Supplementary information

Novel potent and selective dual acetylcholinesterase inhibitors: N-substituted theobromine and theophylline derivatives

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Table of contents

| NMR spectra of Alkylbrominated Intermediates of Theophylline and Theobromine | 5 |
|---|----|
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 1e | 5 |
| DEPT and HSQC spectra in CDCl ₃ of 1e | 6 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 2b | 7 |
| DEPT and HSQC spectra in CDCl ₃ of 2b | 8 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 2c | 9 |
| DEPT and HSQC spectra in CDCl $_3$ of $2c$ | 10 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 2d | 11 |
| DEPT and HSQC spectra in CDCl₃ of 2d | 12 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 2e | 13 |
| DEPT and HSQC spectra in CDCl ₃ of 2e | 14 |
| NMR Spectra of Methylxanthine Derivatives | 15 |
| ¹ H NMR (400 MHz) and ¹³ C NMR (101 MHz) spectra in CDCl ₃ of 3 | 15 |
| HSQC spectra in CDCl_3 of 3 | 16 |
| HRMS (ESI-TOF) of 3 | 16 |
| ¹ H NMR (400 MHz) and ¹³ C NMR (101 MHz) spectra in CDCl ₃ of 4 | 17 |
| HSQC spectra in CDCl_3 of 4 | 18 |
| HRMS (ESI-TOF) of 4 | 18 |
| ¹ H NMR (400 MHz) and ¹³ C NMR (101 MHz) spectra in CDCl ₃ of 5 | 19 |
| DEPT and HSQC spectra in $CDCl_3$ of 5 | 20 |
| HPLC-UV/MS of 5 | 21 |
| ¹ H NMR (400 MHz) and ¹³ C NMR (101 MHz) spectra in CDCl ₃ of 6 | 22 |
| DEPT and HSQC spectra in CDCl ₃ of 6 | 23 |
| HRMS (ESI-TOF) of 6 | 24 |
| ¹ H NMR (400 MHz) and ¹³ C NMR (101 MHz) spectra in CDCl ₃ of 7 | 25 |
| DEPT and HSQC spectra in CDCl ₃ of 7 | 26 |
| HPLC-UV/MS of 7 | 27 |
| ¹ H NMR (400 MHz) and ¹³ C NMR (101 MHz) spectra in CDCl ₃ of 8 | 28 |
| DEPT and HSQC spectra in CDCl₃ of 8 | 29 |
| HPLC-UV/MS of 8 | 30 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 9 | 31 |
| DEPT and HSQC spectra in CDCl ₃ of 9 | 32 |
| HRMS (ESI-TOF) of 9 | 33 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 10 | 34 |

| DEPT and HSQC spectra in CDCl $_3$ of ${f 10}$ | 35 |
|---|-----|
| HRMS (ESI-TOF) of 10 | .36 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 11 | 37 |
| DEPT and HSQC spectra in CDCl ₃ of ${f 11}$ | 38 |
| HRMS (ESI-TOF) of 11 | .39 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 12 | 40 |
| DEPT and HSQC spectra in CDCl ₃ of 12 | 41 |
| HRMS (ESI-TOF) of 12 | .42 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 13 | 43 |
| DEPT and HSQC spectra in CDCl $_3$ of ${f 13}$ | 44 |
| HRMS (ESI-TOF) of 13 | .45 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 14 | 46 |
| DEPT and HSQC spectra in CDCl $_3$ of ${f 14}$ | 47 |
| HRMS (ESI-TOF) of 14 | .48 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 15 | 49 |
| DEPT spectra in CDCl ₃ of 15 | 50 |
| HRMS (ESI-TOF) of 15 | .50 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 16 | 51 |
| DEPT and HSQC spectra in CDCl₃ of 16 | 52 |
| HRMS (ESI-TOF) of 16 | .53 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 17 | 54 |
| DEPT and HSQC spectra in CDCl₃ of 17 | .55 |
| HRMS (ESI-TOF) of 17 | .56 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in MeOD of 18 | 56 |
| DEPT and HSQC spectra in MeOD of 18 | 57 |
| HRMS (ESI-TOF) of 18 | .59 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 19 | 60 |
| DEPT and HSQC spectra in CDCl₃ of 19 | .61 |
| HRMS (ESI-TOF) of 19 | .62 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in 20 | 63 |
| DEPT and HSQC spectra in CDCl₃ of 20 | 64 |
| HRMS (ESI-TOF) of 20 | .65 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in MeOD of 21 | 66 |
| DEPT and HSQC spectra in MeOD of 21 | 67 |
| HRMS (ESI-TOF) of 21 | .68 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 22 | 69 |
| DEPT and HSQC spectra in CDCl₃ of 22 | 70 |
| HRMS (ESI-TOF) of 22 | 71 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl₃ of 23 | 72 |
| DEPT and HSQC spectra in CDCl₃ of 23 | .73 |
| HRMS (ESI-TOF) of 23 | .74 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl₃ of 24 | 75 |
| DEPT and HSQC spectra in CDCl₃ of 24 | .76 |
| HRMS (ESI-TOF) of 24 | .77 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 25 | 78 |
| DEPT and HSQC spectra in CDCl₃ of 25 | 79 |
| HRMS (ESI-TOF) of 25 | .80 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in MeOD of 26 | 81 |

| DEPT and HSQC spectra in MeOD of 26 | 82 |
|---|----|
| HRMS (ESI-TOF) of 26 | 83 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDCl ₃ of 27 | 84 |
| DEPT and HSQC spectra in CDCl ₃ of 27 | 85 |
| HRMS (ESI-TOF) of 27 | 86 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDl ₃ of 28 | 87 |
| DEPT and HSQC spectra in CDCl ₃ of 28 | 88 |
| HRMS (ESI-TOF) of 28 | 89 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in MeOD of 29 | 90 |
| DEPT and HSQC spectra in CDCl ₃ of 29 | 91 |
| HRMS (ESI-TOF) of 29 | 92 |
| ¹ H NMR (300 MHz) and ¹³ C NMR (75 MHz) spectra in CDI_3 of 30 | 93 |
| DEPT and HSQC spectra in CDCl ₃ of 30 | 94 |
| HRMS (ESI-TOF) of 30 | 95 |
| Molecular Docking | 96 |





¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra in CDCl₃ of 1e







 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 2b



DEPT and HSQC spectra in \mbox{CDCl}_3 of ${\bf 2b}$



 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 2c



DEPT and HSQC spectra in $CDCl_3$ of **2c**



 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 2d



DEPT and HSQC spectra in $CDCl_3$ of **2d**



 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 2e



DEPT and HSQC spectra in CDCl₃ of **2e**

^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in CDCl3 of $\boldsymbol{3}$ 7.58 7.32 7.31 7.30 7.26 7.26 7.25 7.25 7.23 7.23 4.42 4.41 4.39 H₂C 0⁄⁄ с́н₃ 1.00 ₹ 4.18 0.90 ₹ 3.07 2.08 4.33H 2.16H 2.54H 2.06₋₁ 2.07^J 2.09_Y 1.06_T 7.5 3.5 2.5 1.5 5.5 4.5 3.0 2.0 .5 8.0 7.0 6.5 6.0 5.0 4.0 1.0 0.5 0.0 f1 (ppm) - 141.59 - 138.57 $\frac{129.26}{128.31}$ ~ 155.28 ~ 151.84 ~ 149.09 -107.02-63.21 ~ 55.14 ~ 52.53 ~ 44.91 ~ 42.76 32.95 31.27 29.92 28.13 0 160 150 140 110 100 30 20 10 130 120 90 80 70 60 50 40 f1 (ppm)

NMR Spectra of Methylxanthine Derivatives

f2 (ppm) f1 (ppm) 20 1 7.57 141.61 {3.58,29.99} {1.35,32.98} {1.80,32.98} 2 7.30 128.33 30 3 7.30 129.32 {2.57,42.78} {2.01,31.32} {4.39,44.94} 40 4 7.24 127.16 {1.97,52.58} {2.81,52.58} 5 4.39 44.94 50 6 3.58 29.99 {3.49,63.21} {2.39,55.24} 60 7 3.49 63.21 8 3.40 28.16 70 9 2.81 52.58 80 (mdd) 102.57 42.78 90 112.39 55.24 ÷ 122.01 31.32 100 131.97 52.58 110 32.98 141.80 151.35 32.98 120 {7.30,129.32} 130 {7.57,141.61} 140 150 -- 160 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 f2 (ppm)

HSQC spectra in $CDCl_3$ of **3**

HRMS (ESI-TOF) of **3**

Qualitative Compound Report





¹H NMR (400 MHz) and ¹³C NMR (101 MHz) spectra in CDCl₃ of $\bf{4}$

HSQC spectra in $CDCl_3$ of 4



Qualitative Compound Report





 ^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in CDCl3 of 5







HPLC-UV/MS of 5





DEPT and HSQC spectra in CDCl_3 of ${\bf 6}$

Qualitative Compound Report

| Data File | 2045 | BBP 1 01.d | | | Sample Name | BBP 1 | | | |
|-------------------------------|-------------------|---------------------|---|---------------|-----------------|-----------|------------|-----------------|------|
| Sample Type | Sampl | e | | | Position | Vial 25 | | | |
| Instrument Name | Instru | ment 1 | | | User Name | | | | |
| Acq Method | ESI A | CN 75 pos L | JNICO CANAL A1.m | | Acquired Time | 12/21/202 | 22 10:04:3 | 34 AM (UTC+01:0 | (00) |
| IRM Calibration Statu | s Succes | s | | | DA Method | DefaultMF | 5.m | | |
| Comment | | | | | | | | | |
| Sample Group | | | Info | | | | | | |
| User | BRUNELLA BISC | USSI | Stream Name | IC | | | | | |
| Acquisition Time | 12/21/2022 10:0 | 4:34 AM | Acquisition SW | 620 | series TOF/6500 | series | | | |
| (Local) | (UTC+01:00) | | Version Q-TOF B.08.00 (B8058. SP1) | | .3 | | | | |
| QTOF Driver Version | 8.00.00 | | QTOF Firmware Version | 2.72 | 3 | | | | |
| Tune Mass Range Max. | 1700 | | | | | | | | |
| Compound Table | | | | | | | Diff | Hits | |
| Compound Label | RT | Mass | Abund | For | mula | Tgt Mass | (ppm) | (DB) | |
| Cpd 1: C22 H30 N6 0 | 02; 0.475 .475 | 410.2437 | 420581 | C22 H3 | 0 N6 O2 | 410.243 | 1.75 | 1 | |
| 5 2 | 68 68 | | 92 92 | | 12/ | 100 | 100 | | |
| Compound Label | m/z | RT | Algorithm | | Mass | | | | |
| Cpd 1: C22 H30 N6 O2 0.475 | ; 411.251 | 0.475 | Find by Formula | | 410.2437 | | | | |
| MS Zoomed Spectrum | | | | | | | | | |
| the about on appears with | | | | | | | | | |
| ×10.5 Cpd 1: C22 H | 30 N6 O2; 0.47 | '5: + FBF Sp | pectrum (rt: 0.475 | min) 204 | 5_BBP_1_01.d \$ | Subtract | | | |
| x10 5 Cpd 1: C22 H | 30 N6 O2; 0.47 | /5: + FBF Sp | pectrum (rt: 0.475 411.2510 | min) 204 | 5_BBP_1_01.d \$ | Subtract | | | |
| x10 5 Cpd 1: C22 H | 30 N6 O2; 0.47 | 25: + FBF Sp ([C | ectrum (rt: 0.475 411.2510 :22H30N6O2]+H) | min) 204 + | 5_BBP_1_01.d \$ | Subtract | | | |
| x10 5 Cpd 1: C22 H | 30 N6 O2; 0.47 | 25: + FBF Sp ([C | ectrum (rt: 0.475 411.2510 :22H30N6O2]+H) | min) 204 + | 5_BBP_1_01.d \$ | Subtract | | | |

390 395 400 405 410 415 420 425 430 435 440 Counts vs. Mass-to-Charge (m/z)

1.

