WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 5.210
Volume 4, Issue 11, 493-504 Review Article ISSN 2278 – 4357

A REVIEW ON ACYL UREAS HAVING DIFFERENT PHARMACOLOGICAL ACTIVITIES

Rakhi Chaudhary*, Dr. Shuaib[1], Dr. S. Riaz Hashim[2], Prem Shankar Mishra[3]

[1]Translam Institute of Pharmaceutical Education and Research, Meerut-250001, India.
[1]KIRAS Meerut, [2]IFTM University Moradabad, [3]Meerut Institute of Engg. & Technology Meerut-250005.

Article Received on
31 Aug 2015,

Revised on 20 Sep 2015,
Accepted on 10 Oct 2015

***Correspondence for Author**
Rakhi Chaudhary
Translam Institute of Pharmaceutical Education and Research, Meerut-250001, India.

ABSTRACT

Acyl ureas are compounds, which essentially incorporate urea and phenyl urea as a sub structural component either in open or cyclic form. Acyl urea derivatives are one of the major classes of bioactives, widely used as CNS (sedative, hypnotic), antimicrobial, anti-inflammatory anti-tumor activities etc. The present review summarizes about the various synthesized acyl ureas derivatives, and the various pharmacological activities of acyl urea moiety. Thus by studying one can say that acyl urea derivatives ring have been explored in past years and is still used for future development of new drugs against many more.

KEYWORDS: Cinnamoyl ureas, Various Pharmacological activity.

INTRODUCTION

Medicinal chemistry has been defined by IUPAC specified commission as discipline that covers the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level.[1]

Medicinal chemistry covers the following stages-

- In the first stage new active substances or drugs are identified and prepared from natural sources, organic chemical reactions through biotechnological processes. They are known as Lead compounds.
- The second stage is optimization of lead structure to improve selectivity and to reduce toxicity.

- Third stage is the development stage, which involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substances to render it clinically useful.[2]

Thus the practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease. Most of the activity in this discipline is directed to new natural or synthetic organic compounds. Once a new pharmaceutical lead compound has been discovered, extensive and costly efforts usually are made to synthesize a series of analogues in the hope that even better activity will be found. Qualitative structure-activity relationship (SAR) for absorption, distribution, metabolism, excretion parameters can be developed within a particular compound series. Even more powerful than these to provide guidance in the design processes are the quantitative structure activity relationships (QSAR) which make use of a variety of statistical methods.

Non-quantitative methods such as the Topliss approach also are popular. Computer aided design, docking studies including quantitative energy calculations and graphical methods have been rapidly introduced in the pharmaceutical industry. It is too early to evaluate the effects of these methods on drug discovery.[3]

Medicinal chemistry is devoted to discovery and development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic organic compounds. Inorganic compounds continue to be important in therapy, for example, as antacids, mineral supplements and radiopharmaceuticals, but organic molecules with increasingly specific pharmacological activities are clearly dominant.

The process of establishing a new pharmaceutical is exceedingly complex and involves the talents of people from a variety of disciplines, including chemistry, biochemistry, molecular biology, physiology, pharmaceutics and medicine. The medicinal chemistry is concerned mainly with the organic, analytical, and biochemical aspects of this process, but its scientists must interact productively with those in other disciplines. The advances in molecular biology and computer science are now having revolutionary influence on drug design and production. Recombinant DNA technology and new cloning methods are making great impact.[4]

Acyl ureas have a long history of human use as a component of plant-derived scents and flavourings. It belongs to the class of auxin, which is recognized as plant hormones regulating

cell growth and differentiation. The cinnamoyl functionality is also present in a variety of secondary metabolites of phenyl propanoid biosynthetic origin.

