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Synthesis and antifungal activity of new thienyl and aryl conazoles

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Abstract
Recent studies reported that an first generation azole (tioconazole) was active against *Candida glabrata* petite mutants, a fluconazole- and voriconazole- resistant strain of fungi characterized as most azole resistant yeast by an overexpression of the efflux pumps. Therefore, monosubstituted 1-[2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazoles differing from tioconazole by the nature of the linker and of the aromatic ring in their side-chain were synthesized and evaluated against the mutant and the wild-type strain of *C. glabrata*. New 2-aryl-1-azolyl-3-thienylbutan-2-ols were then designed and synthesized, and their antifungal activity was evaluated against both strains of *C. glabrata* and two other major human pathogenic fungi, *C. albicans* and *Aspergillus fumigatus*. These new compounds exhibited a broad spectrum activity, as well as good efficiency against the petite mutant, suggesting that they may overcome the increased expression of the efflux pumps usually observed in clinical yeast isolates resistant to current azoles.

Keywords: *Antifungal agents, Candida glabrata, conazole derivatives, azole resistance, efflux pumps*

Introduction

During the past two decades, invasive fungal infections have become an important cause of morbidity and mortality [1]. Such a situation is explained by the growing number of immunodepressed patients as the result of a primary infection (AIDS) or frequent use of chemotherapeutic and immunosuppressive agents. Among current antifungals, conazoles are the most frequently used. First generation imidazoles (e.g., tioconazole **I**; Figure 1) are mostly restricted to the treatment of superficial mycoses. Second generation triazoles (e.g., fluconazole **II**; Figure 1) are characterized by a better metabolic stability and distribution profile [2], and are therefore indicated for the treatment of systemic infections. However, several of those second generation azoles suffer from a narrow spectrum of activity. For instance, some yeast species such as *Candida glabrata* and filamentous fungi (e.g., *Aspergillus*) are poorly or not susceptible to fluconazole. Therefore, new broad spectrum antifungals (e.g., voriconazole **III**; Figure 1) showing a good activity against both *Candida* and *Aspergillus* species have been recently developed [3].

However, the extensive use of azoles in prophylaxis and therapy has given rise to the emergence of resistant isolates which has now become a major concern: in the case of patients with HIV, fluconazole-resistant strains of *Candida* were implicated in 21% of the oropharyngial candidiasis [4]. Recent reports even pointed out that several strains were resistant to fluconazole and also to voriconazole [5–8]. This reduced azole susceptibility was often associated with an overexpression of genes encoding some membrane transporters called efflux pumps. Strikingly, one of these studies [8] reported that tioconazole was active

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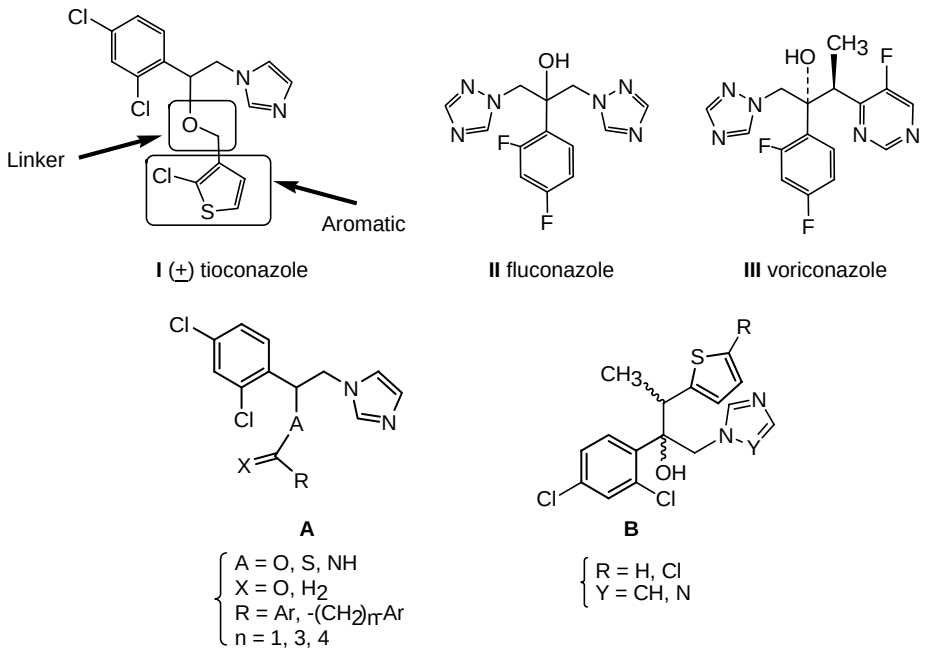


Figure 1. Imidazole and triazole derivatives used in therapy, and the general structure of the new synthesized compounds **A** and **B**.

against *C. glabrata* petite mutant, a fluconazole- and voriconazole-resistant yeast with drug efflux [9,10].

With the aim of discovering new broad spectrum antifungal agents also efficient against fluconazole- and voriconazole-resistant isolates, and taking into account the particular antifungal activity of tioconazole against *C. glabrata* petite mutants, mono-substituted 1-[2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazoles **A** were designed and synthesized in order to evaluate the influence of the nature of the linker and the aromatic ring (Fig. 1) on the antifungal activity against a wild-type strain of *C. glabrata*, and its derived petite mutant chosen as a model of fluconazole- and voriconazole-resistant isolate. From the preliminary results obtained for this first series and related to the first generation of azoles (e.g., tioconazole **I**), a new series of 2-aryl-1-azolyl-3-thienylbutan-2-ols **B** was then synthesized and evaluated for its potential antifungal activity against both strains of *C. glabrata*, as well as against the two other major human pathogenic fungi, i.e. *C. albicans* and *A. fumigatus*.

Materials and methods

Chemistry

Instrumentation. Synthesis of compounds **2b** [11], **3b** [12], **3c** [13], **3d**–**3f** [14], **3g** [15], **3h** [16], **3j** [17], **3o** [17], **3k** [16], **5** [18], **8** [19], **9** [14], **10** [20] and **11** [20] were realized as previously described. Alcohol 1 [16] is commercially available from Acros and used as received. Silicagel 60 (Macherey-Nagel, 230-400 mesh) was used for column chromatography and precoated Silicagel plates (Macherey-Nagel, SIL G/UV254, 0.25 mm) were used for preparative TLC. Melting points were determined with an Electrothermal 8100 melting point apparatus and reported uncorrected. Infrared (IR) spectra were determined on a BRUKER FT IR Vector 22 using KBr discs for solids or neat liquid films for liquids. NMR spectra were recorded in $CDCl_3$ solution on a BRUKER AVANCE DRX 500 spectrometer or a JEOL GSX 270 WB spectrometers.

*1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl 5-chlorothiophene-2-carboxylate (**2a**)*. A solution of 5-chlorothiophene-2-carboxylic acid (1.23 mmol) and thionyl chloride (13.79 mmol) was refluxed for 2 h and evaporated under reduced pressure. The residue was then added to a solution of 1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol 1 (0.97 mmol) and triethylamine (1.94 mmol) in dichloromethane (20 mL) with stirring at 0°C for 1 h. The resulting solution was washed with 5% potassium hydroxide (10 mL) and water (2 × 20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 using dichloromethane/ethanol (97/3) as eluent to give **2a** as a colorless oil (0.75 mmol, 77%). IR?(KBr) ν_{max}: 3110 (C–H_{arom}), 2931 (C–H), 1716 (C=O), 1330 (C–O) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 4.33 (dd, 1H, J = 6.0 and 14.9 Hz, CH_{2a}), 4.43 (dd, 1H, J = 3.2 and 14.9 Hz, CH_{2b}), 6.41 (dd, 1H, J = 3.2 and 6.0 Hz, C*H), 6.81 (s, 1H_{arom}, H-2 imid.), 6.95 (d, 1H_{arom}, J = 4.4 Hz, H-4 thienyl), 7.00 (s, 1H_{arom}, H-3 imid.), 7.01 (d, 1H_{arom}, J = 8.5 Hz,

H-6′), 7.15 (dd, 1H$_{arom}$, J = 2.1 and 8.5 Hz, H-5′), 7.34 (s, 1H$_{arom}$, H-5 imid.), 7.41 (d, 1H$_{arom}$, J = 2.1 Hz, H-3′), 7.62 (d, 1H$_{arom}$, J = 4.4 Hz, H-3-thienyl); ^{13}C-NMR (270 MHz; $CDCl_3$): 49.5 (CH_2), 71.9 (C⋆H), 127.6 (2CH$_{arom}$), 127.7 (2CH$_{arom}$), 129.5 (2CH$_{arom}$), 129.8 (C$_{q/arom}$), 132.1 (C$_{q/arom}$), 132.2 (C$_{q/arom}$), 134.0 (2CH$_{arom}$), 135.2 (C$_{q/arom}$), 135.5 (C$_{q/arom}$), 158.9 (C=O); HRMS (MeOH, APCI +) m/z: 400.9672 (requires: 400.9685).

*General procedure for compounds **3***. Sodium hydride (21.5 mmol) (60% dispersion in mineral oil) was added to a stirred solution of 1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol **1** (3.90 mmol) in anhydrous THF (25 mL) and the mixture was refluxed for 30 min. A solution of the designated halogenalkyl or methanesulfonate derivatives (5.84 mmol) in anhydrous THF (10 mL) was added and the mixture was stirred at room temperature. After 3 h, cold water (10 mL) and dichloromethane (20 mL) were then added. The organic layer was separated, dried (Na_2SO_4), filtered, evaporated under reduced pressure and the product was purified by flash chromatography on SiO_2 using the designated eluent.

