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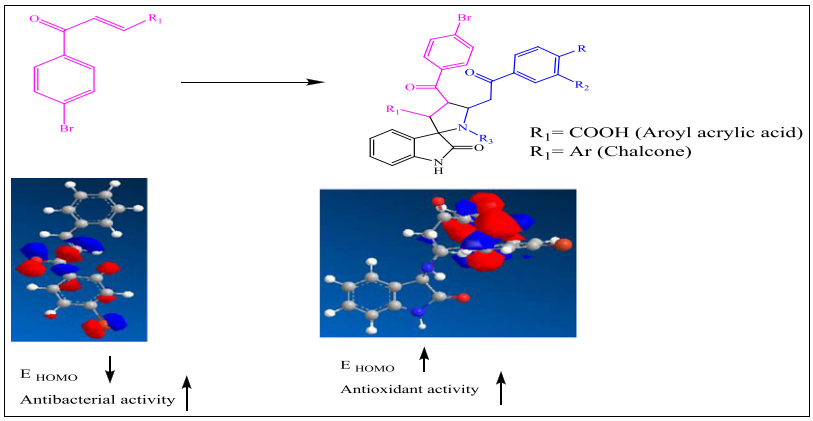

The regioselective spiroindoline derivatives were afforded via multi-componant reaction. Its process was one of the green chemistry (simplicity, mild conditions, and atomic economy). The electron repelling and attracting groups affected on reactivity of the azomethine ylides (increase E_{HOMO} value). All compound structures were confirmed by spectroscopic data and elemental analysis. The antibacterial and antioxidant activities for these synthesized compounds could be investigated; the highly antioxidant activity was observed with compounds, which proved to possess high HOMO values, and the highly antibacterial activity was observed against *S. aureus*, *B. cereus*, *S. marcesens*, and *P. mirabilis*, which proved to possess low HOMO values.

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INTRODUCTION

The antioxidant compounds play an important role in cellular structures particularly in brain [1,2]. They are considered as an attractive target to the treatment of brain problem. The antioxidant reagents could capture the free radicals directly, and so they show a great activity as neuro-protective agents [3,4] and chemo-protective agents [5–11]. Moreover, the spirocyclic compounds have non-planar chiral structure, and so they have been considered as multifunctional agents in biomolecules. Spiroindolines have been contributed as cholinergic, cholinesterase inhibitors, and antioxidants for the treatment of Alzheimer's disease [12–15]. They have attracted considerable attention in recent years because they possess a wide range of biological activities including circadian rhythm, endogenous antioxidant regulation, and the immune system, among others [16–18], and pharmacological activities [19–21]. Also, they are well known as powerful anti-tumor agents because of their kinase inhibitory properties, especially as tyrosine kinase inhibitors [22–24], antidiabetic (11β-HSD1) in liver and adipose tissue [25,26], and pest control acetylcholine transporter [27]. On the other hand, the molecular diversity for construction of spirooxindoles is a wide set of natural and non-natural α-amino acids [28,29], and 1,3-dipolarophiles, for example, α,β-unsaturated ketones [30–39], maleimides [40,41], benzo[*b*]thiophene-1,1-dioxide [42], bis(arylmethylidene) acetones and cycloalkanones [43,44], 1,4-naphthoquinone [45], arylidenemalonodinitriles [46], arylidenerhodanines [47,48], α,β-unsaturated lactones [49], nitrostyrenes [50], acrylonitriles [51], and arylidene [52,53] have been reported.

RESULTS AND DISCUSSION

Chemistry. It has reported [54–59] that the equimolar amounts of isatins **1**, sarcosine and 4-aryl-4-oxo-2-butenoic acids **2** or chalcones **3** in boiling aqueous methanol (1:3) afforded exclusively the spirooxindoles via The multicomponent 1,3-dipolar cycloaddition (MCDC). The authors wanted to prepare the new spirooxindoline derivatives having a high HOMO energy value to increase the efficiency as antioxidant reagents. This does not come only through the amendment of the

installation of α amino acids. The presence of the electron donating groups directly attached for nitrogen ylide and electron withdrawing groups directly attached to carbon ylide was proceeding the rate of the reaction because of the increase value of the HOMO energy [60,61]. The authors outline the effect of the electron repelling and attracting groups on the HOMO energy of the ylides. It will be assumed that HOMO and LUMO of dipolarophile are affected by the same amount. Changing the type of α-amino acids **4** [32–35], the reaction could proceed to afford the spiro derivatives **5** and **6** (Scheme 1). The R_3 groups in 1,3-dipolar precursor (Scheme 1) can be controlled not only in proceeding of the reaction due to further closes in the energy gap between $HOMO_{1,3\text{-dipolar}}$ and $LUMO_{dipolarophile}$ (Type 2) than the other HOMO—LUMO distance in case of sacrosine (Type 1) making this interaction clearly dominant, but also the molecular orbital coefficients in both HOMO and LUMO are unequal and pairing large-large and small-small coefficients (favored orientation) leads to greater stabilization and explains the observed regioselective products **5** and **6** [62,63].

As a consequence, the gain in stabilization through the increased interaction $HOMO_{diene}$–$LUMO_{dienophile}$ overrides the loss due to lengthening the second HOMO—LUMO separation [63]. This follows from the inverse proportionality between stabilization and energy difference of interacting orbitals. Conversely, electron donor substituents will decrease the stabilization, that is, the reactivity is lowered in dipolarophile [64]. Scheme 2 outlines the effect of terminal groups in both 1,3-dipolar and dipolarophile upon E_{HOMO} and molecular orbital coefficients. To explain the regiospecific reaction, the cyclo adduct in [54] (Scheme 1) was not formed as the ($ArCOCH_2$-) moiety directly attached to the amino group in 1,3-dipolar would change its molecular orbital coefficient (Scheme 2, type 2).

