GREEN SYNTHESIS OF GUANIDINES DIRECTLY FROM THIOUREA

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การสังเคราะห์ที่เป็นมิตรต่อสิ่งแวดล้อมของกัวนิดีนโดยตรงจากไทโอยูเรีย

นายจักรกฤษณ์ ศรีษะ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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Field of Study	Chemistry
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จักรกฤษณ์ ศรีษะ : การสังเคราะห์ที่เป็นมิตรต่อสิ่งแวดล้อมของกัวนิดีนโดยตรงจากไทโอยูเรีย. (GREEN SYNTHESIS OF GUANIDINES DIRECTLY FROM THIOUREA) อ.ที่ปรึกษาหลัก : รศ. ดร.สัมฤทธิ์ วัชรสินธุ์, อ.ที่ปรึกษาร่วม : ศ. ดร.มงคล สุขวัฒนาสินิทธิ์

งานวิจัยนี้ได้พัฒนาวิธีการสังเคราะห์กัวนิดีนโดยตรงจากไอโซไทโอไซยาเนต โดยใช้ DIB เป็นสารออกซิไดซ์ ในน้ำที่มีสารลดแรงตึงผิว จากการศึกษาพบว่าการใช้ร้อยละ 1 โดยน้ำหนักของ TPGS-750-M เป็นสารลดแรงตึงผิวในสารละลายโซเดียมไฮดรอกไซด์ที่มีฤทธิ์ด่าง สามารถเปลี่ยนจากอะโรมาติกไอโซไทโอไซยาเนตและเอมีนหลายชนิดเป็นกัวนิดีนที่อุณหภูมิห้อง โดยให้ร้อยละผลิตภัณฑ์ที่ได้ในระดับดีถึงดีเยี่ยม (ร้อยละ 69-95) กระบวนการสังเคราะห์ในน้ำสามารถปรับใช้ในการเตรียมกัวนิดีในปริมาณสารระดับกรัม ตัวกลางไมเซลลาร์ในวัฏภาคน้ำมีความสามารถในการใช้ซ้ำสูง เนื่องจากสามารถเกิดปฏิกิริยาได้หลายรอบโดยปราศจากการสูญเสียประสิทธิผล คุณประโยชน์ของปฏิกิริยานี้ได้แก่ ปราศจากโลหะ ใช้น้ำเป็นตัวทำละลาย และเตรียมได้ง่ายที่อุณหภูมิห้องและระบบเปิด ยิ่งไปกว่านั้นวิธีการที่พัฒนาขึ้นนี้ยังสามารถใช้สังเคราะห์สารให้ความหวาน NC-174 ยา Pinacidil และ ตัวเร่งสำหรับไบโอดีเซล

สาขาวิชา เคมี ลายมือชื่อนิสิต .....

ปีการศึกษา 2561 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

ลายมือชื่อ อ.ที่ปรึกษาร่วม .....

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Jakkrit Srisa : GREEN SYNTHESIS OF GUANIDINES DIRECTLY FROM THIOUREA. Advisor: Assoc. Prof. SUMRIT WACHARASINDHU, Ph.D. Co-advisor: Prof. MONGKOL SUKWATTANASINITT, Ph.D.

In this work, one-pot synthesis of guanidines directly from isothiocyanates using DIB (diacetoxyiodobenzene) as a desulfurizing agent under a micellar condition in water was developed. The optimization study revealed that the use of 1wt%TPGS-750-M as a surfactant with NaOH as a base at room temperature can convert aromatic isothiocyanates and varieties of amines into the corresponding guanidines in good to excellent yields (69 - 95%). This green synthetic process in water can be applied to prepare guanidine at gram-scale quantity. The aqueous micellar medium was also reusable to give relatively the similar reaction yields for at least three cycles. The key benefit of this reaction is metal-free, utilize water as a solvent and operate at room temperature in an open flask. Moreover, the synthetic methodology was also applied to prepare as NC-174 sweetener, pinacidil drug, and biodiesel catalyst

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Student's Signature .....
Advisor's Signature .....
Co-advisor's Signature .....

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Jakkrit Srisa

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LIST OF ABBREVIATION

acetone-d_6	deuterated acetone
ACN	acetonitrile
Ar	aromatic
cat.	catalyst
^{13}C NMR	carbon-13 nuclear magnetic resonance
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
d	doublet (NMR)
dd	doublet of doublet (NMR)
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent (s)
Et_3N	triethylamine
g	gram (s)
h	hour (s)
^1H NMR	proton nuclear magnetic resonance
Hz	Hertz
HRMS	high resolution mass spectrum
h	hour (s)
J	coupling constant
K_a	Association constant

MALDI-TOF MS	matrix assisted laser desorption/ionization-time of flight mass spectrometry
mg	milligram (s)
min	minute (s)
mL	milliliter (s)
mmol	millimole (s)
m	multiplet (NMR)
M	molar
MHz	megahertz
MS	mass spectroscopy
NMR	nuclear magnetic resonance
rt	room temperature
s	singlet (NMR)
t	triplet (NMR)
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
δ	chemical shift
°C	degree Celsius
% yield	percentage yield

CHAPTER I

INTRODUCTIONS

1.1 Overview

The traditional organic synthesis relies on the use of an organic solvent in order to dissolve reactant and catalyst in the reaction mixture. The organic solvent used in the reaction is however considered as major waste in the reaction as it does not corporate in the final product. Moreover, most of them are toxic and environmental pollution. On the other hand, water is nontoxic and can consider as greenness solvent. The neat water or so-called “on-water” reaction was first introduced by Sharpless[1]. Since then many elegant reactions have been reported[2-6]. Although on-water reactions offer many benefits, wide-spread adopted has been limited by the inability of on-water reaction to being adapted to all the traditional chemical transform reactions due to heterogeneous behavior and poor reproducibility. In recent years, new developments in surfactant technology created by Liptutzed[7-15] and others[16-31] have significantly made an improvement for aqueous reactions allowing the reaction to occur “in-water” via the formation of micelles, thereby providing high reproducibility and reactivity.

Guanidines are important moieties that attract many interests in the agricultural and pharmaceutical industry due to their broad spectrum of biological activities. A typical synthesis of guanidine involves two steps reaction from isothiocyanates. The first step is the formation of thiourea and the second step is guanidine formation. However, the reaction needs to conduct in organic solvent and requires toxic desulfurizing agents. Therefore, in this project, we aim to develop more green and efficient method to synthesize guanidine. We plan to use water as reaction medium and less toxic activator reagent under one-pot procedure directly from isothiocyanate.

1.2 Water as the solvent for organic synthesis

Based on the benefits mentioned above, many research groups have been demonstrated the use of water as a solvent. This is because it is wildly available, nontoxic, and inexpensive. The reaction can be classified into two types (**Figure 1.1**). The first one is "on water" reaction which was first developed by Sharpless. The reaction was conducted in neat water. Starting material and reactants are not solute in water medium and become heterogeneous during the course of the reaction. The second one is "in water" reaction in which both starting material and reactants can solute in water medium. This is because of additive surfactant which is added in the reaction mixture.[3]

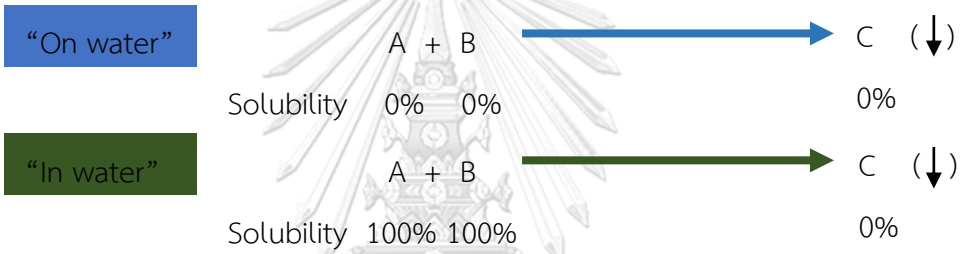


Figure 1.1 Reaction "on water" and "in water"

1.2.1 Examples of reaction on water

Neat water could be used as a reaction medium, it is cheap and easy to handle. Although most of reactants and catalysts could not be soluble in water, in some cases, the reaction on water can proceed in good yields and better than typical in organic solvent. The hypothesis is that the reactants form the hydrogen bond with the water surface (**Figure 1.2**). This hydrogen bonding activates the acceptor and donor ability allowing the reaction to proceed on the surface.[7]

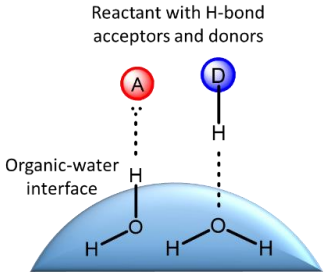
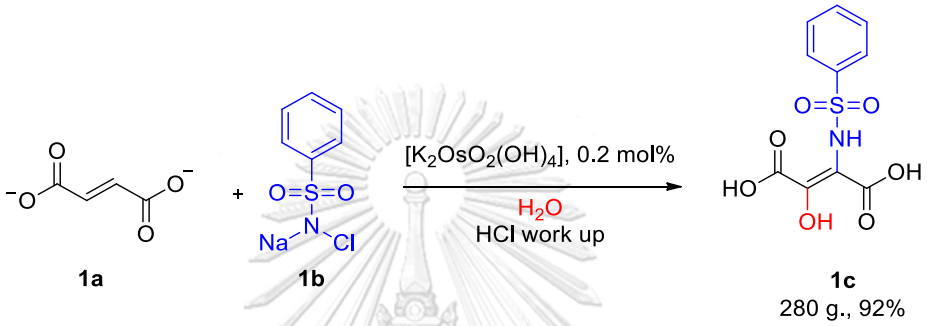


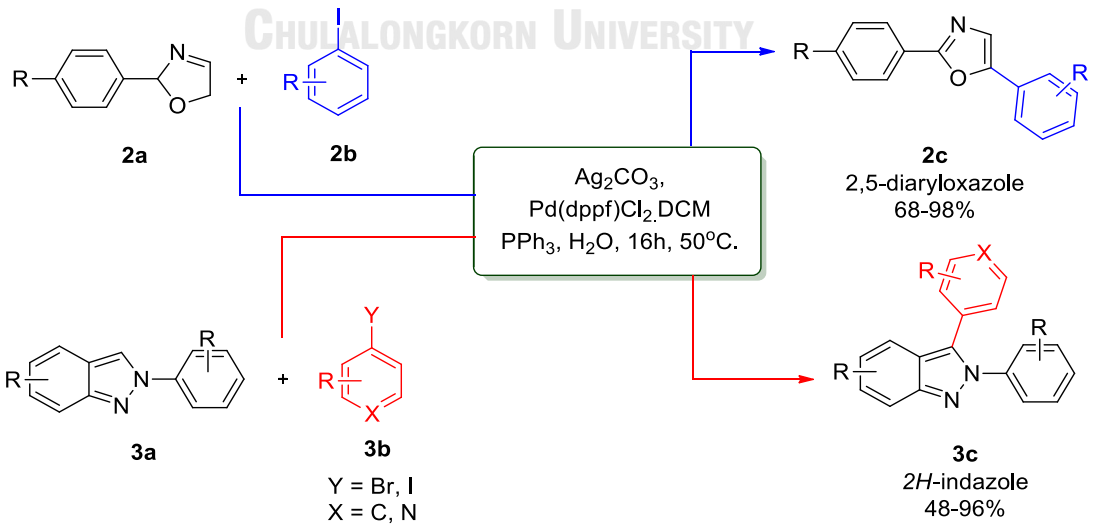
Figure 1.2 Activation of reactants by H-bonding at the aqueous interface

Sharpless and co-worker are an early group to study organic reaction on water. One of highlighted work from Sharpless groups is the synthesis of bioactive compound **1c** in 2001. They synthesized compound **1c** form sodium bicarbonate (**1a**) and fumaric acid (**1b**) in the presence of osmium as a catalyst on water (**Scheme 1.1**). The reaction can proceed at room temperature. Moreover, this method was able to scale up to 280 grams with excellent yield.[32]



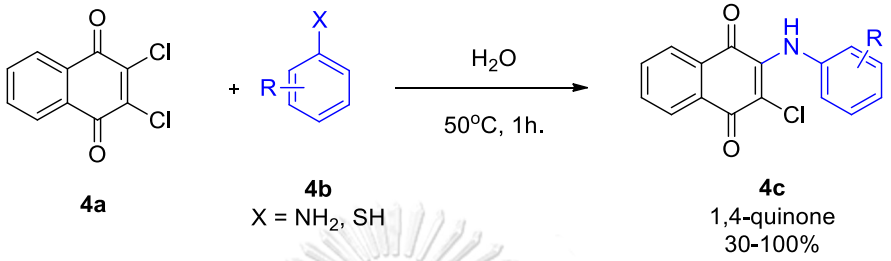
Scheme 1.1 2-hydroxy-3-(phenylsulfonamido)fumaric acid synthesis

In 2008, Greaney and co-worker reported C-C bond formation to prepare 2,5-diaryloxazoles (**2c**) using Pd-catalyst under "on water" condition. The desired products were obtained in good to excellent yields under mild reaction condition (**Scheme 1.2**). Next, in 2010, the same group used similar condition to prepare *2H*-indazoles (**3c**) in moderate to excellent yields as seen in **scheme 1.2**.[33, 34]



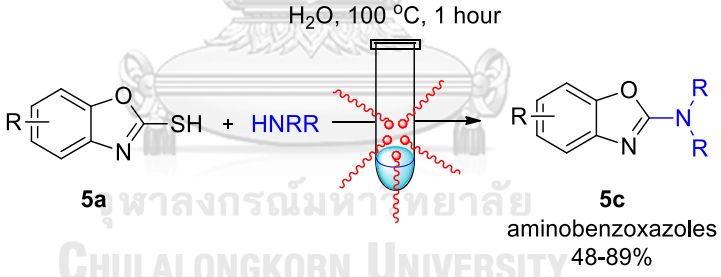
Scheme 1.2 Synthesis of 2,5 diaryloxazole and 2H-indazole

In 2009, Maurya and co-worker synthesized 1,4-quinone (**4c**) from 2,3-dichloro-1,4-naphthoquinone (**4a**) with ether amines or thiols (**4b**) on water (**Scheme 1.3**). The reaction was carried out in short reaction time without the use of a toxic metal catalyst. The products were isolated in good to excellent yields.[35]



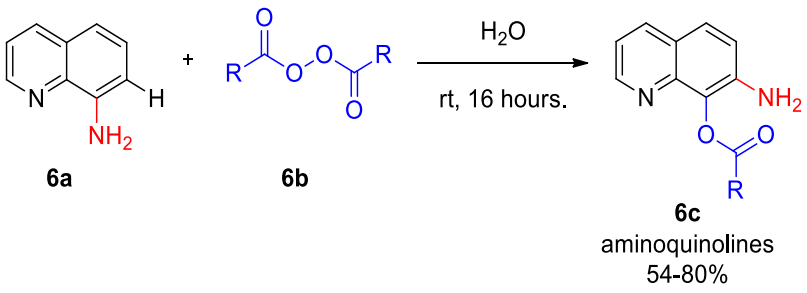
Scheme 1.3 Synthesis of 1,4-ruinone

In 2018, our group developed a simple and efficient method to prepare amino benzoxazoles **5c** from benzoxazole-2-thiols **5a** on water as seen in **scheme 1.4**. The reaction was accelerated by microwave irradiation. After the reaction is completed, the product is precipitated and can be filtered out from water medium.[36]



Scheme 1.4 Synthesis of aminobenzoxazoles

In 2019, Malapaka and co-worker reported the benzoxylation of aminoquinoline (**6a**) into product **6c** on water (**Scheme 1.5**). The reaction involves C-N/C-H bond breaking and C-O/C-N bond forming in one-pot method. The product **6c** was obtained in moderate to good yields under mild reaction condition.[6]



Scheme 1.5 Synthesis of aminoquinolines

1.2.2 Examples of reaction in water

Even though the reaction “on water” is convenient requiring no additive in the reaction but the heterogeneous nature results in the poor reproducibility. Therefore, this issue was solved by using surfactant which makes substrates or catalysts soluble “in water”.

The surfactants compose of hydrophilic and hydrophobic parts as shown in **figure 1.3.** The hydrophilic groups are possessed in anionic (alkyl sulfate, alkyl sulfonate), cationic (tetraalkylammonium, alkyl pyridinium), zwitterionic (trialkylammoniopropanesulfonate), or nonionic (polyoxyethylenealkyl ether, alkyl glycoside) (**Figure 1.4**). On the other hand, the hydrophobic long alkyl chain is an important part to form micelles which make reactants or catalysts solute in the micelle. Moreover, by capping reactants and the catalyst in the micelle, it increases the concentration of substrates offering faster reactions than traditional organic solvent.[15, 37]

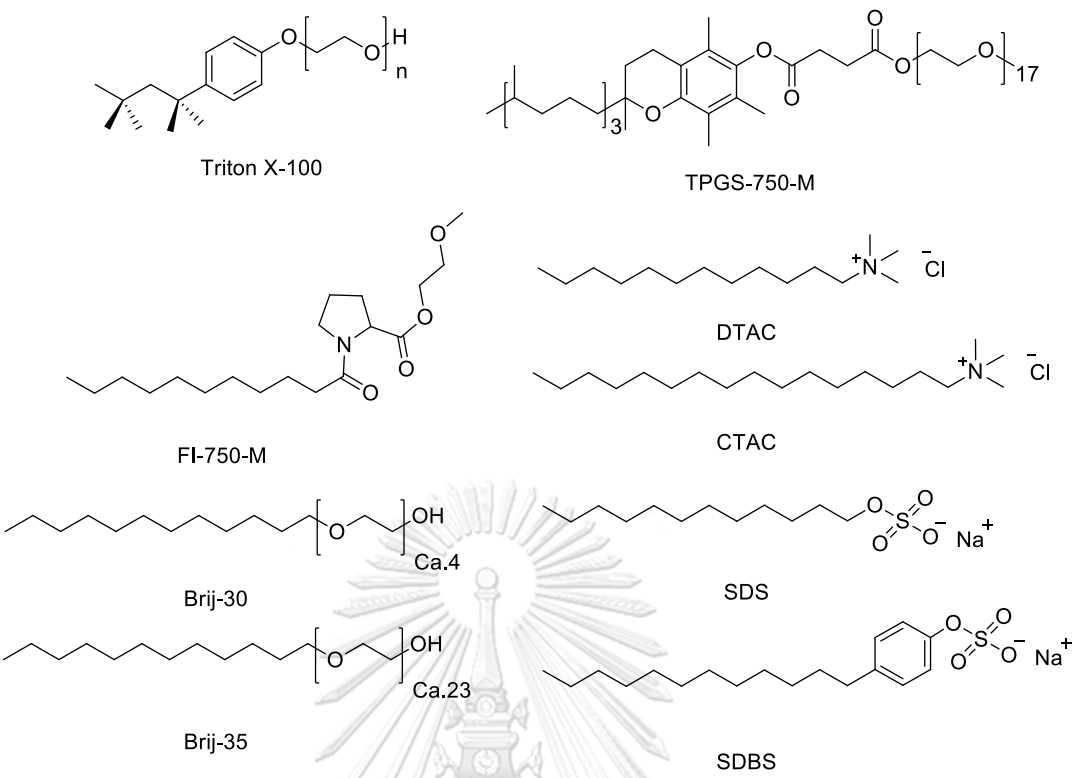


Figure 1.3 Examples of surfactants

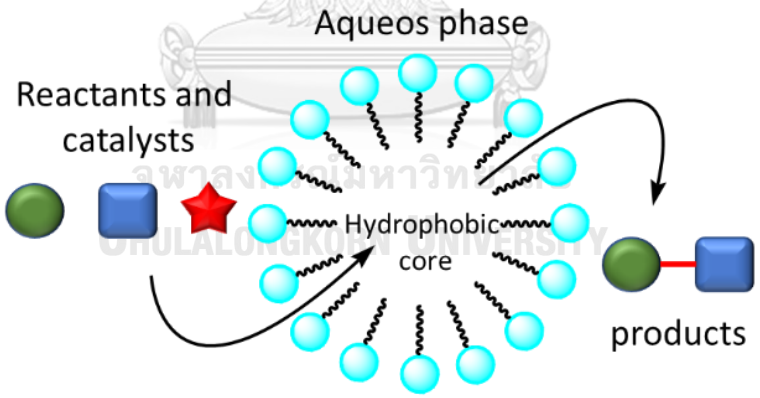
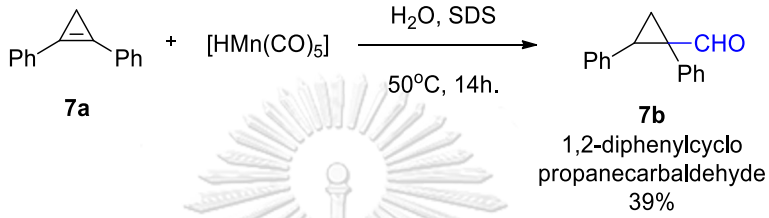


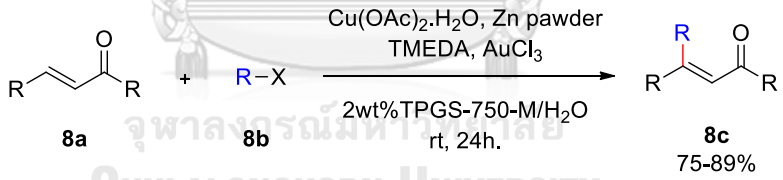
Figure 1.4 Hydrophobic species can react in the micelle interior[7]

In 1983, Orchin and Matsui first demonstrated the use of surfactant for in water reaction. The synthesis of 1,2-diphenylcyclopropanecarbaldehyde (**7c**) was accomplished by using manganese as a catalyst in the presence of SDS as a surfactant in water. The product was obtained in 39% yield as seen in **Scheme 1.6**. This is the first report to inspire other groups developed methodology for organic synthesis in water.[38]



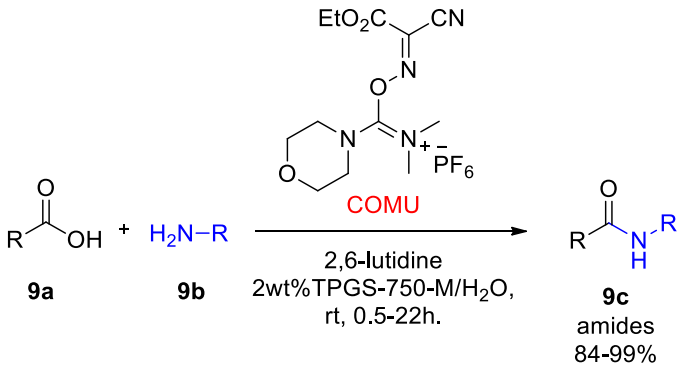
Scheme 1.6 Synthesis of 1,2-diphenylcyclopropanecarbaldehyde

In 2012, Isley and co-worker studied the use of TPGS-750-M as micellar in water for additions of alkyl halides (**8b**) to enones (**8a**) in the presence of copper and zinc powder as catalysts. the reaction was completed in 24 hours at room temperature to give the product **8c** in good yields as seen in **Scheme 1.7**.[8]



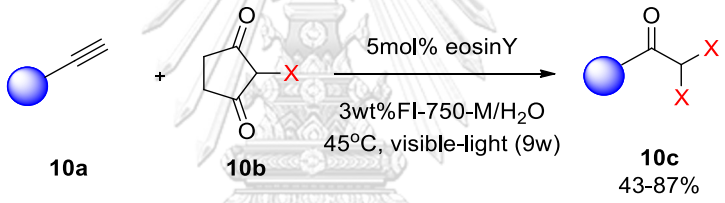
Scheme 1.7 Nucleophilic substitution of enones

In 2015, Lipshutz and co-worker synthesized amides (**9c**) from carboxylic acids (**9a**) and chiral amines (**9b**) using COMU as a mediator under TPGS-750-M/H_2O at room temperature. The aqueous reaction medium can recycle leading to reduce waste and product was obtained in good to excellent yields with no epimerization. (**Scheme 1.8**).[39]



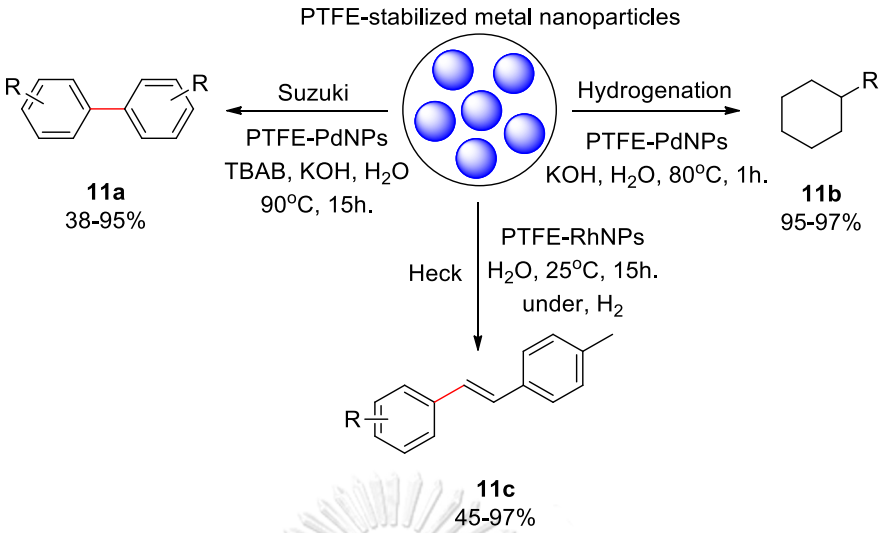
Scheme 1.8 Synthesis of amides

In 2018, Handa and co-worker reported a new surfactant (FI-750-M) in water for oxyhalogenation. The reaction between **10a** and **10b** was a catalyst by eosin-Y under visible-light to produce product **10c** in moderate to good yields (**Scheme 1.9**). The highlight of this method was reusable of the micellar reaction medium.[23]



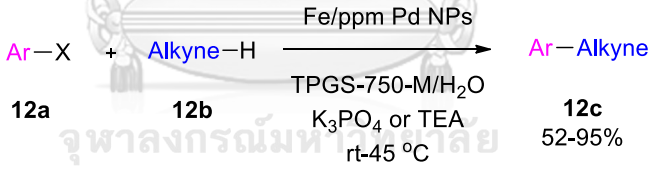
Scheme 1.9 Halogenation of alkynes

In 2018, Uozumi and co-worker prepared polymer-support metal nanoparticle catalysts (PTFE-PdNPs and PTFE-RhNPs) for Suzuki coupling reaction (Compound **11a**), heck reaction (Compound **11c**) and hydrogenation of arene (Compound **11b**) as seen in **scheme 1.10**. PTFE-PdNPs and PTFE-RhNPs compose of long polyethyleneglycol with act as a surfactant. They showed high catalytic activity and reuse-ability in water under mild reaction condition with good yields. Importantly, the catalyst can be reused 5 times without loss of its efficiency.[20]



Scheme 1.10 Suzuki coupling reaction, Heck reaction, and Hydrogenation

In 2019, Lipshutz and co-worker developed methodology for Sonogashira coupling reaction which used nanoparticle $FeCl_3$ in combination with only 500 ppm Pd as catalysts in TPGS-750-M/H_2O (**Scheme 1.11**). The advantage of this method is recyclable reaction medium in 5th cycles and "in-flask" extraction which reduced the use of organic solvent for large scale production.[13]

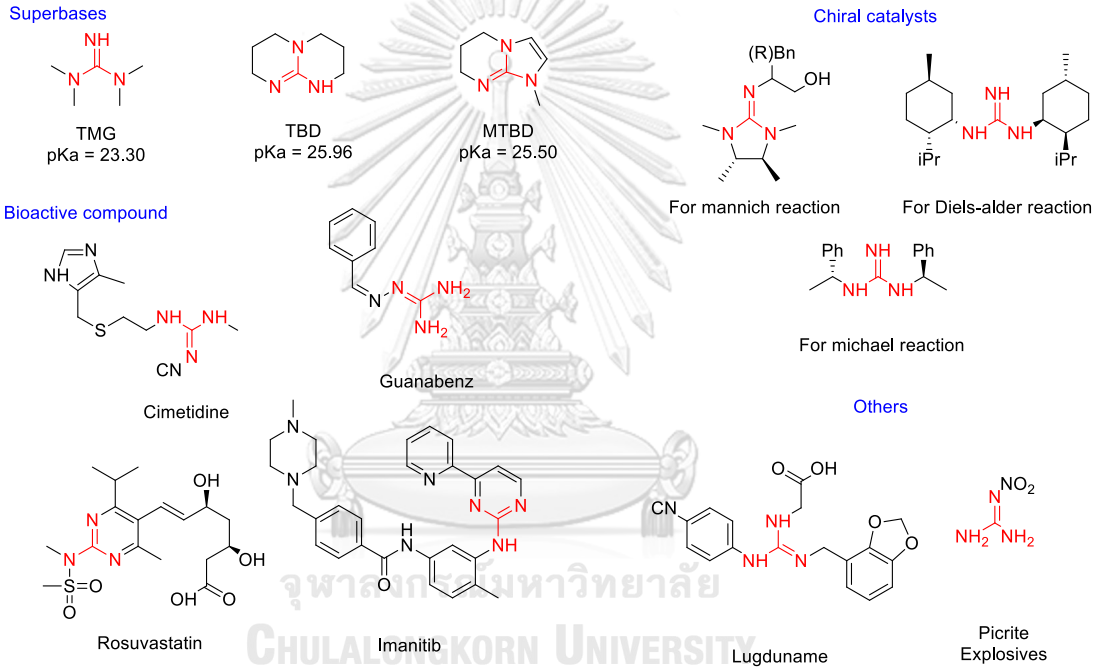


Scheme 1.11 Sonogashira coupling reaction

1.3 Literature reviews on guanidine

The structure of the guanidine compound is a Y-shaped CN_3 functional group as seen in **scheme 1.12** (red line). Guanidine was categorized as an organosuperbase, it is stronger bases than other nitrogen moieties including amidines, amines, pyridines, and diamines. Thus, it has been wildly used in an organic reaction as a base catalyst. Moreover, the chiral guanidines can be used as asymmetric catalysts for various reactions. For pharmaceutical in industry, guanidines demonstrated a broad spectrum of biologically active compounds. For example, Rosuvastatin is a commercial drug from AstraZeneca company which has been used for the treatment

of high cholesterol and prevention of cardiovascular disease. Guanabenz is under clinical trial phase from IVAX Pharmaceuticals, Inc. company as an antihypertensive drug. Imatinib is an anticancer drug from NOVARTIS company which inhibited the Bcr-Abl tyrosine-kinase. Cimetidine is a blockbuster drug from IVAX Pharmaceuticals, Inc. company which has been used to treat peptic ulcers. Moreover, nitroguanidine (Picrite) is used as an explosive propellant. One noteworthy example is Lugduname which is substituted guanidine with an acetic acid functional group. It was produced by the University of Lyon, France in 1996 which is extremely potent sweeteners.[40-43]



Scheme 1.12 structure of guanidine and biologically important compounds

1.4 Typical synthesis of guanidines

A typical synthesis of guanidine involves a reaction between an amine and guanylating agents such as isothioureas, amidine sulfonic acid, cyanamide, carbodiimide, pyrazole-1-carbox imidamides, triflylguanidines and thiourea (**Figure 1.5**).

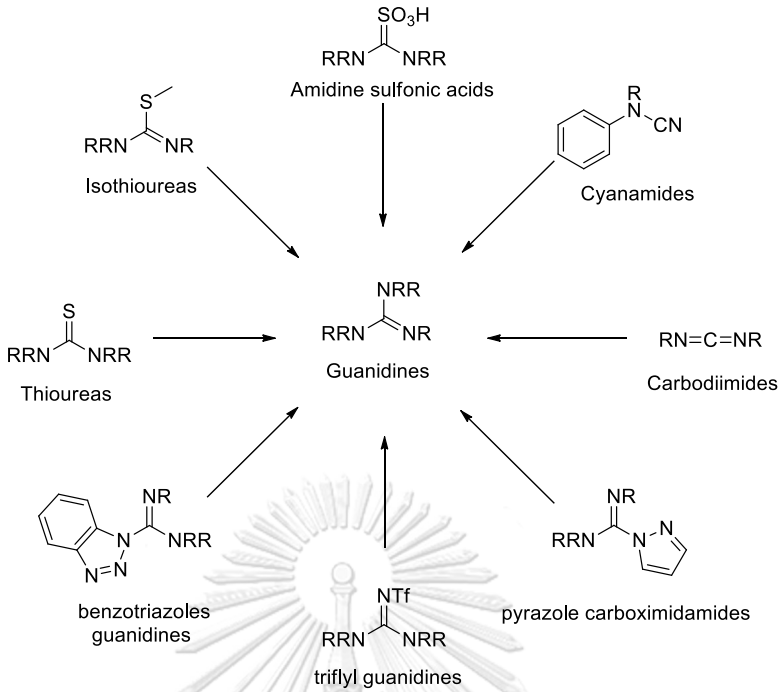
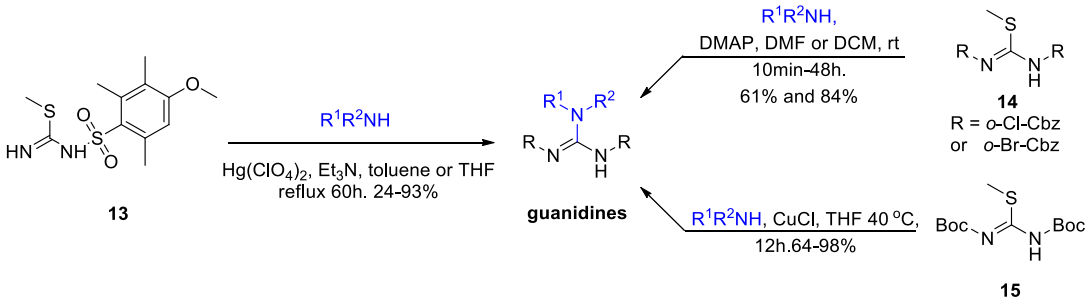


Figure 1.5 Guanylating agents

1.4.1 Isothioureas

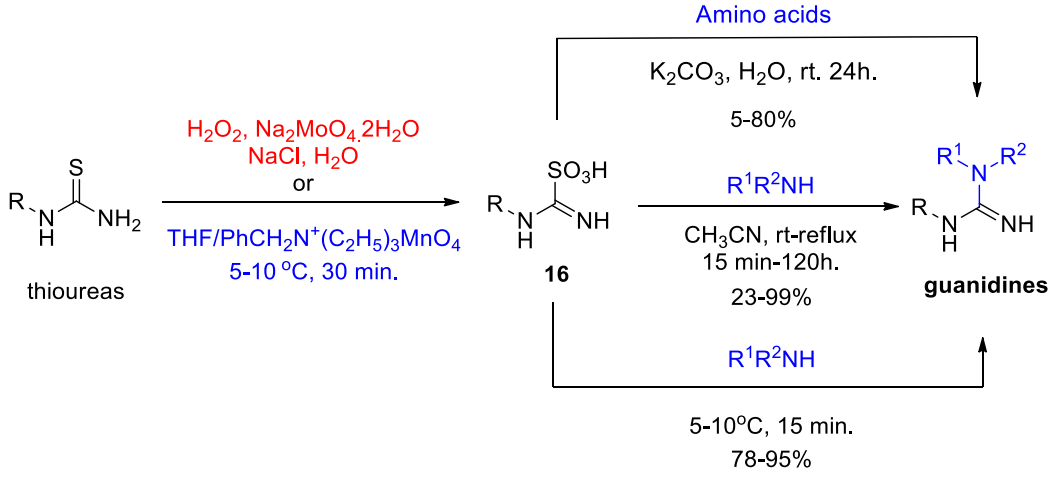
In 1996, Doherty[44] was the first group to prepare guanylating agent, isothiourea **13**, for the synthesis of guanidine. It used mercury as a catalyst under the hash condition and long reaction time (**Scheme 1.13**). The scope of amines is limited and this reaction presents high toxicity of mercury metal. Later, in 2004, Izdebski and co-worker[45] developed isothiocyanate **14** for the synthesis of guanidine (**Scheme 1.13**). This new guanylating agent is highly stable but the scope of the reaction is very narrow (only isobutylamine was examined). Next, in 2007, Terada and co-worker[46] demonstrated the synthesis of guanidine from Boc-isothiourea (**15**). It can couple with a variety of amine using copper salt as a catalyst to obtain guanidines in moderate to high yields (**Scheme 1.13**). The drawback of this method is a long reaction time. Importantly, all mentioned procedures are used as a traditional organic solvent (toluene, THF, DMF or DCM).



Scheme 1.13 Isothiocyanates as guanylating agent for synthesis guanidine

1.4.2 Amidine sulfonic acids

In 1986, Miller and co-worker[47] used amidine sulfonic acids **16** as a guanylating agent to generate guanidino acids under a mild condition in water (**Scheme 1.14**). It can prepare highly soluble di-,tri-substituted guanidine acids. In the same year, Maryanoff and co-worker[48] used the same starting material to prepare guanidines without the use of a metal catalyst or another additive (**Scheme 1.14**). However, amidine sulfonic acids need to prepare from thiourea and using toxic reagent (H_2O_2) and metal catalyst (Na_2MoO_4), including, tedious purification step. To solve this problem, in 2001, Ramadas and co-worker[49] developed a one-pot method for synthesis of guanidines from thiourea. The amidine sulfonic acids **16** was used for next step without purification by using quaternary ammonium permanganate (**Scheme 1.14**). This method presents a one-pot procedure in water with good and excellent yields.

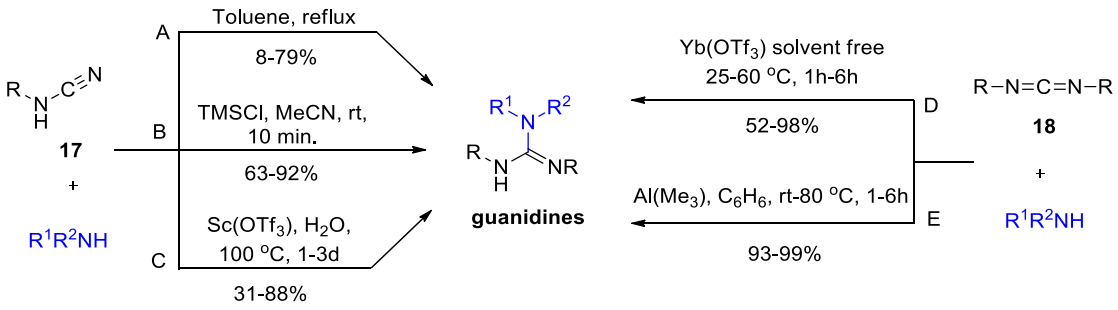


Scheme 1.14 Amidine sulfonic acids as guanylating agent for synthesis guanidine

1.4.3 Cyanamides and carbodiimides

In 1998, Reddy and co-worker[50] demonstrated the use of cyanamides as a guanylating agent to prepare guanidine without the use of any catalyst or mediator (**Scheme 1.15A**). However, this procedure needs to carry out in refluxing toluene and only symmetry guanidine can be prepared. In 2011, Looper and co-worker[51] developed a method for synthesis of monoprotected guanidines by using chlorotrimethylsilane (TMSCl) to generate intermediate *N*-silylcarbodiimide that can couple with a variety of amines (**Scheme 1.15B**). In 2014, Tanaka and co-worker[52] used scandium(III) triflate as a catalyst to synthesize guanidines from cyanamide derivatives in water (**Scheme 1.15C**). However, the reaction was run under the hash condition and required long reaction time (1-3 days).

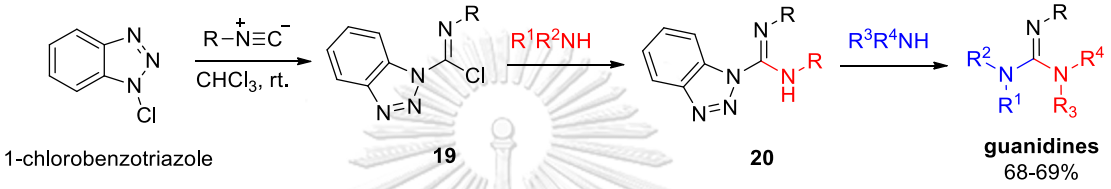
In 2009, Shen and co-worker[53] reported the use of carbodiimide **18** as guanylating agent (**Scheme 1.15D**). The reaction was carried out in the presence of ytterbium triflate as a catalyst under solvent-free condition. The reaction is highly efficient and can react with a variety of amine to product to guanidine in excellent yield. Similarly, Zhang and co-worker[54] reported the use of trimethyl aluminum to activate carbodiimide 18 in benzene (**Scheme 1.15E**). The product was obtained in excellent yield. As mention above, although carbodiimide has high reactivity and converts into guanidine product in high yield, the reaction needs a metal catalyst and organic solvent.



Scheme 1.15 Cyanamides and carbodiimides as guanylating agents for synthesis guanidine

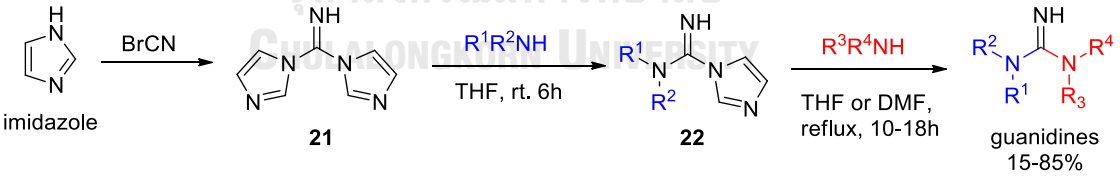
1.4.4 Pyrazole carboximidamides and Benzotriazoles

In 2001, Katritzky and coworker[55] reported new guanylating agent, benzotriazole **19** which was prepared from chlorobenzotriazole and isocyanide under mild condition reaction (**Scheme 1.16**). This new guanylating agent it highly stable and can react with a variety of amine to generate guanidines without the use of catalyst. However, all the reactions were carried out in a highly toxic organic solvent (chloroform).



Scheme 1.16 Benzotriazole as guanylating agents for synthesis guanidine

Then in 2002, di(imidazole-1yl)carboximidamide **21** was prepared by Katritzky group[56] from the reaction between bromocyanamide and imidazole. It was used as a guanylating agent which can convert into guanidine from the replacement of imidazoles with the corresponding amines (**Scheme 1.17**). The reaction can run without toxic metal catalyst but it is hash reaction condition and required an organic solvent.

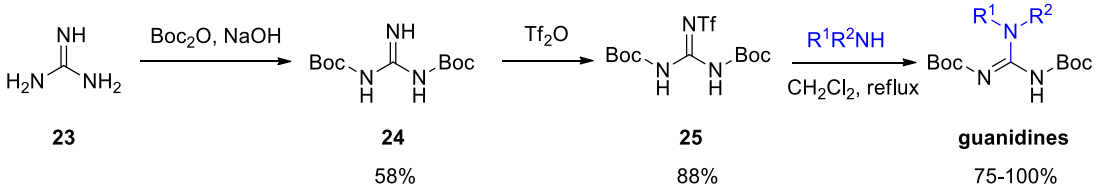


Scheme 1.17 Pyrazole carboximidamides as guanylating agents for synthesis guanidine

1.4.5 Triflil guanidines

Triflyl guanidine **25**, was used as a new guanylating agent by Goodman group[57] for the synthesis of protected guanidine (**Scheme 1.18**). Di-Boc-triflilguanidine **25** efficiently reacted with variety amines and converted to guanidine in good to

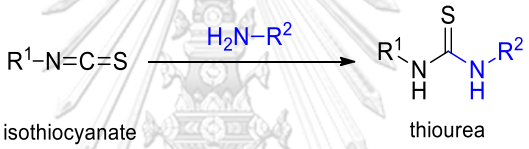
excellent yield. On the other hand, this method required multiple steps and the use of toxic solvent and hash condition.



Scheme 1.18 Triflil guanidines as guanylating agents for synthesis guanidine

1.4.6 Thioureas

Thioureas are the most promising guanylating agent because of their stability and easy to handle. It was synthesized from isothiocyanates and corresponding amines under mild reaction condition (**Scheme 1.19**).

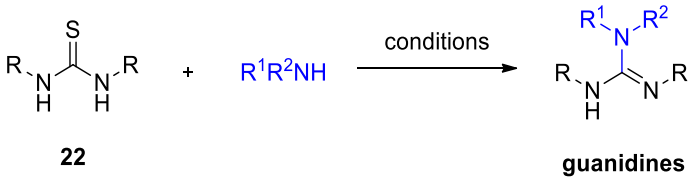


Scheme 1.19 Synthesis of thioureas

In 1995, Ramadas and Srinivasan[58] reported the use of thiourea to synthesize guanidine by using copper sulfate on SiO_2 as a catalyst (**Table 1.1,** entry 1). Guanidines were obtained in good to excellent yields. This report has inspired another research group and thiourea has become a popular guanylating agent. In 1997, Lipton and co-worker[59] developed to use Mukaiyama's reagent for the preparation of guanidine. The reagent is very reactive and guanidines were prepared in excellent yield. (**Table 1.1,** entry 2). In 2006, Cunha and co-worker[60] studied to use bismuth(III) as a catalyst for synthesizing guanines from thioureas (**Table 1.1,** entry 3). Although the catalytic amount of bismuth(III) was used, the $NaBiO_3$ was required as a co-oxidant in stoichiometric amount. In 2012, Akamanchi and co-worker[61] presented the conversion of thioureas into guanidine in acetonitrile using IBX as an oxidizing agent (**Table 1.1,** entry 4). The products were generated in good to excellent yields at room temperature in short reaction time. However, IBX poses serious drawback

because of its potential shock sensitive nature. In 2016, Pattaraworapan and co-worker[62] used trichloro cyanuric acid (TCT) as desulfurization reagent in DCM under ultrasound-assisted to convert thiourea into guanidine (**Table 1.1,** entry 5).

