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NON-CONVENTIONAL AGENTS FOR OPTICAL RESOLUTIONS

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Abstract In this paper we demonstrate the use of chiral drugs and intermediates as resolving agents on 13 examples from our practice. In 11 cases of 13, the configuration of the enantiomers in the precipitated salt is opposite, which support the assumption that the formation of a "quasi racemate" type diastereoisomeric salt may be preffered, when the racemate and the resolving agent are structurally similar or at least there is no significant difference between their molecular weight.

The optical resolution via diastereoisomeric salt formation is one of the most frequently used methods for preparing optically active enantiomers in preparative and process scales.[1,2] In theory, any optically active base or acid can be used as resolving agent, but only about a dozen of them have been applied extensively in practice.[3,4] For instance the tartaric acid and its derivatives are commonly used for the resolution of racemic bases while the naturally occurring basic alkaloids are applied to resolve recemic acids. The main advantage of this is that these optical resolving agents are commercially available at relatively low cost and their usefulness is supported by analogue separations in the literature.

The formation of stable diastereoisomeric salts which possess substancial differences in their physicochemical properties is required for an efficient optical resolution.[5,6] Approximatelly 60% of the diastereoisomeric salts formed between racemates and the most commonly used resolving agents meet this condition.[3] When these reagents fail to work, the more expensive resolving agentsmay be used to obtain the resolution. Therefore it may be advantageous to obtain optical resolutions by using chiral intermediates or end products produced in pharmaceutical industry, especially tose "unwanted" optically active isomers generated during the synthessis of chiral drugs.

In this brief review we demonstrate from our practice the use of several chiral intermediates and endproducts from drug synthesis processes as "new" optical resolving agents to separate 13 racemic compounds.

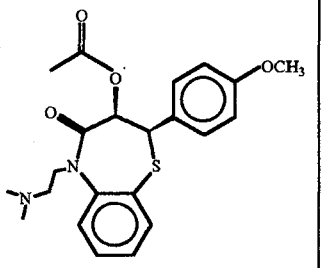
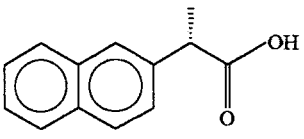
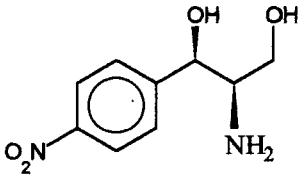
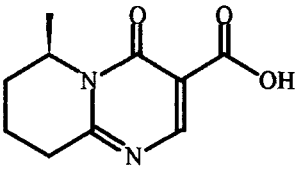
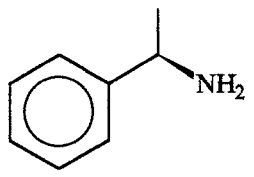
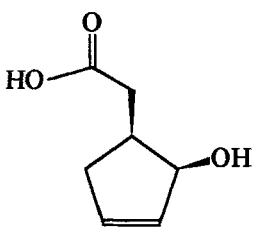
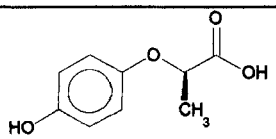
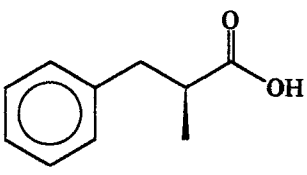
Naproxen (II), a generic antiinflamatory drug, has proven to be an efficient resolving agent for the optical resolution of racemic-Diltiazem (I),[7] which is an important calcium antagonist (Table 1). During the resolution, the R,R-I.S-II salt precipitates with very high optical purity.

The MZ-121 (IV) is a spasmolytic drug candidate, which is useful for the resolution of racemic 2-amino-1,3-hydroxy-1-(4-nitro-phenyl)-propane (III),[8] an intermediate in the production of Chlorocide. An optical purity of 98 % was obtained in the precipitate of the diastereoisomeric salt.

The racemic Corey-lacton VI is the first chiral intermediate from the production of $PGF_{2\alpha}$ in industrial scale. The resolution of the racemic lacton(VI) is achieved by formation and fractional crystallization of diastereoisomeric salt with α-phenylethylamine (V). On the other hand the synthetically produced racemic-α-phenylethylamine can be resolved by using SS-VI as optical resolving agent,[9] byproduct of the syntheses.

