UNIUNEA EUROPEANĂ
GUVERNUL ROMÂNIEI
MINISTERUL MUNCII, FAMILIEI ŞI PROTECŢIEI SOCIALE
AMPOSDRU
Fondul Social European
POSDRU 2007-2013
Instrumente Structurale
2007-2013
MINISTERUL EDUCAŢIEI CERCETĂRII TINERETULUI ŞI SPORTULUI
OIPOSDRU
UNIVERSITATEA BABEŞ-BOLYAI
CLUJ-NAPOCA

BABEŞ-BOLYAI UNIVERSITY
Faculty of Chemistry and Chemical Engineering

SYNTHESIS AND CHARACTERIZATION OF NOVEL FERROCENE AND PHENOTHIAZINE CONTAINING HETEROCYCLES WITH POTENTIAL PHARMACEUTICAL APPLICATIONS

- PhD thesis -

PhD Supervisor
Prof. Dr. Luminiţa Silaghi-Dumitrescu

PhD Candidate:
Kocsis Vasile-Ludovic

CLUJ-NAPOCA
2012

Table of Contents

1. Introduction

"Logic is the beginning of all wisdom, not the end" Spock

The present work is dedicated to the hard working men and women, whose outstanding ideas, experiments and findings fueled the development of Science, Technology and the modem way of living; sharing knowledge and discoveries for the greater good of our species.

Laboratory work has been a life changing experience for me, over the years I tried to shed bad habits, and concentrate of positive thinking, because Preparative Organic Chemistry is never as easy as one may expect. Sometimes it takes months of rigorous work just to isolate a desired compound, and sometimes only one out of a hundred experiments will yield what you desire, but the overwhelming joy of isolating a new compound makes it a unique experience.

Our work addresses three main subjects: synthesis and characterization of beta-carboline alkaloids, ferrocene containing heterocycles and C_2 chiral phenothiazinyl-salen complexes. We have chosen these topics to address issues, which need improvement; we perfected reactions, yielded new compounds with possible pharmaceutical applications, which may be feasible to produce and to use in anticancer treatment or chemotherapy.

The thesis is divided in a literature review part, and an original contributions part, that contains result, and discussion on our work, and an experimental report of our findings.

2. Literature review

2.1 Recent studies of pharmacologically active phenothiazine compounds

The chemistry of phenothiazine[1] has a long tradition in our group and in the Department of Organic Chemistry at Babeș-Bolyai University, it was proven to be a molecule of great industrial and pharmaceutical value since its discovery. A well-known phenothiazine derivative, methylene blue[2] is a widely used antiseptic and colorant, and has been used for a variety of applications over the course of the 19th and 20th century; it is an important dye, used to this day in histology (i.e. staining of several types of cells) it has been proven to possess antimalarial[3] effects as well, it has redox capabilities and is a decent antiseptic. In the 1950's phenothiazine derivatives[4] literally emptied the clinics, revolutionizing psychiatric treatment. Phenothiazines are the oldest group of synthetic antipsychotic drugs; they do not have precursors among natural compounds.

Recent literature suggests that phenothiazine derivatives could play an important role in future development of relatively cheap and effective pharmaceuticals for various applications.

Aftab[5] and coworkers have explored the structure-activity relationships of several known phenothiazine related drugs for the inhibition of protein kinase C, and have found, that trifluoro-substitution on the second carbon on the phenothiazine nucleus has decreased activity of the derivative and it was dramatically increased if a quinoid structure was added to the nucleus. If an alkyl bridge of at least tree carbons connect the terminal amine to the nucleus is essential for activity. The most active side chains have proven to be primary amines and unsubstituted piperazines (Figure 1,Figure 1).

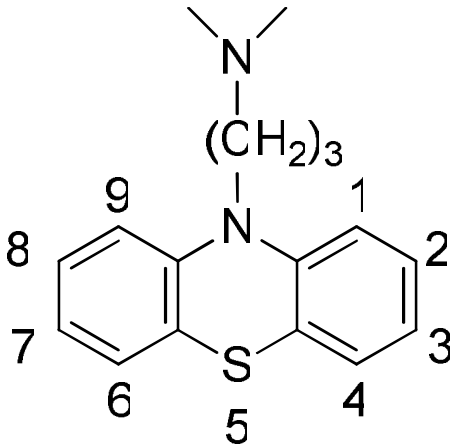


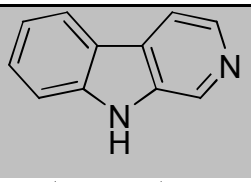
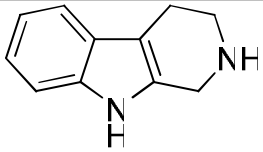
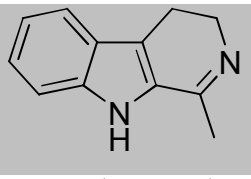
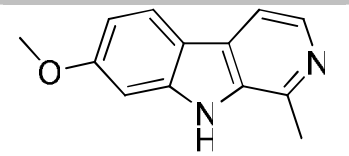
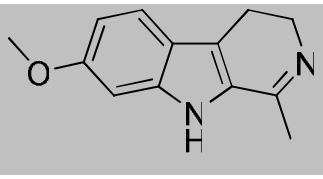
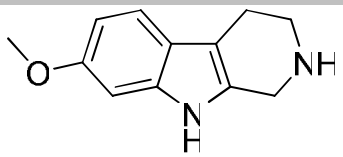
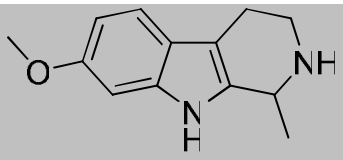
Figure 1 General structure and numbering of phenothiazine compounds

2.2 β-carboline alkaloids

The oldest use of β-carboline alkaloids, more specifically harmala alkaloids was by Amazonian shamans, the drugs were derived from indigenous plants[6] (i.e. *Banisteriopsis caapi*), and used in rituals for cleansing the body and the soul.

2.2.1 General structure and a few examples of important β-carbolines

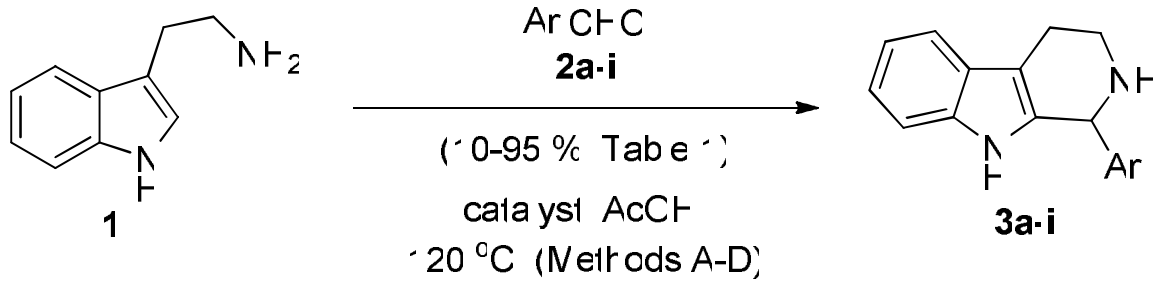
Table 1 Some important β-carbolines are presented below

Name	R_1	R_2	R_3	Structure
β-carboline	H	H	H	
Tryptoline	H	H	H	
Harmane	CH_3	H	H	
Harmine	CH_3	H	OCH_3	
Harmaline (a.k.a Telepathine)	CH_3	H	OCH_3	
Pinoline	H	OCH_3	H	
Tetrahydroharmine	CH_3	H H	OCH_3	

3. Original Contributions

3.1 Perfecting the Pictet-Spengler reaction

In our work we undertook a comparative evaluation of four methods (Methods A-D) employing aromatic aldehydes as substrates and acetic acid as solvent at reflux temperature (120 ^{o}C) in search for more expedient protocols of high efficiency associated with satisfactory yields, reasonable reaction time and facile workup process establishing easy access to representative 1-aryl-β-carbolines **3a-i** (Scheme 1). Transformations **1** → **3a-i** were first attempted by simple heating of the reactants in acetic acid for 2-3 hours (Method A:Table 2). When the reactions were conducted in the presence of TFA employed as catalyst no dramatic increase in the yields could be achieved (Method B:Table 2).



