Bioorganic & Medicinal Chemistry Letters 19 (2009) 1267–1282

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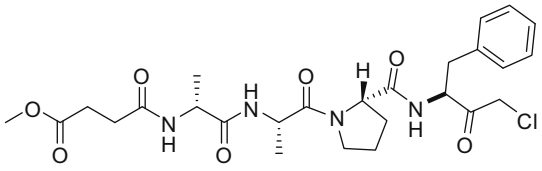
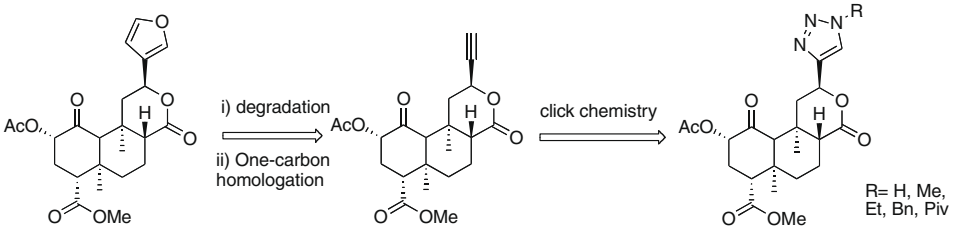
Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 5, 2009

Contents

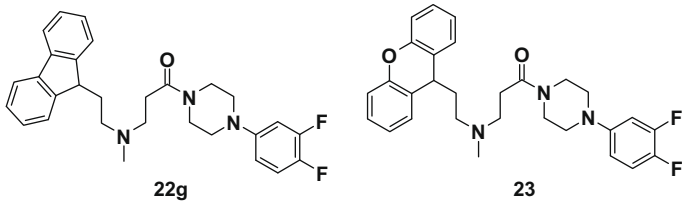
ARTICLES



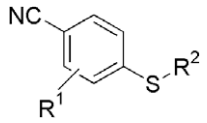
The synthesis and biological evaluation of MeOSuc-Ala-Ala-Pro-Phe-CH_2Cl as potent proteinase K inhibitor is reported.

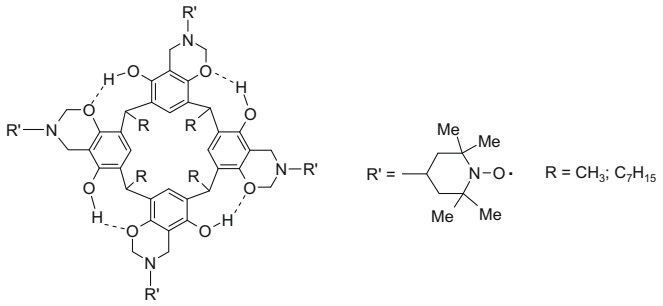


We have carried out the synthesis and biological evaluation of C-12 triazole and oxadiazole analogs of salvinorin A. SAR studies suggest that electronic factors that may affect either the electron density of hydrogen bond acceptor at C-12 or hydrophobic interactions between C-12 moiety and KOPR are critical to salvinorin A templated C-12 analog's affinity for KOPR.

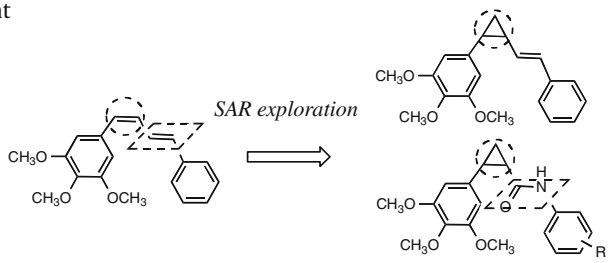


Pharmacophore considerations based on obeline and ergoline somatostatin sst_1 receptor antagonists led to the design of an achiral β-alanine piperazine amide derivative with largely retained sst_1 affinity and selectivity. Systematic optimization of this initial hit afforded highly potent and selective sst_1 receptor antagonists like fluorenyl derivative **22g** or xanthenyl derivative **23**. These achiral, non-peptidic compounds are easily prepared and show promising PK properties in rodents.

