HIGHLY ASYMMETRIC REDUCTION OF NEW BENZOFURYL AND BENZOTHIOPHENYL *α*-AMINO KETONES

Agnieszka Tafelska-Kaczmarek[1], Marcin Kwit[2], Bartosz Stasiak[2]

[1]*Nicolaus Copernicus University in Torun, Faculty of Chemistry, Department of Organic Chemistry, 7 Gagarin Street, 87-100 Torun, Poland*

[2]*Adam Mickiewicz University, Faculty of Chemistry, 89B Umultowska Street, 61-614 Poznan, Poland*

e-mail: tafel@umk.pl

Heterocyclic compounds occupy a central position in organic chemistry. These compounds play an important role in the design and discovery of new pharmacologically active molecules. Heterocycles provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs. Oxygen and sulfur containing heterocyclic systems exhibit diverse biological and pharmacological activities due in part to the similarities with many natural and synthetic molecules with known biological activity [1,2]. Both benzofuran and benzothiophene derivatives display the wide range of biological properties including antihyperglycemic, analgesic, antiparasitic, antimicrobial, antifungal, antitumor, and antidepressant. Several benzofuryl and benzothiophenyl drugs is depicted in Figure 1.

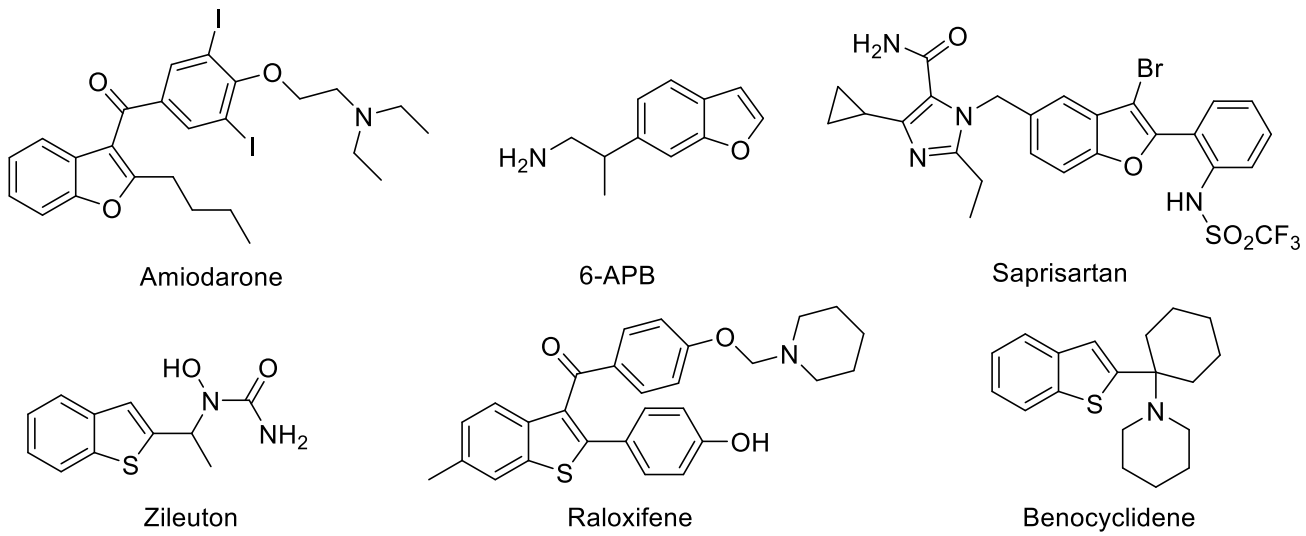


Figure 1. Benzofuryl and benzothiophenyl drugs

On the other hand, the main antifungal drugs for clinical uses are compounds possessing at least two principal pharmacophoric groups: iron coordinating group - the azole ring, able to interact with the heme iron, and the aromatic group, as a hydrophobic moiety adjacent to it [3]. To the azole drugs belong, among others Econazole, Miconazole, Fluconazole, Ketoconazole (Figure 2).

