Articles

Design and Syntheses of 1,6-Naphthalene Derivatives as Selective HCMV Protease Inhibitors

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Through high throughput screening of various libraries, substituted styryl naphthalene **6** was identified as an HCMV protease inhibitor. Optimization of various regions of the lead molecule using parallel synthesis resulted in 1,6-substituted naphthalenes **19d**−**i**. These compounds displayed good potency and were selective over elastase, trypsin, and chymotrypsin. The optimization approach on lead compound **6** in three different regions of the molecule using parallel solution-phase synthesis and the corresponding SAR are discussed in detail.

Introduction

Human cytomegalovirus (HCMV), a member of the betaherpesvirinae family, infects ∼60% of the population in the developed world and >90% of the population in the developing world.[1] However, the physiological and clinical relevance of this virus is underscored by its ability to establish lifelong latent infections. Immunocompromised/immunosupressed patients are at risk for disease[2] wherein reactivation of the virus produces clinical manifestations that include pneumonitis, retinitis, colitis, and oesophagitis. The current treatment[3] for HCMV includes the use of acyclonucleosides and nucleotides (acyclovir, gancyclovir, cidofovir), phosphonate substrate analogues (foscarnet), and antisense therapy (formvirsen). The first three require administration by intravenous injection, and formvirsen requires intraocular injection. Dosing issues combined with liabilities of viral resistance and toxic side effects[4] highlight the need for new drugs that will alleviate these difficulties.

HCMV protease, a serine protease, is a viable target for antiviral chemotherapy because of its critical role in capsid assembly and viral maturation.[5] There is a high degree of homology between the herpes proteases, but little homology exists with the mammalian serine proteases, which support the notion that specific inhibitors of HCMV protease have antiviral activity with therapeutic benefit.[6] This enzyme exists as a dimer, and the crystal structure of HCMV protease has identified Ser-132, His-63, and His-157 to be involved in a unique catalytic triad.[7] Inhibitors that have an effect on dimer and/or force conformational alterations of the enzyme would be effective inhibitors of viral proliferation. The most potent inhibitors described in the literature are chemically reactive to the catalytic serine, Ser-132 and/or, a surface cysteine Cys-161 (Figure 1) acting as Michael acceptors[8] **1** and **2** or electrophiles (e.g. β-lactam inhibitors[9] **4** and **5**, peptidyl trifluromethyl ketones[10] **3**).

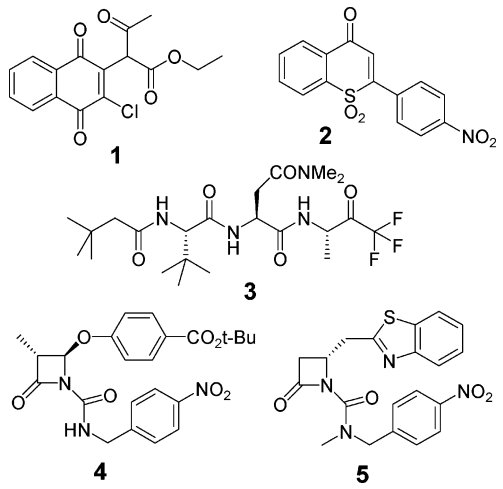

Figure 1. Irreversible inhibitors of HCMV protease.

Our interest toward identifying a reversible HCMVP inhibitor started with the high throughput screening of the various compound libraries. The effort culminated in the identification of stilbene **6** that binds noncovalently and displays competitive inhibition kinetics in both HPLC end-point and fluorescent rate-based assays.[11] This compound does not display time-dependent inhibition kinetics in comparison to the β- and/or *trans*-lactam derivatives, or trifluoromethyl ketones.[10] Biophysical analyses demonstrate the ability of the compound to displace substrate, confirming the competitive mechanism of action. Further 1D NMR analysis indicated that the compound binds to protease with 1:1 stoichiometry and displaces substrate.[13] Stilbene **6** has an IC_{50} value of 66 μM and is selective over elastase[11] and chymotrypsin[12] (>160 μM). This screening hit was

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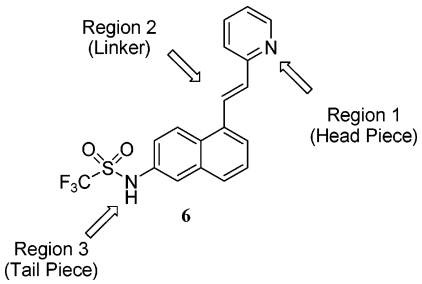
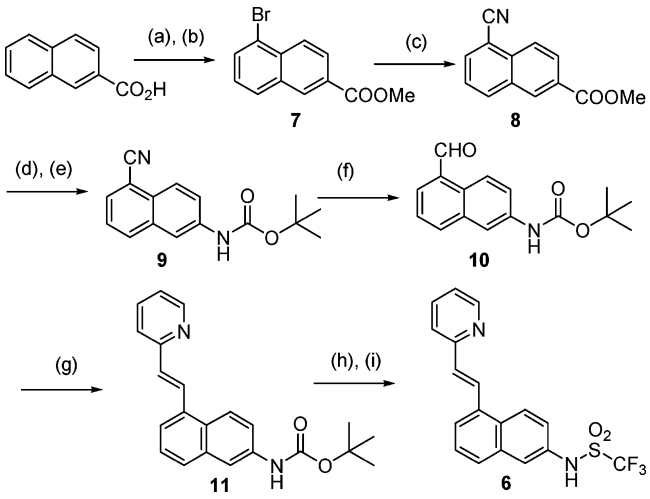


Figure 2.

Scheme 1. Synthesis of Stilbene Derivatives[a]



[a] Reagents and conditions: (a) Br_2,I_2, AcOH, recrystallize, 29%; (b) HCl, MeOH, 98%; (c) CuCN, 66%; (d) 1 N NaOH, 100%; (e) $(PhO)_2PON_3$, t-BuOH, 33%; (f) RaNi, AcOH, NaH_2PO_2, 68%; (g) Wittig salt, TEA, CH_2Cl_2; (h) TFA−CH_2Cl_2; (i) electrophiles, TEA, CH_2Cl_2.

the basis for further modifications in the three regions outlined (Figure 2).

