Bioorganic & Medicinal Chemistry Letters 20 (2010) 4593–4597

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Aryl sulfonamides containing tetralin allylic amines as potent and selective bradykinin B1 receptor antagonists

Qingyian Liu [a,*], Wenyuan Qian [a], Aiwen Li [a], Kaustav Biswas [a], Jian Jeffrey Chen [a], Christopher Fotsch [a], Nianhe Han [a], Chester Yuan [a], Leyla Arik [c], Gloria Biddlecome [a], Eileen Johnson [c], Gondi Kumar [b], Dianna Lester-Zeiner [a], Gordon Y. Ng [d], Randall W. Hungate [a], Benny C. Askew [a]

[a] Chemistry Research and Discovery, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States
[b] Department of Pharmacokinetics and Drug Metabolism, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States
[c] Department of Neuroscience, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States
[d] Department of Inflammation, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320, United States

ARTICLE INFO

Article history:
Received 19 April 2010
Revised 28 May 2010
Accepted 2 June 2010
Available online 8 June 2010

Keywords:
Homobenzylic amines
Allylic amines
Bradykinin B1
Receptor antagonist
Pain

ABSTRACT

The bradykinin B1 receptor has been shown to mediate pain response and is rapidly induced upon injury. Blocking this receptor may provide a promising treatment for inflammation and pain. We previously reported tetralin benzyl amines as potent B1 antagonists. Here we describe the synthesis and SAR of B1 receptor antagonists with homobenzylic amines. The SAR of different linkers led to the discovery of tetralin allylic amines as potent and selective B1 receptor antagonists (hB1 IC_{50} = 1.3 nM for compound **16**). Some of these compounds showed modest oral bioavailability in rats.

Bradykinin B1 and B2 receptors are two distinctive G-protein coupled receptors that mediate pathophysiological pathways in pain and inflammation via similar signaling cascades.[1–5] The B1 and B2 receptors are different not only in the structures of their natural agonists, but also in their biological expressions and patterns of regulation. The B2 receptor is constitutively expressed in the central and peripheral nervous system, vascular and tissue endothelium, and on a number of inflammatory cells. The B1 receptor generally exists at very low levels in normal states, and it is rapidly induced following tissue injury.[3–5] The B2 receptor is quickly desensitized and internalized when activated by its ligands (bradykinin or kallidin). Preclinical studies suggest that the B2 receptor plays a role in

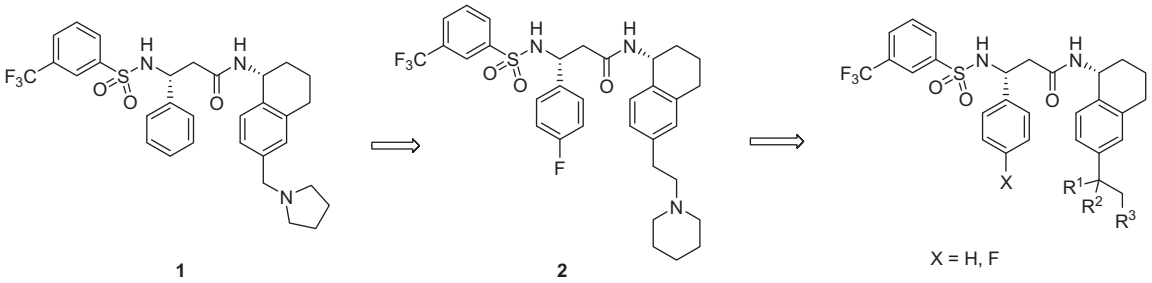
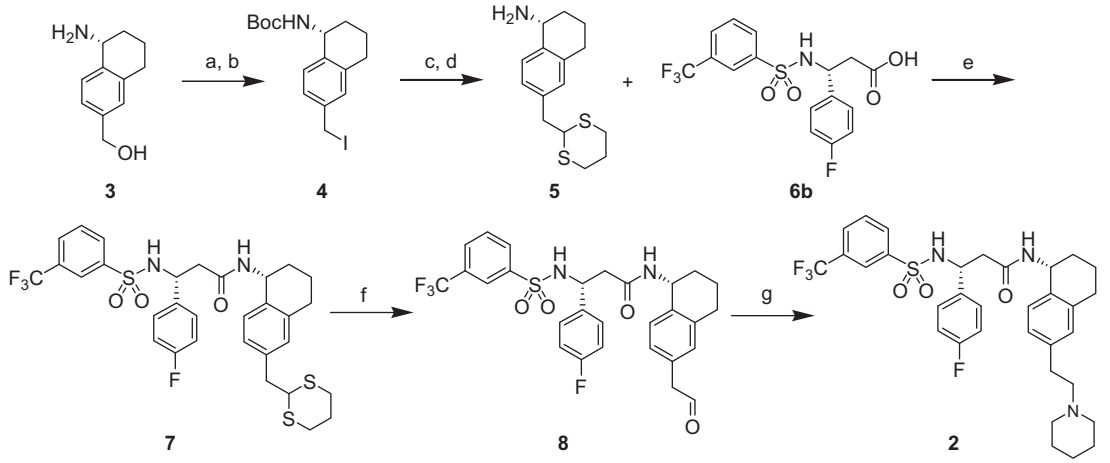


