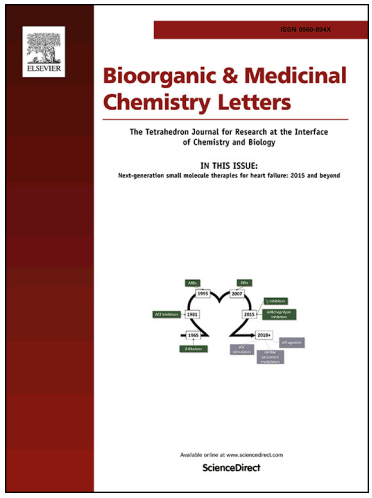
Accepted Manuscript



1-Aryl-3-(4-methoxybenzyl)ureas as potentially irreversible glycogen synthase kinase 3 inhibitors: Synthesis and biological evaluation

Jana Venter, Concepción Perez, Willem A.L. van Otterlo, Ana Martínez, Margaret A.L. Blackie

PII: S0960-894X(19)30281-1
DOI: https://doi.org/10.1016/j.bmcl.2019.04.049
Reference: BMCL 26416

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 26 March 2019
Revised Date: 25 April 2019
Accepted Date: 27 April 2019

Please cite this article as: Venter, J., Perez, C., van Otterlo, W.A.L., Martínez, A., Blackie, M.A.L., 1-Aryl-3-(4-methoxybenzyl)ureas as potentially irreversible glycogen synthase kinase 3 inhibitors: Synthesis and biological evaluation, *Bioorganic & Medicinal Chemistry Letters* (2019), doi: https://doi.org/10.1016/j.bmcl.2019.04.049

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

1-Aryl-3-(4-methoxybenzyl)ureas as potentially irreversible glycogen synthase kinase 3 inhibitors: Synthesis and biological evaluation

Jana Venter[a], Concepción Perez[b], Willem A. L. van Otterlo[a], Ana Martínez[c], Margaret A. L. Blackie[a*]

[a]*Department of Chemistry and Polymer Science, Stellenbosch University, Stellenbosch 7602, South Africa*
[b]*Instituto de Quimica Medica-CSIC, Juan de la Cierva 6, 28003 Madrid, Spain*
[c]*Centro de Investigaciones Biológicas-CSIC, Ramiro de Maeztu 9, 28040 Madrid, Spain*

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Glycogen synthase kinase 3
Alzheimer's disease
Targeted covalent inhibitor
Cysteine 199
Ureas

ABSTRACT

Glycogen synthase kinase 3 (GSK-3) has become known for its multifactorial involvement in the pathogenesis of Alzheimer's disease. In this study, a benzothiazole- and benzimidazole set of 1-aryl-3-(4-methoxybenzyl)ureas were synthesised as proposed Cys199-targeted covalent inhibitors of GSK-3β, through the incorporation of an electrophilic warhead onto their ring scaffolds. The nitrile-substituted benzimidazolylurea **2b** (IC_{50} = 0.086 ± 0.023 μM) and halomethylketone-substituted benzimidazolylurea **9b** (IC_{50} = 0.13 ± 0.060 μM) displayed high GSK-3β inhibitory activity, in comparison to reference inhibitor AR-A014418 (**1**, IC_{50}= 0.072 ± 0.043) in our assay. The results suggest further investigation of **2b** and **9b** as potential covalent inhibitors of GSK-3β, since a targeted interaction might provide improved kinase-selectivity.

As the most prevalent form of dementia, Alzheimer's disease (AD) is defined as a progressive neurodegenerative disease with clinical symptoms of memory loss and cognitive decline, which is characterised at the molecular level by deposits of intracellular neurofibrillary tangles (NFTs) and extracellular β-amyloid (Aβ) plaques in the brain.[1] The global impact of dementia was analysed by Alzheimer's Disease International in the World Alzheimer Report of 2015, which stated that the number of dementia cases would increase from 46.8 million to 74.7 million by 2030.[2] There is currently no cure for AD, and thus far only palliative drugs have successfully reached the market.[3]

AD drug discovery is challenging since the risk factors and molecular mechanisms of AD development are multifactorial and not fully understood.[4,5] The development of disease-modifying therapeutics (DMTs), which can intervene in primary molecular mechanisms of AD to prevent or delay the onset/progression of the disease, is priority.[6] Glycogen synthase kinase 3 (GSK-3) is a promising CNS drug target, since dysregulated GSK-3 activity plays a central role in AD development and provides a link between Aβ plaques, NFTs, inflammatory responses and reduced cholinergic transmission.[7,8]

