www.saber.ula.ve/avancesenquimica
Avances en Química, 19(3), 109-116 (2024)
Artículo científico

A synthetic approach toward symmetrically substituted 1,4-bis(cinnamyl)piperazines

Gheorghe Roman*, Mihaela Balan-Porcărașu

Petru Poni Institute of Macromolecular Chemistry, Iași 700847, Romania

(*) gheorghe.roman@icmpp.ro

Recibido: 05/12/2024 **Revisado**: 27/12/2024 **Aceptado**: 31/12/2024

Abstract

A three-step pathway has been designed for the preparation of symmetrically substituted 1,4-bis(cinnamyl)piperazines starting from β-amino ketones. The approach comprises the bis-N-alkylation of piperazine with hydrochlorides of dimethylamine-based ketone Mannich bases, reduction of the resulting piperazine-containing amino ketones with $NaBH_4$, and subsequent acid-catalyzed dehydration of the intermediate secondary γ-amino alcohols. The proposed method for obtaining the title piperazines has been validated through the synthesis of four analogs having either phenyl, or 4-chlorophenyl, or 4-bromophenyl or 2-naphthalenyl moieties as the aromatic part of the cinnamyl fragment.

Keywords: Mannich bases; Reduction; Amino alcohols; Dehydration

Resumen

Un enfoque sintético para la obtención de 1,4-bis(cinamil)piperazinas sustituidas simétricamente. Se ha diseñado una vía de tres pasos para la preparación de 1,4-bis(cinamil)piperazinas sustituidas simétricamente a partir de β-aminocetonas. El enfoque comprende la bis-N-alquilación de piperazina con clorhidratos de bases de Mannich de cetonas basadas en dimetilamina, la reducción de las aminocetonas resultantes que contienen piperazina con NaBH4 y la posterior deshidratación catalizada por ácido de los γ-aminoalcoholes secundarios intermedios. El método propuesto para obtener las piperazinas del título se ha validado mediante la síntesis de cuatro análogos que tienen restos fenilo, 4-clorofenilo, 4-bromofenilo o 2-naftalenilo como parte aromática del fragmento cinamilo.

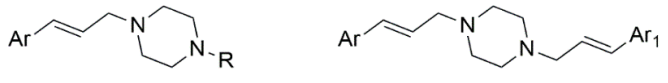
Palabras claves: bases de Mannich; reducción; aminoalcoholes; deshidratación

Introduction

An important number of synthetic substances feature piperazine as part of their molecular structure, and piperazine derivatives are essential components of many industrial products (such as plastics, resins, pesticides, components for brake fluids, etc.). Many synthetic piperazine-containing compounds exhibit important pharmacological properties[1–5]. Piperazine is the core structure in currently marketed drugs for the treatment of *angina pectoris* (ranolazine, trimetazidine), allergic rhinitis (levocetirizine), nausea, vomiting, and dizziness caused by motion sickness (meclizine, cinnarizine), erectile disfunction (sildenafil, vardenafil), or various types of cancer (imatinib). In addition, several in-use antibiotics belonging to fluoroquinolones (ciprofloxacin, norfloxacin), along with macrocyclic antibiotics rifampicine and rifapentine, or oxazolidinone antibiotic ranbezolid present a piperazine moiety in their structure. More importantly, piperazine-containing drugs are used for the treatment of mental and neuropsychological disorders such as major depressive disorder, anxiety disorders or addiction (*e.g.*, buspirone, trazodone, vortioxetine), or in medication primarily used to manage psychosis (aripiprazole, olanzapine, prochlorperazine). While nowadays research directed to the discovery of novel antipsychotics and antidepressants still places piperazine highly amongst the scaffolds to be incorporated into the structures of drug candidates[6,7], piperazines have emerged as molecular fragments in a number of drug candidates developed as substances with antibiabetic activity[8], molecules with analgesic and anti-inflammatory action[9], antivirals and HIV-inhibitors[10,11], anticancer agents[12,13], trypanomicide compounds[14], hybrids with anti-mycobacterial activity[15] or antioxidant properties[16]. Amongst these drug candidates that feature a broad molecular diversity, examples of several *N*-cinnamylpiperazines can be encountered in libraries developed for the inhibition of proliferation of pancreatic cancer cells[17], in a collection of compounds with anti-convulsant activity[18], as substances that could be incorporated as tyrosinase and melanin inhibitors in depigmentation drugs with minimum side effects[19], as GPR4 receptor modulators for treating angiogenesis, pain, autoimmune and inflammatory diseases[20], in a series of antibacterial compounds that inhibit the formation of biofilms[21], in a study aiming at developing derivatives of Incentrom A (1-(9H-carba-

zol-9-yl)-3-(4-cinnamylpiperazin-1-yl)propan-2-ol) as small molecules that perturb the normal functioning of centromere (a specialized chromosomal structure responsible for accurate chromosome segregation) in *Saccharomyces cerevisiae*[22], in libraries of derivatives of bile acid capable of inducing pro-apoptotic processes in several cancer cell lines[23], or as potential candidates for the reversal of P-gp-dependent multidrug resistance in cancer chemotherapy[24]. On the other hand, piperazine-containing compounds have been repurposed from less effective anti-depressant agents or opioid analgesics to designer drugs meant to evade the legal restrictions of the well-known drugs of abuse[25]. As part of the last decade's surge in synthetic non-fentanyl opioid psychoactive substances, several novel recreational drugs that have an *N*-cinnamylpiperazine fragment have been found on the illicit drug market recently. From a structural point of view, they all appear to be close analogs of bucinnazine (1-butyryl-4-cinnamylpiperazine, (*E*)-1-(4-cinnamylpiperazin-1-yl)-butan-1-one) that have at least one additional methyl group in their structure compared to the prototypical compound[26,27].

Several general synthetic approaches have been consistently reported in the literature for the installment of the cinnamyl fragment in the structure of *N*-cinnamylpiperazines **1** (Fig. 1). They rely on the alkylation of piperazine derivatives with cinnamyl halides[24,28–31], on the reductive amination of piperazines with cinnamaldehydes[28,32–34], and on the reduction of piperazine-containing carboxamides[35–37]. Because piperazine itself may act as a bifunctional substrate in these reactions, the previously mentioned approaches for the synthesis of mono-substituted cinnamylpiperazines often use a piperazine derivative substituted at one nitrogen atom with a protective group (*e.g.*, *t*-butoxycarbonyl, formyl) which can be easily removed once the cinnamyl moiety is in place. In contrast to the wealth of information on *N*-cinnamylpiperazines and their derivatives, bis(*N*,*N*′-cinnamyl)piperazines **2** (either symmetrically or unsymmetrically substituted, Fig. 1) are under-represented in scientific literature, as demonstrated by a search that showed that only three distinct compounds **2** (Ar = Ar_1 = C_6H_5; Ar = Ar_1 = 2-$H_3COC_6H_4$; Ar = C_6H_5, Ar_1 = 2-$O_2NC_6H_4$) with this structure can be found in five sources (three articles and two patents).



