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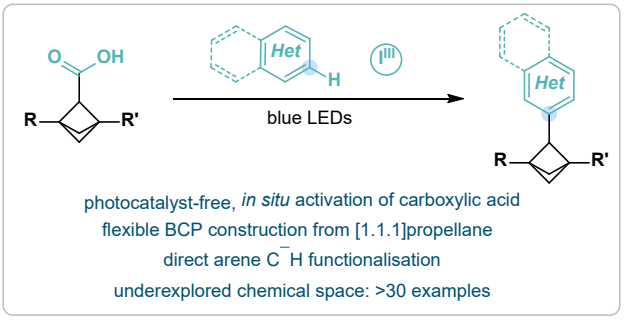
Bridge Heteroarylation of Bicyclo[1.1.1]pentane Derivatives

Joseph M. Anderson[1,2], Nicholas D. Measom[1], John A. Murphy[2], Darren L. Poole*[1]

[1] Medicinal Chemistry, GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, UK, SG1 2NY. [2] Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, UK, G1 1XL.

Supporting Information Placeholder

ABSTRACT: Herein we report the decarboxylative Minisci heteroarylation of bicyclo[1.1.1]pentane (BCP) and 2-oxabicyclo[2.1.1]hexane (oBCH) derivatives at the bridge positions. In an operationally simple, photocatalyst-free process, free bridge carboxylic acids are directly coupled with non-prefunctionalised heteroarenes to provide rare examples of polysubstituted BCP and oBCH derivatives in synthetically useful yields. Additionally, the impact of the BCP core on the physicochemical properties of a representative example compared to its all-aromatic *ortho*- and *meta*-substituted analogues is evaluated.

