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## SUPPLEMENTARY INFORMATION

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# Chemically advanced template search (CATS) for scaffold-hopping and prospective target prediction for 'orphan' molecules

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## General information

All starting materials and solvents were obtained from ABCR Chemicals, Aldrich, Fluka, Alfa Aesar or Acros, and were used without further purification.

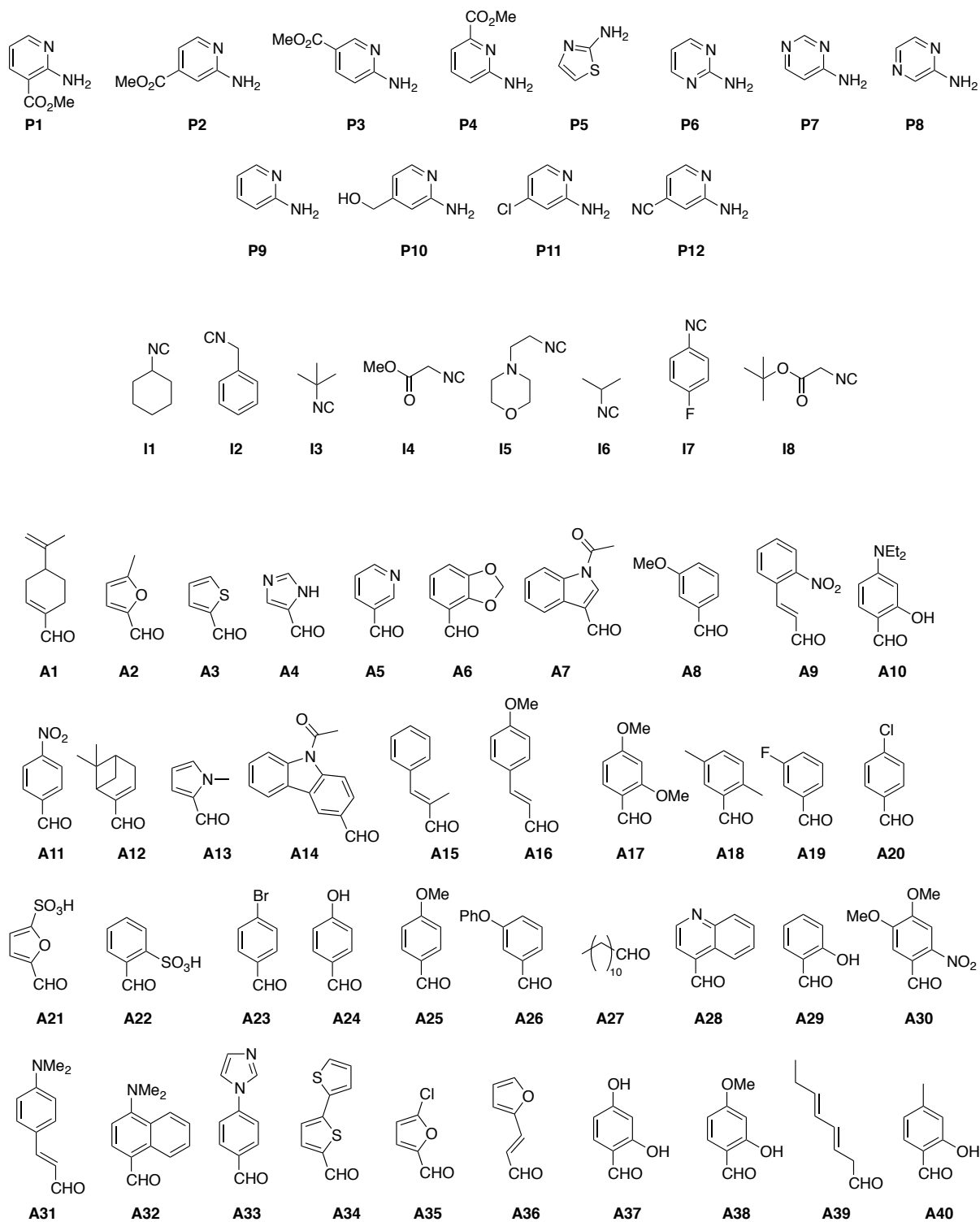
Combinatorial library was built using J-KEM® Scientific robot for mixing the building blocks. Microwave-assisted synthesis was then carried out in a Biotage Initiator reactor.

Analytical HPLC-MS was carried out in a Shimadzu LC-MS2020 system, equipped with a Nucleodur C<sub>18</sub> HTec column, under an appropriate gradient of acetonitrile : H<sub>2</sub>O (+ 0.1% trifluoroacetic acid in each phase), and a total flow rate of 0.5 mL/min. The mass spectrometer was operated in positive-ion mode with ESI. Preparative HPLC was carried out on a Shimadzu LC-8A system, coupled to a Nucleodur 100-5 C<sub>18</sub> HTec column, and a SPD-20A UV/Vis detector.

Proton and carbon nuclear magnetic resonance spectra (<sup>1</sup>H and <sup>13</sup>C NMR, respectively) were recorded on Bruker Avance 400 spectrometer. Chemical shifts (δ) are reported in units of parts per million (ppm) downfield from SiMe<sub>4</sub> (δ 0.0) and relative to the respective solvent's peak. Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (double of doublet) td (triplet of doublet) or m (multiplet). <sup>1</sup>H-<sup>1</sup>H Coupling constants (*J*) are reported in Hertz (Hz).

## Virtual combinatorial library – building blocks

A virtual combinatorial library was built from the building blocks described by Burchak *et al.*<sup>1</sup> The structures of aminopyridines (P), aldehydes (A) and isocyanides (I) are given below.



## General procedure for synthesis of imidazopyridine combinatorial library

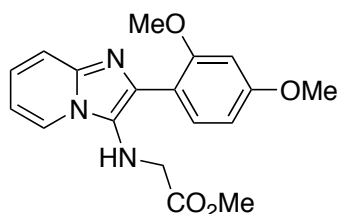


Stock solutions in MeOH were prepared for all building blocks (P, A and I) and catalyst. These solutions had a concentration of 400 mM for P, A and I starting materials, while for perchloric acid a solution of concentration 40 mM was prepared. An automated system dispensed 75  $\mu\text{L}$  of each building block and catalyst, sequentially, into microwave vials. These were sealed and heated for 5 minutes, at 170°C under microwaves. The reaction products were analyzed under HPLC-MS using ACN : H<sub>2</sub>O (+ 0.1% TFA in each phase) as eluent. A typical run used a gradient of 5-50% ACN run in 12 minutes.

## General procedure for synthesis of selected imidazopyridines

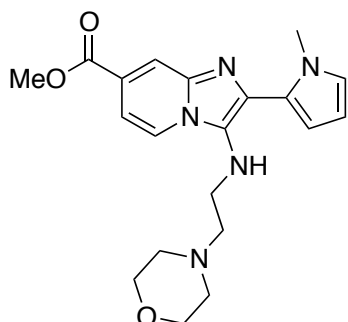
The protocol was adapted from existing literature.<sup>2</sup> 2-Aminopyridine (1.0 molar eq.), aldehyde (1.0 molar eq.) isocyanide (1.0 molar eq.) and perchloric acid (10 mol%) were dissolved in ethanol absolute (2.1 mL/mmol). The solutions were heated at 170 °C for 5 minutes under microwaves. The resulting crudes were purified via preparative HPLC using ACN : H<sub>2</sub>O (+ 0.1% TFA in each phase) as eluent. A typical run used a gradient of 5-50% ACN run over 16 minutes.

### Methyl 2-((2-(2,4-dimethoxyphenyl)imidazo[1,2-a]pyridin-3-yl)amino)acetate, 1



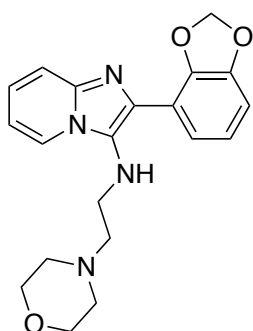
Yellow oil; 81%; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400.13 MHz):  $\delta$  3.44 (3H, s, OCH<sub>3</sub>), 3.67 (2H, s, CH<sub>2</sub>), 3.75 (3H, s, OCH<sub>3</sub>), 3.80 (3H, s, OCH<sub>3</sub>), 6.57-6.61 (2H, m, Ar-H), 7.32-7.36 (1H, m, Ar-H), 7.53 (1H, d,  $J$  = 8.0 Hz, Ar-H), 6.77-7.75 (2H, m, Ar-H), 8.68 (1H, d,  $J$  = 2.4 Hz, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz):  $\delta$  48.54, 52.52, 56.18, 56.48, 99.77, 107.08, 108.44, 112.51, 117.43, 123.13, 126.42, 129.04, 132.62, 133.56, 137.46, 159.91, 164.60, 173.19. HRMS-ESI calc. (C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>+H<sup>+</sup>): 342.1448, found: 342.1448.

**Methyl 2-(1-methyl-1*H*-pyrrol-2-yl)-3-((2-morpholinoethyl)amino)imidazo[1,2-*a*]pyridine-7-carboxylate, 2**



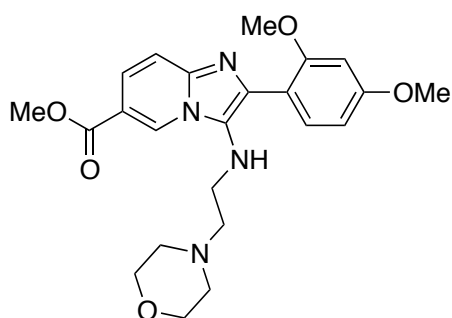
Yellow oil; 74%; (CD<sub>3</sub>OD, 400.13 MHz):  $\delta$  3.08 (2H, m, CH<sub>2</sub>), 3.21 (2H, t,  $J$  = 6.4 Hz, CH<sub>2</sub>), 3.37 (2H, m, CH<sub>2</sub>), 3.45 (2H, t,  $J$  = 6.4 Hz, CH<sub>2</sub>), 3.72 (3H, s, CH<sub>3</sub>), 3.81 (2H, m, CH<sub>2</sub>), 3.97 (2H, m, CH<sub>2</sub>), 4.05 (3H, s, CH<sub>3</sub>), 6.32 (1H, dd,  $J$  = 3.8 Hz, Ar-H), 6.63 (1H, dd,  $J$  = 3.8 Hz, Ar-H), 7.06 (1H, m, Ar-H), 7.93 (1H, dd,  $J$  = 1.6 and 7.2 Hz, Ar-H), 8.40 (1H, m, Ar-H), 8.80 (1H, dd,  $J$  = 0.8 and 7.2 Hz, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz): 35.01, 41.04, 53.33, 53.84, 57.27, 64.81, 110.04, 114.52, 115.63, 116.03, 116.31, 118.78, 126.40, 127.62, 131.28, 134.24, 137.07, 165.19. HRMS-ESI calc. (C<sub>20</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub>+H<sup>+</sup>): 384.2030, found: 384.2031.

**2-(Benzo[*d*][1,3]dioxol-4-yl)-*N*-(2-morpholinoethyl)imidazo[1,2-*a*]pyridin-3-amine, 3**



White solid; mp = 131-133 °C, 75%, <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400.13 MHz):  $\delta$  3.00 (2H, m, CH<sub>2</sub>), 3.21 (3H, t,  $J$  = 6.2 Hz, CH<sub>2</sub> + CH), 3.34 (3H, t,  $J$  = 6.4 Hz, CH<sub>2</sub> + CH), 3.56-3.94 (4H, m, CH<sub>2</sub>), 6.01 (2H, s, CH<sub>2</sub>), 6.87 (1H, dd,  $J$  = 1.8 and 8.2 Hz, Ar-H), 6.92 (1H, t,  $J$  = 8.2 Hz, Ar-H), 7.14 (1H, dd,  $J$  = 1.8 and 8.0 Hz, Ar-H), 7.37 (1H, td,  $J$  = 1.6 and 7.4 Hz, Ar-H), 7.74 (1H, m, Ar-H), 7.82 (1H, m, Ar-H), 8.65 (1H, m, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz):  $\delta$  42.50, 53.47, 57.66, 64.84, 103.47, 109.52, 111.50, 112.97, 118.24, 122.26, 122.86, 124.07, 126.52, 128.89, 134.85, 138.74, 146.90, 149.91. HRMS-ESI calc. (C<sub>20</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>+H<sup>+</sup>): 367.1765, found: 367.1765.

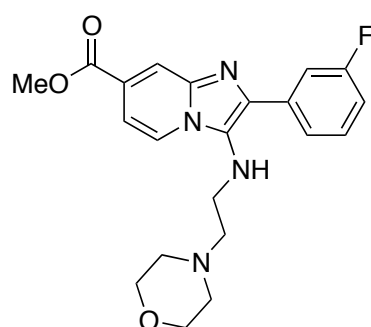
**Methyl 2-(2,4-dimethoxyphenyl)-3-((2-morpholinoethyl)amino)imidazo[1,2-*a*]pyridine-6-carboxylate, 4**



Yellow oil; 92%; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400.13 MHz):  $\delta$  2.90 (2H, m, CH<sub>2</sub>), 3.22 (2H, t,  $J$  = 6.4 Hz, CH<sub>2</sub>), 3.32 (2H, t,  $J$  = 6.4 Hz, CH<sub>2</sub>), 3.39 (2H, d,  $J$  = 11.6 Hz, CH<sub>2</sub>), 3.77 (3H, s, OCH<sub>3</sub>), 3.82 (3H, s, OCH<sub>3</sub>), 3.84-4.00 (4H, m, CH<sub>2</sub>), 4.04 (3H, s, OCH<sub>3</sub>), 6.42 (1H, d,  $J$  = 2.0 Hz, Ar-H), 6.45 (1H, dd,  $J$  = 2.0 and 8.7 Hz, Ar-H), 7.54 (1H, d,  $J$  = 8.8 Hz, Ar-H), 7.83 (1H, dd,  $J$  = 1.0 and 9.2 Hz, Ar-H), 8.20 (1H, dd,  $J$  = 1.6 and 9.4 Hz, Ar-H), 9.11 (1H, s, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz):  $\delta$  41.89, 53.36, 53.59,

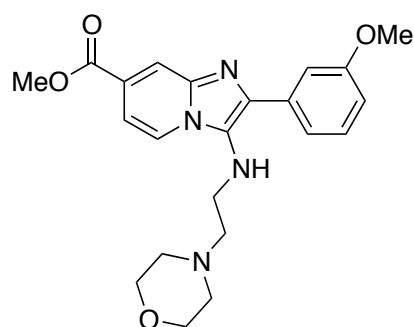
56.22, 56.52, 57.46, 64.79, 99.86, 107.21, 107.91, 112.67, 116.07, 121.89, 125.05, 129.26, 132.88, 133.31, 138.60, 160.23, 165.11, 165.15. HRMS-ESI calc. ( $C_{23}H_{28}N_4O_5+H^+$ ): 441.2132, found: 441.2127.

