REFERENCES

[1] M. Shahini, B. Ramezanzadeh and H. E. Mohammadloo, *Journal of Molecular Liquids* **2021**, *325*, 115110.

[2] M. Yadav, T. Sarkar and I. Obot, *RSC advances* **2016**, *6*, 110053-110069.

[3] S. A. Umoren, I. B. Obot, A. Madhankumar and Z. M. Gasem, *Carbohydrate polymers* **2015**, *124*, 280-291.

[4] L. Huang, W.-Q. Chen, S.-S. Wang, Q. Zhao, H.-J. Li and Y.-C. Wu, *Environmental Chemistry Letters* **2022**, *20*, 3235-3264.

[5] K. K. Alaneme and S. J. Olusegun, *Leonardo Journal of Sciences* **2012**, *20*, 59-70.

[6] K. Shamsheera, A. R. Prasad, P. Jaseela and A. Joseph, *Chemical Data Collections* **2020**, *28*, 100402.

[7] K. Shamsheera, R. P. Anupama and J. Abraham, *Results in Chemistry* **2020**, *2*, 100054.

[8] M. Mobin and M. Rizvi, *Carbohydrate Polymers* **2016**, *136*, 384-393.

[9] S. Umoren, I. Obot, E. Ebenso, P. Okafor, O. Ogbobe and E. Oguzie, *Anti-corrosion methods and materials* **2006**.

[10] M. M. Fares, A. Maayta and M. M. Al-Qudah, *Corrosion Science* **2012**, *60*, 112-117.

Chapter 11

INDOLE - A PROMISING SCAFFOLD IN BIOCHEMISTRY

Dr. Rajeena Pathoor[*] and Dr. Thasnim P[#]

[*]*PG and Research Department of Chemistry, Sir Syed College, Taliparamba, Karimbam (PO), Kannur (Dt), Kerala, Pin: 670142*
E-mail: rajeenapathoor@gmail.com

[#] *PG Department of Chemistry, KAHM Unity Women's College, Manjeri, Narukara (PO), Malappuram (Dt), Kerala, Pin: 676122*
E-mail: thasnim6390@gmail.com

ABSTRACT

ISBN 978-93-5457-774-1

Because of their various applications in the field of drug design, Photochemistry,agrochemicals, dyes etc., heterocycles generally assume an important place in chemistry. Of these, indole scaffolds, which have also paved the way for developing effective targets, have been identified in most of the important synthetic drug molecules. Privileged structures, while helping the development of novel biologically-active compounds, are bound to multiple receptors with high affinity. The derivatives of indoles exhibit such activities as antibacterial, anticancer, anti-oxidants, anti-inflammatory, anti-diabetic, antiviral, and antiproliferative, antituberculosis.Thus this Chapter throws some light on the wide-ranging biological activities ofindole derivatives as evident in the past two decades, which, the chapter will show, is useful for designing more potent drug targets so as to compete with the existing drugs.

INTRODUCTION

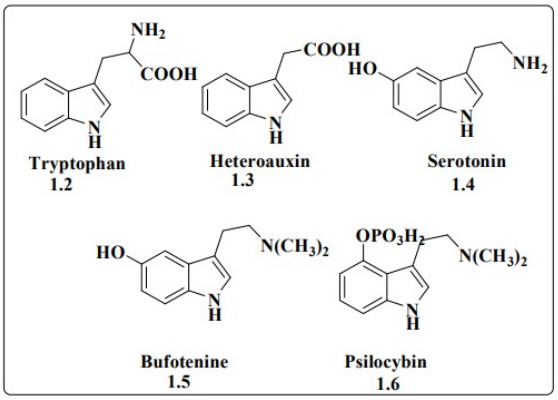
Indole chemistry began with the study of the indigo dye. Indole was first isolated through the treatment of the indigo dye with oleum and hence the name indole which is a portmanteau of the words indigo and oleum. Indole is a benzopyrrole ring system in which the benzene and pyrrole rings are merged through the 2-and 3-positions of the pyrrole nucleus. Indole is wide spread in natural environment and can be produced by a variety of bacteria. The amino acid tryptophan is an indole derivative and the precursor of the neurotransmitter serotonin. Several natural alkaloids with indole as basic ring are therapeutically active. Indole is solid and has the odour of manure, but when highly diluted, it smells like jasmine.

