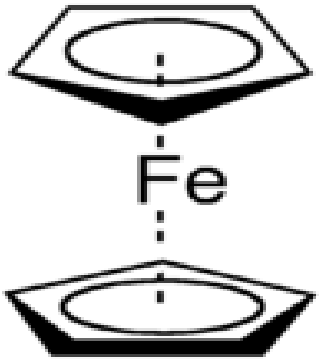
Design and synthesis of multifunctional ferrocene derivatives as potent antimicrobial agents

Toma Nardjes Mouas[1,*], Eric Manoury[2,3]
[1]Université frères Mentouri-Constantine 1, Laboratoire d'Obtention de Substances Thérapeutiques LOST, Campus Chasbet Ersas, 25000 Constantine, Algeria.
[2] CNRS, LCC (Laboratoire de Chimie de Coordination), 205 route de Narbonne, Toulouse Cedex 4, France.
[3]Université de Toulouse, UPS, INPT, F-31077 Toulouse Cedex 4, France.
* Correspondence: mouas.toma.nardjes@umc.edu.dz (T.N.M)

Abstract: In recent year, the chemistry of ferrocene and the design of new compounds containing the ferrocene unit, has received a surge in interest, owing to their utility in many fields such as organic synthesis, catalysis and biotechnology material. In the framework, of attending a new multifunctional ferrocenyl derivatives, two precursors namely DMHF 1 and a ferrocene functionalized in 1,2 position by thiophosphine function 2, were fully characterized by HRMS, IR, NMR ^{1}H, ^{13}C, ^{31}P and UV spectroscopy, then were *in vitro* tested for antibacterial activity against Gram-negative: *Escherichia coli:* ATCC 25922 (for 1,2), *Klebsiella pneumonia:* ATCC 700603 (for 1,2), *Pseudomonas aeruginosa* : ATTC27853 (for 2), *Proteus Sp* (for 2), *Morganella morganii* (for 1,2), *Enterrobacter sp* (for1) *;* Gram-positive: *Staphylococcus aureus:* ATCC 25923 (for 2), *Staphylococcus aureus 2S:* ATCC 43300 (for 1,2), *Bacillus Sp* (for 1,2), fungus: *Aspergillus Niger* (for 2)*, Fusarium oxysprium* (for 2)*, Alternaria Sp* (for 2) and *Penicillium sp* (for 1,2) using disc diffusion method on solid medium MH and Sabouraud respectively. Obtained results were compared to antibiogram and reveled an interesting antimicrobial potent varying from 7 to 10mm of inhibition for DMHF and 7 to 15mm of inhibition for 1,2 dithiophosphine ferrocene compounds, which indicates mostly an improvement of antimicrobial activity with chiral substitution of ferrocene moiety with amine and thiophosphine functions, this encourage future investigations on chirality and substitution role in the improvement of antimicrobial activity.

Keywords: ferrocene; thiophosphine; planar chirality; antimicrobial activity.

