AMERICAN JOURNAL OF PHARMTECH RESEARCH

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Synthesis and Antimicrobial Study of some Novel Schiff bases of Substituted Gallic Acid

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ABSTRACT

A new series of novel substituted Gallic acid derivatives were synthesized by reacting methylated Gallic acid with hydrazine hydrate and then with various substituted aromatic aldehyde in mild and facile synthetic route to form various Schiff base derivatives. Melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using precoated TLC plates (MERCK, 60F) using chloroform: methanol (8:2) solvent system. The developed chromatographic plates were visualized under UV at 254nm. IR spectra were recorded using KBr on Josco FTIR model 8400 spectrophotometer, 1H NMR spectra in DMSO on a BRUKER FT-NMR instrument using TMS as internal standard. FAB mass spectra were recorded on JEOL SX 102 (DA-6000 mass Spectrometer) Data system using Argon (6KV.10MA) as the FAB gas. The designed compounds were screened for Antibacterial activity against *Staphylococcus aureus* and *Escherichia coli and* Antifungal activity against *Aspergillus Niger* in comparison with Ofloxacin and Fluconazole as standard to reveal the potency of synthesized derivatives. In accordance with the data obtained from antimicrobial activity, all the synthesized Schiff bases of substituted gallic acid have shown good activity against the tested microbes. Among these Schiff bases, compound bearing p-chloro group, o-chloro group, p-nitro group and m-nitro group has shown good activity against all the tested bacteria and fungi.

Keywords: Gallic acid, Schiff base, Nutrient Broth, 90% Ethanol, Antimicrobial Activity.

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Received 17 January 2013, Accepted 24 January 2013

Please cite this article in press as Prasad SA *et al.*, Synthesis and Antimicrobial Study of some Novel Schiff bases of Substituted Gallic Acid. American Journal of PharmTech Research 2013.

INTRODUCTION

Schiff bases are the important compound owing to their wide range of biological activities and industrial application. They have been found to posses the pharmacological activities such as antimalarial[1], anticancer[2], antibacterial[3], antifungal[4], antitubercular[5], anti-inflammatory, antimicrobial[6], and antiviral[7], etc. They also serve as a back bone for the synthesis of various heterocyclic compounds.

Gallic acid and its derivatives have been recognised, through various studies, to have properties that make it therapeutically promising. Derivatives of Gallic acid (a strong natural antioxidant[8]) derivative have been found to possess wide spectrum of biodynamic properties such as antitubercular, analgesic[9], antitumour[10], plant growth promoter, antityrosinase activity[11], radical scavenging activities and anti allergic. The chemistry of these substituted derivatives of Gallic acid has been the fascinating field of investigation in medicinal chemistry, as it has been found to exhibit enhanced biological profile. In view of these above biological importance of Schiff bases and Gallic acid, we plan to synthesis of some novel substituted Gallic acid analogs of Schiff bases by Schiff reaction.

The present work is oriented towards synthesis of some Schiff bases of substituted Gallic acid by condensing 3, 4, 5-trimethoxy benzoyl hydrzide with different aromatic aldehydes in the presence of glacial acetic acid and ethanol at 50-60^{o} C (scheme 1.). All the synthesized compounds have been characterized on the basis of their melting point, TLC, IR, 1H NMR and mass spectral data. The antimicrobial activity of these compounds was evaluated by Agar diffusion method. The main aim of the present work is to find new molecules such as these by synthesizing several Schiff bases from substituted Gallic acid.

MATERIALS AND METHODS:

All the chemicals used to synthesize the title compounds were of laboratory grade and purchased from S.D. Fine Chemicals and Sigma Aldrich. All the reactions were carried out under prescribed laboratory conditions. Melting points of the synthesized compounds were determined by open capillary and are uncorrected. The purity of the compounds was checked using precoated TLC plates (MERCK, 60F) using chloroform: methanol (8:2) solvent system. The developed chromatographic plates were visualized under UV at 254nm. IR spectra were recorded using KBr on Josco FTIR model 8400 spectrophotometer, 1H NMR spectra in DMSO on a BRUKER FT-NMR instrument using TMS as internal standard. FAB mass spectra were recorded on JEOL SX 102 (DA-6000 mass Spectrometer) data system using Argon

(6KV.10MA) as the FAB gas.