CHEMICAL AND BIOLOGICAL IMPORTANCE

Indole is the parent substance of a large number of important compounds that occur in nature. Tryptophan (2-amino-3-(3′-indolyl) propionic acid) 1.2, is one of the naturally occurring essential amino acids. In higher plants this tryptophan degrades into heteroauxin (indole-3-acetic acid) 1.3, which is a plant hormone. Serotonin 1.4, is an indole derivative

ISBN 978-93-5457-774-1

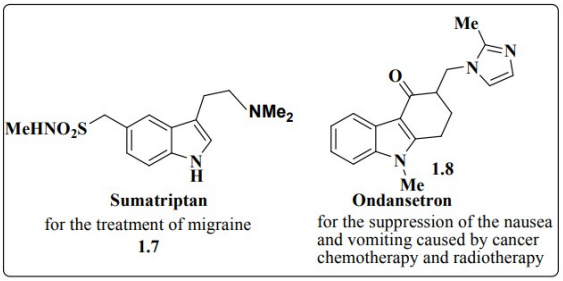
with a hydroxyl group on the benzene ring which is a vasoconstrictor hormone that plays an important role in conducting impulses to the brain. Bufotenine 1.5 and psilocybin 1.6, are indole derivatives that are found in the skins of toads, toxic mushrooms, and West Indian snuff.



Some potent derivatives of indole

Some indole alkaloids exert considerable pharmacological activity. Among the clinically useful alkaloids, three groups are notable: (a) the ergot alkaloids—ergometrine with its direct action on the contraction of uterine muscle, (b) the rauvolfia alkaloids, which is specifically reserpine, and is used as the forerunner of the tranquillisers, (c) the dimeric anti-leukemic alkaloids of catharanthus are vinblastine and vincristine. Tryptophan is an essential amino acid and one of the constituents of most proteins.

The study and classification of 5-hydroxy-tryptamine receptors resulted in the design and synthesis of sumatriptan 1.7, for the treatment of migraine and ondansetron1.8, for the suppression of the nausea and vomiting caused by cancer chemotherapy and radiotherapy.



ISBN 978-93-5457-774-1

Structure of indole derivatives used in chemotherapy

1. BIOLOGICAL ACTIVITIES OF SYNTHETIC MOLECULES CONTAINING INDOLE NUCLEUS

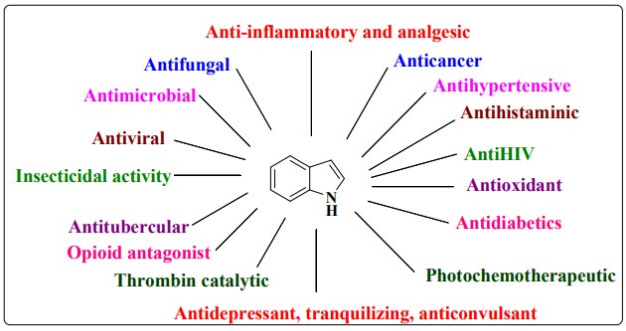
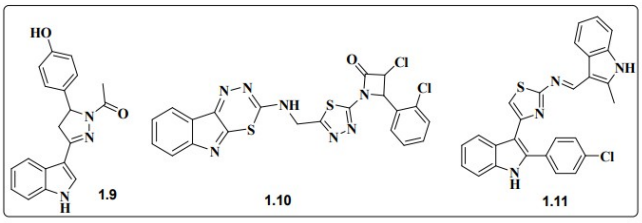


Figure 1.4. Graphical representation of biological activity of indole derivatives.

