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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

A simple method for the synthesis of 1,3-diaminopropan-2-ols derivatives and their *ex vivo* relaxant activity on isolated rat tracheal rings

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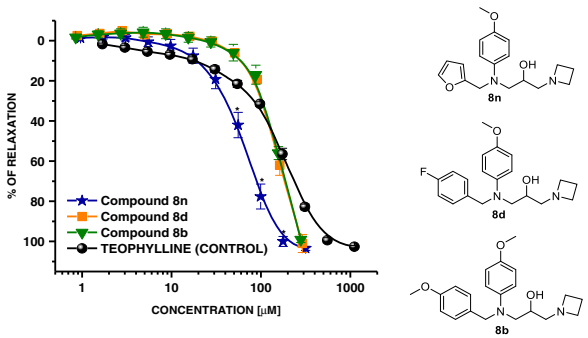
Abstract A mild and eco-friendly method has been developed for the synthesis of a series of 1,3-diaminopropan-2-ols **8a–n**. The epoxide of epichlorohydrin undergoes ring-opening with amines using $MgSO_4$ or mixed metal oxides catalysts under mild and neutral conditions to afford the corresponding β-amino alcohols in excellent yields. Preliminary evaluation of relaxant activity of **8b–n** was carried out on rat tracheal rings contracted by carbachol 1 μM. Most of the tested compounds exhibited significantly relaxant effects in a concentration-dependent manner. Compound **8n** was found to be the most active, being twofolds more potent than theophylline (positive control). This compound has the potential for development as an anti-asthma drug.

Graphical Abstract



Keywords 1,3-Diaminopropan-2-ols · Mixed metal oxides · Rat tracheal relaxation · Anti-asthmatic effect

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Introduction

Asthma is one of the most common chronic diseases, and is characterized by airflow obstruction, bronchial hyper responsiveness, and an underlying inflammation (Busse et al. 2007). Airway smooth muscle plays a central role in almost all the pathophysiologic and clinical aspects of asthma. The most important contractile agonists relevant to asthma are acetylcholine, histamine, leukotrienes, prostaglandins, endothelyn-1, and bradykinin. Asthma drug therapy is centered on counteracting bronchoconstriction and/or inflammation processes using agonists of the β_2 adrenergic receptor (β_2-agonist) and inhaled glucocorticoids, respectively. Combinations of these drugs keep airways open and prevent acute exacerbations (Mendes et al. 2015).

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β-Amino alcohol fragments are versatile intermediates for the syntheses of vast range of biologically active natural and synthetic compounds (Fig. 1). Some exemplary molecules with a β-amino alcohol core and their biological activities are: the salbutamol **I**, a β_2-agonist and effective bronchodilator because of its ability to relax airway smooth muscle (Fuso et al. 2013); compound **II**, a low molecular weight probe for β-secretase inhibition (Kumar et al. 2012); and compound **III**, a Src Kinase inhibitor (Sharma et al. 2010).

One of the most straightforward synthetic procedures for the preparation of β-amino alcohols is ring opening of epoxides with amines (Chang and Ganesan 1997; Van de Weghe and Collin 1995). A variety of activators or promoters, such as metal amides (Cossy et al. 2002; Canas et al. 1991; Caron and Sharpless 1985; Chong and Sharpless 1985), have been used in epoxide ring opening reactions. However, some promoters are dangerous or form emulsions, making work-up difficult. Recent alternative procedures include the use of ionic liquids (Yadav et al. 2003), silica gel-bonded S-sulfonic acid (Tajbakhsh et al. 2012), mesoporous aluminosilicate (Chakravarti et al. 2009), pH-controlled aqueous conditions (Bonollo et al. 2006), and microwave irradiation (Robin et al. 2007).

Mixed metal oxides (MMOs) have important roles in organic transformations because of their ease of handling, decreased reactor and plant corrosion, cost effectiveness, and the fact that most MMOs are reusable and recyclable (Gawande et al. 2012).

Research towards novel molecules based on bronchodilator activity has led to extensive structural modifications in new bronchodilator agents. Developmental attention is focused on *N*-substituents of β-amino alcohols to find new molecules with bronchodilator activity. In this paper, we report the syntheses of a library of 1,3-diaminopropan-2-ols and screen these compounds for their relaxant activity. The biological activities of the reported compounds are compared to that of theophylline.

Results and discussion

Chemistry

A series of 1,3-diaminopropan-2-ols derivatives (**8a–n**) were prepared via four step syntheses (Scheme 1). *N*-Benzylideneanilines **3a–g** were obtained in good yields (87–98%) by a procedure previously reported (Vázquez et al. 2004). The *N*-benzylideneanilines were reduced to give *N*-benzylanilines **4a–g** by two synthetic methods: reductive amination, a direct reaction; or a stepwise/indirect reaction. Several reductants are suitable for these reactions, e.g. molecular hydrogen (Baxter and Reitz 2002; Bódis et al. 2005; Gomez et al. 2004) and metal hydrides (Chandrasekhar et al. 2000; Lopez and Fu 1997; Chen et al. 2001; Blackwell et al. 2000; Kobayashi et al. 1996; Apodaca and Xiao 2001). However, most of these reagents have drawbacks in handling and specificity of functional groups that can be reduced. Cyanoborohydride and tin hydride reagents are highly toxic and generate toxic by-products such as HCN, NaCN, or organotin compounds (Pereyre et al. 1987) and the selective formation of amines with metal hydrides is challenging (Gribble 1998; Dangerfield et al. 2010).

We systematically investigated a number of experimental conditions of the indirect method for the reduction reaction. The reaction was carried out by traditional method with a 1:1:1 mixture of Schiff base **3a**, sodium borohydride and boric acid in tetrahydrofuran/methanol (THF/MeOH) at 0 °C to rt until thin-layer chromatography (TLC) and nuclear magnetic resonance (NMR) showed no further reaction progress and the product **4a** was obtained with good yield (99%). Cho and Kang (2005) have reported the use of boric acid-activated sodium borohydride in absence of a solvent by grinding the solid reagent with reactants to effectively reductively aminate aldehydes and ketones. We applied Cho's method and were unable to obtain satisfactory results and a mixture of solvents were necessary for the reaction to proceed (yield 30%). We next applied this initial methodology to other imines (Scheme 1). The indirect reductive amination procedure was efficient for most of imines trialed and synthesized *N*-benzylanilines **4a–d** and **4g** with good yields. However, reaction of imines containing a 2-thienyl moiety resulted in lower yields of compounds **4e** and **4f**. The low yields of these products is because the 2-thienyl group is readily decomposed (Bell et al. 1969; Billman and Diesing 1957).

Our next challenge was establishing conditions for nucleophilic addition to the epoxide of epichlorohydrin. We evaluated the model reaction in the presence and absence of a base. A range of solvents (THF, CH_3CN, Toluene, *iso*-propyl alcohol, and MeOH) were evaluated without base and after 30 h no reaction had occurred. Various bases

