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Trimethylsilylpyrazoles as novel inhibitors of p38 MAP kinase: A new use of silicon bioisosteres in medicinal chemistry

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Abstract—The synthesis, physicochemical properties and pharmacological profiles of two novel silicon-containing p38 MAP kinase inhibitors are described.

The pharmaceutical industry has an ongoing need for new and safe medicines with a genuine biomedical benefit, a clean IP position and commercial viability. Sila-substitution (C/Si exchange) of existing drugs or development candidates is one possible approach to the search for new drug-like entities that have beneficial biological properties and a clear IP position.[1]

Kinases represent an important family of therapeutically relevant targets for which a marketable compound appears achievable.[2] The p38 mitogen-activated protein kinase (p38 MAP kinase; SAPK2a) is an intracellular serine/threonine kinase that can be activated by a range of environmental stimuli such as stress, or via the immune response. The discovery of novel chemical entities as potent and selective inhibitors of p38 MAP kinase and their efficacy in several animal models of inflammation has validated this enzyme as an important anti-inflammatory target.[3,4]

Recently, there have been many publications describing p38 MAP kinase inhibitors which include small heterocyclic rings such as imidazole and pyrazole, placing severe restrictions on the free patent space for such scaffolds.[5] This is typified by BIRB-796 (Doramapimod, **1**), a non-peptidic p38 MAP kinase inhibitor from Boehringer Ingelheim which recently underwent clinical evaluation for the treatment of several inflammatory diseases, including rheumatoid arthritis, Crohn's disease and psoriasis.[6]

In order to combine scientific data from the literature with our own remit of using silicon as an isostere for carbon in medicinal chemistry, we synthesised compound **2** (the silicon analogue of BIRB-796) and investigated the in vitro activity, physicochemical and pharmacokinetic properties of the silicon–carbon pair. A further compound **3**, in which the silylated pyrazole unit was replaced by an aryl silane, was also investigated (Fig. 1).

The silicon analogue of BIRB-796 was synthesised according to the procedure shown below (Scheme 1). Modification of a known protocol[7] for the [3 + 2] cycloaddition reaction of trimethylsilylacetylene (**4**) to ethyl diazoacetate (**5**) in the absence of solvent led to the pyrazole **6** in good yield. Use of a known procedure[8] for the copper(II)-mediated arylation of pyrazoles utilizing *para*-tolylboronic acid afforded both **7a** (major) and **7b** (minor), which were easily separable by standard column chromatography. Ester **7a** was hydrolysed under basic conditions to afford the corresponding carboxylic acid **8**. This acid was then converted to the isocyanate in situ, which was allowed to react with the known amine **9**[6] to afford the direct silicon analogue of BIRB-796 (**2**) in good overall yield. In order to allow direct comparison within our own assay systems, BIRB-796 was synthesised according to the literature procedure.[6]

