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Design, synthesis, and evaluation of fused heterocyclic analogs of SCH 58261 as adenosine A_{2A} receptor antagonists

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ABSTRACT

SCH 58261 is a reported adenosine A_{2A} receptor antagonist which is active in rat in vivo models of Parkinson's Disease upon ip administration. However, it has poor selectivity versus the A_1 receptor and does not demonstrate oral activity. Quinoline analogs have improved upon the selectivity and pharmacokinetics of SCH 58261, but were difficult to handle due to poor aqueous solubility. We report the design and synthesis of fused heterocyclic analogs of SCH 58261 with aqueous solubility as well as improved A_{2A} receptor binding selectivity and pharmacokinetic properties. In particular, the tetrahydronaphthyridine **4s** has excellent A_{2A} receptor in vitro binding affinity and selectivity, is active orally in a rat in vivo model of Parkinson's Disease, and has aqueous solubility of 100 μM at physiological pH.

As described in the preceding publication,[1] adenosine A_{2A} receptor antagonism is a potential treatment for Parkinson's Disease.[2,3] SCH 58261 (Fig. 1, **1**) has previously been identified as a high-affinity A_{2A} receptor antagonist.[4] However, SCH 58261 is only moderately selective for A_{2A} receptors over A_1 receptors,[5] has poor solubility,[6] and does not produce in vivo activity when dosed orally.[4c] Attempts via phenyl substitution to produce soluble analogs which maintain the biological activity of SCH 58261 were unsuccessful.[6] We have previously demonstrated that quinoline analogs of SCH 58261 can improve A_{2A} selectivity as well as pharmacokinetics and oral efficacy.[1] In addition, replacement of the phenyl group of SCH 58261 with a piperazine moiety can produce potent and selective A_{2A} receptor antagonists.[7] While these modifications have improved upon the in vitro and in vivo properties of SCH 58261, the reported lead compounds all have poor aqueous solubility.[7] To follow up on these discoveries, our plan was to attach fused heterocyclic moieties (**2**) with the SCH 58261 tricyclic core **3** (Scheme 1). Our rationale was that incorporation of the more basic nitrogen present in fused heterocyclic side-chains (**2**) could result in water soluble A_{2A} receptor antagonists (**4**) which also improve the potency and selectivity of SCH 58261. Described herein are the syntheses and structure–activity relationships of novel fused heterocyclic analogs which demonstrate aqueous solubility and improve upon the pharmacological and pharmacokinetic profiles of SCH 58261.

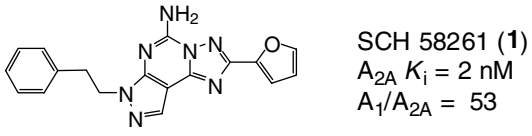

Figure 1. SCH 58261.

The general synthesis of the fused heterocyclic analogs of SCH 58261 is depicted in Scheme 1.[8] Displacement of the tosylate **3**[7a] with the corresponding free amine **2** furnished the desired targets **4** reported throughout this publication. The first heterocyclic analogs we explored were isoindolines, which were synthesized as shown in Scheme 2.[9] Generally, the isoindoline analogs met the in vitro criteria with A_{2A} binding affinity in the range of 5–15 nM and an acceptable selectivity profile (Table 1).[10] Compound **4d** demonstrated improved selectivity and solubility over SCH 58261 and was studied further. Unfortunately, this compound showed low plasma levels in a rat pharmacokinetic assay[11] and was only moderately active in a haloperidol-induced catalepsy assay in rat.[12]

