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Azepino-indazoles as calcitonin gene-related peptide (CGRP) receptor antagonists

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Azepino-indazoles as calcitonin gene-related peptide (CGRP) receptor antagonists

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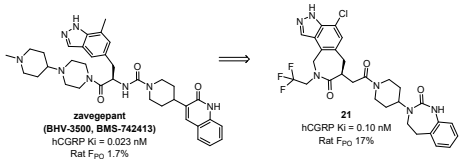

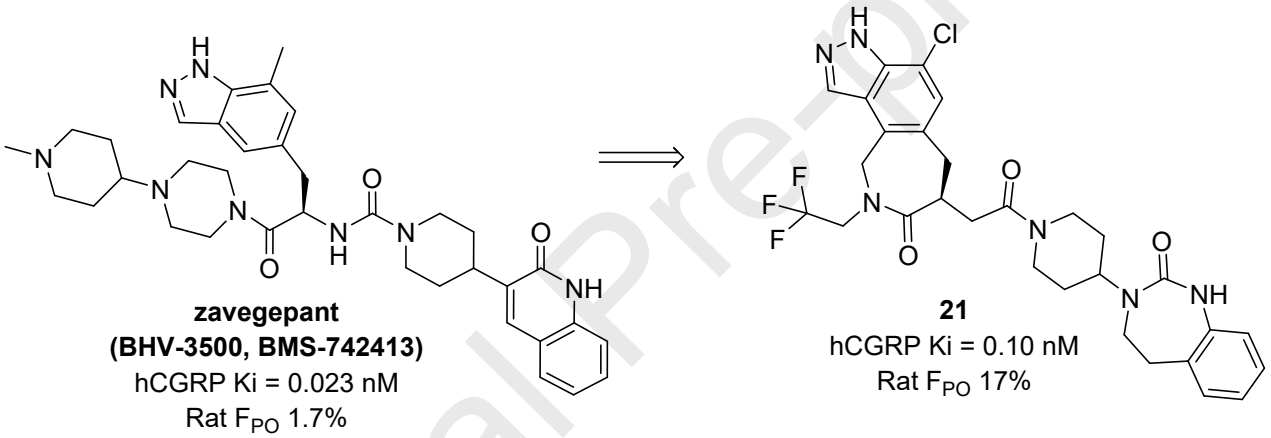

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ABSTRACT

Calcitonin gene-related peptide (CGRP) receptor antagonists have been shown clinically to be effective treatments for migraine. Zavegepant (BHV-3500, BMS-742413) is a high affinity antagonist of the CGRP receptor (hCGRP K_i = 0.023 nM) that has demonstrated efficacy in the acute treatment of migraine with intranasal delivery in a Phase 2/3 trial, despite showing low oral bioavailability in rats (F_{PO} = 1.7%). Using zavegepant as a template, we sought to improve oral bioavailability through a series of azepinones which were designed in an attempt to reduce the number of rotatable bonds. These efforts led to the discovery of compound **21** which was able to mostly maintain high affinity binding (hCGRP K_i = 0.100 nM) and *in vivo* efficacy in the marmoset facial blood flow assay, while greatly improving oral bioavailability (rat F_{PO} = 17%).

