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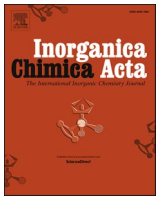

Research paper



Homoleptic pyrazinoic acid transition metal complex as an efficient catalyst toward elegant three-component synthesis of 3,4-dihydro-2*H*-1,3-benzoxazines

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ABSTRACT

In the frame of this study, the Mannich type reaction of primary aliphatic or aromatic amines with phenol and *para*-formaldehyde in the presence of pyrazinoic acid based transition metal complex as catalyst has provided a convenient multicomponent condensation method for efficient producing of 3,4-dihydro-2*H*-1,3-benzoxazines.

1. Introduction

It is an important task to develop new and efficient synthesis strategies for the preparation of versatile organic compounds to be used for different applications. In this context, various transition metal-based complexes are widely used catalytic systems in these strategies, especially in C—C, C—N and C—S coupling reactions [1–5]. Moreover coordination compounds based three-dimensional metal–organic frameworks have recently become very popular in the field of solar cells, gas adsorption etc. [6–9] and the coordination abilities of some *N*-bidentate ligands to different metals have attracted attention [10]. Many effective methods have been developed for the synthesis of heterocyclic compounds by utilizing the catalytic effects of metal complexes containing different ligands [11–14]. Among them, homoleptic or heteroleptic coordination compounds formed by pyrazinoic acid (2-pyrazinecarboxylic acid) with different transition metals are suitable catalysts for a wide range of organic synthesis reactions. In particular, it is stated that pyrazinoic acid and its analogs can act as versatile co-catalysts in many organic transformations, especially in different oxidation reactions, and these compounds are also useful as ligands for in situ generated catalyst systems [15–19]. Experimental and theoretical studies have been carried out on the non-covalent interactions in the structures of various metals coordination complexes of pyrazine- and pyridine-dicarboxylic acids [20,21]. Magnetic and CSD studies were carried out by preparing 1D coordination polymer and mononuclear complex with pyrazine and pyridinedicarboxylic acids under sonochemical conditions [22]. On the other hand, polarization-supported/resonance-supported hydrogen bond interactions and unconventional interactions were investigated in the crystal formations of chelidamic acid-based complexes [23].

Acting as a water-soluble ligand, pyrazinoic acid can maintain its stable molecular structure under variable reaction conditions. It is noted that pyrazinoic acid and some of its derivatives have a wide range of biological activities, among which anti-tuberculosis effects are particularly noteworthy [24–28]. Akhlaghi et al. claimed that these compounds have also anticancer effects [29]. According to a study by Premkumar and Govindarajan, trivalent lighter rare-earth complexes of 2-pyrazinecarboxylate with hydrazinium cation exhibited satisfactory antibacterial and antifungal activities [30]. It has been reported that the Cu(II) complex compound of pyrazine-2-carboxylic acid can rapidly eliminate a toxic cationic dyestuff such as Methyl blue from the aqueous medium in the presence of hydrogen peroxide by acting as a heterogeneous catalyst [31]. In addition, it is a very useful *N*,*O*-bidentate ligand that can form coordination compounds and supramolecular coordination polymers with a wide range of metal ions [32]. Considering all these properties of this versatile ligand, it will be important to evaluate its transition metal complexes as catalysts in different organic transformations. On the other hand, polyoxometalates (POMs) are known for their tremendous properties and due to their various physicochemical properties and especially their modifiable chemical structures, they find widespread application in various fields, especially as heterogeneous catalysts for different organic transformations and for multicomponent

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strategies toward functionalized heterocyclic systems [33–41].

As it is known, 3,4-dihydro-2*H*-1,3-benzoxazines are the leading precursors of polybenzoxazine resins, which exhibit extremely superior properties when compared to other monomers [42–44]. This versatile 1,3-benzoxazine scaffold draws attention among other heterocyclic compounds due to some of its biological activities [45–47]. As mentioned above, it is an important goal to develop suitable methods for synthesizing these compounds, which are important starting materials for the preparation of polybenzoxazine resins. In this context, when the three-component synthesis strategy for the preparation of these compounds is carried out in a catalyst-free environment, relatively long reaction times are required and yields are generally not satisfactory [48–50]. It should be noted that there are few studies on the synthesis of 3,4-dihydro-2*H*-1,3-benzoxazines under catalytic conditions [32,51,52]. Thanks to the advantages such as atom economy, efficiency and generally milder reaction conditions provided by the adoption of catalytic multi-component synthesis strategies, more environmentally friendly chemical processes can be developed. In connection with our researches focused on development of catalytic synthesis strategies for the preparation of 3,4-dihydro-2*H*-1,3-benzoxazines we are interested in catalytic activity of pyrazinoic acid based transition metal complexes. Hence, for the first time herein we report heterogeneous catalytic performance of readily accessible 2-pyrazine carboxylic acid Ni(II) complex ($Ni(pyza)_2(H_2O)_2$) towards the synthesis of a series of 3,4-dihydro-2*H*-1,3-benzoxazines in toluene. It should also be noted that the main difference of this homoleptic heterogeneous catalyst from the other heterogeneous POMs catalysts [33–41] mentioned above is that there is only one active side (Ni atom). Moreover, within the scope of this study, the mechanistic aspect of the catalytic reaction is also discussed.

2. Results and discussion

Within the frame of this study, it was aimed to develop a three-component catalytic method instead of the two-component catalytic method, considering that more environmentally friendly approaches are needed in organic transformations. Thus, without the need for secondary amines, which are obtained by hydrogenation of *Schiff bases*, a series of aliphatic or aryl amines are directly combined with phenol and formaldehyde to form the corresponding *N*-alkyl or *N*-aryl substituted 3,4-dihydro-2*H*-1,3-benzoxazines. For this purpose, the coordination compound, which will be used as a catalyst, was successfully synthesized according to the method given in the literature with some modifications by using pyrazinoic acid and Ni(II) chloride hexahydrate [53]. The chelating potential of the nitrogen atoms in the pyrazine ring depends on the position of the carboxylic acid group attached to this ring system. Pyrazinoic acid can form stable complexes with many transition metals by acting as a bidentate ligand over the *O* atom of the carboxylate group in the 2-position and the *N* atom in the 1-position of the pyrazine heterocycle. The binding mode of pyrazinoic acid ligand with metal ion in coordination compound used in this study is as shown in Fig. 1. As seen in the figure the two water molecules complete the coordination sphere of the transition metal ion. In the IR spectrum of the catalyst, a wide medium absorption band was observed at 3200 cm^{-1} belonging to (O—H), indicating the presence of water molecule of crystallization or it may belong to the water molecule used as the solvent (Supplementary data, S24). However, without a doubt, the medium band (Ni-OH) at 308 cm^{-1} shows that the water molecule is coordinated to the Ni ion. In addition, a sharp peak belonging to the Ni-O bond was obtained at 280 cm^{-1} in the FIR (Far Infrared Spectrum) spectrum of the nickel complex compound (Fig. 1). A sharp stretch band belonging to the carbonyl group of the pyrazinoic acid ligand was observed at 1661 cm^{-1}. On the other hand, a moderate strain band appeared at 460 cm^{-1}, which belongs to the Ni-N bond. All these IR data clearly reveal that the relevant nickel complex compound has been successfully synthesized and that two water molecules are located in the coordination sphere. The magnetic moment for the nickel compound and the coordination of these two water molecules would suggest that the metal atom is in an distorted octahedral environment [53].

