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Biaryl and heteroaryl derivatives of SCH 58261 as potent and selective adenosine A_{2A} receptor antagonists

Unmesh Shah, Craig D. Boyle *, Samuel Chackalamannil, Bernard R. Neustadt, Neil Lindo, William J. Greenlee, Carolyn Foster, Leyla Arik, Ying Zhai, Kwokei Ng, Shiyong Wang, Angela Monopoli, Jean E. Lachowicz

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

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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. We report the design and synthesis of biaryl and heteroaryl analogs of SCH 58261 which improve the A_{2A} receptor binding selectivity as well as the pharmacokinetic properties of SCH 58261. In particular, the quinoline **25** has excellent A_{2A} receptor in vitro binding affinity and selectivity, sustained rat plasma levels upon oral dosing, and is active orally in a rat behavioral assay.

Adenosine is the endogenous ligand for adenosine receptors A_1, A_{2A}, A_{2B}, and A_3, which are G-protein coupled receptors responsible for a variety of physiological functions.[1] In the CNS, adenosine receptors exhibit a discrete localization pattern that includes dopaminergic projection fields such as the striatum. Colocalization with D_2 dopamine receptors in this region[2] led to the hypothesis that A_{2A} receptors might be a target for Parkinson's Disease (PD), a debilitating motor disorder marked by degeneration of dopaminergic neurons.[3] In PD patients, the A_{2A} antagonist istradefylline was shown to improve the response rate and duration of therapeutic efficacy of a subthreshold levadopa dose.[4]

SCH 58261 is a reported A_{2A} receptor antagonist[5] with moderate selectivity over the A_1 receptor.[6] It is active in vivo when dosed intraperitoneally, but is not active upon oral administration.[7] Our goal was to optimize the structure–activity relationship (SAR) of the SCH 58261 series to improve selectivity (>100-fold over A_1) and oral pharmacokinetics in order to discover orally active A_{2A} receptor antagonists with a low potential for A_1 associated side effects.

Our initial plan (Fig. 1) was to produce biphenyl derivatives (A) to develop an SAR for A_{2A} selectivity. Secondary analogs of outer (B) and inner (C) ring heterocycles could possibly maintain an optimal A_{2A} in vitro profile while improving solubility and pharmacokinetic properties. Biphenyl analogs (A) were synthesized as shown in Scheme 1. Suzuki coupling with *p*-bromophenyl ethanol **2** followed by mesylation produced biphenyl left-hand intermediates **3**. The mesylate **3** was displaced by the anion of the SCH 58261 tricyclic core **4**[8] to yield the desired compounds **5**–**7**.[9] Outer heterocyclics (B) were produced by two methods (Schemes 1 and 2).

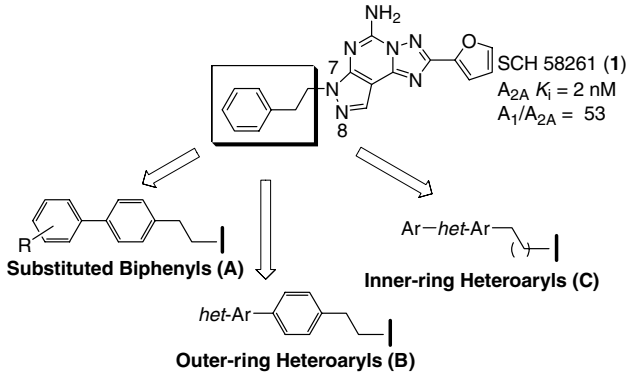

Figure 1. A_{2A} antagonist SCH 58261 and biaryl modification plans.

* Corresponding author. Tel.: +1 908 740 3503; fax +1 908 740 7152.
E-mail address: craig.boyle@spcorp.com (C.D. Boyle).

