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Potent oxadiazole CGRP receptor antagonists for the potential treatment of migraine

Paula L. Nichols [a,*], Jonathan Brand [a], Michael Briggs [b], Mathilde D'Angeli [a], Jennifer Farge [a], Stephen L. Garland [c], Paul Goldsmith [b], Rio Hutchings [a], Ian Kilford [a], Ho Y. Li [a], David MacPherson [a], Fiona Nimmo [a], Francis Dominic Sanderson [d], Sanjeet Sehmi [a], Nicola Shuker [a], John Skidmore [a], Michael Stott [a], Jennifer Sweeting [a], Hasmi Tajuddin [a], Andrew K. Takle [a], Giancarlo Trani [a], Ian D. Wall [c], Robert Ward [a], David M. Wilson [a], David Witty [a]

[a] Department of Medicinal Chemistry, Neurosciences Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK
[b] Department of Drug Metabolism and Pharmacokinetics, Neurosciences Centre of Excellence for Drug Discovery, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK
[c] Computational and Structural Chemistry, Molecular Discovery Research, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK
[d] Early Development Group, Pharmaceutical Development, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

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ABSTRACT

A pharmacophore model was built, based on known CGRP receptor antagonists, and this was used to aid the identification of novel leads. Analogues were designed, modelled and synthesised which incorporated alternative 'LHS' fragments linked via either an amide or urea to a privileged 'RHS' fragment commonly found in CGRP receptor antagonists. As a result a novel series of oxadiazole CGRP receptor antagonists has been identified and the subsequent optimisation to enhance both potency and bioavailability is presented.

Migraine is a chronic neurovascular disorder, which results in episodic headache attacks lasting 4–72 h and is believed to affect more than 10% of adults.[1] The current standard treatment for migraines is the class of 5-$HT_{1B/1D}$ receptor agonists known as the triptans.[2] However, triptans are contraindicated in patients with cardiovascular disease because their mechanism of action involves direct vasoconstriction.[3] Therefore, a novel class of migraine drug that did not result in direct vasoconstriction would offer a significant therapeutic advantage.

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide, present in the CNS and periphery,[4] and is a potent vasodilator.[5] CGRP has been implicated in the pathophysiology of migraine, as enhanced levels of CGRP are observed during migraine attacks and an intravenous (IV) infusion of CGRP can induce migraine-like headaches.[6] Support for this theory initially came from clinical trials of the CGRP receptor antagonist, olcegepant, which demonstrated similar efficacy to the triptans following an IV infusion but without any direct vasoconstriction.[7]

Following on from the successful proof of concept with IV administered olcegepant, our programme aimed to identify a novel orally bioavailable CGRP receptor antagonist for the treatment of migraine. Further support for this came during the course of this work when the first orally bioavailable CGRP receptor antagonist, MK-0974, was reported to be efficacious in a Phase II clinical trial for the treatment of acute migraine.[8]

To aid the design and identification of novel leads, a pharmacophore model was built based on known CGRP receptor antagonists, such as benzodiazepinone **1** and indazole **2**.[9,10] The 'right-hand side' (RHS) fragments were all highly conserved across these molecules and they incorporated key hydrogen-bond acceptor/donor functionality. In addition, the linkers also included another hydrogen-bond acceptor that was believed to be important for binding (Fig. 1).

In order to further improve our understanding of the CGRP pharmacophore, novel analogues were designed, modelled and synthesized. These analogues linked novel 'left-hand side' (LHS) fragments, via an amide or a urea, to a range of privileged RHS

* Corresponding author.
E-mail address: paula.l.nichols@gsk.com (P.L. Nichols).

