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Unexpected Reactions of Azido-*p*-Benzoquinone Derivatives Towards *Lawesson's* Reagent and Molecular Docking Study as a Promising Anticancer Agent

Ahmed A. El-Sayed,* Manal M. T. El-Saidi, Reham R. Khattab
National Research Centre, Photochemistry Department, Industrial Chemical Division, 33 EL Bohouth st., Dokki, Giza 12622, Egypt.

SYNTHESIS of 1,3,2-benzo-aza-phosphole derivatives (**3b-c**) by reaction of *lawesson's Reagent* (*LR*) **1b** with 2-azido-*p*-benzoquinonedibenzenesulfonimine (**2b-c**) has been intercepted. The reaction of 2-azido-*p*-quinonediimine **4** with *Lawesson's Reagent* (*LR*) (**1a**) and/or (**1b**) gave the corresponding compounds **6a** and **6b**. On the other hand, when 2,5-diazido **5** reacted with *LR* (**1b**) has led to the formation of the benzenesulfonamide **10.** The disphospha-5-indacene adduct has been synthesized by the reaction of *LR* **1c** with **5.** Mechanisms accounting for the formation of these compounds are provided. All the synthesized compounds have been subjected to docking study using AutoDock *Vina* software in order to gain insights to their binding modes against cyclin-dependent protein kinase 2 (CDK-2, PDB:1DI8), receptor protein B-cell lymphoma 2 (BCL-2, PDB:2O2F), and Janus kinase 2 (Jak2, PDB:5AEP) that are highly involved in cell cycle and in cell apoptosis. These targets have been selected based on their key roles in cancer progression via the regulation of the cell cycle and DNA replication. Molecular-docking analyses have revealed that compound **12** and **6b** are the best docked ligand against all tested targets. As it is displays the lowest binding energy and critical hydrogen bonds and hydrophobic interactions with these proteins.

Keywords: Azides, *Lawesson's Reagent*, Molecular docking, Benzoazaphosphole derivatives, Benzoquinone diimine derivatives.

Introduction

Azide derivatives are one of those compounds with a wide range of reactions that can be built new Nitrogen–heteroatom or Carbon–Nitrogen bonds [1–5]. Azides chemistry have challenged many scientists in the synthesis of heterocyclic compounds due to their high biological activity from the former investigation of phenyl azide by Peter Grieb in 1864 [6, 7],−Azidothymidine (AZT) is known as the first drug used in treatment of HIV [8]. In recent years, the organic azides photochemistry studies have focused on the potential of their use in "click" reactions. These reactions have been recognized to increase the molecular complexity by bringing together two molecules together in a reliable and stereoselective fashion [9–13]. In addition, azide derivatives yields novel transformations that have emerged and have been widely applied in organic synthesis [14]. The synthetic utility of azides is mostly due to their high chemical reactivity [15] that is driven by the excellent ability of the dinitrogen leaving group. The unique features of the azido group is the wide range functionality as electrophile, nucleophile and radical acceptor [4, 10, 13]. Their amenability to diverse reaction pathways provides great opportunities to generate highly reactive intermediates; this the reason that they have attained an increasingly powerful and practical role in the organic methodology [14, 15]. Few researchers have been concerned with the

*Corresponding author e-mail: ahmedcheme4@yahoo.com
Telephone: 00201008653440; Fax: (202) 33370931
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multifunctional performance of the azido group, especially for mechanism analysis and reaction with *Lawesson's Reagent* [11,13,16–18].

Molecular docking provides a rapid way to evaluate the likely binders from large chemical libraries with minimal costs and it is being widely used as a vital component of the drug discovery process [22]. Molecular docking study has been utilized to determine the possible mechanism action of the tested compounds against three protein cyclin-dependent protein kinase 2 (CDK-2), receptor protein B-cell lymphoma 2 (BCL-2), and Janus kinase 2 (Jak2) that are implicated significantly in cancer progression. These targets are considered to be potential anticancer drug targets [23]. Moreover many benzoquinone derivatives are potential protein kinase inhibitor (especially cyclin dependent kinase 2), and B-cell lymphoma 2 BCL2 protein [24].

Material and Methods

All melting points were uncorrected. The appropriate precautions in handling moisture-sensitive compounds were undertaken. *Lawesson's Reagent*s [25–27] were prepared according to established procedures. 2-Azido-*p*-benzoquin onedibenzenesulfonimine (**4**) and 2,5-diazido-*p*-benzoquinone-dibenzenesulfonimine (**5**) [28] were recrystallized and dried before use.

The IR spectra were run on *Zeiss USA, California infrared-spectrophotometer IMR 1b*. The ^{1}H-NMR spectra were recorded on *Joel JNM-EX 270 FT NMR* system and the chemical shifts were recorded in δ (ppm) relative to TMS. The ^{31}P-NMR spectra were taken on *Joel instrument* (*vs* 85% H_3PO_4). The Mass Spectra were performed at 70eV on *schimadzu GC/MS-Qp1000EX* spectrometer. The Elemental Analysis was carried out at the microanalytical centre, (Cairo University, Egypt). The microanalysis for the new compounds were in good agreement with calculated values (C, H ± 0.1, N ± 0.05, P ± 0.05, S ± 0.05).

Molecular Docking Study

The structures of all tested compounds were modelled using the Chemsketch software (http://www.acdlabs.com/resources/ freeware/) (Figure 1). The structures were optimized and energy minimized using the VEGAZZ software [29]. The optimized compounds were used to perform molecular docking. The three-dimensional structures of the two molecular targets (receptors) were obtained from Protein Data Bank (PDB) (www.rcsb.org): CDK-2 (PDB:1DI8, https://www.rcsb.org/pdb/explore/explore.do?structureId=1di8), BCL-2 (PDB:2O2F, https://www.rcsb.org/pdb/explore/explore.do?structureId=2o2f), Jak2 (PDB:5AEP, https://www.rcsb.org/structure/5AEP). The steps for receptor preparation included the removal of heteroatoms (solvent and ions), the addition of polar Hydrogen and the assignment of Kollman charges. The active sites were defined using grid boxes of appropriate sizes around the bound cocrystal ligands [30]. These compounds were docked into the active site of the CDK-2, BCL-2 and Jak2 to study their interaction in silico and to speculate their anti-cancer activity. The docking study was performed using AutoDock Vina (version 1.5.6) [31] and Chimera for visualization [32].

