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Discovery of BMS-846372, a Potent and Orally Active Human CGRP Receptor Antagonist for the Treatment of Migraine

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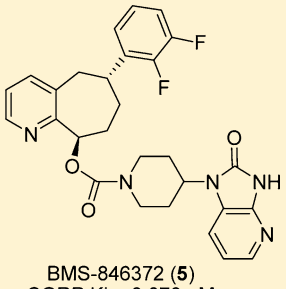
Supporting Information

ABSTRACT: Calcitonin gene-related peptide (CGRP) receptor antagonists have been clinically shown to be effective in the treatment of migraine, but identification of potent and orally bioavailable compounds has been challenging. Herein, we describe the conceptualization, synthesis, and preclinical characterization of a potent, orally active CGRP receptor antagonist **5** (BMS-846372). Compound **5** has good oral bioavailability in rat, dog, and cynomolgus monkeys and overall attractive preclinical properties including strong (>50% inhibition) exposure-dependent in vivo efficacy in a marmoset migraine model.



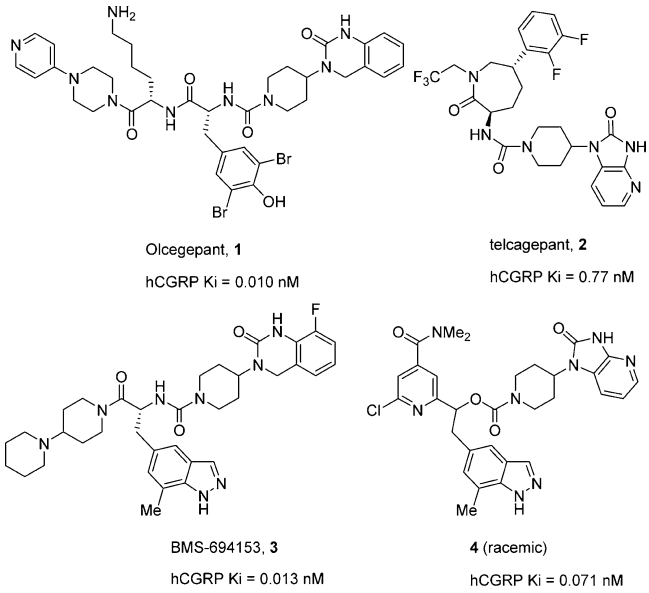
BMS-846372 (**5**)
CGRP Ki = 0.070 nM

KEYWORDS: *migraine, CGRP, CGRP receptor, antagonist*

Migraine is a chronic debilitating disease, affecting roughly 12% of the U.S. population, with women being at least 2-fold more susceptible than men.[1] One early hypothesis, put forward by Wolff, was that migraine pathophysiology was associated with the dilation of cranial blood vessels.[2] More contemporary efforts have focused on neural processes and the potential roles of peripheral[3] and central sensitization[4] in the neurobiology of headache. The triptan class of 5-$HT_{1B/1D}$ agonists is the current standard of care for treating migraines, and they are believed to primarily act by vasoconstriction of cranial vessels with concomitant inhibition of neurotransmitter release from trigeminal afferents.[5] However, triptans are associated with a number of unpleasant side effects including chest and neck tightening and are contraindicated in patients with cardiovascular disease and hypertension.[6]

The calcitonin gene-related peptide (CGRP), a 37 amino-acid peptide, is widely distributed in the nervous system.[7] CGRP is an extremely potent vasodilator that has been implicated in the pathogenesis of migraine.[8−10] Studies have shown that plasma levels of CGRP are elevated during migraine attacks.[11,12] The CGRP receptor is composed of a family B G-protein-coupled receptor (GPCR), named the calcitonin receptor-like receptor (CLR), along with a receptor activity modifying protein 1 (RAMP1).[13] CGRP receptor antagonists are attractive therapeutic targets for the treatment of migraine, and several have demonstrated clinical efficacy. Intravenous administration of the highly potent CGRP receptor antagonist BIBN4096BS (**1**, Chart 1) was accompanied by alleviation of pain in migraineurs without the cardiovascular side effects associated with the use of triptans.[14] While this compound effectively demonstrated the first clinical proof of concept, its route of administration and chemical instability precluded further development.[15] More recently, an oral CGRP receptor antagonist, telcagepant (MK-0974)[16] (**2**, Chart 1), was advanced

