## Supporting Information

# Thiazolylpyrazoles as ΔF508-CFTR Correctors with Improved Hydrophilicity Compared to Bithiazoles

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**10a**: summary of data CCDC 767034
Formula: C18 H24 N4 O3 S1
Unit cell parameters: a 10.2685(15) b 11.2542(17) c 17.123(3)
alpha 72.768(2) beta 88.794(2) gamma 88.903(2)
space group P-1

**9f**: summary of data CCDC 767035
Formula: C21 H23 Br1 N4 O3 S1
Unit cell parameters: a 10.0372(4) b 20.6057(8) c 11.0875(4) beta 107.7350(10)
space group P21/c

**Table 1.** Calculated and extrapolated logP values of active thiazolylpyrazoles **11d**/**14a**/**14b**/**14e**/**14g**/**14h**/**14j** and the bithiazole **1**.

| compound | logP | clogP*[a] | relative difference (%)*[b] |
|---|---|---|---|
| 11d | 5.52 | 5.61 | 1.63593 |
| 14a | 4.75 | 4.17 | 12.28250 |
| 14b | 4.53 | 3.82 | 15.58325 |
| 14e | 5.1 | 4.77 | 6.32385 |
| 14g | 5.70 | 5.78 | 1.42973 |
| 14h | 4.26 | 4.12 | 3.19175 |
| 14j | 3.46 | 3.40 | 1.61200 |
| 1 | 5.71 | 5.6 | 1.91409 |

*[a] calculated with ChemDraw ultra 11(Cambridge Software)

*[b] Relative difference=[Absolute value of (logP-clogP)]/logP

**Table 2.** Logk and logP values of reference compounds (used to establish the logP vs. logk trendline) and thiazolylpyrazole correctors.

| Compound | T1*[a] | (T1-T0)*[b] | logk*[c] | logP |
|---|---|---|---|---|
| **4-chloro-Phenol** | 20.10 | 17.08 | 0.752 | 2.4*[d] |
| **2,4-dichloro-Phenol** | 22.16 | 19.14 | 0.802 | 3.21*[d] |
| **3,4,5-trichloro-Phenol** | 23.61 | 20.59 | 0.834 | 4.36*[d] |
| **pentachlorophenol** | 25.83 | 22.81 | 0.878 | 5.9*[d] |
| **p, p'-DDT** | 28.80 | 25.78 | 0.931 | 6.19*[d] |
| **11d** | 25.48 | 22.46 | 0.871 | 5.52*[e] |
| **14a** | 24.12 | 21.1 | 0.844 | 4.75*[e] |
| **14b** | 23.73 | 20.71 | 0.836 | 4.53*[e] |
| **14e** | 24.71 | 21.69 | 0.856 | 5.09*[e] |
| **14g** | 25.81 | 22.79 | 0.878 | 5.70*[e] |
| **14h** | 23.28 | 20.26 | 0.827 | 4.26*[e] |
| **17** | 22.00 | 18.98 | 0.798 | 3.46*[e] |
| **4a** | 25.83 | 22.81 | 0.878 | 5.71*[e] |
| **KBr** | 3.02 | 0.00 | | |

*[a] Retention time on RP-HPLC.

*[b] The difference between the retention time $T_1$ and the void time $T_0$, which is the retention time of KBr

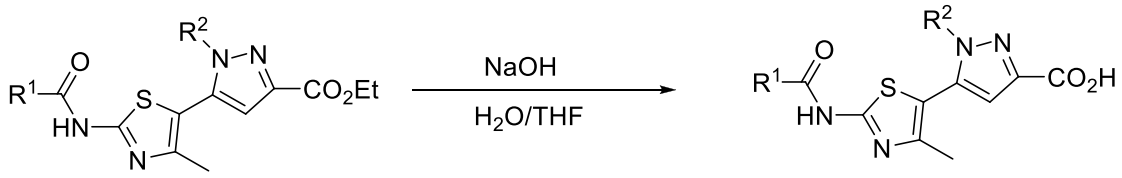
*[c] logk is the capacity factor, which equals to log $[(T_1-T_0)/T_0]$.

*[d] The logP value is found in reference 17.

*[e] The logP value is extrapolated from the trendline that was established based on the values of the reference compounds, the substituted phenols and p,p'-DDT. The equation of the trendline is y = 23.304x - 15.151 and the linear regression square $R^2 = 0.96$.

