King Saud University
College of Pharmacy
Department of Pharmaceutical Chemistry

SYNTHESIS AND BIOLOGICAL TESTING OF NEW 1-ADAMANTYL DERIVATIVES

Submitted in Partial Fulfillment of the Requirements for the *Ph. D.* Degree in Pharmaceutical Sciences "Pharmaceutical Chemistry" in the College of Pharmacy, King Saud University

By

Ebtehal Suliman Al Abdullah
M. Sc. Pharm. Sci.

1428 H
2007 G

CONTENTS

List of Figures

List of Schemes

List of Tables

List of Tables "Cont."

List of Tables "Cont."

List of Abbreviations

AcOH	Acetic acid
AIDS	Acquired immunity deficiency syndrome
Ar	Aryl
ATP	Adenosine triphosphate
BS	*Bacillus subtilis*
Bu	Butyl
CA	*Candida albicans*
CAs	Carbonic anhydrases
$CDCl_3$	Deuteriochloroform
CNS	Central nervous system
COX	Cyclooxygenase
DEPT	Distortionless enhancement by polarization transfer
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Deuteriodimethylsulphoxide
EC	*Escherichia coli*
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
EI-MS	Electron impact mass spectra
ESI-MS	Electrospray ionization mass spectra
Et	Ethyl
EtOH	Ethanol
HCV	Hepatitis C viruses
HIV	Human immunodeficiency viruses
11β-HSD1	11β-Hydroxysteroid dehydrogenase type 1
11β-HSD2	11β-Hydroxysteroid dehydrogenase type 2
HSV	Herpes Simplex virus
5-HT	5-Hydroxytryptamine
IFO	Institute of fermentation of Osaka
IR	Infrared
LD	Lethal dose

Me	Methyl
MeOH	Methanol
MIC	Minimal inhibitory concentration
ML	*Micrococcus luteus*
Mp.	Melting point
NMDA	*N*-Methyl-D-aspartate
NMR	Nuclear magnetic resonance
PA	*Pseudomonas aeuroginosa*
Ph	Phenyl
Pr	Propyl
SA	*Staphylococcus aureus*
SEM	Standard error of mean
TLC	Thin layer chromatography
TNF-α	Tumour necrosis factor-α
μW	Microwave

ABSTRACT

Several adamantane derivatives have long been known for diverse biological properties, mainly as antiviral, antibacterial, antifungal and anti-inflammatory agents. Recently, adamantyl derivatives were recently reported to possess 11β-HSD1 inhibitory activities. In addition, 1,2,4-triazole and 1,3,4-thiadiazole were reported to constitute the pharmacologically active moiety of several compounds. On these bases new series of 1-adamantyl derivatives, in which the adamantyl moiety was attached to 1,2,4-triazole, 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole or 1,3,4-thiadiazole nucleus, have been synthesized as potential bioactive agents. In order to obtain the target compounds, the following routes were adopted:

1. Esterification of adamantane-1-carboxylic acid **140** with methanol in the presence of sulphuric acid to yield methyl adamantane-1-carboxylate **141**, which was reacted with hydrazine hydrate to yield adamantane-1-carboxylic acid hydrazide **142**. The hydrazide **142** was reacted with potassium hydroxide and carbon disulphide to yield Potassium *N*'-(1-adamantylcarbonyl)dithiocarbazate **143**, which was reacted with hydrazine hydrate to yield the key intermediate 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144**.

2. Treatment of 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** with various arylisothiocyantes in *N*,*N*-dimethylformamide (DMF) at room temperature yielded good yields of the corresponding *N*-[5-(1-adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-arylthiourea derivatives **145a-e**. Compounds **145a-e** were cyclized to their 5-(1-Adamantyl)-2-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole analogues **146a-e** *via* microwave irradiation for 5 minutes. Compounds **146a-e** were also prepared through the reaction of compound **144** with the appropriate arylisothiocyante in DMF for 18 hours or *via* microwave irradiation for 8 minutes (Scheme 1).

3. Treatment of 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** with aliphatic isothiocyanates in DMF for 24 hours afforded poor yields of the corresponding 5-(1-adamantyl)-2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazole **149a-e**. Compounds **149a-e** were independently prepared in good overall yields through the reaction of 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** with cyanogen bromide in ethanol to yield 5-(1-adamantyl)-2-amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **148**, which was subsequently reacted with methyl iodide, ethyl iodide, allyl bromide, *n*-butyl bromide or benzyl chloride in ethanol, in the presence of potassium carbonate to afford compounds **149a-e** (Scheme 2).

4. The reaction of 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** with various aromatic aldehydes in ethanol or acetic acid yielded the corresponding 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles **150a-v**. Treatment of 5-(1-adamantyl)-4-(2,6-difluorobenzylideneamino)-3-mercapto-1,2,4-triazole **150o** or 5-(1-adamantyl)-4-(2,6-dichlorobenzylideneamino)-3-mercapto-1,2,4-triazole **150q** with several monosubstituted piperazines and formaldehyde solution in ethanol yielded the corresponding *N*-Mannich bases 5-(1-adamantyl)-4-arylideneamino-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones **151a-p**. The piperidine *N*-Mannich bases 5-(1-adamantyl)-4-arylideneamino-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thiones **152a-n**, were similarly prepared *via* the reaction of the corresponding arylideneamino derivative, ethyl 4-piperidinecarboxylate and formaldehyde solution in ethanol (Scheme 3).

5. Dehydrative cyclization of Potassium *N*'-(1-adamantylcarbonyl)dithiocarbazate **143** using sulphuric acid at room temperature yielded 5-(1-adamantyl)-1,3,4-thiadiazoline-2-thione **153**, which was reacted with benzyl- or 4-substituted benzyl chlorides to yield the corresponding 5-(1-adamantyl)-3-(benzyl or 4-substituted benzyl)-1,3,4-thiadiazoline-2-thiones **154a-d**. The reaction of compound **153** with 1-methyl-, ethyl- or phenylpiperazine and formaldehyde

solution in ethanol yielded the corresponding 5-(1-adamantyl)-3-(4-substituted-1-piperazinylmethyl)-1,3,4-thiadiazoline-2-thiones **155a-c** (Scheme 4).

6. The reaction of compound **153** with ethyl bromoacetate, ethyl 2-bromopropionate or ethyl bromopropionate, in ethanol, in the presence of anhydrous potassium carbonate yielded the corresponding ethyl esters **156**, **158** and **160**, which were simultaneously hydrolyzed by heating in 10% aqueous sodium hydroxide solution to afford the corresponding carboxylic acids **157**, **159** and **161** (Scheme 5).

7. The reaction of adamantane-1-carboxylic acid hydrazide **142**, potassium thiocyanate and hydrochloric acid, in water, yielded 1-(1-adamantylcarbonyl)-3-thiosemicarbazide **162**. Dehydrative cyclization of compound **162** using sulphuric acid at room temperature yielded 5-(1-adamantyl)-2-amino-1,3,4-thiadiazole **163**. Compound **163** was also prepared in higher yield *via* one-step three-component reaction of adamantane-1-carboxylic acid, thiosemicarbazide and phosphorus oxychloride. Compound **163** was reacted with phenyl-, 4-fluorphenyl- or 4-chlorophenylisothiocyanate to yield the corresponding *N*-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-arylthioureas **164a-c** in poor yields. 5-(1-Adamantyl)-1,3,4-thiadiazoline-2-one **165** was prepared through deamination of compound **163** *via* treatment with sodium nitrite in cold aqueous hydrochloric acid solution followed by boiling for 10 minutes (Scheme 6).

In the present investigation, 83 new target compounds were prepared. The purity of the newly synthesized compounds was checked by thin layer chromatography (TLC), and the structures of these compounds were confirmed by Infrared (IR), ^{1}H NMR, ^{13}C NMR, electron impact (EI-MS) or Electrospray ionization (ESI-MS) mass spectra. The synthesis of the target new compounds necessitated the preparation of the following unavailable starting compounds guided with the published literatures:

1. Methyl adamantane-1-carboxylate (**141**).
2. Adamantane-1-carboxylic acid hydrazide (**142**).

3. Potassium *N*'-(1-adamantylcarbonyl)dithiocarbazate (**143**).
4. 5-(1-Adamantyl)-4-amino-3-mercapto-1,2,4-triazole (**144**).
5. 1-(1-Adamantylcarbonyl)-3-thiosemicarbazide (**162**).
6. 5-(1-Adamantyl)-2-amino-1,3,4-thiadiazole (**163**).

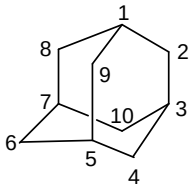
All the newly synthesized compounds were tested for their *in vitro* growth inhibitory activity against a panel of standard strains of pathogenic microorganism including Gram-positive bacteria, Gram-negative bacteria and the yeast-like pathogenic fungus *Candida albicans*. The compounds **145a**, **145b**, **145e**, **150h**, **150o**, **151n**, **152a**, **152e**, **152f**, **152m**, **153**, **157**, **159**, **164b** and **164c** displayed strong inhibitory activity against one or more of the tested microorganisms. Meanwhile, 31 compounds showed moderate activity, 15 compounds exhibited weak activity and 22 compounds were practically inactive against the tested microorganisms. The Gram-positive bacteria *Bacillus subtilis* and to a lesser extent *Staphylococcus aureus* and *Micrococcus luteus* are considered the most sensitive among the tested microorganisms. The activity against the tested Gram-negative bacteria was generally lower than the Gram-positive bacteria, compounds **150h**, **151n**, **152m** and **153** were strongly active against *Escherichia coli*, while only compound **153** was strongly active against *Pseudomonas aeuroginosa*. The inhibitory activity of the compounds against *Candida albicans* was rather lower than their antibacterial activity, only compound **152f** showed strong activity comparable to the antifungal drug Clotrimazole.

In addition, the acute anti-inflammatory activity of 26 representative compounds was determined *in vivo* following the carrageenan-induced paw oedema method in rats. The compounds **151l** and **159** were highly potent at 40 mg/kg dose level compared to the potent anti-inflammatory drug Indomethacin. The oral acute toxicity of compounds **151l** and **159**, which possessed the best anti-inflammatory activity, was determined *via* determination of their lethal doses LD_{16}, LD_{50} and LD_{84} in mice. The antiviral activity of the new derivatives are planned to be evaluated later in an international laboratory after setting suitable screening agreement.

1. INTRODUCTION

1.1. Pharmacological Properties of Adamantane Derivatives

Adamantane **1** is the proprietary name of the hydrocarbon tricyclo[3.3.1.$1^{3,7}$]decane . It occurs as white crystalline powder with characteristic aromatic odour. It exists as a minor constituent of petroleum oil.



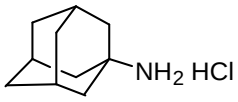
1

Adamantane is a highly lipophilic compound, it is readily soluble in organic solvents, sublimes at 209-212 ^{o}C, crystallizes at –30 ^{o}C and melts in sealed tubes at 268 ^{o}C. Adamantane nucleus was first built up by Prelog and Seiwerth in 1941 *via* aluminum chloride-catalyzed isomerization of tetrahydrodicyclopentadiene,[1] this chemical synthesis was latterly improved *via* catalytic hydrogenation of dicyclopentadiene in the presence of aluminum chloride.[2]

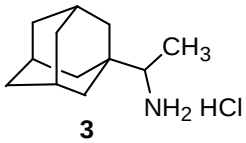
Due to the high lipophilicity of adamantane, the incorporation of the adamantyl moiety into several molecules results in compounds with relatively high lipophilicity, which in turn can modify the biological availability of these molecules. After the discovery of amantadine in 1960 as antiviral and antiparkinsonian drug, adamantane derivatives attracted the attention of several scientists as potential chemotherapeutic agents. As a result of this intensive search, thousands of adamantane derivatives were synthesized and tested for several biological activities. This resulted in the discovery of several drugs which are now available in market. Among the major biological activities displayed by adamantane derivatives, the antiviral, antibacterial, antifungal, anti-inflammatory, central nervous and 11β-HSD1 inhibitory activities are the most important ones.

1.1.1. Antiviral Adamantane Derivatives

Amantadine hydrochloride **2** (1-adamantanamine hydrochloride, Symmetrel®) is the first adamantane derivative to be introduced in medicine as effective therapy against Asian A_2 influenza viruses.[3-5] The pronounced central nervous stimulant and cardiovascular effects of amantadine[6] necessitated the search for newer more potent and less toxic agents for the control of pandemic influenza viruses. Rimantadine **3** (α-methyl-1-adamantanemethylamine hydrochloride**,** Flumadine®)[7] was further developed as more potent and less toxic alternative to amantadine.[8]

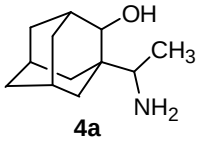


2

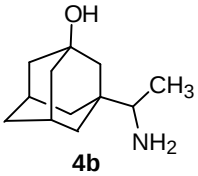


3

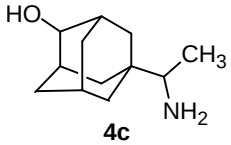
Amantadine and rimantadine inhibit the viral replication during the early stages of infection by blocking the ion channel formed by the transmembrane domain of the M2 protein.[9,10] Although both amantadine and rimantadine are orally active and well absorbed, amantadine is excreted unchanged by the kidney while rimantadine is metabolized in the liver by hydroxylation before excretion in urine giving rise to the metabolites **4a-c**.[11] The three metabolites of rimantadine were found to be active *in vitro* against the wild type influenza A viruses (H3N1 and H1N1) and inactive against influenza B viruses.