1 2

Fig. 1: General structures of *N*-cinnamylpiperazines **1** and bis(*N*,*N*′-cinnamyl)piperazines **2**.

On the other hand, in the century that has passed since the first report on the aminomethylation of aryl methyl ketones, a rich and diversified chemistry that relates to the Mannich reaction and its products generally known as Mannich bases has become accessible for the synthesis of compounds that could be otherwise difficult to obtain[38–40]. The use of piperazines as amine reagents in the Mannich reaction has been reported scarcely, and not always in journals that are readily available. Starting from piperazine-containing ketone bis-Mannich bases, the present study aims at reporting a hitherto unemployed synthetic approach for the preparation of several symmetrically substituted piperazines **2**, and to structurally characterize these compounds that belong to a scarcely known class of compounds.

Experimental

Materials and methods

Piperazine, $NaBH_4$, glacial acetic acid, aq. 36% HCl and the solvents used for the synthesis and purification of intermediates and final products were purchased from Merck–Sigma–Aldrich and were used without prior purification. Direct aminomethylation of the corresponding aryl methyl ketones with paraformaldehyde and dimethylamine hydrochloride using a method that was previously reported[41] provided the starting ketone Mannich base hydrochlorides **3**–**6**, whose analysis using NMR spectroscopy confirmed their structure and purity. NMR spectra were recorded on a Bruker Avance NEO spectrometer at 400 MHz, with a 5 mm probe for direct detection of H, C, F, Si. The residual signals of the deuterated solvents were used as internal standard (DMSO-d_6: δ = 2.51 ppm for ^{1}H and δ = 39.47 ppm for ^{13}C; $CDCl_3$: δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C). The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was based on additional 2D homo- and hetero-nuclear correlation experiments (H,H-COSY, H,C-HSQC and H,C-HMBC). For NMR analysis purposes, the numbering of the carbon atoms in the structure of the compounds reported in this study is given in Scheme 1. Melting points were taken on a Mel Temp II apparatus and are uncorrected. Elemental analysis was performed on a Vario EL III CHNS analyzer.

*Synthesis of piperazine-containing amino ketones **7–10***

A solution of piperazine (344 mg, 4 mmol) in distilled water (10 mL) was added in one portion to the efficiently stirred solution of the ketone Mannich base hydrochloride **3**–**6** (8 mmol) in distilled water (50 mL). The resulting mixture was stirred at room temperature for 24 h, then the solid material was filtered, thoroughly washed with distilled water, air-dried, and recrystallized from the appropriate solvent.

3,3'-(Piperazine-1,4-diyl)bis(1-phenylpropan-1-one) **7**. Colorless crystals from 96% ethanol (1.15 g, 82%), mp 146–147 °C (literature mp 141 °C[42]; literature mp 141.5–144 °C[43]). ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 2.56 (br s, 8H, H1), 2.84 (t, J = 7.6 Hz, 4H, H2), 3.19 (t, J = 7.6 Hz, 4H, H3), 7.42–7.49 (m, 4H, H7), 7.52–7.59 (m, 2H, H8), 7.95 (dd, J = 1.2 and 8.0 Hz, 4H, H6). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.3 (C3), 53.1 (C2), 53.2 (C1), 128.0 (C6), 128.6 (C7), 133.1 (C8), 137.0 (C5), 199.1 (C4).

3,3'-(Piperazine-1,4-diyl)bis[1-(4-chlorophenyl)propan-1-one] **8**. Colorless crystals from 96% ethanol (1.29 g, 77%), mp 168–169 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 2.55 (br s, 8H, H1), 2.82 (t, J = 7.6 Hz, 4H, H2), 3.14 (t, J = 7.6 Hz, 4H, H3), 7.43 (d, J = 8.8 Hz, 4H, H7), 7.89 (d, J = 8.8 Hz, 4H, H6). ^{13}C NMR

($CDCl_3$, 100.6 MHz): δ 36.3 (C3), 53.0 (C2), 53.2 (C1), 129.0 (C7), 129.4 (C6), 135.2 (C5), 139.6 (C8), 197.8 (C4).

3,3'-(Piperazine-1,4-diyl)bis[1-(4-bromophenyl)propan-1-one] 9. Colorless crystals from 96% ethanol (1.42 g, 70%), mp 159–160 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 2.54 (br s, 8H, H1), 2.82 (t, J = 7.2 Hz, 4H, H2), 3.14 (t, J = 7.2 Hz, 4H, H3), 7.60 (d, J = 8.4 Hz, 4H, H7), 7.81 (d, J = 8.4 Hz, 4H, H6). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.3 (C3), 53.0 (C2), 53.2 (C1), 128.3 (C8), 129.5 (C6), 132.0 (C7), 135.6 (C5), 198.0 (C4).

3,3'-(Piperazine-1,4-diyl)bis[1-(naphthalen-2-yl)propan-1-one] 10. Colorless crystals from 96% ethanol–chloroform 1:1 *v*/*v* (1.12 g, 62%), mp 184–185 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 2.62 (br s, 8H, H1), 2.92 (t, J = 7.2 Hz, 4H, H2), 3.33 (t, J =7.2 Hz, 4H, H3), 7.52–7.64 (m, 4H, H10, H11), 7.89 (mM 4H, H7, H9), 7.96 (d, J = 8.0 Hz, 2H, H12), 8.03 (dd, J = 2.0 and 8.4 Hz, 2H, H6), 8.48 (s, 2H, H14). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.3 (C3), 53.2 (C1), 53.3 (C2), 123.8 (C6), 126.8 (C11), 127.8 (C9), 128.5 (C7, C10), 129.6 (C12), 129.7 (C14), 132.5 (C13), 134.2 (C5), 135.6 (C8), 199.1 (C4).

Reduction of piperazine-containing amino ketones 7–10

Small portions of $NaBH_4$ (380 mg, 10 mmol) were added to the suspension of a ketone Mannich base **7**–**10** (2 mmol) in methanol (20 mL), and the resulting mixture was stirred in a stoppered flask at room temperature overnight. The solvent was removed under reduced pressure, water (50 mL) was then added to the solid material, the suspension was further stirred at room temperature for 30 min, then the solid material was filtered, washed thoroughly with water, air-dried, and recrystallized from an appropriate solvent.