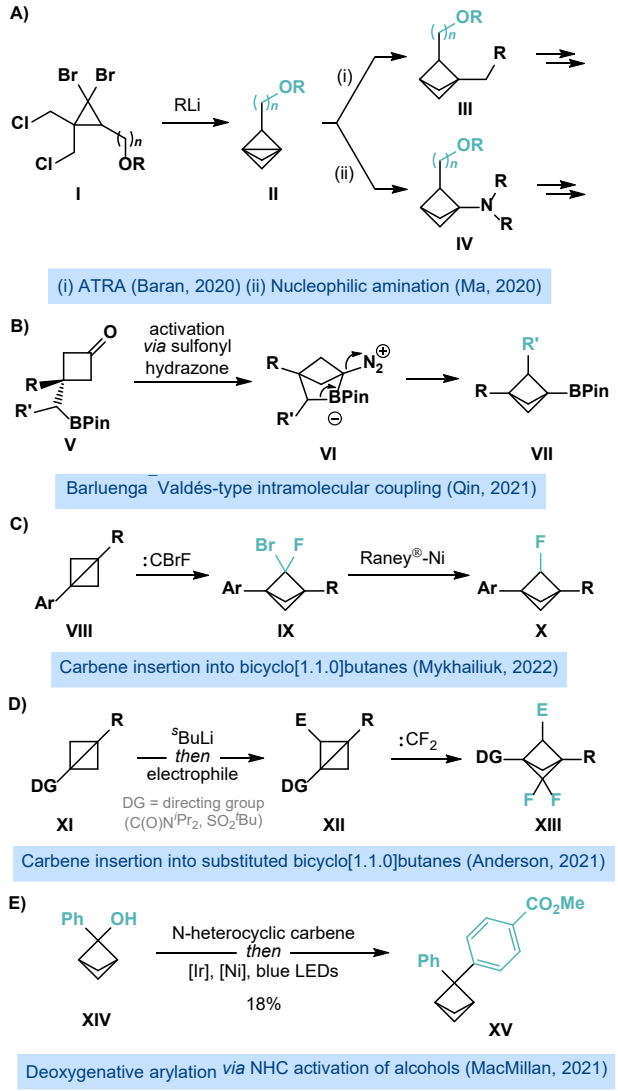


Bicyclo[1.1.1]pentane (BCP) derivatives are powerful bioisosteres for *tert*-butyl groups, alkynes and arenes in drug discovery, facilitating "escape from flatland"[1] with ability to significantly improve the physicochemical and metabolic profiles of lead structures.[2] Recent literature has highlighted particular interest in 1,2- and 1,2,3-substituted BCPs as replacements for *ortho*- and *meta*-substituted arenes. However, challenging syntheses with high step counts, and limited validation of strategies for divergent functionalisation, present severe limitations to the exploration of these motifs.[2] Key reports from Baran[3] and Ma[4] describe the synthesis of 1,2-difunctionalised BCPs through atom transfer radical addition (ATRA) and strain-release nucleophilic amination of appropriate [1.1.1]propellane precursors, respectively (**Scheme 1A**). Qin subsequently reported an intramolecular Barluenga−Valdés coupling providing both BCP and higher bicycloalkane derivatives (**Scheme 1B**).[5] More recently, Mykhailiuk has disclosed a controlled synthesis of elusive bridge mono-fluorinated BCPs (**Scheme 1C**),[6] while difluorocarbene insertion into Anderson's bridge-substituted bicyclo[1.1.0]butanes provides entry to 2-substituted-4,4-difluorinated derivatives (**Scheme 1D**).[7] Additionally, MacMillan's deoxygenative arylation methodology[8] was applied in a single example to bicyclopentanol **XIV**, furnishing arylated product **XV** in moderate yield (**Scheme 1E**).

While BCPs with bridgehead-bound heterocycles are well-known and are accessible through ATRA,[9] cross-coupling,[10] annulative[11] and Minisci-type processes,[12] BCPs with heterocycles at the bridge position are rare and represent a potentially valuable yet highly under-explored area of chemical space.[2,13] Although a Minisci disconnection to these structures is particularly appealing due to no requirement for pre-functionalisation of the heterocycle, controlled radical transformations at BCP bridge positions are still in their infancy.[3,13] The strain energy of the parent BCP hydrocarbon is over twice that of cyclopropane and cyclobutane,[14] and so direct extension of methodologies compatible with these more familiar motifs cannot be guaranteed. Recent evidence has shown that successful application of existing radical-based methodologies to the BCP core often requires significant reaction re-optimisation.[13] Herein, we report the direct Minisci-type reaction of free BCP bridge carboxylic acids under hypervalent iodine activation. Synthesis of the acid precursors from [1.1.1]propellane **2** thus provides a highly modular approach to unsymmetrical 1,2,3-trisubstituted BCP derivatives of medicinal interest. Furthermore, our study provides an assessment of the relative lifetime of the putative BCP radical at different temperatures, which we anticipate will be useful in the application of other reaction radical transformations to this privileged scaffold.

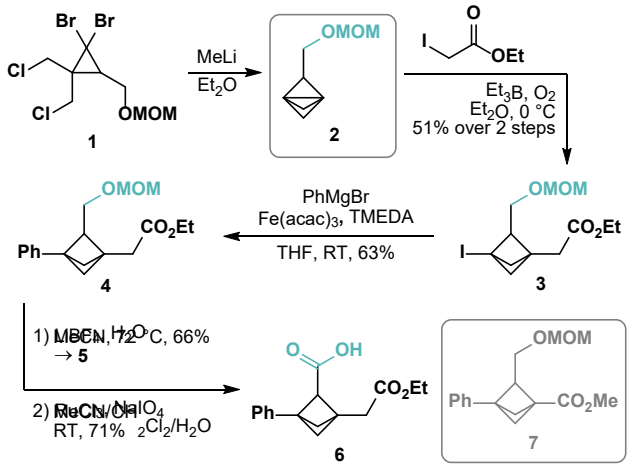
Our investigation began with gram-scale synthesis of model substrate **6** from [1.1.1]propellane **2**[3,15] (**Scheme 2**), building on the ATRA[10] and Kumada[16] cross-coupling methodologies of Anderson. Attempts to access lower homologue **7** from **2** through Knochel's 3-component assembly[17] were unsuccessful (complex mixtures obtained), potentially due to Lewis

acid-promoted loss of methanol from the MOM group at elevated temperatures and subsequent propellane fragmentation.



