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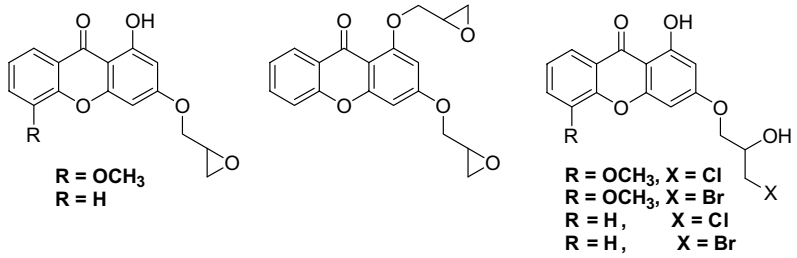
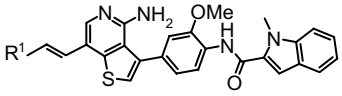
Contents

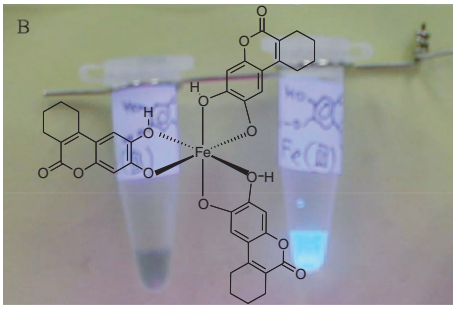
ARTICLES



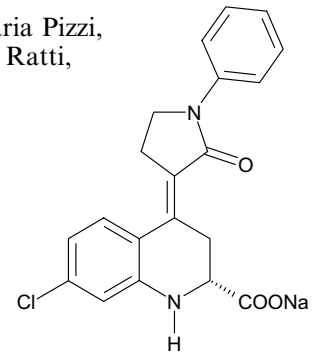


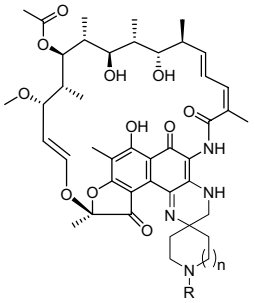
We describe the identification, SAR, and in vivo pharmacology of a new series of Src-family selective Lck inhibitors. These thienopyridines were designed to access the unique residues in the extended hinge region of Lck.

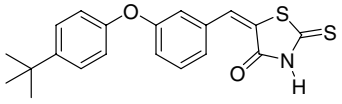
A black precipitate that is formed of three molecules of 3,4-cyclohexenoesculetin per ion of iron III is applied for visual detection of retro-aldol retro-Michael catalytic activity.



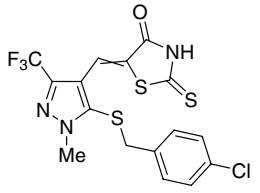
Chiral tetrahydroquinolines have been prepared by an asymmetric Mannich-*type* condensation reaction as in vivo potent anti-hyperalgesic agents in different animal models of chronic pain.





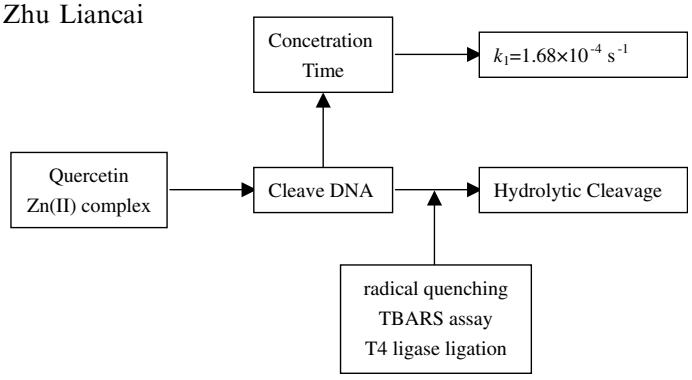


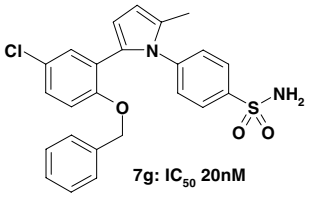
ADAMTS-5 IC_{50}: 1.7 μM



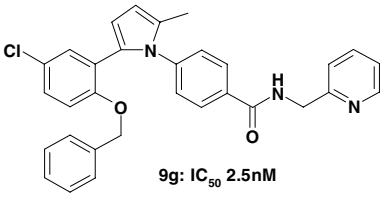
ADAMTS-5 IC_{50}: 1.1 μM
ADAMTS-4 IC_{50}: 44 μM

Carbazole sulfonamides **II** showed potent antiproliferative activity.