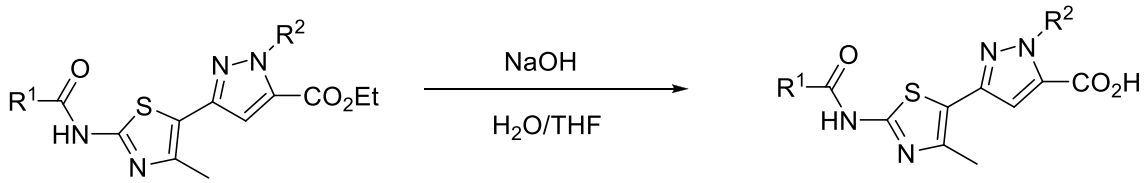
**Preparation of thiazolylpyrazole carboxylic acids.** None of the thiazolylpyrazole carboxylic acids are active in [$I^-$] influx cell assay. General procedure for the preparation of acids **12** and **15** as well as representative structural data.

**Scheme 1:**




**9** **12**

**Scheme 2:**




**10** **15**

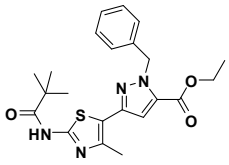
**General procedure of saponification of thiazolylpyrazole esters**: To a 0.2 M solution of the ester (**9** or **10**; 1 equivalent) in 1:1 $H_2O$/THF was added NaOH (4 equiv). The reaction mixture was stirred at room temperature for 24 h. When the reaction was complete, water, in the same volume as the reaction mixture, was added followed by concentrated HCl (dropwise) to adjust the pH to 3. The product, which precipitated, was collected by filtration and dried under vacuum. The $^1$H NMR, $^{13}$C NMR, and low resolution mass spectrometry data of representative acids **12** and **15** are listed below.

**1-(4-Bromophenyl)-5-(4-methyl-2-pivalamidothiazol-5-yl)-1H-pyrazole-3-carboxylic acid (12b).** Ester **9a** (R = H and $R^2$ = *p*-Br-Ph; 100 mg, 0.2 mmol) was reacted with NaOH (33 mg, 0.8 mmol) by the above general procedure and delivered **12b** as an off-white solid (76 mg, 81%). $^1$H NMR (600 MHz, DMSO) δ 13.12 (s, 1H), 12.00 (s, 1H), 7.69 (d, *J* = 8.8, 2H), 7.36 (d, *J* = 8.8, 2H), 7.05 (s, 1H), 2.02 (s, 3H), 1.21 (s, 9H); $^{13}$C NMR (151 MHz, DMSO) δ 177.58, 163.39, 159.33, 147.57, 145.49, 138.83, 136.07, 132.99, 127.60, 122.27, 112.92, 111.40, 104.99, 39.43, 27.15, 16.22; LC/MS(ESI): cal. [M+H$^+$] = 463.04 and [M+2+H$^+$] = 465.04, found 462.93 and 464.98.

**1-Allyl-3-(4-methyl-2-pivalamidothiazol-5-yl)-1H-pyrazole-5-carboxylic acid (15b).** Ester **10a** (R = H and $R^2$ = allyl; 95 mg, 0.25 mmol) was reacted with NaOH (40 mg, 1.0 mmol) by the above general procedure and delivered **15b** as an off-white solid (79 mg, 90%). $^1$H NMR (600 MHz, DMSO) δ 13.60 (s, 1H), 11.78 (s, 1H), 6.97 (s, 1H), 6.00 (ddd, *J* = 5.5, 10.6, 22.5, 1H), 5.13 (dd, *J* = 3.6, 15.5, 3H), 4.98 (dd, *J* = 1.5, 17.1, 1H), 2.41 (s, 3H), 1.21 (s, 9H); $^{13}$C NMR (151 MHz, DMSO) δ 177.28, 160.87, 156.73, 143.54, 134.86, 134.70, 117.67, 117.00, 109.40, 53.96, 39.43, 27.26, 17.00; LC/MS(ESI): cal. [M+H$^+$] = 349.13, found 349.13

