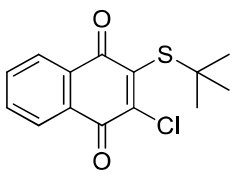
2.1. Quinone, A Promising Lead For Diverse Drug Development and Formulation

Quinones are an important class of compounds found in all respiring animal and plant cells, and exhibit a great variety of functions (Salas *et al.,* 2008). It is widely used as anti inflammatory (Lien *et al.,* 2002), antialergic (Lien *et al.,* 2002), laxative agents, anti-feedant, antiplatelet, apoptotic (Kim *et al.,* 2013) anticancer, neuroprotective, antifungal, anti-tubercular and antibacterial agents. 1,4-Naphthoquinone is a key class of quinone family. A number of derivatives containing this scaffold having anticancer activity are reported by various groups of scientists.

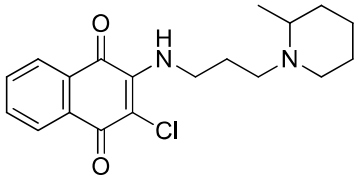
2.2. 1, 4-Naphthoquinones as Anticancer Agents

After years of research in the area of cancer therapeutics, scientists have not yet been able to synthesise or discover novel molecules that could effectively overcome the acquired and inherited resistance to the currently available treatment strategies. Hence, the mortality caused by this non-communicable disease is broadening at an alarming rate. In the next two decades, a population close to 25 million (75%) is anticipated to be the victims of cancer. (Steeg *et al.,* 2006). To find a solution to this, scientists have made an attempt to explore the natural products and their derivatives. Naphthoquinone chromophore is one such class of compounds with potential cytotoxic effect. It is reported that quinodal anthracycline antibiotics are the most utilized anticancer drug ever developed.

Kacmaz *et al.,* (2019) synthesized a series of N(H)-, S- and S,S-substituted 1,4-naphthoquinones with different amines. The newly synthesized compounds were characterized by using various analytical techniques, and evaluated for their antitumor activity through MTT assay against human cervical cancer (HeLa) cell line. The compound **1** (IC_{50} = 10.16 μM) and **2** (IC_{50} = 12.82 μM) revealed the highest antitumor activity against the HeLa cells along with the minimum IC_{50} values.

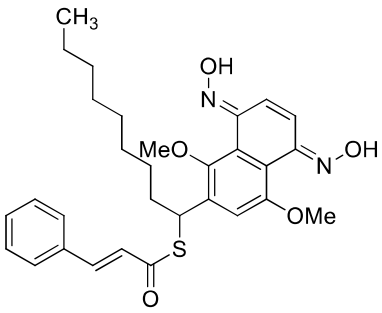


1



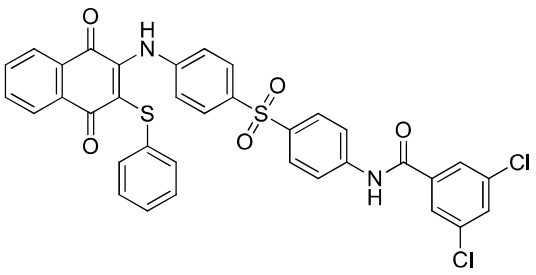
2

Huang *et al.,* (2019) synthesized and evaluated sulfur-containing 1,4-naphthoquinone oxime derivatives against various cancer cell lines for their anticancer potential. Obtained results corroborate high cytotoxic potential *vis-à-vis* positive controls while all the synthesized compounds are reported for safety profile towards the normal cells. 1,4-naphthoquinone oxime derivatives show higher cytotoxicity toward drug-susceptible cell lines. Among all the synthesized derivatives, compound **3** (IC_{50} 0.29 ± 0.01 to 1.33 ± 0.05µM) was recognized as the most potent agent toward MDR cell lines.



3

Phenylaminosulfanyl-1,4-naphthoquinone derivatives were synthesized and characterized by Ravichandiran *et al.,* (2019). Further to ensure the cytotoxicity profile of the newly synthesized compound are reported for anticancer activity against cancer cell lines i.e., HeLa, and MCF-7, A549. Almost all the compounds are represented for cytotoxic activity. In particular, compounds **4, 5** and **6** revealed notable cytotoxic potential. Besides this, all these selected compounds show cytotoxicity towards the normal human kidney i.e., HEK293 cell lines. Thus, the overall result corroborates that the synthesized compound does not shows any renal impairment.



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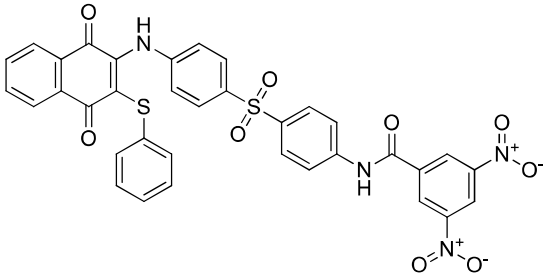

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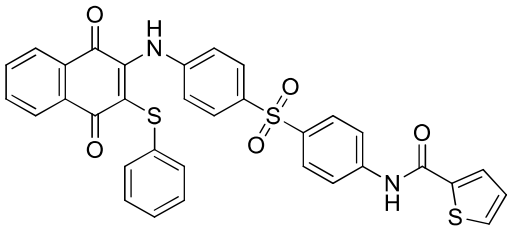
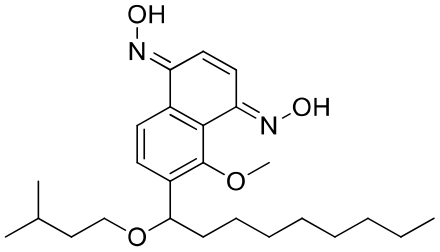


6

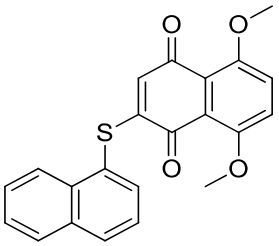
Zhang *et al.,* (2018) synthesised oxime derivatives to improve the safety and efficacy of 1,4-naphthoquinone. The prepared compounds were further evaluated for their anticancer potential in different cancer cell lines *viz.* breast cancer cell (MDA-MB-231), colorectal cancer cell (HCT-15), liver cancer cell (BEL-7402) and ovarian cancer cell (A2780). colorectal cancer cell (HCT-116). Among all the synthesized derivatives, compound 7 revealed the highest anticancer potential with the low IC_{50} values 0.66 ± 0.05 µM (MDA-MB-231), 5.11 ± 0.12 µM (BEL-7402) and 8.26± 0.22 µM (A2780).



7

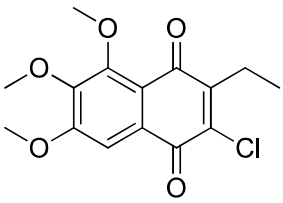
Wang *et al*., (2018) synthesized the novel derivative of naphthoquinone like 2-(naphthalene- 2-thio)-5,8-dimethoxy-1,4-naphthoquinone to enhance the therapeutic performance in the management of cancer. The study corroborates that compound **8** showed the most potent cytotoxic activity in concentration dependent method against

the gastric cancer cells. Notably increased generation of ROS was found on treating with compound **8,** due to induced mitochondrial-related programmed cell death in AGS cells.