Synthesis of 3, 4, 5 trimethoxybenzoic acid:

8 g. (0.2 moles) of sodium hydroxide in 50 ml of water was placed in RBF along with 50 g (0.29 moles) of Gallic acid. The flask was immediately stoperred, and then reaction mixture was shaken occasionally until all the acid was dissolved; 57 ml (0.6 mol) of dimethyl sulphate was then added and the flask was stirred for 1hr, during this temperature was maintained below 30–35°C. The flask was then fitted with a reflux condenser and refluxed for 2 hr. The ester thus produced was saponified by addition of 2 g. of sodium hydroxide dissolved in 3 ml of water and refluxing for 2 hours. The reaction was monitored by TLC. The reaction mixture was then cooled and acidified with dilute HCl, the precipitated 3,4,5-trimethoxybenzoic acid was filtered and washed with cold water. The product 3,4,5-trimethoxybenzoic acid (TMBA) was recrystalized from boiling water using decolorizing carbon. Yield: 85 %, Colour: light brown , Rf value: 0.64, Mp: 183 °C.

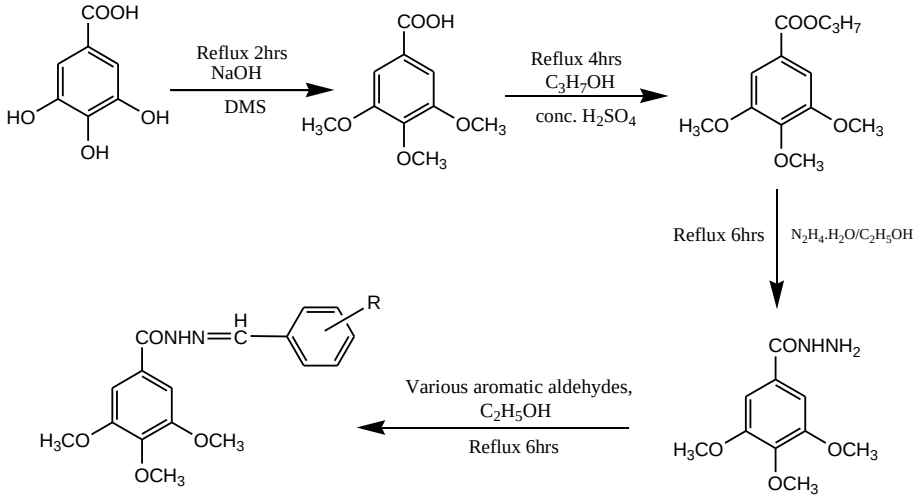

Figure-1: scheme of synthesis:

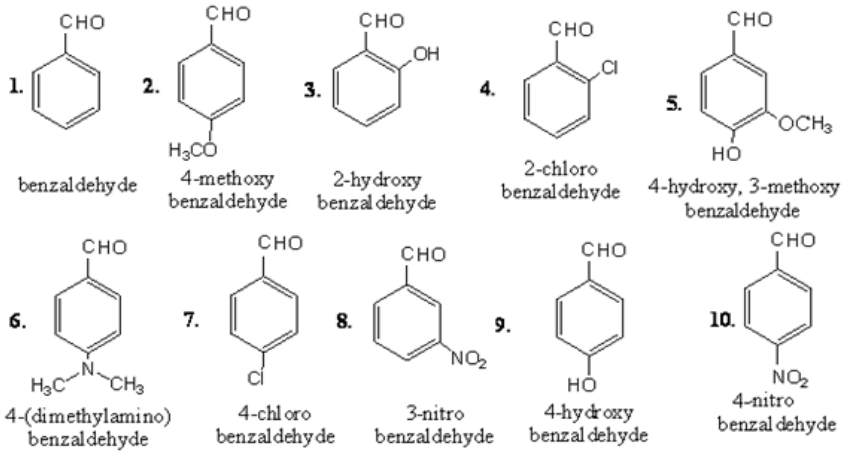

Figure-2: Various aromatic aldehydes used in the synthesis

Synthesis of propyl (3,4,5-trimethoxy) benzoate:

In a round bottom flask 56g (0.246mol) of 3,4,5-trimethoxybenzoic acid, 187ml (150g, 2.5mol) of propanol and 5g (2.7ml) of conc. Sulphuric acid was taken. The mixture was refluxed for 4 hours. Excess of alcohol was distilled off on a water bath and allowed to cool. Poured it slowly and with stirring on to 200g of crushed ice. Added sufficient ammonia solution to render the resulting solution strongly alkaline. Extracted the mixture with five 25 ml portion of ether, dry the combined ethereal extracts over MgSO4, removed the ether and distilled the residue under pressure. Yield: 78 %, Colour: Pale yellow, Rf value: 0.59, Mp: 174 °C.

