International Journal of Drug Development & Research | Jan-March 2010 | Vol. 2 | Issue 2 | ISSN 0975-9344
Available online http://www.ijddr.com

Full Length Research Paper

SYNTHESIS AND CHEMISTRY OF PYRAZOLONE WITH PYRIMIDINE RING AND SCREENING OF ANTIOXIDANT ACTIVITY OF SYNTHESISED HETEROCYCLIC NUCLEUS HAVING UREA/THIOUREA/GUANIDINE LINKAGES

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ABSTRACT

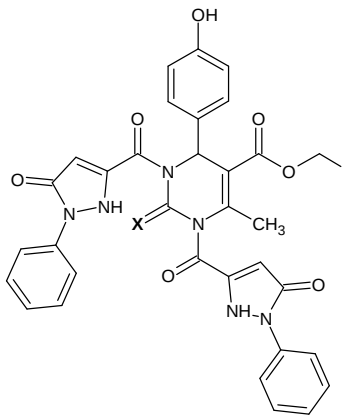
Five member pyrazolone and six member pyrimidine nucleus have been synthesised by multistep synthesis and subjected for antioxidant study for variable electronegative atoms for X=O(urea)/S(thiourea)/NH(guanidine). In-vitro antioxidant activity by reducing power indicated that incresed absorbance with concentration of showed that synthesized compounds have reducing power. By Ferric reducing antioxidant power (FRAP) assay method, it has been concluded that the three synthesized compound are responsible for the antioxidant potential: Compound-C (X=NH) >Compound-B (X=S) >Compound-A (X=O)

Keywords: *Pyrazolone, Pyrimidine, Electronegativity, Ferric Reducing Antioxidant Power (FRAP), Absorbance*

OBJECTIVES:

An antioxidant is a substance or food, like, red grapes, Rooibos Aspalathox, and black strap molasses, that helps prevent or delay oxidative damage caused by reactive oxygen and or reactive nitrogen species. Oxidative damage to the body, cells and tissues may contribute to diseases like cancer and heart disease. Fruits, vegetables, oils, nuts and whole grains have varying levels of antioxidant compounds like carotenoids, lycopene and the vitamins C and E. Flavonoids and phytochemicals, found in foods of plant origin, also act as antioxidants.

Synthesized Compounds: X=O (urea), S (thiourea), NH (guanidine).



MOLECULAR DESIGN

CHEMISTRY:

Phenyl substituted pyrazolone carboxylic acid has been synthesized by reaction between phenyl hydrazine with ethyl acetoacetate to form 5-pyrazolone which on alkaline oxidation with $KmnO_4$/KOH produced free carboxylic acid. Acid chloride of this acid has been condensed with pyrimidine nucleus produced by condensation of 4-hydroxy benzaldehyde with urea/thiourea/guanidine and ethyl acetoacetate[1].

