T.C.
YEDITEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES
DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

THE ANALYSIS OF THE STRUCTURAL SIMILARITY OF SOME ANTIDEPRESSANTS AND ANTI-INFLAMMATORY MOLECULES

MASTER OF SCIENCE THESIS

SARAH ARDAM ABDULQADER ALRADHWANI

İSTANBUL-2018

T.C.
YEDITEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES
DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

THE ANALYSIS OF THE STRUCTURAL SIMILARITY OF SOME ANTIDEPRESSANTS AND ANTI-INFLAMMATORY MOLECULES

MASTER OF SCIENCE THESIS

SARAH ARDAM ABDULQADER ALRADHWANI

SUPERVISOR

Assoc. Prof. Dr. F. Esra ÖNEN BAYRAM

İSTANBUL-2018

THESIS APPROVAL FORM

Institute : Yeditepe University Institute of Health Sciences

Programme : Pharmaceutical Chemistry

Title of the Thesis : The Analysis of the Structural Similarity of Some Antidepressants and Anti-Inflammatory Molecules

Owner of the Thesis : Sarah Ardam Abdulqader Alradhwani

Examination Date : 13.11.2018

This study have approved as a Master Thesis in regard to content and quality by the Jury.

	Title, Name-Surname (Institution)	(Signature)
Chair of the Jury:	Prof. Dr. Hülya AKGÜN	
Supervisor:	Doç. Dr. Filiz Esra ÖNEN BAYRAM	
Member/Examiner:	Prof. Dr. Barkın BERK	
Member/Examiner:	Doç. Dr. Hande SİPAHİ	
Member/Examiner	Dr. Öğr. Ü. Enise Ece GÜRDAL	

APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by Administrative Board of Institute with decision dated 30.11.2018 and numbered 2018/20-03

Prof. Dr. Bayram YILMAZ

Director of Institute of Health Sciences

TEZ ONAYI FORMU

Kurum : Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü

Program : Farmasötik Kimya

Tez Başlığı : Bazı Antidepresan ve Antienflamatuvar Moleküllerin Yapı Benzerliklerinin Tayini

Tez Sahibi : Sarah ardam abdulqader Alradhwani

Sınav Tarihi : 13.11.18

Bu çalışma jurimiz tarafından kapsam ve kalite yönünden Yüksek Lisans Tezi olarak kabul edilmiştir.

	Unvanı, Adı-Soyadı (Kurumu)	İmza
Jüri Başkanı:	Prof. Dr. Hülya AKGÜN	
Tez danışmanı:	Doç. Dr. Filiz Esra ÖNEN BAYRAM	
Üye:	Prof. Dr. Barkın BERK	
Üye:	Doç. Dr. Hande SİPAHİ	
Üye:	Dr. Öğr. Ü. Enise Ece GÜRDAL	

ONAY

Bu tez Yeditepe Üniversitesi Lisansüstü Eğitim-Öğretim ve Sınav Yönetmeliğinin ilgili maddeleri uyarınca yukarıdaki jüri tarafından uygun görülmüş ve Enstitü Yönetim Kurulu'nun .30./.11../..2018.. tarih ve .2018/20-03.... sayılı kararı ile onaylanmıştır.

Prof. Dr. Bayram YILMAZ
Sağlık Bilimleri Enstitüsü Müdürü

DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

13.11.2018

Sarah Alradhwani

DEDICATION

This study is wholeheartedly dedicated to my beloved parents, who have been my source of inspiration, and continually provide their moral, spiritual, emotional and financial support.

To my beloved sister and my best friend Tamarah who have always supported and encouraged me, and to all of my friends and relatives who also have been a great support for me.

ACKNOWLEDGEMENTS

I would like to especially thank my thesis advisor Assoc. Prof. Dr. Filiz Esra Önen Bayram for her support, she was an amazing mentor that I've learned a lot from, her door was always open whenever I ran into a trouble or had a question about my research or writing, she steered me in the right direction whenever she thought I needed it. I was lucky to work with her and I would be always grateful for the support that she gave me.

I would like to give a special thank for the Dr. Gülçin Tuğcu, who performed the calculations, for her tremendous help and her great support for us, and Assoc. Prof. Dr. Hande Sipahi for her advices and ideas.

I would also like to thank Prof. Dr. Hülya Akgün, Prof. Dr. Meriç Köksal Akkoç, Dr. Lec. Enise Ece Gürdal, Assoc. Prof. Dr. Hayati Çelik for the support and knowledge that they gave me.

I would like to thank my friend Pharm. Bengisu Turgutalp for her word of advice and for her encouragement. I would also like to thank my friend and my colleague Nesreen Alhusadi for her advices.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS AND ABBREVIATIONS

5-HT	Serotonin receptors 5-hydroxytryptamine
AA	Arachidonic acid
ACTH	Adrenocorticotrophic hormone
AD	Antidepressant
AE	Antienflamatuvar
AI	Anti-inflammatory
ATGL	Adipose triglyceride lipase
AVP	Vasopressin
BDNF	Brain-Derived Neurotrophic Factor
BH_4	Tetrahydrobiopterin
m-CPP	*meta*- chlorophenyl piperazine
o-CPP	*ortho*- chlorophenyl piperazine
CRF	Adrenocorticotrophic hormone releasing factor
CRP	C-reactive protein
DA	Dopamine
TRP	Tryptophan
sGC	Soluble quanylyl cyclase
cGMP	Cyclic quanosine monophosphate
HPA	Hypothalamic- pituitary-adrenal axis
HPETE-5	Hydroperoxyeicosatetraenoic
HSL	Hormone sensitive lipase
IDO	Indoleamine-2,3-dioxygenase
IFN	Interferon
KMUP-1	7-{2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl}-1,3-dimethylpurine-2,6-dione
LOX	Lipooxygenase enzyme
LTA4	Leukotriene that is responsible for inducing inflammatory reactions
MACCS	Molecular ACCess System
MAO	Monoamine oxidase
MARKs	Mitogen-activated protein kinase
NE	Norepinephrine
NFκB	Nuclear factor κB
NMDA	*N*_methyl_*D*_aspartate
iNOS	Nitric oxide synthase
PGD2	Pro-inflammatory prostaglandin
PGE2	Pro-inflammatory prostaglandin
PLA2	Phospholipase A2
SAD	Seasonal effective disorder
TDO	Tryptophan-2,3-dioxygenase
TNF	Tumor necrosis factor
TRH	Tryptophan hydroxylase

ABSTRACT

Alradhwani, S. A. (2018). The Analysis of the Structural Similarity of Some Antidepressants and Anti-Inflammatory Molecules. Yeditepe University, Institute of Health Science, Department of Pharmaceutical chemistry, M.Sc. Thesis, İstanbul.

Currently many studies link depression to inflammation and mechanism that underlie this connection are being elucidated. Also new treatment strategies for these comorbid diseases that combine the use of antidepressants (AD) with anti-inflammatory agents (AI) are being suggested. However, to the best of our knowledge, no study yet investigated the structural similarity of the compounds used to treat these two diseases. Thus, in this study we examined whether there is any structural similarity between AD and AI molecules in *silico*. We gathered from the literature the AI and AD derivatives using Clarivates Analytics database (Web of Science) and we covered the period from 2008-2017. Then we did a manual search and obtained the most similar structures. In order to be able to discuss our results we also used computational methods and measured the similarity of the compounds using the cosine and Tanimoto similarity coefficients. By this method, we found 12 similar structures two of these, which are 7-{2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl}-1,3-dimethylpurine-2,6-dione known as (KMUP-1) (AI8), and 7-{4-[4-(3-chlorophenyl)piperazin-1-yl]butyl}-1,3-dimethylpurine-2,6-dione (AD10), their similarity was 96%. We found also that the coumarin derivatives AD16 and AD17 are 80% similar to the compound AI12.

Keywords: antidepressant, anti-inflammatory, structure, similarity, comorbid diseases

ÖZET

Alradhwani, S. A. (2018). Bazı Antidepresan ve Antienflamatuvar Moleküllerin Yapı Benzerliklerinin Tayini. Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Farmasötik Kimya Anabilim Dalı, Yüksek Lisans Tezi, İstanbul.

Günümüzde birçok çalışma depresyon ile enflamasyon hastalıklarını ilişkilendirmekte ve bu bağlantının temelini oluşturan mekanizmaları aydınlatmaktadır. Ayrıca aynı anda seyredebilen bu iki hastalığın tedavi stratejilerinde antienflamatuvar (AI) ve antidepresan (AD) moleküllerinin beraber kullanılması da önerilmektedir. Ancak, bildiğimiz kadarıyla, bu iki hastalığın tedavisinde kullanılan bileşiklerin yapılarının benzerliğini araştıran bir çalışma henüz gerçekleştirilmemiştir. Bu nedenle, bu çalışma AI ve AD bileşiklerinin yapı benzerliklerinin bilgisayar ortamında araştırmayı hedeflemektedir. Çalışmada kullanılacak yapılar Clarivates Analytics veritabanı (Web of Science) 2008-2017 aralığında taranarak elde edilmiştir. Elde edilen yapıların benzerlikleri önce manüel olarak daha sonra da bilgisayar ortamında cosine ve Tanimoto katsayıları hesaplanarak belirlenmiştir. Çalışma yapısal benzerlik gösteren birçok molekül ortaya çıkarmış ve bunlardan özellikle ikisinin olduça yakın yapıda olduklarını saptamıştır. Benzer bulunan yapılar KMUP-1 olarak da bilinen 7-{2-[4-(2-klorofenil)piperazin-1-il]butil}-1,3-dimetilpürin-2,6-dion (AI8) ve 7-{4-[4-(3-klorofenil)piperazin-1-il]butil}-1,3-dimetilpürin-2,6-diondur (AD10) 96% benzerlik gösterdi. Çalışma ayrıca AD16 ve AD17 kumarin türevlerinin de AI12 türeviyle %80 oranında yapı benzerliği gösterdiğini ortaya koymuştur.

Anahtar Kelimeler: antidepresan, antienflamatuvar, yapı, benzerlik, komorbid hastalık

1. INTRODUCTION AND PURPOSE

Recently, a bidirectional relationship has been revealed concerning two important diseases, depression and inflammation (1). These two diseases have a great impact on the quality of life for millions of patients around the world and they are responsible for the death of thousands of people every year. Inflammation and depression are affecting and enhancing each other development. People that are suffering from chronic inflammatory diseases such as asthma, cardiovascular diseases, and rheumatoid arthritis are found to be at high risk for developing depression. Also, high levels of inflammatory markers are found to be present in one-third of the depressed patients (2, 3). There are many studies that discuss the possible connections between these two diseases should they be biological, hormonal, and environmental. Pro-inflammatory cytokines that can induce behavioral sicknesses by affecting some specific brain parts like the Hypothalamic-pituitary-adrenal axis (HPA-axis), hippocampus, Brain-Derived Neurotrophic Factor (BNDF) can be an illustration for such a connection (4). The changes in brain's neurotransmitter levels such as serotonin and dopamine which are highly related to depression due to changes in cytokine levels also points out a possible connection between the diseases (5, 6). Some studies also proved that anti-inflammatory drugs such as aspirin has an antidepressant activity when investigated *in vivo* (7). Other studies indicated that antidepressants drugs such as desipramine and fluoxetine possess anti-inflammatory activities (8). However, the structural similarities of the antidepressant and anti-inflammatory drugs have not been studied in details. To the best of our knowledge, Önen et al, were the first who published very recently a study that deals with the analysis of the similarity of the molecular structure of drugs that are marketed as antidepressant and anti-inflammatory agents (9). But, there is still no study that evaluated the structural similarity of molecules that are described in the literature for some *in vitro* and/or *in vivo* antidepressant and anti-inflammatory activities.

Our aim in this study is to investigate the structural similarity of the molecules that were described for their antidepressant and anti-inflammatory activity in the last 10 years (2008 -2018). To obtain these data computational similarity measures will be used. The study will describe the molecules' structures with either the PubChem or Molecular ACCess System (MACCS) fingerprints or the Tanimoto and cosine coefficients were used to calculate to measure the similarity of these structures.

2. LITERATURE REVIEW

2.1. Depression

Depression is a public mental health problem which is represented by the feeling of isolation, worthlessness, and deep feelings of sadness and disappearance that affects people's functioning, thoughts, feelings and interactions. It is also associated with lack of confidence, self-esteem and a feeling of insecurity. These feelings significantly interfere with normal daily life activities and tasks. The continuity of these sensations may even lead to suicidal thoughts if not discovered or treated properly.

Depression strikes at any time and affect different kind of people regardless of their age, race and socioeconomic conditions. Women are more vulnerable than men to depression, depression is twice more common in women (10). Two thirds of people with depression do not realize that they have this disease, so they do not seek for professional help, the misperception of such a disease by public also leads to such ignorance. (11)

2.1.1. Types of depression

There are many factors that play an important role in initiating the presence of depression. Some types of depression are caused by environmental factors, such as climate changes, stress, social and familial status, and even the changes between day and night. Chemical changes also play an essential role in the development of depression, such as the dysfunction of some brains neurotransmitters like serotonin (5-HT), dopamine (DA) and norepinephrine (NE). Other types are enhanced by some hormonal changes such as the dysregulation of the hypothalamic- pituitary- adrenal axis (HPA axis).

1- Major depressive disorders

2- Persistent depression (dysthymia)

3- Manic-depressive disorder (Bipolar disorder)

4- Seasonal effective disorder (SAD), (12).

2.1.1.1 Major depressive disorders

Serious mental disorders have severe symptoms that effect the patient's way in handling their daily life activity, such as working, eating and sleeping. Major depressive disorders occur among children, young and elder people.

Most common symptoms are:

- Despondency : lost spirit
- Anhedonia (joylessness) : reduced interest and pleasure in most activities
- Melancholia : low spirit, being passive, withdrawal and/or lack of energy, slow thinking and delayed reaction time, feelings of failure in everything, sexual disturbance and insomnia
- Appetite change : loss of appetite and weight, sometimes weight gain
- Disrupted sleep or insomnia : difficulty in falling asleep, early waking or too much sleep
- Change in motor activity
- Fatigue, low self-esteem and sense of guilt
- Concentration difficulties
- Suicidal thoughts

In order the patient to be diagnosed with depression at least five of these symptoms should be present, especially despondency and anhedonia. These symptoms should affect work performance and social activities and must be present at least for 2 weeks continuously so the patient could be diagnosed with depression. The most severe form of symptoms of major depressive disorders is melancholia (12, 13).

2.1.1.2 Persistent depression (dysthymia)

Dysthymia can be diagnosed for a patient presenting persistent symptoms of major depressive disorders for at least 2 years and its main symptoms are loss of appetite and insomnia. In children it is enough for the symptoms to last only one year to be diagnosed. Dysthymia occurs more in women than in men (12, 14).

2.1.1.3 Manic-depressive disorder (bipolar disorder)

The disorder is characterized by moods swinging between deep depression and mania episodes, a pathologically overjoyed mood characterized with reduced sleep periods and a strong need to talk in rapid and incomprehensive way. This pathological

condition varies from one person to another, sometimes it happens 2 or 3 times in a life time and sometimes the intervals between periods are short (12, 14).

2.1.1.4 Seasonal effective disorder (SAD)

Seasonal changes, occurs between day and night, light and dark and also warmth and cold affect human mood. The circadian cycle is affected by body temperature, secretion of hormones and other physiological factors. It is regulated by the hormone called melatonin which is only secreted in dark. Melatonin is related to other sleep-wake rhythm related hormones like cortisol, whose levels typically drop when melatonin levels increase. Both of these hormones are involved in mood regulation and their levels are found to be disturbed in depressed people. Seasonal depression shows atypical symptoms of major depressive disorders like increased sleep and appetite. Women appear to be more affected by winter depression. These depression types are found to occur annually at the same time of the year and are also known as seasonal depression (12, 14).

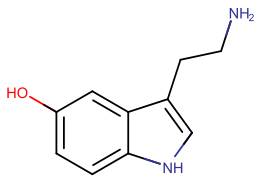
2.1.2. Causes of depression

2.1.2.1 Biological causes

Neurotransmitters

Amines and amino acids are neurotransmitters responsible for the transmission of messages between neurons. These neurotransmitters are affecting our mood and emotions. Neurotransmitters that are found to be connected to depression and anxiety disorders are serotonin, dopamine and noradrenaline (12, 13).

- Serotonin and depression



Serotonin

Serotonin, is a neurotransmitter also known as 5-hydroxytryptamine. In humans, serotonin is synthesized from the L-tryptophan (figure 2.1), an amino acid that is supplied from the diet (15). Monoamine oxidase is the phase 1 enzyme that is involved in the biotransformation of the serotonin into its active metabolites. MAO has 2 isoforms MAO-A and MAO-B. Serotonin is a selective substrate of MAO-A (figure 2.2) (16) .

Serotonin affects several brain functions and emotional responses such as body temperature, circadian rhythm, mood, anxiety and appetite. It is also involved in the perception of external stimuli and impulse control. The imbalance of serotonin secretion may lead to a psychiatric disorders such as depression, eating disturbance and aggressive behavior (17). Also, low levels of serotonin have been linked with increased stress, sleep disturbance and panic attacks (18, 19).

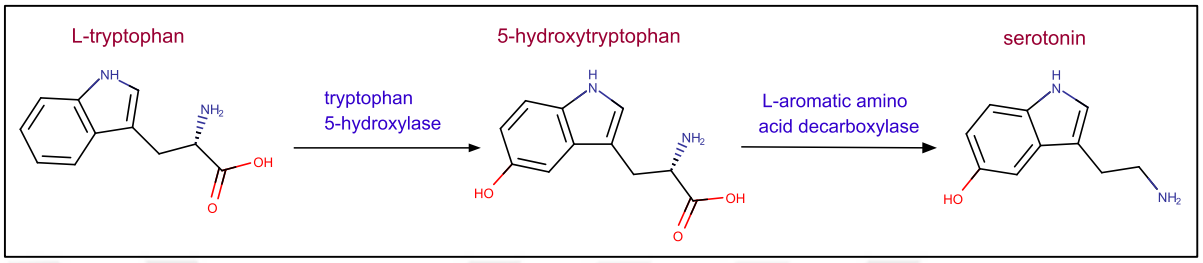


Figure 2.1. Serotonin synthesis pathway

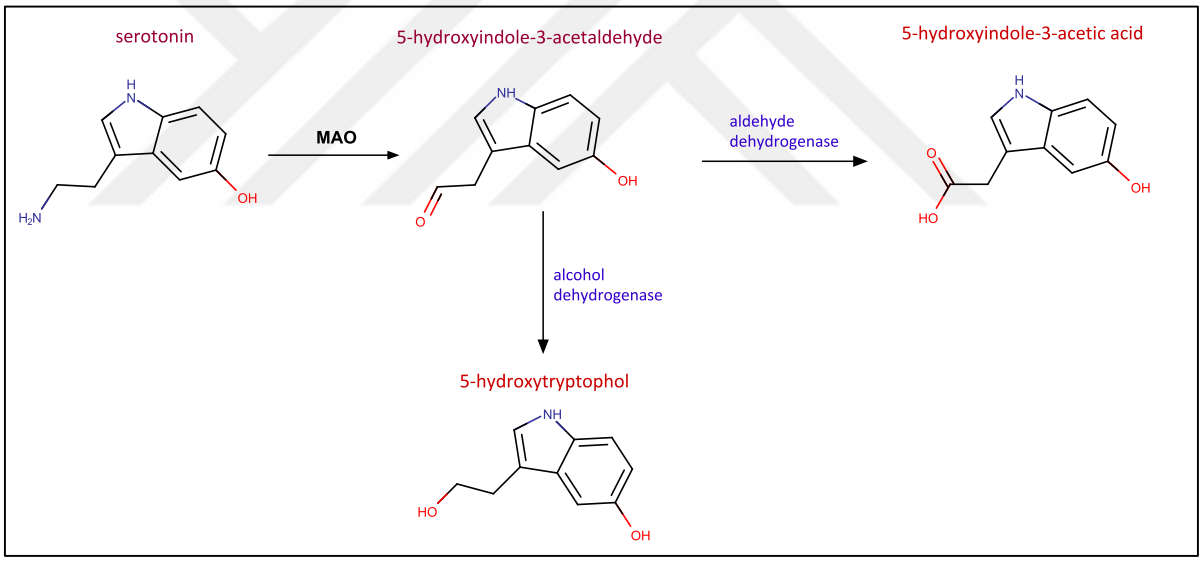


Figure 2.2. The biotransformation of serotonin by MAO

Serotonin receptors 5-hydroxytryptamine 5-HT mediates serotonin function. These receptors consists of 7 families, from 5-TH 1 to 5-TH 7 (figure 2.3) (20, 21). Brain serotonin levels can be increased by using the drugs that inhibit the reuptake of serotonin in the neural synapses and these drugs are found to be effective in treating depression (22, 23).

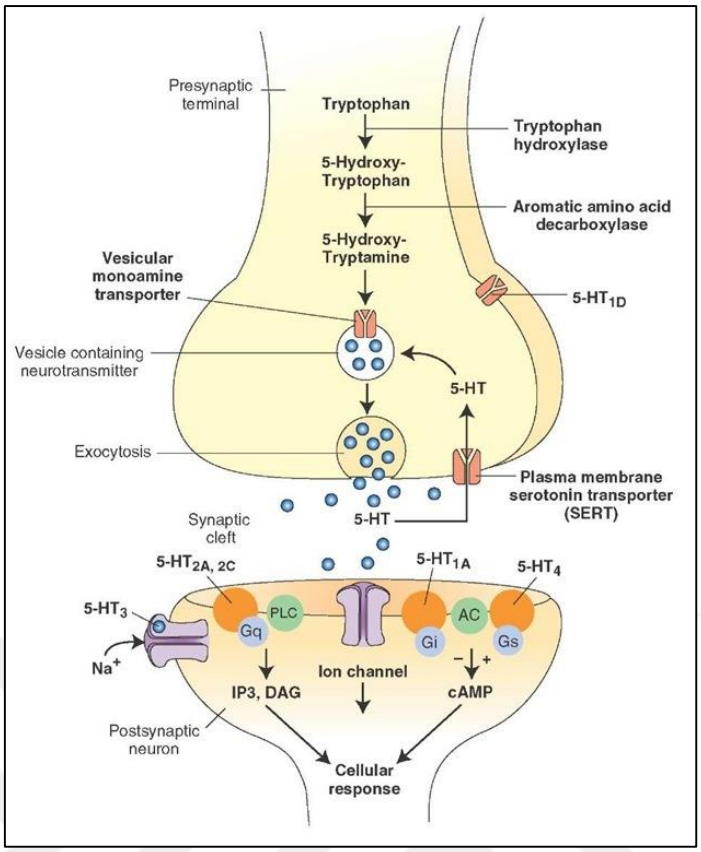
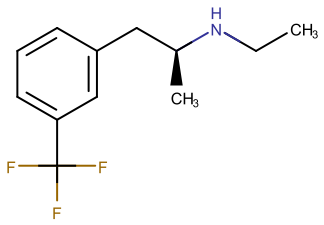


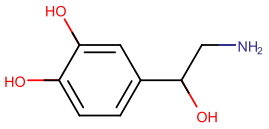
Figure 2.3. Serotonin receptors (24)

Some clinical trials of serotonin functioning showed that people with high serotonin levels were more confident, relaxed and optimistic while people with low levels were aggressive, competitive and impulsive. In this trial, the authors (Graeff FG. et al) applied a stimulated public speaking test in healthy volunteers. They used D-Fenfluramine, a 5-HT uptake blocker. During this test they measured physiological parameters such as heart rate and blood pressure and found that the volunteers who took the drug during the test demonstrated low rates of anxiety and they were more relaxed which is due to the increase in serotonin levels (25).

D-Fenfluramine



- Norepinephrine (NE) and depression



Norepinephrine

Norepinephrine or noradrenaline is a neurotransmitter that plays role in regulating mood, anxiety levels, energy and fear. NE is secreted in cells in case of stressful situations, situations call for alert, attention, and self-defense. NE is secreted in the hypothalamus, amygdala, and the hippocampus (figure 2.4) (26, 27). Reduction in NE synthesis and modulation of NE receptors may lead to depression. NE is activated in response to the acute stress (28, 29). Both chronic and acute stresses are affecting the NE function (30). Noradrenergic system is activated by many types of stressful stimuli such as loud noise, electric shock, hypoglycemia, hypotension and others.(31-33).

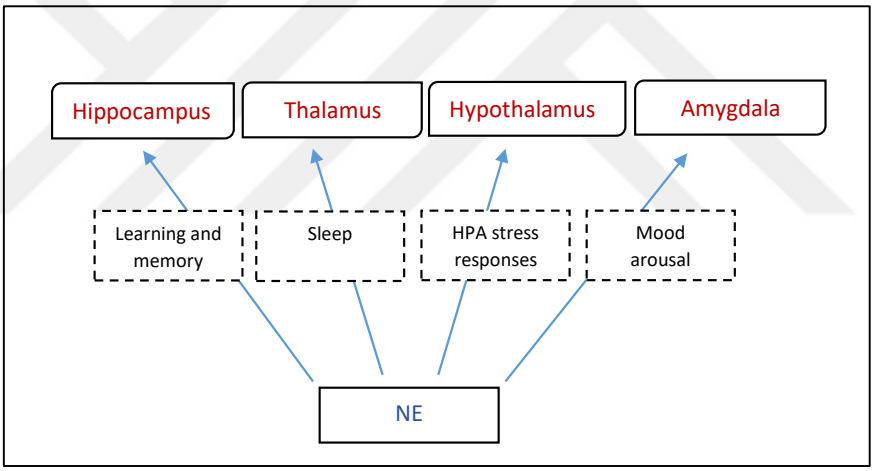


Figure 2.4. NE effect on specific brain parts (27)

The administration of α-adrenergic antagonist yohimbine, an anxiogenic agent resulted in enhancing anxiety-like behavior (figure 2.5). This is because yohimbine is activating the NE release in the limbic forebrain and this activation resulted in enhancing acute stressors release and enhancement of a behavior similar to the one obtained after inducing an acute stress as illustrated in the figure below (26, 27, 34-36).

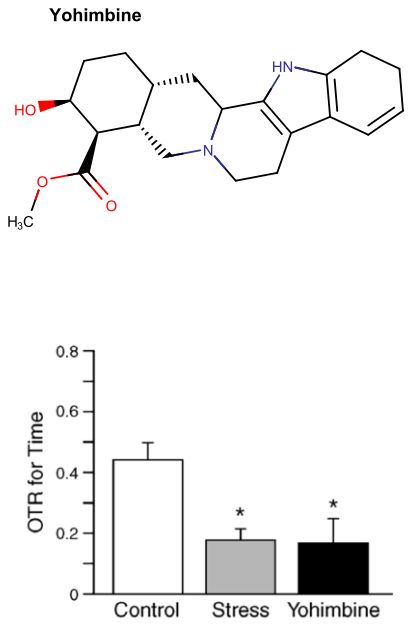
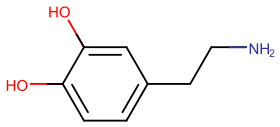


Figure 2.5. The anxiogenic effect of yohimbine which is similer to stress, (adapted from Morilak DA et al) (35).