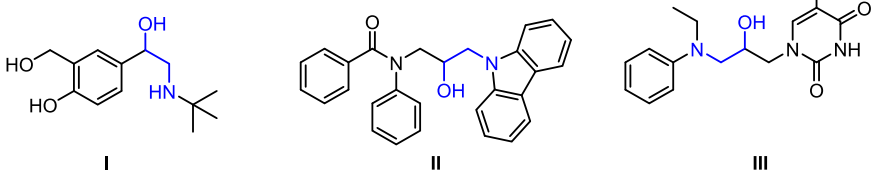
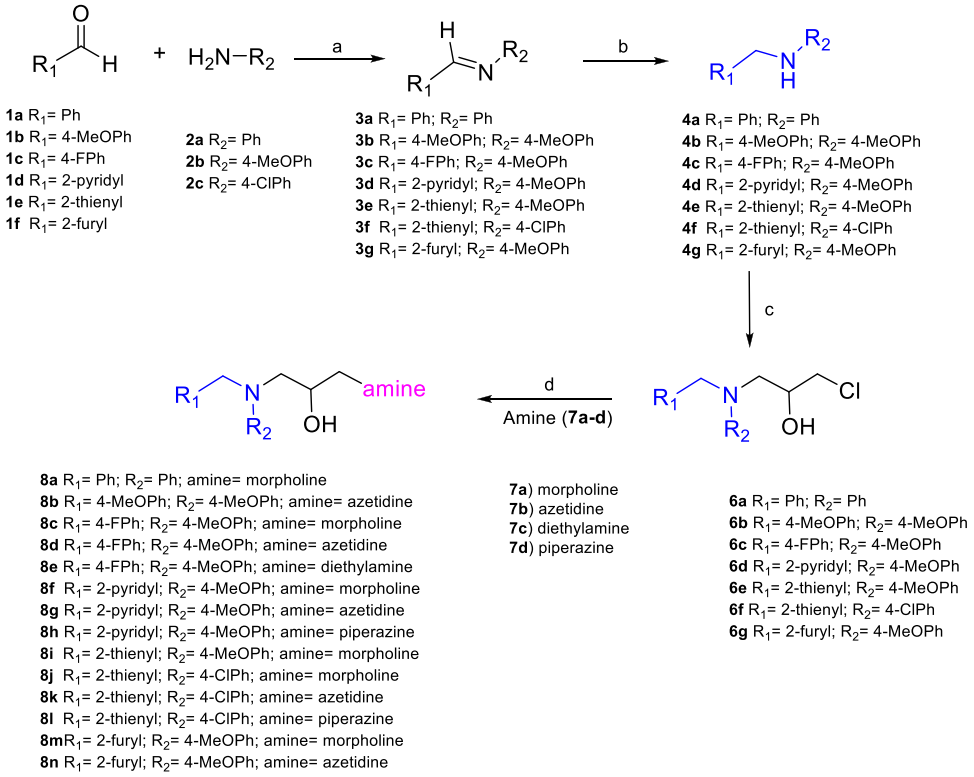


Fig. 1 Three 1-aminopropan-2-ols with potential biological activities



Scheme 1 General synthetic route for 1,3-diaminopropan-2-ols. Conditions: **a 1** (1.5 mmol) and **2** (1.5 mmol), under IR irradiation at 90 °C (50 V). **b** $NaBH_4$ (1 equiv.), H_3BO_3 (1 equiv.), THF/MeOH (1/1, 10 mL) at 0–20 °C. **c 4a–f** (1 equiv), epichlorohydrine **5** (1.5 equiv.), CH_2Cl_2/MeOH (10 mL) at rt with $MgSO_4$ or MMO. **d** NaOH (1.5 M, 2 mL) at 0 °C, then MeOH/H_2O (7:3, 3 mL), amine **7a–d** (2 equiv.) at rt

(NaH, K_2CO_3, KOH, and NaOH) were evaluated and all resulted in poor yields. Adjusting the molar ratio of **4**:epichlorohydrin failed to improve the yield of the desirable product (0–33%).

Condensation of amine **4a** with epichlorohydrin in MeOH with $MgSO_4$ (Bergeron et al. 1997) afforded the desired halohydrin **6a** in acceptable yield (58%). Using a mixture of MeOH/CH_2Cl_2 improved the yield of **6a** (80%). Other solvents (MeOH, THF, and DMF) led to the formation of a polar by-product. Mg/Al MMOs are potential substitutes for common bases such as alkaline hydroxides, ammonia, and ammonium salts. These MMOs are advantageous because they are environmentally friendly, inexpensive, non-toxic, and their basic properties can be tailored to increasing their activity and/or selectivity. They can also be easily separated and recycled because pollutant salts and by-products are not formed in the process (Carbajal Arizaga et al. 2007). We tested MMOs with different Al:Mg ratios ($x = 0.3$, 0.4, and 0.6, where $x = Al/(Mg+Al)$) for the nucleophilic opening of epichlorohydrin. The MMO with Al:Mg $x = 0.4$ showed good activity and afforded **6a** in 75% in short reaction time.

Compounds **6a–g** were prepared by aminolysis of racemic epichlorohydrin with the corresponding secondary amine in CH_2Cl_2/MeOH in the presence of $MgSO_4$ and MMO (Al:Mg, $x = 0.4$) in good yields (Table 1). The opening of the epoxide ring of epichlorohydrin with **4a–g** under these conditions proceed to exclusively form the

Table 1 Addition of nucleophilic amines to epichlorohydrin under two different conditions

Product	*t* (h)	Yield (%)[a]	*t* (h)	Yield (%)[b]
6a	168	80	75	75
6b	13	99	7	90
6c	20	75	12	70
6d	15	72	10	61
6e	28	80	14	80
6f	32	74	18	70
6g	32	100	12	100

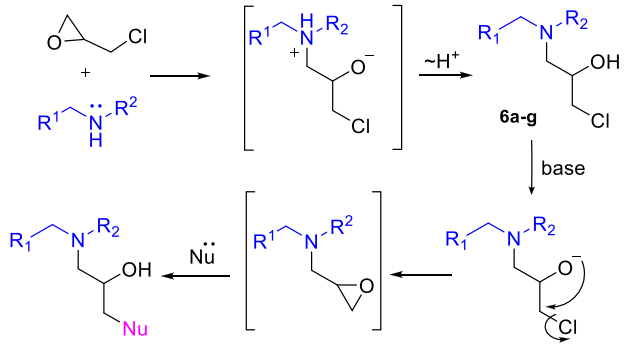
4a–g (1 equiv.), epichlorohydrine **5** (1.5 equiv.), CH_2Cl_2/MeOH (10 mL, 3:7) at rt with $MgSO_4$ or MMO

[a] 25%wt of $MgSO_4$

[b] 15%wt of MMO, Al:Mg $x = 0.4$

secondary alcohol (Scheme 2) (Robin et al. 2007). There were no appreciable differences in the yields for reactions using $MgSO_4$ or the MMO. However, the use of the MMO decreased the reaction time substantially and the catalytic MMO was recovered and reused five times without detriment to the reaction outcome. The MMO was recycled easily by washing with water and reactivating in an oven at 140 °C.

The final step in our syntheses was the addition of different amines, morpholine (**7a**), azetidine (**7b**), diethylamine (**7c**) and piperazine (**7d**), to compounds **6a–g** in the presence of NaOH (1.5 M) in methanol to yield **8a–n** in



Scheme 2 Possible reaction mechanism for the closing and opening of the epoxide

75–80% yield. The reactions presumably proceed by an epoxy opening/closing (Scheme 2). The chemical structures of compounds **8a–n** were confirmed unambiguously by spectral data analysis (^{1}H, ^{13}C, ^{1}H–^{1}H COZY NMR, IR, and HRMS spectroscopy).

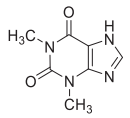
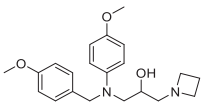
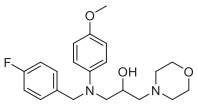
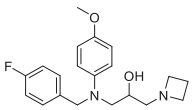
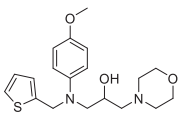
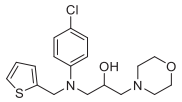
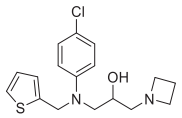
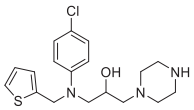
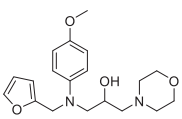
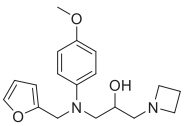
Ex vivo rat tracheal assay

The compounds **8b–d**, **8i–n** [0.8–300 μM] were evaluated for their relaxant effect on tracheal smooth muscle cells in a model of isolated rat tracheal rings pre-contracted with carbachol [1 μM]. The efficacy and potency of each compound is shown in Table 2.

