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Design, Synthesis, and Evaluation of Anticancer Activity of Some New Spiro Indoline-2-one Derivatives

Sabita Kumari*, Subir Samanta

Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Ranchi, Jharkhand, India

ABSTRACT The indoline-2-one derivatives **(SSSK 16-20)** were designed by docking, *in silico* absorption, distribution, metabolism, and excretion (ADME) and predicted toxicity studies. These designed compounds were then synthesized by a three-component coupling reaction. These compounds were characterized by ^{1}H nuclear magnetic resonance (^{1}H NMR), ^{13}C NMR, Fourier transform infrared, and mass spectral data. Then, all synthesized compounds were tested for anticancer activity on MDA-MB-231 and MCF-7 cell lines. The compounds having halogen at isatin ring displayed good binding scores. *In silico*, ADME and toxicity studies were also found significant for most of the compounds. Three compounds **SSSK16, SSSK17,** and **SSSK19** showed significant anticancer potential against MCF-7 with GI_{50} value of 0.44, 0.04, and 21.6 molar.

KEYWORDS Absorption, distribution, metabolism, and excretion, Breast cancer, Docking, Indoline-2-one, MCF-7, MDA-MB-231.

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INTRODUCTION

Cancer is one of the leading causes of death in the world among all chronic diseases and affecting almost 9.6 million of death in 2018.[1,2] Breast cancer is the most prevalent form of cancer diagnosed in women worldwide and affecting 2.1 million women each year. It is accounting approximately 15% of all cancer deaths among women.[2] There are many difficulties in the treatment of cancer, including drug resistance, toxicity, and low specificity.[3] Therefore, there has been an increscent interest in the field of cancer chemotherapy by the discovery and development of novel agents with high efficacy, low toxicity, and minimum side effects.[4] Due to the less selectivity of suitable drugs, drug resistance, and complex mechanisms, the current drug treatment of breast cancer seems to be challenging.[5] Therefore, the development of potent, competent, and having less adverse effect anticancer agents over the synthesis of new molecules is significant in breast cancer research.

Indolin-2-one is an advantageous and highly predominating scaffold in natural and synthetic medicinal compounds, as illustrated in **Figure 1**. Indolin-2-one possesses carbonyl group at the second position of the indoline ring. Due to the possibility of substitution at four different positions of the indoline ring, primarily at nitrogen atom 1, carbonyl group 2, carbon atom 3, and a benzene ring, it exhibits a wide range of pharmacological activities.[6] Indolin-2-one is also an important class of heterocyclic compounds with a wide range of biological activities against mouse double minute 2 homolog p53,[7] anticancer,[6,8] anti-human immunodeficiency virus,[9] antimicrobial,[10] antifungal,[11] anti-inflammatory,[12] antileishmanial,[13] and anticonvulsant.[14] Accordingly, in continuation of our research program to find anti-breast cancer agents and considering the importance of indolin-2-one as anti-breast cancer agents, we report herein the design, synthesis, and anticancer property of indoline-2-one derivatives **(SSSK 16-20)**.

