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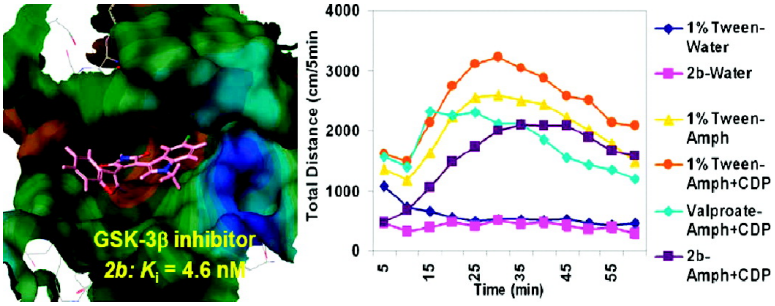

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Structure-Based Design Leads to the Identification of Lithium Mimetics That Block Mania-like Effects in Rodents. Possible New GSK-3β Therapies for Bipolar Disorders

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Abstract: More than two million American adults, or approximately one percent of the population 18 years or older, suffer from bipolar disorder. Current treatments include the so-called "mood stabilizers," lithium and valproic acid. Both are relatively dated drugs that are only partially effective and produce various undesirable side effects including weight gain. Based upon continued efforts to understand the molecular target for lithium, it now appears that specific inhibitors of the enzyme glycogen synthase kinase-3β (GSK-3β) may mimic the therapeutic action of mood stabilizers and might therefore allow for the design of improved drugs for treating patients with bipolar disorder as well as certain neurodegenerative disorders. Furthermore, the pro-apoptotic properties of the GSK-3 enzyme suggest the possible use of such inhibitors as neuroprotective agents. In fact, neuroprotection may contribute to the treatment of mood disorders. The present chemistry, modeling, and biology efforts have identified 3-benzofuranyl-4-indolylmaleimides as potent and relatively selective GSK-3β inhibitors. The best ligand in this series (having a K_i value of 4.6 nM against GSK-3β) was studied in a novel mouse model of mania that has recently been validated with several clinically effective mood stabilizers. This study presents the first demonstration of the efficacy of a GSK-3β inhibitor in this mouse model of mania. Selective brain penetrable GSK-3 ligands like those described herein become valuable research tools in better defining the role of this multifaceted kinase in both physiological and pathophysiological events.

Introduction

On the basis of continued efforts to understand the molecular target for lithium, it now appears that specific inhibitors of the enzyme glycogen synthase kinase-3β (GSK-3β) may mimic the therapeutic action of mood stabilizers and might therefore allow for the design of improved drugs for treating patients with bipolar disorder as well as certain neurodegenerative disorders. GSK-3 is a serine/threonine protein kinase, which was initially described as a key enzyme involved in glycogen metabolism[1,2] but is now known to regulate a diverse array of cell functions.[3] GSK-3 phosphorylates and thereby regulates the function of many metabolic, signaling, and structural proteins.[4] GSK-3 also regulates cell survival, as it facilitates a variety of apoptotic mechanisms.[5] There are two highly homologous forms of GSK-3 in mammals, GSK-3α and GSK-3β.

The line of evidence leading to the proposal that GSK-3 plays an important role in the action of mood stabilizers and possibly in the pathobiology of mood disorders has recently been summarized.[6] The stimulatory action of GSK-3 inhibition on β-catenin protein levels in the hippocampus is currently believed to be at the center of the putative therapeutic action of treatments aimed at moderating mood disorders.[7,8] Furthermore, GSK-3β regulates axon growth and synaptic remodeling under the control of mood stabilizing drugs.[9] In addition, in cultured cells, GSK-3β modulates brain-derived neurotrophic factor signaling.[10] Taken together, these studies have led to speculation on the role of the GSK-3-related Wnt signaling pathway in mood disorders.[11] Dysfunction of the Wnt pathway has also been implicated in the pathophysiology of Alzheimer's disease and schizophrenia.

