Synthesis Characterisation CNS and Analgesic Studies of Thiophene Sybstituted Hydrazone Derivative

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Abstract

In the present work, [1-(thiophen-2-yl] ethylidene] hydrazine and 4, 4'-(hydrazine-1,2-diylidenedimethylylidene)bis(N,N-dimethylaniline) were synthesized, it is condensation between 2-acetyl thiophene and hydrazine, p-dimethyl amino benzaldehyde with hydrazine hydrate. The structures of the synthesized compounds were characterized on the basis of IR and ^{1}HNMR spectral data. Among all synthesized compound I and II are screened for their CNS activity. Chlorpromazine is employed as a reference standard. From the results it is concluded that, compound II show more depressant activity than Compound I. The synthesized compound was subjected to analgesic studies with control saline as a reference standard and shows a significant increase in analgesic activity

Keywords: Aldazines, ethanol, FT-NMR, IR, CNS, hydrazone

Introduction

Azines are organic compounds having azine linkage (=N-N=) in their structures. Based on the chemical moiety, Azines are of two kind Aldazines and ketazines. Aldazines are having their general formulae as RHC=N-N=CHR [1]. They are obtained by the condensation of aldehydes with hydrazine hydrate. These reactions are generally initiated by mineral acids. Ketazines are compounds with general formula R_2C=N-N=CR_2 ketones on condensation with hydrazine hydrate in presence of mineral acids yield ketazines. CNS depressants slow normal brain functions in higher doses, some CNS depressants can become general anaesthetics. Central nervous system depressant is used for the treatment of anxiety, panic, sleep disorders, acute stress reactions and muscle spasms, includes drugs such as valium, Librium and Xanax. Most CNS depressants act on the brain by affecting the neurotransmitter gamma amino butyric acid (GABA). GABA unique ways, it is through their ability to increase GABA activity that they produce a drowsy or calming effect that is beneficial to that suffering room anxiety or sleep disorders. These drugs are also particularly dangerous when mixed with other medications or alcohol; overdose can cause breathing problems and lead to death [2-6]. Although the newer sleep medications such as ambient, lunesta and sonasta appear to have reduced dependence and abuse liabilities. Chlorpromazine is the oldest antipsychotic drug. The molecular structure is 2-Chloro-10-(3-dimethylaminopropyl)-phenothiazine. Chlorpromazine works on a variety of receptors in the central nervous system producing

anticholinergic, antidopaminergic, antihistaminic and antiadrenergic effects [7-11]. Its anticholinergic properties cause constipation, sedation, hypotension and relieve nausea. Its antidopaminergic properties can cause extrapyrimidal symptoms such as akasthisia (restlessness), dystonia and parkinsonism. Chlorpromazine inhibits clathrin-mediated endocytosis [13-18]. It is often administered in acute settings as syrup which has a faster onset of action than tablets [19, 20]. In this present work the condensation of 2-acetyl thiophene with hydrazine hydrate and condensation of p-dimethyl amino benzaldehyde with hydrazine hydrate and it is synthesized. It is subjected to CNS studies when compared with standard drug chlorpromazine. It is subjected to analgesic studies when compared with saline.

2. Materials and Methods

2- acetyl thiophene, p-dimethyl amino benzaldehyde and hydrazine hydrate was purchased from sigma Aldrich. The solvents were analar grade. The solvents used were ethanol, methanol and THF

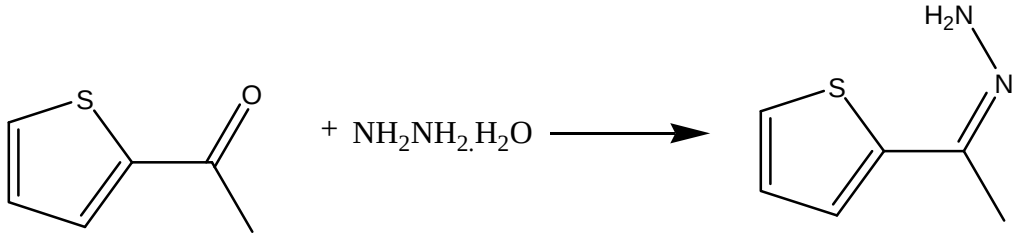
The following materials were used for the analgesic and CNS activity of thiophene substituted hydrazone derivative Albino mice (15-35 g), Syringe 1 ml, Glass Van Tuberculin – BCG Borosilicate glass.

