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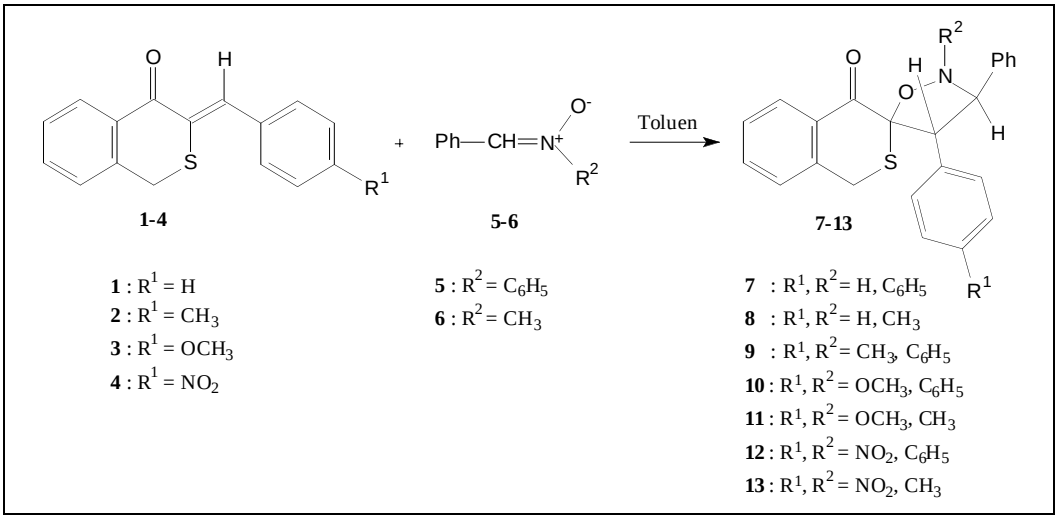

A series of seven new 2',3',4'-substituted spiro[isothiochromene-3,5'-isoxazolidin]-4(1*H*)-ones (**7-13)** has been prepared in the reaction of benzylidene(phenyl)azane oxide (**5**) or benzylidene(methyl)azane oxide (**6**) with (3*Z*)-3-(4-substituted-benzylidene)-1*H*-isothio- chromen-4(3*H*)-one (**1-4**). The reaction occurs by a 1,3-dipolar cycloaddition mechanism that leads to the regiospecific formation of various spiro-isoxazolidines (**7**-**13**).

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Spiro-isoxazolines derivatives have emerged in recent years as candidates for drugs due to their herbicidal, plant-growth regulatory and antitumor activity [1,2]. We have recently investigated the antitubercular activity [3] and anti-breast cancer activity [4] of some spiro-isoxazolines derivatives. The results suggest that spiro-isoxazolines-based compounds may become potent drugs in those areas.

Our group performed also antimicrobial screening of imidazo[1,2-*a*]pyrimidines, in collaboration with Tuberculosis Antimicrobial Acquisition Facility (**TAACF**) of USA. These studies have shown that compounds bearing a formyl-, hydroxyl- or nitrosyl- side chain in position 3 are highly active as antitubercular agents [5] as well as antibacterial agents [6].

General structure/activity relationship observations allowed us to suggest that functionalized side chain(s) characterized by groups such as [O=N-C-N] or [O-C-C-N] are crucial for the bioactivity of certain chemical compounds. The two terminal heteroatoms (O and N) are critical for the interactions with the bacterial cell receptor, therefore are responsible for antimicrobial activities (Figure 1). These interactions usually have precise geometric requirements, which may be described in terms of the distance between the two terminal heteroatoms and their spatial orientation in the pharmacophore.

In this paper we describe our efforts to extend the methodology of the synthesis of pharmacologically important spiro-isoxazolidines. The development of a short and convergent approach to the synthesis allowed us to synthesise derivatives **7-13** (Scheme 1), which will be subjected to further pharmacological investigations. In particular they will be tested against *Mycobacterium Tuberculosis* bacteria and cancer.