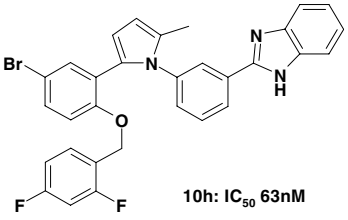




7g: IC_{50} 20nM

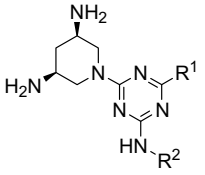


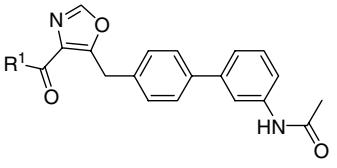
9g: IC_{50} 2.5nM



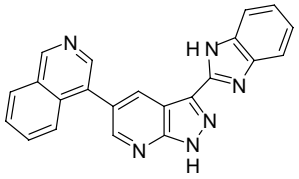
10h: IC_{50} 63nM

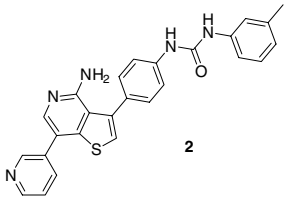
The discovery and SAR of novel non-acidic 1,5-biaryl pyrrole derivatives is described. Several new motifs were discovered that were found to be effective replacements for the carboxylic acid in a series of EP_1 receptor antagonists.

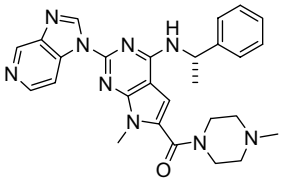


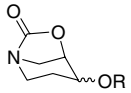


The synthesis and evaluation of 5-(4-phenylbenzyl)oxazole-4-carboxamides as prostacyclin receptor antagonists is reported.

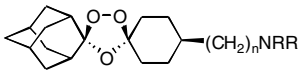




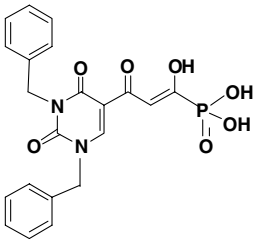


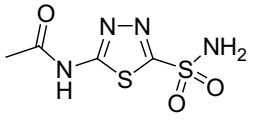


The discovery, SAR, and MoA investigation of a novel non-peptidic protease inhibitor scaffold are described.



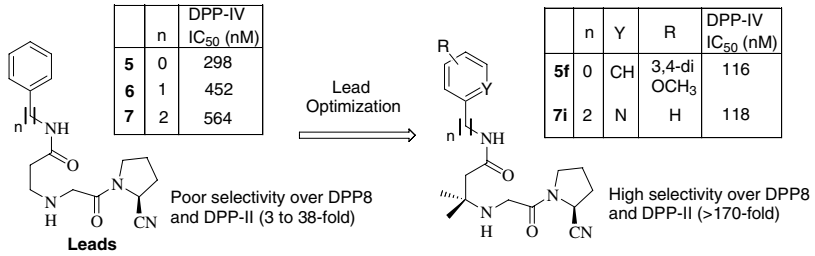
n = 0-2, R = H, alkyl, aryl





AZA

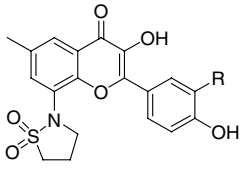
A series of carbonic anhydrase inhibitors, including AZA, have been found to inhibit AQP4 mediated water transport in an in vitro functional assay. AZA has an apparent $IC_{50} = 0.9\ \mu M$ against human AQP4-M23.



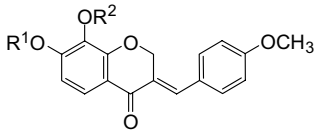
	n	DPP-IV IC_{50} (nM)
5	0	298
6	1	452
7	2	564

	n	Y	R	DPP-IV IC_{50} (nM)
5f	0	CH	3,4-di OCH_3	116
7i	2	N	H	118

Trypanothione reductase (TR) was screened against 134,500 compounds. Four chemotypes were selective for TR over human glutathione reductase. The in vitro activity of 13 purchased compounds against TR and *Trypanosoma brucei* is summarized.



