Issue 71; September 2022

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Recent Publications of ISHC Members

Issue 71; September 2022

Synthesis of MAPA Reagents and 2-Alkyl(aryl)aminopyridines from 2-Bromopyridine Using the Goldberg Reaction

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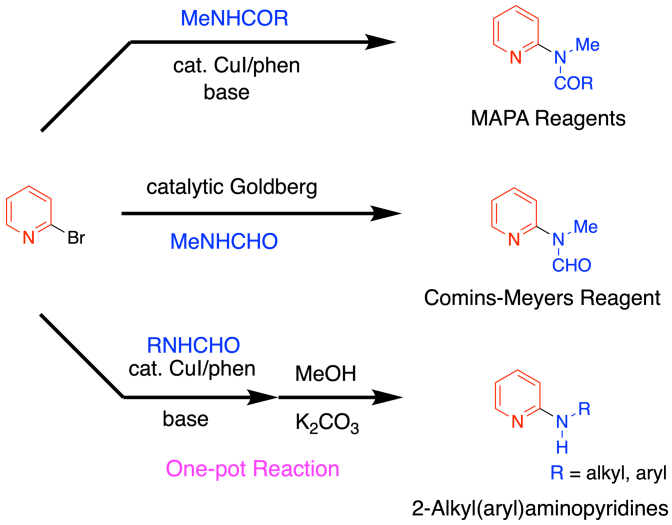
Molecules **2022**, *27*, 1833 (1–10). **DOI:** 10.3390/molecules27061833



Abstract: A short and economical synthesis of various 2-methylaminopyidine amides (MAPA) from 2-bromopyridine has been developed using the catalytic Goldberg reaction. The effective catalyst was formed *in situ* by the reaction of CuI and 1,10-phenanthroline in a 1/1 ratio with a final loading of 0.5–3 mol%. The process affords high yields and can accommodate multigram-scale reactions. A modification of this method provides a new preparation of 2-*N*-substituted aminopyridines from various secondary *N*-alkyl(aryl)formamides and 2-bromopyridine. The intermediate aminopyridine formamide is cleaved in situ through methanolysis or hydrolysis to give 2-alkyl(aryl)aminopyridines in high yields.

Lewis Acid-Catalyzed Diastereoselective Domino Reaction of Ene-Ynamide with Trimethylsilyl Cyanide to Construct Spiroindolines

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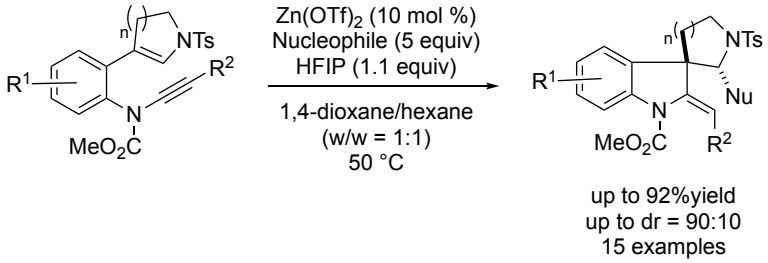
Org. Lett. **2022**, *24*, 4389–4393. **DOI:** 10.1021/acs.orglett.2c01607



Abstract: The Zn(OTf)2-catalyzed domino reaction of enamide-ynamides in the presence of trimethylsilyl cyanide as an external nucleophile to construct spirocyclic indolines was developed. This domino reaction involved cyclization of enamide to ynamide to generate 4′,5′-dihydrospiro[indoline-3,3′-pyrrol]-1′-ium followed by cyanide addition to produce spiroindolopyrrolidines with good diastereoselectivity.

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Regioselective Synthesis of 5- and 3-Hydroxy-*N*-Aryl-1*H*-Pyrazole-4-Carboxylates and Their Evaluation as Inhibitors of *Plasmodium falciparum* Dihydroorotate Dehydrogenase

