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Synthesis of Anti-Fungals, from Chiral imidazolyl-imino and amino Compounds

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Abstract: This work describes the synthesis of novel nonracemic derivatives of imidazole. Some oxidation reactions using Mn(II), Se(II) and nitric acid were employed for the synthesis of the starting materials, imidazolyl carboxaldehydes in straightforward steps. These key step compounds were then subjected to schiff bases and reductive amination processes for the synthesis imidazolylimio and imidazolylamino compounds using standard conditions. Attempts to purify some imidazolylamino compounds using kugelrohr distillation technique have been unsuccessful. However, recrystallization from acetonitrile allowed isolation some compounds in good yields. The new compounds that were synthesised were potential ligands for complexation of metals. Ag(I) was used to synthesis of several metal complexes. These compounds were characterised by nuclear magnetic resonance (NMR) and fourier transform infrared spectroscopy (FTIR) as well as elemental analysis method. These imidazole derivatives have been screened for activity against Candida albicans. Although the S-enantiomer of N-[(1E)-1-benzyl imidazol-2-ylmethylene]-N′-(1-phenylethyl)amine was found inactive against C. albicans, the R-enantiomer showed moderate activity. However, in two instances the activity was greater than that for ketoconazole which is a common agent to cure candida infestation.

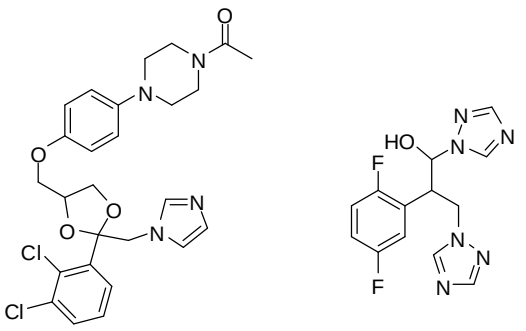
Keywords: Schiff bases, reductive amination, Ag(I) complexes, C. albicans

1.0 Introduction

Fungi are major plant pathogens and are one of the main causes of crop damage and spoilage of foods.[1] Also they are very versatile organisms that live in and on animals as part of their natural flora, but they can also be the cause of numerous infections. For example, superficial mycoses infections are limited to the outermost layers of the skin and hair.[2] One of the most common fungal species to affect humans is the yeast *Candida albicans*. This yeast is dimorphic, that is to say, it exists as single, oval yeast cells, and reproduces by budding. It also has the ability to produce pseudohyphae, where the buds elongate forming a structure known as the germ tube. Germ tubes remain attached to each other to form root-like rhizoids. Rhizoids can penetrate mucosae and intestinal walls causing microscopic holes, which then allow toxins, undigested food, bacteria and fungi to enter the blood stream, giving rise to a condition called Leaky Gut Syndrome.[3] *Candida albicans* is found in humans as a normal part of the bowel flora. In a healthy person, *C. albicans*, in their millions, perform many functions inside the digestive tract, one of which is to destroy harmful bacteria.

Our immune system, together with bacteria, such as *Lactobacillus acidophilus sp.*, helps to keep the growth of *Candida sp.* and other fungal cells under control. However, if the immune system is compromised and the numbers of "friendly" bacteria are reduced, then an overgrowth of *Candida sp.* can occur, giving rise to a condition known as candidiasis.

Ketoconazole **1** (Fig. 1) was the first azole that could be given orally to treat systemic fungal infections. It is effective against several types of fungi, but it is highly toxic to mammalian cells and relapse is common even after seemingly successful treatment. Also, it does not reach therapeutic levels in the central nervous system (CNS) unless administered in very high doses. The main adverse effect of ketoconazole is liver toxicity, which can be fatal.[2] Organ damage can progress even after the treatment has stopped. Ketoconazole can also have adverse reactions with other drugs. The extensive use of the azoles has led to the emergence of fungal resistance, with many fungal strains now resistant to all azoles.[1] Fluconazole **2** (Fig. 1), unlike virtually all other commercially available azoles, is essentially water-soluble and therefore can be given either orally or intravenously. Due to the fact that it reaches high concentrations in the CNS and ocular fluids, it is frequently used in the treatment of fungal meningitis. Fluconazole can also be used for the treatment of fungal infections involving the vagina, mouth, skin tissues and nails. Despite not being a potent antifungal, as judged by *in-vitro* susceptibility tests, it is nevertheless, remarkably effective against a variety of mycoses. Fluconazole is not hepatotoxic at normal dosage levels and side-effects are usually mild. Rare side-effects are hepatitis and exfoliative skin lesions.



