Electronic Supplementary Information

Pd-catalysed general access to 7-membered N/O-heterocyclic compounds as potential agents against inflammation

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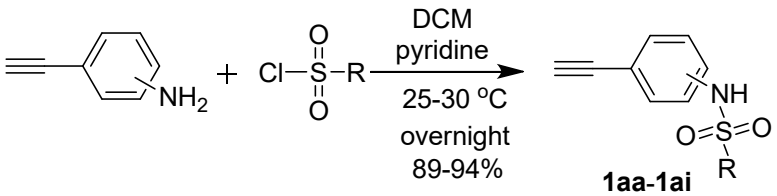
Experimental section

Chemistry

General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), using EtOAc/ *n*-hexane as solvent system and visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution by using 400 and 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. MS spectra were obtained on Agilent 6430 series Triple Quard LC-MS / MS spectrometer. Melting points (mp) were determined by using Buchi B-540 melting point apparatus and are uncorrected. Chromatographic purity by HPLC (Agilent 1200 series Chem Station software) was determined by using area normalization method and conditions specified in each case are as follows: column, mobile phase (range used), flow rate, diluent, detection wavelength, and retention time.

Scheme S-1:



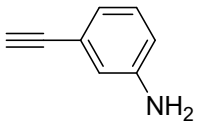
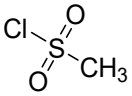
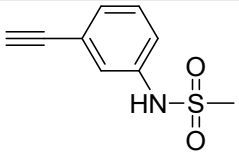
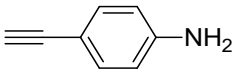
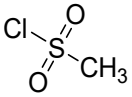
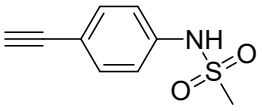
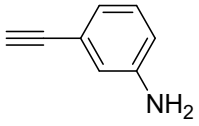
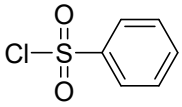
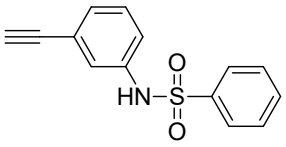
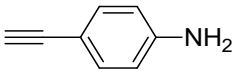
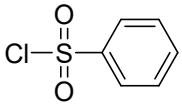
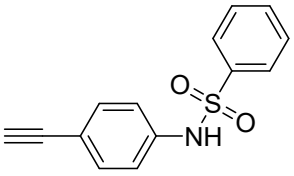
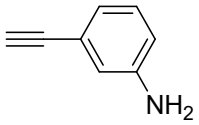
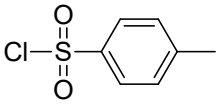
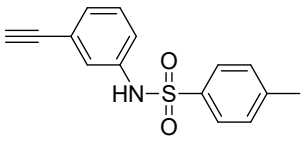
R = methyl, phenyl, *p*-toluenyl, *m*-toluenyl, 2-thienyl

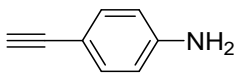
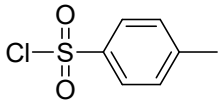
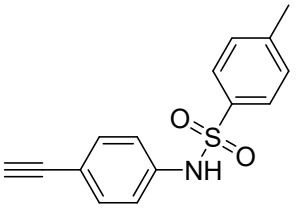
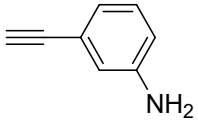
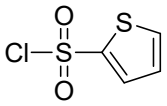
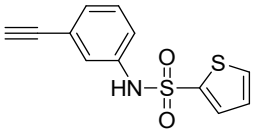
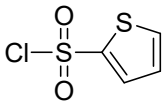
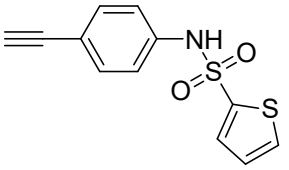
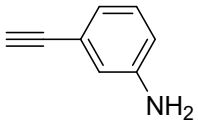
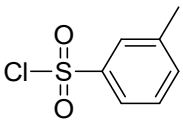
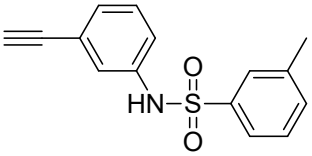
General Procedure for the preparation of compound 1 (1aa-1ai):

Appropriate sulfonyl chloride (1.2 mmol) was added to a solution containing 3-ethynylaniline or 4-ethynylaniline (1.0 mmol), and pyridine (3.0 mmol) in DCM (10 mL) under a nitrogen atmosphere at 0 °C for 10 minutes. The resulting mixture was stirred at room temperature (25-30 °C) for overnight. After completion of the reaction (indicated by TLC) and then DCM was evaporated. The residue was treated with 2N aqueous HCl (10 ml) and the mixture was diluted with ice-water (60 mL) and extracted with ethyl acetate (3 x 15 mL). The

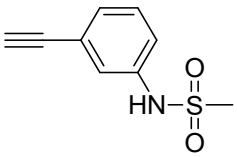
organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The residue was purified by column chromatography using hexane and EtOAc as eluent to afford the title compound. All the compounds (**1aa-1ai**) prepared were characterized by MS, NMR spectra and purity was determined by HPLC method.

Table S-1. List of synthesized compounds **1aa-1ai** from 3/4-ethynylaniline and sulfonyl chlorides (Scheme S-1)

Entry	3/4-Ethynylaniline	Sulfonyl chlorides	Product 1 (Ethynylsulfonamides)	Yield (%)
1			 **1aa**	94
2			 **1ab**	90
3			 **1ac**	93
4			 **1ad**	89
5			 **1ae**	94

6			 **1af**	91
7			 **1ag**	92
8			 **1ah**	89
9			 **1ai**	88

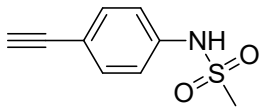
***N*-(3-Ethynylphenyl)methanesulfonamide (1aa)**



Yield: 94%; White solid; mp: 64-66 °C; R_f = 0.40 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.88 (bs, 1H, NH, D_2O exchangeable), 7.37-7.32 (m, 1H, ArH), 7.30-7.23 (m, 2H, ArH), 7.23-7.17 (m, 1H, ArH), 4.20 (s, 1H, ≡C-H), 3.02 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 138.7, 129.8, 126.9, 122.6, 122.2, 120.1, 83.0 (-C≡), 81.0 (-C≡), 39.4 (Me); MS (ES mass): 196.0 (M+1, 100%); HPLC: 99.7%, X-Bridge C-18 150 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90,

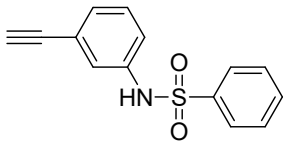
30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 215.0 nm, retention time 10.9 min.

***N-(*4-Ethynylphenyl)methanesulfonamide (1ab)**



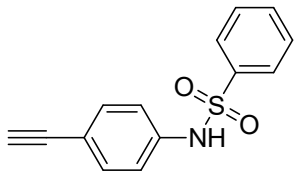
Yield: 90%; White solid; mp: 82-84 °C; R_f = 0.39 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.01 (bs, 1H, NH, D_2O exchangeable), 7.54-7.37 (m, 2H, ArH), 7.23-7.15 (m, 2H, ArH), 4.08 (s, 1H, ≡C-H), 3.03 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 139.0, 132.9 (2C), 118.8 (2C), 116.5, 83.2 (-C≡), 80.1 (-C≡), 39.3 (Me); MS (ES mass): 196.0 (M+1, 100%); HPLC: 99.7%, X-Bridge C-18 150 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/20, 20/90, 30/90, 30/90, 31/20, 35/20; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 220.0 nm, retention time 7.4 min.

***N*-(3-Ethynylphenyl) benzenesulfonamide (1ac)**



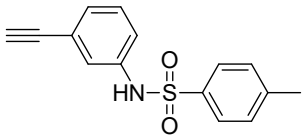
Yield: 93%; White solid; mp: 68-70 °C; R_f = 0.51 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.46 (bs, 1H, NH, D_2O exchangeable), 7.79-7.76 (m, 1H, ArH), 7.76-7.74 (m, 1H, ArH), 7.64-7.59 (m, 1H, ArH), 7.58-7.53 (m, 2H, ArH), 7.27-7.23 (m, 1H, ArH), 7.17-7.10 (m, 3H, ArH), 4.21 (s, 1H, ≡C-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 139.2, 138.0, 133.1, 129.7, 129.3 (2C), 127.3, 126.6 (2C), 122.5, 122.4, 120.4, 82.8 (-C≡), 81.1 (-C≡); MS (ES mass): 258.0 (M+1, 100%); HPLC: 98.1%, X-Bridge C-18 150 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 25/90, 35/90, 36/5, 40/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); Max plot, retention time 15.9 min.

***N*-(4-Ethynylphenyl)benzenesulfonamide (1ad)**



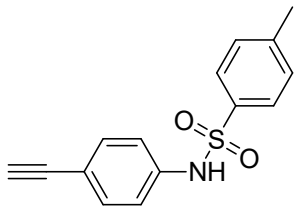
Yield: 89%; White solid; mp: 150-152 °C; R_f = 0.50 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.57 (bs, 1H, NH, D_2O exchangeable), 7.85-7.77 (m, 2H, ArH), 7.63-7.53 (m, 3H, ArH), 7.34 (d, *J* = 8.4 Hz, 2H, ArH), 7.09 (d, *J* = 8.8 Hz, 2H, ArH), 4.05 (s, 1H, ≡C-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 139.3, 138.3, 133.1, 132.7 (2C), 129.3 (2C), 126.6 (2C), 119.3 (2C), 116.9, 83.0 (-C≡), 80.3(-C≡); MS (ES mass): 258.0 (M+1, 100%); HPLC: 96.1%, Eclipse plus C-18 250 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/20, 35/90, 40/90, 41/20, 45/20; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 215.0 nm, retention time 19.8 min.

_N_-(3-Ethynylphenyl)-4-methylbenzenesulfonamide (1ae)



Yield: 94%; White solid; mp: 59-61 °C; R_f = 0.53 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.38 (bs, 1H, NH, D_2O exchangeable), 7.65 (d, *J* = 8.8 Hz, 2H, ArH), 7.35 (d, *J* = 8.8 Hz, 2H, ArH), 7.27-7.08 (m, 4H, ArH), 4.18 (s, 1H, ≡C-H), 2.30 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 143.4, 138.1, 136.4, 129.8 (2C), 129.6, 127.1, 126.6 (2C), 122.4, 122.3, 120.2, 82.8 (-C≡), 81.1 (-C≡), 20.9 (Me); MS (ES mass): 272.0 (M+1, 100%); HPLC: 99.7%, X-Bridge C-18 150 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 15.1 min.

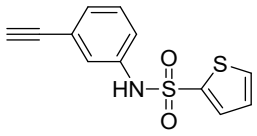
_N_-(4-Ethynylphenyl)-4-methylbenzenesulfonamide (1af)



Yield: 91%; White solid; mp: 81-83 °C; R_f = 0.53 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.49 (bs, 1H, NH, D_2O exchangeable), 7.66 (d, *J* = 8.0 Hz, 2H, ArH), 7.36-7.31 (m, 4H, ArH), 7.12-7.07 (m, 2H, ArH), 4.06 (s, 1H, ≡C-H), 2.32 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 143.5, 138.4, 136.4, 132.7 (2C), 129.7 (2C), 126.6 (2C), 119.2 (2C), 116.7,

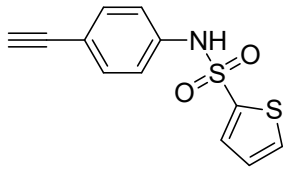
83.0 (-C≡), 80.3 (-C≡), 20.9 (Me); MS (ES mass): 272.0 (M+1, 100%); HPLC: 99.3%, X-Bridge C-18 150 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 25/90, 35/90, 36/5, 40/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); Max plot, retention time 17.2 min.

_N_-(3-Ethynylphenyl)thiophene-2-sulfonamide (1ag)



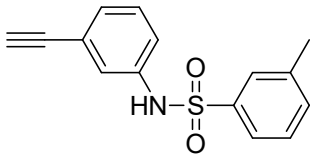
Yield: 92%; White solid; mp: 40-42 °C; R_f = 0.51 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.58 (bs, 1H, NH, D_2O exchangeable), 7.91 (dd, *J* = 4.8, 1.2 Hz, 1H, ArH), 7.56 (dd, *J* = 4.0, 1.2 Hz, 1H, ArH), 7.34-7.26 (m, 1H, ArH), 7.23-7.16 (m, 3H, ArH), 7.13 (m, 1H, ArH), 4.19 (s, 1H, ≡C-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 139.6, 137.7, 133.6, 132.6, 129.7, 127.7, 127.6, 122.8, 122.4, 120.7, 82.8 (-C≡), 81.2 (-C≡); MS (ES mass): 261.9 (M-1, 100%); HPLC: 99.6%, X-Bridge C-18 150 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 220.0 nm,, retention time 13.9 min.

_N_-(4-Ethynylphenyl)thiophene-2-sulfonamide (1ah)



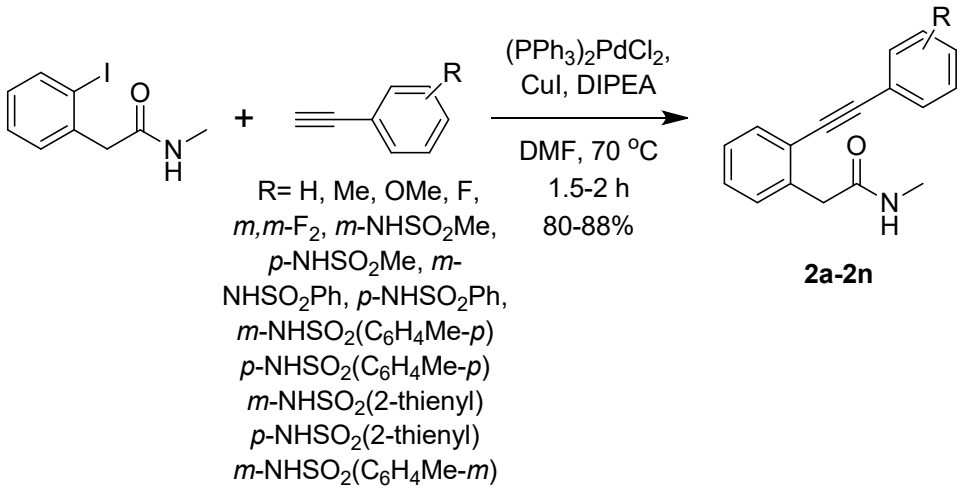
Yield: 89%; White solid; mp: 122-124 °C; R_f = 0.49 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.68 (bs, 1H, NH, D_2O exchangeable), 7.91 (dd, *J* = 4.8, 1.2 Hz, 1H, ArH), 7.58 (dd, *J* = 4.0, 1.2 Hz, 1H, ArH), 7.41-7.36 (m, 2H, ArH), 7.17-7.11 (m, 3H, ArH), 4.09 (s, 1H, ≡C-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 139.7, 138.0, 133.6, 132.7 (2C), 132.6, 127.7, 119.6 (2C), 117.2, 82.9 (-C≡), 80.5 (-C≡); MS (ES mass): 263.8 (M+1, 100%); HPLC: 99.9%, Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 28/90, 30/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm,, retention time 13.4 min.

***N*-(3-Ethynylphenyl)-3-methylbenzenesulfonamide (1ai)**



Yield: 88%; White solid; mp: 45-47 °C; R_f = 0.50 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.41 ((bs, 1H, NH, D_2O exchangeable)), 7.59 (s, 1H, ArH), 7.57-7.51 (m, 1H, ArH), 7.47-7.41 (m, 2H, ArH), 7.28-7.21 (m, 1H, ArH), 7.17-7.10 (m, 3H, ArH), 4.18 (s, 1H, ≡C-H), 2.34 (s, 3H, $ArCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 139.2, 139.1, 138.0, 133.7, 129.7, 129.2, 127.2, 126.7, 123.7, 122.5, 122.4, 120.3, 82.8 (-C≡), 81.1 (-C≡), 20.8 (ArMe); MS (ES mass): 270.2 (M-1, 100%); HPLC: 99.8%, Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm,, retention time 15.2 min.

Scheme S-2:

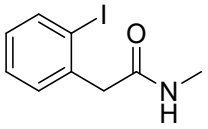
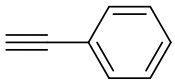
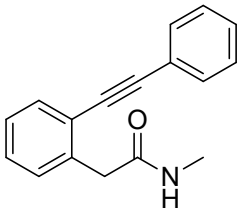
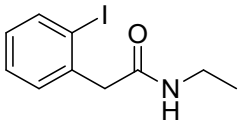
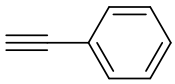
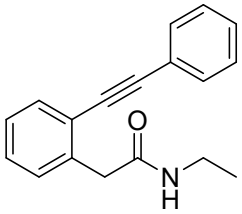
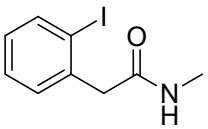
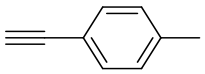
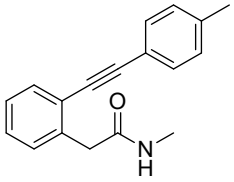
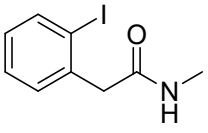
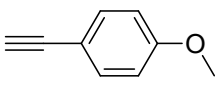
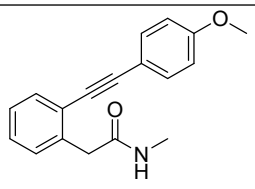


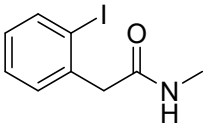
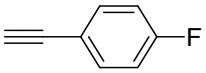
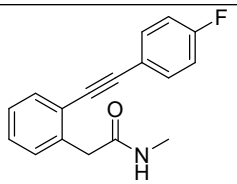
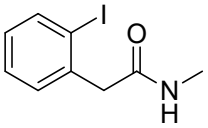
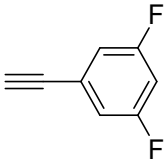
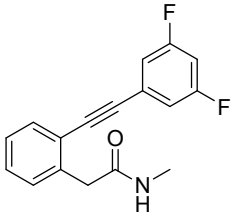
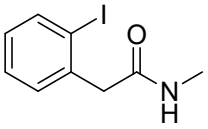
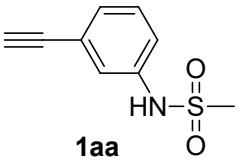
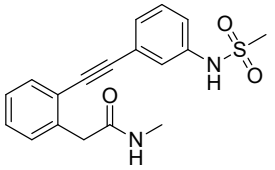
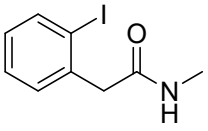
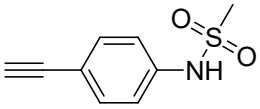
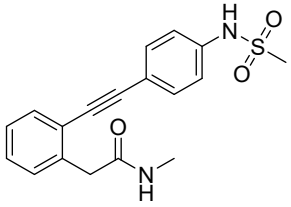
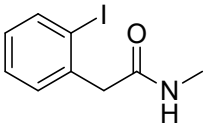
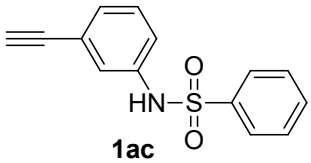
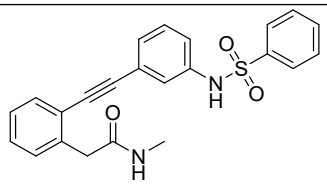
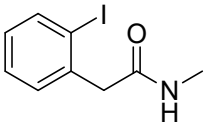
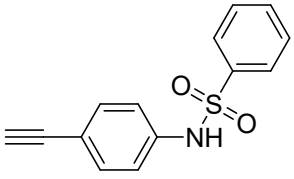
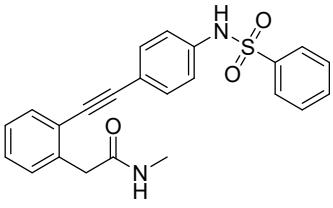
General Procedure for the preparation of compound 2:

