Synthesis of Cinnamide Dimers as Potential Antibacterial and Antifungal Agents

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Abstract: A series of new cinnamide dimers was synthesized (**5a-6a**) and evaluated for their antimicrobial and antifungal activity. All the compounds investigated have shown significant antimicrobial activity against gram-positive and gram-negative bacterial strains, as well as few fungal strains. The compounds having withdrawing group exhibited significant biological activity than their precursors. Moreover all the compounds containing electron withdrawing substituent showed good antimicrobial activity in comparison with the standards.

Keywords: Antibacterial, Antifungal, Cinnamide dimers, Piperazine.

INTRODUCTION

Microorganisms are the major threat to the public health worldwide due to their drug resistance [1]. The multidrug resistant Gram positive bacteria including methicillin resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis* (MRSE) and vancomycin resistant *enterococci* (VRE) are the major drug resistant bacteria and despite the tremendous progress in medicinal chemistry, they are still challenging to the public health [2]. The bacterial resistance to antibiotics is a major health problem and pointed the need to discover novel hybrid compounds with potent antimicrobial activity. The need for the synthesis of antifungal drugs is much required because of limited progress in this field. Recently, cinnamic acid derivates play an important role in medicinal chemistry. Moreover, cinnamic acid derivatives exhibit a wide range of pharmacological activities, such as inhibitors of hepatic glucose-6-phosphate translocase [3], antiatherogenic [4], vanilloid receptor-1 antagonists [5], antagonists of leukocyte function [6], anticonvulsant activity [7], antioxidative [8], antitumor [9], antimicrobial [10-12] and antituberculosis [13,14].

Moreover, previous studies in this laboratory on the synthesis of pyrrolobenzodiazepine (PBD) dimers incorporating a piperazine moiety enhanced the bioavailability as well as bioefficacy [15]. Piperazine is a pharmacologically attractive scaffold that is present in many important drugs such as the Merck HIV protease inhibitor, Crixivan and drugs under development [16]. It is well known that this heterocyclic backbone could act on various pharmacological targets and is known to display anticancer [17-24], calcium channel blocking [25-28], antibacterial [29] and histamine antagonist properties [30,31]. Recently, piperazine derivatives containing tetrazole nucleus have been reported as antifungal Agents [32].

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In continuation of our search for prominent antibacterial and antifungal agents with therapeutic efficacy, in the present invention we have prepared cinnamide dimers with piperzine scaffold and evaluated their antibacterial and antifungal activity. The main objective behind the synthesis of cinnamide dimers with piperzine is to enhance the biological activity and the solubility of these compounds. Some of the cinnamide derivatives reported as antibacterial agents have been shown in Fig. (**1**).

CHEMISTRY

The synthetic pathway (Scheme **1**) involves the use of commercially available substituted cinnamic acid as the starting material, which was treated with thionyl chloride and then coupled to N-Boc piperazine in the presence of a base to give the corresponding compounds **2a-c**. This upon deprotection of Boc by employing TFA in CH_2Cl_2 gives the compounds **3a-c**, which was coupled with substituted cinnamic acid chloride which provides the required cinnamide dimers, **5a-z** and **6a**.

RESULTS AND DISCUSSION

Antimicrobial Activity

Antimicrobial efficacy of the Compounds **5a-z** and **6a** was tested for their minimum inhibitory concentration (MIC) by tube dilution method against various test bacterial strains and antifungal activity against *Aspergillus* and *Candida* sps was tested by well diffusion method [33-35]. The *in vitro* antibacterial activity of the newly synthesized compounds **5a-6a** was studied against the following bacterial strains of gram-positive organisms viz. *Staphylococcus aureus* (MTCC 96), *Staphylococcus epidermidis* (MTCC 435), *Bacillus subtilis* (MTCC 441) and gram-negative organisms viz., *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741) by MIC method. *Aspergillus niger* (MTCC 1344), *Aspergillus parasiticus* (MTCC 2797), *Candida albicans* (MTCC 227) and *Saccharomyces cereviseae* (MTCC 36) which were taken as test fungi to find out the antifungal activity of the synthesized compounds.

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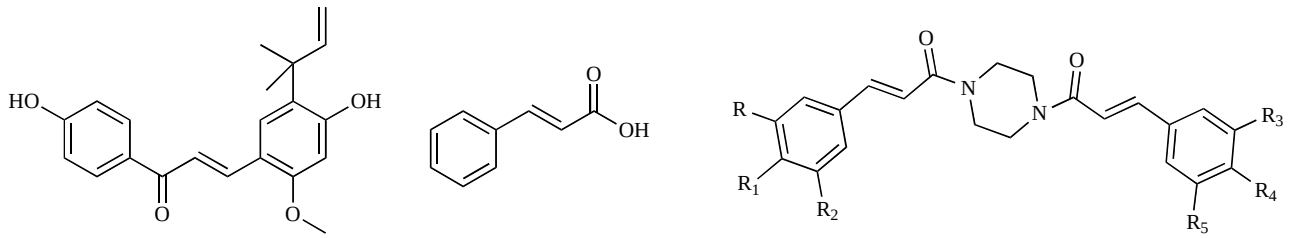
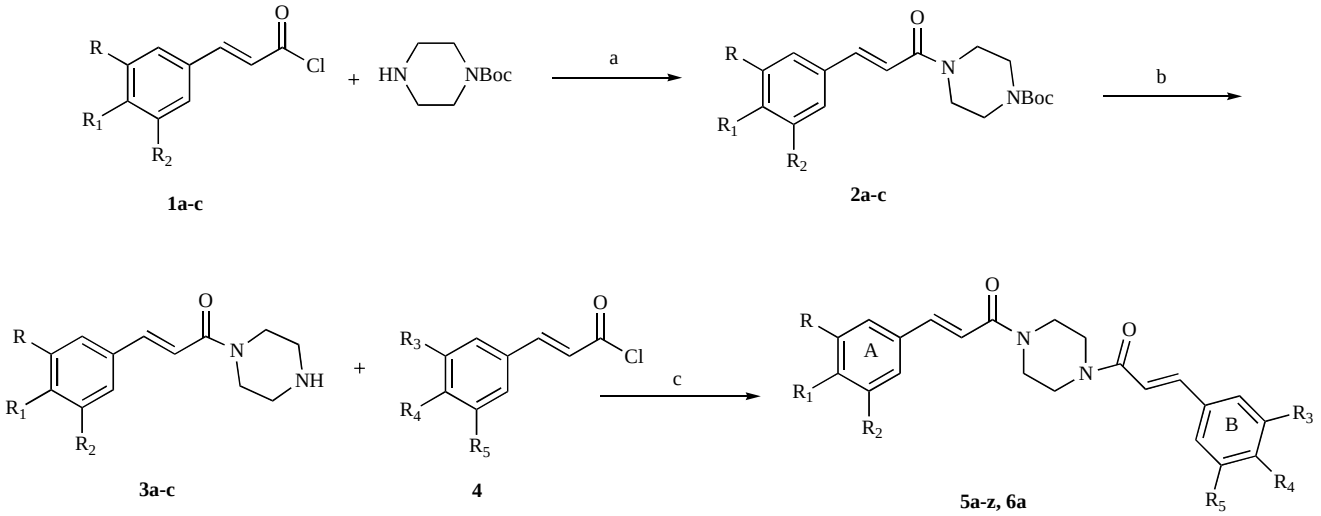


Fig. (1).



