Bioorganic & Medicinal Chemistry Letters 19 (2009) 5275–5288

Contents lists available at ScienceDirect

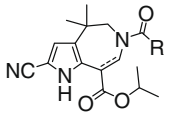
Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

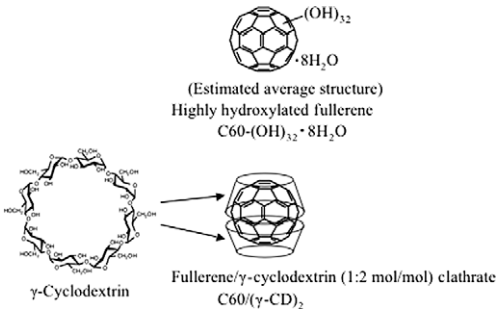
Bioorganic & Medicinal Chemistry Letters Vol. 19, No. 18, 2009

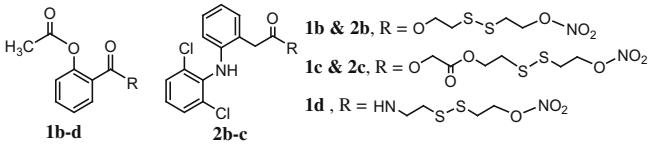
Contents

ARTICLES

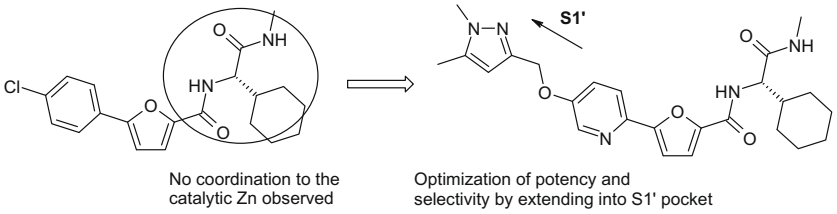


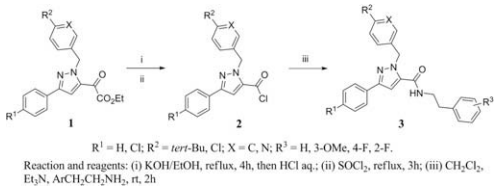
The rational design and discovery of a new series of pyrrole[2,3-*d*]azepino FXR agonists with aqueous solubility and improved pharmaceutical properties is reported.



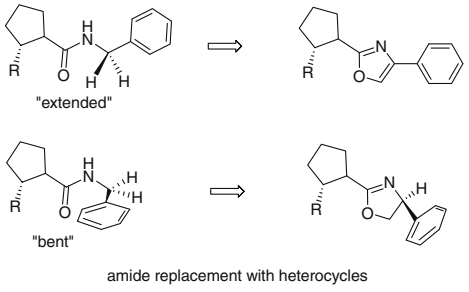


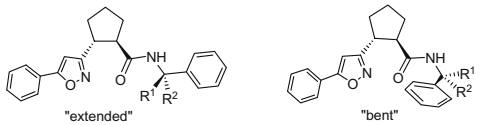
Gastric-sparing NO-NSAIDs were designed, synthesized and evaluated. Among those evaluated, NO-Diclofenac (**2b**) has shown excellent bioavailability, anti-inflammatory activity, NO-releasing profile and gastric-sparing properties.



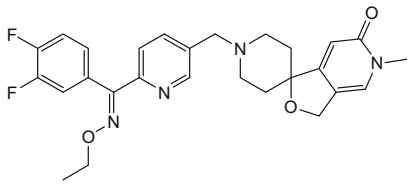


A series of novel 3-aryl-1-arylmethyl-1*H*-pyrazole-5-carboxamide derivatives **3a–l**, were synthesized by the reaction of 3-aryl-1-arylmethyl-1*H*-pyrazole-5-carbonyl chloride with substituted amine in excellent yields. The compounds **3e–h** could suppress A549 lung cancer cell growth. More interestingly, compounds **3e** and **3f** might inhibit the A549 cell growth by inducing apoptosis; whereas compounds **3g** and **3h** with fluorine group might inhibit the A549 cell growth by inducing autophagy.