**Methyl 2-(3-fluorophenyl)-3-((2-morpholinoethyl)amino)imidazo[1,2-a]pyridine-7-carboxylate, 5**



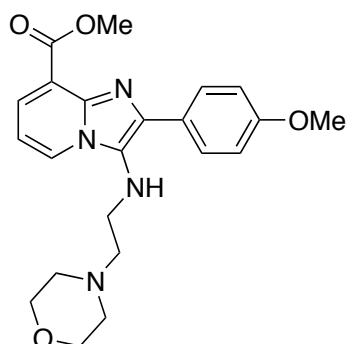
Yellow oil; 70%;  $^1H$  NMR ( $CDCl_3$ , 400.13 MHz):  $\delta$  2.96 (2H, m,  $CH_2$ ), 3.33 (2H, t,  $J = 6.4$  Hz,  $CH_2$ ), 3.44 (2H, t,  $J = 6.4$  Hz,  $CH_2$ ), 3.44-3.49 (2H, m,  $CH_2$ ), 3.90-4.01 (4H, m,  $CH_2$ ), 4.03 (3H, s,  $OCH_3$ ), 7.11 (1H, td,  $J = 2.2$  and 8.4 Hz, Ar-H), 7.45 (1H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.59 (1H, d,  $J = 8.2$  Hz, Ar-H), 7.88 (1H, dd,  $J = 1.6$  and 7.0 Hz, Ar-H), 8.40 (1H, s, Ar-H), 8.71 (1H, dd,  $J = 1.0$  and 7.0 Hz, Ar-H).  $^{13}C$  NMR ( $CD_3OD$ , 100.61 MHz):  $\delta$  42.56, 53.46, 53.86, 57.64, 64.83, 115.00, 116.12, 116.36, 116.62, 118.40, 118.61, 125.44, 126.73, 129.57, 132.77, 134.75, 138.17, 164.52, 165.21. HRMS-ESI calc. ( $C_{21}H_{23}FN_4O_3+H^+$ ): 399.1827, found: 399.1828.

**Methyl 2-(3-methoxyphenyl)-3-((2-morpholinoethyl)amino)imidazo[1,2-a]pyridine-7-carboxylate, 6**



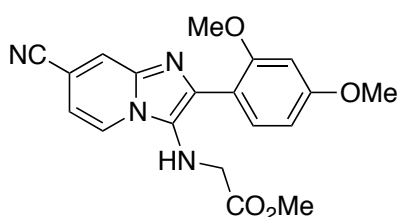
Yellow oil; 93%;  $^1H$  NMR ( $CDCl_3$ , 400.13 MHz):  $\delta$  2.88 (2H, m,  $CH_2$ ), 3.22 (2H, t,  $J = 6.4$  Hz,  $CH_2$ ), 3.29 (2H, t,  $J = 6.4$  Hz,  $CH_2$ ), 3.37 (2H, m,  $CH_2$ ), 3.68 (3H, s,  $CH_3$ ), 3.82-3.91 (4H, m,  $CH_2$ ), 3.95 (3H, s,  $OCH_3$ ), 6.66 (1H, dd,  $J = 1.6$  and 8.2 Hz, Ar-H), 7.06-7.20 (3H, m, Ar-H), 7.72 (1H, dd,  $J = 1.4$  and 7.2 Hz, Ar-H), 8.16 (1H, s, Ar-H), 8.55 (1H, d,  $J = 7.2$  Hz, Ar-H).  $^{13}C$  NMR ( $CDCl_3$ , 100.61 MHz): 41.35, 52.70, 53.52, 55.36, 57.41, 63.53, 112.62, 114.04, 116.17, 116.82, 119.82, 124.39, 126.43, 126.71, 129.48, 130.40, 133.38, 160.18, 161.46, 163.30. HRMS-ESI calc. ( $C_{22}H_{26}N_4O_4+H^+$ ): 411.2027, found: 411.2027.

**Methyl 2-(4-methoxyphenyl)-3-((2-morpholinoethyl)amino)imidazo[1,2-*a*]pyridine-8-carboxylate, 7**



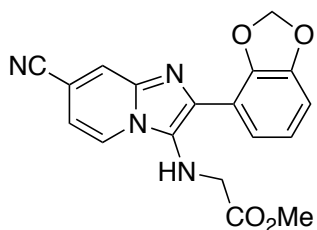
Yellow oil; 72%;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400.13 MHz):  $\delta$  2.88 (2H, m,  $\text{CH}_2$ ), 3.20 (2H, t,  $J = 6.4$  Hz,  $\text{CH}_2$ ), 3.37-3.42 (4H, m,  $\text{CH}_2$ ), 3.81 (3H, s,  $\text{OCH}_3$ ), 3.82-4.03 (4H, m,  $\text{CH}_2$ ), 4.03 (3H, s,  $\text{OCH}_3$ ), 6.98 (2H, d,  $J = 9.0$  Hz, Ar-H), 7.46 (1H, dd,  $J = 7.2$  Hz Ar-H), 7.60 (2H, d,  $J = 9.0$  Hz, Ar-H), 8.38 (1H, dd,  $J = 1.0$  and 7.4 Hz, Ar-H), 7.98 (1H, dd,  $J = 1.0$  and 7.0 Hz, Ar-H).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100.61 MHz):  $\delta$  42.46, 53.37, 53.86, 56.07, 57.63, 64.79, 115.73, 116.53, 117.69, 119.14, 128.30, 129.59, 130.70, 132.39, 136.29, 137.34, 163.12, 164.19. HRMS-ESI calc. ( $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_4 + \text{H}^+$ ): 411.2027, found: 411.2028.

**Methyl 2-((7-cyano-2-(2,4-dimethoxyphenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate, 8**



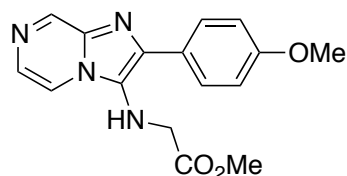
Yellow solid; mp = 60-61 °C; 87%;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400.13 MHz):  $\delta$  3.55 (3H, s,  $\text{OCH}_3$ ), 3.80 (2H, s,  $\text{CH}_2$ ), 3.90 (3H, s,  $\text{OCH}_3$ ), 3.92 (3H, s,  $\text{OCH}_3$ ), 6.73 (1H, d,  $J = 2.4$  Hz, Ar-H), 6.76 (1H, dd,  $J = 4.8$  and 2.0 Hz, Ar-H), 7.62-7.68 (2H, m, Ar-H), 8.28 (1H, s, Ar-H), 8.89 (1H, d,  $J = 7.2$  Hz, Ar-H).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{OD}$ , 100.61 MHz):  $\delta$  48.17, 52.56, 56.22, 56.51, 99.83, 107.29, 108.31, 114.51, 117.25, 117.60, 118.58, 126.04, 127.11, 131.05, 132.79, 135.66, 160.07, 165.05, 173.04. HRMS-ESI calc. ( $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_4 + \text{H}^+$ ): 367.1401, found: 367.1401.

**Methyl 2-((2-(benzo[*d*][1,3]dioxol-4-yl)-7-cyanoimidazo[1,2-*a*]pyridin-3-yl)amino)acetate, 9**



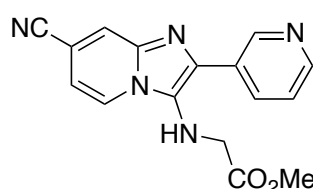
Yellow solid; mp = 160-162 °C; 56%;  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 400.13 MHz):  $\delta$  3.49 (3H, s,  $\text{OCH}_3$ ), 3.84 (2H, d,  $J = 6.4$  Hz,  $\text{CH}_2$ ), 5.61 (1H, t,  $J = 6.4$  Hz, NH), 6.10 (2H, s,  $\text{CH}_2$ ), 6.95-6.97 (2H, m, Ar-H), 7.20 (1H, d,  $J = 7.2$  Hz, Ar-H), 7.31 (1H, dd,  $J = 4.4$  Hz, Ar-H), 8.23 (1H, s, Ar-H), 8.47 (1H, d,  $J = 6.8$  Hz, Ar-H).  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ , 100.61 MHz):  $\delta$  47.53, 51.57, 100.83, 103.97, 107.98, 111.44, 115.88, 118.44, 121.73, 121.77, 123.34, 124.10, 129.74, 131.54, 138.01, 144.21, 147.36, 171.58. HRMS-ESI calc. ( $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_4 + \text{H}^+$ ): 351.1088, found: 351.1087.

**Methyl 2-((2-(4-methoxyphenyl)imidazo[1,2-a]pyrazin-3-yl)amino)acetate, 10**



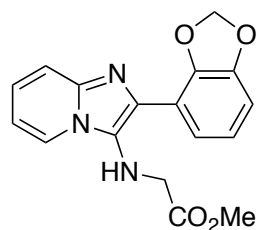
Yellow solid; mp = 150-151 °C; 67%; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400.13 MHz): δ 3.50 (3H, s, OCH<sub>3</sub>), 3.78 (3H, s, OCH<sub>3</sub>), 3.87 (2H, s, CH<sub>2</sub>), 7.00 (2H, d, *J* = 6.8 Hz, Ar-H), 7.83-7.87 (3H, m, Ar-H), 8.56 (1H, d, *J* = 4.8 Hz, Ar-H), 8.92 (1H, s, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz): δ 48.06, 52.67, 55.96, 115.55, 118.72, 123.80, 124.50, 130.54, 133.56, 134.82, 135.96, 141.33, 162.58, 173.27. HRMS-ESI calc. (C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>+H<sup>+</sup>): 313.1295, found: 313.1295.

**Methyl 2-((7-cyano-2-(pyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)amino)acetate, 11**



Yellow solid; mp = 183-185 °C; 39%; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400.13 MHz): δ 3.54 (3H, s, CH<sub>3</sub>), 3.93 (2H, s, CH<sub>2</sub>), 7.28 (1H, dd, *J* = 7.2 and 2.0 Hz, Ar-H), 7.84 (1H, ddd, *J* = 8.0, 5.6 and 0.4 Hz, Ar-H), 8.29 (1H, dd, *J* = 1.6 and 1.2 Hz, Ar-H), 8.63 (1H, dd, *J* = 7.2 and 0.8 Hz, Ar-H), 8.71 (1H, dd, *J* = 5.2 and 0.8 Hz, Ar-H), 8.80 (1H, dt, *J* = 8.0 and 2.0 Hz, Ar-H), 9.40 (1H, d, *J* = 2.0 Hz, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz): δ 47.93, 51.65, 105.81, 111.63, 118.09, 123.53, 125.27, 125.42, 130.11, 130.94, 131.82, 137.72, 138.61, 143.68, 144.48, 171.97. HRMS-ESI calc. (C<sub>16</sub>H<sub>13</sub>N<sub>5</sub>O<sub>2</sub>+H<sup>+</sup>): 308.1142, found: 308.1143.

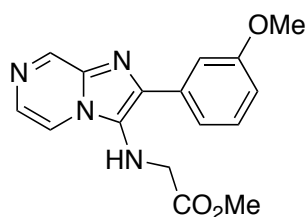
**Methyl 2-((2-(benzo[*d*][1,3]dioxol-4-yl)imidazo[1,2-a]pyridin-3-yl)amino)acetate, 12**



Yellow oil; 80%; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400.13 MHz): δ 3.36 (3H, s, OCH<sub>3</sub>), 3.68 (2H, s, CH<sub>2</sub>), 5.93 (2H, s, CH<sub>2</sub>), 6.76 (1H, d, *J* = 8.0 Hz, Ar-H), 6.82 (1H, t, *J* = 8.0 Hz, Ar-H), 7.10 (1H, d, *J* = 8.0 Hz, Ar-H), 7.29 (1H, t, *J* = 7.2 Hz, Ar-H), 7.65 (1H, d, *J* = 9.2 Hz, Ar-H), 7.72 (1H, m, Ar-H), 8.63 (1H, d, *J* = 6.8 Hz, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz): δ 48.84, 52.57, 103.33, 109.86, 111.18, 112.83, 117.87, 121.63, 123.98, 126.80, 129.62, 134.50, 134.57, 138.48, 146.54, 149.77, 173.17. HRMS-ESI calc. (C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>+H<sup>+</sup>): 326.1135, found: 326.1133.

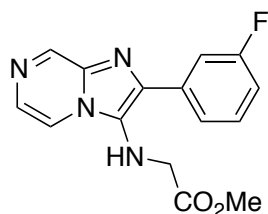


### Methyl 2-((2-(3-methoxyphenyl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate, 13



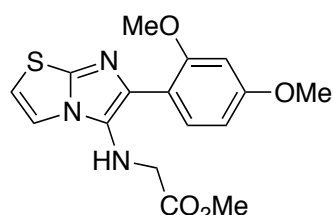
Yellow solid; mp = 137-138 °C; 61%; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400.13 MHz): δ 3.60 (3H, s, OCH<sub>3</sub>), 3.88 (3H, s, OCH<sub>3</sub>), 3.92 (2H, s, CH<sub>2</sub>), 7.06 (1H, ddd, *J* = 8.6, 2.6 and 1.2 Hz, Ar-H), 7.45 (1H, t, *J* = 8.0 Hz, Ar-H), 7.53-7.60 (2H, m, Ar-H), 7.95 (1H, d, *J* = 5.4 Hz, Ar-H), 8.66 (1H, dd, *J* = 5.3 and 1.2 Hz, Ar-H), 9.05 (1H, d, *J* = 0.8 Hz, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz): δ 48.21, 52.66, 55.90, 114.35, 116.45, 118.91, 121.18, 121.24, 124.15, 131.20, 133.94, 135.13, 137.42, 140.56, 161.60, 173.27. HRMS-ESI calc. (C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>+H<sup>+</sup>): 313.1295, found: 313.1294.

### Methyl 2-((2-(3-fluorophenyl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate, 14



Yellow solid; mp = 170-171 °C; 46%; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400.13 MHz): δ 3.50 (3H, s, OCH<sub>3</sub>), 3.87 (2H, s, CH<sub>2</sub>), 7.12 (1H, tdd, *J* = 8.6, 2.4, 0.8 Hz, Ar-H), 7.46 (1H, m, Ar-H), 7.69 (1H, m, Ar-H), 7.77 (1H, m, Ar-H), 7.83 (1H, d, *J* = 5.2 Hz, Ar-H), 8.57 (1H, dd, *J* = 5.2 and 1.2 Hz, Ar-H), 8.97 (1H, d, *J* = 1.0 Hz, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz): δ 48.41, 52.66, 115.41, 115.65, 117.11, 117.32, 119.29, 123.94, 124.72, 131.92, 135.44, 138.33, 163.28, 165.71, 173.31. HRMS-ESI calc. (C<sub>15</sub>H<sub>13</sub>FN<sub>4</sub>O<sub>2</sub>+H<sup>+</sup>): 301.1095, found: 301.1097.