## HPLC chromatograms and mass spectra for thiazolylpyrazole correctors

**10a** (R = H, $R^2$ = Bn)



Calculated (cal. for short) $[M+H^+]$ = 427.18

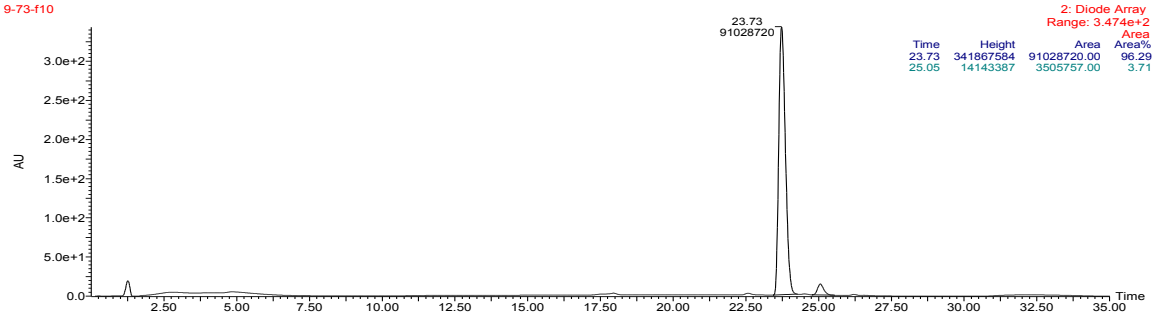



**Figure SI-1. HPLC Chromatogram of compound 10a** (R = H, $R^2$ = Bn)

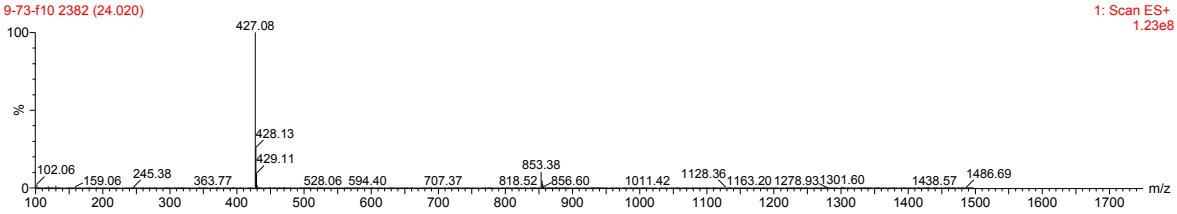
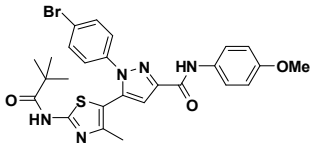