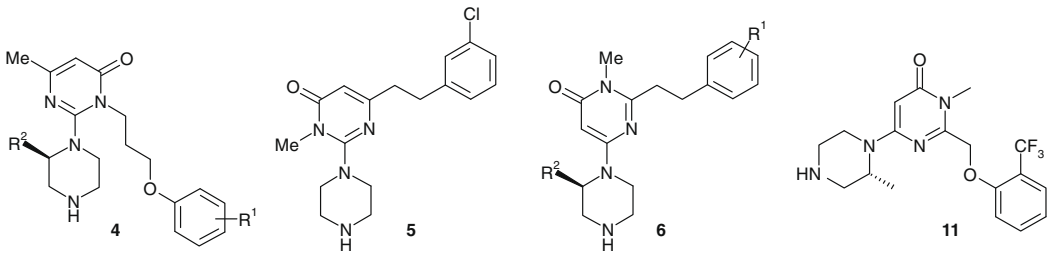


	Energy difference between the two conformation (kcal/mol)	Nav1.7 potency IC_{50} (μM)
R^1, R^2: H	0.07 kcal/mol favor "bent"	> 1 μM
R^1, R^2: $-CH_2CH_2CH_2-$	3.97 kcal/mol favor "bent"	0.12 μM



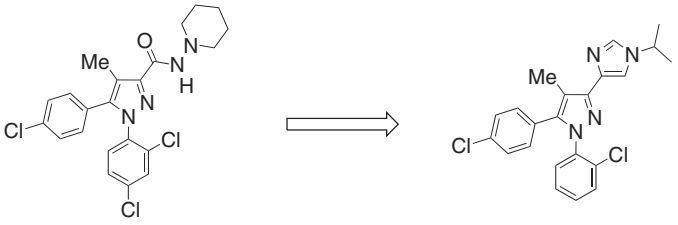
4b: hMCH-1R (IC_{50}) = 6.8 nM

The identification of selective and orally active MCH-1R antagonist **4b** is reported.

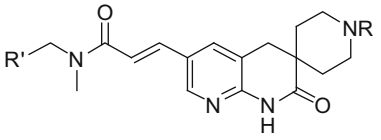


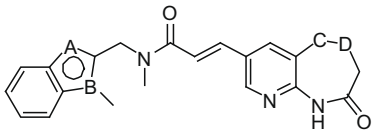
4 **5** **6** **11**

The design, synthesis and biological activity of several novel series of piperazinyl pyrimidinones is described. Compound **11** showed efficacy in a pre-clinical model of urethral function which highlights potential efficacy in stress urinary incontinence.



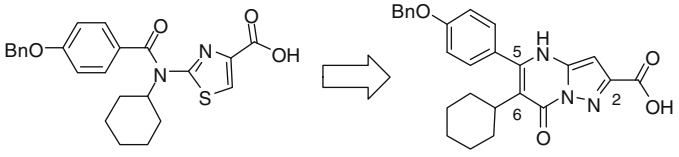
1 (SR141716) **9a**





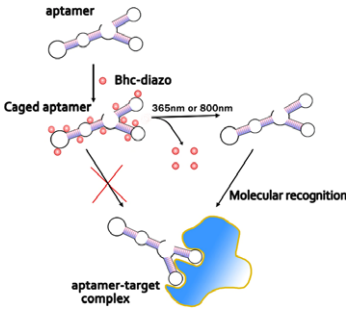
11d, A = O, B = C, C = NH, D = CH_2
16c, A = CH, B = N, C = CH_2, D = NH

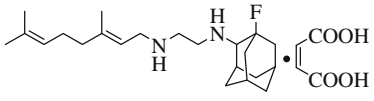
Using a structure guided approach, naphthyridionone FabI inhibitors were expanded to novel 2,3,4,5-tetrahydro-1H-pyrido[2,3-*b* and *e*][1,4]diazepines (e.g., **11d**; FabI IC_{50} = 11 nM). Diazepinone **16c** is shown to be efficacious in a mouse infection model.



1 **2**

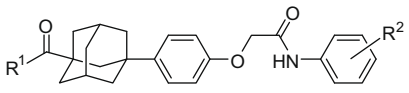
The design, synthesis and evaluation of a series of 4*H*-Pyrazolo[1,5-*a*]pyrimidin-7-ones as potent inhibitors of hepatitis C virus polymerase are described.



