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# Synthesis of new Spiropyrazole derivatives under microwaves irradiation and docking study for inhibition the microbes and COVID-19

Ghada S. Masaret

Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah, Saudi Arabia

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## ABSTRACT

Synthesis of a new series of spiropyrazole derivatives using microwaves irradiation with high yield in minutes was achieved through a cycloaddition reaction of nitrile imines and arylidenes of 5-bromo-indan-1-one. The structure of the new spiropyrazoles was assured based on their available spectral analyses and the comparison of the extracted data with the literature reports. Molecular docking simulations of all new synthesized spiropyrazole derivatives into leucyl-tRNA synthetase editing domain of *Candida albicans* (Pdb: 2WFC) indicated that about seven spiropyrazole derivatives can fit deeply in the active site via the formation of stable complexes. In addition, the docking study was utilized to tested the ability of these spiropyrazoles to inhibit COVID-19 through the interaction with COVID-19 main protease (Pdb: 6LU7). The results were surprising which revealed high docking score ranging from -7.764 to -5.9464 kcal/mol. Moreover, the nitrogen atom of pyrazole, Br atom and the C=O group of indanone are essential parts in the binding mode of almost the active derivatives. The results of the docking study are a glimmer of hope to complete the study on these compounds and examine them in the laboratory to ensure their effectiveness as antimicrobials and antiviral, especially Covid-19. Moreover, pharmacokinetics and physicochemical properties were studied.

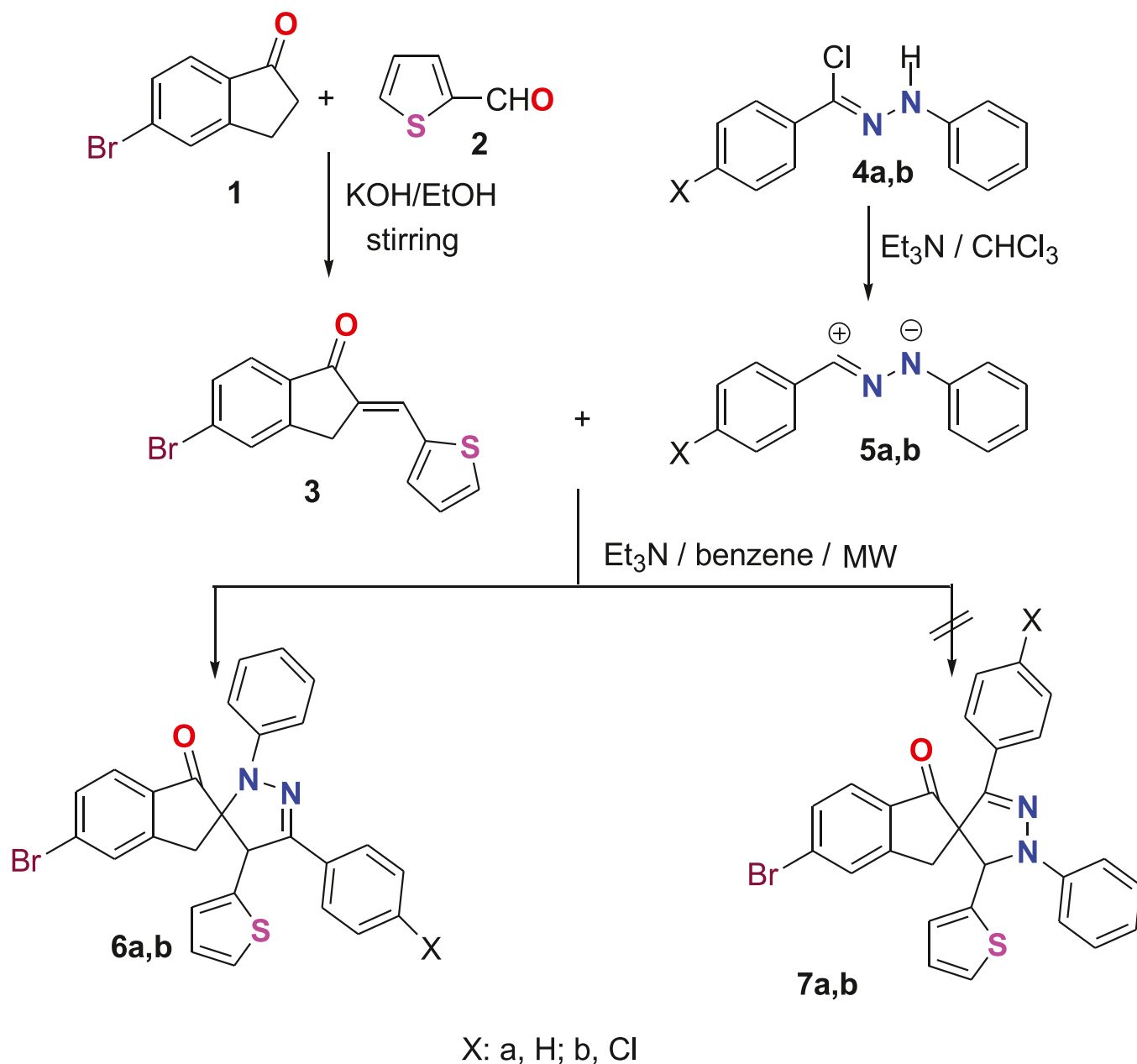
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## 1. Introduction

The continuation of the Corona pandemic (COVID-19) for nearly two years is a big problem, as it takes lives and affects the economic life of the whole world. The outbreak of pneumonia caused by COVID-19 is considered a pandemic according to the World Health Organization in March 2020 [1] that has resulted in millions of infections and deaths worldwide. In this scenario, the development of antiviral agents that interfere with the life cycle of the virus or in virus replication or membrane fusion is urgently needed [2]. Every day, scientists are racing to find effective heterocyclic drugs to stop this epidemic. Recently, many researches have done a theoretical search through docking of compounds with different proteins of viruses related to COVID-19 [3–5]. On the other side, overuse as well as the misuse of antibiotics has led to the expansion of multidrug resistance between various types of microorganism's strains [6]. Accordingly, new antimicrobial agents must be developed that act on new targets to overcome the increasing incidence of microbial resistance to antibiotic therapy. Scientists are also working day and night to search for new compounds with

antimicrobial activity. One of the bioactive drugs is compounds containing pyrazole moiety which are known with their antimicrobial and antiviral activities [7–12]. The class of spiropyrazoles are well known in literature with the phosphodiesterase inhibitors [13], antitumor [14,15], analgesic [16] and anti-inflammatory activities [17]. The synthesis of heterocyclic compounds with biological activity for more than one disease is a difficult goal, in addition to synthesis of these derivatives with high yield in a short reaction time is a good goal. Therefore, using microwave as an energy source increases the yield of the synthesized compounds in a short time [18,19]. Heating using microwave rays helps in the formation of organic compounds in a pure and high rate and in a time of up to a few minutes, because those irradiations can raise the temperature of the reactions to temperatures up to two to four times the boiling points of the reacting compounds in addition to maintaining the atmosphere around chemical reactions of moisture that may affect moisture-sensitive reagents and reduce the formation of unwanted by-product [20]. All the above facts with our expertise in bioactive heterocyclic synthesis [21–24], we focused our effort in this context to synthesize a new series of spiropyrazoles under microwave irradiations and investigated their theoretical activity as antimicrobes and anti-COVID-19 through the docking study with peroxiredoxin 5 (Pdb: 2WFC) and COVID-19 main protease (Pdb:

E-mail address: [gsmasaret@uqu.edu.sa](mailto:gsmasaret@uqu.edu.sa)



**Scheme 1.** Synthesis of spiropyrazoles 6a,b under microwaves irradiation.

6LU7); the overexpressed proteins in *Candida albicans* and severe acute respiratory syndrome coronavirus 2, respectively.