*4-{[1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl) ethoxy]methyl}pyridine (**3a**)*. Eluent: ethylacetate/ethanol (8/2), pale brown oily residue, 30%; IR (KBr) ν_{max}: 3054 (C–H$_{arom}$), 2934 (C–H), 1605 (C=C$_{arom}$), 1099 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 4.07 (dd, 1H, J = 5.4 and 13.5 Hz, CH_{2a}), 4.22 (dd, 1H, J = 2.7 and 13.5 Hz, CH_{2b}), 4.25 (d, 1H, J = 13.5 Hz, $CH_{2a'}$), 4.45 (d, 1H, J = 13.5 Hz, $CH_{2b'}$), 4.97 (dd, 1H, J = 2.7 and 5.4 Hz, C⋆H), 6.90 (s, 1H$_{arom}$, H-2 imid.), 7.03 (m, 3H$_{arom}$, H-5′, H-6′ and H-3 imid.), 7.28 (m, 2H$_{arom}$, H-3′ and H-5 imid.), 7.45 (d, 1H$_{arom}$, J = 9.0 Hz, H-3b and H-3b′ pyridine), 8.51 (d, 2H$_{arom}$, J = 9.0 Hz, H-2a and H-2a′ pyridine); ^{13}C-NMR (270 MHz; $CDCl_3$): 51.5 (CH_2), 68.9 (CH_2), 77.5 (C⋆H), 119.3 (CH$_{arom}$), 121.1 (2CH$_{arom}$), 127.6 (CH$_{arom}$), 127.8 (CH$_{arom}$), 128.9 (CH$_{arom}$), 129.2 (CH$_{arom}$), 132.8 (C$_{q/arom}$), 132.9 (C$_{q/arom}$), 134.7 (C$_{q/arom}$), 137.3 (CH$_{arom}$), 145.2 (C$_{q/arom}$), 149.3 (2CH$_{arom}$); HRMS (EI +) m/z: 347.0582 (requires: 347.0592).

*1-{2-[(3-Chlorobenzyl)oxy]-2-(2,4-dichlorophenyl) ethyl}-1H-imidazole (**3i**)*. Eluent: dichloromethane/ethanol (98/2), pale yellow oil, 84%; IR (KBr) ν_{max}: 3066 (C–H$_{arom}$), 2930 (C–H), 1589 (C=C$_{arom}$), 1095 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 4.01 (dd, 1H, J = 7.5 and 14.6 Hz, CH_{2a}), 4.15 (dd, 1H, J = 2.9 and 14.6 Hz, CH_{2b}), 4.17 (d, 1H, J = 11.7 Hz, $CH_{2a'}$), 4.37 (d, 1H, J = 11.7 Hz, $CH_{2b'}$), 4.92 (dd, 1H, J = 2.9 and 7.5 Hz, C⋆H), 6.85 (s, 1H$_{arom}$, H-2 imid.), 6.98 (m, 2H$_{arom}$, H-5″ and H-6″), 7.09 (s, 1H$_{arom}$, H-3 imid.), 7.19 (m, 2H$_{arom}$, H-2″ and H-4″), 7.22 (dd, 1H$_{arom}$, J = 1.9 and 8.3 Hz, H-5′), 7.26 (d, 1H$_{arom}$, J = 8.3 Hz, H-6′), 7.35 (d, 1H$_{arom}$, J = 1.9 Hz, H-3′), 7.38 (s, 1H$_{arom}$, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 50.9 (CH_2), 70.4 (CH_2), 76.7 (C⋆H), 119.4 (CH$_{arom}$), 125.2 (CH$_{arom}$), 127.2 (CH$_{arom}$), 127.6 (CH$_{arom}$), 127.7 (CH$_{arom}$), 128.1 (CH$_{arom}$), 128.9 (CH$_{arom}$), 129.2 (CH$_{arom}$), 129.5 (CH$_{arom}$), 132.9 (C$_{q/arom}$), 133.5 (C$_{q/arom}$), 133.9 (C$_{q/arom}$), 134.5 (C$_{q/arom}$), 137.5 (C$_{q/arom}$), 138.6 (CH$_{arom}$); HRMS (MeOH, APCI +) m/z: 381.0346 (requires: 381.0328).

*1-{2-(2,4-Dichlorophenyl)-2-[(3-methylbenzyl)oxy] ethyl}-1H-imidazole (**3l**)*. Eluent: dichloromethane/ethanol (97/3), brown oil, 20%; IR (KBr) ν_{max}: 3012 (C–H$_{arom}$), 2924 (C–H), 1091 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 2.33 (s, 3H, CH_3), 4.05 (dd, 1H, J = 7.3 and 14.1 Hz, CH_{2a}), 4.19 (dd, 1H, J = 2.6 and 14.1 Hz, CH_{2b}), 4.20 (d, 1H, J = 11.5 Hz, $CH_{2a'}$), 4.44 (d, 1H, J = 11.5 Hz, $CH_{2b'}$), 4.98 (dd, 1H, J = 2.6 and 7.3 Hz, C⋆H), 6.97 (m, 2H$_{arom}$, H-2″ and H-4″), 6.96 (s, 1H$_{arom}$, H-2 imid.), 7.07 (s, 1H$_{arom}$, H-3 imid.), 7.10 (dd, 1H$_{arom}$, J = 7.7 and 7.9 Hz, H-5″), 7.19 (d, 1H$_{arom}$, J = 7.9 Hz, H-6″), 7.28 (dd, 1H$_{arom}$, J = 1.9 and 8.3 Hz, H-5′), 7.35 (d, 1H$_{arom}$, J = 8.3 Hz, H-6′), 7.43 (d, 1H$_{arom}$, J = 1.9 Hz, H-3′), 7.57 (s, 1H$_{arom}$, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 21.4 (CH_3), 51.6 (CH_2), 71.6 (C⋆H), 76.4 (CH_2), 124.8 (2CH$_{arom}$), 127.8 (CH$_{arom}$), 128.4 (2CH$_{arom}$), 128.4 (CH$_{arom}$), 128.5 (CH$_{arom}$), 128.8 (CH$_{arom}$), 129.5 (2CH$_{arom}$), 133.2 (C$_{q/arom}$), 133.9 (C$_{q/arom}$), 134.8 (C$_{q/arom}$), 136.5 (C$_{q/arom}$), 138.2 (C$_{q/arom}$); HRMS (MeOH, APCI +) m/z: 361.0878 (requires: 361.0874).

*1-{2-(2,4-Dichlorophenyl)-2-[(4-methylbenzyl)oxy] ethyl}-1H-imidazole (**3m**)*. Eluent: dichloromethane/ethanol (97/3), orange oil, 57%; IR (KBr) ν_{max}: 3023 (C–H$_{arom}$), 2923 (C–H), 1589 (C=C), 1086 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 2.36 (s, 3H, CH_3), 4.04 (dd, 1H, J = 7.5 and 14.5 Hz, CH_{2a}), 4.19 (dd, 1H, J = 2.8 and 14.5 Hz, CH_{2b}), 4.22 (d, 1H, J = 11.1 Hz, $CH_{2a'}$), 4.43 (d, 1H, J = 11.1 Hz, $CH_{2b'}$), 4.98 (dd, 1H, J = 2.8 and 7.5 Hz, C⋆H), 6.92 (s, 1H$_{arom}$, H-2 imid.), 7.01 (s, 1H$_{arom}$, H-3 imid.), 7.07 (d, 2H$_{arom}$, J = 8.1 Hz, H-3″ and H-5″), 7.15 (d, 2H$_{arom}$, J = 8.1 Hz, H-2″ and H-6″), 7.28 (dd, 1H$_{arom}$, J = 1.7 and 8.3 Hz, H-5′), 7.36 (d, 1H$_{arom}$, J = 8.3 Hz, H-6′), 7.45 (d, 1H$_{arom}$, J = 1.7 Hz, H-3′), 7.47 (s, 1H$_{arom}$, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 21.1 (CH_3), 51.2 (CH_2), 71.3 (CH_2), 76.5 (C⋆H), 127.7 (2CH$_{arom}$), 128.4 (2CH$_{arom}$), 128.9 (2CH$_{arom}$), 129.1 (2CH$_{arom}$), 129.3 (2CH$_{arom}$), 133.1 (C$_{q/arom}$), 133.6 (C$_{q/arom}$), 134.08 (C$_{q/arom}$), 134.6 (C$_{q/arom}$), 137.6 (C$_{q/arom}$); HRMS (MeOH, APCI +) m/z: 361.0884 (requires: 361.0874).

