Supplementary Information

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1. Reactivity Studies

1.1 General Information

All reagents and buffer components were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, TCI chemicals, or Wako Chemicals without further purification. Notable reagents and their commercial source include Endoxifen (AdooQ BioScience), Doxorubicin Hydrochloride (TCI chemicals), Chloro(1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)gold(I) (TCI chemicals), Dichloro(2-pyridinecarboxylato)gold (Sigma-Aldrich), and Sodium tetrachloroaurate(III) dihydrate (Sigma-Aldrich)

TLC analysis (F-254) were performed with 60 Å silica gel from Merck Millipore. $^1$H and $^{13}$C NMR spectra were measured on either a JEOL AL300 (300 MHz) or AL400 (400 MHz) instrument with the solvent peaks as internal standards. High-resolution mass spectroscopy (HRMS) was carried out on a Bruker MicroTOF-QIII electrospray ionization time-of-flight (ESI-TOF) mass spectrometer.

1.2 HPLC Methods

Reverse-phase HPLC was used to analyze and purify compounds as indicated. The Shimadzu system (Kyoto, Japan) employed two LC-20AP pumps outfitted with a SPD-20AV photodiode array detector, a RF-10AXL fluorescence detector, and a SIL-20A autosampler. The columns used were a semi-preparative 10 × 250 mm Cosmosil 5C$_{18}$-Ar-300 and an analytical 4.6 × 250 mm Cosmosil 5C$_{18}$-Ar-300 from Nacalai Tesque (Kyoto, Japan). Samples were eluted using a combination of mobile phases A (100% H$_2$O), B (100% acetonitrile), C (H$_2$O with 0.1% TFA), and D (acetonitrile with 0.1% TFA). The detector was set to 214 and 254 nm. The different elution methods that were employed in this study are shown in Table S1.

| Method   | Flow rate (ml/min) | Time (min) | %A (100% H$_2$O) | %B (100% ACN) | %C (H$_2$O with 0.1% TFA) | %D (ACN with 0.1% TFA) |
|----------|--------------------|------------|------------------|---------------|-------------------------|------------------------|
| Semi-prep | 3.0                | 0          | 95               | 5             |                         |                        |
| Method 1 |                    | 10         | 95               | 5             |                         |                        |
|          |                    | 40         | 30               | 70            |                         |                        |
|          |                    | 43         | 1                | 99            |                         |                        |
|          |                    | 50         | 1                | 99            |                         |                        |
|          |                    | 58         | 95               | 5             |                         |                        |
|          |                    | 60         | 95               | 5             |                         |                        |
| Semi-prep | 3.0                | 0          | 90               | 10            |                         |                        |
| Method 2 |                    | 10         | 90               | 10            |                         |                        |
|          |                    | 40         | 30               | 70            |                         |                        |
|          |                    | 43         | 1                | 99            |                         |                        |
|          |                    | 50         | 1                | 99            |                         |                        |
|          |                    | 58         | 90               | 10            |                         |                        |
|          |                    | 60         | 90               | 10            |                         |                        |
Table S1 (continued). Gradient profiles for HPLC studies

| Method  | Flow rate (ml/min) | Time (min) | %A (100% H$_2$O) | %B (100% ACN) | %C (H$_2$O with 0.1% TFA) | %D (ACN with 0.1% TFA) |
|---------|--------------------|------------|------------------|---------------|--------------------------|------------------------|
| Method 3 | 3.0                | 0          | 80               | 20            | 80                       | 20                     |
|         | Semi-prep          | 10         | 80               | 20            | 30                       | 70                     |
|         |                    | 40         | 1                | 99            | 1                        | 99                     |
|         |                    | 50         | 1                | 99            | 1                        | 99                     |
|         |                    | 58         | 80               | 20            | 80                       | 20                     |
|         |                    | 60         | 80               | 20            | 80                       | 20                     |
| Method 4 | 3.0                | 0          | 70               | 30            | 70                       | 30                     |
|         | Semi-prep          | 10         | 70               | 30            | 30                       | 70                     |
|         |                    | 40         | 30               | 70            | 1                        | 99                     |
|         |                    | 43         | 1                | 99            | 1                        | 99                     |
|         |                    | 50         | 1                | 99            | 1                        | 99                     |
|         |                    | 58         | 70               | 30            | 70                       | 30                     |
|         |                    | 60         | 70               | 30            | 70                       | 30                     |
| Method 5 | 1.0                | 0          | 95               | 5             | 95                       | 5                      |
|         | Analytical         | 10         | 95               | 5             | 95                       | 5                      |
|         |                    | 35         | 60               | 40            | 60                       | 40                     |
|         |                    | 40         | 5                | 95            | 5                        | 95                     |
|         |                    | 45         | 5                | 95            | 5                        | 95                     |
|         |                    | 50         | 95               | 5             | 95                       | 5                      |
|         |                    | 55         | 95               | 5             | 95                       | 5                      |
| Method 6 | 3.0                | 0          | 60               | 40            | 60                       | 40                     |
|         | Semi-prep          | 5          | 60               | 40            | 60                       | 40                     |
|         |                    | 28         | 5                | 95            | 5                        | 95                     |
|         |                    | 32         | 5                | 95            | 5                        | 95                     |
|         |                    | 33         | 60               | 40            | 60                       | 40                     |
|         |                    | 35         | 60               | 40            | 60                       | 40                     |
| Method 7 | 3.0                | 0          | 65               | 35            | 65                       | 35                     |
|         | Semi-prep          | 5          | 65               | 35            | 65                       | 35                     |
|         |                    | 28         | 5                | 95            | 5                        | 95                     |
|         |                    | 32         | 5                | 95            | 5                        | 95                     |
|         |                    | 33         | 65               | 35            | 65                       | 35                     |
|         |                    | 35         | 65               | 35            | 65                       | 35                     |
| Method | Flow rate (ml/min) | Time (min) | %A (100% H₂O) | %B (100% ACN) | %C (H₂O with 0.1% TFA) | %D (ACN with 0.1% TFA) |
|--------|--------------------|------------|---------------|---------------|------------------------|------------------------|
| 8      | 3.0                | 0          | 85            | 15            |                        |                        |
| Semi-prep | 3                  | 85         | 15            |               |                        |                        |
|        | 5                  | 60         | 40            |               |                        |                        |
|        | 26                 | 50         | 50            |               |                        |                        |
|        | 28                 | 25         | 75            |               |                        |                        |
|        | 32                 | 25         | 75            |               |                        |                        |
|        | 33                 | 85         | 15            |               |                        |                        |
|        | 37                 | 85         | 15            |               |                        |                        |
| 9      | 3.0                | 0          | 70            | 30            |                        |                        |
| Semi-prep | 3                  | 70         | 30            |               |                        |                        |
|        | 18                 | 25         | 75            |               |                        |                        |
|        | 22                 | 25         | 75            |               |                        |                        |
|        | 23                 | 70         | 30            |               |                        |                        |
|        | 27                 | 70         | 30            |               |                        |                        |
| 10     | 3.0                | 0          | 90            | 10            |                        |                        |
| Semi-prep | 3                  | 90         | 10            |               |                        |                        |
|        | 13                 | 75         | 25            |               |                        |                        |
|        | 30                 | 10         | 90            |               |                        |                        |
|        | 35                 | 90         | 10            |               |                        |                        |
|        | 40                 | 90         | 10            |               |                        |                        |
| 11     | 3.0                | 0          | 70            | 30            |                        |                        |
| Semi-prep | 3                  | 70         | 30            |               |                        |                        |
|        | 18                 | 10         | 90            |               |                        |                        |
|        | 22                 | 10         | 90            |               |                        |                        |
|        | 23                 | 70         | 30            |               |                        |                        |
|        | 27                 | 70         | 30            |               |                        |                        |
| 12     | 3.0                | 0          | 65            | 35            |                        |                        |
| Semi-prep | 3                  | 65         | 35            |               |                        |                        |
|        | 18                 | 10         | 90            |               |                        |                        |
|        | 22                 | 10         | 90            |               |                        |                        |
|        | 23                 | 65         | 35            |               |                        |                        |
|        | 27                 | 65         | 35            |               |                        |                        |
## 1.3 HPLC Analysis (Product Standard Curve and Calibration)

To determine yields from HPLC analysis, calibration curves were constructed using product standards of known amounts (shown in Figures S1-S10).

### Method 1

**Product Structure:**

![Product Structure](image)

**HPLC Method**

(see Table S1)

| Calibration Curve |
|--------------------|
| R² = 0.9921 |

| Value | Error (σ) |
|-------|-----------|
| Slope | 335496372.9723 | 17336657.9872 |
| Intercept | 1740214.3807 | 659932.6452 |

**HPLC trace:**

- **rt ≈ 22.9 min**

![HPLC Trace](image)

**Figure S1.** HPLC calibration curve of product 2a

### Method 1

**Product Structure:**

![Product Structure](image)

**HPLC Method**

(see Table S1)

| Calibration Curve |
|--------------------|
| R² = 0.9970 |

| Value | Error (σ) |
|-------|-----------|
| Slope | 387691152.9412 | 12200018.6890 |
| Intercept | 780172.1250 | 267621.8883 |

**HPLC trace:**

- **rt ≈ 22.3 min**

![HPLC Trace](image)

**Figure S2.** HPLC calibration curve of product 2b
| Product Structure | HPLC Method (see Table S1) | Calibration Curve |
|-------------------|----------------------------|-------------------|
| ![2c](image)      | **Method 4**               | ![Calibration Curve](image) |
| **HPLC trace:**   |                            | $R^2 = 0.9982$    |
|                   |                            | Value            |
|                   |                            | Error (σ)        |
|                   |                            | Slope            |
|                   |                            | 431217757.3455   |
|                   |                            | 10529673.9466    |
|                   |                            | Intercept        |
|                   |                            | 1754655.0020     |
|                   |                            | 373645.5652      |
|                   | $rt \approx 23.4 \text{ min}$ |                   |

**Figure S3.** HPLC calibration curve of product 2c

| Product Structure | HPLC Method (see Table S1) | Calibration Curve |
|-------------------|----------------------------|-------------------|
| ![2d](image)      | **Method 3**               | ![Calibration Curve](image) |
| **HPLC trace:**   |                            | $R^2 = 0.9991$    |
|                   |                            | Value            |
|                   |                            | Error (σ)        |
|                   |                            | Slope            |
|                   |                            | 582321369.2265   |
|                   |                            | 10132466.0030    |
|                   |                            | Intercept        |
|                   |                            | 570267.3079      |
|                   |                            | 202655.8148      |
|                   | $rt \approx 20.7 \text{ min}$ |                   |

**Figure S4.** HPLC calibration curve of product 2d
| Product Structure | HPLC Method (see Table S1) | Calibration Curve |
|-------------------|---------------------------|-------------------|
| ![Product Structure](image) | Method 3                  | ![Absorbance vs Mass of Compound](image) |
|                   |                           | \( R^2 = 0.9994 \)  |
|                   |                           | Value | Error (σ) |
|                   |                           | Slope       | 562496460.8295 | 8120349.9246 |
|                   |                           | Intercept   | 369195.6250  | 220042.3389  |
|                   |                           | X          | Y          |
|                   |                           | Absorbance  | Mass of Compound (mg) |

HPLC trace:

Figure S5. HPLC calibration curve of product 2e

| Product Structure | HPLC Method (see Table S1) | Calibration Curve |
|-------------------|---------------------------|-------------------|
| ![Product Structure](image) | Method 2                  | ![Absorbance vs Mass of Compound](image) |
|                   |                           | \( R^2 = 0.9959 \)  |
|                   |                           | Value | Error (σ) |
|                   |                           | Slope       | 691725696.7945 | 25734644.6144 |
|                   |                           | Intercept   | 1823430.8360  | 614330.5589  |
|                   |                           | X          | Y          |
|                   |                           | Absorbance  | Mass of Compound (mg) |

HPLC trace:

rt \( \approx \) 27.3 min

rt \( \approx \) 22.1 min

Figure S6. HPLC calibration curve of product 2f
| Product Structure | HPLC Method (see Table S1) | Calibration Curve |
|-------------------|-----------------------------|-------------------|
| ![structure_2g](image) | **Method 2** | ![calibration_curve_2g](image) |
| **2g** | | |
| **R² = 0.9944** | **Value** | **Error (σ)** |
| | **Slope** | **Intercept** |
| | 607301239.1876 | 1646220.0417 |
| | 26218199.3523 | 608958.3359 |
| **HPLC trace:** | | |
| | | |
| **rt ≈ 23.3 min** | | |

**Figure S7. HPLC calibration curve of product 2g**

| Product Structure | HPLC Method (see Table S1) | Calibration Curve |
|-------------------|-----------------------------|-------------------|
| ![structure_2h](image) | **Method 1** | ![calibration_curve_2h](image) |
| **2h** | | |
| **R² = 0.9992** | **Value** | **Error (σ)** |
| | **Slope** | **Intercept** |
| | 509497867.7419 | 709388.2500 |
| | 8156427.6234 | 168396.1596 |
| **HPLC trace:** | | |
| | | |
| **rt ≈ 25.1 min** | | |

**Figure S8. HPLC calibration curve of product 2h**
Figure S9. HPLC calibration curve of product Doxorubicin

Figure S10. HPLC calibration curve of product Endoxifen
1.4 Reactivity Study

1.4.1 Protocols and Yield Determination

In general, product identification was determined by MS analysis and comparison with retention times of known product standards. Yields were obtained via HPLC analysis (unless otherwise noted). This was carried out via peak integration, followed by calculations based on product calibration curves shown in Supplementary Section 1.3.

For the model reactivity and derivatization studies, compounds 1a-t (0.01 mmol) and Au-1 (concentration adjusted as indicated) were dissolved in solvent (1 ml). The mixtures (in glass test tubes) were then placed on a block temperature-controlled hotplate stirrer (Asynt, UK). Reactions were stirred at the indicated times and temperature. To workup, mixtures were diluted with acetonitrile containing 0.1% TFA (1 ml), filtered, and then injected (50 µl) onto a HPLC with an autosampler. Depending on the desired product, HPLC methods 1-4 were used.

![Figure S11. A) An example of HPLC trace taken from the reaction mixture of 1a incubated with Au-1. Identified is the released amine product 2a. B) HPLC trace of the starting material, compound 1a.](image)

For the individual reactivity studies, prodrugs 3a, 3m, 6a, 6m, or 7 (30 nmol) and metal catalyst (30 nmol) were dissolved in 50% THF in aqueous solvent (50 µl).

For the orthogonal metal reactivity studies, a mixture of prodrug 3a (30 nmol) and either prodrug 4 or 5 (30 nmol) was made in 50% THF in PBS buffer pH 7.4 (50 µl). Depending on the conditions, either Au-4 (30 nmol), Ru-2 (30 nmol), or Pd-3 (30 nmol) was then added.

In general, the mixtures (in eppendorf tubes) were placed in a MD-MINI water bath incubator (Major Science, USA). Without stirring, reactions were left to incubate for 12 hr at 37°C. To workup, mixtures were diluted with 1 mM dodecanethiol in THF (100 µl) to quench the metal catalysts. Since doxorubicin is insoluble unless its primary amine is protonated, 1M HCl (50 µl) was added to ensure the released compound would match the commercial product standards (i.e. doxorubicin...
The solutions were then filtered, and injected (50 µl) onto a HPLC with an autosampler using HPLC method 5.

**Figure S12.** A) An example of HPLC trace taken from the reaction mixture of 3a incubated with Au-4. Identified is the released e/z Endoxifen. B) HPLC trace of prodrug 3a.

**Figure S13.** A) An example of HPLC trace taken from the reaction mixture of 6a incubated with Au-4. Identified is the released Doxorubicin. B) HPLC trace of prodrug 6a.
### 1.4.2 Reactivity Data

In Table S2, the model reaction from 1a to 2a was shown to be time-dependent (entries 1-3) and temperature-dependent (entries 4-5).

Table S2. Investigation into time and temperature dependence

| Entry | Time (hr) | Temp (°C) | Yield of 2a (%) a |
|-------|-----------|-----------|-------------------|
| 1     | 1         | 37        | 19                |
| 2     | 3         | 37        | 44                |
| 3     | 6         | 37        | 54                |
| 4     | 16        | rt        | 46                |
| 5     | 16        | 70        | 69                |

aYields determined by HPLC (peak retention times compared to product standards, followed by MS analysis for confirmation, and then calculation of yields based on product standard curves). bIsolated yields obtained by column chromatography purification. All reactions were standardized to 10 µmol of 1a in 1 ml of solvent (10 mM).

In Table S3, derivatives 1b-t were prepared and tested to investigate the factors that could possibly influence amine release.

**Alkyne substitution (R1 position):** Pentyl, phenyl, and anisole derivatives 1q-s were tested, which all largely showed an increase in reactivity. The only example that falls from this pattern is 1t (entry 20), which may possibly be due to the amine substituent perturbing reactivity by interacting with the Au-catalyst.

**Benzyl substitution (R2, R3, and R4 positions):** Electron-withdrawing group were shown to increase yields of amine release. From comparing simple fluoro substitutions either at the R2, R3, and R4 positions (entries 9-11), it can be observed that the R3 position (para to the alkyne moiety) gave slightly better yields. Subsequently stronger electron-withdrawing groups at the R3 position, such as nitro 1l (56%, entry 12) and trifluoromethyl 1m (74%, entry 13), gave higher yields of amine release. No significant changes in reactivity were seen with substitutions that were weakly electron-donating (methyl, entry 14) and moderately electron-donating (methoxy, entries 15-16). A possible explanation for these observations is that para-positioned electron withdrawing groups likely has a stronger effect in pulling electron density away from the alkyne, thereby better activating it for Au-catalyzed cyclization.
**N-substitution (R<sub>5</sub> position):** Unsubstituted amide 1b showed no detectable levels of Au-triggered amine release (entry 2). Longer and bulkier alkyl groups generally led to lower yields of amine release (c-hexyl, hexyl, isopropyl, and t-butyl, entries 4-7). The same observation was also seen by replacement with an aromatic group (phenyl, entry 3) and an intramolecularly-linked alkane (proline-based amine, entry 8). Likely, the observed reductions in amine release are the outcome of steric bulk outweighing the alpha effects of N-substitution.

**Table S3. Reactivity of Ayba group derivatizes**

| Entry | SM  | R<sub>1</sub> | R<sub>2</sub> | R<sub>3</sub> | R<sub>4</sub> | R<sub>5</sub> | Prod | Yield of 2a-h (%)<sup>a</sup> |
|-------|-----|--------------|--------------|--------------|--------------|--------------|------|----------------------------|
| 1     | 1a  | H            | H            | H            | H            | CH<sub>3</sub> | 2a   | 36                         |
| 2     | 1b  | H            | H            | H            | H            | H            | 2b   | 0                          |
| 3     | 1c  | H            | H            | H            | H            | Ph           | 2c   | 13                         |
| 4     | 1d  | H            | H            | H            | H            | c-hexyl      | 2d   | 15                         |
| 5     | 1e  | H            | H            | H            | H            | hexyl        | 2e   | 20                         |
| 6     | 1f  | H            | H            | H            | H            | iPr          | 2f   | 11                         |
| 7     | 1g  | H            | H            | H            | H            | t-butyl      | 2g   | 5                          |
| 8     | 1h  | H            | H            | H            | H            | H            | 2h   | 21                         |
| 9     | 1i  | H            | F            | H            | H            | CH<sub>3</sub> | 2a   | 45                         |
| 10    | 1j  | H            | H            | F            | H            | CH<sub>3</sub> | 2a   | 47                         |
| 11    | 1k  | H            | H            | H            | F            | CH<sub>3</sub> | 2a   | 41                         |
| 12    | 1l  | H            | H            | NO<sub>2</sub>| H            | CH<sub>3</sub> | 2a   | 56                         |
| 13    | 1m  | H            | H            | CF<sub>3</sub>| H            | CH<sub>3</sub> | 2a   | 74                         |
| 14    | 1n  | H            | CH<sub>3</sub> | H            | CH<sub>3</sub> | 2a   | 43                         |
| 15    | 1o  | H            | OMe          | H            | H            | CH<sub>3</sub> | 2a   | 56                         |
| 16    | 1p  | H            | H            | OMe          | H            | CH<sub>3</sub> | 2a   | 45                         |
| 17    | 1q  | penty1       | H            | H            | H            | CH<sub>3</sub> | 2a   | 62                         |
| 18    | 1r  | Ph           | H            | H            | H            | CH<sub>3</sub> | 2a   | 50                         |
| 19    | 1s  | 4-OH-Ph      | H            | H            | H            | CH<sub>3</sub> | 2a   | 48                         |
| 20    | 1t  | 4-OH-Ph      | H            | H            | H            | CH<sub>3</sub> | 2a   | 30                         |

<sup>a</sup>Yields determined by HPLC (peak retention times compared to product standards, followed by MS analysis for confirmation, and then calculation of yields based on product standard curves). All reactions were standardized to 10 µmol of 1a-t and 5 µmol of Au-1 in 1 ml of solvent (10 mM).
In Table S4, the reactivity of the tested metal catalyst complexes (\textbf{Au-2}, \textbf{Au-3}, \textbf{Au-4}) were compared under aqueous conditions containing either pure water or PBS buffer pH 7.4. Due to the instability of \textbf{Au-2} and \textbf{Au-3} complexes, both 3\textit{a} and 3\textit{m} experienced a noticeable drop in reactivity when switching to buffered conditions.

