IMPROVED METHOD FOR THE SYNTHESIS AND ISOLATION OF SCHIFF BASE FUNCTIONALIZED *N*-HETEROCYCLIC CARBENE LIGAND PRECURSORS

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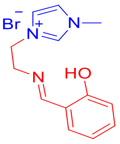
ABSTRACT

We reported herein, the synthesis, and characterization of a series of Schiff base functionalized N-heterocyclic carbene ionic salts, the synthesis involved the heating of the Schiff base and the carbene moieties at 60 ° C for 30 minutes. It does not involves the use of a solvent and all products were isolated in excellent yields between 95 and 98%. The synthesized compounds which are precursors to *N*-hetero cyclic carbene ligands were characterized using spectroscopy.



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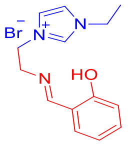

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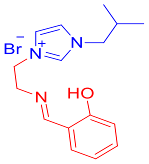

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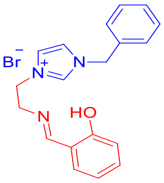

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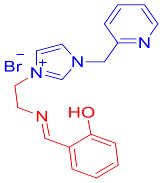

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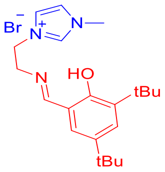

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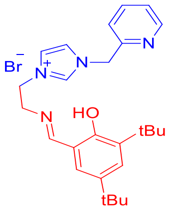

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Keywords

Solvent free, *N*-heterocyclic carbene, Schiff base, green chemistry, ionic salt

INTRODUCTION

Green chemistry also refer to as sustainable chemistry, is an emerging technique that encourages the principle of reduce, reuse and recycle (Banik, *et al*,. 2020). It reduces the generation of hazardous chemicals during chemical reactions including the synthesis of new compounds (Borah & Banik, 2020).

Reactions that are traditionally carried out in solvents could be done neat. The solvent-less reactions are environmentally friendly and economic because they minimize the generation of waste products, reaction time, and save energy (Sahoo & Banik, 2020). This alternate methods of synthesis generally led to improves product yields because no by-product and also workup that often led to the product lose is not required.

N-heterocyclic carbenes (NHCs) are unique and exciting class of hydrocarbons that contains at least one nitrogen atom in a heterocyclic ring system, they are also classified as neutral organic compounds with a divalent carbon atom containing six-electron valence shell, (Krishnan *et al.*, 2015; Waters & Goicoechea, 2015). They are brilliantly used as ligands in the field of coordination chemistry and organometallic compounds. However, their deficient octet electron system makes free carbenes extremely reactive. On this basis, it was traditionally belief that stable carbenes could not be isolated and characterized (Caro *et al.*, 2002; Zhenhong *et al*., 2016)**.** In the early 90s, Arduengo' group successfully isolate and characterized the first stable crystalline carbene (Arduengo *et al.*, 1991). The presence of two nitrogen atoms in the heterocyclic core of the imidazolium based NHCs, provides them an added advantage of having diverse binding modes which allow them to bind in terminal, bridging or chelating coordination modes (Denizaltı *et al.*, 2014; Yang *et al.*, 2016). These two nitrogen are often refers to as wings (Abubakar & Bala, 2018). As a results of this phenomena, imidazolium salts has attracted the attention of researchers in the field of coordination chemistry. They are used as precursors for *N*-heterocyclic carbenes (NHC), which are extensively used as ligands in organometallic chemistry and homogenous catalysis (Andavan *et al.*, 2005; Samanta *et al.*, 2015; Zhu *et al.*, 2014).

On the other hand, Schiff base are brilliant class of ligands which has the ability to stabilize metal centers at different oxidation state (Cozzi, 2004). Hence combining the two ligand motifs of NHC and Schiff base in one ligand framework, is expected to bring a harmonized benefits of enhance stability and reactivity.

Furthermore, the traditional methods for the synthesis of this kind of ligands involves the heating of the NHC motif and the Schiff base motif in a mixture of solvent usually diethyl ether and n-hexane at varying temperatures for several hours or days ( ). Therefore, in order to achieve a greener approach, to the existing procedure, we have design and synthesized several Schiff base functionalized *N*- heterocyclic carbene compounds (**1** - **7**) similar to those reported in the literature (Ibrahim & Bala, 2014; Patel, 2016) without the use of solvent and the reaction was carried out under mild condition and in a very short period of 30 minutes.

MATERIALS AND METHOD

Experimental

General Information

All reactions were performed using standard Schleck techniques under inert atmosphere. All solvents were dried and purified using standard procedures before use. Glassware were dried in oven at temperature above 100 ^{o} C. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance-III 400 MHz spectrometer at ambient temperature with tetramethylsilane (TMS at 0.00 ppm) as internal standard for ^{1}H NMR ($CDCl_3$ ^{1}H 7.27 ppm, DMSO ^{1}H 2.50 ppm). For 13C NMR ($CDCl_3$, δC 77.23 ppm, d_6-DMSO, δC 39.51 ppm) unless otherwise stated. All chemical shifts are quoted in δ (ppm) and coupling constants in Hertz (Hz) using the high frequency positive convention. The abbreviations used for the multiplicity of the NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, dd = doublet of doublet, td = triplet of doublets, dt = doublet of triplet, br s = broad singlet, * implies more than one CH_2 absorbing, etc. Infrared spectra were recorded on a PerkinElmer universal ATR Spectrum 100 FT-IR spectrometer. Mass spectrometry were recorded on Waters Micromass LCT Premier TOF MS-ES$^+$. Thin Layer Chromatography (TLC) was carried out on Machery-Nagel polygramSil/G/UV254 pre-coated plates. Melting point (Mp) analysis was carried out using the Electrothermal 9100 melting point apparatus. All chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification.