8

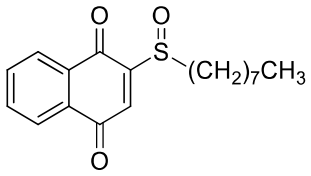
Li *et al.,* (2018) synthesized 1,4-naphthoquinone derivative i.e., 2-chloro-3-alkyl-1,4-naphthoquinone and examined its potential activity towards the myeloid leukaemia and (compound **9)** as most effective anticancer agent against leukaemia cell line (HL-60). The reported shows the damage mtDNA *via* cell cycle arrest at synthesis phase (S phase) followed by a G2/M phase and decrease in protein levels of mtDNA-specific DNA polymerase gamma (poly-gamma) and mtDNA transcription factor A (mt-TFA) after suaitable treatment of overnight.



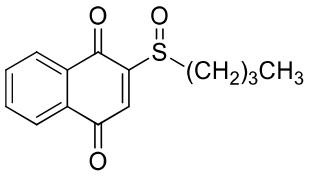
9

Liu *et al.,* (2018) synthesized two different derivatives of 1,4-naphthoquinone. Further, in order to study their effects, it was evaluated on hepatocellular carcinoma cells. Represented that notable increase in programmed cell death, production of reactive oxygen species (ROS) and increased cell cytotoxicity had observed with both the derivative i.e., compound **10** and **11**. Nevertheless, apoptosis was delayed on prior treatment with a specific ROS scavenger i.e., N-acetyl-l-cysteine. Result obtained from

the western blot study shows expression (phosphorylation of p38 and JNK) and supression (phosphorylation of ERK, Akt and STAT3) due to blockage by ROS scavenger on treating with the said derivatives. In addition, both the dervarives showed a significant inhibition in tumor growth and modulated MAPK and STAT3 signalling in mouse xenografts devoid of noticeable effects on body indices like., body weight, hematological parameters, etc. In nutshell, both the derivatives exhbits apoptosis in Hep3B cell line through ROS-mediated p38/MAPK, Akt and STAT3 signalling pathways.

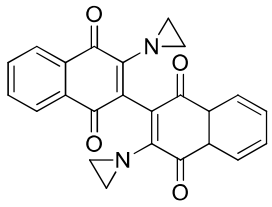


10



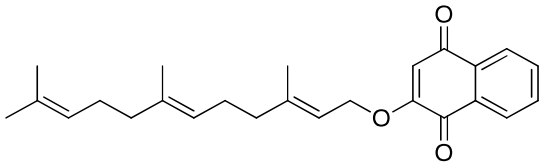
11

Cooper *et al.,* (2017) demonstrate the aziridine as alkylating moiety in the synthesized compound i,e, amino dimeric naphthoquinone (BiQ). Further the newly synthesized compound was evaluated for their cytotoxic potential (antileukemic activity). BiQ showed the enhanced potential against the acute myeloid leukemia (AML) cell lines i.e., decreased proliferation of cancerous cells and it is quite tolerated in NSG mice on systemic administration. Besides, generation of ROS and breaks of DNA fragmentaion was observed with BiQ. However, isostere of BiQ i.e., Bis-dimethylamine BiQ (devoid of alkylating moiety) does not have significant anti-AML activity. The synthesized compound **12** exhibits a superior cytotoxic profile with IC_{50} values i.e., 0.18 ± 0.06, 1.05 ± 0.05 and 0.65 ± 0.30 μM for MOLM-14, MV4-11, and THP-1 cell lines, respectively.



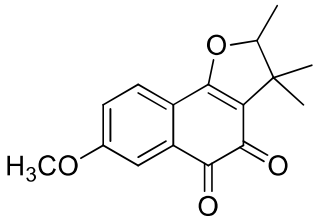
(12)

Wang *et al*., (2015) synthesized derivatives containing 2-O-alkyl-, 3-C-alkyl- or 2/3-N-morpholinoalkyl as substituent. All the synthesized compounds were evaluated for their cytotoxicity employing MTT assay against five different human cancer cell lines (HT-29, SW480, HepG2, MCF-7 and HL-60). Compund **(13)** exhibited utmost cytotoxicity against the above cell lines due to its down-regulation of the HT-29 survival rate. While during Hoechst staining, cells exhibited disruption of nuclear membrane and formation of nuclear bodies leading to apoptosis. While, flow cytometry explain the activity of compound **13** in synthesis phase of cell cycle and effect of concentration-dependent on apoptosis employing Annexin V-FITC/propidium iodide assay over HT-29 cells.



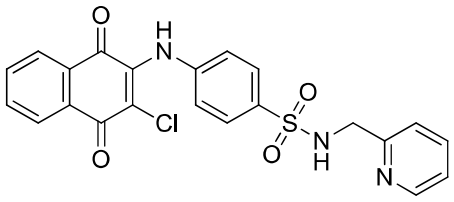
13

Inagaki *et al.,* (2015) described the versatality of naphthoquinones for anticancer potential. They demonstrated that synthetic naphthoquinones slow down cell proliferation against human leukemia cells (HL-60). Among all the compounds, derivative **14** was found to be potentially cytotoxic and to elevate the concentration of intracellular glutathione disulfide.



14

Pingaew *et al.,* (2015) synthesized naphthoquinone derivatives conjugated with sulfonamide moieties (open and closed chain), and evaluated their cytotoxic and antimalarial potential. All derivatives showed cytotoxic potential against four cancer cell lines including HepG2, HuCCA-1, MOLT-3, and A549. Most of the quinones exhibited improved anticancer activity over liver cancer cell (HepG2) as compared to etoposide. Amog the compound **15, 16** and **17** depicted most potential activity with minimun IC_{50}values. Important chemical features related to biological activities was also corelated with quantitative structure-activity relationships.



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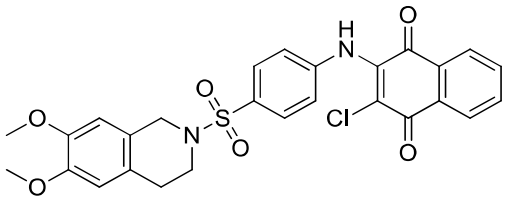

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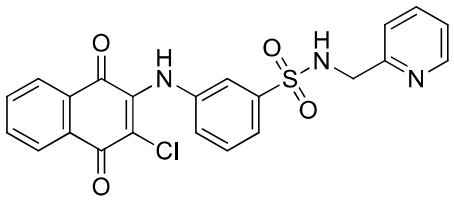
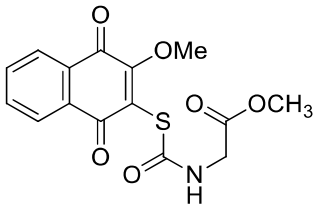


17

A series of semisynthetic naphthoquinone amide analogues synthesized by Sreelatha *et al*., in 2014. The structure of the synthesized compounds were elucidated using spectral (^{1}H NMR, ^{13}C NMR, Mass, IR) and elemental analysis. Anticancer potential of the compounds were screened using SAS and HeLa cell line. 3D-QSAR revealed that enhanced activity against HeLa cells when an electron donating group was in close proximity to sulphur. Among all, compounds **18, 19** and **20** were found to be most potent with IC_{50} values of 16, 12, 14 µM, respectively.