4a



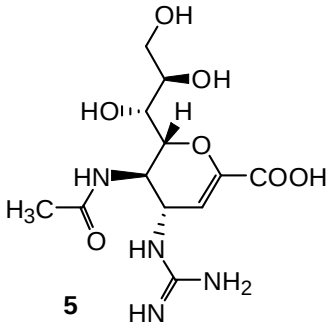
4b



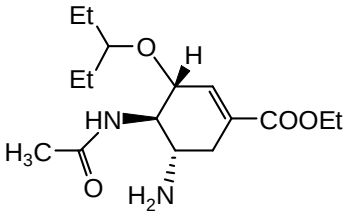
4c

Phenotypic resistance to amantadine was detected shortly after its discovery,[12] and subsequent studies showed the ease of selecting resistant variants *in vivo*.[13] The study of the genetic basis of resistance, ultimately shown to be linked to single nucleotide changes and corresponding single amino acid substitution in the trans-membrane of the M2 ion channel protein, this was critical to understand amantadine's mechanism of action.[14] As a result, influenza A viruses have the ability

to undergo changes and new evolving strains were developed causing serious threat to the human population. Thus pandemic influenza A viruses appeared in Spain in 1918 (H1N1), Asia in 1957 (H2N2), Hong Kong in 1968 (H3N2) and recently the most fatal pandemic in 1997 (H5N1),[15] which occurred in several far Eastern countries and extended during late 2003 and early 2004 to the Middle East region, infecting both human and birds. Despite the viral resistance of the newly developed mutants (H5N1) to the M2 inhibitors as amantadine and rimantadine, recent reports revealed that the combination therapy of M2 inhibitors with the newly developed neuraminidase inhibitors as zanamivir **5** (Relenza®)[16] and oseltamivir **6** (Tamiflu®)[17] is a good option for the control of resistant influenza viral infections till the exploration of other novel drugs.[18]

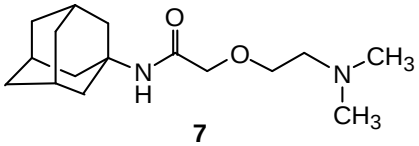


5



6

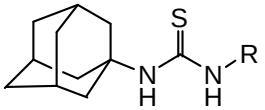
As a result of extensive search based on amantadine and rimantadine, tromantadine **7** (ViruMerz®) was introduced in 1971 as a potent antiviral drug for the treatment of viral skin diseases as Herpes Simplex (HSV).[19] The drug was not approved for systemic use due to its adverse side effects.



7

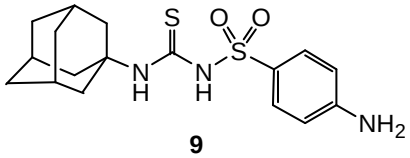
The 1-(1-adamantyl)thiourea derivatives **8**, prepared in 1969, were found to possess good activity against Herpes Simplex viruses (HSV-1).[20] In addition, the antiviral activity of 1-(1-adamantly)-3-[(4-aminophenyl)sulphonyl]thiourea **9** compared favorably with that of amantadine in mice infected with A2/Asian/J305 virus.[21] Meanwhile, the 1-adamantyl secondary and tertiary amines of the general

structures **10** were proved to exhibit potent activity against several strains of pathogenic viruses.[22]

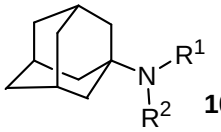


R = H, Me, Et, Pr, *iso*-Pr, Bu, Ph

8



9

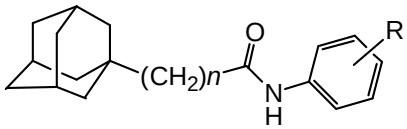


10

R^1, R^2 = H, *n*-$C_{12}H_{25}$, CH_2Ph, $CH(CH_3)CH_2Ph$

NR^1R^2 = *N*-Ph-piperazino, *N*-(4-MePh)piperazino, Piperidino, Morpholino

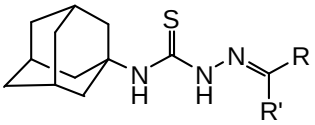
Danilenko *et al*. reported the synthesis and antiviral activity of a series of arylamides of adamantane carboxylic acids of the structure **11**.[23] The derivative (n = 0, R = 3-OCH_3) was the most effective against A2 influenza virus.



n = 0, 1. R = 2, 3, or 4-COOH, 3 or 4-OCH_3

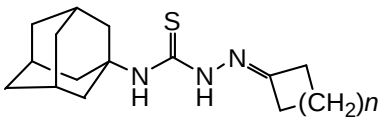
11

The adamantyl thiosemicasbazones **12** and **13**, prepared by Sallay and Childress, were found to be useful antagonists of Herpes Simplex and vaccinia viruses.[24]



R = H, Me, Ph. R' = Me, Ph

12

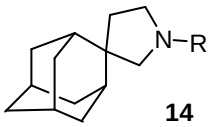


n = 0, 1, 2, 3

13

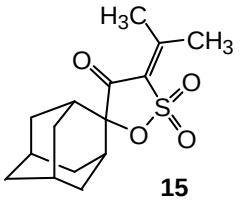
Several adamantane spiro compounds were synthesized and tested for antiviral activity against influenza viruses, of these, the adamantane spiro-3'-

pyrrolidines **14** which were found superior to amantadine in level and spectrum of activity.[25] The adamantane spiro sultone **15** also showed marked antiviral activity.[26]



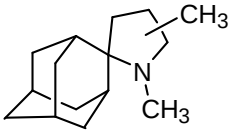
14

R = H, Me, Allyl, *n*-Hexyl, Benzyl, CH_2CH_2OH



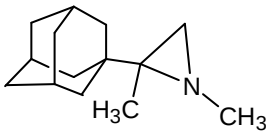
15

The adamantane spiro-2'-pyrrolidines **16** were reported to exhibit potent activity against influenza A H2N2 strains which are not sensitive to amantadine. The structure-activity relationship studies revealed that the 5-methyl substitution was optimal for antiviral activity.[27]

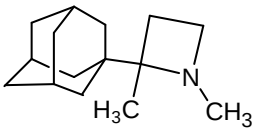


16

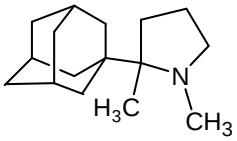
The cyclic rimantadine analogues **17**, **18** and **19** were recently prepared and tested for activity against the resistant strains of influenza A viruses. It was observed that the pyrrolidine analogue **19** is the most potent, as it was 9-fold more potent than rimantadine and 27-fold more potent than amantadine.[28]



17

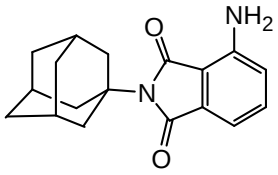


18



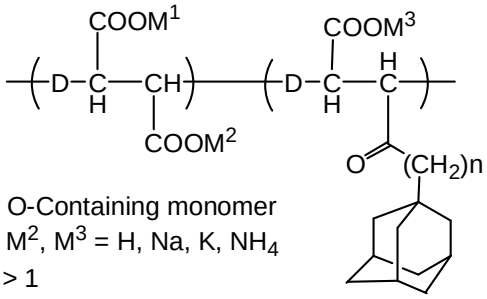
19

Although the classical adamantane derivatives amantadine and rimantadine did not inhibit the replication of human immunodeficiency viruses (HIV), the causative agent of acquired immunity deficiency syndrome (AIDS), several adamantane derivatives were proved to possess marked inhibitory activity. *N*-(1-Adamantyl)-4-aminophthalimide **20**, produced good inhibitory effect against both HIV-1 and HIV-2 in CEM cell cultures.[29]



20

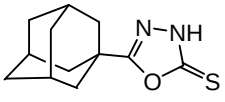
Burstein *et al.* developed the adamantane derivatives **21**, in which the adamantane moiety is chemically linked to a water soluble polyanionic matrix. These derivatives proved to be good inhibitors of early stages of HIV-1 replication.[30]



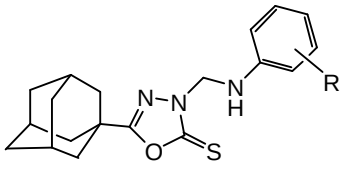
D = O-Containing monomer
M^1, M^2, M^3 = H, Na, K, NH_4
n = > 1

21

5-(1-Adamantyl)-1,3,4-oxadiazoline-2-thione **22**, its 3-arylaminomethyl and 4-substituted-1-piperazinylmethyl derivatives **23** and **24**, respectively, were prepared and tested for chemotherapeutic activities.[31] Compound **22** produced 100, 43, and 37% reduction of HIV-1 viral replication at 50, 10 and 2 μg/ml concentrations, respectively, whereas the derivatives **23** and **24**, which produced good antibacterial activity, were inactive against HIV-1.

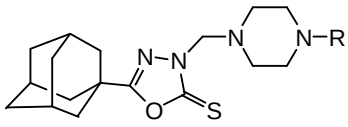


22



R = H, 2-, 3-, 4-Halo or NO2, 2-CN, 4-OCH_3, 2-CF_3, 2,5-F_2

23

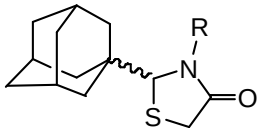


R = Me, Et, COOEt, Ph, 4-FC_6H_4, 2-$MeOC_6H_4$, $PhCH_2$

24

Potent anti-HIV-1 activity was recently observed with a series of (±)-2-(1-adamanthyl-3-alkyl- or arylthiazolidin-4-ones **25**.[32] The derivative with R = 4,6-

dimethyl-2-pyridyl substituent produced the optimal activity and behaved as typical non-nucleoside reverse transcriptase inhibitor.[33]

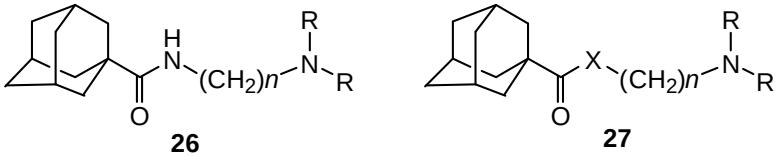


25

In addition to the activity of adamantane derivatives against influenza, herpes and HIV viruses, adamantane derivatives are recently withdrawing the attention of several hepatologists after the exploration of the role of amantadine in improving the clinical therapeutic efficacy of interferon/ribavirin combination against hepatitis C viruses (HCV).[34] The activity of amantadine against HCV is probably due to its ability to inhibit the formation of p7 protein which forms ion channels in the planar lipid bilayers, which is similar to that has been shown for other viral ion channel forming M2 proteins.[35,36]

1.1.2. Antimicrobial Adamantane Derivatives

Several adamantane derivatives have long been known to possess bactericidal and fungicidal activities. The *N*-(dialkylaminoalkyl)adamantane-1-carboxamides **26** were proved to exhibit antibacterial and antifungal activities, in addition to anti-inflammatory, antiprotozoal and antialgal activities.[37] Isosteric replacement of the amide function NH with O or S to get the esters and thioesters **27**, resulted in improving the antibacterial, antifungal and anti-inflammatory activities.[38]

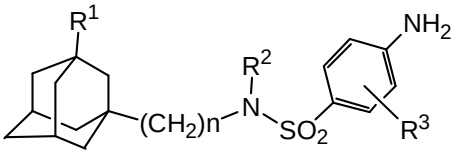


26 **27**

R = Me or Et. *n* = 2, 3 or 7. X = O or S

= Piperidino, Pyrrolidino or 4-Methylpiperazino

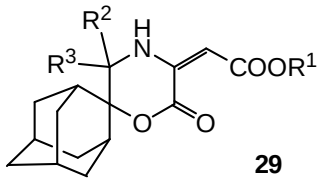
The N^1-(1-adamantyl)sulphanilamide derivatives **28** were found to be useful antibacterial agents against *Staphylococci* and *Diplococci*.[39] Some members of these compounds also exhibited antiviral activity against influenza A-PR8 and hepatic virus MHV3.



28

R^1 = H, Halogen, lower alkyl group or Ph
R^2 = H or lower alkyl group
R^3 = H, Halogen, lower alkyl or alkoxy group
n = 0, 1 or 2

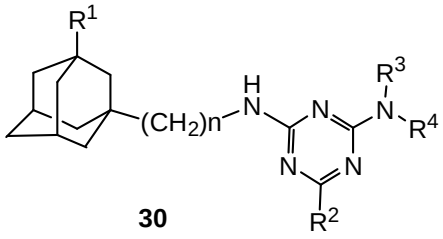
Georgiev and Mullen reported the synthesis of a series of adamantane spiro 3,4,5,6-tetrahydro-1,4-oxazin-2-one derivatives **29**.[40] These derivatives produced potent antibacterial activity against *N. gonorrhea* and anti-inflammatory activity against carrageenan-induced oedema.



29

R^1 = C_1-C_8 alkyl group
R^2, R^3 = C_4-C_8 alkyl group

The 2-(1-adamantyl or 1-adamantylalkylamino)-4-amino-*s*-triazines **30**, prepared by Narayanan, were proved to possess potent antibacterial and hypoglycemic activities.[41]

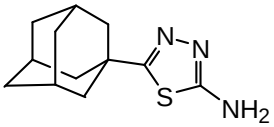


30

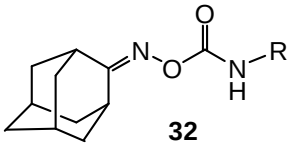
R^1 = H, Me or MeO
R^2 = H or Me
R^3, R^4 = H, Me, Et, or $PhCH_2$
n = 0, 1 or 2

Potent antifungal activity was reported for 2-(1-adamantyl)-5-amino-1,3,4-thiadiazole **31**, which proved to be typical general fungal disinfectant.[42] Meanwhile,

the 2-adamantanone oxime carbamates **32** showed *in vitro* antifungal activity against yeast and systemic mycoses and dermatophytes.[43]



31

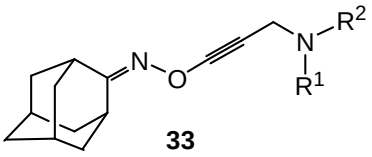


32

R = Cyclohexyl, Ph, 3-$MeOC_6H_4$, 2-ClC_6H_4, 4-BrC_6H_4, $PhCH_2$, Allyl or *iso*-Pr

Another series of 2-adamantanone oxime ethers of the structure **33** were prepared and examined for possible antimicrobial or antiviral activity.[44] Most of these derivatives showed good antifungal activity against wide range of pathogenic fungi and weak antibacterial activity but lacked the antiviral activity.

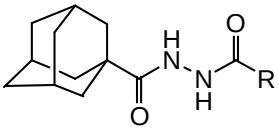
The *N*'-(1-adamantylcarbonyl, isonicotinoyl or aroyl)-1-adamantane carboxylic acid hydrazides **34** were prepared *via* the reaction of adamantane-1-carboxylic acid hydrazide and the corresponding acid chloride.[45] These derivatives were proved to be useful as medicinal bactericides and fungicides.



33

R^1, R^2 = Me, Ph or $PhCH_2$

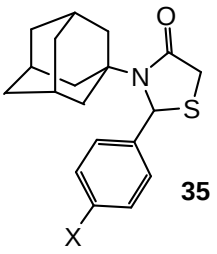
= Morpholino or 4-Methylpiperazino



34

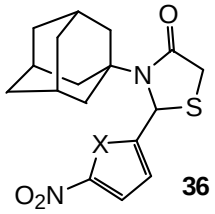
R = 1-Adamantyl, Isonicotinoyl, Ph, 4-FC_6H_4 or 4-$NO_2C_6H_4$

A series of 3-(1-adamantyl)-2-arylthiazolidin-4-ones of the structures **35** and **36** and 3-(1-adamantyl)sydnone **37** were tested for antimicrobial and anti-inflammatory acrivities.[46] Compounds **36** and **37** produced good inhibitory activity against certain strains of pathogenic bacteria and fungi, while compounds **36** produced weak anti-inflammatory activity.



