ELSEVIER

Bioorganic & Medicinal Chemistry Letters

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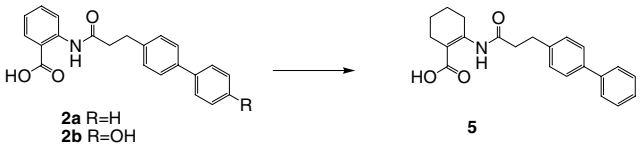
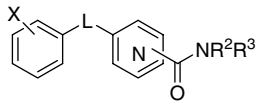
Contents

ARTICLES

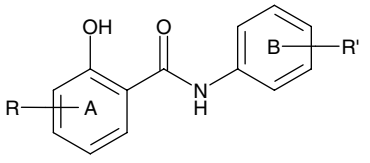


A series of cycloalkene acid-based niacin receptor agonists were designed and synthesized. Several compounds that were potent against the niacin receptor, with enhanced cytochrome P450 selectivity against subtypes CYP2C8 and CYP2C9 and had improved oral exposure in mice were identified.

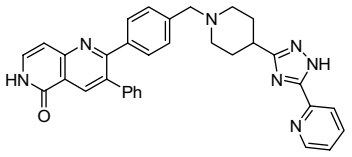


L= CH_2SO_2, CH_2S, CH_2O, S, O, N, bond

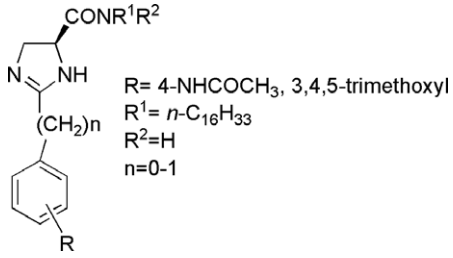
The synthesis and biological evaluation of a series of potent and selective pyridine amide 11β-HSD1 inhibitors is reported.



Halosalicylamide derivatives were evaluated as broad genotype inhibitors of HCV polymerase.



Akt1 IC_{50} = 3.5 nM
Akt2 IC_{50} = 42 nM
Cell Akt1 IC_{50} = 16 nM
Cell Akt2 IC_{50} = 266 nM



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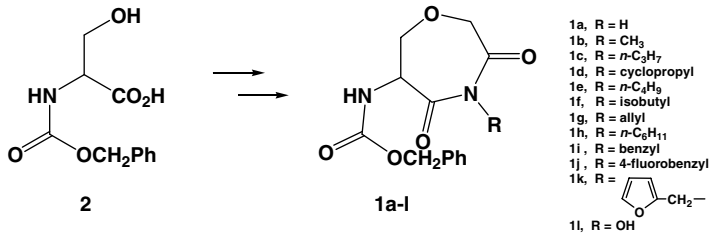
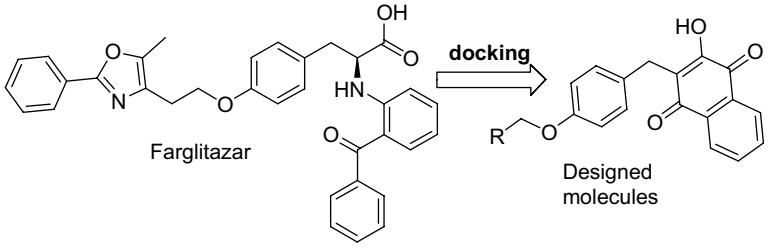
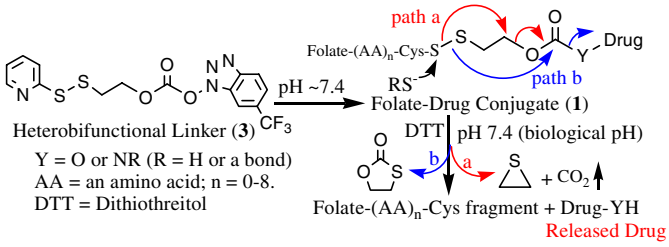


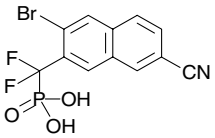
A series of 6-amino-1,4-oxazepane-3,5-dione derivatives, which are 7-membered heterocyclic imides and have N-CO-C-N group in their structures, were designed, synthesized, and their anticonvulsant activities were evaluated by both the MES and PTZ tests.

2-Hydroxy-1,4-naphthoquinone was identified as a novel 'acidic head group' for the design of new series PPARγ ligands using docking studies. Synthesis and receptor-binding studies were used to validate the concept.