The Percentage of carbon, hydrogen, nitrogen ,oxygen and sulphur contents were analyzed using carlo Erba 1108 model elemental analyser using sulphanilamide as a reference standard**.** The infra-red spectra of the compounds were recorded in the conventional region (400-4000cm-1) as KBr pellets. The infra-red spectral measurements were done using FT-IR-Shimadzu spectrometer. The NMR spectroscopy for the thiophene substituted hydrazone derivative is recorded in BRUKER (300MHz) instrument using DMSO as solvent. The analgesiometer (Besto) were used for determining the analgesic activity. Digital actophotometer were used for determining the CNS activity

3. Experimental

3.1) Synthesis of [1-(thiophen-2-yl] ethylidene] hydrazine

Condensation of 2-acetyl thiophene with hydrazine hydrate in the presence of Con.Hcl (5 drops) and absolute ethanol (30 ml) under 6 hrs reflux condition yield orange yellow crystals of 1-(thiophen-2-yl] ethylidene] hydrazine. The yield obtained was 85%



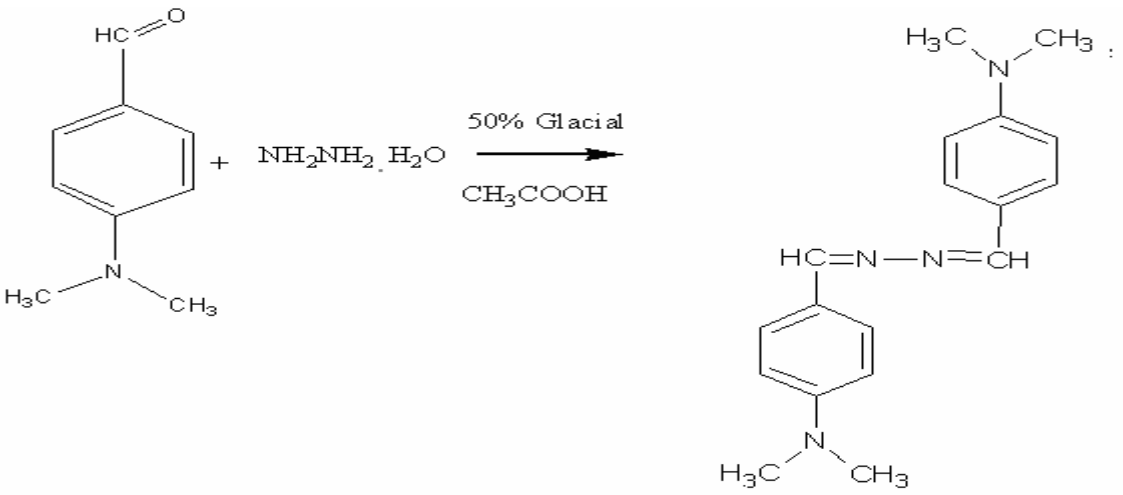
85%

2-acetyl thiophene Product I

Yield – 85% Molecular formula: $C_6H_8N_2S$ Molecular weight: 140.21 Elemental analysis calculated: C (51.40%) H (5.75%) N (19.98%) S (22.87%) found: C (51.37%) H (5.77%) N (19.96%) S (22.88%) Critical temperature 744.96 K Critical Pressure 40.41 Bar ^{1}H NMR (300 MHZ 1% DMSO/D_2O): 7-7.2(m Ar-H) 0.9(s -CH_3) 7 (s -NH); IR (KBR) (cm-1)1733.89 (C=N absorbance) 1105.14 (=N-N absorbance) 713.61 showed thiophene ring stretching 3444.63(-NH asymmetric stretching) 3350.12(-NH symmetric stretching) 842.83(C-S stretching)

3.2) Synthesis of 4, 4'-(hydrazine-1, 2-diylidenedimethylylidene) bis (N, N-dimethylaniline)

Condensing a p-dimethyl amino benzaldehyde with hydrazine hydrate in presence of 50% glacial acetic acid to yielded 80% of yellow green colored precipitate was obtained.