*1-{2-(2,4-Dichlorophenyl)-2-[(2,4-dimethylbenzyl) oxy]ethyl}-1H-imidazole (**3n**)*. Eluent: dichloromethane/ethanol (98/2), orange oil, 27%; IR (KBr) ν_{max}: 3060 (C–H_{arom}), 2935 (C–H), 1589 (C=C, Ar), 1086 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 2.14 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.02 (dd, 1H, J = 7.5 and 14.5 Hz, CH_{2a}), 4.17 (dd, 1H, J = 2.7 and 14.5 Hz, CH_{2b}), 4.21 (d, 1H, J = 11.1 Hz, $CH_{2a'}$), 4.40 (d, 1H, J = 11.1 Hz, $CH_{2b'}$), 4.98 (dd, 1H, J = 2.7 and 7.5 Hz, C*H), 6.88 (s, 1H_{arom}, H-2 imid.), 7.00 (m, 4H_{arom}, H-3″, H-5″, H-6″ and H-3 imid.), 7.28 (dd, 1H_{arom}, J = 1.9 and 8.3 Hz, H-5′), 7.34 (d, 1H_{arom}, J = 8.3 Hz, H-6′), 7.43 (d, 1H_{arom}, J = 1.9 Hz, H-3′), 7.45 (s, 1H_{arom}, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 18.6 (CH_3), 21.1 (CH_3), 51.4 (CH_2), 69.7 (CH_2), 76.5 (C*H), 126.4 (CH_{arom}), 127.8 (CH_{arom}), 128.2 (CH_{arom}), 128.4 (CH_{arom}), 128.5 (CH_{arom}), 128.8 (CH_{arom}), 128.9 (CH_{arom}), 129.5 (CH_{arom}), 131.1 (CH_{arom}), 131.2 ($C_{q/arom}$), 131.6 ($C_{q/arom}$), 134.2 ($C_{q/arom}$), 134.7 ($C_{q/arom}$), 136.6 ($C_{q/arom}$), 138.0 ($C_{q/arom}$); HRMS (MeOH/H_2O, ESI +) m/z: 375.1031 (requires: 375.1030).

*1-{2-(2,4-Dichlorophenyl)-2-[2-(thien-2-yl)ethoxy] ethyl}-1H-imidazole (**3p**)*. Eluent: dichloromethane/ethanol (9/1), pale yellow oil, 60%; IR (KBr) ν_{max}: 3053 (C–H_{arom}), 2986 (C–H), 1098 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 3.07 (t, 2H, J = 6.2 Hz, CH_2), 3.50 (dt, 1H, J = 6.2 and 9.0 Hz,, $CH_{2a'}$), 3.56 (dt, 1H, J = 6.2 and 9.0 Hz, $CH_{2b'}$), 4.00 (dd, 1H, J = 7.1 and 15.5 Hz, CH_{2a}), 4.19 (dd, 1H, J = 2.6 and 14.5 Hz, CH_{2b}), 4.88 (dd, 1H, J = 2.6 and 7.1 Hz, C*H), 6.77 (d, 1H_{arom}, J = 3.2 Hz, H-5 thienyl), 6.85 (s, 1H_{arom}, H-2 imid.), 6.94 (dd, 1H_{arom}, J = 3.2 and 5.1 Hz, H-4 thienyl), 6.99 (s, 1H_{arom}, H-3 imid.), 7.07 (d, 1H_{arom}, J = 8.5 Hz, H-5′), 7.18 (d, 1H_{arom}, J = 5.1 Hz, H-3 thienyl), 7.19 (dd, 1H_{arom}, J = 1.9 and 8.5 Hz, H-4′), 7.40 (d, 1H_{arom}, J = 1.9 Hz, H-3′), 7.41 (s, 1H_{arom}, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 30.5 (CH_2), 51.3 (CH_2), 70.5 (CH_2), 77.9 (C*H), 119.9 (CH_{arom}), 120.8 (CH_{arom}), 122.2 (CH_{arom}), 123.8 (CH_{arom}), 125.4 (CH_{arom}), 126.7 (CH_{arom}), 127.7 (CH_{arom}), 128.4 (CH_{arom}), 128.8 ($C_{q/arom}$), 129.3 (CH_{arom}), 132.9 ($C_{q/arom}$), 134.0 ($C_{q/arom}$), 134.6 ($C_{q/arom}$); HRMS (MeOH, APCI +) m/z: 367.0438 (requires: 367.0439).

*1-{2-(2,4-Dichlorophenyl)-2-[2-(thien-3-yl)ethoxy] ethyl}-1H-imidazole (**3q**)*. Eluent: ethyl acetate/ethanol (95/5), yellow oil, 17%; IR (KBr) ν_{max}: 3113 (C–H_{arom}), 2929 (C–H), 1076 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 2.89 (t, 2H, J = 6.6 Hz, CH_2), 3.48 (dt, 1H, J = 6.6 and 8.9 Hz, $CH_{2a'}$), 3.54 (dt, 1H, J = 6.6 and 8.9 Hz, $CH_{2b'}$), 3.97 (dd, 1H, J = 7.3 and 14.4 Hz, CH_{2a}), 4.16 (dd, 1H, J = 2.6 and 14.4 Hz, CH_{2b}), 4.86 (dd, 1H, J = 2.6 and 7.3 Hz, C*H), 6.85 (s, 1H_{arom}, H-2 imid.), 6.90 (dd, 1H_{arom}, J = 1.3 and 4.9 Hz, H-4 thienyl), 6.95 (dd, 1H_{arom}, J = 1.3 and 2.9 Hz, H-2 thienyl), 7.01 (s, 1H_{arom}, H-3 imid.), 7.05 (d, 1H_{arom}, J = 8.3 Hz, H-5′), 7.18 (dd, 1H_{arom}, J = 1.9 and 8.3 Hz, H-4′), 7.27 (dd, 1H_{arom}, J = 2.9 and 4.9 Hz, H-5 thienyl), 7.40 (d, 1H_{arom}, J = 1.9 Hz, H-3′), 7.42 (s, 1H_{arom}, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 30.5 (CH_2), 51.1 (CH_2), 69.9 (CH_2), 77.6 (C*H), 119.6 (CH_{arom}), 121.2 (CH_{arom}), 125.3 (CH_{arom}), 127.5 (CH_{arom}), 128.1 (CH_{arom}), 128.2 (CH_{arom}), 128.7 (CH_{arom}), 129.1 (CH_{arom}), 132.8 ($C_{q/arom}$), 134.1 ($C_{q/arom}$), 134.4 ($C_{q/arom}$), 137.5 (CH_{arom}), 138.4 ($C_{q/arom}$); HRMS (MeOH, APCI +) m/z: 367.0432 (requires: 367.0439).

*1-{2-(2,4-Dichlorophenyl)-2-[4-(thien-2-yl)butoxy] ethyl}-1H-imidazole (**3r**)*. Eluent: dichloromethane/ethanol (98/2), yellow oil, 47%; IR (KBr) ν_{max}: 3114 (C–H_{arom}), 2939 (C–H), 1076 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 1.67 (m, 4H, $2CH_2$), 2.82 (t, 2H, J = 7.3 Hz, CH_2), 3.25 (dt, 1H, J = 5.8 and 9.2 Hz, $CH_{2a'}$), 3.35 (dt, 1H, J = 6.4 and 9.2 Hz, $CH_{2b'}$), 3.98 (dd, 1H, J = 7.3 and 14.3 Hz, CH_{2a}), 4.17 (dd, 1H, J = 2.7 and 14.3 Hz, CH_{2b}), 4.84 (dd, 1H, J = 2.7 and 7.3 Hz, C*H), 6.77 (dd, 1H_{arom}, J = 1.1 and 3.2 Hz, H-2 thienyl), 6.92 (dd, 1H_{arom}, J = 3.2 and 4.6 Hz, H-4 thienyl), 6.93 (d, 1H_{arom}, J = 5.1 Hz, H-5′), 7.02 (s, 1H_{arom}, H-2 imid.), 7.11 (dd, 1H_{arom}, J = 1.1 and 5.1 Hz, H-4′), 7.25 (dd, 1H_{arom}, J = 1.1 and 4.6 Hz, H-5 thienyl), 7.26 (s, 1H_{arom}, H-3 imid.), 7.41 (d, 1H_{arom}, J = 1.1 Hz, H-3′), 7.44 (s, 1H_{arom}, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 28.03 (CH_2), 28.9 (CH_2), 29.4 (CH_2), 51.3 (CH_2), 69.6 (CH_2), 77.8 (C*H), 119.6 (CH_{arom}), 122.8 (CH_{arom}), 124.1 (CH_{arom}), 126.6 (CH_{arom}), 127.7 (CH_{arom}), 128.4 (CH_{arom}), 129.1 (CH_{arom}), 129.4 (CH_{arom}), 133.0 ($C_{q/arom}$), 134.5 ($C_{q/arom}$), 134.7 ($C_{q/arom}$), 137.7 (CH_{arom}), 144.7 ($C_{q/arom}$); HRMS (MeOH, APCI +) m/z: 395.0750 (requires: 395.0752).

*1-{2-(2,4-Dichlorophenyl)-2-[5-(thien-2-yl)pentoxy] ethyl}-1H-imidazole (**3s**)*. Eluent: dichloromethane/ethanol (98/2), brown oil, 13%; IR (KBr) ν_{max}: 3052 (C–H_{arom}), 2985 (C–H), 1076 (C–O–C) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 1.38 (m, 2H, CH_2), 1.60 (m, 4H, $2CH_2$), 2.81(t, 2H, J = 7.3 Hz, CH_2), 3.22 (dt, 1H, J = 6.4 and 9.0 Hz, $CH_{2a'}$), 3.32 (dt, 1H, J = 6.6 and 9.0 Hz, $CH_{2b'}$), 3.96 (dd, 1H, J = 7.3 and 14.4 Hz, CH_{2a}), 4.15 (dd, 1H, J = 2.8 and 14.4 Hz, CH_{2b}), 4.83 (dd, 1H, J = 2.8 and 7.3 Hz, C*H), 6.77 (m, 1H_{arom}, H-2 thienyl), 6.92 (m, 2H_{arom}, H-4 thienyl and H-5′), 7.01 (s, 1H_{arom}, H-2 imid.), 7.11 (dd, 1H_{arom}, J = 1.3 and 5.1 Hz, H-4′), 7.27 (m, 2H_{arom}, H-5 thienyl and H-3 imid.), 7.42 (m, 1H_{arom}, H-3′), 7.43 (s, 1H_{arom}, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 25.5 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 31.4 (CH_2), 51.4 (CH_2), 69.9 (CH_2), 77.7 (C*H), 119.8 (CH_{arom}), 122.8 (CH_{arom}),

123.9 (CH_{arom}), 126.6 (CH_{arom}), 127.7 (CH_{arom}), 128.3 (CH_{arom}), 128.9 (CH_{arom}), 129.4 (CH_{arom}), 129.4 ($C_{q/arom}$), 133.0 ($C_{q/arom}$), 134.5 ($C_{q/arom}$), 137.7 (CH_{arom}), 144.8 ($C_{q/arom}$); HRMS (MeOH, APCI +) m/z: 409.0923 (requires: 409.0908).