Next, hexadecylamine was used to determine the optimum catalytic reaction conditions for both aliphatic and aromatic amines. Accordingly, 1 equivalent of hexadecylamine, 1 equivalent of phenol and 2 equivalents of paraformaldehyde were reacted in toluene with the catalyst ($Ni(pyza)_2(H_2O)_2$) under the reaction conditions shown in Table 1. As is well known, when benzoxazines are prepared in an aqueous reaction medium, oligomeric by-products are usually formed through the ring opening process of the heterocyclic system [13,54]. Therefore, in order to eliminate these unwanted products and to carry out the synthesis of the related benzoxazine monomers in a heterogeneous environment toluene was chosen as a solvent. Thanks to this chosen solvent, at the end of the reaction, the insoluble catalyst was easily separated from the reaction mixture by simple filtration and reused. When the condensation reaction was carried out in the absence of catalyst, the corresponding benzoxazine monomer **1c** was obtained only in 43% yield (Table 1, entry 1). On the other hand, it was understood that there was a significant increase in product yield when catalyst was used in the reaction. However, as can be seen from the table, increasing the reaction temperature from 90 °C to 100 °C degrees does not cause a remarkable change in product yield (entry 2 and 3). Thus, when the amount of catalyst was doubled at 100 °C, there was a remarkable increase in product yield (entry 5). To optimize the amount of the catalyst, 2.5 mmol % of the complex $Ni(pyza)_2(H_2O)_2$ was added to the medium, but the yield remained unchanged (entry 6). At high temperatures, the isolation of the related benzoxazines becomes more difficult and yields are lower due to the oligomeric by-products formed in the reaction

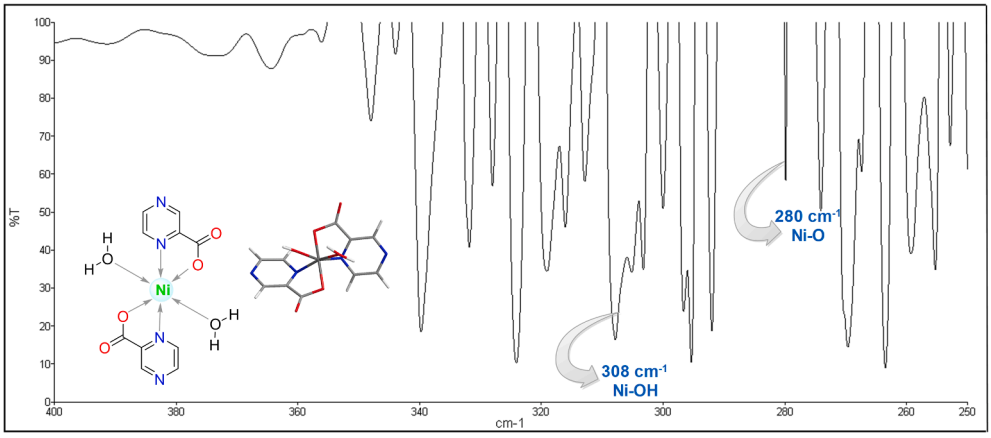
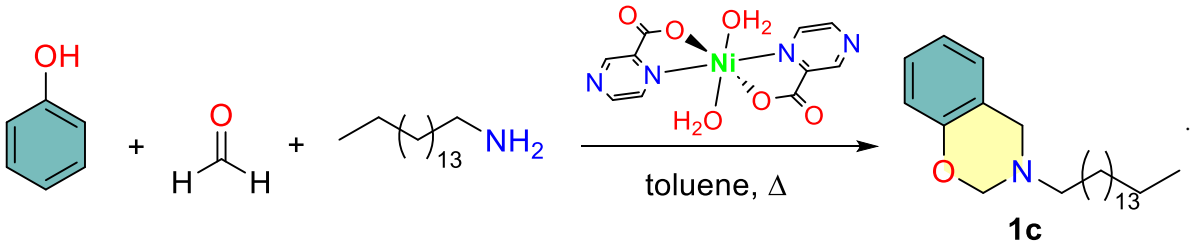


Fig. 1. Binding mode of pyrazinoic acid ligand and optimized 3D structure of the Ni(II) complex and FIR spectrum.

Table 1
Optimization of reaction conditions for the three-component synthesis of 3,4-dihydro-2*H*-1,3-benzoxazines



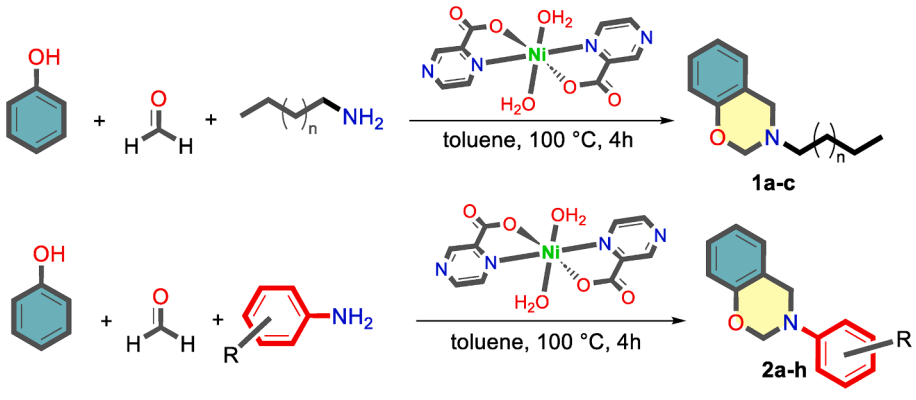
Entry	Catalyst loading (mmol %)	Time (h)	Temperature (°C)	Yield (%)[a]
1	–	4	100	43
2	1	4	90	61
3	1	4	100	62
4	2	2	100	73
5	2	4	100	91
6	2.5	4	100	91
7	2	3	110	90
8	2.5	3	110	89
9	2	4	125	Polymeric side products

[a] Yield after crystallization from acetone/H_2O.

medium (entry 9). Therefore, when the reaction conditions in Table 1 are evaluated, it is understood that the most suitable conditions for the catalytic synthesis of the relevant benzoxazines are as those given in entry 5.

