

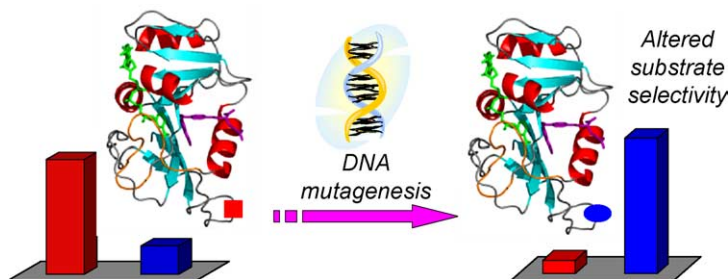
Contents

REVIEW

Altering protein specificity: techniques and applications

pp 2701–2716

Nina M. Antikainen and Stephen F. Martin*

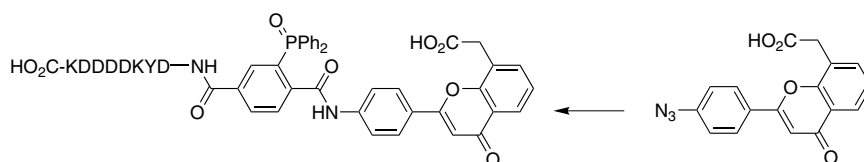


ARTICLES

Synthesis and biological study of a flavone acetic acid analogue containing an azido reporting group designed as a multifunctional binding site probe

pp 2717–2722

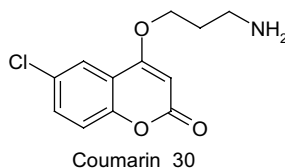
Krishnan Malolanarasimhan, Christopher C. Lai, James A. Kelley, Lynn Iaccarino, Della Reynolds, Howard A. Young and Victor E. Marquez*



Design, synthesis and characterization of a novel class of coumarin-based inhibitors of inducible nitric oxide synthase

pp 2723–2739

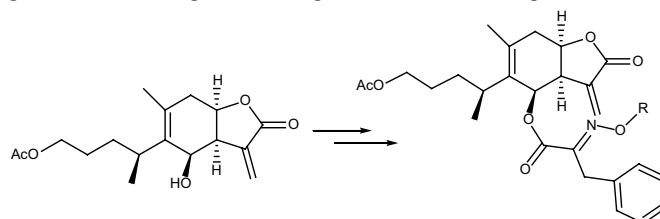
Sharon A. Jackson, Sukhveen Sahni, Lan Lee, Yongyi Luo, Thaddeus R. Nieduzak,* Guyan Liang, Yulin Chiang, Nicola Collar, David Fink, Wei He, Abdelazize Laoui, Jean Merrill, Ray Boffey, Peter Crackett, Bryan Rees, Melanie Wong, Jean-Pierre Guilloteau, Magali Mathieu and Sam S. Rebello



Design, synthesis, and anti-tumor activity of (2-*O*-alkyloxime-3-phenyl)-propionyl-1-*O*-acetylbritannilactone esters

pp 2783–2789

Shouxin Liu, He Liu, Weiying Yan, Li Zhang, Naisheng Bai and Chi-Tang Ho*

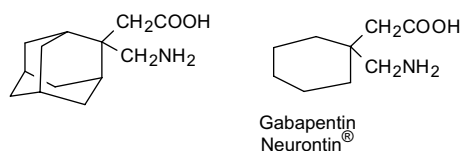


Eight derivatives of 1-*O*-acetylbritannilactone, (2-*O*-alkyloxime-3-phenyl) propionyl-1-*O*-acetylbritannilactone ester are designed and synthesized. Four of these compounds were tested to show inhibitory activity on the growth of human HL-60 and Bel-7402 cell lines.