Scheme 1 Synthesis of 2,3,4,9-tetrahydro-1H-pyrido[3, 4-b]indoles

At this stage we resorted to the use boric acid suspended in acetic acid (Method C:Table **2**) which had been recognised as an efficient catalytic system promoting Biginelli reactions [7] that are related to Pictet-Spengler condensations.

Since Method C proved to be slightly superior to Methods A and B, respectively, resulting in higher yields we attempted its improvement by MW irradiation of the reaction mixture (Method D). Under these conditions the reactions were completed in 30-60 minutes (Table 1). Prolonged irradiation and heating decreased the isolated yields. It is worth to note that the reaction of **2e** performed by Method D afforded **3e** in a relatively low yield (45%), although the transformations of other substrates with decreased electrophilic character including the highly sensitive 10-methyl-10*H*-phenothiazine-3-carbaldehydes (**2g-i**,Table 2) led to significantly higher yields of the targeted β-carbolines. On the other hand, successful transformations of chlorophenothiazines **2h,i** could only be effected by Method D using MW irradiation, however, due to the formation of undefined decomposition products the reaction with 2-chloro derivative **2h** afforded **3h** in low yield (10 %).

Table 2 Yields and reaction times of the used methods (cf. Scheme 1-**Error! Reference source not found.**)

Ar-CHO (**2a-i**)	Yield (%)/ Reaction time (min) Method								Product
	A[(a)]		B[(b)]		C[(c)]		D[(d)]		
4-nitro-benzaldehyde (**2a**)	62	120	76	60	96	120	69	30	**3a**
4-chloro-benzaldehyde (**2b**)	79	120	73	60	75	60	74	30	**3b**
1-naphtaldehyde (**2c**)	51	120	70	120	83	60	83	30	**3c**
4-methoxybenzaldehyde (**2d**)	72	180	84	60	65	90	75	30	**3d**
3,4-dimethoxybenzaldehyde (**2e**)	78	120	37	240	75	60	45	30	**3e**
3-methylbenzaldehyde (**2f**)	70	180	40	240	74	80	69	30	**3f**
10-methyl-10*H*-phenothiazine-3-carbaldehyde (**2g**)	52	360	69	240	83	300	95	30	**3g**
2-chloro-10-methyl-10*H*-phenothiazine-3-carbaldehyde (**2h**)							10	60	**3h**
8-chloro-10-methyl-10*H*-phenothiazine-3-carbaldehyde (**2i**)							48	60	**3i**
2-formylbenzoic acid (**2j**)					82	1440	96	60.	**4**
2-formyl-5-methyl-1*H*-indole-3-carboxylic acid (**2k**)							62	120	**5**
3-formyl-1*H*-indole-4-carboxylic acid (**2l**)							55	120	**6**
4-formyl-1*H*-pyrazole-5-carboxylic acid (**2m**)							79	120	**7**
phtalaldehyde (**2n**)							50	60	**8**

[(a)]acetic acid (2 mL), 120 °C, normal heating, [(b)] TFA (35 µL)/acetic acid (2 mL), 120 °C, normal heating, [(c)] boric acid (35 mg)/acetic acid (2 mL), 120 °C, conventional heating, [(d)] Boric acid (35 mg)/acetic acid (2 mL), 120 °C, 200 W, MW (mono mode).

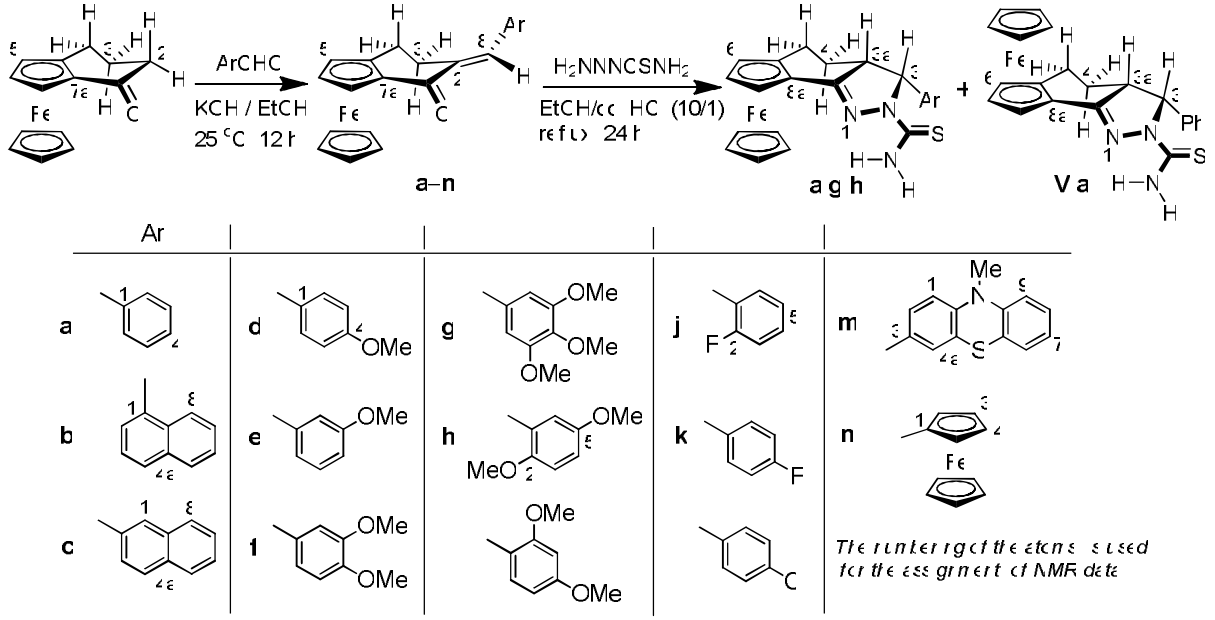
3.2 2-Arylideneferroceno[*e*]cyclohexanones and related 3-aryl-3,3a,4,5-tetrahydroferroceno [*g*]indazoles: synthesis, NMR-, DFT- and x-ray analysis

Prompted advances in the literature review, we extended the frame of our research on compounds with condensed ferrocene unit of potential biological relevance we envisaged the synthesis and structural analysis of several 2-arylidene-3,4-dihydroferroceno[*e*]cyclohex-1-enones (**II a–n**,Scheme 2) and a few related 9errocene[*g*]in-dazoles (**III a**,**g**,**h** and **IV a**,Scheme 2), the first representatives of a novel 9errocene9es-fused heterocyclic skeleton suitable to further functionalisations involving the thiocarbamoyl group in position 2. The novel chalcones and 9errocene[*g*]indazoles are expected to display appreciable activities in ongoing *in vitro* assays on tumorous cell lines and several microorganisms.

