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Two task order assignments were completed during the reporting period. The first assignment consisted of both the preparation of 2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione and studies directed towards the potential syntheses of three additional aza- and diazaisatoic anhydrides. The second assignment was the synthesis of benzamide, 4,4'-[1,5-pentanediylbis-(oxy)bis[N-hydroxy-.

The following target compounds were synthesized during this period: 2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione; 4,4'-[1,5-pentanediylbis(oxy)-bis[N-hydroxy-.

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Azaisatoic anhydrides; bishydroxamic acid.

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Jaroslaw Rozstroy
PI-Signature

16 Feb. 01
Date

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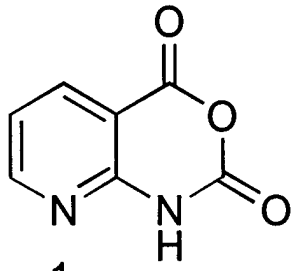
Introduction

The fourth task order assignment of this contract (DAMD17-99-D-0005) consisted of both the preparation of 2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione (1):



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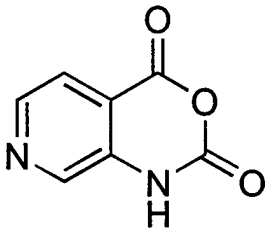
and studies directed towards the potential syntheses of three additional materials (2-4):



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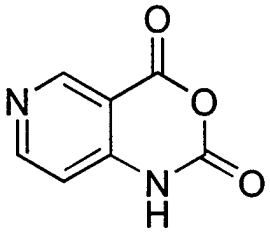

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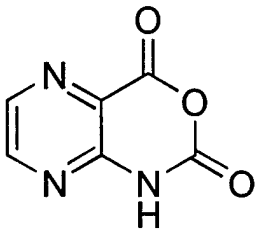

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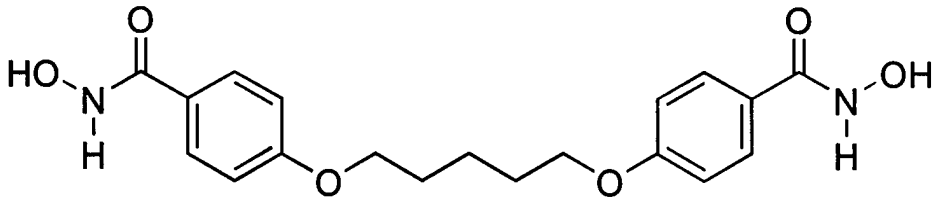
The fifth task order assignment consisted of the synthesis of bishydroxamic acid 5:



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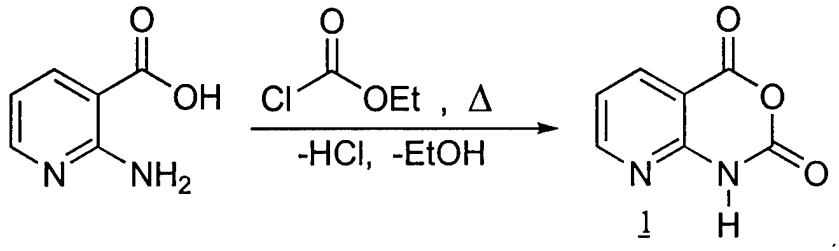
Body

RESEARCH AND KNOWN TARGET COMPOUNDS COMPLETED AND DELIVERED TO WALTER REED ARMY INSTITUTE OF RESEARCH FROM FEBRUARY 15, 2000 TO FEBRUARY 14, 2001

1. 2H-Pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione

The target compound 1 was prepared[1] by the following reaction:



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A stirred suspension of 2-aminonicotinic acid (51.0 g, 369.6 mmol) in ethyl chloroformate (650 mL, 6.8 mol) was heated in a 110°C oil bath, and allowed to reflux for fifteen hours. Additional ethyl chloroformate (650 mL) was added, portionwise over 15h, in order to thin the reaction mixture. The reaction was returned to RT, then diluted with chloroform (250 mL). The solids were collected on a filter, rinsed with chloroform (250 mL), and dried to give a mixture of target, 2-aminonicotinic acid hydrochloride, and a small amount of 2-aminonicotinic acid. These solids were sequentially washed with 500 mL each of water, 0.3N aq. HCl, and aqain with water to remove the starting material (free-base and salt form). The pure target was dried in vacuo at 60°C to give 26.7 g. Starting material was recovered by treating the combined aqueous filtrates with 5% aqueous sodium hydroxide to give pH=5.5, collecting the precipitate, washing with water, and

drying in vacuo at 60°C to give 18.2 g of 2-aminonicotinic acid. The material was suitable for recycling.