### Methyl 2-((6-(2,4-dimethoxyphenyl)imidazo[2,1-*b*]thiazol-5-yl)amino)acetate, 15

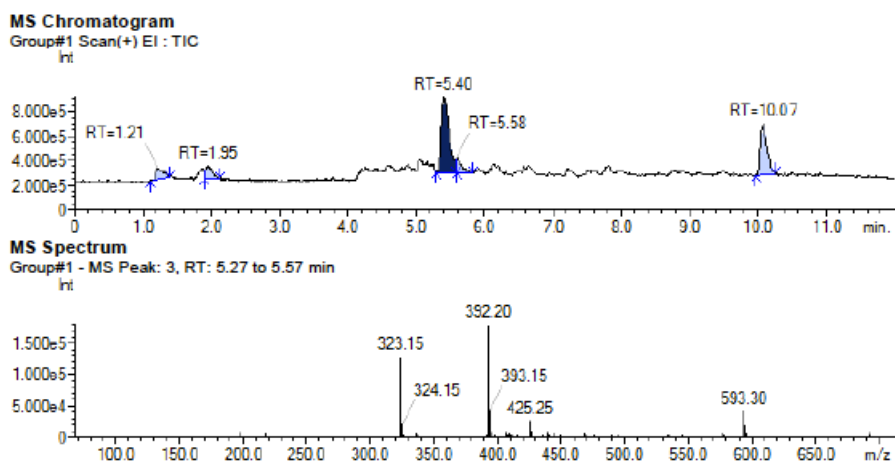


Yellow oil; 52%; <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400.13 MHz): δ 3.39 (3H, s, OCH<sub>3</sub>), 3.58 (2H, s, CH<sub>2</sub>), 3.68 (3H, s, OCH<sub>3</sub>), 3.72 (3H, s, OCH<sub>3</sub>), 6.46-6.53 (2H, m, Ar-H), 7.36 (1H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.96 (1H, dd, *J* = 4.4 and 1.2 Hz, Ar-H). <sup>13</sup>C NMR (CD<sub>3</sub>OD, 100.61 MHz): δ 48.78, 52.53, 56.12, 56.40, 99.75, 106.88, 109.20, 117.89, 121.03, 123.30, 130.74, 132.10, 143.16, 159.66, 164.09, 173.34. HRMS-ESI calc. (C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>S+H<sup>+</sup>): 348.1013, found: 348.1013.

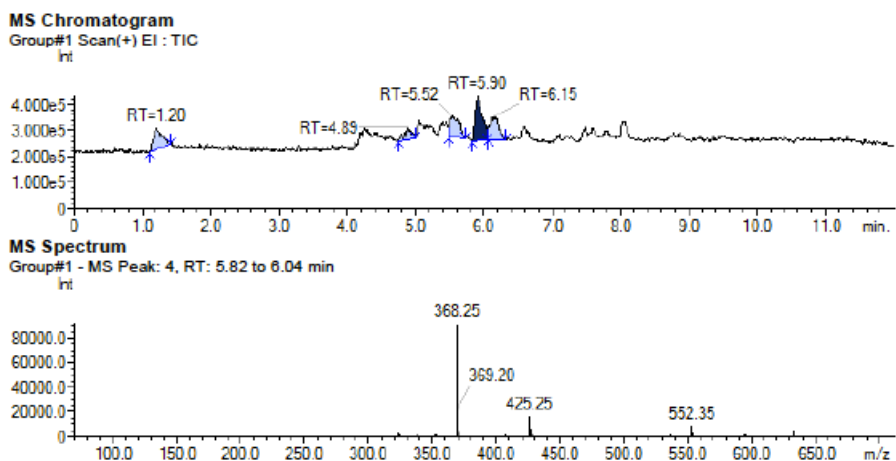
## HPLC chromatograms

For IDs for aminopyridines (P), aldehydes (A) and isocyanides (I), see page S5.