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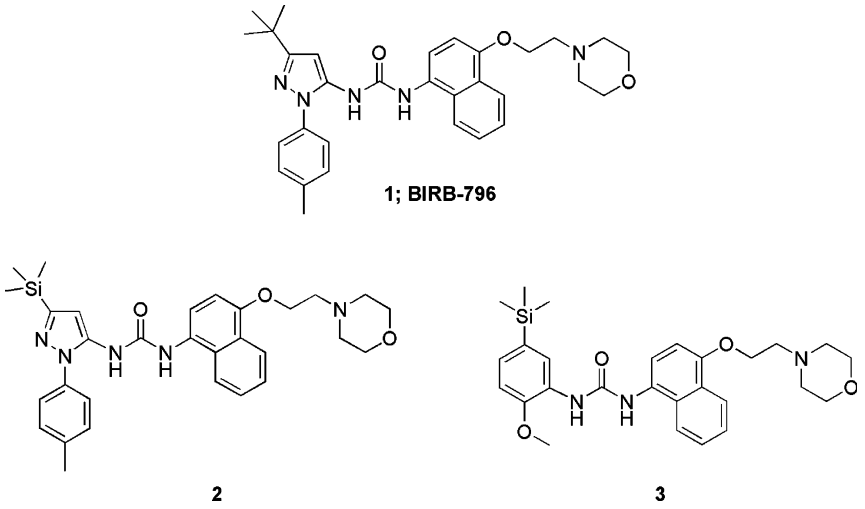
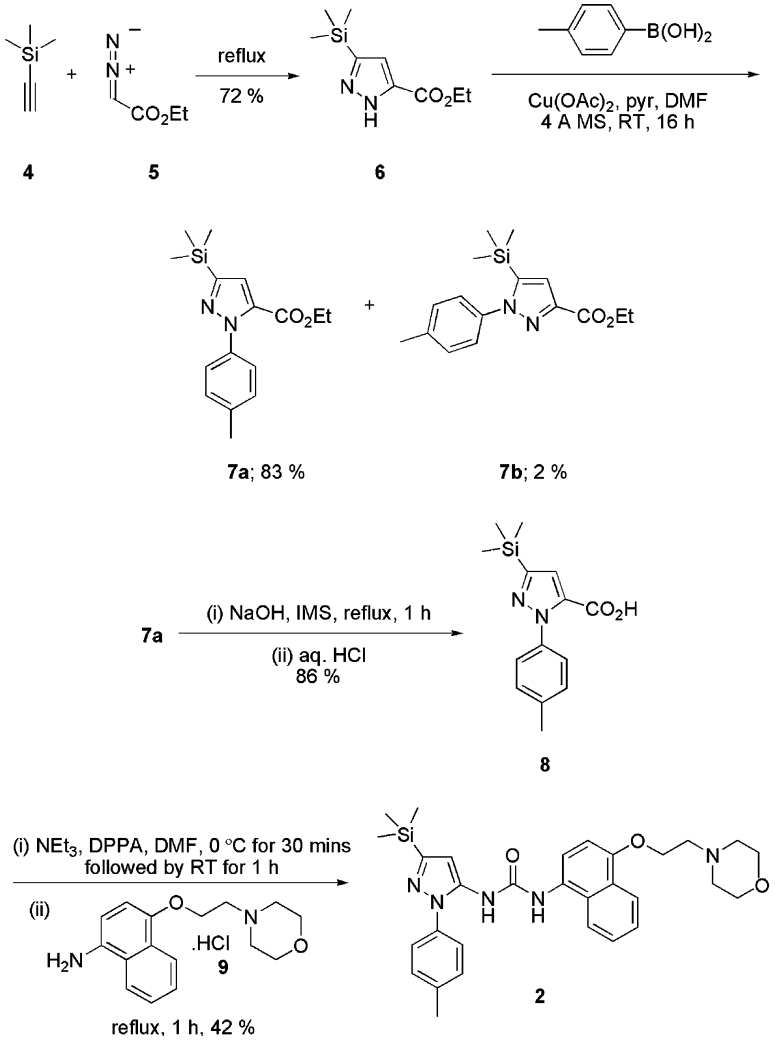


Figure 1. The structures of BIRB-796 and silicon-containing p38 MAP kinase inhibitors.



Scheme 1. The synthetic route to compound **2**. IMS, industrial methylated spirits; DPPA, diphenylphosphoryl azide.

X-ray quality crystals of the acid **8** derived from the major product of the cyclisation reaction (**7a**) were obtained. An X-ray structure determination allowed for the unequivocal assignment of the compound's structure, and in particular the regiochemistry around the pyrazole ring (Fig. 2).[9] By association, the regiochemistry of the final compound can be confirmed.

We were intrigued by the potential replacement of the silylated pyrazole ring with an electron-rich aromatic

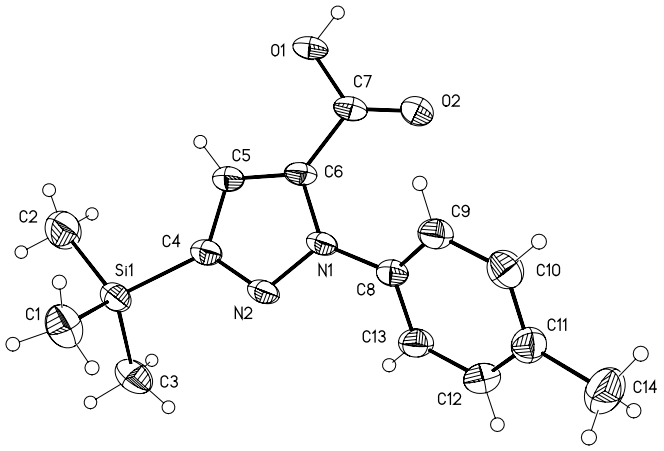


Figure 2. X-ray crystallographic determination of the structure of the acid **8**.

carbocycle which, based on literature precedent,[10] should also provide a highly potent p38 MAP kinase inhibitor. Thus, the amine **10** was allowed to react with phosgene and then the amine **9** in the presence of Hunig's base to afford the aryl silane **3** in good yield (Scheme 2).

The physicochemical parameters for the C/Si analogues **1** and **2** have been measured (Table 1).[11] These data indicate that the exchange of carbon for silicon has an effect on both the pK_a of the aromatic nitrogen heterocycle and the overall lipophilicity of the molecule. Whilst it is common for the lipophilicity of silicon compounds to be equivalent to or greater than their carbon analogues, we were gratified to see in this instance, the silicon compound was moderately less lipophilic than its carbon counterpart.