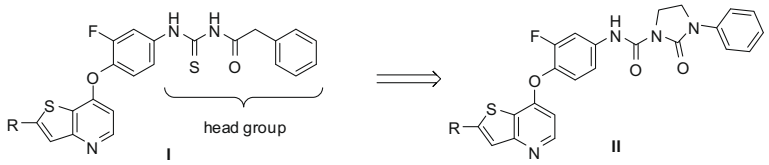




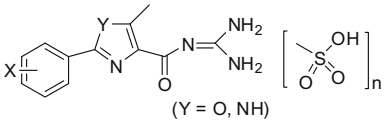
A resorcinarene oxazines bearing four TEMPO fragments at the wide rim exhibit a strong antiradical and antioxidant properties in model systems.



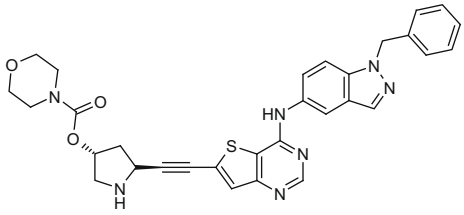
Docking of two representative compounds in the colchicine binding site of tubulin is reported.



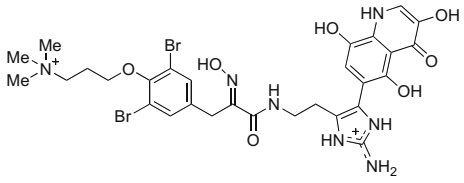
A series of *N*-(3-fluoro-4-(2-arylthieno[3,2-*b*]pyridin-7-yloxy)phenyl)-2-oxo-3-phenylimidazolidine-1-carboxamides (**II**) targeting c-Met and VEGFR2 tyrosine kinases, based on our previous acetylthiourea series (**I**), was designed and synthesized. The new compounds were potent against these two enzymes with IC_{50} values in the low nanomolar range *in vitro*, possessed favorable pharmacokinetic profiles and showed high efficacy *in vivo* in several human tumor xenograft models in mice.



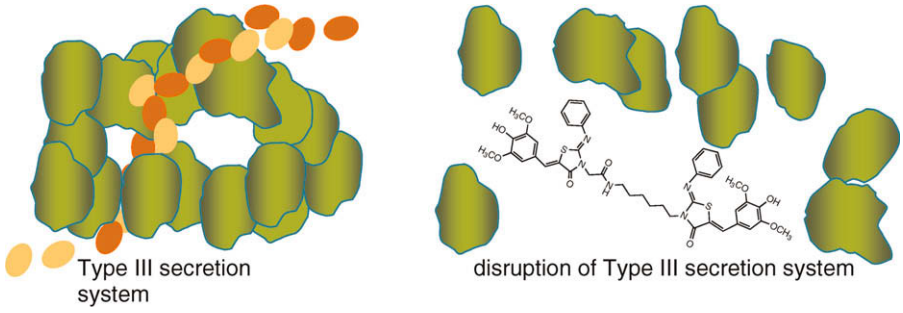
The synthesis and evaluation of (2-aryl-5-methylimidazol-4-ylcarbonyl)guanidines and (2-aryl-5-methyloxazol-4-ylcarbonyl)guanidines as NHE-1 inhibitors are described.

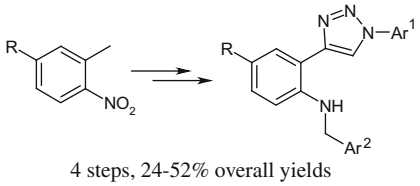


Aniline 'headgroups' were synthesized and incorporated into an alkynyl thienopyrimidine series of EGFR and ErbB-2 inhibitors. Potent inhibition of enzyme activity and cellular proliferation was observed. In certain instances, protein binding was reduced and oral exposure was found to be somewhat improved relative to compounds containing the reference aniline.



tyrokeradine A (**1**)

