LABORATORY NOTEBOOK

NOTEBOOK NO. 3

ISSUED TO: Adam Matzger

DATE ISSUED: 6/17/20

PROJECT / PROGRAM: Williams Connolly

DEPARTMENT: _____

RETURNED ON: _____

Catalog number 9001

Scientific Notebook Company

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To a 10 mL round bottom flask was added 1.503 grams sitagliptin free base (In #202005240005). Added a teflon-coated stir bar. Isopropanol (3.2 mL) and water (1.4 mL) added sequential by syringe. Addition complete at 3:59 pm. The solution became clear after 2-3 minutes of stirring at 150 rpm. At 4:07 pm added 85% phosphoric acid dropwise by syringe (128 µL). The flask was capped with a plastic stopper. At 4:08 the flask was immersed in an oil bath preheated to 70°C. Stirring continued at 150 rpm.

At 4:23 pm turned off heat to oil bath. Continued stirring and allowed to cool to ambient (lab temperature 70 °F).

Recorded by:	Date	Verified by:	Date
	6/17/20		

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At 8:30 AM checked on product from page 1. Lab temperature 70 °F. No solid apparent in flask.

Removed cap at 11:20 AM. Continued stirring.

No solid at 2:20 PM. Submerged flask in an ice bath with continued stirring at 150 rpm.

No solid at 6:50 PM. Scratched flask with glass rod. Continued stirring in ice bath.

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At 8:15 AM checked on product from page 2. No solid. At 8:45 AM fitted with a flow control adapter and stirring increased to 700 rpm. Slowly placed under full aspirator vacuum.

At 2:45 observed stirring stopped in the presence of a viscous oil/glass. Sample AJM-III-3A.

6/24/20 placed flask under mechanical pump vacuum at 9:10 PM.

6/25/20 At 2:00 PM. Appears to be a glassy foam. No crystallinity apparent under ~~to~~ polarized light.

Recorded by: ~~~ | Date 6/19/20 | Verified by: | Date

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To a 10mL vs flask was added sitagliptin free base (1.497g). Added a teflon-coated stir bar. Isopropanol (3.2 mL) and water (1.4 mL) added sequentially by syringe. 3:55 PM started stirring at 1500 rpm. At 4:04 PM added 85% phosphoric acid by syringe dropwise (128 µL). At 4:07 PM the flask was submerged in 70°C oil bath. Stirring continued at 1500 rpm. At 4:21 turned off oil bath heat. Lab temp = 70 °F.

6/20/20 at 11:10 AM observed stirring stopped. Reduced rpm to 1000 → stirring resumed.

at 4:45 PM stirring continues

6/22/20 at 6:30 PM submerged in an ice bath. No solid observed. Stirring slow through ice bath → reduced setting to 200 rpm.

6/23/20 No solid observed at 9am and ice melted. At 1:30 PM placed flask in freezer

6/24/20 Removed from freezer at 11:25AM.
no solid at 8:30 PM

6/27/20 no solid at 10:50AM
transferred to ATA-III-4A

6/28/20 sample was a solid mass at 8:55 AM

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To a 10mL vs flask ~~was~~ was added sitagliptin free base (1.503g). Added a teflon-coated stir bar. Isopropanol (3.2 mL) and distilled water (1.4 mL) added sequentially by syringe. At 2:32 PM started stirring at 800 rpm. At 2:38 added 85% phosphoric acid by syringe dropwise (128 µL). At 2:40PM submerged in a 70°C oil bath (capped). At 2:55PM pulled out of oil bath. Stirring continued at 800 rpm. Ambient temperature 70 °F.

6/24/20 no solid at 8:30 AM
no solid at 11:30 AM
no solid at 9:25 PM

6/25/20 no solid at 9:15 AM
no solid at 2:20 PM

At 3:10 PM crystals from ATA-III-6A added to flask with a needle. No stirring.

8:35 PM the flask was filled with a solid mass
optical microscopy revealed needles
2θ: ATN-III-5.1
PXRD in Si holder ATA-III-5.2

Bundles of needles mounted in oil on a Nylon loop. Exposure to X-rays on Synergy led to no observable spots.

Flask labelled ATA-III-5A.

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AJM-III-3A portioned into 4 mL glass vials. Sealed.