Compounds **8c**, **8i**, **8k**, and **8m** showed significant relaxing effect (greater than 80% at 300 μM) but were less potent than the positive control theophylline at lower concentrations, with concentration–response curves (CRC) shifted to the right of theophyllines (Fig. 2b). Compounds **8b**, **8d**, and **8n** were 100% efficient at 300 μM and were more active than theophylline ($EC_{50} < 150$ μM). The CRC of compound **8n** ($EC_{50} = 62$ μM) is shifted to the left compared to theophylline, and compounds **8b** and **8d** (Fig. 2c), which suggests that compound **8n** is the most potent compound in this series. Compound **8j** ($E_{max} = 62\%$) and **8l** ($E_{max} = 57\%$) had significantly less relaxant effect than theophylline (positive control; $E_{max} = 100\%$; $EC_{50} = 150$ μM; Fig. 2a).

β_2 agonists with longer half-lives have been discovered and called longer-acting β_2 agonists. These longer-acting β_2 agonists allow clinically beneficial once or twice daily administration (Cazzola et al. 2013). Longer-acting β_2 agonists were discovered by *N*-alkyl substitution or introducing substituents on the aromatic ring of short-acting β_2 agonists. These structural changes provide important characteristics such as receptor selectivity, biotransformation, and potency (Cazzola et al. 2013; Graham 1995). In this work, 1,3-diaminopropan-2-ols promote relaxation of contractions induced by carbachol on rat tracheal rings. Compound **8n** was the most potent in vitro relaxation with maximally effective achieved at a concentration half that needed for theophylline. Although the mechanism by which 1,3-diaminopropan-2-ols induce relaxation is unclear, we hypothesized that the azetidine substituent is important for

Table 2 Relaxant effect of 1,3-diaminopropan-2-ol derivatives on rat trachea muscle tissue

Compound	Structure	E_{max} (%)	EC_{50} (μM)
Theophylline (control)		100	150
8b		100	138
8c		88	149
8d		100	154
8i		91	167
8j		62	ND
8k		86	167
8l		57	ND
8m		87	147
8n		100	62

EC_{50} median effective concentration, *E_{max}* maximum effect, *ND* non determined

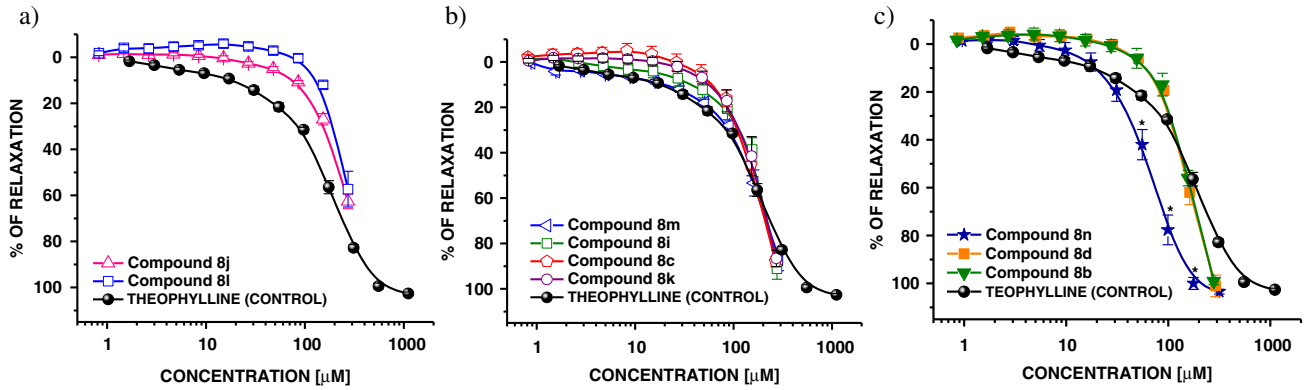


Fig. 2 Concentration response curves of the relaxant effect of 1,3-diaminopropan-2-ol compounds vs. theophylline on rat trachea rings pre-contracted with carbachol 1 μM. **a** Compounds **8j**, **8l** vs. theophylline. **b** Compounds **8c**, **8i**, **8k**, **8m** vs. theophylline. **c** Compounds **8b**, **8d**, **8n** vs. theophylline. All results are expressed as the mean ± standard error of mean from six experiments

potent relaxation activity (Naito et al. 2006; Yun et al. 2014; Ding et al. 2013). This substituent is present on the three most active compounds. Further experiments are necessary to establish the mechanism of action of the more active compounds synthesized.

Conclusion and future prospects

We have synthesized and studied the potential anti-asthmatic activities of a series of 1,3-disubstituted propan-2-ol compounds (**8b–n**). The set of 14 compounds was prepared in good yields via the epoxide ring opening of epichlorohydrin. The use of MMO catalysts improved the reaction time and the catalyst was recovered and reused efficiently up to five times. The simple experimental and product isolation procedures, combined with the ease of catalyst recovery, are expected to contribute to the development of environmentally friendly processes for the synthesis of 1,3-diaminopropan-2-ols of biological and medicinal importance.

Compound **8n** showed significantly improved efficacy and potency as a tracheal smooth muscle relaxant agent compared to theophylline. Compound **8n** provides a led to design a better 1,3-diaminopropan-2-ol containing a azetidine substituent from a chiral precursor that could be an ideal candidate for an anti-asthmatic drug.

Experimental

General procedures

Reaction progress was monitored by TLC, (E. Merck-Kenilworth, NJ, USA, silica gel 60-F_{254} coated aluminum sheets) with a hexanes/EtOAc (8:2) system for the imines and amines and hexanes/EtOAc (7:3) for the final products. Colorless compounds were visualized by irradiation with a 254 nm UV lamp. Reaction promotion by IR radiation was carried out with an Osram industrial IR lamp (250 watts, 127 V). The voltage was regulated with a rheostat, 120 V source, 50/60 Hz, 10 A, 1.4 KVA, 0–140 V in/out.

Commercial reagents used in this project—aldehydes, primary amines, sodium borohydride and epichlorohydrin, carbamylcholine (carbachol), theophylline, dimethyl sulfoxide and ethylic ether were purchased from Sigma-Aldrich (St. Louis, MO, USA). Boric acid, magnesium sulfate, and sodium hydroxide were purchased from Meyer (a subsidiary of Merck). Stock solutions for extractions were made using distilled water and freshly prepared on the day of experimentation.

^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 200 MHz, Varian VNMR 300 MHz or Varian VNMR 500 MHz System in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS, 0.00 ppm, internal reference). Infrared spectroscopy was performed on a Perkin-Elmer FTIR Spectrum 2000 or 1600 FTIR model spectrophotometer using potassium bromide tablets (KBr). X-ray diffraction poder (XRD) powder patterns were collected on a INEL model Equinox System EQUI22102003 using monochromatised Cu Ka radiation ($\lambda = 1.5408$ Å), with 40 KV and 30 mA. Specific surface areas (S_{BET}), were determined by the Brunnauer–Emmet–Teller method. N_2 volumetric measurements were performed at 77 K on a Micromeritic ASAP2010.

*General procedure for the synthesis of imines (**3a–3g**)*

Imines **3a–3g** were prepared using the methodology of Delgado et al. (Vázquez et al. 2004). Briefly, amine **2** (1 equiv.) and aldehyde **1** (1.05 equiv.) were placed in a round bottom flask. This mixture was irradiated with infrared light with a lamp intensity of 30–40 volts (90–120 °C) and the reaction monitored by TLC. The crude reaction mixture was

washed with hexanes and crystallized from cold hexanes or a mixture of cold dichloromethane/hexanes.

