# 2-Aminopyrimidin-4(1H)-one as the novel bioisostere of urea: Discovery of novel and potent CXCR2 antagonists

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# 2-Aminopyrimidin-4(1*H*)-one as the novel bioisostere of urea: Discovery of novel and potent CXCR2 antagonists

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ABSTRACT

2-Aminopyrimidin-4(1*H*)-one was proposed as the novel bioisostere of urea. Bioisosteric replacement of the reported urea series of the CXCR2 antagonists with 2-aminopyrimidin-4(1*H*)-ones led to the discovery of the novel and potent CXCR2 antagonist **3e**. 2-Aminopyrimidin-4(1*H*)-one derivative **3e** demonstrated a good developability profile (reasonable solubility and high permeability) and superior chemical stability especially in simulated gastric fluid (SGF) compared with ureas.



Urea has been one of the most widely used structure components in the discovery of biologically active small molecules.[1] However, the urea-containing compounds frequently suffer from various developability issues such as low aqueous solubility, poor permeability, and poor metabolic/chemical stability, which often limit their potential in pre-clinical and clinical development.[2–4] Bioisosteric replacement is a widely used strategy to maintain biological activity of a functional group/pharmacophore (e.g., urea) at the same time enabling the introduction of structural changes to improve the developability profile.[5–9] The utility of bioisosteric replacement has been established including improving ADME properties, enhancing potency, and obtaining selectivity.[5,6] The urea bioisosteres were extensively explored nevertheless with limited cases of success, including thiourea, *N*-cyanoguanidines, diaminonitroethenes, squaramides, aminothiadiazoles, aminoimidazoles, aminoimidazolones, aminooxazoles, aminooxadiazoles, and aminotriazoles.[7–9] Herein, we propose 2-aminopyrimidin-4(1*H*)-one as a novel bioisostere of urea based on their similar shapes, H-bond donor/acceptor properties, and p$K_a$ values. 2-Aminopyrimidin-4(1*H*)-one shares similar shape and size with urea (bi-phenyl urea as an example, Fig. 1), which should contribute to similar biological activities. They are all planar in structure and overlay well with each other by computer modeling (Fig. 1b). They both have two H-bond donors and 2-aminopyrimidin-4(1*H*)-one has an additional H-bond acceptor which might enable additional interaction with the biological target (Fig. 1a). Further, the N–H on the pyrimidin-4(1*H*)-one moiety is more acidic (p$K_a$: 9.4) than that of the urea (p$K_a$: 11.5), which could potentially provide stronger H-bonding interactions with acceptors. These pieces of evidence support our proposal of 2-aminopyrimidin-4(1*H*)-one as the novel bioisostere of urea.

Bi-arylureas have been the most successful CXCR2 antagonists discovered to date.[10,11] CXCR2, a seven-transmembrane G protein-coupled receptor (GPCR), is a chemokine receptor that plays an important role in regulating neutrophil migration to sites of inflammation and antagonism of CXCR2 has emerged as an appealing strategy for inflammatory diseases such as chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), psoriasis, and rheumatoid arthritis.[12] Since the first discovery of biarylureas as potent CXCR2 antagonists, the medicinal chemistry community has focused on bioisosteric replacements of urea for novel structural scaffolds. A number of urea bioisosteres were explored however with limited success in balancing biological activity and developability profile (e.g., stability, solubility, and permeability).[11] Thus, to develop a novel urea bioisostere will enable the discovery of novel chemotypes as CXCR2 antagonists.

The biarylurea compound **1**[13] (Fig. 2) which demonstrated good CXCR2 antagonism activity (p$IC_{50}$: 8.1) in the β-arrestin assay served as a rational starting point. Bioisosteric replacement of the urea moiety with the proposed 2-aminopyrimidin-4(1*H*)-one