A total of 107.4 g of target 1 (2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione) was obtained from a total of five similar reactions, giving an overall, purified yield of 24% (44% when based on recovered starting material). Two lots were transmitted to WRAIR: 1N4-17-2 (16.5 g; mp 222-225°C) on 3 August '00, and 1N4-21-1 (90.0 g; mp 209-211°C) on 16 August '00. Reported melting data for this material range from 208°C[1] to 224-225°C[2]. We have been able to support both literature values with our results.

Elemental Analysis

$C_7H_4N_2O_3$	%C	%H	%N
164.12 g/mole	51.23	2.46	17.07
1N4-17-2	51.24	2.46	17.00
1N4-21-1	51.15	2.51	17.03

Spectral Data

Infrared (Nujol mull)

υ 3020, 2670, 1935, 1820, 1790-1680, 1665, 1580, 1495, 1285, 1260, 1205, 1190, 995, 960, 905, 855, 810, 755, 725, 690, 640 cm^{-1}.

Nuclear Magnetic Resonance (DMSO-d_6)

δ 12.25 (s, 1H, N-H); 8.66 (dd, 1H, J=4.8 & 1.7 Hz, H-5); 8.31 (dd, 1H, J=7.8 & 1.7 Hz, H-7); 7.31 (dd, 1H, J=7.8 & 4.8 Hz, H-6) at 500 MHz. D_2O exchanged one proton at 12.25 ppm.

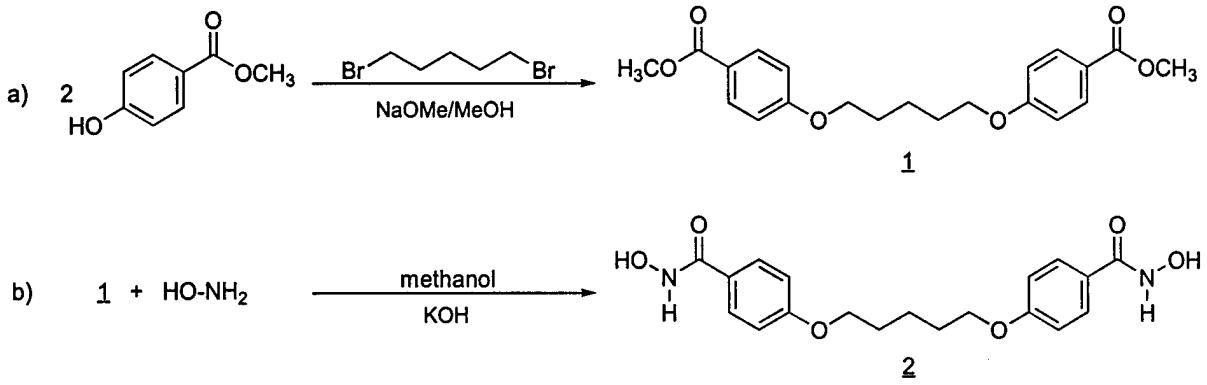
Source of Materials

1. 2-Aminonicotinic acid	Aldrich Chemical Co., Inc.
2. Ethyl chloroformate	Aldrich Chemical Co., Inc.
3. Chloroform	Aldrich Chemical Co., Inc.
4. Hydrochloric acid (conc.)	J.T. Baker Chemical Company
5. Sodium hydroxide	Aldrich Chemical Co., Inc.

2. Benzamide, 4,4'-[1,5-pentanediylbis(oxy)]bis[N-hydroxy-

The target compound 2 was prepared by the following sequence of reactions:

REACTION SCHEME



EXPERIMENTAL

a. 4,4'-[1,5-pentanediylbis(oxy)]bis[benzoic acid] dimethyl ester (1)

A solution of sodium methoxide in methanol (61.0 mL of 0.5 M, 30.5 mmol) was added to a solution of methyl 4-hydroxybenzoate in methanol (4.7 g, 30.9 mmol in 50 mL). After stirring at RT for 30 min, 1,5-dibromopentane (2.4 g, 10.3 mmol) was added. The reaction was then heated at reflux for 24 h. After cooling to RT, the precipitated product was collected on a filter, washed with water (350 mL), and dried in vacuo at 40°C to give 1.5 g (39%) of pure 1. The material was suitable for further transformation.

