



QUINAZOLINE: UNIQUE AND VERSATILE PHARMACOPHORE IN THE FIELD OF CANCER

Gollapalli Naga Raju*, Nomula Venkata Naga Sai Vijaya Lakshmi, Mutyala Sai Meghana,
Rama Rao Nadendla

Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences,
Guntur, Andhra Pradesh, India.

Abstract:

Quinazolines are the most important class of heterocyclic compounds. Quinazoline is a bicyclic compound consisting of a pyrimidine system fused at 5, 6 with benzene ring. Quinazoline is considered as an important chemical synthesis of various physiological significance and pharmacological utility. Cancer is a disease characterized by uncontrollable, irreversible, independent, autonomous, uncoordinated and relatively unlimited and abnormal over growth of tissues. The drugs containing Quinazoline groups were the first effective chemotherapeutic agents which were systematically proved for the prevention and cure of bacterial infection in human beings. Literature revealed that Quinazoline derivatives may serve as an important model on as potent anti-cancer agent. When one biological active molecule is linked to another, resultant molecule generally has increased potency. Most of the derivatives showed enhanced anti-cancer activity. So, Quinazoline derivatives can serve as future therapeutic leads for the discovery of anti-cancer drugs. This review was focused on the Quinazolines and its different derivatives that possess anticancer activities.

Keywords: *Quinazolines, Cancer, Cytotoxic Activity, Antiproliferative Activity, Antitumor activity.*

Corresponding Author:

Gollapalli Naga Raju,

Assistant Professor,

Department of Pharmaceutical Analysis,

Chalapathi Institute of Pharmaceutical Sciences,

Lam, Guntur, Andhra Pradesh - 522034, India.

Email: rajaneeraja@gmail.com

Contact no: +919966788710

QR code



Please cite this article in press as Nagaraju. G et al. *Quinazoline: Unique and Versatile Pharmacophore in the Field Of Cancer*, Indo American J of Pharm Sci, 2015;2(4):827-832.

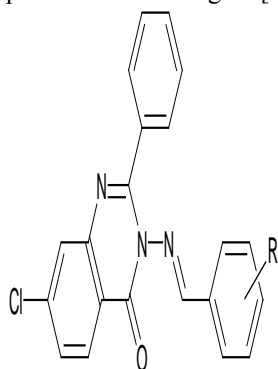
INTRODUCTION:

Heterocyclic chemistry is a chemistry involving the heterocyclic compounds which contain atoms of atleast two different elements as number of ring. The heterocyclic may be inorganic, though the compound has carbon atoms in the ring, the word hetero means different from carbon and hydroge Nitrogen containing heterocyclic compounds plays an important role in medicinal chemistry. Quinazolines are a large class of active chemical compounds exhibiting a broad spectrum of biological activities in animals as well as in humans. Literature studies on quinazolines have shown that these derivatives possess a wide variety of biological activities such as antidiabetic[1], antiviral[2], antibacterial[3], anticonvulsant[4], anti-inflammatory[5], CNS depressant[6], antimalarial[7], antimicrobial[8], antifungal[9], antioxidant[10], anthelmintic[11] activity.

Quinazoline is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. This review was focused on the Quinazolines and its different derivatives that posses anticancer activities.

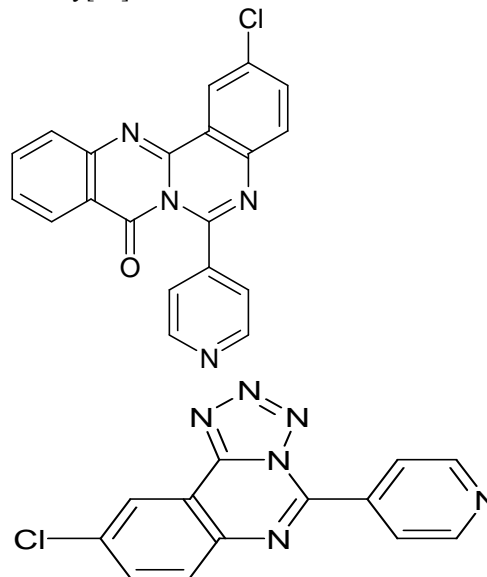
Anticancer activity of Quinazoline derivatives:

A novel 3-(substituted benzylideneamino)-7-chloro-2-phenyl quinazoline-4(3H)-one has been synthesized by Malleshappa N. Noolvi and Harun M. Patel. Rational approach and QSAR techniques enabled the understanding of the pharmacophoric requirement for 2,3,7-tri substituted quinazoline derivatives to inhibit EGFR-*tyrosine kinase* as antitumor agents and could be used as an excellent framework in this field that may lead to discovery of potent anti tumor agent [12].

