IJPSR (2019), Volume 10, Issue 12 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 March 2019; received in revised form, 10 May 2019; accepted, 30 May 2019; published 01 December 2019

DESIGN, SYNTHESIS, AND EVALUATION OF 1,4-NAPHTHOQUINONE DERIVATIVES AS POTENTIAL EPITHELIAL GROWTH FACTOR RECEPTOR INHIBITORS

Mousumi Besan [*1], Manoj K. Gautam [2] and Ankit Jain [2]

Department of Pharmaceutical Engineering and Technology [1], Indian Institute of Technology (Banaras Hindu University), Varanasi - 221005, Uttar Pradesh, India.
University Institute of Pharmaceutical Sciences [2], Panjab University, Chandigarh - 160014, Punjab, India.

Keywords:

Docking, *in-vitro* cytotoxicity, 1,4-Naphthoquinone, Tyrosine Kinase, Epithelial growth factor receptor

Correspondence to Author:
Mrs. Mousumi Besan

Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi - 221005, Uttar Pradesh, India.

E-mail: mousumibesan@gmail.com

ABSTRACT: In this manuscript, we designed and synthesized 1,4-naphthoquinone derivatives. These derivatives were characterized using the different analytical techniques such as ^{1}H NMR, ^{13}C NMR, FTIR, Mass spectroscopy, melting point, and elemental analysis. The synthesized compounds (MB (1-10)) further subjected to assess the anticancer activity using different cancer cell lines such as MCF-7, HeLa, and HepG2. The compound MB-10 was observed to be the most active against these three cancer cell lines *i.e.* MCF-7 (IC_{50} = 16.13± 0.29 µM), HeLa (IC_{50} = 12.98 ± 0.37 µM) and HepG2 (IC_{50} = 18.73 ± 0.65 µM). Compound MB10 has also shown potent tyrosine kinase inhibitory activity with IC_{50} = 1.23 ± 0.12 µM. Moreover, molecular docking investigation revealed that compound MB-10 has strong binding affinity to the amino residue of the active site of enzyme protein tyrosine kinase, which contingent the cytotoxic activities. These outcomes give promising beginning stages to assist in the improvement of cancer as novel and powerful anticancer agents.

INTRODUCTION: Cancer is the quickest developing disease in the world. In developed nations, cancer growth has turned into the main source of mortality, though in developing nations, after cardiovascular diseases, it is the second driving reason for death [1]. By 2030, the yearly number of new cancer patients is expected to be 21 million around the world, about 17 million patients passing of cancer consistently, and 75 million individuals living with cancer [2-4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(12).5327-37

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(12).5327-37

Therefore, the rapid improvement into the diagnostic area and advancement of novel cancer therapy is a very difficult task because of sophisticated biological pathways which participating role to cancer progression [5, 6]. Protein tyrosine kinases play an essential role in initiating various signal transduction pathways inside the cell and are associated with differentiation, cellular proliferation, and numerous monitoring mechanisms [7, 8]. Epidermal growth factor receptor is a type of protein kinase (transmembrane protein) which is responsible for cell growth, proliferation, differentiation, adhesion under typical physiological conditions.

Moreover, the overexpression of Epidermal growth factor receptor (EGFR) has been accompanying with cancer rising and progression in a diversity of

a tumor (cancers) such as head cancer, pancreatic cancer, lung cancer, and neck cancer [9-11]. Thus, EGFR is an alluring focus for the finding of novel anticancer agents. It has three domains *viz*. i. Single transmembrane domain, ii. Intracellular tyrosine kinase domain, iii. Extracellular ligand binding domain. Although the receptor exists as an inactive monomer, dimerization takes place once it is activated by its ligands, resulting from the autophosphorylation of the intracellular tyrosine kinase domain [12-15]. Therefore, most of the reported inhibitors were designed by targeting the kinase domain of EGFR. Therefore, the regulation of EGFR has been deemed as an important strategy for the development of cancer therapy.

OSI -774 (Tarceva) [16], and ZD-1839 (Iressa) [17] are selective, reversible EGFR inhibitors have been recently launched in the market. The various EGFR inhibitors have been reported, including, 4-(phenylamino) pyrimido[5,4-*d*] pyrimidines, 4-(phenylamino) pyrrolo[2,3-*d*] pyrimidines, 4-(phenylamino) quinazolines, and 4-[ar(alk) ylamino] pyrido [4,3-*d*] pyrimidines [18]. Beside this prolonged inhibition and high potency of EGFR functions has been reported for reversible inhibitors. A cluster of bioactivities has been accounted for 1,4-naphthoquinone derivatives to utilized as antiviral [19], anticancer [20] antiplatelet [21, 22] antifungal [23] and antimicrobial [24]. 1,4-Naphthoquinone possessing two electron withdrawing functionality, which is essential for the various biological activities. Structure-activity relationship (SAR) displayed that cytotoxic potency of 1,4-naphthoquinone is firmly connected with their electron accepting ability [25].

MATERIALS AND METHODS:

Instrumentation and Chemicals: The chemical reagents were obtained from various commercially accessible suppliers like HiMedia Laboratories Pvt. Ltd., Mumbai, India, Sigma Aldrich (India), India. Silica gel 60-F_{254} plates, thin-layer chromatography (TLC) were used to monitor the progress of the reaction. The obtained product was recrystallized to get pure products using suitable solvents. The melting point of compounds was recorded using Veego melting point apparatus. PerkinElmer spectrum (Ver 10.03.08) utilized for the FTIR data collection. ^{13}CNMR and ^{1}HNMR of synthesized compounds were collected in solution $CDCl_3$ with the help of Bruker Advance II 400 NMR spectrometer. The chemical shifts (δ) represented as parts per million (ppm). The elemental analyses were performed using Thermo Scientific (FLASH 2000), and Mass spectra were collected by utilizing Waters (Q-TOF Micro).

Molecular Docking: Molecular docking methodologies play a key role in *in-silico* drug design and development. Molecular Docking is a computational technique for relating chemical structures with their biological activities compounds. Moreover, it could afford dynamic pharmacokinetic data, for example, absorption, distribution, metabolism, and excretion (ADME), which is vital factors in the design of a new drug molecule. Epidermal growth factor receptor (EGFR), (PDB: 2GS6) was obtained from the Protein Data Bank (PDB). Molecular docking was performed with the help vLifeMDS (version 15.2). All the synthesized compounds (MB1-MB10**)** were docked using an irreversible inhibitor of EGFR protein as a covalent docking module. First of all, the protein was prepared and refined by excluding water molecules from the complex protein structure followed by the addition of hydrogen atoms as well as deleting the cofactor and ligand. The structures of compounds (2D) were drawn with the help of Chem-Bio Draw Ultra 12.0; then these structures were subjected to conversion from 2D to 3D followed by refinement and energy minimization (Merck Molecular Force Field) method. The analytical gradient and lowest energy conformations were selected for further studies.

Chemistry:

General Procedure for the Synthesis of Compounds (MB1-MB10): Naphthalene-1,4-dione (1) (0.474 g, 3 mmol) was added to 3-mercaptopropionic acid (2) (0.360 g, 3 mmol) in absolute ethanol (50 ml) and the reactant was refluxed for 3-5 h that given product of acid derivative (3). Subsequently, compound 3 was dissolved in dry dichloromethane (DCM) and added thionyl chloride (2 mmol) gradually. The reaction mixture was again refluxed for 3-5 for the formation of acid chloride product. Further different substituted piperazine equimolar ratio was added in dry dichloromethane followed by addition of acid chloride then the reaction mixture were stirred for 9-10 h. When the reaction completed

sodium bicarbonate solution was used to wash the organic layer, evaporated and the final products were purified with the help of column chromatography.

