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Highly selective c-Jun *N*-terminal kinase (JNK) 2 and 3 inhibitors with in vitro CNS-like pharmacokinetic properties prevent neurodegeneration

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ABSTRACT

In this Letter, we describe the discovery of selective JNK2 and JNK3 inhibitors, such as **10**, that routinely exhibit >10-fold selectivity over JNK1 and >1000-fold selectivity over related MAPKs, p38α and ERK2. Substitution of the naphthalene ring affords an isoform selective JNK3 inhibitor, **30**, with approximately 10-fold selectivity over both JNK1 and JNK2. A naphthalene ring penetrates deep into the selectivity pocket accounting for the differentiation amongst the kinases. Interestingly, the gatekeeper Met146 sulfide interacts with the naphthalene ring in a sulfur-π stacking interaction. Compound **38** ameliorates neurotoxicity induced by amyloid-β in human cortical neurons. Lastly, we demonstrate how to install propitious in vitro CNS-like properties into these selective inhibitors.

The c-Jun *N*-terminal kinases (JNKs), a.k.a. stress-activated protein kinases (SAPKs), are serine/threonine targeted members of the mitogen-activated protein kinases (MAPKs).[1] Three variants in the JNK family are known, JNK1, JNK2, and, JNK3; JNK3 is localized primarily in the brain while JNK1 and JNK2 are expressed ubiquitously. JNK1 performs important functions in maintenance and regulation of the central nervous system (CNS), thus JNK1 knockout mice suffer from progressive neurodegeneration.[2] JNK2, JNK3, and dual JNK2 and JNK3 knockout mice were resistant to induced neurodegeneration when compared to their *wild type* counterparts.[3] Since JNK2 and JNK3 both play a prominent role in apoptosis, they are potential therapeutic targets for neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and cerebral ischaemia.[4] Indeed, administration of JNK inhibitors in vivo confers protection against neuronal degradation.[5] In order to avoid untoward side effects, a selective inhibitor[6] would be necessary (e.g., p38α, a closely related MAPK,[7] is involved in maintaining synaptic plasticity in the CNS).[8]

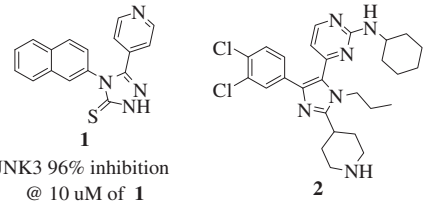

Figure 1. JNK3 kinase inhibitors and selectivity.

Compound **1** was discovered from our in-house compound collection during a screening campaign to identify compounds with JNK activity, and broad selectivity against other kinases (Fig. 1). Of the 262 kinases screened only JNK3 and c-Raf had their activity reduced by more than 50% at 10 μM of **1**.[9] This was all the more

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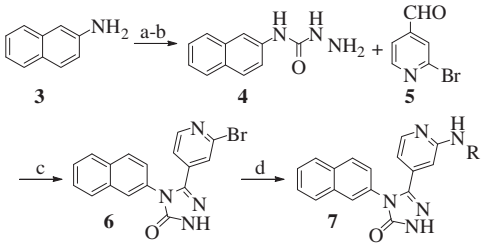
surprising since the closely related analog **2**[10] with the 1,2-dichlorobenzene, a naphthalene ring isostere,[11] does not display much selectivity over p38α or JNK isoforms. This prompted us to investigate if we could improve the activity against JNK while maintaining the selectivity profile. We deemed the thiourea to be pharmaceutically unacceptable,[12] thus the first operation was to replace the thiocarbonyl with a carbonyl so the triazolone **9** (Table 1) became the starting point.

