A new competitive strategy for the industrial synthesis of drugs based on chiral amines via utilizing the waste isomer by flow chemistry

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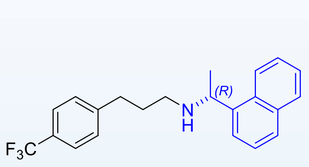
INTRODUCTION

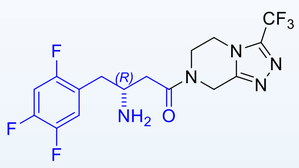
Drug chirality has been recognized as a major factor in the drug discovery process since 1992, when the US Food and Drug Administration (FDA) issued the relevant guidance on the Development of New Stereoisomeric Drugs.

Since then the importance of homochiral drugs has been steadily increasing. Recently, 80% of small-molecule drugs approved by the FDA contained a chiral center, and almost 75% of them were marketed as a single enantiomer. For example, in 2012, of the 25 best-selling drugs on the US market, 14 were low molecular weight compounds, of which 13 consisted of a single enantiomer, and only one was a racemate (the remaining 11 drugs were antibodies obtained by biotechnological methods). Over the last 5 years the value of drugs sold on the US market as single enantiomers almost doubled - from 131 to 225 billion $.

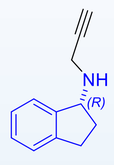
Whenever drug manufacturing process produces a racemate, it has to be separated as only one stereoisomer is useful. The other one usually creates waste. Therefore, development of new, more efficient procedures for the preparation of homochiral drugs is essential. New technologies have therefore focused on stereoselective synthesis and utilization/recycling of undesired isomers.



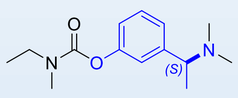
Cinacalcet
(calcimimetic, Amgen)



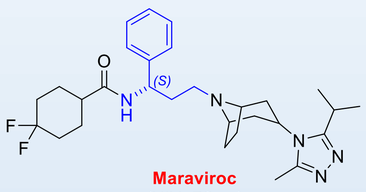
Sitagliptin
(diabetes, Merck & Co)



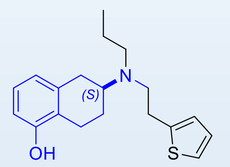
Rasagline
(Parkinson's disease, Teva)



Rivastigmine
(Parkinson's disease, Novartis)



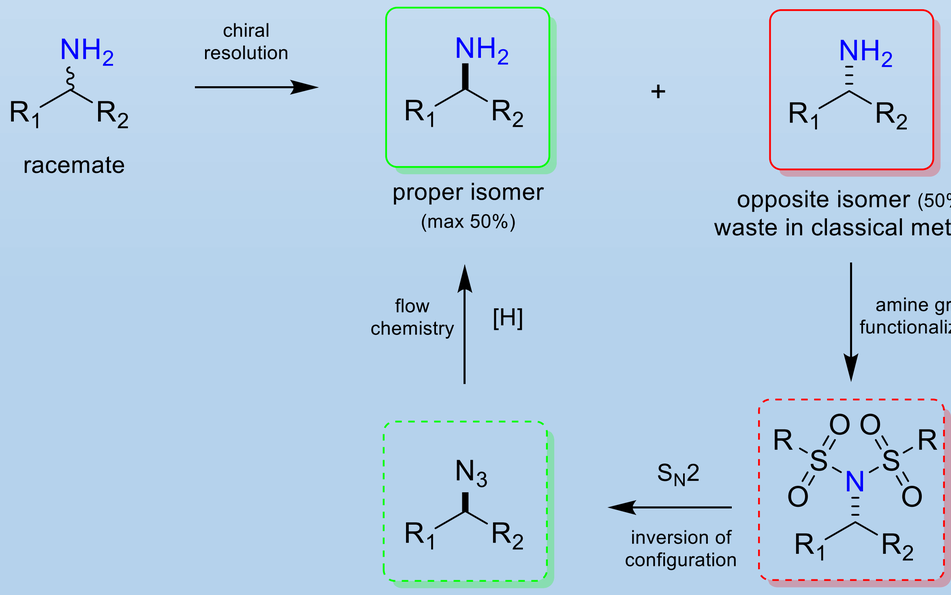
Maraviroc
(HIV, Pfizer)



Rotigotine
(Parkinson's disease, Schwarz)

A significant number of therapeutic substances available on the pharmaceutical market, such as Cinacalcet, Sitagliptin, Rasagline, Rivastigmine, Maraviroc, Rasagline (etc.) contains chiral amine residues. Synthesis of such agents is often based on the preparation of a racemic version of a key intermediate followed by its resolution into individual enantiomers. We describe here a new approach to utilize the undesired enantiomers of the chiral amines by inverting their configuration under flow conditions, which ensures safety and high *ee* of the products, as shown in the Scheme below.

