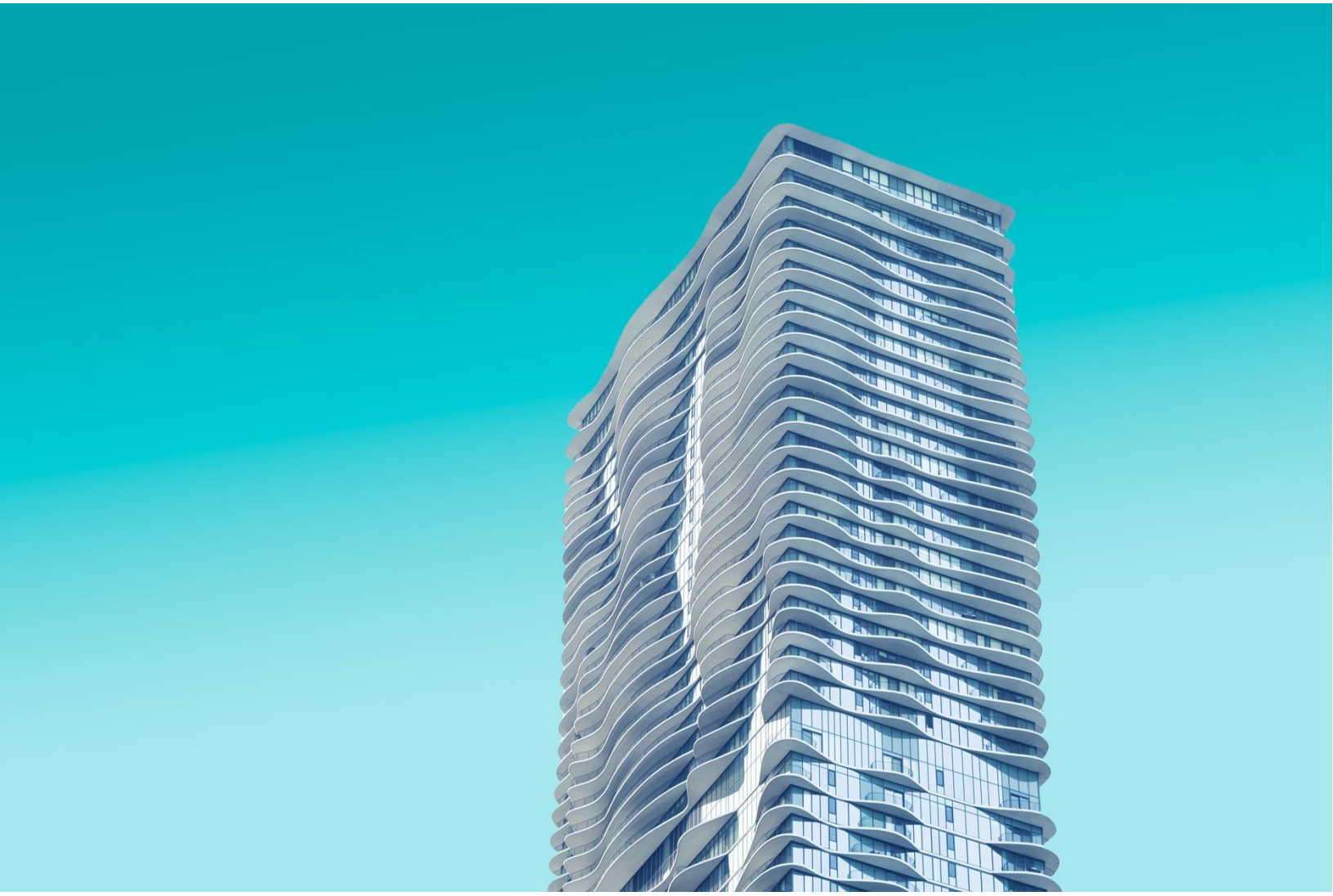
Cortellis™

A Clarivate Analytics solution

BioWorld Science

科睿唯安 2020 年 2 月

创新药研发动态

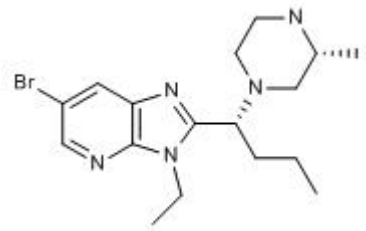


目 录

有关镇痛剂和麻醉剂的新闻报道

2020 年 2 月 17 日，Esteve 公司合成了兼具 mu 阿片类受体配体/电压门控型钙通道 α2/δ-1 亚基配体作用的药物

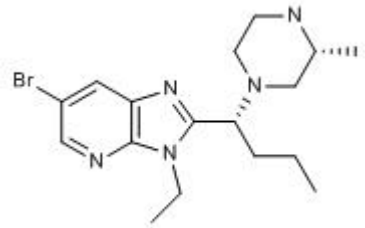
Esteve Pharmaceuticals 发现咪唑并吡啶衍生物兼具双重电压门控型钙通道 α2/δ-1 亚基配体和 mu-阿片类受体配体的作用机制；可用于治疗异常性疼痛、焦虑、抑郁、痛觉过敏、注意力缺陷多动障碍（ADHD）和慢性神经性疼痛。放射性配体结合试验（WO 2020021015）发现，这种例示化合物可抑制[3H]-加巴喷丁与细胞膜表达的人源 Cav2.2 钙通道 α2/δ-1 亚基的结合（Ki < 100 nM），并可抑制[3H]-DAMGO 与在 CHO-K1 细胞膜中转染的人源 mu 阿片类受体的结合（Ki≥500 nM）。



WO 2020021015

Feb 17, 2020. Dual mu-opioid/voltage-gated calcium channels alpha2/delta-1 subunit ligands synthesized at Esteve

Esteve Pharmaceuticals has discovered imidazopyridine derivatives acting as dual voltage-gated calcium channels alpha2/delta-1 subunit and mu-opioid receptor ligands reported to be useful for the treatment of allodynia, anxiety, depression, hyperalgesia, attention deficit hyperactivity disorder (ADHD) and chronic and neuropathic pain. An exemplified compound inhibited binding of [3H]-gabapentin to