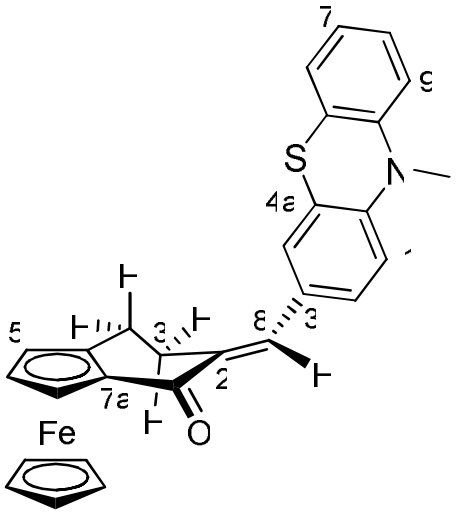
General procedures

3.2.1 Synthesis of novel chalcones and ferroceno[g]indazoles

Chalcones **II a–n** were prepared by the condensation of ferrocenocyclohexenone **I**[8] in low to mediocre yields (27–62%). The reactions were conducted in ethanol in the presence of catalytic amount of potassium hydroxide (4%) at room temperature. Since ketone **I** was used in racemic form, **II a**-**n** were also obtained as racemic mixtures.



Scheme 2 Novel chalcones and ferroceno[*g*]indazoles

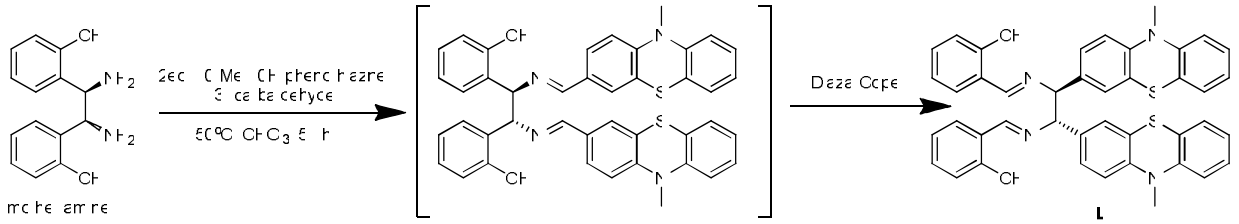


(E)-2-((10-methyl-10H-phenothiazin-3-yl)methylene)-3,4-dihydroferroceno[a]cyclo-hexane-1(2H)-one (II m)

Dark orange solid Yield: 0.387 g (27 %). Mp.: 104-107 °C; IR (cm^{-1}): 1651, 1571, 1461, 1402, 1329, 1280, 1256, 1140, 1184, 1002, 812, 746, 494; ^{1}H NMR ($CDCl_3$): 7.66 (d, *J*=2.2 Hz, 1H, H8); 7.30 (br d, *J*=8.2 Hz, 1H, H2'); 7.28 (br s, 1H, H4'); 7.21 (ddd, *J*=8.2, 7.4 and 1.3 Hz, 1H, H8'); 7.17 (dd, *J*=7.4 and 1.3 Hz, 1H, H6'); 6.98 (t, *J*=7.4 Hz,, 1H, H7'); 6.86 (two overlapping d's, *J*=8.2 Hz, 2H, H1' and H9'); 4.94 (br s, 1H, H7); 4.58 (t, *J*=2.5 Hz,, 1H, H6); 4.52 (br s, 1H, H5); 4.27 (s, 5H, η^5-$C_5\underline{H}_5$); 3.43 (s, 3H, $NC\underline{H}_3$); 3.34 (ddd, *J*=15.0, 5.2 and 2.2 Hz, 1H, $H4_{eq}$); 3.12 (dddd, *J*=15.0, 11.7, 5.8 and 2.2 Hz, 1H, $H3_{ax}$); 2.68 (ddd, *J*=14.8, 5.8 and 2.5 Hz, 1H, $H4_{eq}$); 2.47 (ddd, *J*=14.8, 11.7 and 5.8 Hz, 1H, $H4_{ax}$); ^{13}C NMR ($CDCl_3$): 194.6 (C1); 146.2 (C10a'); 145.6 (C9a'); 135.1 (C2); 134.2 (C8); 131.0 (C3'); 130.4 (C2'); 128.6 (C4'); 128.0 (C8'); 127.7 (C6'); 123.7 (C4a'); 123.27 (C5a'); 123.23 (C7'); 114.7 (C1'); 114.3 (C9'); 92.6 (C4a); 77.1 (C7a); 71.5 (C6); 70.8 (C5); 70.7 (η^5-$\underline{C}_5H_5$); 66.0 (C7); 27.9 (C3); 23.3 (C4): Anal. Calcd. for $C_{28}H_{23}FeNOS$ (477.40): C: 70.44; H: 4.86; N, 2.93; S, 6.72; Found: C: 70.35; H: 4.90; N, 2.83; S, 6.75%.

3.3 Synthesis of novel C_2-chiral diphenothiazinyl- salen complexes and ligands

(Sp)-2-hydroxy-1-phenothiazine chiral salene complexes have been prepared in good yields. The synthesis of the ligand was achieved from the condensation of 2,2'-[(1S,2S)-1,2-diaminoethane-1,2-diyl]diphenol with 10- methyl -10-H- phenothiazine-3-carbaldehyde in chloroform at 50°C (Scheme 3).



Scheme 3 Synthesis of the diphenothiazinlyl-salene ligand

^{1}H NMR confirmed the proposed structure (Figure 2), and all found peeks were correlated.