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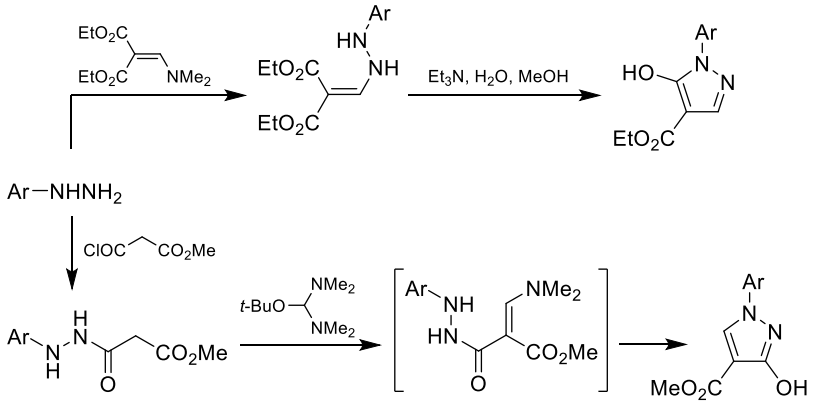
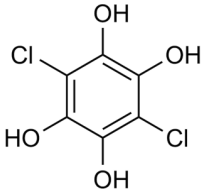
Molecules **2022**, *27*, 4764 (1–18). **DOI:** 10.3390/molecules27154764



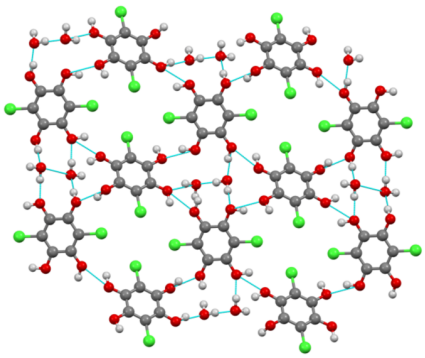
Abstract: *In silico* evaluation of various regioisomeric 5- and 3-hydroxy-substituted alkyl 1-aryl-1*H*-pyrazole-4-carboxylates and their acyclic precursors yielded promising results with respect to their binding in the active site of dihydroorotate dehydrogenase of *Plasmodium falciparum* (*Pf*DHODH). Consequently, four ethyl 1-aryl-5-hydroxy-1*H*-pyrazole-4-carboxylates and their 3-hydroxy regioisomers were prepared by two steps syntheses *via* enaminone-type reagents or key-intermediates. The synthesis of 5-hydroxy-1*H*-pyrazoles was carried out by the literature protocol comprising acid-catalyzed transamination of diethyl [(dimethylamino)methylene]malonate with arylhydrazines followed by base-catalyzed cyclization of the intermediate hydrazones. For the synthesis of isomeric methyl 1-aryl-3-hydroxy-1*H*-pyrazole-4-carboxylates, a novel two-step synthesis was developed. It comprises acylation of hydrazines with methyl malonyl chloride followed by cyclization of the hydrazines with *tert*-butoxy-bis(dimethylamino)methane. Testing the pyrazole derivatives on inhibition of *Pf*DHODH showed that 1-(naphthalene-2-yl)-5-hydroxy-1*H*-pyrazole-4-carboxylate and 1-(naphthalene-2-yl)-, 1-(2,4,6-trichlorophenyl)-, and 1-[4-(trifluoromethyl)phenyl]-3-hydroxy-1*H*-pyrazole-4-carboxylate (~30% inhibition) were slightly more potent than a known inhibitor, diethyl α-{[(1*H*-indazol-5-yl)amino]methylidene}malonate (19% inhibition).

3,6-Dichlorobenze ne-1,2,4,5-tetraol

R. Alan Aitken,* Niti Schindler, and Alexandra M. Z. Slawin (raa@st-and.ac.uk)
Molbank **2022**, *2022*, M1415 (1–5). **DOI:** 10.3390/M1415



X-ray structure



Abstract: The X-ray structure of the title compound as the monohydrate has been determined and shows a complex structure with two independent molecules each of the compound and water and eleven distinct hydrogen bonding interactions. Its melting point has also been recorded for the first time.

