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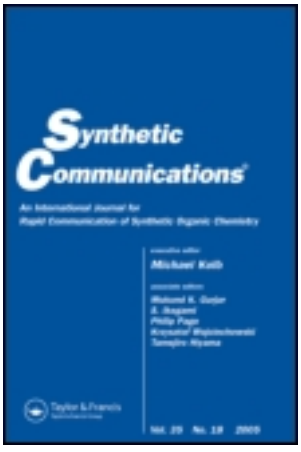

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A Highly Convergent Synthesis of 2-Phenyl Quinoline as Dual Antagonists for NK2 and NK3 Receptors

Hongxing Yan [a], Jeffrey K. Kerns [a], Qi Jin [a], Chongjie Zhu [a], Mary S. Barnette [b], James F. Callahan [a], Douglas W. P. Hay [b], Larry J. Jolivette [c], Mark A. Luttmann [b], Henry M. Sarau [b], Keith W. Ward [c], Katherine L. Widdowson [a] & Zehong Wan [a]

[a] Department of Medicinal Chemistry, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

[b] Department of COPD Biology, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

[c] Department of DMPK, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

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Hongxing Yan, Jeffrey K. Kerns, Qi Jin, and Chongjie Zhu
Department of Medicinal Chemistry, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

Mary S. Barnette
Department of COPD Biology, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

James F. Callahan
Department of Medicinal Chemistry, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

Douglas W. P. Hay
Department of COPD Biology, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

Larry J. Jolivette
Department of DMPK, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

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Address correspondence to Zehong Wan, Department of Medicinal Chemistry, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmith-Kline Pharmaceuticals, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406, USA. E-mail: zehong_2_wan@gsk.com

Mark A. Luttmann and Henry M. Sarau
Department of COPD Biology, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

Keith W. Ward
Department of DMPK, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

Katherine L. Widdowson and Zehong Wan
Department of Medicinal Chemistry, Respiratory & Inflammation Centre of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, King of Prussia, Pennsylvania, USA

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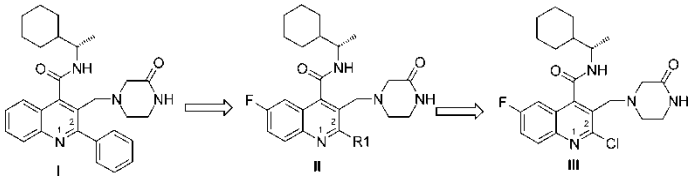
Abstract: A novel and highly convergent synthesis leading to 2-phenyl-quinolines has been developed. As demonstrated in the preparation of 6-fluoro-3-(3-oxo-piperazin-1-ylmethyl)-2-phenyl-quinoline-4-carboxylic acid [(S)-1-cyclohexyl-ethyl]-amide (**8**), the method provides fascile access to this class of analogues via the common intermediate **7**.

Keywords: Array approach, convergent systhesis, quinoline, COPD, NK2, NK3

The mammalian tachykinins (or neurokinins), including substance P (SP), neurokinin A (NKA), and neurokinin B (NKB), are a family of small peptides widely distributed in the central and peripheral neverous system.[1] They interact to different degrees with three G-protein-coupled receptors known as NK1, NK2, and NK3 and have been proposed to play key roles in a wide range of central nervous system (CNS) and peripheral disorders including asthma and chronic obstructive pulmonary disease (COPD).[2] Several research teams have published either selective[2] or nonselective[3] antagonists of the NK1, NK2, and NK3 receptors for the treatment of these conditions. The 2-phenyl-quinolines (**I**, Scheme 1) were disclosed previously as combined NK2/NK3 receptor antagonists;[4] however, very limited variations at C2 of the template were explored. To further expand the structure activity relationship (SAR) around this position, a large number of analogues with aryl or heteroaryl groups (e.g., **II**: R1 = aryl/heteroaryl) at C2 were sought. This posed a challenge when using the previous synthetic routes for this class of molecules because of the need to install the C2 substituents early in the syntheses and the lengthy synthetic steps leading to the target compounds.[4] Fascile access to these analogues might be achieved via a convergent approach (for reviews of convergent synthesis and array approach, see Ref.[5]) where various substituents are introduced at C2 of a



Scheme 1.