Ferrocene moeity propreties

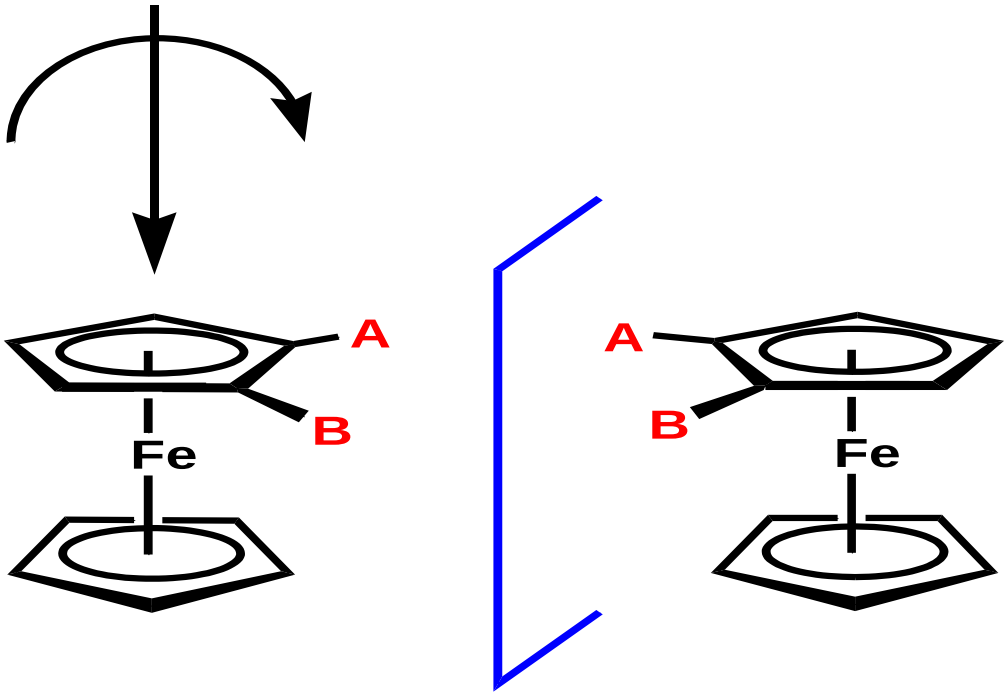


Synthesis

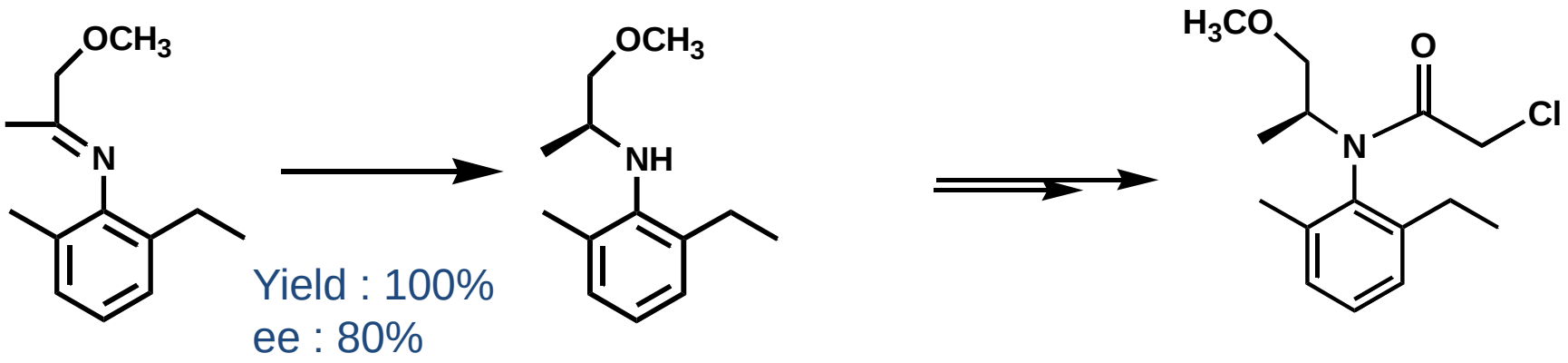
$2\ NaC_5H_5 + FeCl_2 \rightarrow Fe(C_5H_5)_2 + 2\ NaCl$

high stability

The ease introduction of planar cherality.

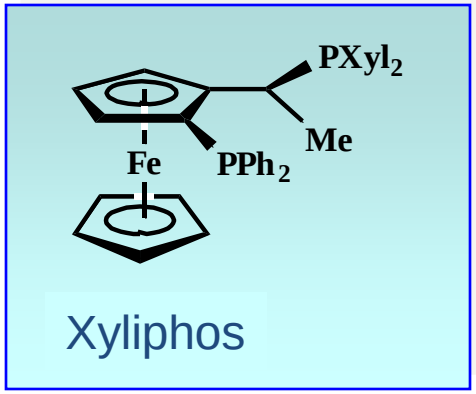


Xyliphos as precursor of (S)-métolachlor



Yield : 100%
ee : 80%