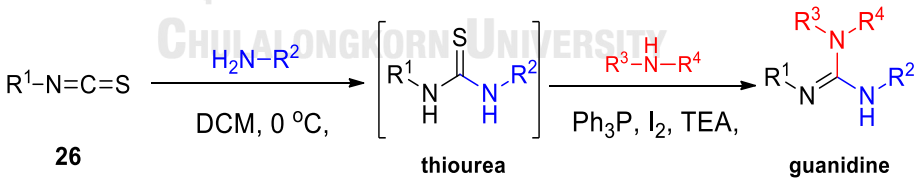
Table 1.1 literature review of thioureas as guanylating agent



22 **guanidines**

Entry	Year	Conditions	Yield (%)
1	1995	$CuSO_4/SiO_2$, TEA, THF, rt, 45-60 min.	75-90%
2	1997	Mukaiyama's Reagent, DMF or DCM, rt	21-92%
3	2006	BiI_3 (5 mol%), $NaBiO_3$, TEA, ACN, reflux, 3-21h.	65-97%
4	2012	IBX, TEA, ACN, rt, 30 min.	78-90%
5	2016	TCT, PPh_3, Na_2CO_3, DCM, rt. 5-10 min.))).	63-92%

Recently, in 2017, Pattarawarapan and co-worker[63] reported the one-pot synthesis of guanidines mediated by the Ph_3P/I_2 system directly from isothiocyanate and amine at 0 °C. The thioureas were generated in situ followed by desulfurization to generate guanidines in good yields (**Scheme 1.20**).



26 **thiourea** **guanidine**

Scheme 1.20 One-pot synthesis of guanidine from isothiocyanate

1.5 Overview of hypervalent iodine reagents

Hypervalent iodine is a useful organic oxidizing agent. It has a high environmental property and also commercially available. It can be categorized into two types: Iodine(III) and iodine(V) (**Figure 1.6**). Both of them are heavily used in organic synthesis for the selective oxidative transformation of complex organic molecules or halogenation reaction.[64] However, hypervalent iodine(V), IBX, were used

in guanidine synthesis the reagent poses serious drawback because of its potential shock sensitive nature.[59] Therefore, in this thesis, decided to use a non-explosive hypervalent (III) as oxidant instead.

Figure 1.6 Hypervalent iodine(III) and iodine(V)

1.6 Introduction to hypervalent iodine (III)

Conrad Willgerodt first synthesized of hypervalent iodine (III) (dichloroiodobenzene) in 1886.[65] It was synthesized from iodobenzene and chlorine gas. Later another more stable hypervalent iodine, for example, iodosylbenzene, (diacetoxyiodo)benzene (DIB) and [hydroxy(tosyloxy)iodo]benzene (HTIB) (**Figure 1.7**). Since then, hypervalent iodine (III) are widely used in organic synthesis for an oxidizing agent, functionalization of carbonyl compounds, rearrangements, and diaryliodonium salt formation.

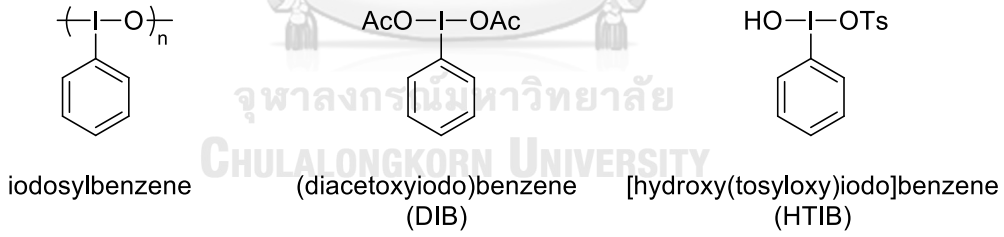


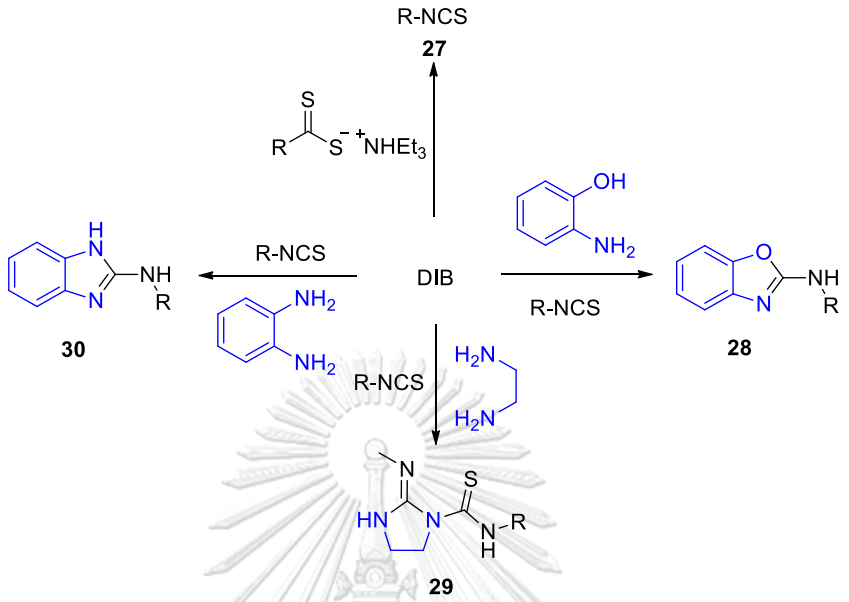
Figure 1.7 Synthesis of common hypervalent iodine(III)

1.6.1 The use of hypervalent iodine (III) for organic synthesis

1.6.1.1 Desulfurization mediated by hypervalent iodine(III)

In 2008, Ghosh and co-worker[66] used DIB as an oxidizing agent for desulfurization of dithiocarbamate salts to generate isothiocyanates **27** in high yields and short reaction time. After that, they applied their methodology to synthesized aminobenzoxazoles **28** and imidazolidenecarbothioamides **29**, and benzimidazoles **30** from *o*-phenylenediamine, *o*-aminophenol and 1,2-diamine, respectively (**Scheme**

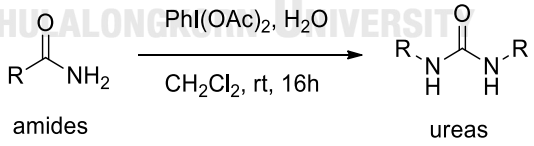
1.21). The products were obtained in good to excellent yields under mild condition by using hypervalent iodine(III) reagent DIB.



Scheme 1.21 Desulfurization reaction

1.6.1.2 Synthesis of symmetrical ureas

In 2010, Kalesse and co-worker[67] synthesized symmetry urea from amides in the presence of DIB as an oxidizing agent in a mixed solvent (water and DCM) under mild condition (**Scheme 1.22**). The products were obtained in modulate yields. This result suggested that DIB is stable in water.

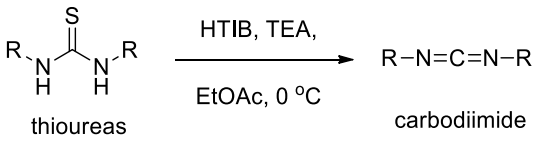


Scheme 1.22 Synthesis of symmetrical ureas

1.6.1.3 Synthesis of carbodiimides

In 2011, Wei and co-worker[68] prepared symmetrical and unsymmetrical carbodiimides, including dialkyl carbodiimide from thiourea derivatives, reacted with HTIB so-called Koser's reagent as seen in **scheme 1.23**. the products were obtained in modulate to good yields. They reported that HTIB is more

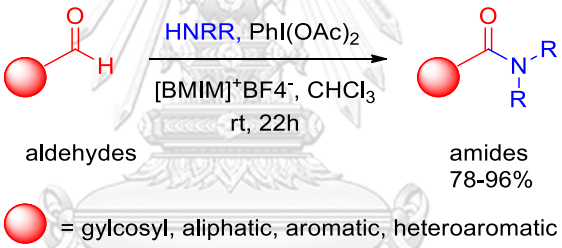
reactive than other hypervalent iodine (III) which required a reaction to proceed at low temperature.



Scheme 1.23 Synthesis of carbodiimides

1.6.1.4 Synthesis of carboxamides from aldehydes

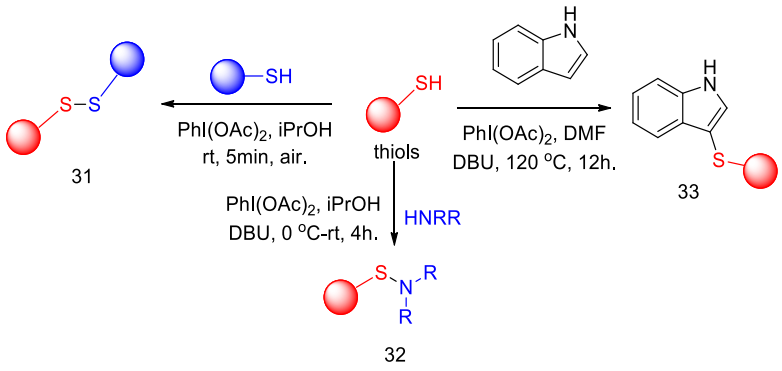
In 2012, Tiwari and co-worker[69] reported the oxidation of aldehydes using DIB in catalytic amounts of ionic liquid ($[BMIM]^+BF_4^-$) to form carboxamides in good to excellent yields (**Scheme 1.24**). The advantage of this method is the one-pot procedure in eco-friendly medium ionic liquid. Moreover, a variety of functional groups were tolerances under mild condition.



Scheme 1.24 Synthesis of amides

1.6.1.5 Formation of S–S, S–N, and S–C Bonds

In 2014, our group[70] demonstrated the use of hypervalent iodine(III) reagent for formation of S-S, S-N, and S-C bonds directly from thiols as shown in **scheme 1.25**. The reaction was successfully under when in the presence of DIB as oxidizing agent mild reaction condition and the product was obtained in high yield.

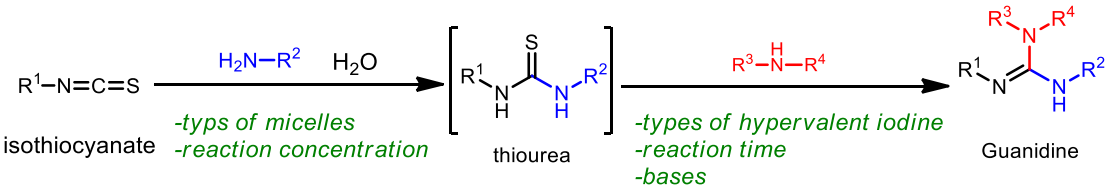


Scheme 1.25 Formation of S–S, S–N, and S–C Bonds

From the above reviews, the synthesis of guanidines has still some problems such as the need for transition metal catalysts or toxic reagents and multiple steps synthesis. Moreover, most reactions require an organic solvent. Based on the advantages of hypervalent iodine(III) reagents which is highly stable, commercially available, and low toxic. We aim to use hypervalent iodine(III) as an oxidizing agent to prepare guanidines. Importantly, we want to develop the one-pot synthesis directly from isothiocyanate and carry out in water containing surfactants as reaction medium. The outcome of our research should provide a green and efficient method to prepare guanidine which is suitable for the both academic and chemical industry.

1.7 The objective of this research

We aim to develop a one-pot synthesis of guanidine directly from isothiocyanate mediated by hypervalent iodine(III) as an oxidant in water (**Scheme 1.26**). For optimization study, we plan to screen surfactants, hypervalent iodine(III), the concentration of reaction and reaction time. Importantly, we will study the scope of amines (highlighted in blue and red lines) and reuse-ability of the reaction medium. Ultimately, we will use our developed method to synthesis the high-value guanidines such as sweetener NC-174, catalyst and pinacidil drug (**Figure 1.8**).



Scheme 1.26 Synthesis of guanidine directly from isothiocyanate

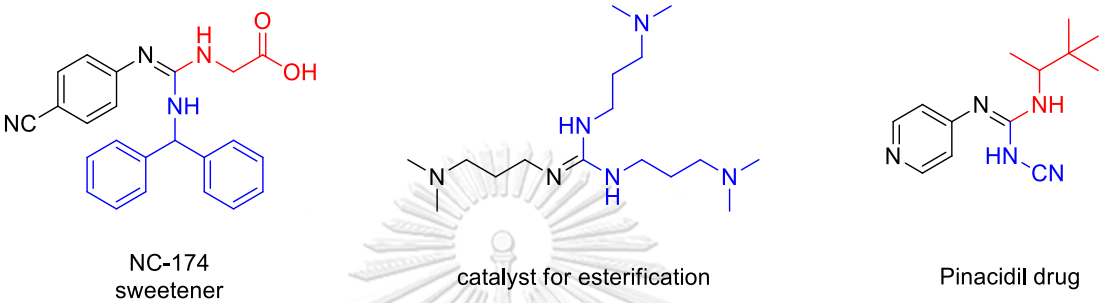


Figure 1.8 Important guanidines

CHAPTER II

EXPERIMENTAL

2.1 Materials and instruments

All chemicals were obtained from commercial suppliers (Sigma Aldrich), Fluka (Switzerland) or Merck (Germany) and were used without further purification. All solvents were used directly without drying. Analytical thin-layer chromatography (TLC) was performed on Kieselgel F254 pre-coated plastic TLC plates from EM Science. Visualization was performed with a 254 nm ultraviolet lamp. Column chromatography was performed by using Merck and silica gel (60, 230–400 mesh) from ICN Silitech. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or Bruker Avance 400 for ^{1}H (400 MHz) and Bruker Avance 400 for ^{13}C (100 MHz) in $CDCl_3$ solution.

2.2 Synthetic procedures

2.2.1 Reaction optimization

For the optimization study was carried out on different parameters, which were listed below along with their selections and values.

-Solvents: Acetonitrile, H_2O, 2wt%TritonX-100/H_2O, 2wt%SDS/H_2O and 2wt%TPGS-750-M/H_2O.

-Hypervalent iodine(III): DIB, BTB, HTIB, and BIB

-Amount of hypervalent iodine(III): 1.2, 1.5 and 2.0 equivalents.

-Bases: NaOH, TEA, and K_2CO_3

-Reactant concentrations: 0.1, 0.5 and 1.0 M.

-Percent of micellar catalyst in water: 2wt%, 1wt%, and 0.1wt%

-Reaction Time: 1.0 h. and 0.5 h.

2.3 The substrate scope of the guanylation reaction

2.3.1 General experimental procedure A: asymmetry guanidines 5a-5p

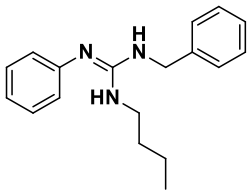
In a 5.0 mL reaction vial containing a magnetic stir bar, isothiocyanate (1.0 equivalent), amine (1.0 equivalent), NaOH (1.5 equivalent) and 1%TPGS-750-M/H_2O (0.4 mL, 0.5M.) were sequentially added. The reaction mixture stirs at room temperature for 1h. After starting material completely was consumed, as monitored by TLC, amine (1.5 equivalent) and DIB (1.2 equivalent) were sequentially added and stirring continued for 30 minutes. Then 1mL of ethyl acetate (1mLx2) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was purified by column chromatography over silica gel by using 25%ethyl acetate in hexane to 100%ethyl acetate as eluent to obtain guanidine derivative.

2.3.2 General experimental procedure B: symmetry guanidines 6a-8e

In a 5.0 mL reaction vial containing a magnetic stir bar, isothiocyanate (1.0 equivalent), amine (2.5 equivalent), NaOH (1.5 equivalent) and 1%TPGS-750-M/H_2O (0.4 mL, 0.5M.) were sequentially added. The reaction mixture stirs at room temperature for 1h. after starting material completely was consumed, as monitored by TLC, DIB (1.2 equivalent) was sequentially added and stirring continued for 30 minutes. Then 1mL of ethyl acetate (1mLx2) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was purified by column chromatography over silica gel by using 25%ethyl acetate in hexane to 100%ethyl acetate as eluent to obtain guanidine derivative.

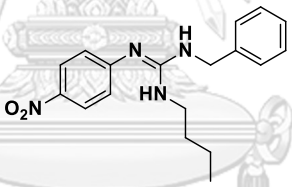
2.3.3 Synthesis derivatives of guanidine

1-benzyl-3-butyl-2-phenylguanidine (**5a**)



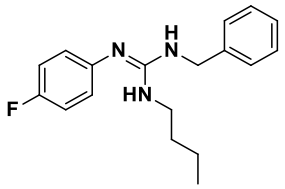
General procedure A was followed, using phenyl isothiocyanate (51.1 mg, 0.3780 mmol), benzylamine (40.5 mg, 0.3780 mmol) and butylamine (41.4 mg, 0.5671 mmol). The compound was obtained in yellow oil (0.9489 g, 83% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.39-7.27 (m, 7H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 4.39 (s, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 1.48-1.41 (m, 2H), 1.31-1.22 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.8, 148.8, 138.9, 129.3, 128.7, 127.5, 127.3, 123.5, 122.0, 46.0, 41.8, 31.7, 19.9, 13.7 $[M+H]^+$: calcd 282.1970, found 282.1983.

1-benzyl-3-butyl-2-(4-nitrophenyl)guanidine (**5b**)



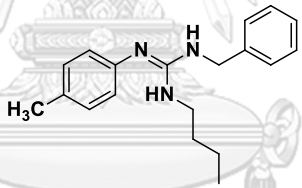
General procedure A was followed, using 4-nitrophenylisothiocyanate (52.0 mg, 0.2886 mmol), benzylamine (31.5 mg, 0.2886 mmol) and butylamine (31.6 mg, 0.4329 mmol). The compound was obtained in yellow solid (0.0855 g, 94% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.06 (d, *J* = 7.6 Hz, 2H), 7.38-7.29 (m, 5H), 6.94 (d, *J* = 7.6 Hz, 2H), 4.41 (s, 2H), 3.14 (t, *J* = 7.2 Hz, 2H), 1.50-1.43 (m, 2H), 1.32-1.23 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 156.8, 152.5, 141.1, 138.1, 128.8, 127.7, 127.3, 125.5, 122.6, 46.1, 41.9, 31.5, 19.9, 13.6. $[M+H]^+$: calcd 327.1821, found 327.1849

1-benzyl-3-butyl-2-(4-fluorophenyl)guanidine (**5c**)



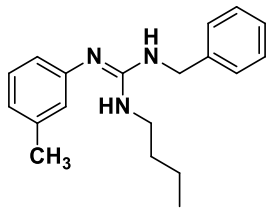
General procedure A was followed, using 4-fluorophenylisothiocyanate (51.0 mg, 0.3330 mmol), benzylamine (36.0 mg, 0.3330 mmol) and butylamine (36.1 mg, 0.4995 mmol). The compound was obtained in colorless oil (0.0917 g, 92% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.43-7.27 (m, 5H), 6.98 (t, *J* = 8.8 Hz, 2H), 6.84 (dd, *J* = 8.2, 5.2 Hz, 2H), 4.40 (s, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 1.54-1.37 (m, 2H), 1.35-1.20 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 158.4 (d, $J_{C\text{-}F}$ = 237.7 Hz), 151.7, 145.9, 138.9, 128.7, 127.5, 127.3, 124.6 (d, $J_{C\text{-}F}$ = 7.7 Hz), 115.9 (d, $J_{C\text{-}F}$ = 21.8 Hz), 46.0, 41.6, 31.8, 19.9, 13.7. $[M+H]^+$: calcd 300.1876, found 300.1893

1-benzyl-3-butyl-2-(*p*-tolyl)guanidine (**5d**)



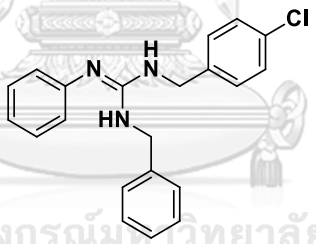
General procedure A was followed, using p-tolylphenylisothiocyanate (50.0 mg, 0.3351 mmol), benzylamine (36.1 mg, 0.3351 mmol) and butylamine (37.3 mg, 0.5027 mmol). The compound was obtained in yellow oil (0.0881 g, 89% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.29-7.22 (m, 3H), 7.17 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 4.28 (s, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.20 (s, 3H), 1.40-1.28 (m, 2H), 1.21-1.11 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.6, 146.9, 139.1, 130.9, 129.9, 128.7, 127.4, 127.3, 123.3, 46.0, 41.6, 31.8, 20.7, 20.0, 13.7. $[M+H]^+$: calcd 296.2127, found 296.2150

1-benzyl-3-butyl-2-(*m*-tolyl)guanidine (**5e**)



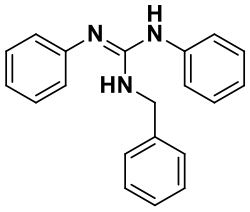
General procedure A was followed, using m-tolylphenylisothiocyanate (52.2 mg, 0.3497 mmol), benzylamine (37.3 mg, 0.3497 mmol) and butylamine (38.1 mg, 0.5246 mmol). The compound was obtained in yellow oil (0.0940 g, 91% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.43-7.27 (m, 5H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.85-6.70 (m, 3H), 4.39 (s, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 1.49-1.42 (m, 2H), 1.33-1.23 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.8, 148.8, 139.0, 129.1, 128.7, 127.4, 127.3, 124.2, 122.7, 120.3, 46.1, 41.8, 31.8, 21.4, 19.9, 13.7. $[M+H]^+$: calcd 296.2127, found 296.2158

1-benzyl-3-(4-chlorobenzyl)-2-phenylguanidine (**5f**)



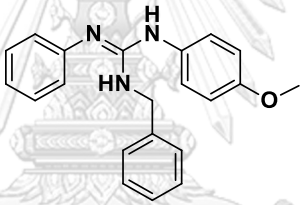
General procedure A was followed, using phenylisothiocyanate (50.9 mg, 0.3771 mmol), 4-chlorobenzylamine (53.2 mg, 0.3771 mmol) and benzylamine (60.9 mg, 0.5657 mmol). The compound was obtained in yellow oil (0.0989 g, 75% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.44-7.18 (m, 9H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 4.34 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.2, 148.6, 138.6, 137.4, 133.1, 129.5, 128.8, 128.8, 128.6, 127.6, 127.2, 123.5, 122.3, 46.1, 45.2. $[M+H]^+$: calcd 350.1424, found 350.1430

1-benzyl-2,3-diphenylguanidine (**5g**)



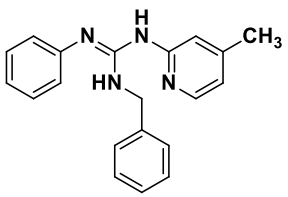
General procedure A was followed, using phenylisothiocyanate (50.5 mg, 0.3746 mmol), aniline (35.5 mg, 0.3746 mmol) and benzylamine (60.1 mg, 0.5620 mmol) The compound was obtained in yellow solid (0.1016 g, 90% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.23-7.12 (m, 9H), 6.94-6.90 (m, 6H), 4.38 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 148.8, 138.8, 129.5, 128.7, 127.6, 127.4, 123.5, 123.0, 46.0. $[M+H]^+$: calcd 302.16, found 302.05.

1-benzyl-3-(4-methoxyphenyl)-2-phenylguanidine (**5h**)



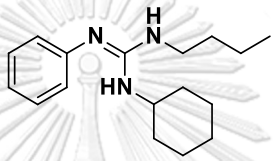
General procedure A was followed, using phenylisothiocyanate (50.8 mg, 0.3764 mmol), 4-methoxyphenylisothiocyanate (46.1 mg, 0.3764 mmol) and benzylamine (60.3 mg, 0.5646 mmol) The compound was obtained in yellow solid (0.0973 g, 78% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.33-7.25 (m, 7H), 7.05 (d, *J* = 7.6 Hz, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.37 (s, 2H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 156.9, 138.6, 129.4, 128.6, 127.6, 127.4, 125.6, 123.4, 123.2, 114.8, 55.4, 46.1. $[M+H]^+$: calcd 332.17, found 332.10.

1-benzyl-3-(4-methylpyridin-2-yl)-2-phenylguanidine (**5i**)



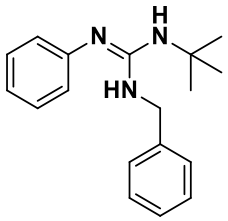
General procedure A was followed, using phenylisothiocyanate (52.1 mg, 0.3854 mmol), 2-amino-4-metylpyridine (42.3 mg, 0.3854 mmol) and benzylamine (62.1 mg, 0.5782 mmol) The compound was obtained in yellow solid (0.0841 g, 69% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.82 (d, *J* = 5.2 Hz, 1H), 7.27-7.06 (m, 8H), 6.88 (m, 2H), 6.39 (d, *J* = 5.2 Hz, 1H), 6.22 (s, 1H), 4.26 (s, 2H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 158.5, 151.3, 148.8, 147.6, 138.7, 129.4, 128.7, 127.4, 127.2, 123.5, 122.0, 115.5, 108.9, 46.0, 20.9. $[M+H]^+$: calcd 317.1766, found 316.1808

1-butyl-3-cyclohexyl-2-phenylguanidine (**5j**)



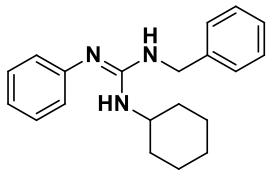
General procedure A was followed, using phenylisothiocyanate (50 mg, 0.3734 mmol), butylamine (27 mg, 0.3734 mmol) and cyclohexylamine (55 mg, 0.5601 mmol) The compound was obtained in yellow solid (0.0908 g, 89% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.17 (t, *J* = 7.6 Hz, 2H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 2H), 3.34-3.29 (m, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 1.92-1.89 (m, 2H), 1.68-0.93 (m, 12H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.2, 129.2, 123.5, 121.6, 50.4, 41.9, 33.7, 31.9, 25.6, 24.8, 20.1, 13.8. $[M+H]^+$: calcd 274.2283, found 274.2284

1-benzyl-3-(*tert*-butyl)-2-phenylguanidine (**5k**)



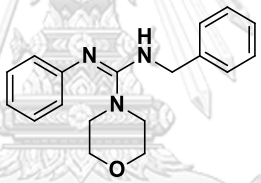
General procedure A was followed, using phenylisothiocyanate (53.0 mg, 0.3921 mmol), t-butylamine (27.3 mg, 0.3921 mmol) and benzylamine (63.2 mg, 0.5881 mmol) The compound was obtained in yellow solid (0.0993 g, 90% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.42-7.26 (m, 7H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 7.2 Hz, 2H), 4.41 (s, 2H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.1, 139.1, 129.3, 128.7, 127.4, 127.4, 123.2, 121.6, 50.9, 46.4, 30.1. $[M+H]^+$: calcd 282.19, found 282.03.

1-benzyl-3-cyclohexyl-2-phenylguanidine (**5l**)



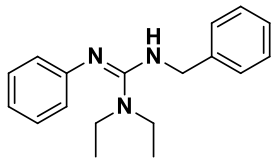
General procedure A was followed, using phenylisothiocyanate (50.0 mg, 0.3702 mmol), benzylamine (40.0 mg, 0.3702 mmol) and cyclohexylamine (55.1 mg, 0.5553 mmol) The compound was obtained in yellow solid (0.0887 g, 78% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.41-7.25 (m, 7H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 2H), 4.41 (s, 2H), 3.42-3.38 (m, 1H), 1.95-1.92 (m, 2H), 1.69-1.51 (m, 3H), 1.39-0.99 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 150.8, 149.3, 139.1, 129.3, 128.7, 127.4, 127.4, 123.5, 121.8, 50.2, 46.0, 33.6, 25.5, 24.7. $[M+H]^+$: calcd 308.2127, found 308.2120

N-benzyl-*N'*-phenylmorpholine-4-carboximidamide (**5m**)



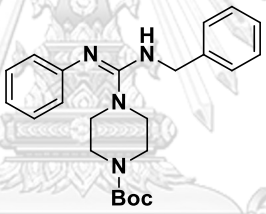
General procedure A was followed, using phenylisothiocyanate (51.0 mg, 0.3772 mmol), benzylamine (40.5 mg, 0.3772 mmol) and morpholine (49.4 mg, 0.5658 mmol) The compound was obtained in yellow oil (0.0802 g, 72% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.33-7.17 (m, 7H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 2H), 4.32 (s, 2H), 3.73 (t, *J* = 4.4 Hz, 4H), 3.29 (t, *J* = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 156.1, 138.6, 129.4, 128.9, 127.7, 127.6, 122.8, 122.1, 66.7, 49.2, 48.5. $[M+H]^+$: calcd 296.1763, found 296.1785

3-benzyl-1,1-diethyl-2-phenylguanidine (**5n**)



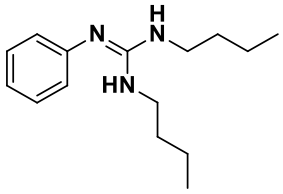
General procedure A was followed, using phenylisothiocyanate (51.0 mg, 0.3775 mmol), benzylamine (40.4 mg, 0.3775 mmol) and diethylamine (41.2 mg, 0.5663 mmol) The compound was obtained in yellow oil (0.0913 g, 86% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.35-7.19 (m, 7H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 2H), 4.20 (s, 2H), 3.30 (q, *J* = 7.2 Hz, 4H), 1.18 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 155.1, 150.3, 139.2, 129.0, 128.5, 127.5, 127.3, 122.1, 121.1, 49.3, 42.7, 13.1. $[M+H]^+$: calcd 282.1970, found 282.1977

tert-butyl-4-(*N*-benzyl-*N'*-phenylcarbamimidoyl)piperazine-1-carboxylate (**5o**)



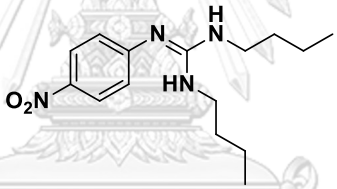
General procedure A was followed, using phenylisothiocyanate (50.1 mg, 0.3705 mmol), benzylamine (40.4 mg, 0.3705 mmol) and *tert*-Butyl-piperazine-1-carboxylate (103.2 mg, 0.5558 mmol) The compound was obtained in yellow oil (0.1198 g, 82% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.34-7.11 (m, 7H), 6.99-6.90 (m, 1H), 6.70 (d, J = 8.4 Hz, 2H), 4.20 (s, 2H), 3.45 (s, 4H), 3.21 (s, 4H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 155.9, 154.7, 148.4, 138.7, 129.2, 128.7, 127.5, 127.4, 127.2, 122.2, 122.2, 79.9, 49.1, 47.6, 46.1, 28.4. $[M+H]^+$: calcd 395.2447, found 395.2433

1,3-dibutyl-2-phenylguanidine (**6a**)



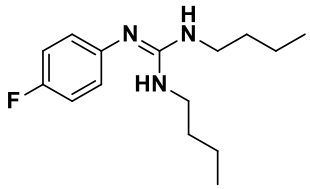
General procedure B was followed, using phenylisothiocyanate (51.7 mg, 0.3748 mmol) and butylamine (68.1 mg, 0.9370 mmol). The compound was obtained in yellow oil (0.082.5 g, 89% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.24 (t, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 3.13 (t, *J* = 8.0 Hz, 4H), 1.53-1.46 (m, 4H), 1.37-1.28 (m, 4H), 0.90 (t, *J* = 8.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 152.3, 148.2, 129.2, 123.4, 122.0, 42.0, 31.8, 20.0, 13.7. $[M+H]^+$: calcd 248.2127, found 248.2127

1,3-dibutyl-2-(4-nitrophenyl)guanidine (**6b**)



General procedure B was followed, using 4-nitroaniline (51.9 mg, 0.3481 mmol), butylamine (63.6 mg, 0.8704 mmol) The compound was obtained in Yellow oil (0.0632 g, 75% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.08 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.55 (s, 2H), 3.15 (t, *J* = 7.2 Hz, 4H), 1.61-1.42 (m, 4H), 1.36-1.29 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 158.0, 152.3, 141.2, 125.7, 123.0, 41.9, 31.9, 20.2, 13.9. $[M+H]^+$: calcd 293.1978, found 293.1972.

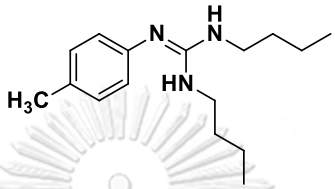
1,3-dibutyl-2-(4-fluorophenyl)guanidine (**6c**)



General procedure B was followed, using 4-fluorophenylisothiocyanate (50.1 mg, 0.3271 mmol) and butylamine (59.8 mg, 0.8177 mmol). The compound was

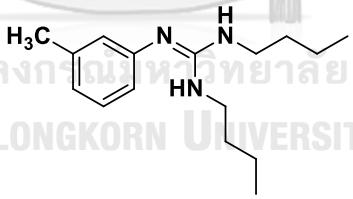
obtained in yellow oil (0.0694 g, 80% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.92 (t, *J* = 8.4 Hz, 2H), 6.78 (dd, *J* = 8.4, 4.8 Hz, 2H) 3.12 (t, *J* = 7.2 Hz, 4H), 1.48 (m, 4H), 1.32 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 158.3 (d, J_{C-F} = 237.6 Hz), 152.0, 145.8, 124.5 (d, J_{C-F}= 7.7 Hz), 115.8 (d, J_{C-F} = 21.8 Hz), 41.6, 31.8, 20.0, 13.7. $[M+H]^+$: calcd 266.2033, found 266.2044

1,3-dibutyl-2-(*p*-tolyl)guanidine (**6d**)



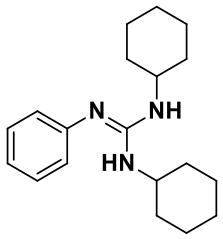
General procedure B was followed, using p-tolylphenylisothiocyanate (51.0 mg, 0.3418 mmol) and butylamine (62.5 mg, 0.8546 mmol). The compound was obtained in Yellow oil (0.0768 g, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.04 (d, *J* = 8 Hz, 2H), 6.75 (d, *J* = 8 Hz, 2H), 3.14 (t, *J* = 7.2 Hz, 4H), 2.27 (s, 3H), 1.53-1.45 (m, 4H), 1.39-1.29 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 6H).^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.7, 147.3, 130.6, 129.8, 123.4, 41.7, 31.9, 20.7, 20.1, 13.8.

1,3-dibutyl-2-(*m*-tolyl)guanidine (**6e**)



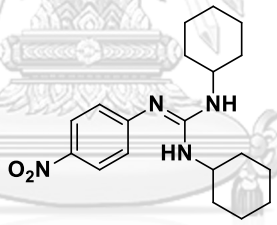
General procedure B was followed, using m-tolylphenylisothiocyanate (52.1 mg, 0.3491 mmol) and butylamine (64.4 mg, 0.8728 mmol). The compound was obtained in yellow oil (0.0739 g, 81% yield.); 1H NMR (400 MHz, CDCl3) **δ** 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 6.73(d, *J* =7.6 Hz, 1H), 6.69(s, 1H), 6.66(d, *J* = 7.6 Hz, 1H), 3.12 (t, *J* = 7.2 Hz, 4H), 2.27 (s, 3H), 1.54-1.44 (m, 4H), 1.39-1.27 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.6, 150.0, 138.9, 129.0, 124.4, 122.3, 120.4, 41.7, 31.9, 21.3, 20.1, 13.8. $[M+H]^+$: calcd 262.2283, found 262.2295

1,3-dicyclohexyl-2-phenylguanidine (**7a**)



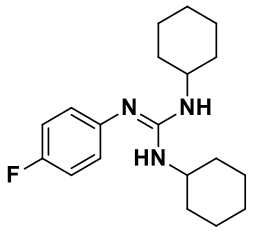
General procedure B was followed, using phenylisothiocyanate (52.5 mg, 0.3887 mmol) and cyclohexylamine (96.3 mg, 0.9717 mmol). The compound was obtained in yellow solid (0.1015 g, 95% yield.);^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.22 (t, *J* = 7.6 Hz, 2H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.6 Hz 2H), 3.37-3.32 (m, 2H), 1.94-1.92 (m, 4H), 1.67-1.53 (m, 6H), 1.29-1.06 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 150.93, 129.29, 123.47, 122.01, 50.62, 33.67, 25.61, 24.93. $[M+H]^+$: calcd 300.2440, found 300.2447

1,3-dicyclohexyl-2-(4-nitrophenyl)guanidine (**7b**)



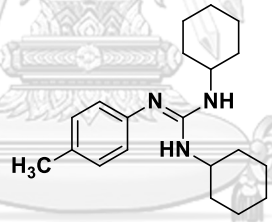
General procedure B was followed, using 4-nitrophenylisothiocyanate (50.1 mg, 0.2782 mmol) and cyclohexylamine (69.2 mg, 0.6955 mmol). The compound was obtained in Yellow solid (0.0881 g, 92% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.08 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 3.40-3.33 (m, 2H), 1.98-1.90 (m, 4H), 1.72-1.53 (m, 6H), 1.33-1.12 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 156.2, 151.2, 141.1, 125.5, 122.1, 50.9, 33.4, 25.3, 24.7. $[M+H]^+$: calcd 345.2291, found 3345.2294

1,3-dicyclohexyl-2-(4-fluorophenyl)guanidine (**7c**)



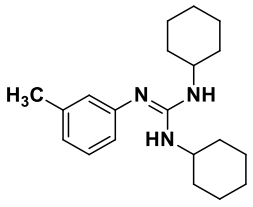
General procedure B was followed, using 4-fluorophenylisothiocyanate (51.1 mg, 0.3337 mmol) and cyclohexylamine (82.7 mg, 0.8343 mmol). The compound was obtained in colorless solid (0.0974 g, 92% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 6.90 (t, *J* = 8.0 Hz, 2H), 6.77 (dd, *J* = 8.0, 4.0 Hz, 2H), 3.35 (s, 2H), 1.95-1.92 (m, 4H), 1.66-1.54 (m, 6H), 1.37-0.96 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 159.6, (d, J_{C-F} = 237.6 Hz), 150.7, 124.5 (d, J_{C-F} = 7.7 Hz), 115.7 (d, J_{C-F} = 21.8 Hz), 50.3, 33.7, 25.6, 24.9. $[M+H]^+$: calcd 318.2346, found 318.2363

1,3-dicyclohexyl-2-(*p*-tolyl)guanidine (**7d**)



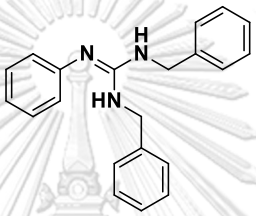
General procedure B was followed, using p-tolylphenylisothiocyanate (50.2 mg, 0.3364 mmol) and cyclohexylamine (73.5 mg, 0.8410 mmol). The compound was obtained in ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.03 (d, *J* = 7.6 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 2H), 3.36 (s, 2H), 2.26 (s, 3H), 1.96-1.94 (m, 4H), 1.67-1.54 (m, 6H), 1.35-1.02 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 150.8, 131.1, 129.8, 123.2, 50.4, 33.6, 25.5, 24.8, 20.7. $[M+H]^+$: calcd 314.2596, found 314.2604

1,3-dicyclohexyl-2-(*m*-tolyl)guanidine (**7e**)



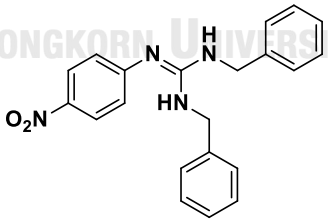
General procedure B was followed, using m-tolylphenylisothiocyanate (50.2 mg, 0.3364 mmol) and cyclohexylamine (83.4 mg, 0.8410 mmol). The compound was obtained in colorless solid (0.0959 g, 91% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.12 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.69 (s, 1H), 6.65 (d, *J* = 7.6 Hz), 3.41-3.36 (m, 2H), 2.27 (s, 3H), 2.06-1.87 (m, 4H), 1.73-1.54 (m, 6H), 1.39-1.03 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 150.2, 138.8, 128.9, 124.3, 122.3, 120.3, 50.2, 33.7, 25.6, 24.9, 21.3. $[M+H]^+$: calcd 314.2596, found 314.2611

1,3-dibenzyl-2-phenylguanidine (**8a**)



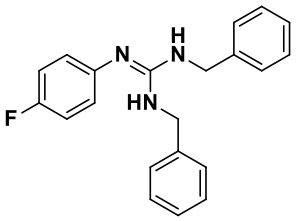
General procedure B was followed, using Phenylisothiocyanate (51.4 mg, 0.3802 mmol) and benzylamine (101.8 mg, 0.9505 mmol). The compound was obtained in yellow oil (0.1008 g, 84% yield.) ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.22-7.00 (m, 12H), 6.91-6.85 (m, 3H), 4.23 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.7, 148.3, 138.6, 129.4, 128.7, 127.4, 127.2, 123.4, 122.2, 46.1. $[M+H]^+$: calcd 316.1814, found 316.1839

1,3-dibenzyl-2-(4-nitrophenyl)guanidine (**8b**)



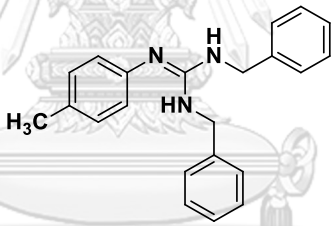
General procedure B was followed, using 4-nitrophenylisothiocyanate (52.0 mg, 0.2886 mmol) and benzylamine (77.3 mg, 0.7216 mmol). The compound was obtained in Yellow solid (0.0998 g, 95% yield.);^{1}H NMR (400 MHz, $CDCl_3$) **δ** 8.10 (d, *J* = 8.0 Hz, 2H), 7.53-7.06 (m, 10H), 7.00 (d, *J* = 8.0 Hz, 2H), 4.41 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 156.9, 151.6, 137.9, 128.9, 127.7, 127.2, 125.5, 123.0, 46.1. $[M+H]^+$: calcd 361.1665, found 361.1659

1,3-dibenzyl-2-(4-fluorophenyl)guanidine (**8c**)



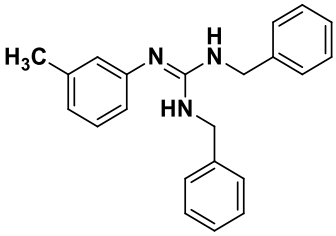
General procedure B was followed, using 4-fluorophenylisothiocyanate (50.9 mg, 0.3328 mmol) and benzylamine (89.1 mg, 0.8320 mmol). The compound was obtained in yellow oil (0.086.5 g, 78% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.36-7.23 (m, 10H), 7.00 (t, *J* = 8.4 Hz, 4H), 6.90 (dd, *J* = 8.4, 5.2 Hz), 4.37 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 158.7 (d, $J_{C\text{-}F}$ = 238.2 Hz), 151.7, 145.0, 138.5, 128.7, 127.5, 127.2, 124.6 (d, $J_{C\text{-}F}$ = 7.7 Hz), 116.0 (d, $J_{C\text{-}F}$ = 11.8 Hz), 46.0. $[M+H]^+$: calcd 3334.17206, found 334.1719

1,3-dibenzyl-2-(*p*-tolyl)guanidine (**8d**)



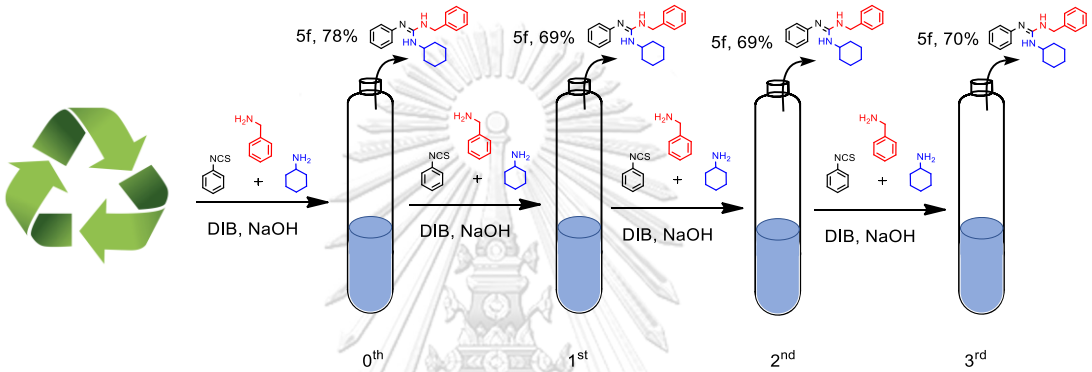
General procedure B was followed, using p-tolylphenylisothiocyanate (53.9 mg, 0.3615 mmol) and benzylamine (96.8 mg, 0.9039 mmol). The compound was obtained in yellow oil (0.0869 g, 73% yield.); ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 7.46-7.17 (m, 10H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 4.38 (s, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) **δ** 151.4, 146.3, 138.8, 131.3, 130.0, 128.7, 127.4, 127.2, 123.3, 46.0, 20.8. $[M+H]^+$: calcd 330.1970, found 330.1977

1,3-dibenzyl-2-(*m*-tolyl)guanidine (**8e**)



General procedure B was followed, using m-tolylphenylisothiocyanate (52.9 mg, 0.3548 mmol) and benzylamine (95.0 mg, 0.8870 mmol). The compound was obtained in yellow oil (0.0818 g, 70% yield.) ;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.15 (m, 11H), 6.85-6.79 (m, 3H), 4.39 (s, 4H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 149.2, 139.1, 138.9, 129.2, 128.7, 127.4, 127.3, 124.3, 122.9, 120.4, 46.0, 21.5. $[M+H]^+$: calcd 330.1970, found 330.1975

2.4 Reusability of reaction medium



I) Initial reaction: In a 5.0 mL reaction vial containing a magnetic stir bar, phenylisothiocyanate (1.0 equiv, 0.7396 mmol), benzylamine (1.0 equiv, 0.7396 mmol), NaOH (1.5 equiv, 1.1095 mmol) and 1wt%TPGS-750-M/H_2O (0.8 mL, 1.0M.) were sequentially added. The reaction mixture was stirred at room temperature for 1h. After starting material completely was consumed, as monitored by TLC (25% ethyl acetate in hexane), cyclohexylamine (1.5 equiv, 1.1095 mmol) and DIB (1.2 equiv, 0.8875 mmol) were sequentially added and stirring continued for 30 minutes. Then 1mL of ethyl acetate (1mLx2) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was purified by column chromatography over silica gel by using 25%ethyl acetate in hexane to 100%ethyl acetate as eluent to obtain guanidine 5l as a yellow solid (0.0887 g, 78% yield.).