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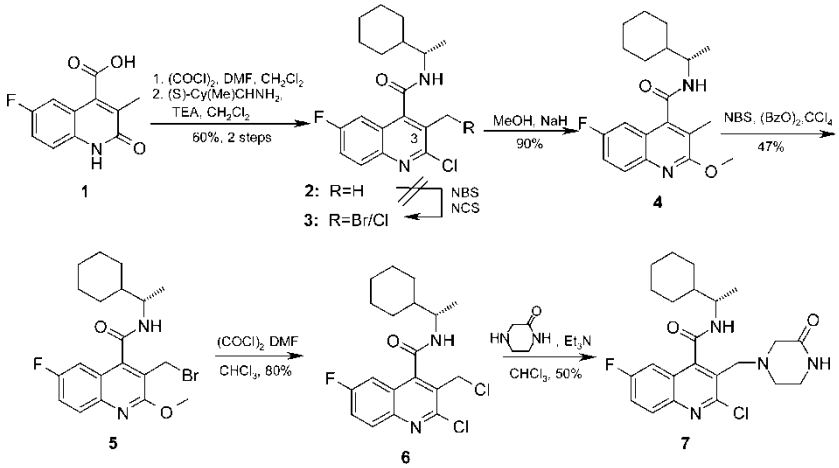
common intermediate (e.g., **III**) in the last step of a synthetic sequence. Our long-standing interest in developing convergent syntheses for SAR studies has prompted us to design a synthetic pathway meeting these requirements.[6a] This article reports a novel and highly convergent synthesis furnishing 2-phenyl-quinolines **II** (e.g., **II:** R1 = Ph).

Our approach started with the synthesis of the 2-chloro-quinoline **7** (Scheme 2), a key intermediate for generating various C2 analogues because of its potential reactivity in transition-metal-mediated cross-coupling reactions. The synthesis commenced with acid **1**, which was readily prepared from 5-fluoroisatin.[7] Treatment with oxalyl chloride completed two conversions: quinolinone to 2-chloro-quinoline and acid to acid chloride. The resultant acid chloride was reacted with (S)-1- cyclohexyl-ethyl-amine to afford the amide **2**. Our next goal was the installation of piperazin-2-one through the displacement of 3-bromomethyl (or chloromethyl)-quinoline (e.g., **3**), a compound we thought could be prepared via reaction with *N*-bromo-succinimide (NBS) (or *N*-chlorosuccinimide [NCS]). Much to our surprise, no reaction was observed under either radical or photochemically initiated



Scheme 2.

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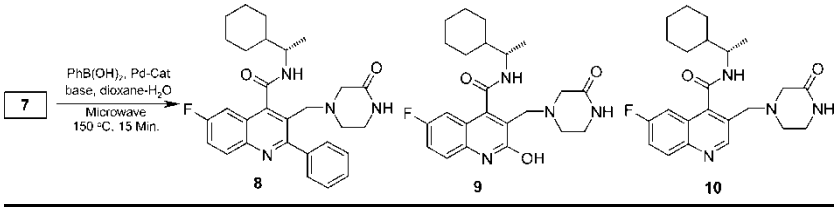
conditions and only the starting material was isolated from the reaction. The poor reactivity of this substrate may be related to the electron-withdrawing nature of the C2 chloride and could be improved by converting to an electron-donating group (e.g., –OMe) at the C2 position. For this purpose, reaction of the 2-chloro-quinoline **2** with methanol provided the 2-methoxy-quinoline **4**. Radical bromination of **4** with NBS furnished the 3-bromo-methyl-quinoline **5** in good yield. Subsequent treatment with oxalyl chloride then reinstalled the chlorine at C2 along with the conversion of the C3 bromo-methyl group to a C3 chloromethyl group, providing compound **6** presumably through halogen exchange. Selective displacement of the C3 chloride with piperazin-2-one then afforded the 2-chloro-quinoline **7**.