Hyperactive GSK-3 may be an early contributory factor in apoptosis and neuronal death. Since GSK-3 inhibition exerts a dramatic neuroprotective action, it has been proposed that the

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(1) Woodgett, J. R. *EMBO J.* **1990**, *9*, 2431.
(2) Welsh, G. I.; Proud, C. G. *Biochem. J.* **1993**, *294*, 625.
(3) Cohen, P.; Frame, S. *Nat. Rev. Mol. Cell. Biol.* **2001**, *2*, 769.
(4) Dominguez, I.; Green, J. B. *Dev. Biol.* **2001**, *235*, 303.
(5) Kim, L.; Kimmel, A. R. *Curr. Opin. Genet. Dev.* **2000**, *10*, 508.
(6) Jope, R. S.; Bijur, G. N. *Mol. Psychiatry* **2002**, *7*, 35.
(7) Gould, T. D.; Chen, G.; Manji, H. K. *Neuropsychopharmacology* **2004**, *29*, 32.
(8) Madsen, T. M.; Newton, S. S.; Eaton, M. E.; Russell, D. S.; Duman, R. S. *Biol. Psychiatry* **2003**, *54*, 1006.
(9) Hall, A. C.; Brennan, A.; Goold, R. G.; Cleverley, K.; Lucas, F. R.; Gordon-Weeks, P. R.; Salinas, P. C. *Mol. Cell Neurosci.* **2002**, *20*, 257.
(10) Mai, J.; Sameni, M.; Mikkelsen, T.; Sloane, B. F. *Biol. Chem.* **2002**, *383*, 1407.
(11) Gould, T. D.; Manji, H. K. *Neuroscientist* **2002**, *8*, 497.

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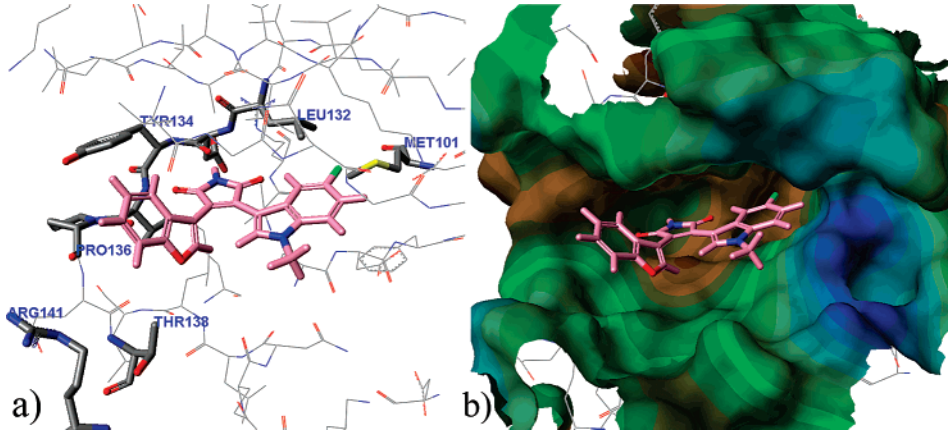


Figure 1. Binding of 3-(benzofuran-3-yl)-4-(indol-3-yl)maleimides to GSK-3β as determined from docking studies: (a) compound **2b** docked to the ATP-binding site of GSK-3β; (b) another rendering of **2b** in complex with GSK-3β in which the protein surface inside the binding site is colored by lipophilic potential (blue = hydrophilic, brown = lipophilic).