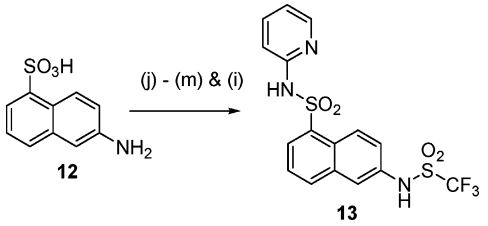
Chemistry. The stilbene analogues were synthesized[14] as shown in Scheme 1 starting from 2-naphthoic acid. Bromination followed by recrystallization to separate the isomers provided the desired bromo compound **7** which was converted to the ester and treated with CuCN to give the nitrile **8**. Hydrolysis followed by treatment with diphenylphosphoryl azide gave the Boc-protected amine **9**. Reduction of **9** to aldehyde **10** provided a key intermediate for further elaboration using solution phase Wittig reaction with different Wittig reagents to optimize region 1 (headpiece). The Boc group was removed, and the free amine was treated with various electrophiles in parallel to optimize region 3 (tailpiece).

Compounds with sulfonamide linkers (Region 2) were synthesized following Scheme 2, while Scheme 3 shows the synthesis of amide analogues. Ethers were synthesized as shown in Scheme 4, and the reverse ethers were made in the same fashion starting from the corresponding naphthol. All these modifications were made by parallel solution-phase synthesis.

Results and Discussion

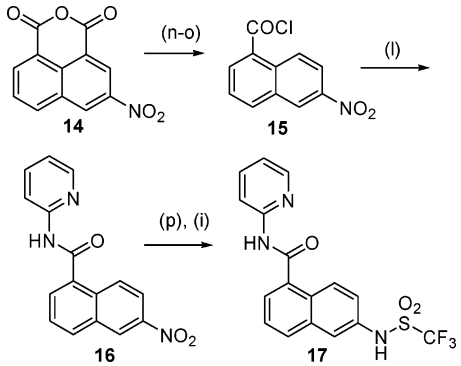
Initial efforts to modify the pyridyl headgroup in stilbenes (Region 1) to quinoline increased the potency significantly while retaining the selectivity for elastase, as shown by **6b** in Table 1. Further probing by introducing susbtituents on the quinoline ring (**6c**−**f**, Table

Scheme 2. Synthesis of Sulfonamide Derivatives[a]



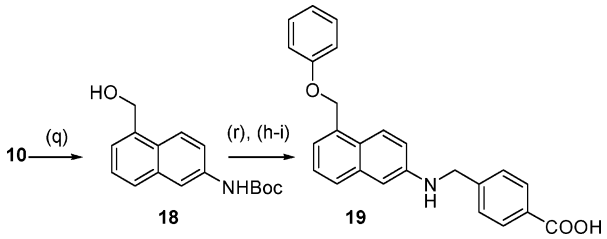
[a] Reagents and conditions: (j) FmocCl, $NaHCO_3$; (k) $SOCl_2$/DMF; (l) amines, pyr; (m) 20% piperidine in DMF.

Scheme 3. Synthesis of Amide Derivatives[a]



[a] Reagents and conditions: (n) HgO, AcOH, separate; (o) $(CO)Cl_2$, toluene; (p) H_2, Pd/C.

Scheme 4. Synthesis of Ether Derivatives[a]

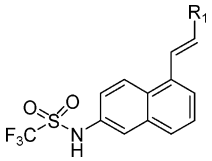


[a] Reagents and conditions: (q) $NaBH_4$, EtOH; (r) PhOH, Ph_3P, DEAD, THF.

1) showed that the region is very flexible and seemed to accommodate a number of substituents such as halogen, methoxy, methyl, or the *N*,*N*-dimethylamino group in the 6-position without loss of potency. While 7-, 8-, and 4- substituents were much less probed, they did seem to tolerate the chloro group and retained selectivity for elastase. Attempts to replace the hetroaromatic headgroup with phenyl or substituted phenyl groups (**6j**−**n** in Table 1) also showed tolerance, accommodating a range of lipophilic substituents such as chloro, trifluoromethyl, or methoxy in the 3 or 4 position. Even bulky substituents such as 2-naphthyl retained potency.

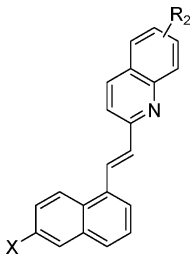
While the headgroup (Region 1) modification significantly increased the potency of **6** and showed flexibility, the modifications on the tailpiece (Region 3) showed limited promise as shown in Table 2. The lead has trifluoromethylsulfonamide as the tailpiece and it was of importance to determine if the acidic NH is necessary for potency. Replacing it with COOH or NH_2 or methylating the NH (**6o**−**q**) led to loss of potency. The sulfonamide was also replaced with amide, urea, or carbamate, and the analogues were found to be inactive. Attempts were also made to replace the trifluoromethylsulfonamide group with other sulfonamide groups

Table 1. Headpiece (Region 1) Modification to Substituted Quinoline and Phenyl Groups



compd	R_1	HCMVP IC_{50} (μM)	elastase IC_{50} (μM)
6	2-pyridyl	66	>50
6b	2-quinolinyl	9.5	>50
6c	6-methyl-2-quinolinyl	6.3	>50
6d	6-methoxy-2-quinolinyl	3.4	>50
6e	6-(*N*-dimethylamino)-2-quinolinyl	3.7	>50
6f	6-chloro-2-quinolinyl	3.2	>50
6g	7-chloro-2-quinolinyl	15.1	>50
6h	8-chloro-2-quinolinyl	3.2	>50
6i	4-chloro-2-quinolinyl	10.5	>50
6j	phenyl	7.5	>50
6k	4-chlorophenyl	4.3	>50
6l	3-trifluoromethylphenyl	6.5	>50
6m	3-methoxyphenyl	6.6	>50
6n	2-naphthyl	15	>50

Table 2. Tailpiece (Region 3) Modifications

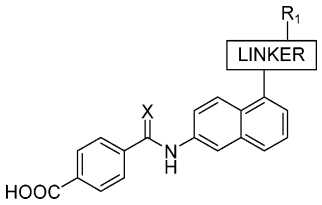


compd	X	R_2	HCMVP IC_{50} (μM)
6f	$NHSO_2CF_3$	6-Cl	3.2
6o	COOH	H	>50
6p	NH_2	7-Cl	>50
6q	$N(CH_3)SO_2CF_3$	6-Cl	>50
6r	$NHSO_2CH_3$	6-Cl	>50
6s	$NHCOCH_3$	6-Cl	43
6u	NHCOOPh	6-Cl	>50
6v	$NHCONHSO_2Ph$	7-Cl	6.7
6w	$NHCONHSO_2$(4-Cl-Ph)	7-Cl	4.7
6x	$NHCONHSO_2$(4-CH_3-Ph)	7-Cl	8.3
6t	NHCOPh	7-Cl	>50
6y	NHCO(4-COOH-Ph)	7-Cl	17.4
6z	$NHCH_2$(4-COOH-Ph)	7-Cl	2.7

such as trichloromethylsulfonamide, aliphatic sulfonamides, or aromatic sulfonamides without much success. However, the sulfonyl ureas in the place of trifluoromethylsulfonamide retained the potency (**6v**−**x** in Table 2), indicating the need for an acidic proton in this region of the molecule. Although the carboxylic acid replacement itself was unsuccessful, the analogues with a benzoic acid moiety attached via an amide or aminomethyl linker (**6y**,**z** in Table 2) were found to retain activity.

