

# Dipole Moment

Subjects: Chemistry, Organic

Contributor: Aparna Das, Bimal Banik

Synthesis, biological activity and structure-activity relationships of diverse compounds are described. The relationships between dipole moment and biological activities are discussed. Despite the progress of interdisciplinary science, the use of dipole moment values of organic compounds to understand their potent medicinal activities in various diseases remains unexplored.

Keywords: Dipole moment, Biological activity, QSAR

---

## 1. Introduction

The dipole is basically a system comprising of two poles, opposite in nature. Dipoles are characterized by their dipole moment ( $\mu$ ), a measure of the system's overall polarity, a vector quantity. The dipole moment values of numerous compounds and their implications on biological activity are discussed here based upon the available data.

### 2-Pyrrolidone:

2-Pyrrolidone is a compound consist of five-membered lactam. Several studies had been performed to calculate the dipole moment of the five-membered lactams, the 2-Pyrrolidone [1].

Kumler *et al.* observed dipole moment of range 3.7-3.9 D in simple amides in dioxane at 30° [2]. Fischer reported a dipole moment value of 3.7 D for 2-pyrrolidone in benzene [3]. Huisgen *et al.* calculated a lower value of 3.55 D for 2-pyrrolidone in benzene at 25° [4]. Earlier than that, Devoto observed a much lower value of 2.3 D for pyrrolidone in benzene [5]. The reduction in dipole moment observed due to the formation of a pyrrolidone dimer [3], a value of 2.2 D reported in dimer in benzene at 25° [4].

### Cholestanone:

Studies showed that the biological activity of steroids is increased by the substitution of fluorine for hydrogen on a carbon atom adjacent to a carbonyl group [6].

Allinger *et al.* calculated the dipole moment of 2-fluorocholestanone [7]. The calculated dipole moment of the 2 $\alpha$ -fluorocholestanone was 4.28D and for 2 $\beta$ -fluorocholestanone, the value was 2.95D. The experimentally measured dipole moment value of the only known 2-fluorocholestanone was 4.39D in the benzene solution.

### Purines, Pyrimidines and Azines:

Mishra *et al.* calculated the dipole moment of the ground and lowest singlet  $\pi - \pi^*$  and  $n - \pi^*$  excited states of biologically important azines, pyrimidines, and purines [8]. Findings showed that in going from the ground to the  $n - \pi^*$  excited state the dipole moment of pyridine changed by -2.3 D, pyridazine changed by -2.0 D and pyrimidine changed by -2.1 D.

Experimentally obtained values for dipole moment changes for pyridine was -3.2D, and -2.84 D and -2.7 D for pyridazine, and pyrimidine, respectively, following the corresponding  $\pi - \pi^*$  excitation [9].

### Thiophene and Carboxamides:

The substituted thiophenes and condensed thiophenes possess pharmacological activities like antiviral [10], antibacterial [11], anticancerous [12], antifungal [13], analgesic and anti-inflammatory activities [14]. Melavanki *et al.* reported the ground and excited state dipole moment of three carboxamides: (E)-2-(4-Chlorobenzylideneamino)- N-(2-chlorophenyl)-4, 5, 6, 7-tetrahydrobenzo[b]thiophene- 3-carboxamide (C<sub>1</sub>), (E)-N-(3-Chlorophenyl)-2-(3, 4- dimethoxybenzylideneamino)-4, 5, 6, 7-tetrahydrobenzo[b] thiophene-3-carboxamide (C<sub>2</sub>) and (E)-N-(3-Chlorophenyl)- 2-(3, 4, 5-trimethoxybenzylideneamino)-4, 5, 6, 7- tetrahydrobenzo[b]thiophene-3-carboxamide (C<sub>3</sub>) [15]

## 2. Dipole Moment and Anticancer Activity

This section describes different types of anticancer drugs and their dipole moment values.

### 2.1. Topovale

Topovale is a potent topoisomerase I inhibitor, also known as ARC-111. Studies showed that ARC-111 (Dibenzo [c,h]-[1,6] naphthyridin-6-one) is one of the effective topoisomerase I (Top I) targeting agent and its analogues exhibit antitumor activities [16]. A series of ARC-111 compounds were considered, for cytotoxicity test against tumor cell lines in RPMI 8402 [17].

The data from chemometric tools, PLS and ANN indicated that dipole moment of ARC-111 analogues had great impacts on antitumor activities.

### 2.2. MDMA:

Riahi *et al.* carried out studies on the effects of the novel drug MDMA as an anticancer drug on the biologic receptor of DNA [18]. For the computational studies, molecular geometries of MDMA and DNA bases (Adenine, Guanine, Cytosine, and Thymine) were optimized. Parameters like dipole moment and energies of the frontier molecular orbitals were calculated.

### 2.3. Efavirenz (EFZ):

Efavirenz (Sustiva or EFZ) is an anti-HIV drug. Description of the interactions between EFZ and DNA base pairs using the density functional tight-binding method were reported [19]. Riahi *et al.* reported a dipole moment value of 4.68D for EFZ [19].

### 2.4. Adriamycin and Daunomycin:

Scientific studies showed that Adriamycin and Daunomycin produce complexes with DNA and block the processes of transcription and replication [20]. Daunomycin is mainly used to treat leukemia, while Adriamycin has a wide range of anticancer activities [21]. The dipole moment of the optimal structures was calculated using HF and B3LYP computational methods [22]. Adriamycin showed a dipole moment value of 5.74D and Daunomycin showed a value of 4.72D [23].

### 2.5. Methotrexate, Temozolomide, Carmustine, Tamoxifen and Hydroxifen:

Methotrexate disrupts the synthesis of DNA, RNA, thymidylates, and proteins [24] by inhibiting the production of folate.

Theoretical calculations were done for anticancer drugs like Methotrexate, Carmustine, Temozolomide, Tamoxifen, and Hydroxifen to study their physicochemical and geometrical properties [25]. Dipole moments of Methotrexate, Carmustine, Temozolomide, Tamoxifen, and Hydroxifen were calculated.