Mammalian GSK-3 exists in two homologous isoforms, known as GSK-3α (51 kDa) and GSK-3β (47 kDa), which share 98% amino acid sequence similarity in their catalytic domain.[9] GSK-3β has been identified as a key kinase responsible for abnormal tau hyperphosphorylation in AD.[10] Tau proteins are microtubule-associated proteins (MAP) which associate to tubulin in order to stabilise cytoskeletal microtubules in CNS nerve cells. Tau hyperphosphorylation thus destabilises association, which result in microtubule degeneration and the aggregation of tau proteins to form NFTs.[11,12] Recent years in GSK-3β inhibitor development were focused on preclinical efforts to address issues involving toxicity and selectivity.[13]

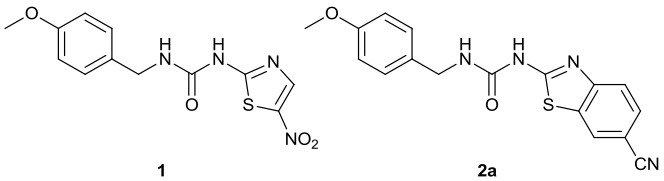


Figure 1. GSK-3β inhibitors, AR-A014418 (**1**, AstraZeneca[14]) and its non-toxic benzothiazole derivative (**2a**, Lo Monte *et al.*[15])

Protein kinases display high sequence conservation in the ATP binding site, therefore kinase inhibitors should display high kinase-selectivity.[7] In 2003, AstraZeneca reported the potent activity (IC_{50} = 104 nm) and high selectivity of the novel GSK-3 inhibitor, AR-A014418 (**1**).[14] This reversible ATP-competitor did not significantly inhibit CDK-2, CDK-5, or the rest of the 26 protein kinases which were assayed. In subsequent work, Lo Monte *et al.* showed that when the thiazole ring of AR-A014418 was replaced with a pyridine or benzothiazole ring structure, the toxicity of the compound diminished in a zebrafish embryo phenotype assay.[15] Their benzothiazole derivative **2a** had a GSK-3 inhibition potency comparative to AR-A014418 (**1**).

Martínez and co-workers were the first to describe irreversible GSK-3β inhibitors, which covalently target Cys199, as a strategy to improve selectivity and to obtain high potency.[16] The ATP binding pocket of GSK-3 uniquely contains a Cys199 residue, which is not conserved in structurally-related kinases.[16] Martínez and co-workers successfully switched reversible GSK-3β inhibitors into irreversible GSK-3β inhibitors, by using an electrophilic moiety which can target Cys199.[17] Recently this hypothesis has been confirmed by X-ray crystallography.[18]

Our aim was to transform the non-toxic, selective, reversible GSK-3β inhibitor **2a** into a Cys199-targeted covalent inhibitor. Different electrophilic warheads would be explored and incorporated onto the ring structure, with the potential to form a covalent bond with Cys199 in the GSK-3 ATP pocket. Thus, a small library of 1-aryl-3-(4-methoxybenzyl)ureas was designed and synthesised, in which the aryl scaffold structure was either a benzothiazole or a benzimidazole ring. The biological activities of the compounds were also tested.