5a: R, R_1, R_2 = OMe, R_3, R_4, R_5 = H
5b: R, R_1, R_2 = OMe, R_3, R_4, R_5 = OMe
5c: R, R_1, R_2 = OMe, R_3, R_5 = H, R_4 = CF_3
5d: R, R_1, R_2 = OMe, R_3 = OCF_3, R_4, R_5 = H
5e: R, R_1, R_2 = OMe, R_3, R_5 = H, R_4 = F
5f : R, R_1, R_2 = OMe, R_3, R_5 = H, R_4 = Cl
5g: R, R_1, R_2 = OMe, R_3, R_5 = H, R_4 = Br
5h: R, R_1, R_2 = OMe, R_3 = H, R_4, R_5 = F
5i : R, R_1, R_2 = OMe, R_3 = H, R_4, R_5 = Cl
5j : R, R_1, R_2 = OMe, R_3 = H, R_4 = OH, R_5 = OMe
5k: R, R_1, R_2 = H, R_3, R_5 = H, R_4 = CF_3
5l : R, R_1, R_2 = H, R_3 = OCF_3, R_4, R_5 = H
5m: R, R_1, R_2 = H, R_3, R_5 = H, R_4 = F
5n: R, R_1, R_2 = H, R_3, R_5 = H, R_4 = Cl
5o: R, R_1, R_2 = H, R_3, R_5 = H, R_4 = Br
5p : R, R_1, R_2 = H, R_3, R_4, R_5 = H
5q: R, R_1, R_2 = H, R_3 = H, R_4, R_5 = F
5r: R, R_1, R_2 = H, R_3 = H, R_4, R_5 = Cl
5s : R, R_1, R_2 = H, R_3 = H, R_4 = OH, R_5 = OMe
5t : R, R_2 = H, R_1 = CF_3, R_3, R_5 = H, R_4 = CF_3
5u : R, R_2 = H, R_1 = CF_3, R_3 = OCF_3, R_4, R_5 = H
5v : R, R_2 = H, R_1 = CF_3, R_3, R_5 = H, R_4 = F
5w: R, R_2 = H, R_1 = CF_3, R_3, R_5 = H, R_4 = Cl
5x: R, R_2 = H, R_1 = CF_3, R_3, R_5 = H, R_4 = Br
5y: R, R_2 = H, R_1 = CF_3, R_3 = H, R_4, R_5 = F
5z : R, R_2 = H, R_1 = CF_3, R_3 = H, R_4, R_5 = Cl
6a: R, R_2 = H, R_1 = CF_3, R_3 = H, R_4 = OH, R_5 = OMe

Scheme 1.Reagents and conditions: a) TEA, *N*-Boc piperazine, dry THF, 0 ^oC to RT, 2h; b) CF_3COOH, $CHCl_3$, RT, 8h; c) TEA, dry THF, 0 ^oC to RT, 2h.

Licochalcone and *trans*-cinnamic acid were used as reference standards.

From the results in Table **1**, it was observed that almost all the compounds in our series exhibited high antibacterial activity against the test bacterial strains viz., Gram-positive organisms viz., *B. subtilis*, *S. aureus* and *S. epidermidis* and Gram-negative organisms viz., *E. coli* and *P. aeruginosa.* Compounds **5i-5q** and **5w** exhibited better or similar activity against *B. subtilis.* The compounds **5r**, **5s**, **5v**, **5w**, **5x**, **5y**, **5z** and **6a** showed equipotent activity against *S. aureus* and compounds **5t**, **5u**, **5v**, **5x**, **5y**, **5z** and **6a** had equipotent activity against *S. epidermidis* in comparison to the standard licochalcone. Only compound **5u** had good activity against *P. aeroginosa*, whereas other compounds **5w**, **5y**, and **6a** were highly active against *E. coli*, though not comparable to the standard. The type I compounds **5a-5j** were designed in such a way that the aromatic ring A would have a strong electron releasing group. These compounds showed moderate or no activity against all organisms tested. The type II compounds **5k-5s** possessing without substitution on ring A showed moderate activity. Similarly, the type III compounds **5t-6a** comprising of electron withdrawing substituent on ring A exhibited better antibacterial activity than type I and type II compounds. From these results the withdrawing group is necessary to get better antibacterial activity on the ring A. It should also be noted that all these compounds showed better antibacterial activity than standard cinnamic acid, as shown in Table **1**.

Antifungal Activity

From the results in Table **2**, it has been observed that most of the compounds exhibited significant *in vitro* inhibitory activity against the fungal strains viz., *A. niger*, *A.*

Table 1. Antibacterial Activity of Compounds 5a-6a

Compound	MIC (μg/ml)				
	Gram-positive			Gram-negative	
	B. subtilis	*S. epidermidis*	*S. aureus*	*P. aeroginosa*	*E. coli*
5a	50	100	100	50	100
5b	50	100	100	100	100
5c	50	12.5	12.5	>100	50
5d	100	25	25	100	50
5e	>100	12.5	>100	>100	50
5f	>100	50	50	>100	50
5g	100	50	>100	>100	50
5h	100	50	50	100	50
5i	25	50	50	25	50
5j	12.5	>100	>100	100	50
5k	25	>100	>100	25	50
5l	25	>100	>100	50	50
5m	25	>100	>100	50	>100
5n	25	50	50	50	50
5o	25	>100	>100	50	50
5p	25	>100	>100	50	50
5q	25	>100	>100	50	50
5r	>100	12.5	6.25	25	50
5s	50	12.5	6.25	25	>100
5t	>100	6.25	12.5	25	>100
5u	>100	6.25	12.5	12.5	50
5v	>100	6.25	6.25	25	>100
5w	12.5	12.5	6.25	>100	12.5
5x	>100	6.25	6.25	>100	>100
5y	>100	6.25	6.25	>100	12.5
5z	>100	6.25	6.25	>100	>100
6a	>100	6.25	6.25	>100	12.5
licochalcone	25	6.25	6.25	12.5	12.5
cinnamic acid	>100	>100	>100	>100	>100