positive action of mood stabilizers on cell survival and adult neurogenesis may underlie the therapeutic behavioral effects of these drugs. The small molecule GSK-3 inhibitor AR-A014418 has been shown to protect N2A neuroblastoma cells against cell death mediated by inhibition of the PI3K/PKB survival pathway.[12] Moreover, a robust body of data suggested a role for GSK-3β in the mechanism of action of lithium, by showing that lithium noncompetitively inhibits the phosphorylation activity of GSK-3β, thus regulating neuronal plasticity through an axonal remodeling and an increasing of synaptic proteins levels. The inhibition of GSK-3β may thus provide the mechanism by which lithium lengthens and stabilizes the period of biological rhythms, an effect which has been linked to its therapeutic efficacy and to its specific action on illness periodicity in mood disorders.[13] These ideas have led in turn to variants of GSK-3β and other components of the molecular clock being considered as possible endophenotypes for bipolar disorder.[14] Klein has recently shown that lithium is able to modulate certain behaviors in mice in a fashion that is paralleled by mice lacking one copy of GSK-3β.[15] Moreover, the molecular changes linked to the inhibition of GSK-3 are observed in vivo in both the lithium-treated and GSK-3$\beta^{\pm}$ mice. These data provide further genetic support for the hypothesis that lithium affects mouse behaviors through direct inhibition of GSK-3β. In summation, there is a reasonable body of information to support the action of lithium in bipolar disorder as working through the inhibition of GSK-3β. Moreover, in light of the accumulating data showing that substantive neuroprotective effects can be achieved through the inhibition of GSK-3, it is likely that properly designed inhibitors will find use not only in the treatment of bipolar disorders, but also neurodegenerative diseases including Alzheimer's disease, Huntington's disease, Parkinson's disease, schizophrenia, and even stroke.

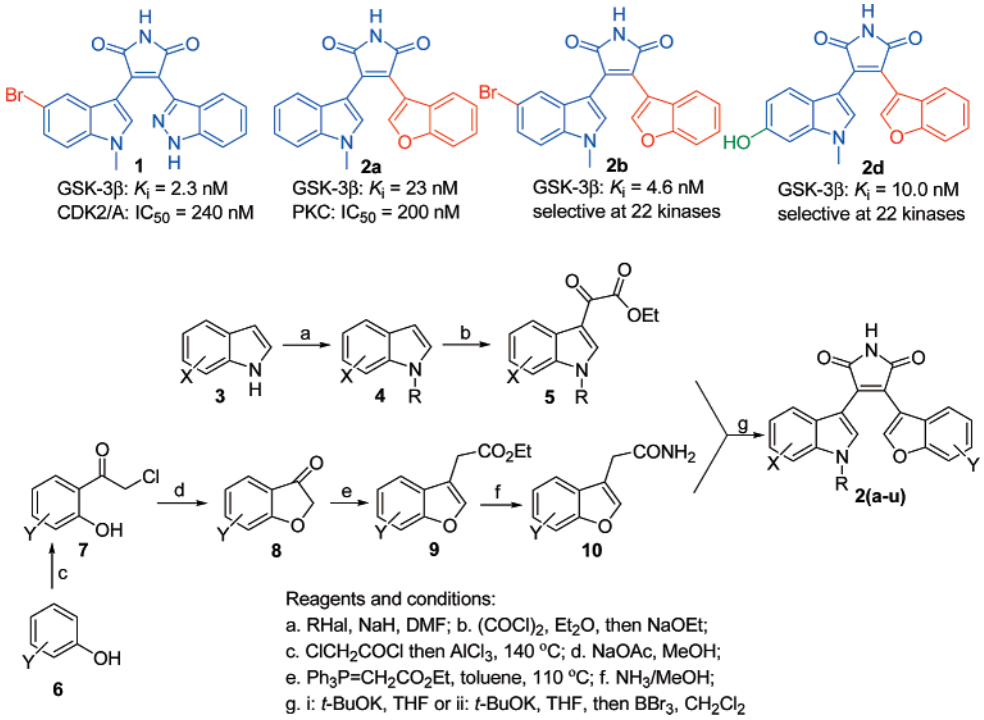
A number of synthetic GSK-3 inhibitors are now currently available,[3] but many of these have not been fully characterized in a battery of biological tests nor are they readily available to academic researchers. These compounds are largely ATP competitive inhibitors whose kinase activity has been determined in vitro; in many cases their true kinase selectivity profiles and their in vivo action remain to be established. As there have been no significant new therapies for treating bipolar disorders in decades, the design of efficacious GSK-3 inhibitors offers promise in fulfilling this unmet medical need.

