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Microwave mediated synthesis of spiro-(indoline-isoxazolidines): mechanistic study and biological activity evaluation☆

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Abstract—Regioisomeric spiro-(indoline-isoxazolidines) have been synthesized in moderate yields by the cycloaddition reaction between ethyl (3-indolylidene)acetate and various substituted α,*N*-diphenylnitrones, using environmentally benign microwave technology. A novel concerted reaction mechanism is described that explains the preferential formation of the regioisomeric spiro-(indoline-isoxazolidine) analogs **6** over **5**. These compounds were screened for anti-mycobacterial and anti-invasive activities against tumor cells.

1. Introduction

The 1,3-dipolar cycloaddition reactions belong to the most important and versatile methods for building five membered heterocycles; they have been applied to the synthesis of natural products such as sugar derivatives,[1] β-lactams,[2] amino acids[3] and alkaloids.[4] Among dipoles, nitrile oxides and nitrile imines have been used extensively. The 1,3-dipolar cycloaddition of nitrones with alkenes in particular has received considerable attention over the past few years in the synthesis of isoxazolidines.[5–9] One of the reasons for the success of the synthetic applications of nitrones is that, contrary to the majority of other 1,3-dipoles, most nitrones are stable compounds which readily undergo cycloadditions to a wide variety of alkenes, affording isoxazolidines and isoxazolines, extremely useful classes of heterocycles.[10]

Recently, a number of publications and reviews have advocated the use of microwave technology in organic synthesis.[11–13] Microwave radiation generally results in enhanced reaction rates and higher product yields as compared to those by conventional heating.[14,15]

In view of above, we have investigated the reaction of indolylidene acetate with a series of nitrones yielding a large number of isomeric spiro-(indoline-isoxazolidines) in a one-pot reaction sequence using microwave radiation. Several of these compounds exhibited interesting anti-tubercular and anti-invasive activities against MCF 7/6 cancer cells.

2. Results and discussion

Spiro-(indoline-isoxazolidines) were synthesized by the cycloaddition reaction between ethyl (3-indolylidene)-acetate (**3**)[16] and various substituted α,*N*-diphenylnitrones **4a–4j** (Scheme 1). The ethoxycarbonylmethylenetriphenyl phosphorane (**2**) was synthesized by the Wittig reaction of triphenylphosphine and ethyl bromoacetate in benzene,[17] which on condensation with the commercially available indoline-2,3 dione (**1**) in acetic acid (glacial) at 80 °C afforded the ethyl (3-indolylidene)acetate (**3**). The nitrones **4a–4j**[18–22] were prepared by the condensation of appropriately substituted aromatic aldehydes with phenylhydroxylamine in ethanol at room temperature. Though, all the nitrones **4a–4j** are known compounds, the spectral

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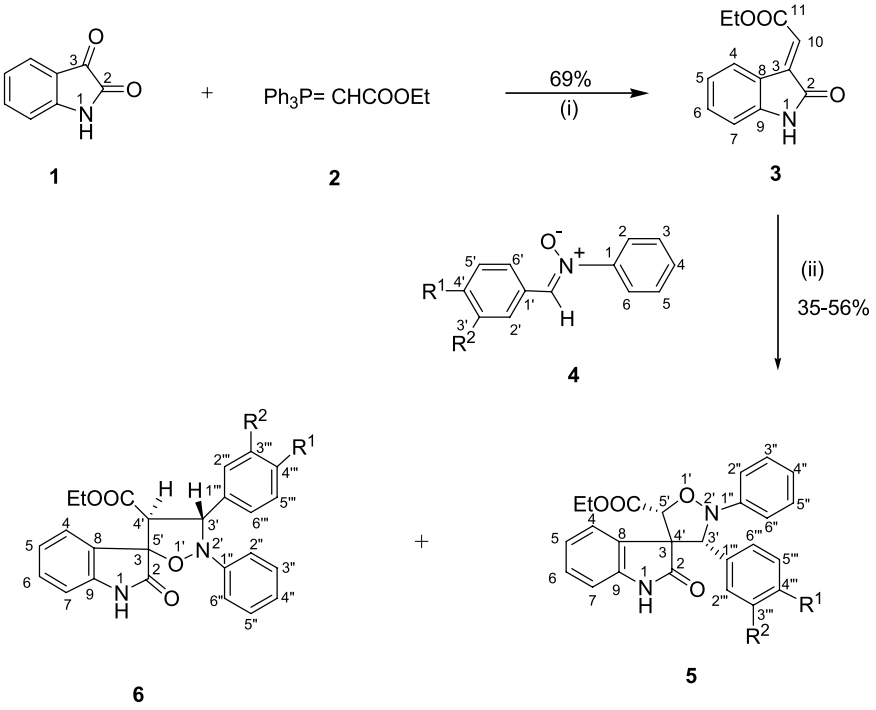


(i) CH_3COOH (glacial), 80 °C, 4 h, 69% yield
(ii) Microwave irradiation, 35 to 56% yield

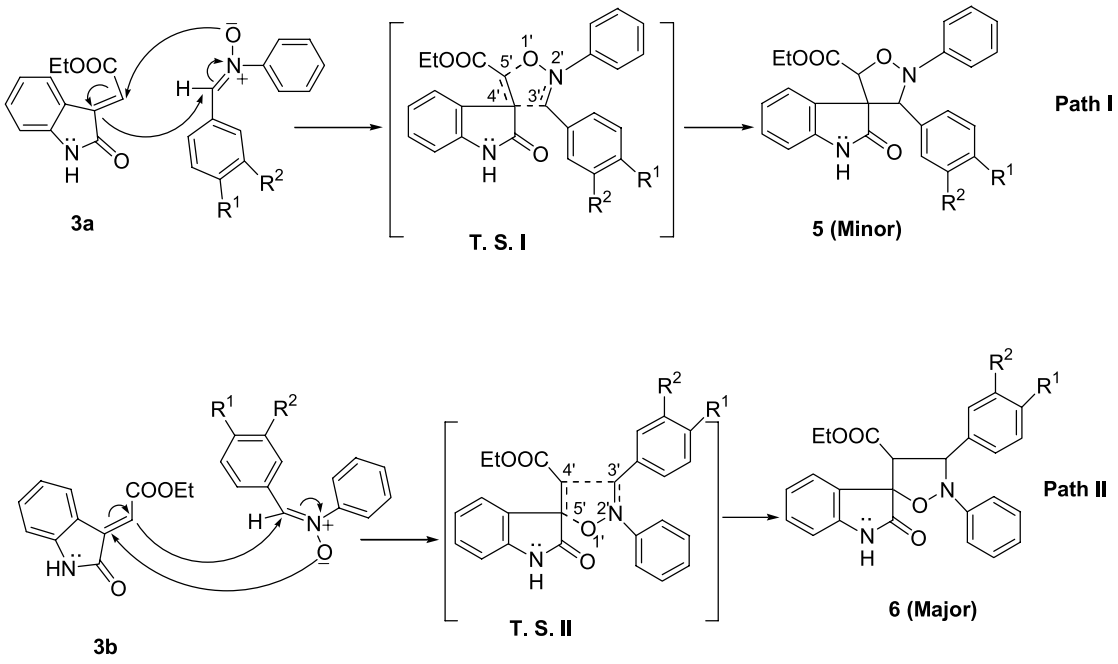
4-6	R^1	R^2	Yield 5 (%)	Yield 6 (%)	MW Irradiation Time (min)
a	Cl	H	22.7	33.8	4.0
b	Br	H	12.1	38.5	4.0
c	NO_2	H	12.8	27.1	5.0
d	F	H	10.0	43.7	4.0
e	CH_3	H	15.6	39.2	4.0
f	H	Cl	21.4	33.0	5.0
g	H	Br	9.1	44.4	4.0
h	H	NO_2	12.1	42.1	4.0
i	H	F	11.7	23.2	5.0
j	H	CH_3	15.8	36.1	4.0

Scheme 1.

data and melting point for α-(3-fluorophenyl)-*N*-phenylnitrone (**4i**) have not been reported earlier. The cycloaddition reaction between the nitrones **4a**–**4j** and ethyl (3-indolylidene)acetate (**3**) in benzene at 60 °C afforded a mixture of two regioisomeric spiro-(indoline-isoxazolidines), that is **5a**–**5j** and **6a**–**6j** in just 10–15% combined yields even after 150–180 h of stirring.