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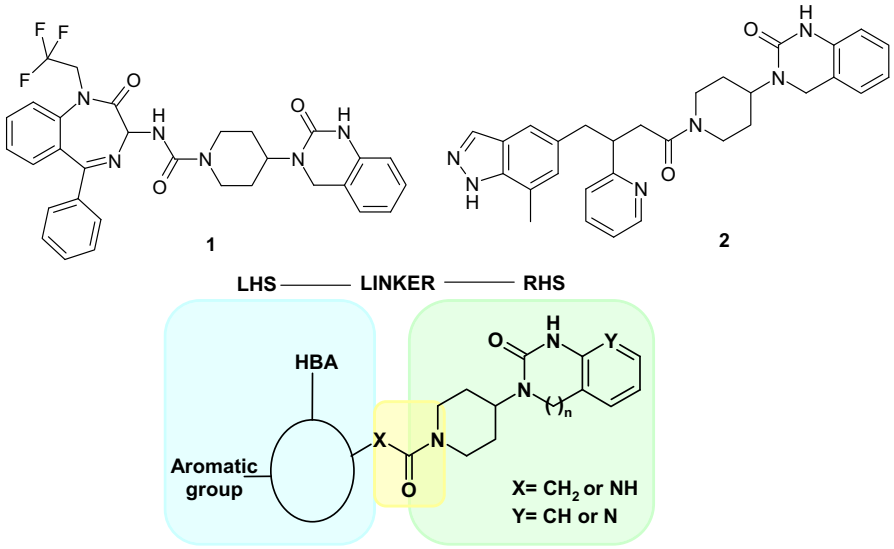
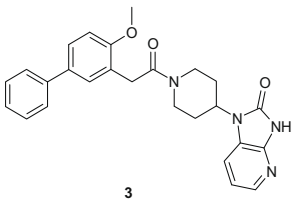


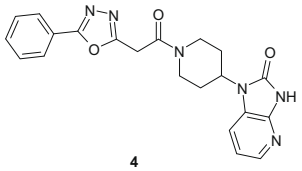
Figure 1. CGRP pharmacophore schematic.

structures commonly found in known CGRP receptor antagonists. The RHS in compounds **1** and **2** was not extensively explored due to stability concerns therefore RHS A,[11] which gave rise to compounds with similar levels of potency, was routinely used. The simplified LHS groups were designed to probe specific elements of the CGRP pharmacophore, such as the necessity and positioning of certain aromatic lipophilic groups and hydrogen-bonding interactions (Fig. 2).

From the analogues prepared, the simple biaryl system **3**, with an appropriately placed hydrogen-bond acceptor in the LHS fragment, was identified as a weak CGRP receptor antagonist (fpK_i 5.6).[12]



3
fpKi 5.6, BEI12.7



4
fpKi 6.7, BEI 16.6

Following the identification of compound **3**, further work to optimise the hydrogen-bonding capacity led to the replacement of the central methoxy-aryl core with a range of alternative 5- and 6-membered heteroaryl systems. The most optimal of these analogues was the 1,3,4-oxadiazole, as exemplified by compound **4**, which demonstrated a significant improvement in potency (fpK_i 6.7) and binding efficiency. It was postulated that the significantly enhanced potency, observed with the 1,3,4-oxadiazole, was due to the optimal hydrogen-bond accepting capacity of this heterocycle.

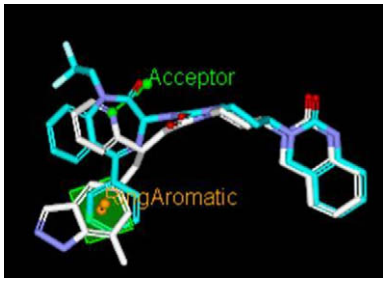


Figure 2. CGRP pharmacophore.

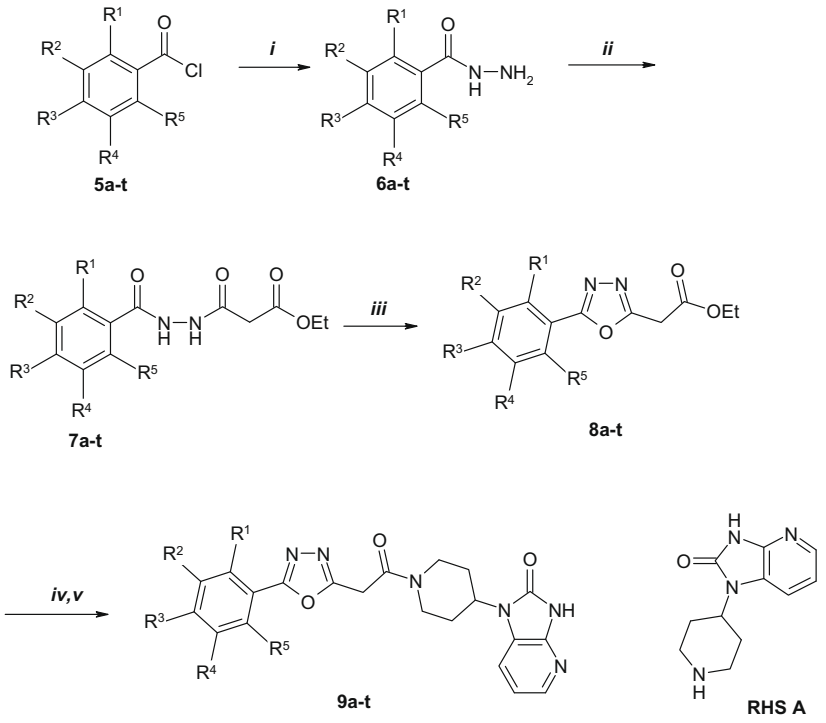
To follow up on this initial oxadiazole lead, a range of substituted-aryl analogues were prepared. Compounds **9a–t** could be prepared, for example, by treatment of the acid chlorides **5a–t** with hydrazine, followed by acylation gave the cyclisation precursors **7a–t**. Subsequent microwave irradiation, in the presence of Burgess reagent, afforded the 1,3,4-oxadiazoles **8a–t** which then underwent ester hydrolysis and amide coupling, with the privileged RHS fragment A[11] motif, to give analogue structures **9a–t** (Scheme 1).[13]

