NOVEL 4-FERROCENYL-8-(PHENYLTHIO)-1,2,3,4-
TETRAHYDROQUINOLINE: DESIGN, SYNTHESIS AND
SPECTRAL CHARACTERIZATION

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ABSTRACT

Herein, we report design, synthesis and spectral characterization of novel 4-ferrocenyl-8-(phenylthio)-1,2,3,4-
tetrahydroquinoline. Desired synthesis was achieved in three reaction steps, with a good overall yield (67%). First
step includedaza-Michael addition of 2-(phenylthio)aniline to 1-ferrocenylpropenone, subsequently, the obtained
ketone was smoothly reduced to the corresponding 1,3-amino alcohol. The final step was an intramolecular
cyclization prompted by acetic acid, proceeding via corresponding a-ferrocenyl carbocation. The synthesized
compounds have been isolated pure, and their structure have been undoubtedly confirmed by standard spectral
techniques (1H NMR, 13C NMR, IR and elemental analyses).

Keywords: Tetrahydroquinoline ring, Ferrocene, Intramolecular cyclization, a-Ferrocenyl carbocation, Spectral
characterization.

INTRODUCTION

As the largest group of organic compounds, heterocycles play an important role in many fields of chemistry (Taylor et al.,
2016). They are known to possess a plethora of biological activities which makes them very important substrates in organic
synthesis (Taylor et al., 2016). Among the heterocycles, quinolines and their hydrogenated derivatives are of particular
importance, since they are known to be biologically active, as well as versatile synths in organic chemistry (Eicher et al.,
2003). A huge number of publications on syntheses and applications of these heterocycles testifies to the great interest of
chemists in these compounds (Sridharan et al., 2011).

On the other hand, usage of metals to induce or enhance
cytotoxicity of natural compounds or known drugs has increased
since the emergence of platinum-based chemotherapy agents in
the treatment of cancer (Kelland, 2007). In addition, metallocenes are also known to exhibit a wide range of
biological activity. Among them, ferrocene has attracted special
attention since it is a neutral, chemically stable and nontoxic
molecule (Togni, 1996). The mentioned metallocene has no
biological activity, but it can be easily derivatized and functionalized to biological important compounds or oxidized to
ferrocenium salts (Köpf-Maier et al., 1984; Houlton et al., 1991;
Kowalski, 2018). Ferrocene derivatives have a unique structure
as well as an excellent redox property, allowing their
applications in medicinal chemistry (Dai et al., 2007). These
compounds display interesting cytotoxic, antitumor, antimalarial,
antifungal and DNA-cleaving activity (Jaouen, 2006). In the
context of antimalarial treatments, it is known that metal-
containing compounds may possess antiparasitic activity
(Gambino & Otero, 2012; Salas et al., 2013; Biot et al., 2012).
Ferroquine (FQ), an analogue of chloroquine (CQ), has been
developed as an important antimalarial drug; it is currently in the
Phase II Sanofi portfolio for uncomplicated P. falciparum
malaria (Malisa et al., 2011; Supan et al., 2012). In terms of
developing new drugs based on FQ, this led to the preparation of
a numerous analogues (NDa & Smith, 2014). It has been
observed that the linker between drug hybrids is an important
determinant into whether or not the novel compound retains the
biological activity of the component parts (Madrid et al., 2006).
However, up to date no analogues have been able to compete
with FQ in terms of antimalarial activity. Thus, the search for
new antimalarials continues and the battle against malaria is far
from over.

As a part of a more comprehensive project aimed at the
synthesis of new potentially bioactive ferrocene derivatives, we
recently reported synthesis of bioactive 2-ferrocenoyl ethyl aryl
amines by aza-Michael additions of 1-ferrocenylpropenone on
anilines (Damljanović et al., 2011; Pejović et al., 2012).
2-Ferrocenoyl ethyl aryl amines - Mannich bases have been
proved to be an excellent starting material for the synthesis of
ferrocene derivatives with heterocyclic scaffold (Minić et al.,
2015; Minić et al., 2017). Bearing all previously mentioned in
mind, we planned to synthesize 1-ferrocenyl-3-((2-
(phenylthio)phenyl)amino)-propan-1-one and employ it as
starting material for a synthesis of novel ferrocene-containing
tetrahydroquinoline derivative. Thus, in this research we put
emphasis on the design, synthesis, as well as assignment of 1H

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and $^{13}$C NMR spectral data of novel 4-ferroceny1-8-(phenylthio)-1,2,3,4-tetrahydroquinoline, a promising privilege structure.

