



Research Article

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# Docking Study of Novel Thiophene Derivatives Synthesized by Stille Cross Coupling with Potent Anti-Cancer Activity



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## Abstract

**Background:** Novel diaryldithiophene and hetero conditions. Isophane Derivatives (7-11) were designed and synthesized under stille cross coupling reaction conditions.

**Materials and Methods:** The new compounds were evaluated for their antitumor activities in 3 different cell lines; MCF7, HEPG2 and Lung Cancer.

**Results:** Compounds 7, 8, 9, 10 and 11 exhibited highly potent cytotoxic activity with IC<sub>50</sub> values in 0.042 - 4.09  $\mu$ M ranges. A docking study of the synthesized compounds was carried out using complex (H10V).

**Conclusion:** Molecular docking simulation was performed to position compounds 7-11 into the EGFR active site to determine the probable binding mode.

**Keywords:** Carbon-Carbon Bond Formation; Stannane; Cytotoxic Activity; Docking Study; CDK2

**Abbreviations:** SRB: Sulforhodamine B; HBV: Hepatitis B Virus; CDK2: Cyclin-Dependent Kinase 2; DMEM: Dulbecco's Modified Eagle's Medium; FBS: Heat Inactivated Fetal Bovine Serum

## Introduction

The development of new anticancer therapeutic agents is one of the fundamental goals in medicinal chemistry as cancer causes about 13 % of all the death [1]. Uracil and other pyrimidine derivatives are effective anticancer agents especially for prostate cancer with cathepsin B inhibition [2], mouse tumor (EAC), human liver (HepG2), breast (MCF-7) and colon (HCT-29) cancer cell lines [3-10]. Also, Pyrimidine derivatives have moderate inhibition activity against HBV with mild cytotoxicity activity [11]. While some pyridine derivatives exhibit considerable vasodilation properties on thoracic aortic rings of Wister rats [12]. On the other hand, Palladium metal was found to be the most effective transition-metal for catalyzing C-C coupling reactions of the last decades [13-17]. This reaction has been used in the syntheses of various biaryl compounds, which are important intermediates in the syntheses of natural products, functionalized polymers, and pharmaceuticals [18]. Pd-complex catalysts are

generally used in cross-coupling reactions, not only in Migitaie Kosugie Stille cross coupling reactions, but also in other relevant cross-couplings such as Suzukie Miyaura [19], Mizorokie Heck [20], and Hiyamae Hatanaka [21] cross-coupling reactions. In continuation of the previous work with Carbon-Carbon coupling reactions of thiophene with various aryl and heterocyclic rings as, tetrahydroisoquinoline bromide, and other allyl halides [22-25], and searching for new effective anticancer agents, this study was performed with the stille cross coupling reaction between thiophene and dihalobiphenyldiol, its benzyloxy derivative, dihalopyridine as well as with monohalopyrimidine-2,4-dione and with monohaloquinoline-3-carbaldehyde to explore the effect of the [Pd]0 catalyst on this reactions. The yielded compounds were tested for their antitumor activity in 3 different cell lines; MCF7, HEPG2 and Lung Cancer which show good activity against the tumor cells with docking study.

## Materials and Methods

### Experimental

#### Chemistry

All melting points were measured using a kofler block apparatus and are uncorrected. Yields listed are of isolated compounds. The IR spectra were recorded on a perkin-Elmer model 1720 FTIR spectrometer for KBr disc.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a varian Gemini 300 BB NMR Spectrometer at 400 MHz. Chemical shifts were reported in  $\delta$  scale (ppm) relative to TMS as a reference standard and the coupling constants  $J$  values are given in Hz. Mass spectra were recorded on GC/MS Finnegan SSQ 7000 spectrophotometer & GC Ms-QP 1000 EX mass spectrometer at 70 eV. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F245. Elemental analyses were performed at the Microanalytical centre at Faculty of science, Cairo University, Egypt. The Antitumor Evaluation of the synthesized compounds was carried out at the faculty of pharmacy, Ain Shams University, Cairo, Egypt.