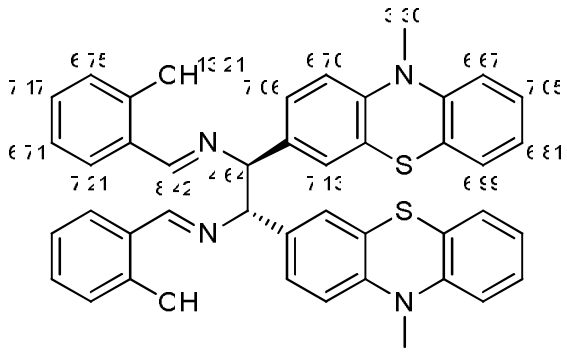
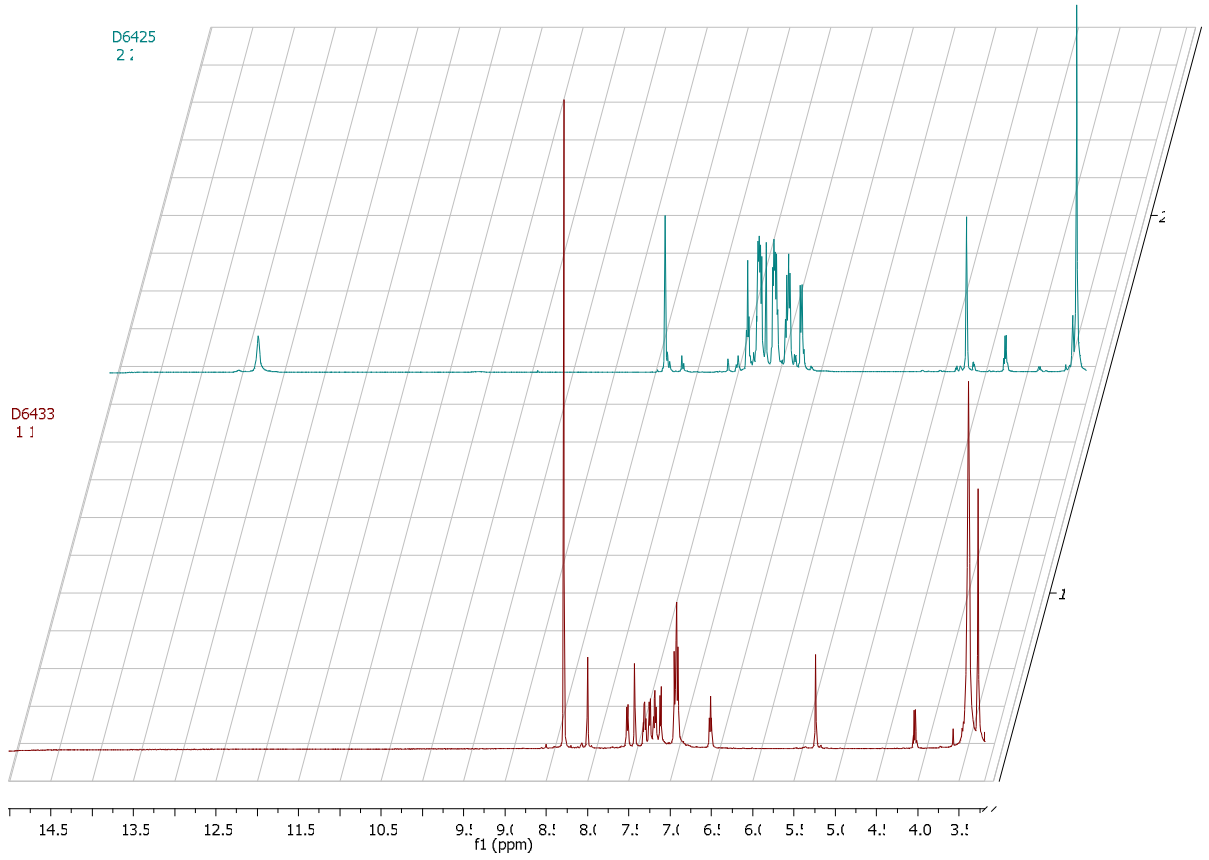


Figure 2 ^{1}H NMR (500 MHz, DMSO-*d6*) spectra assigned to structure

Having the ^{1}H NMR spectra of the ligand and the palladium complex, we had another tool at a disposal to confirm the structural traits of the synthesized complex.



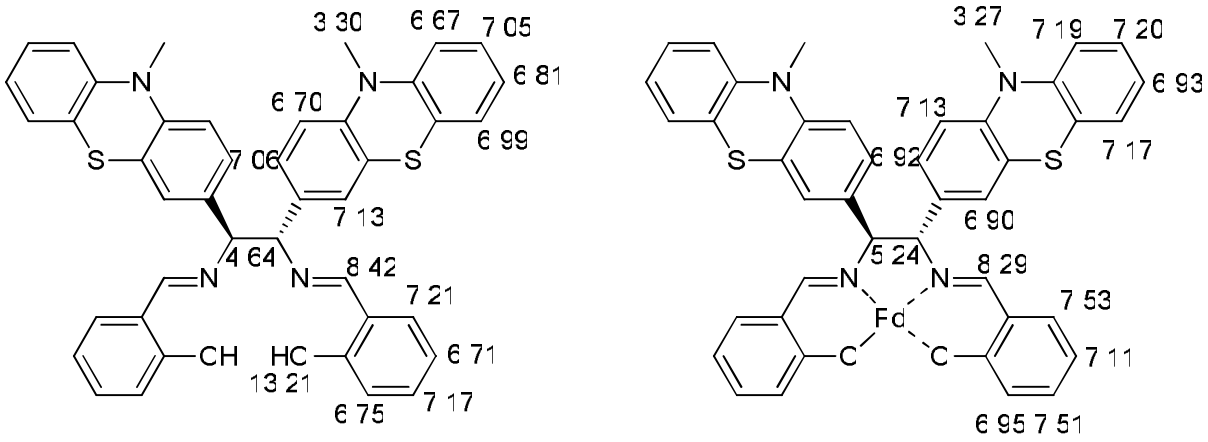


Figure 3 Comparison of ^{1}H NMR spectra of the ligand (blue) with the palladium complex (red)

Comparing of the ^{1}H NMR spectra in DMSO-d_6 of the starting ligand and the palladium (II) complex it is important to note (Figure 3), the disappearance of the proton signal of the OH group at 13.21 ppm, the growth of the proton signal at 8.28 ppm (next to the carbon-nitrogen double bond), and peak 4.64 ppm of the ligand spectrum changed to 5.24 ppm in the product (the chiral protons), we may conclude, that palladium is chelated within our ligand.

5. Overview, general conclusions

Two novel phenothiazine carbaldehydes were synthesized and structurally confirmed (2-chloro-10-methyl-10H-phenothiazine-3-carbaldehyde and 8-chloro-10-methyl-10H-phenothiazine-3-carbaldehyde), and literature methods, for known compounds were improved to save time, and money in the production of starting materials.

We perfected the synthesis of aromatic 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indoles, a field that is a hot topic in current synthetic research; found innovative methods of purification for compounds usually requiring expensive, time and money consuming liquid chromatography. Our simple method yields compounds of analytical purity, employs easy to obtain, relatively inexpensive and safe materials; catalysts and solvents may be reused if required, and the use of microwave reactors has proven to be of great synthetic value.

By extending the groups of aryl aldehydes and hydrazine reagents the reported syntheses of the ferrocene-fused chalcones and ferroceno[*g*]indazoles, the first representatives of a heterocyclic ring system might open up ways to valuable libraries of novel metallocene derivatives of potential biological interest. (Note: the use of roman numerals for ferrocene compounds eased the administration of the large number of compounds synthesized).Moreover, employing a single enantiomer of ketone **I** as precursor, the racemic compounds described in this contribution may become accessible in optically active forms with known relative and consequently – absolute configurations. The elaboration of more efficient conditions and separation methods for the thiosemicarbazide-mediated cyclisations and related reactions of the chalcones type **II** of decreased reactivity is in progress.

Recent literature review of phenothiazine pharmacophores suggested, that there is no compound in this class that was effectively used in cancer therapy by itself, not only aiding, or facilitating the effects of other drugs, that should target cancer DNA.

Our mission is to fill this void, with a new concept, a class of compounds, and the newly synthesized molecule acts as a tetradentate ligand; it coordinated with metal ions with two Schiff base nitrogens and phenolic oxygen atom by deprotonation. The bonding of ligand to metal ion was confirmed by spectroscopic investigation. X-ray diffraction and anticancer studies are under way for all synthesized compounds; the palladium complex looks promising in cytotoxicity tests.

Taking control in the synthesis of a chiral ligand is never an easy job, and the lessons learned here will fuel our enthusiasm for further development of novel multidentate ligands, that

may be used as catalysts or anticancer drugs. Our future goals consist of building new platinum and other d element complexes of the chiral amine, and therapeutical evaluation of both classes of compounds.

We managed to synthesize and structurally confirm several novel compounds, contribute to the chemistry of phenothiazine and ferrocene, publish two articles in the field (a third article is under way), and find possible anticancer drug candidates. A total of 52 compounds were synthesized, out of which 8 were primary materials, 17 were already known and 36 are new.

6. Acknowledgements

I am very grateful to prof. Dr. Csámpai Antal, doctor of the Hungarian Academy of Sciences, my PhD research tutor, and supervisor, at Eötvös Lorand University and prof. Dr. Luminița Silaghi-Dumitrescu, my PhD supervisor at Babeș-Bolyai Uniersity for aiding me in Science and Life in a way only they can.