\textbf{Table S4}. Investigation into the stability between Au(I) and Au(III) catalysts

\begin{center}
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & Substrate & Catalyst & \multicolumn{2}{|c|}{Yield of Release (%)\textsuperscript{a}} \\
& & & 50\% THF & 50\% THF \\
& & & in H\textsubscript{2}O & in PBS buffer \\
\hline
1 & 3\textit{a} & - & <1 & <1 \\
2 & 3\textit{a} & \textbf{Au-2} & 37 & 6 \\
3 & 3\textit{a} & \textbf{Au-3} & 44 & 19 \\
4 & 3\textit{a} & \textbf{Au-4} & 20 & 60 \\
5 & 3\textit{m} & - & <1 & <1 \\
6 & 3\textit{m} & \textbf{Au-2} & 60 & 3 \\
7 & 3\textit{m} & \textbf{Au-3} & 62 & 22 \\
8 & 3\textit{m} & \textbf{Au-4} & 60 & 60 \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a}Yields determined by HPLC (peak retention times compared to product standards, followed by MS analysis for confirmation, and then calculation of yields based on product standard curves). All reactions were standardized to 30 nmol of 3\textit{a,m} and 30 nmol of catalyst in 50 µl of solvent (600 µM).
1.4.3 By-product Identification

For Ayba-decaging to occur, the initial transformation involves a nucleophilic cyclization process where a bond-forming interaction occurs between the lone-pair orbital of the carbonyl-O and the in-plane alkyne π* orbital. Depending on the type of catalyst (and its ligand), either a 5-exo-dig or 6-endo-dig cyclization will proceed. As highlighted in Scheme S1, the resultant by-product 46 was purified from a model substrate 1q. Differentiation between the exo and endo forms can be made by NMR analysis, where protons at the C-1 position of 46 are expected to be down-shifted compared to the substrate.

Scheme S1. Identification of the by-product 46
1.5 Synthetic Schemes

1.5.1 Reactivity Study Substrates

Scheme S2. Synthesis of 2a-c

Preparation of 9a:

N-methylglycine 8a (593 mg, 6.66 mmol) was dissolved in dioxane (10 ml) and H2O (6 ml). NaOH (1.2 g, 30 mmol) dissolved in H2O (2 ml) was added and the mixture was cooled to 0°C. Boc anhydride (1.73 g, 7.92 mmol) dissolved in dioxane (2 ml) was then added dropwise and the mixture was stirred for 16 hr at room temperature. To workup, dioxane in the mixture was evaporated under vacuum and the residual solution was washed with EtOAc. The aqueous layer was then acidified to pH~3 with 1N HCl, which allowed the product to be extracted with CHCl3. The combined organic layer was washed with H2O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 1250 mg, quan. Characterization matched a previous report of this known compound.1H NMR (DMSO-d6, 300 MHz) δ 12.58 (br s, 1H), 3.83 (d, J = 5.2 Hz, 2H), 2.80 (d, J = 10.8 Hz, 3H), 1.36 (d, J = 15.1 Hz, 9H).

Preparation of 9c:

N-Phenylglycine 8c (500 mg, 3.31 mmol) was dissolved in 1:1 acetone/H2O (6 ml). Boc anhydride (2.16 g, 9.89 mmol) dissolved in acetone (1 ml) was then added dropwise and the mixture was stirred for 16 hr at room temperature. To workup, acetone in the mixture was evaporated under vacuum and the residual solution was washed with ether. The aqueous layer was then acidified to pH~3 with 1N HCl, which allowed the product to be extracted with CHCl3. The combined organic layer was washed with H2O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-10% MeOH in CHCl3 was used to purify the desired compound. Yield: 804 mg, 97%. Rf =0.29 (MeOH/CHCl3, 1:10). Characterization matched a previous report of this known compound.2H NMR (DMSO-d6, 400 MHz) δ 12.78 (br s, 1H), 7.34-7.15 (m, 5H), 4.19 (s, 2H), 1.36 (s, 9H).
Preparation of 10a:

![Chemical structure]

Compound 9a (951 mg, 5.03 mmol), benzylamine (550 µl, 5.03 mmol), EDC (1558 mg, 10.06 mmol), HOBT (1357 mg, 10.06 mmol) were dissolved in CHCl₃ (10 ml). NEt₃ (1.4 ml, 10.06 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the solvent was evaporated under vacuum and the mixture redissolved in EtOAc. The organic layer was then washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-50% EtOAc in Hex was used to purify the desired compound. Yield: 1293 mg, 92%. Rf=0.26 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.23 (m, 5H), 4.46 (d, J = 5.9 Hz, 2H), 3.89 (s, 2H), 2.93 (s, 3H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.6, 155.6, 138.2, 128.9, 127.8, 80.9, 53.4, 43.3, 35.9, 28.3. HRMS for C₁₃H₂₄N₂O₃ [M+Na]⁺ calcd. 301.1523 found 301.1517.

Preparation of 10b:

![Chemical structure]

N-Boc-glycine 9b (100 mg, 0.571 mmol), benzylamine (63 µl, 0.571 mmol), EDC (177 mg, 1.14 mmol), HOBT (154 mg, 1.14 mmol) were dissolved in CHCl₃ (10 ml). NEt₃ (160 µl, 1.14 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the solvent was evaporated under vacuum and the mixture redissolved in EtOAc. The organic layer was then washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-50% EtOAc in Hex was used to purify the desired compound. Yield: 538 mg, 89%. Rf=0.21 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.36-7.24 (m, 5H), 6.51 (br s, 1H), 5.19 (br s, 1H), 4.46 (d, J = 5.6 Hz, 2H), 3.82 (d, J = 5.9 Hz, 2H), 1.42 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.6, 156.3, 138.1, 128.9, 127.9, 127.8, 80.6, 44.7, 43.5, 28.3. HRMS for C₁₄H₂₀N₂O₃ [M+Na]⁺ calcd. 287.1366, found 287.1369.

Preparation of 10c:

![Chemical structure]

Compound 9c (830 mg, 3.31 mmol), benzylamine (362 µl, 3.31 mmol), EDC (1025 mg, 6.61 mmol), HOBT (893 mg, 6.61 mmol) were dissolved in CHCl₃ (10 ml). NEt₃ (924 µl, 6.61 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the solvent was evaporated under vacuum and the mixture redissolved in EtOAc. The organic layer was then washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-50% EtOAc in Hex was used to purify the desired compound. Yield: 994 mg, 88%. Rf=0.53 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.36-7.18 (m, 10H), 6.52 (br s, 1H), 4.50 (d, J = 5.8 Hz, 2H), 4.29 (s, 2H), 1.39 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.5, 155.0, 142.7, 138.2, 129.2, 128.9, 127.9, 127.8, 126.5, 125.9, 81.9, 54.6, 43.6, 28.2. HRMS for C₂₀H₂₄N₂O₃ [M+Na]⁺ calcd. 363.1679, found 363.1683.
Preparation of 2a:

Compound 10a (1293 mg, 4.65 mmol) was dissolved in a mixture of TFA:DCM (1 ml:1 ml) and stirred for 60 min at room temperature. Completion of the reaction was determined by disappearance of starting material spot on TLC (100% EtOAc). To workup, the reaction was evaporated under vacuum to an oil. Flash column chromatography using a gradient of 0-10% MeOH in CHCl₃ was used to purify the desired compound. Yield: 828 mg, quan. R_f=0.12 (MeOH/CHCl₃, 1:10). ¹H NMR (CD₃OD, 300 MHz) δ 7.36-7.23 (m, 5H), 4.43 (s, 2H), 3.82 (s, 2H), 2.73 (s, 3H); ¹³C NMR (CD₃OD, 75 MHz): δ 166.5, 139.4, 129.8, 128.8, 128.6, 50.6, 44.2, 33.5. HRMS for C₁₀H₁₄N₂O [M+H]^+ calcd. 179.1179, found 179.1182.

Preparation of 2b:

Compound 10b (235 mg, 0.893 mmol) was dissolved in a mixture of TFA:DCM (1 ml:1 ml) and stirred for 60 min at room temperature. Completion of the reaction was determined by disappearance of starting material spot on TLC (MeOH/CHCl₃, 1:10). To workup, the reaction was evaporated under vacuum to an oil. Flash column chromatography using a gradient of 0-10% MeOH in CHCl₃ was used to purify the desired compound. Yield: 146 mg, quan. R_f=0.03 (MeOH/CHCl₃, 1:10). ¹H NMR (CD₃OD, 300 MHz) δ 7.32-7.18 (m, 5H), 4.39 (s, 2H), 3.68 (s, 2H); ¹³C NMR (CD₃OD, 75 MHz): δ 167.4, 139.5, 129.7, 128.8, 128.6, 44.2, 41.5. HRMS for C₉H₁₂N₂O [M+Na]^+ calcd. 187.0842, found 187.0846.

Preparation of 2c:

Compound 10c (225 mg, 0.661 mmol) was dissolved in a mixture of TFA:DCM (1 ml:1 ml) and stirred for 60 min at room temperature. Completion of the reaction was determined by disappearance of starting material spot on TLC (MeOH/CHCl₃, 1:10). To workup, the reaction was evaporated under vacuum to an oil. Flash column chromatography using a gradient of 0-5% MeOH in CHCl₃ was used to purify the desired compound. Yield: 158 mg, quan. R_f=0.33 (MeOH/CHCl₃, 1:10). ¹H NMR (CDCl₃, 300 MHz) δ 7.57 (br s, 2H), 7.43 (br s, 1H), 7.31-7.17 (m, 6H), 6.94 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 8.3 Hz, 2H), 4.44 (d, J = 6.0 Hz, 2H), 3.91 (s, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.9, 145.1, 137.5, 129.8, 128.9, 127.8(2), 121.4, 115.1, 49.5, 43.5. HRMS for C₁₅H₁₆N₂O [M+H]^+ calcd. 241.1335, found 241.1339.
**Scheme S3. Synthesis of 2d-g**

**Preparation of 12:**

Bromoacetyl bromide 11 (120 μl, 1.38 mmol) was dissolved in DCM (3 ml) and K₂CO₃ (506 mg, 3.66 mmol) was dissolved in water (3 ml). Both mixtures were added simultaneously dropwise over 15 min to a solution of benzylamine (100 μl, 0.92 mmol) in DCM (3 ml) at 0°C. The reaction was then stirred at room temperature for 2 hr. To workup, the reaction was diluted with H₂O and then the organic layer was washed with H₂O (5×), dried over magnesium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 200 mg, 96%. Rᵗ = 0.42 (100% DCM). Characterization matched a previous report of this known compound.³ ¹H NMR (CD₂Cl₂, 300 MHz) δ 7.39-7.26 (m, 5H), 6.73 (br s, 1H), 4.45 (d, J = 5.9 Hz, 2H), 3.91 (s, 2H).

**Preparation of 2d:**

Compound 12 (200 mg, 0.915 mmol) was dissolved in DCM (2 ml). Cyclohexylamine (316 μl, 2.75 mmol) was then added and the mixture was stirred for 16 hr and at room temperature under N₂. To workup, the reaction was evaporated under vacuum to an oil. Flash column chromatography using a gradient of 0-5% MeOH in CHCl₃ was used to purify the desired compound. Yield: 203 mg, 90%. Rᵗ = 0.27 (MeOH/CHCl₃, 1:10). ¹H NMR (CD₂OD, 300 MHz) δ 7.36-7.23 (m, 5H), 4.42 (s, 2H), 3.27 (s, 2H), 2.55-2.46 (m, 1H), 1.93-1.64 (m, 4H), 1.36-1.07 (m, 6H); ¹³C NMR (CD₂OD, 75 MHz): δ 173.2, 139.9, 129.7, 128.8, 128.5, 58.1, 44.0, 33.4, 26.9, 25.9, 18.3. HRMS for C₁₅H₂₂N₂O [M+H]⁺ calcd. 247.1805, found 247.1805.

**Preparation of 2e:**

Compound 12 (209 mg, 0.920 mmol) was dissolved in DCM (2 ml). n-Hexylamine (1.2 ml, 9.220 mmol) was then added and the mixture was stirred for 16 hr at and room temperature under N₂. To workup, the reaction was evaporated under vacuum to an oil. Flash column chromatography using a gradient of 0-5% MeOH in CHCl₃ was used to purify the desired compound. Yield: 194 mg, 85%. Rᵗ = 0.39 (MeOH/CHCl₃, 1:10). ¹H NMR (CD₂OD, 300 MHz) δ 7.36-7.23 (m, 5H), 4.42 (s, 2H), 3.27 (s, 2H), 2.55 (t, J = 7.3 Hz, 2H), 1.54-1.44 (m, 2H), 1.37-1.26 (m, 6H), 0.91 (t, J = 7.0 Hz, 3H); ¹³C NMR (CD₂OD, 75 MHz): δ 174.1, 140.0, 129.7, 128.7, 128.4, 52.8, 50.6, 43.9, 32.8, 30.6, 28.0, 23.6, 14.3. HRMS for C₁₅H₂₄N₂O [M+H]⁺ calcd. 249.1961, found 249.1959.
Preparation of 2f:

Compound 12 (180 mg, 0.791 mmol) was dissolved in DCM (2 ml). 2-Propylamine (339 μl, 3.96 mmol) was then added and the mixture was stirred for 16 hr and at room temperature under N₂. To workup, the reaction was evaporated under vacuum to an oil. Flash column chromatography using a gradient of 0-5% MeOH in CHCl₃ was used to purify the desired compound. Yield: 139 mg, 85%. R_f = 0.28 (MeOH/CHCl₃, 1:10). ¹H NMR (CD₃OD, 300 MHz) δ 7.37-7.22 (m, 5H), 4.41 (s, 2H), 3.29 (s, 2H), 2.78 (quin, J = 6.2 Hz, 1H), 1.09-1.05 (m, 6H); ¹³C NMR (CD₃OD, 75 MHz): δ 174.2, 139.9, 129.7, 128.7, 128.4, 50.4, 43.9, 22.6, 18.3. HRMS for C₁₂H₁₈N₂O [M+H]^⁺ calcd. 207.1492, found 207.1496.

Preparation of 2g:

Compound 12 (216 mg, 0.952 mmol) was dissolved in DCM (2 ml). 2-Methyl-2-propylamine (486 μl, 4.58 mmol) was then added and the mixture was stirred for 16 hr and at room temperature under N₂. To workup, the reaction was evaporated under vacuum to an oil. Flash column chromatography using a gradient of 0-5% MeOH in CHCl₃ was used to purify the desired compound. Yield: 154 mg, 74%. R_f = 0.27 (MeOH/CHCl₃, 1:10). ¹H NMR (CD₃OD, 300 MHz) δ 7.35-7.22 (m, 5H), 4.41 (s, 2H), 3.26 (s, 2H), 1.09 (s, 9H); ¹³C NMR (CD₃OD, 75 MHz): δ 175.0, 139.9, 129.7, 128.7, 128.4, 51.5, 46.4, 43.9, 28.8. HRMS for C₁₃H₂₀N₂O [M+H]^⁺ calcd. 221.1648, found 221.1648.
Scheme S4. Synthesis of 2h

Preparation of 9h:

L-Proline 8h (766 mg, 6.66 mmol) was dissolved in dioxane (6 ml) and H$_2$O (10 ml). NaOH (1.2 g, 30 mmol) dissolved in H$_2$O (2 ml) was added and the mixture was cooled to 0°C. Boc anhydride (1.73 g, 7.92 mmol) dissolved in dioxane (2 ml) was then added dropwise and the mixture was stirred for 16 hr at room temperature. To workup, dioxane in the mixture was evaporated under vacuum and the residual solution was washed with EtOAc. The aqueous layer was then acidified to pH~3 with 1N HCl, which allowed the product to be extracted with CHCl$_3$. The combined organic layer was washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired compound. Yield: 1220 mg, 85%. Characterization matched a previous report of this known compound.\(^4\) \(^1\)H NMR (CDCl$_3$, 300 MHz) δ 8.39 (br s, 1H), 4.44-4.21 (m, 1H), 3.61-3.32 (m, 2H), 2.41-1.84 (m, 4H), 1.59-1.35 (m, 9H).

Preparation of 10h:

Compound 9h (411 mg, 1.91 mmol), benzylamine (210 μl, 1.91 mmol), EDC (592 mg, 3.82 mmol), HOBt (516 mg, 3.82 mmol) were dissolved in CHCl$_3$ (10 ml). NEt$_3$ (534 μl, 3.82 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N$_2$. To workup, the solvent was evaporated under vacuum and the mixture was redissolved in EtOAc. The organic layer was then washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 543 mg, 93%. \(R_f=0.16\) (EtOAc/Hex, 1:1). \(^1\)H NMR (CDCl$_3$, 300 MHz) δ 7.37-7.18 (m, 5H), 6.39 (br s, 1H), 4.63-4.20 (m, 3H), 3.41 (s, 2H), 2.42-1.76 (m, 4H), 1.39 (s, 9H). \(^13\)C NMR (CDCl$_3$, 75 MHz): δ 172.6, 138.4, 128.8, 127.9, 127.5, 80.7, 60.1, 47.2, 43.4, 31.3, 28.3, 24.6, 7.3. HRMS for C$_{17}$H$_{24}$N$_2$O$_3$ [M+Na]$^+$ calcd. 327.1679, found 327.1683.

Preparation of 2h:

Compound 10h (875 mg, 2.88 mmol) was dissolved in a mixture of TFA:DCM (1 ml:1 ml) and stirred for 60 min at room temperature. Completion of the reaction was determined by disappearance of starting material spot on TLC (EtOAc/Hex, 1:1). To workup, the reaction was evaporated under vacuum to an oil. Flash column chromatography using a gradient of 0-10% MeOH in CHCl$_3$ was used to purify the desired compound. Yield: 588 mg, quan. \(R_f=0.18\) (100% EtOAc). \(^1\)H NMR (CD$_2$OD, 300 MHz) δ 7.30-7.18 (m, 5H), 4.38 (s, 2H), 4.24-4.19 (m, 1H), 3.35-3.23 (m, 2H), 2.42-2.32 (m, 1H), 2.04-1.89 (m, 3H). \(^13\)C NMR (CD$_2$OD, 75 MHz): δ 169.9, 139.5, 129.8, 128.8, 128.6, 61.2, 47.3, 44.4, 31.0, 25.1. HRMS for C$_{12}$H$_{16}$N$_2$O [M+H]$^+$ calcd. 205.1335, found 205.1339.
Scheme S5. Synthesis of 1a-p
Preparation of 14a:

2-Iodobenzoic acid 13a (1 g, 4.03 mmol) was dissolved in MeOH (20 ml). Sulfuric acid (2.7 ml) was then slowly added and the mixture was stirred for 16 hr and heated at reflux under N₂. To workup, the reaction was cooled to room temperature, before diluting with ether. The organic layer was then washed with H₂O, brine, dried over magnesium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 847 mg, 80%. Characterization matched a previous report of this known compound.¹ ¹H NMR (CDCl₃, 300 MHz) δ 8.00 (dd, J = 1.0, 7.9 Hz, 1H), 7.80 (dd, J = 1.7, 7.8 Hz, 1H), 7.40 (td, J = 1.1, 7.6 Hz, 1H), 7.15 (td, J = 1.7, 7.7 Hz, 1H), 3.93 (s, 3H).