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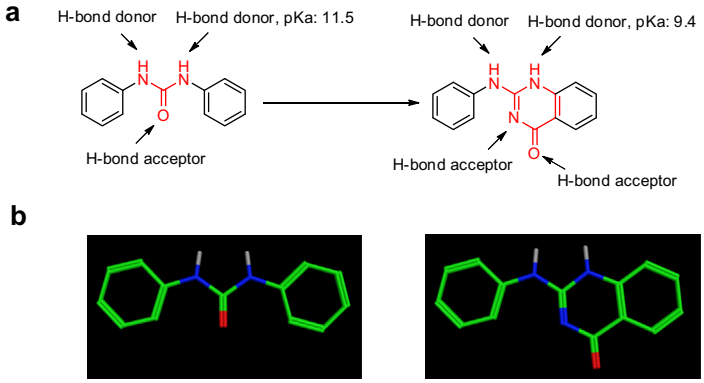



**Figure 1.** Comparison of urea and 2-aminopyrimidin-4(1*H*)-one (alignment for 1b was generated through Flexible Alignment in MOE 2010.1001 with default settings; ligand major macrospecies was determined in Marvin 5.7.0 of ChemAxon at pH 7.4).

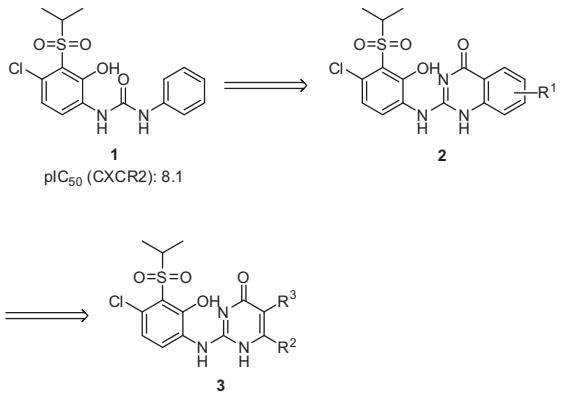
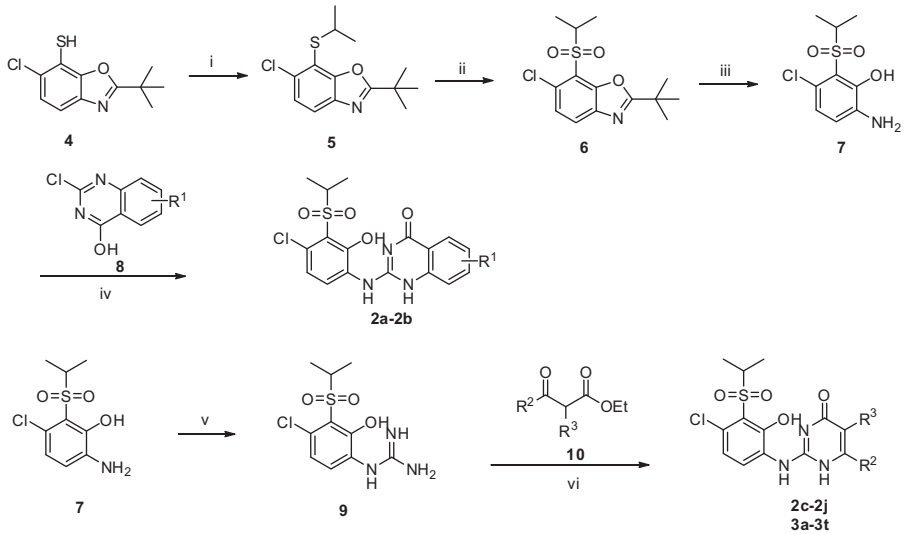



**Figure 2.** 2-Aminopyrimidin-4(1*H*)-ones **2** and **3** as novel urea bioisosteres.

resulted in structures **2**, which should provide reasonable biological activity based on the previously mentioned rationale. Disconnection of the fused benzene ring provides further simplified 2-aminopyridin-4(1*H*)-one analogues **3** which enable both $R^2$ and $R^3$ open for SAR studies.

