Bioorg. Med. Chem. Lett. 43 (2021) 128077

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Calcitonin gene-related peptide (CGRP) receptor antagonists: Heterocyclic modification of a novel azepinone lead

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ARTICLE INFO

*Keywords:*
CGRP receptor antagonist
Imidazolone
Time-dependent CYP3A4 inhibition
Migraine

ABSTRACT

In our efforts to identify orally bioavailable CGRP receptor antagonists, we previously discovered a novel series of orally available azepinone derivatives that unfortunately also exhibited the unwanted property of potent time-dependent human CYP3A4 inhibition. Through heterocyclic replacement of the indazole ring, we discovered a series of heterocycle derivatives as high-affinity CGRP receptor antagonists. Some of them showed reasonable oral exposures, and the imidazolone derivatives that showed good oral exposure also exhibited substantially reduced time-dependent CYP3A4 inhibition. Several compounds showed strong in vivo efficacy in our marmoset facial blood flow assay with up to 87% inhibition of CGRP-induced activity. However, oral bioavailability generally remained low, emphasizing the challenges we and others encountered in discovering clinical development candidates for this difficult Class B GPCR target.

Migraine, is a common and disabling condition, affecting approximately 12% of the adult population in the western world.[1] The nonselective 5-$HT_{1B/1D}$ agonists ("triptans") have been widely used for the acute treatment of migraine, however these have undesirable active vasoconstrictive properties and are contraindicated in patients with uncontrolled hypertension or cardiovascular disease.[2] Approximately 2.6 million Americans with migraine have had a cardiovascular event, condition or procedure that limits the utility of triptans,[3] highlighting the need for new treatments. Although the precise mechanisms underlying the initial triggering event(s) in migraine are not fully understood, great strides have been made in understanding migraine pathophysiology and centers around the trigeminovascular system release of the neuromodulator calcitonin gene-related peptide (CGRP).[4] Therefore, a CGRP receptor antagonist is an attractive therapeutic target for the treatment of migraine.[5] Importantly, blockade of CGRP signaling is not associated with active vasoconstriction providing new treatment options for patients with unmet needs.[6] Initial clinical proof of concept was achieved in the acute treatment of migraine with intravenous administration of the high affinity CGRP receptor antagonist BIBN 4096 BS (olcegepant) showing alleviation of pain without an unwanted cardiovascular signal.[7] Subsequently, clinical development of two orally bioavailable antagonists, MK-0974 (telcagepant) and MK-3207 showed anti-migraine efficacy in clinical trials, but their development was discontinued due to liver safety concerns.[8] Recently, two oral small molecule CGRP receptor antagonists, Ubrelvy™ (ubrogepant)[9] and Nurtec ODT™ (rimegepant)[10] were approved for the acute treatment of migraine. In addition, four injectable monoclonal antibodies, one against the CGRP receptor and three against CGRP itself, have been

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https://doi.org/10.1016/j.bmcl.2021.128077
Received 22 February 2021; Received in revised form 19 April 2021; Accepted 25 April 2021
Available online 29 April 2021