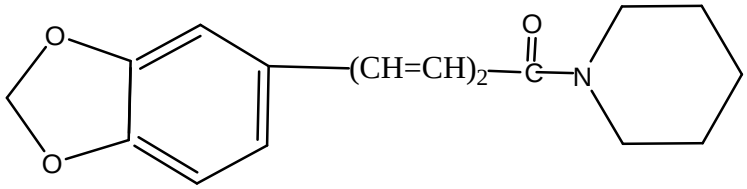
Acyl urea exhibiting various pharmacological activities like Anti tumor, antimicrobial, Anticonvulsant, Sedative-hypnotic activity etc.

Piperine is one of the most useful derivatives of acyl ureas and have been described as effective anticonvulsant agents that antagonize convulsions induced by physical and chemical methods. They also have sedative, hypnotic, tranquilizing and muscle relaxing actions and can intensify depressive actions of other depressants when used in combination. Antiepilepsirine, one of the derivatives of piperine is used as an antiepileptic drug in treating different type of epilepsy.

Acyl Ureas Related Compounds Having Different Pharmacological Activities

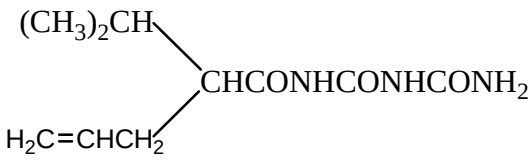
Anticonvulsant activity

On the basis of these findings more than 100 derivatives have been synthesized and anticonvulsant activity of these has been studied. Structural formulae of some of these are as follows:



Piperine

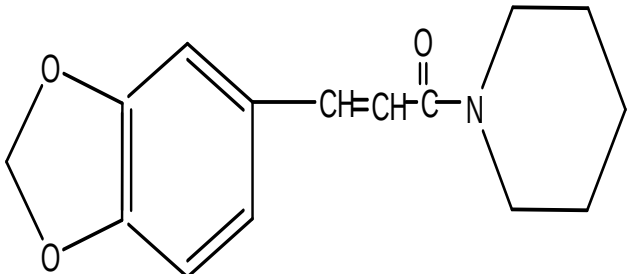
- Now a day's urea derivatives have been used in man for many years and are considered to be safe, short acting mild hypnotics. Urea derivatives have muscle relaxant and anticonvulsant activities also. They can be used in the treatment of agitated states and in the management of withdrawal from alcohol. Long term therapy in geriatrics produced favorable effects in sleep latency.[18]



Sedormid

- Valproic acid (VPA) is a major antiepileptic drug (AED); however, its use is limited by two life-threatening side effects: teratogenicity and hepatotoxicity. Several constitutional isomers of VPA and their amide and urea derivatives were synthesized and evaluated in three different anticonvulsant animal models and a mouse model for AED-induced teratogenicity. The urea derivatives of three VPA constitutional isomers propyl isopropyl acetylurea, di isopropyl acetylurea and 2-ethyl-3-methyl-pentanoylurea displayed a broad spectrum of anticonvulsant activity in rats with a clear superiority over their corresponding amides and acids. These potent urea derivatives caused neural tube defects, but only at doses markedly exceeding their effective dose, whereas VPA showed no separation between its anticonvulsant activity and teratogenicity.

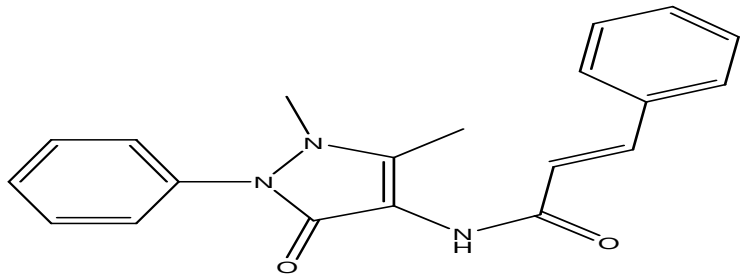
- A survey of literature revealed that Acyl ureas have been synthesized which proves to be an effective antiepileptic drug. Its chemical structure places it in the group of cinnamamides.[19]