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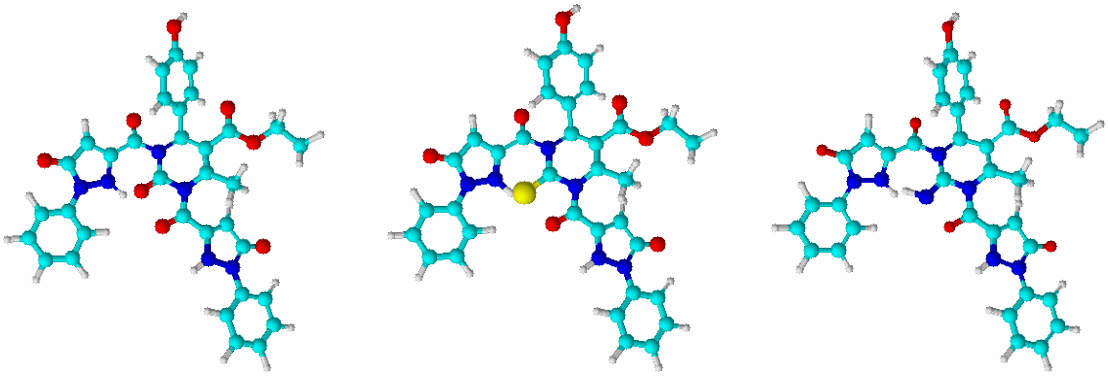
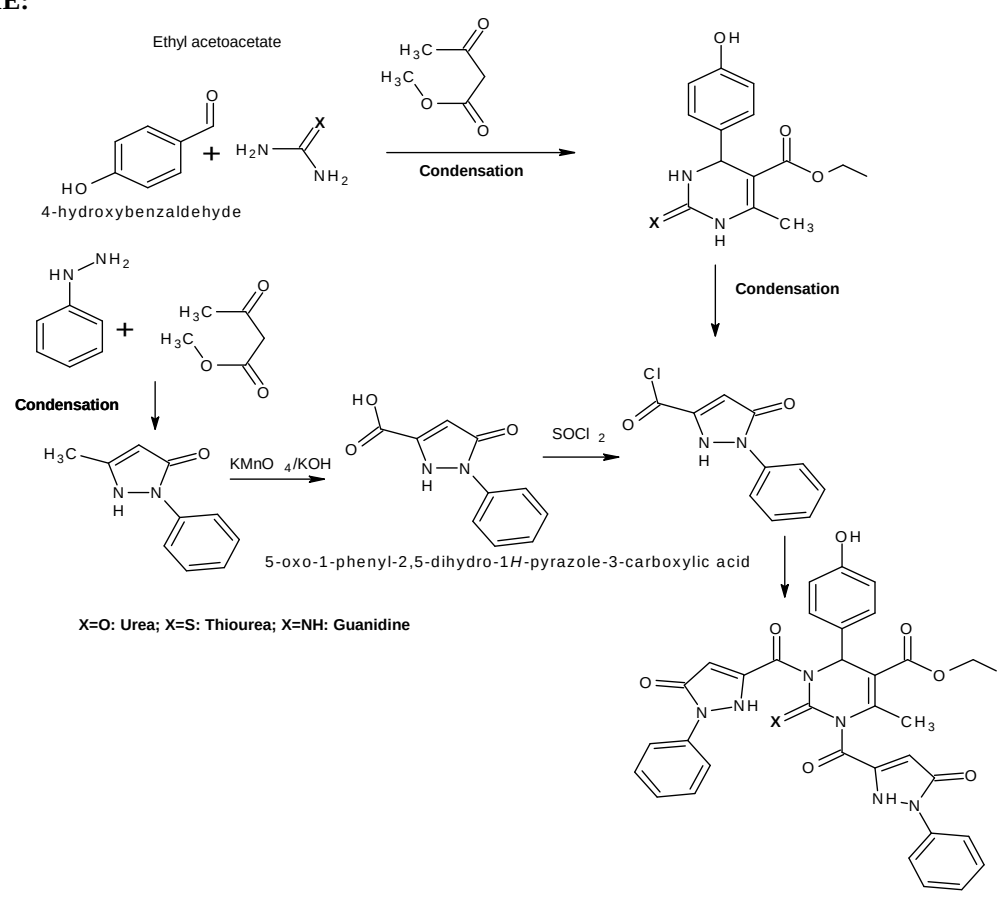
Two moles of this acid chloride conjugates at two imino positions of this pyrimidine nucleus. Finally the free imino group of pyrazolone nucleus has been benzoylated to produce the desired product[2-4]. Here X is variable: X=O (urea), S (thiourea) and NH (guanidine). Three different compounds have been synthesized by keeping X as variable: X=O/S/NH for Compound-A / Compound-B / Compound-C respectively. Electronegativity of oxygen for urea X:O=3.5 and of sulfur for thiourea X:S=2.4 and of nitrogen+hydrogen for guanidine X:NH=3.1+2.2=5.3. So the X=NH shows the maximum electronegativity with combined effect of electronegativity of nitrogen and hydrogen, whereas X=O has two lone pairs and X=S has also two pair of electrons, but in case of NH moiety the electronegativity of nitrogen and hydrogen exceeds the electronegativity of oxygen and sulfur: NH (5.3) > S (2.4) > O (3.5)

Three compounds have characterised by elemental microanalysis by CHN% and spectral datas of UV, IR and Mass spectras.