*Corresponding author: E-mail: sabita16@bitmesra.ac.in

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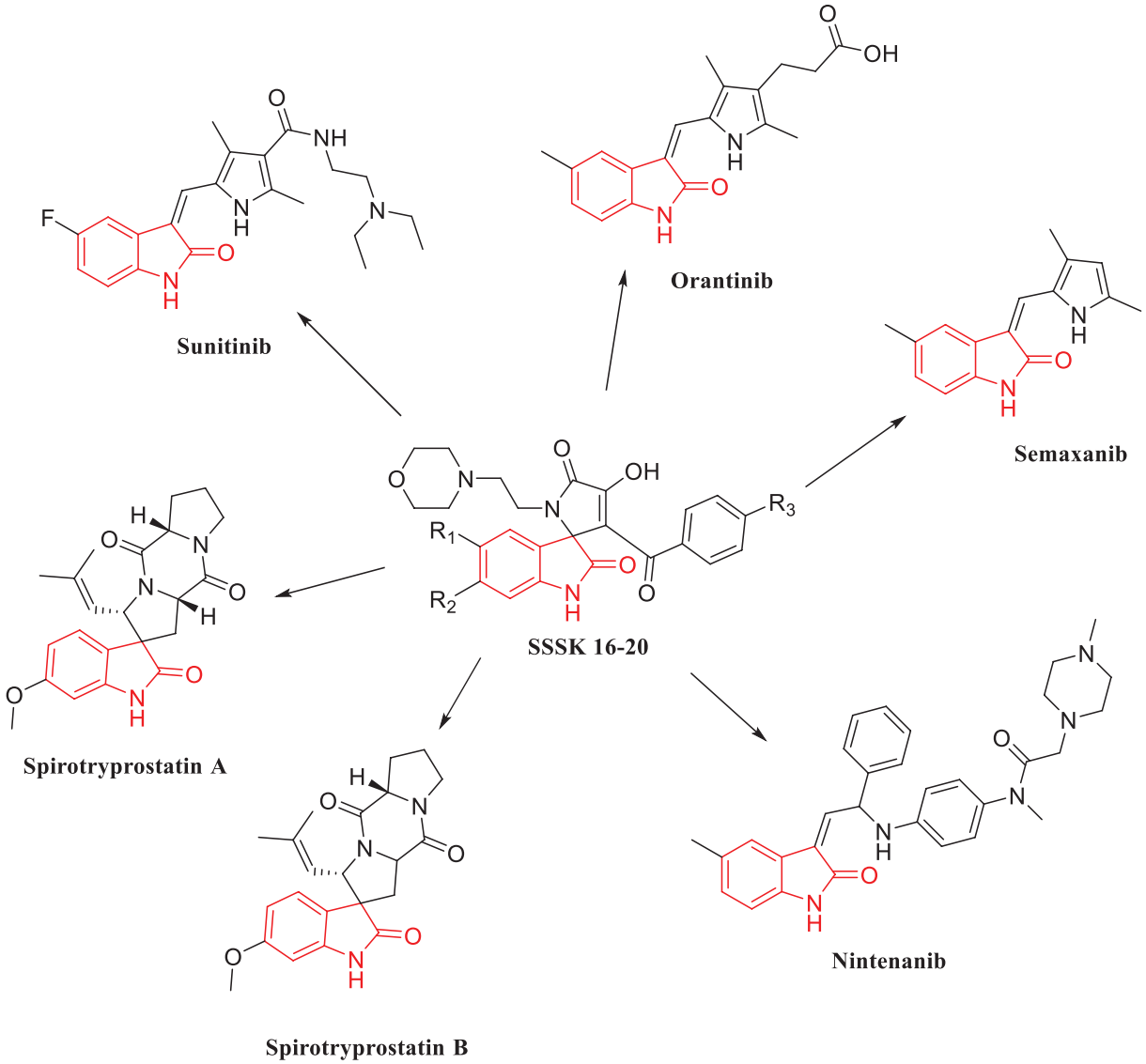


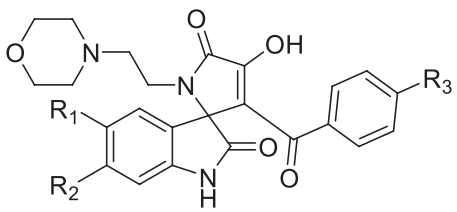
Figure 1: Pharmacophoric pattern of anticancer drugs and targeted compounds (SSSK 16-20)

RESULTS AND DISCUSSION

Molecular docking

The molecular docking studies of compounds **(SSSK 16-20)** were performed by AutoDock 1.4.6 software on estrogen receptor (Protein Data Bank [PDB]: 3EQM) for anti-breast cancer screening [**Table 1**]. The docking score of compounds was ranging between −8.16 and −9.30. All compounds showed better docking scores as compared to the standard drug, Adriamycin (ADR) (−6.86). The compound having isatin ring (**SSSK20**) possessed best score (−9.30) among the series. The compound **SSSK18** having 5-bromo isatin moiety showed a good docking score (−9.12). Other compounds **SSSK16** and **SSSK17** having a 5-chloro substitution at isatin moiety also displayed good scores (−8.65 and −8.50, respectively). Therefore, it could be postulated that compounds having a substitution of halogen at isatin ring displayed good results. Whereas the compound **SSSK20** having halogen substitution at benzoyl ring, displayed less score (−8.16) among the series.

The oxygen of morpholine ring, the >CO of the benzoyl ring and -OH of pyrrole ring in highest docking scored compound **SSSK19** involved in hydrogen bonding interaction with MET374, ALA438, and ARG115, respectively, through -H of –NH [**Figure 2**]. The interaction of standard drug ADR was also shown [**Figure 3**].