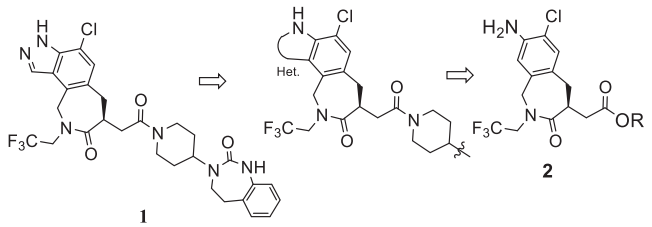
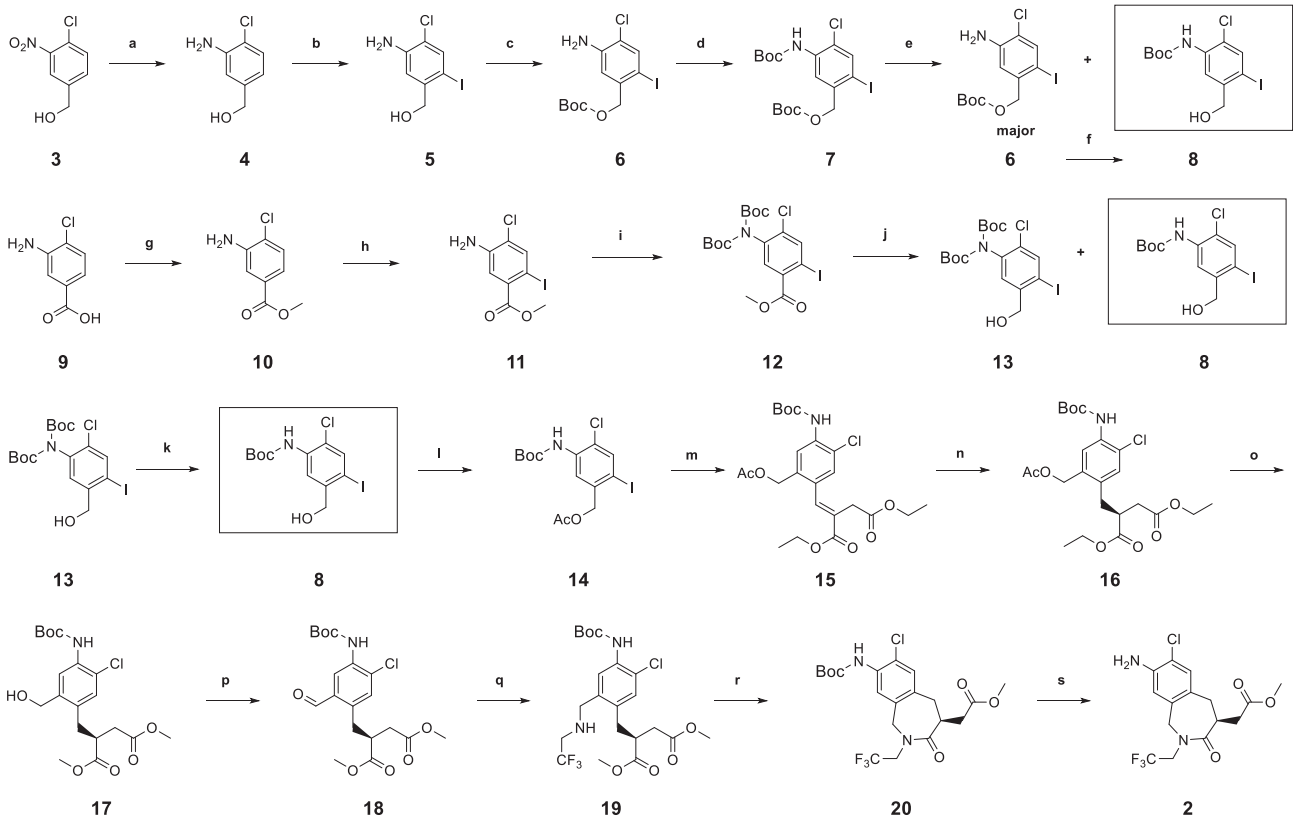



**Fig. 1.** Azepinone CGRP receptor antagonist **1**, proposed heterocyclic replacement and the key intermediate **2**.

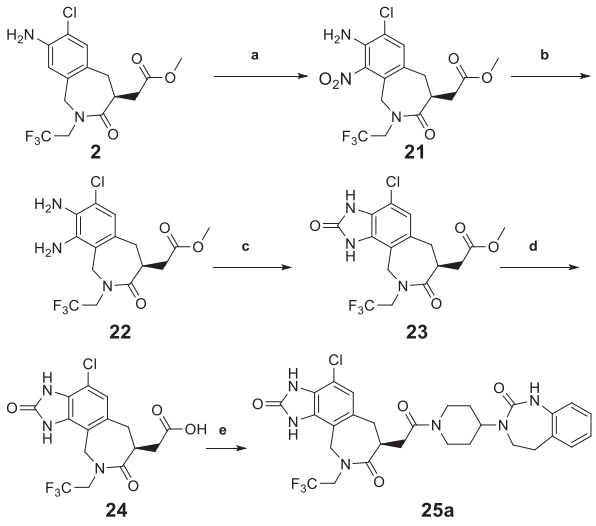
approved for migraine prevention.[11] None of these six agents have shown a liver safety signal which indicates that the early Merck experiences were compound-specific effects and not CGRP-mediated. Most recently, rimegepant and atogepant have demonstrated efficacy in the preventive treatment of migraine, with rimegepant being the only molecule to show efficacy in both acute and preventive treatment of migraine.[12] These data highlight the ongoing importance of these novel oral treatments for migraine.

A recent publication from our laboratories disclosed a high-affinity indazole-containing azepinone CGRP receptor antagonist **1** (Fig. 1) that demonstrated good oral exposure and activity in a marmoset pharmacodynamic assay.[13] However, the compound had potent, time dependent cytochrom P450 isoform 3A4 (CYP3A4) inhibition. Herein, we report focused structure activity relationship (SAR) campaign around the indazole of **1** to address this issue (Fig. 1). Specifically, we wanted to replace the pyrazole portion of the indazole ring with other heterocycles. Since the indazole NH in **1** has been shown to be critical for high-affinity CGRP receptor binding affinity, we decided to retain a hydrogen bond donor as shown in the middle structure (Fig. 1). To access these heterocycles, we envisoned a critical key intermediate, aniline **2**.