Synthesis of 1,3,2-benzoazathiaphosphol-1,5-bis(benzenesulfonamido)-2(4-phenoxy- phenyl)-2-sulfide (3a):

To a suspension of **2a** (0.38 g; 0.001mole) in dry toluene (30 ml) was added **1b** (0.2 g; 0.0005 mole). The reaction mixture was refluxed for 1 hour. The solvent was evaporated. The oil that was left behind was applied to a column prepared by packing slurry of silica gel (30 g) in light petroleum. Toluene-light petroleum (1%) eluted to produce **3a** as colorless crystals (0.5 g), m.p. 127 °C, recrystallized from a chloroform-light petroleum mixture. IR spectrum (KBr, ν, cm^{-1}): 3120 (-NH), 3101 (C-H, Aromatic), 1449 (P-C aryl), 829 (P-N) & 765 (P=S). ^{1}H NMR (DMSO-d_6, δ ppm): 6.71 (d of d, 2H, aromatic), 7.23 (d of d, 2H, aromatic), 7.25-8.39 (m, 18 H, aromatic protons), 11.12 (s, 1H, NH, D_2O exchangeable). ^{31}P-NMR (DMSO-d_6, δ ppm): 85.40. Mass spectra *m/z*, %: 651 [M^++1, 30.02%], 650 [M^+, 25.12%], 388 [M^+-*LR*, 11.10%]. Anal. Calcd. For $C_{30}H_{23}N_2O_5PS_4$, (650.75): C, 55.37%, H, 3.56%, N, 4.30%, P, 4.76%, S**,** 19.71%. Found: C, 55.32%, H, 3.50%, N, 4.26%, P, 4.71%, S**,** 19.65%.

1,3,2-benzoaza-thiaphosphol-1,5-bis(methanesulfonamido)-2(4-phenoxy-phenyl)-2-sulfide (3b)

Similarly To a suspension of **2b** (0.26 g; 0.001 mole) in dry toluene reacted with **1b** (0.2 g; 0.0005 mole) to produce (**3b**) (eluent: toluene-light petroleum 1:6), yield 0.4 g, recrystallized from a chloroform-light petroleum mixture, m.p. 178°C. IR spectrum (KBr, ν, cm^{-1}): 3210 (-NH), 3198 (C-H, Aromatic), 2911 (C-H, Aliphatic),

1448 (P-C aryl), 825 (P-N) & 795 (P=S). ^{1}H NMR (DMSO-d_6, δ ppm): 3.63 (s, 3H, -CH_3), 3.84 (s, 3H, -CH_3), 6.76 (d of d, 2H, aromatic), 7.27 (d of d, 2H, aromatic), 7.35-7.85 (m, 8H, aromatic protons), 9.60 (s, NH, D_2O exchangeable). ^{31}P-NMR (DMSO-d_6, δ ppm): 88.30. Mass spectra *m/z*, %: 527 [M^++2, 40.01%], 526 [M^+, 50.24%]. Anal. Calcd. for $C_{20}H_{19}N_2O_5PS_4$ (526.61): C, 45.62%, H, 3.64%, N, 5.32%, P, 5.88%, S**,** 24.36%. Found: C, 45.59%, H, 3.60%, N, 5.28%, P, 5.83%, S**,** 24.31%.

1,3,2-benzoazathiaphosphol-1,5-bis(thiobenzoylamido)-2(4-phenoxy-phenyl)-2-sulfide (3c)

A suspension of *p*-Quinonedibenzimide **2c** (0.31 g; 0.001 mole) in dry toluene reacted with **1b** (1.2 g; 0.003 mole) to produce **3c** (eluent: toluene-light petroleum l:l0), yield 0.46 g, recrystallized from a chloroform-light petroleum mixture, m.p. 85-87°C. IR spectrum (KBr, ν, cm^{-1}): 3230 (-NH), 3098 (C-H, Aromatic), 1448 (P-C aryl), 820 (P-N) & 790 (P=S). ^{1}H NMR (DMSO-d_6, δ ppm): 6.81 (d of d, 2H, aromatic), 7.07 (d of d, 2H, aromatic), 7.33-8.45 (m, 18 H, aromatic protons), 10.42 (s, 1H, NH, D_2O exchangeable).^{31}P-NMR (DMSO-d_6, δ ppm): 84.12 ppm. Mass spectra *m/z*, %: 610 [M^+, 23.02%]. Anal. Calcd. for $C_{32}H_{23}N_2OPS_4$ (610.77): C, 62.93%, H, 3.80%, N, 4.59%, P, 5.07%, S**,** 21.00%. Found: C, 62.90%, H, 3.78%, N, 4.55%, P, 5.01%, S**,** 20.95%.

Synthesis of N-[5-Amino-3-benzenesulfonyl-2-(4-methoxy-phenyl)-2-thioxo-2,3,3a,6-tetrahydro-2λ^5-benzo[1,3,2]thiazaphosphol-6-yl]-benzenesulfonamide 6a.