1 **2**

Figure1: Ketoconazole and Fluconazole

Complexation

Metal complexes hold an important and divers role in modern medicine. The use of platinum salts in cancer, gold salts in rheumatoid arthritis and silver salts as topical anti-bacterial is witness to this diversity. The term chemotherapy is defined as the use of drugs to injure an invading organism without damage to the host. Although this definition also covers anti-cancer agents, where the invading organism is not strictly different, the treatment has the common aim of the elimination of unwanted cells.[4]

Finally, theses imidazolyl-imino and imidazolyl-amino compounds were employed as various imidazole derivatives ligands for the complexation step using silver perchlorate, Ag (I). In the present work several metal complexes were prepared by the reaction of silver perchlorate with the various imidazole ligands that have been synthesised.

Fungal infections have recently become a focus of major concern with their increasing incidence. Once considered the result rather than cause of infection, fungal diseases are now widely accepted as potentially fatal.[5] *Candida* species, not usually considered highly virulent microorganisms, are widely distributed among vertebrates and humans as commensal microbes.[6] Among all the yeast species *Candida albicans* is one of only a few eukaryotes that has evolved a non-pathogenic association with man. Colonisation largely occurs on the mocusal surfaces of the oral cavity, vaginal tract and gastrointestinal system, where it is kept in check by host defences and the normal microbial flora of the body. *Candida albicans* exhibits structural dimorphism, existing in two morphologies. This characteristic is common to all *Candida* species, however, *Candida albicans* differs in that not only can it exist as ovoid blastspores (yeast cells), but also as true hyphae (germ tubes) (as opposed to pseudohyphae in other *Candida* species). The *Candida* species is a conditionally pathogenic fungus and as such is not considered a highly virulent microorganism. It can cause infection when antibiotics are used or other factors that lead to a reduction in the body's immune system occur. These factors such as illness, or in more recent years the use of immuno suppressive therapy in the combat of AIDS or after organ transplants increase the risk in developing a *candida* fungal infection.[7]

The aim of this work was to design and synthesise novel Schiff base and imidazolylamino ligands as well as their corresponding complexes. These compounds were then screened for anti-*Candida* activity.

2.0 Material and methods

All reagents and starting materials were obtained from commercial sources and used as received. ^{1}H NMR and ^{13}C NMR specra were recorded on a Bruker Avance 300 operated at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C with chemical shift values in ppm relative to tetramethylsilane as the standard. Melting points were determined using an Electrothermal digital Melting Point Apparatus. Infrared spectra of solids (in a KBr matrix) were recorded in the 3700-370 cm^{-1} region on a Nicolet FT-IR Impact 400D infrared spectrometer. Microanalytical data were provided by the Microanalytical Laboratory, National University of Ireland, Cork. The testing of anti-*candida albicans* was carried out by Theresa Tallon in the department of chemistry at the National University of Ireland Maynooth.

2.1 Synthesis of Chiral Schiff Bases Imidazole Derivatives

The aldehyde (1.0 equiv.) was dissolved in acetonitrile (35 mL). (*R*)-(+)-α- methylbenzylamine (0.33 equiv.) was added followed by triethylamine (2.0 equiv.). The reaction mixture was heated at 50 °C for 24 hour.

2.2 Synthesis of Chiral Imidazolylamino Compounds

A solution of aldehyde (1.0 equiv.), (*R*)-(+)-α- methylbenzylamine (1.0 equiv.), and sodium cyanoborohydride (1.0 equiv.) in absolute methanol (2 mL) was stirred at room temperature for 72 h. The methanol was removed in *vacuo*, and the residue was dissolved in 2 N hydrochloric acid (0.5 mL) and extracted with dichloromethane (2 × 5 mL). The aqueous solution was brought to pH >10 with 6 N potassium hydroxide, extracted with dichloromethane (3 × 10 mL). The combined extracts were dried ($MgSO_4$), concentrated to give the chiral imidazolylamino compounds.

2.3 Synthesis of silver complexes

Chiral schiff bases and chiral imidazolylamino of midazole derivativies (1.0 equiv.) and silver perochlorate monohydrate (0.5 equiv.) were dissolved in acetonitrile (30 mL) and refluxed for 30 minutes.