## 2. Results and discussion

5-Bromo-2-(thiophen-2-ylmethylene)indan-1-one **3** was prepared as usual way from the condensation reaction of 5-bromoindan-1-one **1** with 2-thiophene aldehyde **2** in ethanol and in the presence of base catalyst KOH with stirring for 5 h [25]. Previously [26], it was reported that the synthesis of a series of spiropyrazoles took about 50 h under reflux. We tried herein to synthesis a related spiropyrazoles but, carrying bromide atom at the position five of indanone in short reaction time. After several trials using MW irradiations, we able to prepare derivatives **6a,b** from the reaction of hydrazonoyl chlorides **4a,b** with arylidene **3** in benzene at 80 °C for about 40-50 min. Such reaction revealed only one regioisomer **6** rather than **7** (Scheme 1) depending on the compari-

son of their spectral data with the related published derivatives in literature. For instance,

<sup>1</sup>H NMR spectrum of **6b** (Fig. 1) showed all characteristic signals for the existed protons as follows: 2.98 (d, H<sub>a</sub>), 3.44 (d, H<sub>b</sub>), 5.23 (s, pyrazole-H) and fifteen aromatic protons at 6.71-7.78 ppm. The presence of H-4 of pyrazole at  $\delta = 5.23$  ppm [26] ruled out the other regioisomer **7**.

By similar way, the same reaction was repeated under the same reaction condition using arylidene derivatives **9a-h** with nitrile imines **5a,b** afforded the spiropyrazole derivatives **10a-h** in short reaction time (40-50 min) as illustrated in Scheme 2. The signal of pyrazole-H-4 appeared in <sup>1</sup>H NMR of all derivatives **10a-h** at  $\delta = 4.70$ -5.35 ppm, these values discarded the other regioisomer **11a-h**. All IR data of spiropyrazoles **10a-h** have the characteristic absorption bands of C=O at  $\nu = 1673$ -1755 cm<sup>-1</sup>. Another strong evidence for the formation of the spiropyrazole **10** rather than **11**, the <sup>13</sup>C NMR spectrum of compound **10d** (Fig. 2) showed

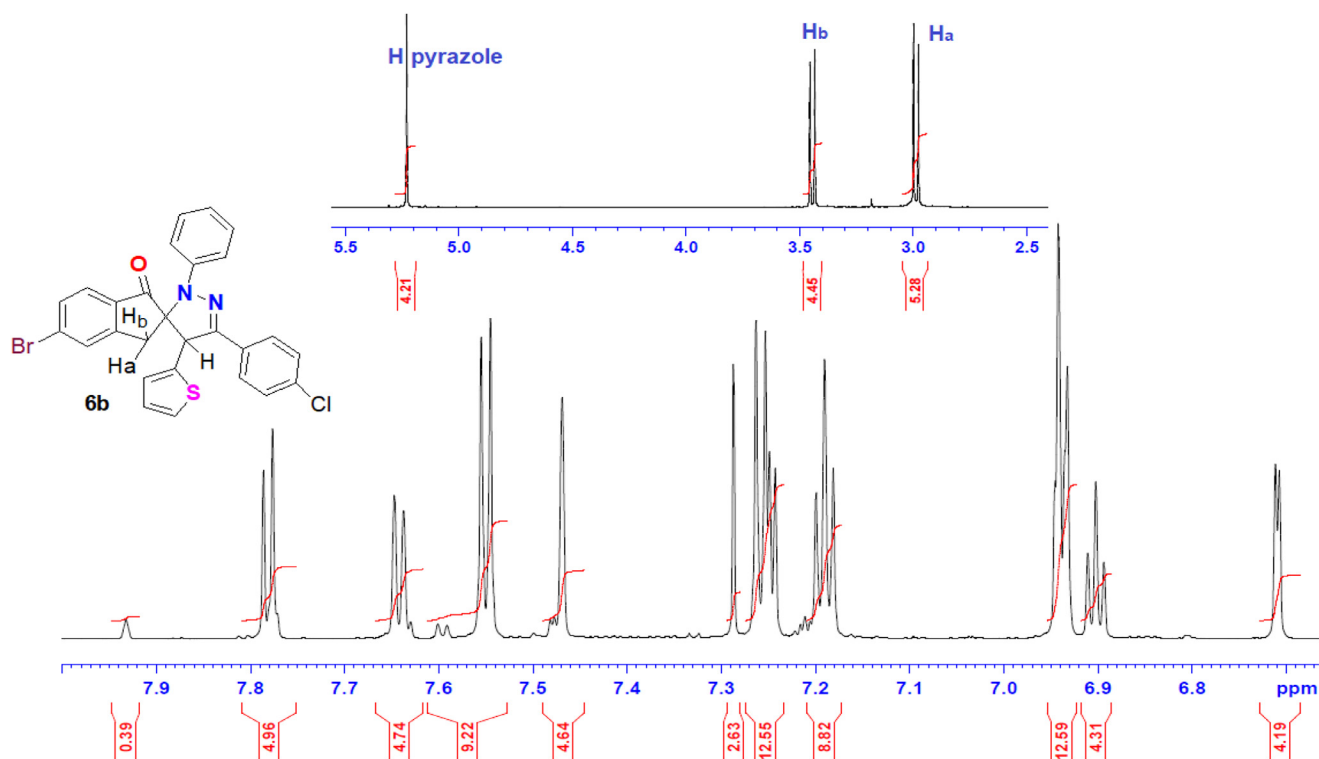


Fig. 1.  $^1\text{H}$  NMR spectrum of spiropyrazole **6b**.

two characteristic carbon signals at 61.2 (C4 pyrazole) and 78.5 (C-spiro) ppm [27,28].

Another two new derivatives of spiropyrazoles **14a,b** were prepared under the same MW irradiations in benzene in the presence of  $\text{Et}_3\text{N}$  from the reaction of nitrileimine **13** and the arylidene of 5-bromo-indan-1-one **9d,e** (Scheme 3). All the results of the spectral analyses for these two spiropyrazoles **14a,b** agreed with the same results for the previous compounds **6** and **10**.

### 3. Docking study

#### 3.1. Docking study for microbial activity

To investigate the ability of the new synthesized spiropyrazole derivatives **6a,b**, **10a-h** and **14a,b**, the molecular docking study have been performed for these derivatives onto the active site

of *Candida albicans* editing domain of cytosolic leucyl-tRNA synthetase to prove their binding affinity and orientation. We used cytosolic leucyl-tRNA synthetase editing domain co-crystallized with benzoxaborole-AMP adduct (PDB code: 2WFG) for docking using MOE 2014 program. The results of docking study were tabulated in Table 1 and the 2D pictures as well as the contact performance for selected derivatives illustrated in Fig. 3. These results revealed docking score ranging from -3.2041 to -6.4628 kcal/mol with different types of interactions as pi-H, H-donor and H-acceptor. The most widely amino-acids involved in the interaction are LYS407, LYS483, LEU317 and THR413. Focusing on the most active spiropyrazole derivatives **10c**, **14b**, **10g** and **10h** with the highest docking scores -6.4628, -6.2704, -5.6246 and -4.8742 kcal/mol, respectively, it was observed that all of them are stabilized by strong-H-bonds and pi-H interactions. Also, we noted that the presence of oxygen atoms as C=O or in nitro group and the bromide atom are essential in interaction. The presence of these strong interactions especially