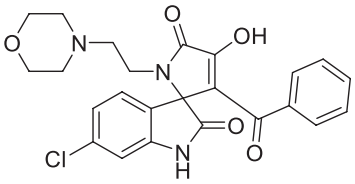
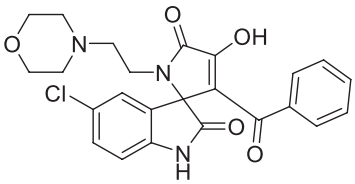
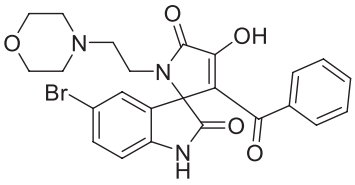
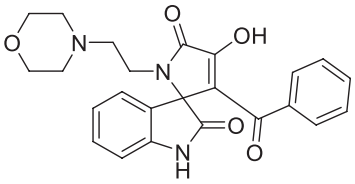
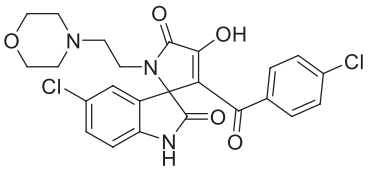


SSSK 16-20

Predicted absorption, distribution, metabolism, and excretion (ADME) studies

All designed compounds **(SSSK 16-20)** showed high gastrointestinal (GI) absorption. None of the

Table 1: Docking scores of designed compounds SSSK 16-20 and standard drug (Adriamycin)

Compounds	Structures	Binding energy (kcal/mol)	No. of H-bonds	Residues involved in the hydrogen bonding	Hydrogen bond length (Å)
SSSK16		−8.65	3	ARG115, TRP141, ARG145	1.921, 1.984, 1.889
SSSK17		−8.50	2	ARG115, ALA438	1.891, 2.238
SSSK18		−9.12	3	ARG115, MET374, ALA438	2.116, 2.073, 2.108
SSSK19		−9.30	3	ARG115, MET374, ALA438	2.214, 2.074, 2.022
SSSK20		−8.16	3	ARG115, MET374, ALA438	2.107, 1.979, 1.893
Adriamycin		−6.86	3	ASP72, GLN92, GLY132	2.216, 2.119, 1.880

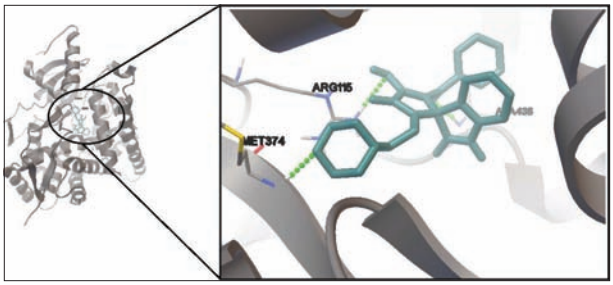


Figure 2: Interaction of SSSK19 against human placental aromatase cytochrome P450 in complex with androstenedione breast cancer cell line Protein Data Bank ID: - 3EQM

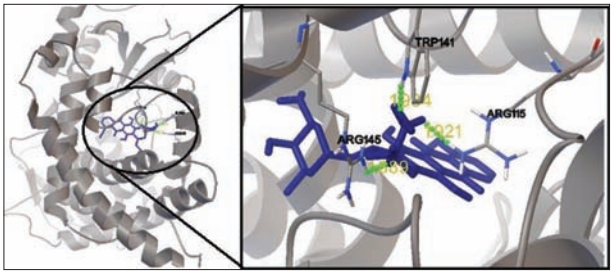


Figure 3: Interaction of Adriamycin against human placental aromatase cytochrome P450 in complex with androstenedione breast cancer cell line Protein Data Bank ID: - 3EQM

compounds showed BBB permeability and inhibition to Cytochrome P450 isomers CYP1A2 and CYP2D6. All compounds displayed inhibition to P-glycoprotein. All compounds followed drug-likeness prediction depending on the selected Lipinski and Veber rule and displayed a significant bioavailability score. It could be seen that the majority of compounds among the series possessed better pharmacokinetic properties [**Table 2**].

Toxicity

All compounds **(SSSK 16-20)** predicted to be non-mutagenic (MUT) and non-carcinogenic. All compounds had significant drug scores (DS) and showed remarkable drug-likeness (DL) values. The compounds **SSSK-16** and **SSSK20** displayed better solubility than other compounds. High cLogP (CLP) values are an estimation of low hydrophilicity and therefore cause low absorption

or permeation. All compounds **(SSSK 16-20)** displayed significant cLogP values [**Table 3**].

