EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 2
783-793
Year: 2018

NEW 2H-CHROMENE-3-CARBOXAMIDE DERIVATIVES: SYNTHESIS AND EVALUATION OF ANTIDEPRESSANT ACTIVITY

Komal Ashok Rajgire*, Ankit Laxman Tupsundar, Rutuja Prabhakar Sonare and Dr. Ashok Pandurang Pingle

Maratha Vdiya Prasarak Samaj's College of Pharmacy Nashik, Department of Pharmaceutical Chemistry.

***Corresponding Author: Komal Ashok Rajgire**
Maratha Vdiya Prasarak Samaj's College of Pharmacy Nashik, Department of Pharmaceutical Chemistry.

Article Received on 15/12/2017 **Article Revised on 05/01/2018** **Article Accepted on 26/01/2018**

ABSTRACT
A series new (Coumarin) 2*H*-chromene-3-carboxamide derivatives **5a-5g** are were synthesized and evaluated as monoamine oxidase A and B (MAO-A and MAO-B) inhibitors and they all are evaluate for the antidepressant activity by using animal model for antidepressant i.e. Force Swim Test (FST) and Tail Suspension Test (TST) on mice the immobility time is recorded for 6 min (360sec) after the treatment with the test compound given to mice by i.p. rout of drug administration, and reference standard used for this test is Fluoxetine the reading is note down after 1hr, 5hr and 24 hr. The result is plotted by using the Mean ± SEM of the group of animal used for the animal activity. The synthesized compound **5b** shows the less Immobility time than **5a** and immobility time is slightly more than the standard drug Fluoxetine.

KEYWORDS: Coumarin, MAO-A, MAO-B, Antidepressant, Force Swim Test, Tail Suspension Test, Fluoxetine.

1. INTRODUCTION
[1-3]Depression is a serious and burdensome psychiatric illness associated with high rates of chronicity, relapse and that is characterized generally, by pervasive low mood, anxiety, cognitive impairment, loss of interest or pleasure in normally enjoyable activities and suicidal behaviors[1-3]. According to WHO estimation, 121 million people worldwide suffer from mental depression. [1-3]The high prevalence of suicide in depressed patients (up to 15%) coupled with complications arising from stress and its effect on the cardiovascular system have suggested, that it will become the second leading cause of premature death or disability worldwide by the year 2020. [1-3]Despite a broad range of antidepressants available today, a significant proportion of these patients will not respond to treatment or will show an only partial response. [1-3]Clinical limitations and adverse effects of currently used antidepressants necessitate the continuous development of novel, efficient and safe drugs for the treatment of depression.

Types of Depression:[6]
The different types of depression also have different symptoms, including:[6]

• Major or Clinical Depressive Disorder:[6]
Along with dysthymic disorder (see below), this is the most common form of depression.[6] Symptoms tend to reduce your ability to perform everyday activities, such as working, sleeping, studying, eating, and most anything that once gave you pleasure. [6]This disabling condition may occur only once in your life, but more often recurs over your lifetime.

• Dysthymic disorder:[6]
This condition, also referred to as dysthymia, tends to be less severe than clinical depression, and may not interfere with your everyday life. [6]It usually lasts for two years or longer, and may lead to clinical depression.

• Postpartum depression:[6]
This form of depression is diagnosed in new mothers who develop a major depressive episode within one month of delivering their baby.

• Psychotic depression:[6]
This is the diagnosis when severe clinical depression is accompanied by a break with reality, hallucinations, delusions, or some other form of psychosis.

• Seasonal affective disorder (SAD):[6]
A form of depression that usually eases during spring and summer months, SAD is associated with the lower levels of natural sunlight that Canadians get during the winter months.

[10]Monoamine oxidases (MAOs) are a protein family of flavin containing amine oxido reductases that play an

important role in the regulation and metabolism of several neurotransmitters, and their inhibitors (MAOIs) could be useful in the treatment of psychiatric and neurological diseases. [10]Two isoforms namely as MAO-A and MAO-B have been identified based on their amino acid sequences, three-dimensional structures, substrate specificity, and inhibitor selectivity. [10]MAO-A has a higher affinity for serotonin and noradrenaline, while MAO-B preferentially deaminates phenylethylamine and benzylamine. [10]Despite of these differences, dopamine and tyramine are common substrates for both isoforms. [10]These properties determine the pharmacological interest of MAOIs. [10]MAO-A inhibitors act as antidepressant and antianxiety agents, whereas MAO-B inhibitors are used alone or in combination to treat Alzheimer's and Parkinson's diseases.[10]

Coumarins are a large family of compounds, of natural and synthetic origin, that display a variety of pharmacological properties.[10] Recently, coumarins and their derivatives were extensively studied to their antioxidative and enzymatic inhibition properties.[10] Numerous functionalized coumarins have been presented as potent MAO and/or AChE inhibitors and some of them have been proposed for treating AD. [10]Structure activity relationship of recent research showed that substitution in position 3 of the coumarin nucleus modulated MAOB inhibitory activity. [10]When introducing an aryl amide group or an alkyl amide group in that position (Fig. [10]1A, B), which could provide them with additional strong selectivity inhibitory activity toward hMAO-B which is used for treatment of Antidepressant activity.

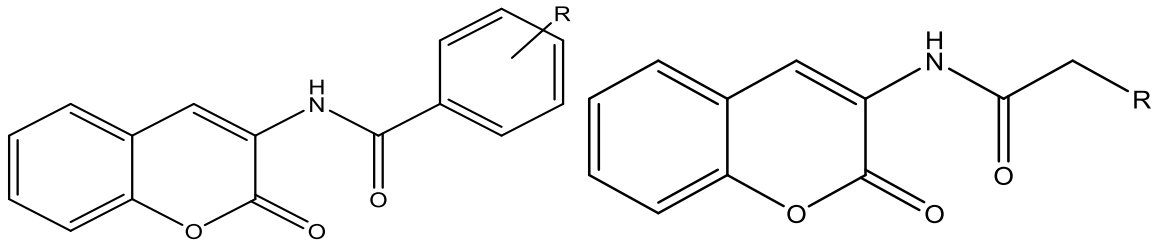


Fig. 1 (A) Fig. 1 (B)

Figure 1: [10]General Structure of coumarin derivatives.