Chart 1. Selected CGRP Receptor Antagonists



Olcegepant, **1**
hCGRP Ki = 0.010 nM

telcagepant, **2**
hCGRP Ki = 0.77 nM

BMS-694153, **3**
hCGRP Ki = 0.013 nM

4 (racemic)
hCGRP Ki = 0.071 nM

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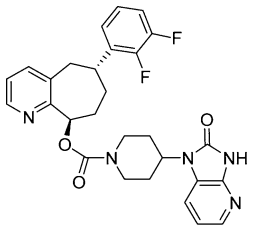
to phase III trials and demonstrated clinical efficacy but was discontinued possibly due to toxicity issues.[17,18]

A recent publication from our laboratories disclosed a potent, indazole-based CGRP receptor antagonist (BMS-694153) (**3**, Chart 1) that showed rapid and efficient intranasal exposure.[19] However, BMS-694153 did not have significant oral bioavailability in either a cynomolgus monkey or a rat primarily due to its poor intrinsic cellular permeability. While intranasal delivery is potentially attractive for migraine treatment, another one of our goals was to discover novel, orally active CGRP antagonists. In a recent publication, we disclosed that pyridine served as an efficient mimetic of the secondary amide in BMS-694153, providing antagonists with excellent binding potency and improved bilayer permeability.[20] Yet, despite this improvement, significant oral exposure was still difficult to achieve in this series. It proved difficult to incorporate optimal physiochemical and pharmacokinetic properties in a single molecule. However, one pyridine derivative (**4**, Chart 1) did demonstrate moderate efficacy (31% inhibition) in the marmoset facial blood flow model[19] at 10 mg/kg when administered orally. To improve oral exposure, we sought to reduce the number of rotatable bonds and improve metabolic stability in our compounds by constraining the pyridyl-containing core and further reducing polarity by replacing the indazole moiety by a 2,3-difluorophenyl ring. Herein, we describe the synthesis of BMS-846372 (**5**), a potent CGRP receptor antagonist with good oral bioavailability (Figure 1).



5

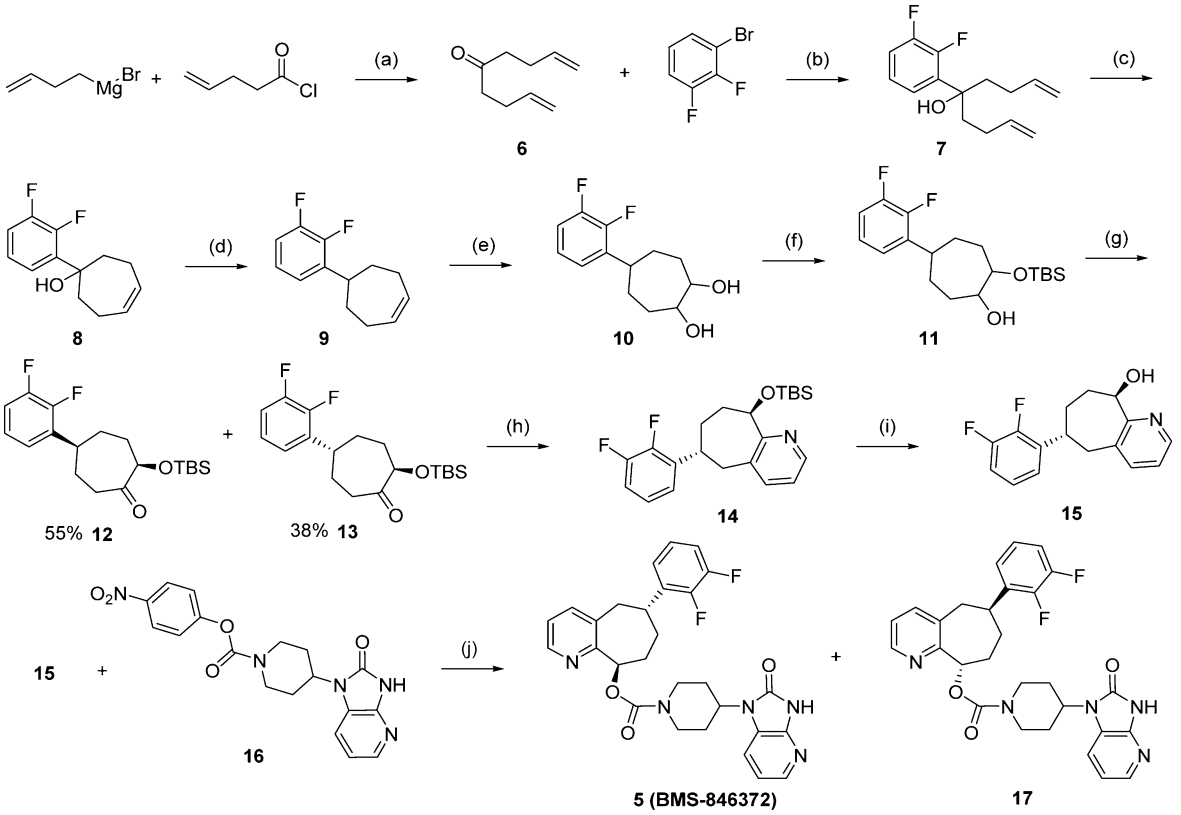
Figure 1. Structure of BMS-846372.