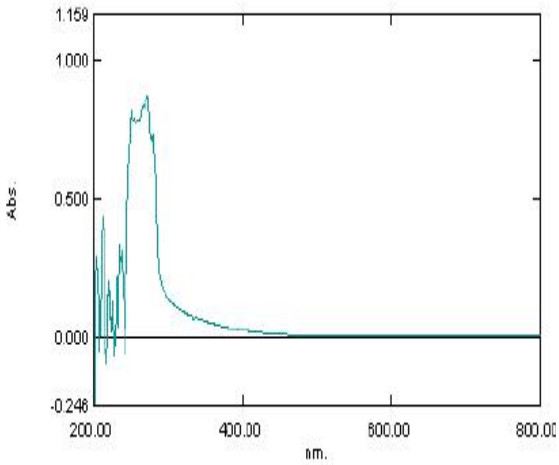


Compound-A **Compound-B** **Compound-C**

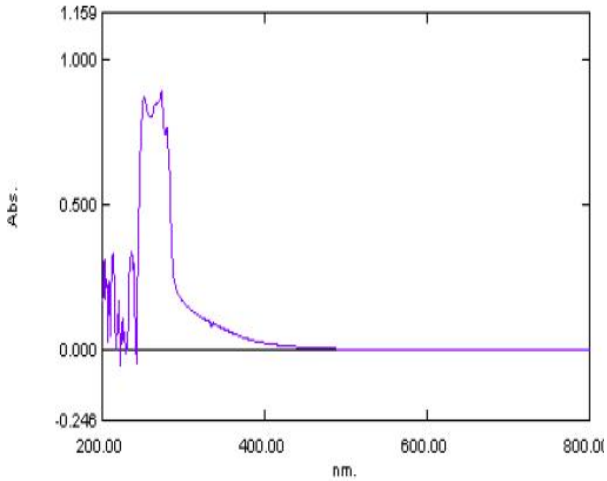
SCHEME:



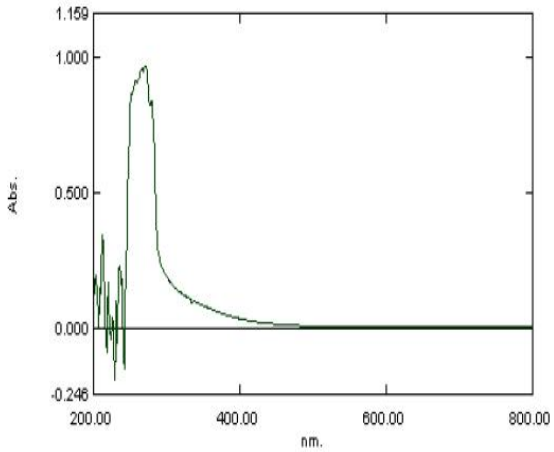
ULTRAVIOLET SPECTRAS OF SYNTHESISED COMPOUNDS



