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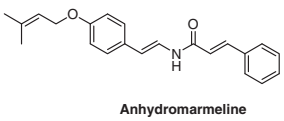
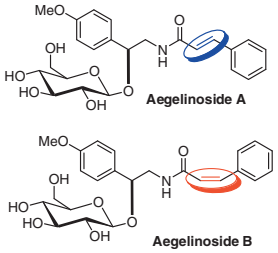
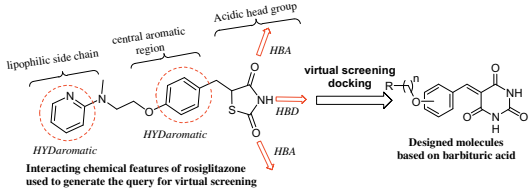
Contents

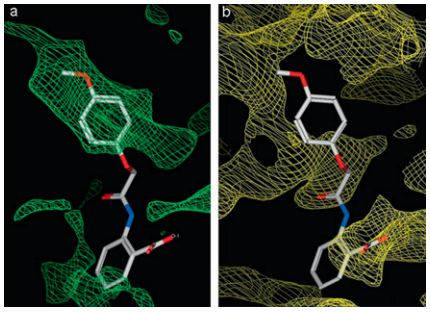
ARTICLES



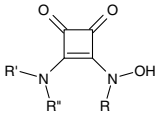




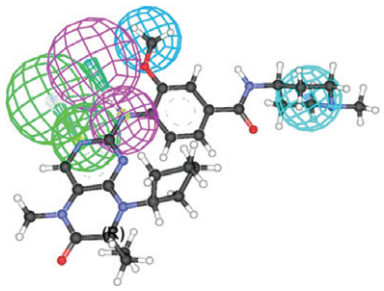
Barbituric acid was identified as a new acid head group for the design of novel PPARγ ligands using virtual screening, synthesis and radio ligand binding analysis.

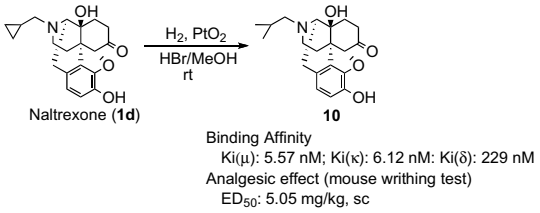


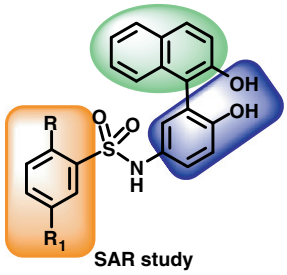
Application of molecular modeling to aid development of potent GPR109A agonists.

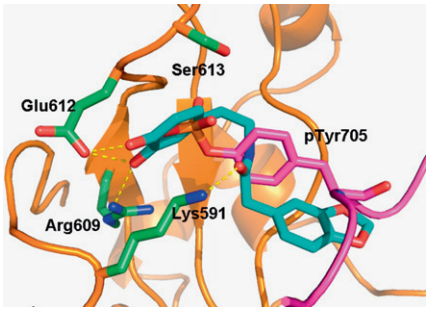


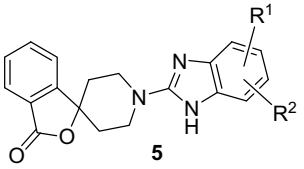
We report here the parallel synthesis of 200 compounds based on squaric acid template. The library was screened on the zinc metalloenzyme ADAMTS-5 and hits with IC_{50} in the range of 1–50 μM were identified.





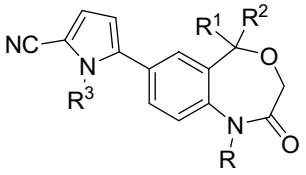






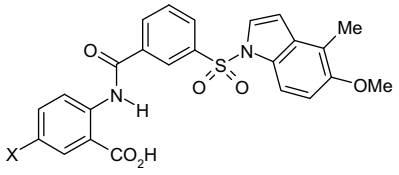
5

Structure–activity relationships of novel 2-(substituted piperidin-1-yl)benzimidazole NPY Y5 receptor antagonists are described.



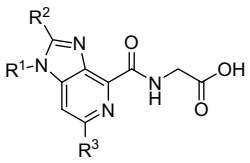
4-24

The functional activities of compounds **4**–**24** as progesterone receptor agonist or antagonist are modulated by the size and nature of R^1 and R^2 substituents.

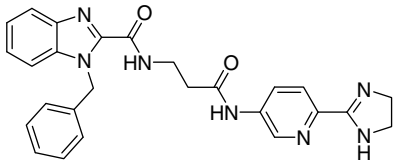


GSK1115 X = Cl
GSK7227 X = Me

The discovery and evaluation of a novel anthranilic acid class of PPARδ partial agonists is described.