Variations on the linker (Region 2) to move away from the styryl moiety in the initial lead **6** was attempted by replacing the double bond with an amide **17** or sulfonamide **13** linker. However, these analogues were inactive. Reducing the double bond to give the saturated analogue retained the activity. This observation prompted us to examine equally flexible linkers such as ethers. As seen from Table 3 both naphthylmethyl ethers (**19a**−**f**) as well as reverse naphthyl ethers (**19g**−**i**) were found to be active with the appropriate tailpiece in position. As observed with the styryl analogues, among the various headpiece groups made, the unsubstituted or the halogenated phenyl groups are favored for good potency. As discussed earlier, an acidic moiety is preferred for the tail region. Apart from the benzoic acid tailpiece shown in Table 3, phenylsulfonyl ureas and trifluoromethylsulfonamides were also active. All these analogues showed very good selectivity for elastase (>50 μM). Some of the potent compounds of interest **19d**−**i** were also selective for trypsin (>80 μM) and chymotrypsin (>50 μM).

Table 3. Linker (Region 2) Modifications



compd	linker	R_1	X	HCMVP IC_{50} (μM)
6aa	CH═CH	3-trifluoromethylphenyl	O	6.9
6ab	CH═CH	3-trifluoromethylphenyl	H,H	6.9
19a	CH_2O	3-chlorophenyl	O	15.3
19b	CH_2O	4-bromophenyl	O	21.3
19c	CH_2O	3-trifluoromethylphenyl	O	15.2
19d	CH_2O	phenyl	H,H	4.8
19e	CH_2O	3-chlorophenyl	H,H	3.1
19f	CH_2O	4-bromophenyl	H,H	2.8
19g	OCH_2	3-chlorophenyl	O	5.1
19h	OCH_2	3-bromophenyl	O	6.1
19i	OCH_2	3-trifluoromethylphenyl	O	7.4

Conclusions

Several naphthalene derivatives were identified as inhibitors of HCMV protease that bind noncovalently with single micro molar potency and display competitive inhibition kinetics in both HPLC end-point and fluorescent rate-based assays. These compounds have time-independent inhibition kinetics and demonstrate the ability to displace substrate confirming the competitive, reversible mechanism of action. Extensive SAR modifications resulted in nonstyryl analogues that are selective for HCMVP.

Experimental Section

General Procedures. Melting points were determined in an open capillary tubes on a Meltemp melting point apparatus and are uncorrected. ^{1}H NMR spectra were determined with s Bruker DPX-300 spectrometer at 300 MHz. Chemical shifts δ are reported in parts per million (δ) relative to residual chloroform (7.26 ppm), TMS (0 ppm), or dimethyl sulfoxide (2.49 ppm) as an internal reference with coupling constants (J) reported in hertz (Hz). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Electrospray (ES) mass spectra were recorded in positive or negative mode on a Micromass Platform spectrometer. Electron impact and high-resolution mass spectra were obtained on a Finnegan MAT-90 spectrometer. Combustion analysis were obtained using Perkin-Elmer Series II 2400 CHNS/O analyzer. The combustion analysis was conducted on the free base. Chromatographic purifications were performed by flash chromatography using Baker 40-μm silica gel. Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF 250 M prescored plates. The terms "concentrated"

and "evaporated" refer to removal of solvents using a rotary evaporator at water aspirator pressure with a bath temperature equal to or less than 60 °C. Unless otherwise noted, reagents were obtained from commercial sources and were used without further purification

5-Bromonaphthalene-2-carboxylic Acid Methyl Ester (7). Anhydrous HCl gas was bubbled through 60 mL of methanol, and to the solution was added 5-bromonaphthalene-2-carboxylic acid (4.02 g). The mixture was stirred at reflux for 5 h, and the solvent was removed under reduced pressure. The solid obtained was washed with hexane and ether several times and dried. Yield: 3.82 g. mp 72−73 °C; ^{1}H NMR (DMSO-d_6): 3.94 (s, 3H), 7.55 (t, J = 8 Hz, 1H), 8.04 (d, J = 10 Hz, 1H), 8.15−8.23 (m, 3H), 8.71 (d, = 2 Hz, 1H). Anal. Calcd for $C_{12}H_9BrO_2$: C, 54.37; H, 3.42; N, 0.00. Found: C, 54.01; H, 3.36; N, 0.02.

5-Cyanonaphthalene-2-carboxylic Acid Methyl Ester (8). 5-Bromonaphthalene-2-carboxylic acid methyl ester **7** (3,7 g; 14 mmol) was dissolved in DMF (20 mL) and pyridine (2 mL), to the solution was added copper cyanide (1.5 g; 16.7 mmol), and the mixture was heated at 160 °C under nitrogen for 6 h. The solution was cooled to room temperature and poured into crushed ice (100 g) and concentrated ammonium hydroxide (50 mL). The precipitate formed was filtered and washed with dilute ammonium hydroxide. The solid was further purified by passing though a plug of silica to give an off white solid (1.9 g). mp 113−115 °C; ^{1}H NMR ($CDCl_3$): 4.02 (s, 3H), 7.62 (t, J = 8 Hz, 1H), 8.04 (d, J = 10 Hz, 1H), 8.2 (d, J = 10 Hz, 1H), 8.27−8.29 (m, 2H), 8.82 (d, = 2 Hz, 1H). Anal. Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.29; N, 6.63. Found: C, 74.09; H, 4.25; N, 6.66.