2- ((3- oxo- 3- (piperazin- 1- yl) propyl) thio) naphthalene-1,4-dione (MB-1): This compound was obtained as a yellow solid in 61% yield; mp 155-157 ºC; IR (KBr) υ_{max} 1157, 1689, 1735, 2890 and 3112 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16 (m, 2H, Ar*H*), 7.72 (m, 3H, Ar*H*), 3.56 (t, 2H, *J*= 4.12 Hz, -N-CH_2), 3.33 (m, 4H, -N-CH_2; -SCH_2), 2.88 (m, 6H, NH(CH_2)$_2$; -CH_2CO), 1.30 (s,1H, -N*H*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.62 (*C*=O), 179.42 (*C*=O), 171.46 (*C*=O), 139.86 (ArC_q), 137.48 (2 × Ar*C*), 133.53 (ArC_q), 132.52 (2 × ArC_q), 130.26 (Ar*C*), 128.87 (Ar*C*), 46.73 (2 × *C*H_2 piperazinyl), 44.32 (2 × *C*H_2 piperazinyl) 35.34 (S-*C*H_2), 29.35 (*C*H_2C=O). MS: m/z 330.40; Anal. Calcd. for $C_{17}H_{18}N_2O_3S$: C, 62.15; H, 5.90; N, 8.20. Found: C, 62.04; H, 5.85; N, 8.2; 8.

2-((3-oxo-3-(4-phenylpiperazin-1-yl)propyl)thio) naphthalene-1,4-dione (MB-2): This compound was obtained as a white solid in 58% yield; mp 202-204 ºC; IR (KBr) υ_{max} 1153,1686, 1731, 2894 and 3101 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.25 (dd, 1H, J_m = 1.36 Hz, J_O = 5.5.84 Hz Ar*H*), 8.17 (dd, 1H, J_m = 1.32 Hz, J_O = 5.84Hz, Ar*H*), 7.74 (m, 2H, Ar*H*), 7.07 (t, 3H, *J*= 5.88 Hz, ArH), 6.62 (m, 3H, ArH), 3.79 (m, 4H, -N(CH_2)$_2$), 3.66 (m, 2H, N-CH_2), 3.46(m, 2H, N-CH_2), 3.13 (t, 2H, *J* = 4.36 Hz, -SCH_2), 3.00 (t, 2H, *J* = 4.40 Hz, -CH_2CO).^{13}C NMR ($CDCl_3$, 100 MHz): δ185.43 (C=O), 178.24 (C=O), 171.83 (C=O), 150.92 (ArC_q), 139.32 (ArC_q), 137.74 (2 × Ar*C*), 133.83 (Ar*C*), 132.93 (2 × ArC_q), 130.53 (ArC_q), 129.35 (2 × Ar*C*), 128.98 (Ar*C*), 120.45 (Ar*C*), 116.63 (2 × Ar*C*), 49.78 (2 × *C*H_2 piperazinyl), 44.21 (2 × *C*H_2 piperazinyl), 35.33 (S-*C*H_2), 29.56 (*C*H_2C=O). MS: m/z: 405.71; Anal. Calcd. for $C_{23}H_{22}N_2O_3S$: C, 67.41; H, 5.70; N, 7.60. Found: C, 67.21; H, 5.76; N, 7.54.

2- ((3-(4-benzhydrylpiperazin-1-yl)-3-oxopropyl) thio)naphthalene-1,4-dione (MB-3): This compound was obtained as a yellow crystalline solid in 63% yield; mp 189-191 ºC; IR (KBr) υ_{max} 1202, 1676, 1729, 2887 and 3092 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.22 (dd, 1H, J_m = 1.34 Hz, J_O = 5.81 Hz Ar*H*), 8.19 (dd, 1H, J_m = 1.35 Hz, J_O = 5.46 Hz Ar*H*), 7.69 (m, 3H, Ar*H*), 7.22 (m, 11H, Ar*H*), 3.63 (t, 2H, *J* = 4.12 Hz, -N-CH_2), 3.88 (t, 2H, *J* = 4.12 Hz, -N-CH_2), 3.24 (t, 2H, *J* = 4.28, -NCH_2), 2.76 (m, 4H, -N-CH_2, -SCH_2), 2.65 (m, 2H, -CH_2CO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.55 (*C*=O), 179.56 (*C*=O), 171.33 (*C*=O), 140.75 (2 ×ArC_q), 139.32 (ArC_q), 137.51 (Ar*C*), 133.65 (ArC_q), 132.42 (2 × Ar*C*), 130.42 (2 × ArC_q), 129.75 (4 × Ar*C*), 128.74 (2 × Ar*C*), 128.64 (Ar*C*), 126.72 (4 × Ar*C*), 77.42 (*C*H), 50.75 (2 × *C*H_2 piperazinyl), 44.95 (2 × *C*H_2 piperazinyl), 35.71 (S-*C*H_2), 28.58 (*C*H_2C=O). MS: *m/z* 495.67; Anal. Calcd. for $C_{30}H_{28}N_2O_3S$, C, 72.32; H, 5.40; N, 5.34. Found: C, 72.35; H, 5.31; N, 5.47

2- ((3-(4-benzylpiperazin-1-yl)-3-oxopropyl)thio) naphthalene-1,4-dione (MB-4): This compound was obtained as brownish solid in 68% yield; mp 162-164 ºC; IR (KBr) υ_{max} 1177,1691, 1739, 2902 and 3100 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (m, 2H, Ar*H*), 7.72 (m, 2H, Ar*H*), 7.21 (m, 5H,Ar*H*), 7.18 (m, 1H, Ar*H*), 3.66 (s, 2H, CH_2), 3.57 (t, 2H, *J* = 4.20 Hz, -N-CH_2), 3.51(t, 2H, *J* = 4.12 Hz -NCH_2), 3.41 (t, 2H, *J*= 4.20 Hz, N-CH_2) 3.00 (t, 2H *J* = 4.12 Hz, N-CH_2), 2.89 (t, 2H *J* = 4.20 Hz, SCH_2),) 2.65 (t, 2H *J*= 4.24, Hz CH_2CO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.54 (*C*=O), 178.84 (*C*=O), 177.25 (*C*=O), 139.92 (ArC_q), 138.63 (ArC_q), 137.73 (Ar*C*), 133.84 (Ar*C*), 132.32 (2 × Ar*C*), 130.23 (2 × ArC_q), 128.51 (2 × Ar*C*), 127.18 (2 × Ar*C*), 127.94 (Ar*C*), 126.64 (Ar*C*), 63.38 (ArC_q), 51.67 (2 × *C*H_2 piperazinyl) 44.65 (2 × *C*H_2 piperazinyl), 35.73 (S-*C*H_2), 29.12 (*C*H_2C=O). MS: *m/z* 420.34; Anal. Calcd. for $C_{24}H_{24}N_2O_3S$, C, 67.64; H, 5.61; N, 6.35. Found: C, 67.52; H, 5.32; N, 6.43.

2- ((3- oxo- 3- (4- (pyridin- 2- yl)piperazin-1-yl) propyl)thio)naphthalene-1,4-dione (MB-5): This compound was obtained as a brownish solid in 65% yield; mp 172-174 ºC; IR (KBr) υ_{max} 1212, 1680, 1721, 2880 and 3078 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.18 (m, 3H, Ar*H*), 7.74 (m, 2H, Ar*H*), 7.72 (m, 1H, Ar*H*), 7.49 (m, 1H, Ar*H*), 6.76 (m, 1H, Ar*H*) 6.68 (m,1H Ar*H*) 3.72 (m, 2H, -NCH_2), 3.66 (m, 2H, -N(CH_2), 3.52 (m, 4H,N(CH_2)$_2$), 3.35 (t, 2H, *J*= 6.40 Hz, -S-CH_2), 2.95 (t, 2H, J = 6.40, -CH_2CO). ^{13}C NMR ($CDCl_3$, 100 MHz):δ 186.41 (*C*=O), 179.73 (*C*=O), 170.14 (*C*=O), 158.75 (ArC_q), 148.85 (*C*H pyridinyl), 140.54 (*C*H_2 pyridinyl), 139.63 (*C*H_2 pyridinyl), 137.53 (Ar*C*), 133.33 (ArC_q), 132.20 (2 × ArC_q), 128.71 (2 ×

Ar*C*), 127.62 (Ar*C*), 113.82 (*C*H_2 pyridinyl), 107.70 (CH_2 pyridinyl), 47.21 (2 × CH_2 piperazinyl) 44.32 (2 × *C*H_2 piperazinyl), 35.44 (S-CH_2), 28.95 (CH_2C=O). MS: *m/z* 407.43; Anal. Calcd. for $C_{22}H_{21}N_3O_3S$: C, 64.21; H, 5.57; N, 10.40. Found: C, 64.32; H, 5.322; N, 10.44.

