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ORIGINAL ARTICLE

Novel Spiro-pyrrolizidine-Oxindole and Spiropyrrolidine-Oxindoles: Green synthesis under Classical, Ultrasonic, and microwave conditions and Molecular docking simulation for antitumor and type 2 diabetes

Dina F. Katowah [a], Huwaida M.E. Hassaneen [b], Thoraya A. Farghaly [a,*]

[a] *Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah, Saudi Arabia*
[b] *Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt*

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Spiropyrrolizineoxindole;
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Abstract Novel spiropyrrolizine / pyrrolidineoxindole moieties were synthesized chemo-, and regio-selectively in high yields from knoevenagel reaction of *bis*[arylmethylidene]piperidin-4-ones, isatin and L-proline or sarcosine under classical, ultrasonic, and microwave conditions. Seven derivatives of the synthesized dispiro-pyrrolizidine-oxindole and spiropyrrolidine were screened for their antitumor activity against two cell lines MCF-7 (breast cancer) and HEPG2 (liver cancer). The results of biological activity indicated that the tested derivatives showed potent activity against breast cancer cell MCF-7. Molecular docking simulation screening studies of the synthesized products with each of the receptors of (3hb5) for breast cancer and (4k9g) for liver cancer and their interaction with 1H5U of glycogen phosphorylase B, type 2 diabetes drug were examined. The docking study of dispiro-pyrrolizidine-oxindole and spiropyrrolidine showed promising results with several derivatives.

1. Introduction

In full swing, scientists are searching day and night for anti-cancer drugs because of the side effects of the drugs circulating in the market, in addition to the body's resistance to these drugs (Richardson et al., 1988). Cancer of all kinds is one of the terrifying diseases whose name is associated with death. The number of deaths from this disease is increasing due to the increase in its causes and the side effects of chemotherapy

* Corresponding author.
E-mail addresses: huwaidah@sci.cu.edu.eg (H.M.E. Hassaneen), tamohamed@uqu.edu.sa, thoraya-f@hotmail.com, thoraya-f@cu.edu.eg (T.A. Farghaly).

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(Sung et al., 2021). On the other hand, diabetes is a well-established disease that occurs when the insulin produced by the pancreas is not sufficiently produced or when the body cannot effectively use the insulin produced. Type 2 diabetes that is not dependent on insulin, or appears in adults, results from the body's ineffective use of insulin. The majority of diabetic patients have type 2 diabetes (Diabetes, 2021). Glycogen phosphorylase (GP) inhibition has been proposed as a therapeutic strategy for type 2 diabetes treatment (Oikonomakos et al., 2005; Somsák et al., 2008). Inhibition of this enzyme by potent and selective inhibitors, will lead to antihyperglycemic drugs. Glycogen phosphorylase is a typical allosteric protein with five different ligand-binding sites, providing multiple opportunities to modulate enzyme activity. Spiro heterocycles are naturally occurring substances with biological activities (James et al., 1990). Also, hybrid molecules like pyrrolidine, pyrrolizine and oxindole pharmacophores which had a wide spectrum of biological activities like antimicrobial and anticancer (Hassaneen et al, 2017; Hati et al., 2016; Freeman-Cook et al., 2007; Engen et al., 2014; Almansour et al., 2014; Mohareb et al., 2014; Khan et al., 2014; Kumar et al., 2021; Wei et al., 2012; Chen et al., 2009; Dandia et al., 2017; Arumugam et al., 2018; Nesi et al., 2013; Hanna et al., 2012). One method from the several methods to generate pyrrolidine ring (Poomathi et al., 2015; Hemamalini et al., 2011; Ghandi et al., 2009; Shahrestani et al., 2019; Altowyan et al., 2022) is 1,3-dipolar cycloaddition of azomethineylides which used to synthesize many dispiroheterocyclic systems with the definite dipolarophiles (Hassaneen et al., 2017; Barakat et al., 2021a; Barakat et al., 2021b; Islam et al., 2021a;Islam et al., 2021b; Islam et al., 2022; Al-Majid et al., 2021; Nájera and Sansano, 2019; Rajkumar et al., 2016). Scientists are making an extensive effort to improve the yield of synthesized heterocyclic compounds by using nano-catalysts or different methods of heating such as microwave, ultrasound or reflux and compare the percentage yield of these methods to get the best results. Nano-catalysts and a variety of heating techniques, such as microwave, ultrasound, and reflux, are among the many tools scientists are using to increase the yield of synthetic heterocyclic compounds, with the goal of determining which approach produces the highest percentage yield. Ultrasound form hot spots during acoustic cavitations which serve to increase reaction rates and yields without using rough conditions (Rezaei et al., 2012; Jadidi et al., 2008; Alaoui et al., 2018; Dandia et al., 2020). Microwave (MW) method has used for synthesis spiropyrrolidine oxindole derivatives, a lot of advantages in using this method than conventional heating (Kefayati et al., 2015; Hoz et al., 2005; Buriol et al., 2010; Engen et al., 2014; Jandourek et al., 2014; Kidwai et al., 1997; Dandia et al., 2021a; Dandia et al., 2021b). Where small volumes and solvent-free MW methods are used that have a high level of chemo-, regio-, and stereoselectivity in them Spiro-oxindole derivatives were made under safe conditions using catalysts in aquas medium (Dandia et al., 2021c; Dandia et al., 2011). There were only a few reports on how to make spirooxindole with each of pyrrolidines and pyrrolizidines under ultrasound, Microwave irradiations, and free solvents.

Following on from the foregoing and in continuation of our research into the synthesis of novel biologically active hybrid heterocyclic compounds using green heating methods, (Shaaban et al, 2022; Alnaja et al., 2021; Bumander et al., 2019; Abbas et al., 2014; Farghaly and Riyadh, 2009), we are interested in synthesising new series of pyrrolidineoxindole and spiropyrrolizidine moieties under microwave irradiation and ultrasonic conditions in order to increase their yields and decrease their reaction time.

Furthermore, we will test the anticancer efficacy of newly synthesised spiropyrrolizidine / pyrrolidineoxindole derivatives for their antitumor activity. In addition, they will utilise the docking research to examine their interaction with two proteins (3hb5) that are associated with breast cancer and (4k9g) that are associated with liver cancer. Additionally, via docking studies of these derivatives with the 1H5U domain of glycogen phosphorylase B, a type 2 diabetes medication, evaluate the capacity of the produced compounds to suppress the development of type 2 diabetes.

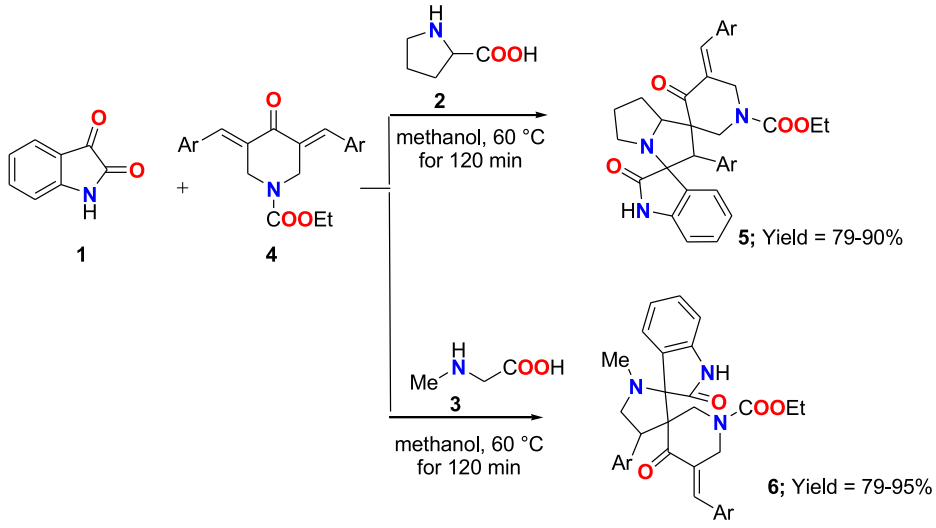
2. Results and discussion

We previously established in our earlier study (Hassaneen et al, 2017) that condensation reaction of isatin **(1)**, amino acids as L-proline **(2)**, or sarcosine **(3)**, and 3,5-*bis*[-phenylmethylidene]-4-oxopiperidine-*N*-carboxylate **(4a-j)**, was carried out in methanol at 60 °C in 120 min Scheme 1 to produce dispiro-pyrrolizidine-oxindoles **(5)**, or spiropyrrolidine **(6)** (Hassaneen et al, 2017).