Results and Discussion

Identification of 3-(Benzofuran-3-yl)-4-(indol-3-yl)-maleimides as Potent GSK-3β Inhibitors: Docking Studies. To date, we have identified some 3-indolyl-4-indazolylmaleimides (**1**), high potency GSK-3β inhibitors that emerged from our SAR studies of staurosporine (Scheme 1).[16] In continuation of this work, we found that certain benzofuranyl bearing maleimides such as **2a** (a 200 nM PKC inhibitor)[17] show very good inhibitory activity toward GSK-3. As benzofurans are more lipophilic than their indazole counterparts, we believed that these relatively unexplored molecules might well serve as better drug development candidates for reasons of blood-brain barrier penetrability. As an aside we note that the related indazoles failed to show any behavioral effects in animal studies. It was our plan to optimize the selectivity of this series by using two approaches: (1) design compounds that would fit "sterically" into the catalytic site of GSK-3 and not into other homologous kinases using the 3D structural features that are unique to GSK-3; and (2) design compounds that are able to bind to amino acids residues that are unique (so-called "selectivity residues") for the ATP binding site of GSK-3 and the areas surrounding it compared to that of other homologous kinases. The closest human homologues of GSK-3β and their alignments were identified using the BLAST search in ExPASy database and these are shown in the Supporting Information. The presence of the phenylalanine (Phe80 in CDK2 corresponds to Leu132 in GSK-3β) residue found in CDK2 as well as CDK3, 7, MAK, and the ICK kinases makes the binding site of these kinases slightly smaller and "hilly" and restricts the entrance of bulkier, more demanding ligands into the catalytic site.[12] From our

(12) Bhat, R.; Xue, Y.; Berg, S.; Hellberg, S.; Ormo, M.; Nilsson, Y.; Radesater, A. C.; Jerning, E.; Markgren, P. O.; Borgegard, T.; Nylof, M.; Gimenez-Cassina, A.; Hernandez, F.; Lucas, J. J.; Diaz-Nido, J.; Avila, J. *J. Biol. Chem.* **2003**, *278*, 45937.
(13) Klemfuss, H. *Pharmacol. Ther.* **1992**, *56*, 53.
(14) Lenox, R. H.; Gould, T. D.; Manji, H. K. *Am. J. Med. Genet.* **2002**, *114*, 391.
(15) O'Brien, W. T.; Harper, A. D.; Jove, F.; Woodgett, J. R.; Maretto, S.; Piccolo, S.; Klein, P. S. *J. Neurosci.* **2004**, *24*, 6791.
(16) Kozikowski, A. P.; Gaisina, I. N.; Petukhov, P. A.; Sridhar, J.; King, L. T.; Blond, S. Y.; Duka, T.; Rusnak, M.; Sidhu, A. *ChemMedChem* **2006**, *1*, 256.
(17) Davis, P. D.; Hill, C. H.; Lawton, G.; Nixon, J. S.; Wilkinson, S. E.; Hurst, S. A.; Keech, E.; Turner, S. E. *J. Med. Chem.* **1992**, *35*, 177.

