Divergent Solution-Phase Synthesis of Diarylpyrimidine Libraries as Selective A_3 Adenosine Receptor Antagonists

Vicente Yaziji,[†] Alberto Coelho,[†] Abdelaziz El Maatougui,[†] José Brea,[‡,§] M. Isabel Loza,[‡] Xerardo Garcia-Mera,[||] and Eddy Sotelo*[,†,||]

Combinatorial Chemistry Unit (COMBIOMED) and Screening Unit (USEF), Institute of Industrial Pharmacy (IFI), and, Departments of Pharmacology and Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, Santiago de Compostela 15782, Spain

Received March 18, 2009

The implementation of flexible and conceptually simple, as well as time- and cost-effective, synthetic methodologies that bring about rapid access to diverse compound libraries is one of the main goals in combinatorial chemistry.[1] This objective is critical in drug discovery because the availability of large libraries of small organic molecules, covering as much chemical space as possible, is seen as the only means to guarantee potential modulation of the many biological targets that are ultimately being unveiled by genomics.[2] The enormous variety of naturally occurring heterocycles and their wide range of biological activities, as well as the results of massive high-throughput screening campaigns, have validated the tremendous importance of drug-like low molecular weight heterocyclic libraries as highly versatile templates in drug discovery.[3] The search for novel potent and selective ligands for the adenosine receptors (ARs)[4] constitutes an excellent example to illustrate this situation, with the availability of highly diverse heterocyclic screening libraries being particularly important in the development of adenosine receptor antagonists, an emerging class of therapeutics that promise conceptually new strategies to address significant unmet medical needs.[4] From a structural point of view, the best known classes of adenosine receptor antagonists encompass highly diverse families of bi-, tri-, tetra-, and to a lesser extent, monocyclic nitrogen-containing aromatic scaffolds (Figure 1).[4] The structural manipulation of these derivatives has permitted the identification of potent and selective antagonists but the search for structurally simpler ligands with improved pharmacokinetic profiles remains a challenge. Several recent examples[5] have addressed the feasibility of the task for most of the adenosine receptor subtypes, in particular a recent paper by Ijzerman[6] concerned a pharmacophore model that enabled the identification of diphenylpyrimidines (Figure 2) as potent and selective A_1 adenosine antagonists.

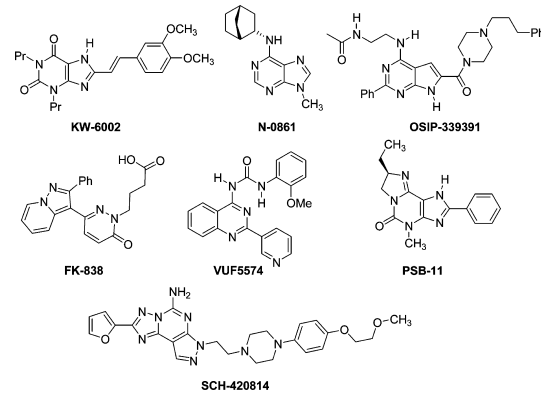
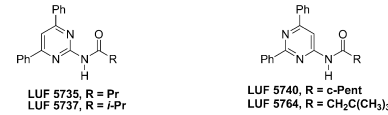


Figure 1. Structures of representative adenosine antagonists.[4]



Code	hA_1[¥]	hA_{2A}[¥]	hA_{2B}[¥]	hA_3[¥]	Code	hA_1[¥]	hA_{2A}[¥]	hA_{2B}[¥]	hA_3[¥]
LUF5735	3.70	7%	54%	38%	**LUF5740**	2.14	196.00	52%	170.00
LUF5737	8.87	44%	79%	45%	**LUF5764**	8.75	32%	4%	39%

[¥] Adenosine binding data is expressed as K_i (nM) or as % of displacement at 1 μM.