Successful preparation of intermediate **2** is outlined in Scheme 1, which involved two diferent approaches to key intermediate **8**. In the first approach reduction of commercial nitro compound **3** afforded the aniline **4**, which was treated with ICl to obtain the iodide **5** in good yield. Mono-Boc protection, however, went exclusively to the primary alcohol to generate **6**. Treatment with excess $Boc_2O$ yielded bis-Boc protected product **7**, which afforded a mixture of the desired alcohol **8** and compound **6** after attempted selective deprotection. Compound **6**, in the presence of a catalytic amount of DMAP, could be completely converted to the more thermodynamically stable **8** in refluxing THF. Alternatvely, a second route to the key intermediate **8** was developed starting with benzoic acid **9**. Ester formation of **10** followed by iodide formation of **11** were achieved in good yields. Mono-Boc protection of the aniline **11** was not feasible and bis-Boc protected interemdiate **12** was obtained in very good yield. Reduction of the ester group to the alcohol by DIBAL, however, led to partial deprotection, generating both **13** and the desired alcohol **8**. Compound **13** could be converted to **8** by treatment with $K_2CO_3$ in MeOH with heating. The alcohol **8** was then protected as the acetate to afford intermediate **14**, which after Heck coupling with itaconic acid diethyl ester, afforded intermediate **15** in excellent yield. Using previously established conditions,[13] chiral reduction was




**Scheme 1.** Reagents and conditions: (a) Fe, AcOH/EtOH (2/1), 95 °C, 2 h, 61%: (b) ICl, $Na_2CO_3$, MeOH, rt, 2 h, 100% (crude); (c) $Boc_2O$ (1.05 equiv.), DMAP (cat.), THF, 75 °C, 4 h; (d) $Boc_2O$ (2.1 equiv.), DMAP (cat.), THF, 75 °C, 6 h; (e) $K_2CO_3$, MeOH/$H_2O$ (4/1), rt, 72 h, **6** (59%) and **8** (38%); (f) DMAP (0.1 equiv.), THF, 75 °C, 24 h, 100% (crude); (g) Trimethyl orthoformate, $H_2SO_4$, MeOH, 60 °C, 28 h, 90%; (h) $I_2$, $Ag_2SO_4$, EtOH, rt, 2 h; (i) $Boc_2O$ (2.4 equiv.), DMAP (cat.), THF, 75 °C, 24 h, 89% for two steps; (j) DIBAL-H, THF, −78 °C, 2 h; (k) $K_2CO_3$, MeOH, 70 °C, 2 h; (l) $Ac_2O$, DMAP (cat.), $CH_2Cl_2$, rt, 2 h; (m) itaconic acid diethyl ester, $PdOAc_2$, tetrabutylammonium chloride hydrate, $Et_3N$, DMF, 50 °C, 88% for three steps; (n) (−)-1,2-Bis((2*R*,5*R*)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium (I) tetrafluoroborate (2.8 mol%), $CH_2Cl_2$, $H_2$ (35 psi), rt, 96 h, 96% (crude); (o) MgO, MeOH, rt, 24 h, 100% (crude); (p) $MnO_2$, $CH_2Cl_2$, 50 °C, 4 h, 100% (crude); (q) 2,2,2-trifluoroethaneamine, $NaBH_3CN$, AcOH, MeOH, rt, 18 h, 88% (crude); (r) AcOH, toluene, 120 °C, 17 h, 64% from **15**; (s) TFA, $CH_2Cl_2$, rt, 5 h, 89%.



**Scheme 2.** Reagents and conditions: (a) 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone, TFA, rt, 2 h, 52%; (b) $SnCl_2$, EtOH, 70 °C, 2 h, 80%; (c) phosgene, $CH_2Cl_2$, 1 h; (d) LiOH, THF, 48 h; (e) 3-(piperidin-4-yl)-4,5-dihydro-1*H*-benzo[d][1,3]diazepin-2(3*H*)-one, Hunig's base, 3-(diethoxyphosphoryloxy)-1,2,3-benzo-triazin-4(3)-one (DEPBT), $CH_2Cl_2$, DMF, rt, 18 h, 77% for 3 steps.

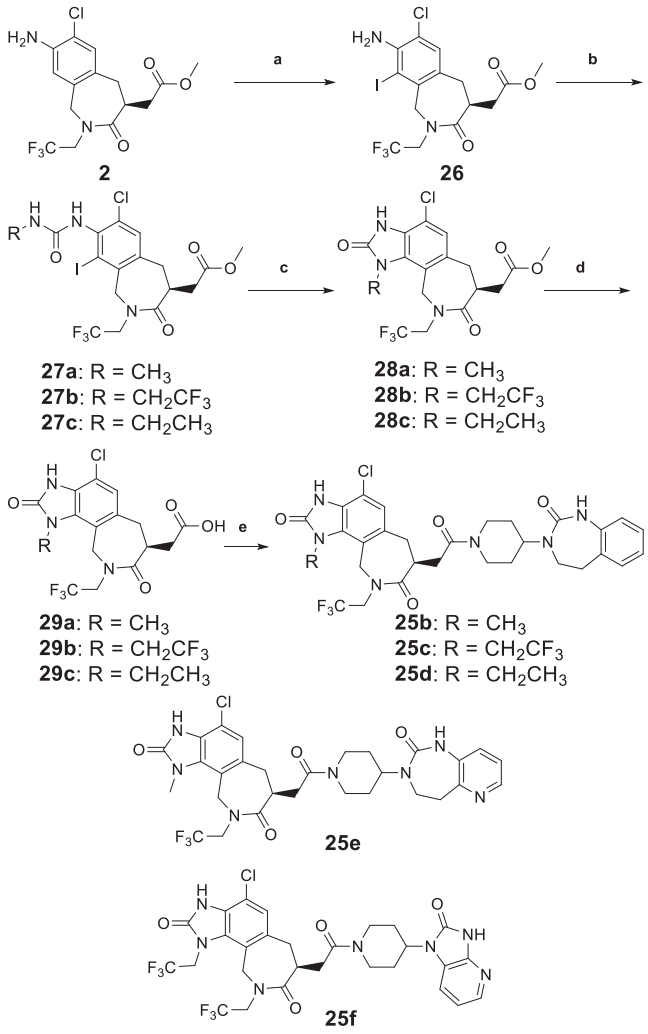
achieved to afford **16** in very good yield. Acetate was removed by hydrolysis with ester exchanged to afford alcohol **17**, which was converted to secondary amine **19** after generation of the aldehyde **18**. Cyclization proceeded smoothly to generate the azepinone **20** in good yield, which afforded the desired intermediate **2** after Boc deprotection.