Yield: 80% Molecular formula $C_{18}H_{22}N_4$ Molecular weight 294.39 Elemental analysis calculated: C (73.44%) H (7.53%) N 19.03%) found C (73.41%) H (7.54%) N (19.05%) Critical temperature 858.79 K Critical Pressure 15.65 Bar ^{1}H NMR (300 MHZ 1% DMSO/D_2O): 6.6-7.4 (m Ar-H) 2.8(s -CH_3) 8.1 (s =CH); IR (KBR) (cm-1) 1602.90 (C=N absorbance) 2910.68 (=N-N absorbance) 812.06 (-C-H Aromatic bending frequency)

4. Results and Discussion

4.1 Elemental Analysis

From the elemental analysis, it is clear that observed micro analytical data (C, H and N) of the compounds are closely comparable with theoretically calculated C, H and N Values. The elemental analysis for Product I: C (51.40%) H (5.75%) N (19.98%) S (22.87%) found: C (51.37%) H (5.77%) N (19.96%) S (22.88%) and for Product II Elemental analysis calculated:: C (73.44%) H (7.53%) N 19.03%) found C (73.41%) H (7.54%) N (19.05%)

4.2 Vibrational Spectroscopy

The infra-red spectra were recorded by using 1% of the sample on KBR pellet with 16 scans and 2cm-1 resolution in a Jasco FT-IR/4100 Spectrophotometer equipped with ATR accessory in the range of 4000-400 cm^{-1} .The FT-IR Spectrum of Product I and II are Shown in Figure 1 and 2[12].

The FT-IR spectra of Product I the peak obtained at 1733.89 cm^{-1} showed C=N absorbance. The Peak obtained at 1105.14 cm^{-1} showed at =N-N absorbance. The Peak obtained at 713.6 cm^{-1} showed thiophene ring stretching. The Peak obtained at 3444.63 cm^{-1} showed -NH asymmetric stretching. The Peak obtained at 3350.12 cm^{-1} showed -NH symmetric stretching. The Peak obtained at 748.33 cm^{-1} showed C-S Stretching.

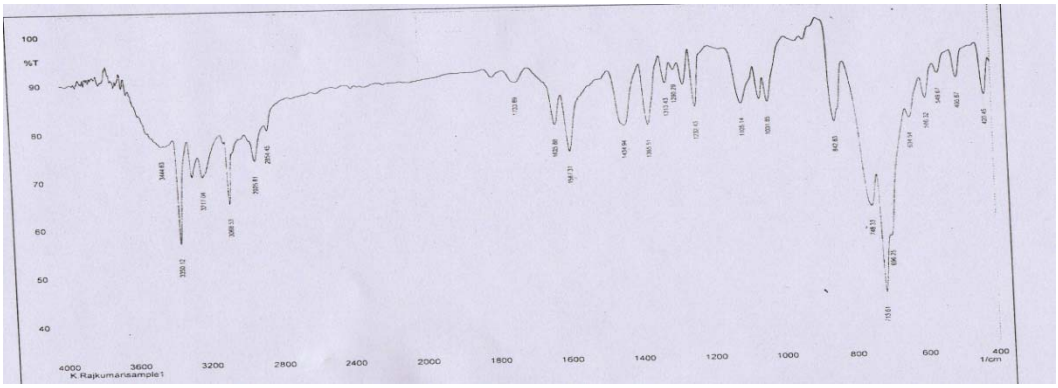


Figure 1 Ft-Ir Spectroscopy Of Product I

The FT-IR Spectra of Product II the peak obtained at 1602.90 cm^{-1} showed –C=N absorbance. The Peak obtained at 2910.68 cm^{-1} showed =N-N absorbance. The Peak at 812.06 cm^{-1} showed –C-H aromatic bending frequency