Antiepilepsirine

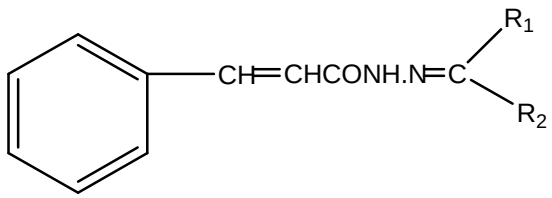
Antimicrobial activity

Jitareanu A *et al., (*2014) synthesized Four new amides of cinnamic acid derivatives (cinnamic acid, p-coumaric acid, ferulic acid and caffeic acid) and 4- aminoantipyrine and their structure was confirmed (1H-NMR, 13C-NMR, FTIR and elemental analysis). Some of their biological properties were evaluated: **antimicrobial and antioxidant** (DPPH radical scavenging activity, Fe3+ reducing power). The tested compounds were more effective against Staphylococcus aureus than the corresponding free acids, but presented no effect on Gram negative bacteria and Candida albicans.

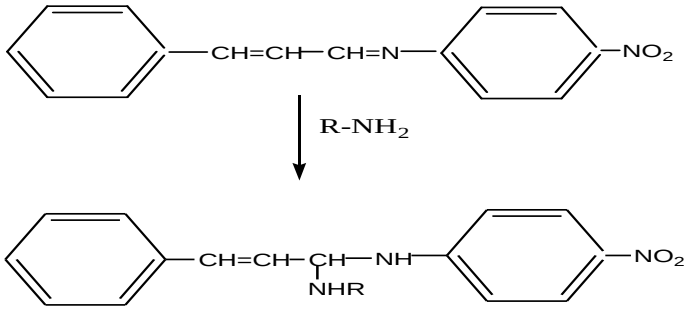


N-(2,3-dimethyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrazol-4-yl) cinnamamide

- **Letcher *et al.*,** have pointed out that hydrazones are most effective as MAO inhibitor than corresponding hydrazines. It was therefore considered of interest to synthesize some cinnamoyl hydrazones for pharmacological evaluation. Twelve new N-cinnamoyl-N'-arylidene hydrazine derivatives were prepared using absolute ethanol or acetic acid as reaction medium. The antibacterial activity of the compounds, in DMF as solvent, was tested by cup-cylinder method. It is evident from the data that almost all Cinnamoyl arylidene hydrazine's exhibit bactericidal action**.** All the Cinnamoyl arylidenehydrazines exhibit bactericidal action on all organisms employed in the study. In general all the compounds show greater antibacterial activity on gram negative organism as compared to gram positive organisms. Furfural cinnamoyl hydrazones is found to be most effective compound.



- Addition of cyanide ion to N-cinnamylidene methylamine and N-cinnamylideneaniline was reported. Mode of addition of primary amines, as nucleophiles to N-cinnamyldiene-p-nitroaniline. The presence of powerful electronegative nitro group helps in boosting its polarization and thus facilitates the addition of the more nucleophilic amine.[25]



Antitumor activity

Sondhi SM *et al.,* synthesized, anticancer and anti-inflammatory activity evaluation of methanesulfonamide and amidine derivatives of 3,4-diaryl-2-imino-4-thiazolines, by Condensation of 3, 4-diaryl-2-imino-4-thiazolines 1a–j with methane sulfonyl chloride gave methane sulfonamide derivatives 2a–j. Condensation of 2-cyanopyrazine, 4-cyanopyridine, and 2-cyanopyridine with 3,4-diaryl-2- imino-4-thiazolines 1h–m in the presence of sodium methoxide afforded amidine derivatives 3a–j. Compounds 2a–j and 3a–j were screened against various human cancer cell lines (COLO-205, HEP-2, A-549, IMR-32) and their percentage growth inhibition profile determined at 1×10^{-5}M. The anti-inflammatory activity of these compounds was assessed using the carrageenan-induced paw edema model.