Synthesis of 3,4,5-trimethoxy benzoyl hydrazide:

Propyl 3,4,5-trimethoxy benzoate 25.4g. (0.1 mol) in ethanol and hydrazine hydrate 10ml.(0.2 mol) were refluxed for 6 h. The excess of solvent was distilled off under reduced pressure using a vacuum pump. The cold residual mass was washed with distilled water, filtered and dried. The crude product obtained was recrystallised from methanol to yield 3,4,5-trimethoxy benzoyl hydrazide. Yield: 85 %, Colour: Pale white, Rf value: 0.61, Mp: 159 °C.

General procedure for the synthesis of schiff bases of 3,4,5-trimethoxy benzoyl hydrazide.

The Schiff base was prepared by reaction of equimole of 3, 4, 5-trimethoxy benzoyl hydrzide and substituted aromatic aldehydes. Each reactant was dissolved in a minimum amount of ethanol, then mixed together and followed by addition of 2 ml glacial acetic acid. The solution was refluxed for 8 h then cools to room temperature and poured in to ice cold water. The solid product was collected through filtration and then dried using drying oven at 80 ºC. The product was redissolved in ethanol for recrystallisation and then dried to give a product. The detailed scheme of synthesis is given in the Figure-1. Various aromatic aldehydes used in the synthesis are given in Figure-2. Physical constants data of synthesized compounds is given in Table- 1

Spectral data of synthesized compounds:

N'-benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBBEN): IR (KBr in cm^{-1}): 1645 (C=N Str);3407 (NH Str); 1356 (C-N Str); 1273 (CO-CH_3 bend); 2964 (CH Str-CH_3); 2990 (Ar-CH Str); 1675 (C=O Str); 770 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.32 (s, 1H, CH=N), 7.42-7.46 (m, 7H, Ar-H), 3.93 (s, 1H, NH), 3.56 (s, 9H, 3(OCH_3)). MS m/z, 314 [M^+]

N'-(4-methoxy) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBANIS): IR (KBr in cm^{-1}): 1640 (C=N Str);3387 (NH Str); 1360 (C-N Str); 1180 (CO-CH_3 bend); 3040 (CH Str-CH_3); 3050 (Ar-CH Str); 1660 (C=O Str); 740 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.31 (s, 1H, CH=N), 7.30-7.46 (m, 6H, Ar-H), 3.91 (s, 1H, NH), 3.45 (s, 12H, 4(OCH_3)). MS m/z, 344 [M^+]

N'-(2-hydroxy) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBSAL):IR (KBr in cm^{-1}): 1650 (C=N Str);3356 (NH Str); 1383 (C-N Str); 1184 (CO-CH_3 bend); 2880 (CH Str-CH_3); 2970 (Ar-CH Str); 1690 (C=O Str); 3590 (OH Str); 720 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.32 (s, 1H, CH=N), 7.30-7.46 (m, 6H, Ar-H), 3.91 (s, 1H, NH), 3.45 (s, 9H, 3(OCH_3)), 2.70 (s, 1H, OH). MS m/z, 330 [M^+]

N'-(2-chloro) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBOCB): IR (KBr in cm^{-1}): 1660 (C=N Str);3410 (NH Str); 1390 (C-N Str); 1210 (CO-CH_3 bend); 2990 (CH Str-CH_3); 2920 (Ar-CH Str); 1710 (C=O Str); 720 (C-Cl Str); 810 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.32 (s, 1H, CH=N), 7.43-7.49 (m, 6H, Ar-H), 3.93 (s, 1H, NH), 3.32 (s, 9H, 3(OCH_3)). MS m/z, 348 [M^+]

N'-(4-hydroxy, 3-methoxy) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBVAN): IR (KBr in cm^{-1}): 1630 (C=N Str);3210 (NH Str); 1400 (C-N Str); 1080 (CO-CH_3 bend); 2980 (CH Str-CH_3); 3110 (Ar-CH Str); 1660 (C=O Str); 3580 (OH Str); 720 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.32 (s, 1H, CH=N), 7.18-7.21 (m, 5H, Ar-H), 3.91 (s, 1H, NH), 3.44 (s, 12H, 4(OCH_3)). MS m/z 360 [M^+]