Selective NE reuptake inhibitors are effective in treating depressed mood, social withdrawal and other symptoms that related to depression and also in treating other stress-related psychiatric disorders (37-39).

- Dopamine (DA) and depression



Dopamine

Dopamine is a neurotransmitter that enhances motor and mental activity. It regulates mental processes that are connected with attention, motivation, concentration and human ability to experience pleasure. Dysfunction in the dopaminergic system and low dopamine levels may result in the discouragement of these abilities (40). DA is synthesized from phenylalanine and tyrosine, amino acids located in the cytoplasm of the presynaptic neurons (figure 2.6). DA exhibit its activity when it interacts with dopamine receptors which are located in the postsynaptic neurons. DA receptors consist of 5-subtypes and these subtypes divided into 2 groups, the D1 family and the D2 family. The D1 family consists of D1 and D5 and the D2 family comprises D2, D3, and D4 (figure 2.7) (41).

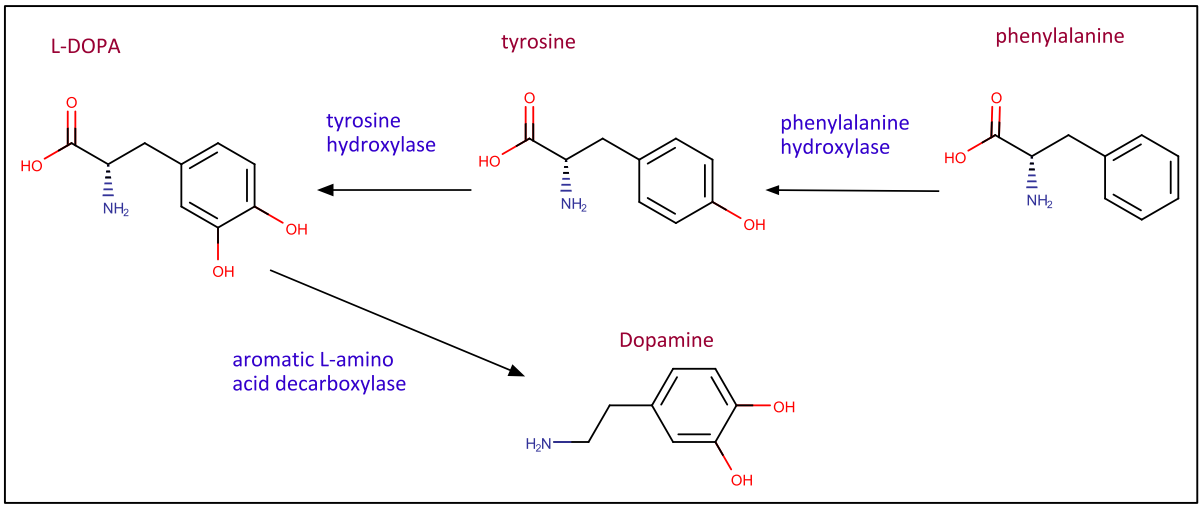


Figure 2.6. Dopamine synthesis pathway

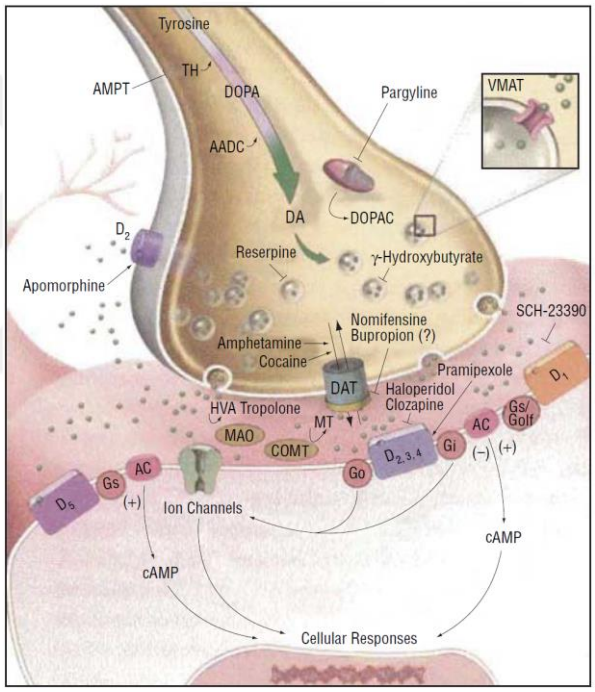


Figure 2.7. Dopaminergic synaptic signaling (adapted from Dunlop BW et al) (42).

The most common symptom of depression is anhedonia, which is caused by the deficiency of dopamine that results from the reduction in dopamine neurotransmission (43-45). Anhedonia is one of the 2 required symptoms for the patient to be diagnosed with depression. Anhedonia, as we mentioned above, is described as the loss of the feeling of pleasure or joylessness. It has been found that it is related to the dysfunction of the dopaminergic system. Especially the dysfunction of the ascending dopaminergic function (the mesolimbic pathway) (figure 2.8) which is found to be playing an important role in

enhancing the motivation and the feeling of the pleasure (42, 46). These findings proves the relationship between the dopamine deficiency and the feeling of joylessness (47-49).

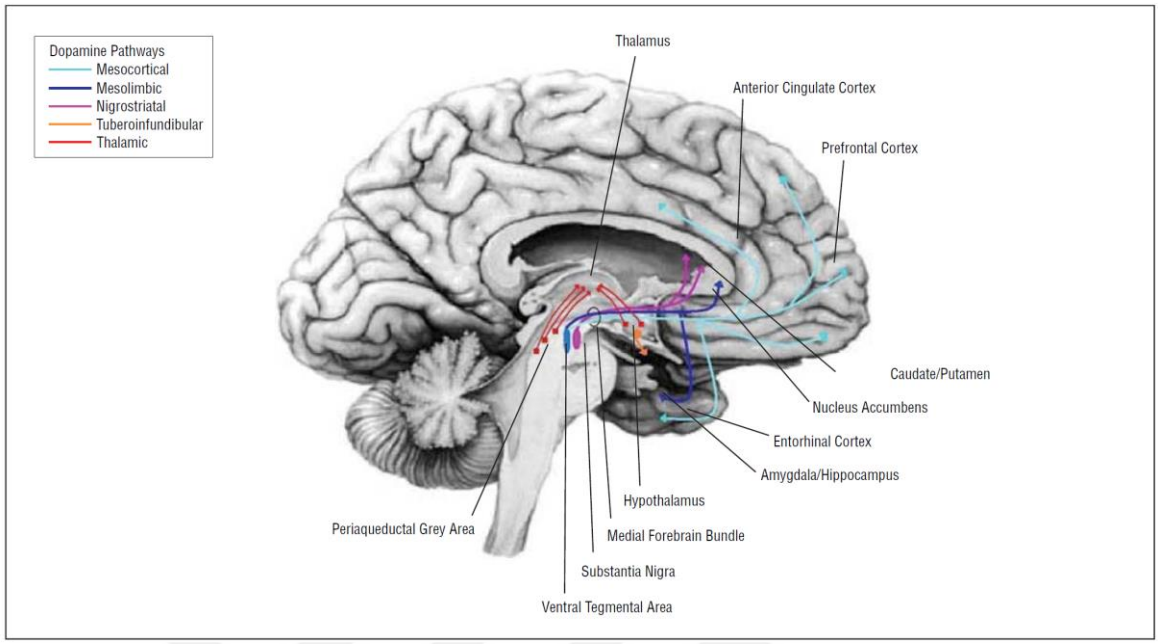


Figure 2.8. Dopaminergic pathways in the human brain, (adapted from Dunlop BW et al) (42).

Memory and concentration are important abilities that controlled by the brain. And these abilities have found to be affected in patients who suffering from depression. As illustrated in (figure 2.8) the mesocortical pathway which is one of the dopaminergic pathways is responsible of these administrative functions. The dysfunction of this pathway resulted in memory and concentration difficulties and these signs are present in depressed patients (42, 46).

The effect of hormones on depression

Hormonal secretion and hormone producing organs are affected by stress and some types of illnesses which can lead to a disturbance in hormonal balance and thus to depression.

- Melatonin and depression

Melatonin as already mentioned is a hormone that regulates our daily rhythm of wakefulness and sleep. Melatonin is synthesized from serotonin, as serotonin is converted to melatonin by a degradation pathway in the pineal gland. Light inhibits the melatonin synthesis and because of this effect, it has been found that melatonin concentration in the pineal gland varies between day and night, its concentration being higher in night (50).

In healthy people, melatonin maximum level is observed between 2.00 am and 4.00 am. Depressed people are shown to present constant levels of melatonin during the whole day which means that melatonin levels do not increase during night (12). As depressed patients present low serotonin levels, melatonin levels cannot increase during night (figure 2.9) which leads to insomnia, one of depression symptoms.

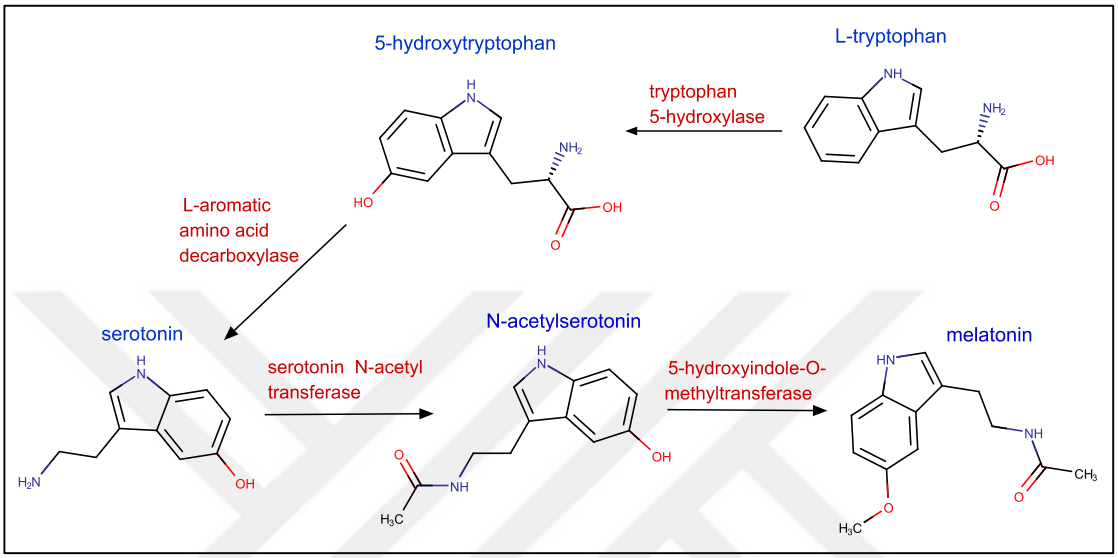


Figure 2.9. Melatonin synthesis pathway

- Prolactin and depression

Prolactin is another hormone that affects our mental health. Depressed individuals who suffer from low self-esteem, week social support and who are experiencing the feeling of powerlessness were shown to present high prolactin levels. Prolactin levels that are normally very low in men can reach extremely high levels when in depressed condition (12, 51).

2.1.2.2 Environmental causes

Stress and depression

To achieve a good mental health there should be a balance in the concentration of neurotransmitters which serve as the basic foundations for normal brain functioning. Chronic and acute forms of stress such as the inability to solve problems, loss of status, humiliation or lack of control are found to be depressogenic and affecting the balance of these neurotransmitters. This leads to elevated noradrenergic response (figure 2.10) and

hypersensitivity of noradrenaline receptors which in return affects both the dopamine and serotonin systems (12, 52-54).

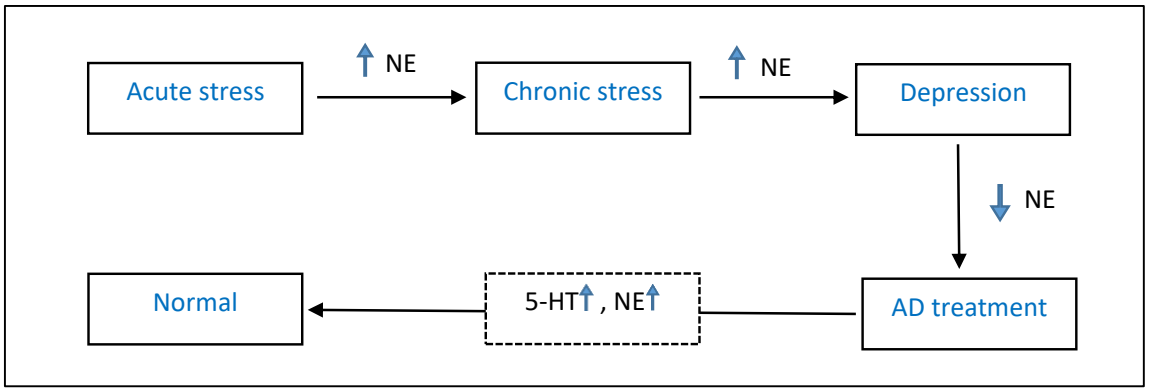


Figure 2.10. The effect of stress on NE (27) AD, antidepressant NE, norepinephrine.

The adrenocorticotrophic hormone releasing factor (CRF) and vasopressin (AVP) are released from the hypothalamus. These 2 hormones are responsible for the activation and stimulation of adrenocorticotrophic hormone ACTH secretion from the pituitary gland. ACTH is responsible for the stimulation of the glucocorticoids secretion (cortisol) from the adrenal cortex (55, 56). Glucocorticoids then activate the HPA axis by interacting with specific receptors that are located on it. Glucocorticoids are controlling many functions such as the size of the hippocampus, neurogenesis, emotional status and the possessions of new memories (56, 57). In stressful situations, the secretion of the CRF and AVP increases and this leads to an increase in the ACTH stimulation which results in increased cortisol secretion and NE (figure 2.11) (58, 59).

The activation of the HPA axis is affecting metabolism, immunity and the brain. In depressed patients, the feedback inhibition of the CRF and AVP from the hypothalamus which is controlled by glucocorticoids are found to be disturbed. Also, depressed patients have increased HPA axis activity and cortisol concentrations. This leads to a conclusion that HPA axis hyperactivity may represent one of the risk factors that appear before depression development (55, 56, 60, 61).

As we mentioned stress increases the production of cortisol which stimulates the hippocampus, a part of the brain which is responsible for learning, memory, spatial navigation and anxiety. The hippocampus is located in brain's temporal lobe and is responsible for converting the short-term-memory to a long-term-memory. The increase in the cortisol concentration leads to some toxic effects including a reduction in cognitive

functions and long-term changes such as hippocampal neuronal degradation which is represented by the reduction in the hippocampus size and neuronal death (54, 62, 63). In fact, in depressed patients the size of the hippocampus is found to be smaller when compared to healthy volunteers. This reduction in the hippocampus size is affecting the efficiency of memory and learning processes, incidents found to be present in depressed patients (56).

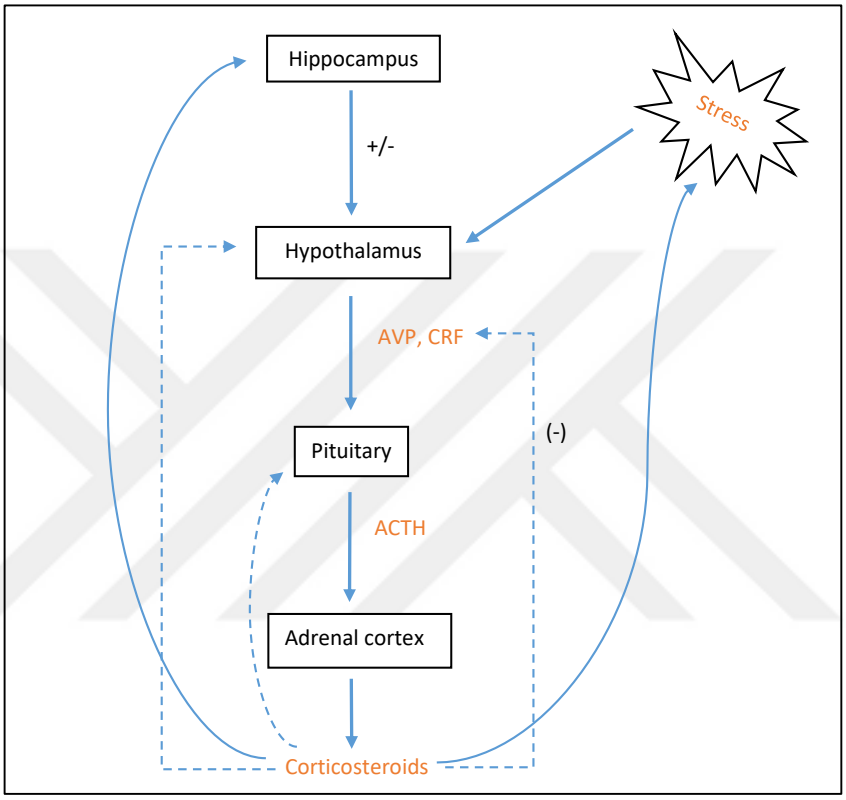


Figure 2.11. The relationship between HPA axis and the hippocampus and the effect of stress (56)

Stress also increases the extracellular concentrations of NE and dopamine by affecting the catecholaminergic neurons. In a clinical study, rats were exposed to an acute and chronic stress, acute tail pressure test and cold chronic test in which the cold was chosen as a chronic stressor. After rats' exposure to these stressors, the NE and dopamine concentrations were obtained and the authors found that NE and dopamine extracellular concentrations were increased. Diazepam a drug used to treat anxiety, was administrated to the rats. Diazepam only reduced the concentration of NE and dopamine in the ones that were exposed to acute stress (64).

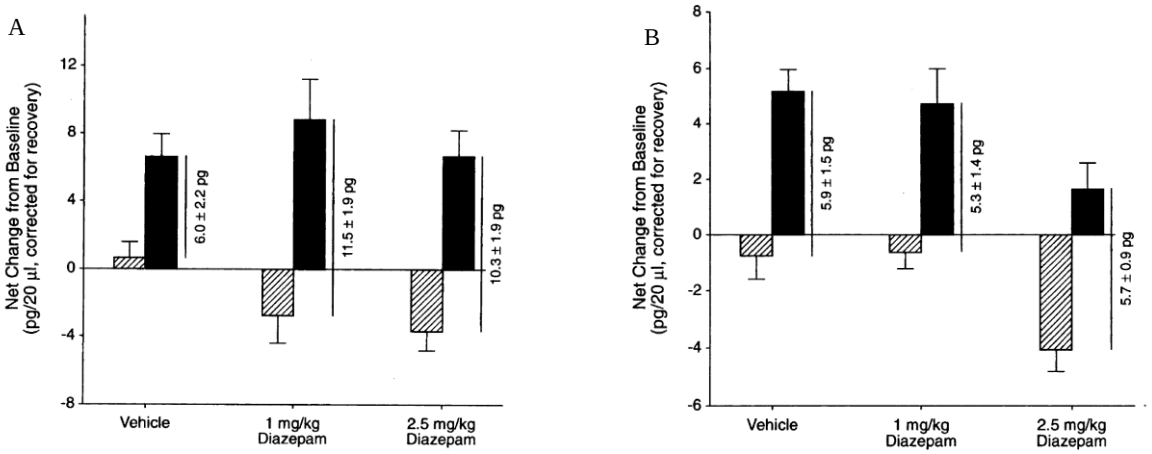


Figure 2.12. Effect of diazepam on the stress-induced increase in extracellular DA in the mPFC of naive rats, 2.12b the effect of diazepam on the stress-induced increase in extracellular NE in the mPFC of naïve rats, (adapted from Finlay J et al) (64).

Acute stressors were found to activate the DA mesocortical pathway, which leads to an increase in the DA concentration in the brain. The prolonged effect of these stressors also leads to an increase in DA concentration *via* the DA mesolimbic pathway. These 2 DA pathways were found to respond oppositely when chronic, uncontrollable and sustained stress is present and the brain falls to adapt to it. This would lead to reduced DA concentration and mesolimbic pathway depletion in case of chronic stress (figure2.12, 2.13) (53, 65-67).

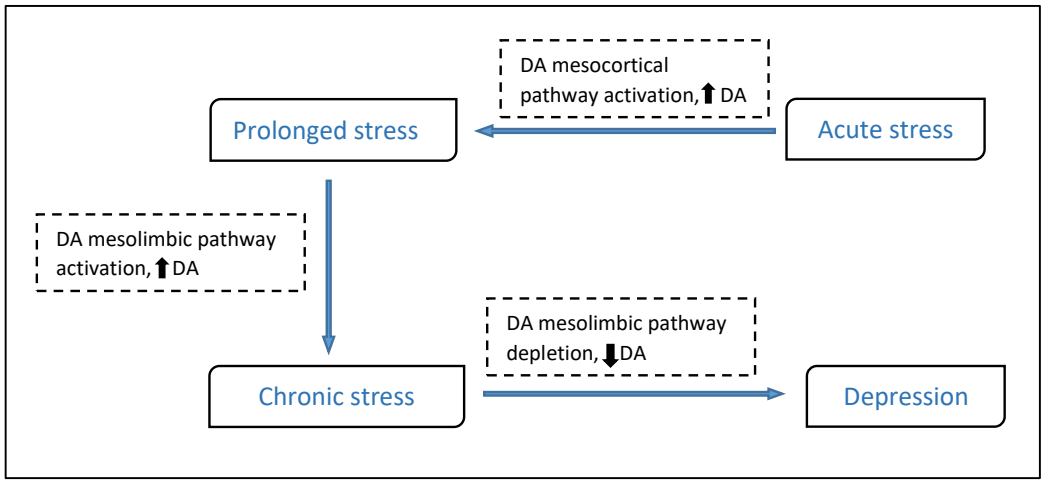


Figure 2.13. The effect of the stress on DA concentration (53)

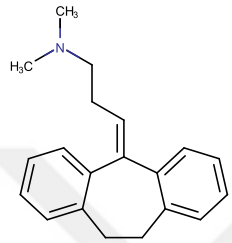
The same thing applies to NE: acute stress is activating the NE release while prolonged, chronic and sustained stress results in decreasing NE levels in brain while the NE extracellular concentration is high (figure 2.10).

2.1.3. Treatment of depression

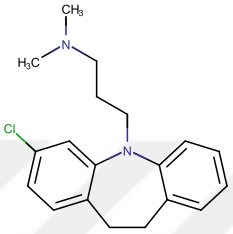
There are many types of antidepressants that are used for treating depression, anxiety and pain. The drug of choice is depending on the condition severity and here is the most common types of antidepressant (12, 13).

2.1.3.1 Non-selective monoamine reuptake inhibitors

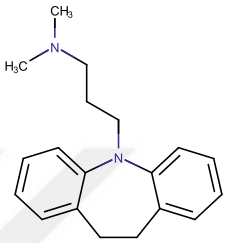
Tricyclic and tetracyclic antidepressants (TCAs): used in severe depression types like melancholia. Such as amitriptyline, clomipramine and imipramine (68).



Amitriptyline



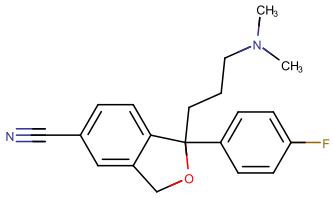
Clomipramine



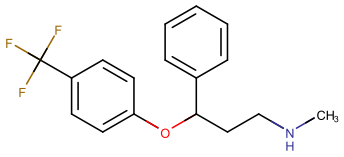
Imipramine

2.1.3.2 Selective serotonin reuptake inhibitors (SSRIs)

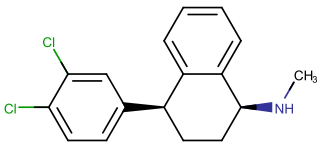
This type of antidepressant is used to increase serotonin concentration by blocking the reuptake of serotonin in the brain, such as citalopram, fluoxetine and sertraline (69).



Citalopram



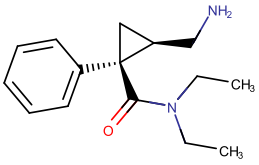
Fluoxetine



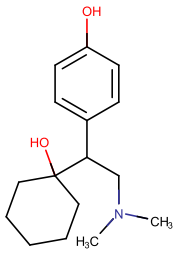
Sertraline

2.1.3.3 Serotonin and noradrenaline reuptake inhibitors (SNRIs)

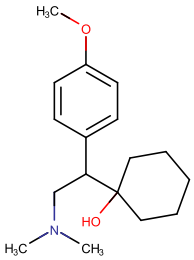
Help to decrease depression symptoms by blocking the reuptake of NE and serotonin such as the drugs below (70).



Levomilnacipran



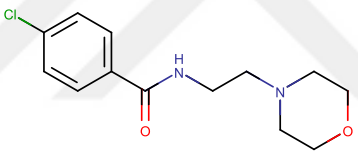
Desvenlafaxine



Venlafaxine

2.1.3.4 Monoamine oxidase (MAO) inhibitors and reversible inhibitors of MAO-A (RIMAs).

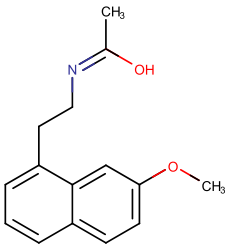
RIMAs are antidepressants that works to increase serotonin and NE levels in the brain by blocking the effect of monoamine oxidase which is responsible of breaking down the serotonin and NE such as moclobemide (71).



Moclobemide

2.1.3.5 Melatonergic antidepressant

Melatonergic antidepressant like the melatonin receptor agonist agomelatine which is a synthetic melatonin working on increasing the melatonin concentration in the brain. This drug used as an alternative drug if the patients have a resistance to other types of antidepressant drugs (72).



Agomelatine

2.2. Inflammation

Inflammation is an immune response and a defense mechanism that aims to protect the body from harmful stimuli. Inflammation plays a main role in the body's healing processes and without the intervention of this mechanism the body's damaged tissues, wound and infections would not be healed.

The immune system consists of 2 types of immune responses, innate immunity and adaptive immunity. Innate immunity is present when the person is born and it is considered as the first line defense against pathogens in which inflammation is considered as a part of it. Adaptive immunity is the type of the immunity that emerges after infections or vaccinations by the effect of antigens that stimulates antibodies production.

Innate immunity consists of phagocytic cells, such as neutrophils, monocytes, and macrophages and inflammatory cells, such as basophiles, mast cells, macrophages, and natural killer cells. These cells induce the secretion of small molecules called cytokines which are playing an important role in regulating inflammatory responses (73-76).

2.2.1. Types of inflammation

2.2.1.1 Acute inflammation (nonspecific)

Acute inflammation has a rapid response with limited time severity. Acute inflammation may last from days to weeks depending on the severity such as acute bronchitis, tonsillitis, dermatitis and skin wounds. Symptoms of acute inflammation are pain, swelling, redness and heat(75).