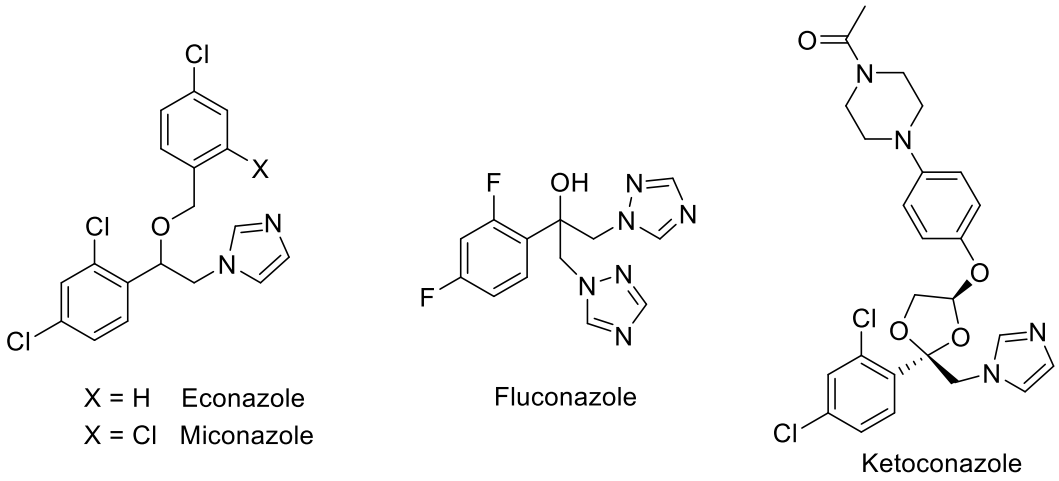
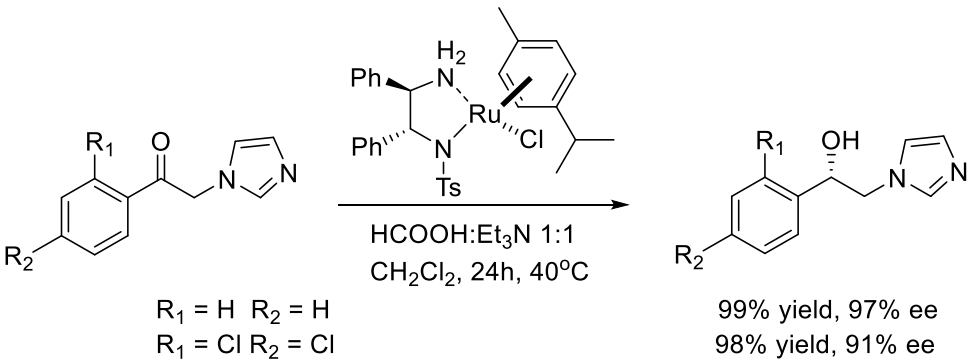


Figure 2. Main azole-antifungal agents

As it shown above the azole-antifungal drugs are *β*-amino alcohols containing imidazole and triazole rings. While the use of racemic amino alcohols is suitable for some of the existing applications, the trend in the pharmaceutical industry is to utilize a single isomer of chiral compound.

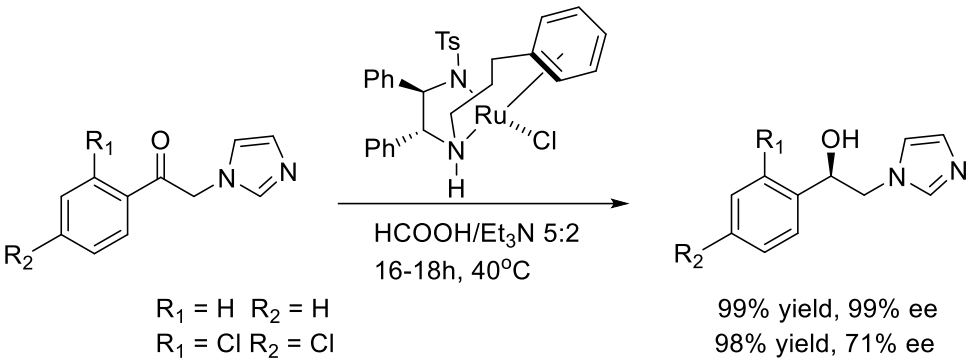
Several chiral 2-(imidazol-1-yl)-1-arylethanols were obtained via the asymmetric hydrogenation of the corresponding *α*-amino ketones. Asymmetric transfer hydrogenation (ATH) is established as an excellent reduction method due to its versatility, operational simplicity, avoidance of explosive hydrogen gas, catalyst robustness, and high stereoselectivity. Imidazole-substituted acetophenones were reduced in this way for the first time by Ramsden and Lennon with the use of RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) as the catalyst precursor [4]. Both (*S*)-*β*-amino alcohols were obtained in high yields and enantioselectivities (Scheme 1).