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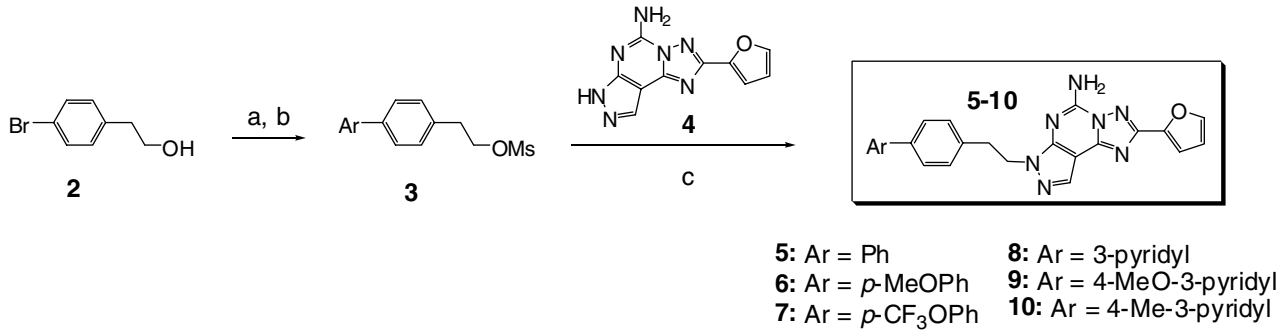
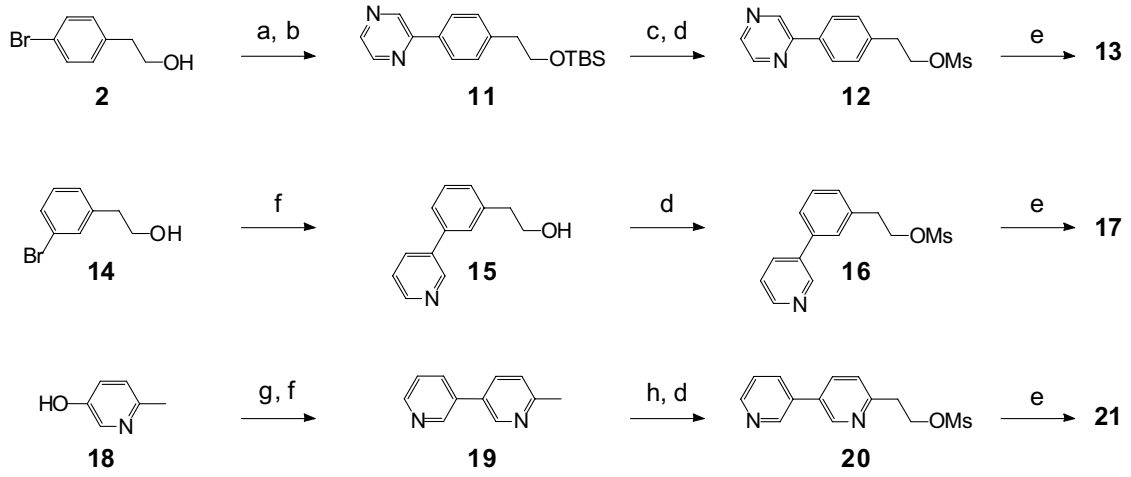


Scheme 1. Synthesis of biphenyl and outer heteroaryl analogs. Reagents and conditions: (a) $ArB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene/H_2O/EtOH, 120 °C, 16 h; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) NaH, DMF, rt, 16 h.



Scheme 2. Synthesis of heterobiaryl analogs. Reagents and conditions: (a) TBSCl, imidazole, DMF; (b) Tributyl(vinyl)tin, $Pd(PPh_3)_4$, toluene, 120 °C; (c) TBAF, THF; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C; (e) **4**, NaH, DMF, rt, 16 h; (f) Pyridine-3-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene/H_2O/EtOH, 120 °C, 16 h; (g) Tf_2O, pyridine; (h) LDA, 0 °C followed by DMF, then $NaBH_4$.

Compounds **8**–**10** were synthesized by the Suzuki coupling of appropriate heterocyclic boronic acids with bromide **2**, followed by *N*-alkylation of the subsequently formed mesylates with the tricyclic amine **4** (Scheme 1). The *m*-pyridyl analog **17** was prepared by a similar route starting from the bromide **14** (Scheme 2). Stille coupling was employed in the synthesis of the pyrazine intermediate **12** of compound **13** (Scheme 2). Inner heterocyclics (C) such as compound **21** were synthesized in a reverse order of steps. The triflate of hydroxypyridine **18** underwent Suzuki coupling to form the biaryl intermediate **19**. Chain extension provided the mesylate **20** (Scheme 2).

The SAR of biaryl analogs is summarized in Table 1. All of the biaryl analogs had excellent A_{2A} receptor affinity.[10] Compared with SCH 58261 (**1**), the biphenyl analogs (**5**–**7**) had improved selectivity for the A_{2A} receptor, but did not improve oral activity. However, incorporation of outer heteroaryl groups generally resulted in improved pharmacokinetics[11] as well as oral in vivo activity in the haloperidol-induced catalepsy assay, a measure of A_{2A} antagonist activity in the basal ganglia.[12] Specifically, compounds **8** and **10** had moderate rat plasma levels and were active orally at 1 h post-dosing. Inner heterocyclics represented by compound **21** generally gave decreased A_{2A} binding affinity and selectivity. Likewise, *m*-biaryl analogs such as **17** did not improve upon the A_{2A} selectivity of SCH 58261 and also had poor pharmacokinetics.

