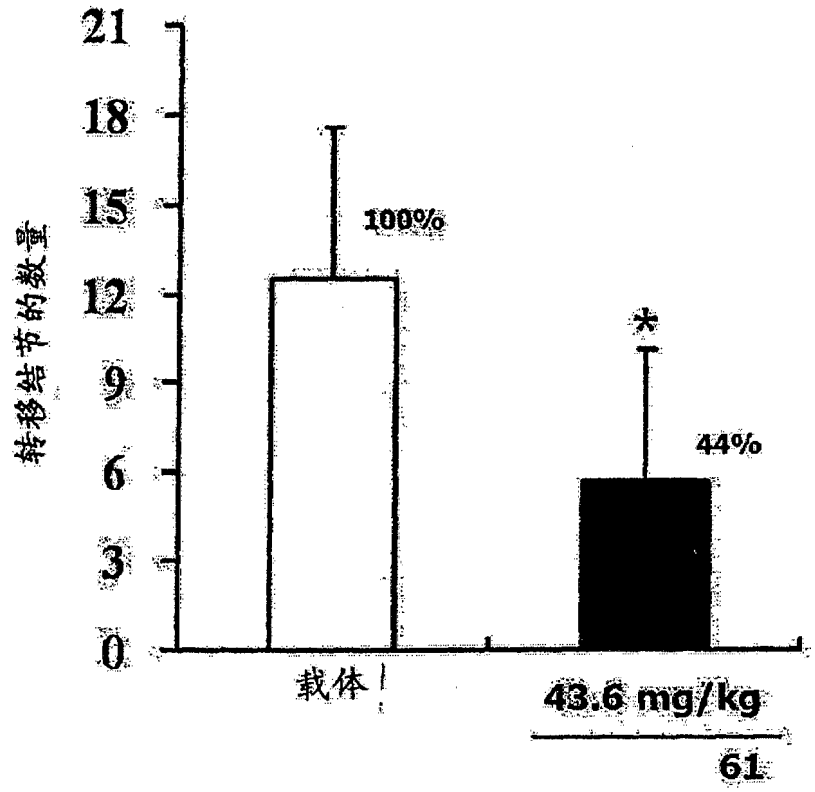
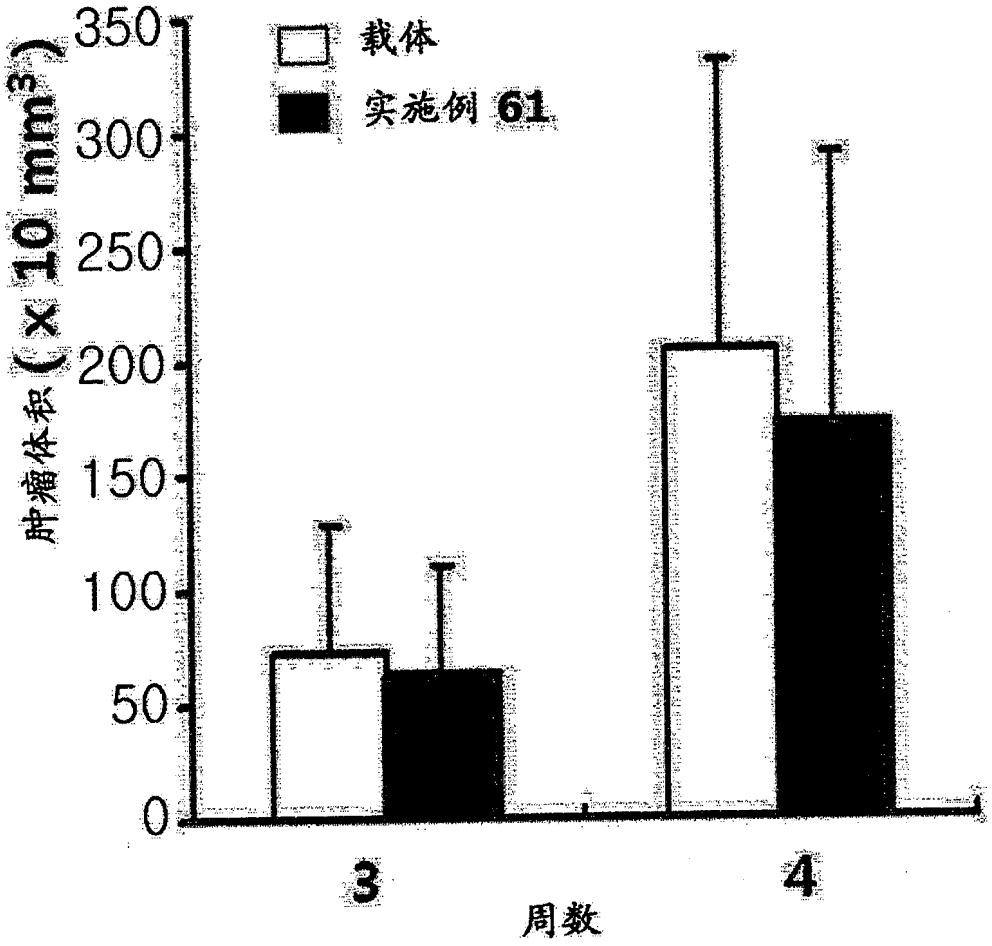


图 11a



数据代表平均值 ± S.D. (n = 8).
*: 与载体组相比有显著性差异 ($p < 0.05$).