*1-(2,4-Dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl methanesulfonate (**4**)*. Methanesulfonyl chloride (3.11 mmol) was added to a stirred solution of 1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol **1** (3.11 mmol) and triethylamine (3.11 mmol) in dichloromethane (20 mL), and the mixture was stirred at 0°C for 1 h. The resulting solution was washed with 5% potassium hydroxide (10 mL) and water (20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash chromatography on SiO_2 using dichloromethane/ethanol (95/5) as eluent to give **4** as white crystals (2.98 mmol, 96%). Mp: 107–109°C; IR (KBr) ν_{max}: 3137 (C–H_{arom}), 2987 (C–H), 1335 and 1192 (SO_2) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 2.71 (s, 3H, CH_3), 4.24 (dd, 1H, J = 7.5 and 15.2 Hz, CH_{2a}), 6.44 (dd, 1H, J = 3.0 and 15.2 Hz, CH_{2b}), 6.07 (dd, 1H, J = 3.0 and 7.5 Hz, C*H), 6.95 (s, 1H_{arom}, H-2 imid.), 7.09 (s, 1H_{arom}, H-3 imid.), 7.31 (m, 2H_{arom}, H-5′ and H-6′), 7.43 (s, 1H_{arom}, H-5 imid.), 7.45 (m, 1H_{arom}, H-3′); ^{13}C-NMR (270 MHz; $CDCl_3$): 38.1 (CH_3), 50.4 (CH_2), 77.8 (C*H), 127.9 (CH_{arom}), 128.1 (CH_{arom}), 128.1 (CH_{arom}), 129.3 (CH_{arom}), 129.6 (CH_{arom}), 129.8 (CH_{arom}), 131.2 ($C_{q/arom}$), 131.8 ($C_{q/arom}$), 136.0 ($C_{q/arom}$); HRMS (MeOH/H_2O, ESI +) m/z: 335.0033 (requires: 335.0024).

*5-Chloro-N-[1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethyl]thiophene-2-carboxamide (**6**)*. A solution of 5-chloro-2-thiophene carboxylic acid (1.23 mmol) and thionyl chloride (13.79 mmol) was refluxed for 2 h and concentrated. The resulting mixture was then added to a solution of 1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanamine **5** (0.49 mmol) and triethylamine (1.94 mmol) in dichloromethane (20 mL). The reaction mixture was then stirred at 0°C for 1 h. The resulting solution was washed with an aqueous 5% potassium hydroxide solution (10 mL) and water (2 × 20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 using dichloromethane/ethanol (96/4) as eluent to give **6** as white crystals (0.45 mmol, 92%). Mp: 102–105°C; IR (KBr) ν_{max}: 3019 (C–H_{arom}), 2958 (C–H), 1649 (C=O), 1542 (N–C=O) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 4.26 (dd, 1H, J = 4.9 and 14.1 Hz, CH_{2a}), 4.37 (dd, 1H, J = 8.9 and 14.1 Hz, CH_{2a}), 5.71 (dd, 1H, J = 4.9 and 8.9 Hz, C*H), 6.69 (d, 1H_{arom}, J = 4.1 Hz, H-4 thienyl), 6.95 (m, 2H_{arom}, H-2 and H-3 imid.), 7.16 (dd, 1H_{arom}, J = 2.1 and 8.5 Hz, H-5′), 7.35 (m, 2H_{arom}, H-6′ and H-5 imid.), 7.37 (d, 1H_{arom}, J = 2.1 Hz, H-3′), 7.40 (d, 1H_{arom}, J = 4.1 Hz, H-3 thienyl), 8.87 (s, 1H, NH); ^{13}C-NMR (270 MHz; $CDCl_3$): 49.1 (CH_2), 52.2 (C*H), 126.9 (CH_{arom}), 127.7 (CH_{arom}), 128.2 (CH_{arom}), 128.8 (2CH_{arom}), 129.7 (CH_{arom}), 129.8 (CH_{arom}), 131.9 (CH_{arom}), 133.4 ($C_{q/arom}$), 134.2 ($C_{q/arom}$), 134.8 ($C_{q/arom}$), 136.0 ($C_{q/arom}$), 136.7 ($C_{q/arom}$), 161.2 (C = O); HRMS (MeOH, APCI +) m/z: 399.9841 (requires: 399.9845).

*N-[(5-Chlorothien-2-yl)methyl]-1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethylamine (**7**)*. To a suspension of lithium aaluminum hydride (1.05 mmol) in anhydrous THF (10 mL) was added amide **6** (0.32 mmol), the reaction mixture was then stirred for 2 h at room temperature. The mixture was hydrolysed with ethanol (10 mL), filtered on Celite® and concentrated under reduced pressure. The resulting residue was diluted with dichloromethane (20 mL), washed with water (3 x 10 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 using dichloromethane/ethanol (95/5) as eluent to give 7 as a brown oil (0.05 mmol, 16%). IR (KBr) ν_{max}: 3248 (N–H), 3105–3009 (C–H_{arom}), 2925 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 3.57 (d, 1H, J = 13.7 Hz, $CH_{2a'}$), 3.75 (d, 1H, J = 13.7 Hz, $CH_{2b'}$), 4.05 (dd, 1H, J = 7.7 and 15.6 Hz, CH_{2a}), 4.18 (dd, 1H, J = 4.3 and 15.6 Hz, CH_{2b}), 4.50 (dd, 1H, J = 4.3 and 7.7 Hz, C*H), 6.50 (d, 1H_{arom}, J = 3.6 Hz, H-3 thienyl), 6.68 (d, 1H_{arom}, J = 3.6 Hz, H-4 thienyl), 6.86 (s, 1H_{arom}, H-2 imid.), 7.06 (s, 1H_{arom}, H-3 imid.), 7.29 (dd, 1H_{arom}, J = 1.9 and 8.5 Hz, H-5′), 7.37 (d, 1H_{arom}, J = 8.5 Hz, H-6′), 7.42 (d, 1H_{arom}, J = 1.9 Hz, H-3′), 7.67 (s, 1H_{arom}, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 46.1 (CH_2), 51.6 (CH_2), 58.0 (C*H), 119.5 (CH_{arom}), 124.4 (CH_{arom}),125.6 (CH_{arom}), 127.9 (CH_{arom}), 129.0 (CH_{arom}), 129.1 (CH_{arom}), 129.8 (CH_{arom}), 129.9 (CH_{arom}), 134.3 ($C_{q/arom}$), 134.5 ($C_{q/arom}$), 134.8 ($C_{q/arom}$), 137.5 ($C_{q/arom}$), 141.8 ($C_{q/arom}$); HRMS (MeOH/H_2O, ESI +) m/z: 385.0874 (requires: 361.0871).

*General procedure for α,β-unsaturated compounds **12** and **13**.* Tetramethyldiaminomethane (11.1 mmol) was added to a stirred solution of ketone **10** or **11** (7.37 mmol) in acetic anhydride (11.1 mmol) and the mixture was refluxed for 3 h. A saturated aqueous solution of potassium carbonate (40 mL) was then added. The organic layer was extracted with dichloromethane (2 × 30 mL), washed with brine (10 mL), dried (Na_2SO_4), filtered and evaporated at

reduced pressure. The crude product was purified by flash chromatography on SiO_2 using the designated eluent.

*2-(2,4-Dichlorophenyl)-1-(thien-2-yl)prop-2-en-1-one (**12**)*. Eluent: dichloromethane/cyclohexane (6/4), yellow oil, 53%; IR (KBr) ν_{max}: 3099 (C–H_{arom}), 2923 (C–H), 1670 (C=O) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 5.98 (s, 1H_{vinyl}, $CH_{2a/vinyl}$), 6.2 (s, 1H_{vinyl}, $CH_{2b/vinyl}$), 7.10 (dd, 1H_{arom}, J = 3.8 and 4.9 Hz, H-4 thienyl), 7.30 (dd, 1H_{arom}, J = 1.9 and 6.8 Hz, H-5′), 7.34 (d, 1H_{arom}, J = 6.8 Hz, H-6′), 7.39 (d, 1H_{arom}, J = 1.9 Hz, H-3′), 7.65 (d, 1H_{arom}, J = 3.8 Hz, H-5 thienyl), 7.67 (d, 1H_{arom}, J = 4.9 Hz, H-3 thienyl); ^{13}C-NMR (270 MHz; $CDCl_3$): 127.3 (CH_2), 127.4 (CH_{arom}), 127.8 (CH_{arom}), 129.3 (CH_{arom}), 132.0 (CH_{arom}), 133.5 (CH_{arom}), 134.1 ($C_{q/arom}$), 134.3 (CH_{arom}), 135.0 ($C_{q/arom}$), 135.9 ($C_{q/arom}$), 142.8 ($C_{q/arom}$), 146.1 ($C_{q/arom}$), 186.2 (C=O).