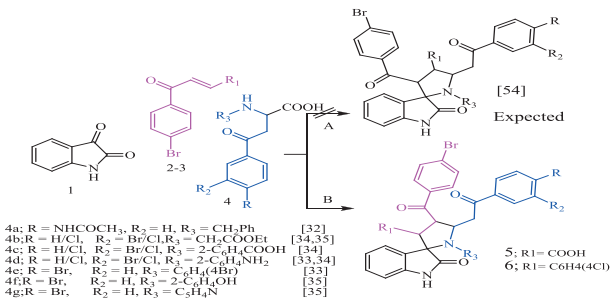
It can be deduced that the electron donor substituents will raise the HOMO and therefore will increase the reaction rate. Any substitution either in the dipolarophile or in the dipolar will increase one HOMO—LUMO interaction and decrease the other one. Because of the inverse proportionality of the stabilization and the energy separation, this implies rate enhancement by any kind of substitution in the dipolar or the dipolarophile [65]. Thus, increasing the electron-donating ability of one end of the dipole (normal demand) or dipolarophile (inverse demand) and increasing the electron withdrawing ability at the other end will encourage one bond to form faster than the other. This creates larger partial charges at the transition state, and the greater the difference in electron demand, the greater the partial charge [65]. The 1,3-dipolar cycloaddition of unsymmetrical dipolarophiles such as chalcone of imidazo[2,1-*b*] 1,3,4-thiadiazole **7a** [30] can occur via the two pathways **A** or **B**, it depended the functional groups on dipolarophile, leading to the formation of the regioisomers 1,3-di-spiro derivatives **8** via pathway **A**. Scheme 3 includes an unsymmetrical arrangement of HOMOs and LUMOs in the dipolarophile will strengthen this dominating interaction and weaken the other one. The orientation of the dipolarophlies are controlled by terminal withdrawing groups, for example, dipolarophiles **7b** and **7c** have reverse orientation differ from **7a** because of change the site of electron withdrawing group that effect on molecular orbital coefficient (Scheme 3).

So if using the exocyclic activating double bond as dipolarophile, for example, 2-aryl-4-benzylidine-5-oxofuran **7b** and 7-benzylidene-10,10-diarylpyrazolo [1′,2′:1,2]-pyrazolo[3,4-*b*]pyrazine-3,6,8-trione **7c** [52] under the same previous reaction condition, it afforded 1,2-di-spirooxindoline derivatives **9** and **10** respectively via pathway **B** (Scheme 4).

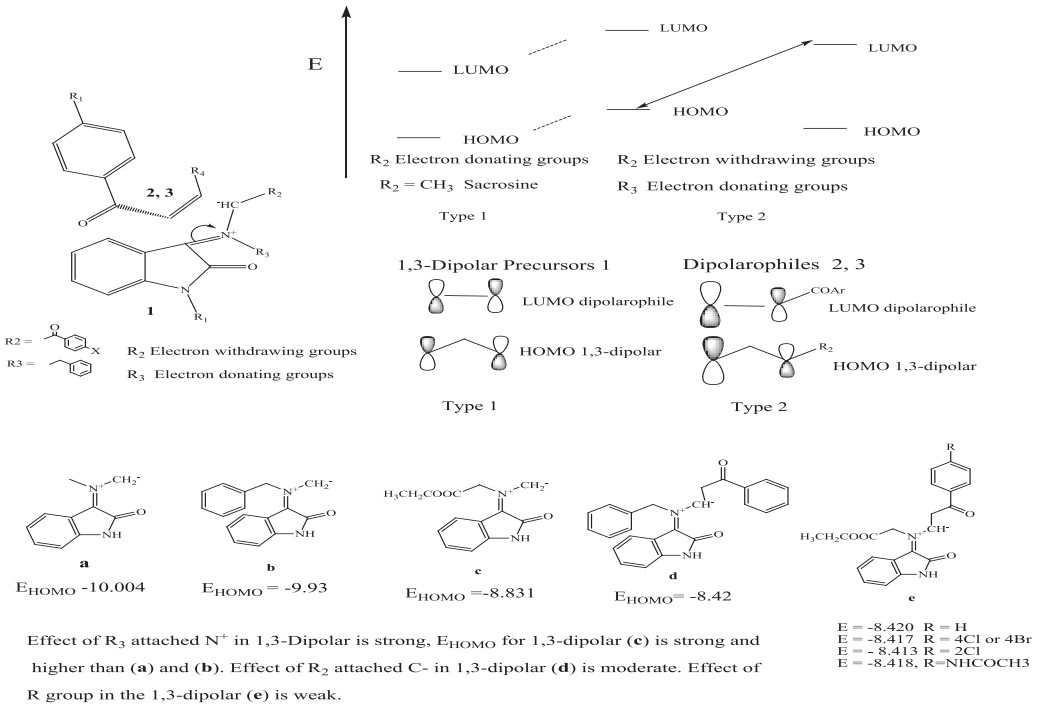
Antibacterial activity evaluation

Filter paper disk-diffusion method. The spiro compounds were tested for their antimicrobial and antioxidant activities, showing weak or no antimicrobial activity and showed promising antioxidant activities [66]. The authors have synthesized spirooxindoline derivatives in good yields for screening them for antibacterial and

Scheme 1. Synthesis of the regiospecific adducts of spirooxindoline by changing α-amino acids via favored pathway **B**. [Color figure can be viewed at wileyonlinelibrary.com]

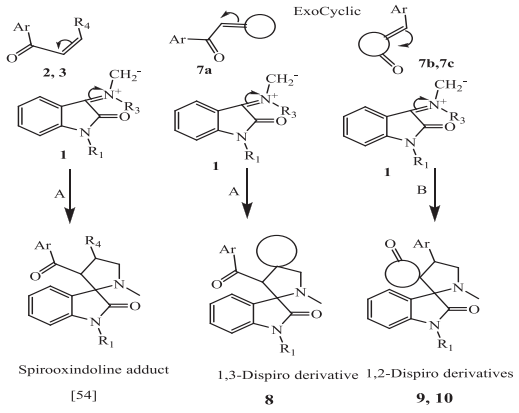


Scheme 2. The effect of terminal groups in both 1,3-dipolar and dipolarophile upon E_{HOMO} and molecular orbital coefficients.