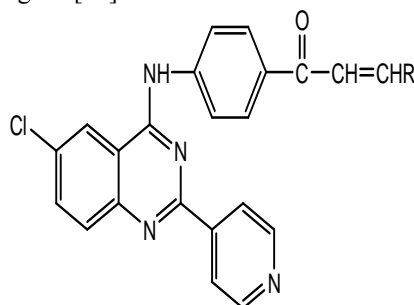


R = H	R = 4-OH
R = 3-Br	R = 2,3-Dmethoxy
R = 4-CN	R = 4-CH ₃
R = 2-Cl	R = 3-NO ₂
R = 4-Cl	R = 4-NO ₂
R = 4-N(CH ₃) ₂	R = 2-NO ₂
R = 2-OCH ₃ , 4-OH	R = 4-Br
R = 4-OCH ₃	R = 4-F
R = 2-OH	R = 3,4-Dihydroxy
	R = 3-OH

Salman et al worked on the Design, synthesis and biological evaluation of Novel Quinazoline Derivatives. Some of the synthesized compounds were screened for human liver cell line (HepG2) activity[13].

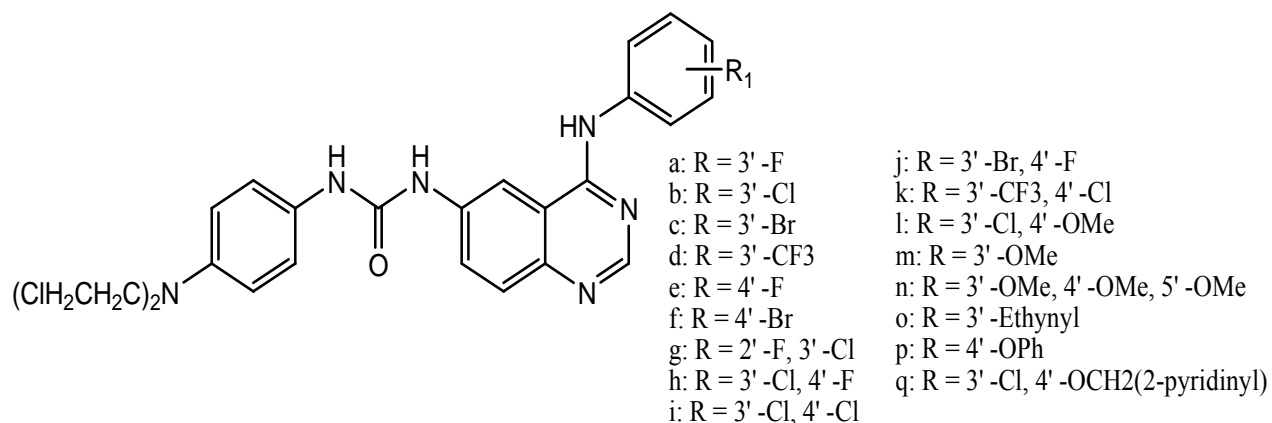


New Quinazoline derivatives were synthesized by Salman et al. All newly synthesized compounds were screened for their anticancer studies. The results revealed that some of the synthesized compounds have a significant biological activity as anticancer agents[14].