Spectral Data

Nuclear Magnetic Resonance ($CDCl_3$)

δ 7.97 & 6.89 (d, 4H each, J=8.7 Hz, Ar-H's); 4.04 (t, 4H, J=6.4 Hz, 2 x OCH_2); 3.88 (s, 6H, 2 x OCH_3); 1.88 (m, 4H, 2 x CH_2); 1.67 (m, 2H, CH_2) at 500 MHz.

b. Benzamide, 4,4'-[1,5-pentanediylbis(oxy)]bis[N-hydroxy- (2)

A solution of KOH in methanol (20.8 g of 85%, 213 mmol in 44 mL, brought to reflux then cooled to 30°C) was added to a solution of hydroxylamine hydrochloride in methanol (14.7 g, 315 mmol in 76 mL, brought to reflux then cooled to 30°C), and the mixture was cooled to 0°C. The precipitated KCl was removed by filtration, and the filtrate was used as a basic, 1.7M methanolic solution of hydroxylamine.

A suspension of 1 (744 mg, 2.0 mmol) in the basic, methanolic hydroxylamine solution (15 mL of 1.7 M, 25.5 mmol) was stirred at RT for 16h. The target was collected on a filter, then suspended in water (20 mL) and stirred for 30 min. The pH was adjusted to ~7 with 1 N aq. HCl, and the solid was recollected on a filter. After rinsing sequentially with water and ether, the target was dried in vacuo at 60°C to give 585 mg (78% yield) of 2, lot number 1N5-5-1; mp 192-193°C, lit. mp[3] 202-203°C. A 140 mg portion was transmitted to WRAIR on 30 November 2000.

Our analysis of this lot gave good agreement with C,H,N elemental analysis, but the melting point was depressed by ~10°C compared to the literature value, and the ^1H NMR indicated an impurity in the aromatic region. Careful analysis with respect to the integration of this spectrum showed that these impurity peaks amounted to 4.6% of the total integrated area in the aromatic region of lot number 1N5-5-1.

Elemental Analysis

374.39 g/mole	%C	%H	%N
$C_{19}H_{22}N_2O_6$	60.95	5.92	7.48
1N5-5-1	60.61	5.86	7.23

Spectral Data

Nuclear Magnetic Resonance (DMSO-d_6)

δ 11.0 & 8.9 (broad, 1H each, NHOH); 7.71 & 6.97 (d, 2H each, J=8.6 Hz, Ar-H's); 4.04 (t, 4H, J=6.3 Hz, 2 x OCH_2); 1.79 (m, 4H, 2 x CH_2) 1.57 (m, 2H, CH_2) at 500 MHz. D_2O exchanged two protons at 11.0 8.9 ppm. The two impurity peaks were observed at 7.8 & 6.9 ppm.

FT-Infrared (KBr pellet)

υ 3286, 3077, 2945, 2762, 1646, 1609, 1569, 1507, 1469, 1414, 1394, 1335, 1304, 1252, 1240, 1222, 1189, 1164, 1115, 1065, 1028, 1011, 947, 902, 848, 816, 755, 700, 649, 550, 493 cm^{-1}.

Additional Efforts

A 400 mg portion of 1N5-5-1 was recrystallized from DMSO/water, rinsed with water, and dried in vacuo at 60°C to constant weight. The target was then suspended in methanol (20 mL), stirred at RT for 30 min, collected on a filter, and dried in vacuo at 60°C to give 344 mg (86% recovery; 67% overall, purified yield) of 2 (lot number 1N5-5-2); mp 192-193°C, lit. mp[1] 202-203°C. Again, we found the melting point

was depressed by ~10°C, and the ^1H NMR indicated the same impurity. Careful analysis with respect to the integration of this spectrum showed that these impurity peaks amounted to 3.8% of the total integrated area in the aromatic region of lot number 1N5-5-2. Additionally, the NMR indicated that this lot had entrained some water and DMSO which we had been unable to remove by washing or drying in vacuo. The presence of solvents was also noted in the C,H,N elemental analysis (carbon analyzed low by 0.74%). We obtained mass spectra of 1N5-5-2 and found, by positive ion electrospray, the molecular ion at *m/z* 375. An attempt to reproduce the literature mass spectrum, which was reportedly obtained by chemical ionization via methane, was not successful.

Elemental Analysis

374.39 g/mole	%C	%H	%N
$C_{19}H_{22}N_2O_6$	60.95	5.92	7.48
1N5-5-2	60.21	5.94	7.19

Spectral Data

Nuclear Magnetic Resonance (DMSO-d_6)

δ 11.0 & 8.9 (broad, 1H each, NHOH); 7.68 & 6.95 (d, 2H each, J=8.6 Hz, Ar-H's); 4.02 (t, 4H, J=6.3 Hz, 2 x OCH_2); 1.77 (m, 4H, 2 x CH_2) 1.57 (m, 2H, CH_2) at 500 MHz. D_2O exchanged two protons at 11.0 8.9 ppm. The two impurity peaks were observed at 7.8 & 6.9 ppm, along with extra water at 3.29 ppm and DMSO at 2.54 ppm.