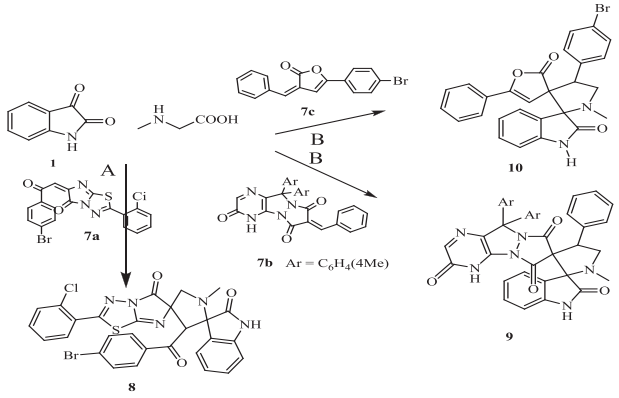


Effect of R_3 attached N^+ in 1,3-Dipolar is strong, E_{HOMO} for 1,3-dipolar (**c**) is strong and higher than (**a**) and (**b**). Effect of R_2 attached C- in 1,3-dipolar (**d**) is moderate. Effect of R group in the 1,3-dipolar (**e**) is weak.

Scheme 3. Synthesis of the regiospecific adducts of spirooxindolines by changing heterocyclic exo-dipolarophile.



Scheme 4. Synthesis of the regiospecific dispiroxindolines via the two pathways **A** or **B**, the orientation depended upon the senior carbonyl groups of the dipolarophiles 7.



antioxidant potentials. The preliminary screening of newly synthesized compounds listed in Table S3 (in supplementary material) were tested and investigated for their antibacterial activity using the filter paper disk-diffusion method. Compounds **2** and **3** possess the highest antibacterial activities that agree with the lowest HOMO energy values [30]. The rest of compounds particularly spirooxindoline derivatives showed low or no sensitivity at all to the bacteria under investigation, and the results are summarized in Table 1.

Antioxidant activity evaluation

Antioxidant screening study in lubricating oil. The oxidation test was carried out according to ASTMD-943 standard method. The oxidation cell in the static mode contained 200 mL base stock, and copper and iron wires as catalysts. The base stock sample was subjected to oxidation at 120°C with pure oxygen (99.95%) at a flow rate of 0.1 L/h for maximum 96 h. The characterized compounds were added with different concentrations (200, 400, and 500 ppm). The oil samples were examined (after 24, 48,

Table 1

Antibacterial activity of the synthesized compounds.

Compound number	Inhibition zone (mm)			
	Staph. aureus	*B. cereus*	*S. marcesens*	*Prot. mirabilis*
2a	17 ± 0.12	16 ± 0.21	15 ± 0.21	16 ± 0.17
2b	18 ± 0.18	17 ± 0.15	16 ± 0.17	16 ± 0.15
2c	17 ± 0.21	16 ± 0.24	16 ± 0.18	16 ± 0.13
3a	16 ± 0.11	16 ± 0.12	15 ± 0.07	15 ± 0.21
3b	16 ± 0.16	17 ± 0.03	16 ± 0.01	16 ± 0.11
3c	16 ± 0.17	16 ± 0.02	15 ± 0.14	15 ± 0.13
5a	09 ± 0.15	08 ± 0.20	07 ± 0.11	08 ± 0.04
5b	09 ± 0.23	09 ± 0.08	08 ± 0.13	08 ± 0.22
5c	08 ± 0.03	08 ± 0.12	08 ± 0.09	08 ± 0.15
6a	09 ± 0.13	08 ± 0.20	07 ± 0.02	06 ± 0.05
6b	06 ± 0.02	08 ± 0.01	07 ± 0.02	06 ± 0.01
6c	05 ± 0.12	04 ± 0.06	05 ± 0.12	04 ± 0.10
7a(*Z-form*)	13 ± 0.15	12 ± 0.13	11 ± 0.11	10 ± 0.15
8	03 ± 0.05	04 ± 0.21	05 ± 0.06	05 ± 0.10
9	07 ± 0.12	08 ± 0.11	09 ± 0.08	07 ± 0.02
10	05 ± 0.11	07 ± 0.12	08 ± 0.08	05 ± 0.20
Ampicillin	18 ± 0.11	19 ± 0.10	20 ± 0.10	19 ± 0.12
Chloramphenicol	19 ± 0.12	20 ± 0.16	20 ± 0.11	20 ± 0.11

The sensitivity of microorganisms to the tested compounds is identified in the following manner: highly sensitive refers to inhibition zone 15–20 mm; moderately sensitive refers to inhibition zone 10–15 mm; slightly sensitive refers to inhibition zone 5–10 mm; not sensitive refers to inhibition zone 0–5 mm; each result represents the average of triplicate readings.

72, and 96 h, respectively) through the change of viscosity and total acid number. The parameters were carried out for the oxidized samples according to ASTM standard test methods D-664, respectively.

Effect of additive concentration. It was interesting to study the effect of concentration of the prepared additives. Thus, three different concentrations, 200, 400, and 500 ppm of each additive were used The data in the Table S4 (in supplementary file) reveal that the most effective concentration in all cases is 200 ppm, that is, the total acid number increase by increasing the concentration of the additives . The most spirooxindoline additive were at optimum concentration correspond to 200 ppm, the order of increasing inhibition efficiency of sporooxindolines were ranked as follows: **9** > **8** > Ascorbic acid > β-Crotene > **10** > **6** > **5** > Lignan > chalcones **3**, **7**, and aroyl acrylic acids **2**, which were consistent with order of higher E_{HOMO} values. The authors disclose that most of the spirooxindolines were in highly efficiency as antioxidant at minimum concentration at 200 ppm (Table 2), and the order of increasing inhibition efficiency of spirooxindolines indicate the scavenging ability toward positive hole, tumor, radical, and oxygen removable depended not only upon E_{HOMO} values but also the number of heteroatom, electron distributions, surface area, and lipophilicity must be considered. Quantum chemical parameters calculations using DFT method with 6–311 g basis set and (Møller–Plesset perturbation theory) [67] used for the calculations of the synthesized compounds are in good agreement with the antioxidant efficiency (see more supplementary material). The high E_{HOMO} are likely to indicate a strong tendency of the molecule to donate electrons. The low values of the energy gap ($\Delta E = E_{LUMO} - E_{HOMO}$) will render good inhibition efficiencies [68,69]. The dipole moment, the hydration energy, the surface area (nm^2), and log P polarizability for spiroindolines carrying hydrophobic groups were agreed an excellent correlation between oxidation inhibition efficiencies. On the other hand, the ionization potential (I, eV), transferred electrons (ΔN), and charge density distribution indicate the greater value of 0.38 for dispirooxindoline **9** indicates the maximum transfer of electron, and hence, greater tendency of scavenging radicals means the compound **9** is the strongest antioxidant. Also, hardness (ή, eV/mol) and softness (, eV^{-1}) confirm the soft molecule is more reactive than a hard molecule because a soft molecule has a lower energy gap. From Table S6 (see more in supplementary file), it is clear that the softness is increased along compounds **9** > **8** > **10** > **6** > **5** with values $0.1491 > 0.1300 > 0.12810 > 0.1180 > 0.1068\ eV^{-1}$, respectively, with the same trend for antioxidant efficiency. In spite of the good correlations between experimental and calculated antioxidant efficiencies, but neglecting some other important factors such as solubility constant, competitive adsorption and surface nature, which might be the reason for obtaining better correlation.