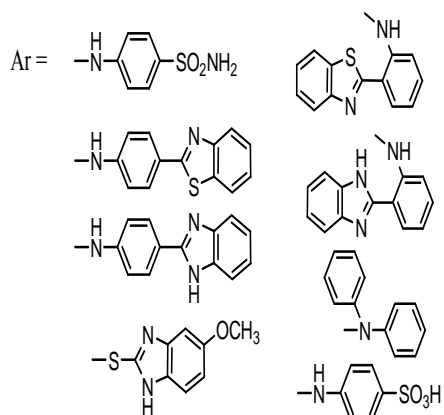
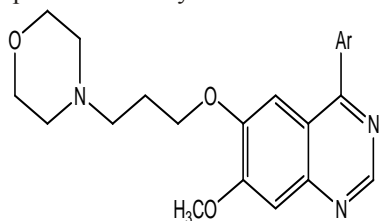


- a. R = Phenyl
- b. R = 4-Methoxyphenyl
- c. R = 4-Chlorophenyl
- d. R = 4-Nitrophenyl

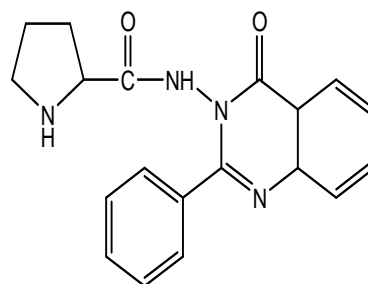
A series of N-mustard-quinazoline conjugates was synthesized by B. Marvania et al and subjected to antitumor studies. The preliminary antitumor studies revealed that these agents exhibited significant antitumor activity in inhibiting various human tumor cell growths *in-vitro*[15].



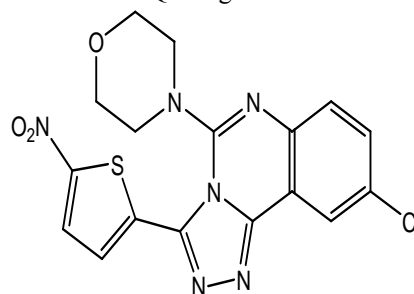
Bhavesh Prajapati et al synthesized Morpholino Propoxy Quinazoline Derivatives. All synthesized compounds were tested for their cytotoxicity by MTT assay. Among all the synthesized derivatives, compound-II was shown promising anticancer activity as compared to other synthesized derivatives[16].



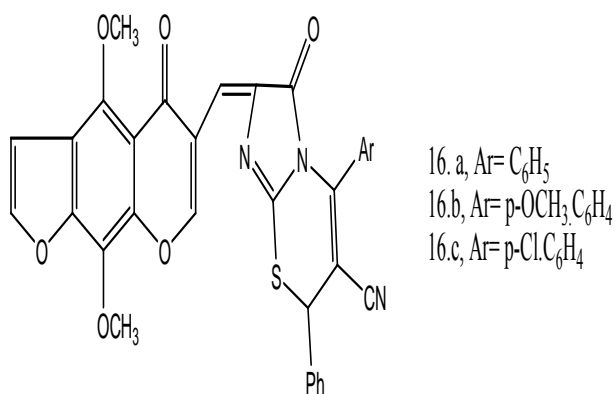
Manish Chaudhari et al synthesized some of the Novel Quinazoline Derivatives and screened for the Anticancer and Anti-Microbial activities[17].



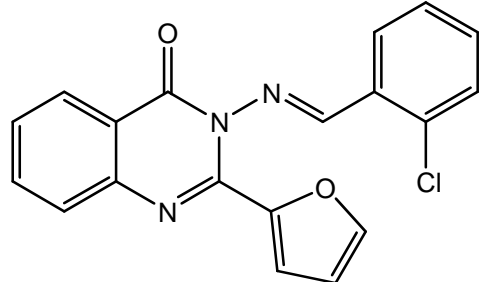
Renata Ovadekova et al studied the Cytotoxicity and Detection of Damage To DNA By 3-(5-Nitro-2-Thienyl)-9-Chloro-5-Morpholin-4-Yl[1,2,4]Triazolo[4,3-C]Quinazoline On Human Cancer Cell Line HeLa. A new synthetically prepared quinazoline derivative was the most effective derivative in our primary cytotoxic screening. In this study, we evaluated cytotoxic/antiproliferative activity of NTCHMTQ using human tumor cell line HeLa[18].