2.4 *N*-[(1*E*)-(1-Benzyl-1*H*-imidazol-2-yl)methylene]-*N*-[(1*R*)-1- phenylethyl]amine (13)

The reaction was carried out according to the reaction 2.1 using 1-benzylimidazole-2-carboxaldehyde **7** (0.15 g, 0.008 mmol), (*R*)-(+)-α-methylbenzylamine (0.03 g, 0.002 mmol) and triethylamine (0.16 g, 0.016 mmol). The solvent was removed under reduced pressure giving *N*-[(1*E*)-(1-benzyl-1*H*-imidazol-2-yl)methylene]-*N*-[(1*R*)-1-phenylethyl]amine **13** as brown oil (0.20 g, 86%). bp 143–145 °C; $[\alpha]_D^{20}$ +21.2 (*c* 0.01, CH_3CH_2OH); δ_H (300 MHz, $CDCl_3$): 1.46 (d, *J*= 6.7 Hz, 3H), 4.41 (q, *J*= 6.6 Hz, 1H), 5.77 (s, 2H), 6.95 (s, 1H), 7.22 (m, 7H), 8.40 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 23.8, 51.1, 70.7, 124.5, 127.0, 127.3, 127.7, 128.0, 128.8, 129.0, 130.1, 137.8, 143.2, 145.1, 152.0 ppm; Analysis: Calculated for $C_{19}H_{19}N_3$: requires C, 78.89; H, 14.53; N, 6.57. Found: C, 78.04; H, 6.57; N, 14.55%.

2.5 *N*-[(1*E*)-(1-Methyl-1*H*-imidazol-2-yl)methylene]-*N*-[(1*R*)-1- phenylethyl]amine (14)

The reaction was carried out according to the reaction 2.1 using 1-methylimidazole-2-carboxaldehyde **8** (0.20 g, 0.02 mmol), (*R*)-(+)-α- methylbenzylamine (0.07 g, 0.006 mmol) and triethylamine (0.36 g, 0.04 mmol). The solvent was removed under pressure giving *N*-[(1*E*) -(1-methyl-1*H*-imidazol-2-yl) methylene]-*N*-[(1*R*)-1-phenyl ethyl] amine **14** as a brown oil (0.3 g, 86%). bp 132–135 °C; $[\alpha]_D^{20}$ +11.65 (*c* 0.01, CH_3CH_2OH); δ_H (300 MHz, $CDCl_3$): 1.55 (d, *J*= 6.6 Hz, 3H), 4.00 (s, 3H), 4.46 (q, *J*= 6.6 Hz, 1H), 6.88 (s, 1H), 7.08 (s, 1H), 7.24 (m, 1H), 7.29 (m, 2H), 7.37 (m, 2H), 8.39 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 25.3, 35.4, 70.3, 124.7, 126.4, 126.8, 128.4, 129.1, 143.1, 145.0, 151.6 ppm.

2.6 Synthesis of *N*-[(1E) -(1*H*-Imidazol-2-yl) methylene]-*N*-[(1*R*)-1- phenylethyl] amine (15)

The reaction was carried out according to the reaction 2.1 using 1*H*-Imidazole-2-carboxaldehyde **11** (0.10 g, 0.010 mmol), (*R*)-(+)-α- methylbenzylamine (0.12 g, 0.003 mmol) and triethylamine (0.10 g, 0.02 mmol).

The solvent was removed under reduced pressure leaving creamy crystals which were recrystalised from acetonitrile to give *N*-[(1*E*)-(1*H*-Imidazol-2-yl)methylene]-*N*-[(1*R*)-1-phenylethyl]amine **15** (0.2 g, 90%) as yellow crystals which were recrystallized from acetonitrile. mp 113–115 °C; ν_{max}/cm^{-1} (KBr): 2300, 1995, 1645, 1470, 1410, 1380, 1265, 1180, 870 cm^{-1}; $[\alpha]_D^{20}$ +13.3 (*c* 0.01, CH_3CH_2OH); δ_H (300 MHz, DMSO): 1.49 (d, *J* = 6.7 Hz, 3H), 4.61 (q, *J* = 6.6 Hz, 1H), 7.07 (s, 1H), 7.24 (m, 2H), 7.31 (m, 2H), 7.40 (m, 2H), 8.29 (s, 1H) ppm; δ_C (75.5 MHz, DMSO): 24.5, 68.3, 69.4, 119.6, 127.0, 128.6, 130.1, 144.8, 151.1, 162.8 ppm; Analysis: Calculated for $C_{12}H_{13}N_3$: requires C, 72.36; H, 6.53; N, 21.10. Found: C, 72.17; H, 6.46; N, 20.98%.