Scheme 1.

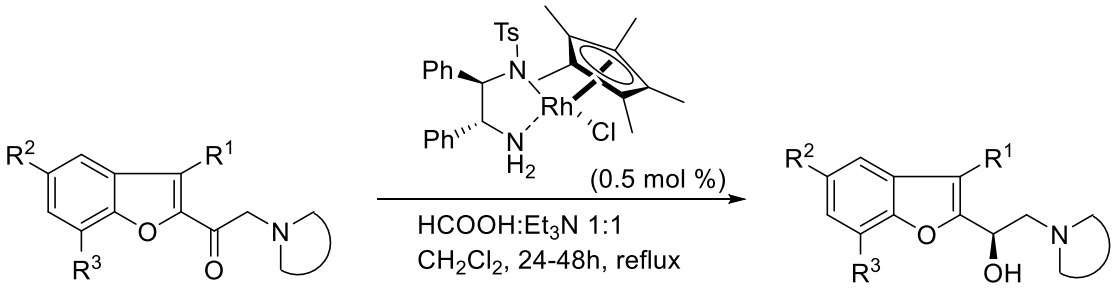
With similarly remarkable enantiomeric excess along with quantitative conversion (*R*)-2-(imidazole-1-yl)-1-phenylethanol was prepared using the “reverse-tethered” catalyst and the standard 5:2 formic acid/triethylamine solvent system/hydrogen source (Scheme 2) [5]. The authors proved that the attachment of a tethering group from the basic nitrogen atom to the arene ligand of a Ru(II) catalyst greatly improves its ability to catalyze asymmetric transfer hydrogenation reactions. However, (*R*)-1-

(2,4-dichlorophenyl)-2-(imidazol-1-yl)ethanol was formed with a significantly poorer selectivity (71% ee).

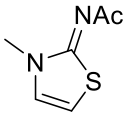


Scheme 2.

Based on these data, we decided to develop a synthesis of new chiral benzofuryl and benzothiophenyl compounds containing azole rings. Twelve differently substituted benzofuryl *α*-amino ketones were prepared by condensation of the corresponding 1-(benzofuran-2-yl)-2-bromoethanones and 1*H*-imidazole, 1*H*-1,2,4-triazole, and 2-aminothiazole according to known procedures [6,7]. When our standard conditions for asymmetric transfer hydrogenation of these ketones (Rh(III)/TsDPEN complex as catalyst, the formic acid/trimethylamine azeotrope (5:2), ethyl acetate as solvent, at room temperature) were applied, no desired products were obtained [8]. Thus, after optimizing the conditions, the hydrogenation was carried out with formic acid as a hydrogen donor, catalyzed by RhCl[(*R*,*R*)-TsDPEN](C_5Me_5), in dichloromethane at reflux for 24h (Scheme 3).



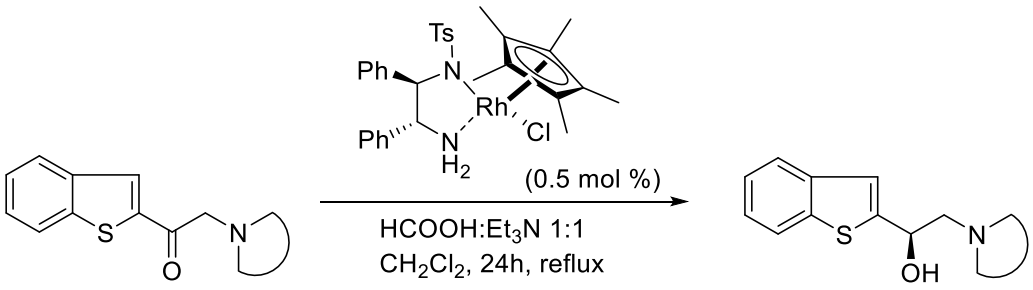
Entry	R^1	R^2	R^3		Yield (%)	Ee (%)
1	H	H	H		79	99
2	H	H	Et		75	96
3	Me	H	H		66	98
4	Me	Me	H		76	98
5	H	H	H		71	96
6	H	H	Et		77	98
7	Me	H	H		57	97
8	Me	Me	H		48	97

9	H	H	H		86	99
10	H	H	Et		69	99
11	Me	H	H		99	93
12	Me	Me	H		91	85

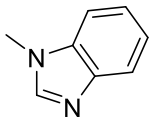
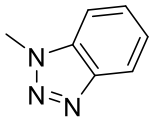
Scheme 3.