FT-Infrared (KBr pellet)

υ 3427, 3286, 3072, 2945, 1646, 1609, 1569, 1507, 1469, 1394, 1305, 1253, 1189, 1165, 1065, 1028, 947, 902, 848, 755, 650, 553 cm^{-1}.

Mass (Electrospray$^+$ in acetone/DMSO)

m/z 375 [$(M+1)^+$], 397 [$(M+Na)^+$], 413 [$(M+K)^+$].

Summary

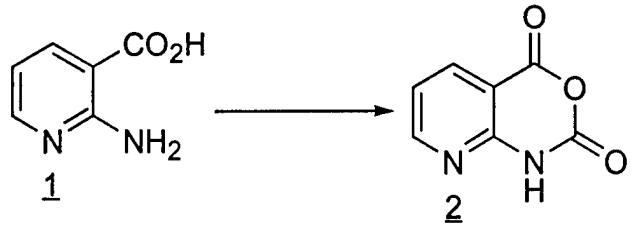
We are confident that this shipment lot contains 92-96% of the desired bis-hydroxamic acid. Purification by crystallization did not increase the melting point, and resulted in trapped solvents. Chromatography was not attempted due to the solubility properties of this material.

Originally, we had tried to convert the bis-ester to the target by using hydroxylamine in water. We also tried hydroxylamine in acidic conditions. Neither attempt gave any reaction at all. Finally, we tried basic conditions and were successful in producing the target, albeit target containing a small amount of a difficult-to-remove impurity. It is possible that neutral conditions could produce the desired target more cleanly than we achieved from our hydroxylamine/KOH conditions, but further efforts would be required.

Key Research Accomplishments

> 3-Azaisatoic anhydride

Ten different sets of reaction conditions were explored in the preparation of 3-azaisatoic anhydride (2) from 2-aminonicotinic acid:

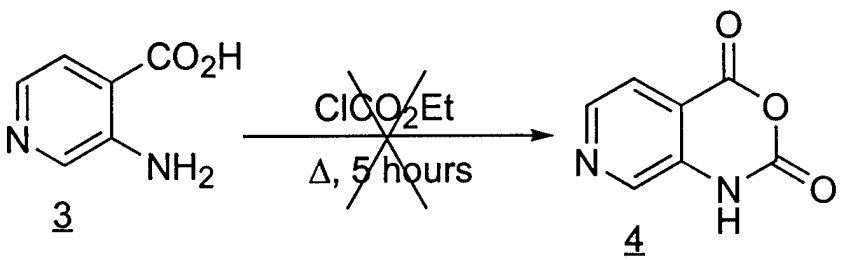


VARIOUS REACTION CONDITIONS
a) phosgene, toluene, water, Na_2CO_3
b) phosgene, toluene, dioxane Na_2CO_3
c) diphosgene, dioxane, Et_3N
d) triphosgene, water, Na_2CO_3
e) $ClCO_2Et$, dioxane, Δ
f) $ClCO_2Et$, dioxane, Et_3N, RT
g) $ClCO_2Et$, dioxane, Et_3N, Δ
h) $ClCO_2Et$, DMF, Δ
i) $ClCO_2Et$, DMF, Et_3N, RT
j) $ClCO_2Et$, Δ

Conditions *"j"* proved to be successful, and 106.5 g of target 2 were transmitted to WRAIR (as 2H-pyrido[2,3-d][1,3]oxazine-2,4(1H)-dione). The preparative details of this synthesis were described on page 2 *(this report)*.

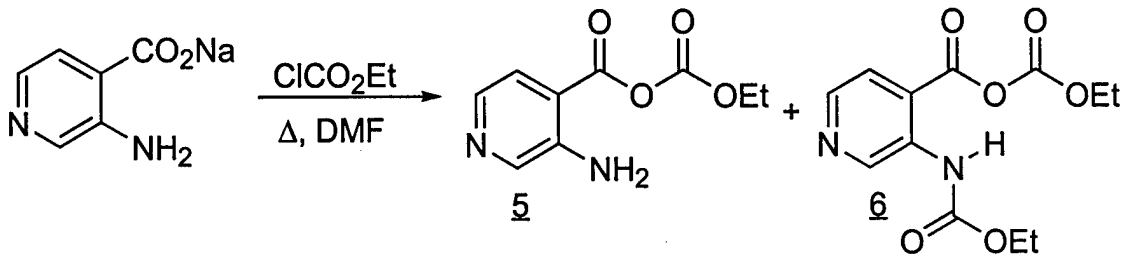
> 4-Azaisatoic anhydride (4)

Repeating the reaction conditions *"j"* on isomeric amino acid 3:



did not produce the desired 4-azaisatoic anhydride. Only starting material 3 was isolated from our two attempts.