N'-(4-dimethylamino) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBDMA): IR (KBr in cm^{-1}): 1640 (C=N Str);3400 (NH Str); 1300 (C-N Str); 1210 (CO-CH_3 bend); 3010 (CH Str-CH_3); 2950 (Ar-CH Str); 1700 (C=O Str); 740 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.31 (s, 1H, CH=N), 7.18-7.21 (m, 6H, Ar-H), 3.91 (s, 1H, NH), 3.45 (s, 9H, 3(OCH_3)),2.19 (s, 6H, N(CH_3)$_2$). MS m/z, 357 [M^+]

N'-(4-chloro) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBPCB) IR (KBr in cm^{-1}): 1660 (C=N Str);3410 (NH Str); 1390 (C-N Str); 1210 (CO-CH_3 bend); 2990 (CH Str-CH_3); 2920 (Ar-CH Str); 1680 (C=O Str); 730 (C-Cl Str); 810 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.32 (s, 1H, CH=N), 7.43-7.49 (m, 6H, Ar-H), 3.93 (s, 1H, NH), 3.32 (s, 9H, 3(OCH_3)). MS m/z, 348 [M^+]

N'-(3-nitro) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBPNB): IR (KBr in cm^{-1}): 1640 (C=N Str);3360 (NH Str); 1410 (C-N Str); 1120 (CO-CH_3 bend); 2920 (CH Str-CH_3); 3210 (Ar-CH Str); 1680 (C=O Str); 1560 (Ar-NO_2 Str); 820 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.31 (s, 1H, CH=N), 7.43-7.49 (m, 6H, Ar-H), 3.93 (s, 1H, NH), 3.32 (s, 9H, 3(OCH_3)). MS m/z,359 [M^+]

N'-(4-hydroxy) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBPHB):IR (KBr in cm^{-1}): 1640 (C=N Str);3356 (NH Str); 1383 (C-N Str); 1184 (CO-CH_3 bend); 2880 (CH Str-CH_3); 2970 (Ar-CH Str); 1690 (C=O Str); 3590 (OH Str); 720 (Ar-ring);. ^{1}H NMR (DMSO, δ

ppm): 8.32 (s, 1H, CH=N), 7.30-7.46 (m, 6H, Ar-H), 3.91 (s, 1H, NH), 3.45 (s, 9H, 3(OCH_3)), 2.70 (s, 1H, OH). MS m/z,330 [M^+]

N'-(4-nitro) benzylidene 3,4,5-trimethoxy benzoyl hydrazide:(SBPNB): IR (KBr in cm^{-1}): 1630 (C=N Str);3360 (NH Str); 1410 (C-N Str); 1120 (CO-CH_3 bend); 2920 (CH Str-CH_3); 3210 (Ar-CH Str); 1700 (C=O Str); 1550 (Ar-NO_2 Str); 760 (Ar-ring);. ^{1}H NMR (DMSO, δ ppm): 8.31 (s, 1H, CH=N), 7.43-7.49 (m, 6H, Ar-H), 3.93 (s, 1H, NH), 3.32 (s, 9H, 3(OCH_3)). MSm/z,359 [M^+]

Antimicrobial activity:

The antimicrobial activity of all the synthesized compounds were examined against Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) and fugal strain Aspergillus niger organisms by measuring zone of inhibition. The antimicrobial activity was performed by Agar diffusion method at the concentration level of 200µg/ml. Ofloxacin and Fluconazole as standard drug at a concentration of 200µg/ml. Nutrient agar was used as culture media for antibacterial activity and Sabouraud dextrose agar was used as culture media for antifungal activity and DMSO as control. The results of the antimicrobial activity are shown in Table 2.