A suspension of compound **4** (0.43 g, 0.001 mol) in dry toluene (30 ml) was treated with **1a** (0.2 g, 0.0005 mol). The reaction mixture was kept at reflux for 24h. After cooling, the solvent was evaporated under reduced pressure and the residue was applied to a column prepared by packing slurry of silica gel (30g) in petroleum ether (40-60 °C). AcOEt/Pet. (3:7; v/v) eluted **6a** as yellow crystals (0.4 g), m.p. 100 °C recrystallized from benzene/pet. ether. IR spectrum (KBr, ν, cm^{-1}): 3420 (-NH_2), 3120 (-NH), 3098 (C-H, Aromatic), 2910 (C-H, Aliphatic), 1448 (P-C aryl), 830 (P-N) & 760 (P=S). ^{1}H NMR ($CDCl_3$-d, δ ppm): 3.75 (s, 3H, MeO-), 4.59 (d, *J=6.20,* 1H, cyclohexane), 4.95 (d, *J=6.30,* 1H, cyclohexane), 5.54 (d, *J=6.35,* 1H, cyclohexane), 5.95 (d, 1H, cyclohexane), 6.08 (s, 2H, -NH_2, D_2O exchangeable), 6.45, 7.30 (d of d, *J=6.25,* 4H, 4-MeOC_6H_4), 7.65-8.01 (m, 10H, aromatic), 10.45 (s, 2H, -NH_2, D_2O exchangeable).^{31}P-NMR ($CDCl_3$-d, δ ppm): 71.20. Mass spectra *m/z*, %: 604 [M-1, 11.05%]$^+$ and 204 [1/2 *LR*, 40.08%]. Anal. Calc. for $C_{25}H_{24}N_3O_5PS_4$ (Mol. Wt. 605.71): C, 49.57%; H, 3.99%; N, 6.94%; P, 5.11%; S, 21.18%; found: C, 49.56%; H, 3.98%; N, 6.95%; P, 5.11%; S, 21.18%.

Synthesis of N-[5-Amino-3-benzenesulfonyl-2-(4-phenoxy-phenyl)-2-thioxo-2,3,3a,6-tetrahydro-2λ^5-benzo[1,3,2]thiazaphosphol-6-yl]-benzenesulfonamide 6b.

Similarly, **1b** (0.27 g) reacted with azide **4** (0.43 g) to produce compound **6b** as orange crystals (0.5 g), m.p. 143°C, recrystallized from $CHCl_3$/pet. ether. IR spectrum (KBr, ν, cm^{-1}): 3400 (-NH_2); 3129(-NH), 3081 (C-H, Aromatic), 2901 (C-H, Aliphatic), 820 (-P-N-), and 760 (-P=S-). ^{1}H NMR ($CDCl_3$-d, δ ppm): 4.54 (d, *J=5.26*, 1H, cyclohexane), 4.89 (d, *J=5.26,* 1H, cyclohexane), 5.65 (d, *J=5.26,* 1H, cyclohexane), 6.02 (d, *J=5.26,* 1H, cyclohexane), 6.80 (s, 2H, -NH_2, D_2O exchangeable), 6.95, 7.50 (d of d, *J=5.26,* 4H, aromatic), 7.55-8.15 (m, 15H, aromatic protons), 10.12 (s, 1H, -NH, D_2O exchangeable). ^{31}P-NMR ($CDCl_3$-d, δ ppm): Mass Spectra (Ms.), *m/z* (%): 666 [M-1, 55.12%]$^+$ and 264 [1/2*LR*, 12.50%]. 78.135. Anal. Calc. for $C_{30}H_{26}N_3O_5PS_4$ (Mol. Wt. 667.78): C, 53.96%; H, 3.92%; N, 6.29%; P, 4.64%; S, 19.21%; found: C, 53.94%; H, 3.90%; N, 6.30%; P, 4.60%; S, 19.18%.

2-Amino-p-phenylenedibenzenesulfonamide 8.

The **6a** derivative treated with EtOH/KOH 10%. The reaction mixture was refluxed for 6 h; evaporate the solvent under vacuum to have compound **8** as yellow ppt. m.p. 250 °C, recrystallized from ethanol, IR spectrum (KBr, ν, cm^{-1}): 3440 (-NH_2); 3081 (C-H, Aromatic), 2954 (C-H, Aliphatic), 1581 (C=N). ^{1}H NMR ($CDCl_3$-d, δ ppm): 4.21 (d, 1H, cyclohexane), 4.63 (d, *J=4.85,* 1H, cyclohexane), 4.95 (d, *J=4.85,* 1H, cyclohexane), 5.32 (d, *J=4.85,* 1H, cyclohexane), 6.23 (s, 2H, -NH_2, D_2O exchangeable), 7.36-8.05 (m, 10H, aromatic protons). Mass Spectra (Ms.), *m/z* (%): 400 [M^+-1, 33.12%]. Anal. Calc. for $C_{18}H_{15}N_3O_4S_2$ (Mol. Wt. 401.46): C, 53.85%; H, 3.77%; N, 10.47%; S, 15.97%; found: C, 53.80%; H, 3.73%; N, 10.45%; S, 15.90%.

Synthesis of N-[4,7-Diazido-3-benzenesulfonyl-2-(4-phenoxy-phenyl)-2-thioxo-2,3-dihydro-2λ^5-benzo[1,3,2]thiazaphosphol-6-yl]-benzenesulfonamide 10.