General procedure for the synthesis of the compounds (1 - 7)

All the compounds **(1 - 7)** were synthesized as described in section 2.1.

2-[2-(3-methylimidazol-1-yl)ethyliminomethyl]phenol (1)

The product was isolated as pale yellow viscous liquid, yield 0.305 g, 98 %, m/z =230.1284 [M$^+$ -Br]. ^{1}H-NMR ($CDCl_3$) 3.97 (s, 3H), 4.15 (t, 2H), 4.73 (t, 2H), 6.82 (m, 2H), 6.97 (m, 1H), 7.23 (m, 2H), 7.34 (dd , 1H), 8.44 (s, 1H), 10.28 (s, 1H), 12.56 (s, 1H, -OH). ^{13}C-NMR ($CDCl_3$) 37.26, 51. 05, 58.59, 116.90, 118.34, 119.23, 122.92, 132.23, 133.15, 133.76, 137.92, 160.68, 169.08.

2-[2-(3-ethylimidazol-1-yl)ethyliminomethyl]phenol (2)

The product was isolated as pale yellow viscous liquid, yield 0.32 g, 98%. ^{1}H-NMR ($CDCl_3$) 1.58 (t, 3H), 4.23 (t, 2H), 4.35 (q, 2H), 4.81 (t, 2H), 6.91 (m, 3H, Ar), 7.27 (m, 2H, Ar), 7.39 (m, 1H, Ar), 8.51 (s, 1H, H-C=N), 10.56 (s, 1H, NCHN), 12.68 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$) 15.72, 51.05, 58.80, 116.90, 119.25, 120.97, 123.01, 132.18, 133.16, 137.38, 169.08.

2-[2-(3-isobutylimidazol-1-yl)ethyliminomethyl]phenol (3)

The product was isolated as yellowish brown solid, yield 0.35, 99%, m/z =272.1771 [M$^+$ -Br]. ^{1}H-NMR ($CDCl_3$) 0.92 (d, 6H), 2.18 (m, 1H), 4.11 (t, 2H), 4.27 (t, 2H), 4.86 (t, 2H), 6.91 (m, 2H, Ar), 7.28 (m, 3H, Ar), 7.53 (m, 2H, Ar), 8.50 (s, 1H, H-C=N), 10.42 (s, 1H, NCHN), 12.48 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$) 19.39, 29.72, 50.83, 57.29, 58.59, 116.86, 118.33, 119.17, 121.87, 122.94, 132.17, 133.10, 137.51, 160.68, 169.30.

2-[-2-(3-benzylimidazol-1-yl)ethyliminomethyl]phenol (4)

The product was isolated as pale yellow moisture sensitive solids, yield 0.298 g, 97%, m/z = 307.1640 [M$^+$ -Br] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.54 (1H, s, OH), 10.29(1H, s, NCHN), 8.45(1H, s, HC=N), 7.61(1H, dd, Ar), 7.46(1H, dd, Ar), 7.33(1H, dd, Ar), 7.32(1H, dd, Ar), 7.27(2H, dd, Ar), 7.26(1H, dd, Ar), 7.24(1H, dd, Ar), 7.20(1H, dd, Ar), 6.84(1H, dd, NCH), 6.82 (H, dd, NCH), 5.48 (2H, s, NCH2C), 4.76 (2H, t, C-CH2-N), 4.18(2H, t, =N-CH2-). ^{13}CNMR (400 MHz, $CDCl_3$) 50.79, 53.69, 58.35, 116.89, 118.32, 119.19, 121.33, 123.05, 128.88, 129.51, 129.60, 132.22, 132.48, 133.10, 133.7, 137.34, 160.64, 168.97. IR 3400 cm-1 (0H), 3095 cm-1 (Ar-C-H), 2930 cm-1 (N=C-H), 1631 -1 (C=N), 1582 cm -1 (Ar-C = C), 1276 cm -1 (C-N), 1148 cm-1 (C – O).

2-[-2-[3-(2-pyridylmethyl) imidazol-1-yl]ethyliminomethyl]phenol (5)

The product was isolated as reddish brown moisture sensitive viscous liquid, yield 0.38 g, 98 %, m/z = 307.1563 [M$^+$ - Br]. ^{1}H-NMR (DMSO) 4.09 (t, 2H), 4.71 (t, 2H), 5.65 (s, 2H), 5.80 (dd, 1H), 6.97 (dd, 2H), 7.45 (m, 3H), 7.91 (m, 3H), 8.20 (m, 1H), 8.58 (s, 1H), 9.41 (s, 1H), 12.69 (s, 1H). ^{13}C-NMR (DMSO) 48.46, 49.54, 57.72, 116.31, 118.57, 118.80, 122.15, 122.53, 122.75, 123.53, 131.82, 132.68, 137.07, 137.54, 149.48, 153.57, 160.03, 167.79.

2, 4-ditert-butyl-6-[2-(3-methylimidazol-1-yl) ethyliminomethyl] phenol (6)

The product was isolated as pale yellow air stable crystalline solid, yield 0.34 g, 99 %, m/z =342.2535 [M$^+$ -Br]^{1}H-NMR (CDCl$_3$) 1.22 (s, 9H), 1.35 (s, 9H), 4.00 (s, 3H), 4.13 (t, 2H), 4.76 (t, 2H), 7.03 (d, 1H), 7.23 (dd, 1H), 7.34 (m, 2H), 8.41 (s, 1H), 10.36 (s, 1H), 12.97 (s, 1H, -OH). 13C-NMR (CDCl3) 29.40, 31.36, 34.40, 37.02 50.95, 58.79, 66.19, 117.80, 123.03, 126.73, 128.25, 136.74, 138.05, 140.88, 157.87, 169.84.