### 2.6. Glutamine:

Glutamine is an  $\alpha$ -amino acid with many functions in the body. It is used in the biosynthesis of proteins and a critical part of the immune system. Glutamine has a special role in intestinal health since the human body naturally produces this amino acid.

To know and detect novel anticancer agents with good selectivity to kill cancer cells and inhibit their proliferation without being toxic [26] is a very difficult task. Non-essential amino acids like Glutamine (GLN) can supply its amide nitrogen atoms in the biosynthesis of other amino acids, amino sugars, purine, pyrimidine bases, and coenzymes [27] via amide transferases [28]. Srikanth *et al.* discussed the antitumor activities of GLN [29]. Elidrissia *et al.* modeled different antitumor glutamines by substituting 5-N-substituted-2-(substituted benzenesulphonyl) glutamines with different substitutions [30]. The theoretical calculations from modeled structures showed that molecular descriptors like dipole moment is a useful tool for the prediction of more active antitumor 5-N-substituted-2-(substituted benzenesulphonyl) glutamines compounds. They also addressed the importance of Quantitative Structure-Activity Relationship (QSAR) Studies for the prediction of new biological active glutamine compounds.

### 2.7. Lantadenes:

Lantadenes are bioactive compounds derived from the weed Lantana Camara. It showed potent cytotoxic activity against a number of cancer cell lines and showed anti-antitumor potentials.

QSAR-based studies including dipole moment calculations were helpful in determining the anticancer activities of Lantadenes Against A549 Cell Lines [31]. They considered a series of forty compounds for the study. Substituent of four selected compounds and their anticancer activity are known.

## 2.8. Xanthone:

Xanthone (9H-xanthene-9-one) is a naturally occurring oxygenated heterocyclic compound with interesting pharmaceutical properties. The compound has dibenzo- $\gamma$ -pyrone as the main structure with the molecular formula  $C_{13}H_8O_2$ . It is prepared by heating of phenyl salicylate. The most significant activities of xanthenes include antibacterial, anticancer, antiviral, antiprotozoal, antimalarial, and anti-inflammatory.

Xanthone compounds showed higher anticancer activity for colorectal cancer (WiDR cell line) [32]. Miladiyah *et al.* made QSAR analysis to predict their activity, based on the biological activity of xanthenes in WiDR cell lines and quantum descriptors of the xanthenes' structures. They selected the AM1 semiempirical method for the optimization of the structure because the AM1 method is fast, requires no complex mathematical calculation [33], and able to predict large molecules and multivalent compounds with good accuracy [34].

## 2.9. Fullerene $C_{60}$ and Benzopyrene:

Because of numerous conjugated double bonds and low-level lowest unoccupied molecular orbital (LUMO) [35], fullerene can easily take up an electron and that makes them an apt antioxidant. Studies demonstrated the biological antioxidant potential of fullerenes [36] and its activity against carcinogenic agents [37].

Benzo( $\alpha$ )pyrene (BaP) can be found in automobile exhaust fumes, in coal tar, in all smoke resulting from the combustion of organic material including tobacco smoke and in many foods, especially grilled and smoked meats [38]. BaP destabilizes the genome by making covalent adducts to DNA [39] and eventually produce cancer [40]. In an enzymatic reaction, BaP turns into a toxic compound by forming benzo( $\alpha$ ) pyrene-7, 8-dihydro diol-9, 10-epoxide [41]. Studies were done to analyze the chemical reactivity of the carcinogenic BaP 7,8 diol 9,10 epoxide using semiempirical (PM3) and density functional theory (DFT) methods [41].

Tavangar *et al.* examined the interaction of fullerenes with the benzo( $\alpha$ ) pyrene 7, 8 epoxide (BaPe) molecule, using the DFT method [37].

## 2.10. Coumarins:

Coumarins acquired attention because of its various therapeutic properties such as antiviral, antimicrobial, anti-tumor, anti-inflammatory, antidiabetic, anticancer, antioxidant, and many others [42]. Ouattara *et al.* have considered the QSAR method to correlate the structure of the compound and its anticancer activity, mainly for breast cancer [43]. The study revealed that the dipole moment is the paramount descriptor for improving anticancer activity.

# 3. Dipole moment and antifungal activity:

There are wide varieties of fungus that can make infections in human. Fungus of the genus *Candida* causes serious illnesses those frequency remains constant despite the development of new therapeutic means, especially in immune-compromised patients.

## 3.1. Thiosemicarbazide:

Siwek *et al.* described the antifungal effect of 4-arylthiosemicarbazides against *Candida* species [44]. The active compounds are also distinguished by high dipole moment, highest occupied molecular orbital energy ( $E_{HOMO}$ ), favorable binding energy ( $E_B$ ), and an electron-accepting heteroaromatic ring at the  $N_1$  position.

## 3.2. Pyrazolopyridines:

Pyrazolopyridines are antidepressant, anti-inflammatory, anti-hyperglycemic, antitumor, antibacterial, anxiolytic agents, and also used for the treatment of Alzheimer's diseases, drugs addiction, and infertility [45]. Quiroga *et al.* showed the synthesis and antifungal *in vitro* activity of pyrazolo [3,4-*b*] pyridines derivatives [46]. To find the correlation between structure and antifungal activity, theoretical calculations were done at the semiempirical level using the PM3 method, and the quantitative parameters like dipole moment and Log P was calculated. As the dipole moment gives the polarity of the compound, Log P determines its ability to penetrate fungal cell membranes and to reach the interacting sites [47].

### 3.3. Oxadiazoles:

Ashtekar *et al.* studied the antifungal activity of 1,3,4-oxadiazole by QSAR approach [48], to design more potent antifungal oxadiazole derivatives. This study suggested that molar refractivity and dipole moment have positive contribution in the antifungal activity of oxadiazole.