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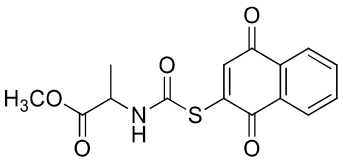

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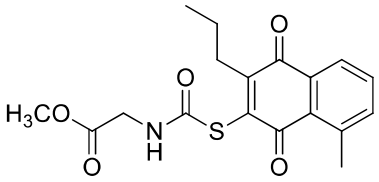
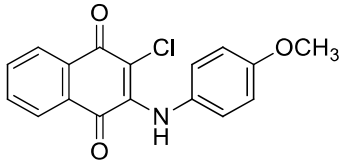


20

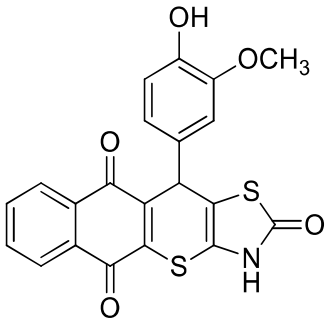
Prachayasittikul *et al*., (2014) synthesized 2-substituted-amino-3-chloro-1,4-naphthoquinone analogues, and evaluated them for anticancer potential in HuCCA-1, HepG2, MOLT-3 and A549 cell lines. Among all the synthesized compounds, derivative **21** exhibited most potent anticancer activity against A549, HuCCA-1 and HepG2 cell line. IT had IC_{50} values of 12.279, 2.364 and 12.279 µM respectively. Where as compound **21** displayed the most cytotoxic potential against cancer cell line (MOLT-3) with an IC_{50} value of 2.118 µM.



21

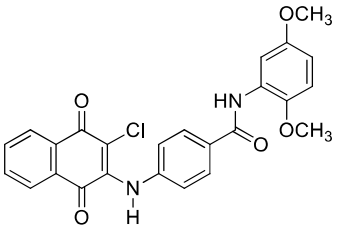
Atamanyuk *et al*., (2014) employed hetero-Diels-Alder reaction to synthesize 11-substituted-3,11-dihydro-2*H*-benzo[6,7]thiochromeno[2,3-d][1,3]-thiazole 2, 5, 10 triones 1,4-naphthoquinone using 5-arylidene-4-thioxo-2-thiazolidinones and 1,4-

naphthoquinone. The synthesized compounds were investigated for their anticancer potential. Among all the synthesized compounds, derivative **22** exhibited moderate selectivity against melanoma cancer cells (UACC-257) with GI_{50} 0.22 μM.



22

Xu *et al*., (2012) synthesized naphthoquinone derivatives and examined them against DU145, A549, KBvin and KB, cancer cell lines. Few compounds **23, 24, 25, 26, 27** and **28** depicted anticancer activities comparable to that of proteasome inhibitor **(**PI-083).Among all, compounds **23, 24, 25, 26, 27** and **28** were established as 20S proteasome inhibitor in cell-based and *in-vitro* assays.



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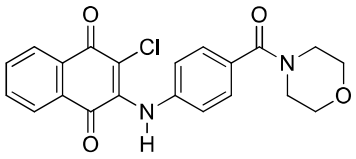

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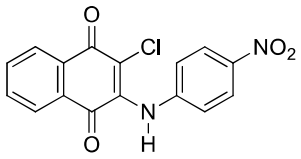

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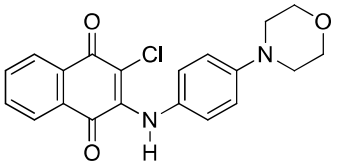

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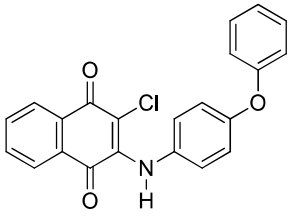

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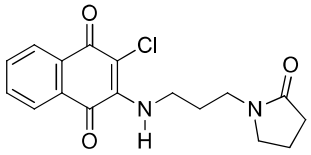
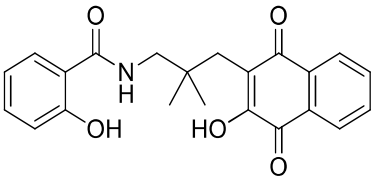


28

Sixteen aromatic amides of naphthoquinone were prepared by Pradidphol *et al.,* (2012) and evaluted for their anticancer potential. *In-vitro* cell based study showed that potent inhibition in NCI-H187 and KB cells lines by compound **29**, **30** and **31**, respectively,

Inhibition of hTopoIIalpha was observed at two different concentration i.e., 20 and 50 µM for compounds **29** and **31** and compounds **30**, and **32**, respectively. Similar trends were observed with docking study.



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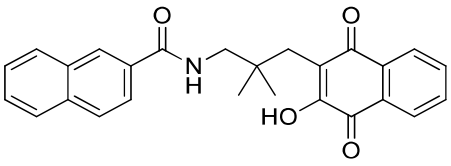

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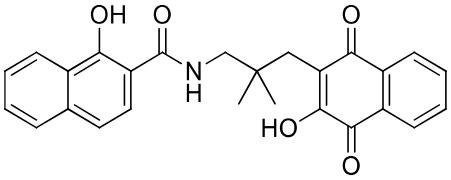

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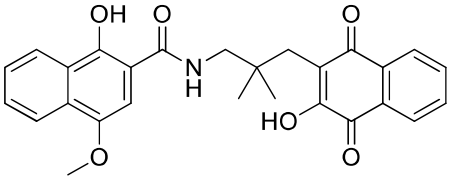
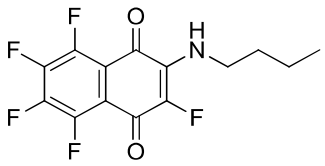


32

Six derivatives of polyfluoro-1,4-naphthoquinone were prepared and their antioxidant and mutagenic properties in Salmonella cells, as well as cytotoxicity in mouse fibroblasts (LMTK), human mammary adenocarcinoma (MCF-7), human myeloma (RPMI 8226), and primary mouse fibroblast cells (PMF) were studied by Zakharova *et al.,* (2010). The growth of tumor cells was efficiently inhibited by compound **33** wheras compound **34** displayed less growth-inhibiting properties towards mammalian cells.. However compound **35** and **36**, exhibited low cytotoxicity and they have no or negligible sign of cytotoxicity towards PMF and LMTK cell lines as compared to tumor human cell lines.



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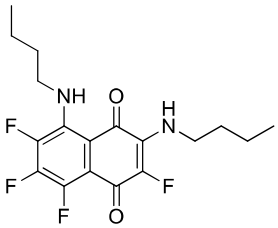

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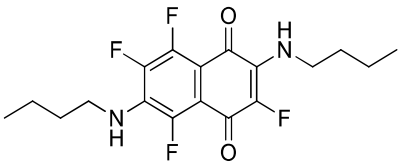
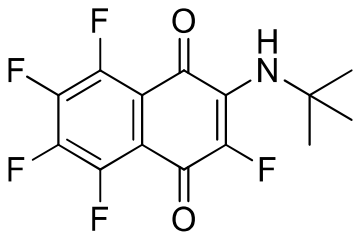


35

Similarly a few naphthoquinone analogs were synthesized and evaluated by Zakharova *et al.*, (2010). Compound **36** inhibited the growth of tumor cells and normal control at the same concentration while 50% decrease in cancer cell growth was observed with compounds **37**, **38** and **39** at low and comparable concentrations in the range of 2.4 to 8.6 μM while being significantly less cytotoxic toward normal PMF and LMTK cells.