N-Benzylidenaniline (**3a**) Yield: 99%; pale yellow crystals; mp 51–52 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (s, 1H, H-1), 7.92 (dd, $J = 6.5$, 2.9 Hz, 2H, H-9, H-13), 7.47 (dd, $J = 11.5$, 7.8 Hz, 5H, H-3, H-4, H-5, H-6, H-7), 7.24 (t, $J = 7.1$ Hz, 3H, H-10, H-11, H-12).

N-(4-methoxybenzylidene)-4-methoxyaniline (**3b**) Yield: 90%; white solid; mp 143–144 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 1H, H-1), 7.30 (d, $J = 8.7$ Hz, 2H, H-3, H-7), 6.89 (d, $J = 8.7$ Hz, 2H, H-10, H-14), 6.79 (d, $J = 9.0$ Hz, 2H, H-6, H-4), 6.61 (d, $J = 9.0$ Hz, 2H, H-11, H-13), 3.81 (s, 3H, H-15), 3.75 (3H, s, H-8).

N-(4-fluorobenzylidene)-4-methoxyaniline (**3c**) Yield: 98%; gray crystals; mp 50–51 °C; ^{1}H NMR (300 MHz, $CDCl_3$,): δ 8.52 (s, 1H, H, H-1), 7.27 (t, $J = 9.0$ Hz, 2H, H-7, H-3), 6.97 (t, $J = 7.6$ Hz, 2H, H-6, H-4), 6.75 (d, $J = 8.9$ Hz, 2H, H-9, H-13), 6.54 (d, $J = 8.9$ Hz, 2H, H-10, H-12), 3.69 (s, 3H, H-14).

N-(pyridin-2-ylmethylene)-4 methoxyaniline (**3d**) Yield: 89%; dark green crystals; mp 26–27 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (d, $J = 4.7$ Hz, 1H, H-6), 8.56 (s, 1H, H-1), 8.10 (d, $J = 7.9$ Hz, 1H, H-4), 7.68 (t, $J = 7.7$ Hz, 1H, H-3), 7.27 (d, $J = 8.8$ Hz, 3H, H-8, H-12, H-5), 6.86 (d, $J = 8.8$ Hz, 2H, H-9, H-11), 3.72 (s, 3H, H-13).

N-(thien-2-ylmethylene)-4 methoxyaniline (**3e**) Yield: 95%; yellow–green crystals; mp 54–55 °C; ^{1}H NMR (300 MHz, $CDCl_3$,): δ 8.30 (s, 1H, H-1), 7.80–7.93 (m, 1H, H-5), 7.45–7.43 (m, 1H, H-4), 7.26 (d, $J = 9.1$ Hz, 2H, H-7, H-11), 7.16–7.13 (m, 1H, H-3), 6.92 (d, $J = 9.0$ Hz, 2H, H-8, H-10), 3.81 (s, 3H, H-12).

N-(thien-2-ylmethylene)-4-chloroaniline (**3f**) Yield: 81%; yellow crystals; mp 73–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (1H, s, H-1), 7.51 (dd, $J = 7.1$, 4.4 Hz, 2H, H-4, H-5), 7.34 (d, $J = 8.5$ Hz, 2H, H-7, H-11), 7.14 (dd, $J = 4.8$, 3.6 Hz, 3H, H-3, H-8, H-10).

N-(furan-2-ylmethylene)-4-methoxyaniline (**3g**) Yield: 89%; dark yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H, H-1), 7.59 (s, 1H, H-5), 7.26 (d, $J = 9.1$ Hz, 2H, H-7, H-11), 6.92 (d, $J = 9.0$ Hz, 3H, H-3, H-8, H-10), 6.57–6.51 (m, 1H, H-4), 3.82 (s, 3H, H-12).

*General procedure for the synthesis of amines (**4a–4g**)*

$NaBH_4$ (1.1 equiv.) then, H_3BO_3 (1.0 equiv.) were slowly added to a solution of imine **3a–g** (1.0 equiv.) in MeOH: THF (1:1) stirred at 0 °C and monitored by TLC. The reaction mixture was washed three times with $NaHCO_3$: CH_2Cl_2, the organic phases dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The product was recrystallized from CH_2Cl_2/petroleum ether.

N-benzylaniline (**4a**) Yield: 99%; white crystals; mp 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.24 (m, 5H, H-9, H-10, H-11, H-12, H-13), 6.78–6.45 (m, 5H, H-3, H-4, H-5, H-6, H-7), 4.25 (s, 2H, H-1), 3.98 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5 (C-8), 139.8 (C-2), 129.6 (C-4, C-6), 128.9 (C-3, C-7), 127.8 (C-10, C-12), 127.5 (C-5), 117.8 (C-11), 113.2 (C-9, C-13), 48.6 (C-1).

4-Methoxy-*N*-(4-methoxybenzyl)aniline (**4b**) Yield: 88%; fawn crystals; mp 90–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, $J = 8.7$ Hz, 2H, H-11, H-13), 6.89 (d, $J = 8.7$ Hz, 2H, H-4, H-6), 6.79 (d, $J = 9.0$ Hz, 2H, H-3, H-7), 6.61 (d, $J = 9.0$ Hz, 2H, H-10, H-14), 4.21 (s, 2H, H-1), 3.81 (s, 4H, H-15, NH), 3.75 (s, 3H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0 (C-5), 152.4 (C-12), 142.7 (C-9), 131.9 (C-2), 128.9 (C-11, C-13), 115.1 (C-3, C-7), 114.2 (C-4, C-6), 55.9 (C-15), 55.4 (C-8), 48.9 (C-1).

N-(4-fluorobenzyl)-4-methoxyaniline (**4c**) Yield: 98%; green olive crystals; mp 25–26 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.23 (m, 2H, H-4, H-6), 6.97 (t, $J = 7.6$ Hz, 2H, H-3, H-7), 6.75 (d, $J = 8.9$ Hz, 2H, H-10, H-12), 6.54 (d, $J = 8.9$ Hz, 2H, H-9, H-13), 4.19 (s, 1H, H-1), 3.69 (s, 3H, H-14); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.6 (C-5), 152.2 (C-11), 142.3 (C-8), 135.5 (C-2), 129.2 (C-4, C-6), 115.4 (C-10, C-12), 114.9 (C-7, C-3), 114.1 (C-13, C-9), 55.6 (C-14), 48.4 (C-1).

4-Methoxy-*N*-(pyridin-2-ylmethyl)aniline (**4d**) Yield: 80%; lilac crystals; mp 73–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (d, $J = 7.9$ Hz, 1H, H-6), 7.68 (t, $J = 7.7$ Hz, 1H, H-4), 7.35 (d, $J = 7.9$ Hz, 1H, H-3), 7.20–7.14 (m, 1H, H-5), 6.28 (d, $J = 8.8$ Hz, 2H, H-9, H-11), 6.25 (d, $J = 8.8$ Hz, 2H, H-8, H-12), 4.46 (s, 2H, H-1), 3.72 (s, 3H, H-13); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.8 (C-2), 152.2 (C-10), 148.1 (C-6), 142.1 (C-7), 136.5 (C-4), 121.9 (C-3), 121.6 (C-5), 114.9 (C-8, C-12), 114.3 (C-9, C-11), 55.7 (C-13), 50.2 (C-1).

4-Methoxy-*N*-(thien-2-ylmethyl)aniline (**4e**) Yield: 62%; lilac crystals; mp 53–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (dd, $J = 4.9$, 1.4 Hz, 1H, H-5), 7.01–6.93 (m, 2H, H-3, H-4), 6.79 (d, $J = 9.0$ Hz, 2H, H-7, H-11), 6.64 (d, $J = 9.0$ Hz, 2H, H-8, H-10), 4.47 (s, 2H, H-1), 3.81 (s, 1H, NH), 3.74 (s, 3H, H-12); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.7 (C-2), 143.4 (C-9), 141.9 (C-6), 126.9 (C-3), 125.0 (C-4),

124.6 (C-5), 115.0 (C-7, C-8), 114.7 (C-10, C-1), 55.8 (C-12), 44.6 (C-1).