Figure 1. Progression of SAR.

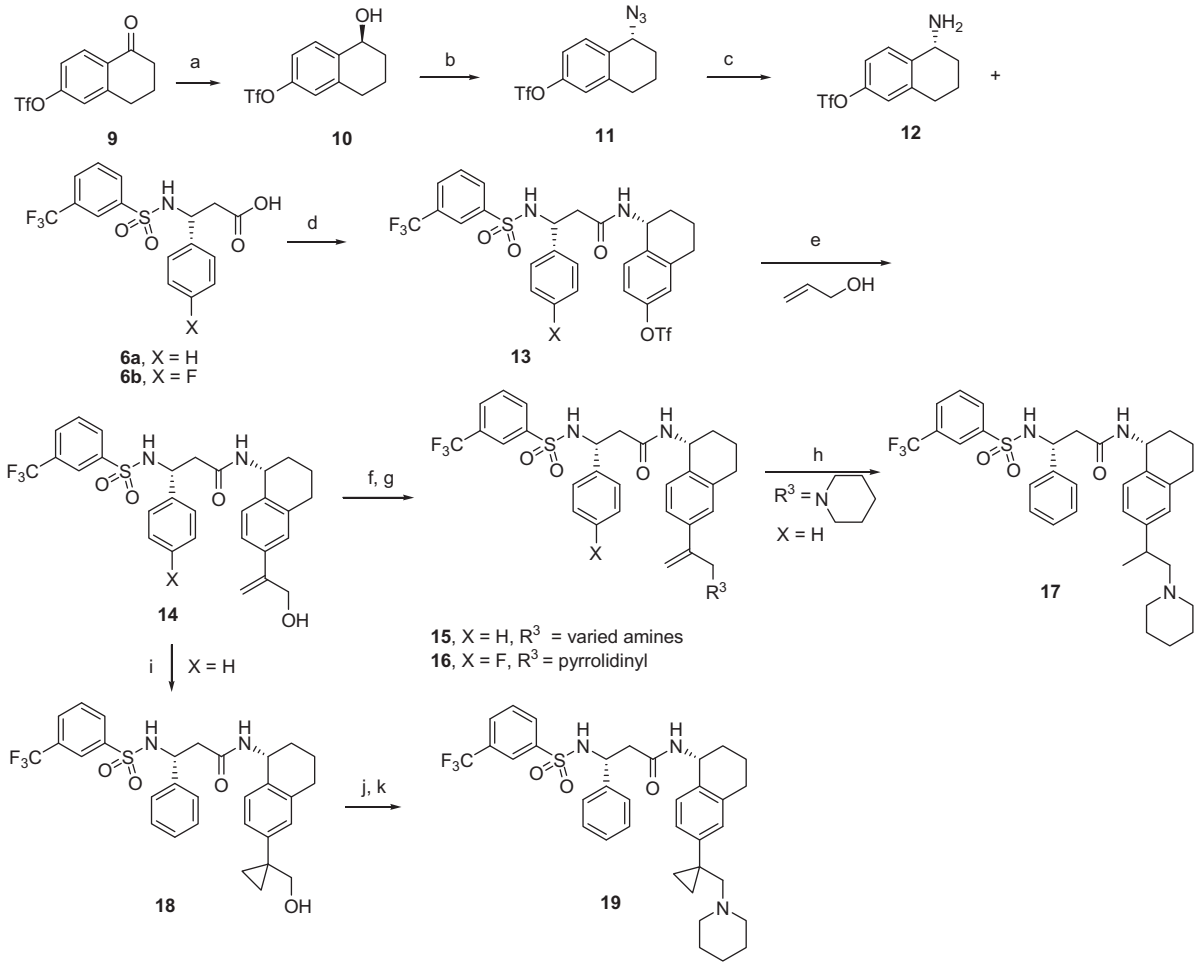
* Corresponding author. Tel.: +1 805 447 1713; fax: +1 805 480 3016.
E-mail address: qingyian@amgen.com (Q. Liu).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.06.010