(5-Cyanonaphthalen-2-yl)carbamic Acid *tert*-Butyl Ester (9). 5-Cyanonaphthalene-2-carboxylic acid methyl ester **8** (10.5 g; 49.8 mmol) was dissolved in 80 mL of methanol, 1 N sodium hydroxide solution (55 mL) was added, and the reaction was stirred at room-temperature overnight. The solvent was removed under reduced pressure, and the solid was dissolved in water and acidified with 1 N hydrochloric acid. The solid obtained was filtered and washed with water and dried (yield: 8.3 g). The acid (9.29 g; 47.2 mmol) obtained was stirred with triethylamine (6.7 mL; 48.2 mmol) in *tert*-butyl alcohol, and to this solution was added phosphorazidic acid diphenyl ester (11.3 mL; 51.8 mmol) dropwise over 30 min. The reaction mixture was stirred at reflux for 24 h and stirred at room temperature for additional 2 days. The solvent was concentrated and quenched with water, extracted with ethyl acetate, dried, and passed through a plug of silica to give the product as a white solid (4.2 g). mp 108−111 °C; ^{1}H NMR ($CDCl_3$): 1.56 (s, 9H), 6.8 (brs, 1H), 7.4−7.56 (m, 2H), 7.8 (d, J = 10 Hz, 1H), 8.0 (d, J = 10, Hz, 1H), 8.15 (d, J = 12 Hz, 1H), 8.2 (s, 1H). Anal. Calcd for $C_{16}H_{16}N_2O_2 \cdot 0.20\ H_2O$: C, 70.67; H, 6.08; N, 10.30. Found: C, 70.76; H, 5.78; N, 10.20.

(5-Formylnaphthalen-2-yl)carbamic Acid *tert*-Butyl Ester (10). mp 96−98 °C dec. (5-Cyanonaphthalen-2-yl)-carbamic acid *tert*-butyl ester **9** (4.01 g; 14.9 mmol) was added to a mixture of pyridine (43 mL) and acetic acid (21 mL) and stirred for 30 min. To this solution was added Raney Ni (∼5 g) in portions over 10 min. After the gas evolution subsided, the mixture was heated to 46 °C for 90 min. The reaction mixture was cooled to room temperature and passed through a pad of Celite and washed with pyridine. The solution was concentrated and diluted with ice−water. A solid precipitated upon standing, which was filtered and purified by silica flash column chromatography to give a white solid (yield: 2.71 g). ^{1}H NMR ($CDCl_3$): 1.56 (s, 9H), 7.4 (dd, J = 12 Hz, J = 3 Hz, 1H), 7.6 (m, 1H), 7.8 (d, J = 10 Hz, 1H), 8.0 (d, J = 10 Hz, 1H), 8.4 (br s, 1H), 9.3 (d, J = 12 Hz, 1H), 10.4 (s, 1H). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.10; H, 6.35; N, 5.42.

***tert*-Butyl 5-[(*E*)-2-(2-Pyridinyl)ethenyl]-2-naphthylcarbamate (11).** A suspension of triphenyl(2-pyridylmethyl)-phosphonium chloride hydrochloride (2.8 g; 7.1 mmol) in THF (40 mL) was cooled to −40 °C under nitrogen. To the suspension was added sodium bis(trimethylsilyl)amide (3.6 mL; 7.2 mmol), and the reaction mixture was warmed to 5 °C over 40 min. To this mixture was added a solution of (5-formylnaphthalen-2-yl)carbamic acid *tert*-butyl ester **10** (1.94 g; 7.15 mmol) in THF dropwise over 20 min at −70 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with addition of saturated ammonium chloride solution, extracted with ethyl acetate, washed with water and brine, dried, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give 2.5 g of the product. ^{1}H NMR (DMSO-d_6): δ 8.7 (d, J = 5 Hz, 1H), 8.40 (d, J = 16 Hz, 1H), 8.3 (d, J = 10 Hz, 1H), 8.2 (s, 1H), 7.8−7.7 (m, 4H), 7.58 (t, J = 8 Hz, 1H), 7.48 (dd, J = 9 Hz; 2.2 Hz, 1H), 7.33−7.4 (m, 2H), 1.5 (s, 9H); Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.59; H, 6.33; N, 7.79.

***C,C,C*-Trifluoro-*N*-[5-(2-pyridin-2-ylvinyl)naphthalen-2-yl]methanesulfonamide (6).** To a solution of *tert*-butyl 5-[(*E*)-2-(2-pyridinyl)ethenyl]-2-naphthylcarbamate **11** (5 mmol) in dichloromethane was added trifluoroacetic acid (10 mmol), and the solution was stirred at room temperature for 6 h. The reaction mixture was concentrated, and the residue was taken up in ethyl acetate and washed with water and sodium bicarbonate. The organic layer was dried and concentrated under reduced pressure and passed through a plug of silica to give the amine. The amine was used for further reactions without purification.

The above amine ((34.6 mg; 0.1 mmol) was dissolved in 4 mL of dichloromethane and triethylaime (0.36 mmol). To the solution was added trifluoromethansulfonyl chloride (0.2 mmol), and the reaction mixture was stirred at room-temperature overnight. The solvent was removed under reduced pressure, and the residue was purified by HPLC. mp 183−185 °C; ^{1}H NMR (DMSO-d_6): δ 8.64 (dd, J = 5 Hz; 1 Hz, 1H), 8.45 (d, J = 16 Hz, 1H), 8.37 (d, J = 10 Hz, 1H), 7.86−7.94 (m, 3H), 7.76−7.81 (m, 2H), 7.58 (t, J = 8 Hz, 1H), 7.48 (dd, J = 9 Hz; 2.2 Hz, 1H), 7.33−7.4 (m, 2H); MS (ESI) m/z 379 (MH); Anal. Calcd for $C_{18}H_{13}F_3N_2O_2S + 0.5\ H_2O$: C, 55.81; H, 3.64; N, 7.23. Found: C, 56.26; H, 3.24; N, 7.08. HRMS Calcd for $C_{18}H_{13}F_3N_2O_2S$: (M + H) 379.07226, found 379.07228.

Compounds **6b**−**z** were prepared by following the procedure described for **6** starting from the appropriate amine and the electrophiles.

***C,C,C*-Trifluoro-*N*-[5-(2-quinolin-2-ylvinyl)naphthalen-2-yl]methanesulfonamide (6b).** mp 143−145 °C; ^{1}H NMR (DMSO-d_6): δ 8.62 (d, J = 16 Hz, 1H), 8.51 (d, J = 11 Hz, 1H), 8.46 (d, J = 11 Hz, 1H), 8.17 (d, J = 9 Hz, 1H), 7.97−8.05 (m, 4H), 7.77−7.83 (m, 2H), 7.64−7.5 (m, 4H); MS (EI) m/z 428; HRMS Calcd for $C_{22}H_{15}F_3N_2O_2S$: (M − H) 427.0734, found 427.07248.