**Figure SI-2. Mass spectrum of 10a** (R = H, $R^2$ = Bn)

**11d**




cal. $[M+H^+]$ = 568.10

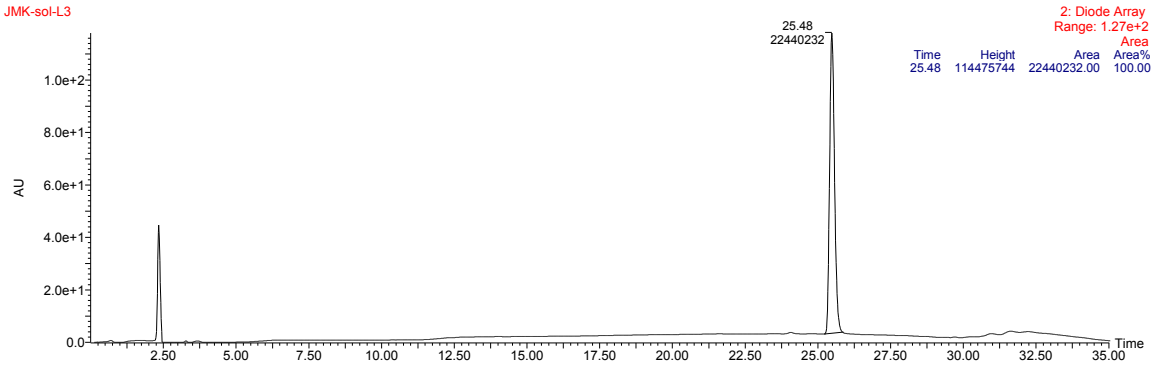



**Figure SI-3. HPLC Chromatogram of compound 11d**

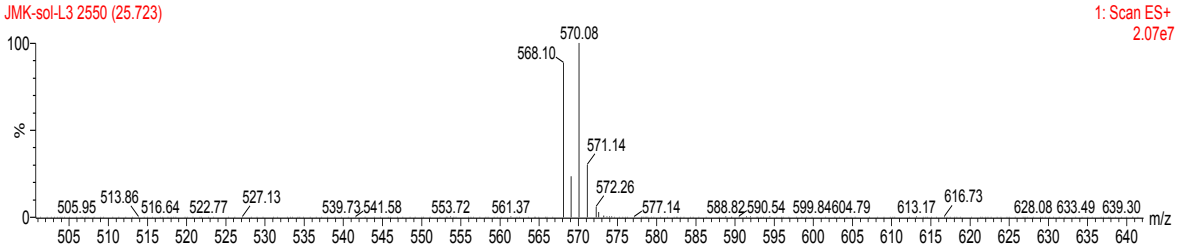
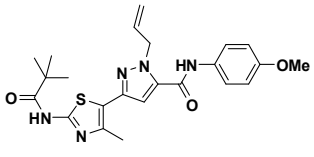



**Figure SI-4. Mass spectrum of 11d**

**14a**




cal. [M+H$^+$]=454.19

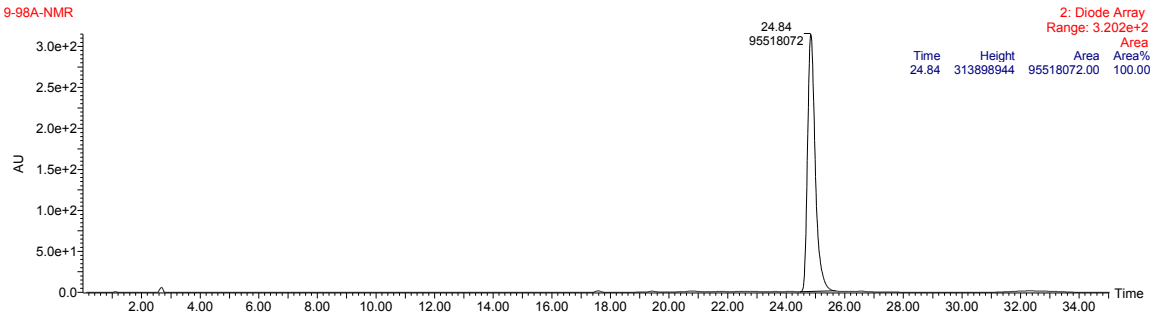



**Figure SI-5. HPLC Chromatogram of compound 14a**

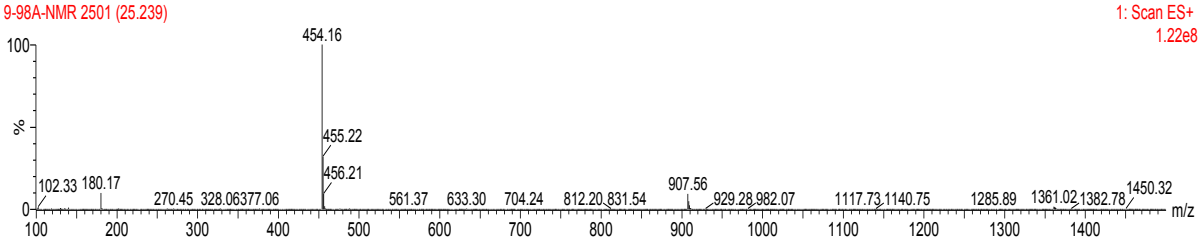
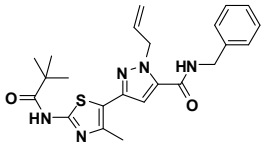