4-Chloro-*N*-(thien-2-ylmethyl)aniline (**4f**) Yield: 67%; yellow crystals; mp 110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (dd, $J = 6.6$, 4.4 Hz, 1H, H-5), 7.34 (d, $J = 8.7$ Hz, 1H, H-3), 7.26–7.15 (m, 2H, H-7, H-11), 6.99–6.98 (m, 1H, H-4), 6.58 (d, $J = 8.8$ Hz, 2H, H-8, H-10), 4.47 (s, 2H, H-1), 4.08 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 162.4 (C-9), 153.4 (C-2), 152.9 (C-6), 142.1 (C-5), 115.2 (C-8, C-10), 115.0 (C-7, C-11), 110.5 (C-3), 107.1 (C-4), 42.8 (C-1).

N-(Furan-2-ylmethyl)-4-methoxyaniline (**4g**) Yield: 80%; white crystals; mp 38–39 °C; ^{1}H NMR (300 MHz, $CDCl_3$,): δ 7.41 (d, $J = 1.9$ Hz, 1H, H-5), 6.83 (d, $J = 9.1$ Hz, 2H, H-7, H-11), 6.69 (d, $J = 9.1$ Hz, 2H, H-8, H-10), 6.39–6.34 (m, 1H, H-3), 6.27 (t, $J = 2.0$ Hz, 1H, H-4), 4.32 (s, 2H, H-1), 3.79 (s, 3H, H-12); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.1 (C-2), 152.6 (C-9), 152.5 (C-6), 141.8 (C-5), 114.9 (C-7, C-11), 114.7 (C-8, C-10), 110.3 (C-3), 106.8 (C-4), 55.6 (C-12), 42.5 (C-1).

*General procedure for the synthesis of tertiary amines (**6a–6g**)*

Epichlorohydrin (2.5 equiv.) was added to a solution of secondary amine **4a–g** (1.0 equiv.) in dry MeOH/CH_2Cl_2 and anhydrous $MgSO_4$ or MMOs (25% wt) and stirred under nitrogen at 30 °C. The crude reaction mixture was filtered through a bed of Celite® and the bed washed with EtOAc. Solvents were removed under reduced pressure to obtain the product.

1-Chloro-3-(benzyl-(phenyl)amino)propan-2-ol (**6a**) Yield: 72%; pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.38 (m, 7H, H-6, H-7, H-8, H-9, H-10, H-13, H-15), 7.01–6.97 (m, 3H, H-12, H-14, H-16), 4.83 (s, 2H, H-4), 4.36 (s, 1H, H-2), 3.85–3.71 (m, 4H, H-1, H-3), 3.00 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.5 (C-8), 159.9 (C-15), 150.0 (C-12), 137.2 (C-5), 131.7 (C-6, C-10), 124.5 (C-7, C-9), 114.7 (C-13, C-17), 107.7 (C-14, C-16), 63.6 (C-2), 54.8 (C-1), 48.6 (C-3).

1-Chloro-3-((4-methoxybenzyl)(4-methoxyphenyl)amino) propan-2-ol (**6b**) Yield: 99%; dark brown-red oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15 (d, $J = 8.7$ Hz, 2H, H-6, H-10), 6.82–6.79 (m, 6H, H-7, H-9, H-13, H-14, H-16, H-17), 4.38 (s, 2H, H-4), 4.37–3.99 (m, 2H, H-2), 3.75 (s, 3H, H-11), 3.73 (s, 3H, H-18), 3.61–3.58 (m, 2H, H-3), 3.54–3.28 (m, 2H, H-1), 2.53 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 158.8 (C-8), 153.2 (C-15), 143.2 (C-12), 130.2 (C-5), 128.7 (C-6, C-10), 117.5 (C-7, C-9), 114.8 (C-13, C-17), 114.0 (C-14, C-16), 68.8 (C-2), 57.2 (C-1), 55.7 (C-11), 55.4 (C-4), 55.3 (C-18), 47.7 (C-3).

1-Chloro-3-((4-fluorobenzyl)(4-methoxyphenyl)amino)propan-2-ol (**6c**) Yield: 80%; brown-red oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.17–7.12 (m, 2H, H-6, H-10), 6.97 (t, $J = 6.0$ Hz, 2H, H-7, H-9), 6.82–6.76 (m, 4H, H-13, H-15, H-12, H-16), 4.42 (s, 2H, H-4), 4.06 (qd, $J = 16.1$, 9.3 Hz, 1H, H-2), 3.75 (s, 3H, H-17), 3.66–3.58 (m, 2H, H-3), 3.54–3.33 (m, 2H, H-1), 2.62 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.7 (C-8), 153.5 (C-14), 142.9 (C-11), 134.0 (C-5), 129.1 (C-6, C-10), 117.8 (C-7, C-9), 115.6 (C-13, C-15), 114.9 (C-12, C-16), 69.0 (C-2), 57.3 (C-1), 55.7 (C-4, C-17), 47.8 (C-3).

1-Chloro-3-((2-pyridin)(4-methoxyphenyl)amino)propan-2-ol (**6d**) Yield: 81%; pale brown solid; mp 91–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (d, $J = 4.7$ Hz, 1H, H-9), 7.80 (s, 1H, OH), 7.71 (t, $J = 7.7$ Hz, 1H, H-7), 7.35 (d, $J = 7.8$ Hz, 1H, H-6), 7.20–7.18 (m, 1H, H-8), 6.75 (d, $J = 9.0$ Hz, 2H, H-11, H-15), 6.58 (d, $J = 9.0$ Hz, 2H, H-12, H-14), 4.70 (d, $J = 16.8$ Hz, 1H, H-4), 4.58 (d, $J = 16.8$ Hz, 1H, H-4), 4.32 (ddd, $J = 8.4$, 6.5, 3.3 Hz, 1H, H-2), 4.03 (d, $J = 14.9$ Hz, 1H, H-3), 3.70–3.68 (m, 1H, H-3), 3.68 (s, 3H, H-16), 3.65–3.63 (m, 1H, H-1), 3.37 (dd, $J = 14.9$, 9.3 Hz, 1H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4 (C-5), 151.5 (C-13), 148.8 (C-9), 141.7 (C-10), 137.4 (C-7), 122.5 (C-8), 122.3 (C-6), 114.8 (C-11, C-15), 113.1 (C-12, C-14), 68.6 (C-2), 59.0 (C-1), 58.8 (C-16), 55.6 (C-4), 46.5 (C-3).

1-Chloro-3-((4-methoxyphenyl)(thien-2-ylmethyl)amino) propan-2-ol (**6e**) Yield: 95%; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.18 (d, $J = 5.1$ Hz, 1H, H-8), 6.94–6.91 (m, 3H, H-6, H-10, H-14), 6.84–6.81 (m, 3H, H-7, H-11, H-13), 4.58 (s, 2H, H-4), 4.01 (dt, $J = 7.9$, 5.0 Hz, 1H, H-2), 3.77 (s, 3H, H-15), 3.63–3.58 (m, 2H, H-3), 3.38 (ddd, $J = 21.9$, 14.0, 6.4 Hz, 2H, H-1), 2.73 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.0 (C-12), 142.6 (C-9), 141.5 (C-5), 126.8 (C-8), 125.8 (C-7), 124.9 (C-6), 118.9 (C-11, C-13), 114.8 (C-10, C-14), 68.7 (C-2), 55.7 (C-1), 55.4 (C-15), 53.7 (C-4), 47.6 (C-3).

