



Supporting Information

Carbene-Catalyzed Activation of Remote Nitrogen Atoms of (Benz)imidazole-Derived Aldimines for Enantioselective Synthesis of Heterocycles

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General methods

All reactions and manipulations involving air-sensitive compounds were carried out using standard Schlenk techniques. Anhydrous THF were distilled from sodium benzophenone ketyl. Anhydrous CH_2Cl_2 was distilled from CaH_2 under an atmosphere of nitrogen. All reactions were monitored by TLC. TLC analysis was performed by illumination with a UV lamp (254 nm). All flash chromatography was packed with silica-gel as the stationary phase. ^1H NMR spectra were recorded on a Bruker BBFO (400 MHz) instrument, and chemical shifts were reported in ppm downfield from internal TMS with the solvent resonance as the internal standard (CDCl_3 , $\delta = 7.26$ ppm). ^{13}C NMR spectra were recorded on a Bruker BBFO (101 MHz) instrument, and chemical shifts were reported in ppm downfield from TMS with the solvent resonance as the internal standard (CDCl_3 , $\delta = 77.16$ ppm). ^{19}F NMR spectra were recorded on a Bruker BBFO (377 MHz) instrument. Optical rotations were measured on a Jasco P-1030 polarimeter. High resolution mass spectra (HRMS) (EI+) were recorded on an a Finnigan MAT 95 XP mass spectrometer. The imines were synthesized according to the literature procedure.^[1]

Conditions optimization for the reaction of imine and trifluoroacetophenone

Table S-1. Preliminary examination of carbene catalysts.^[a]

$\text{1a} + \text{4a} \xrightarrow[\text{DCM, rt, 48 h}]{\text{NHC (20 mol\%)}, \text{DQ (1.2 equiv)}, \text{DIEA (1.0 equiv)}} \text{5a}$

| A: Ar = Mes | | B: Ar = 2,4,6-Cl ₃ C ₆ H ₂ | C: Ar = C ₆ F ₅ | |
|-----------------|-----|---|---|--|
| | | D: Ar = 2,4,6-Cl ₃ C ₆ H ₂ | DQ (oxidant) | |
| Entry | NHC | Conv. [%] ^[b] | er ^[c] | |
| 1 | A | 14 | 81:19 | |
| 2 | B | 23 | 58:42 | |
| 3 | C | trace | - | |
| 4 | D | 20 | 70:30 | |

[a] Reaction conditions: **1a** (0.15 mmol), **4a** (0.1 mmol), DIEA (1.0 equiv), NHC (20 mol%), and DQ (1.2 equiv) in solvent (1.0 mL) at rt. [b] The conversion was determined by ¹⁹F NMR analysis. [c] Enantiomeric ratio of **5a** was determined via HPLC on a chiral stationary phase.

Table S-2. Examination of bases.^[a]

$\text{1a} + \text{4a} \xrightarrow[\text{DCM, rt, 48 h}]{\text{NHC D (20 mol\%)}, \text{DQ (1.2 equiv)}, \text{base (1.0 equiv)}} \text{5a}$

| A: Ar = Mes | | D: Ar = 2,4,6-Cl ₃ C ₆ H ₂ | DQ (oxidant) | |
|-----------------|-------------------------------------|---|-------------------|--|
| Entry | base | Conv. [%] ^[b] | er ^[c] | |
| 1 | DIEA | 20 | 70:30 | |
| 2 | DABCO | trace | - | |
| 3 | NaOAc | trace | - | |
| 4 | K ₂ CO ₃ | 24 | 73:23 | |
| 5 | DBU | 29 | 65:35 | |
| 6 | Cs₂CO₃ | 56 | 70:30 | |

[a] Reaction conditions: **1a** (0.15 mmol), **4a** (0.1 mmol), base (1.0 equiv), NHC (20 mol%), and DQ (1.2 equiv) in solvent (1.0 mL) at rt. [b] The conversion was determined by ¹⁹F NMR analysis. [c] Enantiomeric ratio of **5a** was determined via HPLC on a chiral stationary phase.

Table S-3. The second examination of carbene catalysts with Cs₂CO₃ as base.^[a]

$\text{1a} + \text{4a} \xrightarrow[\text{DCM, rt, 48 h}]{\text{NHC (20 mol\%)}, \text{DQ (1.2 equiv)}, \text{Cs}_2\text{CO}_3 (1.0 \text{ equiv})} \text{5a}$

A: Ar = Mes

D: Ar = 2,4,6-Cl₃C₆H₂

E: Ar = Mes

C: Ar = C₆F₅

G: Ar = Mes

DQ (oxidant)

| Entry | NHC | Conv. [%] ^[b] | er ^[c] |
|-------|----------|--------------------------|-------------------|
| 1 | A | 52 | 73:27 |
| 2 | C | trace | - |
| 3 | D | 56 | 70:30 |
| 4 | E | 23 | 64:36 |
| 5 | G | 55 | 74:26 |

[a] Reaction conditions: **1a** (0.15 mmol), **4a** (0.1 mmol), base (1.0 equiv), NHC (20 mol%), and DQ (1.2 equiv) in solvent (1.0 mL) at rt. [b] The conversion was determined by ¹⁹F NMR analysis. [c] Enantiomeric ratio of **5a** was determined via HPLC on a chiral stationary phase.

Table S-4. Examination of additives.^[a]

$\text{1a} + \text{4a} \xrightarrow[\text{DCM, rt, 48 h}]{\text{NHC G (20 mol\%)}, \text{DQ (1.2 equiv)}, \text{Cs}_2\text{CO}_3 (1.0 \text{ equiv})} \text{5a}$

G: Ar = Mes

DQ (oxidant)

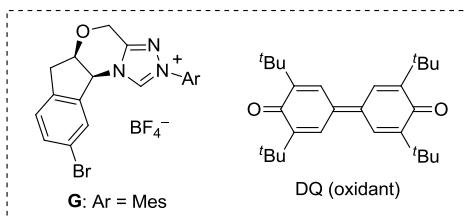
U1

U2

| Entry | Additive | Conv. [%] ^[b] | er ^[c] |
|------------------|----------------------|--------------------------|-------------------|
| 1 | - | 55 | 74:26 |
| 2 ^[d] | LiCl | 50 | 74:26 |
| 3 ^[e] | Cu(OTf) ₂ | trace | - |
| 4 ^[e] | Sc(OTf) ₃ | trace | - |
| 5 ^[e] | U1 | 26 | 74:26 |
| 6 ^[e] | U2 | 53 | 74:26 |
| 7 ^[e] | HOBt | 54 | 74:26 |
| 8 ^[f] | 4Å MS | 60 | 78:22 |

[a] Reaction conditions: **1a** (0.15 mmol), **4a** (0.1 mmol), Cs₂CO₃ (1.0 equiv), NHC (20 mol%), and DQ (1.2 equiv) in solvent (1.0 mL) at rt. [b] The conversion was determined by ¹⁹F NMR analysis. [c] Enantiomeric ratio of **5a** was determined via HPLC on a chiral stationary phase. [d] 1.0 equiv of additive was used. [e] 20 mol% of additive was used. [f] 4 Å MS (100 mg) was used.

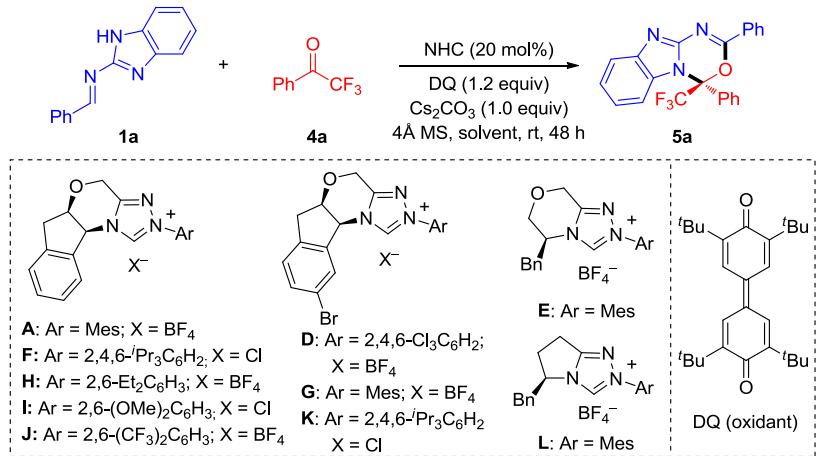
Table S-5. Examination of solvents.^[a]



| Entry | Solvent | Conv. [%] ^[b] | er ^[c] |
|------------------|-----------------------|--------------------------|-------------------|
| 1 | DCM | 60 | 78:22 |
| 2 | THF | 40 | 76:24 |
| 3 | EA | 42 | 67:33 |
| 4 | DMF | 48 | 83:17 |
| 5 | DMSO | 38 | 75:15 |
| 6 | ^t BuOH | 90 | 72:28 |
| 7 ^[d] | ^t BuOH/DMF | 65 | 85:15 |

[a] Reaction conditions: **1a** (0.15 mmol), **4a** (0.1 mmol), Cs_2CO_3 (1.0 equiv), NHC (20 mol%), 4 Å MS (100 mg) and DQ (1.2 equiv) in solvent (1.0 mL) at rt. [b] The conversion was determined by ^{19}F NMR analysis. [c] Enantiomeric ratio of **5a** was determined via HPLC on a chiral stationary phase. [d] ^tBuOH/DMF = 1:1 (1.0 mL).

Table S-6. The third examination of carbene catalysts.^[a]



| Entry | NHC | Solvent | Conv. [%] ^[b] | er ^[c] |
|-------------------|----------|-----------------------|--------------------------|-------------------|
| 1 ^[d] | A | ^t BuOH/DMF | 62 | 82:18 |
| 2 ^[d] | D | ^t BuOH/DMF | 70 | 55:45 |
| 3 ^[d] | E | ^t BuOH/DMF | 32 | 69:31 |
| 4 ^[d] | F | ^t BuOH/DMF | 36 | 94:6 |
| 5 ^[d] | G | ^t BuOH/DMF | 65 | 85:15 |
| 6 ^[d] | H | ^t BuOH/DMF | 63 | 86:14 |
| 7 ^[d] | I | ^t BuOH/DMF | 36 | 76:24 |
| 8 ^[d] | J | ^t BuOH/DMF | 42 | 51:49 |
| 9 ^[d] | K | ^t BuOH/DMF | 50 | 92:8 |
| 10 ^[d] | L | ^t BuOH/DMF | trace | - |
| 11 | K | ^t BuOH | 94 | 90:10 |
| 12 | F | ^t BuOH | 93 (92) | 94:6 |

[a] Reaction conditions: **1a** (0.15 mmol), **4a** (0.1 mmol), Cs₂CO₃ (1.0 equiv), NHC (20 mol%), 4Å MS (100 mg) and DQ (1.2 equiv) in solvent (1.0 mL) at rt. [b] The conversion was determined by ¹⁹F NMR analysis; The data in parenthesis is isolated yield. [c] Enantiomeric ratio of **5a** was determined via HPLC on a chiral stationary phase. [d] ¹BuOH/DMF = 1:1 (1.0 mL).

General procedure for the NHC-catalyzed asymmetric reaction

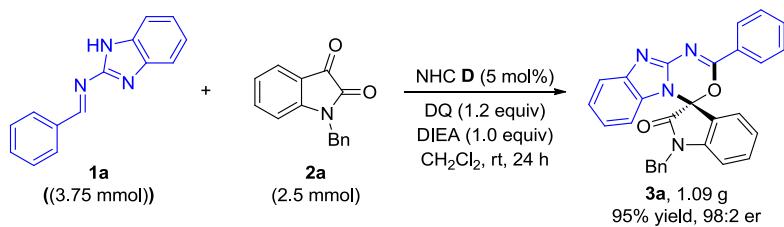
General procedure for the NHC-catalyzed asymmetric reaction of imines with isatins

To a dried 4 mL test tube with a stir bar was added the carbene catalyst (10 mol %), imine (0.15 mmol), isatins (0.1 mmol), DQ (49.8 mg, 1.2 equiv), anhydrous CH₂Cl₂ (1.0 mL) and DIEA (18 μ L, 1.0 equiv). The reaction mixture was stirred at rt for the time indicated in the table, then directly subjected to the preparative thin layer chromatography or column chromatography (Hexane/EA = 2:1).

General procedure for the NHC-catalyzed asymmetric reaction of imines with trifluoroacetophenones

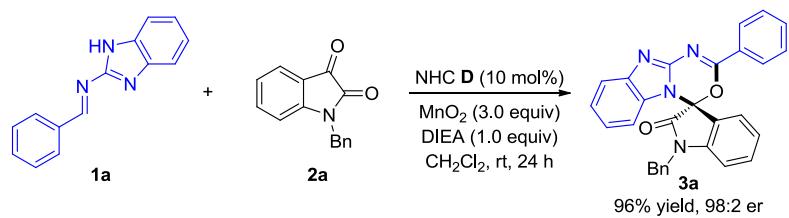
To a dried 4 mL test tube with a stir bar was added the carbene catalyst (20 mol %), imine (0.15 mmol), Cs₂CO₃ (32.6 mg, 1.0 equiv), 4Å MS (100 mg), DQ (49.8 mg, 1.2 equiv), anhydrous ¹BuOH (1.0 mL) and trifluoroacetophenones (0.1 mmol). The reaction mixture was stirred at rt (25–30 °C) for the time indicated in the table, then directly subjected to the preparative thin layer chromatography or column chromatography (Hexane/EA = 4:1).

Procedure for the gram-scale synthesis of **3a**



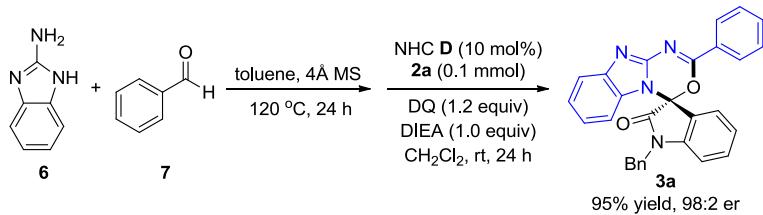
To a 25 mL round bottom flask with a stir bar was added the imine **1a** (3.75 mmol, 0.83 g), isatin **2a** (2.5 mmol, 0.59 g), NHC precatalyst **D** (5 mol %, 70 mg), DQ (1.25 g, 1.2 equiv), anhydrous DCM (12.5 mL) and DIEA (0.45 mL, 1.0 equiv). After stirring at rt for 24 h, the reaction mixture was concentrate under reduced pressure and the residue was directly subjected to column chromatography (Hexane/EA = 15:1 to 3:1) to afford the desired product **3a** (1.09 g) in 95% yield and 98:2 er.

Procedure for the reaction using MnO₂ as oxidant



To a 4 mL test tube with a stir bar was added the imine **1a** (0.15 mmol, 33.2 mg), isatin **2a** (0.1 mmol, 23.6 mg), NHC precatalyst **D** (10 mol %, 5.6 mg), DQ (49.8 mg, 1.2 equiv), anhydrous DCM (1.0 mL) and DIEA (18 uL, 1.0 equiv). After stirring at rt for 24 h, the reaction mixture was directly subjected to column chromatography (Hexane/EA = 15:1 to 3:1) to afford the desired product **3a** (43.7 mg) in 96% yield and 98:2 er.

Procedure for the one-pot synthesis of **3a**



To a test tube with a stir bar was added the amine **6** (0.16 mmol, 21.4 mg), 4 Å MS (200 mg), anhydrous toluene (1.0 mL) and aldehyde **7** (0.15 mmol, 16 uL). The test tube was sealed and stirred at 120 °C for 24 h. Then the reaction mixture was carefully concentrated under reduced pressure to remove the toluene and get the crude imine. To this test tube with the crude imine was added isatin **2a** (0.1 mmol, 23.6 mg), NHC precatalyst **D** (10 mol %, 5.6 mg), DQ (49.8 mg, 1.2 equiv), anhydrous DCM (1.0 mL) and DIEA (18 uL, 1.0 equiv). After stirring at rt for 24 h, the reaction mixture was directly subjected to column chromatography (Hexane/EA = 15:1 to 3:1) to afford the desired product **3a** (43.3 mg) in 95% yield and 98:2 er.

Mechanism studies

Investigation of background reaction

The ¹H spectra analysis of background reaction without carbene catalyst showed that there isn't background reaction for the formation of *N,O*-aminal **6a** and **6b** (figure S-1).

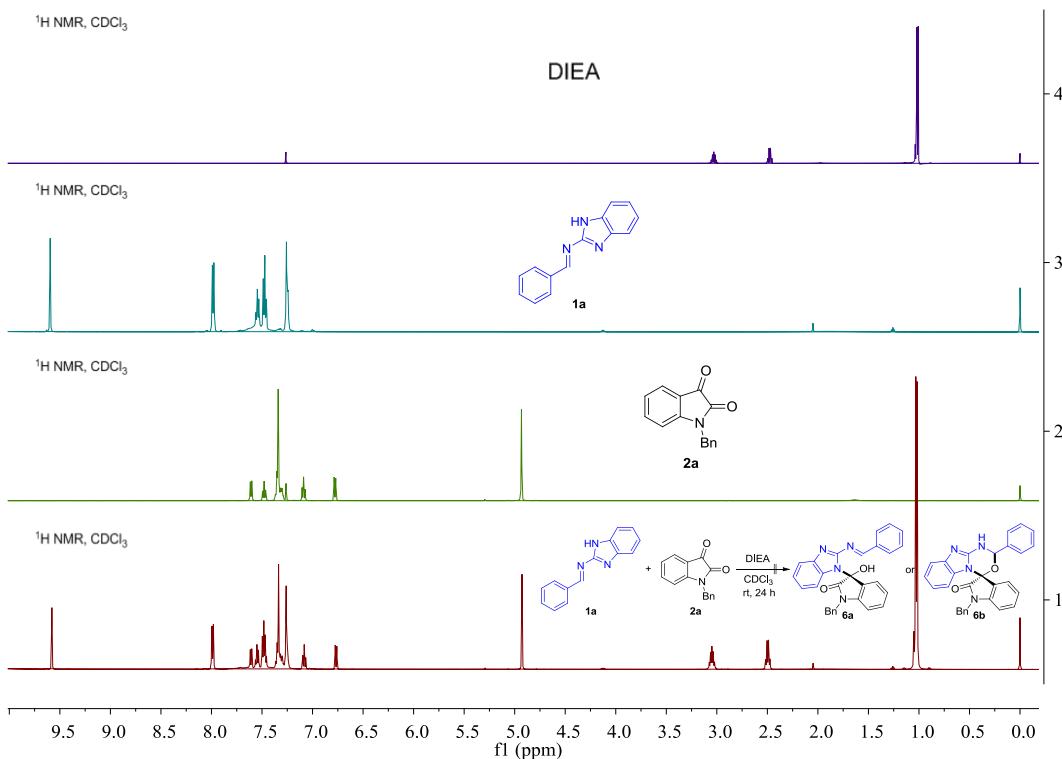
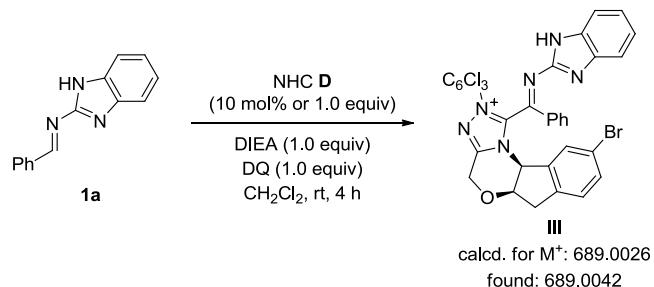


Figure S-1. The ¹H spectra of starting materials and background reaction without carbene catalyst

Detection of the key intermediate via HRMS



The HRMS data of the crude reaction mixture showed an intense peak at 689.0042 (M⁺ of the intermediate III, figure S-2).

| Elemental Composition Report | | | | | | | |
|---|------------|--------|--------|---------|---------|------|--|
| Single Mass Analysis | | | | | | | |
| Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0 | | | | | | | |
| Element prediction: Off | | | | | | | |
| Number of isotope peaks used for i-FIT = 3 | | | | | | | |
| Monoisotopic Mass, Even Electron Ions | | | | | | | |
| 12 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass) | | | | | | | |
| Elements Used: | | | | | | | |
| C: 25-32 | H: 21-22 | N: 1-6 | O: 1-2 | Cl: 3-3 | Br: 0-1 | | |
| Minimum: | | | | -1.5 | | | |
| Maximum: | 5.0 | 20.0 | 50.0 | | | | |
| Mass | Calc. Mass | mDa | PPM | DBE | i-FIT | Norm | Conf(%) |
| 689.0041 | 689.0026 | | 1.5 | 2.2 | 23.5 | 53.8 | n/a |
| | | | | | | | Formula |
| | | | | | | | C ₃₂ H ₂₁ N ₆ OCl ₃ Br |

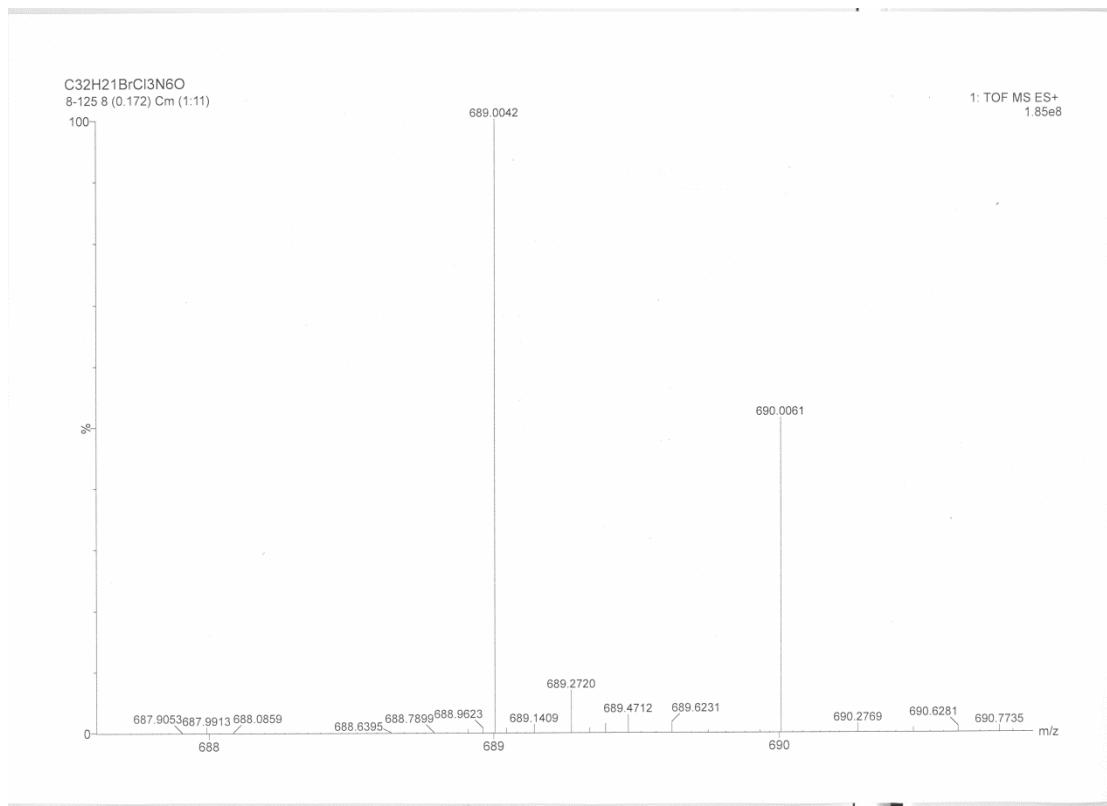


Figure S-2. The HRMS data of intermediate III

Computational methods for mechanism studies

Geometry optimizations in the gas phase were initially carried out using the GFN1-xTB method^[2] as implemented in Entos Qcore Version 0.7.^[3] The resulting structures were further optimized using global hybrid functional M06-2X^[4] with Karlsruhe-family basis set of double- ζ valence def2-SVP^[5,6] for all atoms as implemented in *Gaussian 16* rev. A.03.^[7] Minima and transition structures on the potential energy surface (PES) were confirmed as such by harmonic frequency analysis, showing respectively zero and one imaginary frequency, at the same level of theory. Intrinsic reaction coordinate (IRC) analyses^[8,9] were performed to confirm that the found TSs connect to the right reactants and products.

Single point (SP) corrections were performed using M06-2X functional and def2-TZVP^[1] basis set for all atoms. The implicit SMD continuum solvation model^[10] was used to account for the solvent effect of dichloromethane (DCM) on the overall free energy PES. Gibbs energies were evaluated at the room temperature, as was used in the experiments, using a quasi-RRHO treatment of vibrational entropies.^[11,12]

Vibrational entropies of frequencies below 100 cm⁻¹ were obtained according to a free rotor description, using a smooth damping function to interpolate between the two limiting descriptions. The free energies were further corrected using standard concentration of 1 mol/L, which was used in solvation calculations. SMD(DCM)-M06-2X/def2-TZVP//M06-2X/def2-SVP Gibbs energies are given and quoted in kcal mol⁻¹ throughout. *Unless otherwise stated, these solvent-corrected values are used for discussion throughout the main text and in this supporting information.*

Non-covalent interactions (NCIs) were analyzed using NCIPILOT^[13] calculations. The .wfn files for NCIPILOT were generated at M06-2X/DGDZVP^[14,15] level of theory. NCI indices calculated with NCIPILOT were visualized at a gradient isosurface value of $s = 0.5$ au. These are colored according to the sign of the second eigenvalue (λ_2) of the Laplacian of the density ($\nabla^2 \rho$) over the range of -0.1 (blue = attractive) to +0.1 (red = repulsive). Molecular orbitals are visualized using an isosurface value of 0.05 au throughout. All molecular structures and molecular orbitals were visualized using PyMOL software.^[16]

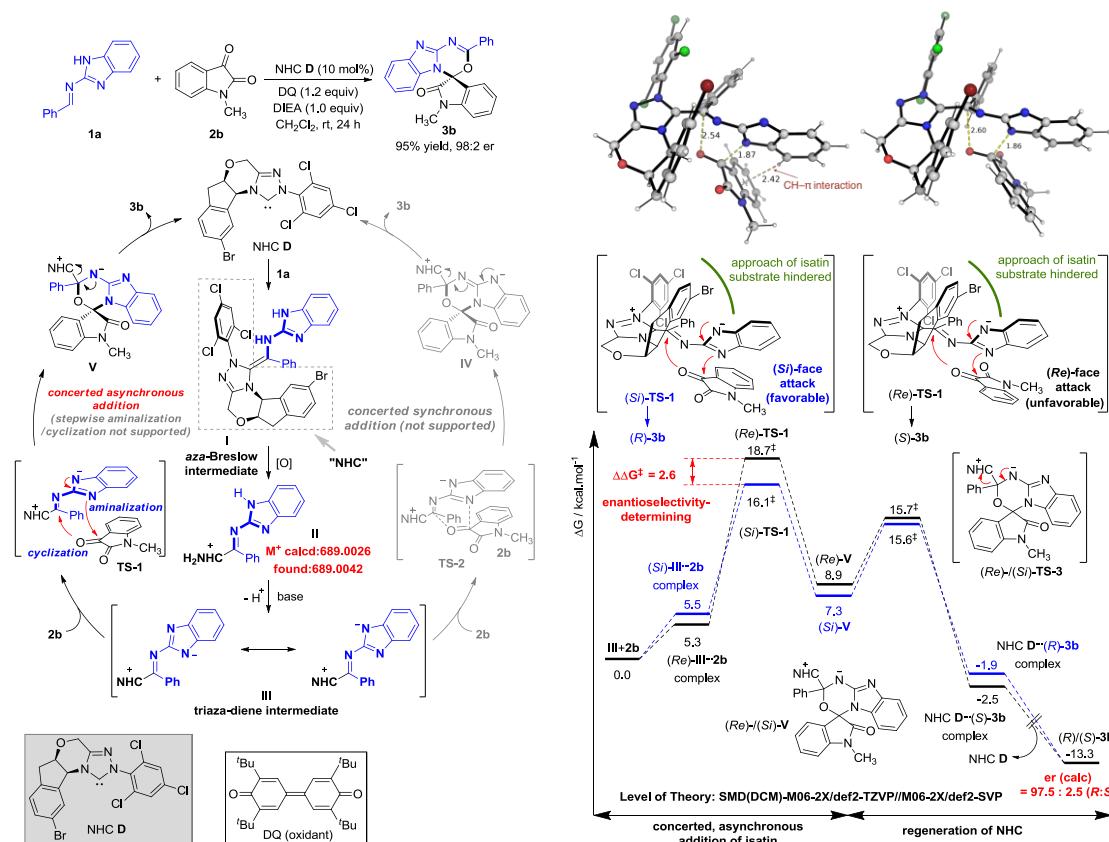
Distortion-interaction^[17,18]/activation strain (DI-AS) model^[18-22] is applied to key TSs to discern the factors affecting stereoselectivity. Geometries are taken from along the IRC reaction coordinate at 0.15 Å interval and single point gas-phase calculations were performed at M06-2x/def2-TZVP level of theory to obtain DI-AS profiles.

Geometries of all optimized structures (in .xyz format with their associated energy in Hartrees) are included in a separate folder named xyz_structures with an associated readme.txt file. All these data have been deposited with this Supporting Information and uploaded to zenodo.org (DOI: 10.5281/zenodo.4314003).

Results and Discussions

For our computational study, we used substrates **1a** and **2b** as shown in Scheme S-1. Experimentally, product **3b** is formed with a 95% yield and an enantiomeric ratio (er) of 98:2. We studied the three possible pathways from triaza-diene intermediate **III**. In pathway 1, intermediate **III** could undergo a concerted [4+2] cycloaddition to give a cycloadduct from which the carbene catalyst NHC **D** can be regenerated. In pathway 2, a stepwise aminalization/cyclization is anticipated, where first a C–N bond forms between intermediate **III** and isatin substrate **2b**.

This can be followed by a nucleophilic substitution at imine to regenerate the carbene catalyst NHC **D**. For concerted asynchronous reaction mechanism (pathway 3), the second cyclization step follows immediately upon the completion of the first aminalization step without the formation of a stable intermediate. We computationally studied the above pathways and found that a concerted, highly asynchronous reaction mechanism is possible (*vide infra*).



Scheme S-1. Possible pathways for imine functionalization and DFT calculations.

Conformational considerations

To determine the most stable form of the key triaza-diene intermediate (**III**), involved in the reaction mechanism, we performed a thorough conformational sampling. We generated a set of rotamers by performing 5-fold rotations about key dihedral angles as shown in Figure S-3. The generated rotamers were then cleaned by removing those species having overlapping atoms. These were performed using the script in the study of conformational effects on physical-organic descriptors by Brethomé *et al.*^[23] A total of 43 resulting rotamers were then subject to geometry optimization using GFN1-xTB in Entos Qcore. The xTB-optimized structures were then clustered to give 3 distinct conformers, which were reoptimized at DFT M06-2X/def2-SVP level. The

resulting structures and their solvent-corrected relative Gibbs energies (SMD(DCM)-M06-2x/def2-TZVP//M06-2x/def2-SVP) are given in Figure S-3. Not surprisingly, the most stable conformer benefits from pi-pi interaction between the phenyl ring on imine substrate (**1a**) and the aryl ring on NHC ligand. The most stable species **III** is used for all subsequent studies.

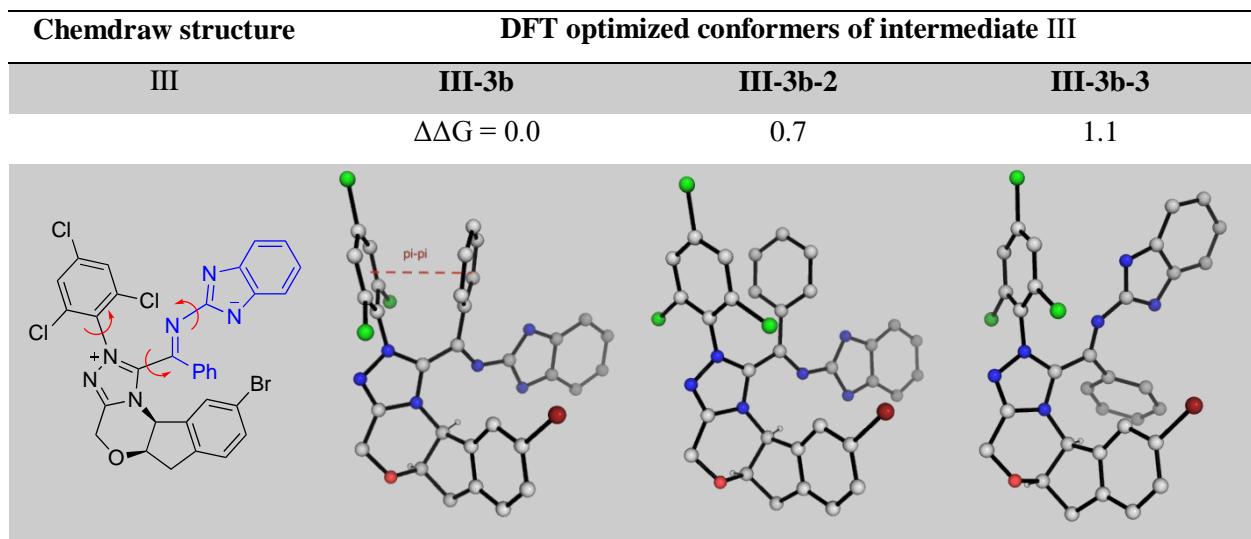
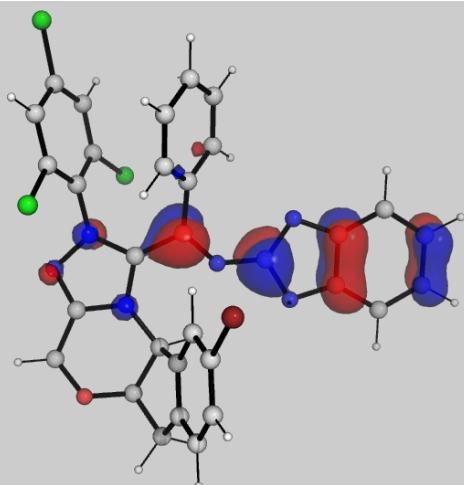
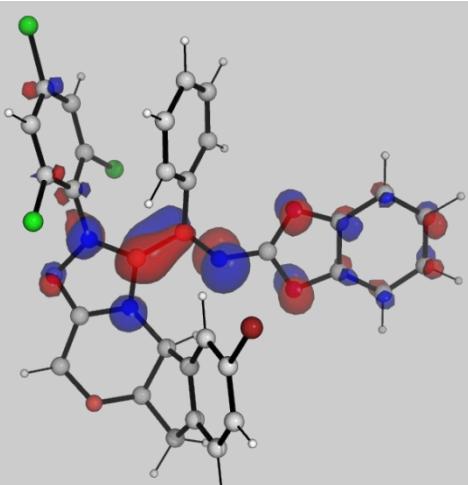


Figure S-3. Chemdraw and DFT optimized conformer structures of key intermediate **III**. Gibbs energy units are given in kcal/mol.

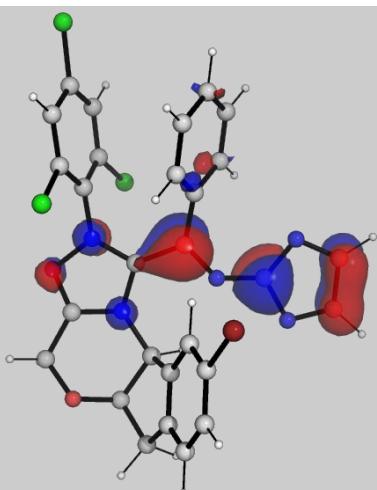
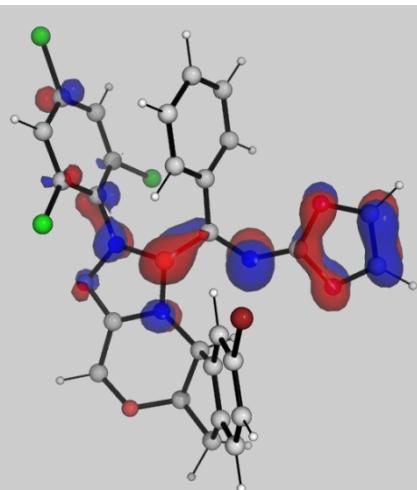
Frontier Molecular Orbitals (FMO) analysis

Figure S-4 shows the frontier molecular orbitals (FMOs) and their associated energies for intermediates **III-3b** (with benzoimidazole protected imine as the substrate) and **III-3ac** (with imidazole protected imine as the substrate) and the isatin substrate **2b** that were used in computation. For the reaction between imine **1b** and isatin **2b** via intermediate **III-3b**, the orbital interaction between the HOMO of **2b** and the LUMO of **III-3b** (HOMO-LUMO gap of 0.203 eV) occurs between the O atom of the ketone group and the C atom of the imine, however, this C–O bond formation does not occur as the TS could not be found computationally. On the other hand, the orbital interaction between HOMO of **III-3b** and LUMO of **2b** has a more compatible orbital interaction and a more favorable HOMO-LUMO gap of 0.176 eV. Thus, the reaction occurs with electrons originating from intermediate **III-3b** and flowing to substrate **2b** (*vide infra*).

Intermediate III-3b

HOMO**-0.24095 eV****LUMO****-0.07809 eV**

Intermediate III-3ac

HOMO**-0.22152 eV****LUMO****-0.05259 eV**

Substrate 2b

HOMO**-0.28085 eV****LUMO****-0.06494 eV**

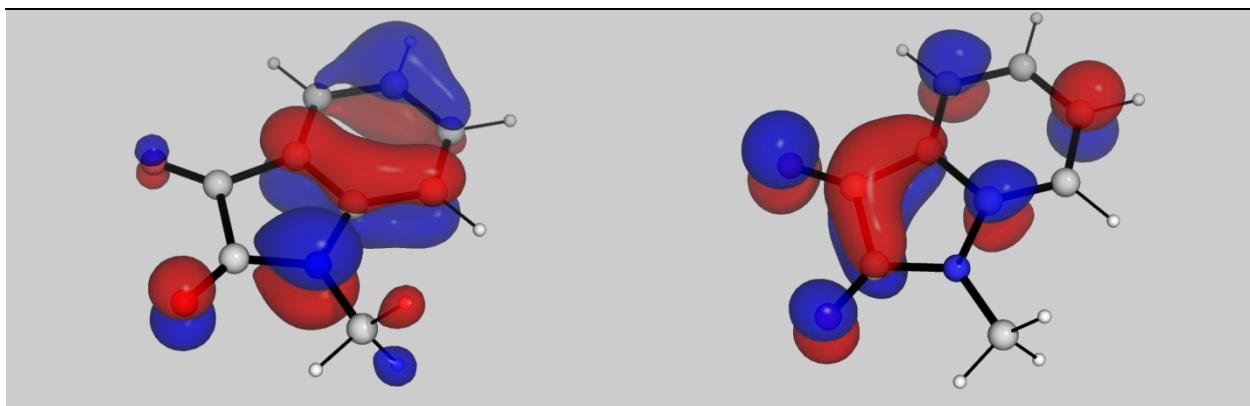


Figure S-4. FMOs, at an isosurface value of 0.05 au, and their associated orbital energies for intermediates **III-3b** and **III-3ac** and substrate **2b**.

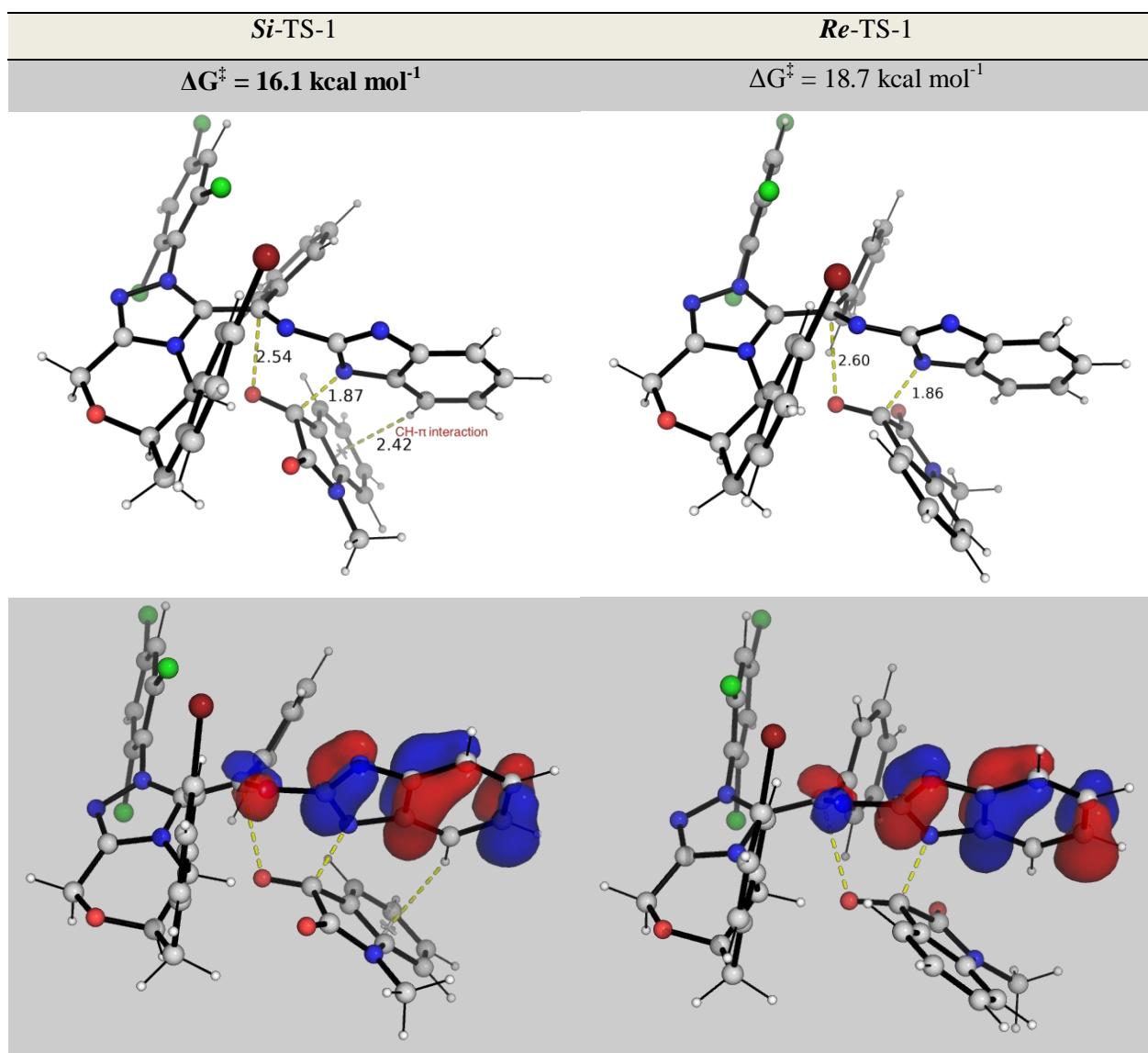
The intermediate **III-3ac** arising from the reaction between imine **1ac** (differs from imine **1b** by a lack of additional Ph-ring) and isatin **2b** has similar FMO shapes as intermediate **III-3b**. The orbital interaction between the HOMO of **2b** and the LUMO of **III-3ac** (HOMO-LUMO gap of 0.228 eV) again has less favorable orbital and HOMO-LUMO energy interactions than the orbital interaction between HOMO of **III-3ac** and LUMO of **2b** (a more favorable HOMO-LUMO gap of 0.157 eV). Thus, similarly, the reaction between **III-3ac** and isatin **2b** occurs with electron flowing from the former to the latter.

Reaction between **III-3b** and **2b**

Key transition state (TS) structures

Figure S-5 shows the optimized TS structures for the concerted, highly asynchronous [4+2] cyclo-addition for NHC-catalyzed imine functionalization. These are the stereo-determining TSs. IRC analyses were used to connect these TSs to their respective reactants and products. The reaction is concerted, highly asynchronous as the products resulting from first C–N bond formation optimizes directly to the [4+2]-cycloadducts **Si-/Re-V** (Figure S-5). The bond lengths in these TSs are also suggestive of a concerted, highly asynchronous mechanism: the C–N bond formation occurs at 1.87 Å (*Si-TS-1*) and 1.86 Å (*Re-TS-1*), while the C–O bonds are much longer at 2.54 Å (*Si-TS-1*) and 2.60 Å (*Re-TS-1*).

The TS for the addition to the *Si*-face of the isatin substrate, *Si-TS-1*, benefits from favorable CH– π interaction between the NHC-activated imine substrate and isatin **2b**. This CH– π interaction is absent in the TS for the addition to the *Re*-face of the isatin substrate, *Re-TS-1*. This can be shown by the NCI plots in Figure S-5. Applying DI-AS model to these TSs (Figure S-6), we see that *Si-TS-1* has a lower activation barrier than *Re-TS-1* due to more favorable interaction energy (in purple), despite having similar strain energy (in blue). Highest occupied molecular orbitals (HOMOs) of both TSs are similar (Figure S-3), suggesting similar electron distribution in these TSs. Thus, the more favorable interaction energy in *Si-TS-1* is likely due to more favorable dispersion energy between its fragments. The difference in the Gibb energy of 2.6 kcal mol⁻¹ predicts an er of 97.5 : 2.5 in favor of *Si*-face adduct, in excellent agreement with experimental findings (er of 98 : 2).



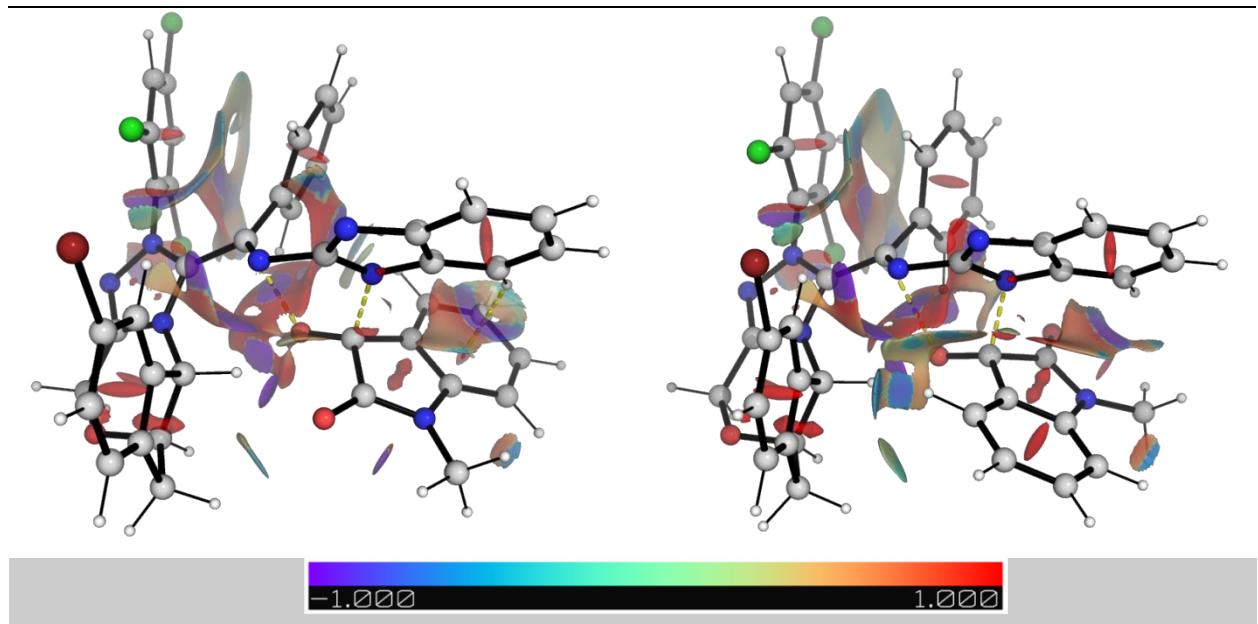


Figure S-5. Optimized TS structures, their HOMO (isosurface value = 0.05 au) and NCI plots. Key bond distances are given in Å.

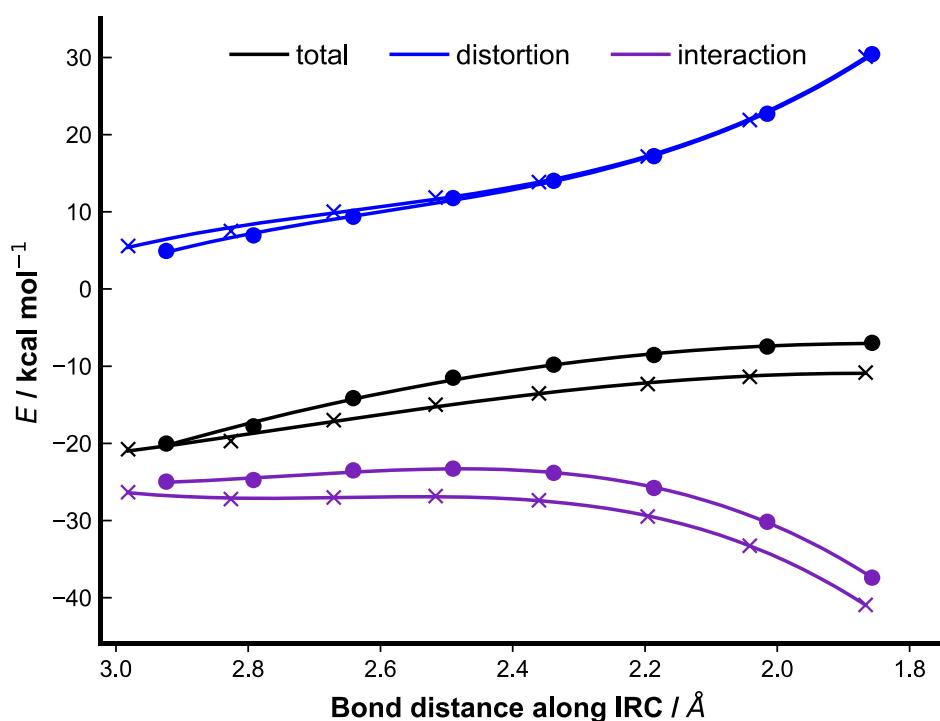
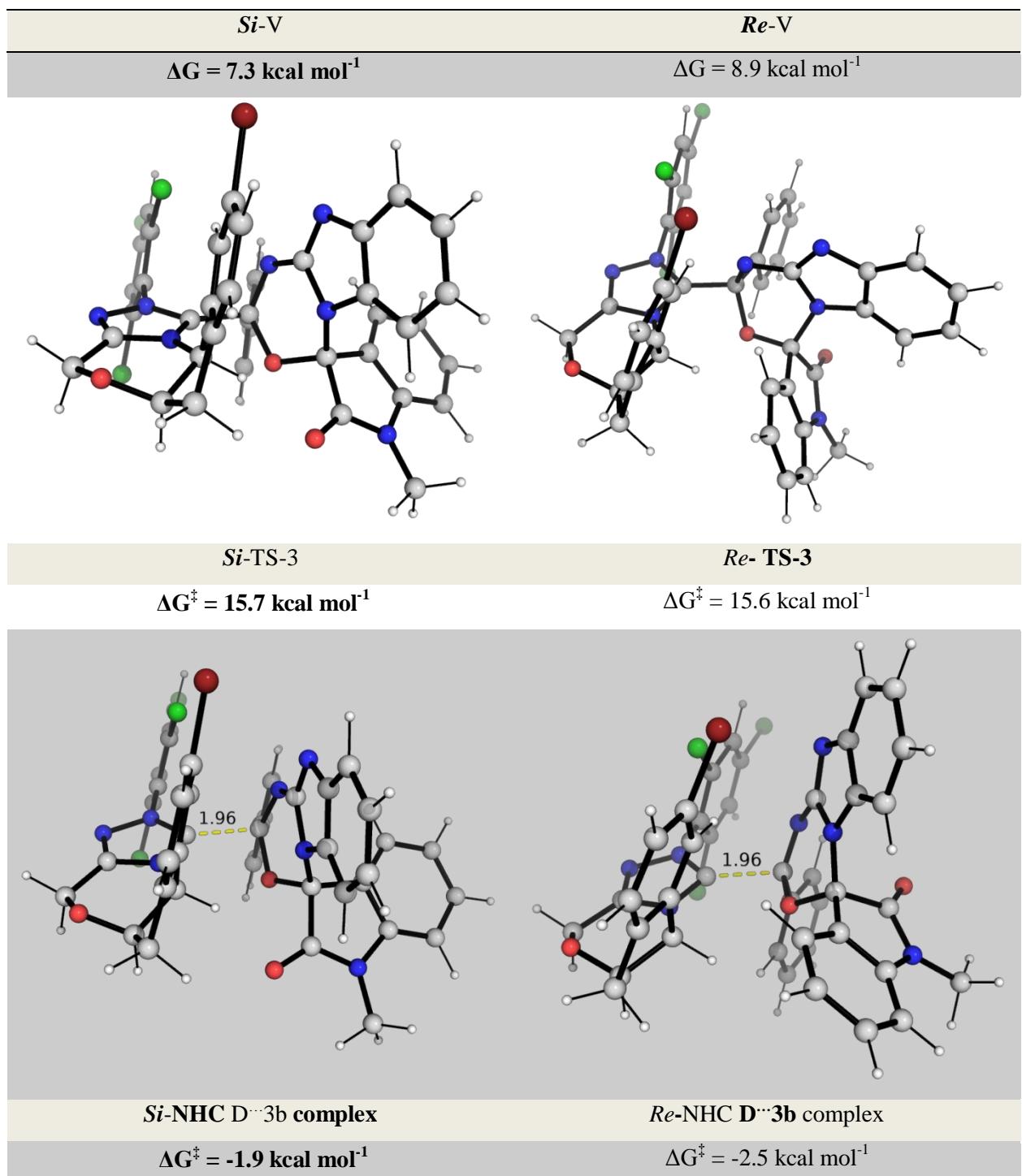


Figure S-6. The activation strain or distortion-interaction analyses applied to the IRC paths along the rate-determining transition state for the addition to the *Si*-face (*Si*-TS-1; cross markers) and the *Re*-face (*Re*-TS-1; full circle markers) of isatin substrate **2b**. All energies are calculated at M06-2X/defTZVPP in gas-phase and used without any further corrections.

Other optimized structures



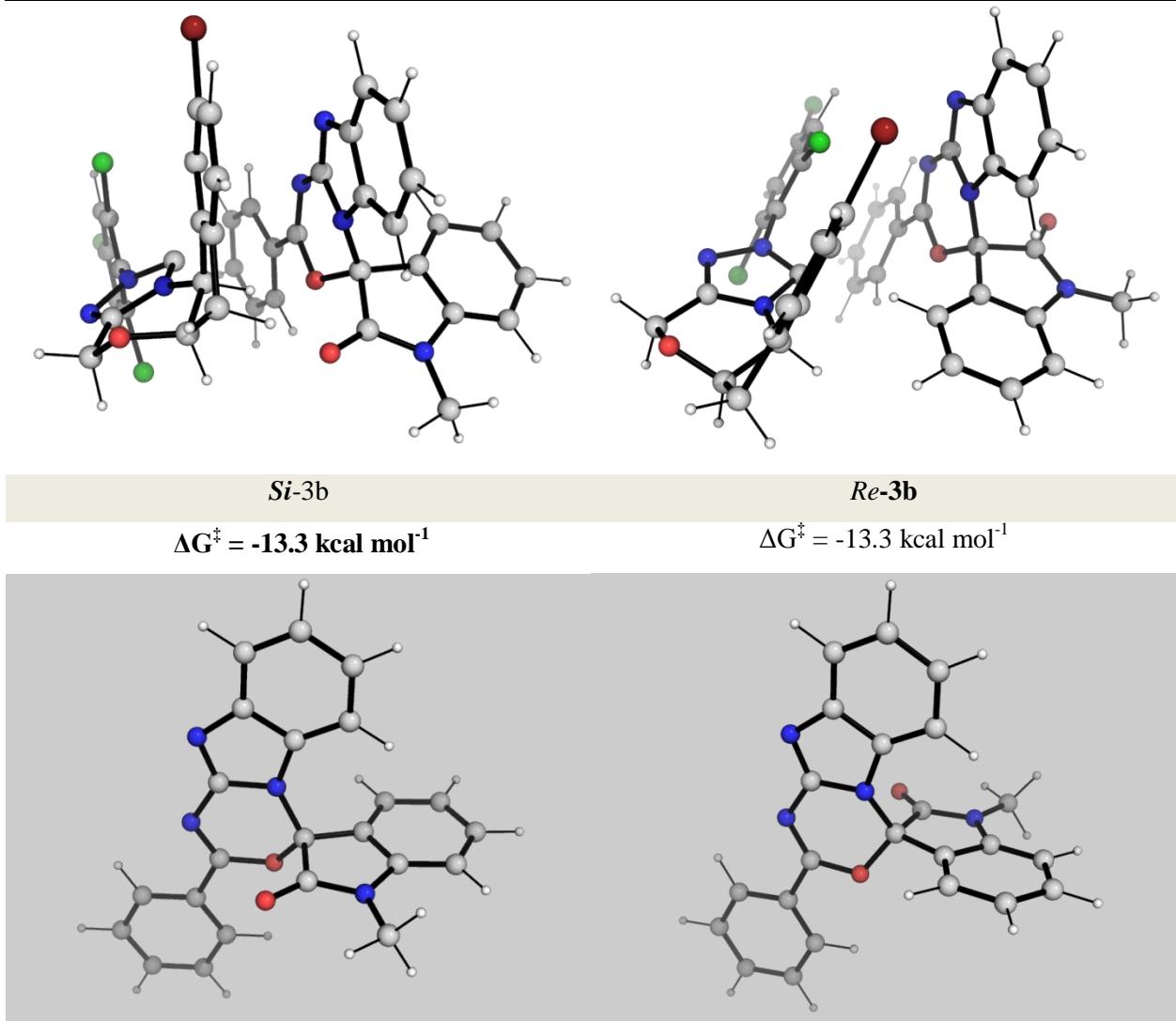


Figure S-7. Optimized structures and their associated Gibbs energies for the reaction between intermediate **III-3b** and isatin substrate **2b**. Key bond distances are given in Å.

Relaxed potential energy surface (PES) scan for concerted, synchronous TSs

Figure S-8 shows the 2-D relaxed PES scans along the two key bonds (C–N and C–O) for the addition of intermediate **III-3b** to isatin **2b**. We see that for addition to either the *Si*-face (Figure S-6a) or the *Re*-face (Figure S-6b), no concerted, synchronous TS structure is possible since no first-order saddle point can be found in this region.

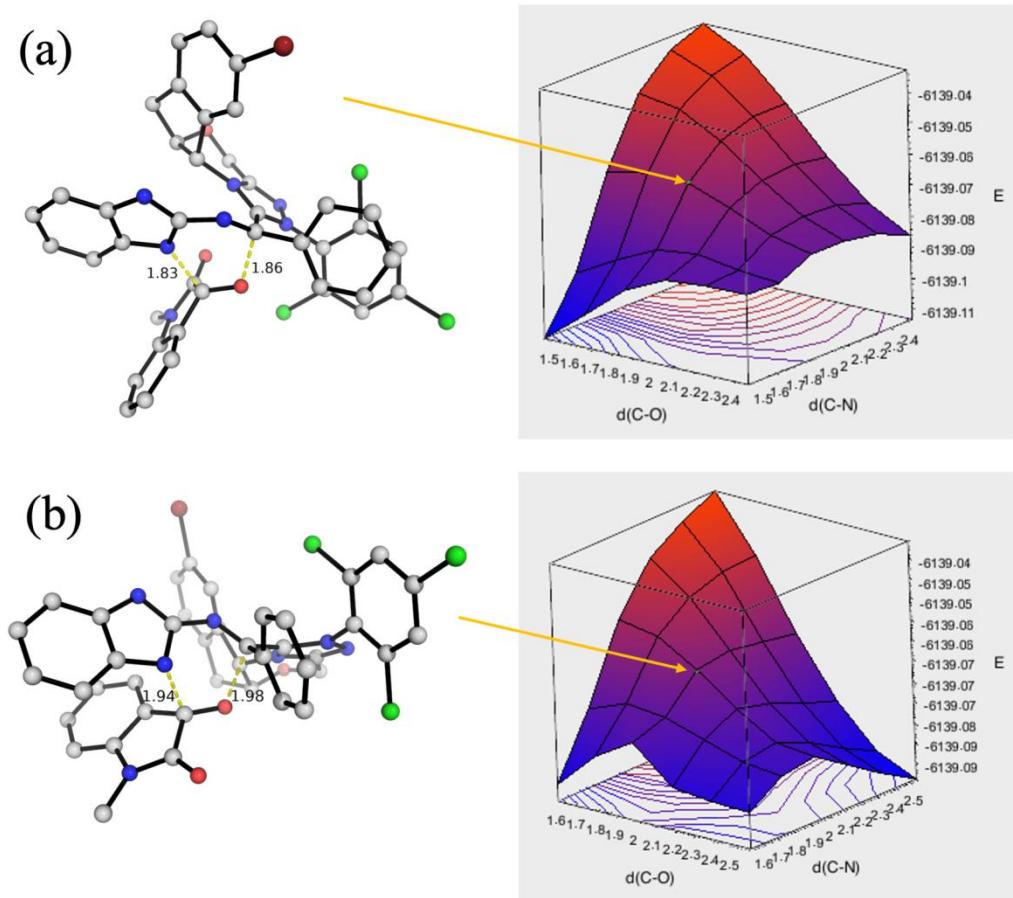


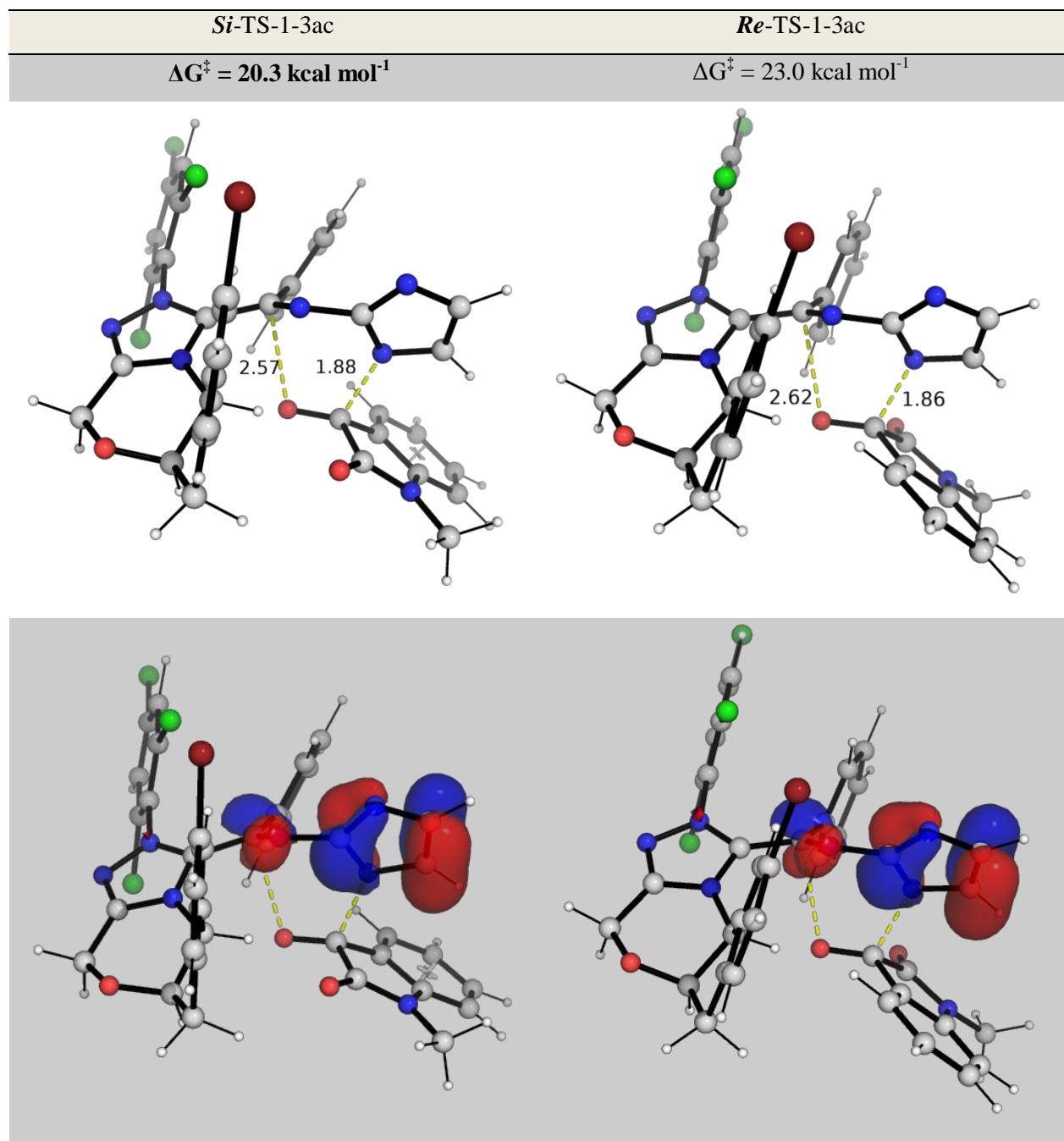
Figure S-8. Two-dimensional relaxed PES scans for formal [4+2] cycloaddition from (a) Si-face and (b) Re-face of the isatin substrate **2b**.

Reaction between **III-3ac** and **2b**

Figure S-9 shows the stereo-determining TS structures for the reaction between intermediate **III-3ac** and isatin substrate **2b** which yield the product **3ac**. The reaction mechanisms are expected to be the same as discussed previously, i.e., the reaction proceeds via a concerted, highly asynchronous mechanism. The bond lengths in these TSs again support such a mechanism: the C–N bond formation occurs at 1.88 Å (*Si-TS-1-3ac*) and 1.86 Å (*Re-TS-1-3ac*), while the C–O bonds are much longer at 2.57 Å (*Si-TS-1-3ac*) and 2.62 Å (*Si-TS-1-3ac*).

The reaction barriers in this case (20.3 and 23.0 kcal mol⁻¹) are higher than that between **III-3b** and **2b** (16.1 and 18.7 kcal mol⁻¹). The lack of a Ph-ring in intermediate **III-3ac** could result in less favorable interaction in this case than in **III-3b**, resulting in higher activation barriers. These computational results are consistent

with experimental finding that the functionalization of imine **1ac** gives a lower yield (52%; reactants recovered) than of imine **1a** (97%).