385



 ^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra in CDCl3 of 7



DEPT and HSQC spectra in CDCl₃ of 7



HPLC-UV/MS of 7



¹H NMR (400 MHz) and ¹³C NMR (101 MHz) spectra in CDCl₃ of ${f 8}$



DEPT and HSQC spectra in $CDCl_3$ of **8**



HPLC-UV/MS of 8



^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of ${\bm 9}$



DEPT and HSQC spectra in CDCl_3 of $\boldsymbol{9}$

Qualitative Compound Report

| Analysis Info | |
|---------------|--|
| Analysis Name | |

Sample Name

Method

Comment

Acquisition Date 12/27/2023 2:37:34 PM

Operator ELB

Instrument micrOTOF-Q II

T6P Sv: MeOH + HCOOH Brunella Biscussi

D:\Data\ggc\23-122610_P1-F-8_01_8413.d Ic_qtof_directospos.m 23-122610

Acquisition Parameter

| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 3.5 Bar | |
|-------------|------------|-----------------------|-----------|------------------|-----------|--|
| Focus | Not active | Set Capillary | 4000 V | Set Dry Heater | 200 °C | |
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 7.0 l/min | |
| Scan End | 1000 m/z | Set Collision Cell RF | 300.0 Vpp | Set Divert Valve | Source | |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 10



Qualitative Compound Report

Analysis Info Acquisition Date 12/27/2023 2:42:42 PM Analysis Name D:\Data\ggc\23-122611_P1-F-9_01_8414.d Operator ELB Method Ic_qtof_directospos.m Operator ELB Sample Name 23-122611 Instrument micrOTOF-Q II Comment T6D Sv: MeOH + HCOOH Brunella Biscussi

Acquisition Parameter

| | 501 | In a Data da | D | Out Make Frank | 0.5.0 | |
|-------------|------------|-----------------------|-----------|------------------|-----------|--|
| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 3.5 Bar | |
| Focus | Not active | Set Capillary | 4000 V | Set Dry Heater | 200 °C | |
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 7.0 l/min | |
| Scan End | 1000 m/z | Set Collision Cell RF | 300.0 Vpp | Set Divert Valve | Source | |
| | | | | | | |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 11




Qualitative Compound Report

| Analysis Info | | | | Acqu | isition Date 12/28 | /2023 1:18:54 PM |
|----------------------|---|-------------------------------|--------------------|------------|---------------------------------|-------------------|
| Analysis Name | D:\Data\ggc\23-122612 | P1-C-1_01_8437.d | | | | |
| Method | Ic gtof directospos.m | | | Operator | ELB | |
| Sample Name | 23-122612 | | | Instrument | micrOTOF-Q II | |
| Comment | T6MP Sv: MeOH + HCOOH Brunella Biscussi | | | | | |
| Acquisition Par | ameter | | | | | |
| Source Type Focus | ESI Not active | Ion Polarity Set Capillary | Positive 4000 V | | Set Nebulizer Set Dry Heater | 3.5 Bar 200 °C |
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | | Set Dry Gas | 7.0 l/min |
| Scan End | 1000 m/z | Set Collision Cell RF | 300.0 Vpp |) | Set Divert Valve | Source |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 12





Qualitative Compound Report

| Analysis Info | | | | Acqu | isition Date | 12/28/20 | 23 1:44:32 PM |
|---|---|--|---|------------------------|---|-----------|--|
| Analysis Name Method Sample Name Comment | D:\Data\ggc\23-122617 Ic_qtof_directospos.m 23-122617 T8P Sv: MeOH + HCOOH Brunella Biscussi | P1-B-5_01_8442.d | | Operator Instrument | ELB microtof | -Q | |
| Acquisition Para | ameter | | | | | | |
| Source Type Focus Scan Begin Scan End | ESI Not active 70 m/z 1000 m/z | Ion Polarity Set Capillary Set End Plate Offset Set Collision Cell RF | Positive 4000 V -500 V 300.0 Vpp | ŝ. | Set Nebulizer Set Dry Heate Set Dry Gas Set Divert Val | er Ive | 3.5 Bar 200 °C 7.0 I/min Source |









Qualitative Compound Report

Analysis Info Acquisition Date 12/28/2023 1:49:41 PM Analysis Name D:\Data\ggc\23-122618_P1-B-6_01_8443.d Operator ELB Method Ic_qtof_directospos.m Operator ELB Sample Name 23-122618 Instrument micrOTOF-Q II Comment T8D Sv: MeOH + HCOOH Sv: MeOH + HCOOH Brunella Biscussi Surger Type ESI Ion Polarity Positive Set Nebulizer 3 5 Bar

| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 3.5 Bar | |
|-------------|------------|-----------------------|-----------|------------------|-----------|--|
| Focus | Not active | Set Capillary | 4000 V | Set Dry Heater | 200 °C | |
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 7.0 l/min | |
| Scan End | 1000 m/z | Set Collision Cell RF | 300.0 Vpp | Set Divert Valve | Source | |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 14



DEPT and HSQC spectra in $CDCl_3$ of **14**

Qualitative Compound Report

| Analysis Info | | | | Acqui | sition Date | 12/28/20 | 23 1:54:50 PM |
|---|--|-------------------|----------|------------------------|-----------------|----------|---------------|
| Analysis Name Method Sample Name Comment | D:\Data\ggc\23-122619 Ic_qtof_directospos.m 23-122619 T8MP Sv: MeOH + HCOOH Brunella Biscussi | _P1-B-7_01_8444.d | | Operator Instrument | ELB micrOTOF | Q | |
| Acquisition Par | ameter | | | | | | |
| Source Type | ESI | Ion Polarity | Positive | | Set Nebulize | r | 3.5 Bar |

| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 3.5 Bar | |
|-------------|------------|-----------------------|-----------|------------------|-----------|--|
| Focus | Not active | Set Capillary | 4000 V | Set Dry Heater | 200 °C | |
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 7.0 l/min | |
| Scan End | 1000 m/z | Set Collision Cell RF | 300.0 Vpp | Set Divert Valve | Source | |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 15

DEPT spectra in CDCl₃ of **15**

HRMS (ESI-TOF) of 15

Analysis Info

Analysis Name Method Sample Name Comment

Acquisition Parameter

D:\Data\ggc\23-122616_P1-B-4_01_8441.d lc_qtof_directospos.m 23-122616 T8PIRR Sv: MeOH + HCOOH Brunella Biscussi Acquisition Date 12/28/2023 1:39:25 PM

Operator ELB Instrument micrOTOF-Q II

nstrument micrOTOF-Q II

| Scan End | 1000 m/z | Set Collision Cell RF | 300.0 Vpp | Set Divert Valve | Source | |
|-------------|------------|-----------------------|-----------|------------------|-----------|--|
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 7.0 l/min | |
| Focus | Not active | Set Capillary | 4000 V | Set Dry Heater | 200 °C | |
| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 3.5 Bar | |
| - | | | | | | |