Chemistry

The synthesis of target compounds **(SSSK 16-20)** was accomplished by a highly efficient three-component coupling reaction of pyruvates **(1)**, chlorosubstituted isatin **(2),** and 2-morpholinoethan-1-amine **(3)**. In all cases, the targeted final indoline-2-one derivatives **(SSSK 16-20)** were obtained in good yield [**Scheme 1 and Table 4**].

The structures of synthesized compounds **(SSSK 16-20)** were confirmed by Fourier transform infrared (FTIR), ^{1}H-nuclear magnetic resonance (^{1}H-NMR), ^{13}C-NMR, and mass spectra. In IR data, compounds **(SSSK 16-20)** displayed a characteristic broad absorption band of the hydroxyl group (-OH, stretch) at 3438–3463 cm^{-1}. All compounds showed an absorption band of the carbonyl group (>CO) at 1726-1710 cm^{-1}. In ^{1}H NMR, the >NH of isatin was observed as a sharp singlet at δ 10.82-10.71 ppm. In the morpholine moiety of all compounds, four protons of $>CH_2$ near to oxygen atom were observed as a singlet at δ 3.71-3.53 ppm and four protons of $>CH_2$ near to nitrogen atom were observed as a multiplet at δ 3.08-2.10 ppm. Other aromatic and aliphatic protons were present at their respective place. In ^{13}C NMR of all compounds, >CO of carbonyl group was observed at δ 186.1–186.9 ppm and >CO of both amide groups were observed at δ 176.4-169.05 ppm. Other aromatic and aliphatic protons were present at their respective place.

In vitro anticancer screening

The synthesized compounds **(SSSK 16-20)** were tested for their *in vitro* anti-breast cancer activity against human cancer cell lines (MCF-7 and MDA-MB-231) using sulforhodamine B assay (SRB Assay).[15] The GI_{50} concentration of all compounds was calculated with reference to a control sample. For each compound, 50% growth inhibition (GI_{50}) was determined from sigmoidal dose-response curves and given in **Table 5**. For reference purposes, ADR data were included in the study.

The resultant data showed that compounds exhibited cytotoxic effects on the human breast cancer MCF-7 cell line. None of the compounds showed anticancer activity on MDA-MB-231 cell line [**Figure 4**]. Among the series,

Table 2: Pharmacokinetic studies (ADME) of compounds (SSSK 16-20)

Compounds	Pharmacokinetics						Drug-likeness			
	GI absorption	BBB permeant	P-gp	CYP1A2	CYP2D6	Log K_p (skin permeation), cm/s	Lipinski	Ghose	Veber	Bioavailability Score
SSKS16	High	No	Yes	No	No	−7.56	Yes	No	Yes	0.56
SSKS17	High	No	Yes	No	No	−7.56	Yes	No	Yes	0.56
SSKS18	High	No	Yes	No	No	−7.78	Yes	No	Yes	0.56
SSKS19	High	No	Yes	No	No	−7.79	Yes	Yes	Yes	0.56
SSKS20	High	No	Yes	No	No	−7.32	Yes	No	Yes	0.56

P-gp: P-glycoprotein, GI: Gastrointestinal, BBB: Blood-brain barrier, CYP1A2: Cytochrome P450 family 1 subfamily A member 2 (PDB: 2HI4), CYP2D6: Cytochrome P450 family 2 subfamily D member 6 (PDB: 5TFT)