Figure 2. Structures and biological data of representative diphenylpyrimidines as selective A_1 adenosine antagonists.[6]

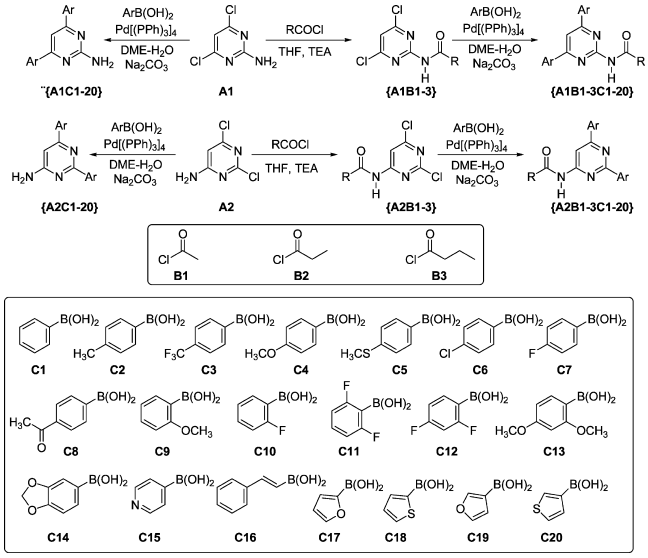
In the context of our ongoing efforts aimed at the development of new adenosine antagonists,[7] we hypothesized that a thorough structural exploration of the pharmacophore model that enabled the discovery of the LUF series (Figure 2), by the introduction of diverse aryl or heteroaryl groups on the central pyrimidine template, should modify the receptorial selectivity profile of these families to afford novel derivatives eliciting affinity by the A_3 receptor subtype. Herein, we document the development of a short, divergent, and practical solution-phase approach to access the target structures based on a Suzuki cross-coupling reaction. The proposed strategy (scheme 1), which exploits the potential for diversity offered by the wide collection of commercially available boronic acids, enabled the rapid synthesis of a large library of compounds and also led to the identification of highly potent and selective A_3 receptor antagonists (Figure 3) with diverse potential therapeutic applications (e.g., treatment of stroke, glaucoma, allergies or anticancer agents).[8]

The Suzuki−Miyaura reaction[9] is currently considered as the reference experimental protocol for introduction of aryl or heteroaryl groups in organic synthesis. As far as other palladium-catalyzed cross-coupling reactions (PCCCR) are concerned,[9] the viability of the transformation is highly dependent on the starting organohalide (or triflate), with the low reactivity of chloroarenes well documented in comparison to their iodo- and bromo-analogues. Such a reactivity profile, which is a consequence of the low reactivity of chloroarenes toward oxidative addition, usually requires either the use of Pd(0)-complexes of superior nucleophilicity or a decrease in the electron density of the π-system in the starting arene.[9] The unique characteristics stemming from the inherently different structural and electronic properties

* To whom correspondence should be addressed. Phone: ++34-981-563100. Fax: ++34-981-528093. E-mail: eddy.sotelo@usc.es.
[†] Combinatorial Chemistry Unit (COMBIOMED).
[‡] Screening Unit (USEF).
[§] Department of Pharmacology.
[||] Department of Organic Chemistry.

10.1021/cc900044k CCC: $40.75
Published on Web 05/27/2009

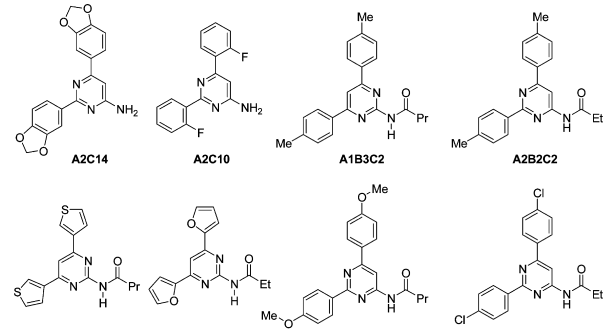
Scheme 1. Synthesis of 2,4- or 4,6-Diarylpyrimidines



of heterocycles support the generally superior reactivity profile observed for chloro-substituents attached to heteroaromatic systems in PCCCR in comparison to the corresponding carbocyclic aryl compounds. Although a comparatively broad experimental scope has been documented for different heterocyclic systems[10] the potential for such systems in library synthesis remains relatively unexplored. Indeed there is a great deal of practical interest in chloro-substituted heteroaryl systems, and this is due to several factors. For example, heteroaryl chlorides are generally less costly, have greater commercial availability, and are more easily prepared than the corresponding bromides and iodides.