In compound **5**, we incorporated an all-carbon 7-membered ring fused to the pyridine to restrict its conformational flexibility. A survey of the literature provided some simple cycloheptapyridine structures, but there were no precedents for our desired substitution pattern, particularly with the incorporation of the two chiral centers. Even without a specific stereogenic synthesis, the core bicyclic ring itself and the trans substitution pattern posed some synthetic challenges. As a potentially general route for exploration of pyridine substitution, our initial attempts focused on the formation of a suitable 7-membered ring on which the pyridine ring could be constructed. As such, the first successful synthetic route to racemic **5** is outlined in Scheme 1 with the formation of a key target intermediate ketone **13**. Thus, the dienyl ketone **6** was formed by reaction of commercially available but-3-enylmagnesium bromide and pent-4-enoyl chloride.[21] The addition of 2,3-difluorophenyl lithium generated from 1-bromo-2,3-difluorobenzene[22,23] afforded alcohol **7** in a 55% yield. The formation of the 7-membered ring **8** was achieved by ring-closure metathesis (RCM) with benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (Grubbs-I) catalyst in 89% yield under high dilution (0.012 M in CH_2Cl_2).[24] Deoxygenation to **9** took place in 88% yield using triethylsilane and trifluoroacetic acid (TFA) in CH_2Cl_2.[25] Dihydroxylation was effected under standard osmium-catalyzed 4-methyl morpholine *N*-oxide (NMO) conditions[26] to give diol **10**, followed by tri-*tert*-butyl-silyl (TBS) protection to afford the monoprotected, inseparable diastereomeric mixture of **11** in 84% yield (two steps). Following Dess-Martin oxidation of the alcohol intermediate **15**, the two diastereomers of the ketone intermediate **12** and **13** were separated. The structure of the trans isomer **13** was identified by X-ray crystallography.[27] Using literature conditions,[28] the formation of the pyridine derivative **14** from the ketone **13** with propargylamine under gold(III) catalysis occurred in 20% yield. Treatment of **14** with tetrabutylammonium fluoride (TBAF) afforded the racemic penultimate intermediate **15** in good yield. The alcohol **15** was coupled with **16**[20] to provide racemic **5** in good yield. The final desired product, **5** (BMS-846372), was separated by chiral preparative high-pressure liquid chromatography (HPLC), from its enantiomer **17**.[29] This 10-step synthesis was used to synthesize the original lots of BMS-846372.