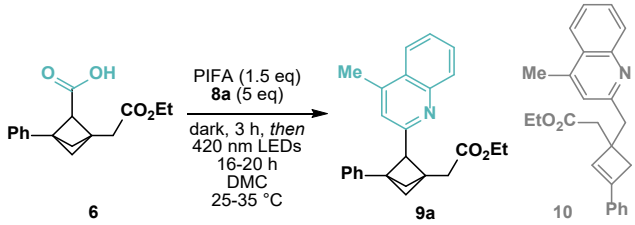
Scheme 1. Recent developments in the synthesis of bridge-functionalised BCP derivatives.

The photochemical Minisci reaction of **6** with lepidine (4-methylquinoline, **8a**) was then pursued. Conditions based on literature reports[18] using inexpensive iodine(III) oxidant PIFA (phenyliodine bis(trifluoroacetate)) were selected as a starting point. Initial control experiments confirmed the observation of Zhang[18b] that exogenous photocatalysts are not necessary to enable reactivity. Further optimisation (see ESI for full details) then identified ethyl acetate and dimethyl carbonate (DMC) as the most effective solvents (**Table 1**, entries 1-5), and that the reaction can be mediated by irradiation wavelengths between 385 nm and 450 nm (entries 6 and 7). A decreased yield was observed when the heterocycle loading was decreased (entry 8), while doubling to 10 eq was of negligible benefit (entry 9). Unexpectedly, increasing PIFA loading above 1.5 eq rapidly decreased the yield (entries 10-11) but without appreciably increasing conversion of carboxylic acid **6**.



Scheme 2. Synthesis of model substrate **6**.

Table 1. Optimisation of Minisci reaction of BCP **6**.



Entry	Deviation from above	Yield 9a (%)[a]
1	None	52 (41[b])
2	EtOAc solvent	40-48[c]
3	EtOAc solvent, 2 eq PIFA	35
4	MeCN solvent, 2 eq PIFA	22
5	DMF solvent, 2 eq PIFA	16
6	EtOAc solvent, 385 nm irradiation, 2 eq PIFA	35
7	EtOAc solvent, 450 nm irradiation, 2 eq PIFA	32
8	EtOAc solvent, 2 eq PIFA, 2 eq lepidine	28
9	EtOAc solvent, 2 eq PIFA, 10 eq lepidine	36
10	EtOAc solvent, 4 eq PIFA	10
11	EtOAc solvent, 6 eq PIFA	3
12	EtOAc solvent, N_2-sparged	29
13	EtOAc solvent, reaction under air	10

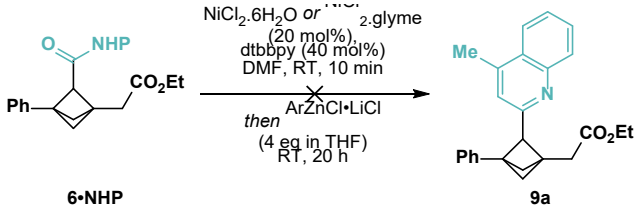
[a] Determined by calibrated liquid chromatography, 15 µmol scale. [b] Isolated yield (n = 2), ~0.175 mmol scale. [c] See ESI.

According to mechanisms proposed in the literature,[18] 1.5 eq PIFA limits the maximum yield of the reaction to 75% (see ESI for further discussion). Addition of larger amounts of PIFA portionwise, or *via* slow addition of a stock solution over several hours, also failed to improve the yield of **9a**. A screen of alternative iodine(III) and iodine(V) reagents[19] confirmed that PIFA remained optimal.