***C,C,C*-Trifluoro-*N*-{5-[2-(6-methyl-quinolin-2-yl)vinyl]-naphthalen-2-yl}methanesulfonamide (6c).** mp 237−240 °C; ^{1}H NMR (DMSO-d_6): δ 8.58 (d, J = 16 Hz, 1H), 8.49 (d, J = 9 Hz, 1H), 8.35 (d, 8 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 7.95−8.00 (m, 3H), 7.82 (d, 2.2 Hz, 1H), 7.76 (s, 1H), 7.60−7.64 (m, 2H), 7.49−7.54 (m, 2H)0.2.51 (s, 3H); MS (EI) m/z 442; HRMS Calcd for $C_{23}H_{17}F_3N_2O_2S$: (M − H) 441.089, found 441.08781.

***N*-{5-[(*Z*)-2-Chloro-2-(6-methoxy-2-quinolinyl)ethenyl]-2-naphthyl}(trifluoro)methanesulfonamide (6d).** ^{1}H NMR (DMSO-d_6): δ 8.60 (d, J = 16 Hz, 1H), 8.48−8.55 (m, 2H), 8.25 (d, 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 7.95−8.00 (m, 2H), 7.80−7.85 (m, 2H), 7.50−7.65 (m, 3H), 4.02 (s, 3H); HRMS Calcd for $C_{23}H_{16}ClF_3N_2O_3S$: (M + H) 493.0595, found 493.05796.

***N*-(5-{(*E*)-2-[6-(Dimethylamino)-2-quinolinyl]ethenyl}-2-naphthyl)(trifluoro)methanesulfonamide (6e).** ^{1}H NMR (DMSO-d_6): δ 8.42 (d, J = 16 Hz, 1H), 8.32 (s, 1H), 8.05−8.15 (m, 2H), 7.95 (d, 8 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 7.62 (d, J = 8H, 1H), 7.28−7.48 (m, 4H), 6.95 (d, J = 3 Hz, 1H), 3.02 (s, 6H); MS (ESI) m/z 472.1 ($(M + H)^+$); HRMS Calcd for $C_{24}H_{20}F_3N_3O_2S$: (M + H) 472.1301, found 472.12879.

***N*-{5-[2-(6-Chloroquinolin-2-yl)vinyl]naphthalen-2-yl}-*C,C,C*-trifluoromethanesulfonamide (6f).** mp 238−240 °C; ^{1}H NMR (DMSO-d_6): δ 8.63 (d, J = 16 Hz, 1H), 8.52 (d, J = 9 Hz, 1H), 8.40 (d, 8 Hz, 1H), 8.2 (d, J = 8 Hz, 1H), 8.13 (s,

1H), 7.98−8.04 (m, 3H), 7.85 (d, 2.2 Hz, 1H), 7.78 (dd, J = 9H; 2.4 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.52−7.57 (m, 2H); MS (ESI) m/z 463 ([M + H]$^+$); Anal. Calcd for $C_{22}H_{14}ClF_3N_2O_2S \cdot 0.75\ H_2O$: C, 55.47; H, 3.28; N, 5.88. Found: C, 55.46; H, 3.38; N, 5.55.

***N*-{5-[2-(7-Chloroquinolin-2-yl)-vinyl]naphthalen-2-yl}-C,C,C-trifluoromethanesulfonamide (6g).** mp 202−204 °C; ^{1}H NMR (DMSO-d_6): δ 8.63 (d, J = 16 Hz, 1H), 8.51 (d, J = 9 Hz, 1H), 8.46 (d, 8 Hz, 1H), 8.16 (d, J = 8 Hz, 1H), 7.98−8.07 (m, 4H), 7.84 (s, 1H), 7.52−7.64 (m, 4H); MS (EI) m/z M$^+$. 462; Anal. Calcd for $C_{22}H_{14}ClF_3N_2O_2S$: C, 57.09; H, 3.05; N, 6.05. Found: C, 56.92; H, 2.90; N, 5.89.

***N*-{5-[(*E*)-2-(8-Chloro-2-quinolinyl)ethenyl]-2-naphthyl}-(trifluoro)methanesulfonamide (6h).** ^{1}H NMR (DMSO-d_6): δ 8.7 (d, J = 16 Hz, 1H), 8.50 (d, J = 9 Hz, 2H), 8.25 (d, 8 Hz, 1H), 8.15 (d, J = 8 Hz, 1H), 7.92−8.02 (m, 3H), 7.85 (d, 2.2 Hz, 1H), 7.75−7.68 (m, 4H); MS (ESI) m/z 463 (M + H)$^+$); HRMS Calcd for $C_{22}H_{14}ClF_3N_2O_2S$: (M + H) 463.0489, found 463.0479.

***N*-{5-[(*E*)-2-(4-Chloro-2-quinolinyl)ethenyl]-2-naphthyl}-(trifluoro)methanesulfonamide (6i).** ^{1}H NMR (DMSO-d_6): δ 8.82 (d, J = 16 Hz, 1H), 8.6−8.68 (m, 2H), 8.25 (t, 8 Hz, 2H), 8.05 (d, J = 8 Hz, 2H), 7.96 (dt, J = 8 Hz, 2.2 Hz, 1H), 7.9 (d, 2.2 Hz, 1H), 7.8 (dt, J = 8 Hz, 2.2 Hz, 1H), 7.60−7.70 (m, 2H), 7.56 (dd, J = 8 Hz, 2,2 Hz, 1H); HRMS Calcd for $C_{22}H_{14}ClF_3N_2O_2S$: (M + H) 463.0489, found 463.04784.

1,1,1-Trifluoro-*N*-{5-[(*E*)-2-phenylvinyl]-2-naphthyl}-methanesulfonamide (6j). LC/MS m/z 376 (M − H) single component 98% (t_R 3.004 min). ^{1}H NMR (DMSO-d_6): δ 8.35 (d, J = 9 Hz; 1 Hz, 1H), 8.05 (d, J = 16 Hz, 1H), 7.95 (d, J = 9 Hz, 1H), 7.75−7.82 (m, 2H), 7.68 (s, 1H), 7.5 (t, J = 7.2 Hz, 1H), 7.00−7.41 (m, 5H), 6.85 (d, J = 12 Hz, 1H); HRMS Calcd for $C_{19}H_{14}F_3NO_2S$: (M − H) 376.0625, found 376.06193.

***N*-{5-[(*E*)-2-(4-Chlorophenyl)vinyl]-2-naphthyl}-1,1,1-trifluoromethanesulfonamide (6k).** LC/MS m/z 410 (M − H) single component 100% (t_R 4.339 min). HRMS Calcd for $C_{19}H_{13}ClF_3NO_2S$: (M − H) 410.0235, found 410.02328.