2.7 Synthesis of *N*-[(1*E*)-(4-Methyl-1*H*-imidazol-5-yl)methylene]-*N*-[(1*R*)-1-phenylethyl]amine (16)

The reaction was carried out according to the reaction 2.1 using 4-(5)-methyl-1*H*-imidazol-5-(4)-carboxaldehyde **10** (0.05 g, 0.004 mmol) and (*R*)-(+)-α- methylbenzylamine (0.02 g, 0.001 mmol). The solvent was removed under reduced pressure giving *N*-[(1*E*)-(4-methyl-1*H*-imidazol-5-yl)methylene]-*N*-[(1*R*)-1-phenyl ethyl]amine **16** as yellow crystals which were recrystallized from acetonitrile (0.07 g, 73%). mp 138–140 °C; ν_{max}/cm^{-1} (KBr): 2170, 1953, 1810, 1710, 1550, 1015, 922, 873, 660; $[\alpha]_D^{20}$ +18.6 (*c* 0.01, CH_3CH_2OH); δ_H (300 MHz, $CDCl_3$) 1.55 (d, *J* = 6.6 Hz, 3H), 2.36 (s, 3H), 4.50 (q, *J* = 6.7 Hz, 1H), 7.25 (m, 6H), 8.31 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$) 12.5, 24.1, 69.3, 124.5, 126.6, 127.1, 128.2, 136.6, 144.4, 148.2, 163.0 ppm; Analysis: Calculated for $C_{13}H_{15}N_3$: requires C, 73.23; H, 7.04; N, 19.71. Found: C, 73.02; H, 7.05; N, 19.84%.

2.8 Synthesis of *N*-[(1*E*)-(2-Butyl-4-chloro-1*H*-imidazol-5-yl)methylene]-*N*′- [(1*R*)-1-phenylethyl] amine (17)

The reaction was carried out according to the reaction 2.1 using 2-butyl-4-chloro-1*H*-imidazol-5-carboxaldehyde **12** (0.20 g, 0.012 mol), (*R*)-(+)-α-methylbenzylamine (0.05 g, 0.004 mol) and triethylamine (0.24 g, 0.024 mmol). The solvent was removed under reduced pressure leaving creamy crystals which were recrystallized from acetonitrile to give *N*-[(1*E*)-(2-butyl-4-chloro-1*H*-imidazol-5-yl)methylene]-*N*′-[(1*R*)-1-phenylethyl]amine **17** (0.25 g, 73%) as white crystals which were recrystallized from acetonitrile. mp 103–105 °C; ν_{max}/cm^{-1} (KBr): 1990, 1920, 1855, 1710, 1660, 1200, 945, 765; $[\alpha]_D^{20}$ +36.25 (*c* 0.01, CH_3CH_2OH); δ_H (300 MHz, $CDCl_3$): 0.84 (t, *J* = 7.3 Hz, 3H), 1.26 (m, 2H), 1.55 (m, 5H), 2.41 (m, 2H), 4.60 (q, *J* = 6.6 Hz, 1H), 7.32 (m, 5H), 8.21 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 13.6, 22.1, 24.1, 28.4, 30.0, 69.2, 123.0, 126.6, 127.3, 128.6, 133.3, 144.0, 146.7, 150.7 ppm; Analysis: Calculated for $C_{16}H_{20}N_3Cl$: requires C, 65.33; H, 6.90; N, 14.51; Cl, 12.24. Found: C, 65.44; H, 6.88; N, 14.52; Cl, 11.99%.

2.9 Synthesis of *N*-[(1-Benzyl-1*H*-imidazol-2-yl)methyl]-*N*′-[(1*R*)-1- phenylethyl]amine (18)

The reaction was carried out according to the reaction 2.2 using 1-benzylimidazol-2-carboxaldehyde **7** (0.10 g, 0.005 mmol), (*R*)-(+)-α- methylbenzylamine (0.06 g, 0.005 mmol), and sodium cyanoborohydride (0.03 g, 0.005 mmol). The solvent was removed under reduced pressure giving *N*-[(1-benzyl-1*H*-imidazol-2-yl)methyl]-*N*′-[(1*R*)-1-phenylethyl]amine **18** as brown oil (0.07 g, 66%). $[\alpha]_D^{20}$ +39.8 (*c* 0.02, C_2H_5OH); δ_H (300 MHz, $CDCl_3$): 1.30 (d, *J* = 6.5 Hz, 3H), 3.62 (q, *J* = 14.3 Hz, 2H), 3.67 (q, *J* = 6.5 Hz, 1H), 5.00 (s, 1H), 6.79 (s, 1H), 6.97 (s, 2H), 7.29 (m, 10H) ppm; δ_C (75.5 MHz, $CDCl_3$): 25.8, 44.2, 51.1, 58.5, 120.8, 127.1, 127.2, 127.7, 128.2, 128.8, 129.2, 137.0, 145.4, 147.0 ppm.