**Figure SI-6. Mass spectrum of 14a**

**14b**



cal. [M+H$^+$]=438.20

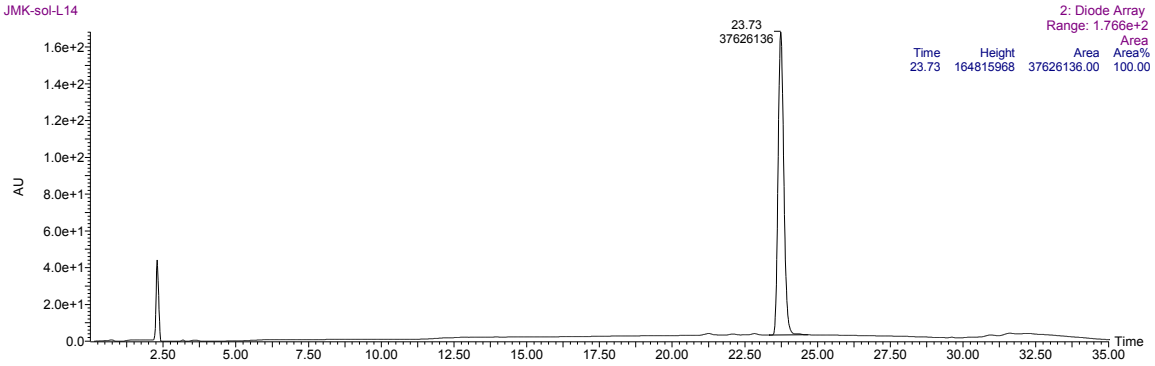



**Figure SI-7. HPLC Chromatogram of compound 14b**

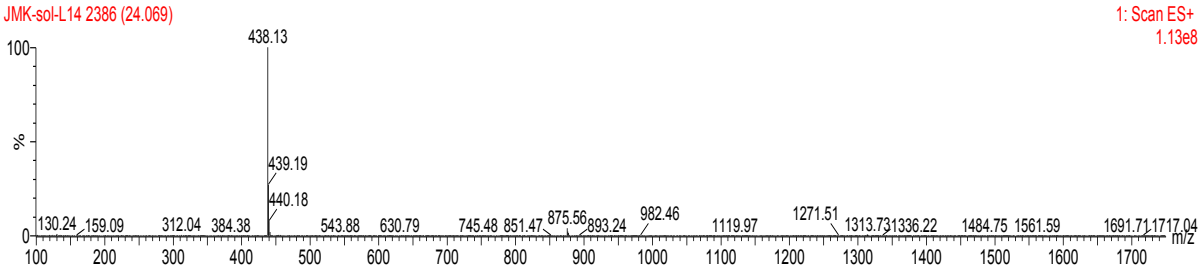
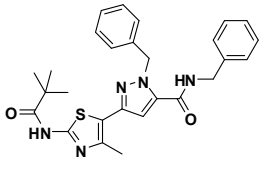



**Figure SI-8. Mass spectrum of 14b**

**14e**



cal. $[M+H^+]$= 488.21

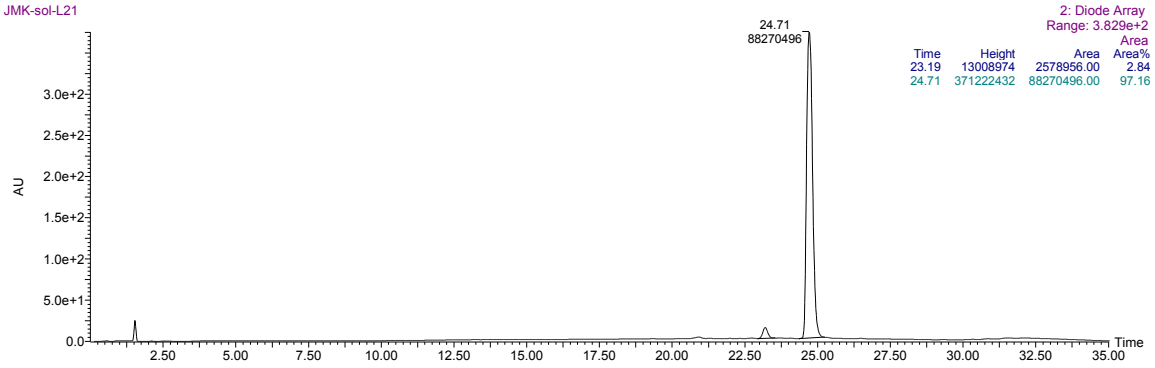



**Figure SI-9. HPLC Chromatogram of compound 14e**

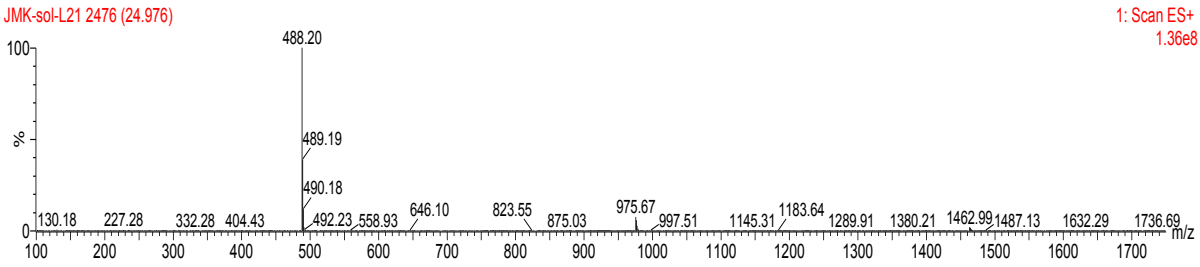
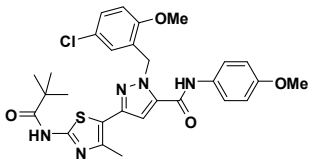