A suspension of compound **5** (0.43g, 0.001 mol) in dry toluene (30 ml) was treated with **1a**

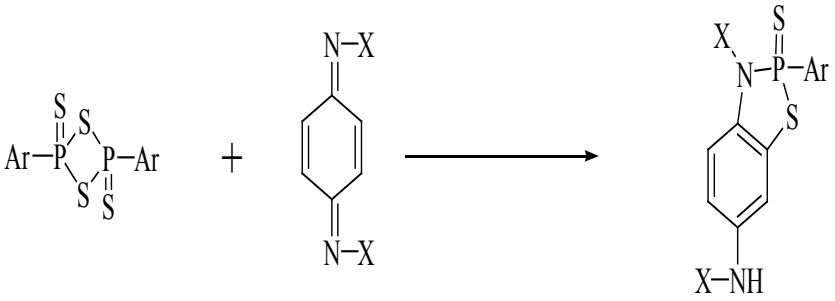
(0.027 g; 0.0005 mol). The reaction mixture was kept at room temperature for 24 hours whereby yellow crystals were separated, filtered off. Washed, dried and proved to be **10**, m.p. 150°C. IR spectrum (KBr, ν, cm^{-1}): 3129(-NH), 3101 (C-H, Aromatic), 2911 (C-H, Aliphatic), 2241, (-CN), 822 (-P-N-), and 765 (-P=S-). ^{1}H NMR (DMSO-d_6, δ ppm): 6.90, 7.31 (d of d, *J=5.42,* 4H, aromatic), 7.48-8.05(m, 16H, aromatic protons), 9.02 (s, 1H, -NH, D_2O exchangeable). ^{31}P-NMR ($CDCl_3$-d, δ ppm): 67.94. Mass Spectra (Ms.), *m/z* (%): 730 [M^+-2, 22.15%]; 698 [M-32, 32.85%]$^+$; 264 [1/2*LR,* 30.35%], 170 [$C_6H_4OC_6H_5$+1, 100%]. Anal. Calc. for $C_{30}H_{21}N_8O_5PS_4$ (Mol. Wt. 732.77): C, 49.17%; H, 2.89%; N, 15.29%; P, 4.23%; S, 17.50%; found: C, 49.15%; H, 2.82%; N, 15.25%; P, 4.22%; S, 17.48%.

Synthesis of 4,8-Bis-sulfonyl-benzeneimino-2,6-bis-phenylsulfanyl-2,6-dithioxo-1,2,3,5,6,7-octahydro-1,5-diaza-2λ5,6λ5-diphospha-s-indacene 12.

A suspension of compound **5** (0.43g, 0.001 mol) in dry toluene (30 ml) was treated with **1c** (0.041 g; 0.0001 mol). The reaction mixture was kept at room temperature for 24 hours whereby yellow crystals were separated, filtered off. Washed, dried and proved to be **12**, m.p. 212°C. IR spectrum (KBr, ν, cm^{-1}): 3229 (-NH), 3121 (C-H, Aromatic), 2923 (C-H, Aliphatic), 1585 (C=N), 820 (-P-N-), and 762 (-P=S-). ^{1}H NMR (DMSO-d_6, δ ppm): 4.94 (s, 2H, -PCH_2-), 5.23 (s, 2H, -PCH_2-), 7.13-7.37 (m, 10H, aromatic protons), 7.55-8.03 (m, 10H, aromatic protons), 9.02 (s, 1H, -NH, D_2O exchangeable), 10.30 (s, 1H, -NH, D_2O exchangeable). ^{31}P-NMR ($CDCl_3$-d, δ ppm): 89.68. Mass Spectra (Ms.), *m/z* (%): 782 [M^+-2, 29.20%]. Anal. Calc. for $C_{32}H_{26}N_4O_4P_2S_6$ (Mol. Wt. 784.91): C, 48.97%; H, 3.34%; N, 7.14%; P, 7.89%; S, 24.51%; found: C, 48.92%; H, 3.30%; N, 7.11%; P, 7.81%; S, 24.50%.

Results and Discussion

Lawesson's Reagent **(1a)** [25–27] is a superior thiating agents for a large number of aliphatic, unsaturated and aromatic compounds. A variety of -O, -N, -S, -P, heterocycles have been synthesized by the action of these *Reagent*s on bifunctional systems in which the substituents are located 1,2 or 1,3 to each other [23, 29–32]. As an extension of our group work using *Lawesson's Reagent* [37]; the synthesis of the 1,3,2-benzoazaphospholes **(3a-c)** by the action of *Lawesson's Reagent* **(1b)** with *p*-benzoquinone diimines **(2a-c)** (Scheme 1).



1 2 3

1, a, Ar = *p*-$C_6H_4OCH_3$ 2, a, X = $SO_2C_6H_5$ 3, a, Ar = *p*-$C_6H_4OC_6H_5$, X=$SO_2C_6H_5$

b, Ar = *p*-$C_6H_4OC_6H_5$ b, X = SO_2CH_3 b, Ar = *p*-$C_6H_4OC_6H_5$, X = SO_2CH_3

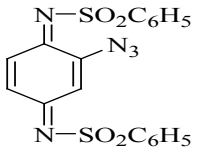
c, Ar = SC_6H_5 c, X= COC_6H_5 c, Ar = *p*-$C_6H_4OC_6H_5$, X = CSC_6H_5

Scheme 1. Synthesis of 1,3,2-benzoazaphospholes (3a-c) by the reaction of L.W. with *p*-benzoquinone diimines.

Structure **3a** is assigned to this product based on several data item. A correct elemental analysis corresponding to $C_{30}H_{23}N_2O_5PS_4$ is obtained; in addition to the mass spectrum of the compound **3a** as an example with signals at *m/z* 651 [M^++1], 650 [M^+] and 388 [M^+-*LR*]. Moreover, the IR spectrum of compound **3a** revealed bands at 3120 (-NH), 1449 (P-C aryl), 829 (P-N) & 765 (P=S) cm^{-1} and ^{1}H-NMR spectrum of compound **3a** has shown a singlet at δ 11.12 due to (-NH) ppm has further confirmed the structure. On the other hand, there appears to be little information in the literature regarding the behaviour of substituted *p*-quinonediimines towards these *LR*. Thus, we have undertaken a study on 2-azido-*p*-benzoqui nonedibenzenesulfonimine **(4)** and 2,5-diazido-*p*-benzoquinone dibenzenesul-donimine **(5)** to investigate the thiating action of *Lawesson's Reagent*s when 2 or 2&5 positions in these diimines are blocked.