2- ((3- oxo- 3- (4- (o-tolyl)piperazin-1-yl)propyl) thio)naphthalene-1, 4-dione (MB-6): This compound was obtained as a creamy solid in 70% yield; mp 210-212 ºC; IR (KBr) υ_{max} 1206, 1679, 1726, 2889 and 3123 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (dd, 1H, J_m= 1.40 Hz, J_O = 5.72 Hz, Ar*H*), 8.22 (dd, 1H, J_m= 1.14 Hz, J_O = 8.60 Hz, Ar*H*), 7.75 (m, 3H, Ar*H*), 6.96 (m, 2H, Ar*H*), 6.59 (m, 2H, Ar*H*), 3.86 (t, 2H, *J*= 3.96 Hz –N-CH_2), 3.73 (t, 2H, J = 4.00 Hz -N-CH_2), 3.53 (t, 2H, J = 4.00 Hz, -N-CH_2), 3.45 (t, 2H, J = 4.00, -N-CH_2), 3.38 (t, 2H, *J*= 6.60 Hz, -S-CH_2), 2.92 (t, 2H, *J*= 6.60 Hz, CH_2CO) 2.27 (s, 3H, CH_3).^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.54 (*C*=O), 174.87 (C=O), 173.42 (C=O), 150.73 (ArC_q), 139.20 (ArC_q), 133.52 (Ar*C*), 132.47 (2 × ArC_q), 130.21 (2 × Ar*C*), 130.06 (ArC_q), 129.43 (ArC_q), 128.43 (Ar*C*), 127.93 (Ar*C*), 127.53 (Ar*C*), 120.34 (Ar*C*), 117.87 (Ar*C*), 50.27 (2 × *C*H_2piperazinyl), 44.24 (2 × *C*H_2 piperazinyl) 35.22 (S-*C*H_2), 29.24 (*C*H_2C=O), 17.63 (*C*H_3). MS: *m/z* 420.84; Anal. Calcd. for $C_{24}H_{24}N_2O_3S$: C, 68.24; H, 5.65; N, 7.05. Found: C, 68.32; H, 5.54; N, 6.90.

2- ((3- (4- (2-chlorophenyl)piperazin-1-yl)-3-oxo-propyl)thio)naphthalene-1,4-dione (MB-7): This compound was obtained as creamy solid in 67% yield; mp 223-225 ºC; IR (KBr) υ_{max} 816, 1147, 1685, 1738, 2883 and 3104 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (m, 2H, Ar*H*), 7.73 (m, 2H, Ar*H*), 7.70 (s, 1H, Ar*H*), 7.14 (m, 1H, Ar*H*), 7.01 (m, 1H, Ar*H*), 6.65 (m, 2H, Ar*H*), 3.89 (t, 2H, *J*= 4.12 Hz, N-CH_2), 3.75(t, 2H, *J*= 4.12 Hz, -N-CH_2), 3.60 (t, 2H, *J*= 4.61 Hz-N-CH_2), 3.54 (t, 2H, *J*= 4.12 Hz, - N-CH_2), 3.47 (t, 2H, *J*= 5.92 Hz,-S-CH_2), 3.03 (t, 2H, *J*= 5.92 Hz, CH_2CO) .^{13}C NMR ($CDCl_3$, 100 MHz): δ187.25 (*C*=O), 175.35 (*C*=O), 170.39 (*C*=O), 148.43 (ArC_q), 139.84 (ArC_q), 137.53 (Ar*C*), 133.84 (ArC_q), 132.30 (2 × ArC_q), 131.15 (2 × Ar*C*), 130.54 (Ar*C*), 128.43 (*C*-Cl), 127.86 (Ar*C*), 127.27 (Ar*C*), 120.56 (Ar*C*), 119.27 (Ar*C*), 50.83 (2 × *C*H_2 piperazinyl), 44.83 (2 × *C*H_2 piperazinyl), 35.12 (S-*C*H_2), 29.21 (*C*H_2C=O). MS: *m/z* 440.23 (M^+ + 1) 442.32 (M^+ + 2); Anal. Calcd. for $C_{23}H_{21}Cl\ N_2O_3S$: C, 62.65; H, 4.35; N, 6.76. Found: C, 62.64; H, 4.41; N, 6.68.

2- ((3- (4- (2, 3-dichlorophenyl)piperazin-1-yl)-3-oxopropyl)thio)naphthalene-1,4-dione (MB-8): This compound was obtained as white crystalline solid in 70% yield; mp 237-239 ºC; IR (KBr) υ_{max} 821, 1150, 1679, 1728, 2884 and 3111 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (dd, 1H, J_m = 1.16 Hz, J_O = 4.81 Hz Ar*H*), 8.15 (dd, 1H, J_m = 1.16 Hz, J_O = 6.10 Hz Ar*H*), 7.75 (m, 2H, Ar*H*), 7.70 (m, 1H, Ar*H*), 6.91 (t, 1H, *J*= 6.00 Hz, Ar*H*), 6.64 (dd, 1H, Ar*H*), 6.49 (dd, 1H, Ar*H*) 3.86 (t, 2H, *J*= 4.00 Hz, N-CH_2), 3.64 (t, 2H, *J*= 4.12 Hz, N-CH_2), 3.53 (m, 4H, -N(CH_2)$_2$, 3.44 (t, 2H, *J*= 4.20 Hz,-SCH_2), 2.98 (t, 2H, *J* = 4.20 Hz, -CH_2CO).^{13}C NMR ($CDCl_3$, 100 MHz): δ 186.46 (*C*=O), 178.21 (*C*=O), 171.54 (*C*=O), 149.64 (ArC_q), 139.40 (ArC_q), 137.23 (Ar*C*), 134.42 (ArC_q), 133.58 (*C*-Cl), 132.12 (2 × ArC_q), 130.37 (2 × Ar*C*), 128.56 (Ar*C*), 128.11 (*C*-Cl), 127.84 (Ar*C*), 121.72 (Ar*C*), 118.98 (Ar*C*), 50.20 (2 × *C*H_2 piperazinyl), 44.32 (2 × *C*H_2 piperazinyl), 35.30 (S-*C*H_2), 29.68 (*C*H_2C=O). MS: *m/z*: 474.45 (M^+ + 1); 476.32 (M^+ + 2). Anal. Calcd. for $C_{23}H_{20}Cl_2\ N_2O_3S$, C, 58.31; H, 4.36; N, 5.46. Found: C, 58.18; H, 4.20; N, 5.43.