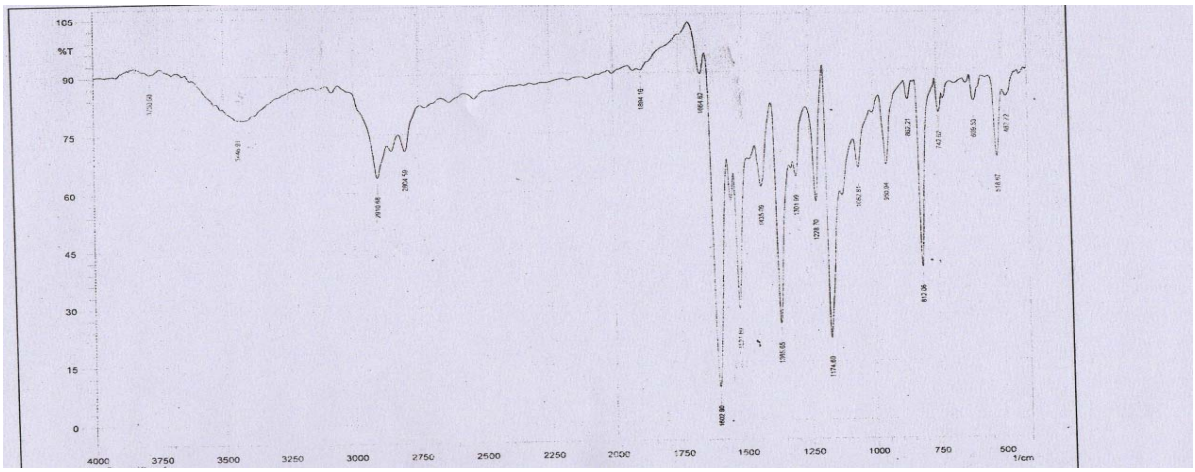


Figure 2 FT –IR Spectroscopy Of Product II

4.3 ^{1}H NMR Spectroscopy

The ^{1}H NMR spectroscopy for the Product I in 1% DMSO/D_2O was analyzed with TMS as Standard. The Structure of Product I is characterized from the assignments of observed chemical shifts to the corresponding protons [21]. The multiplet obtained at 7.3 ppm corresponds to aromatic ring attached to nitrogen moiety. The multiplet obtained at 7 7.0, 7.0, 7.2 corresponds to thiophene ring. A singlet obtained at 0.9 ppm corresponds to the presence of $-CH_3$ group. A singlet obtained at 7 ppm corresponds to the presence of NH group associated with the nitrogen group. It is shown in Figure 3