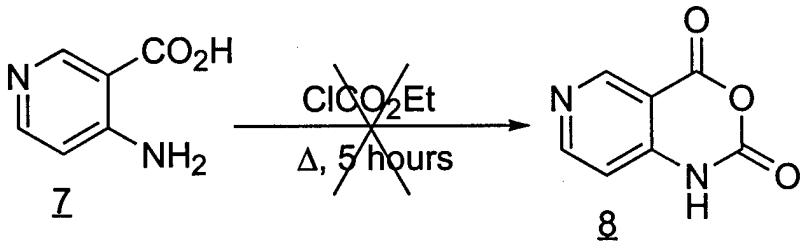
Another trial involved ethyl chloroformate in DMF and aq. sodium carbonate. These conditions resulted in a mixture of products 5 & 6:



High field ^{1}H NMR did not indicate the presence of target 4.

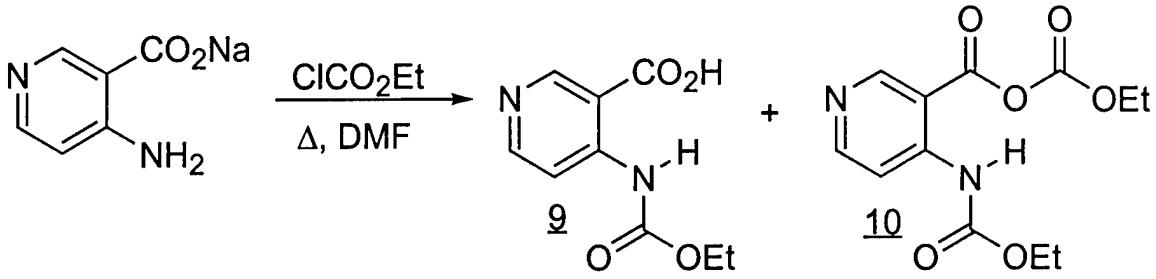
> 5-Azaisatoic anhydride (8)

Applying the original reaction conditions "*j*" to isomeric amino acid 7:



resulted in a complex mixture. The high field ^{1}H NMR of this reaction product possessed ten peaks between 5ppm and 10ppm, as well as aliphatic signals from an -OEt moiety. Isolation of 5-azaisatoic anhydride was not achieved.

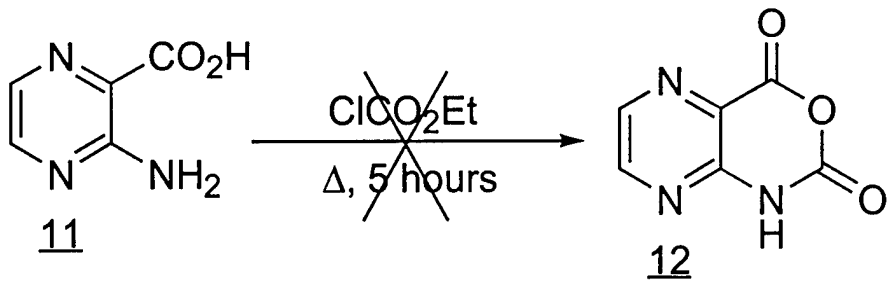
A second attempt involved, as before, the use of ethyl chloroformate in DMF and aq. sodium carbonate. In this instance, however, the reaction proceeded in an alternative fashion, and a different mixture of products (9 & 10) was obtained:



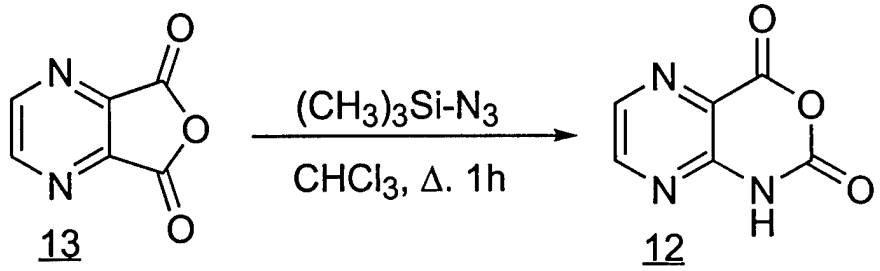
It appears that the nucleophilicity/reactivity of both the carboxylic acid oxygen and the amine nitrogen of amino acids 1, 3, and 7 varies greatly with the position of the heterocyclic ring nitrogen.