A representative example of this trend is the prominent heterocycle pyrimidine, for which the Suzuki arylation of iodo- and bromo-pyrimidines has been widely reported,[11] but the use of chloro-,[12] and especially dichloro-,[13] pyrimidine derivatives as reactive substrates in this transformation remains scarcely studied. A recent report by Slee[14] concerned a lead optimization program that enabled the synthesis of selective A_{2A} adenosine antagonists and this supports the strategy documented here.

The synthetic pathway developed to access the regioisomeric target libraries is presented in Scheme 1. The strategy was designed to fulfill our interest in preparing a large and unexplored collection of pyrimidine derivatives by simultaneous decoration of positions 2 and 4 or 4 and 6 of the central heterocyclic core (**A**) with a diverse range aryl or heteroaryl groups (**C**), thus enabling an in-depth examination of the structure−activity relationships in this series. The feasibility of this strategy relied on the appropriate selection of the 2- or 4-amino dichloropyrimidines (**A**) as precursors (Scheme 1). A preliminary derivatization of these scaffolds was performed by treatment with different acid chlorides (**B1**−**3**, R = Me, Et, Pr),[15] which, in addition to generating the amide group, allowed the incorporation of diverse alkyl fragments. Both of these factors are decisive for the interaction with the receptor. A set of 8 reactive dichloropyrimidines (**A1**−**2** or **A1**−**2B1**−**3**) that incorporate both skeletal and functional diversity was prepared in this way (Scheme 1). The next step involved structural elaboration of the heterocyclic scaffold (Scheme 1). For this purpose we made use of the highly reliable and well-established Suzuki−Miyaura cross-coupling reaction. A collection of 20 commercially available boronic acids (**C1**−**20**), covering the aryl and heteroaryl series (Scheme 1), was employed to introduce structural diversity with the aim of preparing a large library.



Cmpd	hA_1[¥]	hA_{2A}[¥]	hA_{2B}[¥]	hA_3[¥]	Cmpd	hA_1[¥]	hA_{2A}[¥]	hA_{2B}[¥]	hA_3[¥]
A2C14	184.00	34%	1%	7%	**A1B3C2**	36%	2%	10%	131.60
A2C10	7.99	10%	32	299.70	**A1B2C2**	36.90	1%	2%	18.31
A1B3C20	85.70	4568.12	13%	2%	**A2B2C6**	22%	25%	3%	25.30
A1B2C17	1%	1%	2%	142.50	**A2B3C4**	1%	4%	1%	11.00

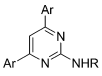
[¥] Adenosine binding data is expressed as K_i (nM) or as % of displacement at 0.1 μM.

Figure 3. Structures and biological data for representative diarylpyrimidines.

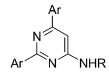
The palladium-catalyzed [$Pd(PPh_3)_4$] phenylations of a set of representative precursors (**A1**,**A2**, **A1B2**, and **A2B2**) by reaction with a slight excess (2.5 equivalents) of phenylboronic acid and sodium carbonate as base in either toluene/ethanol (5:1) or DME/H_2O (3:1) were selected as pilot experiments. This preliminary research not only demonstrated the superiority of DME/H_2O as the solvent for the transformation but also served as a model system in the development of a general optimized protocol to enable library production (Scheme 1). All tested substrates showed a high reactivity toward Suzuki arylation regardless of the highly diverse nature of the selected collection of boronic acids. Complete consumption of the starting materials usually required 4−8 h at 110 °C to afford the desired 2,4- or 4,6-diarylpyrimidines in satisfactory yields (Table 1).[16] The feasibility and broad scope of the sequence is particularly noteworthy as this approach shows significant advantages over more conventional strategies.