Scheme 1. Synthesis of 3-(Benzofuran-3-yl)-4-(indol-3-yl)maleimides



modeling studies (Figure 1), a lipophilic pocket in GSK-3 exists in the vicinity of the 5-position of the indole ring system (made up of the lipophilic portions of Leu130, Leu132, Va110, Met101, Phe201, and Cys199), one that can be nicely filled by a halogen, an acetylenic unit, a methoxy group, or a small ring, like cyclopropyl. Additionally, Tyr-134 in GSK-3 appears to offer the opportunity for locating H-bond acceptor groups within the locus of the 5-position of the heterocyclic ring. In contrast, this site in CDK2 is occupied by Phe82, lacking an OH group. Thus, again this residue may serve as a useful selectivity determinant.[18,19] A library of compounds was designed following recommendations for lead-likeness,[20] oral bioavailability,[21] and Lipinski's "rule of five".[22,23] Solubility and cell-permeability properties of potential inhibitors were verified using molecular spreadsheet capabilities, ClogP, and the Volsurf[24] modules in Sybyl.[25]

Synthesis and Screening of 3-(Benzofuran-3-yl)-4-(indol-3-yl)maleimides. Novel 3-(benzofuran-3-yl)-4-(indol-3-yl)maleimides were readily prepared by condensation[26] of 3-indolylglyoxylic acid esters and the appropriately substituted benzofuranyl-3-acetamides (Scheme 1). N-Alkylation of indoles **3** with various alkyl halides in the presence of sodium hydride followed by acylation of the resulting indoles **4** with oxalyl chloride and then ester formation afforded the precursors **5**. The required reaction partners, benzofuranyl-3-acetamides **10**, were prepared starting from the appropriately substituted anisoles **6**.[27] An acylation of **6** catalyzed by $AlCl_3$, followed by cyclization of aryl ketones **7** in methanolic solution of sodium acetate at elevated temperature yielded 3-benzofuranones **8**. Wittig reaction of **8** with (carboxymethylene)triphenylphosphorane afforded ethyl (1-benzofuran-3-yl)acetates, which were subsequently converted into the corresponding acetamides **10**. All new compounds were screened for their potency to inhibit GSK-3β. As presented in Table 1, the K_i values vary from moderate (1100 nM) to excellent (4.6 nM). Among the variety of compounds we have synthesized and tested to date, the presence of a halogen atom or an acetylenic group in position 5 and a hydroxy group in position 6 of the indole ring turned out to be the best, which supports our strategy for structural modification of the lead scaffold. Compounds **2b**,**c** and the indazole-based compound **1** (Scheme 1) were tested against a panel of 22 kinases, and these results are shown in the Supporting Information. The lead compound **2b** shows a very significant improvement in selectivity against all the off-target kinases as compared to the structurally related indazole.

Behavior Results. Amphetamine/Chlorodiazepoxide-Induced Hyperactivity. While the in vitro data are compelling, the most important measure of success must derive from the animal studies. Animal models for bipolar disorder/mania are scarce and hyperactivity models are often used to mimic the mania associated with bipolar disorder. It was found that a combination of the anxiolytic chlorodiazepoxide (CDP) and the psychostimulant amphetamine (Amph) produces an increase in locomotor activity that is greater than the increase produced by amphetamine alone, and this hyperactivity can be blocked by the putative mood-stabilizers lithium, valproate, and lamotrigine.[28−31] Our best benzofuran-based ligand **2b** was studied in a novel

(18) Shen, M.; Beguin, C.; Golbraikh, A.; Stables, J. P.; Kohn, H.; Tropsha, A. *J. Med. Chem.* **2004**, *47*, 2356.
(19) Zhang, K. Y.; Card, G. L.; Suzuki, Y.; Artis, D. R.; Fong, D.; Gillette, S.; Hsieh, D.; Neiman, J.; West, B. L.; Zhang, C.; Milburn, M. V.; Kim, S. H.; Schlessinger, J.; Bollag, G. *Mol. Cell* **2004**, *15*, 279.
(20) Oprea, T. I.; Davis, A. M.; Teague, S. J.; Leeson, P. D. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1308.
(21) Martin, Y. C. *J. Med. Chem.* **2005**, *48*, 3164.
(22) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.
(23) Lipinski, C. A. *J. Pharmacol. Toxicol. Methods* **2000**, *44*, 235.
(24) Cruciani, C.; Crivori, P.; Carrupt, P. A.; Testa, B. *J. Mol. Struct.* **2000**, *503*, 17.
(25) *SYBYL*, version 7.0; Tripos Inc.: St. Louis, 2004.
(26) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *Tetrahedron Lett.* **1999**, *40*, 1109.
(27) Deshpande, A. R.; Paradkar, M. V. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1992**, *31*, 526.