With the key intermediate **7** in hand, we were ready to investigate the introduction of C2 substituents. Phenylboronic acid was studied as a model system to discover general reaction conditions for the desired transformation. Microwave-assisted Suzuki cross-coupling reaction under $Pd(PPh_3)_4$ catalysis (Entry 1, Table 1), a condition suitable for a heterocyclic chloride,[6b] was employed at first and furnished the desired product **8** in modest yield (32%). A significant amount of the quinolinone **9** was produced, the likely result of hydrolysis of the C2-chloride. (Compounds **9** and **10** were not isolated. Their structure was consistent with molecular weight [LC-MS]). Cross-coupling reactions under anhydrous conditions did not afford any of the side product **9** (Reactions were carried out under the same conditions as **entry 1** except solvent [dioxane] and base [K_2CO_3, *t*-BuOK or *n*-BuLi]), however, diminished yields of the desired product **8** and recovered starting material **7** resulted even after prolonged heating. This

Table 1. Suzuki cross-coupling reactions of **7** with phenylboronic acid



Entry	Catalyst	Base	Component relative ratio[a] **8**	**9**	**10**	**7**	Yield of isolated 8
1	$Pd(PPh_3)_4$	K_2CO_3	1.00	1.05	—	—	32%
2	POPd1	K_2CO_3	1.00	0.25	0.25	1.25	15%
3	POPd2	K_2CO_3	1.00	0.15	0.15	0.20	26%
4	POPd	K_2CO_3	1.00	0.20	0.20	—	44%
5	POPd	*n*-BuLi	1.00	0.10	0.10	—	70%

[a]Based on HPLC measurements of the crude reaction mixture relative to **8** after heated with a microwave for 15 min at 150°C.

suggested the C2 chloride in **7** was not as reactive as that in the unsubstituted 2-chloro-quinoline, for which numerous cross-coupling reactions have been reported (For recent examples of Suzuki cross-coupling reactions with aryl boronic acids, see Ref.[8a–d], transition-metal-mediated cross-coupling reactions with aryl Grinard reagents, see Ref.[8e–h], Stille cross-coupling reactions with aryl Stille reagents, see Ref.[8i]). In light of recent reports[9] that catalysts such as POPd, POPd1, and POPd2 have demonstrated superior efficiency in the coupling reactions of deactivated aryl chlorides with aryl boronic acids, we were interested in evaluating these catalysts for our transformations (Entries 2–4, Table 1). (POPd, POPd1 and POPd2 were purchased from Combiphos Catalysts, Princeton, NJ. POPd = dihydrogen dichlorobis[di-*tert*-butyl phosphinito-κP]palladate[2-], POPd1 = dihydrogen di-μ-chlorotetraskis-[di-*tert*-butylphosphinito-κP]dipalladate[2-], POPd2 = dihydrogen di-μ-chlorodichlorobis[di-*tert*-butylphosphinito-κP]dipalladate [2-]). Experimental results showed that the desired product **8** had been formed with all three catalysts along with two side products: **9** from hydrolysis and **10** arising via reduction of the C2 chloride. The reaction mediated by POPd enjoyed the fastest rate and the best yield, which was further improved to 70% when the catalyst was pretreated with *n*-BuLi (Entry 5, Table 1) (Pd[0] was generated upon the treatment with a base, and we propose that it participates in the catalytic cycle [see Ref. 10]. Pd[0] might be produced in situ more rapidly and more efficiently when treated with *n*-BuLi, a method reported to prepare Ni[0] in situ from $NiCl_2 \cdot L$ ([L = dppf, $2PPh_3$][10]).

In summary, a novel and highly convergent synthesis of 2-phenyl-quinoline as combined antagonists for the NK2 and NK3 receptors was developed (e.g., **8**). Noteworthy is the efficiency of the combination POPd/*n*-BuLi for Suzuki cross-coupling reactions of a relatively unreactive heteroaryl chloride.

