MCR scaffolds as synthons for the development of PET radiotracers

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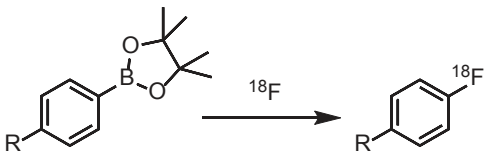
In nuclear medicine and molecular imaging, positron emission tomography (PET) represents a great progress in the clinical development of drugs and diagnostics due to its unique capacity to detect, with high sensitivity, ranges of analytes, in vitro or in vivo, that can go down to the picomolar scale. This imaging technique greatly relies on the development of molecules of interest which incorporate a β^+-emitter element (e.g. ^{15}O, ^{13}N, ^{11}C, ^{18}F…) with very short physical half-lives ranging from 2-110 min. Nonetheless, one of the many challenges is the timely and effective development of molecules (synthons) that can be promptly radiolabeled by appropriately efficient methods. The synthesis of numerous drugs and small drug-like compounds with high structural diversity have already shown to benefit from convergent multicomponent strategies.[1] MCRs also provide a quicker, versatile and proficient way to generate vast libraries of small organic molecules from communal intermediate backbones, allowing a time-efficient approach to investigate how small changes in the overall scaffold may influence functional, biological or pharmacological activity.
The combination of PET radiolabeling with MCR synthesis of biologically active compounds has the potential to greatly simplify radioanalytical and imaging based analyses. It can positively influence the design, synthesis and characterization of active compounds, evaluate their toxicity, PK/PD properties and ultimately shorten the temporal gap among the different clinical trial phases.

Herein, we present a proof of concept study where several structurally different drug-like isocyanide-based MCR scaffolds (e.g. arenes, β-lactam, tetrazole, oxazole) were synthesized to specifically contain a pinacol-derived aryl boronic ester moiety, and used to produce their [^{18}F]fluorinated counterparts. These synthons were used since Cu-mediated oxidative [^{18}F]fluorination of arylboronic acid pinacol ester derivatives tolerate electron-poor and electron-rich arenes with various functional groups.[2]



In summary, reproducible radiochemical conversion yields from 15% to 76% with short reaction times (20 to 30 min.), depending on the scaffolds, were achieved, demonstrating the feasibility of the [^{18}F]fluorination of biologically active molecules synthesized via MCR. The developed method shows the potential to apply [^{18}F]fluorination in line with MCR and also has a latent possibility of incorporating the radiolabeling step in a later stage of this convergent “one-pot” synthesis strategy. Finally, a copper(I)-catalyzed [^{11}C]carboxylation of the boronic acid esters is also a further perspective, which may expand the variability of options beyond fluorine-containing drugs.[3]

References:
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