Tetrahedron Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Optimized synthesis of new LE404-derived azecine-prodrugs

Stephanie Zergiebel [a], Hans-Dieter Arndt [b], Andreas Seeling [a,*]

[a] Institute of Pharmacy, Friedrich-Schiller University Jena, Philosophenweg 14, 07743 Jena, Germany
[b] Institute of Organic Chemistry and Macromolecular Chemistry, Friedrich-Schiller University Jena, Humboldtstr. 10, 07743 Jena, Germany

ARTICLE INFO

Article history:
Received 19 July 2017
Accepted 2 August 2017
Available online xxxx

Keywords:
Azecines
LE404
Prodrugs
Neuroleptics

ABSTRACT

Dibenzoazecines represent a class of high-affinity dopamine and serotonin receptor antagonists. The former synthesis of the lead structure 7-methyl-5,6,7,8,9,14-hexahydrodibenzo[*d*,*g*]azecin-3-ol (LE404) has been 5 steps with a total yield of 13%. The present work enabled the synthesis of LE404 with a much higher yield. Based on this research, further azecin derivatives were synthesized with the aim to improve pharmacokinetic parameters.

© 2017 Elsevier Ltd. All rights reserved.

Introduction

An imbalance of the neurotransmitters dopamine and serotonin is strongly involved in the pathology of schizophrenia. Therefore, the substance class of the benzindoloazecines merge the basic structures of these two neurotransmitters in one molecule.[1]

In further research, the indole ring was substituted by a benzene ring. The dibenzoazecines, obtained in this way, show a similar affinity in receptor binding studies, compared with the benzindoloazecines.[2] In the *in vivo* tests, the substance LE404 (**7**) was clearly superior to the other derivatives. LE404 is equally potent as the tested standard substances haloperidol and risperidone.[2] In addition to that, LE404 has a 5-fold higher therapeutic range than the standard substances. Because the maximum potency of LE404 *in vivo* is quickly reached after 30 min and the effect thereafter falls strongly, the aim is to develop further derivatives with a prolonged half-life.[2] Three ester derivatives were tested *in vitro* and *in vivo*. With the LE404-isobutanoic acid ester, the duration of action has been increased to 120 min.[3] The current work reports an improved synthesis of LE404 and the synthetic pathway to various derivatives of LE404, which could have a longer efficacy *in vivo*. The synthesis of LE404 was reported in 5 steps with an overall yield of 13%.[4] In order to obtain LE404 in sufficient quantity the synthesis was optimized for further derivatizations. The derivatization was focused on various esters and carbamates. Moreover, a propinyl-group has been introduced in various places in the molecule which may inhibit liver metabolism.[5]

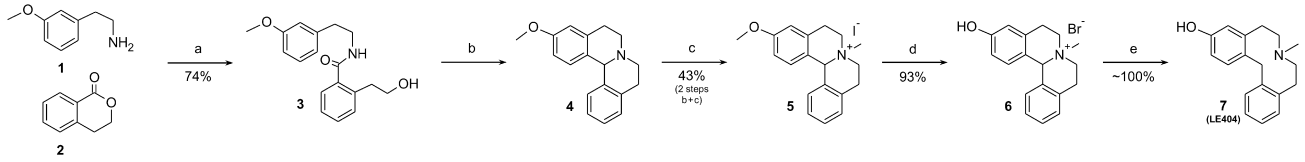
Results and discussion

Scheme 1 illustrates the optimized synthetic pathway leading to LE404. The synthesis is started from commercially available 3-methoxyphenylethylamine **1** and isochromanone **2** to obtain the benzamide **3** in 74% yield. The reaction is catalyzed by potassium cyanide. A Bischler-Napieralski-cyclisation procedure receives the quinolizine **4**. Treatment with methyl iodide afforded the *N*-methylated compound **5** in 43% yield over 2 steps. The ether bond was cleaved with boron tribromide to give phenol **6** in 93% yield. Finally, a Birch reduction yields LE404 by benzylic fragmentation (quantitative conversion). The overall yield was improved to 30%.