**EXPERIMENTAL**

**Materials and measurements**

All chemicals were commercially available and used as received, except the solvents, which were purified by distillation. Ultrasonic cleaner Elmasonic S 10 (Elma, Germany), 30W was used for the ultrasonically supported synthesis. Chromatographic separations were carried out using silica gel 60 (Merck, 230–400 mesh ASTM), whereas silica gel 60 on Al plates, (Merck, layer thickness 0.2 mm) was used for TLC. Melting points were determined on a Mel-Temp capillary melting points apparatus, model 1001, and the given values are uncorrected. The $^1$H and $^{13}$C NMR spectra of the samples in CDCl$_3$ were recorded on a Bruker Avance III 400 MHz ($^1$H at 400 MHz, $^{13}$C at 101 MHz) NMR spectrometer. Chemical shifts are reported in ppm (δ) values relative to TMS (δ$_TMS$ 0 ppm) in $^1$H, $^{13}$C and heteronuclear 2D NMR spectra. The coupling constant (J) are reported in Hz. Multiplicities of proton resonance are designated as singlet (s), a doublet (d), a doublet of doublets (dd), a triplet (t), a pseudo triplet (pt) doublet of doublets of doublets (ddd), a triplet of triplets (tt), a triplet of doublets of triplets (tdd), a triplet of doublets of triplets (tddd) and multiplets (m). 2D spectra ($^1$H-$^1$H COSY, NOESY, HSQC and HMBC) are performed on the same instrument with a standard pulse sequence. IR measurements were carried out with a Perkin-Elmer FTIR 31725-X spectrophotometer. Microanalyses of carbon, hydrogen and nitrogen were carried out with a Carlo Erba 1106 model microanalyzer; these results agreed favorably with the calculated values.

**Synthesis and spectral characterization**

**Synthesis of 1-phenyl-3-((2-(phenylthio)phenylamino)propan-1-one (4)**

A test tube containing a well homogenized mixture of 240 mg (1 mmol) of 1-ferrocenylpropenone, 2 mmol of the 2-(phenylthio)aniline, and 100 mg of montmorillonite K-10 was placed in the ultrasonic cleaner and irradiated for 4 h. Then, CH$_2$Cl$_2$ (10 ml) was added to the mixture, and the contents were filtered off. The solid residue was washed with CH$_2$Cl$_2$, and the collected organic layers were dried (Na$_2$SO$_4$) overnight. After the evaporation of the solvent, the crude mixture was fractioned by flash chromatography on a SiO$_2$ column. The 2-(phenylthio)aniline has been eluted with toluene, whereas the 1-phenyl-3-(2-(phenylthio)phenylamino)propan-1-one has been washed from the column by a mixture of toluene and AcOEt 9 : 1 (v/v). The complete excess of the amines was recovered.

Dark orange solid; mp 86 °C. Rf = 0.7. Yield 70%. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.48 (d, J = 7.5 Hz, 1H, Ar), 7.35 (t, J = 7.7 Hz, 1H, Ar), 7.19 (t, J = 7.5 Hz, 2H, Ar), 7.08 (t, J = 8.6 Hz, 3H, Ar), 6.78 (d, J = 8.2 Hz, 1H, Ar), 6.70 (t, J = 7.4 Hz, 1H, Ar), 5.26 (s, 1H, COCH$_2$CH$_2$NH), 4.72 (pt, J = 1.9 Hz, 2H, 2$^\text{CH}$, C$_p$), 4.48 (pt, J = 1.9 Hz, 2H, 2$^\text{CH}$, C$_p$), 4.10 (s, 5H, 5$^\text{CH}$, C$_p$), 3.58 (d, J = 5.1 Hz, 2H, COCH$_2$CH$_2$NH), 2.92 (t, J = 6.4 Hz, 2H, COCH$_2$CH$_2$NH). $^{13}$C NMR (101 MHz, CDCl$_3$) δ = 202.5 (COCH$_2$CH$_2$NH), 149.1 (C, Ar), 137.9 (C, Ar), 136.9 (C, Ar), 131.9 (C, Ar), 128.9 (C, Ar), 126.5 (C, Ar), 125.3 (C, Ar), 117.1 (C, Ar), 114.5 (C, Ar), 110.5 (C, Ar), 78.8 (C, C$_p$), 72.4 (C, C$_p$), 69.8 (C, C$_p$), 69.2 (C, C$_p$), 38.5 (COCH$_2$CH$_2$NH), 38.4 (COCH$_2$CH$_2$NH). IR (ATR, cm$^{-1}$): ν = 3361 (N-H) cm$^{-1}$; ν = 1655 (C=O) cm$^{-1}$. Anal. Calc. for C$_{32}$H$_{27}$FeNOS: C, 68.03; H, 5.25; Fe, 12.65; N, 3.17; O, 3.62; S, 7.26. Found: C, 68.08, H, 5.21, N, 3.19 %.