Preparation of 14i:

4-Fluoro-2-iodobenzoic acid 13i (300 mg, 1.13 mmol) and K₂CO₃ (234 mg, 1.69 mmol) were dissolved in DMF (10 ml) and stirred for 5 min. CH₃I (105 μl, 1.69 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 300 mg, quan. R₁ =0.58 (EtOAc/Hex, 1:4). Characterization matched a previous report of this known compound.⁶ ¹H NMR (CDCl₃, 300 MHz) δ 7.86 (dd, J = 5.9, 8.8 Hz, 1H), 7.72 (dd, J = 2.5, 8.2 Hz, 1H), 7.11 (td, J = 2.6, 8.7 Hz, 1H), 3.91 (s, 3H).

Preparation of 14j:

5-Fluoro-2-iodobenzoic acid 13j (300 mg, 1.13 mmol) and K₂CO₃ (234 mg, 1.69 mmol) were dissolved in DMF (10 ml) and stirred for 5 min. CH₃I (105 μl, 1.69 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 300 mg, quan. R₁ =0.60 (EtOAc/Hex, 1:4). Characterization matched a previous report of this known compound.⁷ ¹H NMR (CDCl₃, 300 MHz) δ 7.94 (dd, J = 5.4, 8.7 Hz, 1H), 7.54 (dd, J = 3.0, 9.0 Hz, 1H), 6.94 (td, J = 3.0, 7.8 Hz, 1H), 3.94 (s, 3H).

Preparation of 14k:

6-Fluoro-2-iodobenzoic acid 13k (300 mg, 1.13 mmol) and K₂CO₃ (234 mg, 1.69 mmol) were dissolved in DMF (10 ml) and stirred for 5 min. CH₃I (105 μl, 1.69 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 299 mg, quan. R₁ =0.59 (EtOAc/Hex, 1:4). Characterization matched a previous report of this known compound.⁸ ¹H NMR (CDCl₃, 300 MHz) δ 7.68-7.61 (m, 1H), 7.13-7.09 (m, 2H), 3.98 (s, 3H).
Preparation of 14l:

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{NO}_2 \\
\end{align*}
\]

5-Nitro-2-chlorobenzoic acid 13l (216 mg, 1.07 mmol) and K$_2$CO$_3$ (222 mg, 1.61 mmol) were dissolved in DMF (10 ml) and stirred for 5 min. CH$_3$I (100 μl, 1.61 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N$_2$. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 230 mg, quan. $R_t$=0.58 (EtOAc/Hex, 1:4). Characterization matched a previous report of this known compound.$^9$ $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.74-8.72 (m, 1H), 8.31-8.26 (m, 1H), 7.67 (dd, $J$ = 3.5, 8.8 Hz, 1H), 4.00 (s, 3H).

Preparation of 14m:

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{CF}_3 \\
\end{align*}
\]

5-trifluoromethyl-2-chlorobenzoic acid 13m (295 mg, 1.31 mmol) and K$_2$CO$_3$ (272 mg, 1.97 mmol) were dissolved in DMF (10 ml) and stirred for 5 min. CH$_3$I (123 μl, 1.97 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N$_2$. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 313 mg, quan. $R_t$=0.67 (EtOAc/Hex, 1:10). Characterization matched a previous report of this known compound.$^{10}$ $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.11 (s, 1H), 7.69-7.58 (m, 2H), 3.97 (s, 3H).

Preparation of 14n:

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\end{align*}
\]

4,5-Dimethyl-2-iodobenzoic acid 13n (300 mg, 1.09 mmol) and K$_2$CO$_3$ (225 mg, 1.63 mmol) were dissolved in DMF (10 ml) and stirred for 5 min. CH$_3$I (101 μl, 1.63 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N$_2$. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 299 mg, quan. $R_t$=0.60 (EtOAc/Hex, 1:4). Characterization matched a previous report of this known compound.$^{11}$ $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.77 (s, 1H), 7.62 (s, 1H), 3.91 (s, 3H), 2.23 (s, 6H).

Preparation of 14o:

\[
\begin{align*}
\text{MeO} & \quad \text{Cl} \quad \text{O} \\
\end{align*}
\]

4-Methoxy-2-iodobenzoic acid 13o (112 mg, 0.403 mmol) was dissolved in MeOH (2 ml). Sulfuric acid (270 μl) was then slowly added and the mixture was stirred for 16 hr and heated at reflux under N$_2$. To workup, the reaction was cooled to room temperature, before diluting with ether. The organic layer was then washed with H$_2$O, brine, dried over magnesium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 111 mg, quan. $R_t$=0.25 (EtOAc/Hex, 1:10). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.89-7.84 (m, 1H), 7.55-7.52 (m, 1H), 6.94-6.88 (m, 1H), 3.90 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 166.3, 162.3, 132.8, 127.2, 126.3, 113.8, 95.8, 55.7, 52.3. HRMS for C$_8$H$_{10}$O$_3$ [M+H]$^+$ calcd. 292.9669, found 292.9673.
Preparation of 14p:

5-Methoxy-2-chlorobenzoic acid 13p (285 mg, 1.53 mmol) and K₂CO₃ (317 mg, 2.29 mmol) were dissolved in DMF (10 ml) and stirred for 5 min. CH₃I (143 μl, 2.29 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum to give the desired pure compound. Yield: 306 mg, quan. Rᵣ = 0.26 (EtOAc/Hex, 1:10). Characterization matched a previous report of this known compound.¹² ¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.32 (m, 2H), 6.96 (dd, J = 2.9, 8.8 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H).

Preparation of 15a:

Compound 14a (400 mg, 1.53 mmol), CuI (58 mg, 0.31 mmol), and PdCl₂(PPh₃)₂ (107 mg, 0.15 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. (Triisopropylsilyl)acetylene (680 μl, 3.05 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 474 mg, 98%. Rᵣ = 0.70 (EtOAc/Hex, 1:5). ¹H NMR (CDCl₃, 300 MHz) δ 7.89 (dd, J = 1.3, 7.6 Hz, 1H), 7.60 (dd, J = 1.2, 7.8 Hz, 1H), 7.44 (td, J = 1.4, 7.5 Hz, 1H), 7.36 (td, J = 1.4, 7.7 Hz, 1H), 3.91 (s, 3H), 1.15 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 167.5, 135.2, 132.8, 131.6, 130.4, 128.2, 123.6, 105.3, 96.5, 52.3, 18.7, 11.4. HRMS for C₁₉H₂₈O₃Si [M+H]+ calcd. 317.1931, found 317.1935.

Preparation of 15i:

Compound 14i (303 mg, 1.08 mmol), CuI (41 mg, 0.217 mmol), and PdCl₂(PPh₃)₂ (76 mg, 0.108 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. (Triisopropylsilyl)acetylene (482 μl, 2.17 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 350 mg, 96%. Rᵣ = 0.34 (EtOAc/Hex, 1:10). ¹H NMR (CDCl₃, 300 MHz) δ 7.94 (dd, J = 5.8, 8.8 Hz, 1H), 7.28-7.25 (m, 2H), 7.06 (td, J = 2.6, 7.8 Hz, 1H), 3.90 (s, 3H), 1.15 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 166.4, 166.0, 162.7, 133.2, 133.1, 121.9, 121.6, 115.9, 115.6, 104.0, 98.3, 52.3, 18.7, 11.3. HRMS for C₁₉H₂₇FO₃Si [M+H]+ calcd. 335.1837, found 335.1841.
Preparation of 15j:

![Image of compound 15j]

Compound 14j (303 mg, 1.08 mmol), CuI (41 mg, 0.217 mmol), and PdCl₂(PPh₃)₂ (76 mg, 0.108 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. (Triisopropylsilylacetylene) (482 µl, 2.17 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 318 mg, 88%. Rᵣ=0.44 (EtOAc/Hex, 1:10).

^1H NMR (CDCl₃, 300 MHz) δ 7.61-7.56 (m, 2H), 7.18-7.12 (m, 1H), 3.92 (s, 3H), 1.14 (s, 2H); ^13C NMR (CDCl₃, 75 MHz): δ 166.2, 163.6, 160.3, 137.2, 137.1, 119.2, 118.9, 117.6, 117.3, 104.2, 96.3, 52.6, 18.7, 11.4. HRMS for C₁₉H₂₇FO₂Si [M+H]^+ calcd. 335.1837, found 335.1840.

Preparation of 15k:

![Image of compound 15k]

Compound 14k (303 mg, 1.08 mmol), CuI (41 mg, 0.217 mmol), and PdCl₂(PPh₃)₂ (76 mg, 0.108 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. (Triisopropylsilylacetylene) (482 µl, 2.17 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 320 mg, 89%. Rᵣ=0.38 (EtOAc/Hex, 1:10).

^1H NMR (CDCl₃, 300 MHz) δ 7.37-7.29 (m, 2H), 7.12-7.03 (m, 1H), 3.93 (s, 3H), 1.12 (s, 2H); ^13C NMR (CDCl₃, 75 MHz): δ 165.1, 161.2, 157.9, 131.4, 131.3, 129.2(2), 116.4, 116.1, 102.8, 96.7, 52.8, 18.6, 11.2. HRMS for C₁₉H₂₇FO₂Si [M+H]^+ calcd. 335.1837, found 335.1841.

Preparation of 15l:

![Image of compound 15l]

Compound 14l (200 mg, 0.930 mmol), CuI (35 mg, 0.186 mmol), and PdCl₂(PPh₃)₂ (65 mg, 0.093 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. (Triisopropylsilylacetylene) (414 µl, 1.86 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 337 mg, 94%. Rᵣ=0.0.37 (EtOAc/Hex, 1:10). ^1H NMR (CDCl₃, 300 MHz) δ 8.76 (d, J = 2.3 Hz, 1H), 8.28 (dd, J = 2.5, 8.6 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 3.97 (s, 3H), 1.16 (s, 2H); ^13C NMR (CDCl₃, 75 MHz): δ 165.1, 146.7, 136.2, 133.9, 130.0, 125.9, 125.8, 104.4, 103.4, 52.9, 18.7, 11.3. HRMS for C₁₉H₂₇NO₂Si [M+Na]^+ calcd. 384.1602, found 384.1605.
Preparation of 15m:

Compound 14m (282 mg, 1.18 mmol), CuI (45 mg, 0.236 mmol), and PdCl₂(PPh₃)₂ (83 mg, 0.118 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. (Triisopropylsilyl)acetylene (526 μl, 2.36 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 148 mg, 33%. Rₜ=0.43 (EtOAc/Hex, 1:10).

1H NMR (CDCl₃, 300 MHz) δ 8.17 (s, 1H), 7.72-7.65 (m, 2H), 3.94 (s, 3H), 1.16 (s, 21H); 13C NMR (CDCl₃, 75 MHz): δ 166.1, 135.7, 133.3, 130.4, 129.9, 128.1, 128.0, 127.6, 127.5, 103.9, 100.4, 52.6, 18.7, 11.3. HRMS for C₂₀H₁₇F₃O₃Si [M+Na]⁺ calcd. 407.1625, found 407.1629.

Preparation of 15n:

Compound 14n (291 mg, 1.00 mmol), CuI (38 mg, 0.201 mmol), and PdCl₂(PPh₃)₂ (71 mg, 0.100 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. (Triisopropylsilyl)acetylene (446 μl, 2.01 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 337 mg, 97%. Rₜ=0.49 (EtOAc/Hex, 1:10).

1H NMR (CDCl₃, 300 MHz) δ 7.70 (s, 1H), 7.37 (s, 1H), 3.90 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H), 1.16 (s, 21H); 13C NMR (CDCl₃, 75 MHz): δ 167.6, 141.0, 137.3, 136.2, 131.7, 130.0, 121.0, 105.8, 94.8, 52.1, 19.6, 19.5, 18.7, 11.4. HRMS for C₂₁H₁₅O₃Si [M+H]⁺ calcd. 345.2244, found 345.2248.

Preparation of 15o:

Compound 14o (304 mg, 1.04 mmol), CuI (40 mg, 0.208 mmol), and PdCl₂(PPh₃)₂ (73 mg, 0.104 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. (Triisopropylsilyl)acetylene (463 μl, 2.08 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 321 mg, 89%. Rₜ=0.59 (EtOAc/Hex, 1:4).

1H NMR (CDCl₃, 300 MHz) δ 7.91 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 2.7 Hz, 1H), 6.87 (dd, J = 2.7, 8.8 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 1.16 (s, 21H); 13C NMR (CDCl₃, 75 MHz): δ 166.9, 162.0, 132.8, 125.6, 124.9, 120.0, 114.2, 105.4, 96.4, 55.6, 52.0, 18.7, 11.4. HRMS for C₂₀H₁₆O₃Si [M+Na]⁺ calcd. 369.1856, found 369.1860.
Preparation of 15p:

![Chemical Structure](image)

Compound 14p (225 mg, 1.12 mmol), XPhos (107 mg, 0.224 mmol), PdCl\(_2\)(CH\(_3\)CN)\(_2\) (29 mg, 0.112 mmol), and CsCO\(_3\) (914 mg, 2.80 mmol) were dissolved in DMF (5 ml). The mixture was degassed with N\(_2\) for 5 min. (Triisopropylsilyl)acetylene (500 \(\mu\)l, 2.24 mmol) was then added and the mixture was stirred for 16 hr at 90°C under N\(_2\). To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H\(_2\)O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-5% EtOAc in Hex was used to purify the desired compound. Yield: 379 mg, 97%. \(R_t=0.63\) (EtOAc/Hex, 1:4).

\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.53 (d, \(J = 8.6\) Hz, 1H), 7.41 (d, \(J = 2.8\) Hz, 1H), 6.99 (dd, \(J = 2.9, 8.6\) Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 1.15 (s, 21H); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 167.4, 159.4, 136.6, 134.2, 118.3, 115.9, 114.8, 105.3, 94.2, 55.7, 52.3, 18.7, 11.4. HRMS for C\(_{20}\)H\(_{30}\)O\(_3\)Si [M+Na]\(^+\) calcd. 369.1856, found 369.1860.

Preparation of 16a:

Compound 15a (265 mg, 0.839 mmol) was dissolved in MeOH (3 ml) and THF (3 ml) at 0°C. KOH (471 mg, 8.39 mmol) dissolved in H\(_2\)O (3 ml) was then added and the mixture was stirred for 3 hr at rt under N\(_2\). To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H\(_2\)O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-25% EtOAc in Hex was used to purify the desired compound. Yield: 265 mg, quan. \(R_t=0.73\) (EtOAc/Hex, 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 8.07 (d, \(J = 7.8\) Hz, 1H), 7.64 (d, \(J = 7.7\) Hz, 1H), 7.51 (td, \(J = 1.3, 7.5\) Hz, 1H), 7.41 (td, \(J = 1.4, 7.8\) Hz, 1H), 1.16 (s, 21H); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 170.8, 135.2, 132.5, 131.5, 128.4, 124.2, 104.8, 98.7, 18.7, 11.4; HRMS for C\(_{19}\)H\(_{28}\)O\(_2\)Si [M+H]\(^+\) calcd. 303.1775, found 303.1776.

Preparation of 16i:

Compound 15i (361 mg, 1.08 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (607 mg, 10.83 mmol) dissolved in H\(_2\)O (6 ml) was then added and the mixture was stirred for 3 hr at rt under N\(_2\). To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H\(_2\)O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-20% EtOAc in Hex was used to purify the desired compound. Yield: 292 mg, 84%. \(R_t=0.21\) (EtOAc/Hex, 1:4). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 8.09 (dd, \(J = 5.8, 8.8\) Hz, 1H), 7.33-7.29 (m, 2H), 7.10 (td, \(J = 2.6, 8.7\) Hz, 1H), 1.15 (s, 21H); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 170.0, 166.7, 163.3, 134.0, 133.9, 122.1, 121.8, 116.0, 115.7, 103.6, 100.3, 18.6, 11.3. HRMS for C\(_{15}\)H\(_{25}\)FO\(_2\)Si [M+Na]\(^+\) calcd. 343.1500, found 343.1508.
Preparation of 16j:

Compound 15j (361 mg, 1.08 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (607 mg, 10.83 mmol) dissolved in H₂O (6 ml) was then added and the mixture was stirred for 2.5 hr at rt under N₂. To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-25% EtOAc in Hex was used to purify the desired compound. Yield: 300 mg, 87%. Rf=0.25 (EtOAc/Hex, 1:4). ¹H NMR (CDCl₃, 300 MHz) δ 7.78 (dd, J = 2.7, 9.1 Hz, 1H), 7.63 (dd, J = 5.4, 8.6 Hz, 1H), 7.25-7.20 (m, 1H), 1.15 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 165.9, 160.4, 137.1, 137.0, 120.3, 120.0, 118.6, 118.3, 102.8, 99.3, 18.6, 11.3. HRMS for C₁₃H₂₅FO₂Si [M+Na]⁺ calcd. 343.1500, found 343.1501.

Preparation of 16k:

Compound 15k (361 mg, 1.08 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (607 mg, 10.83 mmol) dissolved in H₂O (6 ml) was then added and the mixture was stirred for 3 hr at 50°C under N₂. To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-25% EtOAc in Hex was used to purify the desired compound. Yield: 251 mg, 72%. Rf=0.11 (EtOAc/Hex, 1:4). ¹H NMR (CDCl₃, 300 MHz) δ 7.42-7.35 (m, 2H), 7.14-7.08 (m, 1H), 1.12 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 161.7, 158.4, 132.1, 132.0, 129.5(2), 116.6, 116.3, 102.6, 98.0, 18.6, 11.3. HRMS for C₁₃H₂₅FO₂Si [M+Na]⁺ calcd. 343.1500, found 343.1502.

Preparation of 16l:

Compound 15l (337 mg, 0.878 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (492 mg, 8.78 mmol) dissolved in H₂O (6 ml) was then added and the mixture was stirred for 1 hr at rt under N₂. To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 296 mg, 97%. Rf=0.33 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 8.75 (s, 1H), 8.16 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 1.04 (s, 21H). ¹³C NMR (CDCl₃, 75 MHz): δ 146.6, 136.4, 130.2, 126.3, 126.2, 125.5(2), 104.6, 104.3, 58.8, 18.6, 11.3. HRMS for C₁₃H₂₅NO₂Si [M+Na]⁺ calcd. 370.1445, found 370.1449.
Preparation of 16m:

![Chemical structure of 16m]

Compound 15m (148 mg, 0.385 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (216 mg, 3.85 mmol) dissolved in H₂O (6 ml) was then added and the mixture was stirred for 2.5 hr at rt under N₂. To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 85 mg, 59%. Rᵣ=0.59 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 8.30 (s, 1H), 7.75 (s, 2H), 1.15 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.6, 135.8, 131.9, 130.5, 130.1, 129.0, 128.2, 128.0, 103.5, 102.5, 18.6, 11.3. HRMS for C₁₉H₂₅F₃O₂Si [M+Na]⁺ calcd. 393.1468, found 393.1474.