Based on the X-ray structure MAO-B complex (2BYB. [10]pdb), computer-generated docking molecular models of 2H-chromene- 3-carboxamide derivatives were analyzed, when the position of the carbonyl group with interchangeable (Fig. 2C, D), which favor the formation of a stable binding, should help increase activity against MAO-B. [10]Therefore, on the basis of rational design, we synthesis a series novel 2H-chromene-3-carboxamide derivatives used as selective and efficient MAO inhibitors.

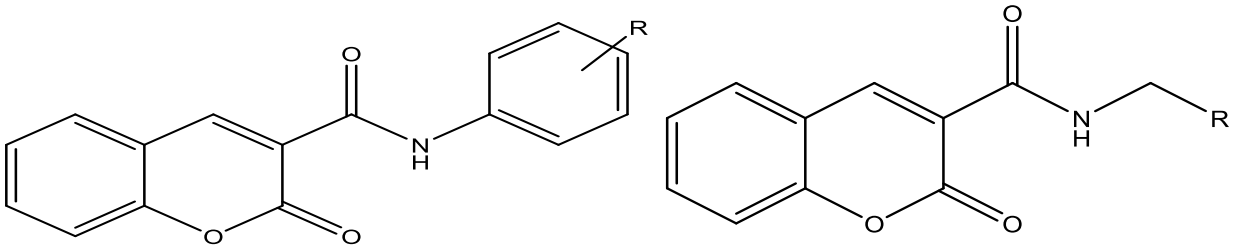


Fig. 2 (C) Fig. 2 (D)

Figure 2: [13]General Structure of novel coumarin derivatives.

2. MATERIALS AND METHODS

2.1: Chemicals: salicylaldehyde, diethyl malonate, piperidine.

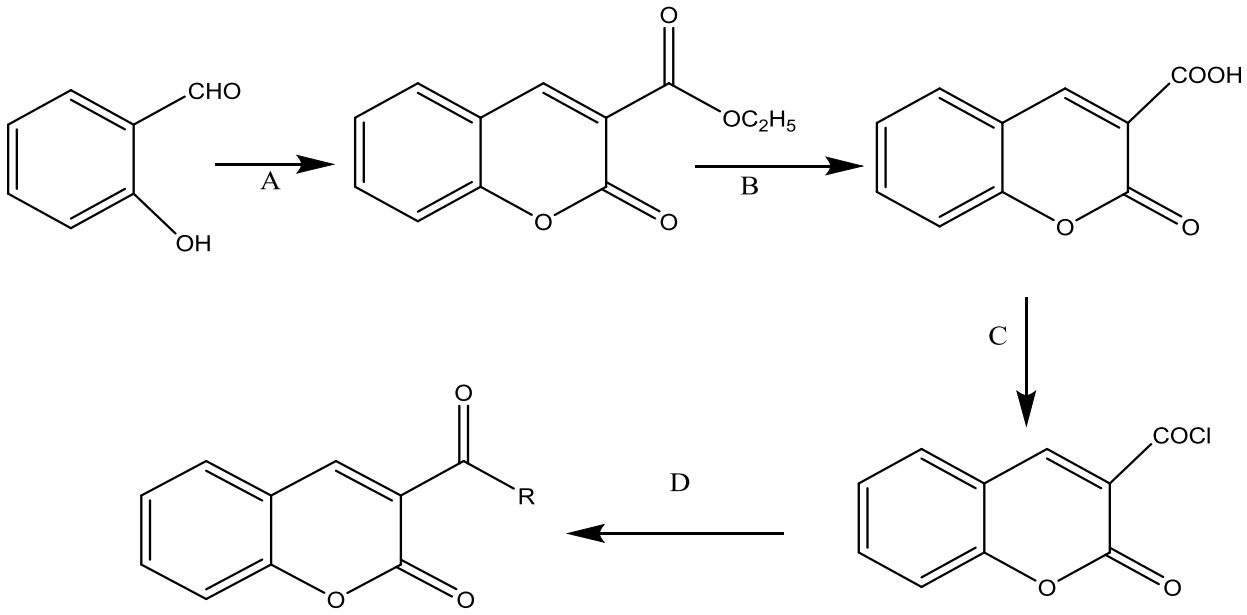
2.2: Animals: Swiss Albino mice was buy from LACSMI Biopharm PVT. LTD. (CPCSEA NO.1277) Pimple Nilakh, Pune, 411027.

Swiss Mice (25-45g) were used for experiment. [37]They were housed in polypropylene cages with husk bedding, renewed every 48 h under 12:12 h light dark circle at around 30 ± 5^0C. [53]The experiment was carried out according to the guideline of the Committee for purpose of control and Supervision of Experimental on Animals (CPCSEA), New Delhi, India, and the Institutional Animal Ethical Committee (IAEC) approved protocol for this study (IAEC /Jan 2017)

2.3: Experimental work:

Coumarin title derivatives 4 were synthesized according to the protocol outlined in Scheme 1. [10]Among them, compounds 1 (ethyl 2- oxo-2H-chromene-3-carboxylate)

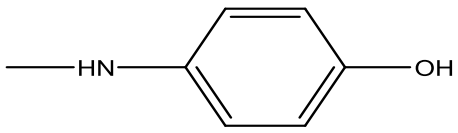
were prepared starting from a condensation of substituted-salicylaldehyde and the diethyl malonate. [10]The reaction was performed in a dry schlenk tube, with piperidine as catalyst, ethanol as solvent, reflux for 2 h. Using simple sodium hydroxide and hydrochloric acid, proved to be an efficient alternative method for the synthesis of compounds 2 (2-oxo-2H-chromene- 3-carboxylic acid). [10]The key intermediate compounds 3 (2- oxo-2H-chromene-3-carbonyl chloride) were obtained through the conventional thionyl chloride and compounds 2, the reaction was performed in a dry schlenk tube, thionyl chloride also used as solvent, reflux for 1 h. The structure of compound 4a-4g was determined by IR, NMR and Mass Spectra of Compound.



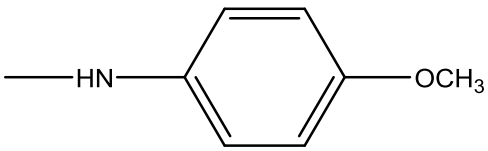
Scheme 1: General Synthetic scheme of 3-carboxamide coumarin derivative.

Reagent and conditions: (A) CH2(COOC2H5)2, urea& $SnCl_2$, reflux 3 h; (B) NaOH, reflux 3 h, HCl, pH ¼ 2; (C) SO_2Cl, reflux 1 h; (D) Substituted amines, 1,4-Dioxane & Pyridine, 25°C, 24hr Stirring.