2.2.1.2 Chronic inflammation (specific)

This type of inflammation has a slow onset of action, last for a long time, from months to years and leads to cell death. This can be caused by some pathogens that cannot be cleared from circulation which keeps the immune responses continuously active. Chronic inflammation is a hallmark of diseases such as rheumatoid arthritis, peptic ulcer and asthma. The symptoms of chronic inflammation are fever, fatigue, abdominal pain, joint pain and rash (75).

2.2.2. Cytokines

Cytokines are low molecular weight proteins that regulate immune responses. They are responsible for mediating and regulating immunity, inflammation and hematopoiesis. Cytokines regulate the immune responses either by inducing or inhibiting the immune system by sending signals to specific receptors when binding to them (77, 78).

Cytokines can act differently on cells, for instance, some cytokines have an autocrine action which means they are acting on the same cells that secreted them, while other can be paracrines (cytokines acting nearby the secreting cells) or endocrines (acting on distant cells) (79).

2.2.2.1 Types of cytokines

Cytokines are named according to the cells that are secreted from,

1. Lymphokines are cytokines secreted by the lymphocytes,
2. Monokines are cytokines secreted from monocytes,
3. Interleukins are cytokines that are secreted from leucocytes and affecting other white blood cells,
4. Interferon's (IFN) are cytokines that are secreted by infected cells and enhance the immunity defenses by interfering with viral replication
5. Chemokines are cytokines shown to be inducing chemotaxis that activates leukocytes immigration.
6. Tumor necrosis factor TNF

Cytokines are produced by basophiles, mast cells, macrophages, and natural killer cells but the predominant producers of cytokines are macrophages and helper T-cells (Th), Macrophages produces IL-12 and INF-ɣ, basophiles and mast cells produce IL-4 and IL-3 (figure2.14) (77-79).

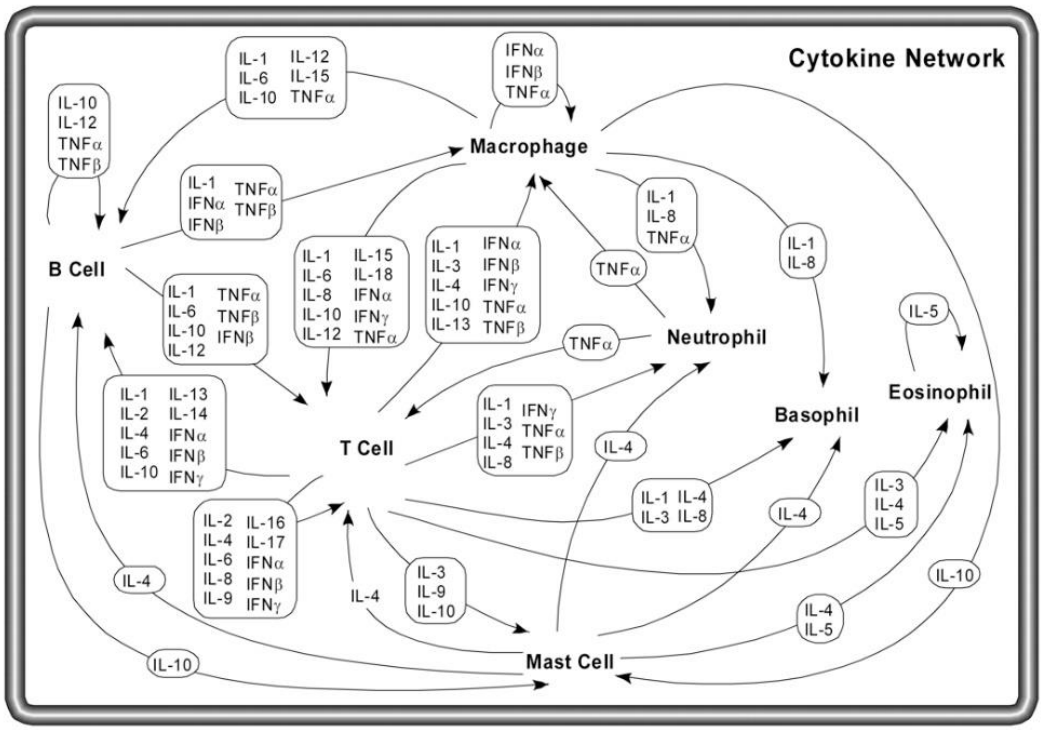


Figure 2.14. Cytokines network, (adapted from Zhang J-M et al) (79).

2.2.3. Inflammatory cytokines

- Pro-inflammatory cytokines
- Anti-inflammatory cytokines
- Inflammatory cascade

2.2.3.1 Pro-inflammatory cytokines:

Immunoregulatory cytokines such as IL-β, TNF-α, and IL-6 that promote inflammation, enhance inflammatory responses and increase inflammation severity by the up-regulation of inflammatory reactions. This happens when the balance between the pro-inflammatory and anti-inflammatory cytokines is disturbed and the secretion of the pro-inflammatory cytokines is increased (figure 2.15). Most of the pro-inflammatory cytokines are secreted by the activated macrophages.

IL-1 and TNF are shown to be pro-inflammatory cytokines as they were administered to humans and after their administration, they induced fever, tissue destruction, inflammation and even shock in some cases (80-82).

2.2.3.2 Anti-inflammatory cytokines:

Anti-inflammatory cytokines are immunoregulatory molecules that suppress the activity of pro-inflammatory cytokines, decrease inflammation severity and promote healing processes. The major anti-inflammatory cytokines are the interleukin (IL)-1 receptor antagonists such as IL-4, IL-6, IL-10, IL-11, and IL-13 (83).

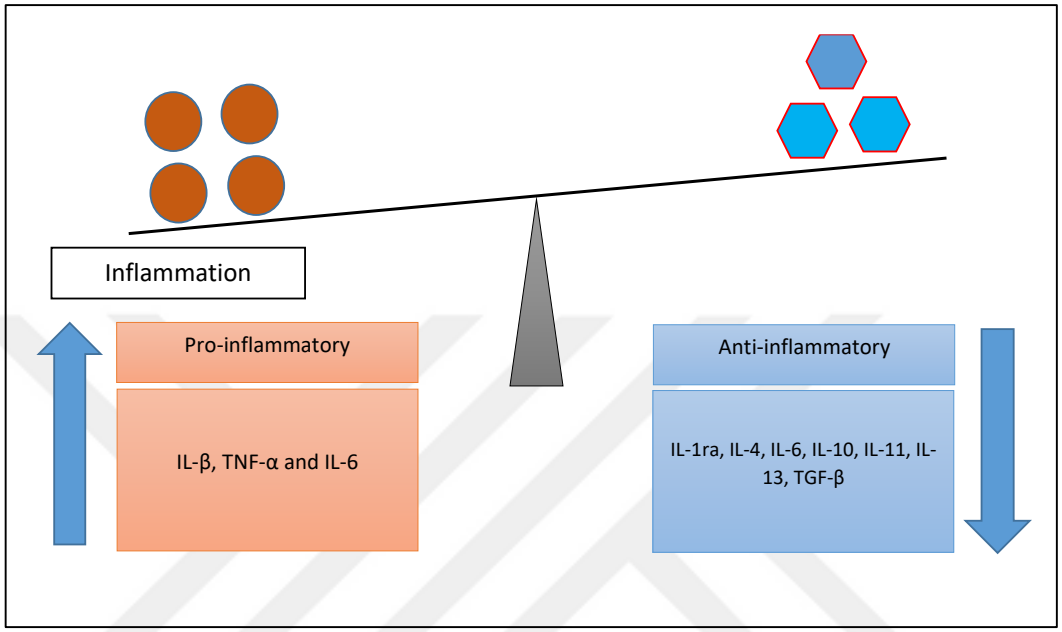


Figure 2.15. The effect of pro-inflammatory and anti-inflammatory cytokines on inflammation

The Inflammatory cascade

In the inflammatory cascade shown in the figure below (figure 2.16). The pro-inflammatory cytokines IL-1, TNF, and INFɣ are responsible for enhancing an inflammatory response by stimulating the secretion of the pro-inflammatory enzymes such as phospholipase A2 (PLA2). The PLA2 is responsible for yielding a free arachidonic acid (AA) from the phospholipids tissue's membrane. The free AA which is unsaturated fatty acid undergo through many pathways, 2 of these pathways are responsible for enhancing inflammatory reactions which are lipooxygenase pathway and cyclooxygenase pathway (84-86).

In the lipooxygenase pathway, the lipooxygenase enzyme (LOX) is responsible for AA oxygenation. This oxygenation is taking place on many Carbone positions such as C-5, C-12, and C-15. In this inflammatory cascade it is affecting C-5 by the enzyme LOX-5. The LOX-5 is an enzyme that results in the inflammatory leukocytes accumulation and converting the free AA to hydroperoxyeicosatetraenoic (HPETE-5). Leukotriene

synthase then converting the HPETE-5 to LTA4. The LTA4 is a leukotriene that is responsible for inducing inflammatory reactions. The LTA4 then transforming to LTC4 by the glutathione-s-transferase. And by an amino acid addition, the LTC4 is converted to LTD4 and LTE4 which are responsible for enhancing vasodilation, edema, and inflammation (85, 87-90).

The cyclooxygenase pathway consists of 2 enzymes COX-1 and COX-2 which are responsible for enhancing inflammation. COX-2 results in the secretion pro-inflammatory prostaglandins like PGE2 and PGD2 by converting the free AA to PGG2 which is a prostaglandin that quickly converts to PGH2. PGH2 converted by the prostacyclin enzyme to PGD2 and PGE2 which are inflammatory mediators that are responsible for enhancing fever and inflammation (85, 91, 92).

The chemokines in this cascade working as facilitators of leukocytes passage to the tissues. The IL-1 and TNF have a synergistic effect on this cascade and they are responsible for initiating the adhesion of the leukocytes to the endothelial surface before their immigration to the tissues. The anti-inflammatory cytokines inhibit this cascade and decrease it severity (80-82)

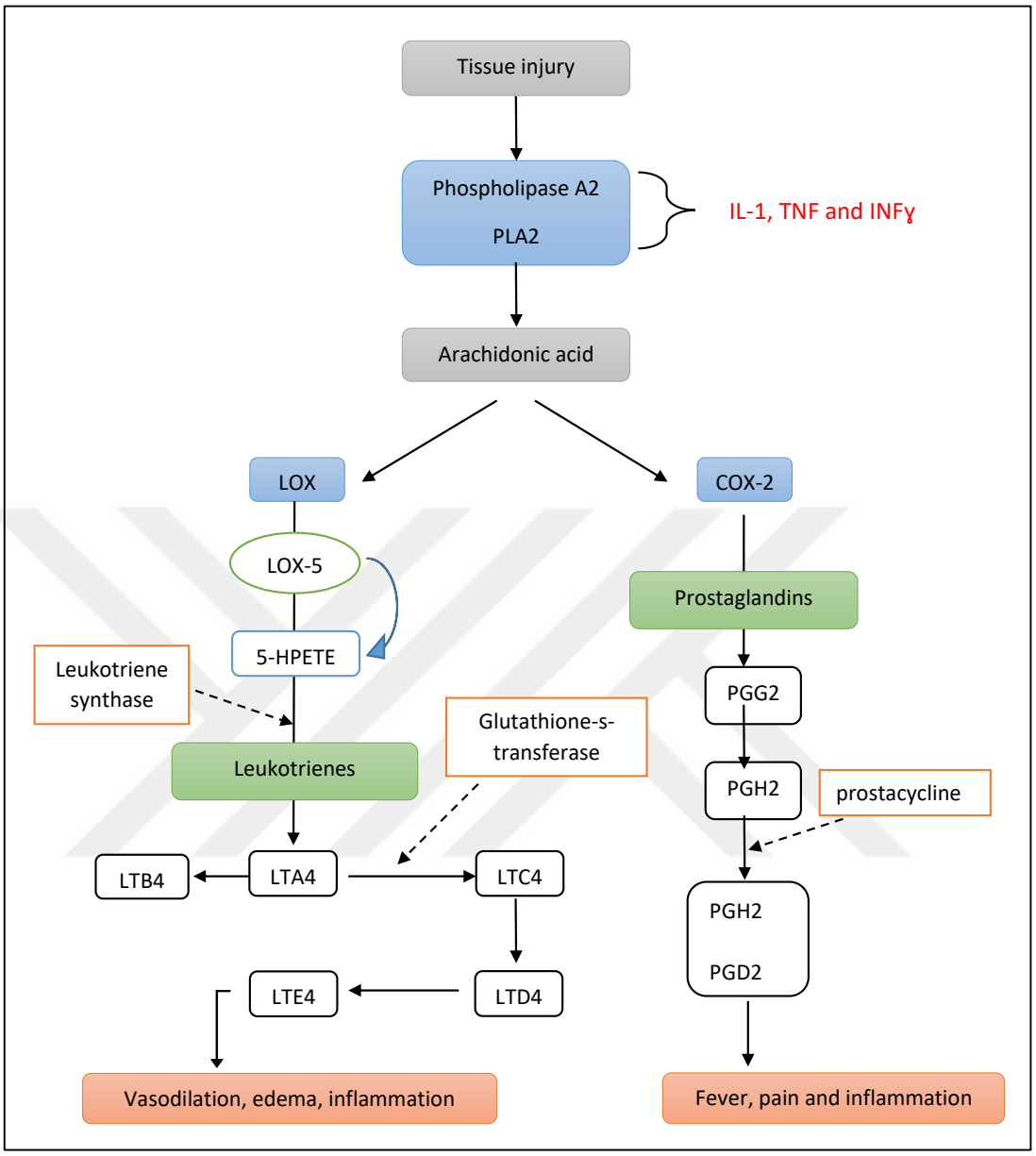


Figure 2.16. The inflammatory cascade

2.2.4. Inflammatory markers

When inflammation occurs, the inflamed site secrets extra proteins and these proteins then traveling through the bloodstream the circulating in it. There is a certain tests that indicates this increase in the levels of these proteins and considered as inflammatory markers (93).

2.2.4.1 Erythrocytes sedimentation rate (ESR)

This test detects the increase of a specific proteins by measuring the red blood cells separation rates from the plasma. The obtained rates of this test are directly proportional to the inflammation rates, which means high inflammation rate is presented when high records of ESR is obtained and it is measured in (mm/h) (93).

2.2.4.2 C-reactive protein

This is a non-specific test that also considered as an inflammatory marker. The CRP is secreted from the liver to the bloodstream in response to inflammatory stimuli. This means that the CRP levels in healthy people would be zero and the presence of this protein in the bloodstream would determine if there is an inflammation or not. The CRP rate is also directly proportional to the inflammation rate. CRP is used to detect some inflammatory diseases such as rheumatoid arthritis and also to check the treatment efficacy (94).

2.2.4.3 Plasma viscosity

This test is similar to the ESR but it is more difficult to perform. It measures the amount of some proteins that located in the blood plasma like the fibrinogen. Fibrinogen levels found to be increased with the presence of inflammation. The increase in the levels of these proteins would also lead to an increase in the plasma viscosity and that means the protein levels and plasma viscosity levels would detect the inflammation presence (95).

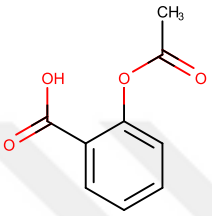
2.2.5. Anti-inflammatory drugs

2.2.5.1 Non-steroidal anti-inflammatory drugs NSAIDs

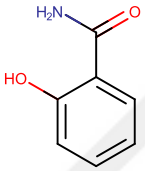
a. Carboxylic acid derivatives:

- Salicylic acid derivatives

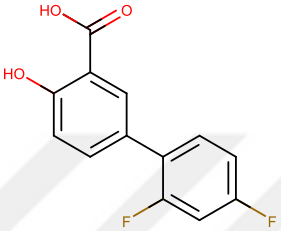
These types of NSAIDs inhibit COX-1 100 times more that COX-2, and have an Anti-inflammatory, analgesic and antipyretic activity, such as acetylsalicylic acid (aspirin), Salicylamide, Diflunisal, Salsalate.



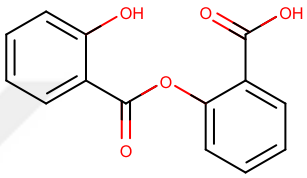
Aspirin



Salicylamide



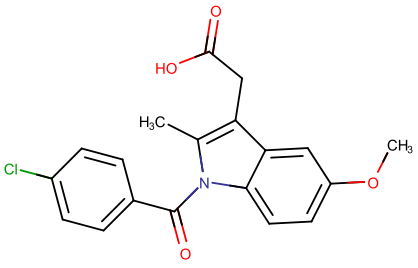
Diflunisal



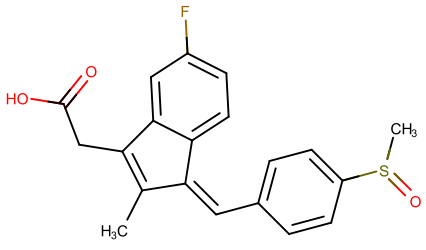
Salsalate

- Aryl and heteroaryl acetic acid derivatives

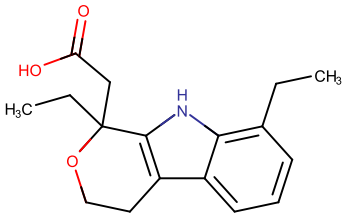
- Indole, indene: Selective COX-1 inhibitors with antipyretic and analgesic activity such as Indomethacin, Sulindac and Etodolac.



Indomethacin



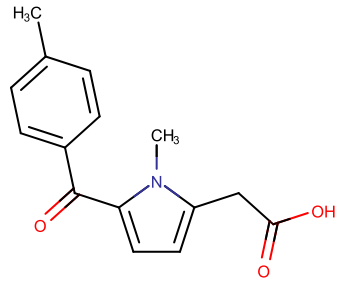
Sulindac



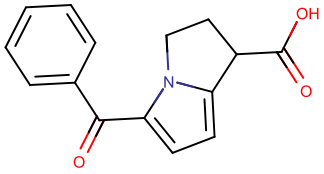
Etodolac

- Pyrrole:

Tolmetin and Ketorolac, Tolmetin is a non-selective cox inhibitor with anti-inflammatory activity and ketorolac is with anti-inflammatory, analgesic and anti-pyretic activity.



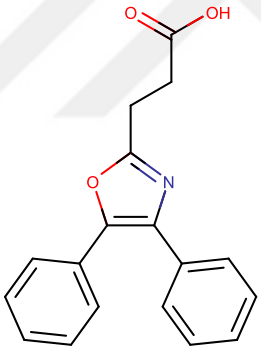
Tolmetin



Ketorolac

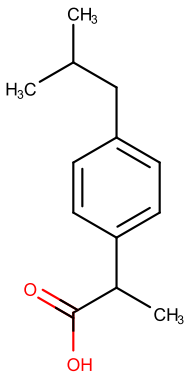
- Oxazole:

Oxaprozin (Daypro), non-selective COX inhibitor

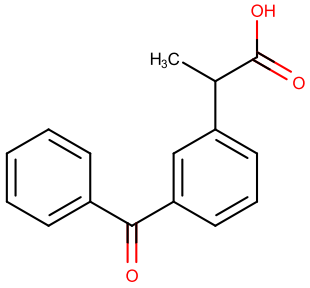


Oxaprozin

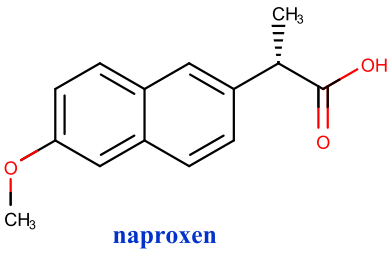
- Propionic acids (Profens)



iboprofen

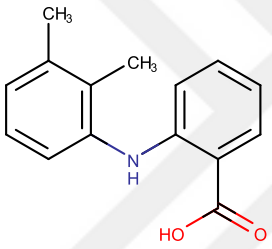


ketoprofen

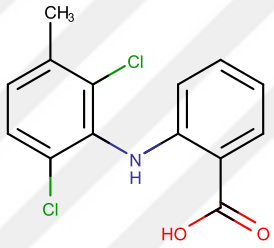


naproxen

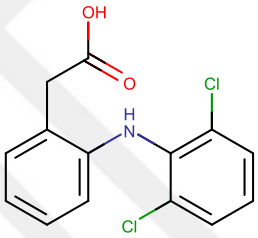
- N-Arylanthranilic acid derivatives (Fenamates)



mefanamic acid



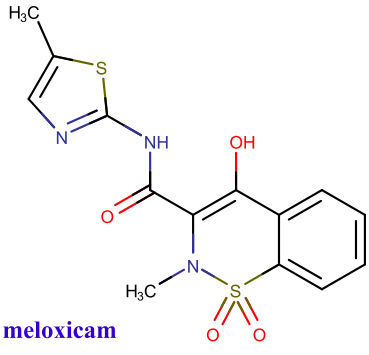
meclofenamate



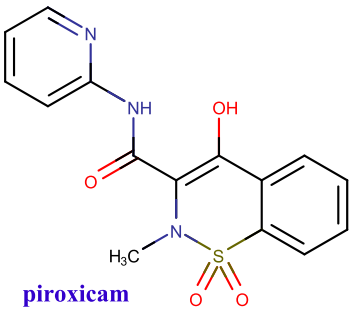
declofenac

b. Enolic acids derivatives

- Oxicams

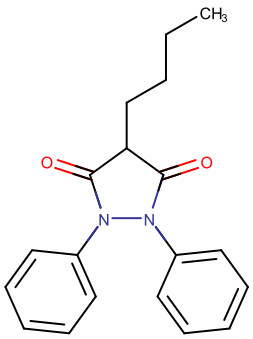


meloxicam



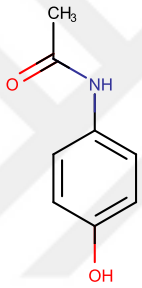
piroxicam

- Phenylpyrazolones derivatives

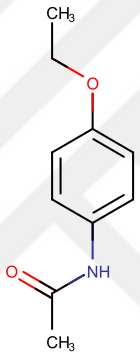


phenylbutazone

c. Anilides derivatives



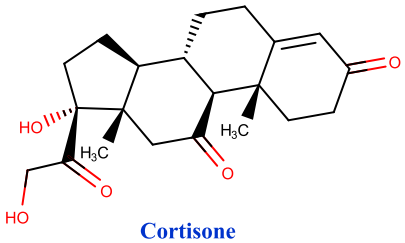
acetaminophen



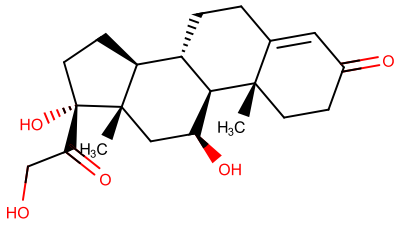
phenacetin

2.2.5.2 Anti-inflammatory Corticosteroids

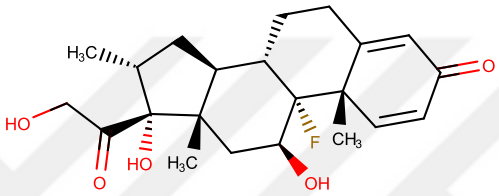
Glucocorticoids, are anti-inflammatory corticosteroids that inhibits inflammation and immune responses ex. Cortisone, hydrocortisone, dexamethasone, prednisolone, methylprednisolone.



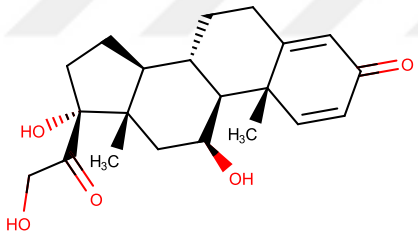
Cortisone



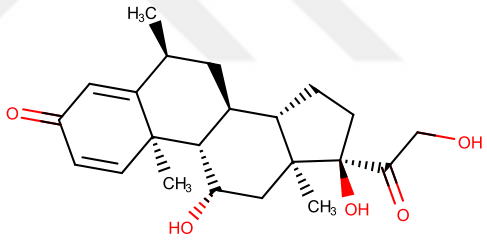
hydrocortisone



dexamethasone



prednisolone



methylprednisolone

2.3. Inflammation and depression

There are some shreds of evidence that links inflammation and depression. The relationship between these two diseases is a bidirectional relationship in which they are both affecting each other. Not only that but also they are contributing to the occurrence of one another by several pathways (1, 4, 6).

The most persuasive evidence that elucidates this relationship is the cytokines, especially the pro-inflammatory cytokines which are considered as inflammatory mediators and markers that are responsible for enhancing inflammatory responses. Inflammatory markers such as IL-β, TNF-α, IL-6, and CRP are found in high concentrations in one-third of patients who are suffering from major depressive disorders MDD (1, 96-98).

Through the clinical studies that investigated this relationship, scientists found that the patients who are suffering from chronic inflammatory diseases such as chronic pain, type 2 diabetes, rheumatoid arthritis and cardiovascular diseases are at high risk of developing depression (2, 5). Also, cancer patients who are treated with cytokines such as interferon-alpha (IFN-α) are developing some symptoms that are related to depression Moreover, during peripheral and CNS inflammatory diseases, a high risk of depression had been observed in these patients. Also, it had been found that inflammatory responses are being activated in response to depression in clinically depressed patients. (1, 3).

2.3.1. Cytokines enhance CNS inflammation and sickness behavior

Cytokines can enhance CNS inflammation when they are present in the brain, and this is accomplished when an infection attacks the body. After this attack the innate immune responses would be stimulated to protect the body and to fight the infection by producing the pro-inflammatory cytokines.

The pro-inflammatory cytokines such as TNF-α, IL-β and IL-6 would reach the brain and, it would affect specific brain regions such as the HPA-axis, the hippocampus, the pituitary gland and the Brain-Derived Neurotrophic Factor (BDNF). The pro-inflammatory cytokines then would induce sickness behaviors similar to the symptoms that present in depressed patients such as decreased appetite, social withdrawal, sleep disturbance and retardation in the motor activity (1, 99-101). The pro-inflammatory cytokines can reach the brain through the blood-brain barrier (BBB) in some specific

cases, or it can be produced inside the brain by the macrophages and the lymphocytes in response to inflammatory *stimuli*.

Cytokines in normal situations cannot cross the (BBB). However, they can get access in specific regions, in regions with no BBB like the circumventricular site, or in regions that have fewer obstacles for the cytokines access by the aid of the passive transport (102-104). Cytokines can cross the BBB in some pathological situations in which the BBB is impaired. In some cases, even cytokines can enhance the impairment in the BBB, just like the TNF-α which is found to have the ability to enhance BBB degeneration. Also, it can reach the brain by the active transport in which specific protein carries would transport the cytokines through the BBB (102, 104-106).

2.3.2. Cytokines and the neurotransmitters

Cytokines are found to be affecting the neurotransmitters concentrations in many ways. Cytokines can increase the reuptake of neurotransmitters like the NE, DA, and serotonin and also interfere with their synthesis pathway by affecting some specific enzymes that play a key role on their synthesis (107).