Compound-A: X=O λmax= 272nm

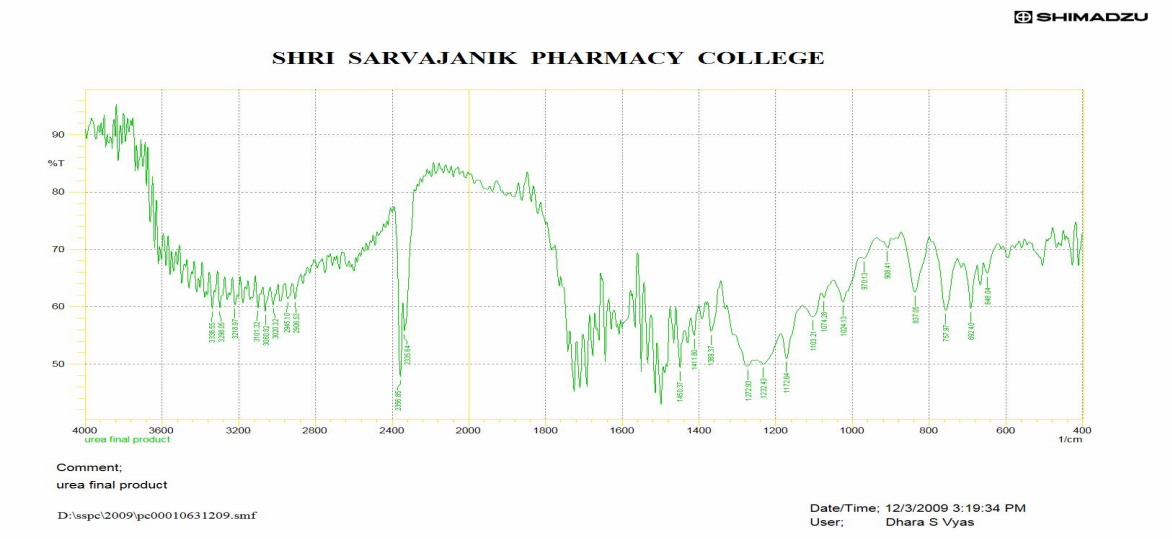


Compound-B: X=S λmax= 273nm

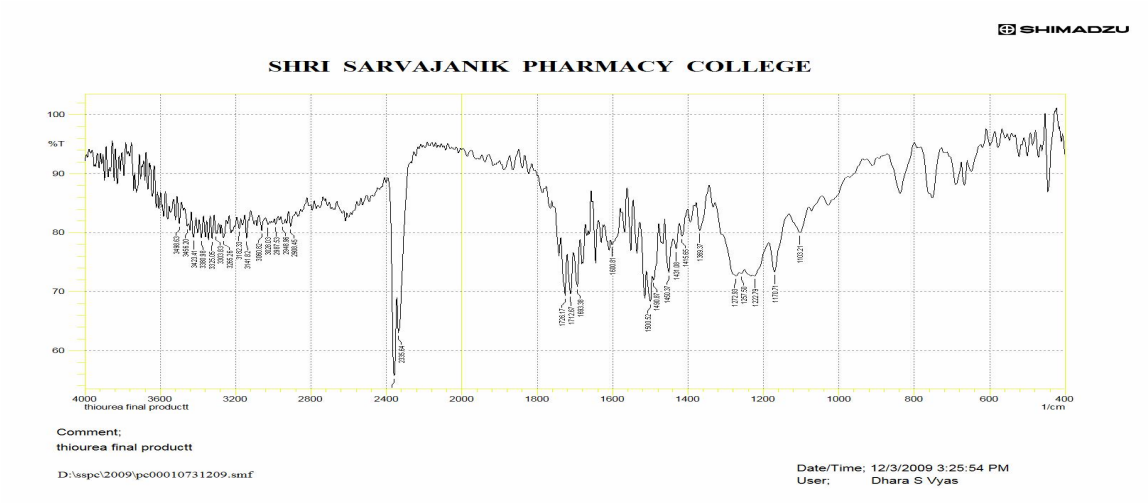


Compound-C: X=NH λmax= 270nm

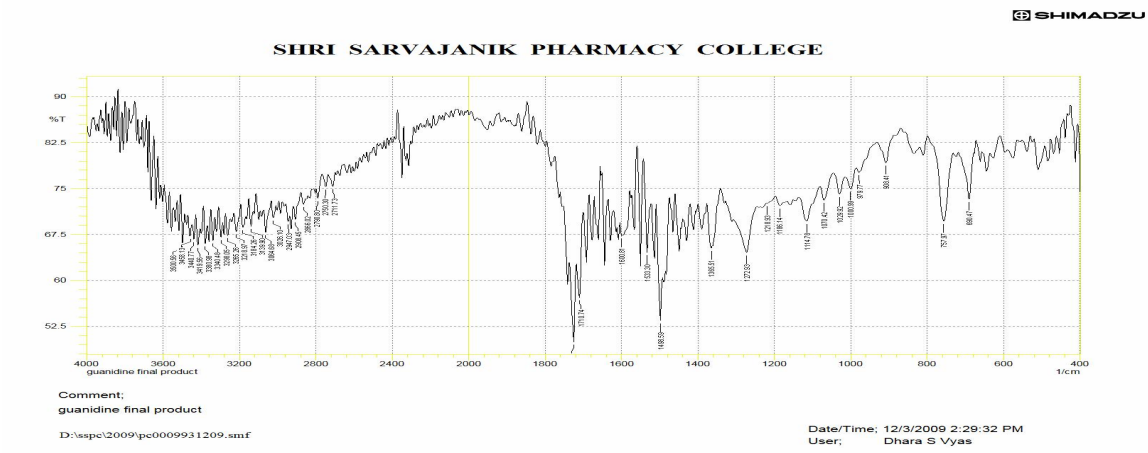
INFRA RED SPECTRAS OF SYNTHESISED COMPOUNDS