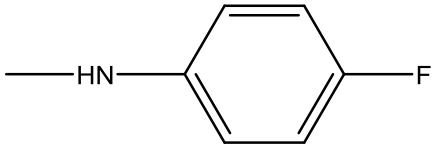
R



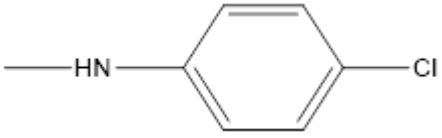
5a



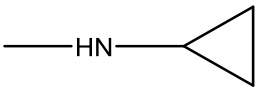
5b



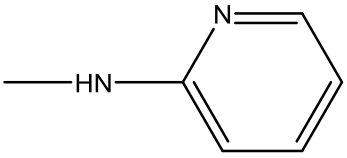
5c



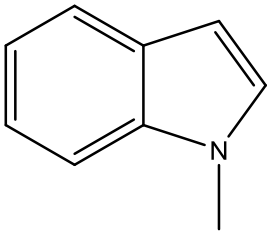
5d



5e



5f



5g

2.4: [39]Evaluation of Antidepressant Activity:

Evaluation of Antidepressant activity of finally synthesized compound is checked by animal model of antidepressant "Force Swim Test" (FST) and "Tail Suspension Test" (TST) in this the synthesized compound is checked against the Fluoxetine as a standard compound as antidepressant, and the immobility time is checked after interval of 1hr, 5hr and 24hrs.

Grouping is done by taking 5 animal is one group for each compound testing.

The Animal ethical committee approval for testing on animal is must.

Force Swim Test:

Equipment: Cylindrical swim tank (small sulo bin is ideal) filled with tepid water to a depth exceeding the length of the rat including tail. [63]Normal laboratory up lighting is required.

Procedure:

Mice of weigh 20-40 g are used. [4]They are brought to the laboratory at least one day before the experiment and are housed separately in Plastic cages with free access to food and water. [4]Naive mices are individually forced to swim inside a vertical Plexiglas cylinder (height: 40 cm; diameter: [4] 18 cm, containing 15 cm of water maintained at 25 °C). [1]Mice placed in the cylinders for the first time are initially highly active, vigorously swimming in circles, trying to climb the wall or diving to the bottom. [4]After 2–3 min activity begins to subside and to be interspersed with phases of immobility or floating of increasing length. [4]After 5–6 min immobility reaches a plateau where the mices remain immobile for approximately 80% of the time. [4]After 15 min in the water the mices are removed and allowed to dry in a heated enclosure (32 °C) before being returned to their home cages. [4]They are again placed in the cylinder 24 h later and the total duration of immobility is measured during a 5 min test. [4]Floating behavior during this 5 min period has been found to be reproducible in different groups of mices. [1]An animal is judged to be immobile whenever it remains floating passively in the water in a slightly hunched but upright position, its nose just above the surface. [12]Test drugs or standard are administered one hour prior to testing. [46]Since experiments with the standard drug (fluoxetine / imipramine) showed that injections 1, 5 and 24 h prior the test gave the most stable results in reducing floating these times are chosen for the experiment.

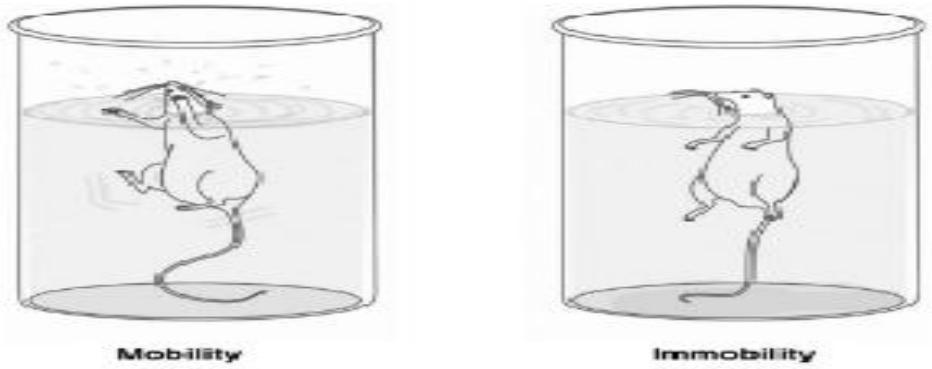


Figure 3: Force Swim Test.

Tail suspension test:

Procedure:

Mice of weigh 20–40 g are used preferentially. [18]They are housed in plastic cages for at least 10 days prior to testing in a 12 h light cycle with food and water freely available. [14]Animals are transported from the housing room to the testing area in their own cages and allowed to adapt to the new environment for 1 h before testing. [21]Groups of 10 animals are treated with the test compounds or the vehicle by intraperitoneal injection (i.p.) [21]30 min prior to testing. [1]For the test the mice are suspended on the edge of a shelf 58 cm above a table top by adhesive tape placed approximately 1 cm from the tip of the tail. [21]The duration of immobility is recorded for a period of 5 min. [1]Mice are considered immobile when they hang passively and completely motionless for at least 1 min.

Figure 4: Tail suspension test.

3. RESULT AND DISCUSSION

An attempt was made to synthesize seven derivatives of coumarin-3-carbonyl chloride and substituted Amine and evaluated for their antidepressant activity. Synthesis of targeted compounds. Establishment of structures of targeted compounds on the basis of Infra-red spectra, NMR spectra and Mass spectrum. Evaluation of targeted compounds for their antidepressant activity by Force Swim Test and Tail Suspension Test.