The synthesis, isolation, and purification of compounds were accomplished using equipment routinely available in laboratories for parallel synthesis. A PLS (6 × 4) Organic Synthesizer was used for compound preparation; isolation of precipitated/triturated products was performed in a 12-channel vacuum manifold from Aldrich, fitted with Aldrich Bond Elut reservoirs. Solvent removal was achieved using standard techniques or an evaporation module from Advanced Chemtech. When necessary, the excess of boronic acid remaining after Suzuki coupling was scavenged by incubation with PS-DIEA at 35 °C during 60 min. Compounds were purified by preparative chromatography or recrystallization and then characterized by spectroscopic and analytical data.[16]

Table 1. Structures and Isolated Yields of Representative 2,4- or 4,6-Diarylpyrimidines Obtained[16]



{A1C1-20}
{A1B1-3C1-20}



{A2C1-20}
{A2B1-3C1-20}

cmpd	R	Ar	yield	cmpd	R	Ar	yield
A1C1	H	Ph	78	**A2C1**	H	Ph	72
A1C4	H	4-OMe-Ph	73	**A2C4**	H	4-OMe-Ph	83
A1C10	H	2-F-Ph	81	**A2C10**	H	2-F-Ph	79
A1C16	H	−CH=CH-Ph	79	**A2C16**	H	−CH=CH-Ph	77
A1C17	H	2-furan	64	**A2C17**	H	2-furan	67
A1B1C1	CO-Me	Ph	79	**A2B1C1**	CO-Me	Ph	76
A1B1C4	CO-Me	4-OMe-Ph	64	**A2B1C4**	CO-Me	4-OMe-Ph	72
A1B1C10	CO-Me	2-F-Ph	59	**A2B1C10**	CO-Me	2-F-Ph	82
A1B1C16	CO-Me	−CH=CH-Ph	80	**A2B1C16**	CO-Me	−CH=CH-Ph	77
A1B1C17	CO-Me	2-furan	61	**A2B1C17**	CO-Me	2-furan	72
A1B2C1	CO-Et	Ph	87	**A2B2C1**	CO-Et	Ph	83
A1B2C4	CO-Et	4-OMe-Ph	83	**A2B2C4**	CO-Et	4-OMe-Ph	78
A1B2C10	CO-Et	2-F-Ph	74	**A2B2C10**	CO-Et	2-F-Ph	94
A1B2C16	CO-Et	−CH=CH-Ph	81	**A2B2C16**	CO-Et	−CH=CH-Ph	63
A1B2C17	CO-Et	2-furan	74	**A2B2C17**	CO-Et	2-furan	78
A1B3C1	CO-Pr	Ph	75	**A2B3C1**	CO-Pr	Ph	82
A1B3C4	CO-Pr	4-OMe-Ph	76	**A2B3C4**	CO-Pr	4-OMe-Ph	90
A1B3C10	CO-Pr	2-F-Ph	78	**A2B3C10**	CO-Pr	2-F-Ph	87
A1B3C16	CO-Pr	−CH=CH-Ph	65	**A2B3C16**	CO-Pr	−CH=CH-Ph	80
A1B3C17	CO-Pr	2-furan	74	**A2B3C17**	CO-Pr	2-furan	78

A preliminary account of the biological data obtained for representative compounds tested in radioligand binding assays[17] is outlined in Figure 3. These assays were aimed at determining the affinities of the compounds at the human adenosine receptor subtypes (namely A_1, A_{2A}, A_{2B}, and A_3). As exemplified for the evaluated compounds (Figure 3), modification of the aryl moieties in both series' had a significant effect on the activity. The most noteworthy result is the identification of new derivatives that elicit a highly potent A_3 antagonistic activity (e.g., **A2B2C17**, **A2B2C6**, and **A2B3C4**), which is complemented by complete selectivity for the other subtypes (figure 3). Further studies to complete the pharmacological characterization of the library at the four adenosine receptor subtypes and also an SAR study are currently in progress in our laboratories and will be published elsewhere.

