

Synthesis of Piperazin-2-one Derivatives via Cascade Double Nucleophilic Substitution

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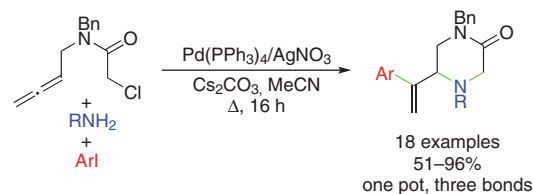
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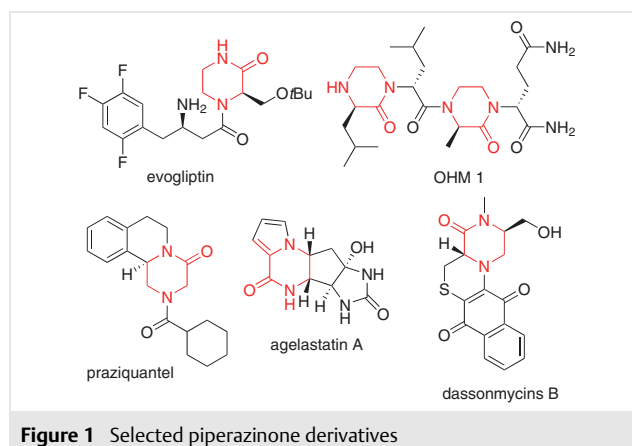
Abstract A cascade, metal-promoted transformation utilizing chloro allenylamide, primary amine, and aryl iodide afforded piperazinones in good yields. Under the optimized conditions the cascade is performed as a one-pot process allowing the formation of three bonds. The synthetic route, controlled by the reaction rates of several processes involved, introduces two points of diversity and is well suited for combinatorial synthesis or related technologies.

Key words piperazinones, cyclization reactions, allenes, nucleophilic substitution, combinatorial synthesis

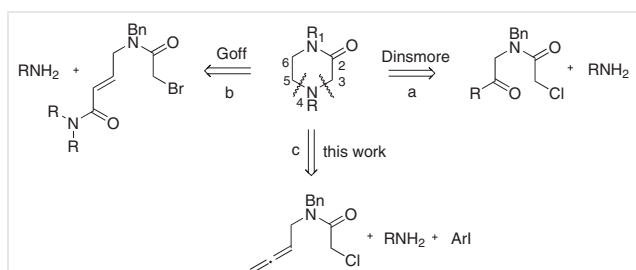
Unique properties of small heterocyclic motifs have made them pivotal participants in drug discovery processes.^{1–5} Their structural varieties provide opportunities to finely balance features of biologically active compounds as they can play various roles.^{6–10} Small heterocyclic rings are used as drug scaffold, bioisosteric replacement or they control specific physicochemical/pharmacokinetic or prodrug properties. Needless to mention, heterocyclic cores are frequently a constitutional part of many natural products as well.^{11,12}

Amongst the heterocyclic skeletons, piperazinones are considered to be a privileged structure in medicinal chemistry.^{13,14} It is a structural part of many drugs and natural products (Figure 1)^{15–18} but its particular value is associated with peptidomimetic properties resulting from the specific positioning of the heteroatoms.^{19,20} Significance of piperazinone motif, perhaps primarily in medicinal chemistry, prompted development of various synthetic methodologies for its preparation.^{21,22}

Amongst them, particularly interesting are those allowing formation of two bonds in one step as they usually provide facile access to structural diversity while simplifying



the synthetic process. These methodologies are widely explored and strategically many of them were developed.²¹ A highly efficient formation of piperazinones outlined in Scheme 1 is based on the simultaneous formation of C(3)–N(4) and N(4)–C(5) bonds and it relies on the nucleophilicity of the amino component employed as the source of N(4). The reported methodologies of this type combine primary amines and typical electrophiles, alkyl halides and aldehyde/ketones (Scheme 1, approach a) or alkyl halides and electron-deficient conjugated double bonds (Scheme 1, approach b).^{23,24} Both processes are very efficient producing piperazinones in high yields. As an alternative to these methods, we developed a related transformation combining electrophilic alkyl halide and allene as a masked electrophile in reaction promoted by Ag(I)/Pd(II) catalysis (Scheme 1, approach c). Interestingly, related process for the formation of the 5-membered ring was reported by the Broggin group but was never explored for the formation of the 6-membered ring.²⁵ In addition, the synthesis of the 5-membered ring was carried out intramolecularly with the pre-



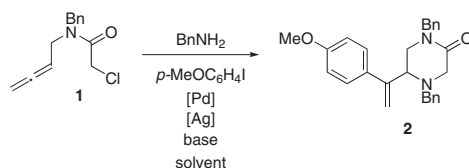
Scheme 1 Synthesis of piperazinones via C(3)–N(4) and N(4)–C(5) bonds formation

formed amine whereas our transformation utilized alkyl chlorides, which was in situ transformed to a nucleophilic secondary amino functionality. The use of aryl iodide to transform allene into the electrophilic moiety ensures additional point of diversity.

Our first experiment (Table 1, entry a) was performed with chloride **1** using benzylamine in excess, aryl iodide, Pd(PPh₃)₄, and Cs₂CO₃ as base in MeCN as solvent. Analysis

of the ¹H NMR spectrum of the crude reaction mixture suggested formation of the expected piperazinone **2** in 43% yield. As the yield was not synthetically fully satisfactory, we next performed the same reaction with the addition of AgNO₃ (entry b) anticipating that it might facilitate the nucleophilic displacement of the chloride. Indeed, the reaction yield increased to 58% and the result prompted surveying few additional Ag-salts (entries c–e). While Ag₂CO₃ and AgOAc proved to be inefficient, AgOTf afforded the expected piperazinone **2** in a yield comparable to that obtained with AgNO₃. As AgOTf is more expensive and hygroscopic, we continued our study with AgNO₃ and further explored several Pd-catalytic systems (entries f–h). Varying Pd-source and the phosphine ligand did not improve the reaction outcome. Two following experiments demonstrated essential role of base and solvent. Namely, performing the reaction in DMF (entry k) or using Et₃N as base (entry i) had detrimental effect on the reaction yield. We finally explored the influence of stoichiometry of AgNO₃ and amine. Decreasing the quantities of Ag-salt to 0.2 or 0.5 equivalent

Table 1 Optimization of the Reaction Conditions for the Synthesis of Piperazinones^a



Entry	[Pd]	[Ag]	BnNH ₂	Base	Solvent	Yield (%) ^b
a	Pd(PPh ₃) ₄	–	3	Cs ₂ CO ₃	CH ₃ CN	43
b	Pd(PPh ₃) ₄	AgNO ₃	3	Cs ₂ CO ₃	CH ₃ CN	58
c	Pd(PPh ₃) ₄	Ag ₂ CO ₃	3	Cs ₂ CO ₃	CH ₃ CN	8
d	Pd(PPh ₃) ₄	AgOAc	3	Cs ₂ CO ₃	CH ₃ CN	18
e	Pd(PPh ₃) ₄	AgOTf	3	Cs ₂ CO ₃	CH ₃ CN	53
f	Pd(OAc) ₂ /PPh ₃ (0.1/0.2 equiv)	AgNO ₃	3	Cs ₂ CO ₃	CH ₃ CN	23
g	Pd(dba) ₂ /PPh ₃ (0.1/0.2 equiv)	AgNO ₃	3	Cs ₂ CO ₃	CH ₃ CN	45
h	Pd(OAc) ₂ /XantPhos (0.1/0.1 equiv)	AgNO ₃	3	Cs ₂ CO ₃	CH ₃ CN	28
i	Pd(PPh ₃) ₄	AgNO ₃	3	Et ₃ N	CH ₃ CN	7
k	Pd(PPh ₃) ₄	AgNO ₃	3	Cs ₂ CO ₃	DMF	3
l	Pd(PPh ₃) ₄	AgNO ₃ (0.2 equiv)	3	Cs ₂ CO ₃	CH ₃ CN	71
m	Pd(PPh₃)₄	AgNO₃ (0.5 equiv)	3	Cs₂CO₃	CH₃CN	74 (63)
n	Pd(PPh ₃) ₄	AgNO ₃ (2.2 equiv)	3	Cs ₂ CO ₃	CH ₃ CN	51
o	Pd(PPh₃)₄	AgNO₃ (1 equiv)	5	Cs₂CO₃	CH₃CN	77
p	Pd(PPh ₃) ₄	AgNO ₃ (1 equiv)	1.5	Cs ₂ CO ₃	CH ₃ CN	27
q	Pd(PPh ₃) ₄	AgNO ₃ (0.5 equiv)	5	Cs ₂ CO ₃	CH ₃ CN	77
r	Pd(dba) ₂ /PPh ₃ (0.1/0.2 equiv)	AgNO ₃ (0.5 equiv)	3	Cs ₂ CO ₃	CH ₃ CN	72 (62)