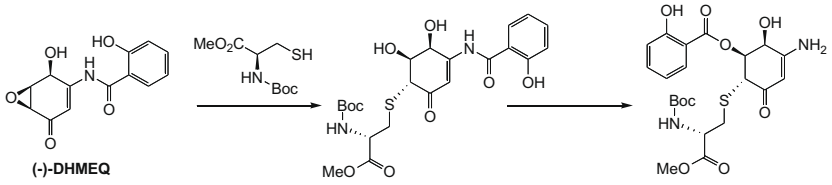


11c

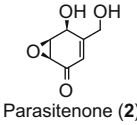
Guided by the metabolism information of **SQ109**, derivatives with substituted geranylamine moiety or substituted admantane ring of **SQ109** were synthesized and evaluated as antituberculosis agents. Among all tested compounds, compound **11c** showed the most potent antituberculosis activity with MIC value of 0.3 μM against *Mycobacterium tuberculosis* H37Rv.



The synthesis and SAR of a new class of potent MDR reversal agents are reported.

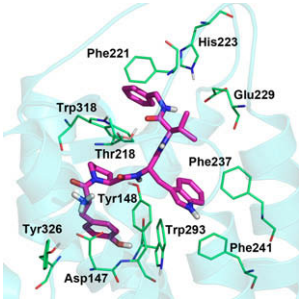


We observed an unusual intramolecular *N→O* acyl group migration in the course or formation of the (−)-DHMEQ and protected cysteine conjugate.

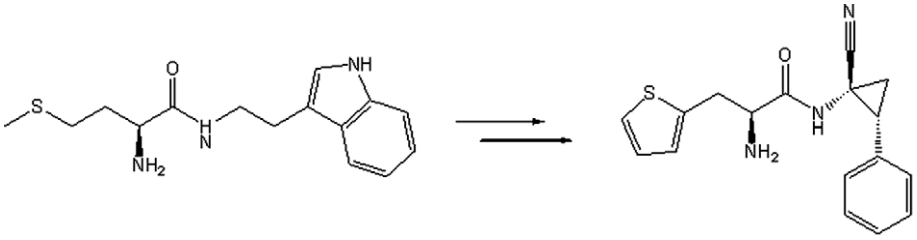


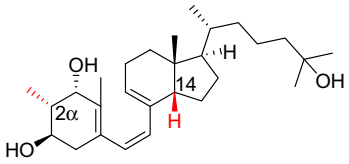
Parasitenone (**2**)

Parasitenon (**2**) was synthesized and the inhibitory activity against NF-κB was assessed.

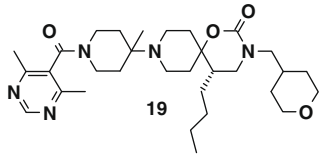


The binding mode of a series of endomorphin analogs in μ opioid receptor is predicted.

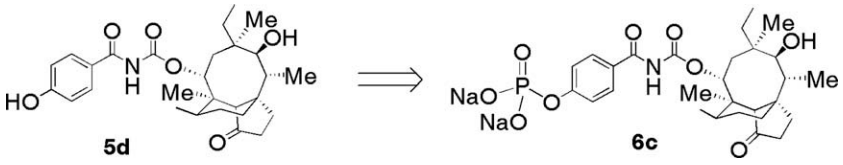




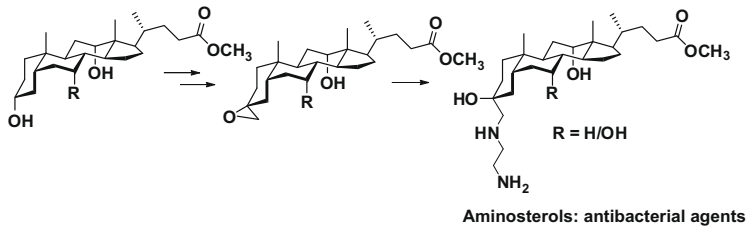
2α-Substituted analogs of 14-epi-previtamin D_3 showed greater genomic activity than 14-epi-previtamin D_3 such as the VDR binding affinity and transactivation activity of osteocalcin promoter in HOS cells.

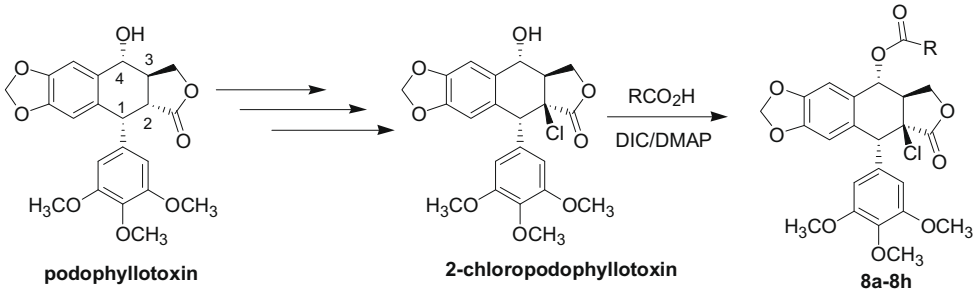


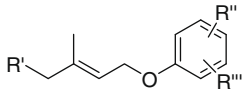
The discovery of a novel series of CCR5 small molecule antagonists is described. Lead optimization was pursued by balancing opposing trends of metabolic stability and potency. Selective and potent analogs with good pharmacokinetic properties were developed as exemplified by compound **19**.