In summary, a simple, divergent and efficient procedure that allows the rapid assembly of a large library of diarylpyrimidines from simple starting materials has been developed. These results contribute to the validation of the potential of the Suzuki reaction in the elaboration of privileged scaffolds, addressing the requirement of highly diverse libraries in a cost- and time-effective manner. Furthermore, these studies enabled the discovery of a structurally simple, highly potent and selective series of A_3 adenosine receptor antagonists that constitutes powerful pharmacological tools for the elucidation of pathophysiological roles of adenosine A_3 receptors.

Acknowledgment. This work was financially supported by the Fondo Europeo de Desarrollo Social (FEDER) and the Galician Government. E.S. is the recipient of a Consolidation Group Research Grant from the Conselleria de Educación (Xunta de Galicia). E.S. and A.C. are researchers of the Isidro Parga Pondal program (Xunta de Galicia, Spain). J.B. is researcher of the Isabel Barreto program (Xunta de Galicia, Spain).

Supporting Information Available. Detailed experimental procedures, spectroscopic data and copies of NMR and mass spectra for representative compounds described. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) *Handbook of Combinatorial Chemistry*; Nicolau, K. C., Hanko, R., Hartwing, W., Eds.; Wiley-VCH: Weinheim, Germany, 2002. (a) *Combinatorial Chemistry: A Practical Approach*; Bannwarth, E., Felder, E., Eds.; Wiley-VCH: Weinheim, Germany, 2000. (b) *Combinatorial Chemistry: Synthesis, Analysis, Screening*; Jung, G., Eds.; Wiley-VCH: Weinheim, Germany, 1999. (c) *The Combinatorial Index*; Bunin, B. A., Eds.; Academic Press: San Diego, CA, 1998.

(2) Bartlett, P. A., Entzeroth, M. *Exploiting Chemical Diversity for Drug Discovery*; RSC Publishing: Cambridge, U.K., 2006. (a) Verheij, H.; Robeson, B. L. *Genomic/Proteomic Technol.* **2002**, *2*, 34–35. (b) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Curr. Opin. Drug Discovery Development* **2006**, *9*, 700–712. (c) Gordon, E. M., Kerwin, J. F., *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Wiley-VCH: Weinheim, Germany, 1998.

(3) For representative examples, see: (a) Geysen, H. M.; Schoenen, F.; Wagner, D.; Wagner, R. *Nature Reviews Drug Discovery* **2003**, *2*, 222–230. (b) *Pharmaceutical Substances: Synthesis, Patents, Applications*; Kleemann, A., Engel, J., Eds.; Thieme: Stuttgart, Germany, 2001. (c) Sperry, J. B.; Wright, D. L. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723–740. (d) Gil, C.; Bräse, S. *J. Comb. Chem.* **2008**, *14*, 175–197. (e) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2008**, *10*, 753–802. (f) Dolle, R. E.; Le Bourdonnec, B.; Goodman, A. J.; Morales, G. A.; Salvino, J. M.; Zhang, W. *J. Comb. Chem.* **2007**, *9*, 855–902.

(4) For representative examples, see: (a) Baraldi, P. G.; Aghadeh, M.; Tabrizi, M. A.; Gessi, S.; Borea, P. A. *Chem. Rev.* **2008**, *108*, 238–263. (b) Jacobson, K. A.; Goao, Z. *Nat. Rev. Drug Discovery* **2006**, *5*, 247–264. (b) Moro, S.; Gao, Z. G.; Jacobson, K. A.; Spallouto, G. *Med. Res. Rev.* **2006**, *26*, 131–159.