Our first priority was to append an amino group bearing a hydrophobic substituent at the 2-position of the pyridine which should lead to a substantial increase in potency based on the literature precedent.[10] A halide at the 2-position of the pyridyl ring would allow for the rapid synthesis of analogs via transition metal-mediated cross-couplings. Synthesis of the key intermediate **6** was accomplished in an expedient manner (Scheme 1). Commercially available starting material **3** was reacted with triphosgene forming an isocyanate that was trapped with hydrazine to yield the semicarbazide **4**. Condensation of **4** with the aldehyde **5** afforded the semicarbazone that was subjected to an in situ oxidative ring closure.[13] This route furnished copious amounts of the synthetically versatile bromide **6** for further elaboration. The preferred method to introduce the amino group was through the use of palladium catalyzed cross-coupling methodologies.[14]

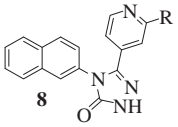
The first target was the cyclohexylamine **10** which resulted in nearly 1000-fold increase in potency relative to the parent **9**

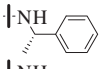
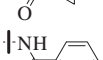


Scheme 1. Reagents and conditions: (a) triphosgene, PhMe, 95 °C; (b) hydrazine, PhMe, 84% over two steps; (c) EtOH, 2 h, then K_3PO_4, 95 °C, 5 min, then $K_3Fe(CN)_6$, H_2O, 95 °C, 48%; (d) H_2N–R, Pd_2dba_3–$CHCl_3$, BINAP or Xantphos, NaO-*t*Bu or Cs_2CO_3, PhMe, 80 °C.

(Table 1). The thiocarbonyl analog of **10** is equipotent (not shown). Gratifyingly, no ERK2 or p38α activity was evident, and the compound was selective for JNK2 and JNK3 over JNK1. Additionally, a screening against a panel of 38 kinases demonstrated that **10** maintained a clean profile.[9] Only when a heteroatom was placed at the 3-position of the newly appended ring, **11** and **18**, was ERK2 activity observed. In fact, a panel screen against the same 38 kinases with **11** exposed a deterioration in the selectivity of inhibitor.[9] Five-membered rings, **13** and **19**, displayed moderate potency against JNK2 and JNK3 but lost all activity against JNK1

Table 1
SAR of amino groups at the pyridyl 2-position[a]



#	R	JNK3 IC_{50} (μM)	JNK2 IC_{50} (μM)	JNK1 IC_{50} (μM)	ERK2 IC_{50} (μM)	P38α IC_{50} (μM)
9	–H	16	32	>50	>50	>50
10		0.024	0.069	1.0	>50	>50
11[b]		0.032	0.13	0.74	22	>50
12		0.085	0.25	1.8	>50	>50
13		0.13	0.35	>50	>50	>50
14		0.070	0.22	1.8	>50	>50
15		0.13	0.39	3.9	>50	>50
16		0.061	0.47	5.7	>50	>50
17		0.040	0.11	2.2	>50	>50
18		0.25	0.95	3.3	14	>50
19		0.21	0.65	>50	>50	>50
20		3.9	>5.0	>5.0	>5.0	>5.0
21		0.41	1.5	7.2	>50	>50
22		0.12	0.44	4.6	>50	>50
23		0.59	4.4	>50	>50	>50

[a] Values are means of at least three experiments at 10 μM ATP concentration, see Supplementary data for experimental details.
[b] 1:1 mixture of enantiomers.

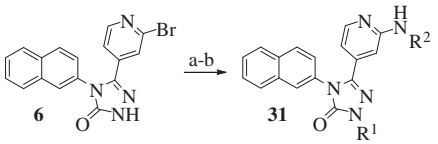
in addition to lack of discernable activity against ERK2 or p38α. We attempted to induce p38α activity with (*S*)-α-methylbenzylamine, **20**, since this piece is known to be quite active against p38α on similar templates,[7] but the naphthalene ring remained the dominant factor in determining the selectivity. Aryl rings, **16** and **17**, in place of saturated ring systems afforded inhibitors with comparable activity and selectivity. Amides **21**–**23** were also explored but the results for JNK2 and JNK3 activity were sub-optimal.