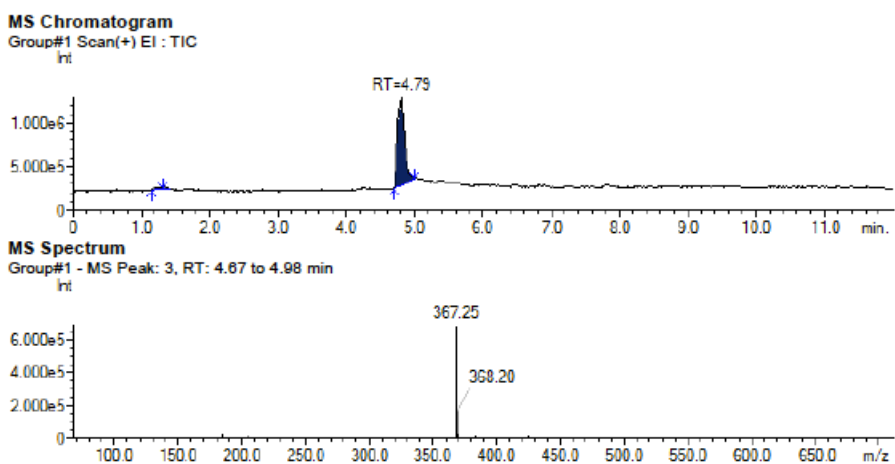
Compound {12, 5, 6}



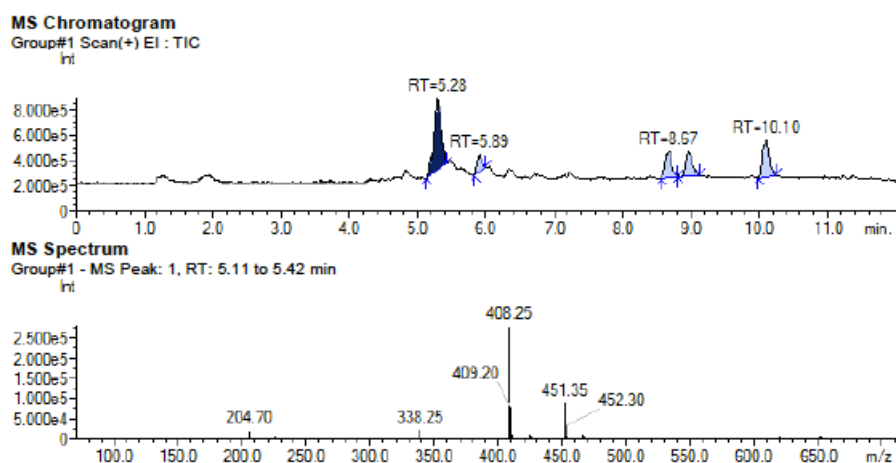
Compound {7, 5, 6}



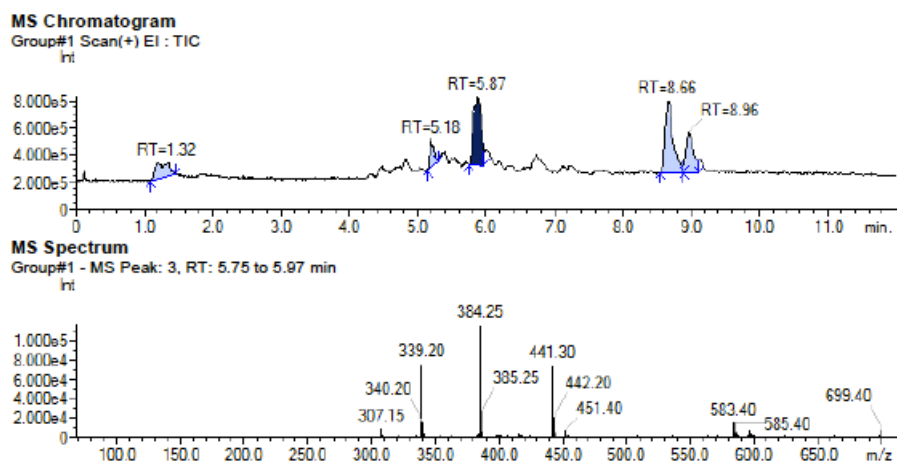
Compound {9, 5, 6}



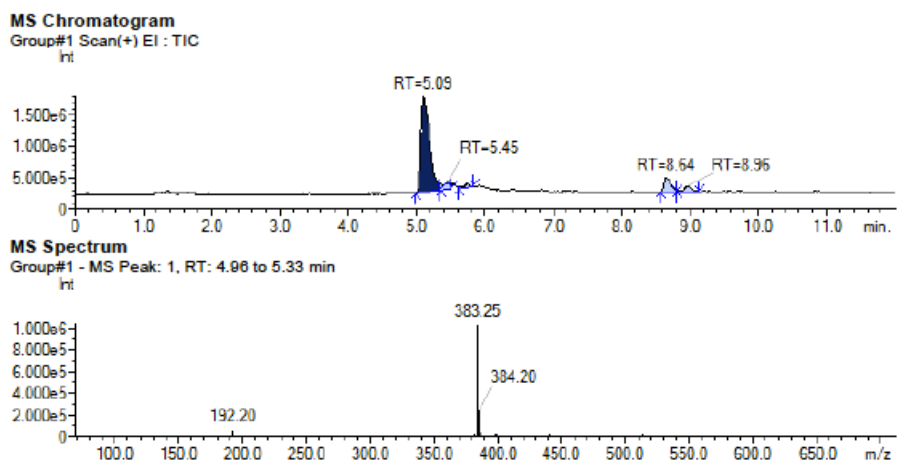
### Compound {12, 5, 17}



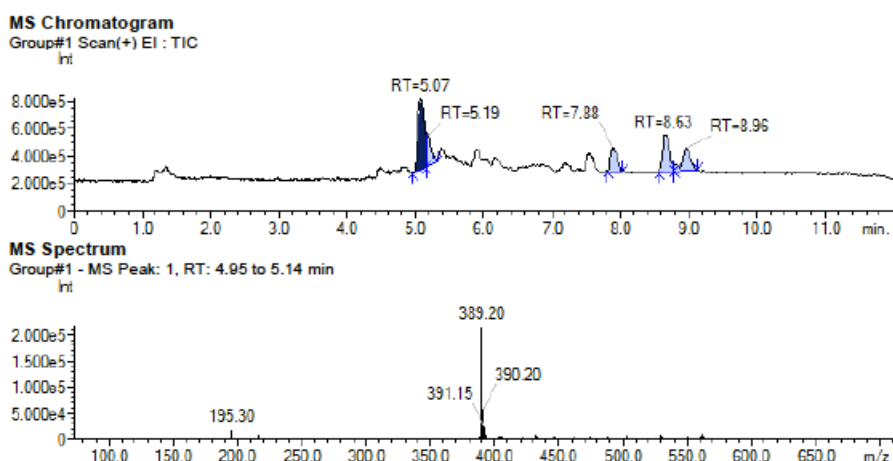
### Compound {7, 5, 17}



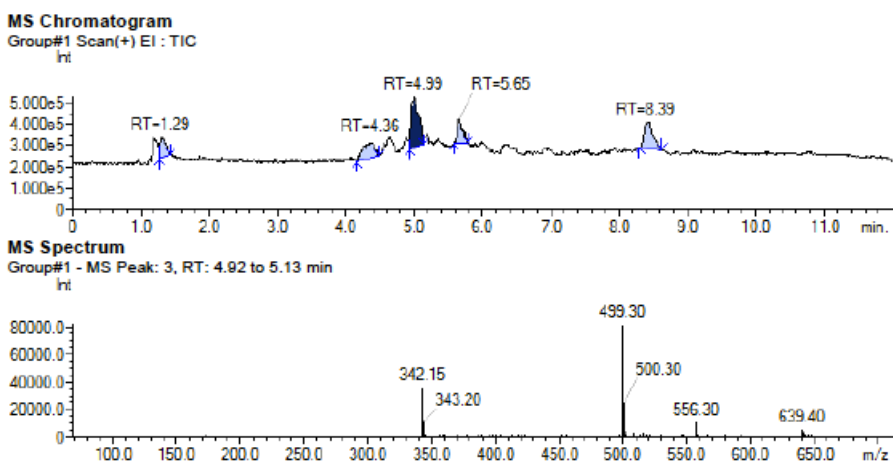
### Compound {9, 5, 17}



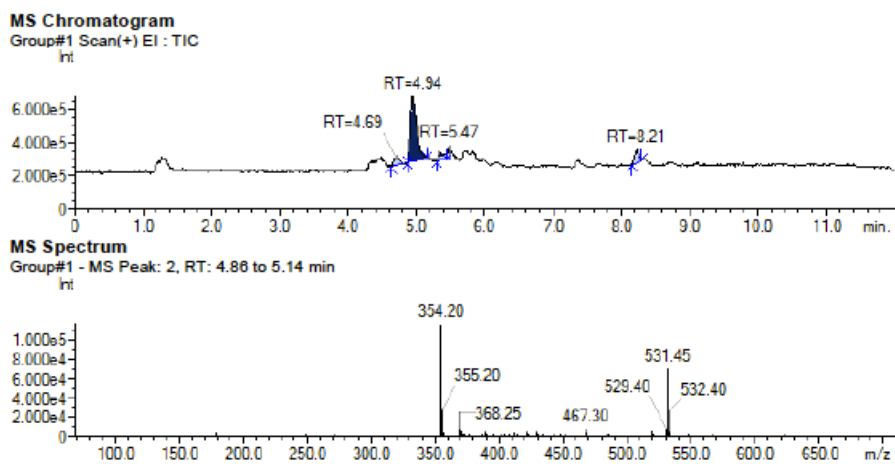
### Compound {5, 5, 17}



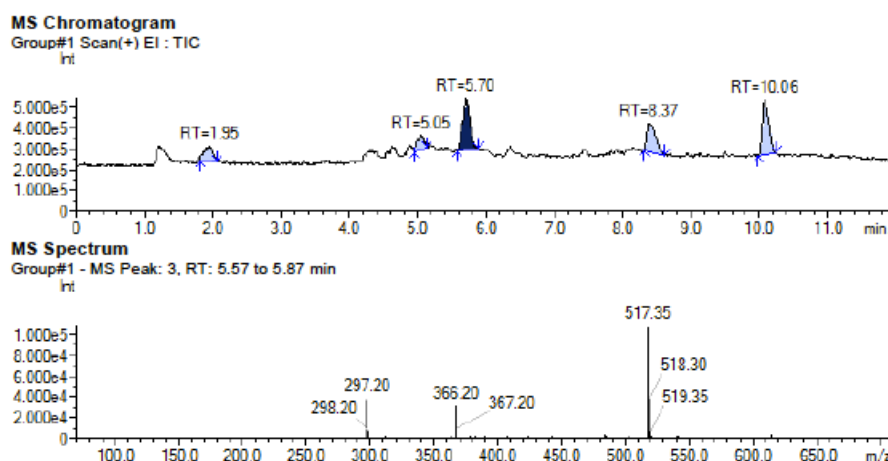
### Compound {8, 5, 19}



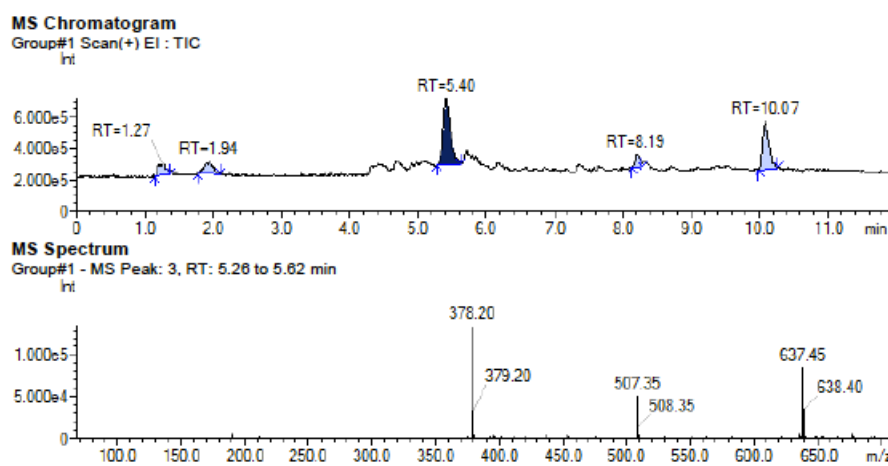
### Compound {8, 5, 8}



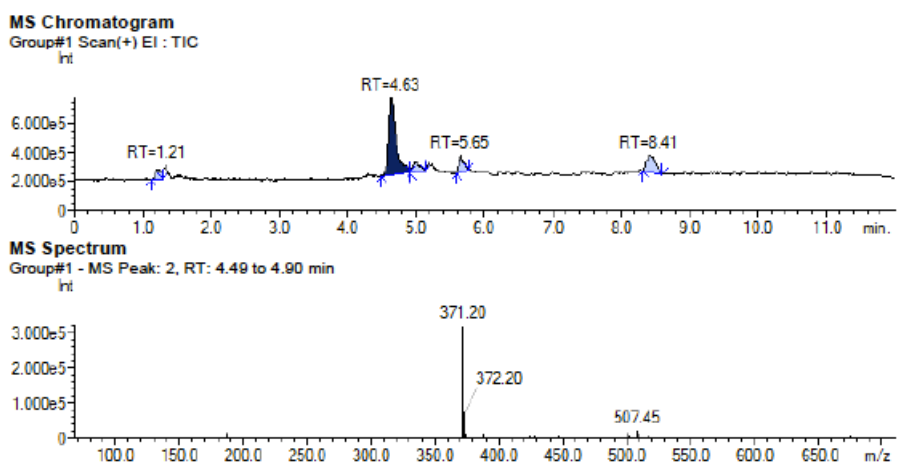
Compound {12, 5, 19}



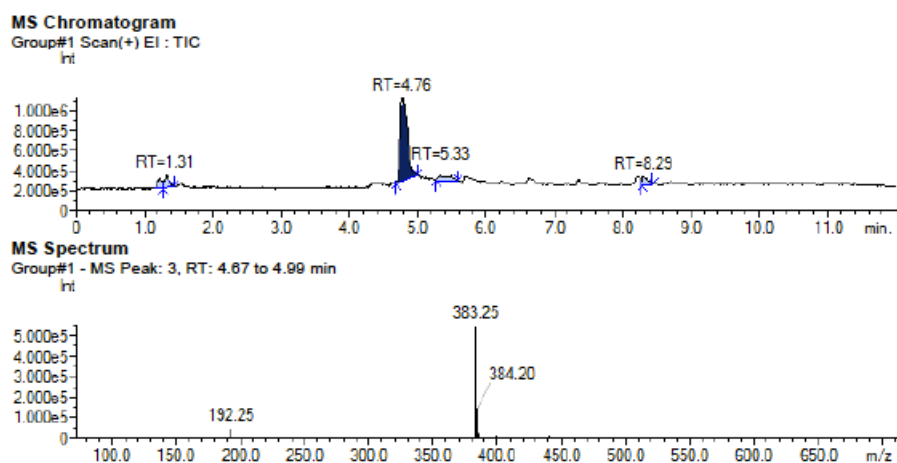
Compound {12, 5, 8}



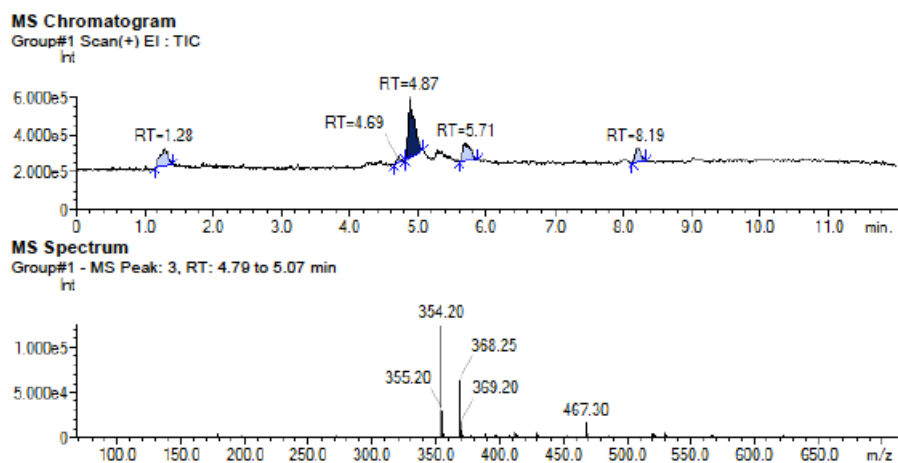
Compound {10, 5, 19}



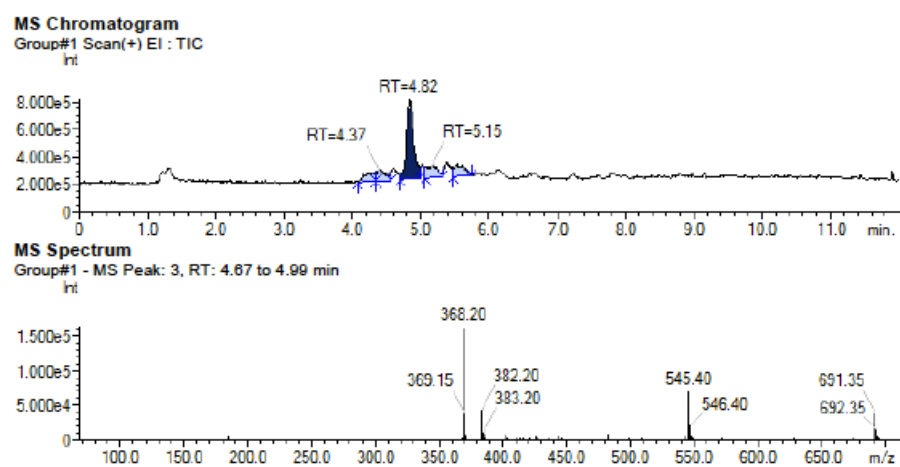
### Compound {10, 5, 8}



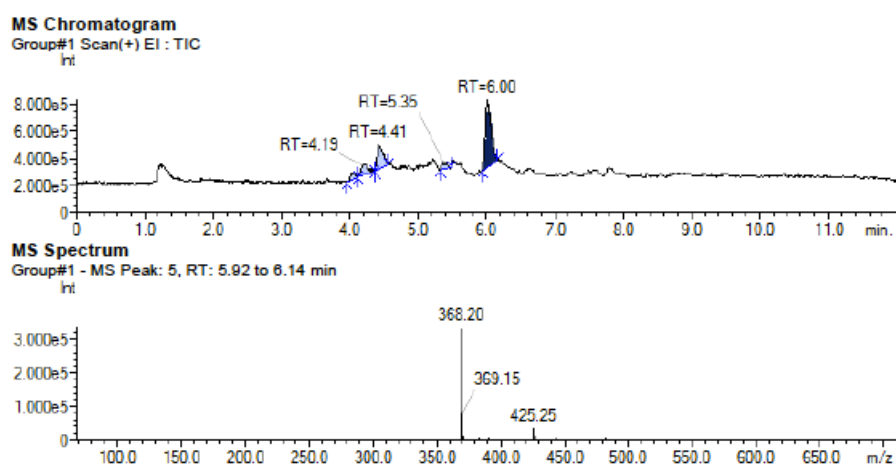
### Compound {8, 5, 25}



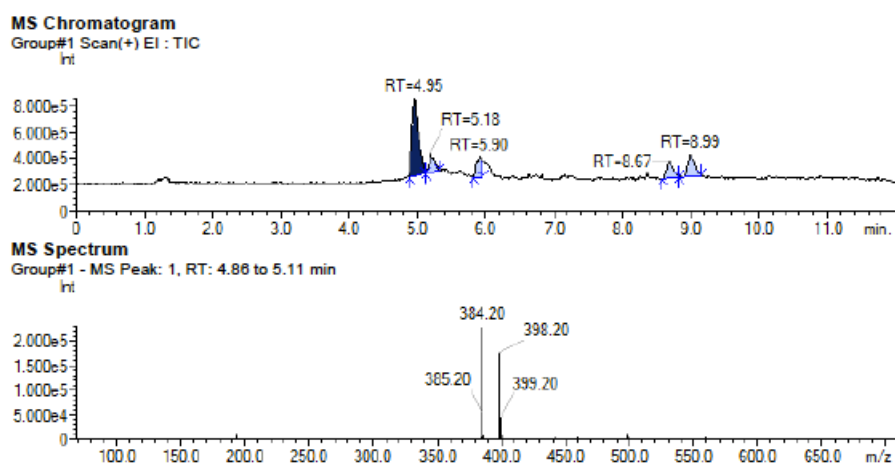