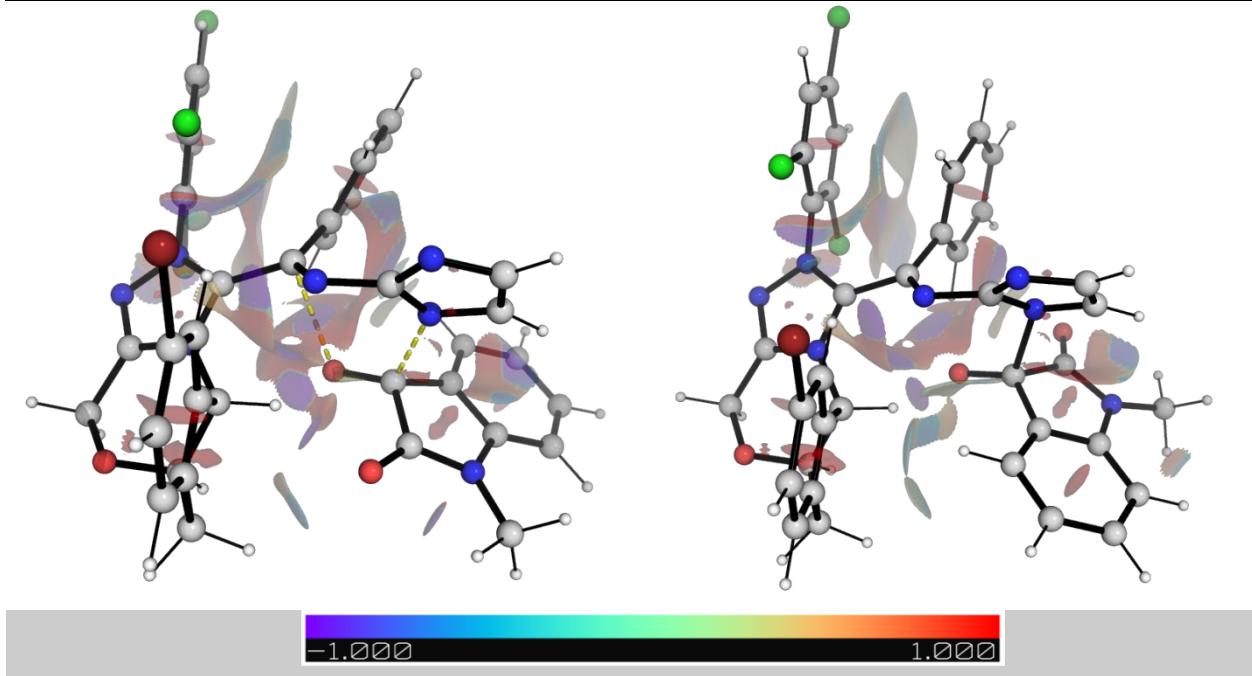


Figure S-9. Optimized TS structures, their HOMO (isosurface value = 0.05 au) and NCI plots for the stereo-determining TSs for the reaction between intermediate **III-3ac** and isatin substrate **2b**. Key bond distances are given in Å.

Optimized structures and absolute energies, zero-point energies

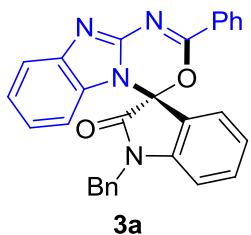
Geometries of all optimized structures (in .xyz format with their associated energy in Hartrees) are included in a separate folder named *xyz_structures* with an associated *readme.txt* file. All these data have been deposited with this Supporting Information and uploaded to zenodo.org (DOI: 10.5281/zenodo.4314003)

Absolute values (in Hartrees) for SCF energy, zero-point vibrational energy (ZPE), enthalpy and quasi-harmonic Gibbs free energy (at 298.15K) for gas-phase M06-2X/def2-SVP optimized structures are given below. Single point corrections in SMD dichloromethane using M06-2X/def2-TZVP functional are also included.

| Structure | E/au | ZPE/au | H/au | T.S/au | G/au | qh-G/au | SP M06- 2X/def2TZVP SMD(DCM) |
|-----------------------------|--------------|----------|------------|----------|-------------|--------------|------------------------------------|
| III-3b | -5587.312242 | 0.464136 | -5586.8134 | 0.101504 | -5586.91492 | -5586.906214 | -5589.941105 |
| IV-3b-c2 | -5587.311914 | 0.464124 | -5586.8131 | 0.100965 | -5586.9141 | -5586.90566 | -5589.940207 |
| IV-3b-c3 | -5587.306555 | 0.464074 | -5586.8076 | 0.102918 | -5586.9105 | -5586.900991 | -5589.938955 |
| 2b | -551.748147 | 0.145384 | -551.59238 | 0.042136 | -551.634513 | -551.634343 | -552.3856815 |
| nhc-c1 | -4884.928065 | 0.261136 | -4884.645 | 0.073281 | -4884.71831 | -4884.713313 | -4886.769456 |
| nhc-c2 | -4884.928065 | 0.261136 | -4884.645 | 0.073275 | -4884.7183 | -4884.71331 | -4886.769457 |
| Re-III⁻2b | | | | | | | |
| complex | -6139.099679 | 0.610953 | -6138.4431 | 0.124072 | -6138.56714 | -6138.556405 | -6142.341829 |
| Re-TS-1 | -6139.078147 | 0.611245 | -6138.4224 | 0.121203 | -6138.54356 | -6138.533208 | -6142.322033 |
| Re-V | -6139.099611 | 0.6139 | -6138.4417 | 0.120293 | -6138.56195 | -6138.551547 | -6142.340797 |
| Re-TS-3 | -6139.095546 | 0.612517 | -6138.4392 | 0.118402 | -6138.55763 | -6138.548074 | -6142.329441 |
| Re-NHC | | | | | | | |
| D ⁻ 3b | | | | | | | |
| complex | -6139.120655 | 0.613393 | -6138.4624 | 0.121885 | -6138.58427 | -6138.573711 | -6142.357847 |
| Re-3b | -1254.16056 | 0.351129 | -1253.7871 | 0.070949 | -1253.85801 | -1253.854073 | -1255.579983 |
| Si-III⁻2b | | | | | | | |
| complex | -6139.101277 | 0.611123 | -6138.4446 | 0.124585 | -6138.56914 | -6138.557948 | -6142.341445 |
| Si-TS-1 | -6139.084959 | 0.611625 | -6138.4288 | 0.121544 | -6138.55035 | -6138.539837 | -6142.326383 |
| Si-V | -6139.111298 | 0.614299 | -6138.4531 | 0.118865 | -6138.57195 | -6138.562344 | -6142.344314 |
| Si-TS-3 | -6139.101713 | 0.613099 | -6138.4449 | 0.118294 | -6138.56323 | -6138.553672 | -6142.330108 |
| Si-NHC | | | | | | | |
| D ⁻ 3b | | | | | | | |
| complex | -6139.123981 | 0.613515 | -6138.4656 | 0.122744 | -6138.58834 | -6138.577371 | -6142.356659 |

| | | | | | | | |
|------------------------|--------------|----------|------------|----------|-------------|--------------|--------------|
| <i>Si</i> -3b | -1254.16056 | 0.351129 | -1253.7871 | 0.070949 | -1253.85801 | -1253.854073 | -1255.579983 |
| III-3ac | -5433.848206 | 0.41673 | -5433.3994 | 0.095036 | -5433.49441 | -5433.487015 | -5436.302217 |
| <i>Si-TS-2-</i> | | | | | | | |
| 3ac | -5985.606936 | 0.563785 | -5985.0011 | 0.115971 | -5985.1171 | -5985.107405 | -5988.68005 |
| <i>Re-TS-2-</i> | | | | | | | |
| 3ac | -5985.599639 | 0.563537 | -5984.994 | 0.11628 | -5985.11031 | -5985.100509 | -5988.675442 |

Characterization data of the catalytic reaction products



(R)-1'-benzyl-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3a): yellow solid, 44.2 mg, 97% yield

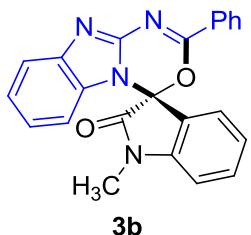
¹H NMR δ 8.22 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.61 – 7.39 (m, 5H), 7.33 – 7.13 (m, 7H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 7.7 Hz, 1H), 5.98 (d, *J* = 8.1 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 169.0, 159.7, 147.7, 143.7, 143.5, 134.4, 133.8, 133.3, 130.2, 130.1, 129.1, 129.0, 128.6, 128.4, 127.6, 126.8, 124.5, 123.6, 123.5, 122.0, 120.5, 111.1, 109.7, 87.2, 44.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 457.1665, found: 457.1669;

HPLC analysis: 98:2 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 13.8 min, t_{major} = 14.7 min), [α]_D²⁵ = -92.30 (c = 1.0, CHCl₃).

Note: Reproduced by the co-author Yongtao Xie gave 96% yield and 98:2 er.



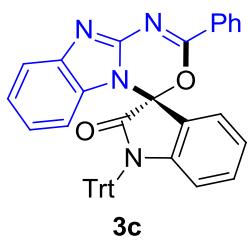
(R)-1'-methyl-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3b): yellow solid, 36.1 mg, 95% yield

¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 7.0 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 6.8 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.26 – 7.16 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.03 (d, *J* = 8.0 Hz, 1H), 3.26 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 168.7, 159.8, 147.7, 144.6, 143.4, 133.9, 133.3, 130.1, 129.1, 129.0, 128.6, 126.7, 124.5, 123.7, 123.4, 122.0, 120.5, 109.9, 109.4, 87.0, 26.7;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 381.1352, found: 381.1356;

HPLC analysis: 98:2 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 13.3$ min, $t_{\text{major}} = 15.0$ min), $[\alpha]_D^{25} = -125.38$ ($c = 1.0$, CHCl₃).

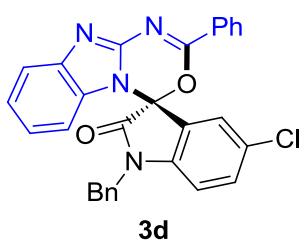


(R)-2-phenyl-1'-tritylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3c): yellow solid, 52.3 mg, 86% yield

¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, $J = 7.5$ Hz, 2H), 7.72 (d, $J = 7.9$ Hz, 1H), 7.58 (t, $J = 7.2$ Hz, 1H), 7.52 – 7.34 (m, 9H), 7.29 – 7.13 (m, 11H), 7.07 (t, $J = 7.3$ Hz, 1H), 6.88 (t, $J = 7.5$ Hz, 1H), 6.58 (d, $J = 8.2$ Hz, 1H), 5.73 (d, $J = 7.9$ Hz, 1H);
¹³C NMR (101 MHz, CDCl₃) δ 170.1, 159.4, 147.8, 144.8, 143.3, 141.1, 133.2, 132.3, 130.4, 130.3, 129.1, 128.8, 128.6, 128.1, 127.4, 126.2, 123.9, 123.4, 123.3, 122.2, 120.3, 117.6, 109.7, 87.0, 75.6;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 609.2291, found: 609.2295;

HPLC analysis: 97:3 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 7.1$ min, $t_{\text{major}} = 7.9$ min), $[\alpha]_D^{25} = +115.08$ ($c = 1.0$, CHCl₃).

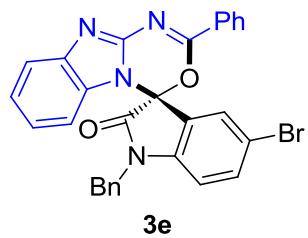


(R)-1'-benzyl-5'-chloro-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3d): yellow solid, 48.1 mg, 98% yield

¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, $J = 7.4$ Hz, 2H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.60 – 7.46 (m, 5H), 7.35 – 7.18 (m, 6H), 7.02 – 6.84 (m, 2H), 6.05 (d, $J = 8.2$ Hz, 1H), 5.05 (d, $J = 15.6$ Hz, 1H), 4.75 (d, $J = 15.7$ Hz, 1H);
¹³C NMR (101 MHz, CDCl₃) δ 168.6, 159.3, 147.3, 143.4, 142.1, 134.0, 133.8, 133.5, 130.2, 130.0, 129.2, 128.9, 128.7, 128.6, 127.5, 127.0, 123.9, 123.8, 123.6, 120.7, 112.2, 109.5, 86.9, 44.6;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 491.1275, found: 491.1273;

HPLC analysis: 95:5 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 20.6$ min, $t_{\text{major}} = 23.7$ min), $[\alpha]_D^{25} = -124.82$ ($c = 1.0$, CHCl₃).



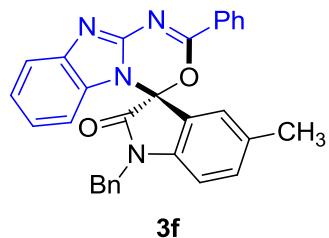
(R)-1'-benzyl-5'-bromo-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3e): yellow solid, 52.3 mg, 98% yield

¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, $J = 7.4$ Hz, 2H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.68 (s, 1H), 7.63 – 7.56 (m, 2H), 7.47 (t, $J = 7.1$ Hz, 2H), 7.30 – 7.23 (m, 6H), 6.97 (t, $J = 7.5$ Hz, 1H), 6.86 (d, $J = 8.3$ Hz, 1H), 6.06 (d, $J = 8.0$ Hz, 1H), 5.04 (d, $J = 15.6$ Hz, 1H), 4.75 (d, $J = 15.6$ Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.4, 159.3, 147.3, 143.4, 142.6, 136.6, 133.9, 133.4, 130.0, 129.9, 129.8, 129.2, 128.9, 128.7, 128.6, 127.5, 124.0, 123.9, 123.8, 120.7, 117.1, 112.6, 109.5, 86.8, 44.5;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 535.0770, found: 535.0775;

HPLC analysis: 95:5 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 21.3$ min, $t_{\text{major}} = 25.0$ min), $[\alpha]_D^{25} = -112.18$ ($c = 1.0$, CHCl₃).



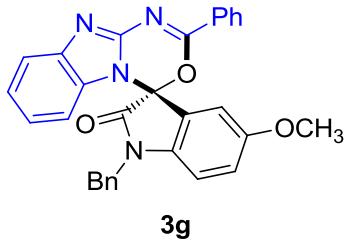
(R)-1'-benzyl-5'-methyl-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3f): yellow solid, 46.1 mg, 98% yield

¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, $J = 7.5$ Hz, 2H), 7.76 (d, $J = 7.9$ Hz, 1H), 7.56 (t, $J = 7.0$ Hz, 1H), 7.46 (t, $J = 7.3$ Hz, 2H), 7.36 (s, 1H), 7.32 – 7.18 (m, 7H), 6.93 (t, $J = 7.6$ Hz, 1H), 6.86 (d, $J = 7.9$ Hz, 1H), 6.03 (d, $J = 8.0$ Hz, 1H), 5.02 (d, $J = 15.6$ Hz, 1H), 4.76 (d, $J = 15.6$ Hz, 1H), 2.29 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 168.9, 159.7, 147.7, 143.4, 141.2, 134.5, 134.4, 134.0, 133.3, 130.3, 130.2, 129.1, 129.0, 128.6, 128.3, 127.6, 127.2, 123.6, 123.5, 122.1, 120.5, 110.9, 109.8, 87.3, 44.4, 21.0;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 471.1821, found: 471.1823;

HPLC analysis: 98:2 er, (CHIRALCEL AS-H column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 11.2 min, t_{major} = 15.2 min), [α]_D²⁵ = -113.54 (c = 1.0, CHCl₃).



(R)-1'-benzyl-5'-methoxy-2-phenylspiro[benzo[4,5]imidazo[1,2-

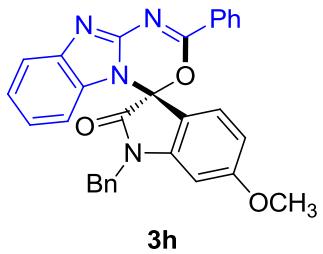
c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3g): yellow solid, 45.2 mg, 93% yield

¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, *J* = 7.3 Hz, 2H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 6.8 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.29 – 7.19 (m, 6H), 7.13 (s, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H), 4.74 (d, *J* = 15.4 Hz, 1H), 3.71 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 168.8, 159.6, 157.1, 147.6, 143.4, 136.7, 134.5, 133.3, 130.2, 130.1, 129.1, 129.0, 128.6, 128.3, 127.6, 123.7, 123.6, 123.0, 120.5, 118.9, 112.7, 111.9, 109.7, 87.4, 56.0, 44.5;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 487.1770, found: 487.1768;

HPLC analysis: 99:1 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 24.0 min, t_{major} = 26.8 min), [α]_D²⁵ = -123.42 (c = 1.0, CHCl₃).



(R)-1'-benzyl-6'-methoxy-2-phenylspiro[benzo[4,5]imidazo[1,2-

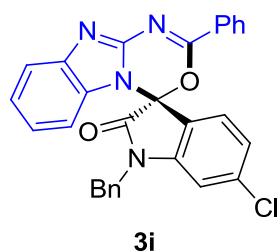
c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3h): yellow solid, 34.1 mg, 70% yield

¹H NMR (400 MHz, CDCl₃) δ 8.32 – 8.12 (m, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.37 – 7.15 (m, 6H), 6.94 (t, *J* = 7.7 Hz, 1H), 6.64 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.51 (d, *J* = 2.1 Hz, 1H), 6.07 (d, *J* = 8.2 Hz, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 4.74 (d, *J* = 15.6 Hz, 1H), 3.83 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 169.5, 164.2, 159.9, 148.0, 145.4, 143.5, 134.5, 133.2, 130.4, 130.3, 129.1, 129.0, 128.6, 128.3, 128.2, 127.5, 123.5, 123.4, 120.5, 113.5, 109.8, 107.9, 99.2, 87.1, 55.9, 44.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 487.1770, found: 487.1773;

HPLC analysis: 99:1 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 26.2.1 min, t_{major} = 32.8 min), [α]_D²⁵ = -81.22 (c = 1.0, CHCl₃).



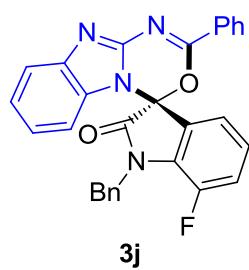
(R)-1'-benzyl-6'-chloro-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3i): yellow solid, 47.0 mg, 96% yield

¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 7.7 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.0 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.37 – 7.14 (m, 7H), 6.98 (s, 2H), 6.06 (d, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.8 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.9, 159.4, 147.5, 144.9, 143.4, 139.9, 133.8, 133.4, 130.0, 129.3, 128.9, 128.7, 128.6, 127.8, 127.5, 124.5, 123.8, 123.7, 120.6, 120.3, 111.8, 109.5, 86.6, 44.5;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 491.1275, found: 491.1278;

HPLC analysis: 97:3 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 17.3 min, t_{major} = 22.6 min), [α]_D²⁵ = -97.42 (c = 1.0, CHCl₃).

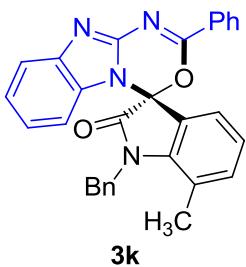


(R)-1'-benzyl-7'-fluoro-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3j): yellow solid, 45.0 mg, 95% yield

¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.10 (m, 9H), 6.91 (t, *J* = 7.7 Hz, 1H), 6.01 (d, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 15.2 Hz, 1H), 4.98 (d, *J* = 15.2 Hz, 1H);
¹³C NMR (101 MHz, CDCl₃) δ 168.8, 159.3, 148.0 (d, *J* = 248.7 Hz), 147.3, 143.4, 135.6, 133.4, 130.3 (d, *J* = 10.0 Hz), 130.0, 129.9, 129.0, 128.9, 128.6, 128.3, 127.8, 125.5 (d, *J* = 6.2 Hz), 124.8 (d, *J* = 2.7 Hz), 123.7 (d, *J* = 10.4 Hz), 122.6 (d, *J* = 3.1 Hz), 122.1, 121.9, 120.6, 109.5, 86.8 (d, *J* = 3.1 Hz), 46.1 (d, *J* = 4.6 Hz);
¹⁹F NMR (377 MHz, CDCl₃) δ -130.2 (1F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 475.1570, found: 475.1573;

HPLC analysis: 95:5 er, (CHIRALCEL AD-H column, *n*-hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 25.5 min, t_{major} = 39.3 min), $[\alpha]_D^{25}$ = -134.26 (c = 1.0, CHCl₃).

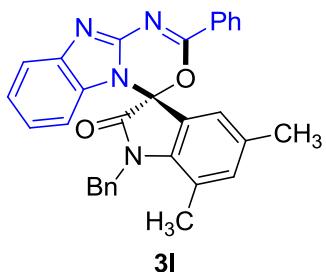


(R)-1'-benzyl-7'-methyl-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3k): yellow solid, 30.6 mg, 65% yield

¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.0 Hz, 1H), 7.46 (s, 3H), 7.35 – 7.05 (m, 8H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.13 (d, *J* = 8.0 Hz, 1H), 5.21 (d, *J* = 16.8 Hz, 1H), 5.10 (d, *J* = 16.8 Hz, 1H), 2.42 (s, 3H);
¹³C NMR (101 MHz, CDCl₃) δ 170.1, 159.8, 148.0, 143.5, 141.8, 137.8, 136.0, 133.3, 130.4, 130.3, 129.2, 129.0, 128.6, 127.8, 125.9, 125.0, 124.6, 123.5, 123.4, 122.6, 122.0, 120.6, 109.9, 86.6, 45.6, 19.0;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 471.1821, found: 471.1826;

HPLC analysis: 99:1 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 21.2 min, t_{major} = 23.6 min), $[\alpha]_D^{25}$ = -116.72 (c = 1.0, CHCl₃).



(R)-1'-benzyl-5',7'-dimethyl-2-phenylspiro[benzo[4,5]imidazo[1,2-

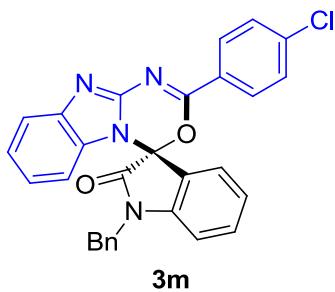
c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3l): yellow solid, 30.5 mg, 63% yield

¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, *J* = 7.3 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.43 (m, 3H), 7.31 – 6.99 (m, 9H), 6.19 (d, *J* = 7.9 Hz, 1H), 5.18 (d, *J* = 16.7 Hz, 1H), 5.08 (d, *J* = 16.7 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 170.1, 159.9, 148.1, 143.5, 139.3, 138.2, 136.1, 134.5, 133.3, 130.4, 130.3, 129.1, 129.0, 128.6, 127.8, 125.9, 125.3, 123.6, 123.5, 122.7, 121.7, 120.5, 110.0, 86.8, 45.6, 20.7, 18.9;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 485.1978, found: 485.1973;

HPLC analysis: 98:2 er, (CHIRALCEL AD-H column, *n*-hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 19.0 min, t_{major} = 31.8 min), [α]_D²⁵ = -93.56 (c = 1.0, CHCl₃).



(R)-1'-benzyl-2-(4-chlorophenyl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-

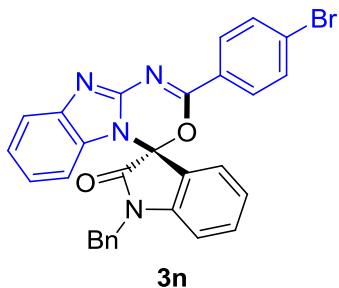
4,3'-indolin]-2'-one (3m): white solid, 46.1 mg, 94% yield

¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, *J* = 7.7 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.60 – 7.38 (m, 4H), 7.33 – 7.15 (m, 7H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 5.97 (d, *J* = 8.0 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.76 (d, *J* = 15.6 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.9, 158.7, 147.4, 143.7, 143.4, 139.8, 134.3, 133.9, 130.2, 130.1, 129.1, 129.0, 128.7, 128.4, 127.5, 126.8, 124.5, 123.8, 123.6, 121.8, 120.6, 111.1, 109.7, 87.2, 44.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 491.1275, found: 491.1279;

HPLC analysis: 97:3 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 20.0$ min, $t_{\text{major}} = 26.4$ min), $[\alpha]_D^{25} = -124.46$ ($c = 1.0$, CHCl₃).



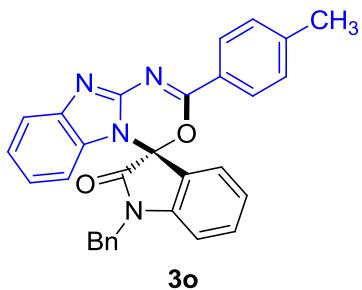
(R)-1'-benzyl-2-(4-bromophenyl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3n): yellow solid, 51.4 mg, 96% yield

¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, $J = 7.5$ Hz, 2H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.65 – 7.45 (m, 4H), 7.36 – 7.14 (m, 7H), 6.98 (d, $J = 7.9$ Hz, 1H), 6.92 (t, $J = 7.5$ Hz, 1H), 5.97 (d, $J = 8.0$ Hz, 1H), 5.03 (d, $J = 15.7$ Hz, 1H), 4.76 (d, $J = 15.6$ Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.9, 158.9, 147.4, 143.7, 143.4, 134.3, 133.9, 132.0, 130.3, 130.1, 129.1, 128.5, 128.4, 127.5, 126.8, 124.5, 123.8, 123.6, 121.8, 120.6, 111.2, 109.7, 87.2, 44.4;

HRMS (ESI, m/z): calcd. for [M+ H]⁺: 535.0770, found: 535.0771;

HPLC analysis: 97:3 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 21.1$ min, $t_{\text{major}} = 28.9$ min), $[\alpha]_D^{25} = -126.14$ ($c = 1.0$, CHCl₃).



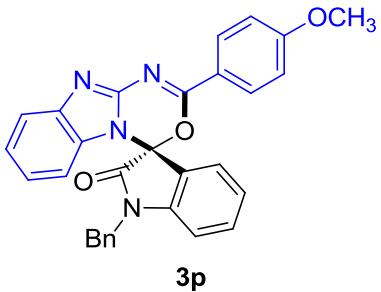
(R)-1'-benzyl-2-(p-tolyl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3o): yellow solid, 45.1 mg, 96% yield

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, $J = 7.3$ Hz, 2H), 7.75 (d, $J = 7.2$ Hz, 1H), 7.55 – 7.48 (m, 2H), 7.36 – 7.12 (m, 9H), 6.97 (d, $J = 7.8$ Hz, 1H), 6.90 (t, $J = 7.5$ Hz, 1H), 5.98 (d, $J = 8.0$ Hz, 1H), 5.02 (d, $J = 15.6$ Hz, 1H), 4.78 (d, $J = 15.6$ Hz, 1H), 2.41 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 169.0, 159.9, 147.9, 144.3, 143.7, 143.4, 134.4, 133.7, 130.1, 129.4, 129.1, 129.0, 128.3, 127.5, 127.3, 126.8, 124.4, 123.4, 122.1, 120.4, 111.0, 109.6, 87.0, 44.4, 21.8;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 471.1821, found: 471.1817;

HPLC analysis: 98:2 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 20.0 min, t_{major} = 22.5 min), [α]_D²⁵ = -125.12 (c = 1.0, CHCl₃).



(R)-1'-benzyl-2-(4-methoxyphenyl)spiro[benzo[4,5]imidazo[1,2-

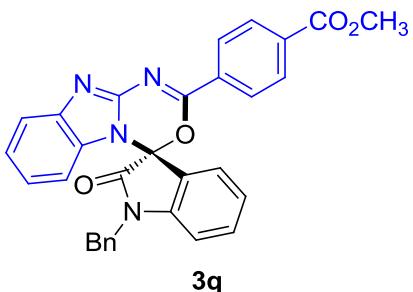
c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3p): yellow solid, 40.3 mg, 83% yield

¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 6.5 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.29 – 7.18 (m, 7H), 7.02 – 6.83 (m, 4H), 5.97 (d, *J* = 7.9 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.77 (d, *J* = 15.6 Hz, 1H), 3.86 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 169.0, 164.0, 159.6, 148.1, 143.7, 134.4, 133.7, 132.1, 131.1, 130.1, 129.1, 128.3, 127.5, 126.8, 124.4, 123.4, 123.5, 122.5, 122.1, 120.3, 114.1, 111.0, 109.6, 86.9, 55.6, 44.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 487.1770, found: 487.1775;

HPLC analysis: 98:2 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 22.2 min, t_{major} = 26.8 min), [α]_D²⁵ = -114.20 (c = 1.0, CHCl₃).



(R)-methyl 4-(1'-benzyl-2'-oxospiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-

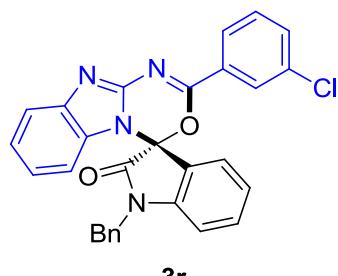
4,3'-indolin]-2-yl)benzoate (3q): yellow solid, 38.0 mg, 74% yield

¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, *J* = 7.5 Hz, 2H), 8.12 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.68 – 7.42 (m, 2H), 7.37 – 7.13 (m, 7H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 5.98 (d, *J* = 8.2 Hz, 1H), 5.04 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.7 Hz, 1H), 3.95 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 168.8, 166.3, 158.7, 147.3, 143.8, 143.4, 134.3, 134.1, 134.0, 133.9, 130.1, 129.7, 129.1, 128.8, 128.4, 127.5, 126.9, 124.5, 123.9, 123.7, 121.7, 120.7, 111.2, 109.8, 87.3, 52.5, 44.4;

HRMS (ESI, m/z): calcd. for [M+ H]⁺: 515.1719, found: 515.1720;

HPLC analysis: 98:2 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 42.9 min, t_{major} = 45.1 min), [α]_D²⁵ = -118.26 (c = 1.0, CHCl₃).



3r

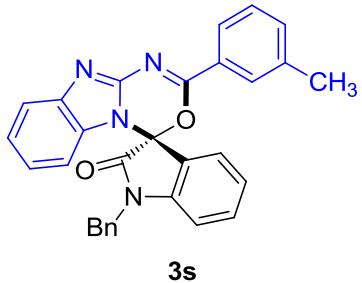
(R)-1'-benzyl-2-(3-chlorophenyl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3r): white solid, 46.5 mg, 95% yield

¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.66 – 7.11 (m, 11H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 5.98 (d, *J* = 8.0 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.77 (d, *J* = 15.6 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.8, 158.4, 147.3, 143.7, 143.4, 134.8, 134.3, 134.0, 133.2, 131.9, 130.1, 130.0, 129.1, 128.7, 128.4, 127.5, 127.1, 126.8, 124.5, 123.9, 123.6, 121.6, 120.6, 111.2, 109.7, 87.3, 44.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 491.1275, found: 491.1277;

HPLC analysis: 98:2 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 18.6 min, t_{major} = 21.9 min), [α]_D²⁵ = -110.32 (c = 1.0, CHCl₃).



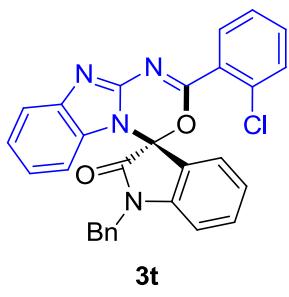
(R)-1'-benzyl-2-(m-tolyl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3s): white solid, 44.1 mg, 94% yield

¹H NMR (400 MHz, CDCl₃) δ 8.12 – 7.88 (m, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.42 – 7.13 (m, 9H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 5.98 (d, *J* = 8.0 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 2.40 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 169.0, 159.9, 147.7, 143.7, 143.4, 138.4, 134.4, 134.1, 133.7, 130.2, 130.1, 129.5, 129.1, 128.6, 128.4, 127.5, 126.8, 126.2, 124.4, 123.6, 123.5, 122.0, 120.5, 111.1, 109.6, 87.1, 44.4, 21.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 471.1821, found: 471.1818;

HPLC analysis: 99:1 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 19.8 min, t_{major} = 21.3 min), [α]_D²⁵ = -103.28 (c = 1.0, CHCl₃).



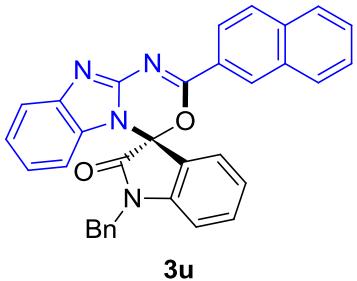
(R)-1'-benzyl-2-(2-chlorophenyl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3t): white solid, 22.1 mg, 45% yield

¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 7.4 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.11 (m, 12H), 6.95 (t, *J* = 8.0 Hz, 2H), 6.01 (d, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.6, 160.0, 147.3, 143.8, 143.4, 134.4, 134.1, 133.8, 133.1, 132.7, 131.2, 130.0, 129.9, 129.1, 128.3, 127.6, 127.0, 126.9, 124.4, 123.9, 123.6, 121.7, 120.7, 111.1, 109.8, 87.3, 44.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 491.1275, found: 491.1278;

HPLC analysis: 90:10 er, (CHIRALCEL AS-H column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 17.4$ min, $t_{\text{major}} = 20.9$ min), $[\alpha]_D^{25} = -52.10$ ($c = 1.0$, CHCl₃).



(R)-1'-benzyl-2-(naphthalen-2-yl)spiro[benzo[4,5]imidazo[1,2-

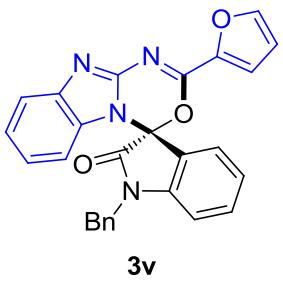
c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3u): white solid, 48.5 mg, 96% yield

¹H NMR (400 MHz, CDCl₃) δ 8.67 (s, 1H), 8.33 (d, $J = 8.4$ Hz, 1H), 7.96 – 7.73 (m, 4H), 7.64 – 7.46 (m, 4H), 7.36 – 7.14 (m, 7H), 7.00 (d, $J = 7.9$ Hz, 1H), 6.92 (t, $J = 7.5$ Hz, 1H), 6.00 (d, $J = 8.0$ Hz, 1H), 5.05 (d, $J = 15.6$ Hz, 1H), 4.79 (d, $J = 15.7$ Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 169.0, 159.8, 147.8, 143.8, 143.5, 135.8, 134.4, 133.8, 132.6, 130.3, 130.2, 129.4, 129.1, 128.6, 128.5, 128.4, 128.0, 127.6, 127.5, 126.9, 124.7, 124.5, 123.6, 123.5, 122.0, 120.5, 111.1, 109.7, 87.2, 44.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 507.1821, found: 507.1826;

HPLC analysis: 98:2 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 85/15, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 30.4$ min, $t_{\text{major}} = 33.7$ min), $[\alpha]_D^{25} = -71.46$ ($c = 1.0$, CHCl₃).



(R)-1'-benzyl-2-(furan-2-yl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-

indolin]-2'-one (3v): yellow solid, 31.2 mg, 70% yield

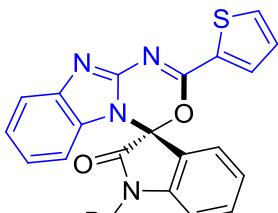
¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, $J = 7.8$ Hz, 1H), 7.66 (s, 1H), 7.57 (d, $J = 7.2$ Hz, 1H), 7.51 (t, $J = 7.7$ Hz, 1H), 7.37 (s, 1H), 7.32 – 7.13 (m, 7H), 6.95 (d, $J = 7.9$

Hz, 1H), 6.90 (t, J = 7.7 Hz, 1H), 6.59 (s, 1H), 5.93 (d, J = 7.9 Hz, 1H), 5.06 (d, J = 15.6 Hz, 1H), 4.74 (d, J = 15.7 Hz, 1H);

^{13}C NMR (101 MHz, CDCl_3) δ 168.8, 151.9, 147.4, 147.3, 144.8, 143.8, 143.4, 134.3, 133.9, 130.3, 129.1, 128.3, 127.5, 126.9, 124.5, 123.6, 123.5, 121.7, 120.5, 118.8, 112.9, 111.1, 109.6, 87.1, 44.4;

HRMS (ESI, m/z): calcd. for $[\text{M}+\text{H}]^+$: 447.1457, found: 447.1460;

HPLC analysis: 93:7 er, (CHIRALCEL AS-H column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 26.7$ min, $t_{\text{major}} = 31.2$ min), $[\alpha]_D^{25} = -97.92$ ($c = 1.0$, CHCl_3).



3w

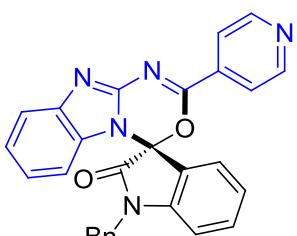
(R)-1'-benzyl-2-(thiophen-2-yl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3w): yellow solid, 27.5 mg, 60% yield

^1H NMR (400 MHz, CDCl_3) δ 7.88 (dd, J = 3.8, 1.1 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.64 (dd, J = 4.9, 1.0 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.51 (td, J = 7.9, 1.1 Hz, 1H), 7.34 – 7.09 (m, 8H), 6.99 – 6.86 (m, 2H), 5.95 (d, J = 8.2 Hz, 1H), 5.03 (d, J = 15.6 Hz, 1H), 4.79 (d, J = 15.7 Hz, 1H);

^{13}C NMR (101 MHz, CDCl_3) δ 168.9, 155.9, 147.6, 143.8, 143.5, 134.3, 134.2, 133.9, 133.7, 133.0, 130.3, 129.1, 128.4, 128.3, 127.5, 126.9, 124.5, 123.5, 121.8, 120.5, 111.1, 109.6, 87.2, 44.4;

HRMS (ESI, m/z): calcd. for $[\text{M}+\text{H}]^+$: 463.1229, found: 463.1230;

HPLC analysis: 97:3 er, (CHIRALCEL AD-H column, *n*-hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 17.9$ min, $t_{\text{major}} = 37.1$ min), $[\alpha]_D^{25} = -82.48$ ($c = 1.0$, CHCl_3).



3x

(R)-1'-benzyl-2-(pyridin-4-yl)spiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-

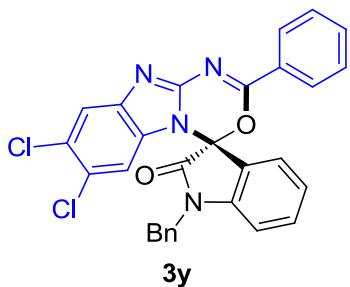
4,3'-indolin]-2'-one (3x): yellow solid, 44.3 mg, 97% yield

¹H NMR (400 MHz, CDCl₃) δ 8.78 (s, 2H), 8.02 (s, 2H), 7.79 (d, *J* = 7.4 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.37 – 6.85 (m, 9H), 5.98 (d, *J* = 8.2 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.76 (d, *J* = 15.7 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.7, 157.8, 150.6, 146.8, 143.8, 143.4, 137.6, 134.2, 134.1, 130.1, 129.1, 128.4, 127.5, 126.9, 124.6, 124.3, 123.8, 121.8, 121.4, 120.9, 111.2, 109.8, 87.5, 44.4;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 458.1617, found: 458.1613;

HPLC analysis: 98:2 er, (CHIRALCEL AS-H column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 23.1 min, t_{major} = 27.6 min), [α]_D²⁵ = -31.96 (c = 1.0, CHCl₃).



(R)-1'-benzyl-7,8-dichloro-2-phenylspiro[benzo[4,5]imidazo[1,2-

c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3y): yellow solid, 48.8 mg, 93% yield

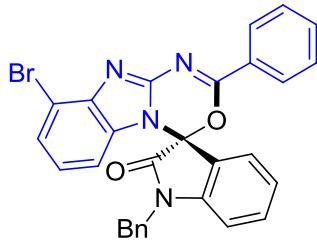
¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 7.4 Hz, 2H), 7.82 (s, 1H), 7.63 – 7.42 (m, 5H), 7.39 – 7.20 (m, 6H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.05 (s, 1H), 5.10 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.7 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.5, 160.6, 149.3, 143.6, 142.9, 134.3, 134.1, 133.7, 129.7, 129.4, 129.3, 129.1, 128.7, 128.5, 127.7, 127.4, 127.3, 126.7, 124.7, 121.6, 121.1, 111.4, 110.9, 87.0, 44.5;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 525.0885, found: 525.0889;

HPLC analysis: 97:3 er, (CHIRALCEL AS-H column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 11.7 min, t_{major} = 22.7 min), [α]_D²⁵ = -68.76 (c = 0.5, CHCl₃).

Note: the solubility of this compound is poor in CH₂Cl₂ and precipitate will form during the reaction.



3z

(R)-1'-benzyl-9-bromo-2-phenylspiro[benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one (3z): yellow solid, 46.4 mg, 87% yield

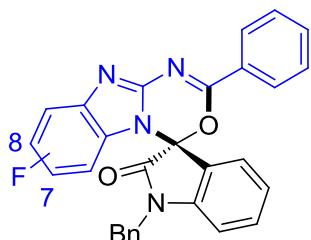
¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, *J* = 7.4 Hz, 2H), 7.64 – 7.37 (m, 6H), 7.35 – 7.18 (m, 6H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.76 (t, *J* = 8.0 Hz, 1H), 5.90 (d, *J* = 8.0 Hz, 1H), 5.06 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 168.7, 160.2, 147.9, 143.8, 142.3, 134.3, 134.0, 133.6, 130.5, 130.0, 129.3, 129.2, 128.7, 128.5, 127.6, 126.9, 126.8, 124.6, 124.3, 121.7, 114.1, 111.1, 108.8, 87.1, 44.5;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 535.0770, found: 535.0773;

HPLC analysis: 99:1 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor} = 17.2 min, t_{major} = 18.7 min), [α]_D²⁵ = -32.16 (c = 0.5, CHCl₃).

Note: the solubility of this compound is very poor in CH₂Cl₂ and precipitate will form during the reaction.



3aa, 8-F/7-F (1.8:1)

yellow oil, 43.6 mg, 92% yield

¹H NMR (400 MHz, CDCl₃) δ 8.30 – 8.13 (m, 5.5H), 7.68 (dd, *J* = 8.9, 4.9 Hz, 1H), 7.61 – 7.40 (m, 16.2H), 7.34 – 7.17 (m, 17.2H), 7.03 – 6.90 (m, 3.8H), 6.65 (td, *J* = 9.2, 2.4 Hz, 1.8H), 5.86 (dd, *J* = 8.9, 4.5 Hz, 1.8H), 5.67 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.06 – 5.01 (m, 2.8H), 4.82 – 4.73 (m, 2.8H);

¹³C NMR (101 MHz, CDCl₃) δ 168.8, 161.0, 160.9, 160.1, 159.7, 158.7, 158.5, 149.2, 148.2, 144.3, 144.2, 143.7, 143.6, 139.8, 134.3, 134.2, 134.1, 134.0, 133.5, 133.4,

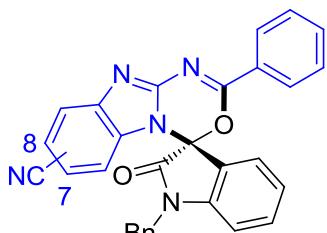
132.2, 130.2, 130.1, 130.0, 129.4, 129.2, 129.1, 129.0, 128.9, 128.7, 128.5, 128.4, 127.5, 127.4, 126.8, 126.7, 126.6, 126.5, 124.6, 124.5, 121.7, 121.4, 121.3, 121.2, 111.7, 111.6, 111.5, 111.4, 111.3, 111.2, 110.0, 109.9, 106.8, 106.6, 97.2, 96.9, 87.1, 87.0, 44.5, 44.4 (the coupling between fluorine and carbon isn't considered here, as the spectrum is complicated for this mixture);

¹⁹F NMR (377 MHz, CDCl₃) δ -116.5 (1F), -118.7 (1.8F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 475.1570, found: 475.1575;

HPLC analysis: 98:2 er and 97:3 er, (CHIRALCEL AD-H column, *n*-hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm, t_{minor-1} = 20.1 min, t_{minor-2} = 25.6 min, t_{major-1} = 43.2 min, t_{major-2} = 48.1 min), [α]_D²⁵ = -127.94 (c = 1.0, CHCl₃).

Note: the two regioisomers could not be separated and the mixture of the two isomers was obtained.



3ab, 8-CN/7-CN (1.8:1)

Yellow oil, 44.7 mg, 93% yield

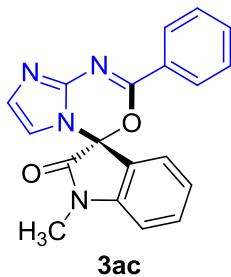
¹H NMR (400 MHz, CDCl₃) δ 8.28 – 8.17 (m, 5.6H), 8.04 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1.8H), 7.65 – 7.53 (m, 8.6H), 7.52 – 7.44 (m, 7.8H), 7.39 – 7.19 (m, 17.6H), 7.14 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.06 – 7.03 (m, 2.8H), 6.25 (s, 1.8H), 5.98 (d, *J* = 8.4 Hz, 1H), 5.07 – 5.03 (m, 2.8H), 4.83 – 4.76 (m, 2.8H);

¹³C NMR (101 MHz, CDCl₃) δ 168.4, 161.5, 161.1, 150.5, 149.5, 146.7, 143.7, 143.6, 143.2, 134.6, 134.3, 134.2, 134.1, 134.0, 132.9, 129.9, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 127.6, 127.4, 126.9, 126.8, 126.7, 124.9, 124.8, 124.7, 121.2, 121.1, 120.9, 119.3, 113.7, 111.6, 111.3, 110.4, 106.1, 87.1, 87.0, 44.6, 44.5;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 482.1617, found: 482.1621;

HPLC analysis: 98:2 er and 98:2 er, (CHIRALCEL AD-H column, *n*-hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 220 nm, t_{minor-1} = 30.0 min, t_{major-1} = 47.7 min, t_{minor-2} = 71.7 min, t_{major-2} = 81.5 min), [α]_D²⁵ = -122.26 (c = 1.0, CHCl₃).

Note:the two regioisomers could not be separated and the mixture of the two isomers was obtained.



(R)-1'-benzyl-2-phenylspiro[imidazo[1,2-c][1,3,5]oxadiazine-4,3'-indolin]-2'-one

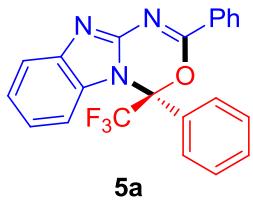
(3ac): yellow oil, 17.1 mg, 52% yield

¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 7.4 Hz, 2H), 7.64 – 7.46 (m, 3H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.09 (s, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.31 (d, *J* = 1.5 Hz, 1H), 3.23 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 169.0, 156.9, 144.6, 143.9, 133.7, 132.6, 130.4, 130.1, 128.6, 128.5, 126.2, 124.4, 122.6, 111.9, 109.7, 86.6, 26.7;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 331.1195, found: 331.1190;

HPLC analysis: 90:10 er, (CHIRALCEL IB column, *n*-hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm, t_{major} = 14.3 min, t_{minor} = 18.9 min), [α]_D²⁵ = -68.92 (c = 0.8, CHCl₃).



(S)-2,4-diphenyl-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5a): yellow solid, 36.1 mg, 92% yield

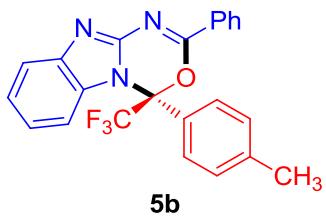
¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, *J* = 7.5 Hz, 2H), 7.78 – 7.46 (m, 9H), 7.23 (t, *J* = 8.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 158.6, 146.5, 142.8, 133.7, 131.8, 131.2, 130.9, 129.4, 129.3, 129.0, 128.9, 127.9, 124.1, 123.6, 123.2 (q, *J* = 293.1 Hz), 120.5, 111.5, 90.6 (q, *J* = 33.5 Hz);

HRMS (ESI, m/z): calcd. for [M+Na]⁺: 416.0987, found: 416.0991;

¹⁹F NMR (377 MHz, CDCl₃) δ -75.4 (3F);

HPLC analysis: 94:6 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, $t_{\text{minor}} = 17.8$ min, $t_{\text{major}} = 22.5$ min), $[\alpha]_D^{25} = +129.73$ (c = 1.0, CHCl₃).



(S)-2-phenyl-4-(p-tolyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5b): yellow solid, 32.5 mg, 80% yield

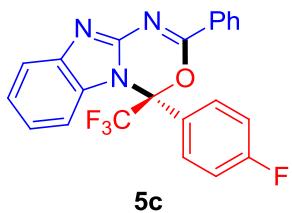
¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 7.3 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.2 Hz, 3H), 7.48 (t, J = 7.7 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.23 (t, J = 7.7 Hz, 1H), 7.05 – 7.01 (m, 1H), 6.45 (d, J = 8.2 Hz, 1H), 2.43 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 158.7, 146.6, 142.8, 142.3, 133.6, 131.0, 130.1, 129.4, 129.0, 128.8, 128.3, 127.8, 124.0, 123.6, 123.2 (q, J = 293.1 Hz), 120.4, 111.6, 90.7 (q, J = 33.5 Hz), 21.5;

¹⁹F NMR (377 MHz, CDCl₃) δ -75.4 (3F);

HRMS (ESI, m/z): calcd. for [M+Na]⁺: 430.1143, found: 430.1141;

HPLC analysis: 95:5 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, $t_{\text{minor}} = 17.7$ min, $t_{\text{major}} = 21.4$ min), $[\alpha]_D^{25} = +49.20$ (c = 1.0, CHCl₃).



(S)-4-(4-fluorophenyl)-2-phenyl-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5c): yellow oil, 33.7 mg, 82% yield

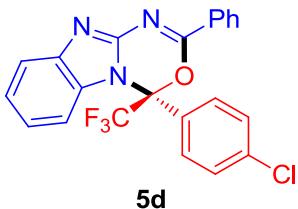
¹H NMR (400 MHz, CDCl₃) δ 8.22 (d, J = 7.8 Hz, 2H), 7.88 – 7.68 (m, 3H), 7.61 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.30 – 7.18 (m, 3H), 7.06 (t, J = 7.8 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 164.4 (d, J = 254.9 Hz), 158.5, 146.4, 142.8, 133.8, 130.8, 130.3 (d, J = 8.9 Hz), 129.2, 128.9, 128.8, 127.3 (d, J = 3.5 Hz), 124.5, 124.2, 123.1 (q, J = 293.2 Hz), 120.6, 116.7 (d, J = 22.0 Hz), 111.3, 90.3 (q, J = 33.8 Hz);

¹⁹F NMR (377 MHz, CDCl₃) δ -75.4 (3F), -106.8 (1F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 412.1073, found: 412.1071;

HPLC analysis: 91:9 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 16.3 min, t_{major} = 19.3 min), [α]_D²⁵ = +59.76 (c = 1.0, CHCl₃).



(S)-4-(4-chlorophenyl)-2-phenyl-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5d): yellow solid, 38.4 mg, 90% yield

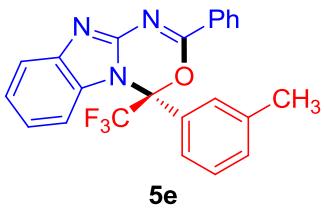
¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 7.4 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.57 (m, 3H), 7.55 – 7.43 (m, 4H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.47 (d, *J* = 8.2 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 158.4, 146.3, 142.8, 138.3, 133.8, 130.7, 129.8, 129.7, 129.3 (q, *J* = 2.0 Hz), 129.2, 128.9, 128.8, 124.3, 123.8, 123.0 (q, *J* = 293.1 Hz), 120.6, 111.3, 90.3 (q, *J* = 33.8 Hz);

¹⁹F NMR (377 MHz, CDCl₃) δ -75.5 (3F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 428.0777, found: 428.0772;

HPLC analysis: 91:9 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 20.1 min, t_{major} = 24.8 min), [α]_D²⁵ = +69.64 (c = 1.0, CHCl₃).



(S)-2-phenyl-4-(m-tolyl)-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5e): slightly yellow oil, 37.8 mg, 93% yield

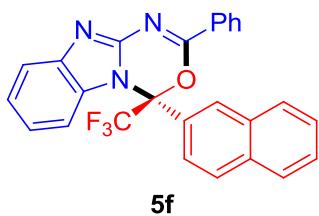
¹H NMR (400 MHz, CDCl₃) δ 8.31 – 8.18 (m, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.56 – 7.34 (m, 6H), 7.25 – 7.17 (m, 1H), 7.08 – 6.98 (m, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 2.38 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 158.6, 146.5, 142.8, 139.5, 133.6, 132.6, 131.1, 131.0, 129.4, 129.2, 129.0, 128.8, 128.4 (q, *J* = 1.9 Hz), 124.8 (q, *J* = 2.3 Hz), 124.0, 123.5, 123.2 (q, *J* = 293.2 Hz), 120.4, 111.5, 90.7 (q, *J* = 33.5 Hz), 21.7;

¹⁹F NMR (377 MHz, CDCl₃) δ -75.3 (3F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 408.1324, found: 408.1321;

HPLC analysis: 96:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 17.3 min, t_{major} = 24.1 min), [α]_D²⁵ = +97.56 (c = 1.0, CHCl₃).



(S)-4-(naphthalen-2-yl)-2-phenyl-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5f): slightly yellow oil, 40.7 mg, 92% yield

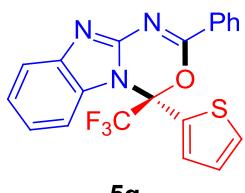
¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 8.29 – 8.16 (m, 2H), 7.99 – 7.89 (m, 3H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.54 (m, 4H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.24 – 7.15 (m, 1H), 7.00 – 6.86 (m, 1H), 6.41 (d, *J* = 8.2 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 158.7, 146.5, 142.9, 134.3, 133.7, 132.4, 130.9, 129.9, 129.4, 129.3, 129.0, 128.9, 128.8, 128.2, 128.1 (q, *J* = 2.6 Hz), 127.9, 127.6, 124.1, 123.9, 123.6, 123.3 (q, *J* = 293.1 Hz), 120.5, 111.5, 90.9 (q, *J* = 33.5 Hz);

¹⁹F NMR (377 MHz, CDCl₃) δ -75.1 (3F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 444.1324, found: 444.1327;

HPLC analysis: 96:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 220 nm, t_{minor} = 19.4 min, t_{major} = 23.8 min), [α]_D²⁵ = +69.62 (c = 1.0, CHCl₃).



(R)-2-phenyl-4-(thiophen-2-yl)-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5g): slightly yellow oil, 21.2 mg, 54% yield

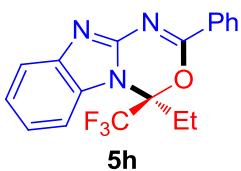
¹H NMR (400 MHz, CDCl₃) δ 8.30 – 8.15 (m, 2H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.64 – 7.59 (m, 3H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.31 – 7.23 (m, 1H), 7.19 (dd, *J* = 5.0, 4.0 Hz, 1H), 7.15 – 7.07 (m, 1H), 6.64 (d, *J* = 8.2 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 158.5, 146.4, 142.8, 133.7, 133.5, 131.1, 130.9, 130.6 (q, *J* = 2.3 Hz), 129.2, 129.0, 128.9, 127.3, 124.3, 123.8, 122.8 (q, *J* = 293.3 Hz), 120.6, 111.6, 88.8 (q, *J* = 35.0 Hz);

¹⁹F NMR (377 MHz, CDCl₃) δ -77.2 (3F);

HRMS (ESI, m/z): calcd. for [M+Na]⁺: 422.0551, found: 422.0555;

HPLC analysis: 96:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 19.5 min, t_{major} = 21.1 min), [α]_D²⁵ = +107.82 (c = 1.0, CHCl₃).



(S)-4-ethyl-2-phenyl-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5h): slightly yellow oil, 31.7 mg, 92% yield

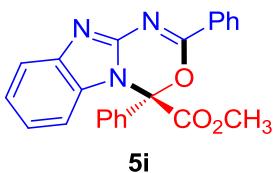
¹H NMR (400 MHz, CDCl₃) δ 8.29 – 8.16 (m, 2H), 7.82 – 7.79 (m, 1H), 7.64 – 7.60 (m, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.28 (m, 3H), 2.94 (dq, *J* = 14.8, 7.3 Hz, 1H), 2.57 (dq, *J* = 14.9, 7.3 Hz, 1H), 1.02 (t, *J* = 7.3 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 158.7, 146.4, 143.0, 133.6, 130.3, 129.2, 128.9, 128.8, 124.4, 123.7, 123.0 (q, *J* = 292.0 Hz), 120.8, 110.9, 91.7 (q, *J* = 33.2 Hz), 24.9, 5.7;

¹⁹F NMR (377 MHz, CDCl₃) δ -82.1 (3F);

HRMS (ESI, m/z): calcd. for [M+Na]⁺: 368.0987, found: 368.0984;

HPLC analysis: 86:14 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 220 nm, t_{minor} = 18.3 min, t_{major} = 21.5 min), [α]_D²⁵ = -89.16 (c = 1.0, CHCl₃).



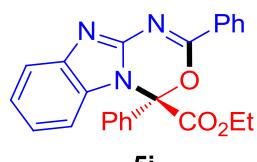
(S)-methyl-2,4-diphenyl-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4-carboxylate (5i): slightly yellow oil, 29.1 mg, 76% yield

¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, *J* = 7.5 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.38 (m, 8H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.02 – 6.98 (m, 1H), 6.31 (d, *J* = 8.2 Hz, 1H), 3.79 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 166.8, 160.6, 147.6, 143.0, 133.4, 132.9, 131.7, 131.6, 129.9, 129.4, 129.3, 128.7, 128.0, 123.5, 123.0, 120.1, 111.9, 92.0, 54.0;

HRMS (ESI, m/z): calcd. for [M+Na]⁺: 406.1168, found: 406.1171;

HPLC analysis: 96:4 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 220 nm, t_{major} = 21.5 min, t_{minor} = 38.1 min), [α]_D²⁵ = +2.20 (c = 1.0, CHCl₃).



5j

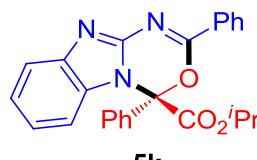
(S)-ethyl 2,4-diphenyl-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4-carboxylate (5j): slightly yellow oil, 29.7 mg, 75% yield

¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, *J* = 7.3 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.40 (m, 8H), 7.25 – 7.16 (m, 1H), 7.04 – 6.95 (m, 1H), 6.33 (d, *J* = 8.3 Hz, 1H), 4.42 – 4.07 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 166.2, 160.6, 147.8, 143.0, 133.4, 133.0, 131.8, 131.6, 130.0, 129.5, 129.3, 128.6, 128.1, 123.4, 123.0, 120.0, 112.0, 92.0, 63.6, 13.9;

HRMS (ESI, m/z): calcd. for [M+Na]⁺: 420.1324, found: 420.1322;

HPLC analysis: 98:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 254 nm, t_{major} = 18.5 min, t_{minor} = 28.6 min), [α]_D²⁵ = -8.36 (c = 1.0, CHCl₃).



5k

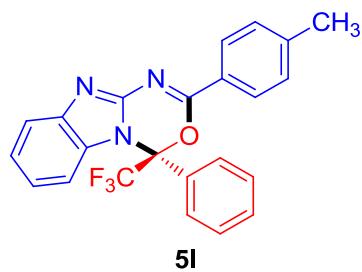
(S)-isopropyl 2,4-diphenyl-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine-4-carboxylate (5k): slightly yellow oil, 28.7 mg, 70% yield

¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, *J* = 7.4 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.39 (m, 8H), 7.24 – 7.13 (m, 1H), 7.06 – 6.90 (m, 1H), 6.32 (d, *J* = 8.2 Hz, 1H), 5.11 – 5.01 (m, 1H), 1.13 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.3 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 165.6, 160.7, 147.9, 143.0, 133.3, 133.0, 131.8, 131.5, 130.1, 129.4, 129.2, 128.6, 128.1, 123.3, 122.9, 120.0, 112.1, 91.9, 72.3, 21.6, 21.5;

HRMS (ESI, m/z): calcd. for [M+H]⁺: 412.1661, found: 412.1658;

HPLC analysis: 98:2 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 1.0 mL/min, λ = 220 nm, t_{major} = 14.0 min, t_{minor} = 19.2 min), [α]_D²⁵ = +1.76 (c = 1.0, CHCl₃).



(S)-4-phenyl-2-(p-tolyl)-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5l): yellow solid, 37.8 mg, 93% yield

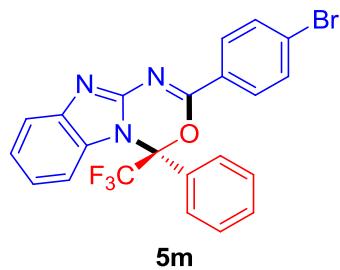
¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, *J* = 8.3 Hz, 2H), 7.76 – 7.70 (m, 3H), 7.64 – 7.46 (m, 3H), 7.35 – 7.15 (m, 3H), 7.06 – 6.94 (m, 1H), 6.42 (d, *J* = 8.2 Hz, 1H), 2.43 (s, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 158.8, 146.7, 144.7, 142.8, 131.7, 131.3, 130.9, 129.6, 129.4, 129.0, 127.8 (q, *J* = 1.9 Hz), 126.5, 123.9, 123.5, 123.2 (q, *J* = 293.0 Hz), 120.3, 111.4, 90.6 (q, *J* = 33.5 Hz), 21.9;

¹⁹F NMR (377 MHz, CDCl₃) δ -75.4 (3F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 408.1324, found: 408.1319;

HPLC analysis: 95:5 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 20.5 min, t_{major} = 23.5 min), [α]_D²⁵ = +59.84 (c = 1.0, CHCl₃).



(S)-2-(4-bromophenyl)-4-phenyl-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5m): yellow solid, 29.7 mg, 63% yield

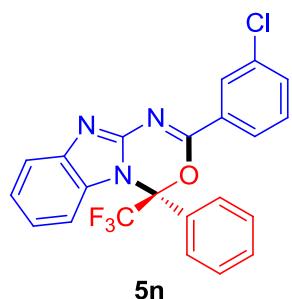
¹H NMR (400 MHz, CDCl₃) δ 8.08 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.68 – 7.49 (m, 5H), 7.26 – 7.18 (m, 1H), 7.09 – 6.95 (m, 1H), 6.41 (d, *J* = 8.3 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 157.8, 146.2, 142.8, 132.2, 131.9, 131.0, 130.9, 130.3, 129.5, 128.9, 128.2, 127.8 (q, *J* = 2.3 Hz), 124.3, 123.7, 123.1 (q, *J* = 293.0 Hz), 120.5, 111.5, 90.8 (q, *J* = 33.6 Hz);

¹⁹F NMR (377 MHz, CDCl₃) δ -75.4 (3F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 472.0272, found: 472.0277;

HPLC analysis: 95:5 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 20.5 min, t_{major} = 35.8 min), [α]_D²⁵ = +63.36 (c = 1.0, CHCl₃).



(S)-2-(3-chlorophenyl)-4-phenyl-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5n): white solid, 38.4 mg, 90% yield

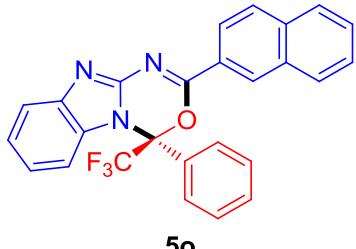
¹H NMR (400 MHz, CDCl₃) δ 8.18 (t, *J* = 1.6 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.65 – 7.49 (m, 4H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.07 – 6.97 (m, 1H), 6.42 (d, *J* = 8.3 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 157.3, 146.0, 142.8, 135.0, 133.6, 132.0, 131.1, 131.0, 130.9, 130.1, 129.5, 128.7, 127.8 (q, *J* = 1.9 Hz), 127.0, 124.5, 124.4, 123.1 (q, *J* = 293.1 Hz), 120.6, 111.5, 90.9 (q, *J* = 33.6 Hz);

¹⁹F NMR (377 MHz, CDCl₃) δ -75.3 (3F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 428.0773, found: 428.0774;

HPLC analysis: 95:5 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 18.3 min, t_{major} = 23.2 min), [α]_D²⁵ = +57.94 (c = 1.0, CHCl₃).



(S)-2-(naphthalen-2-yl)-4-phenyl-4-(trifluoromethyl)-4H-benzo[4,5]imidazo[1,2-c][1,3,5]oxadiazine (5o): slightly yellow oil, 32.3 mg, 73% yield

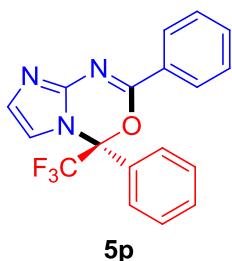
¹H NMR (400 MHz, CDCl₃) δ 8.71 (s, 1H), 8.32 (dd, *J* = 8.7, 1.6 Hz, 1H), 8.00 – 7.84 (m, 3H), 7.83 – 7.72 (m, 3H), 7.65 – 7.44 (m, 5H), 7.25 – 7.21 (m, 1H), 7.07 – 6.97 (m, 1H), 6.45 (d, *J* = 8.2 Hz, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 158.7, 146.6, 142.9, 135.9, 132.6, 131.8, 131.3, 131.0, 130.4, 129.6, 129.5, 128.9, 128.7, 128.0, 127.9 (q, *J* = 2.3 Hz), 127.0, 126.5, 124.4, 124.1, 123.6, 123.2 (q, *J* = 293.2 Hz), 120.4, 111.4, 90.8 (q, *J* = 33.6 Hz);

¹⁹F NMR (377 MHz, CDCl₃) δ -75.3 (3F);

HRMS (ESI, m/z): calcd. for [M+H]⁺: 444.1324, found: 444.1327;

HPLC analysis: 95:5 er, (CHIRALCEL IC column, *n*-hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, t_{minor} = 23.7 min, t_{major} = 30.3 min), [α]_D²⁵ = -24.78 (c = 1.0, CHCl₃).