#### Synthesis of Bis(Dibenzylideneacetone)Palladium(0) Catalyst

A mixture of  $\text{PdCl}_2$  (1.77 g, 0.01 mol) and NaCl (0.58 g, 0.01 mol) was stirred in methanol (50 ml) at room temperature for 16 hrs. The resulting solution was filtered through a cotton plug and the filtrate was diluted to 300 ml with methanol. The diluted filtrate was then heated to  $60^\circ\text{C}$  and 7.28 g of (dibenzylideneacetone) were added to warm, stirred  $\text{Na}_2\text{PdCl}_6$  filtrate. Stirring was continued for further 15 minutes followed by addition of anhydrous sodium acetate (15g) where the reaction commences at once. The solution was stirred for 1 hour till cooling to room temperature; the resulting dark brown precipitate was filtered, washed with (5 x 25 ml) methanol, with (5 x 25 ml) water and with (5 x 25 ml) acetone affording pure  $[\text{Pd}(\text{dba})_2]$  (4.59 g, 80 %).

#### General Procedure for the Preparation of the Stille Coupling Compounds

In a capped flask were placed a solution of the mono or dibromoaryl derivative (0.01 mol),  $\text{Pd}(\text{dba})_2$  (10 mol %) and one or two equivalents of tributyl(thiophen-2-yl)stannane 1 in toluene (20 ml), the flask was sealed under nitrogen and the reaction mixture was heated at  $110^\circ\text{C}$  for 24 hrs., then cooled to room temperature. The reaction mixture was quenched with water (25 ml) and KF (250 mg) was added to the mixture with stirring for 5 hrs., then neutralized with aqueous ammonium chloride solution. The resultant mixture was filtered to remove the unwanted solid ( $\text{Bu}_3\text{SnF}$ ) and the filtrate was evaporated in vacuum to give an oily residue, which was isolated by extraction with ethyl acetate. The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , and evaporated under vacuum to produce the pure products.

#### 5,5'-Bi(Thiophen-2-yl)Biphenyl-2,2'-Diol (7)

Yellowish solid, recrystallized from methanol; yield (45%);

mp  $165\text{--}166^\circ\text{C}$ ; IR (KBr)  $\nu_{\text{max}}$ : 3340, 3248 (OH), 1612 (C=C)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  7.83- 7.12 (m, 12H, Ar-H), 9.0 (b s, 2H, 2 OH) ppm;  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta$  = 117.0 - 140.5 (Ar-C + thiophene-C), 155.5 (C-O) ppm; GC-MS: ( $\text{M}^+$ , %) m/z 350 (25.95), 333 (9.31), 291 (8.65), 233 (8.91), 151 (7.21), 79.95 (100), 72 (8.91); Analysis Calcd. for  $\text{C}_{20}\text{H}_{14}\text{O}_2\text{S}_2$  (350.45) C, 68.55; H, 4.03; S, 18.30; Found C, 68.60; H, 4.15; S, 18.55.

#### 2,2'-Bis-Benzoyloxy-5,5'-Bi(Thiophen-2-yl)-Biphenyl (8)

Green yellowish crystals; recrystallized from ethyl acetate; yield (65%), mp  $170\text{--}171^\circ\text{C}$ ; IR (KBr)  $\nu_{\text{max}}$ : 3062, 3032 (C-H)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  7.90 - 7.10 (m, 22H, Ar-CH), 5.11, 5.07 (2s, 4H, 2 CH<sub>2</sub>) ppm;  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta$  = 71.1 (CH<sub>2</sub>), 115.0 - 140.5 (Ar-C + thiophene-C), 148.5 (C-O) ppm; GC-MS: ( $\text{M}^+$ , %) m/z 530 (59.32), 447 (44.07), 340 (69.49), 256 (60.17), 152 (91.53), 106 (100), 82 (27.12); Analysis Calcd. for  $\text{C}_{34}\text{H}_{26}\text{O}_2\text{S}_2$  (530.70) C, 76.95; H, 4.94; S, 12.08; Found C, 76.75; H, 4.95; S, 12.15.

#### 2,4-Bi(Thiophen-2-yl)Pyridine (9)

Brown yellowish crystals, recrystallized from ethyl alcohol, yield (40%); mp  $140\text{--}141^\circ\text{C}$ , IR (KBr)  $\nu_{\text{max}}$ : 3062, 3032 (C-H), 1603 (C=N)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  8.70 (s, 1H, pyridine-CH), 8.72, 8.65 (2 d,  $J_1 = 2.1$ ,  $J_2 = 2.4$  Hz, 2H, pyridine-CH), 7.90- 7.17 (m, 6H, thiophene-CH) ppm;  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta$  = 112.5 - 152.3 (pyridine-C + Thiophene-C) ppm; GC-MS: ( $\text{M}^+$ , %) m/z 243 (33.67), 159 (29.59, 77 (100), 61 (27.55); Analysis Calcd. for  $\text{C}_{13}\text{H}_9\text{NS}_2$  (243.34) C, 64.17; H, 3.73; N, 5.76; S, 26.35; Found C, 64.05; H, 3.65; N, 5.55; S, 26.50.