Synthesis of the unsubstituted imidazolone derivative **25a** was achieved as shown in Scheme 2. Aniline **2** was nitrated following reported protocols[14] to afford intermediate **21**, which after $SnCl_2$ reduction, generated bis-aniline **22**. Phosgene treatment afforded the imidazolone derivative **23**, which after hydrolysis and 3-(diethyoxyphosphoryloxy)-1,2,3-benzo-triazin-4(3)-one (DEPBT)-mediated amide formation reaction[15] using previously reported amide 3-(piperidin-4-yl)-4,5-dihydro-1*H*-benzo[d][1,3]diazepin-2(3*H*)-one[13], afforded the desired imidazolone derivative **25a** in good yield.

For the synthesis of substituted imidazolone derivatives a different route was developed as shown in Scheme 3. Starting with **2**, iodination in the presence of $Ag_2SO_4$ afforded the iodide **26** in good yield. Formation of ureas **27a-c** was achieved through sequential treatment of **26** with phosgene, followed by reaction with various amines. Intramolecular closure of the substituted imidazolone rings was efficiently achieved by CuI catalysis using 1,10-phenanthroline as the ligand, a protocol adopted from previously reported amination conditions.[16] This transformation represented a new method of preparing specifically substituted imidazolones, and subsequently a similar condition (CuI/DBU) using high temperature microwave heating was reported.[17] The desired products **25b-d** were prepared after ester hydrolysis and amide formation reactions similar to those described for **25a**. Products **25e** and **25f** were prepared from **29a** and **29b**, respectively, using previously reported piperidine-containing G-protein coupled receptor (GPCR) privileged components.[13]

An oxazolidinone derivative **33** was prepared from the iodide intermediate **26** (Scheme 4). Methyl ether formation was achieved in the presence of CuI/1,10-phenanthroline, albeit in low yield. The high reaction temperature required also resulted in ester hydrolysis, affording the acid **30**. The ether in **30** was demethylated by $BBr_3$ to afford amino phenol **31**, which was converted to the oxazolidinone intermediate **32** by phosgene treatment. Amide formation furnished **33** in good yield.

Syntheses of the imidazole (**35**) and triazole (**38**) derivatives were achieved as shown in Scheme 5. The imidazole ring was formed by heating **22** with formic acid and HCl, also resulting in hydrolysis of the

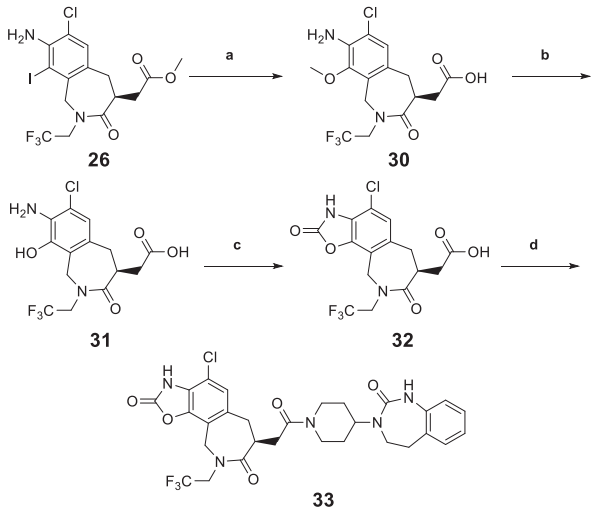


**Scheme 3.** Reagents and conditions: (a) $I_2$, $Ag_2SO_4$, EtOH, rt, 1 h, 91%; (b) phosgene, $CH_2Cl_2$, rt, 30 min–5 h, concentrated to dryness and redissolved in $CH_2Cl_2$, methylamine (**27a**), 2,2,2-trifluoroethylamine (**27b**), or ethylamine (**27c**), rt, 18–72 h; (c) CuI, 1,10-phenanthroline, $Cs_2CO_3$, DME, 80 °C, 16 h, 49% (**28a**), 79% (**28b**), 53% (**28c**); (d) LiOH, THF, rt, 16 h–24 h; (e) 3-(piperidin-4-yl)-4,5-dihydro-1H-benzo[d][1,3]diazepin-2(3H)-one, Hunig's base, DEPBT, $CH_2Cl_2$, DMF, rt, 18 h, 81% for 2 steps (**25b**), 48 h, 83% for 2 steps (**25c**), 70% for 2 steps (**25d**).