2.10 Synthesis of *N*-[(1-Methyl-1*H*-imidazol-2-yl) methyl]-*N*-[(1*R*)-1- phenylethyl] amine (19)

The reaction was carried out according to the reaction 2.2 using 1-methylimidazol-2-carboxaldehyde **8** (0.05 g, 0.004 mmole), (*R*)-(+)-α- methylbenzylamine (0.05 g, 0.004 mmole), and sodium cyanoborohydride (0.03 g, 0.004 mmole). The solvent was removed under reduced pressure giving *N*-[(1-methyl-1*H*-imidazol-2-yl) methyl]-*N*′-[(1*R*)-1-phenylethyl]amine **19** (0.06 g, 62%) as brown oil, which was distilled on Kuglrohr apparatus. $[\alpha]_D^{20}$ +54.8 (*c* 0.01, C_2H_5OH); δ_H (300 MHz, $CDCl_3$): 1.36 (d, *J* = 6.4 Hz, 3H), 3.47 (s, 3H), 3.64 (q, *J* = 12.2 Hz, 2H), 3.81 (d, *J* = 6.2 Hz, 1H), 6.74 (s, 1H), 6.89 (s, 1H), 7.28 (m, 5H) ppm; δ_C (75.5 MHz, $CDCl_3$): 25.3, 52.7, 58.0, 120.3, 127.0, 127.3, 127.6, 129.0, 137.1, 145.5 ppm.

2.11 Synthesis of *N*-[(1-*H*-Imidazol-2-yl) methyl]-*N*′-[(1*R*)-1-phenylethyl] amine (20)

The reaction was carried out according to the reaction 2.2 using imidazole-2-carboxaldehyde **11** (0.05 g, 0.005 mmol), (*R*)-(+)-α-methylbenzylamine (0.06 g, 0.005 mmol), and sodium cyanoborohydride (0.03 g, 0.005 mmol). The solvent was removed under reduced pressure giving *N*-[(1-*H*-imidazol-2-yl) methyl]-*N*′-[(1*R*)-1-phenylethyl] amine **20** (0.06 g, 65%) as brown oil, which was distilled on Kuglrohr apparatus. $[\alpha]_D^{20}$ +50.2 (*c* 0.01, CH_3CH_2OH); δ_H (300 MHz, $CDCl_3$): 1.30 (d, *J* = 6.6 Hz, 3H), 3.68 (s, 2H), 3.76 (q, *J* = 6.6 Hz, 1H), 6.02 (s, 2H), 7.26 (m, 5H) ppm; δ_C (75.5 MHz, $CDCl_3$): 24.3, 45.1, 58.2, 122.0, 127.0, 127.5, 129.0, 145.0, 146.5, 147.7 ppm.

2.12 Synthesis of *N*-[(4-Methyl-1*H*-imidazol-5-yl) methyl]-*N*′-[(1*R*)-1- phenylethyl] amine (21)

The reaction was carried out according to the reaction 2.2 using 4-(5)-methylimidazol-5(4)-carboxaldehyde **10** (0.10 g, 0.001 mmol), (*R*)-(+)-α- methylbenzylamine (0.11 g, 0.001 mmol), and sodium cyanoborohydride (0.05 g, 0.001 mmol). The solvent was removed under reduced pressure giving *N*-[(4-methyl-1*H*-imidazol-5-yl) methyl]-*N*-[(1*R*)-1-phenylethyl] amine **21** (0.01 g, 58%) as brown oil, which was distilled on Kuglrohr apparatus. $[\alpha]_D^{20}$ +38.8 (*c* 0.01, CH_3CH_2OH); δ_H (300 MHz, $CDCl_3$): 1.33 (d, *J* = 6.4

Hz, 3H), 2.04 (s, 3H), 3.55 (s, 2H), 3.78 (q, *J* = 6.6 Hz, 1H), 7.21 (m, 1H), 7.29 (s, 4H), 7.41 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 10.6, 24.1, 42.7, 58.0, 127.1, 127.4, 129.0, 131.0, 133.8, 141.2, 145.4 ppm.