(S)-2,4-diphenyl-4-(trifluoromethyl)-4H-imidazo[1,2-c][1,3,5]oxadiazine (5p): slightly yellow oil, 13.5 mg, 40% yield

¹H NMR (400 MHz, CDCl₃) δ 8.27 – 8.13 (m, 2H), 7.63 – 7.40 (m, 8H), 7.20 (d, *J* = 1.5 Hz, 1H), 6.93 (s, 1H);

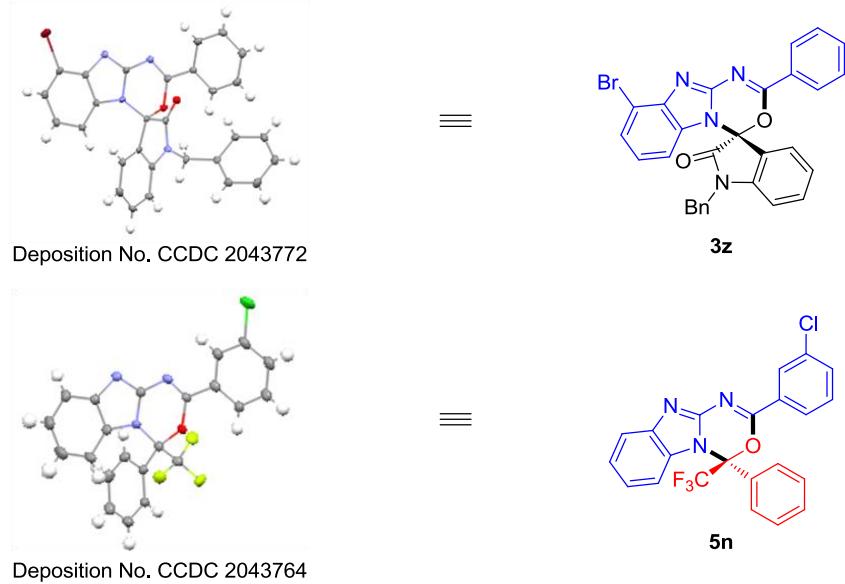
¹³C NMR (101 MHz, CDCl₃) δ 155.3, 143.1, 133.1, 132.4, 131.5, 130.1, 129.6, 129.3, 128.8, 128.5, 126.7 (q, *J* = 2.0 Hz), 122.1 (q, *J* = 289.6 Hz), 114.5, 90.7 (q, *J* = 34.1 Hz);

¹⁹F NMR (377 MHz, CDCl₃) δ -78.0 (3F);

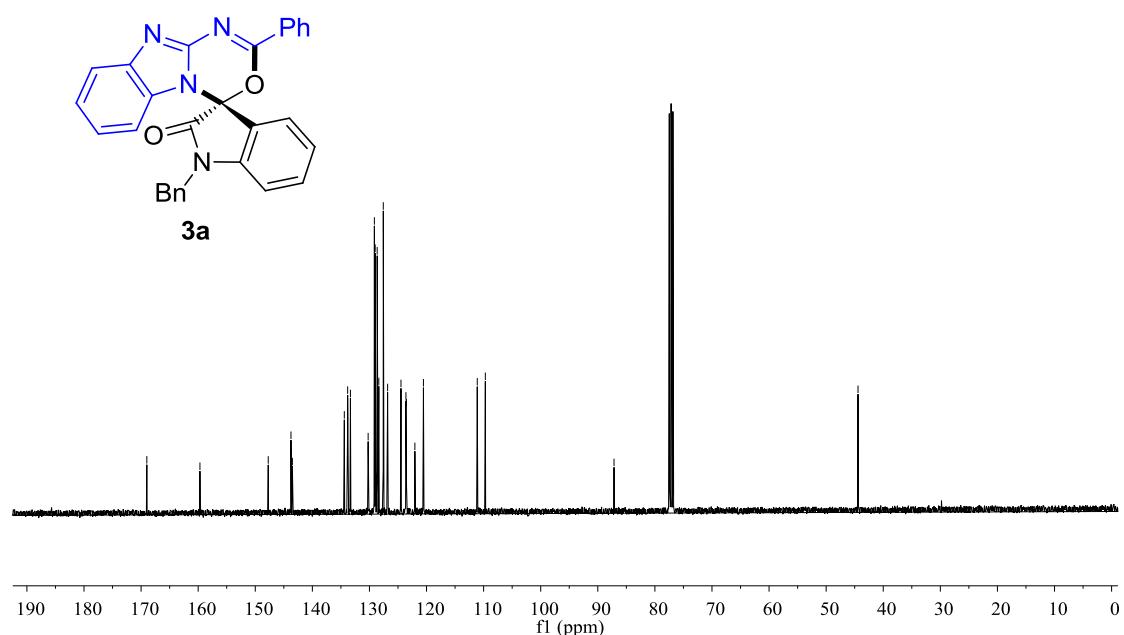
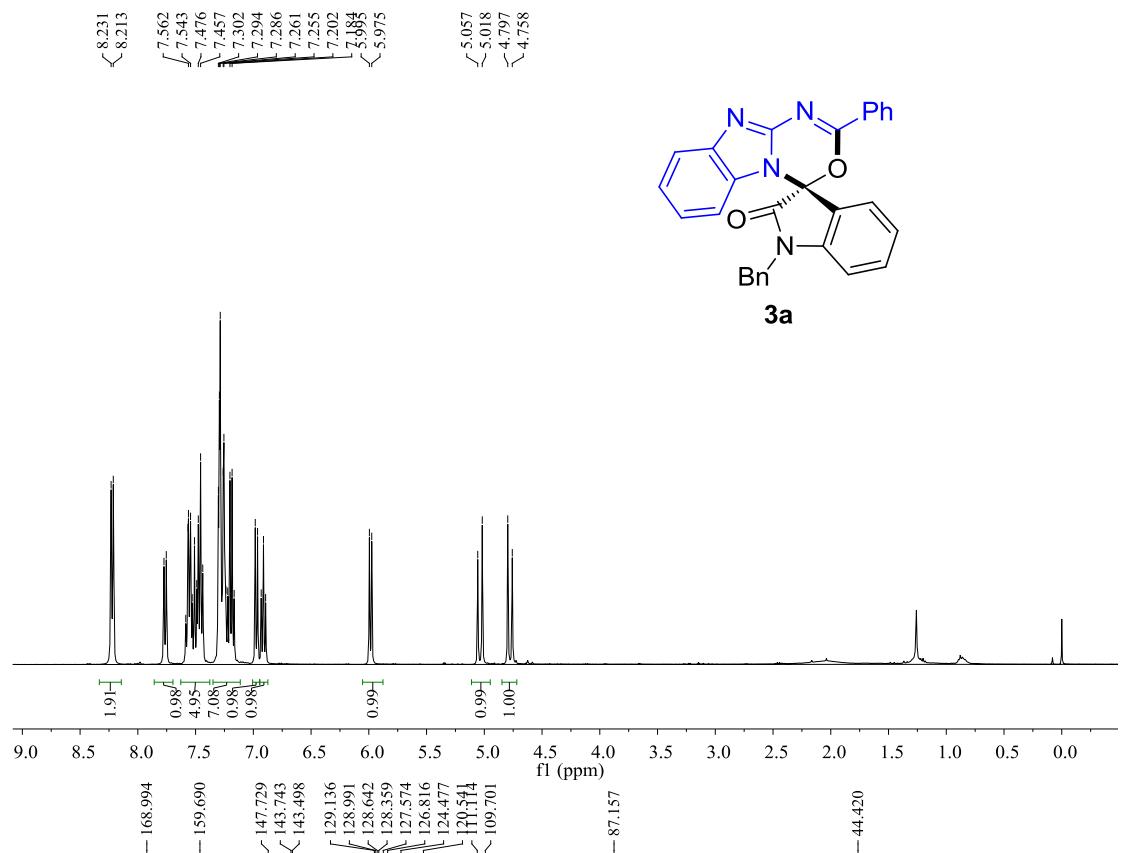
HRMS (ESI, m/z): calcd. for [M+Na]⁺: 366.0830, found: 366.0827;

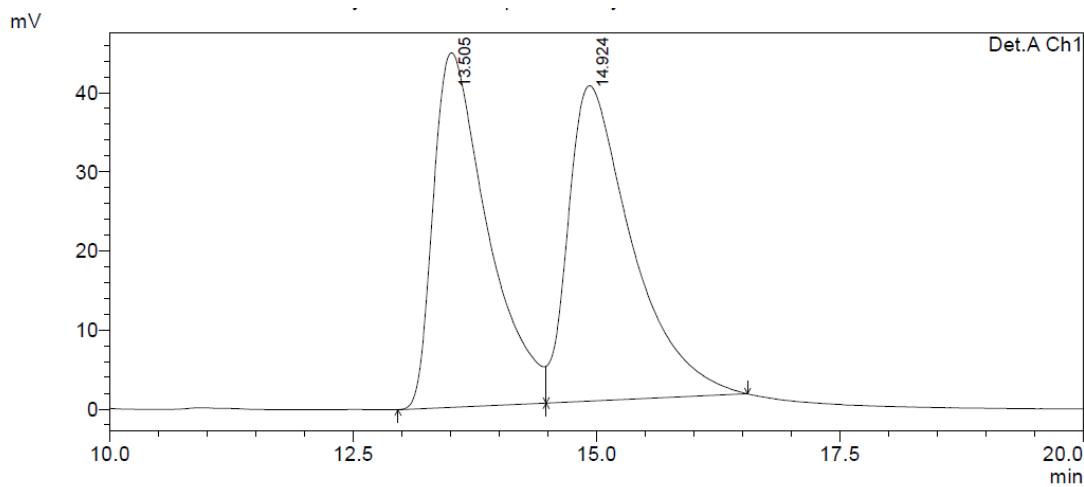
HPLC analysis: 92:8 er, (CHIRALCEL AD-H column, *n*-hexane/*i*-PrOH = 70/30, flow rate = 1.0 mL/min, λ = 254 nm, $t_{\text{minor}} = 10.5$ min, $t_{\text{major}} = 16.9$ min), $[\alpha]_D^{25} = -25.78$ ($c = 0.5$, CHCl₃).

X-ray structure of 3z and 5n



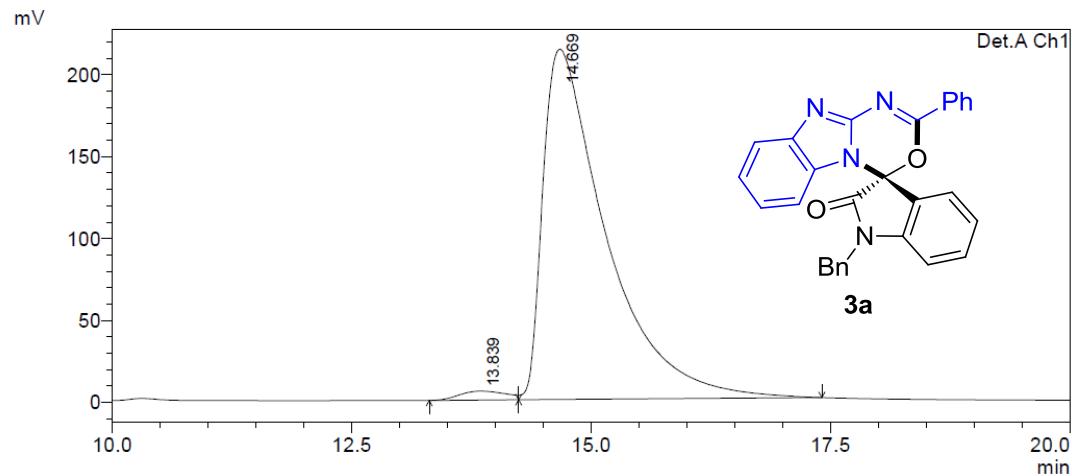
¹H, ¹³C and ¹⁹F spectra and HPLC charts





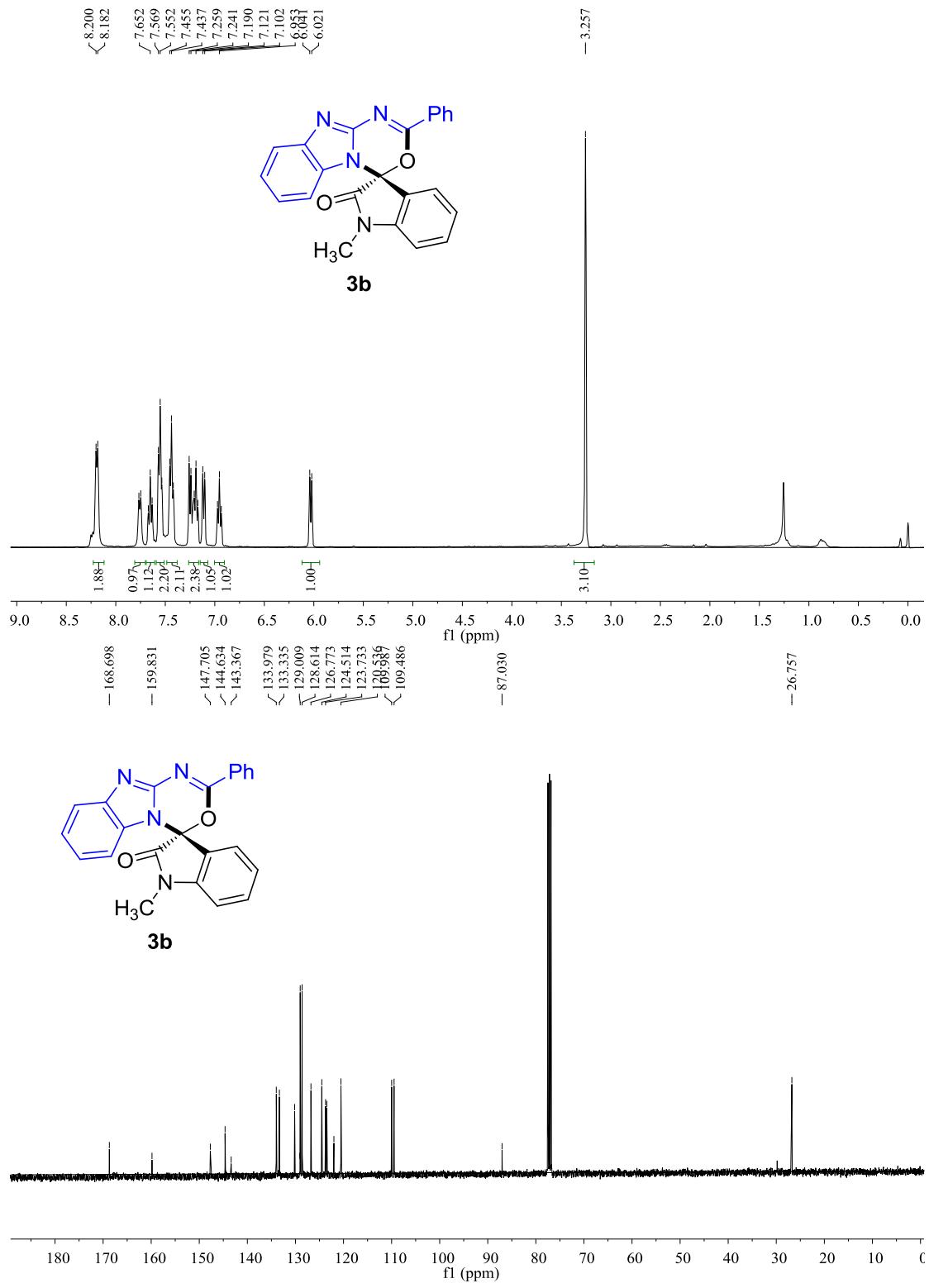
Detector A Ch1 254nm

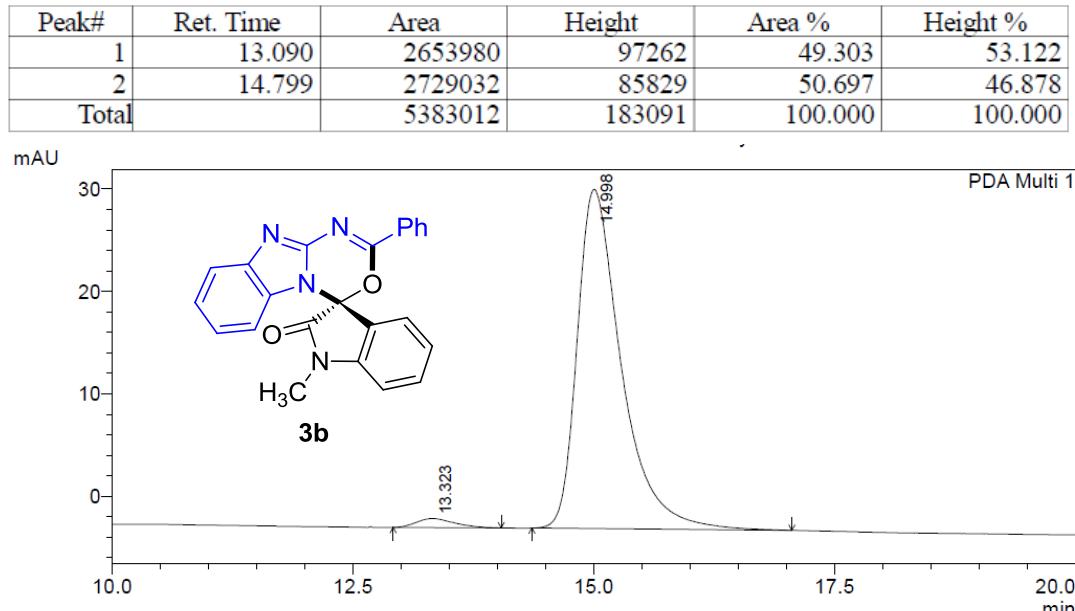
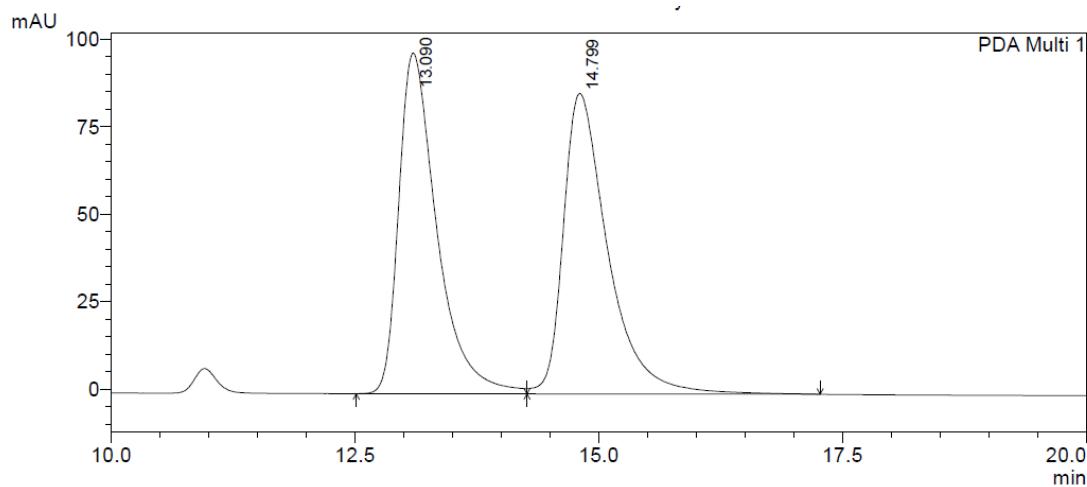
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 13.505 | 1733088 | 44818 | 48.734 | 52.923 |
| 2 | 14.924 | 1823140 | 39868 | 51.266 | 47.077 |
| Total | | 3556227 | 84686 | 100.000 | 100.000 |



Detector A Ch1 254nm

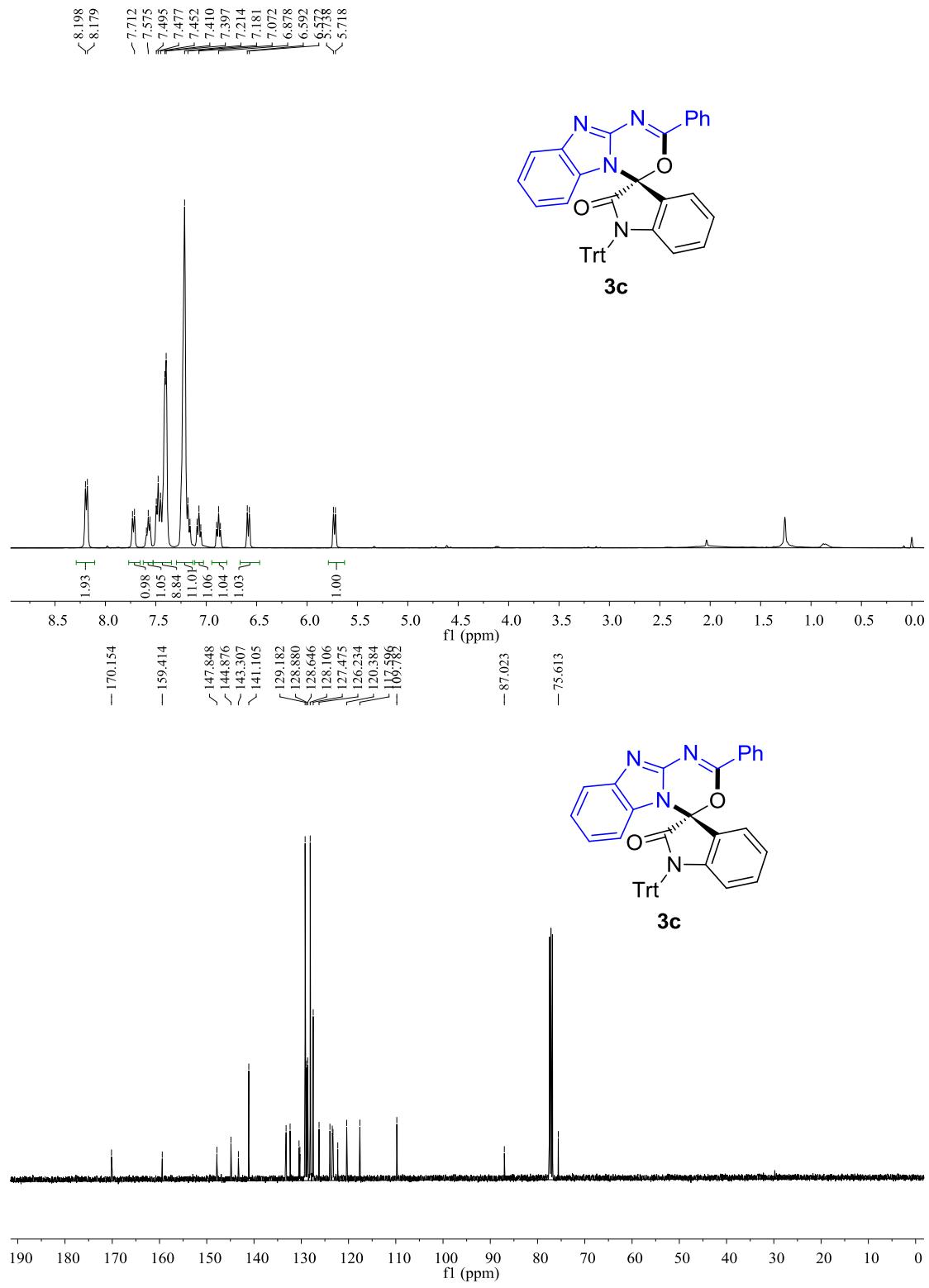
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|----------|--------|---------|----------|
| 1 | 13.839 | 186974 | 5556 | 1.866 | 2.532 |
| 2 | 14.669 | 9830727 | 213886 | 98.134 | 97.468 |
| Total | | 10017701 | 219442 | 100.000 | 100.000 |

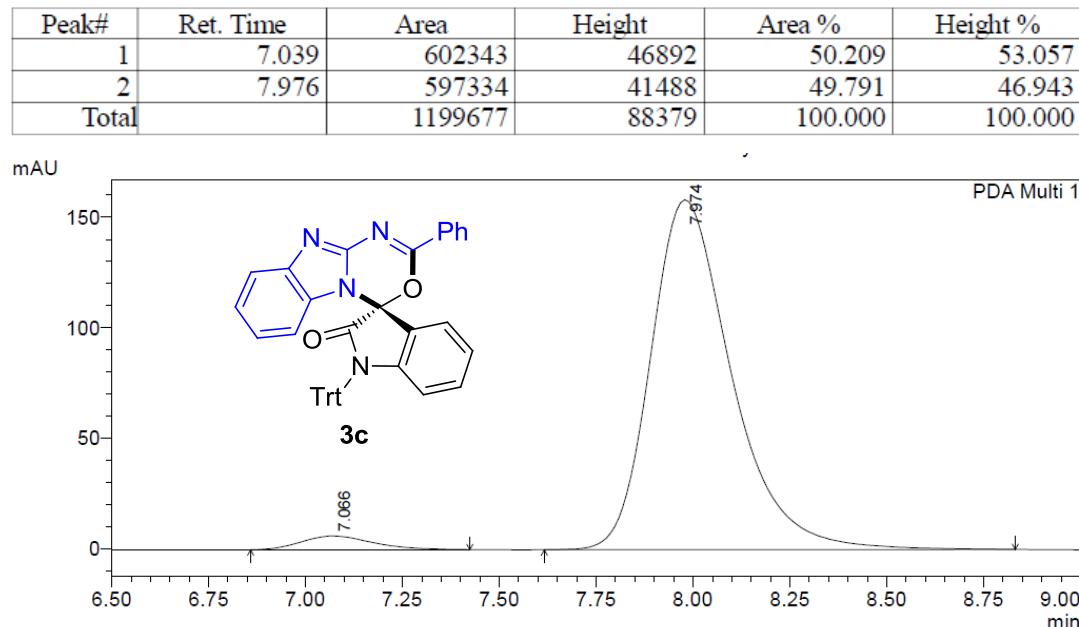
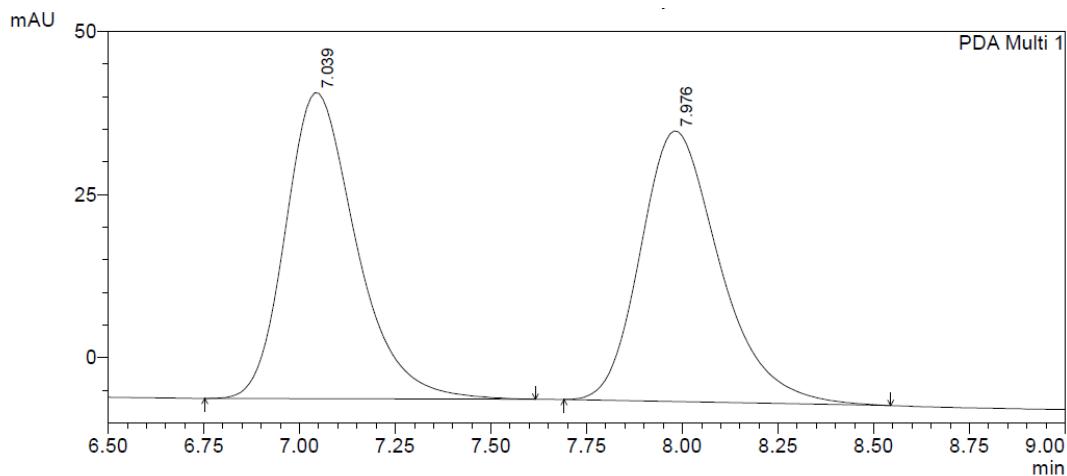


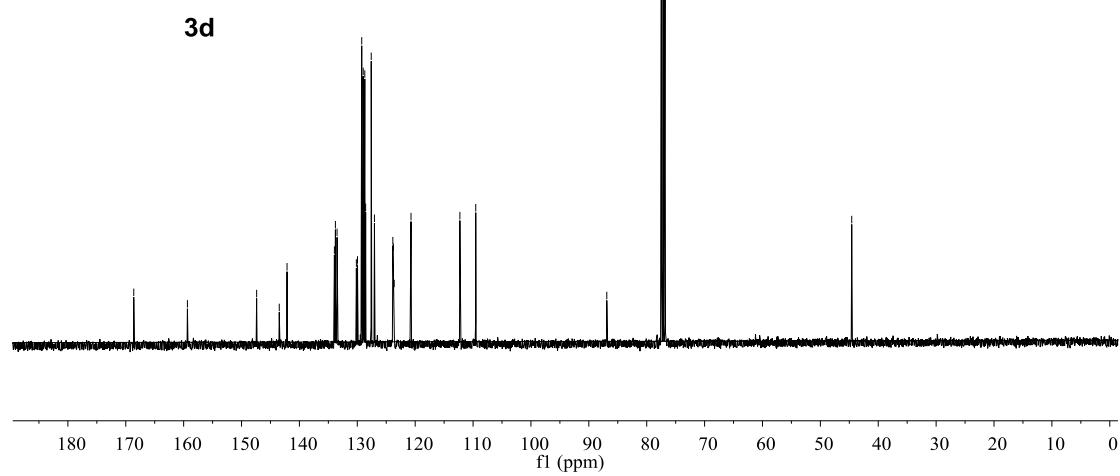
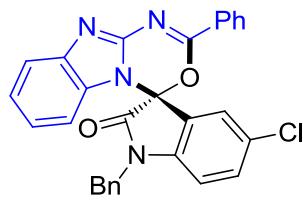
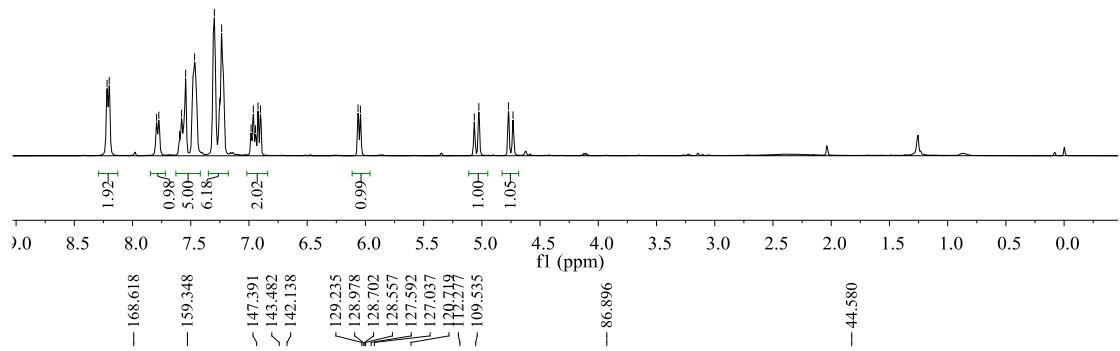
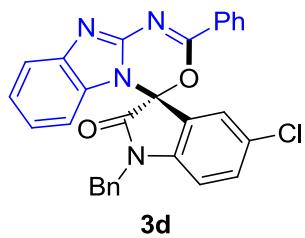


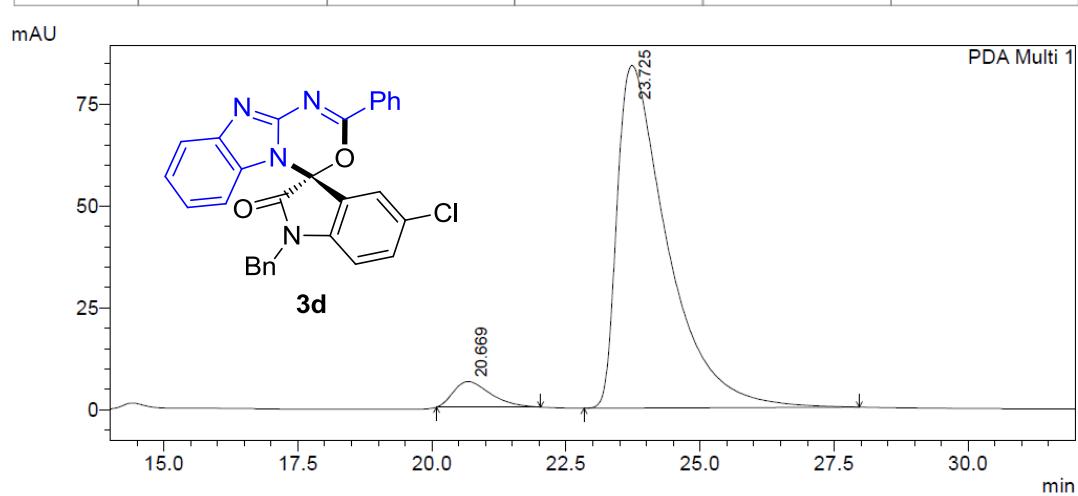
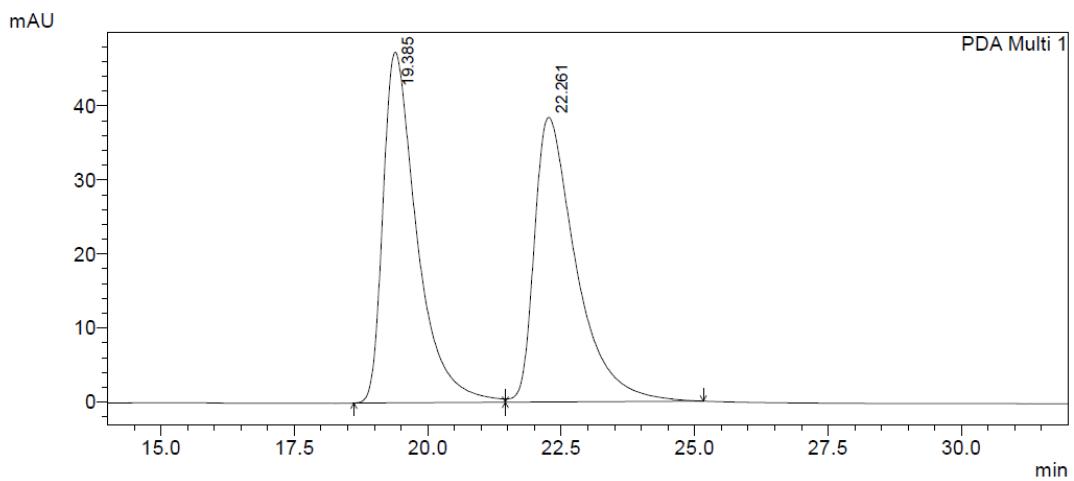
PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 13.323 | 24258 | 879 | 2.244 | 2.587 |
| 2 | 14.998 | 1056982 | 33094 | 97.756 | 97.413 |
| Total | | 1081240 | 33973 | 100.000 | 100.000 |



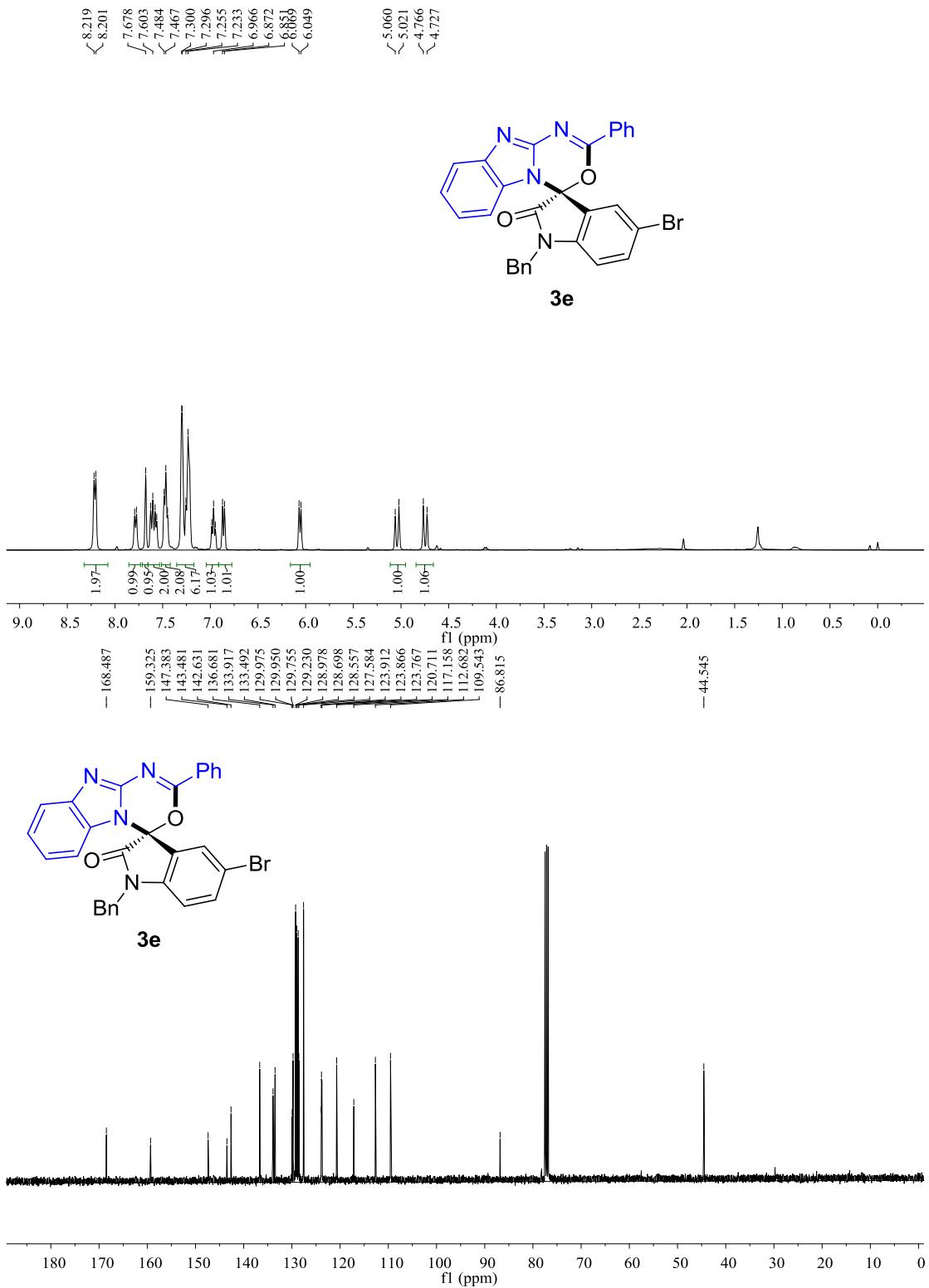


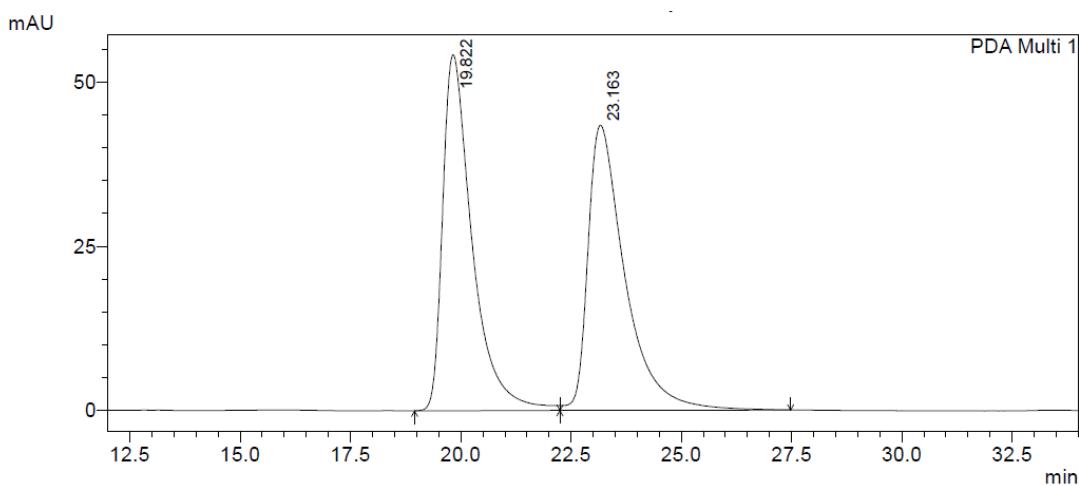




PDA Ch1 254nm 4nm

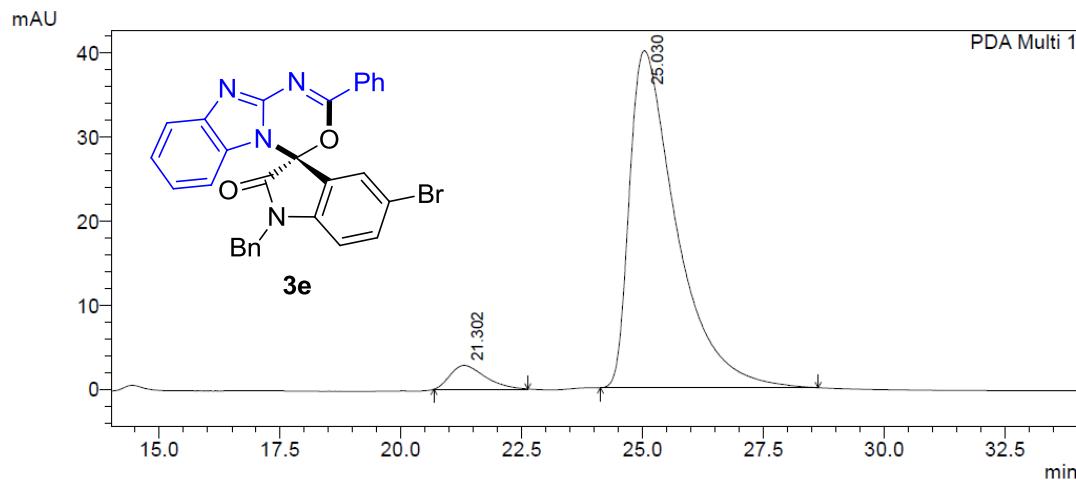
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 20.669 | 303965 | 6301 | 5.222 | 6.959 |
| 2 | 23.725 | 5516498 | 84245 | 94.778 | 93.041 |
| Total | | 5820462 | 90546 | 100.000 | 100.000 |





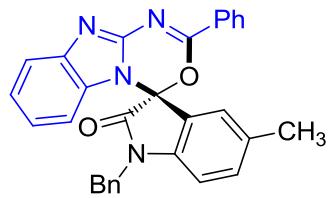
PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 19.822 | 2531846 | 54245 | 49.964 | 55.531 |
| 2 | 23.163 | 2535447 | 43440 | 50.036 | 44.469 |
| Total | | 5067294 | 97685 | 100.000 | 100.000 |

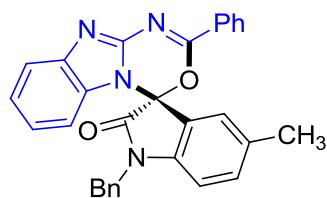
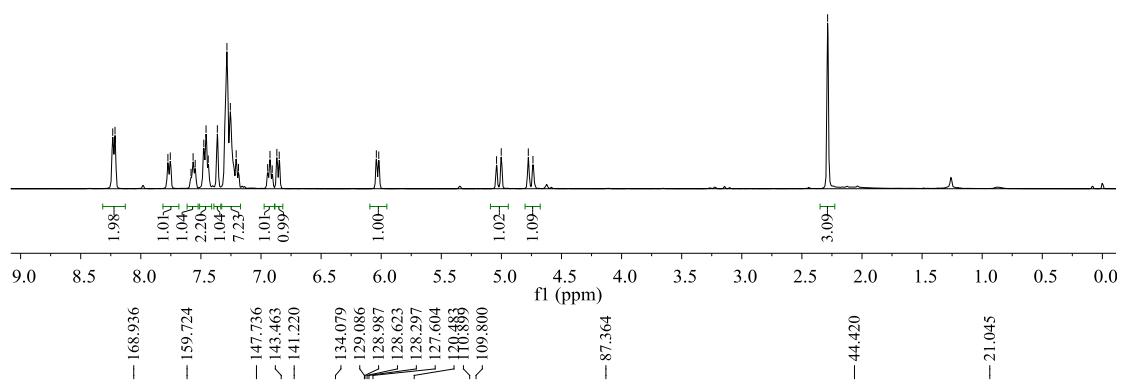


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 21.302 | 140922 | 2810 | 4.951 | 6.557 |
| 2 | 25.030 | 2705364 | 40052 | 95.049 | 93.443 |
| Total | | 2846286 | 42863 | 100.000 | 100.000 |

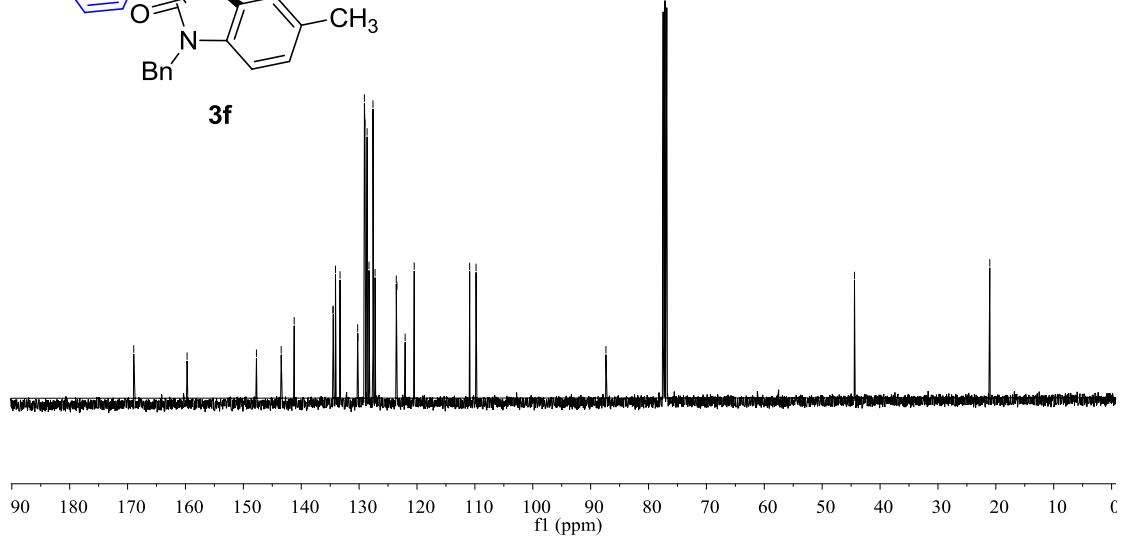
8.233
 8.215
 7.755
 7.565
 7.476
 7.457
 7.363
 7.283
 7.255
 7.206
 6.925
 6.868
 6.848
 6.020

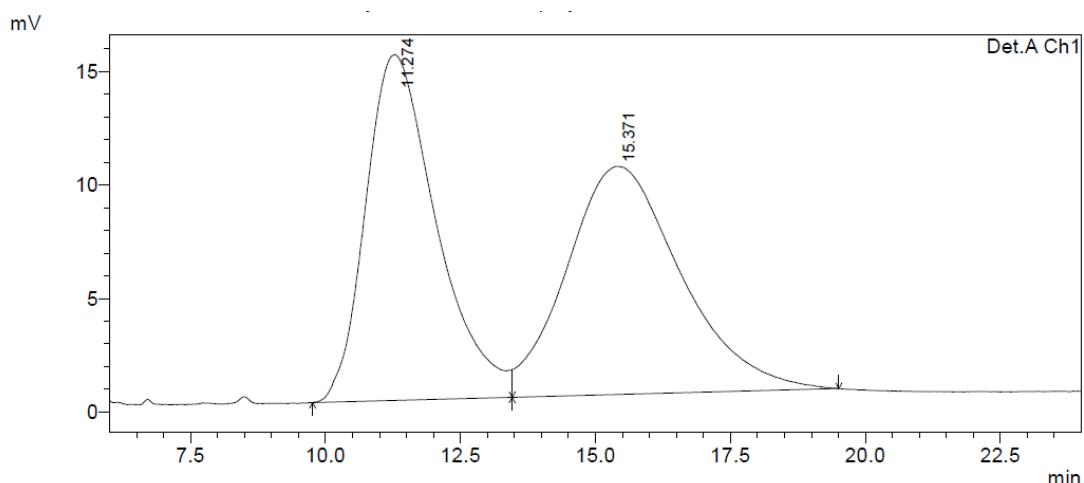


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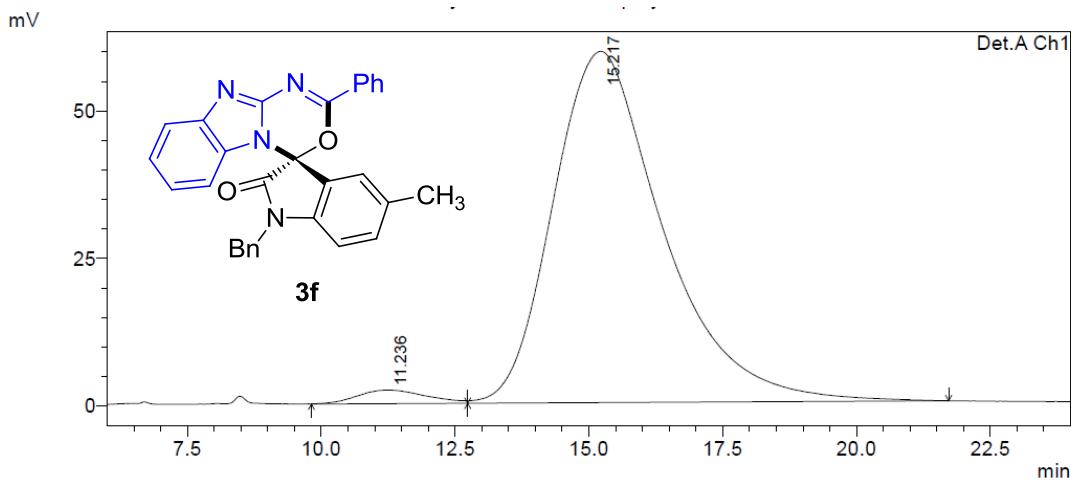
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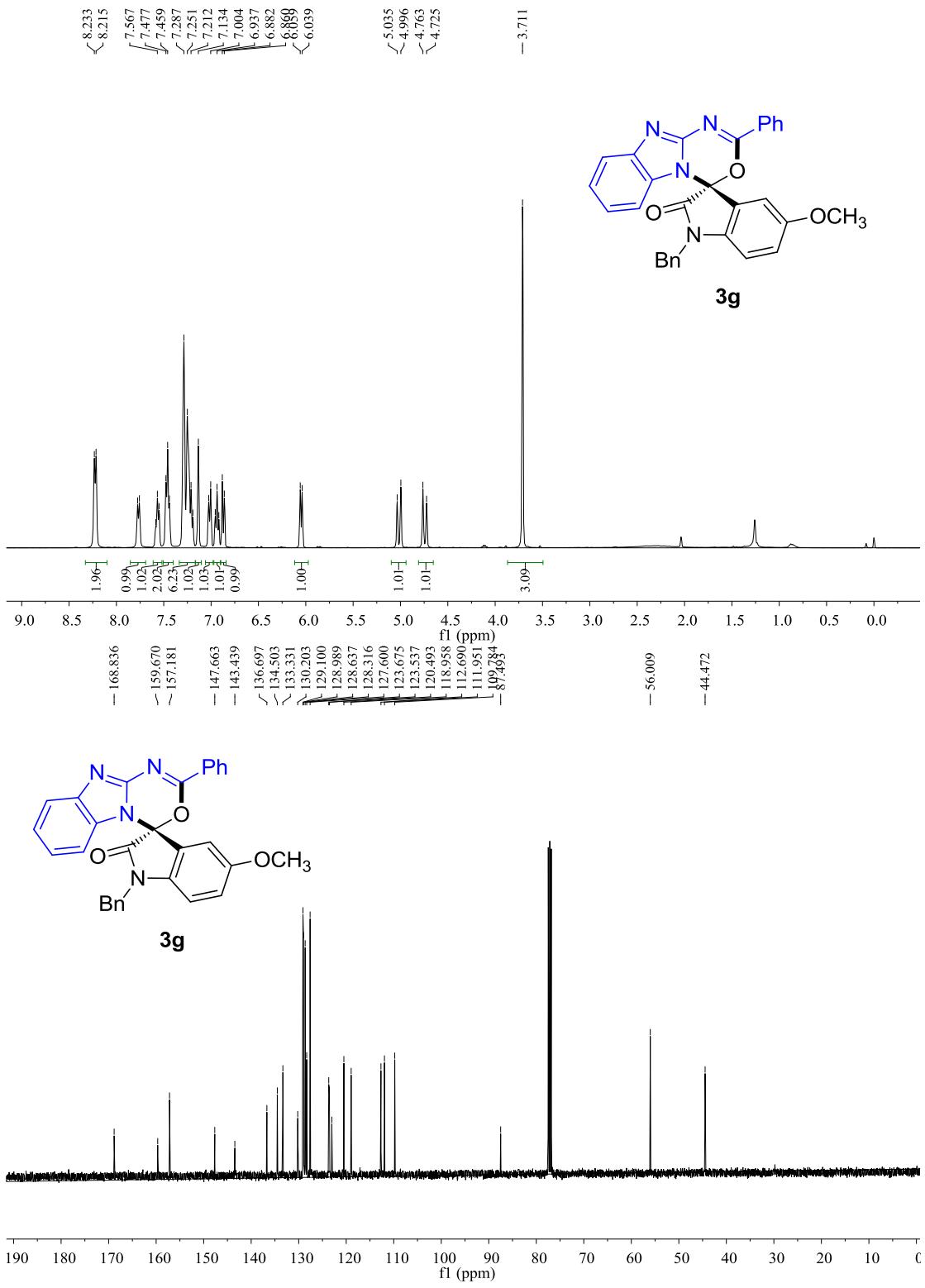
Detector A Ch1 254nm

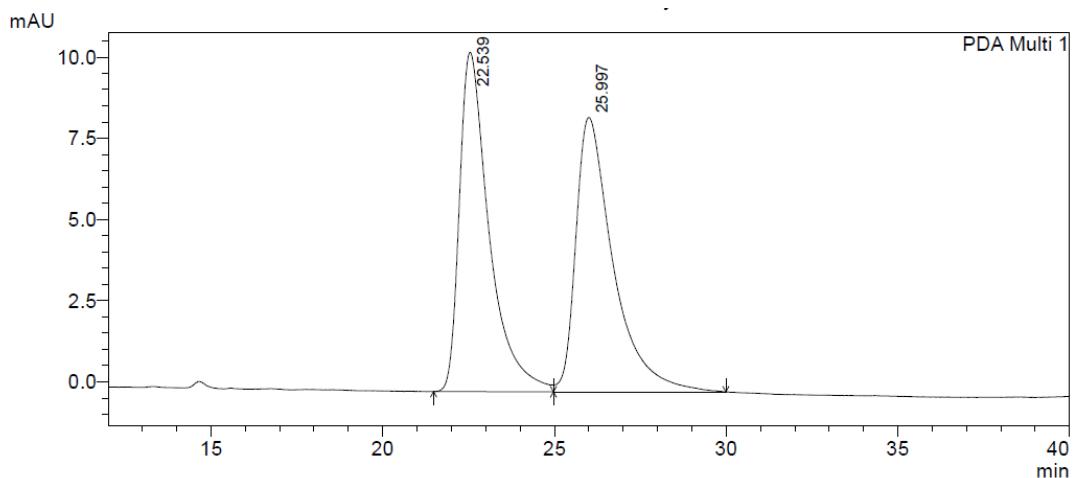
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 11.274 | 1387082 | 15224 | 48.380 | 60.254 |
| 2 | 15.371 | 1479980 | 10042 | 51.620 | 39.746 |
| Total | | 2867061 | 25266 | 100.000 | 100.000 |



Detector A Ch1 254nm

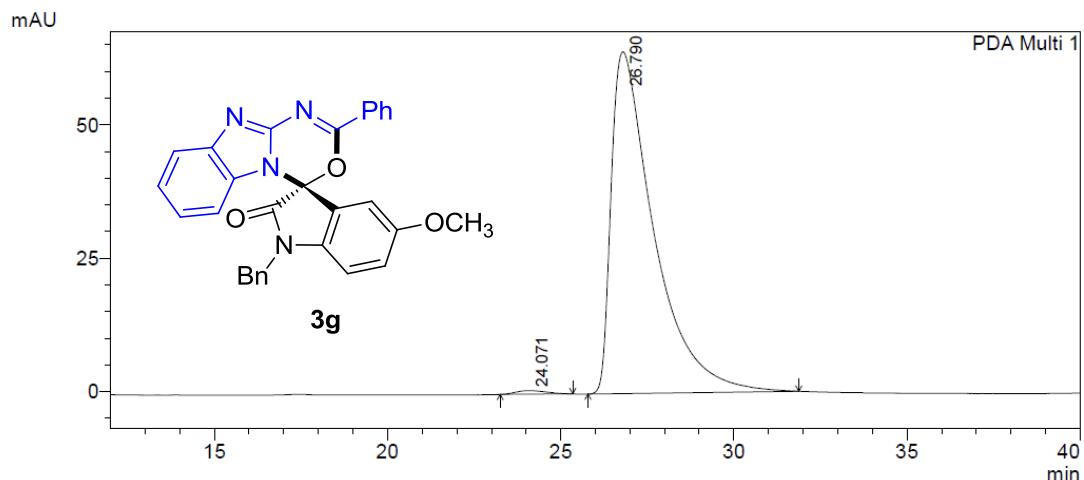
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 11.236 | 205072 | 2304 | 2.352 | 3.727 |
| 2 | 15.217 | 8514184 | 59509 | 97.648 | 96.273 |
| Total | | 8719256 | 61813 | 100.000 | 100.000 |



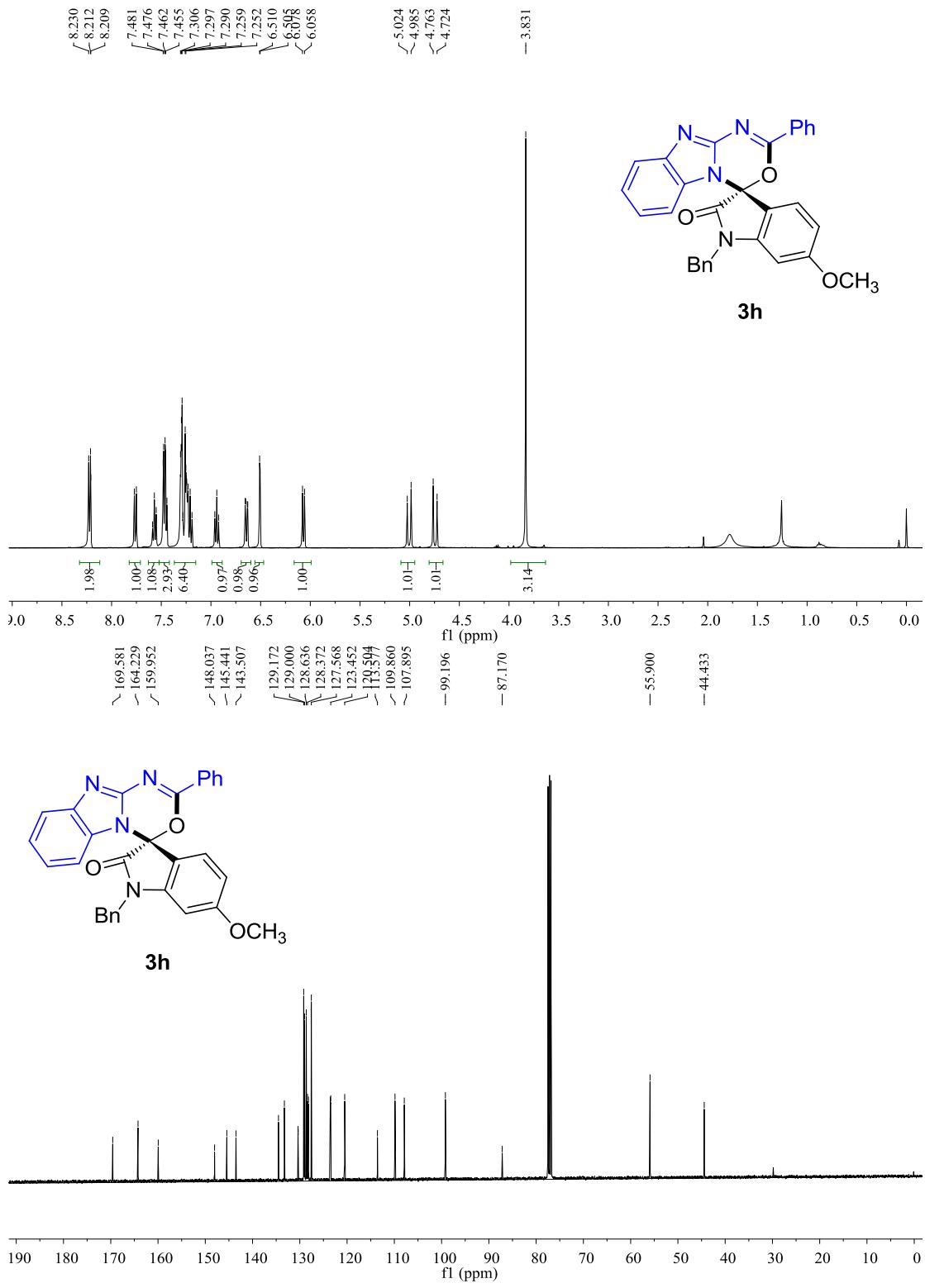


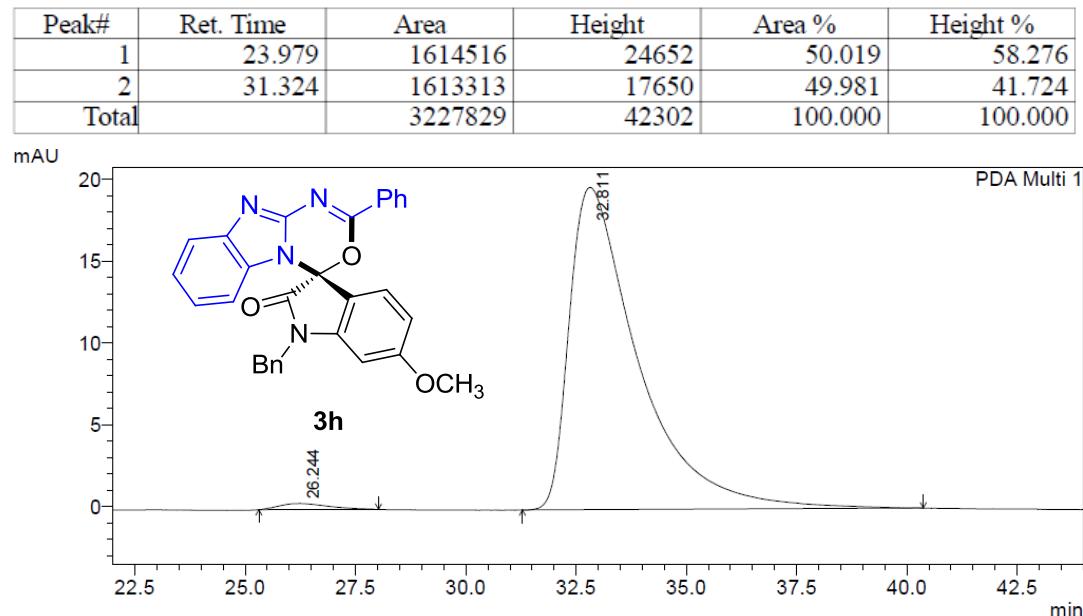
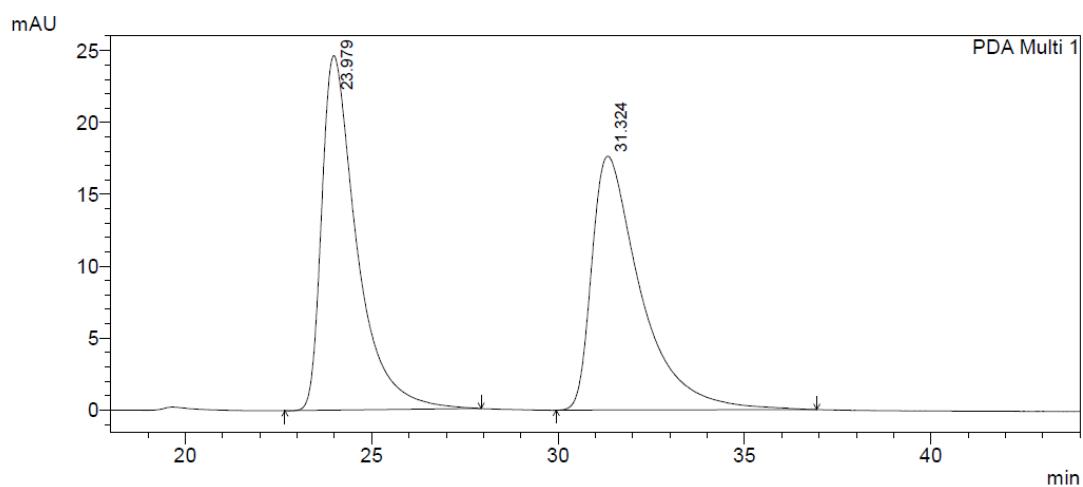
PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 22.539 | 629335 | 10449 | 49.663 | 55.291 |
| 2 | 25.997 | 637871 | 8449 | 50.337 | 44.709 |
| Total | | 1267206 | 18899 | 100.000 | 100.000 |



| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 24.071 | 40159 | 657 | 0.726 | 1.015 |
| 2 | 26.790 | 5492530 | 64064 | 99.274 | 98.985 |
| Total | | 5532689 | 64721 | 100.000 | 100.000 |

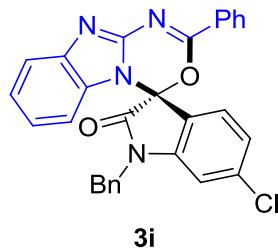




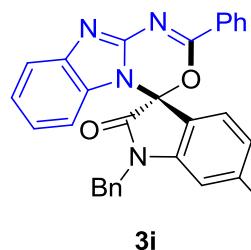
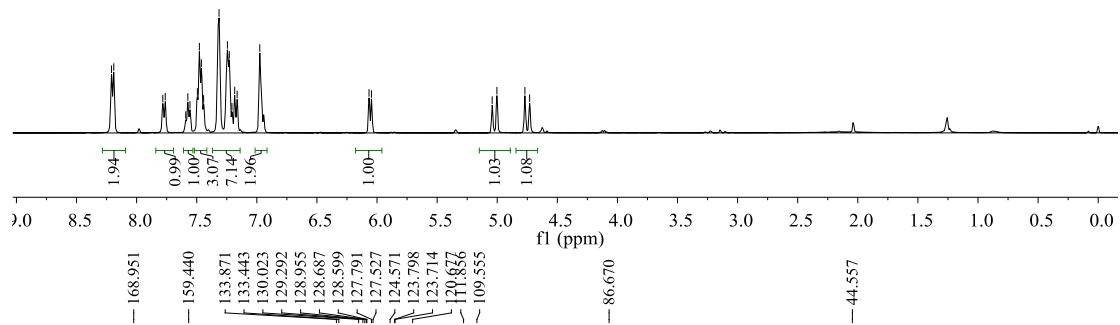
PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 26.244 | 27961 | 375 | 1.284 | 1.870 |
| 2 | 32.811 | 2150111 | 19699 | 98.716 | 98.130 |
| Total | | 2178073 | 20075 | 100.000 | 100.000 |