II) 1st recycle: To the aqueous system obtained from above reaction, phenylisothiocyanate (1.0 equiv, 0.7396 mmol), benzylamine (1.0 equiv, 0.7396 mmol), NaOH (1.5 equiv, 1.1095 mmol) and 1%TPGS-750-M/H2O (0.8 mL, 1.0M.) were

sequentially added. The reaction mixture stirs at room temperature for 1h. After starting material completely was consumed, as monitored by TLC (25% ethyl acetate in hexane), cyclohexylamine (1.5 equiv, 1.1095 mmol) and DIB (1.2 equiv, 0.8875 mmol) were sequentially added and stirring continued for 30 minutes. Then 1mL of ethyl acetate (1mLx2) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was purified by column chromatography over silica gel by using 25%ethyl acetate in hexane to 100%ethyl acetate as eluent to obtain guanidine 5l as a yellow solid (0.0887 g, 69% yield.).

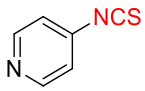
III) 2nd and 3rd, recycle, similar procedures were used as described above. (69%) and (70%) yields were respectively obtained

2.5 Scale-up demonstration of the optimization study

General procedure B was followed, using phenyl isothiocyanate (1.0 g, 7.3969 mmol) and cyclohexylamine (1.8337 g, 18.4922 mmol). The crude product was filtration and then wash the solid with hexane/water without future purification by column chromatography to give guanidine 7e in yellow solid (2.81 g, 98% yield)

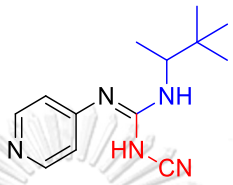
2.6 Synthesis of important guanidines in pharmaceutical and chemical industry

2.6.1 Synthesis of *N''*-cyano-*N'*-(3,3-dimethylbutan-2-yl)-*N*-(pyridin-4-yl)guanidine (Pinacidil drug)



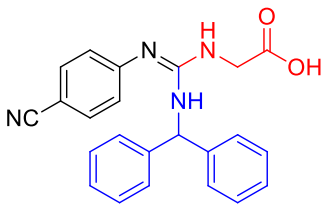
Preparation of 4-pyridineisothiocyanate: In 100 mL round-bottom flask containing a magnetic bar, 4-aminopyridine (500 mg, 5.3129 mmol), CS_2 (606 mg, 7.9693 mmol) and DBU (1.213 g, 7.9693 mmol) in DCM (20 mL). The reaction mixture was stirred at room temperature for 24h. After reaction completed, $FeCl_3$ (1.2926 g, 7.9693 mmol) in H_2O (10 mL) was added to the reaction mixture and it was continuing stirred at room temperature for 1h. After the reaction finished, the organic

layer was separated using a separatory funnel. This extraction was repeated three times using an additional 3 × 10 mL of DCM. The combined extracts were dried over anhydrous sodium sulfate, and volatiles was evaporated under reduced pressure to obtain crude product as orange oil, which was further purified by flash chromatography over silica gel using 100% DCM as eluent. The pure product was obtained as a yellow oil (263 mg, 36% yield).



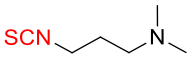
In a 5.0 mL reaction vial containing a magnetic stir bar, 4-pyridineisothiocyanate (100 mg, 0.7343 mmol), cyanamide (30 mg, 0.7343 mmol) and NaOH (mg, mmol) in 1wt%TPGS-750-M/H_2O (0.8 mL. 1.0 M). The reaction mixture was stirred at room temperature for 24h. After starting material completely was consumed, as monitored by TLC (100% ethyl acetate), 3,3-dimethylbutan-2-amine (111 mg, 1.1014 mmol) and DIB (283 mg, 0.8811 mmol) were sequentially added and stirring continued for 30 minutes. Then 1mL of ethyl acetate (1mLx2) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was further purified by flash chromatography over silica gel using 30% ethyl acetate in hexane as eluent to obtain guanidine as a yellow solid (59 mg, 33% yield). ^{1}H NMR (400 MHz, Acetone-d) δ 8.45 (d, *J* = 4.8 Hz, 2H), 7.57 (d, *J* = 4.8 Hz, 2H), 5.98 (d, *J* = 8.0 Hz, 1H), 3.88-3.84 (m, 1H), 1.17 (d, *J* = 4.0 Hz, 3H), 0.98 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 168.0, 151.5, 147.5, 112.8, 57.8, 35.5, 26.9, 16.6.

2.6.2 Synthesis of 2-(3-benzhydryl-2-(4-cyanophenyl)guanidino)acetic acid (Sweetener)



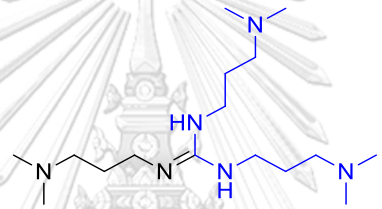
In a 5.0 mL reaction vial containing a magnetic stir bar, 4-cyanophenylisothiocyanate (100 mg, 0.6242 mmol), glycine (47 mg, 0.6242mmol) and NaOH (mg, mmol) in 1wt%TPGS-750-M/H_2O (0.6 mL. 1.0 M). The reaction mixture was stirred at room temperature for 24h. After starting material completely was consumed, as monitored by TLC (100% ethyl acetate), benzhydrylamine (171 mg, 0.9363 mmol) and DIB (mg, mmol) were sequentially added and stirring continued for 30 minutes. Then 1mL of ethyl acetate (1mLx2) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was further purified by flash chromatography over silica gel using 30% ethyl acetate in hexane as eluent to obtain guanidine as a white solid (50 mg, 21% yield). ^{1}H NMR ^{1}H NMR (500 MHz, Acetone) **δ** 8.78 (s, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.60-7.54 (m, 2H), 7.33-7.32 (m, 8H), 7.29-7.21 (m, 2H), 6.40 (t, *J* = 5.0 Hz, 1H), 6.31-6.24 (m, 1H), 4.04 (d, *J* = 5.0 Hz, 2H). ^{13}C NMR (126 MHz, Acetone) **δ** 170.3, 156.1, 146.1, 143.6, 134.2, 129.7, 128.8, 128.4, 120.3, 119.1, 105.2, 58.1, 44.4.

2.6.3 Synthesis of *N,N′,N″*-tris-(3-dimetylaminopropyl)-guanidine (catalysts for transesterification of vegetable oil)



Preparation of 3-isothiocyanato-*N,N*-dimethylpropan-1-amine: In 100 mL round-bottom flask containing a magnetic bar, *N,N*-dimethylpropane-1,3-diamine (500 mg, 4.8934 mmol), CS_2 (557 mg, 7.3401 mmol) and TEA (742 mg, 7.3401mmol) in DCM (20 mL). The reaction mixture was stirred at room temperature for 10 minutes.

After reaction completed, H_2O (10 mL) and CuCl (726 mg, 7.3401 mmol) were added to the reaction mixture and it was continuing stirred at room temperature for 1h. After the reaction finished, the organic layer was separated using a separatory funnel. This extraction was repeated three times using an additional 3 × 10 mL of DCM. The combined extracts were dried over anhydrous sodium sulfate, and volatiles was evaporated under reduced pressure to obtain crude product as orange oil, which was further purified by flash chromatography over silica gel using 100% ethyl acetate as eluent. The pure product was obtained as a yellow oil (402 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) **δ** 3.58 (t, *J* = 6.8 Hz, 4H), 2.36 (t, *J*= 6.8 Hz, 4H), 2.07 (s, 12H), 1.89-1.79 (m, 4H).

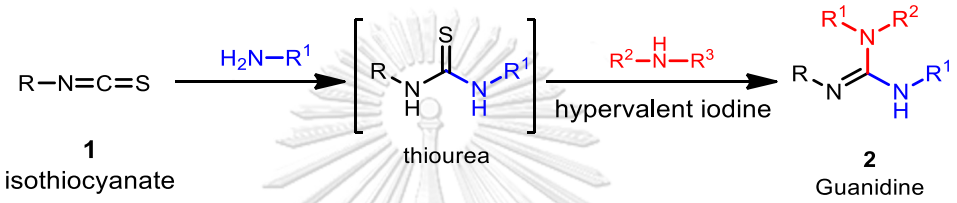


In a 5.0 mL reaction vial containing a magnetic stir bar, 3-isothiocyanato-*N,N*-dimethylpropan-1-amine (100 mg, mmol), *N,N*-dimethylpropane-1,3-diamine (mg, mmol) and NaOH (mg, mmol) in 1wt%TPGS-750-M/H_2O (0.7 mL. 1.0 M). The reaction mixture was stirred at room temperature for 1h. After starting material completely was consumed, as monitored by TLC (100% ethyl acetate), DIB (mg, mmol) were sequentially added and stirring continued for 30 minutes. Then 1mL of ethyl acetate (1mLx2) was added to the reaction mixture, which was stirred for 2 minutes. The organic layer was transferred using a pasteur pipet and evaporated under reduced pressure to give the crude product. The residue was washed with hexane to obtain a complex mixture as a yellow oil.

CHAPTER III

RESULTS AND DISCUSSION

In this study, we developed the one-pot synthesis of guanidine directly from isothiocyanate in water. We hypothesized that the first addition step to form the thiourea could be carried out in the absence of any activator while the second guanylation step might be facilitated with an oxidizing agent such as hypervalent iodine (**Scheme 3.1**).[71]



Scheme 3.1 Proposed the one-pot synthesis of guanidine

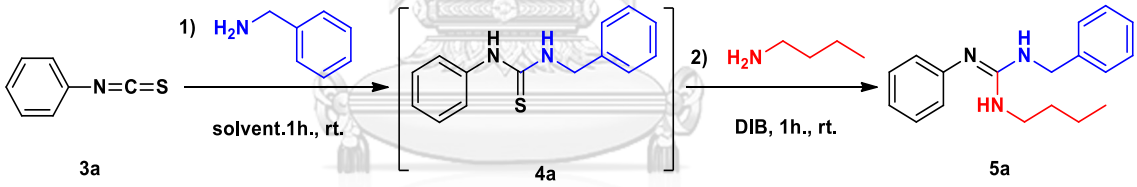
3.1 Reaction optimization

3.1.1 Solvent screening

Phenyl isothiocyanate (**3a**) was selected as starting material to perform the one-pot reaction for the synthesis of guanidine by using benzylamine as a nucleophile for the formation of thiourea (**4a**) and subsequently added butylamine and hypervalent iodine(III), DIB, to facilitate the guanidine formation (**Table 3.1**). For the thiourea formation, we monitored the reaction by TLC to confirm the complete consumption of starting material **3a.** we found that the reaction was completed within 1 hour and *n*-butylamine were subsequently added in the second step. The product was isolated by column chromatography and the results were summarized in **Table 3.1**. The first parameter for the optimization investigation is the solvent systems. Therefore, a variety of surfactants including anionic surfactant (SDS) and nonionic surfactant (TritonX-100 and TPGS-750-M) (**Figure 3.1**), were graded and compared with neat water and typical organic solvent (Acetonitrile) (**Table 3.1**, entry 1-5). The guanidine product **5a** was isolated in 50% along with unreacted intermediate thiourea **4a** in 28% when the reaction was carried out in acetonitrile

(**Table 3.1**, entry 1). Switching from organic solvent to neat water, to our surprise, guanidine **5a** was isolated in 19% yield along with unreacted intermediate thiourea **4a** in 71% yield (**Table 3.1**, entry 2). The poor conversion is due to the heterogeneous nature of the reaction on water as we had seen two layers of the reaction mixtures. Next, the efficiency of surfactant was examined in the model reaction in order to improve the reaction. Low yields (35% and 39%) of **5a** were observed when SDS and TritonX-100 were used as the surfactant a significantly higher yield of guanidine (**Table 3.1**, entry 3 and 4). On the other hand, TPGS-750-M gave the best result, providing guanidine **5a** in 60% yield and thiourea 4a in 20% yield (**Table 3.1**, entry 5). This result probably can be explained by the highly stable and proper size of micelle cavity formed by TPGS-750-M in water which could accelerate the reaction. We also would like to note this reaction under TPGS-750-M gave even higher yield than the reaction in acetonitrile.

Table 3.1 Solvent screening for the synthesis of guanidine **5a**



Entry	Reaction medium	Yield (%)	
		Thiourea (**4a**)	**5a**
1	Acetonitrile	28	50
2	H_2O	71	19
3	2wt%SDS/ H_2O	51	35
4	2wt%TritonX-100/ H_2O	42	39
5	2wt%TPGS-750-M/ H_2O	20	60

[a]Reaction conditions: **3a** (1.0 equiv. 0.37 mmol), benzylamine (1.0 equiv.) and *n*-butylamine (3.0 equiv.) DIB (1.2 equiv.), reaction concentration (0.5 M) at room temperature for 1 h.

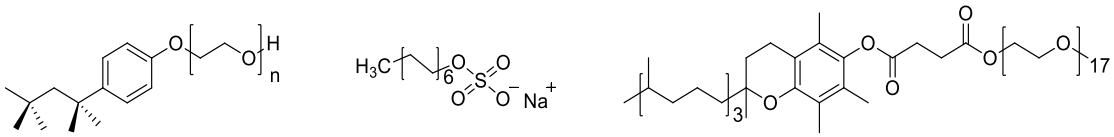


Figure 3.1 The structure of surfactants

3.1.2 Hypervalent iodine screening

Based on the above study, TPGS-750-M was selected as a surfactant to perform the reaction. Next, hypervalent iodine(III) (**Figure 3.2**) such as hydroxy (tosyloxy)iodobenzene (HTIB), [Bis(tert-butylcarbonyloxy)iodobenzene (BIB) and Bis(*tert*-butylcarbonyloxy)iodobenzene (BTB), were screened and results were shown in **table 3.2**. When we changed hypervalent iodine from DIB to HTIB or BIB, the guanidine **5a** did not observe and only intermediate thiourea 4a were obtained in 78% and 81% yields, respectively (**Table 3.2**, entry 2 and 4). This result suggests that HTIB and BIB are sensitive and perhaps decompose in water. Changing to more hydrophobic and stable hypervalent iodine, BTB, it resulted in a slightly lower yield of **5a** in comparison with DIB (**Table 3.2**, entry 3). Base on the above screening, therefore DIB was selected as an oxidizing agent because it provides the best yield of product **5a** in TPGS-750-M system. After that, the amount of DIB was increased to 1.5 equiv. and 2.0 equiv. (**Table 3.2**, entry 5 and 6). Both reactions gave 100% conversion of intermediate thiourea 4a along with 65-70% yields of **5a** which is comparable when DIB was used at 1.2 equivalents.

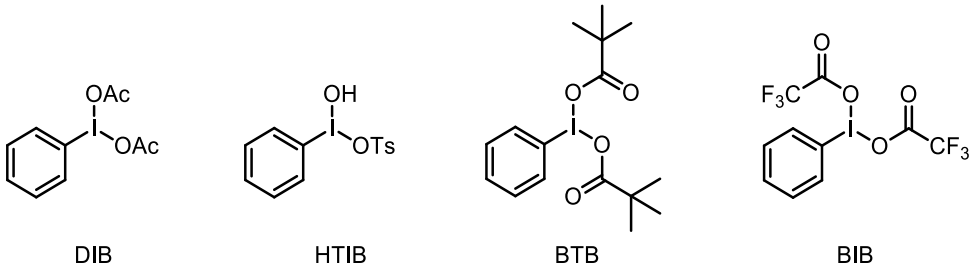
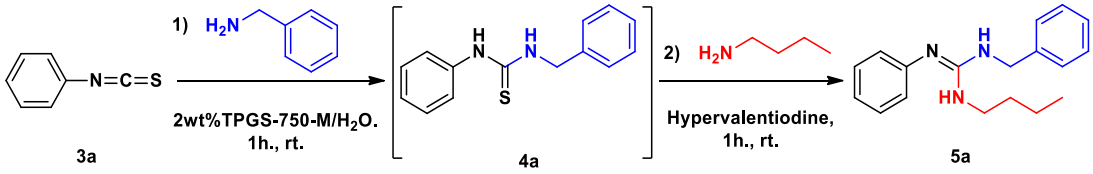


Figure 3.2 The structure of hypervalent iodine

Table 3.2 Hypervalent iodine screening for the synthesis of guanidine **5a**



Entry	Reaction medium	Hypervalent iodine	Yield (%)	
			Thiourea (**4a**)	**5a**
1	2wt%TPGS-750-M/ H_2O	DIB (1.2 eq.)	20	60
2	2wt%TPGS-750-M/ H_2O	HTIB (1.2 eq.)	78	-
3	2wt%TPGS-750-M/ H_2O	BIB (1.2 eq.)	81	-
4	2wt%TPGS-750-M/ H_2O	BTB (1.2 eq.)	15	52
5	2wt%TPGS-750-M/ H_2O	DIB (1.5 eq.)	-	70
6	2wt%TPGS-750-M/ H_2O	DIB (2.0 eq.)	-	65

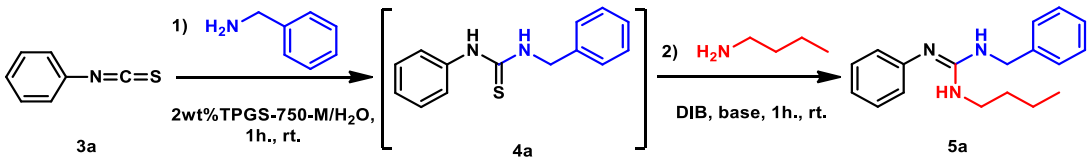
[a]Reaction conditions: 3a (1.0 equiv. 0.37 mmol), benzylamine (1.0 equiv.) and *n*-butylamine (3.0 equiv.) DIB (1.2 equiv.), reaction concentration (0.5 M) at room temperature for 1 h.

3.1.3 Base screening

We plan to study the effects of a base with the idea that those bases must be low toxicity and low cost. Therefore, three inorganic bases (NaOH, KOH, and K_2CO_3) and organic base (TEA) were chosen in this study. Among three bases including NaOH, KOH, and K_2CO_3, we found that only NaOH can improve the reaction and product **5a** in 67% yield along with unreacted of thiourea **4a** in 17% yield (**Table 3.3**, entry 3-5). Meanwhile, TEA was presented a slightly lower yield of **5a** (**Table 3.3**, entry 2). To our delight, the desired guanidine **5a** was obtained in 75% with only 5% intermediate thiourea **4a** when NaOH was increased up to 1.5 equivalents in the reaction (**Table 3.3**, entry 6). As we set the goal to create an atom-economy guanidine synthesis, a large excess of reagents must be reduced as possible. The second amine nucleophile, butylamine, was then reduced from 3 to 1.5 equivalents.

Fortunately, the yield of product **5a** was changed insignificantly (69%, **Table 3.3**, entry 7). Therefore, we designed to use only 1.5 eq of *n*-butylamine for future study.

Table 3.3 base screening for the synthesis of guanidine **5a**



Entry	Reaction medium	Additive	Yield (%)	
			Thiourea (**4a**)	**5a**
1	2wt%TPGS-750-M/ H_2O	-	20	60
2	2wt%TPGS-750-M/ H_2O	NaOH (1.0 eq.)	17	67
3	2wt%TPGS-750-M/ H_2O	K_2CO_3 (1.0 eq.)	19	59
4	2wt%TPGS-750-M/ H_2O	KOH (1.0 eq.)	15	61
5	2wt%TPGS-750-M/ H_2O	TEA (1.0 eq.)	10	54
6	2wt%TPGS-750-M/ H_2O	NaOH (1.5 eq.)	5	75
7*	2wt%TPGS-750-M/ H_2O	NaOH (1.5 eq.)	14	69

[a]Reaction conditions: **3a** (1.0 equiv. 0.37 mmol), benzylamine (1.0 equiv.) and *n*-butylamine (3.0 equiv.) DIB (1.2 equiv.), reaction concentration (0.5 M) at room temperature for 1 h.

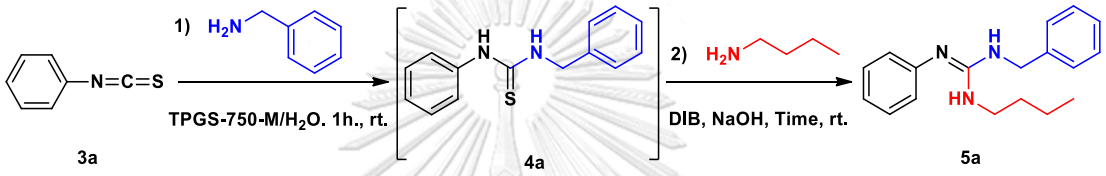
**n*-butylamine (1.5 equiv.)

3.1.4 Percent of micellar catalyst in water, the concentration of reaction medium, and reaction time screening

Based on the above study, we next investigated the amount of TPGS-750-M in water, lowering TPGS-750-M from 2wt% to 1wt% still provided a comparable yield and guanidine **5a** was isolated in 70% yield (**Table 3.4**, entry 2). However, when only 0.1wt% were employed, only 40% of 5a were isolated along with unreacted thiourea **4a** in 40% (**Table 3.4**, entry 3). This was likely due to the critical micelle concentration of TPGS-750-M which at such concentration, the micelle cannot be

formed. After that, we decreased reaction concentration from 0.5 M to 0.1 M. guanidine **5a** was obtained only 30% yield along with unreacted thiourea **4a** in 58% (**Table 3.4**, entry 4) while increases of reaction concentration to 1.0 M resulted in the formation of guanidine **5a** in much better yield (83% yield, **Table 3.4**, entry 5). We would like to note here that not only the reaction yield can be improved but also reaction is shorter completing in 30 minutes.

Table 3.4 percent of micellar catalyst in water and concentration of reaction of **5a** were screen



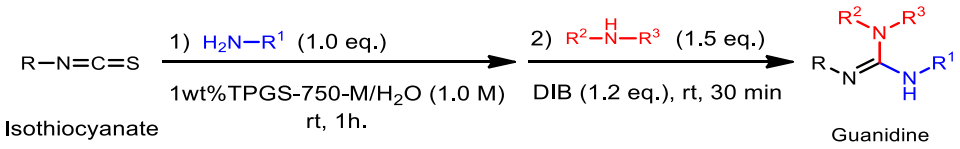
Entry	Reaction medium	Concentration	Yield (%)	
			Thiourea (**4a**)	**5a**
1	2wt%TPGS-750-M/ H_2O	0.5 M.	5	75
2	1wt%TPGS-750-M/ H_2O	0.5 M.	10	70
3	0.1wt%TPGS-750-M/ H_2O	0.5 M.	41	40
4	1wt%TPGS-750-M/ H_2O	0.1 M.	58	30
5*	1wt%TPGS-750-M/ H_2O	1.0 M.	-	83

[a]Reaction conditions: **3a** (1.0 equiv. 0.37 mmol), benzylamine (1.0 equiv.) and *n*-butylamine (1.5 equiv.) DIB (1.2 equiv.), reaction concentration (0.5 M) at room temperature for 1 h.

*reaction time 30 minutes

In summary, we found that 1wt%TPGS-750-M as surfactant is suitable to carry guanylation reaction in water in the present of DIB as oxidizing agent and NaOH as a base (**Scheme 3.2**). The thiourea formation is carried out for 1 hour. while the second step which is guanylation is carried out for 30 minutes. For the purification

step, the crude products were separated by added a small amount of ethyl acetate directly to the reaction mixture to perform in-flask extraction (**Figure 3.3**).



Scheme 3.2 optimized condition for the synthesis of guanidines

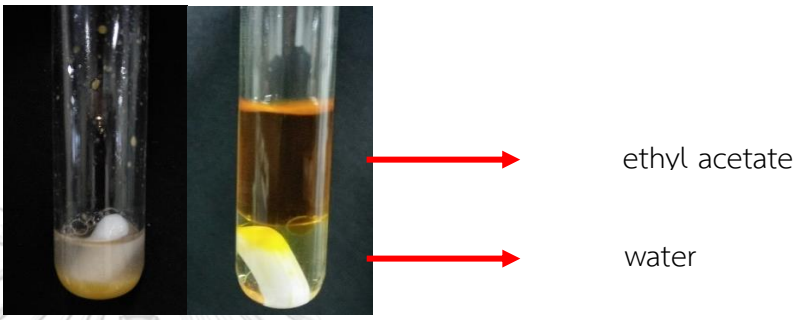


Figure 3.3 A: reaction medium after the reaction finished. B: after added of EtOAc.

3.2 The substrate scope of the guanylation reaction

3.2.1 Synthesis of asymmetry guanidines 5b-5r

With the optimization in hand, a variety of substituted on phenyl isothiocyanates with electron donating group and electron withdrawing group were tested to see the generality the scope of the reaction as seen in black line. Moreover, a variety of amines used in the first step during the formation of thiourea were explored in the blue line. Then, the amines in the second step for the formation of guanidines were investigated in the red line (**Figure 3.4**).

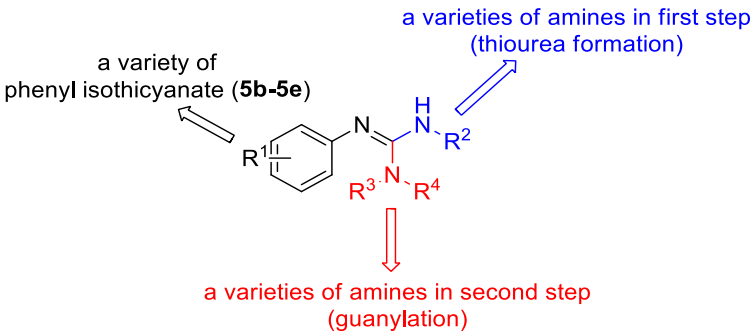


Figure 3.4 scope of guanidines in this work

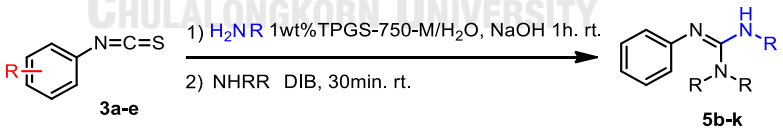
3.2.1.1 Substituted on phenyl isothiocyanates

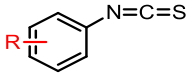
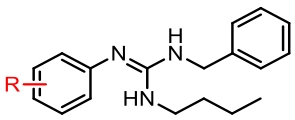
Different substituted isothiocyanates (**3b-e**) were coupled with benzylamine to provide the corresponding intermediate thiourea. Then, *n*-butylamine were subsequently added to generate the corresponding guanidines (**5b-e**) in good yields (**Table 3.5**, entry 1). It was showed that isothiocyanates containing electron withdrawing group on para position (nitro **3b** and fluorine **3c** groups) and electron donating group (*p*-methyl **3d**, *m*-methyl **3e**) has no effect on the reaction efficiency.

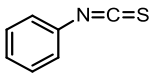
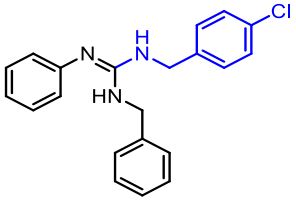
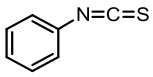
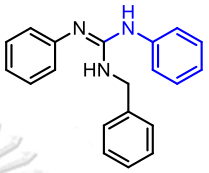
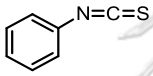
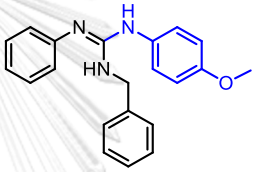
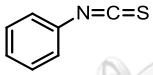
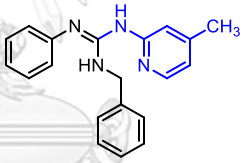
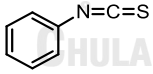
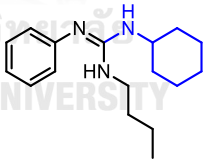
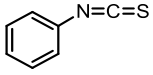
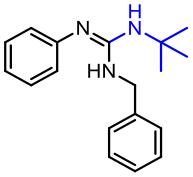
3.2.1.2 A variety of amines used for the formation of thiourea

We next explored the scope of amine in the formation of thioureas. A variety of primary amine containing aliphatic (cyclohexylamine, 4-chloro benzylamine), aromatic (aniline, 4-metoxyaniline) and heterocyclic amine (4-methyl pyridin-2-amine) reacted smoothly with isothiocyanates **3a** which subsequently underwent guanidine formation with either benzylamine or *n*-butylamines to provide products **5f**-**5j** (**Table 3.5**, entry 2-6) in satisfactory yields. Moreover, a stearic amine such as *tert*-butylamine proceeds successfully, offering **5k** in excellent yield (**Table 3.5**, entry 7).

Table 3.5 Substrate scope: substituents on phenyl isothiocyanate and a variety of amines in the first step



Entry	Substrates	Guanidines	Yield of guanidine (%)
1			
	R = *p*-NO_2 **3b**	R = *p*-NO_2 **5b**	94
	p-F **3c**	*p*-F **5c**	92

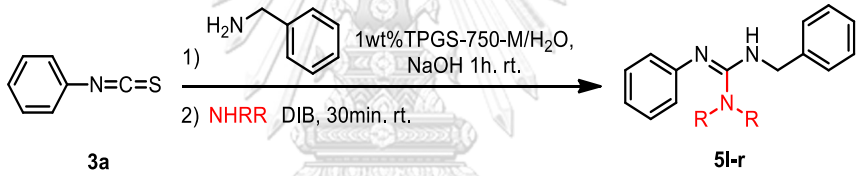
	p-CH_3 **3d**	*p*-CH_3 **5d**	89
	m-CH_3 **3e**	*m*-CH_3 **5e**	91
2	 **3a**	 **5f**	75
3	 **3a**	 **5g**	90
4	 **3a**	 **5h**	78
5	 **3a**	 **5i**	69
6	 **3a**	 **5j**	89
7	 **3a**	 **5k**	90

[a]Reaction conditions: 3 (1.0 equiv. 0.37 mmol) and amine 1 (1.0 equiv.) amine 2 (1.5 equiv.), DIB (1.2 equiv.) in water (1.0 M) under room temperature for 30 min.

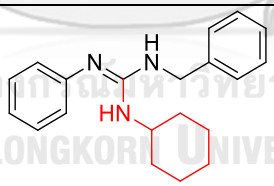
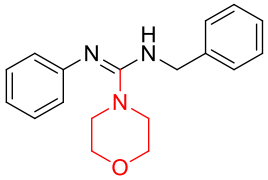
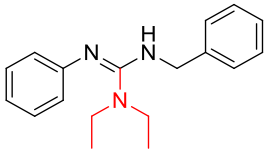
3.2.1.3 A variety of amines used for the formation of guanidine

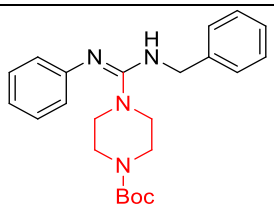
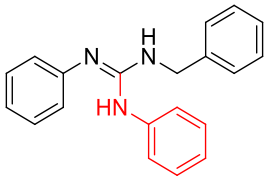
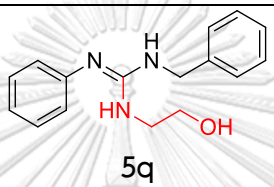
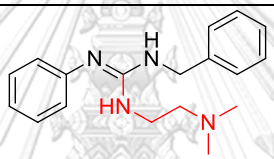
Next, a diversity of amines used in the second step during for the formation of guanidine such as cyclohexylamine, morpholine and diethylamine were tested under the optimized condition to produced products **5l-5n** (**Table 3.6**, entry 1-3) in good yields. Importantly, nucleophilic amine containing acid-sensitive protecting group such as Boc-piperazine tolerated in this micellar in water condition and yielded product **5o** in 82% yield without any deprotected by-product (**Table 3.6**, entry 4). Unfortunately, the aromatic amine, ethanolamine, and diamine gave no reaction (**5p-r Table 3.6**, entry 5) and we observed only unreacted thiourea intermediate in 69% yield. This is probably due to the poor nucleophilic property of aniline.

Table 3.6 Substrate scope: a variety of amines in the second step



3a **5l-r**

Entry	Guanidines	Yield of guanidine (%)
1	 **5l**	78
2	 **5m**	72
3	 **5n**	86

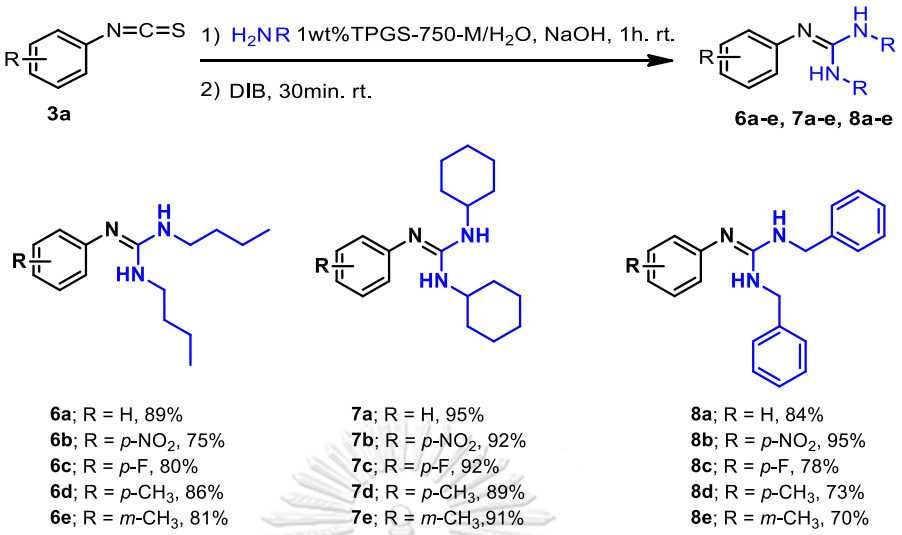
4	 **5o**	82
5	 **5p**	0
6	 **5q**	0
7	 **5r**	0

[a]Reaction conditions: 3 (1.0 equiv. 0.37 mmol) and amine 1 (1.0 equiv.) amine 2 (1.5 equiv.), DIB (1.2 equiv.) in water (1.0 M) under room temperature for 30 min.

3.2.2 Synthesis of symmetry guanidines

We also applied this micellar coupling reaction in water for the synthesis of symmetrical guanidines. For the symmetric guanidine, it allows us to add an excess amine (2.5 equivalents) such as *n*-butylamine, cyclohexylamine, and benzylamine at the first step. After stirring for 1 hour to ensure the complete formation of thiourea, DIB was added to facilitate the guanidine formation with the remaining amines from the first step. As shown in **table 3.7**, both electron-withdrawing (*p*-NO_2 and *p*-F) and electron-donating group (*p*-CH_3 and *m*-CH_3) substituted on isothiocyanates have almost no effect in thiourea formation which further react with the remaining amines to form guanidines **6a**-**e**, **7a**-**e,** and **8a**-**e** respectively in excellent yields.

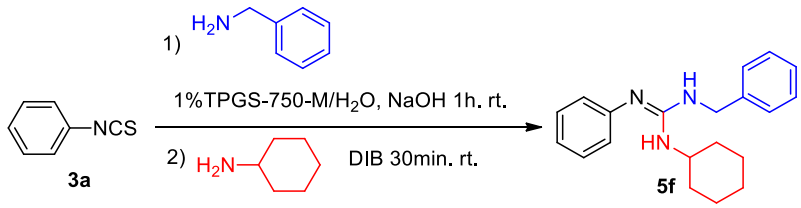
Table 3.7 Substrate scope:



[a]Reaction conditions: 3 (1.0 equiv. 0.37 mmol) and amine (2.5 equiv.) DIB (1.2 equiv.) in water (0.5 M) under room temperature.

3.3 Reusability of reaction medium

To demonstrate the recyclability of the waste medium water containing surfactant TPGS-750-M, we carried out the reaction between isothiocyanate (**3a**) with benzylamine and cyclohexylamine (**Scheme 3.3**) under the optimized condition. After each reaction, a small amount of ethyl acetate was added, and this organic layer containing product **5f** was collected. The aqueous layer containing TPGS-750-M was then reused for three subsequent fresh reaction batches. Excellent results were obtained without any significant loss of the product yields (**Figure 3.5**).



Scheme 3.3 Reuse reaction medium for synthesis of guanidine **5f**

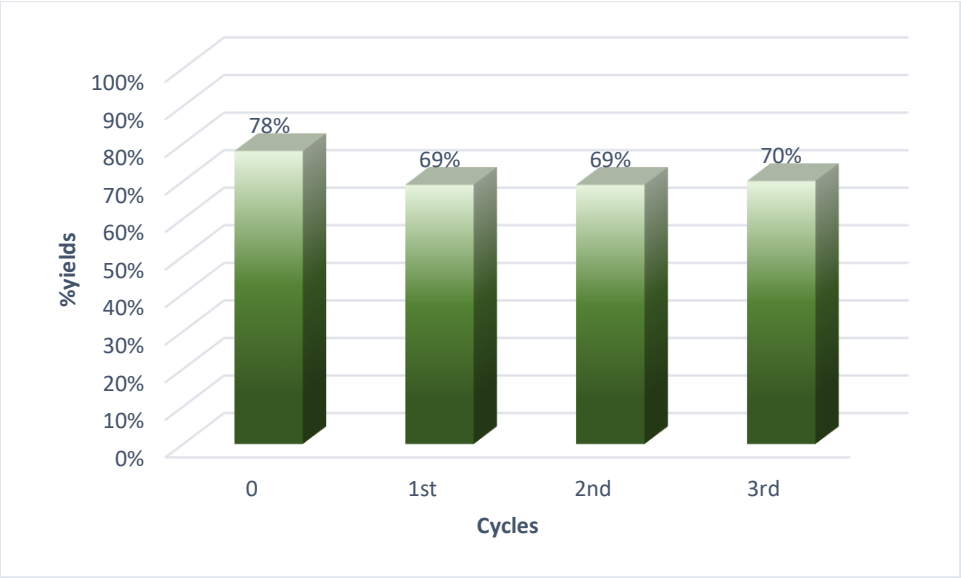
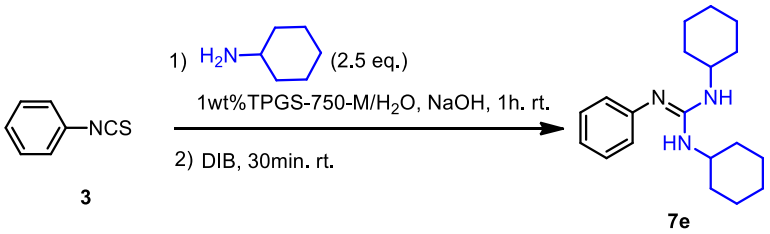


Figure 3.5 Yield of guanidine **5f** in reuse reaction medium 3 cycles

3.4 Multiple gram scale synthesis of guanidine

To demonstrate the scalability of this protocol, the reaction was also performed on a gram scale (**Scheme 3.4**). Treatment of **3a** 1.29 grams with cyclohexylamine 2.36 grams under optimized conditions resulted in the formation of **7e** in nearly quantitative yield. Importantly, in a large scale experiment, the reaction gradually underwent precipitation out of the reaction medium. Therefore, we are able to perform the simple filtration and then wash the solid with hexane/water without the need for column chromatography (**Figure 3.6**). This suggested the possibility of reducing the use of an organic solvent in the extraction and purification process for large scale reaction.



Scheme 3.4 Synthesis of guanidine **7e** in gram scale

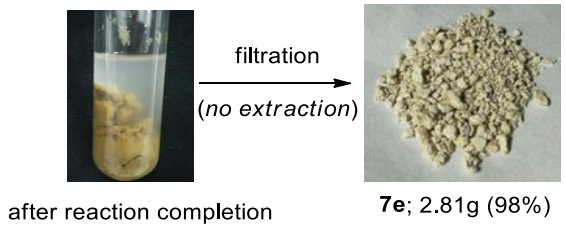


Figure 3.6 Guanidine **7e** after filtration

3.5 Synthesis of important guanidines in pharmaceutical and chemical industry

To demonstrate the applicability of our developed reaction, we aim to synthesize important guanidine compounds such as pinacidil (**10a**), NC-174 (**11a**) and catalyst (**13a**) (**Figure 3.7**). Pinacidil is commercial drug from Leo Pharma company which had been used widely for reducing blood pressure. Next, NC-174 (**11a**) had been reported as a sweetener with a sweetness potency 200,000 times that of sucrose. Lastly, the symmetry guanidine **13a** is heavily used as a commercial catalyst for transesterification of vegetable oil.

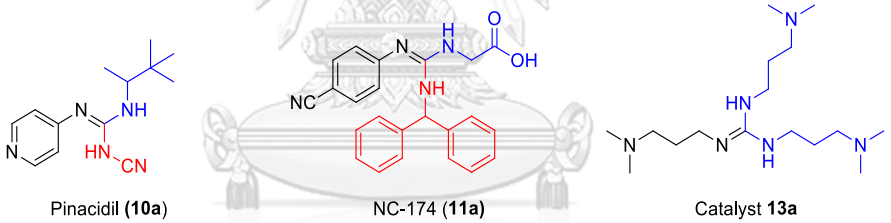
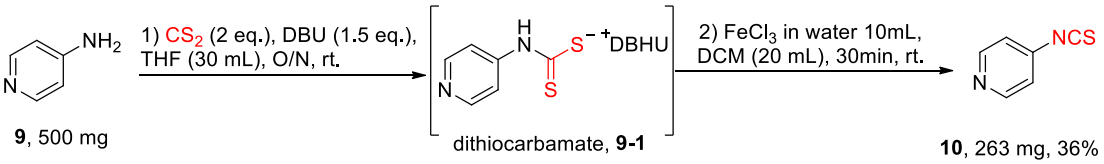


Figure 3.7 Examples of important guanidines

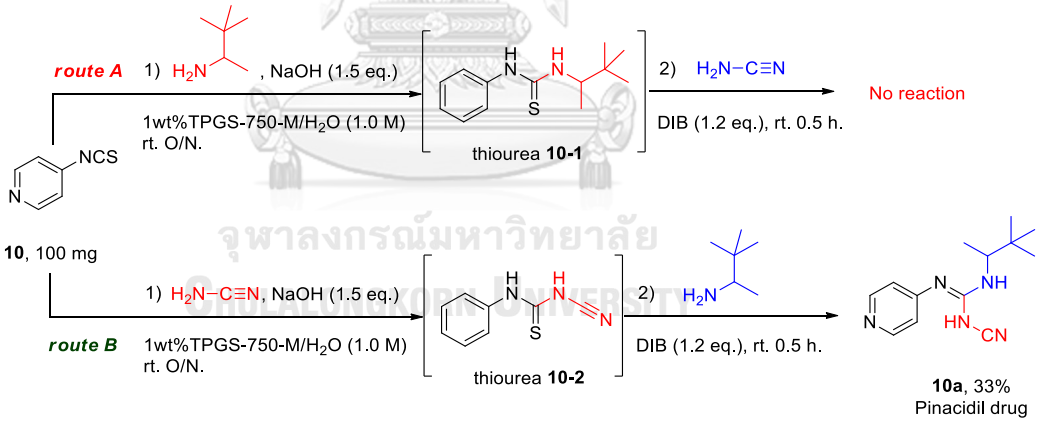
3.5.1 Synthesis of *N''*-cyano-*N'*-(3,3-dimethylbutan-2-yl)-*N*-(pyridin-4-yl) guanidine (Pinacidil, 10a)

Because the starting isothiocyanate (**10**) is not commercially available, we therefore prepared it based on the known literature.[72] First, 4-aminopyridine (**9**) coupled with CS_2 in the presence of DBU as a base to form of dithiocarbamate **9-1**. Then, it undergoes desulfurization using $FeCl_3$ in water to obtain 4-isothiocyanatepyridine (**10**) in 36% yield (**Scheme 3.5**).