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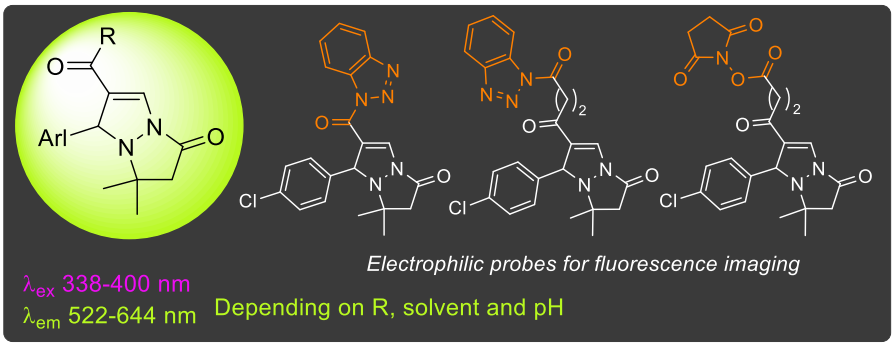
2-Acyl-1-aryl-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole Derivatives: Versatile Fluorescent Probes with Remarkably Large Stokes Shift

Nejc Petek, Bibi Erjavec, Dejan Slapšak, Aljaž Gaber, Uroš Grošelj, Franc Požgan, Sebastijan Ričko, Bogdan Štefane, Marina Klemenčič,* Jurij Svete* (marina.klemencic@fkkt.uni-lj.si or jurij.svete@fkkt.uni-lj.si)

Dyes Pigm. **2022**, *201* 110224 (1–13). **DOI:** 10.1016/j.dyepig.2022.110224

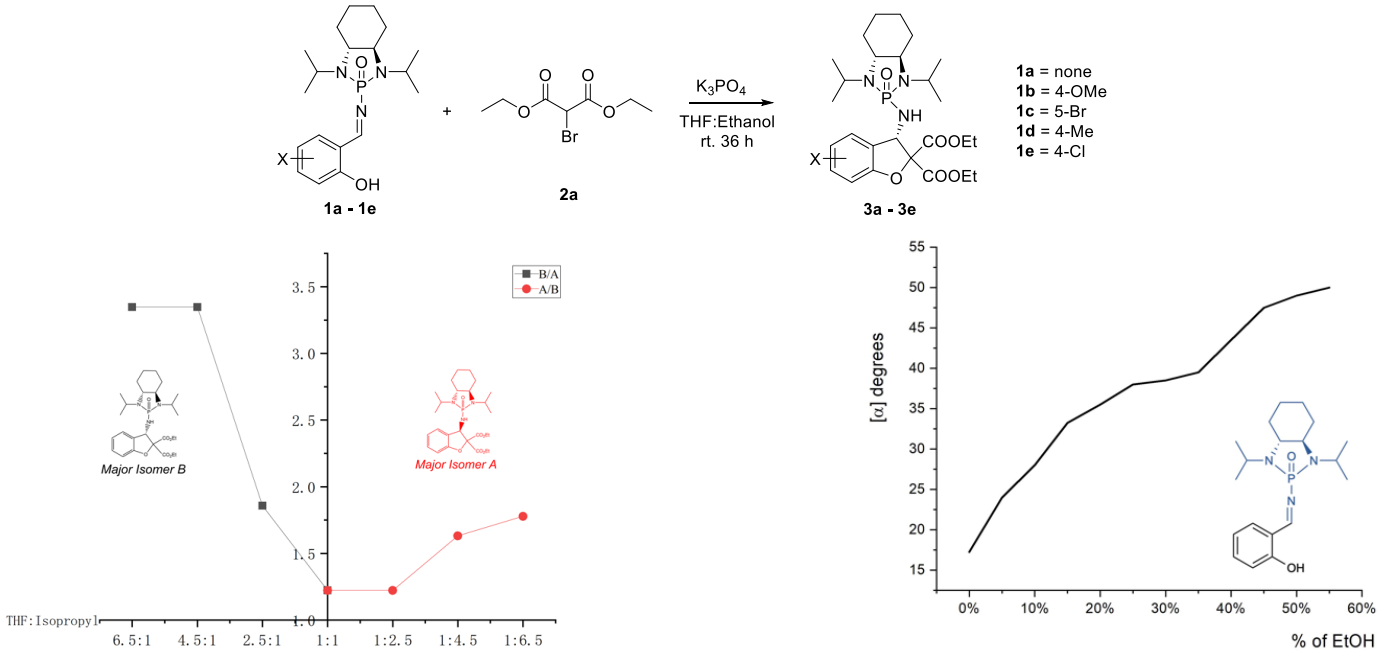


Abstract: A series of thirteen 2-acyl-6,7-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole derivatives were synthesized by using a copper-catalyzed azomethine-imine-alkyne cycloaddition as a key step. These bimane-related fluorescent compounds with λ_{ex} = 338–400 nm and λ_{em} = 522–644 nm exhibit interesting and promising optical properties, including a remarkably large Stokes shift (150–268 nm), positive solvatochromism, and strong dependence of emission intensity on pH in a range of pH 2–10. The benzotriazolide- and *N*-succinimidyl ester-functionalized compounds were successfully used as fluorescent probes for protein labelling.