Table-1: Physical constants data of synthesized compounds:

Sample code	Compound Name	Mol	% Yield	Melting point	Rf value
SBBEN	N'-benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{17}H_{18}N_2O_4$	75	195°C	0.651
SBANIS	N'-(4-methoxy) benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{18}H_{20}N_2O_5$	72	208°C	0.622
SBSAL	N'-(2-hydroxy) benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{17}H_{18}N_2O_5$	69	215°C	0.674
SBOCB	N'-(2-chloro) benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{17}H_{17}N_2O_4Cl$	71	206°C	0.596
SBVAN	N'-(4-hydroxy,3-methoxy) benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{18}H_{20}N_2O_6$	74	184°C	0.712
SBDMA	N'-(4-dimethylamino)benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{19}H_{23}N_3O_4$	78	224°C	0.585
SBPCB	N'-(4-chloro)benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{17}H_{17}N_2O_4Cl$	70	212°C	0.632
SBMNB	N'-(3-nitro) benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{17}H_{17}N_3O_6$	73	218°C	0.664
SBPHB	N'-(4-hydroxy) benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{17}H_{18}N_2O_5$	72	189°C	0.615
SBPNB	N'-(4-nitro) benzylidene 3,4,5-trimethoxy benzoyl hydrazide	$C_{17}H_{17}N_3O_6$	69	214°C	0.687

Table 2: Zone of inhibition (mm) data of synthesized compounds:

Sl.no.	Compound	S.aureus (MRSA 125)		E.coli (MREC 539)		Aspargillus Niger (SFCAN 768)	
		Zone of inhibition (mm)	% inhibition	Zone of inhibition (mm)	% inhibition	Zone of Inhibition (mm)	% Inhibition
1	SBBEN	6.7	33.5	6.2	31.6	8.8	35.7
2	SBANIS	10.1	50.5	9.8	50	9.5	38.6
3	SBSAL	8.8	44	8.3	42	10	40.6
4	SBOCB	11.6	58	10.9	56	15.1	61
5	SBVAN	9.9	49.5	9.2	46.9	12.3	50
6	SBDMA	8.2	41	8.1	41	10.2	41
7	SBPCB	11.8	59	11.2	57.1	14.6	59.3
8	SBMNB	12.7	63.5	11.2	57.1	14.3	58.1
9	SBPHB	8.1	40.5	7.7	39.5	9.8	40
10	SBPNB	12.2	61	11.8	60	15.3	62
11	Ofloxacin	20	100	19.6	100	--	--
12	Fluconazole	--	--	--		24.6	100

RESULTS AND DISCUSSION:

All the synthesized compounds were purified by successive recrystallization using ethanol. The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined on the basis of their FTIR and 1HNMR data and mass spectrum.

The IR spectra of the synthesized compounds showed the presence of C=N stretching bands at 1690-1640 cm^{-1} and NH stretching frequencies at 3500-3060 cm^{-1} corresponding to azomethine compounds. In 1HNMR spectra of the synthesized compounds, the protons of azomethine compounds have given δ ppm 8.31-8.32. In accordance with the data obtained from antimicrobial activity, all the synthesized Schiff bases of methylated Gallic acid have shown good activity against the tested microbes. Among these Schiff bases of methylated Gallic acid, compound bearing Chlorine and nitro substitution has shown good activity against all the tested bacteria and fungi.

CONCLUSION:

Antibacterial and antifungal activity of the synthesized derivatives was done in comparison with Ofloxacin and Fluconazole as standard to reveal the potency of synthesized derivatives. All the selected strains of bacteria and fungi namely S. Aureus, E. Coli, and A. Niger showed sensitivity to all derivatives at concentration of 200µg/ml. Among these Schiff bases of methylated Gallic acid, compound bearing o-chloro, p-chloro, m-nitro and p-nitro substitution has shown good activity against all the tested bacteria and fungi.

ACKNOWLEDGEMENT:

The authors wish to thank Management of Srinivas College of Pharmacy, Valachil, Mangalore and Prof. T. V. Narayana chairman Dr HLT College of pharmacy Kengel Channapatana, for the necessary facilities and encouragement. Also thanks to Indian Institute of Sciences, Bangalore for carrying out IR, HNMR and mass spectra.