2- ((3- (4- (4-chlorophenyl)piperazin-1-yl)-3-oxo-propyl)thio)naphthalene-1,4-dione (MB-9): This compound was obtained as a brownish solid in 63% yield; mp 192-194 ºC; IR (KBr) υ_{max} 816, 1149, 1698, 1738, 2894 and 3108 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (dd, 1H, J_m = 1.16 Hz, J_O = 4.80 Hz, Ar*H*), 8.15 (dd, 1H, J_m= 1.16 Hz, J_O = 6.00 Hz, Ar*H*), 7.78 (m, 1H, Ar*H*), 7.72 (m, 2H, Ar*H*), 7.10 (d, 2H, *J* = 5.96, Ar*H*), 6.56 (d, 2H, *J* = 5.96 Hz, Ar*H*), 3.76 (t, 2H, *J* = 4.00 Hz, -N-CH_2), 3.64 (t, 2H, *J* = 4.04 Hz -NCH_2), 3.55 (t, 2H, *J* = 4.04 Hz –N-CH_2), 3.45 (m, 4H, N-CH_2;S N-CH_2), 2.97 (t, 2H, *J* = 4.32 Hz, -CH_2CO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 186.34 (*C*=O), 165.76 (*C*=O), 173.65 (*C*=O), 150.25 (ArC_q), 139.82 (ArC_q), 132.82 (2 × ArC_q), 137.85 (Ar*C*), 133.24 (ArC_q), 132.67 (2 × Ar*C*), 129.98 (2 × Ar*C*), 128.20 (*C*-Cl), 127.93 (Ar*C*), 117.62 (2 × Ar*C*), 49.12 (2 × *C*H_2 piperazinyl), 44.94 (2 × *C*H_2 piperazinyl), 35.15 (S-*C*H_2), 28.73 (*C*H_2C=O). MS: *m/z* 440.12 (M^+ + 1); 442.27 (M^+ + 2). Anal. Calcd. for $C_{23}H_{21}ClN_2O_3S$, C, 62.75; H, 4.38; N, 6.57. Found: C, 62.40; H, 4.32; N, 6.23

2- ((3- (4- (2- fluorophenyl)piperazin- 1- yl)- 3- oxopropyl)thio)naphthalene-1,4-dione(MB-10): This compound was obtained as creamy solid in 71% yield; mp 179-181 ºC; IR (KBr) υ_{max} 1207, 1676, 1725, 2896 and 3091 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.14 (m, 2H, Ar*H*), 7.72 (m, 2H, Ar*H*), 6.85 (s, 1H, Ar*H*), 6.62 (m, 2H, Ar*H*), 6.58 (m, 2H, Ar*H*), 3.83 (t, 2H, J = 4.00 Hz, N-CH_2), 3.69 (t, 2H, *J* = 4.04 Hz, N-CH_2), 3.64 (t, 2H, J = 4.04 Hz, -N-CH_2), 3.55 (t, 2H, J = 4.16 Hz, -NCH_2), 3.42 (t, 2H, J = 4.00 Hz,-S-CH_2), 3.02 (t, 2H, *J* = 4.16 Hz, -CH_2CO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.54 (*C*=O), 179.82 (*C*=O), 172.92 (*C*=O), 154.83 (*C*-F), 142.45 (ArC_q), 139.34 (ArC_q), 137.53 (Ar*C*), 135.20 (2 × ArC_q), 133.32 (ArC_q), 132.83 (2 × Ar*C*), 127.92 (Ar*C*), 125.63 (Ar*C*), 119.02 (Ar*C*), 118.31 (Ar*C*), 117.03 (Ar*C*), 50.42 (2 × *C*H_2 piperazinyl), 44.35 (2 × *C*H_2 piperazinyl) 35.42 (S-*C*H_2), 29.61 (*C*H_2C=O). MS: *m/z* 424.57 (M^++ 1); 426.43 (M^++ 2). Anal. Calcd. for $C_{23}H_{21}FN_{22}O_3S$: C, 65.83; H, 4.20; N, 6.88. Found: C, 65.54; H, 4.29; N, 6.83.

Molecular Docking: Molecular docking methodologies play a key role in *in-silico* drug design and development. Molecular Docking is a computational technique for relating chemical structures with their biological activities compounds. Moreover, it could afford dynamic pharmacokinetic data, for example, absorption, distribution, metabolism, and excretion (ADME), which is vital factors in the design of a new drug molecule. Epidermal growth factor receptor (EGFR), (PDB: 2GS6) was obtained from the Protein Data Bank (PDB). Molecular docking was performed with the help VlifeMDS (version 15.2).

All the synthesized compounds MB(1-10) were docked using an irreversible inhibitor of EGFR protein as a covalent docking module. First of all, the protein was prepared and refined by excluding water molecules from the complex protein structure followed by the addition of hydrogen atoms as well as deleting the cofactor and ligand. The structure of compounds (2D) was drawn with the help of Chem-Bio Draw ultra 12.0; then these structures were subjected to conversion from 2D to 3D followed by refinement and energy minimization (Merck Molecular Force Field) method. The analytical gradient and lowest energy conformations were selected for further studies.

Cell Culture: Cancer cell lines MCF-7, HeLa, and HeGP 2 were purchased from the National Center for Cell Sciences (NCCS) Pune. Dulbecco's modified Eagle medium (DMEM) supplemented with 1% penicillin-streptomycin (Gibco), 10% (v/v) heat-inactivated FBS and 10% fetal bovine serum (Gibco) was used to culture the procured cancer cell lines. Further, this media was maintained at 37 ºC in a humidity controlled incubator containing 5% carbon dioxide.

***In-vitro* Cytotoxicity (MTT Assay):** *In-vitro* anticancer activity (cytotoxicity) was investigated using MTT assay. The cancer cell lines were spread in 96-well cell culture plate (5×10^3 cells/well) and were allowed to stand in a humidified atmosphere (5% CO_2) overnight at 37 °C. Various concentrations (10, 20, 30, 40 and 50 µM) of synthesized compounds were added after 24 h of incubation. Further cells were incubated for another 24 h. The phosphate buffer solution was utilized for washing the cells in well, subsequently plate was incubated at 37 °C after adding 20 µL MTT staining solution (0.005% w/w in phosphate buffer) to each well. For dissolving the formazan crystals, in each well 100 µL of dimethyl sulfoxide (DMSO) was added, and the absorbance of the resulting solution was observed at 570 nm using microtiter plate reader [30, 31]. The IC_{50} was computed by employing graph Pad Prism Version 5.

Tyrosine Kinase Inhibitory Activity: The kinase activity was evaluated with enzyme-linked immunosorbent assay (ELISA). The assays were performed in 96-well microtiter plates that had been coated overnight with 2.0 µg of a polyGlu-Tyr peptide (4:1) (Sigma P-0275) in 0.1 mL of PBS per well. The purified kinases were diluted in kinase assay buffer (100 Mm Hepes pH 7.5, 100 mM NaCl, and 0.1 mM sodium orthovanadate) and added to all test wells at 5 ng of GST fusion protein per 0.05 mL volume buffer. Test compounds were diluted in 4% DMSO and added to test wells (0.025 mL/well). The kinase reaction was initiated by the addition of 0.025 mL of 40 µM ATP/40 mM $MnCl_2$, and plates were shaken for 10 min before stopping the reactions with the addition of 0.025 mL of 0.5 M EDTA. The final ATP concentration was 10 µM, which is twice the experimentally determined K_m value for ATP. Negative control wells received $MnCl_2$ alone without ATP.

The plates were washed three times with 10 mM Tris pH 7.4, 150 mM NaCl, and 0.05% Tween-20 (TBST). Rabbit polyclonal anti-phosphotyrosine antiserum was added to the wells at a 1:10000 dilution in TBST for 1 h. The plates were then washed three times with TBST. Goat anti-rabbit antiserum conjugated with horseradish peroxidase was then added to all wells (Biosource Cat. No. ALI0404; 1:10000 dilution in TBST) for 1 h. The plates were washed three times with TBST, and the peroxidase reaction was detected with the addition of 2,2′-azinobis(3- ethylbenzthiazoline-6-sulfonic acid) (ABTS) (Sigma A1888). The plate was read using a multiwell spectrophotometer at 492 nm.

The inhibitory rate (%) was calculated with the formula: [1 − treated groups/ control groups)] × 100%. IC_{50} values were calculated from the inhibitory curves.

Statistical Analysis: The statistical analysis was run using Sigma Plot (version 11.1) by applying one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison tests. Statistical significance was considered at $p<0.05$.