Scheme 3.5 synthesis of compound **10**

After that, 4-isothiocyanate-pyridine (**10**) was subjected to our developed method for guanidine synthesis. For the first attempt, it first reacted with 3,3-dimetylbutane-2-amine to form thiourea (**10-1**) which was then treated with cyanamide as a nucleophile for guanidine formation (**Scheme 3.6**, route A). However, the product **10a** was not obtained and we only observed unreacted thiourea 10-1. We hypothesize that the poor reaction attributed to high soluble cyanamide in water and could hardly react with substrates in the micelle. Alternatively, we switched the amide nucleophile order. Cyanamide first reacted with **10** to form thiourea **10-2** and then 3,3-dimetylbutane-2-amine under the optimization. The product **10a** was finally obtained in 33% yield (**Scheme 3.6**, route B).[73]

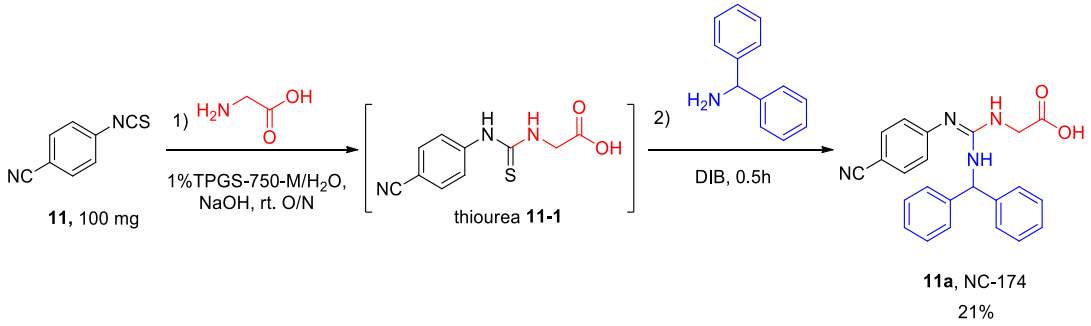


Scheme 3.6 synthesis of pinacidil **10a**

3.5.2 Synthesis of 2-(3-benzhydryl-2-(4-cyanophenyl)guanidino)acetic acid (Sweetener)

NC-174 (**11a**) was synthesized from commercially available starting material, 4-isothiocyanato benzonitrile (**11**) (**Scheme 3.7**). It reacted with glycine to form thiourea intermedium **11-1**, then coupled with benzhydrylamine to form NC-174 **11a** in only 21% yield. we believed that the low yield is governed by the pool

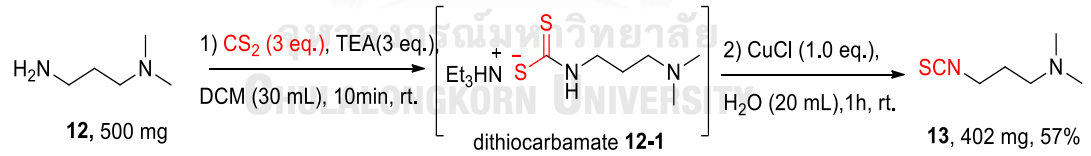
nucleophile of benzhydrylamine and high-water solubility of intermedium thiourea **11-1**.[47]



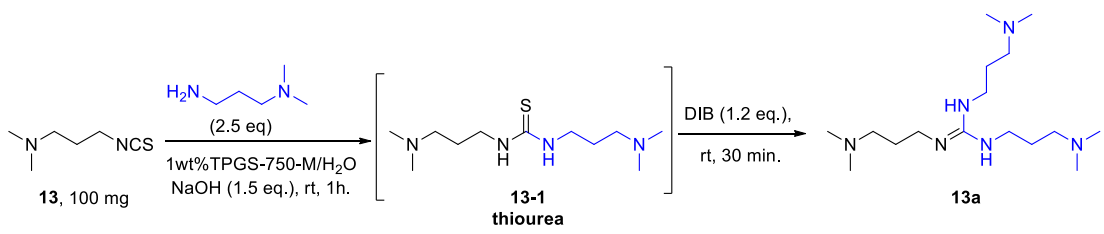
Scheme 3.7 Synthesis of NC-174 11a

3.5.3 Synthesis of *N,N′,N″*-tris-(3-dimetylaminopropyl)-guanidine 13a

We plan to prepare catalyst **13a** from isothiocyanate (**13**) but it is not commercially available. We therefore first prepared the starting material **13** based on the known literature.[74] *N,N*-dimethyl-propylamine (**12**) were coupled with CS_2 in the presence of TEA as a base to form dithiocarbamate **12-1** which was undergoing desulfurization using CuCl in water. We obtained the desired **13** in 57% yield (**Scheme 3.8**). Next, starting material **13** was reacted with an excess amine (2.5 equivalents) under optimization condition. The result was obtained in mixture complex (**13a** + **13-1** thiourea). (**Scheme 3.9**).[75]



Scheme 3.8 Synthesis of *N-N*-dimethylamine**propylisothiocyanate** **13**



Scheme 3.9 Synthesis of catalyst 13a

CHAPTER IV

CONCLUSIONS

In summary, we developed an aqueous micellar synthetic method for synthesis of guanidine directly from isothiocyanate in the presence of DIB as an oxidizing agent. The protocol has high selectivity and high functional group compatibility providing guanidine in high yields under mild reaction condition and short reaction time. The reactions are operationally very simple performing at room temperature in an open-air system in water media. Importantly, micellar can be reused up to 3 cycles, providing a low waste process. Moreover, NC-174 sweetener and pinacidil drug were synthesized using our methodology from the corresponding isothiocyanates in 21% and 36% yields respectively. Our methodology offers an alternative route for large-scale and practical synthesis of guanidine for the chemical industries.

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APPENDIX

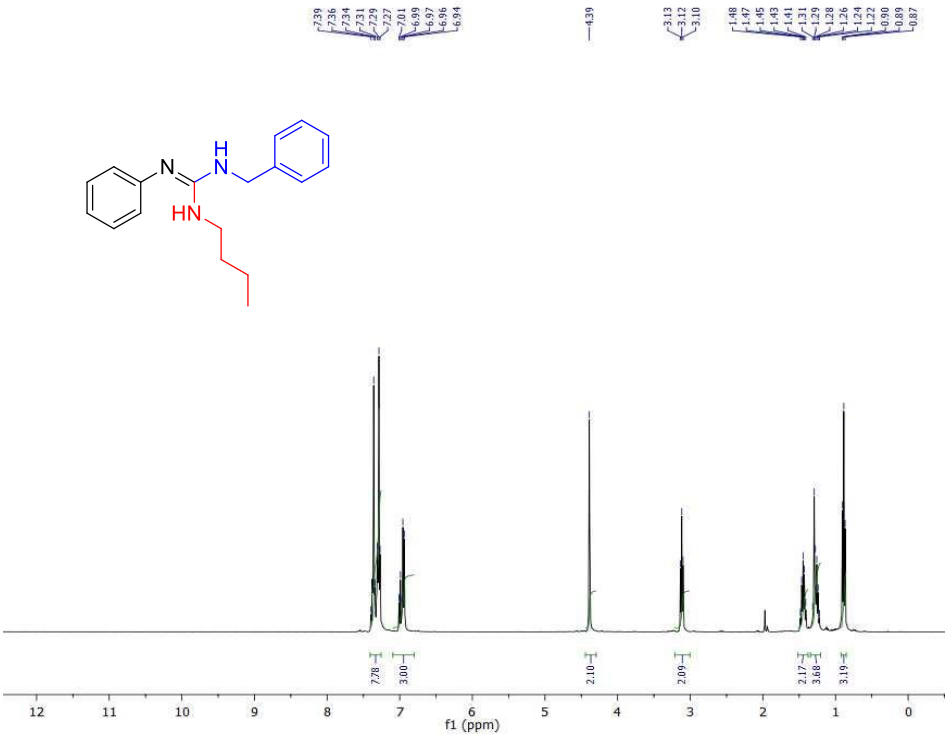

Figure A1 1-benzyl-3-butyl-2-phenylguanidine (**5a**); ^{1}H NMR 400 MHz, $CDCl_3$

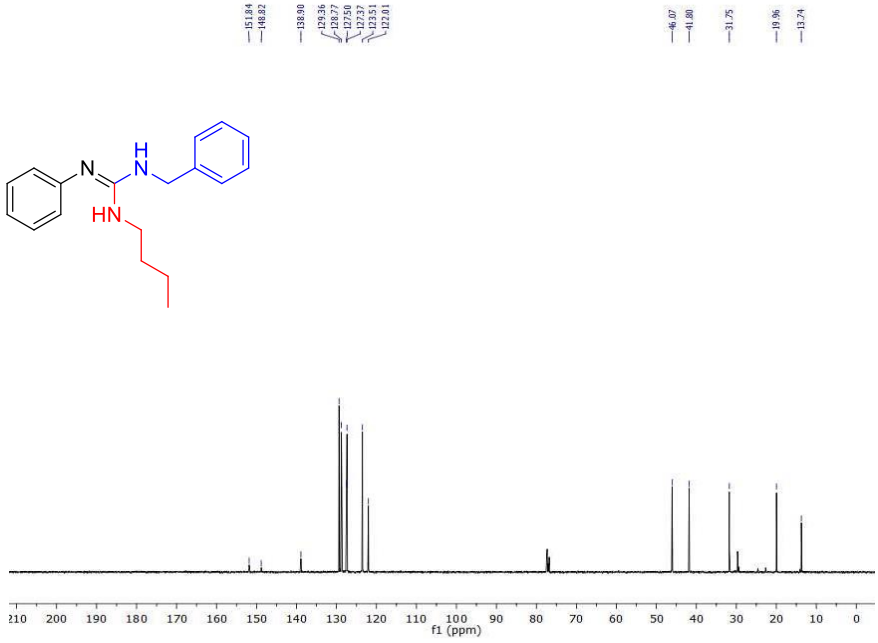

Figure A2 1-benzyl-3-butyl-2-phenylguanidine (**5a**); ^{13}C NMR 100 MHz, $CDCl_3$

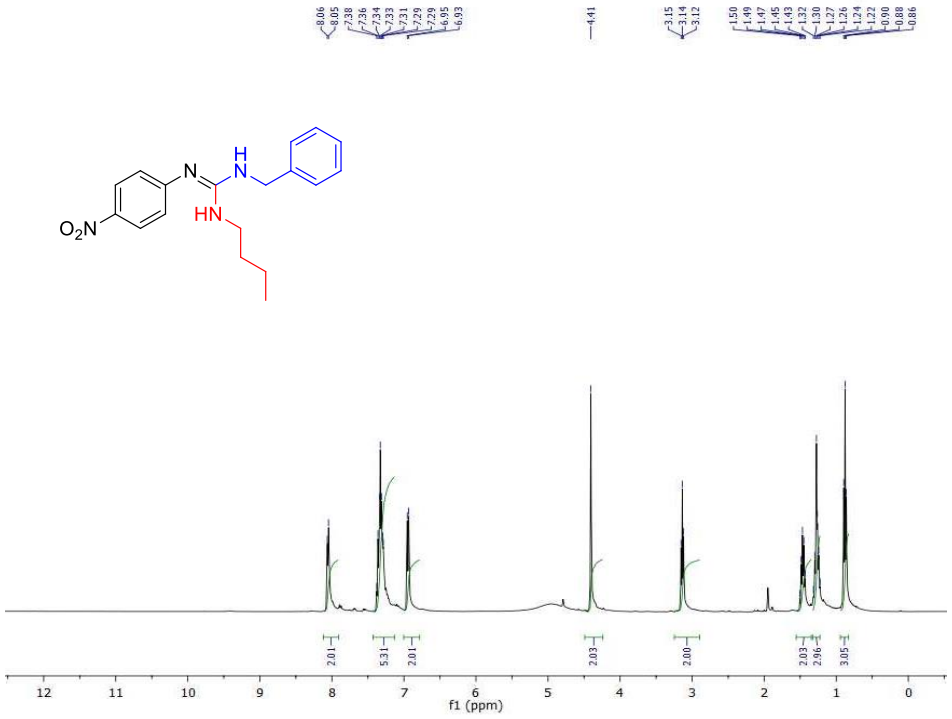

Figure A3 1-benzyl-3-butyl-2-(4-nitrophenyl)guanidine (**5b**); ^{1}H NMR 400 MHz, $CDCl_3$

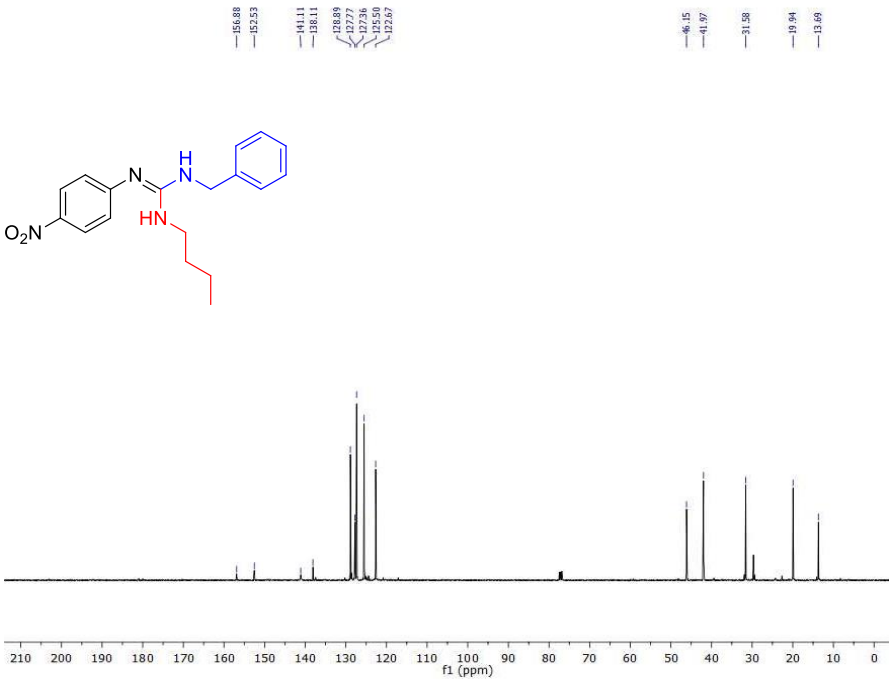

Figure A4 1-benzyl-3-butyl-2-(4-nitrophenyl)guanidine (**5b**); ^{13}C NMR 100 MHz, $CDCl_3$

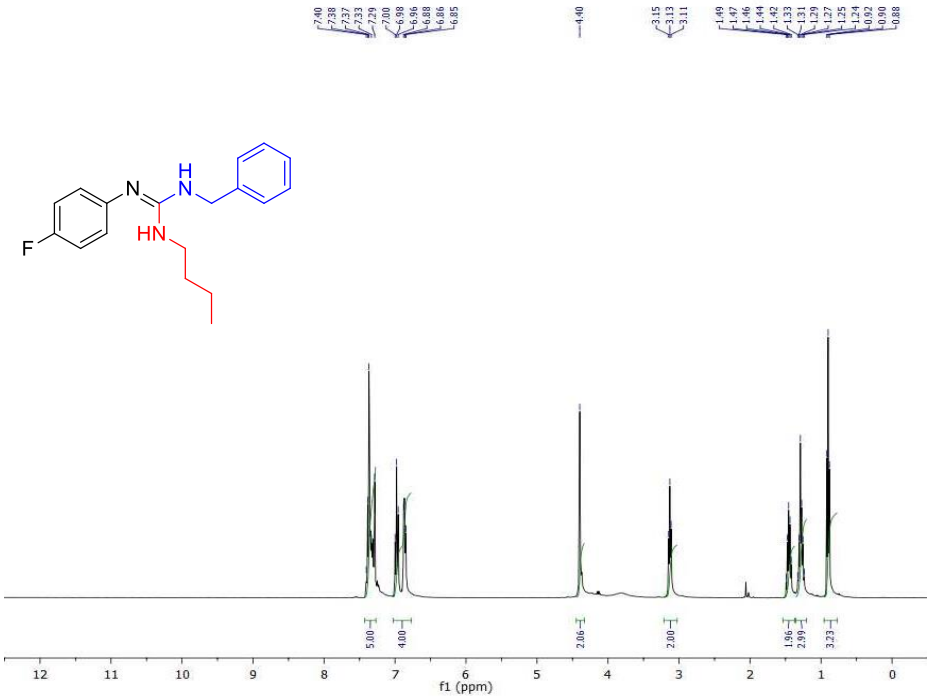

Figure A5 1-benzyl-3-butyl-2-(4-fluorophenyl)guanidine (**5c**); ^{1}H NMR 400 MHz, $CDCl_3$

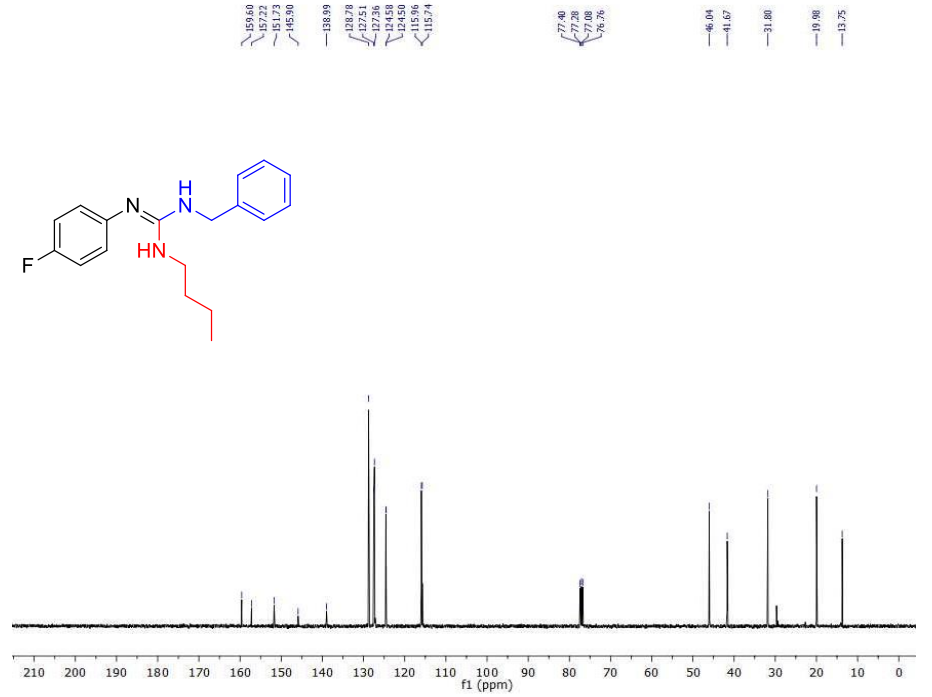

Figure A6 1-benzyl-3-butyl-2-(4-fluorophenyl)guanidine (**5c**); ^{13}C NMR 100 MHz, $CDCl_3$

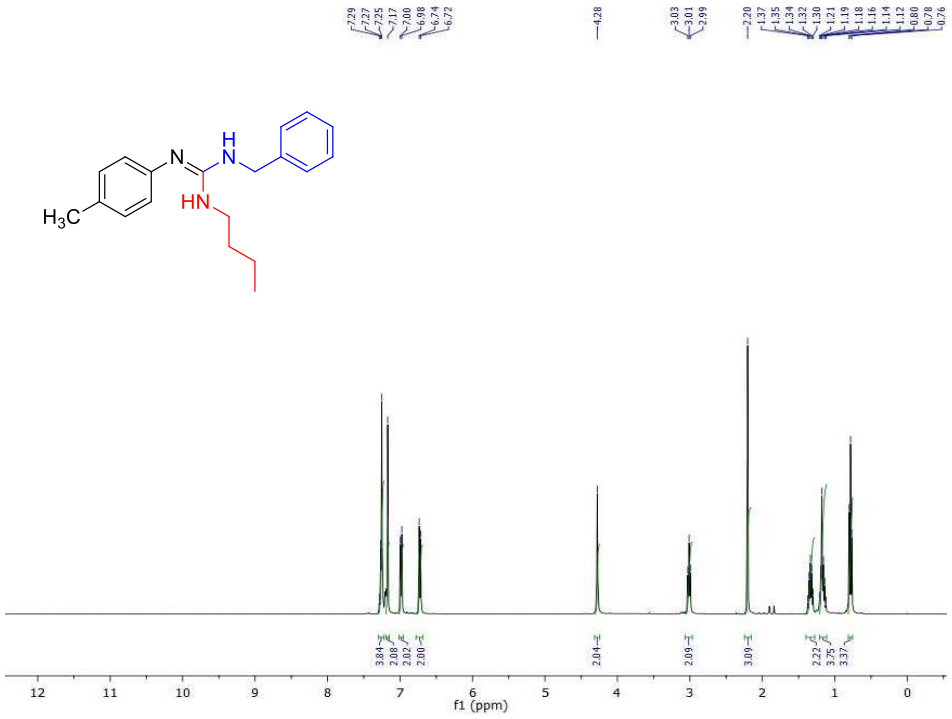

Figure A7 1-benzyl-3-butyl-2-(*p*-tolyl)guanidine (**5d**); ^{1}H NMR 400 MHz, $CDCl_3$

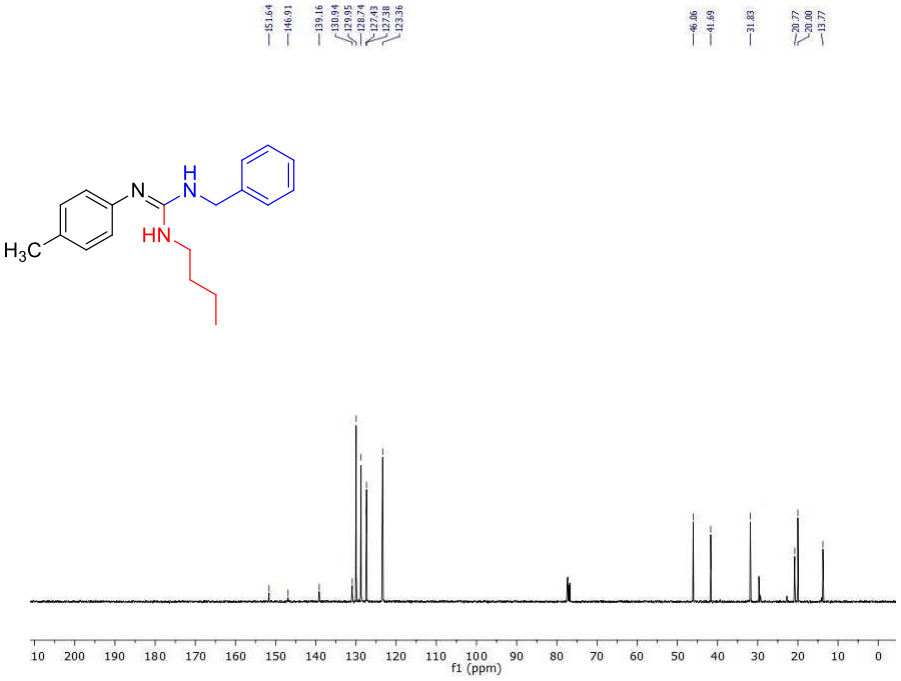

Figure A8 1-benzyl-3-butyl-2-(*p*-tolyl)guanidine (**5d**) ^{13}C NMR 100 MHz, $CDCl_3$

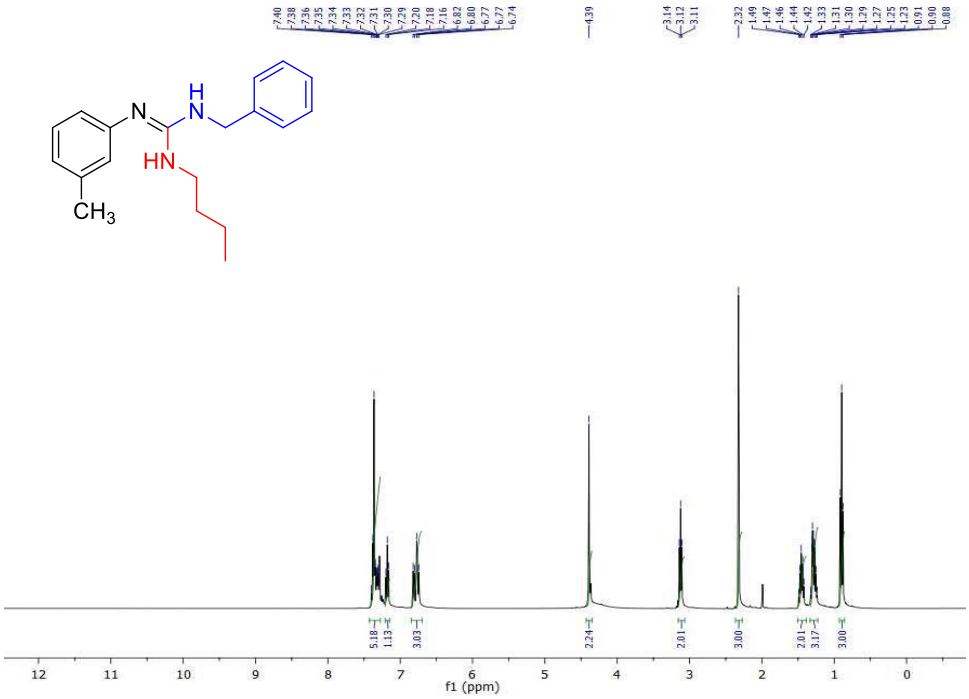

Figure A9 1-benzyl-3-butyl-2-(*m*-tolyl)guanidine (**5e**); ^{1}H NMR 400 MHz, $CDCl_3$

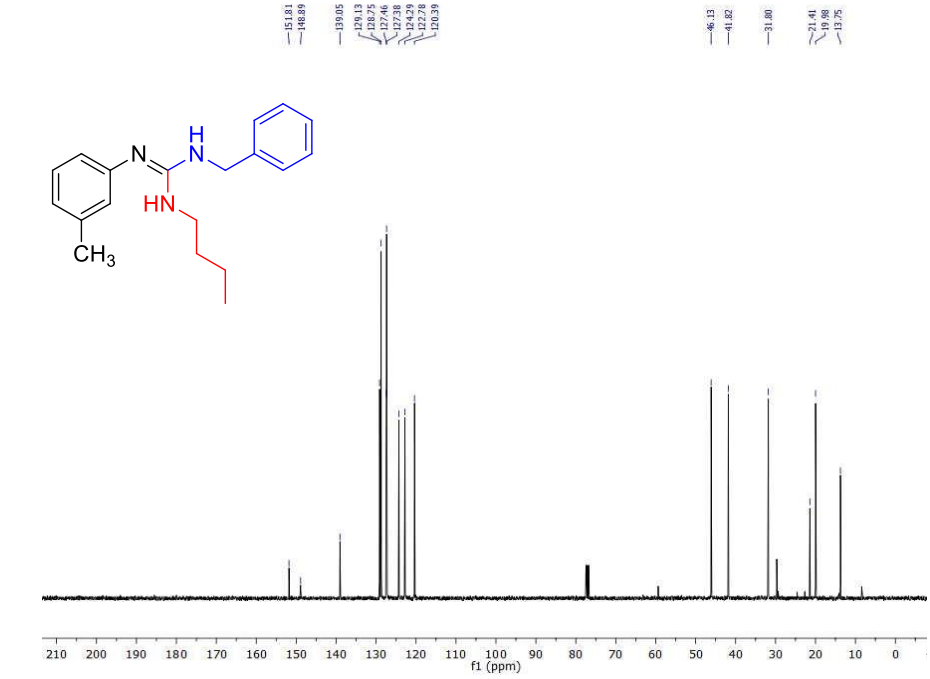

Figure A10 1-benzyl-3-butyl-2-(*m*-tolyl)guanidine (**5e**); ^{13}C NMR 100 MHz, $CDCl_3$

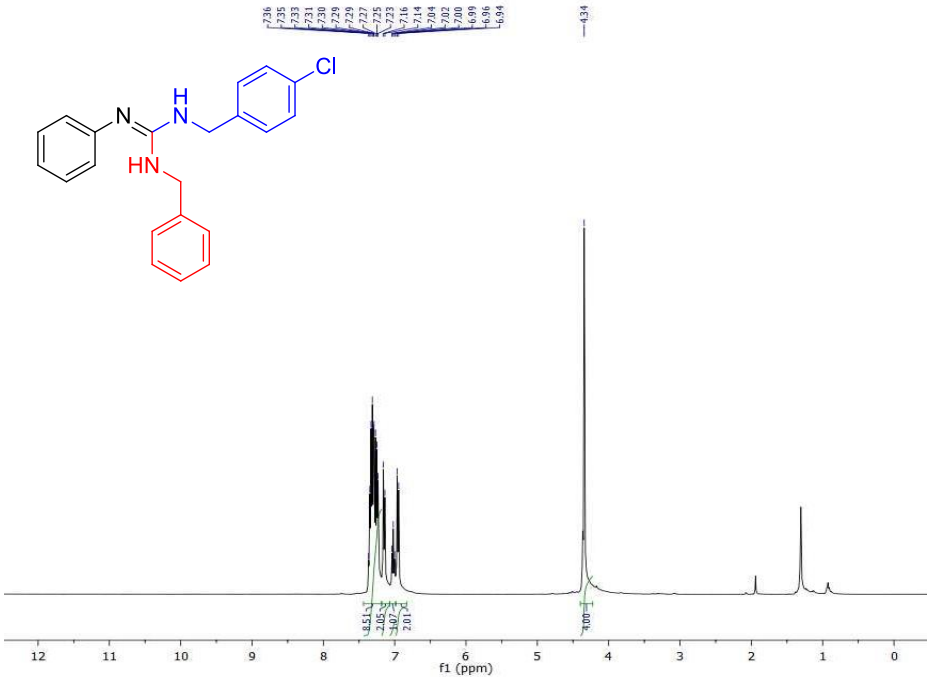

Figure A11 1-benzyl-3-(4-chlorobenzyl)-2-phenylguanidine (**5f**); ^{1}H NMR 400 MHz, $CDCl_3$

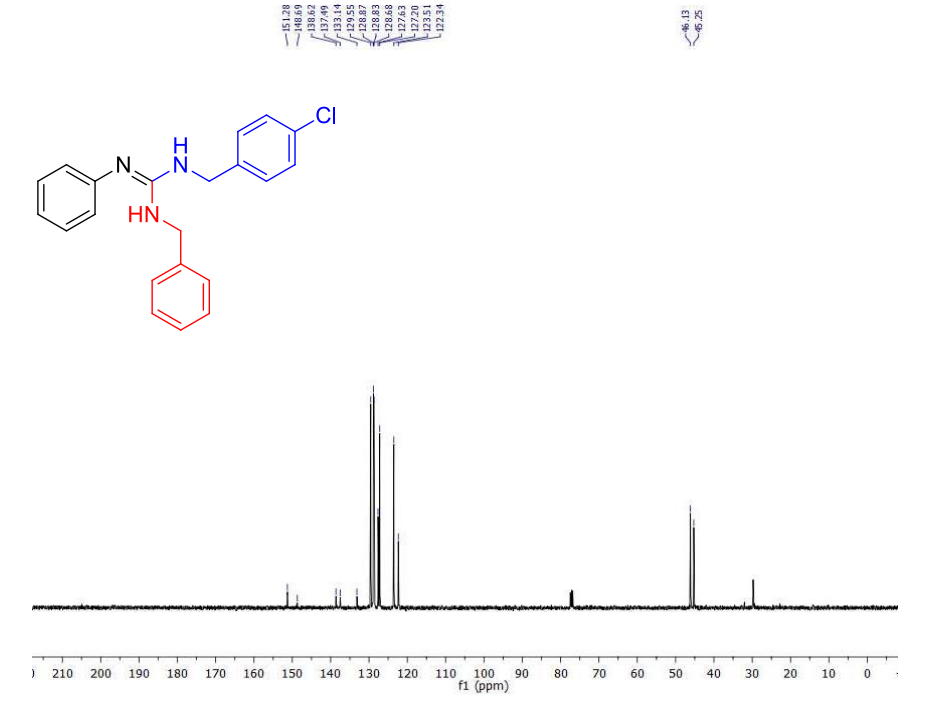

Figure A12 1-benzyl-3-(4-chlorobenzyl)-2-phenylguanidine (**5f**); ^{13}C NMR 100 MHz, $CDCl_3$

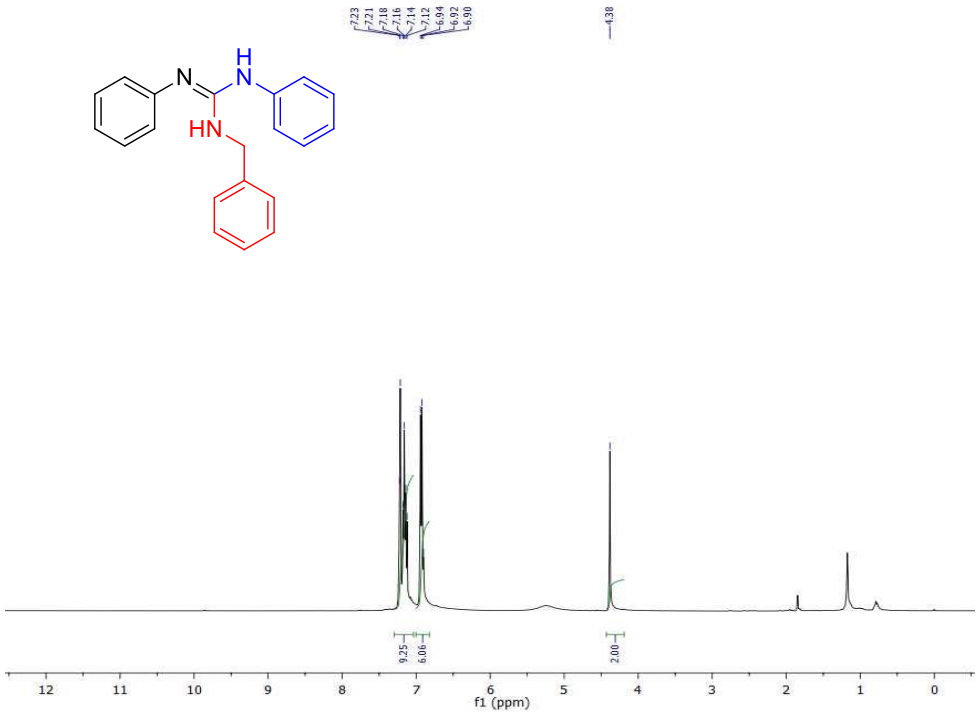

Figure A13 1-benzyl-2,3-diphenylguanidine (**5g**); ^{1}H NMR 400 MHz, $CDCl_3$

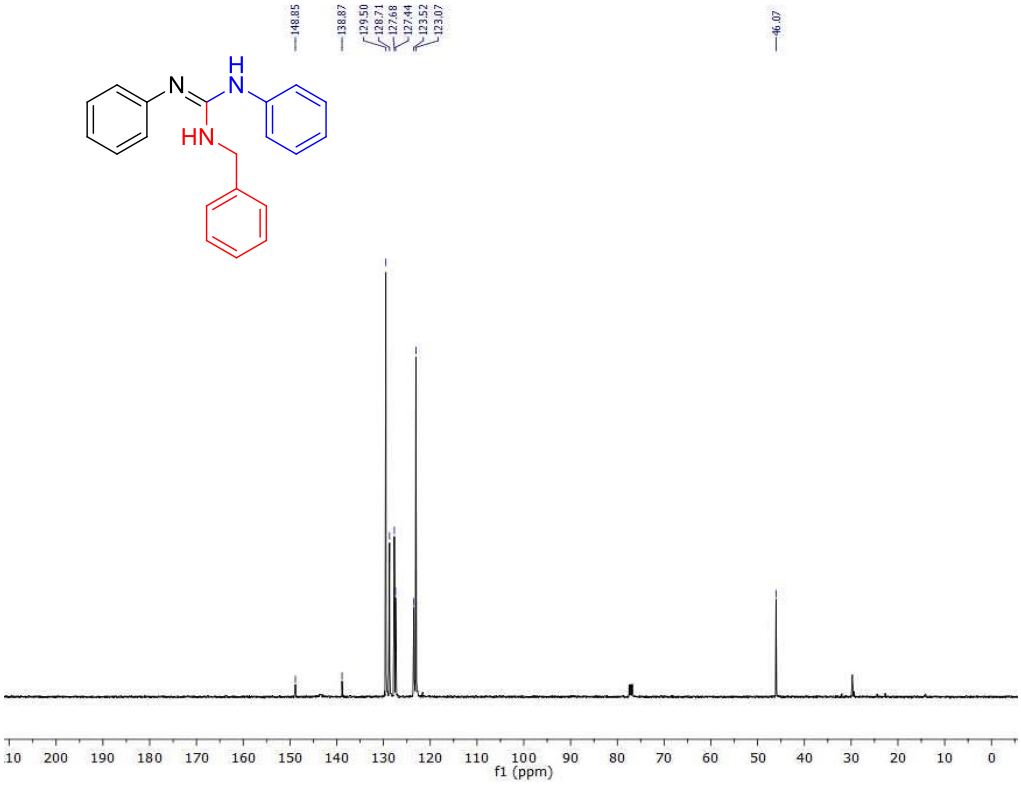

Figure A14 1-benzyl-2,3-diphenylguanidine (**5g**); ^{13}C NMR 100 MHz, $CDCl_3$

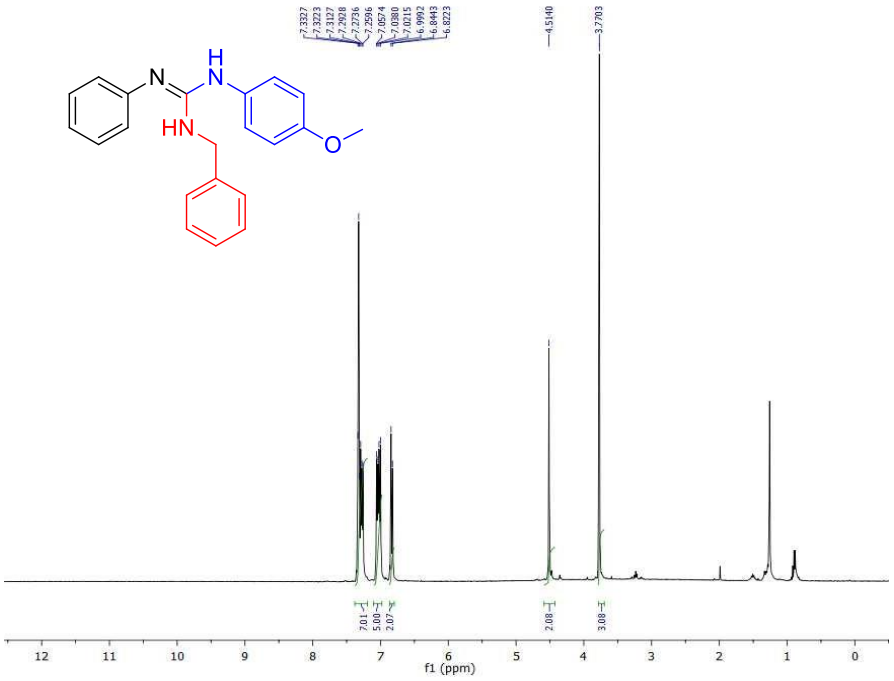

Figure A15 1-benzyl-3-(4-methoxyphenyl)-2-phenylguanidine (**5h**); ^{1}H NMR 400 MHz, $CDCl_3$

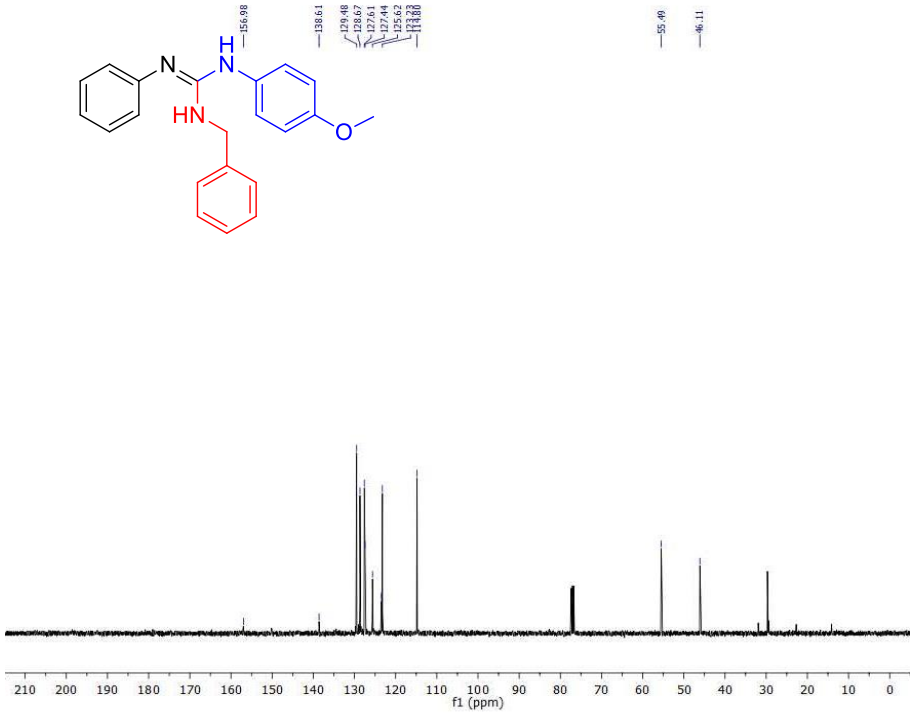

Figure A16 1-benzyl-3-(4-methoxyphenyl)-2-phenylguanidine (**5h**); ^{13}C NMR 100 MHz, $CDCl_3$

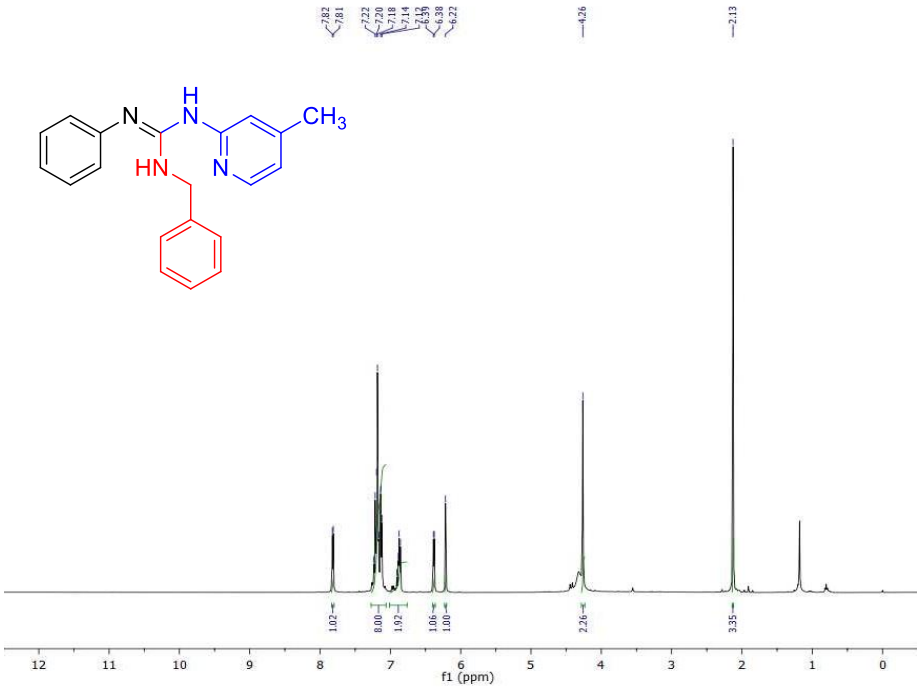

Figure A17 1-benzyl-3-(4-methylpyridin-2-yl)-2-phenylguanidine (**5i**); ^{1}H NMR 400 MHz, $CDCl_3$

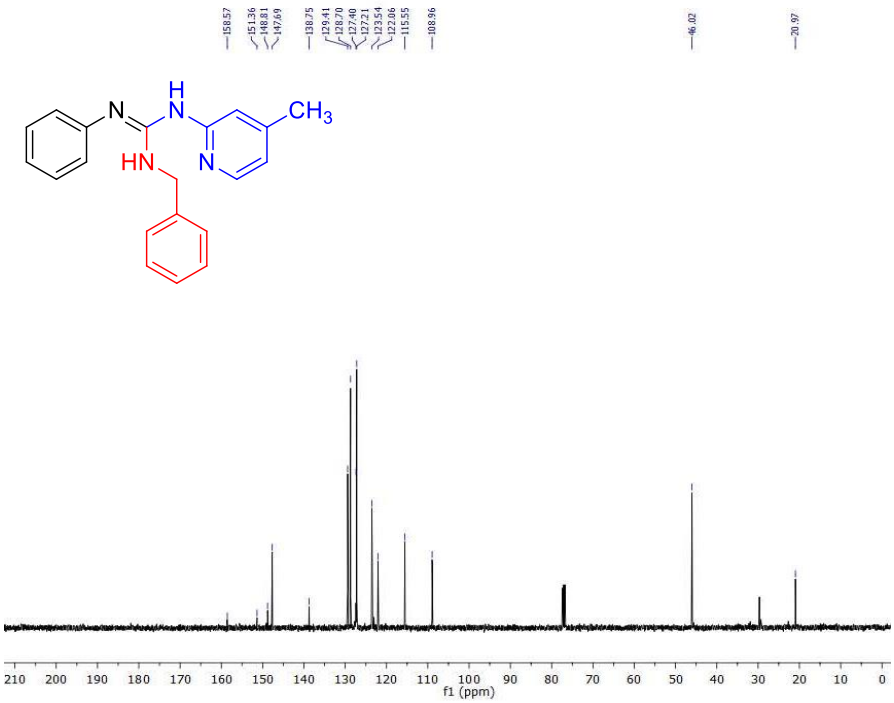

Figure A18 1-benzyl-3-(4-methylpyridin-2-yl)-2-phenylguanidine (**5i**); ^{13}C NMR 100 MHz, $CDCl_3$

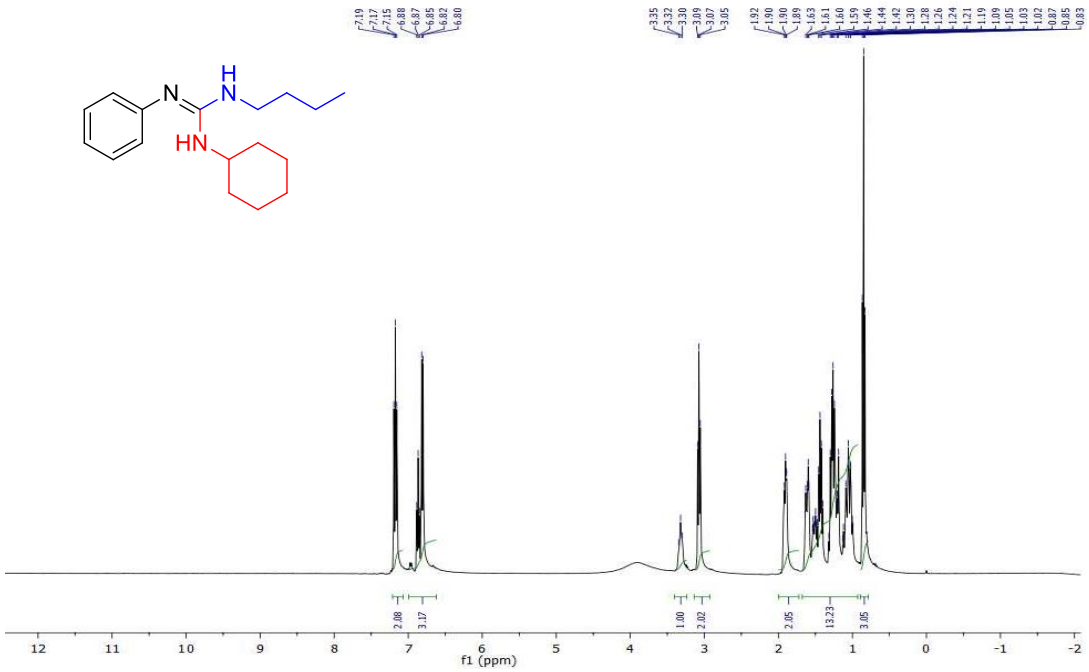

Figure A19 1-butyl-3-cyclohexyl-2-phenylguanidine (**5j**); ^{1}H NMR 400 MHz, $CDCl_3$