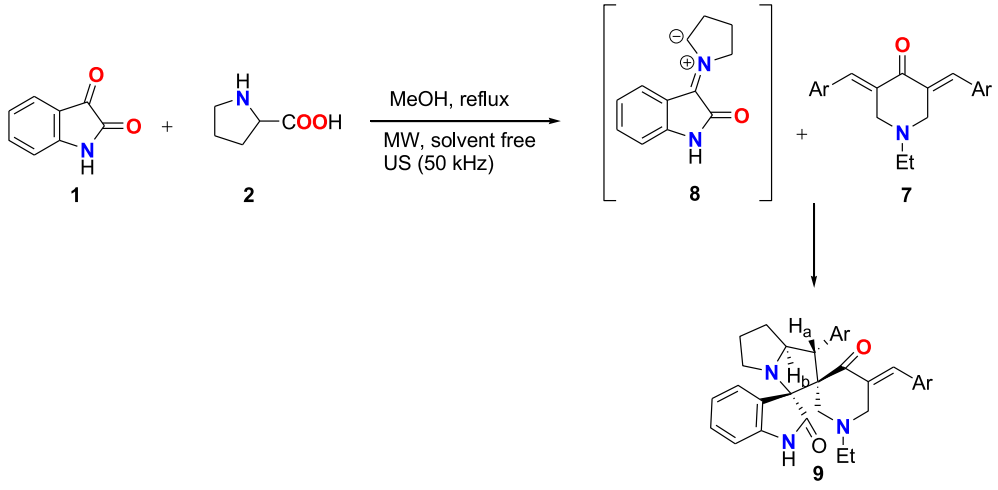
The innovative dispiro-pyrrolizidine-oxindole (**9**) and spiropyrrolidine (**11**) series were produced in this work under solvent-free conditions employing ultrasonic and MW irradiation.

Substituted pyrrolizidines (**9**) were synthesised in high yields using 1,3-dipolar cycloaddition of azomethineylides (**8**) to the adduct (**7**) using standard heating and ultrasonic irradiation (comparative results are shown in Scheme 2, Table 1).

One-pot, three component reaction of isatin (**1**), L-proline (**2**), and adduct of type (**7**) in methanol under reflux. As seen in Scheme 1, the reaction began as a condensation reaction between isatin **1** and L-proline **2**, which was then decarboxylated to generate an *in-situ* azomethine ylide intermediate (**8**). Then, a new form of spiropyrrolizidine-oxinidole (**9**) was synthesised in high quantities by cycloaddition of 3,5-bis[arylmethylidene]-4-oxipiperidine-N-ethyl (**7a-e**) with non-stabilized azomethine ylides (**8**). Highly diastereoselective and regioselective reaction as a single product was produced which confirmed by TLC and GC–mass analysis. Under mild-conditions and low-intensity ultrasound US (cleaning bath) and methanol as a solvent, cycloaddition reactions were carried. It's note that single product **9** was obtained in each reaction condition. So, it can be suggested that the pathway of this homogeneous reaction suggested from a concerted mechanism in a thermolytic method to a US method (Scheme 1). Increase in the rate of decarboxylation and the formation of ylide (**8**) might be the reason in increasing the reaction rate, and cause the frequency of collisions between ylide **(8)** and 3,5-*bis*[-arylmethylidene]-4-oxipiperidine-*N*-ethyl **(7)** to increase. Localized hot spots formed during the cavitational collapse due to the energy of these clashes and formation of ylide **(8)** which provided by short-lived. Next, we decided to change from conventional thermolytic condition for 120 min. to MW heating in a reaction vessel to reduce the reaction time. When heated to 150 °C with a dedicated MW oven, the reaction was completed in 10 min under solvent-free condition,



Scheme 1 Synthesis of dispiro-pyrrolizidine-oxindoles (**5**) and spiropyrrolidine(**6**).



Scheme 2 A proposed mechanism for the synthesis of compound **9a-e.**

Table 1 Synthesis of spiro pyrrolizidine-oxinidole **9a-e.**

Ar		Classical		Ultrasonic	
		Time (min)	Yield%	Time(min)	Yield%[a]
9a	C_6H_5	120	80	30	96
9b	4-MeC_6H_4	120	83	30	88
9c	4-ClC_6H_4	120	82	30	84
9d	2,4-$Cl_2C_6H_3$	120	85	30	90
9e	2-Thionyl	120	70	30	82

a: isolated yield based on isatin.

resulting in a 95% yield of synthesized compound **(9a)** Table 2. Moreover, we confirmed that however method of the conventional thermal-heating affords only moderate yields of the predictable products of the cyclic-condensation reaction, MW irradiation through solvent-free conditions reveals the same products with significantly reduced reaction time and improved yields Table 2. Use of MW equipment for the synthesis allowed conditions Safe and repeatable interaction.

Similar to this, preparation of spiropyrrolidine-oxindoles **(11a-e)** in high yields by a three-component reaction of 3,5-*bis*[arylmethylidene]-4-oxipiperidine-*N*-ethyl **(7a-e)** with two equivalents of both of isatin **1** and sarcosine **3** in methanol at reflux and in ultrasonic condition or microwave under solvent-free conditions to obtain the single product **(11)** Scheme 3, Table 3.

Table 2 % Yield of compound **9a** under MW, solvent-free condition.

Time (min)	Temp(°C)	Yield%[a]
10	200	85
8	200	85
5	200	86
10	150	95
5	150	87
10	80	90
10	65	87

a: isolated yield based on isatin.

The structure of dispiro heterocyclic ring products **11a-e** was proved based on the spectral data that extracted from their NMR, IR, Mass spectra as well as their elemental analysis. The IR spectra of all novel spiropyrrolizidines / pyrrolidineoxindole derivatives **9a-e** and **11a-e** revealed one NH and two C = O at ν = 3421–3251, 1720–1701 and 1716–1678 cm^{-1}, respectively. The ^{1}H NMR spectrum of compound **11c** (Fig. 1) showed the characteristic signals for all protons in the skeleton of this derivative as follows: δ 0.75 triplet signal for CH_3 of ester group, 1.95 singlet signal for N-CH_3 group, 2.94 doublet of doublet for Hb, 3.14 multiplet signal for the two CH_2 groups of pipridinone ring, 3.34 doublet of doublet for Hc, 3.76 quartet signal for CH_2 of ester group, 4.61 doublet of doublet for Ha, 6.56–7.41multiplet with integration of 12 protos for the aromatic protons, 7.54 singlet signal for = CH group and one NH at 10.38 ppm. The regiochemistry of the products spiropyrrolizidine / pyrrolidineoxindole derivatives **9a-e** and **11a-e** was confirmed through checking their ^{13}C NMR data as for example, ^{13}C NMR spectra of derivatives **9a** and **11a** have the characteristic carbon signals at δ 52.7, 54.2 ppm and 83.4, 88.5 ppm for the two spiro carbons in each derivative (Hassaneen et al, 2017). Also, the two downfield carbon signals at δ172.2, and 204.2 ppm in each derivative **9a** and **11a** were due to the C = O of oxindole and keto C = O carbons of piperidinone ring system, respectively. The mass spectra of all products spiropyrrolizidine / pyrrolidineoxindole derivatives **9a-e** and **11a-e** showed expected molecular ion peak for each derivative which confirms the formation of mono-adduct (Fig. 2).

The usage of methanol in the synthesis of new spiropyrrolizidine / pyrrolidineoxindole derivatives **9a-e** and **11a-e** by microwave irradiation or ultrasound demonstrated its effectiveness in terms of high yields for each derivative, a straightforward experimental approach, and ease of isolation.