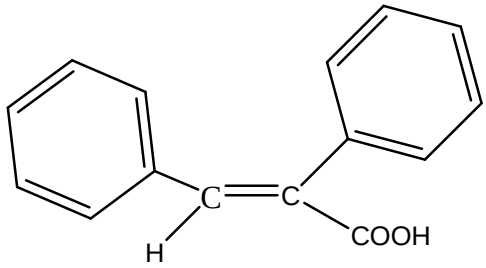
Song DQ *et al.,* reported, Synthesis and activity evaluation of phenylurea derivatives as potent antitumor agents N-3-haloacylaminophenyl-N'-(alkyl/aryl) urea analogs were designed and synthesized. Among these analogs, the compounds 16j bearing bromoacetyl at the N'-end exhibited a potent activity against eight human tumor cell lines, including CEM (leukemia), Daudi (lymphoma), MCF-7 (breast cancer), Bel-7402 (hepatoma), DU-145 (prostate cancer), DND-1A (melanoma), LOVO (colon cancer) and MIA Paca (pancreatic cancer), with the IC(50) values between 0.38 and 4.07 microM. Interestingly, compound 16j killed cancer cells with a mechanism independent of the tubulin-based mechanism, indicating a significant change of the action mode after the structure modification.

Chhikara B S, *et al.,* reported a Fatty acyl amide derivatives of doxorubicin were synthesized with the expectation to improve the lipophilicity and anticancer activity of the drug. The lipophilicity was enhanced with the increase in chain length of fatty acyl moiety. Conjugation of 4'-amino group with fatty acids through an amide bond reduced the anticancer activity in leukemia, breast, ovarian, and colon cancer cell lines, suggesting that the presence of free amino group is required for anticancer activity of doxorubicin. Dodecanoyl-doxorubicin derivative was consistently the most effective among the synthesized derivatives and inhibited the proliferation of colon (HT-29) and ovarian (SK-OV-3) cancer cells by 64% and 58%, respectively, at a concentration of 1 μM after 96 h incubation.

Jiang X, Zhen Y *et al.,* reported the antitumor activity of cinnamamide (CNM), an agent acting on matrix metalloproteinase (MMP), was investigated in the present study. CNM displayed low cytotoxicity. By the MTT assay the IC50 (50% inhibitory concentration) values of CNM on cell proliferation ranged from 1.29 to 1.94 mM in human oral epidermoid

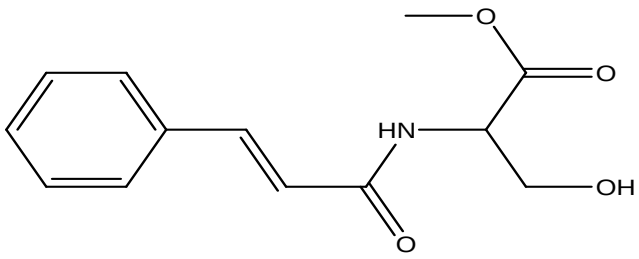
carcinoma KB cells, human hepatoma BEL-7402 cells and human fibrosarcoma HT-1080 cells. Moreover, the IC50 for human fetal lung 2BS cells reached 4.33 mM.

Eleni Pontiki *et al.*, (2014) synthesized cinnamic acids by Knoevenagel condensation reactions and evaluated for the above biological activities. Compound **4ii** proved to be the most **potent LOX inhibitor**. Phenyl substituted acids showed better inhibitory activity against soybean LOX, The compounds have shown very good activity in different antioxidant assays. The antitumor properties of these derivatives have been assessed by their 1/IC50 inhibitory values in the proliferation of HT-29, A-549, OAW-42, MDA-MB-231, HeLa and MRC-5 normal cell lines. The compounds presented low **antitumor activity** considering the IC50 values attained for the cell lines, with the exception of compound **4ii**. Molecular docking studies were carried out on cinnamic acid derivative **4ii** and were found to be in accordance with our experimental biological results.