### 3.4. Beta-Pinene ( $\beta$ -pinene):

Gao *et al.* investigated the synthesis of three series of  $\beta$ -pinene derivatives and their fungicidal activities against three important agricultural pathogens *Rhizoctonia solani*, *Fusarium graminearum*, and *Botrytis cinerea* [49]. The structure-activity relationship (SAR) analysis indicated that the compounds with more net positive charge possessed better fungicidal activity. The study showed that the most important factors affecting the activity were the geometry and charge distribution, which involved dipole moment.

### 3.5. Indol-4-one:

Indole is an aromatic heterocyclic organic compound that has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered pyrrole ring. González *et al.* designed, synthesized, and tested a series of indol-4-one derivatives with 1- and 2-(2,4-substituted phenyl) side chains [50]. González-Chávez and Méndez *et al.* reported a theoretical reactivity study of Indol-4-Ones derivatives and its correlation with antifungal activity [51]. This study suggested that there is a correlation between the relative polarity of the compounds and the antifungal activity.

### 3.6. Aminobenzenesulphonamide Schiff bases:

Santosh *et al.* synthesized a series of Schiff bases derivatives from 4-aminobenzenesulphonamide and tested against the fungi *Aspergillus niger* and *Candida albicans* [52]. Richard *et al.* conducted a SAR study on identical series of compounds to predict more active antifungal agents [53].

### 3.7. Chalcones and Chromanes:

Chalcones are natural compounds that belong to the flavonoid family [54]. These compounds have attracted great interest due to their wide range of pharmacological properties [55]. They have attracted intense interest because of their numerous biological activities [56]. In addition, the structure known as dihydrochromane (or tetrahydropyran) is an important structural fragment of the molecules in many biologically active and natural compounds [57]. In particular, antibiotic activity has been identified for this fragment [58]. A current trend in the discovery and development of highly active compounds is the hybridization of two or more active fragments that may present improved pharmacological activities [59].

Mellado *et al.* synthesized a series of chalcones and dihydrochromane–chalcones hybrids and the compounds were tested against the antifungal activity against *B. cinerea* and *M. fructicola* [60]. The increased polarization of the carbonyl group led to the increased antifungal activity of the compound against *M. fructicola*. This study also presented an increase of antifungal activity of chalcone for *M. fructicola* with an electron donor substituent on the ortho position of C<sub>1</sub>.

## 4. Dipole moment and antibacterial activity:

### 4.1. Copper (II) complexes with quinolones and nitrogen-donor heterocycles:

Quinolones shows a wide range of antibacterial activities. By targeting essential type II bacterial topoisomerases [61], quinolones inhibit DNA replication [62]. They act more effectively in the presence of certain metal ions, like Cu<sup>2+</sup>, Mg<sup>2+</sup> [63]. Several groups reported the synthesis and antibacterial activity of metal compounds with quinolones [64].

Deng *et al.* presented QSAR of a series of Copper (II) complexes with quinolones and nitrogen-donor heterocycles [65]. Different descriptors relating to electronic characteristics, like dipole moment, HOMO, LUMO, energy difference, and net charges, were investigated in the correlation analysis. The theoretical calculations indicated that net HOMO ( $\Sigma_{\text{NHOMO}}$ ) and dipole moment are the most independent parameters affecting the antibacterial activity. They found a positive correlation, antibacterial activity increases with a dipole moment.

### 4.2. Thiourea derivatives:

Thiourea derivatives and their transition metal complexes were studied extensively due to their wide range of pharmacological activities [66].

Soliman reported QSAR on five N-alkyl substituted thiourea ligands (L) and their [ZnL<sub>2</sub>Cl<sub>2</sub>] complexes to investigate their antibacterial activity against *E. coli* and *P. aeruginosa* [67].

Different quantum chemical descriptors were analyzed during this study. The decrease of dipole moment, energy gap and the charge descriptors of these compounds as well as the increase of their molecular polarizabilities due to the N-alkyl substituents enhanced the antibacterial activities of the thiourea derivatives (L).

#### 4.3. Indolylpyrimidines:

Datar made a QSAR analysis to predict the antibacterial activity of indolylpyrimidine derivatives against *Pseudomonas aeruginosa* (PA), a gram-negative pathogen and *Staphylococcus aureus* (SA), a gram-positive pathogen [68]. The dipole moment and antibacterial activity of nine selected derivatives are calculated.

#### 4.4. Terpenes and phenylporpanes:

Terpenes and phenylporpanes are the major constituents of different essential oils. Several groups reported the antibacterial activity [69] and the antimycobacterial activity of essential oils [70].

Chavira *et al.* evaluated the antimycobacterial activity of 25 constituent molecules of essential

oils against *Mycobacterium tuberculosis* H37Rv and *Mycobacterium Bovis* AN5 [71].

Menthol has a higher dipole moment and cymene has the lowest dipole moment. Thymol and carvacrol are the compounds with lower free energy of solvation. The study demonstrated that the lipophilicity alone is not responsible for the antimycobacterial activity of the compounds, but this activity is linked to the electronic characteristics of the phenolic group.

#### 4.5. Quinazolinone:

The quinazolinone derivatives are biologically active compounds [72]. Irfan *et al.* investigated the structural and electronic properties and the antibacterial activity of quinazolinone derivatives [73]. The same group synthesized quinazolinone derivatives as active compounds [74]. The specific compounds exhibited higher dipole moment (5.1D) than compound (3.6D), revealing that this compound has a higher ability of interaction with the surrounding medium and more binding ability resulting in superior biological effects.

#### 4.6. Azole-derived compounds:

The activity of azoles against fungi is based on the inhibition of ergosterol [75]. Azoles also show antibacterial activity by inhibiting the enoyl acyl carrier protein reductase [76]. Among the azole derivatives, triazole compounds showed higher antifungal activity [77], good antimicrobial [78], and antitumor [79] activities. Azoles derivatives in combination with metals are promising to develop new efficient drugs, even against drug-resistant pathogens [80].