EXPERIMENTAL

Commercially available reagents were purchased and used as supplied, unless stated otherwise. Mass spectra were collected on an LCMS system using a Sciex API 150EX instrument [1 × 40 mm Aquasil (C18) column, gradient 4.5%–90% acetonitrile–water (0.02% TFA) over 3.2 min, detection by mass, UV at 214 nm, and evaporative light scattering]. ^{1}H NMR (hereinafter "NMR") spectra were recorded at 400 MHz using a Bruker AM 400 spectrometer or a Bruker Avance 400. Multiplicities indicated are s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet, and br indicates a broad signal. Flash chromatography was run on Merck silica gel 60 (230–400 mesh). Reverse phase preparative HPLC was run using (unless otherwise stated) a 50 × 20-mm internal diameter YMC CombiPrep ODS-A column at 20 mL/min with a 10-min gradient from 10% CH_3CN to 90% CH_3CN in H_2O and a 2-min hold at 90% CH_3CN in H_2O at the end of each

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run. Microwave reactions were conducted in a Smith Creator manufactured by Personal Chemistry.

2-Chloro-6-fluoro-3-methyl-quinoline-4-carboxylic acid [(S)-1-cyclohexyl-ethyl]-amide (2). Oxalyl chloride (2.36 mL, 27.1 mmol) was added slowly to a solution of 6-fluoro-2-oxo-1,2-dihydro-quinoline-4-carboxylic acid (2.0 g, 9.04 mmol) in CH_2Cl_2 (100 mL). The resultant mixture was stirred for 20 min before DMF (2.0 mL) was added. After stirring for 60 min, the reaction mixture was concentrated, CH_2Cl_2 (2 × 50 mL) was added, and the solvent was removed under reduced pressure to provide a brownish liquid residue. This was dissolved in THF (200 mL), and the solution was then mixed with Et_3N (2.54 mL, 18.1 mmol) and (S)-cyclohexyl-ethyl-amine (1.99 mL, 13.4 mmol). After stirring for 30 min, all solvents were removed under reduced pressure and the residue was mixed with H_2O (50 mL). The mixture was extracted with EtOAc (2 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (EtOAc–hexane, 1 : 1) then afforded 2.05 g of the title compound (65%). Mp 196–197°C; LC-MS (ES) m/z 349 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.18 (m, 6H), 1.32 (d, $J = 6.7$ Hz, 3H), 1.51 (m, 1H), 1.80 (m, 4H), 2.53 (s, 3H), 4.24 (m, 1H), 5.83 (s, br, 1H), 7.39 (m, 1H), 7.47 (m, 1H), 7.98 (m, 1H).

6-Fluoro-2-methoxy-3-methyl-quinoline-4-carboxylic acid [(S)-1-cyclohexyl-ethyl]-amide (4). A solution of **2** (0.82 g, 2.35 mmol) in MeOH (16 mL) was mixed with NaH (0.169 g, 60% dispersion in mineral oil, 4.22 mmol). The mixture was heated at 150°C with microwave irradiation for 30 min. After removing all solvents under reduced pressure, the residue was dissolved in EtOAc (40 mL) and washed with H_2O (2 × 20 mL), followed by brine (30 mL). The organic phases were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (EtOAc–hexane, 1 : 2) then afforded 0.73 g of the title compound (90%). Mp 143–144°C; LC-MS (ES) m/z 345 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.09 (m, 6H), 1.21 (d, $J = 6.7$ Hz, 3H), 1.41 (m, 1H), 1.76 (m, 4H), 2.20 (s, 3H), 4.06 (s, 3H), 4.10 (m, 1H), 6.18 (s, br, 1H), 7.20 (m, 1H), 7.28 (m, 1H), 7.74 (m, 1H).

6-Fluoro-2-methoxy-3-bromomethyl-quinoline-4-carboxylic acid [(S)-1-cyclohexyl-ethyl]-amide (5). A solution of **4** (0.72 g, 2.09 mmol) in CCl_4 (72 mL) was mixed with NBS (0.74 g, 4.18 mmol) and dibenzoyl peroxide (0.076 g, 0.31 mmol). The resultant mixture was heated at reflux for 3–5 h, filtered, and concentrated. The resulting residue was dissolved in CH_2Cl_2 (50 mL), and washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (EtOAc–hexane, 1 : 3) then afforded 0.42 g of the title compound (47%). Mp 157–158.5°C; LC-MS (ES) m/z 423 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.18 (m, 6H), 1.33 (d, $J = 6.7$ Hz, 3H), 1.51 (m, 1H), 1.86 (m, 4H), 4.17 (s, 3H), 4.32 (m, 1H), 4.64 (br, 2H), 6.12 (s, br, 1H), 7.42 (m, 2H), 7.84 (m, 1H).

