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Design and synthesis of novel xanthene derivatives

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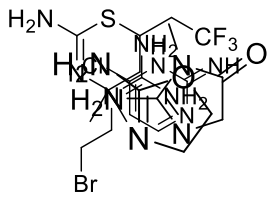
Design and synthesis of novel xanthene derivatives

Graphical Abstract

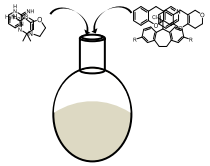
Design
Molecular hybridization



Prediction
Pharmacokinetic/ druglike nature

- Drug likeness
- BBB permeation
- P-gp efflux
- CYP enzymes inhibition
- Lipinski's rules violation
- PAINS

Synthesis
Novel xanthene derivatives



- Design of suitable synthetic pathways
- Application of green chemistry principles

Abstract:
Xanthenes are a special class of oxygen-incorporating tricyclic compounds. Structurally related to xanthones, the presence of different substituents in position 9 presents a large impact on their physical and chemical properties, as well as their biological applications. Xanthene-9-carboxylic acid, 9-hydroxyxanthene (xanthydrol) and their respective derivatives have been reported to exhibit remarkable biological activities, namely neuroprotection, antidiabetic, cytotoxic, and antibacterial.

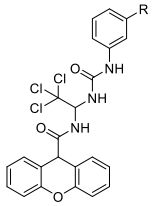
Herein, we report the design of a virtual library of 300 compounds whose pharmacokinetic properties were assessed through computational tools. Synthesis strategies to obtain such drug-like xanthene derivatives - amide coupling, reductive amination, aromatic halogenation and Suzuki coupling - are described. Azaxanthenes and thioxanthenes, important xanthene bioisosters, are also considered for their capacity to establish different biologic interactions for their influence pharmacokinetic properties. Future studies will include the investigation of their potential as bioactive compounds.

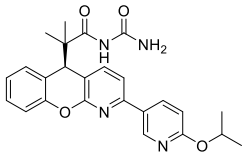
Keywords: drug design, synthesis, xanthene derivatives

Introduction

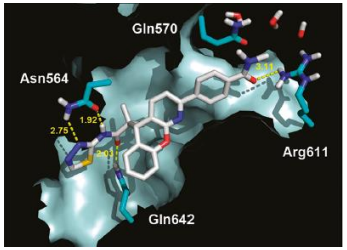
Xanthenes as privileged structures

Antidiabetic[3]

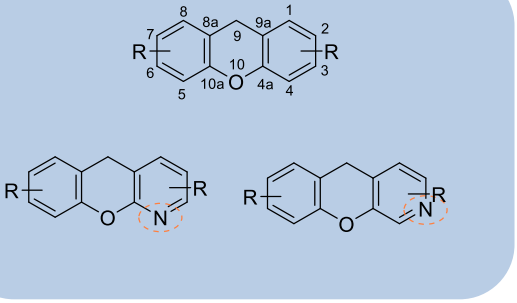


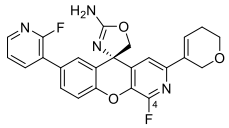


Anti-inflammatory[1]

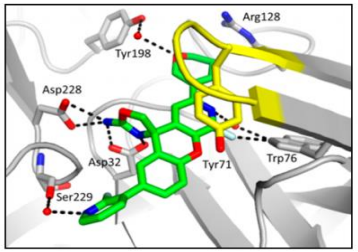


Interaction with glucocorticoid receptor the ligand binding domain[1]

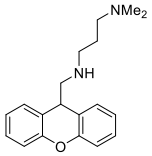




Alzheimers disease[2]



Interaction with the catalytic pocket of BACE1[2]



Antimalarial[4]

[1] Y. Cheng, J. Brown, T.C. Judd, P. Lopez, W. Qian, T.S. Powers, J.J. Chen, M.D. Bartberger, K. Chen, R.T. Dunn, O. Epstein, R.T. Fremeau, S. Harried, D. Hickman, S.A. Hitchcock, Y. Luo, A.E. Minatti, V.F. Patel, H.M. Vargas, R.C. Wahl, M.M. Weiss, P.H. Wen, R.D. White, D.A. Whittington, X.M. Zheng, S. Wood, An Orally Available BACE1 Inhibitor That Affords Robust CNS Aβ Reduction without Cardiovascular Liabilities, ACS Medicinal Chemistry Letters, 6 (2015) 210-215.

