Molecular Modelling Studies of Interaction of Antiarrhythmics with an Anionic Receptor Site

M Remko

Department of Pharmaceutical Chemistry, Comenius University, SK-832 32 Bratislava Slovak Republic

Key words: molecular modelling, antiarrhytmics, receptor sites

The molecular mechanism of action of antiarrhythmics (AA) is still not thoroughly understood With respect to the structural heterogeneity of antiarrhythmics, these drugs were pharmacologically classified in several groups Lidocaine and mexiletine studied in this work are antiarrhythmic agents which belong to the class Ib category Their main antiarrhythmic effect is based on the interaction of these drugs with the sodium channel of the cardiac cell (Nattel 1991) However, the nature of these nonspecific interactions with myocardial membranes is not well defined

In our work theoretical ab initio SCF calculations were employed for the explicit modelling of the AA-receptor interaction The charged carboxylate and amine groups served as target for the binding of AAs to their supposed binding sites in the membrane On the basis of these calculations, a two-centre binding model for the antiarrhythmics to their receptor is proposed Within this model the lidocaine and mexiletine cations are in the first step recognised and bounded at the negatively charged part of the receptor In a subsequent step the interaction between the drug oxygen and cationic amine group of membrane protein may follow The influence of cations (Na^+, K^+, Mg^{2+}, and Ca^{2+}) on the strenght of the drug-anionic site interaction was investigated and the possible proton transfer from the drug towards the receptor was also studied

References

Nattel S (1991) Antiarrhythmic drug classifications A critical appraisal of their history, present status, and clinical relevance Drugs **41**, 672

Analgetically Active Substances Derived from Structures of Anpirtoline and Epibatidine

Stanislav Rádl, Petr Hezký, Jan Proška and Ivan Krejčí

Research Institute for Pharmacy and Biochemistry, Kourimska 17 13060 Prague, Czech Republic

Key words: anpirtoline, epibatidine

Introduction

The key requirement for centrally acting analgesics of non-opioid type is their mode of action not involving opiate receptors These requirements are met by both anpirtoline **I** (2-chloro-6-(piperidin-4-ylthio)pyridine) developed by ASTA Medica (Engel *et al* 1989, Gothert *et al* 1995, Schlicker *et al* 1992) and epibatidine **II** (exo-2-(6-chloro-3-pyridyl)-7-azabicyclo[2 2 1]heptane), an alkaloid isolated from Ecuadorian poisonous frog *Epipedobates tricolor* (Anon 1997, Badio and Daly 1994, Badio *et al* 1994, Polymeropoulos and Kutscher 1995, Spande *et al* 1992) The former is believed to act *via* 5-HT_{1B} receptors, the letter *via* acetylcholine nicotinic receptors Since both compounds contain 2-chloropyridine moiety and amine-containing side chains, we decided to study some hybrids of anpirtoline and epibatidine that could have strong analgesic activity without unwanted toxic effects characteristic of epibatidine For this goal, initial structural analysis of both compounds and analysis of structure-biological activity relationships based on known derivatives were performed

Then we decided to synthesise some compounds having some structural similarity to both compounds We designed a set of compounds consisting of two main series of compounds, the first series contained anpirtoline analogous bearing at the position 2 of the 6-chloropyridine ring a side chain bearing a cyclic amino group (e g pyridine or piperidine) connected to the pyridine ring either directly, or through an alkyl, methylthio, or thio bridge Analogous deaza derivatives containing a chlorophenyl ring instead of the chloropyridine one have been also planed to prepare The second series contained compounds more similar to epibatidine with cyclic amino group bound directly to the position 3 of the 6-chloropyridine ring

All of the compounds of this designed set were studied by molecular modeling using Chem-X software We found that energetically minimised conformations of most of the compounds differed from those computed for both anpirtoline and epibatidine (both (+) and ( ) epibatidine were considered) However, in several cases we have found some conformers of the compounds with energy only 2-3 kcal higher than their energetically minimised conformers On the other hand, for compounds containing an tropan-3-ylthio side chain, no such conformers have been identified Compounds bearing a cyclic amino group connected directly to the position 2 by their nature are not able to provide conformers bearing the side chain nitrogen atom in a near vicinity to nitrogen atoms of epibatidine or anpirtoline minimised conformations Nevertheless, we decided to try to synthesise all of these compounds to get more information concerning possible structure-activity relationships