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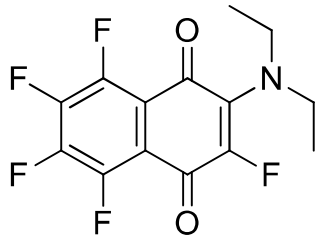

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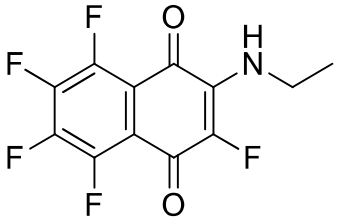

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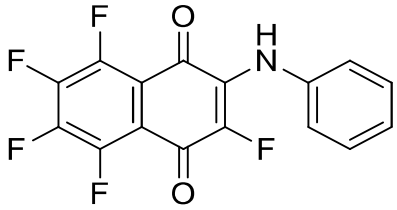
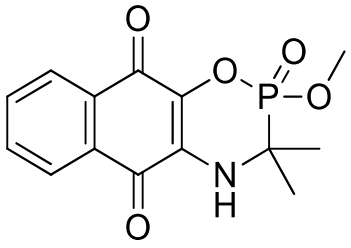


39

Wang *et al*., (2008) synthesized a series of naphthoquinone fused analogs and evaluated for antitumor potential in human cancer cell lines. A significant cytotoxicity with IC_{50} values in a range from 0.019- 5.15 μM were observed by compounds **40**, **41** and **42**. Further, inhibition assays revealed that naphthoquinone derivatives inhibited the topoisomerase II catalytically.



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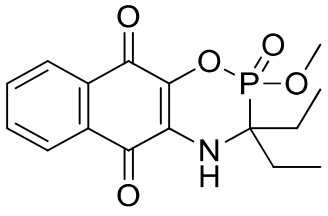

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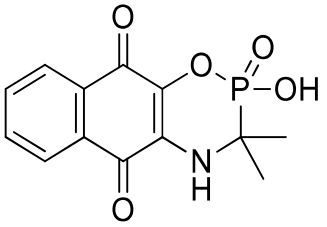
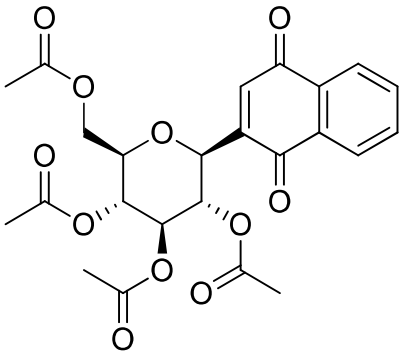


42

Glucosyl and galactosyl naphthoquinone derivatives were synthesized by Lin *et al*., (2008). Cytotoxic acitivity of these compounds were evaluated in vitro against the human melanoma cell line (A375). Compounds **43**, **44**, **45** and **46** depicted an improved cytotoxic potential as compared to 1,4-naphthoquinone.



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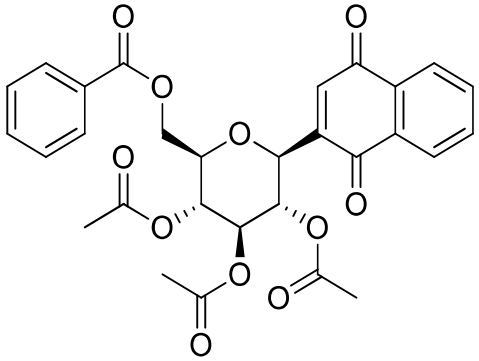

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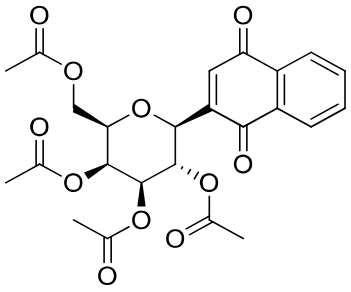

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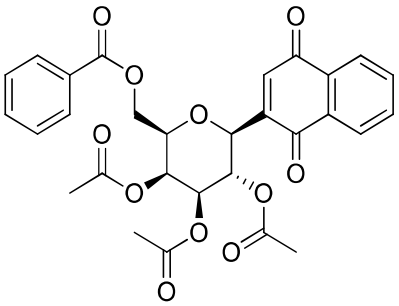
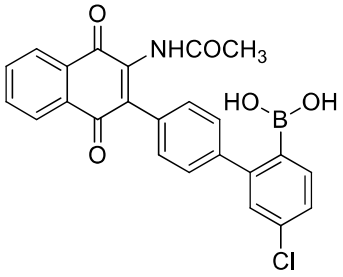


46

Hadden *et al.,* (2009) examined the rationale based designed series of derivatives containing the naphthoquinone moiety for Hsp90 inhibitory activity. The most potent inhibitors showed effective in vitro activity with low IC_{50} values in anticancer and Her2 degradation assays. The compound **47, 48** and **49** exhibited increased anticancer potential against MCF-7 cells over skbr3 cells along with IC_{50} values 0.2 ± 0.03, 1.6 ± 0.4 and 2.0 ± 0.06 μM.



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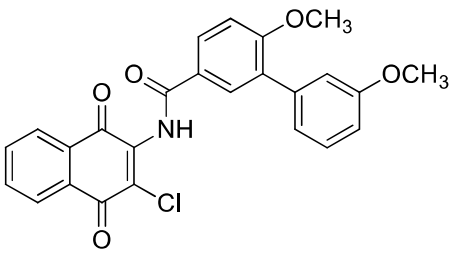

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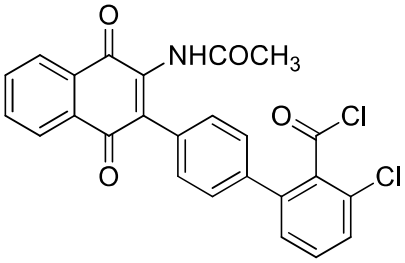
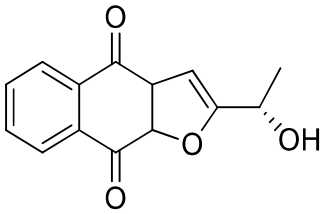


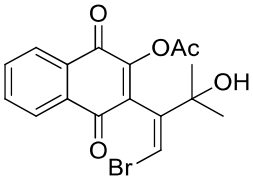
49

Stereoselective synthesis of biologically active naphthoquinones from a Brazilian traditional medicine Tabebuia avellanedae, was achieved by Yamashita *et al*., (2007). Compound **50** showed potent cytotoxicity against various human cancer cell lines, as compared to normal human cell lines as compared with that of mitomycin.



50

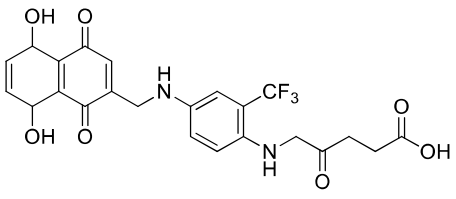
Sacau *et al.,* (2007) synthesized a set of **51** natural naphthoquinones analogs, and evaluated it over human promyelocytic leukaemia cell line (HL-60). Comparative molecular similarity index (CoMSIA) /3D-QSAR studies and Catalyst/HypoGen pharmacophore modelling approach was applied to explain the cytotoxicity of the synthesized compounds.



51

Kim *et al.,* (2006) synthesized 6 or 2-substituted 5,8-dimethoxy-1,4-naphthoquinone and 5,8-dihydroxy-1,4-naphthoquinone analogs, and evaluated their cytotoxic potential against P388 and L1210 cancer cells. Their antitumor potentail was also screened in

mice having S-180 cells in the peritoneal cavity. In comparison with the dimethoxy naphthoquinone derivatives, the dihydroxy naphthoquinone derivatives depicted more potent bioactivities against both P388 and L1210 cells *in-vitro,* and S-180 cells *in-vivo*. The ED_{50} values of dihydroxy and dimethoxy naphthoquinone derivatives against P388 cells were found to be in the range 0.18-1.81 and 0.26-40.41 µg/mL, respectively.It was also found that the 2-substituted analogues **52, 53** and **54** exhibited better antitumor potential in the mice having S-180 cells in the peritoneal cavity.