Preparation of 16n:

![Chemical structure of 16n]

Compound 15n (338 mg, 0.982 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (551 mg, 9.82 mmol) dissolved in H₂O (6 ml) was then added and the mixture was stirred for 2 hr at 50°C under N₂. To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-20% EtOAc in Hex was used to purify the desired compound. Yield: 320 mg, quan. Rᵣ=0.33 (EtOAc/Hex, 1:5). ¹H NMR (CDCl₃, 300 MHz) δ 7.87 (s, 1H), 7.38 (s, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.15 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.6, 142.2, 137.9, 136.0, 132.6, 128.8, 120.9, 105.2, 98.0, 19.7, 19.6, 18.7, 11.4. HRMS for C₂₀H₃₆O₂₅Si [M+H]⁺ calcd. 331.2088, found 331.2080.

Preparation of 16o:

![Chemical structure of 16o]

Compound 15o (360 mg, 1.04 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (584 mg, 10.41 mmol) dissolved in H₂O (6 ml) was then added and the mixture was stirred for 5 hr at rt under N₂. To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-50% EtOAc in Hex was used to purify the desired compound. Yield: 276 mg, 80%. Rᵣ=0.26 (EtOAc/Hex, 1:4). ¹H NMR (CDCl₃, 300 MHz) δ 8.05 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 2.3 Hz, 1H), 6.89 (dd, J = 2.4, 8.8 Hz, 1H), 3.86 (s, 3H), 1.16 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 162.6, 133.7, 128.8, 128.7, 126.0, 119.9, 114.4, 105.0, 98.5, 55.7, 18.7, 11.4. HRMS for C₁₉H₂₅O₃Si [M+H]⁺ calcd. 333.1880, found 333.1872.
Preparation of 16p:

Compound 15p (379 mg, 1.10 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (614 mg, 10.95 mmol) dissolved in H₂O (6 ml) was then added and the mixture was stirred for 1 hr at rt under N₂. To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-50% EtOAc in Hex was used to purify the desired compound. Yield: 361 mg, quan. R₁=0.09 (EtOAc/Hex, 1:4). ¹H NMR (CDCl₃, 300 MHz) δ 7.58-7.54 (m, 2H), 7.04 (dd, J = 2.8, 8.6 Hz, 1H), 3.87 (s, 3H), 1.15 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.4, 159.5, 136.5, 132.9, 119.1, 116.2, 115.6, 104.8, 96.8, 55.7, 18.7, 11.4. HRMS for C₁₉H₂₃O₃Si [M+Na]⁺ calc. 355.1700, found 355.1706.

Preparation of 17a:

Compound 16a (199 mg, 0.660 mmol), 2a (118 mg, 0.660 mmol), EDC (204 mg, 1.32 mmol), HOBt (178 mg, 1.32 mmol) were dissolved in DMF (10 ml). NEt₃ (185 µl, 1.32 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-20% EtOAc in Hex was used to purify the desired compound. Yield: 236 mg, 77%. R₁=0.46 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.55-7.48 (m, 1H), 7.38-7.28 (m, 6H), 7.23-7.14 (m, 2H), 6.98 (br s, 1H), 4.48 (d, J = 5.9, 2H), 3.98 (s, 2H), 3.02 (s, 3H), 1.10 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.0, 168.5, 138.0, 132.8, 129.0, 128.7, 128.5, 127.5, 127.3, 127.2, 126.6, 120.0, 103.3, 94.7, 54.3, 52.0, 43.0, 37.5, 34.0, 18.2, 10.8. HRMS for C₂₅H₃₈N₂O₅Si [M+H]⁺ calc. 463.2775, found 463.2770.

Preparation of 17b:

Compound 16a (100 mg, 0.330 mmol), 2b (54 mg, 0.330 mmol), EDC (102 mg, 0.660 mmol), HOBt (89 mg, 0.660 mmol) were dissolved in DMF (10 ml). NEt₃ (93 µl, 0.660 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-25% EtOAc in Hex was used to purify the desired compound. Yield: 134 mg, 91%. R₁=0.37 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 8.36 (br s, 1H), 8.07-8.04 (m, 1H), 7.59-7.56 (m, 1H), 7.45-7.42 (m, 2H), 7.33-7.23 (m, 5H), 6.71 (br s, 1H), 4.46 (d, J = 5.9, 2H), 4.16 (d, J = 5.8, 2H), 1.13 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.0, 167.2, 138.2, 134.8, 134.3, 131.3, 130.5, 129.3, 128.9, 127.8, 127.7, 120.2, 105.5, 99.8, 44.5, 43.5, 18.7, 11.2. HRMS for C₂₇H₃₆N₂O₅Si [M+H]⁺ calc. 449.2619, found 449.2627.
Preparation of 17c:

![chemical structure]

Compound 16a (222 mg, 0.734 mmol), 2c (177 mg, 0.735 mmol), EDC (228 mg, 1.47 mmol), HOBT (199 mg, 1.47 mmol) were dissolved in CHCl₃ (10 ml). NEt₃ (206 μl, 1.47 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-20% EtOAc in Hex was used to purify the desired compound. Yield: 93 mg, 24%. Rₜ=0.63 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.43-7.23 (m, 8H), 7.15-7.05 (m, 6H), 4.53-4.47 (m, 4H), 1.15 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.9, 168.9, 142.6, 138.4, 133.1, 129.8, 129.2, 129.0(2), 128.8, 128.1, 128.0, 127.9, 127.7, 127.3, 80.4, 80.1, 54.3, 43.7, 18.7, 11.4. HRMS for C₃₃H₄₀N₂O₃Si [M+H]⁺ calcd. 525.2932, found 525.2928.

Preparation of 17d:

![chemical structure]

Compound 16a (110 mg, 0.364 mmol), 2d (90 mg, 0.364 mmol), HCTU (300 mg, 0.728 mmol), HOBT(6-Cl) (123 mg, 0.728 mmol) were dissolved in DMF (5 ml). DIPEA (247 μl, 1.46 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-30% EtOAc in Hex was used to purify the desired compound. Yield: 181 mg, 93%. Rₜ=0.59 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.54-7.50 (m, 1H), 7.43-7.27 (m, 8H), 7.02-6.96 (m, 1H), 4.67-4.49 (m, 2H), 4.39-4.24 (m, 1H), 3.74-3.61 (m, 1H), 3.29-3.19 (m, 1H), 2.00-1.85 (m, 1H), 1.73-1.65(m, 2H), 1.58-1.43 (m, 4H), 1.06 (s, 21H), 1.02-0.85 (m, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 171.7, 170.7, 139.2, 138.6, 133.7, 128.9(2), 128.8, 127.7, 127.5, 125.7, 120.2, 104.0, 95.5, 59.9, 46.5, 43.5, 31.7, 31.0, 30.4, 25.6, 24.9, 18.6, 11.3. HRMS for C₃₃H₄₆N₂O₃Si [M+H]⁺ calcd. 531.3401, found 531.3410.

Preparation of 17e:

![chemical structure]

Compound 16a (121 mg, 0.400 mmol), 2e (99 mg, 0.400 mmol), HCTU (331 mg, 0.801 mmol), HOBT(6-Cl) (136 mg, 0.801 mmol) were dissolved in DMF (5 ml). DIPEA (272 μl, 1.60 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 15-30% EtOAc in Hex was used to purify the desired compound. Yield: 210 mg, quan. Rₜ=0.64 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.12-7.05 (m, 1H), 6.98-6.87 (m,
7H), 6.76-6.66 (m, 2H), 4.12-3.88 (m, 2H), 2.79 (s, 2H), 1.13-1.00 (m, 1H), 0.92-0.85 (m, 1H), 0.74-0.54 (m, 8H), 0.67 (s, 2H), 0.35 (t, J = 6.9, 3H). \(^1\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 171.6, 170.0, 168.4, 138.7, 138.5, 133.3, 129.1, 128.8(2), 127.9, 127.8, 127.6, 126.7, 120.5, 103.8, 95.4, 51.9, 51.8, 43.4, 31.0, 28.4, 26.1, 22.4, 18.7, 13.9, 11.3. HRMS for C\(_{33}\)H\(_{51}\)N\(_2\)O\(_2\)Si [M+Na]\(^+\) calcd. 555.3377, found 555.3387.

Preparation of 17f:

Compound 16a (130 mg, 0.430 mmol), 2f (89 mg, 0.430 mmol), EDC (133 mg, 0.860 mmol), HOBt (116 mg, 0.860 mmol) were dissolved in DMF (5 ml). NEt\(_3\) (240 μl, 1.72 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N\(_2\). To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H\(_2\)O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 15-30% EtOAc in Hex was used to purify the desired compound. Yield: 210 mg, quan. \(R_t=0.54\) (EtOAc/Hex, 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.53-7.56 (m, 1H), 7.28-7.45 (m, 7H), 7.01-7.04 (m, 1H), 4.72-4.52 (m, 2H), 4.41-4.24 (m, 2H), 3.76 (quin, J = 6.7 Hz, 1H), 1.23 (m, 6H), 1.09 (m, 21H); \(^1\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 171.5, 170.6, 138.7, 138.5, 133.3, 129.1, 128.8(2), 128.8, 127.7, 127.5, 125.6, 120.3, 103.9, 95.6, 51.4, 45.5, 43.5, 18.7(2), 11.3. HRMS for C\(_{30}\)H\(_{42}\)N\(_2\)O\(_2\)Si [M+H]\(^+\) calcd. 491.3088, found 491.3092.

Preparation of 17g:

Compound 16a (140 mg, 0.463 mmol), 2g (102 mg, 0.463 mmol), HCTU (383 mg, 0.926 mmol), HOBt(6-Cl) (157 mg, 0.926 mmol) were dissolved in DMF (5 ml). DIPEA (260 μl, 1.85 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N\(_2\). To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H\(_2\)O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-25% EtOAc in Hex was used to purify the desired compound. Yield: 616 mg, 77%. \(R_t=0.14\) (EtOAc/Hex, 1:4). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.46 (d, J = 8.7, 1H), 7.36-7.16 (m, 7H), 7.10 (d, J = 7.1, 1H), 4.40 (d, J = 5.9, 2H), 4.00 (s, 2H), 1.54 (s, 9H), 1.10 (s, 21H); \(^1\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 164.8, 162.6, 137.9, 134.0, 131.8, 129.0, 128.9, 128.6, 128.0, 127.9, 127.5, 126.2, 95.6, 92.5, 58.5, 50.9, 43.6, 28.7, 18.7, 11.3. HRMS for C\(_{31}\)H\(_{44}\)N\(_2\)O\(_2\)Si [M+H]\(^+\) calcd. 505.3245, found 505.3247.

Preparation of 17h:

Compound 16a (132 mg, 0.437 mmol), 2h (89 mg, 0.437 mmol), HCTU (361 mg, 0.873 mmol), HOBt(6-Cl) (148 mg, 0.873 mmol) were dissolved in DMF (5 ml). DIPEA (296 μl, 1.75 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N\(_2\). To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H\(_2\)O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 213 mg, quan. \(R_t=0.42\) (EtOAc/Hex, 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.92-7.82 (m, 2H), 7.71 (d, J=
1.7, 1H), 7.51-7.02 (m, 6H), 4.63-4.38 (m, 1H), 4.26-4.03 (m, 1H), 3.84-3.63 (m, 1H), 3.49-3.25 (m, 2H), 2.32-2.17 (m, 1H), 2.10-1.82 (m, 3H), 1.10 (s, 21H); 13C NMR (CDCl₃, 75 MHz): δ 174.3, 171.4, 134.9, 134.0, 130.5, 130.4, 130.1, 129.6, 128.9, 128.4, 128.2, 127.5, 121.2, 110.5, 63.0, 61.5, 44.0, 33.2, 31.3, 25.7, 23.8, 19.1, 12.4. HRMS for C₃₀H₂₈N₂O₃Si [M+H]+ calcd. 489.2932, found 489.2942.

Preparation of 17i:

Compound 16i (132 mg, 0.413 mmol), 2a (88 mg, 0.495 mmol), EDC (128 mg, 0.825 mmol), HOBT (111 mg, 0.825 mmol) were dissolved in DMF (8 ml). NEt₃ (230 μl, 1.65 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 30-50% EtOAc in Hex was used to purify the desired compound. Yield: 167 mg, 84%. Rᵢ = 0.43 (EtOAc/Hex, 1:1). 1H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.37-7.28 (m, 4H), 7.22-7.16 (m, 3H), 7.10-7.03 (m, 1H), 4.48 (d, J = 5.8, 2H), 4.07 (s, 2H), 3.02 (s, 3H), 1.10 (s, 21H); 13C NMR (CDCl₃, 75 MHz): δ 170.7, 168.8, 163.5, 129.3, 129.0 (2), 128.0, 127.8, 120.0, 116.8, 116.5, 115.8, 102.6, 94.9, 55.8, 52.5, 43.5, 38.0, 25.8, 18.7, 11.2. HRMS for C₂₈H₂₇FN₂O₂Si [M+H]+ calcd. 481.2681, found 481.2685.

Preparation of 17j:

Compound 16j (132 mg, 0.413 mmol), 2a (88 mg, 0.495 mmol), EDC (128 mg, 0.825 mmol), HOBT (111 mg, 0.825 mmol) were dissolved in DMF (8 ml). NEt₃ (230 μl, 1.65 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 15-30% EtOAc in Hex was used to purify the desired compound. Yield: 198 mg, quan. Rᵢ = 0.59 (EtOAc/Hex, 1:1). 1H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.52-7.45 (m, 1H), 7.38-7.28 (m, 3H), 7.15-6.88 (m, 4H), 4.46 (d, J = 5.9, 2H), 3.97 (s, 2H), 3.02 (s, 3H), 1.09 (s, 21H); 13C NMR (CDCl₃, 75 MHz): δ 169.9, 168.5, 167.7, 140.5, 138.3, 135.3, 129.0, 127.7, 116.9, 116.6, 114.6, 114.3, 102.6, 94.9, 54.5, 52.2, 43.5, 37.8, 34.4, 18.6, 11.2. HRMS for C₂₈H₂₇FN₂O₂Si [M+H]+ calcd. 481.2681, found 481.2691.

Preparation of 17k:

Compound 16k (143 mg, 0.447 mmol), 2a (95 mg, 0.536 mmol), HCTU (369 mg, 0.894 mmol), HOBT(6-Cl) (152 mg, 0.894 mmol) were dissolved in DMF (10 ml). DIPEA (303 μl, 1.79 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 15-30% EtOAc in Hex was used to purify the desired compound.
Yield: 181 mg, 84%. Rf = 0.50 (EtOAc/Hex, 1:1). 1H NMR (CDCl3, 300 MHz, mixture of rotamers) δ 7.36-7.28 (m,8H), 7.12-6.97 (m,1H), 6.77 (br s,1H), 4.65-4.37 (m,3H), 3.47-3.37 (m,1H), 2.99 (s,3H), 1.10 (s,21H); 13C NMR (CDCl3, 75 MHz): δ 168.4, 167.8, 166.4, 138.0, 137.6, 130.8, 130.7, 129.0, 128.9, 127.9, 127.7, 122.6, 116.5, 116.2, 102.2, 96.7, 54.8, 52.1, 43.6, 37.3, 34.1, 18.6, 11.2. HRMS for C28H37FN3O2Si [M+H]+ calcd. 481.2681, found 481.2685.

Preparation of 17l:

Compound 16l (207 mg, 0.561 mmol), 2a (120 mg, 0.674 mmol), EDC (174 mg, 1.12 mmol), HOBt (152 mg, 1.12 mmol) were dissolved in DMF (5 ml). NEt3 (314 μl, 2.25 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N2. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H2O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 15-30% EtOAc in Hex was used to purify the desired compound. Yield: 207 mg, 73%. Rf = 0.61 (EtOAc/Hex, 1:1). 1H NMR (CDCl3, 300 MHz, mixture of rotamers) δ 8.26-8.13 (m,2H), 7.71-7.61 (m,1H), 7.43-7.29 (m,5H), 6.87 (br s,1H), 4.48 (d, J = 5.9, 2H), 3.97 (s,2H), 3.03 (s,3H), 1.11 (s,21H); 13C NMR (CDCl3, 75 MHz): δ 168.9, 168.1, 167.2, 147.3, 139.8, 138.2, 134.2, 129.0, 127.8, 127.7, 126.7, 124.1, 122.6, 101.8, 54.4, 52.1, 43.5, 37.9, 34.5, 18.6, 11.1. HRMS for C28H37FN3O4Si [M+H]+ calcd. 508.2626, found 508.2622.

Preparation of 17m:

Compound 16m (85 mg, 0.229 mmol), 2a (41 mg, 0.229 mmol), EDC (72 mg, 0.459 mmol), HOBt (62 mg, 0.459 mmol) were dissolved in DMF (8 ml). NEt3 (128 μl, 0.918 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N2. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H2O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 120 mg, quan. Rf = 0.16 (EtOAc/Hex, 1:4). 1H NMR (CDCl3, 300 MHz, mixture of rotamers) δ 7.66-7.45 (m,4H), 7.37-7.25 (m,4H), 6.94 (br s,1H), 4.48 (d, J = 5.8, 2H), 3.99 (s,2H), 3.02 (s,3H), 1.11 (s,21H); 13C NMR (CDCl3, 75 MHz): δ 169.9, 168.4, 167.5, 139.1, 138.3, 133.6, 128.9, 127.8, 127.7, 126.1, 124.0, 121.7, 102.3, 98.6, 54.5, 52.2, 43.5, 37.9, 34.4, 18.6, 11.2. HRMS for C29H37F3N2O2Si [M+H]+ calcd. 531.2649, found 531.2653.
Preparation of 17n:

Compound 16n (168 mg, 0.509 mmol), 2a (109 mg, 0.610 mmol), EDC (158 mg, 1.02 mmol), HOBt (137 mg, 1.02 mmol) were dissolved in DMF (10 ml). NEt₃ (345 μl, 2.03 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 243 mg, 97%. Rᵣ = 0.53 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.37-7.27 (m, 6H), 7.07-6.99 (m, 1H), 6.95 (br s, 1H), 4.48 (d, J = 5.8, 2H), 4.01 (s, 2H), 3.02 (s, 3H), 2.24 (s, 6H), 1.09 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.8, 169.2, 168.2, 138.5, 138.3, 135.9, 134.0, 128.9, 128.3, 127.7, 127.6, 117.7, 104.2, 93.7, 54.9, 52.7, 43.4, 37.9, 34.3, 19.7, 19.4, 18.7, 11.3. HRMS for C₃₀H₄₂N₂O₂S [M+H]⁺ calcd. 491.3088, found 491.3097.

Preparation of 17o:

Compound 16o (126 mg, 0.379 mmol), 2a (88 mg, 0.493 mmol), EDC (117 mg, 0.758 mmol), HOBt (102 mg, 0.758 mmol) were dissolved in DMF (10 ml). NEt₃ (212 μl, 1.52 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-50% EtOAc in Hex was used to purify the desired compound. Yield: 186 mg, quan. Rᵣ = 0.36 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.36-7.28 (m, 4H), 7.17-7.08 (m, 3H), 6.99-6.87 (m, 2H), 4.47 (d, J = 5.9, 2H), 4.13 (s, 2H), 3.82 (s, 3H), 3.03 (s, 3H), 1.10 (s, 21H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.5, 169.1, 160.2, 138.5, 130.9, 128.9, 128.3, 127.7, 127.6, 117.8, 115.5, 103.8, 95.0, 55.6, 54.9, 52.6, 43.4, 38.0, 34.5, 18.7, 11.3. HRMS for C₂₉H₄₀N₂O₃Si [M+H]⁺ calcd. 493.2881, found 493.2887.

