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Effective Generation of Lead Compounds by High Throughput Organic Synthesis : using Multipurpose Privileged Bezopyrans

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Numerous lead compounds, based on multipurpose privileged structures, can be generated that address a variety of targets from a gene family of interest, irrespective of therapeutic area. Solid-phase organic synthesis has been emerged as a powerful technique in generating combinatorial libraries of small organic molecules useful for drug discovery. Heterocyclic compounds provide scaffolds on which pharmacophores can be arranged to yield potent and selective drugs and a variety of heterocycles have been synthesized on solid support. In our research program for the development of potassium channel activators, and antioxidants, we needed to develop a synthetic strategy and chemistry applicable in a combinatorial approach for the preparation of various benzopyran derivatives. Benzopyrans have attracted significant interests in medicinal chemistry due to their broad biological activities in the areas of antioxidants, diabetes, cardiovascular, multi-drug resistance, anti-HIV agent, and ischemia etc. Therefore, the solid-phase synthesis of benzopyran containing natural and unnatural products has become one of active research fields.

Herein, we would like to report the solid-phase library construction of two thousand analogues of 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2H-1-benzopyran by high throughput organic synthesis. The polymer bound hydroxy-alkoxychromane, produced by nucleophilic reactions with various alcohols on epoxides generated in situ, served as key intermediates for subsequent diversification. Further reactions on this hydroxy-alkoxychromane with various electrophiles such as alkyl halides and acid halides produced the desired 6-amino-2,2-dimethyl-3,4,6-trisubstituted-2H-1-benzopyran analogues.