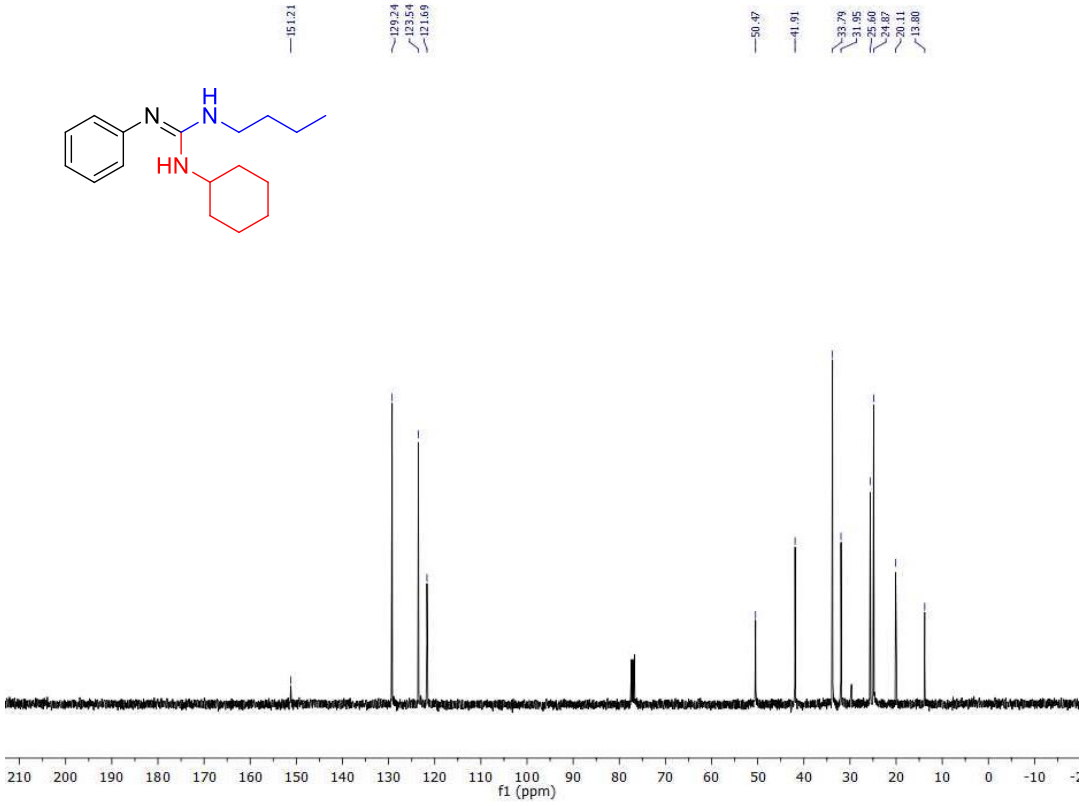

Figure A20 1-butyl-3-cyclohexyl-2-phenylguanidine (**5j**); ^{13}C NMR (100 MHz, $CDCl_3$)

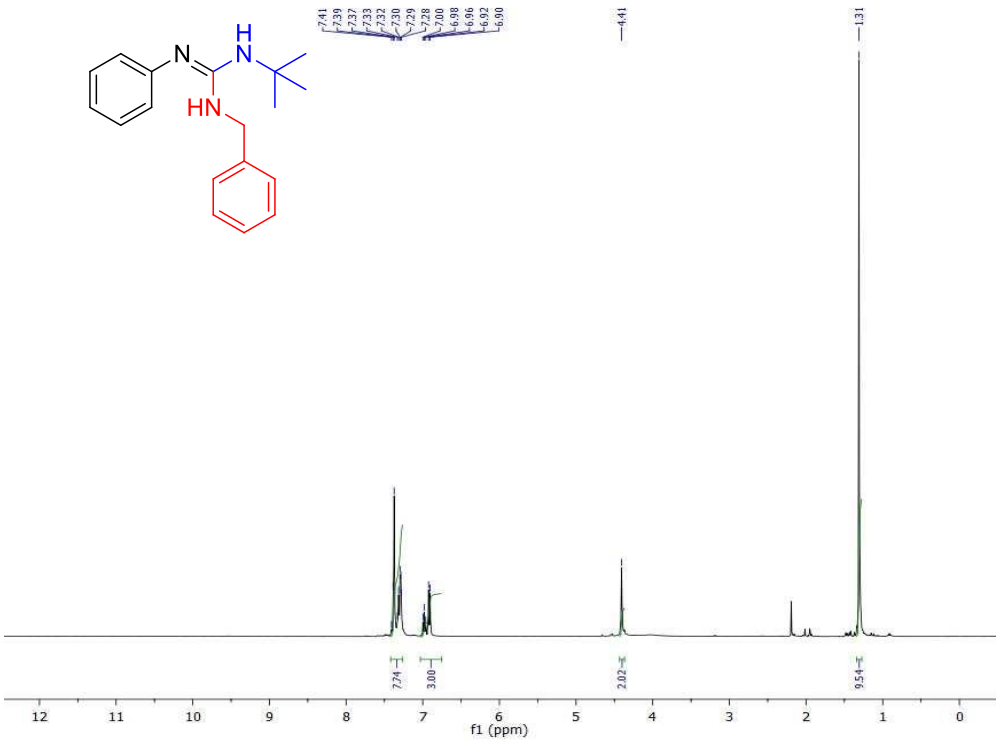

Figure A21 1-benzyl-3-(*tert*-butyl)-2-phenylguanidine (**5k**); ^{1}H NMR 400 MHz, $CDCl_3$

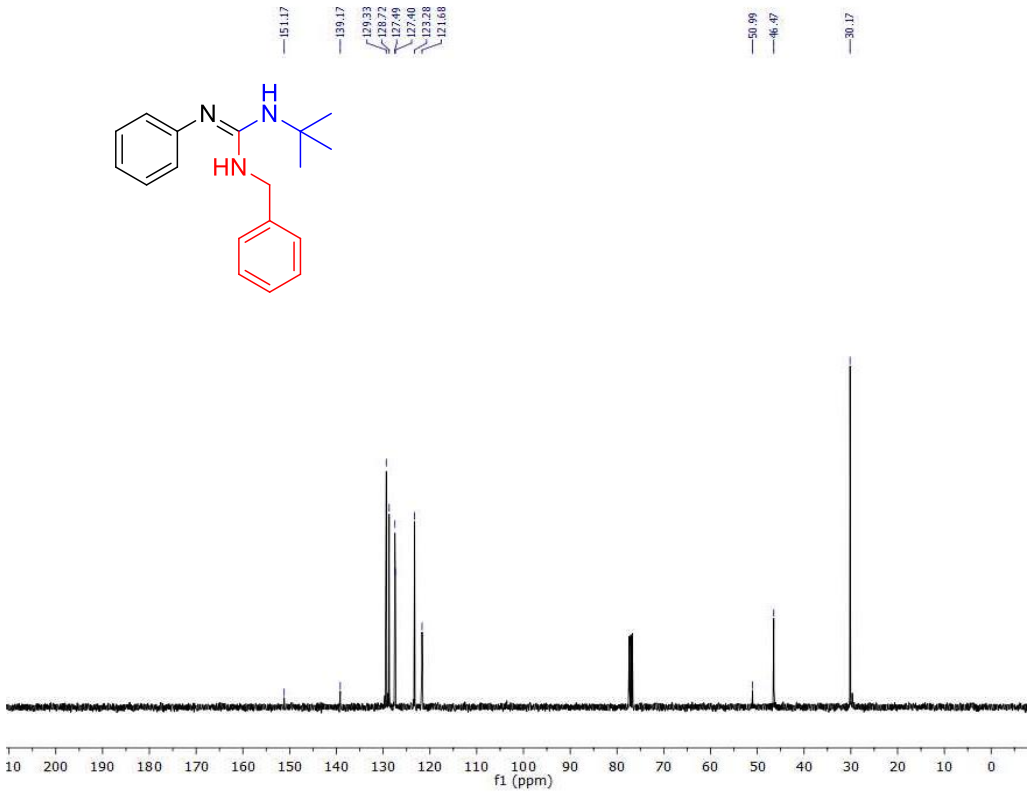

Figure A22 1-benzyl-3-(*tert*-butyl)-2-phenylguanidine (**5k**); ^{1}H NMR 400 MHz, $CDCl_3$

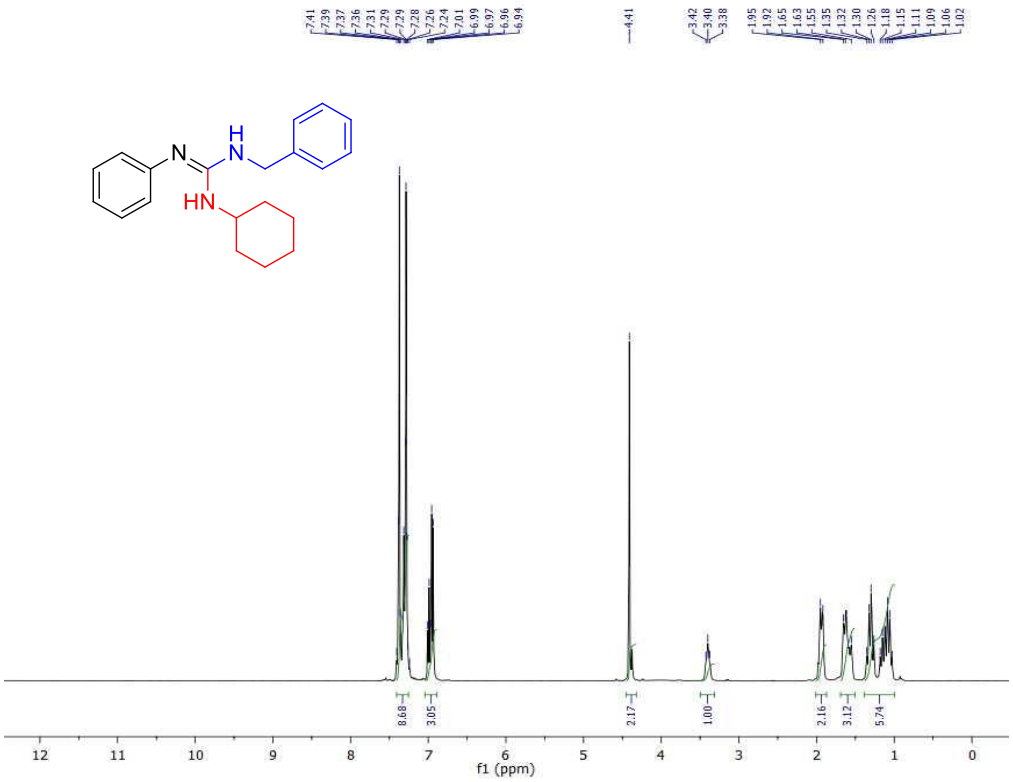

Figure A23 1-benzyl-3-cyclohexyl-2-phenylguanidine (**5l**); ^{1}H NMR 400 MHz, $CDCl_3$

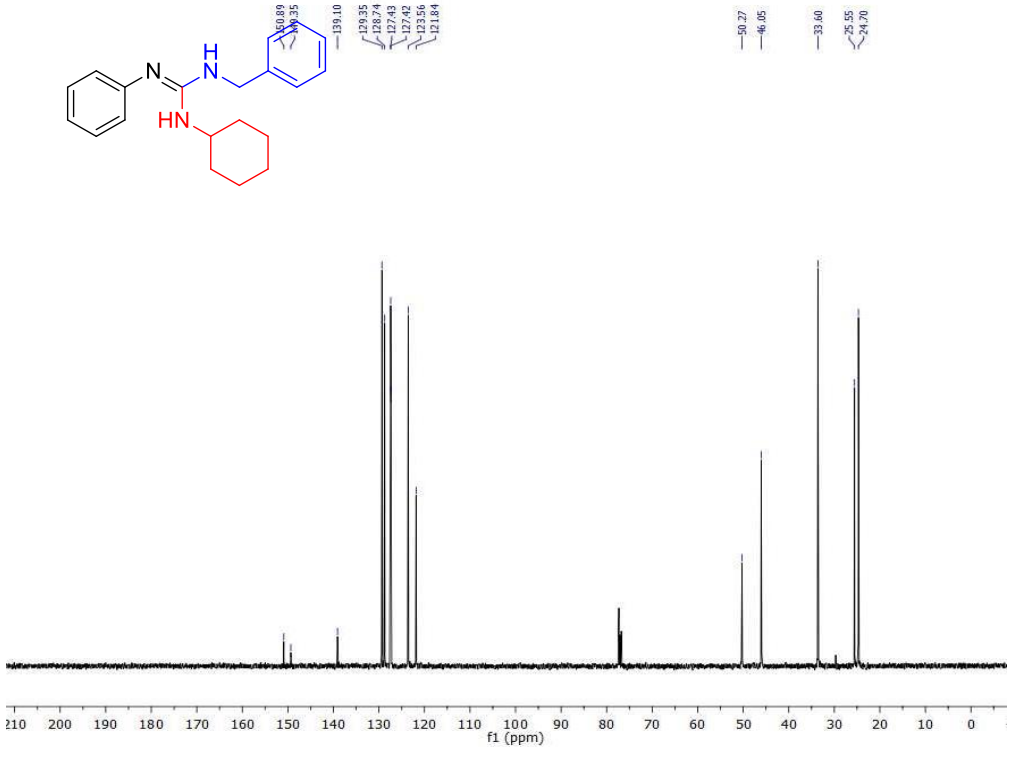

Figure A24 1-benzyl-3-cyclohexyl-2-phenylguanidine (**5l**); ^{13}C NMR 100 MHz, $CDCl_3$

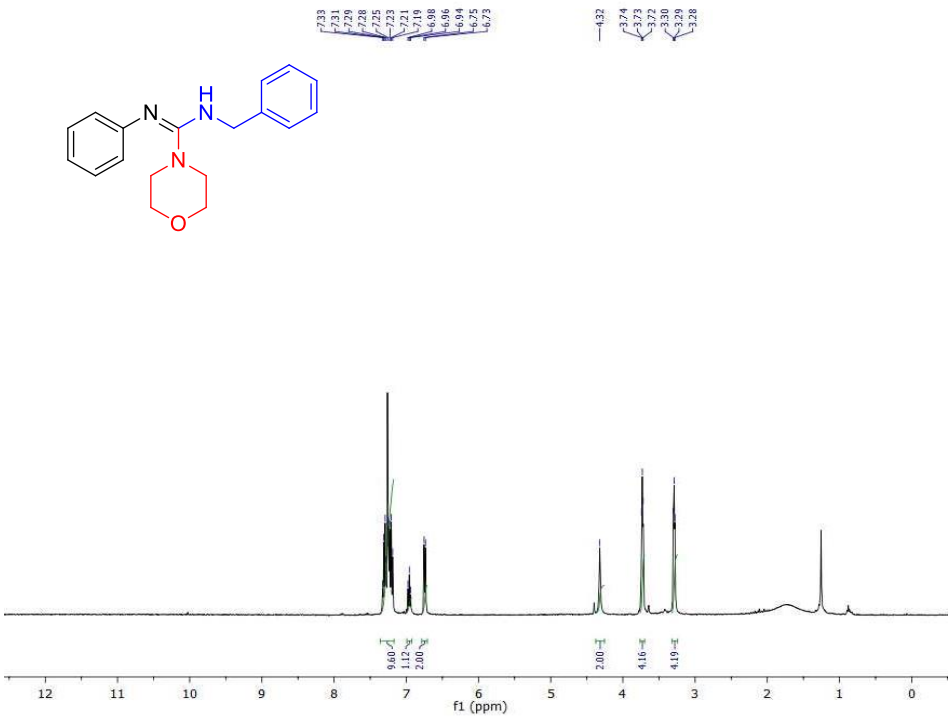

Figure A25 *N*-benzyl-N'-phenylmorpholine-4-carboximidamide (**5m**); ^{1}H NMR 400 MHz, $CDCl_3$

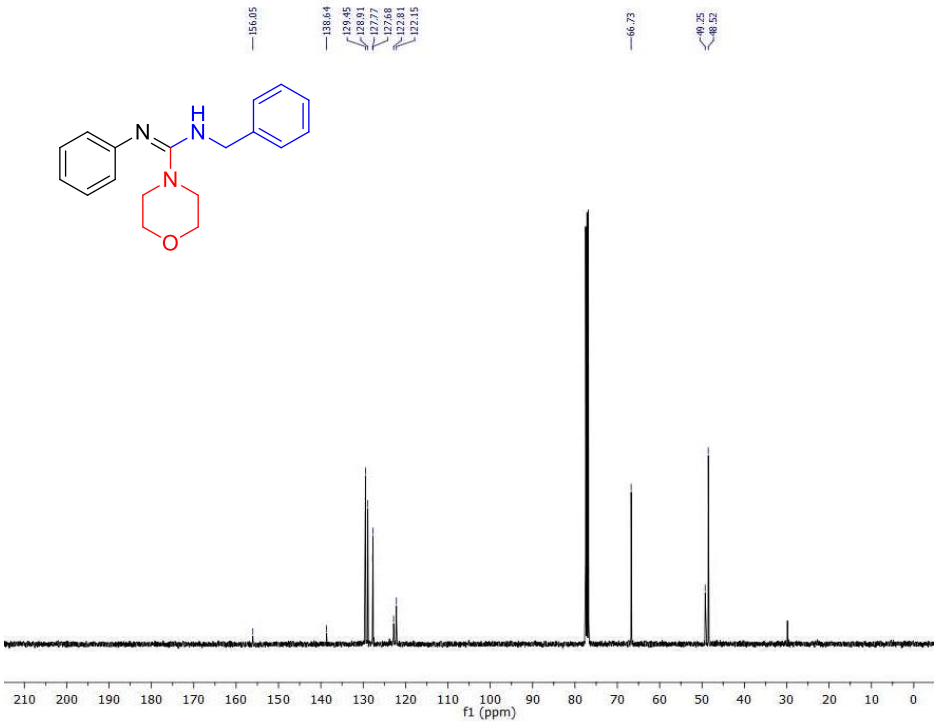

Figure A26 *N*-benzyl-*N'*-phenylmorpholine-4-carboximidamide (**5m**); ^{13}C NMR 100 MHz, $CDCl_3$

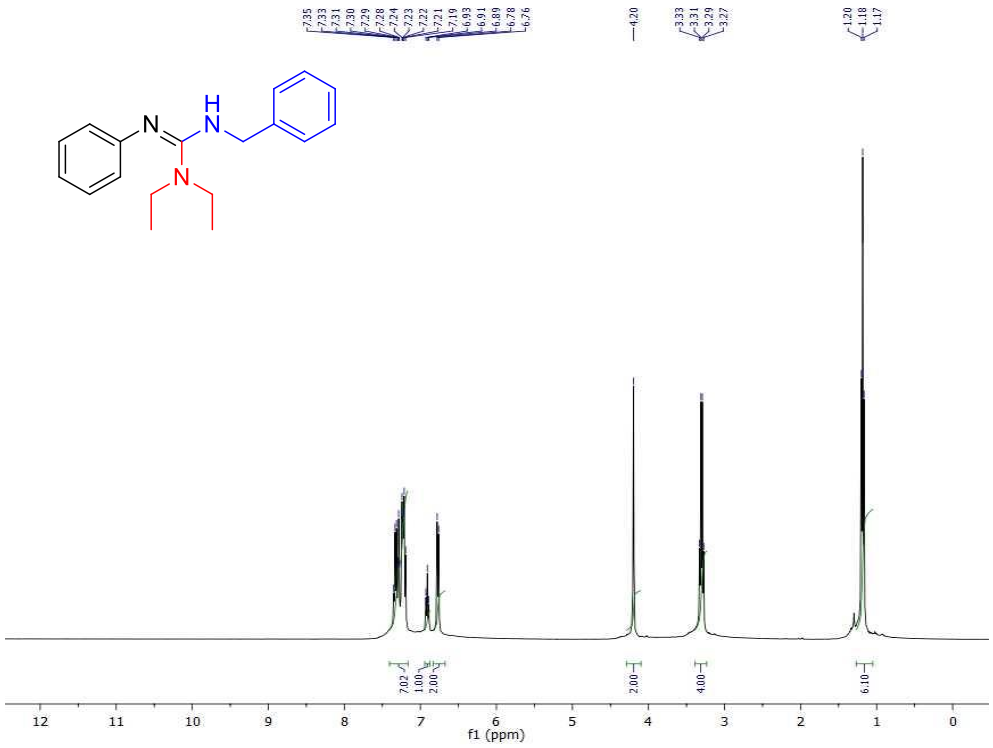

Figure A27 3-benzyl-1,1-diethyl-2-phenylguanidine (**5n**); ^{1}H NMR 400 MHz, $CDCl_3$

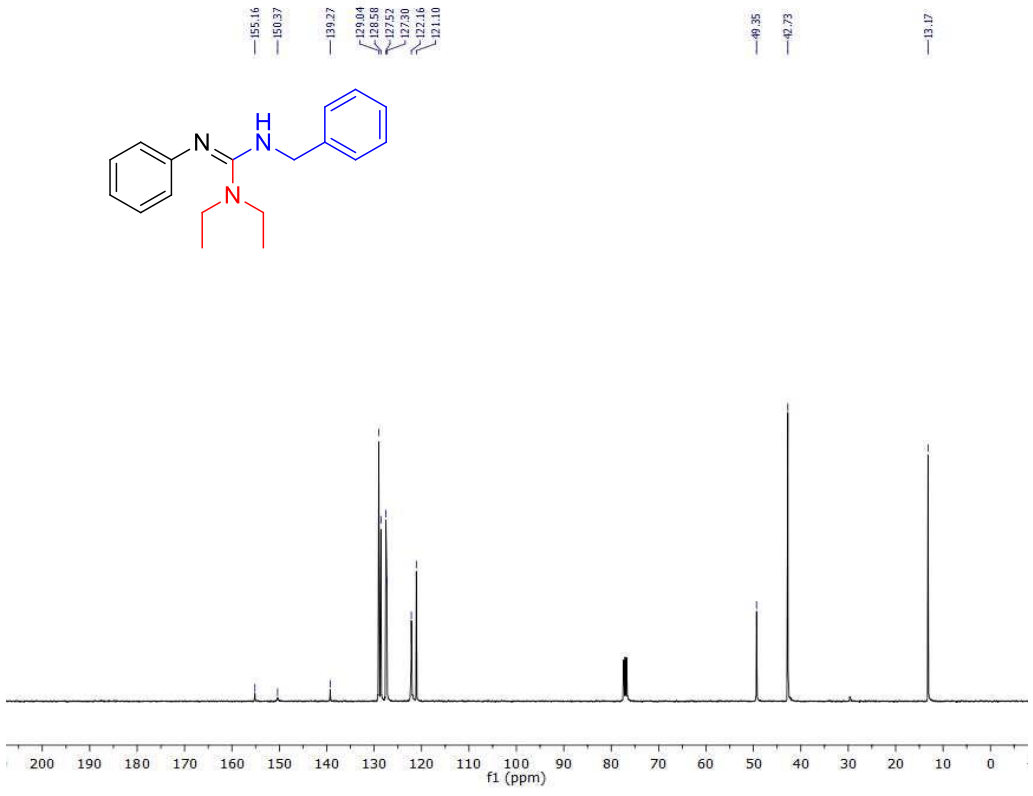

Figure A28 3-benzyl-1,1-diethyl-2-phenylguanidine (**5n**); ^{13}C NMR 100 MHz, $CDCl_3$

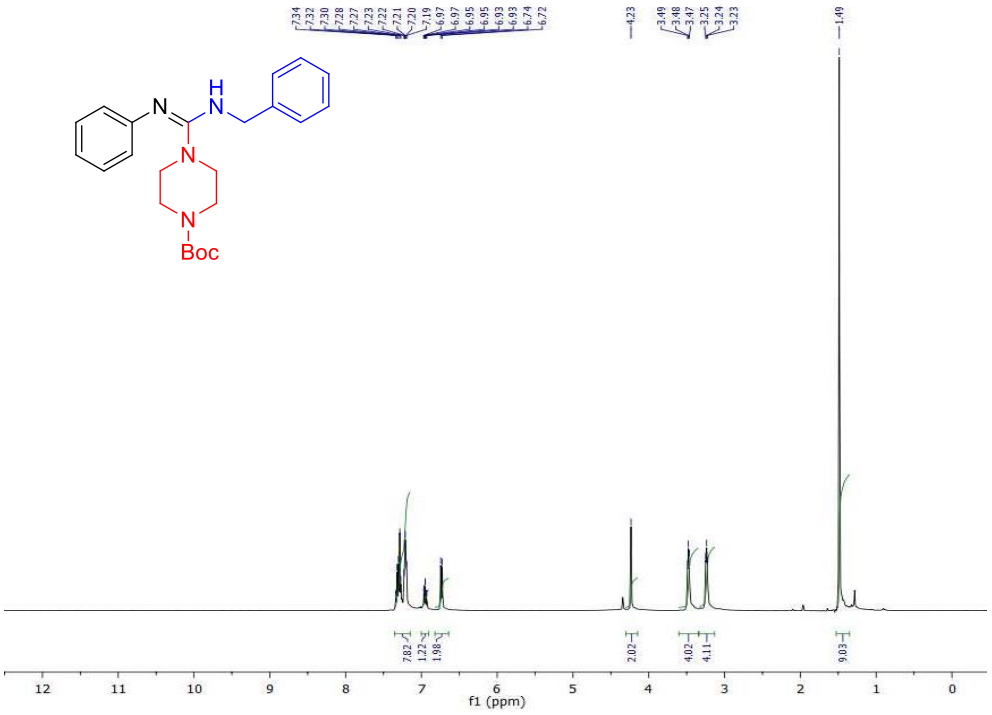

Figure A29 *tert*-butyl-4-(*N*-benzyl-*N*′-phenylcarbamimidoyl)piperazine-1-carboxylate (**5o**); ^{1}H NMR 400 MHz, $CDCl_3$

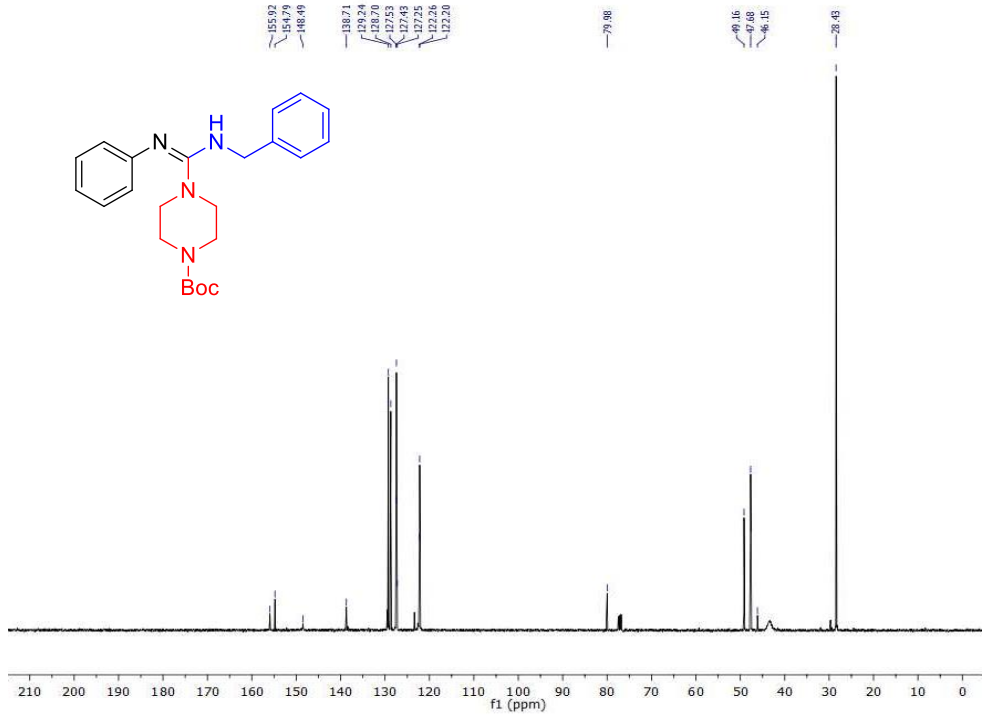

Figure A30 *tert*-butyl-4-(*N*-benzyl-*N*′-phenylcarbamimidoyl)piperazine-1-carboxylate (**5o**); ^{13}C NMR 100 MHz, $CDCl_3$

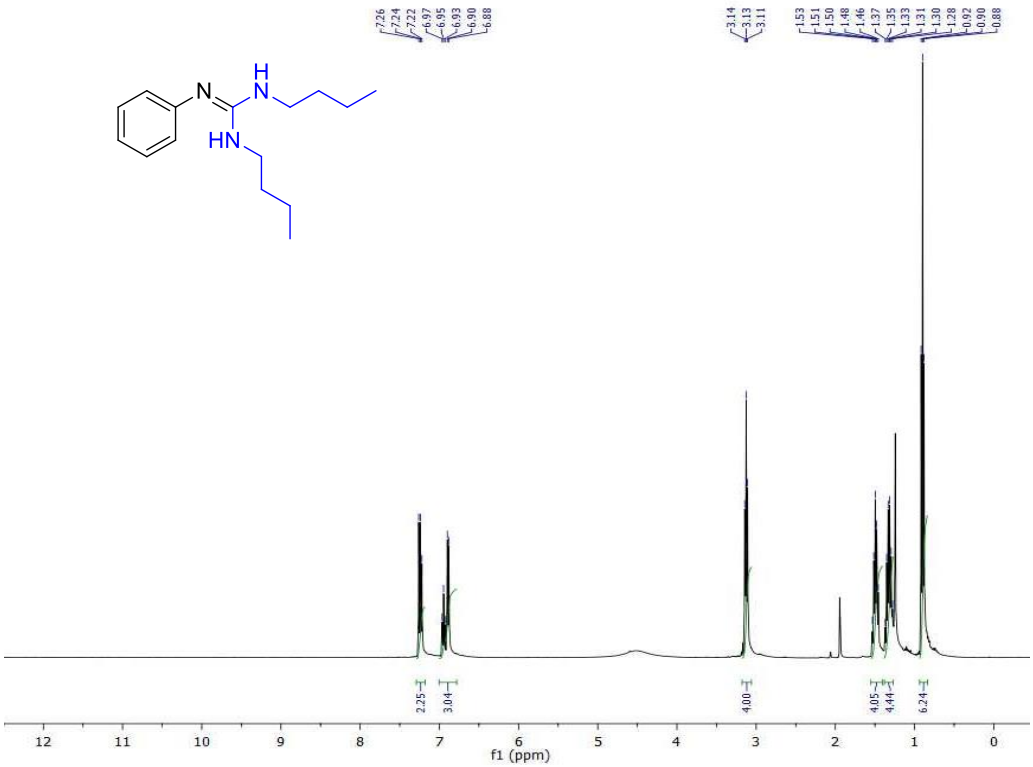

Figure A31 1,3-dibutyl-2-phenylguanidine (**6a**); ^{1}H NMR 400 MHz, $CDCl_3$

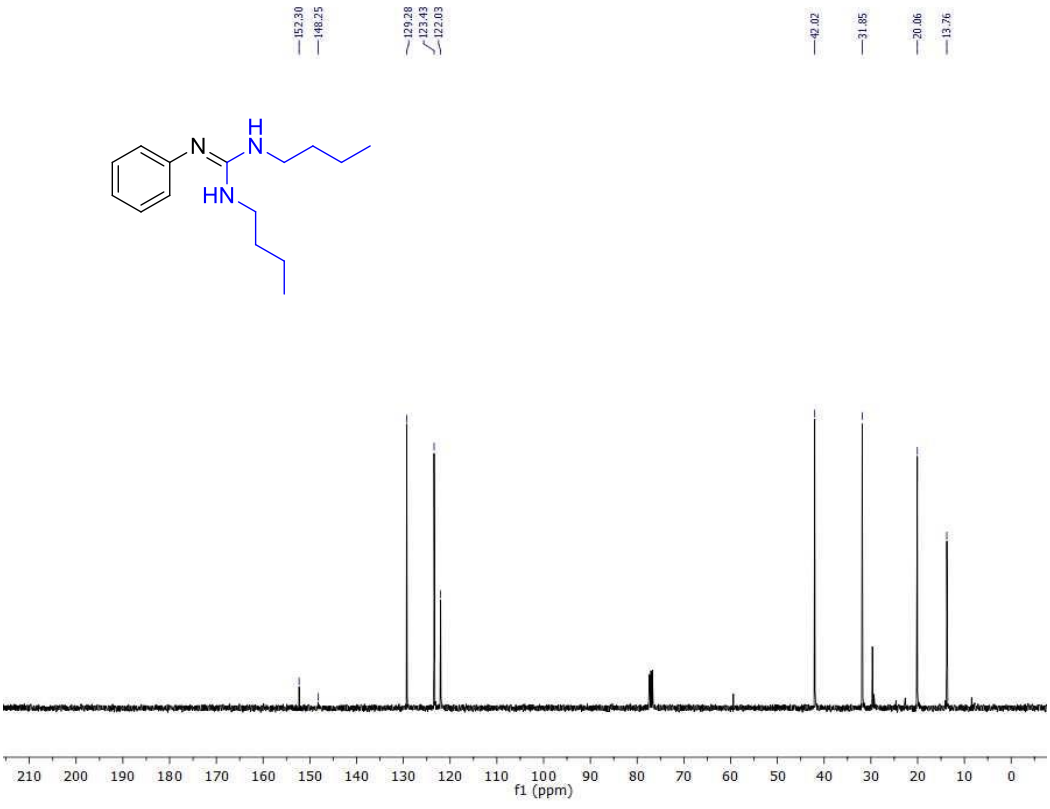

Figure A32 1,3-dibutyl-2-phenylguanidine (**6a**); ^{13}C NMR 100 MHz, $CDCl_3$

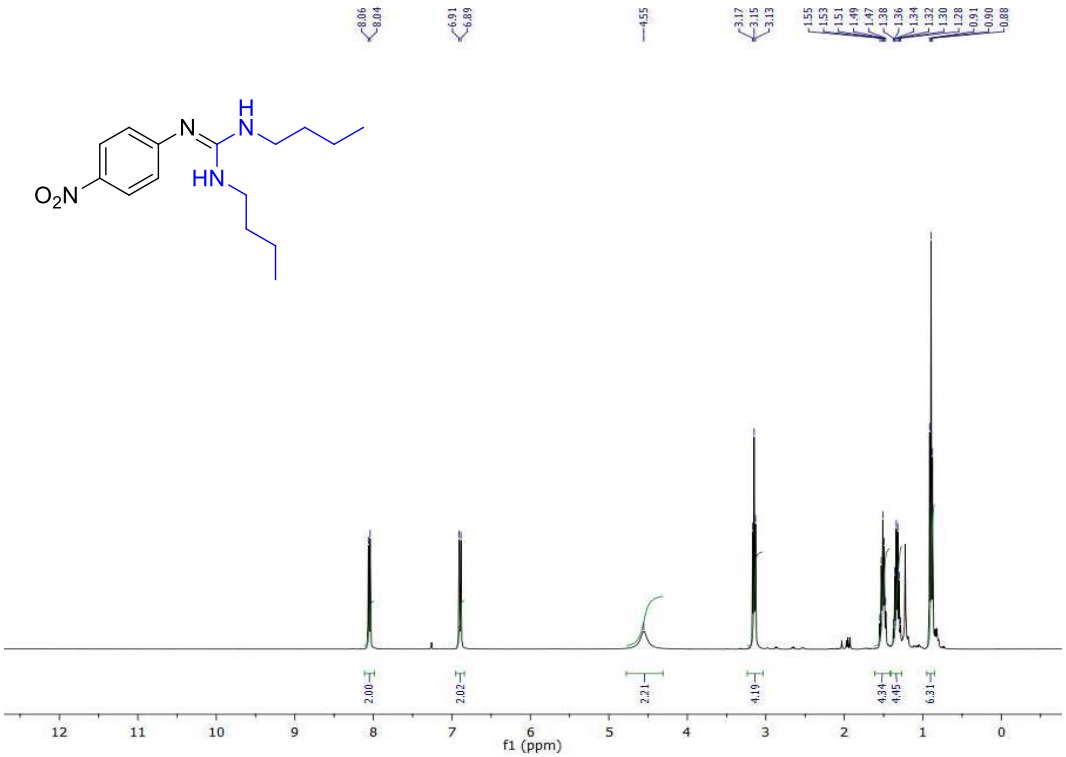

Figure A33 1,3-dibutyl-2-(4-nitrophenyl)guanidine (**6b**); ^{1}H NMR 400 MHz, $CDCl_3$

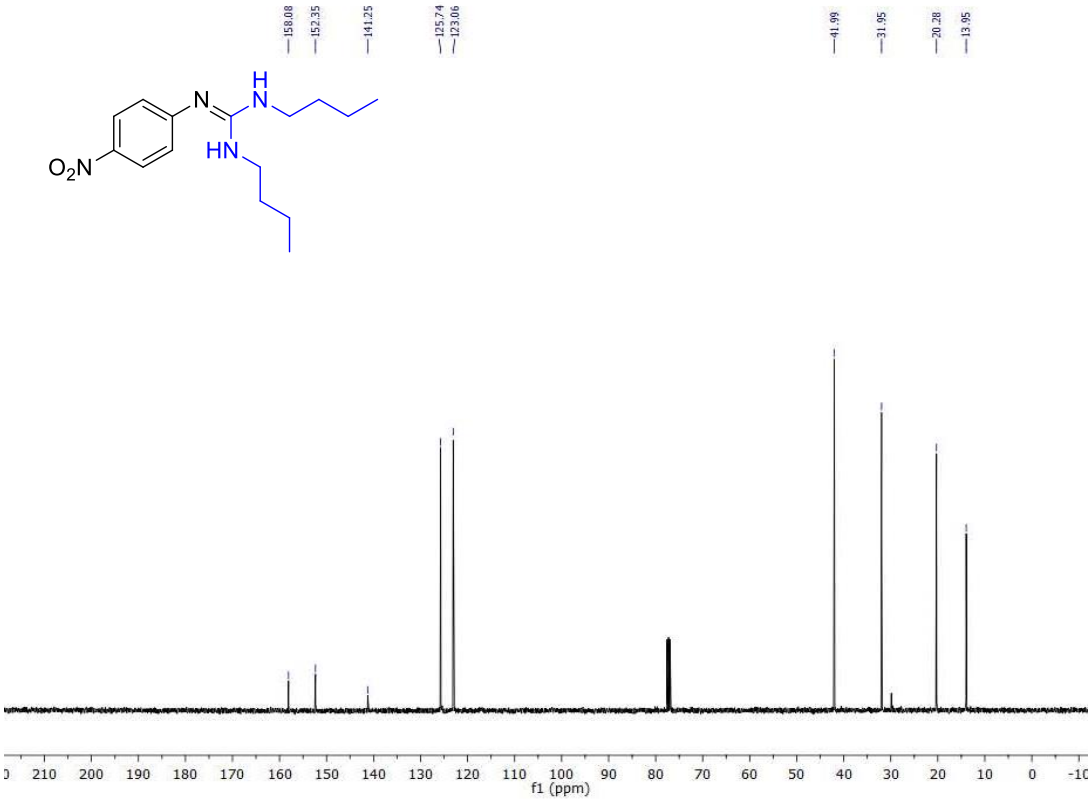

Figure A34 1,3-dibutyl-2-(4-nitrophenyl)guanidine (**6b**); ^{13}C NMR 100 MHz, $CDCl_3$

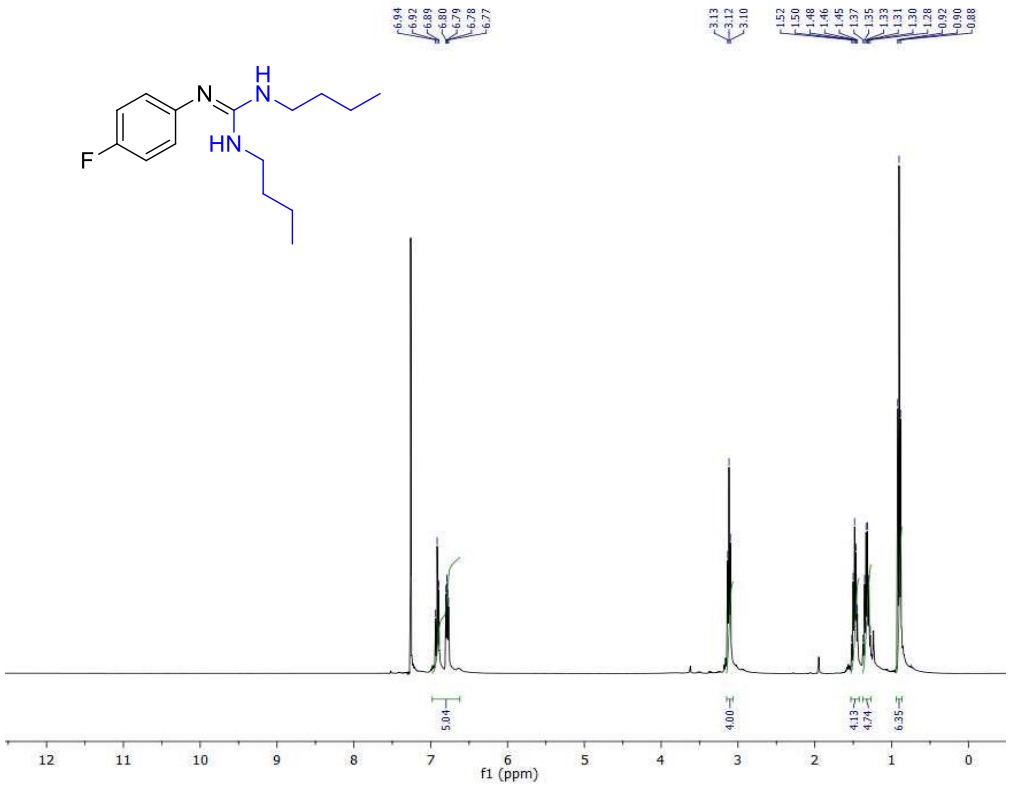

Figure A35 1,3-dibutyl-2-(4-fluorophenyl)guanidine (**6c**); ^{1}H NMR 400 MHz, $CDCl_3$

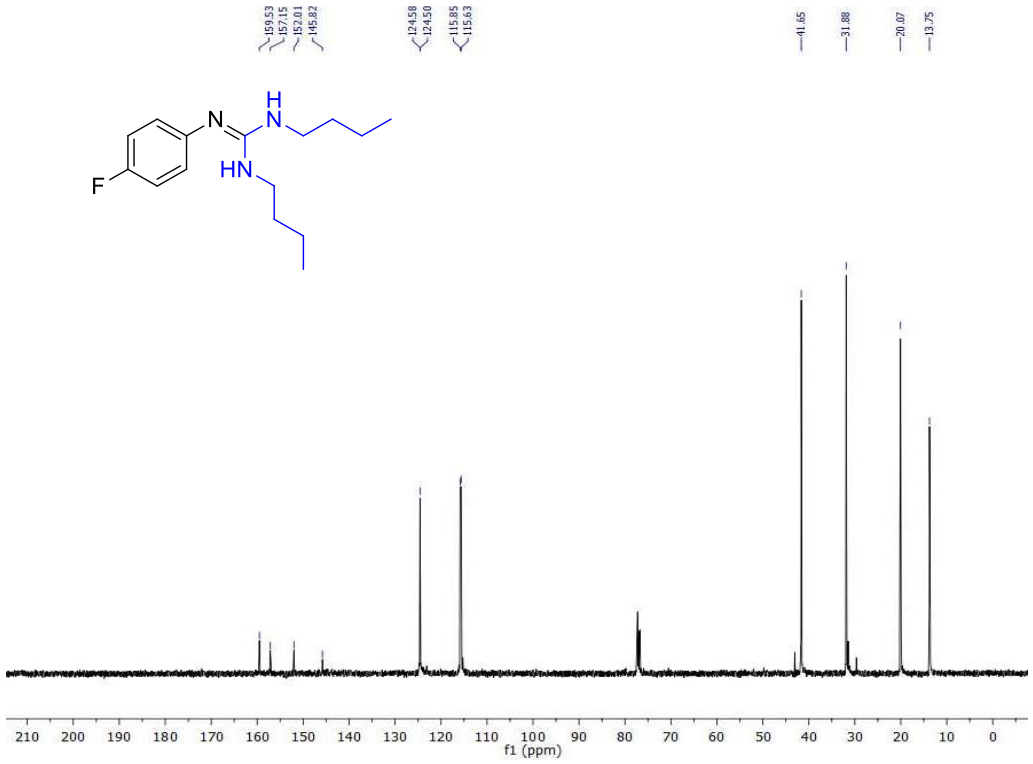

Figure A36 1,3-dibutyl-2-(4-fluorophenyl)guanidine (**6c**); ^{13}C NMR 100 MHz, $CDCl_3$

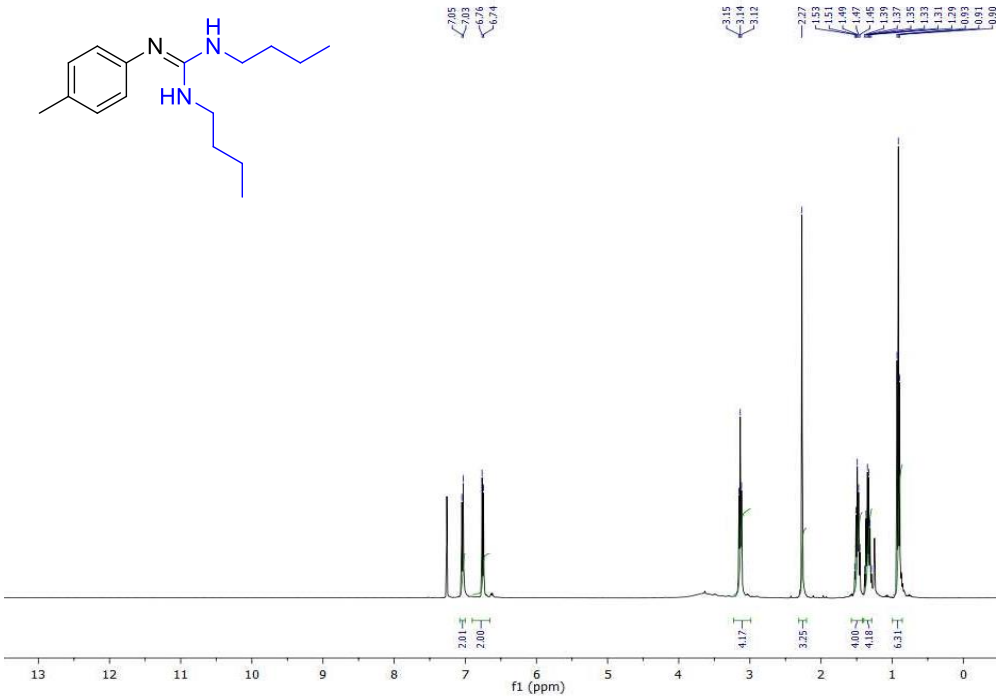

Figure A37 1,3-dibutyl-2-(*p*-tolyl)guanidine (**6d**);^{1}H NMR 400 MHz, $CDCl_3$