*1-(5-Chlorothien-2-yl)-2-(2,4-dichlorophenyl)prop-2-en-1-one (**13**)*. Eluent: dichloromethane/cyclohexane (3/7), yellow oil, 90%; IR (KBr) ν_{max}: 3098 (C–H_{arom}), 2923 (C–H), 1650 (C=O) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 5.97 (s, 1H_{vinyl}, $CH_{2a/vinyl}$), 6.17 (s, 1H_{vinyl}, $CH_{2b/vinyl}$), 6.93 (d, 1H_{arom}, J = 4.1 Hz, H-4 thienyl), 7.33 (dd, 1H_{arom}, J = 1.7 and 8.1 Hz, H-5′), 7.34 (d, 1H_{arom}, J = 8.1 Hz, H-6′), 7.39 (d, 1H_{arom}, J = 1.7 Hz, H-3′), 7.41 (d, 1H_{arom}, J = 4.1 Hz, H-3 thienyl); ^{13}C-NMR (270 MHz; $CDCl_3$): 127.4 (2CH_{arom}), 127.5 ($CH_{2/vinyl}$), 129.4 (CH_{arom}), 132.0 (CH_{arom}), 133.5 ($C_{q/vinyl}$), 133.6 (CH_{arom}), 135.2 ($C_{q/arom}$), 135.6 ($C_{q/arom}$), 140.1 ($C_{q/arom}$), 141.4 ($C_{q/arom}$), 145.4 ($C_{q/arom}$), 185.2 (C=O).

*General procedure for oxirane compounds **14** and **15***. DBU (0.88 mmol) was added to a stirred solution of the α,β-unsaturated compound **12** or **13** (0.71 mmol) and urea-hydrogen peroxide (0.88 mmol) in dried THF (5 mL). After 3 h at room temperature, the mixture was filtered, and the cake washed with chloroform. The filtrate was evaporated under reduced pressure, and the product was purified by flash chromatography on SiO_2.

*[2-(2,4-dichlorophenyl)oxiran-2-yl](thien-2-yl)methanone (**14**)*. Eluent: dichloromethane/cyclohexane (6/4), colorless oil, 66%; IR (KBr) ν_{max}: 3095 (C–H_{arom}), 2926 (C–H), 1660 (C=O) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 3.31 (d, 1$H_{epoxide}$, J = 5.6 Hz, CH_{2a}), 3.54 (d, 1$H_{epoxide}$, J = 5.6 Hz, CH_{2b}), 7,11 (dd, 1H_{arom}, J = 4.1 and 4.7 Hz, H-4 thienyl), 7.30 (dd, 1H_{arom}, J = 1.3 and 8.1 Hz, H-5′), 7.43 (d, 1H_{arom}, J = 8.1 Hz, H-6′), 7.44 (d, 1H_{arom}, J = 1.3 Hz, H-3′), 7.67 (d, 1H_{arom}, J = 4.7 Hz, H-5 thienyl), 8.02 (d, 1H_{arom}, J = 4.1 Hz, H-3 thienyl); ^{13}C-NMR (270 MHz; $CDCl_3$): 53.8 (CH_2), 62.8 (C⋆$_q$), 127.0 (CH_{arom}), 127.9 (CH_{arom}), 129.4 (CH_{arom}), 130.8 (CH_{arom}), 132.8 ($C_{q/arom}$), 134.8 (CH_{arom}), 135.0 ($C_{q/arom}$), 135.1 (CH_{arom}), 135.5 ($C_{q/arom}$), 135.6 ($C_{q/arom}$), 187.4 (C=O).

*(5-Chlorothien-2-yl)[2-(2,4-dichlorophenyl)oxiran-2-yl]methanone (**15**)*. Eluent: dichloromethane/cyclohexane (3/7), yellow oil, 75%; IR (KBr) ν_{max}: 3099 (C–H_{arom}), 2920 (C–H), 1661 (C=O) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 3.33 (d, 1$H_{epoxide}$, J = 5.1 Hz, CH_{2a}), 3.50 (d, 1$H_{epoxide}$, J = 5.1 Hz, CH_{2b}), 6.95 (d, 1H_{arom}, J = 4.1 Hz, H-4 thienyl), 7.29 (dd, 1H_{arom}, J = 1.9 and 8.5 Hz, H-5′), 7.38 (d, 1H_{arom}, J = 8.5 Hz, H-6′), 7.43 (d, 1H_{arom}, J = 1.9 Hz, H-3′), 7.83 (d, 1H_{arom}, J = 4.1 Hz, H-3 thienyl); ^{13}C-NMR (270 MHz; $CDCl_3$): 53.7 (CH_2), 62.9 (C⋆$_q$), 127.1 (CH_{arom}), 127.4 (CH_{arom}), 129.4 (CH_{arom}), 130.9 (CH_{arom}), 132.3 ($C_{q/arom}$), 134.8 ($C_{q/arom}$), 135.7 (CH_{arom}), 135.8 ($C_{q/arom}$), 135.9 ($C_{q/arom}$), 141.0 ($C_{q/arom}$), 186.4 (C=O).

*General procedure for oxiranes **16** and **17***. A solution of 2M butyllithium in cyclohexane (1.84 mmol) was added at 0°C to a solution of methyltriphenylphosphonium bromide (1.84 mmol) in dried THF (4 mL). After 10 min, a solution of oxirane **14** or **15** (1.67 mmol) in dried THF (5 mL) was added, and the mixture was stirred at room temperature for 60 h. Then, the mixture was concentrated and the residue washed with H_2O (2 × 10 mL). The organic residue was extracted with chloroform (2 × 20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 with the designated eluent.

*2-(2,4-Dichlorophenyl)-2-[1-(thien-2-yl)vinyl]oxirane (**16**)*. Eluent: dichloromethane/cyclohexane (3/7), yellow oil, 85%; IR (KBr) ν_{max}: 3099 (C–H_{arom}), 2924 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 3.03 (d, 1$H_{epoxide}$, J = 5.3 Hz, $CH_{2a/epoxide}$), 3.31 (d, 1$H_{epoxide}$, J = 5.3 Hz, $CH_{2b/epoxide}$), 5.28 (s, 1H_{vinyl}, $CH_{2a/vinyl}$), 5.61 (s, 1H_{vinyl}, $CH_{2b/vinyl}$), 6.96 (dd, 1H_{arom}, J = 3.8 and 4.7 Hz, H-4 thienyl), 7.16 (d, 1H_{arom}, J = 3.8 Hz, H-3 thienyl), 7.21 (d, 1H_{arom}, J = 4.7 Hz, H-5 thienyl), 7.24 (dd, 1H_{arom}, J = 1.1 and 8.3 Hz, H-5′), 7.36 (d, 1H_{arom}, J = 1.1 Hz, H-3′), 7.52 (d, 1H_{arom}, J = 8.3 Hz, H-6′); ^{13}C-NMR (270 MHz; $CDCl_3$): 54.1 (CH_2), 60.9 (C⋆$_q$), 119.9 ($CH_{2/vinyl}$), 125.5 (CH_{arom}), 126.2 (CH_{arom}), 126.9 (CH_{arom}), 127.0 (CH_{arom}), 129.2 (CH_{arom}), 131.2 (CH_{arom}), 134.4 ($C_{q/arom}$), 134.6 ($C_{q/arom}$), 135.2 ($C_{q/arom}$), 139.2 ($C_{q/arom}$), 139.4 ($C_{q/vinyl}$).

*2-[1-(5-Chlorothien-2-yl)vinyl]-2-(2,4-dichlorophenyl)oxirane (**17**)*. Eluent: dichloromethane/cyclohexane (3/7), pale oil, 90%; IR (KBr) ν_{max}: 3058

($C-H_{arom}$), 2918 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 3.03 (d, $1H_{epoxide}$, J = 5.1 Hz, $CH_{2a/epoxide}$), 3.29 (d, $1H_{epoxide}$, J = 5.1 Hz, $CH_{2b/epoxide}$), 5.22 (s, $1H_{vinyl}$, $CH_{2a/vinyl}$), 5.55 (s, $1H_{vinyl}$, $CH_{2b/vinyl}$), 6.77 (d, $1H_{arom}$, J = 3.8 Hz, H-4 thienyl), 6.94 (d, $1H_{arom}$, J = 3.8 Hz, H-5 thienyl), 7.38 (d, $1H_{arom}$, J = 1.8 Hz, H-3′), 7.47 (d, $1H_{arom}$, J = 8.2 Hz, H-6″), 7.53 (dd, $1H_{arom}$, J = 1.8 and 8.2 Hz, H-5′); ^{13}C-NMR (270 MHz; $CDCl_3$): 53.9 ($CH_{2/epoxide}$), 60.6 ($C^{\star}_q$), 120.2 ($CH_{2/vinyl}$), 125.6 ($C_{q/arom}$), 125.9 (CH_{arom}), 127.0 (CH_{arom}), 128.3 (CH_{arom}), 129.2 (CH_{arom}), 131.1 (CH_{arom}), 131.8 ($C_{q/arom}$), 133.1 ($C_{q/arom}$), 134.7 ($C_{q/arom}$), 137.6 ($C_{q/arom}$), 138.9 ($C_{q/vinyl}$).