From the examples prepared various SAR trends were observed. In general substitution on the aryl ring at the 2-, and 3-positions was well tolerated but did not enhance potency, whereas substitution at the 4-position had a slightly detrimental effect on potency (Table 1). However, the introduction of two substituents onto the aromatic ring proved to be much more interesting, with 3,5-dichloro-substitution leading to a surprising increase in activity (compound **9h**, Table 1). Several other 3,5-substituent pairs were explored and, in general whilst there was a requirement for a small lipophilic group in the 3-position (e.g., Cl, Me), several groups of varying size were well tolerated in the 5-position. Molecular modelling was employed to aid our understanding of this SAR in relation to the pharmacophore, and this will be reported in a separate communication.

The most promising analogues were explored further and profiled in vivo to understand their pharmacokinetic profile in the rodent. Of particular interest was compound **9o** which combined high levels of permeability and an encouraging pharmacokinetic profile, with clearance approaching 40% liver blood flow (*rat IV, 1 mg/kg*: Cl = 33 mL/min/kg, $t_{1/2}$ = 0.5 h). This compound was also explored in the rat to understand the oral exposure profile (Fig. 3).

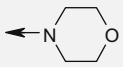
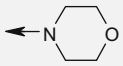
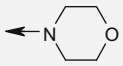
Interestingly, following oral dosing of **9o** in a methylcellulose formulation, the exposure was very limited. However, when dosed in a solubilising formulation, the exposure was significantly enhanced (*rat po, 10 mg/kg*: C_{max} = 0.7 μM, T_{max} = 1.5 h, dose-normalised AUC = 6.3 min kg/L; estimated F = 20%[14]) (Fig. 3). This suggested that exposure for this compound was probably limited by solubility or dissolution rate.

Consequently the next phase of optimisation was focused on improving oral bioavailability by enhancing the solubility of the compounds. Therefore, a strategy of introducing basic substituents onto the terminal aryl ring was employed (compounds **10a–h**, Table 2).



Scheme 1. Synthesis of aryl-oxadiazole analogues. Reagents and conditions: (i) hydrazine hydrate, ethanol, 80 °C; (ii) ethyl 3-chloro-3-oxopropanoate, Et_3N, THF, rt; (iii) burgess reagent, CH_2Cl_2, μW, 100 °C; (iv) LiOH, THF, rt; (v) RHS A, EDC, HOBT, *N*-methyl morpholine, DMF, rt, 2–55% yield over five steps.

Table 1
Aryl-ring SAR

	R^1	R^2	R^3	R^4	R^5	CGRP fpK_i[a]
4	H	H	H	H	H	6.7[b]
9a	Cl	H	H	H	H	6.3[b]
9b	H	Cl	H	H	H	6.5[c]
9c	H	H	Cl	H	H	6.0
9d	Cl	Cl	H	H	H	6.8
9e	Cl	H	H	Cl	H	6.9[b]
9f	Cl	H	H	H	Cl	6.1
9g	H	Cl	Cl	H	H	6.6
9h	H	Cl	H	Cl	H	7.8[d]
9i	H	F	H	F	H	6.9[b]
9j	H	Me	H	Me	H	7.6[c]
9k	H	CF_3	H	CF_3	H	7.6[c]
9l	H	OMe	H	OMe	H	7.3
9m	H	Cl	H	F	H	7.6[c]
9n	H	Cl	H	Br	H	7.9[e]
9o	H	Cl	H	CF_3	H	8.4[f]
9p	H	Cl	H	OMe	H	8.1[c]
9q	H	Cl	H	Ph	H	8.6[g]
9r	H	Cl	H		H	8.2[h]
9s	H	Me	H		H	8.2[i]
9t	H	Ph	H		H	6.7[b]