In the next stage of the study, the scope of primary amines was examined. Optimum reaction conditions determined for hexadecylamine in Table 1 were used in condensation reactions involving all other aliphatic and aromatic amines. The amine compounds selected for this purpose and the general reaction scheme for the synthesis of *N*-alkyl or *N*-aryl substituted 3,4-dihydro-2*H*-1,3-benzoxazine monomers is presented in Scheme 1. The molecular structures of all synthesized benzoxazines are given in Table 2 along with their yields. As can be seen in Table 2, the yields of benzoxazines (**2e-h**) derived from aromatic primary amines containing inductively electron-withdrawing substituents are slightly lower than the yields of benzoxazines derived from other aromatic or aliphatic amines.

In order to investigate the suitability of the catalyst for reuse, phenol, paraformaldehyde and hexadecylamine components were condensed under the reaction conditions given in Table 1, entry 5. At the end of the specified time, when the reaction was completed, the catalyst, which remained as a solid in the environment, was separated from the reaction medium by filtration under vacuum. The insolubility of the catalyst in nonpolar solvents such as toluene indicates the polymeric nature of this compound [53]. On the other hand, the Co-based coordination compound of this ligand was also prepared and it was found that it could catalyze this multicomponent transformation. However, unlike the Ni-based catalyst, it was not preferred to be used in this study because it behaves like a homogeneous catalyst. The recovered catalyst was dried at room temperature and reused in subsequent reactions without any purification. The catalyst recovered in this way was reused four times without any loss in activity, and thus there was no significant decrease in product yield (Fig. 2). The fact that the catalyst maintains this activity

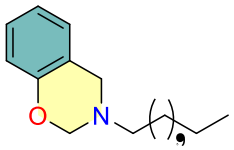
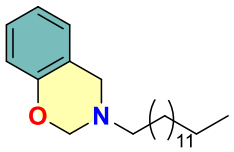
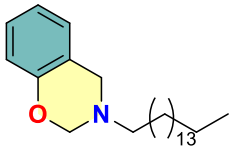
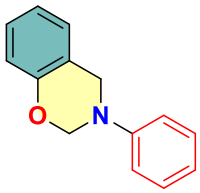
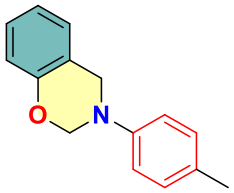
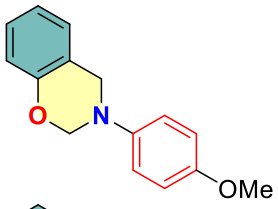
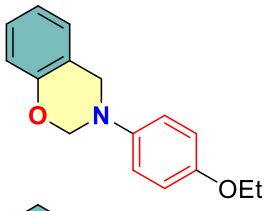
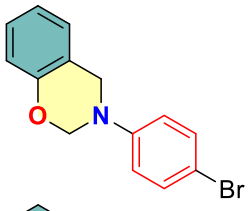
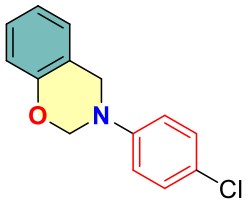
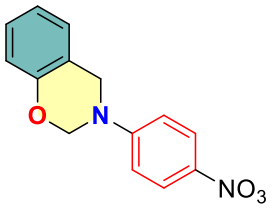
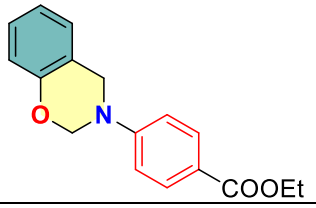


n	compound
9	**1a**
11	**1b**
13	**1c**

R	compound
H	**2a**
p-CH_3	**2b**
p-MeO	**2c**
p-OEt	**2d**
p-Br	**2e**
p-Cl	**2f**
p-NO_2	**2g**
p-COOEt	**2h**

Scheme 1. Synthesis of *N*-alkyl and *N*-aryl substituted 3,4-dihydro-2*H*-1,3-benzoxazines.

Table 2
Structures of 3,4-dihydro-2*H*-1,3-benzoxazines synthesized in the presence of Ni(pyza)$_2$(H$_2$O)$_2$ catalyst.

Compound	Structure	Yield (%)[a]
1a		89
1b		90
1c		91
2a		86
2b		87
2c		89
2d		83
2e		72
2f		71
2 g		70
2 h		73

[a] Yields after crystallization from acetone/H$_2$O.

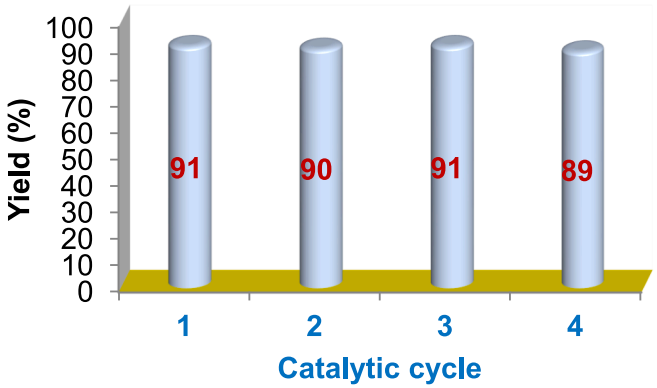


Fig. 2. Reusability of the catalyst for the formation of benzoxazine **1c**.

can be attributed to its polymeric structure formed through the H-bonding between the free carbonyl group in a neighboring unit and the water molecule. As well known, turnover number (*TON*), the number of moles of substrate converted to product per mole of catalyst, and turnover frequency (*TOF*), are valuable metrics generally used to characterize the efficacies of catalysts [55–57]. The *TON* of a catalytic reaction is the number of mole of substrate each mole of catalyst has converted and is calculated according to the following equation (Eq. (1)). On the other hand, activity is generally calculated by working out the catalyst *TOF*, defined by the turnover number per unit time (Eq. (2)). According to these equations the calculated values of *TON* and *TOF* are 46 and 12 h^{-1} respectively.

$$TON = \frac{Substrate\ mole\ x\ Yield}{Catalyst\ mole} \quad (1)$$

$$TOF = \frac{TON}{Reaction\ time\ (h)} \quad (2)$$

In order to reveal the catalytic effect of the Ni(II) complex, the geometry optimizations of the complex, hexadecylamine and formaldehyde compounds were performed and the FMO energies were calculated. Geometry optimizations of the Ni(II) complex, hexadecylamine and formaldehyde were performed using the MM2 force field option through the Chem3D. The calculated Frontier Molecular Orbital (FMO) energetics of these molecules and their optimized geometries are shown in Fig. 3. The energies of the LUMO (Lowest Unoccupied Molecular Orbital) and HOMO (Highest Occupied Molecular Orbital) orbitals of the related molecules are calculated as shown in this figure. As can be seen, the $LUMO_{Ni(II)\ complex}$ - $HOMO_{formaldehyde}$ energy gap is