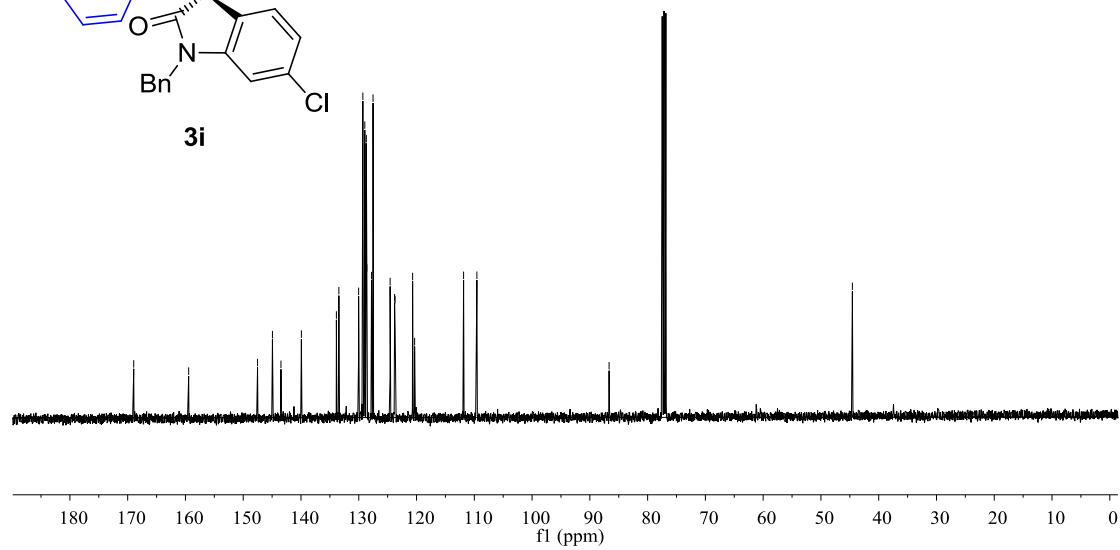
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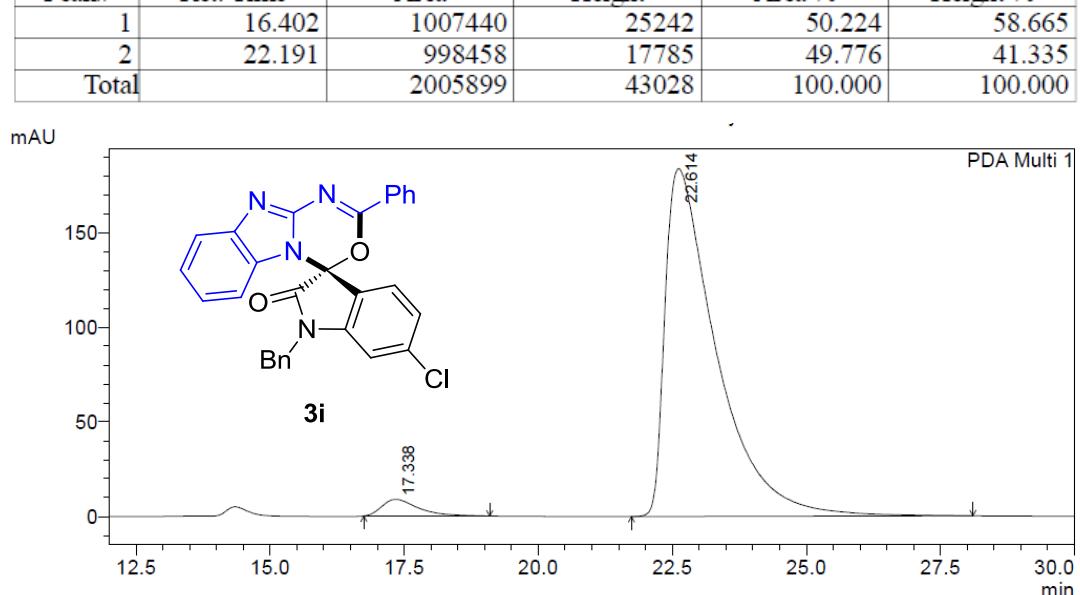
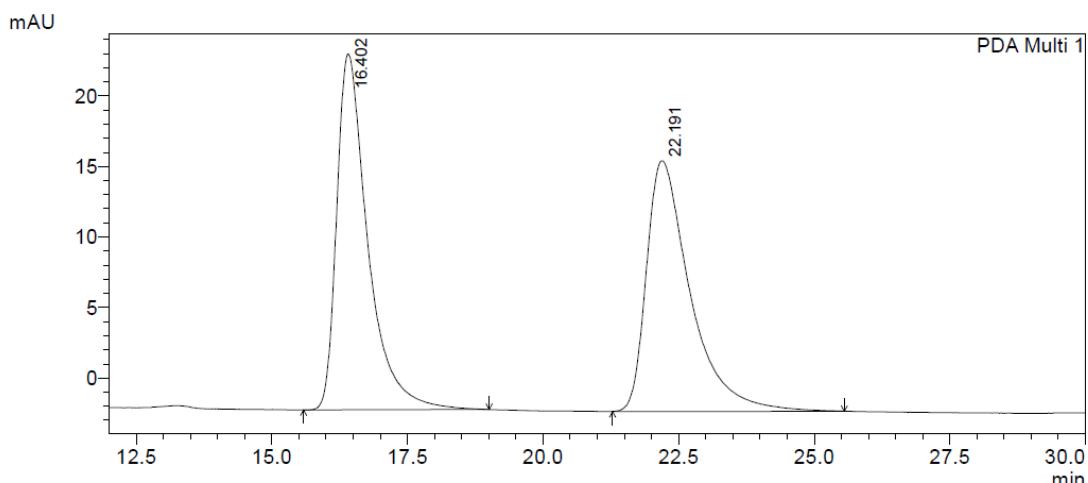


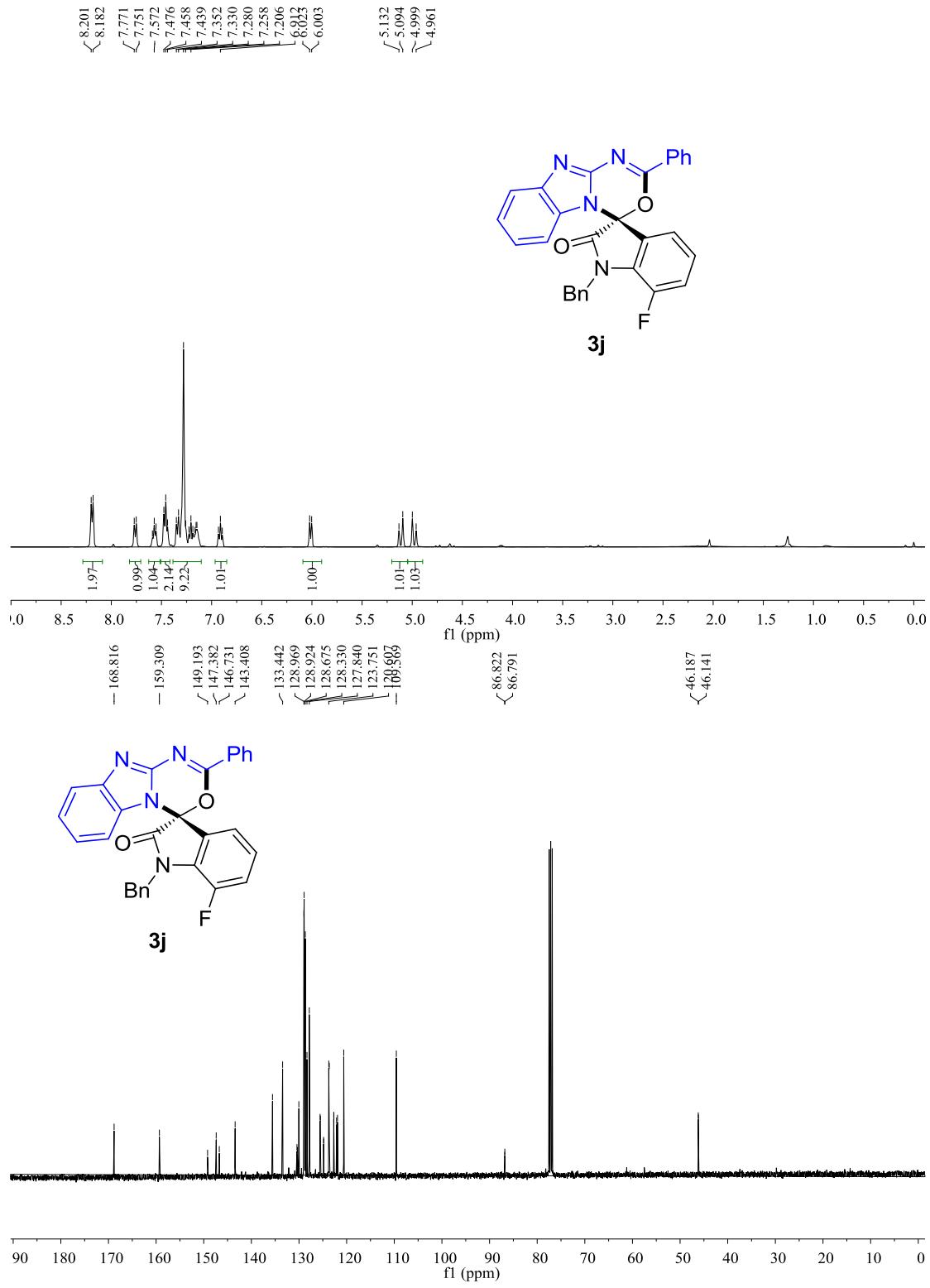
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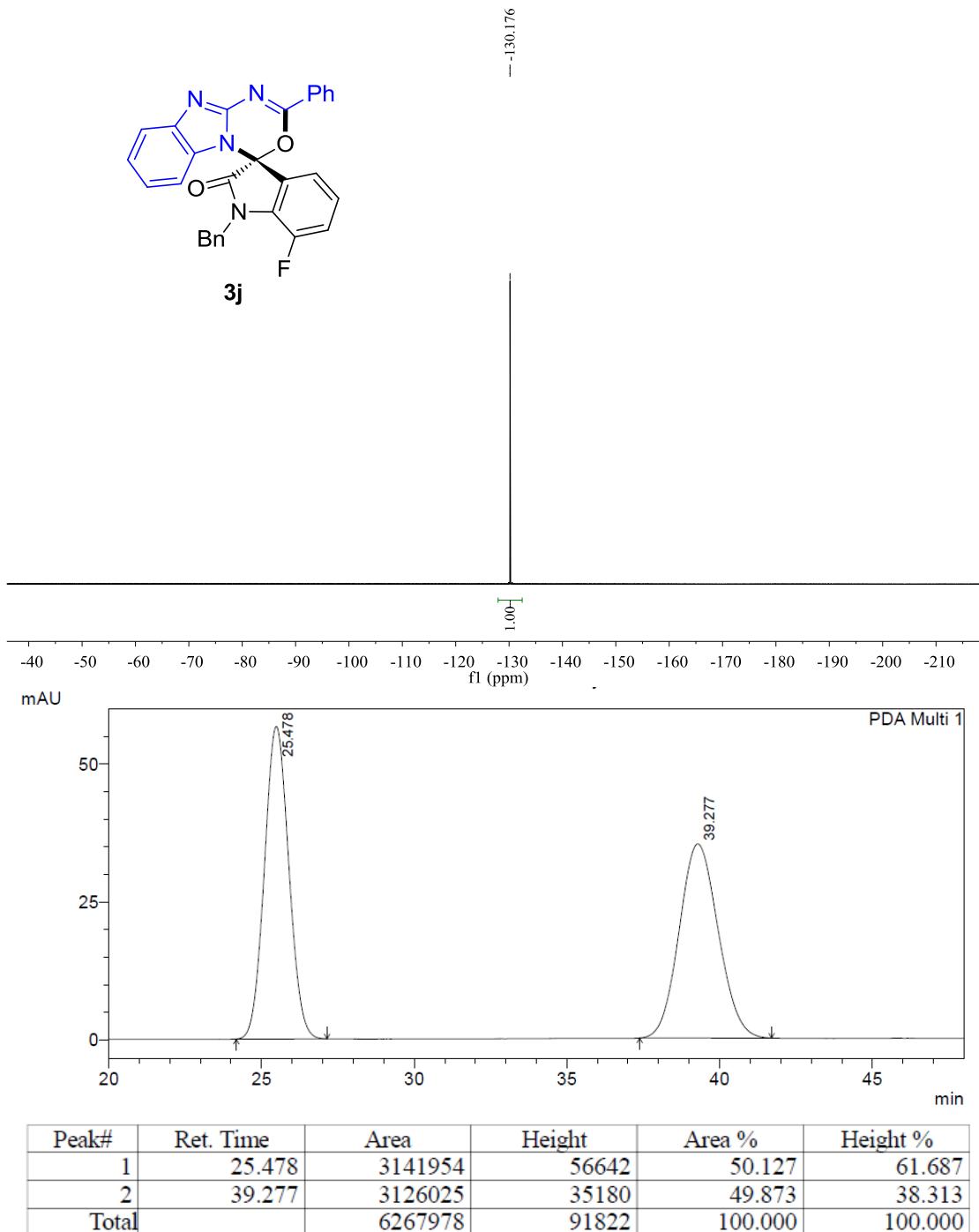


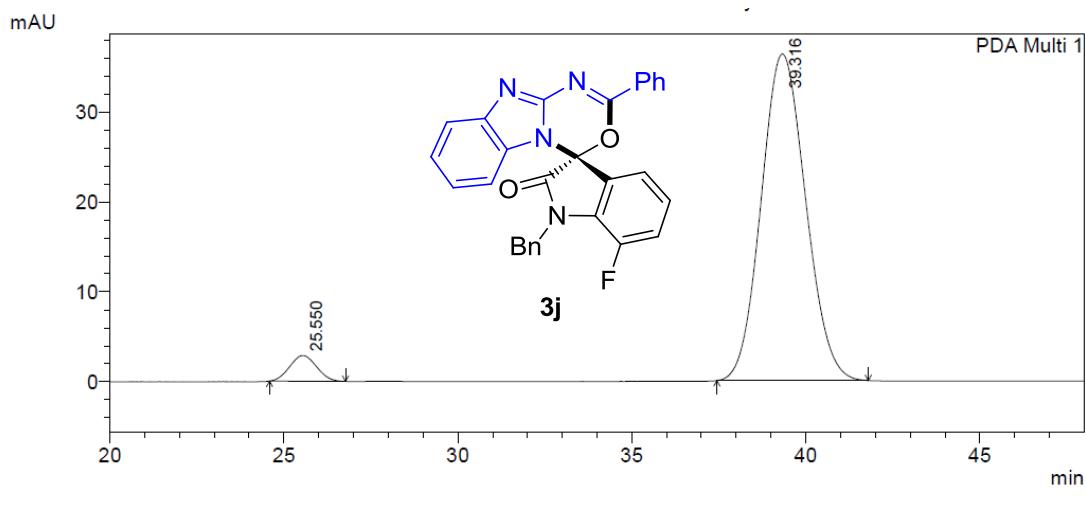
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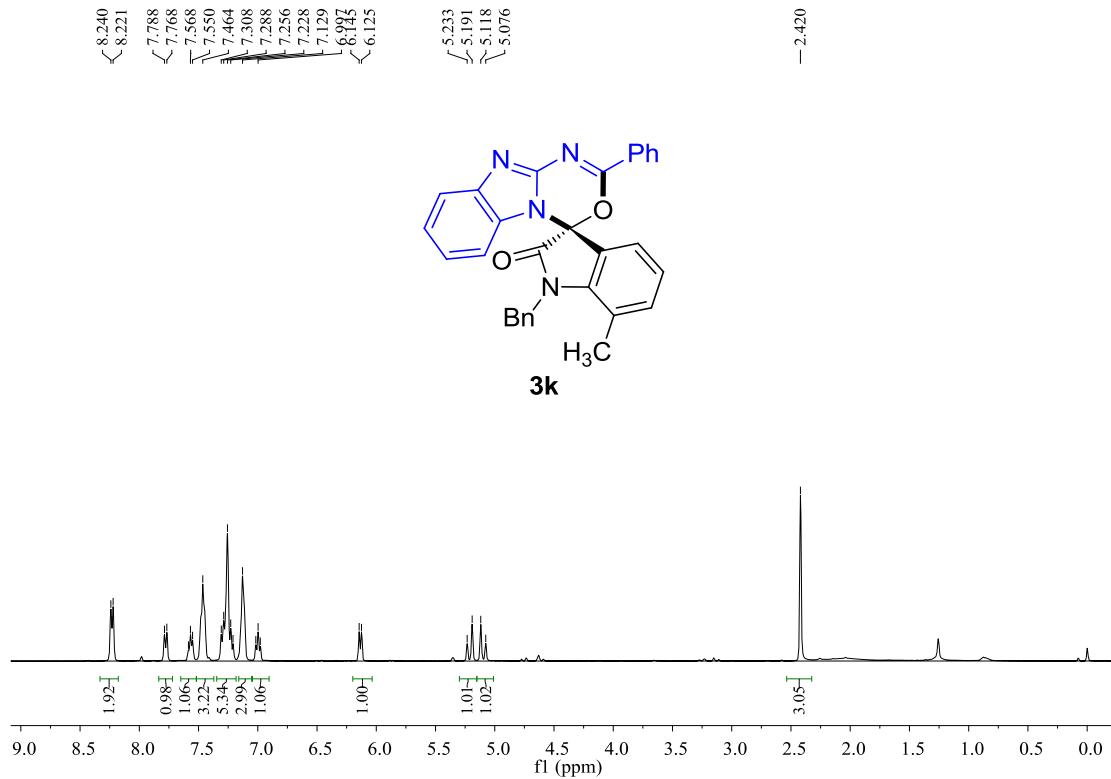


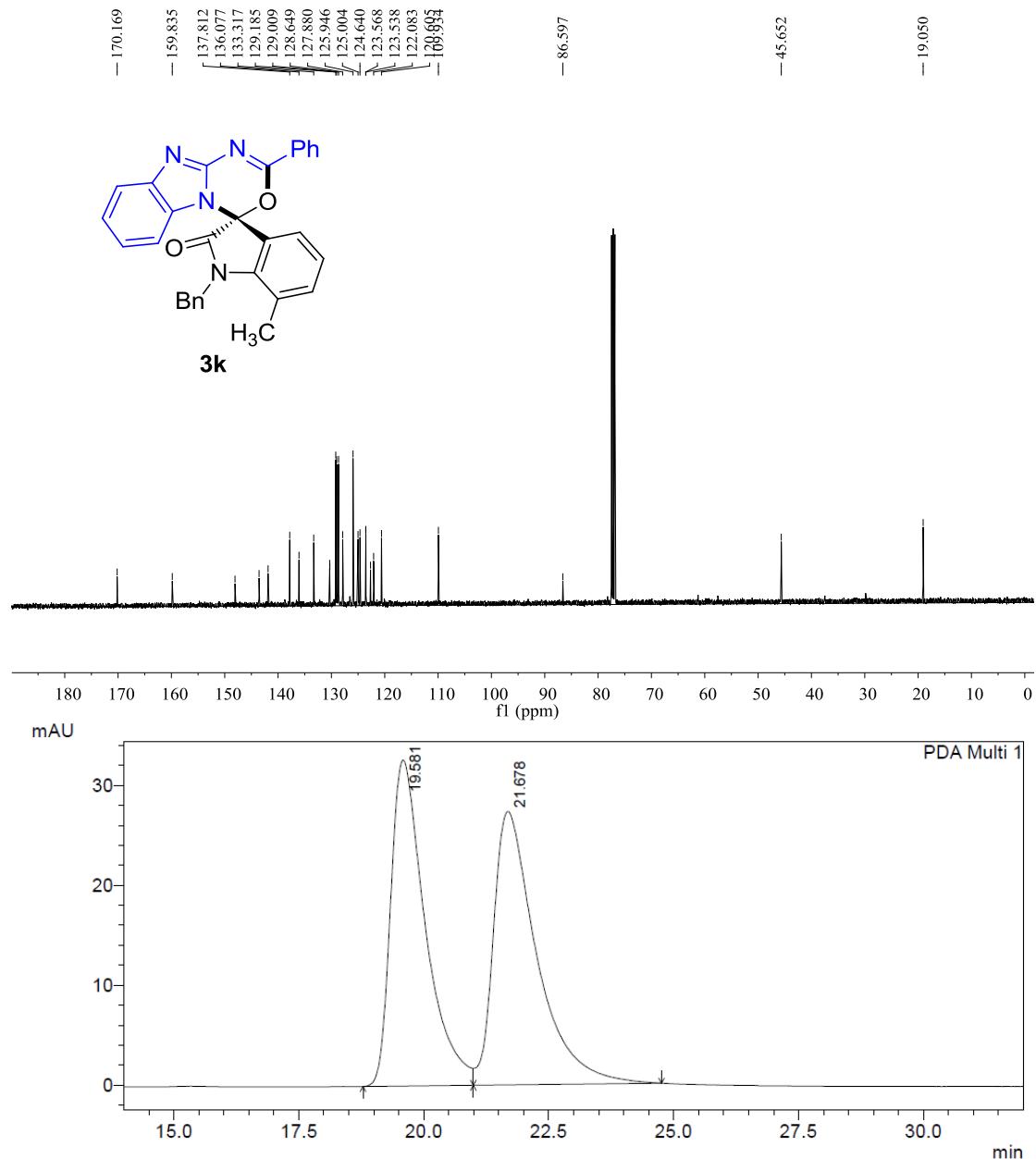






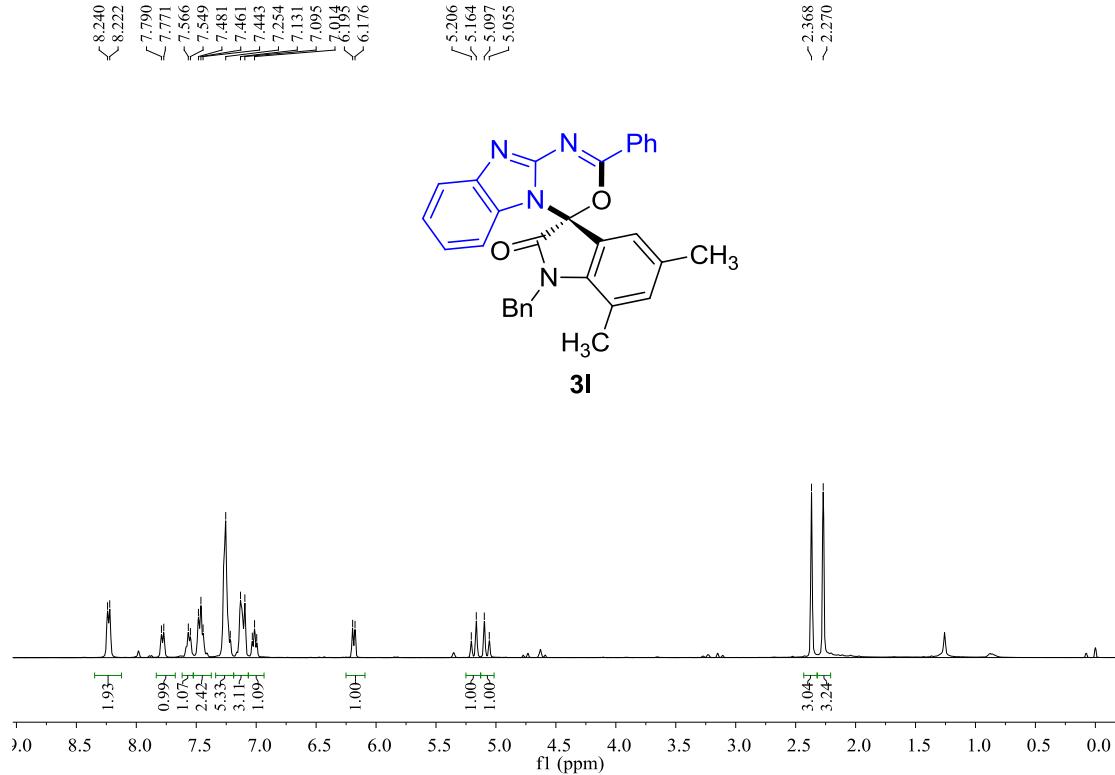
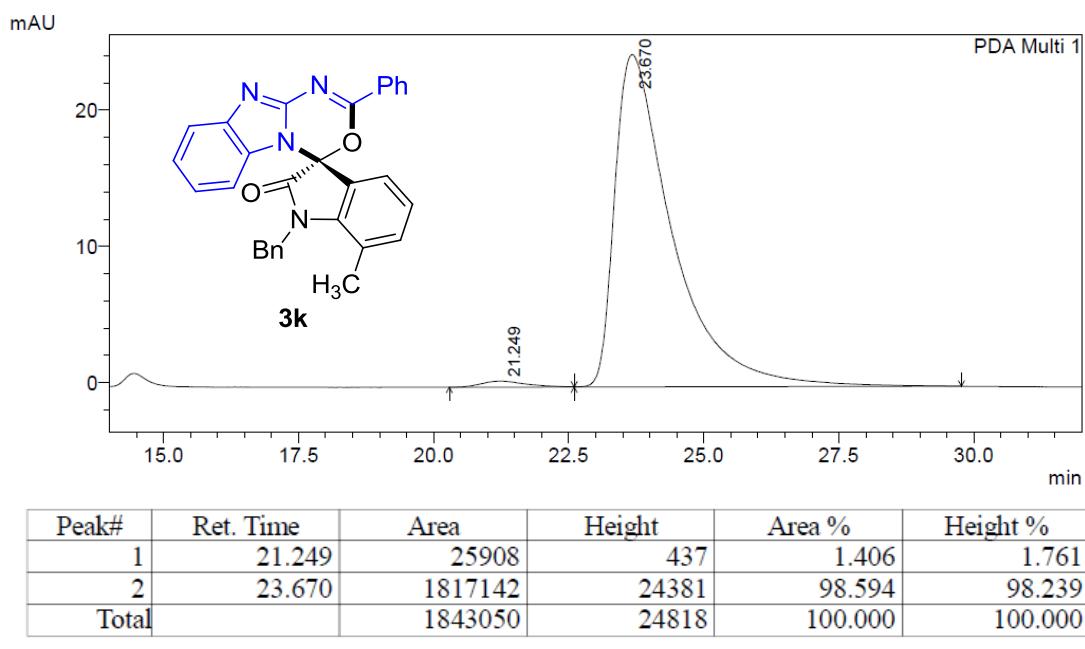
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 25.550 | 154871 | 2872 | 4.573 | 7.320 |
| 2 | 39.316 | 3231478 | 36364 | 95.427 | 92.680 |
| Total | | 3386348 | 39236 | 100.000 | 100.000 |

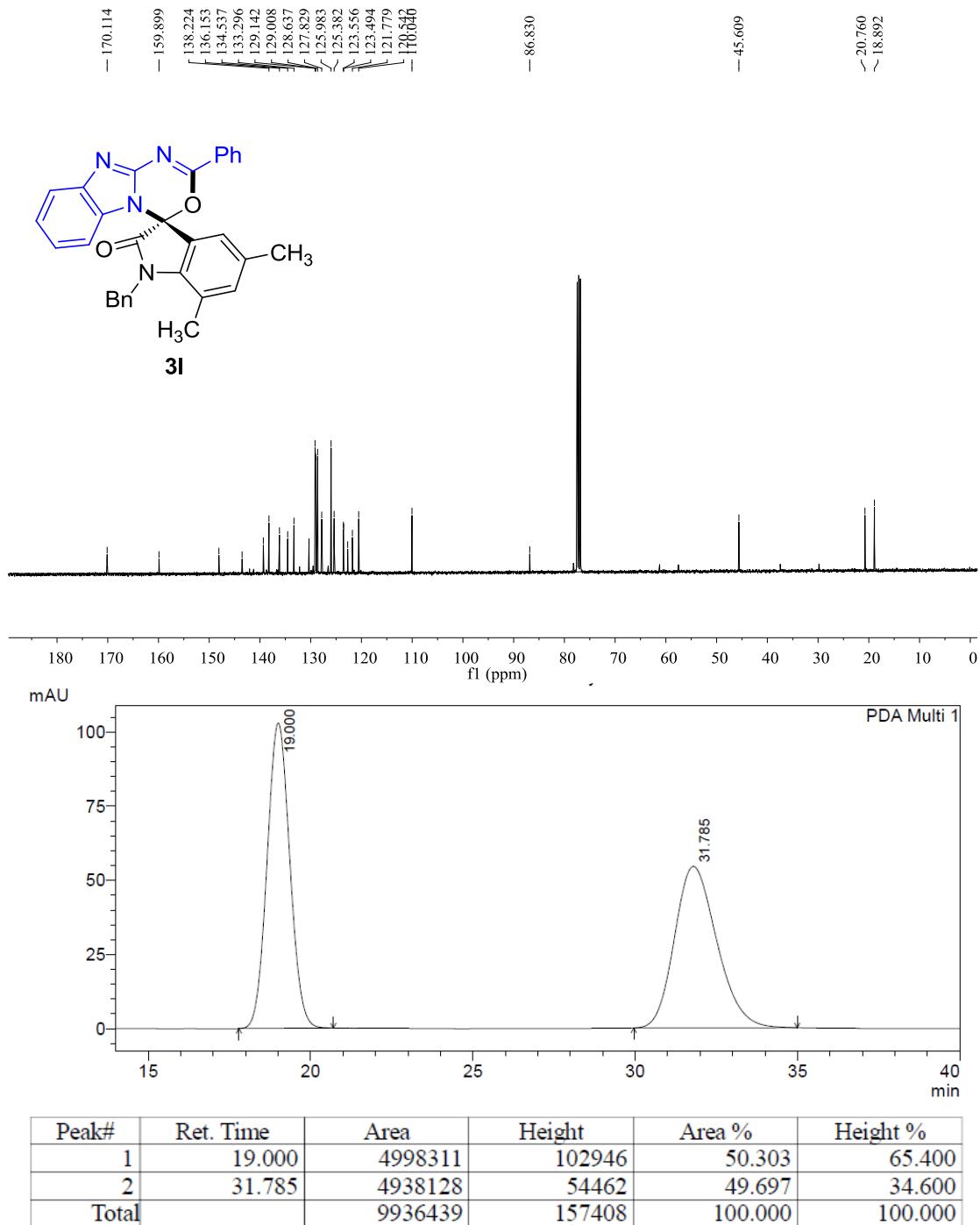


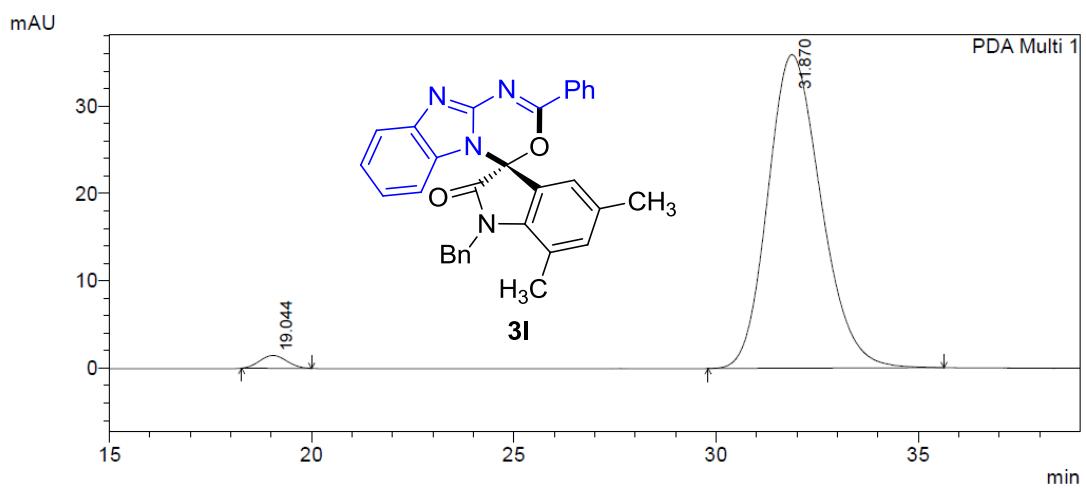


PDA Ch1 254nm 4nm

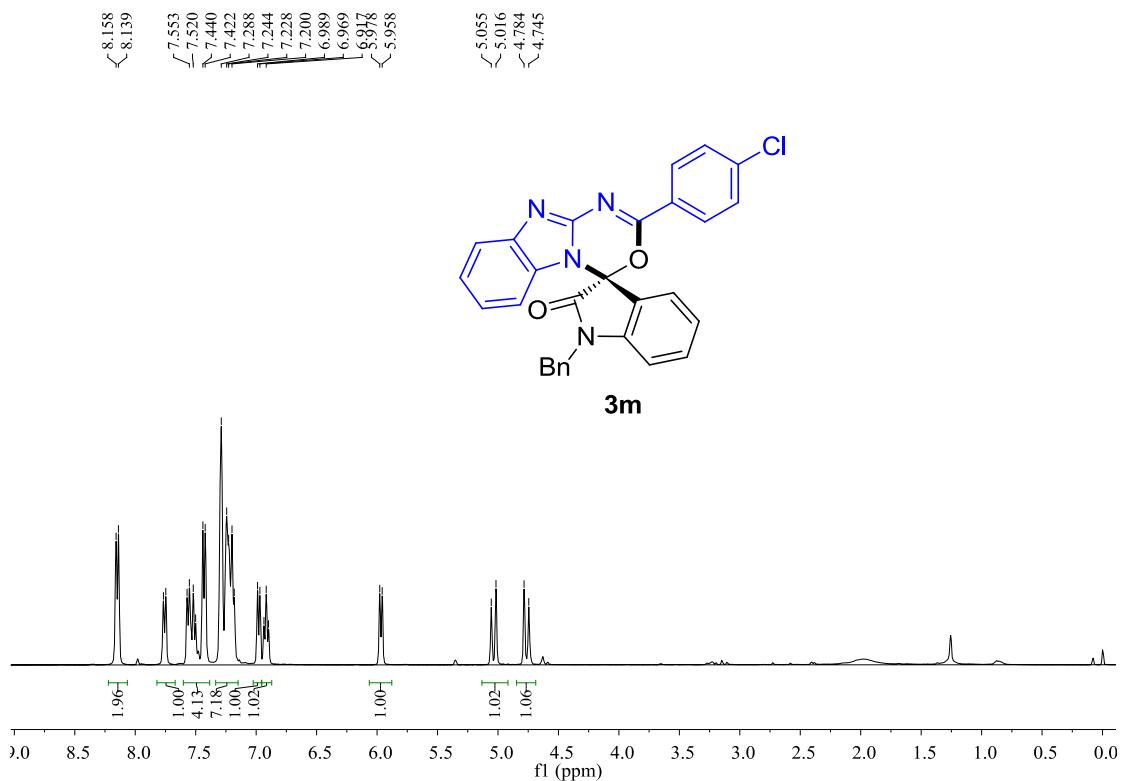
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 19.581 | 1568309 | 32604 | 48.836 | 54.383 |
| 2 | 21.678 | 1643079 | 27349 | 51.164 | 45.617 |
| Total | | 3211388 | 59953 | 100.000 | 100.000 |

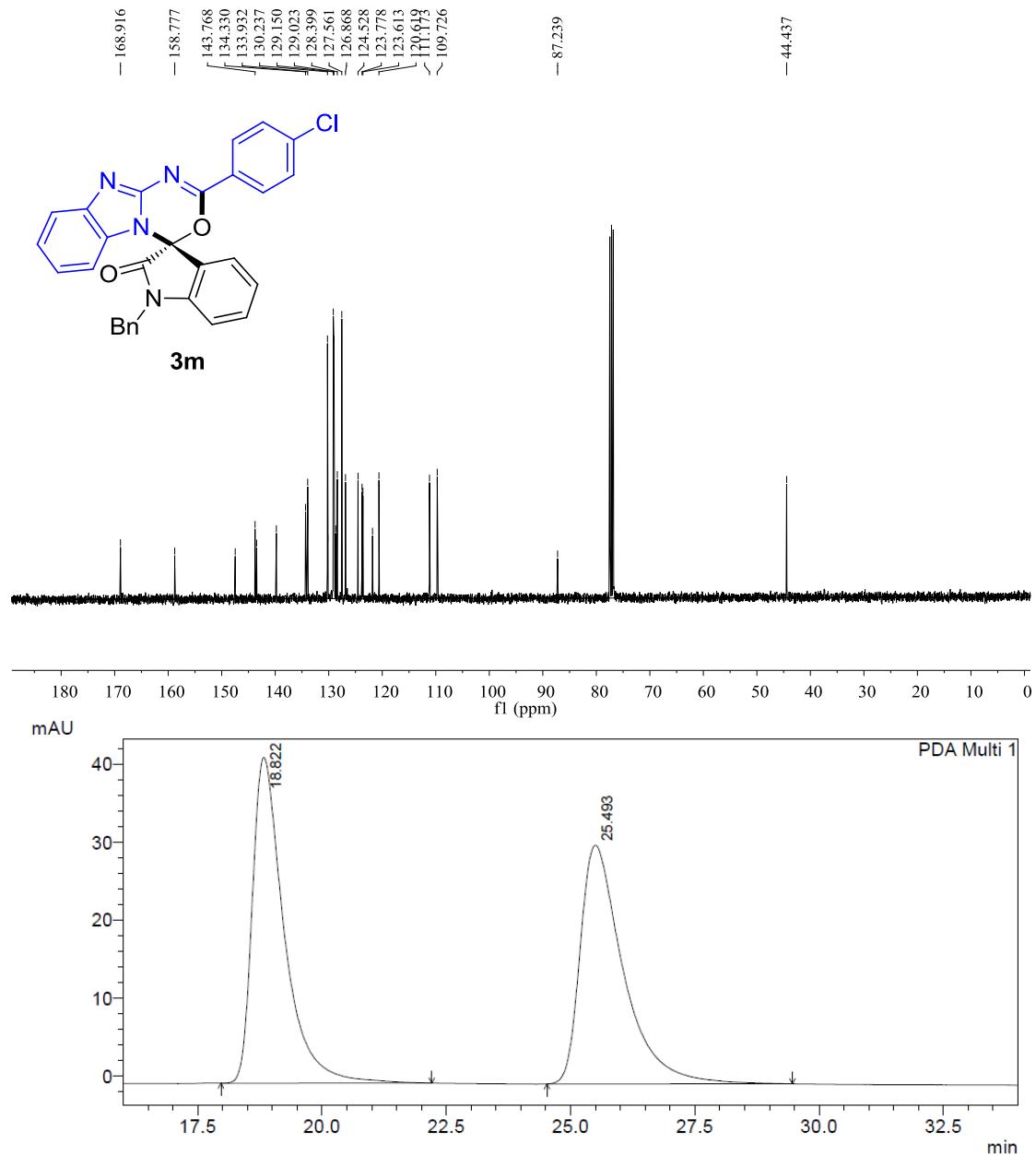




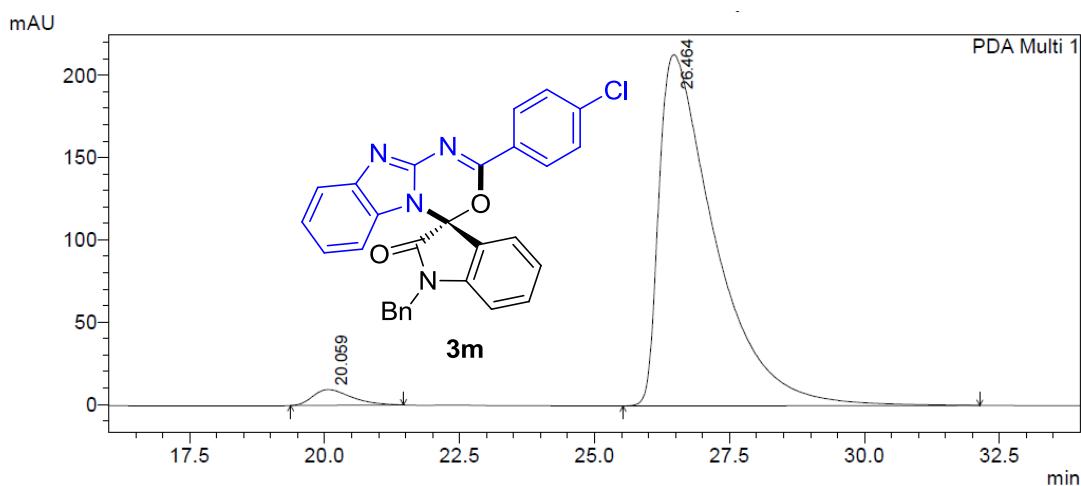


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 19.044 | 68046 | 1467 | 2.029 | 3.925 |
| 2 | 31.870 | 3286016 | 35902 | 97.971 | 96.075 |
| Total | | 3354062 | 37369 | 100.000 | 100.000 |

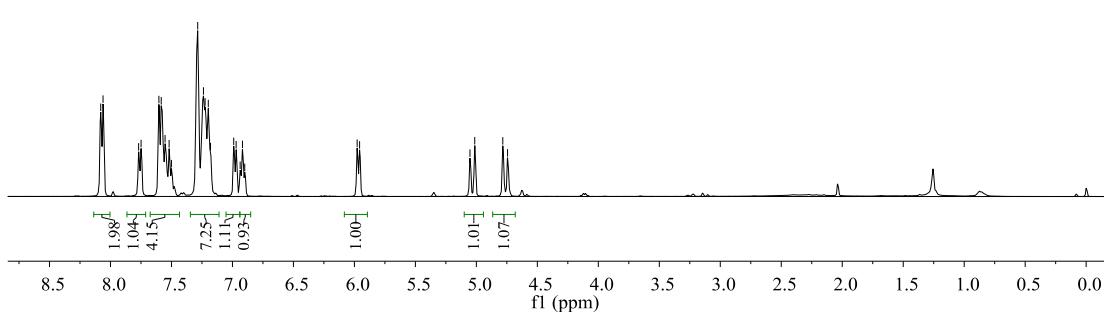
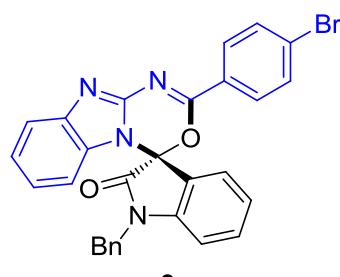


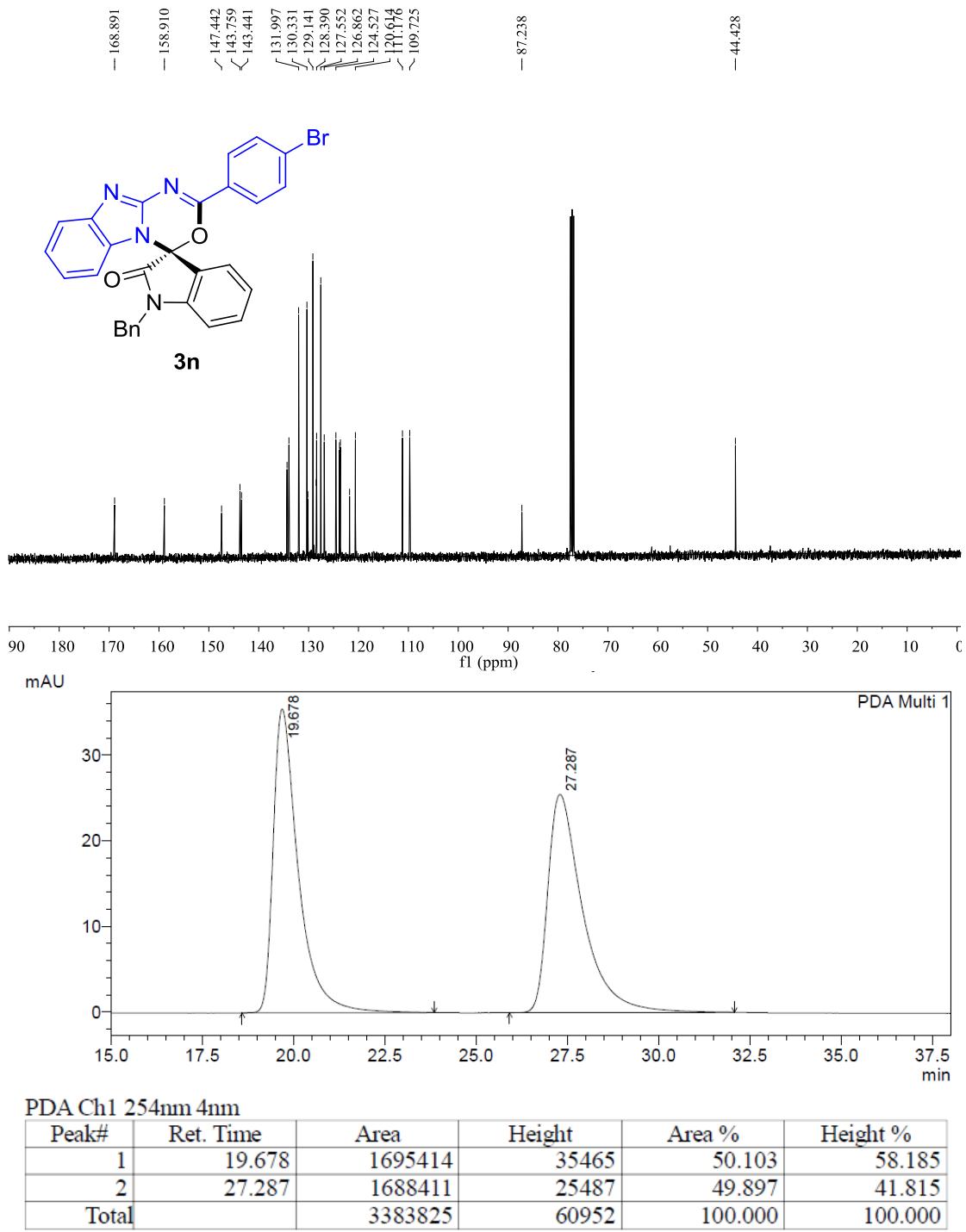


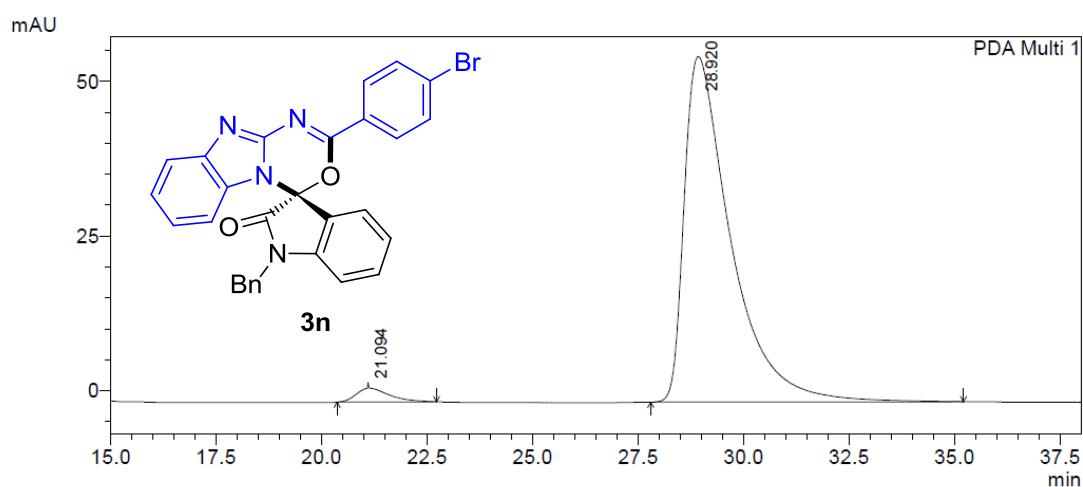
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 18.822 | 1856417 | 41777 | 50.108 | 57.720 |
| 2 | 25.493 | 1848411 | 30601 | 49.892 | 42.280 |
| Total | | 3704828 | 72378 | 100.000 | 100.000 |



| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|----------|--------|---------|----------|
| 1 | 20.059 | 481872 | 9634 | 3.028 | 4.321 |
| 2 | 26.464 | 15432635 | 213305 | 96.972 | 95.679 |
| Total | | 15914507 | 222939 | 100.000 | 100.000 |





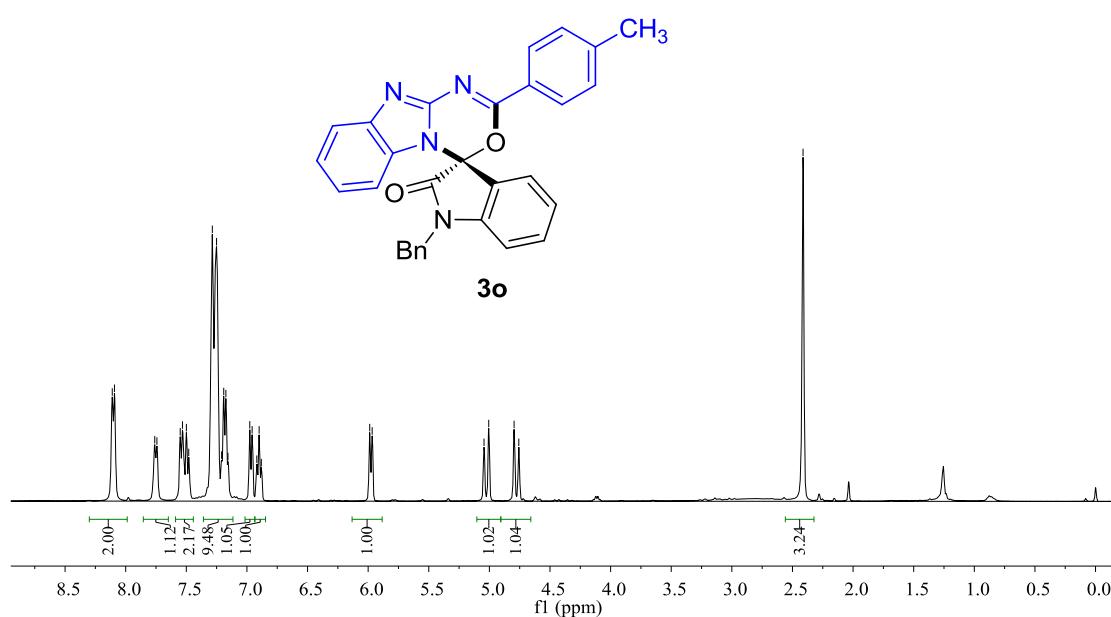


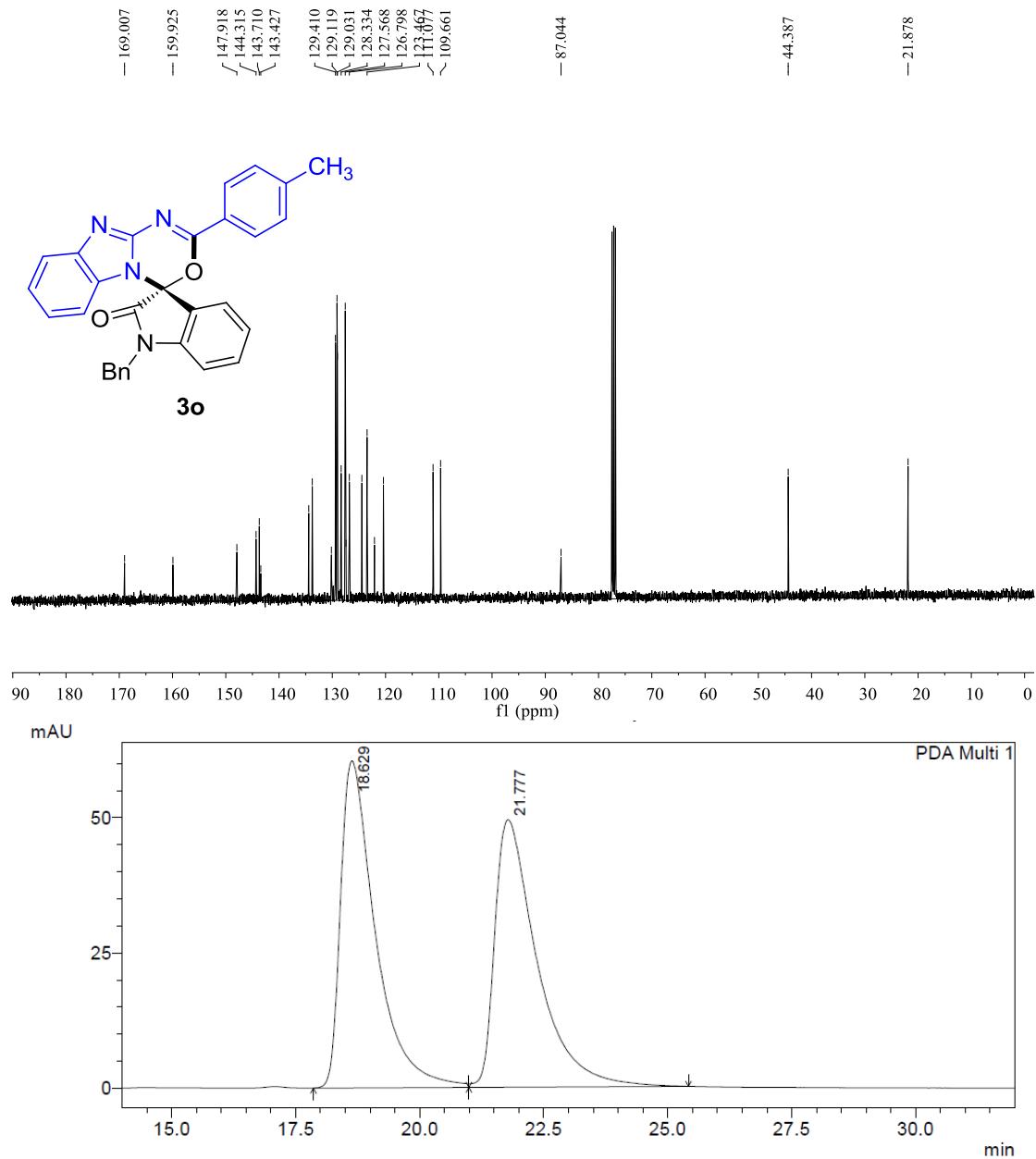
PDA Ch1 254nm 4nm

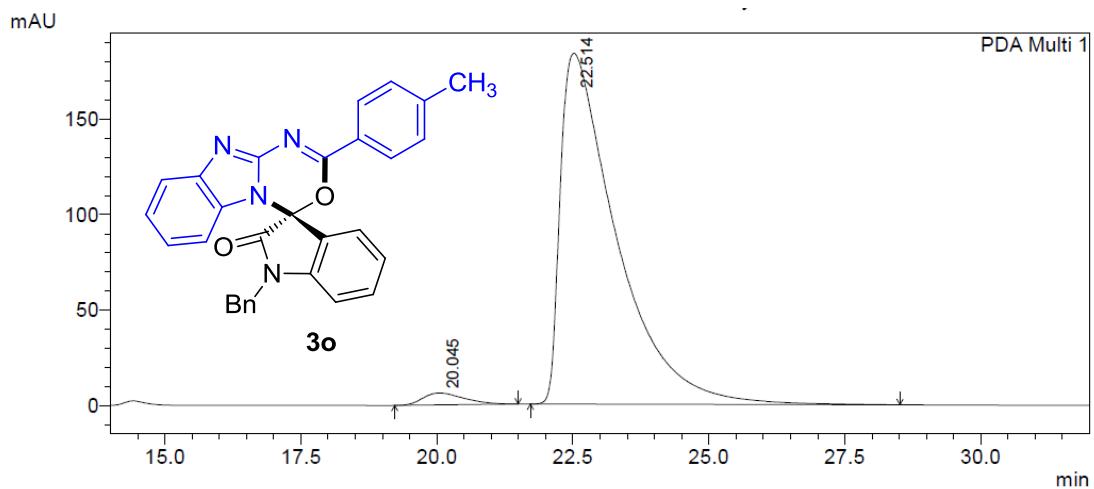
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 21.094 | 122032 | 3141 | 2.768 | 5.326 |
| 2 | 28.920 | 4286951 | 55834 | 97.232 | 94.674 |
| Total | | 4408983 | 58975 | 100.000 | 100.000 |

8.111 8.093 7.760 7.532 7.499 7.285 7.251 7.191 7.174 6.957 6.999 5.967
5.044 5.005 4.796 4.757

-2.413





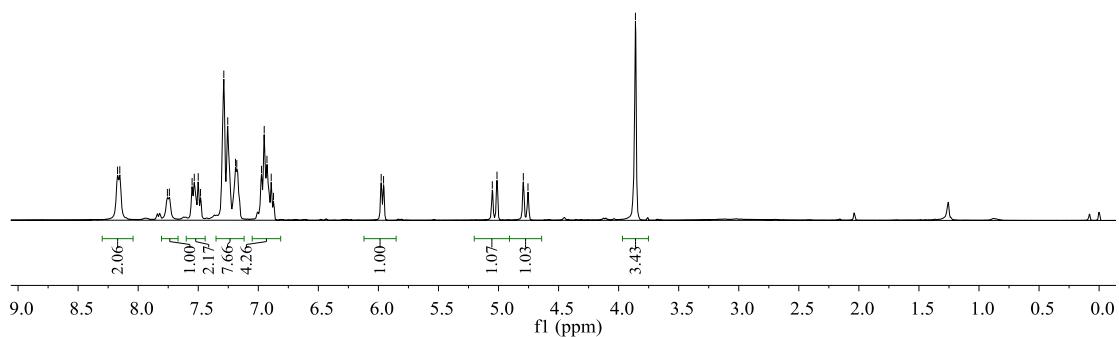
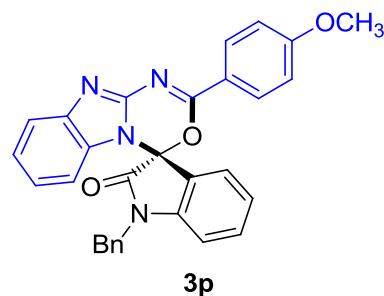


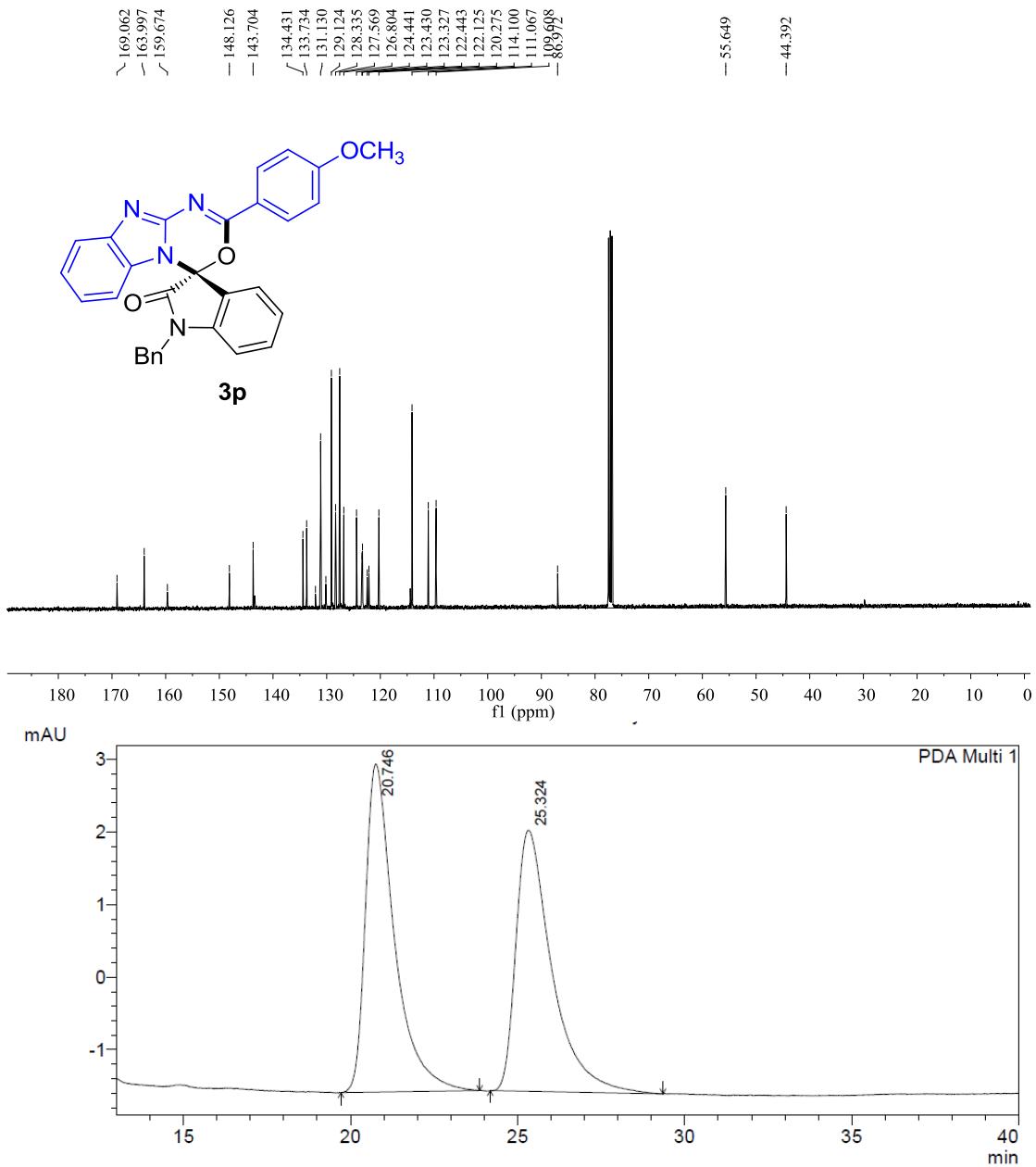
PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|----------|--------|---------|----------|
| 1 | 20.045 | 332820 | 6265 | 2.453 | 3.295 |
| 2 | 22.514 | 13235873 | 183859 | 97.547 | 96.705 |
| Total | | 13568692 | 190124 | 100.000 | 100.000 |

8.172 7.551 7.533 7.500 7.287 7.255 7.190 7.179 6.973 6.951 6.928 6.902 5.957
 5.052 5.013 4.794 4.755

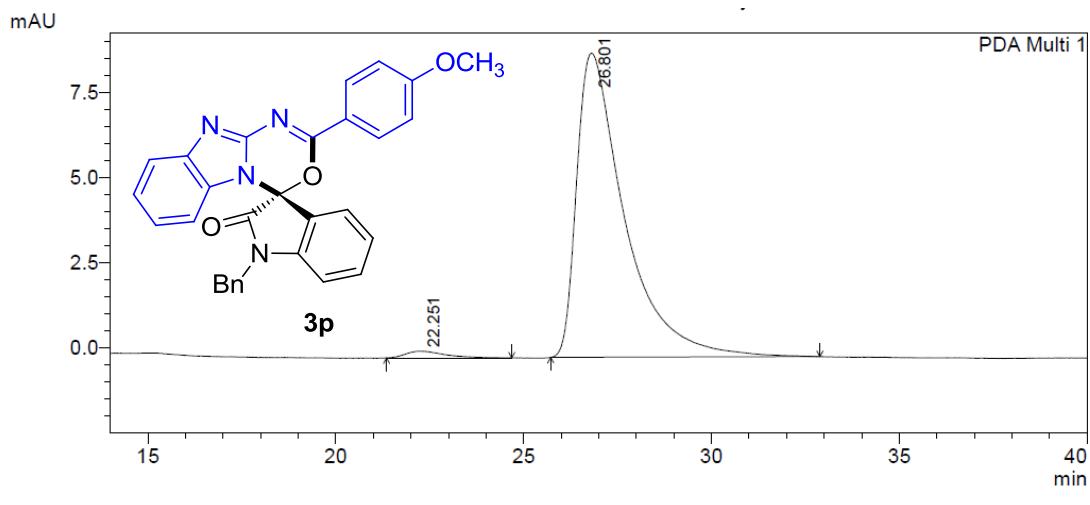
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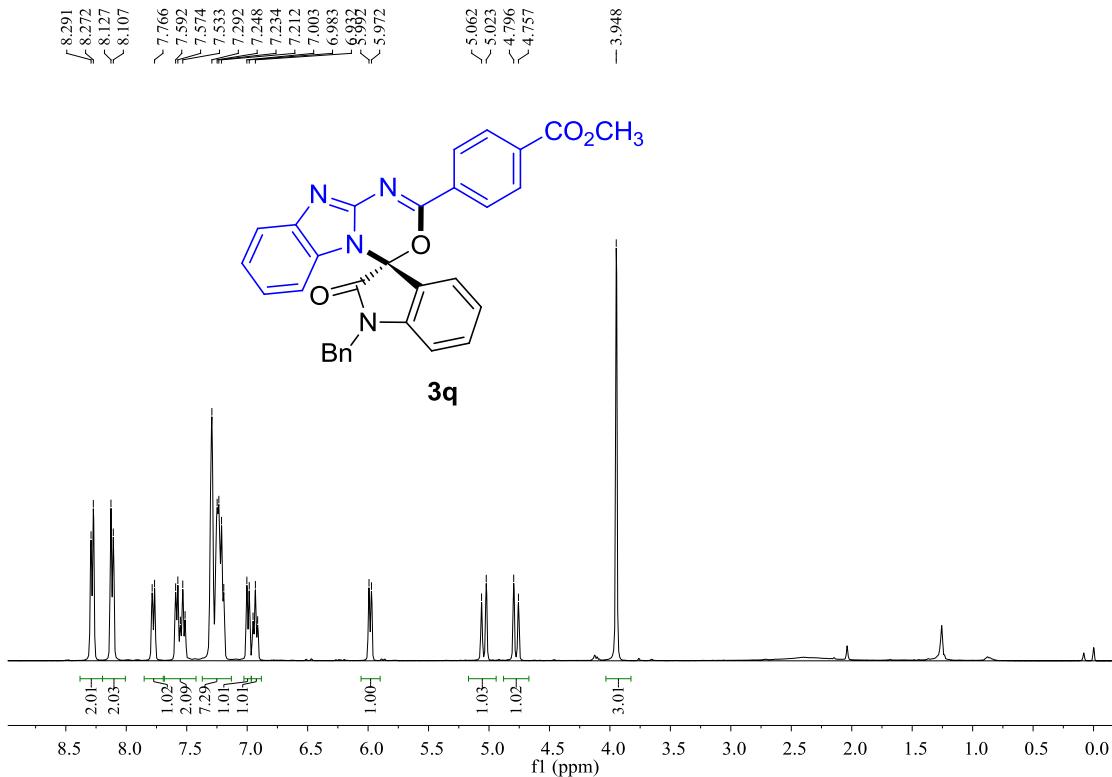
PDA Ch1 254nm 4nm