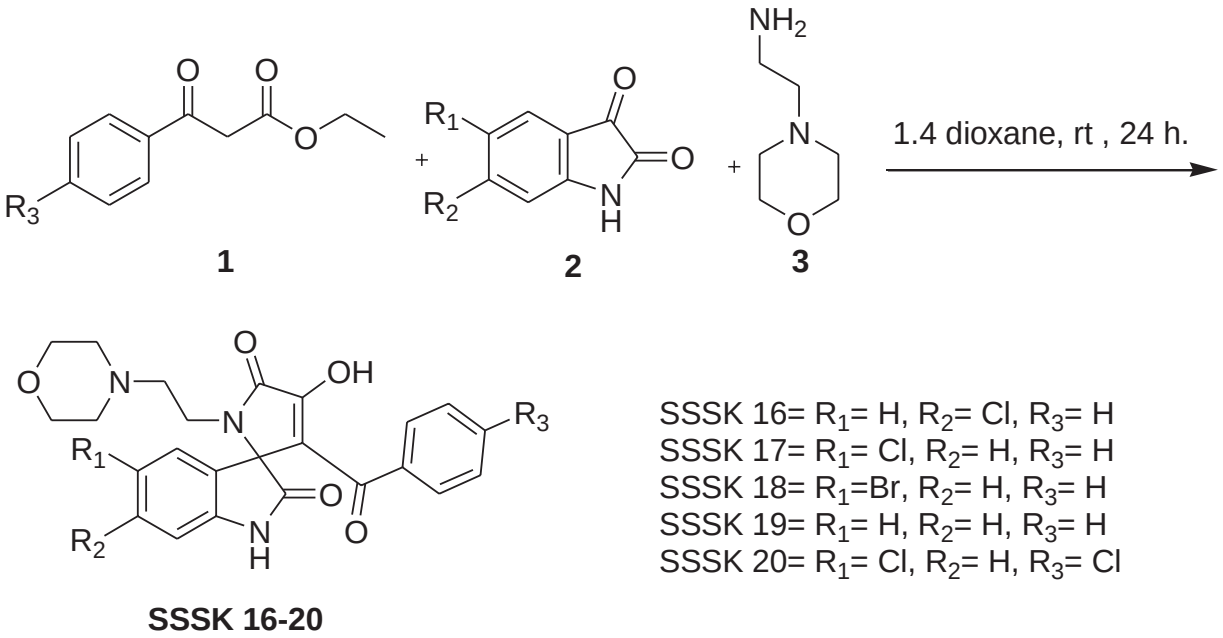
Table 3: Toxicity analysis by Osiris based on compounds (SSSK 16-20).

Compounds	Toxicity risks		Osiris calculations				
	MUT	TUMO	MW	CLP	S	DL	D-S
SSKS16	Green	Green	326	2.88	−3.32	−6.46	0.41
SSKS17	Green	Green	360	3.49	−4.05	−5.73	0.36
SSKS18	Green	Green	404	3.60	−4.15	−8.04	0.34
SSKS19	Green	Green	395	4.02	−4.47	−8.37	0.31
SSKS20	Green	Green	326	2.88	−3.32	−4.43	0.42

Table 4: Compounds (SSSK 16-20) differing in the substitution at R_1, R_2, and R_3

Compounds.[a,b]	R_1	R_2	R_3	Mol. formula	Mol. weight	Yield (%)[c]	MP (°C)
SSSK16	Cl	H	H	$C_{24}H_{22}ClN_3O_5$	467.906	73	247
SSSK17	H	Cl	H	$C_{24}H_{22}ClN_3O_5$	467.906	75	236
SSSK18	Br	H	H	$C_{24}H_{22}BrN_3O_5$	512.360	70	264
SSSK19	H	H	H	$C_{24}H_{23}N_3O_5$	433.464	80	240
SSSK20	H	Cl	Cl	$C_{24}H_{21}Cl_2N_3O_5$	502.348	75	266

[a]Reagents and conditions: **3** (1 mmol), **4** (1 mmol), **5** (1 mmol), 1.4 dioxane, rt, 24 h. [b]Final product was confirmed by the analysis of ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectroscopy. [c]Yield refers to pure products after recrystallization by ethanol



Scheme 1: Synthetic pathway for compounds SSSK 16-20

Table 5: Anti-breast cancer activity of compounds (SSSK 16-20) on MCF-7 and MDA-MB-231 cell lines

Compounds	MCF-7 GI_{50} (M)[a]	MDA-MB-231 GI_{50} (M)[a]
SSSK16	0.44	NE
SSSK17	0.04	NE
SSSK18	NE	NE
SSSK19	21.6	NE
SSSK20	NE	NE
Adriamycin	<E-07	2E-10

[a]GI_{50} (M)=Molar concentration of drug causing 50% inhibition of cell growth

the compound **SSSK17** showed a promising activity (GI_{50} = 0.04 M). The compounds **SSSK16** (GI_{50} = 0.44 M) and **SSSK19** (GI_{50} = 21.6 M) also displayed good activity but less than as compared to standard ADR (GI_{50} <10^{-7} M). It had been found that the presence of the chloro group on isatin moiety accounted for significant activity as in compounds **SSSK16** and **SSSK17**. These compounds also displayed good docking scores than the standard drug. The compound (**SSSK18)** having 5-bromo substitution on isatin exhibited no activity, whereas it exhibited a remarkable docking score. The compound (**SSSK20**) with two chloro group substitution did not show any activity. Therefore, it could be postulated that increasing the electronegative group resulted in a decrease in activity. The results revealed that some compounds were active on the MCF-7 cell line; therefore, it could be postulated that the compounds were active against hormone-dependent estrogen receptors.