 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl₃ of 16

DEPT and HSQC spectra in $CDCl_3$ of **16**

Qualitative Compound Report

Analysis Info Acquisition Date 12/27/2023 2:27:22 PM Analysis Name D:\Data\ggc\23-122608_P1-F-6_01_8411.d Operator ELB Method Ic_qtof_directospos.m Operator ELB Sample Name 23-122608 Instrument micrOTOF-Q II Comment T5-2PP Sv: MeOH + HCOOH Brunella Biscussi Svite of the second second

| Source Type | ESI | Ion Polarity | Positive | Set Nebulizer | 3.5 Bar | |
|-------------|------------|-----------------------|-----------|------------------|-----------|--|
| Focus | Not active | Set Capillary | 4000 V | Set Dry Heater | 200 °C | |
| Scan Begin | 70 m/z | Set End Plate Offset | -500 V | Set Dry Gas | 7.0 l/min | |
| Scan End | 1000 m/z | Set Collision Cell RF | 300.0 Vpp | Set Divert Valve | Source | |

 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of $\boldsymbol{17}$

DEPT and HSQC spectra in \mbox{CDCl}_3 of ${\bf 17}$

Qualitative Compound Report

| Analysis Info | | | | Acqu | isition Date | 12/27/2023 2:32:30 PM | 1 |
|--|-----------------------------|---|------------------------------|-----------------|---|--------------------------------|---|
| Analysis Name D:\Data\ggc\23-122609_P1-F-7_01_8412.d Method lc_qtof_directospos.m Sample Name 23-122609 Comment T5-2MP Sv: MeOH + HCOOH Brunella Biscussi | | | Operator Instrument | ELB microtof | -Q | | |
| Acquisition Par | ameter | | | | | | |
| Source Type Focus Scan Begin | ESI Not active 70 m/z | lon Polarity Set Capillary Set End Plate Offset | Positive 4000 V -500 V | | Set Nebulizer Set Dry Heate Set Dry Gas | 3.5 Bar 200 °C 7.0 I/min | |

1 H NMR (300 MHz) and 13 C NMR (75 MHz) spectra in MeOD of **18**

Qualitative Compound Report

| Data File Sample Type Instrument Name Acq Method IRM Calibration Statu | 2033_BBA_12_(Sample Instrument 1 ESI_ACN_75_pc IS Success | 01.d os_new.m | Sample Nam Position User Name Acquired Tim DA Method | e BBA_12 Vial 12 ne 12/20/2022 2:09:24 PM (UTC+01:00) DefaultMPS.m |
|--|--|-------------------|--|---|
| Comment | 2 | | | |
| Sample Group | | Info. | | |
| User | BRUNELLA BISCUSSI | Stream | Name | LC 1 |
| Acquisition Time (Local) | Acquisition Time 12/20/2022 2:09:24 PM Local) (UTC+01:00) | | ition SW 1 | 6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1) |
| QTOF Driver Version | 8.00.00 | QTOF F Version | irmware 1 | 2.723 |
| Tune Mass Range | 1700 | | | |

Compound Table

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm) | Hits (DB) |
|-----------------------|-------|----------|---------|---------------|----------|---------------|--------------|
| Cpd 1: C18 H29 N5 O2; | 0.352 | 347.2308 | 2037270 | C18 H29 N5 O2 | 347.2321 | -3.95 | 1 |
| 0.352 | | | | s | | | |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|----------|
| Cpd 1: C18 H29 N5 O2; 0.352 | 348.2377 | 0.352 | Find by Formula | 347.2308 |

 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 19

DEPT and HSQC spectra in CDCl_3 of $\boldsymbol{19}$

Qualitative Compound Report

| Data File | 2034_BBA_13_01.d | Sample Name | BBA_13 |
|-----------------------------|--------------------------------------|--------------------|---|
| Sample Type | Sample | Position | Vial 13 |
| Instrument Name | Instrument 1 | User Name | |
| Acq Method | ESI_ACN_75_pos_new.n | Acquired Time | 12/20/2022 2:16:39 PM (UTC+01:00) |
| IRM Calibration Status | s Success | DA Method | DefaultMPS.m |
| Comment | | 0.0000000000 | |
| Sample Group | | Info. | |
| User | BRUNELLA BISCUSSI | Stream Name | LC 1 |
| Acquisition Time (Local) | 12/20/2022 2:16:39 PM (UTC+01:00) | Acquisition SW Ver | rsior 6200 series TOF/6500 series Q- TOF B.08.00 (B8058.3 SP1) |
| QTOF Driver Version | 8.00.00 | QTOF Firmware Ve | rsio 2.723 |
| Tune Mass Range | 1700 | | |
| | | | |

Compound Table

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm | Hits (DB) |
|-----------------------------|-------|----------|----------|---------------|----------|-----------|-----------|
| Cpd 1: C17 H29 N5 O2; 0.347 | 0.347 | 335.2306 | 10149366 | C17 H29 N5 O2 | 335.2321 | -4.58 | 1 |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|----------|
| Cpd 1: C17 H29 N5 O2; 0.347 | 336.2378 | 0.347 | Find by Formula | 335.2306 |

| x107 | Cpd 1: C17 H29 N5 O2; 0.347: + FBF Spectrum (rt: 0.264 min) 2034_BBA_13_01.d Subtract |
|------|---|
| 1- | 336.2378 ([C17H29N5O2]+H)+ |
| 0.8- | - |
| 0.6- | - |
| 0.4- | - |
| 0.2- | - I |
| 0- | 310 315 320 325 330 335 340 345 350 355 360 365 |
| | Counts vs. Mass-to-Charge (m/z) |

 ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in 20

DEPT and HSQC spectra in $CDCl_3$ of **20**

Qualitative Compound Report

| Data File | 2032_BBA_11_ | 01.d | Sample Nam | e BBA_11 |
|------------------------------|--------------------------------------|--------------------|--------------|---|
| Sample Type | Sample | | Position | Vial 11 |
| Instrument Name | Instrument 1 | | User Name | |
| Acq Method | ESI_ACN_75_p | os_new.m | Acquired Tin | 12/20/2022 2:02:14 PM (UTC+01:00) |
| IRM Calibration Statu | IS Success | | DA Method | DefaultMPS.m |
| Comment | | | | |
| Sample Group | | Info. | | |
| User | BRUNELLA BISCUSSI | Stream | Name | LC 1 |
| Acquisition Time (Local) | 12/20/2022 2:02:14 PM (UTC+01:00) | Acquisi Version | tion SW | 6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1) |
| QTOF Driver Version | 8.00.00 | QTOF F | irmware | 2.723 |
| Tune Mass Range Max. | 1700 | | | |