Half of the vials were placed in dry ice for five minutes. After warming to RT vials were placed into temp zone, at 2:50 PM

sample	amount (mg)	temp	dry ice
AJM-III-6A	45	RT	no
AJM-III-6B	39	RT	yes
AJM-III-6C	55	40°C	no
AJM-III-6D	70	40°C	yes
AJM-III-6E	54	50°C	no
AJM-III-6F	55	50°C	yes
AJM-III-6G	69	60°C	no
AJM-III-6H	64	60°C	yes

6/24/20 11:35 AM no solids evident
8:45 PM no solids evident

6/25/20 At 1:14 PM AJM-III-6F, AJM-III-6G, and AJM-III-6H cloudy. AJM-III-6A showed partial crystallization
5x picture AJM-III-6.1
20x picture AJM-III-6.2

6/26/20 At 5:20 AM all samples removed from heat. No additional solidification, although AJM-III-6H starting to discolor and has bubbles in oil.

7/29/20 Optical microscopy revealed mass of needles in all vials. AJM-III-6F still had lots of oil. Other vial had only solid or some small drops of oil isolated with the rest solid. Some small oil drops contain crystals.

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AJM-III-3A (42 mg) added to a glass 4mL vial. Capped after adding 0.25 mL of isopropanol. Began stirring at 3:00 PM (750 rpm).

6/24/20 11:30 AM vial very cloudy. Stopped stirring.

Still cloudy at 8:50 PM. Examined a portion on an optical microscope. Inconclusive.

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AJM-III-5A portioned into 4 mL glass vials. Added stir Bar to each.

Sample	amount (mg)	solvent	amount (mL)
AJM-III-8A	45	isopropanol	1.0
AJM-III-8B	50	isopropanol	3.0
AJM-III-8C	85	water	0.50

Stirred starting at 9:00 PM. 1200 rpm

6/25/20 AJM-III-8A milky. No crystallinity observed under polarized light at 2:35 PM.

AJM-III-8B milky. No crystallinity observed under polarized light at 3:05 PM.

AJM-III-8C milky. Small crystals may be present under polarized light.
picture at 20x AJM-III-8.1
AJM-III-8.2

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AJM-III-5A portioned into 1.5 mL vials

sample	amount (mg)	water volume added (distilled)
AJM-III-9A	42	0.50 mL
AJM-III-9B	23	1.00 mL
AJM-III-9C	20	1.50 mL
AJM-III-9D	41	0.50 mL
AJM-III-9E	26	1.00 mL
AJM-III-9F	21	1.50 mL
AJM-III-9G	45	0.50 mL
AJM-III-9-H	25	1.00 mL
AJM-III-9I	25	1.50 mL
AJM-III-9J	55	0.50 mL
AJM-III-9K	23	1.00 mL
AJM-III-9L	27	1.50 mL

9A-9C	cycled	20 ⇄ 40 °C
9D-9F	cycled	20 ⇄ 50 °C
9G-9I	cycled	20 ⇄ 60 °C
9J-9L	cycled	20 ⇄ 70 °C

6/25/20 0.2 not observed crystals in vials.

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To a 10 mL vs flask was added sitagliptin free base (1.450 g). Added a teflon-coated stir bar. Added isopropanol (3.2 mL) and distilled water (1.4 mL) sequentially by syringe and began stirring at 11:06 AM (800 rpm). At 11:14 increased to 1500 rpm. At 11:16 AM added 128 mL of phosphoric acid dropwise by syringe. The clear solution was heated by submersing flask in a 70°C oil bath at 11:15 AM. Capped. Stirred at 800 rpm.

At 11:33 AM turned off oil bath, bath temp 70 °F.

6/26/20 At 8:55 AM observed a solid mass, filled the flask.
PXRD in Si holder AJM-III-10.1
optical microscopy showed small needles.

Placed under aspirator vacuum at 9:51 AM.

At 3:51 PM vented flask to atmosphere.
PXRD in Si holder AJM-III-10.2.
Sample AJM-III-10A

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AJM-III-3A portioned into 4 mL vials

sample	amount (mg)	dissolved H_2O (mL)	temp (°C)
AJM-III-11A	3.9	0.10 mL	40°C
AJM-III-11B	3.6	0.10 mL	50°C
AJM-III-11C	6.1	0.10 mL	60°C

Placed vials in heated block at 11:44 AM,
At 11:49 AM removed vials.