5a) *N*-(4-methoxyphenyl)-2-oxo-*2H*-chromen-3-carboxamide.
($C_{16}H_{13}NO_4$, **^{1}H-NMR Data**: δ10.74 1H–NH, δ3.84 1H-CH_3 of OCH_3, 7.39-7.76 5H of Aromatic Multiplet, **Mass data:** 296.0913m/z, **m.p:** 245-247 ˚C, Rf: 0.60, Yield: 80%)

***5b)* *N*-(4-hydroxyphenyl)-2-oxo-*2H*-chromen-3-carboxamide.**
($C_{17}H_{11}NO_4$, **^{1}HNMR Data:** δ10.89 1H–NH, δ8.329 1H of CH, δ 6.402-6.432 5H- Aromatic Multiplet, **Mass Data:** 282.5791m/z, m.p.: 290-292˚C, Rf: 0.80, Yield: 75%**)**

5c) *N*-(4-Flurophenyl)-2-oxo-*2H*-chromen-3-carboxamide.
($C_{16}H_{10}FO_3$, **^{1}HNMR Data:** δ10.89 1H–NH, δ9.03 1H of CH, **Mass Data:** 270.25m/z, **m.p:** 310-312˚C, Rf: 0.70, Yield: 60%**)**

5d) *N*-(4-Chlorophenyl)-2-oxo-*2H*-chromen-3-carboxamide.
($C_{16}H_{10}ClO_3$, **^{1}HNMR Data:** δ10.89 1H–NH, δ9.03 1H of CH, δ7.39-**7.77** 5H of Aromatic Multiplet, **Mass Data:** 301.1412m/z, **m.p:** 295-296˚C, Rf: 0.40, Yield: 65%**)**

5e) *N*-cyclopropane-2-oxo-*2H*-chromen-3-carboxamide.
($C_{13}H_{11}NO_3$, **^{1}H-NMR Data:** δ2.510 1H–NH, δ0.846 2H Doublet of Ring, δ7.428-7.894 5H of Aromatic Multiplet, **Mass Data**: 229.0700m/z **m.p.:** 235-237˚C, Rf: 0.55, Yield: 40%**)**

5f) 2-oxo-*N*-(pyridin-2-yl)-2*H*-chromene-3-carboxamide.
($C_{15}H_{10}N_2O_3$ **^{1}H-NMR Data:** δ10.765-1H of NH, δ8.63 1H of CH, δ7.39-7.76 5H of Aromatic Multiplet **Mass Data:** 267.0607 m/z, **m.p:** 220-224˚C, Rf: 0.45, Yield: 60%**)**

5g) 3-(1*H*-indole-1-carbonyl)-2*H*-chromen-2-one.
($C_{18}H_{11}NO_3$, **Mass Data:** 291.06 m/z, **m.p.:** 280-282˚C, Rf: 0.40, Yield: 50%**)**

Result of Antidepressant activity:

1. Result of Force Swim Test:

Table: Result of the Force Swim Test.

Group		Immobility Time (Sec)		
		After 1h (Mean ± SEM)	**After 5h (Mean ± SEM)**	**After 24h (Mean ± SEM)**
I	**Control** (DMSO 1%)	151.6±1.866	158.6±3.586	156.0±2.28
II	**5a** 10mg/kg	121.6± 2.040	98.06±5.718	86.0±4.93
III	**5b** 10mg/kg	92.8± 4.091	95.8±1.855	78.0±6.58
IV	**5c** 10 mg/kg	141.6±3.326	135.4±6.416	135.4±6.416
V	**5d** 10 mg/kg	125.6±2.064	118.0±6.473	138.6±4.32
VI	**5e** 10mg/kg	134.2±3.878	135.4±5.428	120.8±2.083
VII	**5f** 10mg/kg	135.2±1.855	124.4±2.379	122.6±5.092
VIII	**5g** 10mg/kg	166.2±2.482	165.0±3.421	166.2±3.68
IX	**FLX** 10 mg/kg	80.4±1.806	75.40±4.718	73.0±3.2440

Graphical representation of Antidepressant activity by Force Swim Test (FST):

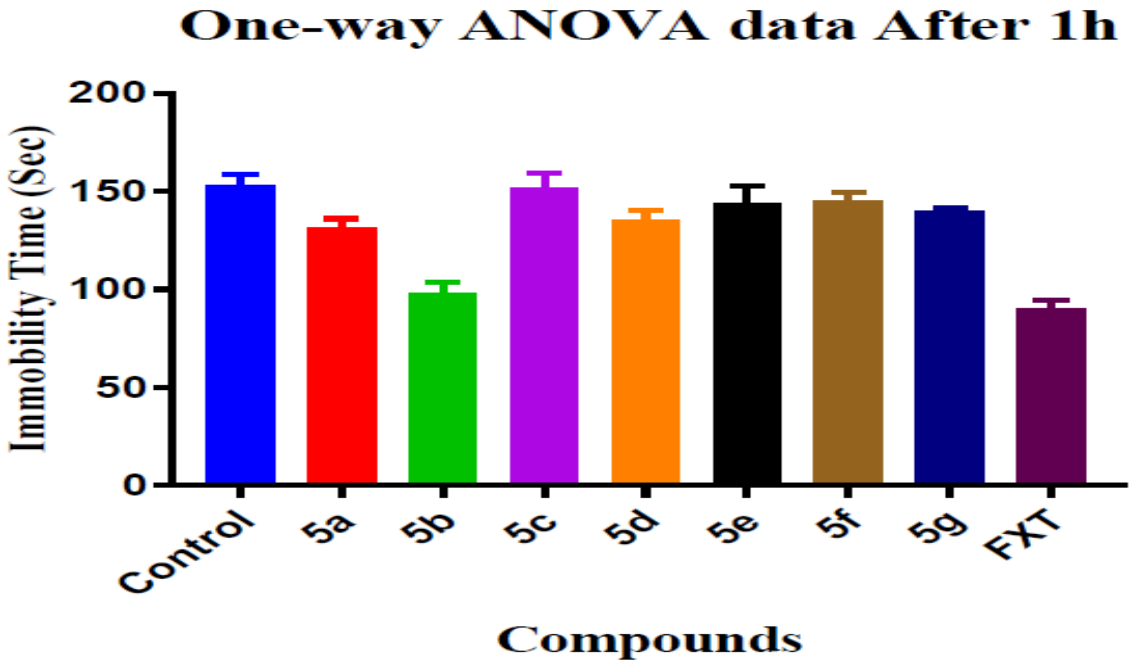


Figure 3.1: Effect of synthesized Coumarin derivative and Standard drug (Fluoxetine i.e.FXT) on mice by FST after 1h.