Modifications of the naphthalene ring were also explored (Table 2). The 4-aminopyran was used to prepare analogs due to better in vitro pharmacokinetic properties associated with it. This will be discussed vide infra (Table 4). Fluoride substitution at R^1, the 6-postion, on the naphthalene ring of **25** was potency neutral for JNK2 and JNK3. However, substituents other than fluorine **26** and **27** at the 6-position led to a decrease in potency. The 8-position, R^2, was more tolerant of substitution as demonstrated by analogs **28**–**30**. The chloride **30** had the JNK3 activity enhanced by sixfold and was approximately 10-fold selective over both JNK1 and JNK2.

Lastly, N-substitutions on the triazolone were explored. The triazolone ring was N-alkylated via a Mitsunobu reaction with intermediate **6** and the amino group was appended subsequently (vida supra Scheme 2).

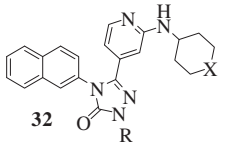
Substitution of the NH of the triazolone ring system led to only modest increases in potency relative to the parent compounds **10** and **12** (Table 3). Analogs with basic piperidine side chains **39** and **40** had a deleterious affect on potency while modulating the basicity of the piperidine[15] as with **41** resulted in an increase in potency relative to the parent **12**. Neutralizing the basicity of the piperidine with the methylcarbamate analog **42** returned full kinase potency. These substituents served a dual purpose: first they augmented the selectivity of inhibitor and secondly they mitigated the Permeability-glycoprotein (P-gp) liability vide infra (Table 4). A panel screen of 38 kinases revealed a modest erosion in the selectivity of **12**, but upon N-substitution of the triazolone the selectivity returned (**12** vs **37**).[9] N-Substitution of **10** did not affect the selectivity profile (**10** vs **34** and **38**).[9] In addition to improving the selectivity profile, N-substitution also appears to be necessary for cellular activity in the human cortical neuronal amyloid-β neurotoxicity assay.[9,16] Compound **38** has an EC_{50} of 12 μM whereas the EC_{50} of the parent compound **10** was >50 μM despite possessing nearly identical activities against JNK1–3 in the biochemical assay. This result indicates that inhibitors of JNK2 and 3 are viable neuroprotective agents.

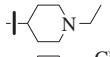
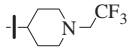
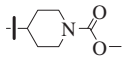
In order for these inhibitors to be effective neuroprotective agents, they must have the appropriate in vitro pharmacokinetic parameters, most notably a high rate of permeability and low P-gp efflux, to pass through the blood–brain barrier and enter into the parenchyma of the brain. Illustrated in Table 4 are the in vitro pharmacokinetic properties of selected analogs. The (tetrahydropyran-4-yl)amine **12** imparts a significant improvement to the passive permeability as is evident when compared to the



Scheme 2. Reagents and conditions: (a) HOR^1, DIAD, polymer support-PPh_2, THF, 0 °C, ca. 50%; (b) H_2NR^2, Pd_2dba_3–$CHCl_3$, BINAP, NaO-*t*Bu, PhMe.

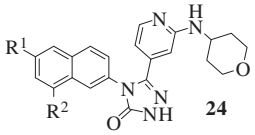
Table 3
SAR of substitution on the triazolone[a]



#	X	R	JNK3 IC_{50} (μM)	JNK2 IC_{50} (μM)	JNK1 IC_{50} (μM)	ERK2 IC_{50} (μM)	P38α IC_{50} (μM)
10	CH_2	–H	0.024	0.069	1.0	>50	>50
12	O	–H	0.085	0.25	1.8	>50	>50
33	CH_2		0.022	0.061	0.42	>50	>50
34	CH_2		0.016	0.097	0.42	>50	>50
35[b]	O		0.092	0.32	3.8	>50	>50
36	O		0.10	0.15	1.4	>50	>50
37	O		0.054	0.093	0.99	>50	>50
38	CH_2		0.029	0.097	0.70	>50	>50
39	O		0.16	0.53	4.5	>5.0	>50
40	O		0.28	2.0	>5.0	na	na
41	O		0.036	0.17	0.90	na	na
42	O		0.024	0.058	0.36	>5.0	>50

[a] Values are means of at least three experiments at 10 μM ATP concentration, see Supplementary data for experimental details.
[b] 1:1 mixture of enantiomers.