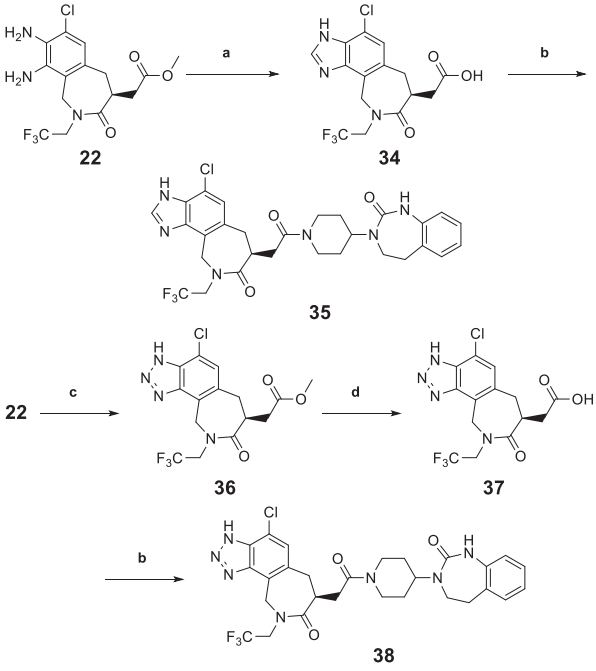
ester, giving acid **34**. Compound **35** was then formed through amide formation. The triazole ring was formed by $NaNO_2$ oxidation of **22** to **36**, which was converted to the triazole **38** after ester hydrolysis and amide formation.

Scheme 6 shows the synthesis of various indole derivatives. Starting from the iodide **26**, Sonogashira coupling with TMS-acetylene afforded **39**, which led to acetylene intermediate **40** after TBAF deprotection. Indole **41** was formed by gold catalysis,[18] and was converted to the indole product **43a** after hydrolysis and amidation. Intermediate **41** could be further derivatized to cyanoindole **44** by known cyanation conditions.[19] After hydrolysis, the cyanoindole acid **45** was converted to either **43b** or **43c** using the two known piperidine derivatives. For synthesis of **43c**, hydrolysis of **44** led to formation of a primary amide side product from nitrile hydrolysis, resulting in the additional formation of **43d** after the coupling reaction and careful separation.

A difluoroindanone derivative **49** was also prepared (Scheme 7). Starting with the indole **41**, oxidation by $CrO_3$ afforded the ketone **46**.[20] The ketone was converted to the corresponding difluoro intermediate **47** by DAST treatment. Hydrolysis of either **46** or **47** by LiOH resulted in opening of the indanone ring.[21] On the other hand, hydrolysis of **47** was



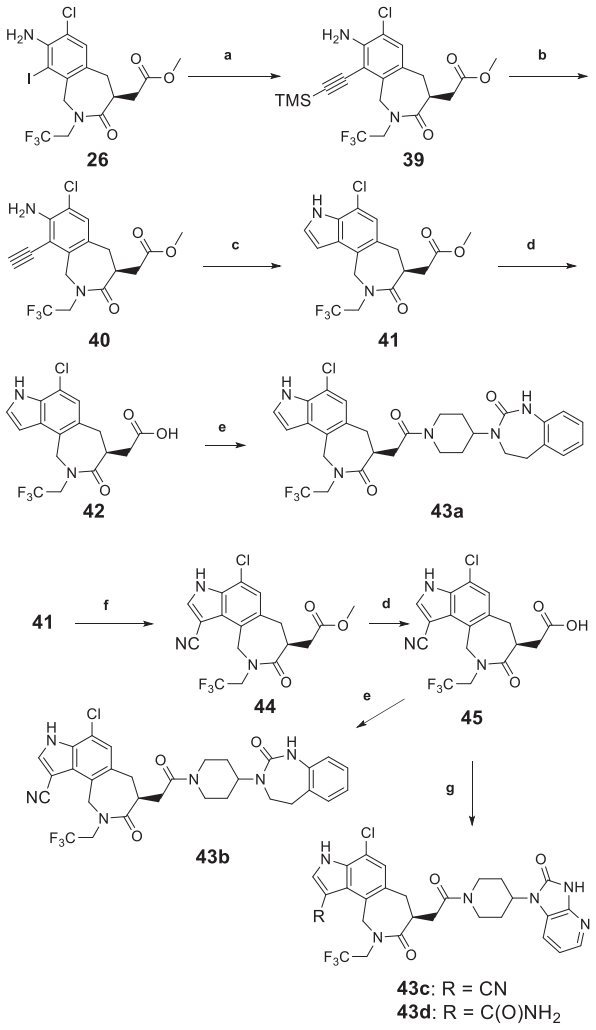

**Scheme 4.** Reagents and conditions: (a) CuI, 1,10-phenanthroline, $Cs_2CO_3$, MeOH, 110 °C (microwave), 24 h, 27%; (b) $BBr_3$, $CH_2Cl_2$, rt, 21 h; (c) phosgene, Hunig's base, $CH_2Cl_2$, 24 h; (d) 1-(piperidin-4-yl)-1*H*-imidazo[4,5-b]pyridin-2(3*H*)-one, Hunig's base, DEPBT, $CH_2Cl_2$, rt, 72 h, 42% for 3 steps.




