

Drug design of new antitubercular agents: 1,3-dipolar cycloaddition reaction of *para*-substituted-benzadoximes and 3-*para*-methoxy-benzyliden-isochroman-4-ones

Ghali Al Houari,^a Abdelali Kerbal,^{a*} Brahim Bennani,^a Mohamed F. Baba,^a Maria Daoudi,^a and Taibi Ben Hadda^{b*}

^aLaboratoire de Chimie Organique, Département de Chimie, Faculté des Sciences Dhar El Mehraz, Université Sidi Mohammed Ben Abdellah, 30000 Fès, Morocco

^bLaboratoire Chimie des Matériaux, Département de Chimie, Faculté des Sciences, Université Mohammed Premier, 60000 Oujda, Morocco

E- mails: kerbal_abdelali@yahoo.fr; tbenhadda@yahoo.com

Abstract

Five new 3',4'-substituted-spiro[isochromene-3,5'-isoxazolin]-4(1H)-ones **7-11** have been prepared in the reaction of *p*-R-benzadoxime **2-6** with 3-*para*-methoxy-benzylidene-isochroman-4-one **1**. The reaction occurs by a 1,3-dipolar cycloaddition mechanism which leads to the regiospecific formation of various spiro-isoxazolines **7-11**. It is concluded that rigid (O^{1'}-C-O^{2'}) group may be responsible for the biological activity observed in antitubercular test with these hyper inter-organised spiro-isoxazoline derivatives. However, subtle alteration by addition of a substituted aryl groups affecting the charge distribution of the terminal heteroatom O^{1'} confers significant improvements in biological effects.

Keywords: Spiroisoxazoline, 1,3-dipolar cycloaddition, tuberculosis, pharmacophore site

Introduction

The spiroisoxazolines 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 activity³ and anti-breast cancer activity⁴ of some spiroisoxazolines derivatives. The results suggest that spiro-isoxazolines-based compounds may become potent drugs in man of those areas.

Our group performed also antimicrobial screening of 3-substituted-imidazo[1,2-a]pyrimidine derivatives. These studies have shown that compounds bearing a formyl-, hydroxyl- or nitroso-

side chains in position 3 are highly active as antitubercular agents⁵ 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 [N-C-N=O], [N-C-C-O] or [N-C-C=O] are crucial for the bioactivity of certain chemical compounds. The two terminal atoms (N and O) are critical for the interactions with the bacterial cell receptor, therefore are responsible for antimicrobial activities, in particularly against *Mycobacterium Tuberculosis* (MBT). These interactions have usually precise geometric requirements, which may be described in terms of the distances between the atoms and their mutual orientation in the pharmacophore.

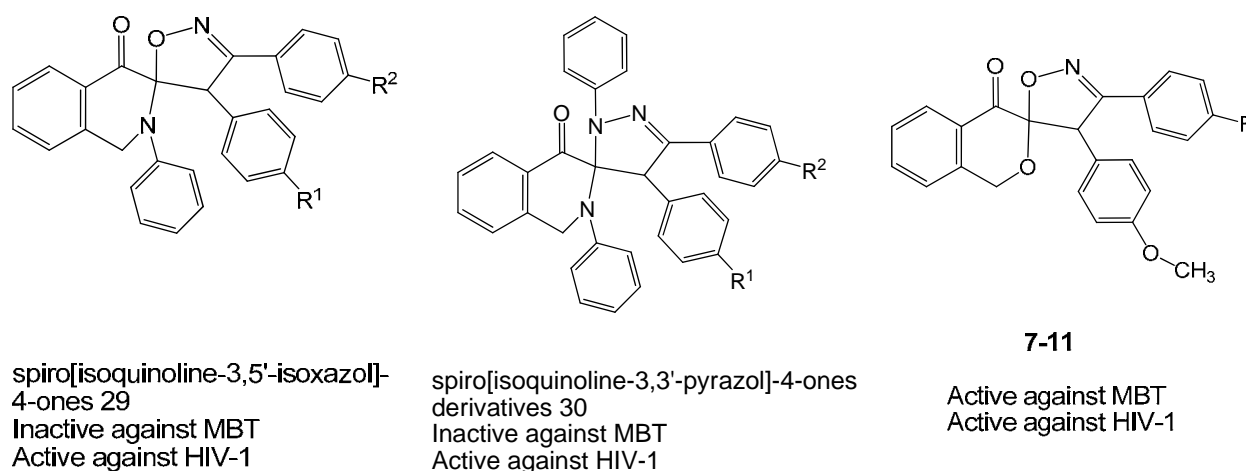


Figure 1. Spiroisoxazolines skeletons containing rigid pharmacophore sites.