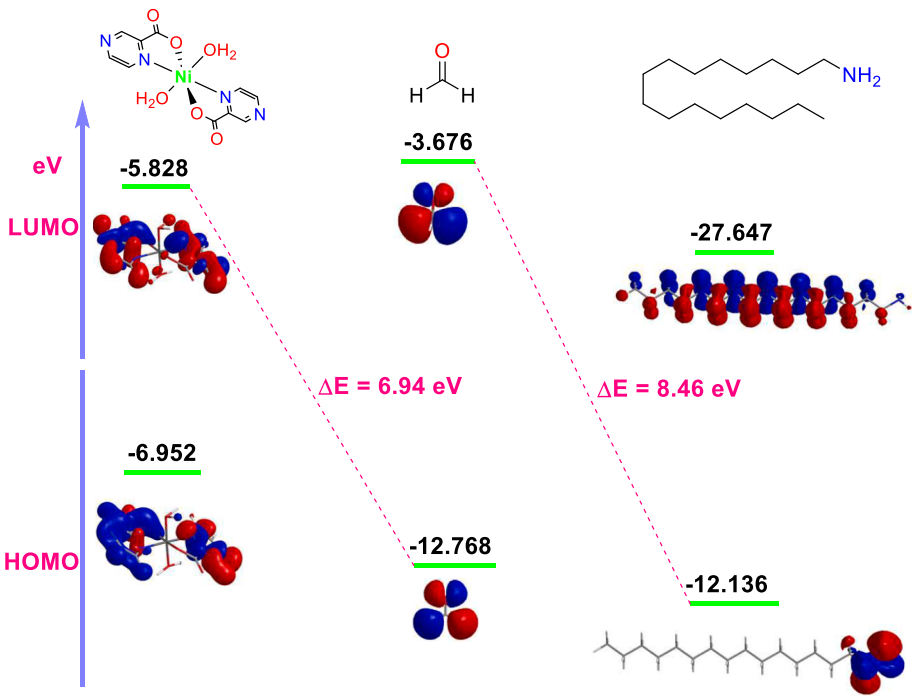


Fig. 3. FMO orbitals of Ni(II) complex, formaldehyde, hexadecylamine and energy gaps.

lower than the $LUMO_{formaldehyde}$ - $HOMO_{hexadecylamine}$ energy gap (6.94 and 8.46 eV, respectively). These energy gaps most likely reveal that the electron flow in the first step of the reaction is from the formaldehyde carbonyl group oxygen atom to the Ni(II) complex [13]. The formaldehyde molecule, which is itself a highly reactive species, reacts more easily with the related amine after this interaction. As a result of this favorite interaction between formaldehyde and the complex, a water molecule is removed from the initial complex compound, and the

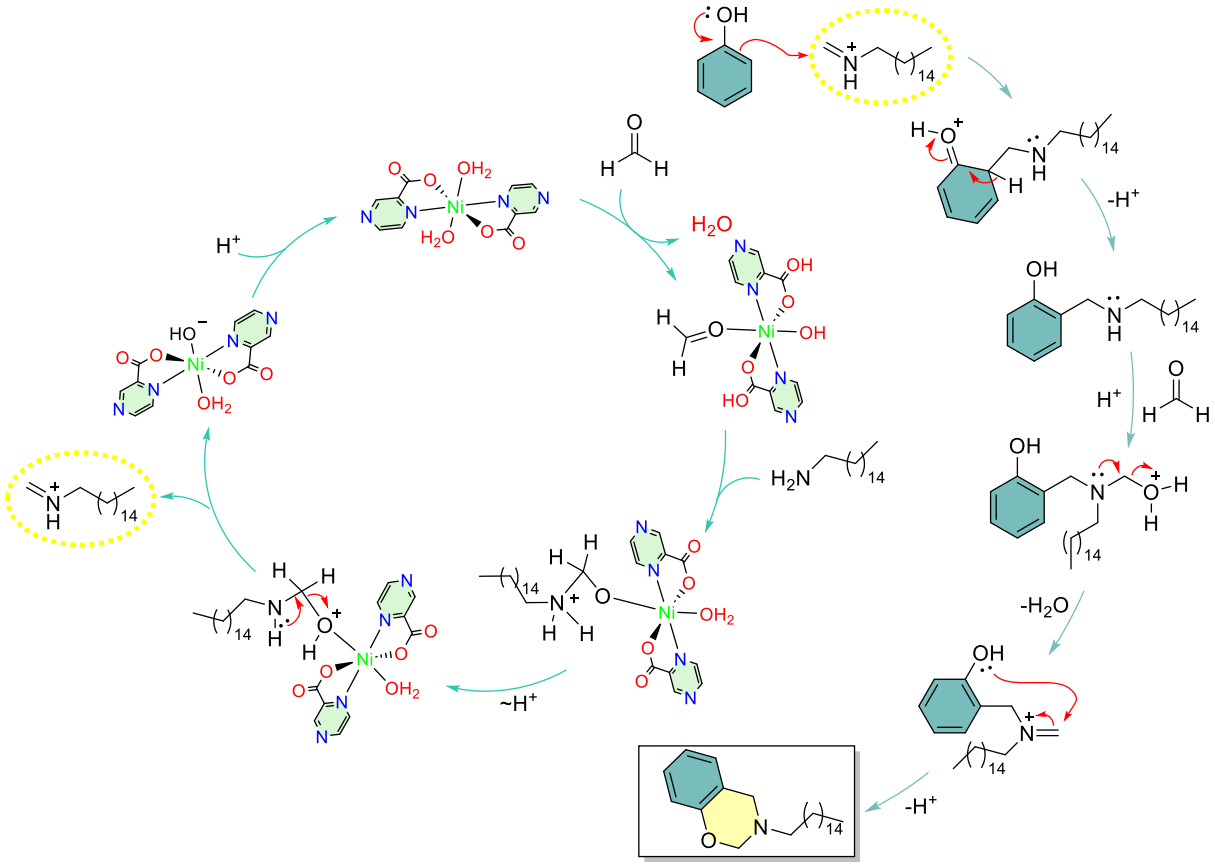


Fig. 4. Plausible reaction mechanism.

nucleophilic attack of the bulky hexadecylamine molecule to the formaldehyde-complex structure formed afterwards becomes quite easy (Fig. 4). After the nucleophilic attack of hexadecylamine on the formaldehyde molecule, a proton transfer takes place at the tetrahedral intermediate formed, followed by the formation of a reactive species, the *N*-methylenehexadecan-1-aminium intermediate. The main catalytic role of the Ni(II) complex in the synthesis of the benzoxazine monomer is probably to accelerate the formation of the *N*-methylenehexadecan-1-aminium intermediate as shown in the catalytic cycle. This cationic intermediate is bonded to the *ortho*-position of the phenol *via* the methylene carbon atom to form a secondary amine intermediate. The secondary amine thus formed attacks the formaldehyde molecule nucleophilically and triggers the formation of a new cationic intermediate. In the last step of the reaction, the phenolic hydroxyl group attacks the methylene carbon of this intermediate and cyclization occurs to form the corresponding benzoxazine product.