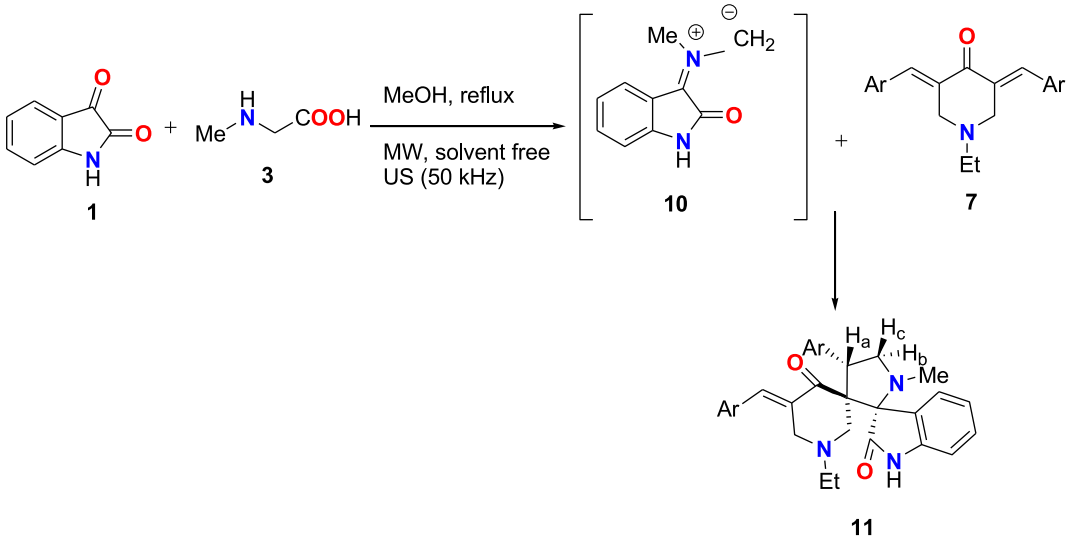
2.1. Antitumor activity

Selected derivatives of the synthesized spiro compounds **9b,c,e** and **11b-e** were screened for their antitumor activity against two cell lines MCF-7 and HEPG2 (Table 4). We observed from the obtained data of IC_{50} in Table 4 that the tested derivatives displayed moderate to excellent cytotoxic activities against the breast cancer **MCF-7** cell line with IC_{50} values ranging from 3.9 to 36.1 μg. 1′′-ethyl-1′-methyl-5′′-(4-methyl benzylidene)-4′-(*p*-tolyl)dispiro[indoline-3,2′-pyrrolidine-3′,3′′-piperidine]-2,4′′-dione **(11b)** is the most reactive derivative with IC_{50} = 3.9 μg in compared with the IC_{50} = 5.20 μg of the reference cisplatin drug. In addition to two derivatives **9b** and **9c** showed good activity with IC_{50} = 7.8 and 9.2 μg. The most potent derivatives as anti-breast cancer derivatives **11b** and **9b** carrying in their skeletons the methyl (EDG). Within the investigation the result for HEPG2 in Table 4, we noted that the most reactive spiro-derivative is **11b** with IC_{50} = 5.7 μg that is near to the IC_{50} = 3.67 μg of the reference cisplatin drug. The other two spiro-derivatives **9c** and **9b** have good activity with IC_{50} = 9.7 and 10.6 μg. The other tested spiropyrazoles showed moderate activity with IC_{50} ranging from 24.8 to 46.2 μg.

2.2. Docking study

2.2.1. Docking study with the receptors of (3hb5) for breast cancer and (4k9g) for liver cancer

To understand the obtained antitumor results depending on a structural bases, all synthesized spiro-derivatives **9a-e** and **11a-e** were evaluated through docking techniques (Table 5 and 6)



Scheme 3 A proposed mechanism for the synthesis of compounds **11a-e**.

Table 3 Synthesis of spiropyrrolizidinoxinidole**11a-e**.

	Ar	Classical		Ultrasonic		Microwave	
		Time (min)	Yield%	Time (min)	Yield%[a]	Time (min)	Yield%[a]
11a	C_6H_5	120	84	30	95	10	95
11b	4-MeC_6H_4	120	79	30	84	10	90
11c	4-ClC_6H_4	120	80	30	93	10	94
11d	2,4-$Cl_2C_6H_3$	120	87	30	88	10	93
11e	2-Thionyl	120	87	30	91	10	94

a: isolated yield based on isatin.

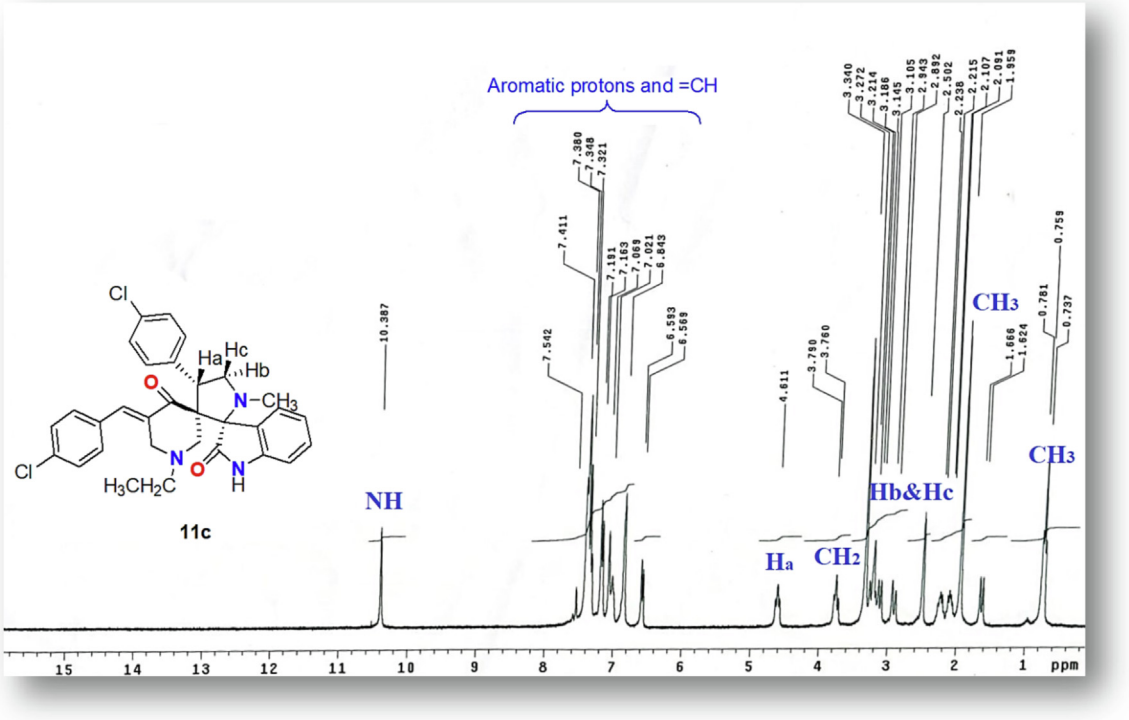


Fig. 1 The ^{1}H NMR (DMSO d_6, 300 MHz) of derivative **11c.**

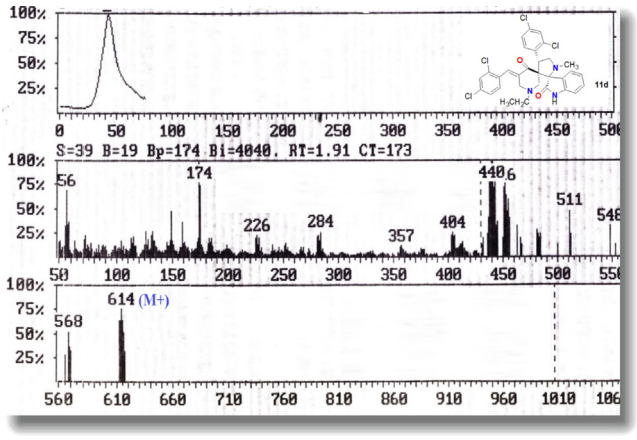


Fig. 2 The mass spectrum of compound **11d (Mwt** = 615.38).

Table 4 The results of IC_{50} (μg) of the antitumor activity of derivatives **9b,c,e** and **11b-e** against two cell lines MCF-7 and HEPG2.

Compd. No.	MCF-7	HEPG2
9b	7.8	10.6
9c	9.2	9.7
9e	21.0	28.7
11b	3.9	5.7
11c	35.9	37.2
11d	18.8	24.8
11e	36.1	46.2
Cisplatin	5.20	3.67

with the receptors of (3hb5) for breast cancer and (4k9g) for liver cancer. Docking simulation was performed in this study using Molecular Operating Environment MOE-Dock 2014

Table 5 Docking results of the new synthesized derivatives **9a-e** and **11a-e** with the receptors of (3hb5) for breast cancer.

