## TABLE OF CONTENTS

Contents	Page No.
Abstract	i-iv
Declaration	v
Certificate	vi
Acknowledgements	vii-viii
Table of Contents	viii-xi
List of Tables	xii
List of Tubics	
List of Figures	xiii-xv
List of Figures	xiii-xv
List of Figures	xiii-xv
List of Figures Abbreviations	xiii-xv
List of Figures Abbreviations CHAPTER-I	xiii-xv xvi-xix

## TABLE OF CONTENTS **Contents** Page No. Chapter II **Review of Literature** 12-51 2.1 Obesity and type 2 diabetes (T2D): Epidemiological prevalence 12 2.2 Obesity mediated type 2 diabetes: Interrelation 13 13-14 2.3 Obesity mediated type 2 diabetes: Interrelation 15-16 2.4Adipose tissue inflammation leading to insulin resistance: Mechanism 2.5 Inflammation and T2D: A brief introduction 17-18 2.6 Adenosine signalling pathway: Role and target of treatment 19-21 21-23 2.7 Toll-like receptor signalling pathway: Introduction and role in resolving obesity underlying inflammation 21 2.7.1 TLRS: Structure and classification 22 2.7.2 TLR4-LPS mediated signaling pathway: Introduction and Mechanism 23 2.7.3 MyD88-dependent pathway 24 2.7.4 MyD88-independent/TRIF-dependent pathway 25 2.8 TLR4 signaling pathway, chronic inflammation and T2D 26 2.9 Protein kinase C (PKC) mediated impairment of insulin signaling 27 2.10 Small molecules and their roles in combating health complications to metabolic disorders 27-28 2.11 Natural products and their derivatives: their role as drug molecules

2.12 Indirubin and Indirubin derivatives	29-32
2.12.1 Indirubin and its derivatives as anti cancer and anti	29-31
inflammatory agent	31-32
2.12.2 Indirubin-3'-monoxime (I3M)	
2.13 Vanillin (VNL): A brief introduction and its anti-cancer, anti-	33-36
microbial and anti-inflammatory attribute	
Bibliography	36-51
CHAPTER III	
Materials and Methods	52-66
3.1 Reagents	52-53
3.2 Cell culture and treatments	53-54
3.3 Development of A <sub>2A</sub> AR stable clone	54
3.4 Radioligand-binding assay	54
3.5 Glucose uptake assay	55
3.6 Cell viability assay	55
3.7 Immunoblotting	56
3.8 Coimmunoprecipitation	56
3.9 Immunofluorescence analysis	57
3.10 Semi-quantitative RT-PCR and real-time quantitative PCR	57
3.11 Enzyme-linked immunosorbent assay (ELISA)	59
3.12 Chromatin immunoprecipitation (ChIP) assay	60
3.13 Cyclic AMP assay	60
3.14 Glycerol release assay	60
3.15 Luciferase reporter assay	61
3.16 RNA interference study	61 62
3.17 Surface plasmon resonance (SPR) analysis	62
3.18 In-vitro IRAK4 kinase assay	63
3.19 Flow cytometric analysis	63
3.20 Site-directed mutagenesis	63
3.21 Animals and treatments	64
3.22 Molecular docking studies	64
3.23 Development of vanillin analogs	64-65
3.24 Statistical analysis	65
Bibliography	65-66

CHAPTER IV	
Study the efficacy of different small molecules on the induction of	67-82
insulin sensitivity through A <sub>2A</sub> AR signalling pathway	
4.1 Introduction	67
4.2 Results	
4.2.1 In-silico studies for screening of potential adenosine 2A	68-69
receptor (A <sub>2A</sub> AR) agonists	
4.2.2 Vanillin (VNL) and indirubin-3'-monoxime (I3M) prevents	70-72
lipid induced insulin resistance through the activation of	
$A_{2A}AR$	
4.2.3 Vanillin stimulates A <sub>2A</sub> AR signalling and promotes anti-	72-75
inflammatory state of adipocytes	
4.2.4 Activation of A <sub>2A</sub> AR by vanillin attenuates lipid induced	76-77
adipocyte inflammation	<b>55.5</b> 0
4.3 Discussions	77-78
Bibliography	79-82
Chapter V	
To investigate the role of indirubin 3'-monoxime (I3M)-induced	83-98
A <sub>2A</sub> AR signalling in alleviating lipid-induced adipocyte insulin	
resistance	
5.1 Introduction	83-84
5.2 Results	
5.2.1 I3M directly binds with and stimulates A <sub>2A</sub> AR signaling	85-87
5.2.2 I3M promotes anti-inflammatory state in adipocytes through	88-90
the activation of A <sub>2A</sub> AR signalling	
5.2.3 Activation of A <sub>2A</sub> AR by I3M attenuates lipid induced	90-92
adipocyte inflammation	
5.3 Discussions	92-94
Bibliography	95-98
CHAPTER VI	00 105
Vanillin acts as a potent IRAK4 inhibitor that impairs LPS-induced	99-125
TLR4 signalling and inflammation 6.1 Introduction	00 100
6.2 Results	99-100
	100-106
6.2.1 Vanillin (VNL) attenuates LPS-induced TLR4 activation	106-108
6.2.2 Vanillin prevents inflammation in macrophages expressing the constitutively active forms of IRAK4/1	
6.2.3: VNL directly binds and inhibits IRAK4 kinase activity	108-114
6.2.4. Vanillin abrogates LPS-induced TLR4 activation and	114-115
inflammation <i>in-vivo</i>	
6.3 Discussion	115-119
Bibliography	120-125

Chapter VII	126-130
Conclusion and future perspectives	
7.1 Conclusion	126-130
7.2 Future Prospects	130
-	
List of Publications	131