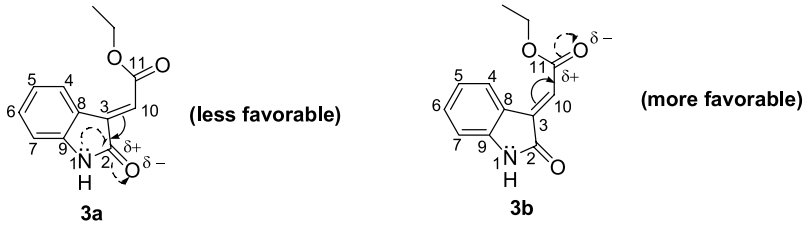
To increase the yield of the spiro-(indoline-isoxazolidines), different reaction conditions and methodologies were attempted, of which a solvent-free reaction coupled with microwave activation provided the desired spiro-(indoline-isoxazolidines) in better yields. Thus, under microwave conditions, spiro compounds **5a**–**5j** and **6a**–**6j** have been prepared just by irradiating the mixture of ethyl (3-indolylidene)acetate (**3**) and the α,*N*-diphenylnitrones **4a**–**4j** in the absence of any solvent for 4–5 min (1 min at a time with 10 s interval) in 35–56% combined yields. The temperature of the reaction mixture under these conditions was observed to reach between 55 and 60 °C. However, by irradiating the reaction mixture in a single attempt for 4–5 min led to a charred mass with the temperature reaching 132–140 °C. The reaction did not proceed when the two reactants were heated (without solvent) in an oil bath at 55 °C for 20 h. Thus, the use of microwave irradiation in dry media resulted in drastic reduction of reaction time and enhancement in yields in comparison to classical heating conditions. In addition, the microwave methodology developed here possesses the currently much demanded 'Green Appeal' and avoids the use of hazardous and toxic solvent(s).

The nitrone addition to the olefinic bond of ethyl (3-indolylidene)acetate (**3**) seems to follow a concerted cyclization mechanism (Scheme 2). The preferential formation of isomers **6** (23–44% yields) over **5** (9–22% yields) indicates that path II is more favorable over path I (Scheme 2). The isomer **6** was found to be the major product in all the cases. This was ascertained by recording the ^{1}H NMR spectra of



Scheme 2.

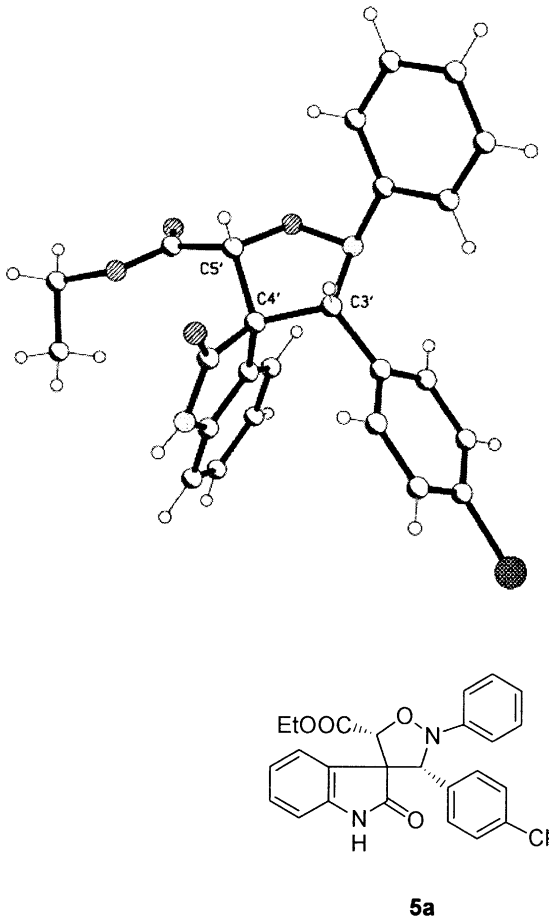
the reaction products containing both the regioisomers **5** and **6**. This mixture was then subjected to isomeric separation by column chromatography, compounds of both the series were obtained in pure forms along with their inseparable mixtures. The relative ratios of the two isomers in the mixtures were determined from ^{1}H NMR spectral analysis and this information was used to calculate the yields of the two isomers, **5** and **6**. The formation of two regioisomeric spiro-(indoline-isoxazolidines) **5a–5j** and **6a–6j** can be explained on the basis of the intermolecular cycloaddition involving exocyclic double bond shifting in **3** in two different modes as depicted mechanistically in Scheme 3. The partial negative charge calculated using the Cache Pro 5.04 (PM3) programme[23] was found to be higher on C-10 (−0.091) as compared to that on C-3 (−0.028). This may be due to the consequence of having an (equivalent of) *o*-aminophenyl substituent on C-3 in **3** conjugated to the ester carbonyl group on C-10, thus the shifting (or polarizability) of the π-electrons towards C-10 is favored over that towards C-3 (Scheme 3). This explains higher yields of the spiro-(indoline-isoxazolidine) isomers **6** over those of **5** (cf. Section 5 and Table 1). Additionally **6** is also calculated to be thermodynamically preferred over **5**. The two regioisomeric spiro-(indoline-isoxazolidines) were well characterized on the basis of their ^{1}H and ^{13}C NMR spectra. In case of the regioisomers **5a–5j**, the two isoxazolidine ring protons appeared as two distinct singlets in the ranges δ 5.24–5.28 and δ 5.30–5.45 (Table 1), indicating them to be on non-adjacent positions. On the other hand, in the case of the regioisomers **6a–6j**, the two isoxazolidine ring protons coupled with each other and appeared as two distinct doublets with J values in the range of 9.0–9.7 Hz (Table 1), suggesting them to be on adjacent ring carbon atoms. Furthermore, the C-3′H appeared quite downfield in **6a–6j** (δ 5.20–5.41, Table 1) as compared to the C-4′H (δ 4.16–4.24, Table 1). The structures of the two regioisomeric spiro derivatives were also compatible with their respective ^{13}C NMR spectra. In the case of regioisomers **6a–6j**, the spiro carbon, that is the C-5 appeared downfield (δ 82.96–83.67) in comparison to the spiro carbon, that is C-4 in compounds **5a–5j** (δ 66.34–68.87, Table 1) because in the former, C-5 is directly attached to the ring oxygen in the isomers **6a–6j**. The structures of two regioisomeric spiro-(indoline-isoxazolidines) were finally confirmed by X-ray crystallographic studies of two compounds, one representative example from each series of two regioisomers, that is of the compounds **5a** and **6c** (Diagrams 1 and 2).[24] Interestingly, the X-ray structures clearly indicate the preference for the C-5′ side chain in **5a** and the C-4′ side chain in **6c** to be *cis* to the larger group at the adjacent spiro carbon (Diagrams 1 and 2).[24] Since both these groups are present in the common starting compound **3**, that is 3-(indolylidene)acetate for both the isomers, the formation of *cis*-products of both the series



Scheme 3.