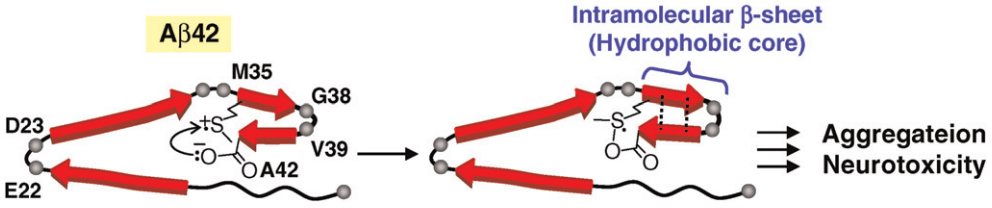


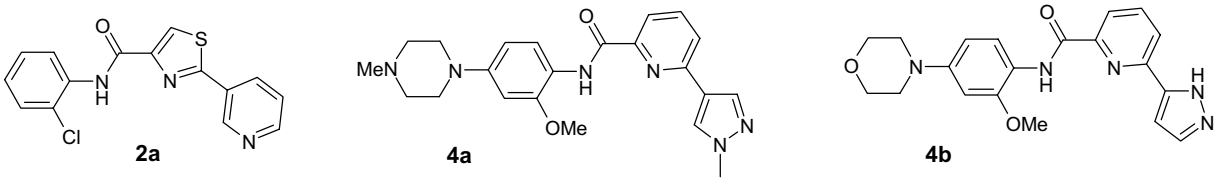
A novel heterobifunctional disulfide-containing linker **3** was synthesized and utilized to create targetable folate–drug conjugates **1** that were shown to release free drugs under biologically relevant pH via sulfhydryl-assisted cleavage.



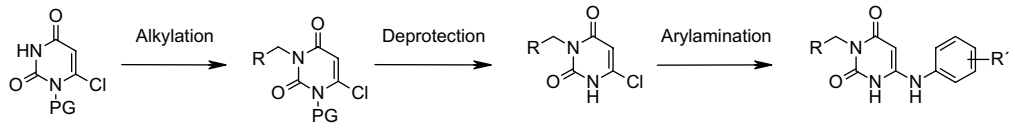
3g IC_{50} = 120 nM

The discovery of the potent and orally active PTP1B inhibitor **3g** (IC_{50} = 120 nM, ED_{50} = 0.8 mg/kg in oGTT) is reported.

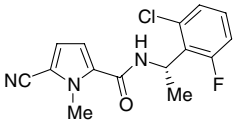


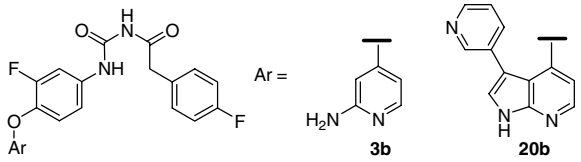


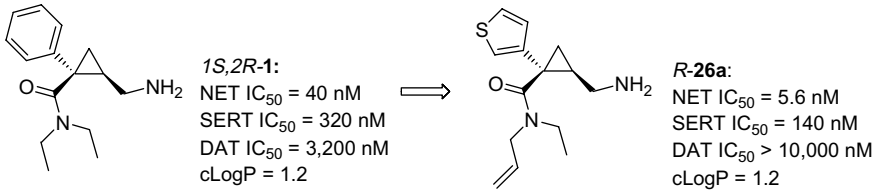
A series of amides, based on the screening hit **2a**, were prepared and profiled. Some potent IRAK-4-inhibitors were identified and two examples, **4a** and **4b**, were progressed into an in vivo PK study.

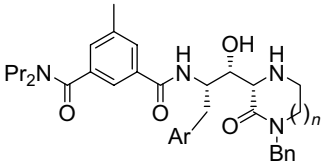


3-Substituted 6-anilinouracils, presently the most promising class of inhibitors of the bacterial DNA polymerase in Gram-positive bacteria, have been prepared by a general and straightforward three-step procedure starting from a readily available 1-benzyloxymethyl-protected derivative of 6-chlorouracil.