^a Reaction conditions: **1** (0.1 mmol), *p*-MeOC₆H₄I (0.12 mmol), BnNH₂ (0.3 mmol) Ag-salt (0.1 mmol), base (0.3 mmol), Pd/ligand source (0.01 mmol), solvent (5 mL), 85–90 °C, 16 h, unless otherwise indicated.

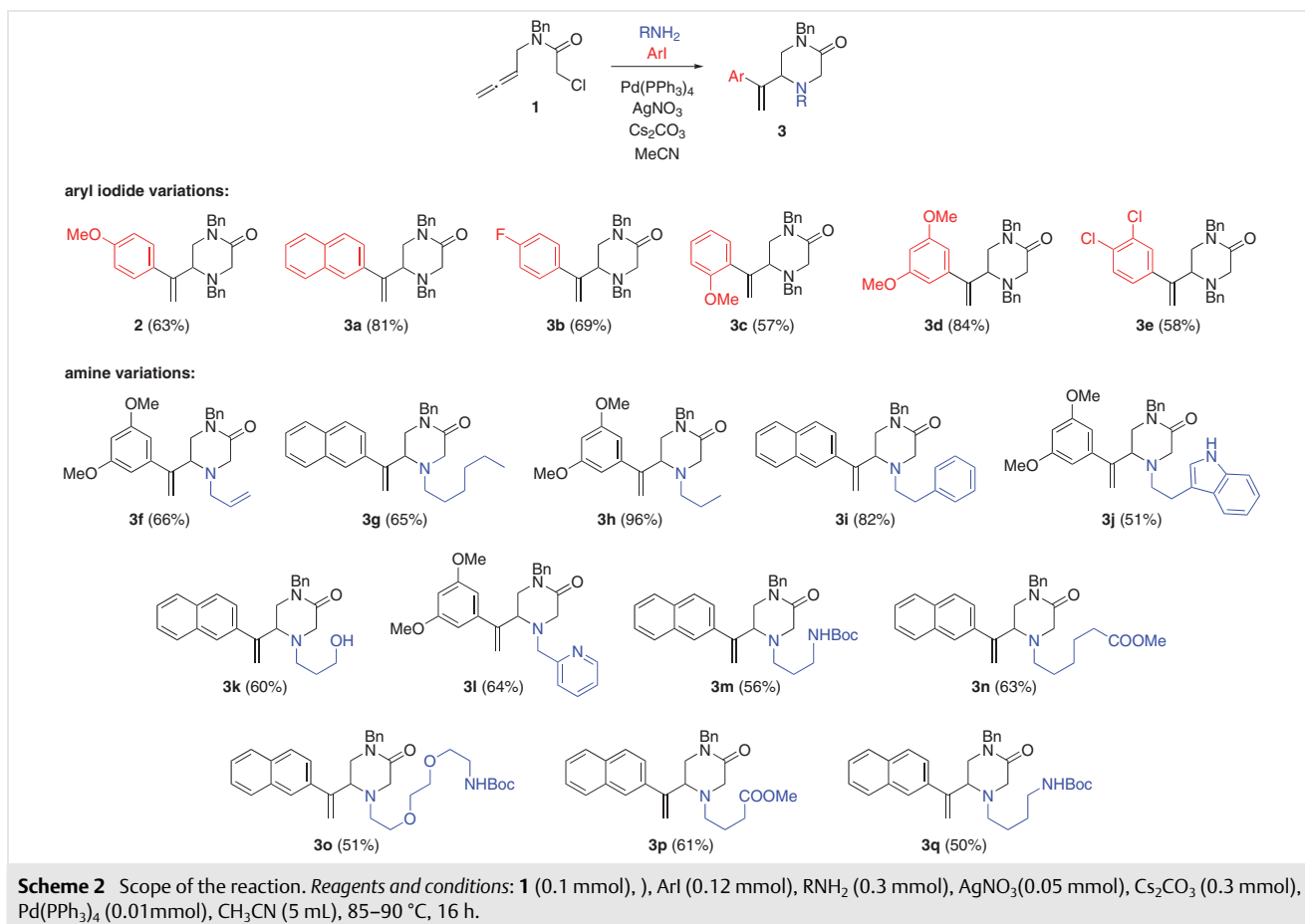
^b Yield calculated from NMR data using pyridine as an internal standard and, in parentheses, isolated yield after column chromatography

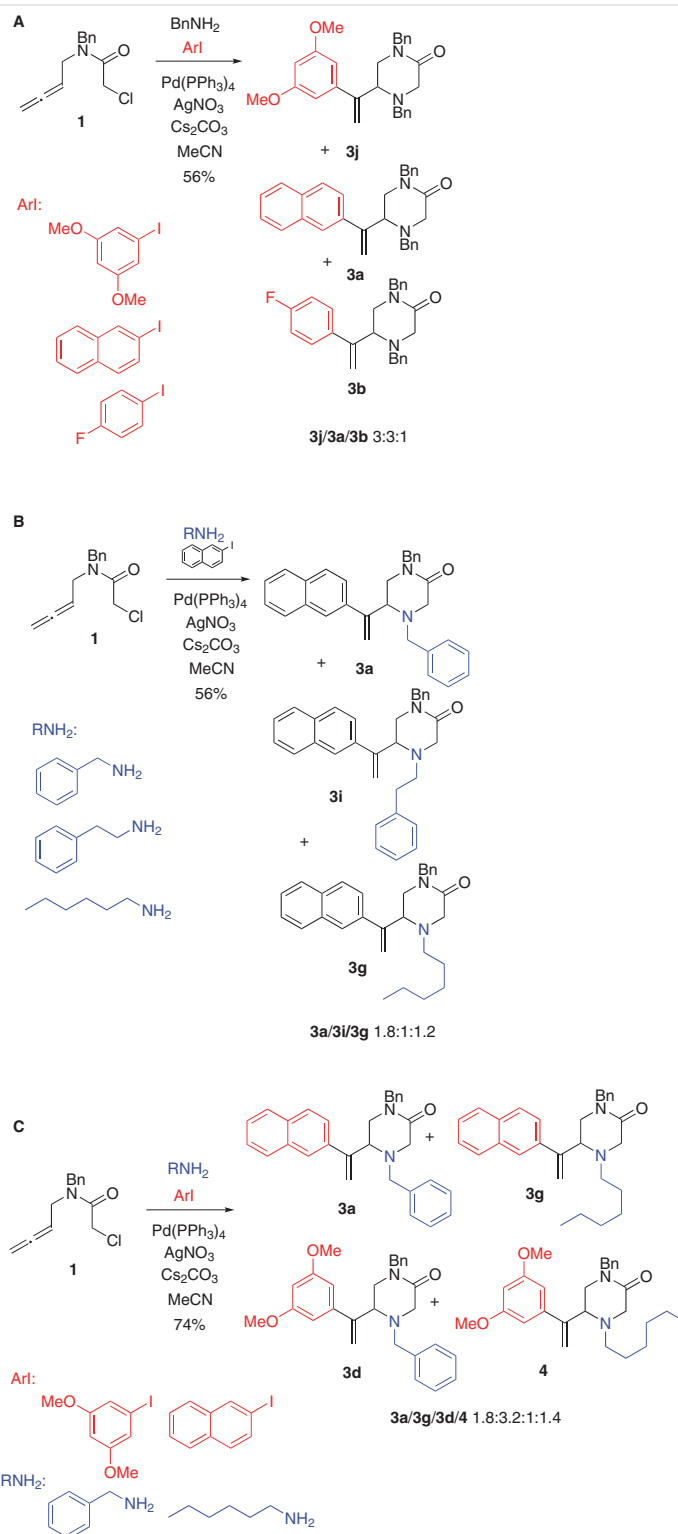
improved the yields to 71% and 74% respectively (entries l, m). A similar effect was observed when $\text{Pd}(\text{dba})_2/\text{PPh}_3$ was used as the catalytic system in conjunction with 0.5 equivalent of AgNO_3 (entry r). Further slight improvement was the consequence of increasing the amount of amine (entries o, q) while completely opposite effect was triggered by reducing the amine quantities (entry p).

