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Discovery of novel quinolinone adenosine A_{2B} antagonists

Brian F. McGuinness [a,*], Koc-Kan Ho [a], Tara M. Stauffer [a], Laura L. Rokosz [a], Neelima Mannava [a], Steven G. Kultgen [a], Kurt Saionz [a], Anthony Klon [a], Weiqing Chen [a], Hema Desai [a], W. Lynn Rogers [a], Maria Webb [a], Juxing Yin [b], Yan Jiang [b], Tailong Li [b], Hao Yan [b], Konghua Jing [b], Shengting Zhang [b], Kanak Kanti Majumdar [c], Vikash Srivastava [c], Samiran Saha [c]

[a] Ligand Pharmaceuticals, 3000 Eastpark Boulevard Cranbury, NJ 08512, USA
[b] WuXi AppTec Co., Ltd, 288 Fute Zhong Road, Shanghai 200131, China
[c] TCG Lifesciences Ltd (Chembiotek), Block BN, Plot-7, Sec-V, Salt Lake City, Kolkata 700 091, India

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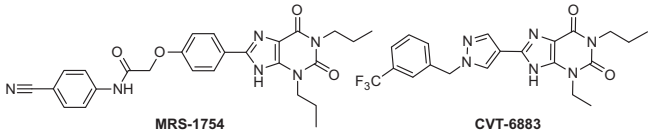
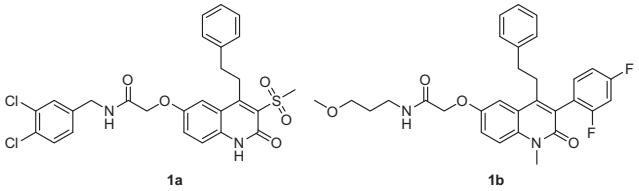
ABSTRACT

A novel series of quinolinone-based adenosine A_{2B} receptor antagonists was identified via high throughput screening of an encoded combinatorial compound collection. Synthesis and assay of a series of analogs highlighted essential structural features of the initial hit. Optimization resulted in an A_{2B} antagonist (**2i**) which exhibited potent activity in a cAMP accumulation assay (5.1 nM) and an IL-8 release assay (0.4 nM).

Extracellular adenosine provides regulatory signals through interaction with a family of G-protein coupled adenosine receptors (subtypes A_1, A_{2A}, A_{2B}, and A_3).[1] In lung tissue, for example, interaction of extracellular adenosine with the A_{2B} receptor has been shown to cause the release of pro-inflammatory cytokines.[2] Hence, antagonism of the A_{2B} adenosine receptor subtype has been proposed as a treatment for respiratory disease.[3] A_{2B} antagonists have also been suggested as treatments for diabetes,[4] diabetic retinopathy,[5] colitis,[6] and cancer.[7] Efforts to develop selective, small molecule A_{2B} antagonists have originally stemmed from xanthine-based lead structures such as MRS-1754.[8] Optimization of this lead led to CVT-6883, a selective A_{2B} antagonist which entered human clinical trials.[9] Non-xanthine-based A_{2B} antagonists have also been discovered including 2-aminopyrimidines,[10] *N*-(5,6-diarylpyridin-2-yl) amides,[11] 2-aminobenzothiazoles,[12] and aminothiazoles.[13]

We have previously described the discovery of various A_{2A} receptor antagonists via the high throughput screening of a large, encoded combinatorial compound collection.[14–16] Herein, we detail the optimization of a novel series of A_{2B} antagonists based on quinolinone hits also discovered from this encoded combinatorial collection.[17]





Two hit molecules, **1a** and **1b**, were initially identified as A_{2B} antagonists. While both were active in a hA_{2B} cAMP accumulation assay (Table 1), neither was stable in a human liver microsome assay (0% remaining after 0.5 h treatment with human liver microsomes).[18] In addition, while these hits proved highly selective against the A_{2A} receptor subtype, they exhibited only minimal A_1 receptor selectivity. Hence, a series of analogs aimed at increasing both human liver microsome (HLM) stability and A_1 receptor selectivity were synthesized.