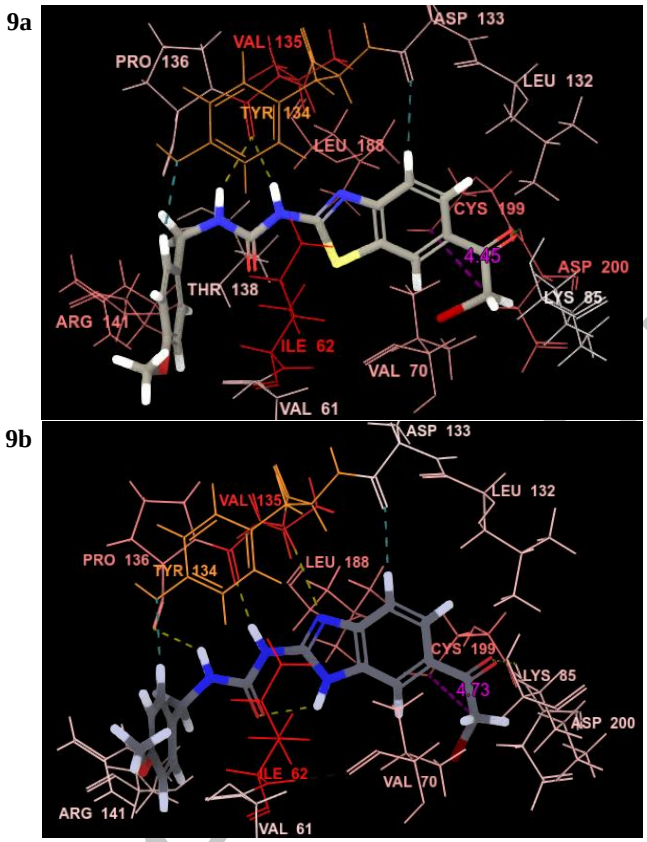


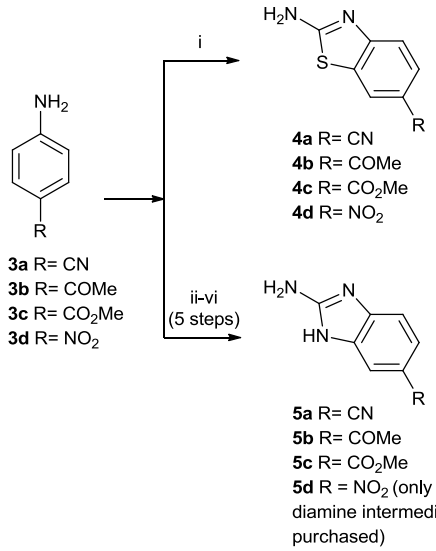
Figure 2. Binding interactions of HMK ligands **9a** and **9b** with the GSK-3β ATP binding pocket. Dashed lines: yellow—hydrogen bond, cyan—aromatic hydrogen bond, purple—Cys199 target distance

Molecular modelling studies with the proposed covalent inhibitors were performed using the Maestro Schrödinger Drug Discovery Suite and the X-ray crystallographic structure of AR-A014418 (**1**) in complex with GSK-3β (PDB ID: 1Q5K). The proposed covalent inhibitors docked similarly to **1** along the hinge region. The reversible docking modes of the halomethylketone (HMK) inhibitors **9a** and **9b** are displayed in Figure 2. The urea functionality of **9a** formed two hydrogen bonds with hinge residue Val135, and weaker aromatic hydrogen bonds with Tyr134 and Asp133. The C_α atom of the HMK moiety was situated 4.5 Å from the sulfur atom of Cys199. Compound **9b** docked similarly, but the imidazole moiety allowed for one additional hydrogen bond with the hinge region, as well as an intramolecular hydrogen bond with the urea carbonyl oxygen.