1-Chloro-3-((4-chlorophenyl)(thien-2-ylmethyl)amino)propan-2-ol (**6f**) Yield: 81%; amber oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–6.94 (m, 3H, H-8, H-10, H-14), 6.88–6.81 (m, 2H, H-6, H-7), 6.79 (d, $J = 6.0$ Hz, 2H, H-1, H-13), 4.71 (s, 2H, H-4), 4.13 (dt, $J = 7.9$, 5.0 Hz, 1H, H-2), 3.66–3.45 (m, 4H, H-3, H-1), 2.40 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0 (C-12), 142.7 (C-5), 141.4 (C-9), 134.8 (C-8), 126.0 (C-10, C-14), 124.7 (C-11, C-13), 118.9 (C-7), 68.7 (C-2), 55.8 (C-1), 55.2 (C-15), 53.7 (C-4), 47.6 (C-3).

1-Chloro-3-((furan-2-ylmethyl)(4-methoxyphenyl)amino) propan-2-ol (**6g**) Yield: 99%; dark yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 1H, H-8), 6.89 (d, $J = 6.7$ Hz, 2H, H-10, H-14), 6.80 (d, $J = 6.6$ Hz, 2H, H-11, H-13), 6.29 (d, $J = 5.0$ Hz, 1H, H-7), 6.12 (d, $J = 3.9$ Hz, 1H, H-6), 4.36 (s, 2H, H-4), 4.03–3.96 (m, 1H, H-2), 3.75 (s, 3H, H-15), 3.64–3.53 (m, 2H, H-3), 3.44 (dd, $J = 14.2$, 4.9 Hz, 1H, H-1), 3.29 (dd, $J = 14.2$, 7.9 Hz, 1H, H-1), 2.85 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0 (C-12), 152.3 (C-5), 143.2 (C-9), 142.3 (C-8), 118.6 (C-10, C-14), 115.0 (C-11, C-13), 110.5 (C-7), 108.2 (C-6), 69.0 (C-2), 56.1 (C-1), 55.9 (C-15), 51.6 (C-4), 47.7 (C-3).

*General procedure for the synthesis of 3-diaminopropan-2-ol derivatives (**8a–8n**)*

An aqueous solution of NaOH (1.5 M) was added dropwise to a solution of a tertiary amine **6a–g** (1.0 equiv.) in MeOH, and stirred for 30 min at 0 °C. A solution of secondary amine **7a–d** (1.1 equiv.) was added slowly. After the reaction was complete, the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phase dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the resulting oil filtered through a Celite® bed and eluted with hexanes/EtOAc (9:1). The solvent was removed under reduced pressure to afford the product.

1-(Benzyl(phenyl)amino)-3-morpholinopropan-2-ol (**8a**) Yield: 98%; pale yellow oil; IR (KBr) ν_{max} (cm^{-1}): 3434, 2924, 2891, 1599, 1506, 1452, 1225, 1117, 748, 730, 695; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.14 (m, 7H, H-6, H-7, H-8, H-9, H-10, H-13, H-15), 6.78–6.66 (m, 3H, H-12, H-14, H-16), 4.65 (d, $J = 8.1$ Hz, 2H, H-4), 4.20–4.05 (m, 1H, H-2), 3.71–3.67 (m, 3H, H-18, H-19), 3.49–3.32 (m, 6H, H-3, H-17, H-18, H-19, H-20), 2.95 (s, 1H, OH), 2.90–2.85 (m, 1H, H-17, H-20), 2.65–2.34 (m, 2H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.7 (C-11), 138.6 (C-5), 129.3 (C-13, C-15), 128.6 (C-7, C-9), 126.8 (C-8), 126.7 (C-6, C-10), 117.0 (C-14), 112.9 (C-12, C-16), 74.5 (C-2), 68.6 (C-1, C-3), 66.9 (C-18, C-19), 59.2 (C-4), 55.2 (C-17, C-20), 54.2 (C-17, C-20); HRMS (EI^+) calculated for $C_{20}H_{27}N_2O_2$: 327.2064, found 327.2073.

1-(Azetidin-1-yl)-3-((4-methoxybenzyl)(4-methoxyphenyl) amino)propan-2-ol (**8b**) Yield: 86%; dark purple oil; IR (KBr) ν_{max} (cm^{-1}): 3434, 2929, 1512, 1241, 1220, 814; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.10 (m, 2H, H-6, H-10), 6.83–6.73 (m, 6H, H-7, H-9, H-13, H-14, H-16), 4.41 (s, 2H, H-4), 3.98 (m, 1H, H-2), 3.80–3.75 (m, 8H, H-3, H-11, H-18), 3.48–3.25 (m, 8H, H-1, H-19, H-20, H-21), 2.60 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1 (C-8), 152.0 (C-15), 141.9 (C-12) 131.5 (C-5), 128.0 (C-6, C-10), 115.6 (C-13, C-17), 114.5 (C-14, C-16), 113.8 (C-7, C-9), 74.4 (C-1), 68.1 (C-2), 59.0 (C-4), 56.3 (C-3), 55.8 (C-11, C-18), 54.5 (C-19, C-20, C-21), 54.2 (C-20); HRMS (EI^+) calculated for $C_{21}H_{28}N_2O_3$: 356.2100, found 356.2110.

1-((4-Fluorobenzyl)(4-methoxyphenyl)amino)-3-morpholinopropan-2-ol (**8c**) Yield: 78%; brown-red oil; IR (KBr) ν_{max} (cm^{-1}): 3435, 2931, 2856, 2832, 1603, 1513, 1242, 1220,1117, 1039, 815, 437; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20–7.11 (m, 2H, H-6, H-10), 6.95 (t, $J = 8.5$ Hz, 2H, H-7, H-9), 6.81–6.74 (m, 4H, H-12, H-13, H-15, H-16), 4.47 (d, $J = 10$ Hz, 2H, H-4), 4.15–3.95 (m, 1H, H-2), 3.72–3.66 (m, 7H, H-17, H-19, H-20), 3.44–3.36 (m, 5H, H-3, H-18, H-21), 2.63–2.33 (m, 3H, H-1, H-18, H-21); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.4 (C-8, $J = 243.0$ Hz), 152.6 (C-14), 143.2 (C-11), 134.3 (C-5), 128.8 ($J = 8.0$ Hz, C-6, C-10), 116.3 (C-12, C-13), 115.5 ($J = 13.5$ Hz, C-7, C-9), 114.7 (C-15, C-16), 74.6 (C-2), 68.4 (C-1), 67.0 (C-19, C-20), 65.4 (C-3), 62.7 (C-4), 59.2 (C-18, C-21), 55.7 (C-17); HRMS (EI^+) calculated for $C_{21}H_{27}N_2O_3F$: 374.2006, found 374.2022.

1-(Azetidin-1-yl)-3-((4-fluorobenzyl)(4-methoxyphenyl) amino)propan-2-ol (**8d**) Yield: 95%; brown-red oil; IR (KBr) ν_{max} (cm^{-1}): 3434, 2929, 2832, 1603, 1512, 1464, 1241, 1220, 1035, 814; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.17–7.12 (m, 2H, H-6, H-10), 6.91 (t, $J = 8.0$ Hz, 2H, H-7, H-9), 6.83–6.73 (m, 4H, H-12, H-13, H-15, H-16), 4.45 (s, 2H, H-4), 4.05 (m, 1H, H-2), 3.73 (s, 3H, H-17), 3.51–3.23 (m, 10H, H-18, H-19, H-20, H-1, H-3), 2.57 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.4 ($J = 243.5$ Hz, C-8), 152.5 (C-14), 143.1 (C-11), 134.3 (C-5), 128.8 ($J = 8.0$ Hz, C-6, C-10), 116.3 ($J = 13.5$ Hz, C-7, C-9), 114.7 (C-12, C-13, C-15, C-16), 74.6 (C-1), 68.4 (C-2), 59.2 (C-4), 56.2 (C-3), 55.7 (C-17, C-18, C-20), 55.1 (C-19); HRMS (EI^+) calculated for $C_{20}H_{26}N_2O_2F$: 345.1978, found 345.1982.