This work was financially supported by the Hungarian Scientific Research Fund (OTKA K-83874) and the European Union and the European Social Fund (grant agreement no. TÁMOP 4.2.1/B-09/KMR-2010-0003).

We are also indebted to the Ph.D. scholarship, the project co-financed by the sectoral operational program (Contract nr.: POSDRU/88/1.5/S/60185 – "Innovative doctoral studies in a Knowledge Based Society") for human resources development 2007–2013.

We gratefully acknowledge the financial support of Romanian National Council of Scientific Research CNCSIS–UEFISCSU (project PN II - ID-PCCE-140/2008).

I am very grateful the American Association for the Advancement of Science for having me among its members since 06/28/2012 and granting access to top scientific news and information.

References

1. Hendrich, A. B.; Wesołowska, O.; Motohashi, N.; Molnár, J.; Michalak, K., *Biochemical and Biophysical Research Communications* **2003,** *304* (2), 260-265.
2. Bernthsen, A., *Berichte der deutschen chemischen Gesellschaft* **1883,** *16* (2), 2896-2904.
3. Bernthsen, A., *Berichte der deutschen chemischen Gesellschaft* **1883,** *16* (1), 1025-1028.
4. Schirmer, R. H.; Coulibaly, B.; Stich, A.; Scheiwein, M.; Merkle, H.; Eubel, J.; Becker, K.; Becher, H.; Muller, O.; Zich, T.; Schiek, W.; Kouyate, B., *REDOX REPORT* **2003,** *8* (5), 272-275.
5. Turner, T., *BMJ* **2007,** *334 Suppl 1* (suppl 1), s7.
6. Dana T. Aftab, L. M. B., Carson R. Loomis, and William N. Halt, *Molecular Pharmacology* **1991,** *40*, 798-805.
7. Nishizuka, Y., *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* **1995,** *9* (7), 484-96.
8. Anderson, P. W.; McGill, J. B.; Tuttle, K. R., *Curr Opin Nephrol Hypertens* **2007,** *16* (5), 397-402.
9. Alcolea Palafox, M.; Gil, M.; Nunez, J. L.; Tardajos, G., *International Journal of Quantum Chemistry* **2002,** *89* (3), 147-171.
10. Litman, T.; Druley, T. E.; Stein, W. D.; Bates, S. E., *Cellular and Molecular Life Sciences* **2001,** *58* (7), 931-959.
11. Liu, R. H.; Sharom, F. J., *BIOCHEMISTRY* **1996,** *35* (36), 11865-11873.
12. Konya, A.; Andor, A.; Satorhelyi, P.; Nemeth, K.; Kurucz, I., *Biochem Biophys Res Commun* **2006,** *346* (1), 45-50.
13. Hollenstein, K.; Dawson, R. J.; Locher, K. P., *Curr Opin Struct Biol* **2007,** *17* (4), 412-8.
14. Okumura, H.; Nakazawa, J.; Tsuganezawa, K.; Usui, T.; Osada, H.; Matsumoto, T.; Tanaka, A.; Yokoyama, S., *Toxicology letters* **2006,** *166* (1), 44-52.
15. Jaszczyszyn, A.; Gasiorowski, K.; Swiatek, P.; Malinka, W.; Cieslik-Boczula, K.; Petrus, J.; Czarnik-Matusewicz, B., *Pharmacological Reports* **2012,** *64* (1), 16-23.
16. Rätsch, C., *The Encyclopedia of Psychoactive Plants: Ethnopharmacology and Its Applications*. Park Street Press: 2005.
17. Samoylenko, V.; Rahman, M. M.; Tekwani, B. L.; Tripathi, L. M.; Wang, Y. H.; Khan, S. I.; Khan, I. A.; Miller, L. S.; Joshi, V. C.; Muhammad, I., *Journal of ethnopharmacology* **2010,** *127* (2), 357-67.
18. Tipton, K. F.; Boyce, S.; O'Sullivan, J.; Davey, G. P.; Healy, J., *Curr Med Chem* **2004,** *11* (15), 1965-82.
19. Hare, M. L., *The Biochemical journal* **1928,** *22* (4), 968-79.
20. Oreland, L.; Hallman, J.; Damberg, M., *Curr Med Chem* **2004,** *11* (15), 2007-16.
21. Herraiz, T., *J. Agric. Food Chem.* **2000,** *48*, 4900–4904.
22. Herraiz, T.; Chaparro, C., *Life sciences* **2006,** *78* (8), 795-802.
23. Barbara Hoefgen, M. D., Patrick Mohr, Astrid M. Schramm, Sherif A. F. Rostom, Hussein El-Subbagh,; Peter M. Schweikert, D. R. R., Matthias U. Kassack, and Jochen Lehmann, *J. Med. Chem.* **2006,** (49), 760-769.
24. Hironori Tsuchiya, H. S. a. M. I., *Chem. Pharm. Bull.* **1999,** *47* (3), 440-443.
25. Herraiz, T., *Journal of Agricultural and Food Chemistry* **1996,** *44* (10), 3057-3065.
26. Herraiz, T., *Journal of Agricultural and Food Chemistry* **1998,** *46* (9), 3484-3490.
27. Herraiz, T.; Ough, C. S., *Journal of Agricultural and Food Chemistry* **1993,** *41* (6), 959-964.