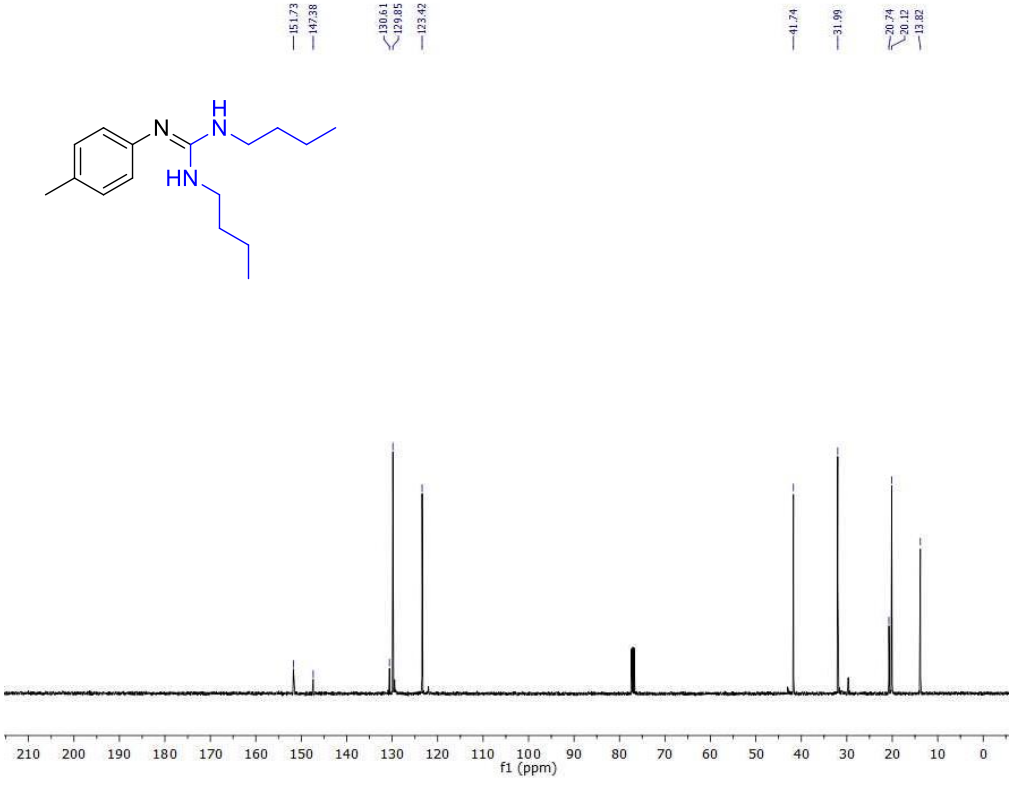

Figure A38 1,3-dibutyl-2-(*p*-tolyl)guanidine (**6d**);^{13}C NMR 100 MHz, $CDCl_3$

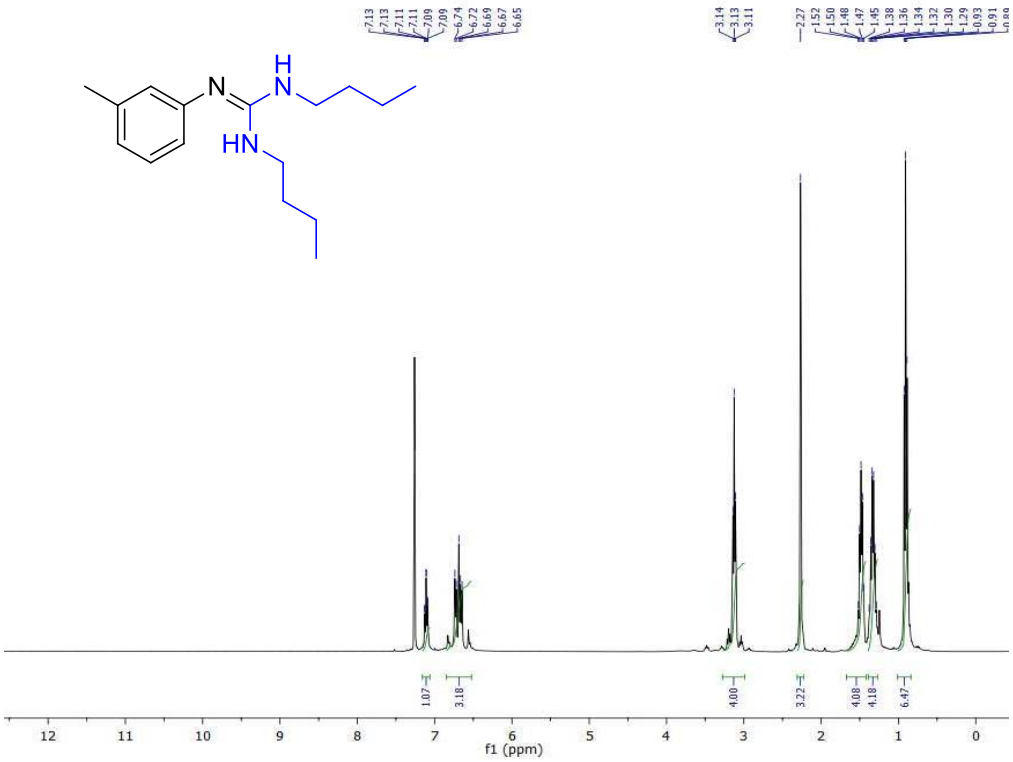

Figure A39 1,3-dibutyl-2-(*m*-tolyl)guanidine (**6e**); ^{1}H NMR 400 MHz, $CDCl_3$

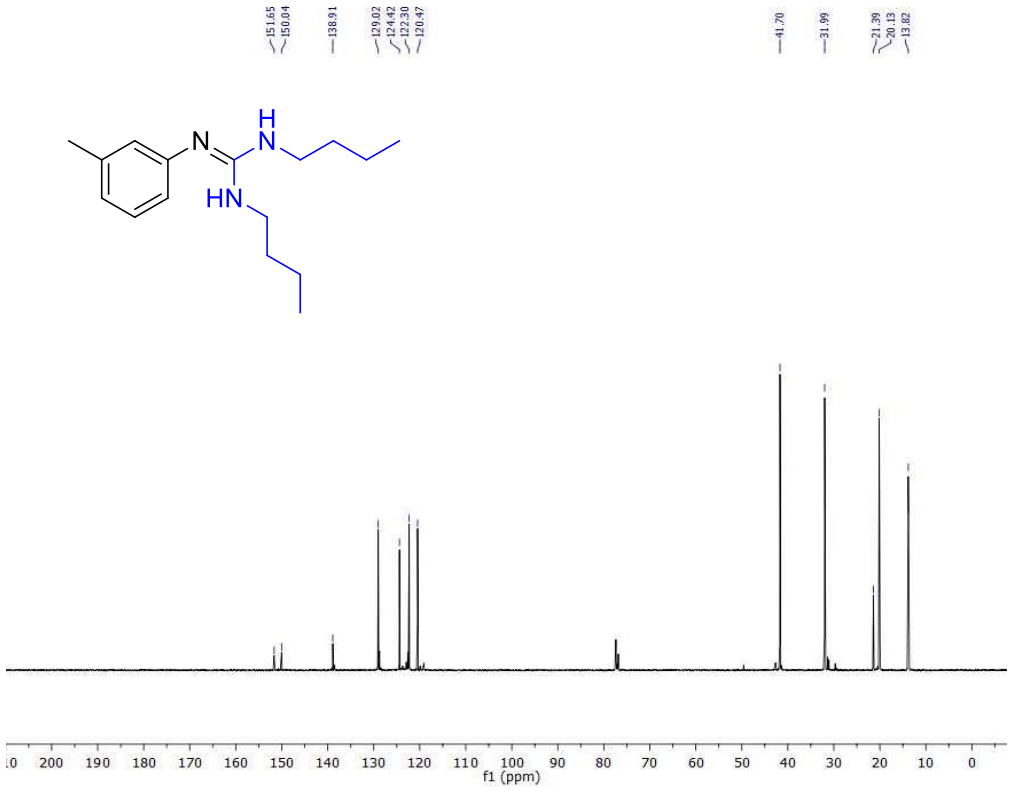

Figure A40 1,3-dibutyl-2-(*m*-tolyl)guanidine (**6e**); ^{13}C NMR 100 MHz, $CDCl_3$

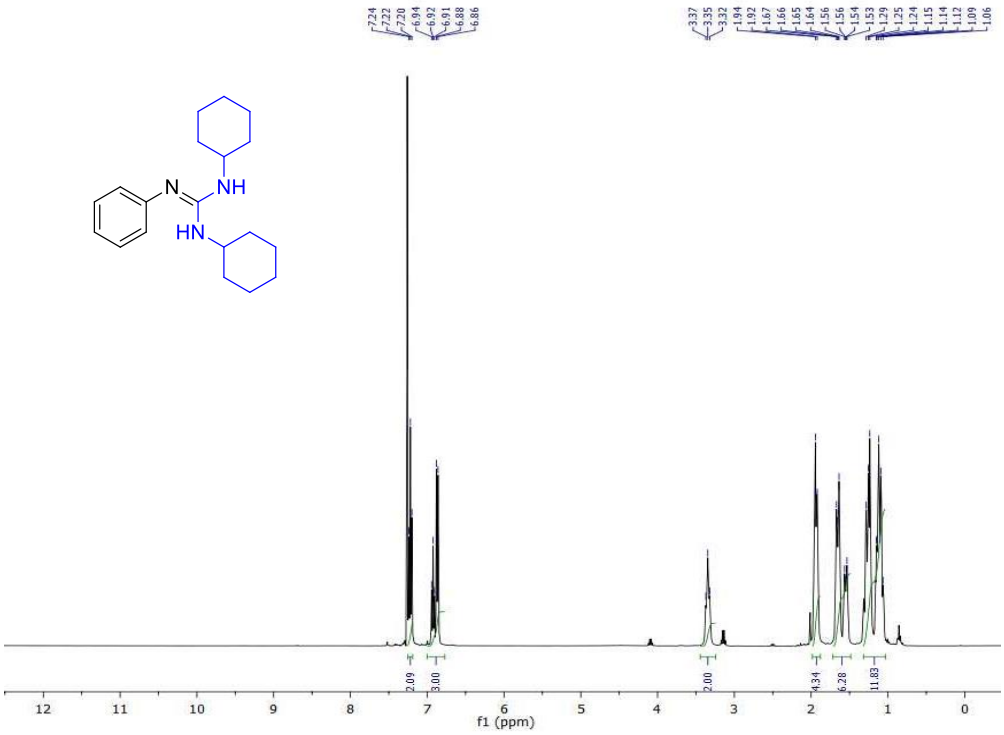

Figure A41 1,3-dicyclohexyl-2-phenylguanidine (**7a**); ^{1}H NMR 400 MHz, $CDCl_3$

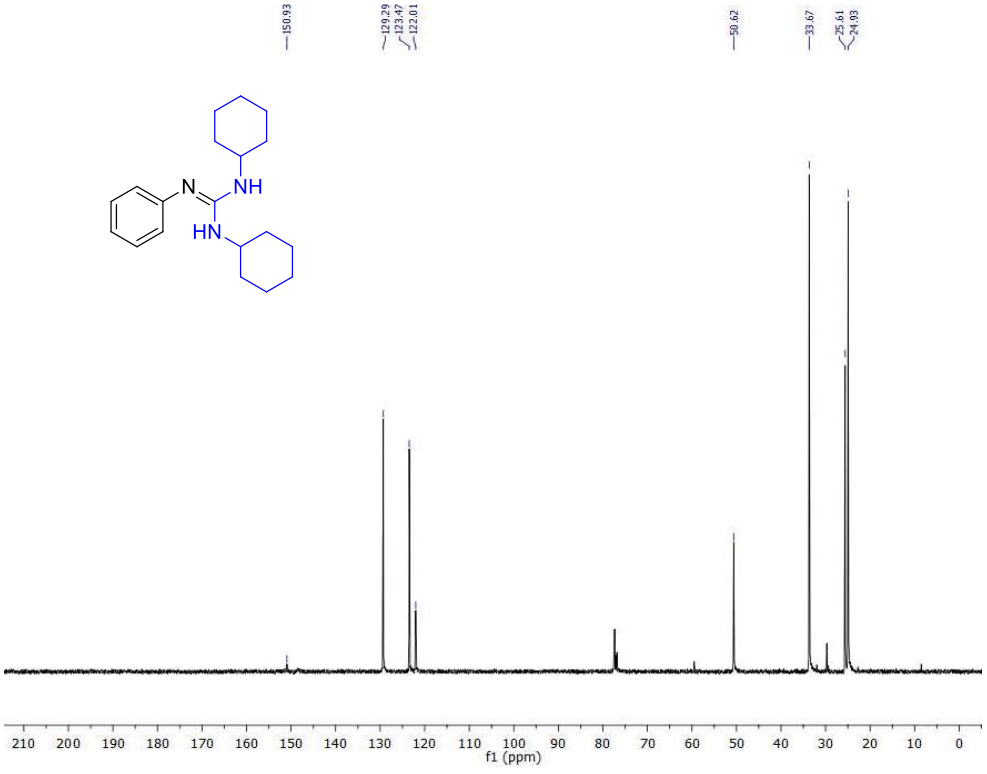

Figure A42 1,3-dicyclohexyl-2-phenylguanidine (**7a**); ^{13}C NMR 400 MHz, $CDCl_3$

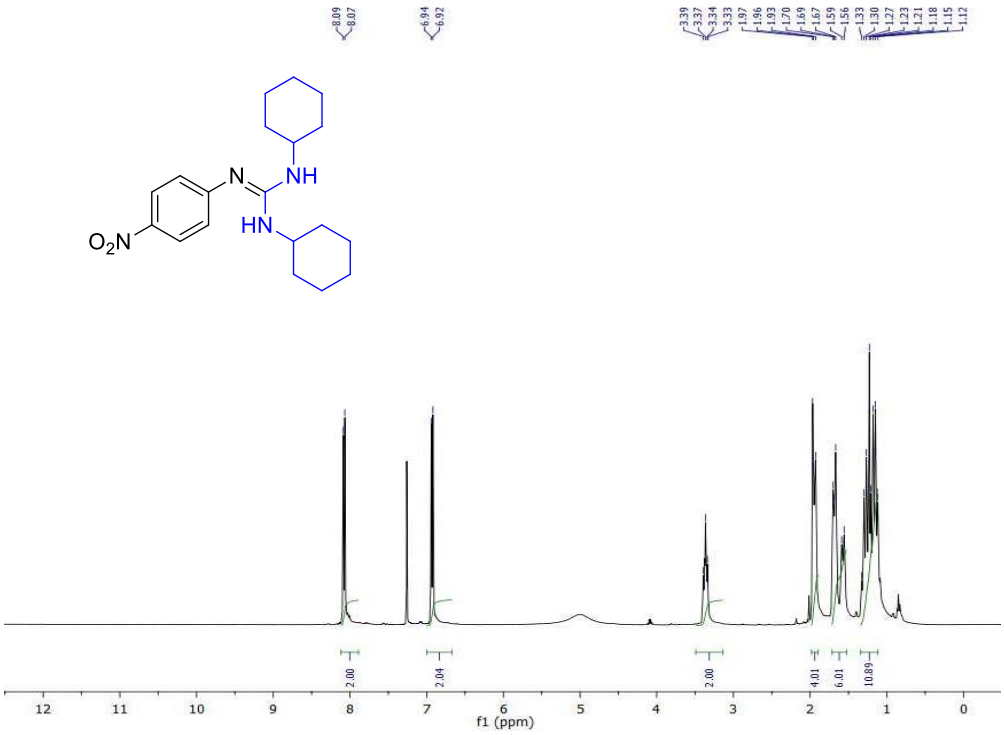

Figure A43 1,3-dicyclohexyl-2-(4-nitrophenyl)guanidine (**7b**); ^{1}H NMR 400 MHz, $CDCl_3$

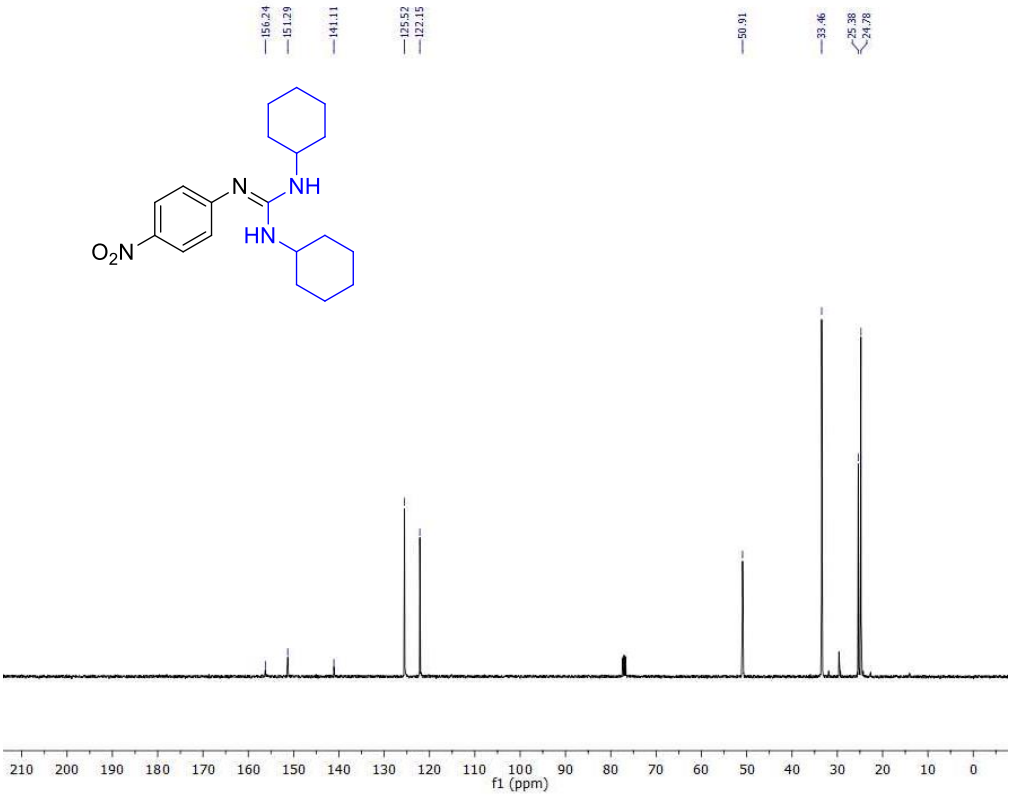

Figure A44 1,3-dicyclohexyl-2-(4-nitrophenyl)guanidine (**7b**); ^{13}C NMR 100 MHz, $CDCl_3$

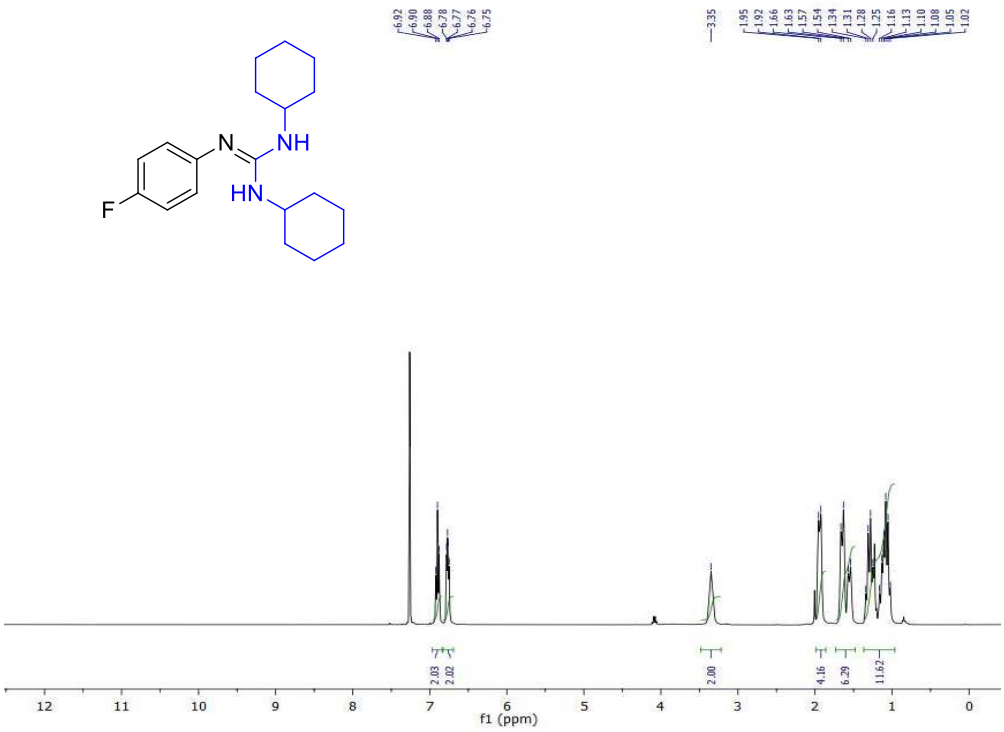

Figure A45 1,3-dicyclohexyl-2-(4-fluorophenyl)guanidine (**7c**); ^{1}H NMR 400 MHz, $CDCl_3$

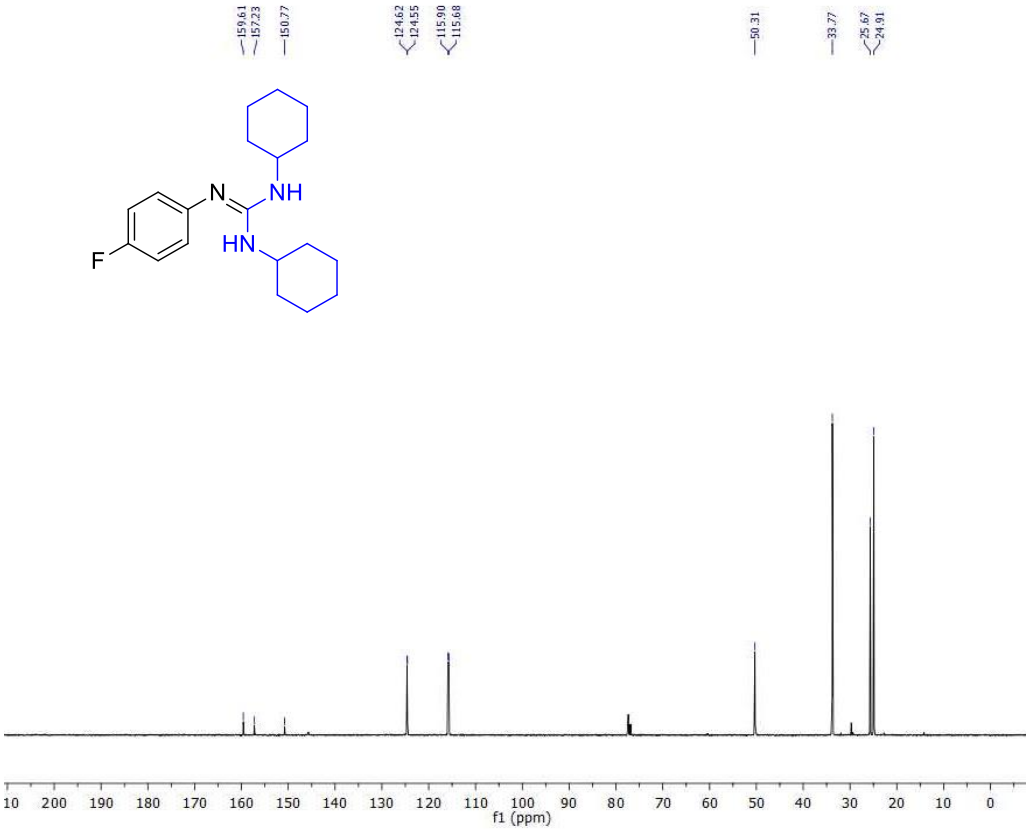

Figure A46 1,3-dicyclohexyl-2-(4-fluorophenyl)guanidine (**7c**); ^{13}C NMR 100 MHz, $CDCl_3$

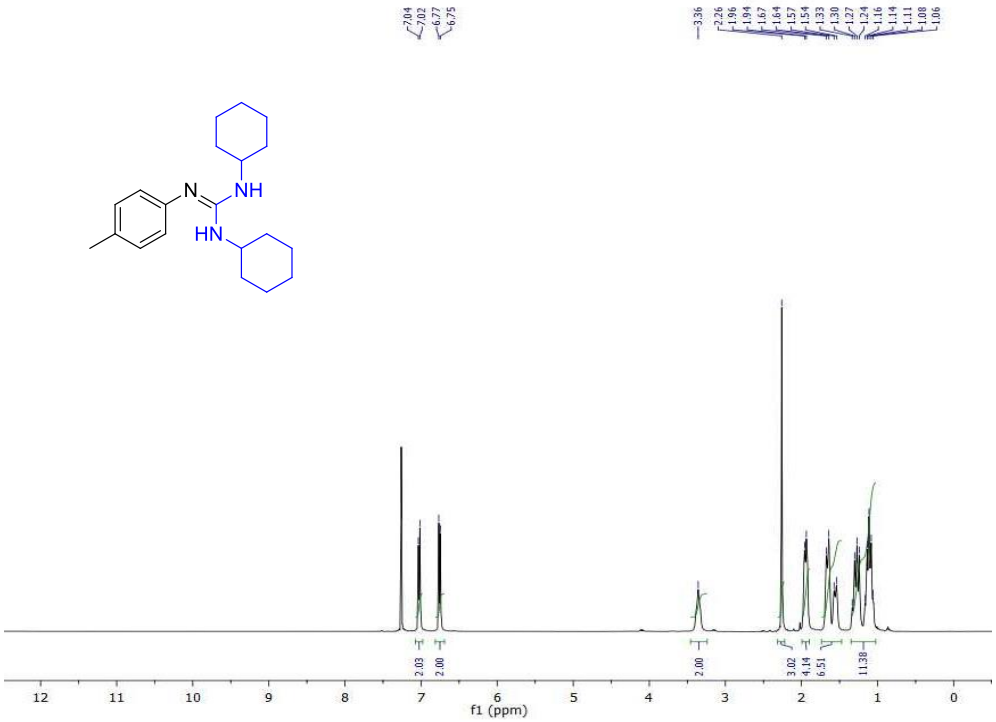

Figure A47 1,3-dicyclohexyl-2-(*p*-tolyl)guanidine (**7d**); ^{1}H NMR 400 MHz, $CDCl_3$

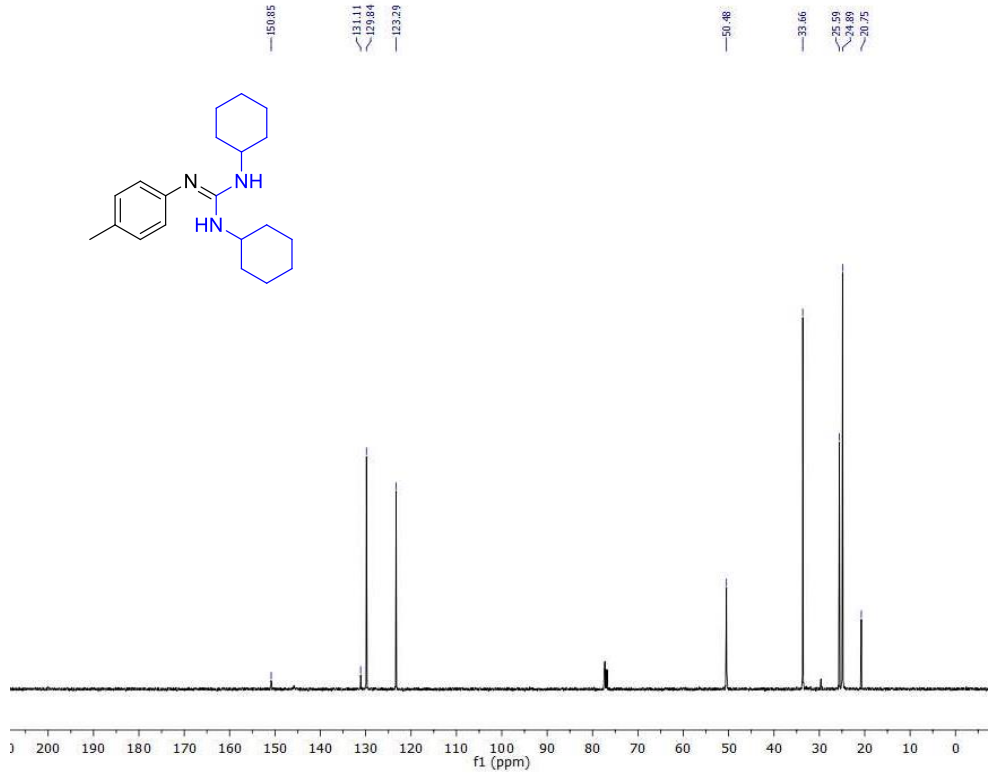

Figure A48 1,3-dicyclohexyl-2-(*p*-tolyl)guanidine (**7d**); ^{13}C NMR 100 MHz, $CDCl_3$

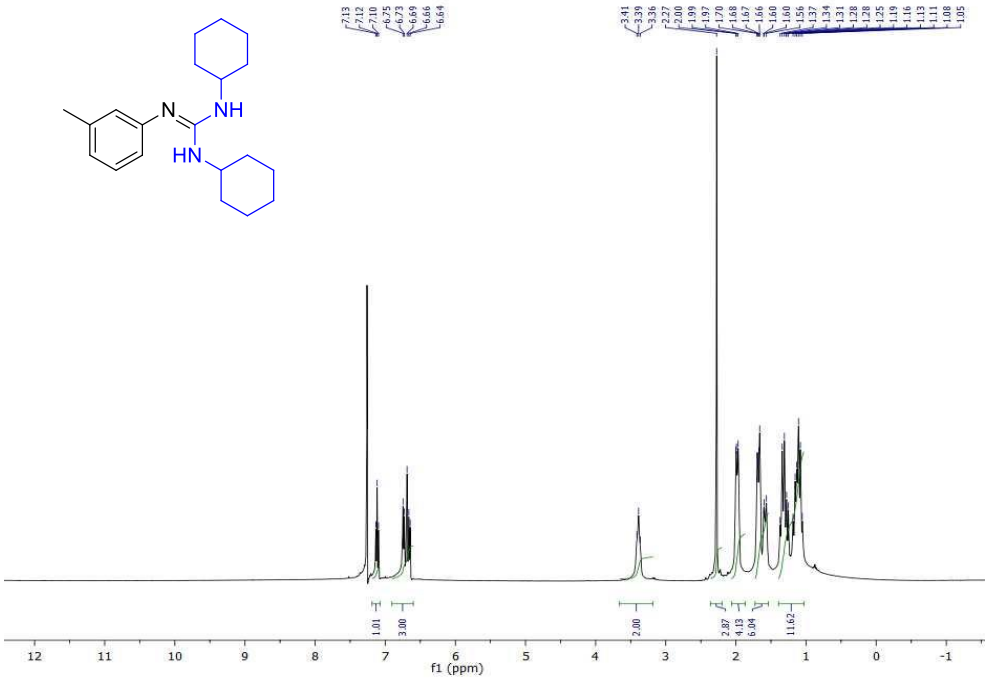

Figure A49 1,3-dicyclohexyl-2-(*m*-tolyl)guanidine (**7e**); ^{1}H NMR 400 MHz, $CDCl_3$

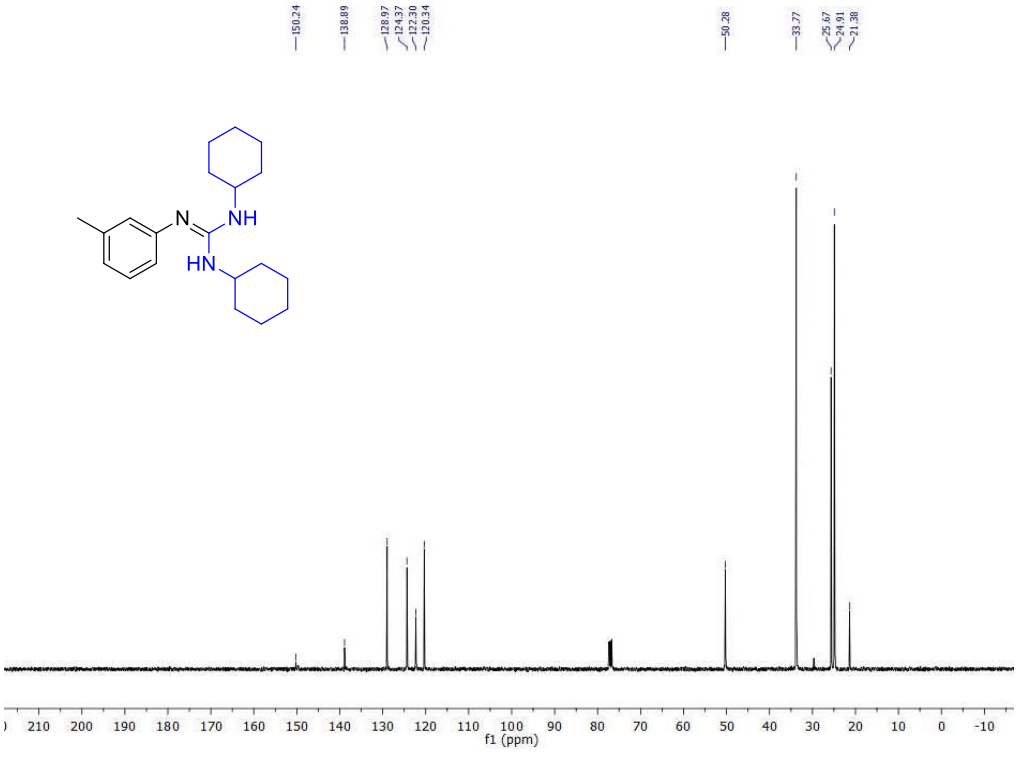

Figure A50 1,3-dicyclohexyl-2-(*m*-tolyl)guanidine (**7e**); ^{13}C NMR 100 MHz, $CDCl_3$

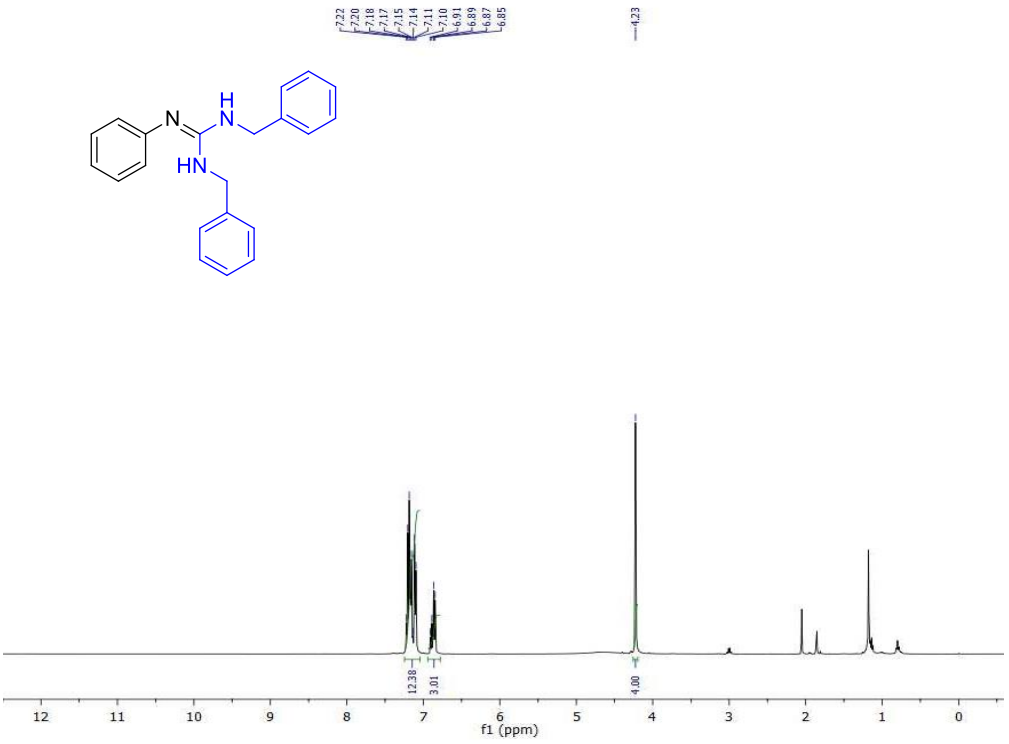

Figure A51 1,3-dibenzyl-2-phenylguanidine (**8a**); ^{1}H NMR 400 MHz, $CDCl_3$

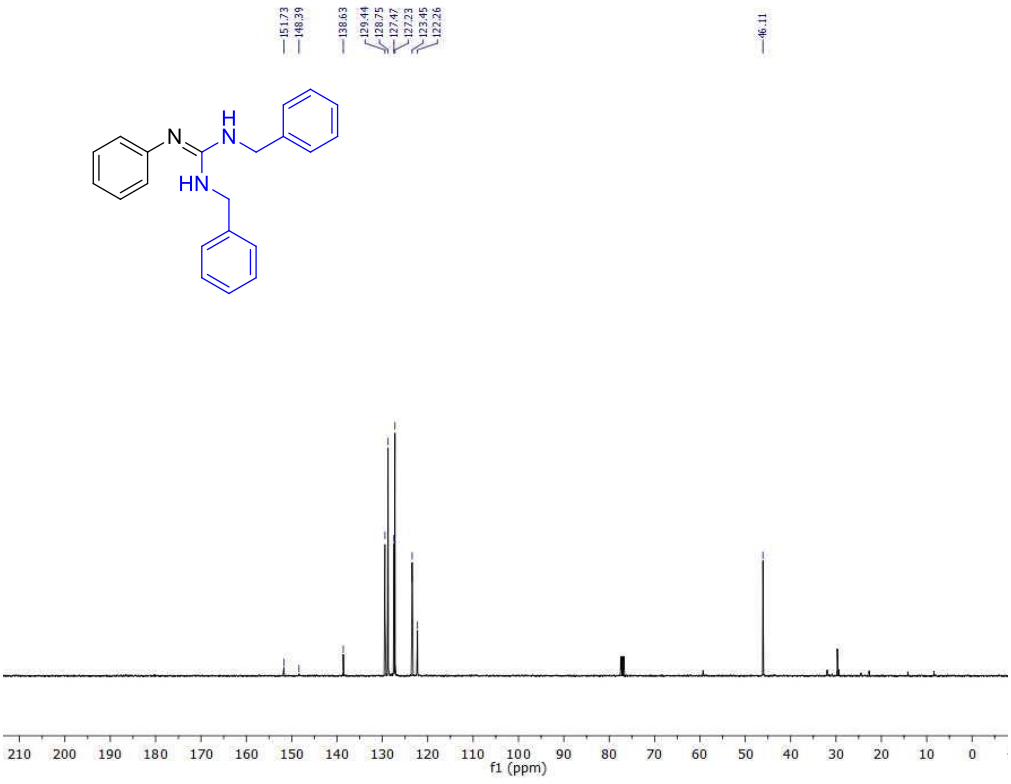

Figure A52 1,3-dibenzyl-2-phenylguanidine (**8a**); ^{13}C NMR 100 MHz, $CDCl_3$

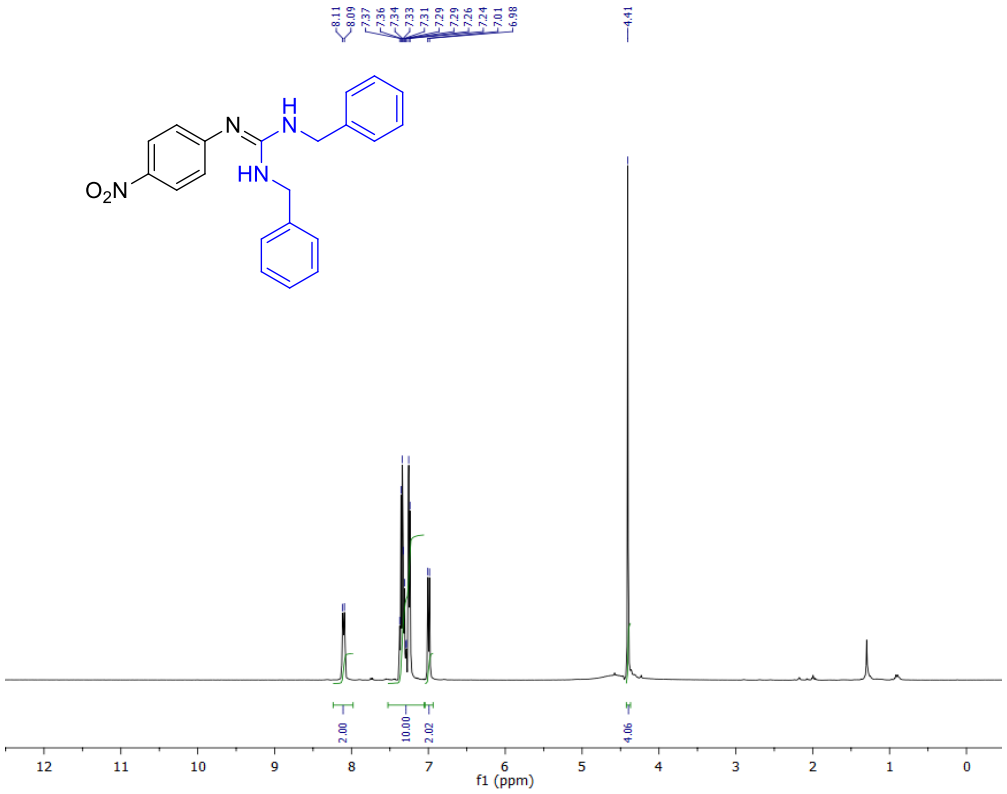

Figure A53 1,3-dibenzyl-2-(4-nitrophenyl)guanidine (**8b**); ^{1}H NMR 400 MHz, $CDCl_3$

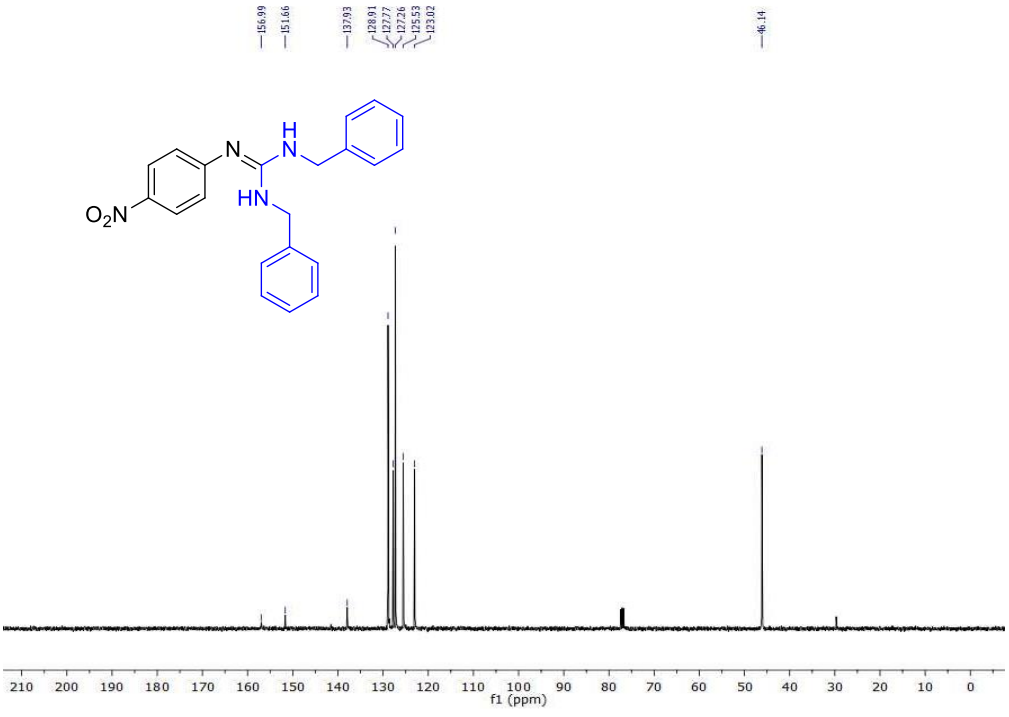

Figure A54 1,3-dibenzyl-2-(4-nitrophenyl)guanidine (**8b**); ^{13}C NMR 100 MHz, $CDCl_3$