In this paper we describe our efforts to extend the methodology of the synthesis of pharmacologically important spiroisoxazoline derivatives. The development of a short and convergent approach to the synthesis allowed us to synthesise derivatives **7-11** (Scheme 1), which will be subjected to further pharmacological investigations. In particular they will be tested on antitubercular, antitumour or anti-HIV activity.

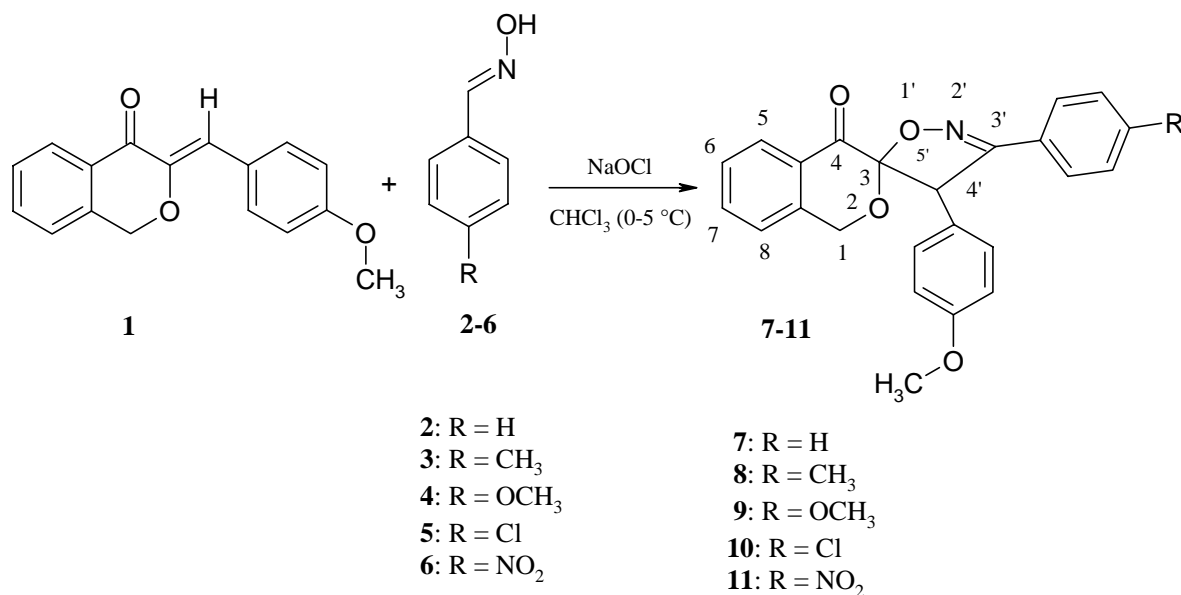
Results and Discussion

Chemistry

In our earlier studies of the dipolar 1,3-cycloaddition reaction, we investigated the action of diarylnitrilimines on dihydroquinoline derivatives,⁷ indene,⁸ and the 3-methoxycarbonyl-4H-1-

benzopyran-4-one, in which the dipolarophilic site is endocyclic.⁹ We also studied the region- and the stereochemistry of the reaction of diarylnitrilimines with the 2-arylidene-indan-1-ones,¹⁰ 3-arylidene-tetraline-4-ones,¹¹⁻¹² 3-arylidene-isothiochroman-4-ones,¹³ and lately the 3-toluidene-2,3-dihydro-4(1H)-isoquinolone,¹⁴ where the dipolarophilic site is exocyclic.

In this work dipolarophile **1** has been prepared by a simple condensation of a *para*-substituted benzaldehyde with the isochroman-4-one in the acidic environment.¹⁵ 1,3-Dipolar cycloaddition of compound **1** with **2-6** in chloroform, at cold temperature, yielded the corresponding spiro-isooxazoline derivatives **7-11** in good yields (Scheme 1).