Table 1. GSK-3β Inhibition by Substituted 3-(Benzofuran-3-yl)-4-(indol-3-yl)maleimides[a]

compd	X	Y	R	IC_{50} (nM)	K_i (nM)
2a	H	H	CH_3	35.0 ± 9.0	23
2b	5-Br	H	CH_3	7.0 ± 3.0	4.6
2c	6-OH	H	CH_3	15.0 ± 3.0	10
2d	6-OH	5-F	CH_3	14.0 ± 3.0	9.3
2e	5-C≡CH	H	CH_3	9.6 ± 4.0	6.4
2f	H	5-F	H	670.0 ± 40.0	446
2g	H	5-Br	CH_3	550.0 ± 20.0	366
2h	H	7-OCH_3	CH_3	180.0 ± 15.0	120
2i	5-F	H	H	360.0 ± 40.0	240
2j	5-F	H	CH_3	26.0 ± 6.0	17
2k	5-Cl	5-F	CH_3	42.0 ± 8.0	28
2l	5-OCH_3	H	CH_3	125.0 ± 35.0	83
2m	5-OBn	H	H	1650.0 ± 200.0	1100
2n	5-OBn	H	CH_3	500.0 ± 60.0	333
2o	5-OBn	H	$(CH_2)_3OH$	220.0 ± 30.0	146
2p	6-OBn	H	CH_3	900.0 ± 80.0	600
2q	6-OBn	5-F	CH_3	160.0 ± 35.0	107
2r	7-OBn	H	CH_3	220.0 ± 45.0	146
2s	5-cyclo-propane	H	CH_3	235.0 ± 15.0	156
2t	5-OH	H	CH_3	690.0 ± 100.0	460
2u	7-OH	H	CH_3	55.0 ± 8.0	36

[a] The concentration of the inhibitor producing a 50% inhibition of the enzyme (IC_{50}) was determined experimentally and used to calculate the apparent equilibrium dissociation constant K_i, by using the Chen-Prusoff equation shown here in its simplified form: $K_i = IC_{50}/(1 + (S/K_m))$, where S is the substrate (ATP) concentration used in the assays (10 μM) and K_m is the Michaelis constant of the substrate for the enzyme (20 μM for ATP).

mouse model of mania that has recently been validated with several clinically effective mood stabilizers.[31,32] In this study, male C57BL/6J mice were pretreated with compound **2b** (50 mg/kg) for 5 min and then injected with amphetamine or a mixture of amphetamine and chlordiazepoxide and locomotor activity was monitored for 60 min (Figure 2). Pretreatment with **2b** inhibited the hyperactivity produced by the combination of amphetamine/chlordiazepoxide, with minimal effects on baseline activity. A 30 min pretreatment with the mood stabilizer valproate (400 mg/kg) produced a similar reduction in admphetamine/chlordiazepoxide-induced hyperactivity. These results clearly demonstrate that our newly synthesized GSK-3β inhibitor **2b** has a profile similar to known mood stabilizers like valproate in the amphetamine/chlordiazepoxide mania model.[32]

Conclusion

Recent biological studies support the idea that bipolar disorders and other mood disorders may be remedied by targeting the enzyme GSK-3. Although it has been conjectured that because of the ubiquitous expression of this enzyme, GSK-3 inhibition may produce side-effects,[33] the fact that known GSK-3 inhibitors such as lithium and valproic acid are not only effective in the treatment of bipolar disorder but are also relatively well tolerated suggests that the development of selective GSK-3 inhibitors may lead to novel and better therapies for mood disorders.