RESULTS AND DISCUSSION:

Molecular Docking: Molecular docking has been applied to designing these compounds. It is the collection of electronic and steric features, which is essential to building considerable supramolecular interactions with a specific biological target that block or activate the biological activity [26]. In the present manuscript, docking studies were done on the epidermal growth factor receptor (EGFR). Docking studies suggested that superior protein-ligand bindings of synthesized compounds with key amino acid on the active site. Methionine residues (MET 793), cytosine (CYS797) and tyrosine (TRY253) are the key residues of the protein-ligand binding [27, 28]. These amino acid residues play a key role in the formation of a bridge within EGFR. Moreover, docking examinations of MB1-MB10 on EGFR demonstrated a considerable binding interaction of the synthesized compounds on the peripheral site and catalytic site of amino acid. All the compounds have been found to possess a good binding affinity with the EGFR and afforded high dock score from -53.82 to -73.11. Amongst all the docked ligand, compound MB-10 has shown a highest binding affinity dock score (73.11) with EGFR. **Table 4** described molecular docking score of synthesized compounds. The 2D/3D and binding pocket representation of the ligand-receptor interactions of the most active compounds MB-9 and MB-10 displayed in **Fig. 1a-c,** and **Fig. 2a-c**.

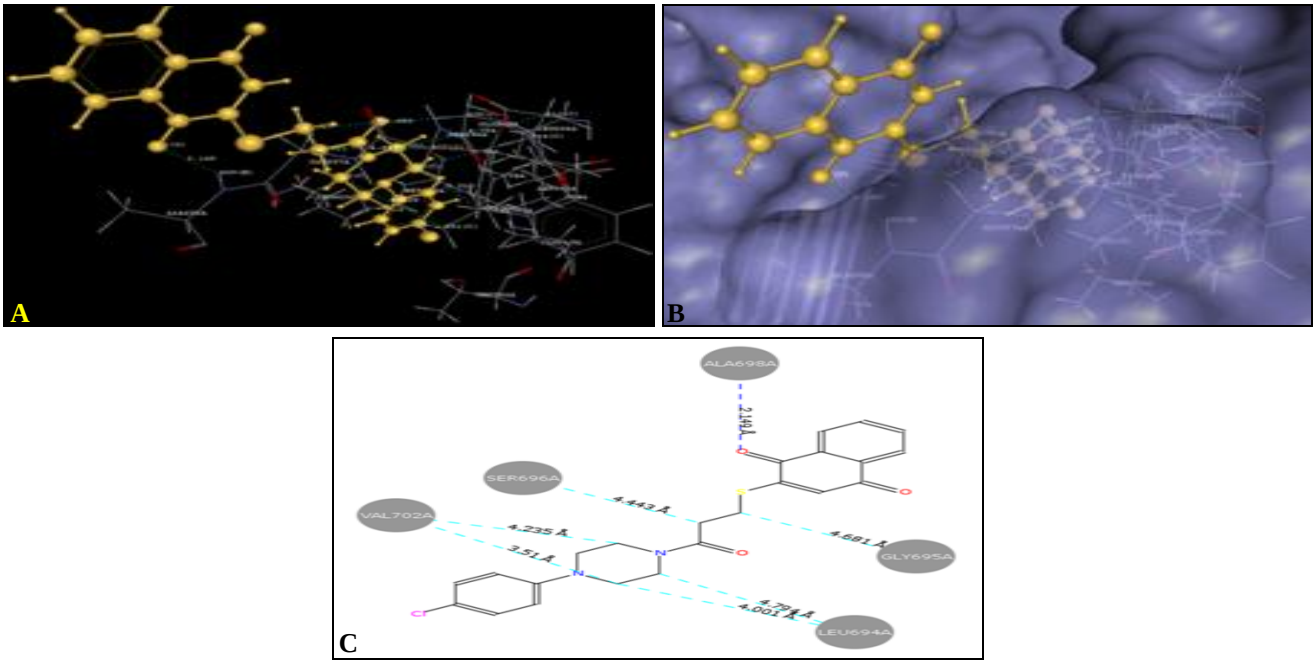


FIG. 1(A-C): (1A) 3D HYDROGEN BONDING INTERACTION OF MB-9 REPRESENTATION SHOWING THE BINDING ORIENTATION OF THE COMPOUNDS MB-9 INTO THE ACTIVE SIDE OF 2GS6, (1B) 3D SURFACE AND HYDROGEN BONDING INTERACTION OF MB-9, (1C) 2D REPRESENTATION SHOWING THE BINDING ORIENTATION OF THE COMPOUNDS MB-9 INTO THE ACTIVE SIDE OF 2GS6

----------: Hydrophobic Interactions; ----------: Hydrogen Bonding

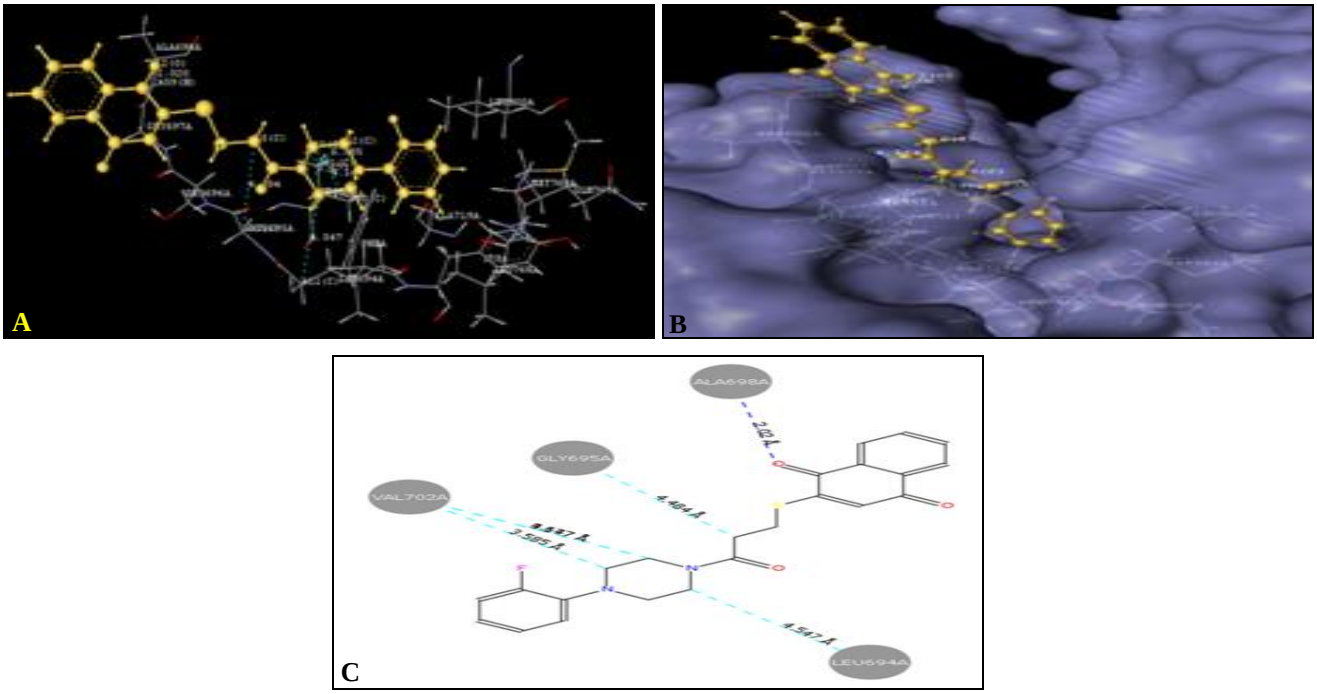


FIG. 2(A-C): (1A) 3D HYDROGEN BONDING INTERACTION OF MB-10 REPRESENTATION SHOWING THE BINDING ORIENTATION OF THE COMPOUNDS MB-9 INTO THE ACTIVE SIDE OF 2GS6, (2B)3D SURFACE AND HYDROGEN BONDING INTERACTION OF MB-10, (2C) 2D REPRESENTATION SHOWING THE BINDING ORIENTATION OF THE COMPOUND MB-10 INTO THE ACTIVE SIDE OF 2GS6