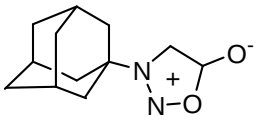
35

X = F, Cl or Br



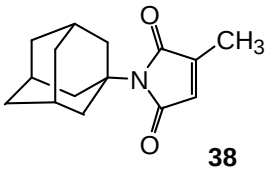
36

X = O or S



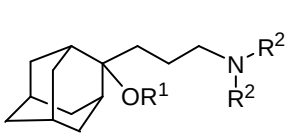
37

Wang *et al.* prepared a series of *N*-(1-adamantyl)maleimides as potential antitumour and antimicrobial agents.[47] The *N*-(1-adamantyl)citraconimide **38** was found to possess specific cytotoxicity against Colo 205, Hep G2, SK-BR-3 and Molt-4 cell line, in addition to good *in vitro* activity against *Staphylococcus aureus* and *Trichophyton mentagrophytes.*

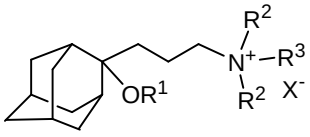


38

Two series of adamantane-2-ol bearing trialkylamines **39**, **40** and adamantane-1-methanol **41**, **42** bearing trialkylamines and their quaternary ammonium salts were synthesized by Antoniadou-Vyza *et al.* and tested for their antibacterial activities.[48] Most of these compounds produced excellent activity against certain strains of resistant Gram-positive and Gram-negative bacteria. The structure-activity relationship studies revealed that the antibacterial activity of these compounds greatly enhanced as the length of terminal nitrogen-attached alkyl group increased from CH_3 to $C_{12}H_{25}$.

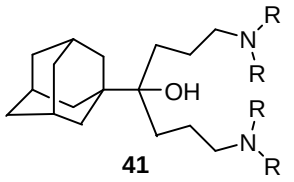


39

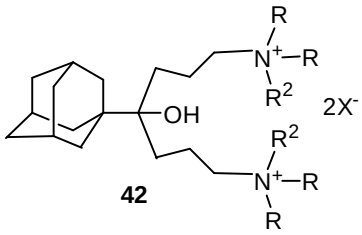


40

R^1 = H or $COCH_3$
R^2 = C_1-C_5 alkyl group
R^3 = H or C_1-C_{12} alkyl group
X = Cl, Br or I



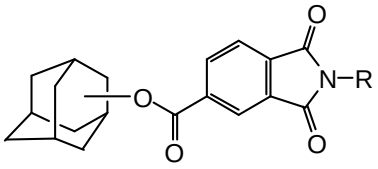
41



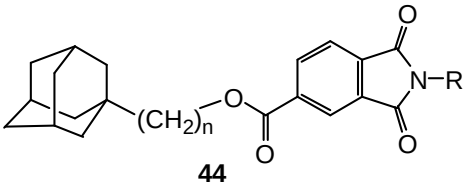
42

R = C_1-C_5 alkyl group
R^2 = H or Me or Et
X = Cl, Br or I

Orzeszko *et al.* reported the synthesis and potent antibacterial activity of series of 4-(1- or 2-adamantyloxycarbonyl)-*N*-substituted phthalimides **43**,[49] and 4-(1-adamantylalkyloxycarbonyl)-*N*-substituted phthalimides **44**.[50]



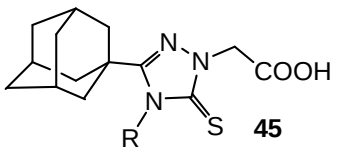
43



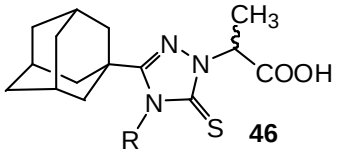
44

R = CH_2COOH, $(CH_2)_2COOH$, $(CH_2)_3COOH$, $(CH_2)_5COOH$ or $(CH_2)_7COOH$
n = 1-3

Al-Deeb *et al.* recently reported the synthesis, antimicrobial and anti-inflammatory activities of novel series of 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]acetic acids **45**, 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]propionic acids **46**, and 2-[2-(1-adamantyl)-1,3,4-oxadiazol-5-ylthio]acetic acid **47**.[51] These compounds produced good antibacterial activity against *Bacillus subtilis* and *Escherichia coli*, and moderate activity against *Staphylococcus aureus*, *Pseudomonas aeuroginosa* and *Candida albicans*. Some members of these series also exhibited potent, dose-dependent anti-inflammatory activity.

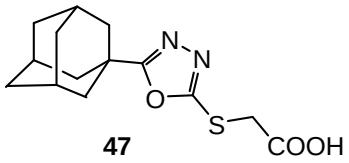


45



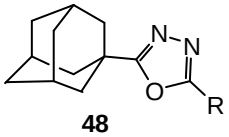
46

R = Me, Et, Allyl, Ph, 4-FC_6H_4, 4-ClC_6H_4, $PhCH_2$ or NH_2



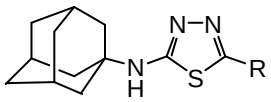
47

Newer series of 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles **48** and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles **49** were recently reported to possess good antimicrobial activity particularly against the tested Gram-positive bacteria *Bacillus subtilis* and moderate activity against the yeast-like pathogenic fungus *Candida albicans*.[52] Some members of these derivatives particularly the oxadiazoles **48** displayed good, dose-dependent anti-inflammatory activity.



48

R = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 3,5-$(NO_2)_2C_6H_3$,3,4-$(MeO)_2C_6H_3$, 2-thienyl or 1-adamantyl

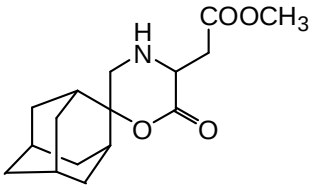


49

R = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 2-thienyl or 1-adamantyl

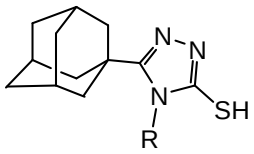
1.1.3. Anti-inflammatory Adamantane Derivatives

Anti-inflammatory activity was reported to several adamantane-containing molecules. In addition to the previously mentioned compounds **26**,[37] **27**,[38] **29**,[40] **35**, **36**, **37**,[46] **45**, **46**,[51] and **48**,[52] which possess anti-inflammatory activity beside the antiviral or antimicrobial activity, several compounds were reported to possess anti-inflammatory activity as the main biological activity. The adamantane spiro tetrahydroxazinone **50** was reported to elicit 30% reduction of the carrageenin-induced paw oedema in rats.[53]



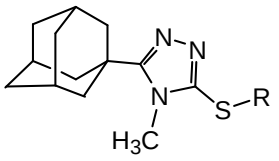
50

A series of 3-(1-Adamantyl)-4-substituted-5-mercapto-1,2,4-triazoles of the general structure **51**, **52** and **53** were prepared and tested for anti-inflammatory and analgesic activities.[54] The derivatives **51** were found to be the most potent among these derivatives. The activity of the derivatives **51** with a methyl, ethyl or benzyl substituents was found comparable to the activity of Indomethacin. The analgesic activity of these compounds correlated to their anti-inflammatory activity.

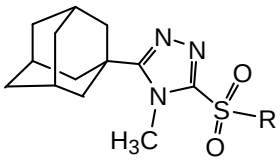


51

R = H, Me, Et, *n*-Bu, Ph or $PhCH_2$



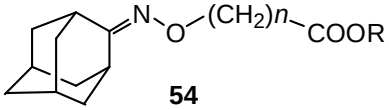
52



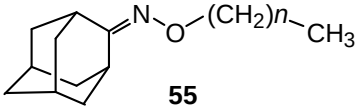
53

R = Et, $PhCH_2$, 4-$FC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 4-$NO_2C_6H_4CH_2$

The adamantane oxime esters **54** and ethers **55** were tested for anti-inflammatory activity.[55] Some of these derivatives exhibited activity comparable to diclofenac against phlogistic-induced mouse paw oedema.



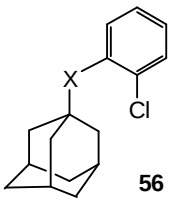
54



55

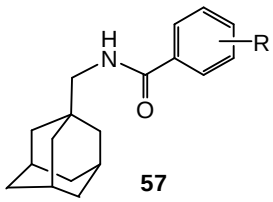
R = C_1-C_3 alkyl group, *n* = 1-5

Baxter *et al.* reported the discovery of the adamantane amides **56**, **57** and **58** as potent $P2X_7$ receptor antagonists.[56] The $P2X_7$ receptor is a ligand-gated ion channel present in a variety of cell types involved in the inflammatory/immune process, specifically macrophages, mast cells and lymphocytes. Activation of $P2X_7$ receptor by the extracellular adenosine triphosphate (ATP) leads to the processing and release of the proinflammatory cytokine interleukin-1β from the monocytes and macrophages. Thus inhibition of $P2X_7$ receptor would results in anti-inflammatory activity.



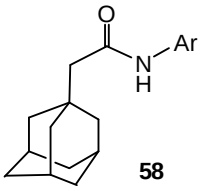
56

X = CH_2NHCO, $CH(Me)NHCO$, $CH_2N(Me)CO$, CH_2NHCH_2, NHCO, $(CH_2)_2NHCO$ or CH_2CONH



57

R = H, 2-Cl, 3-Cl, 2-Br, 2-Me, 2-MeO, 2,3-Cl_2, 3,4-Cl_2, 2,5-Cl_2, 2,6-Cl_2 or 3,5-Cl_2



58

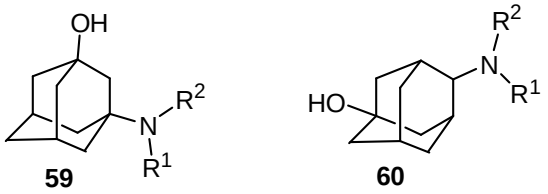
Ar = 2-ClC_6H_4, 2-MeC_6H_4, 2-Cl,5-$MeOC_6H_3$, 2-Me,5-$MeOC_6H_3$, 2-Me,3-$MeOC_6H_3$ or 2-Me-Benzothiazol-6-yl

1.1.4. CNS Activity of Adamantane Derivatives

As a result of the high lipophilicity of adamantane molecule, high lipophilicity is reflected on several adamantane-containing derivatives. The lipophilicity of the adamantane derivatives enables them to pass through the blood brain barriers leading to the existence of high levels of these derivatives in the central nervous system. After the approval of amantadine and rimantadine in the treatment and prophylaxis of influenza infection, the use of these drugs suffered from the undesirable CNS stimulant side effects such as insomnia, nervousness and

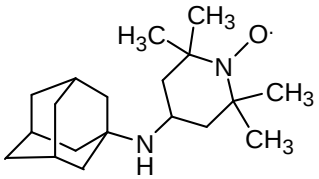
diminished concentration, in addition to the undesirable cardiovascular effectes.[6,57] The therapeutic efficacy of amantadine in the symptomatic treatment of Parkinson's disease was discovered serendipically in 1969, and amantadine is still in use as anti-Parkinsonian drug for more than 30 years.[58] The complete mechanism of action of amantadine still remains elusive. Amantadine is a dopaminergic, noradrenergic and serotonergic substance with neuroprotective properties.[59] Amantadine is known to increase the synthesis, release and uptake of dopamine in the striatum, which is consistent with its amphetamine-like action.[60] Amantadine was found to act as blocker of brain monoamineoxidase A and as non-competitive *N*-methyl-D-aspartate (NMDA)-receptor antagonist thereby influencing the dopamine transmission.[61]

Klimova *et al.* introduced a polar hydroxyl group to some adamantylamines, the derivatives **59** and **60** were found to possess anticataleptic activity, without the undesirable psychomotor-stimulation activity shown by amantadine.[62]



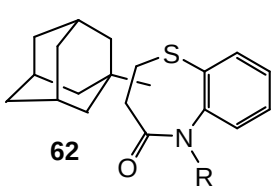
59 **60**

The aminoadamantane derivative of the nitroxyl free radical **61**, prepared by Skolimowski *et al.*, was found to possess potent *in vivo* antiparkinsonian activity in rats.[63]

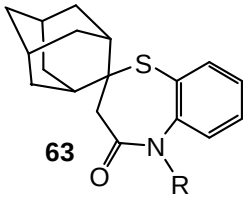


61

Potent antidepressant activity was observed in several adamantane derivatives, of these, the adamantyl 1,5-benzothiazepine-4(H)-ones **62** and its spiro analogues **63**.[64]



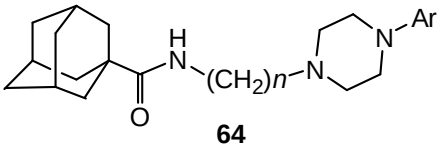
62



63

R = $(CH_2)_2NMe_2$ or $(CH_2)_3NMe_2$

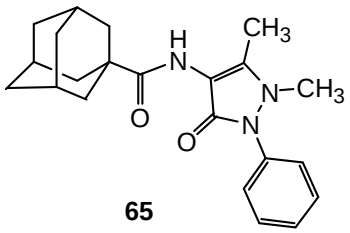
The *N*-(1-adamantylcarboxamidoalkyl)-*N'*-aryl or heteroarylpiperazines **64** were prepared as potential anxiolytic and antidepressant agents.[65] These derivatives demonstrated selective *in vitro* agonistic affinity for 5-HT_{1A} receptors, this affinity was accompanied by significant anxiolytic and antidepressant activity in animal conflict model.