Synthesis and biological properties of phosphate prodrugs of pleuromutilin analogues are disclosed. Compound **6c** was metabolized efficiently to the biologically active parent **5d** in vivo, it also showed excellent antibacterial activity against MSSA and MRSA with comparable ED_{50} as vancomycin by iv administration in mice.

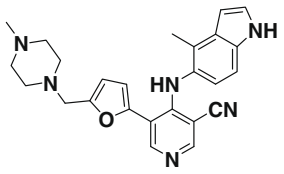






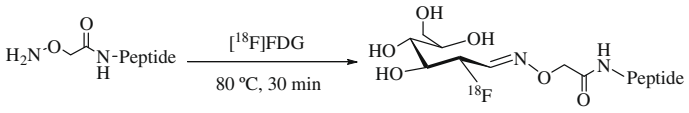
R' = H, isopentenyl, R'' = acetyl, COOH, CH=CH-COOH, *c*-O-CO-CH=CH-, R''' = H, OCH_3

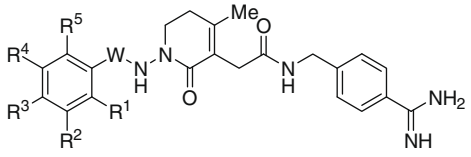
The synthesis and neuroprotective activity (MES test) of selected prenyloxyphenylpropanoids is reported.

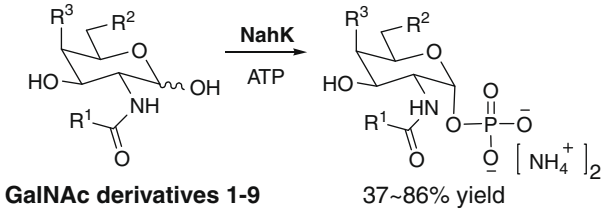


6e

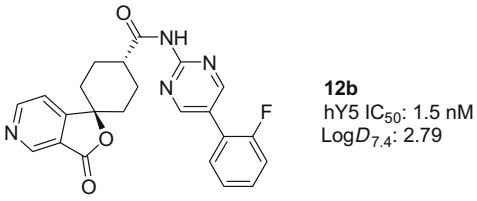
Analog **6e** with a 4-methylindol-5-ylamino group at C-4 and a 5-[(4-methylpiperazin-1-yl)methyl]-2-furyl group at C-5 had an IC_{50} value of 4.5 nM for the inhibition of PKC.



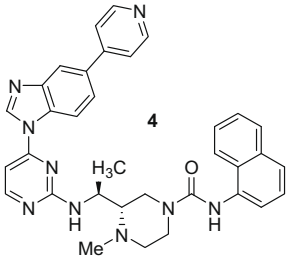




We report herein a bacterial *N*-acetylhexosamine kinase, NahK, with broad substrate specificity towards structurally modified GalNAc analogues, and the production of a GalNAc-1-phosphate library using this kinase.

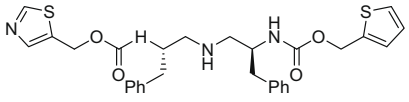


Compound **12b** exhibited an acceptable profile for a PET ligand, and [^{11}C]**12b** was successfully utilized in clinical settings as a Y5 PET ligand.