3,3'-(Piperazine-1,4-diyl)bis(1-phenylpropan-1-ol) 11. Colorless crystals from 96% ethanol (460 mg, 65%), mp 153–155 °C (literature mp 158–161 °C[44]). ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 1.83–1.97 (m, 4H, H3), 1.95–3.67 (m, 12 H, H1, H2), 4.96 (dd, J = 4.4 and 6.8 Hz, 2H, H4), 6.59 (s, 2H, OH), 7.24–7.31 (m, 2H, H8), 7.33–7.43 (m, 8H, H6, H7). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 33.6 (C3), 53.2 (br, C1), 56.9 (C2), 75.6 (C4), 125.5 (C6), 127.0 (C8), 128.2 (C7), 144.7 (C5).

3,3'-(Piperazine-1,4-diyl)bis[1-(4-chlorophenyl)propan-1-ol] 12. Colorless crystals from 96% ethanol (675 mg, 80%), mp 179–181 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 1.72–1.92 (m, 4H, H3), 1.77–3.61 (m, 12 H, H1, H2), 4.91 (dd, J = 4.0 and 7.6 Hz, 2H, H4), 6.65 (s, 2H, OH), 7.30 (s, 8H, H6, H7). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 33.6 (C3), 53.1 (br, C1), 56.9 (C2), 75.0 (C4), 126.9 (C6), 128.4 (C7), 132.6 (C8), 143.3 (C5).

3,3'-(Piperazine-1,4-diyl)bis[1-(4-bromophenyl)propan-1-ol] 13. Colorless crystals from 96% ethanol–DMF (625 mg, 61%), mp 211–213 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 1.69–1.93 (m, 4H, H3), 1.80–3.60 (m, 12 H, H1, H2), 4.89 (dd, J = 3.6 and 7.2 Hz, 2H, H4), 6.66 (s, 2H, OH), 7.24 (d, J = 8.4 Hz, 4H, H6), 7.46 (d, J = 8.0 Hz, 4H, H7). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 33.5 (C3), 53.2 (br, C1), 56.9 (C2), 75.0 (C4), 120.7 (C8), 127.3 (C6), 131.3 (C7), 143.8 (C5).

3,3'-(Piperazine-1,4-diyl)bis[1-(naphthalen-2-yl)propan-1-ol] 14. Colorless crystals from 96% ethanol–DMF (700 mg, 77%), mp 206–207 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 1.88–2.07 (m, 4H, H3), 1.95–3.55 (m, 12H, H1, H2), 5.12 (dd, J = 4.0 and 6.8 Hz, 2H, H4), 6.71 (br s, 2H, OH), 7.38–7.53 (m, 6H, aromatic protons), 7.77–7.94 (m, 8H, aromatic protons). 13C NMR (CDCl3, 100.6 MHz): δ 33.6 (C3), 53.2 (br, C1), 57.0 (C2), 75.6 (C4), 123.9, 124.0, 125.5, 126.0, 127.6, 127.9 (2 carbon atoms), 132.7, 133.4, 142.2 (C5).

*Dehydration of piperazine-containing amino alcohols **11**–**14***

A mixture of an amino alcohol **11**–**14** (1 mmol), glacial acetic acid (5 mL) and aq. 36% HCl (3 mL) was heated at reflux temperature for 3 h. The mixture was allowed to reach room temperature and was then diluted under efficient stirring with water (50 mL). The solid material was filtered and washed thoroughly with water. Its suspension in 96% ethanol (10 mL) was treated with aq. 25% ammonia (0.5 mL) and stirred in a stoppered flask at room temperature for 3 h. The mixture was gradually diluted with water (20 mL), the solid was filtered, washed thoroughly with water, air-dried, and recrystallized from an appropriate solvent.

trans-1,4-Bis[3-(phenyl)prop-2-en-1-yl]piperazine 15. Colorless crystals from 96% ethanol (165 mg, 52%), mp 122–123 °C (literature mp 126–127 °C[45]) ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 2.56 (br s, 8H, H1), 3.20 (d, J = 6.8 Hz, 4H, H2), 6.29 (dt, J = 6.9 and 15.9 Hz 2H, H3), 6.48 (d, J = 16.0 Hz, 2H, H4), 7.23 (t, J = 7.2 Hz, 2H, H8), 7.31 (t, J = 7.5 Hz, 4H, H7), 7.38 (d, J = 7.8 Hz, 4H, H6). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 53.0 (C1), 61.0 (C2), 126.2 (C3), 126.3 (C6), 127.5 (C8), 128.6 (C7), 133.3 (C4), 136.8 (C5). *Anal*. Calc. for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.68; H, 8.05; N, 8.94.

trans-1,4-Bis[3-(4-chlorophenyl)prop-2-en-1-yl]piperazine 16. Colorless crystals from 96% ethanol (250 mg, 64%), mp 139–140 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 22.60 (br s, 8H, H1), 3.16 (d, J = 6.4 Hz, 4H, H2), 6.19–6.30 (m, 2H, H3), 6.54 (d, J = 16.0 Hz, 2H, H4), 7.25–7.30 (m, 8H, H6, H7, overlapped with solvent residual peak). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 53.2 (C1), 60.9 (C2), 127.3 (C3), 127.5 (C7), 128.7 (C6), 131.8 (C4), 133.1 (C8), 135.4 (C5). *Anal*. Calc. for $C_{22}H_{24}Cl_2N_2$: C, 68.22; H, 6.25; N, 7.23. Found: C, 67.96; H, 6.41; N, 7.08.

Hydrochloride 16·HCl. Yield 77%. Colorless solid, mp >280 °C. ^{1}H NMR (DMSO-d_6, 400.1 MHz): δ 3.26 (br s, 8H, H1), 3.85 (d, J = 6.8 Hz, 4H, H2), 6.25 (dt, J = 6.8 Hz and 15.9 Hz, 2H, H3), 6.86 (d, J = 16.0 Hz, 2H, H4), 7.44 (d, J = 8.8 Hz, 4H, H7), 7.52 (d, J = 8.4 Hz, 4H, H6). ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 47.7 (C1), 56.8 (C2), 119.7 (C3), 128.1 (C6), 128.4 (C7), 132.7 (C8), 134.3 (C5), 136.5 (C4).

trans-1,4-Bis[3-(4-bromophenyl)prop-2-en-1-yl]piperazine 17. Colorless crystals from 96% ethanol (325 mg, 68%), mp 163–164 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 2.56 (br s, 8H, H1), 3.15 (d, J = 6.8 Hz, 4H, H2), 6.21–6.32 (m, 2H, H3), 6.46 (d, J = 15.6 Hz, 2H, H4), 7.22 (d, J = 8.4 Hz, 4H, H6), 7.42 (d,