2.3.2.1 Serotonin

The synthesis of serotonin depends on its metabolic precursor tryptophan TRP. When it enters the body TRP undergoes 2 metabolic pathways (figure 2.17). The first one is called the primary pathway in which 99% of the TRP is converted to kynurenine. The second pathway is responsible for converting less than 1% of TRP to serotonin and melatonin. The conversion of TRP to kynurenine is achieved by the enzymes indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO), in which TDO is the predominant enzyme. Conversion of TRP to serotonin (5-HT) is accomplished by the enzyme Tryptophan Hydroxylase (TRH) (108-110)

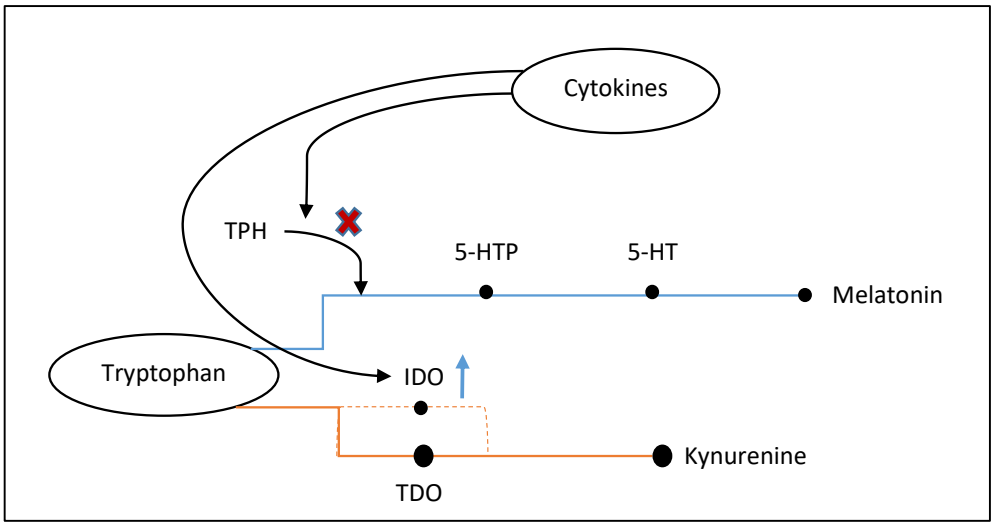


Figure 2.17. The effect of cytokines on serotonin

When an immune activation is present, cytokines such as IL-1, IL-2, IL-6, and INFs can enhance the activity of the IDO enzyme. By this enhancement, the percentage of tryptophan that is converted to kynurenine would be increased. This increase would result in the reduction of the tryptophan that is converted to serotonin by 25% to50% which would result in decreased serotonin levels (109, 111, 112). There is another way by which cytokines can affect serotonin synthesis. Cytokines can decrease serotonin synthesis by decreasing tetrahydrobiopterin (BH_4) levels. BH_4 is an essential co-factor for the enzyme tryptophan hydroxylase which is a rate-limiting enzyme in serotonin synthesis pathway (107, 113).

2.3.2.2 Dopamine

Tetrahydrobiopterin (BH_4) is also an essential co-factor of tyrosine hydroxylase. Tyrosine hydroxylase is the rate-limiting enzyme of the dopamine biosynthesis that is responsible for converting phenylalanine to tyrosine and tyrosine to L-DOPA (figure 2.18) (107, 113).

During some clinical trial, scientists found that the pro-inflammatory cytokines may play an essential role in decreasing dopamine concentrations in some specific brain regions. Some rats were injected with INF-α. The injection of this cytokine decreased BH_4 concentration. The decrease in the BH_4 would then reduce the activity of the tyrosine hydroxylase enzyme, and this would result in less dopamine synthesis (2, 114).

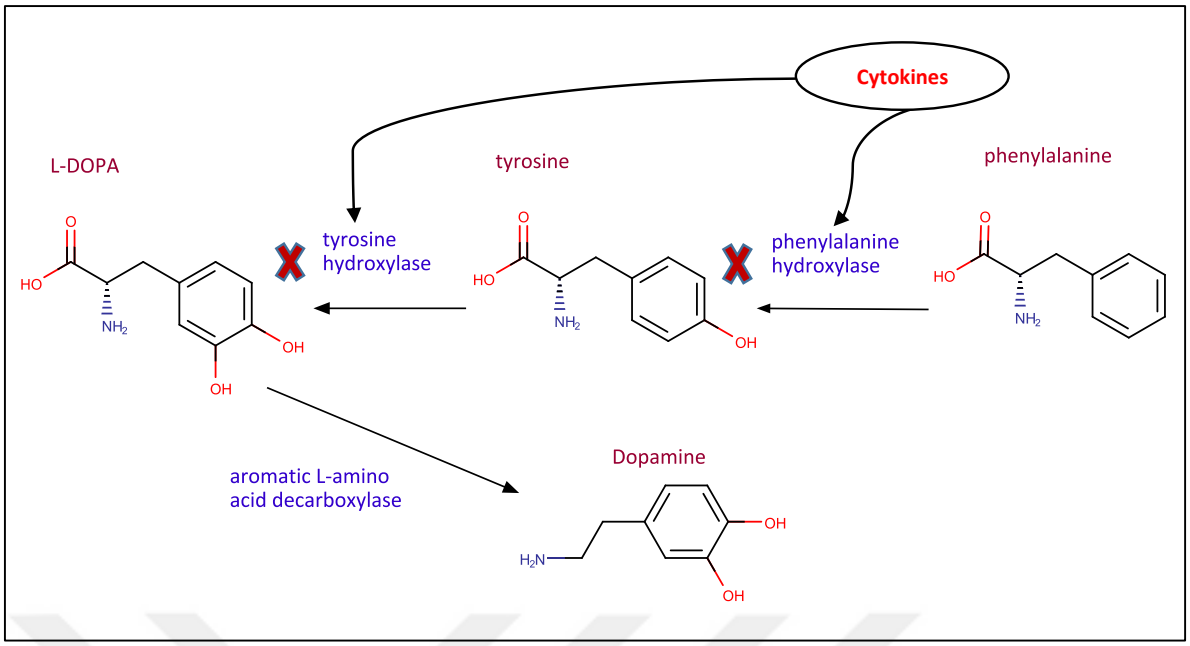


Figure 2.18. The effect of cytokines on dopamine

2.3.2.3 Glutamate

Glutamate is one of the brain's neurotransmitters that have a significant impact on some brain processes like learning and memory. High levels of glutamate are observed in acutely and chronically depressed patients. The excess in glutamate levels is harmful to the brain's neurons and could result in depression. NMDA\ (N_methyl_D_aspartate) is the glutamate receptor that is important for neuronal plasticity and the kynurenic acid and quinolinic acid are the metabolites in the tryptophan metabolic pathway. These two metabolites are affecting glutamate levels in the brain. Kynurenic acid is the NMDA antagonist, and the quinolinic acid is the NMDA agonist. The microglia cells are responsible for enhancing quinolinic acid synthesis. The pro-inflammatory cytokines found to increase quinolinic acid synthesis and by affecting the microglia cells. Moreover, by this, the ratio of quinolinic acid to kynurenic acid would be increased (figure 2.19). This increase in quinolinic acid synthesis would then result in high glutamate concentration (115-118). Astrocytes are types of neuronal cells that work to maintain normal glutamate levels by withdrawing the excess in glutamate concentration and by this they preventing the neurotoxicity. The pro-inflammatory cytokines found to be impairing astrocytes work and by this, it would affect the excess glutamate removal (116, 119, 120).

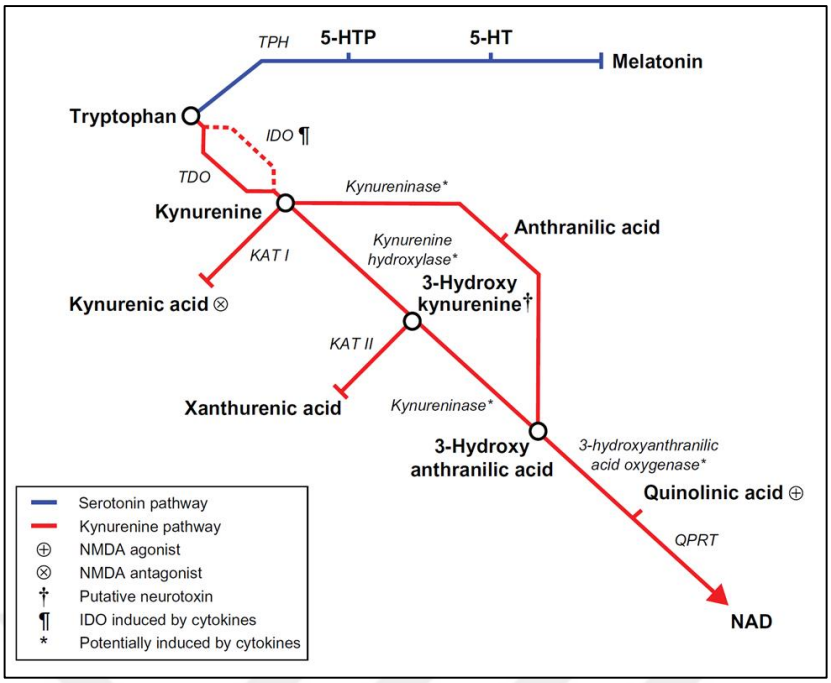


Figure 2.19. The effect of cytokines on glutamate and serotonin, (adapted from Pittenger C et al) (117).

2.3.3. The effect of the cytokines on the hypothalamic-pituitary-adrenal axis (HPA)

The hyperactivity of the HPA-axis and the disruption in the negative feedback inhibition of the corticosteroids is one of the causes of depression. The pro-inflammatory cytokines found to enhance the activation of the HPA-axis and also opposes the negative feedback inhibition of the corticosteroids (103, 121, 122). The pro-inflammatory cytokines impair the negative feedback of corticosteroids by increasing the resistance of the corticosteroids receptors that are located in the hypothalamus and the pituitary gland. This resistance would then result in the reduction of the HPA-axis sensitivity for the high corticosteroids levels. The increase of the corticosteroids concentrations for extended periods would affect specific brain regions such as the hippocampus, pituitary and the hypothalamus which are playing a significant role in developing depression (103, 122, 123). The pro-inflammatory cytokines IL-1 and IL-6 may result in the induction of the HPA-axis activity, and the IL-1 when administered systematically resulted in some disturbances in the HPA-axis (103, 124).

2.3.4. The brain-derived neurotrophic factor (BDNF), depression and cytokines

The brain-derived neurotrophic factor (BDNF) is a protein responsible for the neuronal survival and the neurogenesis. BDNF concentrations are found to be under standard rates in patients who suffer from depression. Acute depression and mania symptoms have been found to be related to the BDNF low levels in the brain (125). Pro-inflammatory cytokines are found to be decreasing the BNDF levels, and this is after the administration of the INF-A which is a cytokine used for the treatment for hepatitis C. Patients with hepatitis C were treated with this cytokine, and their BDNF serum level was investigated before and after the treatment. BDNF serum levels found to be decreased after the treatment, not only that but also the patients start to develop depression symptoms (126-128).

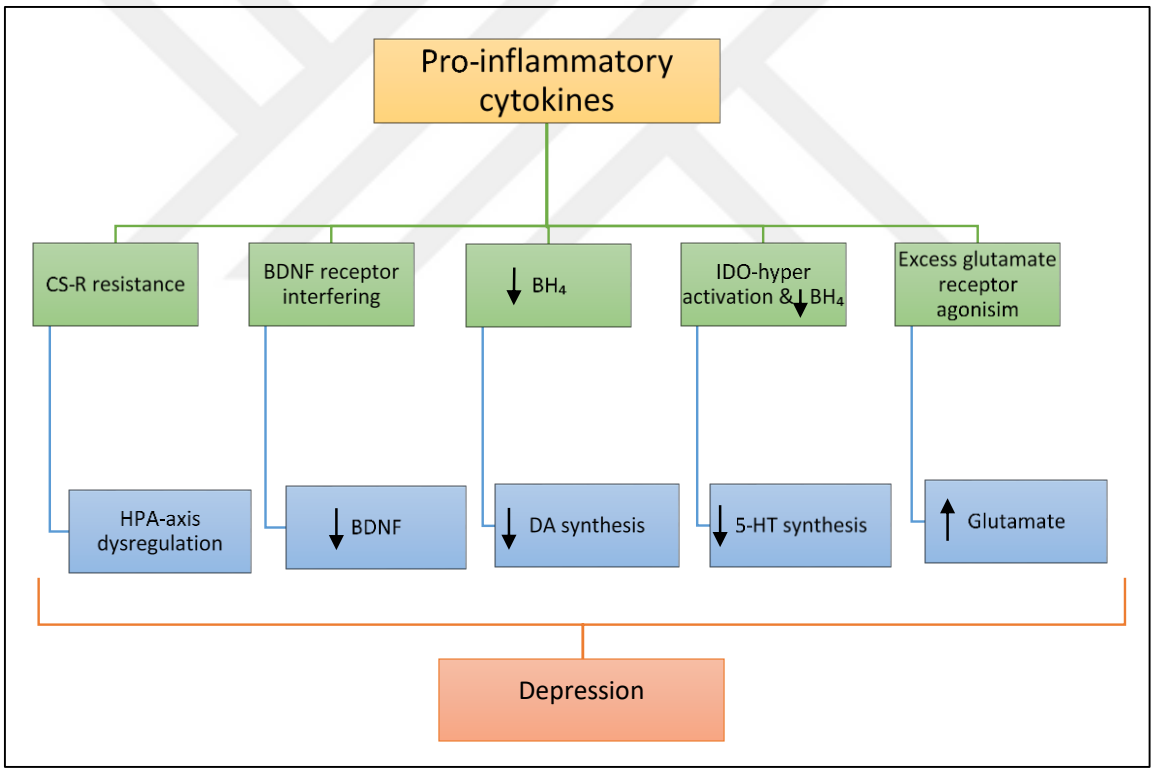


Figure 2.20. The relationship between inflammation and depression

2.3.5. Antidepressants drugs with anti-inflammatory activity

A study investigated the anti-inflammatory activity of two antidepressants drugs, desipramine and fluoxetine (8). The authors used the anti-inflammatory drug prednisolone as a reference drug and injected the mice with LPS (lipopolysaccharide) which is responsible of enhancing systemic inflammation and activating the release of TNF-α. The control was a saline with LPS and TNF-α concentration was measured after 90 min of LPS injection. The authors measured TNF-α concentration after administrating desipramine, fluoxetine and prednisolone. The result showed that TNF-α concentration was reduced when compared to the control (figure 2.21).

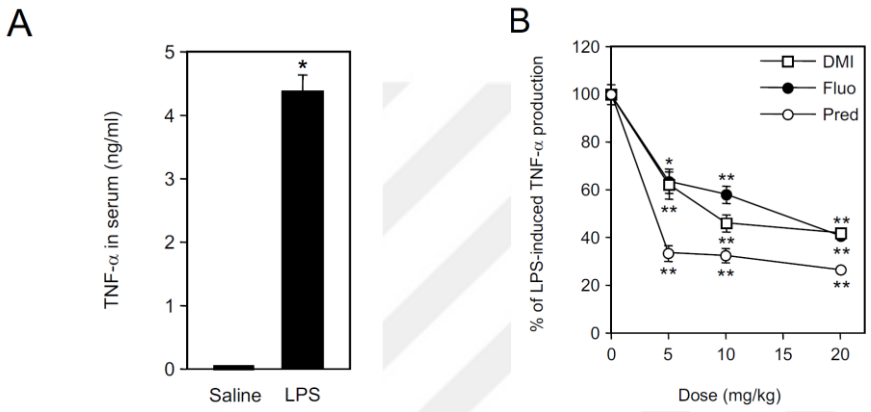


Figure 2.21. The anti-inflammatory effect of desipramine and fluoxetine in mice (taken from Roumestan C et al.) (8)

The authors also determined the rate of the survival of mice that treated either with LPS only or with AD drugs. The findings indicated that the survival rate increased from 10% to 70% in desipramine and prednisolone-treated mice and, 50% in fluoxetine-treated mice.

The authors also treated an isolated human monocyte with LPS. Monocytes constituted the main source of the pro-inflammatory cytokine TNF-α in the blood cells. After the administration of desipramine and fluoxetine TNF-α levels were found to be decreased (figure 2.22) (8) indicating the anti-inflammatory activity of These antidepressant drugs.

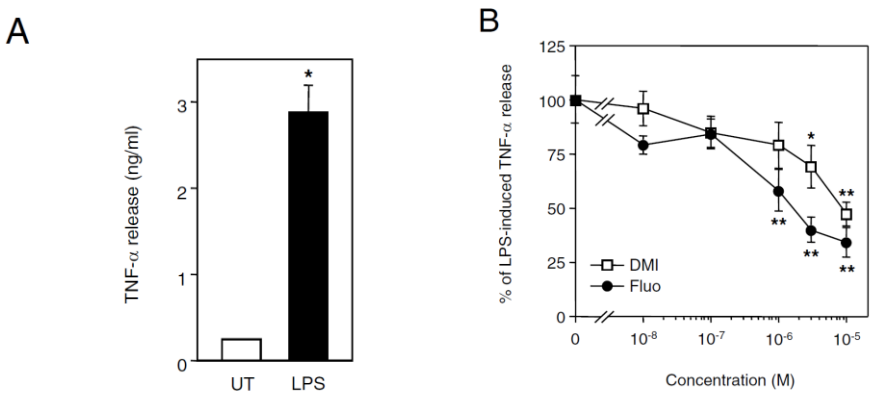
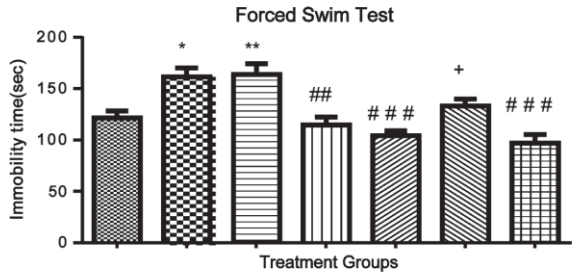


Figure 2.22. The anti-inflammatory effect of desipramine and fluoxetine in human cell (taken from Roumestan C et al.) (8)

2.3.6. Anti-inflammatory drugs with antidepressants activity

In another study mice were treated with interferon α-2b which is considered as an inflammatory mediating cytokine that is responsible for enhancing depressive symptoms. After being treated with interferon α-2b, the rats were treated with aspirin plus amitriptyline and dexamethasone plus amitriptyline for 21 days in which the antidepressant amitriptyline is considered as the reference drug. After the treatment with aspirin and dexamethasone the authors investigated the antidepressant activity of these drugs *via* the forced swimming test and also by measuring serotonin levels and serum cortisol. The authors did not find any good results with dexamethasone but they found that there is a significant decrease in the immobility time. Serotonin levels were also significantly increased and serum cortisol were decreased after aspirin treatment (figures 2.23, 2.24) (7).



Immobility time on day 18 of treatment of interferon-α-2b as observed in forced swim test. Bar diagram represents total immobility time out of 300 seconds swim test. Results are represented as mean + SEM with n=6 rats in each group, ##*P*<.01, ###*P*<.001 when compared with the interferon-α-2b treated group. **P*<.05, ***P*<.001 when compared with the normal group. +*P*<.05 when compared with the interferon-α-2b + amitriptyline + aspirin treated group. (▩) Normal; (▩) interferon-α-2b (IF-α); (▤) IF-α + dexamethasone; (▥) IF-α + aspirin; (▨) IF-α + amitryptilline; (▧) IF-α + ami + dexa; (▦) IF-α + ami + aspirin

Figure 2.23. Forced swimming test results for aspirin, (adapted from Bhatt S et al) (7).

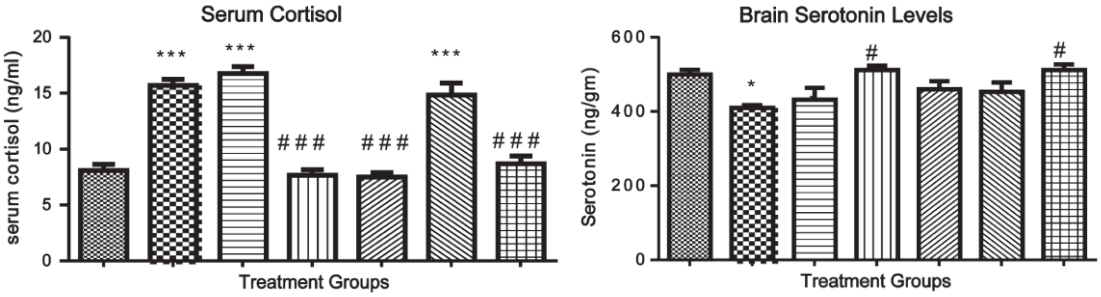


Figure 2. 24 Serotonin and serum cortisol after the administration of aspirin, (adapted from Bhatt S et al) (7)

Other studies also mentioned that other antidepressant drugs such as amitriptyline, imipramine, clomipramine and trazodone were found to possess anti-inflammatory activity (129). Also the anti-inflammatory drug celecoxib was found to be a potent adjunctive antidepressants (130).

Önen et al, recently investigated the similarity of the clinically used antidepressant and anti-inflammatory drugs (9). We will investigate in this study the similarity of the drugs that were recently described for their antidepressant and anti-inflammatory activities and the following part will introduce the methods that can be used for measuring structure similarities in *silico.*

3. MATERIALS AND METHOD

3.1. Listing the anti-inflammatory and antidepressant structures

We aimed to analyze the structures of molecules that are described for their antidepressants and anti-inflammatory activity. In our study, we first searched the literature using from Clarivates Analytics database (Web of Science) for structures described for their anti-inflammatory and anti-depressant activity. Our search comprised the 2008-2017 period and we analyzed the articles for each activity. Then for each relevant study, we determined the most potent structures and constituted thus our database of antidepressant and anti-inflammatory structures.

3.2. Qualitative similarity analysis

The similarity between antidepressant and anti-inflammatory structures was first examined manually and similar structures were gathered in a table. Similar compounds were classified according to their heterocyclic groups.

3.3. Quantitative similarity measures

To determine the similarity of our structures of interest that we obtained from the manual search, first for each compound the SMILES format was obtained using the Marvin Sketch software and the Molecular ACCess System (MACCS) and PubChem fingerprints were calculated using the Padel software as advised in studies that deal with structure similarity searches (131).

The similarity between each pair of molecule anti-inflammatory/anti-inflammatory, anti-inflammatory/antidepressant or antidepressant /antidepressant was determined by calculating the Tanimoto and cosine coefficient and data obtained for the anti-inflammatory/antidepressant pairs have been represented in a table.

In order to investigate the molecular similarity of the molecules *in silico*, specific similarity measures can be applied and these measures determine the efficacy of the similarity search. There are 3 similarity measures, the molecular representations, the weighting scheme, and the similarity coefficient.

The molecular representations can be described as chemical fingerprints or descriptors that consist of small fragments that aim to convert the chemical structure to a readable format. There are 3 types of fingerprints, 1D, 2D and 3D fingerprints.

Concerning the similarity search, 2D fingerprints have been shown to be the most reliable format. These studies showed that molecules that have similar 2D fingerprints can bind to a similar protein target and, drugs with similar 2D fingerprints can act on the same biological target. 2D fingerprints consist of substructural descriptors or fragments that differentiate the molecules according to the presence of a specific substructural features like bonds and atoms (132, 133).

The fingerprints that we used in our research are the MACCS and PubChem 2D fingerprints. These fingerprints are represented by a sequence of a bit binary values (1-0) in which 1 represents the presence of a fingerprint fragment in a molecule and 0 the absence of this fragment.

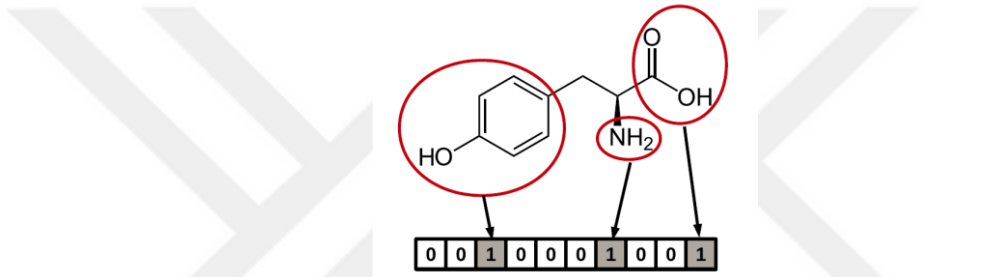


Figure 2.25. Representation of fingerprints, (adapted from Cereto-Massagué et al) (134).

MACCS fingerprint consists of 2 different forms 960 bit and 166 based on SMARTS pattern. SMARTS is a language that characterize the structures by using SMILES supplements. 166 bit is the most used form of MACCS because its shortness allows its easy process by many softwares and it possesses most of the needed chemical features. Examples of fragment information for MACCS fingerprints are given below in (table 2.1) (134, 135).

Table 2.1. MACCS 166 atom symbols (136)

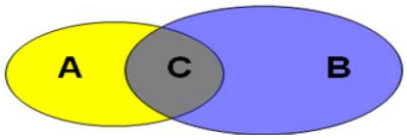
Atom type	
A	Any periodic table element
Q	Hetero atoms
X	Halogens F, Cl, Br, I
Z	Others; other than H, C, N, O, Si, P, S, F, Cl, Br, I
Bond type	
-	Single
=	Double
T	Triple
#	Triple
~	Single or double query bond
%	An aromatic query bond
key descriptors	
21	C=C(Q)Q
50	C=C(C)C
60	S=O
162	Aromatic

PubChem fingerprint is used by PubChem for similarity searching and similarity neighboring. It consists of 881 fundamental structures that makes it more comprehensive than the MACCS fingerprint. Each substructural fragment represents the presence of different substructural features such as atom and ring type and atom pairing. PubChem fingerprints consist of 7 sections, Hierarchic Element Counts which counts the atoms, chemical rings which counts the presence of a chemical ring systems, atom pairs that counts the bonded atom pairs, nearest neighbor of the atom counts the atom nearest neighbor, detailed atom neighborhood which investigates the presence of neighboring pattern like single and double bond, simple SMARTS pattern and complex SMARTS pattern. Some examples are given below (134, 137).

Table 2.2. PubChem fingerprint

Bit position	Bit substructure
Hierarchic Element Counts	
0	>= 4 H
10	>= 4 C
16	4 N
18	>= 1 O
chemical rings	
115	>= 1 any ring size 3
129	>= 1 any ring size 4
142	>= 2 unsaturated non-aromatic heteroatom-containing ring size 4
262	>= 4 hetero-aromatic rings
atom pairs	
263	Li-H
285	C-N
299	N-H
309	O-O
nearest neighbor	
327	C(~Br)(~C)
359	C(~C)(:N)(:N)
378	C(~N)(:C)(:N)
402	N (~O) (: O)
detailed atom neighborhood	
416	C=C
429	C(#N)(-C)
452	C(-O)(=O)
simple SMARTS pattern	
460	C-C-C#C
506	C-C:N:C
553	O=C-C=C
621	N-C:C:C:N
Complex SMARTS pattern	
713	Cc1ccc(C)cc1
775	Brc1c(Br)cccc1
867	OC1C(S)CCC1
880	BrC1C(Br)CCC1

The weighting scheme defines the degree of importance of the components of a given structure while the similarity coefficient measures the similarity between the fingerprints. The most frequently used coefficients to compare the similarity of structures are the Tanimoto and cosine coefficients. To calculate these coefficients, let us assume that there are 2 molecules for which the similarity value would be calculated. A represents the number of bits that are unique to the first molecule, B the number of bits that are unique for the second molecule and C shows the number of bits the common to both A and B (132, 133).