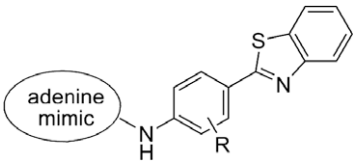


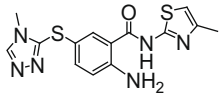


4 steps, 24-52% overall yields

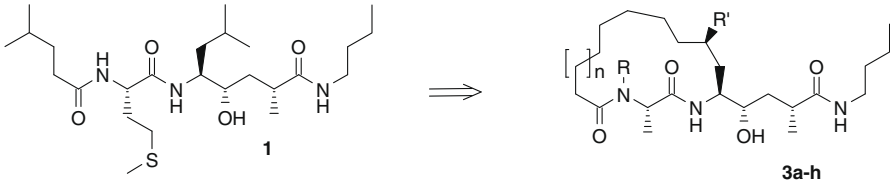
Ar^1	Ar^2	VEGFR-2, enzymatic, IC_{50}, μM[a]	VEGFR-2, cell-based ELISA, IC_{50}, μM[a-c]
3-Cl-(C_6H_4)	4-Pyridine	0.087±0.011	0.16±0.05[a]
3-F_3C-(C_6H_4)	4-Pyridine	0.051±0.05	0.096±0.14
3-F_3CO(C_6H_4)	4-Pyridine	0.066±0.005	0.085±0.02
4-Me-3-F_3C(C_6H_3)	4-Pyridine	0.14±0.03	0.18±0.03
3-Cl-(C_6H_4)	4-Quinolyl	0.19±0.08	0.27±0.06
3-F_3C(C_6H_4)	4-Quinolyl	0.16±0.04	0.31±0.09

Both synthesis and activity of the novel derivatives of (1,2,3-triazol-4-yl)benzenamines are described. Selected molecules of these series are potent and selective inhibitors of vascular endothelial growth factor receptors I and II (VEGFR-1/2).

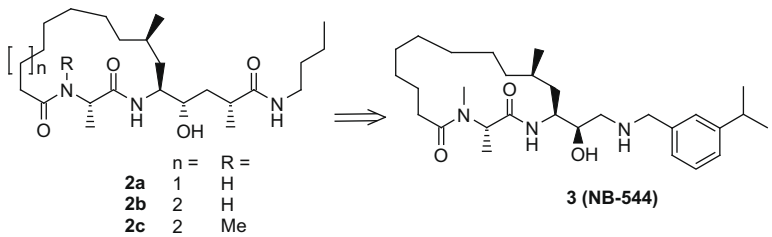




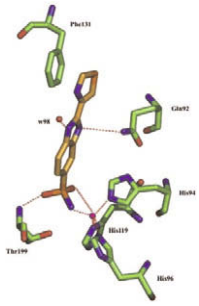
The discovery and structure-activity-relationships of novel 2-amino benzamide glucokinase activators are described.

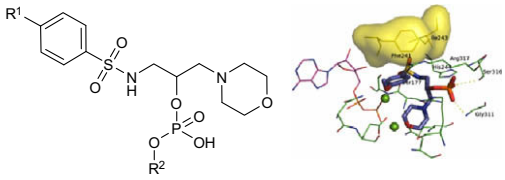


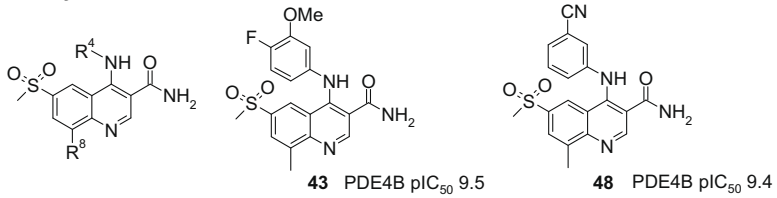
An X-ray co-crystal structure of **1** with BACE-1 allowed the design and syntheses of a series of macrocyclic analogues **3a**–**h**. These inhibitors show improved potency over their open-chain analogue.



The macrocyclic peptidic BACE-1 inhibitors **2a**–**c** were optimized to the highly potent and selective inhibitor **3**. This compound shows inhibition of BACE-1 in the brain of APP51/16 transgenic mice, after intravenous application.