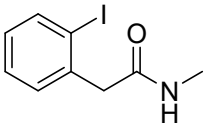
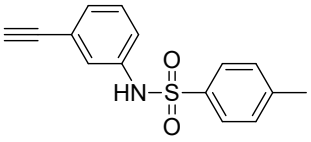
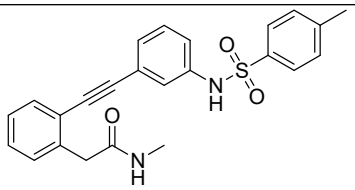
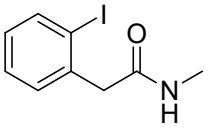
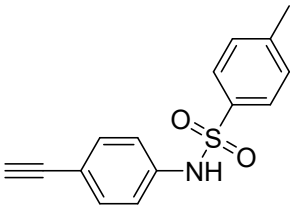
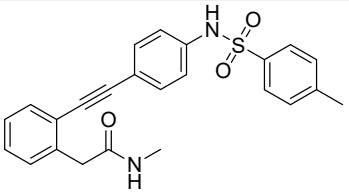
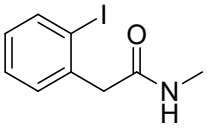
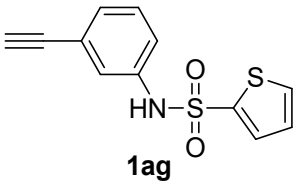
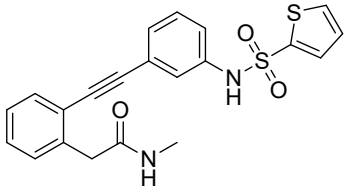
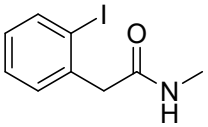
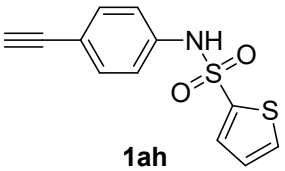
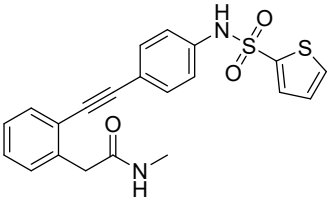
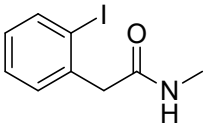
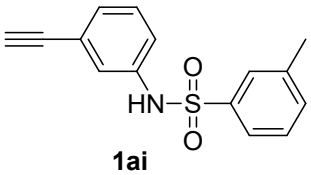
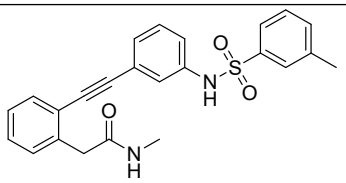
Appropriate terminal alkyne (1.2 mmol) was added to a solution containing 2-(2-iodophenyl)-*N*-methylacetamide (1.0 mmol), $(PPh_3)_2PdCl_2$ (5 mol%), CuI (5 mol%) and *N*,*N*-diisopropylethylamine (DIPEA) (3.0 mmol) in DMF (10 mL) under a nitrogen atmosphere. The mixture was stirred at 70 °C for 1.5-2 h. After completion of the reaction (indicated by TLC), the

mixture was diluted with ice-water (60 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The residue was purified by column chromatography using hexane and EtOAc as eluent to afford the title compound. All the compounds (**2a-2n**) prepared were characterized by MS, NMR spectra and purity was determined by HPLC method.

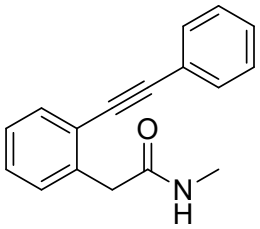
Table S-2. List of synthesized compounds **2a-2n** from 2-(2-iodophenyl)-*N*-alkylacetamide and terminal alkynes (Scheme S-2)

Entry	**2-(2-iodophenyl)-*N*-alkylacetamide**	**Terminal alkyne**	**Product 2 (2a-2n)**	**Yield (%)**
1			 **2a**	88
2			 **2aa**	90
3			 **2b**	86
4			 **2c**	85

5			 **2d**	83
6			 **2e**	80
7		 **1aa**	 **2f**	81
8		 **1ab**	 **2g**	83
9		 **1ac**	 **2h**	85
10		 **1ad**	 **2i**	86

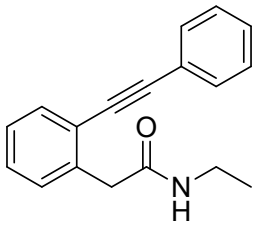
11		 **1ae**	 **2j**	84
12		 **1af**	 **2k**	82
13		 **1ag**	 **2l**	81
14		 **1ah**	 **2m**	83
15		 **1ai**	 **2n**	84

***N*-Methyl-2-{2-(phenylethynyl)phenyl}acetamide (2a)**



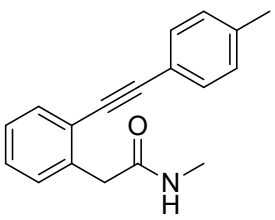
Yield: 88%; White solid; mp: 68-70 °C; R_f = 0.46 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.91 (bs, 1H, NH, D_2O exchangeable), 7.59-7.55 (m, 2H, ArH), 7.52 (d, *J* = 7.6 Hz, 1H, ArH), 7.47-7.42 (m, 3H, ArH), 7.38-7.34 (m, 2H, ArH), 7.32-7.27 (m, 1H, ArH), 3.70 (s, 2H, CH_2), 2.61 (d, *J* = 4.8 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.8 (C=O), 138.3, 131.6, 131.3 (2C), 130.1, 128.7, 128.6 (2C), 128.5, 126.7, 122.5, 122.4, 93.1 (-C≡), 87.8 (-C≡), 40.8 (CH_2), 25.7 (NMe); MS (ES mass): 250.1 (M+1, 100%); HPLC: 96.7%, Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water; UV 220.0 nm, retention time 20.7 min.

_N_-Ethyl-2-{2-(phenylethynyl)phenyl}acetamide (2aa)



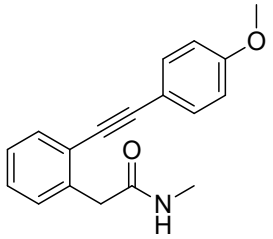
Yield: 90%; White solid; mp: 108-110 °C; R_f = 0.47 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.98 (bs, 1H, NH, D_2O exchangeable), 7.62-7.49 (m, 3H, ArH), 7.42 (s, 3H, ArH), 7.38-7.23 (m, 3H, ArH), 3.68 (s, 2H, CH_2), 3.20-2.96 (m, 2H, Ethyl CH_2), 0.99 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.1 (C=O), 138.4, 131.6, 131.3 (2C), 130.1, 128.7, 128.6 (2C), 128.5, 126.6, 122.5, 122.4, 93.1 (-C≡), 87.9 (-C≡), 40.9 (CH_2), 33.5 (N-CH_2), 14.7 (Me); MS (ES mass): 264.3 (M+1, 100%); HPLC: 98.8%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water; UV 210.0 nm, retention time 14.7 min.

_N_-Methyl-2-{2-(p-tolylethynyl)phenyl}acetamide (2b)



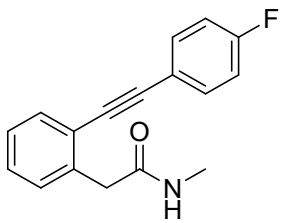
Yield: 86%; White solid; mp: 120-122 °C; R_f = 0.47 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58-7.53 (m, 1H, ArH), 7.42 (d, *J* = 8.0 Hz, 2H, ArH), 7.36-7.27 (m, 3H, ArH), 7.17 (d, *J* = 7.6 Hz, 2H, ArH), 5.56 (bs, 1H, NH, D_2O exchangeable), 3.83 (s, 2H, CH_2), 2.75 (d, *J* = 4.8 Hz, 3H, N-CH_3), 2.37 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1 (C=O), 138.9, 136.9, 132.4, 131.5 (2C), 130.1, 129.3 (2C), 128.8, 127.4, 123.6, 119.6, 94.6 (-C≡), 86.6 (-C≡), 42.7 (CH_2), 26.6 (NMe), 21.5 (ArMe); MS (ES mass): 264.1 (M+1, 100%); HPLC: 99.8%, Eclipse plus C-18 250 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 16.4 min.

2-[2-{(4-Methoxyphenyl)ethynyl}phenyl]-*N*-methylacetamide (2c)



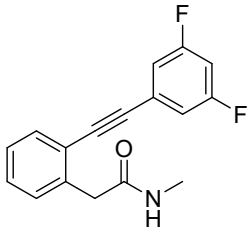
Yield: 85%; White solid; mp: 84-86 °C; R_f = 0.39 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57-7.51 (m, 1H, ArH), 7.50-7.42 (m, 2H, ArH), 7.36-7.26 (m, 3H, ArH), 6.94-6.83 (m, 2H, ArH), 5.56 (bs, 1H, NH, D_2O exchangeable), 3.83 (s, 3H, OCH_3), 3.82 (s, 2H, CH2), 2.75 (d, *J* = 4.8 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2 (C=O), 159.9, 136.7, 133.1 (2C), 132.2, 130.1, 128.7, 127.4, 123.8, 114.8, 114.2 (2C), 94.5 (-C≡), 86.0 (-C≡), 55.3 (OMe), 42.7 (CH_2), 26.6 (NMe); MS (ES mass): 280.1 (M+1, 100%); HPLC: 95.9%, X-Bridge C-18 150 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 220.0 nm, retention time 12.7 min.

2-[2-{(4-Fluorophenyl)ethynyl}phenyl]-*N*-methylacetamide (2d)



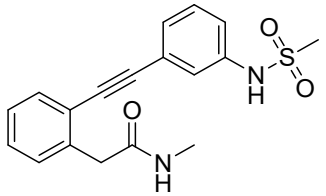
Yield: 83%; White solid; mp: 118-120 °C; R_f = 0.43 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.89 (bs, 1H, NH, D_2O exchangeable), 7.64-7.59 (m, 2H, ArH), 7.51 (d, *J* = 7.2 Hz, 1H, ArH), 7.38-7.34 (m, 2H, ArH), 7.31-7.26 (m, 3H, ArH), 3.68 (s, 2H, CH_2), 2.60 (d, *J* = 4.8 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.8 (C=O), 163.2 (d, C-F *J* = 246.4 Hz), 138.3, 133.6 (2C, d, C-F *J* = 8.6 Hz), 131.5, 130.2, 128.6, 126.7, 122.4, 118.9 (d, C-F *J* = 3.3 Hz), 116.0 (2C, d, C-F *J* = 22.2 Hz), 92.1, 87.6, 40.8 (CH_2), 25.7 (NMe); MS (ES mass): 268.1 (M+1, 100%); HPLC: 99.7%, Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 25/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (50:50); UV 280.0 nm, retention time 13.2 min.

2-[2-{(3,5-Difluorophenyl)ethynyl}phenyl]-*N*-methylacetamide (2e)



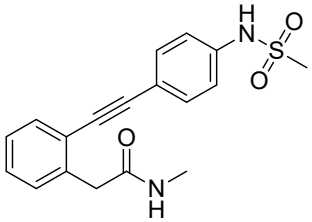
Yield: 80%; White solid; mp: 127-129 °C; R_f = 0.50 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.92 (bs, 1H, NH, D_2O exchangeable), 7.53 (d, *J* = 7.20 Hz, 1H, ArH), 7.49-7.17 (m, 6H, ArH), 3.68 (s, 2H, CH_2), 2.58 (d, *J* = 4.8 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.7 (C=O), 163.5 (2C, dd, C-F *J* = 245.4, 13.9 Hz), 138.7, 131.8, 130.4, 129.3, 126.8, 125.5 (t, C-F *J* = 12.1 Hz), 121.6, 114.7 (2C, dd, C-F *J* = 19.2, 7.7 Hz), 105.2 (t, C-F *J* = 25.8 Hz), 90.8 (t, C-F *J* = 3.9 Hz, -C≡), 89.9 (-C≡), 40.8 (CH_2), 25.7 (NMe); MS (ES mass): 286.0 (M+1, 100%); HPLC: 97.7%, X-Terra C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.05% TFA in water mobile phase B: 0.05% TFA in MeCN (T/%B): 0/2, 5/2, 20/90, 25/90, 26/2, 30/2; flow rate: 1.0 mL/min; Diluent: MeCN: water (10:90); UV 210.0 nm, retention time 17.5 min.

***N*-Methyl-2-[2-{(3-(methylsulfonamido)phenyl)ethynyl}phenyl]acetamide (2f)**



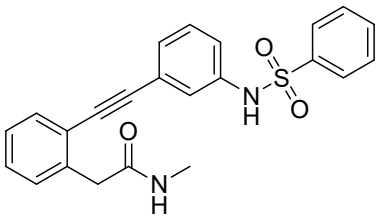
Yield: 81%; white solid; mp: 85-87 °C; R_f = 0.29 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.89 (bs, 1H, NH, D_2O exchangeable), 7.88 (bs, 1H, NH, D_2O exchangeable), 7.52 (d, *J* = 7.2 Hz, 1H, ArH), 7.43-7.33 (m, 4H, ArH), 7.32-7.24 (m, 3H, ArH), 3.67 (s, 2H, CH_2), 3.04 (s, 3H, S-CH_3), 2.61 (d, *J* = 4.8 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.7 (C=O), 138.7, 138.4, 131.7, 130.1, 129.7, 128.8, 126.8, 126.7, 123.3, 122.3, 121.8, 120.1, 92.6 (-C≡), 88.0 (-C≡), 40.8 (CH_2), 39.4 (SMe), 25.7 (NMe); MS (ES mass): 343.0 (M+1, 100%); HPLC: 97.7%, Cosmicsil Aura ODS 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: WATER(80:20); UV 210.0 nm, retention time 12.9 min.

_N_-Methyl-2-[2-{(4-(methylsulfonamido)phenyl)ethynyl}phenyl]acetamide (2g)



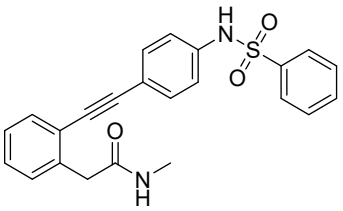
Yield: 83%; white solid; mp: 88-90 °C; R_f = 0.20 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.03 (bs, 1H, NH, D_2O exchangeable), 7.88 (bs, 1H, NH, D_2O exchangeable), 7.54-7.47 (m, 3H, ArH), 7.35-7.31 (m, 2H, ArH), 7.30-7.22 (m, 3H, ArH), 3.67 (s, 2H, CH_2), 3.05 (s, 3H, S-CH_3), 2.60 (d, *J* = 4.4 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.8 (C=O), 138.8, 138.1, 132.5 (2C), 131.4, 130.1, 128.4, 126.7, 122.6, 118.9 (2C), 117.3, 92.9 (-C≡), 87.4 (-C≡), 40.8 (CH_2), 39.5 (SMe), 25.7 (NMe); MS (ES mass): 343.0 (M+1, 100%); HPLC: 99.4%, Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water(80:20); UV 210.0 nm, retention time 11.1 min.

_N_-Methyl-2-[2-{(3-(phenylsulfonamido)phenyl)ethynyl}phenyl]acetamide (2h)



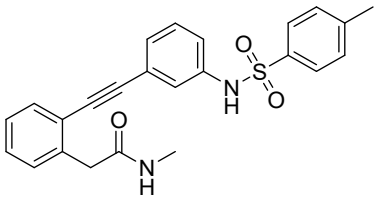
Yield: 85%; white solid; mp: 134-136 °C; R_f = 0.33 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.46 (bs, 1H, NH, D_2O exchangeable), 7.86 (bs, 1H, NH, D_2O exchangeable), 7.79 (d, *J* = 7.2 Hz, 2H, ArH), 7.63 (t, *J* = 7.2 Hz, 1H, ArH), 7.59-7.54 (m, 2H, ArH), 7.50 (d, *J* = 7.2 Hz, 1H, ArH), 7.38-7.32 (m, 2H, ArH), 7.31-7.25 (m, 2H, ArH), 7.22 (d, *J* = 8.8 Hz, 2H, ArH), 7.13 (d, *J* = 7.6 Hz, 1H, ArH), 3.64 (s, 2H, CH_2), 2.59 (d, *J* = 4.4 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.7 (C=O), 139.3, 138.4, 138.0, 133.0, 131.7, 130.1, 129.6, 129.3 (2C), 128.8, 127.1, 126.7, 126.6 (2C), 123.2, 122.3, 122.2, 120.2, 92.4 (-C≡), 88.1 (-C≡), 40.8 (CH_2), 25.7 (NMe); MS (ES mass): 405.1 (M+1, 100%); HPLC: 96.9%, Cosmicsil C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN:water (80:20); UV 210.0 nm, retention time 14.1 min.

N-Methyl-2-[2-{(4-(phenylsulfonamido)phenyl)ethynyl}phenyl]acetamide (2i)



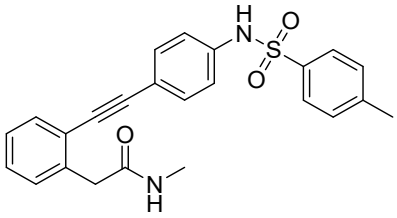
Yield: 86%; white solid; mp: 90-92 °C; R_f = 0.24 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.57 (bs, 1H, NH, D_2O exchangeable), 7.84 (bs, 1H, NH, D_2O exchangeable), 7.81-7.77 (m, 2H, ArH), 7.65-7.61 (m, 1H, ArH), 7.59-7.54 (m, 2H, ArH), 7.46-7.40 (m, 3H, ArH), 7.35-7.29 (m, 2H, ArH), 7.28-7.23 (m, 1H, ArH), 7.14 (d, *J* = 8.4 Hz, 2H, ArH), 3.63 (s, 2H, CH_2), 2.56 (d, *J* = 4.4 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.8 (C=O), 139.3, 138.1, 138.1, 133.1, 132.3 (2C), 131.4, 130.1, 129.3 (2C), 128.4, 126.8, 126.6 (2C), 122.5, 119.4 (2C), 117.7, 92.8 (-C≡), 87.6 (-C≡), 40.8 (CH_2), 25.7 (NMe); MS (ES mass): 405.1 (M+1, 100%); HPLC: 97.5%, Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN:water (80:20); UV 210.0 nm, retention time 14.0 min.