Compd.	Ligand moiety	Receptor site	Interacting residues (Type of interaction)	Distance (°A)	E (kcal/mol)	Docking score (kcal/mol)
9a	6-ring	CG LEU 93 (X)	pi-H	4.07	−0.6	− 5.0609
9b	O 38	NH_2 ARG 37 (X)	H-acceptor	3.12	−1.3	− 5.7909
9c	CL 64	O LEU 64 (X)	H-donor	3.23	−0.5	−5.2109
	N 5	NH2 ARG 37 (X)	H-acceptor	2.99	−3.8	
	6-ring	NE ARG 37 (X)	pi-cation	4.02	−1.0	
	6-ring	NZ LYS 195 (X)	pi-cation	4.23	−0.8	
9d	—	—	—	—	—	—
9e	N 13	NH2 ARG 37 (X)	H-acceptor	3.15	−2.1	−2.1721
	O 41	N GLY 92 (X)	H-acceptor	3.17	−1.3	
	6-ring	NE ARG 37 (X)	pi-cation	3.92	−1.4	
11a	6-ring	6-ring PHE 192 (X)	pi-pi	3.98	−0.0	−5.7153
11b	O 39	N GLY 92 (X)	H-acceptor	2.83	−4.2	−6.5630
	6-ring	NE ARG 37 (X)	pi-cation	3.85	−1.5	
	6-ring	6-ring PHE 192 (X)	pi-pi	3.75	−0.0	
11c	CL 60	OD1 ASN 90 (X)	H-donor	3.42	−0.7	−5.3711
	O 39	NH2 ARG 37 (X)	H-acceptor	2.55	−2.4	
11d	CL 57	O ALA 106 (X)	H-donor	3.59	−1.1	−5.1334
	O 40	NZ LYS 195 (X)	H-acceptor	2.79	−6.1	
11e	N 15	NH2 ARG 37 (X)	H-acceptor	3.22	−1.1	−6.1817
	O 39	NH2 ARG 37 (X)	H-acceptor	2.76	−2.0	
	5-ring	CA GLY 13 (X)	pi-H	4.09	−0.6	

Table 6 Docking results of the new synthesized derivatives **9a-e and 11a-e** with the receptors of (4k9g) for liver cancer.

Compd.	Ligand moiety	Receptor site	Interacting residues (Type of interaction)	Distance (°A)	E (kcal/mol)	Docking score (kcal/mol)
9a	—	—	—	—	—	—
9b	—	—	—	—	—	—
9c	—	—	—	—	—	—
9d	—	—	—	—	—	−5.8396
9e	—	—	—	—	—	—
11a	6-ring	N PRO 1 (A)	pi-cation	3.63	−1.4	−4.8955
11b	O 39	NE1 TRP 108 (A)	H-acceptor	2.84	−2.1	−5.5473
11c	6-ring	CA TYR 36 (A)	pi-H	4.68	−0.6	−5.2285
	6-ring	6-ring TRP 108 (A)	pi-pi	3.88	−0.0	
11d	N 5	NE2 GLN 35 (A)	H-acceptor	3.44	−1.1	−5.4566
	O 39	NE2 GLN 35 (A)	H-acceptor	3.02	−1.4	
11e	5-ring	CA TYR 36 (A)	pi-H	4.02	−0.6	−4.9266

software (MOE, 2014). All the interaction energies and different calculations were calculated. From the docking results of the spiro-synthesized derivatives **9a-e** and **11a-e** with the receptors of (3hb5) for breast cancer, they indicated that all derivatives were interacted with the active cites of (3hb5) with binding energies −6.5630 to −2.1721 Kcal/mol (Figs. 3 and 4) except derivative **9d**. The most reactive derivative in the series of spiro-compounds **9a-e** was found to be **9b** with docking score − 5.7909 Kcal/mol with only H- acceptor from ARG 37 to the C = O of piperidone ring. In case of series **11a-e**, spiro-derivative **11b** is the most reactive compound with binding score = -6.5630 Kcal/mol which formed three types of interactions namely, H-acceptor, pi-cation and pi-pi with the amino acids GLY 92, ARG 37 and PHE 192, respectively. On the other hand, docking the spiro-compounds **9a-e** didn't show any interaction with the active sites of receptor 4k9g (Table 6 & Fig. 5). But, all derivatives **11a-e** involved in the interaction with 4k9g with energy score = -5.5473 to −4.8955 Kcal/mol through H-acceptor, pi-cation and pi-H. The essential parts of the spiro-compounds 11a-d that involved in the interaction to the active site of the protein receptor 4k9g are C = O of indole, nitrogen atom of piperidone, the aryl ring of arylidene moieties.

2.2.2. Docking study with glycogen phosphorylase B (PDB code: 1H5U)

Pyrrolidine and oxindole containing compounds are parts of antidiabetic α-glucosidase inhibitors (Trapero and Llebaria, 2012; Hamed, 2018; Zhu et al., 2021). This finding encourages us to test the interaction of all synthesized dispiro-

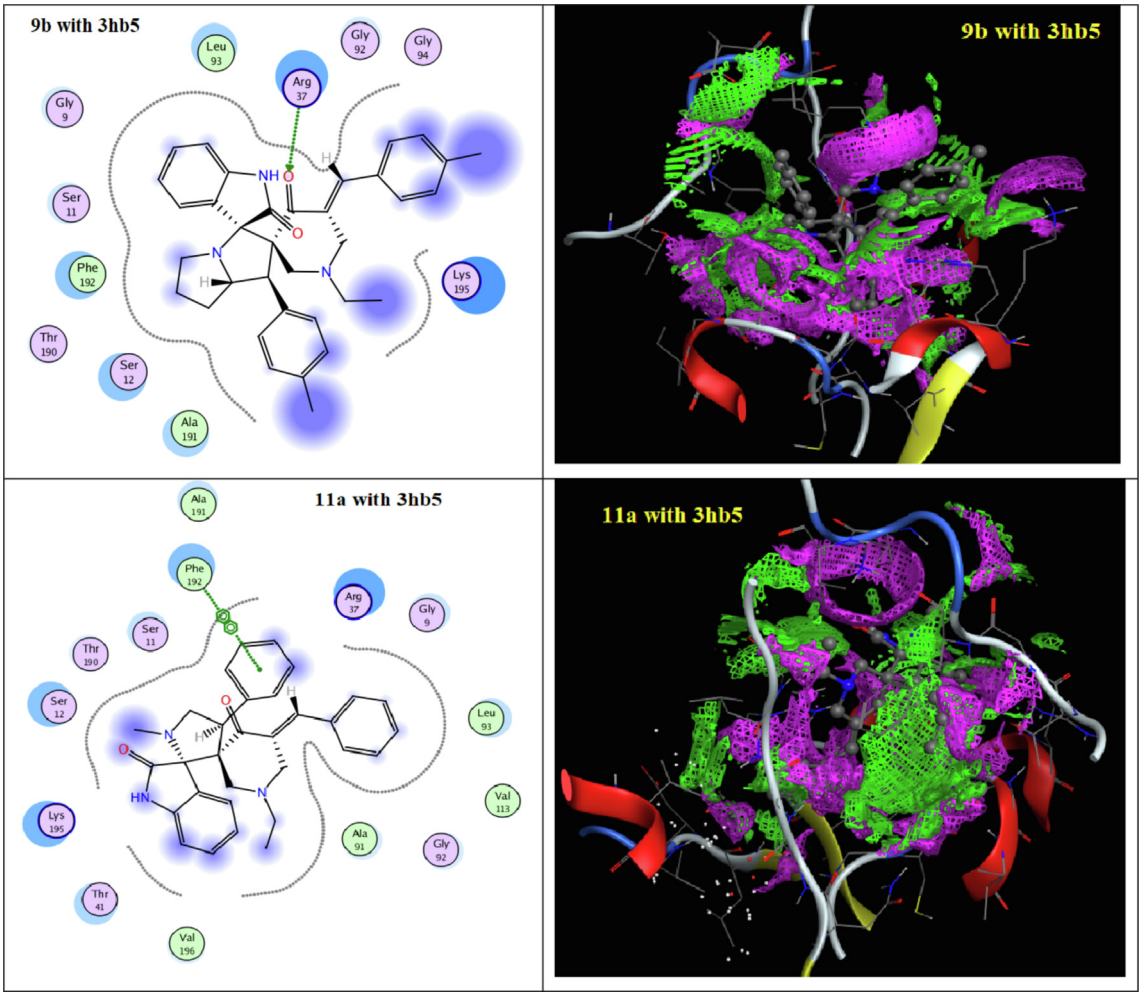


Fig. 3 2D and contact performance of docked compounds **9b** and **11a** into the active site of 3hb5.