#### 5-(Thiophen-2-yl)Uracil (10)

Black crystals; recrystallized from toluene; yield (50%); mp  $155\text{--}156^\circ\text{C}$ ; IR (KBr)  $\nu_{\text{max}}$ : 3162 (NH), 3061, 3029 (C-H), 1698, 1650 (2 C=O), 1603 (C=C)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  11.30, 11.10 (bs, 2H, 2 NH exchangeable), 7.8 (s, 1H, pyrimidine-CH), 7.60 - 7.10 (m, 3H, thiophene-CH) ppm;  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta$  = 112.3 - 137.5 (Pyrimidine-C + thiophene-C), 151.0, 166.0 (2C=O) ppm; GC-MS: ( $\text{M}^+$ , %) m/z 194 (3.5) 178 (26.82), 146.95 (100), 121.95 (68.60), 80 (17.27); Analysis Calcd. for  $\text{C}_8\text{H}_6\text{N}_2\text{O}_2\text{S}$  (194.21) C, 49.48; H, 3.11; N, 14.42; S, 16.51; Found C, 50.0; H, 3.35; N, 14.60; S, 16.32.

#### 2-(Thiophen-2-yl)Quinoline-3-Carbaldehyde (11)

Green crystals, recrystallized from ethyl acetate; yield (60%); mp  $135\text{--}136^\circ\text{C}$ ; IR (KBr)  $\nu_{\text{max}}$ : 3061, 3029 (Ar-CH), 2957, 2851 (Ald-CH), 1655 (C=O), 1616 (C=C)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz) ppm:  $\delta$  10.40 (s, 1H, aldehydes-CH), 9.0 (s, 1H, quinoline-CH), 8.30 (m, 4H, quinoline-CH), 7.46-7.2 (m, 3H, thiophene-CH);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta$  = 120.7 - 154.0 (quinoline-C + thiophene-C), 192.0 (C=O) ppm; GC-MS: ( $\text{M}^+$ , %) m/z 239 (13.7), 210 (1.55), 178 (100), 127 (5.29), 76 (2.56); Analysis Calcd. for  $\text{C}_{14}\text{H}_9\text{NOS}$  (239.29) C, 70.27; H, 3.79; N, 5.85; S, 13.40; Found C, 70.10; H, 3.95; N, 5.60; S, 13.30.

## Biological Evaluation

### Cytotoxicity Assessment

#### Methodology

Each of MCF-7 and HepG2, were grown in RPMI-1640 medium, A549 human lung cancer cells were grown in DMEM, supplemented with 10% heat inactivated FBS, 50 units/mL of streptomycin and maintained at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>. The cells were maintained as “monolayer culture” by serial sub culturing.

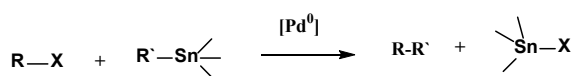
#### SRB Cytotoxicity Assay

Cytotoxicity was determined using SRB method as described by Skehan et al. Exponentially growing cells were collected using 0.25 % Trypsin-EDTA and seeded in 96-well plates at 1000-2000 cells/well in RPMI-1640 supplemented medium. After 24 h, cells were incubated for 72h with various concentrations of the tested compounds. Following 72h treatment, the cells were fixed with 10 % trichloroacetic acid for 1h at 4°C. Wells were stained for 10 min at room temperature with 0.4 % SRB dissolved in 1% acetic acid. The plates were air dried for 24h and the dye was solubilized with Tris-HCl for 5 min on a shaker at 1600 rpm. The optical density (OD) of each well was measured spectrophotometrically at 564 nm with an ELISA microplate reader (ChroMate-4300, FL, USA). The IC<sub>50</sub> values were calculated according to the equation of Boltzman sigmoidal concentration - response curve using the nonlinear regression fitting models (Graph Pad, Prism Version 5).