> 3,6-Diazaisatoic anhydride (12)

Only unreacted 11 was recovered from the following reaction between 3-aminopyrazine-2-carboxylic acid and ethyl chloroformate (under conditions "*j*"):



An alternative route to target 12, utilizing azidotrimethylsilane, was successful in converting 2,3-pyrazinedicarboxylic anhydride to 12:



These conditions produced the target in 27.6% yield. We found that purification by chromatography (SiO_2 eluted with

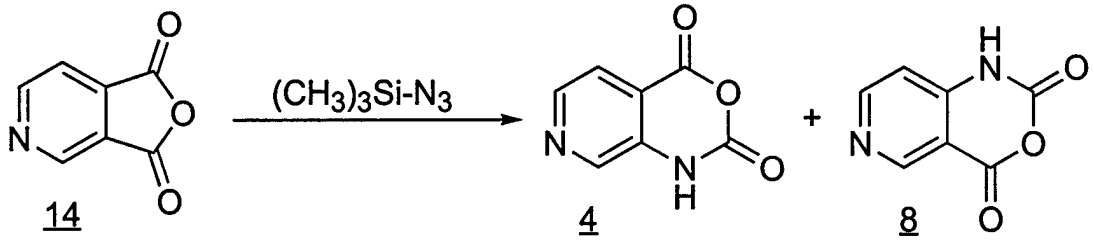
EtOAc/MeOH 2:1) resulted in complete decomposition of the target.

3,6-Diazaisatoic anhydride A stirred suspension of 2,3-pyrazinedicarboxylic anhydride in ethanol-free chloroform (1.2 g, 8.0 mmol in 8 mL) at RT under argon was treated with azidotrimethylsilane (1.1 mL, 8.0 mmol), then heated at reflux for 45 min. The mixture was returned to RT, and stirred under argon overnight. Ethanol (0.4 g, 8.0 mmol) was added, and the mixture was stirred for 15 min. The solids were collected on a filter, rinsed with chloroform (2x10 mL), then dried in vacuo at RT to give 0.9 g of a brownish-gray powder. A portion of this (0.5 g) was heated to reflux in 5 mL of acetonitrile, and the insolubles were removed by filtration and discarded (Note: the material collected on the filter changed form from a purple powder to a black tar). The filtrate was spin evaporated to remove acetonitrile, giving 0.2 g of 3,6-diazaisatoic anhydride (12) as a brown foam.

PROTON NMR SPECTRUM (DMSO-d_6, 400 MHz): δ 12.50 (s, 1H, N-H); 8.68 (d, 1H, J=2.2 Hz, Ar-H); 8.55 (d, 1H, J=2.6 Hz, Ar-H).

> 4-Azaisatoic anhydride & 5-Azaisatoic anhydride (4 & 8 mixture formation trial)

Based on the success of the azidotrimethylsilane reaction, we attempted to convert the unsymmetrical anhydride 14 to the azaisatoic anhydride mixture as shown:



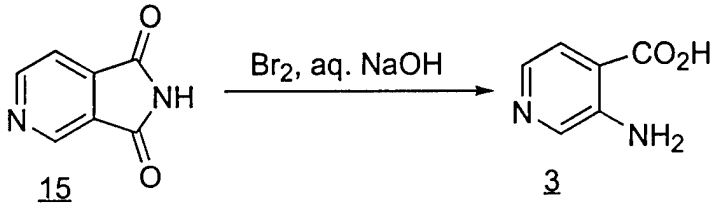
Unfortunately, we found the high field ^{1}H NMR spectrum of the product mixture to be highly complex. It did not indicate that a simple mixture of the desired targets 4 & 8 was formed.

Again, a purification attempt by chromatography (SiO_2 eluted with EtOAc/MeOH 2:1) resulted in decomposition.

> Supplemental Efforts Towards the Azaisatoic Anhydrides

Starting materials 1, 11, 13, and 14 were commercially available, and were purchased. The two amino acids 3 and 7 were not available, and were synthesized.