**Synthesis of 1-phenyl-3-((2-(phenylthio)phenylamino)propan-1-one (5)**

To a stirred solution of the corresponding 1-ferrocenyl-3-((2-(phenylthio)phenylamino)propan-1-one (1 mmol) in MeOH (20 ml) at room temperature, an excess of NaBH$_4$ (5 mmol) was added in several portions (up to 190 mg) and the reaction progress was monitored by TLC. After reduction has been completed (ca. 2 h), methanol was distilled off and the residue diluted with water (20 ml). The mixture was extracted with CH$_2$Cl$_2$ (two 20 ml portions) and the combined organic layers were washed with water and brine, as well as dried with anh. Na$_2$SO$_4$. After filtering off the drying agent and evaporation of the solvent, the crude mixture was purified by column chromatography (SiO$_2$) affording pure 1-ferrocenyl-3-((2-(phenylthio)phenylamino)propan-1-one.

Yellow oil. Rf = 0.4 (Hexane/EtOAc, 7:3 (v/v)). Yield 97%. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.56 – 7.52 (m, 1H, Ar), 7.36 (ddd, J = 8.3, 7.4, 1.6 Hz, 1H, Ar), 7.27 (tt, J = 3.5, 1.9 Hz, 2H, Ar), 7.20 – 7.11 (m, 3H, Ar), 6.73 (ttd, J = 7.0, 4.4, 2.2 Hz, 2H, Ar), 5.22 (s, 1H, CHOCH$_2$CH$_2$NH), 4.31 (dd, J = 8.1, 4.4 Hz, 1H, CHOCH$_2$CH$_2$NH), 4.17 (d, J = 2.5 Hz, 8H, 2$^\text{CH}$, C$_p$), 4.10 (d, J = 1.1 Hz, 1H, CH, C$_p$), 3.38 – 3.19 (m, 2H, CHOCH$_2$CH$_2$NH), 2.02 – 1.81 (m, 3H, overlapping signs from CHOCH$_2$CH$_2$NH and CHOCH$_2$CH$_2$NH). $^{13}$C NMR (101 MHz, CDCl$_3$) δ = 137.8 (C, Ar), 136.0 (C, Ar), 131.5 (C, Ar), 129.0 (C, Ar), 126.3 (C, Ar), 125.9 (C, Ar), 125.3 (C, Ar), 116.7 (C, Ar), 115.4 (C, Ar), 110.5 (C, Ar), 68.7 (C, C$_p$), 68.4 (C, C$_p$), 66.9 (C, C$_p$), 65.4 (C, C$_p$), 40.5 (COCH$_2$CH$_2$NH), 36.9 (CHOCH$_2$CH$_2$NH), 36.8 (COCH$_2$CH$_2$NH). IR (ATR, cm$^{-1}$): ν = 3385 (N-H) cm$^{-1}$; ν = 3068 (O-H) cm$^{-1}$. Anal. Calc. for C$_{32}$H$_{27}$FeNOS: C, 67.72; H, 5.68; Fe, 12.60; N, 3.16; O, 3.61; S, 7.23. Found: C, 67.76, H, 5.66, N, 3.18 %.

**Synthesis of 4-ferrocenyl-8-(phenylthio)-1,2,3,4-tetrahydroquinoline (6)**

The mixture of 1-ferrocenyl-3-((2-(phenylthio)phenylamino)propan-1-one (0.5 mmol) and glacial acetic acid (0.5 ml) was ultrasonicated in an ultrasonic cleaner for 2 h. The reaction mixture was neutralized with NaHCO$_3$ (litmus paper) and
extracted with CH$_2$Cl$_2$ (two 20 ml portions). The combined organic layers were washed with water and dried overnight (anh. Na$_2$SO$_4$). After filtration, the solvent was evaporated, the crude product 4-ferrocenyl-8-((phenylthio)phenyl)amino)propan-1-one in MeOH was employed and we efficiently synthesized the 1-ferrocenyl-3-((2-((phenylthio)phenyl)amino)propan-1-ol (5) in high yields (97%), with a short reaction time and absence of sub products (Scheme 1.). Noteworthy, in spite the efficient reduction, synthesized product must be purified by column chromatography. Moreover, γ-amino alcohols are in general versatile synthons in organic chemistry. Therefore, the obtained product 5 beside promising biological activity, represent excellent starting material for further synthesis of ferrocene-containing compounds with an interest from a biological point of view (antibacterial, antimalarial, anti-inflammatory, antitumor etc.) (Pejović et al., 2015; Minić et al., 2018).