In our earlier studies of the 1,3-dipolar cycloaddition reactions, we investigated the action of diaryl-nitrilimines on dihydroquinoleines [7], indene [8] and the benzopyran-4-ones [9] in which the site of dipolarophiles is endocyclic. We also studied the regio- and the stereo-chemistry of the reaction of diaryl-nitrilimines with the 2-aryliden-indan-1-ones [10], 3-aryliden-tetraline-4-ones [11,12], 3-aryliden-isothiochroman-4-ones [13] and lately some isoquinolones [14], where the site of the dipolarophiles is exocyclic.

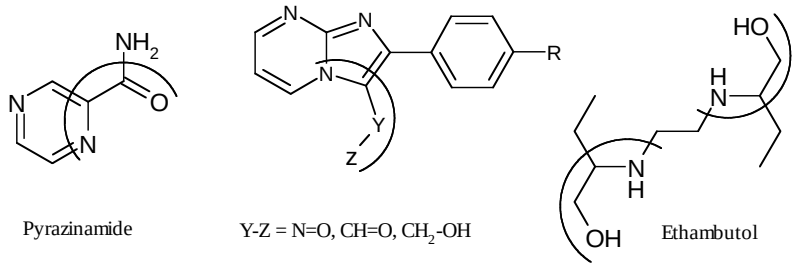


Figure 1. Structure of some clinical antitubercular agents (Pyrazinamide and Ethambutol)

In this work dipolarophiles **1-4** have been prepared by a simple condensation of a *para*-substituted-benzaldehydes with the isothiochroman-4-ones in an acidic environment [15].

1,3-Dipolar cycloaddition of compounds **1-4** with **5-6** in refluxing toluene yielded the corresponding spiro-isooxazolines **7-13** in (30%-45%) yield (Scheme 1).

Compounds **7-13** were characterized using ^{1}H and ^{13}C NMR methods. The ^{1}H NMR data of **7-13** reveals the presence of two protons at 3.5 and 4.6 ppm, as well as two H^{1},$H^{1'}$ protons of the thiopyranic ring (with a J of approximately 16.5 Hz). There are also two others doublets that appear at (4.4-5.1) ppm and (5.2-5.5) ppm respectively, with a J about 10.7-11.0 Hz. These have been attributed to the $H^{3'}$, $H^{4'}$ protons of the isoxazolidine ring (Table 1).

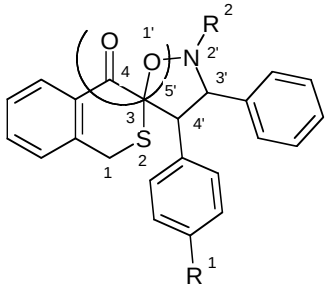


Figure 2. Spiro-isoxazolidine skeleton containing a rigid pharmacophore site (O=C-C-O).

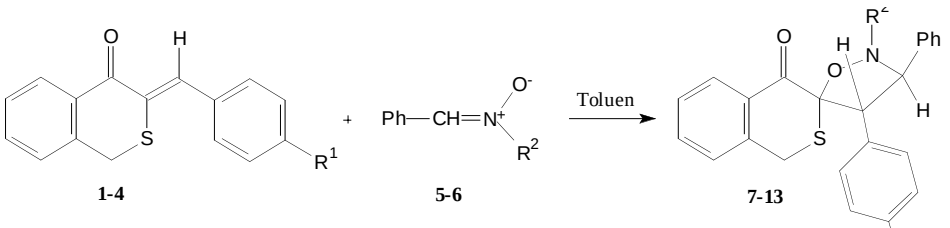
The ^{1}H NMR spectrum confirms that those two $H^{3'}$, $H^{4'}$ protons are positioned on two adjacent carbon atoms $C^{3'}$, $C^{4'}$. The oxygen atom of dipolar precursors **5-6** is fixed at the most substituted carbon atom of dipolarophiles **1-4**. This regiochemistry has been generally observed for reaction of nitrones and asymetric ethylenic dipolarophiles [16-23] and the obtained spiranic products are always the 2'-methyl(phenyl)-3'-phenyl-4'-arylspiro-[isothio-chromene-3,5'-isoxazolidin]- 4(1*H*)-ones **7-13**,

In all cases regio-chemistry was always observed during 1,3-dipolar cycloaddition of nitrones to dipolarophiles leading to the isoxazolidines [25-28]. We have observed this feature in the case of benzopyran-4-one [9] and of the isoquinolone derivatives [14,24].