Preparation of 17p:

Compound 16p (176 mg, 0.530 mmol), 2a (142 mg, 0.795 mmol), EDC (164 mg, 1.06 mmol), HOBt (143 mg, 1.06 mmol) were dissolved in DMF (10 ml). NEt₃ (289 μl, 2.12 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 20-50% EtOAc in Hex was used to purify the desired compound. Yield: 178 mg, 68%. Rᵣ = 0.36 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.45-7.28 (m, 5H), 6.94-6.70 (m, 4H), 4.48 (d, J = 5.9, 2H), 4.13 (s, 2H), 3.78 (s, 3H), 3.04 (s, 3H), 1.09 (s, 21H); ¹³C NMR
(CDCl₃, 75 MHz): δ 171.2, 168.9, 160.2, 140.0, 138.4, 134.8, 128.9, 127.7, 115.9, 112.6, 111.9, 111.7, 103.8, 93.1, 55.6, 55.5, 52.5, 43.4, 37.9, 34.3, 18.7, 11.3. HRMS for C₂₉H₆₀N₂O₅Si [M+H]^+ calcd. 493.2881, found 493.2890.

Preparation of 1a:

Compound 17a (236 mg, 0.510 mmol) was dissolved in DCM (2 ml). TBAF (764 μl of 1.0M solution, 0.764 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-100% EtOAc in Hex was used to purify the desired compound. Yield: 155 mg, quan. Rf =0.13 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.51-7.29 (m, 9H), 6.88 (br s, 1H), 4.49 (d, J = 5.6, 2H), 4.30 (s, 2H), 2.96 (s, 3H), 2.40 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.9, 168.4, 138.7, 138.1, 133.2, 129.7, 129.5, 129.0, 128.3, 127.9, 126.6, 118.9, 81.2, 81.0, 55.0, 52.0, 43.7, 37.9, 34.0. HRMS for C₁₉H₁₈N₂O₂ [M+Na]^+ calcd. 329.1260, found 329.1270.

Preparation of 1b:

Compound 17b (134 mg, 0.299 mmol) was dissolved in DCM (2 ml). TBAF (450 μl of 1.0M solution, 0.448 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum to give a white precipitate, which was then washed with hexanes and filtered to give the desired compound. Yield: 42 mg, 48%. Rf =0.29 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 8.13-8.05 (m, 1H), 7.76-7.69 (m, 1H), 7.56-7.49 (m, 1H), 7.42-7.19 (m, 6H), 4.44 (d, J= 5.7, 2H), 4.24 (d, J= 5.0, 2H), 3.36 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 168.8, 166.8, 138.1, 135.8, 134.3, 130.9, 129.7, 129.4, 128.8, 128.0, 127.7, 119.1, 84.3, 81.9, 44.2, 43.6. HRMS for C₁₈H₁₆N₂O₂ [M+Na]^+ calcd. 315.1104, found 315.1110.

Preparation of 1c:

Compound 17c (93 mg, 0.177 mmol) was dissolved in DCM (2 ml). TBAF (265 μl of 1.0M solution, 0.265 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 20-50% EtOAc in Hex was used to purify the desired compound. Yield: 44 mg, 47%. Rf =0.73 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.39-7.28 (m, 6H), 7.20-7.08 (m, 8H), 4.61 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 2.62 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.7, 168.6, 144.2, 143.7, 142.4, 139.3, 138.2, 133.1, 129.4, 129.1, 129.0, 128.7, 128.4, 127.9, 127.3(2), 81.7, 81.6, 54.6, 43.9. HRMS for C₂₄H₂₆N₂O₂ [M+Na]^+ calcd. 391.1417, found 391.1421.
Preparation of 1d:

Compound 17d (193 mg, 0.364 mmol) was dissolved in DCM (2 ml). TBAF (546 μl of 1.0M solution, 0.546 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 20-50% EtOAc in Hex was used to purify the desired compound. Yield: 124 mg, 90%. Rᵣ=0.31 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.48-7.43 (m, 1H), 7.40-7.25 (m, 7H), 7.19-7.16 (m, 1H), 7.08 (br s, 1H), 4.70-4.50 (m, 2H), 4.40-4.24 (m, 1H), 3.88-3.72 (m, 1H), 3.27-3.17 (m, 1H), 2.18 (s, 1H), 1.93-1.80 (m, 1H), 1.77-1.60(m, 2H), 1.58-1.37 (m, 4H), 1.08-0.85 (m, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.3, 169.8, 139.5, 138.4, 133.2, 129.5, 129.1, 128.9, 128.4, 127.8, 125.6, 118.7, 81.2, 81.1, 59.4, 46.1, 43.7, 31.2, 30.8, 25.5, 25.4, 24.8. HRMS for C₂₄H₂₈N₂O₂ [M+H]⁺ calcd. 375.2067, found 375.2060.

Preparation of 1e:

Compound 17e (213 mg, 0.400 mmol) was dissolved in DCM (2 ml). TBAF (655 μl of 1.0M solution, 0.655 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 130 mg, 86%. Rᵣ=0.35 (EtOAc/Hex, X:X). ¹H NMR (CDCl₃, 300 MHz) δ 7.51-7.44 (m, 1H), 7.41-7.27 (m, 7H), 7.09-7.00 (m, 1H), 4.48 (s, 2H), 3.17 (t, J= 7.8, 2H), 2.35 (s, 1H), 1.81-1.72 (m, 1H), 1.54-1.40 (m, 2H), 1.32-1.00 (m, 7H), 0.80 (t, J= 6.8, 3H); ¹³C NMR (CDCl₃, 75 MHz), δ 171.1, 169.0, 138.9, 138.2, 133.2, 129.5, 129.3, 129.0, 128.3, 127.8, 126.5, 118.9, 81.2, 81.1, 50.5, 49.9, 43.7, 31.1, 28.2, 26.0, 22.4, 13.9. HRMS for C₂₄H₂₈N₂O₂ [M+H]⁺ calcd. 377.2224, found 377.2230.

Preparation of 1f:

Compound 17f (231 mg, 0.472 mmol) was dissolved in DCM (2 ml). TBAF (708 μl of 1.0M solution, 0.708 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 156 mg, 98%, Rᵣ=0.57 (EtOAc/Hex, 3:4). ¹H NMR (CDCl₃, 300 MHz) δ 7.49-7.11 (m, 9H), 7.48-7.25 (m, 7H), 3.83-3.72 (m, 2H), 2.19 (s, 1H), 1.24 (s, 3H), 1.07 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.1, 169.7, 139.4, 138.4, 133.3, 129.6, 129.2, 128.5, 127.8, 125.7, 118.8, 81.2, 51.1, 45.0, 43.7, 20.7. HRMS for C₂₁H₂₂N₂O₂ [M+Na]⁺ calcd. 357.1573, found 357.1565.
Preparation of 1g:

Compound 17g (26 mg, 0.051 mmol) was dissolved in DCM (2 ml). TBAF (76 μl of 1.0M solution, 0.076 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 30-50% EtOAc in Hex was used to purify the desired compound. Yield: 18 mg, 99%. R_f =0.41 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.48-7.43 (m, 1H), 7.37-7.19 (m, 7H), 7.16-7.13 (m, 1H), 4.40 (s, 2H), 3.95 (s, 2H), 2.92 (s, 1H), 1.50 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.7, 169.8, 137.8, 133.4, 129.5, 129.0(2), 128.7, 128.3(2), 128.0, 125.6, 81.4, 58.8, 51.1, 50.1, 43.8, 28.5. HRMS for C₂₂H₂₄N₂O₂ [M+Na]⁺ calcd. 371.1730, found 371.1725.

Preparation of 1h:

Compound 17h (213 mg, 0.437 mmol) was dissolved in DCM (2 ml). TBAF (655 μl of 1.0M solution, 0.655 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 133 mg, 91%. R_f = 0.39 (EtOAc/Hex, 3:4). ¹H NMR (CDCl₃, 300 MHz) δ 7.50-7.22 (m, 9H), 4.93-4.82 (m, 1H), 4.62-4.33 (m, 2H), 3.52-3.42 (m, 1H), 3.27-3.13 (m, 1H), 2.61-2.44 (m, 2H), 2.16-1.81 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.0, 170.0, 140.0, 138.4, 133.2, 129.6, 129.4, 128.9, 128.1, 127.6, 126.4, 118.8, 81.2, 80.8, 60.1, 49.0, 43.7, 28.2, 24.9. HRMS for C₂₁H₂₀N₂O₂ [M+H]⁺ calcd. 333.1598, found 333.1591.

Preparation of 1i:

Compound 17i (167 mg, 0.347 mmol) was dissolved in DCM (2 ml). TBAF (521 μl of 1.0M solution, 0.521 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 87 mg, 77%. R_f = 0.14 (EtOAc/HEX, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.38-7.28 (m, 6H), 7.23-7.10 (m, 2H), 6.79 (br s, 1H), 4.49 (d, J= 5.6, 2H), 4.28 (s, 2H), 2.97 (s, 3H), 2.45 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.2, 168.3, 161.0, 138.1, 129.1, 128.9, 128.8, 128.0, 121.2, 120.2, 119.9, 117.5, 117.2, 82.1, 80.0, 52.2, 43.7, 38.0. HRMS for C₁₉H₁₇FN₂O₂ [M+Na]⁺ calcd. 347.1166, found 347.1176.
Preparation of 1j:

Compound 17j (200 mg, 0.417 mmol) was dissolved in DCM (2 ml). TBAF (630 μl of 1.0M solution, 0.626 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 117 mg, 87%. Rf = 0.20 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.51-7.46 (m, 1H), 7.38-7.29 (m, 6H), 7.11-6.99 (m, 2H), 4.49 (d, J = 5.6, 2H), 4.27 (s, 2H), 2.98 (s, 3H), 2.40 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.5, 168.1, 164.6, 138.0, 135.5, 135.4, 129.1, 128.3, 128.1, 128.0, 117.1, 116.8, 114.4, 114.1, 80.8, 80.2, 52.1, 43.7, 37.8. HRMS for C₁₉H₁₇FN₂O₂ [M+Na]+ calcd. 347.1166, found 347.1172.

Preparation of 1k:

Compound 17k (181 mg, 0.376 mmol) was dissolved in DCM (2 ml). TBAF (565 μl of 1.0M solution, 0.565 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 102 mg, 84%. Rf = 0.21 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.39-7.29 (m, 8H), 7.19-7.09 (m, 1H), 4.69-4.63 (m, 1H), 4.52-4.48 (m, 2H), 4.00-3.95 (m, 1H), 4.00-3.95 (m, 1H), 2.98 (s, 3H), 2.51 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 168.2, 159.8, 138.0, 131.1, 130.9, 129.2, 128.0, 128.2, 127.9, 117.2, 117.0, 82.0, 79.8, 52.0, 43.8, 37.3, 34.0. HRMS for C₁₉H₁₇FN₂O₂ [M+Na]+ calcd. 347.1166, found 347.1169.

Preparation of 1l:

Compound 17l (207 mg, 0.408 mmol) was dissolved in DCM (2 ml). TBAF (612 μl of 1.0M solution, 0.612 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 143 mg, quan. Rf = 0.44 (EtOAc/Hex, 3:4). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 8.24-8.18 (m, 2H), 7.70-7.64 (m, 1H), 7.39-7.29 (m, 5H), 6.73 (br s, 1H), 4.49 (d, J = 5.6, 2H), 4.28 (s, 2H), 3.00 (s, 3H), 2.75 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 168.5, 167.8, 147.8, 140.1, 138.0, 134.3, 129.1, 128.3, 128.0, 125.5, 124.2, 122.2, 86.1, 79.3, 54.6, 52.1, 43.8, 37.9, 34.4. HRMS for C₁₉H₁₇N₃O₄ [M+Na]+ calcd. 374.1111, found 374.1104.
Preparation of 1m:

Compound 17m (84 mg, 0.158 mmol) was dissolved in DCM (2 ml). TBAF (236 μl of 1.0M solution, 0.236 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 58 mg, quan. R₆ = 0.19 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.62-7.57 (m, 3H), 7.38-7.29 (m, 5H), 6.81 (br s, 1H), 4.49 (d, J = 5.6, 2H), 4.27 (s, 2H), 2.98 (s, 3H), 2.61 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.4, 168.0, 167.3, 139.4, 138.0, 133.7, 129.0, 128.2, 127.9, 125.2, 122.7, 83.6, 79.8, 54.6, 52.0, 43.7, 37.9, 34.2. HRMS for C₂₀H₁₇F₃N₂O₂ [M+Na]+ calcd. 397.1134, found 397.1140.

Preparation of 1n:

Compound 17n (243 mg, 0.510 mmol) was dissolved in DCM (2 ml). TBAF (765 μl of 1.0M solution, 0.765 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 159 mg, 93%. R₆ = 0.20 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.37-7.21 (m, 7H), 6.92 (br s, 1H), 4.49 (d, J = 5.6, 2H), 4.29 (s, 2H), 2.97 (s, 3H), 2.36 (s, 1H), 2.26 (s, 3H), 2.24 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.4, 168.0, 167.3, 139.4, 138.0, 133.7, 129.0, 128.2, 127.9, 125.2, 122.7, 83.6, 79.8, 54.6, 52.0, 43.7, 37.9, 34.2. HRMS for C₂₁H₂₂N₂O₂ [M+Na]+ calcd. 357.1573, found 357.1574.

Preparation of 1o:

Compound 17o (208 mg, 0.423 mmol) was dissolved in DCM (2 ml). TBAF (635 μl of 1.0M solution, 0.635 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 75-100% EtOAc in Hex was used to purify the desired compound. Yield: 103 mg, 72%. R₆ = 0.09 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.37-7.20 (m, 6H), 6.98-6.91 (m, 3H), 4.49 (d, J = 5.6, 2H), 4.28 (s, 2H), 3.81 (s, 3H), 2.98 (s, 3H), 2.40 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.0, 168.6, 160.1, 138.1, 131.1, 129.0, 128.4, 128.3, 127.9, 120.3, 117.8, 116.1, 81.3, 80.8, 55.6, 52.2, 43.6, 38.1. HRMS for C₂₀H₂₀N₂O₃ [M+Na]+ calcd. 359.1366, found 359.1370.
Preparation of 1p:

Compound 17p (178 mg, 0.362 mmol) was dissolved in DCM (2 ml). TBAF (550 μl of 1.0M solution, 0.544 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 121 mg, 99%. Rᵢ =0.10 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.42-7.28 (m, 6H), 6.92-6.78 (m, 3H), 4.49 (d, J = 5.6, 2H), 4.29 (s, 2H), 3.82 (s, 3H), 2.98 (s, 3H), 2.32 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.7, 168.4, 160.6, 140.2, 138.0, 134.8, 129.0, 128.3, 128.1, 127.9, 115.8, 111.7, 110.8, 81.4, 79.5, 55.7, 52.0, 43.6, 37.8, 33.9. HRMS for C₂₀H₂₀N₂O₃ [M+Na]⁺ calcd. 359.1366, found 359.1376.

Scheme S6. Synthesis of 1q

Preparation of 15q:

Compound 14a (520 mg, 1.99 mmol), CuI (76 mg, 0.397 mmol), and PdCl₂(PPh₃)₂ (140 mg, 0.199 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. 1-Heptyne (521 μl, 3.97 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-20% EtOAc in Hex was used to purify the desired compound. Yield: 413 mg, 90%. Rᵢ =0.63 (EtOAc/Hex, 1:4). ¹H NMR (CDCl₃, 300 MHz) δ 7.88 (d, J = 7.9, 1H), 7.52-7.28 (m, 3H), 3.92 (s, 3H), 2.47 (t, J = 7.0, 2H), 1.69-1.60 (m, 2H), 1.51-1.31 (m, 4H), 0.93 (t, J = 7.2, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 167.3, 134.4, 132.2, 131.7, 130.3, 127.3, 124.7, 96.2, 79.3, 52.1, 31.2, 28.5, 22.3, 19.8, 14.0. HRMS for C₁₅H₁₈O₂ [M+H]⁺ calcd. 231.1380, found 231.1385.

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Preparation of 16q:

Compound 15q (457 mg, 1.99 mmol) was dissolved in MeOH (6 ml) and THF (6 ml) at 0°C. KOH (1110 mg, 19.85 mmol) dissolved in H₂O (6 ml) was then added and the mixture was stirred for 4.5 hr at rt under N₂. To workup, the mixture was acidified to pH~3 with 1M HCl solution, which allowed the product to be extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-50% EtOAc in Hex was used to purify the desired compound. Yield: 347 mg, 80%. Rf = 0.53 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 8.08 (d, J = 7.9, 1H), 7.56-7.34 (m, 3H), 2.50 (t, J = 7.0, 2H), 1.71-1.61 (m, 2H), 1.52-1.31 (m, 4H), 0.93 (t, J = 7.1, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.4, 134.5, 132.6, 131.5, 130.9, 127.7, 124.7, 98.3, 79.1, 31.2, 28.2, 22.3, 19.8, 14.0. HRMS for C₁₄H₁₆O₂ [M+H]⁺ calcd. 217.1223, found 217.1224.

Preparation of 1q:

Compound 16q (134 mg, 0.620 mmol), 2a (144 mg, 0.806 mmol), EDC (192 mg, 1.24 mmol), HOBt (167 mg, 1.24 mmol) were dissolved in DMF (5 ml). NEt₃ (347 μl, 2.48 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 181 mg, 78%. Rf = 0.26 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.45-7.18 (m, 9H), 7.01 (br s, 1H), 4.51 (d, J = 5.9, 2H), 4.24 (s, 2H), 3.00 (s, 3H), 2.21 (t, J = 7.1, 2H), 1.55-1.45 (m, 2H), 1.37-1.24 (m, 4H), 0.90 (t, J = 7.0, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.7, 168.9, 138.3, 137.9, 132.8, 129.4, 128.9, 128.3, 127.9, 127.8, 127.6, 127.4, 126.7, 121.1, 94.7, 52.5, 43.5, 38.1, 34.0, 31.1, 28.4, 22.2, 19.3, 14.0. HRMS for C₂₄H₂₃N₂O₂ [M+H]⁺ calcd. 377.2224, found 377.2227.
Scheme S7. Synthesis of 1r-t

Preparation of 18:

2-Iodobenzoic acid 13a (320 mg, 1.26 mmol), 2a (225 mg, 1.26 mmol), EDC (391 mg, 2.53 mmol), HOBr (341 mg, 2.53 mmol) were dissolved in CHCl₃ (20 ml). NEt₃ (353 μl, 2.53 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 383 mg, 74%. Rf = 0.11 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.78 (d, J = 8.0, 1H), 7.43-7.06 (m, 8H), 6.94 (br s, 1H), 4.48 (s, 2H), 3.85 (s, 2H), 2.91 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.8, 168.2, 141.6, 139.6, 137.9, 130.8, 129.0, 128.8, 128.5, 127.9, 127.3, 92.3, 52.1, 43.9, 37.9. HRMS for C₁₇H₁₇IN₂O₂ [M+Na]⁺ calcd. 431.0227, found 431.0230.

Preparation of 1r:

Compound 18 (98 mg, 0.240 mmol), CuI (9 mg, 0.048 mmol), and PdCl₂(PPh₃)₂ (17 mg, 0.024 mmol) were dissolved in DMF (2 ml) and NEt₃ (2 ml). The mixture was degassed with N₂ for 5 min. Phenylacetylene (53 μl, 0.480 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-50% EtOAc in Hex was used to purify the desired compound. Yield: 88 mg, 95%. Rf = 0.21 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz, mixture of rotamers) δ 7.59-7.04 (m, 14H), 6.96 (br s, 1H), 4.28 (s, 2H), 4.20 (d, J = 5.6, 2H), 3.06 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.4, 168.8, 138.2(2), 132.6, 131.9, 129.6, 129.2, 129.1, 128.8(2), 127.8, 127.4, 126.9, 122.4, 120.3, 93.0, 86.5, 52.5, 43.2, 38.1. HRMS for C₂₅H₂₂N₂O₂ [M+Na]⁺ calcd. 405.1573, found 405.1577.
Preparation of 1s:

![Chemical Structure Image]

Compound 18 (172 mg, 0.422 mmol), CuI (16 mg, 0.084 mmol), and PdCl$_2$(PPh$_3$)$_2$ (30 mg, 0.042 mmol) were dissolved in DMF (2 ml) and NEt$_3$ (2 ml). The mixture was degassed with N$_2$ for 5 min. 4-Ethynylanisole (109 µl, 0.843 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N$_2$. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 20-40% EtOAc in Hex was used to purify the desired compound. Yield: 45 mg, 26%. $R_f$ = 0.21 (EtOAc/Hex, 1:1). $^1$H NMR (CDCl$_3$, 300 MHz, mixture of rotamers) $\delta$ 7.71-7.11 (m, 13H), 6.83 (d, $J$ = 8.8, 2H), 4.29 (s, 2H), 4.21 (d, $J$ = 5.6, 2H), 3.82 (s, 3H), 3.06 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 171.5, 168.8, 160.4, 138.3, 138.0, 133.4, 132.5, 132.4, 132.2(3), 129.6, 128.8, 128.7, 128.6, 127.4(2), 126.8, 120.7, 114.4, 93.2, 85.4, 55.4, 52.4, 43.2, 38.1. HRMS for C$_{26}$H$_{24}$N$_2$O$_3$ [M+H]$^+$ calcd. 413.1860, found 413.1866.