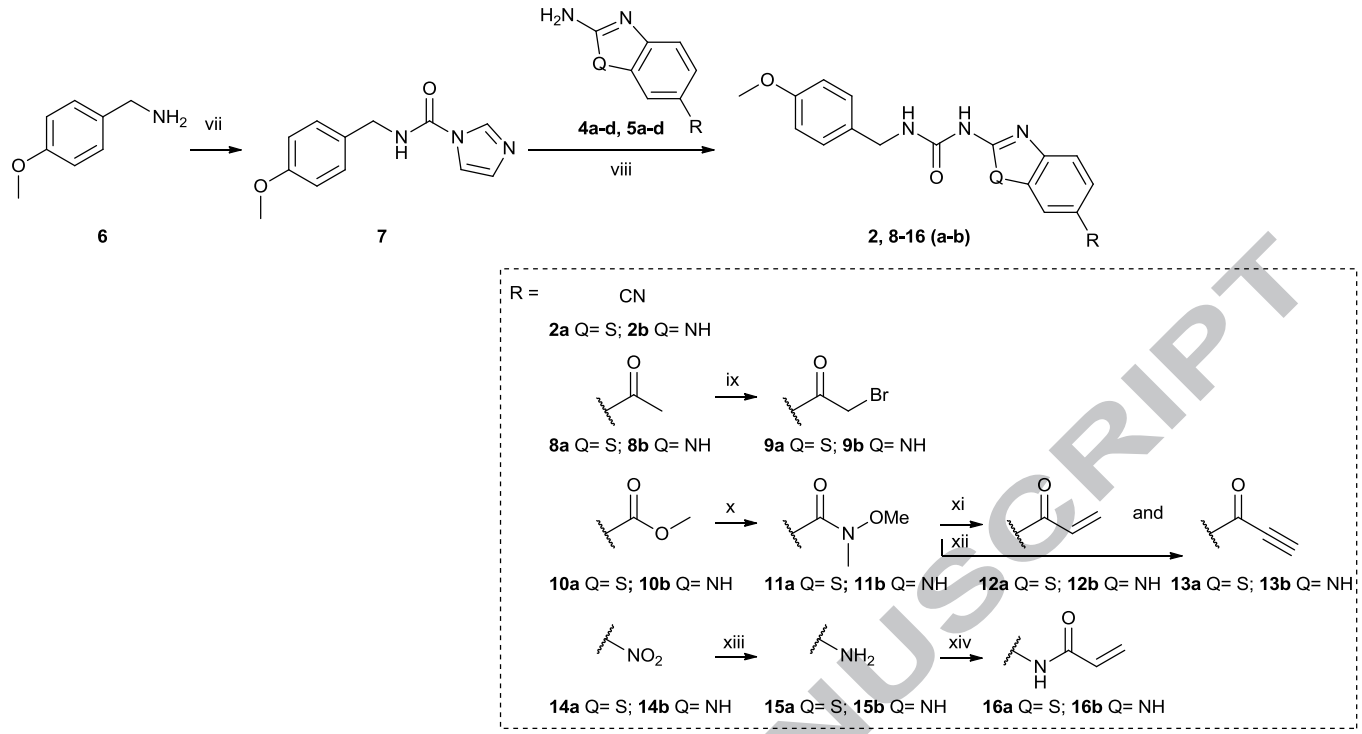
The synthesis of the benzothiazole **4** and benzimidazole **5** heterocycles are depicted in Scheme 1. Cyano-substituted benzothiazole **4a** was synthesised *via* a thiocyanated intermediate, using a modified conventional procedure.[19] The stoichiometric control in the reaction was improved, by use of an organic ammonium tribromide as bromine source.[20] Thus, 4-aminobenzonitrile (**3a**) was thiocyanated with KSCN in glacial acetic acid, utilising phenyltrimethylammonium tribromide ($PhNMe_3Br_3$) as the oxidant. The 4-amino-3-thiocyanatobenzonitrile intermediate was isolated and cyclised with NaH in THF under reflux to yield **4a**. A better cyclisation yield was obtained in basic conditions, than in previously described acidic conditions.

The 2-aminobenzothiazoles **4b-d** were synthesised in one-pot reactions in good to acceptable yields, since these reactions proceeded with fewer by-products and displayed spontaneous cyclisation alongside the thiocyanation step. Thus, the substituted anilines **3b-d** were treated with KSCN/ $PhNMe_3Br_3$ in glacial acetic acid, and after 5 h of stirring at r.t., the crude mixture was heated under reflux for 10 min to form the cyclised product.

The 2-aminobenzimidazoles **5a-c** were synthesised in accordance to published methods.[21–24] The first three steps (ii – iv) entailed acylation of the free amine, nitration *ortho* of the protected amine and deprotection. We found mixed acid nitration with equal volumes of 65% HNO_3 and conc H_2SO_4 (1:1 v/v) to be very convenient. Subsequently, the nitro group was reduced with H_2, Pd/C and the diamine cyclised with CNBr. The diamine precursor of nitro-substituted benzimidazole **5d** was purchased and cyclised.



Scheme 1. (i) 4a: 1. KSCN, glacial AcOH, $PhNMe_3Br_3$, 5 °C – rt, 5 h, 75%; 2. NaH, THF, reflux, 2 h, 85%. **4b-d**: 1. KSCN, glacial AcOH, $PhNMe_3Br_3$, 10 °C – r.t., 5 h, then reflux, 10 min, 54 – 81%. **(ii)** Ac_2O, DCM, 83 – 97%. **(iii) 5a**: KNO_3, conc. H_2SO_4, −15 to −10 °C, 3.5 h, 69%. **5b-c**: 65% HNO_3/ conc. H_2SO_4 (1:1 v/v), 0 °C, 1 h, 69%, 90%. **(iv)** 1 M H_2SO_4, reflux, 2 h, 82 – 96%. **(v)** H_2, 10% Pd/C, EtOAc/MeOH, r.t., 90 – 99%. **(vi)** BrCN, MeOH, H_2O, CH_3CN, r.t., 18 h, 87% – quant.