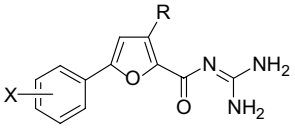
A novel series of 3-hydroxychromones were prepared and found to be CDK inhibitors. Isothiaszolidine 1,1-dioxide analogues showed potent CDK1 and CDK2 inhibitory activities and inhibited proliferation of EJ, HCT116, SW620, and MDA MB468 cancer cells.



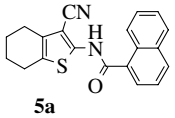
1. $R^1=R^2=H$; **2**. $R^1=CH_3$, $R^2=H$

3. $R^1=H$, $R^2=CH_3$

Intricatin (**2**) has been revised into **3** and antioxidant activity results are reported.



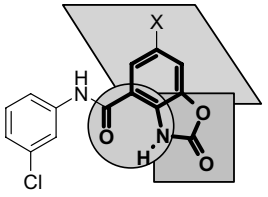
The synthesis and evaluation as NHE-1 inhibitors of 3-substituted-(5-arylfuran-2-ylcarbonyl)guanidines is described.



5a

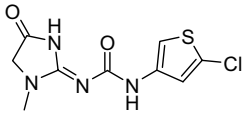
The identification and exploration of a novel, potent and selective series of *N*-(3-cyano-4,5,6,7-tetrahydro-1-benzothien-2-yl)amide inhibitors of JNK2 and JNK3 kinases is described. Compounds **5a** and **11a** were identified as potent inhibitors of JNK3 (pIC_{50} 6.7 and 6.6, respectively), with essentially equal potency against JNK2 (pIC_{50} 6.5). Selectivity within the mitogen-activated protein kinase (MAPK) family, against JNK1, p38α and ERK2, was observed for the series. X-ray crystallography of **5e** and **8a** in JNK3 revealed a unique binding mode, with the 3-cyano substituent forming an H-bond acceptor interaction with the hinge region of the ATP-binding site.

A novel class of potent and stable mGlu5 receptor antagonists was developed by combining information from a high-throughput screening campaign with the structure of the known anxiolytic fenobam.

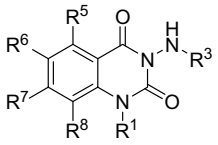


6, X = H Ki: 68 nM
7, X = Cl Ki: 95 nM

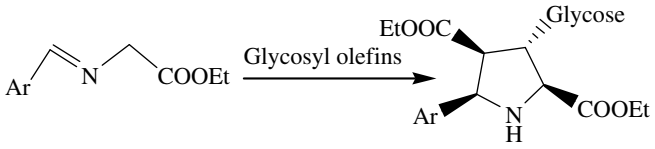
Optimization of affinity and microsomal stability led to identification of the potent, metabolically stable fenobam analog **4l**. Robust in vivo efficacy of **4l** was demonstrated in four different models of anxiety. Additionally, a ligand based pharmacophore alignment of fenobam and MPEP is proposed.

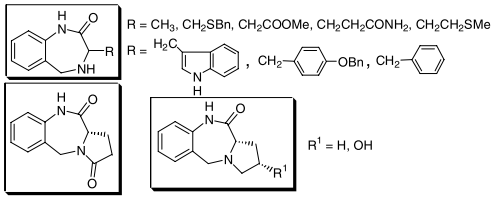


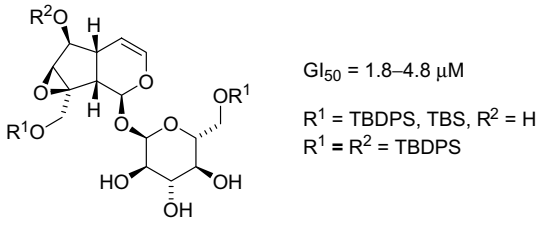
4l
Ki (^{3}H-MPEP): 78 nM
FLIPR: 436 nM



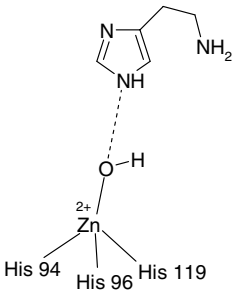
The syntheses and antibacterial SAR of the 3-aminoquinazolinediones are reported.