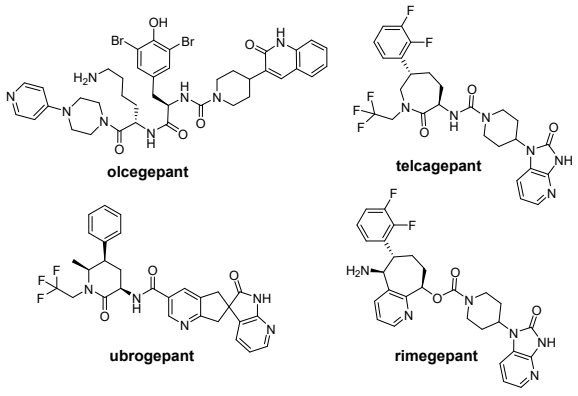
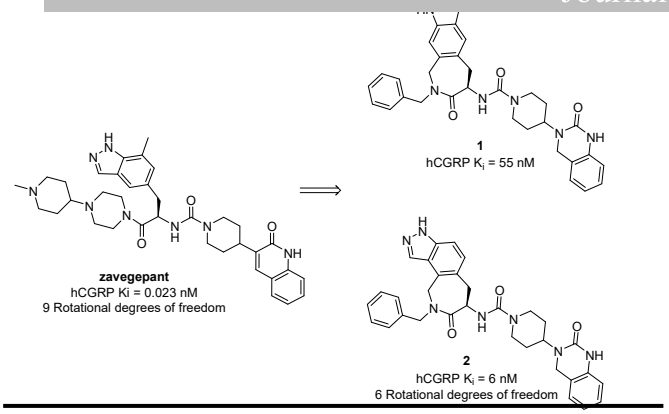


Figure 1: CGRP receptor antagonist clinical candidates

Migraine is a complex neurological disorder characterized by intense headache, often accompanied by nausea with a heightened sensitivity to light, sound and odors, that can last for hours or even several days.[1] Many years of research largely based on the now outmoded idea that dilation of intracranial blood vessels is the underlying pathophysiology of migraine led to the discovery of triptans (5-$HT_{1B/1D}$ agonists),[2] which are active vasoconstrictors. Being non-selective in this respect, triptans are contraindicated in patients with cardiovascular disease or hypertension, and are known to have a number of undesirable side effects.[3]

A number of studies have shown that calcitonin gene-related peptide (CGRP) is involved in the pathogenesis of migraine.[4] Plasma levels of the 37-amino acid peptide, which is widely distributed in the nervous system, are elevated in persons suffering migraine attacks and reduced upon successful treatment.[5] CGRP receptor antagonism has been an attractive approach for the



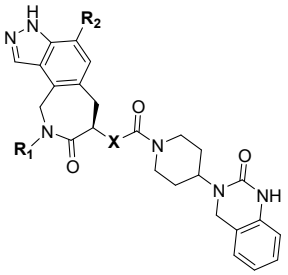
Compound	R_1	R_2	X	hCGRP-R K_i (nM)
2	CH_2Ph	H	NH	12
3	Me	H	NH	370
4	CH_2-4Py	H	NH	22
5	CH_2CH_2-4Py	H	NH	7.1
6	$CH_2CH_2N(Me)_2$	H	NH	170
7	CH_2CH_2-N-morpholine	H	NH	50
8	4-Piperidine	H	NH	290
9	i-Pr	H	NH	59
10	2-Methylpropyl	H	NH	14
11	2,2-Dimethylpropyl	H	NH	4.9
12	CH_2Ph	Cl	NH	1.0
13	2,2-Dimethylpropyl	Cl	NH	1.5
14	2,2-Dimethylpropyl	Cl	CH_2	0.41
15	CH_2CF_3	Cl	CH_2	0.23

treatment for migraine. Initial entries into phase II and III clinical trials, such as olcegepant and telcagepant (Figure 1) provided robust proof of concept for this treatment strategy, showing efficacy comparable to the triptans without the cardiovascular liabilities.[6] Recently a number of treatments targeting the CGRP pathway have been approved.[7] These include four injectable signal blocking monoclonal antibodies as well as two oral small molecule CGRP receptor antagonists, Ubrelvy™ (ubrogepant) and Nurtec™ ODT (rimegepant).[7]