64

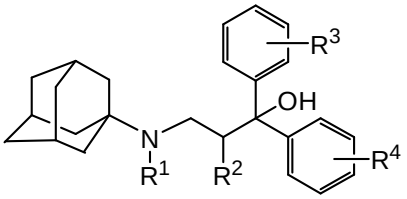
Ar = 2-$MeOC_6H_4$, 3-ClC_6H_4, 3-$CF_3C_6H_4$, $C_6H_5CH_2$,
2,3-$Me_2C_6H_3$ or 2-Pyrimidinyl
n = 1 or 2

Analgesic and antipyretic activities were also reported for several adamantane derivatives. The analgesic activity of the adamantane carboxylic acid amide of 4-aminoantipyrine **65** was found to be 30% higher than that of 4-aminoantipyrine in mice. Moreover, the LD_{50} of this compound was 820 mg/kg, compared with 280 mg/kg for 4-aminoantipyrine.[66]

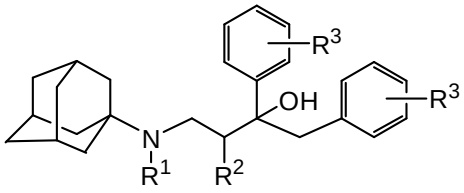


65

Novel series of diaryl 1-adamantylaminopropan-3-ols **66** and diaryl 1-adamantylaminobutan-3-ols **67** were prepared by Delmar Chemicals Ltd.[67] Several derivatives of these series proved to possess marked analgesic activity with generally low toxicity.



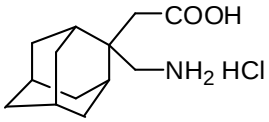
66



67

R^1 = H, Me, Et or *n*-Pr
R^2 = Me, C_2-C_3 alkyl, alkenyl or alkynyl group
R^3, R^4 = H, Halogen, CF_3 or C_2-C_3 alkyl group

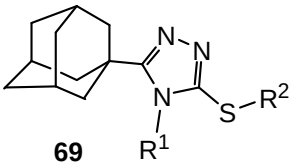
The recently prepared adamantane-γ-aminobutyric acid (AdGABA) **68**, was reported to possess strong anticonvulsant and analgesic activities. The therapeutic action of this compound might be associated with its capability to bind to the neuronal calcium channel $\alpha_2\delta$ auxiliary subunit.[68]



68

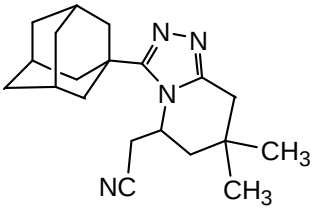
1.1.5. Adamantane Derivatives as 11β-HSD1 Inhibitors

In the late 2003, researchers from Merck & Co. Inc. registered a patent about the synthesis of certain adamantyl 1,2,4-triazoles of the structures **69** and the related compound **70**, as potent inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).[69]



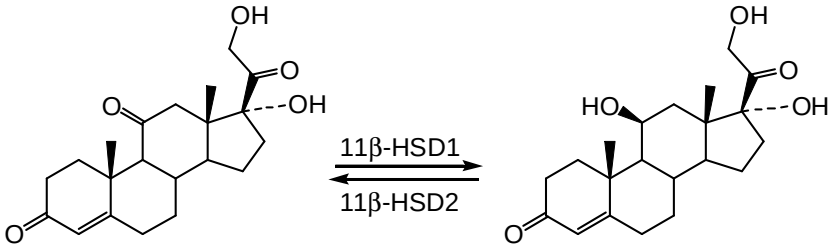
69

R^1 = NH_2, Alkylamino, Akyl or Cycloalkyl
R^2 = Akyl, alkenyl, 1-Adamantyl, CH_2COOH or Cycloalkyl



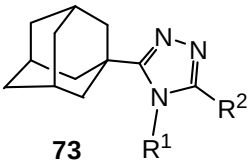
70

11β-Hydroxysteroid dehydrogenase type 1 is an endoplasmic reticulum-associated enzyme that acts as NADPH-dependent reductase which converts inactive cortisone **71** to the active glucocorticoid cortisol **72**. In the liver, cortisol stimulates gluconeogenesis through upregulation of enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, and in adipose tissues, cortisol promotes adipogenesis and lipolysis. As such, 11β-HSD1 is a regulator of intracellular cortisol concentration and has been implicated in a number of metabolic sequela of increased glucocorticoid tone such as visceral adiposity, elevated blood pressure, elevated fasting glucose, and dyslipidemia.[70] On the other hand, the structurally related 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) which is a NAD-dependent dehydrogenase that catalyzes the inactivation of cortisol by conversion to cortisone. 11β-HSD2 is expressed in cells that contain the mineralocorticoid receptors and protects the mineralocorticoids from illicit occupation by cortisol. Inhibition of 11β-HSD2 is known to result in hypokalemia, sodium retention, and hypertension. Thus, the invention of selective 11β-HSD1 inhibitors would be an important therapy for controlling non-insulin-dependent diabetes, hyperglycemia, obesity, insulin resistance, hyperlipidemia, hypertension and other symptoms associated with excessive body cortisol.

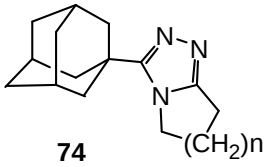


71 **72**

The synthesis, *in vitro*, and *in vivo* 11β-HSD1 inhibitory activity of the adamantyl triazoles **73**, and their cyclic homologues **74** were further carried out. These derivatives were identified as potent and selective inhibitors of 11β-HSD1. The structure-activity relationship studies revealed that the derivatives **73** (R^1 = Me, R^2 = Ph) and **74** (n =3) are the most potent.[71]



73

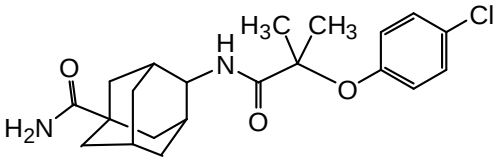


74

R^1 = C_1-C_4 Alkyl group
R^2 = C_1-C_4 Alkyl group, Ph or $PhCH_2$

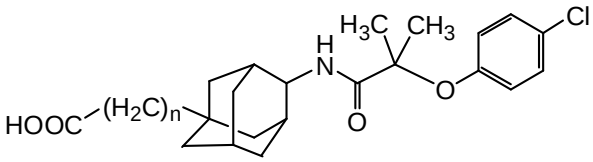
n = 1-7

Shortly after the discovery of the selective 11β-HSD1 inhibitory activity of adamantane derivatives, several structural modifications were carried out to improve the selectivity, potency, and pharmacodynamic profiles. The most interesting of these modifications is the introduction of an amide function into the adamantane structure. Thus, the adamantane amide ether **75** was found to possess potent and selective inhibitory activity against human and mouse 11β-HSD1.[72]



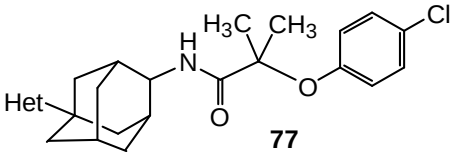
75

The highly active compound **75** was recently modified *via* replacement of the amide function with carboxyalkyl group **76** or a heterocyclic nucleus **77**.[73] These structural modifications resulted in marked increase in the both the potency and 11β-HSD1 inhibitory selectivity.



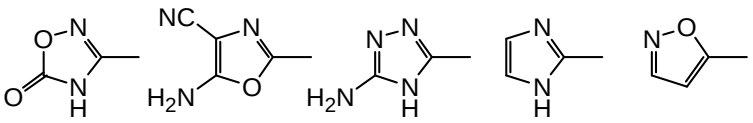
n = 1 or 2

76

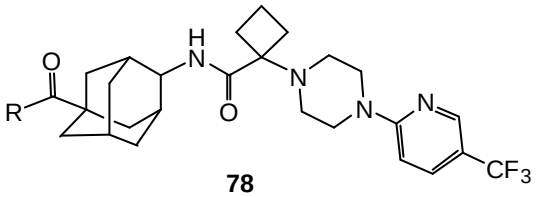


77

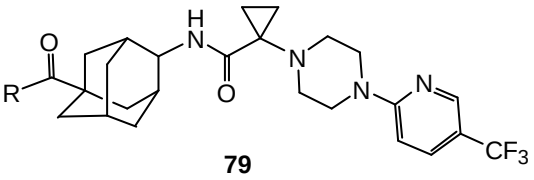
Het =



Optimization of the activity and selectivity was shown in the novel piperazine-containing derivatives **78** and **79**, which are characterized by high metabolic stability and robust pharmacokinetic profiles.[74]



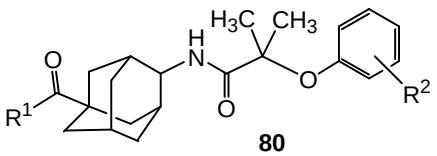
78



79

R = OH or NH_2

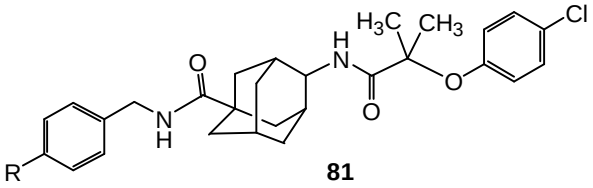
Recently, novel related series of adamantane ethers of the structures **80**, **81**, **82** and **83** were prepared. Although these compounds have lower metabolic stability, their potency and selectivity to human and mouse 11β-HSD1 is more superior.[75]



80

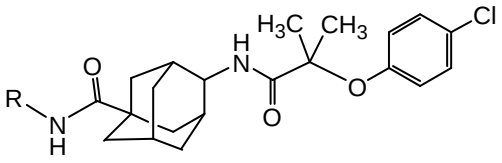
R^1 = OH or NH_2

R^2 = H, 2-Cl, 3-Cl, 4-Cl, 4-OMe



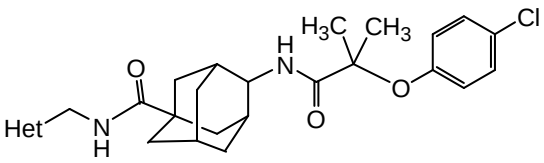
81

R = COOH, SO_2NH_2 or 5-(1*H*)Tetrazolyl



82

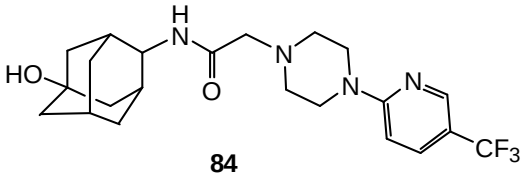
R = CH_2CONH_2 or $CONHCH_3$



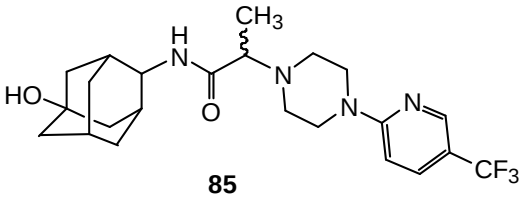
83

Het = 4-Pyridyl or 5-Thiazolyl

Most recently, the highly potent, 11β-HSD1-selective inhibitor *N*-(2-adamantyl)acetamide derivative **84**, and its (±)-methyl derivative **85** were discovered.[76] The methyl analogue **85** has excellent potency, 11β-HSD1 selectivity and improved microsomal stability in both *in vitro* studies on human and mouse 11β-HSD1 and *in vivo* studies on mouse and rats.



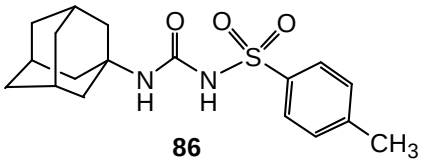
84



85

1.1.6. Miscellaneous Activities of Adamantane Derivatives

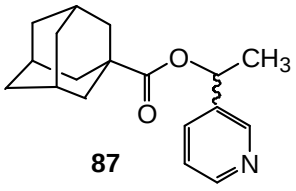
Other biological activities were also observed for some adamantane derivatives. The hypoglycemic potency of the adamantyl analog of tolbutamide, *N*-(*p*-tolylsulphonyl)-*N*'-(1-adamantyl)urea **86** was found to be five times as of tolbutamide, in addition to its rapid onset of action.[77]



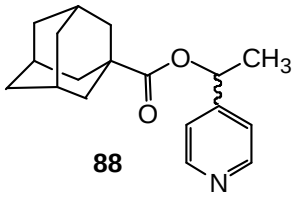
86

Antitumour activity was also reported for some adamantane derivatives, of these, the (*S*)-1-(3- and 4-pyridyl)ethyl adamantane-1-carboxylate **87** and **88**,[78] which characterized by potent inhibitory activity towards 17α-hydroxylase and $C_{17,20}$-lyase

activities of human testicular cytochrome $P450_{17\alpha}$. In addition, these derivatives were found to be resistant to degradation by esterases.

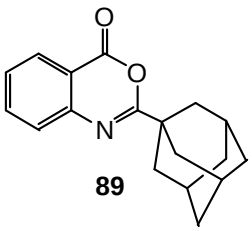


87

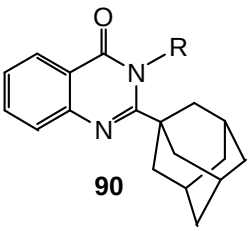


88

The 2-(1-adamantyl)-4*H*-3,1-benzoxazin-4-one **89**, and the 3,4-dihydroquinazolin-4-one analogues **90**, were found to display marked antitumour and anti-HIV-1 activities.[79]



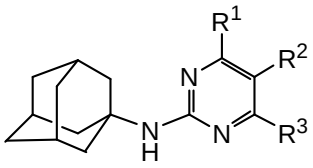
89



90

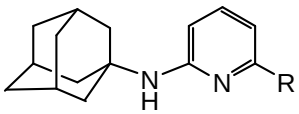
R = NH_2 or Lower alkyl group

The adamantylaminopyrimidines **91**, and adamantylaminopyridines **92** were found to possess potent tumour necrosis factor-α (TNF-α) production-enhancing activity in murine melanoma cells transduced with gene from human TNF-α.[80]



91

R^1, R^2, R^3 = H, Me, NH_2, Cl or Br



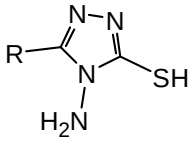
92

R = H or Cl

1.2. Pharmacological Properties of 1,2,4-Triazole Derivatives

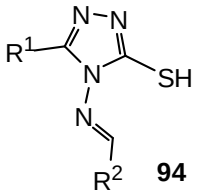
1,2,4-Triazoles (*s*-triazoles) and their fused heterocyclic derivatives are known for their diverse pharmacological activities. The most interesting of these are the anti-inflammatory, analgesic, antibacterial, antifungal and other activities.