The novel GABA adamantane derivative (AdGABA): design, synthesis, and activity relationship with gabapentin

pp 2791–2798

Grigoris Zoidis, Ioannis Papanastasiou, Ioannis Dotsikas, Alejandro Sandoval, Raquel Gouvea Dos Santos, Zeta Papadopoulou-Daifoti, Alexander Vamvakides, Nicolas Kolocouris* and Ricardo Felix

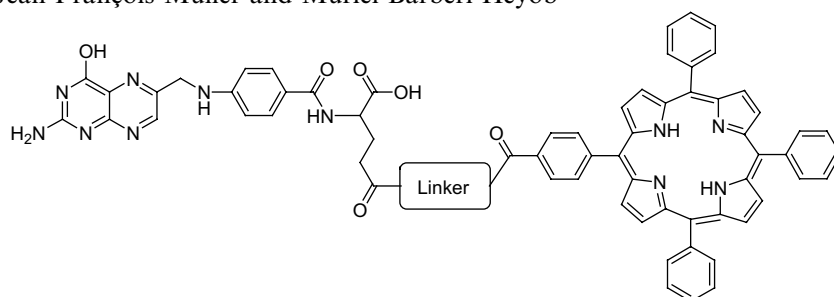


In the current work, we report the design, synthesis (following two different synthetic routes), stability studies, and comprehensive pharmacology of a novel GABA adamantane derivative (AdGABA), which displays a close structure–activity relationship with gabapentin.

Design, synthesis, and biological evaluation of folic acid targeted tetraphenylporphyrin as novel photosensitizers for selective photodynamic therapy

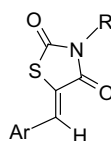
pp 2799–2808

Raphaël Schneider,* Frédéric Schmitt, Céline Frochet, Yves Fort, Natacha Lourette, François Guillemin, Jean-François Müller and Muriel Barberi-Heyob*

**Structure–activity relationships and molecular modelling of 5-arylidene-2,4-thiazolidinediones active as aldose reductase inhibitors**

pp 2809–2823

Rosanna Maccari,* Rosaria Ottanà, Carmela Curinga, Maria Gabriella Vigorita, Dietmar Rakowitz, Theodora Steindl and Thierry Langer

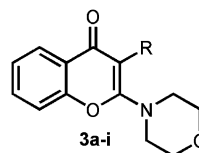


Targeting the gatekeeper residue in phosphoinositide 3-kinases

pp 2825–2836

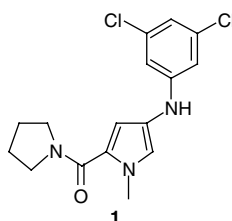
Peter J. Alaimo, Zachary A. Knight and Kevan M. Shokat*

Hck	V	T338	E	Y	M
p110 γ	M	I879	E	I	V
p110 α	L	I	E	V	V
PI3KC2 α	M	V	E	L	V
VPS34	A	I	E	F	I
MEC1	I	L	E	M	V

**Novel non-steroidal/non-anilide type androgen antagonists: discovery of 4-substituted pyrrole-2-carboxamides as a new scaffold for androgen receptor ligands**

pp 2837–2846

Ken-ichi Wakabayashi, Hiroyuki Miyachi, Yuichi Hashimoto and Aya Tanatani*

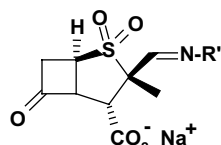


Novel pyrrole-2-carboxamide derivatives were designed and synthesized as androgen antagonists. Compound **1** is more active androgen antagonist than flutamide.

Synthesis and biological evaluation of penam sulfones as inhibitors of β -lactamases

pp 2847–2858

Oludotun A. Phillips,* Andhe V. N. Reddy, Eduardo L. Setti, Paul Spevak, David P. Czajkowski, Herninder Atwal, Sameeh Salama, Ronald G. Micetich and Samarendra N. Maiti



17a-n: R' = OMe, OEt, O-allyl, OCH₂CH₂OH, O-tert-butyl, O-cyclopropylmethyl, O-methoxymethyl, O-pyridin-2-ylmethyl, O-piperidin-2-ylmethyl, etc.

18a-f: R' = NHCOCH₃, NHCOPh, NHCSNH₂, NHCONH₂, NHCOOCH₂Ph, 2-oxo-1-imidazolidinyl

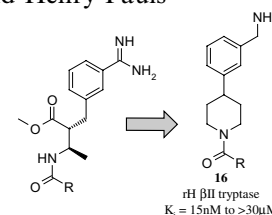
Synthesis of 2 β -substituted-oxyimino and -hydrazone penam sulfones and their β -lactamase inhibitory activities against class A and C β -lactamases are presented.