----------: Hydrophobic Interactions; ----------: Hydrogen Bonding

TABLE 4: DOCKING SCORES OF COMPOUNDS

Compound no.	D-Score
MB-1	-53.82
MB-2	-64.24
MB-3	-60.82
MB-4	-61.53
MB-5	-65.68
MB-6	-63.51
MB-7	-64.64
MB-8	-63.54
MB-9	-68.32
MB-10	- 73.11
Imatinib	-62.92

Grip values docked pose of the fitted ligands were visualized extending deep into the active site pocket and showing several interactions such as Vander Waal's, hydrophobic contacts, hydrogen bonds and π-π stacking interactions with the key residues of the active site catalytic site as well as the peripheral site. The high score of compound MB-9 attributed to its strong hydrogen bonds between amino acid residue ALA698 to the oxygen of the ring naphthoquinone ring along with distance 2.149Å. Compound MB-10 formed hydrogen bonds with ALA698A amino residue of oxygen of the naphthoquinone ring with distance 2.02 Å. Hydrophobic interactions have also been observed in both compounds. The compound 9 with amino acid residues SER696A, VAL702A, LEU694A, and GLY 695A respectively. However, the compound 10have been formed hydrophobic interactions with VAL702A, LEU694A, and GLY 695A. Therefore, compounds 1,4-naphthoquinone derivatives formed considerable interactions with essential amino acid residues and revealed the association of the docking studies with anticancer activity of the compounds.

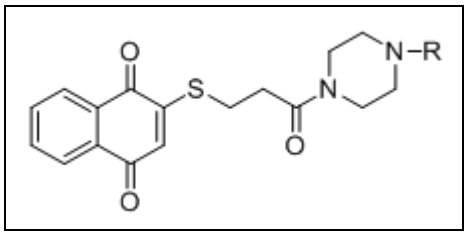
Chemistry: The synthetic pathway for the synthesis of compounds MB1-MB10 has been depicted in Scheme 1. The key 3-((1,4-dioxo-1,4-dihydro naphthalene-2-yl)thio)propanoic acid (3) was synthesized according to the reported method[29]summarized in the proceeding text. Compounds MB-(1-9) were synthesized by refluxing naphthalene-1,4-dione (1) with 4-mercapto propanoic acid (2) in absolute ethanol to form 3-((1,4-dioxo-1,4-dihydro naphthalene-2-yl) thio)propanoic acid (3) which in turn were converted to final compound MB-(1-10) by reaction with thionyl chloride and substituted piperazines.

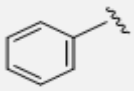
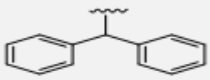
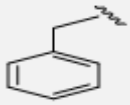
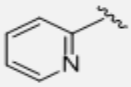
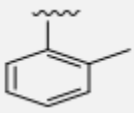
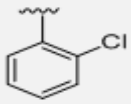
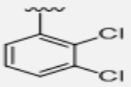
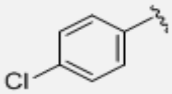
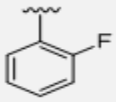
The structures of the synthesized compounds were established using spectral techniques (IR, ^{1}H NMR,

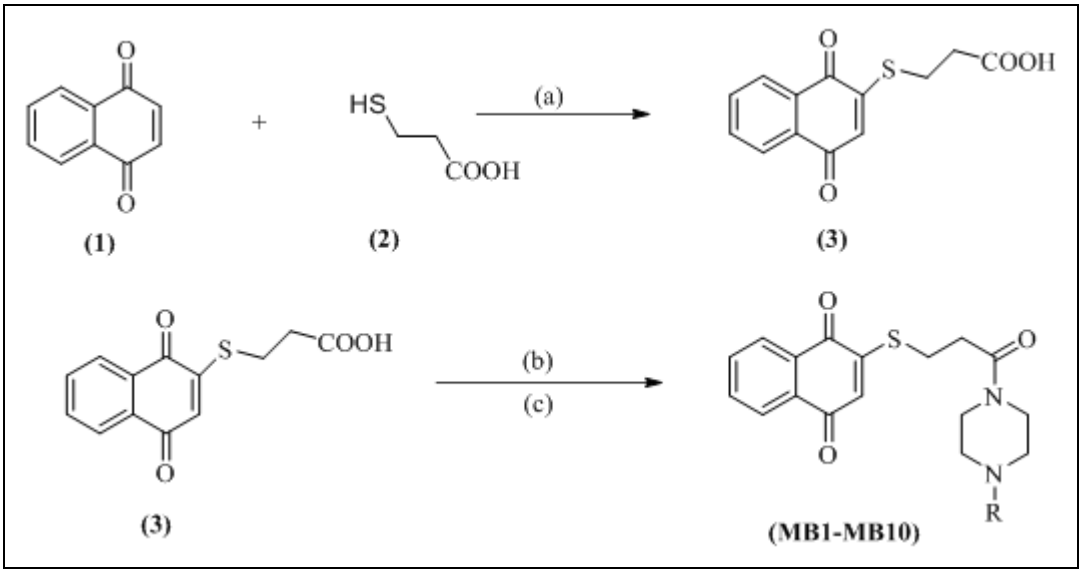
and ^{13}C NMR). The IR spectra and appearance of a characteristic peak of the carbonyl group between 1698 cm^{-1} to 1739 cm^{-1}. In the proton NMR spectra of all the compounds, the disappearance of characteristic broad singlet of the hydroxyl proton at δ 9.47 ppm confirmed the substitution at the hydroxyl group. The aromatic protons resonated in the range of δ 8.37 to 7.04 ppm in the proton NMR spectra of all the compounds are due to the anisotropic effect of the ring. Compounds MB-6 showed singlet at δ 2.32 of the methyl group. There was a characteristic peak of the methylene group in all the compounds at a frequency of ≃ δ 3.64 ppm.

In the ^{13}C NMR spectrum, carbonyl carbon of naphthalene ring was observed at ≃ δ 182.0 ppm and 176.0, whereas carbon of aliphatic carbonyl of the target compounds appeared at ≃ 170.0 ppm. Signals of the ^{13}C NMR spectrum further confirmed the synthesis of the targeted compounds as all the aromatic carbons appeared in the range of δ 160.00-102.00 ppm; however, the methylene carbon peak emerged at δ 31.95-84.36 ppm. The physicochemical data of the synthesized compounds have been listed in **Table 1**.

TABLE 1: CHEMICAL STRUCTURE OF VARIOUS 1,4-NAPHTHOQUINONE DERIVATIVES



Compounds	R	Molecular weight	Melting point (°C)	Appearance	LogP
MB-1	H	330.40	155-157	Yellow	-0.41
MB-2		405.71	202-204	white	2.04
MB-3		495.67	189-191	Yellow	3.41
MB-4		420.34	162-164	Brownish	1.70
MB-5		407.43	172-174	Brownish	1.42
MB-6		420.84	210-212	Creamy	2.53
MB-7		440.23	223-225	Creamy	2.60
MB-8		474.45	237-239	White	3.16
MB-9		440.12	192-194	Brownish	2.60
MB-10		424.57	179-181	Creamy	2.20



SCHEME 1: CHEMICAL REAGENTS AND CONDITIONS: (A) ABSOLUTE ETHANOL, REFLUX, 3-5 h. (B) DRY DCM, THIONYL CHLORIDE, REFLUX, 3-5 h. (C) DRY DCM, SUBSTITUTED PIPERAZINE, STIRRING 9-10 h.