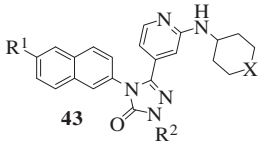
Table 2
SAR of naphthyl substituents[a]



#	R^1	R^2	JNK3 IC_{50} (μM)	JNK2 IC_{50} (μM)	JNK1 IC_{50} (μM)	ERK2 IC_{50} (μM)	P38α IC_{50} (μM)
12	H	H	0.085	0.25	1.8	>50	>50
25	F	H	0.070	0.19	0.74	>50	>50
26	NH_2	H	0.95	5.3	1.7	>50	>50
27	Br	H	0.43	0.78	4.2	>50	>50
28	H	F	0.054	0.38	>0.50	>50	>50
29	H	NH_2	0.094	0.57	2.6	>50	>50
30	H	Cl	0.014	0.15	0.11	na	na

[a] Values are means of at least three experiments at 10 μM ATP concentration, see Supplementary data for experimental details.

Table 4
In vitro pharmacokinetic properties[a]



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#	X	R^1	R^2	JNK3 IC_{50} (μM)	P_{app} (nm/s)	P-gp efflux ratio	Ox. Met.[b] (m, h)
10	CH_2	H	H	0.024	9	2.6	10, 57
12	O	H	H	0.085	157	12	72, 73
25	O	F	H	0.070	73	na	100, 88
35[c]	O	H		0.092	218	1.6	23, 27
36	O	H		0.10	51	1.5	12, 59
37	O	H		0.054	185	1.4	2, 40
38	CH_2	H		0.029	81	na	48, 2

[a] See Supplementary data for experimental details.
[b] Percent remaining after 30 min incubation with liver microsomes (m = mouse and h = human).
[c] 1:1 mixture of enantiomers.

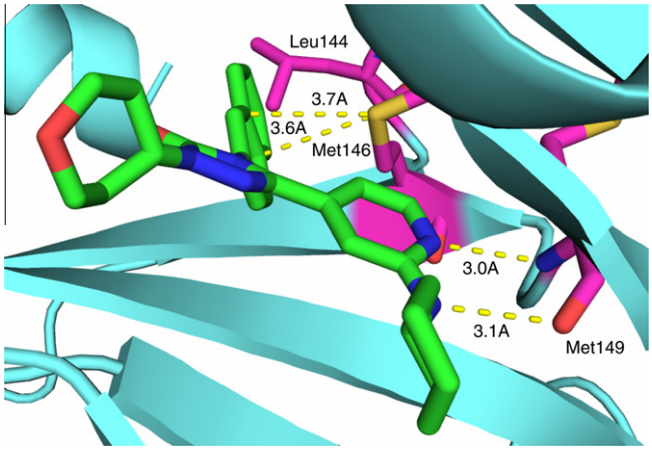

Figure 2. Compound **34** bound to JNK3 kinase (1.7 Å resolution). The aminopyridine is depicted hydrogen bonding with the Met149 of the hinge while the gatekeeper Met146 side chain is depicted interacting with the naphthalene ring via a sulfur-π interaction. The PDB code is 3OY1.

cyclohexylamine analog **10**. Also, this perturbation leads to improved metabolic stability in a microsomal assay (**10** vs **12**). Fluorination on the naphthalene ring at the 6-position, **25**, improves the metabolic stability as well. N-Substitution of the triazolone ring ameliorates the P-gp efflux liability (**12** vs **35**–**37**). This implicates the lone hydrogen bond donor on the triazolone as the egregious moiety inducing the P-gp activity, especially since each appendage bears a hydrogen bond acceptor. Also, N-substitution improves the permeability of the cyclohexyl series.