Structure based design of 4-(3-aminomethylphenyl)piperidinyl-1-amides: novel, potent, selective, and orally bioavailable inhibitors of β II tryptase


pp 2859–2872

Julian Levell,* Peter Astles, Paul Eastwood, Jennifer Cairns, Olivier Houille, Suzanne Aldous, Gregory Merriman, Brian Whiteley, James Pribish, Mark Czekaj, Guyan Liang, Sebastien Maignan, Jean-Pierre Guilloteau, Alain Dupuy, Jane Davidson, Trevor Harrison, Andrew Morley, Simon Watson, Garry Fenton, Clive McCarthy, Joseph Romano, Rose Mathew, Darren Engers, Michael Gardyan, Keith Sides, Jennifer Kwong, Joseph Tsay, Sam Rebello, Liduo Shen, Jie Wang, Yongyi Luo, Odessa Giardino, Heng-Keang Lim, Keith Smith and Henry Pauls

Tryptase is a serine protease implicated in the etiology of asthma. Screening of in-house inhibitors of factor Xa (a closely related serine protease) identified β -amidoester benzamidines as potent inhibitors of recombinant human β II tryptase. X-ray structure driven template modification and exchange of the benzamidine to optimize potency and pharmacokinetic properties gave selective, potent and orally bioavailable 4-(3-aminomethyl phenyl)piperidinyl-1-amides **16**.



pp 2873–2880



11

16a: R = Me
16b: R = MOM
17: R = H

```

graph TD
    A[1006 Anthelmintics] --> B[Dataset of 2630 chemicals in total]
    C[1024 Non-anthelmintics] --> B
    B --> D[2D Atom-based TOMCOOM-CARD Descriptors]
    B --> E[Non-stochastic and Stochastic Quadratic Fingerprinting]
    D --> F(( ))
    E --> F
    F --> G[74 anthelmintic]
    F --> H[250 anthelmintic]
    F --> I[77 non-anthelmintic]
    F --> J[23 non-anthelmintic]
    G --> K([Training Set  
1122 chemicals in total])
    H --> K
    I --> L([Test Set  
508 chemicals in total])
    J --> L
    K --> M[LDA-QSAR Models]
    L --> M
    M --> N[Discovery of new lead anthelmintics]
  
```

pp 2901–2905

$$\begin{array}{ccc} \text{R-CH}_2\text{OH} & & \begin{array}{c} \text{R} \\ \diagup \\ \text{C=O} \\ \diagdown \\ \text{H} \end{array} \\ \text{or} & \xrightarrow[\text{CH}_3\text{CN} / \text{H}_2\text{O, RT}]{[\text{Mn}(\text{TPyP})\text{-CMP}] / \text{NaIO}_4} & \text{or} \\ \begin{array}{c} \text{R} \\ \diagup \\ \text{C-OH} \\ \diagdown \\ \text{R}' \end{array} & & \begin{array}{c} \text{R} \\ \diagup \\ \text{C=O} \\ \diagdown \\ \text{R}' \end{array} \end{array}$$

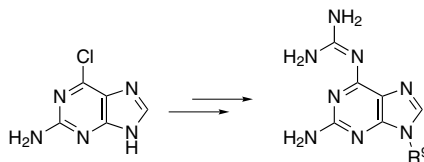
pp 2907–2916

Chemical structures of compounds 3 and 4 are shown. Compound 3 is a disaccharide derivative with a sulfonate group (NaO₃SO) and a long alkyl chain (C₂₅H₅₁). Compound 4 is a disaccharide derivative with a sulfonate group (NaO₃SO) and a long alkyl chain (C₁₄H₂₉).

Synthesis of 9-alkyl and 9-heteroalkyl substituted 2-amino-6-guanidinopurines and their influence on the NO-production in macrophages

pp 2917–2926

Michal Česnek,* Antonín Holý, Milena Masojídková and Zdeněk Zídek



(R)-Goniothalamine: total syntheses and cytotoxic activity against cancer cell lines

pp 2927–2933

Ângelo de Fátima, Luciana Konecny Kohn, Márcia Aparecida Antônio, João Ernesto de Carvalho and Ronaldo Aloise Pilli*