Having optimized the reaction conditions, we then explored the scope of the synthetic route (Scheme 2). Under the above described settings various aryl iodides possessing both electron-donating and electron-accepting groups efficiently participated in the reaction process affording product **3a–e** in good yields. A single example of the aryl iodide having *o*-substituent produced **3c** in 57% yield demonstrating tolerance of the reacting functionality to the proximal sterically more demanding substituent. Comparable results were obtained in the reactions with various amines. All aliphatic amines with no other functionalities in the side chain afforded products **3g, 3h, and 3i** in high yields. Similar results were obtained with amines having relatively inert distal ester groups (**3n, 3p**). The conditions also tolerated several acidic functionalities such as OH, NHBoc or indole-NH yielding the products **3j, 3k, 3m, 3o, 3q** in synthetically acceptable manners. Further to this, chelating aminopyri-

dine derivative employed for the preparation of **3l** did not obstruct the process although two metal species were present in the reaction medium. Finally, double bond was also tolerated suggesting a significantly different rate of the reactions of arylpalladium intermediate with allene or alkene. To demonstrate synthetic utility of the above process, the selected reactions were performed at 1 mmol scale under the otherwise same conditions. Product **3f** was isolated after chromatographic purification in 64% yield (compared to 66% at 0.1 mmol scale) while **3q** was isolated in 59% (compared to 50% at 0.1 mmol scale).

The described process introduces two diversity points into the piperazinone products represented by the amino and the iodo components. Therefore, we briefly explored the combinatorial approach for their preparation (Scheme 3 A–C). The reaction outlined in Scheme 3A was performed under the above described conditions using benzylamine and three iodides to afford the expected **3j, 3a, and 3b** as a mixture in 56% yield and in 3:3:1 ratio, respectively. Similar efficiency was demonstrated by the reaction employing three different amines (Scheme 3B). The products **3a, 3i, and 3g** were obtained in 56% yield and in 1.8:1:1.2 ratio, respectively. Finally, we performed the reaction with different amines and aryl iodides to obtain a clean mixture of four

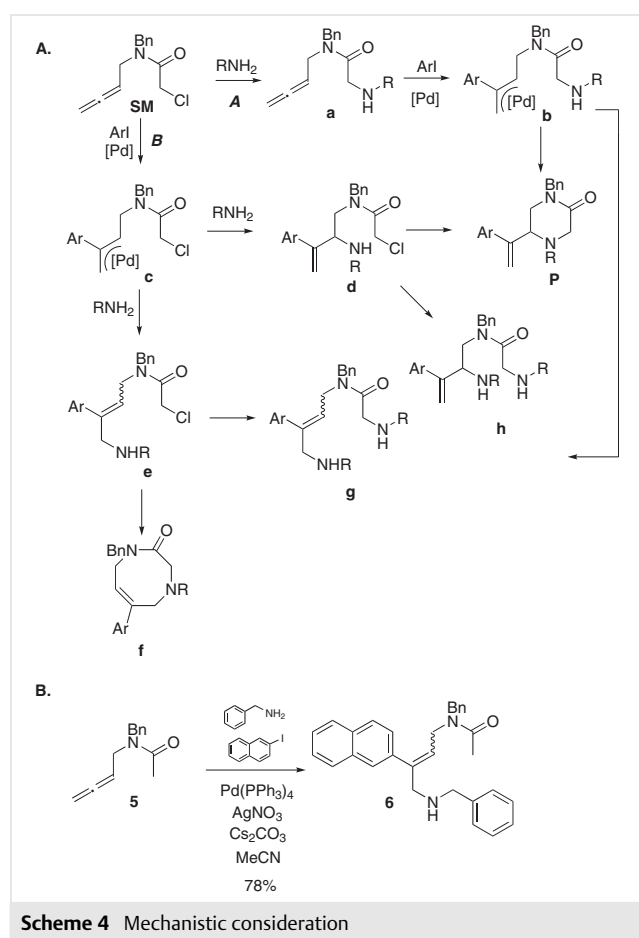




Scheme 3 Combinatorial synthesis of piperazinone derivatives

products **3a**, **3g**, **3d**, and **4** (74% yield, 1.8:3.2:1:1.4 ratio, respectively) (Scheme 3C). The experiments outlined in Scheme 3 demonstrated simplicity and efficiency of the described methodology for the potential combinatorial synthesis of piperazinones.

The depicted cascade transformation combines several processes with compatible reaction rate ideally ordered to yield piperazinone derivatives in good yields. The reaction is likely to start with displacement of chloride in starting allene SM (Scheme 4A) with primary amine creating derivative **a** (Scheme 4A) possessing nucleophilic secondary amino group.



The parallel oxidative addition of the Pd(0) onto the ArI generates an intermediate that reacts with allene moiety creating π -allyl Pd **b** (Scheme 4A). The final step is the well-established nucleophilic substitution involving proximal secondary amine and π -allyl Pd intermediate to create product **P** (Scheme 4A). Alternative pathways which would incorporate initial formation of π -allyl Pd **c** followed by reaction with primary amine to form **d** or **e** and then the cyclized product **f** or **P**, as outlined in Scheme 4A, are unlikely to be effective. Such routes would involve either the reac-

tion of nucleophilic amine with sterically more demanding internal position of π -allyl Pd **c** to form **d** or formation of 8-membered ring product **f** (Scheme 4A). Monitoring of the reaction by ^1H NMR did not reveal any product/by-product that would result from the alternative pathways. In addition, the reaction performed with substrate **5** produced highly regioselectively amine **6** in 78% yield as the product of nucleophilic attack from the less hindered side of the π -allyl Pd-intermediate (Scheme 4B). This result supported nucleophilic displacement of chloride as the first step in the reaction cascade. Our experimental protocol employs an excess of the primary amine nucleophile. However, we did not observe any by-product resulting from the intermolecular reaction of **b** with amine, such as **g** or **h**, (same products would be obtained by reaction of **d/e** with amine), demonstrating the efficiency of the ring closure process.

An efficient cascade process employing chloroallenyl amides for the preparation of piperazinone derivatives was developed. In situ formation of the nucleophilic secondary amine and following nucleophilic displacement onto the proximal π -allyl Pd motif afforded the target compounds in yields typically ~50–90%. Structural variations are easily introduced by appropriate selection of reacting components thus making this transformation well suited for combinatorial synthesis of piperazinone derivatives.