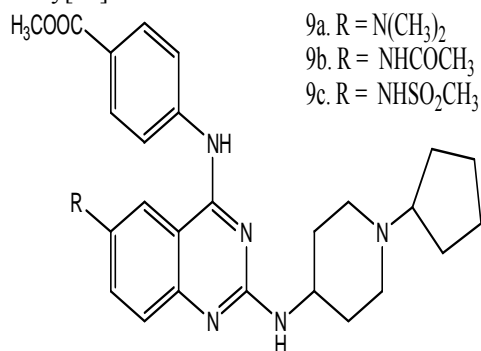
Asmaa A. Magd-El-Din et al carried out the Synthesis of Potent Antitumor Oxo Quinazoline, Pyrazole and Thiazine Derivatives. Compounds were tested against sixteen different human cancer cell lines and most of the compounds were superior to the familiar comparative standards[19].



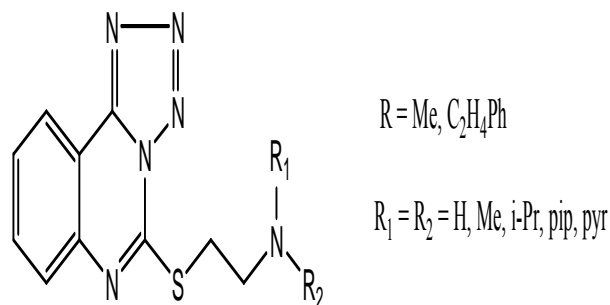
S.N. Manjula, et al was synthesized novel Quinazoline derivatives. These were evaluated for their anti-tumor activity against Ehrlich ascites carcinoma (EAC) and two different concentrations were evaluated for their antitumor activity against Dalton's ascites lymphoma (DLA) bearing Swiss albino mice [20].



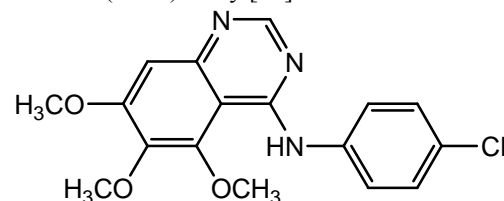
A variety of novel 2-(1-substituted-piperidine-4-ylamino)quinazoline derivatives were prepared WANG Yong-kang, et al, and their antiproliferative activities on five cancer cell lines were evaluated by MTT assay[21].



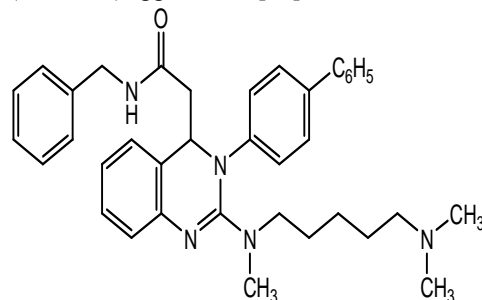
Tetrazolo[1,5-c]quinazoline-5-thione S-Derivatives have been synthesized by L. M. Antypenko et al. The substances were screened for antibacterial and antifungal activities. The substances were screened for their ability to inhibit 60 different human tumor cell lines [22].



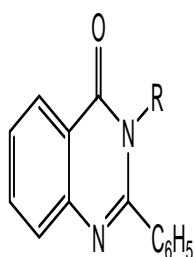
N-(4-chlorophenyl)-5,6,7-trimethoxyquinazolin-4-amine dihydrochloride were synthesized by Huang et al. The anticancer activities of N-(4-chlorophenyl)-5,6,7-trimethoxyquinazolin-4-amine dihydrochloride against four kinds of cell lines were evaluated by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay [23].



A series of 3,4-dihydroquinazoline derivatives were studied by Gi Hyun Kwon et al with anti-cancer activities against human colon cancer HT-29 cell were subjected to three-dimensional quantitative structure-activity relationship (3D-QSAR) studies using the comparative molecular similarity indices analysis (CoMSIA) approaches [24].

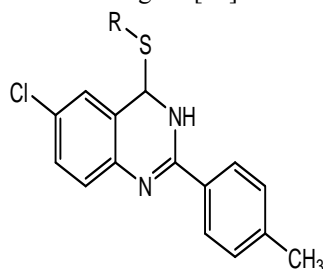


Synthesis of some new quinazoline derivatives were reported by K. Manasa et al. All the synthesized compounds have been screened for their antioxidant and anticancer activity [25].