### Compound {8, 5, 6}



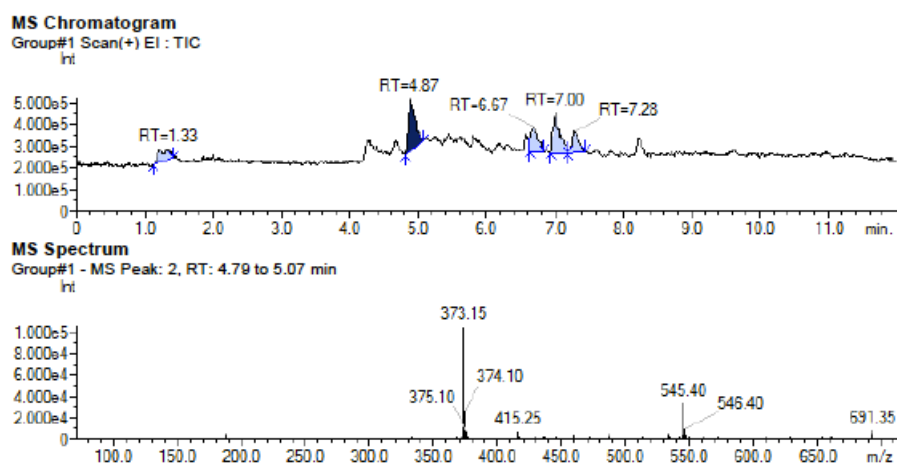
### Compound {6, 5, 6}



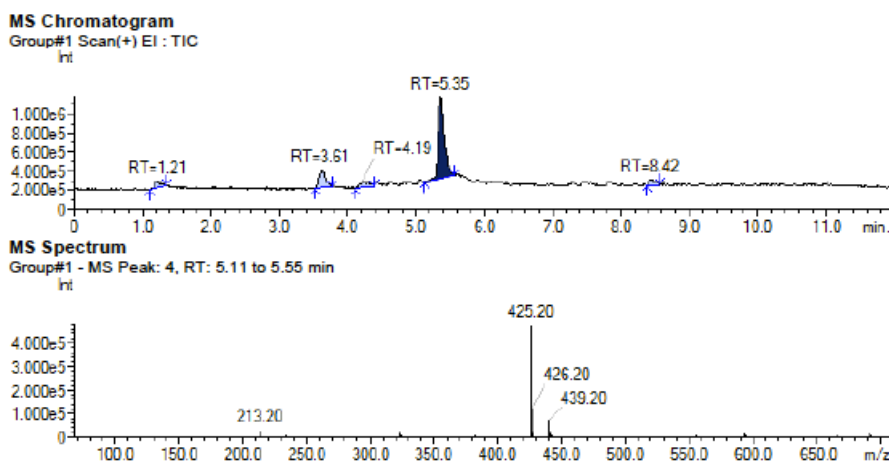
### Compound {8, 5, 17}



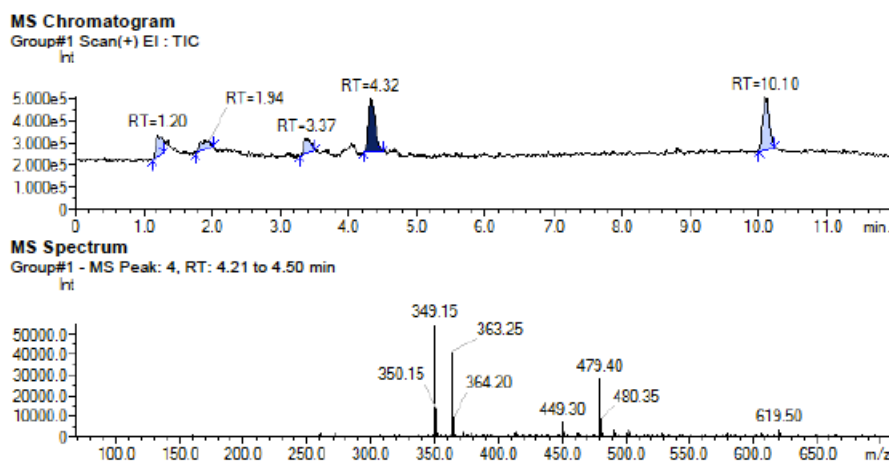
### Compound {5, 5, 6}



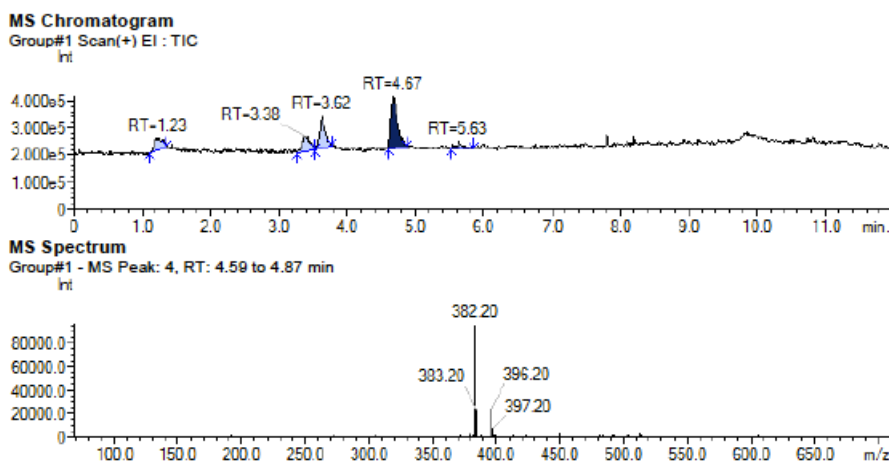
### Compound {2, 5, 6}



### Compound {12, 5, 5}

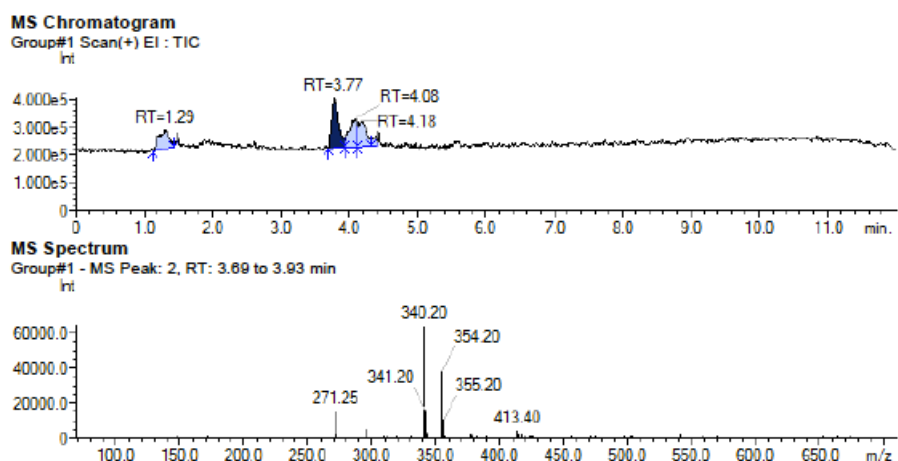


### Compound {2, 5, 5}

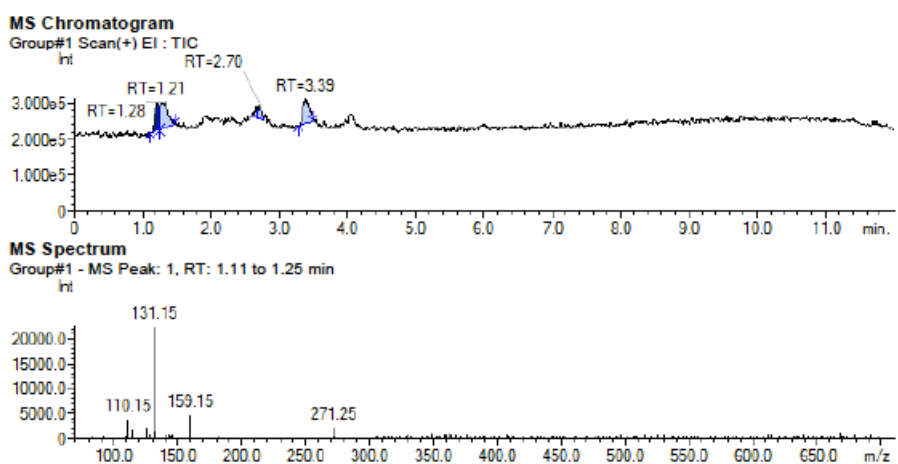




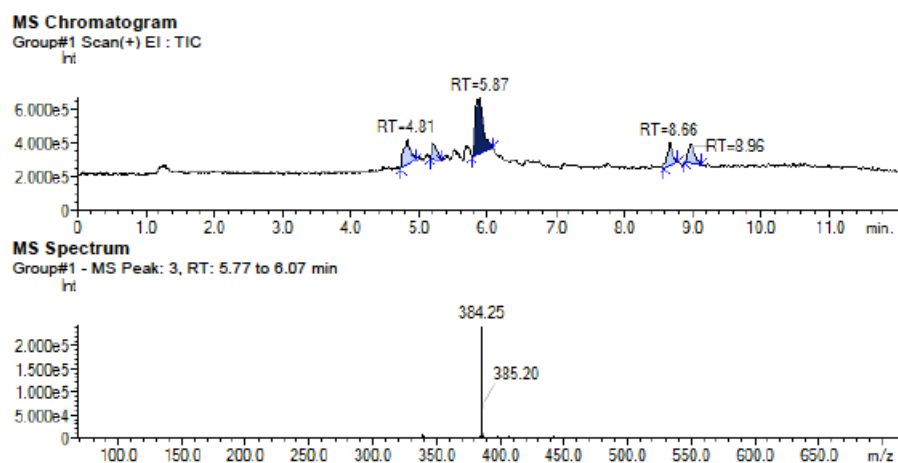
### Compound {8, 5, 24}



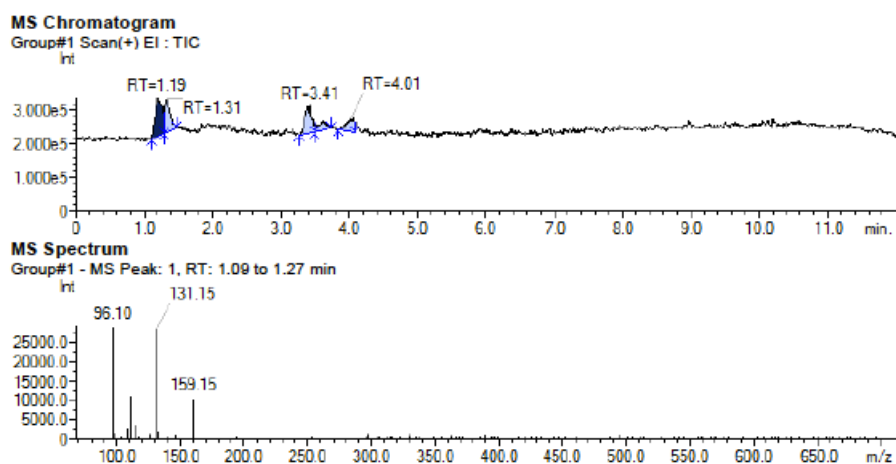
### Compound {8, 5, 5}



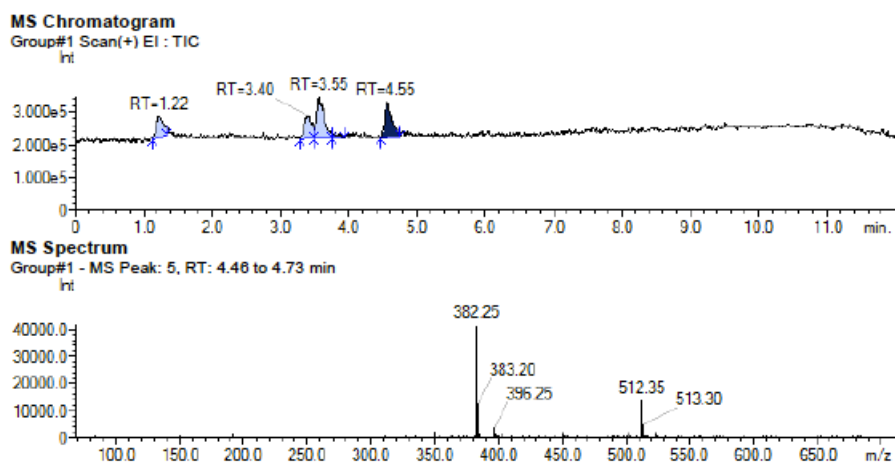
### Compound {6, 5, 17}



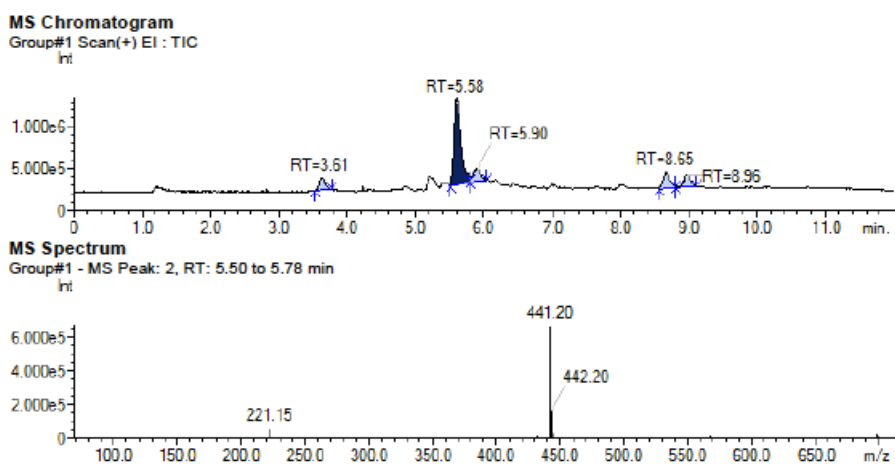
### Compound {7, 5, 5}



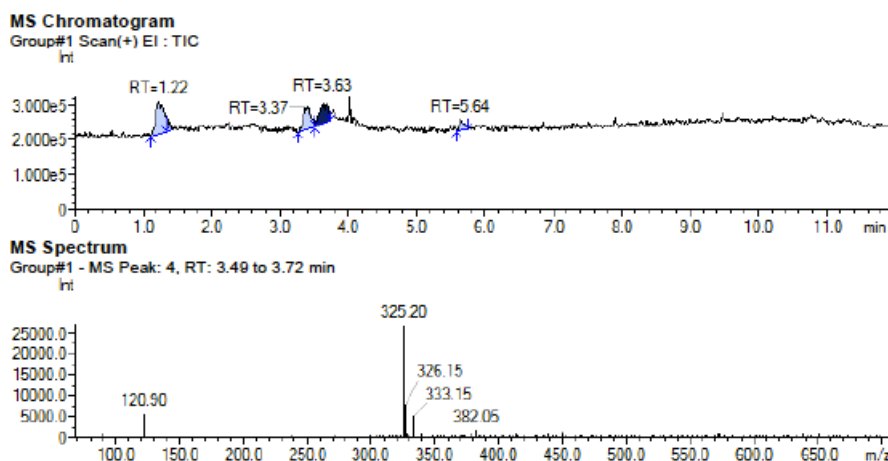
### Compound {3, 5, 5}



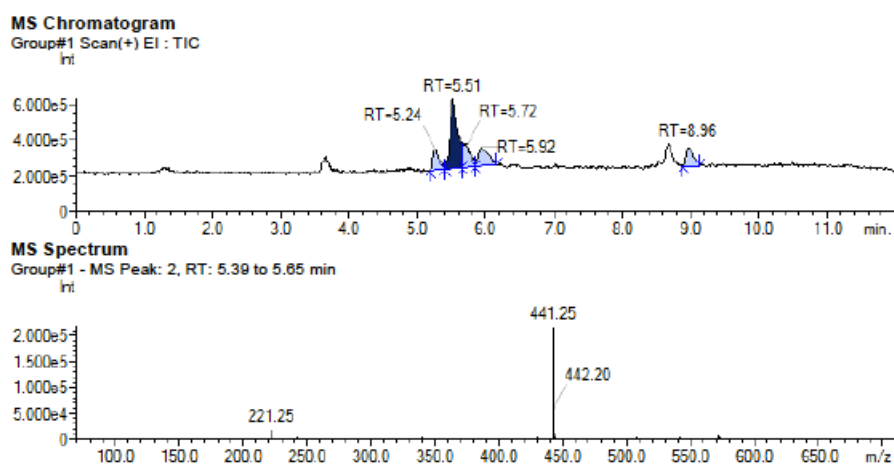
### Compound {2, 5, 17}



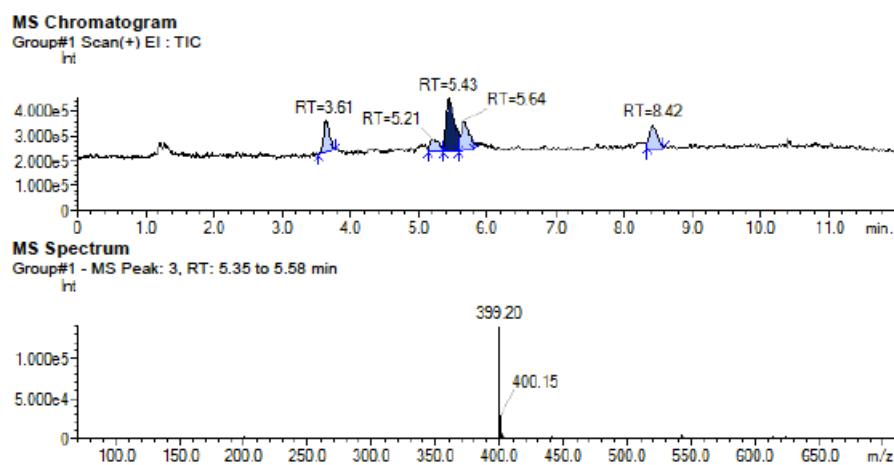
Compound {6, 5, 5}



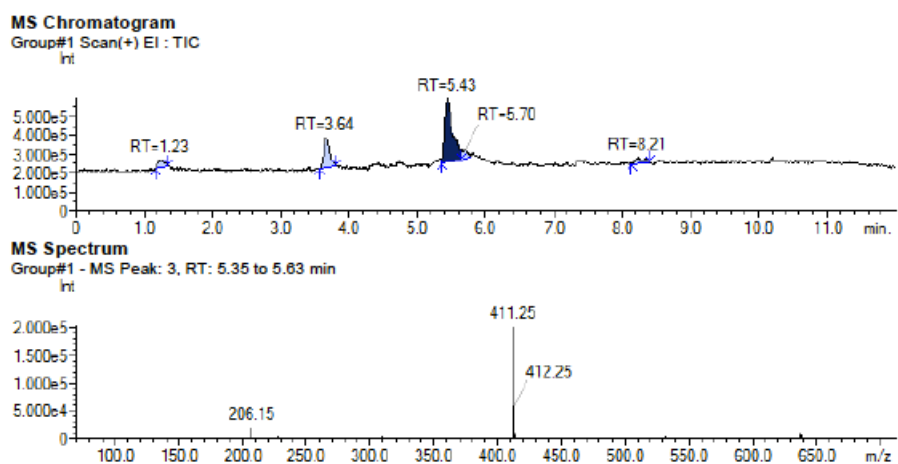