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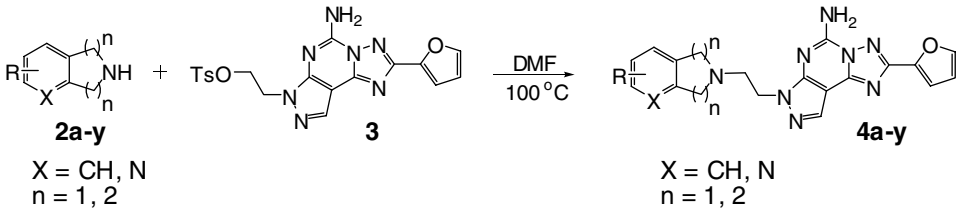
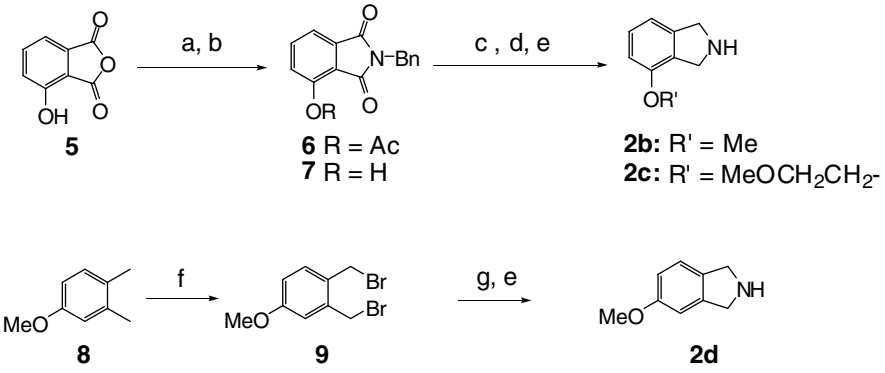
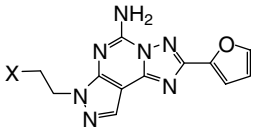


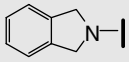
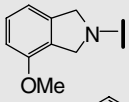
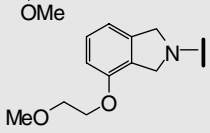
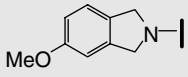
Scheme 1. General synthesis of fused heterocyclic SCH 58261 analogs.



Scheme 2. Synthesis of isoindolines. Reagents and conditions: (a) $BnNH_2$, THF, reflux. (b) Ac_2O, reflux. (c) LAH, THF, reflux. (d) R′X, NaH, DMF. (e) $Pd(OH)_2/C$, HCO_2NH_4, MeOH, reflux. (f) NBS, benzoyl peroxide, CCl_4, reflux. (g) $BnNH_2$, toluene, reflux.

Table 1
Structure–activity relationship of isoindoline analogs

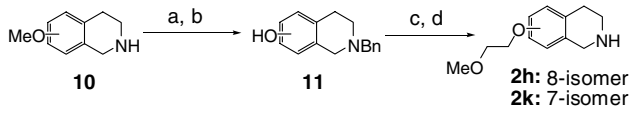


Compound	X	A_{2A} K_i[a] (nM)	A_1/A_{2A}	k. sol.[b] (μM)	Rat AUC[c]	Catalepsy[d] 3 mpk po, 1 h/4 h
4a		14.7	116	37	287	–[e]
4b		6.0	105	–	–	–
4c		7.1	105	75	215	–
4d		5.4	126	37	199	21/24

[a] For a detailed description of the human adenosine receptor binding assays see Ref. 10.
[b] A single measurement of kinetic solubility at pH 7.4.[13]
[c] Area under the curve: h.ng/mL, 0 → 6h, 3 mpk, 20% HPβCD, po.[11]
[d] Inhibition of haloperidol-induced catalepsy is an in vivo measure of A_{2A} antagonist activity (>30% inhibition is considered to be active in this assay).[12]
[e] Not determined.

Tetrahydroisoquinoline analogs were explored next. Commercial tetrahydroisoquinolines and custom synthesized alkoxy intermediates (Scheme 3) displaced the tosylate **3** to yield the final targets **4e**–**4k**.[14] Both 3- and 1-substituted tetrahydroisoquinoline derivatives **4f** and **4g** met the binding criteria and demonstrated good solubility (Table 2). However, these compounds failed to show activity in the catalepsy assay, which was attributed to their poor pharmacokinetic properties.