Scheme 1. Synthesis of spiranic compounds **7-11**.

The synthesis of 4-(4'-méthoxyphényl)-3-aryl-4*H*-spiro[isochromène-3',5'-isoxazol]-4(1*H*)-one **7-11** has been done by reaction of *p*-R-benzaldoxime **2-6** and 3-*para*-méthoxy-benzylideneisochroman-4-one **1** in chloroform and aqueous solution of hypochlorite of sodium (18°). Physical Characterises (I.R and M.S.) of compounds **7-11** are regrouped in Table 1.

Compounds **7-11** were characterized using ¹H and ¹³C NMR methods. The ¹H NMR data of **7-11** reveals the presence of two methylenic protons, H^{1a} and H^{1b}, of the pyronic ring (with a J of approximately 16 Hz) nearly located at 4.7 and 5.5 ppm. There is also one singlet, H^{4'}, of the isoxazolineic ring (Table 2) at 5.9 ppm.

In this work the value of the chemical displacement of the atom at spiranic carbon is between 91.60 and 91.80 ppm, what is in good agreement with the proposed structure **7-11**.^{13,24} The mass spectrometry studies of compounds **7-11** has also been done to validate products of the synthesis.

Table 1. Physical Characterises, I.R et S.M of compounds **7-11**

Compd.	R	% yield	M.p (°C)	IR, ν (C=O) cm ⁻¹	S.M. (m/z)
7	H	78	180-182	1695	m/z: M = 385 [C ₂₄ H ₁₉ NO ₄] (4.28%); 118 (100%)
8	CH ₃	55.9	175-178	1705	m/z: M = 399 [C ₂₅ H ₂₁ NO ₄] (1%); 118 (100%)
9	OCH ₃	79	166-169	1710	m/z: M = 416 [C ₂₅ H ₂₁ NO ₅] (12%); 118 (100%)
10	Cl	45.6	184-187	1700	m/z: M = 419 [C ₂₄ H ₁₈ ClNO ₄] (2.16%); 118 (100%)
11	NO ₂	80.4	168-171	1704	m/z: M = 430 [C ₂₄ H ₁₈ N ₂ O ₆] (1.40%); 118 (100%)

Table 2. ¹H NMR data of compounds **7- 11** (CDCl₃, δ ppm/ TMS, J Hz)

Compd.	R	δ (R)	δ (OCH ₃)	δ (H ^{1a})	δ (H ^{1b})	δ (H ^{4'})	δ (H 3.Ph)
7	H	-	3.74 (s, 3H)	4.76 (d,1H) J = 15.85	5.57 (d,1H)	5.99 (s, 1H)	6.8-8.1 (m, 13H)
8	CH ₃	2.29 (s, 3H)	3.74 (s, 3H)	4.71 (d,1H) J = 15.97	5.55 (d,1H)	5.92 (s, 1H)	6.69-8.05 (m, 12H)
9	OCH ₃	3.75 (s, 3H)	3.72 (s, 3H)	4.71 (d,1H) J = 15.83	5.55 (d,1H)	5.91 (s, 1H)	6.70-8.05 (m, 12H)
10	Cl	-	3.72 (s, 3H)	4.72 (d,1H) J = 15.94	5.54 (d,1H)	5.90 (s, 1H)	6.70-8.05 (m, 12H)
11	NO ₂	-	3.74 (s, 3H)	4.75 (d,1H) J = 15.80	5.55 (d,1H)	5.93 (s, 1H)	6.71-8.17 (m, 12H)

The oxygen atom of *p*-R-benzadoxime **2-6** is fixed at the most substituted carbon atom of dipolarophile **1**. This regiochemistry has been generally observed for reaction of nitrones and dissymmetric ethylenic dipolarophiles,^{16, 23} and the obtained compounds **7-11** are always the 2'-méthyl(phenyl)-3'-phenyl-4'-arylspro[isothio-chromen-3,5'-isoxazolidin]-4(1H)-ones. In all cases regiochemistry was always observed during dipolar 1,3-cycloaddition of benzadoximes to

ethylenic dipolarophiles leading to the isoxazolines.²⁵⁻²⁸ We have observed this feature in the case of 3-méthoxycarbonyl-4H-1-benzopyran-4-one,⁹ and of the 3-toluidene-2,3-dihydro-4(1H)-isoquinolone.^{14, 24} The compounds **7-11** are highly sensitive to pH of solution; they decompose in the presence of traces of acids. So no chromatographic separations the various possible stereoisomers of **7-12** were done.