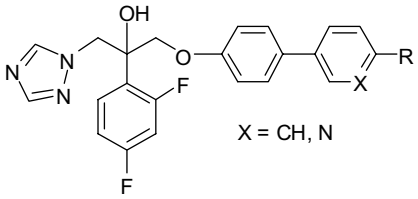




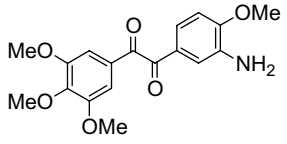
Ar = 3,5-difluorophenyl

n = 1, BACE1 IC_{50} = 3 nM
n = 0, BACE1 IC_{50} = 5 nM

Two novel, potent cyclic amine motifs for BACE1 inhibitors are described, along with their SAR in both the non-prime and prime subsites.

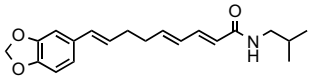


A series of novel biaryloxy-substituted triazole derivatives were synthesized and evaluated for their antifungal activity against eight human pathogenic fungi in vitro. Seventeen compounds showed higher activity than voriconazole against *Candida albicans*.



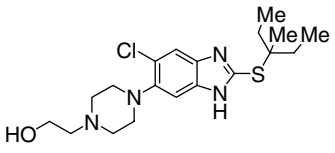
4k IC_{50} = 20-50 nM

Benzil derivatives related to combretastatin A-4 exhibit excellent antiproliferative and antimitotic activities by arresting the cell cycle in G2/M phase.



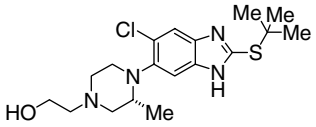
retrofractamide A

Several amide constituents (piperlonguminine and retrofractamides A, B, and C) from the fruit of *Piper chaba* promoted adipogenesis of 3T3-L1 cells. Among them, retrofractamide A was the most active and significantly increased the amount of adiponectin released into the medium and the uptake of 2-deoxyglucose into the cells. Retrofractamide A also increased mRNA levels of adiponectin, peroxisome proliferator-activated receptor γ2 (PPARγ2), glucose transporter 4 (GLUT4), and insulin receptor substrate 1 (IRS-1), but did not act as a PPARγ agonist different from troglitazone.

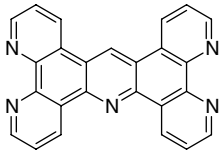


28

A structurally novel ORL1 selective antagonist with a (piperazin-1-yl)benzimidazole scaffold was identified. Among them, an analogue **28** exhibited sub-nanomolar antagonistic activity.



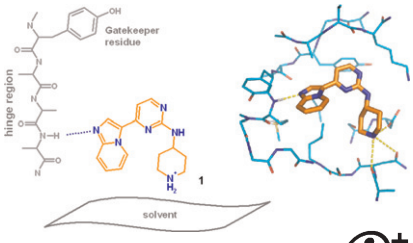
A novel ORL1-selective antagonist with oral bioavailability and brain penetrability, 2-(*tert*-butylthio)-5-chloro-6-[(2*R*)-4-(2-hydroxyethyl)-2-methylpiperazin-1-yl]-1*H*-benzimidazole, was identified in a 5-chloro-6-[piperazin-1-yl]-1*H*-benzimidazole series.

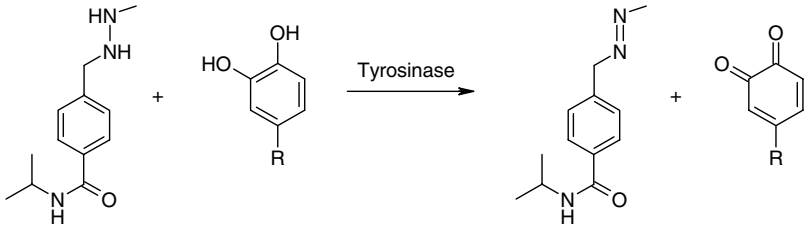


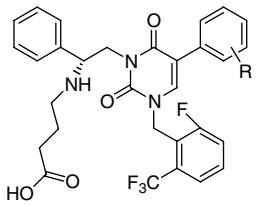
tpac

The nuclease activity of the copper(II)–tpac system induced by visible light is reported.

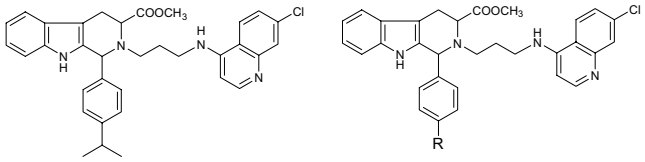
The binding mode of a series of IRAK-4 inhibitors derived screening hit **1** was inferred using a combination of in silico docking into a homology model, surrogate crystal structure analysis and analogue SAR.