1,1,1-Trifluoro-*N*-(5-{(*E*)-2-[3-(trifluoromethyl)phenyl]-vinyl}-2-naphthyl)methanesulfonamide (6l). LC/MS m/z 444 (M − H) single component 96% (t_R 4.316 min). HRMS Calcd for $C_{20}H_{13}F_6NO_2S$: (M − H) 444.0498, found 444.04945.

1,1,1-Trifluoro-*N*-{5-[(*E*)-2-(3-methoxyphenyl)vinyl]-2-naphthyl}methanesulfonamide (6m). LC/MS m/z 406 (M − H) single component 97% (t_R 4.119 min). HRMS Calcd for $C_{20}H_{16}F_3NO_3S$: (M − H) 406.073, found 406.07214.

1,1,1-Trifluoro-*N*-{5-[(*E*)-2-(1-naphthyl)vinyl]-2-naphthyl}methanesulfonamide (6n). LC/MS m/z 426 (M − H) single component 95% (t_R 3.205 min). HRMS Calcd for $C_{23}H_{16}F_3NO_2S$: (M − H) 426.0781, found 426.07654.

5-[(*E*)-2-(7-Chloroquinolin-2-yl)ethenyl]naphthalen-2-amine (6p). LC/MS m/z 331 (M + H) single component 98% (t_R 2.753 min). ^{1}H NMR (DMSO-d_6): δ 8.61 (d, J = 16 Hz, 1H), 8.45 (d, J = 9 Hz, 1H), 8.22 (d, 9 Hz, 1H), 8.14 (d, J = 9 Hz, 1H), 8.08 (dd, J = 3 Hz, 1H), 8.04 (d, J = 9 Hz, 1H), 7.69 (d, J = 9 Hz, 1H), 7.60−7.64 (m, 2H), 7.47 (d, J = 16 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.13 (dd, J = 9 Hz, J = 2 Hz, 1H), 7.01(d, J = 2 Hz, 1H). MS (ESI) m/z 451 (MH); HRMS Calcd for $C_{21}H_{15}ClN$: (M + H) 331.09966, found 331.09957.

***N*-{5-[2-(6-Chloroquinolin-2-yl)-vinyl]naphthalen-2-yl}-*C,C,C*-trifluoro-*N*-methylmethanesulfonamide (6q).** mp 181−183 °C; ^{1}H NMR (DMSO-d_6): δ 8.65 (d, J = 16 Hz, 1H), 8.58 (d, J = 9 Hz, 1H), 8.42 (d, 8 Hz, 1H), 8.19−8.24 (m, 2H), 8.13−8.14 (m, 2H), 8.05−8.08 (m, 2H), 7.79 (dd, J = 6 Hz; 2.5 Hz, 1H), 7.68−7.73 (m, 2H), 7.57 (d, J = 16 Hz, 1H); MS (ESI) m/z 477 (MH); Anal. Calcd for $C_{23}H_{16}ClF_3N_2O_2S$: C, 57.93; H, 3.38; N, 5.87. Found: C, 57.57; H, 3.33; N, 5.78.

***N*-{5-[2-(6-Chloroquinolin-2-yl)vinyl]naphthalen-2-yl}-methanesulfonamide (6r).** mp 256 °C (dec); ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 8.83 (d, J = 16 Hz, 1H), 8.63 (d, J = 9 Hz, 1H), 8.53 (d, 8 Hz, 1H), 8.40 (d, J = 8 Hz, 1H), 8.22−8.25 (m, 2H), 7.90−7.96 (m, 3H), 7.75 (d, J = 2.4 Hz, 1H), 7.58−7.69 (m, 2H), 7.57 (dd, J = 16 Hz; 2.4 Hz, 1H), 3.09 (s, 3H); MS (ESI) m/z 407/409 (M − H); Anal. Calcd for $C_{22}H_{17}ClN_2O_2S \cdot HCl$: C, 59.33; H, 4.07; N, 6.29. Found: C, 59.48; H, 3.93; N, 6.21.

***N*-{5-[2-(6-Chloroquinolin-2-yl)vinyl]naphthalen-2-yl}-acetamide (6s).** mp 213-215 °C; ^{1}H NMR (DMSO-d_6): δ 10.22 (s, 1H), 8.62 (d, J = 16 Hz, 1H), 8.37−8.43 (m, 3H), 8.19 (d, J = 9 Hz, 1H), 8.13 (d, 12 Hz, 1H), 8.05 (d, J = 9 Hz, 1H), 7.92 (d, J = 7 Hz, 1H), 7.86 (d, J = 9 Hz, 1H), 7.78 (dd, J = 9 Hz; 3 Hz, 1H), 7.69 (dd, J = 13 Hz; 6 Hz, 1H), 7.51−7.56 (m, 2H), 2.13 (s, 3H); MS (ESI) m/z 373 ([M + H]$^+$); Anal. Calcd for $C_{23}H_{17}ClN_2O \cdot 0.25H_2O$: C, 74.09; H, 4.60; N, 7.51. Found: C, 73.11; H, 4.40; N, 7.12.

***N*-{5-[(*E*)-2-(7-Chloroquinolin-2-yl)ethenyl]-2-naphthyl}-benzamide (6t).** LC/MS m/z 435 (M + H) single component 96% (t_R 3.763 min). HRMS Calcd for $C_{28}H_{19}ClN_2O$: (M + H) 435.1259, found 435.12495.

{5-[2-(6-Chloroquinolin-2-yl)vinyl]naphthalen-2-yl}-carbamic Acid Phenyl Ester (6u). mp 165 °C; ^{1}H NMR (DMSO-d_6): δ 10.52 (s, 1H), 8.61 (d, J = 16 Hz, 1H), 8.45 (d, J = 9 Hz, 1H), 8.39 (d, 9 Hz, 1H), 8.19 (d, J = 9 Hz, 1H), 8.13 (dd, J = 13 Hz; 2.4 Hz, 1H), 8.04 (d, J = 9 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.85 (d, J = 9 Hz, 1H), 7.75 (dt, J = 9 Hz; 2.4 Hz, 2H), 7.44−7.56 (m, 5H), 7.25−7.28 (m, 3H). MS (ESI) m/z 451 (MH); HRMS Calcd for $C_{28}H_{19}ClN_2O_2$: (M − H) 449.1062, found 449.10599.

