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[99mTc(N)(DASD)(PNPn)]+ (DASD=1,4-dioxa-8-azaspiro[4,5]decandithiocarbamate, PNPn=bisphosphinoamine) for myocardial imaging.

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Aim. 99mTcN-DBODC5 ([DBODC = bis(N-ethoxyethyl)-dithiocarbamate; 5 = bis(dimethoxypropylphosphinoethyl)-ethoxyethylamine]) is the lead candidate of a series of heteroleptic monocationic compounds proposed, for their favorable biodistribution profile, as myocardial perfusion imaging agent (MPIA)[1]. Phase I clinical studies clearly showed that its clinical properties were comparable to those of the commercially available agents. Therefore, modification of 99mTcN-DBODC(5) direct to increase its pharmacokinetic profile, obtaining an ideal myocardial imaging without interference from the adjacent organ activities, would be desirable. This work describes the synthesis, characterization and the biological evaluation of four new cationic 99mTc-nitrido complexes, of general formula [99mTc(N)(DASD)(PNPn)]+ (DASD=1,4-dioxa-8-azaspiro[4,5]decan dithiocarbamate; PNPn=bisphosphinoamine) (Fig 1), abbreviated to 99mTcN-DASD(n), proposed as improved MPIAs [2].
Methods. 99mTcN-complexes were synthetized by a two steps reaction. The chemical nature of the compounds was determined by carrier-added experiments supported by radio/UV-HPLC and LC-MS analyses. Mechanistic studies were performed in-cellulo by using drug sensitive human cancer cell lines and the corresponding drug resistant sublines and in-vivo. Biodistribution studies were performed in rats and compared with the distribution profiles of 99mTcN-DBODC(5) and 99mTc-Sestamibi. The in-vitro and in-vivo metabolisms of the best compounds were evaluated by chromatographic methods.
Results. 99mTcN-DASD(n) compounds were obtained in high yield. Biological studies revealed that the complexes have a fast high initial and persistent heart uptake with rapid clearance from non-target tissues. Among the tested compounds 99mTcN-DASD(5) and 99mTcN-DASD(7) showed improved heart uptake with respect to the gold standard, with a rapid liver washout and superior heart-to-liver ratio. In-cellulo and in-vivo studies demonstrated that the compounds are membrane potential responsive and are avidly transported by Pgp-MRP1. Metabolism studies evidenced a remarkable in-vivo stability of these agents.
Conclusions. 99mTcN-DASD(5) and 99mTcN-DASD(7) are promising MPIAs. The rapid pharmacokinetic profiles, might shortened the duration of imaging protocols below 30 min allowing the early acquisition of images with high quality. In oncological field, the advantage of the in-vivo pharmacokinetic profile can also be applied to tumor imaging.

References

1. Boschi, A.; Uccelli, L.; et.al. J. Nucl. Med. 2003, 44, 806–814.
2. Salvarese, N.; Carta, D.; et. al. J. Med. Chem. 2018, 61, 11114–11126.

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