When 1 mol equivalent of compound **(4)** has been allowed to react with ½ mol equivalent of LR **(1a,b)** in dry toluene at room temperature for 24 hours, no reaction took place (TLC). By raising the temperature to 80°C a crystalline product has been produced in quantitative yield. This adduct is chromatographically pure and shows a sharp melting point (Scheme 2).

Structure **6a** is assigned to this product based on several data item. A correct elemental analysis corresponding to $C_{25}H_{24}N_3O_5PS_4$ is obtained; in addition to the mass spectrum of the compound **6a** with signals at *m/z* 604 [M^+-1] and 204 [1/2 LR]. Moreover, the IR spectrum of compound **6a** shows bands at 3420 (-NH_2), 1448 (P-C aryl), 830 (P-N) & 760 (P=S) cm^{-1} has further confirmed the structure. Finally, the strong C=N absorption band appearing at 1580 cm^{-1} in the spectrum of the diamine **(4)** has vanished completely in the spectrum of compound **6a**. A further confirmation



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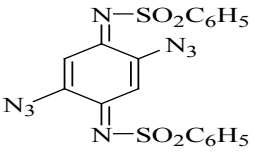

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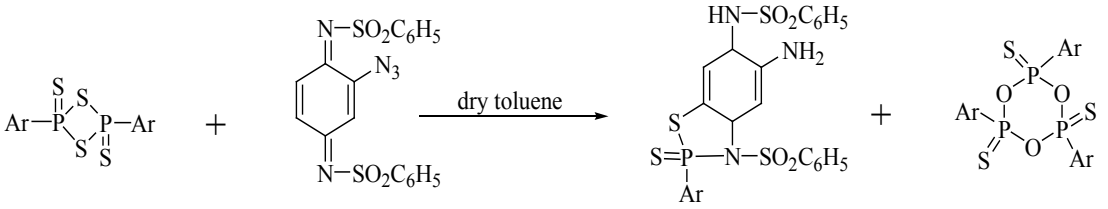


1, a, Ar = *p*-$C_6H_4OCH_3$
b, Ar = *p*-$C_6H_4OC_6H_5$

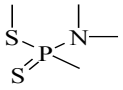
6a, Ar = *p*-$C_6H_4OCH_3$
b, Ar= *p*-$C_6H_4OC_6H_5$

Scheme 2. Synthesis of compound 6a,b by the reaction of L.W. with 2-azido-p-benzoquinonedibenzenesulfonimine.

6a

Ar = *p*-$C_6H_4OCH_3$

8



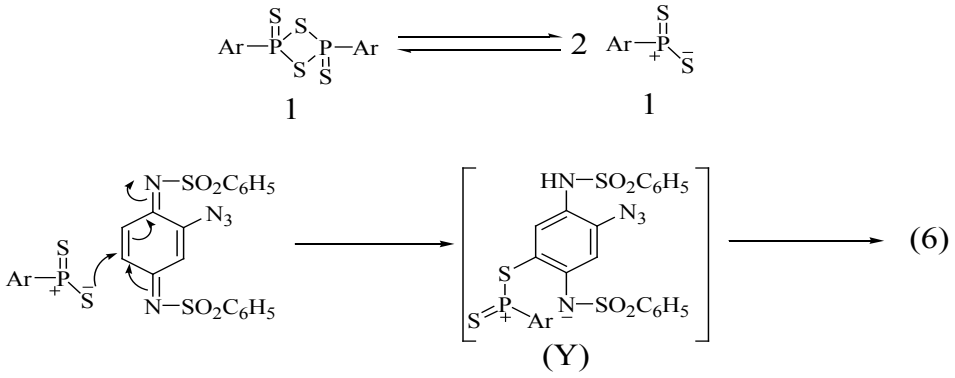
7

by using ^{31}P-NMR chemical shift at δ 71.20 ppm which is in accordance with shifts recorded for structures incorporating moiety **7**.

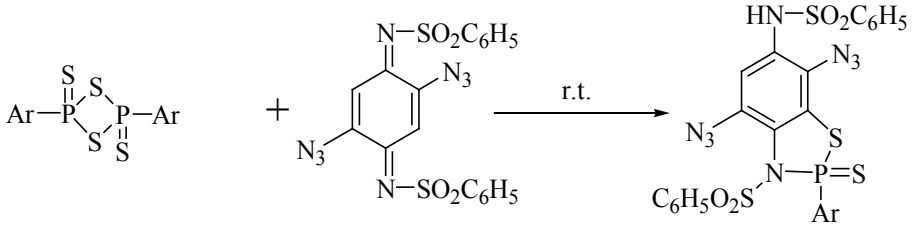
Also, the ^{1}H-NMR spectrum of compound **6a** has shown a singlet at δ 3.75 (3H) ppm for the MeO- protons and two singlet centered at δ 6.18 and 10.45 ppm due to (-NH_2 & NH, D_2O exchangeable). Adduct **6a** has been treated with alcoholic alkali to yield 2-amino-*p*-phenylenedibenzenesulfonamide **8**. Using excess of *Lawesson's Reagent* **(1a)** in this reaction, compound **6a** has been obtained in a high yield. Besides, isolation of a crystalline phosphorus compound has proved to be the trimeric thionophosphine oxide **9** (T.L.C.) chromatography (Scheme 3) [34- 42**,** 35].

Similarly, carrying the reaction of 1 mol equivalent of compound **4** with *LR* **1b** [2] has proceeded in dry toluene to give adduct **6b**; this is based on analytical and spectroscopic data (cf. experimental). A mechanism accounting for the formation of compound **6** is depicted in scheme 3. It is based on the assumption of the nucleophilic Michael type attack of the monomeric species **1** , existing in equilibrium with **1** [38,39] to compound **4** at position-5 yielding the intermediate (**Y**) which collapses to produce **6**. Trimmer **9** has been produced in case of using excess of the *LR*; probably formed by the oxidative cyclization of species **1** by air, giving credibility to the proposed mechanism. The simultaneous reduction of the azido group at position-2 is not surprising since nucleophiles has been known to affect the reduction of azides to the corresponding amines [48].