In this work the value of the chemical displacement of the atom at spiranic carbon is between 91.6 and 91.8 ppm, what is in good agreement with proposed structures **7-13** [13,24]. Mass spectrometry studies of compounds **7-13** have also been done to validate products of the synthesis.

Stereochemistry. An examination of the theoretical models allowed us to visualise four possible conformations of these spiro-compounds (Figure 3).

The analysis of ^{1}H NMR parameters allowed us to propose the conformation of compounds **7-13** while exploiting the effect of solvent ($\Delta\delta = \delta\ CDCl_3 - \delta\ C_6D_6$) based on the signals of $H^{3'}$ and $H^{4'}$ protons. These observations are also in favour of the *trans* position of the



1-4 **5-6** **7-13**

1 : R^1 = H
2 : R^1 = CH_3
3 : R^1 = OCH_3
4 : R^1 = NO_2

5 : R^2 = C_6H_5
6 : R^2 = CH_3

7 : R^1, R^2 = H, C_6H_5
8 : R^1, R^2 = H, CH_3
9 : R^1, R^2 = CH_3, C_6H_5
10 : R^1, R^2 = OCH_3, C_6H_5
11 : R^1, R^2 = OCH_3, CH_3
12 : R^1, R^2 = NO_2, C_6H_5
13 : R^1, R^2 = NO_2, CH_3

Scheme 1 Synthesis of spiro-compounds **7-13**

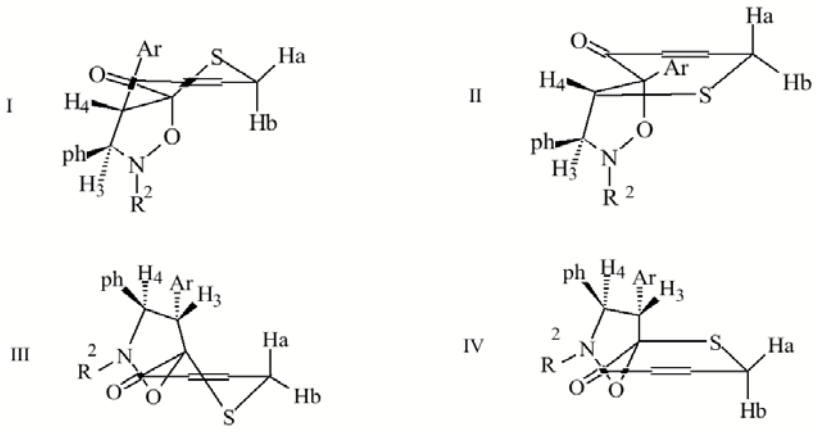


Figure 3

$H^{3'}$ and $H^{4'}$ protons (Figure 1), what is in agreement with data found in the literature [11,24].

NMR studies of compounds 7-13. Replacing the R^1 substituent of the external phenyl group at position $C^{4'}$ of the isoxazolidine ring by an H, OCH_3 or NO_2 group, (see compounds **7**, **10** and **12)** does not significantly affect the structure of the molecule. ^1H and ^{13}C NMR data of these derivatives are similar to those of derivative **9** and are in agreement with the proposed spiro-oxazolidine structure (Table 1).