[a] Values are mean of two experiments carried out in the absence of HSA, unless otherwise indicated.
[b] Values are mean of four experiments.
[c] Values are mean of six experiments.
[d] Values are mean of 12 experiments.
[e] Values are mean of eight experiments.
[f] Values are mean of 11 experiments.
[g] Values are mean of five experiments.
[h] Values are mean of 10 experiments.
[i] Values are mean of 73 experiments.

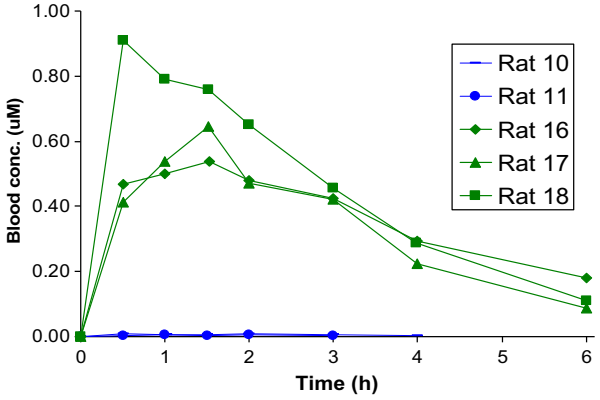
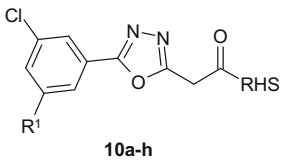
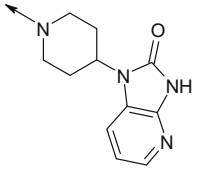


Figure 3. Rat oral administration of **9o**. Rats 16, 17 and 18 were dosed using **9o** formulated at a concentration of 2 mg/mL in 5% NMP, 80% PEG400 diluted to volume with 20% Vitamin E TPGS in water. Rats 10 and 11 were dosed using **9o** formulated at a concentration of 2 mg/mL in 1% (w/v) aq methylcellulose.





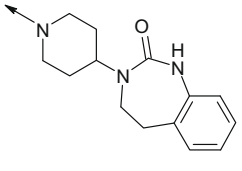
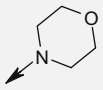
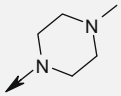
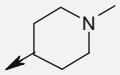
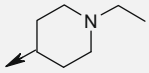
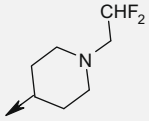
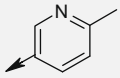
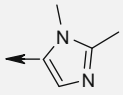
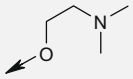
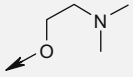


Table 2
Optimisation of the basic substituents

	R[1]	RHS	CGRP fpK_i[a] (−/+HSA)	FaSSIF[15] sol.[g] (μg/ml)	A.M. Perm.[h] (nm/s)	CLb (mL/min/kg)	calcd CHI log D[16]
9r		A	8.2/6.9	40	120	70	1.7
10a		A	8.3[b]/7.6	210	<3	72	—
10b		A	8.4[c]/7.7[c]	531	22	—	0.8
10c		A	8.5[d]/7.8[d]	565	5	—	0.9
10d		A	8.4[b]/7.1[d]	10	200	67	2.4
10e		A	8.6/6.9	<1	220	—	1.7
10f		A	8.8[d]/7.0	390	<3	52	1.2
10g		A	8.3[e]/7.3[f]	330	12	—	0.9
10h		B	7.9[d]/7.8	120	185	50	1.6

[a] Values are mean of two experiments unless otherwise indicated.
[b] Values are mean of eight experiments.
[c] Values are mean of six experiments.
[d] Values are mean of four experiments.
[e] Values are mean of 12 experiments.
[f] Values are mean of three experiments.
[g] Value indicates the amount of compound which had dissolved in a fasted-state simulated intestinal fluid at the one hour time point.
[h] Values were obtained using an in vitro artificial membrane permeability assay.