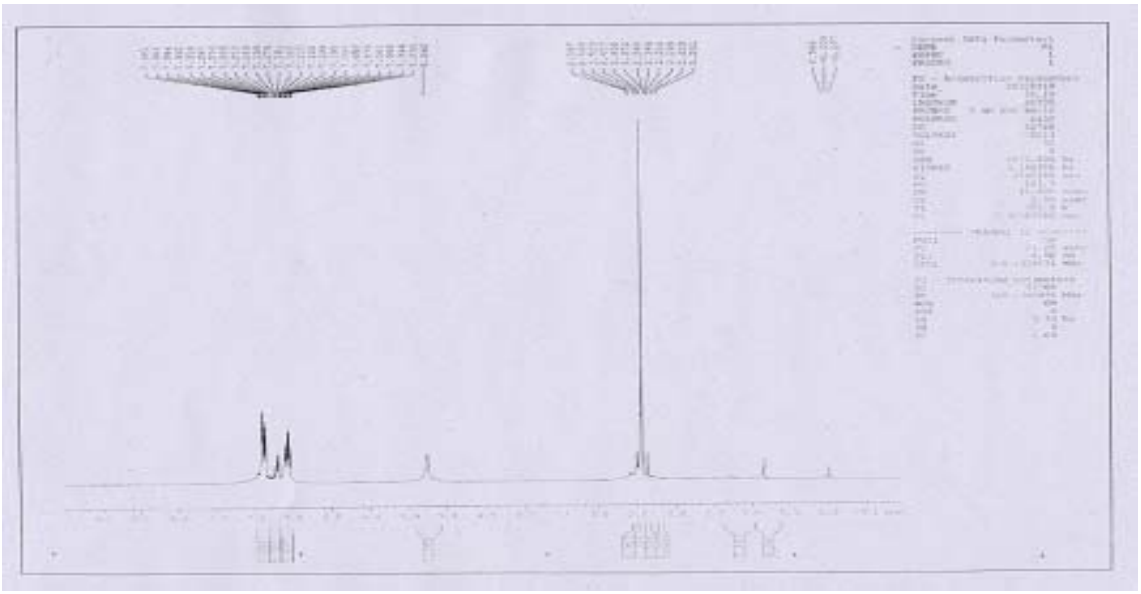


Figure 3: FT-NMR Spectrum of Product I

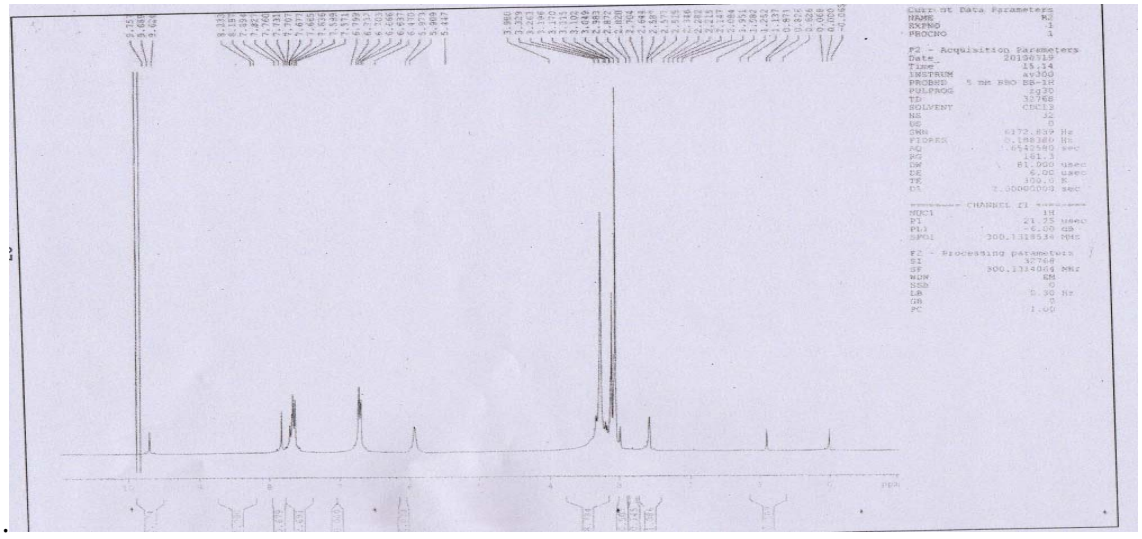


Figure 4: FT-NMR Spectrum of Product II

The FT-NMR Spectrum of product II the multiplet obtained at 6.6-7.4 corresponds to aromatic ring. A singlet obtained at 2.8 ppm corresponds to the presence of $-CH_3$ group. However the value gets increased

due to the presence of nitrogen group and identical protons A singlet obtained at 8.1 ppm corresponds to the presence of =CH group.

4.4 Central Nervous system (CNS) activity

The CNS activity was studied using albino mice through oral route using canula insertion via mouth. The scores from the digital actophotometer were tabulated before and after drug administration [22-24]. The mean % score for a group was plotted as chart likewise the tables and chart for dose of drug (30 mg/10 ml) were drawn.

Then from the mean values and chart the dose dependence of the synthesized compound was studied and it shows positive result.

All the above facts can be observed using the following table and chart.