[2] D.S. Weinstein, H. Gong, A.M. Doweyko, M. Cunningham, S. Habte, J.H. Wang, D.A. Holloway, C. Burke, L. Gao, V. Guarino, J. Carman, J.E. Somerville, D. Shuster, L. Salter-Cid, J.H. Dodd, S.G. Nadler, J.C. Barrish, Azaxanthene Based Selective Glucocorticoid Receptor Modulators: Design, Synthesis, and Pharmacological Evaluation of (S)-4-(5-(1-((1,3,4-Thiadiazol-2-yl)amino)-2-methyl-1-oxopropan-2-yl)-5H-chromeno[2,3-b]pyridin-2-yl)-2-fluoro-N,N-dimethylbenzamide (BMS-776532) and Its Methylene Homologue (BMS-791826), Journal of Medicinal Chemistry, 54 (2011) 7318-7333.

[3] Y. Kwon, P. Song, J.H. Yoon, J. Ghim, D. Kim, B. Kang, T.G. Lee, J.-A. Kim, J.-K. Choi, I.K. Youn, H.-K. Lee, S.H. Ryu, Xanthene Derivatives Increase Glucose Utilization through Activation of LKB1-Dependent AMP-Activated Protein Kinase, PLOS ONE, 9 (2014) e108771.

[4] A. Jarrahpour, E. Ebrahimi, E. De Clercq, V. Sinou, C. Latour, L. Djouhri Bouktab, J.M. Brunel, Synthesis of mono-, bis-spiro- and dispiro-β-lactams and evaluation of their antimalarial activities, Tetrahedron, 67 (2011) 8699-8704.

Results and discussion

Molecular hybridization

Design

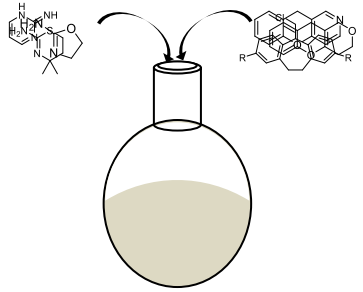
Computational prediction

Pharmacokinetic/ druglike nature

Assessment of suitable synthetic pathways

Synthesis

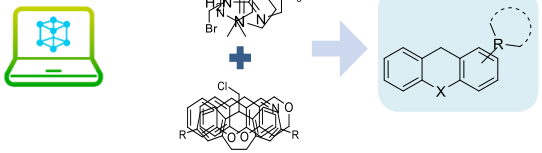
Ongoing work



Results and discussion

Computational prediction

Design of a virtual library of ≈ 300 molecular hybrids



- Calculation of drug likeness properties

- **Lipinski's rule of five**
- **BBB permeation**
- **P-gp efflux**
- **CYP inhibition**
- **PAINS alerts**

Central Nervous System (CNS) drug rules [7]

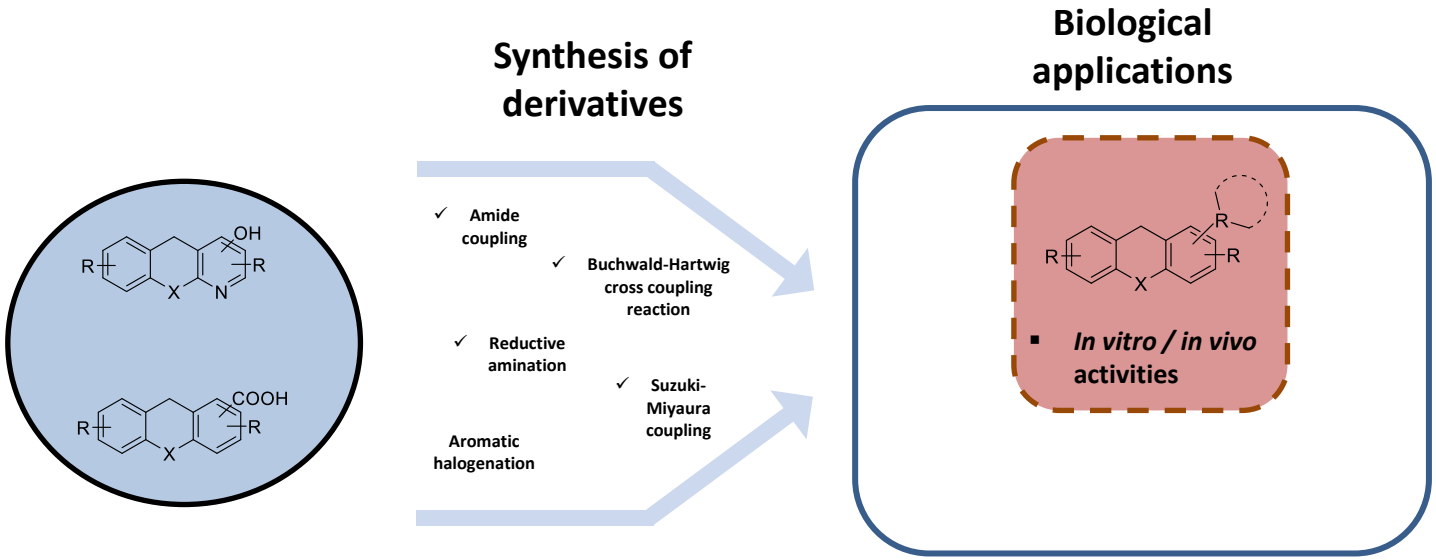
- ✓ Molecular weight < 450
- ✓ logP < 5
- ✓ < 3 H-bond donors
- ✓ < 7 H-bond acceptors (sum of N and O)
- ✓ <8 rotatable bonds
- ✓ TPSA < 70 Å^2

