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4-Substituted-7-azaindoles bearing a ureidobenzofuranone moiety as potent and selective, ATP-competitive inhibitors of the mammalian target of rapamycin (mTOR)

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ABSTRACT

A series of 5-ureidobenzofuranones was discovered as potent and selective inhibitors of mTOR with good cellular activity. Molecular modeling studies revealed several hydrogen bond interactions of the ureido group with the enzyme at the ATP-binding site. Furthermore, modeling showed that the ureido group is best situated at C-5 of the benzofuranone. Syntheses of 4-ureido and 5-ureidobenzofuranones are presented.

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The mammalian target of rapamycin (mTOR) is frequently hyperactivated in human cancers,^{1–3} making it an attractive target for treating cancer.^{4–6} mTOR belongs to a family of unconventional high molecular mass serine/threonine protein kinases and is a key component of the phosphoinositide 3-kinase (PI3K) signaling pathway that plays an important role in regulating cell growth, metabolism and angiogenesis.^{7,8} mTOR is a clinically proven drug target for cancer as demonstrated by rapamycin analogs.⁹ However, rapamycin analogs are allosteric inhibitors, only inhibiting mTORC complex 1 (mTORC1), but not mTORC complex 2 (mTORC2).^{10,11} Inhibition of mTORC1 alone can block a desirable negative feedback mechanism, thereby causing an increase of PI3K-Akt signaling and reducing the effectiveness of the inhibitors.² This negative feedback mechanism can be restored by inhibiting mTORC2. This finding has led the cancer research community to search for small molecule ATP-competitive inhibitors of mTOR. In the PI3K/Akt/mTOR signaling pathway, mTOR and PI3K share high sequence similarity (68%) at their ATP-binding sites, making the search for selective mTOR inhibitors more challenging. Indeed, many reported mTOR inhibitors are dual inhibitors that also inhibit PI3Ka.^{4,12,13} However, recently, quite a few selective mTOR inhibitors have been discovered.^{14–24} Our group has just reported on a series of 2-(4-substituted-pyrrolo[2,3-b]pyridin-3-yl)methylene4-hydroxybenzofuran-3(2H)-ones as potent and selective ATPcompetitive inhibitors of mTOR.²⁵ Through our analoging efforts, we were able to prepare compounds that demonstrated subnanomolar inhibitory activity against mTOR kinase and were selective over PI3Ka. Initially our lead contained two phenolic hydroxyl groups. Since there is no available crystal structure of mTOR, the closely related protein, PI3Ky, was used for co-crystallization studies with our inhibitors. X-ray co-crystallographic structures of inhibitor **1a** with PI3Ky showed the importance of the two phenolic hydroxyl groups for hydrogen bond interactions with Asp2195 and Lys2187 of the enzyme. In an effort to minimize the metabolic liability of the phenolic groups, we eliminated one of the two hydroxyl groups. We now report the replacement of both hydroxyl groups with a ureido group, to completely eliminate the potential liabilities associated with glucuronidation of the phenolic hydroxyl groups, and thus enhance metabolic stability.

Recently, Zask et al.¹⁸ reported that in the pyrazolopyrimidine series, a phenolic hydroxyl group was successfully replaced with a ureido group, a known isostere, to give potent and selective mTOR inhibitors. One of these inhibitors, **2** (Fig. 1), was co-crystallized with PI3K γ to show that the ureido group formed hydrogen bond interactions with Asp841 and Lys833 of PI3K γ (Asp2195 and Lys2187 in mTOR).¹⁸ To determine the best site for a ureido substituent as a 4-OH replacement on the benzofuranone ring, we overlayed the X-ray co-crystal structures of PI3K γ with **1a**²⁵ (PDB code 3LJ3) and **2** (PDB code 3IBE), as shown in Figure 1. The

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Figure 1. Overlay of two X-ray co-crystal structures of PI3Kγ (in dark gray ribbon and carbons) with **1a** (in cyano carbons) and PI3Kγ (in light gray ribbon and carbons) with **2** (in orange carbons). mTOR residue numbering is used in the figure, and the corresponding PI3Kγ numbering is Val882, Lys833, and Asp841.

overlay and subsequent docking studies suggested that a C-5 ureido group on benzofuranone was best positioned to form hydrogen bond interactions with Asp2195 and Lys2187 of mTOR, similar to the interactions observed with a 4,6-dihydroxybenzofuranone, **1a** or the urea **2**. However, a C-4 ureidobenzofuranone is not expected to form these interactions with the enzyme.