Table 2

Total acid number variation with oxidation time at different additive concentrations.

Compound	Concentration (ppm)	Total acid number, mg KOH/g sample × 10^2			
		Oxidation time (h)			
		24	48	72	96
2a	200	51.29	67.30	84.10	187.82
	400	63.90	77.32	93.12	191.75
	500	76.40	84.62	105.68	200.32
3a	200	36.38	70.81	83.21	177.63
	400	49.12	85.23	100.86	190.72
	500	73.5	96.11	119.96	196.6
5a	200	22.97	41.52	68.65	107.85
	400	32.26	53.63	83.99	110.12
	500	44.6	70.45	95.41	164.38
5b	200	21.29	39.30	64.10	107.82
	400	33.94	57.32	83.12	131.75
	500	46.40	64.62	95.68	160.32
5c	200	20.31	28.81	63.21	113.63
	400	39.10	35.23	79.86	140.72
	500	43.5	76.11	89.96	151.62
5d	200	22.27	32.52	58.65	98.85
	400	38.73	43.63	73.99	140.12
	500	44.6	60.45	85.41	164.38
6a	200	12.29	37.30	64.10	91.82
	400	19.90	47.32	83.12	128.75
	500	28.40	64.62	95.68	150.32
6b	200	12.30	48.81	63.21	113.63
	400	19.10	55.23	79.86	140.72
	500	28.50	66.11	99.96	161.6
6c	200	13.89	39.30	71.10	127.82
	400	23.19	47.32	79.12	131.75
	500	36.14	64.62	95.68	150.32
6d	200	11.22	42.81	83.21	123.63
	400	33.18	55.23	89.86	100.72
	500	40.51	70.11	97.96	141.6
7a	200	28.37	39.52	78.65	116.85
	400	48.20	53.63	83.99	130.12
	500	54.6	70.45	105.41	174.38
7b	200	27.59	35.30	74.10	107.82
	400	33.9	57.32	83.12	131.75
	500	46.4	64.62	105.68	170.32
8	200	4.30	21.81	53.21	83.63
	400	8.13	25.23	63.86	100.72
	500	17.11	36.11	79.96	111.6
9	200	1.57	13.52	44.65	61.85
	400	6.23	22.63	49.99	70.12
	500	14.6	30.45	65.41	84.38
10	200	11.29	33.30	67.10	125.82
	400	18.74	47.32	79.12	132.75
	500	26.43	54.62	95.68	150.32
Ascorbic acid	200	10.14	23.81	65.21	94.63
	400	17.11	25.23	73.86	110.72
	500	23.15	36.11	89.96	123.6
Lignin	200	15.29	43.22	74.10	137.82
	400	23.74	55.12	83.12	141.75
	500	36.4	67.12	97.68	160.32
β-Carotene (natural antioxidant)	200	10.94	26.11	66.02	101.63
	400	17.57	27.42	75.36	115.72
	500	24.52	44.23	91.21	136.26
Oil (without additive)	—	94	102	120	202

EXPERIMENTAL

All melting points are corrected and determined on Stuart electric melting point apparatus (Microanalytical center, Cairo, Egypt). Elemental analyses were carried out by Elementar Viro El-Microanalysis at National Research Center, Egypt. IR spectra (KBr) were recorded on infrared spectrometer FT-IR 400D (New York, NY, USA) using OMNIC program and are reported frequency of absorption in terms of cm^{-1}, ^{1}H-NMR spectra recorded on a Bruker spectrophotometer (Rheinstetten, Germany) at 400 MHz using TMS as internal standard and with residual signals of the deuterated solvent δ = 7.26 ppm for $CDCl_3$ and δ 2.51 ppm for DMSO-*d6*. ^{13}C-NMR spectra were recorded on the same spectrometer at 100 MHz and referenced to solvent signals δ = 77 ppm for $CDCl_3$ and δ 39.50 ppm for DMSO-d_6. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer (Kyoto, Japan) used the electron ionization technique at 70 e.v. Homogeneity of all synthesized compounds was checked by TLC.

General procedure for the synthesis of 4-aryl-4-oxo-2-butenoic acids **2**, chalcone derivatives **3**, unnatural amino acids **4**, **7a**, and arylidine **7b**, **7c** were prepared according to the procedures reported in literature [30–36,52]. Typical procedure for the synthesis of spirooxindoline derivatives **5**, **6**, **8**, **9**, and **10** from the three-component reaction of isatins, sarcosine, and 4-aryl-4-oxo-2-butenoic acids /or chalcone derivatives:

A mixture of isatin (1,47 g,0.01 mol), sarcosine (0.9 g; 0.01 mol), and β-aroylacrylic acids **2** or chalcones **3** (0.01 mol) in 10.0 mL aqueous methanol (1:3) was (i) heated in an oil bath to reflux (ii) or stirred at room temperature as the results be shown in Table S3 (in supplementary material). The resulting precipitates were collected by filtration and washed with cold methanol to give the analytically pure products.

