### CONTENTS

#### ABBREVIATIONS

#### INTRODUCTION 1-14

#### REVIEW OF LITERATURE 15-86
- Brain adenosine levels 17
- Brain adenosine receptors: Types, Distribution, Function 19
  - Adenosine $A_1$ receptors 20
  - Adenosine $A_{2A}$ receptors 21
  - Adenosine $A_{2B}$ receptors 22
  - Adenosine $A_3$ receptors 23
- Estimation of endogenous adenosine and its metabolites 23
- Adenosine and Neuroprotection 27
- Neuroprotective role of adenosine in various neuronal disorders 30
  - Cerebral ischemia 30
  - Pain and inflammation 32
  - Parkinson’s disease 33
  - Alzheimer’s disease 34
  - Huntington’s disease 34
  - Schizophrenia 35
- Epilepsy 36
  - Animal models of epilepsy 39
  - Pentylenetetrazol-seizure threshold 40
  - Novel anticonvulsant drugs with adenosinergic mechanism of epilepsy 41
  - Adenosine and GABA 42
  - Adenosine and nitric oxide 45
  - Adenosine and serotonin receptors 48
  - Adenosine and cyclooxygenase 51
- Novel approaches in the therapeutic delivery of adenosine in epilepsy 55
- Drug Addiction and dependence 57
  - Putative neurotransmitters involved in drug addiction 58
  - Drug withdrawal 62
  - Oxidative stress in drug withdrawal 63
  - Mitochondrial enzyme activities and drug withdrawal 67
Existing Therapeutics for drug abuse and withdrawal

Alcohol
- Alcohol withdrawal syndrome
- Adenosine and alcohol withdrawal syndrome

Opioids
- Opioid withdrawal syndrome
- Adenosine and opioid withdrawal syndrome

Benzodiazepines
- Benzodiazepine withdrawal syndrome
- Adenosine and benzodiazepine withdrawal syndrome

AIMS AND OBJECTIVES

CHAPTER 1: DEVELOPMENT AND VALIDATION OF A REVERSE PHASE-HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (RP-HPLC) METHOD FOR THE ESTIMATION OF ADENOSINE AND OTHER NEUROTRANSMITTERS IN BRAIN TISSUES

Part-1: Development and validation of a RP-HPLC method for the estimation of adenosine and related purines in brain tissues of rats
  1.1.1. Introduction
  1.1.2. Experimental
  1.1.3. Results and Discussion

Part-2: Development and validation of a specific RP-HPLC method for the estimation of γ-aminobutyric acid in rat brain tissue samples using benzoyl chloride derivatization and UV/PDA detection
  1.2.1. Introduction
  1.2.2. Experimental
  1.2.3. Results and Discussion

CHAPTER 2: PENTYLENETETRAZOL-SEIZURE THRESHOLD AS A TOOL TO INVESTIGATE THE RELATIVE SENSITIVITY OF ANTIEPILEPTIC DRUGS

  2.1. Introduction
  2.2. Materials and methods
  2.3. Results and Discussion
CHAPTER 3: ON THE FUNCTIONAL INTERACTION OF ADENOSINERGIC SYSTEM WITH OTHER SIGNALING PATHWAYS AGAINST PENTYLENETETRAZOL-SEIZURE THRESHOLD PARADIGM IN MICE

Part-1: On the functional interaction between adenosine and nitric oxide signaling pathway against pentylenetetrazol-seizure threshold in mice

3.1.1. Introduction 157
3.1.2. Materials and methods 159
3.1.3. Results 160
3.1.4. Discussion 163

Part-2: On the functional interaction between adenosine and serotonergic system against pentylenetetrazol-seizure threshold in mice

3.2.1. Introduction 171
3.2.2. Materials and methods 172
3.2.3. Results 174
3.2.4. Discussion 180

Part-3: On the possible involvement of adenosinergic mechanism in the anticonvulsant effect of a selective cyclooxygenase-2 (COX-2) inhibitor against pentylenetetrazol-seizure threshold in mice

3.3.1. Introduction 189
3.3.2. Materials and methods 191
3.3.3. Results 192
3.3.4. Discussion 199

CHAPTER 4: NEUROPROTECTIVE EFFECT OF ADENOSINE A1 AND A2A RECEPTORS IN DRUG WITHDRAWAL SYNDROME

4.1. Introduction 208
4.2. Materials and methods 214
4.3. Results 228
4.4. Discussion 264

SUMMARY AND CONCLUSIONS 281-289

REFERENCES 290-334