Compound {3, 5, 17}



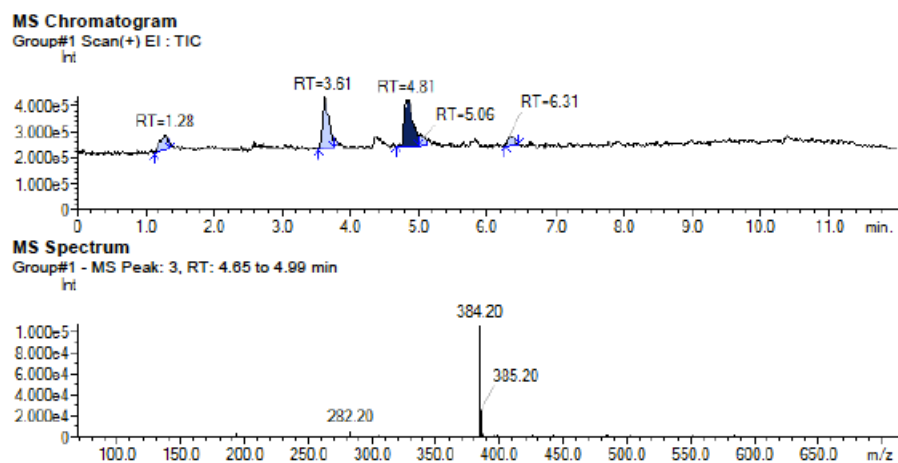
Compound {2, 5, 19}



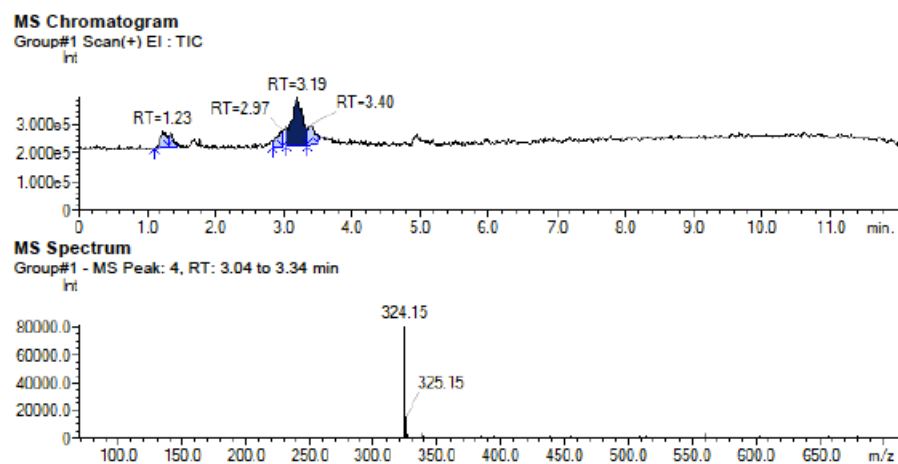
### Compound {2, 5, 8}



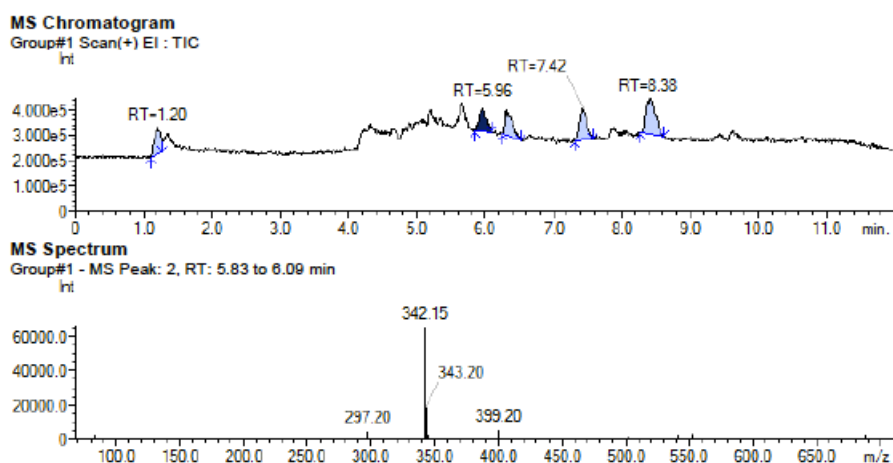
### Compound {2, 5, 13}



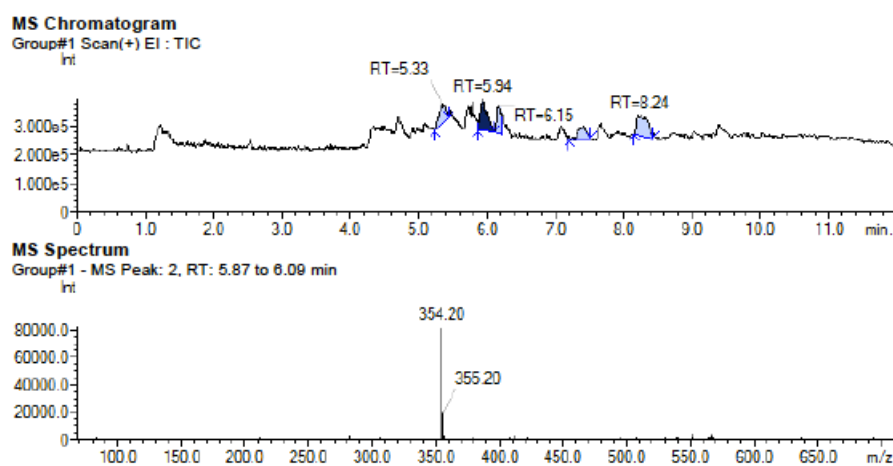
### Compound {9, 5, 5}



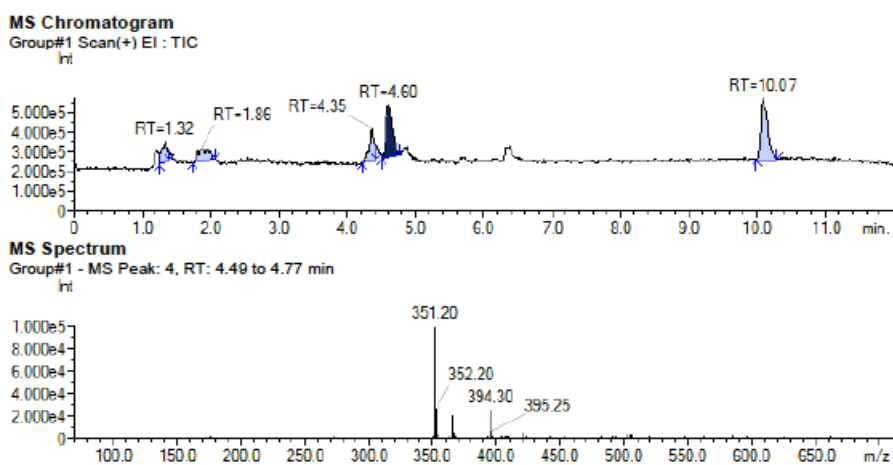
Compound {7, 5, 19}



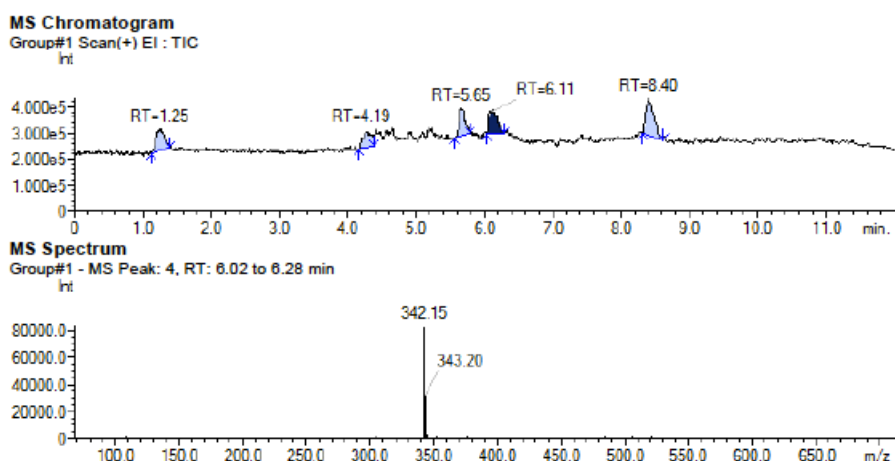
Compound {7, 5, 8}



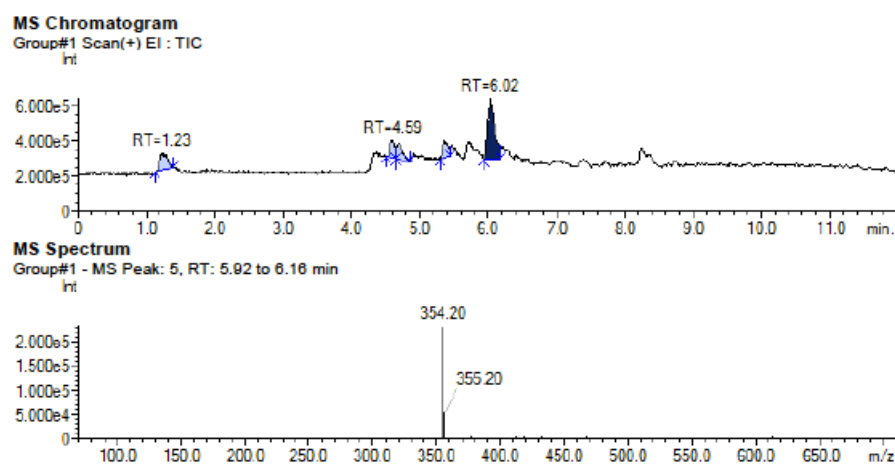
Compound {12, 5, 13}



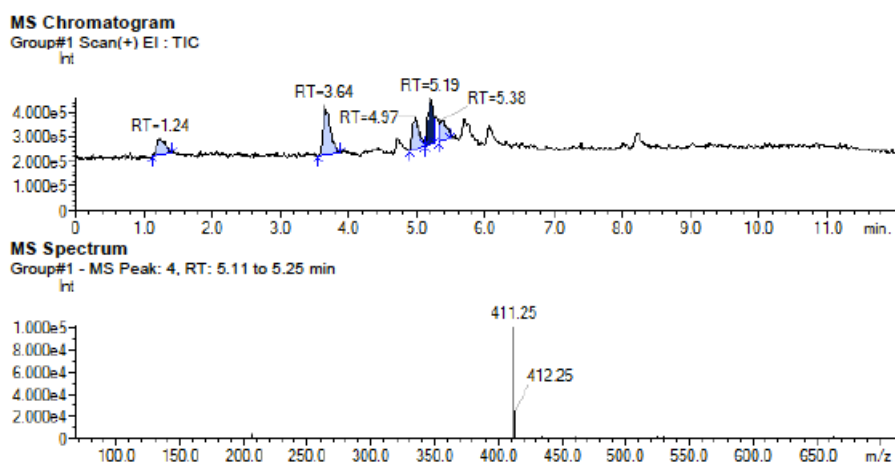
### Compound {6, 5, 19}



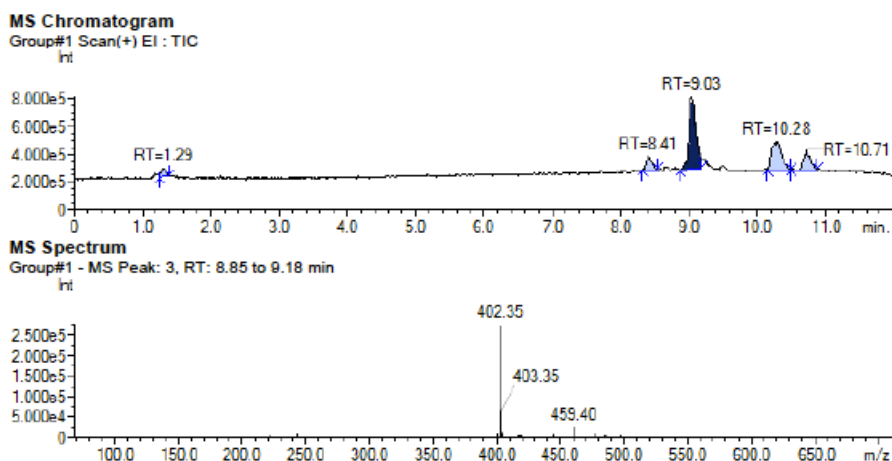
### Compounds {6, 5, 8}



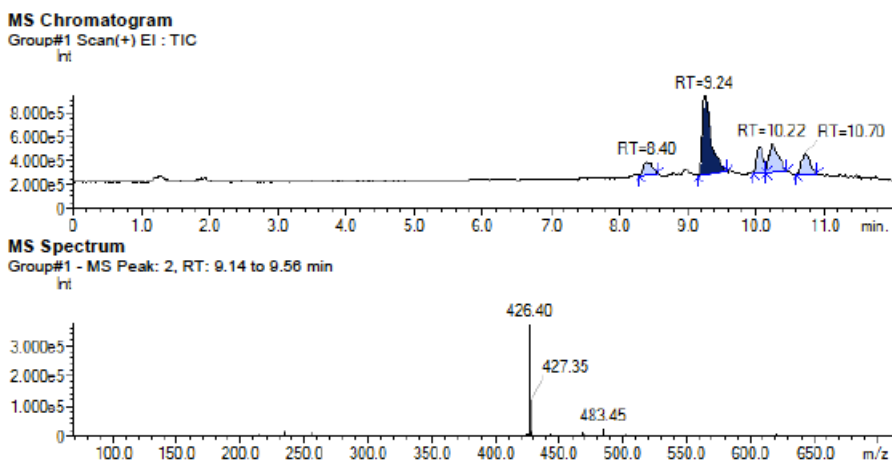
### Compounds {1, 5, 25}



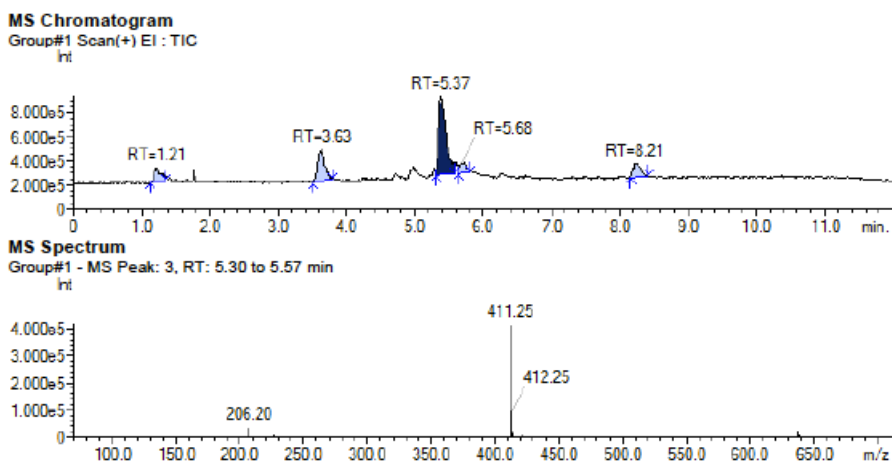
Compounds {8, 5, 27}



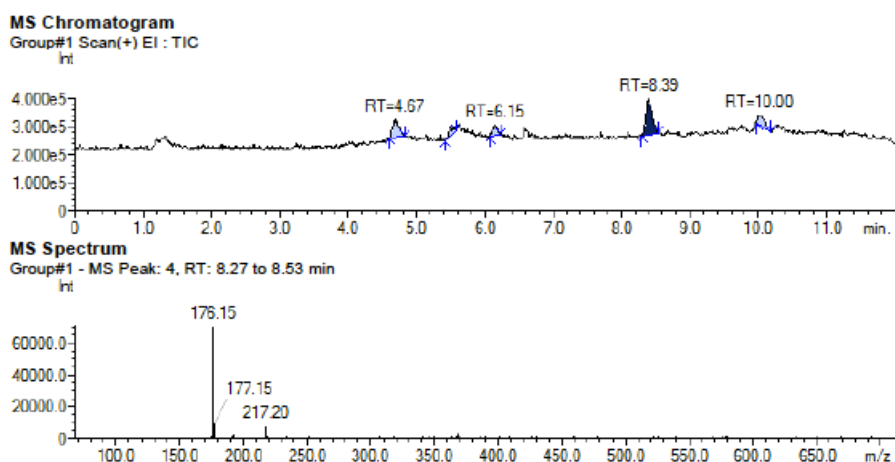
Compound {12, 5, 27}



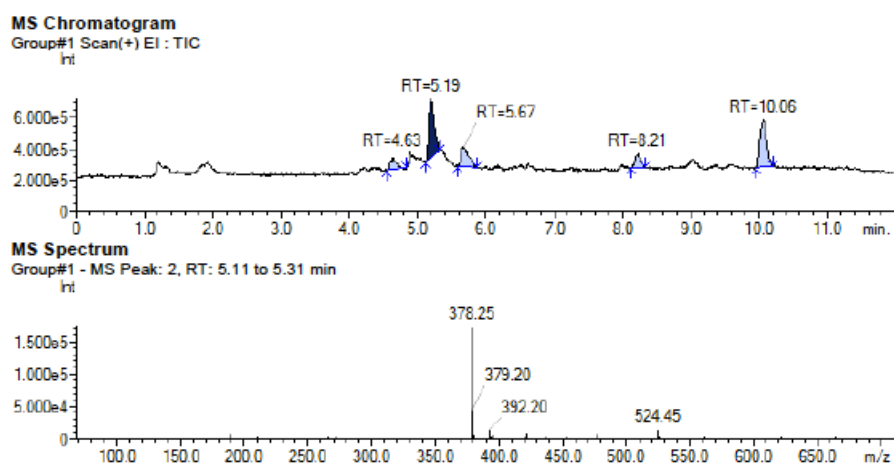
Compound {2, 5, 25}



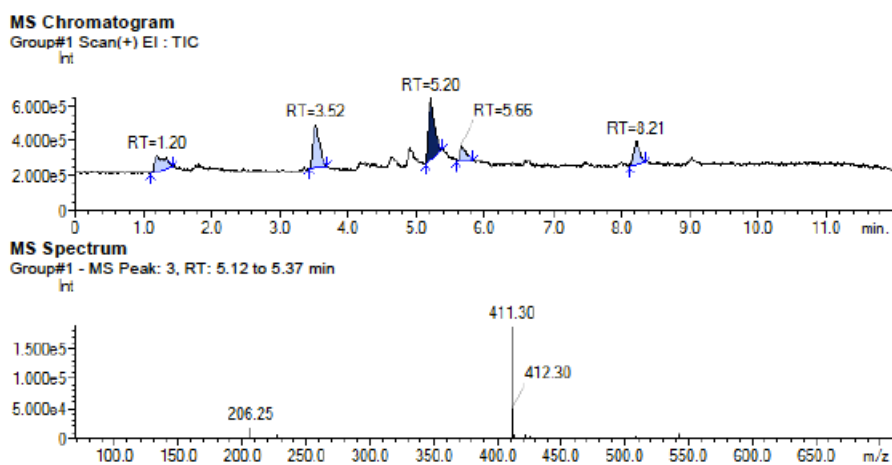
Compound {8, 5, 31}



Compound {12, 5, 25}