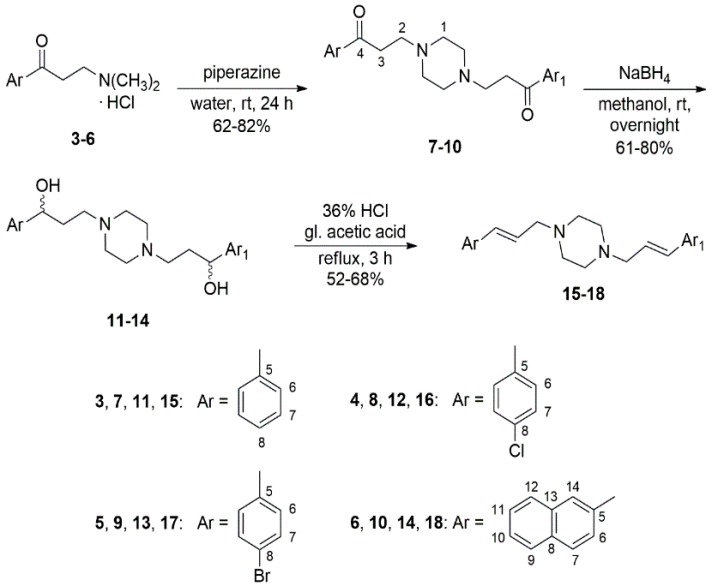
J = 8.4 Hz, 4H, H7). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 53.2 (C1), 60.9 (C2), 121.2 (C8), 127.4 (C3), 127.8 (C6), 131.6 (C7), 131.9 (C4), 135.8 (C5). *Anal.* Calc. for $C_{22}H_{24}Br_2N_2$: C, 55.48; H, 5.08; N, 5.88. Found: C, 55.73; H, 4.98; N, 6.03.

trans-1,4-Bis[3-(naphthalen-2-yl)prop-2-en-1-yl]piperazine 18. Colorless crystals from 96% ethanol–chloroform (225 mg, 54%), mp 189–190 °C. ^{1}H NMR ($CDCl_3$, 400.1 MHz): δ 2.63 (br s, 8H, H1), 3.25 (d, *J* = 6.8 Hz, 4H, H2), 6.42 (dt, *J* = 6.8 Hz and 15.6 Hz, 2H, H3), 6.70 (d, *J* = 15.6 Hz, 2H, H4), 7.38–7.49 (m, 4H, H10, H11), 7.61 (dd, *J* = 1.6 and 8.8 Hz, 2H, H6), 7.72 (s, 2H, H14), 7.74–7.83 (m, 6H, H7, H9, H12). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 53.3 (C1), 61.1 (C2), 123.5 (C6), 125.8 (either C10 or C11), 126.1 (either C10 or C11), 126.2 (C14), 127.0 (C3), 127.6 (C7 or C9), 127.9 (C12), 128.2 (C9 or C7), 132.9 (C8), 133.2 (C4), 133.6 (C13), 134.4 (C5). *Anal.* Calc. for $C_{30}H_{30}N_2$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.79; H, 7.01; N, 6.47.

Results and Discussion

The reaction sequence that has been devised to gain access to the target compounds involves three steps and employs ketone Mannich bases hydrochlorides **3**–**6** as starting materials (Scheme 1). The first step enables the incorporation of the piperazine ring in the structure of amino ketones **7**–**10**. Similar piperazine-containing amino ketones have been usually obtained through a direct Mannich reaction between aryl methyl ketones, paraformaldehyde and piperazine dihydrochloride, followed by the conversion of the piperazine-containing ketone Mannich base dihydrochlorides into the corresponding free bases by treatment with a base[42,43]. This report presents the amine exchange of dimethylamine in ketone Mannich base hydrochlorides **3**–**6** with piperazine as an alternative way for the preparation of amino ketones **7**–**10**. The reaction was conducted at room temperature in water, a solvent in which both compounds **3**–**6** and piperazine are soluble, whereas the products **7**–**10** are not, thus allowing their easy separation from the reaction mixture by filtration. Piperazine should be added to the solution of the ketone Mannich base hydrochloride in the form of aqueous solution; addition of solid piperazine to the reaction mixture may results in its slow dissolution owing to the coating of the piperazine flakes with reaction product, as it was observed in an early attempt toward the synthesis of amino ketone **8**. The reaction products normally begin to precipitate from the reaction mixture in a matter of minutes after piperazine has been added. Nonetheless, complete conversion was not reached in preliminary runs toward the synthesis of amino ketone **7** for which the reaction time was short (1 h, 4 h, or 8 h), as further amounts of piperazine-containing Mannich base continue to separate from the clear filtrate separated after the isolation of the amino ketone that had formed so far. Because only minute amounts of insoluble material could still be observed in the filtrate from one of these initial runs after one day, the reaction time was finally set for 24 h. The investigated amine exchange reaction most likely proceeds through a combination of two mechanisms. The first mechanism involves the nucleophilic substitution of the easily leaving dimethylamino group (in the form of dimethylamine hydrochloride) by piperazine, while the second mechanism entails the slow elimination of dimethylamine hydrochloride from the Mannich base hydrochloride and subsequent fast addition of piperazine to the resulting reactive vinyl ketone. The crude products isolated from this reaction presented high purity (according to their proton NMR spectra), with the exception of the material derived from 3-dimethylamino-1-(naphthalen-2-yl)propan-1-one hydrochloride **6**, whose proton NMR spectra showed signals that were assigned to the free base of compound **6** (based on the presence a singlet at 2.32 ppm that correspond to the protons in the two methyl groups of the dimethylamino moiety, and on the presence of two triplets that appear in the spectrum close and partially superimposed over the triplets associated with protons in the methylene groups of reaction products **10**). This finding suggests that, at least in this case, side reactions also occur during amine exchange. A plausible way for the formation of the free base of compound **6** is a process in which piperazine removes hydrochloric acid from the hydrochloride of Mannich base **6**, although the addition of dimethylamine (formed through the extrusion by piperazine of HCl from dimethylamine hydrochloride – the secondary product in the amine exchange) to the aforementioned reactive intermediate vinyl ketone could not be ruled out. The conversion of ketone Mannich base hydrochlorides **3**–**6** into amino ketones **7**–**10** proceeds with good to excellent yields, but the yields of the pure products are lowered to the values mentioned in Experimental through loss incurred during recrystallization. While amino ketone **7** could be recrystallized easily from 96% ethanol, recrystallization of amino ketone **8** required a rather large volume of the same solvent. Given the high purity of crude amino ketone **9** (that makes the product suitable for direct use in the next step of the reaction sequence), only a small amount (200 mg) required for analysis was recrystallized, and even this quantity necessitated a significant volume of 96% ethanol. It was found out that crude amino ketone **10** could be recrystallized without significant loss from a reasonable volume of a mixture of chloroform and ethanol, which also ensured the removal of the free base of compound **6** present as a minor impurity (approximately 8%) in the crude material isolated from the synthesis. NMR analysis of pure amino ketones **7**–**10** confirmed their structure through the presence in the proton spectra of these compounds of a broad singlet at approximately 2.5–2.6 ppm that integrates for eight protons and was assigned to the hydrogen atoms in the piperazine ring. Additionally, two triplets centered at approximately 2.8–2.9 ppm and 3.1–3.3 ppm that each integrate for four protons could be observed in the proton spectra of compounds **7**–**10**, and these signals were associated with the protons in the methylene groups in the oxopropyl fragment that links piperazine with the aryl moieties in the structure of these compounds. Three peaks, one at approximately 36 ppm and two close to one another and having a chemical shift of approximately 53 ppm,