(S)-metolachlor



Xyliphos

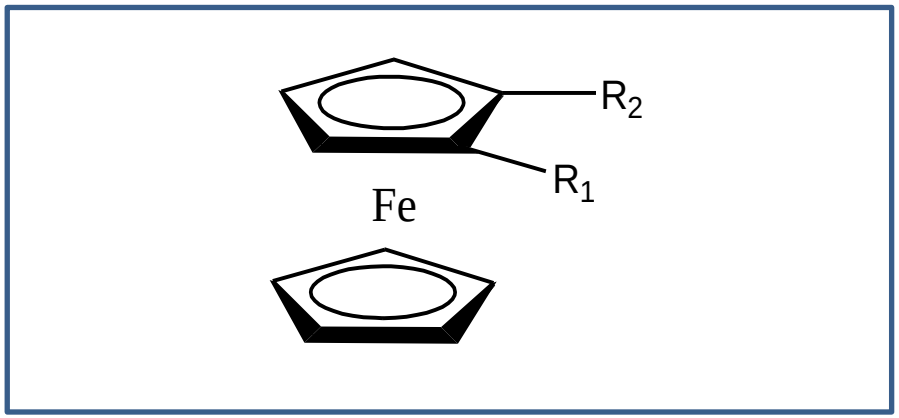
10 000 tons / year
TON : 2 000 000
TOF (h^{-1}) : 400 000

Blaser, H.-U., Brieden, W., Pugin, B., Spindler, F., Studer, M., Togni, A. *Topics in Catalysis.*, (2002), 19, 3-16.

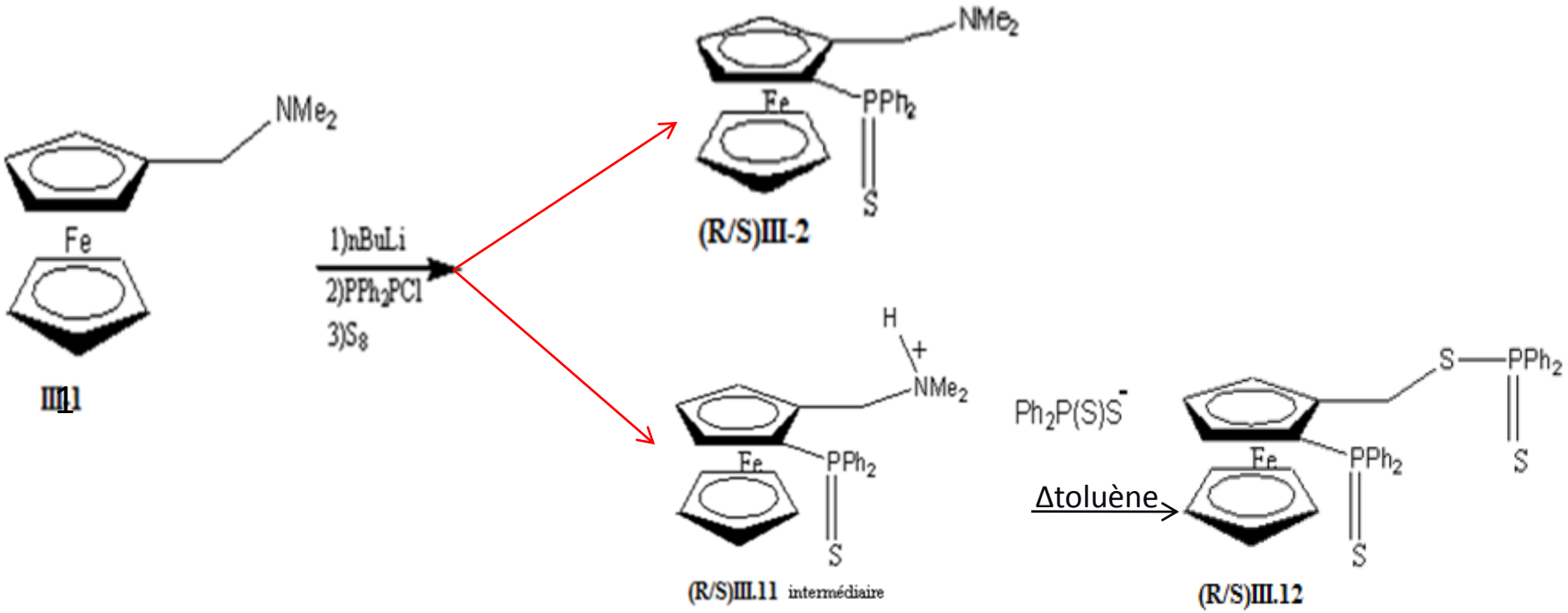
Synthesis and characterization of bidentate ferrocene ligands derivatives :