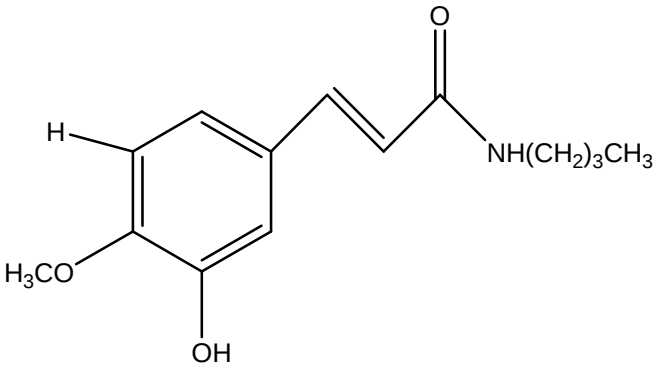
(*E*)-2,3-diphenylacrylic acid

Teni Ernawati *et al.*, *(*2014) synthesized Cinnamic acid derivative compound which firther was investigated for the **anti-cancer inhibitory activity**. To be able to obtain compounds that have bioactivity as above, it is needed to study quantitative structure-activity relationship (QSAR) which is the process by which the chemical structure is quantitatively correlated with biological activity/chemical reactivity. Chemical methods used in synthesizing the chemical of methyl *trans*-cinnamate derivatives are tailored to match their targeted bioactivities. Here, we investigated the anti-cancer inhibitor compound with the method amidation of cinnamic acid derivative compounds.



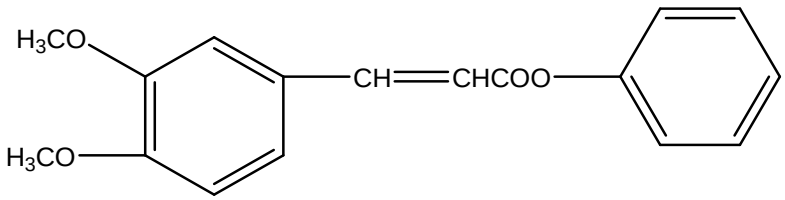
Methyl 2-cinnamamido-3-hydroxy propanoat

Tsenka Milkova *et al.*, *(*2014) synthesized Seventeen cinnamoyl-, feruloyl- and sinapoyl- amino acids amides have been synthesized using the standard methods in peptide chemistry. The antioxidant activity of six feruloyl- and three sinapoyl- amino acid amides was studied on the oxidation stability of a lipid system. Some of the synthesized compounds have been tested for their antibacterial and antiviral activity. Twenty three N-alkylcinnamoyl amides have been prepared in solution and by sonochemical and microwave activated Wittig reaction. Some of the synthesized hydroxycinnamoyl amides were tested for their antiradical activity by DPPH* tests.



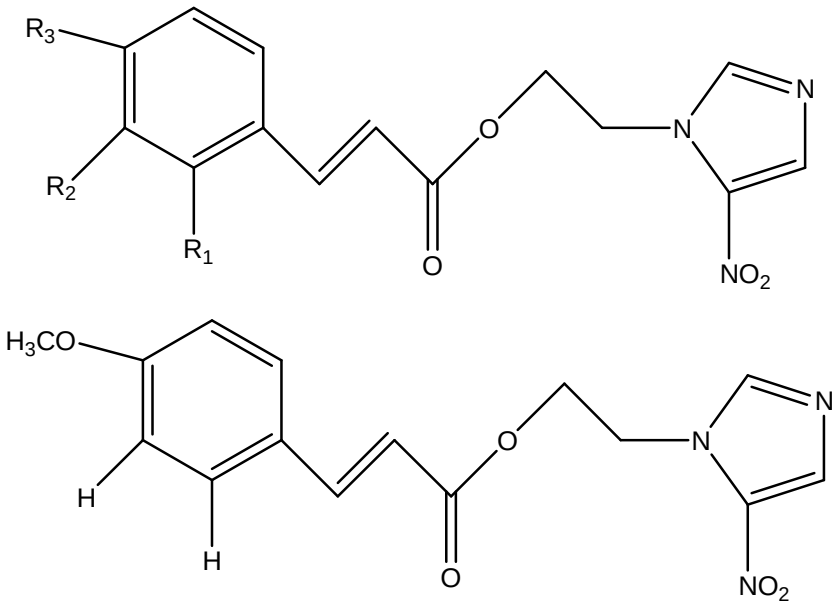
(*E*)-*N*-butyl-3-(3-hydroxy-4-methoxyphenyl)acrylamide