28. Herraiz, T. H., Z.; Ough C. S., *J. Agric. Food Chem.* **1993,** *41*, 455-459.
29. Moura, D. J.; Richter, M. F.; Boeira, J. M.; Pegas Henriques, J. A.; Saffi, J., *Mutagenesis* **2007,** *22* (4), 293-302.
30. Harman, D., *Journal of Gerontology* **1956,** *11* (3), 298-300.
31. Van Raamsdonk, J. M.; Hekimi, S., *PLoS genetics* **2009,** *5* (2), e1000361.
32. Pictet, A.; Spengler, T., *Berichte der deutschen chemischen Gesellschaft* **1911,** *44* (3), 2030-2036.
33. Whaley, W. M.; Govindachari, T. R., The Pictet-Spengler Synthesis of Tetrahydroisoquinolines and Related Compounds. In *Organic Reactions*, John Wiley & Sons, Inc.: 1951; Vol. 6, pp 151-190.
34. Hahn, G.; Ludewig, H., *Berichte der deutschen chemischen Gesellschaft (A and B Series)* **1934,** *67* (12), 2031-2035.
35. Cox, E. D.; Cook, J. M., *Chemical Reviews* **1995,** *95* (6), 1797-1842.
36. Beke, G.; Szabó, L. F.; Podányi, B., *Journal of Natural Products* **2002,** *65* (5), 649-655.
37. Cesati, R. R.; Katzenellenbogen, J. A., *Organic Letters* **2000,** *2* (23), 3635-3638.
38. Allen, M. S.; Hagen, T. J.; Trudell, M. L.; Codding, P. W.; Skolnick, P.; Cook, J. M., *Journal of Medicinal Chemistry* **1988,** *31* (9), 1854-1861.
39. Farzin, D.; Mansouri, N., *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* **2006,** *16* (5), 324-8.
40. Ya-Ching SHEN, C.-Y. C., Pei-Wen HSIEH, Chang-Yih DUH, Yat-Min LIN, and Chin-Lien Ko, *Chem. Pharm. Bull.* **2005,** *53* (1), 32—36.
41. Hotha, S.; Yarrow, J. C.; Yang, J. G.; Garrett, S.; Renduchintala, K. V.; Mayer, T. U.; Kapoor, T. M., *Angew Chem Int Ed Engl* **2003,** *42* (21), 2379-82.
42. Sunder-Plassmann, N.; Sarli, V.; Gartner, M.; Utz, M.; Seiler, J.; Huemmer, S.; Mayer, T. U.; Surrey, T.; Giannis, A., *Bioorganic & medicinal chemistry* **2005,** *13* (22), 6094-111.
43. Sun, C.-M.; Wu, C.-Y., *Synlett* **2002,** *2002* (10), 1709-1711.
44. Grigg, R.; Gunaratne, H. Q. N.; McNaghten, E., *Journal of the Chemical Society, Perkin Transactions 1* **1983**, 185-187.
45. Bratulescu, G., *Tetrahedron Letters* **2008,** *49* (6), 984-986.
46. Hadjaz, F.; Yous, S.; Lebegue, N.; Berthelot, P.; Carato, P., *Tetrahedron* **2008,** *64* (42), 10004-10008.
47. Yokoyama, A.; Ohwada, T.; Shudo, K., *J. Org. Chem.* **1999,** *64* (2), 611-617.
48. Saha, B.; Sharma, S.; Sawant, D.; Kundu, B., *Tetrahedron Letters* **2007,** *48* (8), 1379-1383.
49. Prajapati, D.; Gohain, M., *Synthetic Communications* **2008,** *38* (24), 4426-4433.
50. Aganofov, N. E., Dudin, A. V. , Preobrazhenskii, A. A. and Zhulin, V. M., *Russian Chemical Bulletin, International Edition* **2001,** *50* (3), 560-562.
51. Yu, J.; Wearing, X. Z.; Cook, J. M., *J Org Chem* **2005,** *70* (10), 3963-79.
52. Liu, F.; You, Q. D., *Synthetic Communications* **2007,** *37* (22), 3933-3938.
53. Csámpai, A.; Györfi, A. Z.; Túrós, G. I.; Sohár, P., *Journal of Organometallic Chemistry* **2009,** *694* (22), 3667-3673.
54. Drent, E., *Ferrocenes. Homogeneous Catalysis. Organic Synthesis. Materials Science. A. Togni and T. Hayashi, eds. VCH Verlagsgesellschaft, Weinheim, 1995. 540 pp. DM 248.00 ISBN 3-527-29048-6*. WILEY-VCH Verlag: 2010; Vol. 115, p 448-449.
55. Dombrowski, K. E.; Baldwin, W.; Sheats, J. E., *Journal of Organometallic Chemistry* **1986,** *302* (3), 281-306.

56. Koepf-Maier, P.; Koepf, H., *Chemical Reviews* **1987,** *87* (5), 1137-1152.
57. Neuse, E. W.; Meirim, M. G.; Blom, N. F., *Organometallics* **1988,** *7* (12), 2562-2565.
58. Scarcia, V.; Furlani, A.; Longato, B.; Corain, B.; Pilloni, G., *Inorganica Chimica Acta* **1988,** *153* (1), 67-70.
59. Hill, D. T.; Girard, G. R.; McCabe, F. L.; Johnson, R. K.; Stupik, P. D.; Zhang, J. H.; Reiff, W. M.; Eggleston, D. S., *Inorganic Chemistry* **1989,** *28* (18), 3529-3533.
60. Motohashi, N.; Meyer, R.; Gollapudi, S. R.; Bhattiprolu, K. R., *Journal of Organometallic Chemistry* **1990,** *398* (3), 205-217.
61. Neuse, E. W.; Kanzawa, F., *Applied Organometallic Chemistry* **1990,** *4* (1), 19-26.
62. Houlton, A.; Roberts, R. M. G.; Silver, J., *Journal of Organometallic Chemistry* **1991,** *418* (1), 107-112.
63. Top, S.; Tang, J.; Vessieres, A.; Carrez, D.; Provot, C.; Jaouen, G., *Chemical Communications* **1996,** (8), 955-956.
64. Delhaes, L.; Abessolo, H.; Biot, C.; Berry, L.; Delcourt, P.; Maciejewski, L.; Brocard, J.; Camus, D.; Dive, D., *Parasitol Res* **2001,** *87* (3), 239-44.
65. Klimova, T.; Klimova, E. I.; Martínez García, M.; Vázquez López, E. A.; Alvarez Toledano, C.; Toscano, A. R.; Ruíz Ramírez, L., *Journal of Organometallic Chemistry* **2001,** *628* (1), 107-113.
66. Ma, H.; Hou, Y.; Bai, Y.; Lu, J.; Yang, B., *Journal of Organometallic Chemistry* **2001,** *637–639* (0), 742-744.
67. Top, S.; Vessières, A.; Cabestaing, C.; Laios, I.; Leclercq, G.; Provot, C.; Jaouen, G., *Journal of Organometallic Chemistry* **2001,** *637–639* (0), 500-506.
68. Gerard, J., *Current Medicinal Chemistry* **2004,** *11* (18), 2505-2517.
69. Weber, B.; Serafin, A.; Michie, J.; Van Rensburg, C.; Swarts, J. C.; Bohm, L., *Anticancer Res* **2004,** *24* (2B), 763-70.
70. Bincoletto, C.; Tersariol, I. L.; Oliveira, C. R.; Dreher, S.; Fausto, D. M.; Soufen, M. A.; Nascimento, F. D.; Caires, A. C., *Bioorganic & medicinal chemistry* **2005,** *13* (8), 3047-55.
71. Hillard, E.; Vessieres, A.; Thouin, L.; Jaouen, G.; Amatore, C., *Angew Chem Int Ed Engl* **2005,** *45* (2), 285-90.
72. Moriuchi, T., Hirao, T., Ferrocene–Peptide Bioconjugates. In *Bioorganometallic Chemistry*, Simonneaux, G., Ed. Springer-Verlag Berlin Heidelberg 2006: Heidelberg, 2006; Vol. 17, p 143.
73. Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S., *J Med Chem* **1997,** *40* (23), 3715-8.
74. Loev, B.; Flores, M., *JOURNAL OF ORGANIC CHEMISTRY* **1961,** *26* (9), 3595-3595.
75. Popp, F. D.; Roth, S.; Kirby, J., *Journal of Medicinal Chemistry* **1963,** *6* (1), 83-85.
76. Osella, D.; Ferrali, M.; Zanello, P.; Laschi, F.; Fontani, M.; Nervi, C.; Cavigiolio, G., *Inorganica Chimica Acta* **2000,** *306* (1), 42-48.
77. van Staveren, D. R.; Metzler-Nolte, N., *Chem Rev* **2004,** *104* (12), 5931-85.
78. Neuse, E., *Journal of Inorganic and Organometallic Polymers and Materials* **2005,** *15* (1), 3-31.
79. Allardyce, C. S.; Dorcier, A.; Scolaro, C.; Dyson, P. J., *Applied Organometallic Chemistry* **2005,** *19* (1), 1-10.
80. Fouda, M. F. R.; Abd-Elzaher, M. M.; Abdelsamaia, R. A.; Labib, A. A., *Applied Organometallic Chemistry* **2007,** *21* (8), 613-625.