(5) For representative examples, see: (a) Chang, L. C.; von Frijtag, J. K.; Mulder-Krieger, T.; Spanjersberg, R. F.; Roerink, S. F.; van den Hout, G.; Beukers, M. W.; Brusse, J.; Ijzerman, A. P. *J. Med. Chem.* **2005**, *48*, 2045–2053. (b) Slee, D. H.; Chen, Y.; Zhang, X.; Moorjani, M.; Lanier, M. C.; Lin, E.; Kueter, J. K.; Williams, J. P.; Lechner, S. M., Markinson, S.; Malady, S.; Santos, M.; Gross, R. S.; Jalali, K.; Sai, Y.; Zuo, Z.; Yang, C.; Castro-Palomino, J.; Crespo, M. I.; Prat, M.; Gual, S.; Díaz, J. L.; Saunders, J. *J. Med. Chem.* **2008**, *51*, 1719–1729. (c) Miwatashi, S.; Arikawa, Y.; Matsumoto, T.; Uga, K.; Kanzaki, N.; Imi, Y. N.; Ohkawa, S. *Chem. Pharm. Bull.* **2008**, *56*, 1126–1137. (d) Li, A. H.; Moro, S.; Melman, N.; Ji, X. D.; Jacobson, K. A. *J. Med. Chem.* **1998**, *41*, 3186–3201. (e) van Muijlwijk-Koezen, J. E.; Timmerman, H.; Vollinga, R. C.; von Drabbe, J. F.; de Groote, M.; Visser, S.; Ijzerman, A. P. *J. Med. Chem.* **2001**, *44*, 749–762.

(6) Chang, L. C. W.; Spanjersberg, R. F.; von Frijtag, J. K.; Mulder-Krieger, T.; van den Hout, G.; Beukers, M. W.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2004**, *47*, 6529–6540.

(7) (a) Martínez, A.; Gutiérrez de Terán, H.; Brea, J. M.; Raviña, E.; Loza, M. I.; Cadavid, M. I.; Sanz, F.; Vidal, B.; Segarra, V.; Sotelo, E. *Bioorg. Med. Chem.* **2008**, *16*, 2103–2113. (b) Stefanachi, A.; Brea, J. M.; Cadavid, M. I.; Centeno, N. B.; Esteve, C.; Loza, M. I.; Martínez, A.; Nieto, R.; Raviña, E.; Sanz, F.; Segarra, V.; Sotelo, E.; Vidal, B.; Carotti, A. *Bioorg. Med. Chem.* **2008**, *16*, 2852–2869. (c) Carotti, A.; Cadavid, M. I.; Centeno, N. B.; Esteve, C.;

Loza, M. I.; Martínez, A.; Nieto, R.; Raviña, E.; Sanz, F.; Segarra, V.; Sotelo, E.; Stefanachi, A.; Vidal, B. *J. Med. Chem.* **2006**, *49*, 282–299.

(8) (a) Baraldi, P. G.; Tabrizi, M. A.; Fruttarolo, F.; Borevo, A.; Avitabile, B.; Preti, D.; Romagnoli, R.; Merighi, S.; Gessi, S.; Varani, K.; Borea, P. A. *Drug Dev. Res.* **2003**, *58*, 315–329. (b) Baraldi, P. G.; Fruttarolo, F.; Tabrizi, M. A.; Romagnoli, R.; Preti, D.; Carrion, M.; Iaconinoto, A.; Borea, P. A. *Expert Opin. Ther. Pat.* **2005**, *15*, 1507–1519. (c) Baraldi, P. G.; Tabrizi, M. A.; Bovero, A.; Avitabile, B.; Preti, D.; Fruttarolo, F.; Romagnoli, R.; Varani, K.; Borea, P. A. *Eur. J. Med. Chem.* **2003**, *38*, 367–382.

(9) (a) Miyara, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519. (b) Suzuki, A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles. In *Perspectives in Organopalladium Chemistry For the XXI Century*; Tsuji, J., Ed.; Elsevier: Amsterdam. (c) *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Tsuji, J. Ed.; John Wiley and Sons: Chichester, U.K, 1995. (d) Malleron, J. L., Fiaud, J. C., Legros, J. Y. *Handbook of Palladium-Catalysed Organic Reactions*; Academic Press: San Diego, CA, 1997. (e) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 2004. (f) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley-Interscience; New York, 2002.