Using the corresponding quinoline *N*-oxide or an *N*-methoxyquinolinium salt[20] instead of free heterocycle **8a** provided no benefit. Unexpectedly, deoxygenation of the commercial anhydrous reaction solvent resulted in decreased yields (entry 12), while performing the reaction under air also decreased the yield (entry 13). A wide range of additives were screened without

success. Higher temperatures (≳ 40 °C) failed to improve the yield, instead producing a ring-opened isomer of the desired product arising from β-scission of the intermediate BCP radical (compound **10**). This temperature sensitivity was especially pronounced on larger scale, and necessitated a change of irradiation equipment between reaction optimisation and preparative-scale reactions.

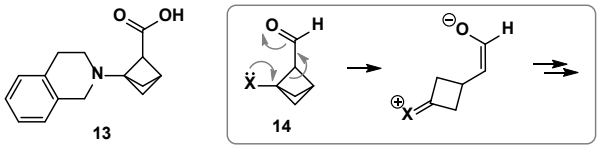
Further optimisation efforts using these model substrates proved unfruitful. Increasing the scale approximately 12-fold (preparative scale for reaction scope assessment) reproducibly provided **9a** in 41% yield. The reaction was scaled up further to 1 mmol scale without further impact on the yield (see ESI). We highlight that this maximum yield is commensurate with other Minisci reactions reported in the literature[12a,21] and is acceptable given that the methodology enables direct fragment coupling without requirement for pre-functionalisation/pre-activation of either component. The operational simplicity of the reaction[13] renders it suitable for parallel synthesis towards rapid library generation, and unreacted starting materials are readily recoverable from reaction mixtures through a combination of basic aqueous workup and chromatography. Finally, to further contextualise the reaction yield, attempted synthesis of **9a** through Baran's Negishi cross-coupling[3] provided only traces of the desired product by LCMS analysis in our hands (**Scheme 3**).



Scheme 3. Unsuccessful synthesis of **9a** through decarboxylative Negishi cross-coupling. NHP = *N*-hydroxyphthalimide.

We next evaluated the scope of the developed reaction (**Figure 1**). Moderately electron-rich (**8b-d, 8m**) and moderately electron-poor (**8e-g, k-l**) quinolines and isoquinolines were tolerated, with products **9c**, **9e-g** and **9k-l** notably containing useful functional handles for further product derivatisation. **9m** was obtained in lower yield due to polymerisation of the heterocycle on addition to the reaction mixture. Substitution adjacent to the heterocycle reactive site presented no issue (**9h**). While **9g** was obtained with excellent regioselectivity about the heterocycle, further increasing the electron deficiency of the quinoline resulted in poor regiocontrol and β-scission of the radical became competitive (example **9i** and 4-cyanoquinoline (see ESI)). This is perhaps expected based on the electron deficiency of the BCP core[2] and consequent philicity mismatch with particularly electron-poor heterocycles. Attempts to increase the electron richness of 4-cyanoquinoline, either by conversion to the *N*-oxide, or running the Minisci reaction in the absence of TFA (using phenyliodine diacetate instead of PIFA, or using PIFA in the presence of bases), provided only marginal improvement and were not explored further. We iterate that our optimisation studies had shown a temperature sensitivity of the intermediate BCP radical, and so raising the reaction temperature to promote arylation with difficult heterocycles is unlikely to be beneficial. 4-Methylanisole, an electron-rich benzenoid and competent coupling partner with aryl radicals,[22] was not trapped by the BCP radical under our reaction conditions. Disappointingly, pyridines (**8o**, **8q**, **8s**), benzoxazole (**8y**) and monocyclic diazines (**8p** and **8x**) proved to be challenging substrates in the developed process (though the amide groups in **8o** are documented as having poor compatibility with PIFA).[18a] **8n** appeared to be a uniquely privileged pyridine substrate: other pyridines with similar substitution patterns gave no detectable product by LCMS analysis (see ESI). In these and other low-yielding cases, various unidentified BCP decomposition products account for the mass balance alongside unreacted starting material **6**. Preliminary experiments to probe the poor performance of monocyclic substrates proved inconclusive (see ESI), but unexpectedly suggested electron donor-acceptor complex formation under the reaction conditions which contrasts with previous literature on PIFA-mediated transformations.[18b] Benzannulated diazines and naphthyridines gave mixed results. Although complex 1,5-naphthyridine **9t** and phthalazine **9v** were isolated in reasonable yields, quinazolines **8u** and **8w** proved more challenging and none of three quinoxalines tested (see ESI) gave any detectable product by LCMS analysis.