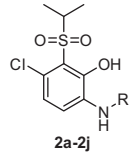
We firstly developed convergent synthetic routes for both **2** and **3** (Scheme 1). The syntheses started from the reported intermediate, thiol **4**.[14] Compound **4** was treated with isopropyl bromide in the presence of potassium carbonate at elevated temperature to afford sulfide **5**. Oxidation of sulfide **5** with *m*-CPBA provided sulfone **6**. The *tert*-butyl oxazole moiety of **6** was hydrolyzed under the acidic condition to give the aminophenol **7**. Treatment of aminophenol **7** with 2-chloro-pyrimidin-4(1*H*)-one intermediates **8**, which were prepared according to reported procedures,[15,16] at elevated temperature produced the 2-aminopyrimidin-4(1*H*)-one derivatives **2a** and **2b**. Alternatively, aminophenol **7** was treated with 1*H*-pyrazole-1-carboximidamide at elevated temperature to afford the guanidine intermediate **9**. Condensation reaction of guanidine **9** with β-ketone esters **10** under microwave radiation in *N*-methyl-2-pyrrolidone (NMP) provided 2-aminopyridin-4(1*H*)-one derivatives **2c**–**2j** and **3a**–**3t**.

With the synthetic routes successfully developed, the activity of 2-aminopyrimidin-4(1*H*)-one derivatives was evaluated (Table 1). The first aminopyrimidin-4(1*H*)-one derivative (**2a**) designed and synthesized demonstrated CXCR2 antagonism activity in the β-arrestin assay, even though the potency was much lower ($pIC_{50}$ = 6.2) than that of the urea analogue **1** ($pIC_{50}$ = 8.1). Introduction of a lipophilic chlorine substitution (**2b**) resulted in marginal improvement in potency. Replacement of the fused benzene ring to the saturated cyclohexyl ring (**2c**) provided similar potency, and the

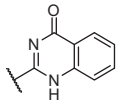
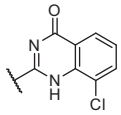
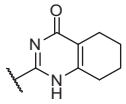
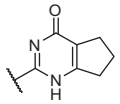
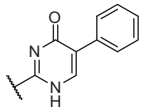
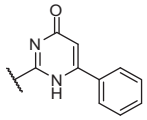
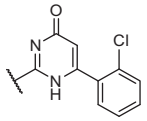
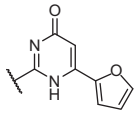
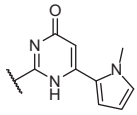
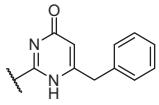



**Scheme 1.** Synthesis of 2-aminopyrimin-(1*H*)-one derivatives **2a**–**2j**, **3a**–**3t**. Reagents and conditions: (i) *i*-PrBr, $K_2CO_3$, DMF, 50 °C, overnight, 91%; (ii) m-CPBA, DCM, 25 °C, 4 h, 96%; (iii) concd HCl, 1,4-dioxane, $H_2O$, 100 °C, overnight, 87%; (iv) DMF, 100 °C, 12 h for **2a**, 3 h for **2b**; (v) 1*H*-pyrazole-1-carboximidamide, DIPEA, DMF, 60 °C, overnight, 25%; and (vi) $Cs_2CO_3$, NMP, mw, 120–160 °C, 1–3 h.

**Table 1**
In vitro CXCR2 β-arrestin potencies for 2-aminopyrimidin-4(1*H*)-one derivatives **2a**–**2j**

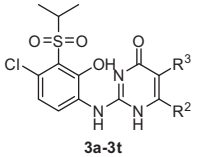


**2a-2j**

| Entry | R | CXCR2 $pIC_{50}$[a] |
|---|---|---|
| **2a** |  | 6.2 |
| **2b** |  | 6.3 |
| **2c** |  | 6.5 |
| **2d** |  | 5.6 |
| **2e** |  | <5.0 |
| **2f** |  | 6.2 |
| **2g** |  | 6.2 |
| **2h** |  | 5.6 |
| **2i** |  | 5.6 |
| **2j** |  | 6.4 |

[a] CXCR2 assay data is the average of at least two determinations.