Hurtado *et al.* reported the synthesis and characterization of new chromium(III) and cobalt(II) complexes derived from triazole ligands and their antifungal, antibacterial, and cytotoxic activities [81]. The calculated molecular dipole moment of these compounds showed values ranging from 2.22 to 12.97 D.

#### 4.7. Polyphenols:

Bordes *et al.* studied the antibacterial activity of 35 polyphenols [82]. Different quantum descriptors like HOMO, LUMO, dipole moment, the polarizability, the maximal and minimal atomic Mulliken charges, the maximal and minimal atomic Hirshfeld charges were considered for QSAR analysis. The calculated data described that both electronic and electric charge (dipole moment, minimum atomic charge (Mulliken)) properties of polyphenols were important for the explanation of Bacterial Load Difference (BLD) with *E. coli*.

## 5. Dipole moment and various other medical disorders

#### 5.1. Hydrazone Analogues:

Hydrazone analogues possess biological activities. Narasimhan *et al.* reported the synthesis, antimicrobial activity of substituted benzoic acid benzylidene/furan-2-yl-methylene hydrazides [83]. The study also showed that the presence of electron-withdrawing groups (-NO<sub>2</sub>, -Cl, -Br) on aromatic ring improved the antimicrobial activity of compounds. Dipole moment was the best descriptor for antibacterial activity of substituted hydrazides against *S. aureus*.

## 5.2. Phenothiazine (PTZ):

Derivatives of phenothiazine are highly bioactive and have widespread use as antipsychotropic [84], antimalarial [85], antimicrobial [86], antitumor [87], antitubercular [88], and analgesic [89]. Bayoumy *et al.* reported the synthesis, biological activity, and molecular modeling of phenothiazine derivatives [90]. The most potent compound against gram-negative bacteria and had the lowest value of dipole moment compared to other compounds [91].

## 5.3. Thiazolidine:

The thiazolidine derivatives have a wide range of medicinal applications such as antiviral [92], antimicrobial [93], anticonvulsant [94], anti-inflammatory [95], and antimalarial activities [96].

Scientific reports showed that these types of compounds have activity against Gram-positive bacteria and Gram-negative bacteria [97].

De Pavia *et al.* reported the synthesis of 5-arylidene-thiazolidine-2,4-dione derivatives and evaluated their antimicrobial activity against *Staphylococcus aureus* ATCC 29213 [98].

Different descriptors were considered for structural-activity analysis and the only selected descriptor that was not exclusively related to the benzene ring was the dipole moment. The data showed that active compounds have lower dipole moment values compared to inactive compounds.

## 5.4. Cinchona alkaloids:

Cinchona alkaloids especially were used for treating *falciparum* malaria [99]. Warhurst *et al.* calculated the dipole moment of different amino alcohol alkaloids [100]. The calculated dipole moment of each active alkaloid was lower than that of its 9-epimer.

## 5.5. Tetraoxanes:

Tetraoxanes are biologically active compounds containing two peroxide groups. Different groups reported the antimalarial activity of tetraoxanes [101]. Paula *et al.* calculated the electron affinity, dipole moment, and logP 1,2,4,5-tetraoxanes and analyzed its correlation with activity against *Plasmodium falciparum* [102].

## 5.6. Chalcones:

Researchers had reported the anti-inflammatory [103], antibacterial [104], trypanocidal [105], antitumoral [106], antiviral [107], and antileishmanial activities [108] of Chalcones. Souza *et al.* described the effects of sulfonamide 4-methoxychalcones against *Leishmania amazonensis* [109]. Different parameters including HOMO, LUMO, electron distribution and dipole moment were calculated.

## 5.7. Cimetidine Analogues:

The cimetidine derivatives like ranitidine [110] and tiotidine [111], showed a better H<sub>2</sub> antagonist activity. Young *et al.* considered a series of cimetidine analogues to investigate H<sub>2</sub> receptor histamine antagonist activity by replacing the cyanoguanidine moiety by other neutral and dipolar groups [112]. The study showed that there was no simple relationship between antagonist activity and dipole moment alone.

## 6. Conclusions:

We have described the significance of dipole moment in determining the biological activity of diverse compounds. Many of the compounds have shown a direct correlation between dipole moment and biological activity.

## Contributors

Aparna Das<sup>1</sup> and Bimal Krishna Banik<sup>2</sup>

<sup>1</sup> Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Prince Mohammad Bin Fahd University, Al Khobar, Kingdom of Saudi Arabia; Email: aparnadasam@gmail.com; adas@pmu.edu.sa

<sup>2</sup> Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Deanship of Research, Prince Mohammad Bin Fahd University, Al Khobar, Kingdom of Saudi Arabia; Email: bimalbanik10@gmail.com; bbanik@pmu.edu.sa

## Acknowledgements:

BKB is grateful to the USA NIH, USA NCI, and USA Private Research Foundation. BKB and AD also thank Prince Mohammad Bin Fahd University for encouragement.