Preparation of 1t:

![Chemical Structure Image]

Compound 18 (81 mg, 0.199 mmol), CuI (8 mg, 0.040 mmol), and PdCl$_2$(PPh$_3$)$_2$ (14 mg, 0.020 mmol) were dissolved in DMF (2 ml) and NEt$_3$ (2 ml). The mixture was degassed with N$_2$ for 5 min. 4-Ethynylaniline (47 mg, 0.397 mmol) dissolved in DMF (0.5 ml) was then added and the mixture was stirred for 16 hr at 30°C under N$_2$. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 80 mg, quan. $R_f$ = 0.33 (EtOAc/Hex, 3:4). $^1$H NMR (CDCl$_3$, 300 MHz, mixture of rotamers) $\delta$ 7.55-6.98 (m, 13H), 6.58 (d, $J$ = 8.5, 2H), 6.53 (br s, 1H), 4.29 (s, 2H), 4.20 (s, 2H), 3.05 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 171.6, 168.9, 147.6, 138.4, 137.8, 133.3, 132.4, 129.5, 128.7, 128.5, 127.4(2), 126.8, 121.0, 114.9, 111.4, 94.1, 84.6, 52.4, 43.2, 38.1. HRMS for C$_{25}$H$_{24}$N$_3$O$_2$ [M+H]$^+$ calcd. 398.1863, found 398.1867.
1.5.2 Endoxifen Derivatives

Scheme S8. Synthesis of 3a

Preparation of 19a:

Compound 14a (405 mg, 1.55 mmol), CuI (59 mg, 0.31 mmol), and PdCl$_2$(PPh$_3$)$_2$ (108 mg, 0.15 mmol) were dissolved in DMF (2 ml) and NEt$_3$ (2 ml). The mixture was degassed with N$_2$ for 5 min. (Trimethylsilyl)acetylene (430 μl, 3.09 mmol) was then added and the mixture was stirred for 16 hr at 30°C under N$_2$. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 5-10% EtOAc in Hex was used to purify the desired compound. Yield: 346 mg, 96%. $R_f$ = 0.41 (EtOAc/Hex, 1:10). $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.91 (d, $J$ = 7.7 Hz, 1H), 7.59 (d, $J$ = 7.5 Hz, 1H), 7.47-7.34 (m, 2H), 3.93 (s, 3H), 0.28 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 167.2, 134.8, 132.8, 131.7, 130.5, 128.4, 123.4, 103.5, 99.8, 52.1, 0.1. HRMS for C$_{13}$H$_{16}$O$_2$Si [M+H]$^+$ calcd. 233.0992, found 233.0992.

Preparation of 20a:

Compound 19a (366 mg, 1.58 mmol) was dissolved in MeOH (5 ml), followed by the addition of aqueous NaOH (5 ml of 2.0M solution). The mixture was then stirred for 2 hr at 40°C. To workup, the H$_2$O layer was washed with EtOAc (1x) and acidified to pH~1 with 1M HCl, which allowed the product to be extracted with EtOAc. The organic layer was then washed with H$_2$O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 30-50% EtOAc in Hex was used to purify the desired compound. Yield: 165 mg, 48%. $R_f$ = 0.14 (EtOAc/Hex, 1:1). Characterization matched a previous report of this known compound. $^1$H NMR (CDCl$_3$, 300 MHz) δ 11.69 (br s, 1H), 8.10 (d, $J$ = 7.8 Hz, 1H), 7.67 (d, $J$ = 7.7 Hz, 1H), 7.55 (td, $J$ = 1.4, 7.5 Hz, 1H), 7.46 (td, $J$ = 1.4, 7.7 Hz, 1H), 3.46 (s, 1H).
Preparation of 21a:

Compound 20a (27 mg, 0.185 mmol), N-hydroxysuccinimide (32 mg, 0.277 mmol), EDC (71 mg, 0.370 mmol), HOBt (50 mg, 0.370 mmol) were dissolved in CHCl₃ (5 ml). NEt₃ (126 μl, 0.740 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the solvent was evaporated under vacuum and the mixture redissolved in EtOAc. The organic layer was then washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-50% EtOAc in Hex was used to purify the desired compound. Yield: 39 mg, 87%. Rᵣ = 0.40 (EtOAc/Hex, 1:1).

### 1H NMR (CDCl₃, 300 MHz) δ 8.16 (d, J = 8.2 Hz, 1H), 7.70-7.57 (m, 2H), 7.47 (t, J = 7.7 Hz, 1H), 3.45 (s, 1H), 2.89 (s, 4H);

### 13C NMR (CDCl₃, 75 MHz): δ 169.4, 160.9, 135.5, 133.9, 131.3, 128.9, 127.1, 124.6, 84.3, 80.9, 25.7.

### HRMS for C₁₃H₉NO₄ [M+Na⁺] calcd. 266.0424, found 266.0421.

Preparation of 3a:

Compound 21a (6.3 mg, 0.026 mmol) and (E/Z)-Endoxifen (4.7 mg, 0.019 mmol) were dissolved in DMF (300 μl). DIPEA (8 μl, 0.043 mmol) was then added and the mixture was stirred for 16 hr at room temperature. To workup, additional DMF (1 ml) was added. The reaction was then filtered and directly purified by reverse phase HPLC using method 6 (retention time ~27.4 min). Yield: 4.1 mg, 42%. 1H NMR (CDCl₃, 400 MHz, mixture of rotamers) δ 7.54-7.46 (m, 1H), 7.41-7.26 (m, 3H), 7.17-7.05 (m, 7H), 6.88 (d, J = 8.7 Hz, 1H), 6.81-6.67 (m, 3H), 6.53 (d, J = 8.8 Hz, 1H), 6.48-6.40 (m, 2H), 4.31 (t, J = 5.0 Hz, 1H), 4.15 (t, J = 4.9 Hz, 1H), 3.77-3.71 (m, 2H), 3.07 (s, 3H), 2.55 (s, 1H), 2.50-2.42 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H);

### 13C NMR (CDCl₃, 75 MHz): δ 170.5, 157.6, 156.8, 154.7, 153.8, 142.9, 141.5, 140.3, 138.0, 136.4, 136.1, 133.1, 132.9, 132.3, 132.2, 130.9, 129.9, 129.4, 129.0, 128.1, 126.4, 126.2, 119.2, 115.2, 114.5, 114.2, 113.4, 81.0, 80.7, 68.1, 47.7, 30.4, 29.1, 13.7. HRMS for C₁₆H₃₁NO₃ [M+H⁺] calcd. 502.2377, found 502.2389.
Scheme S9. Synthesis of 3m

Preparation of 21m:

Compound 16m (170 mg, 0.459 mmol), N-hydroxysuccinimide (79 mg, 0.689 mmol), EDC (176 mg, 0.918 mmol), HOBT (124 mg, 0.918 mmol) were dissolved in CHCl₃ (5 ml). NEt₃ (312 μl, 1.837 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the solvent was evaporated under vacuum and the mixture redissolved in EtOAc. The organic layer was then washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 15-25% EtOAc in Hex was used to purify the desired compound. Yield: 78 mg, 37%. $R_f$ = 0.31 (EtOAc/Hex, 1:4). $^1$H NMR (CDCl₃, 300 MHz) δ 8.35 (s, 1H), 7.82-7.73 (m, 2H), 2.91 (s, 4H), 1.12 (s, 21H); $^{13}$C NMR (CDCl₃, 75 MHz): δ 169.1, 159.8, 136.0, 130.1, 130.0, 129.2, 128.3, 127.6, 121.5, 103.4, 102.5, 25.7, 18.6, 11.2. HRMS for C₃₂H₂₉F₃NO₃Si [M+Na]⁺ calcd. 490.1632, found 490.1634.

Preparation of 3m:

Compound 21m (6.2 mg, 0.013 mmol) and (E/Z)-Endoxifen (2.5 mg, 0.007 mmol) were dissolved in DMF (300 μl), followed by the addition of DIPEA (3 μl, 0.013 mmol). After stirring for 16 hr at room temperature, TBAF (400 μl of 1M solution in THF) was added to the mixture, which was allowed to further stir for 1 hr. To workup, additional DMF (1 ml) was added. The reaction was then filtered and directly purified by reverse phase HPLC using method 7 (retention time ~29.9 min). Yield: 3.3 mg, 87%. $^1$H NMR (CDCl₃, 400 MHz, mixture of rotamers) δ 7.66-7.54 (m, 3H), 7.18-7.05 (m, 7H), 6.89 (d, $J$ = 8.6 Hz, 1H), 6.83-6.68 (m, 3H), 6.56-6.43 (m, 2H), 4.32 (t, $J$ = 4.9 Hz, 1H), 4.16 (t, $J$ = 4.7 Hz, 1H), 3.94-3.79 (m, 2H), 3.01 (s, 3H), 2.62 (s, 1H), 2.51-2.42 (m, 2H), 0.95-0.88 (m, 3H); $^{13}$C NMR (CDCl₃, 75 MHz): δ 168.9, 157.5, 156.7, 155.1, 154.0, 142.8, 141.4, 140.8, 138.1, 137.9, 136.9, 136.6, 136.0, 133.6, 133.3, 132.3, 132.2, 130.9, 129.9, 128.1, 126.2, 125.8, 123.5, 123.0, 115.3, 114.6, 114.1, 113.4, 83.5, 83.3, 66.7, 47.8, 38.9, 29.1, 13.6. HRMS for C₃₅H₃₀F₃NO₃ [M+H]⁺ calcd. 570.2251, found 570.2232.
1.5.3 Doxorubicin Derivatives

Scheme S10. Synthesis of 4 and 5

Preparation of 4:
O-(4-Nitrophenyl)-O’-allylcarbonate (18.1 mg, 0.081 mmol), which was prepared according to literature, was added to Doxorubicin hydrochloride (47 mg, 0.081 mmol) dissolved in DMF (1 ml). DIPEA (28 μl, 0.162 mmol) was then added and the mixture was stirred for 16 hr at room temperature. To workup, additional DMF (1 ml) was added. The reaction was then filtered and directly purified by reverse phase HPLC using method 8 (retention time ~20.8 min). Yield: 20.6 mg, 40%. Characterization matched a previous report of this known compound.

1H NMR (Acetone-d6, 400 MHz) δ 8.02 (dd, J = 7.7, 1.1 Hz, 1H), 7.95-7.91 (m, 1H), 7.67 (d, J = 8.4 Hz, 1H), 6.00-5.83 (m, 2H), 5.11 (d, J = 9.9 Hz, 1H), 4.91 (s, 1H), 4.77-4.73 (m, 2H), 4.59 (d, J = 2.4 Hz, 2H), 4.30-4.24 (m, 1H), 4.07 (s, 3H), 4.05-3.98 (m, 1H), 3.90-3.83 (m, 1H), 3.67-3.63 (m, 2H), 3.21 (d, J = 18.7 Hz, 1H), 3.06 (d, J = 18.7 Hz, 1H), 2.53-2.46 (m, 1H), 2.27-2.22 (m, 1H), 2.02-1.99 (m, 1H), 1.78-1.71 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H). LRMS for C31H33NO13 [M+Na]+ calcd. 650.1, found 650.1.

Preparation of 5:
O-(4-Nitrophenyl)-O’-propargylcarbonate (13.7 mg, 0.062 mmol), which was prepared according to literature, was added to Doxorubicin hydrochloride (39.5 mg, 0.068 mmol) dissolved in DMF (1 ml). DIPEA (16 μl, 0.093 mmol) was then added and the mixture was stirred for 16 hr at room temperature. To workup, additional DMF (1 ml) was added. The reaction was then filtered and directly purified by reverse phase HPLC using method 8 (retention time ~19.3 min). Yield: 17.7 mg, 46%. Characterization matched a previous report of this known compound.

1H NMR (Acetone-d6, 400 MHz) δ 8.02 (dd, J = 7.7, 0.9 Hz, 1H), 7.95-7.91 (m, 1H), 7.67 (d, J = 8.6 Hz, 1H), 5.48 (d, J = 3.8 Hz, 1H), 5.29-5.26 (m, 1H), 4.91 (s, 1H), 4.77-4.73 (m, 2H), 4.59 (d, J = 2.4 Hz, 2H), 4.30-4.24 (m, 1H), 4.07 (s, 3H), 4.05-4.01 (m, 1H), 3.92-3.83 (m, 1H), 3.69-3.63 (m, 2H), 3.22 (dd, J = 18.7, 1.7 Hz, 1H), 3.06 (d, J = 18.7 Hz, 1H), 2.53 (s, 1H), 2.51-2.47 (m, 1H), 2.27 (d, J = 4.6 Hz, 1H), 1.97 (s, 2H), 1.78-1.71 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H). LRMS for C31H33NO13 [M+Na]+ calcd. 648.1, found 648.1.
Scheme S11. Synthesis of 24

Preparation of 23:

Compound 22 (200 mg, 1.62 mmol), NEt₃ (680 μl, 4.86 mmol), and DMAP (60 mg, 0.486 mmol) were dissolved in DCM (10 ml). TBDPS-Cl (520 μl, 2.00 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was quenched with H₂O and the mixture was extracted with EtOAc (3×). The combined organic layers were dried over sodium sulfate and evaporated under vacuum. Flash column chromatography using a gradient of 10-20% EtOAc in Hex was used to purify the desired compound. Yield: 547 mg, 93%. Rᵣ =0.19 (EtOAc/Hex, 1:5). Characterization matched a previous report of this known compound.¹⁷ ¹H NMR (CDCl₃, 300 MHz) δ 7.72-7.65 (m, 4H), 7.45-7.34 (m, 6H), 7.12 (d, J = 8.3 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 4.66 (s, 2H), 3.61 (s, 2H), 1.07 (s, 9H).

Preparation of 24:

Compound 23 (668 mg, 1.85 mmol) and K₂CO₃ (383 mg, 2.77 mmol) were dissolved in DMF (5 ml) and stirred for 5 min. CH₃I (115 μl, 1.85 mmol) was then added in 3 portions of 40 μl that were separated by 15 minutes each time. The mixture was then stirred for 2 hr at 50°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 7-15% EtOAc in Hex was used to purify the desired compound. Yield: 260 mg, 38%. Rᵣ =0.38 (EtOAc/Hex, 1:5). ¹H NMR (CDCl₃, 300 MHz) δ 7.73-7.67 (m, 4H), 7.45-7.34 (m, 6H), 7.16 (d, J = 8.4 Hz, 2H), 6.59 (d, J = 8.5 Hz, 2H), 4.66 (s, 2H), 2.84 (s, 3H), 1.07 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 148.7, 135.9, 134.1, 130.1, 129.8, 127.9, 127.8, 112.4, 65.7, 31.0, 26.9, 19.4. HRMS for C₂₄H₂₉NOSi [M+H]⁺ calcd. 376.2091, found 376.2100.
Scheme S12. Synthesis of 6a,m

Preparation of 25a:

Compound 24 (165 mg, 0.440 mmol), compound 16a (133 mg, 0.440 mmol), HCTU (363 mg, 0.879 mmol), HOBt(6-Cl) (149 mg, 0.879 mmol) were dissolved in DMF (7 ml). DIPEA (246 μl, 1.76 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-15% EtOAc in Hex was used to purify the desired compound. Yield: 163 mg, 56%. Rₜ=0.18 (EtOAc/Hex, 1:5). ¹H NMR (CDCl₃, 400 MHz) δ 7.70-7.57 (m, 4H), 7.48-7.29 (m, 8H), 7.20-7.05 (m, 6H), 4.62 (s, 2H), 3.46 (s, 3H), 1.17 (s, 21H), 1.05 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 140.0, 135.8, 133.5, 133.0, 129.9, 127.9, 127.0, 126.6, 95.1, 65.1, 37.4, 26.9, 19.3, 18.8, 11.4. HRMS for C₄₂H₅₃NO₄Si₂ [M+H]+ calcd. 660.3688, found 660.3680.

Preparation of 25m:

Compound 24 (180 mg, 0.481 mmol), compound 16m (178 mg, 0.481 mmol), HCTU (397 mg, 0.962 mmol), HOBt(6-Cl) (163 mg, 0.962 mmol) were dissolved in DMF (5 ml). DIPEA (163 μl, 0.962 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the reaction was diluted with...
EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-10% EtOAc in Hex was used to purify the desired compound. Yield: 116 mg, 33%. Rf=0.31 (EtOAc/Hex, 1:5). ¹H NMR (CDCl₃, 300 MHz) δ 7.74-7.69 (m, 1H), 7.66-7.57 (m, 3H), 7.44-7.30 (m, 10H), 7.16-7.11 (m, 3H), 4.63 (s, 2H), 3.47 (s, 3H), 1.18 (s, 21H), 1.04 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 142.0, 141.3, 140.7, 135.9, 135.7, 135.0, 133.5, 133.4, 130.2, 130.0, 129.9, 127.9, 127.1, 126.8, 98.5, 65.0, 37.4, 26.6, 19.3, 18.7, 17.7, 12.3, 11.4. HRMS for C₄₃H₅₂F₃NO₂Si₂ [M+H]⁺ calcd. 728.3561, found 728.3555.

Preparation of 26a:

Compound 25a (343 mg, 0.520 mmol) was dissolved in DCM (2 ml). TBAF (2.6 ml of 1.0M solution, 2.60 mmol) was then added and the mixture was stirred for 1 hr at room temperature under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 50-75% EtOAc in Hex was used to purify the desired compound. Yield: 129 mg, 93%. Rf=0.38 (EtOAc/Hex, 3:4). ¹H NMR (CDCl₃, 400 MHz) δ 7.37-7.30 (m, 2H), 7.21-7.02 (m, 7H), 4.55 (s, 2H), 3.49 (s, 3H), 3.28 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 169.9, 139.9, 133.1, 128.6, 128.5, 128.4, 127.5, 127.1, 126.5, 81.6, 81.2, 64.5, 37.4. HRMS for C₁₇H₁₅NO₂ [M+H]⁺ calcd. 266.1176, found 266.1170.

Preparation of 26m:

Compound 25m (116 mg, 0.156 mmol) was dissolved in DCM (2 ml). TBAF (239 μl of 1.0M solution, 0.239 mmol) was then added and the mixture was stirred for 2 hr at 40°C. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 15-30% EtOAc in Hex was used to purify the desired compound. Yield: 27.9 mg, 52%. Rf=0.20 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.51-7.31 (m, 4H), 7.24-7.05 (m, 4H), 4.58 (s, 2H), 3.50 (s, 3H), 3.42 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz): δ 168.4, 142.5, 141.3, 140.4, 133.6, 127.7, 127.3, 125.3, 124.7, 123.6, 121.7, 83.7, 80.4, 64.5, 37.5. HRMS for C₁₆H₁₄F₃NO₂ [M+H]⁺ calcd. 334.1049, found 334.1046.