On the other hand, noncovalent interactions that may occur between phenol and hexadecylamine components, which can also act as either H-bond donors or acceptors, and the appropriate *N* atoms in the pyrazine ring system of the catalyst molecule may also be involved in the reaction mechanism [58–62]. Therefore, the two intermediates shown in Fig. 4 in the proposed mechanistic pathway for benzoxazine **1c** may exhibit noncovalent interactions (H-bonding and pi-pi stacking) as indicated in Fig. 5a and 5b respectively.

3. Experimental section

3.1. General experimental methods

All reagents and solvents were purchased from Merck (Merck, Darmstadt, Germany), Sigma-Aldrich (St. Louis, MO), or Acros Organics (Thermo Fisher Scientific, Geel, Belgium) and used without further purification. Thin layer chromatography was performed using silica gel (60 F_{254}, Merck, Darmstadt, Germany) plates. Melting points were recorded by BÜCHI melting point B-540 apparatus (BÜCHI Labortechnik AG in Flawil, Switzerland). The IR spectra were measured by Spectrum Two FT-IR spectrometer (PerkinElmer, Massachusetts, USA). The NMR spectra were measured using A600a Agilent DD2 600 MHz NMR spectrometer (Santa Clara, California, USA) and chloroform-d ($CDCl_3$) as a solvent. Chemical shifts (δ) are reported in ppm and J values in Hertz. The elemental analyses were performed using an LECO CHNS-932 elemental analyzer (Saint Joseph, MI, USA).

3.2. Chem3D based theoretical calculations

All electronic structure calculations have been carried out using the Chem3D program package [63]. As well-known Chem3D offers two commonly accepted force field calculation methods, MM2 and MMFF94 and these two methods are designed to calculate the molecular properties of the generated organic molecular models. Energy minimizations of hexadecylamine, formaldehyde and catalyst compounds were performed using the MM2 force field calculation method. Parameters used in MM2 calculations are given in Supplementary data.

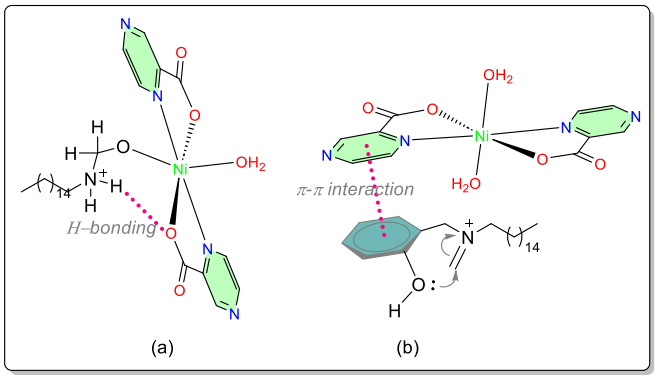


Fig. 5. Noncovalent interactions in proposed intermediates.

3.3. Method for the preparation of catalyst, $(Ni(pyza)_2(H_2O)_2)$

Pyrazinecarboxylic acid (1 g, 8.06 mmol) was dissolved in 100 mL of water. To this solution was added nickel(II) chloride hexahydrate (0.96 g, 4.04 mol) dissolved in 25 mL of water. The resulting solution was stirred for 1 h under heating. After standing for several days, the bluish gray solid of $(Ni(pyza)_2(H_2O)_2)$ formed was filtered off under vacuum. IR (ATR): ν_{max} 3450–3200 (OH, bm), 1661 (C═O, s), 1599, 1585, 1523 (ring, m), 1465 (C—O, m), 1410 (ring, m), 1338, 1149, 1065, 1045, 864, 793, 735, 617, 503, 449, 486, 460 (Ni-N), 404, 308 (Ni-OH), 280 (Ni-O) cm^{-1}.

3.4. General experimental procedure for the three-component preparation of 3,4-dihydro-2H-1,3-benzoxazines

To the weighed quantity of amine (0.241 g, 1 mmol) in a 50-mL flat bottom reaction flask in toluene (2 mL) was added phenol (0.094 g, 1 mmol) and paraformaldehyde (0.060 g, 2 mmol). After addition of the catalyst (2 mmol%), the resulted reaction mixture was stirred in an oil bath at 100 °C for 4 h. After the completion of reaction monitored by TLC, the solvent was removed by rotary evaporator and the resulting solid product was crystallized from acetone-water solvent mixture to give pure 3,4-dihydro-2*H*-1,3-benzoxazines as a white solid.

3.4.1. 3-Dodecyl-3,4-dihydro-2H-benzo[e][1,3]oxazine (**1a**)

White solid; mp 35–37 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11 (t, *J* = 8.8 Hz, 1H, Ar), 6.96 (d, *J* = 8.6 Hz, 1H, Ar), 6.86 (t, *J* = 7.4 Hz, 1H, Ar), 6.77 (d, *J* = 8.2 Hz, 1H, Ar), 4.87 (s, 2H, –NCH_2O-), 3.99 (s, 2H, ArCH_2N-), 2.73 (t, *J* = 11.2 Hz, 2H, ring-NCH_2CH_2-), 1.55 (quin, *J* = 11.1 Hz, 2H, ring-NCH$_2$CH_2CH$_2$-), 1.29–1.25 (m, 18H, 9x-CH_2-), 0.88 (t, *J* = 10.1 Hz, 3H, –CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.19, 127.60, 127.54, 120.42, 120.27, 116.31, 82.41, 51.37, 50.21, 31.92, 29.66, 29.64, 29.62, 29.54, 29.36, 28.14, 27.24, 22.70, 14.15. Anal calc for $C_{20}H_{33}NO$ (303.49): C 79.15, H 10.96, N 4.62. Found: C 79.08, H 10.92, N 4.68.

3.4.2. 3-Tetradecyl-3,4-dihydro-2H-benzo[e][1,3]oxazine (**1b**)

White solid; mp 43–45 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11 (t, *J* = 8.3 Hz, 1H, Ar), 6.96 (d, *J* = 8.2 Hz, 1H, Ar), 6.86 (t, *J* = 7.2 Hz, 1H, Ar), 6.77 (d, *J* = 8.0 Hz, 1H, Ar), 4.87 (s, 2H, –NCH_2O-), 3.99 (s, 2H, ArCH_2N-), 2.73 (t, *J* = 11.2 Hz, 2H, ring-NCH_2CH_2-), 1.55 (quin, *J* = 11.2 Hz, 2H, ring-NCH$_2$CH_2CH$_2$-), 1.31–1.25 (m, 22H, 11x-CH_2-), 0.88 (t, *J* = 10.1 Hz, 3H, –CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.19, 127.60, 127.54, 120.42, 120.27, 116.31, 82.42, 51.37, 50.21, 31.93, 29.70, 29.68, 29.66, 29.62, 29.54, 29.38, 28.14, 27.24, 22.71, 14.15. Anal calc for $C_{22}H_{37}NO$ (331.54): C 79.70, H 11.25, N 4.22. Found: C 79.66, H 11.19, N 4.18.