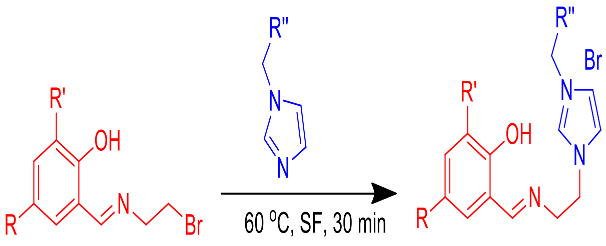
2,4-ditert-butyl-6-[2-[3-(2-pyridylmethyl)imidazol-1-yl]ethyliminomethyl]phenol (7)

The product was isolated as reddish brown air stable solids, yield, 0.41, 98 %. ^{1}H-NMR (CDCl$_3$) 1.31 (s, 9H, t-but J=7.98 Hz), 1.41 (s, 9H, t-but), 4.20 (t, 2H, J=5.26 Hz), 4.77 (t, 2H, J=5.42 Hz), 5.69 (s, 2H), 7.01 (, 2H, Ar, J=5.64 Hz), 7.28 (m, 3H, Ar), 7.41 (m, 3H, Ar J=2.16 Hz), 8.41 (s, 1H, H-C=N, J=7.67 Hz), 10.53 (s, 1H, NCHN), 13.01 (s, 1H, OH). ^{13}C-NMR (CDCl$_3$) 29.38, 31.46, 34.17, 35.06, 50.98, 54.24, 58.64, 117.49, 119.99, 121.30, 122.57, 123.84, 126.68, 127.91, 136.84, 137.82, 140.82, 149.93, 152.25, 157.80, 169.86.

Results and discursion

Synthesis

All the compounds **(1 - 7)** were synthesized by the modification of the literature (Li *et al.,* 2008; Nirmala *et al.,* 2016) where in each case, (1 mmol) equivalent of the Schiff base moiety and the carbene moiety was placed into a clean Schleck tube charged with a stir bar and nitrogen gas and the mixture was heated for 30 minutes in the absence of solvent, leading to the isolation of the product in excellent yield. All the reactions were monitored using thin layer chromatography TLC. The details of the synthesis are reported in the experimental section while the synthetic route is presented in Scheme 1.



Scheme 1. Schematic representation of the synthetic route of compounds **1** to **7**

1 R=R'=R'' = H

2 R=R' = H, R'' = Me

3 R= R' = H, R'' = ^{i}Pr

4 R= R' = H, R'' = Ph

5 R= R' = H, R'' = Py

6 R= R' = tbu, R'' = H

7 R= R' = tbu, R'' = Py

Spectroscopy results

^{1}H-NMR spectrum of compounds **1 - 7** showed all the expected signals typical of an imidazolium salt. The characteristic C2-H imidazolium proton absorption signal was seen downfield between 9.3 to 10.2 ppm in all the compounds (Ibrahim & Bala 2016). The imine and the OH protons were observed at around 8.5 and 12.6 ppm respectively. All other aromatic protons were seen as a multiplet at around 6.8 to 7.5 ppm due to the deshielding effects of the positively charged imidazolium ring system (Gülcemal, *et al.*, 2013). In addition, the ^{13}C NMR spectrum of the compounds showed the characteristic imidazolium C2 signal at 137 ppm for all the seven compounds, this signal is usually observed downfield for all related compounds the carbon alpha to imine (N=C) appears at 167 ppm while the carbon atom that caries the OH group was observed around 160 ppm in all cases (Li *et al.*, 2018). Other spectroscopic techniques including IR confirmed the isolation of the compounds with distinct signals corresponding to the O-H group at (3400 cm^{-1}) and C=N at around (1631 cm^{-1}) functionalities distinctly observed for all the compounds. Positive mode ESI MS analysis gave the molecular ion of the salt with the loss of the Br^{-} counterion(Ndlovu, Ibrahim, & Bala, 2017).

Table 1: Comparison of isolated yield for compounds **1 - 7**

Compounds	Present research		Literature	
	Conditions	**Yield %**	**Conditions**	**Yield %**
1	SF	98	EtOH/60 ° C /1h (Zhu *et al.*, 2012)	NR
2	SF	98	EtOH/60 ° C /1h (Zhu *et al.*, 2012)	NR
3	SF	98	NC	NC
4	SF	97	NC	NC
5	SF	98	NC	NC
6	SF	98	n-hexane/Et$_2$O/60 ° C /4d (Chen *et al.*, 2008)	95
7	SF	98	NC	NC

SF = Solvent free, NR= not reported, NC new compound

As presented in table 1, the results showed that the solventless technique is more robust compared with the procedures that uses solvent. In addition to saving the cost of solvents, the reaction time has also reduced significantly because a reaction that used to take 24h, was concluded in 30 minutes. This is because the solvent mainly serves as a medium of the reaction and the reaction rate often increase with increase in concentration of the reactant particles (Buncel & Stairs 2015). In the absence of solvent, one of the reactant usually the one with lower melting point will act as a solvent and directly consumed the other reactant (Sahoo & Banik 2020). This explain the reason for the observed increase in the percentage yields of the products above the figures reported in the literature. Further, reason is the elimination of the workup process that often led to the products lose.