parasiticus, *C. albicans* and *S. cerevisiae*. Compounds **5n**, **5v**, **5x, 5y** and **6a** showed similar or higher growth inhibition for *A. niger* than the standards used. Compounds **5m-5q, 5s, 5t, 5v, 5y** and **6a** have also shown similar or higher growth inhibition for *A. parasiticus* compared to the standards. Compounds **5h**, **5y** and **6a** were active against *S. cerevisiae* whereas **5w, 5x, 5y** and **6a** were active against *C. albicans.* Interestingly all these compounds showed higher inhibition than one of the precursor cinnamic acid. The newly designed cinnamide dimers may act as cell wall inhibitors and more specifically act on FAS-II, which uses α,β-enoyl systems as substrates, as shown in previous reports [36]. However, these dimer molecules are exhibiting better activity probably based on the synergistic aspects on combination of licochalcone and *trans*-cinnamic acid moieties.

CONCLUSION

In summary, we have synthesized a library of cinnamide dimers with piperazine scaffold and evaluated their antimicrobial activity against various bacterial and fungal strains. Interestingly, compounds **5s-z** and **6a** have shown significant antibacterial as well as antifungal activity when compared to standards. Among the synthesized molecules, compound **6a** shows promising results as an antimicrobial agent that could have potential for commercial application.

Table 2. Antifungal Activity of Compounds 5a-6a

Compd	Zone of inhibition (mm)			
	Filamantous Fungi		Yeast	
	A. *niger*	A. *parasiticus*	C. *albicans*	S. *cervisiae*
5a	12	12	-	-
5b	10	13	-	-
5c	8	14	-	-
5d	12	18	-	-
5e	14	13	8	-
5f	11	12	10	-
5g	12	15	8	-
5h	14	14	14	-
5i	10	13	-	-
5j	10	16	8	-
5k	11	13	8	-
5l	12	14	10	-
5m	20	22	12	15
5n	24	23	11	13
5o	18	25	10	15
5p	19	21	11	14
5q	18	20	-	17
5r	18	19	12	16
5s	21	20	10	18
5t	19	21	13	18
5u	20	16	11	14
5v	22	23	13	16
5w	20	18	11	20
5x	28	11	11	24
5y	22	23	14	22
5z	20	19	12	18
6a	24	21	16	20
licochalcone	22	20	14	20
cinnamic acid	<8	<8	<10	<10

Thus this strategy could prove useful in desiging useful lead compounds for further development as antimicrobial agents.

EXPERIMENTAL SECTION

Antibacterial Assay

The minimum inhibitory concentration (MIC) was tested as per the CLSI/NCCLS standards [37-39]. Sterile capped test tubes were taken and numbered from 1 to 9. 150µg of the compound was weighed and dissolved in 150µl of DMSO. It was added to the first tube and 1 ml of the sterile broth (Muller-Hinton Broth) to all other tubes.1ml of the solution was transferred from first tube to the second tube. Using a separate pipette 1 ml from 2^{nd} tube was transferred to the third tube. The serial dilutions were continued in this manner to the tube number 8. One ml from the 8^{th} tube was discarded and the ninth tube serves as a control. 1 ml of the 10^{-7}CFU/ml culture was taken from the Muller-Hinton broth, which was prepared by incubating overnight. This was done for all the four test bacteria and separate set of dilutions was prepared for all the compounds. The tubes were thoroughly mixed and incubated at 37 ^{o}C for 24 h. The tube which does not contain the visible growth / turbidity after overnight incubation was taken as Minimal Inhibitory Concentration 90 (MIC_{90}). The MIC values obtained from the following experiments were compared with the standards.

Antifungal Assay

Agar cup bioassay was employed for testing antifungal activity**.** The Potato Dextrose Agar (PDA) medium (Himedia) was poured into sterile Petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 0.5 mL of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in DMSO and 100 μg/mL concentrations solutions were prepared. After inoculation, cups were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each cup different compound solutions of concentrations (100 μg/mL) were added. Controls were prepared dissolving clotrimazole in DMSO and maintaining the concentration of solution (100 μg /mL). The treated and the controls were kept at 27 ^{o}C for 48 h. Inhibition zones were measured and the diameter was calculated in millimeter. Triplicates were maintained for each treatment [33, 34].

Characterization

All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthew Company, Ward Hill, MA, USA) and were used without purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with Merck 60-120 mesh silicagel. ^{1}H NMR spectra were recorded on Gemini Varian VXR-unity (400 and 500 MHz) or Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) were reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI^{+} software with capillary voltage 3.98 KV and ESI mode positive ion trap detector. High-resolution mass spectra (HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. Melting points were determined with an Electrothermal melting point apparatus, and were uncorrected.

General procedure for preparation of Tert-butyl 4-[(E)-3-(substituted phenyl)-2-propenoyl]-1-piperazinecarboxylate (2a-c)

To a stirred solution of N-boc piperazine (1.0 mmol) in dry THF was added triethylamine (4.0 mmol) followed by (E)-3-(substituted phenyl)-2-propenoyl chloride (1.0 mmol) at 0 ^{o}C. The reaction mixture was stirred for 2 hours and the reaction was monitored by TLC. After completion of the reaction, THF was evaporated under vacuum to get the crude product. This was further purified by column chromatography (30% EtOAc-Hexane) to afford the pure compounds 2a-c.

Tert-butyl 4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl]-1-piperazinecarboxylate (3a)

Yield 80%; White solid; mp >300 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.64 (d, 1H, J = 15.13 Hz), 6.75 (s, 2H), 6.73 (d, 1H, J = 15.13 Hz), 3.95 (s, 6H), 3.90 (s, 3H), 3.65 (brs, 4H), 3.49-3.45 (m, 4H), 1.49 (s, 9H); ESI-MS: *m*/*z* 407 [M+1]+.

Tert-butyl 4-[(E)-3-phenyl-2-propenoyl]-1-piperazinecarboxylate (3b)

Yield 70%; White solid; mp >300 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.65 (d, 1H, J = 15.29 Hz), 7.51-7.47 (m, 2H), 7.38-7.31 (m, 3H), 6.81 (d, 1H, J = 15.29 Hz), 3.65 (brs, 4H), 3.48-3.44 (m, 4H), 1.47 (s, 9H). ESI-MS: *m*/*z* 317 [M+1]+.