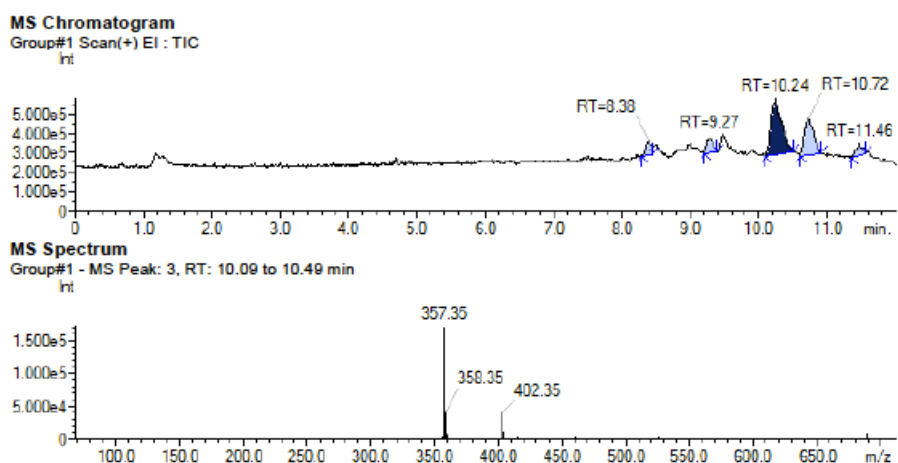


Compound {3, 5, 25}

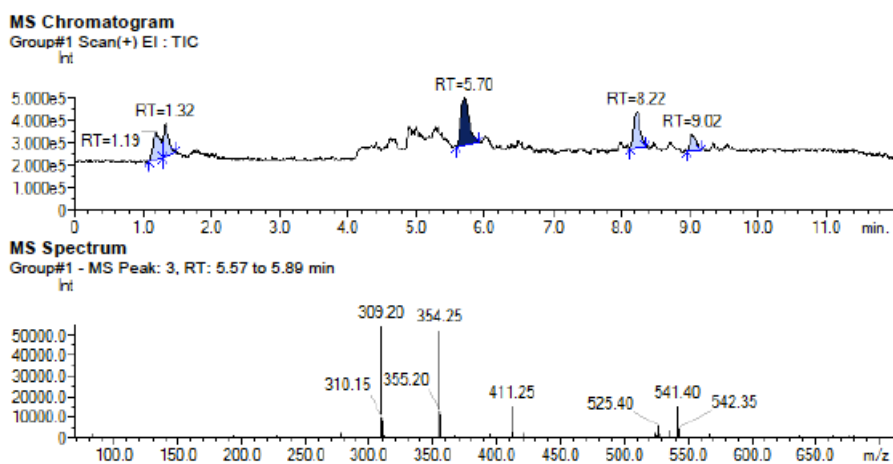




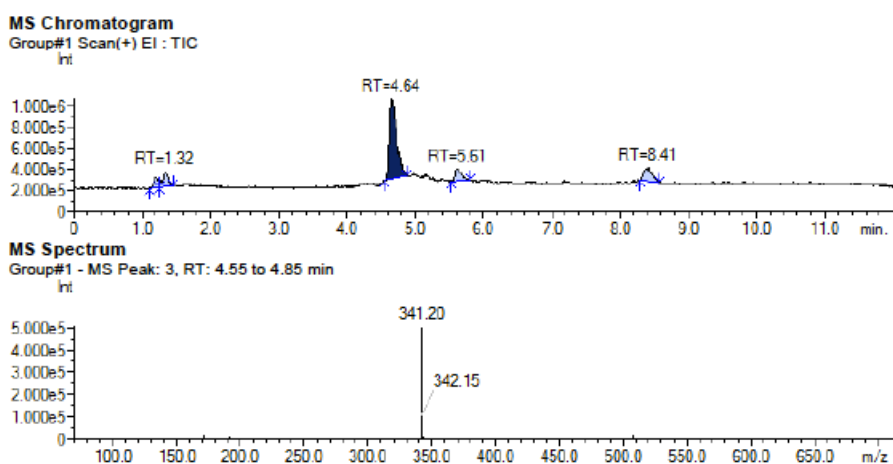
### Compound {7, 5, 27}



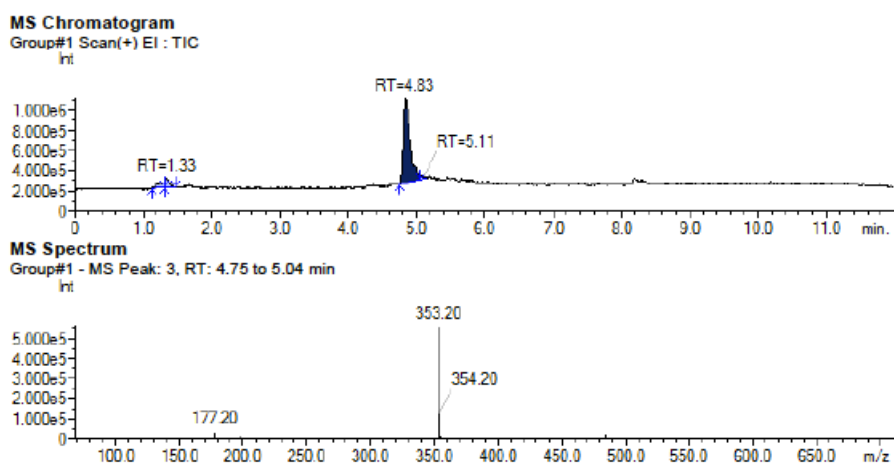
### Compound {7, 5, 25}



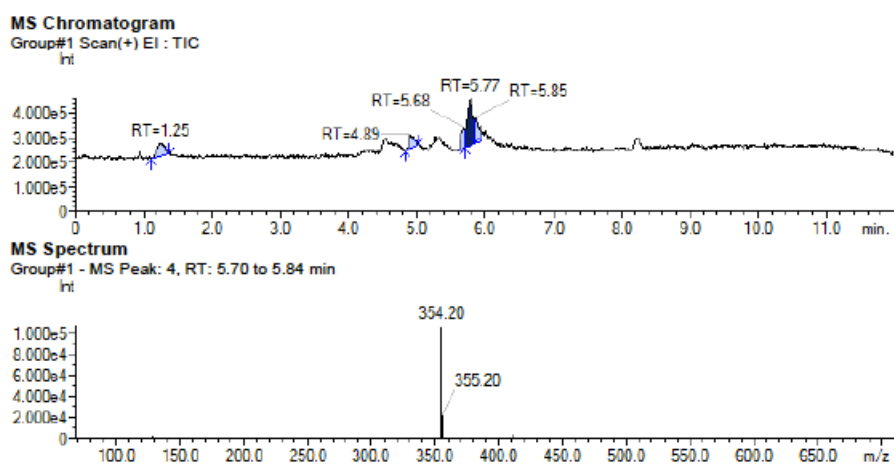
### Compound {9, 5, 19}



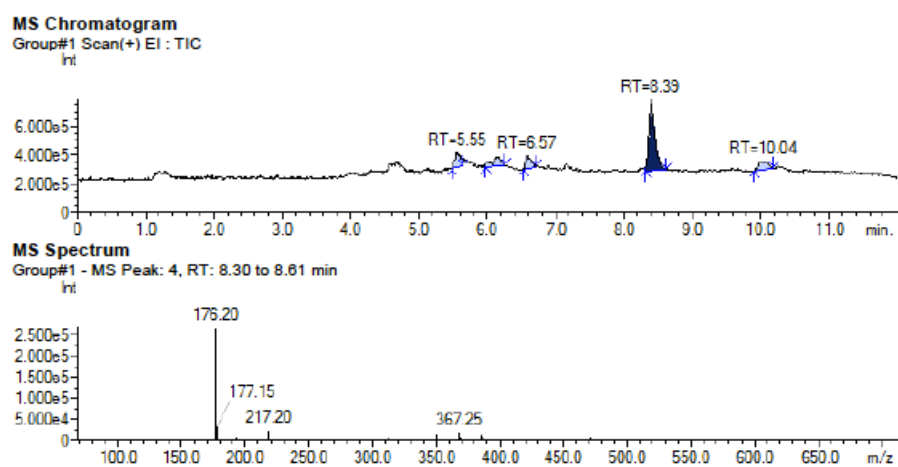
### Compound {9, 5, 8}



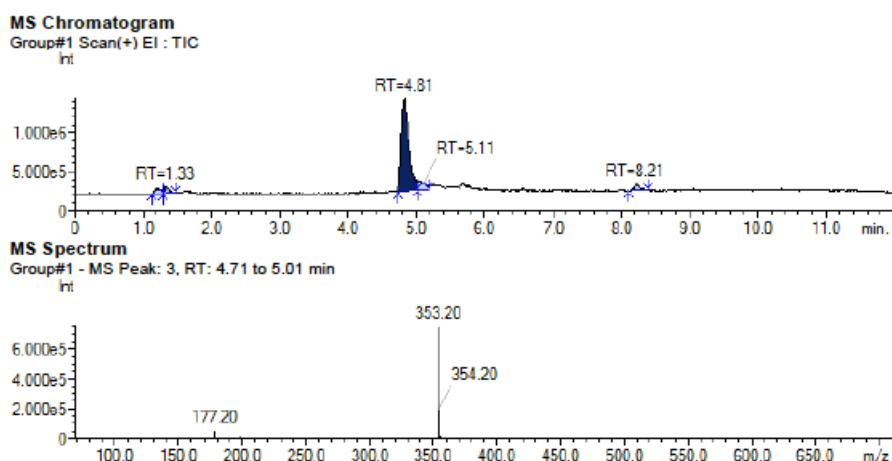
### Compound {6, 5, 25}



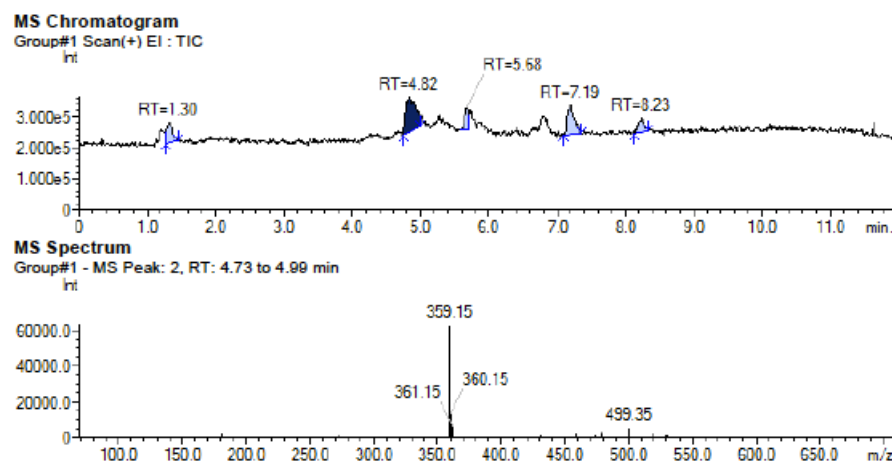
### Compound {7, 5, 32}



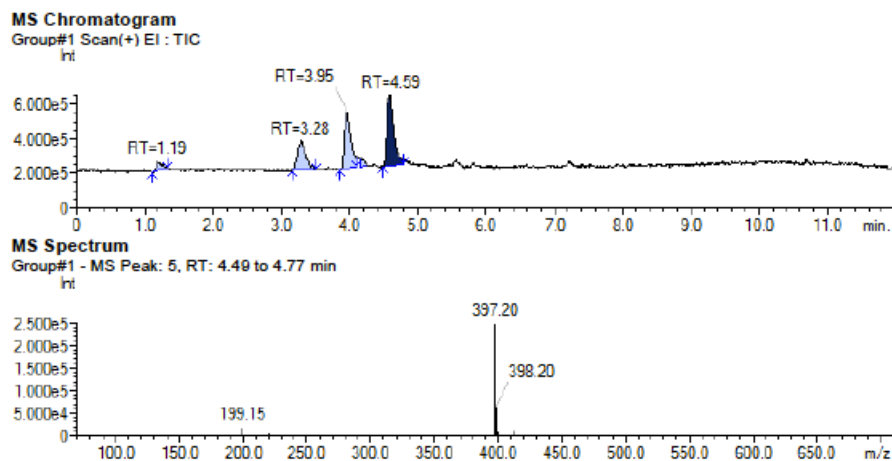
Compound {9, 5, 25}



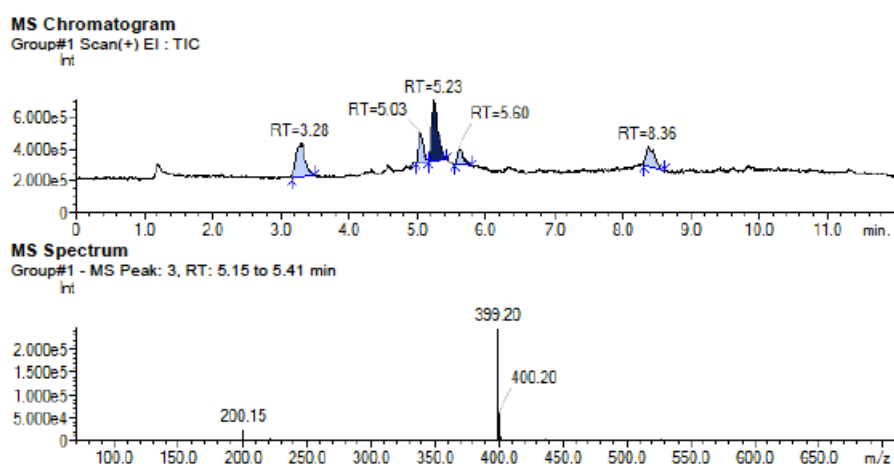
Compound {5, 5, 25}



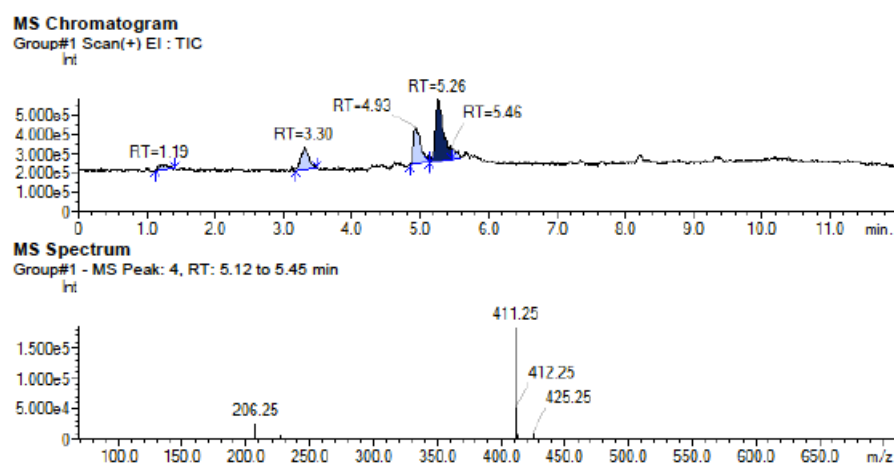
Compound {4, 5, 24}



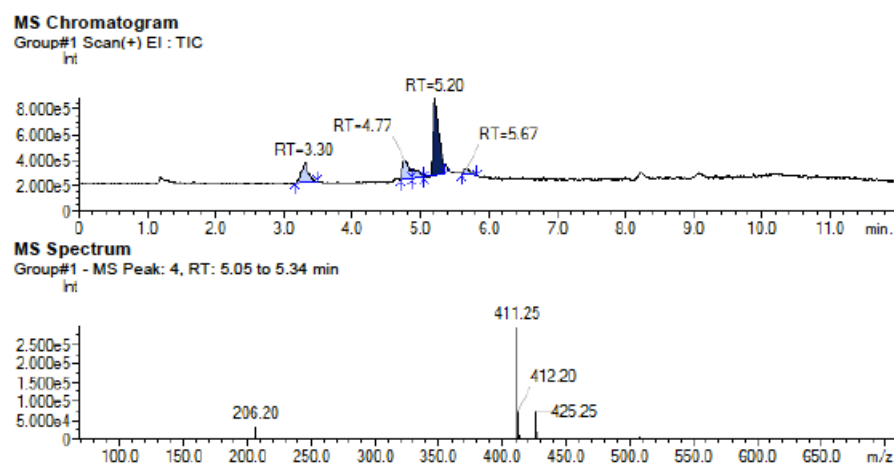
### Compound {4, 5, 19}



### Compound {4, 5, 8}



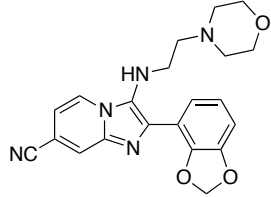
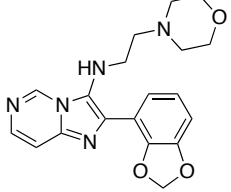
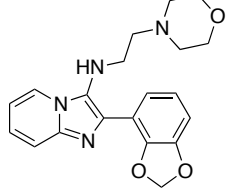
### Compound {4, 5, 25}