CONCLUSION

The solvent less synthesis and characterization of Schiff base functionalized *N*-heterocyclic carbene compounds was reported. Some of the compounds have been reported as ligands in coordination chemistry. The methods is robust, simple and efficient, synthesis was achieved in 30 minutes and a high percentage yield between 95 to 99% was recorded.

ACKNOWLEDGEMENTS

We thank the University of KwaZulu-Natal for spectroscopic analysis. We also thanks Gombe State University for a study fellowship.

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Electronic supporting information

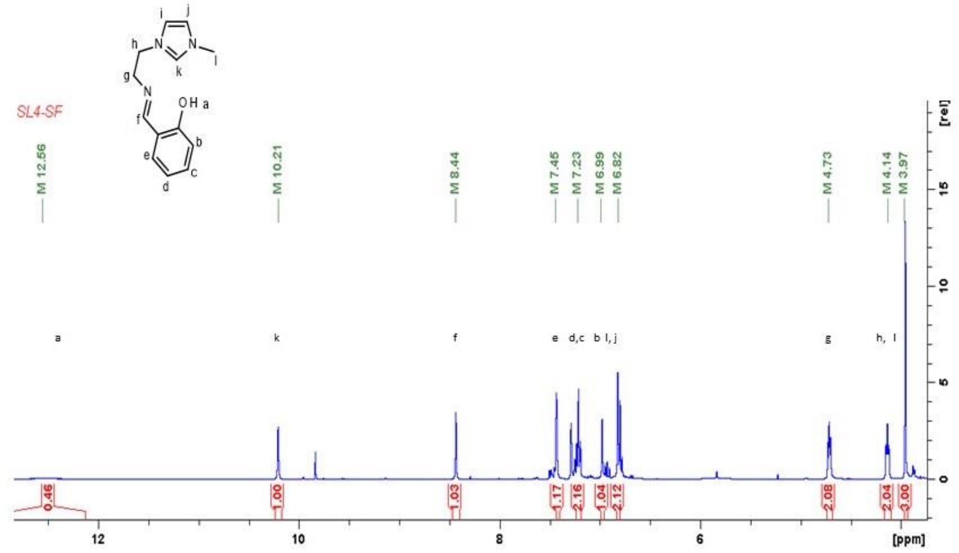
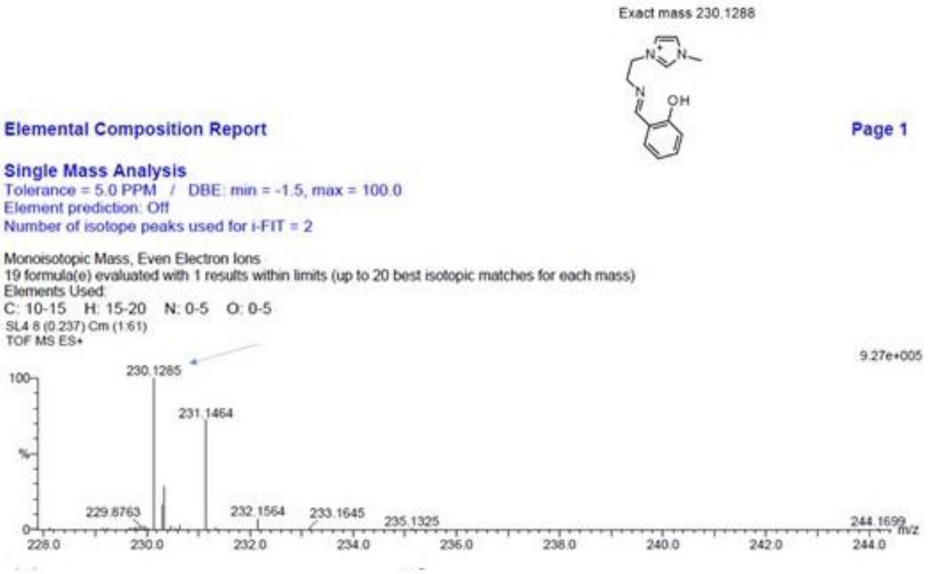


Figure S1 : ^{1}H NMR Spectrum of Compound **1** in $CDCL_3$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Elemental Composition Report

Page 1

Single Mass Analysis
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Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
19 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 10-15 H: 15-20 N: 0-5 O: 0-5
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TOF MS ES+