Previously, our group reported the discovery of the CGRP receptor antagonist BMS-742413,[8] now referred to as zavegepant (BHV-3500).[7] Zavegepant shows good intranasal bioavailability and has demonstrated efficacy in phase II/III clinical trials for the acute treatment of migraine. However, zavegepant has very low oral bioavailability in rats (F_{PO} 1.7%). As an alternative, we were interested in developing a CGRP receptor antagonist that possessed properties conducive to oral delivery. Suspecting that zavegepant possessed too many rotational degrees of freedom, we attempted to constrain the central portion of the molecule into a caprolactam, effectively locking the orientation of the indazole ring system with respect to other components of the indazole, both compounds **1** and **2** were prepared. Compared to **1**, compound **2**, having a less extended core conformation, showed an order of magnitude improved affinity vs. ^{125}I-hCGRP binding in SK-N-MC cell membranes in our previously disclosed assay (Figure 2).[9]

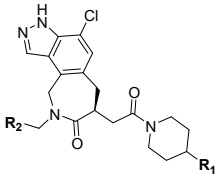
Having determined the preferred regioisomer of the unoptimized indazole, we next set out to explore additional SAR, first focusing on the left side of the molecule (Table 1). We soon learned that lipophilic groups (R_1) were preferred over polar functionality in this region with the 2,2-dimethylpropyl and 2,2,2-trifluoroethyl probes providing the highest affinity. This was in contrast to the unconstrained series that led to zavegepant, and suggested a binding mode for R_1 more like telcagepant than olcegepant, as subsequently observed in structural studies of the receptor complex ectodomain[10]. It was also clear that, as was seen in the non-constrained series, having substitution in the 7-position of the indazole gave us a further boost in affinity. Transforming the linking urea NH, expected to be a liability for permeability, to a methylene group also proved beneficial.

Table 1. SAR of compound **2** modifications



chosen to assess oral exposure. Unfortunately, when **14** was dosed orally in rats at 10 mg/kg it exhibited poor bioavailability (F_{PO} 1.8%). By retaining the amide core (X = CH_2), we sought to improve oral bioavailability by modulating the GPCR-privileged quinazolinone right side of the molecule (Table 2). Addition of a fluorine ortho to the aniline nitrogen (**16**) provided a modest boost in exposure with retention of binding affinity. A similar effect was achieved with naphthyridinones, **17** and **19**. Combining the fluorine with the naphthyridinone in compound **18** provided a further boost in oral bioavailability for compound **18** when compared to compound **17**, but came with a greater than 10-fold loss in binding affinity in each case. The same 10-fold loss of binding affinity was seen when the fluorine was incorporated into the naphtheridinone ring of compound **19** to give **20**. With diazepinone **21** we were able to restore

Figure 2. Constraint of zavegepant (BHV-3500, BMS-742413)



binding affinity while improving oral bioavailability. As with the naphthyridinones, ortho fluorination (**22**) severely degraded binding affinity. Contracting the ring to benzimidazolone **23** also caused a loss in binding affinity, which could be regained by replacing the benzo ring in **23** with a pyrido ring in **24**.

Of all the compounds prepared, **21** showed the best oral bioavailability while retaining a level of CGRP receptor binding affinity that was comparable to the highly polar intranasal compounds. Compound **21** fully antagonized CGRP-induced receptor activation in SK-N-MC cells[8] with an IC_{50} = 0.27 ± 0.15 nM (n = 4). In vitro liver microsomal stability was low ($T_{1/2}$ = 3.6, 2.2, 2.4, and 3.1 minutes in human, rat, monkey and dog, respectively), while human plasma protein binding was in the moderate-to-high range (fu = 2.8%).

Compound **21** was chosen for study in our marmoset facial blood flow assay, used to assess the in vivo pharmacodynamics of CGRP receptor antagonists.[9] Measuring CGRP induced changes in facial blood flow was shown to be a surrogate for the intracranial arterial dilation that occurs when CGRP is released during a migraine attack. In this assay, facial blood flow in anesthetized marmosets is measured using a laser Doppler technique, where four administrations of hαCGRP (10 μg/kg) are delivered intravenously (IV) at 45 minute intervals (-30, 15, 60 and 105 minutes relative to drug delivery), each causing increased