Compound Table

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | (ppm) | (DB) |
|-----------------------|------|----------|--------|---------------|----------|-------|------|
| Cpd 1: C17 H27 N5 O2; | 0.34 | 333.2169 | 738387 | C17 H27 N5 O2 | 333.2165 | 1.26 | 1 |
| 0.340 | | | | | | | |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|------|-----------------|----------|
| Cpd 1: C17 H27 N5 O2; 0.340 | 334.2242 | 0.34 | Find by Formula | 333.2169 |

 1 H NMR (300 MHz) and 13 C NMR (75 MHz) spectra in MeOD of **21**

DEPT and HSQC spectra in MeOD of 21

Qualitative Compound Report

| Data File Sample Type Instrument Name | | 2029_BBA_8_01.0 Sample Instrument 1 | 1 | Sample Nam Position User Name | ne | BBA_8 Vial 8 |
|---|---------------------|---|---------------------|-------------------------------------|-------------------|--|
| Acq Method | | ESI_ACN_75_pos | _new.m | Acquired Tin | ne | 12/20/2022 1:40:29 PM (UTC+01:00) |
| IRM Calibration Statu | s | Success | | DA Method | | DefaultMPS.m |
| Comment | | | | | | |
| Sample Group | | | Info. | | | |
| User | BRUNELL | A BISCUSSI | Stream | Name | LC 1 | and the set of the set of |
| Acquisition Time (Local) | 12/20/20 (UTC+01 | 22 1:40:29 PM :00) | Acquisit Version | tion SW | 620 Q-T SP1 | 0 series TOF/6500 series OF B.08.00 (B8058.3) |
| QTOF Driver Version | 8.00.00 | | QTOF Fi Version | rmware | 2.72 | 23 |
| Tune Mass Range Max. | 1700 | | | | | |

Compound Table

| | Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm) | Hits (DB) |
|---|-----------------------|-------|----------|---------|---------------|----------|---------------|--------------|
| Г | Cpd 1: C19 H31 N5 O2; | 0.354 | 361.2464 | 3576911 | C19 H31 N5 O2 | 361.2478 | -3.9 | 1 |
| L | 0.354 | | | | | | 2 | |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|----------|
| Cpd 1: C19 H31 N5 O2; 0.354 | 362.2538 | 0.354 | Find by Formula | 361.2464 |

 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 22

DEPT and HSQC spectra in CDCl_3 of $\boldsymbol{22}$

Qualitative Compound Report

| Sample Type Instrument Name | Sample | | Position User Name | Vial 5 |
|-------------------------------------|--------------------------------------|---------------------------|--|---|
| Acq Method IRM Calibration State | IS Success | S_UNICO CANAL A1.m | DA Method | 12/22/2022 1:02:07 PM (UTC+01:00) DefaultMPS.m |
| Comment | And California and California | | | |
| Sample Group | | Info. | | |
| User | BRUNELLA BISCUSSI | Stream Name | LC 1 | |
| Acquisition Time (Local) | 12/22/2022 1:02:07 PM (UTC+01:00) | Acquisition SW Version | 6200 series TOF/6500 : Q-TOF B.08.00 (B8058 SP1) | series .3 |
| QTOF Driver Version | 8.00.00 | QTOF Firmware Version | 2.723 | |
| Tune Mass Range Max. | 1700 | | | |

Compound Table

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm) | Hits (DB) |
|--------------------------------|-------|----------|---------|---------------|----------|---------------|--------------|
| Cpd 1: C18 H31 N5 O2; 0.422 | 0.422 | 349.2476 | 2753006 | C18 H31 N5 O2 | 349.2478 | -0.48 | 1 |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|----------|
| Cpd 1: C18 H31 N5 O2; 0.422 | 350.2546 | 0.422 | Find by Formula | 349.2476 |

 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 23

DEPT and HSQC spectra in $CDCl_3$ of 23
Qualitative Compound Report

| Data File Sample Type Instrument Name Acq Method | 2031_BBA Sample Instrumen ESI ACN | _10_01.d t 1 75 pos new.m | Sample Name Position User Name Acquired Tim | e BBA_10 Vial 10 e 12/20/2022 1:55:01 PM (UTC+01:00) |
|---|--|---------------------------------|--|---|
| IRM Calibration State Comment | IS Success | | DA Method | DefaultMPS.m |
| Sample Group | | Info. | | |
| User | BRUNELLA BISCUSS | Stream | Name | LC 1 |
| Acquisition Time (Local) | 12/20/2022 1:55:01 (UTC+01:00) | PM Acquisi Versior | ition SW N | 6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1) |
| QTOF Driver Version | 8.00.00 | QTOF F Version | Firmware N | 2.723 |
| Tune Mass Range Max. | 1700 | | | |

Compound Table

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm) | Hits (DB) |
|-----------------------|-------|----------|--------|---------------|----------|---------------|--------------|
| Cpd 1: C19 H32 N6 O2; | 0.107 | 376.2588 | 113039 | C19 H32 N6 O2 | 376.2587 | 0.46 | 1 |
| 0.107 | | | | | | | |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|----------|
| Cpd 1: C19 H32 N6 O2; 0.107 | 377.2665 | 0.107 | Find by Formula | 376.2588 |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 24



DEPT and HSQC spectra in $CDCl_3$ of 24

Qualitative Compound Report

| Data File Sample Type Instrument Name Acq Method IRM Calibration State | 2028_BBA_7_01 Sample Instrument 1 ESI_ACN_75_pc IS Success | l.d os_new.m | Sample Nam Position User Name Acquired Tin DA Method | e BBA_7 Vial 7 ne 12/20/2022 1:33:15 PM (UTC+01:00) DefaultMPS.m |
|--|--|---------------------------------------|--|---|
| Sample Group User Acquisition Time (Local) | BRUNELLA BISCUSSI 12/20/2022 1:33:15 PM (UTC+01:00) | Info. Stream Acquisi Version | Name tion SW | LC 1 6200 series TOF/6500 series Q-TOF B.08.00 (B8058.3 SP1) |
| QTOF Driver Version | 8.00.00 | QTOF F Version | irmware 1 | 2.723 |
| Tune Mass Range Max. | 1700 | | | |