*General procedure for compounds **18**, **19** and **20***. A stirred solution of vinyloxirane **16** or **17** (1.34 mmol), potassium carbonate (6.70 mmol) and imidazole (6.70 mmol) or 1,2,4-triazole (6.70 mmol) was heated in DMF (3 mL) at 80°C for 5 h. Water (40 mL) was added, and the organic layer was extracted with diethylether (2 x 20 mL), washed with H_2O (10 × 5 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The product was purified by flash chromatography on SiO_2 with the designated eluent.

*2-(2,4-Dichlorophenyl)-1-(1H-imidazol-1-yl)-3-(thien-2-yl)but-3-en-2-ol (**18**)*. Eluent: dichloromethane/ethanol (96/4), yellow oil, 50%; IR (KBr) ν_{max}: 3143 (OH), 3056 ($C-H_{arom}$), 2926 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 4.58 (d, 1H, J = 13.1 Hz, CH_{2a}), 5.02 (d, 1H, J = 13.1 Hz, CH_{2b}), 5.34 (s, $1H_{vinyl}$, $CH_{2a/vinyl}$), 5.62 (s, $1H_{vinyl}$, $CH_{2b/vinyl}$), 6.58 (s, $1H_{arom}$, H-2 imid.), 6.77 (s, $1H_{arom}$, H-3 imid.), 6.85 (dd, $1H_{arom}$, J = 3.5 and 4.5 Hz, H-4-thienyl), 6.89 (dd, $1H_{arom}$, J = 1.2 and 3.5 Hz, H-2 thienyl), 7.04 (dd, $1H_{arom}$, J = 2.1 and 7.9 Hz, H-5′), 7.13 (dd, $1H_{arom}$, J = 1.2 and 4.5 Hz, H-5-thienyl), 7.28 (d, $1H_{arom}$, J = 2.1 Hz, H-3′), 7.43 (s, $1H_{arom}$, H-5 imid.), 7.46 (d, $1H_{arom}$, J = 7.9 Hz, H-6′); ^{13}C-NMR (270 MHz; $CDCl_3$): 29.6 (CH_2), 52.9 ($C^{\star}_q$), 116.5 (CH_2), 120.6 (CH_{arom}), 125.5 (CH_{arom}), 126.6 ($2CH_{arom}$), 126.9 (CH_{arom}), 127.7 (CH_{arom}), 130.2 (CH_{arom}), 131.0 (CH_{arom}), 131.7 ($C_{q/arom}$), 134.3 ($C_{q/arom}$), 137.1 ($C_{q/arom}$), 137.9 (CH_{arom}), 140.7 ($C_{q/arom}$), 143.6 ($C_{q/arom}$).

*2-(2,4-Dichlorophenyl)-3-(thien-2-yl)-1-(1H-1,2,4-triazol-1-yl)but-3-en-2-ol (**19**)*. Eluent: dichloromethane/ethanol (97/3), white oil, 93%; IR (KBr) ν_{max}: 3231 (OH), 3127 ($C-H_{arom}$), 2918 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 4.83 (d, 1H, J = 13.9 Hz, CH_{2a}), 5.25 (s, $1H_{vinyl}$, $CH_{2a/vinyl}$), 5.39 (d, 1H, J = 13.9 Hz, CH_{2b}), 5.59 (s, $1H_{vinyl}$, $CH_{2b/vinyl}$), 6.87 (dd, $1H_{arom}$, J = 3.4 and 5.0 Hz, H-4 thienyl), 7.01 (dd, $1H_{arom}$, J = 1.1 and 3.4 Hz, H-3 thienyl), 7.07 (dd, $1H_{arom}$, J = 2.1 and 8.5 Hz, H-5′), 7.15 (dd, $1H_{arom}$, J = 1.1 and 5.0 Hz, H-5 thienyl), 7.28 (d, $1H_{arom}$, J = 2.1 Hz, H-3′), 7.51 (d, $1H_{arom}$, J = 8.5 Hz, H-6′), 7.78 (s, $1H_{arom}$, H-3 triazol), 8.04 (s, $1H_{arom}$, H-5 triazol); ^{13}C-NMR (270 MHz; $CDCl_3$): 54.7 (CH_2), 78.2 ($C^{\star}_q$), 118.1 (CH_2), 125.7 (CH_{arom}), 126.6 ($2CH_{arom}$), 126.8 (CH_{arom}), 127.1 (CH_{arom}), 130.5 ($2CH_{arom}$), 131.7 ($C_{q/arom}$), 132.0 (CH_{arom}), 134.6 ($C_{q/arom}$), 136.3 ($C_{q/arom}$), 140.1 ($C_{q/arom}$), 141.7 ($C_{q/arom}$).

*3-(5-Chlorothien-2-yl)-2-(2,4-dichlorophenyl)-1-(1H-imidazol-1-yl)but-3-en-2-ol (**20**)*. Eluent: dichloromethane/ethanol (94/6), white oil, 11%; IR (KBr) ν_{max}: 3156 (OH), 3099 ($C-H_{arom}$), 2927 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 4.82 (d, 1H, J = 13.2 Hz, CH_{2a}), 5.08 (d, 1H, J = 13.2 Hz, CH_{2b}), 5.37 (s, $1H_{vinyl}$, $CH_{2a/vinyl}$), 5.57 (s, $1H_{vinyl}$, $CH_{2b/vinyl}$), 6.47 (s, $1H_{arom}$, H-2 imid.), 6.60 (d, $1H_{arom}$, J = 4.1 Hz, H-4 thienyl), 6.71 (d, $1H_{arom}$, J = 4.1 Hz, H-3 thienyl), 6.77 (s, $1H_{arom}$, H-3 imid.), 7.03 (d, $1H_{arom}$, J = 8.3 Hz, H-5′), 7.28 (s, $1H_{arom}$, H-3′), 7.44 (d, $1H_{arom}$, J = 8.3 Hz, H-6′), 7.95 (s, $1H_{arom}$, H-5 imid.); ^{13}C-NMR (270 MHz; $CDCl_3$): 54.85 (CH_2), 76.8 ($C^{\star}_q$), 117.7 ($CH_{2/vinyl}$), 125.6 (CH_{arom}), 126.0 (CH_{arom}), 127.2 (CH_{arom}), 128.4 (CH_{arom}), 128.6 (CH_{arom}), 128.7 ($C_{q/arom}$), 130.2 ($C_{q/arom}$), 130.6 (CH_{arom}), 130.8 (CH_{arom}), 131.7 (CH_{arom}), 132.1 ($C_{q/arom}$), 133.2 ($C_{q/arom}$), 134.8 ($C_{q/arom}$), 138.9 ($C_{q/arom}$).

*General procedure for compounds **21**, **22** and **23***. A suspension of alkene **18**, **19** or **20** (0.27 mmol) and 10% Pd/C (30 mg) in ethanol (5 mL) was vigorously stirred under H_2 at room temperature for 12 h. The resulting mixture was filtered on Celite® and evaporated under reduced pressure. The crude product was purified by flash chromatography on SiO_2 using dichloromethane/ethanol (97/3) as eluent.

*2-(2,4-Dichlorophenyl)-1-(1H-imidazol-1-yl)-3-(thien-2-yl)butan-2-ol (**21**)*. Brown oil, 71%; IR (KBr) ν_{max}: 3210 (OH), 3106 ($C-H_{arom}$), 2923 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 1.07 (d, 3H, J = 7.1 Hz, CH_3), 3.89 (d, 1H, J = 14.3 Hz, CH_{2a}), 4.46 (q, 1H, J = 7.1 Hz, C⋆H), 5.08 (d, 1H, J = 14.3 Hz, CH_{2b}), 6.53 (s, $1H_{arom}$, H-2 imid.), 6.74 (s, $1H_{arom}$, H-3 imid), 7.06 (m, $2H_{arom}$, H-3 thienyl and H-4 thienyl), 7.13 (dd, $1H_{arom}$, J = 1.8 and 8.3 Hz, H-5′), 7.31 (d, $1H_{arom}$, J = 4.7 Hz, H-5 thienyl), 7.40 (d, $1H_{arom}$, J = 1.8 Hz, H-3′), 7.48 (s, $1H_{arom}$, H-5 imid.), 7.57 (d, $1H_{arom}$, J = 8.3 Hz, H-6′); ^{13}C-NMR (270 MHz; $CDCl_3$): 17.7 (CH_3), 39.8 (C⋆H), 53.4 (CH_2), 78.3 ($C^{\star}_q$), 124.2 (CH_{arom}), 125.0 (CH_{arom}), 126.4 (CH_{arom}), 127.0 (CH_{arom}), 127.6 (CH_{arom}), 128.3 (CH_{arom}), 129.9 (CH_{arom}), 130.7 (CH_{arom}), 131.3 (CH_{arom}), 134.5 ($C_{q/arom}$), 135.9 ($C_{q/arom}$), 136.7 ($C_{q/arom}$), 143.4 ($C_{q/arom}$).