(28) Poitou, P.; Boulu, R.; Bohuon, C. *Experientia* **1975**, *31*, 99.
(29) Aylmer, C. G.; Steinberg, H.; Webster, R. A. *Psychopharmacology* **1987**, *91*, 198.
(30) Vale, A. L.; Ratcliffe, F. *Psychopharmacology* **1987**, *91*, 352.
(31) Hanania, T.; Dillon, G. M.; Malekiani, S. A.; Manzano, M. L.; Leahy, E. *Soc. Neurosci. Abstr.* **2005**, 108.9.
(32) Arban, R.; Maraia, G.; Brackenborough, K.; Winyard, L.; Wilson, A.; Gerrard, P.; Large, C. *Behav. Brain Res.* **2005**, *158*, 123.
(33) Woodgett, J. R. *Curr. Drug Targets Immune Endocr. Metabol. Disord.* **2003**, *3*, 281.

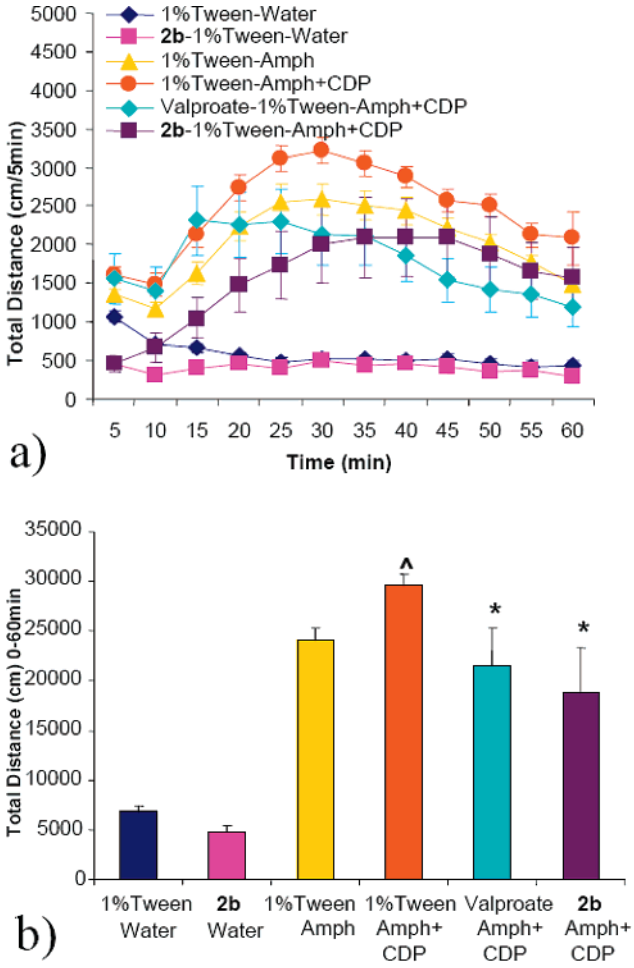


Figure 2. Inhibition of chlordiazepoxide (CDP) and amphetamine (Amph) induced hyperactivity in C57BL/6J mice by **2b** and valproate. (a) Mice were pretreated with either compound **2b** (50 mg/kg), valproate (400 mg/kg), or 1% Tween vehicle. After 5 min or 30 min (valproate group) mice were injected with either water vehicle, amphetamine (4 mg/kg) alone (Amph), or a mixture of amphetamine (4 mg/kg) and chlordiazepoxide (2.5 mg/kg) (Amph + CDP). Locomotor activity was automatically recorded every 5 min for a 60 min period in a square locomotor activity chamber surrounded by infrared beams. (b) Locomotor activity was quantified for a period of 60 min as indicated in the bottom line of the *x*-axis. Each column represents the mean (±SEM) total distance traveled (cm) for at least eight mice. The mixture of Amph + CDP produced greater locomotor activity than Amph alone (∧, $p < 0.05$ 1% Tween−Amph + CDP vs 1% Tween−Amph (Fisher's PLSD). Pretreatment with **2b** and valproate normalized the locomotor activity produced by the Amph + CDP mixture (∗, $p < 0.05$ **2b**−Amph + CDP vs 1% Tween−Amph + CDP (Fisher's PLSD)).