***N*-[({5-[(*E*)-2-(7-Chloroquinolin-2-yl)vinyl]-2-naphthyl}-amino)carbonyl]benzenesulfonamide (6v).** LC/MS m/z 512 (M − H) single component 98% (t_R 3.570 min). ^{1}H NMR (DMSO-d_6): δ 8.70 (s, 1H), 8.58 (dd, J = 16 Hz, J = 2.2 Hz, 1H), 8.42 (d, J = 9 Hz, 1H), 8.21 (d, 9 Hz, 1H), 8.10−8.2 (m, 2H), 8.05 (d, J = 2.4 Hz, 1H), 8.00 (d, J = 9 Hz; 1H), 7.75−7.85 (m, 3H), 7.55−7.68 (m, 3H), 7.35−7.5 (m, 3H). HRMS Calcd for $C_{28}H_{20}ClN_3O_3S$: (M + H) 514.0987, found 514.09801.

4-Chloro-*N*-[({5-[(*E*)-2-(7-chloroquinolin-2-yl)vinyl]-2-naphthyl}amino)carbonyl]benzenesulfonamide (6w). LC/MS m/z 548 (M + H) single component 95% (t_R 3.793 min). ^{1}H NMR (DMSO-d_6): δ 8.73 (s, 1H), 8.58 (d, J = 16 Hz, 1H), 8.45 (d, J = 9 Hz, 1H), 8.21 (d, 9 Hz, 1H), 8.17−8.2 (m, 2H), 8.1 (d, J = 2.4 Hz, 1H), 8.05 (d, J = 9 Hz; 1H), 7.75−7.85 (m, 3H), 7.55−7.7 (m, 3H), 7.4−7.5 (m, 3H). HRMS Calcd for $C_{28}H_{19}Cl_2N_3O_3S$: (M + H) 548.0597, found 548.05857.

***N*-[({5-[(*E*)-2-(7-Chloroquinolin-2-yl)vinyl]-2-naphthyl}-amino)carbonyl]-4-methylbenzenesulfonamide (6x).** LC/MS m/z 528 (M + H) single component 99% (t_R 3.689 min). HRMS Calcd for $C_{29}H_{22}ClN_3O_3S$: (M + H) 528.1143, found 528.11275.

4-[({5-[(*E*)-2-(7-Chloroisoquinolin-3-yl)vinyl]-2-naphthyl}amino)methyl]benzoic acid (6z). LC/MS m/z 465 (M + H) single component 97% (t_R 3.484 min). HRMS Calcd for $C_{29}H_{21}ClN_2O_2$: (M + H) 465.1364, found 465.13588.

4-{[(5-{(*E*)-2-[3-(Trifluoromethyl)phenyl]vinyl}-2-naphthyl)amino]carbonyl}benzoic Acid (6ab). LC/MS m/z 462 (M + H) single component 88% (t_R 4.381 min). HRMS Calcd for $C_{27}H_{18}F_3NO_3$: (M − H) 460.1166, found 460.11646.

(5-Hydroxymethylnaphthalen-2-yl)carbamic Acid *tert*-Butyl Ester (18). (5-Formylnaphthalen-2-yl)carbamic acid *tert*-butyl ester **10** (2.2 g; 8 mmol) in anhydrous ethanol was treated with sodium borohydride (9.7 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for additional 2 h. The reaction mixture was quenched with water and concentrated, and the residue was extracted with ethyl acetate. The organic layer was dried and passed through a plug of silica to give 2.15 g of off-white solid, which was carried forward without further purification.

General Procedure for Preperation of Compounds (19a−i). (5-Hydroxymethylnaphthalen-2-yl)carbamic acid *tert*-butyl ester **18** (0.8 g; 2.9 mmol) in anhydrous THF was treated with triphenylphosphine (847 mg; 3.2 mmol) and diethyl azodicarboxylate (3.2 mmol), to the mixture was added appropriate phenol (3.2 mmol), and the mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and the residue was purified by passing through a plug of silica. Following the procedure described for the synthesis of 6, by reacting with appropriate electrophiles compounds **19a**−**i** were prepared.

4-[({5-[(3-Chlorophenoxy)methyl]-2-naphthyl}amino)carbonyl]benzoic Acid (19a). LC/MS *m/z* 432 (M + H) single component 98% (t_R 3.839 min). ^{1}H NMR (DMSO-d_6): δ 10.65 (s, 1H), 8.54 (d, J = 2 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.09 (s, 4H), 7.89 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 7 Hz, 1H), 7.51 (t, J = 7.32 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.27 (s, 1H), 7.08 (dd, J = 8.4 Hz; J = 2.3 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 5.57 (s, 2H). HRMS Calcd for $C_{25}H_{18}ClNO_4$: (M − H) 430.0852, found 430.08479.

4-[({5-[(4-Bromophenoxy)methyl]-2-naphthyl}amino)carbonyl]benzoic Acid (19b). LC/MS *m/z* 476 (M + H) single component 97% (t_R 3.877 min). ^{1}H NMR (DMSO-d_6): δ 10.65 (s, 1H), 8.53 (d, J = 2 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.08 (s, 4H), 7.89 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 7 Hz, 1H), 7.47−7.51 (m, 3H), 7.09 (d, J = 7.4 Hz, 1H), 5.54 (s, 2H). HRMS Calcd for $C_{19}H_{14}F_3NO_2S$: (M + H), found.

4-[({5-[(3-Trifluoromethylphenoxy)methyl]-2-naphthyl}amino)carbonyl]benzoic Acid (19c). LC/MS *m/z* 466 (M + H) single component 95% (t_R 3.891 min). HRMS Calcd for $C_{26}H_{18}F_3NO_4$: (M − H) 464.11151, found 464.1113.

4-({[5-(Phenoxymethyl)-2-naphthyl]amino}methyl)benzoic Acid (19d). LC/MS *m/z* 384 (M + H) single component 100% (t_R 3.23 min). ^{1}H NMR (DMSO-d_6): δ 7.89 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 9 Hz, 1H), 7.50−7.52 (m, 3H), 7.24−7.32 (m, 4H), 7.10 (dd, J = 9 Hz; 2.3 Hz, 1H), 7.04 (d, J = 9 Hz, 2H), 6.95 (t, J = 7.2 Hz, 1H), 6.68−6.73 (m, 2H), 5.39 (s, 2H), 4.47 (d, J = 5.8 Hz, 2H). HRMS Calcd for $C_{25}H_{21}NO_3$: (M + H) 384.1594, found 384.15883.

4-[({5-[(3-Chlorophenoxy)methyl]-2-naphthyl}amino)methyl]benzoic Acid (19e). LC/MS *m/z* 418 (M + H) single component 99% (t_R 3.5 min). ^{1}H NMR (DMSO-d_6): δ 7.89 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 9 Hz, 1H), 7.45−7.50 (m, 3H), 7.22−7.30 (m, 3H), 7.18 (broad s, 1H), 7.10 (dd, J = 9 Hz, 2.3 Hz, 1H), 7.04 (dt, J = 9 Hz, J = 2.3 Hz, 2H), 6.69−6.73 (m, 2H), 5.40 (s, 2H), 4.46 (d, J = 6 Hz, 2H). HRMS Calcd for $C_{25}H_{20}ClNO_3$: (M + H) 418.1205, found 418.11981.