Preparation of 6a:

4-Nitrophenyl chloroformate (8.3 mg, 0.0413 mmol) was dissolve in THF (300 μl) and cooled to 0°C on an ice bath. Pyridine (4 μl, 0.0413 mmol) was added and after stirring for 20 min, compound 26a (7.3 mg, 0.0275 mmol) dissolved in THF (200 μl) was added and the mixture was stirred for 16 hr at room temperature. To workup, THF was removed and the residue was redissolved in EtOAc. The organic layer was then washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-
50% EtOAc in Hex was used to purify the desired intermediate. Yield: 5.2 mg, 44%. \(R_f=0.67\) (EtOAc/Hex, 3:4). \textbf{HRMS} for C\textsubscript{24}H\textsubscript{18}N\textsubscript{2}O\textsubscript{6} [M+H]+ calc. 431.1238, found 431.1234.

The intermediate compound and doxorubicin hydrochloride (7.0 mg, 0.012 mmol) were dissolved in DMF (300 μl). DIPEA (4 μl, 0.024 mmol) was then added and the mixture was stirred for 16 hr at room temperature. To workup, additional DMF (1 ml) was added. The reaction was then filtered and directly purified by reverse phase HPLC using method 8 (retention time ~28.1 min). Yield: 5.4 mg, 53%. \textbf{\textsuperscript{1}H NMR} (DMSO-d\textsubscript{6}, 400 MHz) \(\delta \) 7.96-7.89 (m, 2H), 7.70-7.64 (m, 1H), 7.33-7.08 (m, 7H), 6.90 (d, \(J = 7.7\) Hz, 1H), 5.46 (s, 1H), 5.27-5.19 (m, 1H), 4.99-4.93 (m, 1H), 4.90-4.77 (m, 3H), 4.70 (d, \(J = 5.3\) Hz, 1H), 4.57 (d, \(J = 6.0\) Hz, 2H), 4.33 (s, 1H), 4.15 (q, \(J = 6.8\) Hz, 1H), 3.99 (s, 3H), 3.43 (s, 3H), 2.98 (d, \(J = 5.0\) Hz, 2H), 2.23-2.08 (m, 2H), 1.88-1.76 (m, 1H), 1.49-1.40 (m, 1H), 1.12 (d, \(J = 6.5\) Hz, 3H); \textbf{\textsuperscript{13}C NMR} (DMSO-d\textsubscript{6}, 75 MHz): \(\delta \) 215.1, 187.9, 187.8, 169.2, 162.2, 157.2, 156.4, 156.1, 144.5, 142.1, 136.7, 136.5, 136.1, 133.4, 129.1, 129.1, 128.3, 127.7, 122.1, 120.6, 120.1, 119.5, 112.3, 112.2, 112.1, 99.8, 92.0, 82.7, 77.7, 76.9, 71.1, 70.0, 63.6, 63.1, 61.5, 56.7, 48.1, 40.7, 30.4, 27.8, 17.1. \textbf{HRMS} for C\textsubscript{45}H\textsubscript{32}F\textsubscript{3}N\textsubscript{2}O\textsubscript{14} [M+Na]+ calc. 857.2528, found 857.2520.

Preparation of 6m:

4-Nitrophenyl chloroformate (3.2 mg, 0.0158 mmol) was dissolved in THF (300 μl) and cooled to 0°C on an ice bath. Pyridine (2 μl, 0.0158 mmol) was added and after stirring for 20 min, compound 26m (3.5 mg, 0.0105 mmol) dissolved in THF (200 μl) was added and the mixture was stirred for 16 hr at room temperature. To workup, THF was removed and the residue was redissolved in EtOAc. The organic layer was then washed with H\textsubscript{2}O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired intermediate. Yield: 2.9 mg, 54%. \(R_f=0.63\) (EtOAc/Hex, 1:1). \textbf{HRMS} for C\textsubscript{25}H\textsubscript{17}F\textsubscript{3}N\textsubscript{2}O\textsubscript{6} [M+Na]+ calc. 521.0931, found 521.0922.

The intermediate compound and doxorubicin hydrochloride (7.0 mg, 0.0114 mmol) were dissolved in DMF (300 μl). DIPEA (3 μl, 0.0171 mmol) was then added and the mixture was stirred for 16 hr at room temperature. To workup, additional DMF (1 ml) was added. The reaction was then filtered and directly purified by reverse phase HPLC using method 9 (retention time ~20.9 min). Yield: 3.9 mg, 75%. \textbf{\textsuperscript{1}H NMR} (DMSO-d\textsubscript{6}, 400 MHz) \(\delta \) 7.94-7.83 (m, 2H), 7.73 (s, 1H), 7.62-7.48 (m, 3H), 7.45-7.35 (m, 1H), 7.24-7.07 (m, 3H), 6.88 (d, \(J = 7.8\) Hz, 1H), 5.42 (s, 1H), 5.21 (s, 1H), 4.98-4.78 (m, 4H), 4.72-4.66 (m, 1H), 4.60-4.56 (m, 3H), 4.18-4.10 (m, 1H), 3.97 (s, 3H), 3.73-3.62 (m, 1H), 3.43 (s, 3H), 2.95 (d, \(J = 7.5\) Hz, 2H), 2.22-2.09 (m, 2H), 1.87-1.77 (m, 1H), 1.49-1.38 (m, 1H), 1.12 (d, \(J = 6.4\) Hz, 3H); \textbf{\textsuperscript{13}C NMR} (DMSO-d\textsubscript{6}, 75 MHz): \(\delta \) 214.0, 186.7, 180.4, 166.9, 161.0, 156.3, 155.3, 142.3, 141.5, 136.3, 136.2, 135.7, 134.9, 133.3, 128.1, 127.1, 125.3, 125.2, 124.7, 124.6, 123.1, 120.2, 120.1, 119.8, 119.1, 110.9, 110.7, 110.5, 100.4, 87.0, 80.2, 75.0, 70.0, 68.0, 66.7, 64.3, 63.7, 56.6, 47.2, 36.7, 32.1, 29.8, 17.0. \textbf{HRMS} for C\textsubscript{46}H\textsubscript{34}F\textsubscript{3}N\textsubscript{2}O\textsubscript{14} [M+Na]+ calc. 925.2402, found 925.2412.
Scheme S13. Synthesis of 30

Preparation of 28:

Compound 27 (500 mg, 2.702 mmol), CuI (103 mg, 0.540 mmol), and PdCl2(PPh3)2 (189 mg, 0.270 mmol) were dissolved in DMF (2 ml) and NEt3 (2 ml). The mixture was degassed with N2 for 5 min. (Triisopropylsilyl)acetylene (1.2 ml, 5.404 mmol) was then added and the mixture was stirred for 16 hr at 40°C under N2. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H2O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 0-10% EtOAc in Hex was used to purify the desired compound. Yield: 770 mg, quan. Rf = 0.52 (EtOAc/Hex, 1:10). Characterization matched a previous report of this known compound.18 1H NMR (CD2Cl2, 300 MHz) δ 9.99 (s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.1 Hz, 2H), 1.15 (s, 21H).

Preparation of 29:

LiAlH4 (205 mg, 5.404 mmol) was suspended in THF (10 ml) and cooled to 0°C on an ice bath. Compound 28 (770 mg, 2.702 mmol) dissolved in THF (20 ml) was then added dropwise and the mixture was stirred for 2 hr at room temperature under N2. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H2O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-25% EtOAc in Hex was used to purify the desired compound. Yield: 463 mg, 60%. Rf = 0.31 (EtOAc/Hex, 1:4). Characterization matched a previous report of this known compound.19 1H NMR (CDCl3, 300 MHz) δ 7.47 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.66 (d, J = 5.3 Hz, 2H), 1.13 (s, 21H).

Preparation of 30:

Compound 29 (463.3 mg, 1.609 mmol) was dissolved in DCM (1 ml). TBAF (2 ml of 1.0M solution, 2.413 mmol) was then added and the mixture was stirred for 2 hr at room temperature. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H2O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 20-40% EtOAc in Hex was used to purify the desired compound. Yield: 212 mg, quan. Rf = 0.24 (EtOAc/Hex, 1:4). Characterization matched a previous report of this known compound.20 1H NMR (CDCl3, 300 MHz) δ 7.47 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.63 (s, 2H), 3.07 (s, 1H).
Scheme S14. Synthesis of 34

Preparation of 32:

Compound 31 (7.5 mg, 0.0183 mmol), and 10% Pd/C (1 mg, 0.006 mmol) were dissolved in EtOH (5 ml). The reaction mixture was first purged with N₂ gas, followed by H₂ gas. The mixture was then stirred for 16 hr at room temperature under H₂. To workup, the reaction was diluted with EtOAc and then filtered through celite. The collected organic layer was dried over sodium sulfate, and evaporated under vacuum to give a clear oil. Yield: 7.0 mg, quan. Characterization matched a previous report of this known compound. HRMS for C₁₇H₃₇NO₈ [M+H]⁺ calcd. 384.2592, found 284.2603.

Preparation of 34:

Compound 32 (8.5 mg, 0.022 mmol), compound 33 (7 mg, 0.022 mmol), EDC (7 mg, 0.044 mmol), HOBT (6 mg, 0.022 mmol) were dissolved in CHCl₃ (0.5 ml). NEt₃ (6 μl, 0.044 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N₂. To workup, the solvent was removed by vacuum and the residue was redissolved in acetonitrile with 1-2 drops of H₂O. The mixture was then filtered and directly purified by reverse phase HPLC using method 10 (retention time ~27.7 min). Yield: 3.9 mg, 25%. H NMR (DMSO-d₆, 400 MHz) δ 7.72-7.29 (m, 8H), 5.04 (d, J = 14.0 Hz, 1H), 3.61 (d, J = 14.0 Hz, 1H), 3.58-3.41 (m, 3H), 3.23 (s, 3H), 2.22-2.13 (m, 1H), 1.89-1.81 (m, 2H), 1.79-1.69 (m, 1H), 1.37-1.10 (m, 4H); C NMR (DMSO-d₆, 75 MHz): δ 172.0, 171.8, 152.0, 148.6, 132.5, 129.6, 129.0, 128.2, 128.1, 127.8, 126.9, 125.3, 122.6, 121.5, 114.5, 108.3, 71.3, 69.8 (br s), 69.7, 69.6, 69.1, 58.1, 54.8, 34.9, 33.9, 24.4. HRMS for C₃₈H₄₆N₄O₁₀ [M+H]⁺ calcd. 699.3851, found 699.3857.
Scheme S15. Synthesis of 7

Preparation of 35:

Compound 13a (306 mg, 1.24 mmol), 24 (309 mg, 0.82 mmol), HCTU (680 mg, 1.65 mmol), HOBt(6-Cl) (279 mg, 1.65 mmol) were dissolved in DMF (5 ml). DIPEA (279 μl, 1.65 mmol) was then added and the mixture was stirred for 16 hr at 50°C under N₂. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 15-25% EtOAc in Hex was used to purify the desired compound. Yield: 112 mg, 15%. R₁=0.17 (EtOAc/Hex, 1:4). ¹H NMR (CDCl₃, 400 MHz) δ 7.73-7.60 (m, 6H), 7.46-7.32 (m, 9H), 7.12-7.02 (m, 2H), 6.89-6.83 (m, 1H), 4.64 (s, 2H), 3.51 (s, 3H), 1.05 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.5, 142.8, 142.2, 140.3, 139.4, 135.7, 133.5, 130.0, 129.9, 128.7, 127.8, 127.5, 127.0, 126.7, 125.8, 93.8, 65.0, 37.5, 26.9, 19.3. HRMS for C₃₁H₃₂NO₂Si [M+H]⁺ calcd. 606.1320, found 606.1345.
Preparation of 36:

![chemical structure](image)

Compound 35 (257 mg, 0.425 mmol), CuI (16 mg, 0.085 mmol), and PdCl\(_2\)(PPh\(_3\))\(_2\) (30 mg, 0.043 mmol) were dissolved in DMF (2 ml) and NEt\(_3\) (2 ml). The mixture was degassed with N\(_2\) for 5 min. Compound 30 (87 mg, 0.552 mmol) dissolved in DMF (0.5 ml) was then added and the mixture was stirred for 16 hr at 40\(^\circ\)C under N\(_2\). To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H\(_2\)O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 30-50% EtOAc in Hex was used to purify the desired compound. Yield: 135 mg, 52%. \(R_t=0.40\) (EtOAc/Hex, 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.71-7.29 (m, 18 H), 7.22-6.98 (m, 4 H), 4.71 (s, 2H), 4.63 (s, 2H), 3.52 (s, 3H), 1.05 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 170.3, 141.7, 139.9, 135.8, 133.6, 132.3, 132.1, 130.0, 128.8, 128.7, 127.9, 127.1, 126.9 (br s), 126.5 (br s), 92.2, 88.6, 65.1, 65.0, 54.4, 26.9, 19.3. HRMS for C\(_{40}\)H\(_{39}\)NO\(_3\)Si [M+H]\(^+\) calcd. 610.2772, found 610.2785.

Preparation of 37:

![chemical structure](image)

Compound 36 (135 mg, 0.221 mmol) was dissolved in THF (5 ml) and cooled to 0\(^\circ\)C on an ice bath. Mesyl chloride (22 µl, 0.287 mmol) and triethylamine (40 µl, 0.287 mmol) was then added and the mixture was stirred for 1 hr at 0\(^\circ\)C under N\(_2\). To workup, the reaction was quenched with cold Na\(_2\)CO\(_3\) and then the product was extracted with DCM. The combined organic layers were dried over sodium sulfate, and evaporated under vacuum to give the intermediate compound as an oil. In the next step, the intermediate compound was dissolved in DMF (5 ml). Sodium azide (29 mg, 0.442 mmol) was then added and the mixture was stirred for 16 hr at room temperature under N\(_2\). To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H\(_2\)O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-25% EtOAc in Hex was used to purify the desired compound. Yield: 140 mg, 99%. \(R_t=0.71\) (EtOAc/Hex, 1:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.51-7.75 (m, 7 H), 7.28-7.44 (m, 11 H), 7.02-7.20 (m, 4 H), 4.64 (s, 2 H), 4.38 (s, 2 H), 3.53 (s, 3 H), 1.05 (s, 9 H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 171.2, 139.9, 136.0, 135.0, 133.6, 132.3, 132.2, 130.0, 128.6, 128.4, 127.9, 126.9 (br s), 126.6 (br s), 92.7, 88.8, 65.1, 60.5, 54.6, 26.9, 19.3. HRMS for C\(_{40}\)H\(_{38}\)N\(_4\)O\(_2\)Si [M+H]\(^+\) calcd. 635.2837, found 635.2840.
Preparation of 38:

Compound 37 (57.3 mg, 0.090 mmol) was dissolved in DCM (1 ml). TBAF (135 μl of 1.0M solution, 0.135 mmol) was then added and the mixture was stirred for 2 hr at 40°C. To workup, the reaction was diluted with EtOAc and then the organic layer was washed with H₂O, brine, dried over sodium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired compound. Yield: 29.9 mg, 84%. Rf = 0.23 (EtOAc/Hex, 1:1). ¹H NMR (CDCl₃, 300 MHz) δ 7.69-7.47 (m, 1H), 7.56 (d, J = 7.9 Hz, 2H), 7.45-7.28 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 4.57 (s, 2H), 4.38 (s, 2H), 3.51 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.2, 139.7, 136.1, 132.4, 132.3, 132.2, 128.5, 128.8, 128.7, 128.5, 128.2, 127.4 (br s), 127.1 (br s), 92.7, 88.2, 64.6, 60.5, 54.6. HRMS for C₂₄H₂₀N₄O₂ [M+H]⁺ calcd. 397.1659, found 397.1663.

Preparation of 39:

4-Nitrophenyl chloroformate (9.0 mg, 0.046 mmol) was dissolve in THF (300 μl) and cooled to 0°C on an ice bath. Pyridine (4 μl, 0.046 mmol) was added and after stirring for 20 min, compound 38 (12.1 mg, 0.031 mmol) dissolved in THF (200 μl) was added and the mixture was stirred for 16 hr at room temperature. To workup, THF was removed and the residue was redissolved in EtOAc. The organic layer was then washed with H₂O, brine, and evaporated under vacuum. Flash column chromatography using a gradient of 25-50% EtOAc in Hex was used to purify the desired intermediate. Yield: 11.7 mg, 68%. Rf = 0.36 (EtOAc/Hex, 1:1). HRMS for C₃₁H₂₃N₅O₆ [M+H]⁺ calcd. 562.1721, found 562.1728.

The intermediate compound and doxorubicin hydrochloride (24.0 mg, 0.042 mmol) were dissolved in DMF (300 μl). DIPEA (7 μl, 0.042 mmol) was then added and the mixture was stirred for 16 hr at room temperature. To workup, additional DMF (1 ml) was added. The reaction was then filtered and directly purified by reverse phase HPLC using method 11 (retention time ~20.4 min). Yield: 10.4 mg, 51%. ¹H NMR (DMF-d7, 400 MHz) δ 8.00-7.92 (m, 2H), 7.73 (dd, J = 7.7, 1.9 Hz, 1H), 7.68-7.49 (m, 4H), 7.47-7.14 (m, 7H), 6.78 (d, J = 8.1 Hz, 1H), 5.57 (s, 1H), 5.40-5.36 (m, 1H), 5.15-5.09 (m, 1H), 5.02-4.82 (m, 3H), 4.80-4.71 (m, 3H), 4.59 (s, 2H), 4.09 (s, 3H), 3.49 (s, 3H), 3.10 (q, J = 18.5 Hz, 2H), 2.45-2.37 (m, 1H), 2.26 (dd, J = 14.5, 5.3 Hz, 1H), 2.03 (td, J = 13.0, 3.8 Hz, 1H), 1.70-1.61 (m, 1H), 1.23 (d, J = 6.5 Hz, 3H); ¹³C NMR (THF-d8, 75 MHz): δ 214.7, 187.8, 187.5, 169.2, 162.3, 157.3, 156.4, 156.0, 144.3, 141.8, 137.4, 136.6, 136.3, 135.8, 134.7, 132.6, 132.4, 129.0, 128.9, 128.8, 128.6, 128.4, 127.6, 127.5, 127.4, 119.8, 119.7, 112.1, 102.1, 92.9, 76.8, 70.7, 69.7, 65.7, 65.5, 56.6, 54.7, 48.0, 36.8, 33.9, 30.8, 17.0. HRMS for C₅₂H₄₇N₅O₁₄ [M+Na]⁺ calcd. 988.3012, found 988.3022.
Preparation of 7:

Compound 39 (5.3 mg, 0.0055 mmol) and 34 (3.9 mg, 0.0055 mmol) were dissolved in a mixture of 1:1:1 PBS/MeOH/ACN (1.2 ml). The mixture was stirred for 16 hr at room temperature. To workup, additional MeOH (1 ml) was added. The reaction was then filtered and directly purified by reverse phase HPLC using method 12 (retention time 17.7 min). Yield: 4.7 mg, 51%.