The primary issues with our original overall scheme were an early high dilution RCM reaction, the low yields of pyridine from the ketone **13**, and the difficulty in controlling both diastereomeric and enantiomeric selectivities. Thus, when gram quantities of **5** were needed for more extensive preclinical evaluations, the route shown in Scheme 1 proved difficult to scale up. Because formation of the pyridine ring (**14**) in Scheme 1 was a very low yielding step, a more focused approach using commercially available pyridines became more attractive. Accordingly, a second route was developed for the synthesis of the penultimate **15**, starting with commercially available 2-bromo-3-pyridinecarboxaldehyde (Scheme 2). A simple Wittig reaction led to the formation of 2-bromo-3-vinylpyridine **18** in good yield.[30] Lithium-halogen exchange of **18** followed by addition of penten-4-al and TIPS-Cl afforded the desired diene **19** in 74% yield. While direct RCM with **19** gave no reaction, treatment of the HCl salt[31,32] of **19** under standard RCM conditions with the (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)-ruthenium (Grubbs-II) catalyst gave the desired cycloheptene **20** in 86% yield. Racemic epoxidation of **20** with a racemic Jacobson's catalyst[33,34] afforded the epoxide **21** in 70% yield. After hydrogenolysis of the epoxide **21**, the resulting alcohol **22** was converted to the ketone **23** by Swern oxidation in good yield. Triflate **24** was formed under standard conditions in 86% yield, and Suzuki coupling with commercially available 2,3-difluorophenylboronic acid also proceeded smoothly to afford **25**. Deprotection with TBAF afforded the unsaturated alcohol **26** in 81% yield. Hydrogenation of **26** gave a mixture of the desired alcohol **15** and its diastereomer **27**. After separation using flash column chromatography (FCC), **27** was converted to **15** by a Mitsunobu reaction. Multigram quantities of **5** were able to be prepared by this route, again through chiral HPLC separation, which allowed for extensive preclinical evaluation of **5**. Compound **5** was crystallized, and its relative stereochemistry was proved by X-ray crystallography.[29]

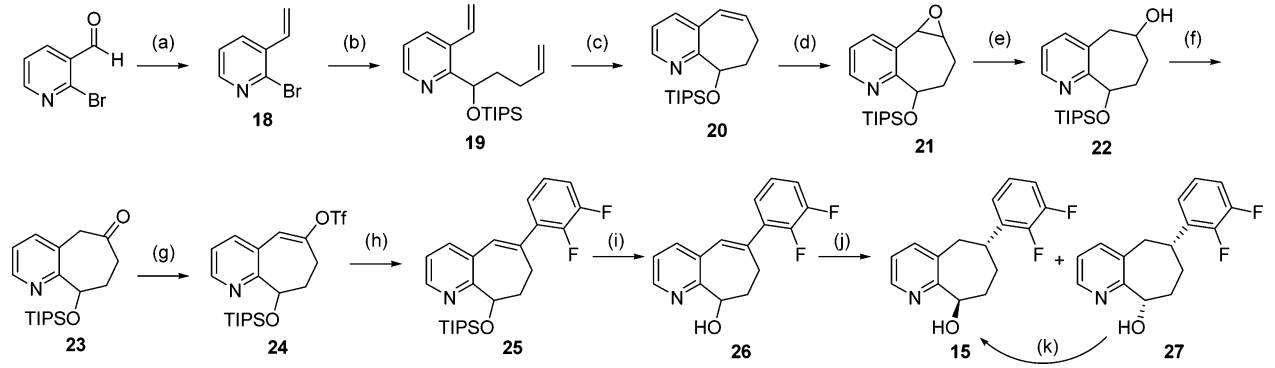
Binding affinities for the human CGRP receptor were determined by inhibition of ^{125}I-CGRP binding in SK-N-MC cell membranes as previously disclosed.[19] Compound **5** displaced ^{125}I-CGRP with a K_i = 0.070 ± 0.021 nM (n = 13), while its enantiomer **17** had significantly reduced affinity with a K_i = 940 nM (Table 1). Functional receptor antagonism for **5** was determined by measuring inhibition of CGRP-stimulated cAMP production in SK-N-MC cells.[19] The compound was

Scheme 1. First Synthesis of 5 (BMS-846372)[a]