Table 3. Selected ¹³C NMR data of compounds **7-11** (CDCl₃, δ ppm/ TMS)

Compd.	R	R	OCH ₃	C ¹	C ⁴	C ^{4'}	C ^{3:5'}
7	H	-	57.34	63.36	185.42	55.11	106.73
8	CH ₃	22.24	58.17	63.34	186.26	55.87	107.36
9	OCH ₃	56.02	58.24	63.32	186.28	55.88	107.29
10	Cl	-	57.94	63.40	186.03	55.90	107.63
11	NO ₂	-	55.21	56.91	186.40	62.80	107.40

Biological Evaluation

Evaluation of anti-tuberculosis activity *invitro*

The products **7-11** are not enantiomerically pure. With an aim of obtaining fast results in anti-tuberculosis screening, compounds **7-11** were tested just as they were obtained. The five compounds (**7-11**) have been evaluated as anti-tuberculosis agents through the TAACF tuberculosis screening program, but only two (**8** and **10**) of them have been shown to inhibit significantly the growth of *Mycobacterium tuberculosis* H37Rv using the Alamar assay at the first level adopted for *in vitro* screening. The three compounds **7**, **9** and **11** displayed modest *in vitro* activity (less than 90%). The anti-tuberculosis data are summarised in Table 4.

Table 4. Antitubercular activity of compounds **7-11**

TAACF Code	Corp ID	R	Tuberculosis Primary Screening			
			Assay	MIC (µg/mL)	% Inh	Activity
297378	7	H	Alamar	>6.25	32	negative
297379	8	CH ₃	Alamar	<6.25	95	positive
297380	9	OCH ₃	Alamar	>6.25	75	negative
297381	10	Cl	Alamar	<6.25	96	positive
297382	11	NO ₂	Alamar	>6.25	79	negative

Conclusions

The spiro-isoxazolines **7-11** can easily be prepared by 1,3-dipolar cycloaddition of 3-para-methoxy-benzylidene-isochroman-4-one (**1**) with the appropriate *p*-R-benzadoxime (**2-6**). These

compounds typically form the highly stable antitubercular pharmacophore site. A number of important points emerge concerning their biological properties and interaction with biological receptors. Based on their pharmacological properties and thermal stability, these compounds may be useful as anti-tubercular agents. Further screening studies are currently in progress in order to elucidate the structure/activity relationships of these derivatives

Experimental Section

General Procedures. Melting points are measured on banc KOFLER without corrections. NMR spectra (^1H , ^{13}C) were recorded on a Bruker Avance (operating at 300 MHz) (Université Paul Sabatier, Toulouse). NMR data are listed in ppm and are reported relative to tetramethylsilane (^1H , ^{13}C), residual solvent peaks being used as internal standard with external calibration. Infrared spectra were recorded in KBr pellets using a Perkin-Elmer 1600 FT-IR spectrometer. Mass spectra were recorded on a Hewlett-Packard 5989A Mass Spectrometer (70 eV) Nermag R 1010 C electronic impact and elemental analysis (CNRS, Université Paul Sabatier, Toulouse, France).

General procedure of the preparation of spiro-isoxazolines 7-11

A mixture of (3*Z*)-3-(4-methoxybenzylidene)-1*H*-isochromen-4(3*H*)-one **1** (0.53 g, 2 mmol) and 2.4 mmol of the oxime **2** was stirred in dry dichlorometane (20 ml) at cold temperature (0°C). To this mixture of **1** and **2-6**, it was added 15 ml of hypochlorite of sodium (18°), portion by portion, over 10 min to keep temperature under 5 °C. The mixture was stirred at room temperature for 16 h until TLC indicated that both precursors have been consumed. After washing the mixture with NaOCl solution until the pH is neutre, the compounds **7-11** were dissolved in ethanol to eliminate non reacting traces of precursors then CHCl_3 is evaporated and then the residue is crystallised in ethanol to yield **7-11** (45-80%) yields.