The in vitro activities of compounds **1**, **2** and **3** in a p38 MAP kinase enzyme assay have been determined (Table 2).[12] When the three compounds were tested in parallel they showed almost equivalent inhibition (*). Thus suggesting that neither the introduction of silicon nor the exchange of the pyrazole for the electron-rich aryl system is detrimental to the potency of the compounds.

The stability of compounds **1**, **2** and **3** to degradation by human liver microsomes has also been determined (Table 3).[13] All compounds demonstrated similar resistance to degradation by such species, the silicon switch compound **2** appearing to be more stable than its carbon analogue.

Table 1. Physicochemical data for compounds **1** and **2**

Compound	pK_a		log P	log D at pH		
	1	**2**		6.0	6.5	7.4
1 (BIRB-796)	1.9	6.4	5.2	4.6	4.9	5.1
2	2.3	6.3	4.7	4.3	4.5	4.7

Table 2. The in vitro activity of compounds **1**–**3** against p38 MAP kinase (human)

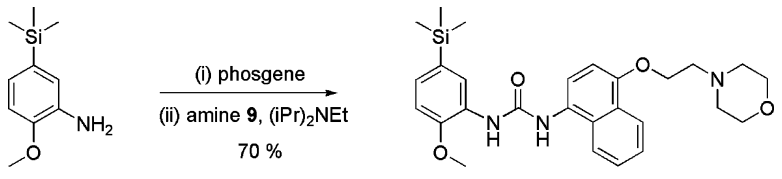
Compound	Human p38 MAP kinase IC_{50}/nM
1 (BIRB-796)	55 ± 51 (n = 3)
2	64 ± 50 (n = 3)
3	3* (n = 1)

* In this assay compound **1**, IC_{50} value = 9 nM and compound **2**, IC_{50} value = 7 nM.

Table 3. The stability of compounds **1**, **2** and **3** in human liver microsomes (percentage turnover after 40 min at 37 °C; 1 μM concentration of compound)

Compound	Microsomal % turnover
1 (BIRB-796)	79 (n = 1)
2	66 (n = 1)
3	94 (n = 1)

These data suggest that the new silicon-derived compound **2** is a potent inhibitor of p38 MAP kinase and is not substantially degraded by human liver microsomes. We therefore proceeded to demonstrate good activity in



Scheme 2. The synthetic route to aryl silane **3**.

Table 4. In vivo effect of BIRB-796 and compound **2** on levels of TNF-α following LPS-challenge

	TNF-α levels (pg/mL)	
Time post dose	30 min	120 min
Vehicle	3546	2950
1 (BIRB-796)	2083 (−41%)	1761 (−40%)
2	1443 (−59%)	1616 (−45%)
Dexamethasone	495 (−86%)	nt[a]

[a] Not tested.

an in vivo efficacy model. Compounds **1** and **2** were tested in an LPS (lipopolysaccharide from *Escherichia coli* 0111:B4)-induced model of TNF-α (tumour necrosis factor) release in mice alongside 3 mg/kg po dexamethasone as a positive control. The animals received either vehicle, or 10 mg/kg po of compounds **1** and **2** at 30 or 120 min prior to challenge with 1 mg/kg ip LPS. Serum TNF-α levels were measured by ELISA (Table 4).[14]

Compound **1** (BIRB-796) is effective in this model as demonstrated by TNF-α suppression at both 30 and 120 min. The silicon compound **2** demonstrated similar efficacy, particularly at the 30 min time-point, where the levels of TNF-α were reduced more than compound **1**.

In conclusion, two new silicon-containing p38 MAP kinase inhibitors (**2** and **3**) have been described. Compound **2** has been demonstrated to have a good physicochemical profile and is also comparable in terms of its stability in human liver microsomes. It appears to be at least as effective as BIRB-796 with respect to both in vitro and in vivo activity and therefore is a promising candidate for further evaluation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.10.044.

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9. We thank Professor Reinhold Tacke and his staff (Institut für Anorganische Chemie, Würzburg, Germany) for performing the X-ray determination. The details of the determination have been lodged with the Cambridge Crystallographic Data Centre (Deposition number 615126).
10. See WO 2002 092576 A1.
11. We thank Ian Cooper (Pharmorphix Ltd, Cambridge, UK) for undertaking these experiments. See the Supplementary Information provided for details of methods.
12. The p38 MAP kinase enzyme assay was carried out at Upstate. Details can be found in the Supplementary Information provided.
13. Microsomal degradation assays were carried out at Inpharmatica Ltd, Cambridge, UK. Details can be found in the Supplementary Information provided.
14. The LPS model was conducted by Cerep, France. For details see Supplementary Information.