81. Zsoldos-Mady, V.; Csampai, A.; Szabo, R.; Meszaros-Alapi, E.; Pasztor, J.; Hudecz, F.; Sohar, P., *ChemMedChem* **2006,** *1* (10), 1119-25.
82. Károlyi, B. I.; Bősze, S.; Orbán, E.; Sohár, P.; Drahos, L.; Gál, E.; Csámpai, A., *Molecules* **2012,** *17* (3), 2316-2329.
83. Gaina, L.; Csampai, A.; Turos, G.; Lovasz, T.; Zsoldos-Mady, V.; Silberg, I. A.; Sohar, P., *Organic & Biomolecular Chemistry* **2006,** *4* (23), 4375-4386.
84. Abrán, Á.; Csámpai, A.; Böcskei, Z.; Sohár, P., *Tetrahedron* **1999,** *55* (17), 5441-5448.
85. Túrós, G.; Csámpai, A.; Czugler, M.; Wamhoff, H.; Sohár, P., *Journal of Organometallic Chemistry* **2001,** *634* (2), 122-130.
86. Túrós, G.; Csámpai, A.; Lovász, T.; Györfi, A.; Wamhoff, H.; Sohár, P., *European Journal of Organic Chemistry* **2002,** *2002* (22), 3801-3806.
87. Csámpai, A.; Túrós, G.; Kudar, V.; Simon, K.; Oeynhausen, H.; Wamhoff, H.; Sohár, P., *European Journal of Organic Chemistry* **2004,** *2004* (4), 717-723.
88. Kiss, K.; Csámpai, A.; Sohár, P., *Journal of Organometallic Chemistry* **2010,** *695* (15-16), 1852-1857.
89. Gál, E.; Cristea, C.; Silaghi-Dumitrescu, L.; Lovász, T.; Csámpai, A., *Tetrahedron* **2010,** *66* (52), 9938-9944.
90. Csámpai, A.; Abrán, Á.; Kudar, V.; Túrós, G.; Wamhoff, H.; Sohár, P., *Journal of Organometallic Chemistry* **2005,** *690* (3), 802-810.
91. Gyömöre, Á.; Csámpai, A., *Journal of Organometallic Chemistry* **2011,** *696* (8), 1626-1631.
92. Manfredini, S.; Bazzanini, R.; Baraldi, P. G.; Guarneri, M.; Simoni, D.; Marongiu, M. E.; Pani, A.; La Colla, P.; Tramontano, E., *Journal of Medicinal Chemistry* **1992,** *35* (5), 917-924.
93. Katayama, H.; Oshiyama, T., *Canadian Journal of Chemistry* **1997,** *75* (6), 913-919.
94. Park, H. J.; Lee, K.; Park, S. J.; Ahn, B.; Lee, J. C.; Cho, H.; Lee, K. I., *Bioorganic & medicinal chemistry letters* **2005,** *15* (13), 3307-12.
95. L. CECCHI, F. M., G. PALAZZINO, G. FILACCHIONI, G. PORRETTA, *FARMACO* **1984,** *39*, 888 - 900.
96. L. CECCHI, F. M., G. PALAZZINO, G. FILACCHIONI, G. PORRETTA, *FARMACO* **1984,** *39*, 953-962.
97. Güniz Küçükgüzel, Ş.; Rollas, S.; Erdeniz, H.; Kiraz, M.; Cevdet Ekinci, A.; Vidin, A., *European Journal of Medicinal Chemistry* **2000,** *35* (7-8), 761-771.
98. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H., *Journal of Medicinal Chemistry* **2000,** *43* (5), 953-970.
99. Bekhit, A., *European Journal of Medicinal Chemistry* **2003,** *38* (1), 27-36.
100. Garg, H. G.; Singhal, A.; Mathur, J. M. L., *Journal of Pharmaceutical Sciences* **1973,** *62* (3), 494-496.
101. Rathelot, P.; Azas, N.; El-Kashef, H.; Delmas, F.; Di Giorgio, C.; Timon-David, P.; Maldonado, J.; Vanelle, P., *Eur J Med Chem* **2002,** *37* (8), 671-9.
102. Eid AI, K. M., Fahmy HH., *J. Pharm. Belg.* **1978,** *33*, 303.
103. Menozzi, G.; Mosti, L.; Fossa, P.; Mattioli, F.; Ghia, M., *Journal of Heterocyclic Chemistry* **1997,** *34* (3), 963-968.
104. Bhat, B. A.; Dhar, K. L.; Puri, S. C.; Saxena, A. K.; Shanmugavel, M.; Qazi, G. N., *Bioorganic & medicinal chemistry letters* **2005,** *15* (12), 3177-80.

105. L. V. Snegur, V. N. B., A. A. Simenel,Yu. S. Nekrasov, L. A. Ostrovskaya, and N. S. Sergeevac, *Russian Chemical Bulletin, International Edition* **2010,** *59* (12), 2167-2178.
106. Dyson, P. J.; Sava, G., *Dalton Trans* **2006,** (16), 1929-33.
107. Williams, D. S.; Atilla, G. E.; Bregman, H.; Arzoumanian, A.; Klein, P. S.; Meggers, E., *Angew Chem Int Ed Engl* **2005,** *44* (13), 1984-7.
108. Gormen, M.; Plażuk, D.; Pigeon, P.; Hillard, E. A.; Plamont, M.-A.; Top, S.; Vessières, A.; Jaouen, G., *Tetrahedron Letters* **2010,** *51* (1), 118-120.
109. Dubar, F.; Khalife, J.; Brocard, J.; Dive, D.; Biot, C., *Molecules* **2008,** *13* (11), 2900-7.
110. Supan, C.; Mombo-Ngoma, G.; Dal-Bianco, M. P.; Ospina Salazar, C. L.; Issifou, S.; Mazuir, F.; Filali-Ansary, A.; Biot, C.; Ter-Minassian, D.; Ramharter, M.; Kremsner, P. G.; Lell, B., *Antimicrobial agents and chemotherapy* **2012,** *56* (6), 3165-73.
111. Pfeiffer, P.; Breith, E.; Lübbe, E.; Tsumaki, T., *Justus Liebigs Annalen der Chemie* **1933,** *503* (1), 84-130.
112. Tsumaki, T., *Bulletin of the Chemical Society of Japan* **1938,** *13* (2), 252-260.
113. Diehl, H.; Hach, C. C.; Bailar, J. C., Bis(N,N'-Disalicylalethylenediamine)-μ -Aquodicobalt(II). In *Inorganic Syntheses*, John Wiley & Sons, Inc.: 1950; pp 196-201.
114. Barkelew, C. H.; Calvin, M., *Journal of the American Chemical Society* **1946,** *68* (11), 2257-2262.
115. Calvin, M.; Bailes, R. H.; Wilmarth, W. K., *Journal of the American Chemical Society* **1946,** *68* (11), 2254-2256.
116. Calvin, M.; Barkelew, C. H., *Journal of the American Chemical Society* **1946,** *68* (11), 2267-2273.
117. Hughes, E. W.; Wilmarth, W. K.; Calvin, M., *Journal of the American Chemical Society* **1946,** *68* (11), 2273-2278.
118. Wilmarth, W. K.; Aranoff, S.; Calvin, M., *Journal of the American Chemical Society* **1946,** *68* (11), 2263-2266.
119. Smith, T. D.; Pilbrow, J. R., *Coordination Chemistry Reviews* **1981,** *39* (3), 295-383.
120. Smith, T. D.; Ruzic, I. M.; Tirant, S.; Pilbrow, J. R., *Journal of the Chemical Society, Dalton Transactions* **1982,** (2), 363-372.
121. Caputo, C. A.; Jones, N. D., *Dalton Transactions* **2007,** (41), 4627.
122. Daly, A. M.; Renehan, M. F.; Gilheany, D. G., *Organic Letters* **2001,** *3* (5), 663-666.
123. Deng, L.; Jacobsen, E. N., *The Journal of Organic Chemistry* **1992,** *57* (15), 4320-4323.
124. Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W., *Journal of the American Chemical Society* **2002,** *124* (7), 1174-1175.
125. Jacobsen, E. N., *Accounts of Chemical Research* **2000,** *33* (6), 421-431.
126. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L., *ChemInform* **1991,** *22* (50), no-no.
127. McGarrigle, E. M.; Gilheany, D. G., *Chemical Reviews* **2005,** *105* (5), 1563-1602.
128. Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N., *Journal of the American Chemical Society* **1994,** *116* (20), 9333-9334.
129. Yoon, T. P.; Jacobsen, E. N., *Science* **2003,** *299* (5613), 1691-3.
130. Zhang, H.; Xiang, S.; Li, C., *ChemInform* **2005,** *36* (29), no-no.
131. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N., *Journal of the American Chemical Society* **1990,** *112* (7), 2801-2803.
132. Hyunwoo Kim, M. S., Alan J. Lough, and Jik Chin, *Organic Letters* **2009,** *11* (1), 157-160.