5'-(2-(4-Acetamidophenyl)-2-oxoethyl)-1'-benzyl-4'-(4-bromobenzoyl)-2-oxospiro[indoline-3,2'-pyrrolidine]-3'-carboxylic acid (5a). Recrystallized from toluene, off white solid, yield (i) 40%, (ii) 36%, m.p.: 222–224°C; IR(KBr), υ, cm^{-1}: 3462 (OH), 3050 (CH_{Ar}), 1689, 1664 (C = O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.05 (3H, s, CH_3CO), 2.46–2.71 (2H, dd, CH_2Aroyl_2), 3.21 (1H, m, CHAroyl), 3.24–3.28 (1H, m, CHN), 3.57 (1H, dd, *J* = 8.4 Hz, CHCOO), 3.68 (2H, s, NCH_2Ph), 6.96 (2H, d, *J* = 8.1 Hz, 2,6–CHAr), 7.01 (2H, d, *J* = 8.1 Hz, 3,5–CHAr), 7.14 [3H, dd, *J* = 8.4 Hz, 3,4,5-CH (Ph)], 7.20–7.28 [2H, dd, *J* = 8.4 Hz, 2,6-CH(Ph)], 7.32–7.40 [2H, dd, *J* = 8.4 Hz, 2,6-CH(BrPh)], 7.52–7.59 [2H, dd, *J* = 9.2 Hz, 3,5-CH(BrPh)], 7.70 [2H, s, 1,4-CH(indol)], 7.81 (2H, d, 2,3-CHindol), 10.45 (1H, s, 1-NH), 11.03 (1H, s, COOH), 12.2 (1H, s, NHCO); ^{13}C-NMR (125 MHz, DMSO-d_6), δ 22.3 (CH_3), 43.1 ($\underline{CH_2}Ph$), 48.1 ($\underline{CH_2}COAr$), 54.2 (C-spiro), 59.6 (CHN), 66.3 ($\underline{C}HCO$), 72.3 ($\underline{C}HCOO$), 108 (C_1Ar), 114.5 (2CHisat), 120.3 (C_4Ph), 123.2 ($C_{2,6}Ph$), 126.1 (2CHisat), 127.2 ($C_{3,5}Ph$), 128.5 (C-Br), 130.4 (C_1Ph), 132.1 ($C_{3,5}Ar$), 136.3 ($C_{2,6}Ar$), 139 ($C_{2,6}Ph$), 142.2 (2Cisat), 143.2 (C_4Ar), 145.3 ($C_{3,4,5}Ph$), 168.2 (CONH), 177.6 (2-CO), 190.30 (2CO-Ar-), 193.5 (COO); found, %: C 63.45, H 4.35, Br 11.68, N 6.03 for $C_{36}H_{30}BrN_3O_6$ (681). Calculated, %: C 63.54, H 4.44, Br 11.74, N 6.17.

4'-(4-Bromobenzoyl)-5'-(2-(3,4-dichlorophenyl)-2-oxoethyl)-1'-(2-ethoxy-2-oxoethyl)-2-oxospiro [indoline-3,2'-pyrrolidine]-3'-carboxylic acid (5b). Recrystallized from toluene, off white solid, yield (i) 45%, (ii) 0%, m.p. 266–268°C; IR(KBr), υ, cm^{-1}: 3455 (OH), 3050 (CH_{Ar}), 1689, 1664 (C = O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 1.3(3H, t, $\underline{CH_3}CH_2COO$), 2.46–2.71 [2H, dd, $CH_2CO(PhCl_2)$], 3.14–3.23 (1H, m, CHAroyl), 3.43–3.47 (1H, m, CHN), 3.68 (2H, q, $CH_3\underline{CH_2}COO$), 3.97 (1H, q, *J* = 8.4 Hz, CHCOO), 5.2 (2H, s, CH_2N), 7.22–7.30 (2H, dd, *J* = 8.4 Hz, BrPh), 7.34 [1H, d, *J* = 8.1 Hz, 5-CH(-$PhCl_2$)], 7.52–7.59 (2H, dd, *J* = 9.2 Hz, BrPh), 7.66 [1H, dd, *J* = 8.4 Hz, 6-CH($PhCl_2$)], 7.70 [2H, s, 2-CH (indol)], 7.81 (2H, d, 3′-CHindol), 7.90 [1H, d, *J* = 8.4 Hz, 2-CH(-$PhCl_2$)], 10.45 (1H, s, 1-NH), 11.08 (1H, s, COOH, which exchanged by D_2O); ^{13}C-NMR (125 MHz, DMSO-d_6), δ 22.3(CH_3), 38.4 (CHN), 57.1($\underline{CH}COAr$), 53.2(C-spiro), 59.6(CHN), 66.3 ($\underline{C}HCO$), 72.3 ($\underline{C}HCOO$), 74.2 ($\underline{CH}COO$),111.3 (C_1Ar), 114.5 (2CHisat), 126.1 (2CHisat), 128.5 (C-Br), 132.1 ($C_{3,5}Ar$), 136.3 ($C_{2,6}Ar$), 139 ($C_{2,6}Ph$), 142.2 (2Cisat), 143.2 (C_4Ar), 145.3–145.8 ($C_{3,4,5}Ph$), 168.2 (CONH), 177.6 (2-CO), 190.30 (2CO-Ar-), 193.5 (COO); found, %: C 54.09, H 3.66, Br 11.61, Cl 10.30, N 4.07for $C_{31}H_{25}BrCl_2N_2O_7$ (688). Calculated, %: C 54.00, H 3.57, Br 11.38, Cl 10.09, N 3.99.