**Scheme 5.** Reagents and conditions: (a) formic acid, HCl, 100 °C (microwave), 10 h; (b) 1-(piperidin-4-yl)-1*H*-imidazo[4,5,b]pyridin-2(3*H*)-one, Hunig's base, DEPBT, DMF, $CH_2Cl_2$, rt, 18 h, 55% for 2 steps (**35**), 76% for 3 steps (**38**; (c) $NaNO_2$, AcOH/$H_2O$ (3/1), rt, 1 h; (d) LiOH, THF, rt, 72 h.

achieved by using bis(tributyltin)oxide in refluxing toluene[22] to afford the intact acid **48**, with subsequent formation of **49a** after amide formation. Product **49b** was prepared in the same manner.

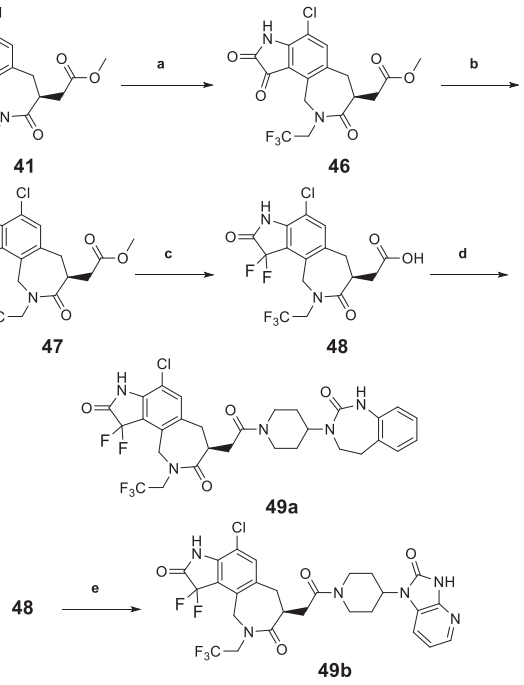
All compounds prepared were tested in a human CGRP receptor binding assay ($K_i$), in competition with [$^{125}$I]CGRP, and selected compounds were tested for antagonist activity (cAMP $IC_{50}$) in a whole-cell assay following previously published protocols.[23] All compounds tested for functional activity were found to be full antagonists of the human CGRP receptor (hCGRP). The hCGRP $K_i$ values are summarized in Table 1, along with single-point liver microsomal stabilities in three species. In addition, $C_{max}$ values from a coarse rat pharmacokinetic (PK) study (10 mg/kg, PO) for selected compounds are also listed in Table 1.




**Scheme 6.** Reagents and conditions: (a) (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$, CuI, $Et_3N$, THF, 50 °C, 20 h, 59%; (b) TBAF, THF, rt, 1.5 h, 100%; (c) $NaAuCl_4{\cdot}2H_2O$, EtOH, rt, 18 h, 62%; (d) LiOH, THF/dioxane, rt, 48 h; (e) 3-(piperidin-4-yl)-4,5-dihydro-1*H*-benzo[d][1,3]diazepin-2(3*H*)-one, Hunig's base, DEPBT, $CH_2Cl_2$, DMF, rt, 18 h, 71% (**43a**) for 2 steps, 83% (**43b**for 2 steps; (f) chlorosulfonyl isocyanate, DMF, MeCN, 0 °C–rt, 2 h; (g) 1-(piperidin-4-yl)-1*H*-imidazo[4,5,b]pyridin-2(3*H*)-one, Hunig's base, DEPBT, $CH_2Cl_2$, DMF, rt, 18 h, 19% (**43c**) and 30% (**43d**) for 2 steps.

The compounds described here were all high-affinity hCGRP receptor antagonists possessing subnanomolar activity. In particular, the imidazolone derivatives **25a-f** achieved low double-digit picomolar binding affinity. Functional activities (cAMP $IC_{50}$) were tested for imidazolones **25b-d** and were 0.060 nM, 0.12 nM, and 0.090 nM, respectively. Unsubstituted imidazolone **25a**, imidazolones with azabenzimidazolone GPCR-privileged components (**25e-f**) demonstrated good microsomal stability but showed poor oral exposure, possibly due to high polarity. Imidazolones **25b-d** had reasonable metabolic stability and oral exposure. Compound **49a** possessed the best oral exposure despite modest rat microsomal stability. Compound **49b**, having the more polar azabenzimidazolone GPCR-privileged component, showed comparatively poor oral exposure, demonstrating the difficult balance needed to be achieved with these chemotypes to achieve good oral bioavailability. Other heterocycle derivatives generally had unacceptable metabolic stability, low oral exposure or other issues.