Table I CNS study of Chlorpromazine

Animals body weight(g)	Drug	Dose mg/kg	Actophotometer activity in 10 min		
			Before treatment	After treatment	% Change in activity
36.18	Chlorpromazine	30 mg/10 ml	230	80	60
34.28			250	98	59.16
35.10			261	123	49.17
35.93			234	70	61.95
36.55			242	84	63.47
				Mean	58.75

Table II CNS study of [1-(thiophen-2-yl] ethylidene] hydrazine

Animals body weight(g)	Drug	Dose mg/kg	Actophotometer activity in 10 min		
			Before treatment	After treatment	% Change in activity
36.18	Chlorpromazine	30 mg/10 ml	192	91	52.6
34.28			238	118	50.42
35.10			242	123	49.5
35.93			204	106	48.39
36.55			230	116	63.47
				Mean	52.87

Table III CNS study of 4, 4'-(hydrazine-1, 2-diylidenedimethylylidene) bis (N, N-dimethylaniline)

Animals body weight(g)	Drug	Dose mg/kg	Actophotometer activity in 10 min		
			Before treatment	After treatment	% Change in activity
36.18	Hydrazone Derivative	30 mg/10 ml	180	75	58.33
34.28			225	118	47.5
35.10			234	123	47.43
35.93			184	110	40.21
36.55			213	94	55.86
				Mean	49.86

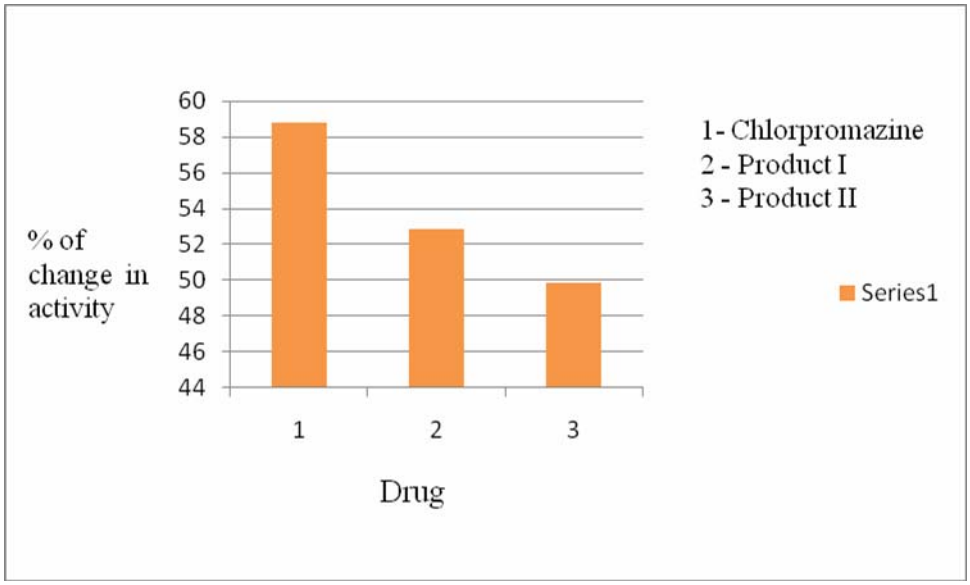


Figure 5: Comparison of Chlorpromazine with Product I and II (30mg/10ml)

4.6 Analgesic Activity:

The doses of Product I and II are prepared with a concentration of 30mg/ 10ml. The doses were given depending upon the body weight of the animal [25, 26].

Table IV Analgesic activity of Product I

Animal body weight(g)	Drug and dose	Basal reading (Seconds)					Reaction time after treatment (Seconds)				
		1	2	3	4	5	15	30	60	90	120
35.83	**Control 1ml saline**	1	1	2	1	1	2	1	1	1	1
31.45		1	1	1	2	1	2	2	1	2	1
30.19		1	1	1	1	1	1	1	2	2	1
	Mean	1.00	1.00	1.33	1.33	1.00	1.66	1.33	1.33	1.66	1.00
33.18	**Test drug (30 mg in 10 ml)**	1	2	2	1	2	2	2	3	4	4
35.16		1	2	1	1	1	2	3	3	5	4
32.56		1	1	1	1	1	3	3	3	4	4
	Mean	1.00	1.66	1.33	1.00	1.33	2.33	2.66	3.00	4.33	4.00
		% of analgesic activity					28.7	50	55.6	61.7	75.0