---

## References

1. C. M. Lee, W. D. Kumler, J. Am. Chem. Soc. 83 (1961) 4593.
2. W. D. Kumler, C. W. Porter, J. Am. Chem. Soc. 56 (1934) 2549.
3. E. Fischer, J. Chem. Soc. (1955) 1382.
4. R. Huisgen, H. Waltz, Chem. Ber. 89 (1953) 2616.
5. G. Devoto, Cazz. chim. ital. 63 (1933) 495.
6. (a) A. H. Nathan, B. J. Magerlein, J. A. Hogg, J. Org. Chem. 24 (1959) 1517; (b) J. S. Mills, A. Bowers, C. Djerassi, H. J. Ringold, J. Am. Chem. Soc. 82 (1960) 3399; (c) H. M. Kissman, A. M. Small, M. J. Weiss, J. Am. Chem. Soc. 82 (1960) 2312.
7. N. L. Allinger, H. M. Blatter, M. A. DaRooge, L. A. Freiberg, J. Org. Chem. 26 (1961) 2550.
8. M. K. Shukla, P. C. Mishra, J. Chem. Inf. Comput. Sci. 38 (1998) 678.
9. P. C. Mishra, R. D. Tewari, Indian J. Pure Appl. Phys. 25 (1987) 387.
10. D. Binder, C. R. Noe, W. Holzer, B. Rosenworth, Arch. Pharm. Weinheim Ger. 318 (1985) 48.
11. A. A. El Maghraby, B. Haroun, N. A. Mohamed, Egypt J. Pharm. Sci. 23 (1982).
12. G. Karminshi-Aamola, M. Bajc, Heterocycles 23 (1985) 1497.
13. J. C. Ramanathan, D. G. Namboothiri, J. Indian Chem. Soc. 55(1978) 822.
14. J. Svoboda, J. Paleki, Cesk Farm 38 (1989) 175.
15. N. R. Patil, R. M. Melavanki, S. B. Kapatkar, N. H. Ayachit, J. Saravanan, J. Fluoresc. 21 (2011) 1213.
16. A. L. Ruchelman, P. J. Houghton, N. Zhou, A. Liu, L. F. Liu, E. J. LaVoie, J. Med. Chem. 48 (2005) 792.
17. Y. Yu, R. Su, L. Wang, W. Qi, Z. He, Med. Chem. Res. 19 (2010) 1233.
18. S. Riahi, S. Eynollahi, M. R. Ganjali, Chem. Biol. Drug Des. 76 (2010) 425.
19. S. Riahi, S. Eynollahi, M.R. Ganjali, P. Norouzi, Int. J. Electrochem. Sci. 5 (2010) 815.
20. (a) A. diMarco, F. Arcamone, F. Zunino, Antibiotics, Springer, Berlin, (1974) 101; (b) M.W. Viswamitra, O. Kennard, P.G. Jones, G.M. Sheldrick, S. Salisbury, L. Falvello, Z. Shakked, Nature 273 (1978) 687.
21. M. Manfait, A.J.P. Alix, P. Jeannesson, J.-C. Jardillier, T. Theophanides, Nucleic Acids Res. 10 (1982) 3803.
22. P.S. Kushwaha, P.C. Mishra, Journal of Molecular Structure 636 (2003) 149.
23. S. Bagheri, Z. Bayat, S. J. Mahdizadeh, E. Taghizadeh, J. Chem. Pharm. Res. 3 (2011) 370.
24. (a) M. R. Sawaya, J. Kraut, Biochemistry 36 (1997) 586; (b) C. A. Fierke, K. A. Johnson, S. J. Benkovic, Biochemistry 26 (1987) 4085; (c) P. J. Cayley, S. M. Dunn, R. W. King, Biochemistry 20 (1981) 874.
25. S. M. Hassani<sup>1</sup>, S. Bagheri, H. Ghahremani, Annals of Biological Research 3 (2012) 2393.
26. A. Kamal, G. Balakrishnan, G. Ramakrishna, T. B. Shaik, K. Sreekanth, M. Balakrishna, Rajender, D. Dastagiri, S. V. Kalivendi, Eur. J. Med. Chem. 45 (2010) 3870.
27. (a) C. Costa, J. F. Huneau, D. Tome, Biochim. Biophys. Acta. 1509 (2000) 95; (b) M. J. Medina, Nutr. 131 (2001) 2539.
28. J. L. Zalkin, J. L. Smith, Adv. Enzymol. Relat. Areas. Mol. Biol. 72 (1998) 87.
29. K. Srikanth, B. Debnath, T. Jha. Bioorg. Med. Chem. 10 (2002) 1841.
30. B. Elidriessia, A. Ousaa, M. A. Ajana, T. Lakhli, M. Bouachrine, Int. J. Sci. Res. Environ. Sci. Toxicol. 3 (2018) 1.
31. Monika, R. Dhingra, A. Gupta, A. kaul, M. Sharma, N. Dhingra, Acta Scientific Pharmaceutical Sciences 2.11 (2018) 41.
32. I. Miladiyah, J. Jumina, S. Mubarika Haryana, M. Mustofa, Drug Design, Development and Therapy 12 (2018) 149.
33. J. J. P. Stewart, J. Mol. Model. 19 (2013) 1.
34. S. Gunasekaran, B. Anita, S. Seshadri, Indian J. Pure Appl. Phys. 48 (2010) 183.