**Table 2**
In vitro CXCR2 β-arrestin potencies for 2-aminopyrimidin-4(1*H*)-one derivatives **3a**–**3t**



**3a-3t**

| Entry | $R^2$ | $R^3$ | CXCR2 $pIC_{50}$[a] |
|---|---|---|---|
| **3a** |  | H | <5.0 |
| **3b** |  | H | 6.6 |
| **3c** |  | H | 6.7 |
| **3d** |  | H | 6.9 |
| **3e** |  | H | 8.2 |
| **3f** |  | H | 6.4 |
| **3g** |  | H | 7.8 |
| **3h** |  | H | 7.7 |
| **3i** |  | H | 7.5 |
| **3j** |  | H | 7.8 |
| **3k** |  | H | 6.9 |
| **3l** |  | H | 7.0 |
| **3m** |  | H | 6.9 |
| **3n** |  | H | 6.2 |
| **3o** |  | H | 5.6 |
| **3p** |  | H | <5.0 |
| **3q** |  | F | 7.6 |
| **3r** |  | F | 7.3 |
| **3s** |  | Me | 6.6 |
| **3t** |  | Me | 6.2 |

[a] CXCR2 assay data is the average of at least two determinations.

cyclopentyl analogue (**2d**) demonstrated decreased potency. Without significant improvement of potencies from these bicyclic fused ring analogues, the monocyclic 2-aminopyrimidin-4(1*H*)-one derivatives were selected for further modification. Phenyl substitution on the 5-position of the 2-aminopyrimidin-4(1*H*)-one (**2e**) was not tolerated in terms of biological activity ($pIC_{50}$ < 5.0). In contrast, 6-position could be substituted by the phenyl ring (**2f**) with CXCR2 inhibition activity comparable to **2a**. The chlorine substitution on the phenyl ring (**2g**) provided very limited improvement in potency. Once the phenyl ring was replaced with the heterocyclic furan or pyrrole rings (**2h** and **2i**), significantly decreased potencies were observed. It was noteworthy that the 6-benzyl substitution (**2j**) demonstrated reasonable potency which indicated aliphatic substitutions could be tolerated. SAR studies were then focused on aliphatic substitutions at the 6-position of the 2-aminopyridin-4(1*H*)-one core to improve potency.

As shown in Table 2, the 6-methyl-2-aminopyrimidin-4(1*H*)-one derivative (**3a**) showed no CXCR2 antagonism activity. The potency was increased when the 6-methyl group was replaced with a more lipophilic and bulkier ethyl group (**3b**). Further increase of lipophilicity at the 6-position with *n*-propyl or *iso*-butyl groups (**3c** and **3d**) resulted in no/marginal improvement in potency. On the other hand, increasing both bulkiness and lipophilicity with *tert*-butyl group