Table 1. Yields and ^{1}H and ^{13}C NMR chemical shift values of key protons and carbon atoms of spiro compounds **5a–5j** and **6a–6j**

Compound	Yield (%)	δ Value of C-3H	δ Value of C-5H	δ Value of C-4	Compound	Yield (%)	δ Value of C-3H (*J* value in Hz)	δ Value of C-4H (*J* value in Hz)	δ Value of C-5
5a	22.7	5.25	5.32	66.34	**6a**	33.8	5.22 (9.5)	4.16 (9.5)	83.51
5b	12.1	5.25	5.30	66.78	**6b**	38.5	5.21 (9.4)	4.16 (9.4)	83.21
5c	12.8	5.26	5.44	68.86	**6c**	27.1	5.41 (9.1)	4.18 (9.2)	83.03
5d	10.0	5.25	5.33	66.55	**6d**	43.7	5.23 (9.5)	4.18 (9.4)	83.23
5e	15.6	5.25	5.32	66.91	**6e**	39.2	5.20 (9.7)	4.21 (9.7)	83.16
5f	21.4	5.24	5.32	68.87	**6f**	33.0	5.23 (9.5)	4.17 (9.5)	82.98
5g	9.1	5.24	5.32	66.58	**6g**	44.4	5.25 (9.5)	4.20 (9.5)	83.67
5h	12.1	5.28	5.45	66.90	**6h**	42.1	5.40 (9.1)	4.17 (9.0)	83.18
5i	11.7	5.24	5.35	66.55	**6i**	23.2	5.27 (9.3)	4.19 (9.3)	83.13
5j	15.8	5.24	5.32	67.08	**6j**	36.1	5.22 (9.7)	4.24 (9.7)	82.96



5a

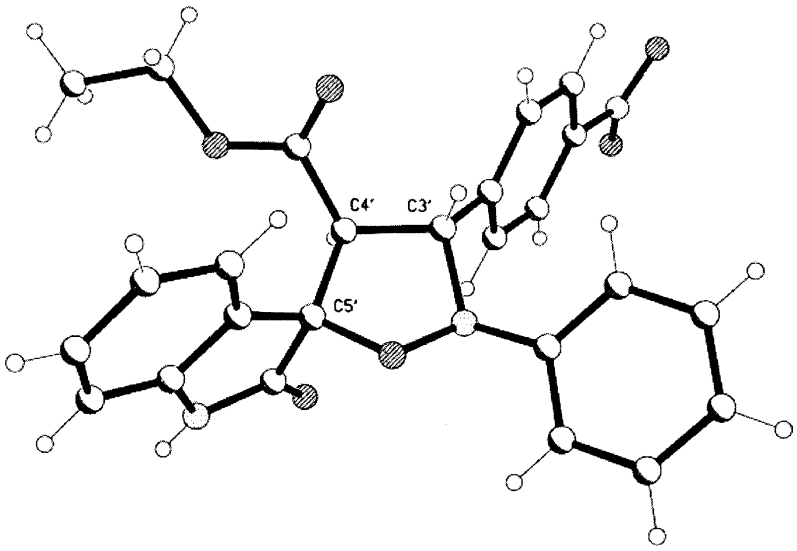
Diagram 1. X-ray crystallography of **5a**.

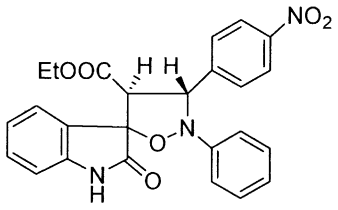
can only be explained if the two groups also have *cis* relationship in the precursor **3**. To establish the geometry, we carried out the NOE experiments on compound **3** but were not able to ascertain the stereo-chemical features in the compound. However, the X-ray crystallographic study on compound **3** (Diagram 3)[24] fully established that ethoxycarbonyl group and phenyl group are in *cis* configuration, this further supports the proposed concerted mechanism.

The ^{1}H and ^{13}C NMR spectra of the spiro-(indoline-isoxazolidines) **5a–5j** and **6a–6j** exhibited only one set of peaks, thereby confirming the formation of single diastereoisomers during the cycloaddition reactions. All 20 spiro-(indoline-isoxazolidines) are new compounds in the literature and have been fully characterized from their spectral data (cf. Section 5).

3. Anti-mycobacterial and anti-invasive activity evaluation of 5a–5j and 6a–6j

All the spiro compounds, viz. **5a–5j** and **6a–6j** were submitted to the NIH Center at SRI (Birmingham, Alabama) for ascertaining their anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294);[25] the spiro-(indoline-isoxazolidines) having structures belonging to series **6** showed better anti-tubercular activities (15–29% inhibition of *Mycobacterium tuberculosis*) than those of the





6c

Diagram 2. X-ray crystallography of **6c**.

spiro compounds belonging to the series **5** (2–8% inhibition, Table 2).

Furthermore, we tested the spiro compounds **5a**–**5j** and **6a**–**6j** in an organotypic assay for invasion. The assay of anti-invasive activity was based on confrontation of invasive human MCF-7/6 mammary carcinoma cells with embryonic chick heart fragments.[26–29] The spiro compounds **5b**, **5c**, **5d**, **5e**, **5g**, **5j**, **6c** and **6e** (Table 3) showed significant inhibition of invasion at 100 μM concentration. The compounds **5c**, **5e** and **6e** showed activity at 10 μM concentration also; none of the compounds exhibited any activity at further dilutions. It is interesting to note that unlike the anti-tubercular activity, the compounds of the series **5** exhibited better anti-invasive activities against tumor cells than the spiro-(indoline-isoxazolidines) **6**.

4. Conclusions

We have synthesized 20 novel spiro compounds taking advantage of the complementarity of the eco-friendly microwave technology under solvent-free conditions. The use of microwave technique resulted in drastic reduction of reaction time and enhancement in yields in comparison to the classical heating method. Furthermore, these compounds showed moderate anti-mycobacterial and anti-invasive activities.

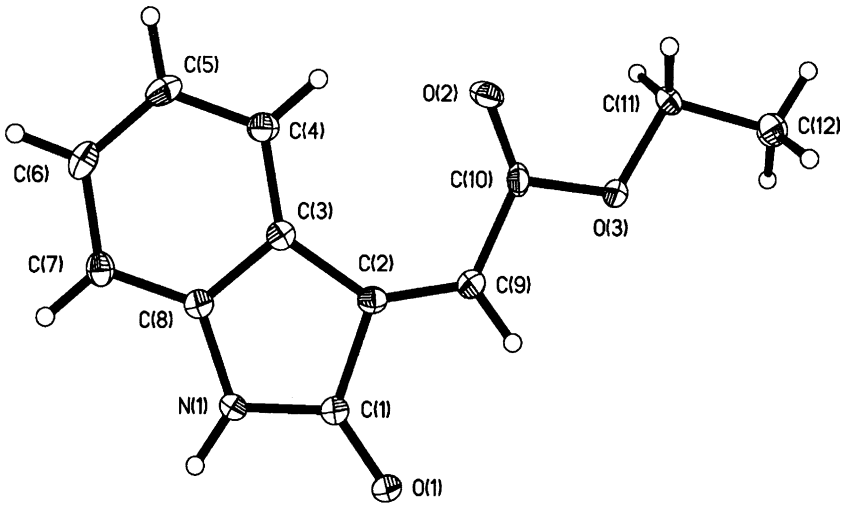
5. Experimental

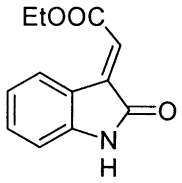
5.1. General

Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. Petroleum ether (60–80 °C) and ethyl acetate were distilled over P_2O_5 and K_2CO_3, respectively prior to use. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrometer. The ^1H NMR and ^{13}C NMR spectra (in $CDCl_3$) were recorded on a Bruker Avance 300 spectrometer at 300 MHz and at 75.5 MHz, respectively using TMS as internal standard. The chemical shifts values are on δ scale and the coupling constants (J) are in Hz. The HRMS determinations were made in FAB positive mode on a JEOL JMS-AX505W high-resolution mass spectrometer using bis-hydroxyethyldisulfide (HEDS) doped with sodium acetate as matrix. All flash chromatographic separations were performed on 100–120 mesh silica gel. Analytical TLCs were performed on Merck silica gel 60 F_{254} plates. Microwave reactions were performed in a domestic microwave oven of 850 W 1.2 Cft (33 L, Infodisplay, Sharp Carosel). Melting points were recorded in a sulphuric acid bath and are uncorrected.

5.2. Preparation of ethyl 2-oxo-3(2*H*)-indolylidene acetate (3)

A mixture of indolin-2,3-dione (**1**, 7.3 g, 50.0 mmol),





3

Diagram 3. X-ray crystallography of **3**.

ethoxycarbonylmethylene-triphenylphosphorane (**2**, 17.3 g, 50.0 mmol) and glacial acetic acid (60 mL) was heated for 4 h at 80 °C.[16] Acetic acid was removed under vacuum, and the residue was washed onto a filter funnel with a small quantity of methanol. Recrystallization from ethanol gave compound **3** (17.6 g, 69%) as an orange solid, mp 168–170 °C (lit.[30] mp 169–170 °C).