4'-(4-Bromobenzoyl)-1'-(2-carboxyphenyl)-5'-(2-(3,4-dichlorophenyl)-2-oxoethyl)-2-oxospiro[indoline-3,2'-pyrrolidine]-3'-carboxylic acid (5c). Recrystallized from toluene, off white solid, yield (i) 45%, (ii) 0%, m.p.: 280–282°C; IR(KBr), υ, cm^{-1}: 3420–3400 (OH), 3050 (CH_{Ar}), 1689, 1664 (C = O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.46–2.71 [2H, dd, $CH_2CO(PhCl_2)$], 3.03–3.07 (1H, m, CHN), 3.07–3.13 (1H, m, CHCOAr), 4.01 (1H, d, *J* = 8.4 Hz, CHCOO), 7.01 [1H, d, *J* = 8.1 Hz, 5-CH($PhCl_2$)], 7.22–7.26 [1H, dd, *J* = 8.4 Hz, 6-CH($PhCl_2$)], 7.32–7.40 (2H, dd, *J* = 8.4 Hz, Brph), 7.52–7.59 (2H, dd, *J* = 9.2 Hz, BrPh), 7.60 [1H, dd, *J* = 8.4 Hz, 2-CH ($PhCl_2$)], 7.62–7.68 (4H, m, 3,4,5,6-CHAr), 7.70 [2H, s, 2-CH (indol)], 7.81 (2H, d, 3′-CHindol), 10.45 (1H, s, 1-NH), 11.11–11.14 (2H, bs, 2COOH, which exchanged by D_2O); found, %: C 56.42, H 3.27, Br 11.04, Cl 9.52, N 3.67 for $C_{34}H_{23}BrCl_2N_2O_7$ (722). Calculated, %: C 56.53, H 3.21, Br 11.06, Cl 9.81, N 3.88.

1'-(2-Aminophenyl)-4'-(4-bromobenzoyl)-5'-(2-(4-bromophenyl)-2-oxoethyl)-2-oxospiro[indoline-3,2'-pyrrolidine]-3'-carboxylic acid (5d). Recrystallized from toluene, off white

solid, yield (i) 50%, (ii) 32%, m.p.: 276–278°C; IR(KBr), υ, cm^{-1}: 3416 (OH), 3050 (CH_{Ar}), 1689, 1664 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.46–2.71 (2H, dd, CH_2Ar), 3.03–3.07 (1H, m, CHN), 3.09–3.15 (1H, m, CHAr), 4.07 (1H, d, *J* = 8.4 Hz, CHCOO), 7.11–7.18 [2H, dd, *J* = 8.1 Hz, 3,5-CH(PhBr)], 7.22–7.26 [2H, dd, *J* = 8.4 Hz, 2,6-CH(PhBr)], 7.32–7.40 (2H, dd, *J* = 8.4 Hz, BrPh), 7.52–7.59 (2H, dd, *J* = 9.2 Hz, BrPh), 7.62–7.68 (4H, m, 3,4,5,6-CHAr), 7.70 [2H, s, 2-CH (indol)], 7.81 (2H, d, 3′-CHindol), 8.02 (2H, s, NH_2Ph), 10.45 (1H, s, 1-NH), 11.13 (1H, s, COOH, which exchanged by D_2O); found: C 56.26, H 3.57, Br 22.64, N 5.72 for $C_{33}H_{25}Br_2N_3O_5$ (703): C 56.35, H 3.58, Br 22.72, N 5.97.

4′-(4-Bromobenzoyl)-1′-(4-bromophenyl)-5′-(2-(4-bromophenyl)-2-oxoethyl)-3′-(4-chlorophenyl) spiro[indoline-3,2′-pyrrolidin]-2-one (6a). Recrystallized from toluene, off white solid, yield (i) 45%, (ii) 0%, m.p. 302–304°C; IR(KBr), υ, cm^{-1}: 3050 (CH_{Ar}), 1689, 1664 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.46–2.71 (2H, dd, CH_2Aroyl_2), 3.03–3.07 (1H, m, 5′-CHN), 2.94–3.03 (1H, m, CHAroyl), 3.99–4.02 [1H, q, *J* = 8.4 Hz, 4′-CH(ClPh)], 7.10–7.13 [2H, dd, *J* = 8.4 Hz, 2,6-CH(-$BrPh_3$)], 7.16–7.20 [2H, dd, *J* = 8.4 Hz, 2,6-CH($BrPh_2$)], 7.22–7.30 [2H, dd, *J* = 8.4 Hz, 2,6-CH($BrPh_1$)], 7.36–7.39 [2H, dd, *J* = 8.4 Hz, 3,5-CH($BrPh_3$)], 7.34–7.45 [2H, dd, *J* = 8.1 Hz, 3,5-CH(PhCl)], 7.52–7.59 [2H, dd, *J* = 9.2 Hz, 3,5-CH($BrPh_2$)], 7.62–7.64 [2H, dd, *J* = 8.4 Hz, 2,6-CH(-PhCl)], 7.66 [2H, dd, *J* = 8.4 Hz, 3,5-CH($BrPh_1$)], 7.70 [2H, s, 2-CH (indol)], 7.81 (2H, d, 3′-CHindol), 10.45 (1H, s, 1-NH); ^{13}C-NMR (125 MHz, DMSO-d_6), δ 38.1 ($\underline{C}H_2COAr_2$), 39.4 (CHN), 46.3 ($\underline{C}HAr_3$), 51.2(C-spiro), 64.3 ($\underline{C}HCOAr_1$), 111.3 (C_1Ar_3), 112.4 [C_1(ClPh)], 114.5 (2CHisat), 116.3 [$C_{2,6}$($BrPh_3$)], 126.1 (2CHisat), 128.5 [C_4($BrPh_3$)], 132.1 ($C_{3,5}Ar_3$), 133.3 [$C_{3,5}$(ClPh)], 136.3 [$C_{2,6}$($BrPh_2$)], 137.8 [$C_{2,6}$(ClPh)], 138.6 [C_4(ClPh)], 139.0 [$C_{2,6}$($BrPh_1$)], 140.2 (C_4Ar_1), 140.6 (2Cisat), 141.3–141.8 ($C_{3,5}Ar_2$), 143.2 (C_4Ar_2), 145.3–145.8 ($C_{3,5}Ar_1$), 146.2 (C_1Ar_2), 146.2 (C_1Ar_1), 177.6 (2-CO), 190.30 (CO-Ar_2) 193.0 (CO-Ar_1); found, %: C 54.63, H 3.11, Br 28.61, Cl 4.12, N 3.22 for $C_{38}H_{26}Br_3ClN_2O_3$ (834). Calculated, %: C 54.74, H 3.14, Br 28.75, Cl 4.25, N 3.36.