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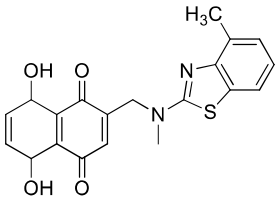

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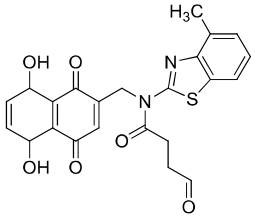
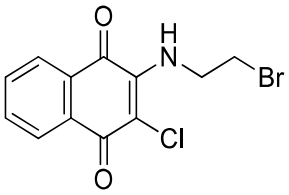


54

Brun *et al*., (2005) reported IC_{50} values in range from 15.40 ± 2.7 to 1.75 ± 0.1µg/mL against CDC25B for the compounds derived from vitamin K_3. These naphthoquinone analogs also showed anticancer activity on HeLa cells and inhibit cell growth at submicromolar concentrations in a clonogenic assay. As a hallmark of apoptosis they increased inhibitory activity of tyrosine 15 phosphorylation of the CDK and induced cleavage of PARP. The compound **55** possessed the best anticancer potential. The ester compounds **56** and **57** also exhibited the potent antiproliferative activity but it was less potent to the compound **55**.



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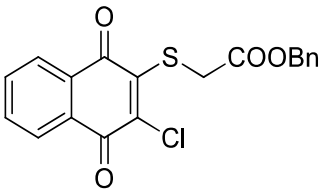

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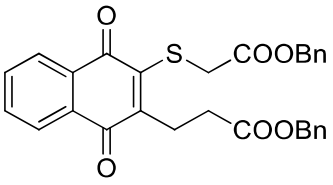
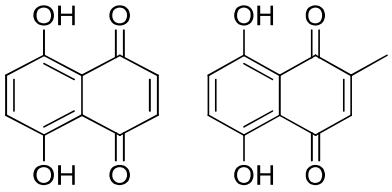


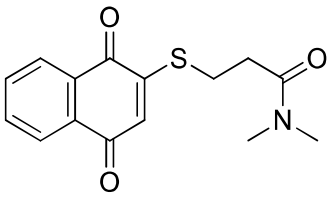
57

Tandon *et al.,* (2004), synthesized a series of 1,4-naphthoquinone analogs and evaluated for antitumor potential on carcinoma cell line (Walker 256). The compounds **58** and **59** were found to be active among all the synthsized compounds against carcinoma cell line.



58 **59**

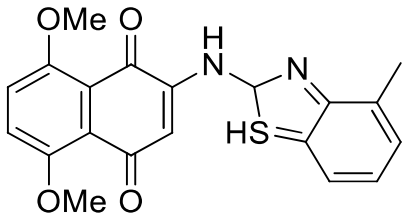
In other study Tandon *et al.,* (2004) synthesized and evaluated few naphthoquinone and benzoquinone derivatives for anticancer activities. The results showed that compound **60** was only active analog against P 388 Lymphoid Leukaemia cells.



(60)

Chung *et al.,* (2004) prepared 6 or 2-Substituted naphthoquinone derivatives and evaluated them for cytotoxic effect against cancer cells SNU-1 and L1210. The antitumor activity was also assessed in mice having S-180 cells in peritoneal cavity and it was observed that 6-substituted naphthoquinone derivatives depicted more potency in both the activities than 2-substituted naphthoquinone analog against L1210 and S-180 cells. Interestingly, it was found that compound 61, exhibited a potent antitumor activity than 6-substituted compounds against SNU-1 and L1210. Compound **61** was found to be equipotent to Adriamycin against L1210 whereas it showed better activity against the solid cancer cell line (SNU-I) when compared with standard Adriamycin.

Besides this, compound **61** also exhibited better *in- vivo* activity against S-180 cells in the peritoneal cavity.



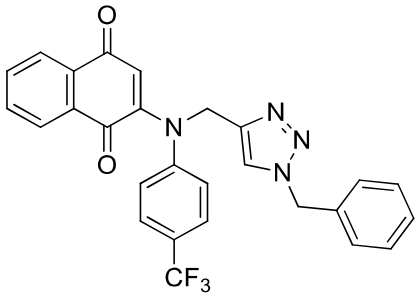
61

2.3. 1,4-Naphthoquinones as Anti-tubercular Agents

According to World Health Organization (WHO), a global population of more than one-third is infected with tuberculosis (T.B.) and an estimated 1.5 million deaths occurred in 2013, out of which 0.36 million people were infected with both human immunodeficiency virus (HIV) and TB (Danne *et al.,* 2018). The long duration therapy generally results in noncompliance of the treatment and finally in multidrug resistance tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), which are highly lethal, extremely expensive and complicated to treat, posing tough challenges for the prevention, treatment and control of TB (Lienhardt *et al.,* 2010). Isoniazid and Rifampicin are effective anti-TB drugs, but MTB has developed resistance against the first-line as well as the second-line drugs which is emerged as a serious problem (Sankar *et al.,* 2013). Therefore, there is an urgent need to develop new inhibitors that reduce the complexity and duration of the current therapeutic treatment as well as effectively treat MDR and XDR tuberculosis (Zaman*et al.,* 2010).

A series of amino-1,4-naphthoquinone appended triazoles was prepared *via* a conventional three-component reaction of substituted N propargyl amino naphthoquinones with 2-bromonaphthalene-1,4- dione/substituted alkyl bromides and sodium azide in the presence of N,N,N-triethyl amine/CuI using water as a solvent by

Bala and Muthusaravanan. Amino naphthoquinone-appended iminochromene-triazole conjugates were also prepared from the amino-1,4-naphthoquinone clubbed-1, 2, 3-triazolyl acetonitriles. All the synthesized compounds were assessed for their *in-vitro* antimycobacterial activity. Among the synthesized compounds, derivative **62** emerged as the most potent one with IC_{50} 1.87 μM, being 6-fold potent than the standard drug, cycloserine, whereas 20-fold more potent than pyrimethamine and comparably active as the standard drug ethambutol (IC_{50}< 1.56 μM).

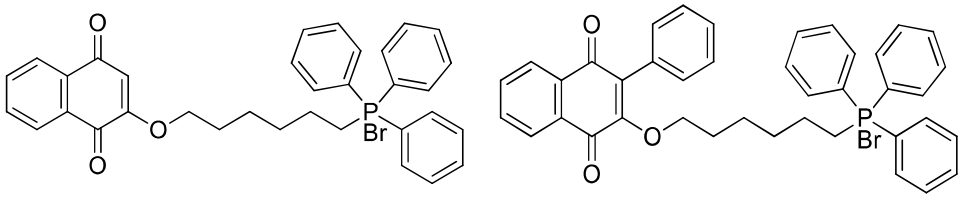


62

2.4. 1, 4-Naphthoquinones as Antimalerial Agents

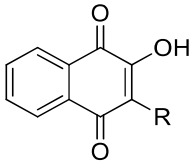
Malaria is a major parasitic disease in the tropical and subtropical regions of the world. In 2015, the World Health Organization (WHO) estimated 214 million new cases resulting in 438,000 deaths, mostly children under 5 years of age were affected. The efficacies of existing anti-malarial drugs are limited by the existence of drug-resistant parasites worldwide (Gama *et al.,* 2010; Segurado *et al.,* 1997). A solution to this is to discover drugs acting on new targets or improve the already in-use drugs. Studies confirmed the anti-parasitic activity of hydroxy-naphthoquinone derivatives against Leishmania braziliensis and Leishmania amazonensis (Souza-Silva *et al.,* 2014),Trypanosomacruzi(Pieretti *et al.,* 2013) and *P.* falciparum (Hussain *et al.,* 2012; de Souza *et al.,* 2014; de Rezende *et al.,* 2014) by means of the inhibition of the mitochondrial electron carrier chain (Ehrhardt *et al.,* 2013).