Functionalization

1,2 position with planar chirality



General procedure



Routaboul, L., Vincendeau, S., Daran, J.-C. & Manoury, E. (2005). Tetrahedron Asymmetry, 16, 2685–2690.

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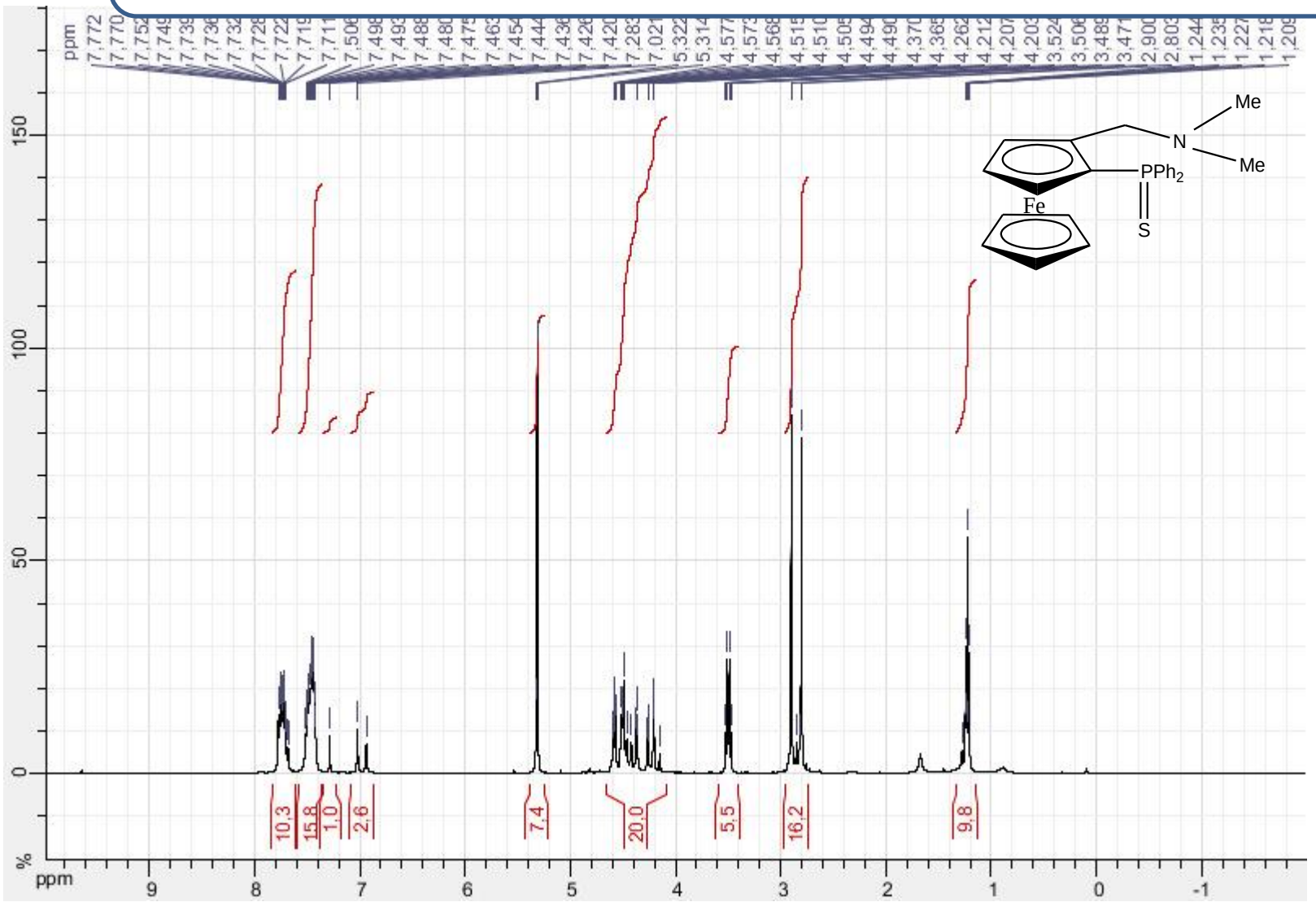
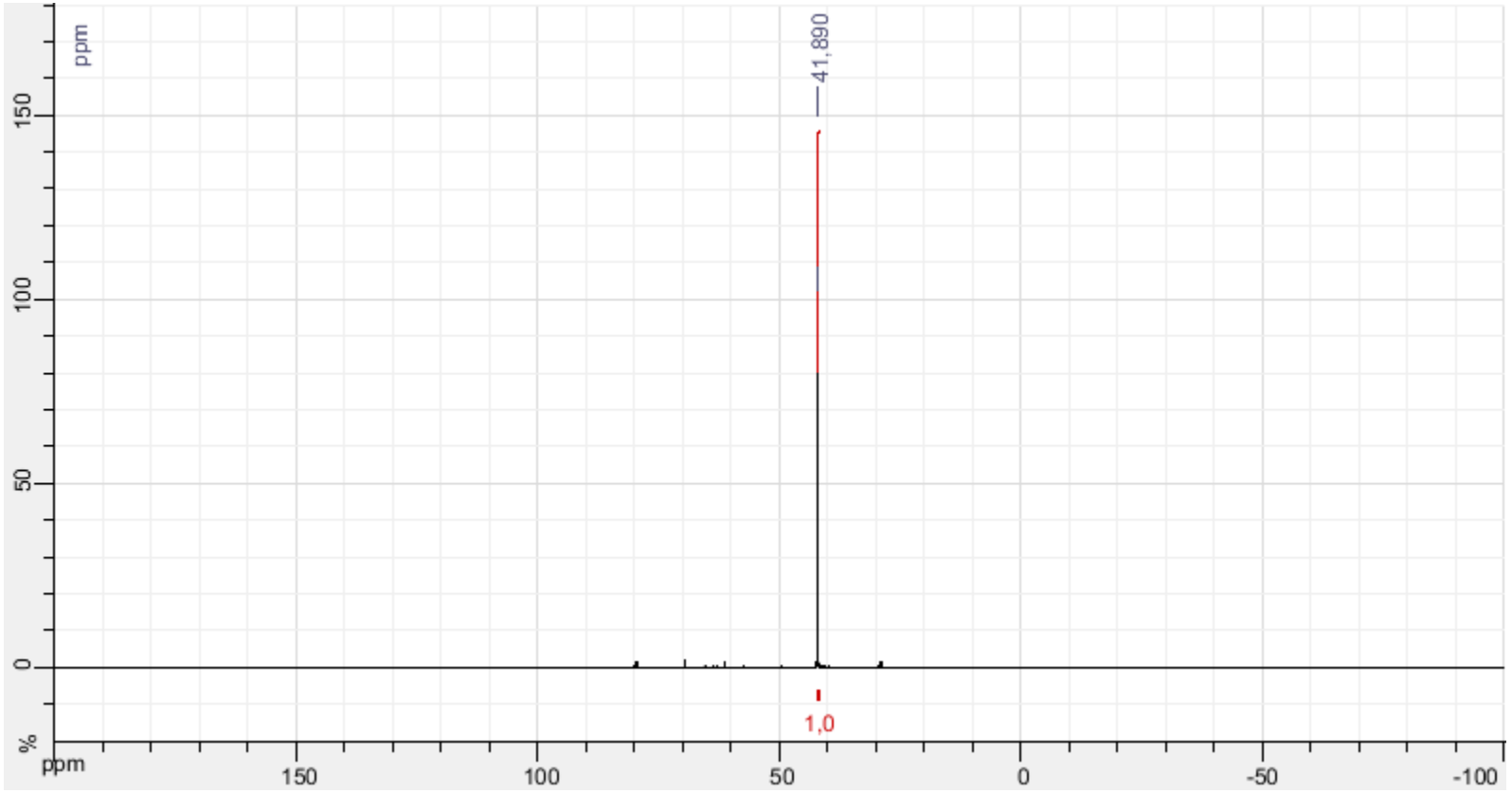
T. N. Mouas, J-C. Daran, H. Merazig and E. Manoury. Acta Cryst. 2014, C70, m460-464.