According to these variables the Tanimoto coefficient can be calculated as follows (133):

$$\frac{c}{a+b-c}$$

And the cosine coefficient is (133):

$$\frac{c}{\sqrt{ab}}$$

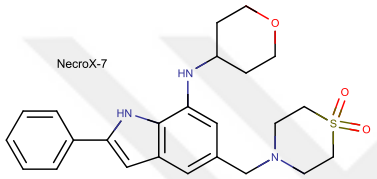
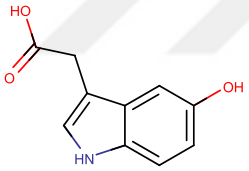
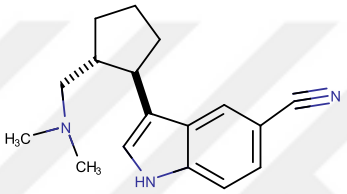
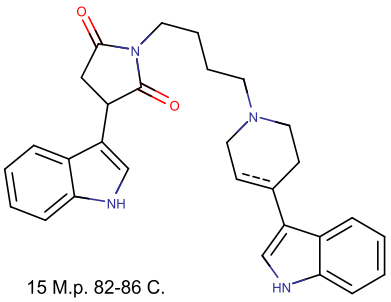
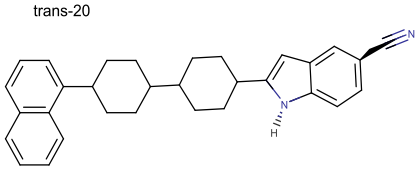
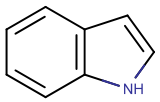
To determine the similarity of our structures of interest *in silico*, first for each compound the SMILES format was obtained and the MACCS and PubChem fingerprints were calculated using the Padel software as advised in studies that deal with structure similarity searches (131) and their similarity were compared calculating the corresponding Tanimoto and cosine coefficient.

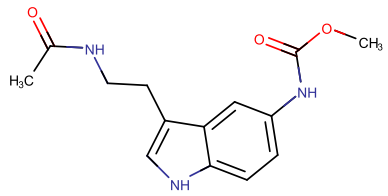
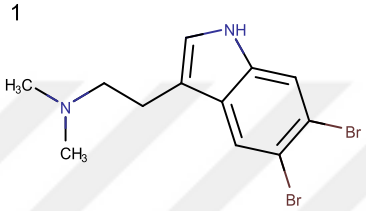
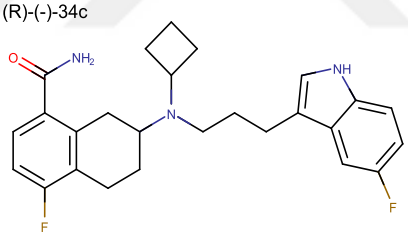
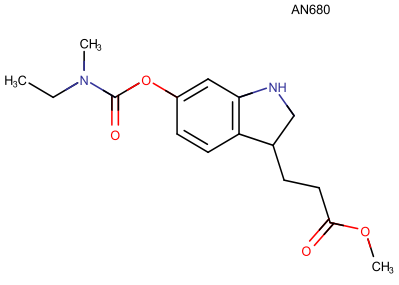
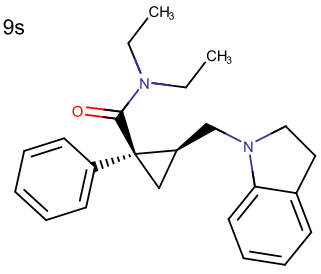
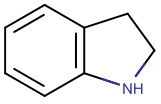
4. RESULTS

4.1. Qualitative similarity search

The manual search performed on the anti-inflammatory and antidepressant derivatives we collected from the literature was achieved by analyzing the nature of the heterocycles present in the structures of the database. Results are given in table 4.1.

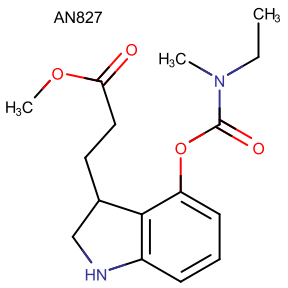
Table 4.1. Antidepressants and anti-inflammatory derivatives

Anti-inflammatory	Antidepressants	
AI1 4-({7-[(oxan-4-yl)amino]-2-phenyl-1H-indol-5-yl}methyl)-1lambda6-thiomorpholine-1,1-dione  NecroX-7 (138) AI2 serotonin derivative , 5-hydroxyindole-3-acetic acid (5-HIAA)  (139)	AD1 1-{2[(dimethylamino)methyl] cyclopentyl}-1H-indole-5-carbonitrile (+)-10b  (140) AD2 3-(1H-indol-3-yl)-1-{4-[4-(1H-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl] butyl} pyrrolidine-2,5-dione  15 M.p. 82-86 C. (141) AD3 2-[4'-(naphthalen-1-yl)-[1,1'-bi(cyclohexane)]-4-yl]-1H-indole-5-carbonitrile trans-20  (142)	 indole

	AD4 methyl N-[3-(2-acetamidoethyl)-1H-indol-5-yl]carbamate 5-MCA-NAT  (143) AD5 [2-(5,6-dibromo-1H-indol-3-yl) ethyl]dimethylamine 1  (144) AD6 7-{cyclobutyl[3-(5-fluoro-1H-indol-3-yl) propyl]amino}-4-fluoro-5,6,7,8-tetrahydronaphthalene-1-carboxamide (R)-(-)-34c  (145)	
AI3 methyl 3-(6-{[ethyl(methyl)carbamoyl]oxy}-2,3-dihydro-1H-indol-3-yl)propanoate AN680 	AD7 (1R,2S)-2-[(2,3-dihydro-1H-indol-1-yl) methyl]-N,N-diethyl-1-phenylcyclopropane-1-carboxamide 9s  (147)	 indoline

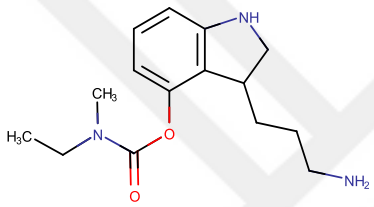
AI4
methyl 3-(4-{[ethyl(methyl)carbamoyl]oxy}-2,3-dihydro-1H-indol-3-yl)propanoate

AN827



AI5
3-(3-aminopropyl)-2,3-dihydro-1H-indol-4-yl N-ethyl-N-methylcarbamate

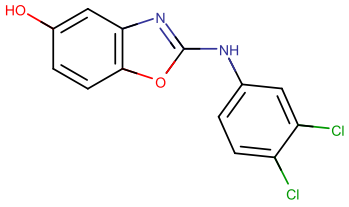
AN917



(146)

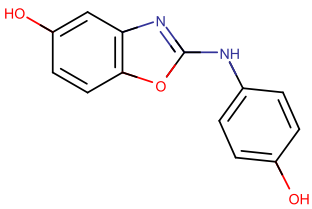
AI6
2-[(3,4-dichlorophenyl)amino]-1,3-benzoxazol-5-ol

DCPAB



AI7
2-[(4-hydroxyphenyl)amino]-1,3-benzoxazol-5-ol

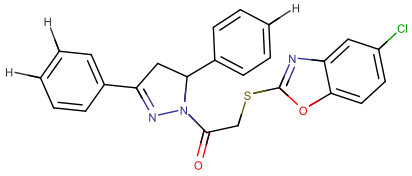
HPAB



(148)

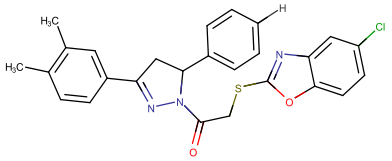
AD8
2-[(5-chloro-1,3-benzoxazol-2-yl)sulfanyl]-1-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one

4a

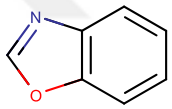


AD9
2-[(5-chloro-1,3-benzoxazol-2-yl)sulfanyl]-1-[3-(3,4-dimethylphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one

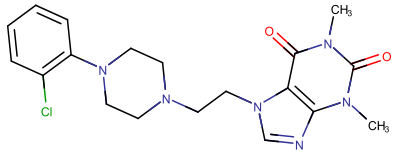
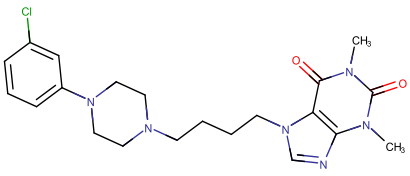
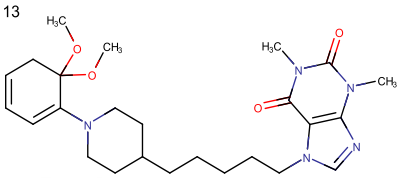
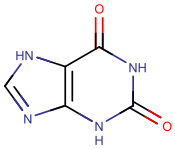
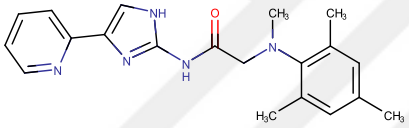
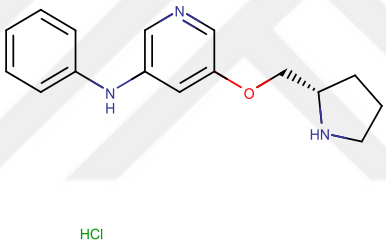
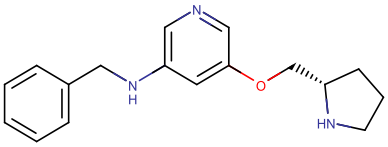
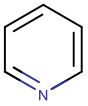
4b



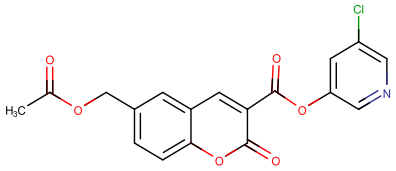
(149)



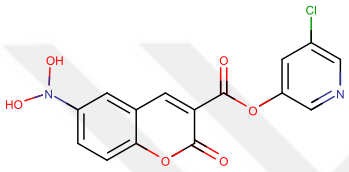
benzoxazol

AI8 7-{2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl}-1,3-dimethylpurine-2,6-dione  (150)	AD10 7-{4-[4-(3-chlorophenyl)piperazin-1-yl]butyl}-1,3-dimethylpurine-2,6-dione 9  AD11 13  (151)	 xanthine
AI9 2-[methyl(2,4,6-trimethylphenyl)amino]-N-[4-(pyridin-2-yl)-1H-imidazol-2-yl] acetamide  (152)	AD12 N-phenyl-5-{[(2S)-pyrrolidin-2-yl]methoxy}pyridin-3-amine 64  HCl AD13 N-benzyl-5-{[(2S)-pyrrolidin-2-yl]methoxy}pyridin-3-amine 65  HCl (153)	 pyridine

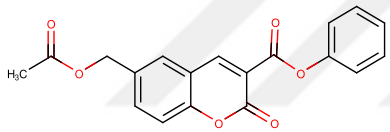
AI10
5-chloropyridin-3-yl 6-[(acetyloxy)methyl]-2-oxo-2H-chromene-3-carboxylate



AI11
5-chloropyridin-3-yl 6-(dihydroxyamino)-2-oxo-2H-chromene-3-carboxylate

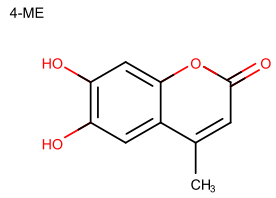


AI12
phenyl 6-[(acetyloxy)methyl]-2-oxo-2H-chromene-3-carboxylate



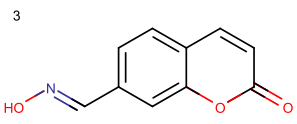
(154)

AI13
6,7-dihydroxy-4-methyl-2H-chromen-2-one

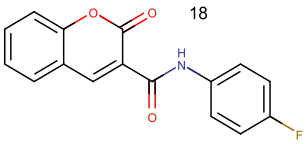


(156)

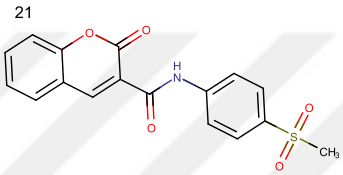
AI14
7-[(1E)-(hydroxyimino)methyl]-2H-chromen-2-one



AD14
N-(4-fluorophenyl)-2-oxo-2H-chromene-3-carboxamide

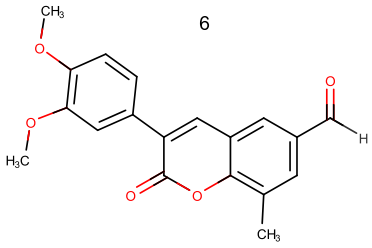


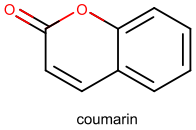
AD15
N-(4-methanesulfonylphenyl)-2-oxo-2H-chromene-3-carboxamide



(155)

AD16
3-(3,4-dimethoxyphenyl)-8-methyl-2-oxo-2H-chromene-6-carbaldehyde

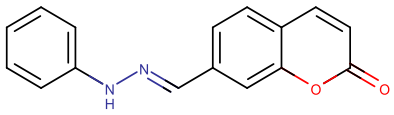




coumarin

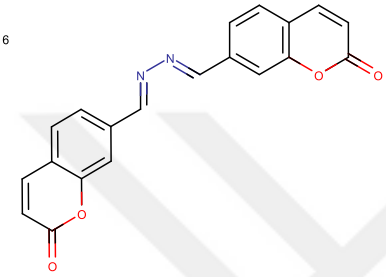
AI15
7-[(1E)-(2-phenylhydrazin-1-ylidene)methyl]-2H-chromen-2-one

5



AI16
7-[(1E)-[(E)-2-[(2-oxo-2H-chromen-7-yl)methylidene]hydrazin-1-ylidene]methyl]-2H-chromen-2-one

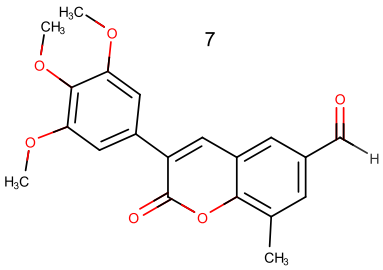
6



(157)

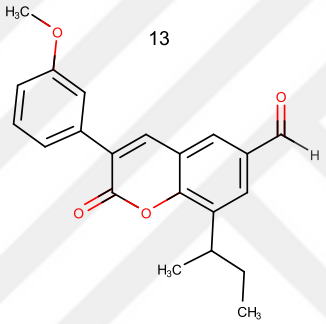
AD17
8-methyl-2-oxo-3-(3,4,5-trimethoxyphenyl)-2H-chromene-6-carbaldehyde

7



AD18
8-methyl-2-oxo-3-(3,4,5-trimethoxyphenyl)-2H-chromene-6-carbaldehyde

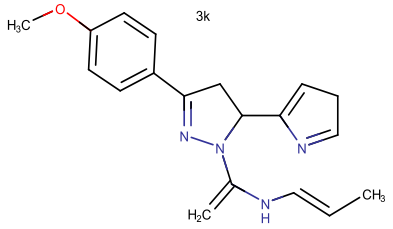
13



(158)

AI21
{1-[3-(4-methoxyphenyl)-5-(3H-pyrrol-5-yl)-4,5-dihydro-1H-pyrazol-1-yl]ethenyl}[(1E)-prop-1-en-1-yl]amine

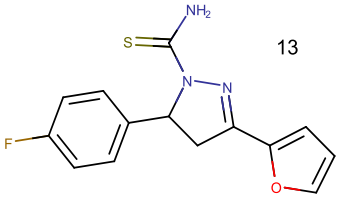
3k



(159)

AD19
5-(4-fluorophenyl)-3-(furan-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

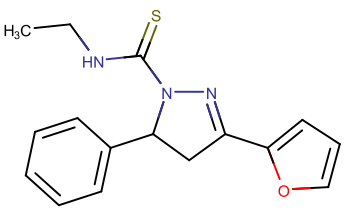
13



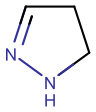
(161)

AD20
N-ethyl-3-(furan-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide

6b

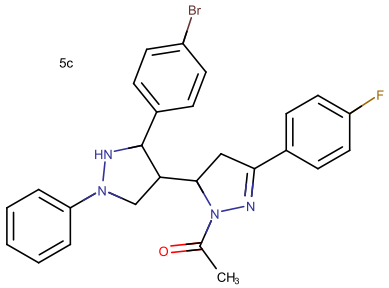


(162)

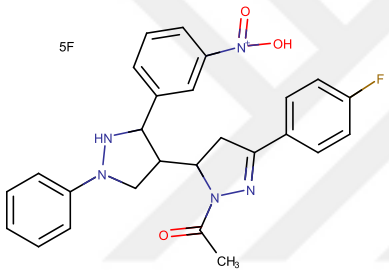


4,5-dihydro-1H-pyrazole (pyrazoline)

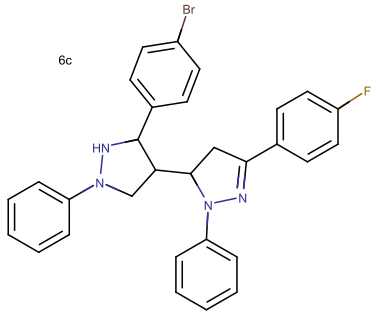
AI17
1-{5-[3-(4-bromophenyl)-1-phenylpyrazolidin-4-yl]-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl}ethan-1-one



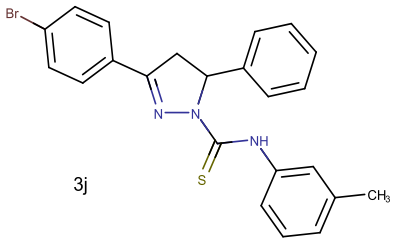
AI18
3-{4-[1-acetyl-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-5-yl]-1-phenylpyrazolidin-3-yl}
-N-hydroxy-N-oxoanilinium



AI19
3-{4-[1-acetyl-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-5-yl]-1-phenylpyrazolidin-3-yl}-N-hydroxy-N-oxoanilinium

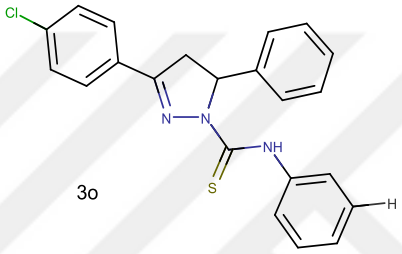


AD21
3-(4-bromophenyl)-N-(3-methylphenyl)-5-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide



3j

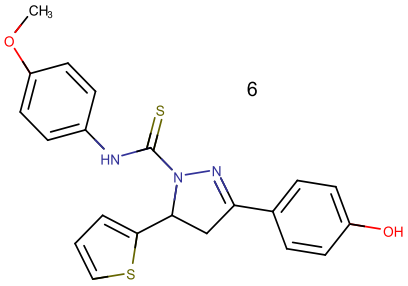
AD22
3-(4-chlorophenyl)-N,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide



3o

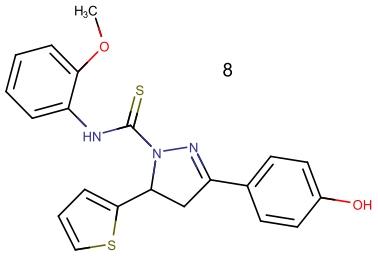
(163)

AD23
3-(4-hydroxyphenyl)-N-(4-methoxyphenyl)-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

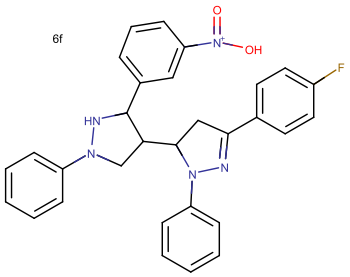
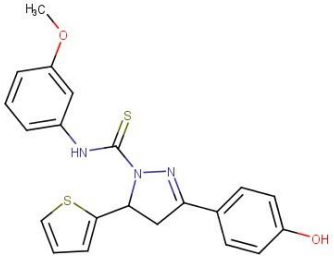
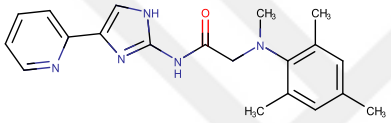
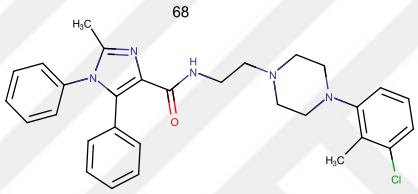
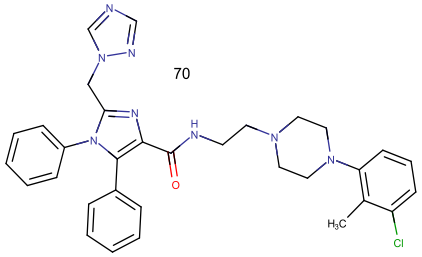
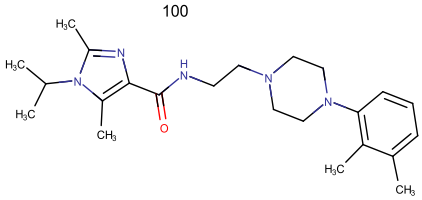


6

AD24
3-(4-hydroxyphenyl)-N-(2-methoxyphenyl)-5-(thiophen-2-yl)- 4,5-dihydro-1H-pyrazole-1-carbothioamide



8

AI20 3-{4-[1-acetyl-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-5-yl]-1-phenylpyrazolidin-3-yl}-N-hydroxy-N-oxoanilinium  (160)	AD25 3-(4-hydroxyphenyl)-N-(3-methoxyphenyl)-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide  (164)	
AI9 2-[methyl(2,4,6-trimethylphenyl)amino]-N-[4-(pyridin-2-yl)-1H-imidazol-2-yl] acetamide  (152)	AD26 N-{2-[4-(3-chloro-2-methylphenyl)piperazin-1-yl]ethyl}-2-methyl-1,5-diphenyl-1H-imidazole-4-carboxamide  AD27 N-{2-[4-(3-chloro-2-methylphenyl)piperazin-1-yl]ethyl}-1,5-diphenyl-2-[(1H-1,2,4-triazol-1-yl) methyl]-1H-imidazole-4-carboxamide  AD28 N-{2-[4-(2,3-dimethylphenyl) piperazin-1-yl]ethyl}-2,5-dimethyl-1-(propan-2-yl)-1H-imidazole-4-carboxamide  (165)	 imidazol

Similar structures were sorted into 8 groups according to the heterocycles they presented. Indeed, similar structures were found to comprise either an indole, indoline benzoxazole, xanthine, pyridine, coumarin, pyrazoline or imidazole cycle. The total number of the compounds are 49 in which there are 28 antidepressant (AD) compounds and 21 anti-inflammatory (AI) compounds. The indole family consists of 6 ADmcompounds and 2 AI compounds. In these compounds we cannot observe high similarity between them, but there are some common intersections. Most of the compounds have the indole ring substituted at their 3^{rd} or 5^{th} positions such as in AD1, AD3, AD4 and AI2. Also the indole ring in the compounds AD1 and AD3 is substituted with carbonitrile in position 3. The indole ring in compounds AD5 and AD6 is substituted in position 3 with an alkyl amine and in position 5 with a halogen.

The compounds in the indoline group are also not highly similar but we can notice that the indoline ring is substituted in position 3 in all the compounds and the compounds AI3, AI4 and AI5 are all containing carbamate group.

The benzoxazole ring of the compounds in the benzoxazole family are all substituted in position 2 and the structures of the compounds AI6 and AI7 are very similar, also the compounds AD8 and AD9 are very similar to each other yet no significant similarity is observed between the ADs and AIs.

In the xanthine family AD10 and AI8 are highly similar to each other with only a slightly change in the chloride position from *m*- chlorophenylpiperazine to *o*-chlorophenylpiperazine and the nature of the linker which is 4-carbon-long in the AD while 2-carbon-long in the AI.

In the pyridine family we can say that the compounds AD12 and AD13 are very similar to each other. Compound AI9 is similar to AD12 and AD13 by the presence of the pyridine and the benzene rings.

In the coumarin family there is also no specific similarity but we can notice that the coumarin ring is substituted at position 3 or /and 6 in most of the compounds such as the compounds AI 10, 11, 12, 13, and AD 14, 15, 16, 17, 18. In compounds AI10, AI11 and AI12 we also can see that they are all containing the ester group and in addition to this, the compounds AI10 and AI11 both comprise a chloropyridine. AI15 and AI 16 are also containing a hydrazine group. AD14 and AD15 are both substituted in position 3

with phenyl carboxamide. The compounds AD16, AD17 and AD18 are very similar to each other.

In the pyrazoline family we can observe some similarities between the structures of the AI and AD compounds especially in the compounds AI17, AI19, AI18 AI20, AI21, and AD19 that all containing 4-florophenyl substituted in the pyrazoline ring in positions 3 and 4. Also the 4-bromophenyl group is present in AI17, AI18 and AD21.

In the imidazole family the imidazole ring is substituted with a carboxamide group in all the compounds. We can notice also that the compounds AD26, AD27 and AD28 are very similar to each other.

To conclude, the analysis reveals the similarity between three family of compounds that are the xanthine derivatives (AD10 and AI8), the coumarin derivatives (AI12 and AD16-17) and the pyrazoline derivatives (AD21 and AI 17-21).

4.2. Quantitative similarity search

We applied the similarity measures using MACCS, PubChem fingerprints and we calculated the similarity of each fingerprint by Tanimoto and Cosine coefficients (tables 4.2, 4.3, 4.4, 4.5).

In Tanimoto and cosine coefficients the results would be in the range between 0 and 1, 0 means there is no similarity between the structures and 1 means they are 100% similar. So the more the results are near 1 the more the structures are similar.