Scheme 2. (vii) 1. 4 M HCl in dioxane, DCM, r.t., 10 min; 2. CDI, DMF, 0 °C, 7 min, quant. yield. **(viii)** NaH, DMF, r.t., 22 h, **2a**: 99%, **2b**: 49%, **8a**: 82%, **8b**: 75%, **10a**: 74%, **10b**: 61%, **14a**: quant., **14b**: 57%. **(ix) 9a**: $PhNMe_3Br_3$, THF, 30 °C, 64 h, 35%. **9b:** 1. TMSOTf, DCM, DIPEA, 0 – 30 °C, 20 h; 2. NBS, THF, $NaHCO_3$, −78 °C, 1.5 h, 48% (over 2 steps). **(x)** MeO(Me)NH·HCl, *i*-PrMgBr, THF, −20 °C to −5 °C, 1 h, **11a**: 81%, **11b**: 78%. **(xi)** 1. vinylmagnesium bromide, THF, −20 °C to 15 °C, 20 h; 2. 1 M aq. $NaHSO_4$, 0 °C, **12a**: 26%, **12b**: 11%. **(xii)** 1. ethynylmagnesium bromide, THF, −20 °C to 15 °C, 20 h; 2. 1 M aq. $NaHSO_4$, 0 °C, **13a**: 76%, **13b**: 15%. **(xiii)** H_2, 10% Pd/C, DMF, MeOH, 60 °C, 4.5 h, **14a**: 40%, **14b**: 85%. **(xiv)** acryloyl chloride, THF, DMF, NEt_3, 0 °C – r.t., 1.25 h, **16a**: 54%, **16b**: 40%.

As depicted in Scheme 2, the prepared heterocycles **4a–d**, **5a–d** were next subjected to 4-methoxybenzylamine (**6**) through a CDI-mediated coupling to form unsymmetrical disubstituted ureas. The well-developed coupling methods of Batey and co-workers,[25,26] were extrapolated into this study to synthesise novel compounds **2b**, **8a–b**, **10a–b**, **14b**, and to improve the literature yields[15] of **2a** and **14a** which were 70% and 26%, respectively, to 99% and a quantitative yield.

To prevent symmetrical urea formation in the first step of Scheme 2 (vii), the ammonium hydrochloride salt of **6** was generated *in situ* using 4 M HCl in dioxane in DCM, whereafter it was reacted with CDI for a shortened time of 7 min to yield the electrophile, *N*-(4-methoxybenzyl) carbamoylimidazole (**7**) in a quantitative yield.[25] Compound **7** was reacted with the 6-substituted 2-aminobenzothiazoles (**4a–d**) in a NaH/DMF system over 22 h at r.t. to afford the 1-(6-substituted benzothiazol-2-yl)-3-(4-methoxybenzyl)ureas (**2a**, **8a**, **10a**, **14a**) in high to quantitative yields. The similar synthesis of the 1-(6-substituted benzimidazol-2-yl)-3-(4-methoxybenzyl)ureas (**2b**, **8b**, **10b**, **14b**) proved more challenging, with moderate yields proposedly due to tautomeric effects in the benzimidazole ring moiety and thus the weaker nucleophilic nature of the 2-aminobenzimidazoles (**5a-d)**.

The ureas were further modified in position 6 of the benzazole portion of the scaffolds, to incorporate the respective electrophilic warheads. Compound **8a** was α-brominated with $PhNMe_3Br_3$ in THF, at 30 °C over 64 h, to afford HMK **9a** with a yield of 35%. To obtain regioselectivity and controlled α-monobromination, **8b** was brominated *via* its silyl enol ether intermediate.[27,28] The crude enol ether intermediate was treated with NBS at −78 °C to yield HMK **9b** in a 48% overall yield.

Vinyl and ethynyl ketones **12a-b**, **13a-b** were prepared from their ester precursors (**10a-b**) by converting the esters into their corresponding Weinreb amides in good yields. A MeO(Me)NH·HCl/*i*-PrMgBr system, inspired by the general Weinreb preparation methods of Williams and co-workers,[29] was utilised. Unfortunately, the subsequent Grignard reactions proceeded in generally low yields, but provided enough material for further reactions.

Acrylamides **16a-b** were synthesised in low to moderate yields by catalytic hydrogenation of their 6-nitro precursors (**14a-b**), and subsequent treatment of the free amines with acryloyl chloride in THF and DMF.

Compound **2a** and newly synthesised compounds **2b**, **8a-8b**, **9a-b**, **12a-b**, **13a-b**, **16a-b**, were evaluated for GSK-3β inhibitory activity using a luminescent assay (see Table 1). Potent GSK-3β inhibitor AR-A014418 (**1,** synthesised according to known procedure[25]) was used as reference standard.