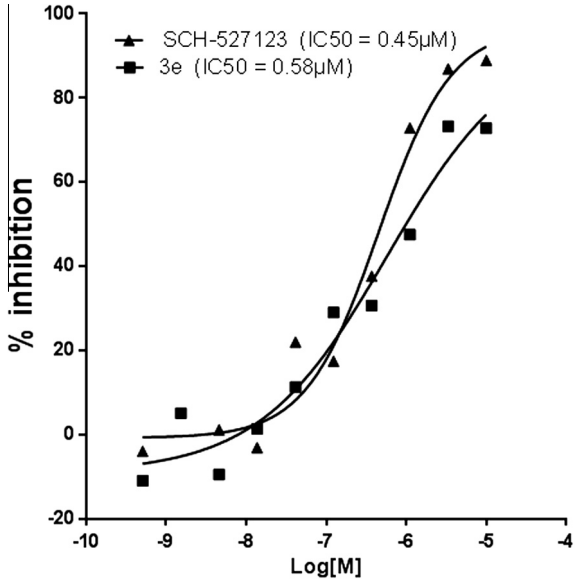



**Figure 3.** Human whole blood CD11b assay data for compounds **3e** and the reported clinical compound SCH-527123.[18]

(**3e**) provided significantly improved potency ($pIC_{50}$: 8.2). We further extended our SAR study to the saturated carbocyclic substitutions at the 6-position. The 3-membered ring (cyclopropyl) analogue (**3f**) demonstrated low potency. Increasing the ring size to the four-membered ring (cyclobutyl, **3g**) provided more than 10-fold potency increase. Whereas further increasing the ring size to the five-membered ring (cyclopentyl, **3h**) led to slightly decreased activity. The methyl-substitution on the cyclopentyl ring (**3i**) resulted in no improvement in potency. Introduction of a *gem*-methyl group to the cyclobutyl ring provided the analogue (**3j**) with good potency, and the improvement of potency was likely due to steric effect. Electronic effect at the 6-substituents was also investigated. Introduction of an electron withdrawing fluorine group to the *tert*-butyl substitution (**3k**) caused ~10-fold decrease in potency compared with its parent compound (**3e**), so did the trifluoro analogue (**3l**). Replacement of one methyl group of **3e** with a fluoride (**3m**) also resulted in significantly decreased potency. Similarities were also observed in the cyclic 6-substituted analogues. For example, the *gem*-difluoro cyclobutyl analogue (**3n**) demonstrated ~15-fold decreased potency than the cyclobutyl analogue (**3g**). On the other hand, introduction of an oxygen atom to the 6-substituents provided compounds (**3o** and **3p**) with marginal/no activity ($pIC_{50}$ = 5.6 and $pIC_{50}$ < 5.0, respectively), indicating that polar functional groups were not tolerated at the 6-position. SAR of the 5,6-disubstitution was also investigated. Based on previous data, bulky substitutions such as phenyl group (**2e**, Table 1) at the 5-position were not tolerated. Focus on the sterically small substitutions at 5-position demonstrated that the 5-fluoro-6-*tert*-butyl analogue (**3q**) had slightly decreased potency ($pIC_{50}$ = 7.6) compared to the 5-hydrogen-6-*tert*-butyl analogue **3e** ($pIC_{50}$ = 8.2), and similarity was also observed with the 5-fluoro-6-cyclobutyl analogue (**3r**). When a more hindered methyl group was introduced at the 5-position, dramatic decrease of potencies were observed (**3s** and **3t**).

The most potent compound **3e** was further assessed in the human whole blood CD11b assay (Fig. 3).[17] Compound **3e** demonstrated good potency with the $IC_{50}$ value of 0.58 μM, comparable to that of the reported clinical compound SCH-527123[18] ($IC_{50}$ = 0.45 μM). It was then further evaluated for its physicochemical properties. In contrast to the urea containing compounds, 2-aminopyrimidin-4(1*H*)-one derivative **3e** demonstrated superior stability in SGF (simulated gastric fluid) and there was no degradation observed at 24 h after incubation in SGF at physiologically relevant temperature (37 °C). In addition, the compound also demonstrated reasonable solubility (33 μg/mL) in FaSSIF (fasted simulated intestinal fluid) at 4 h after incubation. Further, passive permeability of compound **3e** was high (370 nm/s) as evaluated in PAMPA (parallel artificial membrane permeability assay).

In conclusion, bioisosteric replacement of the urea series of the CXCR2 antagonists with 2-aminopyrimidin-4(1*H*)-ones led to the discovery of the novel and potent CXCR2 antagonist **3e**. 2-Aminopyrimidin-4(1*H*)-one derivative **3e** demonstrated better chemical stability especially in SGF compared with ureas which could degrade in acidic conditions. In addition, reasonable solubility and high passive permeability were also observed for 2-aminopyrimidin-4(1*H*)-one compound **3e**. Our result suggested 2-aminopyrimidin-4(1*H*)-one to be a novel bioisostere of urea with a superior developability profile such as chemical stability in particular.