8a: R = 2-F,3-MeO
8d: R = 2-Cl

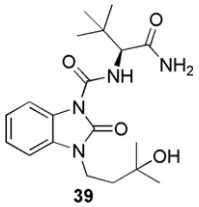


26
MIC: 0.05 μM

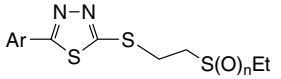
32, R= Me, MIC: 0.06 μM
34, R= Et, MIC: 0.11 μM

A series of hybrid molecules 2-[3-(7-Chloro-quinolin-4-ylamino)-alkyl]-1-(substituted phenyl)-2,3,4,9-tetrahydro-1*H*-β-carbolines have been synthesized and screened for their in vitro antimalarial activity against *Plasmodium falciparum.*

Benzimidazolone derivatives as novel CB2 selective agonists are reported. Compound **39** exhibited excellent metabolic stability and significant attenuation of the visceral allodynia in a rat model by oral administration.

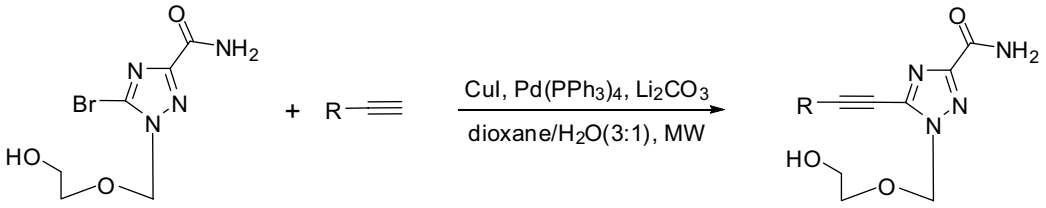


39
hCB2 Ki = 8 nM
HLM T1/2 >120 min

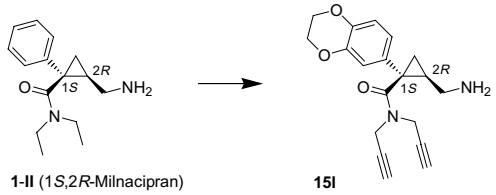


n = 0, 2
Ar = 5-nitrothiophene-2-yl; 5-nitrofuran-2-yl; 1-methyl-5-nitroimidazol-2-yl; nitrophenyl

The synthesis and anti-*Helicobacter pylori* activity of 2-[2-(ethylthio)ethylthio]-5-(nitroaryl)-1,3,4-thiadiazoles and 2-[2-(ethylsulfonyl)ethylthio]-5-(nitroaryl)-1,3,4-thiadiazoles were described.

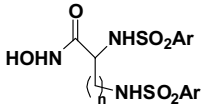


Novel ethynyltriazole acyclonucleosides were synthesized efficiently via a one-step Sonogashira reaction in aqueous solution and under microwave irradiation. Some of them elicit potent antiviral activity against hepatitis C virus, and constitute therefore an interesting structural lead in the search for novel antiviral candidates.



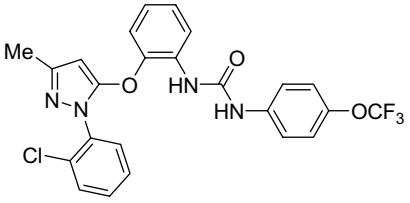
1-II (1*S*,2*R*-Milnacipran)
NET IC_{50} = 40 nM
SERT IC_{50} = 320 nM
DAT IC_{50} = 3,200 nM
cLogP = 1.2