Mono-substitution at the 6- and 7-positions of the tetrahydroisoquinoline moiety resulted in compounds **4i** and **4j**, which showed acceptable A_{2A} potency, but suffered from modest selectivity over A_1. Nevertheless, these compounds were studied further and were shown to possess acceptable rat plasma levels. When tested in vivo, both compounds demonstrated promising anticataleptic activity at 3 mpk. Compound **4j** was also moderately active at 1 mpk in the catalepsy assay. Having seen a good selectivity pro-



Scheme 3. Synthesis of tetrahydroisoquinolines.[14] Reagents and conditions: (a) BnBr, Et_3N, EtOH. (b) BBr_3, CH_2Cl_2, 0 °C → rt. (c) NaH, $MeOCH_2CH_2Br$, DMF. (d) $Pd(OH)_2/C$, HCO_2NH_2, MeOH, reflux.

file for the extended ether **4h**, we synthesized compound **4k**. Unfortunately, it did not improve the selectivity profile and was not studied further.

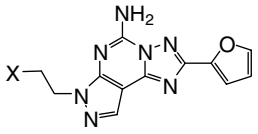
Analogs based on the benzazepine moiety, synthesized as shown in Scheme 4,[15] were also explored. Several compounds of this class showed promising binding affinity and improved selectivity (Table 3) compared to the isoindoline and tetrahydroisoquinoline analogs. Unfortunately, these compounds failed to exhibit acceptable plasma levels and suffered from poor in vivo activity in the catalepsy assay.

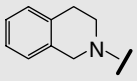
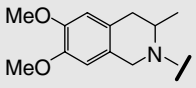
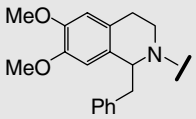
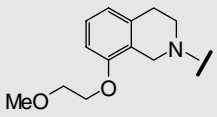
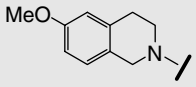
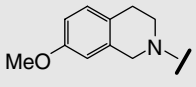
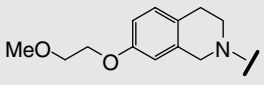
Having seen promising anticataleptic activity for the tetrahydroisoquinoline analogs, we decided to synthesize the corresponding tetrahydronaphthyridine counterparts (Scheme 5).[16–19] The syntheses of intermediates **2r**, **2s**, **2w**, and **2x** have been reported in the literature.[16,19] The remaining tetrahydronaphthyridine intermediates were derived via cyclization of the dinitropyridone **13**[17] to the 3-nitrotetrahydroisoquinoline intermediates **14** and **15**.[18] Intermediates **14** and **15** were reduced to their free amines which underwent Sandmeyer chemistry to form the bromide **2u** and alcohol **16**. Compounds **2u** and **16** were further elaborated to produce **2y**, **2t**, and **2v**.

A comparison of compounds in Table 4 shows that the use of tetrahydronaphthyridine resulted in potent analogs that generally exhibited good rat pharmacokinetics and aqueous solubility. Compounds **4r**, **4s**, and **4u** all had excellent AUC values, and were active in vivo. However, of all of the tetrahydronaphthyridine compounds, only the methyl analog **4s** improved upon the selectivity profile of SCH 58261. It also possessed excellent solubility (100 μM), rat AUC (3491 ng · h/mL, 3 mpk, po), and displayed potent oral anti-cataleptic activity at doses of 3 mpk (80% inhibition @ 1 h) and 1 mpk (65% inhibition @ 1 h). The compound also showed anticataleptic activity at the 4 h time point (~35% inhibition @ 1 mpk).

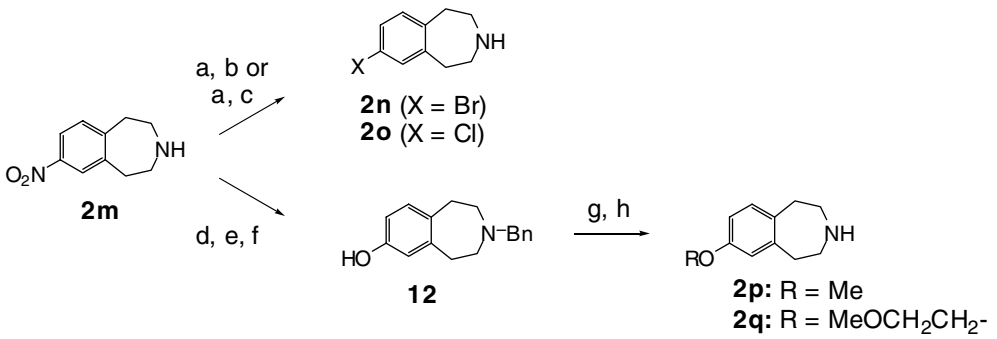
Compound **4s** was studied further and a complete rat pharmacokinetic profile was generated at 3 mpk. It possessed good oral