Results and discussion
Synthesis under controlled athmosphere

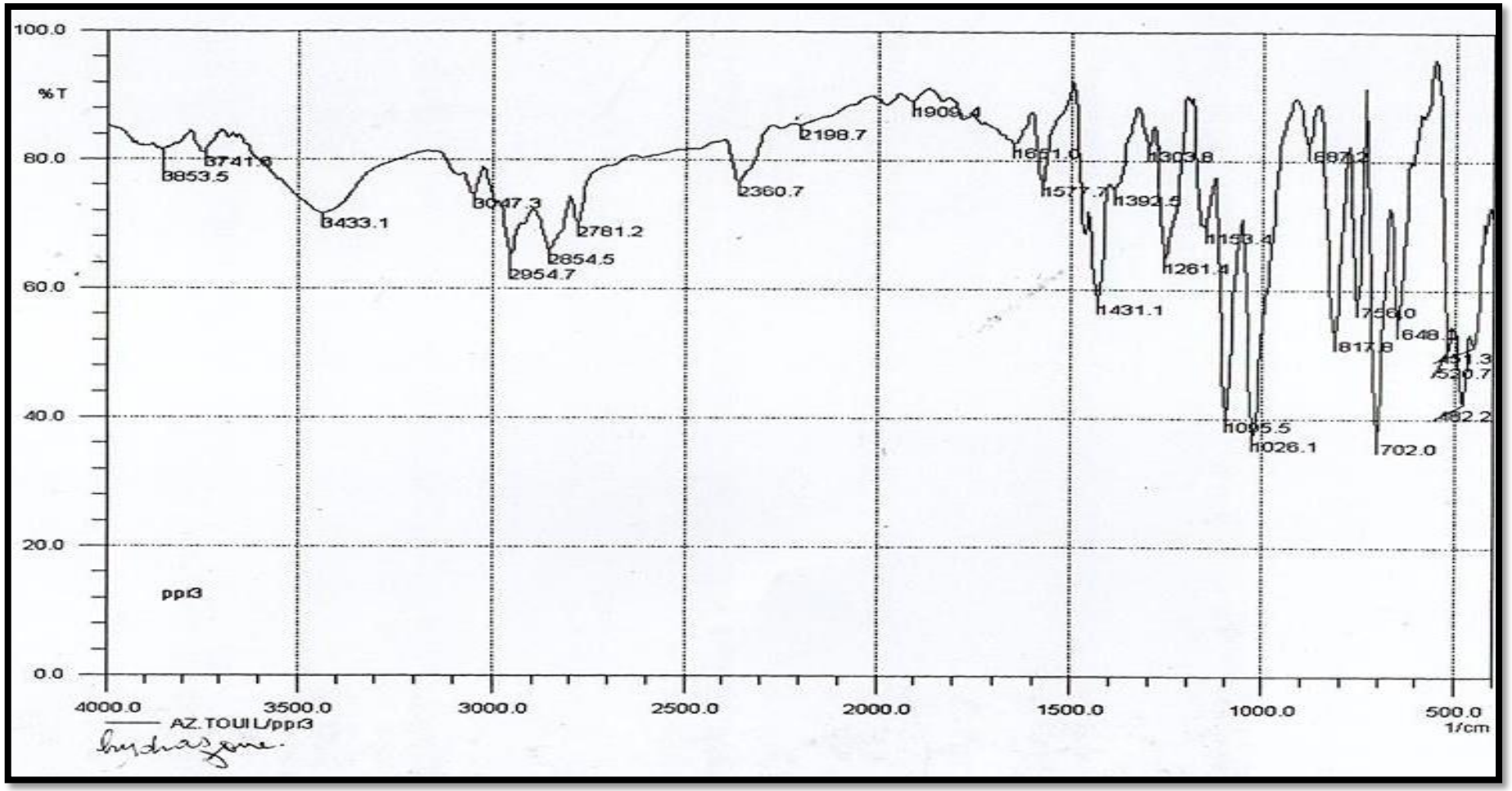
Structural characterization of (R/S)-1



NMR 1H spectra



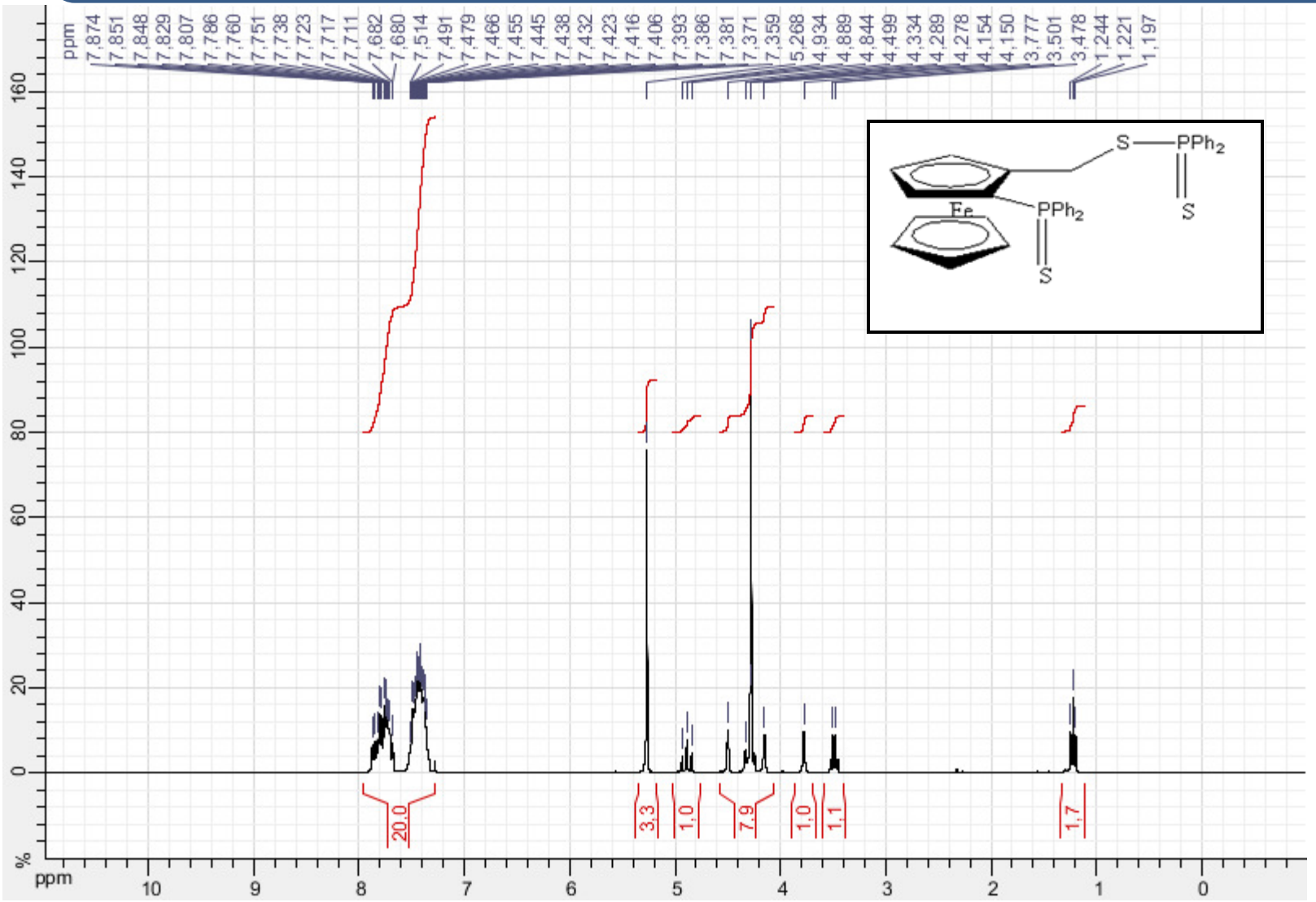
NMR 31P spectra


100.0
%T
80.0
60.0
40.0
20.0
0.0
3853.5
3741.6
3433.1
3047.3
2954.7
2854.5
2781.2
2360.7
2198.7
1903.4
1651.0
1577.7
1392.5
1303.8
1261.4
1153.4
1431.1
1095.5
1026.1
817.8
756.0
702.0
648.8
531.3
520.7
482.2
ppi3
4000.0
3500.0
3000.0
2500.0
2000.0
1500.0
1000.0
500.0
1/cm
AZ.TOUIL/ppi3