Figure S2: HRMS spectrum of compound **1**

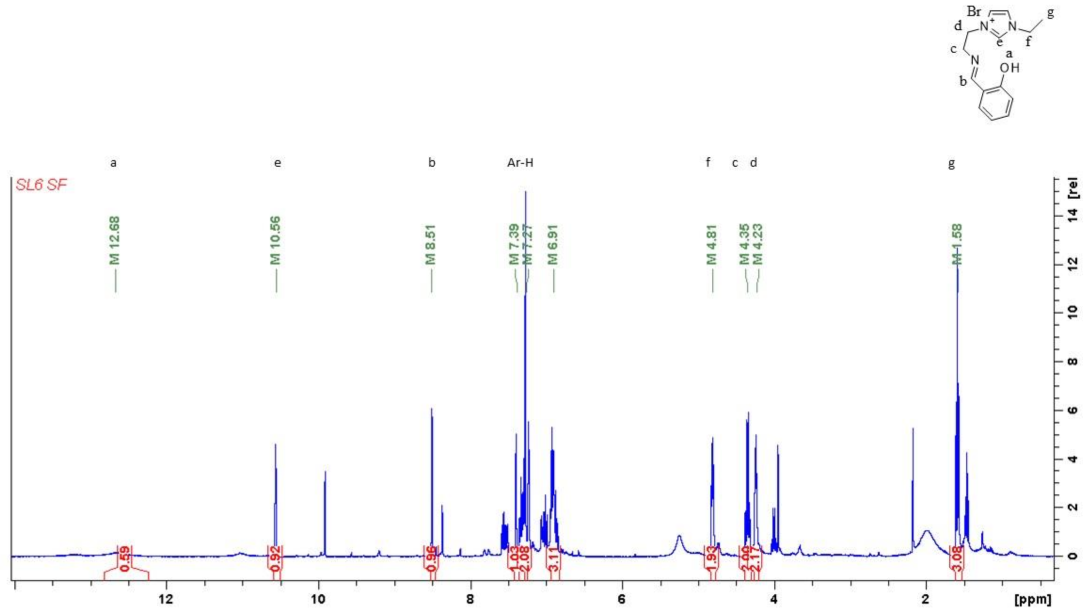


Figure S3: ^{1}H Spectrum of compound **2**

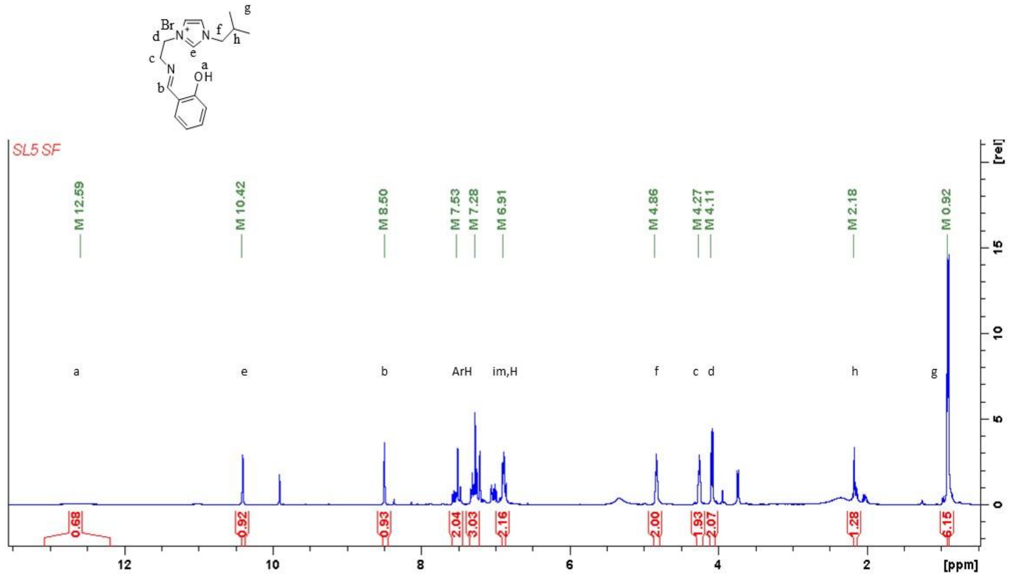
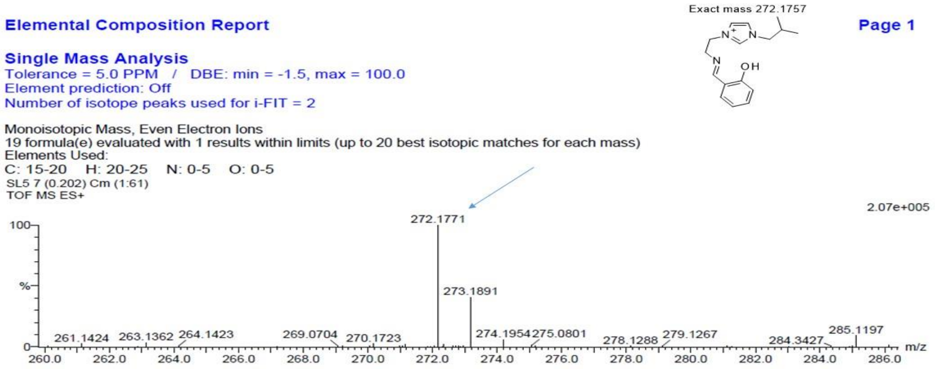


Figure S4: ^{1}H NMR spectrum of compound **3**



Elemental Composition Report

Page 1

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
19 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 20-25 N: 0-5 O: 0-5
SL5 7 (0.202) Cm (1:61)
TOF MS ES+