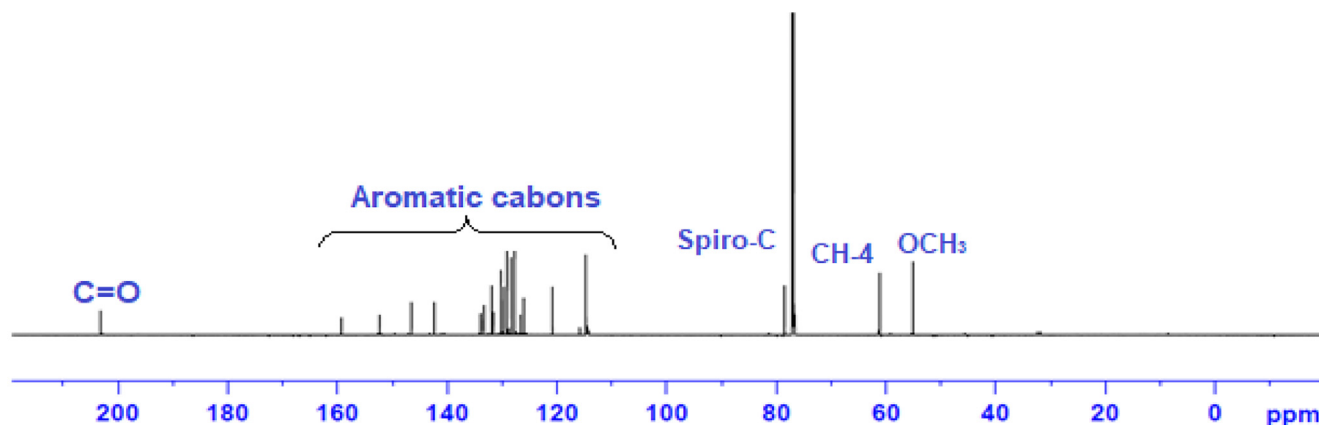
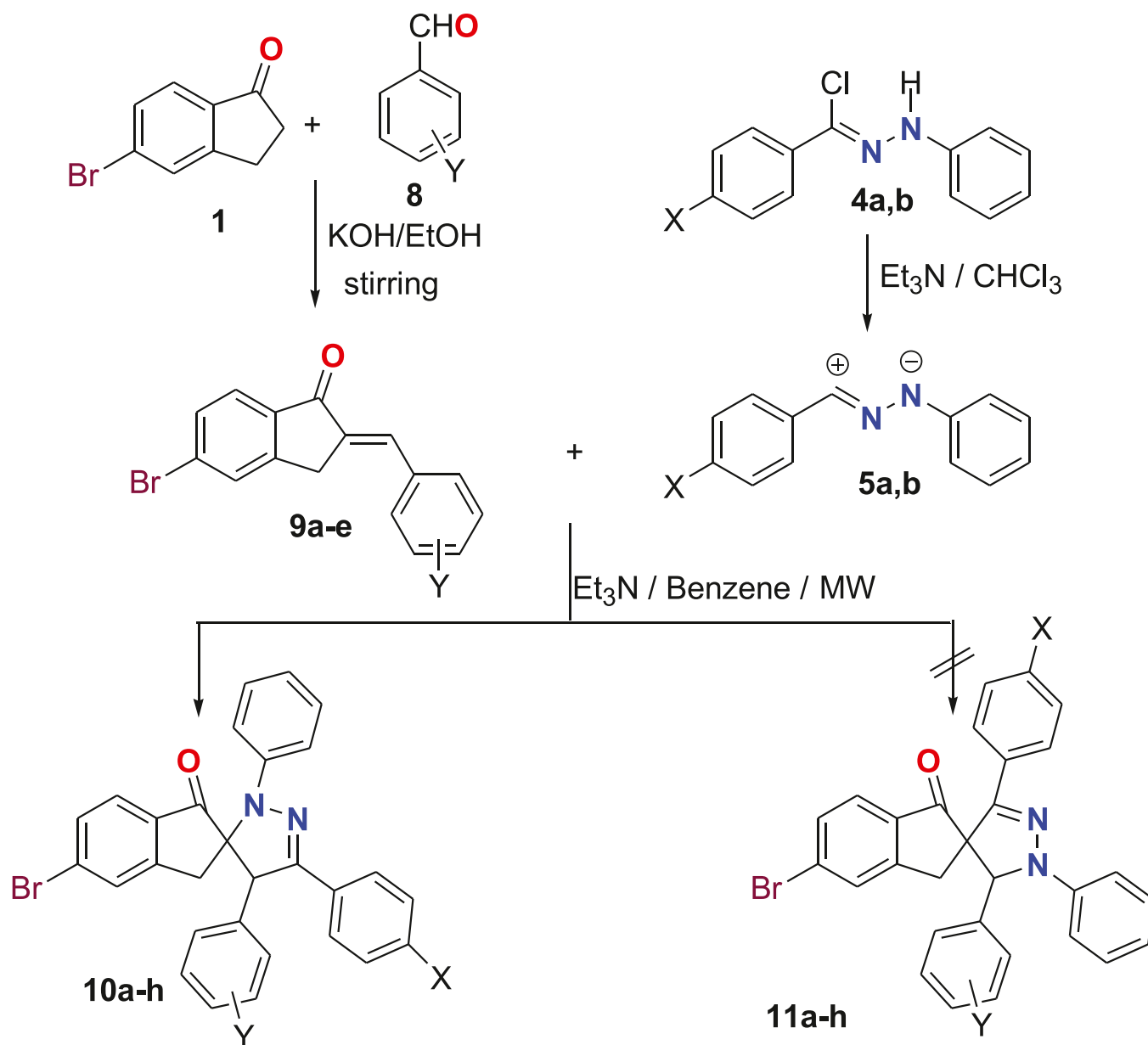


Fig. 2. The  $^{13}\text{C}$  NMR spectrum of spiropyrazole **10d**.



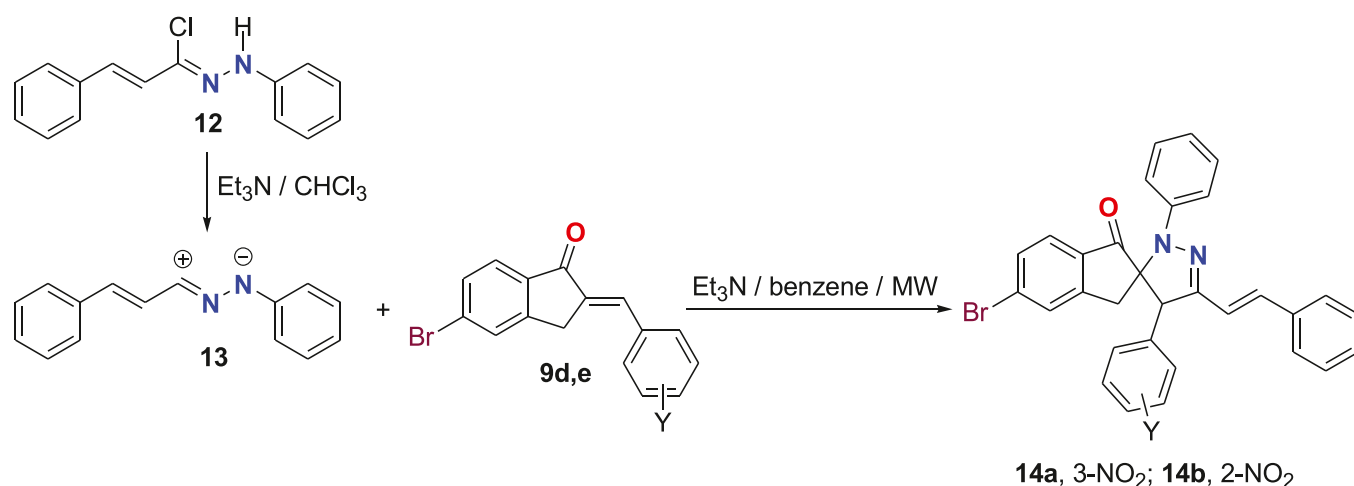
**Scheme 2.** Synthesis of spiropyrazoles **10a-h** under microwaves irradiation.

in derivatives **10c**, **14b**, **10g** and **10h** into the active site of *Candida albicans* editing domain of cytosolic leucyl-tRNA synthetase proves the effectiveness of these spiropyrazoles as antimicrobial agents. Their activity can be investigated experimentally in the future.