[5]. Pajouhesh H, Lenz GR. Medicinal Chemical Properties of Successful Central Nervous System Drugs. *Neurotherapeutics*. 2005;2:541-553. doi:https://doi.org/10.1602/neurorx.2.4.541

Results and discussion

Synthesis

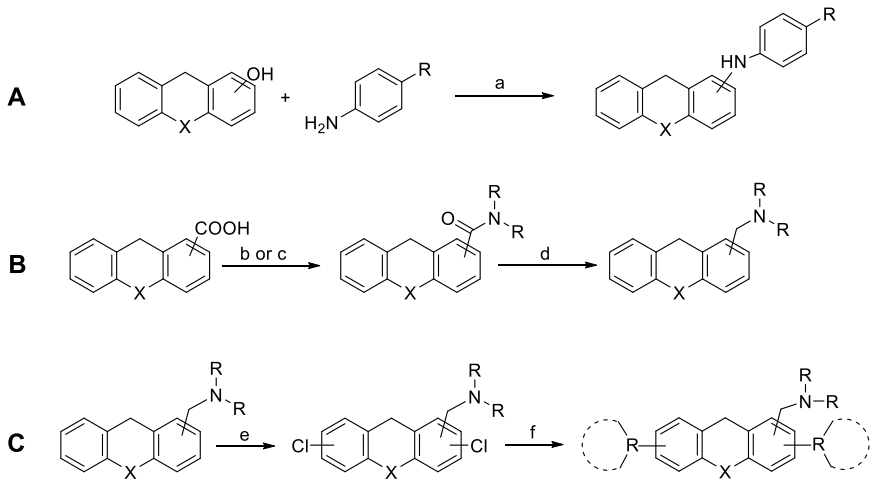
Synthesis of novel xanthene derivatives through distinctive synthetic pathways

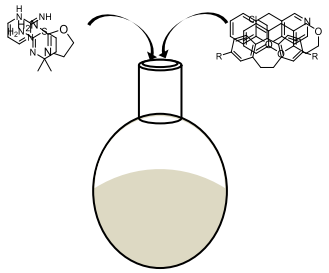


Results and discussion

Synthesis

Synthesis of novel xanthene derivatives through distinctive synthetic pathways





Reagents and conditions: (**a**) acetic acid, 25 °C; (**b**) anhydrous CH_2Cl_2, DIEA, COMU, amine, 0 °C to rt; (**c**) anhydroys THF, TEA, TBTU, amine, rt; (**d**) i) BH_3.THF, THF, 0 ºC to reflux; ii) HCl 6N, 0 °C; (**e**) N-chlorosuccinimide, acetic acid, HCl; (**f**) Suzuki-Miyaura coupling.

Conclusions

- Computational prediction revealed promising druglike compounds with adequate pharmacokinetic properties;
- Preliminary results for the *N*-alkylation of tricyclic moieties and aromatic halogenation showed that suitable synthetic pathways were found to synthesize the desire ligands;
- Future work will focus on *in vitro* studies and further structure modifications for hit to lead optimization.

Acknowledgments

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