The impact of different groups at R^1 and R^2 positions is obvious when looking at the ^1H NMR chemical shifts of hydrogen atoms $H^{3'}$ and $H^{4'}$ of the isoxazolidine ring. In contrast to hydrogen atoms $H^{3'}$ and $H^{4'}$ of the isoxazolidine ring, the two hydrogen atoms H^a and H^b of the iso-thiochroman-4-one ring are non-sensitive to the change of R^1 and R^2 moieties. As expected, the hydrogen atoms of the oxazolidine ring are more strongly influenced by the R^1 moiety ($\delta H^{3'}$ = 4.5 ppm for **8** and ($\delta H^{3'}$ = 5.5 ppm for **12**) than the R^2 group ($\delta H^{4'}$ = 5.1 ppm

Table 1

^1H NMR data of compounds **7-13** ($CDCl_3$, δ ppm/ TMS, J Hz)

Chemical Structure			IR	^1H NMR (δppm/ $CDCl_3$, TMS, J Hz)						
Pdt.	R^1	R^2	ν (CO) cm^{-1}	δ R^1	δ R^2	δ H^a	δ H^b	δ $H^{3'}$	δ $H^{4'}$	δ $H_{Ar.}$
7	H	C_6H_5	1670	-	-	3.5 (d, 1H) J = 16,7	4.6 (d, 1H)	5.4 (d, 1H) J = 10,7	5.1 (d, 1H)	7.0 – 8.2 (m, 19H)
8	H	CH_3	1680	-	2.8 (s, 3H)	3.5 (d, 1H) J = 16,7	4.6 (d, 1H)	4.5 (d, 1H) J = 10,8	5.5 (d, 1H)	6.8 – 8.2 (m, 14H)
9	CH_3	C_6H_5	1670	2.3 (s, 3H)	-	3.5 (d, 1H) J = 16,5	4.6 (d, 1H)	5.3 (d, 1H) J = 10,9	5.1 (d, 1H)	7.0 – 8.2 (m, 18H)
10	OCH_3	C_6H_5	1680	3.7 (s, 3H)	-	3.5 (d, 1H) J = 16,5	4.6 (d, 1H)	5.3 (d, 1H) J = 10,8	5.1 (d, 1H)	6,8-8,2 (m, 18H)
11	OCH_3	CH_3	1680	3.7 (s, 3H)	2.8 (s, 3H)	3.5 (d, 1H) J = 16.7	4.6 (d, 1H)	5.2 (d, 1H) J = 11.0	4.4 (d, 1H)	6.8 – 8.2 (m,13H)
12	NO_2	C_6H_5	1683	-	-	3.5 (d, 1H) J = 16.7	4.6 (d, 1H)	5.3 (s, 2H)		6.9 – 8.2 (m, 18H)
13	NO_2	CH_3	1681	-	2.8 (s, 3H)	3.6 (d, 1H) J = 16.5	4.7 (d, 1H)	5.5 (d, 1H) J = 11.0	4.5 (d, 1H)	7.1- 8.6 (m, 13H)

for **10** and 4.4 ppm for **11**). Protons H^a and H^b of the methylene groups are not affected by either R^1 or R^2 substituents.

The observed changes in chemical shifts of oxazolidine-ring protons (from 4.5 to 5.5 ppm) suggests that various electron-acceptor and/or electron-donor substituents may be used for tuning the electron density on nitrogen and oxygen sp^3 hybridized atoms of these potential therapeutic agents. In the future we are planning to introduce different substituents at positions R^1 and R^2 for greater tuning of the spiroderivatives properties.

performed to obtain more evidence. Crystal structure of compound **9** (R^1 = *para*-methyl-phenyl and R^2 = phenyl) allowed us to confirm that the two $H^{3'}$ and $H^{4'}$ hydrogen atoms adopt *trans* positions (Figure 4). Compound **9** contains an isoxazolidine ring in a twist conformation with the spiro- C atom [0.404 (2) Å] and the adjacent carbon atom [0.266 (2) Å] deviating from the plane of the remaining three atoms. The thiapyran ring adopts a sofa conformation, with the five carbon atoms in the same plane (r.m.s.d. = 0.033 Å) and the sulphur atom deviating by 0.984(2) Å from this plane [29].

