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Modern approaches to the estimation and improvement of the quality of clinical trials: Analysis of international and Russian experience

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Over the last years a number of factors have an influence on the market of clinical trials and prompted changes. Drug developers tend to define intrinsic and extrinsic factors of interregional differences which can influence an outcome of international clinical trials. The increase in R&D costs should be taken into consideration because the activity of trials and developmental activity has been increasing over the last decade, but the number of new drugs' approvals has officially decreased. Analysis of the results of inspections of FDA/EMA and Russian authorities over the last 5 years does not show an improvement in the quality of trials and clinical trials inspections by the IRB/IECs and Sponsor. The results of the FDA inspections related to the frequency of clinical investigator-related deficiencies based on post-inspection correspondence issued showed that the situation has not changed positively either; thus in 2011, out of 407 Domestic and Foreign inspections, 128 had findings (31%), and in 2014, out of 472 inspections - 171 (36%) had findings in the category "Protocol violations". The above-mentioned factors influence the clinical trials' quality and require the compliance to quality standards from all parties who organize and conduct clinical trials. The risk-based management, that is, one of approaches to solving the problem, has been implemented on a wide-scale. On the part of the regulatory authorities (FDA/EMA), regulatory-procedures harmonization is being introduced. The number of risk-based inspections, co-inspections of FDA/EMA/Russian regulatory authorities, is increasing; the training of inspectors is being harmonized.

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Discovery of novel, potent and low-toxic Angiotension II receptor type 1 (AT1) blockers: Design, synthesis, biological evaluation and molecular docking studies of 6-substituted Aminocarbonyl Benzimidazoles with a chiral center

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Novel AT1 receptor blockers bearing 6-substituted carbamoyl benzimidazoles with a chiral center were designed and synthesized as the first step of an investigation devoted to the development of new antihypertensive agents and to the understanding of the pharmacodynamic and pharmacokinetic properties. The newly synthesized compounds were tested for their potential ability to displace [125I] Sar1 Ile8-Ang II specifically bound to human AT1 receptor. These radiolig and binding assays revealed nanomolar affinity in several of the compounds under study. The IC50 values of 9 ligands were found to be higher than Losartan. The screening of lowering blood pressure in spontaneous hypertensive rats displayed that compound 8S (IC50=5.0 nM) was equipotent with Losartan, compound 13R (IC50=7.3 nM), 14R (IC50=6.3 nM) and 14S (IC50=3.5 nM) were slightly ahead of Losartan, and the best activity was given by compound 8R (IC50=1.1nM). What was followed, candidate 8R was identified its excellent efficacy of antihypertension and fairly low toxicity based on plasma analysis, toxicology studies and chronically oral test. Finally, compound 8R exhibited strong and multiple interactions with target active sites of the theoretical AT1 receptor model in docking study.

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