L.P Zhang *et al.*, *(*1992) synthesized nineteen cinnamic acid derivatives, their esters and related styryl ketones. among them Ia, Ib, Ic, II2c showed significant inhibiting effect on croton oil induced mouse ear edema. Ib, II5a, II5c exhibited good activity on HL-60 human cancer cells in vitro.



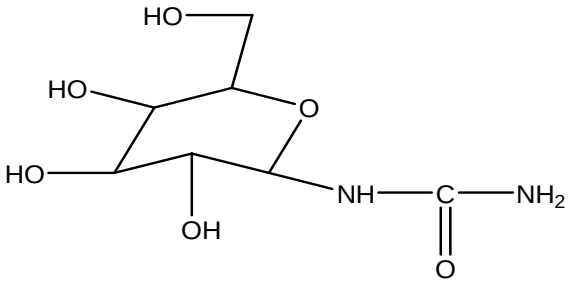
Yong Qian *et al.*, *(*2010) synthesized a series of novel cinnamic acid metronidazole ester derivatives and their biological activities were also evaluated as potential EGFR and HER-2 kinase inhibitors. Compound 3h showed the most potent biological activity (IC50 = 0.62 lM for EGFR and IC50 = 2.15 lM for HER-2). Docking simulation was performed to position compound 3h into the EGFR active site to determine the probable binding model. Antiproliferative assay results demonstrated that some of these compounds possessed good

antiproliferative activity against MCF-7. Compound 3h with potent inhibitory activity in tumor growth inhibition may be a potential anticancer agent.



(*E*)-2-(5-nitro-1*H*-imidazol-1-yl)ethyl 3-(4-methoxyphenyl)acrylate

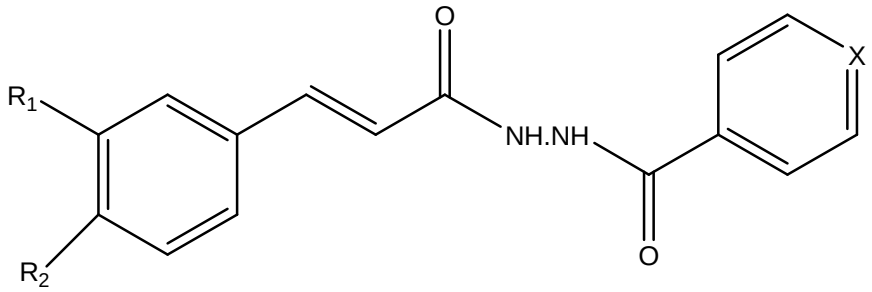
Matthew J. McKay *et al.*, (1987) reviewed about glycosyl urea derivatives that the area of sugar urea derivatives has received considerable attention in recent years because of the unique structural properties and activities that these compounds display. The urea-linkage at the anomeric center is a robust alternative to the naturally occurring O- and N-glycosidic linkages of oligosaccharides and glycoconjugates and the natural products that have been identified to contain these structures show remarkable biological activity.



1-(tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2*H*-pyran-2-yl)urea

Prithwiraj De *et al.*, (2007) synthesized Cinnamic Derivatives by reacting with the suitable cinnamoyl chlorides in the presence of 4-*N*, *N*-dimethylaminopyridine (DMAP) in benzene. All the hydroxyl-cinnamic acids were acetylated to protect the phenolic group before generating the corresponding acid chlorides followed by coupling with the triterpenes. The hydroxycinnamate derivatives of the triterpenes (21d, f, h; 22d, f, h; 23d, f, h) were easily obtained by deacetylation of the acetylated derivatives (21c, e, g; 22c, e, g; 23c, e, g) using

K_2CO_3 in methanol. The biological results indicated that the introduction of unsubstituted or *p*-chlorinated cinnamate ester functionality (21a, b; 22a, b; 23a, b) led to inactive compounds (MIC>200 µg/mL) or without any improvement in the **antimycobacterial activity** of the native triterpenes.