N-Methyl-2-[2-{(3-(4-methylphenylsulfonamido)phenyl)ethynyl}phenyl]acetamide (2j)



Yield: 84%; white solid; mp: 116-118 °C; R_f = 0.40 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.39 (bs, 1H, NH, D_2O exchangeable), 7.86 (bs, 1H, NH, D_2O exchangeable), 7.67 (d, *J* = 8.0 Hz, 2H, ArH), 7.50 (d, *J* = 7.2 Hz, 1H, ArH), 7.39-7.32 (m, 4H, ArH), 7.31-7.25 (m, 2H, ArH), 7.24-7.19 (m, 2H, ArH), 7.13 (d, *J* = 8.0 Hz, 1H, ArH), 3.64 (s, 2H, CH_2), 2.59 (d, *J* = 4.4 Hz, 3H, N-CH_3), 2.33 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.7 (C=O), 143.4, 138.3, 138.1, 136.5, 131.7, 130.0, 129.8 (2C), 129.6, 128.8, 126.9, 126.8, 126.7 (2C), 123.2, 122.2, 122.1, 120.0, 92.5 (-C≡), 88.1 (-C≡), 40.8 (CH_2), 25.7 (NMe), 20.9 (ArMe); MS (ES mass): 419.1 (M+1, 100%); HPLC: 96.5%, Cosmicsil C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN:water (80:20); UV 210.0 nm, retention time 14.8 min.

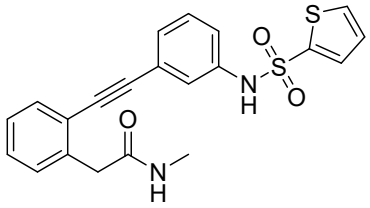
_N_-Methyl-2-{2-{(4-(4-methylphenylsulfonamido)phenyl)ethynyl}phenyl}acetamide (2k)



Yield: 82%; white solid; mp: 86-88 °C; R_f = 0.34 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.49 (bs, 1H, NH, D_2O exchangeable), 7.84 (bs, 1H, NH, D_2O exchangeable), 7.67 (d, *J* = 8.0 Hz, 2H, ArH), 7.46-7.39 (m, 3H, ArH), 7.36 (d, *J* = 8.4 Hz, 2H, ArH), 7.34-7.28 (m, 2H, ArH), 7.28-7.23 (m, 1H, ArH), 7.14 (d, *J* = 8.8 Hz, 2H, ArH), 3.63 (s, 2H, CH_2), 2.55 (d, *J* = 4.4 Hz, 3H, N-CH_3), 2.33 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.8 (C=O), 143.5, 138.2, 138.1, 136.4, 132.3 (2C), 131.4, 130.1, 129.7 (2C), 128.4, 126.7 (2C), 126.6, 122.5, 119.3 (2C), 117.6, 92.8 (-C≡), 87.5 (-C≡), 40.8 (CH_2), 25.7 (NMe), 20.9 (ArMe); MS (ES mass): 419.1 (M+1, 100%); HPLC: 99.5%, X-Bridge C-18 150 * 4.6 mm, 3.5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5,

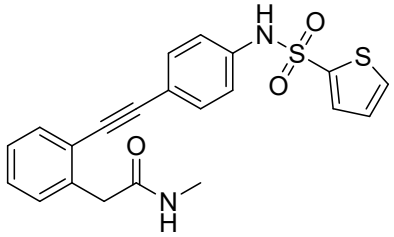
20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 14.7 min.

***N*-Methyl-2-[2-{(3-(thiophene-2-sulfonamido)phenyl)ethynyl}phenyl]acetamide (2l)**



Yield: 81%; white solid; mp: 120-122 °C; R_f = 0.34 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.58 (bs, 1H, NH, D_2O exchangeable), 7.91 (dd, *J* = 4.8, 1.2 Hz, 1H, ArH), 7.87 (bs, 1H, NH, D_2O exchangeable), 7.58 (dd, *J* = 3.6, 1.2 Hz, 1H, ArH), 7.51 (d, *J* = 7.2 Hz, 1H, ArH), 7.38-7.32 (m, 3H, ArH), 7.31-7.26 (m, 3H, ArH), 7.21-7.16 (m, 1H, ArH), 7.15-7.12 (m, 1H, ArH), 3.65 (s, 2H, CH_2), 2.59 (d, *J* = 4.8 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.7 (C=O), 139.7, 138.4, 137.8, 133.6, 132.6, 131.7, 130.1, 129.7, 128.8, 127.7, 127.5, 126.7, 123.3, 122.5, 122.2, 120.6, 92.4 (-C≡), 88.2 (-C≡), 40.8 (CH_2), 25.7 (NMe); MS (ES mass): 411.1 (M+1, 100%); HPLC: 99.4%, Cosmicsil Aura C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 14.7 min.

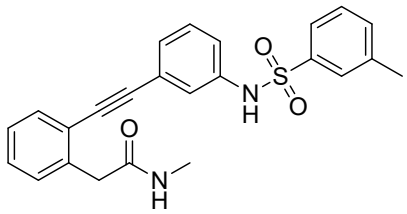
***N*-Methyl-2-[2-{(4-(thiophene-2-sulfonamido)phenyl)ethynyl}phenyl]acetamide (2m)**



Yield: 83%; white solid; mp: 144-146 °C; R_f = 0.32 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.69 (bs, 1H, NH, D_2O exchangeable), 7.92 (dd, *J* = 5.2, 1.2 Hz, 1H, ArH), 7.86 (bs, 1H, NH, D_2O exchangeable), 7.60 (dd, *J* = 4.0, 1.2 Hz, 1H, ArH), 7.46 (d, *J* = 8.4 Hz, 3H, ArH), 7.35-7.31 (m, 2H, ArH), 7.29-7.24 (m, 1H, ArH), 7.21-7.18 (m, 2H, ArH), 7.15-7.12 (m, 1H, ArH), 3.64 (s, 2H, CH_2), 2.58 (d, *J* = 4.8 Hz, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.8 (C=O), 139.7, 138.2, 137.8, 133.6, 132.7, 132.3 (2C), 131.4, 130.1, 128.5, 127.7,

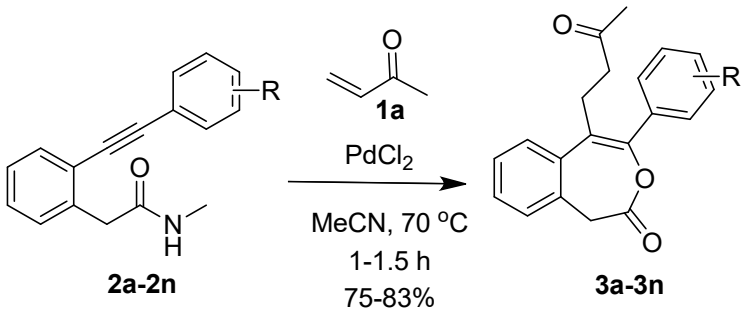
126.7, 122.5, 119.8 (2C), 118.1, 92.7 (-C≡), 87.7 (-C≡), 40.8 (CH_2), 25.7 (NMe); MS (ES mass): 411.0 (M+1, 100%); HPLC: 99.5%, Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 28/90, 30/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 15.1 min.

_N_-Methyl-2-[2-{(3-(3-methylphenylsulfonamido)phenyl)ethynyl}phenyl]acetamide (2n)



Yield: 84%; white solid; mp: 70-72 °C; R_f = 0.44 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.41 (bs, 1H, NH, D_2O exchangeable), 7.86 (bs, 1H, NH, D_2O exchangeable), 7.61 (s, 1H, ArH), 7.59-7.56 (m, 1H, ArH), 7.52-7.49 (m, 1H, ArH), 7.47-7.43 (m, 2H, ArH), 7.32 (m, 4H, ArH), 7.24-7.20 (m, 2H, ArH), 7.15-7.12 (m, 1H, ArH), 3.64 (s, 2H, CH_2), 2.59 (d, J = 4.8 Hz, 3H, N-CH_3), 2.35 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.7 (C=O), 139.3, 139.0, 138.3, 138.1, 133.7, 131.7, 130.0, 129.6, 129.2, 128.8, 127.0, 126.8, 126.7, 123.8, 123.2, 122.2, 122.1, 120.2, 92.5 (-C≡), 88.1 (-C≡), 40.8 (CH_2), 25.7 (NMe), 20.8 (ArMe); MS (ES mass): 419.1 (M+1, 100%); HPLC: 99.9%, Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 28/90, 30/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 16.3 min.

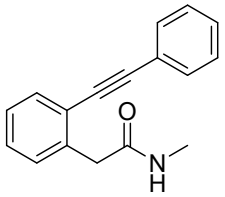
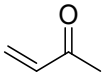
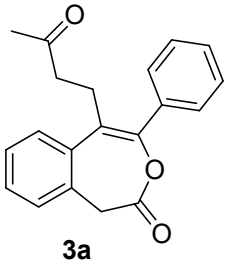
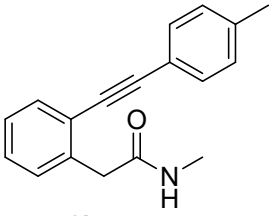
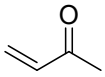
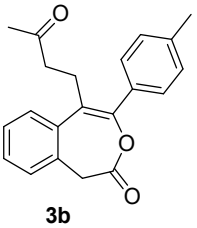
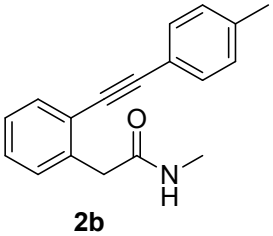
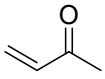
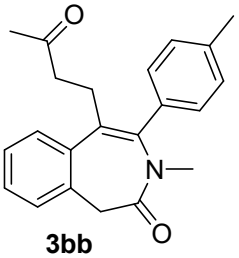
Scheme S-3:

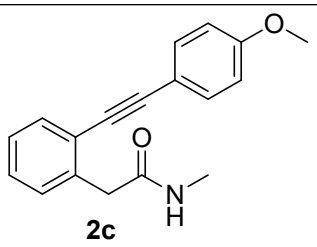
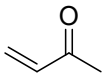
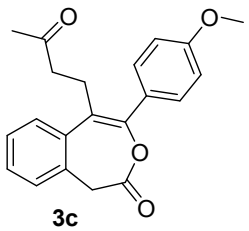
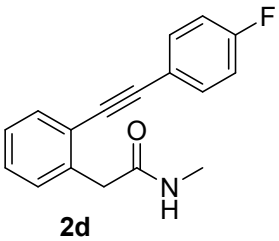
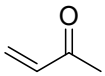
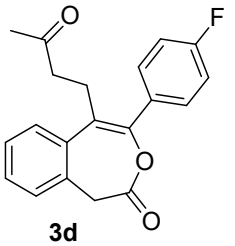
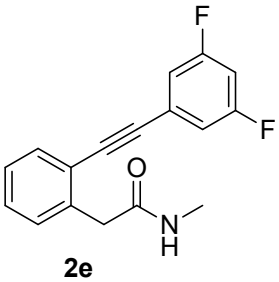
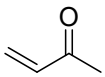
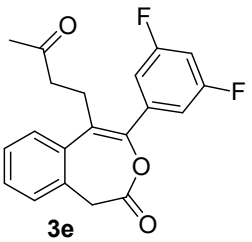
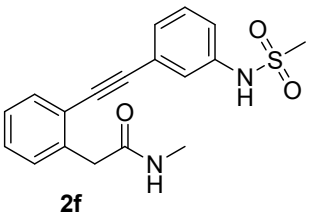
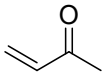
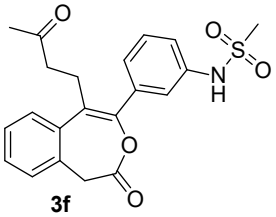
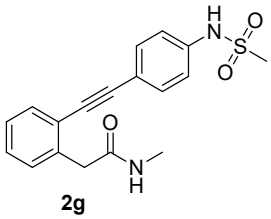
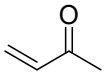
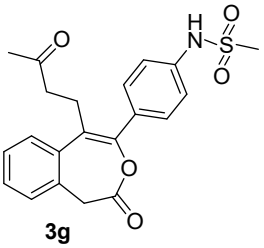
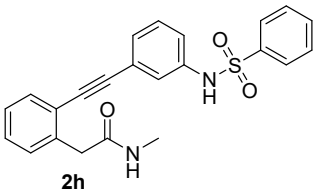
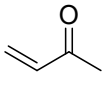
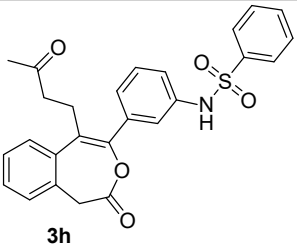


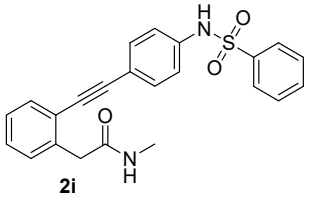
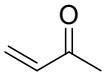
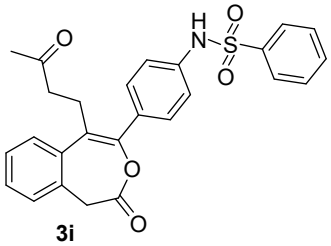
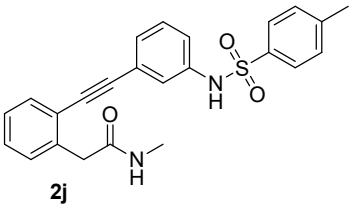
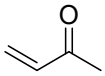
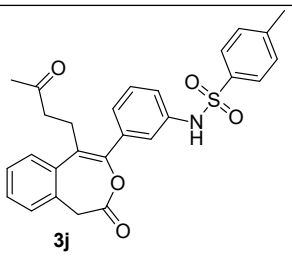
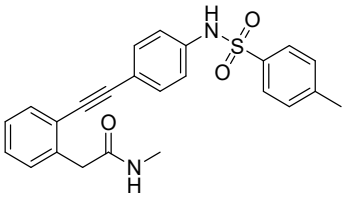
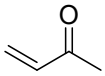
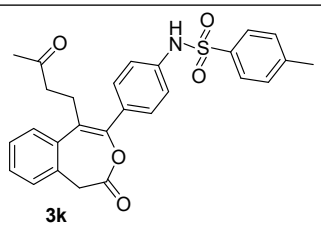
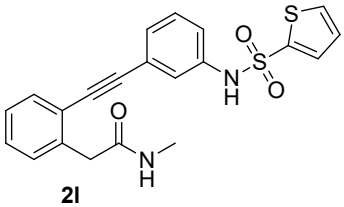
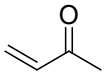
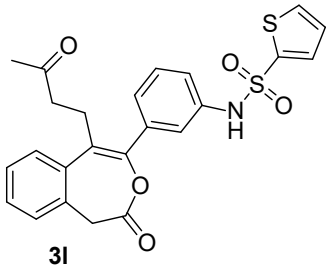
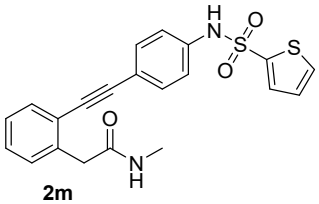
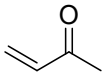
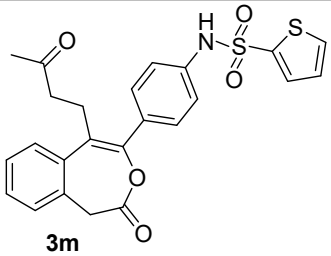
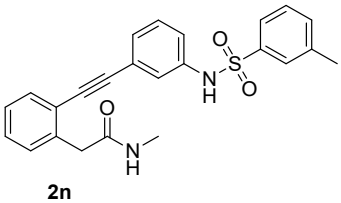
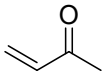
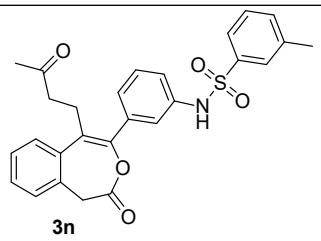
General Procedure for the preparation of compound 3:

To a solution of compound **2** (1.0 mmol) and $PdCl_2$ (10 mol%) in MeCN (10 mL) was added methyl vinyl ketone (**1a**) (2.0 mmol) under a nitrogen atmosphere. The mixture was stirred at 70 °C for 1-1.5 h. After completion of the reaction (indicated by TLC), the mixture was diluted with ice-water (60 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The residue was purified by column chromatography using hexane and EtOAc as eluent to afford the title compound. All the compounds (**3a-3n**) prepared were characterized by MS, NMR spectra and purity was determined by HPLC method.

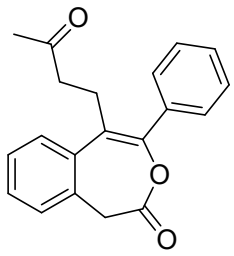
Table S-3. List of synthesized compounds **3a-3n** from compounds **2a-2n** and methyl vinyl ketone (**1a**) (Scheme S-3)

Entry	Product 2 (2a-2n)	1a	Product 3 (3a-3n)	Yield (%)
1	 **2a**		 **3a**	83
2	 **2b**		 **3b**	76
3	 **2b**		 **3bb**	20

4	 **2c**		 **3c**	80
5	 **2d**		 **3d**	81
6	 **2e**		 **3e**	79
7	 **2f**		 **3f**	75
8	 **2g**		 **3g**	77
9	 **2h**		 **3h**	80

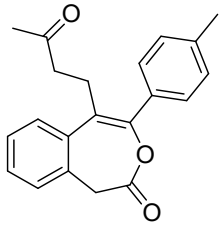
10	 2i		 3i	78
11	 2j		 3j	75
12	 2k		 3k	80
13	 2l		 3l	77
14	 2m		 3m	79
15	 2n		 3n	76

5-(3-Oxobutyl)-4-phenylbenzo[*d*]oxepin-2(1*H*)-one (3a)



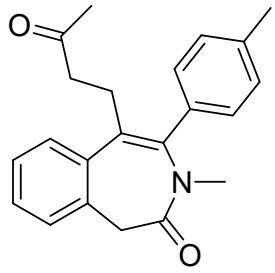
Yield: 83%; White solid; mp: 62-64 °C; R_f = 0.43 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62-7.57 (m, 1H, ArH), 7.42-7.35 (m, 4H, ArH), 7.35-7.28 (m, 3H, ArH), 7.27-7.25 (m, 1H, ArH), 3.70 (s, 2H, CH_2), 3.03-2.96 (m, 2H, CH_2), 2.53-2.46 (m, 2H, CH_2), 2.02 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.3 (C=O, Ketone), 167.6 (C=O, Ester), 142.2, 136.4, 133.2, 131.1, 129.9, 129.3, 128.8 (2C), 128.4 (2C), 127.6, 127.2, 127.1, 125.8, 42.0 (CH_2), 37.3 (CH_2), 29.9 (Me), 26.7 (CH_2); MS (ES mass): 307.1 (M+1, 100%); HPLC: 99.8%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.05% TFA in water mobile phase B: 0.05% TFA in MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 17.7 min.