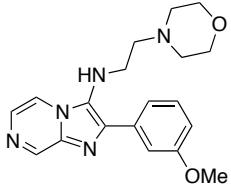
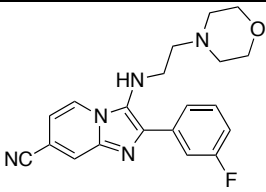
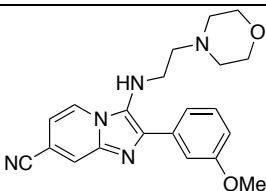
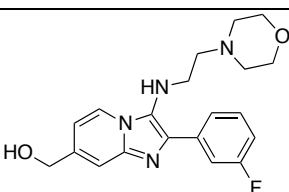
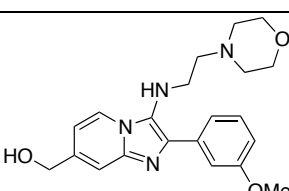
### Preliminary screening data and IC<sub>50</sub> values – PI3K $\alpha$

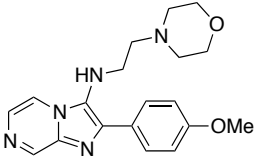
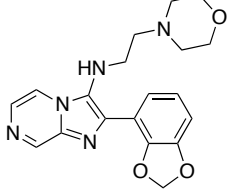
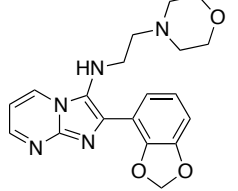
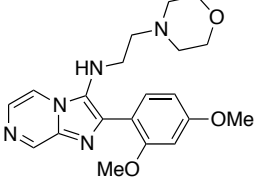
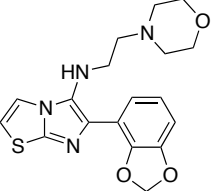
All compounds were tested in a single-dose duplicate at 75  $\mu$ M. The control compound PI-103 was tested in 10-dose IC<sub>50</sub> with 3-fold serial dilution starting at 10  $\mu$ M. All reactions were carried out at 10  $\mu$ M ATP.<sup>3</sup>

**Table 1.** Screening data for selected compounds.

Entry	Compound (P, I, A)	Structure	Screening assay		IC <sub>50</sub> / $\mu$ M	Compound ID in manuscript
			Measurement 1	Measurement 2		
1	12, 5, 6		95.04	93.30	N.T.	
2	7, 5, 6		N.T.	N.T.	N.T.	
3	9, 5, 6		76.32	68.66	>600	3

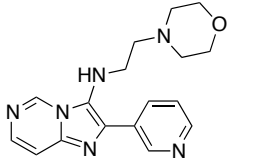
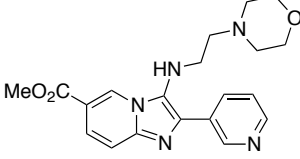
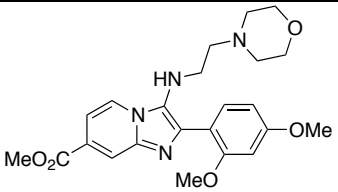
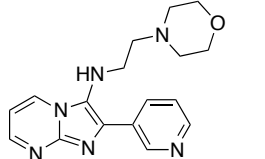
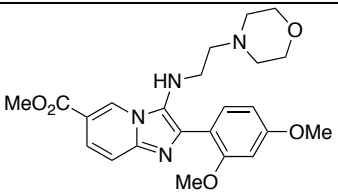
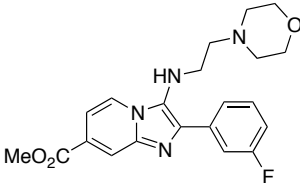
4	12, 5, 17		80.45	92.15	N.T.	
5	7, 5, 17		75.37	85.05	N.T.	
6	9, 5, 17		99.04	99.08	N.T.	
7	5, 5, 17		78.37	89.63	N.T.	
8	8, 5, 19		92.64	106.94	N.T.	

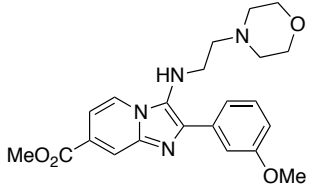
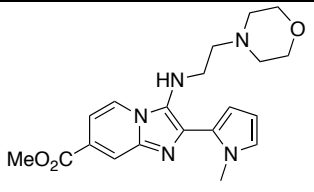
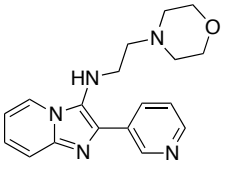
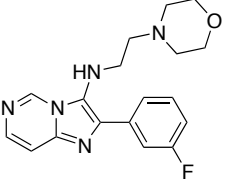
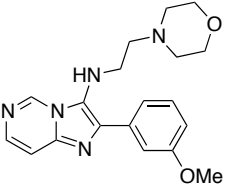
<b>9</b>	8, 5, 8		99.16	82.95	N.T.	
<b>10</b>	12, 5, 19		106.96	87.53	N.T.	
<b>11</b>	12, 5, 8		82.38	83.86	N.T.	
<b>12</b>	10, 5, 19		90.10	80.91	N.T.	
<b>13</b>	10, 5, 8		69.98	84.82	N.T.	

14	8, 5, 25		92.14	91.08	N.T.	
15	8, 5, 6		84.27	94.90	N.T.	
16	6, 5, 6		84.80	95.92	N.T.	
17	8, 5, 17		86.91	84.64	N.T.	
18	5, 5, 6		74.78	79.95	N.T.	

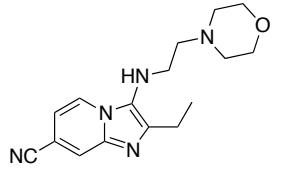
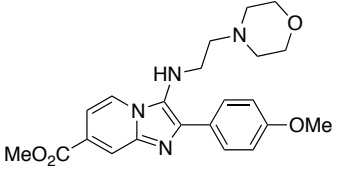
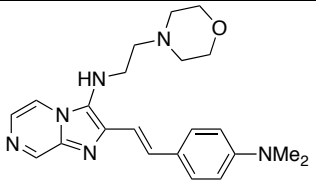
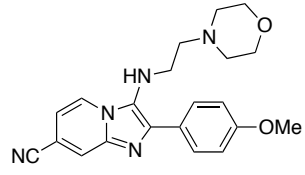
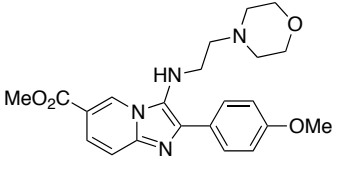
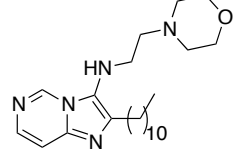


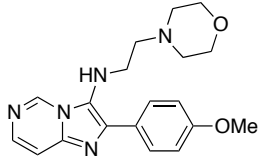
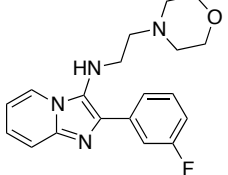
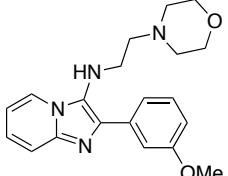
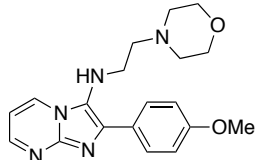
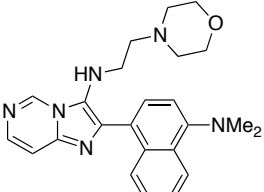
19	2, 5, 6		92.97	97.26	N.T.	
20	12, 5, 5		81.51	86.18	N.T.	
21	2, 5, 5		76.90	78.92	N.T.	
22	8, 5, 24		109.52	90.00	N.T.	
23	8, 5, 5		N.T.	N.T.	N.T.	
24	6, 5, 17		108.51	104.74	N.T.	

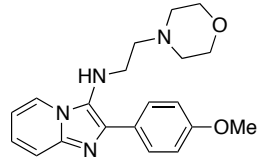
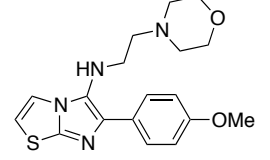
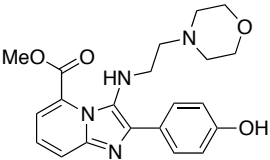
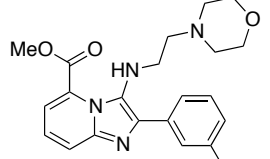
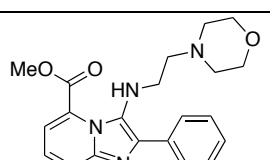
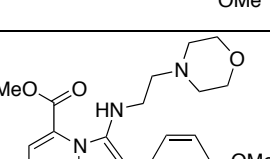
25	7, 5, 5		N.T.	N.T.	N.T.	
26	3, 5, 5		100.18	84.87	N.T.	
27	2, 5, 17		109.20	110.36	N.T.	
28	6, 5, 5		N.T.	N.T.	N.T.	
29	3, 5, 17		61.67	75.44	600	4
30	2, 5, 19		65.38	66.73	>600	5

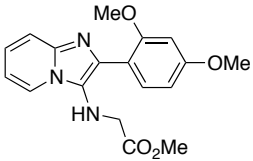
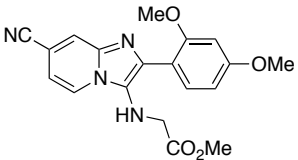
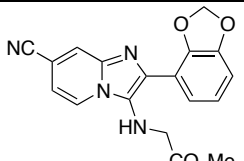
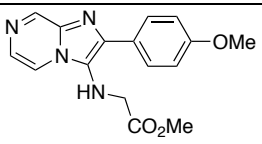
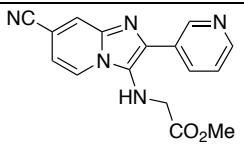
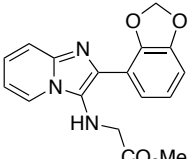
<b>31</b>	2, 5, 8		80.96	67.47	>600	<b>6</b>
<b>32</b>	2, 5, 13		68.57	78.46	232	<b>2</b>
<b>33</b>	9, 5, 5		86.08	76.21	N.T.	
<b>34</b>	7, 5, 19		N.T.	N.T.	N.T.	
<b>35</b>	7, 5, 8		N.T.	N.T.	N.T.	

36	12, 5, 13		93.60	83.34	N.T.	
37	6, 5, 19		100.44	96.85	N.T.	
38	6, 5, 8		89.43	105.98	N.T.	
39	1, 5, 25		70.70	73.69	>600	7
40	8, 5, 27		N.T.	N.T.	N.T.	

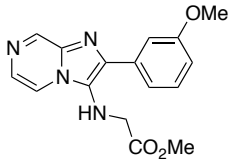
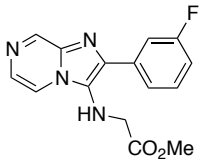
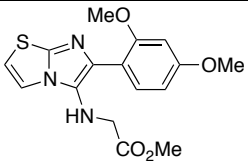
41	12, 5, 27		N.T.	N.T.	N.T.	
42	2, 5, 25		91.17	94.98	N.T.	
43	8, 5, 31		N.T.	N.T.	N.T.	
44	12, 5, 25		99.63	108.34	N.T.	
45	3, 5, 25		85.05	109.83	N.T.	
46	7, 5, 27		N.T.	N.T.	N.T.	

47	7, 5, 25		83.31	99.86	N.T.	
48	9, 5, 19		101.00	93.23	N.T.	
49	9, 5, 8		102.66	98.46	N.T.	
50	6, 5, 25		99.18	98.67	N.T.	
51	7, 5, 32		N.T.	N.T.	N.T.	

52	9, 5, 25		79.98	86.09	N.T.	
53	5, 5, 25		87.95	86.74	N.T.	
54	4, 5, 24		76.83	79.36	N.T.	
55	4, 5, 19		91.21	95.88	N.T.	
56	4, 5, 8		102.98	77.82	N.T.	
57	4, 5, 25		87.73	101.64	N.T.	

<b>58</b>	9, 4, 17		N.T.	N.T.	131	<b>1</b>
<b>59</b>	12, 4, 17		N.T.	N.T.	232	<b>8</b>
<b>60</b>	12, 4, 6		N.T.	N.T.	>600	<b>9</b>
<b>61</b>	8, 4, 25		N.T.	N.T.	>600	<b>10</b>
<b>62</b>	12, 4, 5		N.T.	N.T.	>600	<b>11</b>
<b>63</b>	9, 4, 6		N.T.	N.T.	>600	<b>12</b>



<b>64</b>	8, 4, 8		N.T.	N.T.	289	<b>13</b>
<b>65</b>	8, 4, 19		N.T.	N.T.	>600	<b>14</b>
<b>66</b>	5, 4, 17		N.T.	N.T.	157	<b>15</b>

N.T. – Not tested; PI-103 presented an IC<sub>50</sub> value of 4.05 nM under the assayed conditions.

## References

1. Burchak, O. N.; Mugheri, L.; Ostuni, M.; Lacapère, J. J.; Balakirev, M. Y. *J. Am. Chem. Soc.* **2011**, *133*, 10058-10061.
2. Bienaymé, H.; Bouzid, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2234-2237.
3. Anastassiadis, T.; Deacon, S. W.; Devarajan, K.; Ma, H.; Peterson, R. J. *Nat. Biotechnol.* **2011**, *29*, 1039-1045.