However, longer reaction time (48h) was required for the reduction of the triazole derivatives (Scheme 3, Entry 5-8); the reaction progress was monitored by TLC analysis. In addition, the imino thiazole derivatives required protection by acetyl group (Ac) on the nitrogen atom because this double bond was also reduced (Scheme 3, Entry 9-12). All chiral *β*-amino alcohols were formed in high yields and high enantioselectivities, over 96%. Only two products, the thiazole derivatives of 3-methylbenzofuran and 3,5-dimethylbenzofuran were obtained with lower ee, 93 and 85% respectively (Scheme 3, Entry 11 and 12). The ee values were determined by HPLC analysis on the chiral columns: Daicel Chiralcel OD-H, Daicel Chiralcel OJ, Lux® Cellulose-4, Lux® i-Cellulose-5, Lux® Amylose-1. The appropriate racemic compounds were also prepared and used as standards for ee determination. The absolute configuration (*R*) of products was confirmed by means of ECD spectroscopy supported by theoretical calculations.

Following the same synthetic methodology five benzothiophenyl *α*-amino ketones were prepared by the reaction of 1-(benzothiophen-2-yl)-2-bromoethanone with 1*H*-imidazole, 1*H*-1,2,4-triazole, 2-aminothiazole, 1*H*-1,3-benzimidazole, and 1*H*-benzotriazole [9]. Next, the benzothiophenyl *α*-amino ketones were subjected to the transfer hydrogenation under the above-mentioned conditions (Scheme 4). The reactions were run in dichloromethane at reflux for 24h.



Entry		Yield (%)	Ee (%)
1		78	99
2		95	98

3		74	94
4		98	99
5		76	98

Scheme 4.

The corresponding optically active *β*-amino alcohols were obtained in high yields (74-98%) and excellent enantioselectivities (98-99%). Only (*R*)-1-(benzothiophen-2-yl)-2-(1*H*-benzimidazol-1-yl)ethanol was formed with 94% ee (Scheme 4, Entry 3). The ee values of these products were determined by HPLC analysis on the chiral columns Daicel Chiralcel OD-H and Lux® Amylose-1.

To the best of our knowledge, no chiral benzofuryl and benzothiophenyl *β*-amino alcohols possessing the azole rings have been reported in the literature. Moreover, these compounds as an analogues of known antifungal agents will undergo biological testing in the near future.

References

[1] H. K. Shamsuzzaman, *Eur. J. Med. Chem*. **2015**, *97*, 483-504.

[2] R. S. Keri et al., *Eur. J. Med. Chem*. **2017**, *138*, 1002-1033.

[3] D. De Vita, et al., *Eur. J. Med. Chem.* **2012**, *49*, 334-342.

[4] I. C. Lennon, J. A. Ramsden, *Org. Process Res. Dev*. **2005**, *9*, 110-112.

[5] D. J. Morris, A. M. Hayes, M. Wills, *J. Org. Chem*. **2006**, *71*, 7035-7044.

[6] Y. Wahbi, R. Caujolle, C. Tournaire, M. Payard, M. D. Linas, J. P. Seguela, *Eur. J. Med. Chem.* **1995**, *30*, 955-962.

[7] S. Marquès, R. Buchet, F. Popowycz, M. Lemaire, S. Mebarek, *Bioorg. Med. Chem. Lett*. **2016**, *26*, 1457-1459.

[8] A. Tafelska-Kaczmarek, M. P. Krzemiński, M. Ćwiklińska, *Tetrahedron* **2017**, *73*, 3883-3897.

[9] J. Debray et al., *Bioorg. Med. Chem*. **2013**, *21*, 7981-7987.