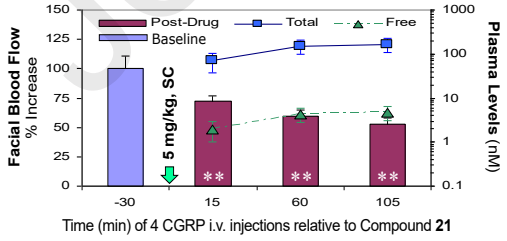
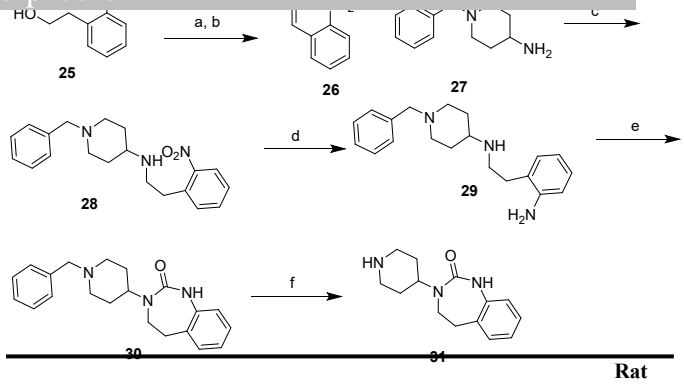


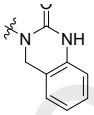
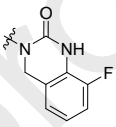
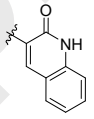
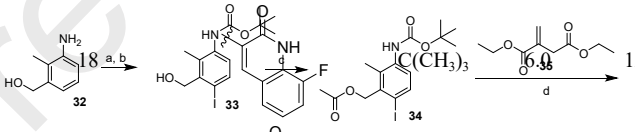
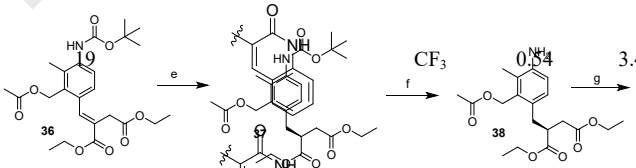
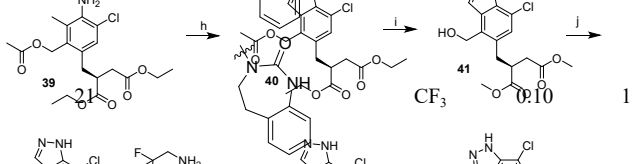
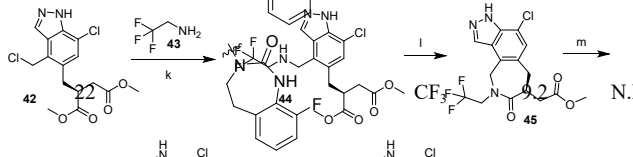
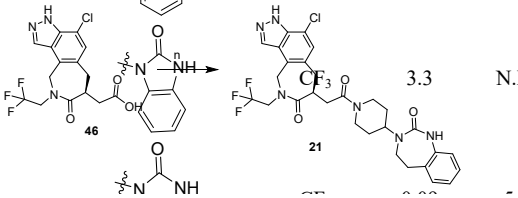
Figure 3. Pharmacodynamic activity of compound **21** in the marmoset facial blood flow assay when challenged with four CGRP IV injections. **p ≤ 0.001 vs. baseline.

facial blood flow. The first delivery establishes a baseline control response, and subsequent deliveries, which are designed to mimic



Scheme 1. Reagents and conditions: (a) methanesulfonyl chloride, TEA,

Table 2. Efforts to improve oral bioavailability through modifications of the GPCR- privileged component

14		$C(CH_3)_3$	0.23	1.8
16		$C(CH_3)_3$	0.31	4.7
17		$C(CH_3)_3$	0.75	4.5
18		$C(CH_3)_3$	6.0	12
19		CF_3	0.54	3.4
20		CF_3	6.0	N.D.
21		CF_3	0.10	17
22		CF_3	9.2	N.D.
23		CF_3	3.3	N.D.