IR spectra were recorded on an IR Thermo Scientific NICOLET iS10 (4950) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Ascend 400 (400 MHz) spectrometer. CDCl_3 was used as a solvent, and chemical shifts are given in parts per million (δ) downfield from TMS as the internal standard. Mass spectral data were recorded using an LTQ Orbitrap XL. Flash chromatography employed silica gel 60 (230–400 mesh), while TLC was carried out using alumina plates with a 0.25 mm silica layer (Kieselgel 60 F254; Merck). Compounds were visualized by staining with KMnO_4 solution. The starting compound *N*-2,3-butadien-1-ylbenzenemethanamine was synthesized following the literature procedure.²⁶

***N*-Benzyl-*N*-buta-2,3-dienyl-2-chloroacetamide (1)**

N-2,3-Butadien-1-ylbenzenemethanamine (4 mmol, 636 mg, 1 equiv) was added to a flame-dried flask under N_2 pressure containing anhyd DCM (10 mL) and Et_3N (8 mmol, 1.11 mL, 2 equiv). Then, chloroacetyl chloride (4.8 mmol, 0.38 mL, 1.2 equiv) was added dropwise to the stirred solution at 0 °C. The solution was stirred for 1 h at 0 °C and then poured into a separatory funnel containing aq 2 M HCl (10 mL). The aqueous layer was extracted with DCM. The organic layers were collected, washed with brine, dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude oil was purified by silica gel flash chromatography (SiO_2 , 1:1 v/v PE– Et_2O) to give a thick orange oil; yield: 735 mg (78%).

IR (ATR): 2927, 1651, 1422, 1139, 850, 698 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.50–7.04 (m, 5 H, *both rotamers*), 5.21–5.04 (m, 1 H, *both rotamers*), 4.88 (dt, J = 6.3, 3.0 Hz, 2 H, *major*), 4.83–4.75 (m, 2 H, *minor*), 4.62 (s, 2 H, *both rotamers*), 4.16 (s, 2 H, *major*), 4.07 (s, 2 H, *minor*), 4.05–3.96 (m, 2 H, *minor*), 3.92–3.84 (m, 2 H, *major*).

^{13}C NMR (101 MHz, CDCl_3): δ = 209.3, 208.5, 166.9, 166.8, 136.6, 135.8, 129.0, 128.7, 128.3, 127.9, 127.6, 126.6, 86.6, 85.6, 78.1, 76.7, 50.7, 48.81, 45.5, 44.7, 41.3, 41.2.

HRMS (ESI): m/z calcd for $[\text{C}_{13}\text{H}_{14}\text{ClNO} + \text{Na}]^+$: 258.06561; found: 258.06528.

Synthesis of Piperazinones; General Procedure

A mixture of **1** (0.1 mmol), ArI (0.12 mmol), RNH_2 (0.3 mmol), AgNO_3 (0.05 mmol), Cs_2CO_3 (0.3 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (0.01 mmol) in CH_3CN (5 mL) was heated in a N_2 atmosphere at reflux for 16 h. After completion of the reaction, the mixture was cooled to rt, and the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography to afford the product.

Combinatorial Synthesis of Piperazinones; General Procedures (Scheme 3)

A: A mixture of **1** (0.2 mmol), three aryl iodides (0.08 mmol each), benzylamine (0.6 mmol), AgNO_3 (0.1 mmol), Cs_2CO_3 (0.6 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (0.02 mmol) in CH_3CN (10 mL) was heated in a N_2 atmosphere at reflux for 16 h. After completion of the reaction, the mixture was cooled to rt, and the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography to afford the products **3j,a,b**.

B: A mixture of **1** (0.2 mmol), 2-iodonaphthalene (0.24 mmol), three amines (0.2 mmol each), AgNO_3 (0.1 mmol), Cs_2CO_3 (0.6 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (0.02 mmol) in CH_3CN (10 mL) was heated in a N_2 atmosphere at reflux for 16 h. After completion of the reaction, the mixture was cooled to rt, and the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography to afford the products **3a,i,g**.

C: A mixture of **1** (0.2 mmol), two aryl iodides (0.12 mmol each), two amines (0.3 mmol each), AgNO_3 (0.1 mmol), Cs_2CO_3 (0.6 mmol), and $\text{Pd}(\text{PPh}_3)_4$ (0.02 mmol) in CH_3CN (10 mL) was heated in a N_2 atmosphere at reflux for 16 h. After completion of the reaction, the mixture was cooled to rt, and the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography to afford the products **3a,g,d,4**.

1,4-Dibenzyl-5-[1-(4-methoxyphenyl)vinyl]piperazin-2-one (2)

Compound **2** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (26.1 mg, 63%) as an orange oil.

IR (ATR): 3028, 1651, 1510, 1246, 698 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.50 (d, J = 8.6 Hz, 2 H), 7.33–7.20 (m, 10 H), 6.87 (d, J = 8.6 Hz, 2 H), 5.50 (s, 1 H), 5.33 (s, 1 H), 4.80 (d, J = 14.7 Hz, 1 H), 4.33 (d, J = 14.6 Hz, 1 H), 4.13 (d, J = 12.9 Hz, 1 H), 3.82 (s, 3 H), 3.63 (dd, J = 9.7, 4.1 Hz, 1 H), 3.55 (d, J = 17.0 Hz, 1 H), 3.50–3.39 (m, 1 H), 3.22 (dd, J = 12.2, 4.1 Hz, 1 H), 3.10 (d, J = 12.9 Hz, 1 H), 2.97 (d, J = 17.0 Hz, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.3, 159.6, 144.9, 137.5, 136.5, 131.8, 128.9, 128.7, 128.4, 128.2, 127.9, 127.6, 127.3, 116.3, 113.8, 64.0, 58.2, 55.7, 55.3, 50.2, 49.4.

HRMS (ESI): m/z calcd for $[\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_2 + \text{H}]^+$: 413.22235; found: 413.22139.

1,4-Dibenzyl-5-(1-naphthalen-2-ylvinyl)piperazin-2-one (3a)

Compound **3a** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (35.1 mg, 81%) as an orange oil.

IR (ATR): 3028, 2922, 1651, 1128, 752, 697 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.04 (s, 1 H), 7.82 (dd, J = 9.3, 5.5 Hz, 3 H), 7.61 (dd, J = 8.6, 1.4 Hz, 1 H), 7.49 (dd, J = 6.4, 3.1 Hz, 2 H), 7.28 (dt, J = 6.3, 5.5 Hz, 10 H), 5.71 (s, 1 H), 5.51 (s, 1 H), 4.81 (d, J = 14.7 Hz, 1 H), 4.34 (d, J = 14.7 Hz, 1 H), 4.21 (d, J = 12.9 Hz, 1 H), 3.79 (dd, J = 9.4, 4.2 Hz, 1 H), 3.62 (d, J = 17.1 Hz, 1 H), 3.51 (dd, J = 12.1, 9.5 Hz, 1 H), 3.30 (dd, J = 12.2, 4.2 Hz, 1 H), 3.19 (d, J = 13.0 Hz, 1 H), 3.03 (d, J = 17.0 Hz, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.3, 145.5, 137.4, 136.7, 136.49, 133.2, 133.0, 128.9, 128.7, 128.4, 128.3, 128.2, 128.1, 127.6, 127.6, 127.4, 126.4, 126.3, 125.7, 124.9, 118.3, 63.7, 58.4, 55.7, 50.1, 49.4.

HRMS (ESI): m/z calcd for $[\text{C}_{30}\text{H}_{28}\text{N}_2\text{O} + \text{H}]^+$: 433.22744; found: 433.22665.

1,4-Dibenzyl-5-[1-(4-fluorophenyl)vinyl]piperazin-2-one (3b)

Compound **3b** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (27.6 mg, 69%) as an orange oil.

IR (ATR): 2921, 1651, 1507, 1226, 840, 698 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.49 (dd, J = 8.4, 5.5 Hz, 2 H), 7.36–7.18 (m, 10 H), 7.01 (t, J = 8.6 Hz, 2 H), 5.51 (s, 1 H), 5.37 (s, 1 H), 4.77 (d, J = 14.6 Hz, 1 H), 4.36 (d, J = 14.6 Hz, 1 H), 4.07 (d, J = 13.0 Hz, 1 H), 3.64–3.68 (m, 1 H), 3.54 (d, J = 17.1 Hz, 1 H), 3.47–3.38 (m, 1 H), 3.24 (dd, J = 12.2, 4.2 Hz, 1 H), 3.15 (d, J = 13.0 Hz, 1 H), 3.00 (d, J = 17.1 Hz, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.2, 162.6 (J_{CF} = 246 Hz), 144.7, 137.3, 136.4, 135.4, 135.4, 128.8, 128.7, 128.6, 128.5, 128.5, 128.2, 127.6, 127.4, 117.7, 115.4, 115.2, 63.5, 58.0, 55.4, 49.6, 49.4.