35. A. Hirsch, M. Brettreich, Fullerenes: Chemistry and Reactions (Weinheim: John Wiley & Sons, Wiley-VCH Verlag GmbH & Co. KGaA (2006).
36. R. Bakry, R. M. Vallant, M. Najam-Ul-Haq, M. Rainer, Z. Szabo, C.W. Huck, G.K. Bonn, International Journal of Nanomedicine 2 (2007) 639.
37. (a) Z. Hajiahmadia, Z. Tavangara, H. Behzadic, Polycyclic Aromatic Compounds (2019); (b) S. Prylutska, A. Burlaka, Y. I. Prylutsky, U. Ritter, P. Scharff, Experimental Oncology 33 (2011) 162.
38. T. H. Ueng, H. W. Wang, Y. P. Huang, and C. C. Hung, Archives of Environmental Contamination and Toxicology 46 (2004) 4.
39. B. D. Jeffy, E. J. Chen, J. M. Gudas, D.F. Romagnolo, Neoplasia 2 (2000) 460.
40. (a) B. Sadikovic, D. I. Rodenhiser, Toxicology and Applied Pharmacology 216 (2006) 458; (b) Q. Shi, L. -E. Wang, M. L. Bondy, A. Brewster, S. E. Singletary, Q. Wei, Carcinogenesis 25 (2004) 1695.
41. P. Huetz, V. Poux, Journal of Molecular Structure: THEOCHEM 764 (2006) 167.
42. Y. Garazd, M. Garazd, R. Lesyk, Saudi Pharmaceutical Journal 25 (2017) 214.
43. L. Ouattara, K. Bamba, M. Guy-Richard Koné, J. S. N'dri, K. N. N'Guessan, O. P. Massapihanoro, D. Fatogoman, Chemical Sciences International Journal 26 (2019) 1.
44. A. Siwek, J. Stefańska, K. Dzitko, A. Ruszczak, J. Mol. Model 18 (2012) 4159.
45. (a) S. Huang, R. Lin, Y. Yu, Y. Lu, P. J. Connolly, G. Chiu, S. Li, S. L. Emanuel, S. A. Middleton, Bioorganic Med. Chem. Lett. 17 (2007) 1243; (b) E. E. Elboray, R. Grigg, C. W. G. Fishwick, C. Kilner, M. a. B. Sarker, M. F. Aly, H. H. Abbas Temirek, Tetrahedron 67 (2011) 5700; (c) S.-A. Thompson, P. B. Wingrove, L. Connelly, P. J. Whiting, K. Wafford, Mol. Pharmacol. 61 (2002) 861.
46. J. Quiroga, Y. Villareal, J. Gálvez, A. Ortíz, B. Insuasty, R. Abonia, M. Raimondi, S. Zacchino, Chemical and Pharmaceutical Bulletin Advance Publication by J-STAGE, (2016)
47. X. Wang, Y. Dong, L. Wang, S. Han, Chemosphere 44 (2001) 447.
48. R. B. Nawale, S. S. Ashtekar, IJRPC 4 (2014) 26.
49. J. Li, X. Tian, Y. Gao, S. Shang, J. Feng, X. Zhang, RSC Adv. 5 (2015).
50. R. González-Chávez, R. Martínez, M. E. Torre-Bouscoulet, M. Gallo, M. M. González-Chávez, Chem. Pharm. Bull. 62 (2014) 16.
51. M. Á. Zermeño-Macías, M. M. González-Chávez, F. Méndez, R. González-Chávez, A. Richaud, Molecules 22 (2017) 427.
52. K. Santosh, M. S. Niranjana, K. C. Chaluvaraju, C. M. Jamakhandi, K. Dayanand, Journal of Current Pharmaceutical Research (2010)
53. N. J. Stéphane, K. M. Guy-Richard, K. C. Guillaume, A. S. Thomas, K. A. Landry Claude, O. Z. Adama, Z. Nahossé, IO SR Journal of Pharmacy 7 (2017) 27.
54. A. Agrawal, Int. J. Pharm. Sci. Nanotech. 4 (2011) 1394.
55. (a) V. R. Yadav, S. Prasad, B. Sung, B. B. Aggarwal, Int. Immunopharmacol. 11 (2011) 295; (b) M. Pilatova, L. Varinskaya, P. Perjesi, M. Sarissky, L. Mirossay, P. Solar, A. Ostro, J. Mojzis, Toxicol. Int. 24 (2010) 1347; (c) Y. Luo, R. Song, Y. Li, S. Zhang, Z. J. Liu, J. Fu, H. L. Zhu, Bioorg. Med. Chem. Lett. 22 (2012) 3039.
56. (a) E. Romano, A. B. Raschi, A. M. Gonzalez, G. Jaime, M. A. Fortuna, L. R. Hernandez, H. Bach, A. M. Benavente, Plant Physiol. Bioch. 49 (2011) 671; (b) C. S. Jeffrey, M. D. Leonard, A. E. Glassmire, C. D. Dodson, L. A. Richards, M. J. Kato, L. A. Dyer, J. Nat. Prod. 77 (2014) 148.
57. (a) M. A. Sanz, T. Voigt, H. Waldmann, Adv. Synth. Catal. 348 (2006) 1511; (b) A. K. Ghosh, D. D. Anderson, Future Med. Chem. 3 (2011) 1181.
58. C. F. Thompson, T. F. Jamison, E. N. Jacobsen, J. Am. Chem. Soc. 123 (2001) 9974.
59. (a) E. Otero, S. Vergara, S. M. Robledo, W. Cardona, M. Carda, I. D. Velez, C. Rojas, F. Otalvaro, Molecules 19 (2014) 13251; (b) G. Singh, A. Arora, S. S. Mangat, S. Rani, H. Kaur, K. Goyal, R. Sehgal, I. K. Maurya, R. Tewari, D. Choquesillo-Lazarte, S. Sahoo, N. Kaur, Eur. J. Med. Chem. 108 (2016) 287.
60. M. Mellado, L. Espinoza, A. Madrid, J. Mella, E. Chavez-Weisser, K. Diaz, M. Cuellar, Molecular Diversity (2019).
61. K. Drlica, X. L. Zhao, Microbiol. Mol. Biol. Rev. 61 (1997) 377.
62. H. C. Neu, Am. J. Med. America 82 (1987) 395.