图 11b



数据代表平均值 ± S.D. (n = 6)。

图 11c

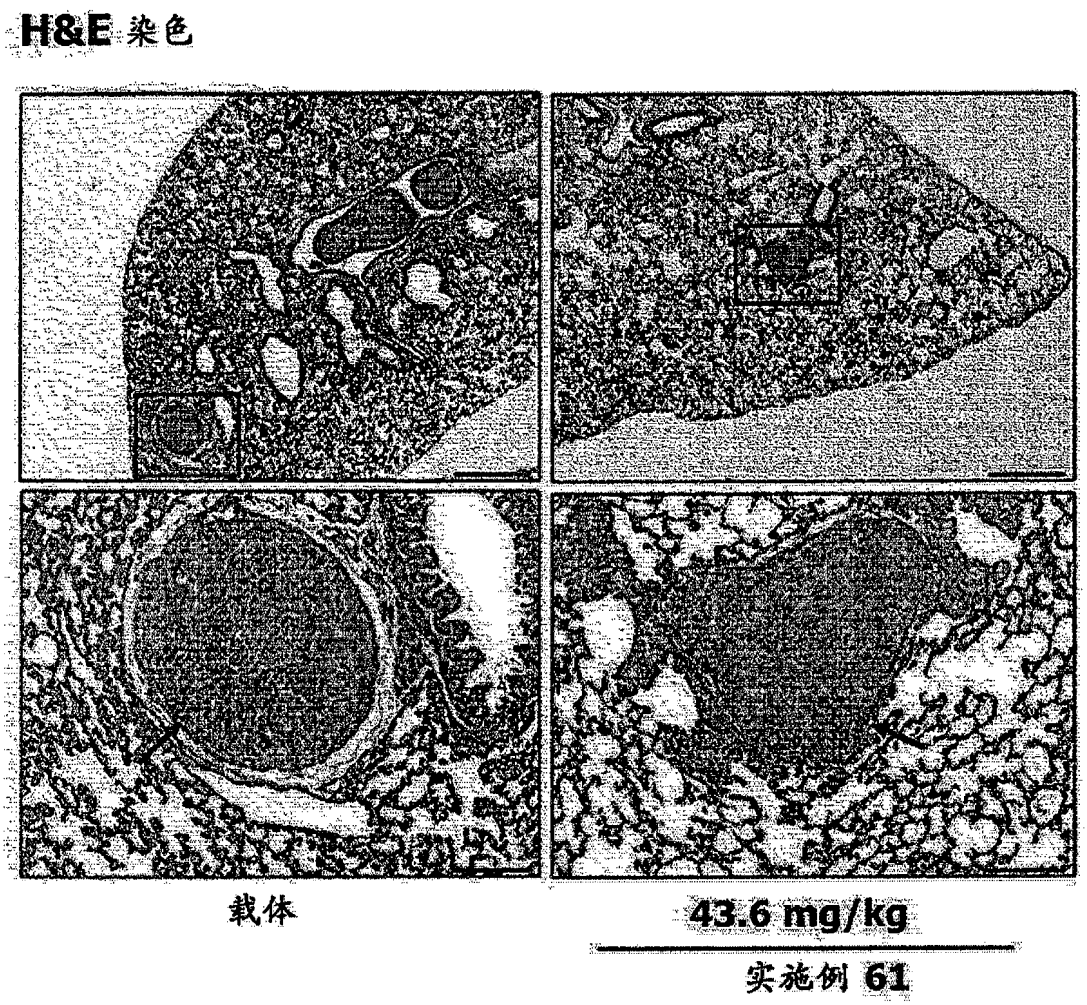
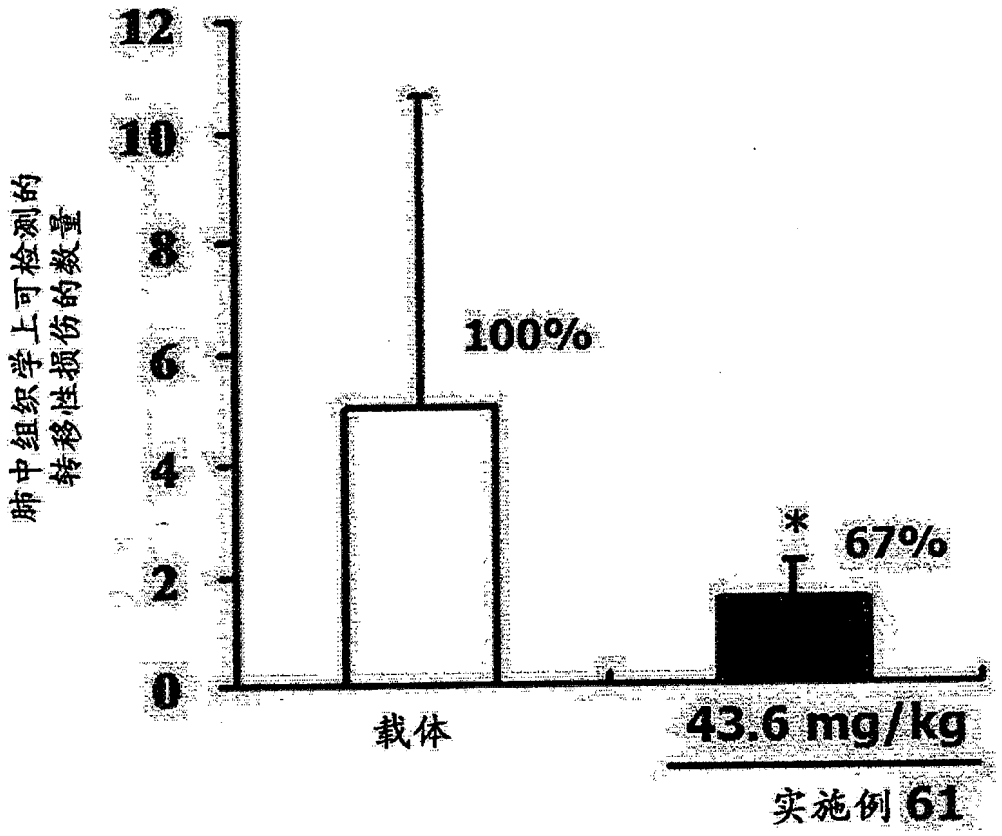


图 12a



数据代表平均值 ± S.D. (n = 3).
*: 与载体组相比有显著性差异 ($p < 0.05$).