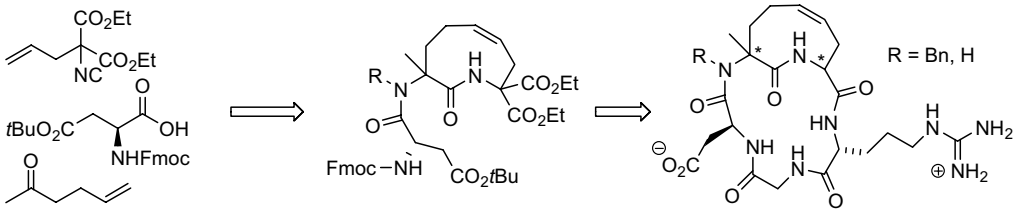


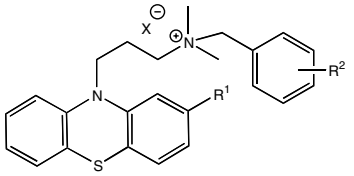




A series of new silylated catalpol analogs inhibit in a dose-dependent manner the proliferation of a panel of diverse human cancer cell lines through G_0/G_1 phase arrest.

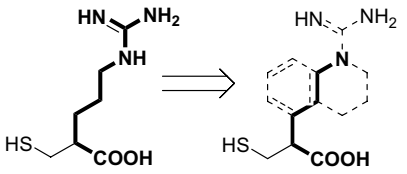


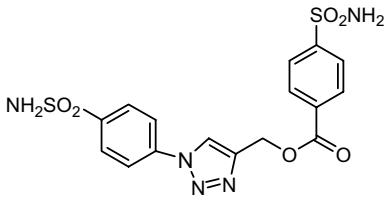


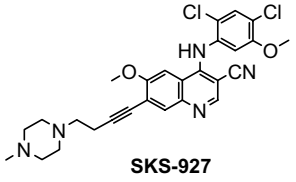


Quaternized promazine derivatives **4b** ($R^1 = CF_3$, R^2 = 4-Cl; X = Cl) and **4c** ($R^1 = CF_3$; R^2 = 3-Cl; X = Cl) inhibit actively growing and non-replicating *Mycobacterium tuberculosis* at <4 and <8 μM, respectively.

A novel series of cyclic potent, selective, small molecule, thiol-based inhibitors of activated Thrombin Activatable Fibrinolysis Inhibitor (TAFIa) are described. Inhibition of TAFIa with (rac)**2a** resulted in dose dependent acceleration of human plasma clot lysis in vitro and was efficacious as an adjunct to tPA in an in vivo rabbit jugular vein thrombolysis model.

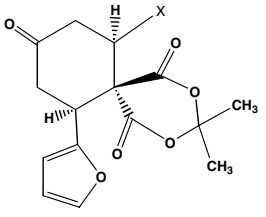




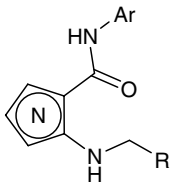


SKS-927

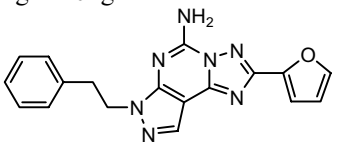
Of a series of 7-ethynyl-3-quinolinecarbonitriles, the most potent Src inhibitory activity was observed with SKS-927.



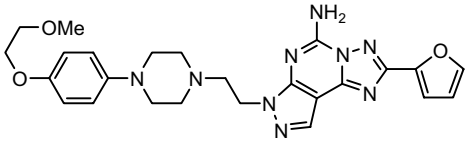
X = furan-2-yl, indol-3-yl, Ph, 4-MeOC$_6$H$_4$,C$_6$H$_4$, 4-Br-C$_6$H$_4$, 2-Cl-C$_6$H$_4$, 4-MeO-3-OH-C$_6$H$_3$, 3-MeO-4-MeO-C$_6$H$_3$, 2- Me-4-MeO-C$_6$H$_3$, 2-MeO-3-MeO-C$_6$H$_3$.



A novel series of potent *ortho*-substituted azole derivatives active against kinases VEGFR-1 and VEGFR-2 is described. Both specific and dual ATP-competitive inhibitors of VEGFR-2 were identified.