1.1. ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY

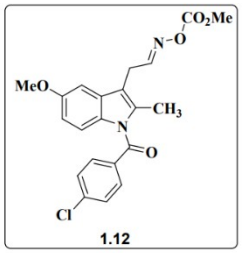
Inflammation is a complex biological response of body tissues due to the hurtful stimuli such as pathogens, irritants and damaged cells. The literature survey has shown that only a few indole based natural anti-inflammatory agents have been reported. A series of bis-indole derivatives were synthesized and evaluated for anti-inflammatory activity by Singh et al. From the study it was confirmed that the bis-indole derivative 1.11 was the most active compound (53.3% at 50 mg/kg dose) of the synthesized series, which showed higher percent of inhibition of oedema, lower ulcerogenic liability and acute toxicity than phenyl butazone (38.8% at 50 mg/kg dose)



ISBN 978-93-5457-774-1

Bis Indole derivatives with potent anti-inflammatory activity

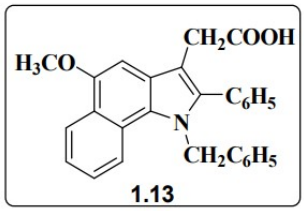
Similarly, indole oximes exhibit analgesic and anti-inflammatory activities. Indole oxime 1.12 was found to be the most active analgesic and anti-inflammatory agent.



1.12

Indole oxime as anti-inflammatory agent

Indole-3-acetic acids were synthesized and evaluated for their in vivo anti-inflammatory activity. It was reported that the compound 1,2-disubstituted-5-methoxy-indole/benz(g)indole-3-acetic acid 1.13 showed significant vivo anti-inflammatory activity.

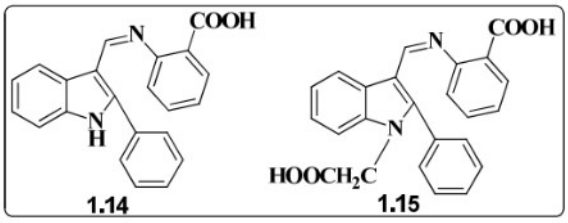


1.13

1,2-disustituted-5-methoxy-indole/benz(g)indole-3-acetic acid

ISBN 978-93-5457-774-1

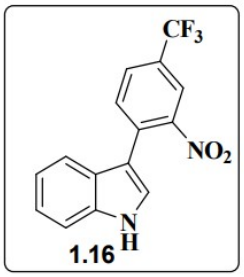
Indole triazole derivatives have been reported as potent analgesic and anti-inflammatory agents. The compounds 2-Phenyl-3- (20-carboxyphenyliminomethyl)-indole 1.14 and 2-pheny l-3-(20- carboxy phenyl imino methyl) -indol-1-acetic acid 1.15 are found to be the most potent.



2-phenyl-3-(20-carboxy phenyl imino methyl) and indole and 2-phenyl-3-(20-carboxy phenyl-imino-methyl)-indol-1-acetic acid

1.2. ANTI-MICROBIAL AND ANTI-FUNGAL ACTIVITY

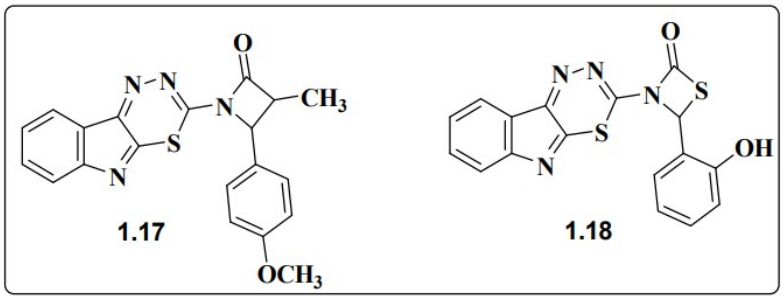
Microbial infections are due to the activity of a range of microbes, including bacteria and fungi, such as enterococcus, aspidosperma, plasmodium, staphylococcus and seudomonas. Resisting such microbes has become a global concern. Structurally novel molecules with new mode of action are required for the treatment of bacterial infections. Some substituted 3-(aryl) and 3- (heteroaryl) indoles were synthesized by Hiari et al. and were evaluated for antibacterial activity. Of the synthesized compounds, the most active compound was 3-(4-trifluoromethyl-2-nitrophenyl) indole 1.16, exhibiting MIX~ 7 µg/cm3 against Escherichia coli and Staphylo-coccus aureus.