Table 2
Structure–activity relationship of tetrahydroisoquinoline analogs



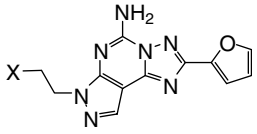
Compound	X	A_{2A} K_i[a] (nM)	A_1/A_{2A}	k. sol.[b] (μM)	Rat AUC[c]	Catalepsy[d] 3 mpk po, 1 h/4 h
4e		4.1	94	50	60	35/0
4f		1.9	149	37	0	0/26
4g		2.3	146	12	0	28/20
4h		1.5	313	37	31	0/0
4i		2.5	68	25	688	65/35
4j		3.2	60	37	357	50/58 26/61 (1 mpk)
4k		5.1	56	50	—[e]	—

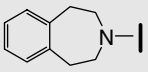
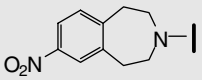
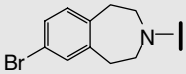
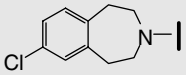
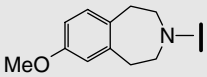
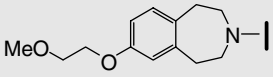
[a] For a detailed description of the human adenosine receptor binding assays see Ref. 10.
[b] A single measurement of kinetic solubility at pH 7.4.[13]
[c] Area under the curve: h.ng/mL, 0 → 6h, 3 mpk, 20% HPβCD.[11]
[d] Inhibition of haloperidol-induced catalepsy is an in vivo measure of A_{2A} antagonist activity (>30% inhibition is considered to be active in this assay).[12]
[e] Not determined.



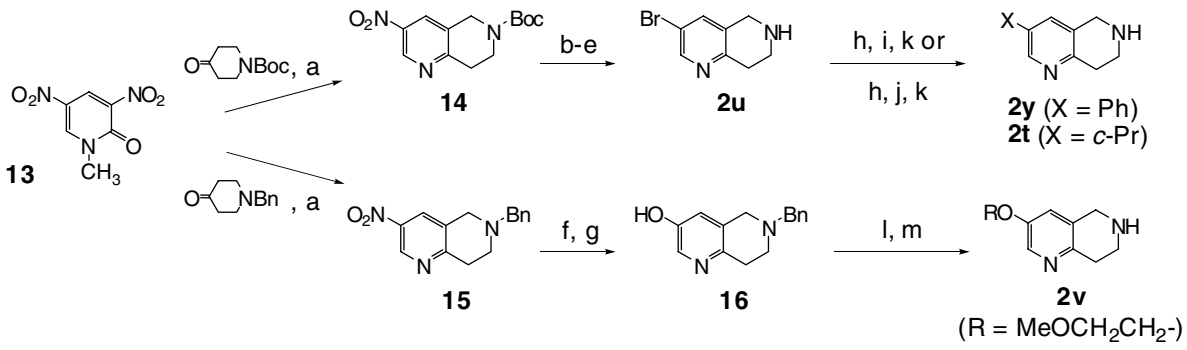
Scheme 4. Synthesis of benzazepines.[15] Reagents and conditions: (a) 10% Pd/C, H_2, MeOH. (b) i—48% HBr, $NaNO_2/H_2O$, 0 °C; ii—CuBr, HBr, H_2O. (c) i—20% HCl, $NaNO_2/H_2O$, 0 °C; ii—CuCl, HCl/H_2O. (d) BnBr, Et_3N, EtOH. (e) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0 ° C → rt. (f) i—5% aq. H_2SO_4, $NaNO_2/H_2O$, 0 °C; ii—5% aq. H_2SO_4, 100 °C. (g) RBr, NaH, DMF, 0 °C → rt. (h) $Pd(OH)_2/C$, HCO_2NH_4, MeOH, reflux.