were identified in the aliphatic region of the carbon spectra of amino ketones **7**–**10** as the signals corresponding to the carbon atom from the methylene group adjacent to the carbonyl group and to the two magnetically similar carbon atoms from the two distinct types of methylene groups (in the oxopropyl bridge and in the piperazine ring) adjacent to the nitrogen atom, respectively. The carbon atom of the carbonyl group was assigned the peak close to 200 ppm. The correct number of aromatic protons and aromatic carbon atoms was identified in the NMR spectra of each amino ketone **7**–**10**.



Scheme 1: Three-step synthetic approach to 1,4-bis(cinnamyl)piperazines from ketone Mannich bases.

Hydrogenation of the carbonyl group in amino ketones (either as free bases or as hydrochlorides) has been usually conducted using sodium borohydride in low molecular weight alcohols as solvents[38], although lithium aluminum hydride[46,47] or molecular hydrogen (very often in conjunction with catalysts designed to induce stereoselectivity)[48–50] have been also employed as reducing agents in this type of process. As both the stereoselectivity of the process and the configuration of the resulting secondary amino alcohols were not critical for the next stage of the reaction sequence leading to bis(cinnamyl)piperazines, reduction of piperazine-containing ketone Mannich bases **7**–**10** was conducted using an excess of sodium borohydride as reducing agent in methanol as solvent (Scheme 1). Given the low solubility of these specific amino ketones in cold methanol, the suspension of these Mannich bases was gradually treated with portions of the reducing agent over one hour. As reduction proceeded, the suspension of compound **7** gradually turned into a clear solution, whereas a solid material was present in the reaction flask throughout the reaction in the case of compounds **8**–**10**, indicating that the amino alcohols **12**–**14** are less soluble in methanol than analog **11**. In order to guarantee that the transformation of the substrate is complete, reduction was allowed to take place overnight in flask that was well-stoppered, with a view to facilitate the persistence of hydrogen in the reaction mixture. Removal of the solvent at the end of the reaction time was preferred as the more general approach toward the isolation of the crude reaction product, although direct dilution of the reaction mixture with a five-fold volume of water and filtration of the solid also allowed the isolation of amino alcohols **13** and **14** in amounts that were comparable to those recorded for the same compounds in runs in which removal of methanol was done prior to addition of water. The yields of the crude amino alcohols **11**–**14** are very good (95% to 85%), but recrystallization of compound **11** from 96% ethanol and of compound **13** from a mixture of DMF and 96% ethanol could not be accomplished without moderate loss of material. On the other hand, a large volume of 96% ethanol was required to recrystallize the crude sample of amino alcohol **12**. The structure analysis of amino alcohols **11**–**14** by NMR spectroscopy revealed several significant changes in the proton spectra of these compounds compared to the proton spectra of the parent amino ketones **7**–**10**. First, the peak corresponding to the protons in piperazine ring in the spectra of amino ketones **7**–**10** (which was already broad) becomes nearly flat in the spectra of amino alcohols **11**–**14**. This very broad peak superimposes the two multiplets associated with the diastereotopic protons of the methylene group in the hydroxypropyl fragment adjacent to the secondary alcohol group, while the multiplet assigned to the protons of the methylene group in the hydroxypropyl fragment neighboring piperazine's nitrogen atom shifts up-field compared to the position of the corresponding triplet associated with the same protons in the ^{1}H NMR spectra of amino ketones **7**–**10**. The proton at the carbon atom of the secondary alcohol function appears as a doublet of doublets at approximately 4.9 ppm in amino alcohols **11**–**13**, while the deshielding effect of the naphthalene moiety in compound **14** brings the value of this signal at 5.1 ppm. The use of $CDCl_3$ as NMR solvent for the spectroscopic analysis of these compounds also allowed the identification of the hydroxyl proton as a broad signal at approximately 6.6–6.7 ppm. As for ^{13}C NMR spectra of amino alcohols **11**–**14**, both the absence of any peak above 145 ppm and the presence of a signal at approximately 75 ppm confirm the transformation of the carbonyl group in amino ketones **7**–**10** into the secondary alcohol function in the aforementioned amino alcohols. Because the peaks in the aromatic region of the ^{1}H and 2D NMR spectra of compound **14** overlap one another to a large extent, the exact assignment of the protons and carbons from the naphthalene moiety could not be done.

Dehydration of amino alcohols obtained from ketone Mannich bases has been investigated only for a small number of substrates, and our best endeavor has identified mostly individual examples of dehydration of secondary γ-amino alcohols that are scattered over several isolated studies[51–58]. These processes take place in the presence of strong acids (HCl, HBr, H_2SO_4), except for one report in which anhydrous $CuSO_4$ was employed as dehydrating agent[51]. An initial attempt at the dehydration of piperazine-containing amino alcohol **12** was conducted in 48% HBr according to a procedure that was used for the preparation of 3-(dimethylamino)-1-(4-fluorophenyl)propene[56]. Rapid for-

