Ain Shams University
Faculty of Science
Chemistry Department

Radiochemical and Biological Characterization of some Radiolabeled Drugs for Nuclear Medicine Applications

Thesis submitted for the degree of PhD in Chemistry

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Approval Sheet

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Radioiodination and Biological Evaluation of Tizanidine as a Potential Brain Imaging Agent

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Labeling was carried out by direct iodination of tizanidine (100 µg) with radioiodine (^{125}I) in a fast single step at room temperature, to produce ^{125}I-tizanidine (^{125}I-TZN). 50 µg chloramine-T (CAT) was used as an oxidizing agent to oxidize the iodide ion to the iodonium ion, at neutral pH = 7 within 15 min. A high radiochemical yield of 92.8 % ± 0.1 was obtained. ^{125}I-TZN was stable for 2 h without detection of any by-products in the reaction mixture. The partition coefficient value of ^{125}I-TZN was 2.21 ± 0.02, showing that it is very lipophilic and can easily cross the blood brain barrier. Biodistribution studies and *in vivo* imaging showed that the initial brain uptake correlated fairly well with the brain-binding affinity of the compound. The brain uptake of ^{125}I-TZN was as high as 5.2 % and 8.0 % in biodistribution studies and *in vivo* imaging at 120 min post injection, respectively. Thus, ^{125}I-TZN is promising in radioreceptor assays for brain imaging.

Keywords: Radioiodination - Tizanidine - Biodistribution- Brain Imaging - SPECT

Introduction

Nuclear medicine imaging involves the detection and spatial mapping of the radiation emitted by a radiopharmaceutical labeled with a specific radionuclide. The objectives of a nuclear medicine scan of the brain may include, for example, the detection of lesions, the evaluation of regional cerebral blood flow (rCBF), or the quantitative determination of a particular metabolic process such as the rate of regional glucose utilization [1]. The development of emission tomography is a good example of the fusion of a number of scientific and medical disciplines to produce an effective imaging technique. There are two different techniques of emission tomography: positron emission tomography (PET), based on radionuclides which decay by positron emission, and single photon

emission computed tomography (SPECT) which is based on radionuclides which emit gamma rays or X-rays. While PET has some inherent technical advantages over SPECT, the economic reality dictates that SPECT is usually the only technique available in routine clinical practice. Recent innovations in the design of multi-head SPECT systems, which allow them to detect positron-emitting radionuclides, have diminished the sharp distinction between the two techniques [2].

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LIST OF ABBREVIATIONS

Abbreviation	*Item*
EC	electron capture
IT	isomeric transition
LET	linear energy transfer
CAT	chloramine-T
SPECT	single-photon emission computed tomography
PET	positron emission tomography
BBB	blood-brain barrier
CT	computed tomography
FDG	fluorodeoxyglucose
rCBF	regional cerebral blood flow
TZN	tizanidine
QTP	quetiapine
CBP	cyclobenzaprine
NPs	nanoparticles
NODCAR	National Organization for Drug Control and Research
BDH	British Drug Houses
SG-TLC	silica gel thin-layer chromatography
HPLC	high-performance liquid chromatography
HEGAP-Par	high energy general all purpose-parallel
Br	brain
Bl	blood
GIT	gastrointestinal tract
fMRI	functional magnetic resonance imaging

ABSTRACT

Candidate Name: Mai Adel Abd Ellatif Mourad

Title of Thesis: Radiochemical and Biological Characterization of some Radiolabeled Drugs for Nuclear Medicine Applications

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This study aimed to take advantages from drugs that are able to cross the blood-brain barrier for the development of potential radiopharmaceuticals for non-invasive brain imaging. Tizanidine hydrochloride, quetiapine fumarate and cyclobenzaprine hydrochloride were successfully labeled with radioactive iodine (^{125}I) using chloramine-T via an electrophilic substitution reaction.^{125}I-tizanidine, ^{125}I-quetiapine and ^{125}I-cyclobenzaprine gave maximum labeling yields of 92.8 % ± 0.1, 94.5 % ± 1.5 and 91.7 % ± 0.6, respectively. Biodistribution studies showed that the maximum uptake of radioiodinated tizanidine and quetiapine by the brain of mice was 5.2 % and 3.5 %, respectively, at 120 min post injection while the maximum uptake of radioiodinated cyclobenzaprine was 2.9 % at 240 min post injection. The SPECT imaging confirmed the results of biodistribution studies.

Keywords: Radiopharmaceuticals, Radioiodination, Tizanidine, Quetiapine, Cyclobenzaprine, Brain imaging, Biodistribution, SPECT.

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