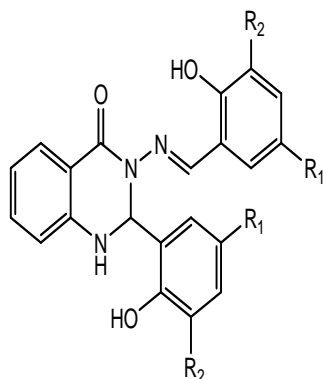
R = Phenyl, p-Chlorophenyl, p-Nitrophenyl,
p-Bromophenyl, 3-Chlorophenyl, p-Tolyl

Novel derivatives of quinazoline have been synthesized by A.S. El-Azab et al and tested for their antitumor activity against three tumor cell lines among these cell lines the human breast carcinoma cell line (MCF-7) in which EGFR is highly expressed. All tested compounds showed potent and selective activity against breast cancer (MCF-7) with IC₅₀ range of 3.35e6.81 mg/ml [26].



1: R=CH₃
2: R=CH₂Ph
3: R=CH₂CN
4: R=allyl
5: R=3-NO₂-2-pyridine
6: R=CH₂CH₂OH

Two new synthesized and characterized quinazoline Schiff bases were investigated for anticancer activity against MCF-7 human breast cancer cell line by Fadhil Lafta Faraj et al. Results showed significant activity towards MCF-7 cells via either intrinsic or extrinsic mitochondrial pathway and are potential candidate for further *in-vivo* and clinical breast cancer studies [27].



(1) R₁ = Br
(2) R₂ = H, OCH₃

CONCLUSION:

Quinazoline exhibits a wide range of biological properties due to its potent biological activities. It is a versatile tool in the field of cancer amongst all activities. It produces anticancer activities not only by interacting with heterocyclic ring but also through various inorganic complexes. It can be concluded that this class of compounds certainly holds great promise

towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress. The biological profiles of these new generations of Quinazolines represent much progress with regard to the older compounds. Hence this unique molecule must act like a boon in the field of developing various synthetic anticancer agents.

ACKNOWLEDGEMENT:

The authors are grateful to Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, Guntur for providing facilities to perform this review work.

REFERENCES:

1. Srinivas S et al, Design, Synthesis, Biological Evaluation and Molecular Docking Studies of Novel Quinazoline Derivatives as GSK-3 β Inhibitors, *World Journal of Pharmacy and Pharmaceutical Sciences*, Volume 2, Issue 6, 5842-5851.
2. Suresh Kumar Krishnan et al, Synthesis, Antiviral and Antimicrobial Activities of Quinazoline Urea Analogues, *International Journal of Drug Design and Discovery*, Volume 4, Issue 4, October–December 2013.
3. Nagaraju Gollapalli et al, Synthesis and Biological Evaluation of Phenyl- Quinazoline Derivatives, *A J P A M C*. 1(1), 2013, 48- 53.
4. L. M. Antypenko et al, Design and Evaluation of Novel Antimicrobial and Anticancer Agents Among Tetrazolo[1,5-c]quinazoline-5-thione S-Derivatives, *Sci Pharm*. 2013; 81: 15–42.
5. Sinha et al, A Novel Approach towards Development of Quinazoline Derivatives in Pain Management, *Asian J Pharm Clin Res*, Vol 6, Suppl 3, 2013, 200-204.
6. M. Shahar Yar et al, Synthesis and Antihypertensive Screening of New Derivatives of Quinazolines Linked with Isoxazole, *BioMed Research International*, Volume 2014, Article ID 739056, 13 pages.
7. Mohammed Hussien Bule et al, Synthesis and *In-Vivo* Pharmacological Evaluation of Some Novel 4(3H)-Quinazolinone Derivatives as Potential Anti-Malarial Agents, *Indo American Journal of Pharmaceutical Research*, Vol 5, Issue 02, 2015.
8. Dhaval J. Patel et al, Synthesis and antimicrobial activity of some new quinazoline derivatives, *Der Chemica Sinica*,