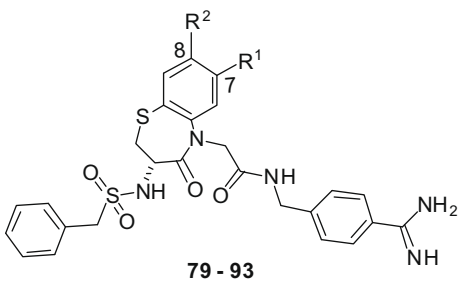






43 PDE4B pIC_{50} 9.5 **48** PDE4B pIC_{50} 9.4

A series of quinoline-3-carboxamides has been identified as potent inhibitors of PDE4. The SAR has been explored and these studies have highlighted compounds **43** and **48** which show good potency, selectivity and rat PK suitable for oral dosing. The crystal structure of an example quinoline bound into the active site of PDE4 is also described.



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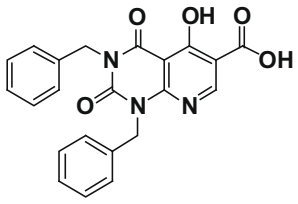
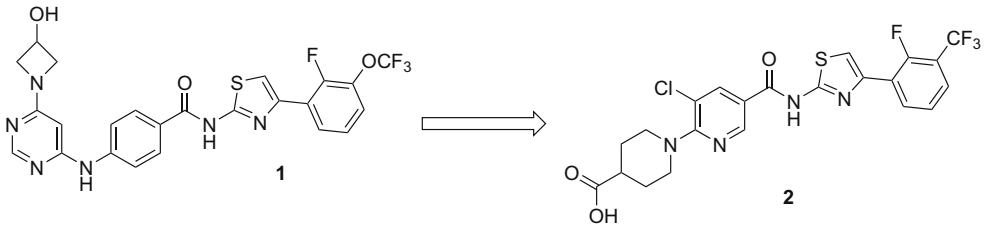
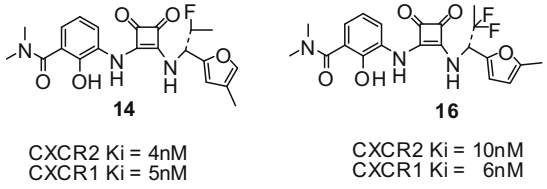
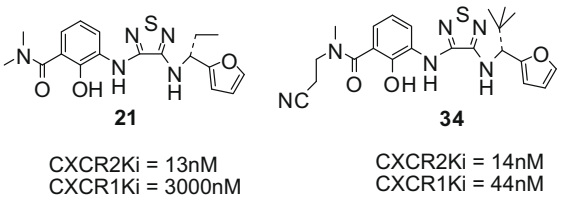




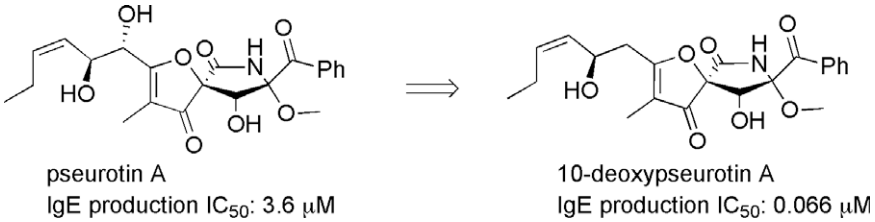
Progress towards the identification of bioavailable drug-like thrombopoietin agonist is reported.

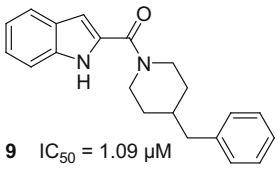


A series of potent and orally bioavailable 3,4-diaminocyclobutenediones with various fluoroalkyl groups as α side chain were prepared and found to show significant improvements in the binding affinities towards both CXCR2 and CXCR1 receptors.

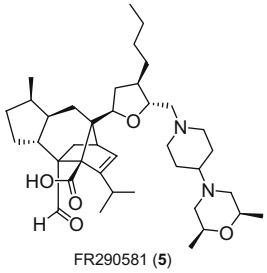


A novel series of potent and selective 3,4-diamino-1,2,5-thiadiazoles were prepared as CXCR2 receptor antagonists.