2.13[Ag.(*N*-[(1*E*)-1-Benzyl-1*H*-imidazol-2-ylmethylene]-*N*-[(1*R*)-1-phenylethyl]amine) (ClO_4).H_2O] (22)

The reaction was carried out according to the reaction 2.4. Concentration gave complex **22** (0.10 g, 67%) as brown crystals. mp 64–66 °C; ν_{max}/cm^{-1} (KBr): 1810, 1715, 1660, 1575, 1430, 1345, 1290, 1175, 710; δ_H (300 MHz, $CDCl_3$); 1.47 (d, *J*6.6 Hz, 3H), 4.76 (q, *J*6.4 Hz, 1H), 5.45 (s, 2H), 6.87 (s, 1H), 7.10 (m, 5H), 7.25 (s, 1H), 7.31 (m, 5H), 8.51 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 23.6, 50.4, 68.4, 125.0, 127.2, 128.0, 128.4, 129.0, 129.6, 130.2, 135.7, 143.0, 147.4 ppm; Analysis: Calculated for $C_{38}H_{40}N_6O_5ClAg$: requires: C, 56.01; H, 4.98; N, 10.27. Found: C, 55.70; H, 4.62; N, 9.82 %.

2.14 [Ag.(*N*-[(1*E*)-1-Methyl-1*H*-imidazol-2-ylmethylene]-*N*-[(1*R*)-1-phenylethyl]amine) (ClO_4).H_2O] (23)

The reaction was carried out according to the reaction 2.4. Concentration gave complex **23** (0.20 g, 76%) as brown oil. δ_H (300 MHz, $CDCl_3$); 1.56 (d, *J*6.6 Hz, 3H), 3.93 (s, 3H), 4.85 (q, *J*6.6 Hz, 1H), 7.25 (m, 7H), 8.60 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 21.2, 31.4, 51.8, 66.2, 124.0, 125.0, 126.0, 126.4, 126.8, 128.0, 140.8, 141.0, 145.8 ppm.

2.15 [Ag.(*N*-[(1*E*)-1*H*-imidazol-2-ylmethylene]-*N*-[(1*R*)-1-phenylethyl]amine) (ClO_4)] (24)

The reaction was carried out according to the reaction 2.4. Concentration gave complex **24** (0.11 g, 72%) as creamy crystals. mp 71–73 °C. ν_{max}/cm^{-1} (KBr): 1860, 1810, 1775, 1730, 1690, 1570, 1490, 1375, 1280, 1175, 985, 750; δ_H (300 MHz, $CDCl_3$); 1.53 (d, *J*6.6 Hz, 3H), 4.65 (q, *J*6.5 Hz, 1H), 7.10 (s, 1H), 7.15 (m 5H), 7.25 (s, 1H), 8.49 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 23.4, 68.4, 126.7, 127.7, 128.5, 130.0, 142.5, 143.5, 148.5, 163.0 ppm; Analysis: Calculated for $C_{24}H_{28}N_6O_5ClAg$: requires: C, 46.30; H, 4.50; N, 13.50. Found: C, 46.45; H, 4.24; N, 13.02%.

2.16 [Ag.(*N*-[(1*E*)-2-Butyl-4-chloro-1*H*-imidazol-5-ylmethylene]-*N*-[(1*R*)-1-phenylethyl]amine) (ClO_4)] (25)

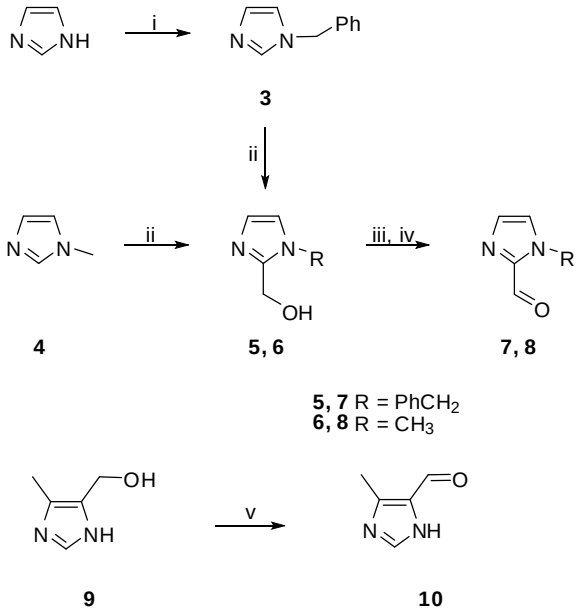
The reaction was carried out according to the reaction 2.4. Concentration gave complex **25** (0.31 g, 66%) as yellow crystals. mp 50–52 °C. ν_{max}/cm^{-1} (KBr): 2680, 2310, 1955, 1775, 1650, 1440, 1280, 1195, 1075, 810, 700; δ_H (300 MHz, $CDCl_3$): 0.74 (t, *J*6.4 Hz, 3H), 1.25 (m, 2H), 1.69 (m, 5H), 2.62 (m, 2H), 4.62 (q, *J*6.6 Hz, 1H), 7.31 (m, 5H), 8.30 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 14.0, 15.0, 20.2, 22.7, 23.3, 28.8, 30.0, 53.3, 127.1, 127.3, 129.2, 129.6, 137.1, 151.3 ppm.