mation of a copious amount of the insoluble dihydrobromide of the starting amino alcohol produced a solid mass that could no longer be rendered homogenous through stirring, and successive addition of small volumes of 48% HBr up to 5 mL did not improve the situation significantly. After workup, the crude product that was isolated was analyzed by thin layer chromatography and by proton NMR spectroscopy. Both investigations showed that the viscous oil that was isolated contained the desired compound, along with some starting material and at least two unknown impurities. Purification by crystallization with 96% ethanol and subsequent recrystallization of the obtained solid from 2-propanol allowed the isolation of the expected bis(cinnamyl)piperazine **16** in low yield (14%). To address the solubility issue during synthesis, a second attempt at obtaining compound **16** was performed in a mixture of acetic acid and 36% HCl, according to a previously reported procedure for the dehydration of tertiary amino alcohols[59] (Scheme 1). The solid substrate dissolved readily in the mixture of solvents, and reaction mixture remained homogenous for two hours, when a solid started to separate. More solid precipitated from the reaction mixture at the end of the reaction time when the mixture was slowly allowed to reach room temperature. Workup of the reaction mixture gave a solid, whose analysis by NMR proved that it was the pure dihydrochloride of the target bis(cinnamyl)piperazine **16** (yield 77%). Given its low solubility in DMSO-d_6, the dihydrochloride was converted into the free base by treatment of its suspension in ethanol with 25% aqueous ammonia. The procedure allowed a 94% recovery of the pure free base, whose structure was confirmed by recording its NMR spectra in $CDCl_3$.The same approach was then used to prepare the remaining bis(cinnamyl)piperazines **15**, **17** and **18** with high purity and in good yields (ranging from 70% to 91% for the crude product), which were further reduced by recrystallization that was performed in order to obtain the analytical samples of each compound. Analysis of their structure by proton NMR showed that the protons in the piperazine ring give a broad singlet (like the signal of the same protons in amino ketones **7**–**10**) at approximately 2.6 ppm, while the signal associated with the protons in the methylene group of the allyl fragment appears as a doublet close to 3.2 ppm. The signal assigned to the vinylic proton at the carbon adjacent to the methylene group presents as a partially superimposed doublet of triplets approximately in the range of 6.2–6.3 ppm (the signal is slightly deshielded in the case of naphthalene-containing derivative **18**). The remaining vinylic proton gives a doublet with a large value of the coupling constant (16 ppm), which indicates that the configuration at the double bond in these compounds is *trans*. The aliphatic region of the carbon NMR spectra of bis(cinnamyl)piperazines **15**–**18** presents only two peaks (one for the magnetically equivalent carbon atoms in the piperazine ring, and the second for the carbon atom of the methylene group in the allyl fragment), while correlation spectroscopy experiments allowed the identification of the two carbon atoms of the double bond at 126–127 ppm and 131–133 ppm, as well as the correct assignment of the peaks for the aromatic carbon atoms in the structure of each target bis(cinnamyl)piperazine.

Conclusions

This study is proof-of-concept that the designed approach toward symmetrically substituted 1,4-bis(cinnamyl)piperazines allows the preparation of these compounds. The required intermediates can be obtained in a facile manner, and very often sufficiently pure to be used as such in the next step. Nonetheless, the intermediate compounds in the devised reaction sequence can be purified using recrystallization from organic solvents, without any need for chromatographic separation, although purification results in reduction of yields. Because of this, even though the yields for each of the three steps are good to very good, the total yield (calculated by considering the purification process) for a specific 1,4-bis(cinnamyl)piperazine described in this report is modest (in the range of 25% to 40%). However, this approach could be a viable alternative for the synthesis of such compounds in those cases when the appropriately substituted cinnamyl halide required for the direct alkylation of piperazine is neither available nor easily accessible through synthesis. Furthermore, the use of ketone Mannich bases derived from propiophenone and its analogs, or from benzofused cyclic ketones such as α-tetralone and similar compounds according to this approach could allow the preparation of piperazines that would be otherwise obtained only in a difficult manner.

References

1. M Faizan, R Kumar, A Mazumder, Salahuddin, N Kukreti, A Kumar, *et al*. The medicinal chemistry of piperazines: A review. **Chemical Biology & Drug Design, 103(6)**, e14537 (2024).

2. MN Romanelli, D Manetti, L Braconi, S Dei, A Gabellini, E Teodori. The piperazine scaffold for novel drug discovery efforts: the evidence to date. **Expert Opinion on Drug Discovery, 17(9)**, 969–984 (2022).

3. A Rafiq, S Aslam, NA Mohsin, M Ahmad. Synthetic routes for the development of piperazine-based acetanilides and their medicinal importance. **Polycyclic Aromatic Compounds, 44(7)**, 4979–5007 (2023).

4. AK Rathi, R Syed, HS Shin, RV Patel. Piperazine derivatives for therapeutic use: a patent review (2010-present). **Expert Opinion on Therapeutic Patents, 26(7)**, 777–797 (2016).

5. A Sharma, S Wakode, F Fayaz, S Khasimbi, FH Pottoo, A Kaur. An overview of piperazine scaffold as promising nucleus for different therapeutic targets. **Current Pharmaceutical Design, 26(35)**, 4373–4385 (2020).

6. A Rathore, V Asati, SK Kashaw, S Agarwal, D Parwani, S Bhattacharya, *et al*. The recent development of piperazine and piperidine derivatives as antipsychotic agents. **Mini-Reviews in Medicinal Chemistry, 21(3)**, 362–379 (2021).

7. RR Kumar, B Sahu, S Pathania, PK Singh, MJ Akhtar, B Kumar. Piperazine, a key substructure for antidepressants: Its role in developments and structure-activity relationships. **ChemMedChem, 16(12)**, 1878–1901 (2021).