Scheme 1. Reagents and conditions: (a) Boc_2O, DMF, rt, 12 h, 100%; (b) I_2, PPh_3, imidazole, ether/DCM, rt, 2 h, 91%; (c) 1,3-dithiane, BuLi, THF, −30 to 0 °C, 3 h, 60%; (d) HCl, MeOH, rt, 12 h, 100%; (e) EDCI, HOBT, DMF, rt, 12 h, 90%; (f) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O, rt, 1 h, 45%; (g) $NaBH(OAc)_3$, piperidine, DCE, rt, 12 h, 55%.

acute wpain processing. In contrast, the B1 receptor is believed to play a more active role in persistent pain and inflammation because this receptor is not desensitized after activation by its natural ligands (des-Arg(9)-BK or des-Arg(10)-kallidin).[1] In animal models, B1 receptor agonists cause hyperalgesia, an effect that can be reversed by peripherally restricted peptide B1 receptor antagonists. This result can be further supported by the fact that B1 receptor knockout mice have shown reduced sensitivity towards painful stimuli.[6,7] These experiments have demonstrated the therapeutic potential for novel B1 antagonists as new treatments for inflammation and pain.



Scheme 2. Reagents and conditions: (a) (*R*)-CBS, BMS, 93%; (b) DPPA, DBU, 85%; (c) PPh_3, THF/H_2O, 70%; (d) EDC, HOBt, 97%; (e) DPPF, $Pd(OAc)_2$, Et_3N, DMF, 62%; (f) MsCl, NEt_3, DCM; (g) Amines, DCM, 50–70% (over two steps); (h) H_2, 5%Pd/Al_2O_3, 44%; (i) Et_2Zn, $ClCH_2I$, DCE, 70%; (j) Dess–Martin oxidation, 68%; (k) piperidine, $NaBH(OAc)_3$, DCE, 48%.

Several classes of non-peptidic B1 antagonists have been reported.[8–14] A pharmacophore found in one of the major classes of B1 antagonists contains a lipophilic sulfonamide, a linker group, and a basic amine. We have previously identified aryl sulfonyl substituted β-phenylalanine tetralin and chroman system as novel B1 antagonists by adding conformational constraints.[15–17] It was demonstrated that an aryl sulfonamide and a benzylic amine group were essential for potency (e.g., compound **1**). To better understand the spatial requirement of the basic amine, the methylene linker was extended by one more carbon, which resulted in compound **2**, our lead of the homobenzylic amine series.

One strategy that has been used by medicinal chemists to increase potency is to decrease the flexibility of a compound. To fine-tune the conformation of the tetralin system, we began by introducing different substituents at the benzylic position of the tetralin using the parent β-phenylalanine trifluoromethylphenylsulfonamide **2** (Fig. 1). After the favored substituents at the benzylic position were identified, the SAR of different amine moieties was explored.

The compounds of interest were prepared by two different synthetic routes as shown in Schemes 1 and 2. The synthesis of elongated 1,6-disubstituted tetralin derivatives **2** started from tetralin aminoalcohol **3**[17] (Scheme 1). Selective Boc-protection of the amino group followed by iodination of the benzylic alcohol afforded **4**. Iodide displacement with the lithium salt of 1,3-dithiane and cleavage of the Boc group provided amine **5**. Coupling of **5** with acid **6b**[16] gave amide **7**. Treatment of **7** with $Hg(ClO_4)_2$ provided the aldehyde functionality in **8**. Reductive amination of **8** with piperidine provided homobenzylic amine **2**.