### 3.2. Docking study for COVID-19 proliferation

To investigate the ability of the spiropyrazoles **6a,b**, **10a-h** and **14a,b** to interact with COVID-19 main protease (Pdb: 6LU7), the molecular docking simulation was performed using the same MOE 2014 program and the results were tabulated in [Table 2](#). At first

glance to the results in [Table 2](#), we noted that all spiropyrazole derivatives showed high docking score ranging from -7.764 to -5.9464 kcal/mol. The common atoms involved in the interaction in the active site of 6lu7 are Br, oxygen atoms as well as the aromatic ring of indanone. The common amino acid residue involved in the interaction is GLY143 form pi-H with the aromatic ring of indanone. Compound **14a** with the highest docking score (-7.764) is strongly fitted in the active site of 6lu7 with H-bond between Br in indanone and the oxygen atom of THR26 and pi-H between the aromatic ring of indanone and the nitrogen atom of GLY143 ([Fig. 4](#)). The promising data for docking simulation using the ma-



**Scheme 3.** Synthesis of spiropyrazoles **14a,b** under microwaves irradiation.

**Table 1**  
Docking results of the new synthesized derivatives 6a-b and 10a-h with the receptors of (2WFC) for microbes.

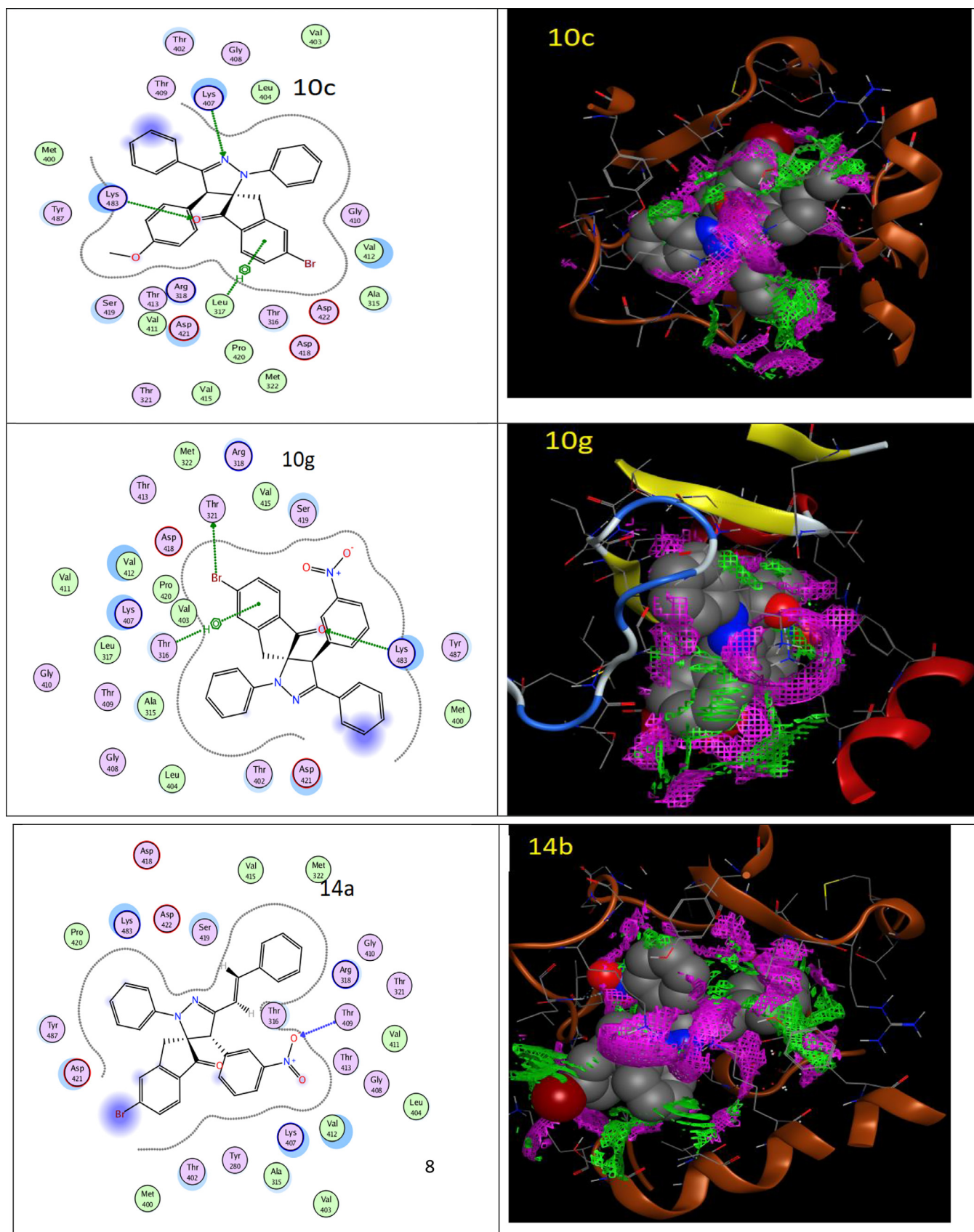
Compd.	Ligand moiety	Receptor site	Interacting residues(Type of interaction)	Distance (°A)	E (kcal/mol)	Docking score (kcal/mol)
6a	6-ring	CD LYS 407 (A)	pi-H	3.81	-0.9	- 4.5946
6b	-	-	-	-	-	- 5.7907
10a	-	-	-	-	-	-4.9668
10b	O 15	NZ LYS 407 (A)	H-donor	3.06	-8.6	-3.8321
	6-ring	CD LYS 407 (A)	pi-H	2.80	-0.9	
10c	O 15	NZ LYS 483 (A)	H-acceptor	2.70	-5.3	-6.4628
	N 21	NZ LYS 407 (A)	H-acceptor	3.72	-1.3	
10d	6-ring	N LEU 317 (A)	pi-H	4.17	-1.8	-3.8721
	6-ring	N LEU 317 (A)	pi-H	4.64	-0.6	
10e	6-ring	CD LYS 407 (A)	pi-H	4.01	-0.8	-3.2041
	-	-	-	-	-	
10f	CL 54	O THR 413 (A)	H-donor	3.39	-1.4	-4.1968
	O 15	NZ LYS 483 (A)	H-acceptor	2.63	-5.0	
10g	N 21	NZ LYS 407 (A)	H-acceptor	3.70	-1.4	-5.6246
	6-ring	N LEU 317 (A)	pi-H	4.13	-2.2	
10h	BR 16	OG1 THR 321 (A)	H-donor	3.41 2.82	-0.9	-4.8742
	O 55	NZ LYS 483 (A)	H-acceptor	3.87	-6.8	
	6-ring	CA THR 316 (A)	pi-H	-	-0.7	
14a	BR 16	OG1 THR 321 (A)	H-donor	3.40	-0.8	-4.1252
	O 15	NZ LYS 483 (A)	H-acceptor	2.77	-7.4	
	6-ring	CA THR 316 (A)	pi-H	3.91	-0.6	
14b	O 60	N THR 409 (A)	H-acceptor	2.80	-1.7	-6.2704
	O 59	CA VAL 403 (A)	H-acceptor	3.25	-0.8	
	O 60	N LEU 404 (A)	H-acceptor	3.08	-1.0	
	6-ring	CB SER 419 (A)	pi-H	3.86	-0.8	

for protease of COVID-19 (Pdb: 6LU7) encourage us to recommend this spiropyrazoles for *in vitro* investigation of these derivatives as COVID-19 inhibitors.