A crystal structure of **34** bound to JNK3 reveals that the naphthalene ring juts deep into the selectivity pocket (Fig. 2). Other MAPKs do not have the capacity to accommodate the naphthalene ring in the selectivity pocket, thus accounting for the high degree of selectivity for this scaffold within the MAPK family. The isoform selectivity for JNK2 and JNK3 over JNK1 can be rationalized as well: JNK1 has a bulky Ile106 residue in the selectivity pocket that will not accommodate the naphthalene substituent, whereas JNK2 and JNK3 are less sterically encumbered with Leu144 at that location. The tactic of targeting these residues for isoform selectivity has been exploited previously with different templates.[17] Similar templates have not reported selectivity for the JNKs over the MAPKs to the extent we have reported here.[18] The distances between the malleable sulfide side chain of the gatekeeper Met146 and the bridgehead carbons of the naphthalene ring are 3.6 Å and 3.7 Å suggesting a sulfur-π stacking interaction is present.[19]

In summary, we have developed a series of highly selective JNK2 and JNK3 inhibitors. This selectivity originates from the naphthalene ring protruding deep into the selectivity pocket. Additionally, these inhibitors exhibit auspicious in vitro CNS-like pharmacokinetic properties. This amalgamated data suggests these compounds are promising agents for neurodegenerative disorders.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.11.010.