## Results and Discussion

### Chemistry

Tributyl(thiophen-2-yl)stannane 1 was prepared according to a previous procedure and was separated by chromatography using neutral Alumina [26]. Coupling of compound 1 with 5,5'-dibromobiphenyl-2,2'-diol (2) in 10% mol of Pd(dba)<sub>2</sub> under reflux in toluene in a nitrogen atmosphere afforded 5,5'-di(thiophen-2-yl)biphenyl-2,2'-diol (7) with 45% yield. The reaction mechanism includes coupling of two thiophene moieties at the 5 and 5' positions of the 5,5'-dibromobiphenyl-2,2'-diol reagent via the common stille coupling mechanism which suggests that when an aryl halide was coupled with a thiophenestannane derivative in the presence of [Pd] salt as a catalyst, the product is the arylthiophene beside tributylstannylbromide as a by-product as shown in [Equation 1] [27].



**Equation 1:** Reaction of alkyl halide with alkyltributylstannane in the presence of Pd [0] catalyst [28].

The toxic by-product was precipitated by stirring the product with KF and removed by filtration. The IR spectrum of compound 7 revealed a broad band at  $\nu_{\text{max}} = 3340$  and  $3248 \text{ cm}^{-1}$  attributed to two OH groups. While its <sup>1</sup>H NMR spectrum showed signals of the aromatic C-H and thiophene groups from  $\delta$  7.83 - 7.12 ppm while the OH protons were appeared as singlet at  $\delta$  9.0 ppm and the <sup>13</sup>C NMR spectrum showed signals of the aromatic-C and thiophene-C groups at  $\delta = 117.0 - 140.5$  in addition to C-O group at 155.5 ppm. The GC-MS of compound 7 showed the [M<sup>+</sup>] with  $m/z = 350$  by 26 % rel. Int. Reaction of the stannane 1 with the benzyloxy derivative of the compound 2 named, 2,2'-(benzyloxy)-5,5'-dibromobiphenyl (3) afforded 2,2'-bis-benzyloxy-5,5'-di(thiophen-2-yl)-biphenyl (8). The reaction product was found to have more yield product (65% yield) than the one with the hydroxyl derivative and so the antitumor activity is much better than the one with the hydroxyl derivative 7, which indicated that the reactivity of the coupling reaction was increased with increasing the aromaticity of the aryl bromide because of increasing the electron withdrawing effect of the benzyloxy moiety of the halide reagent. The IR spectrum of 8 revealed strong bands for aromatic C-H at  $\nu_{\text{max}} = 3062, 3032 \text{ cm}^{-1}$ . While its <sup>1</sup>H NMR spectrum showed the signals of the aromatic and thiophene moiety in addition to two singlet signals at  $\delta = 5.1$  and  $5.07$  ppm attributed to two methylene groups of the benzyl moiety and the <sup>13</sup>C NMR spectrum showed signals of two CH<sub>2</sub> groups at  $\delta = 71.1$  ppm. The GC-MS of 8 showed the [M<sup>+</sup>] with  $m/z = 530$  by 59 % rel. Int. (Figure 1).

#### Scheme-1

On the other hand, the reaction of stannane 1 with 2,4-dibromopyridine (4) under the same reaction conditions afforded 2,4-di(thiophen-2-yl)pyridine (9) with 40 % yield. The reaction proceeds with the same stille coupling reaction mechanism. The IR spectrum of 9 showed bands at  $\nu_{\text{max}} = 3061, 3032$  and  $1603 \text{ cm}^{-1}$  attributed to aromatic C-H and C=N groups respectively. Its <sup>1</sup>H NMR spectrum revealed signals at  $\delta = 8.70$ - $8.65$  ppm for the pyridine moiety and at  $\delta = 7.90$  -  $7.17$  ppm for the thiophene moiety and the <sup>13</sup>C NMR spectrum showed signals of the pyridine and thiophene moieties. The GC-MS of 9 showed the [M<sup>+</sup>] with  $m/z = 243$  by 34 % rel. Int (Figure 2).

Reaction of the stannane 1 with 5-bromouracil (5) under the same conditions afforded 5-(thiophen-2-yl)uracil (10) in 50 % yield. The reaction mechanism includes coupling of one thiophene moiety with 5-bromopyrimidinone moiety at the 5 positions. The IR spectrum of 10 revealed a band at  $\nu_{\text{max}} = 3162 \text{ cm}^{-1}$  for the NH group in addition to two bands at  $\nu_{\text{max}} = 1698$  and  $1650 \text{ cm}^{-1}$  for the two C=O groups of uracil moiety. Its <sup>1</sup>H NMR spectrum revealed two singlet signals at  $\delta = 11.3, 11.1$  ppm attributed to two NH groups and the <sup>13</sup>C NMR spectrum of 10 showed signals of pyrimidine and thiophene carbons in addition to two signals of two C=O groups at  $\delta = 151.0, 166.0$  ppm. The GC-MS of the same compound showed the [M<sup>+</sup>] with  $m/z = 194$  by 3.5 % rel. Int.