Lu and his coworkers (2012), synthesized hydroxy-substituted-1,4-naphthoquinones and screened for antiplasmodial activity against P. falciparum. The atovaquone derivatives were observed to be inactive as antagonists for parasite growth; it was due to dissociation of acidic hydroxyl moiety. Upon alteration to an alkoxy group, the antiplasmodial potential was restored in the sub-100 nM range. Optimal inhibitors showed lower IC_{50} against heteroresistant P. falciparum W2. Antiplasmodial investigation showed that the 2-alkoxy derivatives **63** (IC_{50} = 28.5 ± 3.0) and **64** (IC_{50} = 46.7 ± 4.4 nM) exhibited significantly enhanced activity.



63 **64**

Gokhale *et al.,* (2006), reported the complex of 3-arylazo-4-hydroxy-1,2-naphthoquinone with copper II. The *in-vitro* antimalarial effect of prepared complex molecules against P. falciparum strain (3D7) showed relation with metal redox couple, showing component of electron transport chain of parasite as a possible target.The compound **65**, (ED_{50} = 3.5 µg/ml) was observed to be the most potent. It exhibited approximately 10-fold increase in the antimalarial potential.



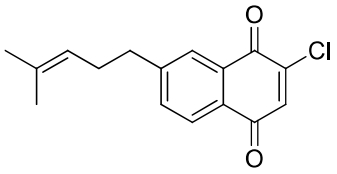
65

2.5. 1, 4-Naphthoquinones as Antifungal Agents

Based on its primary area of infection, fungal infection in humans can be categorized as superficial and systemic mycoses. Systemic fungal infections are increasing the

morbidity and mortality rate of hospitalized patients with impaired immune systems brought about by the use of cytotoxic drugs, immunosuppressive therapy, or human immunodeficiency virus infection. Anti-fungal agents like fluconazole and itraconazole are widely used in clinical settings but have weaker pharmacokinetic and pharmacodynamic profile. Resistance to these drugs have arouse the strong need of developing effective antifungal drug (Lee *et al*., 1999; Charlier *et al.,* 2006).

Castro *et al.,* (2013) prepared heterocycle-fused-1,4-naphthoquinones and 1,4-anthracenediones and evaluated their *in vitro* antifungal potential against Candida species. (human pathogenic yeasts) and filamentous fungi (Trichophyton species, Fusarium species and Aspergillus species). The most active compounds **66**, **67**, **68**, **69** and **70**, showing MIC values in the low µg/mL range, were those possessing one or two halogen atoms particularly chlorine, substituted in the quinone ring.



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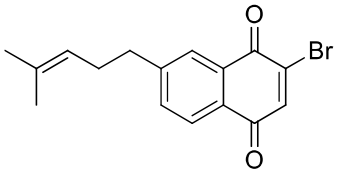

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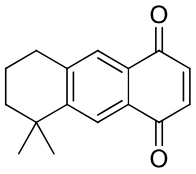

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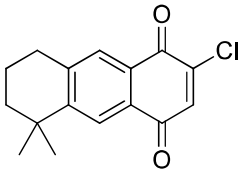

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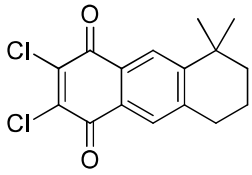
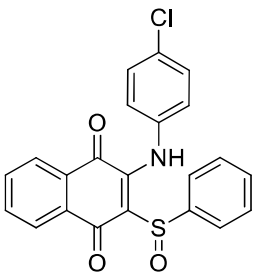


70

A library of naphthoquinone and naphthalene derivatives were synthesized and evaluated against several fungi by Errante *et al.,* (2006). The activities of these compound **71**, **72** and **73** were found to be more compared to amphotericin B against all the tested strains, only excepting Candida albicans.



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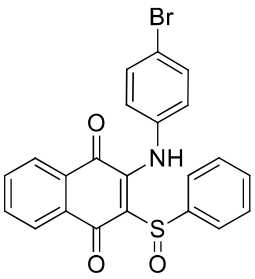

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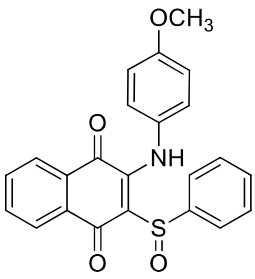
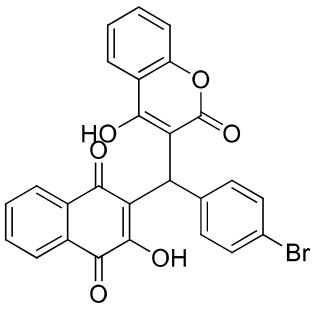


73

2.6. 1, 4-Naphthoquinones as Antibacterial Agents

Escalating resistance towards conventional antibiotics have grabbed attention for the discovery and development of antimicrobials with greater efficacy, safety and a novel mechanism of action. Triazole scaffold has been consistently rewarded as a promising versatile lead molecule with a pivotal position in modern medicinal chemistry (Kharb *et al.,* 2011).

Hueso *et al.,* (2017) prepared a library of naphthoquinone-coumarin hybrids based on preceeded Topoisomerase II in-silico studies of naphthoquinone derived molecules *via* a multicomponent reaction of 4-hydroxycoumarin, aromatic aldehydes and 2-hydroxynaphthoquinone. The conjugated structures were examined against the human topoisomerase II (hTopoIIalpha), E. coli DNA Gyrase and E. coli Topoisomerase I. The compounds **74**, **75**, **76** and **77** inhibited the relaxation of hTopoII alpha-mediated negatively supercoiled circular DNA mediated by human topoisomerase II (hTopoIIalpha) in the low μM range. As results showed that DNA Gyrase and Topoisomerase I were not affected which suggested that the inhibition was specific to human topoisomerase II (hTopoIIalpha). Studies also showed that conjugates were acting by catalytically inhibiting the alpha isoform of human topoisomerase II. In silico studies further strengthened the observation that mechanism of action strongly related to the hTopoIIalpha ATP-binding site.



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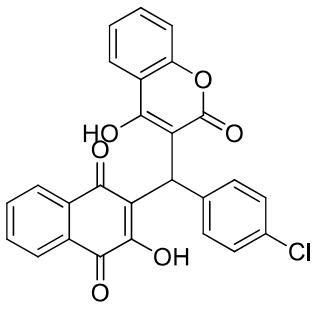

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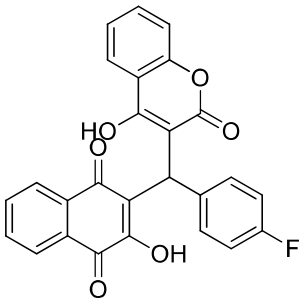

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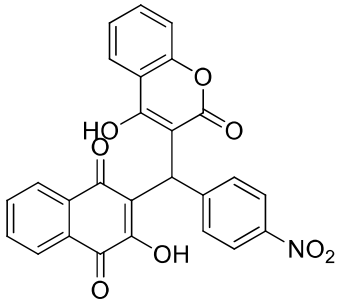
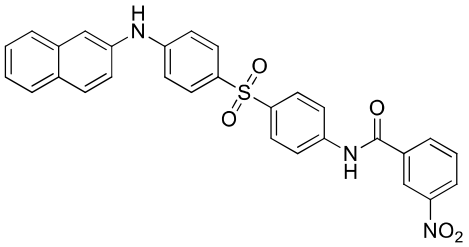


77

Ravichandiran *et al.,* (2014), synthesized a library of 1,4-naphthoquinone analog bearing carbazole-6,11-dione scaffold. Further these derivatives has been tested for *in-vitro* antibacterial activities against various Gram- positive and negative bacterias, and many of the synthesized analog depicted better antibacterial effect and the minimum inhibitory concentrations were comparable to the standard drugs. Compound **78** showed good antibacterial potential among all the molecules with the MIC of 2.1 µg/mL against. B. subtilis. To know the molecular interactions with proteins, the CADD studies of all the synthesized analogs were carried out. Results were in coroboration with in vitro studies. Compound **77** showed best E model and glide score -95.37 and -7.73, respectively. Among all docked molecules, derivative **79** showed least E model and glide score of -101.56 and -4.55, respectively.