A further investigation has been carried out as a reaction of *Lawesson's Reagent* **1b** with diazide **5** in dry toluene solution at room temperature. Compound **10** has formed as an adduct and its structure has been assigned on the basis of the data. Correct elemental analysis corresponding to $C_{30}H_{21}N_8O_5PS_4$ has been obtained. The mass spectra of compound **10** has showed signals at *m/z* 730 [M^+-2]; 698 [M^+-32]; 264 [1/2 LR] and 170 [$C_6H_4OC_6H_5$+1]. Also, the IR spectrum of compound **10** has shown an absorption band 2241 cm^{-1} due to the azide moiety. The ^{31}P-NMR chemical shift for compound **10** has a signal at δ 67.94 ppm. Compound **10** is assumed to be formed by a similar betaine mechanism (cf. Scheme 3). The azide group does not suffer reduction since the reaction proceeded smoothly at room temperature. The possibility to modify



(Scheme 3)



1 5 10

1b, Ar = *p*-$C_6H_4OC_6H_5$ Ar= *p*-$C_6H_4OC_6H_5$

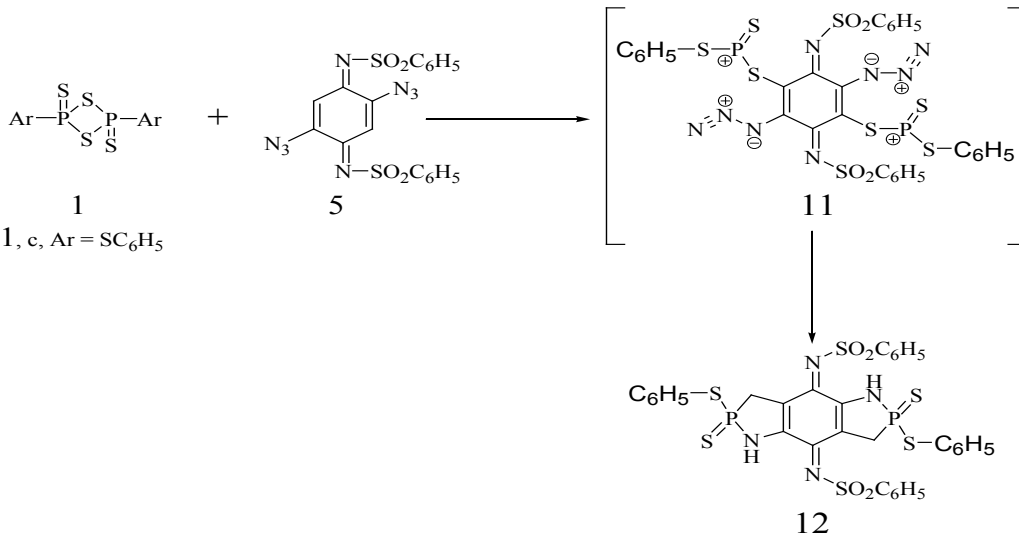
functional groups in an organic molecule without affecting the azide moiety has been previously described [49].

A different path has been intercepted upon reaction of *Lawesson's Reagent* **1c** towards azide **5**, in dry toluene at room temperature; a yellow crystalline compound has been produced and has been assigned structure **12**. The mass spectrum of compound **12** has shown a signal at *m/z* 782 [M^+-2] with a corresponding ^{31}P-NMR spectrum with a signal at δ 89.68 ppm. As for the ^{1}H-NMR spectrum, aromatic protons appears as two multiples at δ 7.13-7.37 (10 H) and 7.55-8.03 (10 H) ppm. The exchangeable (D_2O) protons (-NH) has appeared as a broad two singlet centered at δ 9.02 and 10.30 ppm. A similar obtained mechanism (cf. Scheme 1) may account for the formation of this adduct. The high polarity of the monomeric species of **1c** has initiated the addition of the highly nucleophilic sulfur at both 3 and 6 positions of the diimine to give the intermediate **11**. A subsequent cyclization involving the azido nitrogen attached to the ring has followed by a loss of two Nitrogen atoms from each azido group producing the final product **(12)** (Scheme 4).

Molecular Docking results

To test our docking proposition and to guarantee that the coupling stances of the docked ligands spoke to ideal and substantial potential restricting modes, the docking parameters and strategies have been approved by redocking the cocrystal ligand in request to decide the capacity of AutoDock vina to reproduce the orientation and position of the ligand has been seen in the crystal structure. The redocking of cocrystal ligands to their respective molecular targets exhibited an RMSD value of <2Å between the original cocrystal ligand position and the docked poses, as the RMSD was1.047Å for 1DI8 receptor, it was 1.343Å for 2O2F receptor, and it was the RMSD was1.047Å for 5AEP receptor. This confirmed that the ligands were closely bound to the true conformation of their targets indicating the reliability of the docking protocols and parameters [26,42].

The molecular docking studies has revealed that the compounds **12** (-9.1 kcal/mol), and **6b** (-8.6 kcal/mol) were the most promising compounds against CDK2 protein, that is explained by lowest binding energy even less than the reference ligand (-8.3 kcal/mol) (**Table 1**). While the docking results against Jak2 protein has depicted that **6b** (-10.2 kcal/mol), **5** (-9.6 kcal/mol), **4**, (-9.4 kcal/mol), and **6a** (-9.2 kcal/mol) were the best docked compounds; the free energy of binding for reference ligand was (-9.1 kcal/mol). In addition, compounds **4** (-9.0 kcal/mol), had the lowest free energy of binding upon docking against BCL-2 protein. From these results, it was obvious that compounds **5b** was the best potential compounds against all tested proteins based on low free energy of binding, Hydrogen bond formation (**6b** formed: H-bond with GLN131 residue with H-bond with LYS88 residue with length 3.340Å CDK2 ; H-bond with GLY142 residue of BCL-2 with length 1.878Å; H-bond with ASP976 residue with length of 2.129



(Scheme 4).

