Synthesis of 1,2,3-triazole-4-carboxamides as nucleobase analogues

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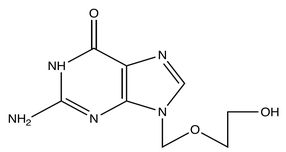
Difficulty in developing antiviral drugs

Viruses, such as Herpes, are difficult to fight because they force host cells to replicate the virus. As a result, antiviral drugs must attack viral cells without killing healthy cells.[1] Antiviral drugs must be disguised in order to trick the body while still targeting the virus with extreme specificity.



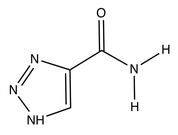
Acyclovir

The antiviral drug Acyclovir is used to treat the Herpes virus.[2]

1

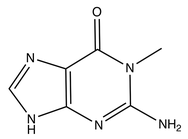
1,2,3-triazole-4-carboxamides resemble purine nucleobases

Antiviral drugs resemble certain chemical structures in human cells in order to attack viruses without being rejected by the body. 1,2,3-triazole-4-carboxamides (**1**) are analogues of the purine nucleoside bases guanine (**2**) and adenine as they share structural and hydrogen-bonding similarities.[3]



1,2,3-triazole-4-carboxamide as a guanine analogue

1



guanine

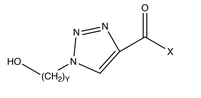
2

2

Table of Final Products

14 products were formed, with four possible alkyl chains and four possible carbonyl groups attached to the triazole.

Length of R Chain	Carbonyl Group	Percent Yield of Final Compound
2	COOH	83%
2	CO-NH_2	77%
2	CO-NH-NH_2	64%
2	CO-NH-OH	62%
3	COOH	--
3	CO-NH_2	78%
3	CO-NH-NH_2	quant.
3	CO-NH-OH	77%
4	COOH	69%
4	CO-NH_2	68%
4	CO-NH-NH_2	73%
4	CO-NH-OH	52%
5	COOH	83%
5	CO-NH_2	61%
5	CO-NH-NH_2	56%
5	CO-NH-OH	--



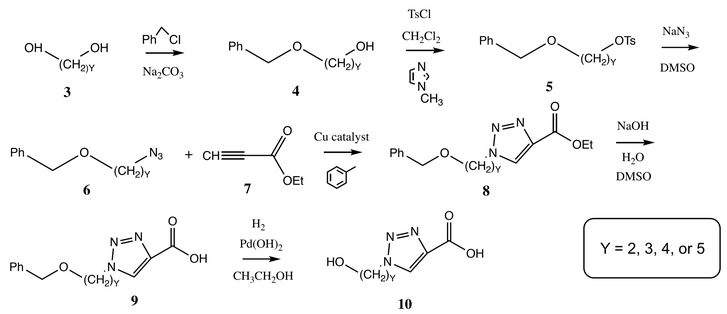
Y = 2, 3, 4, or 5
X = OH, NH_2, NH-NH_2, or NH-OH

Structure of final products

3

Synthetic Route to a Carboxylic Acid

A diol (**3**) was monobenzylated (**4**) and then tosylated (**5**) to form an azide (**6**). (**6**) underwent a Cu-catalyzed Click reaction[4] with ethyl propialote (**7**) to form a triazole (**8**). (**8**) was hydrolyzed (**9**) and then hydrogenated to form a 1,2,3-triazole-4-carboxylic acid (**10**).