References and notes

1. (a) Siddiqui, M. S.; Reddy, P. A. *J. Med. Chem.* **2010**, *53*, 3005; (b) Bogoyevitch, M. A.; Ngoei, K. R. W.; Zhao, T. T.; Yeap, Y. Y. C.; Ng, D. C. H. *Biochim. Biophys. Acta* **2010**, *1804*, 463; (c) Haeusgen, W.; Boehm, R.; Zhao, Y.; Herdegen, T.; Waetzig, V. *Neuroscience* **2009**, *161*, 951; (d) LoGrasso, P.; Kamenecka, T. *Mini-Rev. Med. Chem.* **2008**, *8*, 755; (e) Bogoyevitch, M. A.; Arthur, P. G. *Biochim. Biophys. Acta* **2008**, *1784*, 76; (f) Bogoyevitch, M. A.; Kobe, B. *Microbiol. Mol. Biol. Rev.* **2006**, *70*, 1061; (g) Bogoyevitch, M. A. *BioEssays* **2006**, *28*, 923; (h) Karin, M.; Gallagher, E. *IUBMB Life* **2005**, *57*, 283.
2. Chang, L.; Jones, Y.; Ellisman, M. H.; Goldstein, L. S.; Karin, M. *Dev. Cell* **2003**, *4*, 521.
3. (a) Hunot, S.; Vila, M.; Teismann, P.; Davis, R. J.; Hirsch, E. C.; Przedborski, S.; Rakic, P.; Flavell, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 665; (b) Yang, D. D.; Kuan, C.-Y.; Whitmarsh, A. J.; Rincón, M.; Zheng, T. S.; Davis, R. J.; Rakic, P.; Flavell, R. A. *Nature* **1997**, *389*, 865.
4. (a) Kim, E. K.; Choi, E.-J. *Biochim. Biophys. Acta* **2010**, *1802*, 396; (b) Salh, B. *Expert Opin. Ther. Targets* **2007**, *11*, 1339; (c) Borsello, T.; Forloni, G. *Curr. Pharm. Des.* **2007**, *13*, 1875; (d) Zhang, G.-Y.; Zhang, Q.-G. *Expert Opin. Investig. Drugs* **2005**, *14*, 1373; (e) Kuan, C.-Y.; Burke, R. E. *Curr. Drug Targets CNS Neurol. Disord.* **2005**, *4*, 63; (f) Wang, W.; Ma, C.; Mao, Z.; Li, M. *Drug News Perspect.* **2004**, *17*, 646; (g) Resnick, L.; Fennell, M. *Drug Discovery Today* **2004**, *9*, 932; (h) Harper, S. J.; Wilkie, N. *Expert Opin. Ther. Targets* **2003**, *7*, 187; (i) Manning, A. M.; Davis, R. J. *Nat. Rev. Drug Disc.* **2003**, *2*, 554; (j) Kuan, C.-Y.; Whitmarsh, A. J.; Yang, D. D.; Liao, G.; Schloemer, A. J.; Dong, C.; Bao, J.; Banasiak, K. J.; Haddad, G. G.; Flavell, R. A.; Davis, R. J.; Rakic, P. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 15184.
5. (a) Braithwaite, S. P.; Schmid, R. S.; He, D. N.; Sung, M.-L. A.; Cho, S.; Resnick, L.; Monaghan, M. M.; Hirst, W. D.; Essrich, C.; Reinhart, P. H.; Lo, D. C. *Neurobiol. Dis.* **2010**, *39*, 311; (b) Carboni, S.; Boschert, U.; Gaillard, P.; Gotteland, J.-P.; Gillon, J.-Y.; Vitte, P.-A. *Br. J. Pharmacol.* **2008**, *153*, 157; (c) Rawal, N.; Parish, C.; Castelo-Branco, G.; Arenas, E. *Cell Death Diff.* **2007**, *14*, 381; (d) Carboni, S.; Hiver, A.; Szyndralewiez, C.; Gaillard, P.; Gotteland, J.-P.; Vitte, P.-A. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 25; (e) Borsello, M.; Clarke, P. G. H.; Hirt, L.; Vercelli, A.; Repici, M.; Schorderet, D. F.; Bogousslavsky, J.; Bonny, C. *Nat. Med.* **2003**, *9*, 1180.
6. (a) Miloso, M.; Tredici, G. *Curr. Enzyme Inhib.* **2007**, *3*, 298; (b) Thaimattam, R.; Banerjee, R.; Miglani, R.; Iqbal, J. *Curr. Pharm. Des.* **2007**, *13*, 2751; (c) Graczyk, P. P. *J. Med. Chem.* **2007**, *50*, 5773; (d) Scapin, G. *Curr. Drug Targets* **2006**, *7*, 1443; (e) Knight, Z. A.; Shokat, K. M. *Chem. Biol.* **2005**, *12*, 621; (f) McInnes, C.; Fischer, P. M. *Curr. Pharm. Des.* **2005**, *11*, 1845; (g) Fischer, P. M. *Curr. Med. Chem.* **2004**, *11*, 1563; (h) Luo, Y. *Curr. Opin. Mol. Ther.* **2005**, *7*, 251; (i) Parang, K.; Sun, G. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 617; (j) Parang, K.; Till, J. H.; Ablooglu, A. J.; Kohanski, R. A.; Hubbard, S. R.; Cole, P. A. *Nat. Struct. Biol.* **2001**, *8*, 37.
7. (a) Peifer, C.; Wagner, G.; Laufer, S. *Curr. Top. Med. Chem.* **2006**, *6*, 113; (b) Wrobleski, S. T.; Doweyko, A. M. *Curr. Top. Med. Chem.* **2005**, *5*, 1005; (c) Bolós, J. *Mini-Rev. Med. Chem.* **2005**, *5*, 857; (d) Norris, J. L.; Williams, K. P.; Janzen, W. P.; Hodge, C. N.; Blackwell, L. J.; Popa-Burke, I. G. *Lett. Drug Des. Discovery* **2005**, *2*, 516; (e) Chen, Z.; Gibson, T. B.; Robinson, F.; Silvestro, L.; Pearson, G.; Xu, B. e.; Wright, A.; Vanderbilt, C.; Cobb, M. H. *Chem. Rev.* **2001**, *101*, 2449; (f) Adams, J. L.; Badger, A. M.; Kumar, S.; Lee, J. C. *Prog. Med. Chem.* **2001**, *38*, 1; (g) Lee, J. C.; Kassis, S.; Kumar, S.; Badger, A.; Adams, J. L. *Pharmacol. Ther.* **1999**, *82*, 389.