Compound-A: X=O



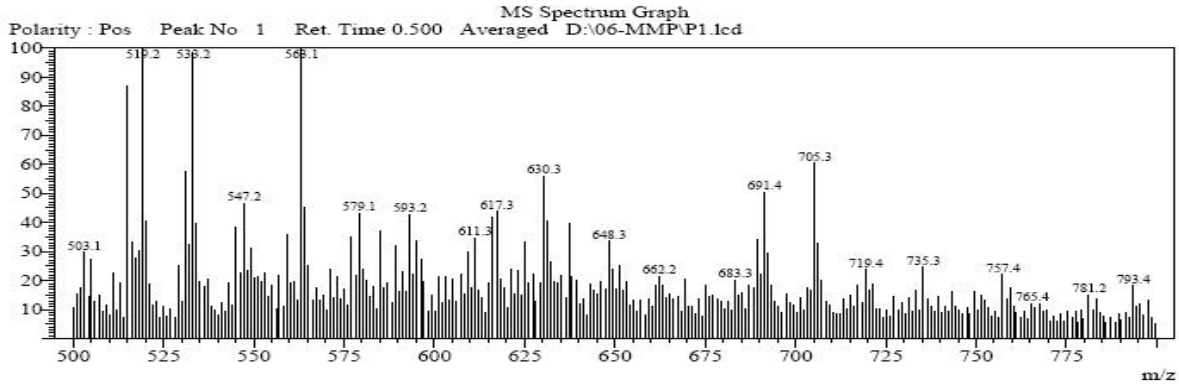
Compound-B: X=S



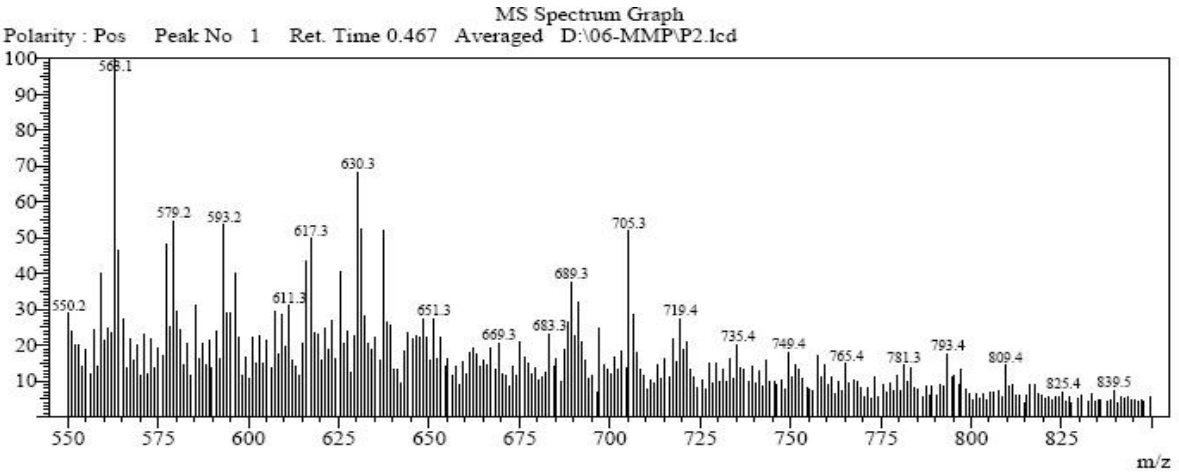
Compound-C: X=NH

Compounds	Spectral data of IR spectroscopy (KBr ; cm^{-1})
2a	1099(Ar-OH), 860(p-substitution), 1750-1650(Strong peak of C=O), 1452(Ar-C=O in ether), 1161.07(R-O in ether), 1644(C=C), 1705(C=O of Urea), 1680(O-substituted six member ring), 837,788,640(m-di substituted six member ring)
2b	1089(Ar-OH), 860(p-substitution), 1750-1650(Strong peak of C=O), 1452(Ar-C=O in ether), 1161.07(R-O in ether), 1638(C=C), 1112(C=S of Thiorea), 1681.21(O-substituted six member ring), 833,784,642(m-di substituted six member ring)
2c	1091(Ar-OH), 862(p-substitution), 1750-1650(Strong peak of C=O), 1451(Ar-C=O in ether), 1161.07(R-O in ether), 1642(C=C), 1654(C=N of Guanidine), 1680(O-substituted six member ring), 833,788,652(m-di substituted six member ring)
5	1725(C=O), 1645(C=C), 1498(Aromatic ring), 690(Mono substituted aromatic ring), 680,754,837(m-di substitution in six member ring), 1679(m-di substitution in five member ring), 1710.13(Carboxylic acid), 3200-2400(broad peak of Carboxylic acid), 1625(di substituted tertiary amide), 1750(aromatic amide)
7a or A	1103.21(Ar-OH), 837(p-substitution), 1680(O-substituted six member ring), 1750(C=O), 1450(Ar-C=O in ether), 1705(Amide), 1172(R-O in ether), 1645(C=C), 690(Mono substituted aromatic ring),1680-1620(Secondary & Tertiary amides)
7b or B	1103.21(Ar-OH), 837.05(p-substitution), 1693.38(O-substituted six member ring), 1726.17(C=O), 1450(Ar-C=O in ether), 1712.67(Amide), 1170.71(R-O in ether), 1645(C=C), 690(Mono substituted aromatic ring),1726-1600(Secondary & Tertiary amides), 1103.21(C=S)
7c or C	1114.78(Ar-OH), 908(p-substitution), 1691.46(O-substituted six member ring), 1720.74(C=O), 1450.37(Ar-C=O in ether), 1710.74(Amide), 1186.14(R-O in ether), 1645(C=C), 690(Mono substituted aromatic ring),1725-1600(Secondary & Tertiary amides)