the human alpha2/delta-1 subunit of Cav2.2 calcium channels expressed in membranes (Ki < 100 nM) and [3H]-DAMGO to human mu-opioid receptors transfected in CHO-K1 cell membranes (Ki = 500 nM or greater) in radioligand binding assays (WO 2020021015).



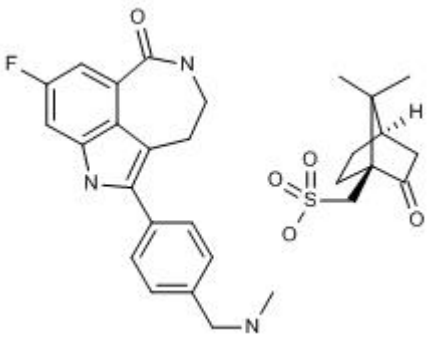
WO 2020021015

有关恶性肿瘤的新闻报道

2020 年 2 月 19 日，由于 rucaparib 在 ATLAS 研究中缺乏对转移性尿路上皮癌（mUC）治疗的药物活性而导致该研究暂停

Clovis Oncology 的研究人员提供了 PARP 抑制剂（PARPi）rucaparib 的 II 期 ATLAS 研究数据，目前正在对该药在复发性、局部晚期或转移性尿路上皮癌（mUC）患者中的疗效进行评价（ClinicalTrials.gov 识别码 NCT03397394）。在数据截止日时，97 例具有可测量病灶且既往接受过 1 ~ 2 种治疗方案后发生疾病进展患者被纳入到开放的 II 期 ATLAS 研究，该研究旨在评价 rucaparib 在既往经治的局部晚期/不可手术切除的尿路上皮癌（UC）或转移性尿路上皮癌（mUC）患者中的安全性和疗效。患者入组时不考虑其肿瘤同源重组缺陷（HRD）状态，但须排除既往使用过 PARPi 的患者。入组研究的受试者治疗方案为 rucaparib 600 mg 口服，每日 2 次。在入组的 97 例患者中，20 例（20.6%）为 HRD 阳性，30 例（30.9%）为 HRD 阴性，47 例（48.5%）的 HRD 状态未知。4 例患者携带致病的 BRCA1/2 突变。在数据截止日时，患者的中位治疗时间为 54 天，目前尚未报告已经得到证实的治疗反应。在 96 例可评估的患者中，27 例（28.1%）的最佳治疗反应为疾病稳定，临床获益率（CBR）为 12.5%，中位无进展生存期为 1.8 个月。未观察到 HRD 状态与临床活动性之间的相关性。共有 93 例患者（95.9%）中止治疗，主要原因是由于出现放射学或临床进展（73.1%）。报告最多的任何级别的治疗相关不良事件（AE）为全身无力/疲乏、恶心和贫血。基于这些结果可以得出结论：rucaparib