8. (a) Aouadi, M.; Binetruy, B.; Caron, L.; Le Marchand-Brustel, Y.; Bost, F. *Biochimie* **2006**, *88*, 1091; (b) Guan, Z.; Kim, J.-H.; Lomvardas, S.; Holick, K.; Xu, S.; Kandel, E. R.; Schwartz, J. H. *J. Neurosci.* **2003**, *23*, 7317; (c) Bolshakov, V. Y.; Carboni, L.; Cobb, M. H.; Siegelbaum, S. A.; Belardetti, F. *Nat. Neurosci.* **2000**, *3*, 1107; (d) Fukunaga, K.; Miyamoto, E. *Mol. Neurobiol.* **1998**, *16*, 79.
9. See Supplementary data.
10. (a) Scapin, G.; Patel, S. B.; Lisnock, J.; Becker, J. W.; LoGrasso, P. V. *Chem. Biol.* **2003**, *10*, 705; (b) ATP concentration of 1 μM was kindly communicated to us by Professor Philip V. LoGrasso.
11. Lima, L. M.; Barreiro, E. *J. Curr. Med. Chem.* **2005**, *12*, 23.
12. Kalgutkar, A. S.; Gardner, I.; Obach, R. S.; Schaffer, C. L.; Callegari, E.; Henne, K. R.; Mutlib, A. E.; Dalvie, D. K.; Lee, J. S.; Nakai, Y.; O'Donnell, J. P.; Boer, J.; Harriman, S. P. *Curr. Drug Metab.* **2005**, *6*, 161.
13. Husain, S.; Srinivasan, V. R.; Surendra Nath, T. G. *Ind. J. Chem.* **1971**, *9*, 642.
14. (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043; (b) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101; (c) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
15. Morgenthaler, M.; Schweizer, E.; Hoffman-Röder, A.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diederich, F.; Kansy, M.; Muller, K. *ChemMedChem* **2007**, *2*, 1100.
16. (a) Wright, S.; Malinin, N. L.; Powell, K. A.; Yednock, T.; Rydel, R. E.; Griswold-Prenner, I. *Neurobiol. Aging* **2007**, *28*, 226; (b) Wogulis, M.; Wright, S.; Cunningham, D.; Chilcote, T.; Powell, K.; Rydel, R. E. *J. Neurosci.* **2005**, *25*, 1071.
17. (a) Christoper, J. A.; Atkinson, F. L.; Bax, B. D.; Brown, M. J. B.; Champigny, A. C.; Chuang, T. T.; Jones, E. J.; Mosley, J. E.; Musgrave, J. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2230; (b) Angell, R. M.; Atkinson, F. L.; Brown, M. J.; Chuang, T. T.; Christopher, J. A.; Cichy-Knight, M.; Dunn, A. K.; Hightower, K. E.; Malkakorpi, S.; Musgrave, J. R.; Neu, M.; Rowland, P.; Shea, R. L.; Smith, J. L.; Somers, D. O.; Thomas, S. A.; Thompson, G.; Wang, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1296; (c) Swahn, B-M.; Xue, Y.; Arzel, E.; Kallin, E.; Magnus, A.; Plobeck, N.; Viklund, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1397; (d) Swahn, B-M.; Huerta, F.; Kallin, E.; Malmström, J.; Weigelt, T.; Viklund, J.; Womack, P.; Xue, Y.; Öhberg, L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5095.
18. (a) Humphries, P. S.; Lafontaine, J. A.; Agree, C. S.; Alexander, D.; Chen, P.; Do, Q.-Q. T.; Li, L. Y.; Lunney, E. A.; Rajapakse, R. J.; Siegel, K.; Timofeevski, S. L.; Wang, T.; Wilhite, D. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2099; (b) Graczyk, P. P.; Khan, A.; Bhatia, G. S.; Palmer, V.; Medland, D.; Numata, H.; Oinuma, H.; Catchick, J.; Dunne, A.; Ellis, M.; Smales, C.; Whitfield, J.; Neame, S. J.; Shah, B.; Wilton, D.; Morgan, L.; Patel, T.; Chung, R.; Desmond, H.; Staddon, J. M.; Sato, N.; Ioune, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4666.
19. (a) Bissantz, C.; Kuhn, B.; Stahl, M. *J. Med. Chem.* **2010**, *53*, 5061; (b) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210; (c) Traxler, P.; Green, J.; Mett, H.; Séquin, U.; Furet, P. *J. Med. Chem.* **1999**, *42*, 1018.