## Acknowledgment

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## References and notes

1. Batra, S.; Tusi, Z.; Madapa, S. *Anti-Infect. Agents Med. Chem.* **2006**, *5*, 135.
2. Dörward, F. Z. *Lead Optimization for Medicinal Chemists: Pharmacokinetic Properties of Functional Groups and Organic Compounds*, 1st ed.; Wiley-VCH Verlag GmbH & Co. KGaA, 2012. Chapter 38.
3. Brown, N. *Bioisosteres in Medicinal Chemistry*, 1st ed.; Wiley-VCH Verlag GmbH & Co. KGaA, 2012. p 44.
4. McCleland, B. W.; Davis, R. S.; Palovich, M. R.; Widdowson, K. L.; Werner, M. L.; Burman, M.; Foley, J. J.; Schmidt, D. B.; Sarau, H. M.; Rogers, M.; Salyers, K. L.; Gorycki, P. D.; Roethke, T. J.; Stelman, G. J.; Azzarano, L. M.; Ward, K. W.; Busch-Petersen, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1713.
5. Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563.
6. Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147.
7. Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.
8. Chen, X.; Wang, W. *Annu. Rep. Med. Chem.* **2003**, *38*, 333.
9. Poindexter, G. S.; Bruce, M. A.; Breitenbucher, J. G.; Higgins, M. A.; Sit, S. Y.; Romine, J. L.; Martin, S. W.; Ward, S. A.; McGovern, R. T.; Clarke, W.; Russell, J.; Antal-Zimanyi, I. *Bioorg. Med. Chem.* **2004**, *12*, 507.
10. (a) Widdowson, K. L. WO Patent 1997/49286, 1997; (b) Jin, Q.; McCleland, B. W.; Palovich, M. R.; Widdowson, K. L. WO Patent 2000/035442, 2000; (c) Busch-Petersen, J.; Palovich, M. R.; Widdowson, K. L. WO Patent 2004/039775, 2004; (d) Busch-Petersen, J. WO Patent 2007/124423, 2007; (e) Busch-Petersen, J. US Patent 2007/249672, 2007; (f) Widdowson, K. L.; Elliott, J. D.; Veber, D. F.; Nie, H.; Rutledge, M. C.; McCleland, B. W.; Xiang, J. N.; Jurewicz, A. J.; Hertzberg, R. P.; Foley, J. J.; Griswold, D. E.; Martin, L.; Lee, J. M.; White, J. R.; Sarau, H. M. *J. Med. Chem.* **2004**, *47*, 1319; (g) Stevenson, C. S.; Coote, K.; Webster, R.; Johnston, H.; Atherton, H. C.; Nicholls, A.; Giddings, J.; Sugar, R.; Jackson, A.; Press, N. J.; Brown, Z.; Butler, K.; Danahay, H. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2005**, *288*, L514.
11. (a) Busch-Petersen, J.; Wang, Y. *Expert Opin. Ther. Patents* **2008**, *18*, 629; (b) Wang, Y.; Busch-Petersen, J.; Wang, F.; Ma, L.; Fu, W.; Kerns, J. K.; Jin, J.; Palovich, M. R.; Shen, J.; Burman, M.; Foley, J. J.; Schmidt, D. B.; Hunsberger, G. E.; Sarau, H. M.; Widdowson, K. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3864.
12. (a) Chapman, R. W.; Phillips, J. E.; Hipkin, R. W.; Curran, A. K.; Lundell, D.; Fine, J. S. *Pharmacol. Ther.* **2009**, *121*, 55; (b) Donnelly, L. E.; Barnes, P. J. *Drugs Future* **2011**, *36*, 465.
13. Compound **1** is an internal CXCR2 program compound and the activity was not previously published.
14. Busch-Petersen, J. U.S. Patent 0,249,672, 2007.
15. Samrin, F.; Sharma, A.; Khan, I. A.; Puri, S. *J. Heterocycl. Chem.* **2012**, *49*, 1391.
16. Feng, J.; Zhang, Z.; Wallace, M. B.; Stafford, J. A.; Kaldor, S. W.; Kassel, D. B.; Navre, M.; Shi, L.; Skene, R. J.; Asakawa, T.; Takeuchi, K.; Xu, R.; Webb, D. R.; Gwaltney, S. L., II *J. Med. Chem.* **2007**, *50*, 2297.
17. The curves were generated from the average of two donors.
18. (a) Gonsiorek, W.; Fan, X.; Hesk, D.; Fossetta, J.; Qiu, H.; Jakway, J.; Billah, M.; Dwyer, M.; Chao, J.; Deno, G.; Taveras, A.; Lundell, D. J.; Hipkin, R. W. *J. Pharmacol. Exp. Ther.* **2007**, *322*, 477; (b) Chapman, R. W.; Minnicozzi, M.; Celly, C. S.; Phillips, J. E.; Kung, T. T.; Hipkin, R. W.; Fan, X.; Rindgen, D.; Deno, G.; Bond, R.; Gonsiorek, W.; Billah, M. M.; Fine, J. S.; Hey, J. A. *J. Pharmacol. Exp. Ther.* **2007**, *322*, 486.