In addition to the previously mentioned adamantyl triazoles **45**, **46**,[51] **51**, **52** and **53**,[54] anti-inflammatory activity was early observed for several 5-alkyl or aryl-4-amino-1,2,4-triazole-3-thiols **93**, 5-alkyl-4-alkylidene-, arylideneamino-1,2,4-triazole-3-thiols **94**, and their thioether **95** derivatives.[81]



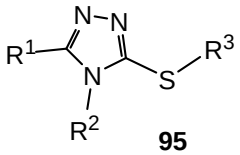
93

R = Me, Et, $(CH_2)_2Me$, $(CH_2)_3Me$, $(CH_2)_4Me$, CH_2OMe, CF_3, Ph or $3,4,5(MeO)_3C_6H_2$



94

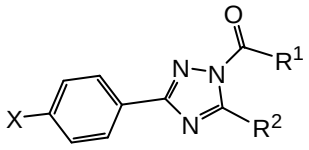
R^1 = Et or CF_3
R^2 = Me, $CH(Me)_2$, Cyclopentenyl, $4\text{-}FC_6H_4$, $4\text{-}MeOC_6H_4$ or 4-Pyridyl



95

R^1 = Et, R^2 = NH_2, $N{=}C(Me)_2$, $N(COCH_3)_2$,NHCOMe or NHCOBu
R^3 = $C_6H_5CH_2$, $CH_2CH_2NEt_2$ or *n*-C_4H_9

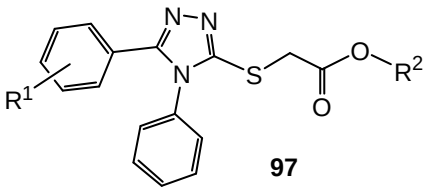
A series of 1-acyl-3-substituted-5-alkyl-1,2,4-triazoles of the structures **96** was prepared for evaluation as anti-inflammatory agent. Most of these derivatives exhibited good anti-inflammatory activity in the mouse active arthus (MAA) reaction method.[82]



96

R^1 = Me, Et or Ph
R^2 = Me or Et
X = H, Me, Cl or CF_3

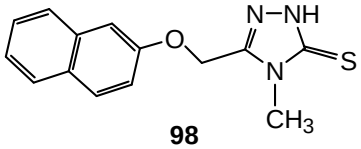
The derivatives of 1-(4-phenyl-5-aryl-1,2,4-triazol-3-ylthio)acetic acid and their ethyl esters **97** displayed good *in vitro* superoxide scavenging activity and *in vivo* anti-inflammatory activity against carrageenin-induced rat paw oedema.[83]



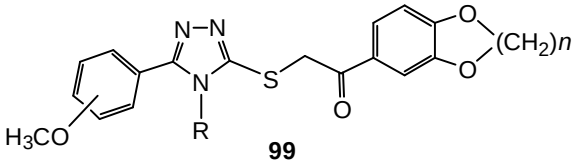
97

R^1 = H, 4-MeO, 3,4-$(MeO)_2$, 3,4,5-$(MeO)_3$ or 4-OH
R^2 = H or Et

In the last decade, there has been a growing interest in the anti-inflammatory activity of 1,2,4-triazole derivatives and hundreds of publications reported the synthesis and good anti-inflammatory activity of substituted 1,2,4-triazoles, of these compounds the naphthyloxymethyl derivative **98**,[84] the 2, 3, and 4-methoxyphenyl derivatives **99**,[85] the 2,6-dichloroanilinobenzyl derivatives **100**,[86] and the highly potent COX-2 selective inhibitor **101**.[87]

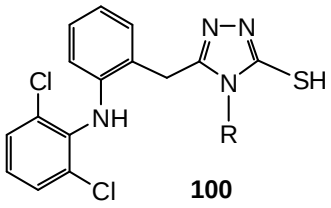


98



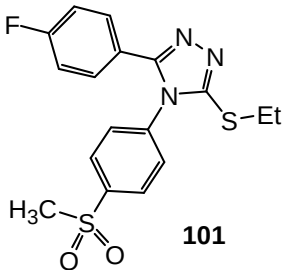
99

R = H or Ph
n = 1-3



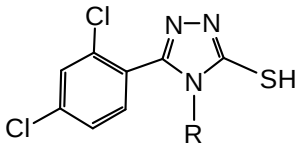
100

R = *n*-Bu, Cyclohexyl, 2-MeC_6H_4, 4-MeC_6H_4, 2-MeOC_6H_4, 4-ClC_6H_4 or 4-FC_6H_4

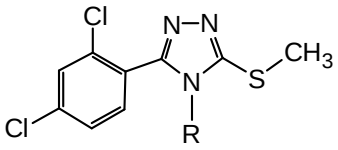


101

In addition to the reported antimicrobial activity of the previously mentioned adamantyl triazoles **45**, **46** and **47**,[51] potent antibacterial and antifungal activities were also reported for several 1,2,4-triazole derivatives. The 3-(2,4-dichlorophenyl)-4-substituted-1,2,4-triazole-5-thiols **102** and their methyl thioethers **103** displayed marked *in vitro* broad spectrum activity against several strains of pathogenic bacteria.[88]



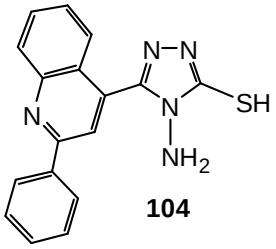
102



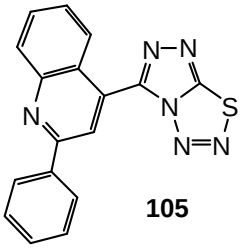
103

R = Me, NH_2, 2-MeC_6H_4, 4-MeC_6H_4, 2-MeOC_6H_4, 4-MeOC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4 or 4-BrC_6H_4

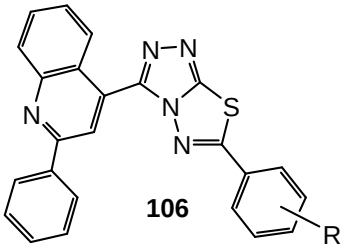
4-Amino-5-cinchophenyl-3-thiol **104** and its fused thiatriazoles **105** and thiadiazoles **106** were also reported to exhibit good inhibitory effect against certain strains of pathogenic bacteria.[89]



104



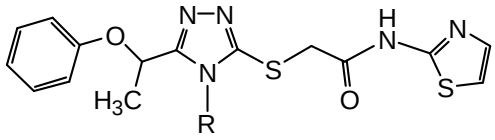
105



106

R = 4-Me, 3-Me, 3-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 4-Br or 4-I

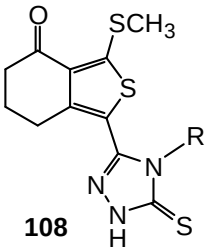
Strong antifungal activity was reported for the 4-phenyl or cyclohexyl-5-(1-phenoxyethyl)-3-[*N*-(2-thiazolyl)acetamido]thio-1,2,4-triazole derivatives **107**.[90]



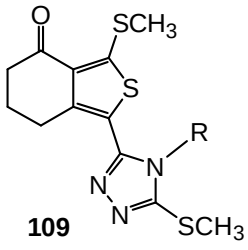
107

R = Ph or Cyclohexyl

The 1-(1,2,4-triazol-3-yl)-3-methylthio-6,7-dihydrobenzo[*c*]thiophen-4(5*H*)-one derivatives **108** and their methyl analogues **109** possessed good antibacterial activity, particularly against Gram-positive bacteria.[91]



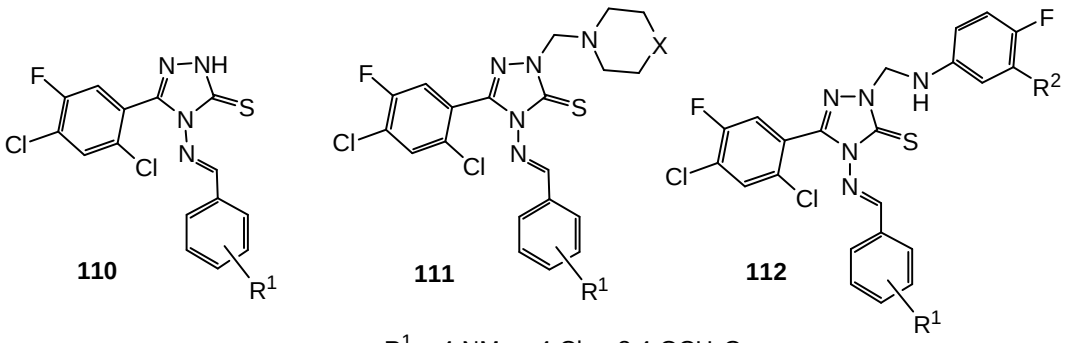
108



109

R = Me, Et, *n*-Bu, Cyclohexyl, 4-FC_6H_4,
4-$NO_2C_6H_4$ or 4-$MeOC_6H_4$,

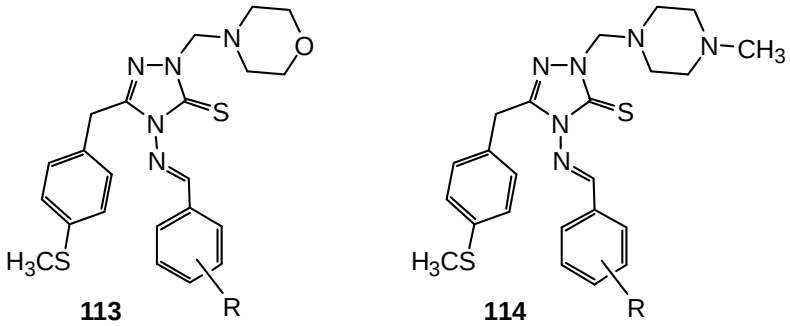
The Schiff's bases of the *N*-amino-1,2,4-triazoles **110** and their *N*-Mannich bases **111** and **112** exhibited promising antibacterial and antifungal activities compared with ciprofloxacin and flucanozole, respectively.[92]



110 **111** **112**

R^1 = 4-NMe_2, 4-Cl or 3,4-OCH_2O
R^2 = H or Cl
X = O, NMe or CH_2

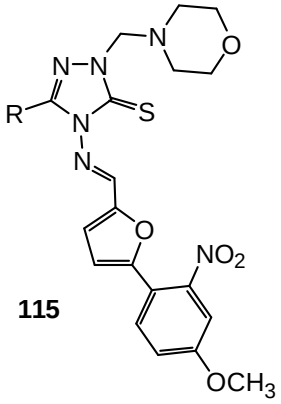
The *N*-Mannich bases of 1,2,4-triazoline-3-thiones of the structures **113** and **114** were recently reported to possess significant antibacterial and antifungal activities.[93]



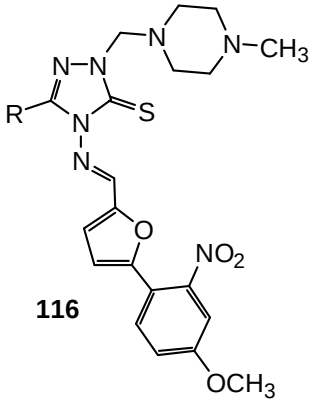
113 **114**

R = 4-Me, 4-MeO, 4-MeS, 4-F, 4-Cl, 2,4-Cl_2, 3,4-OCH_2O

Meanwhile, the structurally-related *N*-Mannich bases **115** and **116** were reported to possess anticancer activity against a panel of 60 cell lines derived from seven cancer types.[94]



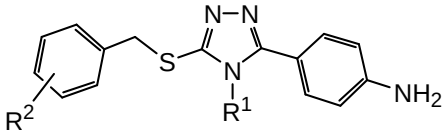
115



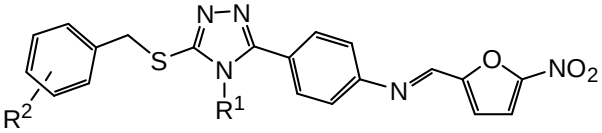
116

R = H, Me, Et, *n*-Pr, 2-$ClC_6H_4OCH_2$ or 2,4-$Cl_2C_6H_3OCH_2$.

The 3-arylmethylthio-4-alkyl or aryl-5-(4-aminophenyl)-1,2,4-triazole derivatives **117** were reported to posses anticonvulsant activity, while their related Schiff's base **118** showed marginal activity against *Mycobacterium tuberculosis* H37Rv. [95]



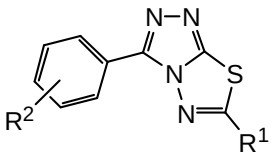
117



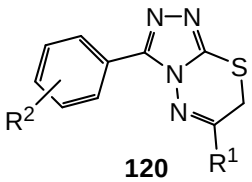
118

R^1 = C_1-C_3 alkyl or aryl
R^2 = Me, Cl, Br or NO_2

Fused triazoles were also reported to possess significant biological activities. The triazolo-1,3,4-thiadiazoles **119** and the triazolo-1,3,4-thiadiazines **120** showed marked antibacterial and antifungal activities.[96]



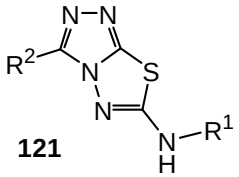
119



120

R^1 = NH_2, NHPh or Ph
R^2 = H, 4-Me, 4-MeO, 2-Cl, 4-Cl, 3-Br or 4-Br

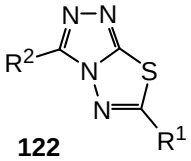
The related 2-substituted aminotriazolo-1,3,4-thiadiazoles **121** were reported to display potent fungicidal and pesticidal activities against *Asperigillus niger* and *Helminthosporium oryzae*.[97]



121

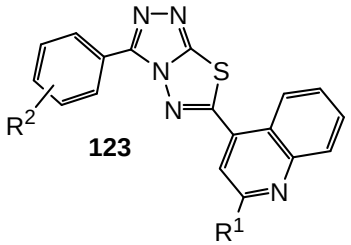
R^1 = Me, Et or Cyclopentyl
R^2 = Cyclohexyl, Ph or 4-$MeOC_6H_4$

Swamy *et al.* recently reported the synthesis and potent antibacterial and antifungal activities of the triazolo-1,3,4-thiadiazoles **122**.[98] Meanwhile, Mathew *et al.* reported the synthesis, significant anti-inflammatory and analgesic activities of the triazolo-1,3,4-thiadiazoles **123**.[99]



122

R^1 = 2-ClC_6H_4 or $CH(C_3H_7)_2$
R^2 = Me, Et, Ph, 4-MeC_6H_4 or 4-ClC_6H_4



123

R^1 = Me or Ph
R^2 = 4-Me_2N, 2-MeNH or 1-Naphthylmethyl

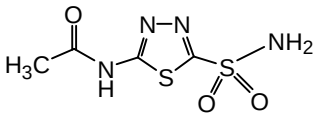
1.3. Pharmacological Properties of 1,3,4-Thiadiazole Derivatives

1,3,4-Thiadiazole nucleus constitutes the active part of several biologically active compounds. The most interesting are carbonic anhydrase inhibitory activity, antibacterial and antifungal activities.