EXPERIMENTAL SECTION

Molecular docking

Molecular docking studies were carried out to understand the interaction of the synthesized compound on the AutoDock tool 1.5.6 against two different cell lines (PDB ID: 3EQM). The crystal structure of the receptor was downloaded from PDB (rcsb.org) and protein was prepared and refined by assigning bond orders, the addition of hydrogen and deletion of the water molecule, and save as protein pdbqt file. The ligand was also prepared by ligand preparation wizard and save as lig.pdbqt file. Grid was generated from grid generation wizard using pdbqt file of protein and ligand and save as grid.gpf file. The doc file was also prepared using docking wizard and saved as doc.dpf file. Finally, docking was performed and the result was analyzed using doc.dlg file.

Predicted ADME studies

The ADME properties of compounds **(SSSK 16-20)** such as predicted GI absorption, P-glycoprotein, blood-brain barrier, and drug-likeness prediction such as Lipinski, Ghose, and Veber rules and bioavailability score were predicted by online tool SwissADME of Swiss Institute of Bioinformatics (http://www.sib.swiss). ChemBioDraw Ultra version 15.0 (Cambridge Software) was used for drawing of 2D structural models and SMILES of each compound was translated into molfile by online Smiles translator and structure file generator found in Online tool Swiss ADME.

Toxicity

Toxicity prediction studies were performed by Osiris Property Explorer. The Osiris Property Explorer includes the mol inspiration software through which the data may obtain. MUT and tumorigenic properties were predicted using Osiris molecular property explorer. Green color predicts low toxicity; yellow shows moderate toxicity, while the red color predicts a high tendency for toxicity. D-S of a compound predicts the compound's overall potential to qualify for a drug. It provides results based on molecular

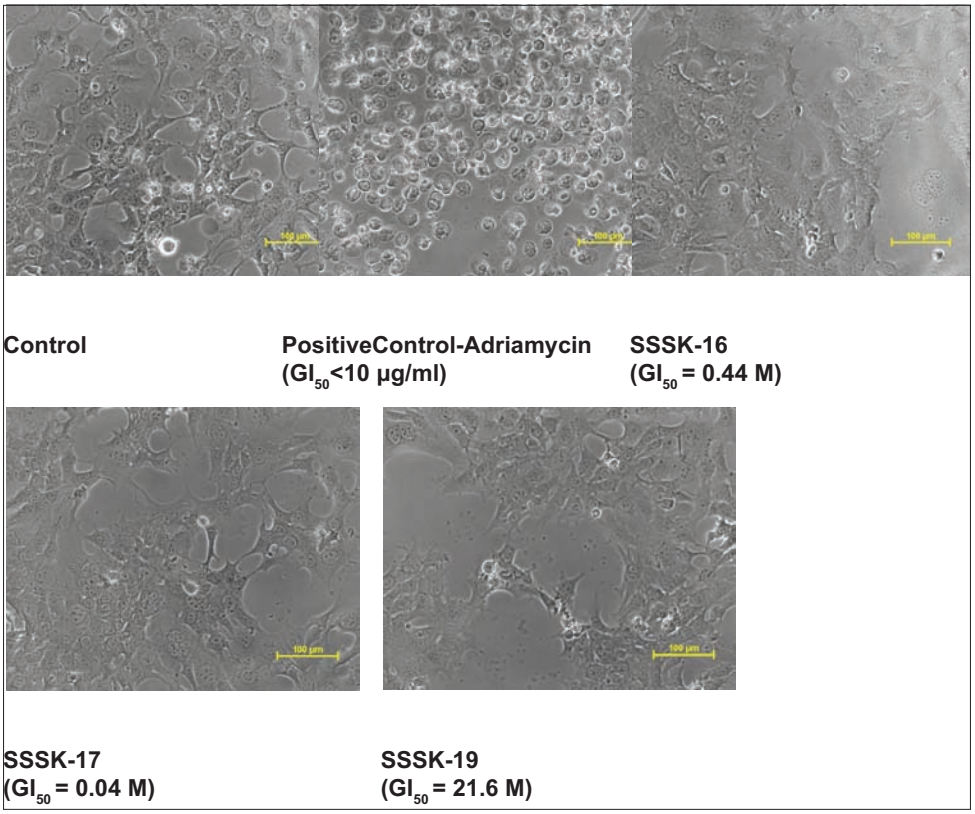


Figure 4: The growth inhibition (GI50) of MCF-7 cancer cells by SSSK16, SSSK17, SSSK19, and positive control (Adriamycin)

weight (MW), cLogP, log S, drug-likeness, and toxicity risks. DL values are based on topological descriptors, the fingerprint of molecular structure, or other properties such as MW, solubility, and cLogP.