**Figure SI-10. Mass spectrum of 14e**

## 14g




cal. [M+H$^+$]=568.18

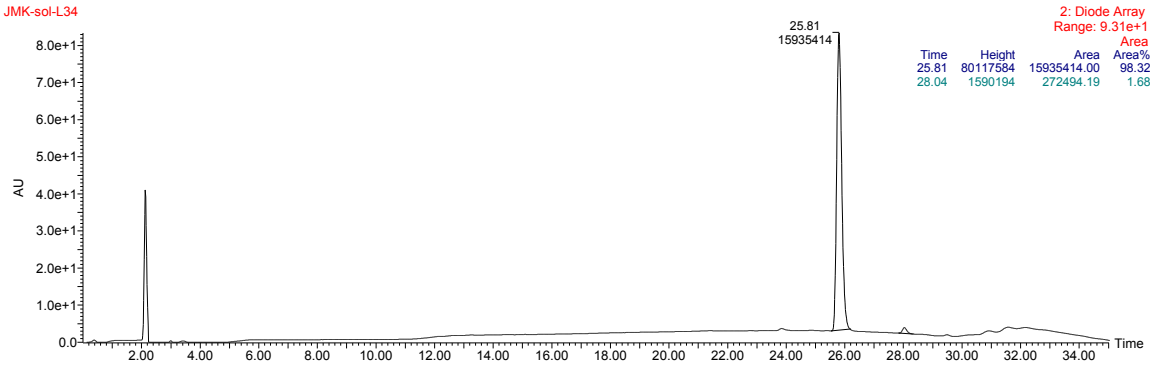



**Figure SI-11. HPLC Chromatogram of compound 14g**

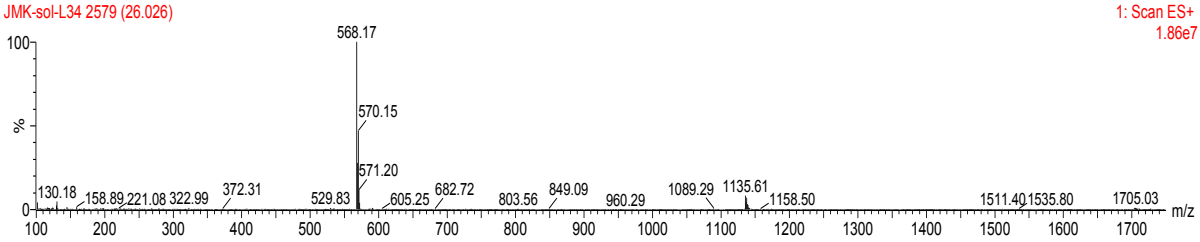
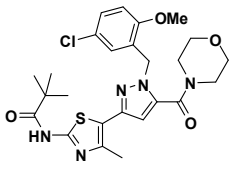