图 12b

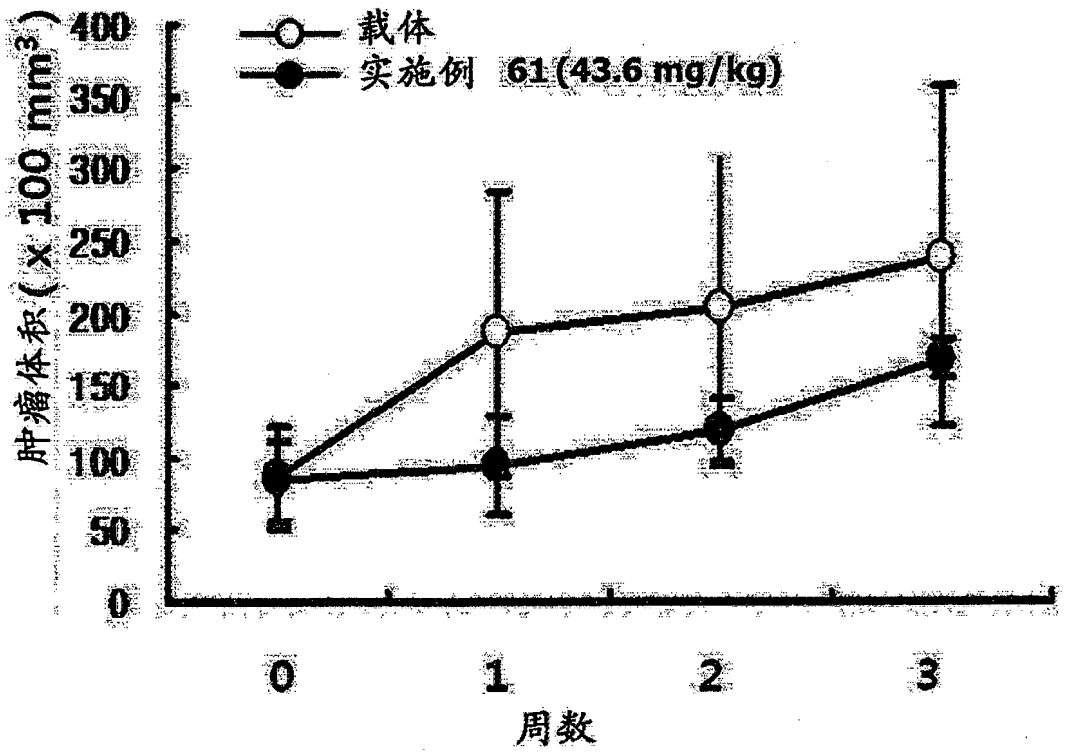

载体
实施例 61(43.6 mg/kg)
肿瘤体积(x 100 mm³)
400
350
300
250
200
150
100
50
0
0
1
2
3
周数
数据代表平均值 ± S.D. (n = 3).

图 12c

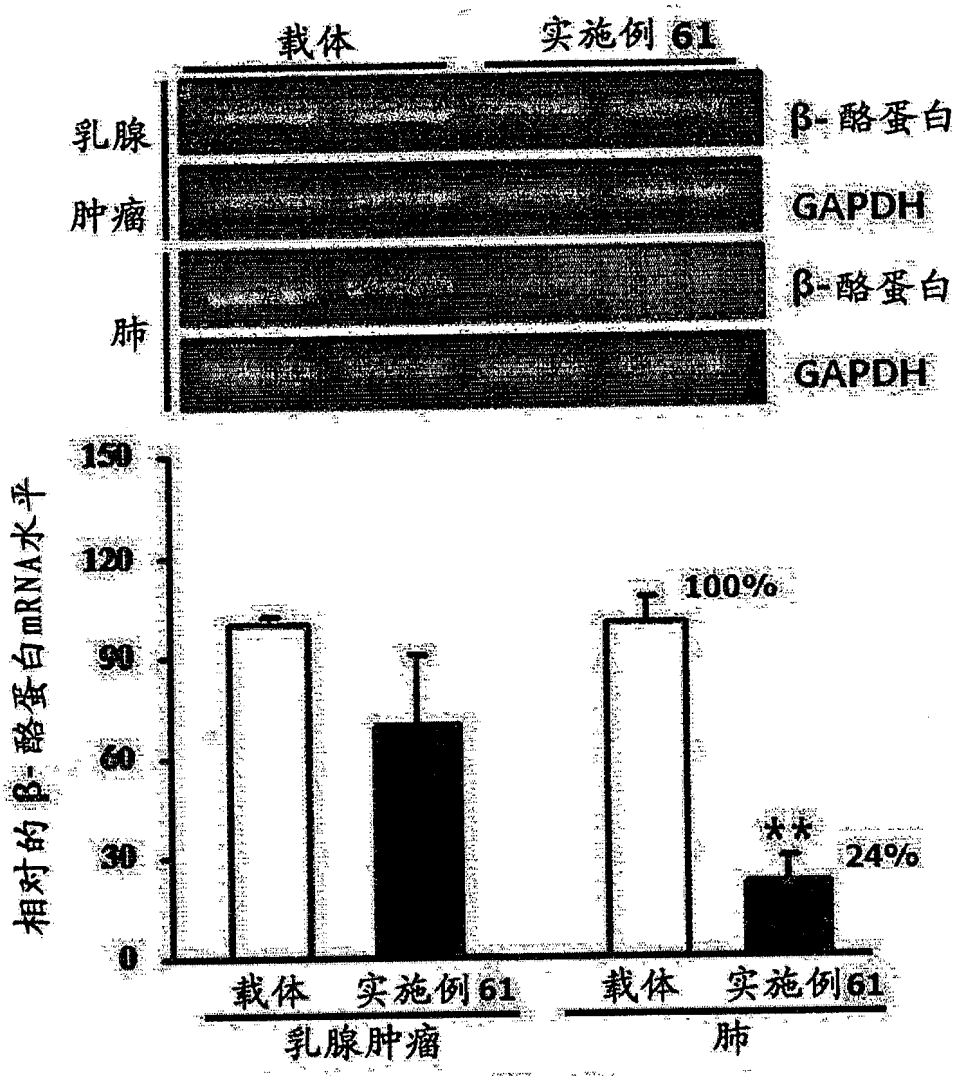
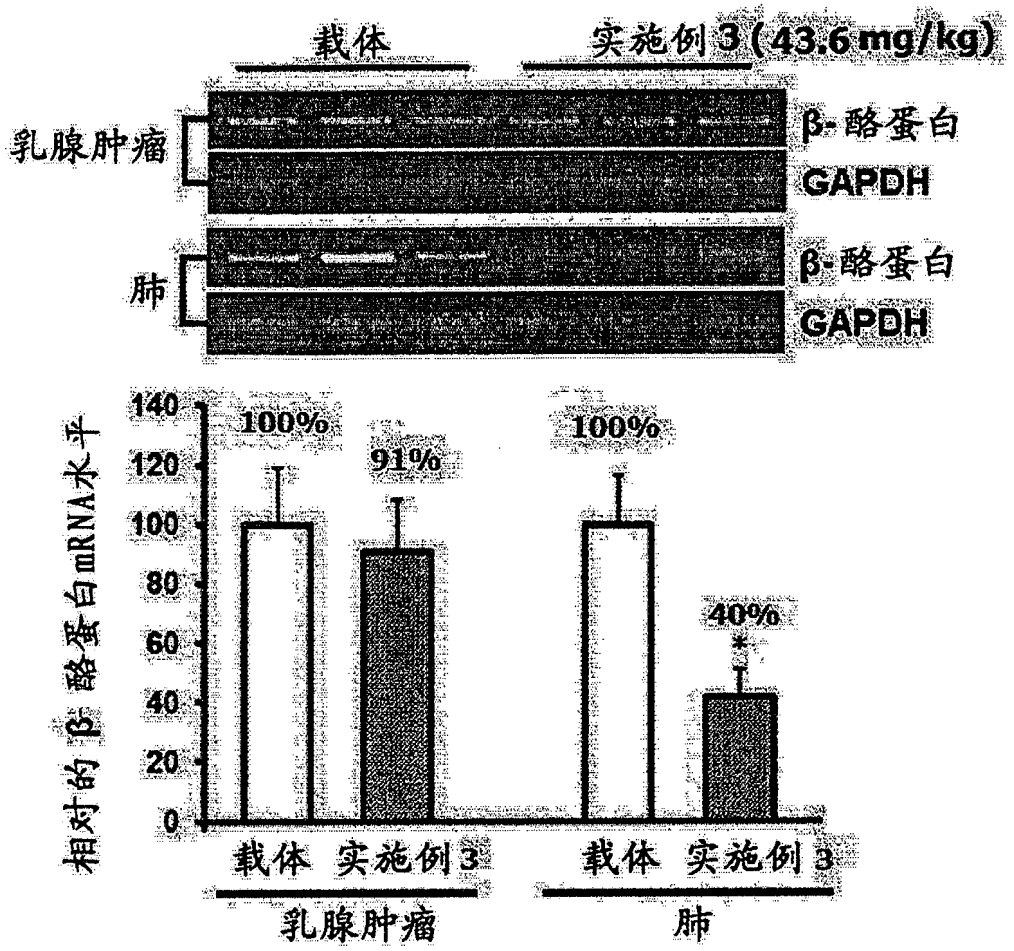