The scope of the BCP partner was next evaluated. Minisci adducts bearing aryl fluoride (**11a-b**), sulfone (**11c**), dialkyl phosphonate (**11d**) and α-difluoroester (**11e**) motifs were all obtained in synthetically useful yields (16-41%). Additionally, 2-oxabicyclo[2.1.1]hexanes **12a**[23] and **12b** were accessed in 28% and 12% yield, respectively. Attempts to prepare BCP substrate **13** through $RuCl_3/NaIO_4$-mediated oxidation of the corresponding primary alcohol provided a complex mixture of compounds (**Scheme 4**), consistent with the observations of Baran for related BCP bridgehead carbamates and sulfides. It appears that "push-pull" 1-amino/1-thio BCP derivatives bearing electron acceptor groups at the bridge position (generalised as **14**) are inherently unstable, presumably due to their ability to undergo ring-opening with associated release of ring strain.



Scheme 4. Proposed instability of general structure **14**.

Finally, the impact of the BCP core on the physicochemical properties of a representative Minisci adduct was evaluated. Compound **9a** was derivatised to amide **15** and the two regioisomers of its all-aromatic analogue (**16** and **17**) were prepared (**Figure 1**, panel). Incorporation of the BCP moiety provided increased solubility over **16** and **17** without detriment to metabolic stability or membrane permeability (see ESI). **15** was more lipophilic at physiological pH (highest ChromLogD at pH 7.4), however this was reversed at pH 2 suggesting that the quinoline nitrogen atom is more basic in **15** than in **16** and **17**.