pyrrolizidine-oxindoles (**9a-e**) and spiropyrrolidinebisoxindoles (**11a-e**) with glycogen phosphorylase B to inhibit the type 2 diabetes. The X- ray crystallography structure was reported for (PDB code: 1H5U). The behaviour of the synthesised products in binding site of the target protein was shown in Fig. 6 which predict the binding modes, affinities, and orientations of compounds (**9a-e, 11a-e**) at the active sites of the protein, docking scores were listed in Table 7. Dispiro-pyrrolizidine-oxindoles (**9**) showed more activity than spiropyrrolidinebisoxindoles (**11**). The carbonyl group of isatin has high activity as it bound with amino acids. In which **9a** bounded with Arg 569 (bond length: 2.7 Å), in **9b** Arg 589 (bond length: 2.4 Å), In **9d** Lys 576 (bond length: 2.4 Å) and Arg 589 (bond length: 1.6 Å), and in **11b**. Lys 680(bond length: 2.1 Å) and Thr 676 (bond length: 3.0 Å).The Nitrogen atom of *N*-ethylpiperidin-4-one also showed activity towards amino acids Lys 576 as in **9a** (bond length: 2.3 Å), in **9b** (bond length: 2.1 Å), in **9d** (bond length: 2.78 Å), and Asn 284 (bond length: 2.5 Å), and in **11b** (bond length: 2.4 Å). The carbonyl group of same rings piperidin-4-one showed high activity in binding with amino acids of (PDB code: 1H5U), in **9a** Thr 676 (bond length: 2.8 Å), Gly 677 (bond length: 2.8 Å), in **9b** Thr 676 (bond length: 2.7 Å), Gly 677 (bond length: 2.6 Å), and in **11b** Thr 676 (bond length: 2.4 Å). The data showed that **9a, 9b, 9d, 11b** have promising activity.

3. Conclusion

Novel of spiropyrrolizidine / pyrrolidineoxindole moieties were synthesized under classical, ultrasonic, and microwave conditions in high yields. US method applied in methanol at 30 min and lower reaction temperature with high yield. In MW the reaction was completed in 10 min under solvent-free condition, resulting in high yield of synthesized compounds. Seven derivatives of the synthesized dispiro-pyrrolizidine-oxindoles and spiropyrrolidine were screened for their antitumor activity against two cell lines MCF-7 (breast cancer) and HEPG2 (liver cancer). The results of biological activity indicated that the tested derivatives have potent activity against breast cancer cell MF-6. Molecular docking simulation screening studies of the synthesized products with each of the receptors of (3hb5) for breast cancer and (4k9g) for liver cancer and their interaction with 1H5U of glycogen phosphorylase B, type 2 diabetes drug were examined. The docking study of dispiro-pyrrolizidine-oxindoles and spiropyrrolidine showed promising results with several derivatives.

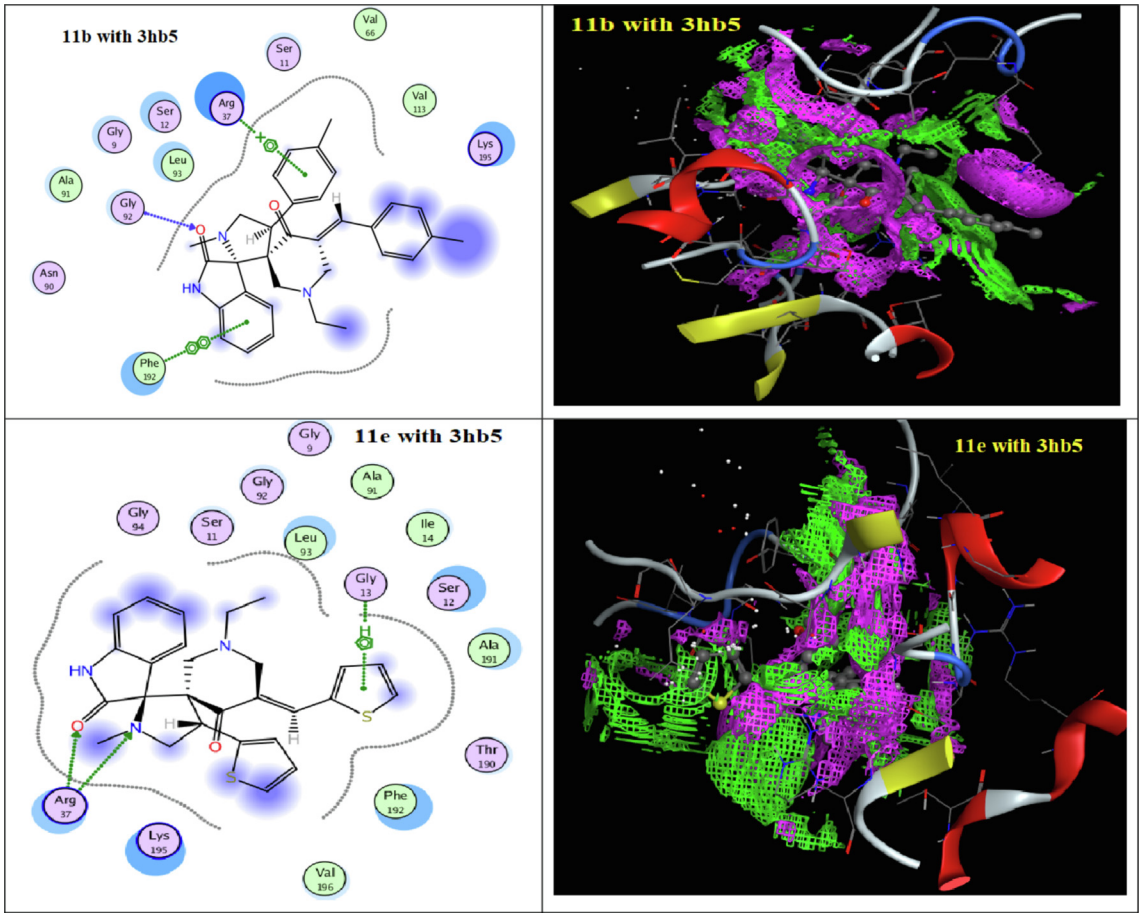


Fig. 4 2D and contact performance of docked compounds **11b** and **11e** into the active site of 3hb5.

4. Experimental section

4.1. Instrumentation

All instruments with their description were cited in supplementary file.

4.2. Classical heating

Under normal reflux, a mixture of 10 mmol of each of isatin, L-proline or sarcosine, and 5 mmol of 3,5-*bis*[-arylmethylidene]-4-oxipiperidine-*N*-ethyl in 30 mL of methanol was heated (Table 1-3). When the reaction was completed by checking the progress of the reaction using TLC, the solid of **9a-e** or **11a-e** was collected and purified by recrystallization in ethanol. The physical and spectral data for **9a-e** and **11a-e** are listed below and their yields are tabulated in Table 1-3.

4.3. Ultrasound irradiation

Irradiation at 25–30 °C of a mixture of 1 mmol of each isatin, amino acids as L-proline, or sarcosine and 0.5 mmol of 3,5-bis [arylmethylidene]-4-oxipiperidine-*N*-ethyl in 10 mL for 30 min using ultrasound irradiation in a water-bath of an ultrasonic cleaner (to avert from the rising of the vapor pressure of methanol and to realize effective cavitation's in this solvent, bath 50 kHz). The formed solid of **9a-e** or **11a-e** was filtered and recrystallized from ethanol. The physical and spectral data for **9a-e** and **11a-e** are listed below and their yields are tabulated in Table 1-3.

4.4. MW Irradiation

A 10 mL microwave vessel equipped with a standard cap (vessel commercially furnished by CEM Discover) was filled with isatin (2 equiv), the appropriate L-proline (2 equiv), or sarcosine (2 equiv) and 3,5-bis[arylmethylidene]-4-oxipiperidine-*N*-ethyl (1equiv) solvent-free at ambient temperature for 10 min, and the products **9a-e** and **11a-e** were separated in a pure form without further purification. The physical and spectral data for **9a-e** and **11a-e** are listed below and their yields are tabulated in Table 1-3.