5-(3-Oxobutyl)-4-(p-tolyl)benzo[*d*]oxepin-2(1*H*)-one (3b)



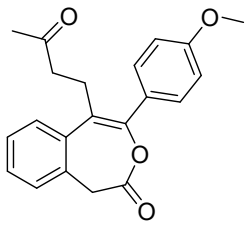
Yield: 76%; White solid; mp: 70-72 °C; R_f = 0.45 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.68-7.65 (m, 1H, ArH), 7.45-7.39 (m, 3H, ArH), 7.25-7.20 (m, 4H, ArH), 3.86 (s, 2H, CH_2), 2.87-2.82 (m, 2H, CH_2), 2.49-2.45 (m, 2H, CH_2), 2.33 (s, 3H, $ArCH_3$), 1.97 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.2 (C=O, Ketone), 167.8 (C=O, Ester), 141.4, 136.6, 133.8, 131.5, 129.3, 129.2, 128.7 (2C), 128.6 (2C), 127.2, 127.1, 126.9, 125.5, 41.3 (CH_2), 36.4 (CH_2), 29.6 (Me), 26.3 (CH_2), 20.8 (ArMe); MS (ES mass): 319.2 (M-1, 100%); HPLC: 99.1%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 16.5 min.

3-Methyl-5-(3-oxobutyl)-4-(p-tolyl)-1*H*-benzo[*d*]azepin-2(3*H*)-one (3bb)



Yield: 20%; White solid; mp: 67-69 °C; R_f = 0.48 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.56-7.52 (m, 1H, ArH), 7.40-7.33 (m, 3H, ArH), 7.33-7.26 (m, 4H, ArH), 3.65 (d, *J* = 12.0 Hz, 1H, CH_2), 3.53 (d, *J* = 12.0 Hz, 1H, CH_2), 2.90-2.82 (m, 1H, CH_2), 2.75-2.64 (m, 1H, CH_2), 2.42 (s, 3H, N-CH_3), 2.36 (s, 3H, ArCH_3), 2.16-1.98 (m, 2H, CH_2), 1.73 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.3 (C=O, Ketone), 169.8 (C=O, Amide), 138.4, 137.6, 135.9, 135.2, 133.4, 129.7 (2C), 129.1 (2C), 128.5, 128.3, 127.5, 126.9, 126.7, 41.8 (CH_2), 41.8 (CH_2), 33.0 (NMe), 29.1 (Me), 26.9 (CH_2), 20.8 (ArMe); MS (ES mass): 334.1 (M+1, 100%); HPLC: 99.7%, Column: Cosmicsil C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 260.0 nm, retention time 14.9 min.

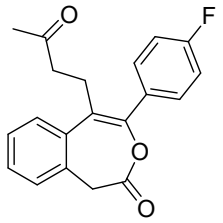
4-(4-Methoxyphenyl)-5-(3-oxobutyl)benzo[*d*]oxepin-2(1*H*)-one (3c)



Yield: 80%; White solid; mp: 94-96 °C; R_f = 0.36 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.66 (d, *J* = 4.0 Hz, 1H, ArH), 7.42 (d, *J* = 3.6 Hz, 3H, ArH), 7.30 (d, *J* = 8.4 Hz, 2H, ArH), 6.98 (d, *J* = 8.4 Hz, 2H, ArH), 3.86 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 2.86 (t, *J* = 7.2 Hz, 2H, CH_2), 2.48 ((t, *J* = 7.2 Hz, 2H, CH_2), 1.98 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.2 (C=O, Ketone), 167.8 (C=O, Ester), 158.4, 141.3, 131.5, 130.0 (2C), 129.5, 129.4, 129.1, 128.7, 127.2, 126.9, 125.2, 113.6 (2C), 55.0 (OMe), 41.4 (CH_2), 36.4 (CH_2), 29.6 (Me), 26.3 (CH_2); MS (ES mass): 335.2 (M-1, 100%); HPLC: 98.9%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN

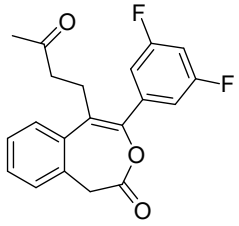
(T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 15.4 min.

4-(4-Fluorophenyl)-5-(3-oxobutyl)benzo[*d*]oxepin-2(1*H*)-one (3d)



Yield: 81%; White solid; mp: 78-80 °C; R_f = 0.38 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.70-7.65 (m, 1H, ArH), 7.46-7.37 (m, 5H, ArH), 7.28-7.22 (m, 2H, ArH), 3.88 (s, 2H, CH_2), 2.91-2.81 (m, 2H, CH_2), 2.49-2.45 (m, 2H, CH_2), 1.97 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.1 (C=O, Ketone), 167.6 (C=O, Ester), 162.5 (d, C-F *J* = 242.7 Hz), 141.7, 133.1 (d, C-F *J* = 3.3 Hz), 131.5, 130.9 (2C, d, C-F *J* = 7.9 Hz), 129.3, 129.1, 127.2, 127.0, 126.9, 124.5, 115.1 (2C, d, C-F *J* = 21.1 Hz), 41.1 (CH_2), 36.4 (CH_2), 29.6 (Me), 26.3 (CH_2); MS (ES mass): 323.2 (M-1, 100%); HPLC: 99.8%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 260.0 nm, retention time 15.4 min.

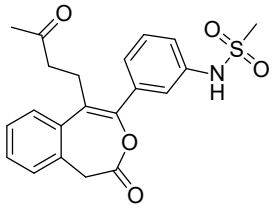
4-(3,5-Difluorophenyl)-5-(3-oxobutyl)benzo[*d*]oxepin-2(1*H*)-one (3e)



Yield: 79%; White solid; mp: 144-146 °C; R_f = 0.40 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.66 (dd, *J* = 6.0, 2.4 Hz, 1H, ArH), 7.48-7.40 (m, 3H, ArH), 7.26-7.18 (m, 1H, ArH), 7.16-7.10 (m, 2H, ArH), 3.92 (s, 2H, CH_2), 2.89-2.82 (m, 2H, CH_2), 2.49-2.46 (m, 2H, CH_2), 1.99 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.1 (C=O, Ketone), 167.4 (C=O, Ester), 163.4 (2C, dd, C-F *J* = 244.6, 13.5 Hz), 142.3, 140.9 (t, C-F *J* = 10.0 Hz), 131.7, 129.6, 128.6, 127.3, 127.1, 127.0, 123.4, 112.4 (2C, dd, C-F *J* = 18.5, 6.7 Hz), 103.1 (t, C-F *J* = 25.6

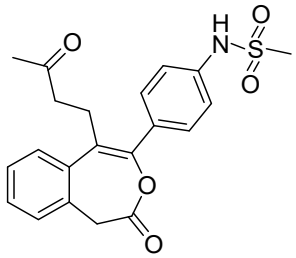
Hz), 40.9 (CH_2), 36.3 (CH_2), 29.7 (Me), 25.9 (CH_2); MS (ES mass): 341.1 (M-1, 100%); HPLC: 98.7%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 15.8 min.

_N_-[3-{4-Oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[_d_]oxepin-2-yl}phenyl]methanesulfonamide (3f)



Yield: 75%; white solid; mp: 80-82 °C; R_f = 0.37 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.78 (bs, 1H, NH, D_2O exchangeable), 7.72-7.67 (m, 1H, ArH), 7.47-7.35 (m, 4H, ArH), 7.22-7.14 (m, 2H, ArH), 7.09 (d, *J* = 8.0 Hz, 1H, ArH), 3.87 (s, 2H, CH_2), 3.02 (s, 3H, S-CH_3), 2.86-2.82 (m, 2H, CH_2), 2.51-2.49 (m, 2H, CH_2), 1.98 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.2 (C=O, Ketone), 167.6 (C=O, Ester), 141.8, 138.2, 137.9, 131.5, 129.4, 129.1, 129.0, 127.3, 127.0, 126.9, 125.1, 124.1, 119.9, 118.7, 41.1 (CH_2), 39.2 (SMe), 36.3 (CH_2), 29.7 (Me), 26.3 (CH_2); MS (ES mass): 398.1 (M-1, 100%); HPLC: 99.7%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: WATER(80:20);UV 210.0 nm, retention time 15.1 min.

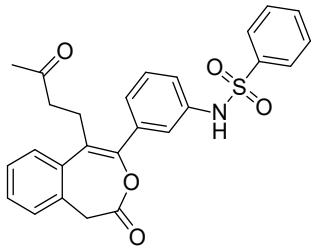
_N_-[4-{4-Oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[_d_]oxepin-2-yl}phenyl]methanesulfonamide (3g)



Yield: 77%; white solid; mp: 154-156 °C; R_f = 0.32 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.82 (bs, 1H, NH, D_2O exchangeable), 7.67-7.64 (m, 1H, ArH), 7.46-7.39

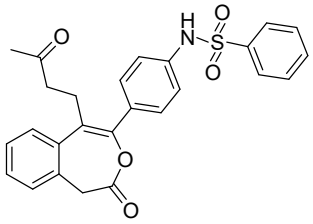
(m, 3H, ArH), 7.33 (d, J = 8.4 Hz, 2H, ArH), 7.23 (d, J = 8.8 Hz, 2H, ArH), 3.86 (s, 2H, CH_2), 3.06 (s, 3H, SCH_3), 2.85 (t, J = 7.6 Hz, 2H, CH_2), 2.49-2.45 (m, 2H, CH_2), 1.98 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.2 (C=O, ketone), 167.7 (C=O, ester), 141.5, 137.5, 131.9, 131.5, 129.8 (2C), 129.3, 129.2, 127.3, 127.0, 126.9, 124.9, 119.0 (2C), 41.3 (CH_2), 39.5 (SMe), 36.4 (CH_2), 29.7 (Me), 26.2 (CH_2); MS (ES mass): 398.2 (M-1, 100%); HPLC: 99.7%, Column: Eclipse plus C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 28/90, 30/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20);UV 210.0 nm, retention time 12.6 min.

_N_-[3-{4-Oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[_d_]oxepin-2-yl}phenyl]benzenesulfonamide (3h)



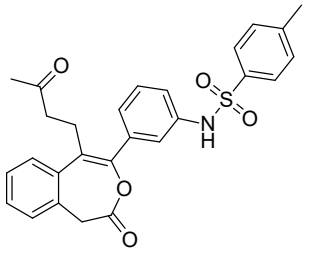
Yield: 80%; white solid; mp: 111-113 °C; R_f = 0.42 (40% EtOAc/ n-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.29 (bs, 1H, NH, D_2O exchangeable), 7.78 (d, J = 7.2 Hz, 2H, ArH), 7.66 (d, J = 7.6 Hz, 1H, ArH), 7.60 (t, J = 7.2 Hz, 1H, ArH), 7.53 (t, J = 7.6 Hz, 2H, ArH), 7.45-7.38 (m, 3H, ArH), 7.25 (t, J = 7.6 Hz, 1H, ArH), 7.10 (s, 1H, ArH), 7.00 (t, J = 7.2 Hz, 2H, ArH), 3.85 (s, 2H, CH_2), 2.73 (t, J = 7.6 Hz, 2H, CH_2), 2.32 (t, J = 7.6 Hz, 2H, CH_2), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.0 (C=O, Ketone), 167.5 (C=O, Ester), 141.7, 139.3, 137.8, 137.5, 132.8, 131.5, 129.4, 129.3, 129.2 (2C), 129.0, 127.3, 127.0, 126.9, 126.7 (2C), 124.9, 124.6, 120.4, 119.2, 40.9 (CH_2), 36.3 (CH_2), 29.7 (Me), 26.4 (CH_2); MS (ES mass): 460.1 (M-1, 100%); HPLC: 98.4%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20);UV 210.0 nm, retention time 14.9 min.

_N_-[4-{4-Oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[_d_]oxepin-2-yl}phenyl]benzenesulfonamide (3i)



Yield: 78%; white solid; mp: 137-139 °C; R_f = 0.37 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.40 (bs, 1H, NH, D_2O exchangeable), 7.82-7.79 (m, 2H, ArH), 7.65-7.60 (m, 2H, ArH), 7.59-7.55 (m, 2H, ArH), 7.44-7.37 (m, 3H, ArH), 7.24-7.21 (m, 2H, ArH), 7.12-7.09 (m, 2H, ArH), 3.83 (s, 2H, CH_2), 2.81-2.77 (m, 2H, CH_2), 2.38 (t, *J* = 7.6 Hz, 2H, CH_2), 1.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.1 (C=O, Ketone), 167.6 (C=O, Ester), 141.5, 139.7, 136.8, 132.9, 132.8, 132.2, 131.5, 129.7 (2C), 129.3, 129.2 (2C), 129.2, 127.2, 126.9, 126.6 (2C), 124.8, 119.4 (2C), 41.2 (CH_2), 36.4 (CH_2), 29.6 (Me), 26.1 (CH_2); MS (ES mass): 460.2 (M-1, 100%); HPLC: 99.6%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20);UV 210.0 nm, retention time 15.1 min.

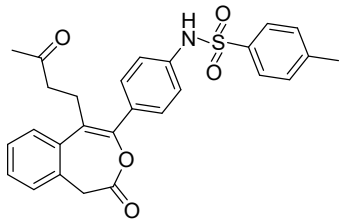
4-Methyl-*N*-[3-{4-oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[*d*]oxepin-2-yl}phenyl]benzenesulfonamide (3j)



Yield: 75%; white solid; mp: 168-170 °C; R_f = 0.49 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.21 (bs, 1H, NH, D_2O exchangeable), 7.68-7.64 (m, 3H, ArH), 7.46-7.40 (m, 3H, ArH), 7.32 (d, *J* = 8.0 Hz, 2H, ArH), 7.27-7.22 (m, 1H, ArH), 7.09 (t, *J* = 2.0 Hz, 1H, ArH), 7.02-6.97 (m, 2H, ArH), 3.85 (s, 2H, CH_2), 2.76-2.72 (m, 2H, CH_2), 2.35-2.31 (m, 5H, CH_2, $ArCH_3$), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.0 (C=O, Ketone), 167.5 (C=O, Ester), 143.2, 141.7, 137.8, 137.7, 136.5, 131.5, 129.6 (2C), 129.5, 129.4, 129.2, 128.9, 127.2, 126.9, 126.7 (2C), 124.9, 124.5, 120.2, 119.1, 40.9 (CH_2), 36.3 (CH_2), 29.6 (Me), 26.4

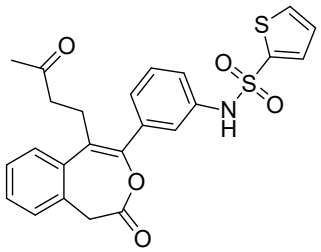
(CH_2), 20.9 (ArMe); MS (ES mass): 474.1 (M-1, 100%); HPLC: 99.4%, Column: Cosmicsil C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20);UV 210.0 nm, retention time 15.7 min.

4-Methyl-*N*-[4-{4-oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[*d*]oxepin-2-yl}phenyl]benzenesulfonamide (3k)



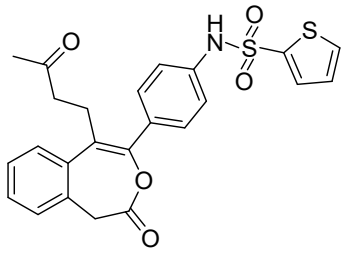
Yield: 80%; white solid; mp: 108-110 °C; R_f = 0.44 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.33 (bs, 1H, NH, D_2O exchangeable), 7.69 (d, *J* = 8.0 Hz, 2H, ArH), 7.64-7.60 (m, 1H, ArH), 7.43-7.35 (m, 5H, ArH), 7.22 (d, *J* = 8.8 Hz, 2H, ArH), 7.09 (d, *J* = 8.8 Hz, 2H, ArH), 3.83 (s, 2H, CH_2), 2.81-2.77 (m, 2H, CH_2), 2.38 (t, *J* = 8.0 Hz, 2H, CH_2), 2.34 (s, 3H, $ArCH_3$), 1.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.1 (C=O, Ketone), 167.7 (C=O, Ester), 143.3, 141.5, 137.0, 136.9, 132.0, 131.5, 129.7 (2c), 129.6, 129.3, 129.2, 127.5, 127.2, 126.9 (2c), 126.7 (2c), 124.8, 119.2 (2c), 41.2 (CH_2), 36.4 (CH_2), 29.6 (Me), 26.1 (CH_2), 20.9 (ArMe); MS (ES mass): 474.1 (M-1, 100%); HPLC: 96.8%, Column: Eclipse plus C-18 250 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20);UV 210.0 nm, retention time 17.8 min.

***N*-[3-{4-Oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[*d*]oxepin-2-yl}phenyl]thiophene-2-sulfonamide (3l)**



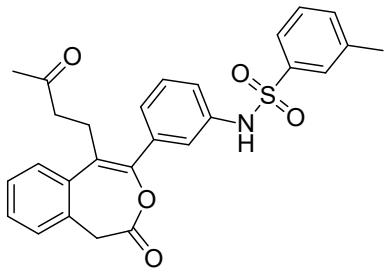
Yield: 77%; white solid; mp: 102-104 °C; R_f = 0.47 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.44 (bs, 1H, NH, D_2O exchangeable), 7.89 (dd, *J* = 4.8, 1.2 Hz, 1H, ArH), 7.71-7.64 (m, 1H, ArH), 7.57 (dd, *J* = 4.0, 1.2 Hz, 1H, ArH), 7.46-7.38 (m, 3H, ArH), 7.30 (t, *J* = 8.0 Hz, 1H, ArH), 7.12 (t, *J* = 1.6 Hz, 1H, ArH), 7.11-6.99 (m, 3H, ArH), 3.83 (s, 2H, CH_2), 2.77 (t, *J* = 8.0 Hz, 2H, CH_2), 2.37 (t, *J* = 8.0 Hz, 2H, CH_2), 1.96 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.0 (C=O. ketone), 167.5 (C=O, ester), 141.8, 139.8, 137.9, 137.3, 133.2, 132.5, 131.5, 129.4, 129.1, 129.0, 127.6, 127.3, 127.0, 126.9, 125.0, 124.9, 120.6, 119.5, 40.9 (CH_2), 36.4 (CH_2), 29.7 (Me), 26.4 (CH_2); MS (ES mass): 466.1 (M-1, 100%); HPLC: 99.2%, Column: X-Bridge C-18 150 * 4.6 mm, 3.5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20);UV 260.0 nm, retention time 14.9 min.