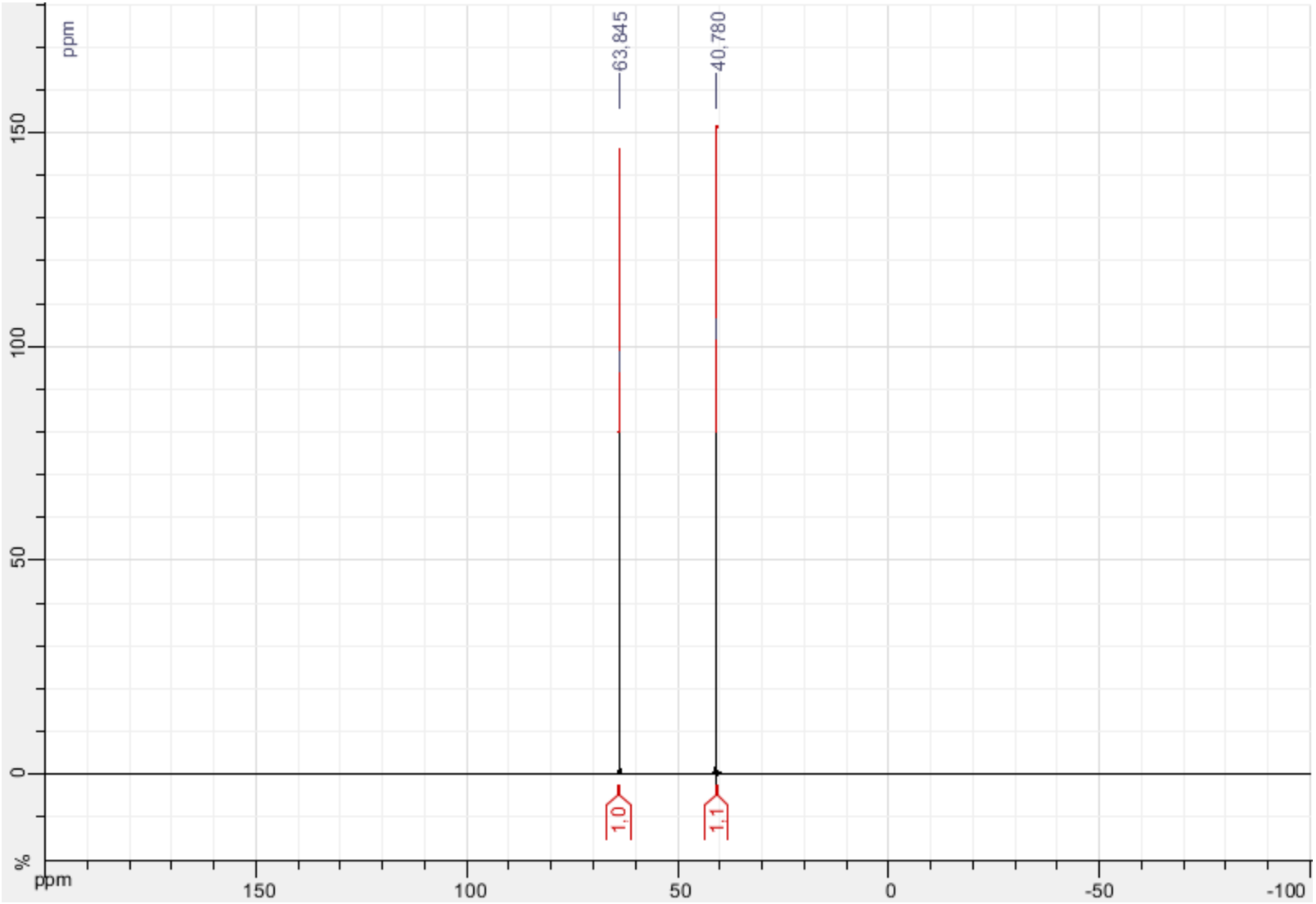
IR spectra

UV spectra

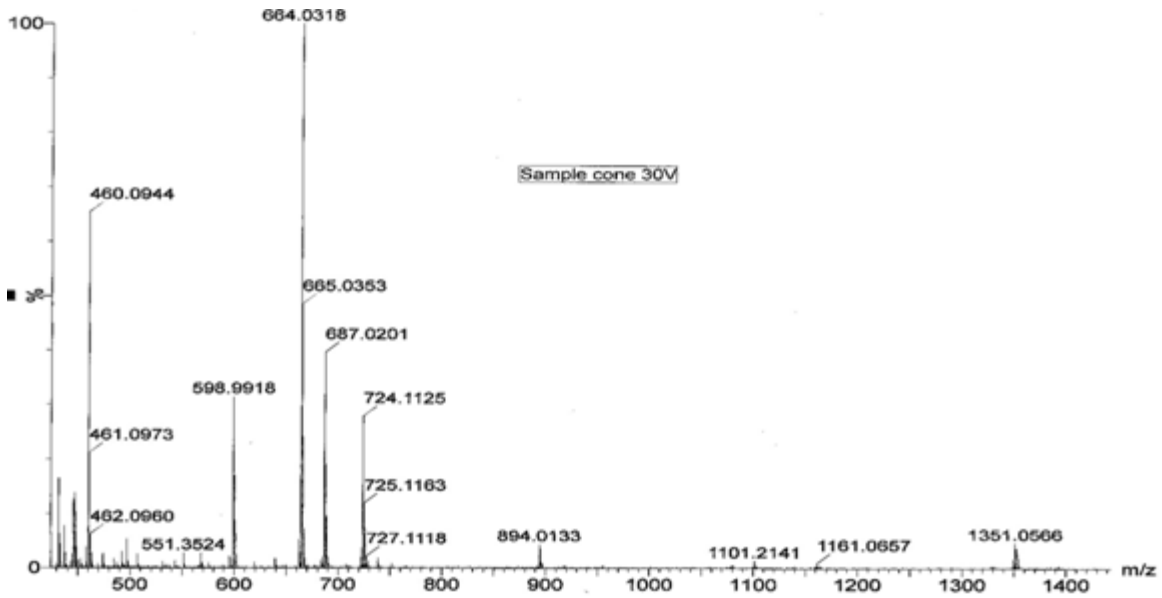
Structural characterization of (R/S)-2



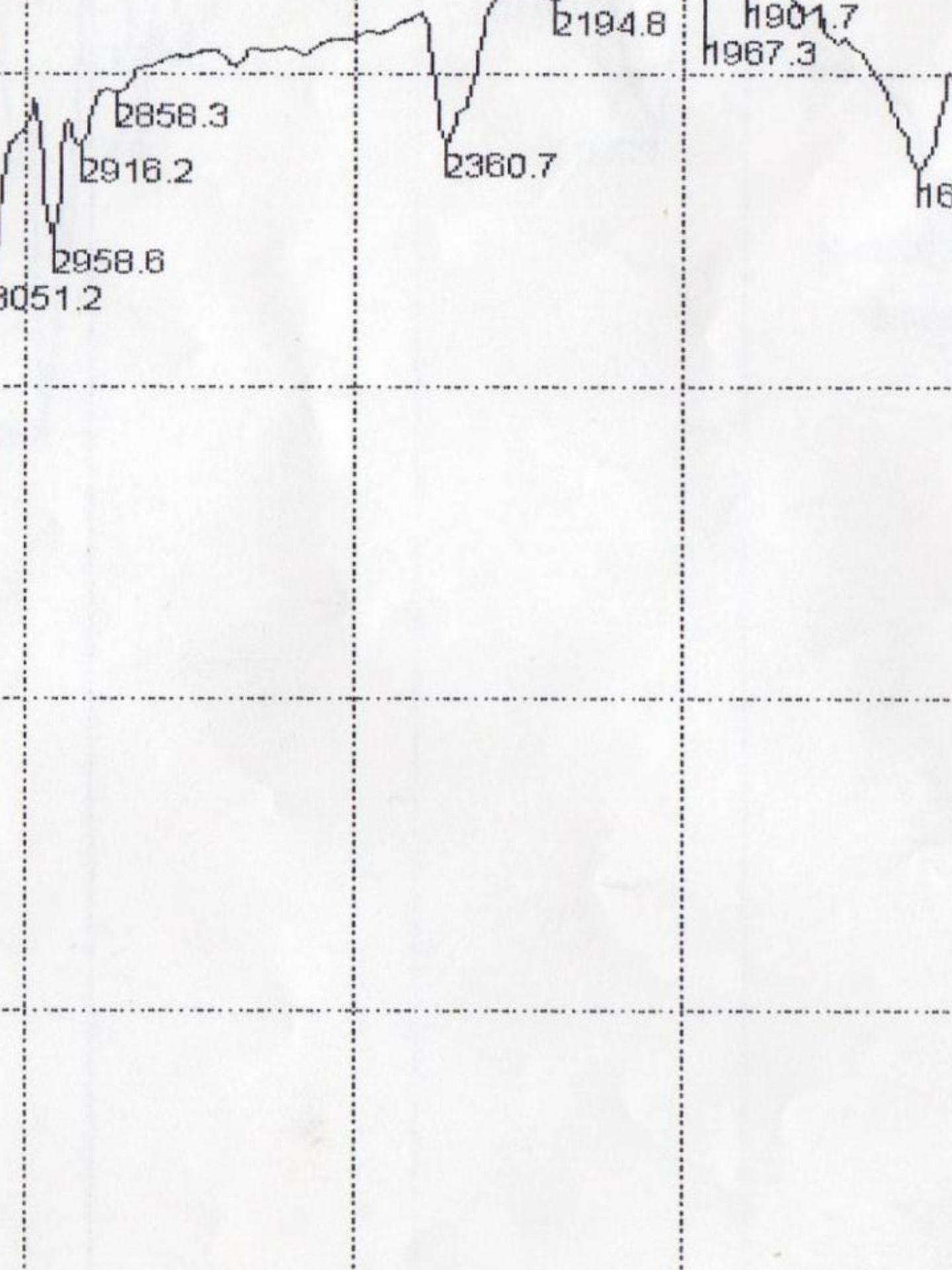
NMR 1H spectra

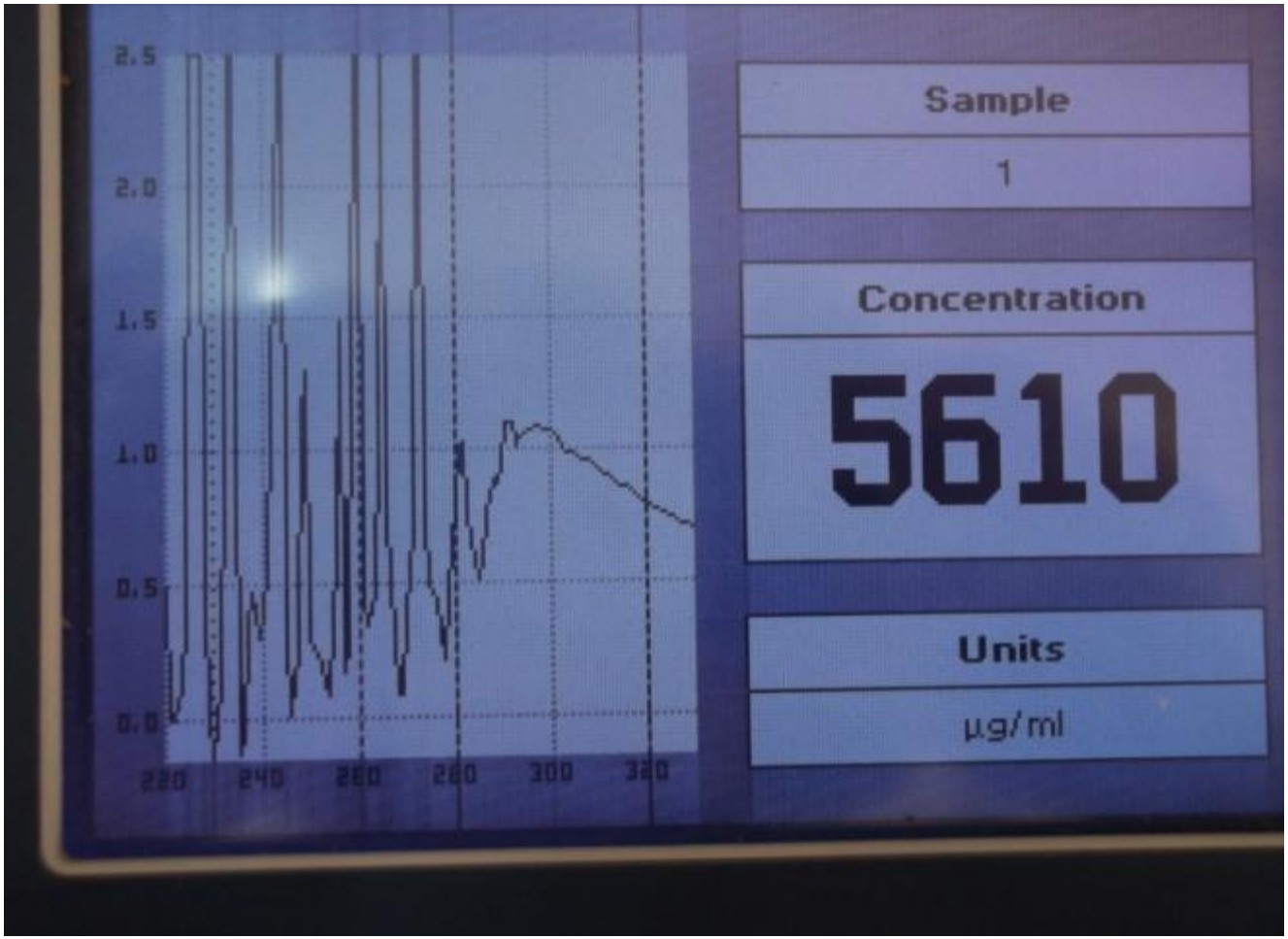


NMR 31P spectra



HR MS spectra


2194.8
1901.7
1967.3
2858.3
2916.2
2360.7
2958.6
3051.2


2.5
2.0
1.5
1.0
0.5
0.0
220
240
260
280
300
320
Sample
1
Concentration
5610
Units
µg/ml

UV spectra

Antimicrobial activity

Gram-negative:

Escherichia coli: ATCC 25922 tested for both compounds 1,2 exhibits a resistance even at high dose

Klebsiella pneumonia: ATCC 700603 , compound 1 exhibits a better MIC= 3,13µ/ml than compound 1 (MIC= 50µ/ml), however inhibition diameter are substantially the same.

Pseudomonas aeruginosa : ATTC27853 and *Proteus Sp* tested only for compound 2, exhibits the same MIC= 1,56 µ/ml.