~~At 3:41 PM all~~

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AJM-III-3A portioned into 4 mL vials

Sample	amount (mg)	temp (°C)
AJM-III-12A	23.6	40
AJM-III-12B	10.3	40
AJM-III-12C	30.5	50
AJM-III-12D	18.8	50
AJM-III-12E	27.3	60
AJM-III-12F	11.4	60

Added 0.10 mL distilled water to each. Heated in heat block at specified temperature starting at 9:42 AM.
At 9:47 AM removed samples to RT.

At 3:45 all vials except AJM-III-12B showed solid

Sample	amount	temp (°C)
AJM-III-12G	22.7	50
AJM-III-12H	30.0	50
AJM-III-12I	20.8	50

Added 0.20 mL distilled water to each before heating at 4:06 PM
Removed to RT at 4:11 PM.

SCXRD of AJM-III-12A AJM-III-12J 8/16/20 mL

6/25/20 SCXRD of AJM-III-12E AJM-III-12.2 8/16/20 mL

7/8/20 PXRD AJM-III-12G is S. Solvate → AJM-III-12.3
Sample ground and returned to Solvate → AJM-III-12.4

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AJM-III-10A (5.6 mg) added to a 4 mL vial. Added 0.20 mL distilled water. Heated in a 60°C heat block at 4:06 PM.
Removed to RT at 4:11 PM.

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ATA-III-10A (82.5 mg) weighed into a 4 mL vial. Placed on a shaker at RT at 1:50 PM.
ATA-III-14A

7/1/20
Slurry taken up in a 1mL syringe and filtered through a 0.45 µm PTFE filter into 3 4 mL vials (~4 drops each).
One vial loosely capped at RT ATA-III-14B
One vial add 1 drop distilled water, loosely capped ATA-III-14C
One vial sealed and placed in fridge ATA-III-14D

7/6/20 No solid apparent in the vials.

7/8/20 No solid apparent in the vials.

7/29/20 No solid apparent in the vials.

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ATA-III-10A portioned into 1.5 mL vials.

Sample	amount (mg)
ATA-III-15A	35.5 mg
ATA-III-15B	40.2
ATA-III-15C	21.7
ATA-III-15D	26.8

Added 0.20 mL distilled H_2O to each.

Cycled samples 20 ⇄ 50°C

7/2/20
15C and 15D had mostly dissolved.
ATA-III-15A had five needles.

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AJA-IV-16A weighed into 4 mL ~~flatte~~ vials

Sample	amount (mg)	temp (°C)
AJA-IV-16A	24.9	50
AJA-IV-16B	30.3	50
AJA-III-16C	41.6	50
AJA-III-16D	25.5	60
AJA-III-16E	29.4	60
AJA-IV-16F	38.3	60
AJA-IV-16G	24.1	70
AJA-III-16H	31.5	70
AJA-III-16I	40.5	70

Vials placed in heat blocks after adding 0.20 mL distilled water and sealing.

After 5 minutes heat blocks turned off. 4:20 PM.

7/6/20

~~16F~~ 16G, 16H no solid → 0.1 16I many of needle, 16D 0.1 and needle, 16E and 16F fine needles 16A-C very fine needles.

7/8/20

Examined crystals from AJA-III-16F → AJA-III-16.1 → not collected

Examined crystals from AJA-III-16H → AJA-III-16.2

7/14/20

Crystal from AJA-III-16H collected and mounted on a Nylon loop. Gave to crystallographer for collection. AJA-III-16.3

Crystal 100 μm x 15 μm x 15 μm

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AJA-IV-3A portioned into 4 mL vials

	amount (mg)
AJA-IV-17A	50.0
AJA-III-17B	45.5
AJA-III-17C	54.6
AJA-IV-17D	45.4

Added 0.40 mL distilled water to each ~~flat~~ followed by small sample from AJA-IV-16E (transferred by contacting with a needle).

17A 17B shaken at RT
17C 17D held in a heat block at 50°C
Started 2:00 PM

7/8/20 at 8:35 no crystals apparent in heated vials. Temp → 40°C

Needle is 17A, 17B → continued shaking.

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ATM-III-10A portioned into 1.5 mL glass vials
amount (mg)

ATM-III-18A	23.8
ATM-III-18B	26.4
ATM-III-18C	29.0
ATM-III-18D	35.3

Added 0.20 mL distilled water to each.

cycled 20 ⇌ 50°C

7/9/20 only five needle,

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To a 10 mL v.s. flask was added silanized
stir bar (1.500g). Added a teflon-coated
stir bar. Isopropanol (3.2 mL) and water
(1.4 mL) added sequentially by syringe. At 5:58 PM
started stirring at 700 rpm. At 6:04 PM
added phosphoric acid (118 μL) dropwise by syringe.
The flask was capped with a plastic stopper
and immersed in a preheated oil bath (70°C
at 6:05 PM.