4-[({5-[(4-Bromophenoxy)methyl]-2-naphthyl}amino)methyl]benzoic Acid (19f). LC/MS *m/z* 462 (M + H) single component 100% (t_R 3.54 min). ^{1}H NMR (DMSO-d_6): δ 7.89 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 9 Hz, 1H), 7.45−7.52 (m, 4H), 7.22−7.27 (m, 2H), 7.10 (dd, J = 9 Hz, 2.3 Hz, 1H), 7.04 (d, J = 9 Hz, 2H), 6.69−6.73 (m, 2H), 5.40 (s, 2H), 4.46 (d, J = 6 Hz, 2H). HRMS Calcd for $C_{25}H_{20}BrNO_3$: (M + H) 462.0699, found 462.06942.

4-[({5-[(3-Chlorobenzyl)oxy]-2-naphthyl}amino)carbonyl]benzoic Acid (19g). LC/MS *m/z* 432 (M + H) single component 98% (t_R 2.91 min).). ^{1}H NMR (DMSO-d_6): δ 10.6 (s, 1H), 8.45 (d, J = 2 Hz, 1H), 8.19 (d, J = 8.2 Hz, 2H), 8.06 (s, 4H), 7.82 (dd, J = 9.2 Hz, J = 2.2 Hz, 1H), 7.63 (s, 1H), 7.55 (d, J = 8 Hz, 1H), 7.39−7.50 (m, 4H), 6.98 (d, J = 7.4 Hz, 1H), 5.33 (s, 2H). HRMS Calcd for $C_{25}H_{18}ClNO_4$: (M + H) 432.09972, found 432.09894.

4-[({5-[(3-Bromobenzyl)oxy]-2-naphthyl}amino)carbonyl]benzoic Acid (19h). LC/MS *m/z* 476 (M + H) single component 92% (t_R 2.95 min). ^{1}H NMR (DMSO-d_6): δ 10.60 (s, 1H), 8.45 (d, J = 2 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.06 (s, 4H), 7.96 (s, 1H), 7.83 (dd, J = 8.4 Hz, J = 2.3 Hz, 1H), 7.77 (s, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.39−7.44 (m, 3H), 6.98 (d, J = 7.4 Hz, 1H), 5.32 (s, 2H). HRMS Calcd for $C_{25}H_{18}BrNO_4$: (M − H) 474.03464, found 474.03514.

4-{[(5-{[3-(Trifluoromethyl)benzyl]oxy}-2-naphthyl)amino]carbonyl}benzoic Acid (19i). LC/MS *m/z* 466 (M + H) single component 94% (t_R 2.95 min). δ 10.58 (s, 1H), 8.40 (d, J = 2 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.0 (s, 4H), 7.96 (s, 1H), 7.83 (dd, J = 8.4 Hz, J = 2.3 Hz, 1H), 7.77 (s, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.39−7.44 (m, 3H), 6.98 (d, J = 7.4 Hz, 1H), 5.32 (s, 2H). HRMS Calcd for $C_{26}H_{18}F_3NO_4$: (M + H) 466.12607, found 466.12538.

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(11) HCMVP A144L (125 nM), elastase (Calbiochem)(150 nM), and trypsin (Worthington) (1 nM) were assayed in a 96-well format in the presence and absence of compound (DMSO final concentration 1%) in a final volume of 200 μL in the presence of 5 μM of the fluorescent substrate (Dabcyl-RGVVNASSRLA-Edans (ANASPEC) for 20 min. The buffer conditions for HCMV P were 50 mM HEPES (pH 7.5), 15% glycerol, and 0.6M Na-citrate, while elastase and trypsin were assayed in 50 mM HEPES pH 8.0, 25 mM NaCl, and 5% glycerol. The assays were terminated by the addition of TFA to a final concentration of 0.1% and incubation at 80 °C for 10 min. Samples (100 μL) were analyzed by reverse-phase HPLC at 1.5 mL min^{-1} using a HP 1100 series coupled to a diode array and fluorescence detector. Substrates and products were resolved on a 50 × 4.6 mm 5 μM C_{18} column. Gradient: 20.5−25% ACN for 1.5 min and 25 to 95% ACN for 1 min. The quantity of substrate cleaved in each assay was derived from the empirically determined product specific activity. This value was determined as 2331 ± 89 mAu·S/nmol.

(12) Chymotrypsin (Worthington, 8 nM) was assayed in a 96-well format using the Diapharma peptide substrate S2586 (80 μM) in the presence of 50 mM Tris (8.5), 150 mM NaCl, 3 mM $CaCl_2$, and 1% DMSO in a final volume of 200 μL. Substrate cleavage was monitored with a Bio-Tek Kinetics reader EL340i. IC_{50} values were determined from the reaction rates over a 20 min in 1 min intervals.

(13) μM of stilbene I was titrated with CMVP at a compound-to-protein ratio of 10:1, 5:1, 2:1, and 1:1 in 10 mM KPO_4, 10% glycerol, pH 7.5 buffer in D_2O. Line-width and intensity change of the compound resonances was consistent with stoichiometric binding. Similarly the substrate (DABCLY-Arg-Gly-Val-Val-Asn-Ala-Ser-Ser-Arg-Leu-Ala-EDANS) was determined to bind stoichiometrically with inactive CMVP R166A. Stilbene I displaces the binding of the substrate.

(14) Compounds were purified by HPLC and the purity was >90%. LC Conditions: HP 1100, 23 °C, 10 μL injected; column: YMC−ODS-A 4.6 × 50 5 μm; gradient A: 0.05% TFA/water, B: 0.05% TFA/acetonitrile; time 0 and 1 min: 98%A and 2%B; 7 min: 10%A and 90%B; 8 min: 10%A and 90%B; 8.9 min: 98%A and 2%B; post time 1 min; flow rate 2.5 mL/min; detection: 215 and 254 nm, DAD. Semiprep HPLC: Gilson with Unipoint software; column: Phenomenex C18 Luna 21.6 mm × 60 mm, 5 μM; solvent A: water (0.02% TFA buffer); solvent B: acetonitrile (0.02% TFA buffer); solvent gradient: time 0: 5% B; 2.5 min: 5% B; 12 min: 95% B; hold 95% B 3 min; flow rate: 22.5 mL/min; detection: 215 and 254 nm.

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