Scheme 2. Reagents and conditions: (a) urea hydrogen peroxide, iodine, THF; (b) $(Boc)_2O$, TEA, THF; (c) Ac_2O, NaOAc, THF, 40% for 3 steps; (d) $Pd(OAc)_2$ (5 mole%), $Bu_4N^+Cl^-$, TEA, DMF, 90%; (e) H_2, (-)-1,2-Bis((2R,5R)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium (I) tetrafluoroborate (2 mole%), CH_2Cl_2, 98%; (f) TFA, CH_2Cl_2, 98%; (g) NCS, DMF, 90%; (h) isoamyl nitrite, potassium acetate, 5% acetic acid – toluene, 70%; (i) $Mg(OMe)_2$, MeOH, 95%; (j) 2M thionyl chloride in CH_2Cl_2, 50%; (k) K_2CO_3, CH_3CN; (l) toluene, acetic acid, 120 °C, 46 h, 60% 2 steps; (m) LiOH, THF, H_2O, 99%; (n) TBTU, **31**, DIEA, DMF, 60%.

receptor antagonist **21** dosed at 0 minutes. The ideal route of administration in the marmoset assay is subcutaneous (SC) delivery, since anesthesia delays gastric emptying, subsequently altering the PK profile of oral administration. When given SC at 5 mg/kg, compound **21** produced statistically significant ($p \leq 0.001$) reductions in marmoset facial blood flow of 27%, 41% and 47% at 15, 60 and 105 minutes respectively, compared to baseline (Figure 3).

Compound **21** was synthesized in a convergent manner in which the diazepinone (**31**) and constrained indazole (**46**) portions of the molecule were prepared separately and then coupled in a final step. The synthesis of the right side diazapinone is outlined in Scheme 1 the key steps being elimination of the alcohol from **25** to form 2-vinylnitrobenzene (**26**), followed by condensation with 4-amino-1-benzylpiperidine (**27**) to yield compound **28**. Reduction of the nitro group preceded formation of the urea **30**. Deprotection of the piperidine nitrogen produced intermediate **31** (Scheme 1).

The indazole azepinone portion of **21** was synthesized starting from 3-amino-2-methylbenzyl alcohol **32**, which was iodinated using iodine monochloride to give **33**, followed by protection of the aniline amine and alcohol (Scheme 2). Coupling of **34** with itaconic acid diethyl ester **35** was carried out under Heck-like conditions.[11] The olefin in **36** underwent rhodium(II) catalyzed asymmetric hydrogenation to impart the desired stereochemistry to **37**.[12] Aniline deprotection was followed by introduction of chlorine on the aromatic ring, gave **39**. To introduce the indazole **40** we devised a novel mild, one pot diazotization and cyclization reaction using isoamyl nitrite and potassium acetate in a solvent system consisting of 5% acetic acid in toluene. Deprotection of the benzyl alcohol using magnesium methoxide in methanol also resulted in transesterification to the dimethyl esters **41**. The unmasked alcohol was then converted to the chloride **42**, which in turn was displaced by 2,2,2-trifluoroamine **43** in the presence of potassium carbonate in acetonitrile. A solution of the newly formed secondary amine **44** in toluene was then heated at reflux in the presence of acetic acid to form the azepinone ring system **45**. The resulting ester was saponified to generate the carboxylic acid **46**, which was coupled with compound **31** under standard amide-forming conditions to yield compound **21**.

In conclusion, we developed a series of azepinone based CGRP receptor antagonists that exhibited high affinity *in vitro* hCGRP receptor binding with improved rat oral bioavailability, as compared to our intranasal lead, zavegepant. A lead compound from this series, compound **21**, exhibited statistically significant inhibitory activity at all three time points against a robust CGRP agonist challenge designed to mimic severe migraine in a marmoset facial blood flow assay when dosed at 5 mg/kg SC. Although a comprehensive dose-response was not conducted to identify the maximal pharmacodynamic (PD) effect of compound **21**, these data are consistent with the PD profile of the clinical assets rimegepant[13] and zavegepant[8] which likewise showed early onset and durable effects across the same time points in the marmoset assay. Encouraged by our ability to modify the highly polar chemotype from which our intranasal compounds originated into one in which significant oral bioavailability was possible, we continued to optimize this series. Results of those efforts will be disclosed in due course.