5.3. General method for preparation of α,*N*-diphenylnitrones 4a–4j

Phenylhydroxylamine (1 mmol)[31] and appropriately substituted benzaldehydes (1 mmol) were dissolved in ethyl alcohol (20 mL). The reaction mixture was stirred overnight at room temperature when a solid precipitated out; the desired compounds **4a–4j**[18–22] after recrystallization from ethyl alcohol were obtained as crystalline solids in 69–85% yields.

5.3.1. α-(3-Fluorophenyl)-*N*-phenylnitrone (4i). Obtained as a white solid (3.63 g, 74%), mp 100–102 °C (from ethanol); R_f: 0.45 (petroleum ether–ethyl acetate 4:1); ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.46–7.51 (3H, m, C-2H, C-4H and C-6H), 7.58–7.62 (2H, m, C-3H and C-5H), 7.74–7.78 (2H, m, C-2′H and C-5′H), 7.89 (1H, s, α-H) and 8.28 (2H,

Table 2. Anti-tuberculosis activity data of spiroisoxazolidines in Alamar assay at 6.25 μg/mL MIC level

Compound	% Inhibition
5c	5
5d	4
5e	5
5f	8
5i	5
5j	2
6a	16
6b	26
6c	15
6d	27
6e	20
6f	29

Table 3. Effect of Spiroisoxazolidines on invasion of MCF-7/6 Cells in vitro

Compound no.	100 μM	10 μM	1 μM
5a	−	0	0
5b	+	0	0
5c	+	+	−
5d	+	−	−
5e	+	+	−
5f	0	−	−
5g	+	0	0
5h	−	0	0
5i	−	0	0
5j	+	−	−
6a	−	0	0
6b	−	0	0
6c	+	0	0
6d	−	0	0
6e	+	+	0
6f	−	0	0
6g	Toxic	0	0
6h	0	0	0
6i	0	0	0
6j	0	0	0

+, anti-invasive; −, not anti-invasive; 0, not tested.

d, $J=8.6$ Hz, C-4′H and C-6′H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 115.5 (d, $J=24.7$ Hz, C-2′), 118.1 (d, $J=21.7$ Hz, C-4′), 122.0 (C-4), 125.4 (d, $J=2.4$ Hz, C-6′), 129.6 (C-3 and C-5), 130.3 (d, $J=6.9$ Hz, C-5′), 130.5 (C-2 and C-6), 132.9 (d, $J=7.2$ Hz, C-1′), 133.75 (C-α), 149.3 (C-1) and 162.9 (d, $J=245.47$ Hz, C-3′). HRMS Calcd for $C_{13}H_{10}FNO$: 215.0746. Found: 215.0735.

5.4. General method of preparation of spiro-(indoline-3,4′/3,5′-isoxazolidines)

(a) By conventional heating. To a solution of ethyl (3-indolylidene)acetate (**3**, 9.21 mmol) in benzene (50 mL), various substituted α,*N*-diphenylnitrones **4a–4j** (9.21 mmol) were added, and the reaction mixture was heated at 60 °C. Progress of the reaction was monitored by TLC; after 150–180 h, the reaction mixture was concentrated under reduced pressure. Crude products were chromatographed over silica gel using ethyl acetate–petroleum ether as eluent to afford **5a–5j** and **6a–6j** as light yellow solids, which were recrystallized from ethyl acetate–petroleum ether to afford the white to light yellow crystals of regioisomeric spiro derivatives in combined yields of 10–15%.

(b) By microwave method. A mixture of ethyl (3-indolylidene)acetate (**3**, 1.84 mmol) and variously substituted α,*N*-diphenylnitrones **4a–4j** (1.84 mmol) were irradiated in a microwave (850 W 1.2 Cft). The progress of the reaction was monitored by TLC; after irradiating the reaction mixture for 4–5 min (1 min at a time with 10 s interval), the mixture was chromatographed over silica gel using ethyl acetate–petroleum ether as eluent to afford the spiro compounds **5a–5j** and **6a–6j** as light yellow solids, which were recrystallized from ethyl acetate–petroleum ether to afford the white to light yellow crystals of regioisomeric spiro derivatives in combined yields of 35–56%.

5.4.1. 3′-(4-Chlorophenyl)-5′-ethoxycarbonyl-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5a). Obtained as a white solid (188 mg, 22%), mp 158–159 °C (from petroleum ether–ethyl acetate), R_f: 0.34 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3272 (NH), 1737 ($COOC_2H_5$), 1616 (CONH), 1486, 1230, 1078, 1011 and 751 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.80–3.98 (2H, m, $COOCH_2CH_3$), 5.25 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.68 (1H, d, $J=7.7$ Hz, C-7H), 6.93 (1H, t, $J=7.1$ Hz, C-4″H), 7.00–7.13 (6H, m, C-2″H, C-3″H, C-5″H, C-6″H, C-2‴H and C-6‴H), 7.21–7.29 (4H, m, C-5H, C-6H, C-3‴H and C-5‴H), 7.53 (1H, d, $J=7.4$ Hz, C-4H) and 7.78 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.4 ($COOCH_2CH_3$), 61.3 ($COOCH_2CH_3$), 66.3 (C-4′), 77.5 (C-3′), 81.9 (C-5′), 109.3 (C-4″), 115.7 (C-2″ and C-6″), 122.6 (C-7), 123.1 (C-5), 124.6 (C-9), 126.9 (C-6), 127.9 (C-3″ and C-5″), 128.4 (C-2‴ and C-6‴), 128.9 (C-3‴ and C-5‴), 129.2 (C-4), 133.8 (C-8 and C-1‴), 140.0 (C-1″), 150.8 (C-4‴), 165.5 (CONH) and 173.7 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{35}ClO_4$: 448.1190. Found: 448.1205.

5.4.2. 3′-(4-Chlorophenyl)-4′-ethoxycarbonyl-2′-phenyl-spiro[indoline-3,5′-isoxazolidine]-2-one (6a). Obtained as a white solid (280 mg, 33%), mp 159–160 °C (from petroleum ether–ethyl acetate), R_f: 0.37 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3205 (NH), 1729 ($COOC_2H_5$), 1621 (CONH), 1491, 1339, 1192, 1031 and 903 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.69 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.65–3.82 (2H, m, $COOCH_2CH_3$), 4.16 (1H, d, $J=9.5$ Hz, C-4′H), 5.22 (1H, d, $J=9.5$ Hz, C-3′H), 6.87 (1H, d, $J=7.8$ Hz, C-7H), 6.92–6.99 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.09–7.19 (3H, m, C-5H, C-6H and C-4‴H), 7.35 (2H, d, $J=8.4$ Hz, C-2‴H and C-6‴H) and 7.63–7.66 (3H, m, C-4H, C-3‴H and C-5‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.7 ($COOCH_2CH_3$), 61.7 ($COOCH_2CH_3$), 64.8 (C-4′), 71.2 (C-3′), 83.5 (C-5′), 110.9 (C-4″), 117.5 (C-2″ and C-6″), 123.4 (C-7), 123.9 (C-5), 126.0 (C-9), 126.6 (C-6), 129.0 (C-3″ and C-5″), 129.6 (C-2‴ and C-6‴), 129.7 (C-3‴ and C-5‴), 131.1 (C-4), 134.6 (C-1‴), 137.2 (C-8), 141.8 (C-1″), 149.8 (C-4‴), 167.8 (CONH) and 176.0 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{35}ClO_4$: 448.1190. Found: 448.1187.