8. D Zolotareva, A Zazybin, A Dauletbakov, Y Belyankova, B Giner Parache, S Tursynbek, *et al*. Morpholine, piperazine, and piperidine derivatives as antidiabetic agents. **Molecules, 29(13)**, 3043 (2024).
9. A Jain, J Chaudhary, H Khaira, B Chopra, A Dhingra. Piperazine: A promising scaffold with analgesic and anti-inflammatory potential. **Drug Research (Stuttgart, Germany), 71(2)**, 62–72 (2021).
10. K Walayat, NA Mohsin, S Aslam, N Rasool, M Ahmad, A Rafiq, *et al*. Recent advances in the piperazine based antiviral agents: A remarkable heterocycle for antiviral research. **Arabian Journal of Chemistry, 16(12)**, 105292 (2023).
11. CA Salubi, HS Abbo, N Jahed, S Titinchi. Medicinal chemistry perspectives on the development of piperazine-containing HIV-1 inhibitors. **Bioorganic & Medicinal Chemistry, 99**, 117605 (2024).
12. V Sharma, R Das, D Sharma, S Mujwar, DK Mehta. Green chemistry approach towards piperazine: Anticancer agents, **Journal of Molecular Structure, 1292**, 136089 (2023).
13. K Walayat, NA Mohsin, S Aslam, M Ahmad. An insight into the therapeutic potential of piperazine-based anticancer agents. **Turkish Journal of Chemistry, 43(1)**, 1–23 (2019).
14. F Gomes Pernichelle, E Tavares Marcelino Alves, RA Massarico Serafim, E Igne Ferreira. The importance of the piperazine ring for the development of trypanomicide compounds. **ChemistrySelect, 8(33)**, e202302697 (2023).
15. PS Girase, S Dhawan, V Kumar, SR Shinde, MB Palkar, R Karpoormath. An appraisal of anti-mycobacterial activity with structure-activity relationship of piperazine and its analogues: A review. **European Journal of Medicinal Chemistry, 210**, 112967 (2021).
16. S Begum, M Rashida Anjum, G Poojitha Harisree, N Sivalakshmi, P Priyanka, K Bharathi. Antioxidant activity of piperazine compounds: A brief review. **Asian Journal of Chemistry, 32(9)**, 2105–2118 (2020).
17. AK Laskowska, AK Puszko, P Sosnowski, K Różycki, P Kosson, J Matalińska, *et al*. Opioid tripeptides hybridized with *trans*-1-cinnamylpiperazine as proliferation inhibitors of pancreatic cancer cells in two- and three-dimensional in vitro models. **ChemMedChem, 12(19)**, 1637–1644 (2017).
18. C Hu, Z-G Sun, C-X Wei, Z-S Quan. Synthesis and anticonvulsant activity of some cinnamylpiperazine derivatives. **Letters in Drug Design & Discovery, 7(9)**, 661–664 (2010).
19. H Raza, MA Abbasib, Aziz-ur-Rehman, SZ Siddiquib, M Hassan, Q Abbas, *et al*. Synthesis, molecular docking, dynamic simulations, kinetic mechanism, cytotoxicity evaluation of *N*-(substituted-phenyl)-4-{(4-[(E)-3-phenyl-2-propenyl]-1-piperazinyl} butanamides as tyrosinase and melanin inhibitors: *In vitro*, *in vivo* and *in silico* approaches. **Bioorganic Chemistry, 94**, 103445 (2020).
20. J Velcicky, W Miltz, B Oberhauser, D Orain, A Vaupel, K Weigand, *et al*. Development of selective, orally active GPR4 antagonists with modulatory effects on nociception, inflammation, and angiogenesis. **Journal of Medicinal Chemistry, 60(9)**, 3672−3683 (2017).
21. MA Abbasi, M Nazir, Aziz-ur-Rehman, SZ Siddiqui, SAA Shah, M Shahid. Synthesis and structure-activity relationship of 1-[(*E*)-3-phenyl-2-propenyl] piperazine derivatives as suitable antibacterial agents with mild hemolysis. **Scientia Iranica, Transaction C: Chemistry, Chemical Engineering, 26(6)**, 3375–3386 (2019).
22. H-Y Lee, Y Jung, W Kim, JH Kim, M-S Suh, SK Shin, *et al*. Structure–activity relationship studies of the chromosome segregation inhibitor, Incentrom A. **Bioorganic & Medicinal Chemistry Letters, 18(16)**, 4670–4674 (2008).
23. D Brossard, L El Kihel, M Clément, W Sebbahi, M Khalid, C Roussakis, *et al*. Synthesis of bile acid derivatives and in vitro cytotoxic activity with pro-apoptotic process on multiple myeloma (KMS-11), glioblastoma multiforme (GBM), and colonic carcinoma (HCT-116) human cell lines. **European Journal of Medicinal Chemistry, 45(7)**, 2912–2918 (2010).
24. S Dei, M Coronnello, G Bartolucci, D Manetti, MN Romanelli, C Udomtanakunchai, *et al*. Design and synthesis of new potent *N*,*N*-bis(arylalkyl)piperazine derivatives as multidrug resistance (MDR) reversing agents. **European Journal of Medicinal Chemistry, 147**, 7–20 (2018).
25. MD Arbo, ML Bastos, HF Carmo. Piperazine compounds as drugs of abuse. **Drug and Alcohol Dependence, 122(3)**, 174–185 (2012).
26. MM Vandeputte, A Cannaert, P Christophe, CP Stove. In vitro functional characterization of a panel of non-fentanyl opioid new psychoactive substances. **Archives of Toxicology, 94(11)**, 3819–3830 (2020).
27. JB Zawilska, P Adamowicz, M Kurpeta, J Wojcieszak. Non-fentanyl new synthetic opioids – An update. **Forensic Science International, 349,** 111775 (2023).
28. H Cai, W Chen, J Jiang, H Wen, X Luo, J Li, *et al*. Artificial intelligence-assisted optimization of antipigmentation tyrosinase inhibitors: *De novo* molecular generation based on a low activity lead compound. **Journal of Medicinal Chemistry, 67(9)**, 7260–7275 (2024).
29. J Penjisević, V Sukalović, D Andrić, S Kostić-Rajacić, V Soskić, G Roglić. 1-Cinnamyl-4-(2-methoxy-phenyl)piperazines: Synthesis, binding properties, and docking to dopamine (D2) and serotonin (5-HT1A) receptors. **Archiv der Pharmazie (Weinheim, Germany), 340(9)**, 456–465 (2007).
30. JI Andrés, J Alcázar, JM Alonso, RM Alvarez, MH Bakker, I Biesmans, *et al*. Discovery of a new series of centrally active tricyclic isoxazoles combining serotonin (5-HT) reuptake inhibition with α2-adrenoceptor blocking activity. **Journal of Medicinal Chemistry, 48(6)**, 2054–2071 (2005).
31. S Paudel, S Acharya, G Yoon, K-M Kim, SH Cheon. Design, synthesis and in vitro activity of 1,4-disubstituted piperazines and piperidines as triple reuptake inhibitors. **Bioorganic & Medicinal Chemistry, 25(7)**, 2266–2276 (2017).
32. L Liu, R Luo, J Tong, J Liao. Iridium-catalysed reductive allylic amination of α,β-unsaturated aldehydes. **Organic & Biomolecular Chemistry, 22(3)**, 585–589 (2023).

33. A Wu, Y Xu, X Qian, J Wang, J Liu. Novel naphthalimide derivatives as potential apoptosis-inducing agents: Design, synthesis and biological evaluation. **European Journal of Medicinal Chemistry, 44(11)**, 4674–4680 (2009).

34. S Boutin, R Maltais, J Roy, D Poirier. Synthesis of 17β-hydroxysteroid dehydrogenase type 10 steroidal inhibitors: Selectivity, metabolic stability and enhanced potency. **European Journal of Medicinal Chemistry, 209**, 112909 (2021).

35. IA Moussa, SD Banister, FN Akladios, SW Chua, M Kassiou. Effects of linker elongation in a series of *N*-(2-benzofuranylmethyl)-*N*′-(methoxyphenylalkyl)piperazine σ_1 receptor ligands. **Bioorganic & Medicinal Chemistry Letters, 21(19)**, 5707–5710 (2011).