3.4.3. 3-Hexadecyl-3,4-dihydro-2H-benzo[e][1,3]oxazine (**1c**)

White solid; mp 51.8–52 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 (t, *J* = 8.5 Hz, 1H, Ar), 6.96 (d, *J* = 8.8 Hz, 1H, Ar), 6.86 (t, *J* = 7.4 Hz, 1H, Ar), 6.77 (d, *J* = 8.2 Hz, 1H, Ar), 4.87 (s, 2H, –NCH_2O-), 3.99 (s, 2H, ArCH_2N-), 2.73 (t, *J* = 11.4 Hz, 2H, ring-NCH_2CH_2-), 1.55 (quin, *J* = 11.4 Hz, 2H, ring-NCH$_2$CH_2CH$_2$-), 1.29–1.25 (m, 26H, 13x-CH_2-), 0.88 (t, *J* = 10.6 Hz, 3H, –CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.19, 127.61, 127.55, 120.43, 120.28, 116.32, 82.42, 51.38, 50.22, 31.94, 29.71, 29.69, 29.67, 29.62, 29.55, 29.38, 28.14, 27.25, 22.71, 14.16. Anal calc for $C_{24}H_{41}NO$ (359.60): C 80.16, H 11.49, N 3.90. Found: C 80.22, H 11.52, N 3.85.

3.4.4. 3-Phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2a**)

White solid; mp 53–54 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27–7.23

(m, 2H, Ar), 7.11–7.09 (m, 3H, Ar), 7.00 (d, J = 7.6 Hz, 1H, Ar), 6.94–6.86 (m, 2H, Ar), 6.80 (d, J = 8.2 Hz, 1H, Ar), 5.35 (s, 2H,–NC$\underline{H}_2$O-), 4.62 (s, 2H, ArC$\underline{H}_2$N-). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.39, 148.42, 129.31, 127.90, 126.78, 121.47, 120.93, 120.84, 118.30, 116.98, 79.49, 50.45. Anal calc for $C_{14}H_{13}NO$ (211.26): C 79.59, H 6.20, N 6.63. Found: C 79.63, H 6.18, N 6.68.

*3.4.5. 3-(p-Tolyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2b**)*

White solid; mp 80–82 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11–6.98 (m, 6H, Ar), 6.86 (t, J = 8.6 Hz, 1H, Ar), 6.79 (d, J = 8.2 Hz, 1H, Ar), 5.32 (s, 2H,–NC$\underline{H}_2$O-), 4.58 (s, 2H, ArC$\underline{H}_2$N-), 2.25 (s, 3H, –CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.79, 145.52, 130.53, 129.25, 127.29, 126.21, 120.36, 120.19, 118.10, 116.34, 79.43, 50.08, 20.01. Anal calc for $C_{15}H_{15}NO$ (225.29): C 79.97, H 6.71, N 6.22. Found: C 79.92, H 6.76, N 6.18.

*3.4.6. 3-(4-Methoxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2c**)*

Glassy transparent crystals; mp 76–78 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.14 (t, J = 8.2 Hz, 1H, Ar), 7.10–7.08 (m, 2H, Ar), 7.01 (d, J = 7.6 Hz, 1H, Ar), 6.90 (t, J = 7.5 Hz, 1H, Ar), 6.84–6.81 (m, 3H, Ar), 5.31 (s, 2H,–NC$\underline{H}_2$O-), 4.57 (s, 2H, ArC$\underline{H}_2$N-), 3.76 (s, 3H, –OC$\underline{H}_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.59, 154.00, 142.00, 127.53, 126.44, 120.57, 120.45, 120.41, 116.53, 114.15, 80.42, 55.18, 50.79. Anal calc for $C_{15}H_{15}NO_2$ (241.29): C 74.67, H 6.27, N 5.81. Found: C 74.63, H 6.23, N 5.77.

*3.4.7. 3-(4-Ethoxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2d**)*

Yellowish solid; mp 53–54 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.12 (t, J = 8.8 Hz, 1H, Ar), 7.07 (d, J = 8.9 Hz, 2H, Ar), 7.01 (d, J = 7.6 Hz, 1H, Ar), 6.89 (t, J = 7.5 Hz, 1H, Ar), 6.82–6.80 (m, 3H, Ar), 5.30 (s, 2H,–NC$\underline{H}_2$O-), 4.56 (s, 2H, ArC$\underline{H}_2$N-), 3.97 (q, J = 6.9 Hz, 2H, –OC$\underline{H}_2$CH$_3$), 1.38 (t, J = 7.0 Hz, 3H, –OCH$_2$C$\underline{H}_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.36, 154.29, 142.23, 127.84, 126.76, 120.93, 120.75, 120.71, 116.86, 115.13, 80.74, 63.69, 51.10, 14.93. Anal calc for $C_{16}H_{17}NO_2$ (255.32): C 75.27, H 6.71, N 5.49. Found: C 75.31, H 6.67, N 5.45.

*3.4.8. 3-(4-Bromophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2e**)*

White solid; mp 80–81 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, J = 8.9 Hz, 2H, Ar), 7.13 (t, J = 8.9 Hz, 1H, Ar), 7.01–6.98 (m, 3H, Ar), 6.90 (t, J = 7.5 Hz, 1H, Ar), 6.81 (d, J = 7.0 Hz, 1H, Ar), 5.32 (s, 2H,–NC$\underline{H}_2$O-), 4.60 (s, 2H, ArC$\underline{H}_2$N-). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.15, 147.49, 132.11, 128.07, 126.76, 121.01, 120.48, 119.99, 116.99, 113.86, 79.20, 50.58. Anal calc for $C_{14}H_{12}BrNO$ (289.01): C 57.95, H 4.17, N 4.83. Found: C 57.99, H 4.21, N 4.87.

*3.4.9. 3-(4-Chlorophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2f**)*

White solid; mp 54–56 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21 (d, J = 8.9 Hz, 2H, Ar), 7.13 (t, J = 8.6 Hz, 1H, Ar), 7.05–7.01 (m, 3H, Ar), 6.90 (t, J = 7.5 Hz, 1H, Ar), 6.81 (d, J = 8.0 Hz, 1H, Ar), 5.32 (s, 2H,–NC$\underline{H}_2$O-), 4.60 (s, 2H, ArC$\underline{H}_2$N-). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.17, 147.05, 129.31, 129.20, 128.06, 126.76, 126.5, 121.00, 120.51, 119.65, 116.99, 79.36, 50.66. Anal calc for $C_{14}H_{12}ClNO$ (245.71): C 68.44, H 4.92, N 5.70. Found: C 68.39, H 4.97, N 5.74.