The last resolution in Table 1. is the resolution of p-hydroxy-phenyl-propionic acid by phenylalanine.[10] In spite of the resembleance of the two molecules, the optical purity of the precipitated salt is lower than that in any other examples.

Table 1. Resolutions by chiral intermediates or end products

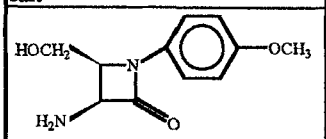
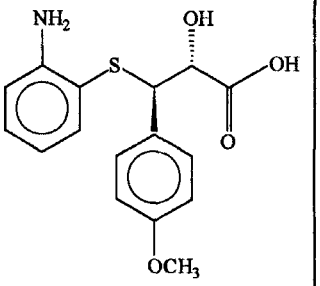
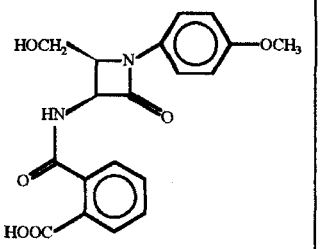
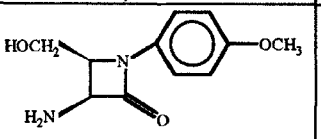
Enantiomer in the precipitated salt	Resolving agent	OP %	Y %	S
 R,R-I	 S-II	93.3	98.6	0.92[7]
 S,S-III	 R-IV	98.0	50.8	0.50[8]
 R-V	 S,S-VI	93.0	55.9	0.52[9]
 R-XIX	 S-XVII	48.8	90.4	0.44[10]

The efficiency (0<S<1) of the optical resolution has been defined as the product of the optical purity (0< OP<1) and the yield (0<Y<1) of the precipitated salt: S= OPxY, in Fogassy,E.; Lopata,A.; Faigl,F.; Darvas,F.; Ács,M; Tőke,L. Tetrahedron Lett., 21:647-653, 1980

All the compounds having two chiral centers was the mixture of S,S and R,R enantiomers.

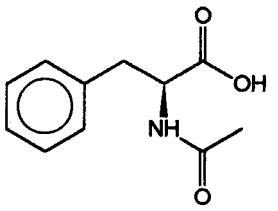
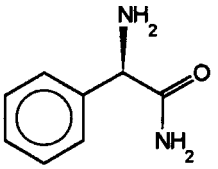
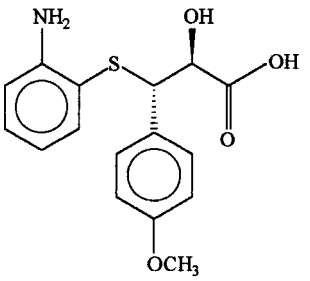
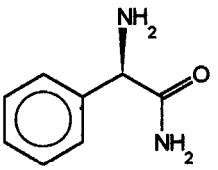
The VII β-lactame derivative can be resolved by VIII[11] which is an intermediate in the production of Diltiazem (I). Compound IX the acidic derivative of VII, can be resolved by the basic β-lactame(VII),[12] both resolution being highly efficient (Table 2).

Table 2. Resolution of β-lactame derivetives

Enantiomer in the precipitated salt	Resolving agent	OP %	Y %	S
 S,S-VII	 R,R-VIII	100	95.7	0.96[11]
 S,S-IX	 S,S-VII	100	85.5	0.86[12]

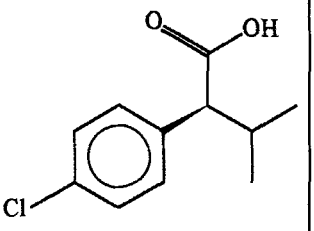
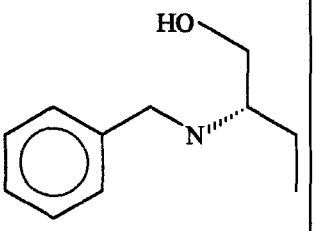
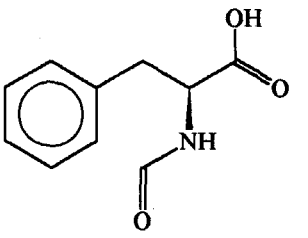
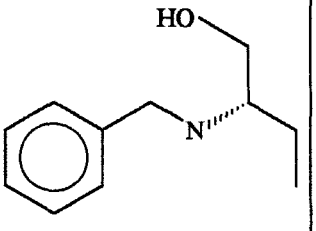
The resolution of phenylglycine can be accomplished by the formation and crystallization of diastereoisomeric salts between the 2R,3R-tartaric acid and phenylglycine amide (R-XI), the basic derivative of phenylglicine. The inexpensive phenylglycine amide (R-XI) was found to be a good basic resolving agent, for the optical resolutions of X[13] and VIII[14] (Table 3.)