Compound 3 was prepared[4] in one step from 3,4-pyridinedicarboximide:



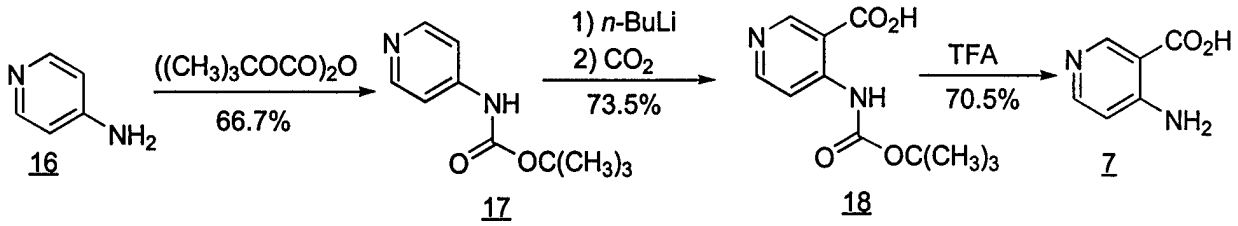
15 3

This reaction was repeated twice to give 3.9 g (51% yield) of 3.

3-Amino-4-pyridinecarboxylic acid A stirred solution of 3,4-pyridinedicarboximide in 10% aq. sodium hydroxide(4.9 g, 33.1 mmol in 80 mL) was cooled in an ice-water bath while bromine (5.4 g, 33.7 mmol) was added dropwise over five minutes. The reaction flask was then immersed in a hot oil bath at 80°C, and the reaction mixture was stirred for one hour. After cooling in an ice-water bath, the pH was adjusted with glacial acetic acid to pH=5.5, and the precipitated target was collected on a filter, rinsed with water (2x100 mL), and dried in vacuo to constant weight to give 2.3 g (51% yield) of 3. Additional 3-amino-4-pyridinecarboxylic acid was prepared in a similar manner.

PROTON NMR SPECTRUM (DMSO-d_6 , 500 MHz): δ 10.0-8.5 (broad, NH_2 + CO_2H); 8.20 (s, 1H, Ar-H); 7.73 (d, 1H, J=5 Hz, Ar-H); 7.46 (d, 1H, J=5 Hz, Ar-H). D_2O exchanged the broad peak at 10.0-8.5 ppm.

The preparation of 7 involved a three step reaction sequence:



A 2.4 g portion of 7 was prepared in 34.5% overall yield.

4-Amino-3-Pyridinecarboxylic acid A mixture of 4-aminopyridine (5.1 g, 54.2 mmol), *tert*-butyl alcohol (10 mL), and KOH (10.7 g of 85%, 162.6 mmol) in water (25 mL) was cooled in an ice-water bath, then di-*tert*-butyl dicarbonate (17.7 g, 81.3 mmol) was added dropwise. The reaction mixture was stirred at RT for six days, then diluted with water (50 mL). The organics were extracted with chloroform (50 mL), then ethyl acetate (2x50 mL). The combined extracts were dried ($MgSO_4$), filtered, and spin-evaporated to give a white solid (which proved to be a mixture of starting material 16 and carbamate 17). Purification by chromatography (200 g SiO_2 eluted with EtOAc) resulted in 7.0 g of pure 17 (66.7% yield). The material was suitable for further transformation.

A solution of 17 in THF (4.0 g, 20.6 mmol in 50 mL) was stirred under argon at -78°C, then treated with the dropwise addition of *n*-butyllithium (26 mL of 2M in cyclohexane, 52.0 mmol). After stirring at 0°C for 3 hours, the reaction mixture was again cooled to -78°C before being poured onto excess dry ice in ether (150 mL). This was stirred over the weekend, then diluted with water (20 mL). The pH of the reaction mixture was brought to pH=7 with acetic acid, and the precipitate was collected on a filter. The solid was washed with water (2x20 mL), and dried in vacuo at 60°C to give 3.6 g (73.5% yield) of carboxylic acid 18. The material was suitable for further transformation.

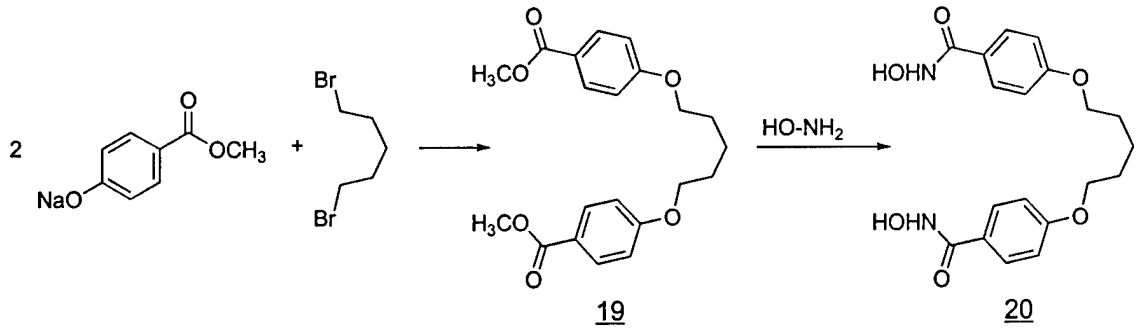
Solid 18 (2.7 g, 11.33 mmol) was added to a mixture of trifluoroacetic acid (12 mL) in dichloromethane (20 mL), and stirred at RT for 16h. After spin-evaporation, the yellow residue was dissolved in water (40 mL), and the pH adjusted to pH=4.2 with 5% aq. sodium hydroxide. The precipitate was collected on a filter, and dried in vacuo at 60°C to constant weight to give 1.1

g (70.5% yield) of target 7. Additional 4-amino-3-pyridinecarboxylic acid was prepared in a similar manner.