REFERENCES:

1. Li Y, Yang ZS, Zhang H, Cao BJ and Wang FD, Artemisinin Derivatives Bearing Mannich Base Group: Synthesis and Anti-malarial Activity. Bio org and Med Chem. 2003; 11:4363-4368.
2. Villar R, Encio I, Migliaccio M, Gil MG, Martinez-Merino V. Synthesis and cytotoxic activity of lipophilic sulphanamide derivatives of the benzo[b] thiophene 1,1-dioxode. Bioorga Med Chem.2004;12:963-968.
3. Venugopal KN, Jayashree BS. Microwave-induced synthesis of Schiff bases of brom coumarins as antibacterials. Indian J Pharm. Sci.2008; 70:88-91.
4. Pandey SN, Lakshmi VS, Pandey A. Biological activity of Mannich bases. Indian J Pharm Sci.2003; 65: 213-222.
5. Bhat MA, Imran M, Khan SA, Siddiqui N. Biologicbal activities of sulfonamides. J Pharm Sci.2005; 67:151-159.
6. S. J. Wadher, M. P. Puranik, N. A. Karande, PG. Yeole, Synthesis and Biological Evaluation of Schiff base of Dapsone and their derivative as Antimicrobial agents. Int J PharmTech Res 2009;1(1) :22-33.
7. Karthikeyan MS, Dasappa Jagadeesh Prasad, Boja Poojary, Subrahmanya Bhat K, Bantwal Shivaram Holla, synthesis and biological activity of Schiff and Mannich bases bearing 2, 4-dichloro-5-flourophenyl moiety. Bioorg and Med. Chem.2006; 14:7482-7489.
8. Sohi KK, Mittal N, Hundal MK, Khanduja KL. Gallic acid, an antioxidant, exhibits anti apoptotic potential in normal human lymphocytes: a Bcl-2 independent mechanism. J. Nutr. Sci. Vitaminol. 2003;49: 221–227.
9. Krogh R.; Yunes R.A.; Andricopulo A.D. Structure-activity relationships for the analgesic activity of gallic acid derivatives, Farmaco 2000;55(11):730-735(6)
10. Sakaguchi N,Inoue M, Isuzugawa K, Ogihara Y, Hosaka K. Cell death-inducing activity by gallic acid derivatives. Biol Pharm Bull 1999;22:471-475

11. Nagendra PK, Yang B, Yang S, Yulong C, ouming Z, Ashraf M, Jiang Y. Identification of phenolic compounds and appraisal of antioxidant and antityrosinase activities from litchi (Litchi sinensis Sonn.) seeds. Food Chem 2009; 116: 1 – 7.
12. Ilango, S Arunkumar. Synthesis, Antimicrobial and Anti-tubercular Activities of Some Novel Trihydroxy Benzamido Azetidin-2-one Derivatives. Tropical J Pharma Res 2011; 10 (2): 219-229.
13. S. Arunkumar, K ilango, RS manikandan, N Ramalakshmi. synthesis and anti-inflammatory activity of some novel pyrazole derivatives of gallic acid. e-Journal of Chemistry 2009;6(S1):123-s128.
14. Arun kumar Subramani, Ilango Kaliapan, Ravindar Bairam, Ramalakshmi N. Synthesis and biological evaluation of some novel triazolo, thiadiazole derivatives of gallic acid. Der Pharma Chemica 2009;1 (1):70-77.
15. Sudeep Mandal, Dibyajyoti Saha, Bindu Jain and Vibhor K Jain, Synthesis, Characterization and Evaluation of Anti-Tubercular Activity of Some Novel Triazole Derivative of Gallic Acid, Int J Res Pharma Biomedical Sci 2011;2(1): 167-174.
16. Weiming Xu, Baoan Song , Pinaki Bhadury, Yang Song and Deyu Hu, Synthesis and Crystal Structure of Novel Sulfone Derivatives Containing 1,2,4-Triazole Moieties, Molecules 2010;15:766-779.
17. K. Ilango, S. Arunkumar, synthesis and ntitubercular activity of novel 2-aryl n-(3,4,5-trihydroxy benzamido)-4-thiazolidinone derivatives. Rasayan J Chem 2010;3(3): 493-496.
18. Xiu-Fang Cao,a Yun-Shen Wang,a Shao-Wei Li,a Chang-Shui Chena and Shao-Yong Ke, Synthesis and Biological Activity of a Series of Novel N-Substituted 2-Lactams Derived from Natural Gallic Acid. J Chinese Chemical Society, 2011, 58, 35-40.
19. Arvind Singh Negi, Mahinder P. Darokar, Sunil K. Chattopadhyay, Ankur Garg, Synthesis of a novel plant growth promoter from gallic acid, Bioorganic & Medicinal Chemistry Letters 2005;15:1243–1247.
20. Abraham, DJ. In Burgers Medicinal Chemistry and Drug Discovery**,** Vol 1, 5th Ed, John Wiley and Sons, 1995, 3-4.