Tert-butyl 4-(E)-3-[4-(trifluoromethyl)phenyl]-2-propenoyl-1-piperazinecarboxylate (3c)

Yield 85%; White solid; mp >300 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.64 (d, 1H, J = 15.10 Hz), 7.61 (s, 4H), 6.87 (d, 1H, J = 15.10 Hz), 3.66 (brs, 4H), 3.49-3.47 (m, 4H), 1.47 (s, 9H). ESI-MS: *m*/*z* 385 [M+1]+.

General Procedure for Preparation of (E)-1-piperazino-3-(substitute phenyl)-2-propen-1-one) (3a-c)

To a solution of boc-protected compounds 2a-c (1 mmol) in dry dichloromethane was added trifluoroacetic acid (11 mmol) at 0 ^{o}C and stirred under nitrogen for 12 h, the reaction mixture was concentrated under vacuum to afford compounds 3a-c and then it was used directly in the next step.

General Procedure for Preparation of Compounds 5a-6a

To a stirred solution of (*E*)-1-piperazino-3-(substitute phenyl)-2-propen-1-one) **3a-c** (1.0 mmol) in dry THF was added triethylamine (1.5 mL) followed by (*E*)-3-(substituted phenyl)-2-propenoyl chlorides **(4)** in dry THF (1.0 mmol) at 0 ^{o}C. The reaction mixture was stirred for 2 hours and the reaction was monitored by TLC. After completion of the reaction, THF was evaporated under vacuum to get the crude product. This was further purified by column chromatography ($CHCl_3$-MeOH) to afford the pure compounds **5a-6a**.

(E)-3-Phenyl-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl]piperazino-2-propen-1-one (5a)

Yield 85%; White solid; mp 168-173 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.68 (d, 1H, J = 15.29 Hz), 7.59 (d, 1H, J = 15.29 Hz), 7.52-7.47 (m, 2H), 7.40-7.34 (m, 3H), 6.83 (d, 1H, J = 15.29 Hz), 6.70 (s, 2H), 6.68 (d, 1H, J = 15.10 Hz), 3.89 (s, 6H), 3.84 (m, 3H), 3.75 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.5, 153.3, 143.6, 143.5, 139.6, 134.8, 130.4, 129.7, 128.7, 127.7, 116.2, 115.4, 104.9, 60.8, 56.1, 45.4, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3473 (br), 2929, 1642, 1583, 1505, 1419, 1384, 1340, 1274, 1253, 1218, 1154, 1038, 1000, 988, 974, 817; ESI-MS: *m*/*z* 437 [M+1]+, HRMS calcd for $C_{25}H_{28}N_2O_5Na$ [M+Na]+ 459.1895, found 459.1909.

(E)-3-(3,4,5-Trimethoxyphenyl)-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl]piperazino-2-propen-1-one (5b)

Yield 72%; White solid; mp 139-143 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.63 (d, 2H, J = 15.29 Hz), 6.74 (s, 4H), 6.74 (d, 2H, J = 15.10 Hz), 3.90 (s, 12H), 3.88 (s, 6H), 3.83-3.70 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.6, 153.3, 143.7, 139.8, 130.4, 115.4, 105.1, 60.9, 56.1, 45.6, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3434 (br), 2926, 1648, 1608, 1582, 1504, 1459, 1419, 998, 816; ESI-MS: *m*/*z* 550 [M+Na]+, HRMS calcd for $C_{28}H_{34}N_2O_8Na$ [M+Na]+ 550.2332, found 550.2322.

(E)-3-[4-(trifluoromethyl)phenyl]-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2propenoyl]piperazino-2-propen-1-one (5c)

Yield 83%; White solid; mp 138-142 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.70 (d, 1H, *J* = 15.32 Hz), 7.50 (d, 1H, *J* = 14.87), 7.32 (d, 2H, *J* = 8.00 Hz), 6.97 (d, 1H, *J* = 15.32), 6.82 (d, 1H, *J* = 14.87), 6.73 (s, 2H), 3.92 (s, 6H), 3.87 (s, 3H), 3.78 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.5, 164.9, 153.3, 143.7, 141.7, 139.7, 138.2, 131.0, 130.3, 127.8, 125.7, 118.8, 115.3, 105.0, 60.8, 56.1, 45.5, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3433 (br), 2922, 1606, 1584, 1505, 1447, 1418, 1183, 1123, 1067, 1037, 991, 829; ESI-MS: *m*/*z* 505 [M+1]+, HRMS calcd for $C_{26}H_{27}N_2O_5F_3Na$ [M+Na]+ 527.1769, found 527.1749.

(E)-3-[3-(Trifluoromethoxy)phenyl]-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl] piperazin-2-propen-1-one(5d)

Yield 87%;White solid; mp 260-265 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.65 (d, 1H, *J* = 15.10 Hz), 7.60 (d, 1H, *J* = 14.32 Hz), 7.43 (s, 2H), 7.37 (s, 1H), 7.27-7.23 (m, 1H), 6.86 (d, 1H, *J* = 15.10 Hz), 6.74 (s, 3H), 3.90 (s, 6H), 3.87 (s, 3H), 3.78 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.5, 165.0, 153.3, 149.4, 143.7, 141.7, 139.7, 136.9, 130.3, 130.1, 126.3, 121.8, 119.6, 118.1, 115.4, 104.9, 60.8, 56.0, 45.5, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3448 (br), 2927, 1646, 1607, 1581, 1506, 1456, 1426, 1267, 1211, 1128, 1032, 989, 823; ESI-MS: *m*/*z* 521 [M]+, HRMS calcd for $C_{26}H_{27}N_2O_6F_3Na$ [M+Na]+ 543.1718, found 543.1732.

(E)-3-(4-Fluorophenyl)-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl]piperazino-2-propen-1-one (5e)

Yield 67%; White solid; mp 172-178 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.62 (d, 1H, *J* = 15.10 Hz), 7.56 (d, 1H, *J* = 15.10 Hz), 7.50 (dd, 2H, *J* = 5.28 Hz), 7.06 (2H, t),6.73 (d, 1H, *J* = 15.10 Hz), 6.70 (s, 2H), 6.66 (d, 1H, *J* = 14.80), 3.89 (s, 6H), 3.84 (s, 3H), 3.75 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.5, 165.4, 153.3, 143.7, 142.3, 139.8, 131.1, 130.4, 129.6, 116.0, 115.4, 105.0, 60.8, 56.1, 45.2, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3448 (br), 2924, 1608, 1583, 1508, 1446, 1274, 1247, 1126, 1033, 1001, 986, 829; ESI-MS: *m*/*z* 455 [M+1]+, HRMS calcd for $C_{25}H_{27}N_2O_5FNa$ [M+Na]+ 477.1801, found 477.1807.