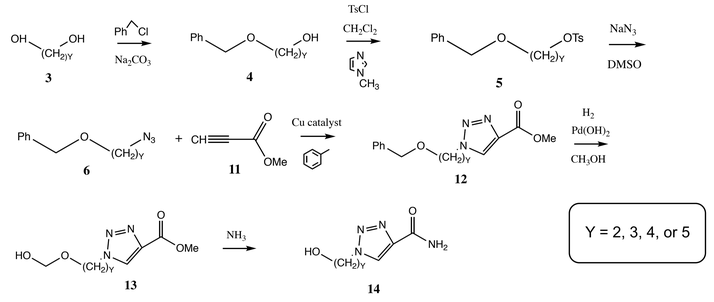


Y = 2, 3, 4, or 5

4

Synthetic Route to an Amide

A diol (**3**) was monobenzylated (**4**) and then tosylated (**5**) to form an azide (**6**). (**6**) underwent a Cu-catalyzed Click reaction[4] with methyl propiolate (**11**) to form a triazole (**12**). (**12**) was hydrogenated (**13**) and then reacted with ammonia to form a 4-carbamoyl-1,2,3-triazole (**14**).

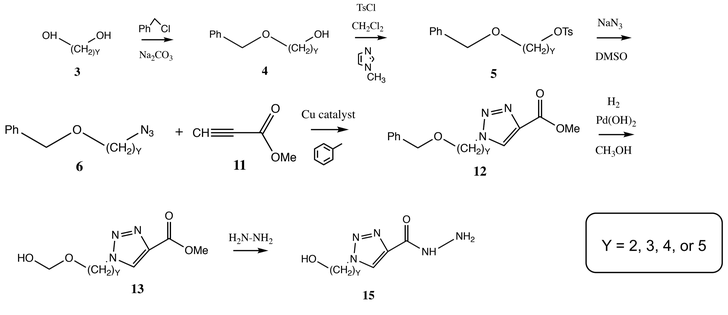


Y = 2, 3, 4, or 5

5

Synthetic Route to a Hydrazide

A diol (**3**) was monobenzylated (**4**) and then tosylated (**5**) to form an azide (**6**). (**6**) underwent a Cu-catalyzed Click reaction[4] with methyl propiolate (**11**) to form a triazole (**12**). (**12**) was hydrogenated (**13**) and then reacted with hydrazine to form a 4-aminocarbamoyl-1,2,3-trizaole (**15**).

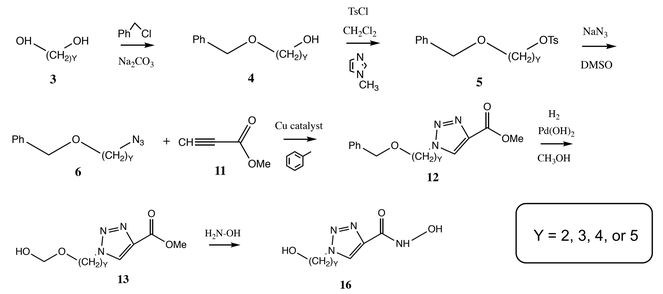


Y = 2, 3, 4, or 5

6

Synthetic Route to a Hydroxamic Acid

A diol (**3**) was monobenzylated (**4**) and then tosylated (**5**) to form an azide (**6**). (**6**) underwent a Cu-catalyzed Click reaction[4] with methyl propiolate (**11**) to form a triazole (**12**). (**12**) was hydrogenated (**13**) and then reacted with hydroxylamine to form a 4-hydroxycarbamoyll-1,2,3-triazole (**16**).



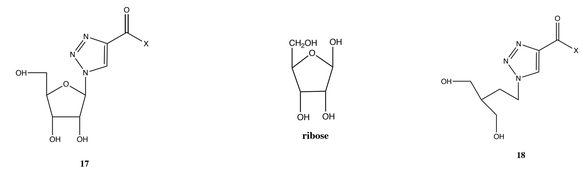
Y = 2, 3, 4, or 5

7

Future Work

Future work includes testing compounds for antiviral activity through the NIAID antiviral screening program, the NCI 60-line screen program, and commercial screening programs such as the one at Eli Lilly.

The triazole chemistry can be expanded to synthesize ribose analogues, such as **17** and **18**.



ribose

X = NH_2, NH-NH_2, NH-OH

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References

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