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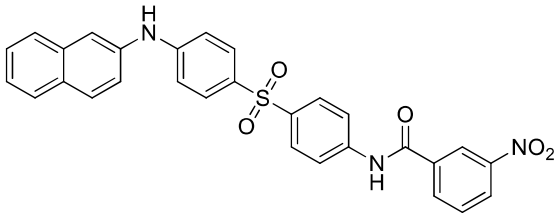
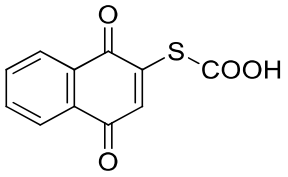


79

A Library of naphthoquinone compounds were synthesized and screened for antiviral and antibacterial potential by Tandon *et al*., (2005). The compounds were also studied for structure-activity relationships. The results revealed that all the analogs displayed *in-vitro* antibacterial activity. Most potent inhibitory effects against poliovirus type 2 infected HeLa cells induced by RNA dependent RNA polymerase was observed by two compound **80** and **81**.



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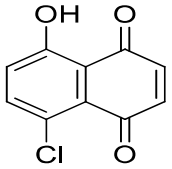


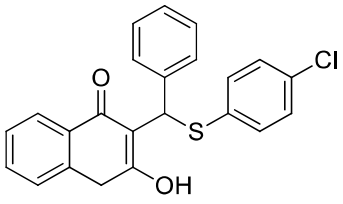
81

2.7. 1, 4-Naphthoquinones as Anti-Trypanosomal Agents

Half a billion population of least developed countries are at risk of lethal parasitic diseases like leishmaniasis (causative agent: *Leishmania donovani, L. major, L.tropica*), Chagas' disease (causative agent: *Trypanosomacruzi*), African sleeping sickness (causative agent: *Trypanosomabrucei* with the two sub-species *T. b. gambiense* and *T. b. rhodesiense*. Ignorance of the epidemiological significance have left the therapy of trypanosomatid infections as an unmet challenge (Pink *et al.,* 2005; Gelb *et al.,* 2002). No vaccines are currently available to prevent these diseases, and the recommended drugs have high toxicity and limited efficacy.

Lara and his coworkers (2018), examined the efficacy of a library of 2-hydroxy-3-phenylsulfanylmethyl-[1,4]-naphthoquinones against various T. cruzi (discrete type

units of relevant clinical forms of Chagas disease). They also studied cytotoxic and trypanocidal effect of naphthoquinone analogs were assessed in mammalian cells, trypomastigotes and intracellular amastigotes. Most of the tested compounds dipslayed low cytotoxic effect. Compound **82** and **83** had IC_{50} values less than benzimidazole. Compound **82** showed higher potency against trypomastigotes from various T. cruzi.



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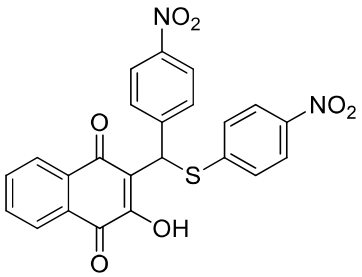
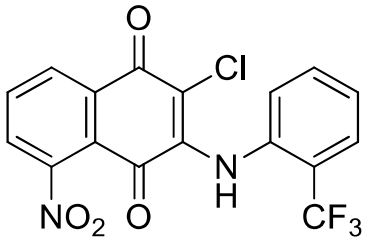


83

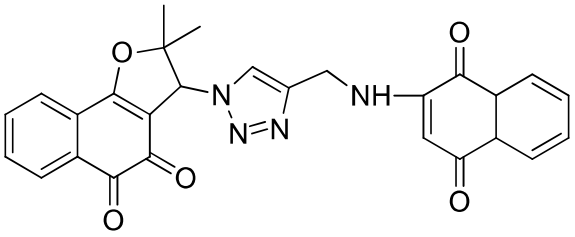
Samant and Chakaingesu (2013), prepared a library of naphthoquinone analog and evaluated for their pharmacological activity against human African trypanosomiasis. The use of reverse micellar medium exhibited selective reaction and also enhanced the rate of conversion. Among all the synthesized derivatives, compound **84** displayed inhibitory effect against T. brucei when tested *in-vitro*. Compound also showed low incidence of cytotoxicity.



84

Diogo *et al*., (2013) prepared a series of para and ortho-naphthoquinone derivatives. These synthesized compounds were screened out against T. cruzi, (the etiological cause of Chagas disease). Compound **85**, **86** and **87** possessed IC_{50} values between 6.8 and

80.8 nM, which is more potent than standard drug benznidazole. Compound **87** showed selectivity index of 34.3 by virtue of this it was subjected to *in vivo* studies.



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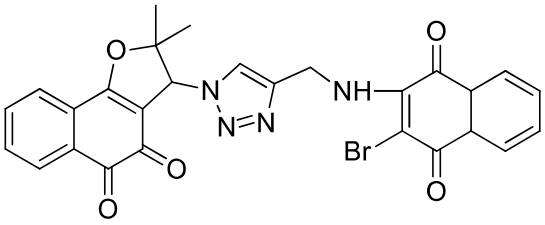

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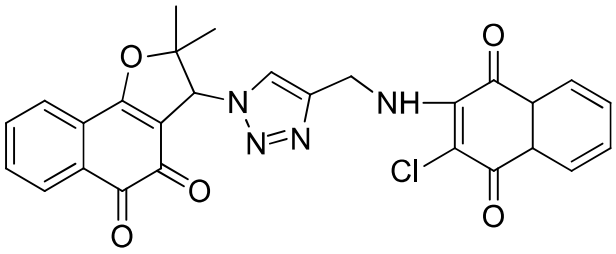
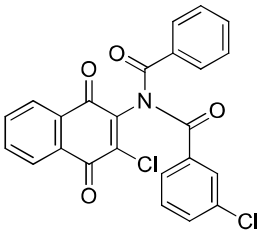


87

Khraiwesh *et al.,* (2012), reported the anti-trypanosomal activity of imido subsitituted naphthoquinone derivatives and nifurtimox. They also studied cytotoxicity, and selectivity index for all the molecules. All the naphthoquinone derivatives showed better IC_{50} ranging from 0.7 µM to 6.1 µM ($p < 0.05$) against T. cruzi when compared with nifurtimox (IC_{50} = 10.67 µM). Molecules **88**, **89**, **90** and **91** displayed selectivity indices of 275.3, 31.83, 53.97 and 60.25 respectively.Whereas selectivity index for nifurtimox was 10.86.