(E)-3-(4-Chlorophenyl)-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl]piperazino-2-propen-1-one (5f)

Yield 84%; White solid; mp 153-158 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.60 (d, 1H, *J* = 15.10 Hz), 7.56 (d, 1H, *J* = 14.35 Hz), 7.43 (d, 2H, *J* = 9.06 Hz), 7.32 (d, 2H, *J* = 8.30 Hz),6.78 (d, 1H, *J* = 15.10 Hz), 6.70 (s, 2H), 6.66 (d, 1H, *J* = 13.80), 3.89 (s, 6H), 3.84 (s, 3H), 3.74 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.6, 165.3, 153.3, 143.7, 142.2, 139.8, 135.6, 133.3, 130.4, 129.0, 128.9, 116.8, 115.4, 105.0, 60.9, 56.1, 45.3, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3429 (br), 2924, 1644, 1604, 1584, 1491, 1446, 1432, 1340, 1275, 1248, 1156, 1124, 1090, 1038, 1010, 991, 980, 820; ESI-MS: *m*/*z* 471 [M]+, HRMS calcd for $C_{25}H_{27}N_2O_5ClNa$ [M+Na]+ 493.1506, found 493.1514.

(E)-3-(4-Bromophenyl)-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl]piperazino-2-propen-1-one (5g)

Yield 79%; White solid; mp 155-160 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.59 (d, 2H, *J* = 15.10 Hz), 7.47 (d, 2H, *J* = 8.30 Hz), 7.36 (d, 2H, *J* = 7.55 Hz), 6.82 (d, 1H, *J* = 15.10 Hz),6.73 (d, 1H, *J* = 15.10 Hz), 6.70 (s, 2H), 3.87 (s, 6H), 3.85 (s, 3H), 3.75 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.5, 165.2, 152.3, 143.8, 142.1, 138.8, 134.6, 133.5, 130.2, 129.2, 128.7, 115.8, 115.2, 105.2, 60.7, 56.3, 45.2, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3483 (br), 2931, 1644, 1603, 1584, 1505, 1488, 1420, 1273, 1217, 1156, 1127, 1072, 1038, 989, 816; ESI-MS: *m*/*z* 515 [M]+, HRMS calcd for $C_{25}H_{27}N_2O_5BrNa$ [M+Na]+ 537.1001, found 537.0987.

(E)-3-(3,4-Difluorophenyl)-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl]piperazino-2-propen-1-one (5h)

Yield 75%; White solid; mp 143-150 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ*: 7.57 (d, 2H, *J* = 15.60 Hz), 7.37-7.33 (m, 2H), 7.18-7.13 (m, 1H), 6.74 (d, 1H, *J* = 15.60 Hz),6.70 (s, 2H), 6.66 (d, 2H, *J* = 15.60 Hz), 3.89 (s, 6H), 3.84 (s, 3H), 3.74 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.5, 165.0, 153.3, 143.7, 141.2, 130.3, 124.6, 124.5, 117.8, 117.5, 117.4, 115.9, 115.7, 115.4, 105.0, 60.8, 56.1, 45.5, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3421 (br), 2937, 1647, 1605, 1586, 1507, 1434, 1419, 1337, 1296, 1277, 1248, 1220, 1126, 1049, 992, 814; ESI-MS: *m*/*z* 495 [M+Na]+, HRMS calcd for $C_{25}H_{26}N_2O_5F_2Na$ [M+Na]+ 495.1707, found 495.1709.

(E)-3-(3,4-Dichlorophenyl)-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl]piperazino-2-propen-1-one (5i)

Yield 83%; White solid; mp 168-173 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.62 (d, 2H, *J* = 14.87 Hz), 7.42-7.38 (m, 2H), 7.20-7.17 (m, 1H), 6.82 (d, 1H, *J* = 14.87 Hz),6.68 (s, 2H), 6.52 (d, 1H, *J* = 14.87 Hz), 3.89 (s, 6H), 3.82 (s, 3H), 3.71 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.6, 165.1, 153.2, 143.8, 141.4, 130.2, 124.8, 124.5, 117.8, 117.6, 117.4, 115.9, 115.6, 115.3, 105.2, 60.8, 56.1, 45.5, 42.2; IR (KBr) (Umax/cm^{-1}): υ 3453 (br), 2936, 1646, 1602, 1581, 1552, 1504, 1455, 1384, 1337, 1272, 1255, 1124, 1028, 990, 922, 819; ESI-MS: *m*/*z* 505 [M]+, HRMS calcd for $C_{25}H_{26}N_2O_5Cl_2Na$ [M+Na]+ 527.1116, found 527.1129.

(E)-3-(4-Hydroxy-3-methoxyphenyl)-1-4-[(E)-3-(3,4,5-trimethoxyphenyl)-2-propenoyl] piperazino-2-propen-1-one (5j)

Yield 87%; White solid; mp 180-185 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.65 (d, 1H, *J* = 15.10 Hz), 7.62 (d, 1H, *J* = 15.10 Hz), 7.09 (d, 1H, *J* = 8.30 Hz), 7.00 (s, 1H),6.90 (d, 1H, *J* = 8.30 Hz), 6.74 (d, 1H, *J* = 14.35 Hz), 6.72 (s, 2H), 6.68 (d, 1H, *J* = 14.35 Hz), 6.19 (brs, 1H), 3.93 (s, 3H), 3.90 (s, 6H), 3.87 (s, 3H), 3.76 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.9, 165.5, 153.3, 147.7, 146.8, 143.8, 143.7, 130.4, 127.3, 122.0, 115.5, 114.8, 113.5, 109.9, 105.0, 60.8, 56.1, 55.9, 45.5, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3448 (br), 2928, 1639, 1607, 1572, 1506, 1431, 1384, 1337, 1247, 1125, 1032, 989, 822; ESI-MS: *m*/*z* 460 [M+1]+, HRMS calcd for $C_{26}H_{30}N_2O_7Na$ [M+Na]+ 505.1950, found 505.1975.

(E)-3-Phenyl-1-(4-(E)-3-[4-(trifluoromethyl)phenyl]-2-propenoylpiperazino)-2-propen-1-one (5k)

Yield 76%; White solid; mp 182-187 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ*: 7.82 (s, 3H), 7.72 (d, 2H, *J* = 14.32 Hz), 7.67 (d, 2H, *J* = 8.23 Hz), 7.62-7.54 (m, 1H),7.42 (d, 1H, *J* = 14.32 Hz), 7.39 (s, 3H), 7.32 (d, 1H, , *J* = 14.28 Hz), 3.76 (brs, 4H), 3.72 (brs, 4H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.4, 153.2, 143.8, 143.4, 139.7, 134.8, 130.6, 129.8, 128.4, 127.6, 116.4, 115.2, 105.3, 45.4, 42.1; IR (KBr) (Umax/cm^{-}

^{1}): υ 3438 (br), 2919, 1644, 1600, 1496, 1435, 1411, 1364, 1328, 1280, 1224, 1167, 1127, 1110, 1068, 1039, 1016, 995, 967, 827, 761; ESI-MS: *m/z* 415 [M+1]+, HRMS calcd for $C_{23}H_{21}N_2O_2F_3Na$ [M+Na]+ 437.1452, found 437.1464.