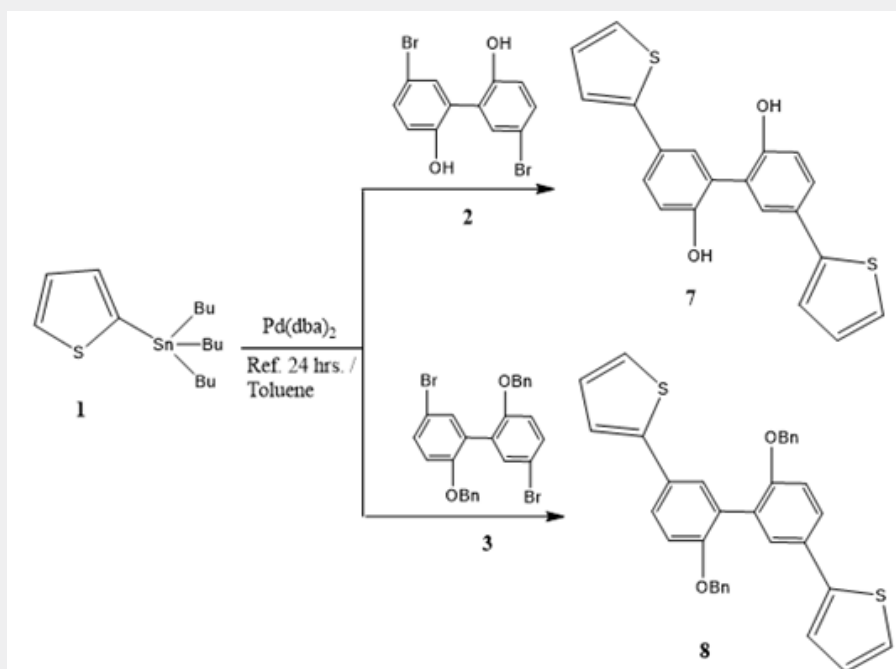


Figure 1: Synthesis of compounds 7,8.

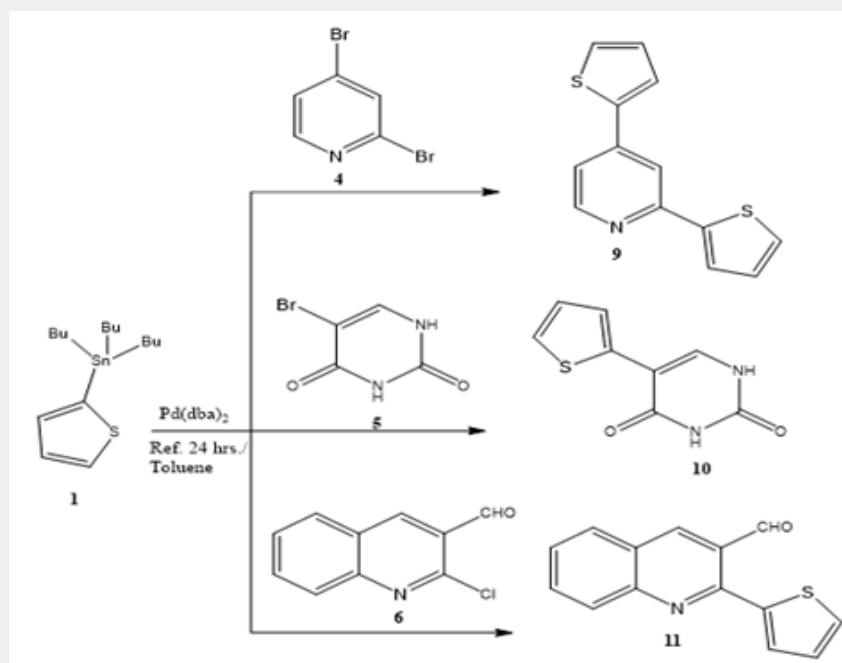


Figure 2: Synthesis of compounds (9-11).