3-(4-trifluoromethyl-2-nitrophenyl)indole

ISBN 978-93-5457-774-1

Substituted azetidonyl and thiazolidinonyl-1,3,4-thiadiazino [6,5-b]indoles were reported as promising antimicrobial agents. Of the synthesized compounds, the compounds 1.17 and 1.18 were found to exhibit most inhibitory effects against E. coli and S. aureus.



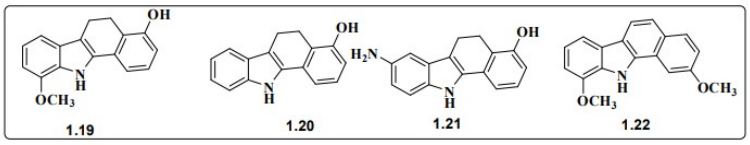
Substituted azetidonyl and thiazolidinonyl-1,3,4-thiadiazino(6,5-b) indole

1.3. ANTICANCER ACTIVITY

Cancer, otherwise known as malignancy, is an extraordinary growth of the cells. There are different varieties of cancer such as breast cancer, skin cancer, lung cancer, colon cancer, prostate cancer and lymphoma. Breast cancer is commonly found in women and is one of the causes for the increased female death rate. The high mortality rate is also an indication of the limited efficacy of the various cancer treatments available now, such as radiation, chemotherapy and surgery. An increasing interest has been shown by scientists and researchers to invent more effective medicine for curing the disease without side effects.

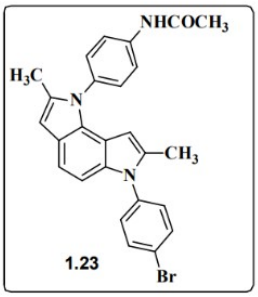
Indole has become, by virtue of its excellent cytotoxic activities, an ideal choice for the development of new anticancer drugs. Hong et al. synthesized a series of various tricyclic and tetracyclic indoles and evaluated their anticancer activity where in the compounds 1.19, 1.20, 1.21 and 1.22 were found to exhibit the highest in vitro activity against human nasopharyngeal carcinoma (HONE-1) and gastric adenocarcinoma (NUGC-3) cell lines.

ISBN 978-93-5457-774-1



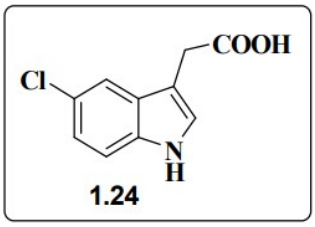
Tricyclic and tetracyclic indoles with potent anti-cancer activity

Garcia and coworkers reported pyrrolo [2,3-e] indole derivatives and evaluated the in vitro cytotoxic activity. The compound 1.23 was found to be the potent one in PC-3 (prostate) cell line.



Pyrrolo (2,3-e) indole derivatives as potent one in PC-3(prostate)cell line

A series of halogenated indole-3-acetic acids were reported for targeted cancer therapy and of the synthesized compounds, the halogenated indole-3-acetic acid 1.24 was found to possess the highest cytotoxicity suitable for targeted cancer therapy.