The benzimidazole-derived compounds (Q = NH) were generally better inhibitors than their benzothiazole equivalents (Q= S), supposedly due to their ability to form one additional hydrogen bond with the hinge region of the GSK-3β ATP pocket. The most potent inhibitor in the library was 1-(6-cyano-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-methoxybenzyl)urea (**2b**) with an IC_{50} value of 0.086 ± 0.023 μM, which compared well to the reference inhibitor (**1**), which displayed an IC_{50} value of 0.072 ± 0.043 μM in our assay. The inhibitory ability of its benzothiazole equivalent, **2a**, is known in the literature.[15]

The benzimidazole-derived HMK, **9b,** displayed satisfactory inhibitory activity with an IC_{50} value of 0.13 ± 0.060 μM. The HMK inhibitors **9a** and **9b** were more potent than their corresponding acetyl-derivatives, **8a** and **8b**, confirming the structure-activity influence of the halomethylketone moiety to increase inhibitory activity. Furthermore, the biological activities of the vinyl and ethynyl ketones (**12a-b**, **13a-b**) were low,

whereas the acrylamides (**16a-b**) displayed insignificant inhibition.

Table 1. The GSK-3β inhibitory activity (IC_{50}) and results of reversible docking studies of compounds produced in Scheme 2.

Substituent	Compd	IC_{50} (μM)	XP dock-ing Gscore (kcal/mol)	Dist from reactive atom to Cys 199 (Å)
Nitrile	**2a**	0.11 ± 0.040	-7.561	4.01
Acetyl	**8a**	2.26 ± 0.41	n.d.[a]	n.d.
HMK	**9a**	0.77 ± 0.037	-7.305	4.45
Vinyl ketone	**12a**	4.05 ± 0.39	-7.305	5.53
Ethynyl ketone	**13a**	4.21 ± 0.33	-7.206	5.16
Acrylamide	**16a**	>10	-7.562	5.08
Nitrile	**2b**	0.086 ± 0.023	-9.089	3.95
Acetyl	**8b**	0.26 ± 0.030	n.d.	n.d.
HMK	**9b**	0.13 ± 0.060	-8.859	4.73
Vinyl ketone	**12b**	1.82 ± 0.22	-9.338	3.84
Ethynyl ketone	**13b**	2.47 ± 0.32	-8.596	5.15
Acrylamide	**16b**	>10	-9.180	5.20
Reference	**1**	0.072 ± 0.043	-7.005	n.a.

[a]n.d. – not determined; [b] n.a. not applicable

The IC_{50} values were compared with the molecular modelling studies. Both reversible and irreversible modes were examined. There was no difference in the trend shown between the two modes, so only the reversible modes are reported here, because the distance from the reactive atom to the sulfur atom of the cysteine was determined under the same conditions. The acetyl derivatives were only included later in the study as they had to be made on the route to the bromomethylketone derivatives.

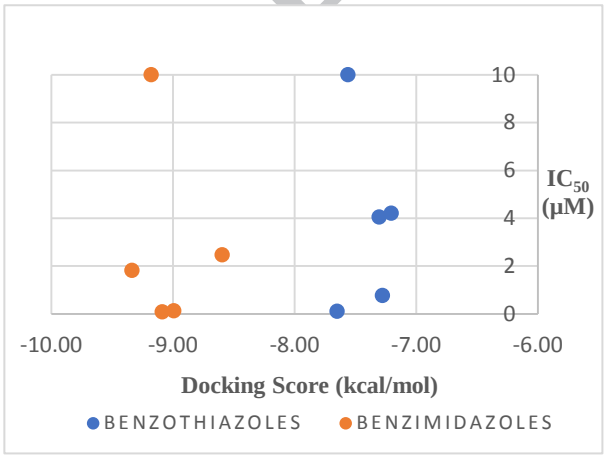
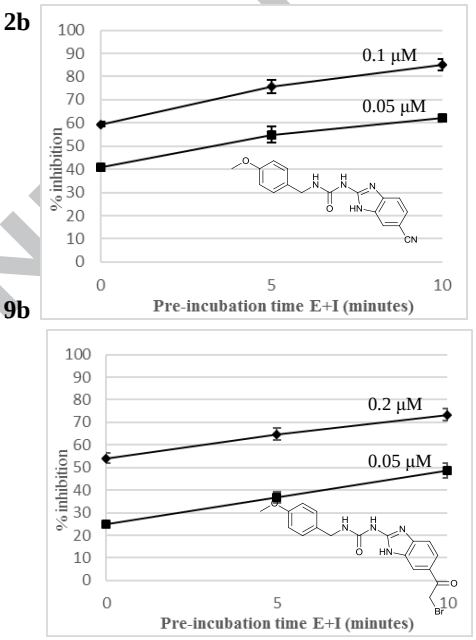


Figure 3. Docking score (reversible binding) and biological activity (IC_{50})

Neither the docking score, nor the distance from the reactive atom to Cys 199 was shown to correlate well with the observed biological activity (Figure 3). This is most clearly observed in the values obtained for the acrylamides **16a** and **16b**.