4.4.1. 5′′-benzylidene-1′′-ethyl-1′-phenyl-5′,6′,7′,7a′-tetrahydro-1′H-dispiro[indoline-3,3′-pyrrolizidine-2′,3′′-piperidine]-2,4′′-dione (9a)

M.p. 234–236 °C (Yellow crystals) IR (KBr) cm^{-1}: 3400 (NH), 1720, 1712 (2CO);^{1}H NMR (DMSO d_6) δ 0.86 ($CH_2\underline{\mathbf{CH_3}}$, t, 3H, J = 7.2 Hz), 2.08 ($2CH_2$, m, 4H), 2.13–2.16 (CH_2, m, 2H), 2.14–2.20 (1Hb, m, 1H), 2.50 (1Ha, d, J = 10.2 Hz), 2.55–3.20 (m, 4H, $2CH_2$), 4.93 ($\underline{\mathbf{CH_2}}CH_3$, q, 2H,

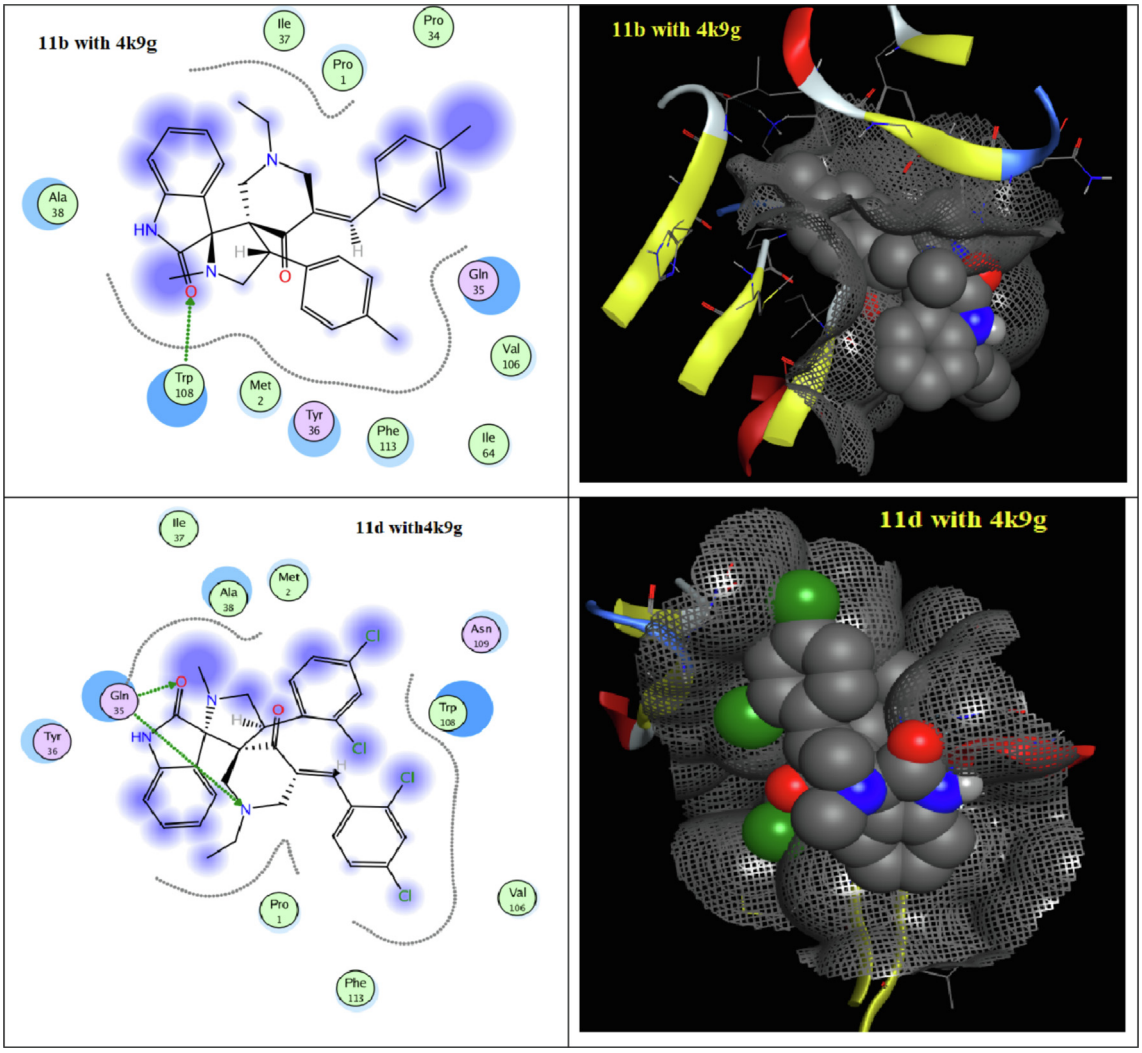


Fig. 5 2D and surface interaction of docked compounds **11b** and **11d** into the active site of 4k9g.

J = 7.2 Hz), 6.68 (Ar-H, d, J = 7.5 Hz, 2H), 6.94 (Ar-H, d, J = 7.5 Hz, 2H), 7.13–7.49 (Ar-H, m, 10*H*), 7.58 (=CH, s, 1H), 10.34 (NH, brs, 1H) ppm; ^{13}C NMR (DMSO d_6): δ 13.4 (CH_3), 22.5, 26.4, 31.8, 52.7, 56.9, 60.1, 62.1, 68.2, 83.4, 114.5, 122.2, 126.1, 126.2, 127.9, 128.0, 128.6, 134.0, 134.9, 136.1, 137.5, 139.5, 152.5, 172.2 (C = O), 204.2 (C = O) ppm; MS, m/z (%): 503.26 (100.0%). Anal. calcd.(Found) for $C_{33}H_{33}N_3O_2$ (503.63): C, 78.70(78.83); H, 6.60(6.58); N, 8.34(8.23).

4.4.2. 1′′-ethyl-5′′-(4-methylbenzylidene)-1′-(p-tolyl)-5′,6′,7′,7a′-tetrahydro-1′H-dispiro-[indoline-3,3′-pyrrolizidine-2′,3′′-piperidine]-2,4′′-dione (9b)

M.p. 249–251 °C (Yellow crystals) IR (KBr) cm^{-1}: 3421 (NH), 1715, 1710 (2CO);^{1}H NMR (DMSO d_6) δ 0.86 ($CH_2\underline{\mathbf{CH_3}}$, t, 3H, J = 7.2 Hz), 1.08 ($2CH_2$, m, 4H), 2.08 (2CH, m, 2H), 2.13 (1Hb, m, 1H), 2.31 (CH_3, s, 3H), 2.42 (CH_3, s, 3H), 2.55 (1Ha, d, J = 10.2 Hz), 2.57 (m, 4H, $2CH_2$), 4.93 ($\underline{\mathbf{CH_2}}$-$CH_3$, q, 2H, J = 7.2 Hz), 6.57 (Ar-H, d, J = 7.5 Hz, 2H), 6.78 (Ar-H, d, J = 7.5 Hz, 2H), 7.09 (Ar-H, d, J = 7 Hz, 2H), 7.16 (Ar-H, d, J = 7.5 Hz, 2H), 7.21–7.48 (Ar-H, m, 4H), 7.58 (=CH, s, 1H), 10.34 (NH, s, 1H) ppm; MS, m/z (%): 531.29 (100.0%). Anal. calcd.(Found) for $C_{35}H_{37}N_3O_2$ (531.69): C, 79.06(79.13); H, 7.01(6.94); N, 7.90(7.87).