The synthesis of allylic amine derivatives **15** and **16** is outlined in Scheme 2. Corey–Bakshi–Shibata reduction of tetralone **9**[17] led to *S*-alcohol **10** in >99% ee. Compound **10** was then subjected to treatment with DPPA and DBU to provide *R*-azide **11**. Selective reduction using PPh_3 gave the corresponding tetralin amine **12**. This amine was then coupled with acid **6a** or **6b** to give amide **13** with a triflate group at the 6-position of the tetralin core. Palladium mediated cross-coupling with allylic alcohol gave compound **14**.[18,19] Final installation of the amino diversity at the allylic position in **15** and **16** was achieved in two steps: the allylic alcohol in **14** was converted to the mesylate, which was displaced with amines. Reduction of the double bond with 5% palladium on alumina gave compound **17** as a mixture of two diastereomers. The cyclopropylmethyl amine **19** was prepared from **14** through cyclopropylation of the double bond, oxidation of the alcohol and reductive amination with piperidine.

The compounds synthesized in Schemes 1 and 2 were tested in the human B1 receptor binding assay and human B1 agonist-induced cellular calcium flux functional assay. Both assays have been discussed previously.[15] Results are reported as the average of at least two independent experiments. The variance in the measurements is expressed as the standard error of the mean (SEM). The SAR studies disclosed below were based on the IC_{50} data from the cellular calcium flux functional assay. Similar trends were observed for the K_i values in the binding assay.

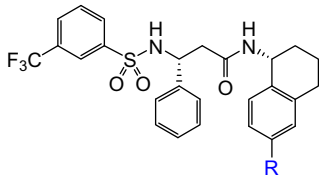
Compound **2** was an early example from our efforts of a homobenzylic amine that showed moderate potency (hB1 binding K_i = 15 nM, hB1 functional IC_{50} = 66 nM). Encouraged by this initial result, we focused on improving the potency of this series. We first investigated the effect of different linkers on the potency. All the compounds were derived from **6a**, which had an unsubstituted central aromatic ring. We intended to modulate the conformation of the tetralin substituents (R) by varying the size of the benzylic substitutions (see Table 1). Compound **17**, which is similar to compound **2** except the α-methyl and 4-F groups, had an IC_{50} = 316 nM. Replacing the benzylic methyl with a cyclopropyl group resulted in compound **19**, which was threefold more potent than **17**. Incorporating a double bond (compound **15a**) further boosted the potency to 41 nM.

Encouraged by the result from the tetralin allyl piperidine **15a**, we explored in detail the effect of different amine substitutions on the allyl linker (Table 2). Pyrrolidine compound **15b** with an IC_{50} = 10 nM, was threefold more potent than piperidine analog **15a** (previous SAR in the benzylamine series showed that piperidine provided the most potent compound[20]). Tertiary amine analogs with small substituents (**15e** and **15f**) were much less potent than pyrrolidine analogs (**15b**–**15d**). Interestingly, the stereochemistry of the 3-hydroxy group on the pyrrolidine ring had an impact on the potency as demonstrated by the 3–4-fold IC_{50} difference between **15c** and **15d**. For analogs with secondary amines (**15g**–**15m**), 2-methoxyethanamine **15h** was the most potent with IC_{50} = 23 nM. Cyclopropylmethylamine was the least potent amine (compound **15i**, IC_{50} = 105 nM). In the chroman benzyl amine series[16], the replacement of β-phenylalanine with 4-F-β-phenylalanine resulted in a significant increase in potency. Thus a similar analog **16** was prepared and indeed it was sevenfold more potent than the parent compound **15b**. Compared to the original lead **2**, a 40-fold improvement in functional potency was achieved with compound **16** (IC_{50} = 1.3 nM). In addition, all compounds were selective for the B1 receptor with IC_{50}s >20 μM against B2.

Finally, we examined the pharmacokinetics of selected compounds in rats (Table 3). Similar rat PK properties were observed for compounds with allylic amines (compounds **15b** and **15k**) and the benzylic amine (compound **1**). These compounds showed moderate in vivo and in vitro clearance and gave 10–15% oral bioavailability.

In summary, we have described our efforts toward expanding structural diversity of B1 antagonists with tetralin homobenzyl amines having different α-substitutions. The SAR of different linkers led to the discovery of allylic amines as potent B1 antagonists. The most potent compound in this series, compound **16**, showed a potency of 1.3 nM in the B1 functional assay, which represented a 40-fold improvement compared to the initial lead, compound **2**. Compounds **15b** and **15k** showed moderate rat in vivo clearance.