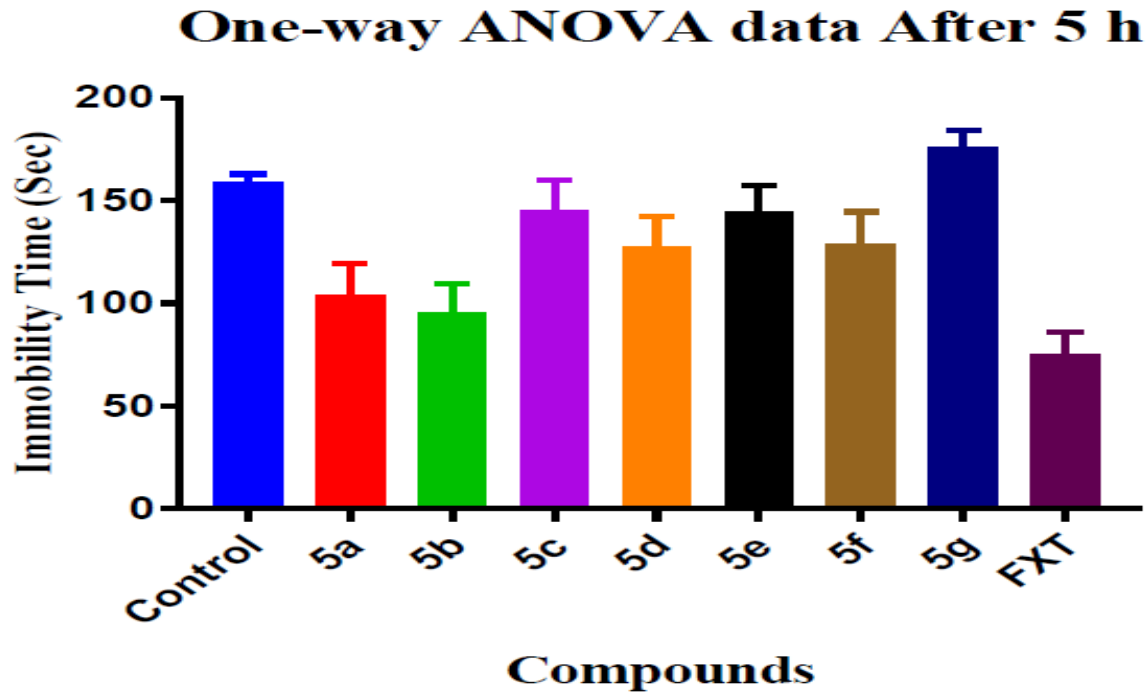


Figure 3.2: Effect of synthesized Coumarin derivative and Standard drug (Fluoxetine i.e.FXT) on mice by FST after 5h.

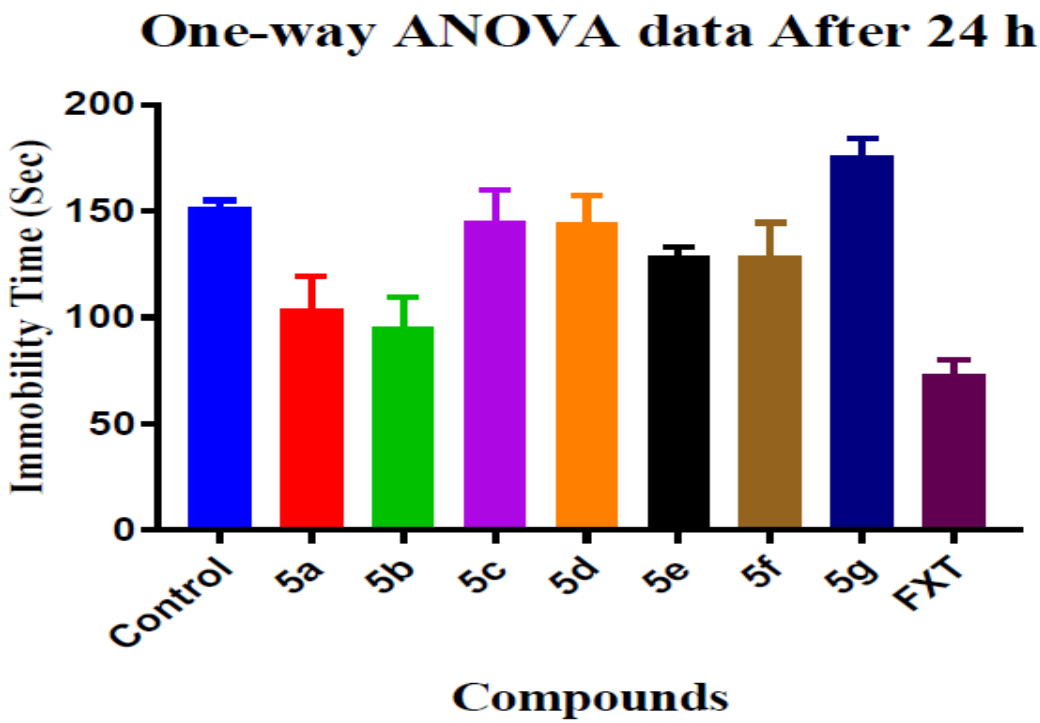


Figure 3.3: Effect of synthesized Coumarin derivative and Standard drug (Fluoxetine i.e.FXT) on mice by FST after 24h.

2: Result of Tail Suspension Test:

Table: Result of Tail Suspension Test.

Group		Immobility Time (Sec)		
		After 1h (Mean ± SEM)	**After 5h (Mean ± SEM)**	**After 24h (Mean ± SEM)**
I	**Control** (DMSO 1%)	189.8±2.01	185.6 ± 3.750	183.6± 3.60
II	**5a** 10mg/kg	131.6 ±2.04	103.8 ±6.90	128.8 ± 1.93
III	**5b** 10mg/kg	101.8 ± 4.2	95.2 ±6.445	95.2 ± 6.44
IV	**5c** 10 mg/kg	151.6 ± 3.32	145.4 ±6.416	145.4 ± 6.41
V	**5d** 10 mg/kg	135.6±2.06	127.8±6.35	144.6 ± 5.81
VI	**5e** 10mg/kg	144.2±3.87	144.6±5.81	103.8±6.90
VII	**5f** 10mg/kg	145.2±1.85	128.6±7.153	128.6±7.15
VIII	**5g** 10mg/kg	176.4±2.48	176.2±3.597	176.2±3.59
IX	**FLX** 10 mg/kg	90.4 ± 1.80	75.40±4.71	73.0±3.24

Group I=Vehicle treated (without any compound),
Group II to VIII = Synthesized Compounds [5(a) to 5(g)] (10 mg/kg)
Group IX= Standard Drug [Fluoxetine] (10mg/kg)

Graphical representation of Antidepressant activity by Tail Suspension Test (TST):