Chemistry

Compounds containing a sulphur bridge at the position 2

Alkylation of sodium salt of 6-chloropyridine-2-thiol with 3-chloro-1-methylpiperidine in DMF provided the corresponding thioether **IIIa** which was then treated with ethyl chloroformate to give, after acidic hydrolysis with hydrochloric acid, 2-chloro-6-(piperidin-3-ylthio)pyridine **IIIb**, a positional isomer of anpirtoline Similar treatment using 2-chloromethyl-1-methylpiperidine provided the corresponding *N*-methyl- (**IIIc**) and *N*-unsubstituted (**IIId**) derivatives Using 3- and 4-chloromethyl-1-methylpiperidine, we synthesised also the respective *N*-methyl derivatives **IIIe** and **IIIf**, as well as the corresponding *N*-unsubstituted compounds **IIIg** and **IIIh** Similarly, 3-chloromethyl-1-methylpyrrolidine gave *N*-methyl and *N*-unsubstituted compounds **IIIi** and **IIIj**, respectively From

most of these derivatives also their deazaanalogues were prepared using sodium salt of 3-chlorothiophenol instead of the pyridine precursor

In order to prepare compounds more similar to epibatidine, we designed to prepare compounds bearing at the position 2 tropan-3-ylthio moiety However, calculations showed that minimum energy conformations of these derivatives could not fit with minimum energy conformations of anpirtoline and epibatidine Nevertheless, we decided to prepare these compounds We again started with sodium salt of 6-chloropyridine-2-thiol which was treated with tropine mesylate to give exclusively the corresponding 3-b derivative **IVa** Unfortunately, we failed to demethylate this compound We also prepared the deaza analog of **IVa** (**IVb**), which was then easily demethylated by the ethyl chloroformate method to give **IVc**

Compounds containing a methylene bridge at the position 2

Treatment of 6-chloro-2-picoline with butyllithium in ether at −78 °C provided its lithium salt which was treated at the same temperature with 1-methyl-4-piperidone to give the corresponding alcohol **Va** Its deaza analog **Vb** was obtained by reaction of 3-chlorobenzyl magnesium chloride with 1 methyl-4-piperidone Treatment of **Va** and **Vb** with ethyl chloroformate gave hydrochlorides of the corresponding ethoxycarbonyloxy derivatives **Vc** and **Vd**, respectively The salt of **Vb** was transferred to its base and then treated again with ethyl chloroformate to give the corresponding *N*-ethoxycarbonyl derivative, which upon acidic hydrolysis provided 3-(3-chlorobenzyl)piperidin-3-ol (**Ve**) Unfortunately, the same treatment of **Vd** gave unseparable mixture

Compounds without a bridge at the position 2

Starting 2-bromo-6-chloropyridine was lithiated with butyllithium and then treated with 1-methylpiperidin-4-one to give, after the workout, good yields of **Via** Similarly, starting from 1-bromo-3-chlorobenzene, the corresponding alcohol **Vibe** was obtained Attempts to demethylate **Via** and **Vibe** at this stage with ethyl chloroformate failed and hydrochlorides of the respective ethoxycarbonyloxy derivatives **Iv** and **Via** were the only isolable products These compounds were transferred into their bases by the bases were without purification treated with ethyl chloroformate to give the corresponding *N*-ethoxycarbonyl derivatives **VIIIa** and **VIIIb**, respectively These compounds upon prolonged heating in a mixture of acetic and hydrochloric acids yielded directly *N*-unsubstituted 3-piperidine derivatives **IXa** and **IXb**, products of hydrolysis of the carbamate group and elimination of the ethoxycarbonyloxy group

All attempts to achieve dehydration of compounds **VIa** and **VIb** under mild conditions failed Finally the corresponding *N*-methyl-3-piperidine bearing at the position 4 6-pyridin-2 yl (**IXc**) and 3 phenyl (**IXd**) groups, were obtained when the corresponding hydroxy derivatives **VI** were refluxed with trifluoroacetic acid Hydrogenation of hydrochloride of **IXd** in methanol using Pt catalyst on carbon produced hydrochloride of its piperidine analog **Xa** without any side products This compound was then demethylated by a standard procedure using ethyl chloroformate and following acidic hydrolysis of the formed carbamate lead to the required compound **Xb** However, attempts to hydrogenate **IXc** by the above described method provided a mixture containing mainly the starting compound and a product of reductive dechlorination on the pyridine ring with little formation of the desired compound Therefore, a different strategy was used Starting 2-bromo-6-methoxypyridine was treated with n-butyllithium and the intermediate pyridinlithium reacted with 1-methylpiperidin-2-one to give hydroxy derivative **VIc**