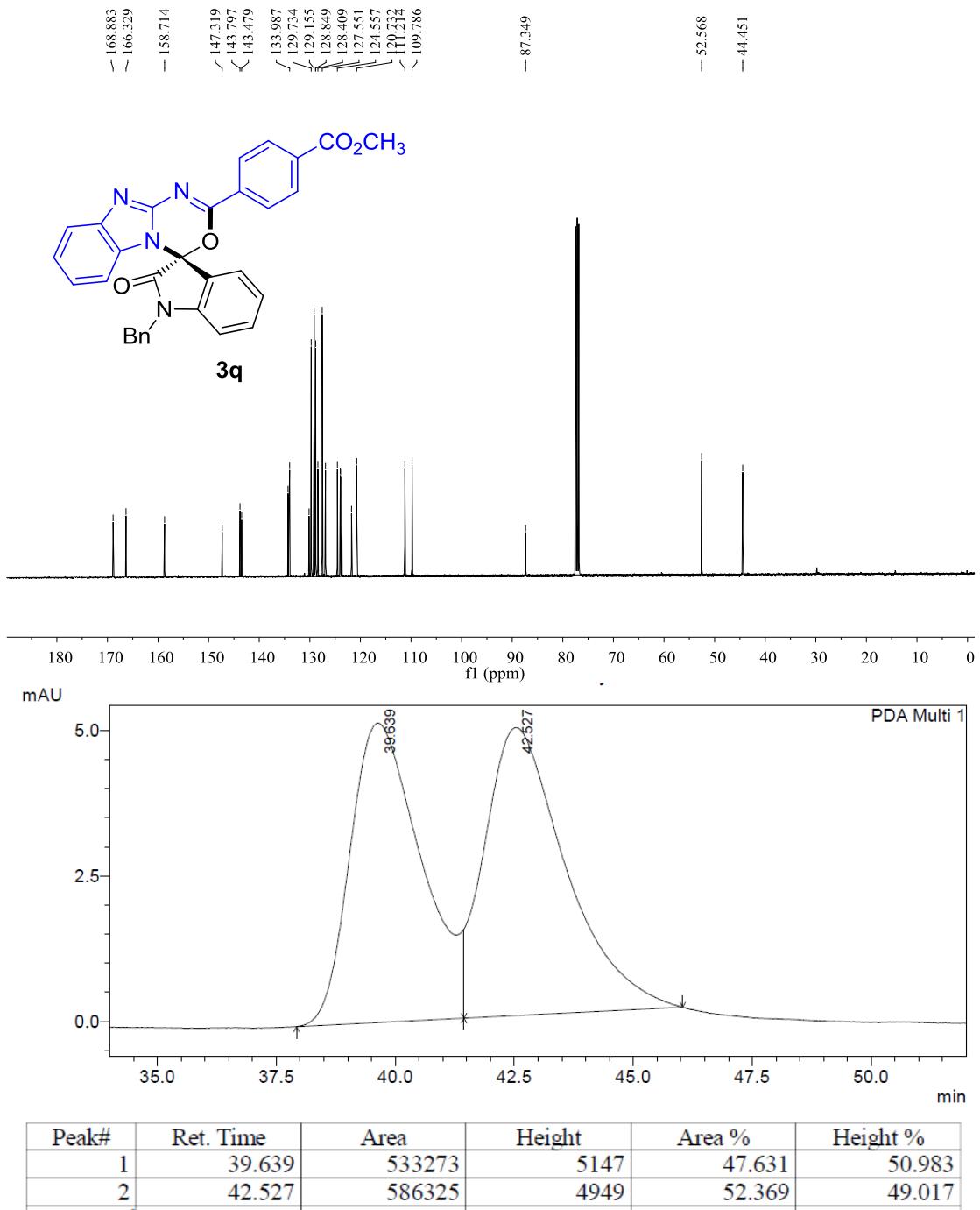
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1 | 20.746 | 272482 | 4519 | 50.345 | 55.657 |
| 2 | 25.324 | 268747 | 3601 | 49.655 | 44.343 |
| Total | | 541229 | 8120 | 100.000 | 100.000 |

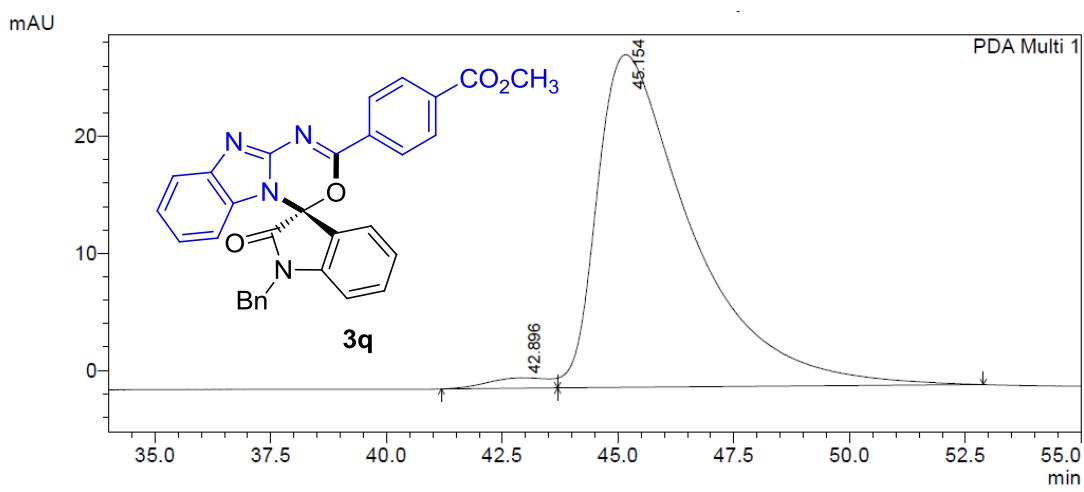


PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1 | 22.251 | 14594 | 202 | 1.808 | 2.209 |
| 2 | 26.801 | 792387 | 8931 | 98.192 | 97.791 |
| Total | | 806981 | 9133 | 100.000 | 100.000 |





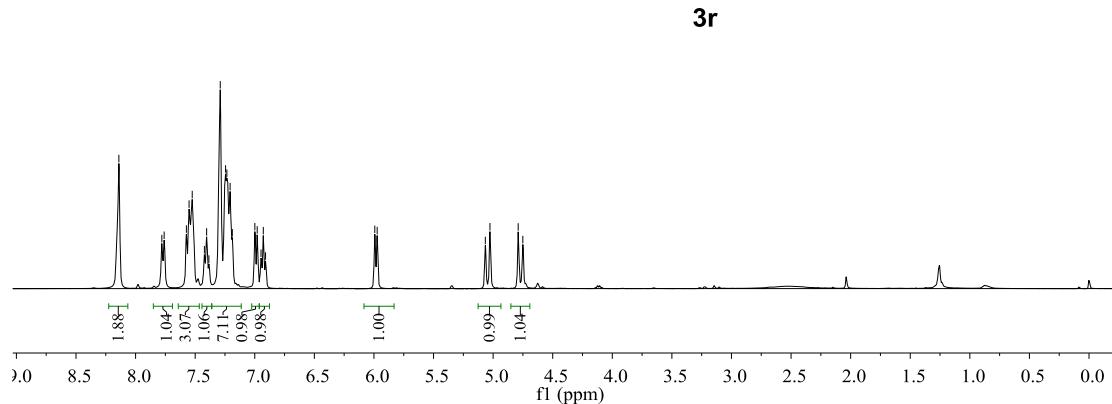
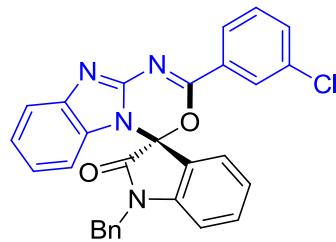


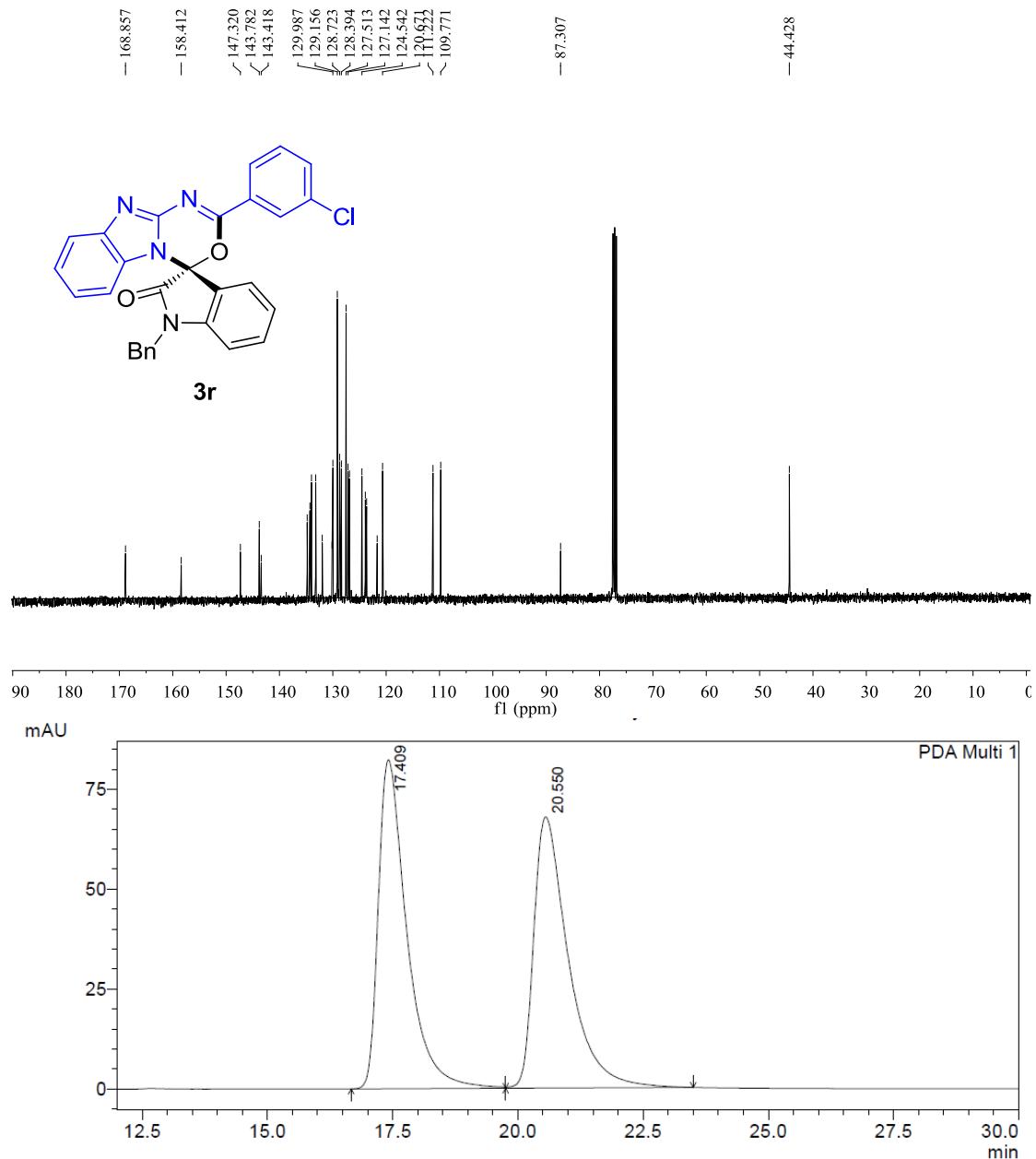
PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 42.896 | 83216 | 902 | 2.010 | 3.078 |
| 2 | 45.154 | 4057890 | 28412 | 97.990 | 96.922 |
| Total | | 4141106 | 29315 | 100.000 | 100.000 |

-8.140
-7.574
-7.551
-7.525
-7.404
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-7.245
-7.234
-7.207
-7.188
-6.999
-6.980
-6.938
-5.973

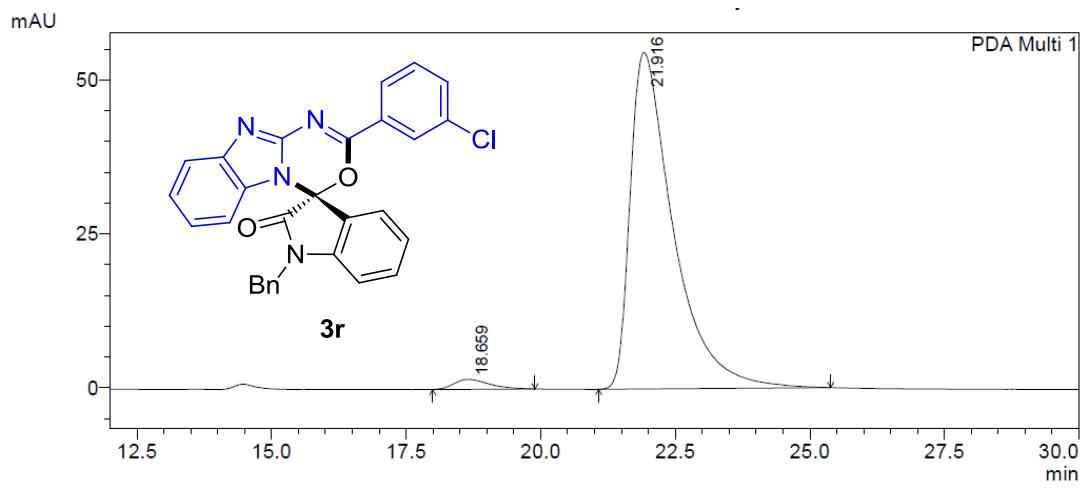
5.065
5.027
4.790
4.751



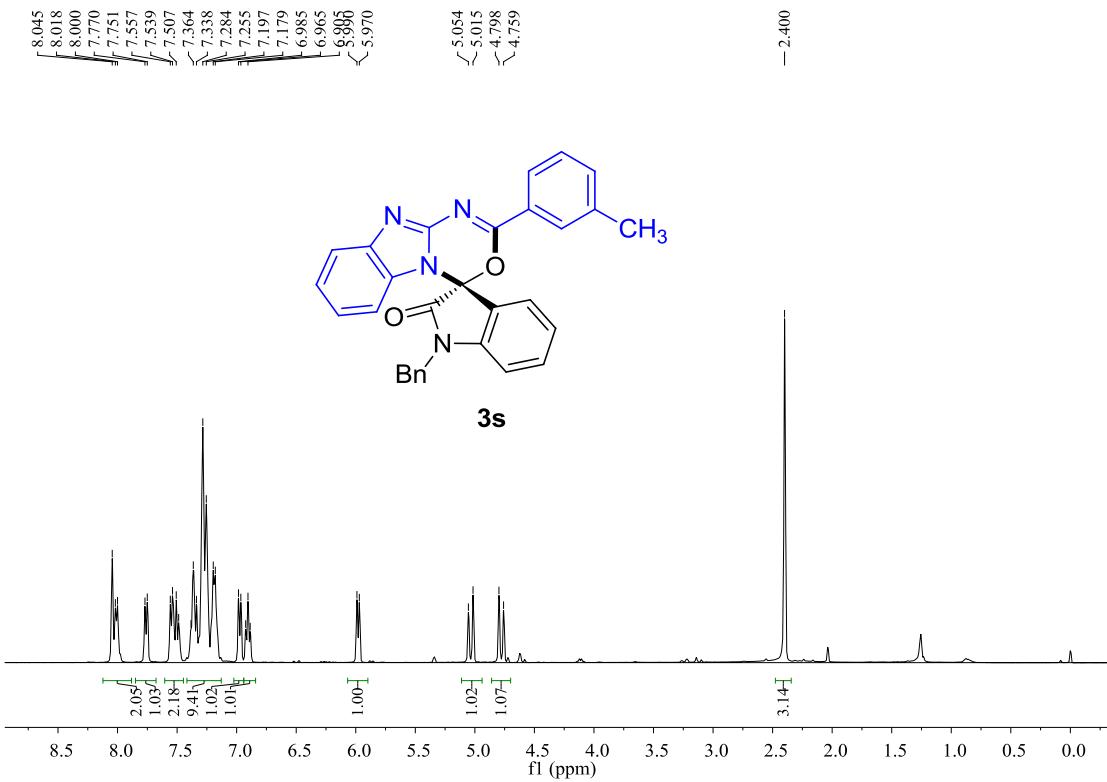


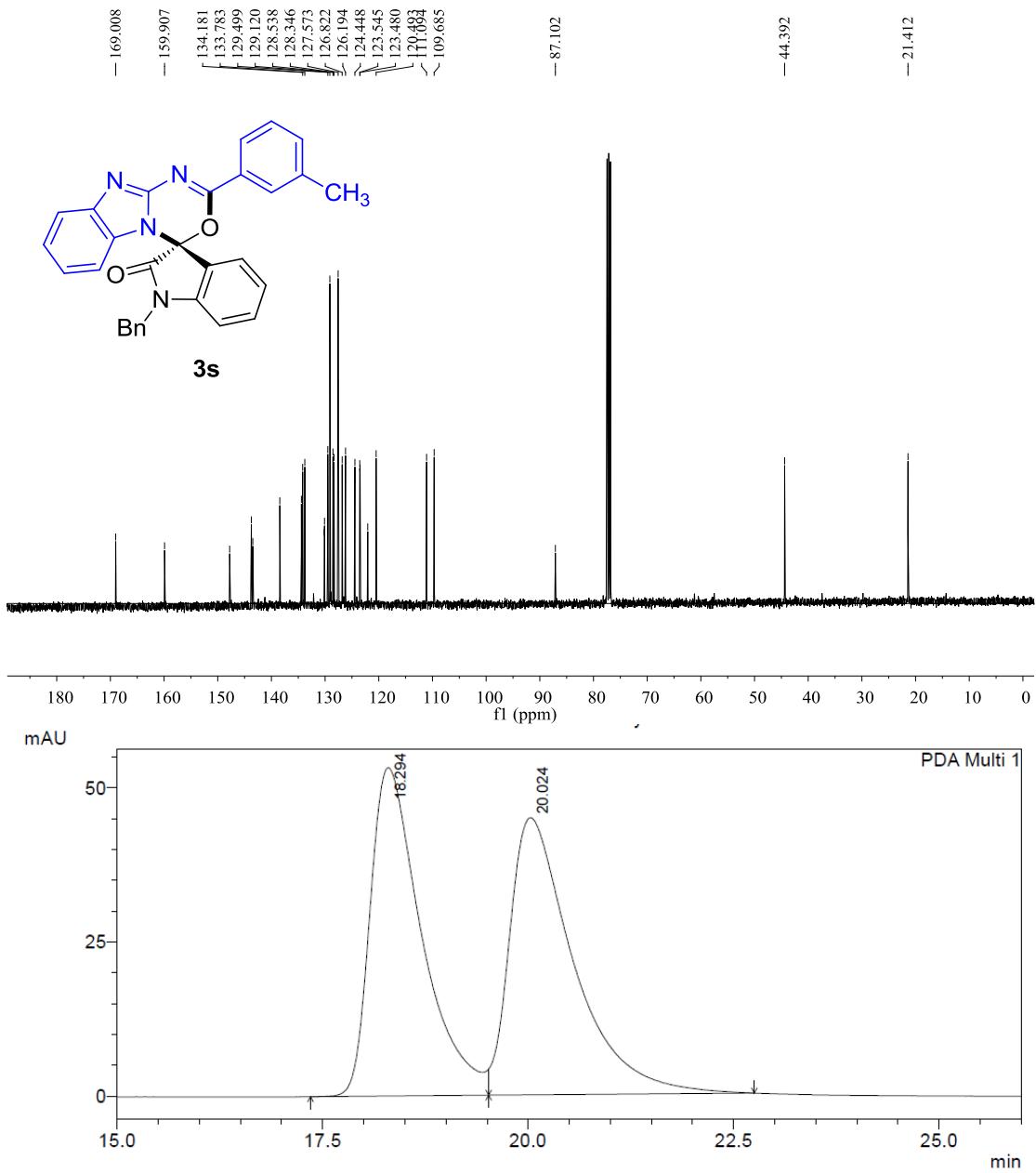
PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 17.409 | 3263748 | 82286 | 50.078 | 54.816 |
| 2 | 20.550 | 3253596 | 67828 | 49.922 | 45.184 |
| Total | | 6517344 | 150114 | 100.000 | 100.000 |



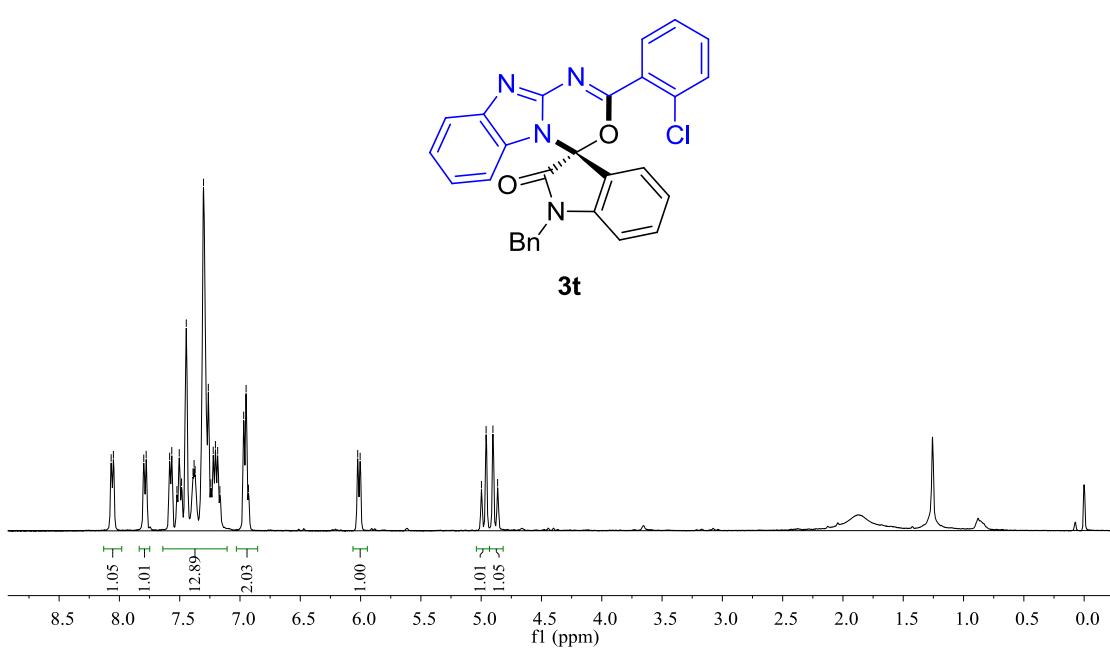
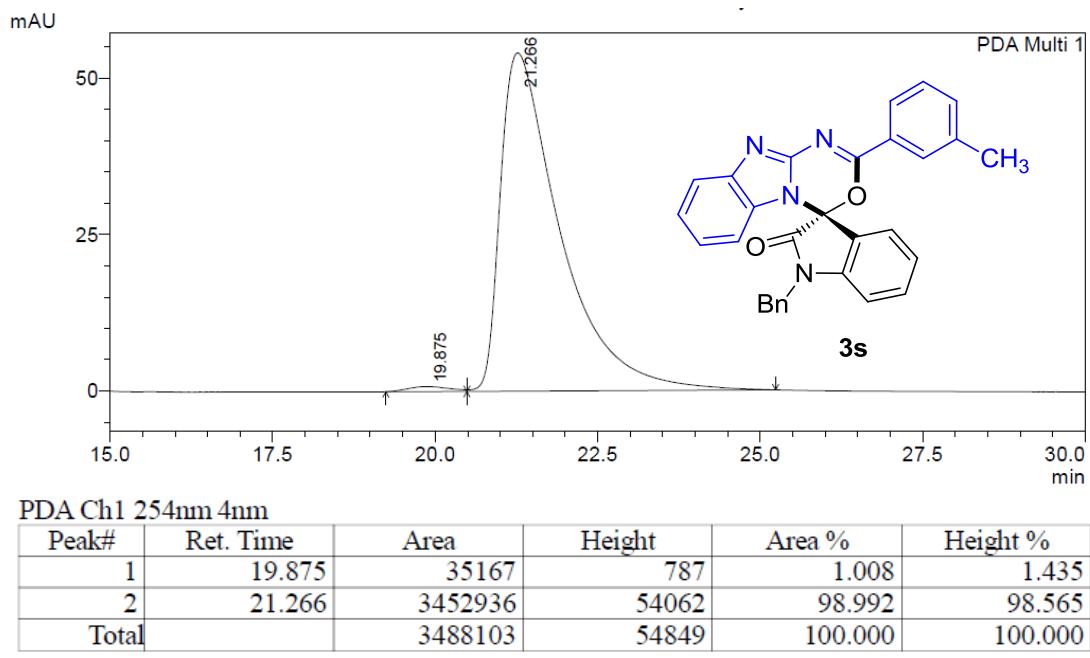
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 18.659 | 74199 | 1630 | 2.368 | 2.895 |
| 2 | 21.916 | 3059424 | 54681 | 97.632 | 97.105 |
| Total | | 3133623 | 56311 | 100.000 | 100.000 |

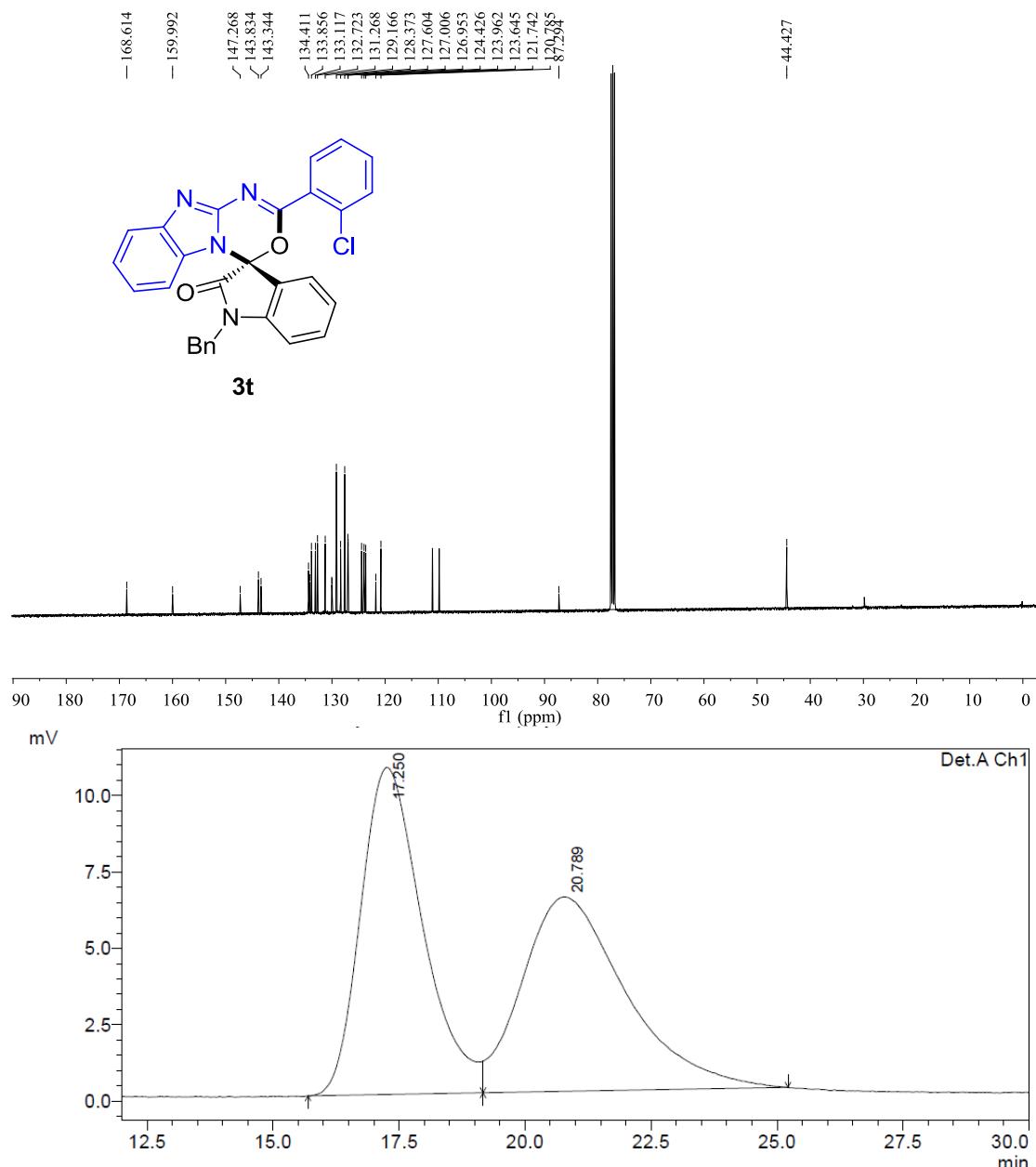




PDA Ch1 254nm 4nm

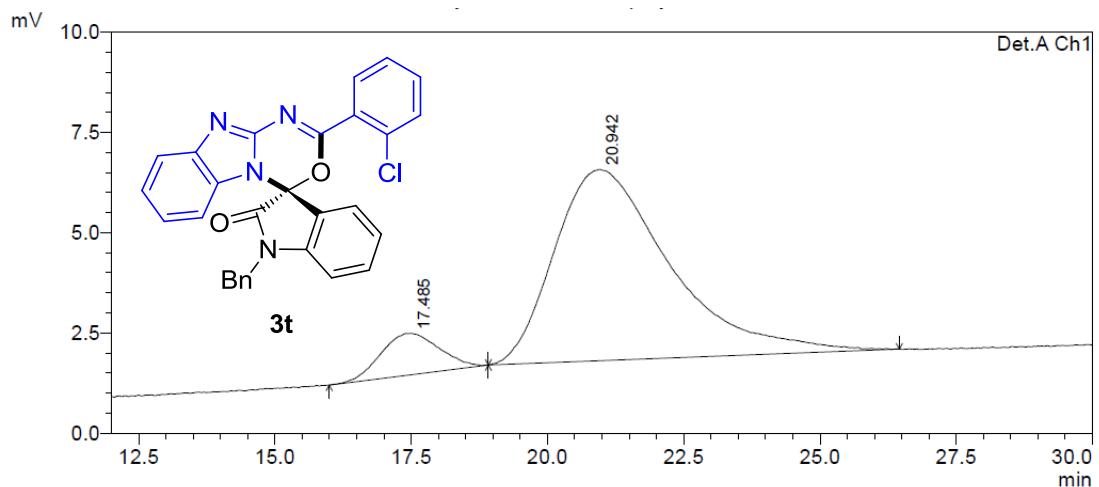
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 18.294 | 2311022 | 53224 | 48.841 | 54.220 |
| 2 | 20.024 | 2420739 | 44939 | 51.159 | 45.780 |
| Total | | 4731761 | 98163 | 100.000 | 100.000 |





Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 17.250 | 914048 | 10700 | 50.138 | 62.731 |
| 2 | 20.789 | 909016 | 6357 | 49.862 | 37.269 |
| Total | | 1823064 | 17057 | 100.000 | 100.000 |

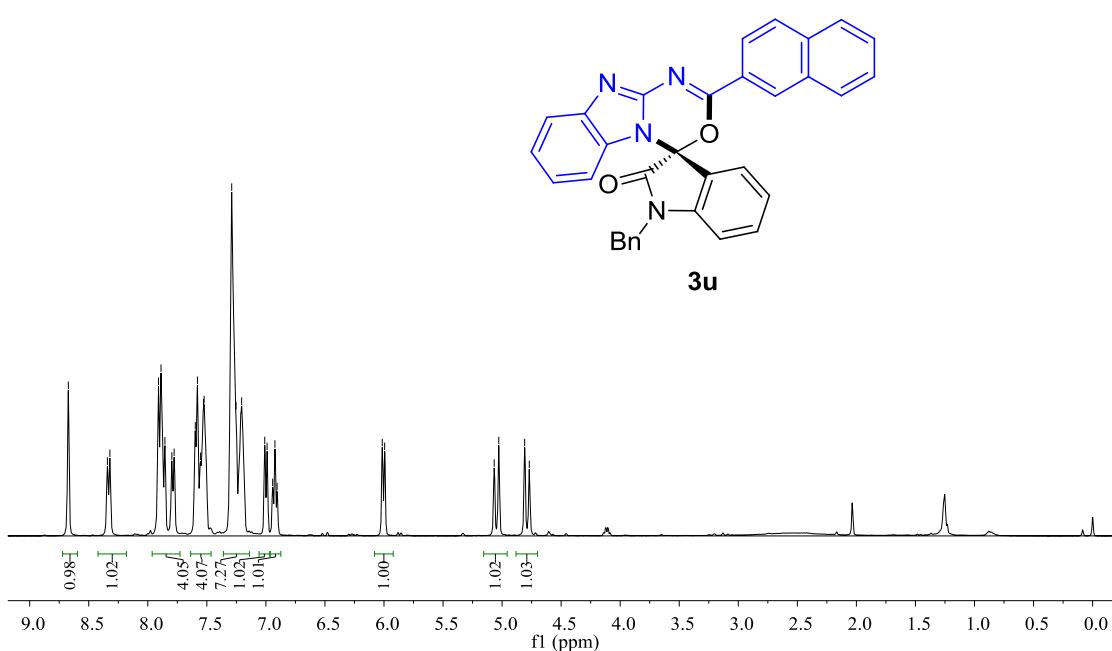
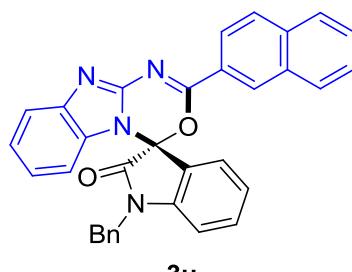


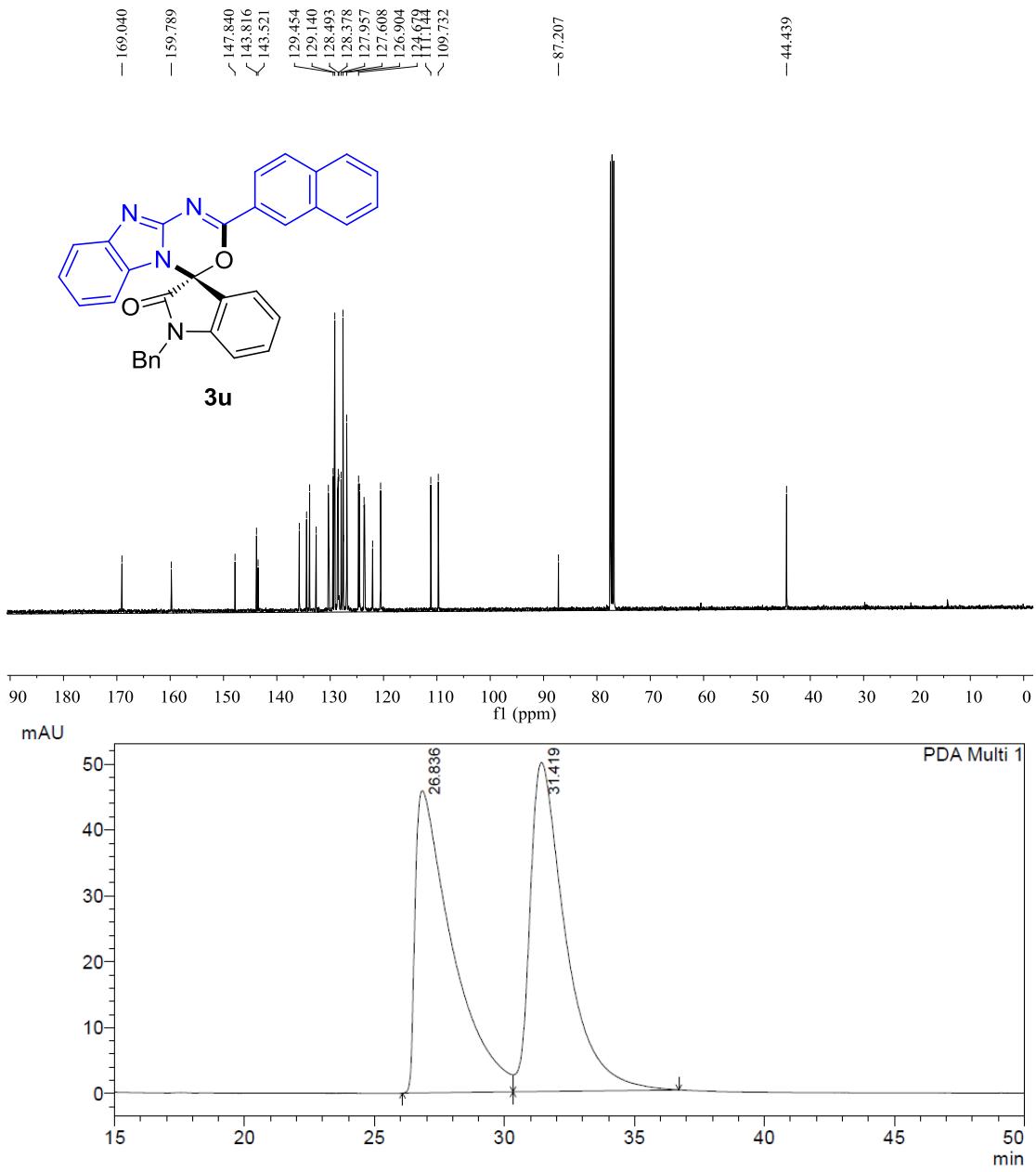
Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1 | 17.485 | 77191 | 1034 | 9.886 | 17.831 |
| 2 | 20.942 | 703644 | 4765 | 90.114 | 82.169 |
| Total | | 780836 | 5798 | 100.000 | 100.000 |

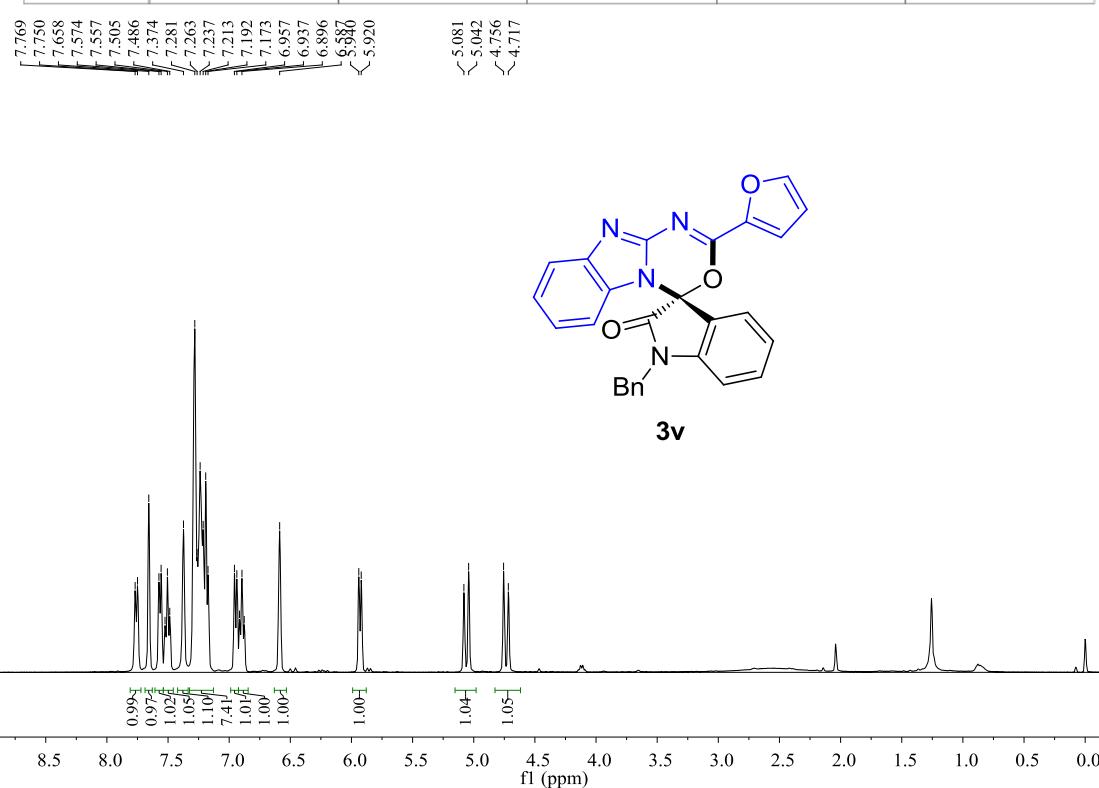
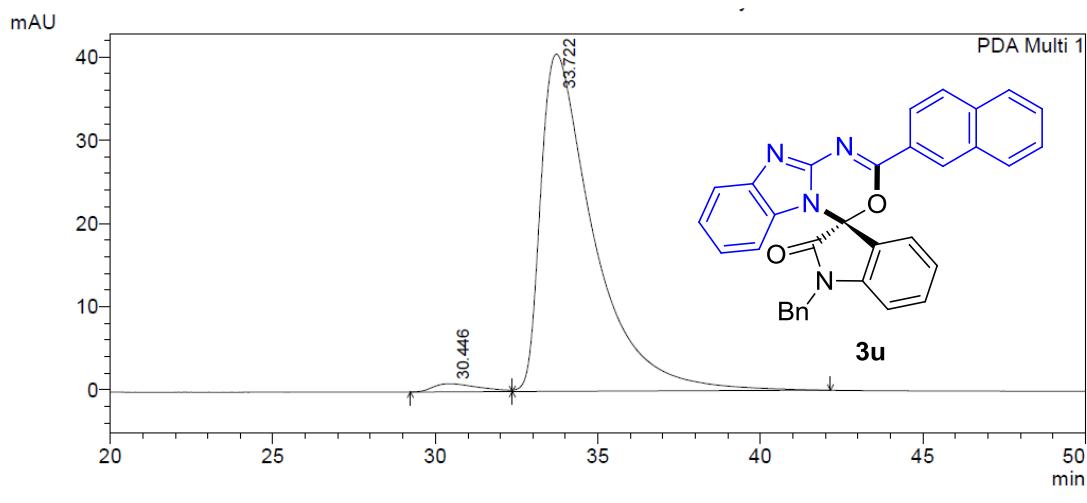
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<8.321
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7.580
7.523
7.522
7.205
7.010
6.924
6.803
<5.995

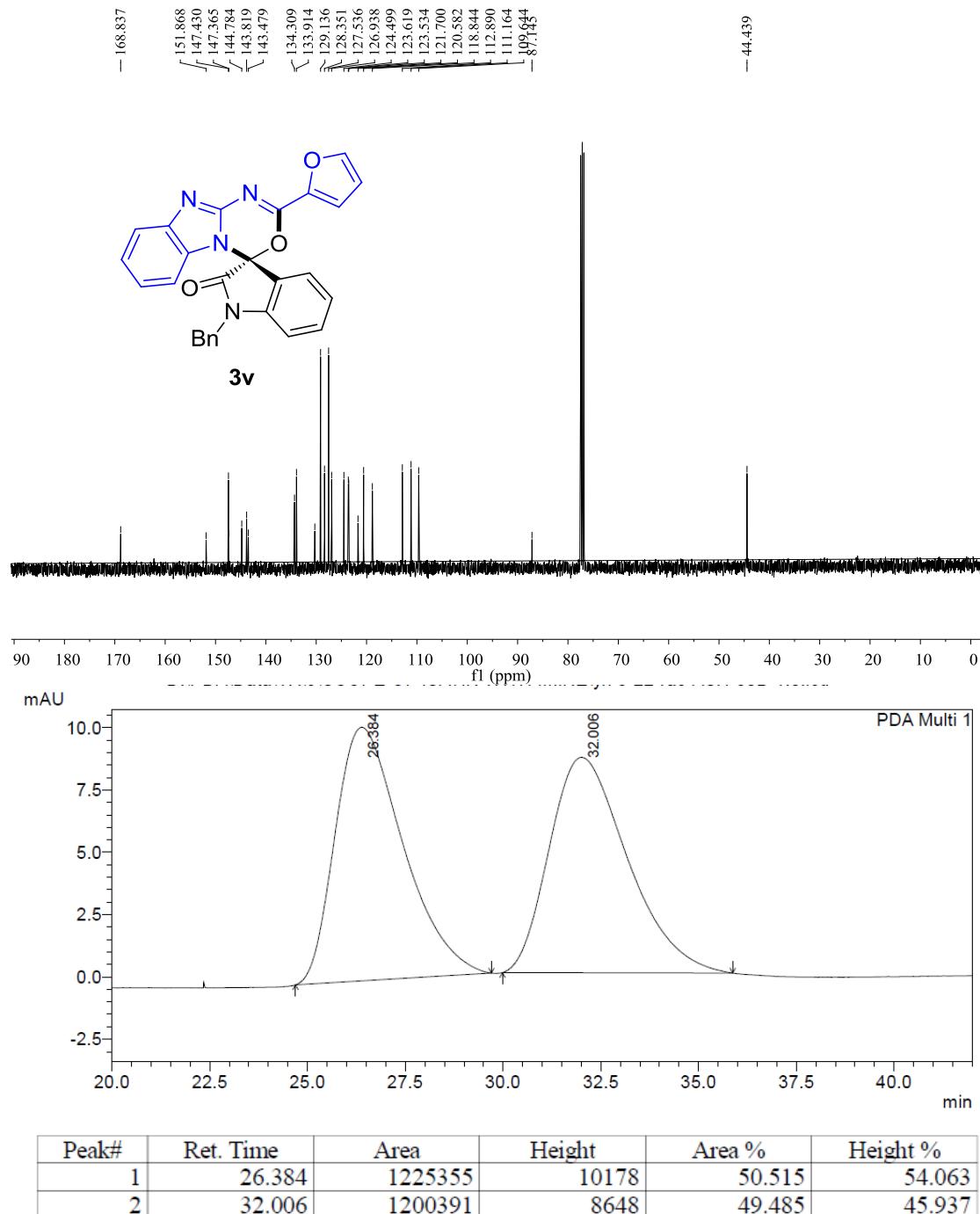
5.067
5.028
4.809
<4.770

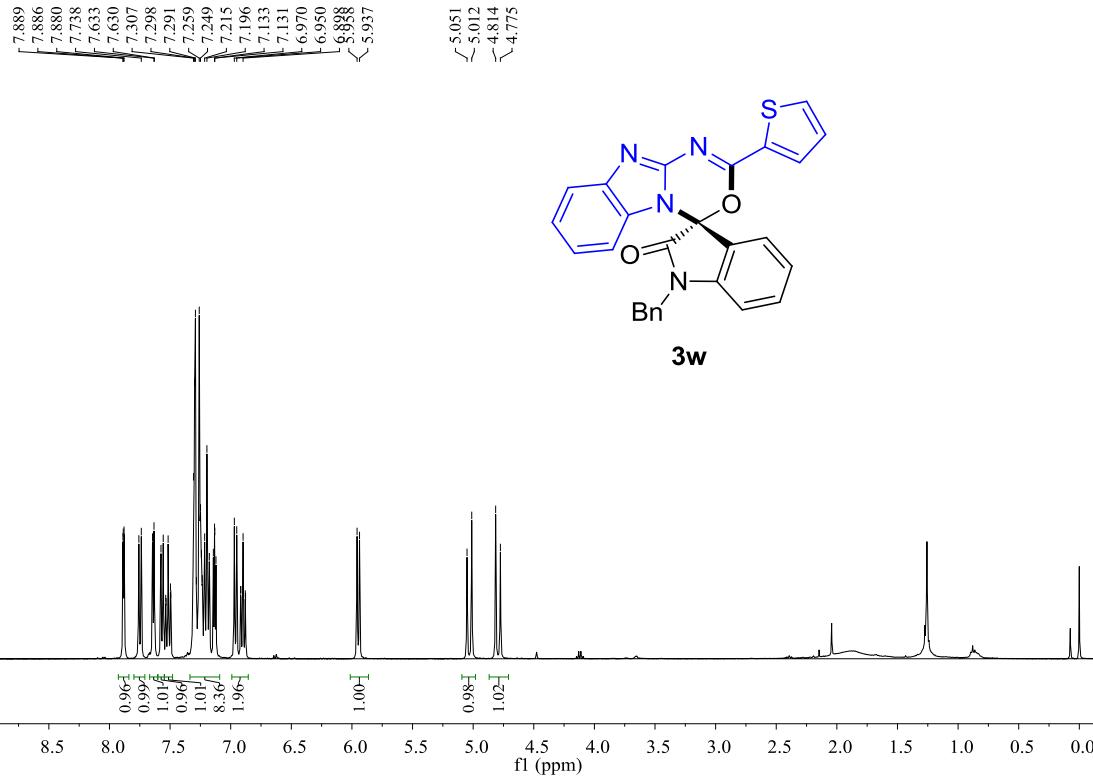
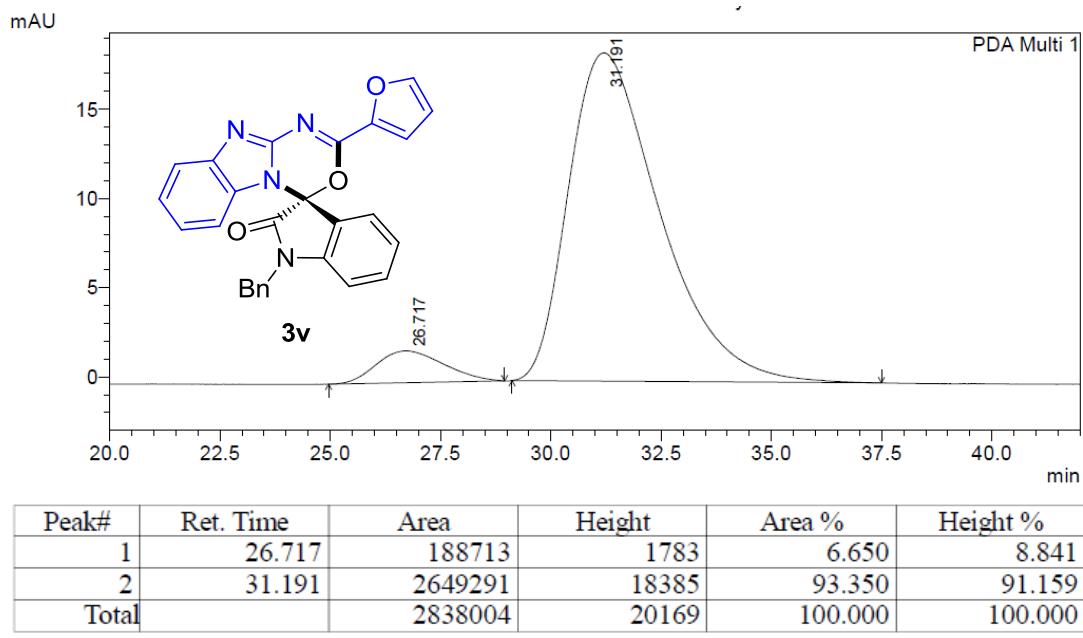


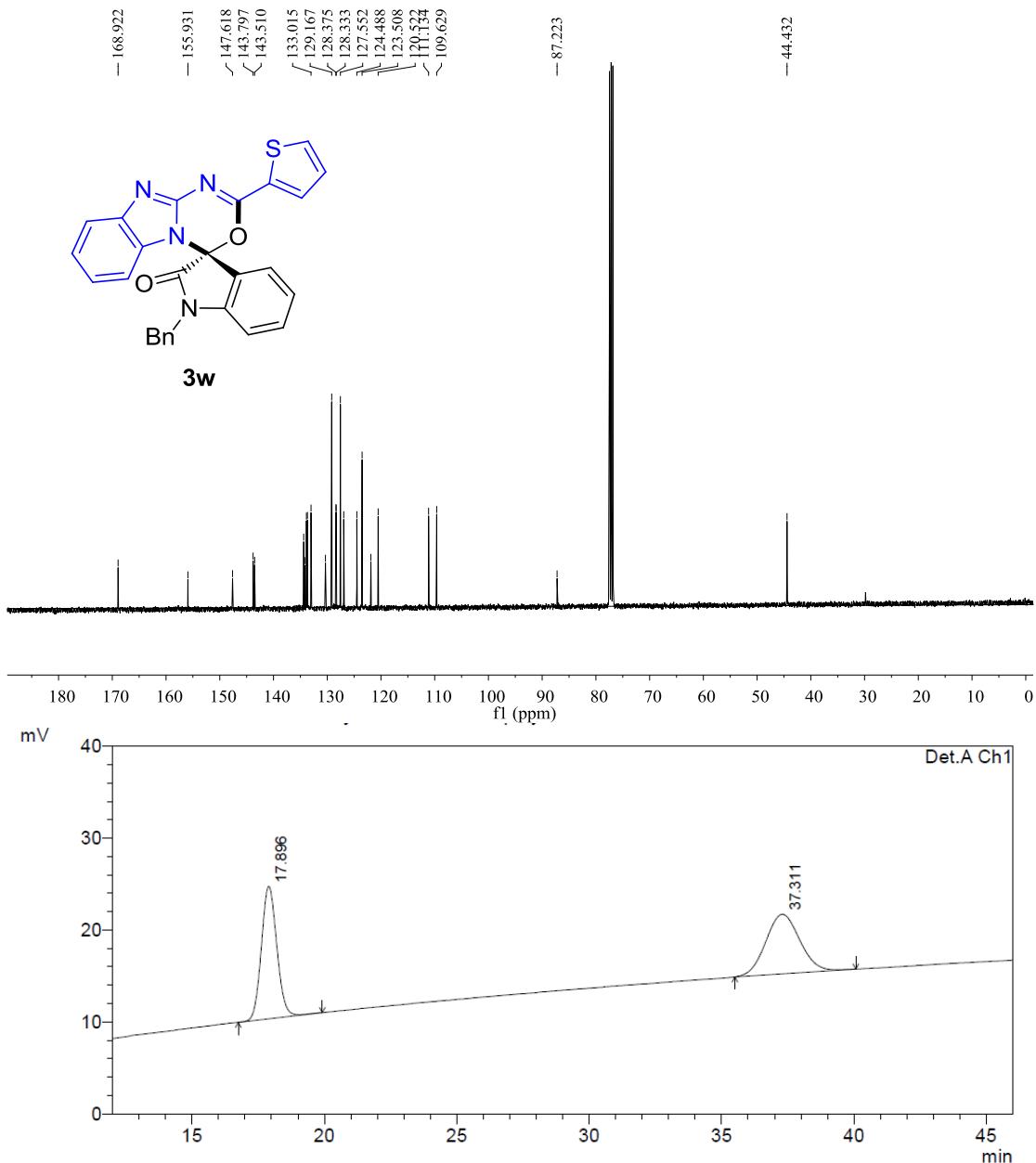


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 26.836 | 4524812 | 45868 | 48.708 | 47.873 |
| 2 | 31.419 | 4764915 | 49944 | 51.292 | 52.127 |
| Total | | 9289727 | 95812 | 100.000 | 100.000 |



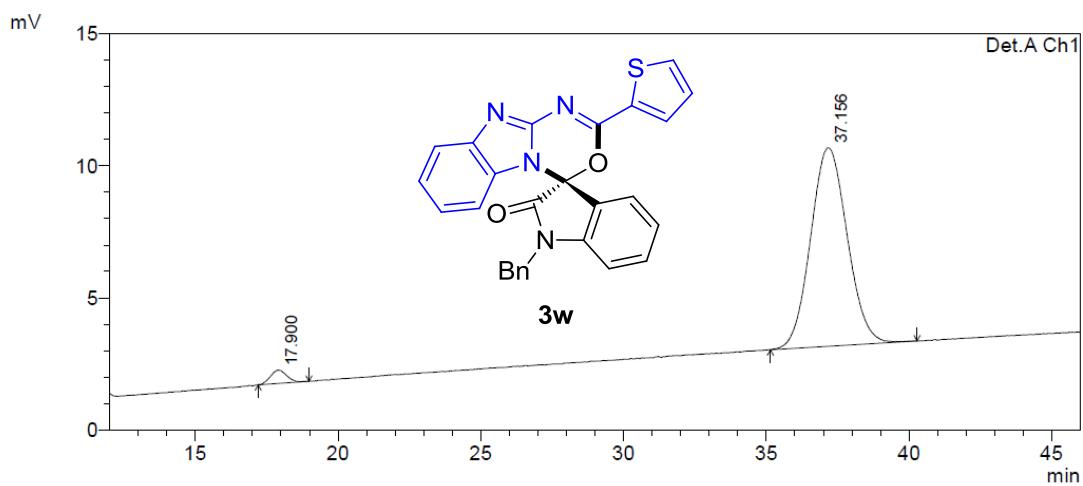






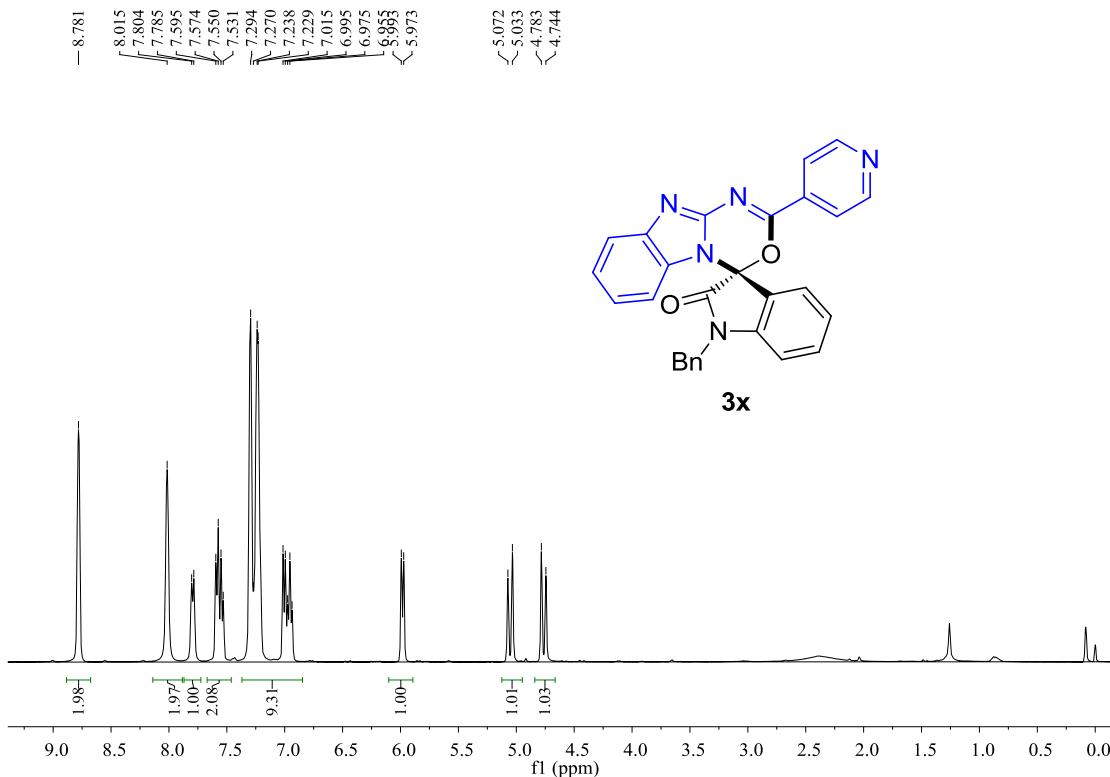
Detector A Ch1 254nm

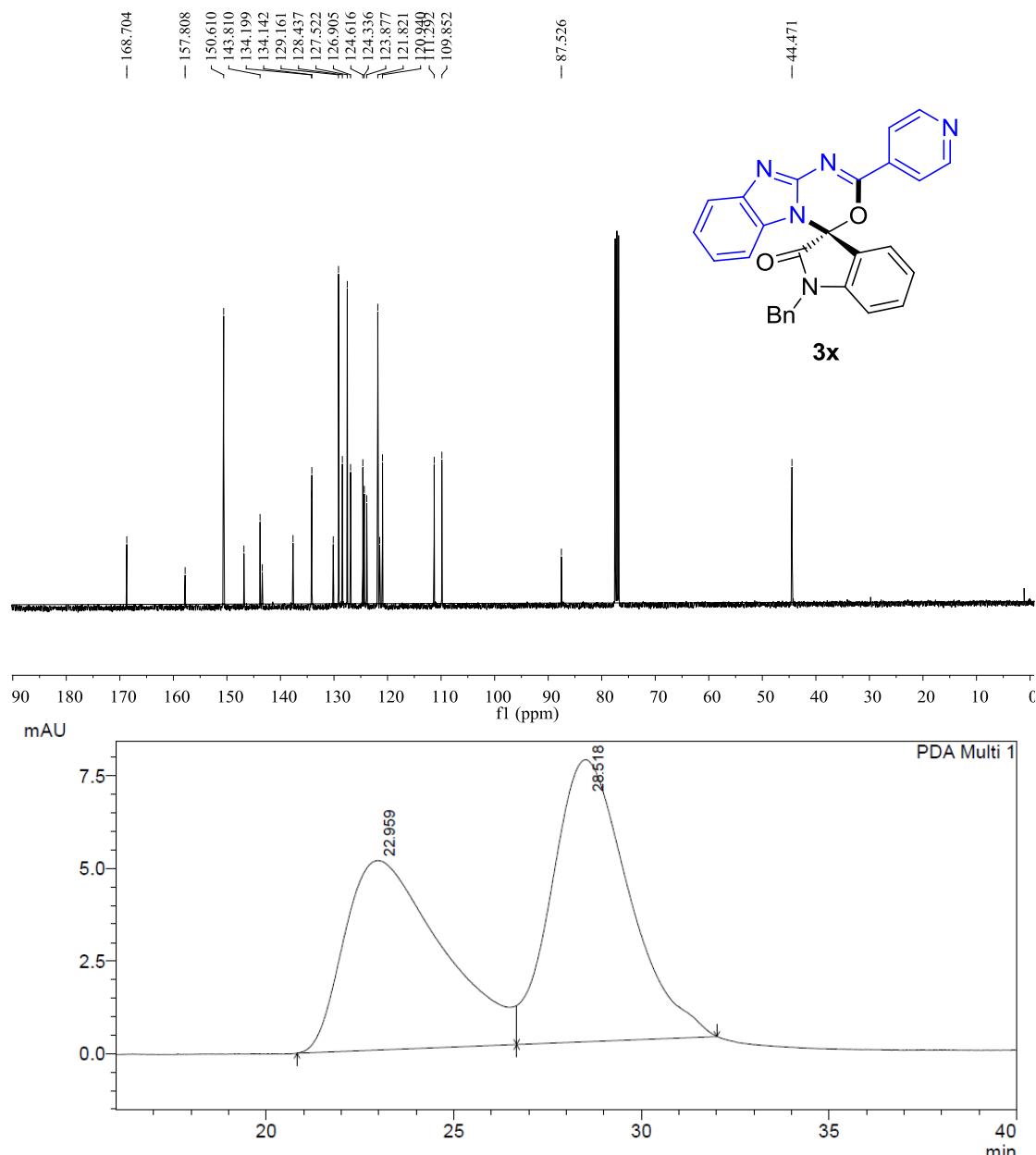
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 17.896 | 584047 | 14401 | 50.238 | 68.979 |
| 2 | 37.311 | 578522 | 6476 | 49.762 | 31.021 |
| Total | | 1162569 | 20878 | 100.000 | 100.000 |

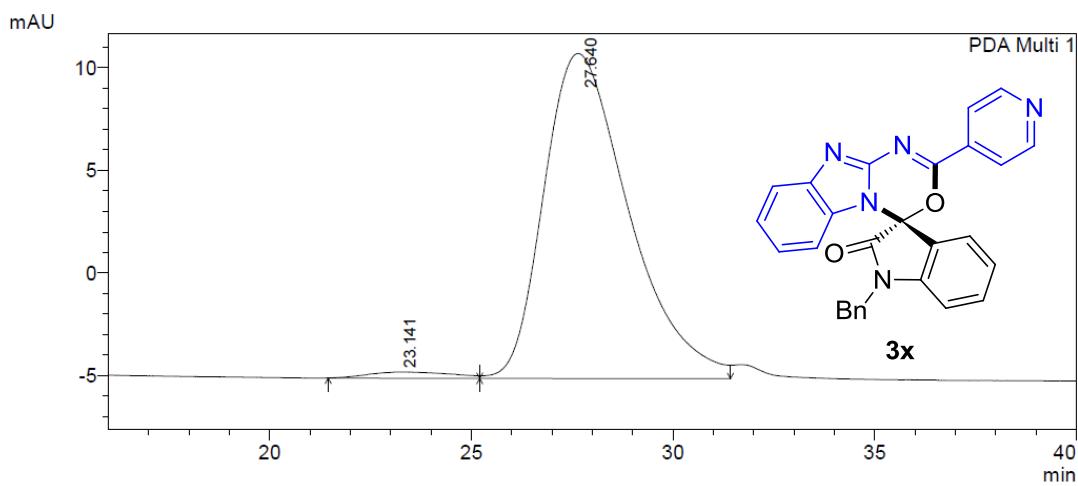


Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1 | 17.900 | 19814 | 505 | 2.873 | 6.299 |
| 2 | 37.156 | 669914 | 7515 | 97.127 | 93.701 |
| Total | | 689728 | 8020 | 100.000 | 100.000 |



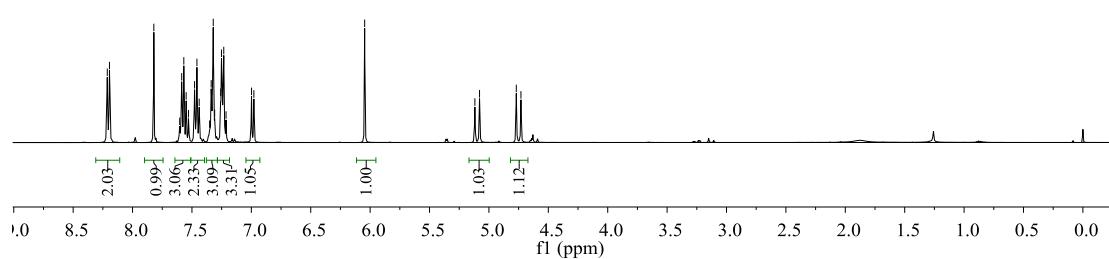
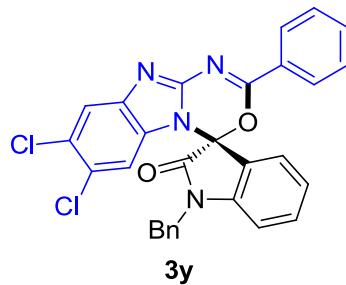