In the last step, ferrocene-containing tetrahydroquinoline compound 6 was premised (Scheme 1). For this synthetic transformation we choose method previously reported by us (Minić et al., 2017), which is efficient and require mild reaction conditions. This investigation started with an ultrasonication of a solution of 0.5 mmol 5 in 0.5 ml of glacial acetic acid. The desired heterocyclic scaffold 6 was isolated after purification by means of column chromatography. It has been shown that 1-ferrocenyl-3-((2-((phenylthio)phenyl)amino)propan-1-ol (5) can smoothly undergo an intramolecular Friedel-Crafts-type reaction promoted by acetic acid, giving rise to the corresponding heterocycle in excellent yield (98%). In addition, this ferrocene-containing heterocycle can be regarded as interesting compound with a variety of applications particularly as novel potent antimalarial.

A plausible reaction mechanism of this intramolecular Friedel-Crafts alkylation is illustrated in Scheme 2. Initially, corresponding α-ferrocenyl carbocation II has been formed by the protonation of 1,3-amino alcohol 5 (oxonium ion I), followed by dehydration. α-Ferrocenyl carbocation II is stabilized by the presence of ferrocene core (Bleiholder et al., 2009), moreover, this cation is electrophilic enough to be attacked by the π-electronic system of the benzene ring (considerably activated by the presence of amine nitrogen), making arenium ion III. Deprotonation of III leads to the final alkylation product 6.

**Spectral characterization**

The three newly synthesized compounds, 4, 5 and 6 described in this work have been fully characterized by standard spectroscopic techniques (IR, $^1$H and $^{13}$C NMR), as well as elemental analyses. All spectral data were fully consistent with the proposed structures.

In the IR spectra of 4, sharp, medium intensity absorption of NH stretching vibration is observed below 3400 cm$^{-1}$, indicating that all NH groups are involved in H-bonding interactions. The CO stretching vibration band of the 1'-ferrocene-carbonyl group appear at 1655 cm$^{-1}$, suggesting the existence of inter- and/or intramolecular H-bonds to the CO functional group. The $^1$H and $^{13}$C NMR spectra of compound 4 display all signals expected for the proposed composition. The $^1$H NMR data for the newly synthesized compound 4 is typical

**RESULTS AND DISCUSSION**

**Synthesis**

First step in target synthesis was finding suitable method for the preparation of 1-ferrocenyl-3-((2-((phenylthio)phenyl)amino)propan-1-one. Few years ago, we designed and optimized reaction conditions for synthesis of 3-arylamino-1-ferrocenylpropan-1-ones in high yields, which shown to be biological active compounds and excellent starting material (Damijanović et al., 2011; Pejović et al., 2012; Minić et al., 2015; Minić et al., 2017). Thus, we decided to use this protocol. For the test reaction we put 1 mmol of 1-ferrocenylpropeneone (synthesized by previously described method (Minić et al., 2017), 2 mmol of 2-phenylthio)aniline and 100 mg of clay montmorillonite K-10 (see Scheme 1.) and flask has been placed in an ultrasound bath. After heating and the usual workup, as well as column chromatography (SiO$_2$), unfortunately, we obtain desired product in only 6% yield, therefore, we decided to increase reaction time on 4 hours. Indeed, when we set reaction under these conditions, to our delight, we successfully synthesized 1-ferrocenyl-3-((2-((phenylthio)phenyl)amino)propan-1-one (4) in 70% yield. These results did not require additional screenings, so we accepted them as the optimal ones.

The obtained ketone 4 was then converted into the corresponding 1,3-amino alcohol. For the reduction of 4, NaBH$_4$ (five equivalents) in MeOH was employed and we efficiently synthesized the 1-ferrocenyl-3-((2-((phenylthio)phenyl)amino)propan-1-ol (5) in high yields (97%), with a short reaction time...
Scheme 1. The synthesis of 4-ferrocenyl-8-(phenylthio)-1,2,3,4-tetrahydro-quinoline (6) starting from ferrocene (1).