(E)-3-Phenyl-1-(4-(E)-3-[3-(trifluoromethoxy)phenyl]-2-propenoylpiperazino)-2-propen-1-one (5l)

Yield 69%; White solid; mp 162-165 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.76 (s, 3H), 7.72 (d, 2H, *J* = 13.78 Hz), 7.62 (d, 1H, *J* = 7.90 Hz), 7.48 (s, 2H), 7.41 (d, 1H, *J* = 7.89 Hz), 6.92 (d, 2H, *J* = 13.78 Hz), 6.81 (s, 1H), 3.78 (brs, 4H), 3.68 (brs, 4H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.7, 165.2, 153.1, 149.4, 143.7, 141.8, 139.6, 136.9, 130.2, 130.3, 126.5, 121.8, 119.6, 118.2, 115.5, 105.2, 45.6, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3447 (br), 2923, 1645, 1601, 1496, 1452, 1435, 1364, 1279, 1219, 1167, 1041, 988, 973, 849, 802, 762, 700, 681; ESI-MS: *m/z* 431 [M+1]+, HRMS calcd for $C_{23}H_{21}N_3O_3F_3Na$ [M+Na]+ 453.1401, found 453.1424.

(E)-3-(4-Fluorophenyl)-1-4-[(E)-3-phenyl-2-propenoyl]piperazino-2-propen-1-one (5m)

Yield 74%; White solid; mp 151-155 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.67 (d, 1H, *J* = 15.17 Hz), 7.58 (d, 1H, *J* = 15.17 Hz), 7.52-7.42 (m, 2H), 7.38-7.32 (m, 3H), 7.27 (d, 2H, *J* = 7.82 Hz), 7.18 (d, 2H, *J* = 8.02 Hz), 6.84 (d, 1H, *J* = 15.16 Hz), 6.68 (d, 1H, *J* = 15.17 Hz), 3.65 (brs, 4H), 3.42 (brs, 4H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.6, 165.3, 153.2, 142.8, 141.2, 139.8, 134.6, 133.2, 130.2, 129.3, 128.7, 116.5, 115.0, 105.8, 45.3, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3428, (br), 2930, 1636, 1614, 1490, 1433, 1410, 1360, 1325, 1270, 1210, 1152, 1120, 1090, 1012, 990, 960, 820, 786; ESI-MS: *m/z* 365 [M+1]+, HRMS calcd for $C_{22}H_{21}N_2O_2FNa$ [M+Na]+ 387.1484, found 387.1474.

(E)-3-(4-Chlorophenyl)-1-4-[(E)-3-phenyl-2-propenoyl]piperazino-2-propen-1-one (5n)

Yield 84%; White solid; mp 250-255 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ*: 7.83 (s, 1H), 7.78 (d, 2H, *J* = 16.79 Hz), 7.77 (s, 1H), 7.58-7.51 (m, 4H), 7.47-7.41 (m, 3H), 7.36 (d, 1H, *J* = 16.79 Hz), 7.32 (d, 1H, *J* = 16.79 Hz), 3.80 (brs, 4H), 3.68 (brs, 4H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.5, 165.2, 152.3, 144.7, 142.6, 139.9, 135.4, 132.3, 130.4, 129.3, 128.6, 117.8, 115.2, 105.3, 45.1, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3434 (br), 3031, 2861, 1646, 1599, 1491, 1435, 1405, 1294, 1274, 1217, 1035, 1012, 988, 818, 789, 763; ESI-MS: *m/z* 381 [M]+, HRMS calcd for $C_{22}H_{23}ClN_2O_2$ [M+H]+ 381.1380, found 381.1391.

(E)-3-(4-Bromophenyl)-1-4-[(E)-3-phenyl-2-propenoyl]piperazino-2-propen-1-one (5o)

Yield 78%; White solid; mp 248-252 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.72 (s, 3H), 7.70 (d, 2H, *J* = 13.62 Hz), 7.60 (d, 2H, *J* = 8.30 Hz), 7.55-7.42 (m, 1H), 7.40 (d, 1H, *J* = 13.59 Hz), 7.39 (s, 3H), 7.27 (d, 1H, *J* = 13.59 Hz), 3.76 (brs, 4H), 3.62 (brs, 4H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.5, 165.2, 151.3, 142.8, 142.0, 138.6, 135.6, 133.3, 130.6, 129.3, 127.7, 115.4, 115.0, 105.4, 45.2, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3436 (br), 3030, 2860, 1647, 1600, 1486, 1455, 1434, 1401, 1273, 1216, 1035, 1008, 986, 814, 786; ESI-MS: *m/z* 425 [M]+, HRMS calcd for $C_{22}H_{21}BrN_2O_2Na$ [M+H]+ 448.0639, found 448.0653.

(E)-3-Phenyl-1-4-[(E)-3-phenyl-2-propenoyl]piperazino-2-propen-1-one (5p)

Yield 87%; White solid; mp 234-239 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ*: 7.71 (d, 2H, *J* = 15.12 Hz), 7.51 (d, 4H, *J* = 5.50 Hz), 7.37-7.36 (m, 6H), 6.85 (d, 2H, *J* = 15.12 Hz), 3.79 (brs, 4H), 3.72 (brs, 4H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.2, 153.4, 143.4, 142.5, 139.1, 133.8, 130.6, 129.8, 128.4, 127.5, 116.2, 115.7, 105.0, 45.6, 42.3; IR (KBr) (Umax/cm^{-1}): υ 3430 (br), 2975, 2936, 1645, 1600, 1498, 1453, 1435, 1397, 1330, 1275, 1220, 1038, 986, 976, 761; ESI-MS: *m/z* 347 [M+1]+, HRMS calcd for $C_{22}H_{23}N_2O_2$ [M+H]+ 347.1759, found 347.1775.