Table 4.2. MACCS-Cosine

Proximity Matrix																					
	Cosine of Vectors of Values																				
	29:AI1	30:AI2	31:AI3	32:AI4	33:AI5	34:AI6	35:AI7	36:AI8	37:AI9	38:AI10	39:AI11	40:AI12	41:AI13	42:AI14	43:AI15	44:AI16	45:AI17	46:AI18	47:AI19	48:AI20	49:AI21
1:AD1	0.627	0.551	0.711	0.711	0.723	0.455	0.471	0.680	0.695	0.410	0.347	0.360	0.269	0.261	0.390	0.309	0.603	0.561	0.611	0.567	0.556
2:AD2	0.732	0.640	0.697	0.697	0.726	0.582	0.602	0.789	0.721	0.602	0.541	0.567	0.497	0.437	0.538	0.522	0.638	0.627	0.597	0.590	0.566
3:AD3	0.634	0.660	0.588	0.588	0.621	0.521	0.539	0.601	0.562	0.417	0.398	0.354	0.308	0.329	0.447	0.383	0.598	0.557	0.650	0.604	0.539
4:AD4	0.651	0.706	0.819	0.819	0.815	0.602	0.643	0.703	0.739	0.542	0.487	0.522	0.426	0.391	0.495	0.431	0.656	0.660	0.577	0.572	0.566
5:AD5	0.601	0.569	0.683	0.683	0.695	0.517	0.465	0.692	0.667	0.495	0.404	0.381	0.265	0.258	0.386	0.305	0.635	0.573	0.669	0.601	0.529
6:AD6	0.656	0.609	0.628	0.628	0.714	0.617	0.572	0.746	0.688	0.489	0.459	0.385	0.327	0.317	0.456	0.361	0.733	0.683	0.694	0.663	0.500
7:AD7	0.631	0.514	0.733	0.733	0.765	0.511	0.529	0.779	0.719	0.467	0.399	0.452	0.341	0.331	0.453	0.377	0.687	0.640	0.618	0.594	0.523
8:AD8	0.622	0.528	0.517	0.517	0.542	0.672	0.615	0.738	0.673	0.557	0.586	0.412	0.340	0.440	0.597	0.542	0.763	0.726	0.700	0.684	0.614
9:AD9	0.612	0.519	0.541	0.541	0.567	0.661	0.605	0.758	0.695	0.566	0.577	0.427	0.357	0.433	0.587	0.533	0.767	0.730	0.688	0.672	0.639
10:AD10	0.678	0.511	0.678	0.678	0.705	0.706	0.653	1.000	0.784	0.613	0.567	0.483	0.395	0.362	0.498	0.462	0.705	0.688	0.624	0.612	0.594
11:AD11	0.667	0.578	0.790	0.790	0.742	0.630	0.670	0.867	0.755	0.647	0.582	0.613	0.537	0.481	0.544	0.554	0.618	0.619	0.537	0.530	0.658
12:AD12	0.770	0.704	0.681	0.681	0.766	0.681	0.705	0.706	0.705	0.578	0.538	0.513	0.439	0.426	0.576	0.490	0.675	0.628	0.673	0.644	0.660
13:AD13	0.770	0.704	0.681	0.681	0.766	0.681	0.705	0.706	0.705	0.578	0.538	0.513	0.439	0.426	0.576	0.490	0.675	0.628	0.673	0.644	0.660
14:AD14	0.510	0.594	0.566	0.566	0.536	0.720	0.698	0.615	0.485	0.720	0.747	0.686	0.664	0.644	0.747	0.686	0.536	0.555	0.453	0.461	0.465
15:AD15	0.659	0.533	0.555	0.555	0.513	0.561	0.601	0.529	0.470	0.620	0.678	0.657	0.640	0.599	0.685	0.635	0.479	0.510	0.390	0.414	0.492
16:AD16	0.424	0.576	0.563	0.563	0.484	0.474	0.516	0.469	0.403	0.748	0.627	0.845	0.853	0.686	0.615	0.732	0.308	0.348	0.263	0.289	0.492
17:AD17	0.418	0.568	0.555	0.555	0.477	0.467	0.508	0.483	0.397	0.762	0.640	0.861	0.870	0.676	0.606	0.722	0.304	0.344	0.259	0.284	0.485
18:AD18	0.427	0.579	0.623	0.623	0.549	0.454	0.495	0.470	0.430	0.741	0.602	0.838	0.791	0.658	0.590	0.703	0.338	0.374	0.298	0.320	0.495
19:AD19	0.592	0.505	0.453	0.453	0.497	0.626	0.582	0.606	0.618	0.438	0.524	0.306	0.271	0.382	0.581	0.495	0.755	0.703	0.760	0.724	0.706
20:AD20	0.636	0.500	0.556	0.556	0.583	0.557	0.577	0.617	0.686	0.434	0.464	0.373	0.293	0.379	0.576	0.490	0.747	0.696	0.733	0.699	0.718
21:AD21	0.593	0.473	0.448	0.448	0.475	0.581	0.534	0.625	0.638	0.409	0.502	0.292	0.254	0.345	0.577	0.462	0.779	0.708	0.825	0.747	0.708
22:AD22	0.599	0.478	0.434	0.434	0.461	0.609	0.540	0.632	0.625	0.413	0.527	0.270	0.231	0.349	0.583	0.467	0.749	0.697	0.813	0.755	0.695
23:AD23	0.661	0.656	0.570	0.570	0.614	0.676	0.699	0.612	0.643	0.477	0.554	0.449	0.469	0.524	0.682	0.584	0.667	0.638	0.686	0.673	0.804
24:AD24	0.655	0.650	0.565	0.565	0.609	0.690	0.713	0.623	0.655	0.493	0.566	0.445	0.465	0.520	0.676	0.579	0.678	0.648	0.680	0.667	0.797
25:AD25	0.671	0.650	0.582	0.582	0.626	0.690	0.713	0.623	0.655	0.473	0.549	0.445	0.465	0.520	0.676	0.579	0.678	0.648	0.680	0.667	0.797
26:AD26	0.669	0.507	0.650	0.650	0.695	0.633	0.576	0.886	0.845	0.518	0.483	0.369	0.295	0.286	0.453	0.369	0.797	0.742	0.700	0.667	0.614
27:AD27	0.683	0.494	0.618	0.618	0.661	0.618	0.562	0.848	0.807	0.506	0.521	0.360	0.287	0.322	0.522	0.423	0.843	0.785	0.754	0.717	0.652
28:AD28	0.681	0.516	0.678	0.678	0.707	0.566	0.586	0.834	0.877	0.449	0.421	0.375	0.300	0.291	0.461	0.375	0.759	0.707	0.656	0.626	0.625

Table 4.3. PubChem-cosine

Proximity Matrix																					
	Cosine of Vectors of Values																				
	29:AI1	30:AI2	31:AI3	32:AI4	33:AI5	34:AI6	35:AI7	36:AI8	37:AI9	38:AI10	39:AI11	40:AI12	41:AI13	42:AI14	43:AI15	44:AI16	45:AI17	46:AI18	47:AI19	48:AI20	49:AI21
1:AD1	0.815	0.789	0.663	0.661	0.681	0.567	0.589	0.653	0.845	0.641	0.632	0.434	0.390	0.483	0.587	0.494	0.716	0.716	0.732	0.729	0.643
2:AD2	0.782	0.828	0.709	0.706	0.683	0.614	0.638	0.710	0.828	0.646	0.655	0.465	0.415	0.511	0.615	0.533	0.762	0.769	0.726	0.737	0.635
3:AD3	0.820	0.729	0.632	0.630	0.648	0.587	0.610	0.615	0.778	0.593	0.591	0.456	0.396	0.474	0.596	0.509	0.712	0.712	0.743	0.740	0.587
4:AD4	0.817	0.828	0.720	0.718	0.733	0.617	0.642	0.696	0.840	0.675	0.690	0.482	0.452	0.546	0.634	0.547	0.747	0.768	0.701	0.727	0.655
5:AD5	0.758	0.772	0.627	0.625	0.651	0.553	0.575	0.624	0.788	0.607	0.617	0.398	0.385	0.469	0.566	0.472	0.747	0.671	0.765	0.684	0.606
6:AD6	0.799	0.809	0.677	0.675	0.651	0.624	0.649	0.673	0.821	0.652	0.655	0.482	0.411	0.513	0.616	0.536	0.742	0.749	0.720	0.730	0.610
7:AD7	0.681	0.694	0.782	0.780	0.750	0.553	0.575	0.654	0.700	0.582	0.588	0.530	0.480	0.524	0.624	0.544	0.781	0.781	0.727	0.732	0.590
8:AD8	0.687	0.702	0.711	0.709	0.703	0.805	0.780	0.662	0.630	0.749	0.754	0.590	0.534	0.619	0.702	0.642	0.675	0.681	0.637	0.646	0.699
9:AD9	0.685	0.694	0.709	0.707	0.701	0.790	0.765	0.654	0.634	0.750	0.740	0.598	0.530	0.620	0.700	0.642	0.668	0.674	0.624	0.634	0.692
10:AD10	0.654	0.603	0.572	0.571	0.574	0.688	0.651	0.985	0.818	0.625	0.634	0.415	0.374	0.446	0.532	0.464	0.639	0.646	0.592	0.604	0.550
11:AD11	0.591	0.560	0.563	0.561	0.550	0.576	0.599	0.816	0.741	0.583	0.569	0.427	0.377	0.437	0.487	0.463	0.563	0.570	0.512	0.524	0.552
12:AD12	0.713	0.744	0.720	0.724	0.740	0.713	0.747	0.646	0.717	0.793	0.794	0.583	0.535	0.645	0.725	0.650	0.621	0.621	0.620	0.625	0.727
13:AD13	0.740	0.770	0.748	0.752	0.769	0.698	0.731	0.632	0.744	0.816	0.817	0.621	0.573	0.682	0.755	0.686	0.653	0.653	0.654	0.659	0.758
14:AD14	0.618	0.693	0.817	0.828	0.833	0.667	0.693	0.567	0.596	0.771	0.779	0.807	0.713	0.771	0.853	0.783	0.667	0.674	0.631	0.643	0.686
15:AD15	0.648	0.657	0.787	0.797	0.797	0.633	0.657	0.544	0.572	0.743	0.745	0.780	0.690	0.731	0.809	0.749	0.619	0.625	0.577	0.589	0.657
16:AD16	0.472	0.581	0.701	0.698	0.648	0.527	0.548	0.399	0.430	0.715	0.623	0.899	0.847	0.791	0.739	0.810	0.461	0.468	0.431	0.444	0.637
17:AD17	0.458	0.566	0.684	0.682	0.632	0.513	0.533	0.387	0.417	0.704	0.614	0.886	0.872	0.772	0.721	0.791	0.447	0.454	0.418	0.431	0.621
18:AD18	0.479	0.596	0.725	0.723	0.672	0.535	0.556	0.405	0.437	0.725	0.633	0.913	0.828	0.803	0.750	0.823	0.475	0.482	0.445	0.459	0.647
19:AD19	0.589	0.680	0.716	0.720	0.696	0.648	0.679	0.497	0.556	0.671	0.650	0.674	0.623	0.721	0.747	0.725	0.643	0.643	0.629	0.634	0.804
20:AD20	0.613	0.689	0.745	0.748	0.720	0.656	0.688	0.516	0.593	0.674	0.642	0.680	0.622	0.712	0.751	0.723	0.648	0.648	0.628	0.633	0.834
21:AD21	0.720	0.624	0.637	0.635	0.653	0.555	0.577	0.613	0.704	0.540	0.558	0.457	0.411	0.491	0.643	0.526	0.856	0.790	0.876	0.806	0.701
22:AD22	0.714	0.632	0.637	0.635	0.653	0.617	0.584	0.675	0.705	0.598	0.609	0.454	0.408	0.497	0.650	0.532	0.777	0.777	0.803	0.800	0.702
23:AD23	0.691	0.714	0.752	0.744	0.761	0.663	0.706	0.551	0.630	0.654	0.650	0.620	0.607	0.644	0.741	0.655	0.687	0.693	0.684	0.694	0.828
24:AD24	0.685	0.691	0.746	0.731	0.748	0.689	0.716	0.546	0.625	0.665	0.650	0.615	0.602	0.638	0.735	0.650	0.681	0.688	0.678	0.688	0.821
25:AD25	0.689	0.706	0.785	0.771	0.790	0.692	0.719	0.545	0.623	0.641	0.627	0.613	0.600	0.637	0.733	0.648	0.679	0.686	0.676	0.686	0.818
26:AD26	0.733	0.671	0.641	0.639	0.622	0.711	0.679	0.863	0.835	0.612	0.620	0.436	0.396	0.465	0.565	0.494	0.703	0.703	0.669	0.673	0.602
27:AD27	0.703	0.665	0.615	0.613	0.597	0.682	0.652	0.850	0.823	0.608	0.615	0.418	0.379	0.453	0.566	0.487	0.698	0.698	0.666	0.669	0.626
28:AD28	0.746	0.675	0.661	0.659	0.660	0.653	0.679	0.851	0.858	0.568	0.589	0.444	0.415	0.474	0.567	0.483	0.712	0.725	0.668	0.686	0.626

Table 4.4. MACCS-Tanimoto

	29:AI1	30:AI2	31:AI3	32:AI4	33:AI5	34:AI6	35:AI7	36:AI8	37:AI9	38:AI10	39:AI11	40:AI12	41:AI13	42:AI14	43:AI15	44:AI16	45:AI17	46:AI18	47:AI19	48:AI20	49:AI21
1:AD1	0.4359	0.3793	0.5373	0.5373	0.5538	0.2941	0.3077	0.5	0.5231	0.2571	0.2073	0.2187	0.1538	0.1493	0.2424	0.1818	0.4225	0.375	0.4375	0.3889	0.3824
2:AD2	0.5696	0.4603	0.5333	0.5333	0.5694	0.4085	0.4265	0.6479	0.5634	0.4286	0.3704	0.3846	0.3182	0.2714	0.3623	0.3433	0.4675	0.4524	0.4247	0.4177	0.3947
3:AD3	0.4167	0.4894	0.3881	0.3881	0.4219	0.3448	0.3636	0.3971	0.3692	0.2581	0.2361	0.2143	0.1818	0.1964	0.2857	0.2364	0.4	0.3514	0.4643	0.4062	0.3548
4:AD4	0.4762	0.5333	0.6912	0.6912	0.6866	0.4286	0.4697	0.5395	0.5857	0.3699	0.3214	0.3433	0.2609	0.2361	0.3239	0.2676	0.4868	0.4878	0.4054	0.4	0.3947
5:AD5	0.4125	0.3966	0.5072	0.5072	0.5224	0.3485	0.303	0.5143	0.4925	0.3284	0.25	0.2344	0.1515	0.1471	0.2388	0.1791	0.4571	0.3875	0.5	0.4225	0.3571
6:AD6	0.475	0.4333	0.4533	0.4533	0.5507	0.4462	0.4	0.5857	0.5217	0.3239	0.2963	0.2353	0.1912	0.1857	0.2941	0.2174	0.5735	0.5065	0.5312	0.493	0.3333
7:AD7	0.443	0.3443	0.5672	0.5672	0.6094	0.3433	0.3594	0.6212	0.5538	0.3043	0.2469	0.2903	0.2031	0.197	0.2923	0.2308	0.5147	0.4545	0.4462	0.4167	0.3521
8:AD8	0.4494	0.3472	0.3483	0.3483	0.3721	0.5	0.4366	0.5844	0.5065	0.3816	0.4146	0.25	0.1948	0.2703	0.4143	0.3571	0.6164	0.5679	0.5352	0.5195	0.4416
9:AD9	0.4396	0.3378	0.3708	0.3708	0.3953	0.4861	0.4247	0.6104	0.5325	0.3896	0.4048	0.2597	0.2051	0.2632	0.4028	0.3472	0.6216	0.5732	0.5205	0.5063	0.4675
10:AD10	0.5114	0.3289	0.5122	0.5122	0.5443	0.5352	0.4722	1	0.6438	0.4342	0.3953	0.3026	0.2308	0.2099	0.3205	0.2857	0.5443	0.5233	0.4487	0.4405	0.4198
11:AD11	0.5	0.3797	0.65	0.65	0.5854	0.4444	0.4805	0.7632	0.6	0.4625	0.4066	0.4079	0.3333	0.2927	0.3537	0.3544	0.4444	0.4479	0.3596	0.3579	0.4819
12:AD12	0.6133	0.5345	0.5135	0.5135	0.6176	0.5156	0.541	0.5405	0.5429	0.4058	0.3671	0.3385	0.2727	0.2647	0.4	0.3182	0.5068	0.4512	0.5075	0.473	0.4928
13:AD13	0.6133	0.5345	0.5135	0.5135	0.6176	0.5156	0.541	0.5405	0.5429	0.4058	0.3671	0.3385	0.2727	0.2647	0.4	0.3182	0.5068	0.4512	0.5075	0.473	0.4928
14:AD14	0.3294	0.4211	0.3867	0.3867	0.36	0.5614	0.5357	0.4324	0.3158	0.5614	0.5873	0.5192	0.4902	0.4717	0.5962	0.5192	0.36	0.3704	0.2917	0.2949	0.3014
15:AD15	0.4884	0.3521	0.3837	0.3837	0.3448	0.3867	0.4225	0.3596	0.3068	0.4444	0.5132	0.4687	0.4444	0.4091	0.5077	0.4462	0.3146	0.3404	0.2414	0.2609	0.3253
16:AD16	0.25	0.4038	0.3714	0.3714	0.3056	0.3065	0.3448	0.2895	0.2432	0.5882	0.4375	0.7317	0.7436	0.5217	0.4423	0.5778	0.175	0.1977	0.1486	0.1625	0.3182
17:AD17	0.2471	0.3962	0.3662	0.3662	0.3014	0.3016	0.339	0.3026	0.24	0.6078	0.4531	0.7561	0.7692	0.5106	0.434	0.5652	0.1728	0.1954	0.1467	0.1605	0.3134
18:AD18	0.2558	0.4074	0.4348	0.4348	0.3662	0.2923	0.3279	0.2949	0.2667	0.5849	0.4179	0.7209	0.6512	0.4898	0.4182	0.5417	0.1975	0.2184	0.1733	0.1852	0.3235
19:AD19	0.4118	0.3333	0.2907	0.2907	0.3293	0.4545	0.4091	0.4304	0.4459	0.28	0.3544	0.1781	0.1528	0.2319	0.4062	0.3231	0.6029	0.5325	0.6129	0.5652	0.5455
20:AD20	0.4578	0.3284	0.3827	0.3827	0.4103	0.3857	0.403	0.443	0.5211	0.2763	0.3012	0.2254	0.1667	0.2286	0.4	0.3182	0.5942	0.5256	0.5781	0.5352	0.5606
21:AD21	0.4096	0.3077	0.2857	0.2857	0.3086	0.4091	0.3636	0.4474	0.4648	0.2568	0.3333	0.169	0.1429	0.2059	0.4032	0.2969	0.6308	0.5333	0.7018	0.5909	0.5469
22:AD22	0.4146	0.3125	0.2738	0.2738	0.2963	0.4375	0.3692	0.4533	0.4507	0.2603	0.3553	0.1549	0.1286	0.209	0.4098	0.3016	0.5909	0.52	0.6842	0.6	0.5312
23:AD23	0.4881	0.4762	0.3976	0.3976	0.443	0.5075	0.5312	0.439	0.4737	0.3117	0.3827	0.2817	0.2941	0.3433	0.5079	0.4	0.5	0.4643	0.5217	0.5067	0.6719
24:AD24	0.4824	0.4687	0.3929	0.3929	0.4375	0.5224	0.5469	0.4512	0.4868	0.3247	0.3951	0.2778	0.2899	0.3382	0.5	0.3939	0.5132	0.4762	0.5143	0.5	0.6615
25:AD25	0.5	0.4687	0.4096	0.4096	0.4557	0.5224	0.5469	0.4512	0.4868	0.3077	0.378	0.2778	0.2899	0.3382	0.5	0.3939	0.5132	0.4762	0.5143	0.5	0.6615
26:AD26	0.5	0.3288	0.4815	0.4815	0.5325	0.4583	0.3973	0.7941	0.7313	0.3462	0.3182	0.2179	0.1646	0.1605	0.2857	0.2179	0.662	0.5875	0.5352	0.5	0.4416
27:AD27	0.5172	0.3158	0.4471	0.4471	0.4938	0.44	0.3816	0.7361	0.6761	0.3333	0.3523	0.2099	0.1585	0.1829	0.3421	0.2564	0.7286	0.6456	0.6	0.5584	0.4805
28:AD28	0.5119	0.338	0.5128	0.5128	0.5467	0.3919	0.4085	0.7143	0.7812	0.2875	0.2667	0.2237	0.1688	0.1646	0.2933	0.2237	0.6111	0.5432	0.4861	0.4557	0.4533

Table 4.5. PubChem-Tanimoto

	29:AI1	30:AI2	31:AI3	32:AI4	33:AI5	34:AI6	35:AI7	36:AI8	37:AI9	38:AI10	39:AI11	40:AI12	41:AI13	42:AI14	43:AI15	44:AI16	45:AI17	46:AI18	47:AI19	48:AI20	49:AI21
1:AD1	0.6851	0.6458	0.495	0.4925	0.5158	0.3871	0.412	0.4829	0.7288	0.4661	0.4558	0.2759	0.2419	0.3163	0.4158	0.3266	0.5574	0.5574	0.5771	0.5739	0.4737
2:AD2	0.6414	0.7056	0.5485	0.5459	0.5172	0.4387	0.4664	0.5502	0.7068	0.4764	0.4851	0.2977	0.2588	0.3365	0.4434	0.3589	0.6138	0.6223	0.5661	0.5798	0.4634
3:AD3	0.691	0.5678	0.4604	0.4581	0.4792	0.405	0.4317	0.4423	0.6324	0.4159	0.413	0.2944	0.2464	0.3093	0.4242	0.3402	0.5525	0.5525	0.5906	0.5872	0.4154
4:AD4	0.6885	0.7021	0.5619	0.559	0.5784	0.438	0.467	0.5323	0.7222	0.5046	0.5205	0.315	0.2905	0.3717	0.4646	0.3744	0.5967	0.6236	0.5385	0.5698	0.4869
5:AD5	0.6094	0.6244	0.4567	0.4545	0.4822	0.3755	0.3992	0.4528	0.6489	0.4323	0.4416	0.2464	0.2374	0.3035	0.3942	0.3073	0.5967	0.5052	0.6185	0.5189	0.4343
6:AD6	0.665	0.6782	0.5117	0.5093	0.481	0.4506	0.479	0.5069	0.6959	0.4829	0.4852	0.3116	0.2554	0.3381	0.4439	0.3602	0.5876	0.5959	0.5573	0.5707	0.436
7:AD7	0.5054	0.5156	0.631	0.6272	0.5939	0.3632	0.3881	0.4762	0.5272	0.3972	0.4009	0.3605	0.3152	0.3547	0.45	0.3736	0.6352	0.6352	0.5687	0.575	0.4167
8:AD8	0.5187	0.5388	0.5451	0.5427	0.5307	0.6736	0.6387	0.4898	0.4563	0.5975	0.6049	0.3974	0.3498	0.4241	0.5286	0.4509	0.4978	0.5043	0.4526	0.4632	0.5223
9:AD9	0.5142	0.5278	0.5397	0.5375	0.5256	0.652	0.6179	0.4802	0.4591	0.5976	0.5857	0.4017	0.344	0.4217	0.5236	0.4478	0.4874	0.4937	0.4375	0.4477	0.5108
10:AD10	0.4862	0.4316	0.4009	0.3991	0.4018	0.5188	0.4809	0.9695	0.6927	0.4534	0.4622	0.2579	0.2275	0.2824	0.3616	0.2982	0.4686	0.4757	0.4183	0.43	0.3779
11:AD11	0.4189	0.3872	0.3919	0.3901	0.3796	0.3992	0.4244	0.6882	0.5879	0.4093	0.3951	0.2689	0.2311	0.2762	0.3214	0.2986	0.3915	0.3981	0.3427	0.3538	0.381
12:AD12	0.5534	0.5913	0.5622	0.5672	0.5864	0.5474	0.5926	0.4769	0.5583	0.6537	0.6538	0.4051	0.3623	0.4677	0.5677	0.4762	0.4493	0.4493	0.4478	0.4527	0.5691
13:AD13	0.5874	0.625	0.597	0.602	0.623	0.5314	0.574	0.4619	0.5922	0.6878	0.6875	0.441	0.3961	0.5054	0.6042	0.5132	0.4831	0.4831	0.4826	0.4876	0.6064
14:AD14	0.4455	0.5266	0.6893	0.7045	0.7143	0.4892	0.5231	0.3945	0.4233	0.62	0.6287	0.671	0.5523	0.6226	0.7439	0.6398	0.5	0.5079	0.4603	0.4734	0.5217
15:AD15	0.4793	0.4888	0.6492	0.6632	0.6612	0.4575	0.4871	0.3734	0.4	0.5888	0.5899	0.6272	0.5215	0.5657	0.6778	0.5909	0.4471	0.4541	0.4038	0.4155	0.4874
16:AD16	0.307	0.4045	0.5368	0.534	0.4789	0.348	0.3702	0.2479	0.2723	0.5463	0.4439	0.8129	0.7333	0.6513	0.5852	0.6797	0.2991	0.3052	0.2749	0.2857	0.4677
17:AD17	0.2961	0.3911	0.5179	0.5153	0.4615	0.3373	0.3583	0.2387	0.2625	0.5359	0.4361	0.7902	0.7718	0.6242	0.5635	0.6519	0.2877	0.2936	0.2639	0.2744	0.4503
18:AD18	0.3125	0.4186	0.5652	0.5622	0.5054	0.3537	0.3766	0.2521	0.2771	0.5572	0.4521	0.837	0.7067	0.6689	0.5988	0.698	0.311	0.3173	0.2864	0.2976	0.478
19:AD19	0.4178	0.5138	0.5572	0.5622	0.533	0.4733	0.511	0.3305	0.3853	0.5022	0.4784	0.5	0.4485	0.5543	0.5957	0.5618	0.4729	0.4729	0.4573	0.4623	0.6705
20:AD20	0.442	0.5251	0.593	0.598	0.5612	0.4836	0.5219	0.3473	0.4211	0.5066	0.4703	0.5054	0.4467	0.5419	0.6	0.558	0.478	0.478	0.4554	0.4604	0.7126
21:AD21	0.5579	0.4481	0.4646	0.4623	0.484	0.373	0.3974	0.439	0.5389	0.3636	0.3793	0.2953	0.2585	0.3245	0.4734	0.3564	0.7468	0.6527	0.78	0.675	0.5398
22:AD22	0.5503	0.4545	0.4643	0.4619	0.4839	0.431	0.4027	0.5052	0.5393	0.4182	0.4279	0.2932	0.2562	0.3297	0.4811	0.3622	0.6347	0.6347	0.6709	0.6667	0.5402
23:AD23	0.527	0.5556	0.601	0.5905	0.61	0.4941	0.5447	0.3796	0.4592	0.4855	0.4816	0.4363	0.4265	0.46	0.5842	0.4752	0.519	0.5263	0.5122	0.5245	0.6973
24:AD24	0.52	0.5281	0.5924	0.5748	0.5931	0.524	0.5574	0.375	0.4534	0.4979	0.4818	0.43	0.4206	0.4532	0.5756	0.4683	0.5117	0.5189	0.5048	0.5169	0.6862
25:AD25	0.5244	0.5459	0.6439	0.625	0.6465	0.528	0.5617	0.3735	0.4515	0.4715	0.4563	0.4279	0.4186	0.451	0.5728	0.466	0.5093	0.5164	0.5024	0.5144	0.6825
26:AD26	0.5773	0.5042	0.4698	0.4678	0.4474	0.5502	0.5143	0.7563	0.7143	0.4409	0.4492	0.27	0.241	0.2931	0.3898	0.319	0.5352	0.5352	0.493	0.4977	0.4248
27:AD27	0.5381	0.496	0.4395	0.4378	0.418	0.517	0.4828	0.7321	0.693	0.4361	0.444	0.253	0.2264	0.2794	0.3871	0.3089	0.5244	0.5244	0.4844	0.4889	0.4444
28:AD28	0.5942	0.5088	0.4931	0.4908	0.4905	0.4819	0.5128	0.7407	0.7513	0.396	0.416	0.2793	0.2586	0.3041	0.3946	0.3136	0.55	0.5657	0.4975	0.5176	0.4524

We chose the structures with high similarity values from 0.7 and above. According to this we found many similar structures (table 4.7) two of them being exceptionally similar table (4.6). The structures in table (4.7) are Xanthine derivatives one with anti-inflammatory activity which is the compound 7-{2-[4-(2-chlorophenyl)piperazin-1-yl]ethyl}-1,3-dimethylpurine-2,6-dione, and the compound with antidepressants activity is 7-{4-[4-(3-chlorophenyl)piperazin-1-yl]butyl}-1,3-dimethylpurine-2,6-dione. The values of their similarity were MACCS-Tanimoto = 1, PubChem-Tanimoto =0.9695, MACCS-Cosine=1.000, and PubChem-Cosine=0.985.