Table V Analgesic activity of Product II

Animal body weight(g)	**Drug and dose**	**Basal reading (Seconds)**					**Reaction time after treatment (Seconds)**				
		1	2	3	4	5	15	30	60	90	120
35.83	**Control 1ml saline**	1	1	2	1	1	1	1	1	1	1
31.45		1	1	1	2	1	2	2	1	2	1
30.19		1	1	1	1	1	1	1	2	2	1
	Mean	1.00	1.00	1.33	1.33	1.00	1.33	1.33	1.33	1.66	1.00
33.18	**Test drug (30 mg in 10 ml)**	1	2	2	1	2	2	3	3	5	5
35.16		1	2	1	1	1	3	3	4	5	5
32.56		1	1	1	1	1	3	3	3	4	6
	Mean	1.00	1.66	1.33	1.00	1.33	2.33	3.00	3.33	4.33	5.33
		% of analgesic activity					50	55.6	60.2	64.5	81.3

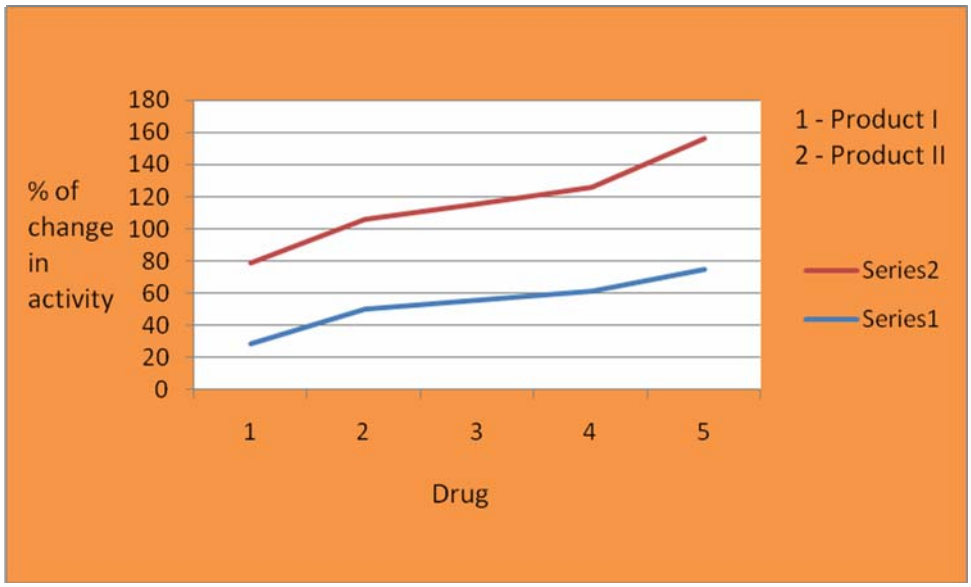


Figure 6: Comparison of analgesic activity of product I and II

5. Conclusion

During this research work the compound [(1-thiophen-2-yl) ethylidene] hydrazine and the compound 4,4' – (hydrazine-1,2-diylidenedimethylylidene)bis(N,N- dimethyl aniline) was synthesized. The Structure characterized with the support of, IR, TLC ^{1}H NMR Spectral data. The FT-IR spectra of Product I the peak obtained at 1733.89 cm^{-1} showed C=N absorbance. In product II the Peak at 812.06 cm^{-1} showed – C-H aromatic bending frequency. The synthesized product I was confirmed by TLC with ethyl acetate and hexane (8:2) and product II was confirmed by TLC with Chloroform and benzene(4.5:0.5).In FT-NMR spectrum of product I the multiplet obtained at 7.0-7.2 corresponds to thiophene ring. The FT-NMR Spectrum of product II the multiplet obtained at 6.6-7.4 corresponds to aromatic ring. A singlet obtained at 2.8 ppm corresponds to the presence of $–CH_3$ group. However the value gets increased due to the presence of nitrogen group and identical protons. The synthesized hydrazone derivative was screened for CNS activity using animal screening model with digital actophotometer. From the result it is found that the newly synthesized product II showed more CNS depressant activity than Product I. The synthesized product II showed more analgesic activity compared with Product I with different time intervals.