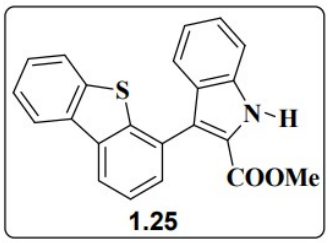


Halogenated indole-3-acetic acids with highest cytotoxicity

The synthesis and inhibitory activity of heteroaryl indoles on the inhibition of human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and SF-268 (CNS cancer) were reported by Queiroz et al. From the study it was observed that methyl

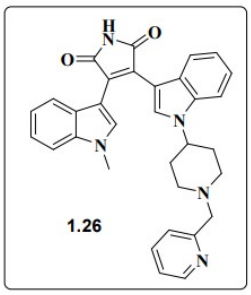
ISBN 978-93-5457-774-1

3-(dibenzothien-4-yl) indole-2-carboxylate 1.25 had the most potent growth inhibitory activity in all the tumour cell lines that were tested (with GI50 values ranging from11to 17 lM).



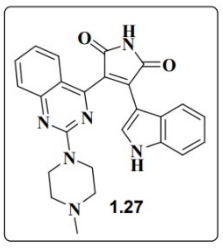
Hetero-aryl indoles as most potent growth inhibitor activity in all the tumor cell lines tested

Enzastaurin 1.26 is an indolebased drug, currently under clinical evaluation, for the treatment of lymphoma, breast cancer, prostate cancer, NSCLC, leukemia, colorectal cancer, ovarian cancer, renal cell carcinoma and pancreatic cancer.



Enzastaurin.

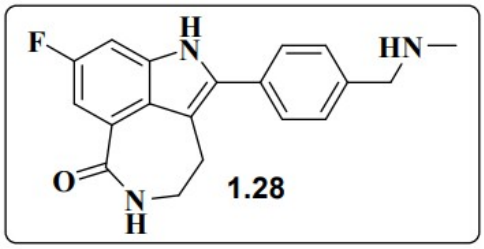
Sotrastaurin 1.27 was developed by Novartis and has been evaluated for the effectiveness in the treatment of lymphocytic leukemia, lymphoma, melanoma and kidney transplantation.



ISBN 978-93-5457-774-1

Sotrastaurin

Similarly, Agouron pharmaceuticals reported Rucaparib 1.28, which is an investigational candidate for advanced solid tumor, breast and ovarian cancer with BRCA1 and BRCA2 mutation.



Rucaparib

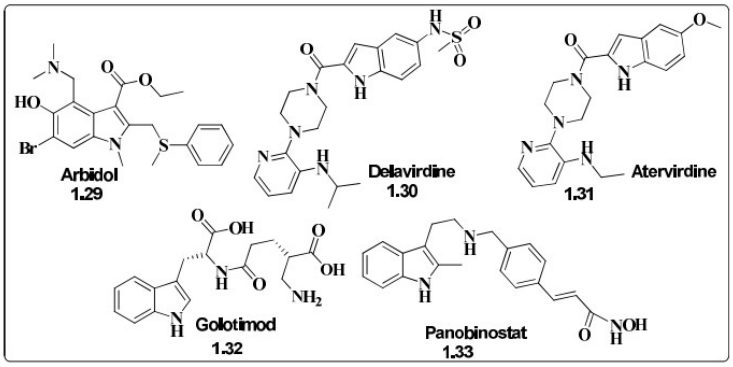
1.4. ANTIVIRAL ACTIVITY

Viruses are the main agents responsible for various disease classes like influenza (seasonal, pandemic), smallpox, dengue and chikungunya. They are also involved in chronic diseases in the form of human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV, respectively), coronaviruses (Middle east respiratory Syndrome), MERS, severe acute respiratory syndrome (SARS), viral hemorrhagic fevers (Ebola) etc. Most anti-virals are used for specific viral infections, while a broad-spectrum of antiviral is effective against a wide range of viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development. The literature on this has revealed that the indole scaffolds, by virtue of their high affinity and specificity to bind with different molecular targets, are considered as efficient antiviral agents.