Figure S5: HRMS spectrum of compound **3**

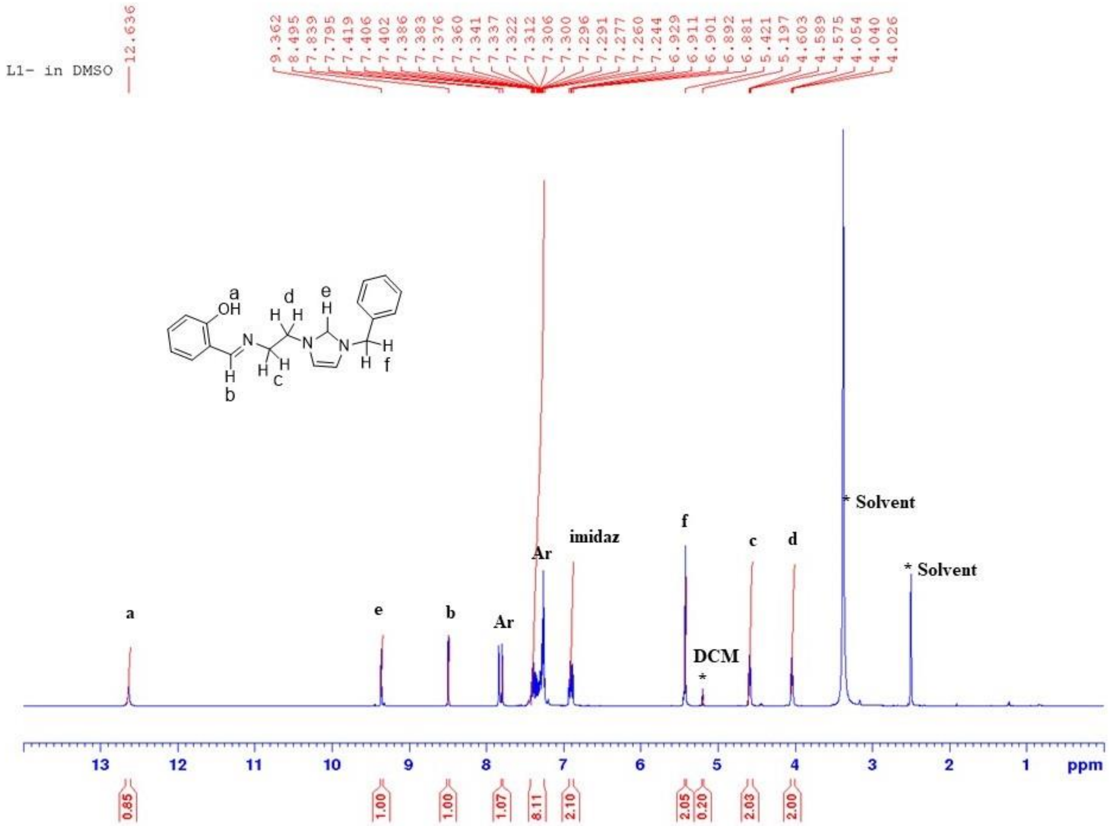
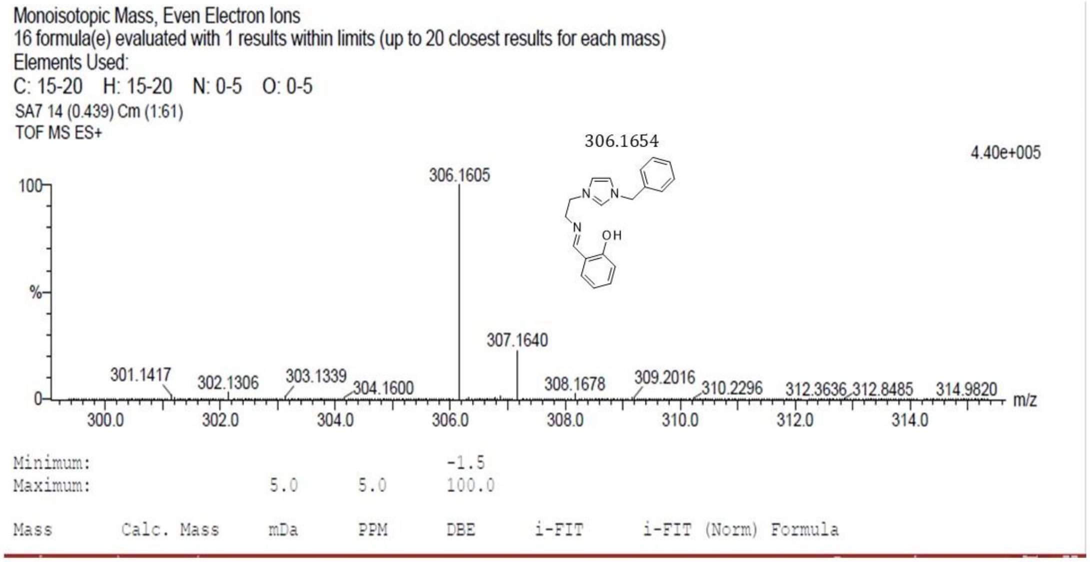


Figure S6: ^{1}H NMR spectrum of compound **4** in CDCl$_3$



```
Monoisotopic Mass, Even Electron Ions
16 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)
Elements Used:
C: 15-20   H: 15-20   N: 0-5   O: 0-5
SA7 14 (0.439) Cm (1:61)
TOF MS ES+
```

```
Minimum:                                    -1.5
Maximum:                  5.0       5.0     100.0

Mass      Calc. Mass      mDa       PPM     DBE      i-FIT      i-FIT (Norm) Formula
```