5.4.3. 3′-(4-Bromophenyl)-5′-ethoxycarbonyl-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5b). Obtained as a light yellow solid (111 mg, 12%), mp 170–171 °C (from petroleum ether–ethyl acetate), R_f: 0.41 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3274 (NH), 1737 ($COOC_2H_5$), 1618 (CONH), 1476, 1399, 1230, 1075 and 750 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 3.80–3.98 (2H, m, $COOCH_2CH_3$), 5.25 (1H, s, C-3′H), 5.30 (1H, s, C-5′H), 6.69 (1H, d, $J=7.7$ Hz, C-7H), 6.93 (1H, t, $J=7.5$ Hz, C-4″H), 7.03–7.10 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.15–7.17 (2H, m, C-2‴H and C-6‴H), 7.23–7.29 (4H, m, C-5H, C-6H, C-3‴H and C-5‴H) and 7.53 (1H, d, $J=7.4$ Hz, C-4′H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.9 ($COOCH_2CH_3$), 61.8 ($COOCH_2CH_3$), 66.7 (C-4′), 78.0 (C-3′), 82.5 (C-5′), 102.9 (C-4″), 109.9 (C-2″ and C-6″), 122.5 (C-9), 123.1 (C-7), 123.6 (C-5), 125.1 (C-1‴), 127.4 (C-6), 128.7 (C-3″ and C-5″), 129.4 (C-2‴ and C-6‴), 129.7 (C-4), 131.9 (C-3‴ and C-5‴), 134.8 (C-8), 140.5 (C-1″), 151.2 (C-4‴), 166.0 (CONH) and 174. 2 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{79}BrO_4$: 492.0685. Found: 492.0670.

5.4.4. 3′-(4-Bromophenyl)-4′-ethoxycarbonyl-2′-phenyl-spiro[indoline-3,5′-isoxazolidine]-2-one (6b). Obtained as a light yellow solid (351 mg, 39%), mp 161–162 °C (from petroleum ether–ethyl acetate), R_f: 0.43 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3426 (NH), 1729 ($COOC_2H_5$), 1619 (CONH), 1474, 1190, 1023 and 755 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.69–3.78 (2H, m, $COOCH_2CH_3$), 4.16 (1H, d, $J=9.4$ Hz, C-4′H), 5.21 (1H, d, $J=9.4$ Hz, C-3′H), 6.85 (1H, d, $J=7.5$ Hz, C-7H), 6.93–6.97 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.09–7.19 (3H, m, C-5H, C-6H and C-4″H) and 7.49–7.60 (5H, m, C-4H, C-2‴H, C-3‴H, C-5‴H and C-6‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.7 ($COOCH_2CH_3$), 61.6 ($COOCH_2CH_3$), 64.8 (C-4′), 71.2 (C-3′), 83.2 (C-5′), 110.5 (C-4″), 117.6 (C-2″ and C-6″), 122.8 (C-1‴), 123.4 (C-7), 123.9 (C-5), 126.0 (C-9), 126.7 (C-6), 128.9 (C-3″ and C-5″), 130.0 (C-2‴ and C-6‴), 131.1 (C-4), 132.5 (C-3‴ and C-5‴), 137.8 (C-8), 141.5 (C-1″), 149.7 (C-4‴), 167.8 (CONH) and 175.2 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2^{79}BrO_4$: 492.0685. Found: 492.0682.

5.4.5. 5′-Ethoxycarbonyl-3′-(4-nitrophenyl)-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5c). Obtained as a light yellow solid (109 mg, 12%), mp 169–170 °C (from petroleum ether–ethyl acetate), R_f: 0.34 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3280 (NH), 1724 ($COOC_2H_5$), 1619 (CONH), 1474, 1344, 1230, 1075 and 834 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.81 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.81–3.99 (2H, m, $COOCH_2CH_3$), 5.26 (1H, s, C-3′H), 5.44 (1H, s, C-5′H), 6.68 (1H, d, $J=7.7$ Hz, C-7H), 6.91–6.94 (1H, m, C-4″H), 7.00–7.10 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.27–7.31 (2H, m, C-2‴H and C-6‴H), 7.47–7.50 (4H, m, C-5H, C-6H, C-3‴H and C-5‴H) and 7.98–8.01 (2H, m, C-4′H and NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 15.9 ($COOCH_2CH_3$), 63.9 ($COOCH_2CH_3$), 68.8 (C-4′), 79.9 (C-3′), 84.7 (C-5′), 111.9 (C-4″), 117.9 (C-2″ and C-6″), 125.3 (C-7), 125.9 (C-5), 126.0 (C-3″ and C-5″), 126.6 (C-9), 129.2 (C-6), 129.8 (C-2‴ and C-6‴), 131.5 (C-3‴ and C-5‴), 132.0 (C-4), 142.4 (C-1‴), 145.4 (C-8), 150.0 (C-1″), 152.9 (C-4‴), 167.6 (CONH) and 175.8 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_3O_6$: 459.1430. Found: 459.1435.

5.4.6. 4′-Ethoxycarbonyl-3′-(4-nitrophenyl)-2′-phenyl-spiro[indoline-3,5′-isoxazolidine]-2-one (6c). Obtained as a light yellow solid (229 mg, 27%), mp 171–172 °C (from petroleum ether–ethyl acetate), R_f: 0.38 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3203 (NH), 1729 ($COOC_2H_5$), 1621 (CONH), 1599, 1472, 1243, 1029 and 855 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.68–3.85 (2H, m, $COOCH_2CH_3$), 4.18 (1H, d, $J=9.2$ Hz, C-4′H), 5.41 (1H, d, $J=9.1$ Hz, C-3′H), 6.90–7.01 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.08 (1H, d, $J=7.3$ Hz, C-4″H), 7.15–7.20 (2H, m, C-5H and C-6H), 7.25–7.31 (1H, m, C-4H), 7.91 (2H, d, $J=8.7$ Hz, C-2‴H and C-6‴H), 8.12 (1H, br s, NH) and 8.26 (2H, d, $J=8.7$ Hz, C-3‴H and C-5‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.2 ($COOCH_2CH_3$), 61.4 ($COOCH_2CH_3$), 64.3 (C-4′), 70.2 (C-3′), 83.0 (C-5′), 110.2 (C-4″), 116.9 (C-2″ and C-6″), 123.0 (C-7), 123.6 (C-5), 124.1 (C-3″ and C-5″), 125.2 (C-9), 126.1 (C-6), 128.6 (C-2‴ and C-6‴), 128.7 (C-3‴ and C-5‴), 130.8 (C-4), 141.1 (C-1‴), 145.8 (C-8), 147.9 (C-1″), 148.7 (C-4‴), 167.1 (CONH) and 174.4 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_3O_6$: 459.1430. Found: 459.1451.

5.4.7. 5′-Ethoxycarbonyl-3′-(4-florophenyl)-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5d). Obtained as a white solid (80 mg, 10%), mp 154–155 °C (from petroleum ether–ethyl acetate), R_f: 0.42 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3277 (NH), 1738 ($COOC_2H_5$), 1617 (CONH), 1473, 1226, 1153, 908 and 754 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 3.80–3.98 (2H, m, $COOCH_2CH_3$), 5.25 (1H, s, C-3′H), 5.33 (1H, s, C-5′H), 6.66 (1H, d, $J=7.6$ Hz, C-7H), 6.77–6.95 (3H, m, C-4″H, C-2‴H and C-6‴H), 7.00–7.12 (5H, m, C-2″H, C-3″H, C-5″H, C-6″H and C-3‴H), 7.23–7.29 (3H, m, C-5H, C-6H and C-5‴H), 7.48 (1H, br s, NH) and 7.54 (1H, d, $J=7.3$ Hz, C-4H); ^{13}C NMR (300 MHz; $CDCl_3$): δ 13.5 ($COOCH_2CH_3$), 61.3 ($COOCH_2CH_3$), 66.5 (C-4′), 77.7 (C-3′), 82.0 (C-5′), 109.3 (C-4″), 115.1 (d, $J=7.2$ Hz, C-6‴), 115.4 (d, $J=22.4$ Hz, C-5‴), 115.9 (C-2″ and C-6″), 122.6 (C-7), 123.2 (C-5), 124.9 (C-9), 127.1 (d, $J=6.9$ Hz, C-2‴), 128.2 (C-6), 128.4 (d, $J=21.8$ Hz, C-3‴), 128.9 (C-3″ and C-5″), 129.2 (C-4), 131.1 (d, $J=2.9$ Hz, C-1‴), 140.1 (C-8), 150.9 (C-1″), 162.3 (d, $J=247.0$ Hz, C-4‴), 165.7 (CONH), 173.9 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}FN_2O_4$: 432.1485. Found: 432.1505.