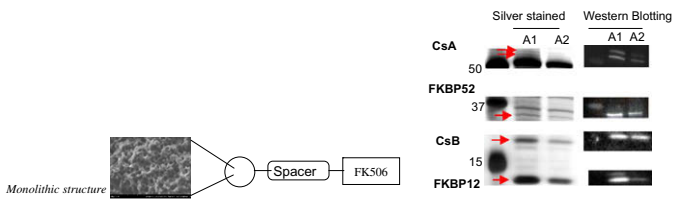




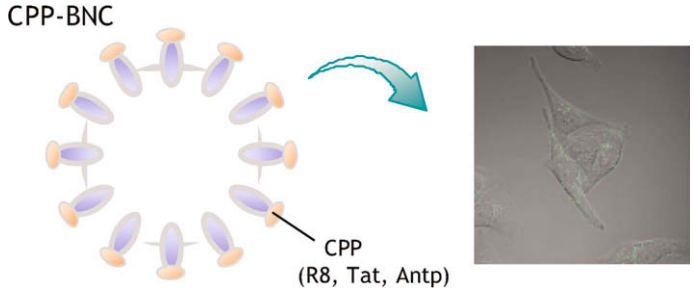
Heterocyclic 2-amides were identified as novel lead structures for p38 MAP kinase inhibition, and a SAR analysis of 25 compounds was executed.



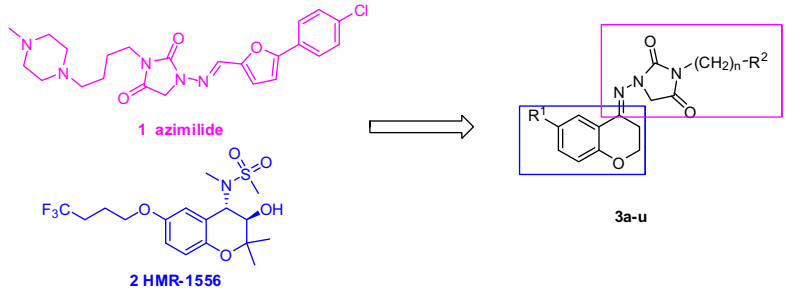
We have discovered the novel sordarin derivative FR290581, which exhibited superior activity, a good pharmacokinetic profile and good in vivo activity.



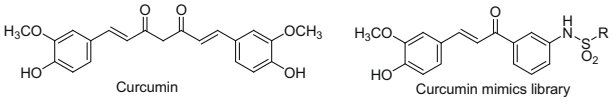
Introduction effects of spacer to monolithic solid material on identification of specific binding protein was analyzed using benzensulfonamide as a bait, which exhibited introduction of ω-substituted heptanoic acid as spacer enabled affinity resins effectively to capture carbonic anhydrase type 2 from rat brain lysate with little amount of non-specific protein absorption. The same material with the optimized spacer bearing FK506 successfully captured FKBP52, calcineurin A and B at silver stained level as well, while that without spacer has failed.

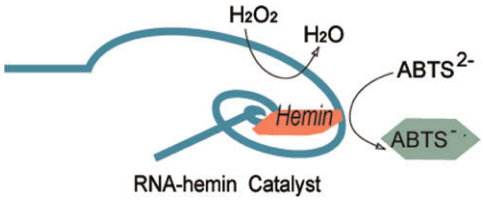


Bionanocapsules displaying cell-penetrating peptide (CPP-BNC) was constructed. CPP-BNC was efficiently internalized into various cell lines in a short time, compared with original BNC.

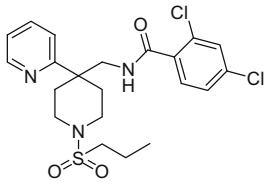


On the rationale of molecular hybridization of azimilide and HMR-1556, a novel series of I_{Kr} and I_{Ks} dual blockers were designed, synthesized and evaluated.