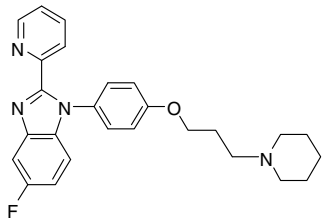


We report the structure-based design and synthesis of a novel series of aza-benzimidazoles as PHD2 inhibitors. These efforts resulted in compound **22**, which displayed highly potent inhibition of PHD2 function in vitro.

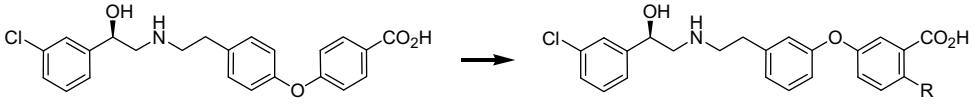


38g *c*BK B_1 EC_{50} = 2 nM
rBK B_1 EC_{50} = 0.8 nM

The design, synthesis, and structure–activity studies of a novel series of BK B_1 receptor antagonists based on a 1-benzylbenzimidazole chemotype are described. A number of compounds, for example, **38g**, with excellent affinity for the cynomolgus macaque and rat BK B_1 receptor were discovered.



A series of non-imidazole histamine H_3 receptor antagonists based on the (3-phenoxypropyl)amine motif have been identified. Compound **8a** displays a good pharmacokinetic profile in the rat.

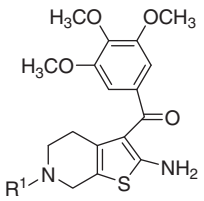


2a
β_3 EC_{50} = 100 nM

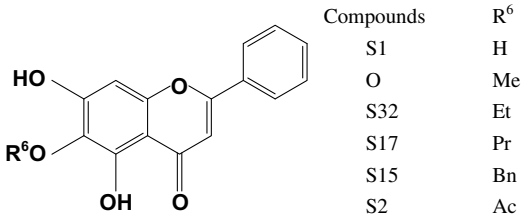
7g: R = O-*i*-Pr
β_3 EC_{50} = 3.4 nM
β_1 / β_3 = 238

7k: R =
β_3 EC_{50} = 6.6 nM
β_1 / β_3 = >152

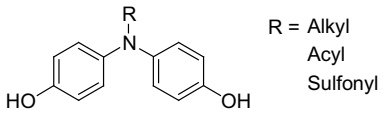
SAR study of phenoxybenzoic acid derivatives as β_3-AR agonist is described. Compounds **7g** and **7k**, exhibiting excellent β_3-AR activity and selectivity, were discovered.



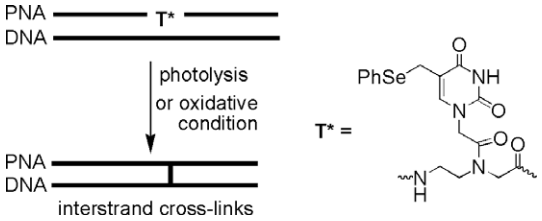
R^1=alkyl, acyl, C(X)Yalkyl
with X=O or S and Y=O or NH.



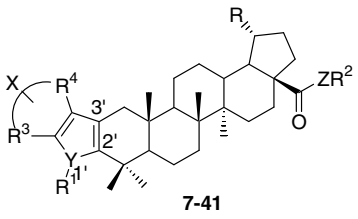
SAR and effect on the NF-κB, AP-1, or CREB mediated transcription of baicalein analogs with modification of the 6th position of A ring.



Novel diphenylamine-type estrogen receptor ligands were designed and synthesized, and showed moderate estrogenic activities. We propose that the diphenylamine skeleton may be a privileged core structure for various nuclear receptor ligands.

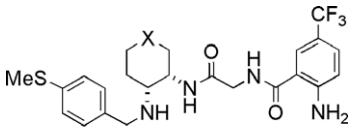


PNA/DNA interstrand cross-links were formed from modified PNA base upon photolysis or oxidative conditions.