[a]Reagents and conditions: (a) THF, −78 °C to rt, 3 h (68%). (b) *n*-BuLi, THF, −78 °C to rt, 1 h (55%). (c) Grubbs-I, CH_2Cl_2 (0.012 M), 40 °C, 2 h (89%). (d) Triethylsilane, TFA, CH_2Cl_2, rt, 3 h (88%). (e) OsO_4, NMO, acetone/water, 1 h. (f) TBS-Cl, DMF, rt, 5 h (84% for two steps). (g) Dess-Martin periodinane, CH_2Cl_2, rt, 17 h (55% of **12** + 38% of **13**). (h) Propargylamine, $NaAuCl_4 \cdot 2H_2O$, EtOH, 80 °C, 5 h (20%). (i) TBAF, THF, rt, 19 h (84%). (j) NaH, THF; rt, 18 h (46%), then chiral separation.

Scheme 2. Second Synthesis of BMS-846372 (5)[a]



[a]Reagents and conditions: (a) Methyltriphenylphosponium bromide, *n*-BuLi, THF, 72 h (89%). (b) *n*-BuLi, THF, 4-pentenylaldehyde, then TIPS-Cl, −78 °C to rt (74%). (c) HCl; Grubbs-II, CH_2Cl_2, 40 °C, 4 h (86%). (d) (±)-[1,2-Cyclohexanediamino-*N*,*N*′-bis(3,5-di-*t*-butylsalicylidene)]-manganese(III) chloride, NaOCl, Na_2HPO_4, CH_2Cl_2 (70%). (e) Pd/C/hydrogen (25 psi), EtOH, rt, 4 h (99%). (f) Oxalyl chloride, DMF (cat.), −50 °C, CH_2Cl_2, Et_3N (49%). (g) LDA, $PhNTf_2$, THF, −78 °C to rt, 18 h (86%). (h) 2,3-Difluorophenylboronic acid, Na_2CO_3, $Pd(PPh_3)_4$, toluene, 110 °C, 1.5 h (65%). (i) TBAF, THF, rt, 1 h (81%). (j) Pd/C/hydrogen (1 atm) (16% **15** and 74% **27**). (k) 4-Nitrobenzoic acid, PPh_3, DIAD, THF, 0 °C to rt, 5 h; LiOH, rt, 3 h (77%).

Table 1. In Vitro Data for 5 and Its Enantiomer 17

compd	5	17
hCGRP K_i (nM)	0.070 (±0.021)	940
cAMP IC_{50} (nM)	0.22	
PAMPA (pH 5.5/pH 7.4) (nm/s)	1500/880	

shown to be an antagonist with an IC_{50} = 0.22 ± 0.05 nM (n = 2). BMS-846372 completely inhibited CGRP-mediated elevation of cAMP.

A novel noninvasive marmoset recovery model for in vivo efficacy assessment of CGRP-receptor antagonists was developed in our laboratories, which utilized facial blood flow

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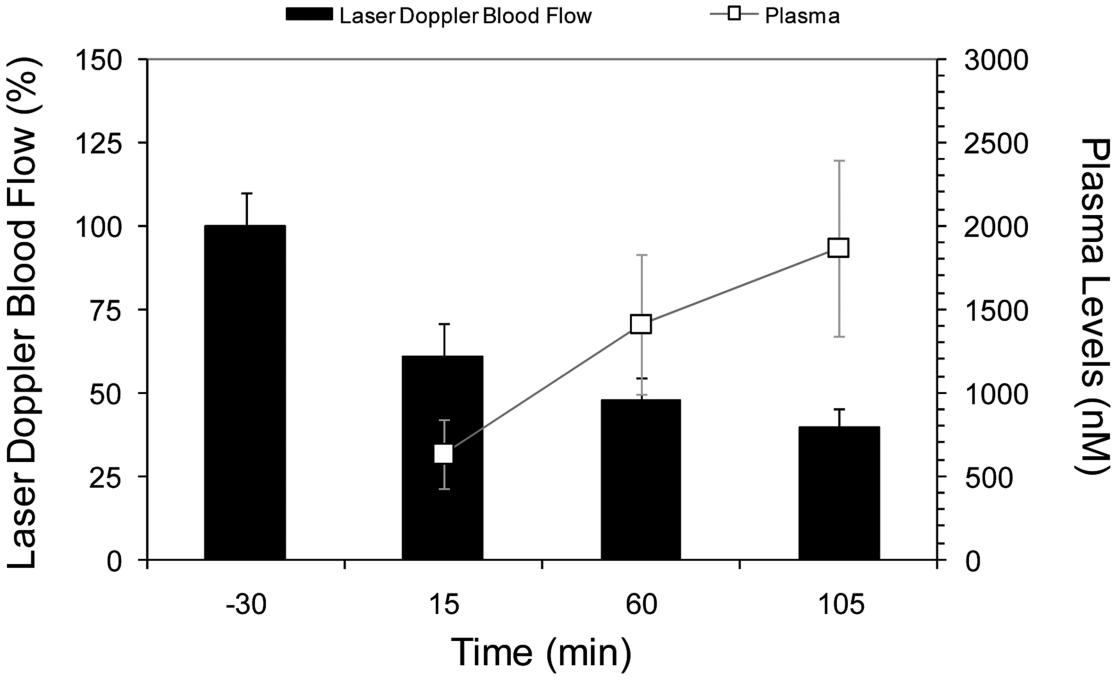