Several compounds were tested for *in vitro* CYP3A4 time dependent inhibition after 30 min incubation. Values for imidazoles **25b** and **25c** ($IC_{50}$ = 8.1 μM and 8.4 μM, respectively), were greatly improved over lead azepinone **1** ($IC_{50}$ = 0.1 μM). Compound **49b** was found to have no




**Scheme 7.** Reagents and conditions: (a) $CrO_3$, acetone/AcOH/$H_2O$ (1/5/1.5), rt, 4 h, 39% from **41**; (b) DAST, $CH_2Cl_2$, rt, 72 h; (c) bis(tributyltin)oxide, toluene, 80 °C, 36 h; (d) 3-(piperidin-4-yl)-4,5-dihydro-1*H*-benzo[d][1,3]diazepin-2(3*H*)-one, Hunig's base, DEPBT, $CH_2Cl_2$, DMF, rt, 4 h, 42% for 2 steps; (e) 1-(piperidin-4-yl)-1*H*-imidazo[4,5,b]pyridin-2(3*H*)-one, Hunig's base, DEPBT, $CH_2Cl_2$, DMF, rt, 66 h, 60% for 3 steps.

**Table 1**
Selected data for the products.

| Compound | hCGRP $K_i$[a] (nM) | Microsomal stability (%)[b] (H/R/M) | $C_{max}$ (nM)[c] (coarse rat PK) |
|---|---|---|---|
| 25a | 0.019 (±0.010) | 60/41/71 | 3 |
| 25b | 0.015 (±0.008) | 36/35/75 | 96 |
| 25c | 0.020 (±0.006) | 58/54/87 | 270 |
| 25d | 0.014 (±0.003) | 44/22/59 | 230 |
| 25e | 0.043 (±0.008) | 73/56/100 | 11 |
| 25f | 0.026 (±0.009) | 90/90/41 | 3 |
| 33 | 0.12 (±0.05) | 49/64/63 | 36 |
| 35 | 0.17 (±0.05) | 26/7/24 | NT |
| 38 | 0.44 (±0.04) | 62/90/64 | 15 |
| 43a | 0.85 (±0.04) | 0.9/0.8/1.6 | NT |
| 43b | 0.06 (±0.04) | 38/11/26 | NT |
| 43c | 0.060 (±0.002) | 40/40/7 | NT |
| 43d | 0.40 (±0.30) | 80/80/70 | NT |
| 49a | 0.069 (±0.014) | 22/35/8.1 | 480 |
| 49b | 0.13 (±0.07) | 91/82/28 | 4 |

[a] Values are the mean of at least three experiments.
[b] Percent remaining after 10 min incubation in liver microsomes at 0.5 M (H = human, R = rat, M = monkey).
[c] Dosed at 10 mg/kg PO in 80%PEG400/10%DMAC/10%TW80. NT = Not tested.

observable time dependent CYP3A4 inhibition (>40 μM at 30 min).

Compounds **25b-d** and **49a-b** were tested in the marmoset facial blood flow assay as previously described.[23] The results for **25b-c** and **49b** were shown in Fig. 2. 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, 105 min) (Fig. 2). The effect of different doses of antagonists, delivered subcutaneously (sc) at 0 min, on the hαCGRP-induced increases in facial blood flow was measured by laser Doppler flowmetry. In this assay, compounds **25b-c**, and **49** showed exposure-dependent inhibition of CGRP-induced