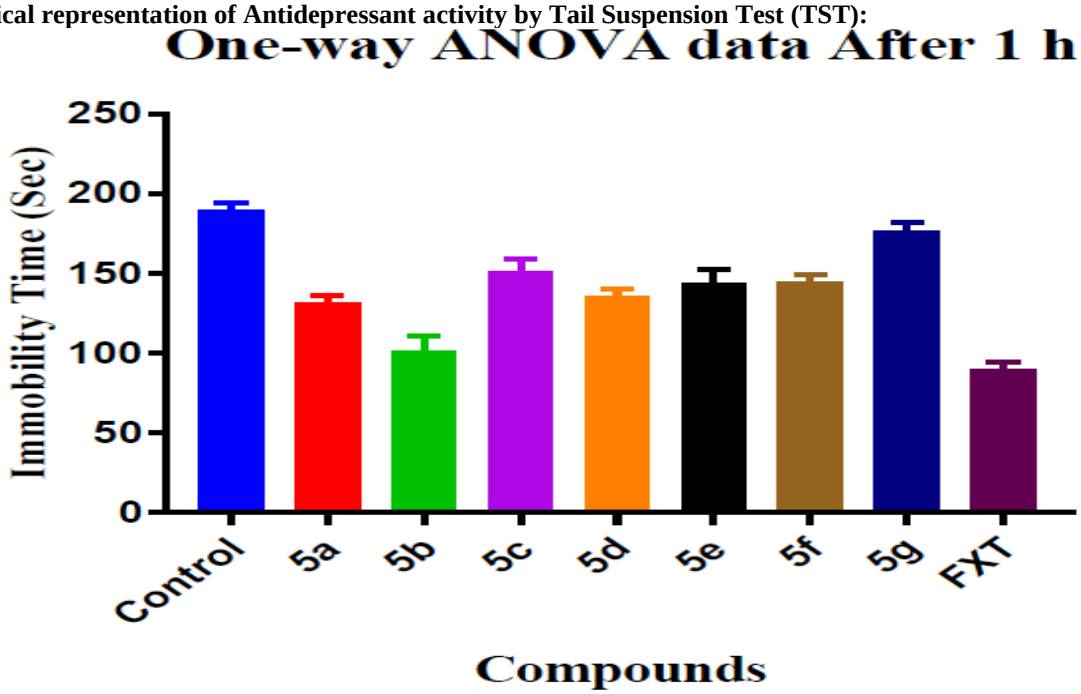


Figure 4.1: Effect of synthesized Coumarin derivative and Standard drug (Fluoxetine i.e.FXT) on mice by TST after 1h.

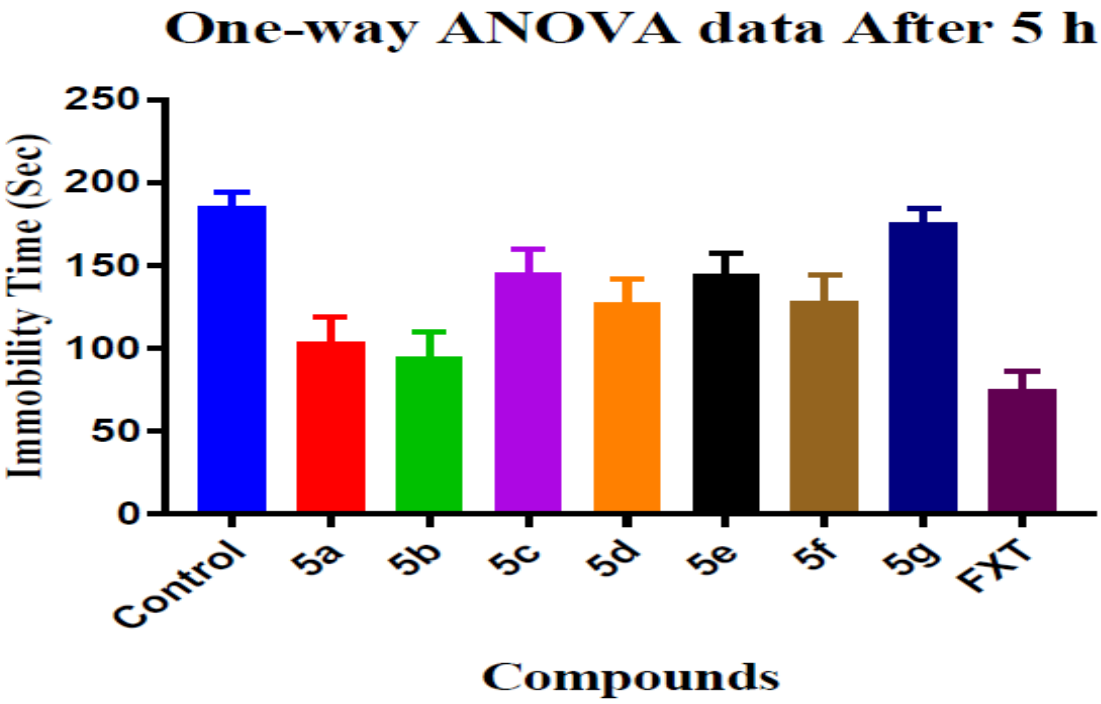


Figure 4.2: Effect of synthesized Coumarin derivative and Standard drug (Fluoxetine i.e.FXT) on mice by TST after 5h.