Coupling of the stannane 1 with 2-chloroquinoline-3-carbaldehyde (6) under the same reaction conditions afforded 2-(thiophen-2-yl)quinoline-3-carbaldehyde (11) in 60 % yield.

The reaction mechanism includes coupling of one thiophene moiety at the position 2 of the 2-chloroquinoline-3-carbaldehyde moiety. The IR spectrum of compound 11 revealed bands at  $\nu_{\max}$  =



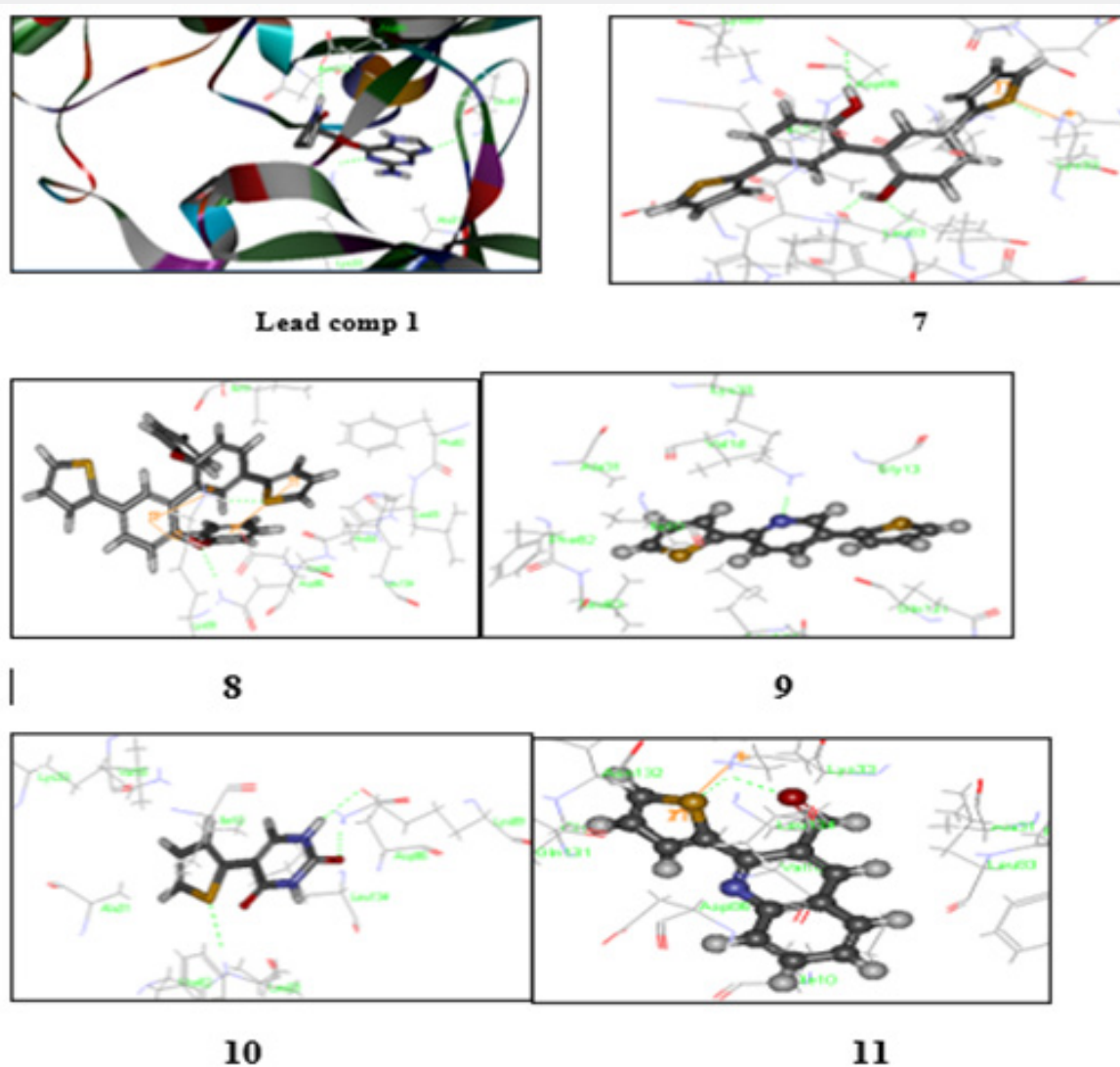
2957, 2852, 1655 and 1616  $\text{cm}^{-1}$  attributed to the aldehyde C-H, C=O and C=C respectively, the  $^1\text{H}$  NMR of the same compound revealed signals at  $\delta = 10.39, 9.0, 8.30, 8.0, 7.82, 7.46, 7.28, 7.25$  and 7.20 ppm due to C-H group of the aldehyde and 8 aromatic CH groups of the quinoline and thiophene moieties and the  $^{13}\text{C}$  NMR spectrum of 11 showed signals of quinoline and thiophene carbons in addition to a signal of C=O group of the aldehyde at  $\delta = 192.0$  ppm. The GC-MS of the same compound showed the  $[\text{M}^+]$  with  $m/z = 239$  by 13.7 % rel. Int (Figure 2).