^1H NMR (1,4-Dioxane-d8, 400 MHz) δ 8.04 (d, J = 7.7 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.61-7.43 (m, 7H), 7.40-7.21 (m, 6H), 6.93 (s, 1H), 6.84 (s, 1H), 6.22-5.98 (m, 1H), 5.90-5.66 (m, 1H), 5.41-5.35 (m, 1H), 5.25-5.19 (m, 1H), 4.97-4.80 (m, 2H), 4.78-4.75 (m, 1H), 4.72 (t, J = 5.8 Hz, 1H), 4.30-4.22 (m, 1H), 4.03 (s, 3H), 3.85-3.73 (m, 4H), 3.56-3.40 (m, 35H), 3.30 (s, 3H), 3.21-3.06 (m, 2H), 2.46-2.35 (m, 1H), 2.20-2.08 (m, 1H), 2.03-1.87 (m, 2H), 1.84-1.73 (m, 1H), 1.72-1.52 (m, 2H), 1.43-1.27 (m, 4H), 1.23 (d, J = 6.5 Hz, 3H); ^13C NMR (1,4-Dioxane-d8, 75 MHz): δ 214.9, 187.8, 187.7, 172.8, 172.4, 162.1, 157.1, 156.3, 156.0, 141.9, 140.1, 139.3, 137.8, 137.6, 137.2, 136.5, 136.0, 135.9, 135.6, 135.5, 135.4, 134.8, 133.3, 132.9, 132.8, 132.1, 131.2, 130.5, 130.3, 130.0, 129.8, 129.4, 129.1, 129.0, 128.9, 128.8, 128.0, 127.5, 125.5, 122.0, 120.8, 119.9, 119.3, 112.2, 112.1, 110.0, 101.8, 76.7, 72.5, 71.1, 70.7, 58.7, 56.6, 47.9, 41.0, 39.6, 36.1, 33.9, 30.8, 25.4, 24.8, 16.9. HRMS for C$_{90}$H$_{101}$N$_7$O$_{24}$ [M+Na]$^+$ calcd. 1686.6796, found 1686.6798.
1.5.4 Gold Catalyst Complexes

Scheme S16. Synthesis of Au-5

Preparation of 41:

Compound 40 was prepared according to the previous literature. Compound 40 (275.0 mg, 844.9 µmol) and Boc-amino-3-oxapentanoic acid (277.8 mg, 1.270 mmol) were dissolved in DCM. EDC (1.270 mmol) and HOBt (1.270 mmol) were added and the mixture was stirred at rt for 20 min. To workup, H₂O was added to the mixture and the product was extracted to CH₂Cl₂. The organic layer was dried over Na₂SO₄ and then evaporated under vacuum after the filtration. Flash column chromatography using a gradient of 25-50% of EtOAc in Hex was used to purify the desired compound. Yield: 311.5 mg, 70%. Rᵣ=0.74 (CHCl₃/MeOH, 9:1). ¹H NMR (CDCl₃, 400 MHz) δ 7.08 (m, 1H), 6.81 (s, 2H), 6.79 (s, 2H), 3.94 (s, 2H), 3.72-3.60 (m, 2H), 3.60-3.50 (m, 2H), 3.46-3.21 (m, 4H), 3.09 (dd, J=12.4, 6.0 Hz, 1H), 2.90 (dd, J=12.4, 5.2 Hz, 1H), 2.25 (s, 6H), 2.22 (s, 3H), 2.20 (s, 3H), 2.19 (s, 6H), 1.43 (s, 9H) ¹³C NMR (CDCl₃, 100 MHz): δ 170.0, 156.0, 143.3, 141.3, 131.7, 131.4, 130.2, 130.0, 129.1, 79.8, 71.0, 70.5, 56.9, 51.2, 42.1, 40.5, 28.5, 20.6, 19.1, 18.5. HRMS for C₃₀H₄₈N₄O₄ [M+H]+ calcd. 527.3592, found 527.3597.
Preparation of 42:

![Chemical structure of compound 41](image)

Compound 41 (314.9 mg, 591.4 µmol) was dissolved in 4.6 M HCl solution in MeOH (8.3 mL). The reaction solution was stirred at rt for 2 h. To workup, the reaction solution was neutralized with 1.5 g of NaOH and sat. aq. NaHCO₃. The product was extracted to CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered, and then evaporated to obtain the desired compound. Yield: 172.5 mg, 68%. Rᵥ = 0.23 (CHCl₃/MeOH, 4:1). ¹H NMR (CDCl₃, 400 MHz) δ 7.52 (m, 1H), 6.81 (s, 2H), 6.78 (s, 2H), 3.98 (s, 2H), 3.65-3.47 (m, 4H), 3.42 (dt, J = 13.6, 5.6 Hz, 1H), 3.07 (dd, J = 12.4, 6.0 Hz, 1H), 2.88 (dd, J = 12.4, 5.2 Hz, 1H), 2.83 (dd, J = 5.6, 4.4 Hz, 2H), 2.24 (s, 6H), 2.21 (s, 3H), 2.19 (s, 3H), 2.17 (s, 6H). ¹³C NMR (CDCl₃, 100 MHz): δ 170.6, 143.5, 141.3, 131.5, 131.3, 130.0, 129.6, 129.0, 74.0, 70.5, 57.0, 51.0, 41.7, 41.5, 20.6, 19.2, 18.5. HRMS for C₂₅H₃₈N₄O₂ [M+H]⁺ calcd. 427.3068, found. 427.3071.

Preparation of 44:

![Chemical structure of compounds 42 and 43](image)

Compound 42 (160.7 mg, 376.7 µmol) and 43 (108.3 mg, 414.4 µmol) were dissolved in DCM (15 mL). EDC (79.4 mg, 414.4 µmol) and HOBt (55.6 mg, 414.4 µmol) were added and the mixture was stirred at rt for 2 h. Then, EDC (79.4 mg, 414.4 µmol) and HOBt (55.6 mg, 414.4 µmol) were added and the mixture was stirred further for 1 hr. To workup, H₂O was added to the mixture and the product was extracted to CH₂Cl₂. The organic layer was dried over Na₂SO₄ and then evaporated under vacuum after the filtration. Flash column chromatography using a gradient of 0-5% of MeOH in CHCl₃ was used to purify the desired compound. Yield: 231.2 mg, 92%. Rᵥ = 0.53 (CHCl₃/MeOH, 9:1). ¹H NMR (CDCl₃, 400 MHz) δ 9.07 (m, 1H), 8.60 (s, 1H), 7.31 (d, J = 9.2 Hz, 1H), 6.724 (s, 2H), 6.716 (s, 2H), 6.61 (dd, J = 9.2, 2.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 4.02 (s, 2H), 3.69-3.49 (m, 7H), 3.45 (q, J = 7.2 Hz, 4H), 3.05 (dd, J = 12.8, 5.6 Hz, 1H), 2.86 (dd, J = 12.8, 4.4 Hz, 1H), 2.21 (s, 6H), 2.16 (s, 6H), 2.15 (s, 6H), 1.25 (t, J = 7.2 Hz, 6H). ¹³C NMR (CDCl₃, 100 MHz) δ 170.3, 163.5, 163.0, 157.7, 148.3, 143.7, 141.5, 133.5, 131.3, 131.2, 130.9, 130.0, 129.8, 129.5, 129.2, 110.1, 110.0, 108.5, 96.6, 70.6, 70.6, 57.0, 50.7, 45.2, 41.7, 39.3, 20.6, 19.1, 18.5, 12.6. HRMS for C₃₉H₅₅N₅O₅ [M+H]⁺ calcd. 670.3963, found. 670.3977.
Preparation of 45:

\[
\begin{align*}
\text{Compound 44 (165.6 mg, 247.2 µmol) was dissolved in CH(OEt)}_3 (3.0 \text{ mL). NH}_4 \text{Cl (13.2 mg, 247.2 µmol) was added and the mixture was stirred at 120 °C for 7 hrs. After cooled to rt, the mixture was filtered and the filtrate was concentrated under vacuum. The product was sedimentated in Et}_2 \text{O, filtered with Celite, and recovered with CHCl}_3. \text{ The resulting solution was evaporated under vacuum. Flash column chromatography using a gradient of 5-15% of MeOH in CHCl}_3 \text{ was used to purify the desired compound. From the extract in Et}_2 \text{O, the 76% yield of the starting material 44 was purified with flash column chromatography using a gradient of 0-7.5% of MeOH in CHCl}_3. \text{ Yield: 23.6 mg, 13% (54% brsm), R}_f = 0.56 (\text{CHCl}_3/\text{MeOH, 8:2}). & \text{(CDCl}_3, 400 MHz) 9.55 (s, 1H), 8.99 (m, 1H), 8.63 (s, 1H), 8.01 (t, J=6.0 Hz, 1H), 7.42 (d, J=9.2 Hz, 1H), 6.96 (s, 2H), 6.92 (s, 2H), 6.67 (dd, J=8.8, 2.4 Hz, 1H), 6.44 (d, J=2.4 Hz, 1H), 5.32 (m, 1H), 4.58 (t, J=12.0 Hz, 1H), 4.48 (dd, J=12.0, 8.0 Hz, 1H), 4.03-3.86 (m, 3H), 3.76-3.59 (m, 5H), 3.53-3.42 (m, 5H), 2.47 (s+brs, 3H+3H), 2.44 (s, 3H), 2.36 (brs, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 1.27 (t, J=7.2 Hz, 6H). & \text{13C NMR (CDCl}_3, 100 MHz) 171.0, 163.4, 163.1, 160.4, 157.8, 152.9, 148.4, 140.8, 140.6, 135.2, 131.4, 130.7, 130.5, 130.2, 129.0, 124.5, 121.9, 110.3, 110.0, 108.5, 96.5, 70.7, 70.4, 62.5, 55.6, 45.3, 40.1, 39.3, 29.9, 21.2, 19.0, 18.7, 12.6. & \text{HRMS for C}_{40}\text{H}_{50}\text{N}_5\text{O}_5\text{Cl [M-Cl]}^+ \text{ calcd. 680.3806, found. 680.3846.}
\end{align*}
\]

Preparation of Au-5:

\[
\begin{align*}
\text{Compound 45 (23.6 mg, 32.7 µmol) was dissolved in DCM (3.0 mL). Ag}_2 \text{O (3.8 mg, 16.4 µmol) was added and the mixture was stirred at rt for 4 hrs. The mixture was filtered with Celite to remove the precipitated salt. To the filtrate was added chloro(dimethylsulfide)gold (I) (8.7 mg, 32.7 µmol) and stirred at rt for 13 hrs. The mixture was filtered with Celite and the filtrate was evaporated under vacuum to obtain Au-5 as a brown powder. Yield: 28.9 mg, 97%. & \text{(CDCl}_3, 400 MHz) 9.03 (m, 1H), 8.64 (s, 1H), 7.40 (d, J=9.6 Hz, 1H), 7.04 (dd, J=7.2, 4.8 Hz, 1H), 6.93 (s, 1H), 6.90 (s, 3H), 6.69 (dd, J=8.8, 2.4 Hz, 1H), 6.47 (d, J=2.4 Hz, 1H), 4.67 (m, 1H), 4.13 (t, J=9.6 Hz, 1H), 3.98-3.84 (m, 4H), 3.67-3.47 (m, 8H), 3.33 (dt, J=13.2, 4.8 Hz, 1H), 2.41 (s, 3H) 2.38 (s, 3H), 2.29 (s, 3H), 2.27 (s, 6H), 1.29 (t, J=7.2 Hz, 1H). & \text{13C NMR (CDCl}_3, 100 MHz) 171.0, 163.4, 163.1, 160.4, 157.8, 152.9, 148.4, 140.8, 140.6, 135.2, 131.4, 130.7, 130.5, 130.2, 129.0, 124.5, 121.9, 110.3, 110.0, 108.5, 96.5, 70.7, 70.4, 62.5, 55.6, 45.3, 40.1, 39.3, 29.9, 21.2, 19.0, 18.7, 12.6. & \text{HRMS for C}_{40}\text{H}_{50}\text{N}_5\text{O}_5\text{AuCl [M-Cl]}^+ \text{ calcd. 877.3394, found. 876.3455.}
\end{align*}
\]
1.5.5 Reaction by-products

Preparation of 46:

Compound 1q (50 mg, 0.133 mmol) and Au-1 (42 mg, 0.106 mmol) were dissolved in THF (2 ml) and PBS buffer pH 7.4 (2 ml). The mixture was stirred for 16 hr at 37 °C. To workup, the reaction was diluted with diethyl ether and then the organic layer was extracted, dried over magnesium sulfate, and evaporated under vacuum. Flash column chromatography using a gradient of 10-25% EtOAc in Hex was used to purify the desired compound. Yield: 19 mg, 40% based on Au. Rf =0.30 (EtOAc/Hex, 1:4). \textbf{^{1}H NMR} (CDCl$_3$, 300 MHz) δ 7.22-6.99 (m, 4H), 1.81 (t, $J$= 7.4, 2H), 1.41-1.17 (m, 6H), 0.87 (t, $J$= 6.8, 3H); \textbf{^{13}C NMR} (CDCl$_3$, 75 MHz): δ 157.0, 156.1, 135.9, 131.2, 128.6, 128.4, 127.6, 120.0, 97.5, 33.0, 31.3, 25.9, 22.4, 14.0. \textbf{LRMS} for C$_{14}$H$_{15}$O$_2$AuCl [M-Cl]$^+$ calcd. 412.2, found. 412.2.
2. Cell-based Assays

2.1 General Cell Culture Protocol

In this study, the following cell lines were obtained from the RIKEN Cell Bank. Cells were grown in 37 °C incubators supplemented with 5% CO₂ gas. Specific growth media used are indicated as follows:

| Name       | Type                          | Medium                                      | FBS  | Penicillin-Streptomycin |
|------------|-------------------------------|---------------------------------------------|------|-------------------------|
| HeLa S3    | human cervix adenocarcinoma    | DMEM (High Glucose) w/ L-glutamine and phenol red | 10%  | 1%                      |
| PC3        | human prostate cancer cells    | DMEM (High Glucose) w/ L-glutamine and phenol red | 10%  | 1%                      |
| A549       | human lung adenocarcinoma cells| DMEM (High Glucose) w/ L-glutamine and phenol red | 10%  | 1%                      |
| MCF7       | human breast cancer cells      | RPMI w/ L-glutamine                         | 10%  | 1% (charcoal stripped)  |

2.2 Cell Viability Studies

2.2.1 MTS Assay Protocol

Cell viability was determined using an MTS assay, which is a colorimetric method to monitor the reduction of MTS tetrazolium salts to formazan via mitochondrial dehydrogenase of metabolically active cells. The commercial kit used in this study was the CellTiter 96® AQueous One Solution Cell Proliferation Assay (Promega, Wisconsin, USA).

Based on cell titration experiments (data not shown), cells were plated and grown overnight on 96-well Falcon® microplates (1000 cells/well for HeLa; 1000 cells/well for PC3; 1000 cells/well for A549; 2000 cells/well for MCF7). The media was then removed, followed by the incubation of various concentrations of compounds used in this study. Generally, 10 μl of compounds were added to 90 μl of media. Following an incubation time of 4 days, cell viability was detected by first removing the media and replacing it with 20 μl MTS reagent and 80 μl media. Following incubation at 37 °C for 2 hr, end-point absorbance was acquired at 490 nm, via a SpectraMax® iD3 Multi-Mode Microplate Reader (Molecular Devices, California, USA). The background control for this assay was the incubation of 20 μl MTS reagent and 80 μl media in the absence of cells. Obtained EC₅₀ values were calculated via GraphPad Prism (version 7.0d) software using fitting based on the sigmoidal dose response equation.

2.2.2 Controls

Before cell toxicity studies, various controls experiments were performed. The first was to determine the toxicity of DMSO (Figure S14), which was used to dissolve the compounds used in this study. This experiment led to the standardization of 1% DMSO. The next control was to determine the toxicity of Au-5 (Figure S15). From the acquired growth curves, it was decided that the addition of Au-5 to a final concentration of 10 μM would be ideal for the tested cell lines (HeLa S3, PC3, A549, and MCF7).
Figure S14. Cell growth curves aimed at exploring the effects of DMSO supplementation to cultures of A) HeLa cells, B) A549 cells, C) PC3 cells, and D) MCF7 cells.

Figure S15. Cell growth curves aimed at exploring the effects of Au-5 supplementation to cultures of A) HeLa cells, B) A549 cells, C) PC3 cells, and D) MCF7 cells.
2.2.3 Cell Toxicity Results

Cell growth curves to monitor toxicity of the tested compounds (3a, 3m, 6a, 6m, and 7) are shown in Figures S16-S19. A summary of the calculated EC$_{50}$ values obtained in tests against MCF7 cells using prodrugs 3a,m are shown in Table S5.

| Compound       | EC$_{50}$ (µM) |
|----------------|----------------|
| 3a             | 55             |
| 3a/Au-5        | 26             |
| 3m             | 57             |
| 3m/Au-5        | 41             |
| Endoxifen      | 25             |

Table S5. Summary of cytotoxic activity of endoxifen-based prodrugs

![Figure S16](image_url). Cell growth curves of MCF7 cancer cells aimed at exploring the effects of supplementation with A) prodrug 3a (orange) and mixture 3a/Au-5 (purple), as well as B) prodrug 3m (grey) and mixture 3m/Au-5 (turquoise). Endoxifen (brown) was used as a control.
Figure S17. Cell growth curves aimed at exploring the effects of either prodrug 6a (red), mixture 6a/Au-5 (blue), or doxorubicin (green) supplementation to cultures of A) HeLa cells, B) A549 cells, and C) PC3 cells.

Figure S18. Cell growth curves aimed at exploring the effects of either prodrug 6m (red), mixture 6m/Au-5 (blue), or doxorubicin (green) supplementation to cultures of A) HeLa cells, B) A549 cells, and C) PC3 cells.
Figure S19. Cell growth curves aimed at exploring the effects of either prodrug 7 (red), mixture 7/Au-5 (blue), or doxorubicin (green) supplementation to cultures of A) HeLa cells, B) A549 cells, and C) PC3 cells.
2.3 Cell Permeability Studies

2.3.1 Incubation and Imaging Protocol

To monitor the penetration of compounds under study, fluorescent cell imaging was performed. Given that doxorubicin (and similar derivatives) are known to produce fluorescence ($\lambda_{\text{EX}} = 470 \text{ nm} / \lambda_{\text{EM}} = 560 \text{ nm}$), cell penetration can be comparatively quantified via fluorescent imaging of cells incubated under various conditions.

HeLa cells were first plated onto ibidi µ-Slide 8 well chamber slides at approximately 30,000 cells/well and grown overnight. In each well, 280 µl of fresh DMEM media was then added, followed by 20 µl of compound (150 µM stock solution), which gave a final concentration of 10 µM doxorubicin, 6a, or 7. After incubations at 37°C for set time intervals (1, 2, 4, 8 hr), cells were washed with DMEM media (2×) and PBS buffer pH 7.4 (2×). Imaging studies were then carried out using a Keyence BZ-X710 All-in-one Fluorescence Microscope® at 20× magnification. Brightfield images (color) were obtained at a 1/150 sec exposure setting and fluorescent images were obtained at a 1.2 sec exposure setting.

2.3.2 Cell Imaging Results

Cells from obtained images were randomly chosen (n=15) and their fluorescence was quantified via ImageJ. Shown in Figures S20-S31 are the cropped images of the cells used for quantification. Under set time intervals (1, 2, 4, 8 hours), incubations were carried out using either doxorubicin, 6a, or 7.

| Doxorubicin Time: 1 hr |
|-----------------------|
| ![Imaging Studies](image-url) |

Figure S20. Imaging studies of HeLa cells incubated with Doxorubicin (10 µM) for 1 hr.
Figure S21. Imaging studies of HeLa cells incubated with Doxorubicin (10 µM) for 2 hr.

Figure S22. Imaging studies of HeLa cells incubated with Doxorubicin (10 µM) for 4 hr.
**Figure S23.** Imaging studies of HeLa cells incubated with Doxorubicin (10 μM) for 8 hr.

**Figure S24.** Imaging studies of HeLa cells incubated with compound 6a (10 μM) for 1 hr.
Figure S25. Imaging studies of HeLa cells incubated with compound 6a (10 µM) for 2 hr.

Figure S26. Imaging studies of HeLa cells incubated with compound 6a (10 µM) for 4 hr.
Figure S27. Imaging studies of HeLa cells incubated with compound 6a (10 µM) for 8 hr.

Figure S28. Imaging studies of HeLa cells incubated with compound 7 (10 µM) for 1 hr.
Figure S29. Imaging studies of HeLa cells incubated with compound 7 (10 µM) for 2 hr.

Figure S30. Imaging studies of HeLa cells incubated with compound 7 (10 µM) for 4 hr.
Figure S31. Imaging studies of HeLa cells incubated with compound 7 (10 μM) for 8 hr.
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