### 3.3. Pharmacokinetics, and ADME activity

ADMET investigation on the selected synthesized spiropyrazole derivatives 6a, 10c, 10g, 19h, 14a and 14b was done using SwissADME website (<http://www.swissadme.ch/index.php>). SwissADME is a web tool that computes the key pharmacokinetic, physicochemical parameters and drug-likeness for molecules [29]. The data of Physicochemical properties were collected in Tables 3a & 3b which including molecular weight (MW), molecular refractivity (MR), polar surface area (PSA), partition coefficient (log Po/w) hydrogen bond acceptors and donors counts, and the number of rotatable bonds in a molecule count of specific atom types. Drug similarity can be assumed as a correct balance between molecular

parameters that influence the pharmacokinetics and pharmacodynamics of molecules that finally influence their absorption, distribution, metabolism and excretion (ADME) in the human body as a drug. From Tables 3a & 3b, the molecular weight of only derivative 6a < 500 [30] which increases the transmissibility of this spiropyrazole derivative to membranes and speed the transport and absorption. All spiropyrazole derivatives 6a, 10c, 10g, 19h, 14a and 14b showed topological polar surface area (TPSA) between 41.90 and 78.49 Å<sup>2</sup> which are in the correct range < 140 Å<sup>2</sup> [31]. The Lipophilicity (Log P) value of spiropyrazole derivatives 6a, 10c, 10g, 19h, 14a and 14b are ranged between 4.14 – 3.18 Which agrees with Lipinski's rule of five. All derivatives contain only the number of HBA (hydrogen bond acceptors) in agreement value with Lipinski's rule for drug-likeness (for HBA < 10). The above results indicated that the physicochemical properties of the tested indole derivatives within the acceptable range. In addition, tested spiropyrazole derivatives 6a, 10c, 10g, 19h, 14a and 14b showed high GI



**Fig. 3.** The 2D docked model and contact performance of derivatives 10c, 10h and 14b into the active site of 2WFG.

**Table 2**  
Docking results of the new synthesized derivatives 6a-b, 10a-h and 14a-b with the receptors of (6lu7) for COVID-19.

Compd.	Ligand moiety	Receptor site	Interacting residues(Type of interaction)	Distance (°A)	E (kcal/mol)	Docking score (kcal/mol)
6a	O 15	SG CYS 145 (A)	H-donor	3.19	- 1.0	- 6.5155
6b	O 15	SG CYS 145 (A)	H-donor	3.25	-0.8	- 6.6631
	C 25	OE1 GLN 189 (A)	H-donor	2.86	-0.8	
10a	N 28	N GLU 166 (A)	H-acceptor	3.19	-0.9	
	BR 16	O THR 26 (A)	H-donor	3.36	-1.6	-6.5876
	C 18	OE1 GLN 189 (A)	H-donor	3.16	-1.1	
	N 21	N GLU 166 (A)	H-acceptor	3.27	-2.0	
10b	-	-	-	-	-	-6.3476
10c	6-ring	N GLY 143 (A)	pi-H	4.61	-0.6	-6.7045
10d	6-ring	N GLY 143 (A)	pi-H	4.56	-0.7	-6.9558
10e	BR 16	O THR 26 (A)	H-donor	3.80	-0.5	-6.7893
	6-ring	N GLY 143 (A)	pi-H	4.27	-0.7	
10f	BR 16	O THR 26 (A)	H-donor	3.84	-0.4	-5.9464
	6-ring	N GLY 143 (A)	pi-H	4.53	-1.1	
10g	6-ring	N GLY 143 (A)	pi-H	4.18	-0.7	-7.0122
10h	O 15 6-ring	SG CYS 145 (A)	H-donor	3.84	-0.7	-7.2934
		N GLY 143 (A)	pi-H	4.14	-0.7	
14a	BR 16	O THR 26 (A)	H-donor	3.64 4.12	-0.6	-7.764
	6-ring	N GLY 143 (A)	pi-H		-1.2	
14b	BR 16	O THR 26 (A)	H-donor	3.60	-1.4	-7.6202
	O 60	NE2 HIS 163 (A)	H-acceptor	3.28	-1.3	

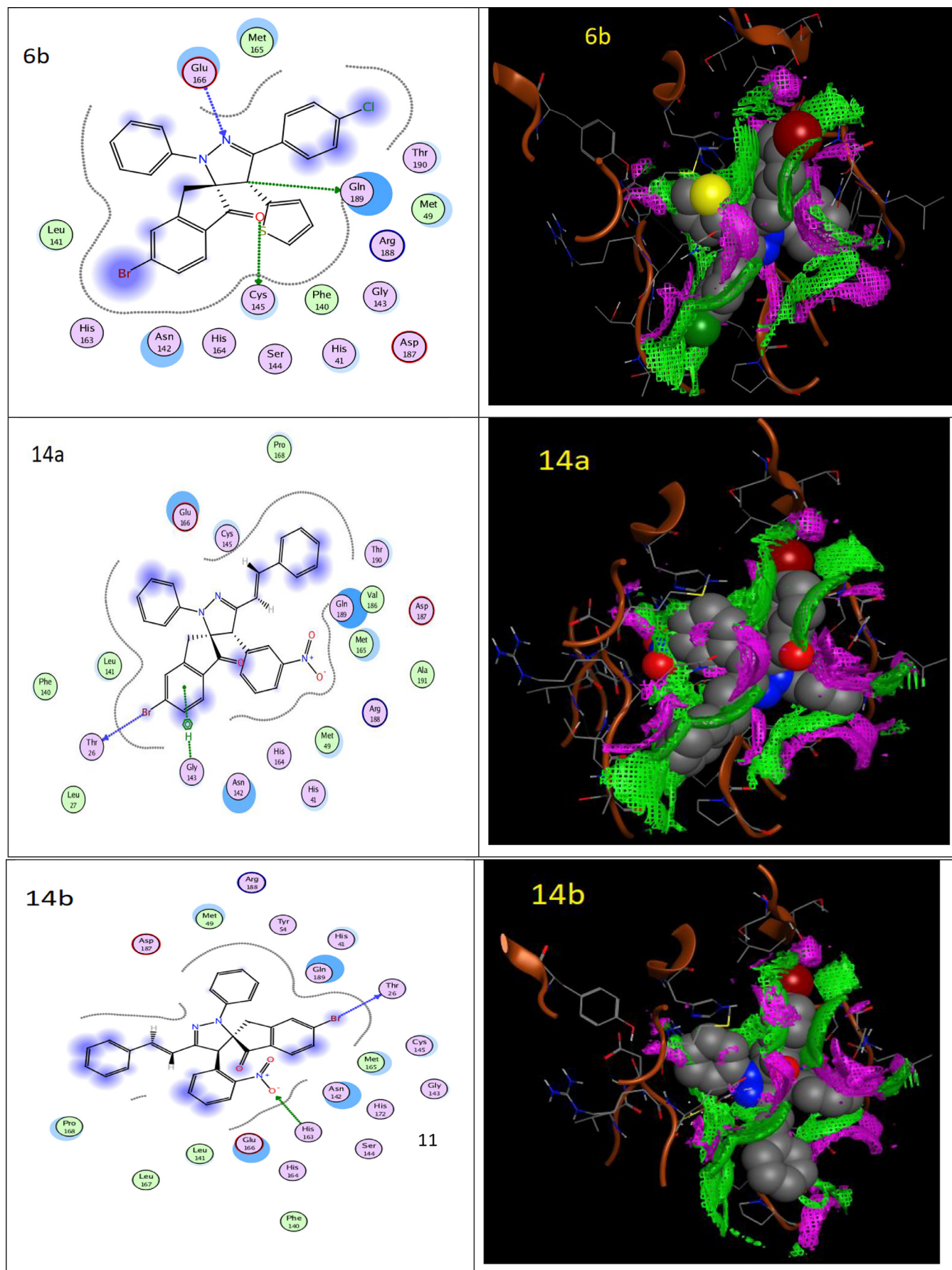
**Table 3a**  
Physicochemical and Pharmacokinetics properties for tested spiropyrazole derivatives 6a, 10c, 10g, 19h, 14a and 14b.