4'-(4-Methoxyphenyl)-3'-phenyl-4'*H*-spiro[isochromen-3,5'-isoxazol]-4(1*H*)-one (7). This compound was obtained as white powder. Yield = 78%. M.p. = 180-182 °C. IR ν (C=O) = 1695 cm^{-1} . $^1\text{H-NMR}$: 3.74 (s, 3H, OCH_3); 4.76 (d, 1H, H^{1a} , $^2\text{JH}^{1a}\text{-H}^{1b}$ = 15.85); 5.57 (d, 1H, H^{1b} , $^2\text{JH}^{1b}\text{-H}^{1a}$ = 15.85); 5.99 (s, 1H, $\text{H}^{4'}$); 6.8-8.1 (m, 13H, Aromatic H). $^{13}\text{C-NMR}$: 57.34 (OCH_3); 63.36 (C^1); 106.73 ($\text{C}^{3,5'}$); 185.42 (C^4); 160.53 (C^3); 55.11 (C^4); (Aromat. C) : 113.76; 123.4; 124.17; 127.86; 128.13; 128.30; 128.34; 128.48; 130.18; 131.61; 134.53; 141.42; 159.21. MS (EI, 70 eV): $[\text{M}]^+$ = 385 (17); 118 (100). Anal. Calcd. For $\text{C}_{24}\text{H}_{19}\text{NO}_4$: C, 74.79; H, 5.39; N, 3.63. Found: C, 73.85; H, 5.17; N, 3.55.

4'-(4-Methoxyphenyl)-3'-(4-methylphenyl)-4'*H*-spiro[isochromen-3,5'-isoxazol]-4(1*H*)-one (8). This compound was obtained as white powder. Yield = 56%. M.p. = 175-178 °C. IR ν (C=O) = 1705 cm^{-1} . $^1\text{H-NMR}$: 2.29 (s, 3H, CH_3); 3.74 (s, 3H, OCH_3); 4.71 (d, 1H, H^{1a} , $^2\text{JH}^{1a}\text{-H}^{1b}$ = 15.97); 5.55 (d, 1H, H^{1b} , $^2\text{JH}^{1b}\text{-H}^{1a}$ = 15.97); 5.92 (s, 1H, $\text{H}^{4'}$); 6.69-8.05 (m, 12H, Aromatic H). $^{13}\text{C-NMR}$: 58.17 (OCH_3); 22.24 (CH_3); 63.34 (C^1); 107.36 ($\text{C}^{3,5'}$); 186.26 (C^4); 161.20 (C^3); 55.85 (C^4); (Aromat. C): 114.47; 124.34; 124.94; 126.13; 128.50; 129.13; 129.99; 132.39;

135.29; 141.22; 142.23; 159.91. MS (EI, 70 eV): $[M]^+$ = 399 (16); m/z = 90 (20); 118 (100). Anal. Calcd. For $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 74.93; H, 5.39; N, 3.37.

4'-(4-Methoxyphenyl)-3'-(4-methoxyphenyl)-4'H-spiro[isochromen-3,5'-isoxazol]-4(1H)-one (9). This compound was obtained as white powder. Yield = 79 %. M.p. = 166-169 °C. IR ν (C=O) = 1710 cm^{-1} . 1H NMR: 3.72 (s, 3H, OCH₃); 3.75 (s, 3H, OCH₃); 4.71 (d, 1H, H^{1a}, $^2JH^{1a}-H^{1b}$ = 15.83); 5.55 (d, 1H, H^{1b}, $^2JH^{1b}-H^{1a}$ = 15.83); 5.91 (s, 1H, H⁴); 6.70-8.05 (m, 12H, Aromatic H). ^{13}C -NMR: 58.24 (OCH₃); 56.02 (OCH₃); 63.32 (C¹); 107.29 (C^{3,5'}); 186.28 (C⁴); 161.80 (C^{3'}); 55.88 (C^{4'}); (Aromat C): 107.29; 114.47; 121.39; 124.42; 124.93; 128.48; 129.14; 130.22; 132.42; 135.27; 142.24; 159.91; 160.80. MS (EI; 70 eV): $[M]^+$ (%) = 416 (17); 120.9 (100). Anal. Calcd. For $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37. Found: C, 73.03; H, 5.19; N, 3.31.