36. DB Lewis, D Matecka, Y Zhang, L-W Hsin, CM Dersch, D Stafford, *et al*. Oxygenated analogues of 1-[2-(diphenyl-methoxy)ethyl]- and 1-[2-[bis(4-fluorophenyl)-methoxy]ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909) as potential extended-action cocaine-abuse therapeutic agents. **Journal of Medicinal Chemistry, 42(24)**, 5029–5042 (1999).

37. M Kurokawa, F Sato, Y Masuda, T Yoshida, Y Ochi, K Zushi, *et al*. Synthesis and biological activity of 11-[4-(cinnamyl)-1-piperazinyl]-6,11-dihydrodibenz[*b*,*e*]oxepin derivatives, potential agents for the treatment of cerebrovascular disorders. **Chemical & Pharmaceutical Bulletin, 39(10)**, 2564–2573 (1991).

38. M Tramontini. Advances in the chemistry of Mannich bases. **Synthesis, 1973(12)**, 703–775 (1973).

39. MM Hammouda, KM Elattar. Recent progress in the chemistry of β-aminoketones. **RSC Advances, 12(38)**, 24681–24712 (2022).

40. H Lv, Y Du, H Zhang, Y Zheng, Z Yan, N Dong. Advances in Mannich-type reactions based on the classification of compounds with activated α-H. **ChemistrySelect, 8(21)**, e202300173 (2023).

41. G Roman. Novel aminobenzenesulfonamides as potential inhibitors of carbonic anhydrases. **Revue Roumaine de Chimie, 69(3–4)**, 111–117 (2024).

42. C Mannich, D Lammering. Über die Synthese von β-Keto-basen aus fett-aromatischen Ketonen, Formaldehyd und sekundären Aminen. **Chemische Berichte, 55(10)**, 3510–3526 (1922).

43. V Valenta, M Bartošová, M Protiva. 1-[3-(2-Alkoxyphenoxy)-3-phenylpropyl]piperazines and some related compounds. **Collection of Czechoslovak Chemical Communications, 46(5)**, 1280–1287 (1981).

44. RE Lutz, NH Shearer. Antimalarials. Some piperazine derivatives. **Journal of Organic Chemistry, 12(6)**, 771–775 (1947).

45. H. Terayama, T Naruke, S Kasai, M Numata, H Nakayama, T Saito, *et al*. Studies on analgesic agents. XIII. Metabolic fate of 1-butyryl-4-cinnamylpiperazine hydrochloride (BCP-HCl) in rats. **Chemical & Pharmaceutical Bulletin, 21(1)**, 12–20 (1973).

46. S Huecas, L Araújo-Bazán, FM Ruiz, LB Ruiz-Ávila, RF Martínez, A Escobar-Peña, *et al*. Targeting the FtsZ allosteric binding site with a novel fluorescence polarization screen, cytological and structural approaches for antibacterial discovery. **Journal of Medicinal Chemistry, 64(9)**, 5730–5745 (2021).

47. F Lehmann, A Pettersen, EA Currier, V Sherbukhin, R Olsson, U Hacksell, *et al*. Novel potent and efficacious nonpeptidic urotensin II receptor agonists. **Journal of Medicinal Chemistry, 49(7)**, 2232–2240 (2006).

48. J Wang, D Liu, Y Liu, W Zhang. Asymmetric hydrogenation of β-amino ketones with the bimetallic complex RuPHOX-Ru as the chiral catalyst. **Organic & Biomolecular Chemistry, 11(23)**, 3855–3861 (2013).

49. MB Widegren, ML Clarke. Towards practical earth abundant reduction catalysis: Design of improved catalysts for manganese catalysed hydrogenation. **Catalysis Science & Technology, 9(21)**, 6047–6058 (2019).

50. X Zhao, Z Yang, Y Cheng, A Huang, F Hu, F Ling, *et al*. Divergent synthesis of β-hydroxy amides (esters) and γ-amino alcohols via Ir/*f*-diaphos catalyzed asymmetric hydrogenation. **Advanced Synthesis & Catalysis, 364(17)**, 3074–3080 (2022).

51. T Magdziarz, B Lozowicka, R Gieleciak, A Bak, J Polanski, Z Chilmonczyk. 3D QSAR study of hypolipidemic asarones by comparative molecular surface analysis. **Bioorganic & Medicinal Chemistry, 14(5)**, 1630–1643 (2006).

52. E Rudinger-Adler, J Büchi. Synthese einiger Benzyloxyphenyl-Derivative mit lokalanaesthetischer Wirkung. **Arzneimittel-Forschung, 29(9)**, 1326–1331 (1979).

53. H Igarashi, T Kurihara. Synthesis and pharmacology of basic sec-, tert-alcohols and derivatives (in Japanese). **Yakugaku Zasshi, 93(5)**, 554–565 (1973).

54. H Ohtaka, M Miyake, T Kanazawa, K Ito, G Tsukamoto. Benzylpiperazine derivatives. I. Syntheses and biological activities of 1-(2,3,4-trimethoxybenzyl)piperazine derivatives. **Chemical & Pharmaceutical Bulletin, 35(7)**, 2774–2781 (1987).

55. NJ Bunce. Photolysis of aryl chlorides with aliphatic amines. **Journal of Organic Chemistry, 47(10)**, 1948–1955 (1982).

56. M Van der Auweraer, A Vannerem, FC De Schryver. The electronic structures of intramolecular exciplexes with aliphatic amines as donors. **Journal of Molecular Structure, 84**, 343–352 (1982).

57. V Valenta, M Vlkova, M Valchar, K Dobrovsky, Z Polivka. Potential antidepressants: 3-Aryl-3-(arylthio)propylamines as selective inhibitors of 5-hydroxytryptamine re-uptake in the brain. **Collection of Czechoslovak Chemical Communications, 56(7)**, 1525–1533 (1991).

58. J Hine, MJ Skoglund. Double-bond-stabilizing abilities of 1-methyl-2-pyrrolyl, 9-anthryl, and *o*-tolyl substituents. **Journal of Organic Chemistry, 47(24)**, 4758–4766 (1982).

59. AF Casy, JL Myers, P Pocha. Studies of the elimination of 1,2-diaryl-4-dimethylaminobutan-2-ols—I: Acid-catalysed elimination of 1,2-diaryl-4-dimethylamino-3-methylbutan-2-ols and base-catalysed elimination of related 2-chloro derivatives. **Tetrahedron, 22(3)**, 1001–1009 (1966).