Compound Table

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm) | Hits (DB) |
|-----------------------|-------|----------|---------|---------------|----------|---------------|--------------|
| Cpd 1: C18 H29 N5 O2; | 0.332 | 347.2311 | 3050682 | C18 H29 N5 O2 | 347.2321 | -2.88 | 1 |
| 0.332 | | | | | | | |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|----------|
| Cpd 1: C18 H29 N5 O2; 0.332 | 348.2382 | 0.332 | Find by Formula | 347.2311 |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of 25



DEPT and HSQC spectra in CDCl₃ of 25

Qualitative Compound Report

| Data File Sample Type Instrument Name | 2026_BBA_5_01. Sample Instrument 1 | d | Sample Nam Position User Name | BBA_5 Vial 5 | |
|---|--|---------------------|-------------------------------------|---|---------------------------|
| Acq Method | ESI_ACN_75_pos | _new.m | Acquired Tin | 12/20/202 | 22 1:18:46 PM (UTC+01:00) |
| IRM Calibration State | IS Success | | DA Method | DefaultM | PS.m |
| Comment | | | | | |
| Sample Group | | Info. | | | |
| User | BRUNELLA BISCUSSI | Stream | Name | C 1 | |
| Acquisition Time (Local) | 12/20/2022 1:18:46 PM (UTC+01:00) | Acquisit Version | tion SW | 5200 series TO Q-TOF B.08.00 SP1) | F/6500 series (B8058.3 |
| QTOF Driver Version | 8.00.00 | QTOF Fi Version | rmware | 2.723 | |
| Tune Mass Range Max. | 1700 | | | | |

Compound Table

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm) | Hits (DB) |
|-----------------------|-------|----------|----------|---------------|----------|---------------|--------------|
| Cpd 1: C20 H33 N5 O2; | 0.284 | 375.2635 | 39219620 | C20 H33 N5 O2 | 375.2634 | 0.18 | 1 |
| 0.284 | | | | | | | |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|----------|
| Cpd 1: C20 H33 N5 O2; 0.284 | 376.2714 | 0.284 | Find by Formula | 375.2635 |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in MeOD of $\mathbf{26}$



DEPT and HSQC spectra in MeOD of 26

Qualitative Analysis Report

| Data Filonamo | 2027 PPA 6 02 | 4 | Sample Name | PPA 6 |
|------------------------------|------------------------|--------------------------|------------------------------|------------------------------------|
| Cample Tune | 2027_DBA_0_02. | u | Desition | Nol 4 |
| Sample Type | Sample | | Position | Vial 4 |
| Instrument Name | Instrument 1 | | User Name | |
| Acq Method | ESI_ACN_75_pos | UNICO CANAL A1.m | Acquired Time | 12/22/2022 12:54:48 PM (UTC+01:00) |
| IRM Calibration State | Is Success | | DA Method | DefaultMPS.m |
| Comment | | | | |
| Sample Group | | Info. | | |
| User | BRUNELLA BISCUSSI | Stream Name | LC 1 | |
| Acquisition Time | 12/22/2022 12:54:48 PM | Acquisition SW | 6200 series TOF/6500 : | series |
| (Local) | (UTC+01:00) | Version | Q-TOF B.08.00 (B8058 SP1) | 3 |
| QTOF Driver Version | 8.00.00 | QTOF Firmware Version | 2.723 | |
| Tune Mass Range Max. | 1700 | | | |

Spectra

| +ESI Scan (rt: 0.8 | 73-1.188 min, 20 so | cans) Frag=150.0V 2027 | BBA_6_02.0 | d Subtract | |
|--------------------|---------------------|--------------------------------|--|---|--|
| 36 | 2.2544 | | | | |
| - | | | | | |
| - | | | | | |
| - | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| 200 | 400 60 | 0 800 | 1000 | 1200 | 1400 |
| 200 | Cou | ints vs. Mass-to-Charge | (m/z) | | |
| | 36 200 | 362.2544 200 400 600 Cou | 200 400 600 800 Counts vs. Mass-to-Charge | 200 400 600 800 1000 Counts vs. Mass-to-Charge (m/z) | 200 400 600 800 1000 1200 Counts vs. Mass-to-Charge (m/z) |



 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDCl3 of $\boldsymbol{27}$



Qualitative Compound Report

| Data File | | 2025_BBA_4_01. | d | Sample Nan | ne | BBA_4 |
|-----------------------------|---------------------|------------------------|---------------------|--------------|-------------------|--|
| Sample Type | | Sample | | Position | | Vial 4 |
| Instrument Name | | Instrument 1 | | User Name | | |
| Acq Method | | ESI_ACN_75_pos | _new.m | Acquired Tir | me | 12/20/2022 1:11:36 PM (UTC+01:00) |
| IRM Calibration State | IS | Success | | DA Method | | DefaultMPS.m |
| Comment | | | | | | |
| Sample Group | | | Info. | | | |
| User | BRUNELL | A BISCUSSI | Stream | Name | LC 1 | L |
| Acquisition Time (Local) | 12/20/20 (UTC+01 | 22 1:11:36 PM ::00) | Acquisit Version | tion SW | 620 Q-T SP1 | 0 series TOF/6500 series OF B.08.00 (B8058.3) |
| QTOF Driver Version | 8.00.00 | | QTOF Fi Version | rmware | 2.72 | 23 |
| Tune Mass Range Max. | 1700 | | | | | |

Compound Table

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm) | Hits (DB) |
|--------------------------------|-------|----------|----------|---------------|----------|---------------------------------------|--------------|
| Cpd 1: C19 H31 N5 O2; 0.322 | 0.322 | 361.2485 | 37944788 | C19 H31 N5 O2 | 361.2478 | P.01 | 1 |
| | · | 8 | 6 8 | | 0 | · · · · · · · · · · · · · · · · · · · | 2 |

| Compound Label | m/z | RT | Algorithm | Mass | |
|--------------------------------|----------|-------|-----------------|----------|--|
| Cpd 1: C19 H31 N5 O2; 0.322 | 362.2562 | 0.322 | Find by Formula | 361.2485 | |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDl₃ of 28