for monosubstituted ferrocene (a characteristic intensity pattern of 2 : 2 : 5 for the H-atoms of ferrocene). Two slightly deshielded triplets (or better pseudo triplets) are observed for the cyclopentadienyl (Cp) ring H-atoms at 4.72 ppm (\(J = 1.9\) Hz) and 4.48 ppm (\(J = 1.9\) Hz). These are down fielded to the singlets assigned to the unsubstituted Cp ring at \(\delta(H)\) 4.10, which is characteristic for ferrocenes with electron-withdrawing substituents (due to deshielding effect with the increased delocalization of electron density toward the C=O substituent [39]). The first region (0-4 ppm) contains the signals of protons on the aliphatic part of molecules, CO\(\text{CH}_2\text{CH}_2\text{NH}\) (\(\delta(H) = 3.58\) ppm) and CO\(\text{CH}_2\text{CH}_2\text{NH}\) (\(\delta(H) = 2.92\) ppm). The signal of proton attributed to amine group was observed at 5.26 ppm. The aromatic region related to the benzene core is located 7.48-6.70 ppm.

Scheme 2. Plausible mechanism for the intramolecular Friedel-Crafts alkylation of compound 5.

The \(^{13}\)C NMR spectra can be analyzed in an analogous manner to the proton spectra, with signals corresponding to the carbonyl group (\(\delta(C) = 202.5\) ppm), aromatic core above 110.5 ppm, ferrocene moiety between 69 and 79 ppm and aliphatic carbons at ca 38 ppm.

Infrared spectra of the 1-ferrocenyl-3-((2-(phenylthio)phenyl)amino)propan-1-ol (5) show characteristic bands associated to N-H stretching vibrations (\(\nu = 3385\) cm\(^{-1}\)) and C-OH stretching vibrations (\(\nu = 3068\) cm\(^{-1}\)). Additionally, lack of signal for C=O undoubtedly confirms that the reduction really occurs. The \(^1\)H NMR spectra of 5 contain characteristic signals for aliphatic, hydroxy, ferrocene, amino and quinoline protons located in the expected regions. In that context, ferrocene moiety exhibits two signals assigned to hydrogens of the substituted Cp ring and one singlet originated to five protons of the unsubstituted Cp ring. Characteristic signal for H-atom of
amino NH was observed as the singlet in area (5.22 ppm) while aromatic rings show the signals in a little bit higher range of 7.56 – 6.73 ppm. Moreover, in the $^{13}$C NMR spectra of the 5 signals of the aliphatic, ferrocene and aromatic groups can be recognized in appropriate regions. Additionally, absence of signal attributed to carbonyl group in $^{13}$C NMR spectra of compound 5 unambiguously confirmed proposed product structure.

Figure 1. $^1$H NMR (CDCl$_3$, 400 MHz) spectrum of compound 6.

Figure 2. $^{13}$C NMR (CDCl$_3$, 101 MHz) spectrum of compound 6.
The main common feature of the IR spectra of synthesized compound 6 is strong band at 3345 cm⁻¹, which is attributed to the N-H stretching. Noteworthy, in the ¹H NMR spectra of product 6 signals of the unsubstituted Cp ring are down fielded to of the singlets assigned to the substituted Cp ring (δ = 4.17 ppm for the unsubstituted, and 4.12 – 3.87 ppm for substituted rings, respectively). Furthermore, in the ¹H NMR spectra of compound 6 characteristic signals for aromatic and aliphatic protons appear in the expected regions (see Experimental part and Figure 1).

In the ¹³C NMR spectra of the 4-ferrocenyl-8-(phenylthio)-1,2,3,4-tetrahydro-quinoline (6) signals of the ferrocene and tetrahydroquinoline core can be recognized in appropriate regions. Aromatic and ferrocene carbons show signals in characteristic areas (110–145 and 65–94 ppm, respectively). Aliphatic carbons from tetrahydroquinoline core were relatively non-sensitive to the neighboring NH -group occurring at δ(C) = 38.5 for FeCH₂CH₂NH δ(C) = 36.3 for FeCH₂CH₂NH and δ(C) = 28.5 for FeCH₂CH₂NH (see Experimental part and Figure 2.).

CONCLUSION

Briefly, the intramolecular cyclization of ferrocene-containing 1,3-aminoalcohol via corresponding α-ferrocynyl carbocation have been described. This protocol is practically convenient and proceeds under relatively mild conditions providing easy access to novel 4-ferrocenyl-8-(phenylthio)-1,2,3,4-tetrahydro-quinoline (6) in a good overall yield (67%). Structures of novel compounds were undoubtedly confirmed by standard spectroscopic techniques (IR and 1D and 2D NMR), as well as elemental analyses. Eventually, the synthesized compounds could be of interest for the bioactivity studies, therefore, further work to extend this methodology for the synthesis of other nitrogen fused heterocycles is under progress.

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