Figure 2. Marmoset facial blood flow.

as a surrogate for intracranial artery diameter, and the dilation of arteries, which characterize a migraine.[19] Briefly, marmosets were anesthetized, and facial blood flow was increased by intravenous (iv) administration of hαCGRP (10 μg/kg) at 45 min intervals (−30, 15, 60, and 105 min). The effect of different doses of antagonist **5**, delivered SC at 0 min, on the hαCGRP-induced increases in facial blood flow was measured by laser Doppler flowmetry. In this model, compound **5** showed exposure-dependent inhibition of CGRP-induced increases in marmoset facial blood flow upon subcutaneous (sc) dosing (Figure 2).[35] As compared to predose vehicle control (−30 min), strong (>50%) inhibition of CGRP-induced effects on facial blood flow was observed with 7 mg/kg of **5** at 60 and 105 min postdose (52−60%) (Figure 2). In comparing exposure versus efficacy with 7 mg/kg of **5** at the 60 and 105 min postdose test times, plasma levels of **5** were above 1000 and 1500 nM, respectively, and both times were associated with strong in vivo efficacy (>50% inhibition).

With a 10 mg/kg dose po and 1 mg/kg iv, compound **5** exhibited significant oral bioavailability in the rat (F_{po} = 29%), dog (F_{po} = 34%), and cynomolgus monkey (F_{po} = 38%), certainly in part because of its high bilayer permeability (PAMPA: 880−1500 nm/s, Table 1). Compound **5** is reasonably stable in human liver microsome with 74% remaining after 10 min (0.5 μM) and with a $t_{1/2}$ = 24 min. In addition, compound **5** at 10 μM showed no significant potential for off-target liabilities in a panel of receptor, ion channel, and enzyme activity assays.

In conclusion, BMS-846372 is a potent CGRP antagonist, with good oral bioavailability, strong exposure-dependent in vivo efficacy, and acceptable off-target liabilities. It is active in vivo and represents an opportunity for human dosing. Additional preclinical studies of BMS-846372 will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data for the preparation of compounds **6**−**15** and **17**−**27** and full characterization of BMS-846372. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

CGRP, calcitonin gene-related peptide; GPCR, G-protein-coupled receptor; CLR, calcitonin receptor-like receptor; RAMP1, receptor activity modifying protein 1; THF, tetrahydrofuran; RCM, ring-closure metathesis; TFA, trifluoroacetic acid; NMO, 4-methyl morpholine *N*-oxide; TBS, tri-*tert*-butylsilyl; TBAF, tetrabutylammonium fluoride; DIAD, diisopropyl azodicarboxylate; HPLC, high-pressure liquid chromatography; TIPS, tri-isopropyl-silyl; LCMS, liquid chromatography mass spectrometry; Grubbs-I, benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium, bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride; Grubbs-II, (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium; FCC, flash column

chromatography; NMR, nuclear magnetic resonance; sc, subcutaneous; po, taken orally; iv, intravenous

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