Water is used for several purposes in houses and industrial applications, which results in the generation of considerable amounts of wastewater. Wastewater should be handled appropriately which is required from legal, environmental as well as economic and societal perspectives. Wastewater treatment plant (WWTP) design is a formidable challenge. One of the key steps involved is the process synthesis - defined as the selection of treatment processes as a combination of unit operations and processes to create the process flow diagram. As a consequence of the emerging technological developments and resulting increase in the number of alternative wastewater treatment technologies, as well as stricter effluent limit values imposed by regulations; it became increasingly harder to identify the most feasible decision regarding the WWTP network design. Retrofitting of existing treatment plants can also be formulated as a process synthesis challenge in the sense that a new task can be added to the existing treatment line or one or several existing processes can be changed as a result of the emerging needs. Existing plants need retrofitting due to a number of reasons such as: change in the wastewater flow and composition, change in the effluent limitations, as well as changes in the wastewater treatment trends, e.g. from nutrient removal to nutrient recovery. Similarly, recovery possibilities for clean water, energy and materials shifted the perception about wastewater towards being a valuable resource rather than being a waste. While the regulations change to impose stricter effluent limit values for the contaminants, the increasing population and the size of the cities put a barrier on the expansion of the existing WWTPs. Therefore, the retrofitting task has become a complex integrated decision making problem where a number of aspects have to be accounted for in the early stage decision making. WWTP layouts are currently developed based on expert and experience-based designs. However, as a result of the above-mentioned considerations, it is evident that making the most feasible decision with this experience-based approach will be increasingly difficult if not subjective. In this study, a systematic framework based on mathematical programming is proposed to handle the complex process synthesis problem by a superstructure optimization approach to generate a novel and optimal WWTP process selection for treatment of domestic wastewaters. The framework has been implemented as a tool which consists of the superstructure covering all relevant treatment alternatives and a database storing design parameters and performances for each alternative technology. The solution of the optimization problem provides an optimal process selection and the optimal flows through the selected network. Finally, the framework is applied to two case studies constituting typical examples for the different scales of wastewater treatment design (BSM2) and retrofitting studies (Lynetten WWTP of 750,000 PE, and Avedøre WWTP of 265,000 PE) in order to highlight and validate the use of the developed methodology and database.