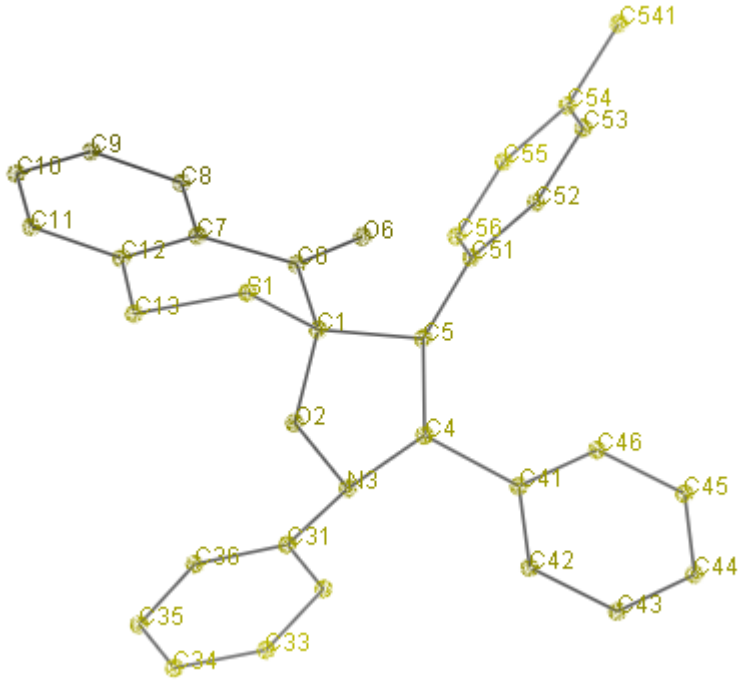


Figure 4. ORTEP of compound **9** [29]. The protons have been omitted for the clarity.

Table 2

^{13}C NMR data of compounds **7-13** ($CDCl_3$, δ ppm/ TMS)

Chemical Structure			Selected data ($CDCl_3$, δ pm/ TMS)						
Pdt.	R^1	R^2	δ R^1	δ R^2	δ $C^{1'}$	δ C^4	δ C^3	δ $C^{5;3'}$	δ $C^{4'}$
7	H	C_6H_5	-	-	28.00	61.20	73.50	91.60	185.80
8	H	CH_3	-	21.30	27.70	60.10	73.40	91.60	186
9	CH_3	C_6H_5	21.20	-	27.90	61	73.30	91.70	184
10	OCH_3	C_6H_5	55.20	-	28.00	60.80	73.40	91.60	184.10
11	OCH_3	CH_3	55.20	21.90	27.70	60.75	73.40	91.70	185.90
12	NO_2	C_6H_5	-	-	27.90	61.30	74.30	91.80	184.20

Although the ^1H NMR results and, in particular, the value of the ^3J coupling constant ($H^{3'}$-$H^{4'}$) suggests a *trans*-disposition of the two $H^{3'}$ and $H^{4'}$ protons, an X-Ray diffraction study of one of the compounds **7-13** was

CONCLUSION

We have shown that 2'-, 3'- and 4'-substituted spiro-isoxazolidines **7-13** bearing alkyl or aryl moieties, exist in

spiranic forms in both the solution and the solid state. The rigid three bonds pharmacophore system (O=C-C-O) observed in compounds **7-13** is of major interest for the design of new drugs [6]. Further screening studies are currently in progress in order to elucidate the structure/activity relationships of these derivatives on the basis of functionalization of thiachroman-4-one with electron-donating and withdrawing groups. We are also planning to examine chemical interactions of similar bis-bidentate O,O-ligands with transition metals.

EXPERIMENTAL

NMR spectra (^{1}H, ^{13}C) were recorded on a Bruker Spectrospin (operating at 80 MHz) (Université Paul Sabatier, Toulouse), or on a Brüker AC 200 (operating at 200 MHz) spectrometer (Université de Franche-Compté, Besançon, France). NMR data are listed in ppm and are reported relative to tetramethylsilane (^{1}H, ^{13}C), residual solvent peaks being used as internal standard with external calibration. Infra-red spectra were recorded in KBr pellets using a Beckman 310 spectrometer. Mass spectra were recorded on a Hewlett-Packard 5989A Mass Spectrometer (70 eV) and elemental analysis (CNRS, Université Paul Sabatier, Toulouse, France).