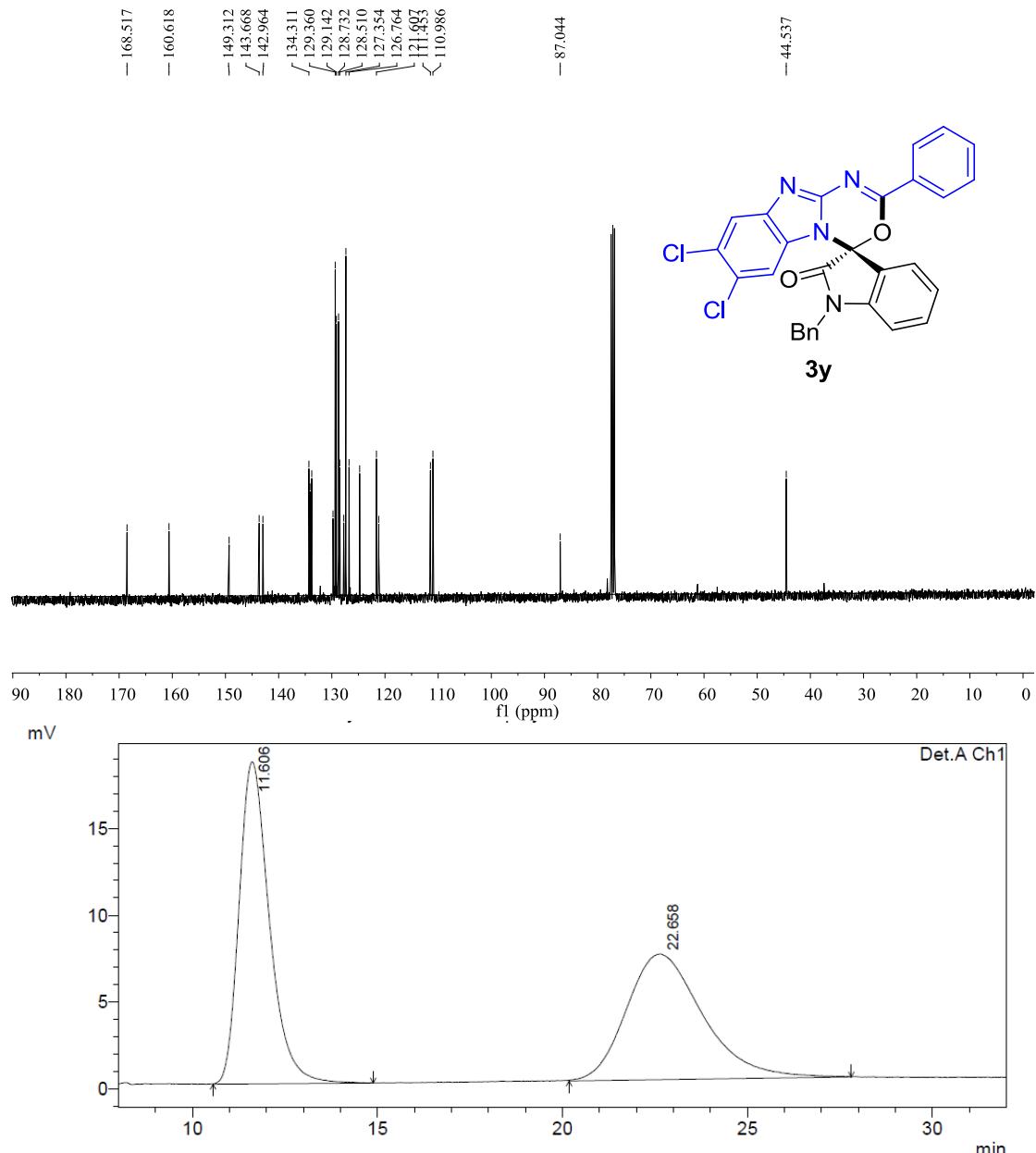


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 23.141 | 43527 | 300 | 1.844 | 1.858 |
| 2 | 27.640 | 2316932 | 15839 | 98.156 | 98.142 |
| Total | | 2360458 | 16139 | 100.000 | 100.000 |

8.213
8.194
7.821
7.586
7.568
7.478
7.458
7.338
7.321
7.258
7.251
7.232
6.998
6.946

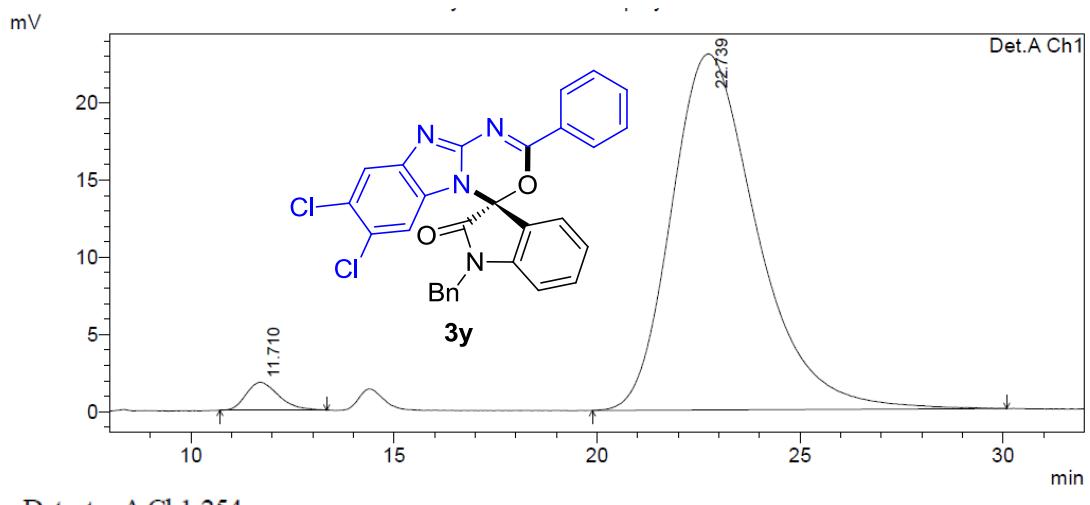
5.118
5.079
4.770
4.730





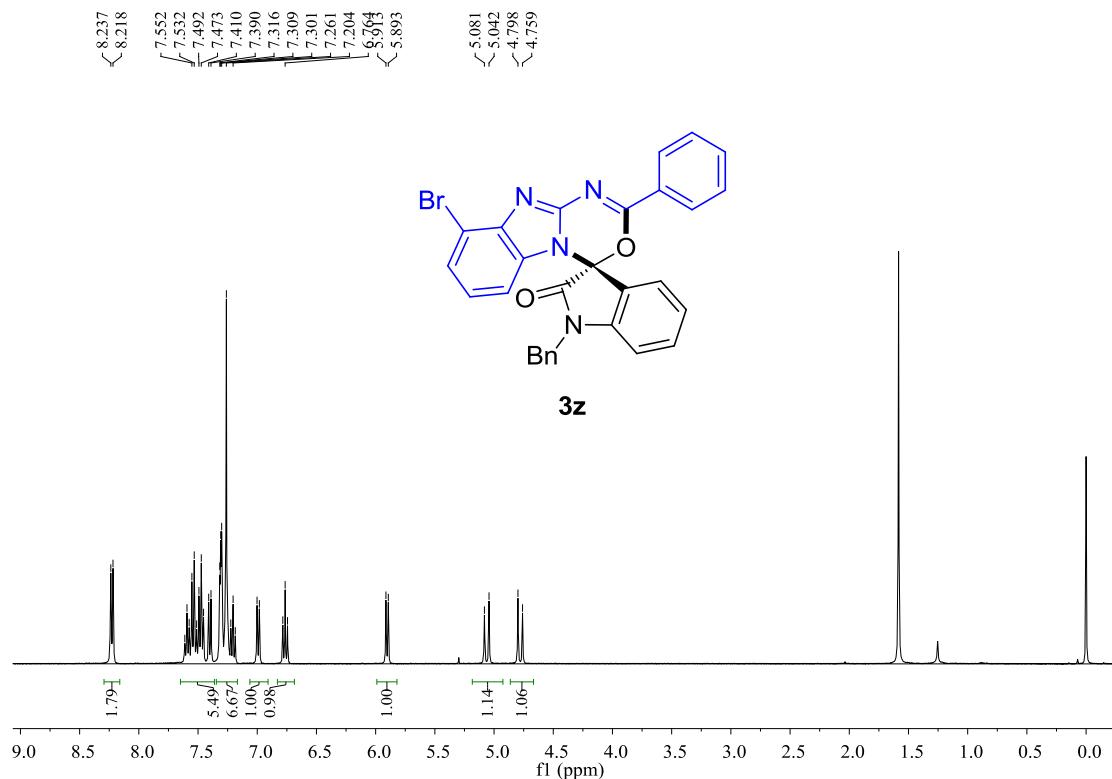
Detector A Ch1 254nm

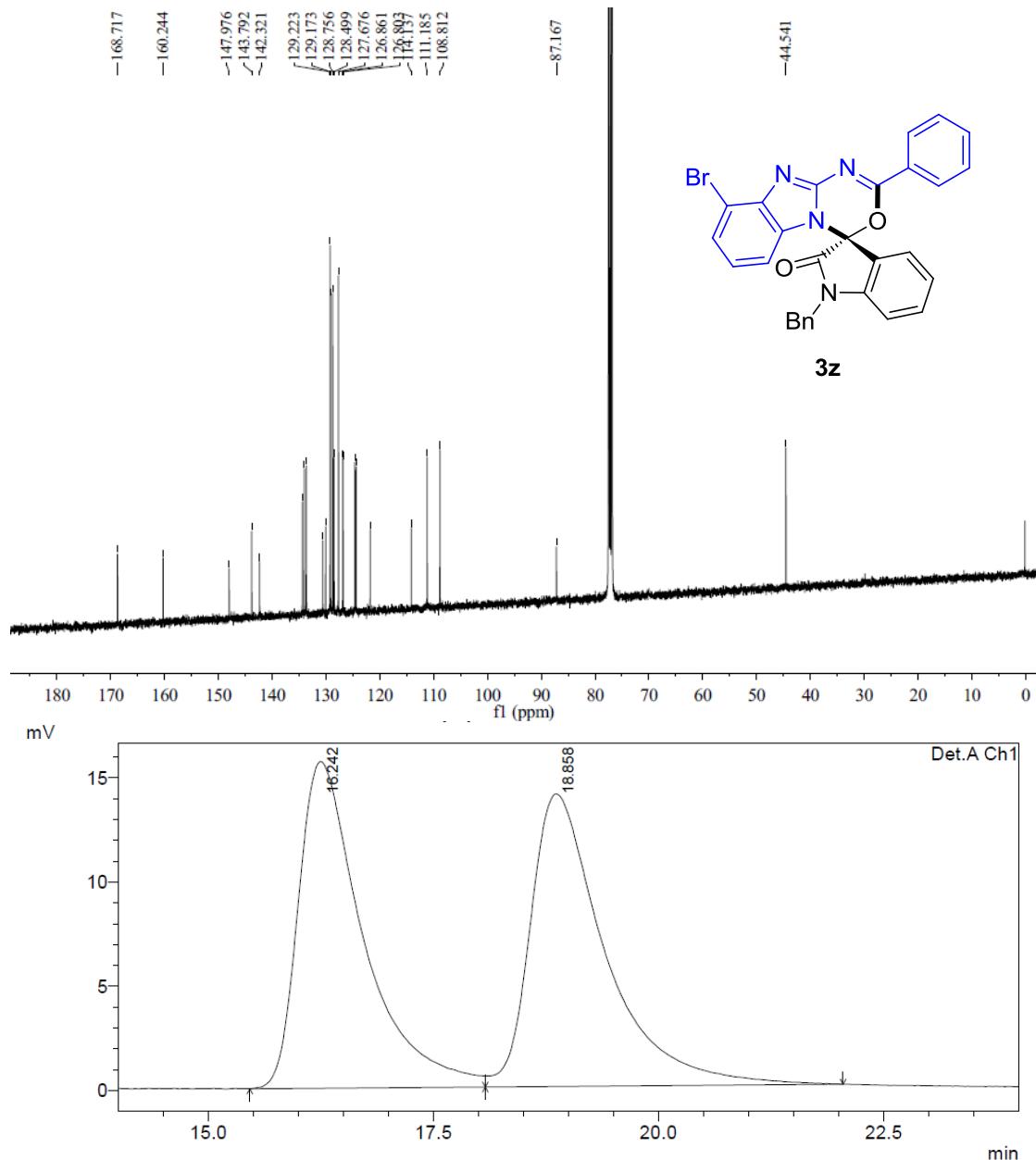
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 11.606 | 1056552 | 18547 | 50.492 | 71.969 |
| 2 | 22.658 | 1035971 | 7224 | 49.508 | 28.031 |
| Total | | 2092524 | 25771 | 100.000 | 100.000 |



Detector A Ch1 254nm

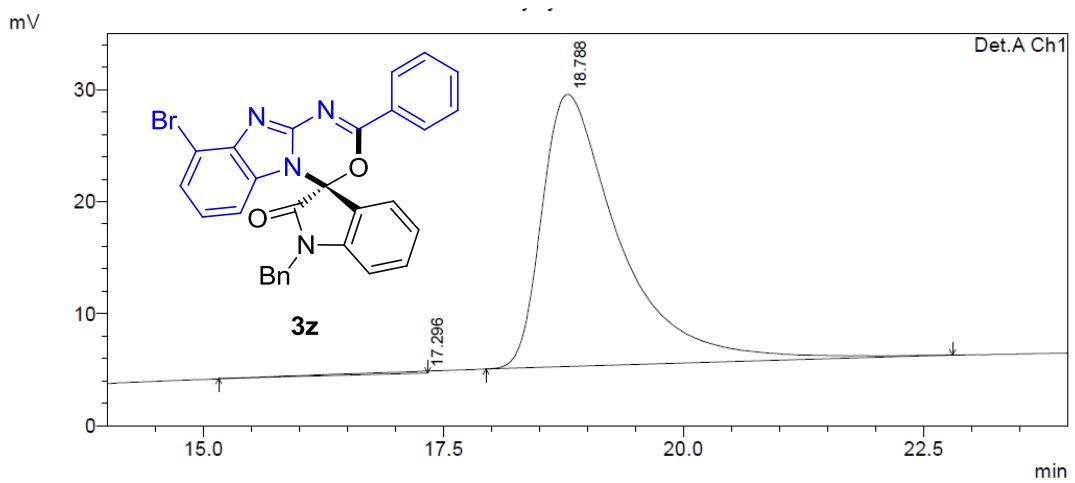
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 11.710 | 101303 | 1808 | 2.901 | 7.273 |
| 2 | 22.739 | 3390551 | 23054 | 97.099 | 92.727 |
| Total | | 3491854 | 24862 | 100.000 | 100.000 |



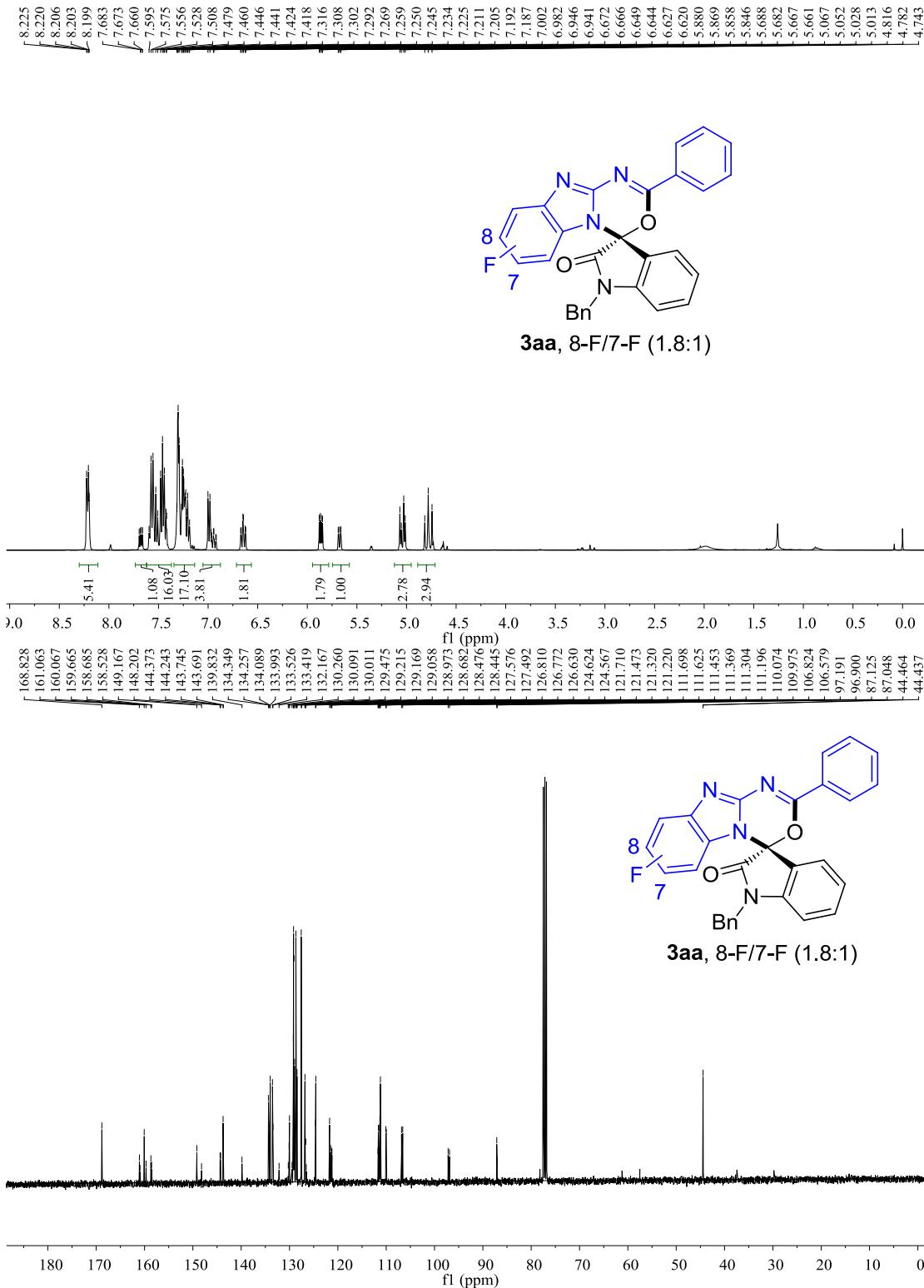


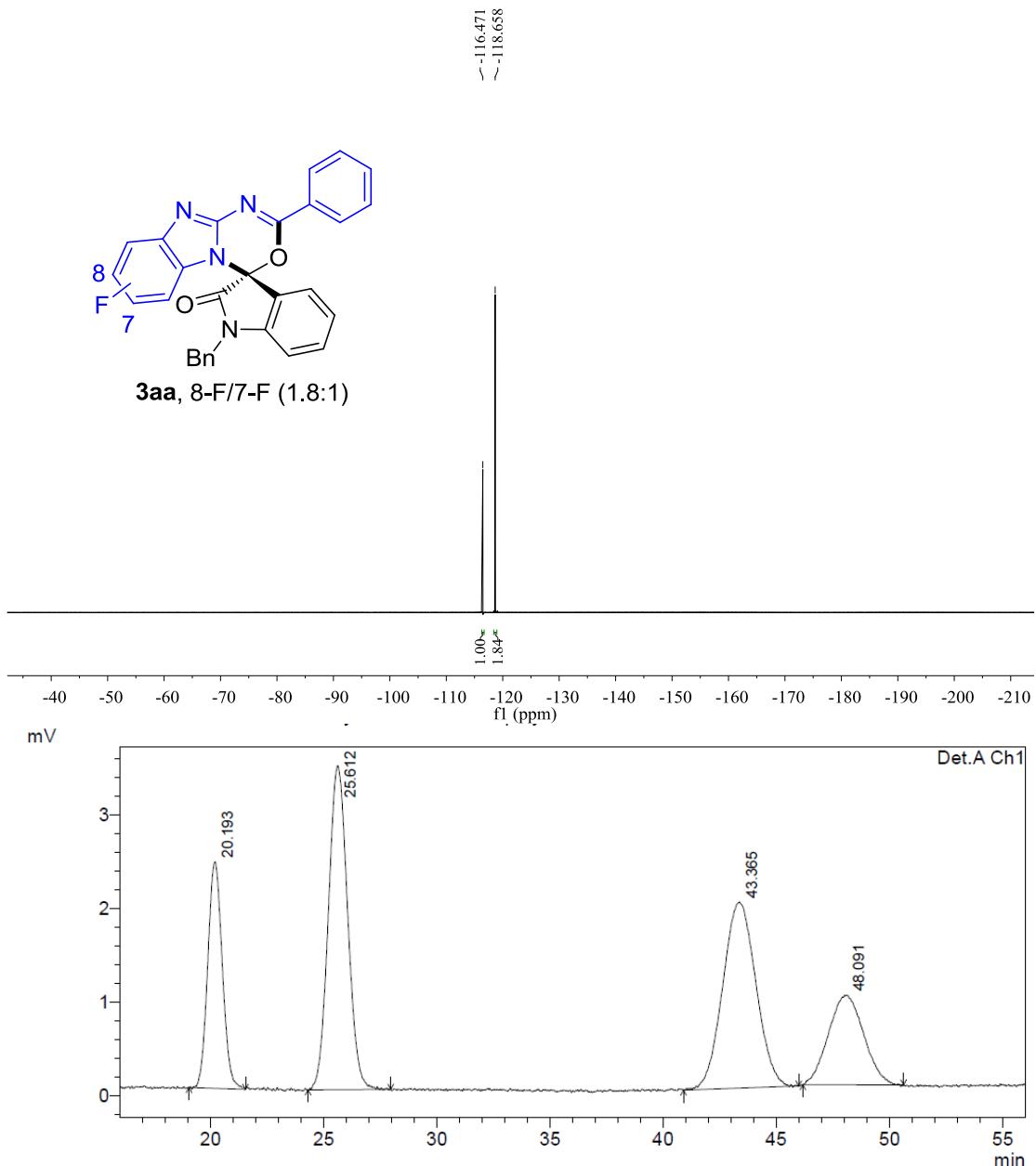
Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 16.242 | 783602 | 15672 | 49.167 | 52.754 |
| 2 | 18.858 | 810169 | 14036 | 50.833 | 47.246 |
| Total | | 1593771 | 29708 | 100.000 | 100.000 |

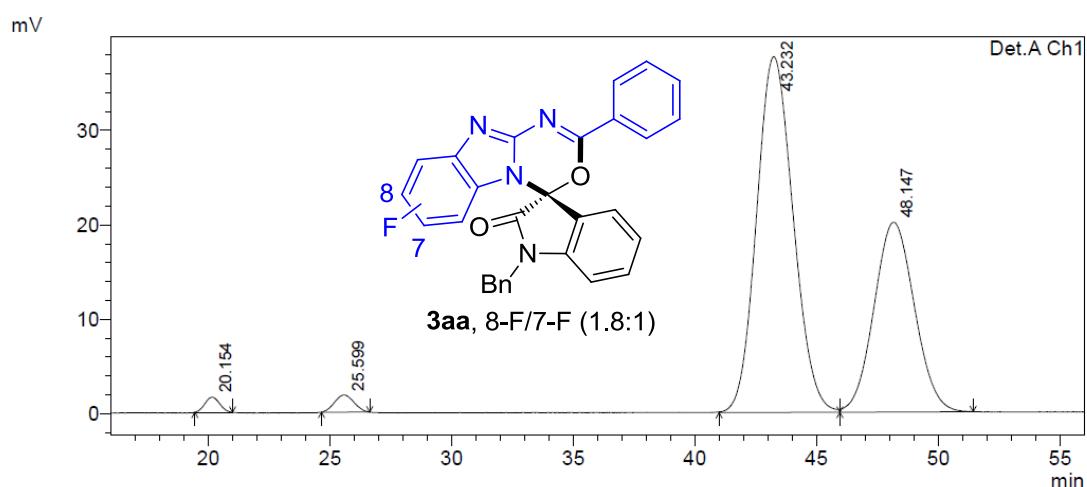


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 17.296 | 11672 | 179 | 0.841 | 0.732 |
| 2 | 18.788 | 1375682 | 24295 | 99.159 | 99.268 |
| Total | | 1387355 | 24474 | 100.000 | 100.000 |



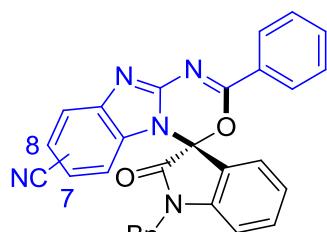


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1 | 20.193 | 108301 | 2425 | 17.466 | 27.414 |
| 2 | 25.612 | 204667 | 3469 | 33.008 | 39.210 |
| 3 | 43.365 | 203300 | 1993 | 32.787 | 22.527 |
| 4 | 48.091 | 103787 | 960 | 16.738 | 10.849 |
| Total | | 620055 | 8847 | 100.000 | 100.000 |

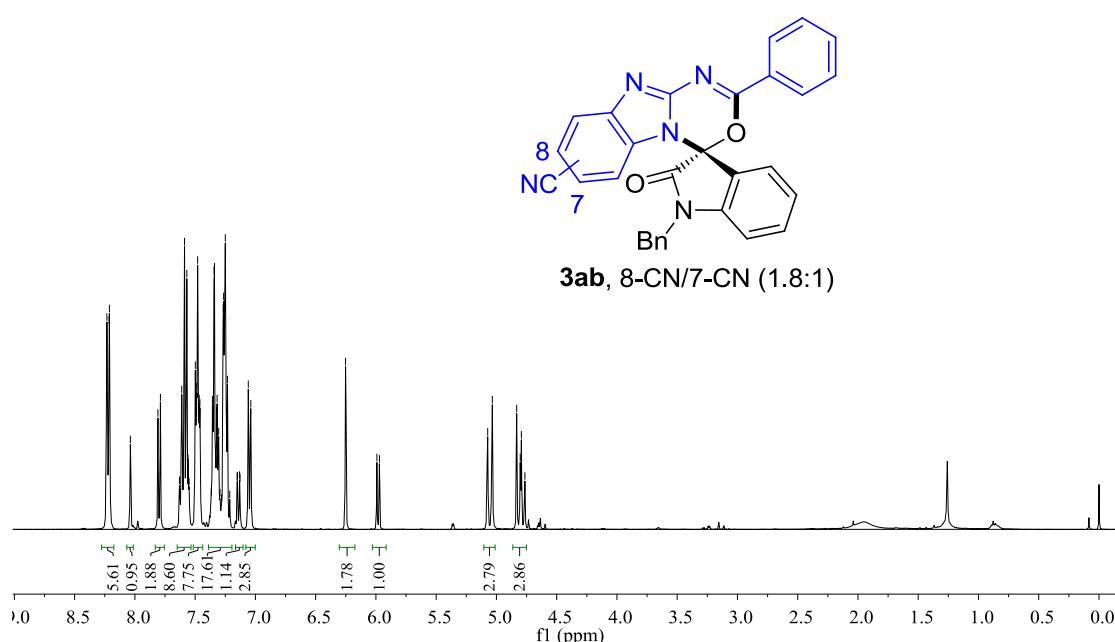


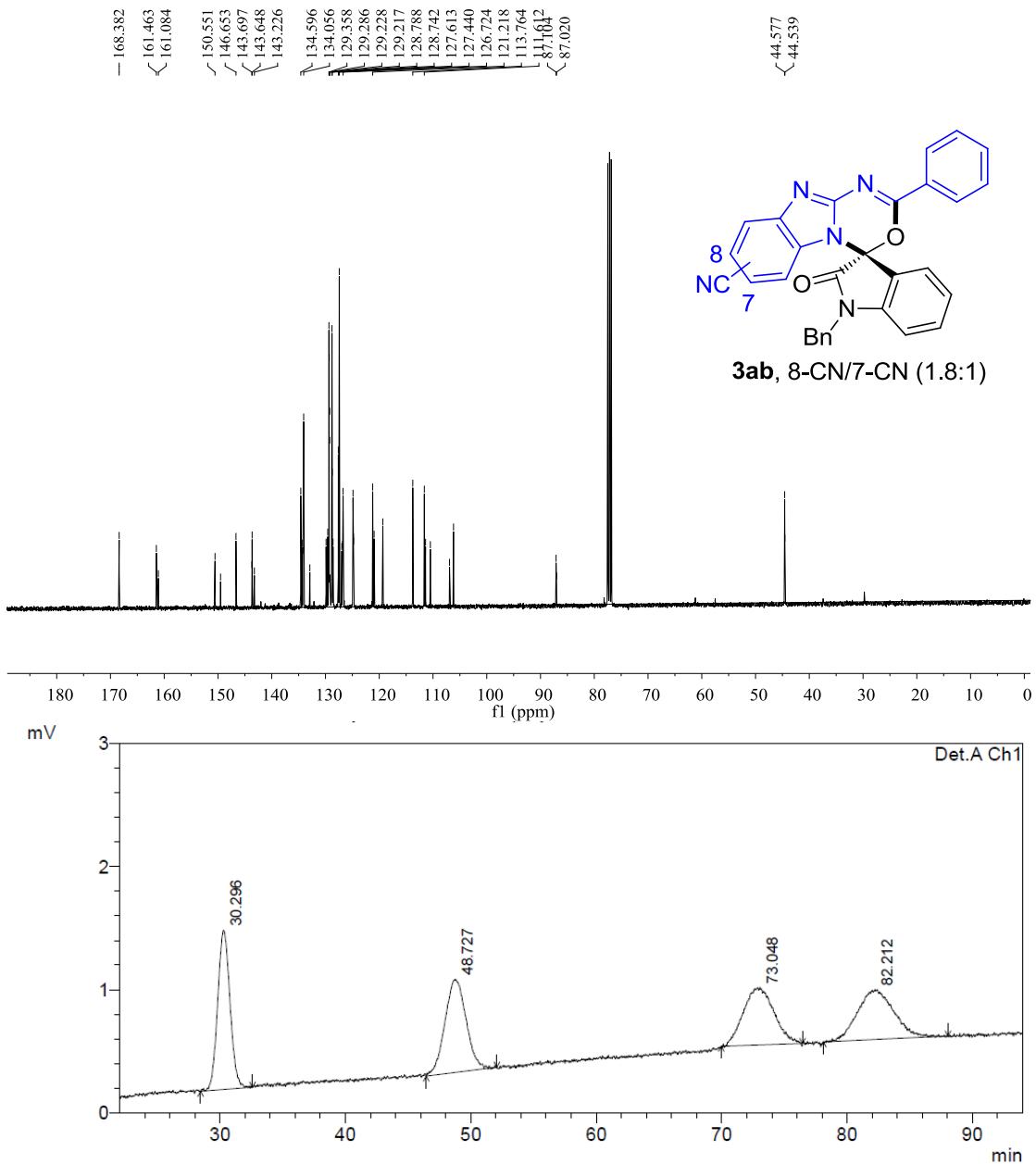
Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 20.154 | 67588 | 1610 | 1.050 | 2.631 |
| 2 | 25.599 | 100335 | 1811 | 1.559 | 2.960 |
| 3 | 43.232 | 3943501 | 37663 | 61.256 | 61.559 |
| 4 | 48.147 | 2326322 | 20098 | 36.136 | 32.850 |
| Total | | 6437746 | 61182 | 100.000 | 100.000 |

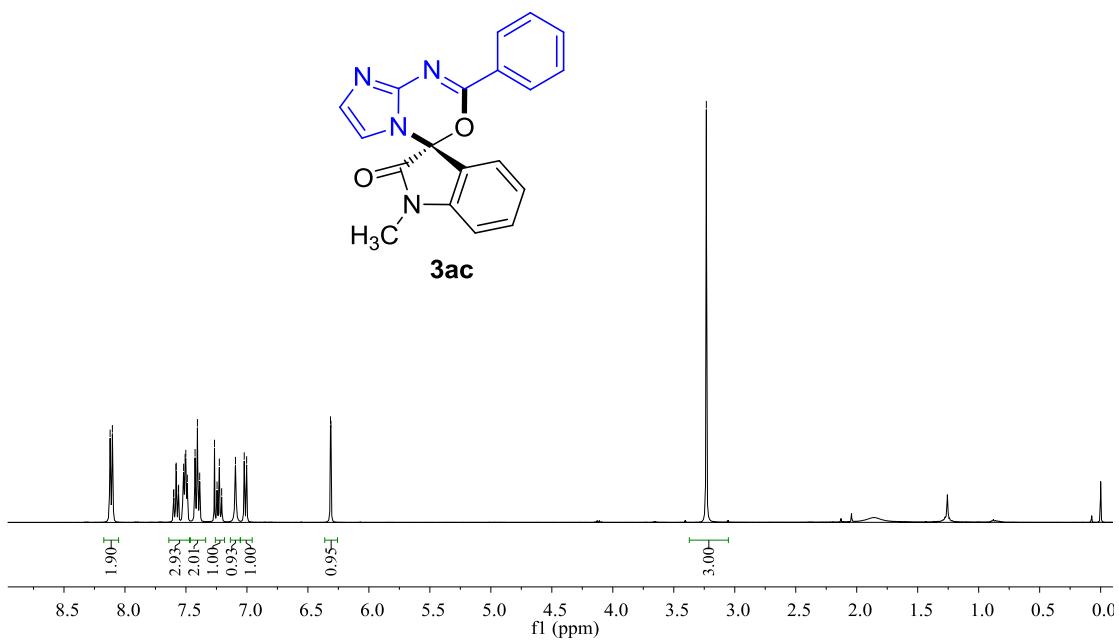
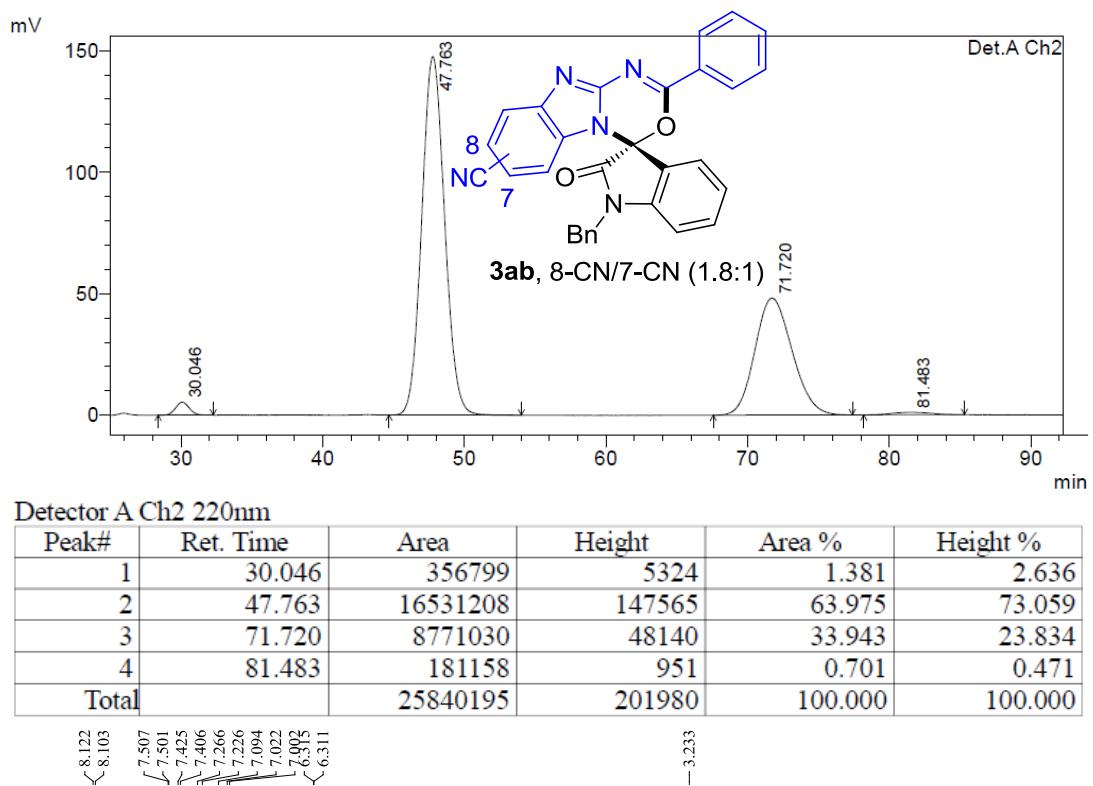


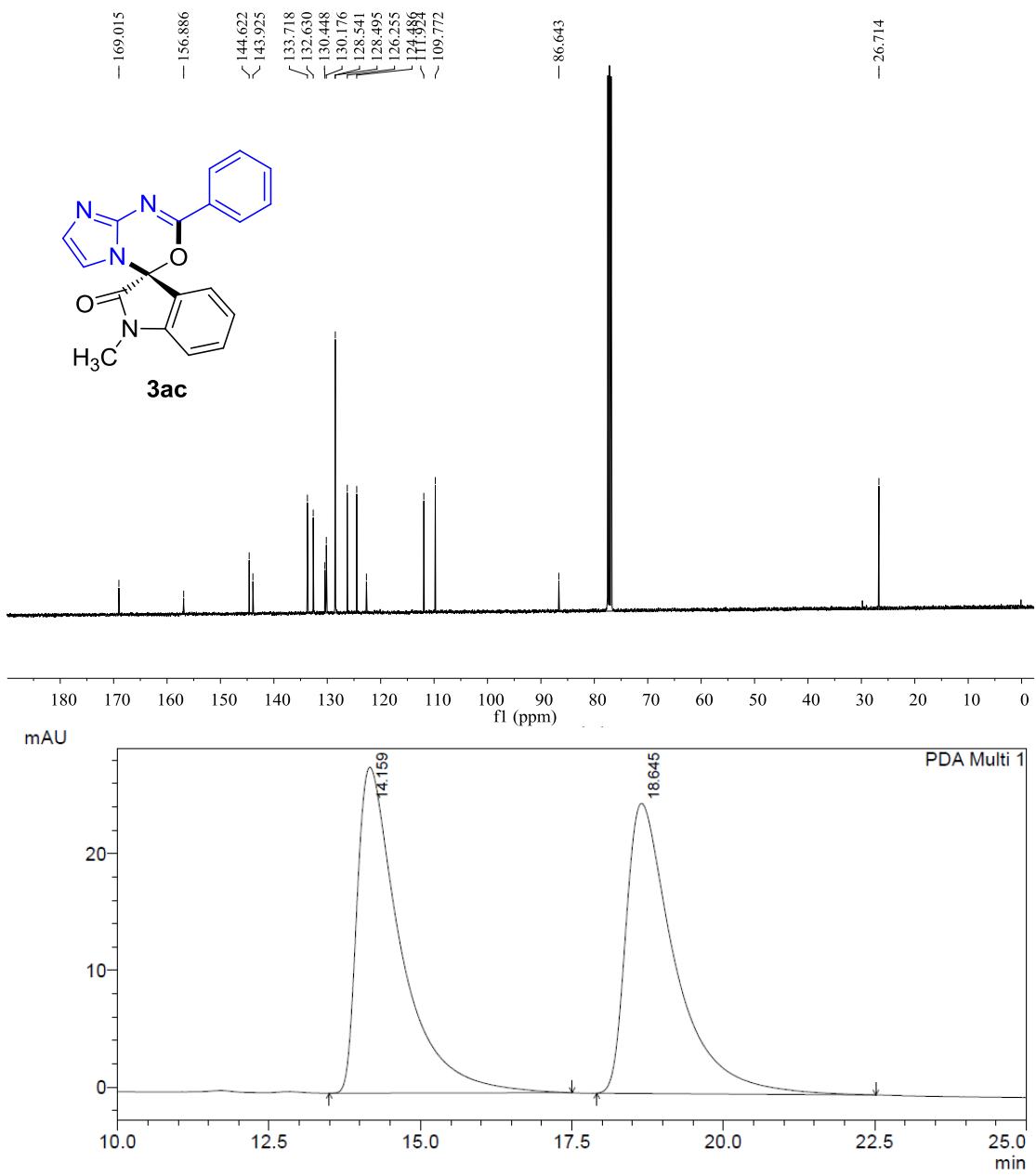
3ab, 8-CN/7-CN (1.8:1)





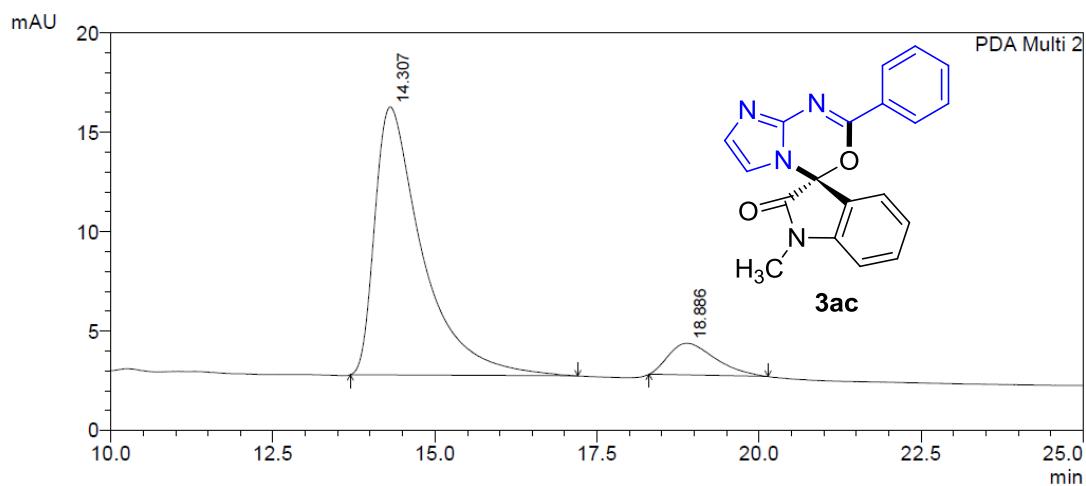
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1 | 30.296 | 88665 | 1293 | 26.307 | 44.217 |
| 2 | 48.727 | 88674 | 759 | 26.310 | 25.943 |
| 3 | 73.048 | 78963 | 467 | 23.429 | 15.988 |
| 4 | 82.212 | 80735 | 405 | 23.954 | 13.852 |
| Total | | 337037 | 2924 | 100.000 | 100.000 |





PDA Ch2 220nm 4nm

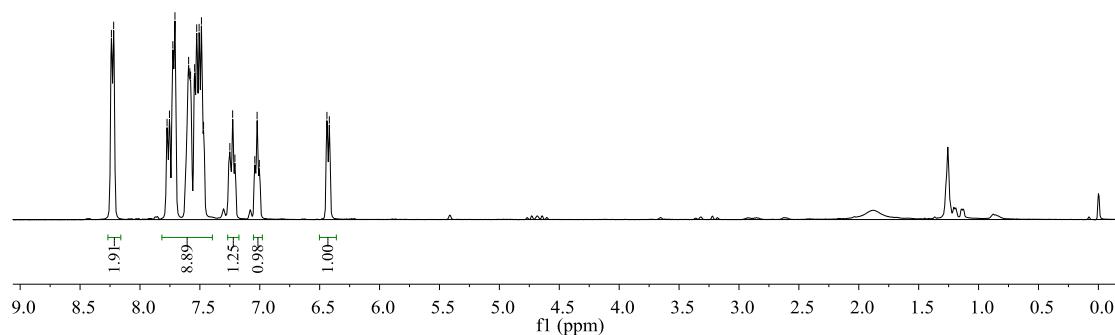
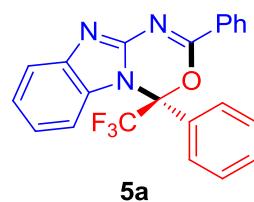
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 14.160 | 2832672 | 57183 | 49.892 | 52.880 |
| 2 | 18.645 | 2844948 | 50954 | 50.108 | 47.120 |
| Total | | 5677620 | 108136 | 100.000 | 100.000 |

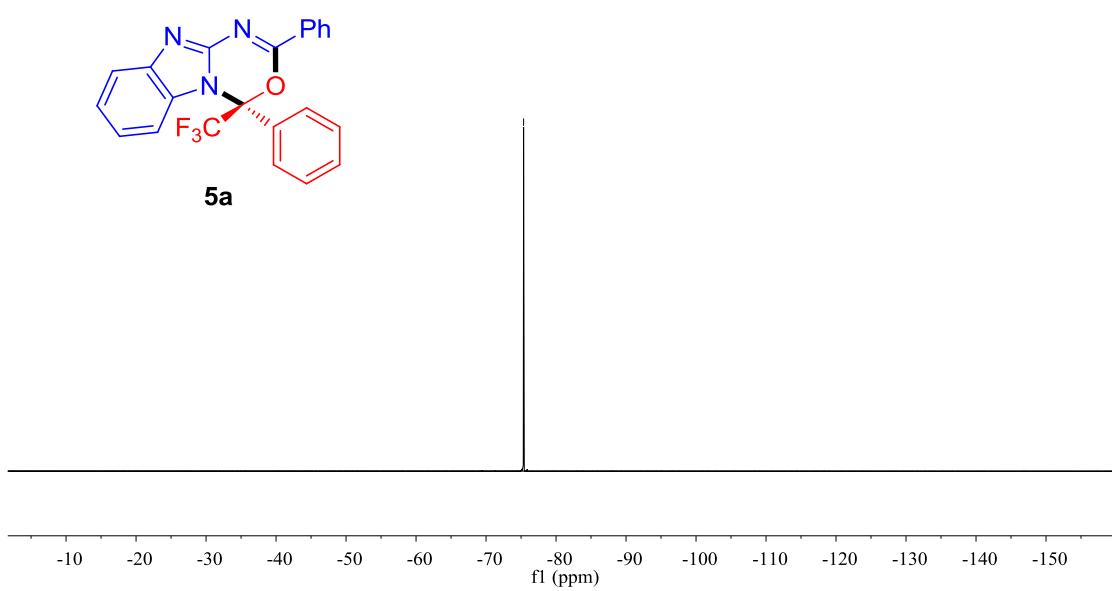
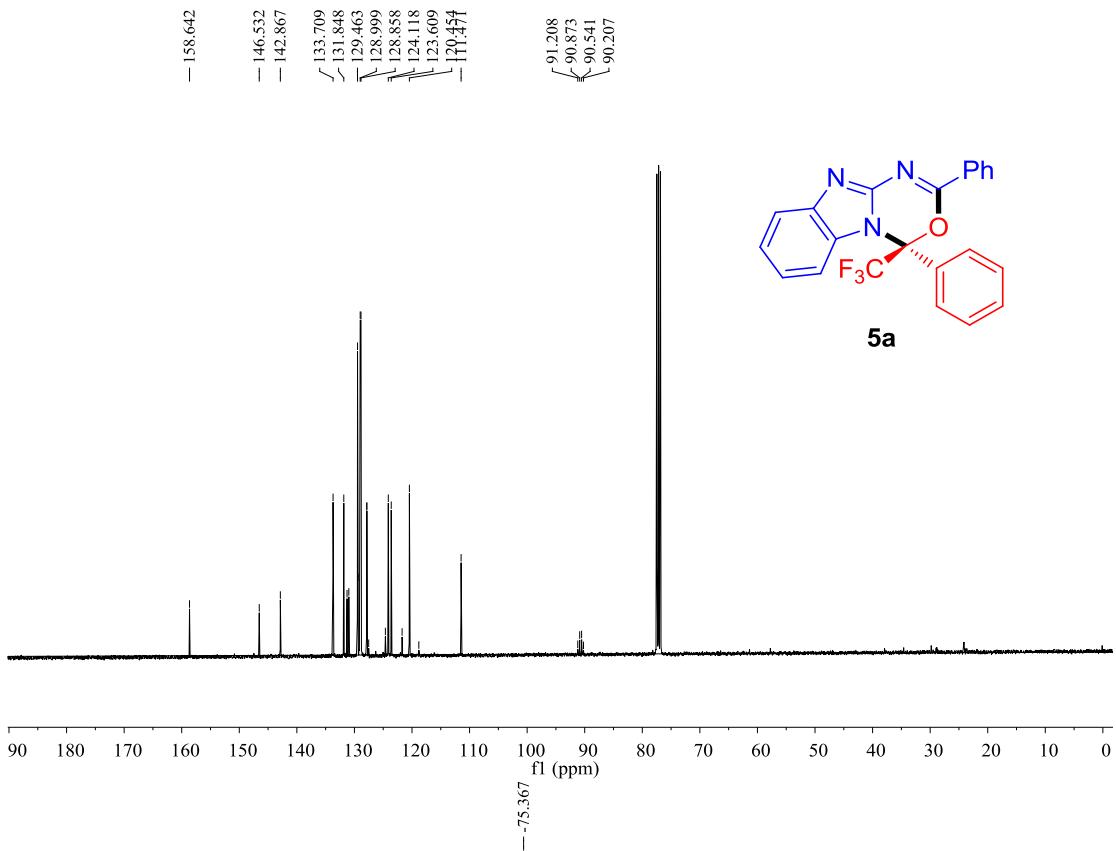


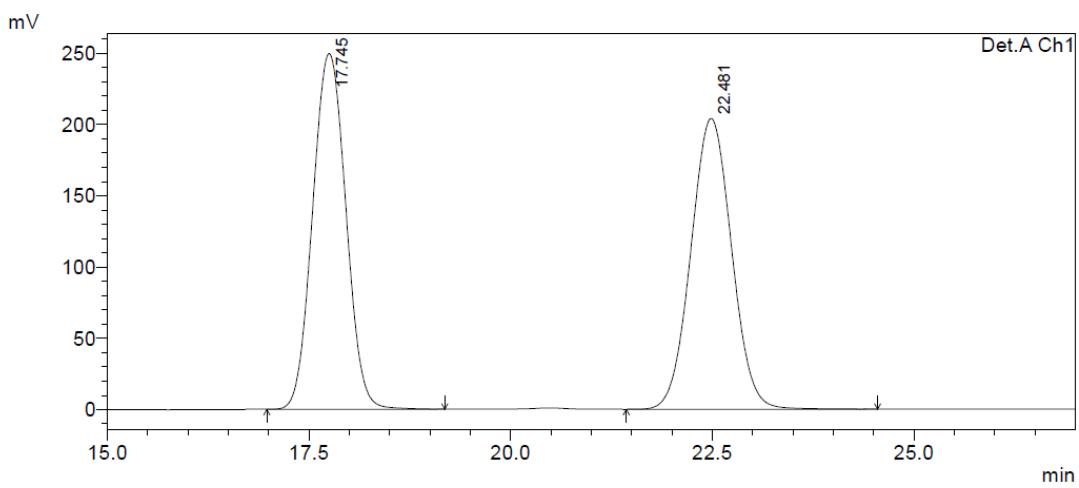
PDA Ch2 220nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1 | 14.307 | 690200 | 13487 | 89.618 | 89.433 |
| 2 | 18.886 | 79957 | 1593 | 10.382 | 10.567 |
| Total | | 770157 | 15080 | 100.000 | 100.000 |

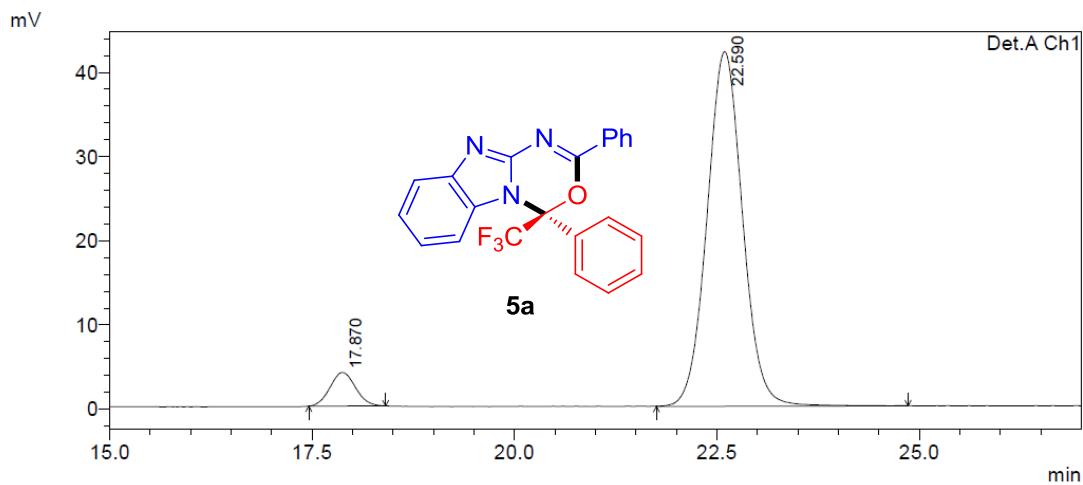
8.220
7.725
7.708
7.594
7.584
7.577
7.544
7.526
7.506
7.487
6.419





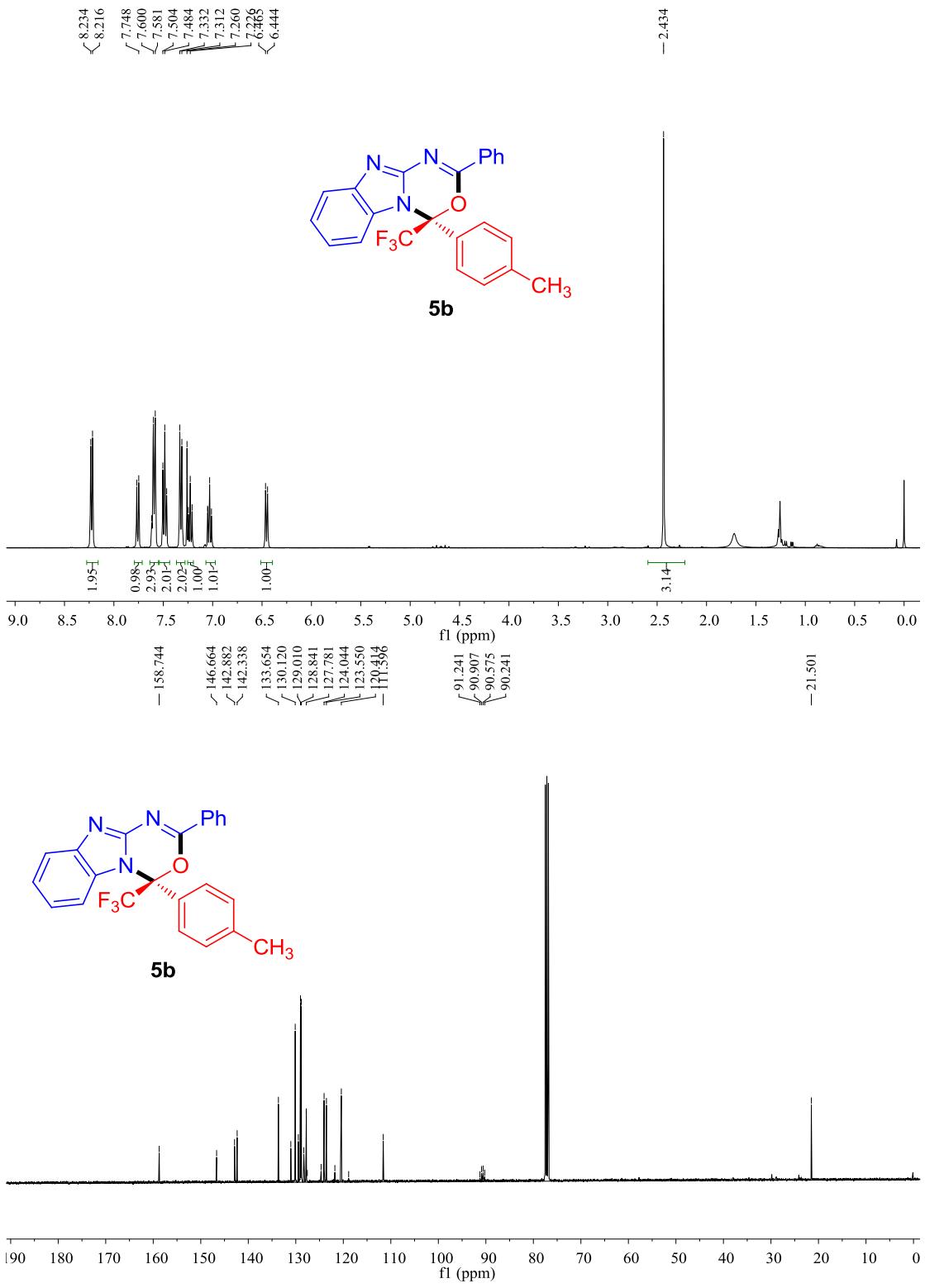


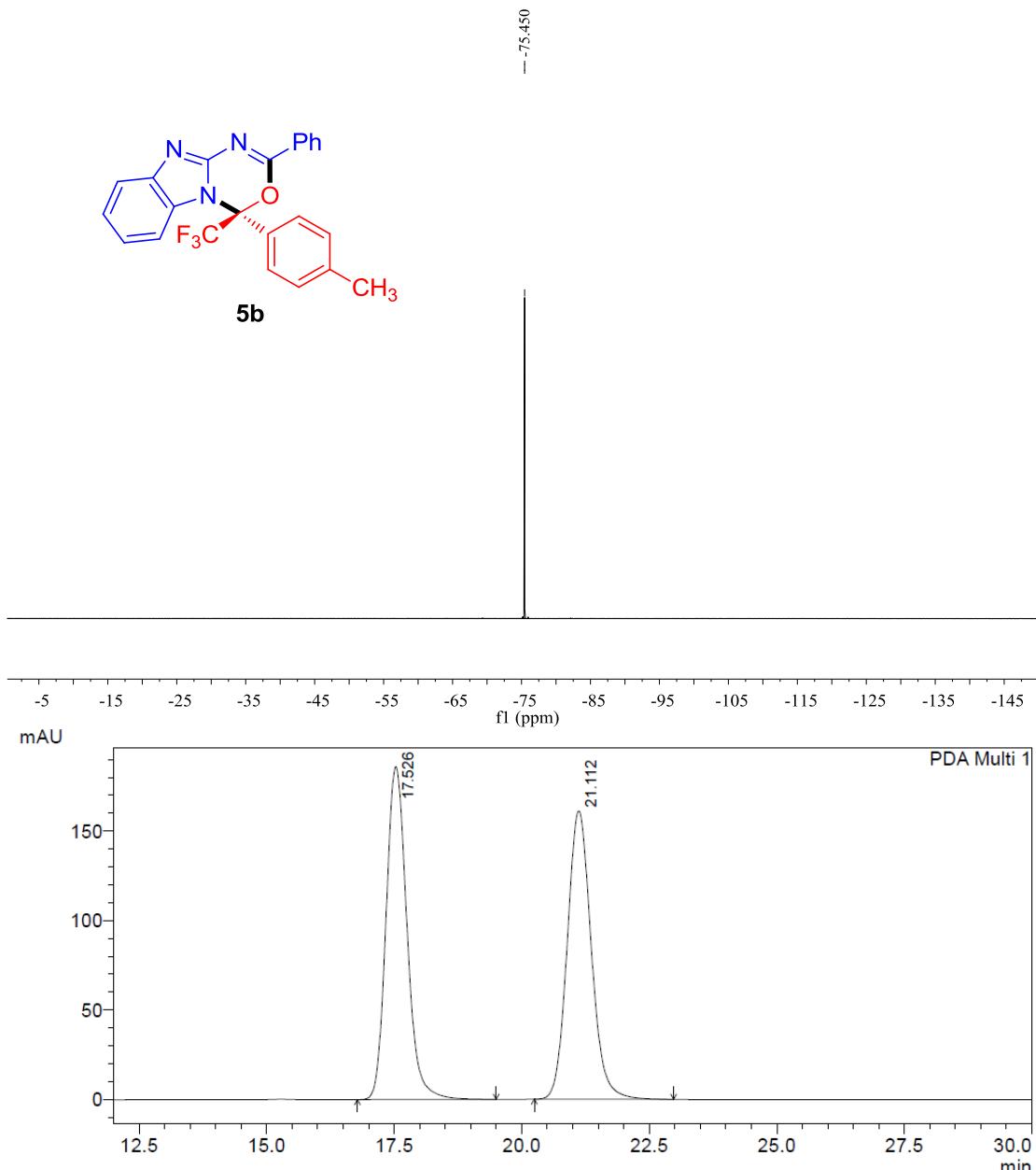
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|----------|--------|---------|----------|
| 1 | 17.745 | 7158937 | 249690 | 49.990 | 55.030 |
| 2 | 22.481 | 7161768 | 204048 | 50.010 | 44.970 |
| Total | | 14320705 | 453739 | 100.000 | 100.000 |



Detector A Ch1 254nm

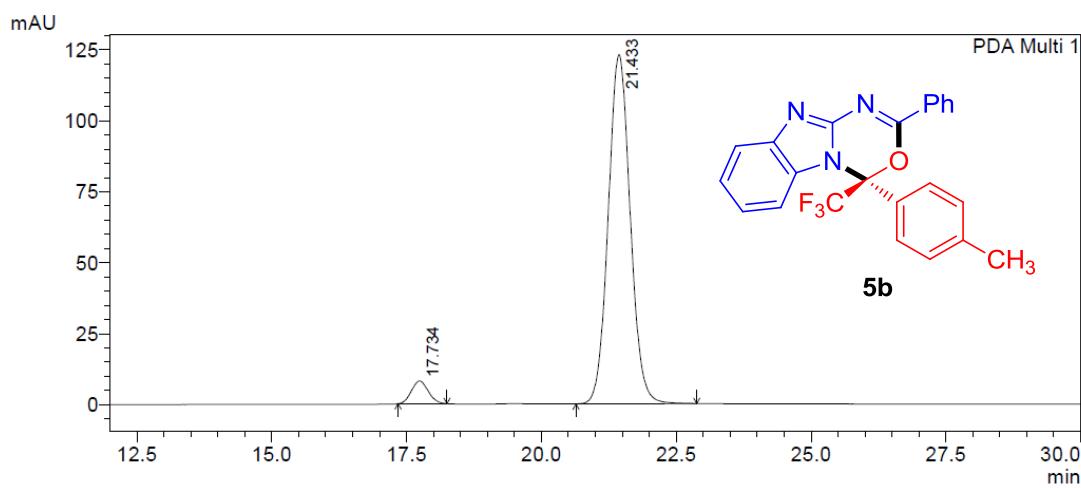
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 17.870 | 86833 | 3976 | 6.335 | 8.620 |
| 2 | 22.590 | 1283963 | 42147 | 93.665 | 91.380 |
| Total | | 1370796 | 46123 | 100.000 | 100.000 |