Pharmacological Evaluation:

***In-vitro* Cytotoxic Activity:** All the synthesized compounds MB1-MB10 were evaluated *in-vitro* for their anticancer activity. The cytotoxic effects of all newly synthesized compounds (1,4-naphthoquinone derivatives) were subjected to assess *in-vitro* anticancer potency using various cancer cell lines, such as MCF-7, (breast carcinoma), HepG2 (liver carcinoma) and cervical carcinoma (Hela) using imatinib as a positive control. *In-vitro* cytotoxicity results suggested that the cytotoxicity were dose-dependent. Almost all the compound showed anticancer activity in dose-dependent. Cell viability decreased, and cytotoxicity increases with increase in the concentration of the compounds.

The synthesized compounds exposed that the cytotoxicity was found to be poor to strong comparatively to the control drugs **Table 2**. The compounds MB (9, 10) exhibited intense anticancer activity on HeLa cell line. Especially, MB-9, MB-10 exhibited stronger activity than Imatinib. Two compounds MB (4, 10) against MCF-7 cell line demonstrated great antineoplastic action. The compounds MB (2, 10) exposed extensive cytotoxic with HepG2 cell lines. Moreover, the remaining synthesized compounds MB (1, 3, 5, 6, 7, and 8) devoid any critical cytotoxic action against tested cancer cell lines **Fig. 3**. Thus, the compound MB10 revealed as a most potent anticancer agent against MCF-7, HepG2, and HeLa cell lines when compared to standard drug imatinib.

TABLE 2: *IN-VITRO* CYTOTOXICITY OF COMPOUNDS. THE DIFFERENCES IN CYTOTOXICITY IS STATISTICALLY SIGNIFICANT (P<0.05) ± SEM

Compounds	HeLa cell IC_{50}(µM)	MCF-7 cell IC_{50}(µM)	HepG2 cell IC_{50}(µM)
MB-1	84.71 ± 0.52	76.28 ± 1.26	>100
MB-2	69.88 ± 1.07	48.12 ± 1.08	20.72 ± 1.27
MB-3	44.32 ± 0.24	74.06 ± 1.43	23.47 ± 1.88
MB-4	22.02 ± 0.69	21.13 ± 0.29	37.35 ± 0.33
MB-5	23.67 ± 0.74	58.08 ± 0.37	25.36 ± 1.43
MB-6	67.37 ± 1.38	41.02 ± 1.50	24.50 ± 1.05
MB-7	93.82 ± 0.78	>100	>100
MB-8	>100	82.36 ± 2.63	96.29 ± 1.04
MB-9	15.05 ± 0.62	27.47 ± 0.29	37.20 ± 0.49
MB-10	12.98 ± 0.37	16.13 ± 0.29	18.73 ± 0.65
Imatinib	20.43 ± 0.76	28.19 ± 0.34	25.85 ± 0.79

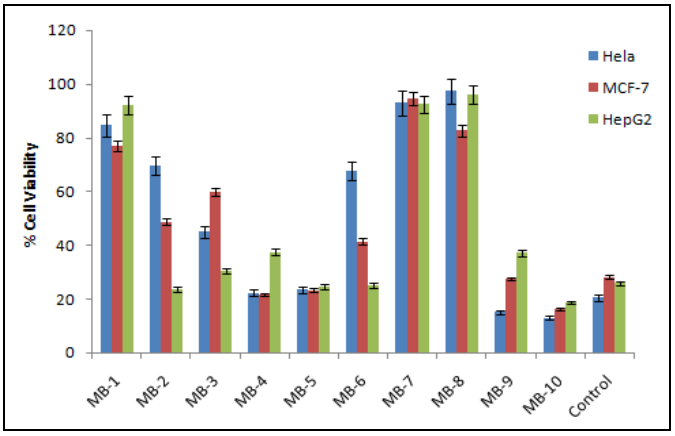


FIG. 3: *IN-VITRO* CYTOTOXICITY OF COMPOUNDS. THE DIFFERENCES IN THE PERCENTAGE OF CELL CYTOTOXICITY OF COMPOUNDS MB-9 AND MB-10 COMPARED TO THE CONTROL (IMATINIB) ARE STATISTICALLY SIGNIFICANT P <0.05 (n=3)

***In-vitro* Enzymatic Assay (EGFR Kinases Inhibition):** After *in-vitro* cytotoxicity screening of synthesized compound against the MCF-7, HeLa

and HepG-2 cell lines were subjected to assess EGFR kinases inhibition with the help of self-made kit of tyrosine kinase using Imatinib as standard drug. The majority of compounds indicated pronounced tyrosine kinase inhibition. **Table 3** summarized the inhibition IC_{50} values of all the synthesized compounds. Compounds MB-4 and MB-9 possess more comparable inhibitory effect against EGFR. While compound MB-10 have most potent inhibition (IC_{50} = 1.23 ± 0.12 µM), approximately three times more than (IC_{50} = 3.60 ± 0.79 µM) **Fig. 4**. Thus, compound MB-10 is a hopeful, kinase inhibitor.

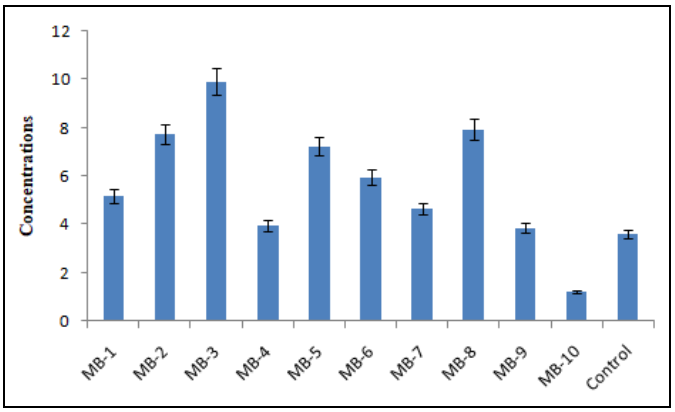


FIG. 4: ENZYME INHIBITORY ACTIVITY OF PROTEIN TYROSINE KINASE OF COMPOUNDS. THE PERCENTAGE OF INHIBITION OF COMPOUND MB-9 AND MB-10 COMPARED TO THE CONTROL DRUG (IMATINIB) ARE STATISTICALLY SIGNIFICANT P <0.05 (n=3)

TABLE 3: ENZYME INHIBITORY ACTIVITY OF PROTEIN TYROSINE KINASE OF COMPOUNDS. THE DIFFERENCES IN TYROSINE KINASE INHIBITORY ACTIVITY COMPARED TO THE CONTROL GROUPS ARE STATISTICALLY SIGNIFICANT (P <0.05)

Compounds	Tyrosine kinase inhibitory activity IC_{50} (µM) ± SEM
MB-1	5.16 ± 0.31
MB-2	7.74 ± 0.19
MB-3	9.32 ± 0. 66
MB-4	3.96 ± 0.47
MB-5	7.23 ± 0.14
MB-6	5.96 ± 0.14
MB-7	4.65 ± 0.03
MB-8	7.92 ± 0.15
MB-9	3.85 ± 0.09
MB-10	1.23 ± 0.12
Imatinib	3.60 ± 0.79

CONCLUSION: We have successfully synthesized a series of piperazine substituted 1,4-naphthoquinone derivatives. The compounds were evaluated for their cytotoxic effect using MCF-7, HeLa, and HepG-2 cancer cell lines. Almost all the synthesized derivatives possess considerable anticancer activity. Compound MB-10 revealed the utmost powerful anticancer agent. Furthermore, on the enzyme inhibition assay compound MB-10 showed the good promising inhibitory activity with IC_{50} = 1.23 ± 0.12 µM. Molecular docking study revealed the strong binding capability with the active sites of enzymes. Therefore, these findings suggested that the rational design of piperazine substituted 1,4-naphthoquinone as a hopeful potential anticancer agent for auxiliary expansion in cancer therapy.

ACKNOWLEDGEMENT: The authors gratefully acknowledge IIT-BHU for the funding of this work. The authors also acknowledge thanks to Panjab University, Chandigarh and NIPER Mohali, Punjab to provide spectral and cell line facilities.