HRMS (ESI): m/z calcd for $[\text{C}_{26}\text{H}_{25}\text{FN}_2\text{O} + \text{H}]^+$: 401.20237; found: 401.20150.

1,4-Dibenzyl-5-[1-(2-methoxyphenyl)vinyl]piperazin-2-one (3c)

Compound **3c** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (23.4 mg, 57%) as light brown, amorphous solid; mp 46–51 °C.

IR (ATR): 2912, 1640, 1492, 1245, 744, 700 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.34–7.21 (m, 9 H), 7.18 (d, J = 7.2 Hz, 2 H), 7.11 (dd, J = 7.3, 1.1 Hz, 1 H), 6.91 (t, J = 7.4 Hz, 1 H), 6.82 (d, J = 8.3 Hz, 1 H), 5.54 (s, 1 H), 5.37 (s, 1 H), 4.82 (d, J = 14.5 Hz, 1 H), 4.35 (d, J = 14.6 Hz, 1 H), 4.19 (d, J = 13.1 Hz, 1 H), 3.68 (dd, J = 8.5, 3.8 Hz, 1 H), 3.55 (s, 3 H), 3.54–3.47 (m, 2 H), 3.36 (dd, J = 12.0, 8.7 Hz, 1 H), 3.04 (dd, J = 24.5, 15.2 Hz, 2 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.6, 156.5, 146.6, 138.3, 136.8, 131.3, 130.2, 129.1, 128.7, 128.6, 128.4, 128.3, 127.5, 127.1, 120.8, 117.9, 110.6, 61.2, 57.8, 55.5, 54.9, 50.6, 49.4.

HRMS (ESI): m/z calcd for $[\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_2 + \text{H}]^+$: 413.22235; found: 413.22128.

1,4-Dibenzyl-5-[1-(3,5-dimethoxyphenyl)vinyl]piperazin-2-one (3d)

Compound **3d** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (37.2 mg, 84%) as a light yellow oil.

IR (ATR): 2935, 1651, 1588, 1154, 734, 698 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.40–7.17 (m, 10 H), 6.65 (d, J = 2.1 Hz, 2 H), 6.42 (s, 1 H), 5.58 (s, 1 H), 5.42 (s, 1 H), 4.76 (d, J = 14.7 Hz, 1 H), 4.36 (d, J = 14.7 Hz, 1 H), 4.16 (d, J = 13.0 Hz, 1 H), 3.77 (s, 6 H), 3.64–3.36 (m, 3 H), 3.23 (dd, J = 12.2, 4.1 Hz, 1 H), 3.12 (d, J = 13.0 Hz, 1 H), 2.98 (d, J = 17.0 Hz, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.2, 160.7, 145.7, 141.8, 137.5, 136.5, 128.8, 128.7, 128.4, 128.2, 127.6, 127.4, 118.1, 105.1, 99.9, 63.7, 58.3, 55.7, 55.4, 50.3, 49.4.

HRMS (ESI): m/z calcd for $[\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_3 + \text{H}]^+$: 443.23292; found: 443.23235.

1,4-Dibenzyl-5-[1-(3,4-dichlorophenyl)vinyl]piperazin-2-one (3e)

Compound **3e** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (26.2 mg, 58%) as an orange oil.

IR (ATR): 2922, 1647, 1453, 908, 728, 697 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.68 (d, J = 1.6 Hz, 1 H), 7.37–7.21 (m, 12 H), 5.56 (s, 1 H), 5.40 (s, 1 H), 4.77 (d, J = 14.6 Hz, 1 H), 4.39 (d, J = 14.6 Hz, 1 H), 4.03 (d, J = 12.9 Hz, 1 H), 3.63 (dd, J = 8.8, 4.5 Hz, 1 H), 3.54 (d, J = 17.1 Hz, 1 H), 3.40 (dd, J = 12.2, 9.0 Hz, 1 H), 3.25 (dd, J = 12.3, 4.4 Hz, 1 H), 3.19 (d, J = 13.0 Hz, 1 H), 3.00 (d, J = 17.1 Hz, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.1, 143.6, 139.1, 136.9, 136.3, 132.6, 132.1, 130.3, 128.8, 128.7, 128.7, 128.6, 128.5, 128.24, 127.7, 127.6, 126.1, 119.2, 63.0, 58.2, 55.1, 49.4, 48.9.

HRMS (ESI): m/z calcd for $[\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O} + \text{H}]^+$: 451.13385; found: 451.13339.

4-Allyl-1-benzyl-5-[1-(3,5-dimethoxyphenyl)vinyl]piperazin-2-one (3f)

Compound **3f** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (26.1 mg, 66%) as an orange oil.

IR (ATR): 2929, 1652, 1589, 1453, 1154, 697 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.33–7.19 (m, 5 H), 6.65 (d, J = 2.1 Hz, 2 H), 6.41 (s, 1 H), 5.89–5.64 (m, 1 H), 5.52 (s, 1 H), 5.31 (s, 1 H), 5.19 (t, J = 12.8 Hz, 2 H), 4.79 (d, J = 14.7 Hz, 1 H), 4.32 (d, J = 14.7 Hz, 1 H), 3.82–3.67 (m, 7 H), 3.63–3.43 (m, 2 H), 3.40–3.29 (m, 1 H), 3.14 (dd, J = 12.1, 4.1 Hz, 1 H), 3.02 (d, J = 17.0 Hz, 1 H), 2.77 (dd, J = 13.5, 7.6 Hz, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.3, 160.7, 145.3, 141.6, 136.5, 134.0, 128.6, 128.1, 127.5, 118.6, 118.6, 105.1, 99.8, 63.8, 56.8, 55.7, 55.4, 50.2, 49.3.

HRMS (ESI): m/z calcd for $[\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_3 + \text{H}]^+$: 393.21727; found: 393.21712.

1-Benzyl-4-hexyl-5-(1-naphthalen-2-ylvinyl)piperazin-2-one (3g)

Compound **3g** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (27.9 mg, 65%) as an orange oil.

IR (ATR): 2926, 1651, 1453, 1270, 820, 699 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.01 (s, 1 H), 7.82–7.74 (m, 3 H), 7.58 (dd, J = 8.6, 1.7 Hz, 1 H), 7.49–7.43 (m, 2 H), 7.30–7.22 (m, 5 H), 5.63 (s, 1 H), 5.38 (s, 1 H), 4.83 (d, J = 14.7 Hz, 1 H), 4.28 (d, J = 14.7 Hz, 1 H), 3.84 (d, J = 16.9 Hz, 1 H), 3.63 (dd, J = 9.7, 4.0 Hz, 1 H), 3.40 (dd, J = 12.0, 9.9 Hz, 1 H), 3.18 (dd, J = 12.1, 4.1 Hz, 1 H), 3.05 (d, J = 16.9 Hz, 1 H), 2.93–2.86 (m, 1 H), 2.20–2.13 (m, 1 H), 1.50–1.44 (m, 2 H), 1.30 (s, 2 H), 1.20 (d, J = 3.3 Hz, 2 H), 0.89 (d, J = 3.6 Hz, 2 H), 0.82 (t, J = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.5, 145.5, 136.8, 136.5, 133.2, 132.9, 128.6, 128.3, 128.2, 127.9, 127.5, 126.3, 126.2, 125.7, 124.9, 118.4, 64.6, 55.8, 53.9, 50.2, 49.3, 31.7, 26.3, 26.6, 22.6, 14.0.

HRMS (ESI): m/z calcd for $[\text{C}_{29}\text{H}_{34}\text{N}_2\text{O} + \text{H}]^+$: 427.27439; found: 427.27465.

1-Benzyl-5-[1-(3,5-dimethoxyphenyl)vinyl]-4-propylpiperazin-2-one (3h)

Compound **3h** was synthesized following the general procedure. Flash chromatography (SiO_2 , 2:1 v/v PE-Et₂O) afforded the product (38.0 mg, 96%) as an orange oil.