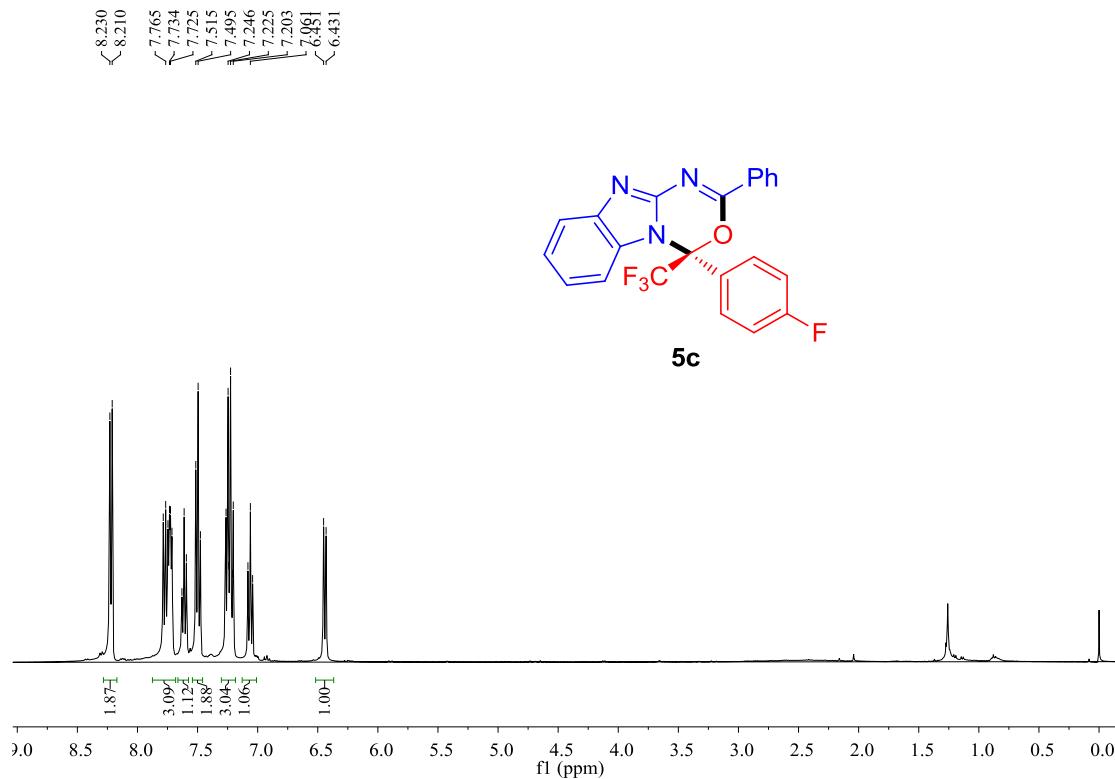


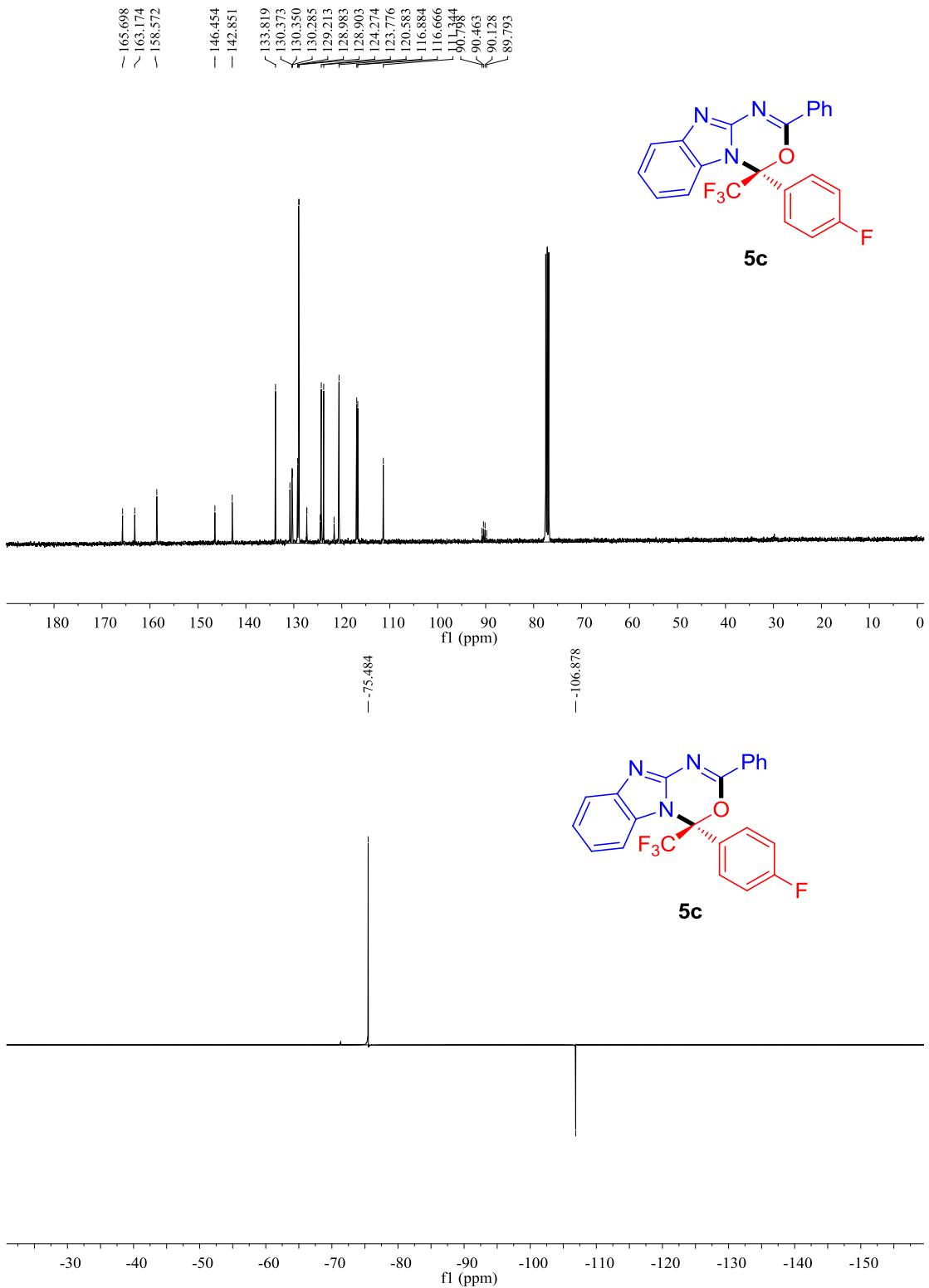
PDA Ch1 254nm 4nm

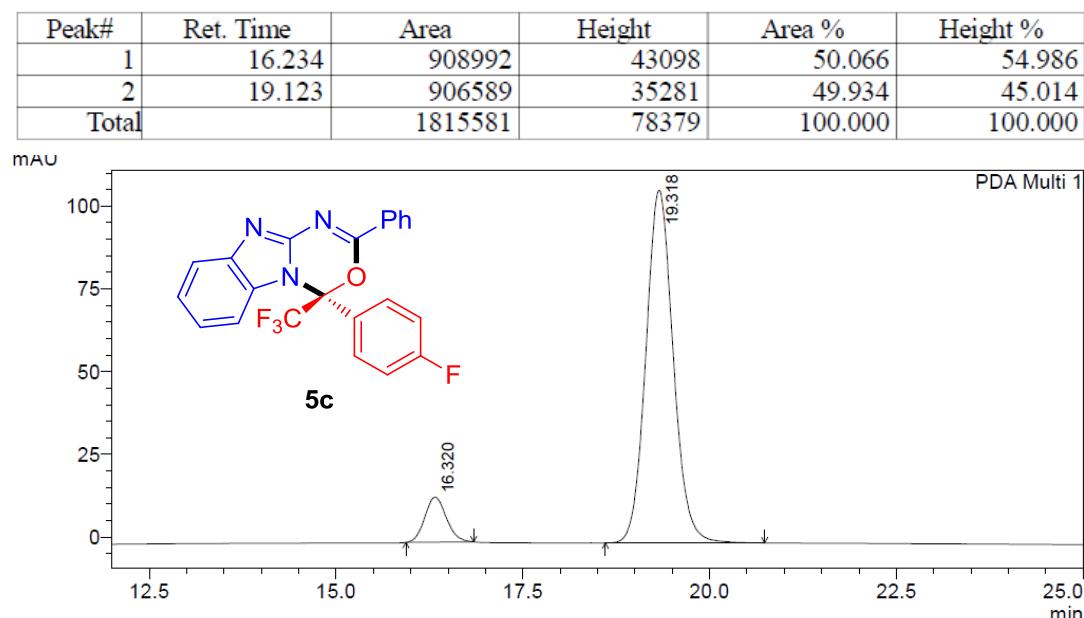
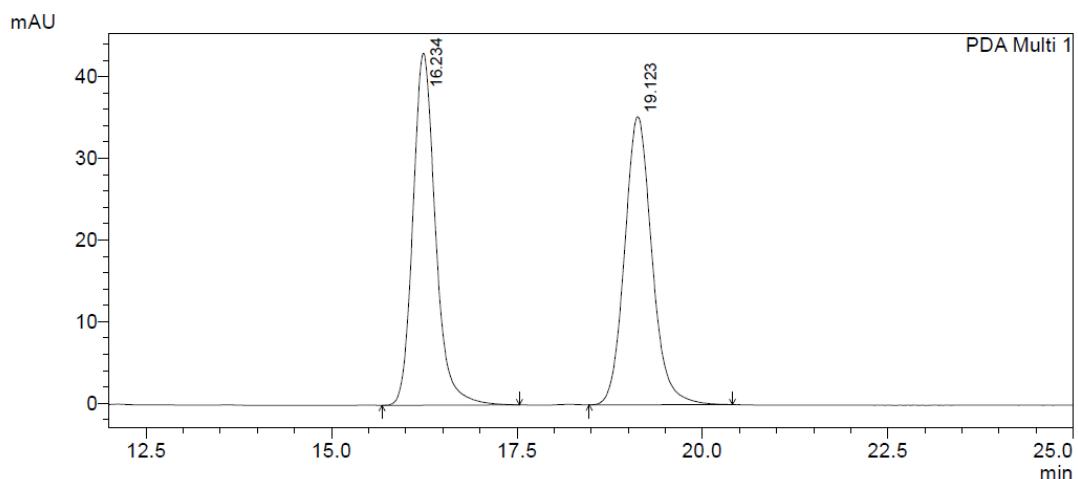
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|----------|--------|---------|----------|
| 1 | 17.526 | 5284806 | 185872 | 50.043 | 53.585 |
| 2 | 21.112 | 5275801 | 161001 | 49.957 | 46.415 |
| Total | | 10560607 | 346873 | 100.000 | 100.000 |

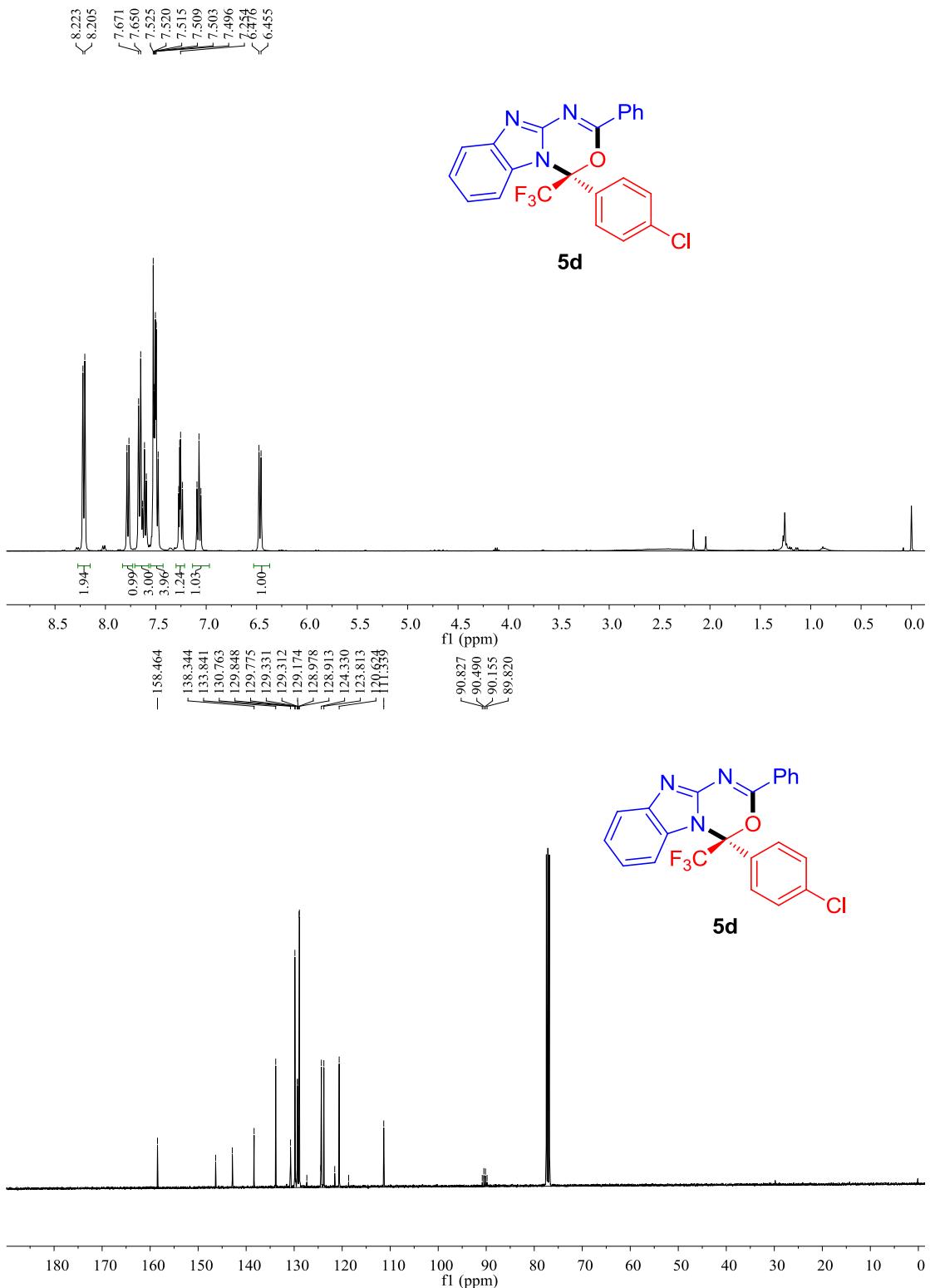


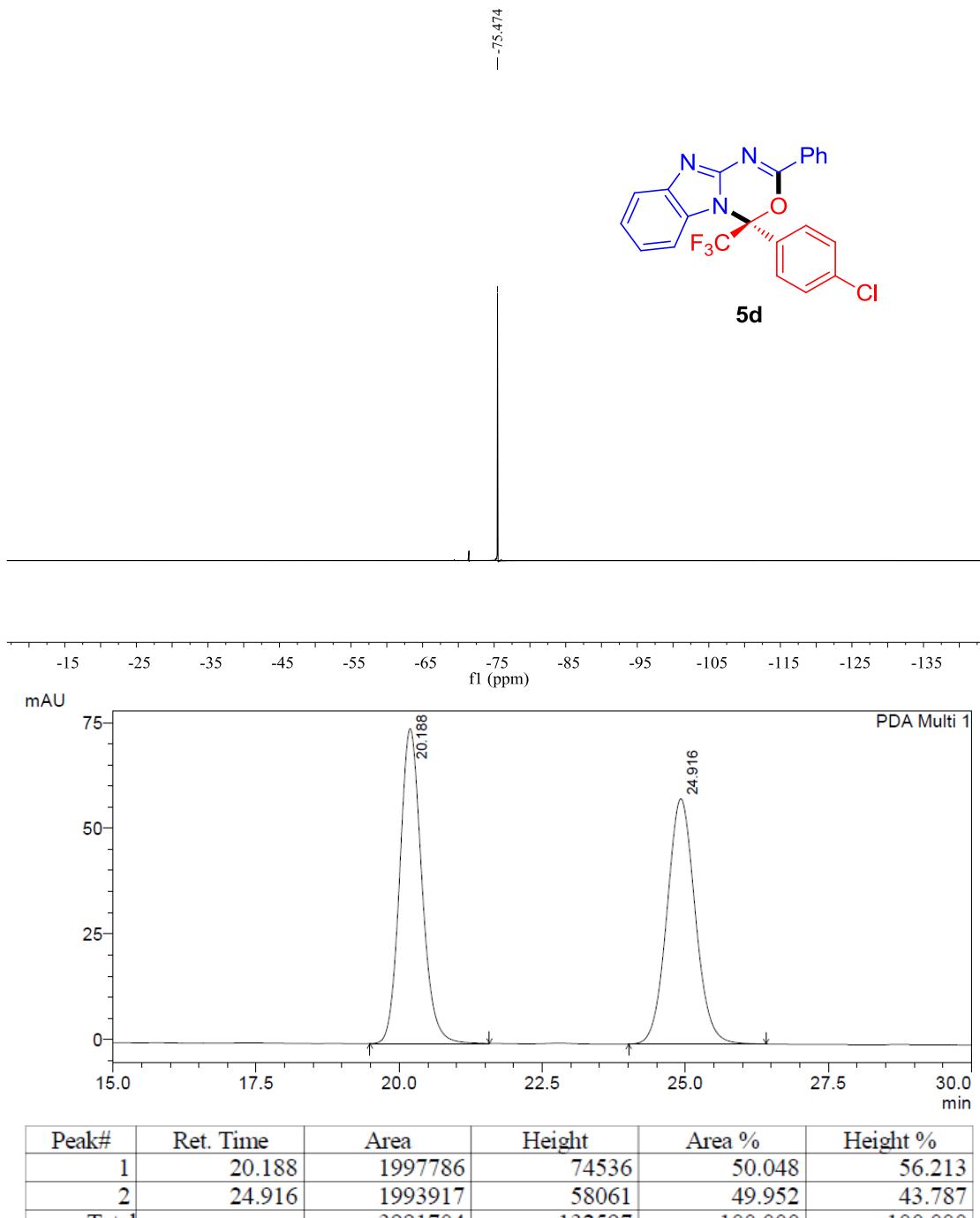
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 17.734 | 174520 | 8005 | 4.761 | 6.108 |
| 2 | 21.433 | 3490934 | 123043 | 95.239 | 93.892 |
| Total | | 3665455 | 131048 | 100.000 | 100.000 |

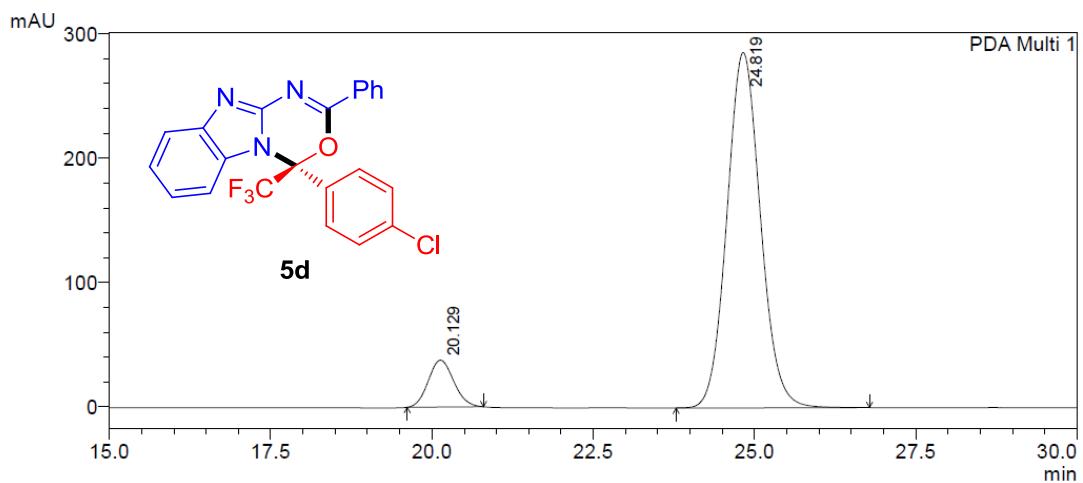






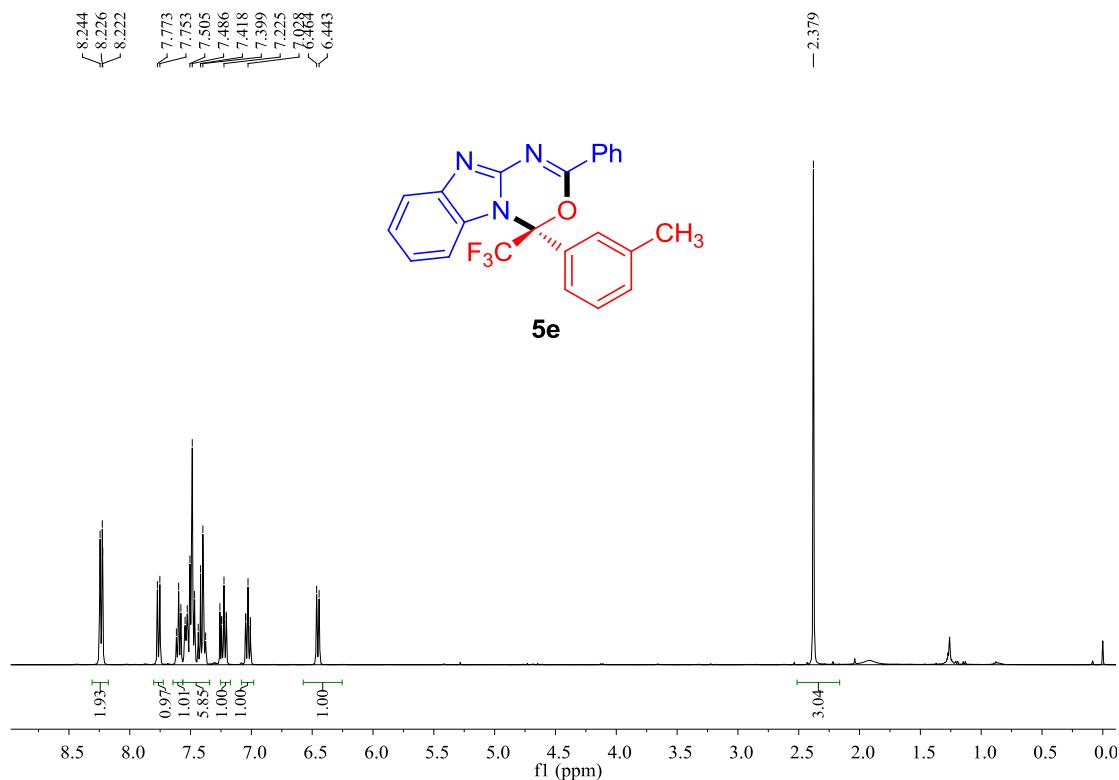


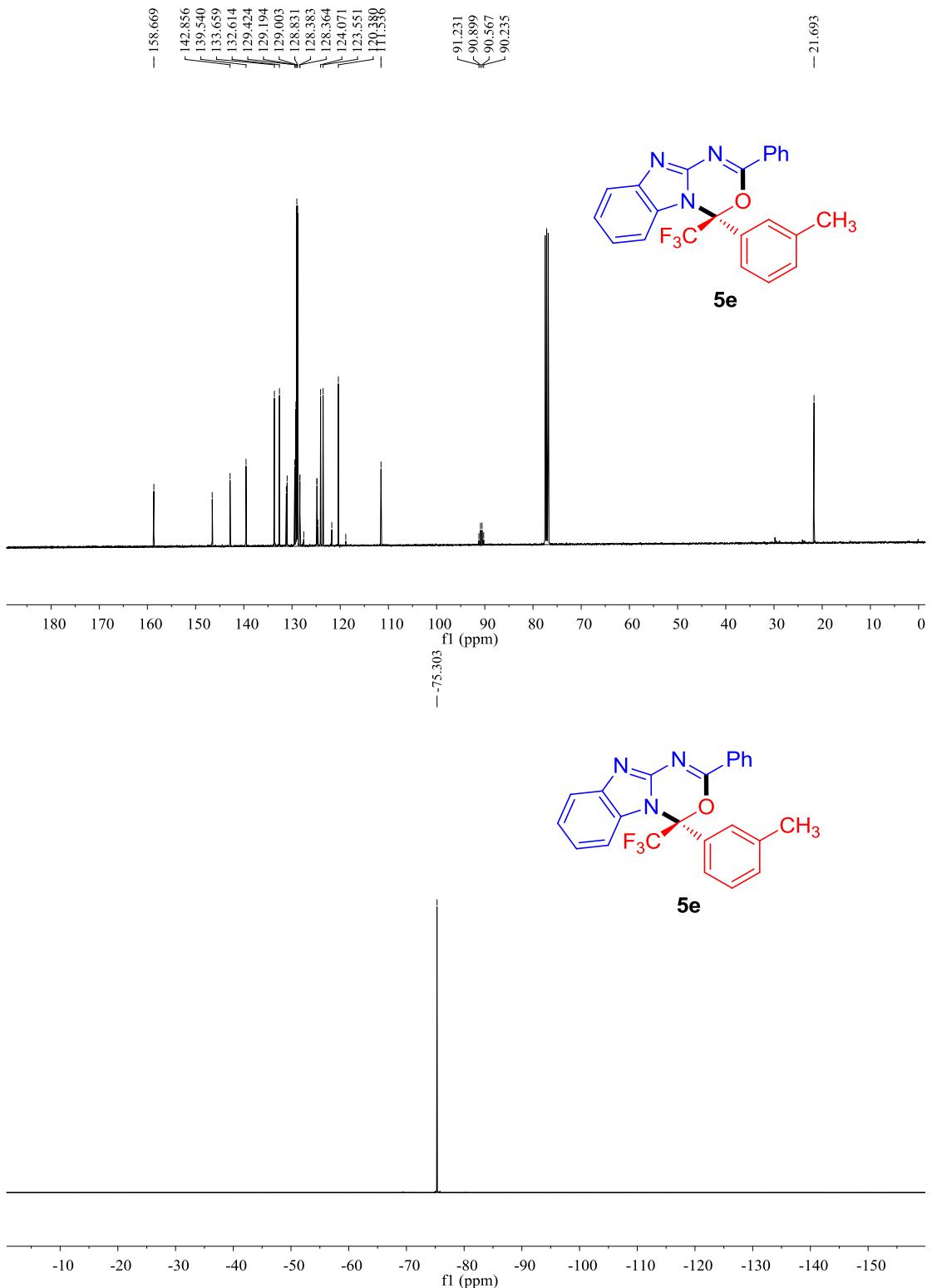


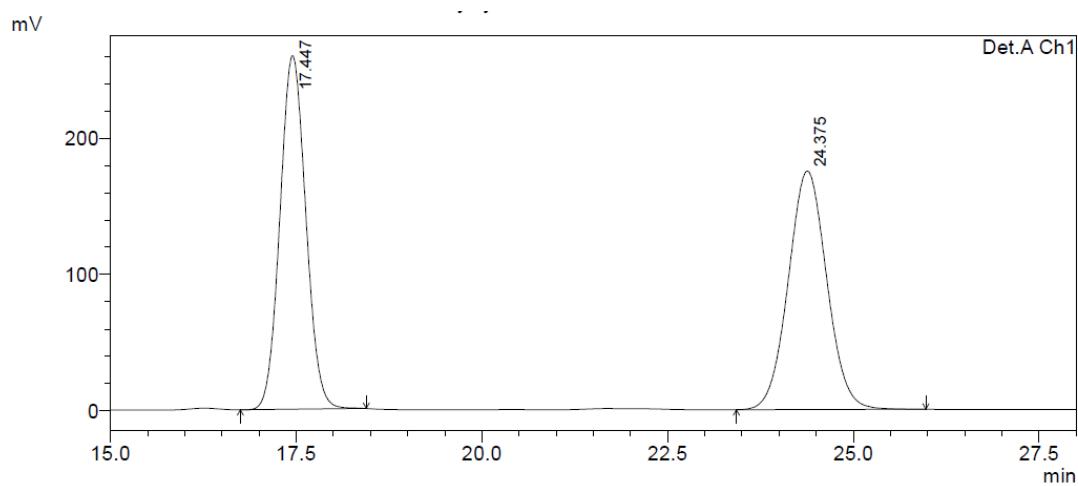


PDA Ch1 254nm 4nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|----------|--------|---------|----------|
| 1 | 20.129 | 1043982 | 37813 | 9.172 | 11.678 |
| 2 | 24.819 | 10338819 | 285988 | 90.828 | 88.322 |
| Total | | 11382801 | 323802 | 100.000 | 100.000 |

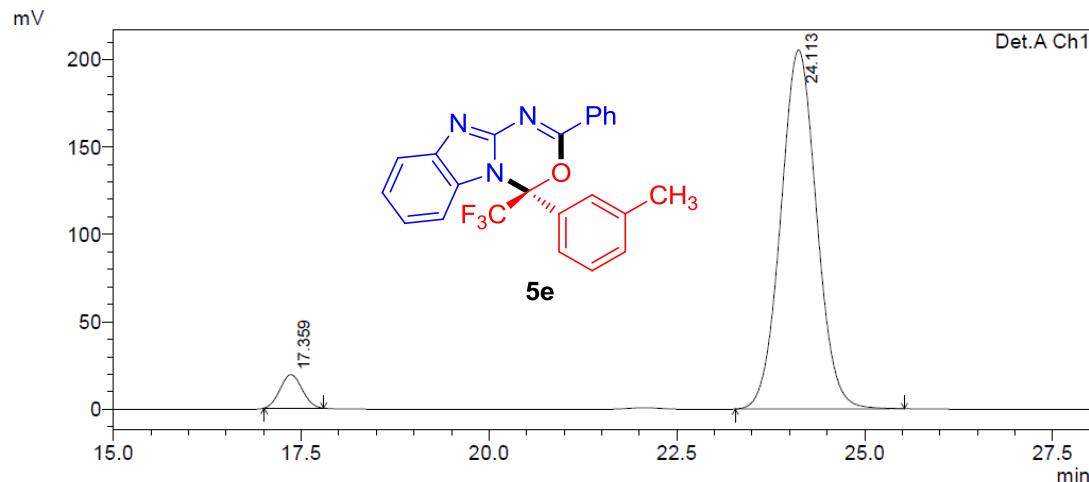






Detector A Ch1 254nm

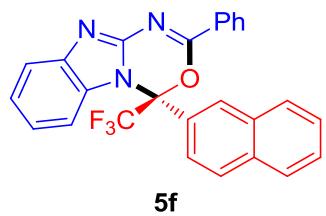
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|----------|--------|---------|----------|
| 1 | 17.447 | 6294922 | 259633 | 49.904 | 59.716 |
| 2 | 24.375 | 6319062 | 175148 | 50.096 | 40.284 |
| Total | | 12613984 | 434780 | 100.000 | 100.000 |



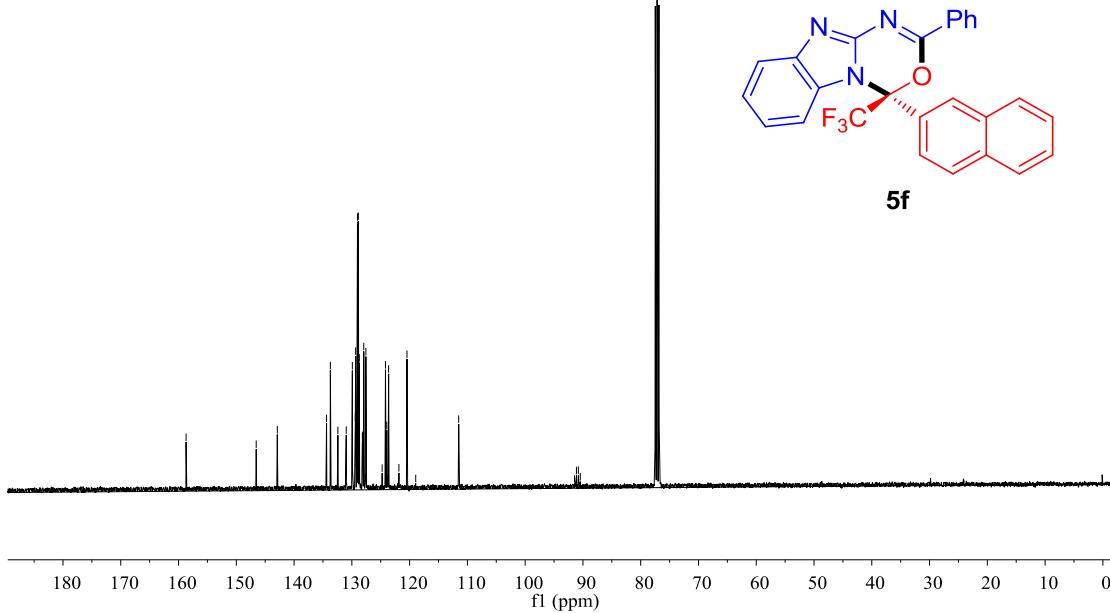
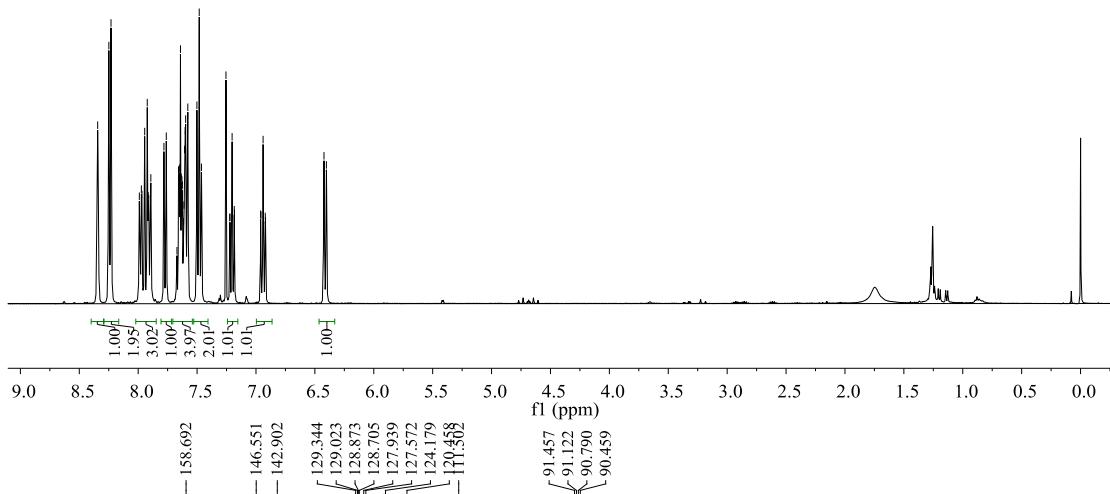
Detector A Ch1 254nm

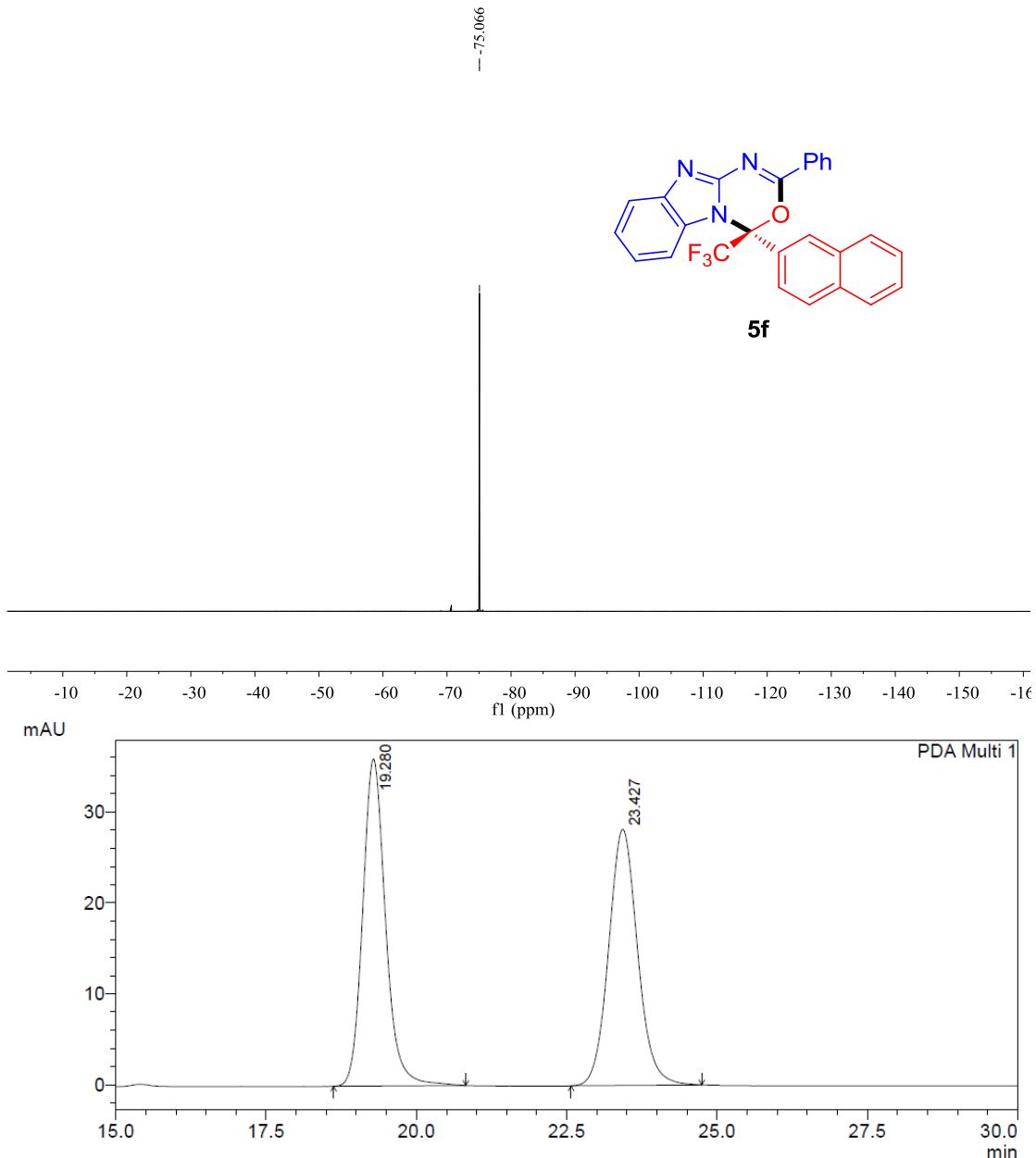
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 17.359 | 390078 | 19191 | 5.411 | 8.551 |
| 2 | 24.113 | 6819398 | 205242 | 94.589 | 91.449 |
| Total | | 7209476 | 224433 | 100.000 | 100.000 |

8.344
8.249
8.231
8.228
7.945
7.923
7.761
7.641
7.601
7.597
7.579
7.501
7.482
7.255
6.402
6.403



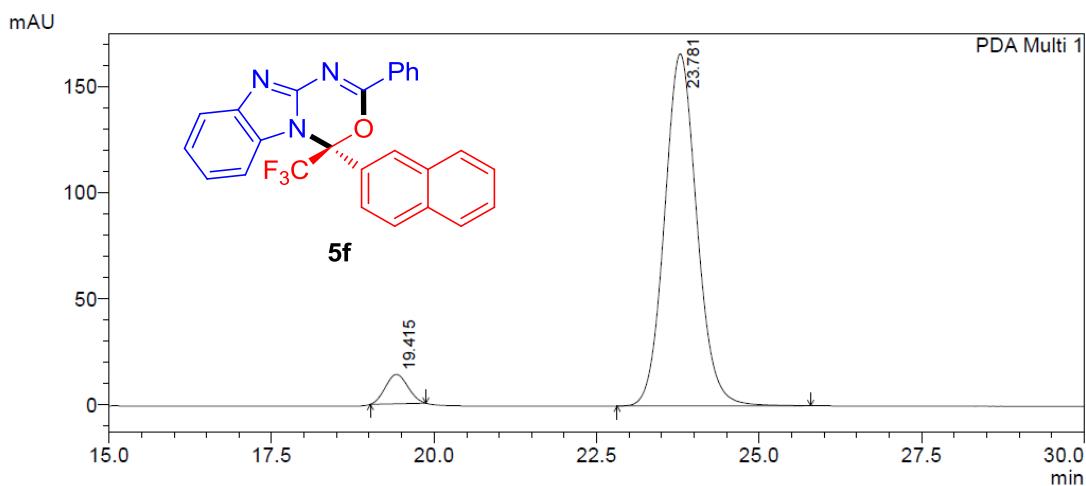
5f





PDA Ch1 254nm 4nm

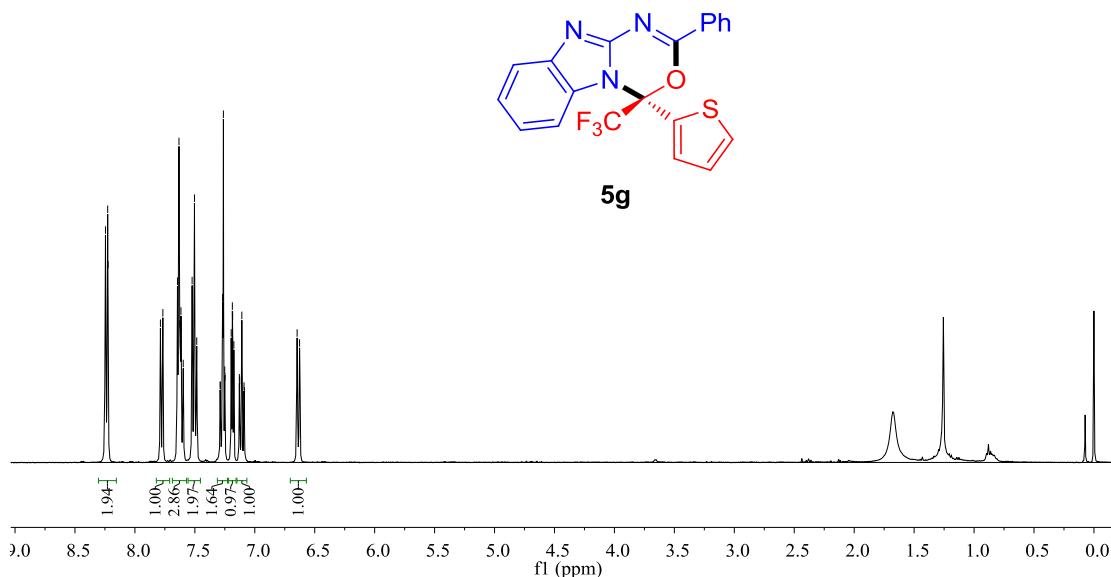
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 19.280 | 948251 | 35976 | 50.152 | 56.083 |
| 2 | 23.427 | 942517 | 28171 | 49.848 | 43.917 |
| Total | | 1890768 | 64148 | 100.000 | 100.000 |

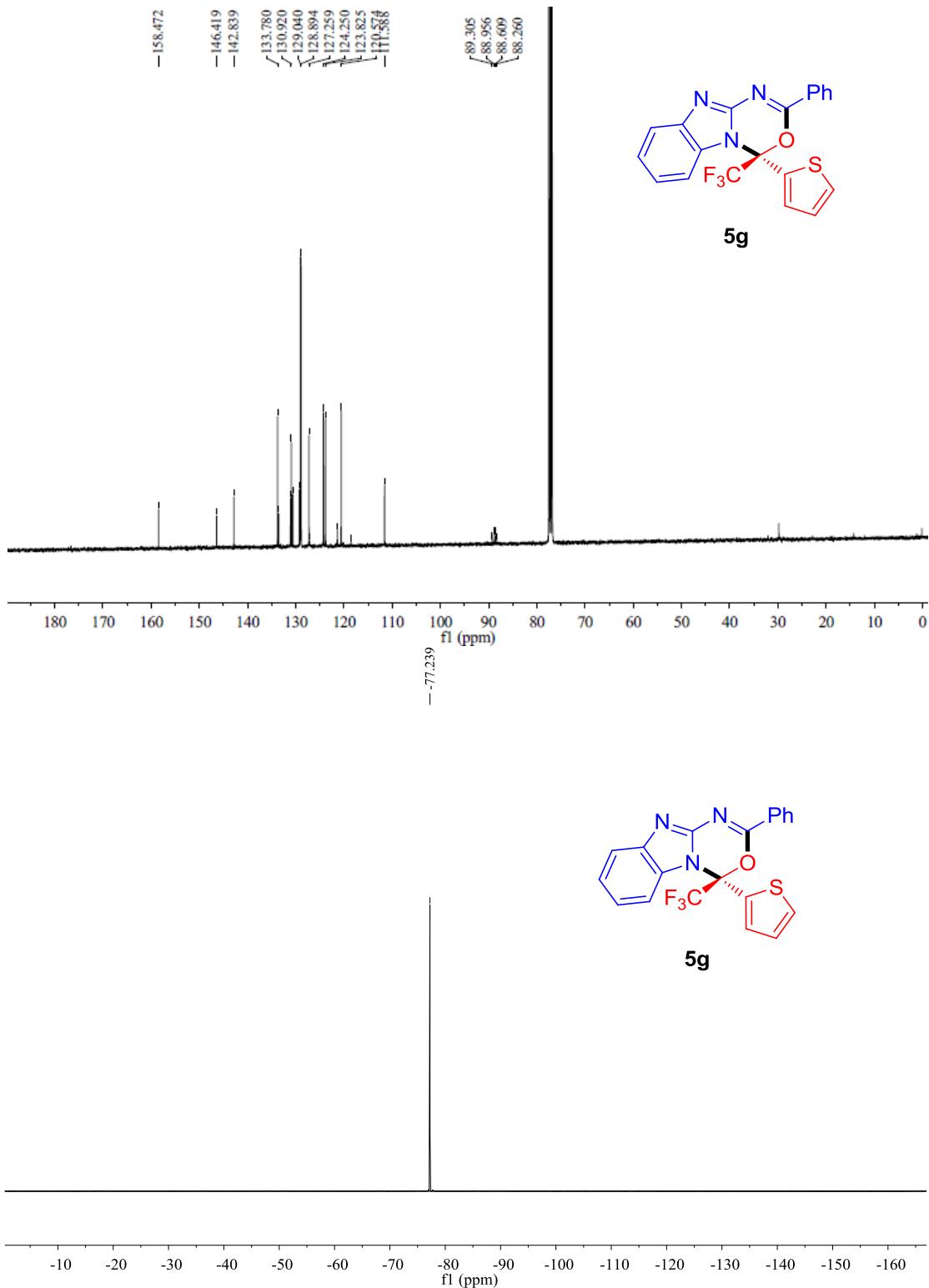


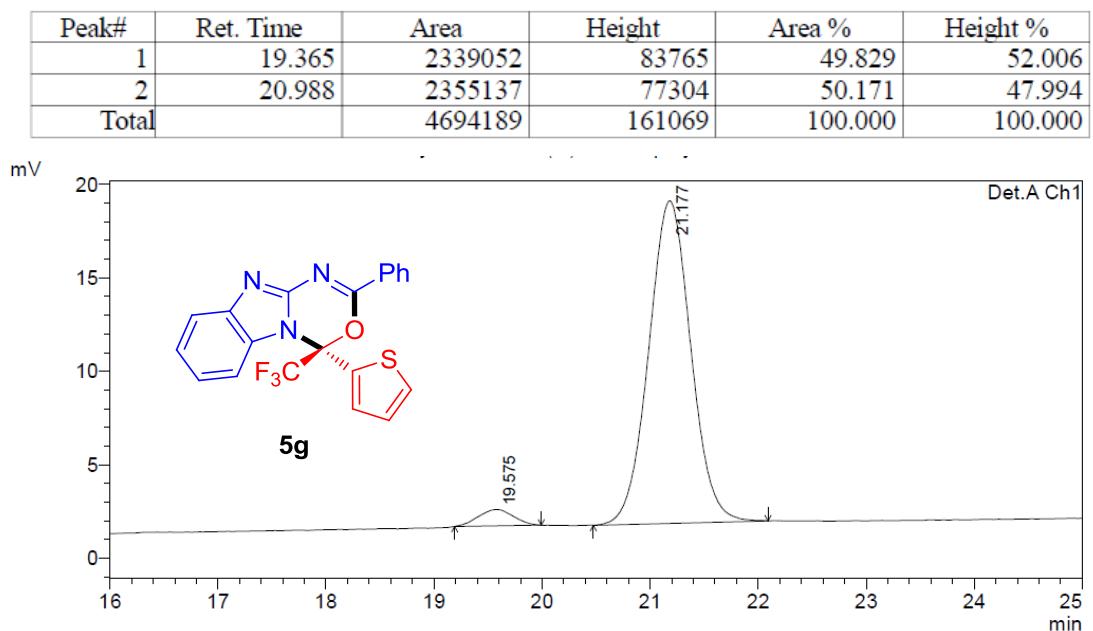
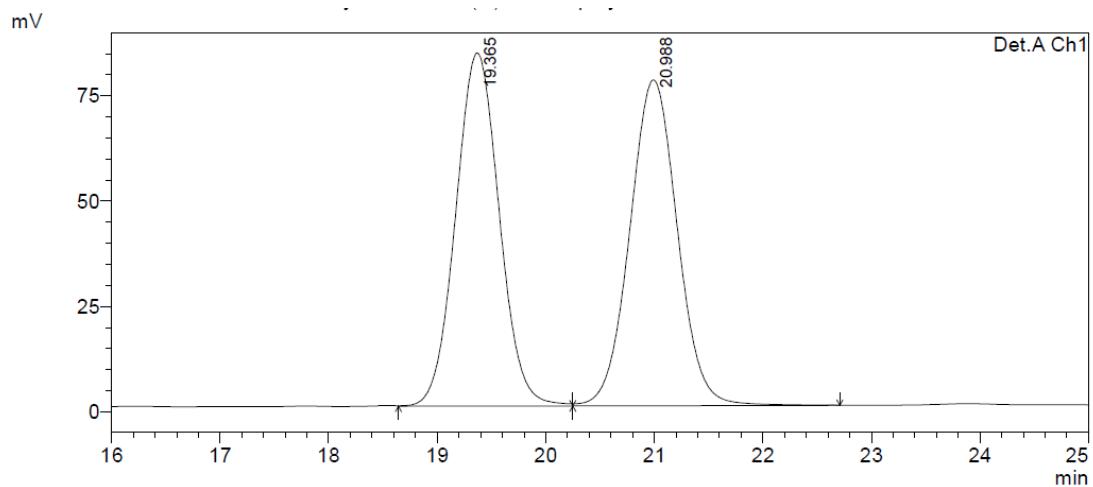
PDA Ch1 254nm 4nm

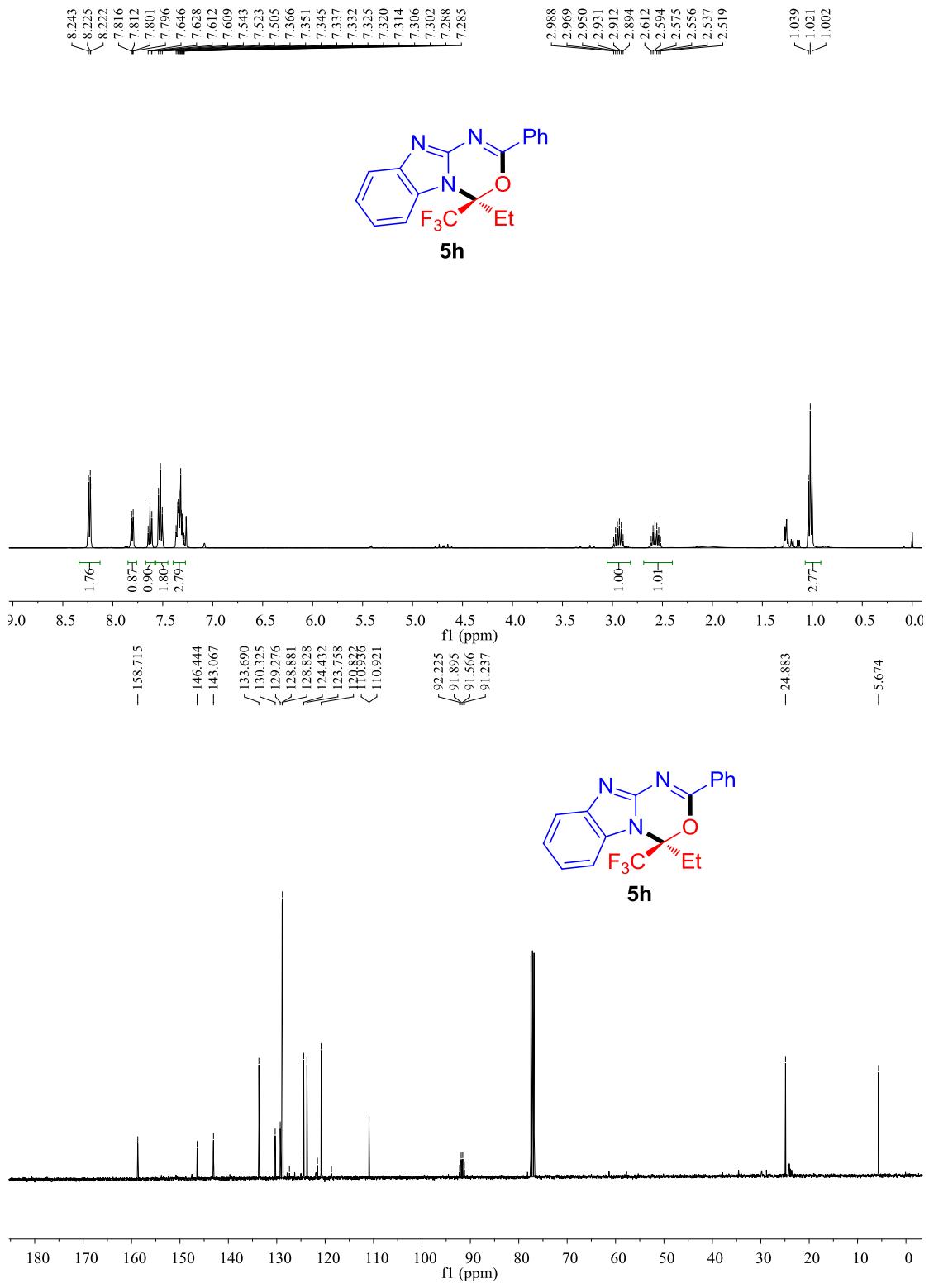
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 19.415 | 332933 | 13842 | 5.481 | 7.696 |
| 2 | 23.781 | 5741908 | 166018 | 94.519 | 92.304 |
| Total | | 6074841 | 179861 | 100.000 | 100.000 |

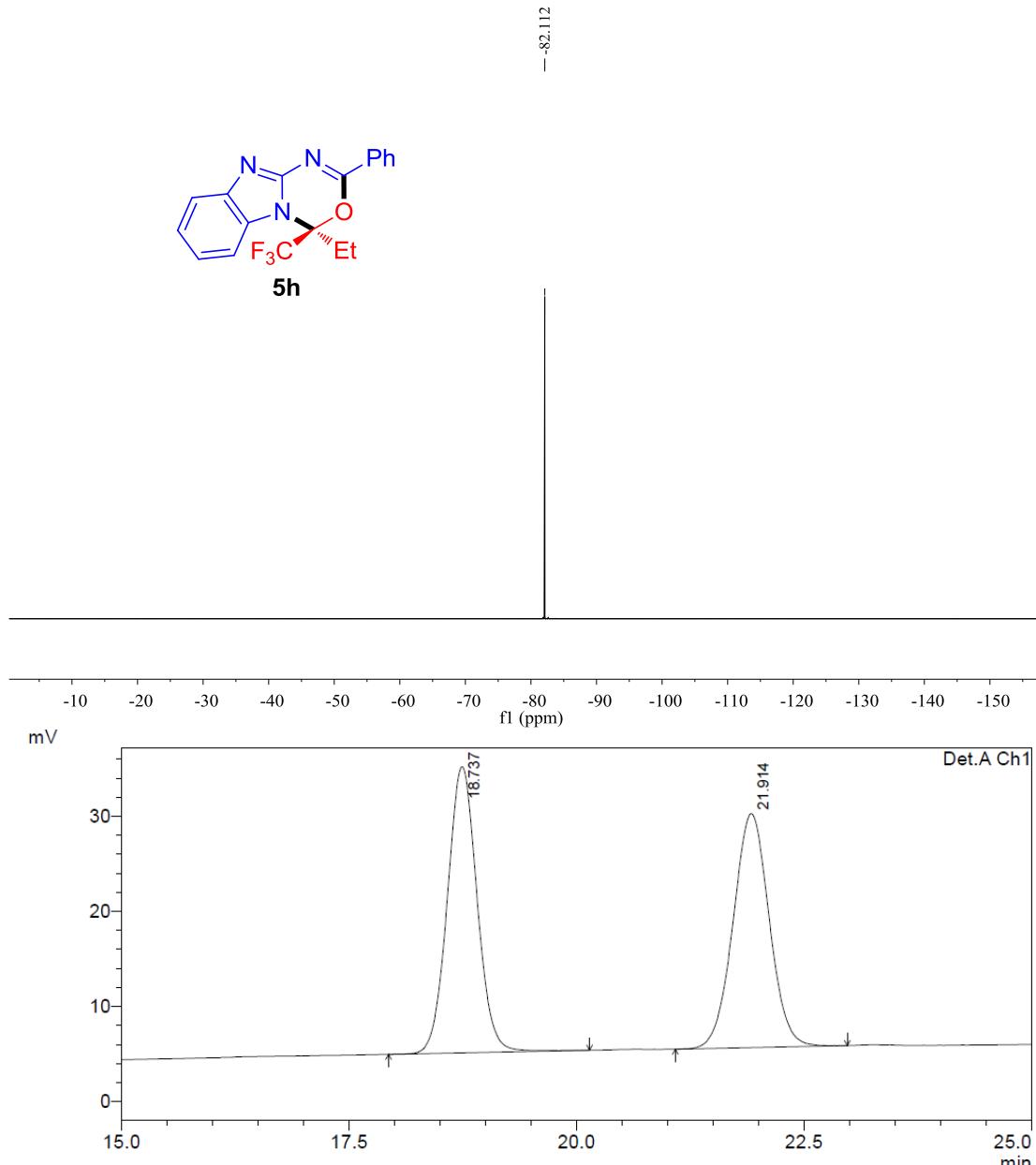
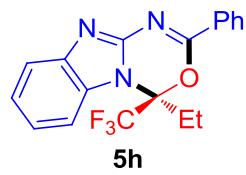
8.246
8.227
7.645
7.632
7.523
7.503
7.269
7.262
6.187
6.147
6.626





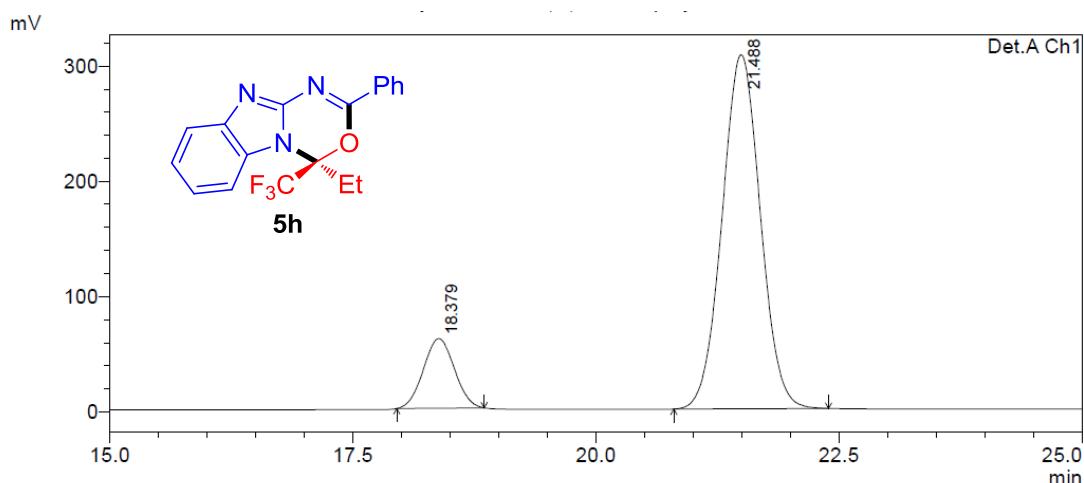






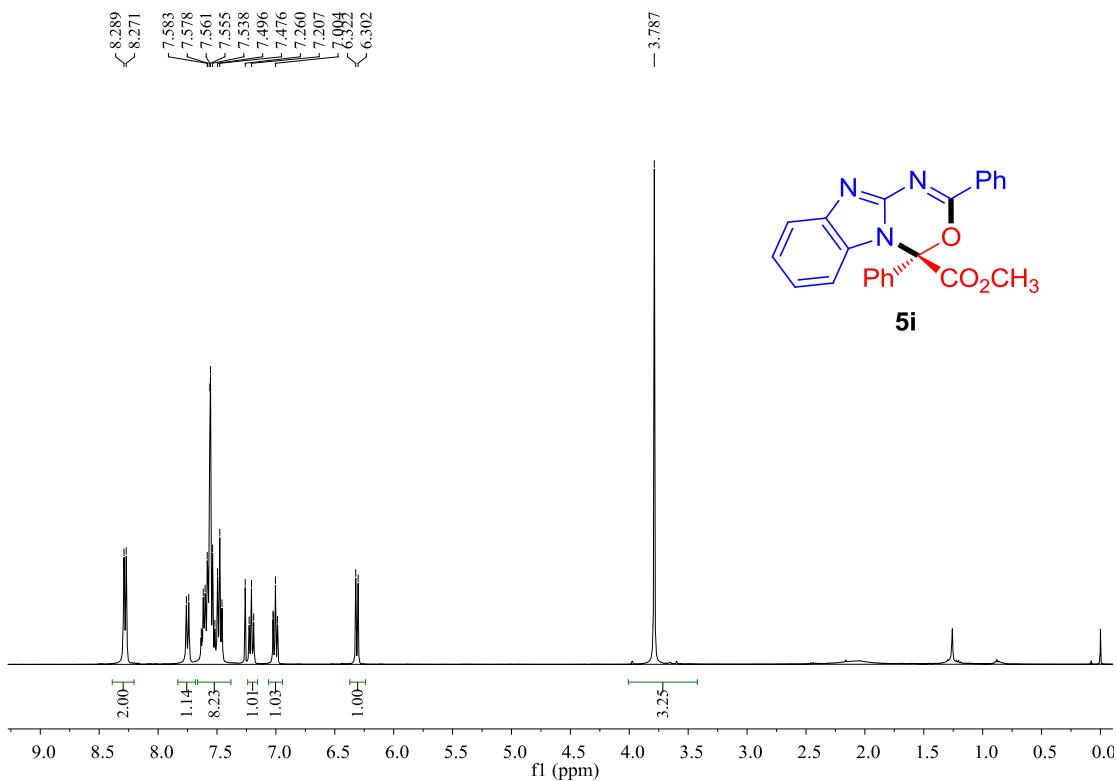
Detector A Ch1 254nm

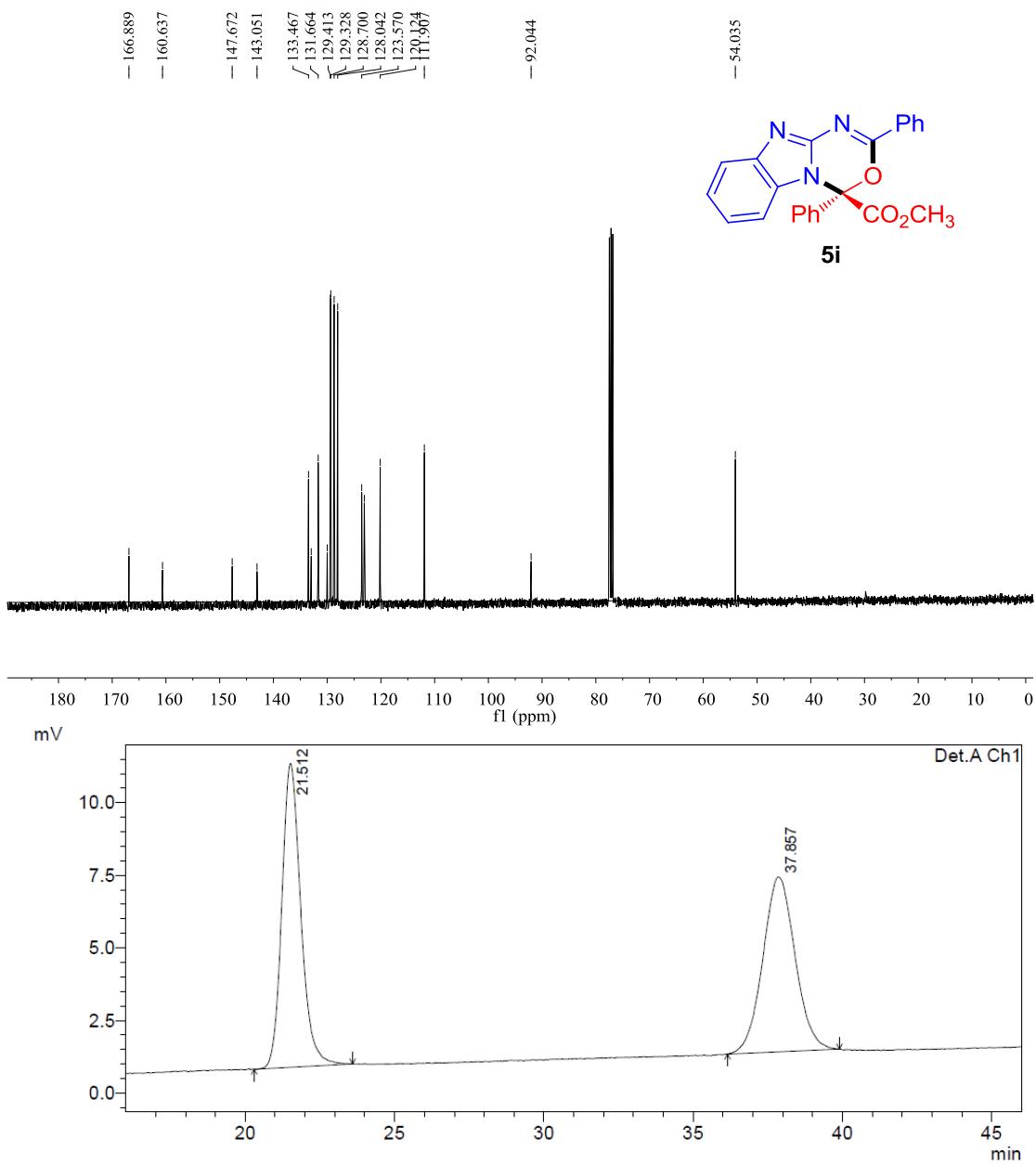
| Detector A CH ₄ 254nm | | | | | |
|----------------------------------|-----------|---------|--------|---------|----------|
| Peak# | Ret. Time | Area | Height | Area % | Height % |
| 1 | 18.737 | 683744 | 30093 | 50.139 | 55.016 |
| 2 | 21.914 | 679939 | 24605 | 49.861 | 44.984 |
| Total | | 1363683 | 54699 | 100.000 | 100.000 |



Detector A Ch1 254nm

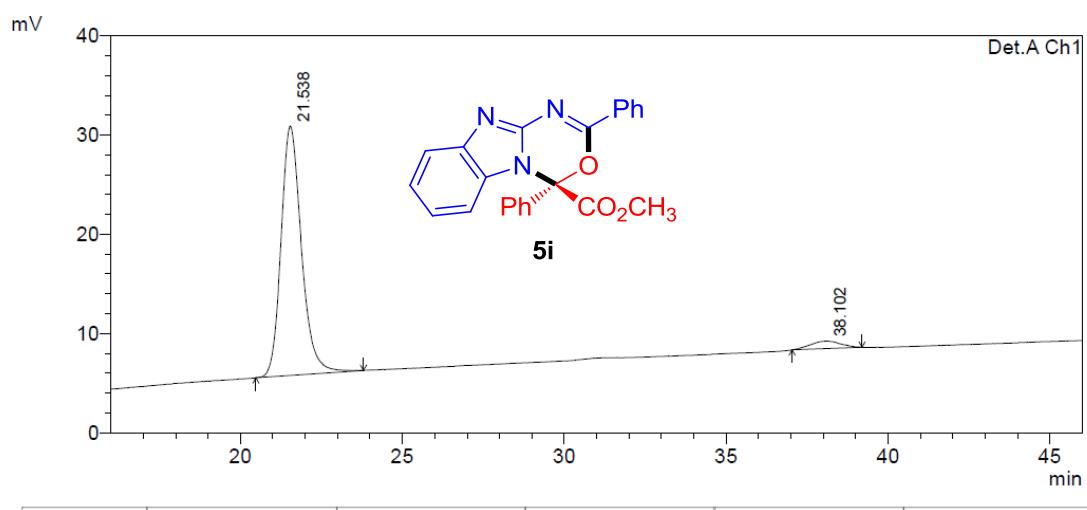
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 18.379 | 1339620 | 60353 | 13.745 | 16.429 |
| 2 | 21.488 | 8406537 | 307003 | 86.255 | 83.571 |
| Total | | 9746156 | 367356 | 100.000 | 100.000 |