载体
实施例 61
乳腺肿瘤
肺
β-酪蛋白
GAPDH
β-酪蛋白
GAPDH
相对的β-酪蛋白mRNA水平
150
120
90
60
30
0
100%
**
24%
载体
实施例61
载体
实施例61
乳腺肿瘤
肺
数据代表平均值±S.D. (n = 6).
**.在肺中与载体组相比有显著性差异(p < 0.01).

图 12d



数据代表平均值 ± S.E. (n = 7–10).
*：在肺中与载体组相比有显著性差异 ($p < 0.05$).

图 13a

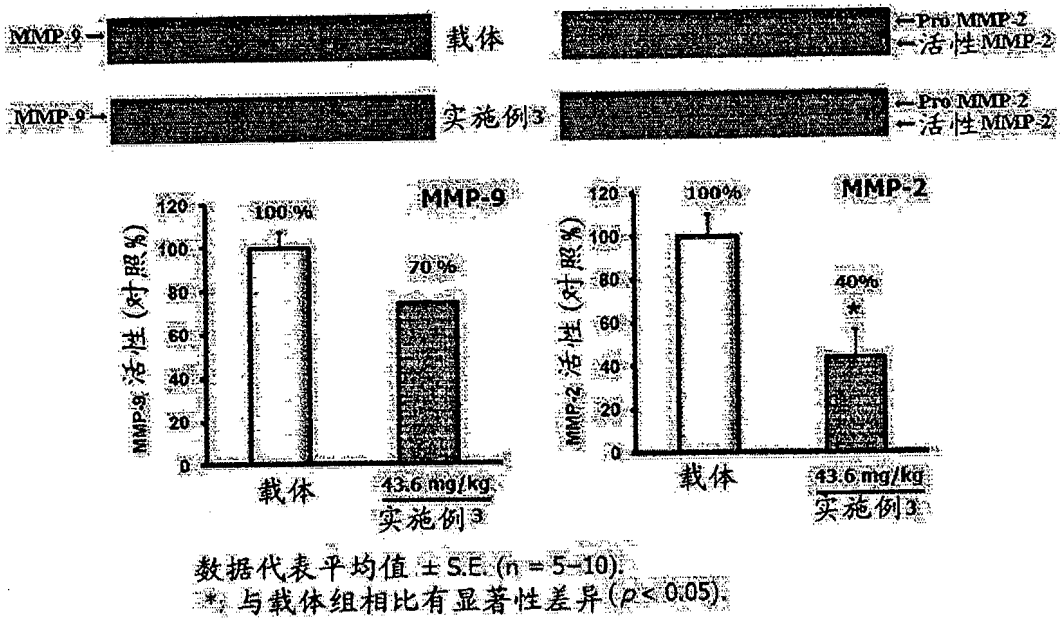
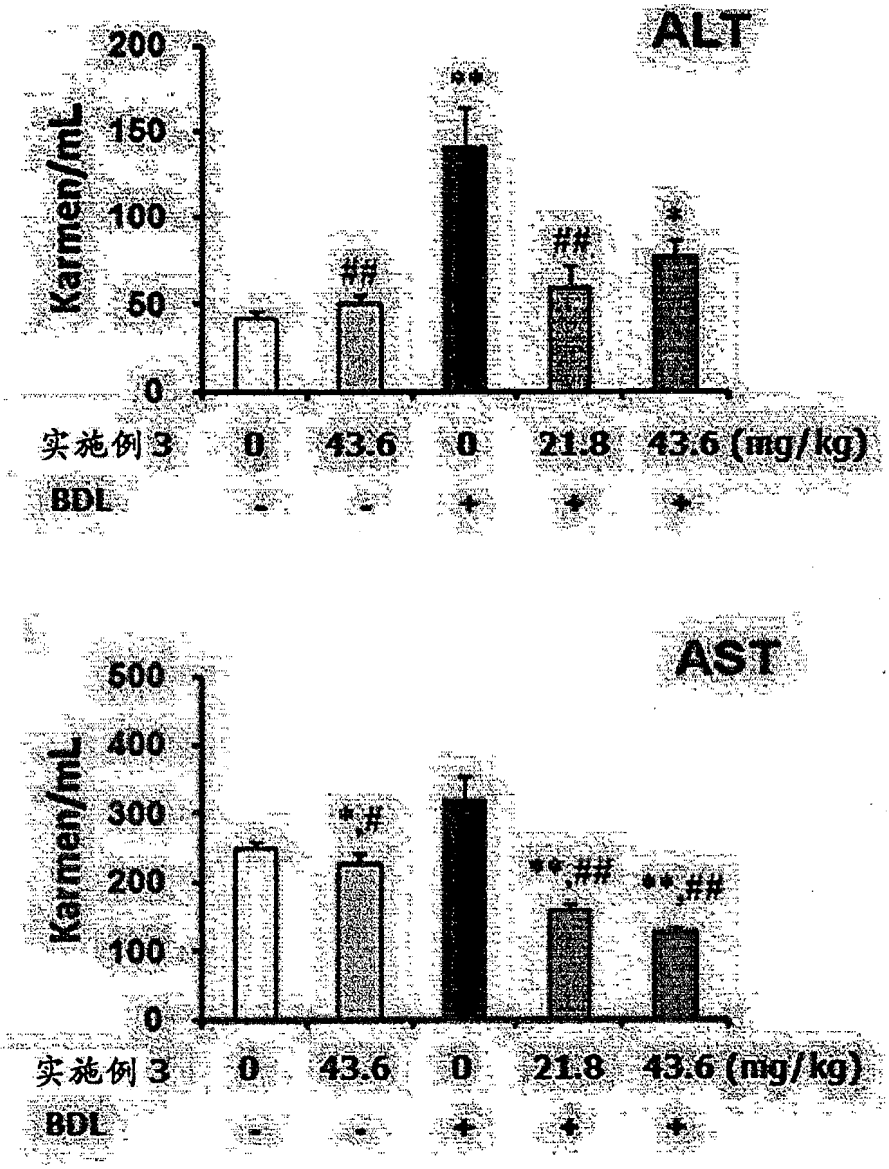