Properties	Compounds		
	6a	10c	10g
Formula	C <sub>27</sub> H <sub>19</sub> BrN <sub>2</sub> O <sub>5</sub>	C <sub>30</sub> H <sub>23</sub> BrN <sub>2</sub> O <sub>2</sub>	C <sub>29</sub> H <sub>20</sub> BrN <sub>3</sub> O <sub>3</sub>
Molecular weight	499.42 g/mol	523.42 g/mol	538.39 g/mol
Num. of heavy atoms	32	35	36
Num. of aromatic heavy atoms	23	24	24
Num. of rotatable bonds	3	4	4
Num. H-bond acceptor (HBA)	2	3	4
Num. H-bond donors (HBD)	0	0	0
Molar reactivity	140.44	149.06	151.39
Topological Polar Surface area (TPSA)	60.91 Å <sup>2</sup>	41.90 Å <sup>2</sup>	78.49 Å <sup>2</sup>
Lipophilicity (Log P)	3.90	4.14	3.18
Water solubility (Log S)	-7.67 (InSoluble)	-7.90 (InSoluble)	-7.88 (inSoluble)
Pharmacokinetics (GI absorption)	High	High	High
Pharmacokinetics (BBB permeant)	No	Yes	No
Pharmacokinetics (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibitors)	No, No, Yes, No, No (respectively)	No, No, Yes, No, No (respectively)	No, Yes, Yes, No, No (respectively)
Druglikeness (Lipinski)	Yes; 1 violation: MLOGP>4.15	No; 2 violations: MW>500, MLOGP>4.15	No; 2 violations: MW>500, MLOGP>4.15

**Table 3b**  
Physicochemical and Pharmacokinetics properties for tested spiropyrazole derivatives 6a, 10c, 10g, 19h, 14a and 14b.

Properties	Compounds		
	10h	14a	14b
Formula	C <sub>29</sub> H <sub>20</sub> BrN <sub>3</sub> O <sub>3</sub>	C <sub>31</sub> H <sub>22</sub> BrN <sub>3</sub> O <sub>3</sub>	C <sub>31</sub> H <sub>22</sub> BrN <sub>3</sub> O <sub>3</sub>
Molecular weight	538.39 g/mol	564.43 g/mol	564.43 g/mol
Num. of heavy atoms	36	38	38
Num. of aromatic heavy atoms	24	24	24
Num. of rotatable bonds	4	5	5
Num. H-bond acceptor (HBA)	4	4	4
Num. H-bond donors (HBD)	0	0	0
Molar reactivity	151.39	161.32	161.32
Topological Polar Surface area (TPSA)	78.49 Å <sup>2</sup>	78.49 Å <sup>2</sup>	78.49 Å <sup>2</sup>
Lipophilicity (Log P)	3.86	3.54	3.59
Water solubility (Log S)	-7.88 (inSoluble)	-8.22 (inSoluble)	-8.22 (inSoluble)
Pharmacokinetics (GI absorption)	High	High	High
Pharmacokinetics (BBB permeant)	No	No	No
Pharmacokinetics (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibitors)	No, Yes, Yes, No, No (respectively)	No, No, Yes, No, No (respectively)	No, No, Yes, No, No (respectively)
Druglikeness (Lipinski)	No; 2 violations: MW>500, MLOGP>4.15	No; 2 violations: MW>500, MLOGP>4.15	No; 2 violations: MW>500, MLOGP>4.15





**Fig. 4.** The 2D docked model and contact performance of derivatives 6b, 14a and 14b into the active site of 6LU7.

absorption with no BBB permeant except 10c. all derivatives able to inhibit CYP2C9 in addition derivatives 10c, 10g and 10h able to inhibit CYP2C19.

#### 4. Conclusion

In this context, we synthesized a new series of spiro-pyrazole derivatives from cycloaddition reaction of nitrile imines and arylidene of 5-bromo-indan-1-one under microwaves irradiation. The new spiro-pyrazoles were formed in excellent yield in short reaction time. The structure of the new spiro-pyrazoles was assured based on their available spectral analyses and the comparison of the extracted data with the literature reports. Molecular docking simulations of all new synthesized spiro-pyrazole derivatives into leucyl-tRNA synthetase editing domain of *Candida albicans* (Pdb: 2WFC) indicated that about seven spiro-pyrazole derivatives can fit deeply in the active site via the formation of stable complexes. In addition, the docking study was utilized to test the ability of these spiro-pyrazoles to inhibit COVID-19 through the interaction with COVID-19 main protease (Pdb: 6LU7). The results were surprising which revealed high docking score ranging from -7.764 to -5.9464 kcal/mol. The results of the docking study are a glimmer of hope to complete the study on these compounds and examine them in the laboratory to ensure their effectiveness as antimicrobials and antiviral, especially Covid-19. Moreover, pharmacokinetics and physicochemical properties were studied.

#### 5. Experimental

##### 5.1. Material and method

Reaction's progress was monitored by thin-layer chromatography (TLC) on silica gel-(G60 F254 (Merck)) of 0.5 mm thickness, visualizing with ultraviolet light (254 and 365 nm) or with iodine vapour. Melting points were determined using a Buchi B-540 capillary apparatus. NMR spectra were recorded on a Bruker Advance 850 MHz spectrometer (850 MHz for  $^1\text{H}$  NMR and 212.5 MHz for  $^{13}\text{C}$  NMR) respectively in  $\text{CDCl}_3$  solvent and tetramethyl silane as reference. Elemental analysis was carried out on Euro EA 3000 elemental analyser. Mass spectra were recorded on a Shimadzu GC-MS-QP-2010 mass spectrometer in EI (70 eV) model using the direct inlet probe technique. IR spectra of all spiro-pyrazole compounds were recorded on the IR Affinity 1S spectrometer (Shimadzu). Microwave synthesiser CEM mars machine was used for microwave irradiation.

##### 5.1.1. Synthesis of spiro-pyrazole derivatives 6a,b, 10a-h and 14a,b

Equimolar quantity (0.002 mol) of arylidene derivatives of 5-bromo-indan-1-one 3 or 9 and hydrazonoyl halides 4a,b or 12 placed in Microwave-vial (HP-500) in 20 mL benzene for each reaction. All derivatives in each vial were irradiated at the same time by microwaves irradiation (400 W power) under pressure at 80 °C for 40–50 min. We tracked the reaction using TLC test. After making sure that the reactions were completed, the products were collected after the solvent was evaporated. The solid-colored products were crystallized after drying from dioxane/ethanol mixture.