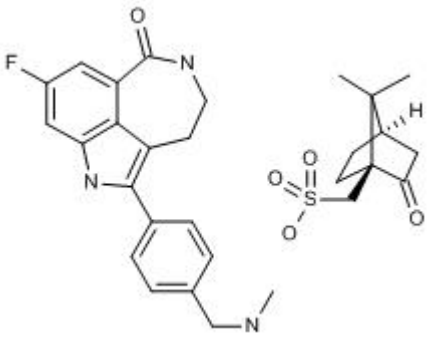
单药治疗对既往经治的晚期尿路上皮癌患者无效。ATLAS 研究在首次中期分析时暂停纳入受试者 (Grivas,P. et al.Genitourin Cancers Symp (Feb 13-15, San Francisco) 2020, Abst 440).



Feb 19, 2020. ATLAS study of rucaparib in mUC suspended due to lack of activity

Researchers from Clovis Oncology presented data from the phase II ATLAS study of the PARP inhibitor (PARPi) rucaparib being evaluated in patients with recurrent, locally advanced or metastatic urothelial carcinoma (mUC) (ClinicalTrials.gov Identifier NCT03397394). At the time of data cut-off, 97 patients with measurable disease who had progressed after 1-2 prior regimens were enrolled in the open-label phase II ATLAS study, designed to evaluate the safety and efficacy of rucaparib in previously treated locally advanced/unresectable UC or mUC. Patients were enrolled regardless of tumor homologous recombination deficiency (HRD) status, and prior PARPi was not allowed. The enrolled subjects were treated with oral rucaparib 600 mg, given twice daily. Of the 97 enrolled patients, 20 (20.6%) were HRD-positive, 30 (30.9%) were HRD-negative and 47 (48.5%) had unknown HRD status. Four patients had a deleterious BRCA1/2 alteration. At the time of data cut-off, median time on treatment was 54 days, with no confirmed responses reported to date. Of 96 evaluable patients, 27 (28.1%) had a best response of stable disease, with the clinical benefit rate (CBR) being 12.5% and the median progression-free survival being 1.8 months. No relationship was observed between HRD status and clinical activity. A total of 93 patients (95.9%) discontinued treatment, mainly due to radiologic or clinical progression (73.1%). The most frequent reported treatment-emergent adverse events (AEs) of any grade were asthenia/fatigue, nausea and anemia. Based on these findings, it could be concluded that single agent rucaparib did not show activity in patients with previously treated advanced UC. Enrollment in the ATLAS

study was suspended at the first interim analysis (Grivas, P. et al. Genitourin Cancers Symp (Feb 13-15, San Francisco) 2020, Abst 440).

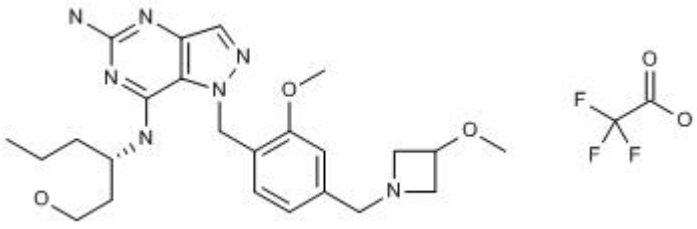


2020 年 2 月 21 日，百时美施贵宝开发 toll 样受体 7 激动剂

有研究报道，百时美施贵宝公司开发的专利药物 toll 样受体 7（TLR7）激动剂，用于治疗恶性肿瘤并用作疫苗佐剂。

分泌型胚胎碱性磷酸酶(SEAP)报告基因转基因试验（WO 2020028608）发现，这种 1H-吡唑并[4,3-d]嘧啶例示化合物[I]对 HEK-Blue 细胞表达的人 TLR-7 受体表现出激动活性（EC50=1.2 nM）。

SEAP 报告基因转基因试验（WO 2020028610）发现，这种 2H-吡唑并[4,3-d]嘧啶例示化合物[II]对 HEK-Blue 细胞表达的人 TLR-7 受体表现出激动活性（EC50=130 nM）。



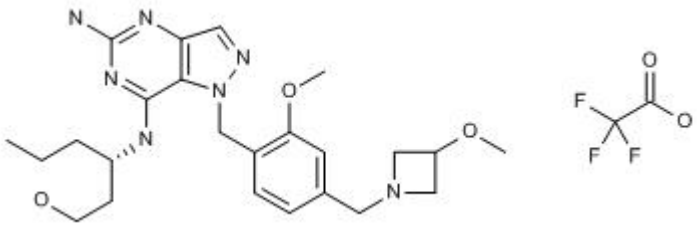
[I] WO 2020028608

Feb 21, 2020. Bristol-Myers Squibb discovers toll-like receptor 7 agonists

Bristol-Myers Squibb has patented toll-like receptor 7 (TLR7) agonists reported to be useful for the treatment of cancer and as vaccine adjuvants.