Table 4.6. The most similar antidepressant and anti-inflammatory suructures

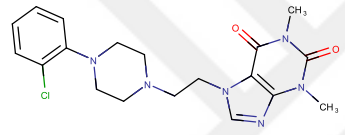
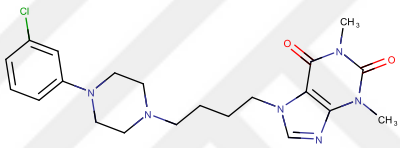
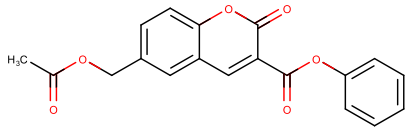
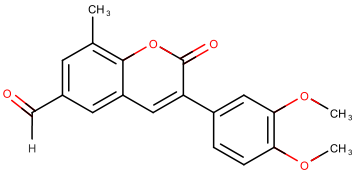
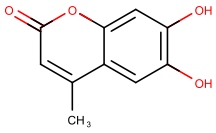
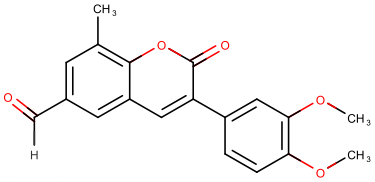
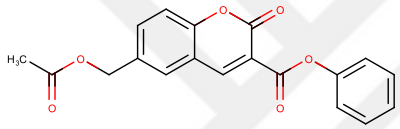
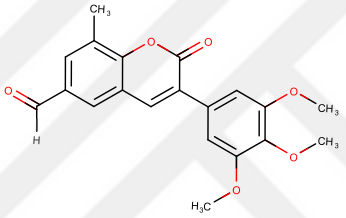
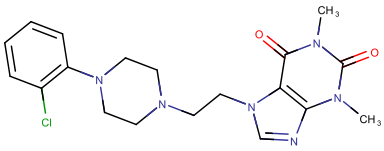
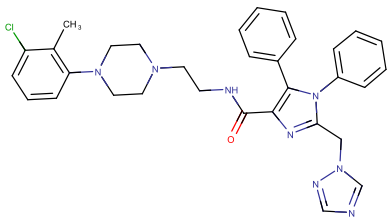
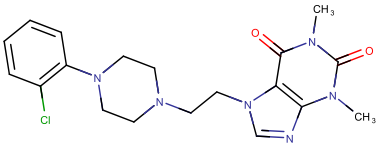
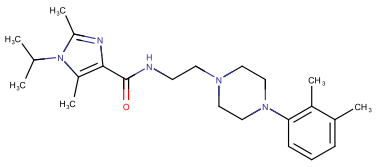
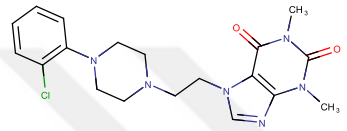
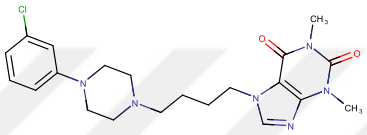
Anti-inflammatory	antidepressants	Similarity results
AI8  (150)	AD10  (151)	MACCS-Tanimoto=1 PubChem-Tanimoto=0.9695, MACCS-Cosine=1.000 PubChem-Cosine=0.985

Table 4.7. Other similar antidepressant and anti-inflammatory derivatives

Anti-inflammatory derivatives	Antidepressants derivatives	Similarity results
AI12  (154)	AD16  (158)	MACCS-Cosine=0.845 PubChem-Cosine=0.899 MACCS-Tanimoto = 0.7317 PubChem-Tanimoto =0.8129
A13  (156)	AD16  (158)	MACCS-Cosine=0.853 PubChem-Cosine=0.847 MACCS-Tanimoto = 0.7436 PubChem-Tanimoto =0.7333
AI12  (154)	AD17  (158)	MACCS-Cosine=0.861 PubChem-Cosine=0.886 MACCS-Tanimoto = 0.7561 PubChem-Tanimoto =0.7692
AI8  (150)	AD26  (165)	MACCS-Cosine=0.886 PubChem-Cosine=0.863 MACCS-Tanimoto =0.7941 PubChem-Tanimoto =0.7563
AI8  (150)	AD28  (165)	MACCS-Cosine=0.834 PubChem-Cosine=0.851 MACCS-Tanimoto = 0.7143 PubChem-Tanimoto =0.7812

5. DISCUSSION AND CONCLUSION

The molecules found to be surprisingly similar to each other are two theophylline derivatives presenting a chlorophenylpiperazine moiety in their structures. The molecule described for its anti-inflammatory and analgesic properties in rats is the KMUP-1 molecule. KMUP-1 is a theophylline derivative that was first synthesized by the japanese pharmaceutical company Eisai Pharmaceuticals in 1984 (166). Since that time it has been described for many different biological activities.

Anti-inflammatory	Antidepressant	Similarity results
AI8, KMUP-1  (150)	AD10  (151)	MACCS-Tanimoto=1 PubChem-Tanimoto=0.9695, MACCS-Cosine=1.000 PubChem-Cosine=0.985

KMUP-1 has been found to be reducing pulmonary dysfunction in mice by altering the activation of the protein kinase A and G (PKA and PKG) activating soluble guanylyl cyclase (sGC)/cGMP/PKG and inhibiting the pro-inflammatory cytokine TNF-α (167).

KMUP-1 was also found to be reducing steatohepatitis by activating cyclic adenosine monophosphate (cAMP) and cyclic quanosine monophosphate (cGMP) that would then activate the PKA and PKG enzymes. PKA and PKG are responsible for enhancing liver lipolysis by the stimulation of the hormone sensitive lipase (HSL) and the adipose triglyceride lipase (ATGL) that are responsible for liver lipolysis. KMUP-1 also reduced the TNF-α levels, TNF-α is the pro-inflammatory cytokine that causes the accumulation of fats in liver by affecting the lipid metabolism (168).

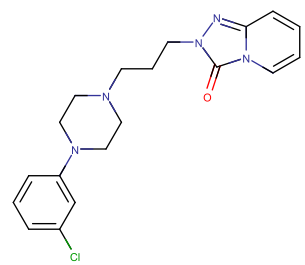
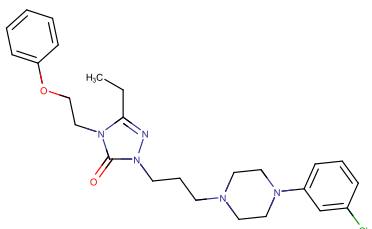
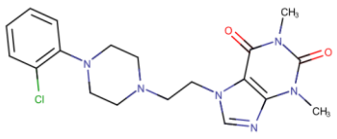
This molecule has been also investigated recently for its anti-inflammatory in 2014 activity that made it appear in our screening where it was found to reduce inflammation and hyperlagesia. Hyperalgesia is a neuropathic pain caused by nerve injury. This pain is promoted by the release of TNF-α and IL-1ß. Nuclear factor κB (NFκB) is responsible for controlling the production of these cytokines. Mitogen activated protein kinase (MAPKs) is responsible for activating or inhibiting the neuronal pain. After being treated with KMUP-1, rats were found to show a decrease in the increased TNF-α and IL-1ß

levels. The molecule was demonstrated to also inhibit the NFκB activation, MAPK and COX-2 enzymes and to induce nitric oxide synthase (iNOS), factors that are important in the inflammatory process (150).

Interestingly, when we investigated the possible antidepressant activity of this molecule, we came up with some studies that connected KMUP-1 to serotonin levels. Indeed, serotonin is found to be affecting cardiac growth in patients with heart failure in which high levels of serotonin have been observed. This is believed to be because of the deficiency in serotonin clearance or by increased serotonin secretion that is caused by chronic treatment that can cause cardiac hypertrophy. KMUP-1 has been found to be inhibiting the serotonin-induced cardiomyocyte hypertrophy by inhibiting PKA and PKC enzymes that play a key role in the serotonin receptor 5-HT$_{2A}$ activation and, by activating PKG (169).

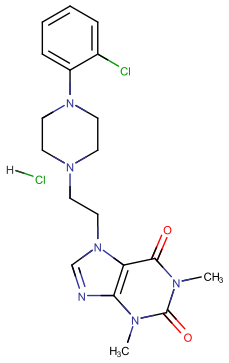
Moreover, KMUP-1 has also been protected for its possible antidepressant activity by Chen I-J in 2010. In his patent the author refers to the trazodone molecule, a marketed antidepressant that is a triazolopyridine linked with a three-carbon-long spacer to a m-chlorophenylpiperazine (m-CCP) and the nefazodone that is also an antidepressant that also presents m-CPP moiety in its structure (Table 5.1). He mentions that these two molecules could present their antidepressant activity thanks to the CPPs that would be release when the drugs are metabolized.

Table 5.1. Trazodone, Nefazodone and KMUP-1

Trazodone	Nefazodone	KMUP-1
		

When protecting its idea, the author pointed out that o-chlorophenyl piperazine (o-CPP) was described for demonstrating some serotonin receptor antagonism and m-chlorophenyl piperazine (m-CPP) was known for having both anti-histaminic activity and serotonin receptor antagonism. In order to investigate whether the theophylline linked

CPP derivatives possess antidepressant activity Chen I-J 2010 used the pharmaceutically accepted salt form of KMUP-1 named as pulmodil.

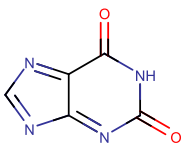


pulmodil

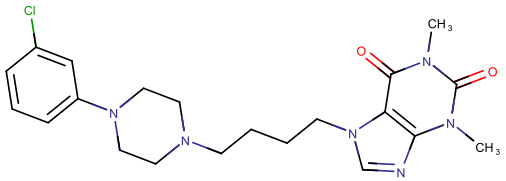
After the administration of pulmodil in mice and comparing it with other NO/ cGMP regulators, its antidepressant activity have been proved by its effect in regulating NO/cGMP pathway and by serotonergic receptor antagonism (170) . Nitric oxide (NO) and cyclic quanosine monophosphate (cGMP) are playing an important role in depression (170). NO found to be altering the serotonergic neurotransmission while cGMP found to be affecting learning, memory and inducing stress when its activity is enhanced (171). The concentrations of the cGMP in the brain found to be increased by the effect of serotonin receptors 5-HT$_{2A}$ 5-HT$_{1A}$. This increase in cGMP levels can be prevented by using drugs that antagonize the serotonin receptor 5-HT$_{1A}$ (170). The detected antidepressant effect was related to the release of o-chlorophenylpiperazine after the metabolism of the KMUP-1 molecule.

Concerning the AD10 molecule, that was found to be very similar to AI8 KMUP-1 in our similarity search study, it has been developed as some purine-2,6-dione derivatives substituted with phenylpiperazines that were previously synthesızed were found to exhibit some antidepressant activity.

Purine-2,6-dione

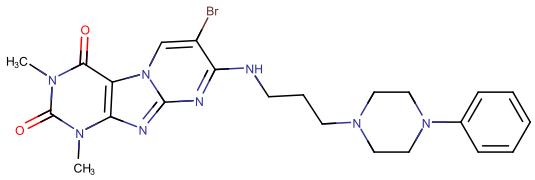


AD10



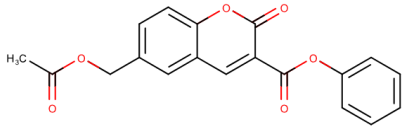
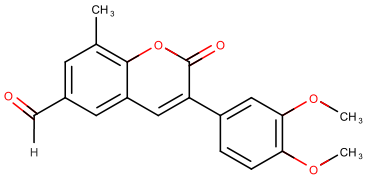
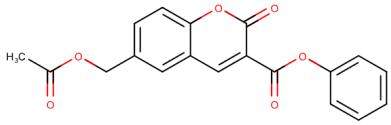
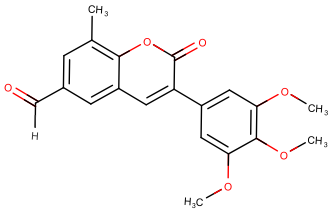
Givent their data, the authors wanted to investigate the impact of the alkoxyl and morpholine heterocycle on the bioactivity of the molecules and for this purpose they decided to synthesize unsubsituted xanthine derivatives as shown above (151). When proposing such structures the authors mentioned the similarity of these structures with KMUP-1 (AI8) (166). The compound AD10 was found to be a serotonin receptor 5-HT$_{2A}$ antagonist when evaluated and we think that this antagonism is due to the phenylpiperazine moiety as they mentioned in Chen I-J in 2010 (170). The forced swimming test indicated that compound AD10 was more effective than the marketed antidepressant imipramine. Also according to the results obtained from the four-plate test, compound AD10 was found to exhibit some anxiolytic activity and was more potent than diazepam (151).

In another study that investigated the antidepressant and anxiolytic activity of long-chain arylpiperazine derivatives Jurczyk S et al, found that many of these compounds possess high affinity for the 5-HT$_{2A}$ and 5-HT$_{1A}$ receptors ligands was shown to be either fully, partial agonists and antagonists. These compounds have been evaluated in *vivo* and in *vitro*. The author mentioned that the compound 1,3-Dimethyl-7-bromo-8-[3-(4-phenylpiperazin-1-yl)-propylamino]-1H,3H-pyrimido[2,1-f]purine-2,4-dione in the figure below which is a 5-HT$_{1A}$ receptor agonist was found to possess anxiolytic activity when evaluated in rats in the Vogel test and antidepressant activity in the Porsolt test (172).



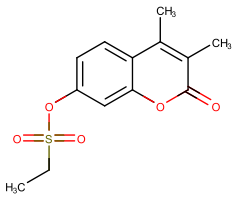
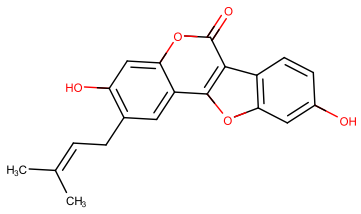
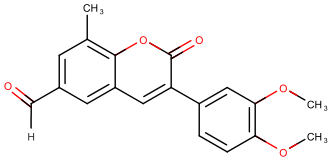
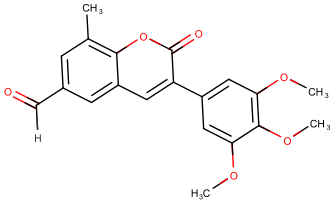
Our screening search also revealed the similarity of some coumarin structures as molecules AD16 with AI12 were found to have a similarity coefficient of MACCS-Cosine=0.845, PubChem-Cosine=0.899, MACCS-Tanimoto = 0.7317, PubChem-Tanimoto =0.8129 and, AD17 with AI12 with similarity coefficient of MACCS-Cosine=0.861, PubChem-Cosine=0.886, MACCS-Tanimoto = 0.7561, PubChem-Tanimoto =0.7692.

Table 5.2.Similarity of coumarin derivatives

AI12 	AD16 	MACCS-Cosine=0.845 PubChem-Cosine=0.899 MACCS-Tanimoto = 0.7317 PubChem-Tanimoto =0.8129
AI12 	AD17 	MACCS-Cosine=0.861 PubChem-Cosine=0.886 MACCS-Tanimoto = 0.7561 PubChem-Tanimoto =0.7692

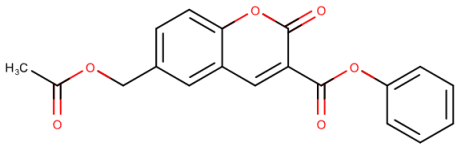
The structure of the coumarin derivative AD16 and AD17 were developed from the coumarin containing antidepressant drugs like Esuprone and Psoralidin which are MAO inhibitors (Table 5.2). The authors investigated the antidepressant activity of the novel 3-phenyl coumarin derivatives AD16 and AD17 by administrating them to mice. Their data obtained with the forced swimming test indicated that compounds AD16 and AD17 were potent antidepressants (158).

Table 5.3.Esuprone, Psoralidin, AD16 and AD17

Esuprone 	Psoralidin 
AD16 	AD17 

Coumarin derivatives were also found to be active anti-inflammatory agents as they were shown to inhibit the arachidonic acid metabolism by blocking COX-2 and LOX (173, 174). Also they were described for reducing pro-inflammatory cytokines levels such as prostaglandins and blocking NFκB (175, 176).

AI12



In the study that examined the anti-inflammatory activity the coumarin compound AI12 which our results showed to be similar to the AD16 and AD17 (80 %), the authors showed that this coumarin derivative was found possess some anti-inflammatory activity by inhibiting the alveolar macrophages (154). No data concerning the antidepressant effect of AI12 and, the anti-inflammatory effect of AD16 and AD17 was found in the literature.

Our investigation focused on the structural similarity of the anti-inflammatory and antidepressants derivatives collected from the literature, revealed that 12 compounds with high similarity values. According to the results the theophylline derivatives AD10 and AI8 were 96% similar. Interestingly AI8 found to be already mentioned in the literature for its antidepressant activity as the author referred (166). Moreover, our analysis also indicated that the coumarin derivatives AD16, AD17 and AI12 were representing a similarity of 80%. Though, no data that deals with the antidepressant activity of AI8 or anti-inflammatory activity of AD16 and AD17 were found to be memorized in the literature. Thus, we believe that our approach can reveal structures that can be evaluated for activities that are different from the activities for which they were first developed.

6. REFERENCES

1. Kiecolt-Glaser JK, Derry HM, Fagundes CP. Inflammation: depression fans the flames and feasts on the heat. American Journal of Psychiatry. 2015;172(11):1075-91.
2. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacology & therapeutics. 2011;130(2):226-38.
3. Eyre H, Baune BT. Neuroplastic changes in depression: a role for the immune system. Psychoneuroendocrinology. 2012;37(9):1397-416.
4. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychological bulletin. 2014;140(3):774.
5. Hashmi AM, Butt Z, Umair M. Is depression an inflammatory condition? A review of available evidence. J Pak Med Assoc. 2013;63(7):899-906.
6. Shelton RC, Miller AH. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. Progress in neurobiology. 2010;91(4):275-99.
7. Bhatt S, Pundarikakshudu K, Patel P, Patel N, Panchal A, Shah G, et al. Beneficial effect of aspirin against interferon-α-2b—induced depressive behavior in Sprague Dawley rats. Clinical and Experimental Pharmacology and Physiology. 2016;43(12):1208-15.
8. Roumestan C, Michel A, Bichon F, Portet K, Detoc M, Henriquet C, et al. Anti-inflammatory properties of desipramine and fluoxetine. Respiratory research. 2007;8(1):35.
9. Bayram F, Reis R, Tuncer B, Sipahi H. The importance of the structure similarity of drugs used for depression and inflammation, two comorbid diseases. Current topics in medicinal chemistry. 2018.
10. Gholipour B. Depression: Causes, Symptoms and Treatments Live Science2017 [Available from: https://www.livescience.com/34718-depression-treatment-psychotherapy-anti-depressants.html.
11. Health TNIoM. Depression: National Institute of Mental Health; 2018 [updated February 2018. Available from: https://www.nimh.nih.gov/health/topics/depression/index.shtml.
12. Wasserman D. Depression: OUP Oxford; 2011.
13. Iyer K, Khan Z. Review Paper Depression–A Review. Research Journal of Recent Sciences _____ ISSN.2277:2502.
14. Benazzi F. Various forms of depression. Dialogues in clinical neuroscience. 2006;8(2):151.
15. Kema IP, de Vries EG, Muskiet FA. Clinical chemistry of serotonin and metabolites. J Chromatogr B Biomed Sci Appl. 2000;747(1-2):33-48.
16. Shih J, Chen K. Regulation of MAO-A and MAO-B gene expression. Current medicinal chemistry. 2004;11(15):1995-2005.
17. Lucki I. The spectrum of behaviors influenced by serotonin. Biol Psychiatry. 1998;44(3):151-62.
18. Cowen PJ, Browning M. What has serotonin to do with depression? World Psychiatry. 2015;14(2):158-60.
19. Karege F, Widmer J, Bovier P, Gaillard JM. Platelet serotonin and plasma tryptophan in depressed patients: effect of drug treatment and clinical outcome. Neuropsychopharmacology. 1994;10(3):207-14.

20. Barnes NM, Sharp T. A review of central 5-HT receptors and their function. Neuropharmacology. 1999;38(8):1083-152.
21. Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav. 2002;71(4):533-54.
22. Gershon MD. Review article: serotonin receptors and transporters -- roles in normal and abnormal gastrointestinal motility. Aliment Pharmacol Ther. 2004;20 Suppl 7:3-14.
23. Manocha M, Khan WI. Serotonin and GI Disorders: An Update on Clinical and Experimental Studies. Clin Transl Gastroenterol. 2012;3:e13.
24. what-when-how.com. serotonin synapse [Available from: http://what-when-how.com/wp-content/uploads/2012/04/tmp1476_thumb1.jpg.
25. Graeff FG, Guimarães FS, De Andrade TG, Deakin JF. Role of 5-HT in stress, anxiety, and depression. Pharmacology Biochemistry and Behavior. 1996;54(1):129-41.
26. Dremencov E, Blier P. Brain norepinephrine system as a target for antidepressant and mood stabilizing medications. Current drug targets. 2009;10(11):1061-8.
27. Goddard AW, Ball SG, Martinez J, Robinson MJ, Yang CR, Russell JM, et al. Current perspectives of the roles of the central norepinephrine system in anxiety and depression. Depression and anxiety. 2010;27(4):339-50.
28. Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo–pituitary–adrenocortical axis. Trends in neurosciences. 1997;20(2):78-84.
29. Sawchenko P, Li H, Ericsson A. Circuits and mechanisms governing hypothalamic responses to stress: a tale of two paradigms. Progress in brain research. 2000;122:61-80.
30. Flak JN, Myers B, Solomon MB, McKlveen JM, Krause EG, Herman JP. Role of paraventricular nucleus-projecting norepinephrine/epinephrine neurons in acute and chronic stress. European Journal of Neuroscience. 2014;39(11):1903-11.
31. Abercrombie ED, Jacobs BL. Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and nonstressful stimuli. Journal of Neuroscience. 1987;7(9):2837-43.
32. Cecchi M, Khoshbouei H, Javors M, Morilak D. Modulatory effects of norepinephrine in the lateral bed nucleus of the stria terminalis on behavioral and neuroendocrine responses to acute stress. Neuroscience. 2002;112(1):13-21.
33. Morilak DA, Fornal CA, Jacobs BL. Effects of physiological manipulations on locus coeruleus neuronal activity in freely moving cats. II. Cardiovascular challenge. Brain research. 1987;422(1):24-31.
34. Charney DS, Woods SW, Goodman WK, Heninger GR. Neurobiological mechanisms of panic anxiety: biochemical and behavioral correlates of yohimbine-induced panic attacks. The American journal of psychiatry. 1987.
35. Morilak DA, Barrera G, Echevarria DJ, Garcia AS, Hernandez A, Ma S, et al. Role of brain norepinephrine in the behavioral response to stress. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2005;29(8):1214-24.
36. Van Moffaert M, Dierick M. Noradrenaline (Norepinephrine) and Depression. CNS Drugs. 1999;12(4):293-305.
37. Ferguson JM, Mendels J, Schwartz G. Effects of reboxetine on Hamilton Depression Rating Scale factors from randomized, placebo-controlled trials in major depression. International clinical psychopharmacology. 2002;17(2):45-51.
38. Nelson JC. A review of the efficacy of serotonergic and noradrenergic reuptake inhibitors for treatment of major depression. Biological Psychiatry. 1999;46(9):1301-8.

39. Versiani M, Cassano G, Perugi G, Benedetti A, Mastalli L, Nardi A, et al. Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. The Journal of clinical psychiatry. 2002.
40. Association AP. Practice Guideline for the Treatment of Patients with Major Depression, 2000. Diagnostic and Statistical Manual of Mental Disorders.
41. Mansour A. Biochemical anatomy: Insights into cell biology and pharmacology of the dopamine and serotonin systems in the brain. Textbook of Psychophamacology. 1998.
42. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Archives of general psychiatry. 2007;64(3):327-37.
43. Willner P. Dopamine and depression: a review of recent evidence. I. Empirical studies. Brain Research Reviews. 1983;6(3):211-24.
44. Willner P. Dopamine and depression: a review of recent evidence. II. Theoretical approaches. Brain Research Reviews. 1983;6(3):225-36.
45. Willner P. Dopamine and depression: a review of recent evidence. III. The effects of antidepressant treatments. Brain Research Reviews. 1983;6(3):237-46.
46. Ben-Jonathan N, Hnasko R. Dopamine as a prolactin (PRL) inhibitor. Endocrine reviews. 2001;22(6):724-63.
47. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain research reviews. 1998;28(3):309-69.
48. Heinz A, Schmidt L, Reischies F. Anhedonia in schizophrenic, depressed, or alcohol-dependent patients: neurobiological correlates. Pharmacopsychiatry. 1994.
49. Wise RA. The dopamine synapse and the notion of 'pleasure centers' in the brain. Trends in neurosciences. 1980;3(4):91-5.
50. knowledge pd. Serotonin - Metabolism: pharmacorama drug knowledge [Available from: https://www.pharmacorama.com/en/Sections/Serotonin_2_1.php.
51. Mendlewicz J, Van Cauter E, Linkowski P, L'Hermite M, Robyn C. I. The 24-hour profile of prolactin in depression. Life sciences. 1980;27(22):2015-24.
52. Brown GW, Harris T. Social origins of depression: A study of psychiatric disorder in women: Routledge; 2012.
53. Pizzagalli DA. Depression, stress, and anhedonia: toward a synthesis and integrated model. Annual review of clinical psychology. 2014;10:393-423.
54. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neuroscience & Biobehavioral Reviews. 2011;35(3):537-55.
55. Pariante CM. The glucocorticoid receptor: part of the solution or part of the problem? Journal of psychopharmacology. 2006;20(4_suppl):79-84.
56. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends in neurosciences. 2008;31(9):464-8.
57. Herbert J, Goodyer I, Grossman A, Hastings M, De Kloet E, Lightman S, et al. Do corticosteroids damage the brain? Journal of neuroendocrinology. 2006;18(6):393-411.
58. Tsigos C, Chrousos GP. Physiology of the hypothalamic-pituitary-adrenal axis in health and dysregulation in psychiatric and autoimmune disorders. Endocrinology and metabolism clinics of North America. 1994;23(3):451-66.
59. Tsigos C, Chrousos GP. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. Journal of psychosomatic research. 2002;53(4):865-71.
60. Heim C, Nemeroff CB, editors. Neurobiology of early life stress: clinical studies. Seminars in Clinical Neuropsychiatry; 2002.