MMP-9
载体
←Pro MMP-2
←活性MMP-2
MMP-9
实施例3
←Pro MMP-2
←活性MMP-2
MMP-9
MMP-2
MMP-9活性（对照%）
MMP-2活性（对照%）
100%
70%
40%
*
载体
43.6 mg/kg
实施例3
数据代表平均值 ± S.E. (n = 5–10)
*: 与载体组相比有显著性差异 ($p < 0.05$)

图 13b

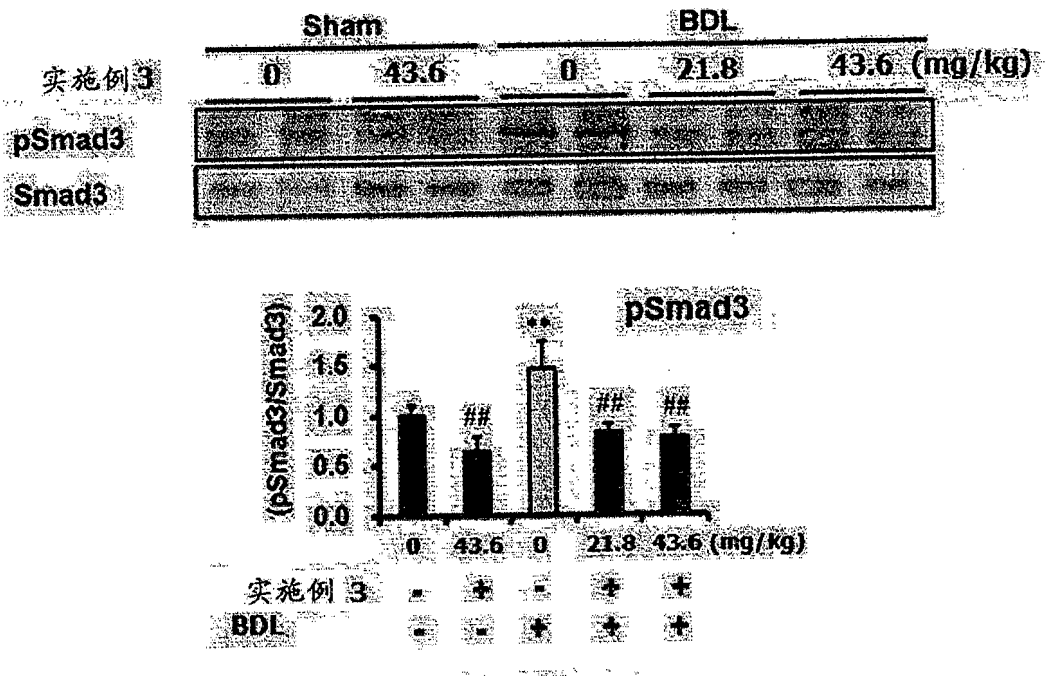


数据代表平均值 ± S.E. (n = 5–8).

*: $p < 0.05$ 相对于 sham. **: $p < 0.01$ 相对于 sham.

#: $p < 0.05$ 相对于 BDL. ##: $p < 0.01$ 相对于 BDL.

图 14a



数据代表平均值 ± S.E. (n = 5).