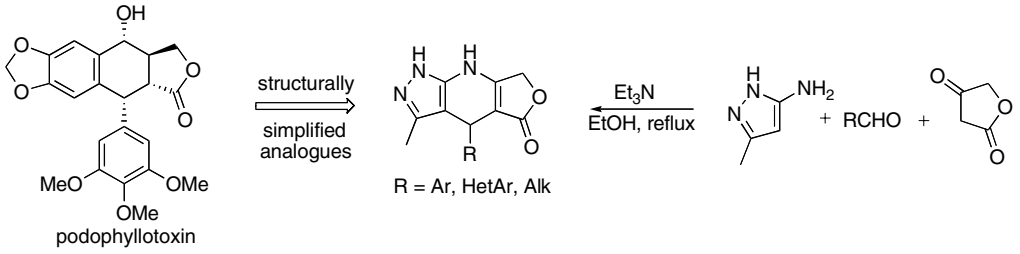


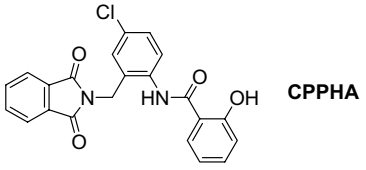
SCH 58261



SCH 420814 A_{2A} Ki = 1.1nM, A_1/A_{2A} = 1340 X

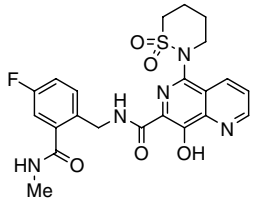
Starting from the known adenosine A_{2A} antagonist SCH 58261, SAR-guided structural optimization led to SCH 420814, which is a potent and selective A_{2A} antagonist, with good pharmacokinetics and excellent oral activity in rodent models of Parkinson's disease.

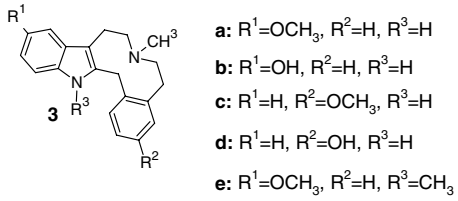




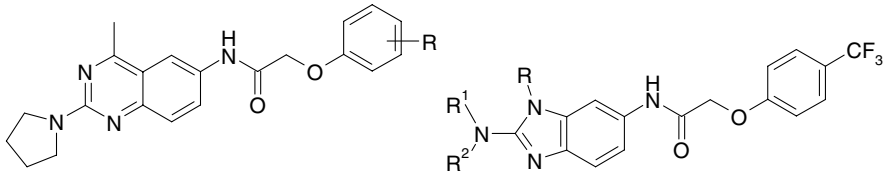
CPPHA

EC_{50} ~250 nM human
EC_{50} ~1025 nM rat
5.3- to 7.3-fold potentiation





To explore SAR, the synthesis of novel azecine-styled dopamine antagonists and screening was performed at all human-cloned dopamine receptor subtypes. The benz-indolo-azecine with the highest affinity for D_5 until now, turned out to be **3e** K_i = 0.23 nM.

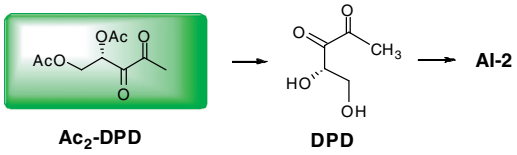


The discovery, synthesis, evaluation and structure–activity relationships of a series of quinazolines and benzimidazoles as MCH-1R antagonists are described.

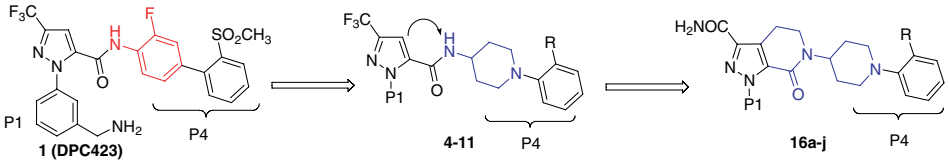
We have developed a number of hydroxamate and non-hydroxamate inhibitors of TACE that possess the selective quinolinemethoxy P1′ group. Using the X-ray co-crystal structure of our hydroxamate IK682 and TACE, and a co-crystal structure of a pyrimidinetrione in MMP-8, we have developed a highly plausible pharmacophore model of how our pyrimidinetrione and hydantoin inhibitors bind to TACE.