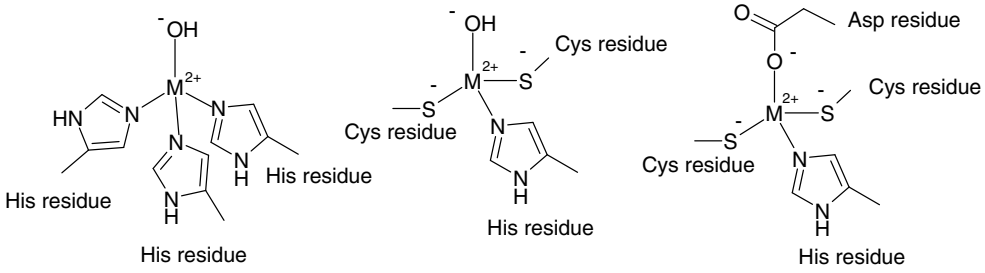
7-41

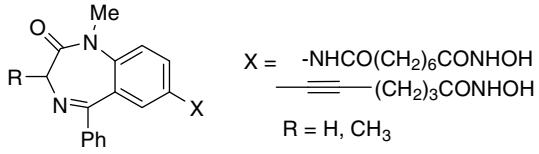
A new series of betulinic acid derivatives have been synthesized by introducing heterocyclic ring between C-2 and C-3 positions of betulinic acid. Compound **11** has showed IC_{50} of 2.44, 2.5, and 2.7 μg/ml on MIAPaCa, PA-1, and SW620 cancer cell lines, respectively. While compound **38** showed IC_{50} of 0.67 μg/ml on MIAPaCa cell line.



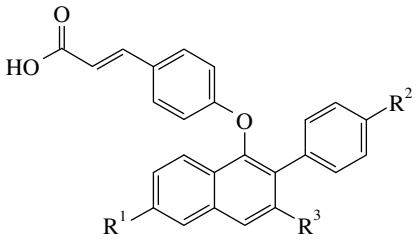
2 X = CH_2; CCR2 IC_{50} = 1180 nM
14 X = NH; CCR2 IC_{50} = 6.3 nM

A series of *cis*-3,4-disubstituted piperidines was synthesized and evaluated as CC chemokine receptor 2 (CCR2) antagonists. Several derivatives have excellent binding, functional antagonism, and selectivity.

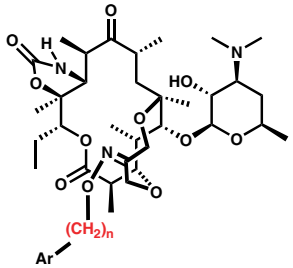




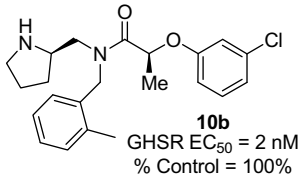
The design and evaluation of new HDAC-inhibitors carrying a 5-phenyl-benzo[*e*][1,4]diazepin-2-one nucleus are reported.



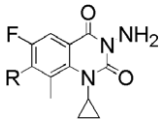
A novel series of 3-alkyl naphthalenes and their activity against estrogen receptor are reported.



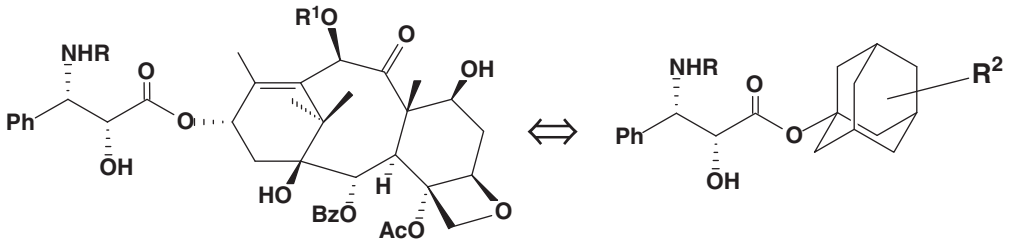
We designed and synthesized a series of novel 3,6-bicyclolide oximes, possessing linkers of varying lengths to the secondary binding site. The *E* isomers exhibited excellent antibacterial profiles against a broad spectrum of resistant pathogens.

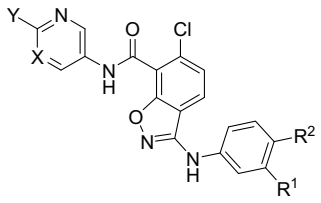


The discovery of single-digit nanomolar full agonists (e.g., **10b**) of the Growth Hormone Secretagogue receptor (GHSR) is reported, starting with a micromolar screening hit identified from a GPCR-targeted solid-phase library. The 'library pedigree' of this series greatly facilitated its rapid optimization.

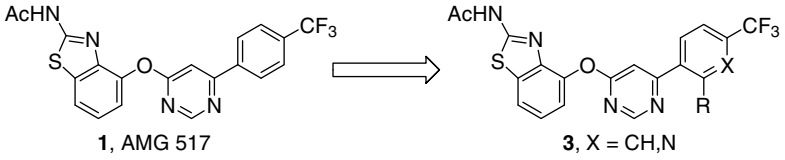


The synthesis and structure–activity relationship of a novel series of bacterial topoisomerase (3-aminoquinazolinediones) inhibitors is described.