Before we embarked our analoging efforts on 5-ureidobenzofuranaones, we prepared both 5-methylurea **3a** and 4-methylurea **3b** to verify the preference for 5- versus 4-ureidobenzofuranones, as suggested by crystallography and modeling. The synthesis of **3a** is shown in Scheme 1. The 4-bromide **4** was converted into the 4-phenyl compound **5a**, under Suzuki coupling conditions,²⁵ followed by condensation with 5-ureidobenzofuranone **11** where R is a methyl group. Compound **11** was prepared from 2-hydroxyacetophenone **7**. Alpha bromination of **7**,²⁶ followed by nitration²⁷ gave **8**, which was readily cyclized under basic conditions to yield **9**. After reduction of **9**, the resulting amine **10** was treated with isocyanate to afford **11**. The preparation of 4-ureidobenzofuranone **3b** started from 2-hydroxy-6-pivalamidobenzoic acid **12**,²⁸ as shown in Scheme 2. After esterification, the resulting intermediate **13** was reacted with sodium ethoxide and bromoacetate to yield **14**, which was then cyclized to 4-pivalamidobenzofuranone **15**. Attempts to deprotect the pivaloyl group of **15** resulted in decomposition. We then coupled **15** directly with the 4-phenyl-7-azaindole core by heating with HCl in dioxane. To our delight, the pivaloyl group was also removed and the resulting amine **16** was further converted to the corresponding isocyanate, followed by treatment with methylamine to yield **3b**. Clearly, **3a** was 100-fold more potent than **3b** in inhibiting mTOR kinase, as shown in Table 1, confirming the modeling hypothesis. However, **3a** was 10-fold less potent and fourfold



Scheme 1. Reagents and conditions: (i) for **5a**: 4,4,5,5-tetramethyl-2-phenyl-1,3,2dioxaborolane, PS-Pd(PPh₃)₄, Na₂CO₃, DME, heat; for **5b**: NHR¹R², Pd₂(dba)₃, 2'-(dicyclohexylphosphino)-*N*,*N*-dimethylbiphenyl-2-amine, K₂HPO₄, dioxane or DME, heat; (ii) 5-ureidobenzofuranone **11**, EtOH, HCl, heat; (iii) CuBr₂, EtOAc, CHCl₃, reflux; (iv) HNO₃, HOAc; (v) Hunig base, EtOAc, room temperature; (vi) Fe, HOAc, H₂O, EtOAc, heat; (vii) R-NCO, CH₂Cl₂ or THF.

less selective compared to the corresponding 4-OH derivative **1b**. We then prepared a new methylurea **6a**, where a bridged morpholine was introduced at C-4 of the azaindole core instead of a 4-phenyl substituent shown in **3a**. To our delight, **6a** showed enhanced potency in mTOR and cells as well as selectivity, compared to **3a**. Therefore, we focused our optimization efforts on varying the 4-amino substituent on the azaindole core and the 5-ureido substituent on the benzofuranone of **6**. Derivatives **6** were prepared by converting the 4-bromide **4** to the 4-amino analogs **5b**, under Buchwald coupling conditions,²⁵ followed by condensation with a variety of 5-ureidobenzofuranones **11**, as depicted in Scheme 1.

A variety of substituted ureas, **6a–6f**, were prepared and evaluated for mTOR potency as shown in Table 2. Methylurea **6a** showed good potency (mTOR IC₅₀ = 9.5 nM) with 61-fold selectivity over



Scheme 2. Reagents and conditions: (i) SOCl₂, EtOH; (ii) NaOEt, BrCH₂CO₂Et; (iii) NaH, toluene, then NaOH, followed by HCl; (iv) **5a**, HCl, dioxane; (v) triphosgene, Et₃N, THF, followed by MeNH₂.