Aggregation-Induced Synthesis (AIS): Asymmetric Synthesis via Chiral Aggregates

Hossein Rouh, Yao Tang, Ting Xu, Qingkai Yuan, Sai Zhang, Jia-Yin Wang, Shengzhou Jin, Yu Wang, Junyi Pan, Hannah L Wood, James D. McDonald, and Guigen Li* (guigenli@nju.edu.cn)

Research **2022**, 9865108 (1–9). **DOI:** 10.34133/2022/9865108



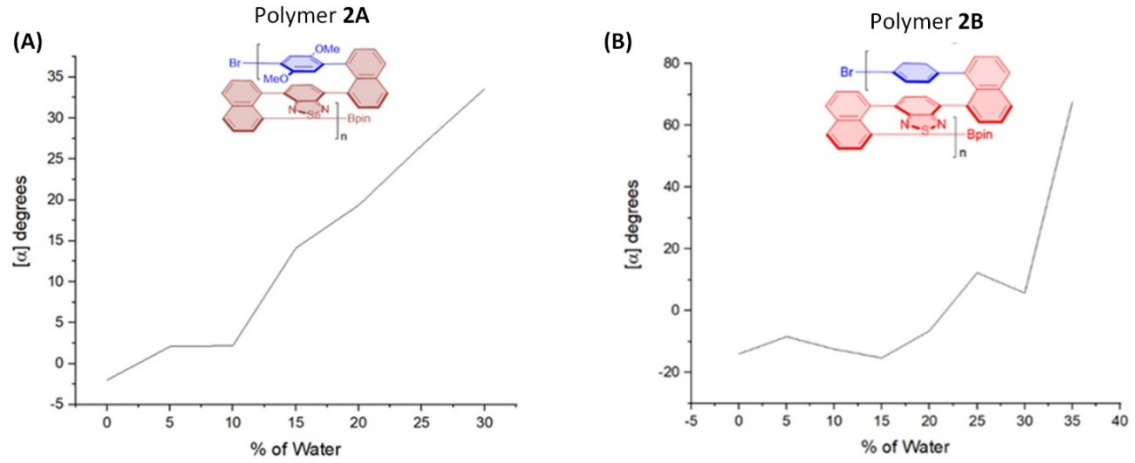
Opposite Control of Chiral Aggregate-Induced Asymmetric Synthesis and AIP

Abstract: A new chiral aggregate-based tool for asymmetric synthesis has been developed by taking advantage of chiral aggregates of GAP (Group-Assisted Purification) reagents, *N*-phosphonyl imines. This tool was proven to be successful in the asymmetric GAP synthesis of functionalized 2,3-dihydrobenzofurans by reacting salicyl *N*-phosphonyl imines with dialkyl bromomalonates bromomalonates in various co-solvent systems. The chiral induction can be controlled by differentiating between two asymmetric directions simply by changing the ratios of co-solvents which are commonly adopted in AIE (aggregation-induced emission) systems. The formation of chiral aggregates was witnessed by a new analytical tool – aggregation-induced polarization (AIP). The present synthetic method will be broadly extended for general organic synthesis, particularly, for asymmetric synthesis and asymmetric catalysis in the future.

Aggregation-Induced Polarization (AIP): Optical Rotation Amplification and Adjustment of Chiral Aggregates of Folding Oligomers and Polymers

Yao Tang, Sai Zhang, Ting Xu, Qingkai Yuan, Jia-Yin Wang, Shengzhou Jin, Yu Wang, Junyi Pan, Isaac Griffin, Daixiang Chen, and Guigen Li* (guigenli@ttu.edu)

Front. Chem. **2022**, *10*, 962638 (1–9)/ **DOI:** 10.3389/fchem.2022.962638



Aggregation-induced polarization (AIP) of multi-layer 3D chiral folding polymers.