The previous work reported a yield of 13% over all 5 steps.[4] By adding KCN as a catalyst, the yield of the ester aminolysis in the first step (a) was improved from 60% to 74% (Scheme 1). In the second step (b), the starting material was dissolved in acetonitrile and $POCl_3$ was added dropwise under ice cooling. Due to the higher dilution of components and lowering the reaction temperature compared to earlier procedures,[4] the selectivity of the reaction could be improved and thus the yield could be increased. Furthermore, if the crude product was reacted with methyl iodide directly (step c) it resulted in a higher yield than when amine **4** was first purified, because the recrystallization of **5** proceeded effectively, whereas the purification of amine **4** resulted in loss of material. In the next step (d), the methyl ether was cleaved with boron tribromide instead of 47% hydrogen bromide solution, increasing the yield by 9%. In the last step (e), Birch reduction of ammonium salt **6** was carried out in liquid ammonia at −78 °C instead of −40 °C, and for extraction chloroform instead of diethyl ether

* Corresponding author.
E-mail address: b8sean@rz.uni-jena.de (A. Seeling).

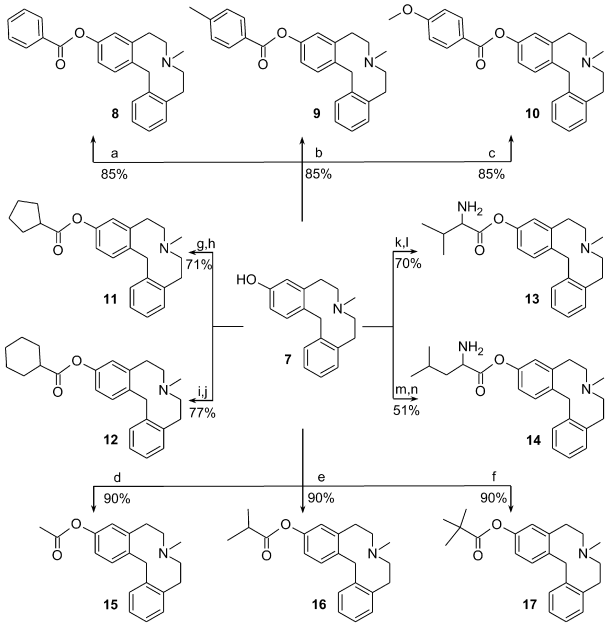
http://dx.doi.org/10.1016/j.tetlet.2017.08.007
0040-4039/© 2017 Elsevier Ltd. All rights reserved.



Scheme 1. Reagents and conditions: a) KCN, 70 °C, 7 d; b) phosphoryl chloride, MeCN, 0 °C to rt, reflux 24 h; c) methyl iodide, MeCN, reflux, 48 h; d) boron tribromide, chloroform, 0 °C to rt, 24 h; e) Na^0, liq. ammonia, -78 °C to rt, 12 h.

was used, followed by silica gel filtration. The yield could such be improved from 72%[4] to nearly 100%.

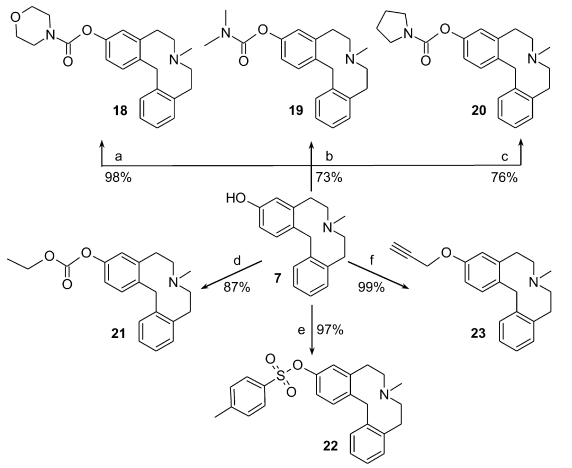
The obtained lead structure **7** was first converted into ten different esters (Scheme 2). Esterification of **7** afforded **8**, **9** and **10**, respectively, in 85% yield using the appropriate acid chloride (step a: benzoyl chloride, step b: p-methylbenzoyl chloride, step c: p-methoxybenzoyl chloride) and sodium hydride to deprotonate the phenol as previously described for **15**, **16** and **17**.[3] The compounds **11** and **12** were also prepared from the acid chlorides, but in this case the acid chlorides were obtained from the carboxylic acids and not purchased commercially. The yield over two steps is 71% for **11** and 77% for **12**. The synthesis was carried out over two steps without purification of the acid chloride because this is very sensitive to hydrolysis and the yield is significantly higher when the crude product is directly converted. To obtain the amino acid esters **13** and **14**, first a Steglich esterification was carried out with the Boc-protected amino acids[6] (yield: 74% for *N*-(tert-butoxycarbonyl)-L-valine-ester, yield: 54% for *N*-(tert-butoxycarbonyl)-L-leucine-ester). In the next step, the protective group was cleaved by hydrochloric acid in dioxane, and the chloride salts of the azecines were obtained simultaneously. The yield for **13** and **14** was 95%, respectively.