Table 3
Structure–activity relationship of benzazepine analogs



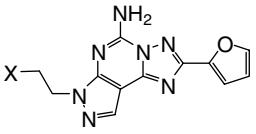
Compound	X	A_{2A} K_i[a] (nM)	A_1/A_{2A}	k. sol.[b] (μM)	Rat AUC[c]	Catalepsy[d] 3 mpk po, 1 h/4 h
4l		2.0	215	0	48	0/17
4m		0.7	71	< 5	—[e]	—
4n		1.1	62	6	—	—
4o		3.3	33	—	—	—
4p		1.9	463	< 2.5	0	5/8
4q		2.0	306	< 2.5	103	0/0

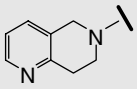
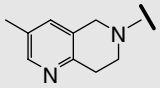
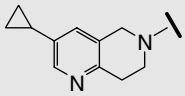
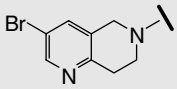
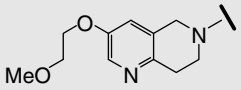
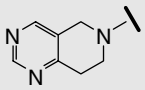
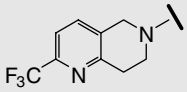
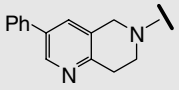
[a] For a detailed description of the human adenosine receptor binding assays see Ref. 10.
[b] A single measurement of kinetic solubility at pH 7.4.[13]
[c] Area under the curve: h.ng/mL, 0 → 6 h, 3 mpk, 20% HPβCD, po.[11]
[d] Inhibition of haloperidol-induced catalepsy is an in vivo measure of A_{2A} antagonist activity (>30% inhibition is considered to be active in this assay).[12]
[e] Not determined.



Scheme 5. Synthesis of tetrahydronaphthyridines.[17] Reagents and conditions: (a) 7 N NH_3 in MeOH, reflux.[18] (b) TFA, CH_2Cl_2. (c) H_2, 10% Pd/C, MeOH. (d) $NaNO_2$, HBr, 0 °C. (e) CuBr, HBr, 100 °C. (f) $SnCl_2{\cdot}2H_2O$, concd HCl, EtOH, 50 °C.[18] (g) i—5% aq. H_2SO_4, $NaNO_2/H_2O$, 0 °C; ii—5% aq. H_2SO_4, 100 °C. (h) Ph_3CCl, Et_3N, DMAP, CH_2Cl_2. (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, 100 °C. (j) i—Tributyl(vinyl)tin, $Pd(PPh_3)_4$, DMF, 100 °C; ii—CH_2N_2,Et_2O. (k) 3 N HCl, acetone. (l) $MeOCH_2CH_2Br$, NaH, DMF, 0 °C → rt. (m) $Pd(OH)_2/C$, HCO_2NH_4, MeOH, reflux.

Table 4
Structure–activity relationship of tetrahydronaphthyridine analogs



Compound #	X	A_{2A} K_i[a] (nM)	A_1/A_{2A}	k. sol.[b] (μM)	Rat AUC[c]	Catalepsy[d] 3 mpk po, 1 h/4 h
4r		4.8	64	>250	1792	50/30 15/0 (1 mpk)
4s		2.0	179	100	3491	85/30 60/35 (1 mpk)
4t		1.9	53	75	214	0/0
4u		1.6	61	37	2018	65/30
4v		3.1	82	175	477	—[e]
4w		6.2	23	>250	467	—
4x		5.0	20	37	1237	—
4y		17.9	27	—	—	—

[a] For a detailed description of the human adenosine receptor binding assays see Ref. 10.
[b] A single measurement of kinetic solubility at pH 7.4.[13]
[c] Area under the curve: h.ng/mL, 0 → 6 h, 3 mg/kg, 20% HPβCD, po.[11]
[d] Inhibition of haloperidol-induced catalepsy is an in vivo measure of A_{2A} antagonist activity (>30% inhibition is considered to be active in this assay).[12]
[e] Not determined.