An initial GSK-3β time-dependent study, performed according to the methods of Martínez and co-workers,[17] suggested that active compounds, nitrile **2b** and HMK **9b**, react in an irreversible fashion. Berteotti et al have shown that such an interaction is theoretically possible.[30] As seen in Figure 4, inhibitors **2b** and **9b** displayed increased inhibition percentage, when the inhibitor was pre-incubated with the enzyme for a longer time. These findings potentially support a covalent interaction between the incorporated electrophilic warhead and Cys199 in the GSK-3β ATP pocket. However, more extensive studies are necessary to ascertain a Cys199-targeted covalent interaction, and to confirm whether this interaction is irreversible on the biological timescale.



In this study, two sets of 1-aryl-3-(4-methoxybenzyl)ureas were transformed into proposed Cys199-targeted covalent inhibitors, by incorporation of an electrophilic warhead onto their ring scaffolds. The compounds were designed by way of modelling, synthesised and biologically evaluated. No clear correlation was observed between the modelled interaction and the biological inhibition observed. High GSK-3β inhibitory activity was measured for inhibitors **2b** and **9b**. The potential covalent interaction of these inhibitors with Cys199, a unique residue in the GSK-3 ATP binding pocket, may potentially provide enhanced kinase-selectivity which is highly desirable in GSK-3 kinase inhibitors.

Acknowledgments

This research was financially supported by the National Research Foundation (Innovation Master's Scholarship 2017 – 2018), Stellenbosch University and MINECO (grant no. SAF2016-76693-R). We acknowledge the Central Analytical Facilities (CAF) at Stellenbosch University for assisting with

Figure 4. Time-dependent GSK-3β inhibition studies with inhibitors **2b** and **9b**, respectively.

NMR, MS and UPLC-MS data.

Supplementary Material

Supplementary material associated with this article can be found online at doi:

References

(1) Hooper, C.; Killick, R.; Lovestone, S. *J. Neurochem.* **2008**, *104*, 1433.

(2) Prince, M.; Wimo, A.; Guerchet, M.; Ali, G.-C.; Wu, Y.-T.; Prina, M. *World Alzheimer Report 2015: The Global Impact of Dementia*; Alzheimer's Disease International: London, **2015**.

(3) Mangialasche, F.; Solomon, A.; Winblad, B.; Mecocci, P.; Kivipelto, M. *Lancet Neurol.* **2010**, *9*, 702.

(4) Bachurin, S. O.; Bovina, E. V.; Ustyugov, A. A. *Med. Res. Rev.* **2017**, *37*, 1186.

(5) Huang, Y.; Mucke, L. *Cell* **2012**, *148*, 1204.

(6) Cummings, J.; Lee, G.; Ritter, A.; Zhong, K. *Alzheimer's Dement. Transl. Res. Clin. Interv.* **2018**, *4*, 195.

(7) Martinez, A.; Gil, C.; Perez, D. I. *Int. J. Alzheimer's Dis.* **2011**, *2011*, 1.

(8) Llorens-Martín, M.; Jurado, J.; Hernández, F.; Ávila, J. *Front. Mol. Neurosci.* **2014**, *7*, 1.

(9) Woodgett, J. R. *EMBO J.* **1990**, *9*, 2431.

(10) Ishiguro, K.; Shiratsuchi, A.; Sato, S.; Omori, A.; Arioka, M.; Kobayashi, S.; Uchida, T.; Imahori, K. *FEBS Lett.* **1993**, *325*, 167.

(11) Panza, F.; Solfrizzi, V.; Seripa, D.; Imbimbo, B. P.; Lozupone, M.; Santamato, A.; Zecca, C.; Barulli, M. R.; Bellomo, A.; Pilotto, A.; Daniele, A.; Greco, A.; Logroscino, G. *Biomed. Res. Int.* **2016**, *2016*, 1.