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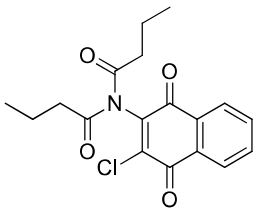

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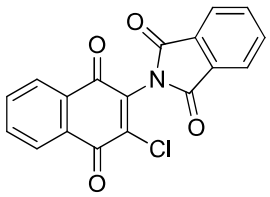

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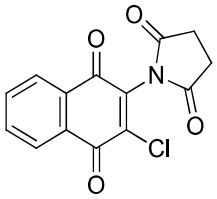
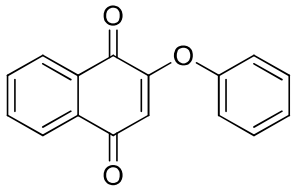


91

Bolognesi *et al.,* (2008) designed and prepared a series of 2-phenoxy-1,4-naphthoquinone analogs. The synthesis was carried out by parallel approach. All the synthesized analogs expressed inhibitory effect towards either Leishmania or Trypanosoma species. Compound **92** was found to be most active derivative against the tested organisms Leishmania donovani, Trypanosoma brucei rhodesiense and Trypanosoma cruzi cells.



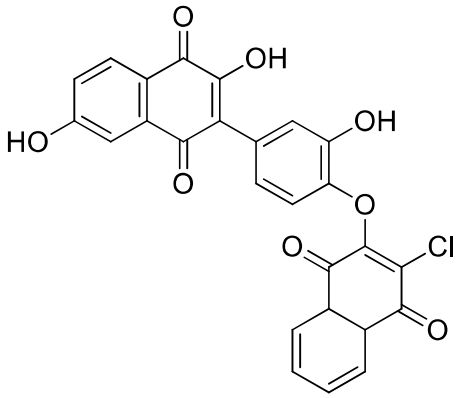
92

2.8. 1, 4-Naphthoquinones as Anti-Inflammatory Agents

Cyclo-oxygenases (COXs) are the key enzymes in the biosynthesis of prostaglandin (PG) from arachidonic acid (AA). This prostaglandin play an important role in inflammation. COX-1 isoforom is constitutive and responsible for cytoprotection of gastrointestinal tract (GIT), while the inducible COX-2 mediates inflammation (Xie *et al.,* 1991). Analgesics and antipyretics are the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs). Gastro-intestinal complications like perforation, bleeding, ulcer, obstruction etc. may be observed on long-term use of NSAIDs.

Ivana *et al.,* (2015) investigated the inhibition of rat lens aldose reductase by naphthoquinone derivative in comparison with the parent quercetin. The inhibitory effect of compound **93**, established by IC_{50} in micro molar range, better than other

synthesized compound. Compound **93** significantly inhibited aggregation of sorbitol in concentration-dependent way, which suggested that it was readily taken up by the cells of eye lens and interfered with cytosolic aldose reductase.

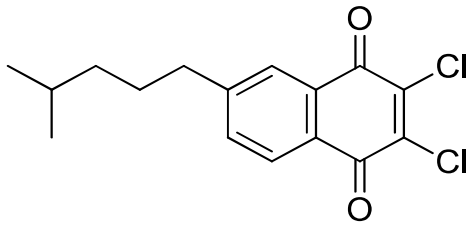


93

2.9. 1, 4-Naphthoquinones as Antiviral agents

The African and Asian population is at high risk of human immunodeficiency virus type 1 (HIV-1) infection. A record of 2.6 million cases of HIV-1 infection was reported in 2009. Reverse transcriptase (RT), protease and integrase inhibitors are costly therapeutic options. In 2011, only 50% could access this medically effective treatment; therefore, to overcome these limitations ideal strategies are explored to develop novel preventives, such as a a topical microbicide or an oral pre exposure prophylactic (PrEP).

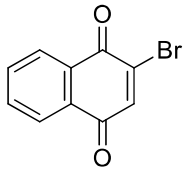
Linares *et al.,* (2019) evaluated terpenyl-1,4-naphthoquinone, 1,4-anthraquinone and heterocycle-fused quinone derivatives for their anti-herpetic and anti-dengue potential against Human Herpesvirus (HHV) type 1 and 2, and Dengue virus serotype 2 (DENV-2). The compound **94** was found to be the best antiviral activity against Herpes viruses (EC_{50}: <0.4 µg/mL, <1.28 µM) and DENV-2 (1.6 µg/mL, 5.1µ) on pre-infective stages. Moreover, compound **94** disrupted the viral attachment of HHV-1 to Vero cells (EC50: 0.12 µg/mL, 0.38 µM) with a very high selectivity index (SI = 1728).



94

2.10. 1, 4-Naphthoquinones as Miscellaneous Agents

Cardoso *et al.*, (2018) reported the synthesis of 1,4-naphthoquinone and their action on dermal wound healing and migration of fibroblasts in diabetic mice. Various spectroscopic techniques were employed to characterize the synthesized derivatives. In scratch assay, compounds **95** and **96**, prompted the migration of fibroblasts, wheras analogue 94, 95 and 96 enhanced the rate of wound closure as compared to untreated diabetic mice. While, analog **95** was optimal for the propagation of epithelization, thereby enhancing the number of blood vessels and keratinocyte layers and lowering diffuse cellular infiltration when compared to derivatives **96** and **97**.



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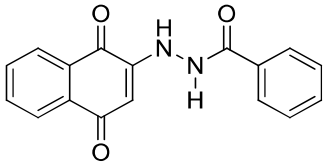

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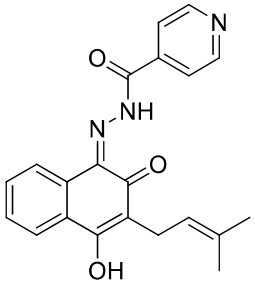
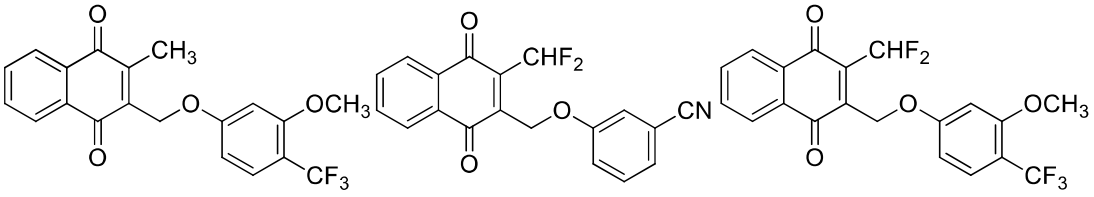


97

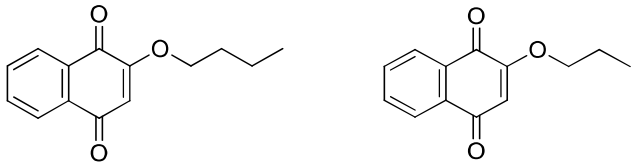
Johann *et al.*, (2015) synthesized some 1,4-naphthoquinone analogs and these synthesized compounds were observed as active anti-schistosomal agents as they specifically inhibit Schistosoma mansoni thioredoxin-glutathione reductase (SmTGR). The derivatives were also screened for specificity of the enzymatic inhibition assays using human glutathione (hGR) and thioredoxin reductase (hTrxR). Further, the

analogs **98**, **99** and **100** displayed time-dependent inactivation of SmTGR, relating with potent anti-schistosomal action in worms. All the compounds did not exhibit in *vivo* activity, indicating that the limited bioavailability might have interfered with compound activity.



98 **99** **100**

In search for antiallergic, antiinflammatory and antiplatelet agents, 1,4-naphthoquinone bearing 2-alkoxy derivatives were prepared by Lien *et al*.,(2002). A few of the synthesized compounds displayed significant anti-allergic, anti-inflammatory and anti-platelet activities. Among all the prepared analogs, compound **101** and **102** showed potent inhibitory activity on neutrophil superoxide anion production.



101 **102**