**: $p < 0.01$相对于sham. ##: $p < 0.01$相对于BDL.

图 14b

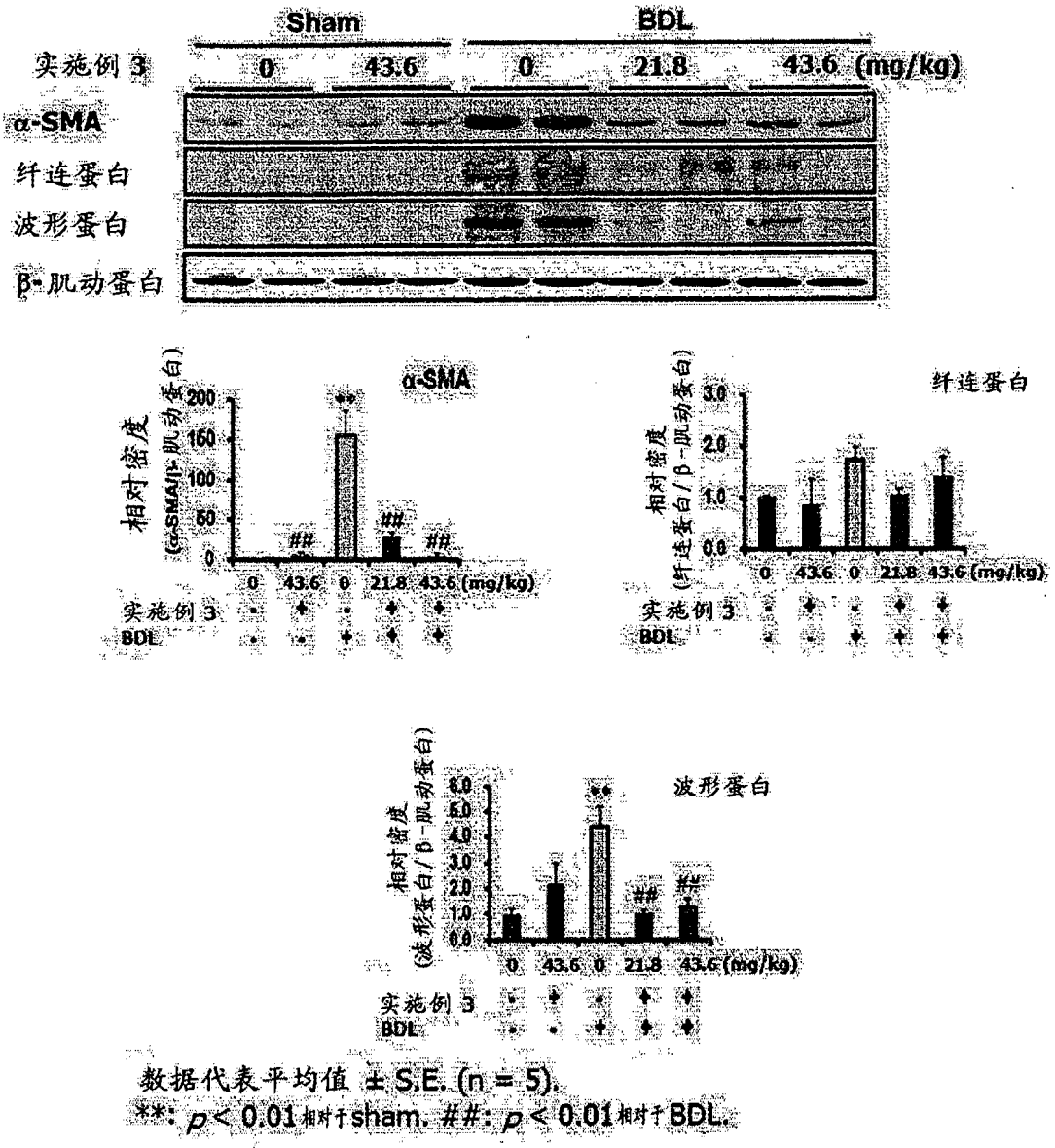

Sham
BDL
实施例 3
0
43.6
0
21.8
43.6 (mg/kg)
α-SMA
纤连蛋白
波形蛋白
β-肌动蛋白
相对密度
(α-SMA/β-肌动蛋白)
α-SMA
(纤连蛋白/β-肌动蛋白)
纤连蛋白
(波形蛋白/β-肌动蛋白)
波形蛋白
0 43.6 0 21.8 43.6 (mg/kg)
实施例 3
BDL
数据代表平均值 ± S.E. (n = 5).
**: p < 0.01 相对于 sham. ##: p < 0.01 相对于 BDL.

图 14c

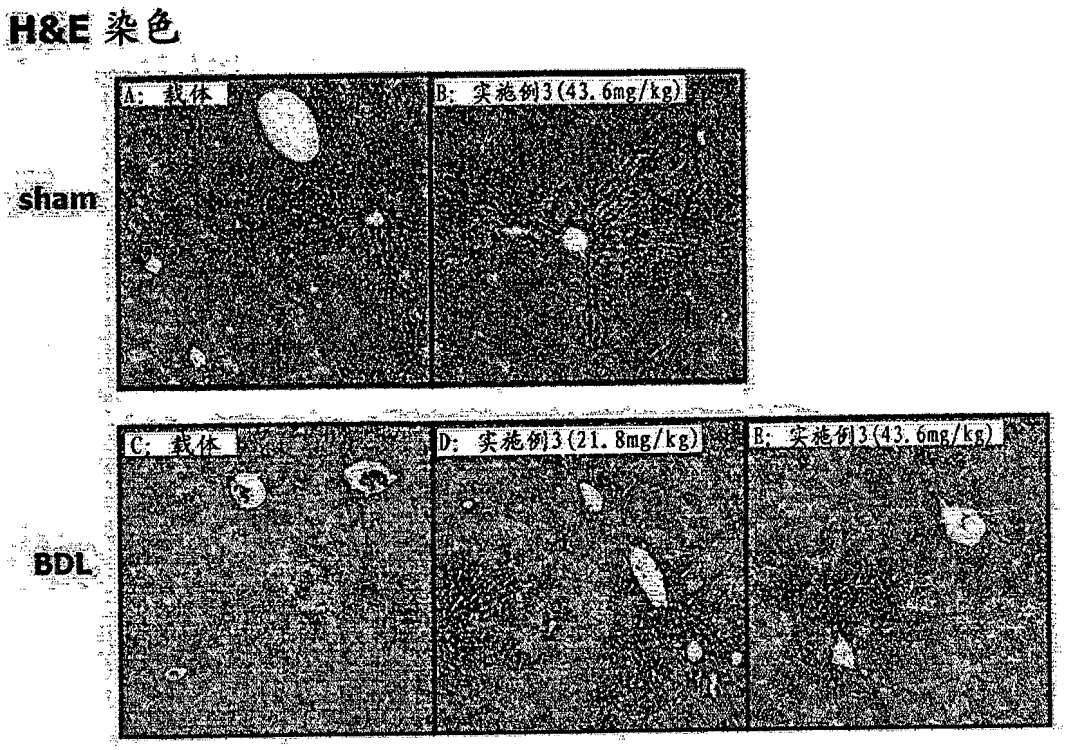
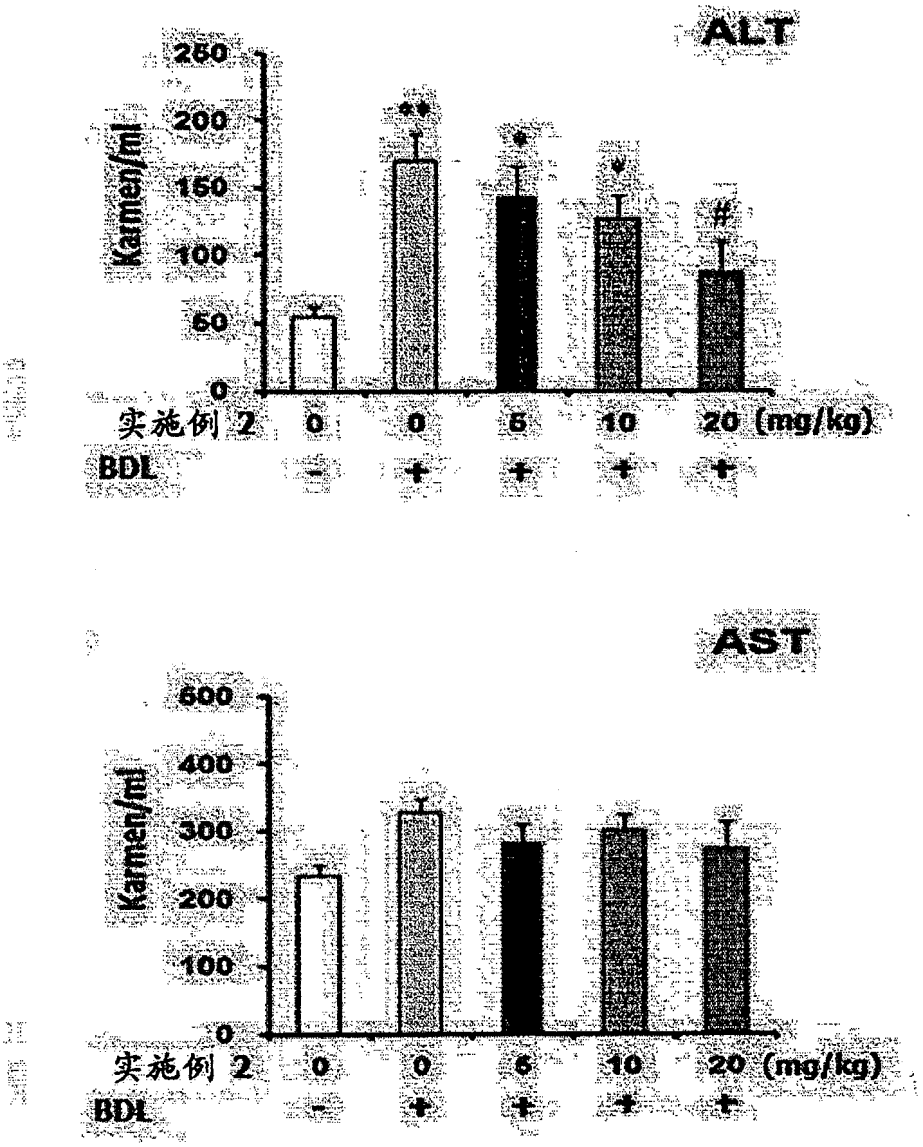