5.4.8. 4′-Ethoxycarbonyl-3′-(4-florophenyl)-2′-phenyl-spiro[indoline-3,5′-isoxazolidine]-2-one (6d). Obtained as a light yellow solid (348 mg, 43%), mp 149–150 °C (from petroleum ether–ethyl acetate), R_f: 0.45 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3449 (NH), 1729 ($COOC_2H_5$), 1621 (CONH), 1473, 1193 and 754 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.69 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 3.69–3.80 (2H, m, $COOCH_2CH_3$), 4.18 (1H, d, $J=9.5$ Hz, C-4′H), 5.23 (1H, d, $J=9.5$ Hz, C-3′H), 6.88 (1H, d, $J=7.8$ Hz, C-7H), 6.92–6.99 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.04–7.19 (5H, m, C-4H, C-5H, C-6H, C-2‴H and C-6‴H), 7.23–7.29 (1H, m, C-4″H), 7.66–7.70 (2H, m, C-3‴H and C-5‴H) and 7.83 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.7 ($COOCH_2CH_3$), 61.6 ($COOCH_2CH_3$), 64.8 (C-4′), 71.2 (C-3′), 83.2 (C-5′), 110.6 (C-4), 116.1 (d, $J=6.8$ Hz, C-6‴), 116.4 (d, $J=21.8$ Hz, C-5‴), 117.6 (C-2″ and C-6″), 123.4 (C-7), 123.8 (C-5), 126.0 (C-9), 126.6 (d, $J=7.1$ Hz, C-2‴), 128.9 (C-3″ and C-5″), 129.9 (C-6), 130.0 (d, $J=22.6$ Hz, C-3‴), 131.0 (C-4), 134.3 (d, $J=3.1$ Hz, C-1‴), 141.5 (C-8), 149.7 (C-1″), 163.2 (d, $J=247.0$ Hz, C-4‴), 167.8 (CONH) and 175.5 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}FN_2O_4$: 432.1485. Found: 432.1494.

5.4.9. 5′-Ethoxycarbonyl-3′-(4-methylphenyl)-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5e). Obtained as a light yellow solid (123 mg, 15%), mp 155–156 °C (from petroleum ether–ethyl acetate), R_f: 0.46 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 2924 (NH), 1739 ($COOC_2H_5$), 1593 (CONH), 1475, 1401, 1233, 1074 and 742 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 2.17 (3H, s, C_6H_4–CH_3), 3.79–3.97 (2H, m, $COOCH_2CH_3$), 5.25 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.64 (1H, d, $J=7.7$ Hz, C-7H), 6.89–6.93 (3H, m, C-4″H, C-2‴H and C-6‴H), 7.00–7.08 (4H, m, C-3″H, C-5″H, C-6″H and C-2″H), 7.15 (2H, d, $J=8.0$ Hz, C-3‴H and C-5‴H), 7.21–7.24 (2H, m, C-5H and C-6H), 7.39 (1H, br s, NH) and 7.58 (1H, d, $J=7.2$ Hz, C-4H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.9 ($COOCH_2CH_3$), 21.4 ($C_6H_4CH_3$), 61.7 ($COOCH_2CH_3$), 66.9 (C-4′), 78.5 (C-3′), 82.3 (C-5′), 109.6 (C-4″), 116.2 (C-2″ and C-6″), 122.9 (C-7), 123.3 (C-5), 125.5 (C-9), 126.9 (C-3″ and C-5″), 127.5 (C-6), 129.2 (C-4) 129.3 (C-3‴, C-5‴, C-2‴, C-6‴), 132.5 (C-1‴), 138.1 (C-8), 140.5 (C-1″), 151.6 (C-4‴), 166.2 (CONH) and 174. 5 ($COOC_2H_5$); HRMS Calcd for $C_{26}H_{24}N_2O_4$: 428.1736. Found: 428.1725.

5.4.10. 4′-Ethoxycarbonyl-3′-(4-methylphenyl)-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6e). Obtained as a light yellow solid (309 mg, 39%), mp 160–162 °C (from petroleum ether–ethyl acetate), R_f: 0.48 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 2924 (NH), 1728 ($COOC_2H_5$), 1619 (CONH), 1471, 1376, 1243, 1027 and 828 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.69 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 2.34 (3H, s, $C_6H_4CH_3$), 3.63–3.80 (2H, m, $COOCH_2CH_3$), 4.21 (1H, d, $J=9.7$ Hz, C-4′H), 5.20 (1H, d, $J=9.7$ Hz, C-3′H), 6.84

(1H, d, $J=7.7$ Hz, C-7H), 6.92–6.98 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.12–7.23 (6H, m, C-4H, C-5H, C-6H, C-4‴H, C-2‴H and C-6‴H), 7.44 (1H, br s, NH) and 7.58 (2H, d, $J=8.0$ Hz, C-3‴H and C-5‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.7 ($COOCH_2\mathit{C}H_3$), 21.5 ($C_6H_4\mathit{C}H_3$), 61.4 ($COO\mathit{C}H_2CH_3$), 64.9 (C-4′), 71.7 (C-3′), 83.1 (C-5′), 110.4 (C-4″), 117.6 (C-2″ and C-6″), 123.3 (C-7), 123.6 (C-5), 126.2 (C-9), 126.7 (C-6), 128.2 (C-3″ and C-5″), 128.8 (C-2‴ and C-6‴), 130.0 (C-3‴ and C-5‴), 130.9 (C-4), 135.5 (C-1‴), 138.5 (C-8), 141.5 (C-1″), 150.1 (C-4‴), 167.9 (CONH) and 175.5 ($\mathit{CO}OC_2H_5$); HRMS Calcd for $C_{26}H_{24}N_2O_4$: 428.1736. Found: 428.1721.

5.4.11. 3′-(3-Chlorophenyl)-5′-ethoxycarbonyl-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5f). Obtained as a light yellow solid (177 mg, 21%), mp 158–159 °C, (from petroleum ether–ethyl acetate), R_f: 0.35 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3317 (NH), 1741 ($COOC_2H_5$), 1619 (CONH), 1595, 1399, 1230, 1075 and 750 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.81 (3H, t, $J=7.0$ Hz, $COOCH_2C\mathit{H}_3$), 3.80–3.98 (2H, m, $COOC\mathit{H}_2CH_3$), 5.24 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.68 (1H, d, $J=7.7$ Hz, C-7H), 6.91–6.96 (1H, m, C-5‴H), 7.01–7.17 (7H, m, C-2″H, C-3″H, C-4″H, C-5″H, C-6″H, C-2‴H and C-6‴H), 7.25–7.31 (3H, m, C-5H, C-6H and C-4‴H), 7.51 (1H, d, $J=7.4$ Hz, C-4H) and 7.62 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 15.94 ($COOCH_2$-$\mathit{C}H_3$), 63.8 ($COO\mathit{C}H_2CH_3$), 68.8 (C-4′), 80.0 (C-3′), 84.5 (C-5′), 111.75 (C-4″), 117.9 (C-2″ and C-6″), 125.0 (C-7), 125.5 (C-5), 127.0 (C-6), 127.2 (C-9), 129.0 (C-5‴), 129.4 (C-6‴), 130.7 (C-4), 131.4 (C-3″ and C-5″), 131.7 (C-4‴), 131.9 (C-2‴), 136.7 (C-1‴), 140.0 (C-8), 142.4 (C-1″), 153.3 (C-3‴), 167.9 (CONH) and 176.0 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{35}ClO_4$: 448.1190. Found: 448.1182.