Abstract: The phenomenon of aggregation-induced polarization (AIP) was observed showing optical rotation amplification and adjustment. The relationship between optical rotations of chiral aggregates of multi-layered chiral folding oligomers and polymers with water% in THF (f_w) has been established accordingly. New multi-layered chiral oligomers were synthesized under the asymmetric catalytic systems established by our lab recently. These products were well characterized by UV-vis, NMR and MALDI-TOF spectra. Absolute stereochemistry (enantio- and diastereochemistry) was assigned by comparison with similar asymmetric induction by the same catalyst in our previous reactions. The present AIP work can serve as a new tool to determine chiral aggregates, especially for those that cannot display emission. AIP would also complement AIE-based CPL since AIP serves as a new tool providing enhanced right- or left-hand polarized lights with individual wavelengths. It will find many applications in chemical and materials sciences in the future.

Development of an Orally Active Small-Molecule Inhibitor of Receptor Activator of Nuclear Factor κB Ligand

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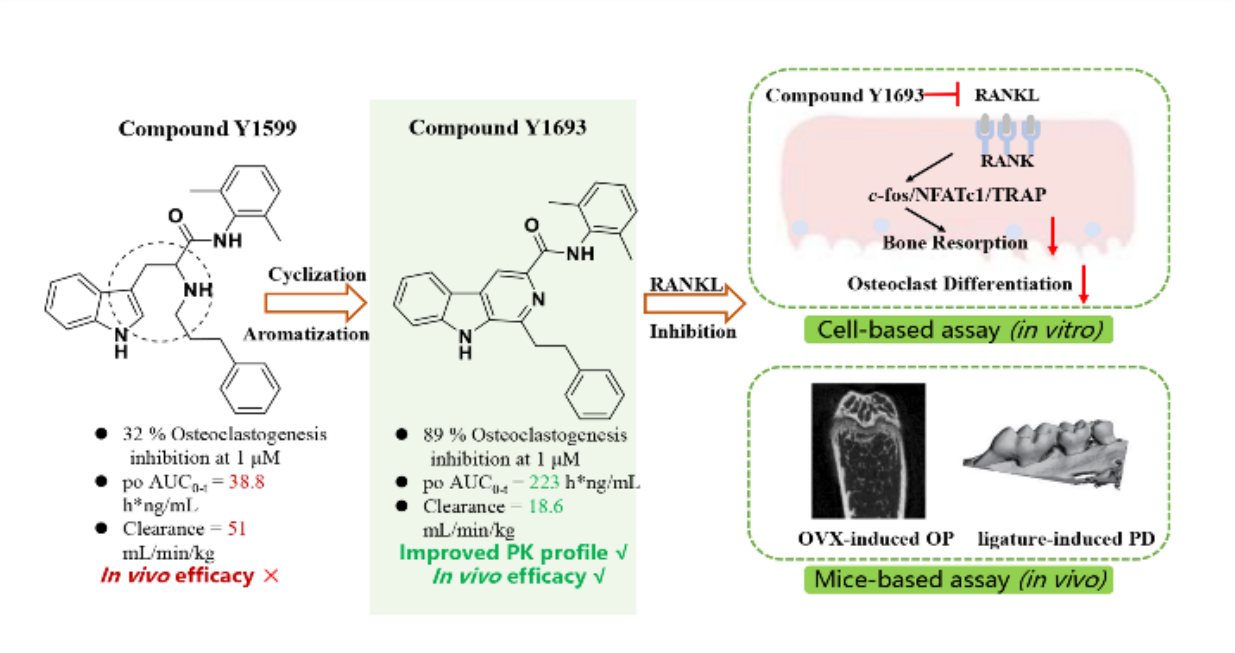
J. Med. Chem. **2022**, *65*, 10992–11009. **DOI:** 10.1021/acs.jmedchem.2c00081