*3.4.10. 3-(4-Nitrophenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine (**2 g**)*

Yellow solid; mp 177–178 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (d, J = 7.0 Hz, 2H, Ar), 7.17 (t, J = 7.2 Hz, 1H, Ar), 7.07–7.06 (m, 3H, Ar), 6.96 (t, J = 7.4 Hz, 1H, Ar), 6.87 (d, J = 7.0 Hz, 1H, Ar), 5.42 (s, 2H,–NC$\underline{H}_2$O-), 4.75 (s, 2H, ArC$\underline{H}_2$N-). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.01, 152.94, 140.36, 128.36, 126.79, 125.87, 121.62, 120.07, 117.31, 115.06, 76.96, 49.50. Anal calc for $C_{14}H_{12}N_2O_3$ (256.26): C 65.62, H 4.72, N 10.93. Found: C 65.65, H 4.69, N 10.90.

*3.4.11. Ethyl 4-(2H-benzo[e][1,3]oxazin-3(4H)-yl)benzoate (**2 h**)*

White solid; mp 85–86 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, J = 8.8 Hz, 2H, Ar), 7.13 (t, J = 7.7 Hz, 1H, Ar), 7.08–7.04 (m, 3H, Ar), 6.92 (t, J = 7.5 Hz, 1H, Ar), 6.84 (d, J = 8.3 Hz, 1H, Ar), 5.39 (s, 2H,–NC$\underline{H}_2$O-), 4.69 (s, 2H, ArC$\underline{H}_2$N-), 4.33 (q, J = 7.1 Hz, 2H, –OC$\underline{H}_2$CH$_3$), 1.37 (t, J = 7.1 Hz, 3H, –OCH$_2$C$\underline{H}_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.44, 154.19, 151.66, 131.26, 128.09, 126.80, 122.23, 121.19, 120.56, 117.13, 115.79, 77.79, 60.58, 49.66, 14.41. Anal calc for $C_{17}H_{17}NO_3$ (283.33): C 72.07, H 6.05, N 4.94. Found: C 72.02, H 6.09, N 4.89.

4. Conclusions

In summary, an efficient synthetic approach based on readily available Ni(pyza)$_2$(H$_2$O) catalyzed, three-component Mannich type condensation of phenol, paraformaldehyde and primary amines (aliphatic or aromatic) has been developed for the preparation of a series of 3,4-dihydro-2*H*-1,3 benzoxazine monomers. The most advantageous aspect of this developed catalytic method is that higher reaction yields can be achieved in a relatively short time. Moreover, this complex compound catalyzes the corresponding reaction without significant loss of activity even after four times of use.

CRediT authorship contribution statement

Ayhan Yıldırım: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization. **M. Suat Aksoy:** Conceptualization, Methodology, Investigation, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ica.2023.121583.

References

[1] X. Jia, P. Penga, Org. Biomol. Chem. 16 (2018) 8984.
[2] S. Sain, D. Kishore, S. Jain, V. Sharma, M. Srivastava, N. Sankararamakrishnan, S. Mishra, J. Dwivedi, S.M. Wabaidur, S. Sharma, Inorg. Chem. Commun. 122 (2020), 108230.
[3] E.R. Felipe, R.N.O. Yáñez, M. Vera, H. Valdés, L.G. Sebastián, A.R. Sanchez, D. M. Morales, Polyhedron 204 (2021), 115220.
[4] A. Jedidi, M.S. Al-Harbi, S.G. Aziz, O.I. Osman, L. Cavallo, J. Mol. Graph. 117 (2022), 108281.
[5] S. Priyarega, J. Haribabu, R. Karvembu, Inorganica Chim. Acta 532 (2022), 120742.
[6] H.E. Hosseini, M. Mirzaei, S. Zarghami, A. Bauzá, A. Frontera, J.T. Mague, M. Habibid, M. Shamsipur, CrstEngComm 16 (2014) 1359.
[7] R. Khajavian, M. Mirzaei, H. Alizadeh, Dalton Trans. 49 (2020) 13936.
[8] M. Mirzaei, H.E. Hosseini, Z. Karrabi, K. Molčanov, E. Eydizadeh, J.T. Mague, A. Bauzád, A. Frontera, CrstEngComm 16 (2014) 5352.
[9] A. Hassanpoor, M. Mirzaei, M.N. Shahrak, A.M. Majcher, Dalton Trans. 47 (2018) 13849.
[10] M. Bazargan, M. Mirzaei, A. Franconetti, A. Frontera, Dalton Trans. 48 (2019) 5476.
[11] R.I. Khusnutdinov, A.R. Bayguzina, U.M. Dzhemilev, J. Organomet. Chem. 768 (2014) 75.
[12] M. Khajehzadeh, M. Moghadam, S. Jamehbozorg, Inorganica Chim. Acta 485 (2019) 173.
[13] A. Yıldırım, M. Göker, Appl. Organomet. Chem. 35 (2021) e6425.
[14] M. Abd El Aleem Ali Ali El-Remaily, T. El-Dabea, M. Alsawat, M.H.H. Mahmoud, A. A. Alfi, N. El-Metwaly, A.M. Abu-Dief, ACS Omega 6 (2021) 21071.
[15] Y.N. Kozlov, G.V. Nizova, G.B. Shul'pin, J. Mol. Catal. A Chem. 227 (2005) 247.
[16] E.V. Gusevskaya, L. Menini, L.A. Parreira, R.A. Mesquita, Y.N. Kozlov, G. B. Shul'pin, J. Mol. Catal. A Chem. 363–364 (2012) 140.
[17] A.M. Kirillov, G.B. Shul'pin, Coord. Chem. Rev. 257 (2013) 732.