(12) Kramer, T.; Schmidt, B.; Lo Monte, F. *Int. J. Alzheimers Dis.* **2012**, *2012*, 1.

(13) Medina, M. *Int. J. Mol. Sci.* **2018**, *19*, 1160.

(14) Bhat, R.; Xue, Y.; Berg, S.; Hellberg, S.; Ormö, M.; Nilsson, Y.; Radesäter, A. C.; Jerning, E.; Markgren, P. O.; Borgegård, T.; Nylöf, M.; Giménez-Cassina, A.; Hernández, F.; Lucas, J. J.; Díaz-Nido, J.; Avila, J. *J. Biol. Chem.* **2003**, *278*, 45937.

(15) Monte, F. Lo; Kramer, T.; Boländer, A.; Plotkin, B.; Eldar-Finkelman, H.; Fuertes, A.; Dominguez, J.; Schmidt, B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5610.

(16) Perez, D. I.; Conde, S.; Pérez, C.; Gil, C.; Simon, D.; Wandosell, F.; Moreno, F. J.; Gelpí, J. L.; Luque, F. J.; Martínez, A. *Bioorg. Med. Chem.* **2009**, *17*, 6914.

(17) Perez, D. I.; Palomo, V.; Pérez, C.; Gil, C.; Dans, P. D.; Luque, F. J.; Conde, S.; Martínez, A. *J. Med. Chem.* **2011**, *54*, 4042.

(18) Redenti, S.; Marcovich, I.; De Vita, T.; Pérez, C.; De Zorzi, R.; Demitri, N.; Perez, D. I.; Bottegoni, G.; Bisignano, P.; Bissaro, M.; Moro, S.; Martinez, A.; Storici, P.; Spalluto, G.; Cavalli, A.; Federico, S. *ChemMedChem* **2019**, *14*, 310.

(19) Sawhney, S. N.; Boykin, D. W. *J. Org. Chem.* **1979**, *44*, 1136.

(20) Jordan, A. D.; Luo, C.; Reitz, A. B. *J. Org. Chem.* **2003**, *68*, 8693.

(21) Fairley, T.; Tidwell, R.; Donkor, I.; Naiman, N.; Ohemeng, K.; Lombardy, R.; Bentley, J.; Cory, M. *J. Med. Chem.* **1993**, *36*, 1746.

(22) Starcevic, K.; Caleta, I.; Cincic, D.; Kaitner, B.; Kralj, M.; Ester, K.; Karminski-Zamola, G. M. *Heterocycles* **2006**, *68*, 2285.

(23) Maji, B.; Kumar, K.; Kaulage, M.; Muniyappa, K.; Bhattacharya, S. *J. Med. Chem.* **2014**, *57*, 6973.

(24) Tawar, U.; Jain, A. K.; Dwarakanath, B. S.; Chandra, R.; Singh, Y.; Chaudhury, N. K.; Khaitan, D.; Tandon, V. *J. Med. Chem.* **2003**, *46*, 3785.

(25) Duspara, P. A.; Sadequl Islam, M.; Lough, A. J.; Batey, R. A. *J. Org. Chem.* **2012**, *77*, 10362.

(26) Grzyb, J. A.; Shen, M.; Yoshina-Ishii, C.; Chi, W.; Brown, R. S.; Batey, R. A. *Tetrahedron* **2005**, *61*, 7153.

(27) Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785.

(28) Bartolomé-Nebreda, J. M.; Alonso De Diego, S. A.; Artola, M.; Delgado, F.; Delgado, Ó.; Martín-Martín, M. L.; Martínez-Viturro, C. M.; Pena, M. Á.; Tong, H. M.; Van Gool, M.; Alonso, J. M.; Fontana, A.; Macdonald, G. J.; Megens, A.; Langlois, X.; Somers, M.; Vanhoof, G.; Conde-Ceide, S. *J. Med. Chem.* **2015**, *58*, 978.

(29) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(30) Berteotti, A.; Vacondio, F.; Lodola, A.; Bassi, M.; Silva, C; Mor, M.; Cavalli, A. *ACS Med. Chem. Lett.* **2014**, *5*, 501

Graphical Abstract

1-Aryl-3-(4-methoxybenzyl)ureas as potentially irreversible glycogen synthase kinase 3 inhibitors: Synthesis and biological evaluation

Leave this area blank for abstract info.

Jana Venter, Concepción Perez, Willem A. L. van Otterlo, Ana Martínez, Margaret A. L. Blackie