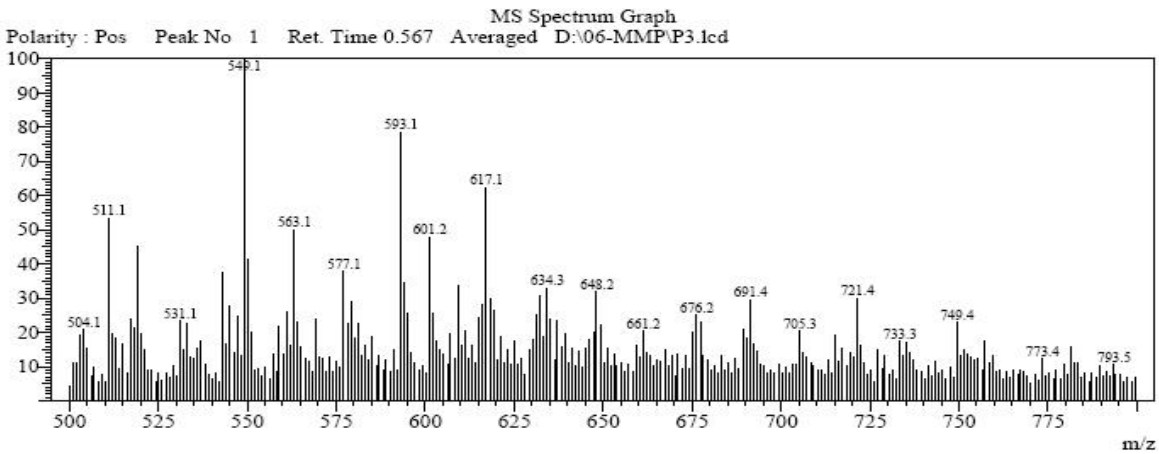
MASS SPECTRAS OF SYNTHESISED COMPOUNDS



Compound-A: X=O



Compound-B: X=S



Compound-C: X=NH

COMPOUNDS	SPECTRAL DATA OF MASS SPECTROSCOPY m/z (Abundance)
A X=O	648.3(M+, 34), 630.3(56), 593.2(44), 563.1(100), 533.2(98), 519.2(99), 503(30)
B X=S	669.3(M+, 23), 651.3(29), 630.3(70), 617.3(51), 611.3(32), 593.2(56), 579.2(56), 563.1(100), 550.2(30)
C X=NH	648.2(M+, 32), 634.3(33), 617.1(64), 601.2(47), 577.1(38), 563.1(50) 549.1(100), 531.1(24), 511.1(53), 504.1(21)

PHYSICOCHEMICAL PARAMETERS:

COMPOUNDS	% YIELD	D.P. ºC	POLARITY	MOL. FORMULA	N% CALCD	N% FOUND
Compound-A : X=O	87.78	195	Semipolar	$C_{34}H_{28}N_6O_8$	12.96	12.93
Compound-B : X=S	81.56	183	Semipolar	$C_{34}H_{28}N_6O_7S$	12.64	12.62
Compound-C : X=NH	81.63	173	Semipolar	$C_{34}H_{29}N_7O_7$	15.14	15.12