61. Nemeroff CB, Vale WW. The neurobiology of depression: inroads to treatment and new drug discovery. The Journal of clinical psychiatry. 2005;66:5-13.
62. Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology. 2000;23(5):477.
63. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Archives of general psychiatry. 2000;57(10):925-35.
64. Finlay J, Zigmond M, Abercrombie E. Increased dopamine and norepinephrine release in medial prefrontal cortex induced by acute and chronic stress: effects of diazepam. Neuroscience. 1995;64(3):619-28.
65. Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ. Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. Journal of neurochemistry. 1989;52(5):1655-8.
66. Cabib S, Puglisi-Allegra S. The mesoaccumbens dopamine in coping with stress. Neuroscience & Biobehavioral Reviews. 2012;36(1):79-89.
67. Rossetti ZL, Lai M, Hmaidan Y, Gessa GL. Depletion of mesolimbic dopamine during behavioral despair: partial reversal by chronic imipramine. European journal of pharmacology. 1993;242(3):313-5.
68. Annette (Gbemudu) Ogbru P, MBA. tricyclic antidepressants (tcas) RXlist; [Available from: https://www.rxlist.com/tricyclic_antidepressants_tcas/drugs-condition.htm.
69. Staff MC. Selective serotonin reuptake inhibitors (SSRIs) 2018 [Available from: https://www.mayoclinic.org/diseases-conditions/depression/in-depth/ssris/art-20044825.
70. Staff MC. Serotonin and norepinephrine reuptake inhibitors (SNRIs) 2016 [Available from: https://www.mayoclinic.org/diseases-conditions/depression/in-depth/antidepressants/art-20044970.
71. Fowler JS, Logan J, Azzaro AJ, Fielding RM, Zhu W, Poshusta AK, et al. Reversible inhibitors of monoamine oxidase-A (RIMAs): robust, reversible inhibition of human brain MAO-A by CX157. Neuropsychopharmacology. 2010;35(3):623-31.
72. Manikandan S. Agomelatine: A novel melatonergic antidepressant. J Pharmacol Pharmacother. 2010;1(2):122-3.
73. Calder PC, Yaqoob P. Diet, immunity and inflammation: Elsevier; 2013.
74. Fox SI. Fundamentals of human physiology: McGraw-Hill; 2009.
75. Nordqvist C. Everything you need to know about inflammatio: medical news today; 2017 [updated 24 November 2017. Available from: https://www.medicalnewstoday.com/articles/248423.php.
76. Parkin J, Cohen B. An overview of the immune system. The Lancet. 2001;357(9270):1777-89.
77. Berman JW, Guida MP, Warren J, Amat J, Brosnan CF. Localization of monocyte chemoattractant peptide-1 expression in the central nervous system in experimental autoimmune encephalomyelitis and trauma in the rat. The Journal of Immunology. 1996;156(8):3017-23.
78. Xie W-R, Deng H, Li H, Bowen T, Strong J, Zhang J-M. Robust increase of cutaneous sensitivity, cytokine production and sympathetic sprouting in rats with localized inflammatory irritation of the spinal ganglia. Neuroscience. 2006;142(3):809-22.
79. Zhang J-M, An J. Cytokines, inflammation and pain. International anesthesiology clinics. 2007;45(2):27.
80. biological s. Inflammatory Cytokines review: sino biological; [Available from: https://www.sinobiological.com/Inflammatory-Cytokines.html.

81. biological s. Proinflammatory cytokines review: sino biological; [Available from: https://www.sinobiological.com/Proinflammatory-cytokines.html.
82. Dinarello CA. Proinflammatory cytokines. Chest. 2000;118(2):503-8.
83. biological s. Anti-inflammatory cytokines review: sino biological; [Available from: https://www.sinobiological.com/Anti-inflammatory-cytokines.html.
84. Dennis EA, Norris PC. Eicosanoid storm in infection and inflammation. Nature Reviews Immunology. 2015;15(8):511.
85. Hanna VS, Hafez EAA. Synopsis of arachidonic acid metabolism: A review. Journal of advanced research. 2018.
86. Jayadev S, Linardic CM, Hannun YA. Identification of arachidonic acid as a mediator of sphingomyelin hydrolysis in response to tumor necrosis factor alpha. Journal of Biological Chemistry. 1994;269(8):5757-63.
87. Chavis C, Vachier I, Godard P, Bousquet J, Chanez P. Lipoxins and other arachidonate derived mediators in bronchial asthma. Thorax. 2000;55(suppl 2):S38-S41.
88. Newcomer ME, Brash AR. The structural basis for specificity in lipoxygenase catalysis. Protein Science. 2015;24(3):298-309.
89. Smith WL, Murphy RC. The eicosanoids: cyclooxygenase, lipoxygenase and epoxygenase pathways. Biochemistry of Lipids, Lipoproteins and Membranes (Sixth Edition): Elsevier; 2015. p. 259-96.
90. Vogel R, Jansen C, Roffeis J, Reddanna P, Forsell P, Claesson H-E, et al. Applicability of the triade-concept for the positional specificity of mammalian lipoxygenases. Journal of Biological Chemistry. 2009:jbc. M109. 057802.
91. Drenjančević I, Jukić I, Mihaljević Z, Ćosić A, Kibel A. The Metabolites of Arachidonic Acid in Microvascular Function. Microcirculation Revisited-From Molecules to Clinical Practice: InTech; 2016.
92. Harizi H, Gualde N. The impact of eicosanoids on the crosstalk between innate and adaptive immunity: the key roles of dendritic cells. Tissue antigens. 2005;65(6):507-14.
93. Tidy DC. Blood Tests to Detect Inflammation: patient; [updated 18 July 2018. Available from: https://patient.info/health/blood-tests/blood-tests-to-detect-inflammation.
94. Stöppler MC. C-Reactive Protein CRP Test, Ranges, Symptoms, and Treatment: MedicineNet; 2018 [updated 8/3/2018. Available from: https://www.medicinenet.com/c-reactive_protein_test_crp/article.htm#what_is_c-reactive_protein_crp.
95. NHS H. Plasma Viscosity: Homerton NHS; [updated 17 February 2015. Available from: http://www.homerton.nhs.uk/our-services/services-a-z/p/pathology/haematology/haematology-tests/p/plasma-viscosity/.
96. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biological psychiatry. 2010;67(5):446-57.
97. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosomatic medicine. 2009;71(2):171-86.
98. Liu Y, Ho RC-M, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. Journal of affective disorders. 2012;139(3):230-9.
99. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain, behavior, and immunity. 2007;21(2):153-60.
100. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature reviews neuroscience. 2008;9(1):46.

101. Hart BL. Biological basis of the behavior of sick animals. Neuroscience & Biobehavioral Reviews. 1988;12(2):123-37.
102. Dantzer R, Aubert A, Bluthe R-M, Gheusi G, Cremona S, Laye S, et al. Mechanisms of the behavioural effects of cytokines. Cytokines, stress, and depression: Springer; 1999. p. 83-105.
103. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2005;29(2):201-17.
104. Watkins LR, Maier SF, Goehler LE. Cytokine-to-brain communication: a review & analysis of alternative mechanisms. Life sciences. 1995;57(11):1011-26.
105. Banks WA, Farr SA, Morley JE. Entry of blood-borne cytokines into the central nervous system: effects on cognitive processes. Neuroimmunomodulation. 2002;10(6):319-27.
106. Chandler S, Miller K, Clements J, Lury J, Corkill D, Anthony D, et al. Matrix metalloproteinases, tumor necrosis factor and multiple sclerosis: an overview. Journal of neuroimmunology. 1997;72(2):155-61.
107. Miller AH, Haroon E, Raison CL, Felger JC. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depression and anxiety. 2013;30(4):297-306.
108. Bender DA. Biochemistry of tryptophan in health and disease. Molecular aspects of medicine. 1983;6(2):101-97.
109. Christmas DM, Potokar J, Davies SJ. A biological pathway linking inflammation and depression: activation of indoleamine 2, 3-dioxygenase. Neuropsychiatric disease and treatment. 2011;7:431.
110. Schwarcz R, Pellicciari R. Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. Journal of Pharmacology and Experimental Therapeutics. 2002;303(1):1-10.
111. Fuchs D, Forsman A, Hagberg L, Larsson M, Norkrans G, Reibnegger G, et al. Immune activation and decreased tryptophan in patients with HIV-1 infection. Journal of interferon research. 1990;10(6):599-603.
112. WERNER ER, FUCHS D, HAUSEN A, JAEGER H, REIBNEGGER G, WERNER-FELMAYER G, et al. Tryptophan degradation in patients infected by human immunodeficiency virus. Biological chemistry Hoppe-Seyler. 1988;369(1):337-40.
113. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology. 2012;37(1):137.
114. Kitagami T, Yamada K, Miura H, Hashimoto R, Nabeshima T, Ohta T. Mechanism of systemically injected interferon-alpha impeding monoamine biosynthesis in rats: role of nitric oxide as a signal crossing the blood–brain barrier. Brain research. 2003;978(1-2):104-14.
115. Bhagwagar Z, Wylezinska M, Jezzard P, Evans J, Ashworth F, Sule A, et al. Reduction in occipital cortex γ-aminobutyric acid concentrations in medication-free recovered unipolar depressed and bipolar subjects. Biological psychiatry. 2007;61(6):806-12.
116. McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: a literature review. CNS spectrums. 2008;13(6):501-10.
117. Pittenger C, Sanacora G, Krystal JH. The NMDA receptor as a therapeutic target in major depressive disorder. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2007;6(2):101-15.
118. Sanacora G, Gueorguieva R, Epperson CN, Wu Y-T, Appel M, Rothman DL, et al. Subtype-specific alterations of γ-aminobutyric acid and glutamatein patients with major depression. Archives of general psychiatry. 2004;61(7):705-13.

119. Rosi S, Vazdarjanova A, Ramirez-Amaya V, Worley P, Barnes C, Wenk G. Memantine protects against LPS-induced neuroinflammation, restores behaviorally-induced gene expression and spatial learning in the rat. Neuroscience. 2006;142(4):1303-15.
120. Vercellino M, Merola A, Piacentino C, Votta B, Capello E, Mancardi GL, et al. Altered glutamate reuptake in relapsing-remitting and secondary progressive multiple sclerosis cortex: correlation with microglia infiltration, demyelination, and neuronal and synaptic damage. Journal of Neuropathology & Experimental Neurology. 2007;66(8):732-9.
121. Murphy BEP. Steroids and depression. The Journal of steroid biochemistry and molecular biology. 1991;38(5):537-59.
122. Young EA, Haskett RF, Murphy-Weinberg V, Watson SJ, Akil H. Loss of glucocorticoid fast feedback in depression. Archives of general psychiatry. 1991;48(8):693-9.
123. Miller AH, Pariante CM, Pearce BD. Effects of cytokines on glucocorticoid receptor expression and function. Cytokines, stress, and depression: Springer; 1999. p. 107-16.
124. Tilders J, Schmidt E. Cross-sensitization between immune and non-immune stressors. Cytokines, stress, and depression: Springer; 1999. p. 179-97.
125. Tri. What is BDNF and What Does it Do? : examin edexistence; [Available from: https://examinedexistence.com/what-is-bdnf-and-what-does-it-do/.
126. Kaneko N, Kudo K, Mabuchi T, Takemoto K, Fujimaki K, Wati H, et al. Suppression of cell proliferation by interferon-alpha through interleukin-1 production in adult rat dentate gyrus. Neuropsychopharmacology. 2006;31(12):2619.
127. Kenis G, Prickaerts J, van Os J, Koek GH, Robaeys G, Steinbusch HW, et al. Depressive symptoms following interferon-α therapy: mediated by immune-induced reductions in brain-derived neurotrophic factor? International Journal of Neuropsychopharmacology. 2011;14(2):247-53.
128. Lotrich FE, Albusaysi S, Ferrell RE. Brain-derived neurotrophic factor serum levels and genotype: association with depression during interferon-α treatment. Neuropsychopharmacology. 2013;38(6):985.
129. Abdel-Salam OM, Nofal SM, El-Shenawy SM. Evaluation of the anti-inflammatory and anti-nociceptive effects of different antidepressants in the rat. Pharmacological research. 2003;48(2):157-65.
130. Abbasi S-H, Hosseini F, Modabbernia A, Ashrafi M, Akhondzadeh S. Effect of celecoxib add-on treatment on symptoms and serum IL-6 concentrations in patients with major depressive disorder: randomized double-blind placebo-controlled study. Journal of affective disorders. 2012;141(2-3):308-14.
131. Yap CW. PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints. Journal of computational chemistry. 2011;32(7):1466-74.
132. Willett P. Similarity methods in chemoinformatics. Annual review of information science and technology. 2009;43(1):1-117.
133. Willett P. The calculation of molecular structural similarity: principles and practice. Molecular informatics. 2014;33(6-7):403-13.
134. Cereto-Massagué A, Ojeda MJ, Valls C, Mulero M, Garcia-Vallvé S, Pujadas G. Molecular fingerprint similarity search in virtual screening. Methods. 2015;71:58-63.
135. Sud M. Fingerprints/MACCSKeys.pm: mayachemtools; 2018 [Available from: http://www.mayachemtools.org/docs/modules/html/MACCSKeys.html.
136. Sud M. Fingerprints/MACCSKeys.pm: MayaChemTools; 2018 [cited 2018. Available from:

http://www.mayachemtools.org/docs/modules/html/MACCSKeys.html#GenerateMACCSKeys.
137. Han L, Wang Y, Bryant SH. Developing and validating predictive decision tree models from mining chemical structural fingerprints and high–throughput screening data in PubChem. BMC bioinformatics. 2008;9(1):401.
138. Chung HK, Kim YK, Park JH, Ryu MJ, Chang JY, Hwang JH, et al. The indole derivative NecroX-7 improves nonalcoholic steatohepatitis in ob/ob mice through suppression of mitochondrial ROS/RNS and inflammation. Liver International. 2015;35(4):1341-53.
139. Afarideh M, Behdadnia A, Noshad S, Mirmiranpour H, Mousavizadeh M, Khajeh E, et al. Association of peripheral 5-hydroxyindole-3-acetic acid, a serotonin derivative, with metabolic syndrome and low-grade inflammation. Endocrine Practice. 2015;21(7):711-8.
140. Denhart DJ, Deskus JA, Ditta JL, Gao Q, King HD, Kozlowski ES, et al. Conformationally restricted homotryptamines. Part 5: 3-(trans-2-aminomethylcyclopentyl) indoles as potent selective serotonin reuptake inhibitors. Bioorganic & medicinal chemistry letters. 2009;19(15):4031-3.
141. Wróbel MZ, Chodkowski A, Herold F, Gomółka A, Kleps J, Mazurek AP, et al. Synthesis and biological evaluation of novel pyrrolidine-2, 5-dione derivatives as potential antidepressant agents. Part 1. European journal of medicinal chemistry. 2013;63:484-500.
142. Zhou D, Zhou P, Evrard DA, Meagher K, Webb M, Harrison BL, et al. Studies toward the discovery of the next generation of antidepressants. Part 6: Dual 5-HT 1A receptor and serotonin transporter affinity within a class of arylpiperazinyl-cyclohexyl indole derivatives. Bioorganic & medicinal chemistry. 2008;16(14):6707-23.
143. Oxenkrug GF, Bachurin SO, Prakhie IV, Zefirov NS. Quinone reductase 2 and antidepressant effect of melatonin derivatives. Annals of the New York Academy of Sciences. 2010;1199(1):121-4.
144. Kochanowska AJ, Rao KV, Childress S, El-Alfy A, Matsumoto RR, Kelly M, et al. Secondary metabolites from three Florida sponges with antidepressant activity. Journal of natural products. 2008;71(2):186-9.
145. Hatzenbuhler NT, Baudy R, Evrard DA, Failli A, Harrison BL, Lenicek S, et al. Advances toward new antidepressants with dual serotonin transporter and 5-HT1A receptor affinity within a class of 3-aminochroman derivatives. Part 2. Journal of medicinal chemistry. 2008;51(21):6980-7004.
146. Shifrin H, Moradov D, Bejar C, Schorer-Apelbaum D, Weinstock M. Novel indoline derivatives prevent inflammation and ulceration in dinitro-benzene sulfonic acid-induced colitis in rats. Pharmacological Reports. 2016;68(6):1312-8.
147. Chen C, Dyck B, Fleck BA, Foster AC, Grey J, Jovic F, et al. Studies on the SAR and pharmacophore of milnacipran derivatives as monoamine transporter inhibitors. Bioorganic & medicinal chemistry letters. 2008;18(4):1346-9.
148. Oh YJ, Kim D, Oh S, Jang EJ, Won HY, Jeong H, et al. Novel benzoxazole derivatives DCPAB and HPAB attenuate Th1 cell-mediated inflammation through T-bet suppression. Scientific Reports. 2017;7:42144.
149. Can ÖD, Özkay ÜD, Kaplancıklı ZA, Öztürk Y. Effects of some 1, 3, 5-trisubstitued-2-pyrazoline derivatives on depression and anxiety parameters of mice. Archives of pharmacal research. 2009;32(9):1293-9.
150. Dai Z-K, Lin T-C, Liou J-C, Cheng K-I, Chen J-Y, Chu L-W, et al. Xanthine derivative KMUP-1 reduces inflammation and hyperalgesia in a bilateral chronic

constriction injury model by suppressing MAPK and NFκB activation. Molecular pharmaceutics. 2014;11(5):1621-31.
151. Partyka A, Chłoń-Rzepa G, Wasik A, Jastrzębska-Więsek M, Bucki A, Kołaczkowski M, et al. Antidepressant-and anxiolytic-like activity of 7-phenylpiperazinylalkyl-1, 3-dimethyl-purine-2, 6-dione derivatives with diversified 5-HT 1A receptor functional profile. Bioorganic & medicinal chemistry. 2015;23(1):212-21.
152. Tanaka K, Kanno T, Yanagisawa Y, Yasutake K, Inoue S, Hirayama N, et al. A novel acylaminoimidazole derivative, WN1316, alleviates disease progression via suppression of glial inflammation in ALS mouse model. PloS one. 2014;9(1):e87728.
153. Liu J, Eaton JB, Caldarone B, Lukas RJ, Kozikowski AP. Chemistry and Pharmacological Characterization of Novel Nitrogen Analogues of AMOP-H-OH (Sazetidine-A, 6-[5-(Azetidin-2-ylmethoxy) pyridin-3-yl] hex-5-yn-1-ol) as α4β2-Nicotinic Acetylcholine Receptor-Selective Partial Agonists. Journal of medicinal chemistry. 2010;53(19):6973-85.
154. Bissonnette EY, Tremblay GM, Turmel V, Pirotte B, Reboud-Ravaux M. Coumarinic derivatives show anti-inflammatory effects on alveolar macrophages, but their anti-elastase activity is essential to reduce lung inflammation in vivo. International immunopharmacology. 2009;9(1):49-54.
155. Chimenti F, Secci D, Bolasco A, Chimenti P, Bizzarri B, Granese A, et al. Synthesis, molecular modeling, and selective inhibitory activity against human monoamine oxidases of 3-carboxamido-7-substituted coumarins. Journal of medicinal chemistry. 2009;52(7):1935-42.
156. Hemshekhar M, Sunitha K, Thushara R, Santhosh MS, Sundaram MS, Kemparaju K, et al. Antiarthritic and antiinflammatory propensity of 4-methylesculetin, a coumarin derivative. Biochimie. 2013;95(6):1326-35.
157. Kontogiorgis CA, Savvoglou K, Hadjipavlou-Litina DJ. Antiinflammatory and antioxidant evaluation of novel coumarin derivatives. Journal of enzyme inhibition and medicinal chemistry. 2006;21(1):21-9.
158. Sashidhara KV, Kumar A, Chatterjee M, Rao KB, Singh S, Verma AK, et al. Discovery and synthesis of novel 3-phenylcoumarin derivatives as antidepressant agents. Bioorganic & medicinal chemistry letters. 2011;21(7):1937-41.
159. Gökhan-Kelekçi N, Yabanoğlu S, Küpeli E, Salgın U, Özgen Ö, Uçar G, et al. A new therapeutic approach in Alzheimer disease: some novel pyrazole derivatives as dual MAO-B inhibitors and antiinflammatory analgesics. Bioorganic & medicinal chemistry. 2007;15(17):5775-86.
160. Jadhav SY, Shirame SP, Kulkarni SD, Patil SB, Pasale SK, Bhosale RB. PEG mediated synthesis and pharmacological evaluation of some fluoro substituted pyrazoline derivatives as antiinflammatory and analgesic agents. Bioorganic & medicinal chemistry letters. 2013;23(9):2575-8.
161. Chimenti F, Carradori S, Secci D, Bolasco A, Bizzarri B, Chimenti P, et al. Synthesis and inhibitory activity against human monoamine oxidase of N1-thiocarbamoyl-3, 5-di (hetero) aryl-4, 5-dihydro-(1H)-pyrazole derivatives. European journal of medicinal chemistry. 2010;45(2):800-4.
162. Zamfir A, Schenker S, Bauer W, Clark T, Tsogoeva SB. Silicon lewis acid catalyzed [3+ 2] cycloaddition reactions of hydrazones/cyclopentadiene: Mild access to pyrazolidine derivatives. European Journal of Organic Chemistry. 2011;2011(20-21):3706-9.
163. Siddiqui N, Alam P, Ahsan W. Design, Synthesis, and In-Vivo Pharmacological Screening of N, 3-(Substituted Diphenyl)-5-phenyl-1H-pyrazoline-1-carbothioamide

Derivatives. Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry. 2009;342(3):173-81.
164. Karuppasamy M, Mahapatra M, Yabanoglu S, Ucar G, Sinha BN, Basu A, et al. Development of selective and reversible pyrazoline based MAO-A inhibitors: Synthesis, biological evaluation and docking studies. Bioorganic & medicinal chemistry. 2010;18(5):1875-81.
165. Seo HJ, Park E-J, Kim MJ, Kang SY, Lee SH, Kim HJ, et al. Design and synthesis of novel arylpiperazine derivatives containing the imidazole core targeting 5-HT2A receptor and 5-HT transporter. Journal of medicinal chemistry. 2011;54(18):6305-18.
166. Sugimoto H, Nakamura T, Hamazo S, Igarashi T, Daiku Y. Theophylline and theobromine derivatives. Google Patents; 1984.
167. Wu B-N, Chen C-W, Liou S-F, Yeh J-L, Chung H-H, Chen J. Inhibition of proinflammatory tumor necrosis factor-α-induced inducible nitric-oxide synthase by xanthine-based 7-[2-[4-(2-chlorobenzene) piperazinyl] ethyl]-1, 3-dimethylxanthine (KMUP-1) and 7-[2-[4-(4-nitrobenzene) piperazinyl] ethyl]-1, 3-dimethylxanthine (KMUP-3) in rat trachea: the involvement of soluble guanylate cyclase and protein kinase G. Molecular pharmacology. 2006;70(3):977-85.
168. Wu B-N, Kuo K-K, Chen Y-H, Chang C-T, Huang H-T, Chai C-Y, et al. Theophylline-Based KMUP-1 Improves Steatohepatitis via MMP-9/IL-10 and Lipolysis via HSL/p-HSL in Obese Mice. International journal of molecular sciences. 2016;17(8):1345.
169. Kuo H-F, Lai Y-J, Wu J-C, Lee K-T, Chu C-S, Chen J, et al. A xanthine-derivative K+-channel opener protects against serotonin-induced cardiomyocyte hypertrophy via the modulation of protein kinases. International journal of biological sciences. 2014;10(1):64.
170. Chen J. Pharmaceutical compositions comprising chlorophenyl piperazine derived compounds and use of the compounds in producing medicaments. Google Patents; 2010.
171. Straub VA, Grant J, O'Shea M, Benjamin PR. Modulation of serotonergic neurotransmission by nitric oxide. Journal of neurophysiology. 2007;97(2):1088-99.
172. Jurczyk S, Kołaczkowski M, Maryniak E, Zajdel P, Pawłowski M, Tatarczyńska E, et al. New arylpiperazine 5-HT1A receptor ligands containing the pyrimido [2, 1-f] purine fragment: synthesis, in vitro, and in vivo pharmacological evaluation. Journal of medicinal chemistry. 2004;47(10):2659-66.
173. Grimm EL, Brideau C, Chauret N, Chan C-C, Delorme D, Ducharme Y, et al. Substituted coumarins as potent 5-lipoxygenase inhibitors. Bioorganic & medicinal chemistry letters. 2006;16(9):2528-31.
174. Hoult J, Forder RA, de las Heras B, Lobo IB, Payá M. Inhibitory activity of a series of coumarins on leukocyte eicosanoid generation. Agents and actions. 1994;42(1-2):44-9.
175. Corsini E, Lucchi L, Binaglia M, Viviani B, Bevilacqua C, Monastra G, et al. Cloricromene, a semi-synthetic coumarin derivative, inhibits tumor necrosis factor-α production at a pre-transcriptional level. European journal of pharmacology. 2001;418(3):231-7.
176. Kim H-J, Jang SI, Kim Y-J, Chung H-T, Yun Y-G, Kang T-H, et al. Scopoletin suppresses pro-inflammatory cytokines and PGE2 from LPS-stimulated cell line, RAW 264.7 cells. Fitoterapia. 2004;75(3-4):261-6.

7. CURRICULUM VITAE

Personal Informations

Name	Sarah Ardam Abdulqader	**Surname**	Alradhwani
Place of Birth	Baghdad	**Date of Birth**	15/6
Nationality	Iraqi	**TR ID Number**	99928370524
E-mail	Sarah_aljumaily92@yahoo.com	**Phone number**	0538558809

Education

Degree	Department	The name of the Institution Graduated From	Graduation year
University	Pharmacy	Al Ahliyya Amman University	2016
High school	Science School	Baghdad High School	2010

Languages	Grades
English	Intermediate (B2)
Turkish	Intermediate

Work Experience (Sort from present to past)

Position	Institute	Duration (Year - Year)

Computer Skills

Program	Level
Microsoft Office	Intermediate
Microsoft Power Point	Intermediate