Table 3. Resolutions by phenylglycine amide

Enantiomer in the precipitated salt	Resolving agent	OP %	Y %	S
 S-X	 R-XI	100	86.1	0.86[13]
 S,S-VIII	 R-XI	98.2	67.3	0.66[14]

The optically active aminobutanol is an oily intermediate from the production of the antitubercular Ethambutol. Its benzyl-derivative is a crystalline compound (XIII). It has been used as the optical resolving agent for the separation of racemic mandelic acid.[15] We found that benzyl-aminobutanol is a good resolving agent for different types of racemates, as illustrated in Table 4. The resolution of XII[16] and XIV[13] can be accomplished with good efficiency (S=0.75), but neither the optical purity nor the yield reach the 100%.

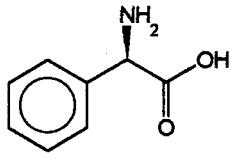
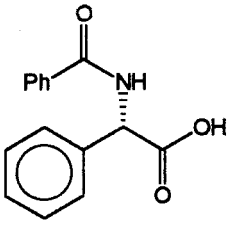
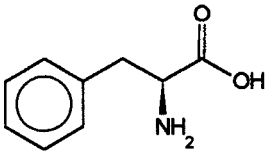
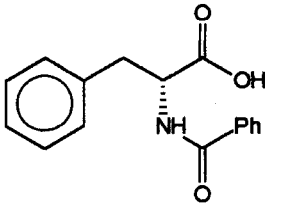
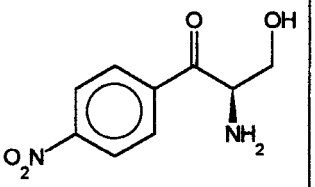
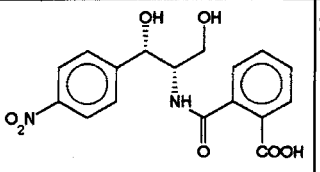
Table 4. Resolutions by benzyl-aminobutanol

Enantiomer in the precipitated salt	Resolving agent	OP %	Y %	S
 S-XII	 S-XIII	81.8	90.0	0.74[16]
 R-XIV	 S-XIII	84.5	89.0	0.75[13]

In Table 5 phenylglycine (XV)[10] and phenylalanine (XVII)[17] were resolved by forming diastereoisomeric salts with their acidic (N-benzoyl) derivatives. The optical purities of the precipitated salts in both cases are extremely high.

During the optical resolution of XX using its acidic derivatives (XXI)[18] as resolving agents asymmetric transformation takes place (when the S-isomer of XX transformed into the R isomer during the resolution yielding about 0.95 mole R isomer starting from one mole racemate).

Table 5. Resolutions by acetyl derivatives

Enantiomer in the precipitated salt	Resolving agent	OP %	Y %	S
 R-XV	 S-XVI	95.4	90.0	0.86[10]
 S-XVII	 R-XVIII	100	80.0	0.80[17]
 R-XX	 S,S-XXI	81.0	190.0	1.54[18]

These examples illustrate well that chiral drugs and intermediates can act as efficient resolving agents, but their use are limited, because of their limited availability.

The racemates can crystallizes either heterochiral or homochiral forms. The heterochiral packing is the thermodynamically preferred, about 90% of the racemates form racemic molecular compound, in which the R and S enantiomers crystallizes together.[19,20] We suggested in a recent paper,[21] that the heterochiral packing may determine the results of optical resolutions too. The precipitating, more stable salt can contain that enantiomer of the racemate of which having opposite configuration as the resolving agent.

In 11 cases of 13 analysed in this paper, the configuration of the enantiomers in the precipitated salt is opposite, which support the assumption that the formation of a "quasi racemate" type diastereoisomeric salt may be preferred, when the racemate and the resolving agent are structurally similar or at least there in no big difference between their molecular weight.

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