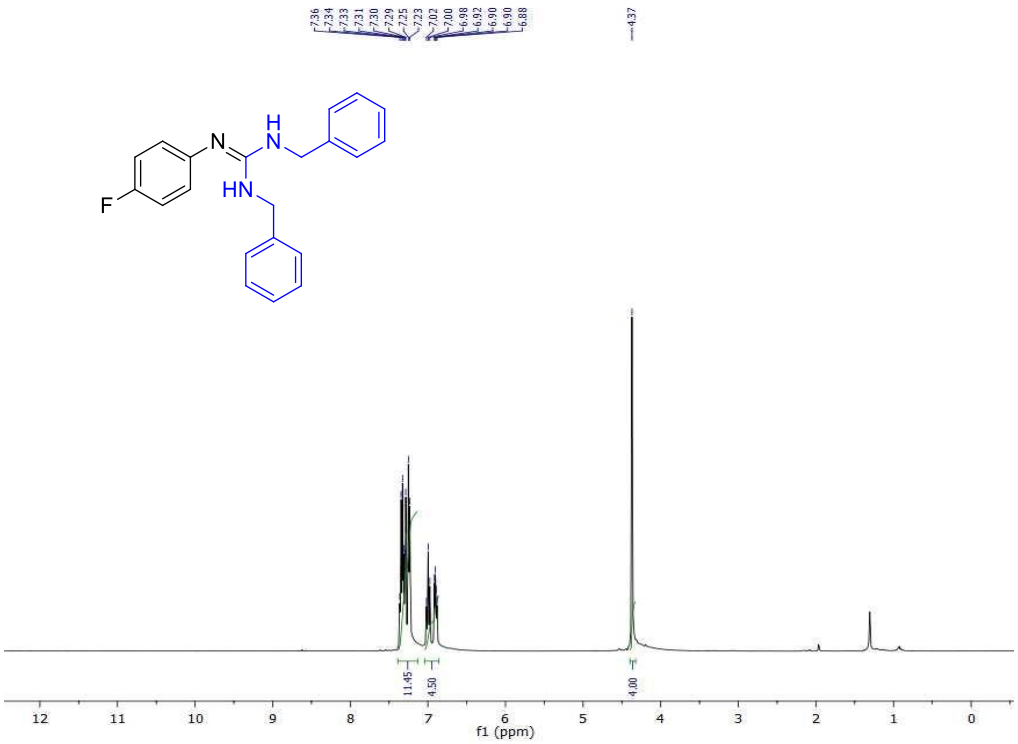

Figure A55 1,3-dibenzyl-2-(4-fluorophenyl)guanidine (**8c**); ^{1}H NMR 400 MHz, $CDCl_3$

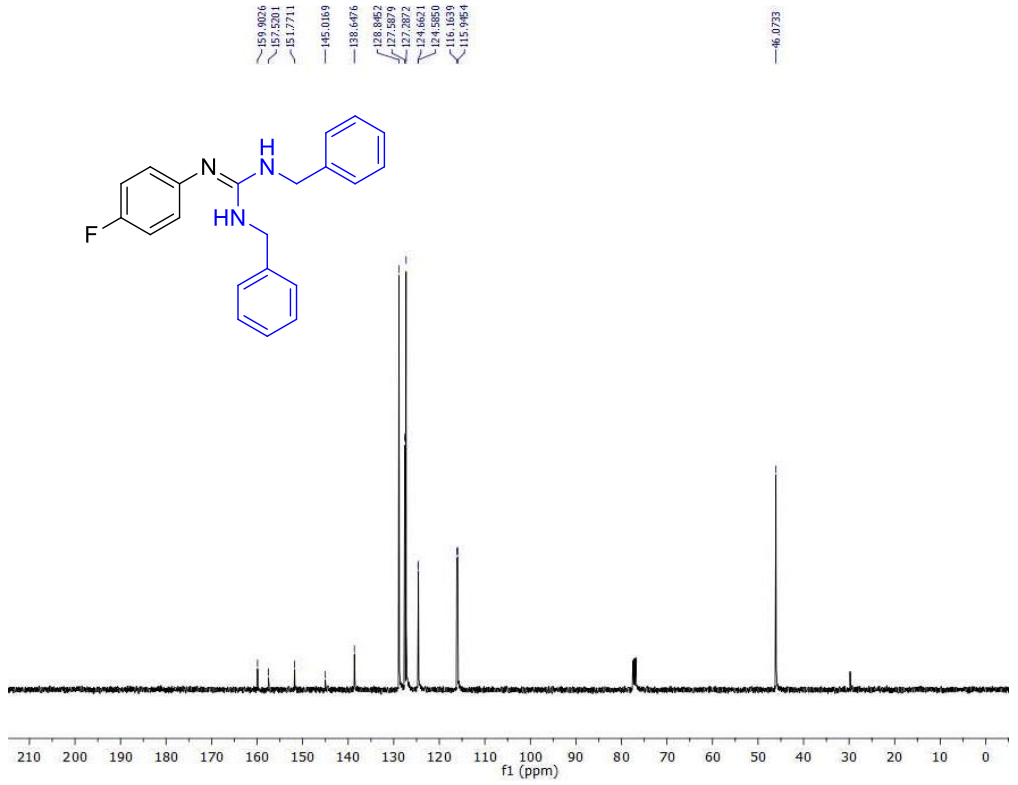

Figure A56 1,3-dibenzyl-2-(4-fluorophenyl)guanidine (**8c**); ^{13}C NMR 100 MHz, $CDCl_3$

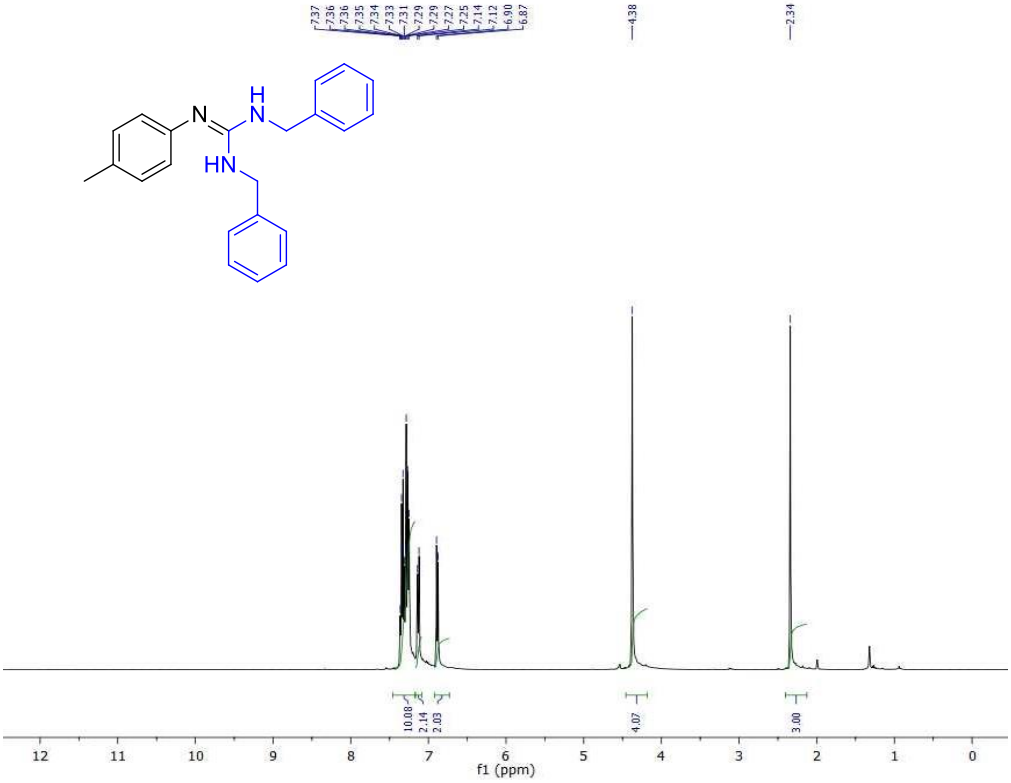

Figure A57 1,3-dibenzyl-2-(*p*-tolyl)guanidine (**8d**); ^{1}H NMR 400 MHz, $CDCl_3$

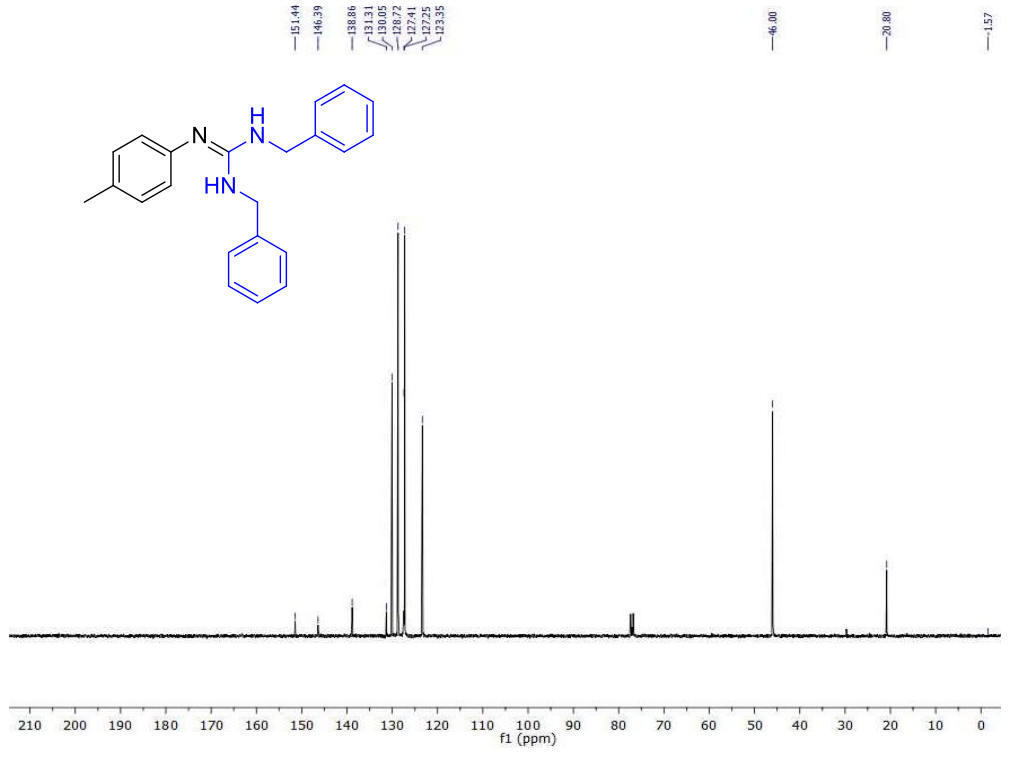

Figure A58 1,3-dibenzyl-2-(*p*-tolyl)guanidine (**8d**); ^{13}C NMR 100 MHz, $CDCl_3$

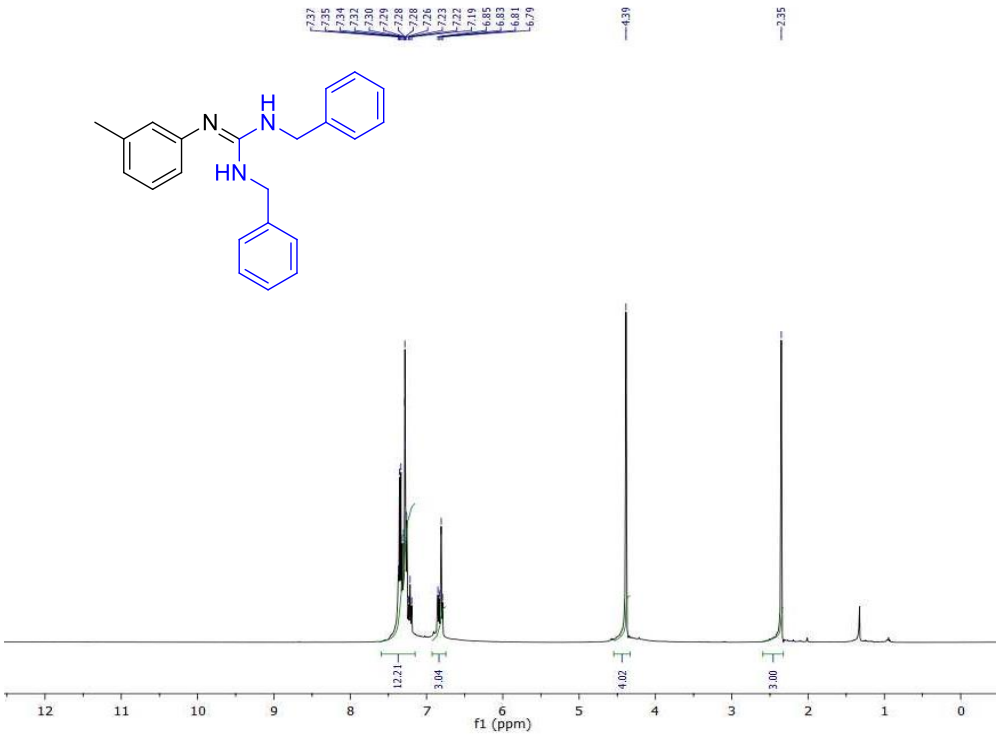

Figure A59 1,3-dibenzyl-2-(*m*-tolyl)guanidine (**8e**); ^{1}H NMR 400 MHz, $CDCl_3$

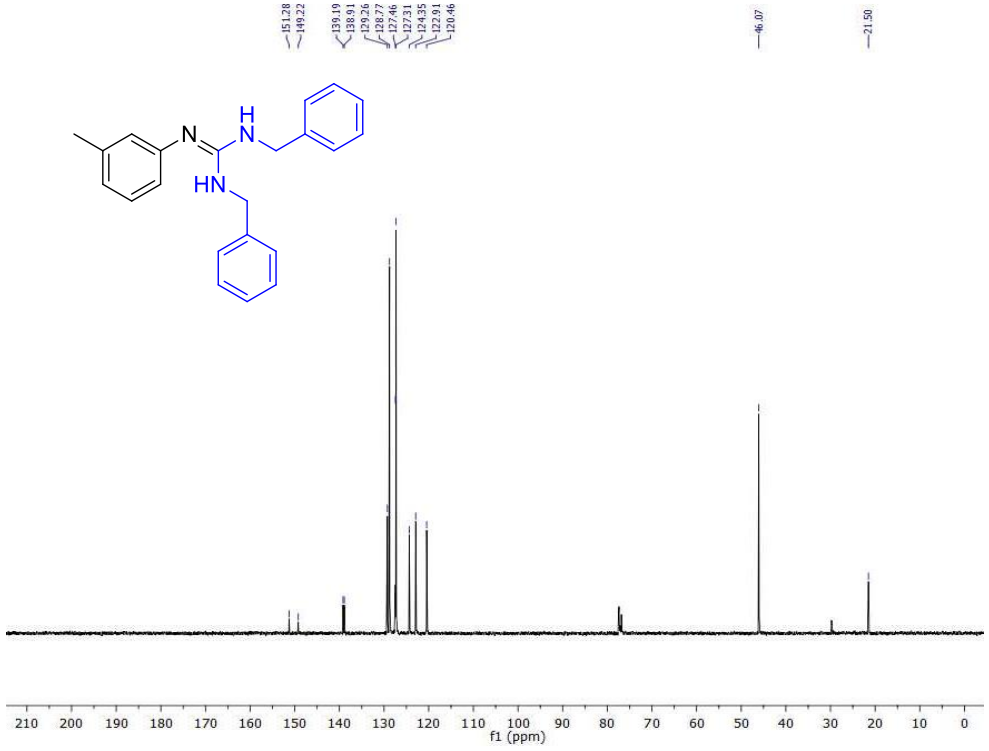

Figure A60 1,3-dibenzyl-2-(*m*-tolyl)guanidine (**8e**); ^{13}C NMR 100 MHz, $CDCl_3$

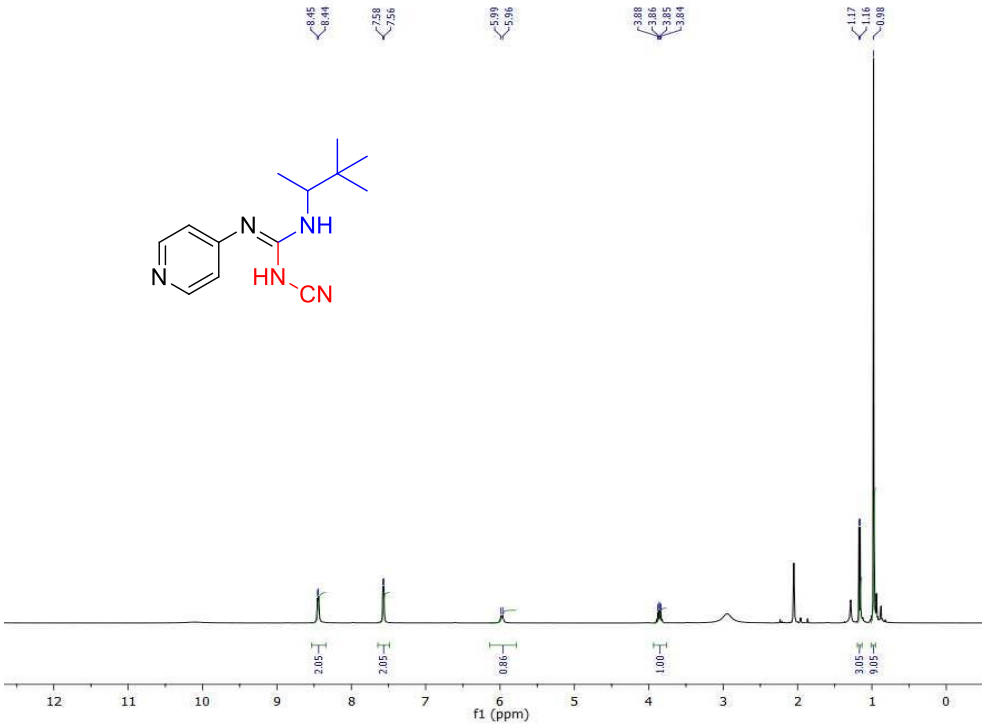

Figure A61 Pinacidil drug (**10a**); ^{1}H NMR 400 MHz, $CDCl_3$

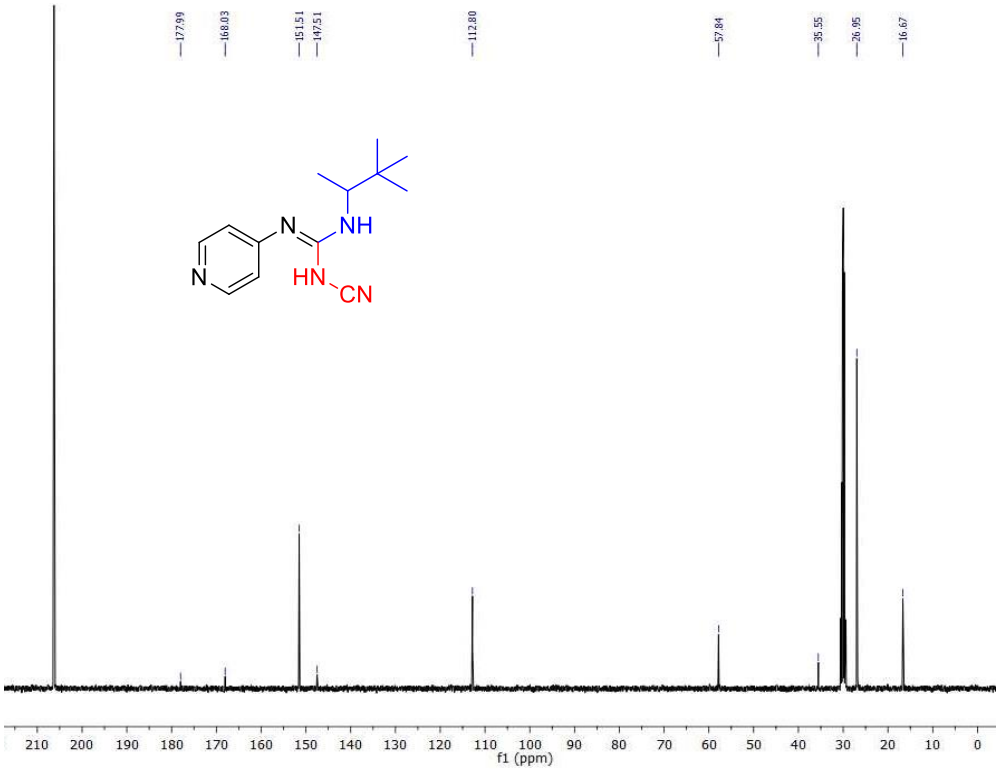

Figure A62 Pinacidil drug (**10a**); ^{13}C NMR 100 MHz, $CDCl_3$

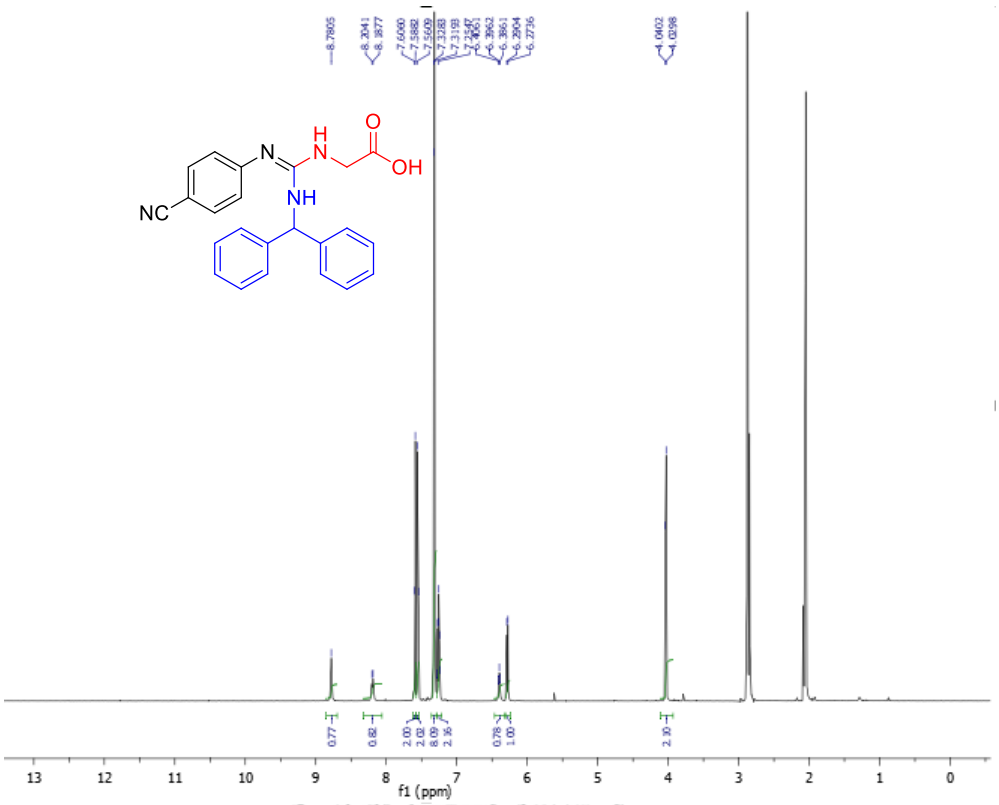

Figure A63 NC-174 (**11a**); ^{1}H NMR 500 MHz, Acetone-d_6

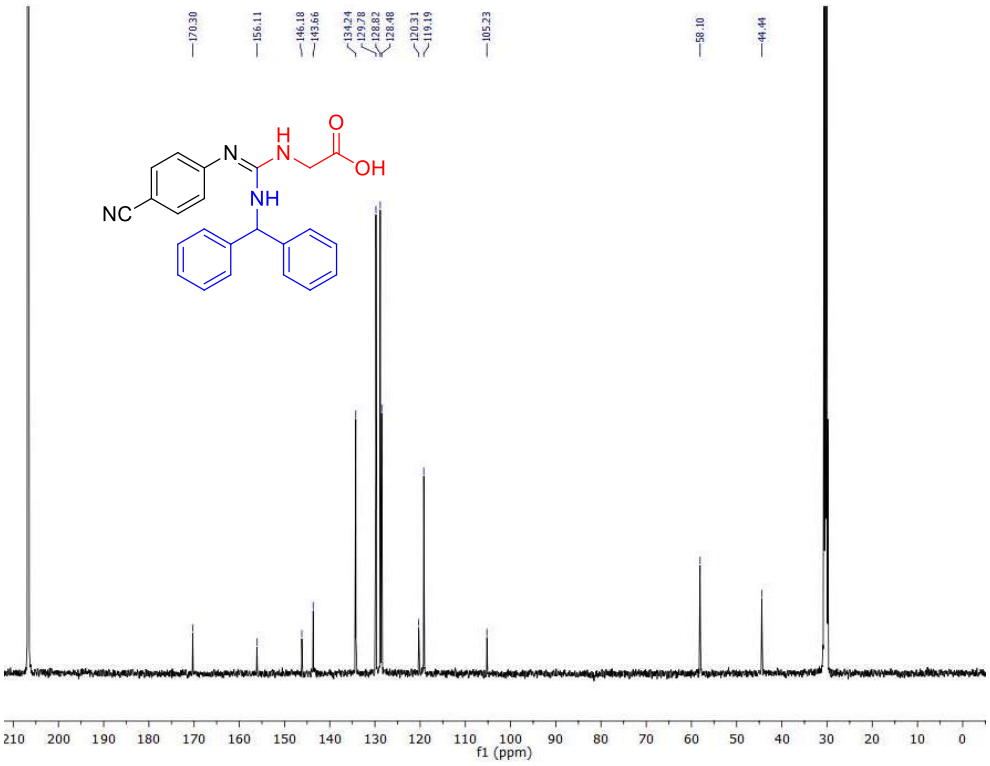

Figure A64 NC-174 (**11a**); ^{13}C NMR 126 MHz, Acetone-d_6

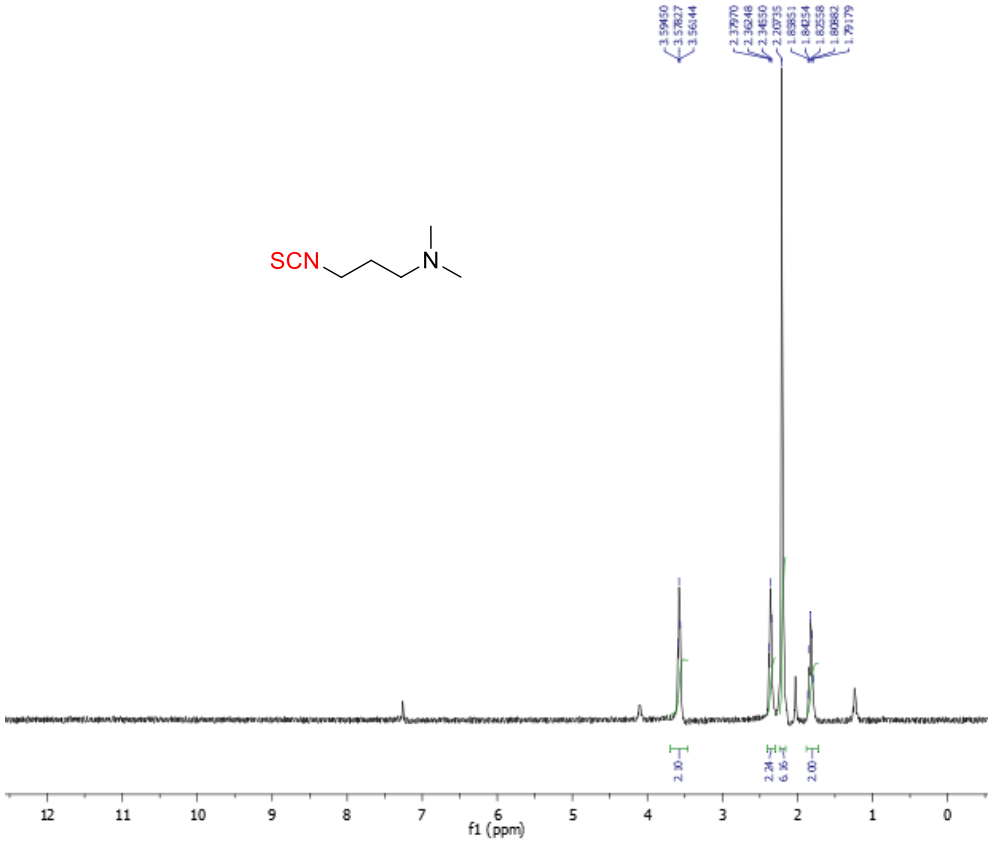

Figure A65 *N,N*-dimethylamine propyl isothiocyanate (**13**); ^{1}H NMR 400 MHz, $CDCl_3$

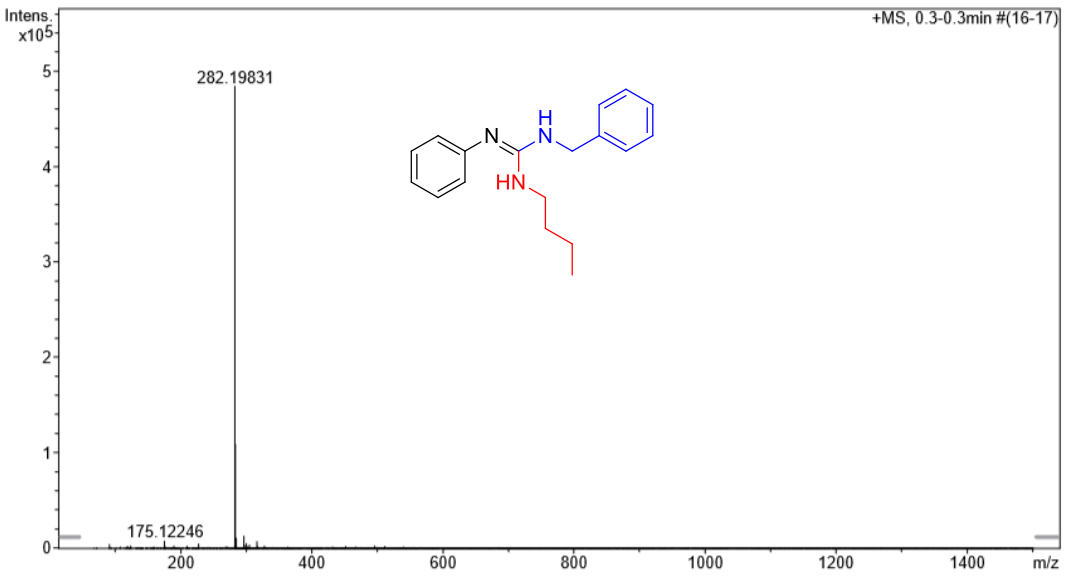

Figure A66 HRMS of 1-benzyl-3-butyl-2-phenylguanidine (**5a**)

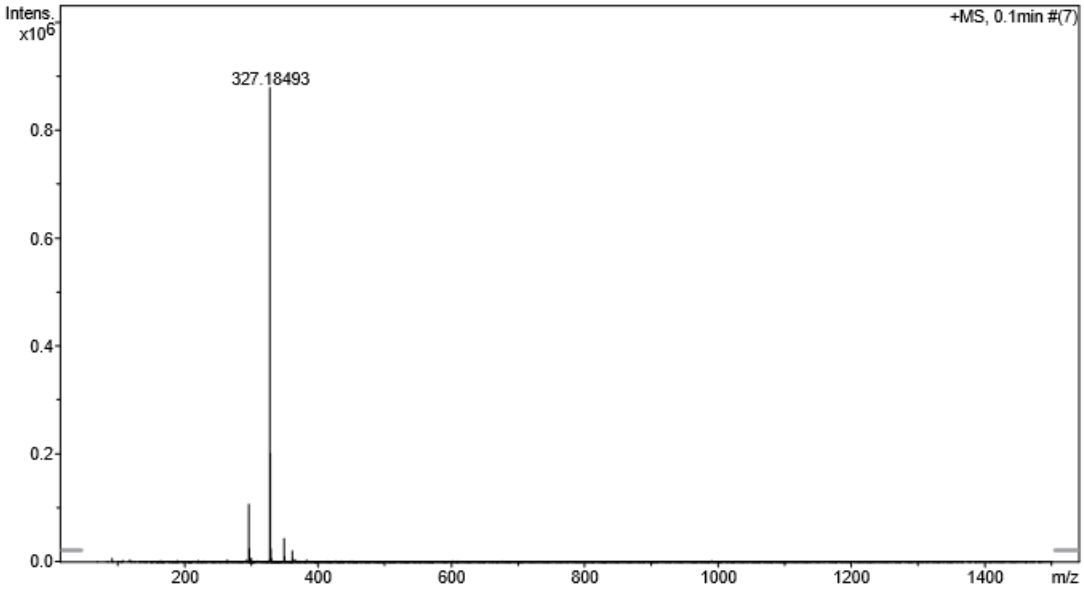

Figure A67 HRMS of 1-benzyl-3-butyl-2-(4-nitrophenyl)guanidine (**5b**)

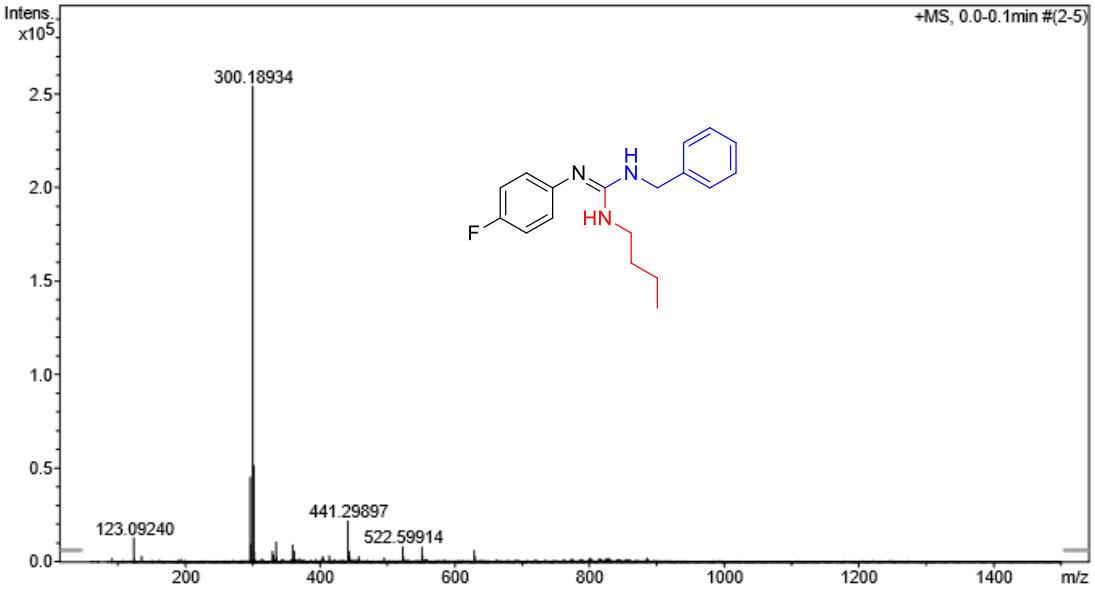

Figure A68 HRMS of 1-benzyl-3-butyl-2-(4-fluorophenyl)guanidine (**5c**)

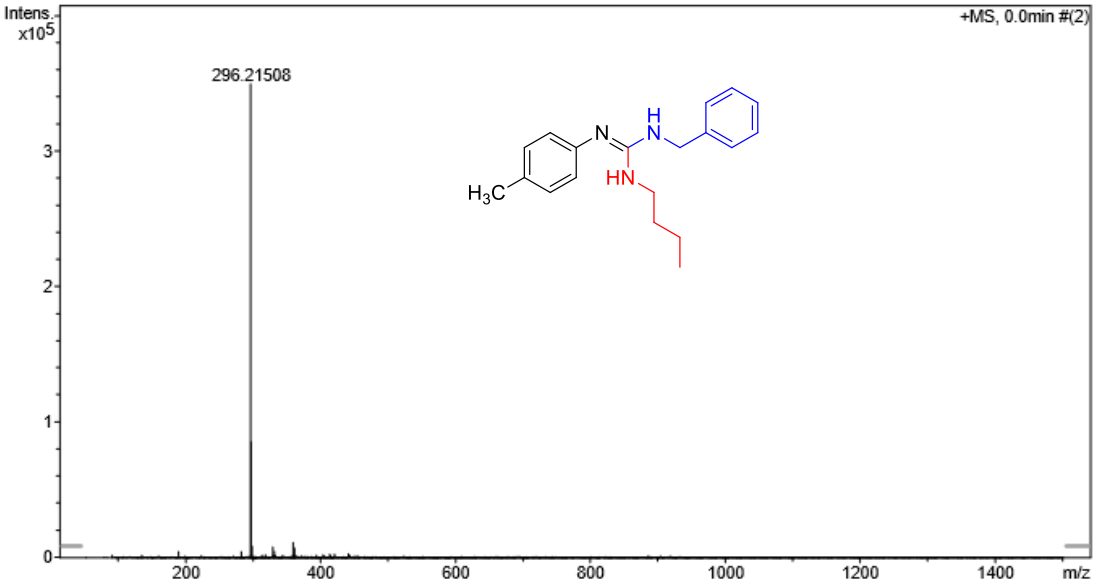

Figure A69 HRMS of 1-benzyl-3-butyl-2-(*p*-tolyl)guanidine (**5d**)

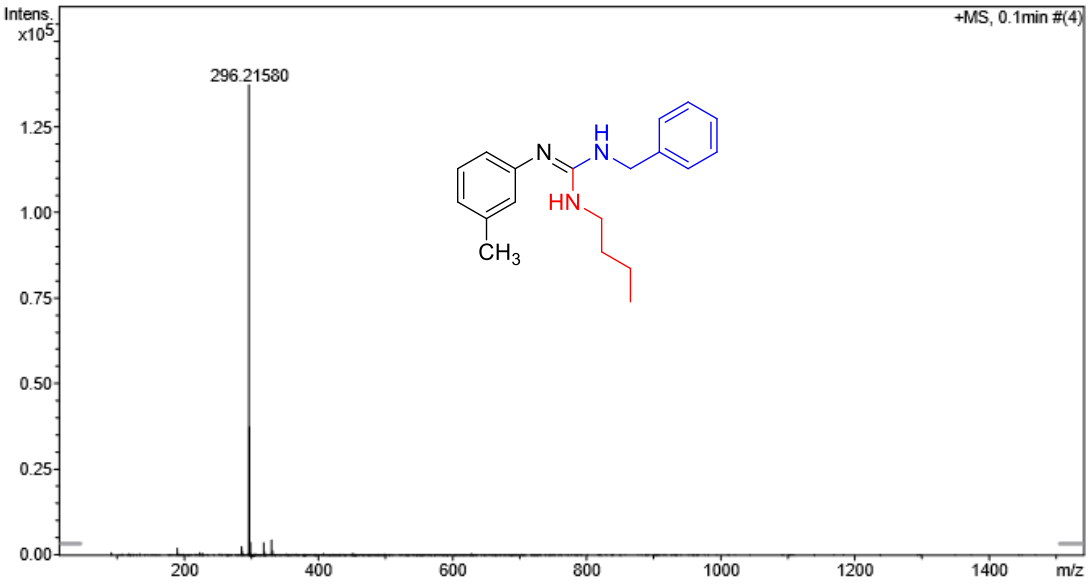

Figure A 70 HRMS of 1-benzyl-3-butyl-2-(*m*-tolyl)guanidine (**5e**)

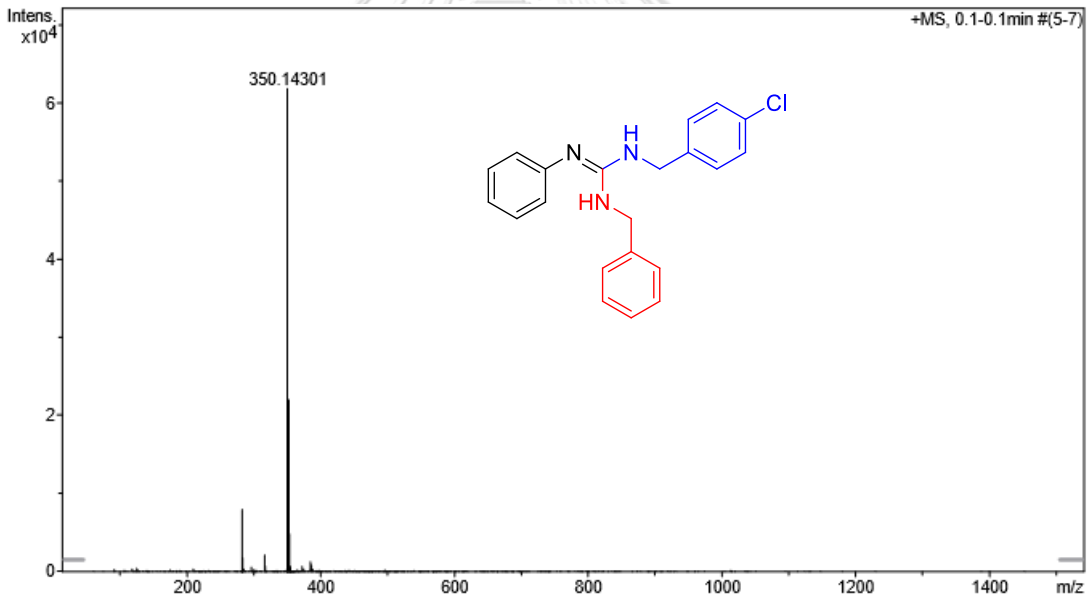

Figure A71 HRMS of 1-benzyl-3-(4-chlorobenzyl)-2-phenylguanidine (**5f**)

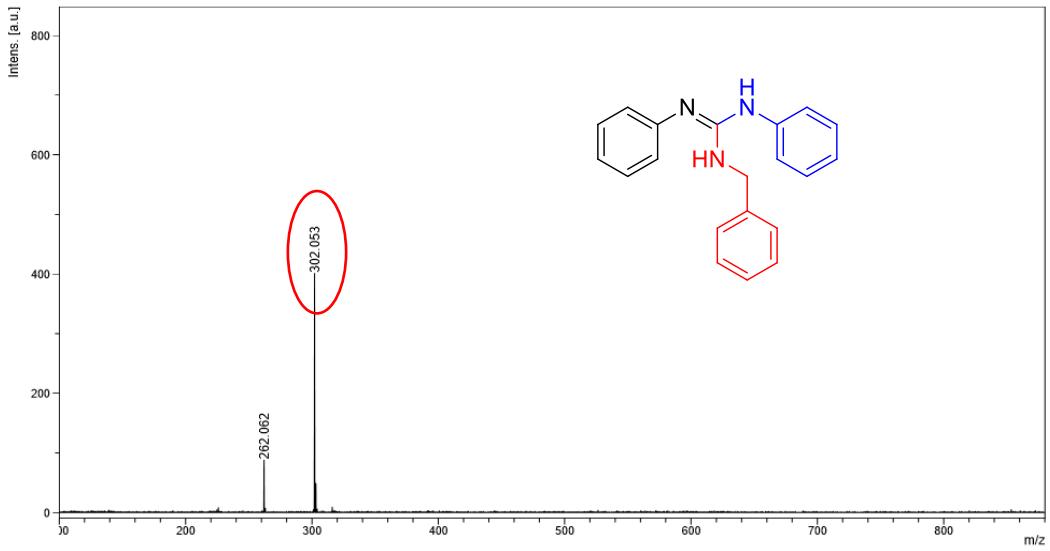

Figure A72 MALDI-TOF MS of 1-benzyl-2,3-diphenylguanidine (**5g**)

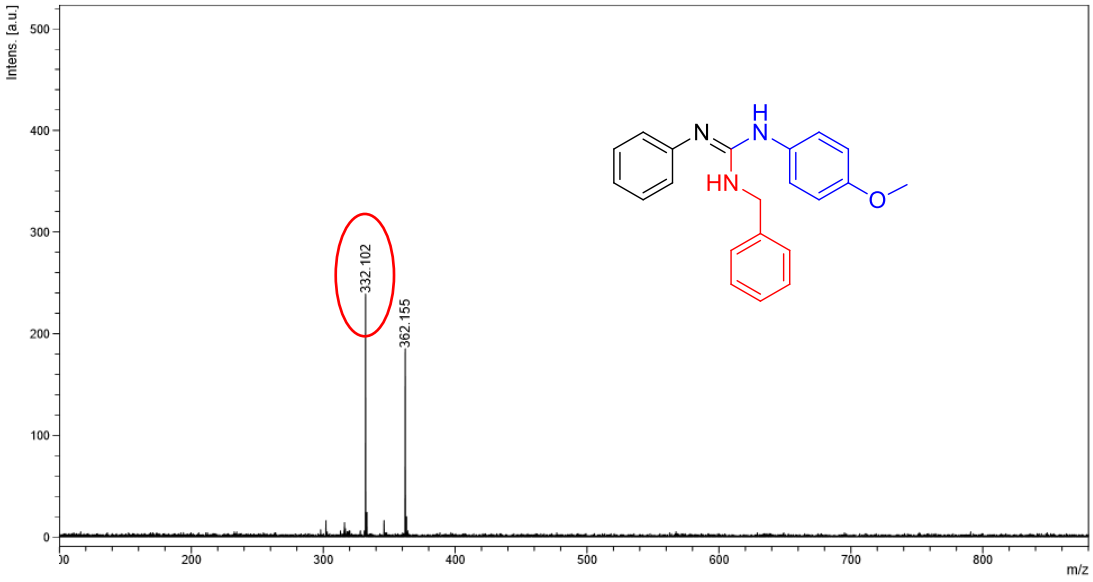

Figure A73 MALDI-TOF MS of 1-benzyl-3-(4-methoxyphenyl)-2-phenylguanidine (**5h**)