Table 1
SAR of different linkers



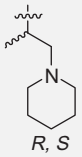
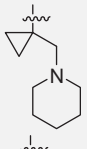
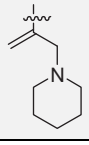
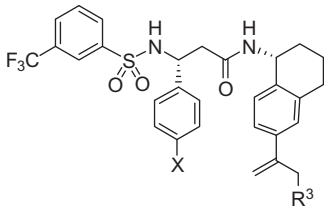
Compd	R	Binding K_i ± SEM (nM)	Functional IC_{50} ± SEM (nM)
17	 *R, S*	34 ± 10	316 ± 54
19		14 ± 1	88 ± 75
15a		3.3 ± 0.1	41 ± 12

Table 2
SAR of allylic amines



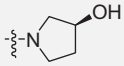
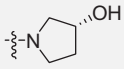
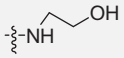
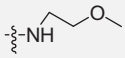
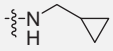
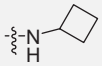
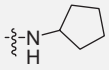
Compd	X	R^3	Binding $K_i \pm$ SEM (nM)	Functional $IC_{50} \pm$ SEM (nM)
15a	H		3.3 ± 0.1	41 ± 12
15b	H		0.7 ± 0.1	9.7 ± 2.9
15c	H		3.5 ± 0.9	3.9 ± 1.3
15d	H		12 ± 0.3	15 ± 0.1
15e	H		12 ± 2	206 ± 36
15f	H		78 ± 12	154 ± 39
15g	H		21 ± 6	32 ± 18
15h	H		42 ± 4	23 ± 7
15i	H		16 ± 2	105 ± 54
15j	H		11 ± 5	78 ± 4
15k	H		4.6 ± 0.5	42 ± 18
15l	H		3.4 ± 0.6	44 ± 22
15m	H		30 ± 15	47 ± 2
16	F		ND	1.3 ± 0.0

Table 3
Rat pharmacokinetics of selected compounds

Compd	$t_{1/2}$[a] (h)	Cl[a] (mL/h/kg)	V_{ss}[a] (mL/kg)	Oral %F[b]	RLM (μL/min/mg)
1	1.2	1890	2952	13%	388
15b	1.5	1834	3616	10%	282
15k	2.4	1992	5860	15%	240

[a] Dosed IV (1 mg kg^{-1}) in DMSO.
[b] Dosed PO (10 mg kg^{-1}) in 2% HPMC/1% Tween 80 in water.

The SAR results on the allylic amine portion could be applied to other scaffolds for further optimization.

References and notes

1. Marceau, F.; Regoli, D. *Nat. Rev. Drug Disc.* **2004**, *3*, 845.
2. Howl, J.; Payne, S. J. *Expert Opin. Ther. Targets* **2003**, *7*, 277.
3. Bock, M. G.; Longmore, J. *Curr. Opin. Chem. Biol.* **2000**, *4*, 401.
4. Bock, M. G.; Hess, J. F.; Pettibone, D. J. *Annu. Rep. Med. Chem.* **2003**, *38*, 111.
5. Dray, A.; Perkins, M. *Trends Neurosci.* **1993**, *16*, 99.
6. Ferreira, J.; Beirith, A.; Mori, M. A. S.; Araujo, R. C.; Bader, M.; Pesquero, J. B.; Calixto, J. B. *J. Neurosci.* **2005**, *25*, 2405.
7. Ferreira, J.; Campos, M. M.; Araujo, R.; Bader, M.; Bader, M.; Pesquero, J. B.; Calixto, J. B. *Neuropharmacology* **2002**, *43*, 1188.
8. Gougat, J.; Ferrari, B.; Sarran, L.; Planchenault, C.; Poncelet, M.; Maruani, J.; Alonso, R.; Cudennec, A.; Croci, T.; Guagnini, F.; Urban-Szabo, K.; Martinolle, J.-P.; Soubrie, P.; Finance, O.; Le Fur, G. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 661.
9. Kuduk, S. D.; DiMarco, C. N.; Chang, R. K.; Wood, M. R.; Schirripa, K. M.; Kim, J. J.; Wai, J. M. C.; DiPardo, R. M.; Murphy, K. L.; Ransom, R. W.; Harrell, C. M.; Reiss, D. R.; Holahan, M. A.; Cook, J.; Hess, J. F.; Sain, N.; Urban, M. O.; Tang, C.; Prueksaritanont, T.; Pettibone, D. J.; Bock, M. G. *J. Med. Chem.* **2007**, *50*, 272.
10. Kuduk, S. D.; Di Marco, C. N.; Chang, R. K.; Wood, M. R.; Kim, J. J.; Schirripa, K. M.; Murphy, K. L.; Ransom, R. W.; Tang, C.; Torrent, M.; Ha, S.; Prueksaritanont, T.; Pettibone, D. J.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2791.
11. Su, D.-S.; Markowitz, M. K.; Murphy, K. L.; Wan, B.-L.; Zrada, M. M.; Harrell, C. M.; O'Malley, S. S.; Hess, J. F.; Ransom, R. W.; Chang, R. S.; Wallace, M. A.; Raab, C. E.; Dean, D. C.; Pettibone, D. J.; Freidinger, R. M.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6045.
12. Wood, M. R.; Kim, J. J.; Han, W.; Dorsey, B. D.; Homnick, C. F.; Dipardo, R. M.; Kuduk, S. D.; MacNeil, T.; Murphy, K. L.; Lis, E. V.; Ransom, R. W.; Stump, G. L.; Lynch, J. J.; O'Malley, S. S.; Miller, J.; Chen, T.-B.; Harrel, C. M.; Chang, R. S. L.; Sandhu, P.; Ellis, J. D.; Bondiskey, J.; Pettibone, D. J.; Freidinger, R. M.; Bock, M. G. *J. Med. Chem.* **2003**, *46*, 1803.
13. Su, D.-S.; Marknwitz, M. K.; DiPardo, R. M.; Murphy, K. L.; Harrell, C. M.; O'Malley, S. S.; Ransom, R. W.; Chang, R. S. L.; Ha, S.; Hess, F. J.; Pettibone, D. J.; Mason, G. S.; Boyce, S.; Freidinger, R. M.; Bock, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 7516.