3'-(4-Chlorophenyl)-4'-(4-methoxyphenyl)-4'H-spiro[isochromen-3,5'-isoxazol]-4(1H)-one (10). This compound was obtained as white powder. Yield = 45%. M.p. = 184-187 °C. IR ν (C=O) = 1700 cm^{-1} . 1H NMR: 3.72 (s, 3H, OCH₃); 4.72 (d, 1H, H^{1a}, $^2JH^{1a}-H^{1b}$ = 15.94); 5.54 (d, 1H, H^{1b}, $^2JH^{1b}-H^{1a}$ = 15.94); 5.90 (s, 1H, H⁴); 6.70-8.05 (m, 12H, Aromatic H). ^{13}C -NMR: 57.94 (OCH₃); 63.40 (C¹); 107.63 (C^{3,5'}); 186.03 (C⁴); 160.40 (C^{3'}); 55.90 (C^{4'}); (Aromat. C): 107.63; 114.62; 123.76; 124.96; 127.55; 128.55; 129.00; 129.60; 129.87; 132.36; 135.40; 137.04; 142.10; 160.09. MS (EI, 70 eV) : $[M]^+$ = 419 (35); 118 (100). Anal. Calcd. For $C_{24}H_{18}ClNO_4$: C, 68.66; H, 4.32; N, 3.34. Found: C, 67.05; H, 4.39; N, 3.37.

4'-(4-methoxyphenyl)-3'-(4-nitrophenyl)-4'H-spiro[isochromen-3,5'-isoxazol]-4(1H)-one (11): Yield = 80%. M.p. = 168-171 °C. IR ν (C=O) = 1704 cm^{-1} . 1H NMR: 3.74 (s, 3H, OCH₃); 4.75 (d, 1H, H^{1a}, $^2JH^{1a}-H^{1b}$ = 15.80); 5.55 (d, 1H, H^{1b}, $^2JH^{1b}-H^{1a}$ = 15.80); 5.93 (s, 1H, H⁴); 6.71-8.17 (m, 12H, Aromatic H). ^{13}C -NMR: 55.21 (OCH₃); 62.80 (C⁴); 104.40 (C^{3,5'}); 186.40 (C⁴); 159.58. (C^{3'}); 62.80 (C^{4'}); (Aromat C): 107.40; 114.09; 122.31; 123.76; 124.27; 127.86; 127.97; 128.08; 128.67; 131.55; 134.53; 134.86; 141.20; 148.49; 159.06. MS (EI, 70 eV): $[M]^+$ = 430 (19); 118 (100). Anal. Calcd. For $C_{24}H_{18}N_2O_6$: C, 66.97; H, 4.22; N, 6.51. Found: C, 67.12; H, 4.43; N, 6.74.

Acknowledgements

This work was supported by the "Programme de la Recherche Globale de l'Université Mohammed Premier N°: PGR-Ump-BH-2005" Grant from the Ministry of National Education of Morocco. Antimycobacterial data were provided by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) through a research and development contract with the U.S. National Institute of Allergy and Infectious Diseases.