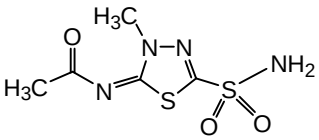
1,3,4-Thiadiazole-2-sulphonamides were early known as carbonic anhydrase inhibitors. Carbonic anhydrase enzymes (CAs) are ubiquitous zinc enzymes. These enzymes catalyze the interconversion between carbon dioxide and the bicarbonate

ion and thus involved in crucial physiological processes connected with respiration and transport of CO_2/HCO_3^- between metabolizing tissues and the lungs, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissues and organs, biosynthetic reactions such as gluconeogenesis, lipogenesis and ureagenesis, bone resorption, calcification, tumourigenicity and several other physiological and pathological processes. Inhibition of CAs would be clinically useful in the treatment of various diseases such as glaucoma, epilepsy, congestive heart failure, mountain sickness, gastric and duodenal ulcers and other neurological disorders.[100]

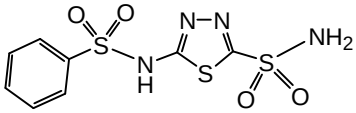
Several 1,3,4-thiadiazole-2-sulphonamides including acetazolamide **124**, methazolamide **125** and benzolamide **126** were early introduced as useful therapeutic agents for the treatment of glaucoma.[101]



124

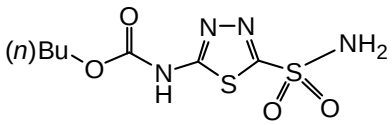


125



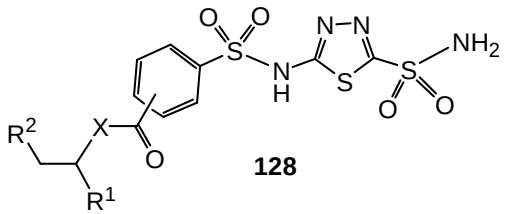
126

As a result of extensive search based on acetazolamide, several newer 1,3,4-thiadiazole derivatives were prepared for testing their CAs inhibitory activity as potential anticonvulsants and/or antiglucoma agents. The *t*-butoxycarbonylamido derivative **127**, prepared by Chufán *et al.*, showed potent *in vitro* inhibitory activity against CA isoenzyme II, and more potent, less toxic *in vivo* anticonvulsant activity compared to acetazolamide in mice.[102]



127

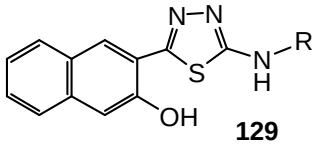
The ester and amide analogues of benzolamide **128** showed higher *in vitro* CAs inhibitory activity than acetazolamide and benzolamide. In addition, they were more effective as topical antiglucoma agents with longer duration of action in rabbits.[103]



128

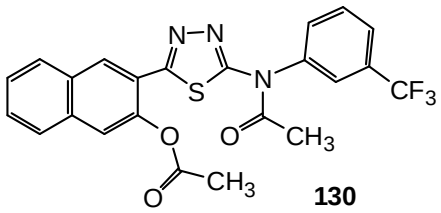
X = O or NH
R^1 = H or Me
R^2 = OH, MeO, Me_2N, Et_2N,
or $Me_2NCH_2CH_2O$

A series of 2,5-disubstituted-1,3,4-thiadiazoles of the general structures **129** and **130** were tested for anticonvulsant and antibacterial activities. The derivatives **129** (R = Et and 3-FC_6H_4) produced 90% and 70% protection against pentylenetetrazole-induced convulsions in mice, respectively. Meanwhile, the activity of compound **130** against Garm-positive bacteria was equal to that of benzylpenicillin.[104]



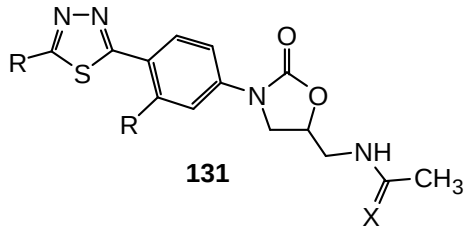
129

R = Et, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-FC_6H_4
4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4 or 3-$CF_3C_6H_4$,



130

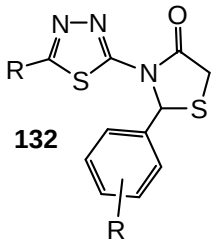
Potent and broad spectrum antibacterial activity was reported for a series of 1,3,4-thiadiazole phenyl oxazolidinones of the general structure **131**.[105] Meanwhile, most of the thiadiazolyl thiazolidinones **132** showed high antifungal activity against *Aspergillus clavatus* and *Aspergillus fumigatus*, and bactericidal activity against *Klebsiella* species.[106]



131

R = H, OH, Me, Et, FCH_2, $MeOCH_2$, $AcOCH_2$, EtOOC, $MeCO(CH_2)_2$, $MeSCH_2$, $HOCH_2$, H_2NCO, H_2NCOCH_2, $MeSOCH_2$, H_2NCH_2 or $MeNHCH_2$

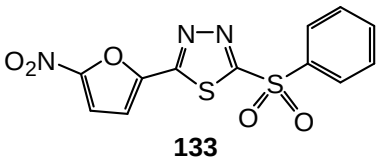
X = O or S



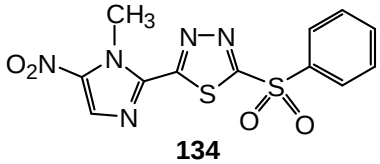
132

R = Ph, 2-Furanyl or PhS

The antifungal activity of the phenylsulphonyl-1,3,4-thiadiazoles **133** and **134** against several pathogenic Candida strains was found to be superior to the antifungal drug miconazole.[107]

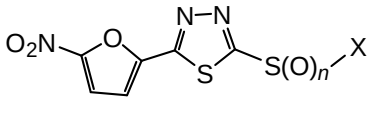


133

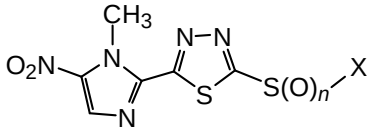


134

Several 2,5-disubstituted-1,3,4-thiadiazoles were reported to possess marked antituberculous activity, of these the nitrofuryl **135** and the nitroimidazolyl **136** thiadiazole derivatives, which exhibited very good activity against *Mycobacterium tuberculosis* H37Rv.[108,109] In addition, the activity of the nitrothienyl analogues of **135** was comparable to their nitrofuryl derivatives.[110]



135

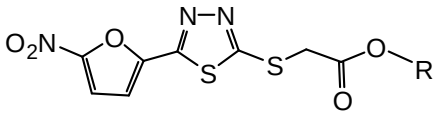


136

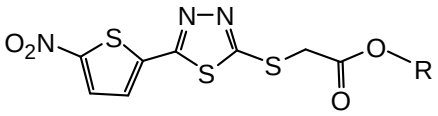
n = 0, 1 or 2

X = H, COOEt, $CONH_2$ or $CONHNH_2$

The alkyl α-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-ylthio]acetates **137**,[110] and their nitrothienyl analogues **138**,[111] were equally and highly active against *Mycobacterium tuberculosis* H37Rv.



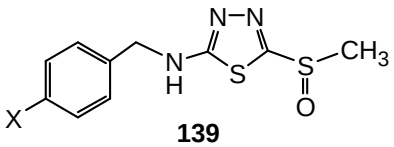
137



138

R = Me, Et, *n*-Pr, *n*-Bu, $PhCH_2$

Potent anti-inflammatory activity was recently observed among a series of 2-benzylamino or 4-halobenzylamino-1,3,4-thiadiazole-5-methylsulphoxides **139**.[112] The 4-fluoro derivative was identified as the most potent of these derivatives as it was more active than the selective COX-2 inhibitor celecoxib at the same molar concentration against carrageenan-induced rat paw oedema.



139

X = H, F, Cl or Br

2. RESEARCH OBJECTIVES

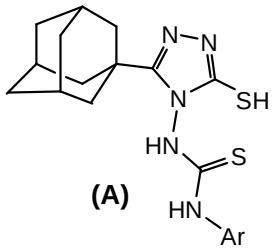
Research for the development of new therapeutic agents is becoming the major interest in many academic and industrial research laboratories all over the world with the aim to discover newer, more potent molecules, with higher specificity and reduced toxicity than the existing ones. In addition, the various types of resistant microorganisms that are discovered nowadays are becoming a great challenge for the scientists.

As shown in the introductory part, the adamantane nucleus was found to be a very important pharmacophore in many therapeutic agents. In addition, the incorporation of an adamantyl moiety into a pharmacologically-active molecule resulted in many cases in improving the therapeutic profile of the parent drug. Since the discovery of amantadine **2** in 1966 as the first antiviral therapy for systemic use, several hundreds or even thousands of 1-adamantyl, 2-adamantyl and adamantane-spiro derivatives were synthesized and proved to be effective against several pathogenic microorganisms and beneficial in improving various physiological disorders.

One of the most important concepts of drug design is the covalent conjugation of biologically active moieties, acting by different mechanisms that would lead; in a favourable case, to synergism that leads to compounds with improved activity and reduced toxicity. Based on this concept, and taking in consideration the pharmacological activities shown by various adamantane derivatives, 1,2,4-triazoles, fused 1,2,4-triazolo derivatives and 1,3,4-thiadiazoles, the aim of the present investigation is a trial to combine the structural features of adamantane derivatives with 1,2,4-triazoles, fused 1,2,4-triazoles or 1,3,4-thiadiazoles. The target compounds which are structurally-related to previously reported pharmacologically-active compounds are expected to possess antiviral, anti-inflammatory and/or antimicrobial activities.

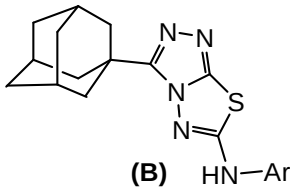
As previously mentioned, adamantyl 1,2,4-triazole derivatives were reported to possess various biological activities including antimicrobial, anti-

inflammatory,[51,54] and 11β-HSD1 inhibitory activities.[69,71] In addition, the conjugation of an adamantyl moiety with thiourea resulted in improving the chemotherapeutic activity.[20,21,24] Based on these observations, a series of *N*-[5-(1-adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-arylthioureas of the general structure (**A**) were synthesized.

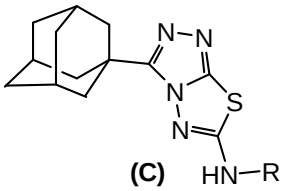


(A)

In view of the reported antibacterial,[89,96-98] antifungal[97,98] and anti-inflammatory[99] activities of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles, two series of 5-(1-adamantyl)-2-aryl or alkylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles of the general structures (**B** and **C**) were synthesized.

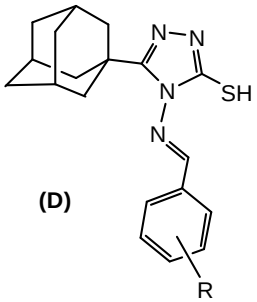


(B)



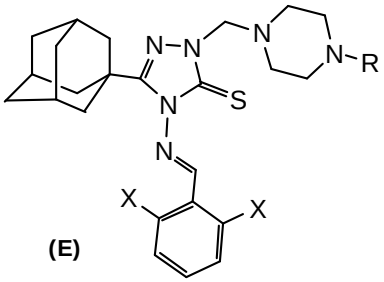
(C)

Taking into consideration, the anti-inflammatory activity,[81] and potent antibacterial and antifungal activities[92] of several arylideneamino-1,2,4-triazole-3-thiols, a series of 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles of the general structures (**D**) was synthesized.



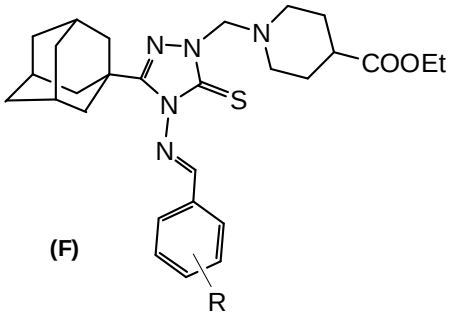
(D)

The incorporation of a 4-substituted-1-piperazinylmethyl moiety into 1,2,4-triazole and 1,3,4-oxadiazoles was reported to be endowed with anti-HIV,[31] antimicrobial,[92,93] and anticancer activities.[94] Thus, the *N*-Mannich bases namely, 5-(1-adamantyl)-4-arylideneamino-1-(4-substituted-1-piperazinyl-methyl)-1,2,4-triazoline-3-thiones (**E**) and their 4-ethoxycarbonylpiperidine analogues, 5-(1-adamantyl)-4-arylideneamino-1-(4-ethoxycarbonyl-1-piperidyl-methyl)-1,2,4-triazoline-3-thiones (**F**) were synthesized.



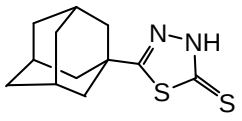
(E)

X = F or Cl

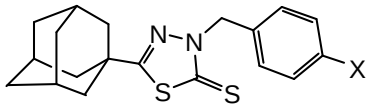


(F)

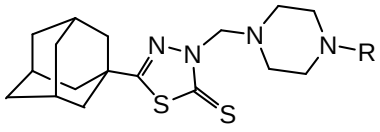
In view of the potent antifungal activity of the adamantyl 1,3,4-thaidiazole **31**,[42] the antimicrobial activity of the adamantylamino 1,3,4-thiadiazoles **49**,[52] the carbonic anhydrase inhibitory activity,[101-103] the antimicrobial activity,[104-110] and the anti-inflammatory activity[112] of various 1,3,4-thiadiazole, it was of interest to prepare 5-(1-adamantyl)-1,3,4-thiadiazoline-2-thione (**G**), its benzyl or 4-substituted benzyl derivatives (**H**), the *N*-piperazinomethyl Mannich bases (**I**), in addition to the *N*-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-arylthiourea derivatives (**J**).



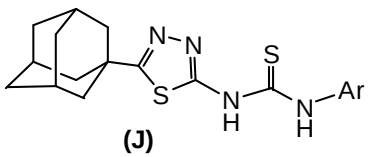
(G)



(H)

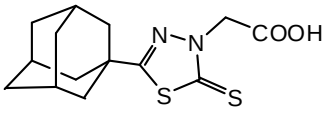


(I)

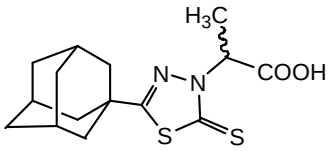


(J)

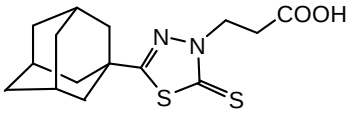
Acetic acid and propionic acid derivatives constitute the most important class of nonsteroidal anti-inflammatory agents.[113] Accordingly, the new adamantyl 1,3,4-thiadiazole-acetic or propionic acid derivatives (**K**, **L** and **M**) were prepared.