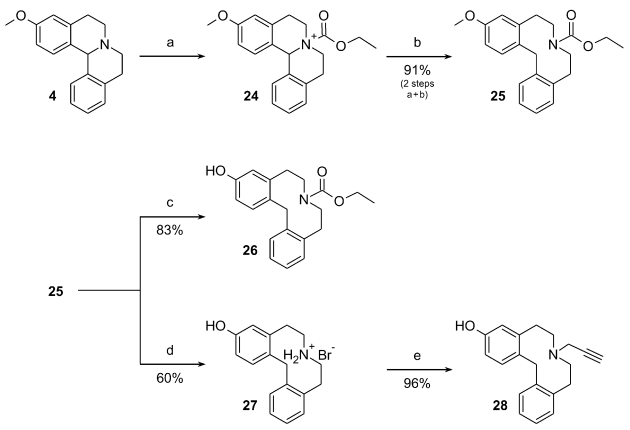
Scheme 2. Reagents and conditions: a) benzoyl chloride, NaH, DCM, 0 °C to rt, 30 min; b) p-methylbenzoyl chloride, NaH, DCM, 0 °C to rt, 30 min; c) p-methoxybenzoyl chloride, NaH, DCM, 0 °C to rt, 30 min; d) acetyl chloride, NaH, DCM, 0 °C to rt, 30 min3; e) isobutyryl chloride, NaH, DCM, 0 °C to rt, 30 min3; f) pivaloyl chloride, NaH, DCM, 0 °C to rt, 30 min3; g) cyclopentanecarboxylic acid, oxalyl chloride, DMF, DCM, 0 °C to rt, 60 min; h) **7**, TEA, 0 °C to rt, 24 h; i) cyclohexanecarboxylic acid, oxalyl chloride, DMF, DCM, 0 °C to rt, 60 min; j) **7**, TEA, 0 °C to rt, 24 h; k) *N*-(tert-butoxycarbonyl)-L-valine, DCC, DMAP, DMF, rt, 24 h; l) HCl in dioxane, MeCN, 0 °C to rt, 2 h; m) *N*-(tert-butoxycarbonyl)-L-leucine, DCC, DMAP, DMF, rt, 24 h; n) HCl in dioxane, MeCN, 0 °C to rt, 2 h.

Treatment of **7** with various carbamoyl chlorides gave the carbamates **18**, **19** and **20** (Scheme 3). The yield ranged between 73% and 98%, depending on the carbamoyl chloride used. After 24 h the conversion was quantitative (monitored by TLC). Moreover, Scheme 3 shows three further derivatives. Reaction of **7** with ethyl chloroformate afforded **21** in 87% yield as a colorless solid after silica column purification. To obtain the toluene-4-sulfonic acid ester, **7** was deprotonated with sodium hydride and was then treated with toluene-4-sulfonic acid chloride. The used solvent was a mixture of THF and DCM, to accommodate the different solubilities of substrates and reagents. The optimal final mixing ratio of THF/DCM was 3:1 and afforded sulfonate **22** in 97% yield. The reaction conditions for the synthesis of the propargyl ether derivative **23** could be greatly simplified compared to the literature[7] by using sodium hydride for deprotonation and a solvent mixture of toluene/DMF (1:1). The transformation was found to be complete in 1 h. In addition, it was possible to carry out the reaction at room temperature without refluxing, with a final yield of 99%.