Dehydration of this compound with trifluoroacetic acid then afforded piperideine derivative **IXe**, which was hydrogenated on Pd/C to give piperidine derivative **Xc** For the conversion of the methoxy group in **Xc** into the chlorine atom we employed Vilsmeier reagent generated from phosphorus oxychloride and DMF The chloropyridine **Xd** was demethylated to 2-chloro-6-(piperidin-4-yl)pyridin (**Xe**) by an usual procedure involving treatment with ethyl chloroformate and consecutive acidic hydrolysis

Compounds without a bridge at the position 3

Starting from 2-chloro-5-bromopyridine and 1-methyl-4-piperidone and using methodology described in the previous chapter, the following simplified epibatidine derivatives were prepared 2-chloro-5-(4-hydroxy-1-methylpiperidin-4-yl)pyridine (**XIa**), 2-chloro-5-(4-ethoxycarbonyloxy-1-methylpiperidin-4-yl)pyridine (**XIb**), 2-chloro-5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)pyridine (**XIIa**), 2-chloro-5-(1,2,3,6-tetrahydropyridin-4-yl) pyridine (**XIIb**), 5-(4-hydroxy-1-methylpiperidin-4-yl)-2-methoxypyridine (**XIc**), 5-(1,2,3,6-tetrahydropyridin-4-yl)-2-methoxypyridine (**XIIc**), 5-(1-methylpiperidin-4-yl)-2-methoxypyridine (**XIIIa**), 2-chloro-5-(1-methylpiperidin-4-yl) pyridine (**XIIIb**), and 2-chloro-5-(piperidin-4-yl) pyridine (**XIIIc**)

The initial set contains more than 40 derivatives, most of them have been and some are being tested for their binding to 5-HT_{1A}, 5-HT_{1B}, M_1 and M_2 receptor subtypes Their pharmacological testing on selected animal models (hot plate and intraperitoneal tests in mice) is in progress The results together with the structure-activity studies will be published separately

Acknowledgements. This work was supported by Copernicus network and by the Grant Agency of the Czech Republic (grant No 203/96/0112)

References

Anon (1997) Epibatidine Drugs Fut **22**, 1210-1220

Badio D , Daly J W (1994) Epibatidine, a potent analgesic and nicotinic agonist Mol Pharmacol **45**, 562-569

Badio B , Garraffo H M , Spande T F , Daly J W (1994) Epibatidine Discovery and definition as a potent analgesic and nicotinic agonist Med Chem Res **4**, 440-148

Engel J , Scheffler G , Nickel B , Thiemer K , Tibes U , Wermer U , Szelenyi I (1989) Anpirtoline Drugs Fut **14**, 614-616

Polymeropoulos E E , Kutscher B (1995) Epibatidine A new lead for the design of non-opiate analgesics In QSAR and Molecular Modelling Concepts, Computational Tools and Biological Applications (Eds R Sanz, J Giraldo and F Manaut) pp 608-610, Prous Science Publishers, Barcelona

Schlicker E , Werner U , Hamon M , Gozlan H , Nickel B , Szelenyi I , Gothert M (1992) Anpirtoline, a novel, highly potent 5-HT_{1B} receptor agonist with antinociceptive/antidepressant-like actions in rodents Br J Pharmacol **105**, 732-738

Spande T F , Garaffo H M , Edwards M W , Yeh H J C , Pannell L , Daly J W (1992) Epibatidine A novel (chloropyridyl)azabicycloheptane with potent analgesic activity from Ecuadoran poison frog J Am Chem Soc **114**, 3475-3478

Swetberg M D B , Shannon, H E , Nickel B , Goldberg S R (1992) D-16949 (Anpirtoline) A novel serotonergic (5-HT_{1B}) psychotherapeutic agent assessed by its discriminative effects in the rat J Pharmacol Exp Ther **263**, 1015-1022