CONFLICTS OF INTEREST: The authors declare that they have no competing interests with whomsoever.

REFERENCES:

1. Mudasir NP, Parvez K, Kamal A, MdImtaiyaz H and Amir A: Synthesis, characterization and biological evaluation of tertiary sulfonamide derivatives of pyridyl-indole based heteroarylchalcone as potential carbonic anhydrase IX inhibitors and anticancer agents. Eur J Med Chem 2018; 55: 13-23.
2. Guichard N, Guillarme D, Bonnabry P and Fleury SS: Antineoplastic drugs and their analysis: a state of the art review. Analyst 2017; 142: 2273-21.
3. Rebucci M and Michiels C: Molecular aspects of cancer cell resistance to chemotherapy. Biochem Pharmacol 2013; 85: 1219-26.
4. Holohan C, Van Schaeybroeck S, Longley DB and Johnston PG: Cancer drug resistance: an evolving paradigm. Nat Rev Cancer 2013; 13: 714-26.
5. Belpomme D, Irigaray P, Sasco AJ, Newby JA, Howard V, Clapp R and Hardell L: The growing incidence of cancer: role of lifestyle and screening detection. Int J Oncol 2007; 30: 1037-49.
6. Bridges AJ: Chemical inhibitors of protein kinases. Chem Rev 2001; 101: 2541-72.
7. Ullrich A and Schlessinger J: Signal transduction by receptors with tyrosine kinase activity. Cell 1990; 61: 203-12.
8. Gschwind A, Fischer OM and Ullrich A: The discovery of receptor tyrosine kinases: targets for cancer therapy. Nat Rev Cancer 2004; 4: 361-70.
9. Steuer CE, Khuri FR and Ramalingam SS: The next generation of epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of lung cancer. Cancer 2015; 121: E1-6.
10. Ping W and Zhixiang W: Epidermal Growth Factor Receptor Cell Proliferation Signaling Pathways. Cancers 2017; 9: 52-96.
11. Li J, Tan JZ, Chen LL, Zhang J, Shen X, Mei CL, Fu LL, Lin LP, Ding J, Xiong B and Xiong XS: Design, synthesis and antitumor evaluation of a new series of N-

substituted-thiourea derivatives. Acta Pharmacologica Sinica 2006; 27: 1259-71.
12. Fry DW, Kraker AJ, McMichael A, Ambroso LA, Nelson JM, Leopold WR, Connors RW and Bridges AJ: A specific inhibitor of the epidermal growth factor receptor tyrosine kinase. Science 1994; 265: 1093-95.
13. Chinkers M and Brugge JS. Characterization of structural domains of the human epidermal growth factor receptor obtained by partial proteolysis. J Biol Chem 1984; 259: 11534-42.
14. Araujo RP, Petricoin EF and Liotta LA: A mathematical model of combination therapy using the EGFR signaling network. Biosystems 2005; 80: 57-69.
15. Asano T, Yoshikawa T, Usui T, Yamamoto H, Yamamoto Y, Uehara Y and Nakamura H: Benzamides and benzamidines as specific inhibitors of epidermal growth factor receptor and v-Src protein tyrosine kinases. Bioorg Med Chem 2004; 12: 3529-42.
16. Norman P. ZD-1839 (astraZeneca): Curr Opin Investig Drugs 2001; 3: 428-434.
17. Norman P: OSI-774 OSI pharmaceuticals: Curr Opin Investig Drugs 2001; 2: 298-04.
18. Smaill JB, Palmer BD, Rewcastle GW, Denny WA, McNamara DJ, Dobrusin EM, Bridges AJ, Zhou H, Showalter HH, Winters RT and Leopold WR: Tyrosine kinase inhibitors. 15. 4-(Phenylamino) quinazoline and 4-(phenylamino) pyrido[d]pyrimidine acrylamides as irreversible inhibitors of the ATP binding site of the epidermal growth factor receptor. J Med Chem 1999; 42: 1803-15.
19. Ilina TV, Semenova EA, Pronyaeva TR, Pokrovskii AG, Nechepurenko IV, Shults EE, Andreeva OI, Kochetkov SN and Tolstikov GA: Inhibition of HIV-1 reverse transcriptase by aryl-substituted naphto-and anthraquinones: In Doklady Biochemistry and Biophysics. Kluwer Academic Publishers-Plenum Publishers 2002; 382(1-6): 56-59.
20. Verma RP: Anti-cancer activities of 1,4-naphthoquinones: a QSAR study. Anti-Cancer Agents Med Chem 2006; 6: 489-99.
21. Jin YR, Ryu CK, Moon CK, Cho MR and Yun YP: Inhibitory effects of J78, a newly synthesized 1, 4-naphthoquinone derivative, on experimental thrombosis and platelet aggregation. Pharmacology 2004; 70: 195-00.
22. Lien JC, Huang LJ, Teng CM, Wang JP and Kuo SC: Synthesis of 2-alkoxy 1,4-naphthoquinone derivatives as antiplatelet, anti-inflammatory, and antiallergic agents. Chem Pharm Bull 2002; 50: 672-74.
23. Tandon VK, Yadav DB, Maurya HK, Chaturvedi AK and Shukla PK: Design, synthesis, and biological evaluation of 1, 2, 3-trisubstituted-1, 4-dihydro benzo [g] quinoxaline-5, 10-diones and related compounds as antifungal and antibacterial agents. Bioorg Med Chem 2006; 14: 6120-26.
24. Ryu CK and Kim DH: The synthesis and antimicrobial activities of some 1,4-naphthoquinones (II). Archives Pharmacal Res 1992; 15: 263-68.
25. Prachayasittikul V, Pingaew R, Worachartcheewan A, Nantasenamat C, Prachayasittikul S, Ruchirawat S and Prachayasittikul V: Synthesis, anticancer activity and QSAR study of 1, 4-naphthoquinone derivatives. Eur J Med Chem 2014; 84: 247-63.
26. Hong S, Kim J, Seo JH, Jung KH, Hong SS and Hong S: Design, synthesis, and evaluation of 3, 5-disubstituted 7-azaindoles as Trk inhibitors with anticancer and antiangiogenic activities. J Med Chem 2012; 55: 5337-49.
27. Srivastava JK, Pillai GG, Bhat HR, Verma A and Singh UP: Design and discovery of novel monastrol-1, 3, 5-triazines as potent anti-breast cancer agent *via* attenuating epidermal growth factor receptor tyrosine kinase. Scientific Reports 2017; 7: 5851-69.
28. Al-Anazi M, Al-Najjar B and Khairuddean M: Structure-based drug design studies toward the discovery of novel chalcone derivatives as potential epidermal growth factor receptor (EGFR) inhibitors. Molecules 2018; 23: 3203-19.
29. Tandon VK, Singh RV and Yadav DB: Synthesis and evaluation of novel 1,4-naphthoquinone derivatives as antiviral, antifungal and anticancer agents. Bioorganic Med. Chem. Lett 2004; 14: 2901-04.
30. Ravichandiran P, Subramaniyan SA, Kim SY, Kim JS, Park BH, Shim KS and Yoo DJ: Synthesis and anticancer evaluation of 1,4-naphthoquinone derivatives containing a phenylaminosulfanyl moiety. Chem Med Chem 2019; 14: 532-44.
31. Hemaiswarya S and Doble M: Combination of phenylpropanoids with 5-fluorouracil as anti-cancer agents against human cervical cancer (HeLa) cell line. Phytomedicine 2013; 20: 151-58.

How to cite this article:
Besan M, Gautam MK and Jain A: Design, synthesis, and evaluation of 1,4-naphthoquinone derivatives as potential epithelial growth factor receptor inhibitors. Int J Pharm Sci & Res 2019; 10(12): 5327-37. doi: 10.13040/IJPSR.0975-8232.10(12).5327-37.