Table 1

Ureas versus hydroxyl derivatives



Compd	Sub		IC_{50}^{a} (nM)		
		mTOR	ΡΙ3Κα	Sel ^b	LNCap
1b 3a	5-	3.5 37	89 233	25.4 6	0.2 60
3b	4-	3500	>10,000	>2.9	>60

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = $(IC_{50} PI3K\alpha)/(IC_{50} mTOR)$.

PI3Ka. However, ethylurea 6b was sixfold less potent against mTOR compared to **6a**. Surprisingly, dimethylaminoethylurea **6c** was as potent as **6a**, but suffered a decrease in selectivity. Compared to methylurea 6a, phenylurea 6d was 15-fold less potent. However, 3-pyridylurea 6e was equipotent to 6a against mTOR, with higher selectivity and 10-fold higher cellular potency $(IC_{50} = 15 \text{ nM})$. Introducing a morpholine substituent on the 3-pyridyl ring gave 6f, which was as potent as 6e, however with significant loss in cellular activity. So we focused our analoging efforts on 3-pyridylureas and further investigated the effect of 4-bridged morpholines²³ on mTOR potency. Compared to morpholine **6g**, bridged morpholines **6e**, **6h**, **6i** showed enhanced mTOR potency and cellular activity, as shown in Table 3. Among them, 2,6-bridged morpholine 6e showed the highest selectivity (145-fold) over PI3Ka, whereas 3,6-bridged morpholine 6h was the most potent one in inhibiting mTOR kinase (IC₅₀ = 7.5 nM) and cellular proliferation (IC₅₀ = 1.8 nM). Other 4-substituted analogs carrying 4-pipe-





Compd	R	$IC_{50}^{a}(nM)$			$I{C_{50}}^a(\mu M)$
		mTOR	ΡΙ3Κα	Sel ^b	LNCap
6a	ξ́—CH₃	9.5	580	61	0.14
6b	≹−CH₂CH₃	57.0	311	5.5	2.8
6c	\$N	5.6	24	4	0.06
6d	₹-	145.0	498	3.4	0.28
6e	₹-√_N	14.3	2080	145	0.015
6f	₹-√_N_O	29.0	2220	76.6	>60

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = $(IC_{50} PI3K\alpha)/(IC_{50} mTOR)$.

Table 3

Morpholine versus bridged morpholines



Compd	NR ¹ R ²		$IC_{50}^{a}(nM)$			
		mTOR	ΡΙ3Κα	Sel ^b	LNCap	
6e	§−N_O	14.3	2080	145	0.015	
6g	ξ−N_O	71.0	275	4	0.05	
6h	§−N∕∕O	7.5	249	33	0.0018	
6i	§−N_O	42.0	128	3	0.006	

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = $(IC_{50} PI3K\alpha)/(IC_{50} mTOR)$.

ridinylamides, were also prepared as mTOR kinase inhibitors (Table 4). Their synthesis began with Buchwald coupling of 4 and 4-piperidinyl ester. The resulting ester was hydrolyzed and condensed with a variety of amines via mixed anhydride method²⁵ to yield amides. Final coupling of the amides with ureidobenzofuranone 11 yield 6j-6y. Dimethylamide 6j showed good mTOR potency and 193-fold selectivity. However, diethylamide 6k lost 10-fold in mTOR potency, compared to **6***i*, and was not selective. The morpholinylamides **61–6n** were all potent and selective mTOR inhibitors, with **6n** showing the highest selectivity (644-fold). Compared to morpholinylamide 61, N-Me-piperazinylamide 60 and piperidinylamide 6q showed reduced mTOR potency and selectivity, but enhanced cellular activity. Pyrrolidinylamide 6p was superior to piperidinvlamide **6a** in terms of mTOR potency and selectivity. To enhance the water solubility of **6p**, dimethylamino and ethoxy groups were introduced on the pyrrole ring (6r and 6s, respectively). Although both 6r and 6s were as potent as 6p, and more selective, they exhibited much reduced cellular activity. 3-Pyridylmethylaminoamide **6t** was found to be a potent (IC₅₀ = 9 nM) and selective (450-fold) mTOR inhibitor; unfortunately, it lacked cellular activity. This prompted us to prepare three isomers of *N*-methyl-(3-pyridylmethyl)aminoamides **6u–6w**. These three isomers were as potent as **6t**, however, with reduced selectivity. Analogs 6v and 6w showed good cellular activity. Interestingly, replacement of the pyridyl group of **6u** with a phenyl gave 6x that showed 10-fold reduction of mTOR potency. However, removal of the methylene bridge between the pyridine ring and N from **6u** did not affect the mTOR potency of the resulting derivative 6y and provided 4-fold and 10-fold enhancement in selectivity and cellular activity, respectively, as shown in Table 4.