5.4.12. 3′-(3-Chlorophenyl)-4′-ethoxycarbonyl-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6f). Obtained as a light yellow solid (272 mg, 33%), mp 159–160 °C (from petroleum ether–ethyl acetate), R_f: 0.38 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3205 (NH), 1729 ($COOC_2H_5$), 1620 (CONH), 1472, 1339, 1292, 1033, 1097 and 841 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, $J=7.1$ Hz, $COOCH_2C\mathit{H}_3$), 3.69–3.82 (2H, m, $COOC\mathit{H}_2CH_3$), 4.17 (1H, d, $J=9.5$ Hz, C-4′H), 5.23 (1H, d, $J=9.5$ Hz, C-3′H), 6.89–6.99 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.05 (1H, d, $J=7.4$ Hz, C-6‴H) 7.15–7.20 (2H, m, C-4″H and C-5‴H), 7.23–7.33 (3H, m, C-5H, C-6H and C-4‴H), 7.60–7.62 (1H, m, C-4H), 7.73 (1H, br s, C-2‴H) and 8.13 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.3 ($COOCH_2\mathit{C}H_3$), 61.3 ($COO\mathit{C}H_2CH_3$), 64.4 (C-4′), 70.6 (C-3′), 82.9 (C-5′), 110.1 (C-4″), 116.8 (C-2″ and C-6″), 123.0 (C-7), 123.3 (C-5), 125.4 (C-9), 125.9 (C-6), 126.3 (C-5‴), 127.8 (C-6‴), 128.6 (C-4, C-3″ and C-5″), 130.2 (C-4‴), 130.6 (C-2‴), 134.8 (C-1‴), 140.5 (C-8), 141.0 (C-1″), 149.4 (C-3‴), 167.2 (CONH) and 174.6 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{35}ClO_4$: 448.1190. Found: 448.1183.

5.4.13. 3′-(3-Bromophenyl)-5′-ethoxycarbonyl-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5g). Obtained as a light yellow solid (83 mg, 9%), mp 160–161 °C (from petroleum ether–ethyl acetate), R_f: 0.36 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3284 (NH), 1739 ($COOC_2H_5$), 1618 (CONH), 1469, 1231, 1073, 753 and 694 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.0$ Hz, $COOCH_2C\mathit{H}_3$), 3.80–3.98 (2H, m, $COOC\mathit{H}_2CH_3$), 5.24 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.69 (1H, d, $J=7.7$ Hz, C-7H), 6.91–7.12 (6H, m, C-2″H, C-3″H, C-5″H, C-6″H, C-2‴H and C-6‴H), 7.19–7.23 (2H, m, C-4″H and C-5‴H), 7.25–7.30 (2H, m, C-5H and C-6H) 7.47–7.51 (2H, m, C-4H and C-4‴H) and 7.89(1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.5 ($COOCH_2\mathit{C}H_3$), 61.4 ($COO\mathit{C}H_2CH_3$), 66.5 (C-4′), 77.6 (C-3′), 82.2 (C-5′), 109.4 (C-4″), 115.5 (C-2″ and C-6″), 122.5 (C-7), 123.1 (C-5), 124.7 (C-9), 125.1 (C-6), 127.0 (C-4), 129.0 (C-3″ and C-5″), 129.3 (C-6‴), 129.6 (C-5‴), 129.8 (C-4‴), 131.2 (C-2‴), 137.9 (C-8 and C-1‴), 140.1 (C-1″), 150.9 (C-3‴), 165.5 (CONH) and 173.8 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{79}BrO_4$: 492.0685. Found: 492.0696.

5.4.14. 3′-(3-Bromophenyl)-4′-ethoxycarbonyl-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6g). Obtained as a light yellow solid (402 mg, 44%) mp 145–146 °C (from petroleum ether–ethyl acetate), R_f: 0.38 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3206 (NH), 1730 ($COOC_2H_5$), 1620 (CONH), 1474, 1338, 1192, 1027 and 834 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, $J=7.0$ Hz, $COOCH_2C\mathit{H}_3$), 3.67–3.84 (2H, m, $COOC\mathit{H}_2CH_3$), 4.20 (1H, d, $J=9.5$ Hz, C-4′H), 5.25 (1H, d, $J=9.5$ Hz, C-3′H), 6.90–7.00 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.04 (1H, d, $J=7.2$ Hz, C-6‴H), 7.15–7.20 (2H, m, C-4″H and C-5‴H), 7.23–7.29 (2H, m, C-5H and C-6H), 7.44–7.47 (1H, m, C-4‴H), 7.65 (1H, d, $J=7.7$ Hz, C-4H), 7.89–7.90 (1H, m, C-2‴H) and 8.47 (1H, br s, NH); ^{13}C NMR (300 MHz; $CDCl_3$): δ 13.7 ($COOCH_2\mathit{C}H_3$), 61.7 ($COO\mathit{C}H_2CH_3$), 64.8 (C-4′), 71.1 (C-3′), 83.6 (C-5′), 110.9 (C-4″), 117.2 (C-2″ and C-6″), 123.4 (C-7), 123.7 (C-5), 125.9 (C-9), 126.6 (C-6), 126.9 (C-4), 129.0 (C-3″ and C-5″), 130.9 (C-6‴), 131.1 (C-5‴), 131.1 (C-4‴), 132.0 (C-2‴), 141.2 (C-8 and C-1‴), 141.7 (C-1″), 149.9 (C-3‴), 167.6 (CONH) and 175.6 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{79}BrO_4$: 492.0685. Found: 492.0704.

5.4.15. 5′-Ethoxycarbonyl-3′-(3-nitrophenyl)-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5h). Obtained as a light yellow solid (123 mg, 12%), mp 165–166 °C (from petroleum ether–ethyl acetate), R_f: 0.28 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3310 (NH), 1741 ($COOC_2H_5$), 1619 (CONH), 1474, 1348, 1231, 1076 and 830 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.81 (3H, t, $J=$ 7.0 Hz, $COOCH_2C\mathit{H}_3$), 3.81–3.99 (2H, m, $COOC\mathit{H}_2CH_3$), 5.28 (1H, s, C-3′H), 5.45 (1H, s, C-5′H), 6.68 (1H, d, $J=$ 7.7 Hz, C-7H), 6.87–6.93 (1H, m, C-5‴H), 7.03–7.10 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H),7.29–7.35 (3H, m, C-5H, C-6H and C-4″H), 7.49 (1H, d, $J=7.3$ Hz, C-4H), 7.63–7.67 (2H, m, C-2‴H and C-6‴H), 7.95–7.98 (1H, m, C-4‴H) and 8.16 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.9 ($COOCH_2\mathit{C}H_3$), 61.9 ($COO\mathit{C}H_2CH_3$), 66.9 (C-4′), 77.9 (C-3′), 82.7 (C-5′), 109.9 (C-4″), 116.0 (C-2″ and C-6″), 121.9 (C-7), 123.2 (C-5), 123.5 (C-6), 123.9 (C-6‴), 124.7 (C-9), 127.2 (C-5‴), 129.5 (C-3″ and C-5″), 129.8 (C-4‴), 129.9 (C-2‴), 132.9 (C-4), 138.5 (C-1‴), 140.4 (C-8), 148.5 (C-1″), 150.9 (C-3‴), 165.7 (CONH) and 173.8 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_3O_6$: 459.1430. Found: 459.1438.

5.4.16. 4′-Ethoxycarbonyl-3′-(3-nitrophenyl)-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6h). Obtained as a light yellow solid (356 mg, 42%), mp 159–160 °C (from petroleum ether–ethyl acetate), R_f: 0.32 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3093 (NH), 1730 ($COOC_2H_5$), 1619 (CONH), 1472, 1351, 1198, 1024 and 906 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.68 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 3.66–3.83 (2H, m, $COOCH_2CH_3$), 4.17 (1H, d, J=9.0 Hz, C-4′H), 5.40 (1H, d, J=9.1 Hz, C-3′H), 6.86–6.97 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.05 (1H, d, J=7.3 Hz, C-4″H), 7.12–7.27 (3H, m, C-5H, C-6H and C-6‴H), 7.55 (1H, t, J=7.9 Hz, C-5‴H), 7.87 (1H, br s, NH), 8.07–8.17 (2H, m, C-4H and C-4‴H) and 8.53 (1H, br s, C-2‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.2 ($COOCH_2CH_3$), 61.4 ($COOCH_2CH_3$), 64.2 (C-4′), 70.3 (C-3′), 83.1 (C-5′), 110.3 (C-4″), 116.9 (C-2″ and C-6″), 122.9 (C-7), 123.0 (C-5), 123.3 (C-6), 123.6 (C-6‴), 125.3 (C-9), 126.1 (C-5‴), 128.6 (C-3″ and C-5″), 129.9 (C-4), 130.8 (C-4‴), 133.8 (C-2‴), 140.8 (C-1‴), 141.1 (C-8), 148.6 (C-1″), 148.8 (C-3‴), 167.1 (CONH) and 174.6 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_3O_6$: 459.1430. Found: 459.1425.