4′-(4-Bromobenzoyl)-5′-(2-(4-bromophenyl)-2-oxoethyl)-3′-(4-chlorophenyl)-1′-(2-hydroxyphenyl) spiro[indoline-3,2′-pyrrolidin]-2-one (6b). Recrystallized from toluene, off white solid, yield (i) 42%, (ii) 0%, m.p.: 310–312°C; IR (KBr), υ, cm^{-1}: 3490 (OH), 3050 (CH_{Ar}), 1689, 1664 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.46–2.71 (2H, dd, CH_2Aroyl_2), 3.03–3.07 (1H, m, CHN), 3.14–3.23 [1H, m, CH($BrPh_1$)], 4.02–4.07 [1H, q, *J* = 8.4 Hz, CH(ClPh)], 7.10–7.13 [2H, dd, *J* = 8.4 Hz, 2,4-C$\underline{H}$(OHPh)], 7.16–7.20 [2H, dd, *J* = 8.4 Hz, 2,6-CH($BrPh_2$)], 7.22–7.30 [2H, dd, *J* = 8.4 Hz, 2,6-CH(-$BrPh_1$)], 7.36–7.39 [2H, dd, *J* = 8.4 Hz, 3,5-C$\underline{H}$(OHPh)], 7.34–7.45 [2H, dd, *J* = 8.1 Hz, 3,5-CH(PhCl)], 7.52–7.59 [2H, dd, *J* = 9.2 Hz, 3,5-CH($BrPh_2$)], 7.62–7.64 [2H, dd, *J* = 8.4 Hz, 2,6-CH(PhCl)], 7.66 [2H, dd, *J* = 8.4 Hz, 3,5-CH($BrPh_1$)], 7.70 [2H, s, 2-CH (indol)], 7.81 (2H, d, 3′-CHindol), 10.45 (1H, s, 1-NH), 12.01 (1H, s, OH); found, %: C 59.13, H 3.47, Br 20.68, Cl 4.51, N 3.52 for $C_{38}H_{27}Br_2ClN_2O_4$ (770). Calculated, %: C 59.21, H 3.53, Br 20.73, Cl 4.60, N 3.63.

4′-(4-Bromobenzoyl)-5′-(2-(4-bromophenyl)-2-oxoethyl)-3′-(4-chlorophenyl)-1′-(pyridin-2-yl)spiro [indoline-3,2′-pyrrolidin]-2-one (6c). Recrystallized from toluene, off white solid, yield (i) 34%, (ii) 0%, m.p. 300–302°C; IR(KBr), υ, cm^{-1}: 3050 (CH_{Ar}), 1689, 1664 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.46–2.71 (2H, dd, CH_2Aroyl_2), 3.03–3.07 (1H, m, 5′-CHN), 3.14–3.23 (1H, m, 5′-$CHAroyl_1$), 4.11–4.17 [1H, q, *J* = 8.4 Hz, CH(ClPh)], 7.16–7.20 [2H, dd, *J* = 8.4 Hz, 2,6-CH(-$BrPh_2$)], 7.22–7.30 [2H, dd, *J* = 8.4 Hz, 2,6-CH($BrPh_1$)], 7.36–7.39 [2H, dd, *J* = 8.4 Hz, 3,5-CH(Py)], 7.34–7.37 [2H, dd, *J* = 8.1 Hz, 3,5-CH(PhCl)], 7.40–7.43 [2H, dd, *J* = 8.4 Hz, 4,6-CH(Py)], 7.52–7.59 [2H, dd, *J* = 9.2 Hz, 3,5-CH($BrPh_2$)], 7.62–7.64 [2H, dd, *J* = 8.4 Hz, 2,6-CH(-PhCl)], 7.66 [2H, dd, *J* = 8.4 Hz, 3,5-CH($BrPh_1$)], 7.70 [2H, s, 1,4-CH (indol)], 7.81 (2H, d, 2,3-CHindol), 10.45 (1H, s, 1-NH); found, %: C 58.70, H 3.41, Br 21.06, Cl 4.56, N 5.43 for $C_{37}H_{26}Br_2ClN_3O_3$ (755). Calculated, %: C 58.79, H 3.47, Br 21.14, Cl 4.69, N 5.56.

3′-(4-Bromobenzoyl)-2-(2-chlorophenyl)-1′-methyl-5H-dispiro[imidazo[2,1b] [1, 3, 4] thiadiazole-6,4′-pyrrolidine-2′,3″-indoline]-2″,5-dione (8). Recrystallized from dioxane, off white solid, yield (i) 40%, (ii) 0%, m.p. 270–272°C; IR(KBr), υ, cm^{-1}: 3320 (NH), 3050 (CHAr), 1689, 1673, 1664 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.28 (3H, s, 1′-NCH_3), 2.64–2.73 (2H, m, 5′-CH_2), 4.43 (1H, s, 7-CH), 7.21 [1H, d, *J* = 8.1 Hz, 5-CH(Ph)], 7.36 [2H, dd, *J* = 8.4 Hz, 3,5-CH (Ph)], 7.40 [2H, s, 2-CH (indol)], 7.41 (2H, d, 3′-CHindol), 7.43 [1H, s, 5-CH (Ph)], 7.52–7.50(2H, dd, *J* = 9.4 Hz, BrPh), 7.72–7.69(2H, dd, *J* = 8.4 Hz, ClPh), 10.55 (1H, s, 1-NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ 38.4(CH_3N), 54.6(CH_2N), 56.5($\underline{C}HCO$), 71.2(C-spiro$_1$), 77.2(C-spiro$_2$), 114.5(2CHisat), 120.3 (C_4Ph), 123.4(C_1Ar) 126.1(2CHisat), 127.2($C_{3,5}$Ph) 128.5(C-Br) 130.4(C_1Ph), 131.1($C_{2,6}$Ph), 132.1($C_{3,5}$Ar), 136.3($C_{2,6}$Ar), 142.2(2Cisat), 162.2(Ph$\underline{C}$=N), 167.4 (COimid), 171.4(CN_2S), 177.6(2-CO), 195.00(CO-benzoyl); found, %: C 54.15, H 3.00, Br 12.75, Cl 5.64, N 11.16, S 5.08 for $C_{28}H_{19}BrClN_4O_5S$ (620). Calculated, %: C 54.16, H 3.08, Br 12.87, Cl 5.71, N 11.28, S 5.16.