[18] Q. Liu, H.G. Wu, C. R. Chim. 16 (2013) 451.
[19] A. Karmaka, L.M.D.R.S. Martins, L.F.C.G. da Silva, S. Hazra, A.J.L. Pombeiro, Catal. Lett. 145 (2015) 2066.
[20] H.E. Hosseini, M. Mirzaei, M. Biabani, V. Lippolis, M. Chahkandic, C. Bazzicalupi, CrstEngComm 15 (2013) 6752.
[21] M. Mirzaei, H.E. Hosseini, A. Bauzá, S. Zarghami, P. Ballester, J.T. Maguee, A. Frontera, CrstEngComm 16 (2014) 6149.
[22] A. Hassanpoor, M. Mirzaei, H.E. Hosseinia, A. Majcher, CrstEngComm 20 (2018) 3711.
[23] M. Mirzaei, H.E. Hosseini, M. Shamsipur, M. Saeedi, M. Ardalani, A. Bauzá, J. T. Mague, A. Fronterac, M. Habibi, RSC Adv. 5 (2015) 72923.
[24] M. Dolezal, P. Cmedlova, L. Paleka, J. Vinsova, J. Kunes, V. Buchta, J. Jampilek, K. Kralova, Eur. J. Med. Chem. 43 (2008) 1105.
[25] M.F. Simões, E. Valente, M.J.R. Gómez, E. Anes, L. Constantino, Eur. J. Pharm. Sci. 37 (2009) 257.
[26] H. Sayahi, O. Zimhony Jr., W.R. Jacobs, A. Shekhtman, J.T. Welch, I. Bioorg, Med. Chem. Lett. 21 (2011) 4804.
[27] Y.D. Maldonado, G. Scalese, K.F. Manieri, F.R. Pavan, L.D.A. Méndez, D. Gambino, J. Inorg. Biochem. 227 (2022), 111683.
[28] S. Alghamdi, M. Asif, Russ. J. Bioorganic Chem. 48 (2022) 491.
[29] S. Akhlaghi, A. Mostoufi, H. Kalantar, M. Fereidoonnezhad, Med. Chem. Res. 31 (2022) 580.
[30] T. Premkumar, S. Govindarajan, World J. Microbiol. Biotechnol. 22 (2006) 1105.
[31] S. El-din, H. Etaiw, M.M. El-bendary, Appl. Organomet. Chem. 32 (2018) e4213.
[32] S. El-din, H. Etaiw, M.M. El-bendary, J. Lumin. 199 (2018) 232.
[33] M. Ghanbarian, S.Y.S. Beheshtiha, M.M. Heravi, M. Mirzaei, V. Zadsirjan, N. Lotfian, J. Clust. Sci. 31 (2020) 1295.
[34] M.M. Heravi, T. Hosseinnejad, M. Tamimi, V. Zadsirjan, M. Mirzaei, J. Mol. Struct. 1205 (2020), 127598.
[35] S.H. Baghan, M. Mirzaei, H.E. Hosseini, V. Zadsirjan, M.M. Heravi, J.T. Mague, Appl. Organomet. Chem. 34 (2020) e5793.
[36] M. Daraie, N. Lotfian, M.M. Heravi, M. Mirzaei, React. Kinet. Mech. Catal. 129 (2020) 391.
[37] N. Lotfian, M.M. Heravi, M. Mirzaei, M. Daraie, J. Mol. Struct. 1199 (2020), 126953.
[38] M.M. Heravi, T. Momeni, M. Mirzaei, V. Zadsirjan, M. Tahmasebi, Inorg. Nano-Met. Chem. 51 (2021) 896.
[39] M. Daraie, M. Mirzaei, M. Bazargan, V.S. Amiri, B.A. Sanati, M.M. Heravi, Sci. Rep. 12 (2022) 12004.
[40] M. Malmir, M.M. Heravi, Z.Y. Ghasemi, M. Mirzaei, Sci. Rep. 12 (2022) 11573.
[41] Z.Y. Ghasemi, M.M. Heravi, M. Malmir, G. Jahani, M.B. Bisafar, M. Mirzaei, Inorg. Chem. Commun. 140 (2022), 109456.
[42] Y. Xing, X. He, R. Yang, K. Zhang, S. Yang, Polymers 12 (2020) 2794.
[43] D. Trybuła, A.M. Harych, M. Gazińska, S. Berski, D. Jędrzkiewicz, J.N. Ejfler, Macromolecules 53 (2020) 8202.
[44] S. Abdous, M. Derradji, O. Mehelli, R. Belgacemi, S. Soudjrari, N. Ramdani, K. Khiari, M. El Amine Kadi, W. Liu, High Perform. Polym. 34 (2022) 455.
[45] S. Yamamoto, S. Hashiguchi, S. Miki, Y. Igata, T. Watanabe, M. Shiraishi, Chem. Pharm. Bull. 44 (1996) 734.
[46] H. Mizufune, H. Irie, S. Katsube, T. Okada, Y. Mizuno, M. Arita, Tetrahedron 57 (2001) 7501.
[47] K. Hiramatsu, T. Honjo, V. Rauniyar, F.D. Toste, ACS Catal. 6 (2016) 151.
[48] Z. Tang, W. Chen, Z. Zhu, H. Liu, Synth. Commun. 42 (2012) 1372.
[49] S. Ohashi, V. Pandey, C.R. Arza, P. Froimowicz, H. Ishida, Polym. Chem. 17 (2016) 2245.
[50] A.A. Pindel, A.M. Harych, E. Gębarowska, T. Gębarowski, D. Jędrzkiewicz, E. Pląskowska, D. Zalewski, N. Gulia, S. Szafert, J. Ejfler, New J. Chem. 43 (2019) 12042.
[51] A. Yıldırım, M. Göker, ChemistrySelect 5 (2020) 6971.
[52] A. Yıldırım, Y. Kaya, M. Göker, Carbohydr. Res. 510 (2021), 108458.
[53] J.R. Allan, A.D. Paton, K. Turvey, H.J. Bowley, D.L. Gerrard, Inorganica Chim. Acta 132 (1987) 41.
[54] H. Ishida, Y. Rodriguez, J. Appl. Polym. Sci. 58 (1995) 1751.
[55] S. Kozuch, J.M.L. Martin, ACS Catal. 2 (2012) 2787.
[56] Q. Yue, Y. Lu, Z. Zhang, H. Tian, H. Wang, X. Lia, S. Liu, New J. Chem. 44 (2020) 16913.
[57] S. Layek, B. Agrahari, A. Kumar, N. Dege, D.D. Pathak, Inorg. Chim. Acta 500 (2020), 119222.
[58] A. Frontera, D. Quiñonero, P.M. Deyà, Wiley Interdiscip. Rev. Comput. Mol. Sci. 1 (2011) 440.
[59] M. Lafrance, C.N. Rowley, T.K. Woo, K. Fagnou, J. Am. Chem. Soc. 128 (2006) 8754.
[60] M. Sen, B. Emayavaramban, N. Barsu, J.R. Premkumar, B. Sundararaju, ACS Catal. 6 (2016) 2792.
[61] Z. Ma, A.V. Gurbanov, A.M. Maharramov, F.I. Guseinov, M.N. Kopylovich, F. I. Zubkov, K.T. Mahmudov, A.J.L. Pombeiro, J. Mol. Catal. A: Chem. 426 (2017) 526.
[62] K.T. Mahmudov, A.V. Gurbanov, F.I. Guseinov, M.F.C.G. da Silva, Coord. Chem. Rev. 387 (2019) 32.
[63] Chem3D v.2022, PerkinElmer Informatics.