An mTOR homology model was built based on the X-ray crystal structure of PI3K γ . The X-ray structure of our 4,6dihydroxybenzofuranone inhibitor **1a** bound to PI3K γ was used as the basis for docking studies in the mTOR homology model. Binding studies of urea **6h** with this homology model showed a hydrogen bond between N-7 and Val2240 in the hinge region of the ATP-binding domain of the enzyme as shown in Figure 2. Furthermore, the urea group forms three hydrogen bonds with the enzyme, namely the two NHs with Asp2195 and the carbonyl with Lys2187, consistent with what was predicted from the overlay studies shown in Figure 1. The homology model also showed an additional hydrogen bond between the 3-pyridyl nitrogen and Gln2167. Since the phenyl urea **6d** is not expected to form this Table 4

Piperidinylamides



Compd	NR ¹ R ²	$IC_{50}^{a}(nM)$			$I{C_{50}}^a(\mu M)$
		mTOR	ΡΙ3Κα	Sel ^b	LNCap
6j	≹—NMe₂	10.5	2030	193	0.08
6k	≹—NEt₂	115.0	308	2.7	0.05
61	ξ−N_O	18.0	2660	148	3.2
6m	§−N_O	17.0	1677	98.6	0.09
6n	§−N_O	5.4	3477	644	0.2
60	ξ−N_N−	70.0	4598	65.7	0.33
6p	Ş_N	8.2	909	111	0.012
6q	₹-N_	47.5	600	12.6	0.018
6r	§−NN	11.0	>10,000	>909	2.3
6s	§−N_−O	8.2	2310	282	0.19
6t	t termine termine ter	9.0	4040	450	60
6u		10.9	1030	94	3.2
6v	₹-N	9.3	1230	132	0.023
6w	↓ N ↓	8.4	1570	187	0.04
6x	Į−N ,	102.5	>10,000	>98	0.020
6y		13.0	4960	380	0.3

^a Determinations were done in duplicate and repeat values agreed, on average, with a mean twofold difference.

^b Selectivity = $(IC_{50} PI3K\alpha)/(IC_{50} mTOR)$.

specific hydrogen bond interaction, it is not surprising to see that 6d showed 10-fold reduction of mTOR potency compared to the corresponding 3-pyridyl urea 6e (Table 2). Furthermore, Gln2167 in mTOR is Lys776 in PI3Ka. The lysine likely prefers to interact with solvent, rather than the inhibitor. This may lead to the high selectivity (145-fold) of **6e** over PI3Ka. The bridged morpholines at C-4 of the azaindole core sit below the glycine-rich loop and the pocket in this region is quite large, especially compared to the region directly adjacent to the hinge region. It is likely that the bridged morpholines are able to fill more space in this area, resulting in increased potency (Table 3). However, the resolution of the homology model is not sufficiently high to help explain selectivity for groups (i.e., C-4 substituents) away from the hinge region. It is clear from the model that the amide substituent NR¹R² (Table 4) at C-4 point towards solvent, providing opportunity for future design of inhibitors.



Figure 2. Docking of 6h (in orange carbons) in an mTOR homology model based on the PI3K γ crystal structure. Hydrogen bonds are shown with black dashed lines and residue numbers are indicated for hydrogen bonding partners.