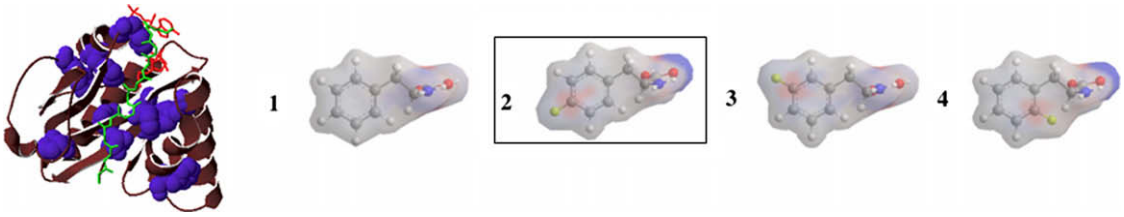
4

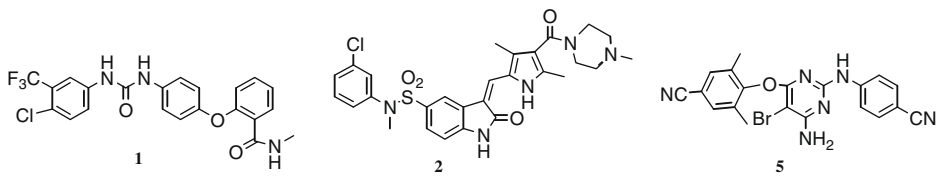
Compound **4** was found to be a potent inhibitor of Lck activity (IC_{50} = 0.1 nM) and cellular IL2 release (IC_{50} = 8 nM).



8

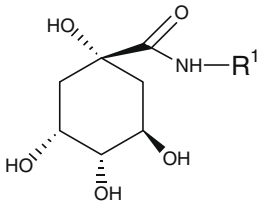
The structural elements of ritonavir were used to design a series of compounds which inhibit CYP3A. Compound **8** was found to strongly enhance plasma levels of lopinavir and compares favorably to ritonavir.



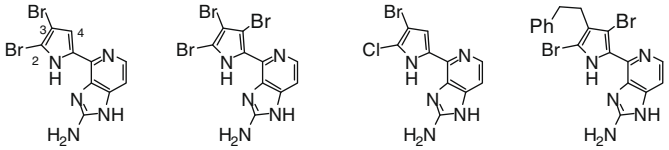


1 2 5

A new flow cytometry method that uses an optimized DNA and RNA staining strategy to monitor the growth and development of the *Plasmodium falciparum* strain W2mef has been used in a pilot study and has identified Bay 43-9006 **1**, SU 11274 **2**, and TMC 125 **5** as compounds that exhibit potent (<1 μM) overall and ring stage in vitro antimalarial activity.

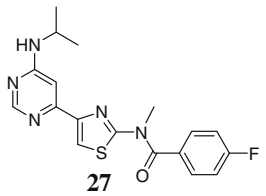


Quinic Acid Derivatives



MMP-12 inhibitory activity IC_{50}

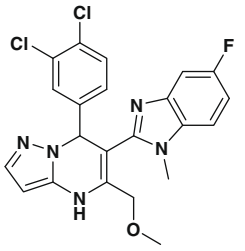
The three ageladine A analogs **4a**, **c**, and **o** were found to show more potent MMP-12 inhibitory activity than natural ageladine A.



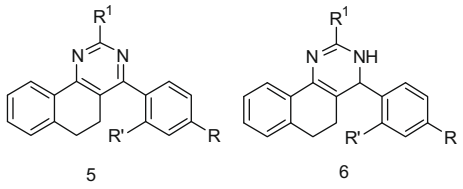
27

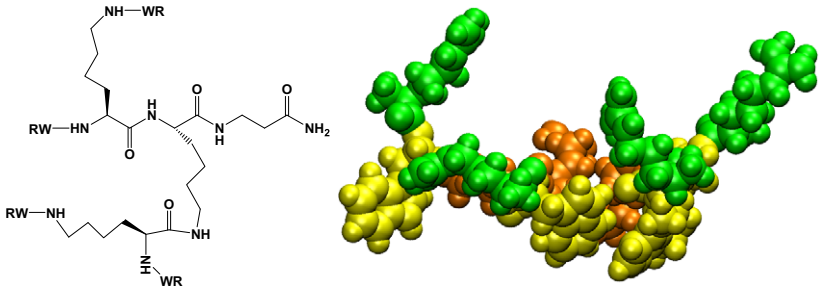
We identified 4-fluoro-*N*-[4-[6-(isopropylamino)pyrimidin-4-yl]-1,3-thiazol-2-yl]-*N*-methylbenzamide **27** as a potent mGluR1 antagonist. The compound possessed excellent subtype selectivity and good PK profile in rats. It also demonstrated relatively potent antipsychotic-like effects in several animal models.

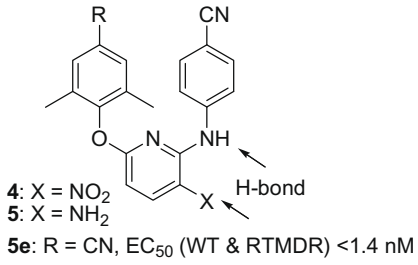
$K_V1.5$ blockers have the potential to be selective agents for the treatment of atrial fibrillation. Dihydropyrazolopyrimidines provide a template for the synthesis of potent and selective $K_V1.5$ blockers.