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6. References

[1] Ravikumar & ujjanimatada, Indian Journal of Chemistry, Section B, March 2008 (541)
[2] William Kemp Organic Spectroscopy, MC Milan Press Ltd., London, III edition. 1991
[3] Robert M Silverstein, Spectroscopic Identification of Organic Compounds, John Wiley & Sons INC. edition, 1991
[4] Brindaban C.R. and Dispak. C.S. J.org Chem, 53,1988,878
[5] Graham L. Patrick, An Introduction to Medicinal Chemistry II edition, Oxford University Press 2002.
[6] Ujjinamatada. R. K., Appala. R. S. and Agassimundin. Y. S; J. Heterocyclic chemistry, 43;2006,437
[7] Kadam S. S, Mahadik, R. Bothara. K.G.Principles of Medicinal Chemistry, Vol 1, Nirali Prakashan, X edition (2002)
[8] Green T.W and Wuts PG. M; Protective groups in Organic Synthesis (Wiley, New York) 1991, Page No(214-215)
[9] Hersberg E. B. J.Org Chemistry, 13, 1948;542
[10] Gatta. F and Settimj.G, J. Heterocyclic chemistry 21, 1984, 937
[11] R. S. Satoskar, S.D. Bhandarkar, S.S. Ainapure, Pharmacology and pharmacotherapeutics, Popular Prakashan, Mumbai, Revised XVIII edition 2002
[12] L. J. Bellamy, the Infrared Spectra of Complex Molecules, Chapman and Hall, London, (1978).
[13] B.C. Baguley, M.Lebret, Biochemistry, 23 (1984) p. 937-943.
[14] B. Altural, Y. Akcamur, E. Saripinar, M. Yildirim, G. Kollenz,. Monatsh. Chem., 120 (1989) p. 1015.
[15] Vogels text book of Practical organic chemistry, Arthur Israel Vogel, B.S. Furniss – Science – 1989
[16] M. Weitzer, S. Brooker, Dalton Trans., 14 (2005) p. 2448.
[17] M. Sönmez, M. Berber, J. Med. Chem., 41 (2005) p. 101.
[18] K. Y. El-Baradie, Monatsh. Chem., 136 (2005) p. 677.
[19] Emregul, K. C.; Abdulkadir Akay, A.; Atakol, O. Mater. Chem. Phys. 2005, 93, p. 325–35.
[20] Gupta, V. K.; Singh, A. K.; Mehtab, S.; Gupta, B. Anal. Chim. Acta 2006, 566, p. 5–10.
[21] Organic chemistry Seventh edition Francis A. Carey the McGraw Hill companies 2008 p. 539.
[22] Venkanna Lunavath and Estari Mamidala* Preliminary Phytochemical Screening and Antibacterial Studies of the Leaves of Eclipta Alba (L) International Journal of Pharma and Bio sciences Vol 4 issue 3 July- September 2010, p. 380-384.
[23] *B. Parimala Devi and R. Ramasubramaniaraja Pharmacognostical and Antimicrobial screening of Gymnema Sylvestre R.BR, and Evaluation of Gurmar Herbal Tooth Paste and Powder, composed of Gymnema Sylvestre R.BR, Extracts in Dental, International journal of pharma and bio sciences Vol 1 issue 3 July-September 2010 p. 1-16
[24] Anil Kumar Sharma 1*, Rajeev Kharb1 and Rajandeep Kauri, Pharmacognostical Aspects of Calotropis procera (Ait.) R. (Ait.) R. Br. International Journal of Pharma and Bio sciences Vol 2 issue 3 July-September 2011, p. 380-384
[25] NM. Goudgaon* and Rohini Yerram Reddy, Analgesic and Anti-inflammatory activities of 2-(4-Fluorobenzylthio)-N-(Substituted Phenyl) Pyrimidine-4-Amine, International Journal of Pharmaceutical, chemical and biological sciences Vol 4 issue 1 January- March 2014 p. 64-68.
[26] P. Deivanayagam1,2,3*, R.Pa. Boopathy1, S. Thanikaikarasan2 Synthesis, Characterization, Antimicrobial, Analgesic and CNS studies of Schiff base Cu(II) complex derived from 4-choro-o-phenylene diamine Vol 2 issue 2 October 2014 P. 166-170