##### 5.1.2. Spiro-pyrazole derivative 6a

87% Yield; mp = 212–214 °C; yellow solid; IR (KBr):  $\nu$  3058 ( $\text{sp}^2$  CH), 1720 (C=O), 1596 (C=N), 1498, 1376, 1208, 1088  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.98 (d,  $J$  = 17.85 Hz, 1H, Ha), 3.43 (d,  $J$  = 17.85 Hz, 1H, Hb), 5.23 (s, 1H, pyrazole-H), 6.71 (d,  $J$  = 4.25 Hz, 1H, thiophene-H), 6.89 (t,  $J$  = 6.8 Hz, 1H, ArH), 6.93–7.29 (m, 9H, ArH and thiophene-H), 7.46 (s, 1H, Ar-H), 7.55 (d,  $J$  = 8.5 Hz, 2H, Ar-H), 7.63 (d,  $J$  = 7.7 Hz, 1H Ar-H), 7.77 (d,  $J$  = 8.5 Hz, 1H, Ar-H). MS m/z (%): 499 ( $\text{M}^+$ , 16), 472 (74), 437 (46), 393 (39), 320

(19), 171 (25), 142 (54), 139 (100), 130 (50), 79 (43). Anal. Calcd for  $\text{C}_{27}\text{H}_{19}\text{BrN}_2\text{OS}$  (499.42): C, 64.93; H, 3.83; N, 5.61%. Found C, 64.76; H, 3.79; N, 5.53%.

##### 5.1.3. Spiro-pyrazole derivative 6b

90% Yield; mp = 207–210 °C; yellow solid; IR (KBr):  $\nu$  3058 ( $\text{sp}^2$  CH), 2965 ( $\text{sp}^3$  CH), 1720 (C=O), 1596 (C=N), 1491, 1377, 1317, 1267, 1246, 1208, 1154, 1119, 1088, 1011  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.98 (d,  $J$  = 18.7 Hz, 1H, Ha), 3.44 (d,  $J$  = 18.7 Hz, 1H, Hb), 5.23 (s, 1H, pyrazole-H), 6.71 (d,  $J$  = 3.4 Hz, 1H, thiophene-H), 6.89 (t,  $J$  = 7.65 Hz, 1H, ArH), 6.94 (d,  $J$  = 7.65 Hz, 3H, Ar-H), 7.17–7.26 (m, 5H, ArH and thiophene-H), 7.45 (s, 1H, Ar-H), 7.55 (d,  $J$  = 7.65 Hz, 2H, Ar-H), 7.68 (d,  $J$  = 8.5 Hz, 1H Ar-H), 7.78 (d,  $J$  = 7.65 Hz, 1H, Ar-H). MS m/z (%): 534 ( $\text{M}^+$ +1, 19), 533 ( $\text{M}^+$ , 24), 516 (46), 475(24), 463 (22), 451 (34), 439 (25), 433 (46), 385 (44), 334 (100), 328 (36), 296 (46), 281 (62), 246 (24), 213 (29), 208 (57), 187 (72), 167 (28), 147 (42), 132 (49), 106 (42), 79 (37), 77 (25). Anal. Calcd for  $\text{C}_{27}\text{H}_{18}\text{BrClN}_2\text{OS}$  (533.87): C, 60.74; H, 3.40; N, 5.25%. Found C, 60.65; H, 3.31; N, 5.09%.

##### 5.1.4. Spiro-pyrazole derivative 10a

91% Yield; mp = 155–160 °C; yellow solid; IR (KBr):  $\nu$  3060 ( $\text{sp}^2$  CH), 2934 ( $\text{sp}^3$  CH), 1755 (C=O), 1485, 14713, 1345, 1260, 1098, 1064  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.77 (d,  $J$  = 17.5 Hz, 1H, Ha), 3.56 (d,  $J$  = 17.5 Hz, 1H, Hb), 4.70 (s, 1H, pyrazole-H), 6.35–7.84 (m, 17H Ar-H). MS m/z (%): 572 ( $\text{M}^+$ , 56), 566 (56), 559 (50), 549 (100), 544 (62), 529 (53), 509 (76), 460 (45), 294 (55), 194 (64), 172 (55), 122 (69), 115 (55), 96 (70), 83 (51). Anal. Calcd for  $\text{C}_{29}\text{H}_{20}\text{Br}_2\text{N}_2\text{O}$  (572.29): C, 60.86; H, 3.52; N, 4.89%. Found C, 60.75; H, 3.48; N, 4.76%.

##### 5.1.5. Spiro-pyrazole derivative 10b

90% Yield; mp = 125–126 °C; yellow solid; IR (KBr):  $\nu$  3058 ( $\text{sp}^2$  CH), 1755 (C=O), 1489, 1471, 1316, 1262, 1091, 1024, 1014  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.92 (d,  $J$  = 17.5 Hz, 1H, Ha), 3.42 (d,  $J$  = 17.5 Hz, 1H, Hb), 5.12 (s, 1H, pyrazole-H), 6.75–7.81 (m, 16H Ar-H). MS m/z (%): 606 ( $\text{M}^+$ , 40), 598 (24), 556 (66), 476 (30), 439 (46), 308 (43), 289 (34), 223 (53), 217 (54), 208 (49), 199 (40), 177 (43), 175 (100), 156 (65), 145 (34). Anal. Calcd for  $\text{C}_{29}\text{H}_{19}\text{Br}_2\text{ClN}_2\text{O}$  (606.73): C, 57.41; H, 3.16; N, 4.62%. Found C, 57.27; H, 3.04; N, 4.58%.

##### 5.1.6. Spiro-pyrazole derivative 10c

89% Yield; mp = 142–144 °C; yellow solid; IR (KBr):  $\nu$  3058 ( $\text{sp}^2$  CH), 2996, 1947 ( $\text{sp}^3$  CH), 1724 (C=O), 1593 (C=N), 1494, 1380, 1269, 1246, 1028  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.80 (d,  $J$  = 18.0 Hz, 1H, Ha), 3.38 (d,  $J$  = 18.0 Hz, 1H, Hb), 3.77 (s, 3H,  $\text{OCH}_3$ ), 4.91 (s, 1H, pyrazole-H), 6.74 (d,  $J$  = 8.5 Hz, 1H, Ar-H), 6.82 – 6.85 (m, 2H, ArH), 6.91 (d,  $J$  = 7.65 Hz, 1H, Ar-H), 7.06–7.75 (m, 13H Ar-H). MS m/z (%): 523 ( $\text{M}^+$ , 27), 445 (54), 417 (36), 369 (25), 263 (20), 207 (32), 193 (15) 152 (35), 106 (67), 77 (100). Anal. Calcd for  $\text{C}_{30}\text{H}_{23}\text{BrN}_2\text{O}_2$  (523.42): C, 68.84; H, 4.43; N, 5.35%. Found C, 68.67; H, 4.32; N, 5.19%.

##### 5.1.7. Spiro-pyrazole derivative 10d

92% Yield; mp = 162–164 °C; yellow solid; IR (KBr):  $\nu$  3060 ( $\text{sp}^2$  CH), 2836 ( $\text{sp}^3$  CH), 1727 (C=O), 1593 (C=N), 1309, 1247, 1154  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.79 (d,  $J$  = 18.7 Hz, 1H, Ha), 3.36 (d,  $J$  = 18.7 Hz, 1H, Hb), 3.76 (s, 3H,  $\text{OCH}_3$ ), 4.87 (s, 1H, pyrazole-H), 6.75–6.86 (m, 5H, Ar-H), 6.89 (d,  $J$  = 8.5 Hz, 2H, Ar-H), 7.10 (t,  $J$  = 9.35 Hz, 2H, Ar-H), 7.18 (d,  $J$  = 8.5 Hz, 2H, Ar-H), 7.36 (s, 1H, Ar-H), 7.46 (d,  $J$  = 9.35 Hz, 2H, Ar-H), 7.59 (d,  $J$  = 7.65 Hz, 1H Ar-H), 7.74 (d,  $J$  = 8.5 Hz, 1H, Ar-H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  55.2 ( $\text{OCH}_3$ ), 61.2 (C4 pyrazole), 78.5 (C-spiro), 114.4, 114.8, 115.8, 120.9, 126.0, 126.7, 127.7, 128.3, 128.4, 129.9, 130.4, 131.6, 131.8, 131.8, 133.9, 134.2, 142.4, 146.5, 152.3, 159.3, 203.3 (C=O). MS m/z (%): 557 ( $\text{M}^+$ , 24), 522 (20), 348 (41), 338 (72), 329 (30), 229 (23), 206 (32), 111

(32), 107 (25), 105 (33), 77 (100). Anal. Calcd for  $C_{30}H_{22}BrClN_2O_2$  (557.86): C, 64.59; H, 3.97; N, 5.02%. Found C, 64.41; H, 3.84; N, 4.95%.