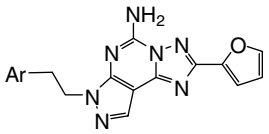
Although the *p*-heterobiaryls **8** and **10** improved upon the A_{2A} selectivity of SCH 58261 and demonstrated oral activity, their aqueous solubility was poor, and their oral pharmacokinetics suffered from fast clearance. This resulted in a low duration of in vivo activity in the oral catalepsy model. To address these issues, quinoline analogs were designed as fused heteroaryl isosteres of the biaryl moiety.

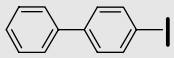
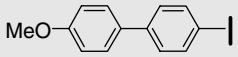
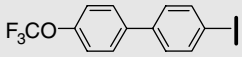
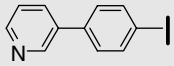
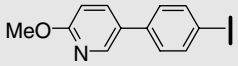
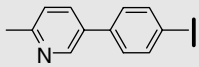
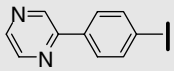
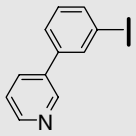
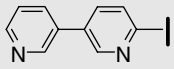
Bromoquinoline **22** was used as a starting material for most of the quinoline targets (Scheme 3). Stille coupling and hydroboration provided the alcohol **23**, which was converted to **25** from the mesylate **24**. The common aldehyde intermediate **26** was also synthesized from **23** via silyl protection and benzylic oxidation.

Aldehyde **26** proved to be a versatile intermediate in the synthesis of quinoline analogs (Scheme 3). Wittig chain extension and hydrogenation provided the ethyl intermediate **27**. Aldehyde **26** was also reduced or treated with methyl Grignard reagent to yield primary and secondary alcohols which were subsequently alkylated to form the methoxyethoxy intermediates **29** and **31**. Reductive amination of aldehyde **26** and its methyl ketone analog with morpholine gave the intermediates **33** and **36**. A slightly different route was employed to synthesize the 2-morpholinoquinoline analog (Scheme 4). The bis-chloroquinoline **38** was displaced by morpholine, and the ethanol portion of intermediate **39** was constructed via Stille coupling and hydroboration.

As shown in Table 2, the quinoline analogs generally exhibited excellent A_{2A} receptor binding affinity and selectivity over A_1. Oral rat pharmacokinetics were variable, but several compounds exhibited good plasma exposure. Most of the quinoline derivatives also

Table 1
Structure–activity relationship of biaryl analogs



Compound #	Ar	A_{2A} K_i[a] (nM)	A_1/A_{2A}	k. sol.[b] (μM)	Rat AUC[c]	Catalepsy[d] 1 or 3 mpk po, 1 h/4 h
5		1.1	109	—[e]	—	—
6		0.5	2124	<5	0	30/5 (1 mpk)
7		7.8	100	<5	67	20/0
8		1.5	255	<4	351	40/25 (1 mpk)
9		1.9	283	<5	0	—/0 (3 mpk)
10		0.6	257	<5	199	60/25
13		0.9	372	<4	114	—/3 (3 mpk)
17		5.5	66	25	0	—
21		11.4	30	—	—	—