ACKNOWLEDGEMENT

We thank Prof. S. Riaz Hashim (Faculty of Chemistry, Ex Research Scientist, Hyderabad), Prof. Shuaib, Mr. Prem Shankar Mishra for progressive discussion and support for research study.

REFERENCES

1. Speranta Avram a*, I. Svab b, C. Bologa c, Maria-Luiza Flonta "A cyclic urea derivatives used as HIV-1 protease inhibitors, A 3D-QSAR-CoMFA method for new antiviral drug design" J. Cell. Mol. Med., 2003; 7(3): 287-296.
2. Xiao-hui MA, Xiao-yi ZHANG, Jian-jun TAN, Wei-zu CHEN, Cun-xin WANG2 "Exploring binding mode for styrylquinoline HIV-1 integrase inhibitors using comparative molecular field analysis and docking studies"; Acta Pharmacol Sin., 2004 Jul; 25(7): 950-958.
3. Eduardo Borges De Melo; "A QSAR Study of Matrix Metalloproteinases Type 2 (MMP-2) Inhibitors with Cinnamoyl Pyrrolidine Derivatives"; Sci Pharm., 2012; 80: 265–281.
4. S Prakash1, D Maji 2*, S Samanta 2 and RK Sinha3 Design, "Synthesis and Antidiabetic, Cardiomyopathy Studies of Cinnamic Acid-Amino Acid Hybrid Analogs" Med chem, an open access journal, 2014; 4(2): 345-350.
5. Nuzul Wahyuning Diyah*, Juni Ekowati*, Siswandono "synthesis and antitumor activity evaluation of n, n'-dibenzoyl-n, n'-diethylurea against human breast cancer cell line (mcf-7)" International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6(2): 0975-1491.

6. Amita Mishra and Sanjay Batra* "Thiourea and Guanidine derivatives as Antimalarial and Antimicrobial agents" Current Topics in Medicinal Chemistry, 2013; 13(16): 2011-25.
7. Eleni Pontiki [1,]*, Dimitra Hadjipavlou-Litina [1,]*, Konstantinos Litinas[2] and George Geromichalos "Novel Cinnamic Acid Derivatives as Antioxidant and Anticancer Agents: Design, Synthesis and Modeling Studies" Molecules, 2014; 19(7): 9655-9674.
8. Wei-Ming Zhang,[ab] Man Xing,[ab] Ting-Ting Zhao,[ab] Yu-Jia Ren,[ab] Xian-Hui, Yang,[ab] Yu-Shun Yang,[ab] Peng-Cheng Lv*[ab] and Hai-Liang Zhu*[a] "Synthesis, molecular modeling and biological evaluation of cinnamic acid derivatives with pyrazole moieties as novel anticancer agents" RSC Advances, 2014; 4: 37197-37207.
9. Ram Thaimattam Ram Thaimattam, Pankaj Daga, Shaikh Abdul Rajjak, Rahul Banerjee, Javed Iqbal "3 D QSAR COMFA,COMSIA Studies on substituted ureas as RAF-1 Kinase inhibitors and its confirmation with structure based studies" Bioorg. Med. Chem., 2004 Dec; 12(24): 6415-25.
10. Valentina Anuta, George Mihai Nitulescu*, Cristina Elena Dinu-Pîrvu and Octavian Tudorel Olaru; "Biopharmaceutical Profiling of New Antitumor Pyrazole Derivatives" Molecules, 2014; 19: 16381-16401.
11. Xin Zhai, Qiang Huang, Nan Jiang, Di Wu, Hongyu Zhou and Ping Gong* "Discovery of Hybrid Dual N-Acylhydrazone and Diaryl Urea Derivatives as Potent Antitumor Agents.
12. Bedia Kocyigit-Kaymakcioglu 1,* Ahmet Ozgur Celen 1, Nurhayat Tabanca 2, Abbas Ali 2, Design, Synthesis and Cytotoxicity Evaluation" Molecules, 2013; 18: 2904-2923.
13. Shabana I. Khan 2, 3, Ikhlas A. Khan 2, 3 and David E. Wedge Synthesis and Biological Activity of Substituted Urea and Thiourea Derivatives Containing 1, 2, 4-Triazole Moieties Molecules, 2013; 18: 3562-3576.
14. Ali Mohammad1, Fauzia Bano Faruqi1 and Jamal Mustafa2; "Edible compounds as antitumor agents" Indian Journal of Science and Technology, May 2009; 2(5): 62-69.
15. Yong Qian, Hong-Jia Zhang, Hao Zhang, Chen Xu*, Jing Zhao*, Hai-Liang Zhu* "Synthesis, molecular modeling and biological evaluation of cinnamic acid metronidazole ester derivatives as novel anticancer agents" Bioorganic & Medicinal Chemistry, 2010; 18: 4991–4996.
16. Yoshimi Aoyagi, 1 Norio Masuko, Shuichi Ohkubo, Makoto Kitade, Kentaro Nagai, Shinji Okazaki, Konstanty Wierzba, Tadafumi Terada, Yoshikazu Sugimoto and Yuji Yamada Cancer Sci, | September 2005 | vol. 96 | no. 9 | 614– 619.