We have discovered novel hydantoins that are drug-like, non-hydroxamate inhibitors of the matrix metalloprotease TACE with nM potency. Synthesis and SAR of these inhibitors is described as well as their selectivity against other MMPs.

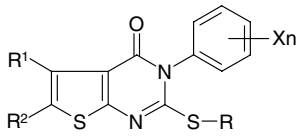
A high-throughput screening campaign of a library of 100,000 lead-like compounds identified 2-iminobenzimidazoles (I) as a novel class of trypanothione reductase inhibitors. These 2-iminobenzimidazoles display potent trypanocidal activity against *Trypanosoma brucei rhodesiense*, do not inhibit closely related human glutathione reductase and have low cytotoxicity against mammalian cells.



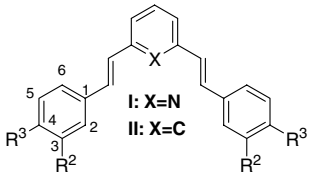
Ac_2-DPD induces bioluminescence in *Vibrio harveyi* and β-galactosidase activity in *Salmonella enterica* Typhimurium, and inhibits biofilm formation in *Bacillus cereus*. Its biological activity is most likely due to in situ hydrolysis into DPD. Ac_2-DPD can thus be considered as a stable and storable precursor of DPD.



The synthesis, SAR, pharmacokinetic profile, and modeling studies of both monocyclic and fused pyrazoles containing substituted *N*-arylpiperidinyl P4 moieties that are potent and selective factor Xa inhibitors will be discussed. Fused pyrazole analog **16a**, with a 2′-methylsulfonylphenyl piperidine P4 group, was shown to be the best compound in this series (FXa $K_i = 0.35$ nM) based on potency, selectivity, and pharmacokinetic profile.

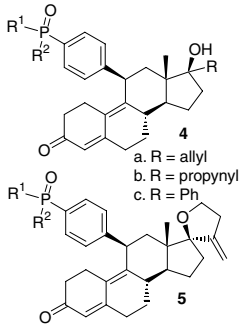


Structural effect of substituents on Nec-5, a new class of small molecule inhibitors of necroptosis, was described. Significant influence was found in structural variation of R, R^1, R^2, and Xn in the parent molecule.

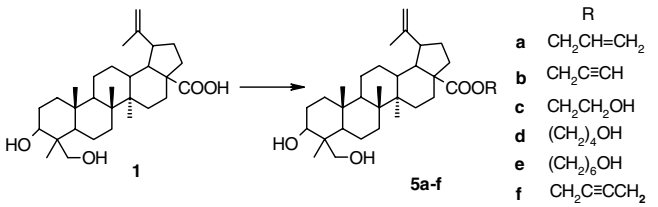


The new bis-styrylpyridine and bis-styrylbenzene derivatives were designed and synthesized. Most of them showed excellent inhibitory activities for Aβ fibril formation at IC_{50} of 0.1–2.7 μM which is comparable to curcumin (IC_{50} of 0.8 μM). In particular, **I–7** and **II-2** exhibited the best combination of inhibitory activity and compound cytotoxicity.

The synthesis and biological activities of the glucocorticoid receptor antagonists **4** and **5** are reported.



The derivatives **5a–f** of 23-hydroxy betulinic acid have better cytotoxicity than 23-hydroxy betulinic acid and betulinic acid in vitro. And they are also more potent than 23-hydroxy betulinic acid in vivo. The research results have been applied. China Patent: CN 10040277.2, 2006.



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Typical snapshot of **7b** bound to HIV-RT from an MC simulation. Carbon atoms of **7b** are gold; from the left, Tyr181, Tyr188, Phe227, Leu100, Lys101; Trp229 at the top, Val106 at the bottom. H-bond with Lys101 O on right. Some residues in front including Glu138 have been removed for clarity. The water on N5 is also H-bonded to a carboxylate O of Glu138. [Thakur, V. T.; Kim, J. T.; Hamilton, A. D.; Bailey, C. M.; Domaoal, R. A.; Wang, L.; Anderson, K. S.; Jorgensen, W. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5664.]

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