*2-(2,4-Dichlorophenyl)-3-(thien-2-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol (**22**)*. Yellow oil, 71%; IR (KBr) ν_{max}: 3417 (OH), 3121 (C–H_{arom}), 2926 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 1.09 (d, 3H, J = 7.1 Hz, CH_3), 4.05 (d, 1H, J = 14.3 Hz, CH_{2a}), 4.26 (q, 1H, J = 7.1 Hz, C⋆H), 5.41 (d, 1H, J = 14.3 Hz, CH_{2b}), 7.01 (dd, $1H_{arom}$, J = 3.3 and 5.1 Hz, H-4 thienyl), 7.09 (d, $1H_{arom}$, J = 3.3 Hz, H-3 thienyl), 7.13 (dd, $1H_{arom}$, J = 1.9 and 8.5 Hz, H-5′), 7.28 (d, $1H_{arom}$, J = 5.1 Hz, H-5 thienyl), 7.34 (d, $1H_{arom}$, J = 1.9 Hz, H-3′), 7.65 (d, $1H_{arom}$, J = 8.5 Hz, H-6′), 7.75 (s, $1H_{arom}$, H-5 triazol), 8.04 (s, $1H_{arom}$, H-3 triazol); ^{13}C-NMR (270 MHz; $CDCl_3$): 18.1 (CH_3), 40.1 (C⋆H), 55.2 (CH_2), 78.9 ($C⋆_q$), 125.1 (CH_{arom}), 126.0 (CH_{arom}), 126.2 (CH_{arom}), 127.4 (CH_{arom}), 128.9 ($C_{q/arom}$), 129.7 ($C_{q/arom}$), 130.7 (CH_{arom}), 131.4 (CH_{arom}), 134.5 ($C_{q/arom}$), 137.3 (CH_{arom}), 139.2 (CH_{arom}), 144.1 ($C_{q/arom}$).

3-(5-Chlorothien-2-yl)-2-(2,4-dichlorophenyl)-1-(1H-imidazol-1-yl)butan-2-ol (23). Yellow oil, 31%; IR (KBr) ν_{max}: 3272 (OH), 3149 (C–H_{arom}), 2924 (C–H) cm^{-1}; ^{1}H-NMR (270 MHz; $CDCl_3$): 1.09 (d, 3H, J = 7.1 Hz, CH_3), 4.39 (m, 2H, CH_{2a} and C⋆H), 5.16 (d, 1H, J = 14.3 Hz, CH_{2b}), 6.63 (s, $1H_{arom}$, H-2 imid.), 6.90 (s, $1H_{arom}$, H-3 imid.), 7.07 (d, $1H_{arom}$, J = 3.6 Hz, H-3 thienyl), 7.15 (d, $1H_{arom}$, J = 3.6 Hz, H-4 thienyl), 7.09 (s, $1H_{arom}$, H-5 imid.), 7.28 (m, $1H_{arom}$, H-5′), 7.39 (d, $1H_{arom}$, J = 1.9 Hz, H-3′), 7.67 (d, $1H_{arom}$, J = 8.7 Hz, H-6′); ^{13}C-NMR (270 MHz; $CDCl_3$): 17.5 (CH_3), 39.7 (C⋆H), 55.2 (CH_2), 77.8 ($C⋆_q$), 118.0 (CH_{arom}), 121.1 (CH_{arom}), 124.7 (CH_{arom}), 126.8 (CH_{arom}), 127.3 (CH_{arom}), 127.5 ($C_{q/arom}$), 127.9 (CH_{arom}), 129.5 ($C_{q/arom}$), 130.5 (CH_{arom}), 132.0 (CH_{arom}), 136.1 ($C_{q/arom}$), 136.4 ($C_{q/arom}$), 142.2 ($C_{q/arom}$).

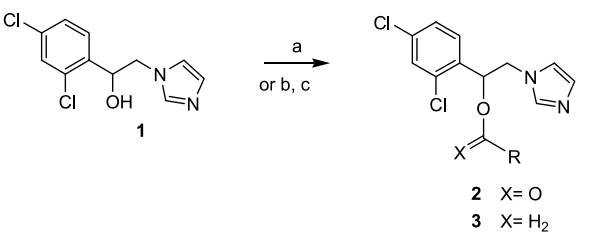
Antifungal activity

Antifungal susceptibilities were evaluated on the following fungi: one azole-susceptible strain of *Candida glabrata* designated 94.5579, its derived fluconazole-resistant petite mutant, *Candida albicans* (ATCC 66-390) and *Aspergillus fumigatus* (CBS 113-26). They were previously cultured on yeast peptone dextrose agar at 37°C during 48 h for yeasts and 72 h for *Aspergillus*. For yeasts, the test was performed following the guidelines of the approved reference method [21]. MICs (Minimum Inhibitory Concentration) were determined using a microdilution assay in RPMI-1640 culture medium, inoculated with 0.5–2.5 × 10^3 cells /mL. The test was performed using sterile 96 flat shaped-well microtitre plates. Serial two-fold drug dilutions were made in DMSO. Each dilutions of the compounds were dispensed at a volume of 5 μL per well, to obtain final concentrations ranging from 250 μg/mL to the concentration where inhibition was not seen. After 48 h at 37°C, the absorbance was measured at 630 nm and $MICs_{80}$ were calculated at the minimum concentration required to inhibit at least 80% of the fungal growth compared to the drug-free control. The *Aspergillus* suspension was prepared by fragmenting the culture in sterile distilled water with a ground-glass grinder and the fungal suspension was finally adjusted spectrophotometrically to an A_{450} of 0.6 [22].

Results and discussion

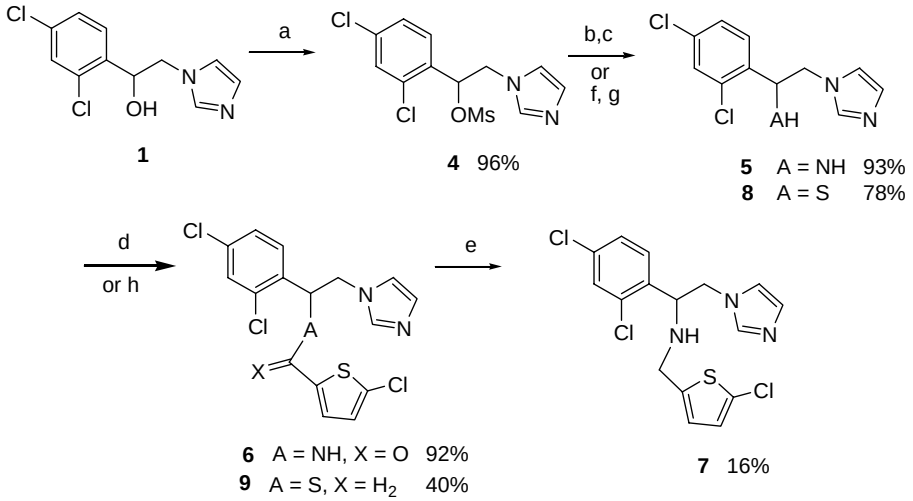
Chemistry

Synthesis of 1-[2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole derivatives was achieved following classical pathways (Schemes 1 and 2). Depending on the nature of the desired benzylic heteroatom, **1** was either directly *O*-acylated to ester **2** [11], *O*-alkylated to ether **3** [12–16] (Scheme 1) or activated as a methanesulfonate **4** in order to access to the amine **7** and the thioether **9** (Scheme 2). Substitution of **4** by NaN_3 led to the corresponding azide [23], which was reduced by treatment with lithium aluminum hydride to give the primary amine **5** [18,23]. The secondary amine **7** was then efficiently obtained in a two step sequence consisting first in an acylation leading



Compound	R	Yield (%)
2a	5-chloro-2-thienyl	77
2b	-Ph	98
3a	4-pyridyl	30
3b	2-quinolyl	40
3c	2-furyl	25
3d	5-chloro-2-thienyl	9
3e	2-thienyl	55
3f	3-thienyl	60
3g	-Ph	*40*
3h	*o*-Cl-C_6H_4-	84
3i	*m*-Cl-C_6H_4-	63
3j	*p*-Cl-C_6H_4-	32
3k	*o*-CH_3-C_6H_4-	23
3l	*m*-CH_3-C_6H_4-	20
3m	*p*-CH_3-C_6H_4-	57
3n	2,4-$(CH_3)_2$-C_6H_3-	27
3o	2,4-Cl_2-C_6H_3-	82
3p	-CH_2-(2-thienyl)	60
3q	-CH_2-(3-thienyl)	17
3r	-$(CH_2)_3$-(2-thienyl)	47
3s	-$(CH_2)_4$-(2-thienyl)	13

Scheme 1. Synthesis of compounds **2** and **3**. Reagents: (a) RCOCl, TEA, dichloromethane; (b) NaH, THF; (c) RCH_2X or RCH_2OMs, THF.



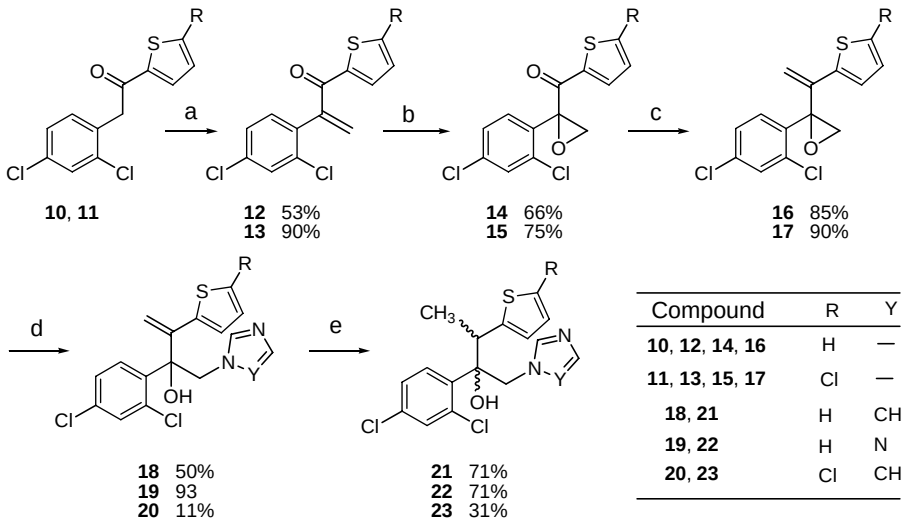
Scheme 2. Synthesis of compounds **4**–**9**. Reaction conditions: (a) MsCl, TEA, dichloromethane, 96%; (b) NaN_3, DMF; (c) $LiAlH_4$, THF; (d) 5-chloro-2-thienylcarbonyl chloride, TEA, dichloromethane, 92%; (e) $LiAlH_4$, THF, 16%; (f) CH_3COSK, THF; (g) NaOH, THF, H_2O; (h) 2-chloro-5-(chloromethyl)thiophene, NaH, THF.

to amide **6**. Its reduction using lithium aluminum hydride gave the expected amine **7**. Starting from the methanesulfonate **4**, the desired thioether **9** [14] was prepared in a classical way by alkylation of the thiol **8** [19].