(K)



(L)



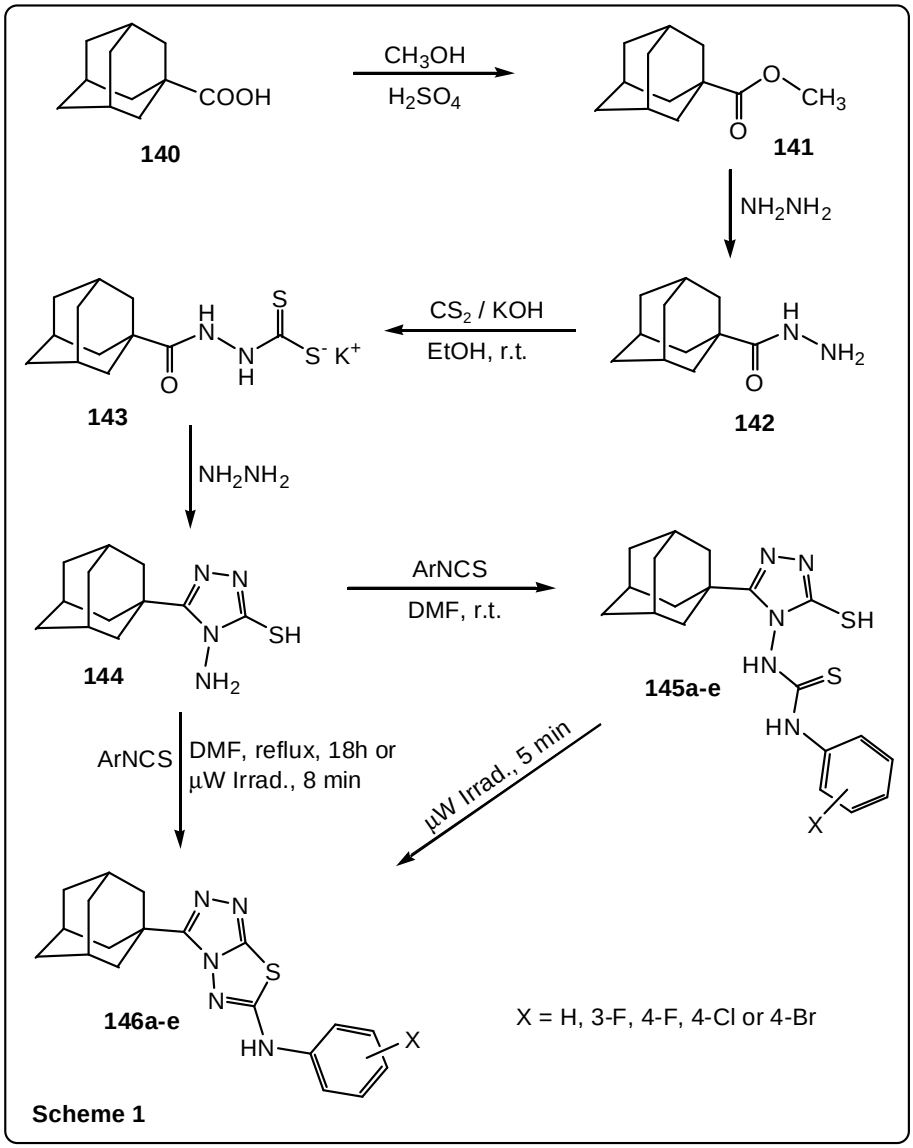
(M)

The main research objectives of this study is the synthesis of new adamantane derivatives, whose structures (**A**-**M**) are related to previously reported biologically-active derivatives.

3. THEORETICAL DISCUSSION OF THE EXPERIMENTAL WORK

Considering the previously mentioned objectives of this study to obtain the new target derivatives of the general structures (**A-M**), in which the 1-adamantyl moiety was attached to 1,2,4-triazole, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole or 1,3,4-thiadiazole nucleus, the schemes (1-6) were adopted.

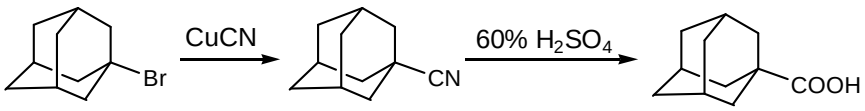
3.1. Synthesis of *N*-[5-(1-adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-arylthioureas (145a-e) and 5-(1-adamantyl)-2-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (146a-e) (Scheme 1)



Scheme 1

3.1.1. Methyl adamantane-1-carboxylate (141)

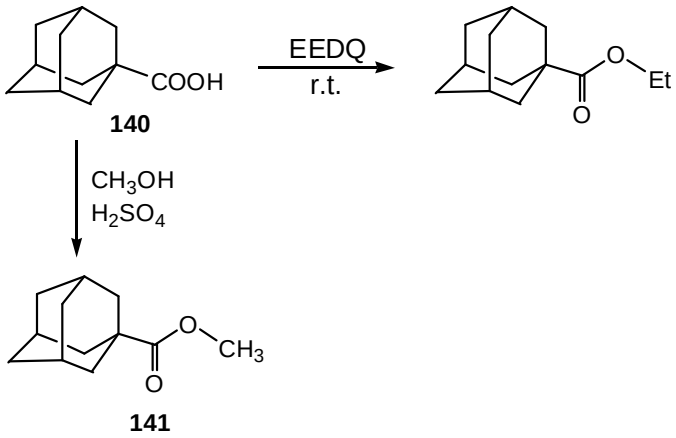
The starting material adamantane-1-carboxylic acid **140** is commercially-available. It was prepared by Nomura *et al.* through cyanation of 1-bromoadamantane with cuprous cyanide followed by hydrolysis with 60% sulphuric acid as follows:[114]



140

Several procedures were reported for the esterification of adamantane-1-carboxylic acid. The most recent procedure for the preparation of ethyl adamantane-1-carboxylate was described by Zacharie *et al.*,[115] through the reaction of the carboxylic acid with 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) under neutral and mild conditions. This method is suitable for the preparation of ethyl esters of heat and acid sensitive carboxylic acids.

In this investigation, methyl adamantane-1-carboxylate **141** was easily prepared following the classical esterification method by heating adamantane-1-carboxylic acid with pure methanol in the presence of sulphuric acid as dehydrating agent to yield the target ester in 98% yield.[54] The ethyl ester was also prepared in similar manner but with lower yield (65%). The methyl ester was found to be more beneficial than the ethyl ester because of its relatively higher melting point and the relative higher yield.

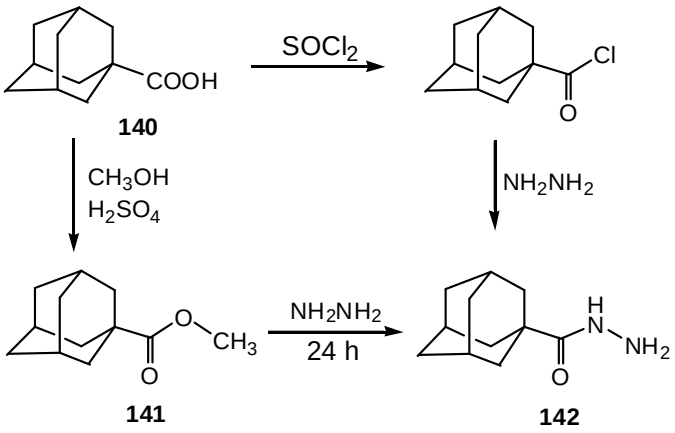


140 **141**

3.1.2. Adamantane-1-carboxylic acid hydrazide (142)

Several methods were reported for the preparation of carboxylic acid hydrazides. These methods mainly utilize the carboxylic acid ester (usually the methyl or the ethyl ester) with hydrazine in ethanol, or the acid halides with hydrazine in the presence of triethylamine.

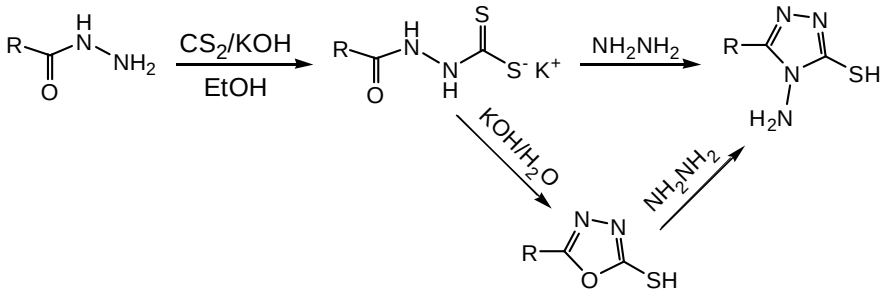
Ficarra *et al*. prepared adamantane-1-carboxylic acid hydrazide **142** by the reaction of adamantane-1-carbonyl chloride (prepared by the reaction of adamantane-1-carboxylic acid and thionyl chloride) with hydrazine hydrate in the presence of triethylamine in diethyl ether as a solvent.[45] Adamantane-1-carboxylic acid hydrazide **142** was also prepared in 98% yield *via* prolonged heating of compound **141** with hydrazine hydrate in the absence of solvent.[54] The latter procedure was adopted in this study for its high yield and the lack of the use of the harmful thionyl chloride.



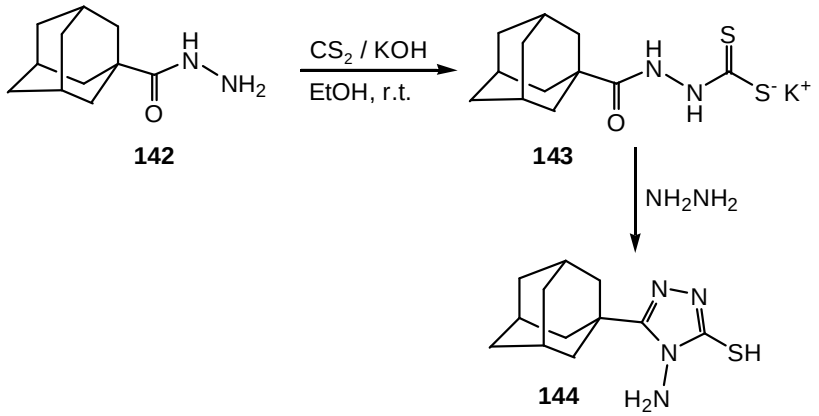
3.1.3. 5-(1-Adamantyl)-4-amino-3-mercapto-1,2,4-triazole (144)

4-Amino-5-substituted-3-mercapto-1,2,4-triazoles are useful intermediates for the synthesis of various condensed 1,2,4-triazolo derivatives. The most widely utilized method for the preparation of these derivatives depends on the condensation of the carboxylic acid hydrazide with carbon disulphide in ethanolic potassium hydroxide to yield the corresponding potassium 3-acyldithiocarbazate, which are converted to the corresponding 4-amino-5-substituted-3-mercapto-1,2,4-triazoles *via*

reaction with hydrazine. Alternatively, the cyclization of the 3-acyldithiocarbazates *via* heating with aqueous potassium hydroxide yields the corresponding 5-substituted-2-mercapto-1,3,4-oxadiazoles, which yield the corresponding 4-amino-5-substituted-3-mercapto-1,2,4-triazoles upon heating with hydrazine.[116] The reaction sequences are outlined as follows:



The previously reported 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** was prepared according to the method of El-Emam *et al.*,[117] through the condensation of adamantane-1-carboxylic acid hydrazide **142** with carbon disulphide in ethanolic potassium hydroxide to yield the corresponding potassium *N*'-(1-adamantylcarbonyl)dithiocarbazate **143**, which upon heating with hydrazine yielded 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** in good overall yield.



142 **143** **144**

3.1.4. N-[5-(1-Adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-arylthioureas (145a-e)

In the present study, trials to react 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** with arylisothiocyanates to get the corresponding disubstituted

thiourea derivatives **145a-e** *via* prolonged heating in ethanol or methanol up to 24 hours were unsuccessful, and the reactants were separated unchanged. The reaction seemed to be solvent-dependent, carrying out the reaction in *N*,*N*-dimethylformamide (DMF) at room temperature for 24 hours yielded the target *N*,*N'*-disubstituted thiourea derivatives **145a-e** in excellent yields (89-95%). Attempted reaction of compound **144** with methyl-, ethyl-, allyl-, *n*-butyl- or benzylisothiocyanate under the same conditions ended with failure, and the reactants were recovered unchanged. A similar observation was previously observed by Molina and Tárraga.[118]

The structures of compounds **145a-e** were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic absorption peaks at 3210-3278 cm^{-1} (NH), 3023-3180 cm^{-1} (Ar C-H), 2885-2954 cm^{-1} (Adamantane C-H) and 1495-1633 cm^{-1} (C=N). The ^{1}H NMR spectra are characterized by the presence of the adamantyl protons (15H) as a singlet at δ 1.70-1.72 ppm (6H) and a multiplet or two singlets at δ 1.96-2.08 ppm for the other 9 adamantane protons. The two NH protons appeared as two singlets at δ 9.77-9.98 and 10.02-10.81 ppm, while the SH protons came as singlet at δ 13.47-13.64 ppm. The ^{13}C NMR spectra are characterized by the presence of the adamantyl carbons as four peaks at δ 27.80-27.88, 34.65-34.85, 36.52-36.88 and 38.37-38.48 ppm. The assignment of the aryl carbons, triazoles C-3 and triazoles C-5 is rather complicated, particularly in cases of the fluorine-containing derivatives **145b** and **145c**. Taking into consideration the previously reported ^{13}C NMR data of similar substituted triazoles, the triazoles C-5 and C-3 could be safely assigned at δ 136.08-142.60 and 157.08-163.02 ppm, respectively. The assignment is also based on the exclusion of the characteristic aryl C-F and its neighbouring C-H carbons in the downfield region which appear as doublets with $J_{C\text{-}F}$ 92-94 and 23-26 Hz, respectively. Meanwhile, the C=S carbon appeared at δ 167.73-167.90 ppm. The detailed NMR and mass spectral data of the compounds **145a-e** are given in the experimental part (section *4.6*). As an example, the NMR data of compound **145b** are shown in Figure 1.