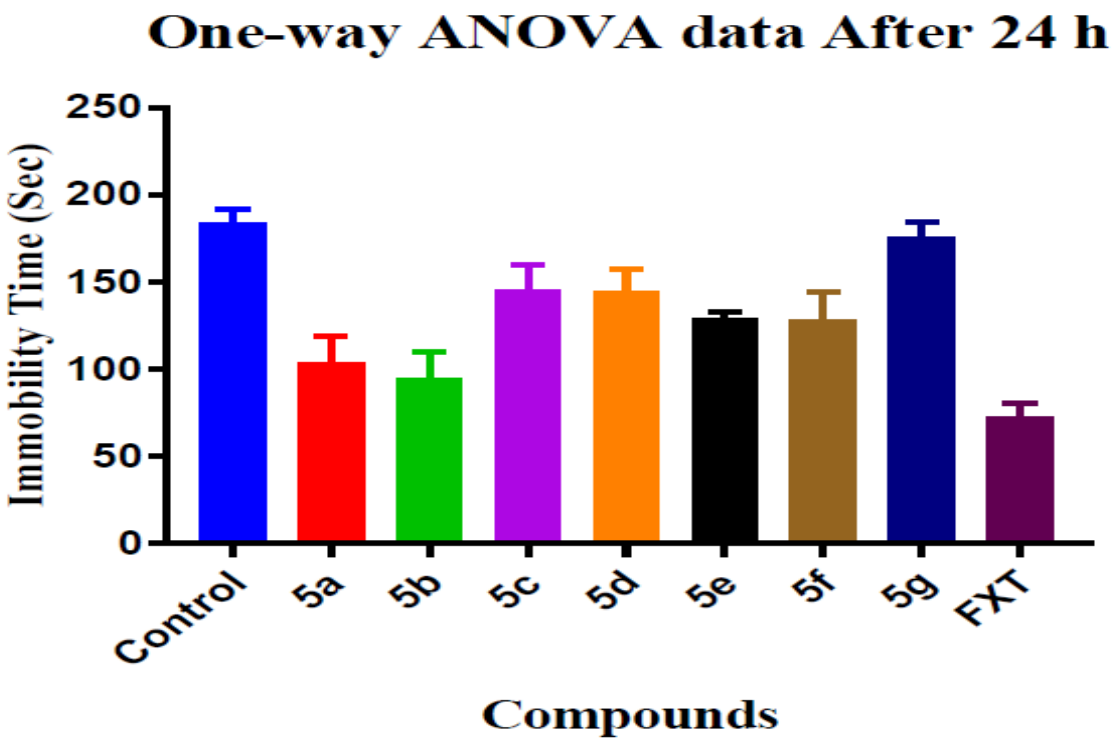


Figure 4.3: Effect of synthesized Coumarin derivative and Standard drug (Fluoxetine i.e.FXT) on mice by TST after 24h.

4. CONCLUSION

All the synthesized compounds have been screened for their Antidepressant activities.

Antidepressant activity is checked by Force Swim Test and Tail suspension model in that the Compound Code 5(b) is more active than 5(a) i.e. shows the markedly decrease in immobility then all other compounds.

The all compound is compared to the Fluoxetine as standard antidepressant drug (Brand name: Fludac 20mg Cap. Mfg by CADILA Pharmaceutical).

FLX > 5(b) > 5 (a)

The one way ANOVO study shows the data is significant.

[30]Coumarins are a group of heterocyclic compounds currently being of great interest. [30]For this reason, the isolation and the structural characterization of novel derivatives, together with the development of new synthetic methods and biological properties, are topics of growing interest for a great number of research groups. [30]It is therefore, of utmost importance that the study of this topic, and the development of new synthetic strategies, is one of the areas of most up-to-date research and primordial. It is even more important to stress that the metabolic studies related to the biotransformation of coumarin and derivatives, that have already been initiated, are actually an emergent area of research.

In this synthesis, new class of 3–substituted coumarin derivatives were synthesized and evaluated for Antidepressant activity.

5. ACKNOWLEDGEMENTS

I would like to thank all people who have helped and inspired me during my M. Pharm research work.

I am very much thankful to the principal, MVP Samaj's College of pharmacy, Nashik, for providing infrastructure and all the necessary facilities for this research work.

Once again I would like to thank all the people mentioned & those that I have unknowingly failed to mention but have been instrumental in the culmination of this project into a successful endeavor.

REFERENCES

1. An article on Depression, by Anxiety and Depression Association of America (ADAA), www.adaa.org 2016.
2. Mood Disorders Society of Canada. Quick Facts: Mental Illness and Addiction in Canada, 3rd Edition. November 2009. Available at. www.mooddisorderscanada.ca/page/quick-facts.
3. National Institute of Mental Health. Depression. Revised 2008. Available at www.nimh.nih.gov/health/publications/depression/index.shtml.
4. MayoClinic.com Depression (Major Depressions) Symptoms Accessed June 4, 2010 Available at,