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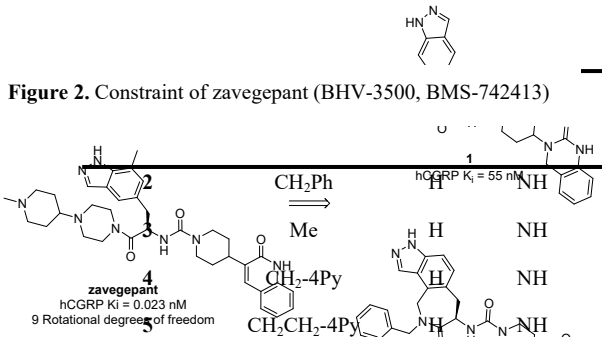
Table 1. SAR of compound **2** modifications

				hCGRP-F (nM)
2	CH_2Ph	H	NH	12
3	Me	H	NH	370
4	CH_2-4Py	H	NH	22
5	CH_2CH_2-4Py	H	NH	7.1
6	$CH_2CH_2N(Me)_2$	H	NH	170
7	CH_2CH_2-N-morpholine	H	NH	50
8	4-Piperidine	H	NH	290
9	i-Pr	H	NH	59
10	2-Methylpropyl	H	NH	14
11	2,2-Dimethylpropyl	H	NH	4.9
12	CH_2Ph	Cl	NH	1.0
13	2,2-Dimethylpropyl	Cl	NH	1.5
14	2,2-Dimethylpropyl	Cl	CH_2	0.41
15	CH_2CF_3	Cl	CH_2	0.23

Figure 2. Constraint of zavegepant (BHV-3500, BMS-742413)



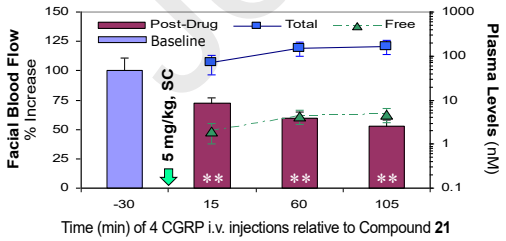
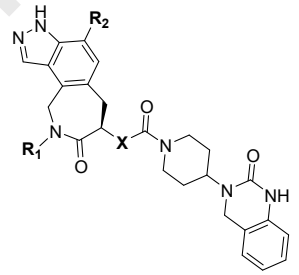


Figure 3. Pharmacodynamic activity of compound **21** in the marmoset facial blood flow assay when challenged with four CGRP IV injections. **p ≤ 0.001 vs. baseline.

Scheme 1. Reagents and conditions: (a) methanesulfonyl chloride, TEA, THF; (b) DBU, CH_2Cl_2, 98%; (c) neat, 120 °C, 21 h, 78%; (d) H_2, PtO_2, EtOH, 99%; (e) CDI, CH_3CN, 80%; (f) H_2, Pd/C, 85%.