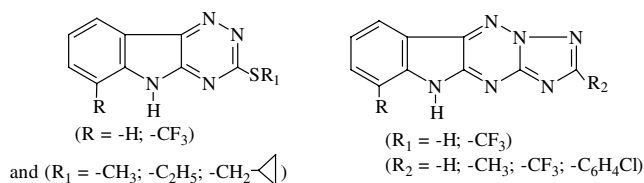
The total syntheses of (*R*)-goniothalamine (**1**) via catalytic asymmetric allylation of α -benzyloxyacetaldehyde (**2**), followed by ring-closing metathesis and Wittig olefination and via catalytic asymmetric allylation of *trans*-cinnamaldehyde followed by ring-closing metathesis are reported. The antiproliferative activities of (*R*)-**1** and its *Z*-isomer **10** as well as of the synthetic dihydropyranone intermediates **7** and **8** against eight different cancer cell lines are also described.



1,2,4-Triazino-[5,6*b*]indole derivatives: effects of the trifluoromethyl group on in vitro antimalarial activity

pp 2935–2942

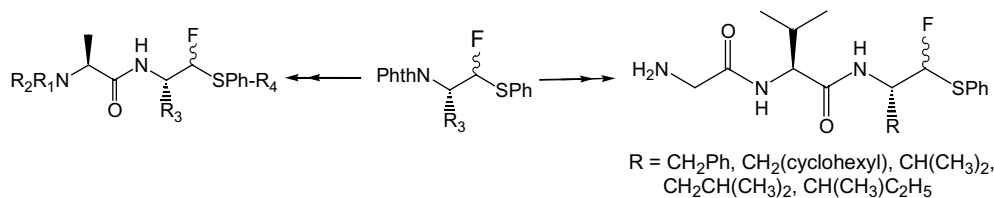
Joseph L. Kgekong,* Peter P. Smith and Gilbert M. Matsabisa



Novel fluoro-peptidomimetics: synthesis, stability studies and protease inhibition

pp 2943–2958

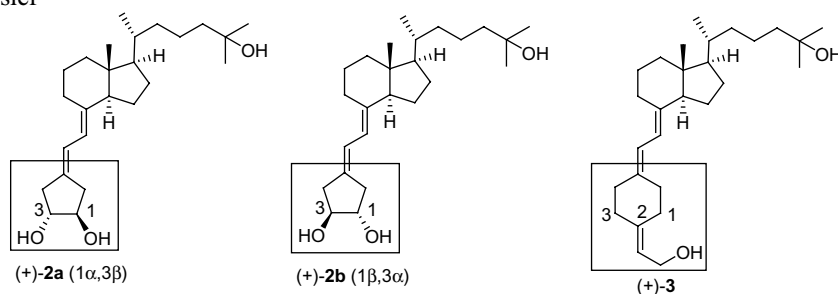
Subhash C. Annedi, Kanchana Majumder, Lianhu Wei, Catherine E. Oyiliagu, Sheeba Samson and Lakshmi P. Kotra*



Novel A-ring analogs of the hormone $1\alpha,25$ -dihydroxyvitamin D_3 : synthesis and preliminary biological evaluation

pp 2959–2966

Gary H. Posner,* S. H. Tony Lee, Hyung Jin Kim, Sara Peleg, Patrick Dolan and Thomas W. Kensler

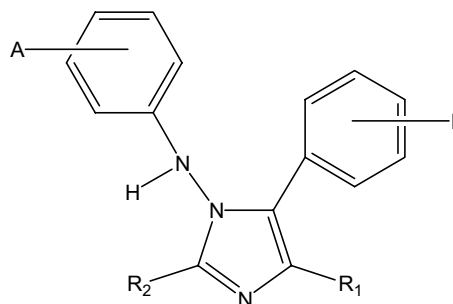


QSAR by LFER model of cytotoxicity data of anti-HIV 5-phenyl-1-phenylamino-1*H*-imidazole derivatives using principal component factor analysis and genetic function approximation

pp 2967–2973

Kunal Roy* and J. Thomas Leonard

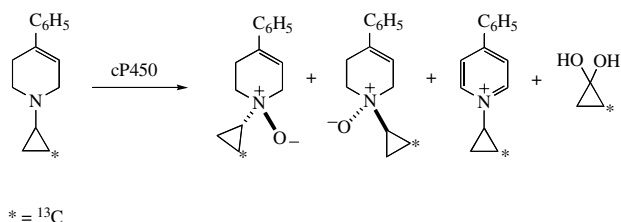
Cytotoxicity data of anti-HIV (human immunodeficiency virus) 5-phenyl-1-phenylamino-1*H*-imidazole derivatives have been subjected to quantitative structure–activity relationship (QSAR) study by linear free energy related (LFER) model of Hansch using principal component factor analysis and genetic function approximation.