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2-Chloro-6-fluoro-3-chloromethyl-quinoline-4-carboxylic acid [(S)-1-cyclohexyl-ethyl]-amide (6). A solution of **5** (1.0 g, 2.36 mmol) in $CHCl_3$ (50 mL) was mixed with oxalyl chloride (2.06 mL, 23.6 mmol) and DMF (1.0 mL). The mixture was stirred at 60°C for 1 h and upon cooling was washed with H_2O (20 mL) and brine (20 mL). The organic phases were collected, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (EtOAc–hexane, 1 : 2.5) then afforded 0.73 g of the title compound (80%). Mp 196–196.5°C; LC-MS (ES) m/z 383 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.11 (m, 6H), 1.27 (d, $J = 6.8$ Hz, 3H), 1.46 (m, 1H), 1.75 (m, 4H), 4.15 (m, 1H), 4.70 (br, 2H), 6.43 (s, br, 1H), 7.35 (m, 1H), 7.49 (m, 1H), 7.94 (m, 1H).

2-Chloro-6-fluoro-3-(3-oxo-piperazin-1-ylmethyl)-quinoline-4-carboxylic acid [(S)-1-cyclohexyl-ethyl]-amide (7). A solution of **6** (1.0 g, 2.61 mmol) in CH_2Cl_2 (100 mL) and MeCN (10 mL) was mixed with Et_3N (0.77 mL) and piperazin-2-one (0.29 g, 2.89 mmol). The resultant mixture was heated to reflux for 20 h. All solvents were then removed under reduced pressure and the resulting residue was dissolved in EtOAc (100 mL) and washed with H_2O (50 mL) and brine (50 mL). The organic phase was collected, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (EtOAc) then afforded 0.59 g of the title compound (50%). Mp 132–133.5°C; LC-MS (ES) m/z 447 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.10 (m, 6H), 1.29 (d, $J = 6.8$ Hz, 3H), 1.47 (m, 1H), 1.72 (m, 4H), 2.62 (s, 2H), 3.30 (s, 4H), 3.90 (m, 2H), 4.12 (m, 1H), 7.19 (s, br, 1H), 7.41 (s, br, 1H), 7.51 (m, 2H), 7.97 (m, 1H).

6-Fluoro-2-phenyl-3-(3-oxo-piperazin-1-ylmethyl)-quinoline-4-carboxylic acid [(S)-1-cyclohexyl-ethyl]-amide (8). A solution of POPd (1.2 mg, 0.0022 mmol) in dioxane (1.0 mL) was treated with *n*-BuLi (0.028 mL, 1.6 M in THF, 0.045 mmol) for 5 min. H_2O (0.33 mL), K_2CO_3 (0.025 g, 0.18 mmol), **7** (20 mg, 0.045 mmol), and phenyl boronic acid (0.011 g, 0.090 mmol) were then added to the reaction mixture. The resultant mixture was heated with microwave irradiation at 170°C for 30 min. All solvents were then removed under reduced pressure. Reverse phase preparative HPLC then afforded 0.016 g of the title compound (73%). Mp 230°C; LC-MS (ES) m/z 489 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 1.12 (m, 6H), 1.30 (d, $J = 6.7$ Hz, 3H), 1.49 (m, 1H), 1.75 (m, 4H), 2.45 (m, 2H), 2.95 (m, 2H), 3.15 (m, 2H), 3.82 (s, 2H), 4.25 (m, 1H), 5.79 (s, 1H), 6.88 (s, br,1H), 7.54 (m, 5H), 7.66 (m, 2H), 8.16 (m, 1H).