63. (a) G. Palu, S. Valisena, G. Ciarrocchi, B. Gatto, M. Palumbo, *Proc. Natl. Acad. Sci.* 89 (1992) 9671; (b) C. Sissi, M. Andreoli, V. Cecchetti, A. Fravolini, B. Gatto, M. Palumbo, *Bioorg. Med. Chem.* 6 (1998) 1555.
64. (a) I. Turel, A. Golobi, A. Klavžar, B. Pihlar, P. Buglyó, E. Tolis, et al., *J. Inorg. Biochem.* 95 (2003) 199; (b) M. P. López-Gresa, R. Ortiz, L. Perelló, J. Latorre, M. Liu-González, S. García-Granda, et al., *J. Inorg. Biochem. Spain* 92 (2002) 65.
65. S. Deng, X. Zeng, W. Hu, X. Liu, *International Conference on Biomedical Engineering and Biotechnology* (2012).
66. (a) F.-Y. Wu, L.-N. Zhang, Z.-J. Ji, X.-F. Wan, *J. Lumin* 130 (2010) 1280; (b) M.R. Malik, V. Vasylyeva, K. Merz, N. Metzler-Nolte, M. Saleem, S. Ali, A.A. Isab, K.S. Munawar, S. Ahmad, *Inorg. Chim. Acta* 376 (2011) 207; (c) S.A. Khan, N. Singh, K. Saleem, *Eur. J. Med. Chem.* 43 (2008) 2272.
67. S. M. Soliman, *Asian Journal of Chemistry* 26 (2014) 1161.
68. P. A. Datar, *Journal of Computational Medicine*, (2014).
69. L. Hernández-Ochoa, C. A. Macías-Castañeda, G. V. Nevárez-Moorillón, E. Salas-Muñoz, F. Sandoval-Salas, *CyTA J. Food.* 10 (2012) 85.
70. S. Andrade-Ochoa, K. F. Chacón-Vargas, G. V. Nevárez-Moorillón, B. E. Rivera-Chavira, L. R. Hernández-Ochoa, *Adv. in Biol. Chem.* 3(2013) 480.
71. S. Andrade-Ochoa, G. V. Nevárez-Moorillón, L. E. Sánchez-Torres, M. V.-García, B. E. Sánchez-Ramírez, L. M. Rodríguez-Valdez, B. E. Rivera-Chavira, *BMC Complementary and Alternative Medicine* 15 (2015) 332.
72. (a) N. C. Desai, A. Dodiya, N. Shihory, *J. Saudi. Chem. Soc.* 17 (2013) 259; (b) K. P. Rakesh, H. M. Manukumar, D. C. Gowda, *Bioorg. Med. Chem. Lett.* 25 (2015) 1072.
73. A. G. Al-Sehemi, A. Irfan, S. A. Alrumman, A. El-Latif Hesham, *Bull. Chem. Soc. Ethiop.* 30 (2016) 307.
74. (a) A. G. Al-Sehemi, *JKAU: Sci.* 18 (2006) 47; (b) A. G. Al-Sehemi, M. A. M. Al-Melfi, A. Irfan, *Struct. Chem.* 24 (2013) 499.
75. M. K. Kathiravan, A. B. Salake, A. S. Chothe, P. B. Dudhe, R. P. Watode, M. S. Mukta, S. Gadhwe, *Bioorg. Med. Chem.* 20 (2012) 5678.
76. D. J. Shrinivas, R. D. Sheshagiri, A. M. Uttam, A. Tejjaraj, H. K. Venkatrao, K. G. Andanappa, *Mini Rev. Med. Chem.* 14 (2014) 678.
77. H. Bendaha, L. Yu, R. Touzani, R. Souane, G. Giaever, C. Nislow, C. Boone, S. El Kadiri, G. W. Brown, M. Bellaoui, *Eur. J. Med Chem.* 46 (2011) 4117.
78. K. Singh, D. P. Singh, M. S. Barwa, P. Tyagi, Y. Mirza, *J. Enzyme Inhib. Med. Chem.* 21 (2006) 557.
79. B. S. Holla, K. N. Poojary, B. S. Rao, M. K. Shivananda, *Eur. J. Med. Chem.* 37 (2002) 511.
80. (a) O. A. El-Gammal, M. M. Bekheit, M. Tahoona, *Spectrochim. Acta AMol. Biomol. Spectrosc.* 135 (2015) 597; (b) J. Hurtado, L. Ibarra, D. Yepes, P. García-Huertas, M. A. Macías, O. Triana-Chavez, E. Nagles, L. Suescun, A. Muñoz-Castro, *J. Mol. Struct.* 1146 (2017) 365; (c) A. -N. M. A. Alaghaz, R. A. Ammar, *Eur. J. Med. Chem.* 45 (2010) 1314.
81. R. A. Murcia, S. M. Leal, M. V. Roa, E. Nagles, A. M. -Castro, J. J. Hurtado, *Molecules* 23 (2018) 2013.
82. L. B.- Chibane, V. Forquet, P. Lantéri, Y. Clément, L. L.- Akkari, N. Oulahal, P. Degraeve, C. Bordes, *Frontiers in Microbiology* 10 (2019) 1.
83. P. Kumar, B. Narasimhan, D. Sharma, *ARKIVOC* 13 (2008) 159.
84. G. Lin, K. K. Midha, E. M. Hawes, *J. Heterocycl. Chem.* 28 (1991) 215.
85. J. N. Dominguez, S. Lopez, J. Charris, L. Iarruso, G. Lobo, A. Semenow, J. E. Olson, P. J. Rosenthal, *J. Med. Chem.* 40 (1997) 2726.
86. J. Raval, K. K. Desai, *ARKIVOC* xiii (2005) 21.
87. N. Motohashi, M. Kawase, S. Saito, H. Sakagami, *Curr. Drug Target* 10. 1 (2000) 237.
88. M. Viveros, L. Amaral, *Int. J. Antimicrob. Ag.* 17 (2001) 225.
89. L. Amaral, J. E. Kristiansen, *Int. J. Antimicrob. Agents*, phenothiazine: an alternative to conventional therapy for the initial management of suspected multidrug resistant tuberculosis. *Acall for studies.* 14 (2000) 173.
90. A. A. Fadda, A. Fekri, N. M. Bayoumy, *RSC Advances*
91. R. N. Jones, A. L. Barry, T. L. Gavan, I. I. J. A. Washington, in: E.H. Lennette, A. Ballows, W.J. Hausler Jr., H.J. Shadomy (Eds.), *Manual of Clinical Microbiology*, Fourth ed., Am. Soc. Microbiol. (1972), Washington DC, (1985).
92. A. Verma, S. K. Saraf, *Eur. J. Med. Chem.* 43 (2008) 897.