AUC (7980 ng · h/mL), a long half-life ($t_{1/2}$ = 11.3 h), and low plasma clearance (4.7 mL/min/kg). Compound **4s** also exhibited excellent oral bioavailability (F = 71%).

In conclusion, we have discovered novel heterocyclic analogs of SCH 58261 as promising adenosine A_{2A} receptor antagonists. Several compounds displayed single digit A_{2A} binding affinity and were highly selective over the A_1 receptor. Additionally, by incorporating polar heterocyclic moieties, we achieved improved aqueous solubility. The highly soluble tetrahydronaphthyridine analog **4s** demonstrated potent oral anticataleptic activity and a promising pharmacokinetic profile in rats. Further characterization of the compound **4s** and related analogs is currently in progress.

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References and notes

1. Shah, U.; Boyle, C. D.; Chackalamannil, S.; Neustadt, B. R.; Lindo, N.; Greenlee, W. J.; Foster, C.; Arik, L.; Zhai, Y.; Lachowicz, J. E.; Ng, K.; Wang, S.; Monopoli, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4199.
2. Fredholm, B. B.; Abbracchio, M. P.; Burnstock, G.; Daly, J. W.; Harden, T. K.; Jacobson, K. A.; Leff, P.; Williams, M. *Pharmacol. Rev.* **1994**, *46*, 143.
3. (a) Ferre, S.; von Euler, G.; Johansson, B.; Fredholm, B. B.; Fuxe, K. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 7238; (b) Schwarzschild, M. A., guest editor. *Prog. Neurobiol.* **2007**, *83*, 261. Special Issue: Targeting Adenosine A_{2A} Receptors in Parkinson's Disease and Other CNS Disorders.
4. (a) Zocchi, C.; Ongini, E.; Conti, A.; Monopoli, A.; Negretti, A.; Baraldi, P. G.; Dionisotti, S. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 398; (b) Baraldi, P. G.; Cacciari, B.; Spalluto, G.; Pineda de Villatoro, M. J.; Zocchi, C.; Dionisotti, S.; Ongini, E. *J. Med. Chem.* **1996**, *39*, 1164; (c) Ongini, E. *Drug Dev. Res.* **1997**, *42*, 63.
5. (a) Selectivity over A_1 is necessary to avoid cardiac side-effects.; (b) Bara-Jimenez, W.; Sherzai, A.; Dimitrova, T.; Favit, A.; Bibbiani, F.; Gillespie, M.; Morris, M. J.; Mouradian, M. M.; Chase, T. N. *Neurology* **2003**, *61*, 293; (c) Hauser, R. A.; Hubble, J. P.; Truong, D. D. *Neurology* **2003**, *61*, 297; (d) Francis, J.

E.; Cash, W. D.; Psychoyos, S.; Ghai, G.; Wenk, P.; Friedmann, R. C.; Atkins, C.; Warren, V.; Furness, P.; Hyun, J. L.; Stone, G. A.; Desai, M.; Williams, M. *J. Med. Chem.* **1988**, *31*, 1014; (e) Sarges, R.; Howard, H. R.; Browne, R. G.; Lebel, L. A.; Seymour, P. A.; Koe, B. K. *J. Med. Chem.* **1990**, *33*, 2240.