H&E 染色
A：载体
B：实施例3(43.6mg/kg)
sham
C：载体
D：实施例3(21.8mg/kg)
E：实施例3(43.6mg/kg)
BDL

图 14d

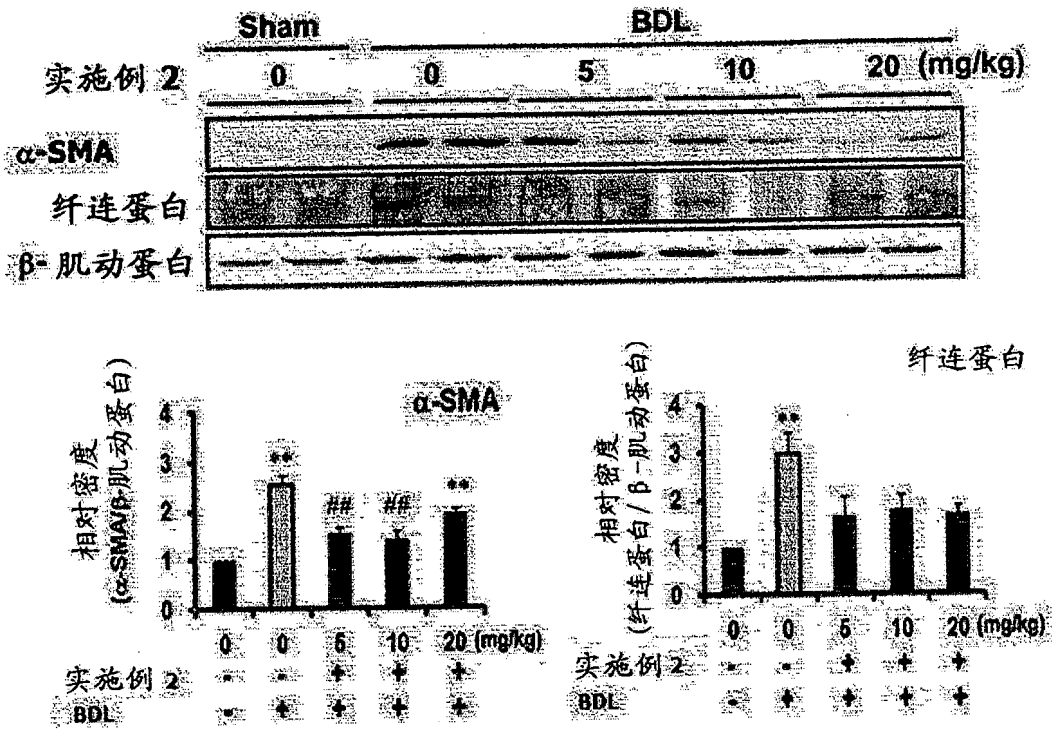


数据代表平均值 ± S.E. (n = 5–8).

*: $p < 0.05$ 相对于 sham. **: $p < 0.01$ 相对于 sham.

#: $p < 0.05$ 相对于 BDL.

图 15a



数据代表平均值 ± S.E. (n = 5).