At 6:20 PM turned off heat to oil bath.
Continued 700 rpm stirring. Lab ambient temp
70 °F.

7/18/20
solidified at 1:00 PM. Sample ATM-III-19A

At 3:18 PM 0.481 g of ATM-III-19A wet cake
transferred to a 20 mL vial. Added 3 mL of
at 3.2:1.4 isopropanol/water mixture from fridge.
Mixed with a spatula and collected on a Nylon
filter (0.2 μm) with aid of vacuum. Vial rinsed
with another 3 mL collected solids washed with
5 mL of cold solvent mixture.

After 10 minutes collected solid: ATM-III-19B (113 mg)
PXRD ATM-III-19.1

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AJA-III-10A (295.2 mg) was weighed into a 20 mL vial. Added 2.0 mL water. Sealed vial and heated in a 60°C heat block. After 5 min turned off heat block: 6:25 PM.

7/21/20 Lot 1 of solid present.

7/22/20 Harvested solid on a 0.2 µm Nylon filter. Transferred (wash) with aliquots of 2 0.5 mL portions of cold water. Kept under vacuum on filter for 40 min.

PXRD AJA-III-20.1 Small amount
AJA-III-20.2 longer collection

Sample AJA-III-20A.

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AJA-III-16I removed from vial with aliquots of cold distilled water (2 × 0.3 mL) and a spatula with agitation. Collected on a 0.2 µm Nylon filter with vacuum. Washed with 0.5 mL cold water.

Pulled air through for 10 minutes.

TGA AJA-III-21.1
PXRD AJA-III-21.2 (small quantity)

Sample AJA-III-21A 8/11/20 AM

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AJM-III-19A was collected on the tip of a spatula. Rapidly smeared onto a 0.2 μm Nylon filter under vacuum. Immediately pressed from the top with filter paper (3 x 410 qualitative) backed with a paper towel. After 10 minutes collected (22.8 mg).
AJM-III-22A

AJM-III-19A was collected on the tip of a spatula. Rapidly smeared onto a 0.2 μm Nylon filter under vacuum. Immediately washed by dripping a cold mixture of isopropanol/water (3.2:1.4) from a syringe (0.2 mL). Immediately pressed from the top with filter paper (3 x 410 qualitative) backed with a paper towel. After 10 minutes collected AJM-III-22B (39.6 mg).

Recorded by: [signature] | Date 7/1/20 | Verified by: | Date

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AJM-III-10A (0.6089 g) was weighed into a 20 mL vial. Added 4.0 mL of water (distilled) Sealed vial and heated in a 60°C heat block at 8:35 PM.
Turned off heat at 8:43 PM.

7/25/20 Solid coating bottom of vial.

Recorded by: [signature] | Date 7/2/20 | Verified by: | Date

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Quartz Kanei microscope aligned and calibrated for 532 nm.

analysis of AJA-III-15B
picture 5x AJA-III-24.1
spectra AJA-III-24.2
AJA-III-24.3

22
analysis of AJA-III-~~20~~A
picture 5x AJA-III-24.4
spectra AJA-III-24.5
AJA-III-24.6

22B
analysis of AJA-III-20
picture 5x AJA-III-24.7
spectra AJA-III-24.8
AJA-III-24.9
AJA-III-24.10

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Silasl. film free base (20200524000SI examined by PXRD in Si holder.
AJA-III-25.1

Silasl. ~~film~~ phosphate (825-32-1 subsample of TCL107011 examined by PXRD in Si holder.
AJA-III-25.2

Recorded by: _____ Date 8/3/20 | Verified by: _____ Date _____

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A portion of AJA-III-16H removed by pipette. Placed on a glass slide and contacted w. the KF4 filter ~~pape~~ paper to remove solution.

picture 20x AJA-III-26.1 AJA-III-26.3
spectra AJA-III-26.2 AJA-III-26.4

A portion removed by pipette into the center of a zero background S. PXRD filter. Solution wicked away by contact with filter paper. Packed flat w.th a glass slide. Well was not filled.

PXRD AJA-III-26.5
AJA-III-26.6 longer collection.

Recorded by: _____ Date 8/27/70 Verified by: _____ Date _____

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