PROCESS SCHEME

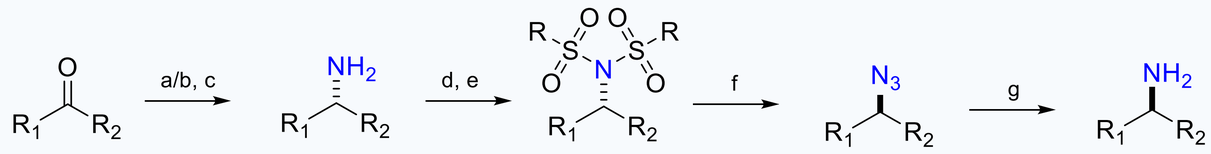


EQUIPMENT

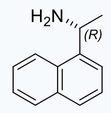
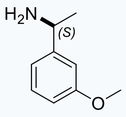
Flow Chemistry
Reactor
VAPOURTEC R2
PUMP MODEL

Project "Development of new chiral amines synthetic methods for the pharmaceutical industry" co-financed by the European Regional Development Funds under the Measure 1.1.1. Operational Program - Smart Growth (POIR.01.01.01-00-1200/15-00)

RESULTS

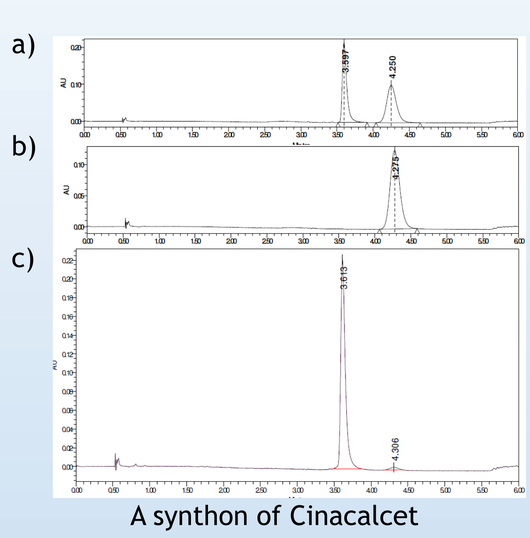


Reactions: (a) reductive amination (b) reduction of oxime; (c) chiral resolution – crystallization; (d) MsCl (or TsCl), various bases, solvents, and temperatures; (e) MsCl (or TsCl), various bases, solvents, and temperatures; (f) NaN_3, various solvents, temperatures, time (flow rate); (g) H_2, Pd/C

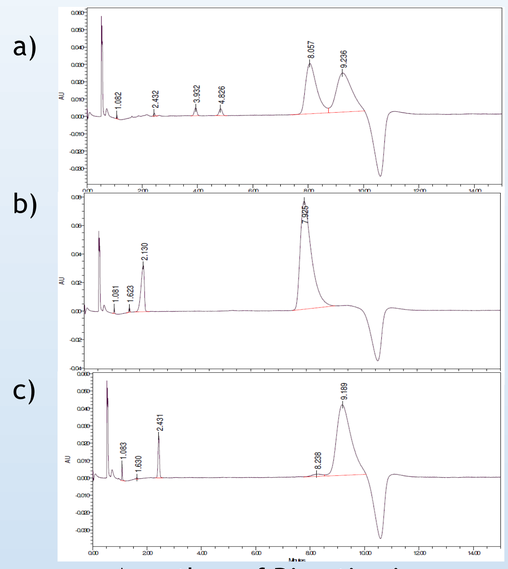
Synthon of	Structure	Yield of Step d [%]	Yield of Step e [%]	Step f – classical chemistry Yield [%]	Step f – classical chemistry *ee* [%]	Step f – flow chemistry Yield [%]	Step f – flow chemistry *ee* [%]	Step g Yield [%]	Step g *ee* [%]
Cinacalcet		99[A]	100[A]	91[A]	**69[A]**	84[A]	**91[A]**	90	**92[A]**
		99[B]	100[B]	84[B]	**90[B]**	77[B]	**94[B]**		**96[B]**
Rivastigmine		100[A]	89[A]	95[A]	**89[A]**	82[A]	**93[A]**	95	**89[A]**
		100[B]	84[B]	81[B]	**95[B]**	77[B]	**97[B]**		**95[B]**

[A] R - Tosyl
[B] R - Mesyl

Selected chiral analysis: a) racemate b) starting material enantiomer c) opposite enantiomer (after inversion of configuration)



A synthon of Cinacalcet



A synthon of Rivastigmine

CONLUSION

A new efficient and safe method for inversion of configuration of chiral amines has been developed.

Several homochiral amine synthons were synthesized. Two of them (Cinacalcet and Rivastigimine) were converted into di-tosyl and di-mesyl derivatives. Inversion of configuration of the chiral center was achieved by substitution of the disulfonimide moiety using NaN_3 under flow conditions to give an organic azide. The reaction has been fully optimized (temperature, flow rate and solvent) in a flow reactor, which ensured the safety of the whole process. The organic azides were obtained in satisfactory yields and over 90% *ee*. The azides could be reduced to the desired amines by standard hydrogenation, which should also be achievable under flow conditions. We also intend to expand the method to other amines to make it as widely applicable as possible.

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