The Wnt signaling pathway blocks GSK-3 phosphorylation of β-catenin leading to its translocation to the nucleus with the subsequent transcription of genes needed for neuronal growth and neuronal plasticity and ultimately to behavioral changes beneficial to the treatment of mood disorders.[5] In the absence of Wnt, the GSK-3 mediated phosphorylation of β-catenin leads to its degradation by the proteasome. Many of the components found in the Wnt signaling pathway are overexpressed or mutated in several types of cancers. Many colon cancers are known to come about from an initiating mutation in APC or mutations in β-catenin that make it resistant to degradation. Consequently, GSK-3 inhibitors have been considered to possibly mimic the Wnt signaling pathway and to be potentially oncogenic. GSK-3 is also known to phosphorylate the transcription factors c-JUN and c-MYC, and thus the GSK-3-inhibitor-

promoted dephosphorylation of these proto-oncogenes might be anticipated to lead to their activation. However, in spite of these concerns, it is well-known that lithium, which has been used for many years for the treatment of bipolar disorder, is not known to be associated with an increased risk of cancer. The administration of the GSK-3 inhibitor CHIR 99021 in ZDF rats for up to 20 h was found not to cause an observable increase in β-catenin or cyclin D1 mRNA in brain, liver, lung, adipose tissue, or colon. The effects of GSK-3 inhibition by lithium were studied in the APC multiple intestinal neoplasia mouse model, a model of tumorigenesis. Chronic lithium treatment in this model did not increase the number of tumors indicating that GSK-3 inhibitors may not exacerbate intestinal polyp formation and may pose a low risk for the tumor development.[34] Other studies suggest that stabilization of β-catenin in the CNS does not result in brain tumors.[35] Moreover, lithium actually increases survival rates of patients with adenocarcinomas.[36] Thus, perhaps, the inhibition of GSK-3 by itself may be unable to elevate β-catenin levels in primary cells; such elevations may require that the cell lines have already undergone some prior transforming events. While these results would suggest that the GSK-3 inhibitors may be free of oncogenic effects, it is clear that longer term studies employing a wide variety of GSK-3 inhibitors possessing diverse chemical scaffolds should be undertaken to completely eliminate such concerns as well as to ascertain whether some chemical scaffolds are problematic for reasons relating to their off-target activity.

Using structure-based design methods, we have designed and synthesized a new series of 3-benzofuranyl-4-indolylmaleimides as potent and relatively selective GSK-3β inhibitors. This study presents the first demonstration of the efficacy of a GSK-3β inhibitor in this novel mouse model of mania. Future studies will determine if these behavioral effects generalize to other mania models such as enhancement of prepulse inhibition. As more than 2 million people per year experience bipolar disorders in the United States, the present work may eventually lead to desperately needed improved therapies.

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Supporting Information Available: Methods of biological assay and detailed experimental procedures with spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(34) Gould, T. D.; Gray, N. A.; Manji, H. K. *Pharmacol. Res.* **2003**, *48*, 49.
(35) Kratz, J. E.; Stearns, D.; Huso, D. L.; Slunt, H. H.; Price, D. L.; Borchelt, D. R.; Eberhart, C. G. *BMC Cancer* **2002**, *2*, 33.
(36) Johnson, C. D.; Puntis, M.; Davidson, N.; Todd, S.; Bryce, R. *Br. J. Surg.* **2001**, *88*, 662.