Studies on the cytochrome P450 catalyzed oxidation of ^{13}C labeled 1-cyclopropyl-4-phenyl-1,2,3,6-tetrahydropyridine by ^{13}C NMR

pp 2975–2980

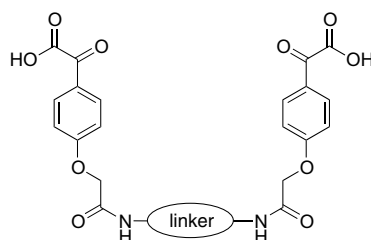
Philippe Bissel and Neal Castagnoli, Jr.*



Investigations of linker structure on the potency of a series of bidentate protein tyrosine phosphatase inhibitors

pp 2981–2991

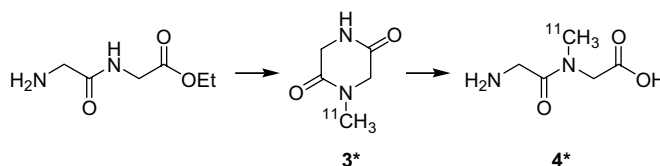
Jian Xie and Christopher T. Seto*



[¹¹C]Glycylsarcosine: synthesis and in vivo evaluation as a PET tracer of PepT2 transporter function in kidney of *PepT2* null and wild-type mice

pp 2993–3001

Nabeel B. Nabulsi, David E. Smith and Michael R. Kilbourn*

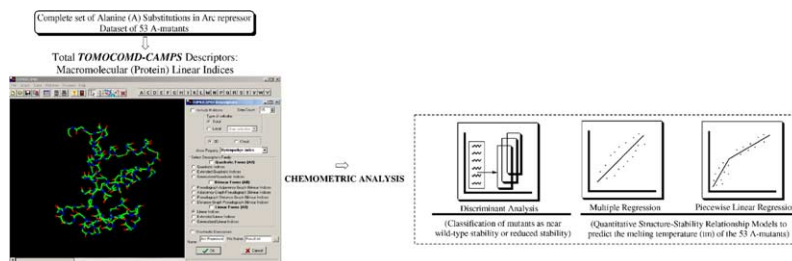


C-11 labeled (Gly-Sar) **4*** and [¹¹C]*cyclo*(Gly-Sar) [1-methylpiperazine-2,5-dione] **3*** were synthesized as potential radiotracers to investigate the localization and in vivo function of the peptide transporter PepT2 in mouse kidney.

Protein linear indices of the ‘macromolecular pseudograph α -carbon atom adjacency matrix’ in bioinformatics. Part 1: Prediction of protein stability effects of a complete set of alanine substitutions in Arc repressor

pp 3003–3015

Yovani Marrero-Ponce,* Ricardo Medina-Marrero, Juan A. Castillo-Garit, Vicente Romero-Zaldivar, Francisco Torrens and Eduardo A. Castro

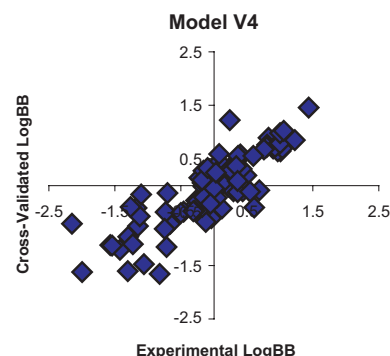


In silico ADME modelling: prediction models for blood–brain barrier permeation using a systematic variable selection method

pp 3017–3028

Ramamurthi Narayanan* and Sitarama B. Gunturi

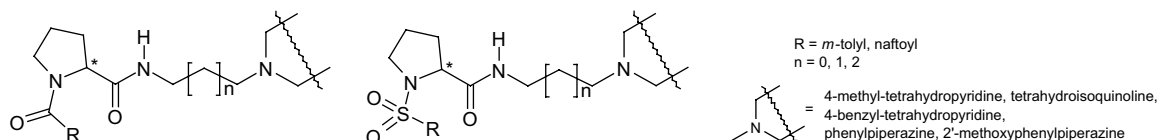
Predictive models for blood–brain barrier permeation were derived using 116 diverse compounds, 324 molecular descriptors, VSMP, a systematic variable selection method and multiple linear regression. Validation tests demonstrate that the models possess excellent predictive power and can be applied to virtual screening studies.