93. (a) S. G. Alegaon, K. R. Alagawadi, *Med. Chem. Res.* 21 (2012) 816; (b) M. J. Naim, M. J. Alam, S. Ahmad, F. Nawaz, N. Shrivastava, M. Sahu, O. Alam, *Eur. J. Med. Chem.* 129 (2017) 218.
94. C. D. Barros, A. A. Amato, T. B. de Oliveira, K. B. R. Iannini, A. L. da Silva, T. G. da Silva, E. S. Leite, M. Z. Hernandez, M. C. A. de Lima, S. L. Galdino, *Bioorg. Med. Chem.* 18 (2010) 3805.
95. (a) L. C. Santos, F. T. Uchôa, A. R. P. A. Canas, I. A. Sousa, R. O. Moura, M. C. A. Lima, S. L. Galdino, I. R. Pitta, J. Barbe, *Heterocycl. Commun.* 11 (2005) 121; (b) R. Maccari, A. del Corso, M. Giglio, R. Moschini, U. Mura, R. Ottana, *Bioorg. Med. Chem. Lett.* 21 (2011) 200.
96. (a) M. P. Anthony, J. N. Burrows, S. Duparc, J. J. Moehrle, T. N. Wells, *Malar. J.* 11 (2012) 316; (b) R. K. Sharma, Y. Yonis, G. Mugumbate, M. Njoroge, J. Gut, P. J. Rosenthal, K. Chibale, *Eur. J. Med. Chem.* 90 (2015) 507.
97. (a) S. K. Bharti, G. Nath, R. Tilak, S. K. Singh, *Eur. J. Med. Chem.* 45 (2010) 651; (b) B. F. Abdel-Wahab, H. A. Abdel-Aziz, E. M. Ahmed, *Eur. J. Med. Chem.* 44 (2009) 2632.
98. Raíssa K. C. de Paiva, a Jamerson F. da Silva, Hudieyllen A. Moreira, Osvaldo G. Pinto, Lilian T. F. M. Camargo, c, d Plínio L. F. Naves, Ademir J. Camargo, d Luciano Ribeiro, d L. M. Ramos, *J. Braz. Chem. Soc.* 30 (2019) 164.
99. H. M. Gilles, World Health Organisation GENEVA 56 (1991).
100. C. Warhurst, J. C. Craig, I. S. Adagu, D. J. Meyer, S. Y. Lee, *Malaria Journal* 2 (2003).
101. (a) J. L. Vennerstrom, H. N. Fu, W. Y. Ellis, A. L. Ager, J. K. Wood, S. L. Andersen, L. Gerena, W. K. Milhous, *J. Med. Chem.* 35 (1992) 3023; (b) H. Atheaya, S. I. Khan, R. Mamgain, D. S. Rawat *Bioorg. Med. Chem. Lett.* 18 (2008) 1446; (c) G. L. Ellis, R. Amewu, C. Hall, K. Rimmer, S. A. Ward, P. M. O'Neill, *Bioorg. Med. Chem. Lett.* 18 (2008) 1720.
102. M. C. de Paula, M. S. Valle, J. R. Pliego Jr., *Med. Chem. Res.* 23 (2014) 5197.
103. H. K. Hsieh, T. H. Lee, J. P. Wang, J. J. Wang, C. N. Lin, *Pharm Res* 15 (1998) 39.
104. L. Ni, C. Q. Meng, J. A. Sikorski, *Expert Opin Ther Pat* 14 (2004) 1669.
105. F. Lunardi, M. Guzela, A. T. Rodrigues, R. Correa, I. Eger-Mangrich, M. Steindel, E. C. Grisard, J. Assreuy, J. B. Calixto, A. R. Santos, *Antimicrob Agents Chemother* 47 (2003) 1449.
106. T. Owa, T. Okauchi, K. Yoshimatsu, N. H. Sugi, Y. Ozawa, T. Nagasu, N. Koyanagi, T. Okabe, K. Kitoh, H. Yoshino, *Bioorg Med Chem Lett* 10 (2000) 1223.
107. (a) F. Uchiumi, T. Hatano, H. Ito, T. Yoshida, S. I. Tanuma, *Antiviral Res* 58 (2003) 89; (b) J. H. Wu, X. H. Wang, Y. H. Yi, K. H. Lee, *Bioorg. Med. Chem. Lett.* 13 (2003) 1813.
108. (a) G. Bhattacharya, J. Herman, D. Delfin, M. M. Salem, T. Barszcz, M. Mollet, G. Riccio, R. Brun, K. A. Werbovets *J Med Chem* 47 (2004) 1823; (b) P. Boeck, C. A. B. Falcaño, P. C. Leal, R. A. Yunes, V. Cechinel Filho, V. E. C. Torres-Santos, B. Rossi-Bergmann, *Bioorg Med Chem* 14 (2006) 1538.
109. (a) C. R. Andrighetti-Frohner, K. N. Oliveira, D. Gaspar-Silva, L. K. Pacheco, A. C. Joussef, M. Steindel, C. M. O. Simões, A. M. T. Souza, U. O. Magalhães, I. F. Afonso, C. R. Rodrigues, R. J. Nunes, H. C. Castro, *Eur. J. Med. Chem.* 44 (2009) 755; (b) A. M. T. Souza, H. C. Castro, M. A. Brito, C. R. Andrighetti-Frohner, U. Magalhaes, K. N. Oliveira, D. Gaspar-Silva, L. K. Pacheco, A. C. Joussef, M. Steindel, C. M. O. Simoes, D. O. Santos, M. G. Albuquerque, C. R. Rodrigues, R. J. Nunes, *Curr. Microbiol.* 59 (2009) 374.
110. J. Bradshaw, R. T. Brittain, J. W. Clitherow, M. J. Daly, D. Jack, B. J. Price, R. Br. Stables, *J. Pharmacol.* 66 (1979) 464 P.
111. T. O. Yellin, S. H. Buck, D. J. Gilman, D. F. Jones, J. M. Wardleworth, *Life Sci.* 25 (1979) 2001.
112. R. C. Young, G. J. Durant, J. C. Emmett, C. R. Ganellin, M. J. Graham, R. C. Mitchell, H. D. Prain, M. L. Roantree, *Journal of Medicinal Chemistry* 29 (1986).
113. R. C. Young, G. J. Durant, J. C. Emmett, C. R. Ganellin, M. J. Graham, R. C. Mitchell, H. D. Prain, M. L. Roantree, *Journal of Medicinal Chemistry* 29 (1986).