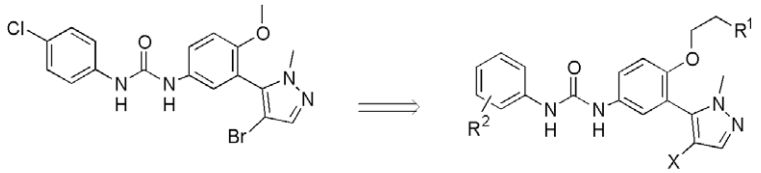


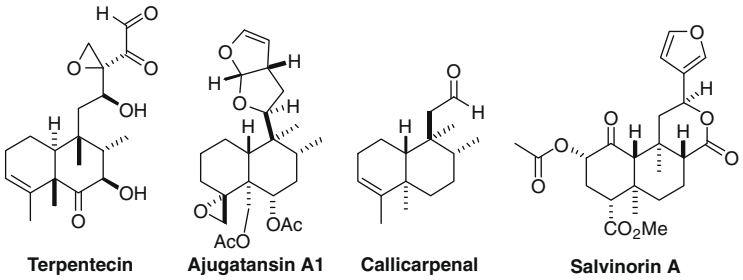
31a $K_V1.5$ IC_{50} 0.030 uM

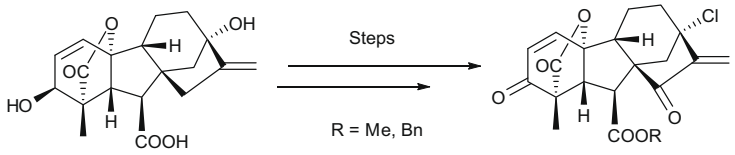




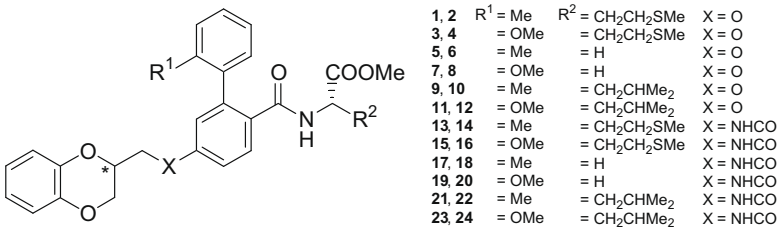




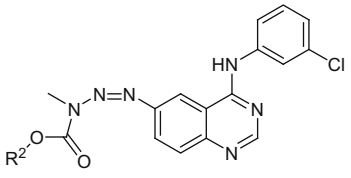




A series of gibberellin based molecules were designed and synthesized. Gibberellin derivatives bearing two α,β-unsaturated ketone units showed strong anticancer activities in MTT assay towards a number of human cancer cell lines including HT29, A549, HepG2 and MKN28. The most potent gibberellin derivative (R = Me, IC_{50} = 2.9 μM against HT29) inhibited completely the topoisomerase I activity at 8 μg/mL level.



	R^1	R^2	X
1, **2**	= Me	= CH_2CH_2SMe	X = O
3, **4**	= OMe	= CH_2CH_2SMe	X = O
5, **6**	= Me	= H	X = O
7, **8**	= OMe	= H	X = O
9, **10**	= Me	= CH_2CHMe_2	X = O
11, **12**	= OMe	= CH_2CHMe_2	X = O
13, **14**	= Me	= CH_2CH_2SMe	X = NHCO
15, **16**	= OMe	= CH_2CH_2SMe	X = NHCO
17, **18**	= Me	= H	X = NHCO
19, **20**	= OMe	= H	X = NHCO
21, **22**	= Me	= CH_2CHMe_2	X = NHCO
23, **24**	= OMe	= CH_2CHMe_2	X = NHCO



The synthesis and biological activities of stabilized 3-alkyl-1,2,3-triazene-based EGFR-DNA targeting molecules are described.

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.]

Indexed/Abstracted in: Beilstein, Biochemistry & Biophysics Citation Index, CANCERLIT, Chemical Abstracts, Chemistry Citation Index, Current Awareness in Biological Sciences/BIOBASE, Current Contents: Life Sciences, EMBASE/Excerpta Medica, MEDLINE, PASCAL, Research Alert, Science Citation Index, SciSearch, TOXFILE

ELSEVIER

ISSN 0960-894X