IR (ATR): 2960, 1652, 1589, 1203, 1154, 698 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.32–7.22 (m, 5 H), 6.66 (d, J = 2.0 Hz, 2 H), 6.40 (s, 1 H), 5.50 (s, 1 H), 5.28 (s, 1 H), 4.80 (d, J = 14.7 Hz, 1 H), 4.30 (d, J = 14.7 Hz, 1 H), 3.81–3.76 (m, 7 H), 3.46 (dd, J = 9.7, 3.9 Hz, 1 H), 3.41–3.28 (m, 1 H), 3.11 (dd, J = 12.0, 3.9 Hz, 1 H), 3.00 (d, J = 16.9 Hz, 1 H), 2.82 (dt, J = 12.1, 8.3 Hz, 1 H), 2.17–2.05 (m, 1 H), 1.56–1.46 (m, 2 H), 0.86 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.4, 160.6, 145.5, 141.7, 136.5, 128.6, 128.1, 127.5, 118.4, 105.1, 99.8, 64.5, 55.8, 55.8, 55.3, 50.2, 49.3, 19.9, 11.6.

HRMS (ESI): m/z calcd for $[\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_3 + \text{H}]^+$: 395.23292; found: 395.23166.

1-Benzyl-5-(1-naphthalen-2-ylvinyl)-4-phenethylpiperazin-2-one (3i)

Compound **3i** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE-Et₂O) afforded the product (36.5 mg, 82%) as an orange oil.

IR (ATR): 3026, 1651, 1495, 1129, 909, 698 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 7.90 (s, 1 H), 7.81–7.76 (m, 1 H), 7.73 (dd, J = 8.8, 3.7 Hz, 2 H), 7.51 (d, J = 8.6 Hz, 1 H), 7.46 (dd, J = 6.3, 2.8 Hz, 2 H), 7.32–7.25 (m, 3 H), 7.25–7.15 (m, 5 H), 7.07 (d, J = 7.2 Hz, 2 H), 5.60 (s, 1 H), 5.32 (s, 1 H), 4.83 (d, J = 14.7 Hz, 1 H), 4.27 (d, J = 14.7 Hz, 1 H), 3.96 (d, J = 16.8 Hz, 1 H), 3.70 (dd, J = 9.7, 4.0 Hz, 1 H), 3.41–3.32 (m, 1 H), 3.18 (ddd, J = 20.7, 19.5, 12.6 Hz, 3 H), 2.77 (t, J = 7.8 Hz, 2 H), 2.57–2.46 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.3, 145.3, 139.6, 136.7, 136.4, 133.2, 132.9, 128.7, 128.7, 128.4, 128.3, 128.1, 127.9, 127.6, 127.5, 126.2, 126.2, 126.1, 125.6, 124.9, 118.6, 64.2, 55.8, 55.6, 50.2, 49.4, 33.3.

HRMS (ESI): m/z calcd for $[\text{C}_{31}\text{H}_{30}\text{N}_2\text{O} + \text{H}]^+$: 447.24309; found: 447.24324.

1-Benzyl-5-[1-(3,5-dimethoxyphenyl)vinyl]-4-[2-(1H-indol-3-yl)ethyl]piperazin-2-one (3j)

Compound **3j** was synthesized following the general procedure. Flash chromatography (SiO_2 , Et₂O) afforded the product (25.6 mg, 51%) as an orange oil.

IR (ATR): 2928, 1639, 1589, 1154, 908, 730 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 8.04 (s, 1 H), 7.45 (d, J = 7.9 Hz, 1 H), 7.32–7.22 (m, 6 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.05 (t, J = 7.4 Hz, 1 H), 6.91 (d, J = 1.7 Hz, 1 H), 6.64 (d, J = 2.1 Hz, 2 H), 6.40 (s, 1 H), 5.48 (s, 1 H), 5.26 (s, 1 H), 4.79 (d, J = 14.7 Hz, 1 H), 4.36 (d, J = 14.7 Hz, 1 H), 3.98 (d, J = 16.8 Hz, 1 H), 3.74 (s, 6 H), 3.59 (dd, J = 9.6, 3.9 Hz, 1 H), 3.43–3.32 (m, 1 H), 3.29–3.12 (m, 3 H), 3.02–2.81 (m, 2 H), 2.57–2.42 (m, 1 H).

^{13}C NMR (101 MHz, CDCl_3): δ = 167.4, 160.7, 145.5, 141.8, 136.5, 136.2, 128.7, 128.1, 127.5, 127.4, 121.9, 121.7, 119.2, 118.7, 118.2, 113.7, 111.1, 105.2, 99.8, 63.9, 55.9, 55.3, 54.5, 50.3, 49.4, 30.3, 23.0.

HRMS (ESI): m/z calcd for $[\text{C}_{31}\text{H}_{33}\text{N}_3\text{O}_3 + \text{H}]^+$: 496.25947; found: 496.25915.

1-Benzyl-5-[1-(3,5-dimethoxyphenyl)vinyl]-4-(3-hydroxypropyl)piperazin-2-one (3k)

Compound **3k** was synthesized following the general procedure. Flash chromatography (SiO₂, EtOAc) afforded the product (24.4 mg, 60%) as an orange oil.

IR (ATR): 2933, 1636, 1589, 1203, 1154, 1062 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.38–7.21 (m, 5 H), 6.53 (d, *J* = 2.0 Hz, 2 H), 6.41 (s, 1 H), 5.54 (s, 1 H), 5.26 (s, 1 H), 4.73 (d, *J* = 14.6 Hz, 1 H), 4.43 (d, *J* = 14.6 Hz, 1 H), 3.88 (s, 1 H), 3.77 (s, 6 H), 3.68–3.55 (m, 2 H), 3.43–3.34 (m, 1 H), 3.23 (dd, *J* = 12.3, 4.1 Hz, 1 H), 3.14–3.00 (m, 2 H), 2.84–2.73 (m, 1 H), 2.42–2.32 (m, 1 H), 2.06 (s, 1 H), 1.84–1.76 (m, 1 H), 1.66–1.58 (m, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ = 166.8, 160.8, 145.6, 142.0, 136.3, 128.7, 128.2, 127.7, 117.8, 105.0, 104.3, 99.7, 63.2, 62.5, 55.4, 55.2, 52.2, 49.8, 49.5, 28.5.

HRMS (ESI): *m/z* calcd for [C₂₄H₃₀N₂O₄ + H]⁺: 411.22783; found: 411.22693.

1-Benzyl-5-[1-(3,5-dimethoxyphenyl)vinyl]-4-pyridin-2-ylmethylpiperazin-2-one (3l)

Compound **3l** was synthesized following the general procedure. Flash chromatography (SiO₂, EtOAc) afforded the product (28.3 mg, 64%) as an orange oil.

IR (ATR): 2936, 1651, 1589, 1204, 1154, 727 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.53 (d, *J* = 4.3 Hz, 1 H), 7.63 (t, *J* = 8.1 Hz, 1 H), 7.29 (dt, *J* = 15.4, 8.1 Hz, 6 H), 7.18–7.13 (m, 1 H), 6.64 (d, *J* = 1.6 Hz, 2 H), 6.41 (s, 1 H), 5.56 (s, 1 H), 5.42 (s, 1 H), 4.76 (d, *J* = 14.7 Hz, 1 H), 4.38 (d, *J* = 14.7 Hz, 1 H), 4.29 (d, *J* = 13.9 Hz, 1 H), 3.76 (d, *J* = 10.1 Hz, 6 H), 3.75–3.70 (m, 1 H), 3.60 (d, *J* = 17.0 Hz, 1 H), 3.50–3.37 (m, 2 H), 3.27 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.14 (d, *J* = 17.0 Hz, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ = 167.0, 160.7, 158.0, 149.3, 145.6, 141.9, 136.6, 136.4, 132.2, 132.1, 128.7, 128.4, 128.2, 127.6, 122.7, 122.2, 118.3, 105.2, 99.8, 63.5, 59.8, 56.0, 55.4, 50.2, 49.4.