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REFERENCES

1. Regoli, D.; Boudon, A.; Fauchere, J.-L. *Pharmacol. Rev.* **1994**, *46*, 551.
2. (a) Giardina, G. A. M.; Raveglia, L. F.; Grugni, M. *Drugs Future* **1997**, *22*, 1235; (b) Gao, Z.; Peet, N. P. *Curr. Med. Chem.* **1999**, *6*, 375; (c) Seward, E. M.; Swain, C. J. *Expert Opin. Ther. Pat.* **1999**, *9*, 571; (d) Giardina, G. A. M.; Grugni, M.; Raveglia, L. F. *Expert Opin. Ther. Pat.* **2000**, *10*, 939; (e) Mackenzie, A. R.; Marchington, A. P.; Middleton, D. S.; Newman, S. D.; Selway, C. N.; Terrett, N. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2211.
3. (a) Gerspacher, M.; Vecchia, L. L.; Mah, R.; Sprecher, A.-V.; Anderson, G. P.; Subramanian, N.; Hauser, K.; Bammerlin, H.; Kimmel, S.; Pawelzik, V.; Ryffel, K.; Ball, H. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3081; (b) Bernstein, P. R.; Aharony, D.; Albert, J. S.; Andisik, D.; Barthlow, H. G.; Bialecki, R.; Davenport, T.; Dedinas, R. F.; Dembofsky, B. T.; Koether, G.; Kosmider, B. J.; Kirkland, K.; Ohnmacht, C. J.; Potts, W.; Rumsey, W. L.; Shen, L.; Shenvi, A.; Sherwood, S.; Stollman, D.; Russell, K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2769; (c) Ting, P. C.; Lee, J. F.; Shih, N.-Y.; Piwinski, J. J.; Anthes, J. C.; Chapman, R. W.; Rizzo, C. A.; Hey, J. A.; Ng, K.; Nomeir, A. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2125; (d) Gerspacher, M.; Lewis, C.; Ball, H. A.; Howes, C.; Subramanian, N.; Ryffel, K.; Fozard, J. R. *J. Med. Chem.* **2003**, *46*, 3508.
4. Blaney, F. E.; Raveglia, L. F.; Artico, M.; Cavagnera, S.; Dartois, C.; Farina, C.; Grugni, M.; Gagliardi, S.; Luttmann, M. A.; Martinelli, M.; Nadler, G. M. M. G.; Parini, C.; Petrillo, P.; Sarau, H. M.; Scheideler, M. A.; Hay, D. W. P.; Giardina, G. A. M. *J. Med. Chem.* **2001**, *44*, 1675.
5. (a) Coe, D. M.; Storer, R. *Ann. Rep. Combinatorial Chem. Molecular Diversity* **1999**, *2*, 1; (b) Flynn, D. L. *Med Res. Rev.* **1999**, *19*, 408.
6. (a) Wan, Z.; Boehm, J. C.; Bower, M. J.; Kassis, S.; Lee, J. C.; Zhao, B.; Adams, J. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1191; (b) Wan, Z.; Yan, H. Unpublished results.
7. Batt, D. G.; Petraitis, J. J.; Sherk, S. R.; Copeland, R. A.; Dowling, R. L.; Taylor, T. L.; Jones, E. A.; Magolda, R. L.; Jaffee, B. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1745.
8. (a) Nishimura, M.; Ueda, M.; Miyaura, N. *Tetrahedron* **2002**, *58*, 5779; (b) Carles, L.; Narkunan, K.; Penlou, S.; Rousset, L.; Bouchu, D.; Ciufolini, M. *J. Org. Chem.* **2002**, *67*, 4304; (c) Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8657; (d) Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8661; (e) Furstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856; (f) Bonnet, V.; Mongin, F.; Trécourt, F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, *6*, 1008; (g) Bonnet, V.; Mongin, F.; Trecourt, F.; Queguiner, G.; Knochel, P. *Tetrahedron* **2002**, *58*, 4429; (h) Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 3547; (i) Legros, J.-Y.; Primault, G.; Fiand, J.-C. *Tetrahedron* **2000**, *57*, 2507.
9. (a) Li, G. Y.; Zheng, G.; Noonan, A. *J. Org. Chem.* **2001**, *66*, 8677; (b) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643.
10. Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024.