An exemplified 1H-Pyrazolo[4,3-d]pyrimidine, compound [I], displayed agonistic activity at human TLR7 receptors expressed in HEK-Blue cells (EC50 = 1.2 nM) in secreted embryonic alkaline phosphatase (SEAP) reporter transgene assays (WO 2020028608).

An exemplified 2H-Pyrazolo[4,3-d]pyrimidine, compound [II], also displayed agonistic activity at human TLR7 receptors expressed in HEK-Blue cells (EC50 = 130 nM) in SEAP reporter transgene assays (WO 2020028610).

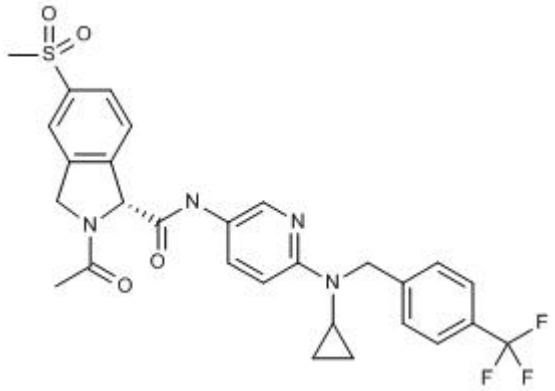


[I] WO 2020028608

有关皮肤病的新闻报道

2020 年 2 月 28 日，丹麦利奥制药公司成功开发出 RORC 配体

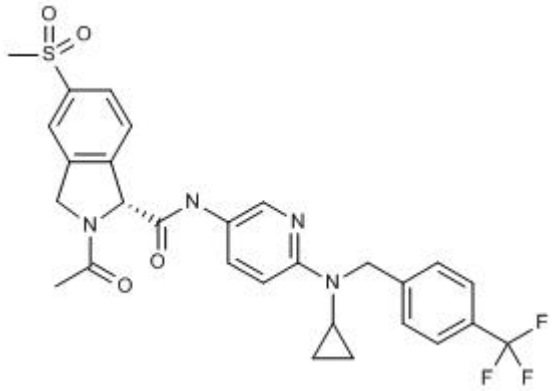
利奥公司已开发出核受体 ROR-γ（RORC）（特异性 T 细胞亚型 2）配体用于治疗银屑病。亲近闪烁试验表明这种例示化合物可抑制[3H]-25-羟基胆固醇与人 RORC 配体结合域蛋白的结合（EC50=9.12 nM）。α-LISA 试验发现，该药对抗 CD3/抗 CD8 刺激的人外周血单个核细胞中 IL-17A 的生成具有抑制作用（EC50=5.69 nM）。α-LISA 试验（WO 2020035556）还显示该药对人全血中 IL-17A 的生成具有抑制作用（EC50=18.6 nM）。



WO 2020035556

Feb 28, 2020. Leo Pharma A/S presents RORC ligands

Leo Pharma A/S has identified nuclear receptor ROR-gamma (RORC) (T cell-specific isoform 2) ligands reported to be useful for the treatment of psoriasis. An exemplified compound inhibited the binding of [3H]-25-hydroxycholesterol to human RORC ligand-binding domain protein (EC50 = 9.12 nM) in scintillation proximity assays. It suppressed IL-17A production in anti-CD3/anti-CD8-stimulated human peripheral blood mononuclear cells (EC50 = 5.69 nM) in alpha-LISA assays. It also inhibited IL-17A production in human whole blood (EC50 = 18.6 nM) in alpha-LISA assays (WO 2020035556).