References and Notes

1. Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, 4603.
2. Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, 1291.
3. Bennani, B.; Kerbal, A.; Ben Larbi, N.; Ben Hadda, T.; Synthesis and application of spiroisoxazolines as new anti-tubercular agents, *OMPIC, Moroccan Patent No. 2769*, 2004.
4. Bennani, B.; Kerbal, A.; Ben Larbi, N.; Ben Hadda, T. Synthesis and application of isothiochromeno[3,4-e][1,2]oxazine (TCO) as new antitumoral agents, *OMPIC, Moroccan Patent No 2771*, 2004.
5. Benchat, N.; El Bali, B.; Abouricha, S.; Moueqqit, M.; Mimouni, M.; Ben Hadda, T. *Med. Pharm. Chem.* **2003**, 1.
6. Anafloous, A.; Benchat, N.; Mimouni, M.; Abouricha, S.; Ben Hadda, T.; El Bali, B.; Hakkou, A.; Hacht, B. *Lett. Drug Des. Disc.* **2004**, 1, 35.
7. Tshiamala, K.; Kerbal, A.; Vebrel, J.; Laude, B. *J. Chem. Res.(S)* **1988**, 3, 106.
8. Kerbal, A.; Vebrel, J.; Cerutti, E.; Laude, B. *J. Chem. Soc., Chem. Commun.* **1989**, 632.
9. Filali Baba, B.; Kerbal, A.; Bitit, N.; El Bali, B.; Escudie, J.; Ranaivonjatovo, H.; Bolte, M. *Acta. Cryst.* **2000**, C56, 205.
10. Kerbal, A.; Tshiamala, K.; Vebrel, J.; Laude, B. *Bull. Soc. Chim. Belg.* **1988**, 97, 149.
11. Kerbal, A.; Tshiamala, K.; Vebrel, J.; Laude B.; Mercier, M. F. *Bull. Soc. Chim. Belg.* **1991**, 2, 159.
12. Theobala, F.; Rodier, N.; Kerbal, A.; Tshiamala, K.; Laude, B. *Acta. Cryst.* **1990**, C46, 1312.
13. Kerbal, A.; Vebrel, J.; Roche, M.; Laude, B. *Tetrahedron Lett.* **1990**, 31, 4145.
14. Badri, R.; Kerbal, A.; El Bali, B.; Escudie, B.; Ranaivonjatovo, H.; Bolte, M. *Acta Cryst.* **1999**, C55.
15. Pivnenko, N. S.; Orlov, V. D.; Nodel'Man, O. A.; Mikhed'Kina, E. I.; Lavrushin, V.F. *Zh. Org. Khim.* **1980**, 16, 1945.
16. Cacciarini, M.; Cordero, F. M.; Faggi, C.; Goti, A. *Molecules* **2000**, 5, 637.
17. Chiacchio, U.; Casucelli, F.; Corsaro, A.; Rescifina, A.; Romeo, G.; Uccella, N. *Tetrahedron* **1994**, 50, 6671.
18. Christl, R.; Huisgen, M. *Chem. Ber.* **1973**, 106, 345.
19. Jones, A. D.; Knight, D.; Thornton, S.R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1, 337.
20. Fornefeld, E. J.; Pike, J. *J. Org. Chem.* **1979**, 44, 835.
21. Asrof Ali, S.K.; Wazeer Mazhar-UI-Haque, M.I. *Tetrahedron* **1990**, 46, 7207.
22. Chaner-Reny, J.; Chrmier-Junuario, M. O.; Vessièrè, R.; Zuccarelli, M. *J. Heterocyclic Chem.* **1997**, 31, 1667.
23. Rastelli, A.; Gandolfi, R.; Amade, M. S.; *Advances In Quantum Chemistry.* **2000**, 36,151.
24. Bennani, B.; Filali Baba, B.; EL-Fazazi, A.; Al Houari, G.; El Bali, B.; Bolte, M.; Ben Larbi, N.; Kerbal, A. *J. Mar. Chim. Hétéroc.* **2003**, 1, 1.
25. Christl, M.; Huisgen, R.; Sustmann, R. *Chem. Ber.* **1973**, 106, 3235, 1,3-Dipolar cycloaddition chemistry, A. Padwa, Wiley: New York, 337.
26. Christl, M.; Huisgen, R. *Chem. Ber.* **1973**, 106, 345.
27. Bast, K.; Christl, M.; Huisgen, R.; Mach, W. *Chem. Ber.* **1973**, 106, 3312.

28. Alami, A.; Soufiaoui, M. *J. Soc. Mar. Chim.* **1992**, *1*, 3589.
29. Ben Hadda, T.; Badri, R.; Kerbal, A.; Filali Baba, B.; Akkurt, M.; Demailly, G.; Benazza, M. Looking for a new antitubercular pharmacophore site: synthesis and bioactivity of spiroheterocycles 2,3',4'-tri-substituted-1,2-dihydro-4H,4'H-spiro[isoquinoline-3,5'-isoxazol]-4-ones. Manuscript submitted to *Arkivoc*.
30. Ben Hadda, T.; Badri, R.; Kerbal, A.; Filali Baba, B.; Akkurt, M.; Demailly, G.; Benazza, M. *Arkivoc* **2007**, (*xiv*), 276.