Å, and H-bond with ARG980 residue with length of 2.158 Å of Jak2 protein)), and hydrophobic interaction (**6b** formed:hydrophobic interaction ILE10, VAL18, ALA31, PHE82, PHE80, LEU134 residue with CDK2 ; hydrophobic interaction ILE144, VAL145, VAL130, LEU134, LEU198, PHE101, PHE109, PHE150 residue of BCL-2; hydrophobic interaction LEU997, LEU 983, LEU 932, LEU 860, LEU 855, PHE895, PHE995, PHE860, VAL863, VAL911residue of

TABLE 1. The results of molecular docking withCDK-2(1di8), BCL2 (2O2F), and Jak2 (5AEP) receptors.

Drugs	Free energy of binding (Kcal/mol)		
	CDK2	BCL2	Jak2
Reference ligand	-8.3	-10.6	-9.1
4	-8.6	-8.7	-9.4
5	-8.6	-8.7	-9.6
6a	-8.1	-8.5	-9.2
6b	-8.4	-9.0	-10.2
10	-6.6	-8.3	-8.1
12	-9.1	-8.4	-8.7

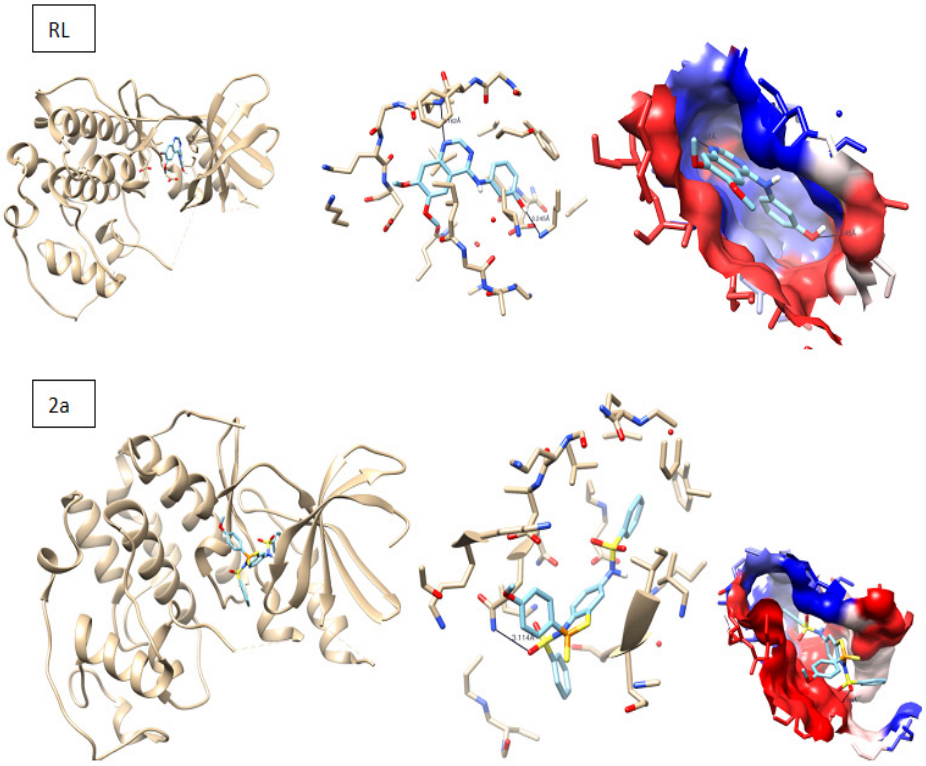


Fig. 1. 3D of hydrogen bond interaction between reference ligand (RL), and the most promising compound 6b with CDK-2 protein.