_N_-[4-{4-Oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[*d*]oxepin-2-yl}phenyl]thiophene-2-sulfonamide (3m)



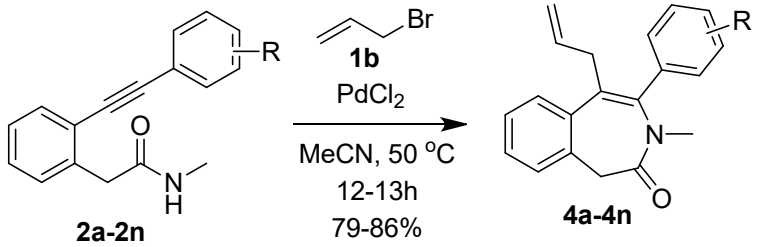
Yield: 79%; white solid; mp: 142-144 °C; R_f = 0.42 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.54 (bs, 1H, NH, D_2O exchangeable), 7.91 (dd, *J* = 4.8, 1.2 Hz, 1H, ArH), 7.66-7.62 (m, 1H, ArH), 7.59 (dd, *J* = 4.0, 1.2 Hz, 1H, ArH), 7.45-7.38 (m, 3H, ArH), 7.30-7.25 (m, 2H, ArH), 7.17-7.12 (m, 3H, ArH), 3.84 (s, 2H, CH_2), 2.85-2.79 (m, 2H, CH_2), 2.41 (t, *J* = 8.0 Hz, 2H, CH_2), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.2 (C=O, Ketone), 167.6 (C=O, Ester), 141.5, 140.2, 136.6, 133.3, 132.6, 132.4, 131.5, 129.7 (2C), 129.3, 129.2, 127.6, 127.2, 126.9, 124.8, 120.1, 119.7 (2C), 41.2 1 (CH_2), 36.4 1 (CH_2), 29.6 (Me), 26.1 (CH_2); MS (ES mass): 466.1 (M-1, 100%); HPLC: 97.4%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 28/90, 30/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20);UV 210.0 nm, retention time 16.5 min.

3-Methyl-*N*-[3-{4-oxo-1-(3-oxobutyl)-4,5-dihydrobenzo[*d*]oxepin-2-yl}phenyl]benzenesulfonamide (3n)

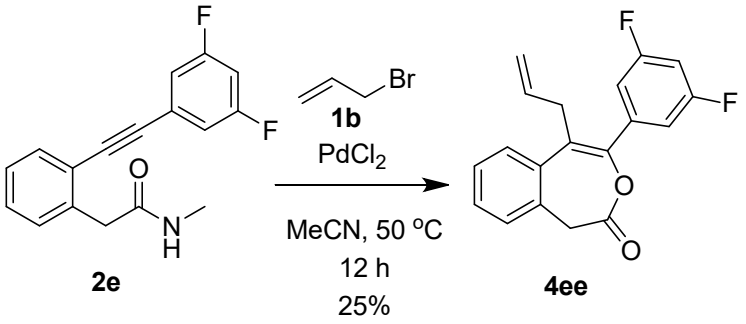


Yield: 76%; white solid; mp: 153-155 °C; R_f = 0.50 (40% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.25 (bs, 1H, NH, D_2O exchangeable), 7.68-7.65 (m, 1H, ArH), 7.61-7.55 (m, 2H, ArH), 7.46-7.38 (m, 5H, ArH), 7.26 (d, *J* = 8.0 Hz, 1H, ArH), 7.09 (t, *J* = 1.6 Hz, 1H, ArH), 7.05-6.96 (m, 2H, ArH), 3.85 (s, 2H, CH_2), 2.78-2.72 (m, 2H, CH_2), 2.35-2.28 (m, 5H, CH_2, $ArCH_3$), 1.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 207.0 (C=O, Ketone), 167.5 (C=O, Ester), 141.7, 139.4, 138.9, 137.8, 137.6, 133.5, 131.5, 129.4, 129.2, 129.0, 128.9, 127.3, 127.0, 126.9, 126.8, 124.9, 124.6, 123.9, 120.2, 119.1, 40.9 (CH_2), 36.4 (CH_2), 29.6 (Me), 26.4 (CH_2), 20.8 (ArMe); MS (ES mass): 474.2 (M-1, 100%); HPLC: 96.8%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20);UV 210.0 nm, retention time 15.3 min.

Scheme S-4:



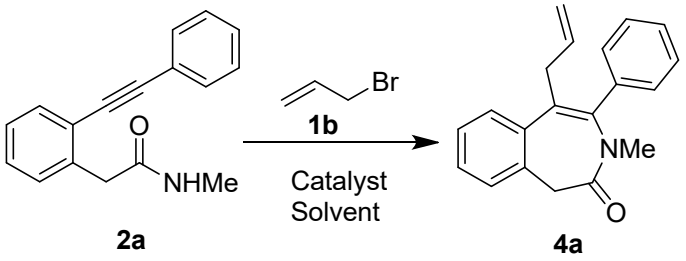
Formation of 5-allyl-4-(3,5-difluorophenyl)benzo[*d*]oxepin-2(1*H*)-one (4ee):



General Procedure for the preparation of compound 4:

To a solution of compound **2** (1.0 mmol) and $PdCl_2$ (10 mol%) in MeCN (5 mL) was added Allyl bromide (1.5 mmol) under a nitrogen atmosphere. The mixture was stirred at 50 °C for 12-13 h. After completion of the reaction (indicated by TLC), the mixture was diluted with ice-water (60 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under low vacuum. The residue was purified by column chromatography using hexane and EtOAc as eluent to afford the title compound. All the compounds (**4a-4n**) prepared were characterized by MS, NMR spectra and purity was determined by HPLC method.

Table S-4. Effect of reaction conditions on *7-endo-dig* cyclization of amide **2a** in the presence of **1b**.[a]



Entry	Catalyst	Solvent[b]	T (ºC); t (h)	% yield[c]
1.	$PdCl_2$	MeCN	50; 12	86
2.	$Pd(OAc)_2$	DMF	50; 20	0
3.	$(PPh_3)_2PdCl_2$	DMF	50; 20	0
4.	$Cu(OAc)_2$	DMF	70; 6	0
5.	$PdCl_2$	DMF	50; 20	15
6.	$Pd(OAc)_2$	MeCN	50; 20	0

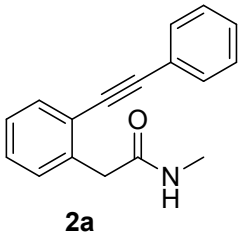
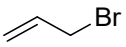
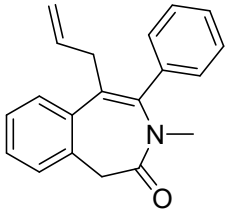
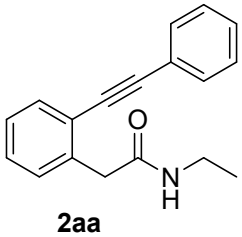
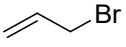
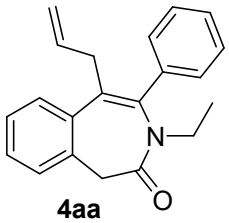
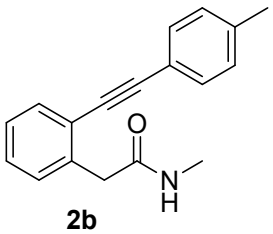
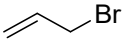
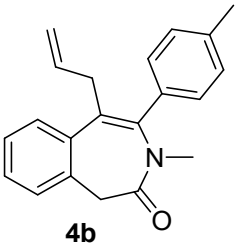
7.	$PdCl_2$	PEG-400	50; 13	30
8.	$PdCl_2$	PEG-400	70; 1	20
9.	$PdCl_2$	1,4-Dioxane	50; 13	35
10.	CuI	MeCN	50; 20	0
11.	$PdCl_2$	DMSO	50; 20	0
12.	$CuCl_2$	MeCN	50; 20	0

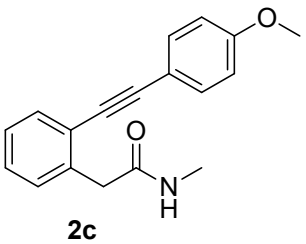
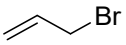
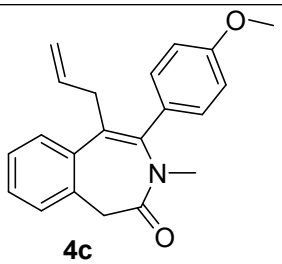
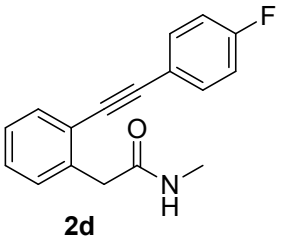
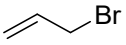
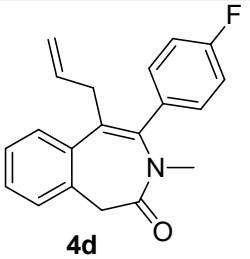
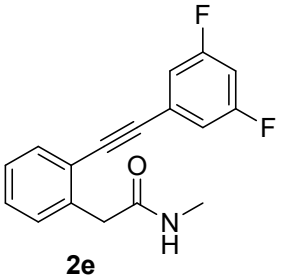
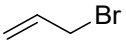
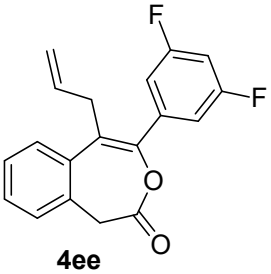
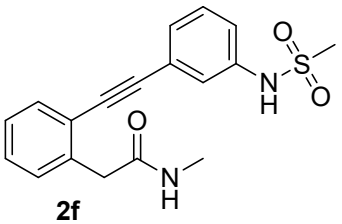
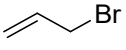
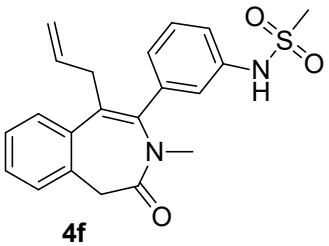
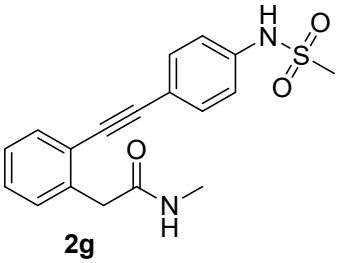
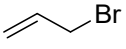
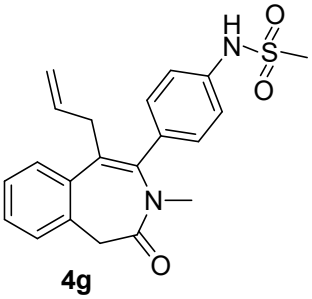
[a]All the reactions were performed using **2a** (1.0 mmol), **1b** (1.5 mmol) and catalyst (10 mol%) in an aqueous solvent (10 mL) under nitrogen atmosphere.

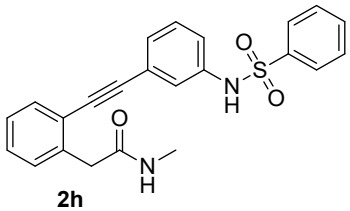
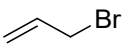
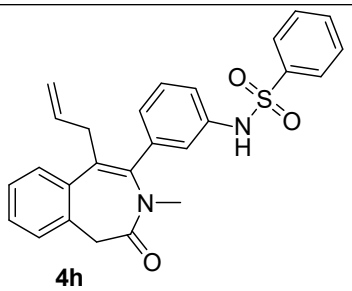
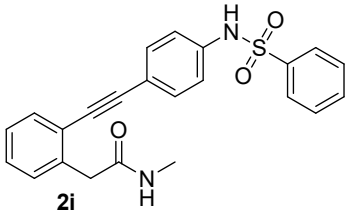
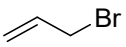
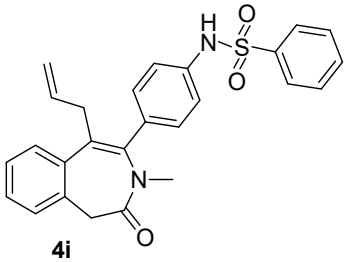
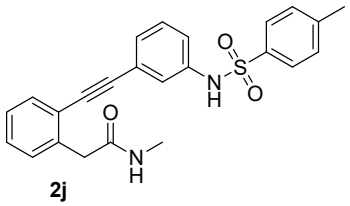
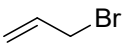
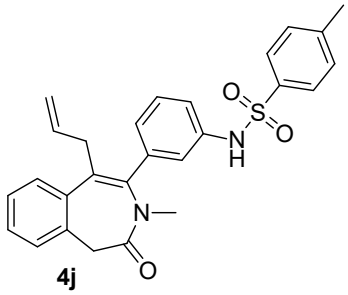
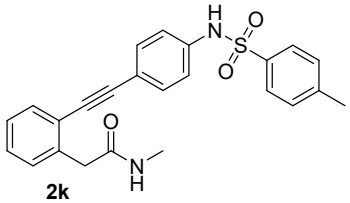
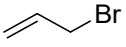
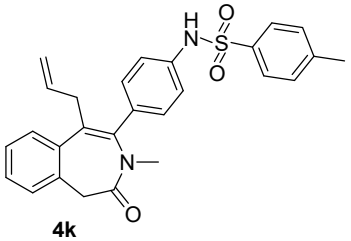
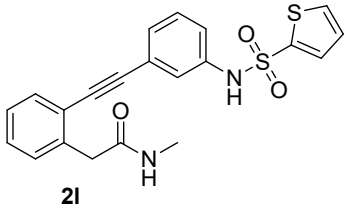
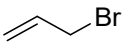
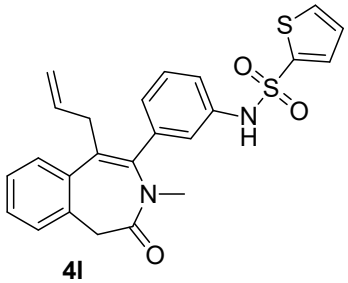
[b]The aqueous solvent i.e. 1% H_2O in the solvent was used.

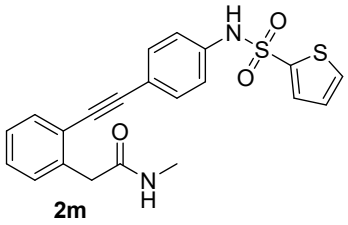
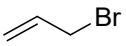
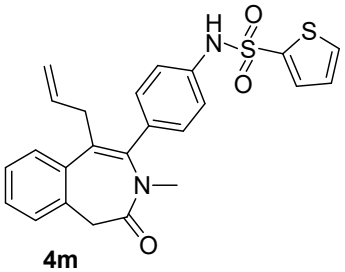
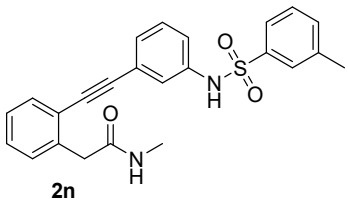
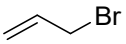
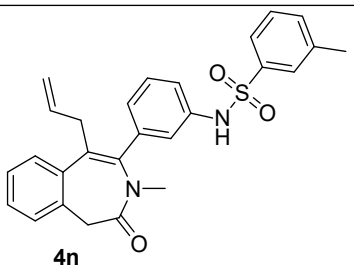
[c]Isolated yield.

Table S-5. List of synthesized compounds **4a-4n** from compounds **2a-2n** and allyl bromide (**1b**) (Scheme S-4)

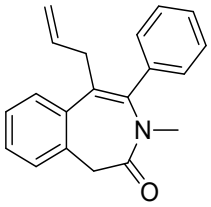
Entry	Product 2 (2a-2n)	1b	Product 4 (4a-4n)	Yield (%)
1	 **2a**		 **4a**	86
2	 **2aa**		 **4aa**	70
3	 **2b**		 **4b**	81

4	 **2c**		 **4c**	85
5	 **2d**		 **4d**	83
6	 **2e**		 **4ee**	25
7	 **2f**		 **4f**	79
8	 **2g**		 **4g**	81

9	 **2h**		 **4h**	80
10	 **2i**		 **4i**	82
11	 **2j**		 **4j**	84
12	 **2k**		 **4k**	83
13	 **2l**		 **4l**	80

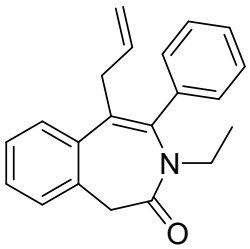
14	 **2m**		 **4m**	82
15	 **2n**		 **4n**	83

5-Allyl-3-methyl-4-phenyl-1*H*-benzo[*d*]azepin-2(3*H*)-one (4a)



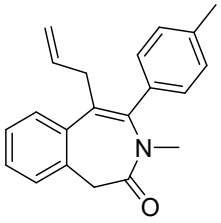
Yield: 86%; White solid; mp: 48-50 °C; R_f = 0.70 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57-7.52 (m, 1H, ArH), 7.48-7.38 (m, 3H, ArH), 7.38-7.31 (m, 5H, ArH), 5.55-5.43 (m, 1H, allylic CH), 4.81 (dd, *J* = 10.4, 1.6 Hz, 1H, =CH_2), 4.76 (dd, *J* = 17.2, 1.6 Hz, 1H, =CH_2), 3.66 (s, 2H, CH_2), 3.30 (d, *J* = 6.4 Hz, 2H, allylic CH_2), 2.64 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7 (C=O), 139.3, 136.7, 136.2, 135.9, 135.6, 129.8 (2C), 128.7, 128.6 (2C), 128.5, 128.4, 127.7, 126.9, 126.8, 116.1, 42.6 (CH_2), 37.9 (allylic CH_2), 33.7 (NMe); MS (ES mass): 290.1 (M+1, 100%); HPLC: 99.3%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 16.9 min.

5-Allyl-3-ethyl-4-phenyl-1*H*-benzo[*d*]azepin-2(3*H*)-one (4aa)



Yield: 70%; Red liquid, vial; R_f = 0.74 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.63-7.59 (m, 1H, ArH), 7.49-7.41 (m, 5H, ArH), 7.37-7.32 (m, 3H, ArH), 5.55-5.33 (m, 1H, allylic CH), 4.76 (dd, *J* = 10.4, 1.6 Hz, 1H, =CH_2), 4.71 (dd, *J* = 10.4, 1.6 Hz, 1H, =CH_2), 3.69-3.37 (m, 4H, CH_2, N-CH_2), 3.20-3.13 (m, 1H, allylic CH_2), 2.63-2.54 (m, 1H, allylic CH_2), 0.53 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.4 (C=O), 139.1, 137.6, 136.7, 136.0, 135.7, 135.6, 129.7 (2C), 129.3, 128.5 (2C), 128.4, 127.4, 126.9, 126.8, 115.9, 42.2 (CH_2), 38.7 (N-CH_2), 37.3 (allylic CH_2), 12.6 (Me); MS (ES mass): 304.4 (M+1, 100%); HPLC: 92.8%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 17.9 min.

