Ruthenium-catalyzed cyclization reactions in pursuit of molecules that inhibit DXP synthase

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OBJECTIVE

DXP synthase is a bacterial enzyme of the non-mevalonate pathway and is being explored as a target for the development of potential antibiotics. The objective is to synthesize a small library of TPP (enzyme cofactor)-resembling triazole compounds using a diverse set of aromatic or heteroaromatic cores alongside an internal alkyne using ruthenium catalysts.

METHODS

Standard synthetic chemistry methods are employed. A set of aryl or heteroaryl cores (that mimic the enzyme cofactor) were selected. These core bear either a primary alcohol or alkyl halide, which are converted to their corresponding azides. The isolated azides are cyclized in the presence of a specific ruthenium catalyst to yield the corresponding aryl/heteroaryl triazole, which resembles the central ring of the enzyme cofactor, TPP. Product yields of these 8 compounds vary depending upon the type of solvent, catalyst, and temperature used. These compounds will be evaluated in biological assays.

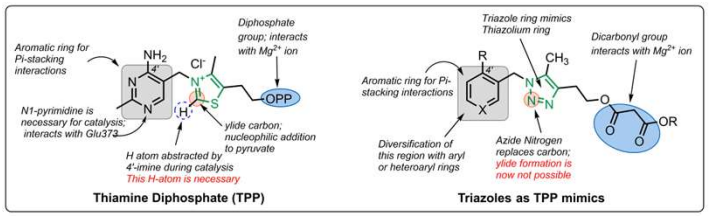
RESULTS

An array of suitable aryl/heteroaryl triazoles (~8-10) have been created using ruthenium catalysts. These will be evaluated in cell-based assays to help identify lead compounds or scaffolds towards the inhibition of bacterial DXP synthase.

CONCLUSIONS

Ruthenium-based triazole generating reactions are less commonly studied, compared to their more famous metathesis counterparts. Nevertheless, they yield excellent results when traditional copper-based "click" chemistry does not work on internal alkynes. In this study, we demonstrate the utility of this procedure towards the synthesis of suitable enzyme inhibitors.

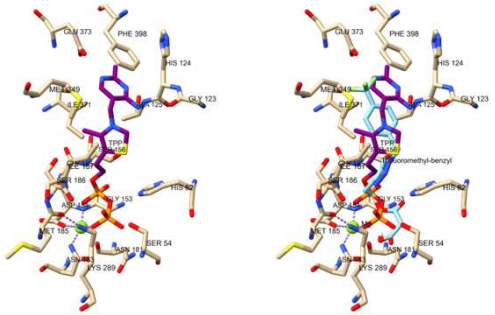
RATIONAL DESIGN



RATIONAL DESIGN

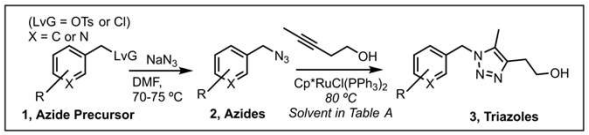
The key step in DXP synthase mechanism is 4'-NH2-mediated creation of the thiazolyl ylide (at C2), in order to realize the C-C bond formation involving pyruvate and G3P. As a TPP-mimicking molecule, 1,2,3-triazole is a suitable thiazole replacement as it lacks the ability to form an ylide, while maintaining hydrophobic interactions in the active site. This hypothesis is confirmed by our docking results, which supports the efforts to synthesize potential DXP synthase inhibitors.

TPP in active site *Comparison of native TPP with SRM15*

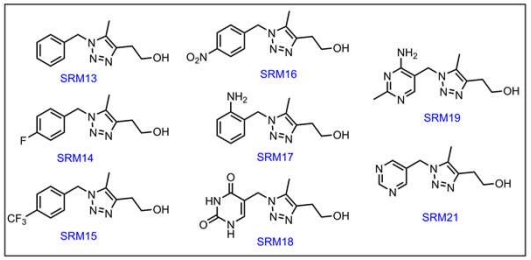


CHEMISTRY

The creation of a small series of 1,2,3-triazoles was accomplished using Ru-based "click" chemistry reaction, which are less common when compared to their Cu-based cousins. These reactions include Cp*RuCl(PPh_3)$_2$. a specific Ru-catalyst, as well as specific azides and the internal alkyne, 3-pentynol. The dicarbonyl anchors the molecule to the Mg2+ ion in the active site.



Using this synthetic scheme, we obtained the following triazoles.



OPTIMIZATION

Different solvents were used to accomplish the synthesis of these triazoles. For the set of substituted phenyl azides (SRM13 to SRM17), benzene provided the best yields of the corresponding triazoles, while for the heteroaryl azides, a combination of 1,4-dioxane w/ 5% DMF was found to be most suitable. All reactions were conducted at 80 °C.

Azide precursor of	Solvent	Time (hr)	Average Yields (%)
SRM13, SRM14, SRM15, SRM16, SRM17	Benzene	6.5	45
	Toluene	8.5	20
	1,4-Dioxane	12	20
	THF	11	15
SRM18, SRM19, SRM21	1,4-Dioxane w/ 5% DMF	12	40
	THF	16	20
	Dioxane	16	No Reaction
	Benzene	16	No Reaction
	Toluene	16	No Reaction

REACTION YIELDS

Based on the results from our solvent studies (above), the following triazoles were synthesized. Reaction yields are low, due to the formation of regioisomeric products that are not easily separated. Based on NMR results, the distribution of regioisomers (e.g., 13a:13b) is ~70:30 across the board.

Code	Solvent	Time (hr)	Yield (%)
SRM13	Benzene	6.5	54
SRM14	Benzene	6.5	55
SRM15	Benzene	6.5	56
SRM16	Benzene	6.5	51
SRM17	Benzene	6.5	55
SRM18	THF	18	11
SRM19	1,4-Dioxane: 5%DMF	16	37
SRM21	THF	16	22

CHALLENGES AND FUTURE DIRECTIONS

- Despite using a variety of methods detailed in literature, we are unable to achieve the complete removal of Ru from the final product. We continue to explore additional strategies to scavenge Ru metal.
- Biological studies are currently underway in the form of both isolated enzyme assays and whole cell assays on selected bacteria.

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