Morganella morganii (for 1,2), exhibits a MIC= 0,78µ/ml for compound 1, and was resistant to c ompound 2.

Enterrobacter sp (for1) *;* tested only for 1, exhibits a MIC= 3,13µ/ml.

Gram-positive:

Staphylococcus aureus: ATCC 25923 (for 2), was resistant to tested compound 2.

Staphylococcus aureus 2S: ATCC 43300 tested for both compounds 1,2 exhibit a MIC= 3,13µ/ml for compound 1, and was resistant to compound 2.

Bacillus Sp (for 1,2), was resistant to compound 2, and gave a MIC=1,56µ/ml for compound 1.

Fungus:

Aspergillus Niger (for 2), compound 2gave a MIC=1,56µ/ml

Fusarium oxysprium (for 2), tested compound 2 exhibits a MIC=3,13µ/ml

Alternaria Sp (for 2) was resistant to tested compound 2.

Penicillium sp (for 1,2) was resistant to compound 2, on the other hand compound 1 exhibits an

Conclusion

Ferrocene planar chiral derivatives 1 and 2 were efficiently synthesized, characterized and fully screened for its antimicrobial potential against several gram+, gram- and fungus referential strains. The obtained bidendate ligands, exhibit mostly better results in case of functionalization with amine and thiophosphine groups. Investigations on molecular structures and comparison with observed effect could help to explain the structure activity relationship that may or not improve observed therapeutically effect of functionalized ferrocene.

This encouraging results lead to invest more ferrocene derivatives as potent antimicrobial agents and face microbial resistant phenomenon in clinical and alimental medium.

Acknowledgments

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