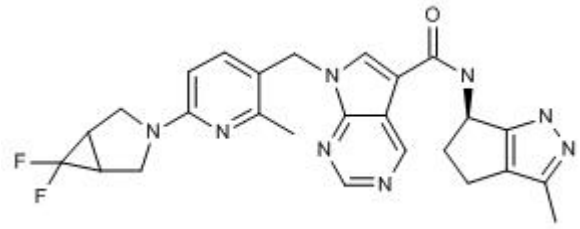


WO 2020035556

有关眼部疾病的新闻报道

2020 年 2 月 28 日，勃林格殷格翰为 KLKB1 抑制剂申报专利

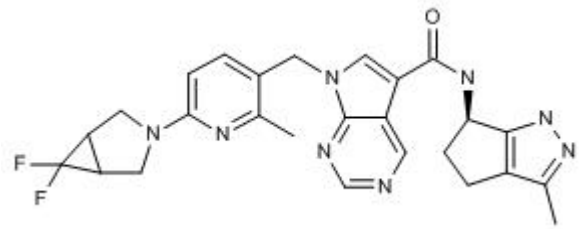
勃林格殷格翰宣布，其已开发出甲酰胺衍生物这种血浆激肽释放酶（KLKB1）抑制剂，可用于治疗糖尿病性黄斑水肿、年龄相关性黄斑变性和脉络膜新生血管形成。荧光试验发现，这种例示化合物对人激肽释放酶（KLK）B1 具有抑制作用（Ki=0.1 nM），对组织激肽释放酶 1 具有选择性抑制作用（WO 2020035540）。



WO 2020035540

Feb 28, 2020. Boehringer Ingelheim Pharma patents KLKB1 inhibitors

Boehringer Ingelheim Pharma has divulged carboxamide derivatives acting as plasma kallikrein (KLKB1) inhibitors reported to be useful for the treatment of diabetic macular edema, age-related macular degeneration and choroidal neovascularization. An exemplified compound inhibited human KLKB1 activity (Ki = 0.1 nM) with selectivity over tissue kallikrein 1 in fluorescence-based assays (WO 2020035540).

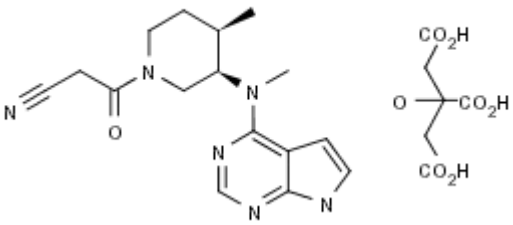


WO 2020035540

有关代谢性疾病的新闻报道

2020 年 2 月 21 日，JAK 抑制剂可诱导骨修复，无需炎性刺激

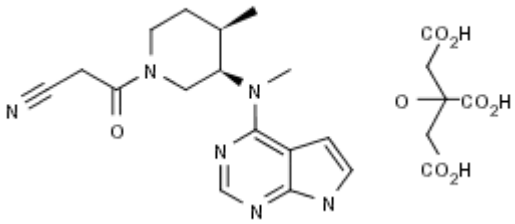
Janus 激酶（JAK）的活化可触发促炎细胞因子的信号转导，JAK 抑制剂 Xeljanz（枸橼酸托法替尼，辉瑞公司）和 Olumiant（baricitinib，礼来公司）获批用于治疗类风湿性关节炎。德国 Erlangen 大学附属医院的研究人员现已证明，即使在没有炎性刺激的情况下，这两种药物均可对骨形成带来获益。这些研究人员在动物模型中发现，使用 Xeljanz 和 Olumiant 治疗可刺激具有骨修复作用的成骨细胞的生成并且能够增加骨量，对未发生骨丢失的患者以及因雌激素水平下降和炎症导致骨丢失的患者均有疗效。作者得出结论：无论骨丢失是由炎症或其他因素引起，他们的结果均“支持[JAK 抑制]是促进成骨细胞功能和骨形成的强效治疗方法”（Adam,S. et al.Sci Transl Med 2020, 12(530): eaay4447).



Feb 21, 2020. JAK inhibitors build bone, no inflammation necessary

Janus kinase (JAK) activation sets off signaling by proinflammatory cytokines, and JAK inhibitors Xeljanz (tofacitinib citrate, Pfizer) and Olumiant (baricitinib, Eli Lilly) are approved for the treatment of rheumatoid arthritis. Now, researchers at University Hospital Erlangen have demonstrated that both drugs had beneficial effects on bone formation even in the absence of inflammation. They showed that in animal models, treatment with Xeljanz and Olumiant stimulated bone-building osteoblast cells and increased bone mass both in the absence of bone loss, and after bone loss due to estrogen loss as well as inflammation. The authors concluded that their results "support that [JAK inhibition] is a potent therapeutic tool for

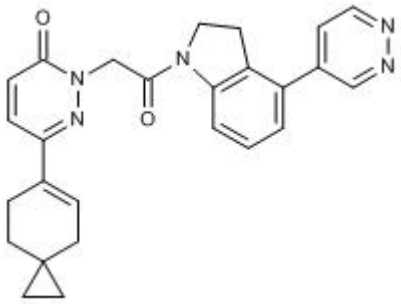
increasing osteoblast function and bone formation" regardless of whether the bone loss was caused by inflammation or other factors (Adam, S. et al. Sci Transl Med 2020, 12(530): eaay4447).