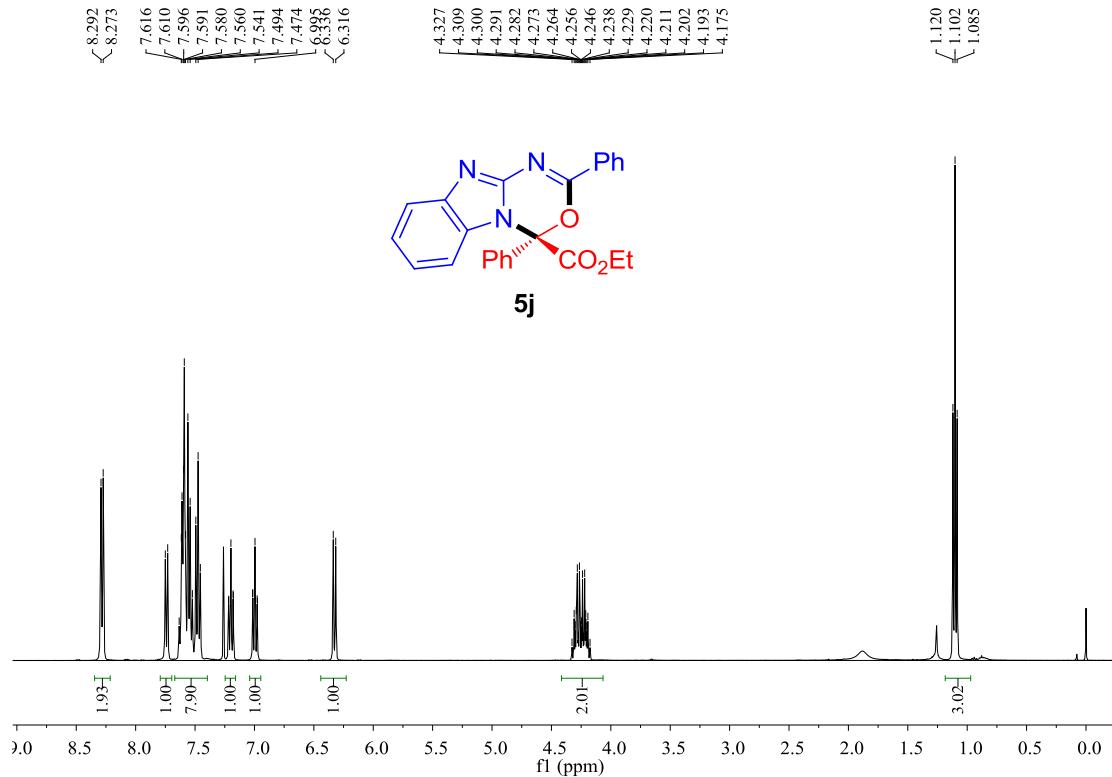


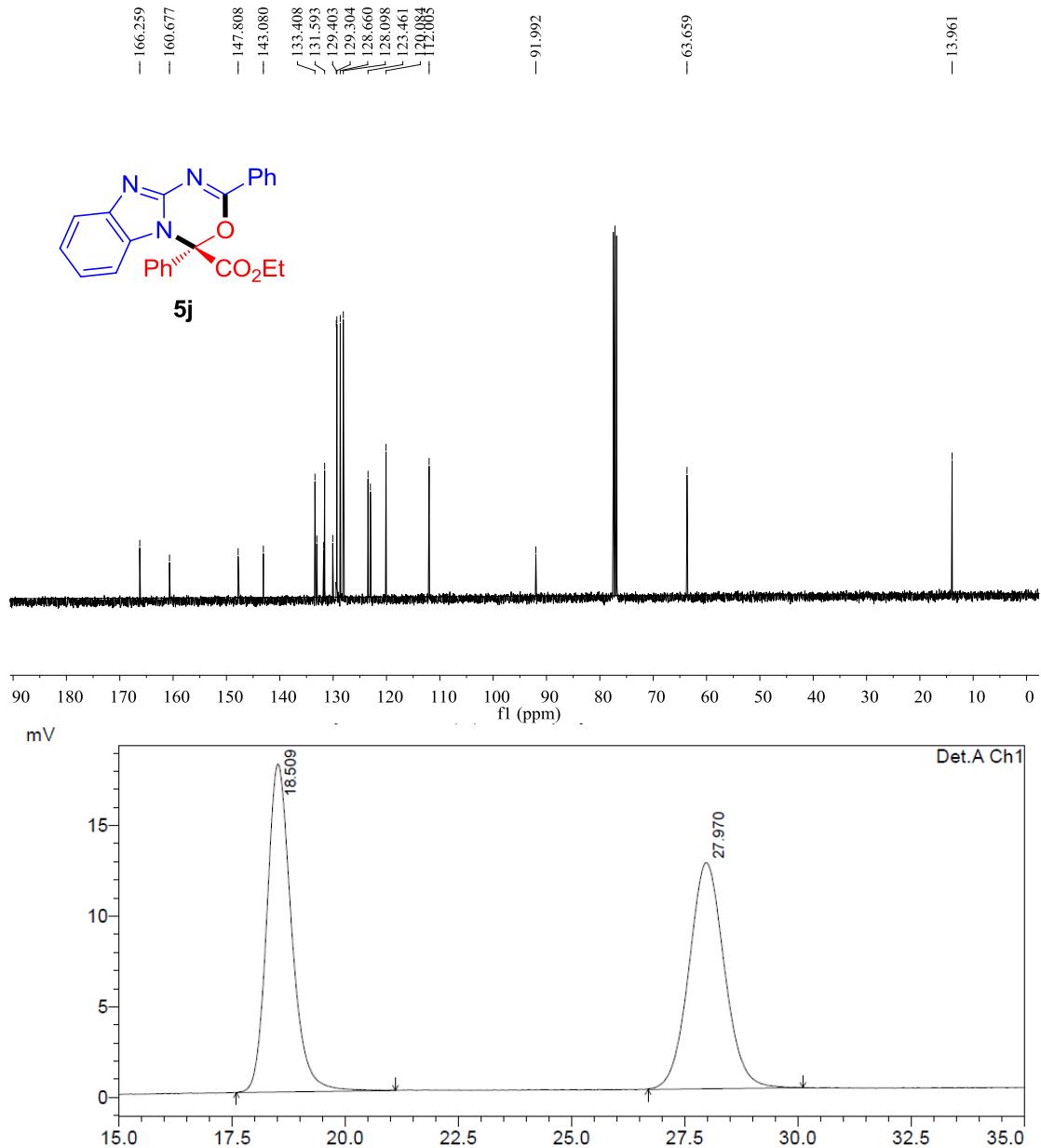
Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1 | 21.512 | 462392 | 10467 | 50.518 | 63.462 |
| 2 | 37.857 | 452916 | 6026 | 49.482 | 36.538 |
| Total | | 915308 | 16493 | 100.000 | 100.000 |

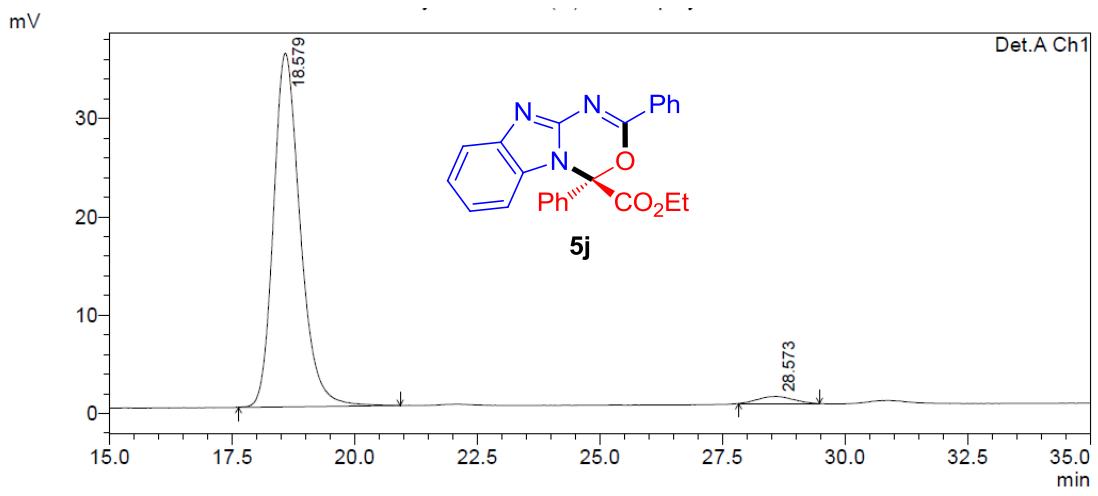


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 21.538 | 1100278 | 25128 | 95.755 | 97.107 |
| 2 | 38.102 | 48780 | 749 | 4.245 | 2.893 |
| Total | | 1149058 | 25877 | 100.000 | 100.000 |



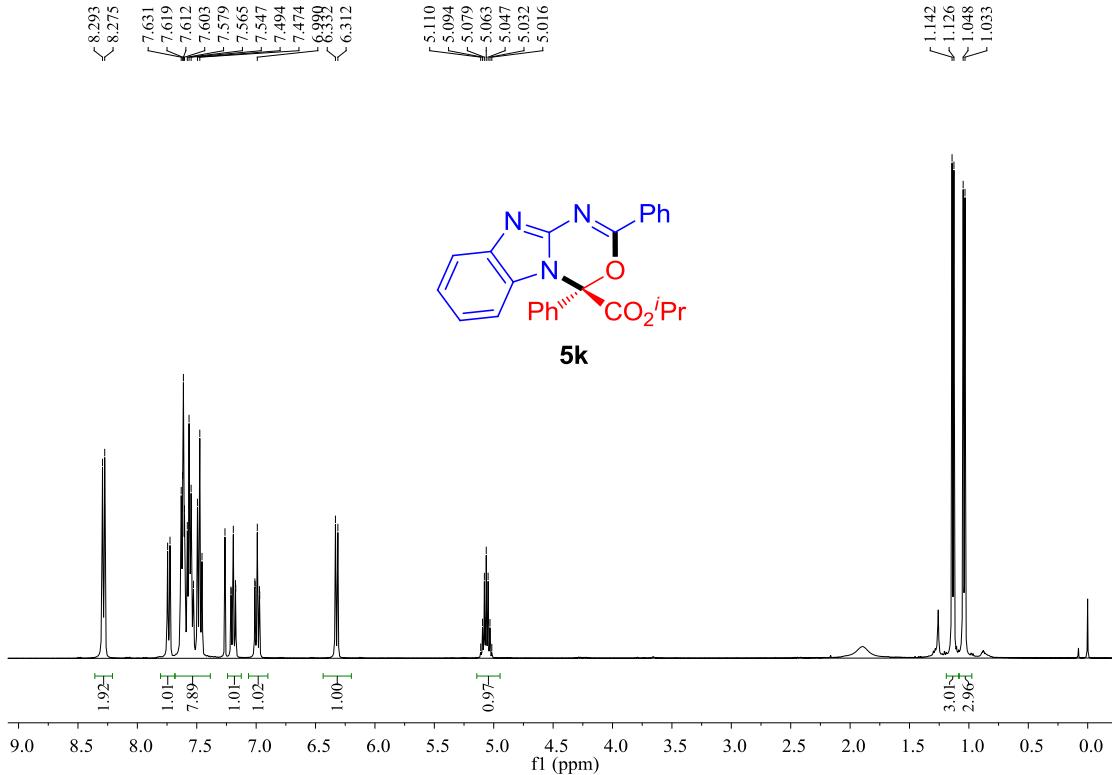


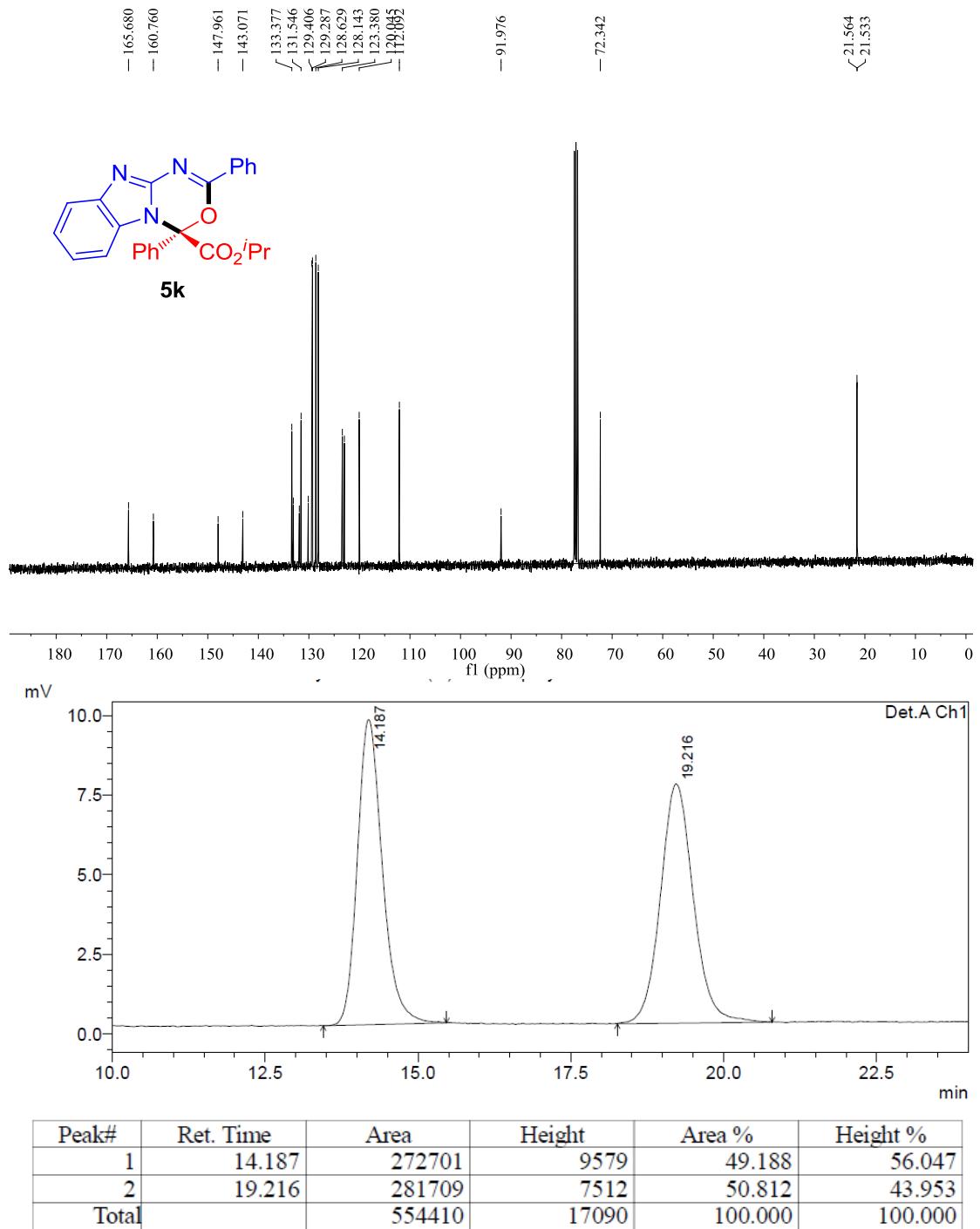
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 18.509 | 684895 | 18091 | 50.135 | 59.175 |
| 2 | 27.970 | 681205 | 12481 | 49.865 | 40.825 |
| Total | | 1366100 | 30572 | 100.000 | 100.000 |

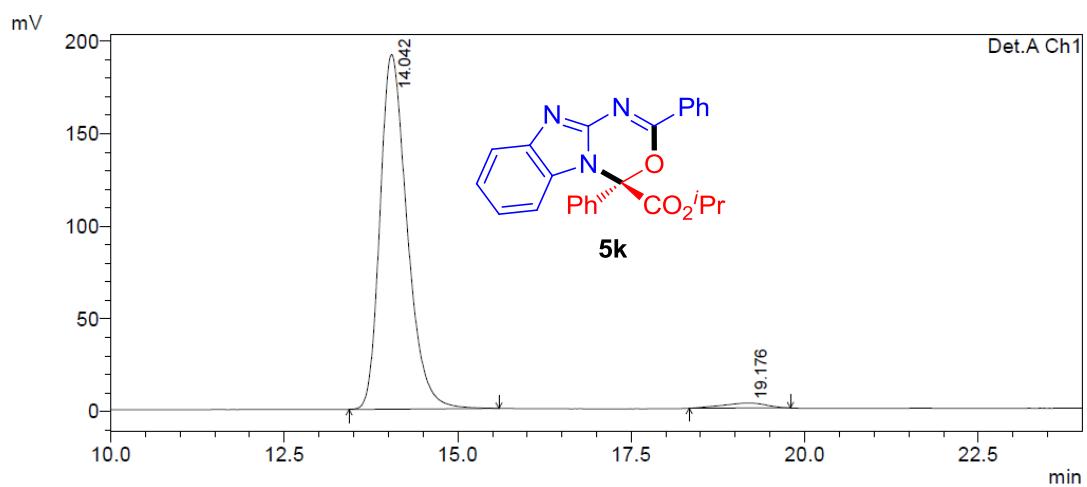


Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 18.579 | 1366836 | 35977 | 97.442 | 98.021 |
| 2 | 28.573 | 35886 | 726 | 2.558 | 1.979 |
| Total | | 1402723 | 36703 | 100.000 | 100.000 |

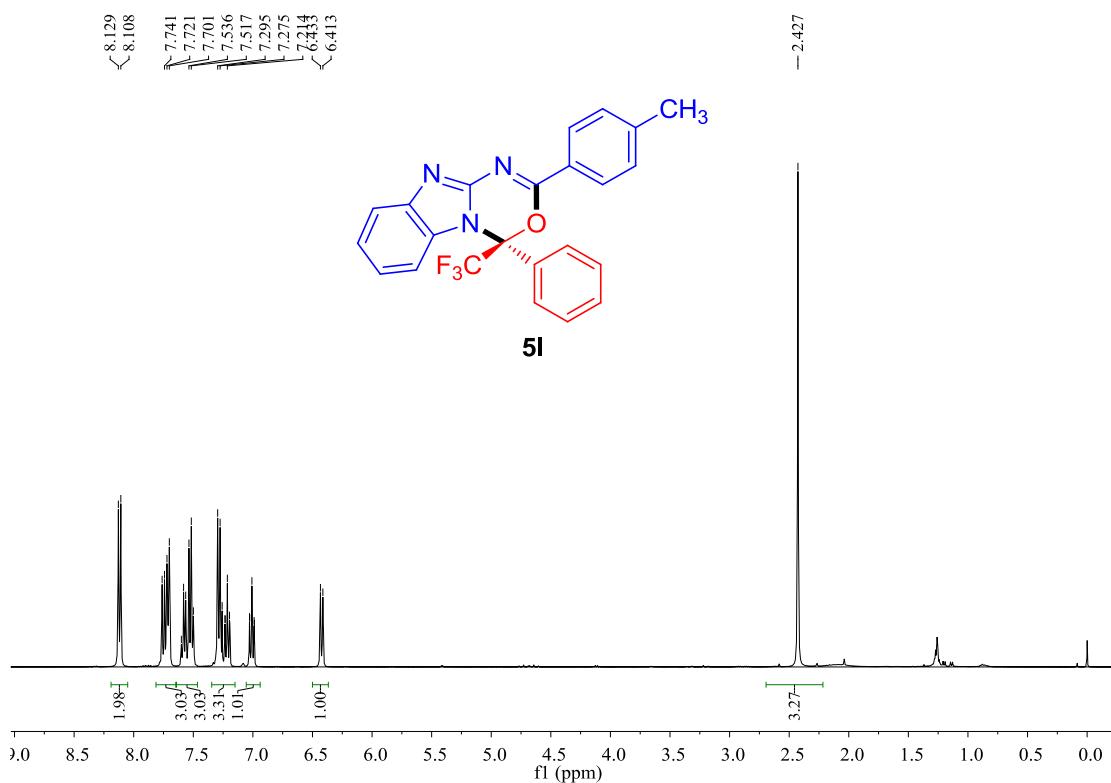


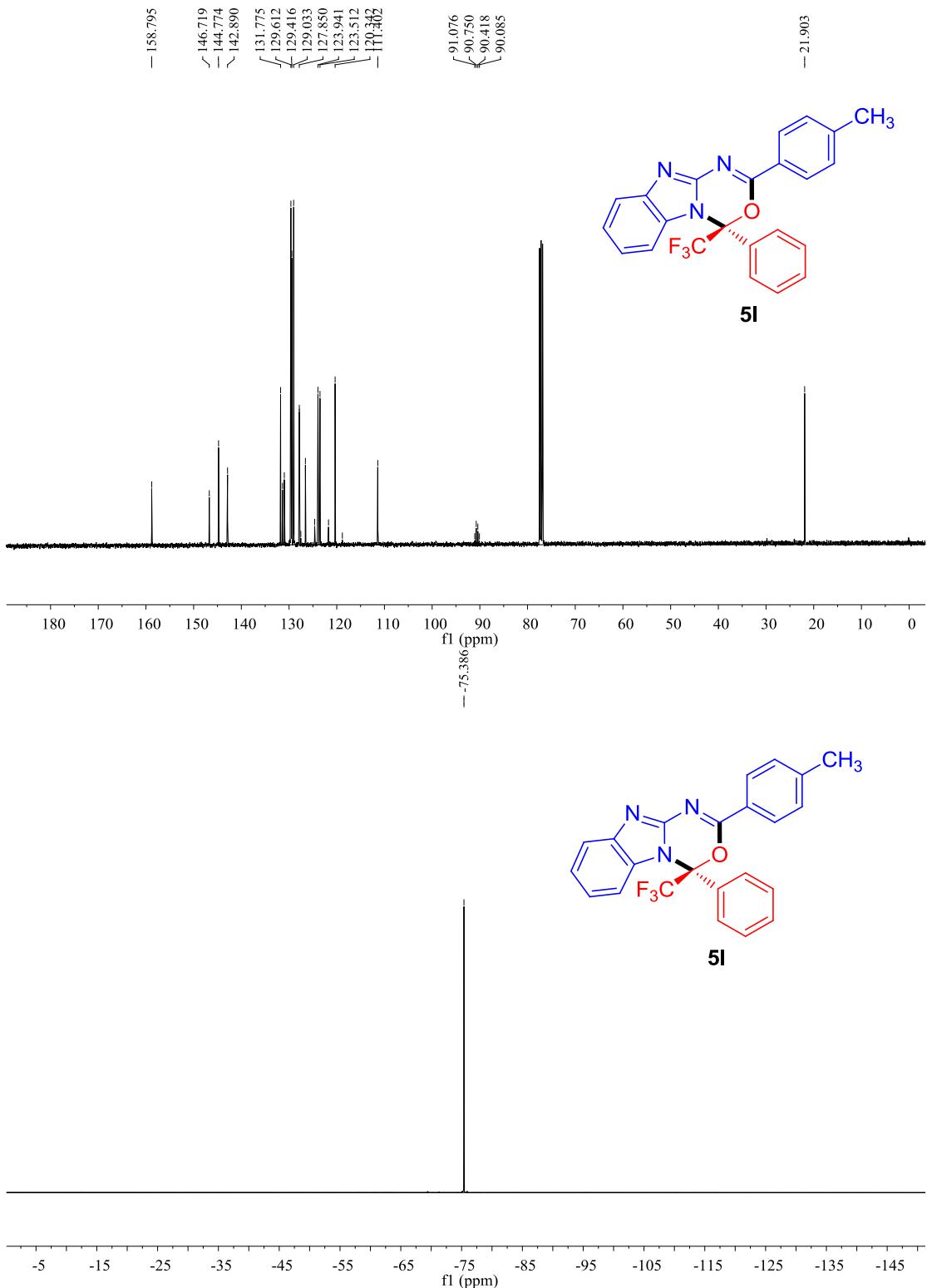


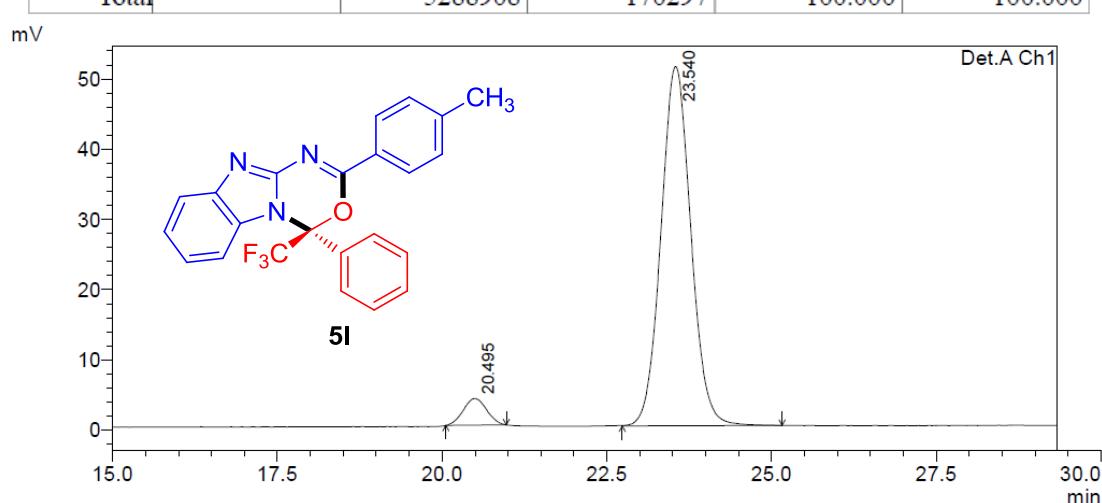
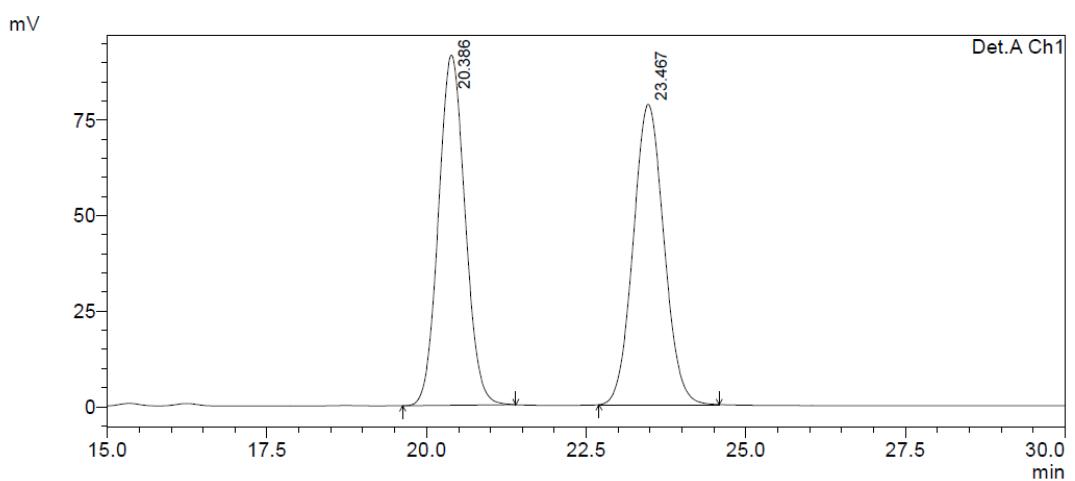


Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 14.042 | 5215689 | 191618 | 97.744 | 98.589 |
| 2 | 19.176 | 120389 | 2743 | 2.256 | 1.411 |
| Total | | 5336077 | 194361 | 100.000 | 100.000 |

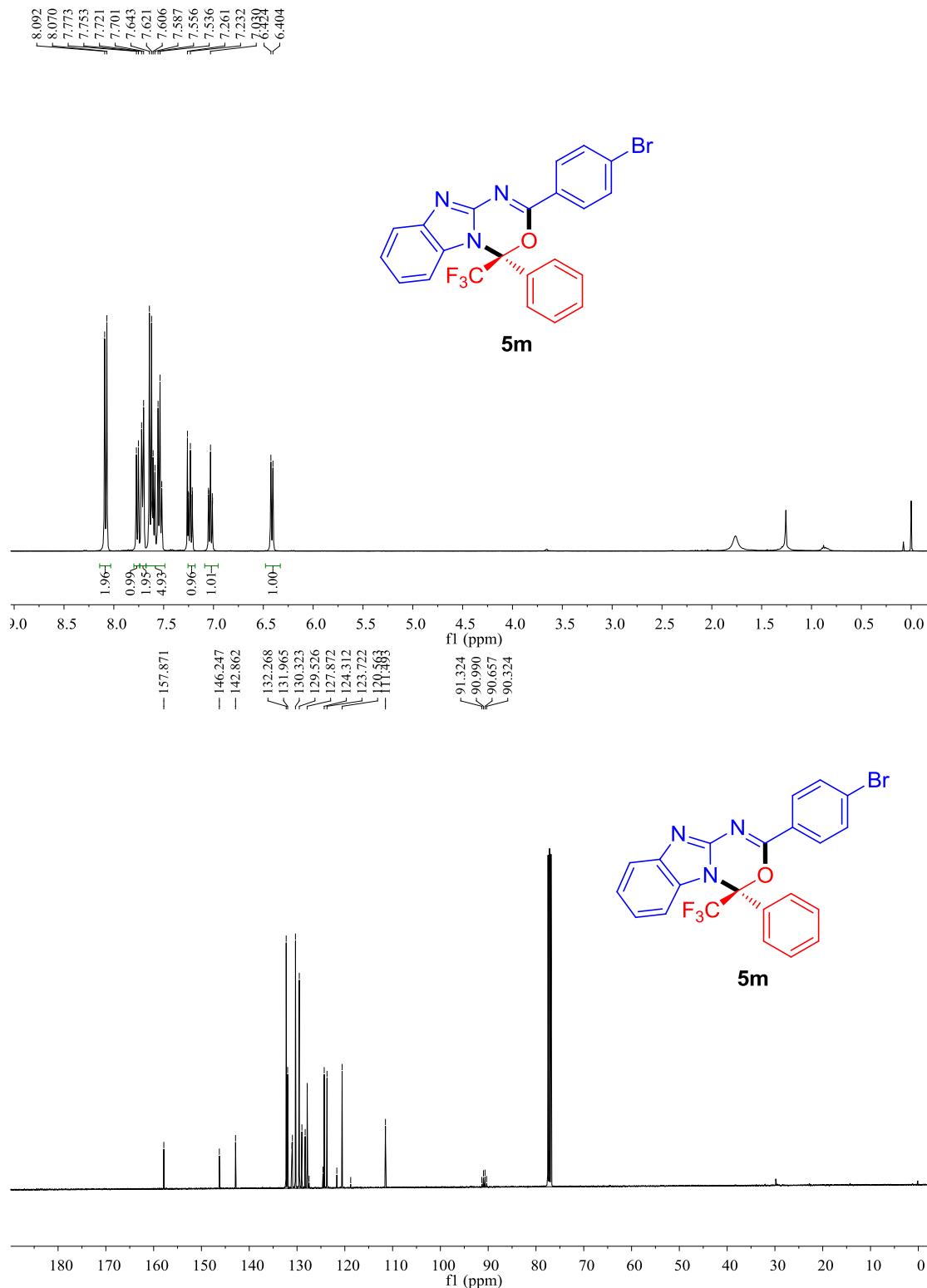


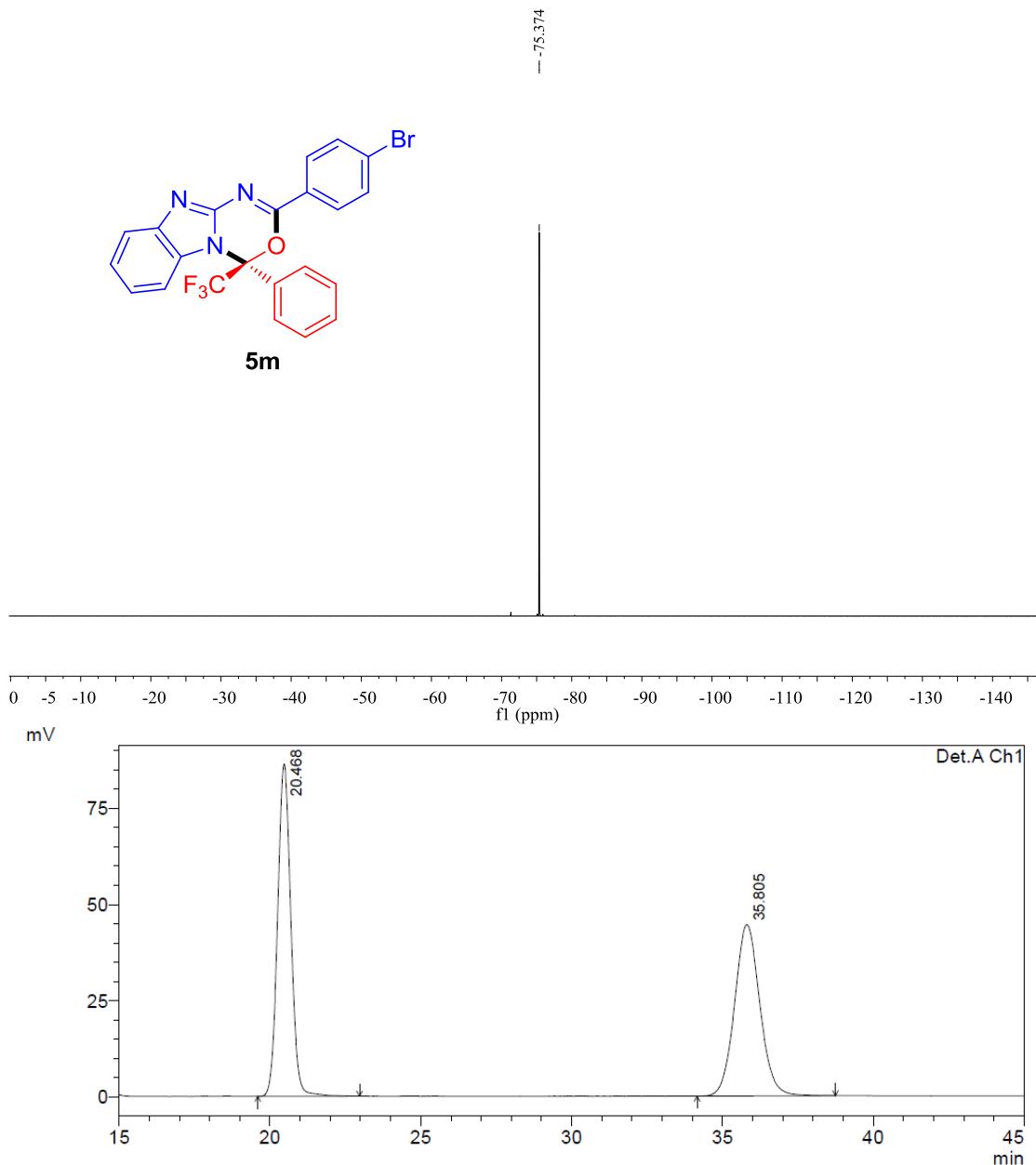




Detector A Ch1 254nm

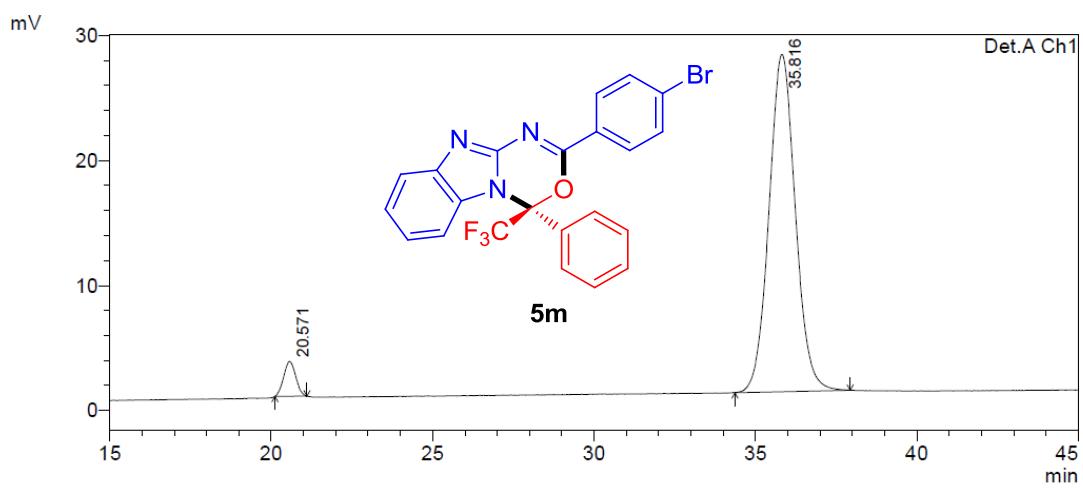
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 20.495 | 93878 | 3798 | 5.499 | 6.908 |
| 2 | 23.540 | 1613213 | 51172 | 94.501 | 93.092 |
| Total | | 1707092 | 54969 | 100.000 | 100.000 |



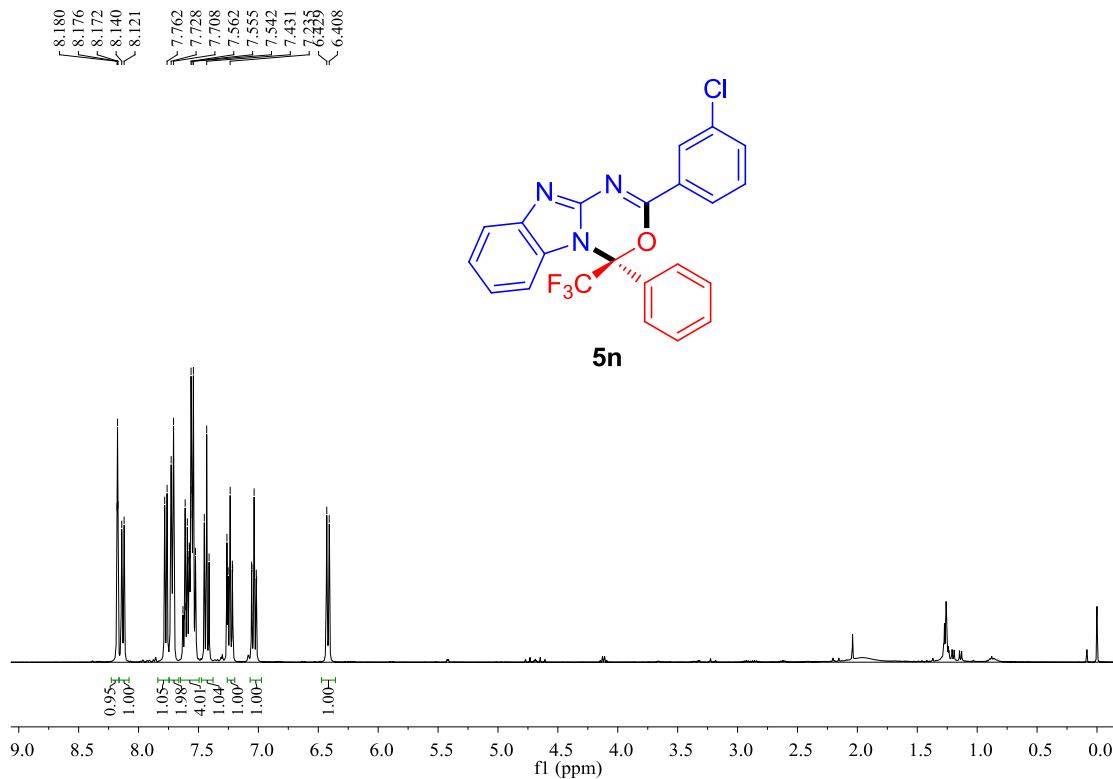


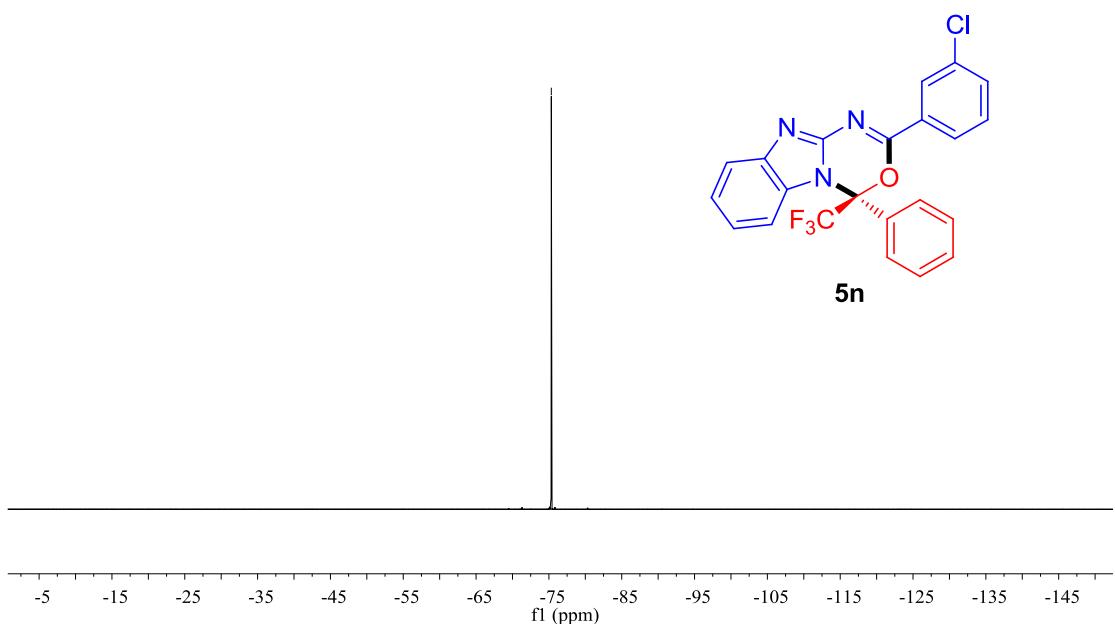
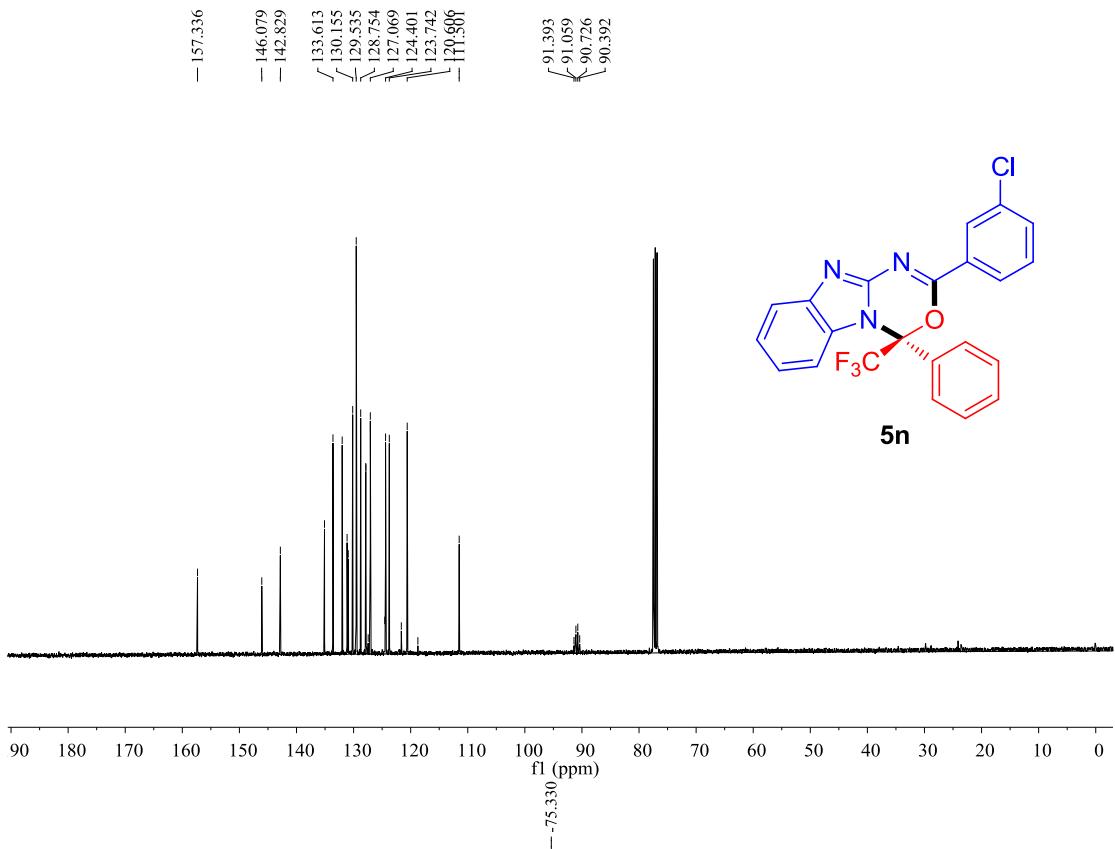
Detector A Ch1 254nm

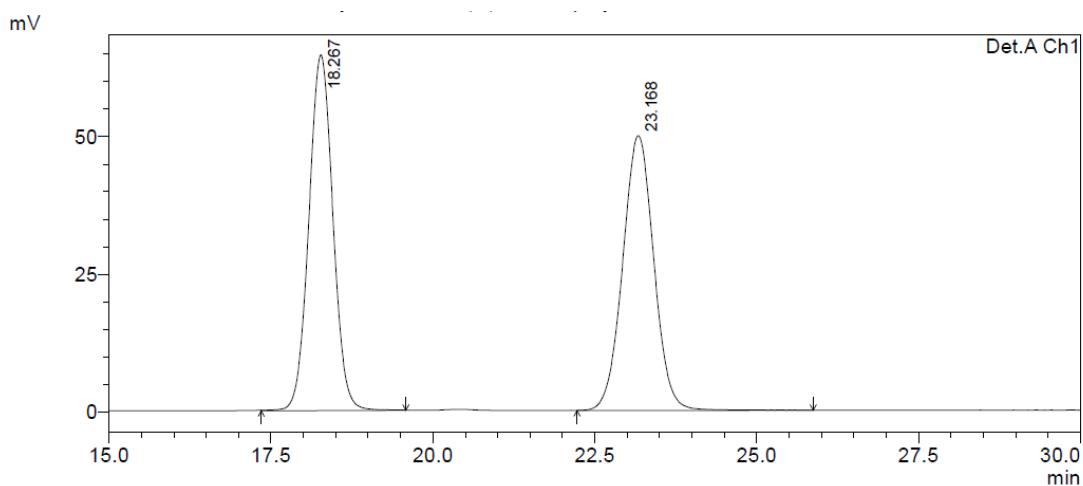
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 20.468 | 2628901 | 86267 | 50.302 | 65.972 |
| 2 | 35.805 | 2597337 | 44496 | 49.698 | 34.028 |
| Total | | 5226238 | 130763 | 100.000 | 100.000 |



| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 20.571 | 72456 | 2789 | 4.510 | 9.360 |
| 2 | 35.816 | 1534162 | 27008 | 95.490 | 90.640 |
| Total | | 1606617 | 29797 | 100.000 | 100.000 |

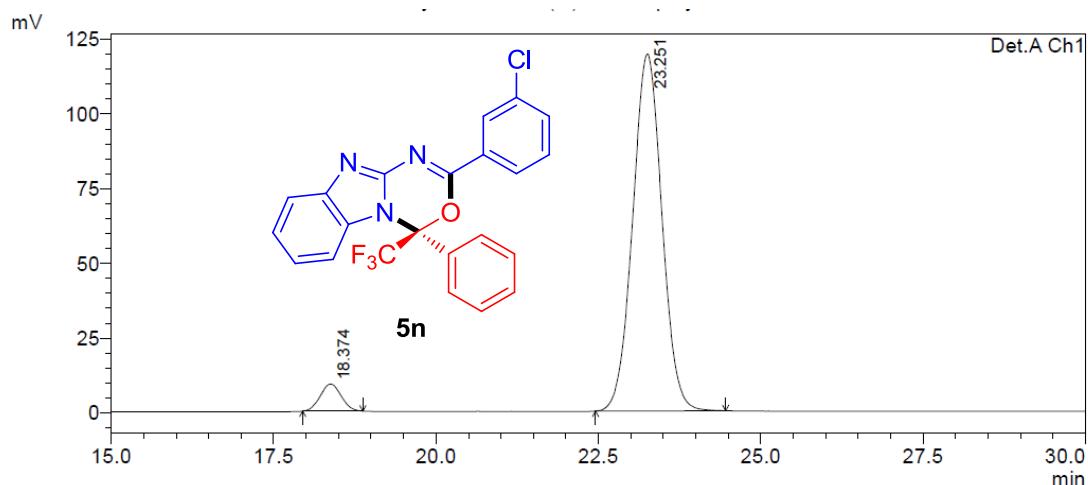






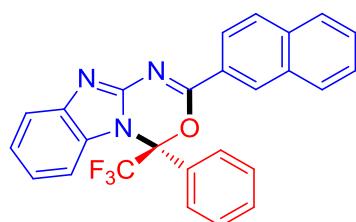
Detector A Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 18.267 | 1666653 | 64569 | 49.982 | 56.422 |
| 2 | 23.168 | 1667883 | 49869 | 50.018 | 43.578 |
| Total | | 3334536 | 114438 | 100.000 | 100.000 |

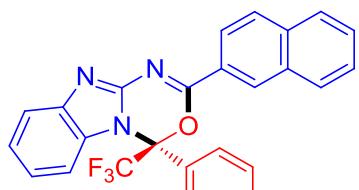
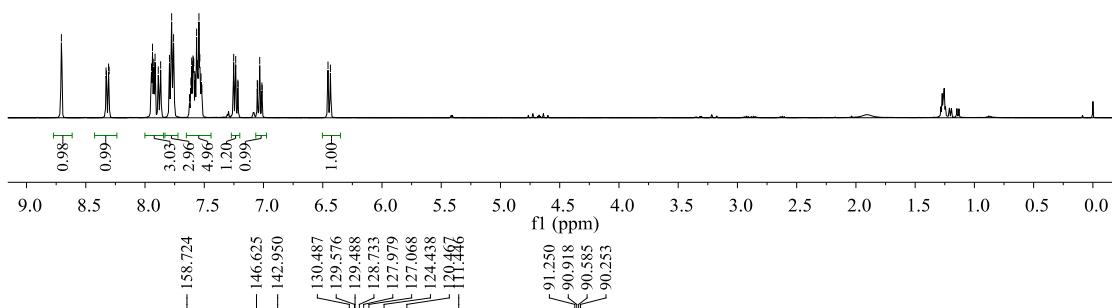


| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 18.374 | 203055 | 9070 | 5.146 | 7.058 |
| 2 | 23.251 | 3742501 | 119432 | 94.854 | 92.942 |
| Total | | 3945555 | 128502 | 100.000 | 100.000 |

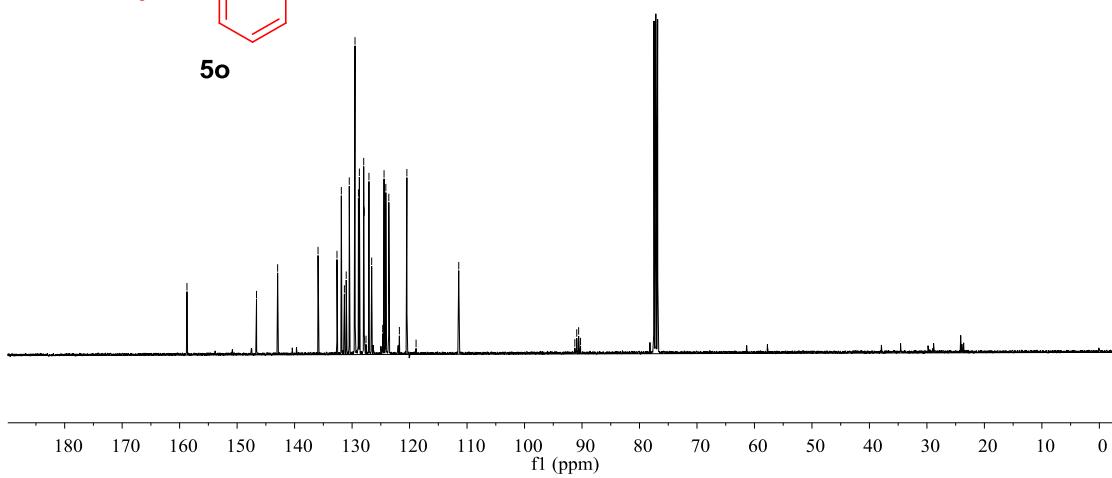
- 8.706
 8.329
 8.307
 8.303
 7.937
 7.915
 7.794
 7.775
 7.759
 7.565
 7.545
 7.537
 7.256
 6.435

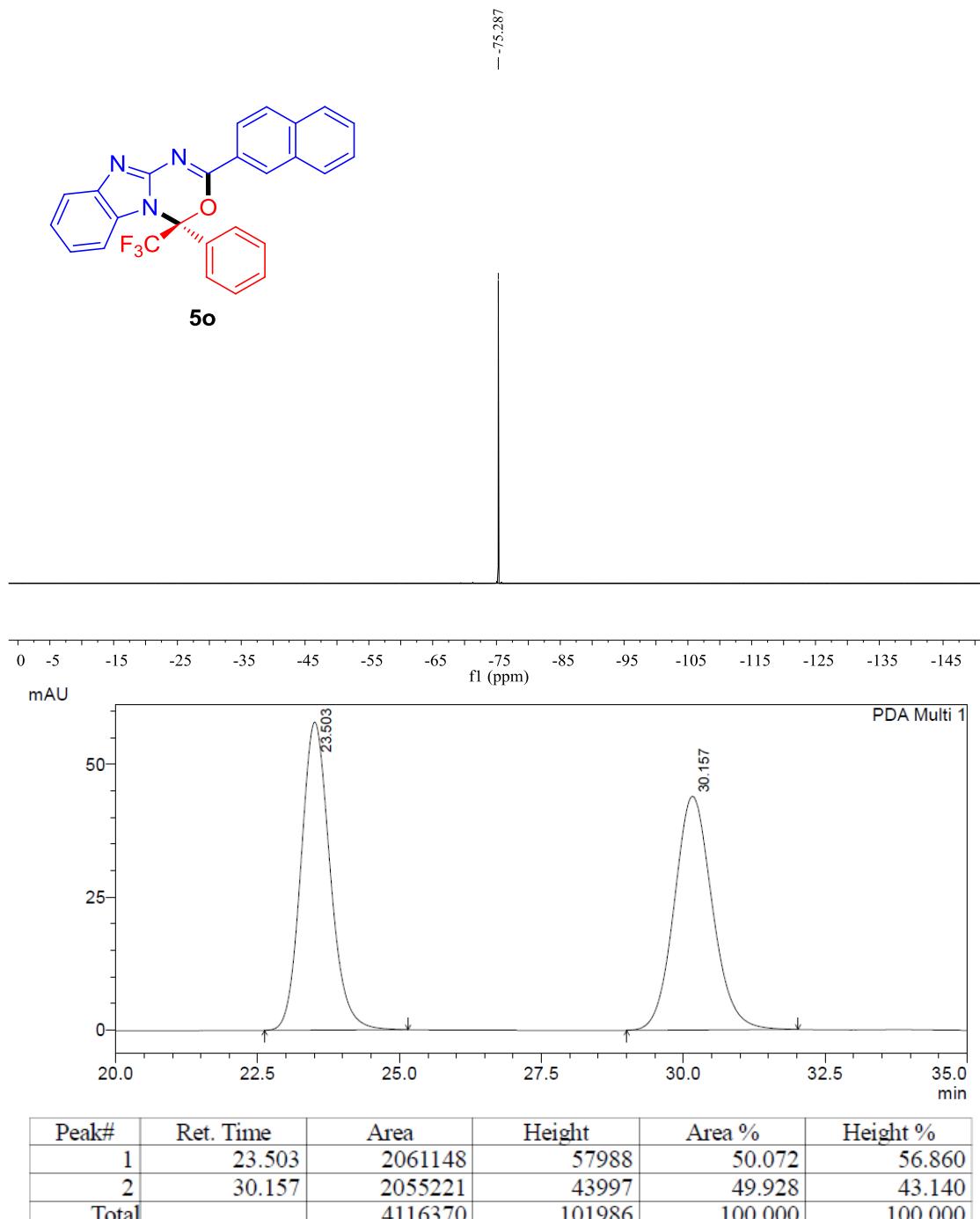


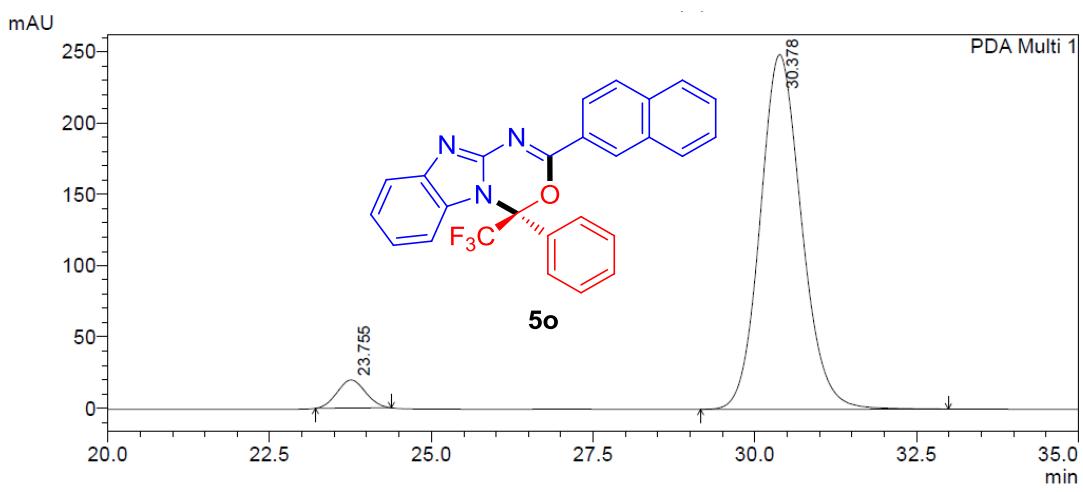
5o



5o

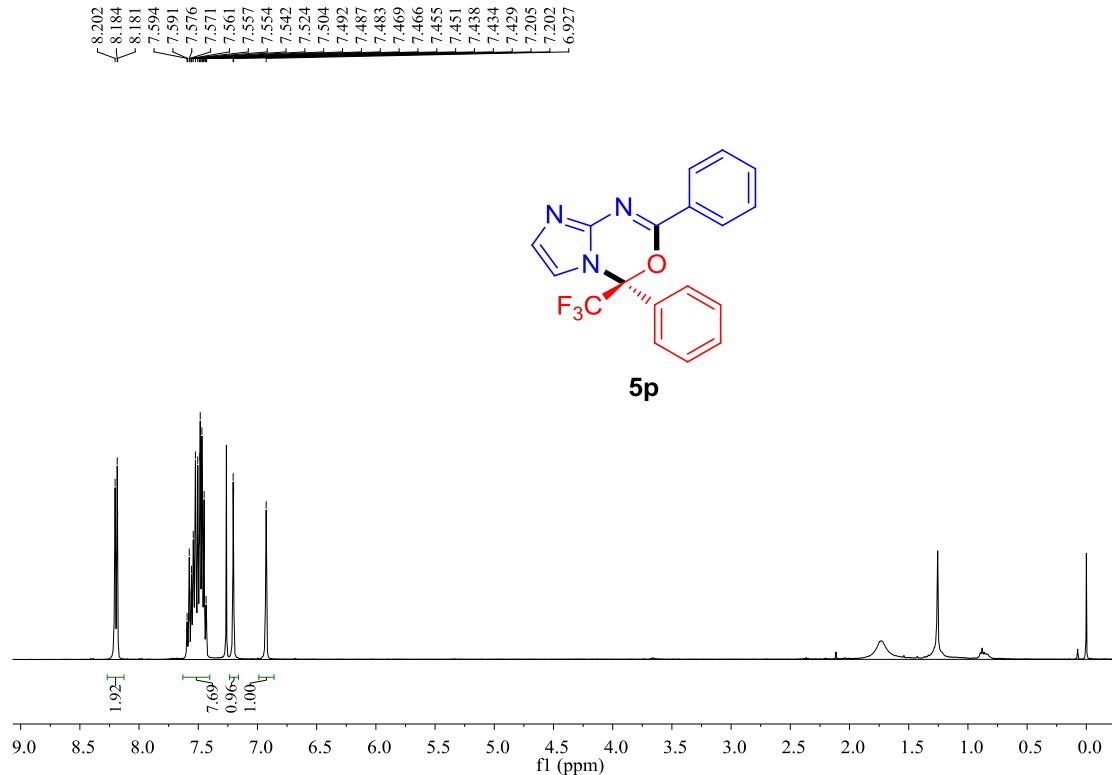


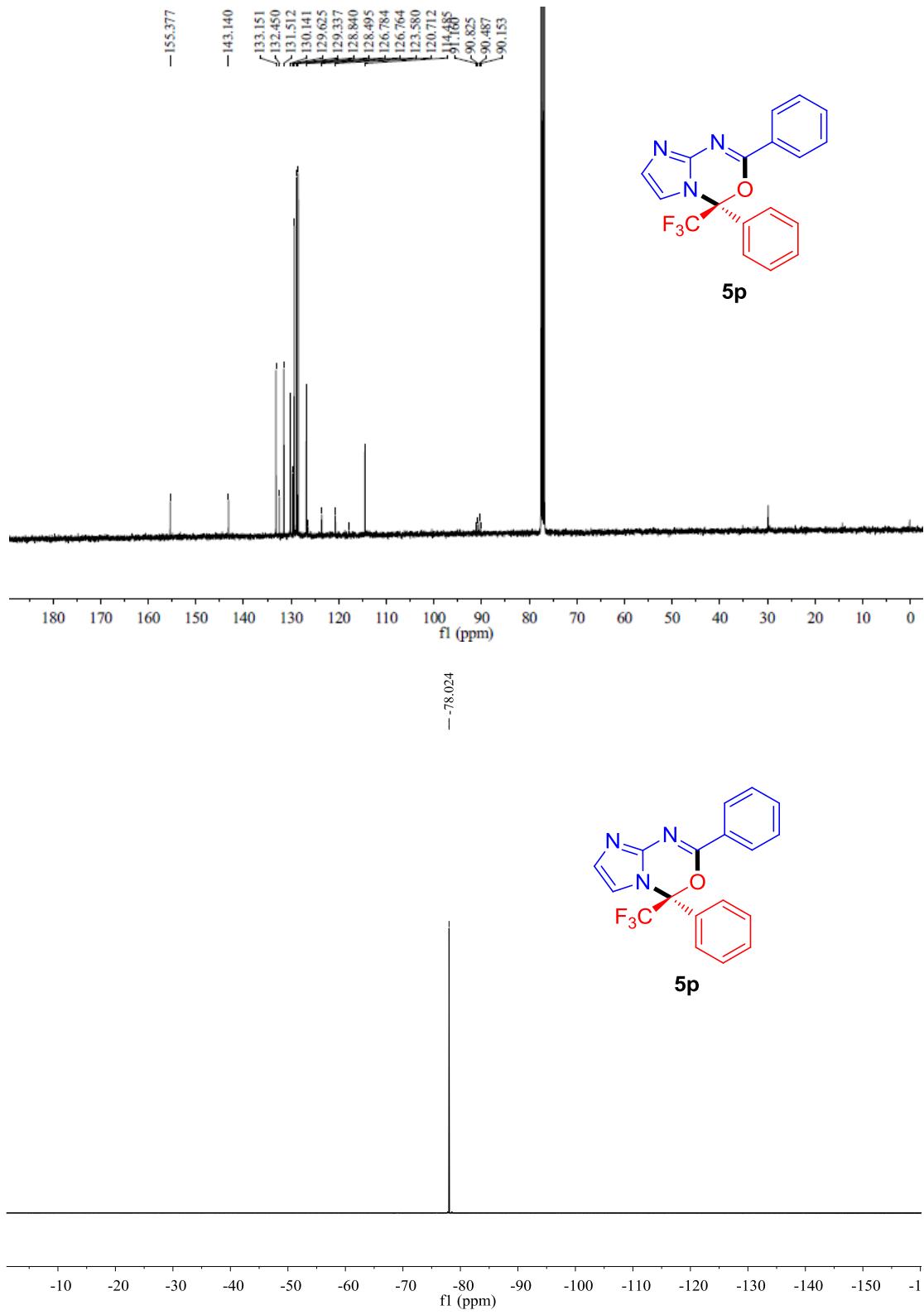


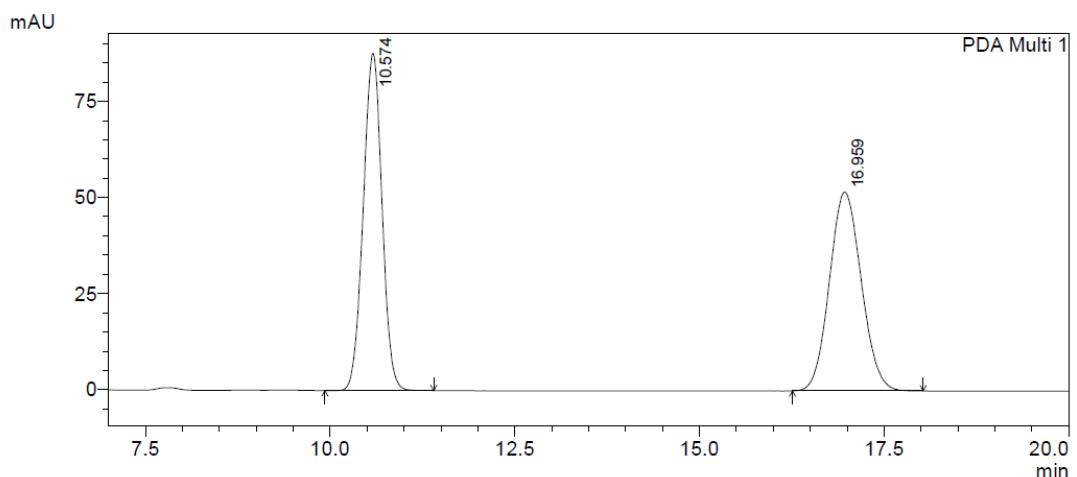


PDA Ch1 254nm 4nm

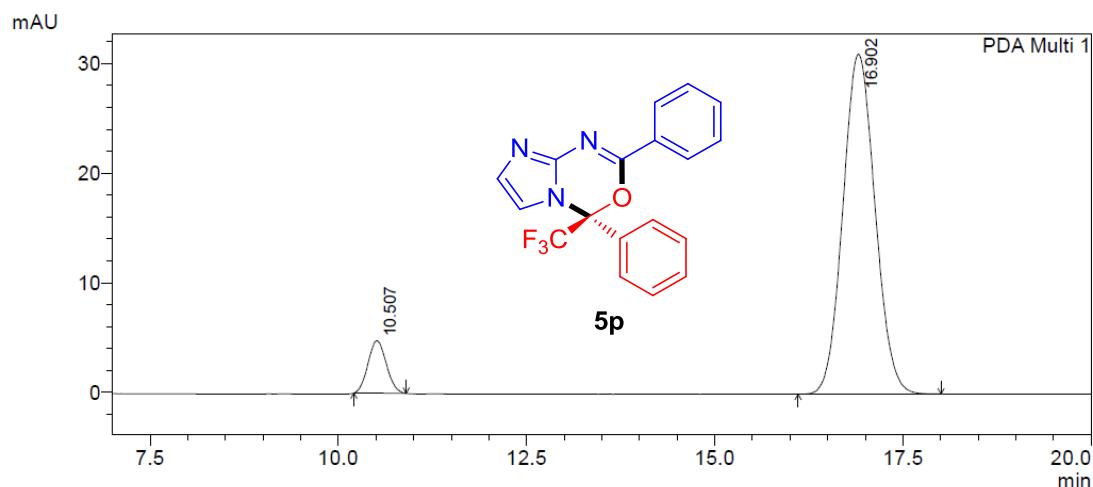
| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|----------|--------|---------|----------|
| 1 | 23.755 | 604609 | 19703 | 5.189 | 7.344 |
| 2 | 30.378 | 11047612 | 248601 | 94.811 | 92.656 |
| Total | | 11652221 | 268305 | 100.000 | 100.000 |







| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 10.574 | 1550560 | 87761 | 49.967 | 62.937 |
| 2 | 16.959 | 1552608 | 51682 | 50.033 | 37.063 |
| Total | | 3103169 | 139443 | 100.000 | 100.000 |



| Peak# | Ret. Time | Area | Height | Area % | Height % |
|-------|-----------|---------|--------|---------|----------|
| 1 | 10.507 | 80846 | 4769 | 8.063 | 13.328 |
| 2 | 16.902 | 921835 | 31016 | 91.937 | 86.672 |
| Total | | 1002681 | 35785 | 100.000 | 100.000 |

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