In conclusion, we have shown that 5-ureidobenzofuranones are attractive replacements for 4-hydroxybenzofuranones. Overlays of co-crystal structures of PI3Ky with 4,6-dihydroxylbenzofuranone 1a and pyrazolopyrimidine 2 suggested a ureido replacement for the 4,6-dihydroxy groups would be optimal at the 5-position. Molecular modeling studies of 6h suggested that potentially three hydrogen bonds can be formed between the urea group and the enzyme, and that these interactions were best achieved with the urea appendage on the 5-position. An additional hydrogen bond interaction between the pyridyl nitrogen and the enzyme appears to provide further enhancement of potency with 3-pyridylurea. Optimization of the C-4 substituents on the azaindole led to discovery of potent (low nanomolar) and selective (up to 132-fold) inhibitors of mTOR, with good cellular activity ($IC_{50} = 1.8-23 \text{ nM}$).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.02.012.

References and notes

- Yuan, T. L.; Cantley, L. C. Oncogene 2008, 27, 5497. 1.
- Carracedo, A.; Pandolfi, P. P. Oncogene 2008, 27, 5527. 2.
- Inoki, K.; Corradetti, M. N.; Guan, K. L. Nat. Genet. 2005, 37, 19. 3.
- Verheijen, J.; Yu, K.; Zask, A. Annu. Rep. Med. Chem. 2008, 43, 189. 4 5
- Strimpakos, A. S.; Karapanagiotou, E. M.; Saif, M. W.; Syrigos, K. N. Cancer Treat. Rev. 2009, 35, 148.
- 6. Baldo P. Cecco S. Giacomin E. Lazzarini R. Ros B. Marastoni S. Curr. Cancer Drug Targets 2008, 8, 647.
- 7 Guertin, D. A.; Sabatini, D. M. Cancer Cell 2007, 12, 9.
- Chiang, G. G.; Abraham, R. T. Trends Mol. Med. 2007, 13, 433. 8
- Fasolo, A.; Sessa, C. Expert Opin. Investig. Drugs 2008, 17, 1717. 9 10. Choi, J.; Chen, J.; Schreiber, S. L.; Clardy, J. Science 1996, 273, 239.
- 11. Liang, J.; Choi, J.; Clardy, J. Acta Crystallogr., Sect. D 1999, 55, 736.
- Maira, S.-M.; Staffer, F.; Brueggen, J.; Furet, P.; Schnell, C.; Fritsch, C.; Brachmann, S.; Chene, P.; De Pover, A.; Schoemaker, K.; Fabbro, D.; Gabriel, D. Staffer, M. Marche, J. 2010. D.; Simonen, M.; Murphy, L.; Finan, P.; Sellers, W.; Garcia-Echeverria, C. Mol. Cancer Ther. 2008, 7, 1851.
- 13. Folkes, A. J.; Ahmadi, K.; Alderton, W. K.; Alix, S.; Baker, S. J.; Box, G.; Chuckowree, I. S.; Clarke, P. A.; Depledge, P.; Eccles, S. A.; Friedman, L. S.; Hayes, A.; Hancox, T. C.; Kugendradas, A.; Lensun, L.; Moore, P.; Olivero, A. G.; Pang, J.; Patel, S.; Pergl-Wilson, G. H.; Raynaud, F. I.; Robson, A.; Saghir, N.; Salphati, N. C.; Wiesmann, C.; Workman, P.; Zhyvoloup, A.; Zvelebil, M. J.; Shuttleworth, S. I. J. Med. Chem. 2008, 51, 5522.
- 14. Feldman, M. E.; Apsel, B.; Uotila, A.; Loewith, R.; Knight, Z. A.; Ruggero, D.; Shokat, K. M. PLoS Biol. 2009, 7, 371.