4.4.3. 5′′-(4-chlorobenzylidene)-1′-(4-chlorophenyl)-1′′-ethyl-5′,6′,7′,7a′-tetrahydro-1′H-dispiro[indoline-3,3′-pyrrolizidine-2′,3′′-piperidine]-2,4′′-dione. (9c)

M.p. 230–233 °C (Yellow crystals) IR (KBr) cm^{-1}: 3251 (NH), 1720, 1710 (2CO); ^{1}H NMR (DMSO d_6) δ 0.74 ($CH_2\underline{\mathbf{CH_3}}$, t, 3H, J = 7.2 Hz), 1.91 ($2CH_2$, m, 4H), 2.00 (2 CH, m, 2H), 2.20 (1Hb, m, 1H), 3.29 ($2CH_2$, m, 4H), 3.34 ($\underline{\mathbf{CH_2}}CH_3$, q, 2H, J = 7.2 Hz), 4.42 (1Ha, d, J = 10.2 Hz), 6.83–7.33 (Ar-H, m, 12H), 7.36 (=CH, s, 1H), 10.43 (NH, s, 1H) ppm; MS, m/z: 571.18 (100.0%). Anal. calcd.(Found) for $C_{33}H_{31}Cl_2N_3O_2$ (572.52): C, 69.23(69.16); H, 5.46(5.43); N, 7.34(7.57).

4.4.4. 5′′-(2,4-dichlorobenzylidene)-1′-(2,4-dichlorophenyl)-1′′-ethyl-5′,6′,7′,7a′-tetrahydro-1′H-dispiro[indoline-3,3′-pyrrolizidine-2′,3′′-piperidine]-2,4′′-dione. (9d)

M.p. over 300 °C (Yellow crystals) IR (KBr) cm^{-1}: 3255 (NH), 1710, 1681 (2CO); ^{1}H NMR (DMSO d_6) δ 0.67 ($CH_2\underline{\mathbf{CH_3}}$, t, 3H, J = 7.2 Hz), 1.92 (2 CH_2, m, 4H), 2.00 (2 CH, m, 2H), 2.20 (1Hb, m, 1H), 3.34 ($2CH_2$, m, 4H), 3.77 ($\underline{\mathbf{CH_2}}CH_3$, q,

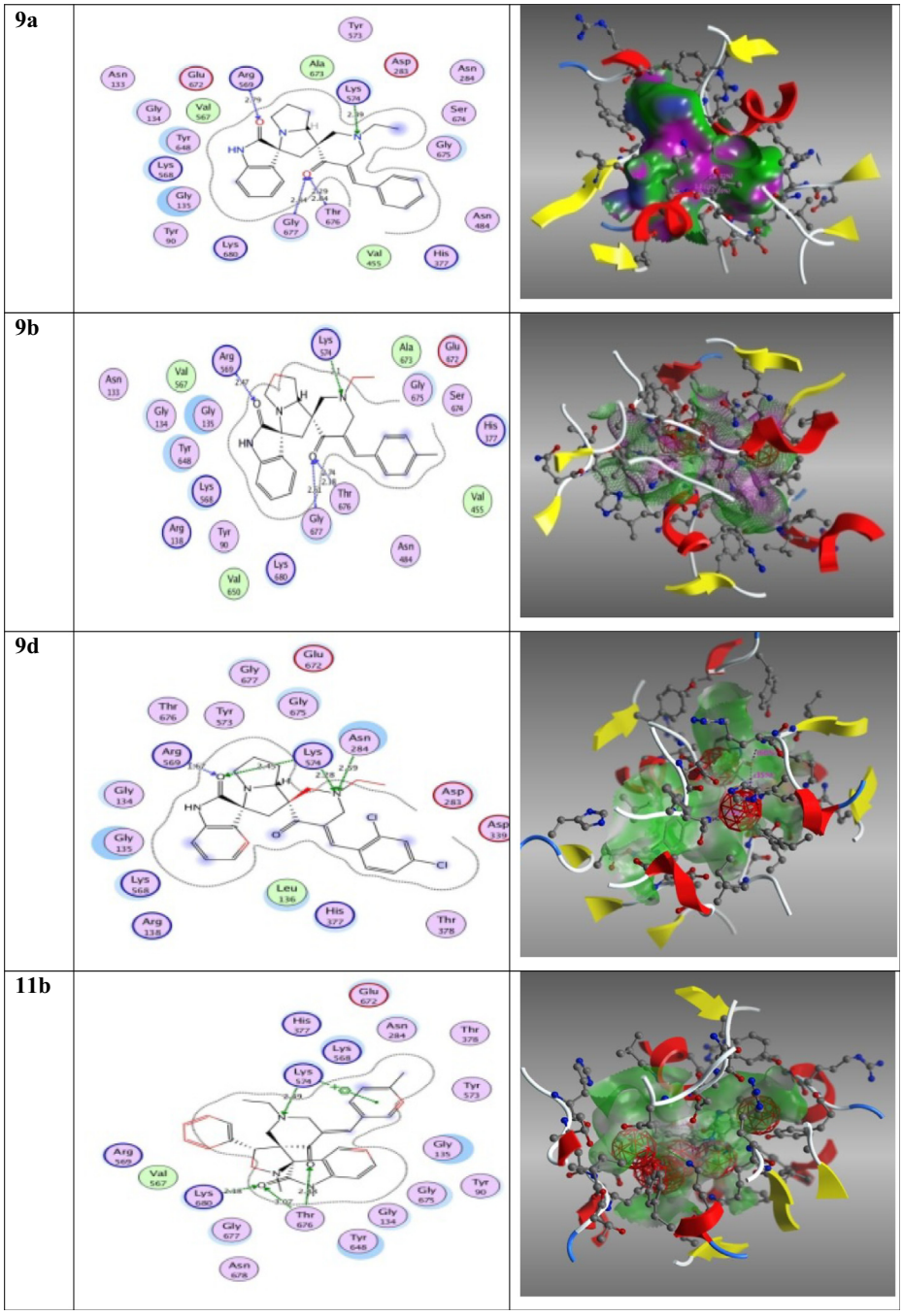


Fig. 6 2D, 3D of the promising compounds against glycogen phosphorylase B (PDB code: 1H5U).

2H, J = 7.2 Hz), 4.82 (1Ha, d, J = 10.2 Hz), 6.64 (Ar-H, d, J = 7.5 Hz, 1H), 6.83 (Ar-H, d, J = 7.5 Hz, 1H), 7.07–7.67 (ArH, m, 8H), 7.95 (=CH, s, 1H), 10.59 (NH, s, 1H) ppm;; MS, m/z (%): 639.10 (78.2%). Anal. calcd. (Found) for $C_{33}H_{29}Cl_4N_3O_2$ (641.41): C, 61.79(61.69); H, 4.56(4.41); N, 6.55 (6.49).

4.4.5. 1′′-Ethyl-5′′-(2-thienyl)-1′-(2-thienyl)-5′,6′,7′,7a′-tetrahydro-1′H-dispiro[indoline-3,3′-pyrrolizidine-2′,3′′-piperidine]-2,4′′-dione (9e)

M.p over 300 °C (Yellow crystals) IR (KBr) cm^{-1}: 3253 (NH), 1701, 1678 (2CO); ^{1}H NMR (DMSO d_6) δ 1.11 ($CH_2\underline{\mathbf{CH_3}}$, t, 3H, J = 7.2 Hz), 1.64 (2 CH_2, m, 4H), 2.18 (2 CH, m, 2H), 2.20 (1Hb, m, 1H), 2.40 ($2CH_2$, m, 4H), 3.78 ($\underline{\mathbf{CH_2}}CH_3$, q, 2H, J = 7.2 Hz), 4.50 (1Ha, d, J = 10.2 Hz), 6.81–7.93 (Ar-H and thiophene-H, m, 10H), 7.81 (=CH, s, 1H), 10.45 (NH, s, 1H,) ppm; MS, m/z: 517 (M^+ + 2, 27%), 515 (M^+, 49%). Anal. calcd. (Found) for $C_{29}H_{29}N_3O_2S_2$ (515.69): C, 67.54(67.32); H, 5.67(5.45); N, 8.15(8.03).

4.4.6. 5′′-Benzylidene-1′′-ethyl-1′-methyl-4′-phenyldispiro[indoline-3,2′-pyrrolidine-3′,3′′-piperidine]-2,4′′-dione. (11a)

M.p. 232–234 °C (Colourless crystals) IR (KBr) cm^{-1}: 3253 (NH), 1720, 1713 (2CO); ^{1}H NMR (DMSO d_6): δ 0.74 (CH_2-

Table 7 Molecular docking simulation of compounds **9a-e, 11a-e** with glycogen phosphorylase B (PDB code: 1H5U).