DEPT and HSQC spectra in $CDCl_3$ of 28

Qualitative Compound Report

| Data File Sample Type Instrument Name Acq Method IRM Calibration Statu Comment | IS | 2023_I Sample Instrur ESI_AC Succes | BBA_2_02. e ment 1 CN_75_pos s | .d s_UNI | (CO CANAL A1.n | 1 | Sample Name Position User Name Acquired Tim DA Method | e BBA_2 Vial 2 e 12/22/20 DefaultM | 22 12:40:2 PS.m | 1 PM (UTC+ | -01:00) |
|---|---|---|--|---|--------------------------------|-------------------|---|---|--------------------|------------|---------|
| Sample Group | | | ICCI | I | ifo. | 16.1 | | | | | |
| Acquisition Time (Local) | e 12/22/2022 12:40:21 PM (UTC+01:00) | | A | Acquisition SW 6200 series TOF/6500 serie Version Q-TOF B.08.00 (B8058.3 SP1) | | 00 series 58.3 | | | | | |
| QTOF Driver Version | OF Driver Version 8.00.00 | | | Q | QTOF Firmware 2.723 Version | | | | | | |
| Tune Mass Range Max. | 1700 | | | | | | | | | | |
| Compound Table | | | | | | | | | D:# | Uita | |
| Compound Label | | RT | Mass | | Abund | For | mula | Tgt Mass | (ppm) | (DB) | |
| Cpd 1: C19 H32 N | 6 O2; 0.978 | 0.978 | 376.25 | 84 | 107805 | C19 H3 | 2 N6 O2 | 376.2587 | -0.79 | 1 | |
| Compound Labol | | 1/7 | D | т | Algorithm | | Mass | | | | |
| Cpd 1: C19 H32 N6 O 0.978 | 2; 3 | 77.2657 | 0 | .978 | Find by For | mula | 376.2584 | | | | |
| MS Zoomed Spectrum | | | | | | | | | | | |





¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra in MeOD of **29**

DEPT and HSQC spectra in CDCl₃ of 29



Qualitative Compound Report

| Data File Sample Type Instrument Name Acq Method IRM Calibration State | 2024_BBA_3_02.c Sample Instrument 1 ESI_ACN_75_pos IS Success | J _UNICO CANAL A1.m | Sample Name Position User Name Acquired Time DA Method | BBA_3 Vial 3 12/22/2022 12:47:32 PM (UTC+01:00) DefaultMPS.m |
|--|---|---|--|---|
| Sample Group User Acquisition Time (Local) | BRUNELLA BISCUSSI 12/22/2022 12:47:32 PM (UTC+01:00) | Info. Stream Name Acquisition SW Version | LC 1 6200 series TOF/6500 s Q-TOF B.08.00 (B8058, SP1) | series 3 |
| QTOF Driver Version | 8.00.00 | QTOF Firmware Version | 2.723 | |
| Tune Mass Range Max. | 1700 | | | |
| Compound Table | | | | |

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | (ppm) | Hits (DB) |
|--------------------------------|-------|---------|--------|---------------|----------|-------|--------------|
| Cpd 1: C19 H32 N6 O2; 2.299 | 2.299 | 376.259 | 645896 | C19 H32 N6 O2 | 376.2587 | 0.87 | 1 |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|---------|
| Cpd 1: C19 H32 N6 O2; 2.299 | 377.2664 | 2.299 | Find by Formula | 376.259 |





 ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in CDl_3 of 30



DEPT and HSQC spectra in $CDCl_3$ of **30**

Qualitative Compound Report

| Data File 2022_BBA_1_02.d Sample Type Sample Instrument Name Instrument 1 | | d | Sample Name Position | BBA_1 Vial 1 | |
|---|------------------------|--------------------------|--------------------------------|------------------------------------|--|
| Aca Method FSI ACN 75 pos | | LINICO CANAL A1 m | User Name | 12/22/2022 12:33:09 PM (UTC+01:00) | |
| IRM Calibration Status Success | | | DA Method | DefaultMPS.m | |
| Comment | | | | | |
| Sample Group | | Info. | | | |
| User | BRUNELLA BISCUSSI | Stream Name | LC 1 | | |
| Acquisition Time | 12/22/2022 12:33:09 PM | Acquisition SW | 6200 series TOF/6500 : | series | |
| (Local) (UTC+01:00) | | Version | Q-TOF B.08.00 (B8058.3 SP1) | | |
| QTOF Driver Version | 8.00.00 | QTOF Firmware Version | 2.723 | | |
| Tune Mass Range | 1700 | | | | |

Compound Table

Max.

| Compound Label | RT | Mass | Abund | Formula | Tgt Mass | Diff (ppm) | Hits (DB) |
|--------------------------------|-------|----------|-------|---------------|----------|---------------|--------------|
| Cpd 1: C18 H30 N6 O2; 1.923 | 1.923 | 362.2427 | 28818 | C18 H30 N6 O2 | 362.243 | -0.8 | 1 |

| Compound Label | m/z | RT | Algorithm | Mass |
|--------------------------------|----------|-------|-----------------|----------|
| Cpd 1: C18 H30 N6 O2; 1.923 | 363.2501 | 1.923 | Find by Formula | 362.2427 |



Molecular Docking

| | | Dor | nepezil | |
|--------|---------|--------|---------|--------------|
| | coul | vdW | h-bond | distance (Å) |
| TYR72 | -1.374 | -1.881 | 0 | 2.748 |
| ASP74 | -25.178 | -0.82 | 0 | 4.107 |
| THR83 | -0.095 | -0.235 | 0 | 5.135 |
| TRP86 | -0.292 | -4.769 | 0 | 2.647 |
| GLY121 | 1.331 | -1.527 | 0 | 2.958 |
| GLY122 | 0.457 | -0.317 | 0 | 5.097 |
| TYR124 | -1.29 | -2.546 | 0 | 2.346 |
| SER125 | -0.791 | -0.406 | 0 | 4.027 |
| TYR133 | -0.161 | -0.509 | 0 | 2.901 |
| GLU202 | 0.51 | -1.02 | 0 | 2.381 |
| SER203 | 1.807 | -0.171 | 0 | 3.208 |
| TRP286 | 0.955 | -5.594 | 0 | 3.001 |
| SER293 | -0.762 | -0.986 | 0 | 2.41 |
| VAL294 | 0.106 | -1.599 | 0 | 2.843 |
| PHE295 | -1.569 | -1.263 | -1.0 | 2.031 |
| PHE296 | 10.305 | -0.939 | 0 | 3.433 |
| PHE297 | 0.454 | -1.972 | 0 | 2.119 |
| TYR337 | -1.6 | -1.515 | 0 | 2.327 |
| PHE338 | -1.258 | -4.285 | 0 | 2.444 |
| TYR341 | -1.313 | -7.101 | 0 | 2.664 |
| HIS447 | -3.421 | -3.093 | 0 | 2.073 |

Table 1. Electrostatic (coul), van der Waals (vdW), and hydrogen bond (h-bond) energies of protein-ligand complex (Kcal/mol) and calculated per-residue distances.