MW and aqueous solubility (S) were also predicted. The low aqueous solubility of a compound affects its absorption and distribution characteristics.

Materials

All chemicals and solvents were of analytical grade and purchased from Merck, Sigma Aldrich, Alfa Assar, Fischer, and Rankem. All the reaction was performed in magnetic stirrer with the hot plate. Thin-layer chromatography was performed on 0.25 mm pre-coated plates with silica gel GF-254 (Merck) and viewed under UV light. Melting points were determined using OptiMelt digital melting point apparatus. ECX-500 spectrometer (JEOL) was used to record NMR spectra, 500 MHz for Proton (^{1}H), and 125 MHz for carbon (^{13}C). Dimethyl sulfoxide was used as a solvent for NMR spectroscopy. The chemical shifts were noted in (δ, ppm) using tetramethylsilane (TMSH) as an internal standard. Thermo Scientific, USA, ultimate 3000 mass spectrometry was used to record the mass spectra (m/z value) of all synthesized compounds. The infrared (IR) spectra were recorded on an FTIR (Shimadzu) using Potassium Bromide (KBr). The *in-vitro* anticancer study was done at Advanced Centre for Treatment Research and Education in Cancer (ACTREC), anticancer drug screening facility (ACDSF), Tata Memorial Centre, Navi Mumbai, India.

Synthesis

General procedure for the synthesis of substituted spiro indoline-2-one derivatives (SSSK 16-20)

The substituted isatin **2** (1 mmol) and 2-morpholinoethan-1-amine **(3)** (1 mmol) were mixed in 1,4-dioxane (5 mL). After stirred for 20 min, a solution of compound **1** (1 mmol) in 1,4-dioxane (1 mL) was dropped slowly into the reaction mixture. Then, the mixture was stirred for 24 h. The resulting precipitate was filtered off and recrystallized from ethanol to give compounds **SSSK 16-20.**

3'-Benzoyl-6-chloro-4'-hydroxy-1'-(2-morpholinoethyl) spiro[indoline-3,2'-pyrrole]-2,5'(1'H)-dione (SSSK16)

IR (KBr, ν, cm^{-1}): 3450 (OH), 2968, 1726, 1710, 1614, 1480; ^{1}H-NMR (500 MHz, DMSO-d$_6$, ppm): 10.82 (s, 1H, >NH), 7.67 (d, *J* = 7.3 Hz, 2H), 7.39 (d, *J* = 6.4 Hz, 1H), 7.30 (t, *J* = 7.0 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.86 (s, 1H), 3.58 (s, 4H, >CH$_2$), 3.20 (d, *J* = 14 Hz, 2H, >CH$_2$), 3.09 (d, *J* = 13.7 Hz, 2H, >CH$_2$), 2.71-2.61 (m, 4H, >CH$_2$); ^{13}C-NMR (125MHz, DMSO-d$_6$): 186.1, 176.4, 169.9, 145.8, 139.7, 134.1, 131.4, 129.2, 127.9, 126.7, 125.9, 122.0, 110.5, 68.7, 64.9, 55.1, 52.6, 36.9; HR-MS: 466.1179 (M+H)+, calcd. 466.1170.

3'-Benzoyl-5-chloro-4'-hydroxy-1'-(2-morpholinoethyl) spiro[indoline-3,2'-pyrrole]-2,5'(1'*H*)-dione (SSSK17)

IR (KBr, ν, cm^{-1}): 3445 (OH), 2925, 1725, 1619, 1583, 1477, 1388; ^{1}H-NMR (500 MHz, DMSO-d$_6$, ppm): 10.80 (s, 1H, >NH), 7.70 (d, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.0 Hz,

1H), 7.31 (t, *J* = 7.0 Hz, 2H), 7.23 (d, *J* = 6.1 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 1H), 3.58 (s, 4H, >CH_2), 3.20 (t, *J* = 7.3 Hz, 1H, >CH_2), 3.11 (t, *J* = 6.4 Hz, 1H, >CH_2), 2.80-2.30 (m, 6H, >CH_2); ^{13}C-NMR (125MHz, DMSO-d_6): 186.2, 176.3, 169.8, 145.9, 139.8, 134.2, 131.3, 129.3, 127.8, 126.8, 125.8, 122.1, 110.6, 68.8, 64.8, 55.2, 52.5, 36.8; HR-MS: 466.1174 (M+H)+, calcd. 466.1170.