(10) For representative examples, see: (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Elsevier: Amsterdam, 2007. (b) Turck, A.; Plé, N.; Mojovic, L.; Quéguiner, G. *Bull. Soc. Chim. Fr.* **1993**, *130*, 488–492. (c) Sturmer, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3307–3308. (d) Maes, B. U.; R'kyek, O.; Kosmrlj, J.; Lemiere, G. L. F.; Esmans, E.; Rozenski, J.; Dommisse, R. A.; Haemers, A. *Tetrahedron* **2001**, *57*, 1323–1330. (d) Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8661–8667. (e) Buron, F.; Plé, N.; Turck, A.; Quéguiner, G. *J. Org. Chem.* **2005**, *70*, 2616–2621. (f) Itoh, T.; Mase, T. *Tetrahedron Lett.* **2005**, *46*, 3573–3577.

(11) For representative examples, see: (a) Wheelhouse, R. T.; Jennings, S. A.; Philips, V. A.; Pletsas, D.; Murphy, P. M.; Garbertt, N. C.; Chaires, J. B.; Jenkins, T. C. *J. Med. Chem.* **2006**, *49*, 5187–5198. (b) Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388–390. (c) Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125–7128. (d) Wellmar, U.; Hornfeldt, A. B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 1159–1163. (e) Gong, Y.; Pauls, H. *Synthesis* **2000**, 829–831. (e) Wong, K. T.; Hung, T. S.; Lin, Y.; Wi, C. C.; Lee, G. H.; Peng, S. M.; Chio, C. H.; Su, Y. O. *Org. Lett.* **2002**, *4*, 513–516. (f) Benderitter, P.; de Araújo Júnior, J. X.; Schmitt, M.; Bourguignon, J. J. *Tetrahedron* **2007**, *63*, 12465–12470.

(12) Cooke, G.; de Cremiers, H. A.; Rotello, V. M.; Tarbit, B.; Vanderstraeten, P. E. *Tetrahedron* **2001**, *57*, 2787–2789. (a) Mitchell, M., B.; Walbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273–2276. (c) Wade, J. V.; Krueger, C. A. *J. Comb. Chem.* **2003**, *5*, 267–272. (d) Luo, G.; Chen, L.; Poindexter, G. S. *Tetrahedron Lett.* **2002**, *43*, 5739–5742.

(13) Epple, R.; Azimioara, M.; Russo, R.; Bursulaya, B.; Tian, S. S.; Gerken, A.; Iskandar, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2969–2973.

(14) Zhang, X.; Tellew, J. E.; Luo, Z.; Moorjani, M.; Lin, E.; Lanier, M. C.; Chen, Y.; Willians, J. P.; Saunders, J.; Lechner, S. M.; Markison, S.; Joswig, T.; Petroski, R.; Piercey, J.; Kargo, W.; Malany, S.; Santos, M.; Gross, R. S.; Wen, J.; Jalali, K.; O'Brien, Z.; Stotz, C. E.; Crespo, M. I.; Díaz, J. L.; Slee, D. *J. Med. Chem.* **2008**, *51*, 7099–7110.

(15) Scribner, A.; Dennis, R.; Hong, J.; Lee, S.; McIntyre, D.; Perrey, D.; Feng, D.; Fisher, M.; Wyvratt, M.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D.; Biftu, T. *Eur. J. Med. Chem.* **2007**, *42*, 1334–1357. (a) Helgen, C.; Bochet, C. G. *Heterocycles* **2006**, *67*, 797–805.

(16) Reported yields refer to at least the mean of 2 different experiments. Complete description of the spectroscopic and analytical data for representative compounds is included in the Supporting Information.

(17) Radioligand binding competition assays were performed *in vitro* using A_1, A_{2A}, A_{2B} and A_3 human receptors expressed in transfected CHO (A_1), HeLa (A_{2A} and A_3) and HEK-293 (A_{2B}) cells. For a detailed description of the experiment, see: Bosch, M. P.; Campos, F.; Niubo, I.; Rosell, G.; Diaz, J. L.; Brea, J.; Loza, M. I.; Guerrero, A. *J. Med. Chem.* **2004**, *47*, 4041.

CC900044K