(E)-3-(3,4-Difluorophenyl)-1-4-[(E)-3-phenyl-2-propenoyl]piperazino-2-propen-1-one (5q)

Yield 90%; White solid; mp 249-254 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.57 (d, 2H, *J* = 15.62 Hz), 7.53 (m, 2H), 7.38-7.31 (m, 5H), 7.20-7.19 (m, 1H), 6.74 (d, 2H, *J* = 15.62 Hz), 3.87 (brs, 4H), 3.64 (brs, 4H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.6, 165.2, 153.4, 143.6, 141.3, 130.4, 124.5, 124.3, 117.8, 117.7, 117.3, 115.8, 115.7, 115.4, 105.2, 45.5, 42.2; IR (KBr) (Umax/cm^{-1}): υ 3435 (br), 3032, 2858, 1647, 1601, 1515, 1498, 1434, 1299, 1276, 1220, 1115, 1039, 976, 817, 763; ESI-MS: *m/z* 383 [M+1]+, HRMS calcd for $C_{22}H_{21}N_2O_2F_2$ [M+H]+ 383.1571, found 383.1569.

(E)-3-(3,4-Dichlorophenyl)-1-4-[(E)-3-phenyl-2-propenoyl]piperazino-2-propen-1-one (5r)

Yield 69%; White solid; mp 230-235 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.62 (d, 2H, *J* = 15.42 Hz), 7.58 (m, 2H), 7.42-7.37 (m, 5H), 7.32-7.20 (m, 1H), 6.89 (d, 2H, *J* = 15.42 Hz), 3.82 (brs, 4H), 3.54 (brs, 4H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.4, 165.0, 153.4, 143.7, 141.6, 130.4, 124.6, 124.7, 117.8, 117.4, 117.2, 115.9, 115.6, 115.2, 105.0, 45.2, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3430 (br), 2976, 1643, 1602, 1475, 1439, 1397, 1383, 1218, 1171, 1075, 1036, 983, 850, 808, 762; ESI-MS: *m/z* 415 [M]+, HRMS calcd for $C_{22}H_{20}Cl_2N_2O_2Na$ [M+H]+ 438.0752, found 438.0764.

(E)-3-(4-Hydroxy-3-methoxyphenyl)-1-4-[(E)-3-phenyl-2-propenoyl]piperazino-2-propen-1-one (5s)

Yield 83%; White solid; mp 248-253 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.64 (d, 1H, *J* = 15.12 Hz), 7.62 (d, 1H, *J* = 15.12 Hz), 7.53 (m, 2H), 7.36-7.32 (m, 3H), 7.09 (d, 1H, *J* = 8.23 Hz), 7.00 (s, 1H), 6.89 (d, 1H, *J* = 8.23 Hz), 6.74 (d, 1H, *J* = 15.12 Hz), 6.68 (d, 1H, *J* = 15.12 Hz), 3.87 (s, 3H), 3.64 (brs, 8H); ^{13}C NMR (DMSO-d6, 150 MHz): δ 165.7, 165.3, 153.1, 147.5, 146.8, 143.7, 143.4, 130.4, 127.3, 122.2, 115.3, 114.8, 113.2, 109.9, 105.3, 56.7, 45.4, 42.3; IR (KBr) (Umax/cm^{-1}): υ 3428 (br), 2977, 1647, 1600, 1490, 1432, 1368, 1280, 1212, 1170, 1032, 986, 852, 800, 760, 680; ESI-MS: *m/z* 393 [M+1]+, HRMS calcd for $C_{23}H_{24}Cl_2N_2O4Na$ [M+H]+ 415.3720, found 415.3732.

(E)-3-[3-(Trifluoromethoxy)phenyl]-1-(4-(E)-3-[4-(trifluoromethyl)phenyl]-2-propenoylpiper-azino)-2-propen-1-one (5t)

Yield 76%; White solid; mp 145-150 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.71 (d, 2H, *J* = 15.29 Hz), 7.63 (s, 4H), 7.43-7.37 (m, 3H), 7.21 (s, 1H), 6.88 (d, 1H, *J* = 16.80 Hz), 6.85 (d, 1H, *J* = 16.05 Hz), 3.75 (s, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.4, 165.1, 153.4, 149.5, 143.5, 141.5, 140.4,

136.9, 130.4, 130.3, 126.3, 121.8, 119.9, 118.1, 115.4, 105.4, 45.6, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3446 (br), 2921, 1646, 1604, 1491, 1448, 1437, 1330, 1278, 1218, 1168, 1068, 1039, 1017, 987, 848, 829, 803, 748; ESI-MS: *m*/*z* 499 [M+1]+, HRMS calcd for $C_{24}H_{20}N_2O_3F_6Na$ [M+H]+ 521.1275, found 521.1266.

(E)-3-[4-(Trifluoromethyl)phenyl]-1-(4-(E)-3-[4-(trifluoro-methyl)phenyl]-2-propenoylpiperaz-ino)-2-propen-1-one (5u)

Yield 80%; White solid; mp 279-284 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.72 (d, 2H, *J* = 15.12 Hz), 7.51 (d, 4H, *J* = 5.50 Hz), 7.37-7.36 (m, 6H), 6.85 (d, 2H, *J* = 15.12 Hz), 3.79 (brs, 4H), 3.72 (brs, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.8, 153.2, 143.4, 139.6, 130.2, 115.6, 105.2, 45.6, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3432 (br), 2929, 1650, 1617, 1577, 1435, 1413, 1364, 1323, 1277, 1126, 1157, 1111, 1066, 1035, 1016, 987, 831, 749; ESI-MS: *m*/*z* 483 [M+1]+, HRMS calcd for $C_{24}H_{20}N_2O_2F_6Na$ [M+H]+ 505.1326, found 505.1336.

(E)-3-(4-Fluorophenyl)-1-(4-(E)-3-[4-(trifluoromethyl) phenyl]-2-propenoylpiperazino)-2-propen-1-one (5v)

Yield 73%; White solid; mp 225-230 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.70 (d, 1H, *J* = 15.10 Hz), 7.64 (d, 1H, *J* = 15.10 Hz), 7.60 (s, 4H), 7.54-7.47 (m, 2H), 7.06 (t, 2H, *J* = 8.30 Hz), 6.93 (d, 1H, *J* = 15.10 Hz), 6.76 (d, 1H, *J* = 15.86 Hz), 3.75 (brs, 8H); ^{13}C NMR (CDCl3, 150 MHz): δ 165.3, 165.2, 153.1, 142.6, 141.0, 139.6, 134.7, 133.1, 130.4, 129.5, 128.4, 116.7, 115.2, 105.9, 45.2, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3422 (br), 2977, 1649, 1613, 1475, 1433, 1412, 1384, 1364, 1326, 1277, 1215, 1171, 1158, 1114, 1067, 1037, 990, 850, 807; ESI-MS: *m*/*z* 433 [M+1]+, HRMS calcd for $C_{23}H_{20}N_2O_2F_4Na$ [M+H]+ 455.3067, found 455.3055.