## Scheme 2

### Molecular Docking Study of CDK2 Inhibitors and Binding Conformation

The Molecular Docking study for the new synthesized

compounds into CDK2 was carried out by using Discovery Studio 2.5 software to investigate the detailed intermolecular interactions between the ligand and the target protein. The structure of the enzyme and lead compound 1 (H10V) having resolution of 1.95 was used in the determination of the important amino acids in the predicted binding pocket. [24] Re-docking lead 1 with the same binding site showed docking energy = - 37.45 kcal/mol with small RMSD (0.045) deviation in comparison to its crystal structure. The small RMSD values proved the validity of the used docking processes [29]. Interactive docking using C-DOCKER protocol for all compounds 7-11 was carried out relative to the selected active site and each docked compound was assigned according to binding mode. The score according to its binding mode onto the binding site was calculated [27]. The predicted binding energies and the corresponding experimental values were outlined in (Figure 3).



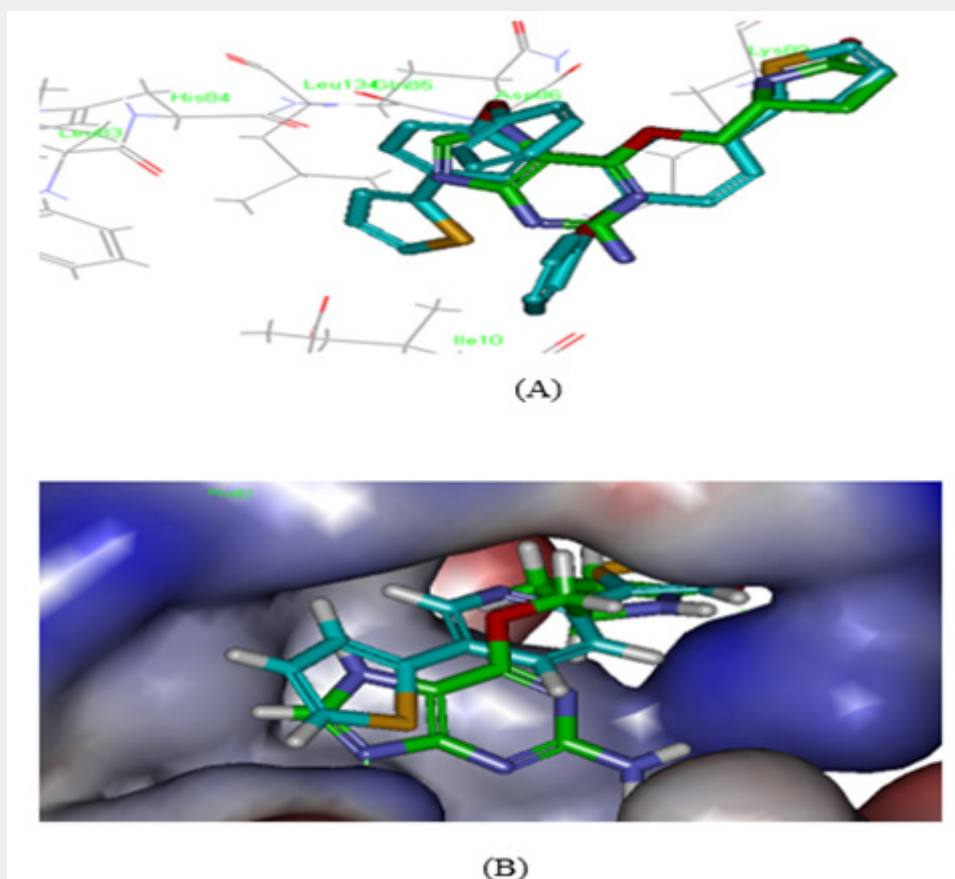
**Figure 3:** The proposed binding mode of Molecular docking modeling of compounds (7-11) and lead compound 1 with CDK2: for clarity, only interacting residues are displayed in the binding site of CDK2 resulting from docking respectively. The most important amino acids are shown together with their respective numbers.