2.17 [Ag.(*N*-[(4-Methyl-1*H*-imidazol-5-yl)methyl]-*N*-[(1*R*)-1-phenylethyl]amine). (ClO_4)] (26)

The reaction was carried out according to the reaction 2.4. Concentration gave complex **26** (0.10 g, 80%) as brown crystals. mp 64–66 °C. δ_H (300 MHz, $CDCl_3$): 1.34 (d, *J*6.6 Hz, 3H), 2.07 (s, 3H), 3.47 (d, *J*5.0 Hz, 2H), 3.68 (q, *J*6.6 Hz, 1H), 7.22 (m, 6H), 7.55 (s, 1H) ppm; δ_C (75.5 MHz, $CDCl_3$): 23.5, 42.63, 58.0, 125.0, 126.6, 127.6, 128.7, 135.6, 143.8, 163.2 ppm.

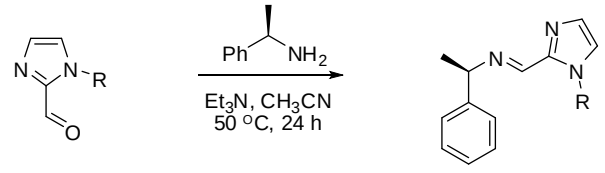
3. Results and discussion

Our approach for the synthesis of the imidazolyl-imino and imidazolyl-amino compounds and their complexes were successfully achieved using Schiff bases and Reductive amination processes respectively of suitably derived imidazolyl carboxaldehydes **7**, **8**, **10**, **11** and **12**. These key imidazolyl carboxaldehydes required for this study, aldehydes **11** and **12** are commercially available. However, compounds **7**, **8** and **10** were synthesised in few steps from the corresponding commercially available imidazoles as shown in Scheme 1. Initially, *N*-benzylimidazole **3** which was prepared from imidazole and *N*-methylimidazole **4** were converted to the corresponding hydroxylimidazoles **5**, **6** respectively in excellent yields using *p*-formaldehyde. This followed by oxidation of compounds **5** and **6** using selenium dioxide and manganese oxide to give imidazolyl carboxyldehydes **7** and **8**.[8] As such, commercially available, hydroxylimidazole **9** was also subjected to the oxidation reaction using pyman procedure to give aldehyde **10**.[9]



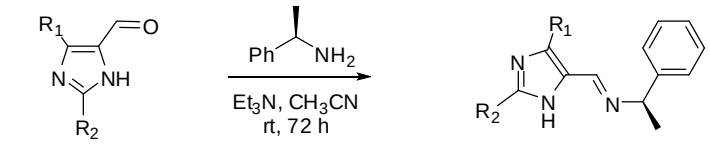
Scheme 1 *Reagents and conditions*: i. $PhCH_2Br$, $(CH_3OCH_2)_2$, MeONa, 0 °C, 1 h, (91%); ii. HCHO, toluene, 110 °C, 18 h, **5** (86%), **6** (88%); *cond.* iii for **7**. SeO_2, 1,4-dioxane, H_2O, reflux, 72 h, (77%); *cond.* iv for **8**. MnO_2, 1,4-dioxane, reflux, 2 h, (75%); v. Na_2CO_3, H_2O, HNO_3, (69%).

With imidazolyl carboxaldehydes **7**, **8**, **10**, **11** and **12** in hand, these were subjected to a Schiff bases reaction. Nonracemic Schiff bases derivatives of imidazole **13**, **14**, **15**, **16** and **17** were synthesised in good yields by treatment of imidazole carboxaldehydes with enantiopure (*S*)-phenylethyl amine in the presence of a weak base such as triethylamine Scheme 2. The resulting products **13** and **14** came out as oils which did not recrystalise.