Pleasingly, replacement of the trifluoromethyl group in **9o** with a piperazine or a piperidine resulted in maintenance of potency and a significant improvement in aqueous solubility (compounds **10a**, **10b** and **10c**). However, these analogues generally had sub-optimal metabolic stability and permeability was limited due to the presence of the strongly basic centre.

As a result, substituents with reduced basicity were targeted as a means of achieving the optimum balance of solubility and permeability. The pyridyl analogue **10e** maintained a good level of potency but was not sufficiently basic to give the desired increase in solubility, whereas the imidazole analogue displayed good levels of solubility but was poorly permeable. Oxy-linked analogues such as **10g** were, again, highly soluble but did not have the desired level of permeability.

It was evident from an analysis of the series that good permeability could be achieved with compounds where the calculated CHI log D was greater than 1.7 but increasing this beyond 2.0 often resulted in reduced solubility. In this regard, compound **10h** which incorporated an oxypropylamine LHS with the privileged RHS fragment B,[17] gave the most optimal balance of permeability and solubility of all the analogues prepared. These optimal attributes were believed to be due to basicity-reducing effect of the β-oxygen, resulting in increased permeability whilst retaining some solubility, and the compound having an overall log D close to the desired range. This compound was selected for further profiling in the rodent.

Gratifyingly the compound had a very encouraging pharmacokinetic profile (*rat IV, 1 mg/kg*: Cl = 50 mL/min/kg; $t_{1/2}$ = 1.9 h) and demonstrated encouraging exposure when dosed orally using a standard methylcellulose formulation (*rat po, 10 mg/kg*: C_{max} = 0.25 μM, T_{max} = 3 h, dose-normalised AUC = 2.5 min kg/L; estimated F = 14%[14]), albeit with a delayed absorption profile (Fig. 4).

In summary, a novel series of aryl-oxadiazole CGRP receptor antagonists was designed using a pharmacophore model based on previously reported CGRP receptor antagonists. The initial lead was optimised via both modification of the central core and introduction of suitable substituents in the LHS terminal aryl group. In addition a strategy of balancing solubility, permeability and log D

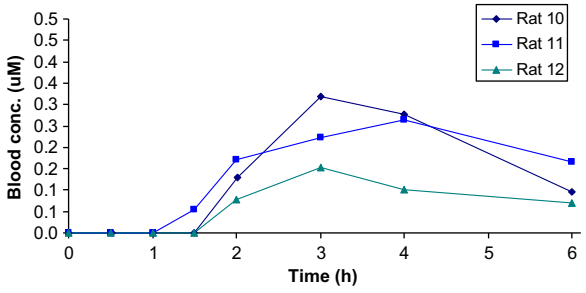


Figure 4. Rat oral administration of **10h**, formulated at a concentration of 2 mg/mL in 1% methylcellulose.

successfully delivered compounds with encouraging levels of oral exposure in the rat. However, the delayed absorption profile observed with **10h** is not ideal as an acute migraine therapeutic. Consequently further optimisation work aimed at improving the bioavailability, in particular the T_{max}, is required and will be reported at a later date.

Acknowledgements

The authors would like to thank the drug metabolism and pharmacokinetic group for providing in vivo data. Thanks also go to the pharmaceutical development group for the solubility analysis and formulation work.

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12. The functional pK_i (fpK_i) for antagonism of CGRP-stimulated increases in intracellular cAMP was determined in HEK 293 cells expressing the human recombinant receptor. Compounds which had encouraging potency in the absence of HSA were then screened in the presence of HSA to give a better prediction of the in vivo potency. For details of this assay, see: Nichols, P. L.; Skidmore, J.; Ward, R. W.; Wilson, D. M. WO2009/000819 A1.
13. Scheme 1 details the most common route used to synthesise compounds of the type **9a**–**t**. Alternative syntheses can be found in Nichols, P. L.; Skidmore, J.; Ward, R. W.; Wilson, D. M. WO2009/000819 A1.
14. F (%) was estimated, using data obtained with different animals in separate IV and oral studies, using following calculation: F (%) = (AUC(0–t)/D po)/(AUC(0–t)/D iv) × 100.
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