#### 5.1.8. Spiropyrazole derivative 10e

88% Yield; mp = 183–184 °C; yellow solid; IR (KBr):  $\nu$  3063 ( $sp^2$  CH), 2928 ( $sp^3$  CH), 1713 (C=O), 1593 (C=N), 1475, 1413, 1313, 1260, 1210, 1107, 1037  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.73(d,  $J$  = 18 Hz, 1H, Ha), 3.27 (d,  $J$  = 18 Hz, 1H, Hb), 4.70 (s, 1H, pyrazole-H), 7.03 (s, 1H, Ar-H), 7.05–7.18 (m, 10H, Ar-H), 7.22 (d,  $J$  = 7.65 Hz, 2H, Ar-H), 7.32 (t,  $J$  = 8.5 Hz, 1H, ArH), 7.40 (d,  $J$  = 8.5 Hz, 1H, Ar-H), 7.54 (d,  $J$  = 7.65 Hz, 1H, Ar-H), 7.62 (d,  $J$  = 8.5 Hz, 1H, Ar-H). MS  $m/z$  (%): 527 ( $M^+$ , 12), 525 (6), 519 (22), 505 (20), 465 (28), 441 (36), 405 (42), 399 (52), 367 (48), 362 (85), 346 (53), 316 (56), 294 (88), 275 (100), 244 (35), 138 (20), 121 (41), 96 (68), 78 (19). Anal. Calcd for  $C_{29}H_{20}BrClN_2O$  (527.84): C, 65.99; H, 3.82; N, 5.31%. Found C, 65.78; H, 3.73; N, 5.20%.

#### 5.1.9. Spiropyrazole derivative 10f

93% Yield; mp = 190–192 °C; yellow solid; IR (KBr):  $\nu$  3063 ( $sp^2$  CH), 2927 ( $sp^3$  CH), 1716 (C=O), 1592 (C=N), 1438, 1413, 1313, 1260, 1210, 1107, 1037  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.73(d,  $J$  = 17.85 Hz, 1H, Ha), 3.30 (d,  $J$  = 17.85 Hz, 1H, Hb), 5.35 (s, 1H, pyrazole-H), 7.03 (s, 1H, Ar-H), 7.09–7.80 (m, 15H, Ar-H). MS  $m/z$  (%): 562 ( $M^+$ , 51), 537 (68), 498 (84), 432 (72), 390 (100), 305 (80), 201 (83), 191 (91), 149 (82), 142 (74), 102 (59). Anal. Calcd for  $C_{29}H_{19}BrCl_2N_2O$  (562.28): C, 61.95; H, 3.41; N, 4.98%. Found C, 61.78; H, 3.34; N, 4.86%.

#### 5.1.10. Spiropyrazole derivative 10g

92% Yield; mp = 176–180 °C; yellow solid; IR (KBr):  $\nu$  3065 ( $sp^2$  CH), 1717 (C=O), 1593 (C=N), 1529, 1491, 1350, 1317, 1208, 1058  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.92 (d,  $J$  = 18 Hz, 1H, Ha), 3.43 (d,  $J$  = 18 Hz, 1H, Hb), 5.05 (s, 1H, pyrazole-H), 6.93 (d,  $J$  = 8.5 Hz, 1H, Ar-H), 7.15–7.83 (m, 14H, ArH), 8.01 (d,  $J$  = 7.65 Hz, 1H, Ar-H), 8.09 (d,  $J$  = 8.5 Hz, 1H, Ar-H). MS  $m/z$  (%): 540 ( $M^+$ +2, 2), 538 ( $M^+$ , 36), 514 (11), 480 (29), 383 (13), 316 (15), 259 (34), 72 (51), 64 (100). Anal. Calcd for  $C_{29}H_{20}BrN_3O_3$  (538.39): C, 64.69; H, 3.74; N, 7.80%. Found C, 64.56; H, 3.66; N, 7.73%.

#### 5.1.11. Spiropyrazole derivative 10h

89% Yield; mp = 222–224 °C; yellow solid; IR (KBr):  $\nu$  3060 ( $sp^2$  CH), 1674 (C=O), 1596 (C=N), 1491, 1368, 1297, 1195, 1090  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.09 (d,  $J$  = 17.85 Hz, 1H, Ha), 3.45 (d,  $J$  = 17.85 Hz, 1H, Hb), 4.98 (s, 1H, pyrazole-H), 6.67–8.42 (m, 17H, ArH). MS  $m/z$  (%): 572 ( $M^+$ , 20), 599 (84), 476 (33), 416 (34), 339 (65), 294 (100), 249 (72), 187 (44), 94 (45), 65 (86). Anal. Calcd for  $C_{29}H_{20}BrN_3O_3$  (572.84): C, 60.80; H, 3.34; N, 7.34%. Found C, 60.72; H, 3.18; N, 7.20%.

#### 5.1.12. Spiropyrazole derivative 14a

91% Yield; mp = 200–203 °C; yellow solid; IR (KBr):  $\nu$  3060–3030 ( $sp^2$  CH), 1717 (C=O), 1595 (C=N), 1498, 1348, 1265, 1122, 1058  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  2.98 (d,  $J$  = 17.5 Hz, 1H, Ha), 3.71 (d,  $J$  = 17.5 Hz, 1H, Hb), 4.85 (s, 1H, pyrazole-H), 6.0 (d,  $J$  = 12 Hz, 1H, CH=CH), 6.87–8.27 (m, 18H, Ar-H and CH=CH). MS  $m/z$  (%): 564 ( $M^+$ , 25), 516 (30), 460 (19), 441 (32), 355 (42), 344 (25), 220 (25), 209 (26), 122 (52), 105 (36), 103 (12), 77 (52). Anal. Calcd for  $C_{31}H_{22}BrN_3O_3$  (564.43): C, 65.97; H, 3.93; N, 7.44%. Found C, 65.78; H, 3.90; N, 7.36%.

#### 5.1.13. Spiropyrazole derivative 14b

90% Yield; mp = 205–207 °C; yellow solid; IR (KBr):  $\nu$  3058–3026 ( $sp^2$  CH), 1663 (C=O), 1596 (C=N), 1496, 1339, 1195, 1071  $cm^{-1}$ .  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.08 (d,  $J$  = 17.85 Hz, 1H, Ha), 3.70 (d,  $J$  = 17.85 Hz, 1H, Hb), 4.75 (s, 1H, pyrazole-H), 6.20 (d,

$J$  = 12 Hz, 1H, CH=CH), 7.03–8.70 (m, 18H, ArH and CH=CH). MS  $m/z$  (%): 564 ( $M^+$ , 26), 561 (48), 538 (47), 501 (52), 468 (64), 400 (28), 371 (37), 348 (69), 306 (33), 284 (48), 253 (100), 241 (60), 192 (66), 106 (52), 77 (26). Anal. Calcd for  $C_{31}H_{22}BrN_3O_3$  (564.43): C, 65.97; H, 3.93; N, 7.44%. Found C, 65.85; H, 3.79; N, 7.32%.

### Declaration of Competing Interest

The authors declare no conflict of interest.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2022.133581.

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