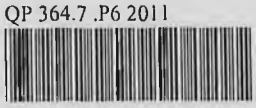
THE C-F BOND AS A CONFORMATIONAL PROBE IN AGONIST RECEPTOR INTERACTIONS.

POH WAI CHIA



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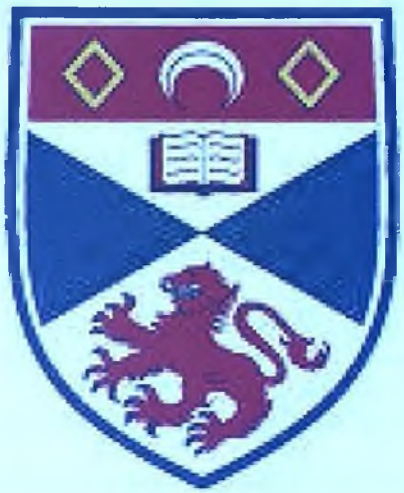

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I, Poh Wai Chia, hereby certify that this thesis, which is approximately 96,088 words in length, has been written by me, that is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree. I was admitted as a research student I September 2008 and as a candidate for the degree of Doctor of Philosophy in August 2009; the higher study for which this is a record was carried out in the University of St. Andrews between 2008 and 2011.

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Abbreviation

α	alpha
Å	amstrong
Bn	benzyl
B	beta
Boc_2O	tert-butoxycarbonyl anhydride
br	broad
cat.	catalytic
CNS	Central Nervous System
CI	chemical ionization
COSY	correlation spectroscopy
de	diastereomeric excess
Deoxofluor™	(bis(2-methoxyethylamino) sulfur trifluoride)
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
ee	enantiomeric excess
EI	electron impact
GABA	γ-aminobutyric acid
GABA-AT	γ-aminobutyric acid aminotransferase
GCMS	gass-chromatography mass spectroscopy
HMBC	heteronuclear multiple bond correlation
Hz:	Hertz
J:	coupling constant

m:	multiplet
NMDA:	*N*-methyl-D-aspartate
NMR:	Nuclear magnetic resonance
ppm:	parts per million
singlet:	singlet
triplet:	triplet
TBAF:	*N*-tetrabutylammonium fluoride

Abstract

Chapter 1 gives an introduction on the physical and electronic properties of fluorine and the C-F bond. The application of fluorine in organic chemistry, which is mainly attributed to the electronic properties of fluorine is described. The role of fluorine in neuropsychiatric drug development and for influencing the conformational study of bioactive amines is also illustrated.

Chapter 2 of the thesis describes the synthesis of the two fluorinated stereoisomers (2*R*, 3*S*) and (2*S*, 3*S*) 3-fluoro *N*-methyl–D-aspartate (NMDA). These were prepared as analogues to study the binding conformation of NMDA on the glutameric NMDA receptor. The (2*S*, 3*S*)-3-fluoro NMDA D-**72** was successfully prepared from diethyl D-tartrate. The (2*S*,3*R*)- stereoisomer was prepared by separation of diastereoisomers generated by reaction of a *meso*- epoxide with an enantiomerically pure amine, followed by fluorination. Both the (2*S*,3*R*)- and (2*R*,3*S*)- enantiomers were prepared separately, however assignment of the absolute configuration to each enantiomer could not be unambiguously proven. The fluorinated 3F-NMDA stereoisomers were assessed by dose response analysis and TEVC analysis in the rat glutamate receptor. The biological results show that the (2*S*, 3*S*)-3F NMDA D-**72** is a good agonist, whereas (2*R*, 3*S*)- and (2*S*, 3*R*)-3-fluoro NMDA are inactive stereoisomers. The result of this study indicates that (*2S, 3S*)-3F NMDA D-**72** is the only relevant agonist that can access a conformation for binding to NMDA receptor.

Chapter 3 describes the preparation of fluorinated analogues of the calcium receptor agonist Cinacalcet. The (2*R*,1'*R*)-**123** and (2*S*,1'*R*)-**124** fluoro Cinacalcet diastereoisomers were prepared from 3'-(trifluoromethyl)cinnamic acid and 3''-SF_5-**137** Cinacalcet was synthesized from pentafluorosulfanyl benzyl alcohol. The biological assessment in the calcium receptor (CaR) revealed that both (2*R*,1'*R*)-**123** and (2*S*,1'*R*)-**124** fluoro Cinacalcet is slightly lower in potency compared to the non-fluorinated Cinacalcet 117. This suggests that the Cinacalcet 117 adopts an extended conformation when bound to the receptor. The 3''-SF_5-**137** Cinacalcet possesses equipotent activity with Cinacalcet **117**.