- 2014, 5(2):37-43.
9. Sharma GVR et al, A Formal and Simple Synthesis of an Antifungal Quinazolinone of Marine Source, *Nat Prod Chem Res* 2014, 2:4.
 10. K. Manasa et al, Synthesis, antioxidant and anticancer activity of quinazoline derivatives, *CPR* 1(2), 2011, 101-105.
 11. Theivendren P. Selvam et al, Synthesis, characterization, and anthelmintic activity of novel 6,7,8,9-tetrahydro-5H-5-phenyl-2-benzylidene-3-substituted hydrazino thiazolo (2,3-b) quinazoline derivatives and analogues, *Drug Discoveries & Therapeutics*. 2010; 4(6):392-398.
 12. Malleshappa N. Noolvi and Harun M. Patel, Synthesis, method optimization, anticancer activity of 2,3,7-trisubstituted Quinazoline derivatives and targeting EGFR-tyrosine kinase by rational approach, *Arabian Journal of Chemistry* (2013) 6, 35–48.
 13. Salman et al, Design, synthesis and biological evaluation of Novel Quinazoline Derivatives as Potential Anticancer Agent, *IJRPC* 2014, 4(3), 501-508.
 14. Salman et al, Synthesis and anti-cancer properties of novel quinazoline derivatives, *IJRPC* 2015, 5(1), 34-40.
 15. B. Marvania et al, Design, synthesis and antitumor evaluation of phenyl N-mustard-quinazoline conjugates, *Bioorg. Med. Chem.* 19 (2011) 1987–1998.
 16. Bhavesh Prajapati et al, Synthesis and Preliminary in-vitro Cytotoxic Activity of Morpholino Propoxy Quinazoline Derivatives, *Int.J. ChemTech Res.*2014,6(1),pp 547-555.
 17. Manish Chaudhari et al, Synthesis, Anticancer and Anti-Microbial Characterization of Some Novel Quinazoline Derivatives, *International Journal of Science and Research (IJSR)*, Volume 3 Issue 11, November 2014, 3195-3198.
 18. Renata Ovadekova et al, Cytotoxicity and Detection of Damage To DNA By 3-(5-Nitro-2-Thienyl)-9-Chloro-5-Morpholin-4-Yl[1,2,4]Triazol[4,3-C]Quinazoline On Human Cancer Cell Line HeLa, *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2005, 149(2):455–9.
 19. Asmaa A. Magd-El-Din et al, Synthesis of Potent Antitumor Oxo Quinazoline, Pyrazole and Thiazine Derivatives, *Australian Journal of Basic and Applied Sciences*, 6(3): 675-685, 2012.
 20. S.N. Manjula, et al, *In-vivo* anti-tumour activity of novel Quinazoline derivatives, *European Review for Medical and Pharmacological Sciences*, 2012; 16: 1753-1764.
 21. WANG Yong-kang, et al, Synthesis and antitumor activity of novel 2-(1-substituted-piperidin-4-ylamino)quinazolines as antitumor agents, *Acta Pharmaceutica Sinica* 2012, 47 (9): 1164–1178.
 22. L. M. Antypenko et al, Design and Evaluation of Novel Antimicrobial and Anticancer Agents Among Tetrazolo[1,5-c]quinazoline-5-thione S-Derivatives, *Sci Pharm.* 2013; 81: 15–42.
 23. Huang et al, Antitumor effect of N-(4-chlorophenyl)-5,6,7-trimethoxyquinazolin-4-amine dihydrochloride on tumor cells *in-vitro*, *African Journal of Pharmacy and Pharmacology* Vol. 6(21), pp. 1536-1544, 8 June, 2012.
 24. Gi Hyun Kwon et al, CoMSIA 3D-QSAR Analysis of 3,4-Dihydroquinazoline Derivatives Against Human Colon Cancer HT-29 Cells *Bull. Korean Chem. Soc.* 2014, Vol. 35, No. 11.
 25. K. Manasa et al, Synthesis, antioxidant and anticancer activity of quinazoline derivatives, *CPR* 1(2), 2011, 101-105.
 26. A.S. El-Azab et al, Design, synthesis and biological evaluation of novel quinazoline derivatives as potential antitumor agents: Molecular docking study *European Journal of Medicinal Chemistry* 45 (2010) 4188-4198.
 27. Fadhil Lafta Faraj et al, Synthesis, Characterization, and Anticancer Activity of New Quinazoline Derivatives against MCF-7 Cells, *The Scientific World Journal* Volume 2014, Article ID 212096, 15 pages.