1′-Methyl-4′-phenyl-10″,10″-di-p-tolyl-4″,10″-dihydro-3″H,6″H,8″H-dispiro [indoline- 3,2′-pyrrolidine-3′,7″-pyrazolo[1′,2′:1,2]pyrazolo[3,4-b]pyrazine]-2,3″,6″,8″-tetraone (9). Recrystallized from dioxane, off white solid, yield (i)

42%, (ii) 0%, m.p. 308–310°C; IR(KBr), υ, cm^{-1}: 3410, 3333(NH), 3050 (CH_{Ar}), 1689, 1664 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.06(6H, s, $2CH_3$), 2.18 (3H, s, 1′-NCH_3), 3.34–3.23 (2H, m, 5′-CH_2), 4.43 (1H, dd, *J* = 8.4 Hz, 6-CH), 7.12–7.17(4H, dd, *J* = 8.4 Hz, CH_3Ph), 7.18–7.29(4H, dd, *J* = 9.2 Hz, $2CH_3$Ph), 7.31 [1H, d, *J* = 8.1 Hz, 5-CH(Ph)], 7.36 [3H, dd, *J* = 8.4 Hz, 3,4,5-CH (Ph)], 7.40 [2H, s, 2-CH (indol)], 7.41 (2H, d, 3′-CHindol), 7.43 [1H, s, 5-CH (Ph)], 10.45 (1H, s, 1-NH); ^{13}C-NMR (125 MHz, DMSO-d_6) δ δ 23.2($2\underline{C}H_3$), 32.8(CH_3N), 38.4(CH_3N), 43.1(<u>CH</u>Ph), 54.6(CH_2N), 56.5(<u>CH</u>CO), 64.4[C(2Ar)] 71.2(C-spiro$_1$), 83.2(C-spiro$_2$), 114.5(2CHisat), 118.5($\underline{2C}$-CH_3), 120.3(C_4Ph), 123.2($2C_{2,6}$Ph), 124.2(2C=), 126.1(2CHisat), 127.2($2C_{3,5}$Ph), 130.4(C_1Ph), 131.1($C_{3,5}$Ph), 132.1($C_{2,6}$Ar), 136.3($C_{2,6}$Ar), 142.2(2Cisat), 161.2(C=N), 168.3(CONH), 171.4(2CON), 177.6(2-CO); found,%: C 72.05, H 4.85, N 12.76 for $C_{39}H_{32}N_6O_4$ (648). Calculated, %: C 72.21, H 4.97, N 12.95.

4′-(4-Bromophenyl)-1′-methyl-5-phenyl-2H-dispiro[furan-3,3′-pyrrolidine-2′,3″-indoline]-2,2″-dione (10). Recrystallized from dioxane, off white solid, yield (i) 45%, (ii) 34%, m.p. 292–294°C; IR(KBr), υ, cm^{-1}: 3402, 3370 (NH), 3050 (CH_{Ar}), 1773, 1664 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6), δ, ppm, (*J*, Hz): 2.08 (3H, s, 1′-NCH_3), 3.14–3.23 (2H, m, 5′-CH_2), 4.97 (1H, q, *J* = 8.4 Hz, 4′-CH), 5.61 (1H, s, C=fur), 7.01 [1H, d, *J* = 8.1 Hz, 5-CH(Ph)], 7.06 [3H, dd, *J* = 8.4 Hz, 3,4,5-CH (Ph)], 7.12–7.20(2H, dd, *J* = 8.4 Hz, BrPh), 7.22–7.29(2H, dd, *J* = 9.2 Hz, BrPh), 7.40 [2H, s, 2-CH (indol)], 7.41 (2H, d, 3′-CHindol), 7.43 [1H, s, 5-CH (Ph)], 10.45 (1H, s, 1-NH); ^{13}C-NMR (125 MHz, DMSO-d_6), δ 38.4 (CH_3N), 43.1(<u>CH</u>Ph), 54.6(CH_2N), 71.2(C-spiro$_1$), 75.2 (C-spiro$_2$), 108.5(CH=fur), 111.3(C_4Ar), 114.5(2CHisat), 120.3(C_4Ph), 123.2($C_{2,6}$Ph), 126.1(2CHisat), 127.2 ($C_{3,5}$Ph) 128.5(C-Br) 130.4(C_1Ph), 132.1($C_{3,5}$Ar), 136.3 ($C_{2,6}$Ar), 142.2(2Cisat), 145.3(PhC=), 177.6(2-CO), 190.30(CO-furanone); found, %: C 64.58, H 4.15, Br 15.78, N 5.36 for $C_{27}H_{21}BrN_2O_3$ (500). Calculated, %: C 64.68, H 4.22, Br 15.94, N 5.59.

CONCLUSION

The 1,3-dipolar cycloaddition of azomethine ylides to 4-aryl-4-oxo-but-2-enoic acids and/or chalcone derivatives afforded the regiospecific spirooxindoles **4** and **5** in moderate to good yields. Changing of the dipolarophiles and α-amino acids structures can be effected upon the regiospecificity. The structures of the new compounds were elucidated using IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy. Some of the newly synthesized compounds were screened against bacterial strains, the compounds **2** and **3** (low E_{HOMO}) were showed with high antibacterial activities, and the others **9** > **8** > Ascorbic acid > β-Crotene > **10** > **6** > **5** > Lignan (high E_{HOMO}) were showed with high antioxidant activities. There are relationships between antibacterial and antioxidant agents from point of view quantum chemical parameter. Increasing in the E_{HOMO} values refer to no antibacterial activity and high antioxidant activity that were identical to identical to the experimental results. More than 16 parameters can be confirmed, for example, E_{HOMO}, E_{LUMO}, the energy gap (ΔE), the dipole moment, the hydration energy, the surface area (nm^2), log P polarizability, total energy, Ionization potential, softness, and charge densities are calculated using single method using DFT could be confirmed aforementioned.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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