PROTON NMR SPECTRUM (DMSO-d_6 , 400 MHz): δ 14.0 (broad, 1H, CO_2H); 8.96 & 8.64 (s, 1H each, NH_2); 8.74 (s, 1H, Ar-H); 8.14 (d, 1H, J=7 Hz, Ar-H); 6.97 (d, 1H, J=7 Hz, Ar-H). D_2O exchanged three protons at 14.0, 8.96, and 8.64 ppm.

> Benzamide, 4,4'-[1,5-pentanediylbis(oxy)]bis[N-hydroxy-

The two-step synthesis of target 20 was completed in 26% overall yield:



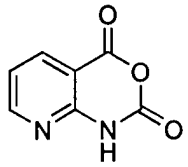
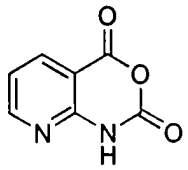
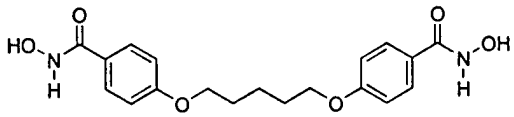
19 20

A 140 mg portion of this material was transmitted to WRAIR.

Conclusions

CUMULATIVE LIST OF REQUESTED COMPOUNDS DELIVERED TO WALTER REED ARMY INSTITUTE OF RESEARCH (WRAIR) FROM FEBRUARY 15, 2000 TO FEBRUARY 14, 2001

The previous Cumulative List covering the period from February 15, 1999 to February 14, 2000 may be found in Starks Associates, Inc. Annual Report dated March 2000, page 103, Contract No. DAMD17-99-D-0005. The list covering the period from December 1, 1992 to March 31, 1999 may be found in Starks Associates, Inc. Final Report dated May 1999, page 48, Contract No. DAMD17-93-C-3003. The list covering the period from March 15, 1989 to November 30, 1992 may be found in Starks Associates, Inc. Final Report dated November 30, 1992, page 35, Contract No. DAMD17-89-C-9058. The list covering the period from September 15, 1983 to March 14, 1989 may be found in Starks Associates, Inc. Final Report dated March 14, 1989, page 55, Contract DAMD17-83-C-3206. The list covering the period from September 29, 1979 to September 14, 1983 may be found in Starks Associates, Inc. Final Summary Report dated September 1983, page 56, Contract No. DAMD17-79-C-9170. The list covering the period from July 1, 1973 to September 28, 1979 may be found in Starks Associates, Inc. Final Summary Report dated September 1979, page 82, Contract No. DAMD17-73-C-3159. The list covering the period from July 1, 1965 to June 30, 1973 may be found in Starks Associates, Inc. Final Summary Report dated June 1973, page 54, Contract No. DA49-193-MD-2751.

Cumulative No.	Compound	Amount	BN#	WR#	Starks Assoc. Report
					
1278	2H-Pyrido[2,3-d]-[1,3]-oxazine-2,4-(1H)-dione	16.8 g			141
					
1279	2H-Pyrido[2,3-d]-[1,3]-oxazine-2,4-(1H)-dione	90.0 g			141
					
1280	Benzamide, 4,4'-[1,5-pentanediylbis-(oxy)]bis[N-hydroxy-	140 mg			142

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1. Sonnenburg, R.; Neda, I.; Fischer, A.; Jones, P.G.; Schmutzler, R. *Chem. Ber.* **1995**, *128*, pp. 627-634.

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4. Chenard, B.L.; Welch, Jr., W.M. *US Patent #5,962,457* **1999**. Assigned to Pfizer, Inc.

Appendices

ACKNOWLEDGEMENT

The following technical personnel were assigned to syntheses which have been requested by Walter Reed Army Institute of Research: Dr. J.F. Novotny (Supervisor), Dr. J.W. Givens, and Dr. Ji-Long Jiang.

We would like to acknowledge the technical help of CPT M.J. Novak.

Distribution

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