General Procedure of the Preparation of spiroisoxazolines 7-13. Under atmospheric nitrogen, a suspension of (3*Z*)-3-(4-arylidene)-1*H*-isothiochromene-4(3*H*)-one **1-4** (5 mmol) was stirred in dry toluene (25 ml) at room temperature. A mixture of *p*-substituted-benzaldoxime **5-6** (5 mmol) and toluene (25 ml) was added portion by portion over 10 min. The mixture was stirred and refluxed for 12 h until TLC indicated that both precursors have been consumed. After removing toluene, the compounds **7-13** were dissolved in ethanol to eliminate non reacting traces of precursors then precipitated or crystallised for **9** in ethylic ether to yield **7-13** (30-50%) yield as a white precipitate or crystals for **9**.

2',3',4'-Triphenylspiro[isothiochromene-3,5'-isoxazolidin]-4(1*H*)-one (7). This compound was obtained as white powder, mp 158-159°, ir: CO 1670 cm^{-1}; ^{1}H nmr (selected data): δ 3.50 (d, 1H), 4.60 (d, 1H, CH^{21}, J = 16.70 Hz), 5.10 (d, 1H), 5.40 (d, 1H, CH$^{3',4'}$, J = 10.7 Hz), 7.00-8.20 ppm (m, 19H aromatic), ^{13}C nmr (selected data): C^1 (28.00), C$^{4'}$ (61.20), C$^{3''}$ (73.50), C$^{5',3}$ (91.30), C$^{4'}$ (185.80); ms: m/z : 449 (M$^+$ or $C_{29}H_{23}NO_2S^+$). *Anal.* Calcd. For $C_{29}H_{23}NO_2S$: C, 77.48; H, 5.16; N, 3.12. Found: C, 77.32; H, 5.03; N, 3.19.

2'-Methy-3',4'-diphenylspiro[isothiochromene-3,5'-isoxazolidin]-4(1*H*)-one (8). This compound was obtained as white powder, mp 168-170°, ir: CO 1680 cm^{-1}. ^{1}H nmr: δ 2.80 (s, 3H, OCH_3), 3.50 (d, 1H), 4.60 (d, 1H, CH^{21}, J = 16.50 Hz), 4.50 (d, 1H), 5.50 (d, 1H, CH$^{3',4'}$, J = 10.80 Hz), 6.80-8.20 (m, 14H aromatic). ^{13}C nmr (selected data): CH^3 (21.30), C1 (27.70), C$^{4'}$ (60.10), C$^{3''}$ (73.40), C$^{5',3}$ (91.60), C$^{4'}$ (186.00), ms: m/z : 387 (M$^+$ or $C_{24}H_{21}NO_2S^+$). *Anal.* Calcd. For $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46; N, 3.61. Found: C, 73.95; H, 5.39; N, 3.35.

2',3'-Diphenyl-4'(4-methylphenyl)spiro[isothiochromene-3,5'-isoxazolidin]-4(1*H*)-one (9). This compound was obtained as white powder, mp 155-157°, ir: CO 1670 cm^{-1}. ^{1}H nmr: δ 2.30 (s, 3H, CH_3), 3.50 (d, 1H), 4.60 (d, 1H, CH^{21}, J = 16.50 Hz), 5.10 (d, 1H), 5.30 (d, 1H) CH$^{3',4'}$, J = 10.90 Hz), 7.00-8.20 (m, 18H aromatic). ^{13}C nmr (selected data): CH_3 (21.20), C1 (27.90), C$^{4'}$ (61.00), C$^{3''}$ (73.30), C$^{5',3}$ (91.70), C$^{4'}$ (184.00), ms: m/z : 463 (M$^+$ or $C_{30}H_{25}NO_2S^+$). *Anal.* Calcd. For $C_{36}H_{25}NO_2S$: C, 77.72; H, 5.44; N, 3.02. Found: C, 77.53; H, 5.37; N, 2.98.