Parallel solid-phase synthesis and characterization of new sulfonamide and carboxamide proline derivatives as potential CNS agents

pp 3029–3035

Paweł Zajdel,* Gilles Subra, Andrzej J. Bojarski, Beata Duszyńska, Maciej Pawłowski and Jean Martinez



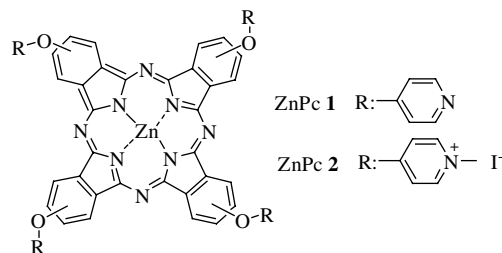
The parallel solid-phase synthesis of a series of sulfonamide and carboxamide proline derivatives and their in vitro binding affinities for serotonin 5-HT₇, 5-HT_{1A} and dopamine D₂ receptors are presented.

Synthesis, properties, and photodynamic inactivation of *Escherichia coli* using a cationic and a noncharged Zn(II) pyridyloxophthalocyanine derivatives

pp 3037–3045

Inés Scalise and Edgardo N. Durantini*

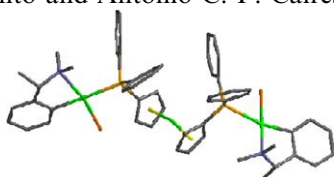
The photodynamic effect of a cationic Zn(II) *N*-methylpyridyloxophthalocyanine (ZnPc 2) and a noncharged Zn(II) pyridyloxophthalocyanine (ZnPc 1) has been compared in both homogeneous media bearing photooxidizable substrates and in vitro using a typical Gram-negative bacterium *Escherichia coli*. These studies show that cationic ZnPc 2 is an efficient phototherapeutic agent with potential applications in photodynamic inactivation of bacteria.



Chiral cyclopalladated complexes derived from *N,N*-dimethyl-1-phenethylamine with bridging bis(diphenylphosphine)ferrocene ligand as inhibitors of the cathepsin B activity and as antitumoral agents

pp 3047–3055

Cláudia Bincoletto, Ivarne L. S. Tersariol, Carlos R. Oliveira, Simone Dreher, Daniela M. Fausto, Marco Antonio Soufen, Fábio D. Nascimento and Antonio C. F. Caires*



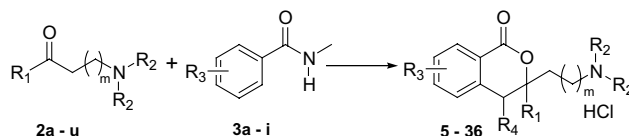
Chiral cyclopalladated complexes derived from *N,N*-dimethyl-1-phenethylamine and the coordinating ligand 1,1'-bis(diphenylphosphine)ferrocene were synthesized and studied as Cathepsin B inhibitors and antitumoral agents against solid tumors. The results presented in this work introduce the title cyclopalladated complexes as promising antitumoral drugs with reduced toxicity in experimental studies.



Isochromanone-based urotensin-II receptor agonists

pp 3057–3068

Fredrik Lehmann, Erika A. Currier, Roger Olsson, Uli Hacksell and Kristina Luthman*




OTHER CONTENTS

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Contributors to this issue
Instructions to contributors

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*Corresponding author

* Supplementary data available via ScienceDirect

COVER

Protocols that are commonly employed for altering the substrate specificity and selectivity profiles of proteins include rational and random DNA mutagenesis methods as well as techniques that entail selection and screening. This figure was designed using the programs pyMOL, Microsoft Powerpoint, and Microsoft Excel [Antikainen, N. M.; Martin, S. F. *Bioorg. Med. Chem.* **2005**, *13*, 2701–2716].

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