HRMS (ESI): *m/z* calcd for [C₂₇H₂₉N₃O₃ + H]⁺: 444.22817; found: 444.22770.

{3-[4-Benzyl-2-(1-naphthalen-2-ylvinyl)-5-oxopiperazin-1-yl]-propyl}carbamic Acid *tert*-Butyl Ester (3m)

Compound **3m** was synthesized following the general procedure. Flash chromatography (SiO₂, Et₂O) afforded the product (27.1 mg, 56%) as a thick, yellow oil.

IR (ATR): 2973, 1699, 1645, 1497, 1168, 728 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.91 (s, 1 H), 7.79 (dd, *J* = 11.1, 5.7 Hz, 3 H), 7.54 (d, *J* = 8.5 Hz, 1 H), 7.49–7.45 (m, 2 H), 7.34–7.22 (m, 5 H), 5.64 (s, 1 H), 5.35 (s, 1 H), 4.76 (d, *J* = 14.6 Hz, 1 H), 4.55 (s, 1 H), 4.40 (d, *J* = 14.6 Hz, 1 H), 3.80 (d, *J* = 16.9 Hz, 1 H), 3.71 (dd, *J* = 9.3, 3.9 Hz, 1 H), 3.49–3.37 (m, 1 H), 3.24 (dd, *J* = 12.2, 4.0 Hz, 1 H), 3.12–3.07 (m, 3 H), 2.92 (dt, *J* = 12.6, 7.6 Hz, 1 H), 2.30–2.20 (m, 1 H), 1.64 (dd, *J* = 14.4, 7.2 Hz, 2 H), 1.37 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ = 167.1, 155.8, 145.5, 143.3, 136.8, 136.4, 133.2, 132.9, 130.5, 128.9, 128.7, 128.4, 128.2, 128.2, 128.1, 127.6, 127.5, 126.4, 126.3, 125.4, 124.7, 118.1, 78.9, 63.6, 55.3, 51.3, 49.9, 49.4, 38.6, 30.3, 28.4, 26.9.

HRMS (ESI): *m/z* calcd for [C₃₁H₃₇N₃O₃ + Na]⁺: 522.27271; found: 522.27227.

6-[4-Benzyl-2-(1-naphthalen-2-ylvinyl)-5-oxopiperazin-1-yl]hexanoic Acid Methyl Ester (3n)

Compound **3n** was synthesized following the general procedure. Flash chromatography (SiO₂, Et₂O) afforded the product (29.5 mg, 63%) as an orange oil.

IR (ATR): 2929, 1733, 1651, 1434, 1170, 728 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.99 (s, 1 H), 7.78 (t, *J* = 5.9 Hz, 3 H), 7.57 (d, *J* = 8.5 Hz, 1 H), 7.49–7.44 (m, 2 H), 7.27 (dt, *J* = 16.1, 7.1 Hz, 5 H), 5.63 (s, 1 H), 5.37 (s, 1 H), 4.81 (d, *J* = 14.7 Hz, 1 H), 4.30 (d, *J* = 14.7 Hz, 1 H), 3.81 (d, *J* = 16.9 Hz, 1 H), 3.68–3.60 (m, 4 H), 3.49–3.34 (m, 1 H), 3.19 (dd, *J* = 12.1, 3.9 Hz, 1 H), 3.05 (d, *J* = 16.9 Hz, 1 H), 2.89 (dt, *J* = 12.3, 7.9 Hz, 1 H), 2.21 (t, *J* = 7.5 Hz, 2 H), 1.61–1.47 (m, 5 H), 1.32 (dd, *J* = 14.2, 6.8 Hz, 1 H), 1.21 (dd, *J* = 14.0, 6.5 Hz, 1 H).

¹³C NMR (101 MHz, CDCl₃): δ = 174.0, 167.4, 145.4, 136.7, 136.5, 133.2, 132.9, 128.6, 128.2, 128.2, 127.9, 127.5, 127.5, 126.3, 126.2, 125.6, 124.9, 118.4, 64.4, 55.6, 53.6, 51.4, 50.1, 49.4, 33.9, 26.6, 26.3, 24.8.

HRMS (ESI): *m/z* calcd for [C₃₀H₃₄N₂O₃ + H]⁺: 471.26422; found: 471.26375.

[2-(2-[4-Benzyl-2-(1-naphthalen-2-ylvinyl)-5-oxopiperazin-1-yl]ethoxy)ethoxy]ethylcarbamic Acid *tert*-Butyl Ester (3o)

Compound **3o** was synthesized following the general procedure. Flash chromatography (SiO₂, EtOAc) afforded the product (29.0 mg, 51%) as an orange oil.

IR (ATR): 2867, 1704, 1645, 1171, 1118, 697 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.95 (s, 1 H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2 H), 7.67 (dd, *J* = 11.8, 7.1 Hz, 1 H), 7.55 (d, *J* = 1.7 Hz, 1 H), 7.49–7.46 (m, 2 H), 7.27 (dt, *J* = 10.3, 7.5 Hz, 5 H), 5.64 (s, 1 H), 5.39 (s, 1 H), 5.17 (s, 1 H), 4.79 (d, *J* = 14.6 Hz, 1 H), 4.33 (d, *J* = 14.7 Hz, 1 H), 3.95 (d, *J* = 17.1 Hz, 1 H), 3.77 (dd, *J* = 9.4, 4.0 Hz, 1 H), 3.65–3.45 (m, 8 H), 3.46–3.37 (m, 1 H), 3.25 (dt, *J* = 7.8, 5.6 Hz, 4 H), 3.18–3.10 (m, 1 H), 2.55–2.43 (m, 1 H), 1.43 (s, 9 H).

¹³C NMR (101 MHz, CDCl₃): δ = 167.4, 156.1, 145.5, 136.9, 136.5, 133.2, 132.9, 132.2, 132.1, 132.1, 131.9, 131.9, 129.0, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.6, 127.5, 126.9, 126.3, 126.2, 125.6, 124.9, 118.4, 79.1, 70.4, 70.3, 70.2, 69.5, 63.9, 56.5, 52.9, 49.9, 49.4, 40.4, 28.4.

HRMS (ESI): *m/z* calcd for [C₃₄H₄₃N₃O₅ + H]⁺: 574.32755; found: 574.33039.

4-[4-Benzyl-2-(1-naphthalen-2-ylvinyl)-5-oxopiperazin-1-yl]butyric Acid Methyl Ester (3p)

Compound **3p** was synthesized following the general procedure. Flash chromatography (SiO₂, Et₂O) afforded the product (27.1 mg, 61%) as a yellow oil.

IR (ATR): 2923, 1732, 1651, 1258, 1129, 699 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.93 (s, 1 H), 7.79 (dd, *J* = 12.2, 8.9 Hz, 3 H), 7.53 (d, *J* = 8.6 Hz, 1 H), 7.50–7.44 (m, 2 H), 7.28 (dt, *J* = 15.8, 7.5 Hz, 5 H), 5.63 (s, 1 H), 5.36 (s, 1 H), 4.77 (d, *J* = 14.6 Hz, 1 H), 4.36 (d, *J* = 14.7 Hz, 1 H), 3.82 (d, *J* = 16.9 Hz, 1 H), 3.68 (dd, *J* = 9.4, 4.0 Hz, 1 H), 3.55 (s, 3 H), 3.40 (dd, *J* = 18.9, 9.4 Hz, 1 H), 3.22 (dd, *J* = 12.2, 4.1 Hz, 1 H), 3.08 (d, *J* = 16.9 Hz, 1 H), 2.93 (dt, *J* = 12.4, 7.9 Hz, 1 H), 2.37–2.20 (m, 3 H), 1.81 (dd, *J* = 11.7, 5.8 Hz, 2 H).

¹³C NMR (101 MHz, CDCl₃): δ = 173.7, 167.2, 145.4, 136.8, 136.4, 133.2, 132.9, 128.9, 128.3, 128.2, 128.0, 127.6, 127.5, 126.3, 126.2, 125.5, 124.8, 118.2, 63.9, 55.4, 52.8, 51.4, 50.1, 49.4, 31.3, 21.9.