有关精神疾病的新闻报道

2020 年 2 月 10 日，日本住友制药公司开发出了新型 Nav1.1 通道激活剂

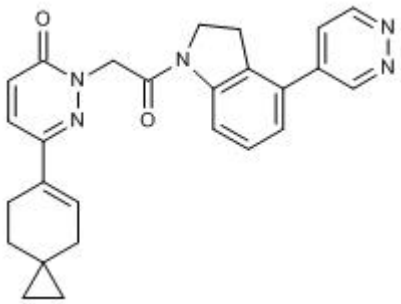
日本住友制药公司已合成哒嗪酮衍生物这种钠通道蛋白 1 型亚基 α（Nav1.1）通道激活剂，该药可用于治疗注意力缺陷多动障碍（ADHD）、抑郁症、癫痫、精神分裂症和帕金森病。自动膜片钳分析（WO 2020017587）发现，这种例示化合物可激活在 HEK-293 细胞中稳定表达的人 Nav1.1 通道（在 1 mcM 时增强率=499%），对在 CHO-K1 细胞中稳定表达的人 Nav1.5 通道具有选择性激活作用（在 1 mcM 时为 1%）。



WO 2020017587

Feb 10, 2020. Sumitomo Dainippon Pharma describes new Nav1.1 channel activators

Sumitomo Dainippon Pharma has synthesized pyridazinone derivatives acting as sodium channel protein type 1 subunit alpha (Nav1.1) channel activators reported to be useful for the treatment of attention deficit hyperactivity disorder (ADHD), depression, epilepsy, schizophrenia and Parkinson's disease. An exemplified compound activated human Nav1.1 channels stably expressed in HEK-293 cells (enhancing rate = 499% at 1 mcM) with selectivity over human Nav1.5 channels stably expressed in CHO-K1 cells (enhancing rate = 1% at 1 mcM) in automated patch clamp assays (WO 2020017587).



WO 2020017587

靶点研发风险评估及警示

基于以上的创新药进展，在立项思路上必须同时考虑可能的风险。为此，科睿唯安顾问团队基于 OFF-X 数据库，对于标靶及药物已观察到的不良反应，提取部分内容供参。

靶标	药物	不良反应	警示级别(level of evidence)	警示日期
Opioid mu receptor	naldemedine	腹痛(abdominal pain) 腹泻(Diarrhoea)	Confirmed/ Reported	2020/02/25
JAK1/2	Baricitinib/ tofacitinib	静脉血栓栓塞和肺栓塞	Confirmed/Reported	2020/02/03
Retinoid Z receptor gamma antagonist (RORC)	AZD0284	首次人体试验，主要不良事件是鼻咽炎；其他还有头痛、便秘	Suspected Confirmed/Reported	2020/03/05
Plasma prekallikrein	BCX7353	ACAAI 报道三期临床不良事件有腹痛、紫癜、消化不良，恶心，呕吐和肝功能异常	Suspected	2019/1108
scn9a sodium channel subunit inhibitor (SCNA9)	N/A	线粒体变性、神经变性、神经纤维毒性、小纤维神经病变	Suspected (target alert)	2019/12/23

科睿唯安药物新闻

周一至周五动态更新的药物新闻和 EMAIL 跟踪提醒

- 每周一至五，科睿唯安药物新闻（Clarivate Analytics BioWorld Science）精选最新、最重要的药物研发新闻在线发布，并以简明扼要的格式发送提醒邮件至您的邮箱，帮助您快速锁定重要的新闻事件
- 您可以在线检索我们所有的新闻资源，并设定检索条件（限定新闻发生的时间、药名、专利号、公司、大学、机构、治疗类别/分组、化合物类型、信息源）找到与您研究相关的内容。药物新闻（BioWorld Science）内容可回溯至 1996 年，并可查看化学结构式。

药物新闻（BioWorld Science）提供如下内容：

- 从海量信息源中总结出的摘要报告。
- 在全球重要会议中披露的新闻信息。
- 每周更新的邮件提醒服务，以表格的形式告知您进入临床前开发最有前景的化合物、lead compounds 和最新的作用机制。
- 每周更新的邮件提醒服务，告知您在研药物研发状态的变更。

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