15l
NET IC_{50} = 1.7 nM
SERT IC_{50} = 25 nM
DAT IC_{50} >10,000 nM
cLogP = 0.7

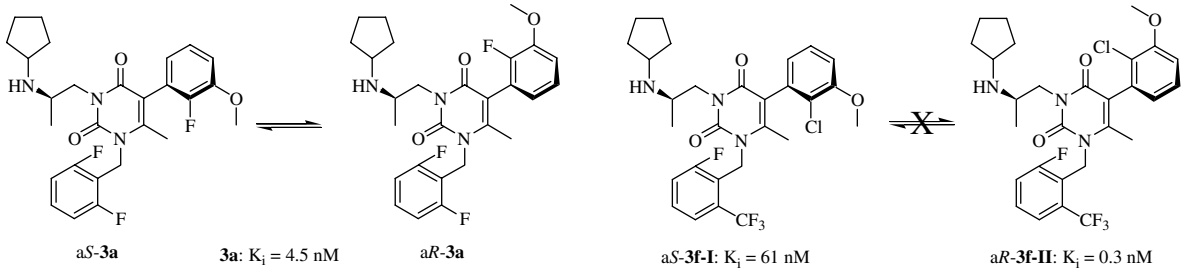


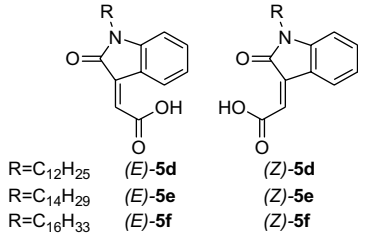
K_i = 1.8 μM (MMP-7)
2.6 nM (MMP-9)
1.6 μM (MMP-10)

The syntheses of a series of selective MMP inhibitors are described.

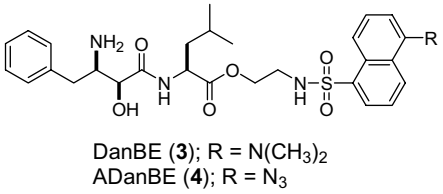


This manuscript describes the synthesis and evaluation of a series of $P2Y_1$ receptor antagonists for the treatment of platelet aggregation disorders.

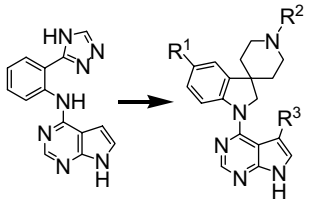


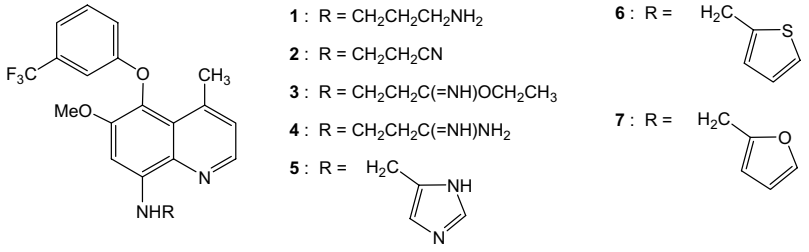


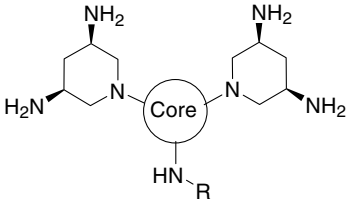
N-Alkyl oxindolylidene acetic acids (*E*)-**5d**–**f** and (*Z*)-**5d**–**f** were designed and synthesized, and were found to show strong inhibitory activity towards Cdc25A (IC_{50} = 1.6–2.9 μM).



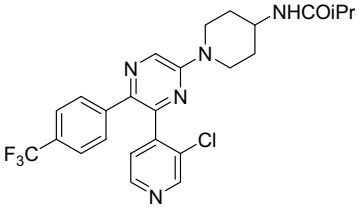
Fluorescent bestatin ester analogs **3** and **4** were designed and synthesized. Direct binding of cIAP1-BIR3 domain protein and these probes was observed in fluorescence polarization assay and photoaffinity labeling assay.



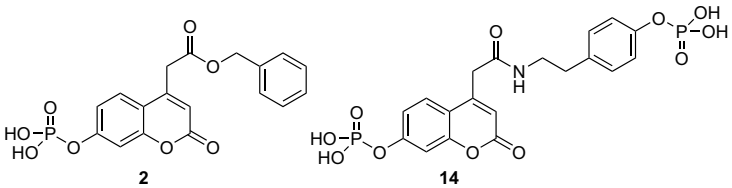




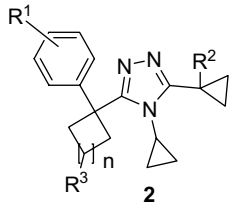
Core = triazine, pyridine, pyrimidine or purine



18c, hCB1 K_i = 0.24 nM



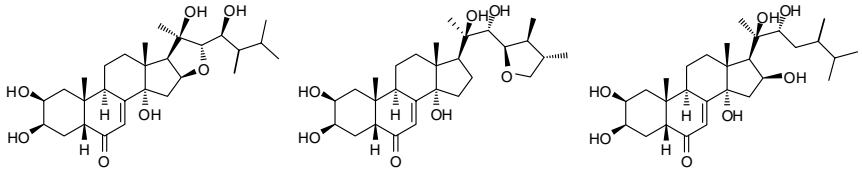
We have prepared and evaluated nine novel analogs of 4-methylumbelliferone phosphate (MUP) with a variety of additional groups occupying the second phosphate binding pocket of PTP1B. Surprisingly, the simple benzyl ester **2** was an equivalent substrate for the enzyme as phosphotyrosine mimic **14**.