* Corresponding author. Tel.: +1 609 570 1095 x1527; fax: +1 609 570 1050.
E-mail address: bmcguinness@venenumbiodesign.com (B.F. McGuinness).

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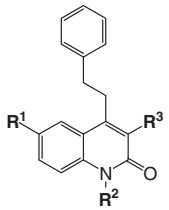
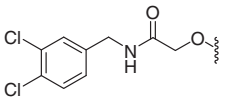
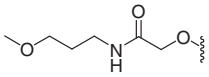
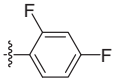
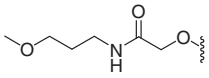
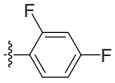
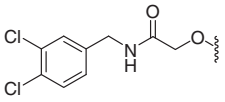
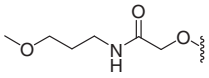
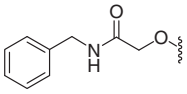
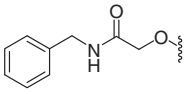
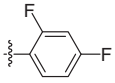
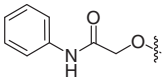
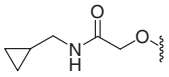
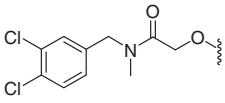
Table 1
SAR of quinolinone analogs



Compd	R^1	R^2	R^3	CHO-hA_{2B} cAMP K_i (nM)	Human A_{2B} binding av K_i (nM)	Human A_{2A} binding av K_i (nM)	A1 binding av K_i (nM)	HLM stability (% remaining-0.5 h)[13]
1a		H		315 ± 102	211 ± 36	>10,000	811 ± 6	0
1b		Me		633 ± 83	677 ± 44	>10,000	3623 ± 1536	0
1c		H		>5000	>10,000	>10,000	6050 ± 3175	ND
1d		Me		>5000	>7000	ND	>10,000	ND
1e		H		>5000	ND	>10,000	10,443 ± 5032	ND
1f		H		352 ± 227	70 ± 19	>10,000	159 ± 34	0
1g		Me		>5000	3655 ± 1332	>10,000	7027 ± 616	ND
1h		H		3474 ± 739	11,310 ± 470	>10,000	>10,000	28
1i		H		1675 ± 671	>10,000	>10,000	1334 ± 309	67
1j		H		>5000	>10,000	ND	>10,000	ND
1k		H		1017 ± 37	710 ± 44	>10,000	602 ± 25	0

The synthetic route used to generate the majority of the analogs in this study is outlined in Scheme 1. The hydroxyl moiety of 4-aminophenol was protected as the *t*-butyldimethylsilyl ether followed by protection of the amino group as the *t*-butoxycarbamate. The dianion of this protected intermediate was reacted with tributyltin chloride to generate stannane **4** which was employed in a Stille coupling with the appropriate acid chloride to yield ketone **5**. Deprotection of the phenol and alkylation with methyl bromoacetate produced **6** which was further deprotected by TFA treatment to yield aniline **7**.

Various methods were employed at this stage to generate the quinolinone ring (**8**) depending on the targeted R^3 group. For the methanesulfonyl and 2,4-difluorophenyl R^3 analogs, a two step procedure of amide formation followed by base-mediated cyclization was required. For the 2-thiazolyl R^3 analogs, however, cyclization occurred spontaneously with warming during the EDC-mediated amide formation conditions. The required 2-thiazolylacetic acid was prepared by the homologation route described in Scheme 2. Although phosphorus oxychloride (employed for the synthesis of analogs **2n**–**2q**) was also effective in producing a cyclized structure, the 2-chloroquinoline was isolated. Subsequent treatment with acetic acid under microwave heating was employed to produce the desired quinolinone **8**.

If desired, methylation of the R^2 position was completed at this stage (**8**) via methyl iodide treatment in the presence of potassium carbonate. Ultimately, base-mediated deprotection of the methyl ester followed by amide bond formation yielded the completed analogs.

A similar route was followed to generate the aminomethyl quinolinones **2d**–**2f** (Scheme 3). 4-Chloroaniline was Boc-protected and