2',3'-Diphenyl-4'(4-methoxlphenyl)spiro[isothiochromene-3,5'-isoxazolidin]-4(1*H*)-one (10). This compound was obtained as white powder, mp 187-189°, ir: CO 1680 cm^{-1}. ^{1}H nmr: δ 3.70 (s, 3H, OCH_3), 3.50 (d, 1H), 4.60 (d, 1H, CH^{21}, J = 16.50 Hz), 5.10 (d, 1H), 5.30 (d, 1H, CH$^{3',4'}$, J = 10.90 Hz), 6.80-8.20 ppm (m, 18H aromatic). ^{13}C nmr (selected data): CH_3 (28.00), C^1(27.90), C$^{4'}$ (60.80), C$^{3''}$ (73.40), C$^{5',3}$ (91.60), C$^{4'}$ (184.10). ms: m/z 479 (M$^+$ or $C_{30}H_{25}NO_3S^+$). *Anal.* Calcd. For $C_{30}H_{25}NO_3S$: C, 75.13; H, 5.25; N, 2.92. Found: C, 74.97; H, 5.19; N, 2.85.

2'-Methyl-3'-phenyl-4'(4-methoxylphenyl)spiro[isothiochromene-3,5'-isoxazolidin]-4(1*H*)-one (11). This compound was obtained as white powder, mp 153-154 °, ir: CO 1680 cm^{-1}. ^{1}H nmr: δ 2.80 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.50 (d, 1H), 4.60 (d, 1H, CH21, J = 16.70 Hz), 4.40 (d, 1H), 5.20 (d, 1H, CH$^{3',4'}$, J = 11.00 Hz), 6.80-8.20 ppm (m, 13H aromatic). ^{13}C nmr (selected data): OCH_3 (55.20), CH_3 (21.90), C^1 (27.70), C$^{4'}$ (60.75), C$^{3''}$ (73.40), C$^{5',3}$ (91.70), C$^{4'}$ (185.90). ms: m/z 417 (M$^+$ or $C_{25}H_{23}NO_3S^+$). *Anal.* Calcd. For $C_{25}H_{23}NO_3S$: C, 71.92; H, 5.55; N, 3.35. Found: C, 72.03; H, 5.63; N, 5.49.

2',3'-Diphenyl-4'-(4-nitropheny)lspiro[isothiochromene-3,5'-isoxazolidin]-4(1*H*)-one (12). This compound was obtained as white powder, mp 145-146 °, ir: CO 1683 cm^{-1}. 1H nmr: δ 3.50 (d, 1H), 4.60 (d, 1H, CH^{21}, J = 16.70 Hz), 5.30 (s, 2H), 6.90-8.20 ppm (m, 18H aromatic). ^{13}C nmr (selected data): C^1 (27.90), C$^{4'}$ (61.30), C$^{3''}$ (74.30), C$^{5',3}$ (91.80), C$^{4'}$ (184.20). ms: m/z : 494 (M$^+$ or $C_{29}H_{22}N_2O_4S^+$). *Anal.* Calcd. For $C_{29}H_{22}N_2O_4S$: C, 70.43; H, 4.48; N, 5.66. Found: C, 70.25; H, 4.52; N, 5.58.

2'-Methyl-3'-phenyl-4'(4-nitrophenyl)spiro[isothiochromene-3,5'-isoxazolidin]-4(1*H*)-one (13). This compound was obtained as white powder, mp 140-141°, ir CO 1681 cm^{-1}. ^{1}H nmr: δ 2.80 (s, 3H, CH_3), 3.60 (d, 1H), 4.70 (d, 1H, CH^{21}, J = 16.70), 4.50 (d, 1H), 5.50 (d, 1H, CH$^{3',4'}$, J = 11.00), 7.10-8.60 ppm (m,13H aromatic). ms: m/z : 432 (M$^+$ or $C_{24}H_{20}N_2O_4S^+$). *Anal.* Calcd. For $C_{24}H_{20}N_2O_4S$: C, 66.65; H, 4.66; N, 6.48. Found: C, 67.03; H, 4.54; N, 6.39.

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