14. Kuduk, S. D.; Ng, C.; Feng, D.-M.; Wai, J. M.-C.; Chang, R. S. L.; Harrell, C. M.; Murphy, K. L.; Ransom, R. W.; Reiss, D.; Mason, G.; Boyce, S.; Tang, C.; Prueksaritanont, T.; Freidinger, R. M.; Pettibone, D. J.; Bock, M. G. *J. Med. Chem.* **2004**, *47*, 6439.
15. D'Amico, D. C.; Aya, T.; Human, J.; Fotsch, C.; Chen, J. J.; Biswas, K.; Riahi, B.; Norman, M. H.; Willoughby, C. A.; Hungate, R.; Reider, J.; Biddlecome, G.; Lester-Zeiner, D.; VanStaden, C.; Johnson, E.; Kamassah, A.; Arik, L.; Wang, J.; Viswanadhan, V. N.; Groneberg, R. D.; Zhan, J.; Suzuki, H.; Toro, A.; Mareska, D. A.; Clarke, D. E.; Harvey, D. M.; Burgess, L. E.; Laird, E. R.; Askew, B.; Ng, G. *J. Med. Chem.* **2007**, *50*, 607.
16. Biswas, K.; Li, A.; Chen, J. J.; D'Amico, D. C.; Fotsch, C.; Han, N.; Human, J.; Liu, Q.; Norman, M. H.; Riahi, B.; Yuan, C.; Suzuki, H.; Mareska, D. A.; Zhan, J.; Clarke, D. E.; Toro, A.; Groneberg, R. D.; Burgess, L. E.; Lester-Zeiner, D.; Biddlecome, G.; Manning, B. H.; Arik, L.; Dong, H.; Huang, M.; Kamassah, A.; Loeloff, R.; Sun, H.; Hsieh, F. Y.; Kumar, G.; Ng, G. Y.; Hungate, R. W.; Askew, B. C.; Johnson, E. *J. Med. Chem.* **2007**, *50*, 2200.
17. Fotsch, C.; Biddlecome, G.; Biswas, K.; Chen Jian, J.; D'Amico Derin, C.; Groneberg Robert, D.; Han Nianhe, B.; Hsieh, F.-Y.; Kamassah, A.; Kumar, G.; Lester-Zeiner, D.; Liu, Q.; Mareska David, A.; Riahi Babak, B.; Wang Yueh-Ju, J.; Yang, K.; Zhan, J.; Zhu, J.; Johnson, E.; Ng, G.; Askew Benny, C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2071.
18. Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7235.
19. Park, N.; Jung, Y.; Park, C.; Seong, C.; Lim, H. *Bull. Korean Chem. Soc.* **2001**, *22*, 139.
20. Chen, J.; Qian, W.; Biswas, K.; Viswanadhan, V.; Askew, B. C.; Hitchcock, S.; Hungate, R. W.; Arik, L.; Johnson, E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4477.