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Bioorthogonal Transfer Hydrogenation Mediated by Small Molecule Catalyst

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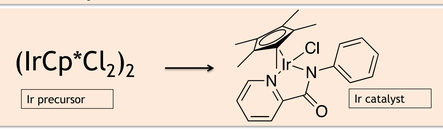
Introduction

Background
- Increasing threat of drug resistant diseases
- Need of new therapeutic solutions
- Most of the drugs available are either organic molecules or biologics
- Inorganic metal complexes can undergo ligand exchange reaction
- Metal centers exist in different oxidation states and form more than four bonds unlike carbon
- Inorganic medicinal chemistry is underexplored

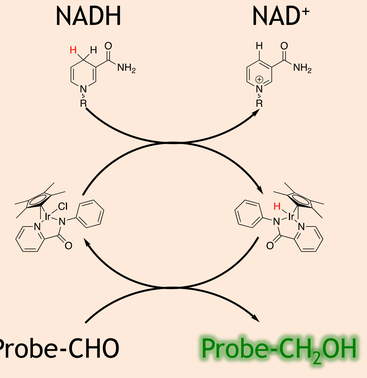
Goal
- Engineer unprotected metal catalyst
- Carry out bioorthogonal transfer hydrogenation

Challenges
- Catalyst should be stable in water, air, biological pH and non toxic
- Catalyst should be active in presence of cellular nucleophiles

Benefits
- Catalytic drugs do not need in stoichiometric amount
- New mechanism may overcome drug resistant problem

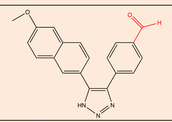
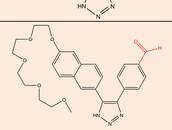
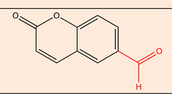
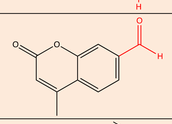
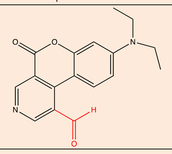
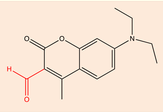
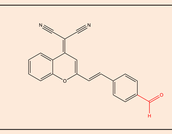


Approach

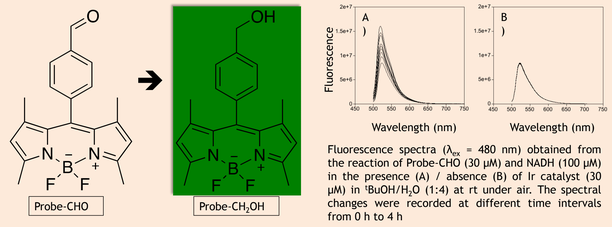


Probe Selection

Goal
- Low energy excitation
- Good conversion under physiological condition
- Difference in photophysical properties

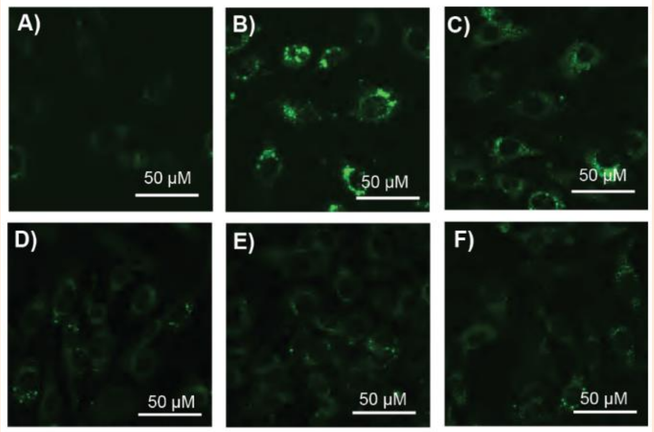
Probe Scanned	Drawback
	High energy excitation Bad solubility Poor conversion
	Very poor conversion
	High energy excitation Over reduction
	High energy excitation Alcohol is dimly emissive
	No conversion
	No conversion
	Non-fluorescent

Achievement
- QY from 0.26 to 0.61
- Λ_{ex} = 480 nm
- 20% conversion under physiological condition

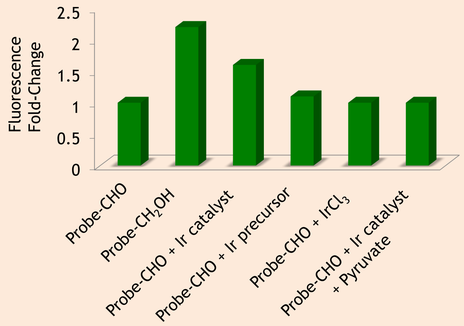


Fluorescence spectra (λ_{ex} = 480 nm) obtained from the reaction of Probe-CHO (30 μM) and NADH (100 μM) in the presence (A) / absence (B) of Ir catalyst (30 μM) in $^tBuOH/H_2O$ (1:4) at rt under air. The spectral changes were recorded at different time intervals from 0 h to 4 h

Results

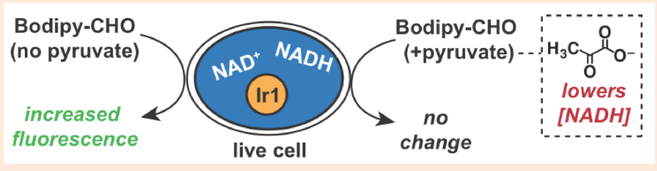


Fluorescence confocal microscope images (40x) of NIH-3T3 cells treated with A) Probe-CHO (30 μM); B) Probe-CH_2OH (30 μM); C) Probe-CHO (30 μM)/Ir catalyst (20 μM); D) Probe-CHO (30 μM)/Ir precursor (10 μM); E) Probe-CHO (30 μM)/$IrCl_3$ (20 μM); and F) Probe-CHO (30 μM)/Ir catalyst (20 μM)/sodium pyruvate (10 mM)



	Probe-CHO	Probe-CH_2OH	Ir catalyst
IC_{50} (μM)	>500	79 ± 20	108 ± 3

NIH-3T3 mouse fibroblast cells treated with Probe-CHO/ Probe-CH_2OH/ Ir catalyst for 3 h and the cell viability percentage was determined using a colorimetric MTS assay



Effect of Pyruvate as NADH Modulator

Conclusions and Future Direction

- Transfer Hydrogenation using endogenous NADH in live cells
- Unprotected small molecule iridium catalyst
- Interaction of the catalyst with other cellular components is under investigation

References

- Sletten, E. M.; Bertozzi, C. R. Angew. Chem., Int. Ed. 2009, 48, 6974–6998
- Ngo, A. H.; Ibañez, M.; Do, L. H. ACS Catal. 2016, 6, 2637– 2641
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