6. Baraldi, P. G.; Cacciari, B.; Romagnoli, R.; Spalluto, G.; Monopoli, A.; Ongini, E.; Varani, K.; Borea, P. A. *J. Med. Chem.* **2002**, *45*, 115.
7. (a) Neustadt, B. R.; Hao, J.; Lindo, N.; Greenlee, W. J.; Stamford, A. W.; Tulshian, D.; Ongini, E.; Hunter, J.; Monopoli, A.; Bertorelli, R.; Foster, C.; Arik, L.; Lachowicz, J.; Ng, K.; Feng, K-I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1376; (b) Silverman, L. S.; Caldwell, J. P.; Greenlee, W. J.; Kiselgof, E.; Matasi, J. J.; Tulshian, D. B.; Arik, L.; Foster, C.; Bertorelli, R.; Monopoli, A.; Ongini, E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1659.
8. All compounds in this publication were isolated and tested in free base form.
9. Intermediate **2a** is commercially available from Aldrich Chemical Company, Inc., Milwaukee, WI.
10. *Binding Assay*: Matasi, J. J.; Caldwell, J. P.; Hao, J.; Neustadt, B.; Arik, L.; Foster, C.; Lachowicz, J.; Tulshian, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1333. footnote 11. Functional assays run on selected compounds throughout the A_{2A} program indicate that similar pyrazolotriazolopyrimidines are antagonists with K_b values approximating the binding assay derived K_i values. In addition, affinity for the rat A_1 and A_{2A} receptors did not differ from affinity for the human receptor.
11. Procedure described in: Cox, K. A.; Dunn-Meynell, K.; Korfmacher, W. A.; Broske, L.; Nomeir, A. A.; Lin, C.-C.; Cayen, M. N.; Barr, W. H. *Drug Discovery Today* **1999**, *4*, 232. %CV values typically range from 10 to 30 in this assay ($n = 2$).
12. (a) Inhibition of haloperidol-induced catalepsy is an in vivo assay used to evaluate Parkinson's drugs (>30% inhibition is considered to be active in this assay); (b) Mandhane, S. N.; Chopde, C. T.; Ghosh, A. *Eur. J. Pharmacol.* **1997**, *328*, 135; Procedure described in: (c) Matasi, J. J.; Caldwell, J. P.; Zhang, H.; Fawzi, A.; Cohen-Williams, M. E.; Varty, G. B.; Tulshian, D. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3670.
13. The nephelometric (light scattering) method was used to determine the kinetic solubility of compounds. The test compound (1.0 mg) was dissolved in DMSO at 25 mM.A serial dilution into DMSO was performed and 3 μl of the compound in DMSO at various concentrations was added to the buffer (10 mM phosphate, pH 7.4). Presence of precipitate was detected by nephelometry. Solubility was defined as the highest concentration of material that did not scatter light Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **2001**, *46*, 3.
14. Tetrahydroisoquinolines **2i**, **2j**, and **10** were synthesized as described in: Sall, D. J.; Grunewald, G. L. *J. Med. Chem.* **1987**, *30*, 2208. Intermediates **2e**–**2g** are commercially available from Acros Organics, Morris Plains, NJ.
15. Benzazepine **2m** was synthesized as described in: Pecherer, B.; Sunbury, R. C.; Brossi, A. *J. Heterocycl. Chem.* **1971**, *8*, 779. The unsubstituted intermediate **2l** is commercially available from Scientific Exchange, Inc., Center Ossipee, NH.
16. The synthesis of intermediate **2r** is reported in the following reference: Shiozawa, A.; Ichikawa, Y.-I.; Ishikawa, M.; Kogo, Y.; Kurashige, S.; Miyazaki, H.; Yamanaka, H.; Sakamoto, T. *Chem. Pharm. Bull.* **1984**, *32*, 995; The synthesis of intermediate **2s** is reported in the following reference: Shiozawa, A.; Ichikawa, Y.-I.; Komuro, C.; Kurashige, S.; Miyazaki, H.; Yamanaka, H.; Sakamoto, T. *Chem. Pharm. Bull.* **1984**, *32*, 2522.
17. Intermediate **13** was synthesized as described in: Matsumura, E.; Ariga, M.; Tohda, Y. *Bull. Chem. Soc. Jpn.* **1979**, *39*, 2413.
18. Cyclization of **13** to form a 3-nitrotetrahydronaphthyridine is reported in: Harling, J. D.; Harrington, F. P.; Thompson, M. *Synth. Commun.* **2001**, *31*, 787.
19. The synthesis of intermediate **2w** is reported in: Fukui, H.; Inoguchi, K.; Nakano, J. *Heterocycles* **2002**, *56*, 257; The synthesis of intermediate **2x** is described in: Ashton, W. T.; Caldwell, C. G.; Duffy, J. L.; Mathvink, R. J.; Wang, L.; Weber, A. E. WO Patent 2004069162, 2004.