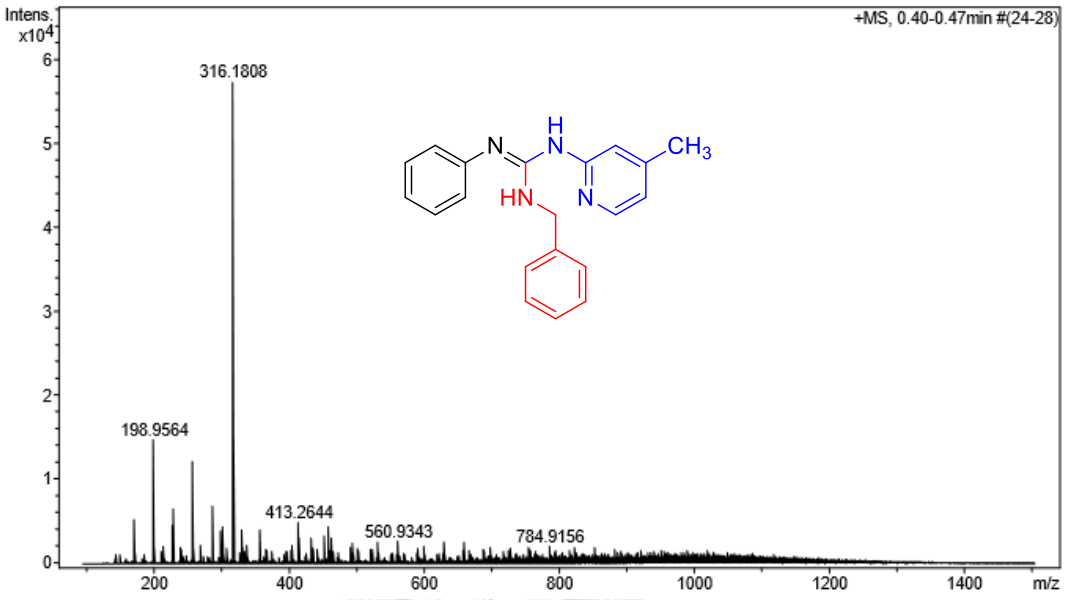

Figure A74 HRMS of 1-benzyl-3-(4-methylpyridin-2-yl)-2-phenylguanidine (**5i**)

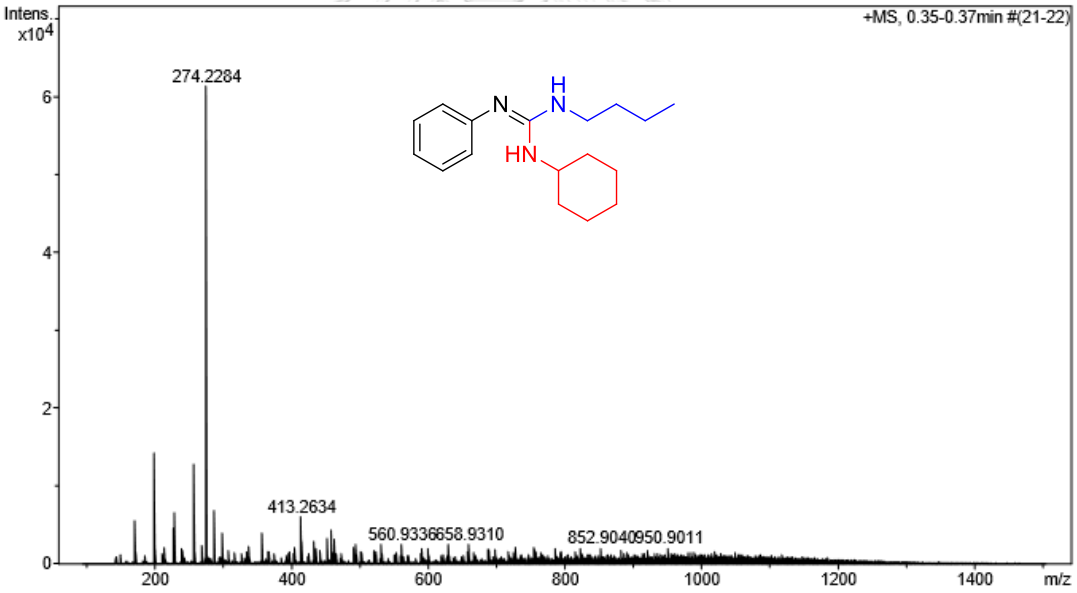

Figure A75 HRMS of 1-butyl-3-cyclohexyl-2-phenylguanidine (**5j**)

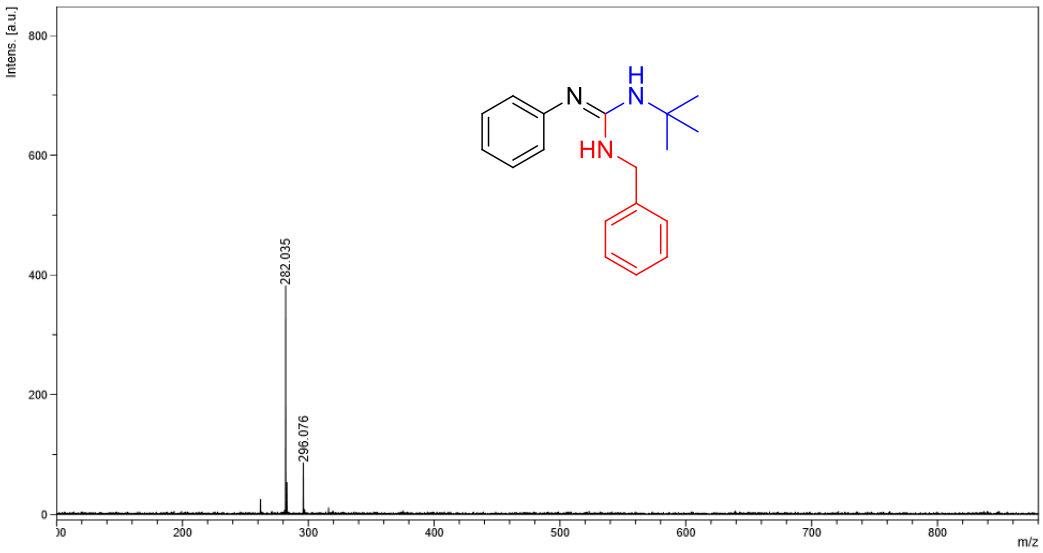

Figure A76 MULDI-TOF MS of 1-benzyl-3-(*tert*-butyl)-2-phenylguanidine (**5k**)

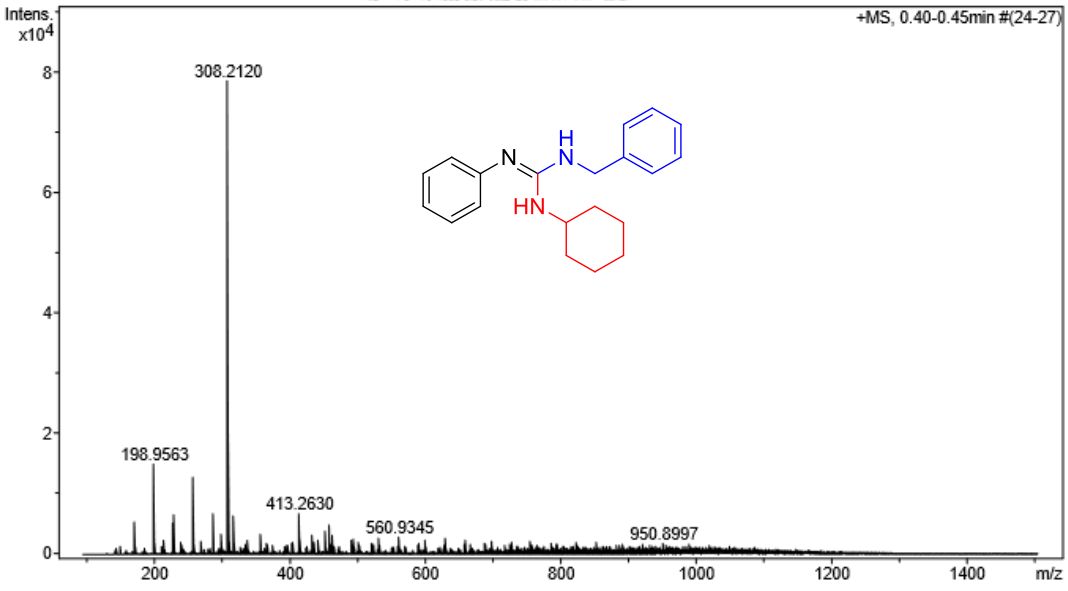

Figure A77 HRMS of 1-benzyl-3-cyclohexyl-2-phenylguanidine (**5l**)

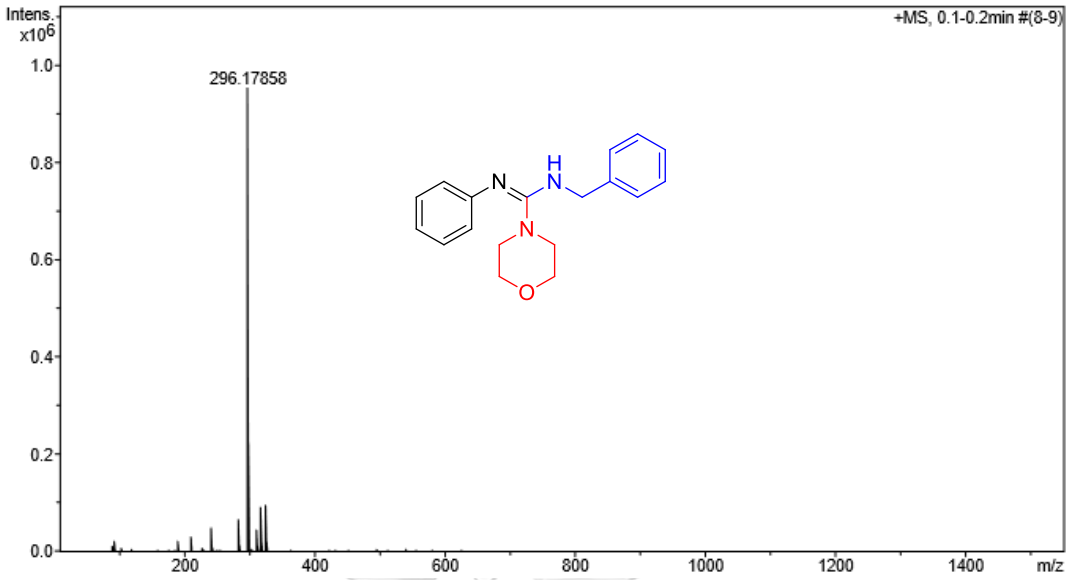

Figure A78 HRMS of *N*-benzyl-*N'*-phenylmorpholine-4-carboximidamide (**5m**)

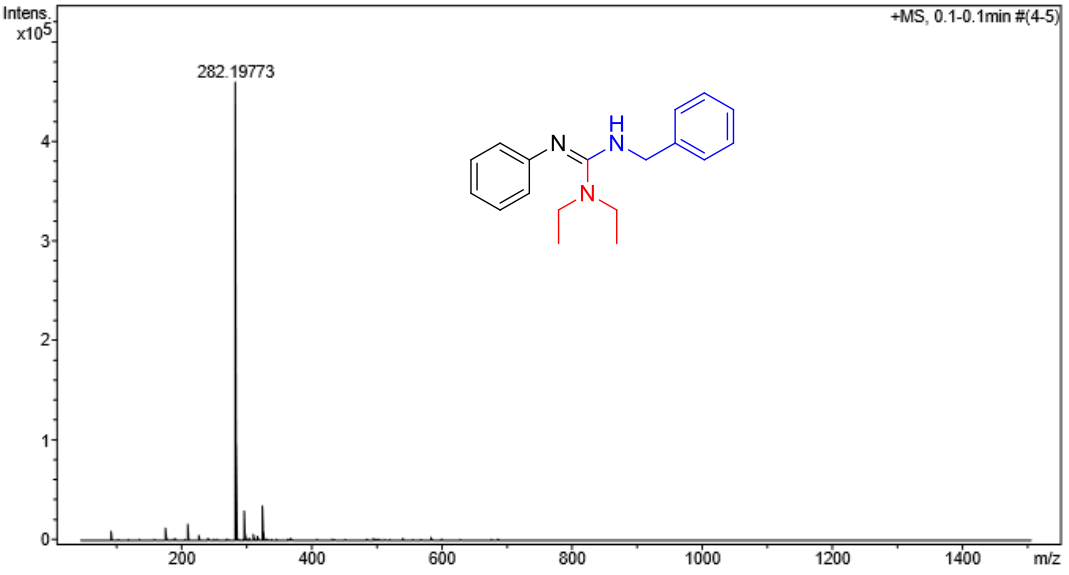

Figure A79 HRMS of 3-benzyl-1,1-diethyl-2-phenylguanidine (**5n**)

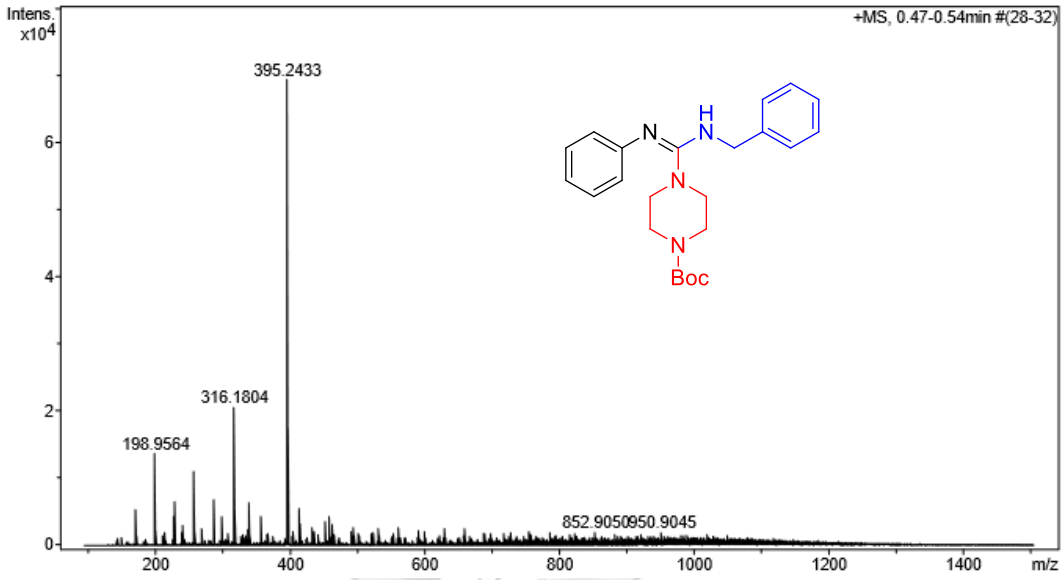

Figure A80 HRMS of *tert*-butyl-4-(*N*-benzyl-*N'*-phenylcarbamimidoyl)piperazine-1-carboxylate (**5o**)

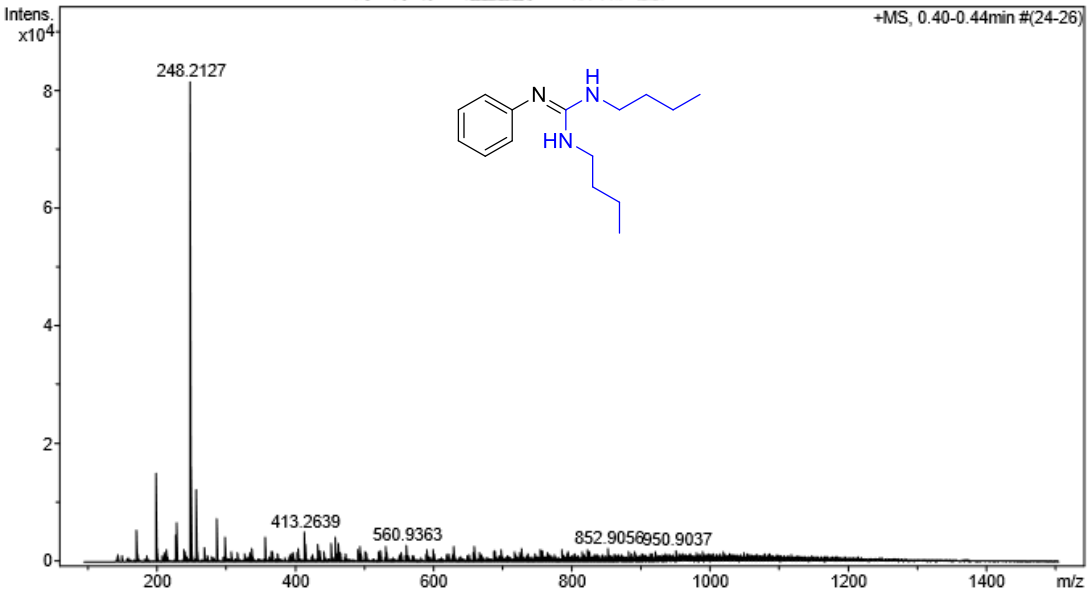

Figure A81 HRMS of 1,3-dibutyl-2-phenylguanidine (**6a**)

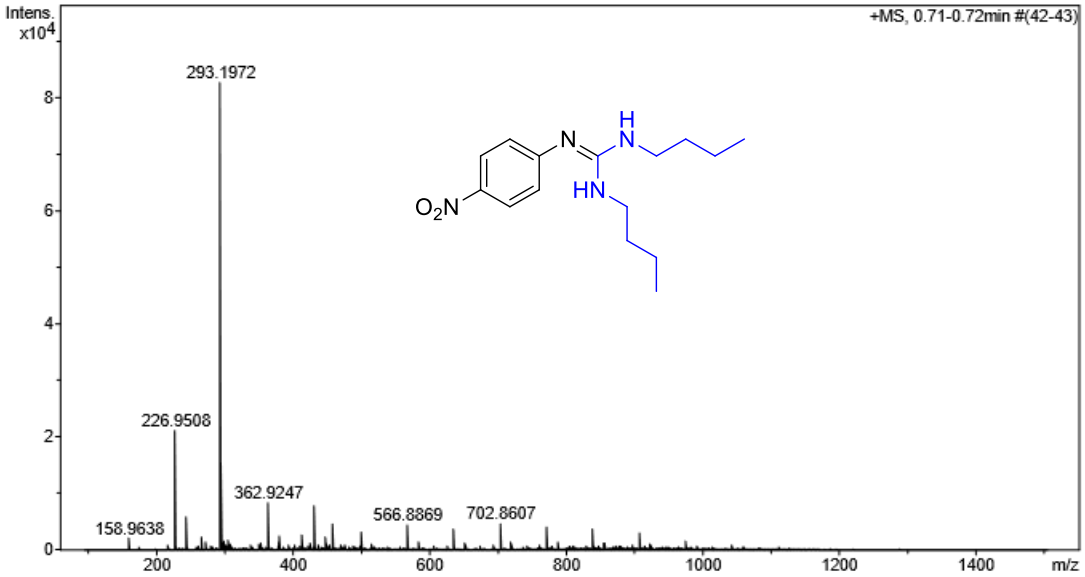

Figure A82 HRMS of 1,3-dibutyl-2-(4-nitrophenyl)guanidine (**6b**)

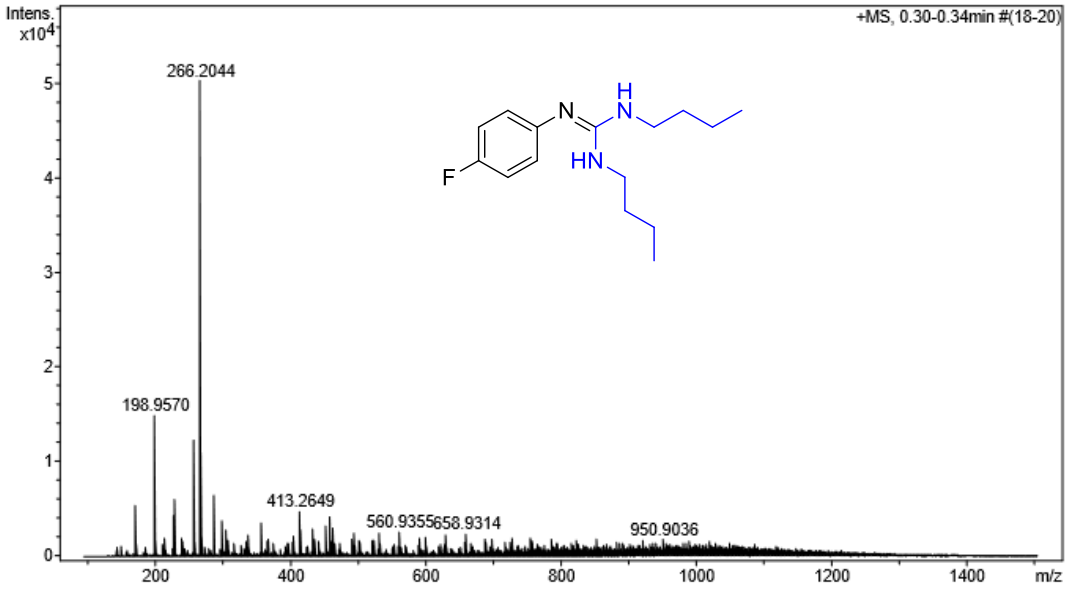

Figure A83 HRMS of 1,3-dibutyl-2-(4-fluorophenyl)guanidine (**6c**)

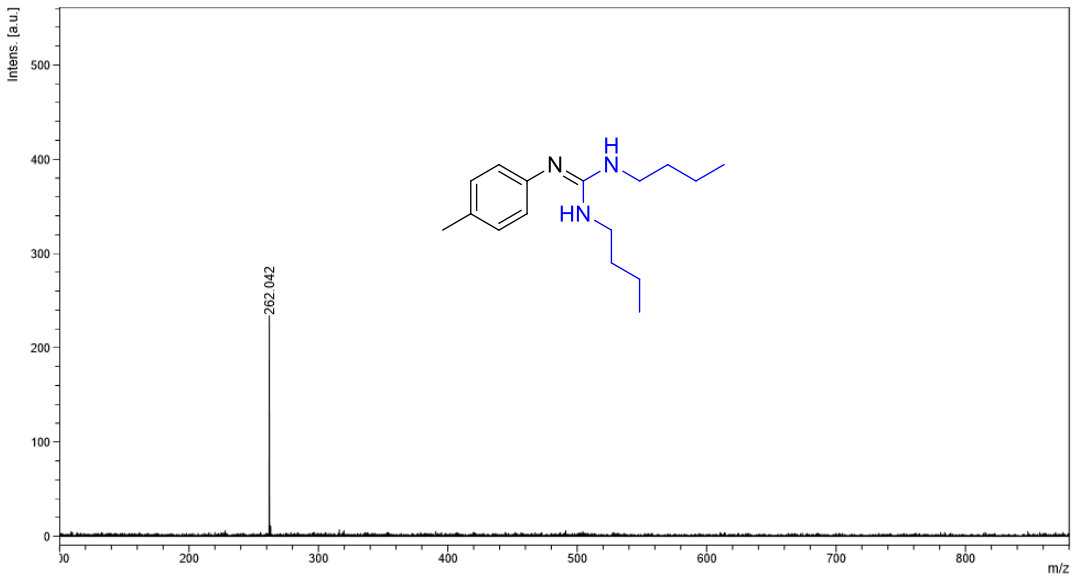

Figure A84 HRMS of 1,3-dibutyl-2-(*p*-tolyl)guanidine (**6d**)

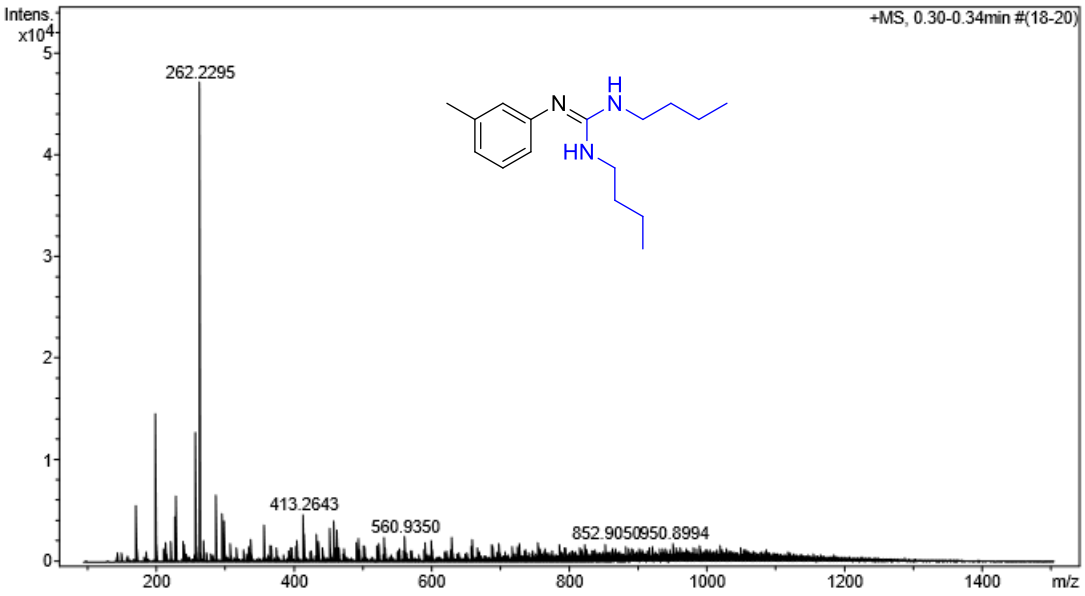

Figure A85 HRMS of 1,3-dibutyl-2-(*m*-tolyl)guanidine (**6e**)

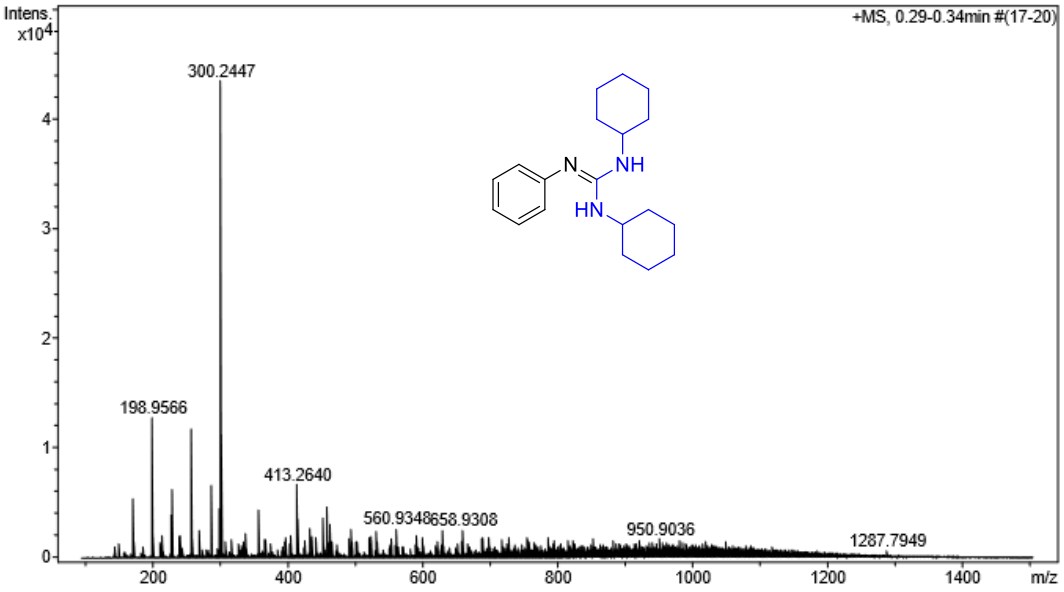

Figure A86 HRMS of 1,3-dicyclohexyl-2-phenylguanidine (**7a**)

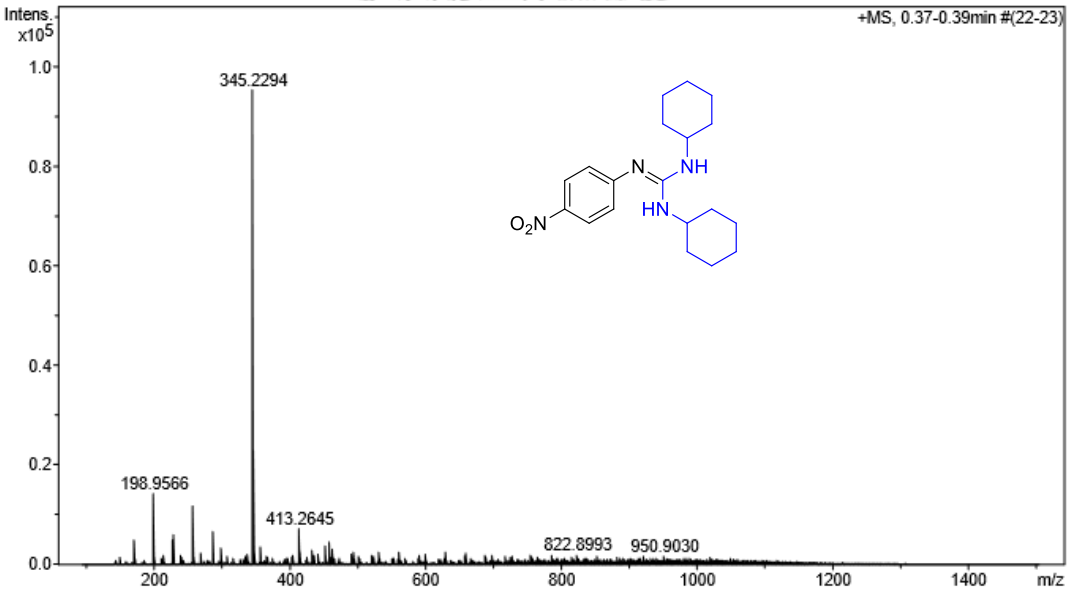

Figure A87 HRMS of 1,3-dicyclohexyl-2-(4-nitrophenyl)guanidine (**7b**)

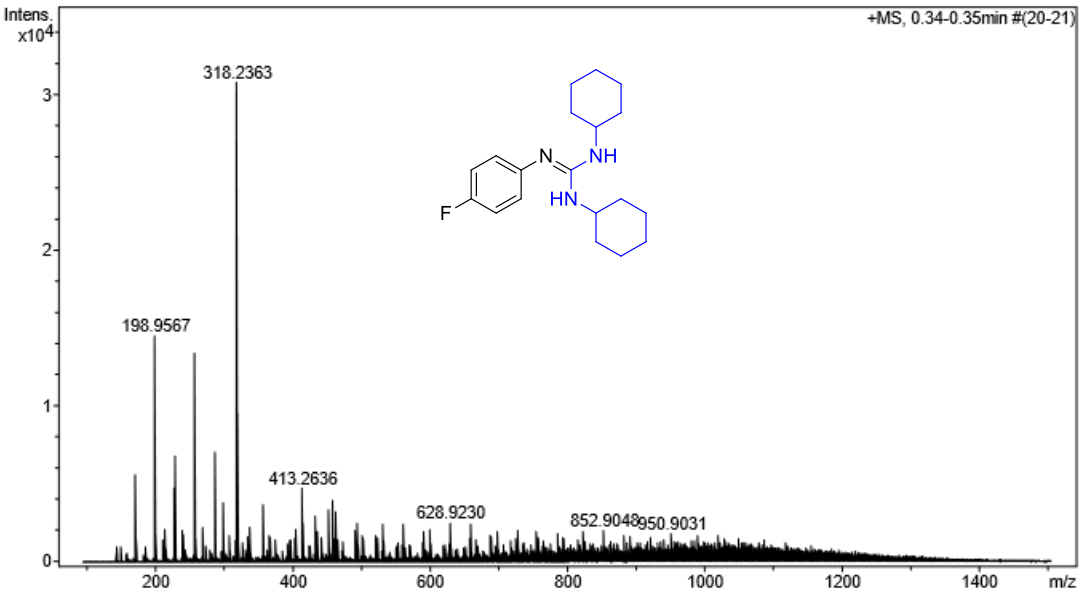

Figure A88 HRMS of 1,3-dicyclohexyl-2-(4-fluorophenyl)guanidine (**7c**)

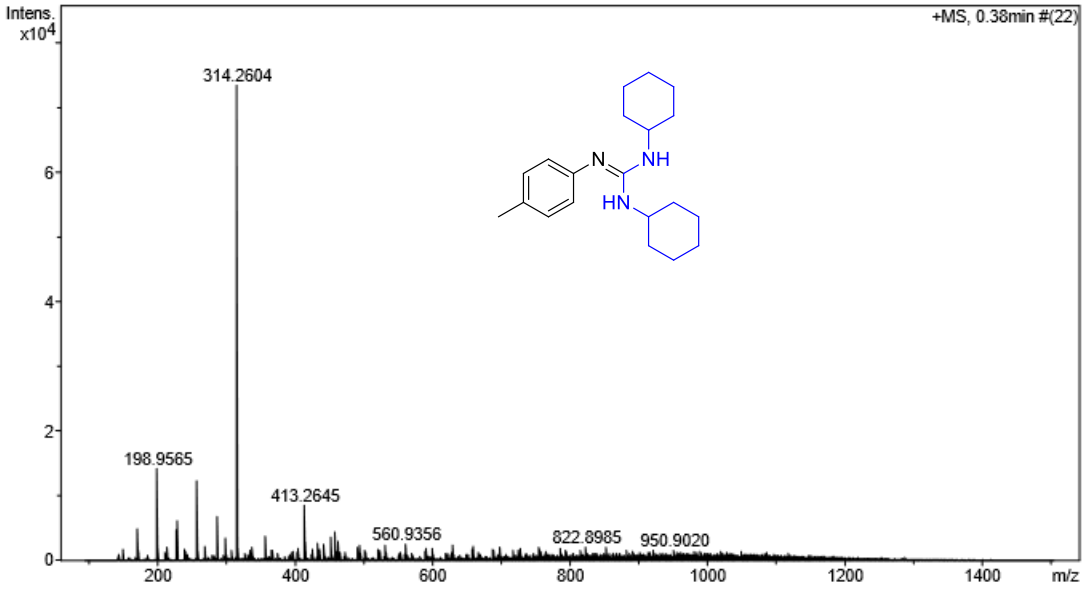

Figure A89 HRMS of 1,3-dicyclohexyl-2-(*p*-tolyl)guanidine (**7d**)

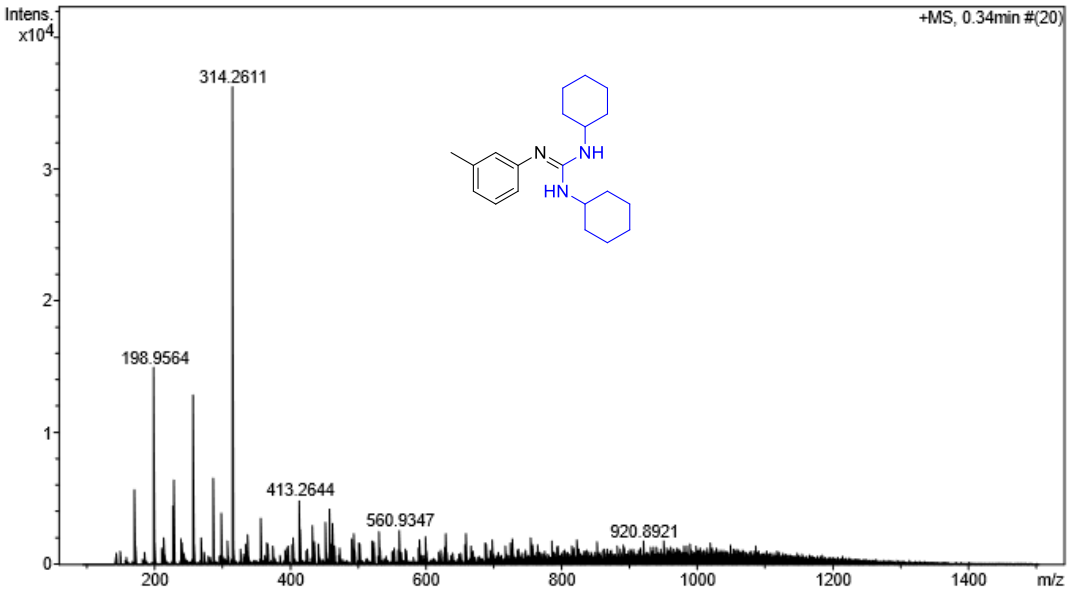

Figure A90 HRMS of 1,3-dicyclohexyl-2-(*m*-tolyl)guanidine (**7e**)

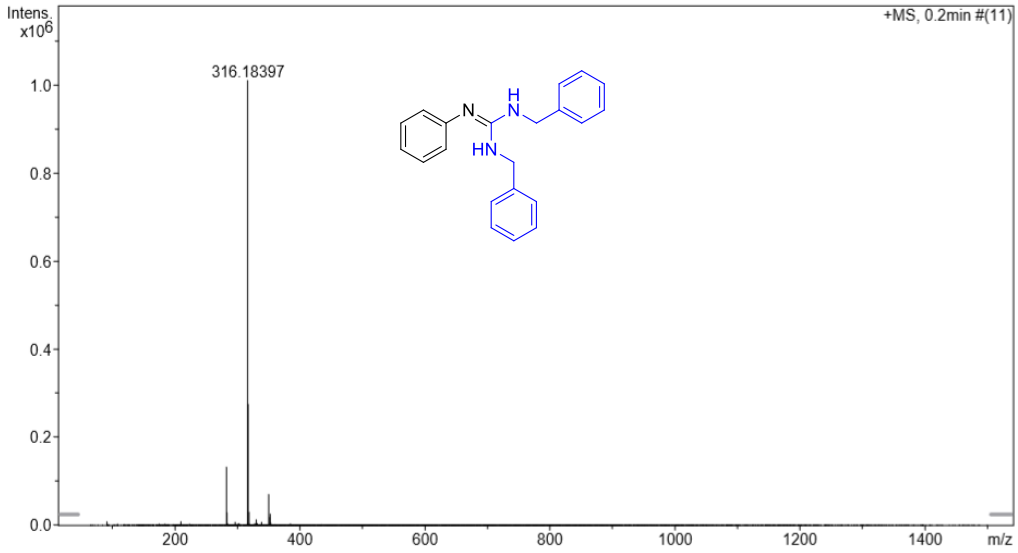

Figure A91 HRMS of 1,3-dibenzyl-2-phenylguanidine (**8a**)

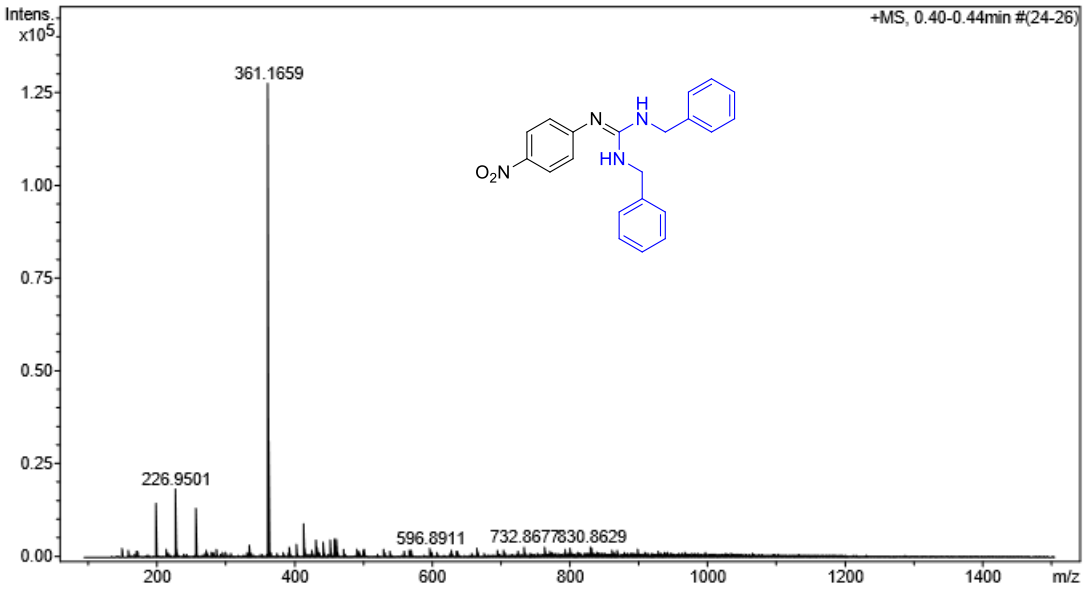

Figure A92 HRMS of 1,3-dibenzyl-2-(4-nitrophenyl)guanidine (**8b**)

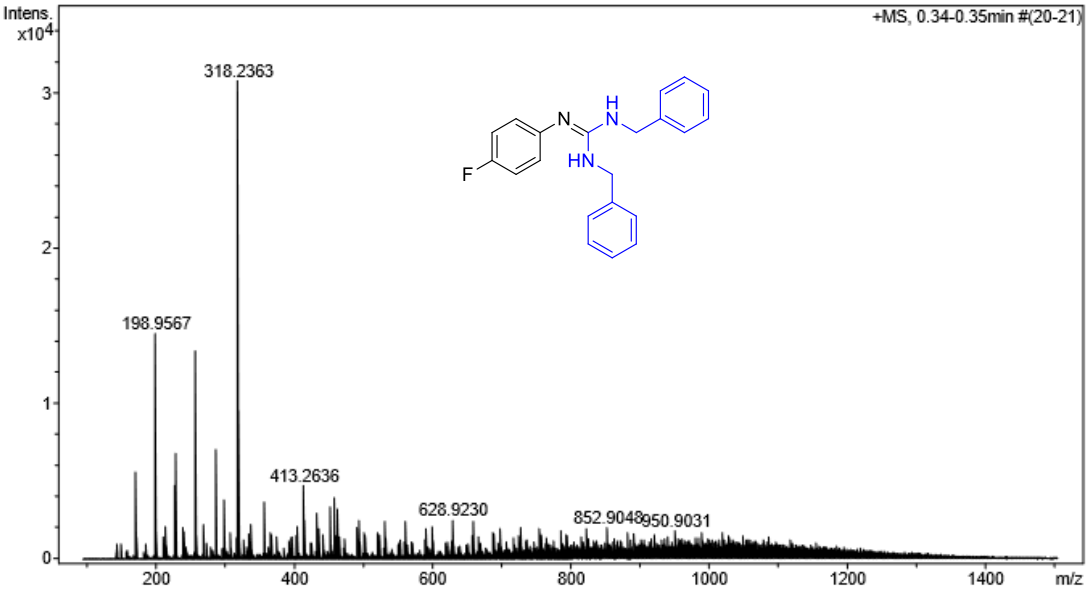

Figure A93 HRMS of 1,3-dibenzyl-2-(4-fluorophenyl)guanidine (**8c**)

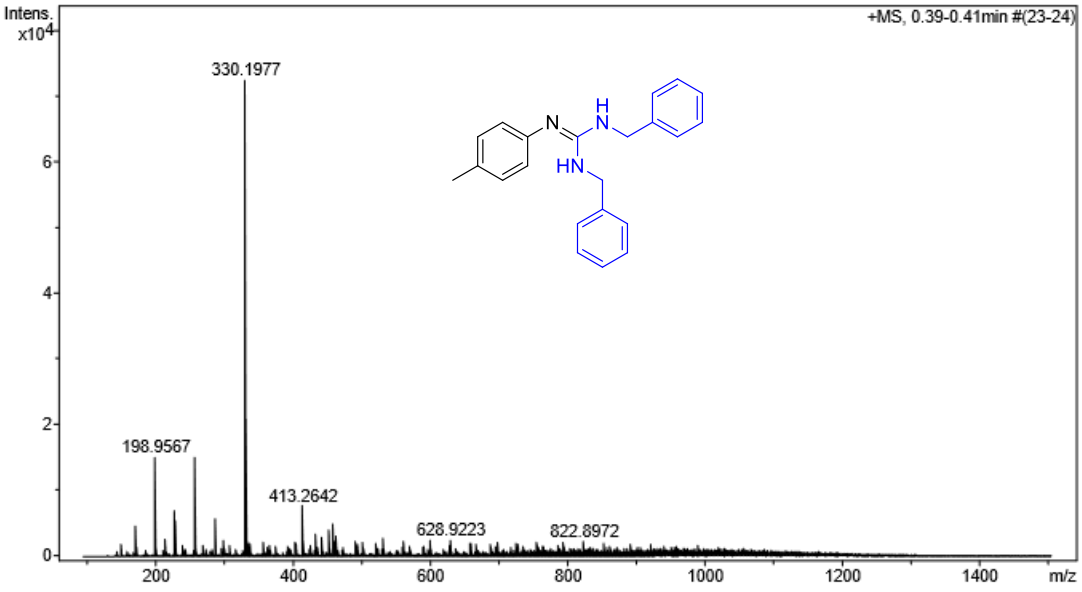

Figure A94 HRMS of 1,3-dibenzyl-2-(p-tolyl)guanidine (**8d**)

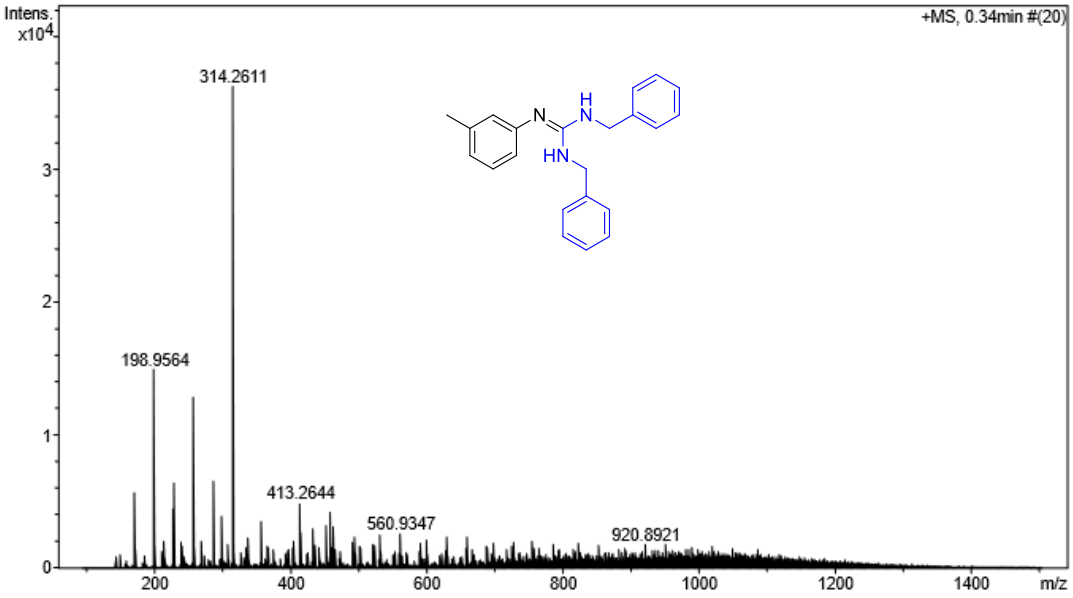

Figure A95 HRMS of 1,3-dibenzyl-2-(m-tolyl)guanidine (**8e**)

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