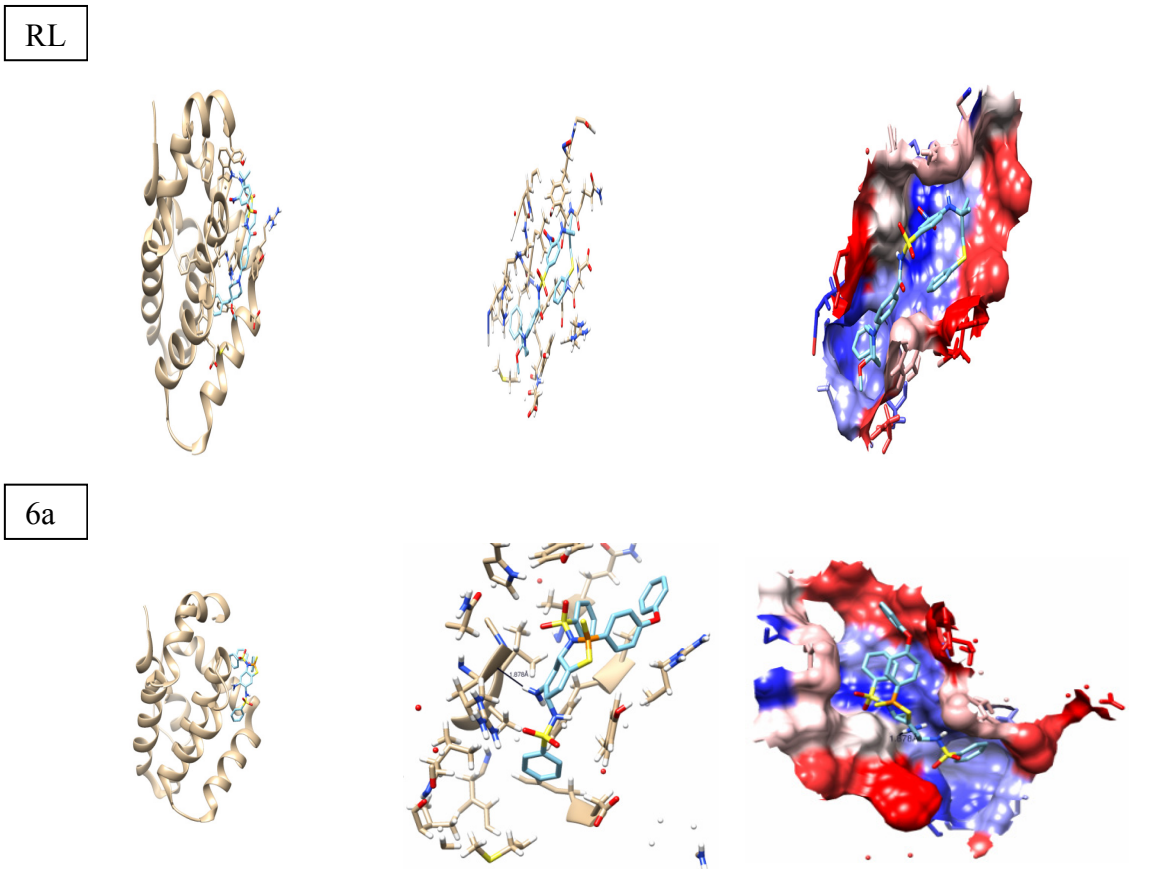


Fig. 2. 3D of hydrogen bond interaction between reference ligand (RL), and the most promising compound 6b with BCL-2 protein.

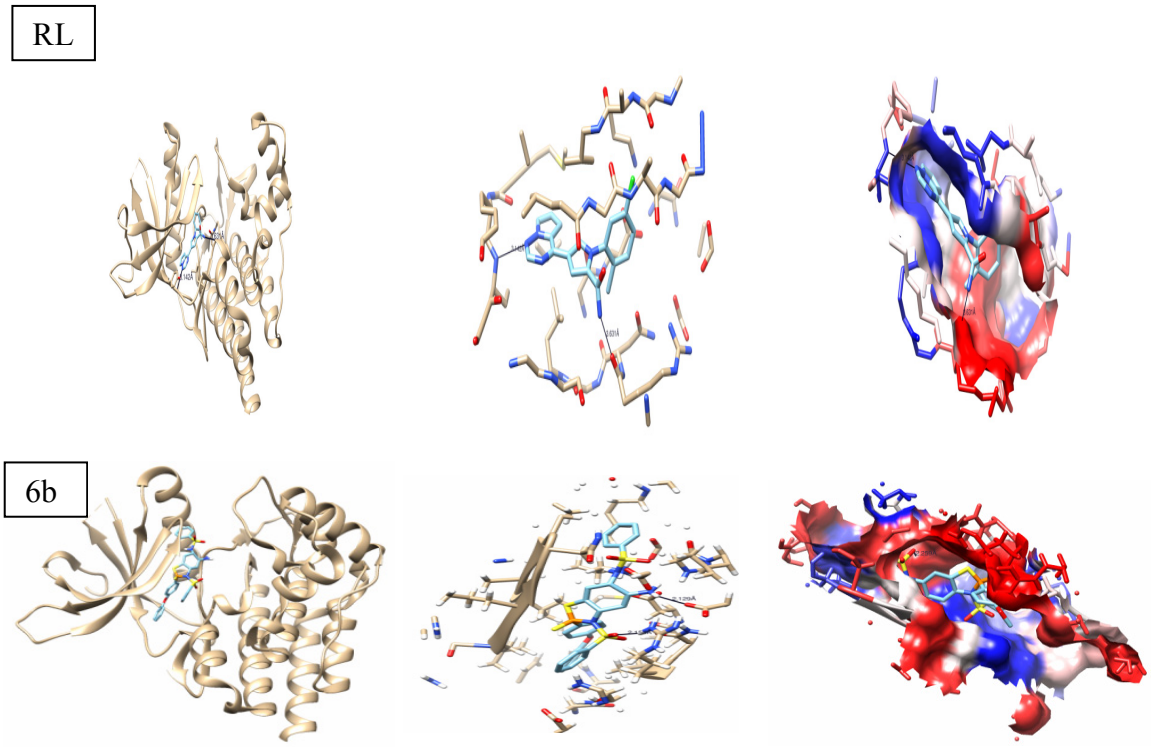


Fig. 3. 3D of hydrogen bond interaction between reference ligand (RL), and the most promising compound 6b with Jak2 protein.

Jak2 protein)) (Figure 1, 2 & 3).

These results has shed a light on compound **6b** as promising anticancer agents and further lab experimentation are to be carried out for activity verification.

(H-bond with GLN131 residue with H-bond with LYS88 residue with length 3.340 Å CDK-2; H-bond with GLY142 residue of BCL-2 with length 1.878 Å; H-bond with ASP976 residue with length of 2.129 Å, and H-bond with ARG980 residue with length of 2.158 Å of Jak2 protein), and hydrophobic interaction (6b formed hydrophobic interaction ILE10, VAL18, ALA31, PHE82, PHE80, and LEU134 residue with CDK-2; hydrophobic interaction ILE144, VAL145, VAL130, LEU134, LEU198, PHE101, PHE109, and PHE150 residue of BCL-2; and hydrophobic interaction LEU997, LEU 983, LEU 932, LEU 860, LEU 855, PHE895, PHE995, PHE860, VAL863, and VAL911 residue of Jak2 protein) [42-45] (Figs 1–3).

Conflicts of interest

The authors declare that they have no conflict of interest.

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