www.mayoclinic.com/health/depression/DS00175/DSECTION=symptoms.
5. https://en.wikipedia.org/wiki/List_of_antidepressants, February 20, 2017, 12.30pm.
6. Ross J, Baldessarini in, Goodman & Gilman's, The Pharmacological Basis of Therapeutics 11th edition Drug Therapy of Depression and Anxiety Disorders by page no. 429-455.
7. Rosenzweig-Lipson, S.; Beyer, C. E.; Hughes, Z. A.; Khawaja, X.; Rajarao, S. J.; Malberg, J. E.; Rahman, Z.; Ring, R. H.; Schechter, L. E. Pharmacology. Theory. 2007, Page no. 113,134.
8. Borges1 F, Roleira F, Milhazes N, Santana L, Uriarte E. Simple coumarins and analogues in Medicinal Chemistry: Occurrence, Synthesis and Biological Activity, Current Medicinal Chemistry, 2005; 12: 887-916.
9. Jain PK, Joshi H. Coumarin: Chemical and Pharmacological Profile. Journal of applied Pharmaceutical Science, 2012; 02(06): 236-240.
10. Zhou X, Li M, Wang X, Wang T and Kong L. Synthesis of benzofuran derivatives via rearrangement and their inhibitory activity on acetylcholinesterase. Molecules, 2010; 15: 8593-8601.
11. Sripathi SK, Logeeswari K. Synthesis of 3-aryl coumarin derivatives using ultrasound. International journal of organic chemistry, 2013; 3: 42-47.
12. Arora RB and Mathur CN. Relationship between structure and anticoagulant activity of coumarin derivatives. Brit. J. Pharmacol, 1963; 20: 29-35.
13. Lin H, Tsai S, Chen C, Chang Y, Lee C, Lai Z, Lin C. Structure–activity relationship of coumarin derivatives on xanthine oxidase-inhibiting and free radical-scavenging activities. biochemical pharmacology, 2008; 75: 1416–1425.
14. Abdel-Wahab1 BF, Mohamed HA, Farhat A A. Ethyl coumarin-3-carboxylate: Synthesis and chemical properties. Organic Communication, 2014; 7(1): 1-27.
15. Sashidhara KV, Kumar A, Chatterjee M, Rao KB, Singh S, Verma A, Palit G, Discovery and synthesis of novel 3-phenylcoumarin derivatives as antidepressant agents, Bioorganic & Medicinal Chemistry Letters, 2011: 1937–1941.
16. Sashidhara KV, Modukuri RK, Singh S, Rao KB, Teja GA, Gupta S, Shukla S. Design and synthesis of new series of coumarin–aminopyran derivatives possessing potential anti-depressant-like activity. Bioorganic & Medicinal Chemistry Letters, 2014; 21: 1617-1622.
17. Han L, Huang B, Xiong Z, Yan C, One-pot synthesis of potential antioxidant agents, 3-carboxylate coumarin derivative, 2015; 9(13): 435-444.
18. Asadipour A, Alipour M, Jafari M, Khoobi M, Emami S, Nadri H, Sakhteman A, Moradi A, Sheibani V, Moghadam FH, Shafiee A, Foroumadi A, Novel coumarin-3-carboxamides bearing N-benzylpiperidine moiety as potent acetylcholinesterase inhibitors. European Journal of Medicinal Chemistry, 2013; 70: 623-630.
19. Rendenbach-Muller B, Schlecker R, Traut M, and Weifenbach H. Synthesis of coumarins as subtype-selective inhibitors of Monoamine oxidase. Bioorganic & Medicinal Chemistry Letters, 1994; 4(10): 1195-1198.
20. Daniela S, Carradori S, Bolasco A, Chimenti P, Yanez M, Ortuso F, Alcaro S. Synthesis and selective human monoamine oxidase inhibition of 3-carbonyl, 3-acyl, and 3-carboxyhydrazido coumarin derivatives. European Journal of Medicinal Chemistry, 2011; 46: 4846-4852.
21. Zhou X, Wang X, Wang T, Kong L. Design, synthesis, and acetylcholinesterase inhibitory activity of novel coumarin analogues. Bioorganic & Medicinal Chemistry, 2008; 16: 8011–8021.
22. Castro A., Martınez A., Mini-Rev. Medicinal Chemistry, 2001; 1: 267.
23. Brufola G, Fringuelli F, Piermatti O and Pizzo F. Simple and efficient one-pot preparation of 3-substituted coumarins in water. Heterocycles, 1996; 43(6): 1257-1266.
24. Chimenti F, Secci D, Bolasco A, Chimenti P, Bizzarri B, Orallo F, Ortuso F, Alcaro S. Synthesis, Molecular Modeling, and Selective Inhibitory Activity against Human Monoamine Oxidases of 3-Carboxamido-7-Substituted Coumarins. Journal of Medicinal Chemistry, 2009; 52(7): 1935–1942.
25. Emami S and Dadashpour S. Current developments of coumarin-based anti-cancer agents in medicinal chemistry. European Journal of Medicinal Chemistry, 2015; 102: 611-630.
26. Khar RK , Mukherjee R and Jain SK. Three Dimensional Pharmacophore Modelling of Monoamine oxidase-A (MAO-A) inhibitors. International Journal of Molecular Sciences, 2007; 8: 894-919.
27. Wahab A, Bakra F, Hanan A and Abdelbasset A. Ethyl coumarin-3-carboxylate: Synthesis and chemical properties, Organic Communication, 2014; 7(1): 1-27.
28. Xin-Hua Liu et al, New 2H-chromene-3-carboxamide derivatives: Design, synthesis and use as inhibitors of MAO. European Journal of Medicinal Chemistry, 2014; 80: 278-284.
29. Sashidhara KV, Palnati GR, Avula SR, Kumar A. Efficient and General Synthesis of 3-Aryl Coumarins Using Cyanuric Chloride. Synlett, 2012; 23: 611–621.
30. Bhosale SH. et. al, Pharmacophore modeling and atom-based 3D-QSAR studies of tricyclic selective monoamine oxidase A inhibitors. Scholars Research Library Der of Pharma Chemica, 2010; 2(6): 171-182.
31. Olmedo D, Sancho R, Bedoya LM and López-Pérez JL. 3-Phenylcoumarins as Inhibitors of HIV-1 Replication. Molecules, 2012; 17: 9245-9257.

32. Perkin WH. Artificial production of coumarin and formation of its homologues. Journal of Chemistry Scoiety, **1868**; 21: 181.
33. Dighe NS, Tambe DL, Dighe AS, Musmade DS and Nirmal SA. Design, Synthesis and Anti-Depressant Activity of Some Novel Coumarin Derivatives. Journal of Analytical & Pharmaceutical Research, 2016; 2(4): 00026 1-6.
34. Patil PO, Bari SS, Firke SD and Deshmukh PK. Review: A comprehensive review on synthesis and designing aspects of coumarin derivatives as monoamine oxidase inhibitors for depression and Alzheimer's disease. Bioorganic & Medicinal Chemistry, 2013; 21: 2434–2450.
35. Jain K S, Bariwal JB, Kathiravan MK, Phoujdar MS. Recent advances in selective a1-adrenoreceptor antagonists as antihypertensive agents. Bioorganic & Medicinal Chemistry, 2008; 16: 4759–4800.
36. Hassan G S. Design & Synthesis of some piperazinomethyl Benzofuran Derivatives & Preliminary Investigation of their hypotensive activity as α1Adrenoreceptor Antagonists. International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3(4): 441-449.
37. He B, Lin Z, Synthesis of 2-oxo-2H-1-benzopyran-3-carboxylic acid ethyl ester under microwave irradiation conditions. Huaxue Gongchengshi, 2007; 21: 9-10.
38. Pavia DL, Lampman GM, George SK and Janmes RV. Spectroscopy, Depatment of chemistry, 2007; 26-86, 108-138.
39. Asadipour A, Alipour M, Jafari M, Khoobi M, Emami S, Nadri H, Sakhteman A, Moradi A, Sheibani V, Moghadam FH, Shafiee A, Foroumadi A. Novel coumarin-3-carboxamides bearing N-benzylpiperidine moiety as potent acetylcholinesterase inhibitors. European Journal of Medicinal Chemistry, 2013; 70: 623-630.
40. Tiwari M. et al, Pharmacological evaluation of novel 1-[4-(4-benzo[1,3] dioxol-5-ylmethyl-piperazin-1-yl)-phenyl]-3-phenyl-ureaas potent anticonvulsant and antidepressant agent, Pharmacological Reports. 2015; 394: 1–9
41. Carotti A. et al, In silico design of novel 2H-chromen-2-one derivatives as potent and selective MAO-B inhibitors, European Journal of Medicinal Chemistry, 2015; 89: 98-105.
42. Anand P, Singh B, Singh N. A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. Bioorganic & Medicinal Chemistry, 2012; 20: 1175–1180.
43. Castro A., Martınez A., Mini-Rev. Medicinal Chemistry, 2001; 1: 267.
44. Guo B, Fan H, Xin Q. Synthesis and evaluation of novel and potential antibacterial agents. Bioorganic and Medicinal chemistry Letters, 2013; 23: 3697-3699.
45. Varshney S, Saxena V. Design, Synthesis ,Charactrization and biological evaluation of some novel cannolo piperazine derivatives. International journal of Pharmacy and Pharmacetical science, 2014; 6: 246-48.