5.4.17. 5′-Ethoxycarbonyl-3′-(3-florophenyl)-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5i). Obtained as a light yellow solid (93 mg, 11%), mp 169–170 °C (from petroleum ether–ethyl acetate), R_f: 0.35 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3296 (NH), 1741 ($COOC_2H_5$), 1615 (CONH), 1484, 1379, 1296, 1024 and 904 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 3.81–3.98 (2H, m, $COOCH_2CH_3$), 5.24 (1H, s, C-3′H), 5.35 (1H, s, C-5′H), 6.67 (1H, d, J=7.7 Hz, C-7H), 6.78–6.80 (1H, m, C-4″H), 6.92 (1H, t, J=7.0 Hz, C-5‴H), 7.04–7.06 (7H, m, C-4H, C-2″H, C-3″H, C-5″H, C-6″H, C-4‴H and C-6‴H), 7.26–7.30 (2H, m, C-5H and C-6H) and 7.50–7.52 (2H, m, C-2‴H and NH); ^{13}C NMR (300 MHz; $CDCl_3$): δ 13.6 ($COOCH_2CH_3$), 61.4 ($COOCH_2CH_3$), 66.5 (C-4′), 77.7 (C-3′), 82.2 (C-5′), 109.4 (C-4″), 113.7 (d, J=2.9 Hz, C-6‴), 115.1 (d, J=8.2 Hz, C-5‴), 115.6 (C-2″ and C-6″), 122.1 (d, J=22.9 Hz, C-4‴), 122.7 (C-7), 123.2 (C-5), 124.8 (C-9), 127.8 (C-6), 129.0 (C-3″ and C-5″), 129.3 (C-4), 129.9 (d, J=22.4 Hz, C-2‴), 138.3 (d, J=7.9 Hz, C-1‴), 140.2 (C-8), 151.0 (C-1″), 162.7 (d, J=246.8 Hz, C-3‴), 165.6 (CONH) and 173.9 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}FN_2O_4$: 432.1485. Found: 432.1492.

5.4.18. 4′-Ethoxycarbonyl-3′-(3-florophenyl)-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6i). Obtained as a light yellow solid (185 mg, 23%), mp 144–145 °C (from petroleum ether–ethyl acetate), R_f: 0.38 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3210 (NH), 1730 ($COOC_2H_5$), 1618 (CONH), 1473, 1341, 1229, 1132, 1090 and 961 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.71 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 3.67–3.80 (2H, m, $COOCH_2CH_3$), 4.19 (1H, d, J=9.3 Hz, C-4′H), 5.27 (1H, d, J=9.3 Hz, C-3′H), 6.87 (1H, d, J=7.7 Hz, C-7H), 6.90–7.01 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.03–7.08 (2H, m, C-4″H and C-5‴H), 7.14–7.19 (2H, m, C-5H and C-6H), 7.31–7.38 (1H, m, C-4‴H) and 7.42–7.50 (3H, m, C-4H, C-2‴H and C-6‴H); ^{13}C (75.5 MHz; $CDCl_3$): δ 13.3 ($COOCH_2CH_3$), 61.3 ($COOCH_2CH_3$), 64.4 (C-4′), 70.7 (C-3′), 83.1 (C-5′), 110.3 (C-4″), 114.8 (d, J=2.9 Hz, C-6‴), 115.4 (d, J=8.0 Hz, C-5‴), 116.9 (C-2″ and C-6″), 123.0 (C-7), 123.3 (C-5), 123.4 (d, J=22.6 Hz, C-4‴), 125.5 (C-9), 126.3 (C-6), 128.6 (C-3″ and C-5″), 130.5 (d, J=21.2 Hz, C-2‴),130.7 (C-4), 141.1 (d, J=6.4 Hz, C-1‴), 141.2 (C-8), 149.4 (C-1″), 162.9 (d, J=246.7 Hz, C-3‴), 167.4 (CONH) and 175.0 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}FN_2O_4$: 432.1485. Found: 432.1464.

5.4.19. 5′-Ethoxycarbonyl-3′-(3-methylphenyl)-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5j). Obtained as a light yellow solid (126 mg, 15%), mp 158–160 °C (from petroleum ether–ethyl acetate), R_f: 0.32 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3304 (NH), 1733 ($COOC_2H_5$), 1617 (CONH), 1378, 1227, 1076 and 750 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 2.17 (3H, s, $C_6H_4CH_3$), 3.80–3.98 (2H, m, $COOCH_2CH_3$), 5.24 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.64 (1H, d, J=7.7 Hz, C-7H), 6.87–7.00 (3H, m, C-4″H, C-5‴H and C-6‴H), 7.03–7.10 (5H, m, C-2″H, C-3″H, C-5″H, C-6″H and C-2‴H), 7.22–7.28 (3H, m, C-5H, C-6H and C-4‴H) and 7.54–7.56 (2H, m, C-4H and NH); δ (75.5 MHz; $CDCl_3$) 13.9 ($COOCH_2CH_3$), 21.6 ($C_6H_4CH_3$), 61.6 ($COOCH_2CH_3$), 67.0 (C-4′), 78.6 (C-3′), 82.4 (C-5′), 109.6 (C-4″), 116.0 (C-2″ and C-6″), 122.7 (C-7), 123.2 (C-5), 124.0 (C-6), 125.5 (C-9), 127.5 (C-5‴), 127.6 (C-6‴), 128.4 (C-4‴), 129.1 (C-3″ and C-5″), 129.2 (C-2‴), 129.4 (C-4), 135.6 (C-1‴), 138.2 (C-8), 140.7 (C-1″), 151.7 (C-3‴), 166.2 (CONH) and 174.8 ($COOC_2H_5$); HRMS Calcd for $C_{26}H_{24}N_2O_4$: 428.1736. Found: 428.1720.

5.4.20. 4′-Ethoxycarbonyl-3′-(3-methylphenyl)-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6j). Obtained as a light yellow solid (287 mg, 36%), mp 139–140 °C (from petroleum ether–ethyl acetate), R_f: 0.35 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3216 (NH), 1732 ($COOC_2H_5$), 1618 (CONH), 1470, 1377, 1293, 1110, 1051 and 906 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 2.37 (3H, s, $C_6H_4CH_3$), 3.64–3.81 (2H, m, $COOCH_2CH_3$), 4.24 (1H, d, J=9.7 Hz, C-4′H), 5.22 (1H, d, J=9.7 Hz, C-3′H), 6.87–6.97 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.07–7.17 (4H, m, C-5H, C-6H, C-4″H and C-5‴H), 7.22–7.29 (2H, m, C-4‴H and C-6‴H), 7.48–7.54 (2H, m, C-4H and C-2‴H) and 8.00 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.2 ($COOCH_2CH_3$), 21.3 ($C_6H_4CH_3$), 61.0 ($COOCH_2CH_3$), 64.5 (C-4′), 71.3 (C-3′), 82.9 (C-5′), 110.1 (C-4″), 116.8 (C-2″ and C-6″), 122.8 (C-7), 122.9 (C-5), 124.9 (C-6), 125.7 (C-9), 126.3 (C-4), 128.2 (C-6‴), 128.3 (C-3″ and C-5″), 128.7 (C-5‴), 129.0 (C-4‴), 130.5 (C-2‴), 138.1 (C-1‴), 138.6 (C-8), 141.1 (C-1″), 149.8 (C-3‴), 167.3 (CONH) and 175.1 ($COOC_2H_5$); HRMS Calcd for $C_{26}H_{24}N_2O_4$: 428.1736. Found: 428.1718.

6. X-ray crystallography

The crystallographic measurements on compounds **3**, **5a** and **6c** were made using a Siemens SMART area-detector diffractometer. Graphite monochromated Mo-K_α radiation was used in all cases. The structures were solved using SHELXTL-PLUS[32] and refined with SHELXL-96.[33]

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