3'-Benzoyl-5-bromo-4'-hydroxy-1'-(2-morpholinoethyl) spiro[indoline-3,2'-pyrrole]-2,5'(1'H)-dione (SSSK18)

IR (KBr, ν, cm^{-1}): 3439 (OH), 3101, 1711, 1615, 1583, 1474, 1386, 1304; ^{1}H-NMR (500 MHz, DMSO-d_6, ppm): 10.79 (s, 1H, >NH), 7.69 (s, 2H), 7.34 (s, 5H), 6.81 (s, 1H), 3.57 (s, 4H, >CH_2), 3.20 (d, *J* = 2.0 Hz, 1H, >CH_2), 3.08 (s, 1H, >CH_2), 2.80-2.10 (m, 6H, >CH_2); ^{13}C-NMR (125MHZ, DMSO-d_6): 186.9, 175.8, 169.0, 144.2, 139.4, 131.8, 130.2, 129.2, 128.1, 127.0, 124.5, 122.3, 110.6, 69.2, 65.3, 55.3, 52.8, 37.3; HR-MS: 512.0654 (M+2H)+, calcd. 512.0821.

3'-Benzoyl-4'-hydroxy-1'-(2-morpholinoethyl) spiro[indoline-3,2'-pyrrole]-2,5'(1'H)-dione (SSSK19)

IR (KBr, ν, cm^{-1}): 3463 (OH), 3084, 2869, 1723, 1706, 1618, 1583, 1471, 1388; ^{1}H-NMR (500 MHz, DMSO-D^6, ppm): 10.71 (s, 1H, >NH), 7.66 (d, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.87-6.85 (m, 2H), 3.53 (s, 4H, >CH_2), 3.21 (m, 1H, >CH_2), 3.07-3.01 (m, 1H, >CH_2), 2.50-2.32 (m, 6H, >CH_2); ^{13}C-NMR (125 MHZ, DMSO-D^6): 184.2, 175.8, 168.9, 144.2, 139.3, 131.9, 130.2, 129.2, 128.1, 126.9, 124.6, 122.3, 110.6, 69.2, 65.4, 55.4, 52.9, 37.4; HR-MS: 434.1713 (M+H)+, calcd. 434.1716.

5-chloro-3'-(4-chlorobenzoyl)-4'-hydroxy-1'-(2-morpholinoethyl)spiro[indoline-3,2'-pyrrole]-2,5'(1'H)-dione (SSSK20)

IR (KBr, ν, cm^{-1}): 3445 (OH), 3100, 2866, 1714, 1618, 1545, 1477, 1384; ^{1}H-NMR (500 MHz, DMSO-d_6, ppm): 10.74 (s, 1H, >NH), 7.73 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 7.9 Hz, 1H), 3.62 (s, 4H, >CH_2), 3.20-3.19 (m, 1H, >CH_2), 3.18-3.13 (m, 1H, >CH_2), 3.08-2.54 (m, 6H, >CH_2); ^{13}C-NMR (125 MHZ, DMSO-d_6): 186.8, 175.9, 169.1, 144.3, 139.5, 131.7, 131.7, 130.3, 129.3, 128.2, 127.1, 124.6, 122.2, 110.5, 69.1, 65.4, 55.2, 52.7, 37.4; HR-MS: 500.0781 (M+H)+, calcd. 500.0780.

In vitro anticancer activity by SRB assay

In-vitro, anticancer study for five compounds was done against two cancer cell lines (MCF-7 and MDA-MB-231). Anticancer screening of final compounds was determined by SRB assay procedure, taking ADR as a standard drug.[15,16] All compounds were evaluated in triplicate in four concentrations 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} and the average of these molar drug concentrations was considered as the final value. The absorbance of all the aliquots was measured using Elisa plate reader at a wavelength of 540 nm with a 690 nm reference wavelength. Results were plotted with reference to the dose-response curve as molar drug concentration and percent control growth.

CONCLUSION

Three compounds **SSSK16, SSSK17,** and **SSSK19** exhibited anticancer activity on MCF-7 cell line. None of the compounds showed anticancer activity on MDA-MB-231 cell line. Results of docking, *in silico* ADME and toxicity studies, were also favorable for the synthesis of compounds. The presence of isatin moiety and its substitution with chloro group (**SSSK16**, **SSSK17,** and **SSSK19**) were favorable for binding as well as anti-breast cancer activity. Further evaluation of the detail mechanism pathway involved in an activity needs to be investigated.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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