Arbidol (Umifenovir) 1. 29 exhibits broad-spectrum antiviral activity against a number of enveloped and non-enveloped viruses by inhibiting the fusion of viral capsid with the host cell membrane. The drug possesses high potency against influenza A, B and C

ISBN 978-93-5457-774-1

viruses, respiratory syncytical virus, hepatitis B virus, hepatitis C virus, human rhinovirus type 14, coxsackie B3 virus, adenovirus type-7. Delavirdine (Rescriptor) 1.30 acts as non-nucleoside reverse transcriptase inhibitor (NNRTI) and is used for the treatment of human immunodeficiency virus (HIV). It is also an inhibitor of chytochrome P450 enzyme CYP3A4 and can interact with many medications.[24]Atevirdine (U-87201E) 1.31 is a bis-heteroaryl piperazine with an in-vitro activity against human immunodeficiency virus (HIV-1).[25] GSK2248761 (Fosdevirine) is another NNRTI which is under Phase 2 clinical evaluation. This compound has been reported to have sub 13 nano-molar activity against NNRTI resistant mutant HIV. Golotimod (SCV-07) 1.32 is an orally bio-available synthetic peptide containing the amino acids D-glutamine and L-tryptophan connected by a gammaglutamyl linkage with potential immune-stimulating, antimicrobial and anti-neoplastic activities. Panobinostat (LBH589) 1.33 is a non-selective histone deacetylase inhibitor (HDACinhibitor) for treatment of Multiple Myeloma (Phase III) and Acute Myeloid Leukemia (Phase II).



Some indole derived antiviral compounds

CONCLUSIONS

In conclusion, this chapter summarizes the wide range of biological and drug like properties make indole an attractive privileged scaffold. A single scaffold can impart potent and selective ligands for a range of diverse biological targets through their functional group

ISBN 978-93-5457-774-1

modification. The aromatic heterocyclic scaffold, which sound like various protein structures, has received diligence from organic and medicinal chemists. Numerous heterocycles have been identified and reinvestigated as privileged scaffolds, of which Indole ring is a prominent privileged scaffold and has been reported in various bioactive molecular syntheses. The literature on this reveals that the indole-functionalized scaffolds can provide ligands for diverse receptors and can interact with unrelated and undruggable targets.This chapter try to describes the importance indole derivatives as a promising heterocycle in drug discovery.

REFERENCES

1. L. Palego, L. Betti, A. Rossi and G. Giannaccini, J Amino Acids, 2016
2. M. Berger, J. A. Gray and B. L. Roth, Annu. Rev. Med., 2009, 60, 335–366
3. W. S. Chilton, J. Bigwood and R. E. Gensen, J. Psychedelic Drugs, 1979, 11, 61–69.
4. N. K. Kaushik , N. Kaushik , P. Attri , N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, Molecules, 2013, 18, 6620-6662.
5. E. F. Mueschenborn and A. Fox, Headache, 2005, 45, 632–637.
6. J. A. Generali and D. J. Cada, Hospital Pharmacy, 2009, 44, 670– 671.
7. P. Singh, P. Prasher, P. Dhillon and R. Bhatti, Eur. J. Med. Chem., 2015, 97, 104 – 123.
8. E. Abele, R. Abele, O. Dzenitis and E. Lukevics, Chem Heterocycl Compd., 2003, 39, 3.
9. G. P. Kalaskar, M. Girisha, M. G. Purohit, B. S. Thippeswamy and B. M. Patil, Indian J Heterocycl Chem., 2007, 16, 325.
10. M. Amir, N. Dhar and S. K. Tiwari, Indian J Chem., 1997, 36B, 96.
11. H. Panwar, R. S. Verma and V. K. Srivastava, A. Kumar, Indian J Chem., 2006, 45B, 2099.
12. Y. M. A Hiari, A. M Qaisi, M. M. Abadelah and W. Voelter, Monatshefte Fur Chemie., 2006, 137, 243.
13. P. Singh, Eur. J. Med. Chem., 2014, 74, 440–450.
14. J. Khazir, I. Hyder, J. L. Gayatri, L. Prasad, N. Nalla, G. Chasoo, A. Mahajan, A. K. Saxena, M. S. Alam, G. N. Qazi and H. M. Sampath, Eur. J. Med. Chem., 2014, 82, 255–262.
15. N. Panathur, U. Dalimba, P. Venkat, M. Alvala, P. Yogeeswari, D. Sriram and V. Kumar, Eur. J. Med. Chem., 2013, 69, 125–138.
16. B. C. Hong, Y. Jiang, Y. Chang and S. Lee, J Chin Chem. Soc., 2006, 53, 647.
17. L. C. Garcia and R. Martinez, Eur J Med Chem., 2002, 37, 261.
18. S. Rossiter, L. K. Folkes, P. Wardman, Bioorg. Med. Chem., 2002, 12, 2523.