In order to derivatize the nitrogen in the 10-membered azecine ring, access to the secondary amine was necessary. The synthetic pathway is shown in Scheme 4. Step a and b afforded carbamate **25** in 91% yield, which was synthesized according to a literature method.[8] Following the work of Enzensperger et al. [9] succeeded in cleaving simultaneously the urethane and the methyl ether with boron tribromide to form the secondary amine **27**, albeit under drastic conditions (reflux for 24 h, 10 equivalents boron tribromide). Under controlled conditions, it was possible to cleave the methyl ether selectively (step c) in 85% yield (→ **26**). By using a sterically hindered base (*N*,*N*-diisopropylethylamine), the nitrogen alkylation was successful without a protective group on the phenol. Hence, amine **27** was directly converted with propargyl bromide to amine **28** (yield: 96%).



Scheme 3. Reagents and conditions: a) 4-morpholine-carbonylchloride, NaH, DCM, 0 °C to rt, 24 h; b) dimethylcarbamoyl chloride, NaH, DCM, 0 °C to rt, 24 h; c) 1-pyrrolidinecarbonyl chloride, NaH, DCM, 0 °C to rt, 24 h; d) ethyl chloroformate, NaH, DCM, 0 °C to rt, 3 h; e) toluene-4-sulfonic acid chloride, NaH, THF/DCM (3:1), 0 °C to rt, 2 h; f) propargyl bromide, NaH, toluene/DMF (1:1), 0 °C to rt, 1 h.



Scheme 4. Reagents and conditions: a) ethyl chloroformate, THF, −78 °C (4 h) to rt (12 h);[8] b) sodium cyanoborohydride THF, −78 °C (4 h) to rt (12 h);[8] c) boron tribromide, chloroform, rt, 24 h; d) boron tribromide, chloroform, reflux, 24 h; e) propargyl bromide, *N*,*N*-diisopropylethylamine, DCM, 0 °C to rt, 12 h.

Conclusion

To diversify the lead structure **7** broadly, an optimization of the synthesis of azecine **7** was necessary. It succeeded to increase the yield of the synthesis to 30%. Moreover, seventeen different derivatives were synthesized from the core structure of **7**. Several structural variations have been obtained which are intended to increase the half-life of these dopamine and serotonin receptor antagonists *in vivo* by different mechanisms. In order to establish a relationship between derivatization and stronger protraction, these compounds will now be tested for stability in physiological media, metabolic stability, as well as duration of action *in vivo*.

Experimental

Experimental procedures, characteristics and analytical data (^{1}H NMR, ^{13}C NMR, IR, HRMS, elemental analysis, mp) of the compounds can be found in the Supplementary data file.

Acknowledgement

The authors would like to thank Dr. Christoph Enzensperger for the constructive scientific discussion.

Supplementary data

Supplementary data (experimental procedures, analytical data, materials, equipment parameters) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.08.007.

References

1. Witt T, Hock FJ, Lehmann J. *J Med Chem*. 2000;43:2079–2081.
2. Schulze M, Siol O, Robaa D, et al. *Drug Res*. 2012;62:252–260.
3. Zergiebel S, Fleck C, Arndt HD, Enzensperger C, Seeling A. *Drug Res*. 2017. http://dx.doi.org/10.1055/s-0043-108651. in press.
4. Lehmann J, Mohr P, Schweikert PM, Decker M, Hoefgen B/Assignee: Friedrich-Schiller-Universitaet Jena, Germany. Patent: DE 10 2005 025 625 A1 2006.12.07.
5. Blobaum AL. *Drug Metab Dispos*. 2006;34:1–7.
6. Dhokchawle BV, Tauro SJ, Bhandari AB. *Drug Res*. 2016;66:46–50.
7. Mathur D, Rana N, Olsen CE, Parmar VS, Prasad AK. *J Heterocycl Chem*. 2015;52:701–710.
8. Robaa D, Eldin AS, Lehmann J, Enzensperger C. *Chem Biodivers*. 2011;8:431–439.
9. Enzensperger C, Müller FK, Schmalwasser B, Wiecha P, Traber H, Lehmann J. *J Med Chem*. 2007;50:4528.