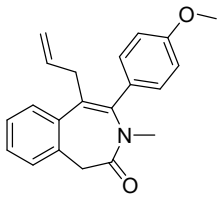
5-Allyl-3-methyl-4-(p-tolyl)-1*H*-benzo[*d*]azepin-2(3*H*)-one (4b)



Yield: 81%; Red liquid, vial; R_f = 0.73 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.65-7.56 (m, 1H, ArH), 7.36-7.28 (m, 7H, ArH), 5.48-5.34 (m, 1H, allylic CH), 4.75 (dd, *J* = 13.6, 1.6 Hz, 1H, =CH_2), 4.72 (dd, *J* = 13.6, 1.6 Hz, 1H, =CH_2), 3.64 (d, *J* = 12.4 Hz, 1H, CH_2), 3.55 (d, *J* = 12.0 Hz, 1H, CH_2), 3.40-3.34 (m, 1H, allylic CH_2), 3.23-3.15 (m, 1H, allylic CH_2), 2.48 (s, 3H, N-CH_3), 2.36 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.6 (C=O), 138.9, 137.7, 136.1, 135.8, 135.5, 133.5, 129.5 (2C), 129.1 (2C), 128.4, 127.4, 127.3, 127.0, 126.7, 115.9, 41.9 (CH_2), 37.1 (allylic CH_2), 32.9 (NMe), 20.8 (ArMe); MS (ES mass): 304.2 (M+1, 100%); HPLC: 90.0%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile

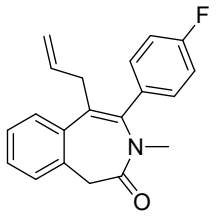
phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 28/90, 30/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 21.0 min.

5-Allyl-4-(4-methoxyphenyl)-3-methyl-1*H*-benzo[*d*]azepin-2(3*H*)-one (4c)



Yield: 85%; White solid; mp: 53-55 °C; R_f = 0.57 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55-7.51 (m, 1H, ArH), 7.36-7.26 (m, 5H, ArH), 6.96 (d, *J* = 8.4 Hz, 2H, ArH), 5.56-5.44 (m, 1H, allylic CH), 4.88-4.72 (m, 2H, allylic =CH_2), 3.86 (s, 3H, OCH_3), 3.69-3.59 (m, 2H, CH_2), 3.31 (d, *J* = 6.0 Hz, 2H, allylic CH_2), 2.62 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8 (C=O), 159.5, 139.1, 136.3, 136.2, 135.6, 131.0 (2C), 128.9, 128.6, 128.2, 127.6, 126.9, 126.8, 116.1, 113.9 (2C), 55.3 (OMe), 42.7 (CH_2), 38.0 (allylic CH_2), 33.7 (NMe); MS (ES mass): 320.1 (M+1, 100%); HPLC: 98.0%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 18.6 min.

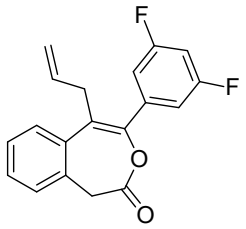
5-Allyl-4-(4-fluorophenyl)-3-methyl-1*H*-benzo[*d*]azepin-2(3*H*)-one (4d)



Yield: 83%; White solid; mp: 49-51 °C; R_f = 0.67 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.62-7.59 (m, 1H, ArH), 7.55-7.50 (m, 2H, ArH), 7.38-7.30 (m, 5H, ArH), 5.49-5.37 (m, 1H, allylic CH), 4.79-4.70 (m, 2H, allylic =CH_2), 3.67 (d, *J* = 12.4 Hz, 1H, CH_2), 3.57 (d, *J* = 12.4 Hz, 1H, CH_2), 3.39 (dd, *J* = 15.6, 6.8 Hz, 1H, allylic CH_2), 3.15 (dd, *J* = 15.6, 5.6 Hz, 1H, allylic CH_2), 2.50 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.6 (C=O), 162.9 (d, C-F *J* = 244.2 Hz), 137.9, 135.9, 135.7, 135.5, 132.8 (d, C-F *J* = 3.4 Hz), 132.0 (2C, d, C-F *J* = 8.4 Hz), 128.5, 127.9, 127.4, 127.1, 126.8, 116.0, 115.6 (2C, d, C-F *J* = 21.1 Hz), 42.0

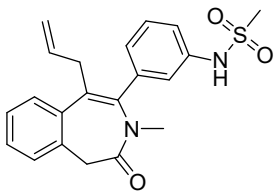
(CH_2), 37.1 (allylic CH_2), 32.9 (NMe); MS (ES mass): 308.1(M+1, 100%); HPLC: 97.4%, Column: X-Terra C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.05% TFA in water mobile phase B: 0.05% TFA in MeCN (T/%B): 0/2, 5/2, 20/90, 25/90, 26/2, 30/2; flow rate: 1.0 mL/min; Diluent: MeCN: water (10:90); UV 210.0 nm, retention time 18.5 min.

5-Allyl-4-(3,5-difluorophenyl)benzo[*d*]oxepin-2(1*H*)-one (4ee)



Yield: 25%; White solid; mp: 95-97 °C; R_f = 0.65 (20% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.67-7.63 (m, 1H, ArH), 7.51-7.41 (m, 3H, ArH), 7.23-7.14 (m, 3H, ArH), 5.90-5.79 (m, 1H, allylic CH), 5.19-5.09 (m, 2H, allylic =CH_2), 3.95 (s, 2H, CH_2), 3.42 (d, *J* = 5.6 Hz, 2H, allylic CH_2); ^{13}C NMR (100 MHz DMSO-d_6) δ: 167.2 (C=O), 163.3 (2C, dd, C-F *J* = 244.1, 13.6 Hz), 143.7, 141.4 (t, C-F *J* = 10.1 Hz), 134.9, 131.5, 129.8, 128.3, 127.4, 127.0, 126.5, 121.2, 117.5, 112.6 (2C, dd, C-F *J* = 18.5, 6.9 Hz), 103.0 (t, C-F *J* = 25.5 Hz), 36.3 (CH_2), 36.2 (allylic CH_2); MS (ES mass): 311.3(M-1, 100%); HPLC: 99.9%, Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.05% TFA in water mobile phase B: 0.05% TFA in MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 24.5 min.

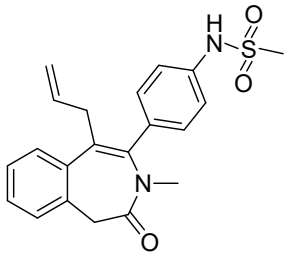
***N*-{3-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]azepin-4-yl)phenyl}methanesulfonamide (4f)**



Yield: 79%; White solid; mp: 79-81 °C; R_f = 0.53 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.84 (bs, 1H, NH, D_2O exchangeable), 7.65-7.60 (m, 1H, ArH), 7.48-7.44 (m, 1H, ArH), 7.37-7.34 (m, 3H, ArH), 7.28-7.25 (m, 2H, ArH), 7.20 (d, *J* = 7.6 Hz, 1H, ArH), 5.47-5.37

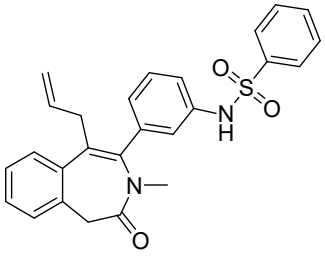
(m, 1H, allylic CH), 4.78-4.70 (m, 2H, allylic =CH_2), 3.63-3.55 (m, 2H, CH_2), 3.39 (dd, J = 15.6, 6.8 Hz, 1H, allylic CH_2), 3.21 (dd, J = 15.6, 5.6 Hz, 1H, allylic CH_2), 3.04 (s, 3H, S-CH_3), 2.51 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.6 (C=O), 138.6, 138.4, 137.4, 135.9, 135.7, 135.4, 129.7, 128.6, 127.8, 127.4, 127.1, 126.8, 125.2, 120.9, 119.8, 116.1, 41.9 (CH_2), 39.3 (SMe), 37.1 (allylic CH_2), 32.9 (NMe); MS (ES mass): 383.2(M+1, 100%); HPLC: 95.1%, Column: Cosmicsil Aura ODS 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 220.0 nm, retention time 14.9 min.

_N_-{4-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1_H_-benzo[_d_]azepin-4-yl)phenyl}methanesulfonamide (4g)



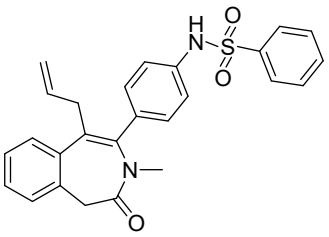
Yield: 81%; White solid; mp: 60-62 °C; R_f = 0.48 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.96 (bs, 1H, NH, D_2O exchangeable), 7.62-7.58 (m, 1H, ArH), 7.42 (d, J = 8.4 Hz, 2H, ArH), 7.36-7.33 (m, 3H, ArH), 7.30 (d, J = 8.8 Hz, 2H, ArH), 5.47-5.35 (m, 1H, allylic CH), 4.78-4.71 (m, 2H, allylic =CH_2), 3.65-3.54 (m, 2H, CH_2), 3.39 (dd, J = 15.6, 6.8 Hz, 1H, allylic CH_2), 3.19 (dd, J = 15.6, 6.0 Hz, 1H, allylic CH_2), 3.07 (s, 3H, S-CH_3), 2.50 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.6 (C=O), 138.5, 138.4, 136.1, 135.8, 135.5, 131.5, 130.8 (2C), 128.4, 127.6, 127.4, 127.1, 126.7, 119.0 (2C), 116.0, 42.0 (CH_2), 39.6 (SMe), 37.1 (allylic CH_2), 33.0 (NMe); MS (ES mass): 383.1(M+1, 100%); HPLC: 95.8%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 13.3 min.

_N_-{3-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1_H_-benzo[_d_]azepin-4-yl)phenyl}benzenesulfonamide (4h)



Yield: 80%; White solid; mp: 150-152 °C; R_f = 0.72 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.36 (bs, 1H, NH, D_2O exchangeable), 7.77-7.72 (m, 2H, ArH), 7.62-7.57 (m, 2H, ArH), 7.55-7.50 (m, 2H, ArH), 7.38-7.31 (m, 4H, ArH), 7.15-7.08 (m, 3H, ArH), 5.33-5.22 (m, 1H, allylic CH), 4.69 (dd, *J* = 10.0, 1.2 Hz, 1H, =CH_2), 4.60 (dd, *J* = 17.2, 1.6 Hz, 1H, =CH_2), 3.58-3.50 (m, 2H, CH_2), 3.26 (dd, *J* = 15.6, 6.8 Hz, 1H, allylic CH_2), 2.97 (dd, *J* = 15.6, 6.0 Hz, 1H, allylic CH_2), 2.33 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.5 (C=O), 138.9, 138.1, 137.8, 137.2, 135.6, 135.5, 135.3, 132.9, 129.6, 129.2 (2C), 128.6, 127.8, 127.4, 127.1, 126.8, 126.7 (2C), 125.5, 121.5, 120.7, 116.0, 41.8 (CH_2), 36.9 (allylic CH_2), 32.7 (NMe); MS (ES mass): 445.1(M+1, 100%); HPLC: 97.8%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.05% TFA in water mobile phase B: 0.05% TFA in MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 18.3 min.

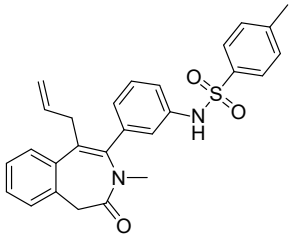
_N_-{4-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1_H_-benzo[_d_]azepin-4-yl)phenyl}benzenesulfonamide (4i)



Yield: 82%; White solid; mp: 90-92 °C; R_f = 0.69 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.43 (bs, 1H, NH, D_2O exchangeable), 7.78-7.76 (m, 1H, ArH), 7.76 (d, *J* = 1.6 Hz, 1H, ArH), 7.62-7.58 (m, 1H, ArH), 7.57-7.51 m, 3H, ArH), 7.36-7.30 (m, 4H, ArH), 7.29 (s, 1H, ArH), 7.17 (d, *J* = 8.4 Hz, 2H, ArH), 5.38-5.38 (m, 1H, allylic CH), 4.70 (dd, *J* = 10.0, 1.6 Hz, 1H, =CH_2), 4.60 (dd, *J* = 17.2, 1.6 Hz, 1H, =CH_2), 3.59-3.50 (m, 2H, CH_2), 3.29 (dd, *J* = 15.6, 6.8 Hz, 1H, allylic CH_2), 3.05 (dd, *J* = 15.6, 6.0 Hz, 1H, allylic CH_2), 2.41 (s, 3H, N-CH_3);

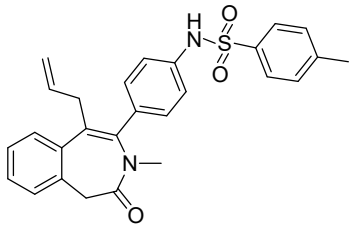
^{13}C NMR (100 MHz DMSO-d_6) δ: 169.6 (C=O), 139.3, 138.3, 137.6, 135.8, 135.7, 135.4, 132.9, 132.1, 130.6 (2C), 129.2 (2C), 128.4, 127.5, 127.4, 127.0, 126.7, 126.6 (2C), 119.9 (2C), 115.9, 41.9 8 (CH_2), 37.1 (allylic CH_2), 32.8 (NMe); MS (ES mass): 445.2(M+1, 100%); HPLC: 95.3%, Column: Eclipse plus C-18 250 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 18.1 min.

_N_-{3-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1_H_-benzo[_d_]azepin-4-yl)phenyl}-4-methylbenzenesulfonamide (4j)



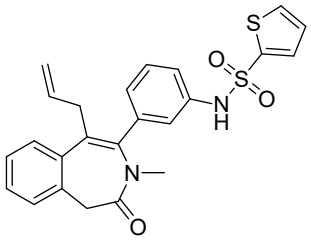
Yield: 84%; White solid; mp: 56-58 °C; R_f = 0.77 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.27 (bs, 1H, NH, D_2O exchangeable), 7.65-7.58 (m, 3H, ArH), 7.37-7.30 (m, 6H, ArH), 7.13-7.08 (m, 3H, ArH), 5.33-5.22 (m, 1H, allylic CH), 4.69 (d, *J* = 9.6 Hz, 1H, =CH_2), 4.60 (d, *J* = 16.8 Hz, 1H, =CH_2), 3.58-3.50 (m, 2H, CH_2), 3.27 (dd, *J* = 15.6, 6.8 Hz, 1H, allylic CH_2), 2.96 (dd, *J* = 15.6, 6.0 Hz, 1H, allylic CH_2), 2.34 (s, 3H, N-CH_3), 2.30 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.5 (C=O), 143.3, 138.1, 137.9, 137.2, 136.6, 136.1, 135.6, 135.5, 135.4, 129.6 (2C), 129.5, 128.6, 127.9, 127.4, 127.1, 126.8 (2C), 125.4, 121.5, 120.6, 116.0, 41.8 (CH_2), 36.9 (allylic CH_2), 32.7 (NMe), 20.9 (ArMe); MS (ES mass): 459.2(M+1, 100%); HPLC: 98.1%, Column: Cosmicsil C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 16.4 min.

_N_-{4-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1_H_-benzo[_d_]azepin-4-yl)phenyl}-4-methylbenzenesulfonamide (4k)



Yield: 83%; White solid; mp: 190-192 °C; R_f = 0.73 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.35 (bs, 1H, NH, D_2O exchangeable), 7.66 (s, 1H, ArH), 7.64 (s, 1H, ArH), 7.58-7.54 (m, 1H, ArH), 7.35-7.30 (m, 6H, ArH), 7.29 (s, 1H, ArH), 7.18 (s, 1H, ArH), 7.16 (s, 1H, ArH), 5.39-5.29 (m, 1H, allylic CH), 4.70 (dd, *J* = 10.0, 1.6 Hz, 1H, =CH_2), 4.60 (dd, *J* = 17.2, 1.6 Hz, 1H, =CH_2), 3.59-3.50 (m, 2H, CH_2), 3.29 (dd, *J* = 15.6, 6.8 Hz, 1H, allylic CH_2), 3.05 (dd, *J* = 15.6, 6.0 Hz, 1H, allylic CH_2), 2.42 (s, 3H, N-CH_3), 2.31 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.6 (C=O), 143.3, 138.3, 137.8, 136.5, 135.8, 135.7, 135.4, 131.9, 130.6 (2C), 129.6 (2C), 128.6, 127.6, 127.4, 127.0, 126.8, 126.7 (2C), 119.8 (2C), 115.9, 41.9 (CH_2), 37.1 (allylic CH_2), 32.9 (NMe), 20.9 (ArMe); MS (ES mass): 459.2(M+1, 100%); HPLC: 95.7%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 5 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 18.8 min.

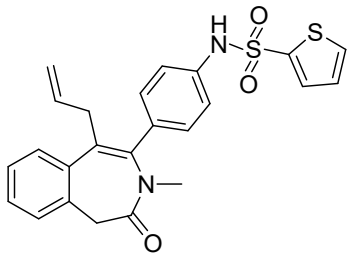
_N_-{3-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1_H_-benzo[_d_]azepin-4-yl)phenyl}thiophene-2-sulfonamide (4l)



Yield: 80%; White solid; mp: 153-155 °C; R_f = 0.72 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.49 (bs, 1H, NH, D_2O exchangeable), 7.89 (dd, *J* = 5.2, 1.6 Hz, 1H, ArH), 7.65-7.58 (m, 1H, ArH), 7.54 (dd, *J* = 3.6, 1.2 1H, ArH), 7.42-7.38 (m, 1H, ArH), 7.37-7.31 (m, 3H, ArH), 7.18 (d, *J* = 7.2 Hz, 3H, ArH), 7.11-7.09 (m, 1H, ArH), 5.38-5.27 (m, 1H, allylic CH), 4.72 (dd, *J* = 10.0, 1.6 Hz, 1H, =CH_2), 4.65 (dd, *J* = 17.2, 1.6 Hz, 1H, =CH_2), 3.60-3.51 (m, 2H, CH_2), 3.30 (dd, *J* = 15.6, 6.8 Hz, 1H, allylic CH_2), 3.06 (dd, *J* = 15.6, 6.0 Hz, 1H, allylic CH_2), 2.39 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.6 (C=O), 139.4, 138.1, 137.6,

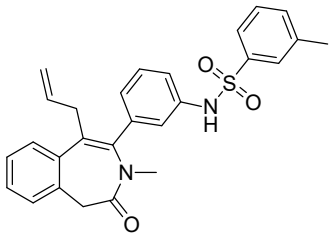
137.3, 135.7, 135.5, 135.4, 133.5, 132.6, 129.6, 128.6, 127.9, 127.6, 127.4, 127.1, 126.8, 125.9, 121.9, 120.9, 116.1, 41.8 (CH_2), 36.9 (allylic CH_2), 32.8 (NMe); MS (ES mass): 451.1(M+1, 100%); HPLC: 96.9%, Column: Cosmicsil Aura ODS 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 220.0 nm, retention time 16.6 min.