7 R = $PhCH_2$
8 R = CH_3
11 R = H

13 R = $PhCH_2$ (86%)
14 R = CH_3 (88%)
15 R = H (90%)

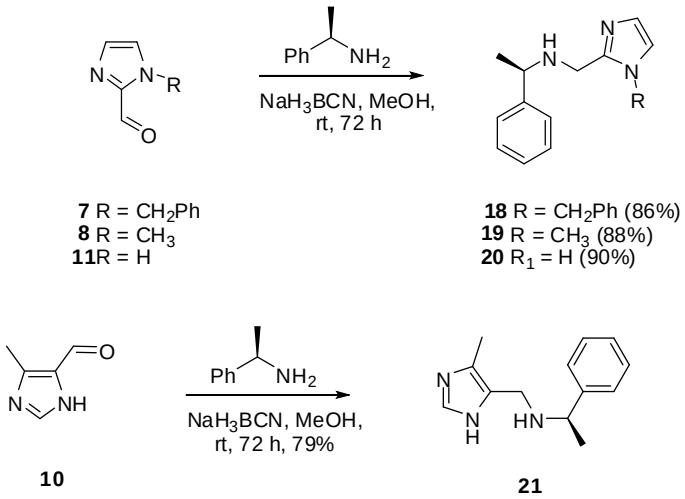


10 R_1 = CH_3, R_2 = H
12 R_1 = Cl, R_2 = *n*-Bu

16 R_1= CH_3, R_2 = H (73%)
17 R_1= Cl, R_2= *n*-Bu (79%)

Scheme 2. Synthesis of Chiral derivatives of Imidazolyl-imino Compounds

Having achieved the first part of this work, we have been also utilised reductive amination step for the synthesis of chiral imidazolyl amino compounds, **18**, **19**, **20** and **21** using sodium cyanoborohydride as a reducing agent Scheme 3. Attempts to recrystalise the resulting products from a variety of solvents were unsuccessful. The ^{1}H NMR spectra of the resulting compounds indicated to present of small amount of impurities, and for further synthesis steps the crude oils can be used. As most of the final products of imidazolylamino compounds and Schiff bases ligands were difficult to purify and also difficult to obtain them as solids, we therefore decided to convert these resulting products to their corresponding picrates by reaction with picric acid. This allowed recrystallization of the desired products smoothly using acetonitrile giving satisfactory results for the elemental analyses. Finally, coordination of imidazolylimino and amino compounds with Ag(I) was achieved successfully to give several complexes **22**, **23**, **24**, **25** and **26**.



Scheme 3. Synthesis of Chiral derivatives of Imidazolyl-amino Compounds

The results of the anti-*candida* activity for these compounds are shown in Table 1. Previous study demonstrated that Ketoconazole **1** was the first azole that could be given orally to treat systemic fungal infections. It is also found to be more effective than triazole compounds such as fluconazole and intraconazole against several different types of fungi. Under our conditions of testing the MIC for ketoconazole is 2.5 µg/ml.[10] Two of the silver complexes (entries 3 and 5) show greater activity. Although, the *S*-enantiomer of *N*-[(1*E*)-1-benzyl imidazol-2-ylmethylene]-*N*′-(1-phenylethyl)amine, **13** and its picrate were inactive against *C. albicans*, the *R*-enantiomer (entry 1) showed moderate activity. This is the only ligand which showed activity independent of complexing to a metal.

Table 1: Minimum Inhibitory Concentration (MIC) against *Candida albicans*

ENTRY	Compound	MIC (µg/ml)
1	*R*-(**13**)	10
2	[Ag.(**13**)$_2$(ClO_4)] **(22)**	5
3	[Ag.(**14**)$_2$(ClO_4).H_2O] **(23)**	1.25
4	[Ag.(**15**)$_2$(ClO_4).H_2O] **(24)**	5
5	[Ag.(**17**)$_2$(ClO_4)] **(25)**	1.25
6	[Ag.(**21**)$_2$(ClO_4).H_2O] **(26)**	10

4. Conclusions:

In summary, series of chiral imidazolyl-imino and imidazolyl-amino compounds and their Ag(I) complexes were synthesised using Schiff bases and reductive amination processes. These target compounds are an important class of *anti-candida albicans*. These silver-imidazole antifungal drugs would become the next generation in the fight against fungal infections. Further investigation of the synthesis and use of other imidazole derivatives sush as ureas and their Zn(II) complexes is currently underway.

5. Acknowledgements

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