Compound	S (score)
9a	−10.61
9b	−12.37
9c	−12.41
9d	−12.40
11a	−8.79
11b	−6.14
11c	−9.96
11d	−12.00

CH$_3$, t, 3H, *J* = 7 Hz), 1.96 (CH_3, s, 3H), 2.82 (Hb, dd, 1H, *J* = 9.0, 7.0 Hz), 3.15 ($2CH_2$, m, 4H), 3.30 (1Hc, dd, 1H, *J* = 10.7, 7.0 Hz), 3.78 (**CH$_2$**CH_3, q, 2H, *J* = 7.2 Hz), 4.60 (1Ha, dd, 1H, *J* = 10.7, 9.0 Hz), 6.55–7.17 (Ar-H, m, 14H), 7.20 (=CH, s, 1H), 10.27 (NH, s, 1H) ppm; ^{13}C NMR (DMSO d_6) δ 13.7, 29.8, 40.1, 53.3, 54.2, 56.9, 57.2, 64.2, 88.5, 114.5, 122.2, 125.7, 126.3, 126.4, 127.4, 127.8, 128.2, 128.6, 134.2, 135.4, 137.0, 139.5, 140.2, 152.9, 172.2, 204.2 ppm; MS, *m*/*z* (%):477.24 (100.0%). Anal. calcd. (Found) for $C_{31}H_{31}N_3O_2$ (477.60): C, 77.96(77.87); H, 6.54 (6.42); N, 8.80(8.74).

4.4.7. 1′′-Ethyl-1′-methyl-5′′-(4-methylbenzylidene)-4′-(p-tolyl) dispiro[indoline-3,2′-pyrrolidine-3′,3′′-piperidine]-2,4′′-dione. (11b)

M.p. 242–245 °C (Yellow crystals) IR (KBr) cm^{-1}: 3251 (NH), 1720, 1712 (2CO); ^{1}H NMR (DMSO d_6): δ 0.76 (CH_2**CH$_3$**, t, 3H, *J* = 7 Hz), 1.95 (CH_3, s, 3H), 2.70 (CH_3, s, 3H), 2.92 (Hb, dd, 1H, *J* = 9.0, 7.0 Hz), 3.14 ($2CH_2$, m, 4H), 3.17 (CH_3, s, 3H), 3.28 (**CH$_2$**CH_3, q, 2H, *J* = 7.2 Hz), 3.89 (1Hc, dd, 1H, *J* = 10.7, 7.0 Hz), 4.62 (1Ha, dd, 1H, *J* = 10.7, 9.0 Hz), 6.57–7.16 (Ar-H, m, 12H), 7.19 (=CH, s, 1H), 10.27 (NH, s, 1H) ppm; MS, *m*/*z* (%):505 (7.3%), 506 (1.5%). Anal. calcd. (Found) for $C_{33}H_{35}N_3O_2$ (505.65): C, 78.38(78.29); H, 6.98(6.82); N, 8.31(8.20).

4.4.8. 5′′-(4-chlorobenzylidene)-4′-(4-chlorophenyl)-1′′-ethyl-1′-methyldispiro[indoline-3,2′-pyrrolidine-3′,3′′-piperidine]-2,4′′-dione. (11c)

M.p. 253–255 °C (Yellow crystals) IR (KBr) cm^{-1}: 3251 (NH), 1718, 1710 (2CO); ^{1}H NMR (DMSO d_6) δ 0.75 (CH_2**CH$_3$**, t, 3H, *J* = 7.2 Hz), 1.95 (CH_3, s, 3H), 2.94 (Hb, dd, 1H, *J* = 9.0, 7.0 Hz), 3.14 ($2CH_2$, m, 4H), 3.34 (1Hc, dd, 1H, *J* = 10.7, 7.0 Hz), 3. (**CH$_2$**CH_3, q, 2H, *J* = 7.2 Hz), 4.61 (1Ha, dd, 1H, *J* = 10.7, 9.0 Hz), 6.57 (Ar-H, d, *J* = 8 Hz, 2H), 6.84 (Ar-H, d, *J* = 8 Hz, 2H), 7.02–7.41 (Ar-H, m, 8H), 7.54 (=CH, s, 1H), 10.38 (NH, s, 1H) ppm; MS, *m*/*z* (%): 546.17 (33.5%). Anal. Calcd. (Found) for $C_{31}H_{29}Cl_2N_3O_2$ (546.49): C, 68.13 (68.01); H, 5.35 (5.29); N, 7.69 (7.86).

4.4.9. 5′′-(2,4-dichlorobenzylidene)-4′-(2,4-dichlorophenyl)-1′′-ethyl-1′-methyldispiro-[indoline-3,2′-pyrrolidine-3′,3′′-piperidine]-2,4′′-dione. (11d)

M.p. over 300 °C (Yellow crystals) IR (KBr) cm^{-1}: 3340 (NH), 1716, 1710 (2CO); ^{1}H NMR (DMSO d_6): δ 0.69 (CH_2**CH$_3$**, t, 3H, *J* = 7.2 Hz), 1.93 (CH_3, s, 3H), 2.51 (Hb, dd, 1H, *J* = 9.0, 7.0 Hz), 2.88 ($2CH_2$, m, 4H), 2.94 (1Hc, dd, 1H, *J* = 10.7, 7.0 Hz), 3.77 (**CH$_2$**CH_3, q, 2H, *J* = 7.2 Hz), 4.96 (1Ha, dd, 1H, *J* = 10.7, 9.0 Hz), 6.65 (Ar-H, d, *J* = 7 Hz, 1H), 6.82 (Ar-H, d, *J* = 7 Hz, 1H), 7.07–7.87 (Ar-H, m, 8H), 7.99 (=CH, s, 1H), 10.55 (NH, s, 1H) ppm; MS, *m*/*z* (%):615.09 (4.3%). Anal. calcd. (Found) for $C_{31}H_{27}Cl_4N_3O_2$ (615.38): C, 60.50 (60.78); H, 4.42 (4.31); N, 6.83 (6.70).

4.4.10. 1′′-Ethyl-1′-methyl-5′′-(2-thienyl)-4′-(2-thienyl)-dispiro [indoline-3,2′-pyrrolidine-3′,3′′-piperidine]-2,4′′-dione (11e)

M.p. over 300 °C (Yellow crystals) IR (KBr) cm^{-1}: 3400 (NH), 1720, 1716 (2CO); ^{1}H NMR (DMSO d_6): δ 0.86 (CH_2**CH$_3$**, t, 3H, *J* = 7.2 Hz), 1.94 (CH_3, s, 3H), 2.72 (Hb, dd, 1H, *J* = 9.0, 7.0 Hz), 2.72 ($2CH_2$, m, 4H), 3.26 (**CH$_2$**CH_3, q, 2H, *J* = 7.2 Hz), 3.68 (1Hc, dd, 1H, *J* = 10.7, 7.0 Hz), 4.82 (1Ha, dd, 1H, *J* = 10.7, 9.0 Hz), 6.61 (Ar-H, d, *J* = 7.5 Hz, 1H), 6.71–7.38 (Ar-H and thiophene-H, m, 7H), 7.46 (thiophene-H, d, *J* = 4.8 Hz, 1H), 7.62 (=CH, s, 1H), 7.83 (thiophene-H, d, *J* = 4.8 Hz, 1H), 10.40 (NH, s, 1H) ppm; MS, *m*/*z* (%):649 (64%). Anal. calcd. (Found) for $C_{27}H_{27}N_3O_2S_2$ (489.65): C, 66.23 (66.07); H, 5.56 (5.38); N, 8.58 (8.61).

4.5. Antitumor assay

The method for antitumor assay were reported in the literature report (Mosmann, 1983).

4.6. Molecular docking studies

Molecular docking study was carried out for spiropyrrolizidines / pyrrolidineoxindoles **9a-e** and **11a-e** using MOE-Dock 2014 software (Inc, 2016). Chemical structures of spiropyrrolizidines / pyrrolidineoxindoles **9a-e** and **11a-e** were drawn by the MOE-builder and the program force field MMFF94x minimized them. After download the protiens 3hb5, 4k9g and 1H5U for breast cancer, liver cancer and type2 diabetes, respectively, all hydrogen atoms were aded followed by removal the water molecules. After that, docking of spiropyrrolizidines / pyrrolidineoxindoles **9a-e** and **11a-e** were done.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.arabjc.2022.103930.

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