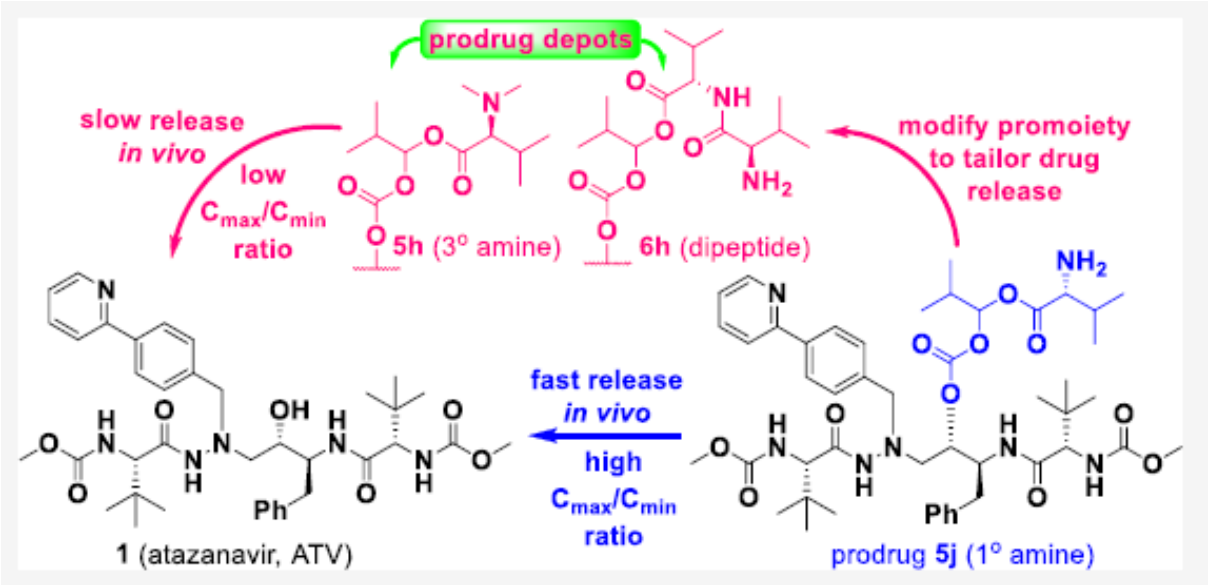


Abstract: Receptor activator of nuclear factor-κB (RANK) and its ligand, RANKL, play pivotal roles in bone remodeling. The monoclonal antibody denosumab successfully inhibited the maturation of osteoclasts (OCs) by binding to RANKL in the clinic. We continued our efforts to develop small-molecule inhibitors of RANKL. In this work, 41 β-carboline derivatives were synthesized based on previously synthesized compound **Y1599** to improve its drug-like properties. Compound **Y1693** was identified as a potent RANKL inhibitor that improved absorption–distribution–metabolism–excretion properties and effectively prevented RANKL-induced osteoclastogenesis and bone resorption. Furthermore, Y1693 also suppressed the expression of OC marker genes. Moreover, **Y1693** demonstrated good tolerability and efficacy in an orally administered mouse model of osteoporosis as well as the ability to rescue alveolar bone loss *in vivo* caused by periodontal disease. Collectively, the above findings may provide a valuable direction for the development of novel antiresorptive therapies that target RANKL.

Improving Drug Delivery While Tailoring Prodrug Activation to Modulate C_{max} and C_{min} by Optimization of (Carbonyl)oxylalkyl Linker-Based Prodrugs of Atazanavir

Murugaiah A. M. Subbaiah,* Lakshumanan Subramani, Thangeswaran Ramar, Salil Desai, Sarmistha Sinha, Sandhya Mandlekar, John F. Kadow, Susan Jenkins, Mark Krystal, Murali Subramanian, Srikanth Sridhar, Shweta Padmanabhan, Priyadeep Bhutani, Rambabu Arla, and Nicholas A. Meanwell (murugaiah.andappan@syngeneintl.com)

J. Med. Chem. **2022**, *65*, 11150–11176. **DOI:** 10.1021/acs.jmedchem.2c00632



Abstract: Structure–property relationships associated with a series of (carbonyl)oxyalkyl amino acid ester prodrugs of the marketed HIV-1 protease inhibitor atazanavir (**1**), designed to enhance the systemic drug delivery, were examined. Compared to previously reported prodrugs, optimized candidates delivered significantly enhanced plasma exposure and trough concentration (C_{min} at 24 h) of **1** in rats while revealing differentiated PK paradigms based on the kinetics of prodrug activation and drug release. Prodrugs incorporating primary amine-containing amino acid promoieties offered the benefit of rapid bioactivation that translated into low circulating levels of the prodrug while delivering a high C_{max} value of **1**. Interestingly, the kinetic profile of prodrug cleavage could be tailored for slower activation by structural modification of the amino terminus to either a tertiary amine or a dipeptide motif, which conferred a circulating depot of the prodrug that orchestrated a sustained release of **1** along with substantially reduced C_{max} and a further enhanced C_{min}.