_N_-{4-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1_H_-benzo[_d_]azepin-4-yl)phenyl}thiophene-2-sulfonamide (4m)



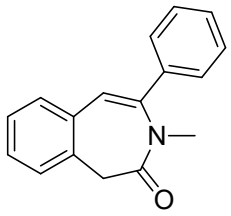
Yield: 82%; White solid; mp: 141-143 °C; R_f = 0.68 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.56 (bs, 1H, NH, D_2O exchangeable), 7.90 (dd, *J* = 5.2, 1.6 Hz, 1H, ArH), 7.61-7.56 (m, 2H, ArH), 7.38-7.32 (m, 5H, ArH), 7.24-7.21 (m, 2H, ArH), 7.13-7.10 (m, 1H, ArH), 5.42-5.33 (m, 1H, allylic CH), 4.72 (dd, *J* = 10.4, 1.6 Hz, 1H, =CH_2), 4.65 (dd, *J* = 16.8, 1.6 Hz, 1H, =CH_2), 3.61-3.51 (m, 2H, CH_2), 3.35 (dd, *J* = 15.0, 6.8 Hz, 1H, allylic CH_2), 3.10 (dd, *J* = 15.0, 6.0 Hz, 1H, allylic CH_2), 2.44 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.6 (C=O), 139.8, 138.3, 137.4, 135.8, 135.7, 135.4, 133.4, 132.5 (2C), 130.6, 128.5, 127.6, 127.5, 127.4, 127.0, 126.7, 120.3 (2C), 119.7, 115.6, 41.9 (CH_2), 37.1 (allylic CH_2), 32.9 (NMe); MS (ES mass): 451.0 (M+1, 100%); HPLC: 93.3%, Column: Eclipse PLUS C-18 250 * 4.6 mm, 5µm, mobile phase A: 0.1% TFA in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 28/90, 30/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 17.3 min.

_N_-{3-(5-Allyl-3-methyl-2-oxo-2,3-dihydro-1_H_-benzo[_d_]azepin-4-yl)phenyl}-3-methylbenzenesulfonamide (4n)



Yield: 83%; White solid; mp: 63-65 °C; R_f = 0.78 (60% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.31 (bs, 1H, NH, D_2O exchangeable), 7.62-7.53 (m, 3H, ArH), 7.40 (d, *J* = 5.6 Hz, 2H, ArH), 7.37-7.31 (m, 4H, ArH), 7.11 (m, 3H, ArH), 5.33-5.22 (m, 1H, allylic CH), 4.69 (d, *J* = 9.6 Hz, 1H, =CH_2), 4.60 (d, *J* = 16.8 Hz, 1H, =CH_2), 3.58-3.51 (m, 2H, CH_2), 3.27 (dd, *J* = 15.6, 6.8 Hz, 1H, allylic CH_2), 2.99 (dd, *J* = 15.6, 5.6 Hz, 1H, allylic CH_2), 2.34 (s, 3H, N-CH_3), 2.30 (s, 3H, ArCH_3); ^{13}C NMR (100 MHz DMSO-d_6) δ: 169.6 (C=O), 139.0, 138.9, 138.2, 137.9, 137.2, 135.6, 135.5, 135.4, 133.6, 129.6, 129.1, 128.6, 127.7, 127.4, 127.1, 126.9, 126.8, 125.5, 123.9, 121.4, 120.7, 116.0, 41.8 (CH_2), 36.9 (allylic CH_2), 32.7 (NMe), 20.8 (ArMe); MS (ES mass): 459.1(M+1, 100%); HPLC: 95.2%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5, 35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 16.3 min.

3-Methyl-4-phenyl-1*H*-benzo[*d*]azepin-2(3*H*)-one (5a)



Yield: 26%; White solid; mp: 120-122 °C; R_f = 0.68 (30% EtOAc/ *n*-hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.59 (d, *J* = 7.2 Hz, 2H, ArH), 7.48 (t, *J* = 7.2 Hz, 3H, ArH), 7.44-7.39 (m, 1H, ArH), 7.38-7.31 (m, 3H, ArH), 6.95 (s, 1H, ArH), 3.62 (s, 2H, CH_2), 2.72 (s, 3H, N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.7 (C=O), 142.7, 137.4, 133.6, 133.4, 128.9, 128.8 (2C), 128.6, 128.1, 127.7, 127.3 (2C), 126.9, 119.7, 42.3 (CH_2), 34.6 (NMe); MS (ES mass): 250.3 (M+1, 100%); HPLC: 99.8%, Column: Eclipse XDB C-18 150 * 4.6 mm, 5µm, mobile phase A: 10 mM Ammonium acetate in water mobile phase B: MeCN (T/%B): 0/5, 20/90, 30/90, 31/5,

35/5; flow rate: 1.0 mL/min; Diluent: MeCN: water (80:20); UV 210.0 nm, retention time 15.9 min.

Compound characterization:

All the compounds **3** and **4** synthesized were characterized by spectral (NMR, MS) data. The CH_2 protons of the 7-membered ring could be detected for most of the compounds in their ^{1}HNMR spectra generally as a singlet near δ 3.8 and as a multiplet near δ 3.5-3.6 in case of **3** and **4** respectively. The corresponding ^{13}C NMR signal appeared near 36 and 41 ppm, respectively. The ^{13}C NMR signal near 167 and 169 ppm was due to the C=O group of benzo[*d*]oxepin-2(1*H*)-one (in case of **3**) and 3-benzazepin-2-one ring (in case of **4**) respectively. The partial ^{1}H and ^{13}C NMR data of two representative compounds **3l** and **4l** are shown in Fig S-1. In case of **3l** the NH and C=O group of the 3-oxobutyl side chain appeared near δ 10.4 (D_2O exchangeable broad singlet) and 207 ppm in the ^{1}H and ^{13}C NMR spectra, respectively. The presence of side chain was further indicated by the ^{1}H NMR signals at δ 1.96 (CH_3), 2.37 (CH_2) and 2.77 (CH_2) as well as ^{13}C NMR signal at 29.7 (CH_3), 26.4 (CH_2) and 40.9 (CH_2) ppm. In case of **4l** the presence of allyl side chain was indicated by the ^{1}H NMR signals at δ 5.38-5.27 (m, =CH), 4.72 & 4.65 (dd, =CH_2) and 3.30 & 3.06 (dd, CH_2). The NCH_3 group appeared at δ 2.39 and 32.8 ppm in ^{1}H and ^{13}C NMR spectra respectively.

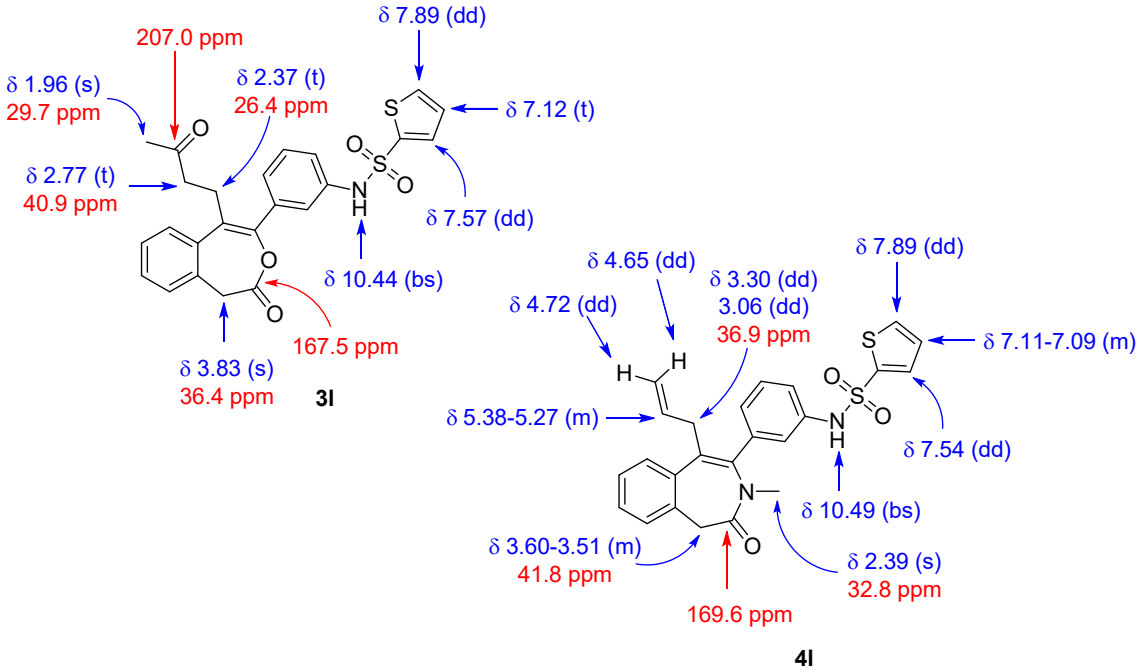
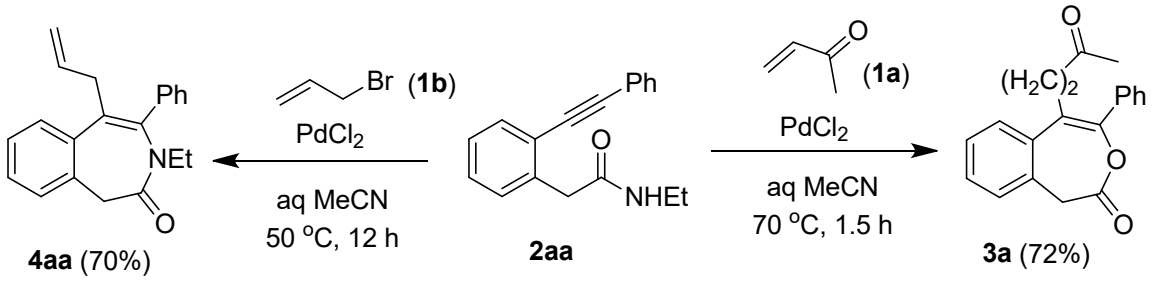


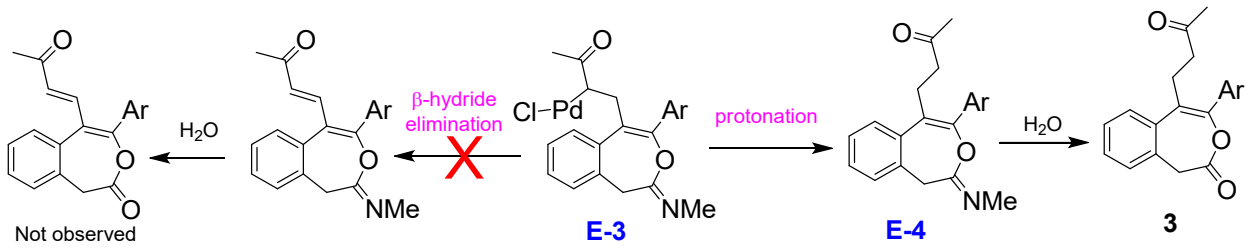
Fig S-1. Partial representation of ^{1}H as well as ^{13}C NMR spectral data of compound **3l** and **4l**.



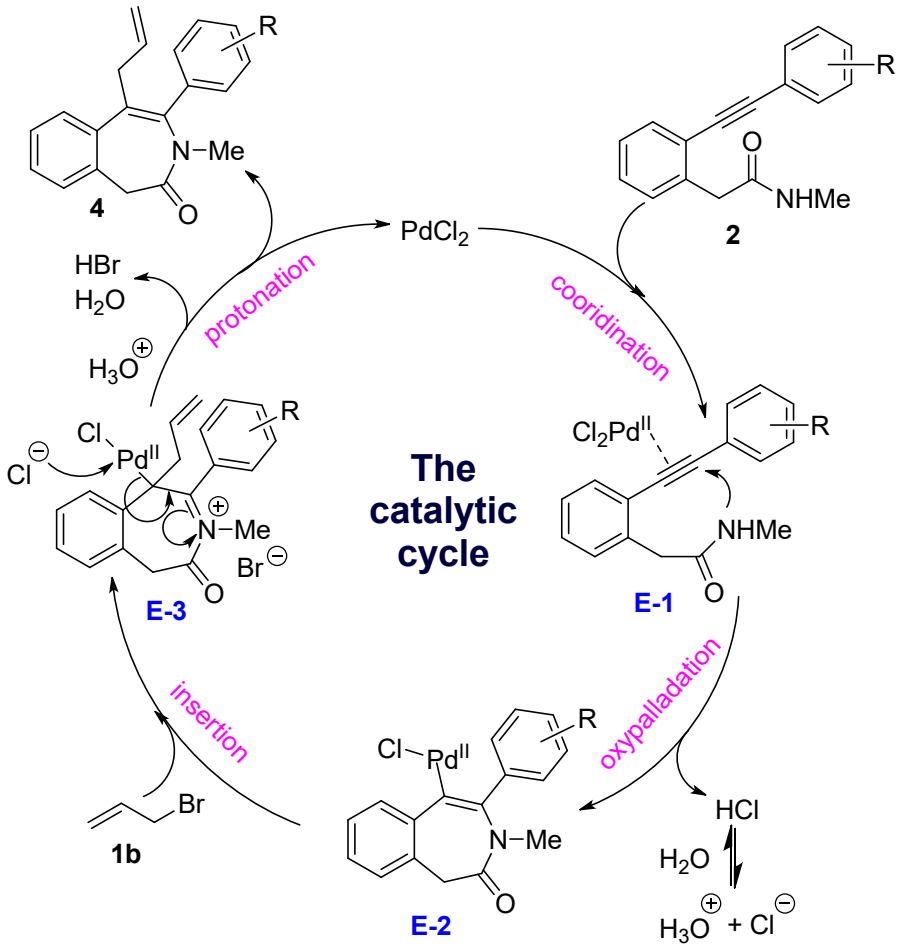
Scheme S-5. The Pd-catalyzed *7-endo-dig* cyclization of amide *N*-ethyl-2-(2-(phenylethynyl)phenyl)acetamide (**2aa**) in the presence of **1a** and **1b**.

The proposed reaction mechanism

Mechanistically, the formation of **3** (Scheme 3, see the main manuscript) may involve (i) the formation of initial coordinated complex **E-1** followed by (ii) oxypalladation leading to **E-2** and (iii) alkene insertion to give **E-3** and (iv) finally protonation of the Pd-enolate **E-3** (or the corresponding *O*-Pd enolate) to give **E-4** [with the regeneration of Pd (II) catalyst to complete the catalytic cycle] followed by subsequent hydrolysis to afford **3**. Notably, the β-hydride elimination of **E-3**, a competing process leading to the formation of the alternative Heck-type product was not observed in this case perhaps due to the fact that the protonation of the Pd-enolate (e.g. **E-3** in the current study) is favoured over the β-hydride elimination in the presence of polar protic solvent (or excess of halide salt), e.g. aqueous MeCN in the current study (see ref 22 and 23 in the main manuscript).



A reaction mechanism similar to Scheme 3 of main manuscript could be proposed for the formation of **4** as follows involving all these steps except the hydrolysis step.



Scheme S-6. Proposed reaction mechanism for the formation of **4**.

While the reason for selective formation of *O*-heterocycle in the presence of methyl vinyl ketone (**1a**) and *N*-heterocycle in the presence of allyl bromide (**1b**) was not clear however the possible explanation for this observation could be presented as follows. It is evident from the Scheme 2 (see the main manuscript) that the reaction affords *N*-heterocycle when performed in the absence of **1a** or **1b** indicating the preferred participation of the N-nucleophilic center over the O-center in the Pd-catalysed *7-endo-dig* cyclization of amide **2a** in the absence of any influencing agents or additives. However, the nucleophilic attack by amidic NH was somewhat hindered in the presence of **1a** perhaps due to its H-bonding with the carbonyl oxygen of **1a** thereby allowing O-center to participate in the cyclization. Needless to mention that such type of H-bond interaction was not possible when **1b** was employed and hence the participation of NH was facilitated in the cyclization. Nevertheless, further study is ongoing to understand this phenomenon.

Biology

***In vitro* enzymatic assay**

Enzymes were procured from BPS Biosciences

PDE4B assay: The inhibition of PDE4B enzyme was measured using PDE light HTS cAMP phosphodiesterase assay kit (Lonza) according to manufacturer's recommendations. Briefly, 20 pg of PDE4B enzyme was pre-incubated either with DMSO (vehicle control) or compound for 15 min before incubation with the substrate cAMP (5 µM) for 1 h. The reaction was halted with stop solution followed by incubation with detection reagent for 10 minutes in dark. Luminescence values (RLUs) were measured by a Multilabel plate reader (Perkin Elmer 1420 Multilabel counter). The percentage of inhibition was calculated using the following formula and IC_{50}s were computed using GraphPad Prism Version 5.04 software.

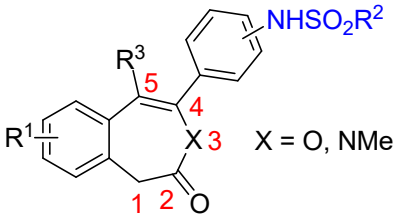
$$\% \text{ Inhibition} = \frac{\text{RLU of vehicle control} - \text{RLU of Inhibitor}}{\text{RLU of vehicle control}} \times 100$$

Data Analysis: The PDE activity assays were performed in duplicate at each concentration. Fluorescence intensity is converted to fluorescence polarization using the Tecan Magellan6 software. The fluorescence polarization data were analyzed using the computer software, Graphpad Prism. The fluorescence polarization (FP_t) in absence of the compound in each data set was defined as 100% activity. In the absence of PDE and the compound, the value of fluorescent polarization (FP_b) in each data set was defined as 0% activity. The percent activity in the presence of the compound was calculated according to the following equation:

% Activity = $(FP-FP_b) / (FP_t-FP_b) \times 100\%$

Where FP = the fluorescence polarization in the presence of the compound.

Table S-6. *In vitro* evaluation of compound **3** and **4** against PDE4B.

Compound	% inhibition at 10 µM	Remarks
3a	5.76	 None of the benzo[*d*]oxepin-2(1*H*)-one derivatives (**3**; X=O) showed significant inhibition (< 50%) of PDE4B whereas 3-
3e	9.78	
3f	17.42	
3h	25.22	
3j	38.48	
3k	29.65	
3l	36.70	
3n	27.96	
4a	4.75	

4c	19.24	benzazepin-2-one derivatives (X = NMe) (**4a**, **4c**, **4d** etc) devoid of an aminosulfonyl moiety was also fund to be less active. On the other hand 3-benzazepin-2-one derivatives containing an aminosulfonyl moiety are generally active except **4f**, **4l** etc. It seems the activity was influenced by the C-4 aryl substituent present in compound **4** in the order $C_6H_4NHSO_2Ph$-*m* (**4h**) > $C_6H_4(NHSO_2C_6H_4Me$-*m*$)$-*m* (**4n**) > $C_6H_4[NHSO_2$ (2-thienyl)]-*p* (**4m**) > $C_6H_4NHSO_2Ph$-*p* (**4i**).
4d	33.01	
4f	27.35	
4g	40.04	
4h	76.12	
4i	66.36	
4j	45.33	
4k	47.99	
4l	36.24	
4m	67.77	
4n	71.82	
Rolipram	77.31	

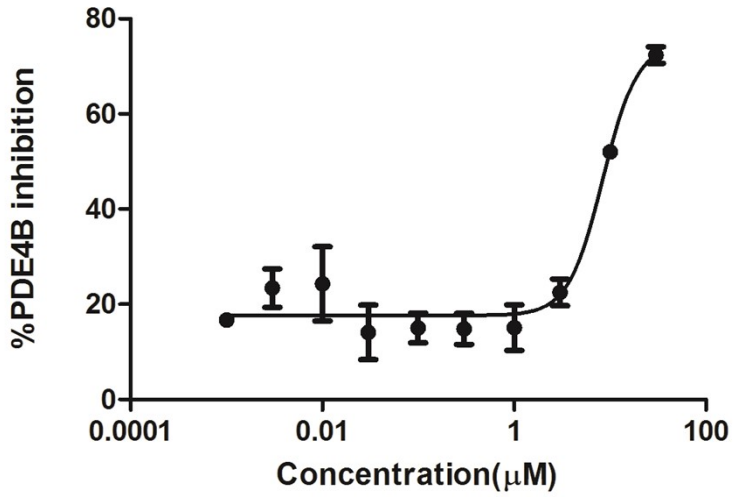


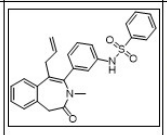
Fig. S-2. Concentration dependent inhibition of PDE4B by compound **4n** *in vitro.*

MTT assay

Cell line: Raw 264.7 cell line was obtained from American type culture collection (ATCC), India and grown at 37ºC in a humidified atmosphere of 5% CO_2 using DMEM (Lonza), supplemented with 10% FBS (Himedia) and antibiotic solution 1X-Pencillin-streptomycin (Thermo Fisher scientific). About 80% confluent cells were used for MTT assay.