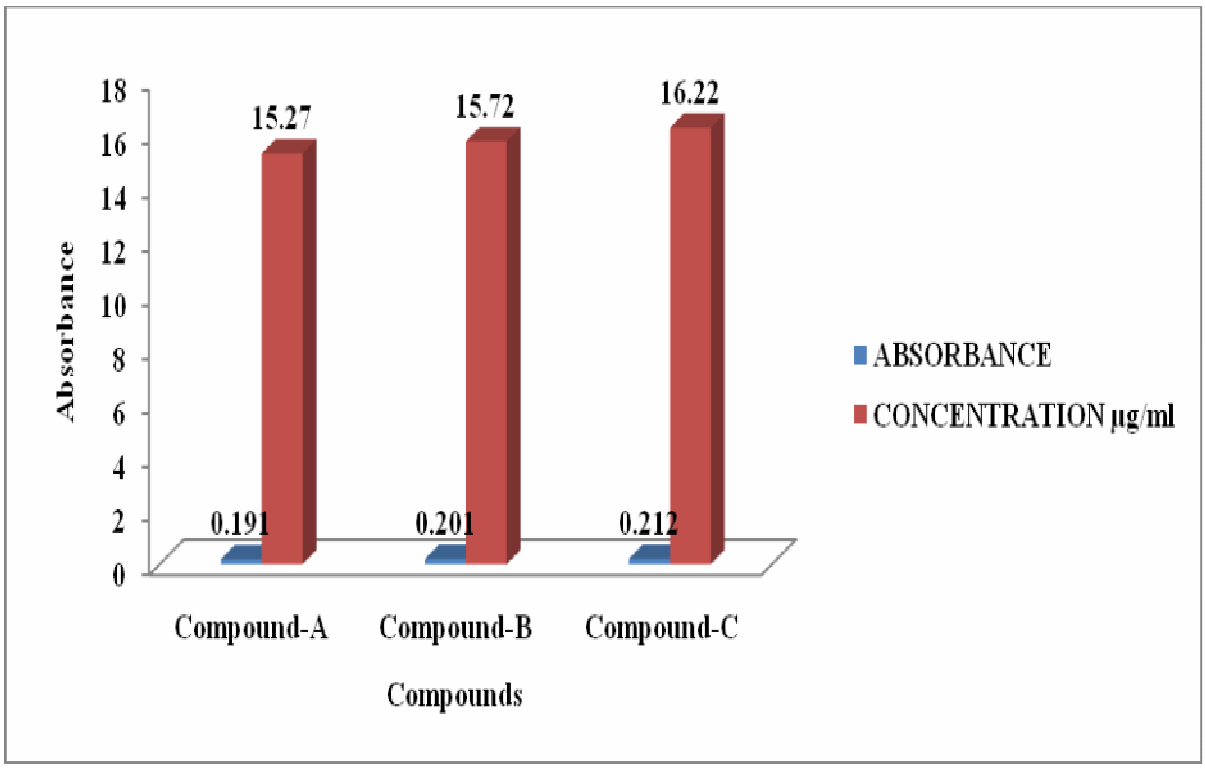
D.P.= Decomposition point ºC

EXPERIMENTAL METHOD:

FERRIC REDUCING ANTIOXIDANT POWER

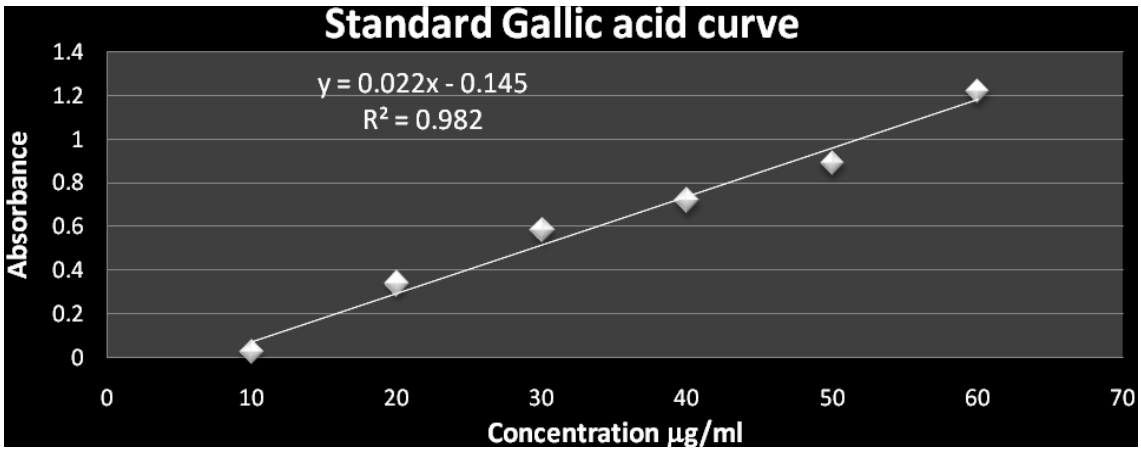
Serially Diluted extracts (10-100 mcg/ml) were mixed with 2.5 ml of potassium phosphate buffer (0.2M, pH 6.6) & 2.5 ml of potassium ferricyanide (1g/100ml) the mix was incubated at 50 for 20 minute. A total of 2.5 ml of 10% trichloroacetic acid was added to the mixture to stop the reaction. Equal volume of ultra pure water was added to 2.5 ml of the mixture before the addition of 0.5 ml of $FeCl_3$(0.1 g/100 ml) The sample was allowed to stand for 30 min. before measuring the absorbance at 700 nm. The absorbance obtained was converted to Gallic acid equivalents in mg/gram compound (mg GAE/g) using a Gallic acid standard curve[5-7].