(E)-3-(4-Chlorophenyl)-1-(4-(E)-3-[4-(trifluoromethyl) phenyl]-2-propenoylpiperazino)-2-propen-1-one (5w)

Yield 84%; White solid; mp 280-285 °C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ*: 7.72 (d, 1H, *J* = 14.67 Hz), 7.65 (d, 1H, *J* = 14.67 Hz), 7.64 (s, 4H), 7.46 (d, 2H, *J* = 7.82 Hz), 7.35 (d, 2H, *J* = 8.80 Hz), 6.92 (d, 1H, *J* = 15.65 Hz), 6.82 (d, 1H, *J* = 15.65 Hz), 3.81 (brs, 4H), 3.73 (brs, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.4, 165.2, 152.4, 144.6, 142.5, 140.2, 135.6, 132.4, 130.5, 129.6, 128.6, 117.6, 115.2, 105.1, 45.3, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3421 (br), 2925, 1649, 1615, 1492, 1433, 1412, 1364, 1325, 1277, 1216, 1157, 1123, 1089, 1066, 1011, 991, 960, 821, 788; ESI-MS: *m*/*z* 471 [M+Na]+, HRMS calcd for $C_{23}H_{20}N_2O_2F_4Na$ [M+H]+ 471.8612, found 471.8604.

(E)-3-(4-Bromophenyl)-1-(4-(E)-3-[4-(trifluoromethyl) phenyl]-2-propenoylpiperazino)-2-prop- -en-1-one (5x)

Yield 78%; White solid; mp 290-295 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.71 (d, 1H, *J* = 15.10 Hz), 7.63 (s, 4H), 7.61 (d, 1H, *J* = 16.61 Hz), 7.50 (d, 2H, *J* = 7.55 Hz), 7.37 (d, 2H, *J* = 8.30 Hz), 6.91 (d, 1H, *J* = 16.61 Hz), 6.82 (d, 1H, *J* = 16.61 Hz), 3.75 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.3, 165.1, 151.5, 142.6, 142.2, 138.7, 135.3, 133.6, 130.6, 129.5, 127.4, 115.2, 115.2, 105.2, 45.1, 42.2; IR (KBr) (Umax/cm^{-1}): υ 3436 (br), 2926, 1649, 1615, 1488, 1432, 1412, 1399, 1363, 1324, 1277, 1216, 1122, 1067, 1041, 1006, 991, 832, 817, 749; ESI-MS: *m*/*z* 493 [M]+, HRMS calcd for $C_{23}H_{20}BrN_2O_2F_3Na$ [M+H]+ 516.3120, found 516.3108.

(E)-3-(3,4-Difluorophenyl)-1-(4-(E)-3-[4-(trifluoromethyl) phenyl]-2-propenoylpiperazino)-2-propen-1-one (5y)

Yield 65%; White solid; mp 215-220 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.70 (d, 1H, *J* = 15.86 Hz), 7.64 (s, 4H), 7.59 (d, 1H, *J* = 15.10 Hz), 7.43-7.34 (m, 2H), 7.18 (s, 1H), 6.94 (d, 1H, *J* = 15.86 Hz), 6.80 (d, 1H, *J* = 15.10 Hz), 3.77 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.7, 165.1, 153.2, 143.7, 141.3, 130.1, 124.6, 124.3, 117.9, 117.6, 117.2, 115.9, 115.6, 115.3, 105.0, 45.3, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3435 (br), 2976, 1649, 1612, 1475, 1435, 1413, 1397, 1383, 1365, 1325, 1270, 1219, 1171, 1113, 1067, 1037, 990, 850, 820; ESI-MS: *m*/*z* 451 [M+1]+, HRMS calcd for $C_{23}H_{19}N_2O_2F_5Na$ [M+Na]+ 473.1264, found 473.1257.

(E)-3-(3,4-Dichlorophenyl)-1-(4-(E)-3-[4-(trifluoromethyl) phenyl]-2-propenoylpiperazino)-2-propen-1-one (5z)

Yield 72%; White solid; mp 230-235 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.69 (d, 1H, *J* = 15.10 Hz), 7.64 (s, 4H), 7.59 (d, 1H, *J* = 15.86 Hz), 7.44 (s, 1H), 7.36 (dd, 2H, *J* = 8.30, 6.04 Hz), 6.93 (d, 1H, *J* = 15.86 Hz), 6.85 (d, 1H, *J* = 15.10 Hz), 3.76 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.7, 165.2, 153.2, 143.6, 141.4, 130.2, 124.7, 124.3, 117.8, 117.5, 117.2, 115.9, 115.5, 115.3, 105.0, 45.6, 42.1; IR (KBr) (Umax/cm^{-1}): υ 3435 (br), 2977, 2938, 1648, 1612, 1475, 1434, 1412, 1397, 1384, 1364, 1325, 1281, 1215, 1171, 1125, 1066, 1037, 990, 850, 826; ESI-MS: *m*/*z* 483 [M]+, HRMS calcd for $C_{23}H_{19}N_2O_2F_3Cl_2Na$ [M+Na]+ 505.0673, found 505.0671.

(E)-3-(4-Hydroxy-3-methoxyphenyl)-1-(4-(E)-3-[4-(trifluo-romethyl)phenyl]-2-propenoylpipera zino)-2-propen-1-one (6a)

Yield 59%; White solid; mp 260-265 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*: 7.72 (d, 1H, *J* = 15.32 Hz), 7.65 (s, 4H), 7.62 (d, 1H, *J* = 15.32 Hz), 7.06 (d, 1H, *J* = 8.30 Hz), 6.92 (s, 1H), 6.87 (d, 1H, *J* = 8.30 Hz), 6.76 (d, 1H, *J* = 15.32 Hz), 6.65 (d, 1H, *J* = 15.32 Hz), 6.06 (brs, 1H), 3.98 (s, 3H), 3.78 (brs, 8H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 165.6, 165.1, 153.1, 147.7, 146.4, 143.8, 143.3, 130.4, 127.1, 122.4, 115.5, 114.6, 113.4, 110.6, 105.0, 55.8, 45.5, 42.0; IR (KBr) (Umax/cm^{-1}): υ 3436 (br), 2978, 1640, 1605, 1496, 1432, 1360, 1280, 1210, 1172, 1036, 982, 850, 807, 760, 684; ESI-MS: *m*/*z* 461 [M+1]+, HRMS calcd for $C_{24}H_{23}N_2O_4F_3Na$ [M+Na]+ 483.4422, found 483.4412.

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