Figure S7: HRMS spectrum of compound **4**

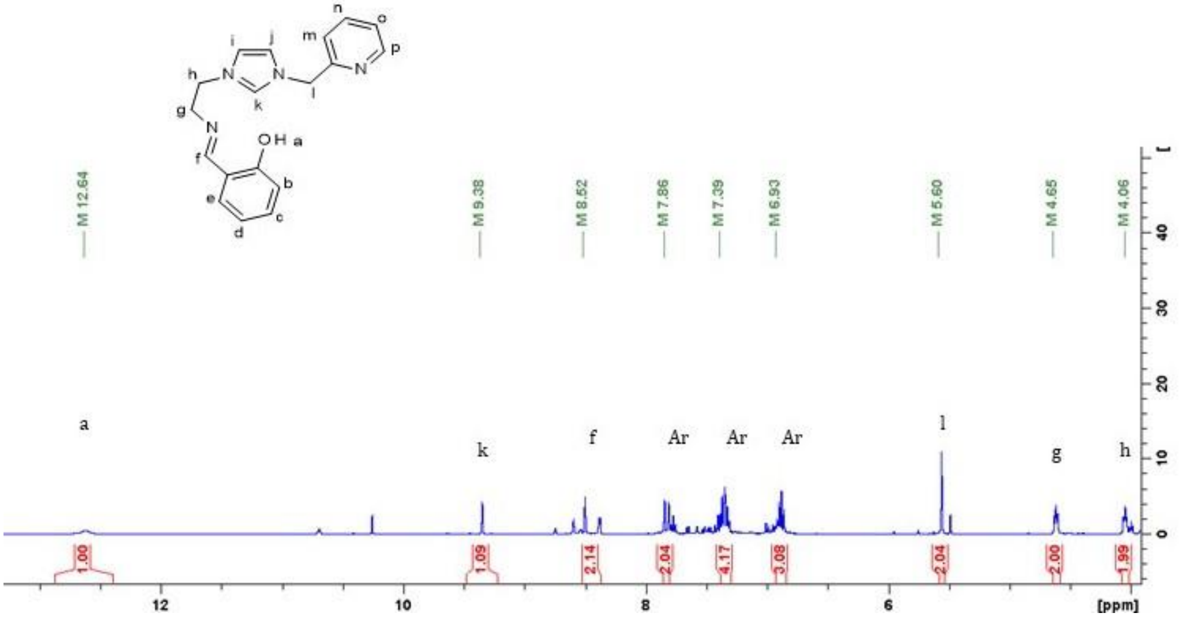
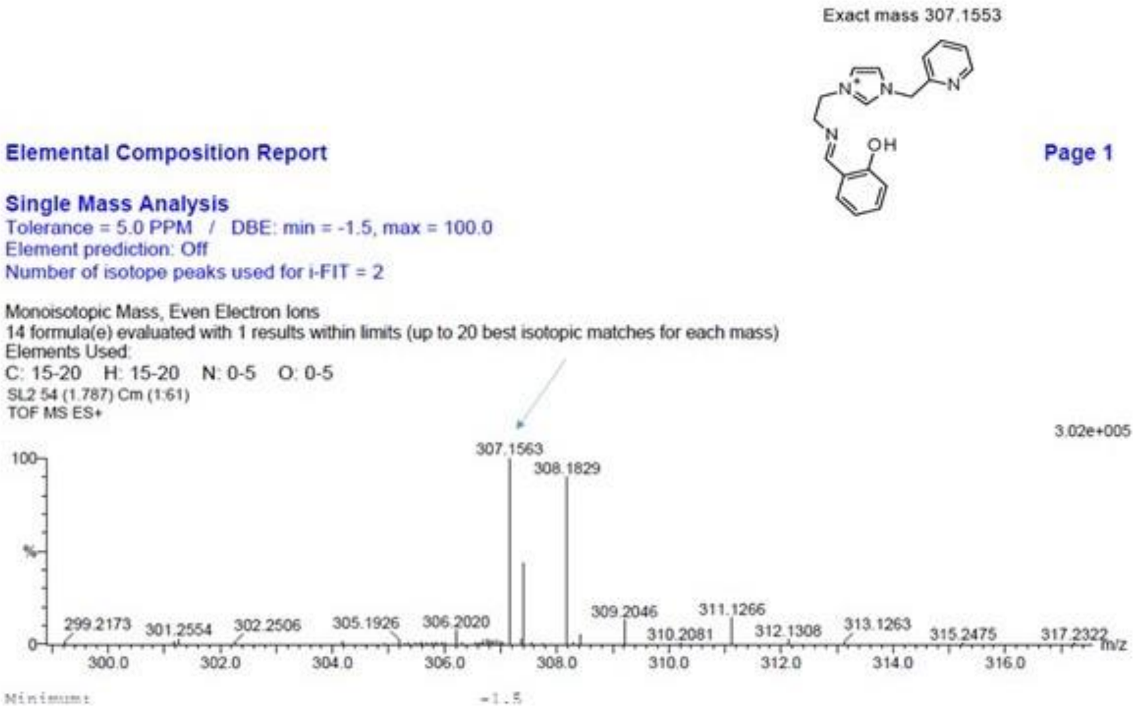


Figure S8: ^{1}H NMR Spectrum of compound **5** in DMSO-d6



Exact mass 307.1553

Elemental Composition Report

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Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
14 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 15-20 N: 0-5 O: 0-5
SL2 54 (1.787) Cm (1:61)
TOF MS ES+