HRMS (ESI): m/z calcd for $[C_{28}H_{30}N_2O_3 + H]^+$: 443.23292; found: 443.23237.

{4-[4-Benzyl-2-(1-naphthalen-2-ylvinyl)-5-oxopiperazin-1-yl]butyl}carbamic Acid *tert*-Butyl Ester (3q)

Compound **3q** was synthesized following the general procedure. Flash chromatography (SiO_2 , Et_2O) afforded the product (25.7 mg, 50%) as a light yellow oil.

IR (ATR): 2929, 1704, 1645, 1502, 1167, 733 cm^{-1} .

1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.82–7.74 (m, 3 H), 7.55 (d, J = 8.6 Hz, 1 H), 7.51–7.42 (m, 2 H), 7.28 (ddd, J = 15.9, 12.2, 6.7 Hz, 5 H), 5.64 (s, 1 H), 5.36 (s, 1 H), 4.80 (d, J = 14.7 Hz, 1 H), 4.46 (s, 1 H), 4.33 (d, J = 14.7 Hz, 1 H), 3.80 (d, J = 16.9 Hz, 1 H), 3.67 (dd, J = 9.5, 4.0 Hz, 1 H), 3.47–3.38 (m, 1 H), 3.21 (dd, J = 12.2, 4.1 Hz, 1 H), 3.04 (dd, J = 18.2, 11.2 Hz, 3 H), 2.94–2.83 (m, 1 H), 2.27–2.16 (m, 1 H), 1.48 (s, 4 H), 1.42 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3, 155.9, 145.4, 136.8, 136.5, 133.2, 132.9, 128.7, 128.2, 128.2, 127.9, 127.6, 127.5, 126.3, 126.2, 125.6, 124.8, 118.2, 79.1, 64.1, 55.5, 53.3, 50.0, 49.4, 40.3, 30.3, 28.4, 27.6, 23.9.

HRMS (ESI): m/z calcd for $[C_{32}H_{39}N_3O_3 + H]^+$: 514.30642; found: 514.07750.

1-Benzyl-5-[1-(3,5-dimethoxyphenyl)vinyl]-4-hexylpiperazin-2-one (4)

Compound **4** was synthesized following the general procedure. Flash chromatography (SiO_2 , 1:2 v/v PE- Et_2O) afforded the product (28.8 mg, 66%) as an orange oil.

IR (ATR): 2927, 1652, 1590, 1204, 1154, 698 cm^{-1} .

1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 5 H), 6.65 (d, J = 2.1 Hz, 2 H), 6.40 (s, 1 H), 5.50 (s, 1 H), 5.28 (s, 1 H), 4.80 (d, J = 14.7 Hz, 1 H), 4.30 (d, J = 14.7 Hz, 1 H), 3.82 (d, J = 9.4 Hz, 1 H), 3.76 (s, 6 H), 3.46 (dd, J = 9.7, 4.0 Hz, 1 H), 3.38–3.29 (m, 1 H), 3.11 (dd, J = 12.0, 3.9 Hz, 1 H), 2.99 (d, J = 16.9 Hz, 1 H), 2.85 (dt, J = 12.2, 8.1 Hz, 1 H), 2.17–2.07 (m, 1 H), 1.51–1.44 (m, 2 H), 1.31–1.21 (m, 6 H), 0.86 (t, J = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.4, 160.7, 145.5, 141.8, 136.5, 128.6, 128.1, 127.5, 118.3, 105.2, 99.8, 64.5, 55.8, 55.3, 54.0, 50.3, 49.3, 31.8, 26.9, 26.7, 22.6, 14.0.

HRMS (ESI): m/z calcd for $[C_{27}H_{36}N_2O_3 + H]^+$: 514.30642; found: 514.30775.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References

- Costa, R. F.; Turones, L. C.; Cavalcante, K. V. N.; Rosa Júnior, I. A.; Xavier, C. H.; Rosseto, L. P.; Napolitano, H. B.; da Castro, P. F. S.; Neto, M. L. F.; Galvão, G. M.; Menegatti, R.; Pedrino, G. R.; Costa, E. A.; Martins, J. L. R.; Fajemiroye, J. O. *Front. Pharmacol.* **2021**, *12*, 666725.
- Heravi, M.; Zadsirjan, V. *RSC Adv.* **2020**, *10*, 44247.
- Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. *Org. Biomol. Chem.* **2016**, *14*, 6611.
- Zhang, T. Y. *Adv. Heterocycl. Chem.* **2017**, *121*, 1.
- St. Jean, D. J. Jr.; Fotsch, C. J. *Med. Chem.* **2012**, *55*, 6002.
- Peerzada, M. N.; Hamel, E.; Bai, R.; Supuran, C. T.; Azam, A. *Pharmacol. Therap.* **2021**, *225*, 107860.
- Kumari, S.; Carmona, A. V.; Tiwari, A. K.; Trippier, P. C. *J. Med. Chem.* **2020**, *63*, 12290.
- Subbaiah, M. A. M.; Meanwell, N. A. *J. Med. Chem.* **2021**, *64*, 14046.
- Ali, I.; Lone, M. N.; Al-Othman, Z. A.; Al-Warthan, A.; Sanagi, M. *Curr. Drug Targets* **2015**, *16*, 711.
- Poulie, C. B. M.; Bunch, L. *ChemMedChem* **2013**, *8*, 205.
- Gao, B.; Yang, B.; Feng, X.; Li, C. *Nat. Prod. Rep.* **2022**, *39*, 139.
- Joule, J. A. *Adv. Heterocycl. Chem.* **2016**, *119*, 81.
- Magriotis, P. A. *RSC Med. Chem.* **2020**, *11*, 745.
- Xu, S.; Sun, L.; Zalloum, W. A.; Huang, T.; Zhang, X.; Ding, D.; Shao, X.; Jiang, X.; Zhao, F.; Cocklin, S.; De Clercq, E.; Pannecouque, C.; Dick, A.; Liu, X.; Zhan, P. *Molecules* **2022**, *27*, 8415.
- Zou, P.; Guo, M.; Hu, J. *Expert Rev. Clin. Pharmacol.* **2022**, *15*, 747.
- Zhang, X.; Chen, S.; Zhang, L.; Zhang, Q.; Zhang, W.; Chen, Y.; Zhang, W.; Zhang, H.; Zhang, C. *Org. Lett.* **2021**, *23*, 2858.
- Doenhoff, M. J.; Cioli, D.; Utzinger, J. *Curr. Opin. Infect. Dis.* **2008**, *21*, 659.
- D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Puset, J.; Leroy, S.; Pietra, F. J. *Chem. Soc., Chem. Commun.* **1993**, 1305.
- Usmanova, L.; Dar'in, D.; Novikov, M. S.; Gureev, M.; Krasavin, M. *J. Org. Chem.* **2018**, *83*, 5859.
- Golebiowski, A.; Jozwik, J.; Klopfenstein, S. R.; Colson, A.-O.; Grieb, A. L.; Russell, A. F.; Rastogi, V. L.; Diven, C. F.; Portlock, D. E.; Chen, J. J. *J. Comb. Chem.* **2002**, *4*, 584.
- Dinsmore, C. J.; Beshore, D. C. *Org. Prep. Proced. Int.* **2002**, *34*, 367.
- Kolter, T.; Dahl, C.; Giannis, A. *Liebigs Ann. Chem.* **1995**, 625.
- Dinsmore, C. J.; Zartman, C. B. *Tetrahedron Lett.* **2000**, *41*, 6309.
- Goff, D. A. *Tetrahedron Lett.* **1998**, *39*, 1473.
- Beccalli, E. M.; Broggin, G.; Clerici, F.; Galli, S.; Kammerer, C.; Rigamonti, M.; Sottocornola, S. *Org. Lett.* **2009**, *11*, 1563.
- Jovanovic, M.; Petkovic, M.; Jovanovic, P.; Simic, M.; Tasic, G.; Eric, S.; Savic, V. *Eur. J. Org. Chem.* **2019**, 295.