Compd 21

Compd 32

| | coul | vdW | h-bond | distance (Å) | coul | vdW | h-bond | distance (Å) |
|--------|---------|--------|--------|--------------|---------|--------|--------|--------------|
| TYR72 | -1.591 | -1.469 | 0 | 2.204 | -0.754 | -0.82 | 0 | 3.344 |
| ASP74 | -21.231 | -0.979 | 0 | 3.881 | -24.206 | -0.763 | 0 | 4.101 |
| THR83 | -0.631 | -0.26 | 0 | 4.255 | -0.674 | -0.283 | 0 | 4.267 |
| TRP86 | -2.807 | -5.15 | 0 | 2.186 | -2.802 | -5.654 | 0 | 2.385 |
| GLY121 | 1.96 | -1.656 | 0 | 2.174 | 1.832 | -1.358 | 0 | 2.444 |
| GLY122 | 0.421 | -0.25 | 0 | 3.842 | 0.36 | -0.216 | 0 | 4.689 |
| TYR124 | -0.687 | -2.275 | 0 | 2.753 | -0.557 | -2.009 | 0 | 2.669 |
| SER125 | -1.285 | -0.341 | 0 | 4.330 | -1.28 | -0.284 | 0 | 4.364 |
| TYR133 | -0.457 | -0.562 | 0 | 3.015 | -0.436 | -0.373 | 0 | 3.467 |
| GLU202 | -0.23 | -1.333 | 0 | 2.476 | -0.162 | -1.081 | 0 | 2.645 |
| SER203 | 0.021 | -0.792 | 0 | 2.836 | 0.069 | -0.498 | 0 | 3.202 |
| TRP286 | 0.024 | -6.529 | 0 | 2.765 | 0.871 | -5.592 | 0 | 2.801 |
| SER293 | -0.299 | -1.199 | 0 | 2.625 | -0.423 | -1.857 | 0 | 2.242 |
| VAL294 | -0.42 | -2.105 | 0 | 2.015 | 0.615 | -2.401 | 0 | 2.001 |

| PHE295 | -1.558 | -1.143 | -1 | 1.987 | -0.721 | -1.915 | -0.485 | 2.204 |
|--------|--------|--------|--------|-------|--------|--------|--------|-------|
| PHE296 | 8.979 | -0.855 | 0 | 3.256 | 9.378 | -2.558 | 0 | 1.542 |
| PHE297 | 0.338 | -1.537 | 0 | 2.470 | 0.263 | -2.039 | 0 | 2.181 |
| TYR337 | -0.983 | 0 | -3.326 | 2.371 | -1.108 | -2.343 | 0 | 2.209 |
| PHE338 | -0.396 | -3.161 | 0 | 2.641 | -0.479 | -2.895 | 0 | 2.235 |
| TYR341 | -0.242 | -8.333 | 0 | 2.681 | -1.11 | -6.173 | 0 | 2.497 |
| HIS447 | -4.159 | -2.231 | 0 | 2.258 | -4.099 | -2.35 | 0 | 2.124 |

| | Compd 28 | | | | Compd 16 | | | |
|--------|----------|--------|--------|--------------|----------|--------|--------|--------------|
| | coul | vdW | h-bond | distance (Å) | coul | vdW | h-bond | distance (Å) |
| TYR72 | -1.805 | -1.427 | 0 | 2.233 | -1.392 | -1.880 | 0 | 2.095 |
| ASP74 | -27.573 | -1.124 | -0.406 | 2.043 | -30.648 | -1.978 | 0 | 2.009 |
| THR83 | -0.793 | -0.728 | 0 | 3.231 | -0.537 | -0.727 | 0 | 3.552 |
| TRP86 | -2.158 | -6.09 | 0 | 2.568 | -0.716 | -4.637 | 0 | 2.13 |
| GLY121 | 1.877 | -1.22 | 0 | 2.501 | 1.348 | -0.972 | 0 | 2.654 |
| GLY122 | 0.261 | -0.218 | 0 | 4.642 | 0.189 | -0.222 | 0 | 4.968 |
| TYR124 | -0.552 | -2.99 | 0 | 2.460 | -0.676 | -3.046 | 0 | 1.701 |
| SER125 | -1.365 | -0.345 | 0 | 4.190 | -1.188 | -1.048 | 0 | 2.713 |
| TYR133 | -0.269 | -0.249 | 0 | 3.811 | -0.145 | -0.074 | 0 | 5.447 |
| GLU202 | -0.311 | -0.812 | 0 | 3.048 | 0.018 | -0.112 | 0 | 5.334 |
| SER203 | -0.061 | -0.382 | 0 | 3.765 | 0.105 | -0.103 | 0 | 5.997 |
| TRP286 | 0 | -6.317 | 0 | 2.642 | -0.055 | -5.719 | 0 | 2.775 |
| SER293 | -0.362 | -1.177 | 0 | 2.666 | -0.058 | -1.034 | 0 | 2.501 |
| VAL294 | -0.302 | -2.101 | 0 | 2.067 | -0.085 | -2.063 | 0 | 2.285 |
| PHE295 | -1.144 | -1.248 | -0.758 | 2.197 | 0.065 | -1.648 | -0.380 | 2.198 |
| PHE296 | 8.949 | -0.844 | 0 | 3.520 | 9.547 | -0.921 | 0 | 3.628 |
| PHE297 | 0.398 | -1.575 | 0 | 2.165 | 0.513 | -1.970 | 0 | 2.161 |
| TYR337 | -1.317 | -3.248 | 0 | 2.640 | -0.474 | -3.883 | 0 | 2.469 |
| PHE338 | -0.392 | -2.311 | 0 | 2.497 | -0.349 | -3.780 | 0 | 2.139 |
| TYR341 | -0.976 | -7.891 | -0.071 | 2.394 | -1.035 | -8.119 | 0 | 2.338 |
| HIS447 | -3.649 | -2.31 | 0 | 2.343 | -2.622 | -1.217 | 0 | 2.009 |



Figure S1. 2D representation of best docking poses and protein–ligand interactions of donepezil (A), compd **21** (B), compd **32** (C), compd **16** (D)and compd **28** (E).



Fig. S2. Docking validation, a comparison of the redocked binding mode and the co-crystallized pose (green) of donepezil.