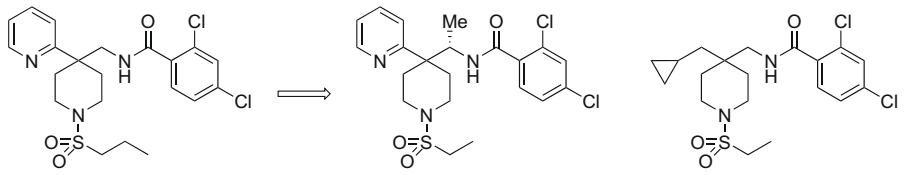


In vitro selection of catalytic RNA with peroxidase activity is reported.



GlyT1 (IC_{50}) 4.4 nM

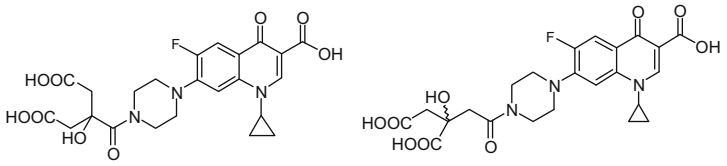
Solublility in water (850 ug/mL, HCl salt)



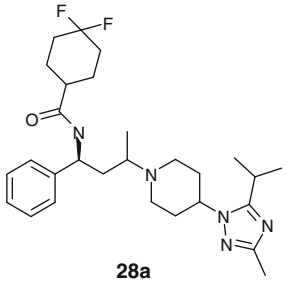
GlyT1 IC_{50} 4.4 nM
Dog $t_{1/2}$ 2.3 h

GlyT1 IC_{50} 11 nM
Dog $t_{1/2}$ 5 h

GlyT1 IC_{50} 26 nM
Dog $t_{1/2}$ 11.8 h

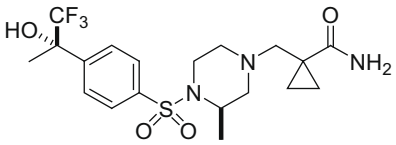


Citrate-functionalized ciprofloxacin conjugates have been synthesized and antimicrobial activities against clinically-relevant bacteria determined. Uptake mechanisms were investigated using wild-type and *ompF* deletion strains of *Escherichia coli* K-12.



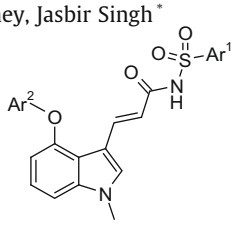
28a

Optimisation of a series of compound 4-piperidinyltriazoles led to the identification of **28a** which showed good whole cell antiviral activity, excellent selectivity over the hERG ion channel and complete oral absorption.

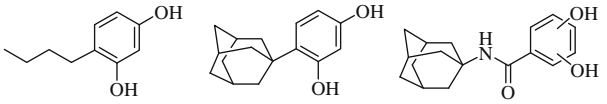


(S)-28

The synthesis and SAR of a series of arylsulfonylpiperazine inhibitors of 11β-HSD1 are described. Optimization rapidly led to potent, selective, and orally bioavailable inhibitors demonstrating efficacy in a cynomolgus monkey ex vivo enzyme inhibition model.



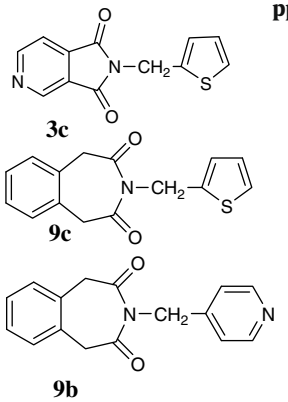
A series of potent and selective EP_3 receptor antagonists are described. Utilizing a pharmacophore model developed for the EP_3 receptor, a series of 3,4-disubstituted indoles were found to be efficient ligands for this target. These compounds showed high selectivity over IP, FP and other EP receptors. An optimized molecule **7c** featured a sound profile and potency in the functional rat and human platelet aggregation assays.



4-*n*-butyl resorcinol **1** **6a-e**

Dihydroxyl benzamide derivatives **6a–e** significantly suppressed the cellular melanin formation without tyrosinase inhibitory activities.

A number of N-substituted cyclic imides have been synthesized and screened for anticancer been synthesized and screened for anticancer **9c** exhibited good anticancer activity against colon (COLO-205) cancer and **9b** exhibited good anti-inflammatory activity.



3c

9c

9b

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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