**Figure 3**

**Alignment Study of Docked Compound 8 And 9 With the Lead Compound 1 Inside the Binding Pocket Of CDK2, As Shown In Figure 2 Revealed That**

For compound 8, the Biphenyl moiety of 8 was perfectly aligned with purine nucleus of ligand 1, Benzyloxy group of 8

superimposed with 4-amino substituent of lead compound 1, the 2-thiophene part of 8 was aligned with o-pyrrolidin-2-one methyl substituent of ligand 1, also both compound 8 and ligand 1 make the same hydrogen bonding interaction with Asp86 and Lys33. Additionally, compound 8 makes two hydrophobic interactions with Lys33. Also, compound 9 revealed good alignment with lead compound 1 (Figure 4 A&B).



**Figure 4:** (A) Alignment of docked compound 8 (cyan colour) with lead compound (1) (green colour) in the binding site of CDK2, shows amino acids in contact in the same position, (B) Alignment of docked compound 9 (cyan colour) with lead compound (1) (green colour) in the binding site of CDK2, shows amino acids in contact in the same position.

**Figure 4**

### Cytotoxicity Evaluation

The synthesized compounds 7-11 were screened for their cytotoxicity against A549 (Lung Cancer), MCF7 (breast) and HEPG2 (liver) human tumor cell lines utilizing the Sulfo-Rhodamine-B (SRB) standard method [28-33]. From the observed results (Table 1), it has been concluded that compounds 8, 9, 10 and 11 exhibited highly potent anti-tumor activity against MCF7 (breast) and A549 (Lung Cancer) cell lines more than that of Doxorubicin that was

used as a reference standard during this study (Table 1), while, compounds 8, 9 and 10 revealed highly potent cytotoxicity against HEPG2 (liver cancer) and A549 (Lung Cancer) cell lines more than that of Doxorubicin.

**Table 1**

The high docking results and biological activities can be explained by; first, the thiophene ring in all the new compounds increases the hydrophobic binding interaction with the deep hydrophobic pocket created by His84, Phe82, Glu81 and Ala31.

Second, hydrogen bonding interactions were found to happen between the compounds (7-11) with the high docking scores and N-H group of Lys33, N-H of Lys89 and Asp86. H-bond is displayed as line. Compounds 8 and 9 are nicely bound to the CDK2. The oxygen atom of 8 projects toward the side chain NH group of Asp86, forming a more optimal H-bond interaction. Also, the sulfur atom of the thiophene ring of compound 8 forms

hydrogen bond with Lys33. For compound 9 its N atom of pyridine ring make hydrogen bonding interaction with the N-H of Lys33. The docking results had provided us with useful information to understand the binding mode and the structural features of the target and chemical structure of the ligand. This was extended to the successful designing of highly active analogs of CDK2 inhibitor; (Table 1 and Figure 3,4).

**Table 1:** C-Docking interaction energy and Cytotoxicity properties of the synthesized compounds (7-11).

Compd. No.	C-Docker interaction Energy (-)	Lung cancer (A549) IC <sub>50</sub> (μM)	Brest cancer (MCF7) IC <sub>50</sub> (μM)	HPG2 cancer (HepG2) IC <sub>50</sub> (μM)
Ligand 1	37.45			
7	41.17	0.619	4.09	3.68
8	49.74	0.066	0.272	0.042
9	48.89	0.023	0.096	1.225
10	49.04	0.118	0.229	0.119
11	39.11	0.175	0.626	2.432
Doxorubicin	-	0.411	1.172	0.877

## Conclusion

We have successfully synthesized a series of new mono and bithiophene compounds (7-11) by using stille cross coupling technique of one or two moles of Tributyl(thiophen-2-yl) stannane with aryl halides and/or mono or dihaloheterocyclic compounds. The new synthesized compounds were evaluated for their antitumor activities in 3 different cell lines; MCF7, HEPG2 and A549 where compounds 8, 9 and 10 exhibited highly potent cytotoxicity activity comparable to that of Doxorubicin. A Molecular Docking study for the new synthesized compounds into CDK2 was carried out by using Discovery Studio 2.5 software.

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