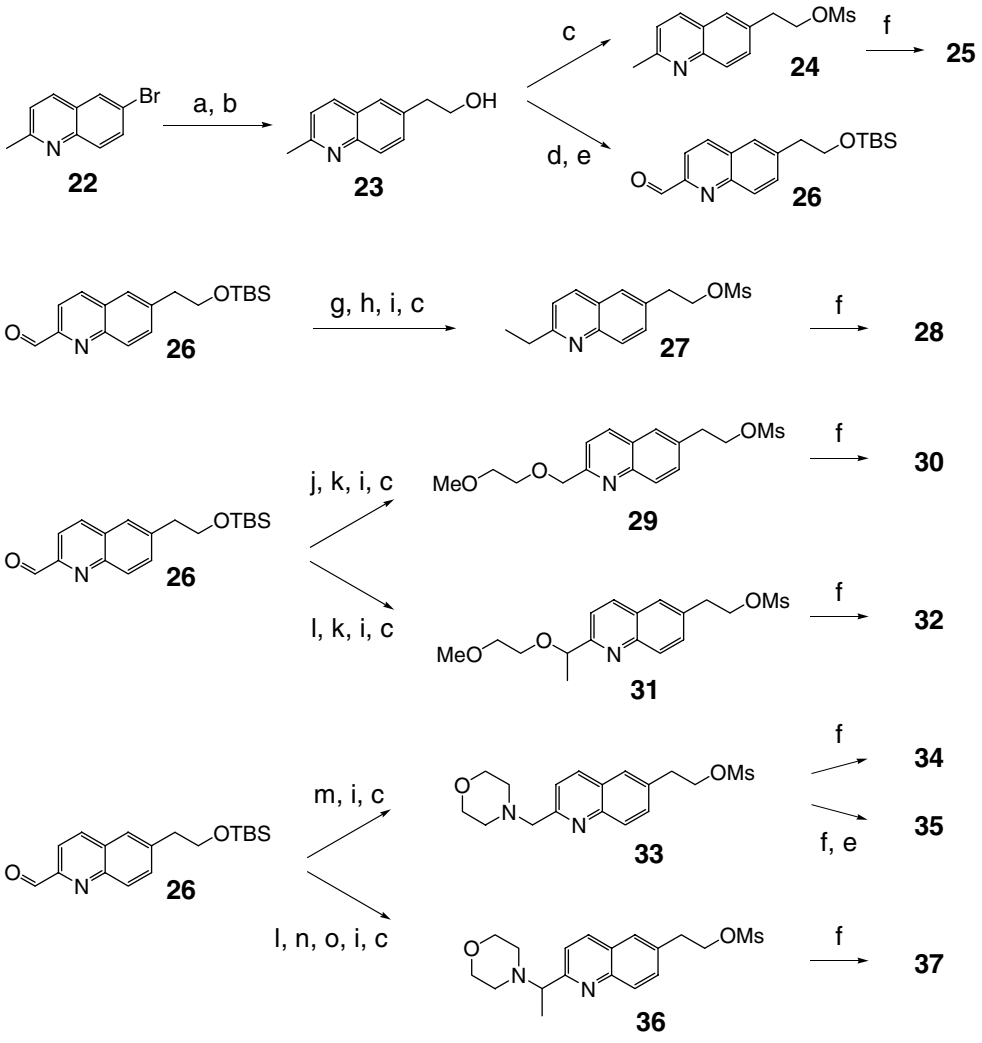
[a] For a detailed description of the human adenosine receptor binding assays see Ref. 10.
[b] A single measurement of kinetic solubility at pH 7.4.[13]
[c] Area under the curve: h.ng/mL, 0 → 6 h, 3 mpk, 20% HPβCD, po.[11]
[d] Inhibition of haloperidol-induced catalepsy is an in vivo measure of A_{2A}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

improved upon the solubility of their biaryl counterparts. However, the more soluble compounds such as **34**, **35** and **37** tended to be less active in the catalepsy assay, which could be due to a lower ability of polar compounds to reach the striatum. The methylquinoline **25** had a good pharmacokinetic profile with sustained plasma levels over 4 h (Fig. 2). The in vivo duration of compound **25** was supported by the catalepsy assay, as activity was demonstrated at both 1 and 4 h post-dosing. Furthermore, quinoline **25** was dosed down to 1 mpk in the catalepsy assay and was also active at the 4-h timepoint.

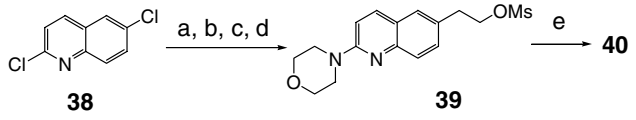
In conclusion, initial biaryl targets based on the SCH 58261 template improved A_{2A} receptor selectivity over A_1, and outer heteroaryl analogs showed a modest pharmacokinetic improvement. Quinoline isosteres maintained excellent in vitro properties while improving upon the pharmacokinetics of SCH 58261. Ultimately, the methylquinoline analog **25** proved to be a superior A_{2A} receptor antagonist in terms of binding affinity, selectivity, PK and oral activity in the catalepsy assay. Further optimization of this series of A_{2A} receptor antagonists will be disclosed in future publications.

Acknowledgments

The authors thank Professors Ronald Breslow and Scott Rychnovsky, Drs. Michael Graziano, John Hunter, John Piwinski, Andrew Stamford, Catherine Strader and Geoffrey Varty for helpful discussions. We also thank Drs. Mark Liang, Jesse Wong and Mr. Y. Jin for providing the tricyclic intermediate **4**. In addition, we thank Drs. Charles McNemar, William Windsor, and Mr. Ashwin Ranchod for providing solubility data. We also thank Drs. Pradip Das and Ben Pramanik for obtaining analytical data.