133. Jik Chin, F. M., Nirusha Thavarajah, Donghyung Lee, Alan Lough, and Doo Soo Chung, *J. Am. Chem. Soc.* **2003,** *125*, 15276-15277.
134. Kim, H. J.; Kim, H.; Alhakimi, G.; Jeong, E. J.; Thavarajah, N.; Studnicki, L.; Koprianiuk, A.; Lough, A. J.; Suh, J.; Chin, J., *Journal of the American Chemical Society* **2005,** *127* (47), 16370-1.
135. Kiss, K.; Holczbauer, T.; Czugler, M.; Sohár, P.; Bodor, A.; Csámpai, A., *Journal of Organometallic Chemistry* **2012,** *706-707*, 46-51.
136. Ronald Gust, I. O., Diana Posselt, and Klaus Sommer, *J. Med. Chem.* **2004,** *47*, 5837-5846.
137. Li, Y.; Yang, Z.-y., *Inorganica Chimica Acta* **2009,** *362* (13), 4823-4831.
138. Ansari, K. I.; Kasiri, S.; Grant, J. D.; Mandal, S. S., *Journal of biomolecular screening* **2011,** *16* (1), 26-35.
139. Rosalind A. Rosenthal, B. F., Richard P. Hill, Karl D. Huffman, Zelmira Lazarova,Javed Mahmood, Meetha Medhora, Robert Molthen, John E. Moulder, Stephen T. Sonis, Philip J. Tofilon and Susan R. Doctrow, *Anti-Cancer Agents in Medicinal Chemistry* **2011,** *11*, 359-372.
140. Azam, M.; Hussain, Z.; Warad, I.; Al-Resayes, S. I.; Khan, M. S.; Shakir, M.; Trzesowska-Kruszynska, A.; Kruszynski, R., *Dalton Trans* **2012,** *41* (35), 10854-64.
141. Proetto, M.; Liu, W.; Hagenbach, A.; Abram, U.; Gust, R., *Eur J Med Chem* **2012,** *53* (0), 168-75.
142. Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J., *Tetrahedron Letters* **1986,** *27* (3), 279-282.
143. Mingos, D. M. P.; Baghurst, D. R., *Chemical Society Reviews* **1991,** *20* (1), 1-47.
144. Kappe, C. O., *Angewandte Chemie International Edition* **2004,** *43* (46), 6250-6284.
145. Kiss, K.; Csampai, A.; Sohar, P., *Journal of Organometallic Chemistry* **2010,** *695* (15-16), 1852-1857.
146. Hoefgen, B.; Decker, M.; Mohr, P.; Schramm, A. M.; Rostom, S. A.; El-Subbagh, H.; Schweikert, P. M.; Rudolf, D. R.; Kassack, M. U.; Lehmann, J., *J Med Chem* **2006,** *49* (2), 760-9.
147. Becke, A. D., *The Journal of Chemical Physics* **1993,** *98* (2), 1372.
148. C. Lee, W. Y., and R. G. Parr, *Phys. Rev. B* **1988,** *37*, 785-789
149. Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J., *The Journal of Physical Chemistry* **1994,** *98* (45), 11623-11627.
150. Wiberg, K. B., *Journal of Computational Chemistry* **1986,** *7* (3), 379-379.
151. Hill, E. A.; Richards, J. H., *Journal of the American Chemical Society* **1961,** *83* (20), 4216-4221.
152. Etter, M. C.; MacDonald, J. C.; Bernstein, J., *Acta Crystallographica Section B* **1990,** *46* (2), 256-262.
153. Saenger, W.; Lindner, K., *Angewandte Chemie International Edition in English* **1980,** *19* (5), 398-399.
154. Weber, E.; Josel, H. P., *Journal of Inclusion Phenomena and Macrocyclic Chemistry* **1983,** *1* (1), 79-85.
155. Weber, E.; Csoregh, I.; Stensland, B.; Czugler, M., *Journal of the American Chemical Society* **1984,** *106* (11), 3297-3306.
156. Lóránd, T.; Kocsis, B.; Emôdy, L.; Sohár, P., *European Journal of Medicinal Chemistry* **1999,** *34* (11), 1009-1018.

157. Jagtap, P. G.; Degterev, A.; Choi, S.; Keys, H.; Yuan, J.; Cuny, G. D., *Journal of Medicinal Chemistry* **2007,** *50* (8), 1886-1895.
158. Pearson, R. G., *Chemical Hardness: Applications from Molecules to Solids*. Wiley-VCH:: Weinheim, Germany, 1997.
159. Kohn, W.; Becke, A. D.; Parr, R. G., *The Journal of Physical Chemistry* **1996,** *100* (31), 12974-12980.
160. Izumi, T.; Tamura, F.; Sasaki, K., *Bulletin of the Chemical Society of Japan* **1992,** *65* (10), 2784-2788.
161. A. Jalon, F.; Lopez-Agenjo, A.; R. Manzano, B.; Moreno-Lara, M.; Rodriguez, A.; Sturm, T.; Weissensteiner, W., *Journal of the Chemical Society, Dalton Transactions* **1999,** (22), 4031-4039.
162. Ketata, I., *Open Journal of Inorganic Chemistry* **2012,** *02* (02), 33-39.
163. Frisch, M. J. T., G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A, *GAUSSIAN 03, Rev. A. 1*. Gaussian, Inc: Pittsburgh, PA, 2003.
164. Yang, C. J.; Chang, Y. J.; Watanabe, M.; Hon, Y. S.; Chow, T. J., *Journal of Materials Chemistry* **2012,** *22* (9), 4040-4049.
165. Iwaoka, T.; Kondo, M., *Chemistry Letters* **1978,** *7* (7), 731-734.
166. Jovanovic, M. V.; Biehl, E. R.; De Meester, P.; Chu, S. S. C., *Journal of Heterocyclic Chemistry* **1986,** *23* (3), 801-807.
167. Jovanovic, M. V. B., Edward R., *Organic Magnetic Resonance* **1984,** *22* (8), 491-504.
168. Ebdrup, S., *Journal of the Chemical Society, Perkin Transactions 1* **1998,** (6), 1147-1150.
169. Srinivasan, N.; Ganesan, A., *Chemical Communications* **2003,** (7), 916-917.