**: $p < 0.01$ 相对于 sham. ##: $p < 0.01$ 相对于 BDL.

图 15b

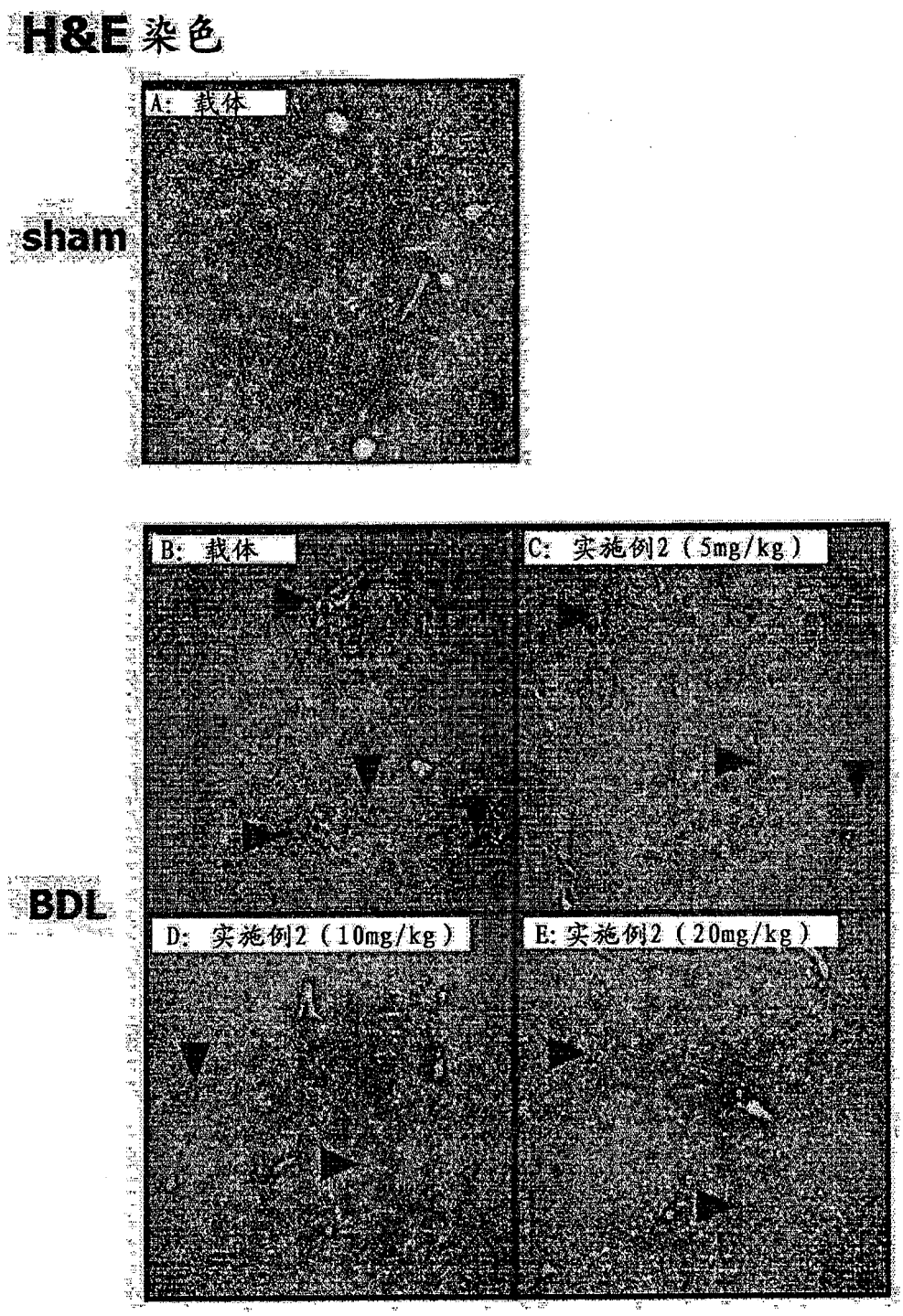


图 15c

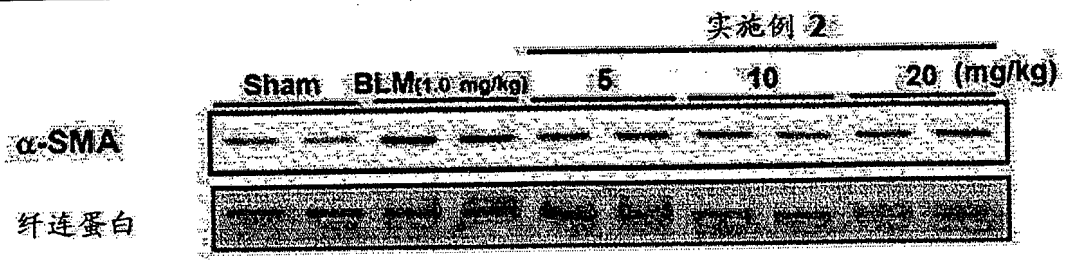

实施例 2
Sham
BLM(1.0 mg/kg)
5
10
20 (mg/kg)
α-SMA
纤连蛋白

图 16a

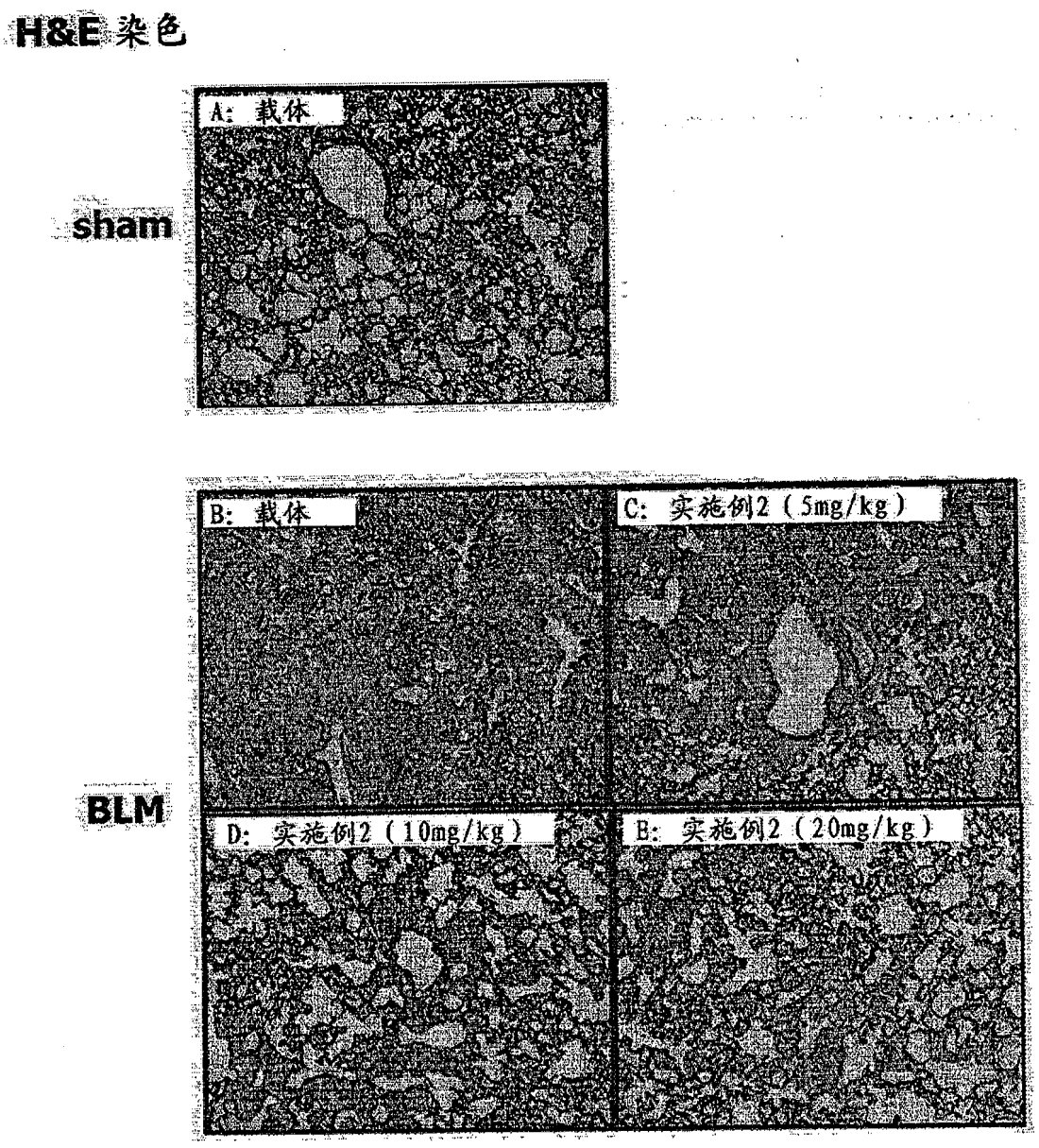

H&E 染色
sham
A: 载体
BLM
B: 载体
C: 实施例2 (5mg/kg)
D: 实施例2 (10mg/kg)
E: 实施例2 (20mg/kg)

图 16b