1-(Diethylamino)-3-((4-fluorobenzyl)(4-methoxyphenyl) amino)propan-2-ol (**8e**) Yield: 80%; dark purple oil; IR (KBr) ν_{max} (cm^{-1}): 3455, 2931, 2832, 1600, 1535, 1455, 1242, 1220, 1117, 1009, 815; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.15 (m, 2H, H-6, H-10), 6.98 (t, $J = 8.0$ Hz, 2H, H-7, H-9), 6.59 (dd, $J = 6.6$, 6.7 Hz, 4H, H-12, H-13, H-15, H-16), 4.78 (s, 1H, OH), 4.52 (s, 2H, H-4), 4.02–3.96 (m, 1H, H-2), 3.73 (s, 3H, H-17), 3.39–3.36 (m, 2H, H-3), 2.80–2.45 (m, 6H, H-1, H-18, H-21), 1.14 (t, $J = 7.5$ Hz, 6H, H-19, H-20); HRMS (EI^+) calculated for $C_{20}H_{19}N_2O_2$: 361.2307, found 361.2291.

1-(Azetidin-1-yl)-3-((4-methoxyphenyl)(pyridin-2-ylmethyl)amino)propan-2-ol (**8g**) Yield: 79%; amber oil; IR (KBr) ν_{max} (cm^{-1}): 3427, 2919, 1514, 1243, 1039; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, $J = 4.5$ Hz, 1H, H-9),

7.70 (td, $J = 7.6$, 1.6 Hz, 1H, H-7), 7.33 (d, $J = 7.8$ Hz, 1H, H-6), 7.18 (dd, $J = 7.1$, 5.2 Hz, 1H, H-8), 6.75 (d, $J = 9.1$ Hz, 2H, H-11, H-15), 6.58 (t, $J = 6.4$ Hz, 2H, H-12, H-14), 4.64 (dd, $J = 14.9$, 2.2 Hz, 2H, H-4), 4.28–4.23 (m, 1H, H-2), 3.89 (dd, $J = 14.9$, 2.2 Hz, 1H, H-3), 3.79–3.72 (m, 1H, H-18), 3.70 (s, 3H, H-16), 3.52 (ddd, $J = 14.9$, 9.6, 5.3 Hz, 2H, H-1), 3.44 (s, 4H, H-17, H-19), 3.41–3.36 (m, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7 (C-5), 151.5 (C-13), 149.1 (C-9), 142.1 (C-10), 137.3 (C-7), 122.4 (C-8), 122.2 (C-6), 114.9 (C-11, C-15), 113.2 (C-12, C-14), 74.9 (C-1), 68.0 (C-2), 59.4 (C-17, C-19), 58.9 (C-4), 58.4 (C-3), 55.8 (C-16, C-18); HRMS (EI^+) calculated for $C_{19}H_{26}N_3O_2$: 328.2025, found 328.2038.

1-((4-Methoxyphenyl)(pyridin-2-ylmethyl)amino)-3-(piperazin-1-yl)propan-2-ol (**8h**) Yield: 85%; amber oil; IR (KBr) ν_{max} (cm^{-1}): 3390, 2932, 1659, 1594, 1514, 1436, 1244, 1181, 1039, 817, 760; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.11 (m, 3H, H-8, H-11, H-13), 6.90 (dd, $J = 9.2$, 4.2 Hz, 2H, H-6, H-7), 6.74 (dd, $J = 9.1$, 2.2 Hz, 2H, H-10, H-14), 4.72 (d, $J = 9.1$ Hz, 2H, H-4), 4.10–3.97 (s, 1H, H-2), 3.52–3.33 (m, 5H, H-3, H-15, H-18), 3.01–2.85 (m, 3H, H-16, H-17), 2.61–2.24 (m, 4H, H-1, H-3, H-16, H-17), 1.30 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0 (C-13), 148.5 (C-9), 136.6 (C-7), 122.4 (C-5), 122.3 (C-6), 122.2 (C-10), 120.4 (C-8), 114.8 (C-11, C-15), 113.2 (C-12, C-14), 74.8 (C-2), 68.0 (C-1), 64.1 (C-3, C-17, C-20), 59.4 (C-4), 55.7 (C-18, C-19); HRMS (EI^+) calculated for $C_{18}H_{25}ClN_3OS$: 366.1407, found 366.1375.

1-((4-Methoxyphenyl)(thien-2-ylmethyl)amino)-3-morpholinopropan-2-ol (**8i**) Yield: 85%; amber oil; IR (KBr) ν_{max} (cm^{-1}): 3430, 2932, 2830, 1635, 1512, 1455, 1242, 1116, 1036; ^{1}H NMR (200 MHz, $CDCl_3$,): δ 7.19–7.13 (m, 1H, H-8), 6.93–6.75 (m, 6H, H-6, H-7, H-10, H-11, H-13, H-14), 4.65 (s, 2H, H-4), 4.03–3.89 (m, 1H, H-2), 3.78–3.65 (m, 7H, H-15, H-17, H-18), 3.35–3.25 (m, 2H, H-3), 3.13 (s, 1H, OH), 2.68–2.52 (m, 2H, H-16, H-19), 2.49–2.36 (m, 4H, H-1, H-16, H-19); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.0 (C-5), 143.1 (C-12), 142.5 (C-9), 126.7 (C-8), 125.2 (C-7), 124.5 (C-6), 117.2 (C-11, C-13), 114.7 (C-10, C-14), 67.1 (C-17, C-18), 65.5 (C-2), 62.7 (C-1), 56.4 (C-3), 55.7 (C-15), 53.9 (C-16, C-19), 52.8 (C-4); HRMS (EI^+) calculated for $C_{19}H_{26}N_2O_3S$: 362.1664, found 362.1678.

1-((4-Chlorophenyl)(thien-2-ylmethyl)amino)-3-morpholinopropan-2-ol (**8j**) Yield: 78%; amber oil; IR (KBr) ν_{max} (cm^{-1}): 3429, 2926, 2891, 2821, 1596, 1501, 1454, 1417, 1366, 1326, 1221, 1192, 1116, 1007, 909, 510, 731, 702; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.15 (dd, $J = 7.0$, 4.5 Hz, 3H, H-8, H-10, H-14), 6.91 (dd, $J = 8.9$, 4.0 Hz, 2H, H-6, H-7), 6.75 (dd, $J = 9.1$, 2.3 Hz, 2H, H-11, H-13), 4.73 (d, $J = 8.8$ Hz, 2H, H-4), 4.13–3.95 (s, 1H, H-2), 3.72–3.63 (m, 2H, H-3), 3.48–3.38 (m, 5H, H-15, H-16, H-17, H-18), 2.90–2.85 (m, 1H, H-15, H-18), 2.66–2.58 (m, 2H, H-1), 2.56–2.29 (m, 2H, H-15, H-18); ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.8 (C-5), 141.9 (C-12), 129.0 (C-11, C-13), 126.8 (C-8), 125.0 (C-7), 124.3 (C-6), 122.3 (C-9), 114.6 (C-10, C-14), 74.3 (C-2), 68.5 (C-1), 66.9 (C-16, C-17), 65.5 (C-3), 62.4 (C-4), 59.2 (C-15, C-18), 54.0 (C-15, C-18); HRMS (EI^+) calculated for $C_{20}H_{19}N_2O_2$: 367.1247, found 367.1243.

1-(Azetidin-1-yl)-3-((4-chlorophenyl)(thien-2-ylmethyl) amino)propan-2-ol (**8k**) Yield: 96%; amber oil; IR (KBr) ν_{max} (cm^{-1}): 3434, 2891, 1597, 1500, 1366, 1219, 1125, 1101, 810, 701; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–6.95 (m, 3H, H-8, H-11, H-13), 6.92–6.88 (m, 2H, H-6, H-7), 6.86–6.74 (d, $J = 6.8$ Hz, 2H, H-10, H-14), 4.71 (s, 2H, H-4), 4.10–4.01 (s, 1H, H-4), 3.51–3.32 (m, 8H, H-1, H-3, H-15, H-16, H-17), 2.43 (s, 1H, H-1), 1.26–0.87 (s, 1H, H-3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.8 (C-5), 141.7 (C-12), 129.0 (C-11, C-13), 126.9 (C-8), 125.1 (C-7), 124.4 (C-6), 122.4 (C-9), 114.7 (C-10, C-14), 74.3 (C-1), 68.6 (C-2), 59.2 (C-15, C-17), 54.0 (C-4), 51.1 (C-3, C-16); HRMS (EI^+) calculated for $C_{17}H_{22}ClN_2OS$: 337.1141, found 337.2051.