Test compounds	Absorbance	Concentration (µg/ml)
Compound-A	0.191	15.27
Compound-B	0.201	15.72
Compound-C	0.212	16.22



ABSORBANCE OF GALLIC ACID:

Gallic Acid µgm/ml	Absorbance
10	0.026
20	0.34
30	0.584
40	0.719
50	0.891
60	1.22



RESULT AND DISCUSSION:

The spectral data for the absorption for the three compounds was compared with gallic acid for the plot was calculated by the equation: y=0.022x-0.1458 (R^2=0.982) and found that the antioxidant property of the compounds have the mentioned profle: Compound-C>Compound-B>Compound-A. Compound-C is guanidine moiety having X=NH so according to the highest electronegativity profile this is more potent than other two when compared with the total reducing capacity property. (Compound-A: 15.27µg, Compound-B: 15.72µg, Compound-C: 16.22µg) It was expressed as GAE means that reducing power of 60µg/ml of each compound is equivalent to reducing power of µg of gallic acid or expressed as µgGAE/mg of compound.

CONCLUSION:

In-vitro antioxidant activity by Reducing Power indicated that incresed absorbance with concentration of showed that synthesized compounds have reducing power. By Ferric reducing antioxidant power (FRAP) assay method, it has been concluded that the three synthesized compound are responsible for the antioxidant potential.

Compound-C (X=NH) >Compound-B (X=S) >Compound-A (X=O)

Acknowledgement: All the authors are thankful to the research group of Shri Sarvajanik Pharmacy College, Mehsana, Gujarat, India for providing the necessary equipments, chemicals, instruments and library facility for performing this project

successfully under the guidance of Prof. Dr. Dhrubo Jyoti Sen who has guided nicely these synthetic as well as spectroscopical antioxidant experiments under his expertise. The authors are also thankful to Oxygen Healthcare, Ahmedabad for Mass Spectras of the synthesised compounds.

REFERENCES:

1) *Vogel A I, Textbook of Practical Organic Chemistry, 3rd ed., (Longmans, Green and Co., Ltd.), 1956, 403.*
2) *Blicke F F, Organic Reactions Vol-I, 6th ed., (John Wiley and Sons, Inc., London), 1957, 303-341.*
3) *Maxwell Charles E, Org Syn Coll Vol-III, 3rd ed., 1955, 305.*
4) *Sen D J, PhD Thesis, Jadavpur University, Kolkata, 2000.*
5) *Aderogba M.A. ogundaini A.O. and Eloff J.N. (2006). Isolation of two flavonoids from bauhini monandra (kurz) leaves and their antioxidative effects. African journal of traditional, complementary and alternative medicine, 3(4): 59-65.*
6) *Farnsworth N., (1966). Biological and phytochemical screening of plants. J. pharm. Sci. 55 (3): 225-286.*
7) *Kirtikar K.R. and Basu B.D., (1995). Indian medicinal plants, international books distributor, dehradun, 1, 815-818.*

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Dilip R. Chavda, Priya R. Modiya and Hiren M. Marvaniya are the M.Pharm. students of Pharmaceutical Chemistry, studying in Shri Sarvajanik Pharmacy College, Mehsana and completed this project under the guidance of Prof. Dr. Dhrubo Jyoti Sen

Article History: IJDDR-10-073

Date of Submission: 30-03-2010

Date of Acceptance: 16-05-2010

Conflict of Interest: Medicinal Chemistry

Source of Support: Shri Sarvajanik Pharmacy College, Mehsana-384001, Gujarat