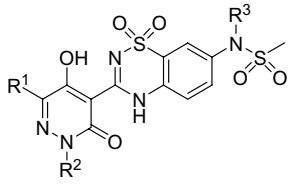
2

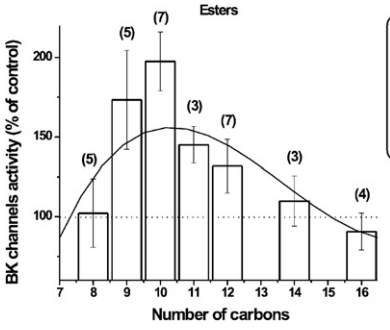
The synthesis and biological activity of selective inhibitors of 11β-hydroxysteroid dehydrogenase type I are reported.

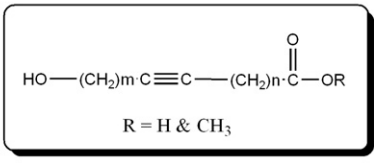
Three new ergostane-type ecdysteroids along with five known ecdysteroids were isolated from the sclerotium of *Polyporus umbellatus* under bioassay-guided purification. All compounds exhibited potent anti-inflammatory activity in the test of TPA-induced inflammation in mice.



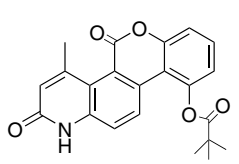
1 2 3





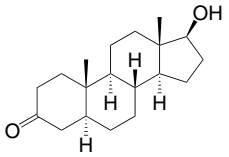


C-8	m = 2	n = 3
C-9	m = 2	n = 4
C-10	m = 3	n = 4
C-11	m = 3	n = 5
C-12	m = 4	n = 5
C-14	m = 4	n = 7
C-16	m = 4	n = 9



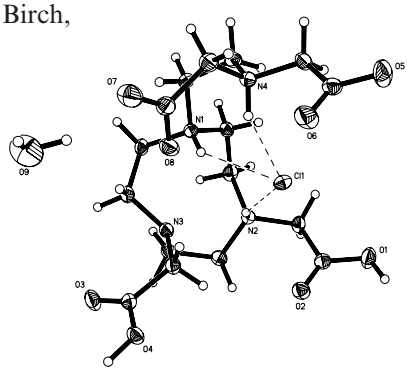
5d

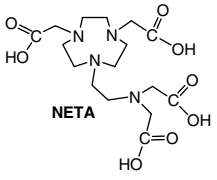
hAR EC_{50} (Eff.) = 1.1 nM (132%)



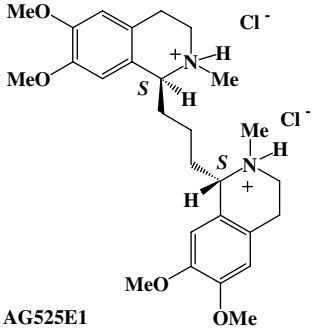
DHT

hAR EC_{50} (Eff.) = 5.1 nM (100%)





NETA



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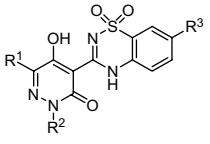

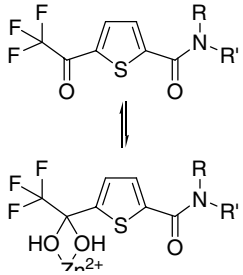

OTHER CONTENTS

*Corresponding author

ⓘ+ Supplementary data available via ScienceDirect

COVER

Overlay of high resolution co-crystal structures of *R*-**22**-ADP (cyan) and **1**-ADP (green) bound in an allosteric binding site of the mitotic kinesin KSP. [Roecker, A. J.; Coleman, P. J.; Mercer, S. P.; Schreier, J. D.; Buser, C. A.; Walsh, E. S.; Hamilton, K.; Lobell, R. B.; Tao, W.; Diehl, R. E.; South, V. J.; Davide, J. P.; Kohl, N. E.; Yan, Y.; Kuo, L. C.; Li, C.; Fernandez-Metzler, C.; Mahan, E. A.; Prueksaritanont, T.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5677.]

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