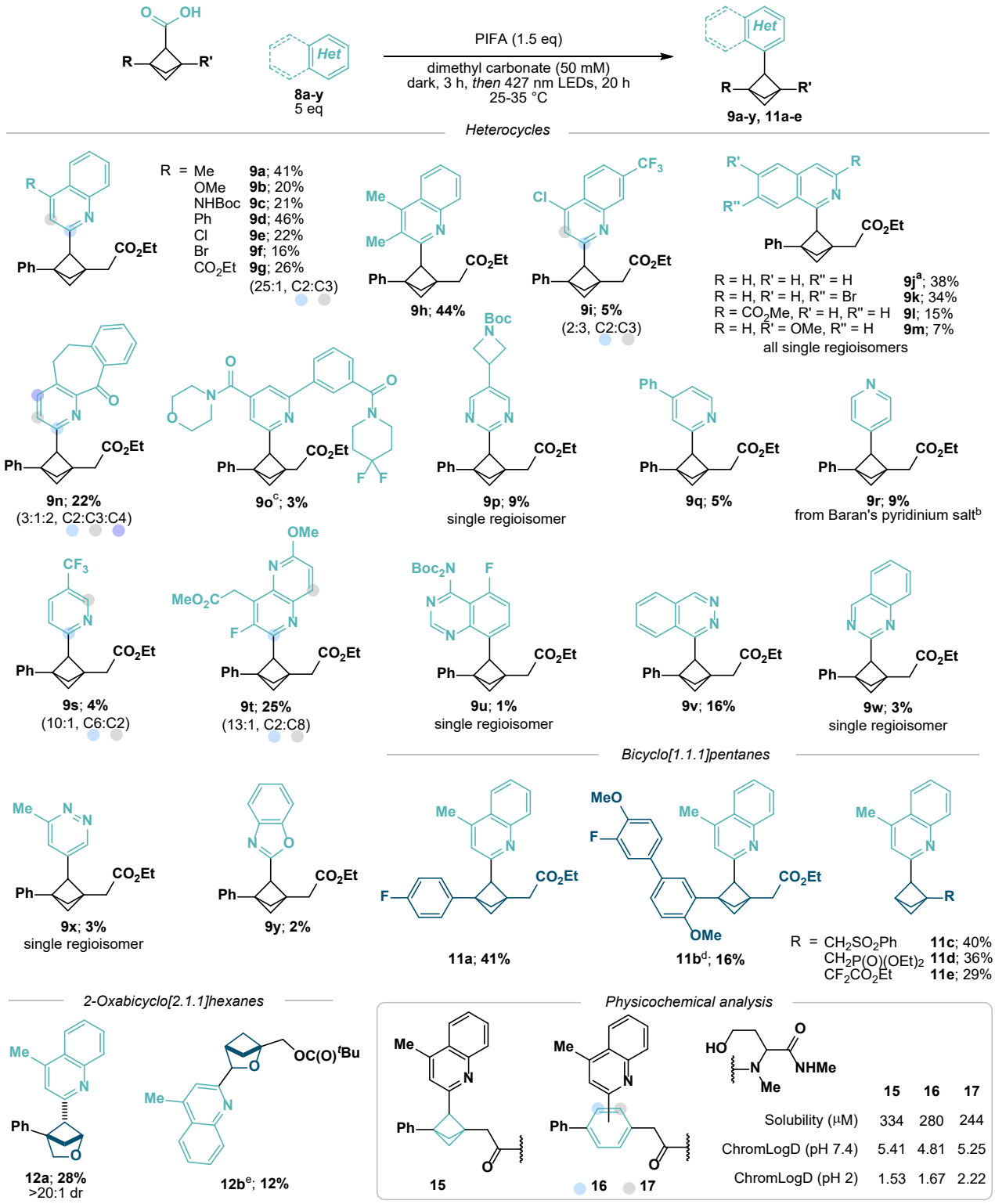


Figure 1. Reaction scope; isolated yields reported on approximately 0.175 mmol scale. [a] 7.5 eq heterocycle used. [b] 1,4-diethyl 2-(1-pyridin-1-ium-yl)butanedioate ethylsulfate used as heterocycle, followed by DBU-mediated elimination of the auxiliary (see ESI).[21b] Yield reported is that over two steps. [c] 0.112 mmol scale. [d] 0.103 mmol scale. [e] 0.06 mmol scale. CAD = charged aerosol detection.

In summary, we report the direct photochemical coupling of BCP bridge carboxylic acids with heteroarenes under hypervalent iodine activation. Although the yields are moderate, the methodology provides straightforward access to products that were inaccessible in our hands through established protocols. Experiments have shown that effective temperature control ($T \lesssim 40$ °C), and fast reaction kinetics, are critical for successful retention of the BCP scaffold in reactions of bridge-centered radicals.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Extended optimisation tables, experimental procedures, analytical data for synthesized compounds, and copies of NMR spectra for novel compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

Darren L. Poole – Medicinal Chemistry, GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, UK, SG1 2NY.

Email: darren.l.poole@gsk.com

Authors

Joseph M. Anderson – Medicinal Chemistry, GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, UK, SG1 2NY; and Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, UK, G1 1XL.

Nicholas D. Measom – Medicinal Chemistry, GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, UK, SG1 2NY.

John A. Murphy – Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, UK, G1 1XL.

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