In the second part of our study, the synthesis of new 2-aryl-1-azolyl-3-thienylbutan-2-ols, **21**–**23**, was performed in five steps through a nucleophilic opening of a thienyloxirane by an imidazolyl or a triazolyl anion as the key step. Therefore, oxirane synthesis started from thienylketones **10** and **11** [20] which were condensed with *N,N,N′,N′*-tetramethyldiaminomethane in acetic anhydride leading to the α,β-unsaturated carbonyls **12** and **13**, respectively [24]. Their oxidation under basic conditions (urea.hydrogen peroxide, DBU) gave the oxiranes **14** and **15** [25]. Nucleophilic attack of these epoxides would give substituted propan-2-ols instead of the desired 2-aryl-1-azolyl-3-thienylbutan-2-ols; therefore, Wittig reaction of methylphosphorane and epoxyketones **14** and **15** gave the allylic epoxides **16** and **17** with the required number of carbon atoms. Imidazole or triazole potassium salts were alkylated by these compounds **16**–**17** to yield the allylic alcohols **18**–**20**. In the last step, a catalytic hydrogenation (H_2, Pd/C) led to the stereomeric mixture of 2-aryl-1-azolyl-3-thienylbutan-2-ols **21**–**23** (Scheme 3).

Antifungal activity

In vitro antifungal susceptibility testing of the monosubstituted 1-[2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazoles indicated out that all of them were active against the parent strain of *C. glabrata* ($MIC_{80} \leq 16$ μg/mL; Table I) [26]. The antifungal activity against *C. glabrata* petite mutant, ranged from inactive ($MIC_{80} = 125$ μg/mL) to a level of activity similar to that of tioconazole. In the first part of the study, the influence of the nature of the linker between the 1-[2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole backbone and the aromatic ring in the side chain was evaluated (Table I). Comparison of the antifungal activity of thienyl compounds **3p**–**3s** established that the length of the linker should be limited: contrary to **3r**, **3s** ($MIC_{80} = 125$ μg/mL) was inactive against the mutant, whereas both compounds showed equal MIC_{80} values of 4 μg/mL against the parent strain. Concerning the nature of the linker, the presence of an ester function did not improve the antifungal activity against the voriconazole-resistant mutant: **2a** and **2b** were respectively less active than the corresponding ethers **3d** and **3g**. The influence of the nature of the heteroatom directly linked to the 1-[2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole backbone was evaluated by comparison of the antifungal activity of the ether **3d** ($MIC_{80} = 4$ μg/mL), amine **7** ($MIC_{80} = 16$ μg/mL) and thioether **9** ($MIC_{80} = 4$ μg/mL). This revealed that the presence of a nitrogen in the linker reduced the antifungal activity. The antifungal activity was also significantly affected for amide **6**, whose MIC_{80} increased to 125 μg/mL. The similar activities of **3d** and **9** ($MIC_{80} = 4$ μg/mL) highlighted that the ether or thioether function are the two best types of linkage. The influence of the nature of the aromatic ring in the side chain was also determined. The replacement of the 2-chloro-3-thienyl moiety by other pyridyl (**3a**), quinolyl (**3b**) and furyl (**3c**) heteroaromatic rings resulted in a decrease of the antifungal activity with MIC_{80} ranging from 16 to 125 μg/mL. This effect was particularly obvious in the case of a nitrogen aromatic ring (**3a**,**3b**), the pyridinic compound 3a being almost inactive against the resistant mutant of *C. glabrata*.



Compound	R	Y
10, **12**, **14**, **16**	H	—
11, **13**, **15**, **17**	Cl	—
18, **21**	H	CH
19, **22**	H	N
20, **23**	Cl	CH

Scheme 3. Synthesis of compounds **12**–**23**. Reaction conditions: (a) $(CH_3)_2NCH_2N(CH_3)_2$, Ac_2O; (b) H_2O_2.urea, DBU, THF; (c) $(C_6H_5)_3PCH_3$. Br, BuLi, THF, 0°C; (d) imidazole or triazole, K_2CO_3, DMF 80°C; (e) H_2, Pd/C, ethanol.

Table I. MIC_{80} for the monosubstituted 1-[2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazoles against a wild strain of *Candida glabrata* and its azole-resistant petite mutant isolate.

	MIC_{80}* (μg/mL)	
	Candida glabrata	
Compound	Parent	Mutant
2a	16	16
2b	16	62
3a	16	125
3b	16	31
3c	8	16
3d	0.25	4
3e	0.5	1
3f	0.5	1
3g	0.5	4
3h	0.5	2
3i	4	4
3j	8	2
3k	1	16
3l	4	8
3m	0.5	8
3n	8	4
3o	4	8
3p	4	4
3q	1	8
3r	4	8
3s	4	125
6	8	125
7	2	16
9	1	4
11	0.25	4
Tioconazole	4	0.5
Fluconazole	8	> 250
Voriconazole	0.5	> 250

[a] Minimun inhibitory concentration required to reduce growth by 80% relative to the control.

Replacement of the thiophene ring of tioconazole by another five membered aromatic ring led to the less active furan **3c**. Among the thienyl derivatives, unsubstituted thiophenes (**3e**,**3f**) were almost as efficient as tioconazole, whatever the orientation of the thiophene. Results of those antifungal evaluations also indicated that the change of thiophene by a phenyl ring led to active compounds against the voriconazole-resistant strain. However all the phenyl derivatives (**3g**–**3o**) were generally less active than the most efficient compound of the thiophenyl series (**3d**–**3f**).

At this point, several parameters may be considered as critical in creating antifungal activity against the voriconazole-resistant strain of *C. glabrata*. The length of the side chain must be limited, otherwise the antifungal activity decreases dramatically (**3s**). Moreover, the lack of a strong hydrogen acceptor such as nitrogen in the spacer or the aromatic ring is also necessary to insure activity against the drug effluxing mutant. The presence of a weak hydrogen bonding atom such as sulfur could be tolerated in the linker or the aromatic ring. As a matter of fact, tioconazole bearing a thiophenyl ring remained the most efficient compound against *C. glabrata* petite mutant.

All the compounds tested so far against the voriconazole-resistant strain were monosubstituted 1-[2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazoles reminiscent of conazoles of the first generation (e.g. tioconazole). Therefore, like several last generation antifungal conazoles (e.g. fluconazole, voriconazole), a tertiary alcohol next to the dihalogenophenyl ring would probably lead to compounds with better pharmacokinetic profile or activity. Recent studies also pointed out that a methyl group in the side chain (e.g. voriconazole) enhanced the binding to the

Table II. MIC_{80} for the tested compounds against several fungal strains.

	MIC_{80}⋆ (μg/mL)			
	Candida glabrata		*C. albicans*	*A. fumigatus*
Compound	Parent	Mutant		
21	0.5	0.25	4	0.5
22	1	0.5	8	0.5
23	0.25	1	8	0.25
Tioconazole	4	0.5	8	0.5
Fluconazole	8	>250	2	>250
Voriconazole	0.5	>250	0.062	8

⋆ Minimun inhibitory concentration required to reduce growth by 80% relative to the control.

conazole target [27], the lanosterol 14-α-demethylase, involved in the synthesis of sterols of the fungal membrane. Therefore, new 2-aryl-1-azolyl-3-thienyl-butan-2-ols **17-21**, bearing a thiophenyl ring separated by a short linker from the backbone of the molecule would probably combine the advantages of the last generation of azoles [3], and the structural requirement in the lateral chain for an activity against *C. glabrata* petite mutant.

Indeed, contrary to fluconazole and voriconazole, the mixture of diastereomers **21** ($MIC_{80} = 0.25$ μg/mL), **22** ($MIC_{80} = 0.5$ μg/mL) and **23** ($MIC_{80} = 1$ μg/mL) were active against the resistant strain of *C. glabrata* (Table II) with MIC_{80}s as high as that tioconazole ($MIC_{80} = 0.5$ μg/mL). Moreover, their antifungal activity was also evaluated against major human pathogenic fungi (*C. albicans* and *A. fumigatus*) and they showed activity against both of them.

In conclusion, several structural features necessary to the escape of tioconazole to the efflux pumps have been defined. In addition, new thienyl conazoles **21**–**23** were synthezised as mixture of diastereomers, and in vitro susceptibility testing showed their high activity against major human pathogenic fungi, but also against an azole-resistant petite mutant. Although these results have to be confirmed using other well characterized azole-resistant isolates, they suggest that these compounds may be broad spectrum antifungals capable of overcoming the increased expression of the efflux pumps usually responsible for the acquired resistance to azoles. The identification of the most potent stereoisomers is also under investigation in our laboratory, prior to the design of an adequate asymmetrical synthesis.

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