**Figure SI-12. Mass spectrum of 14g**

## 14h




cal. [M+H$^+$]= 532.18

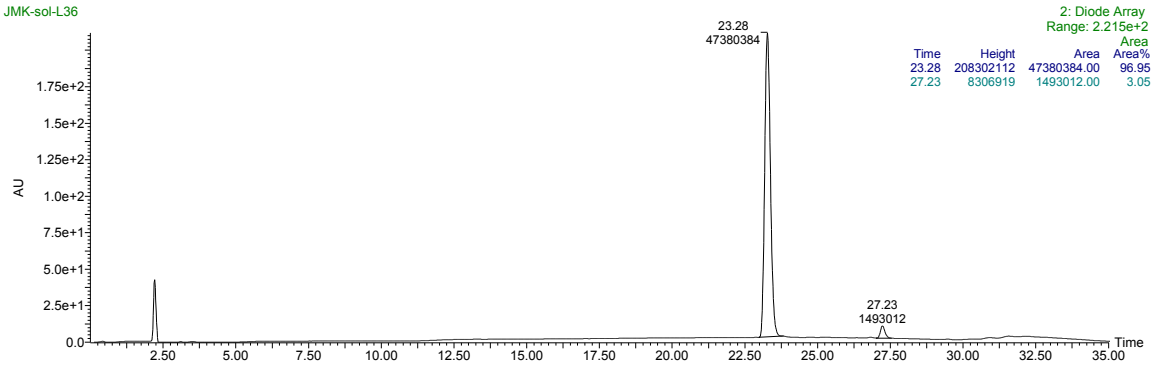



**Figure SI-13. HPLC Chromatogram of compound 14h**

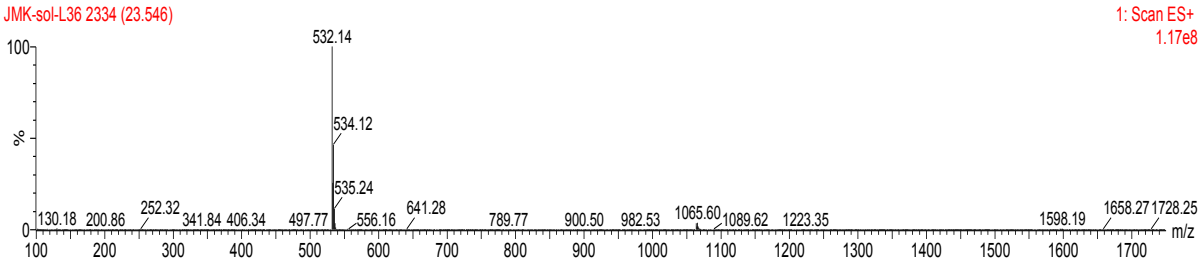
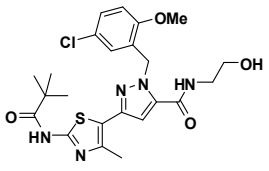



**Figure SI-14. Mass spectrum of 14h**

**14j**




cal. [M+H$^+$]=506.16

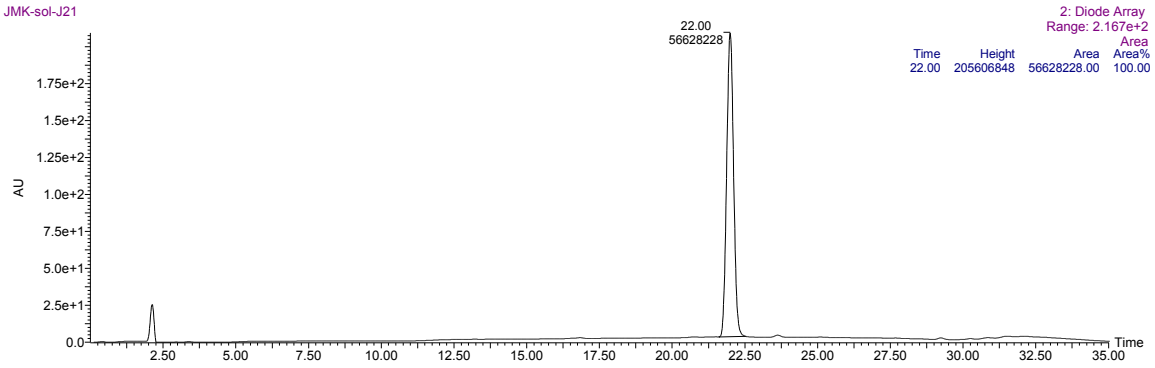



**Figure SI-15. HPLC Chromatogram of compound 14j**

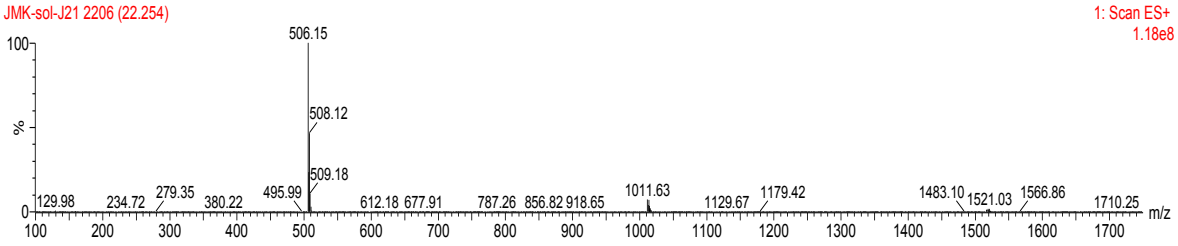



**Figure SI-16. Mass spectrum of 14j**