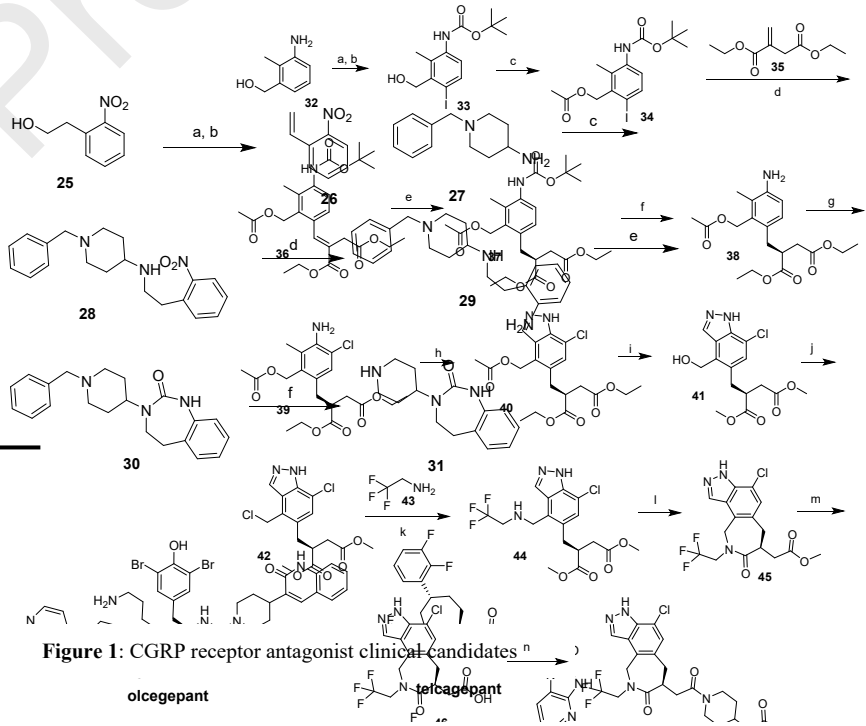
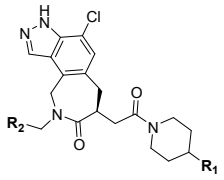
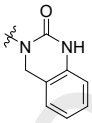
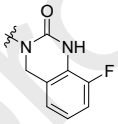
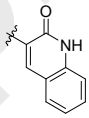
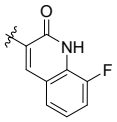
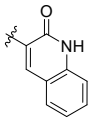
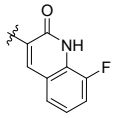
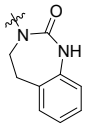
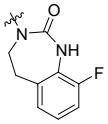
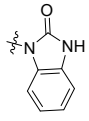
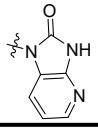


Figure 1: CGRP receptor antagonist clinical candidates

Scheme 2. Reagents and conditions: (a) urea hydrogen peroxide, iodine, THF; (b) $(Boc)_2O$, TEA, THF; (c) Ac_2O, NaOAc, THF, 40% for 3 steps; (d) $Pd(OAc)_2$ (5 mole%), $Bu_4N^+Cl^-$, TEA, DMF, 90%; (e) H_2, (-)-1,2-Bis((2R,5R)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium (I) tetrafluoroborate (2 mole%), CH_2Cl_2, 98%; (f) TFA, CH_2Cl_2, 98%; (g) NCS, DMF, 90%; (h) isoamyl nitrite, potassium acetate, 5% acetic acid – toluene, 70%; (i) $Mg(OMe)_2$, MeOH, 95%; (j) 2M thionyl chloride in CH_2Cl_2, 50%; (k) K_2CO_3, CH_3CN; (l) toluene, acetic acid, 120 °C, 46 h, 60% 2 steps; (m) LiOH, THF, H_2O, 99%; (n) TBTU, **31**, DIEA, DMF, 60%.

Table 2. Efforts to improve oral bioavailability through modifications of the GPCR- privileged component



Compound	R_1	R_2	hCGRP-R K_i (nM)	Rat F_{PO} at 10 mg/kg (%)
14		$C(CH_3)_3$	0.23	1.8
16		$C(CH_3)_3$	0.31	4.7
17		$C(CH_3)_3$	0.75	4.5
18		$C(CH_3)_3$	6.0	12
19		CF_3	0.54	3.4
20		CF_3	6.0	N.D.
21		CF_3	0.10	17
22		CF_3	9.2	N.D.
23		CF_3	3.3	N.D.
24		CF_3	0.09	5.5