Minimum: -1.5

Figure S9: HRMS spectrum of compound **5**

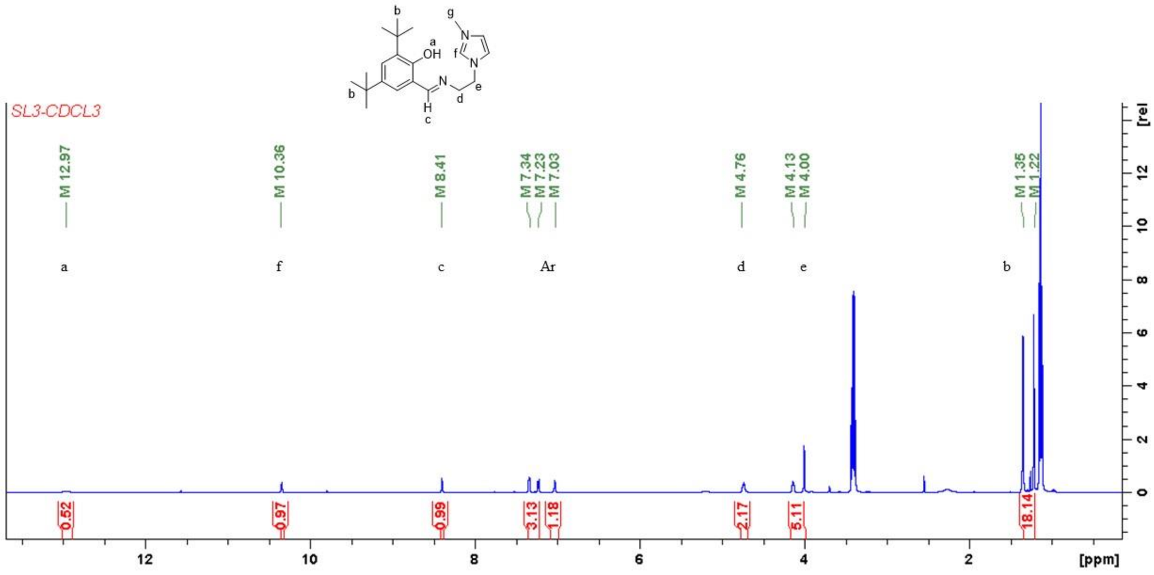
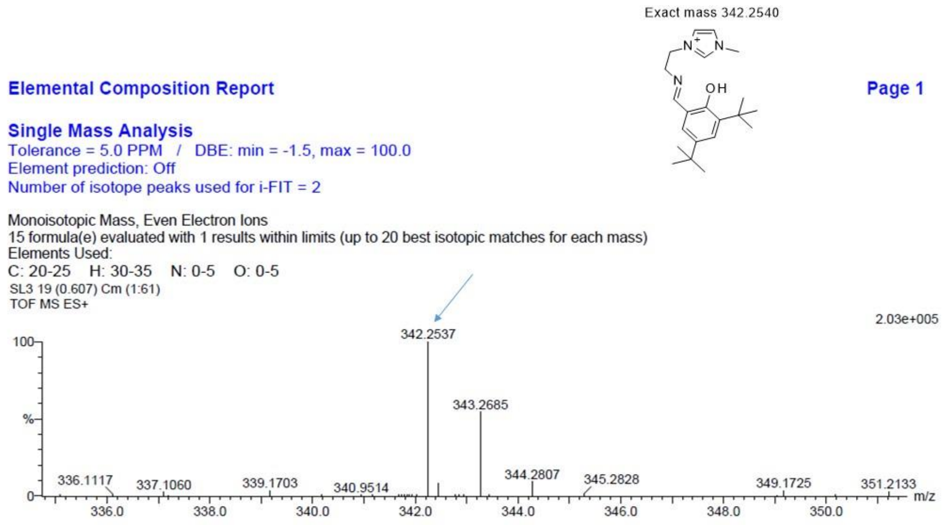


Figure S10: ^{1}H NMR spectrum of compound **6**



Exact mass 342.2540

Elemental Composition Report

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Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 20 best isotopic matches for each mass)
Elements Used:
C: 20-25 H: 30-35 N: 0-5 O: 0-5
SL3 19 (0.607) Cm (1:61)
TOF MS ES+

Figure S11: HRMS spectrum of compound **6**

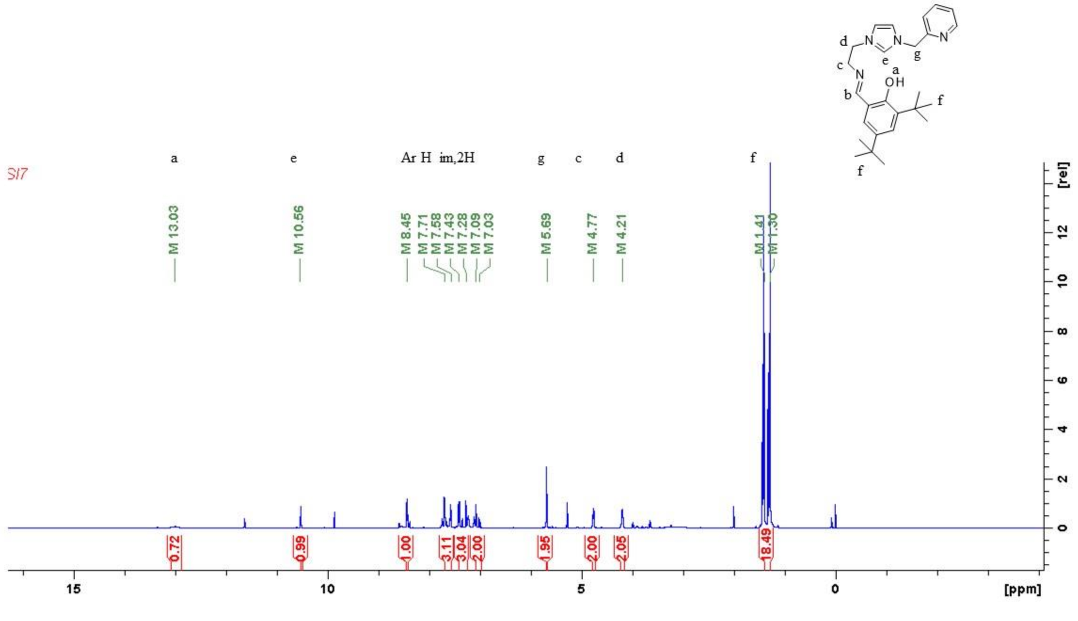

Figure S12: ^{1}H NMR spectrum of compound **7** in DMSO-d6