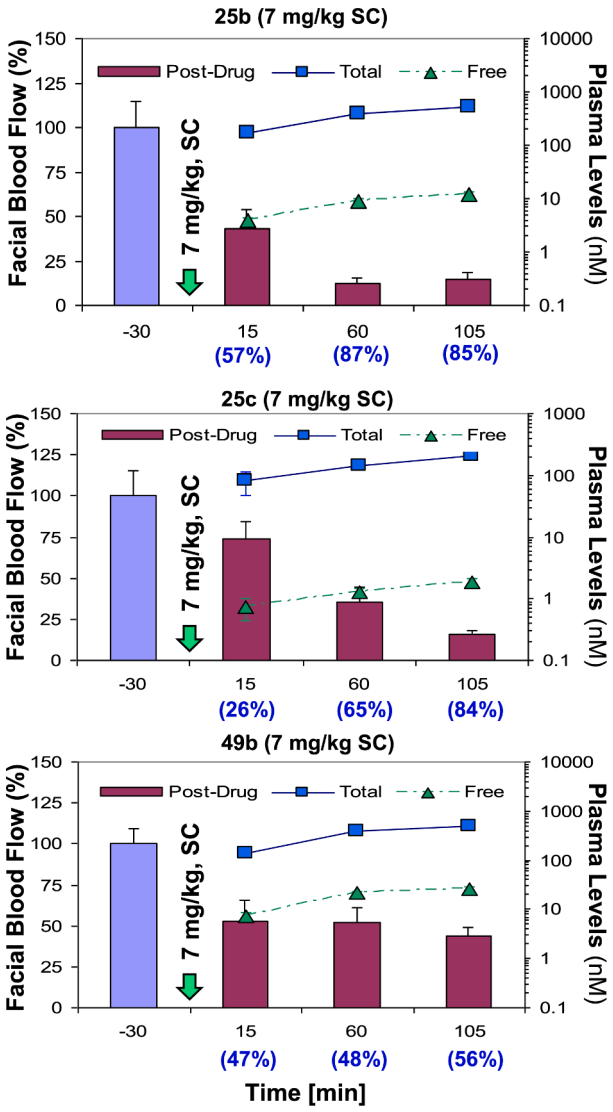



**Fig. 2.** Marmoset laser Doppler blood flow assay. Each marmoset received 4 iv injections of hαCGRP, designed to mimic waves of CGRP release during severe migraine, delivered at −30 min (baseline), and +15, +60 and +105 min relative to compound (0 min).

increases in marmoset facial blood flow upon sc dosing (only 7 mg/kg dose is shown in Fig. 2). As compared to predose vehicle control (−30 min), strong inhibition (>50%) of CGRP-induced effects on facial blood flow was observed with 7 mg/kg of **25b** at all time points (15, 60, and 105 min postdose test times). Total plasma levels of **25b** were above 170 and 510 nM (3.9–11.8 nM free with fu = 2.3%) and all times were associated with strong in vivo efficacy (>50 inhibition). Even at 3 mg/kg of **25b**, strong efficacy (up to 79%) was seen for total plasma levels of **25b** above 40–200 nM (data not shown). For **25c**, the strong inhibition was observed at 60 and 105 min post-dose test times (65–84%) and total plasma levels of **25c** were above 80 and 210 nM (0.7–1.9 nM free with fu = 0.9%). Imidazolone **25d** was also tested in this assay and was similar to **25c** with the peak efficacy of 67% (not shown). For **49b**, around 50% inhibition was observed at all time points (47–56%) with slightly stronger inhibition at the 105 min postdose test time (56%). The total plasma levels of **49b** were above 140–490 nM (7.4–26.3 nM free with fu = 5.4%).

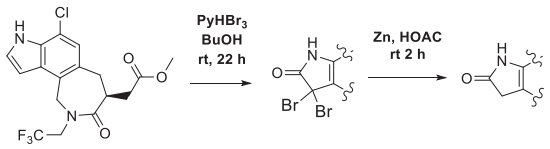
Pharmacokinetic studies also assessed oral exposures in vivo. With a 10 mg/kg oral dose, compound **25b** exhibited only 1% bioavailability in the rat with Cmax of 29 nM (less than the 4 h coarse PK Cmax of 96 nM).

**Table 2**
Selected data for 25b, 25c and 49b.

| Compound | 25b | 25c | 25f | 49b |
|---|---|---|---|---|
| MW | 633 | 701 | 674 | 627 |
| H-bond D/A[a] | 2/8 | 2/8 | 2/9 | 2/8 |
| cLogP[b] | 3.31 | 3.60 | 3.09 | 3.03 |
| tPSA[b] | 105 | 105 | 118 | 114 |
| PAMPA (nm/s) pH5.5/7.4 | NT/192 | 513/NT | 28/23 | 99/87 |
| Caco-2 Pc A-B/B-A (nm/*sec*) | <15/196 | <15/24 | <15/165 | <15/257 |
| Solubility[c] (μg/ml) | <1 | <1 | <1 | 15 |

[a] Numbers of hydrogen bond donor and acceptor.
[b] Calculated by Chemdraw 16.
[c] Measured in 50 mM phosphate buffer (pH 7) as an amorphous solid. NT = Not tested.

Compound **25b** was dosed in the cynomolgus monkey (cyno) at 10 mg/kg and revealed a Cmax of 35 nM, while the Cmax of **25c** and **25d** were 87 and 230 nM, respectively, when dosed in cynomologous monkeys at 10 mg/kg. Poor oral bioavailability is likely due to overall poor physicochemical properties of these rigid molecules with high molecular weight (MW), which appeared to be P-glycoprotein (P-gp) substrates (Table 2). Furthermore pharmaceutics challenges remained (i.e., very poor aqueous solubility, Table 2) and it seemed to be unlikely that all of the required molecular features for good oral bioavailability could be incorporated into one molecule in this series of CGRP antagonists, despite our extensive SAR studies around the azepinone core.




**41**

In summary, we have modified a novel CGRP receptor antagonist azepinone series by replacing the fused indazole portion with various heterocycles. In general, these compounds showed excellent binding affinities against the human CGRP receptor. Five compounds tested in the marmoset facial blood flow assay showed very good efficacy. However, oral bioavailability remained low, emphasizing the challenges we and others have encountered in discovering development candidates for this difficult Class B GPCR target. However, during the same time of these efforts, our team was successful in a different series of CGRP receptor antagonists, leading to rimegepant (BMS-927711)[24] that was approved as Nurtec™ ODT.[10]

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.128077.

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