- Garcia-Martinez, J. M.; Moran, J.; Clarke, R. G.; Gray, A.; Cosulich, S. C.; Chresta, C. M.; Alessi, D. R. *Biochem. J.* **2009**, 421, 29. 15
- Thoreen, C. C.; Kang, S. A.; Chang, J. W.; Liu, Q.; Zhang, J.; Gao, Y.; Reichling, L. J.; 16 Sim, T.; Sabatini, D. M.; Gray, N. S. J. Biol. Chem. 2009, 284, 8023.
- 17 Yu, K.; Toral-Barza, L.; Shi, C.; Zhang, W.-G.; Lucas, J.; Shor, B.; Kim, J.; Verheijen, J.; Curran, K.; Malwitz, D. J.; Cole, D. C.; Ellingboe, J.; Ayral-Kaloustian, S.; Mansour, T. S.; Gibbons, J. J.; Abraham, R. T.; Nowak, P.; Zask, A. Cancer Res. 2009, 69, 6232.
- Zask, A.; Verheijen, J. C.; Curran, K.; Kaplan, J.; Richard, D. J.; Nowak, P.; 18 Malwitz, D. J.; Brooijmans, N.; Bard, J.; Svenson, K.; Lucas, J.; Toral-Barza, L.; Zhang, W.-G.; Hollander, I.; Gibbons, J. J.; Abraham, R. T.; Ayral-Kaloustian, S.; Mansour, T. S.; Yu, K. J. Med. Chem. 2009, 52, 5013.
- 19. Menear, K. A.; Gomez, S.; Malagu, K.; Bailey, C.; Blakburn, K.; Cockroft, X.-L.; Ewen, S.; Fundo, A.; Le Gall, A.; Hermann, G.; Sebastian, L.; Sunose, M.; Presnot, T.; Torode, E.; Hickson, I.; Martin, N. M. B.; Smith, G. C. M.; Pike, K. G. Bioorg. Med. Chem. Lett. 2009, 19, 5898.
- 20. Richard, D. J.; Verheijen, J. C.; Curran, K.; Kaplan, J.; Toral-Barza, L.; Hollander, I.; Lucas, J.; Yu, K.; Zask, A. Bioorg. Med. Chem. Lett. 2009, 19, 6830.
- 21 Nowak, P.; Cole, D. C.; Brooijmans, N.; Bursavich, M. G.; Curran, K. J.; Ellingboe, J. W.; Gibbons, J. J.; Hollander, I.; Hu, Y.; Kaplan, J.; Malwitz, D. J.; Toral-Barza, L.; Verheijen, J. C.; Zask, A.; Zhang, W.-G.; Yu, K. J. Med. Chem. 2009, 52, 7081.
- 22. Verheijen, J.; Richard, D. J.; Curran, K.; Kaplan, J.; Lefever, M.; Nowak, P.; Malwitz, D. J.; Brooijmans, N.; Toral-Barza, L.; Zhang, W.-G.; Lucas, J.; Hollander, I.; Ayral-Kaloustian, S.; Mansour, T.; Yu, K.; Zask, A. J. Med. Chem. 2009, 52, 8010.
- 23. Zask, A.; Kaplan, J.; Verheijen, J. C.; Richard, D. J.; Curran, K.; Brooijmans, N.; Bennett, E. M.; Toral-Barza, L.; Hollander, I.; Ayral-Kaloustian, S.; Yu, K. J. Med. Chem. 2009, 52, 7942.
- Kaplan, J.; Verheijen, J. C.; Brooijmans, N.; Toral-Barza, L.; Hollander, I.; Yu, K.; 24. Zask, A. Bioorg. Med. Chem. Lett. 2009, 20, 640.
- 25 Tsou, H.-R.; MacEwan, G.; Birnberg, G.; Grosu, G.; Bursavich, M. G.; Bard, J.; Brooijmans, N.; Toral-Barza, L.; Hollander, I.; Mansour, T. S.; Ayral-Kaloustian, S.; Yu, K. Bioorg. Med. Chem. Lett., 2010, doi:10.1016/j.bmcl.2010.01.135.
- King, L. C.; Ostrum, G. K. J. Org. Chem. 1964, 29, 3459. 26.
- 27. Joshi, S. S.; Singh, H. J. Am. Chem. Soc. 1954, 76, 4993.
- 28. Hillis, L. R.; Gould, S. J. J. Org. Chem. 1985, 50, 718.