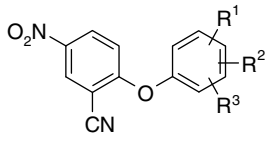


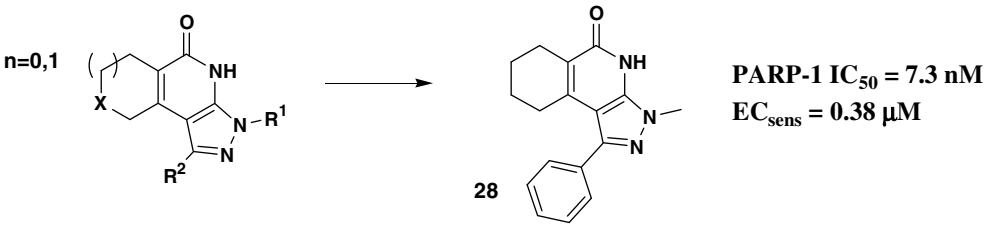


A novel series of 7-amido-3-(arylamino)-benzisoxazoles are herein disclosed as potent inhibitors of the receptor tyrosine kinase c-Kit, with IC_{50} values in the nanomolar range.

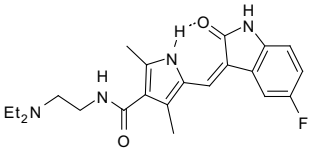


Analogs with various substituents at the R region of **3** were prepared to improve the solubility while maintaining the potent TRPV1 activity of clinical candidate AMG 517.

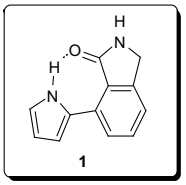




Potent PARP-1 inhibitors were identified in a tricyclic pyrazolo pyridine-2-one series with nanomolar binding affinity and submicromar activity in a cell-based chemosensitization assay.



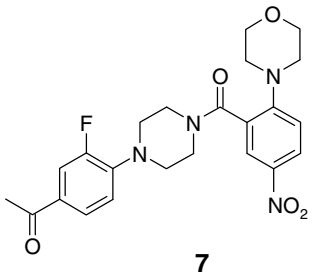
SU-11248 (sunitinib)
VEFG-R2 inhibitor



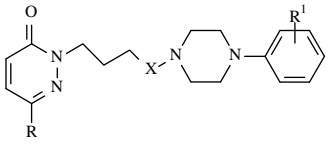
1

The design of a new kinase inhibitor scaffold **1** based on known VEGF-R2 kinase inhibitors is described. The series designed to be inhibitors of VEGF-R2 kinase were synthesized and found to potently inhibit VEGF-R2 and Aurora-A kinases. The structure-based design, synthesis, initial SAR, and in vivo efficacy of the series are discussed.

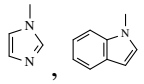
Screening of the Roche compound library led to the identification of the benzoylpiperazine **7** as a structurally novel GlyT1 inhibitor. The SAR which was developed in this series resulted in the discovery of highly potent compounds displaying excellent selectivity against the GlyT2 isoform, drug-like properties, and in vivo efficacy after oral administration.



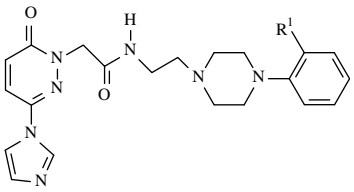
7



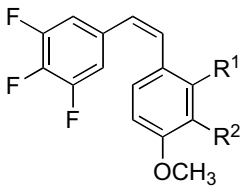
R=



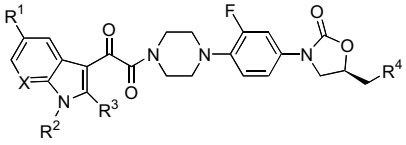
R^1= *o*-OCH_3;
R^1= *o*-OC_2H_5;
R^1= *o*-$OCH(CH_3)_2$
R^1= *m*-CF_3
X= CH_2
X= CO



In continuing our search for selective α_1-AR antagonists, new alkoxyarylpiperazinylalkylpyridazinone derivatives were designed and synthesized. The new compounds were tested for their affinity toward α_1-AR, α_2-AR, and toward 5-HT_{1A} receptors. The ability of these compounds to inhibit the serotonin transporters (SERT) was also determined.



A series of nitrogen-containing fluoro combretastatin structural modifications have been synthesized and evaluated for potential anti-cancer activity.



The synthesis and antibacterial activity of novel oxazolidinones possessing indolylglyoxamide moiety on piperazine scaffold have been disclosed.

*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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