ISBN 978-93-5457-774-1

19. M. R. P. Queiroz, A. S. Abreu, M. S. D. Carvalho, P. M. T. Ferreira, N. Nazareth and M. S. Nascimento, Bioorg. Med. Chem., 2008, 16, 5584.
20. (a) M. J. Robertson, B. S. Kahl, J. M. Vose, S. de Vos, M. Laughlin, P. J. Flynn, K. Rowland, J. C. Cruz, S. L. Goldberg and L. Musib, J. Clin. Oncol., 2007, 25 , 1741-1746; (b) M. Crump, S. Lepp€a, L. Fayad, J. J. Lee, A. Di Rocco, M. Ogura, H. Hagberg, F. Schnell, R. Rifkin and A. Mackensen, J. Clin. Oncol., 2016, 34, 2484-2492.
21. (a) T. L. Naylor, H. Tang, B. A. Ratsch, A. Enns, A. Loo, L. Chen, P. Lenz, N. J. Waters, W. Schuler and B. D€orken, Cancer Res., 2011, 71, 2643-2653; (b) S. Friman, W. Arns, B. Nashan, F. Vincenti, B. Banas, K. Budde, D. Cibrik, L. Chan, J. Klempnauer and S. Mulgaonkar, Am. J. Transpl., 2011, 11, 1444-1455.
22. M. Ihnen, C. Z. Eulenburg, T. Kolarova, J. W. Qi, K. Manivong, M. Chalukya, J. Dering, L. Anderson, C. Ginther, A. Meuter, Mol. Cancer Ther., 2013, 12, 1002-1015.
23. Y. Boriskin, I. Leneva, E. I. Pecheur and S. Polyak, Curr. Med. Chem., 2008, 15, 997-1005.
24. (a) J. R. Palmer, D. L. Romero, P. A. Aristoff, R. C. Thomas, H. W. Smith, in: Google Patents, 1996. US5563142; (b) D. L. Romero, R. A. Morge, M. J. Genin, C. Biles, M. Busso, L. Resnick, I. W. Althaus, F. Reusser, R. C. Thomas and W. G. Tarpley, J. Med. Chem., 1933, 36, 1505-1508.
25. G. D. Morse, R. C. Reichman, M. A. Fischl, M. Para, J. Leedom, W. Powderly,L. M. Demeter, L. Resnick, Y. Bassiakos, J. Timpone, Antivir. Res., 2000, 45, 47-58.
26. S. Castellino, M. R. Groseclose, J. Sigafoos, D. Wagner, M. de Serres, J. W. Polli, E. Romach, J. Myer, B. Hamilton, Chem. Res. Toxicol., 2012, 26, 241- 251.
27. J. Aspinall and P. J. Pockros, Curr. Opin. Investig. Drugs., 2006, 7, 180-185.
28. P. Atadja, Cancer Lett., 2009, 280, 233-241.

Chapter 12

SELF-ASSEMBLED GOLD NANOCLUSTERS FOR BIOPHOTONIC APPLICATIONS

Furhan

Ph.D scholar, University of Grenoble Alpes,Department of Molecular Chemistry and Institute for Advanced BioScience Grenoble, France

ISBN 978-93-5457-774-1