1-((4-Chlorophenyl)(thien-2-ylmethyl)amino)-3-(piperazin-1-yl)propan-2-ol (**8l**) Yield: 85%; amber oil; IR (KBr) ν_{max} (cm^{-1}): 3400, 2936, 2882, 2820, 1596, 1499, 1366, 1219, 1127, 1101, 809, 700; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15–7.11 (m, 3H, H-8, H-11, H-13), 6.90 (dd, $J = 9.2$, 4.2 Hz, 2H, H-6, H-7), 6.74 (dd, $J = 9.1$, 2.2 Hz, 2H, H-10, H-14), 4.72 (d, $J = 9.1$ Hz, 2H, H-4), 4.10–3.97 (s, 1H, H-2), 3.52–3.33 (m, 5H, H-3, H-15, H-18), 3.01–2.85 (m, 3H, H-16, H-17), 2.61–2.24 (m, 4H, H-1, H-3, H-16, H-17), 1.30 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.9 (C-5), 142.0 (C-12), 128.9 (C-11, C-13), 126.8 (C-8), 125.2 (C-7), 124.4 (C-6), 122.1 (C-9), 114.8 (C-10, C-14), 74.1 (C-2), 68.6 (C-1), 59.1 (C-3, C-15, C-18), 54.2 (C-4), 51.1 (C-16, C-17); HRMS (EI^+) calculated for $C_{18}H_{25}ClN_3OS$: 366.1407, found 366.1375.

1-((Furan-2-ylmethyl)(4-methoxyphenyl)amino)-3-morpholinopropan-2-ol (**8m**) Yield: 92%; dark orange oil; IR (KBr) ν_{max} (cm^{-1}): 3434, 2927, 2854, 1513, 1243, 1116, 1037; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 1H, H-9), 6.87–6.78 (m, 4H, H-10, H-11, H-13, H-14), 6.27 (s, 1H, H-7), 6.11 (s, 1H, H-6), 4.43 (s, 2H, H-4), 3.98–3.91 (m, 1H, H-2), 3.75–3.68 (m, 7H, H-15, H-17, H-18), 3.35–3.25 (m, 2H, H-3), 2.60–2.56 (m, 2H, H-16, H-19), 2.43–2.31 (m, 4H, H-1, H-16, H-19); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.5 (C-12), 143.3 (C-5), 141.7 (C-8, C-9), 116.7 (C-10, C-14), 114.5 (C-11, C-13), 110.1 (C-7), 107.6 (C-6), 66.8 (C-17, C-18), 65.4 (C-2), 62.5 (C-1), 56.4 (C-3), 55.6 (C-15), 53.9

(C-16, C-19), 50.3 (C-4); HRMS (EI^+) calculated for $C_{19}H_{26}N_2O_4$: 346.1893, found 346.1855.

1-(Azetidin-1-yl)-3-((furan-2-ylmethyl)(4-methoxyphenyl) amino)propan-2-ol (**8n**) Yield: 84%; light yellow oil; IR (KBr) ν_{max} (cm^{-1}): 3435, 2931, 2832, 1513, 1464, 1244, 1183, 1183, 1126, 1104, 1074, 1038, 815, 737; ^1H NMR (200 MHz, $CDCl_3$): δ 7.26 (s, 1H, H-8), 6.78 (d, $J = 8.5$ Hz, 2H, H-10, H-14), 6.72 (d, $J = 9.0$ Hz, 2H, H-11, H-13), 6.20 (s, 1H, H-7), 6.05 (s, 1H, H-6), 4.30 (s, 2H, H-4), 3.89 (m, 1H, H-2), 3.79–3.72 (m, 1H, H-17), 3.80 (s, 3H, H-15), 3.36 (dt, $J = 6.7$, 3.3 Hz, 1H, H-3), 3.35–3.31 (m, 2H, H-1), 3.30–3.26 (m, 4H, H-16, H-18), 3.21 (dd, $J = 14.4$, 7.9 Hz, 1H, H-3), 2.72 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.1 (C-12), 152.4 (C-5), 143.2 (C-9), 142.0 (C-8), 117.2 (C-10, C-14), 114.9 (C-11, C-13), 110.3 (C-7), 107.8 (C-6), 74.5 (C-1), 68.2 (C-2), 59.3 (C-16, C-18), 55.7 (C-4, C-15), 55.2 (C-3), 50.7 (C-17); HRMS (EI^+) calculated for $C_{18}H_{25}N_2O_3$: 317.1865, found 317.1875.

Pharmacological test

Animals

Healthy male Wistar rats (250–300 g) were used and maintained under standard laboratory conditions. All animal procedures were conducted in accordance with local regulations for animal experimentation and care (NOM-062-ZOO-1999, México), and approved by the institutional animal care and use committee based on US National Institute of Health publication (No. 85-23, revised 1985). All experiments were carried out using six animals per group. The animals used were euthanized by cervical dislocation. Efforts were made to minimize animal suffering and the number of animals used.

Trachea ring assay procedure

The previous described protocol was used to assess the relaxant effect of synthetic compounds on rat trachea rings (Sánchez-Recillas et al. 2014). The rat trachea was removed, dissected, cleaned of connective tissue and mucus, and immediately cut into 4–5 mm length rings. Tissue segments were mounted on stainless steel hooks under an optimal tension of 1.96×10^{-2} N in 10 mL organ baths containing warmed (37 °C) and oxygenated (O_2/CO_2, 95:5) Krebs solution (composition, mM: NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; EDTA, 0.026 and glucose, 11.1, at pH 7.4). Changes in tension were recorded by Grass-FT03 forced transducers (Astromed, West Warwick, RI, USA) connected to a MP100 analyzer (BIOPAC Instruments, Santa Barbara, CA, USA) as previously described (Sánchez-Recillas et al. 2014). The rings were allowed to equilibrate and contracted by addition of carbachol [1 μM] and washed every 40 min for 2 h. Test samples (compounds, vehicle, and positive control) were each added to a bath in a volume of 100 μL and the cumulative concentration–response curves were obtained for each ring (0.8–300 μM). The relaxant effect of the compounds and positive control (theophylline, inhibitor of phosphodiesterase; 1.67–550 μM) were determined by comparing the muscular tone of the contraction before and after addition of the test materials. Muscular tone was calculated from the tracings, using Acknowledge software (Biopac®).

MMOs procedure

Salts of Al and Mg [$Al_2(SO_4)_3$ and $MgSO_4$] in aqueous solutions were used to produce MMOs with different molar ratios (x). In a three-necked flask, a solution of Al and Mg salts was slowly added dropwise to a solution of Na_2CO_3 (0.5 M), maintained at a pH 12 and 60 °C with stirring at 200 rpm. The mixture was filtered and the solid heated from rt to 450 °C. The dried mixed oxides were characterized by XRD, nitrogen physisorption (S_{BET}), infrared spectroscopy (FT-IR), and thermoanalysis (TGA/DTA), and found to be layered structures.

Data analysis

Experimental results were expressed as a mean of six experiments ± standard error of mean. CRCs and experimental data were plotted and the CRCs adjusted by the nonlinear curve-fitting program Origin 8.0 (Microcal Software Inc., USA). Significance was evaluated using ANOVA followed by Tukey's test. Significant pharmacological effects were determined by a p value < 0.05 in the *ex vivo* experiments.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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