17. Evandro Luís de Oliveira Niero and Gláucia Maria Machado-Santelli* "Cinnamic acid induces apoptotic cell death and cytoskeleton disruption in human melanoma cells" Journal of Experimental & Clinical Cancer Research, 2013; 32: 31.
18. Prithwiraj De1, 2, Damien Veau1, 2, Florence Bedos-Belval1, 2, Stefan Chassaing1, 2 and Michel Baltas1, 2 "Cinnamic Derivatives in Tuberculosis" www.intechopen.com, 337-339.
19. Tingting Yang and Guohua Gao* "Synthesis and characterization of novel N-acyl cyclic urea derivatives", ARKIVOC, 2012; (vi): 304-316.
20. Anatoly D. Shutalev*, Ekaterina A. Kishko, Natalie V. Sivova and Aleksei Yu. Kuznetsov, "A New Convenient Synthesis of 5-Acyl-1, 2, 3, 4-tetrahydropyrimidine-2-thiones/ones" Molecules, 1998; 3: 100–106.
21. Sham M Sondhi, Reshma Rani, P P Gupta, "Synthesis, anticancer and anti-inflammatory activity evaluation of methanesulfonamide and amidine derivatives of 3, 4-diaryl-2-imino-4-thiazolines" Molecular Diversity Volume 13, Number 3, 357-366, DOI: 10.1007 /s 11030-009-9125.
22. Dan-Qing Song[†], Na-Na Du[†], Yue-Ming Wang, "Synthesis and activity evaluation of phenylurea derivatives as potent antitumor agents"; Bioorganic & Medicinal Chemistry, 1 June 2009; 17(11): 3873–3878.
23. Chhikara BS, St Jean N, Mandal D, Kumar A, Parang K; "Fatty acyl amide derivatives of doxorubicin: synthesis and in vitro anticancer activities" Eur J Med Chem., 2011 Jun; 46(6): 2037-42.
24. Jiang X, Zhen Y Cinnamamide, "An antitumor agent with low cytotoxicity acting on matrix metalloproteinase". Anticancer Drugs., 2000 Jan; 11(1): 49-54.
25. Balsamo, P. L. Barili, P. Crotti, B. Macchia, F. Macchia, A. Pecchia, A. Cuttica, N. Passerini "Structure-activity relations in cinnamamides, Synthesis and pharmacological evaluation of some (E)- and (Z)-N-alkyl-.alpha., beta.-dimethylcinnamamides" J. Med. Chem., 1975; 18(8): 842–846.