Scheme 3. Synthesis of quinoline analogs. Reagents and conditions: (a) Tributyl(vinyl)tin, $Pd(Ph_3P)_4$, DMF, 100 °C; (b) 9-BBN, THF; then aq NaOH, H_2O_2; (c) MsCl, Et_3N, CH_2Cl_2; (d) TBSCl, imidazole, DMAP, DMF; (e) SeO_2, dioxane, 100 °C; (f) **4**, NaH, DMF, rt, 16 h; (g) *n*-BuLi, THF, 0 °C, $MePPh_3Br$; then **26**; (h) H_2, 10% Pd/C, MeOH; (i) TBAF, THF; (j) $NaBH_4$, MeOH; (k) NaH, DMF, $BrCH_2CH_2OMe$; (l) MeMgBr, THF, 0 °C; (m) Morpholine, AcOH, $NaBH_3CN$, MeOH; (n) Dess–Martin periodinane, CH_2Cl_2, $NaHCO_3$; (o) Morpholine, AcOH, $NaBH(OAc)_3$, DCE.



Scheme 4. Synthesis of morpholine analog. Reagents and conditions: (a) Morpholine, K_2CO_3, DMF, 120 °C; (b) Tributyl(vinyl)tin, $Pd_2(dba)_3$, P^tBu_3, CsF, dioxane, 90 °C; (c) 9-BBN, THF; then aq NaOH, H_2O_2; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C; (e) **4**, NaH, DMF, rt, 16 h.

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5. (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.
6. (a) Selectivity over A_1 is necessary to avoid cardiac side effects.; (b) Hauser, R. A.; Hubble, J. P.; Truong, D. D. *Neurology* **2003**, *61*, 297; (c) 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; (d) Sarges, R.; Howard, H. R.; Browne, R. G.; Lebel, L. A.; Seymour, P. A.; Koe, B. K. *J. Med. Chem.* **1990**, *33*, 2240; (e) Also see Ref. 4.
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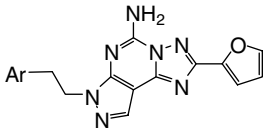
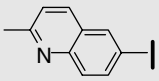
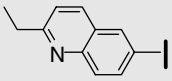
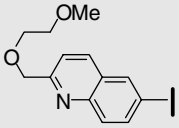
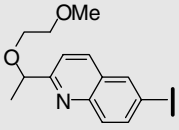
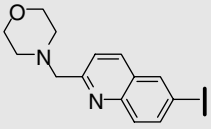
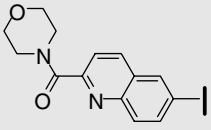
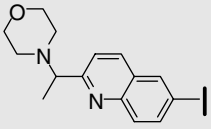
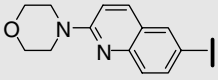
9. All of the final compounds in this publication were synthesized by the mesylate alkylation of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine **4** shown in Scheme 1. A mixture of 7- and 8-alkylated products was formed. The *N*-8 alkylated analogs were generally inactive.
10. *Binding Assay:* Matasi, J. J.; Caldwell, J. P.; Hao, J.; Neustadt, B.; Arik, L.; Foster, C. J.; Lachowicz, J.; Tulshian, D. B. *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 Discov. Today* **1999**, *4*, 232. %CV values typically range from 10 to 30 in this assay ($n = 2$).

Table 2
Structure–activity relationship of quinoline analogs



Compound #	Ar	A_{2A} K_i[a] (nM)	A_1/A_{2A} (μM)	k. sol.[b]	Rat AUC[c]	Catalepsy[d] 3 mpk po, 1 h/4 h
25		2.4	169	6	1405	86/38
28		2.7	242	<2.5	450	43/38
30		2.8	436	12	68	0/0
32		1.5	1320	–[e]	0	–
34		2.3	364	37	656	0/0
35		1.6	501	100	–	23/13
37		1.3	1278	100	7489	28/13
40		1.8	2139	–	6	–

[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.

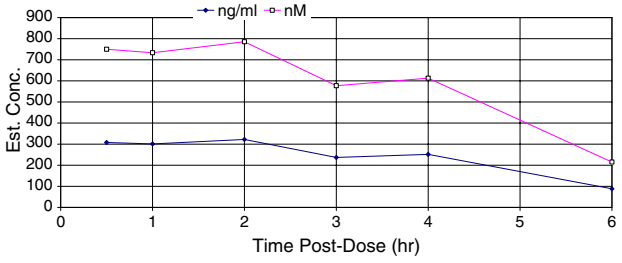


Figure 2. Rat AUC of compound **25**.

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. K. *Eur. J. Pharmacol.* **1997**, *328*, 135; (c) Procedure described in 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 Deliv. Rev.* **2001**, *46*, 3.