Cytoxicity assay: The cytotoxic effect was evaluated using MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay according to the method published by Mosmann et al [1]. The cells (100µl; $2.5*10^4$) were seeded into 96 well microtitre plates and left to adhere for 16 hours. The medium was then removed from the wells and replaced with 100µl of media

containing compounds. Cells were incubated with different concentrations of drug (1-100µM) for the next 24hours. MTT (10µl; 5mg/ml in PBS) was added to each well and further incubated for 2h. The medium was removed and DMSO (200µl) was added. The absorbance was read at 570 nm and the cell viability was expressed as percent of control.

4h		STRUCTURE	set-1	set-2	% Viability	% Viability	avg	std	% Cell dea	% Cell dea	avg	std
CTRL			1	1	100	100	100	0	0	0	0	0
4h (0.3µM)			1.00719	1.01158	100.719	101.158	100.939	0.31093	-0.71875	-1.15847	-0.93861	0.31093
4h (1µM)			0.98888	0.99226	98.8881	99.2257	99.0569	0.23878	1.11195	0.77426	0.9431	0.23878
4h (3µM)			1.01512	0.98584	101.512	98.5835	100.048	2.07089	-1.51221	1.41646	-0.04788	2.07089
4h (10µM)			0.59212	0.81432	59.2117	81.432	70.3218	15.7121	40.7883	18.568	29.6782	15.7121
4h (30µM)			0.66581	0.72716	66.5811	72.7155	69.6483	4.33771	33.4189	27.2845	30.3517	4.33771
4h (100µM)			0.53334	0.66778	53.3338	66.7782	60.056	9.50663	46.6662	33.2218	39.944	9.50663

MTT IC_{50} > 100 µM

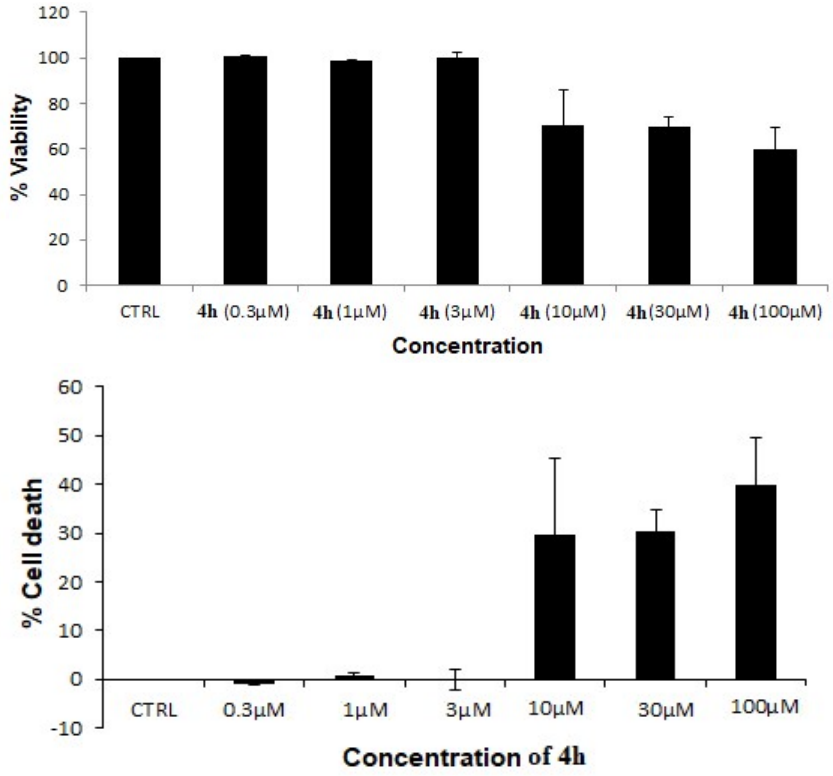
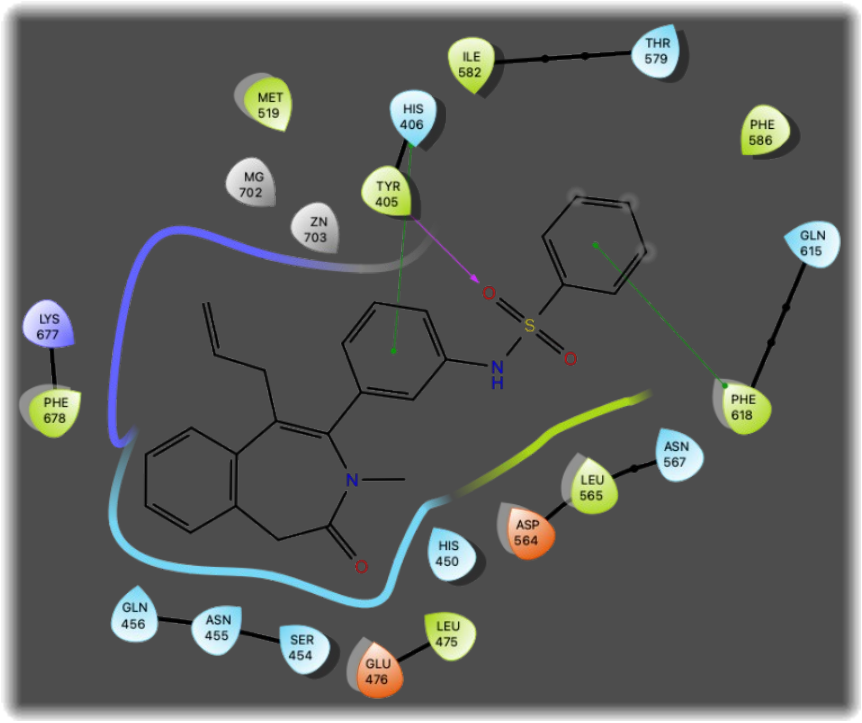


Fig. S-3. MTT assay results of compound **4h**.

Reference

[1] T. Mosmann, Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods* 1983, **65**, 55-63.

Molecular docking studies



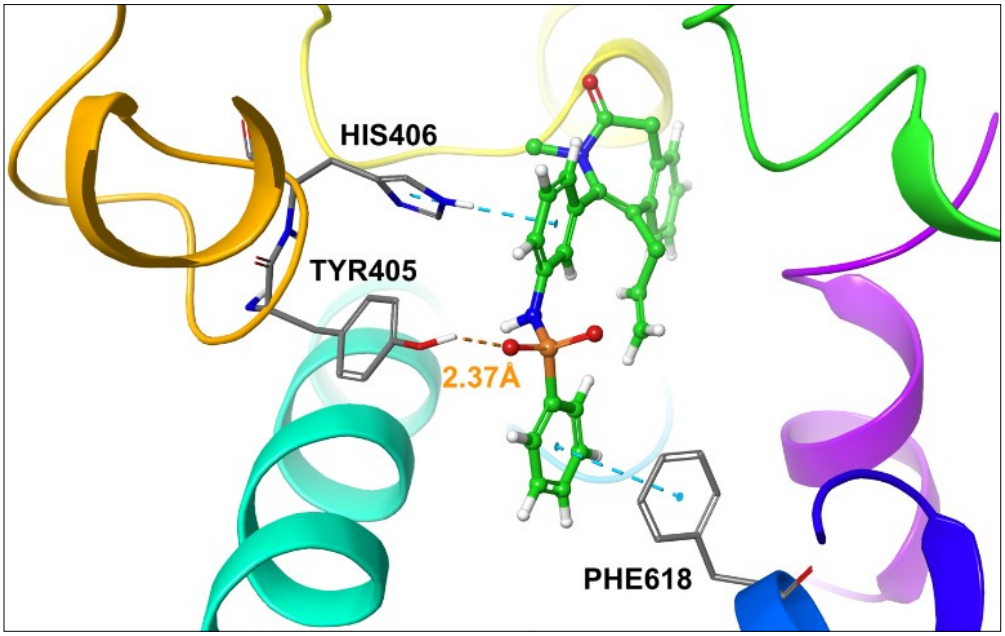


Fig. S-4. The 2D (where H-bond, pi-pi and pi-cation interactions are shown in magenta, green and red coloured line, respectively) and 3D interaction diagram (where H-bond, π-cation and π-π stacking are shown in orange, green and cyan dashed lines respectively) of **4h** with PDE4B (PDB ID: 4MYQ), that were prepared in Maestro visualizer (Schrödinger, LLC).

According to the study of Fox et al. [1] the PDE4B inhibitors interact with a C-terminal regulatory helix, now termed CR3 (Control Region 3), located in between catalytic domain and C-terminal. They deposited the crystal structure of PDE4B (ID 4MYQ) in Protein Data Bank (PDB, https://www.rcsb.org/) bound with a co-crystal ligand, that we have utilized for our present study.

Loop Modelling: Because of high degree of flexibility, few portions were missing in the above mentioned crystal structure, and among them we thought that region between SER659 to ASP670 (Fig S-5) was important for our predictive *in-silico* studies as that region was near to catalytic domain and connected with CR3.

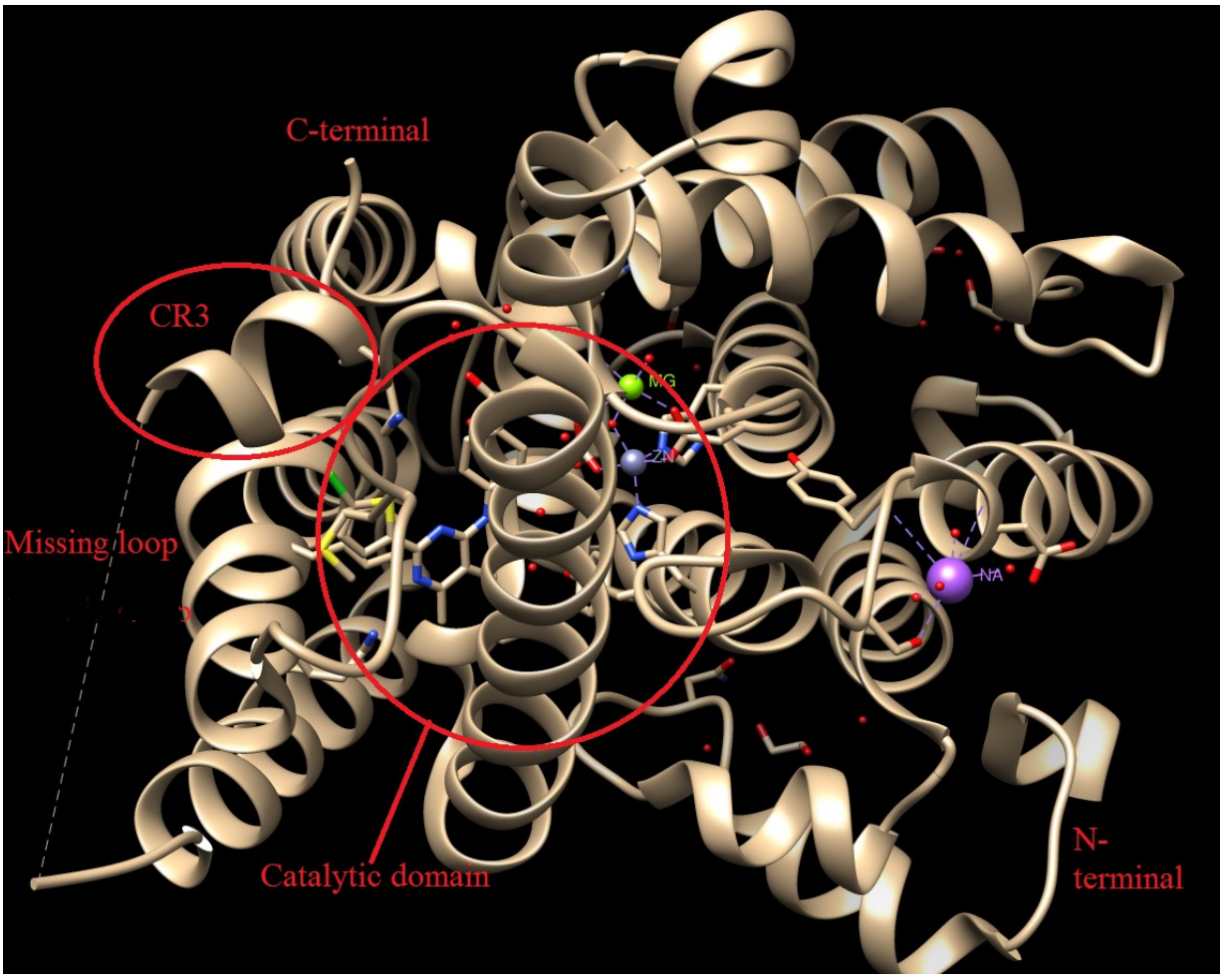


Fig. S-5. Structure of PDE4B (ID 4MYQ) (before loop modelling), indicated with different region of the enzyme.

For generating that missing loop we have used ModLoop web-tool [2] which relied on the loop modelling routine in MODELLER [3] (uses MODELLER loop refinement Python

script) and predicted the loop conformations by satisfaction of spatial restraints. Before development of the loop confirmation, we have added dummy coordinate for those 10 amino acid residues in our PDB file (as it was required for ModLoop) and then the final model was extracted (Fig S-6).

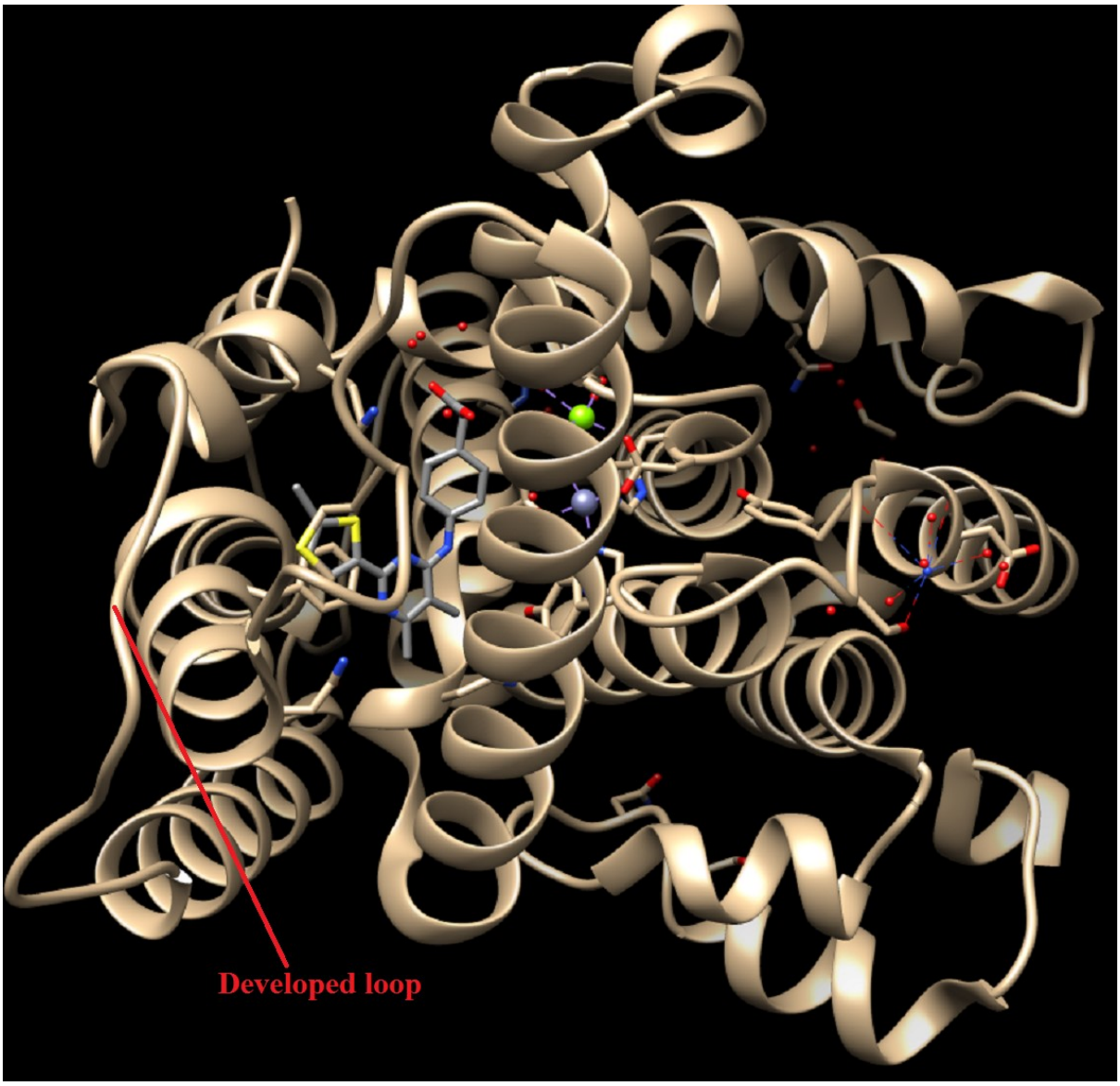


Fig. S-6. Structure of PDE4B with developed loop.

Material and Methods: To predict the probable interactions between the test ligands and target protein (PDE4B), we have performed molecular docking studies. The structures of all the test ligands were constructed in MarvinSketch [4]. Protein and all ligands were prepared (means optimization, charge calculation, deletion of co-crystal ligand, addition of hydrogen, and

rotatable bonds assignment etc.) using AutoDock tool [5]. As some water mediated interactions with PDE4B has been reported [1], we kept all the water molecules in the PDB structure. AutoGrid was utilized to generate the grid box with -18.33, 35.5, and -6.14 as center_X, center_Y, and center_Z respectively (as we have targeted the position of co-crystal ligand), and points 20X20X20 with internal spacing 1 Å. Then all ligands were docked using reliable open-source tool AutoDock Vina [6]. To search all possible conformation of ligands thoroughly, exhaustiveness value of 20 were used, which made the process little more time consuming, but allowed us to find out the best pose of individual ligand accurately. Finally, complexes with lowest binding energy were retrieved.

References

1. D. Fox 3rd, A. B. Burgin and M. E. Gurney, *Cell. Signal.*2014, **26**, 657-663.
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