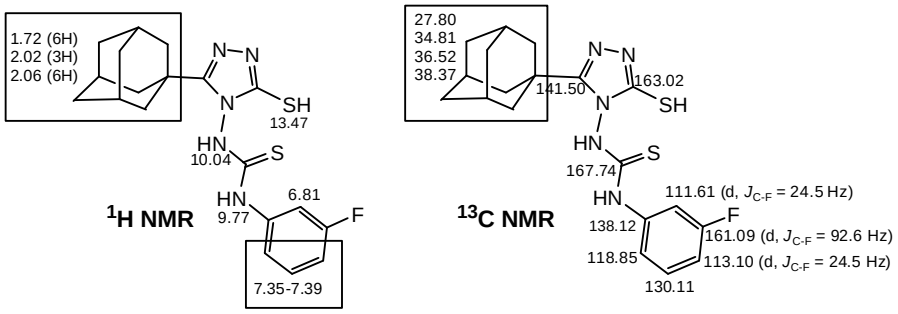


Figure 1: ^{1}H and ^{13}C NMR data of compound **145b**.

The relative intensity of the molecular ion peaks (M^+) of compounds **145a-e** (section *4.6*) in electron impact (EI) mass spectra were very low (1-2%) or even absent as in case of compound **145b**, but all of them showed characteristic peaks at (M^+ -34) characteristic for the dehydrosulphurized fragments. This behaviour was also observed for some *N*-[5-alkyl or aryl-3-mercapto-1,2,4-triazol-4-yl]-*N*'-(4-bromophenyl)thioureas.[118]

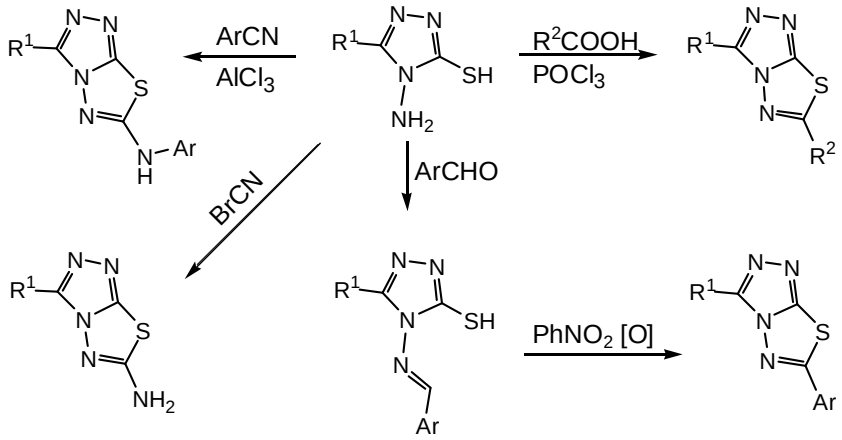
The following new *N*-[3-(1-adamantyl)-5-mercapto-1,2,4-triazol-4-yl]-*N*'-arylthioureas **145a-e** were prepared in this part:

1. *N*-[5-(1-Adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-phenylthiourea **154a**.
2. *N*-[5-(1-Adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-(3-fluorophenyl)thiourea **145b**.
3. *N*-[5-(1-Adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-(4-fluorophenyl)thiourea **145c**.
4. *N*-[5-(1-Adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-(4-chlorophenyl)thiourea **145d**.
5. *N*-[5-(1-Adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-(4-bromophenyl)thiourea **145e**.

3.1.5. 5-(1-Adamantyl)-2-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (146a-e)

Several methods were reported for the synthesis of 2,5-disubstituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles utilizing either 1,3,4-thiadiazoles or 1,2,4-triazoles

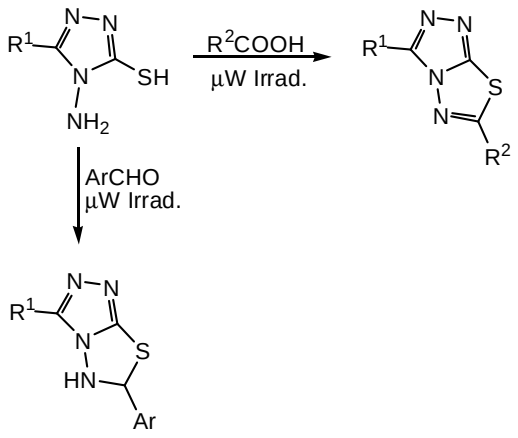
as starting materials. The use of 1,3,4-thiadiazoles as precursors for 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles utilizes mainly the 2-hydrazino-1,3,4-thiadiazoles as starting materials through reaction with alkyl orthoformate, cyanogen bromide or carbon disulphide. The main disadvantages of these methods are the numerous steps for the preparation of the starting materials and the poor overall yields. 4-Amino-5-mercapto-3-substituted-1,2,4-triazoles are excellent precursors for 2,5-disubstituted-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. The reactions utilizing these precursors include dehydrative ring closure by heating with carboxylic acids and phosphorus oxychloride,[96,99,117,119-122] heating with arylnitriles in the presence of aluminum chloride,[123] and oxidative cyclization of the 4-arylideneamino derivatives using nitrobenzene.[124] 2-Amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives were efficiently prepared from their corresponding 4-amino-3-mercapto-1,2,4-triazole derivatives *via* reaction with cyanogen bromide.[96,125,126] The condensation reactions of 4-amino-3-mercapto-1,2,4-triazoles to their 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles may be summarized as follows:



Eweiss *et al.* reported that the reaction of 4-amino-3-mercapto-1,2,4-triazoles with alkyl- or arylisothiocyanate in ethanol yields the corresponding 2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles,[96] in contrary to the observations of Molina and Tárraga who reported that 4-amino-3-mercapto-1,2,4-triazoles are unreactive towards alkyl- or arylisothiocyanate in ethanol, while they react only with arylisothiocyanate in DMF at room temperature to yield acyclic thiourea derivatives. Meanwhile, prolonged heating in DMF yields the 2-arylamino-1,2,4-triazolo[3,4-

b][1,3,4]thiadiazole derivatives.[118] In the present study, prolonged heating of compound **144** with phenyl-, 3-fluorophenyl-, 4-fluorophenyl-, 4-chlorophenyl- or 4-bromophenylisothiocyanate in DMF for 18 hours yielded the cyclic dehydrosulphurized products **146a-e** in 51-63% yields (Method A).

In the last decade, microwave irradiation was introduced as a useful alternative to the traditional heating for the synthesis of several heterocyclic derivatives.[127-129] Some 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles and their dihydro derivatives were recently prepared through the reaction of 4-amino-3-mercapto-1,2,4-triazoles with carboxylic acids,[98,130] or aldehydes[131] under microwave irradiation.



To our knowledge, microwave-assisted intramolecular dehydrosulphurization was not reported. It was of interest to attempt the cyclization of compounds **145a-e** to their cyclic dehydrosulphurized analogues **146a-e** *via* exposure to microwave irradiation. Thus, compounds **145a-e** were exposed to microwave irradiation in a domestic microwave oven in the absence of solvents. Several pilot experiments were carried out to optimize the irradiation time and intensity. Microwave irradiation for five minutes at 454 W (58%) was found to be the optimum condition for this reaction. The result of this technique was very interesting and compounds **145a-e** were successfully cyclized to compounds **146a-e** in high yields (92-95%) in a very short time (Method B). The reaction of 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** with phenyl- 3-fluorophenyl-, 4-fluorophenyl-, 4-chlorophenyl- or 4-

bromophenylisothiocyanate was similarly carried out *via* microwave irradiation for eight minutes to yield the corresponding cyclic products **146a-e** in 82-89% yields (Method C).

The structures of compounds **146a-e** were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic absorption peaks at 3257-3289 cm^{-1} (NH), 3044-3169 cm^{-1} (Ar C-H), 2888-2901 cm^{-1} (Adamantane C-H) and 1480-1667 cm^{-1} (C=N). The ^{1}H NMR spectra are characterized by the presence of the adamantyl protons (15H) as three singlets at δ 1.72-1.79 ppm (6H), δ 1.98-2.10 ppm (3H) and δ 2.08-2.15 ppm (6H). The NH protons appeared as separated singlet within the aromatic protons or as a multiplet at δ 7.06-7.60 ppm. The ^{13}C NMR spectra are characterized by the presence of the adamantyl carbons as four peaks at δ 27.40-27.86, 34.18-35.12, 35.99-36.80 and 38.30-39.15 ppm. The assignment of the C-2, C-5 and C-8 of the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole system is also rather complicated. According to the analysis of the ^{13}C NMR data of compounds **146a-e**, the assignment of the C-5, C-2 and C-8, it would be possible to conclude that the C-5 at δ 149.68-149.90 ppm, C-2 at δ 153.14-159.85 ppm and C-8 at δ 176.08-180.05 ppm. The detailed NMR and mass spectral data of compounds **146a-e** are given in the experimental part (section *4.7*). As an example, the NMR data of compound **146e** are shown in Figure 2.

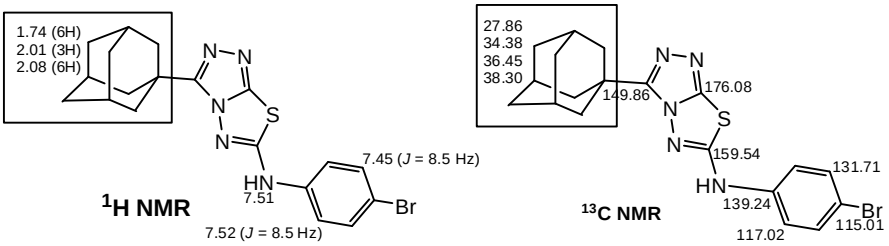


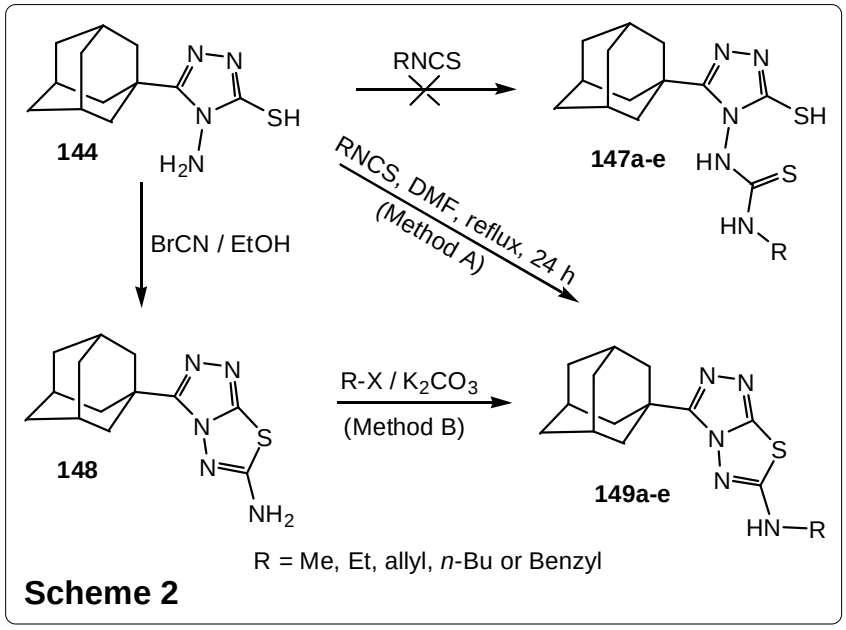
Figure 2: ^{1}H and ^{13}C NMR data of compound **146e**.

The following new 5-(1-adamantyl)-2-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **146a-e** were prepared in this part:

1. 5-(1-Adamantyl)-2-phenylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **146a**.

2. 5-(1-Adamantyl)-2-(3-fluorophenylamino)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **146b**.
3. 5-(1-Adamantyl)-2-(4-fluorophenylamino)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **146c**.
4. 5-(1-Adamantyl)-2-(4-chlorophenylamino)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **146d**.
5. 5-(1-Adamantyl)-2-(4-bromophenylamino)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **146e**.

3.2. Synthesis of 5-(1-adamantyl)-2-amino-1,2,4-triazolo[3,4-*b*][1,3,4]thia-diazole (148), and 5-(1-adamantyl)-2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (149a-e) (Scheme 2)



Scheme 2

3.2.1. 5-(1-Adamantyl)-2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadia-zoles (149a-e) (Method A)

As previously mentioned, attempted reaction of compound **144** with methyl-, ethyl-, allyl-, *n*-butyl- or benzylisothiocyanate to get the disubstituted thioureas **147a-e** or the cyclic derivatives **149a-e** was unsuccessful in ethanol and methanol at

room or reflux temperature or in DMF at room temperature. On carrying out the reaction in DMF for 24 hours at reflux temperature (Method A), the target compounds **149a-e** were obtained in fair yields (34-42%). In contrary to the reaction of compound **144** with arylisothiocyanate, microwave irradiation was unsuitable to assist the reaction with the aliphatic isothiocyanates. Increasing the irradiation time more than 10 minutes or irradiation intensity resulted in carbonization of the reactants.

3.2.2. 5-(1-Adamantyl)-2-amino and substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazoles (148 and 149a-e) (Method B)

Compounds **149a-e** were independently prepared in good overall yields (Method B) through the reaction of compound **144** with cyanogen bromide in ethanol according to the previously reported general procedures,[96,125,126] to yield 5-(1-adamantyl)-2-amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **148** in 76% yield. Compound **148** was successfully reacted with the appropriate halides namely; methyl iodide, ethyl iodide, allyl bromide, *n*-butyl bromide or benzyl chloride in ethanol, in the presence of potassium carbonate to afford good yields (82-92%) of the corresponding 5-(1-adamantyl)-2-substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]thia-diazole derivatives **149a-e**.

The structures of compounds **148** and **149a-e** were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic absorption peaks at 3243-3331 cm^{-1} (NH and NH_2), 3034 and 3152 cm^{-1} (Ar C-H and allyl C-H of compounds **149e** and **149c**, respectively), 2865-2924 cm^{-1} (Adamantane and alkyl C-H) and 1392-1643 cm^{-1} (C=N). The ^{1}H NMR spectra are characterized by the presence of the 15 adamantyl protons as three singlets or multiplets at δ 1.71-2.16 ppm. The NH_2 of compound **148** as singlet at δ 6.14 ppm and the NH of compounds **149a-e** as singlets at δ 5.25-5.72 ppm. The alkyl, phenyl and allyl protons were also distinguished. In addition to the adamantyl, alkyl, phenyl and allyl carbons, the ^{13}C NMR spectra showed the C-2, C-5 and C-8 of the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole system approximately as in

compounds **146a-e**. The detailed NMR and mass spectral data of the compounds are given in the experimental part (sections *4.8* & *4.9*). As an example, the NMR data of compound **149c** are shown in Figure 3.

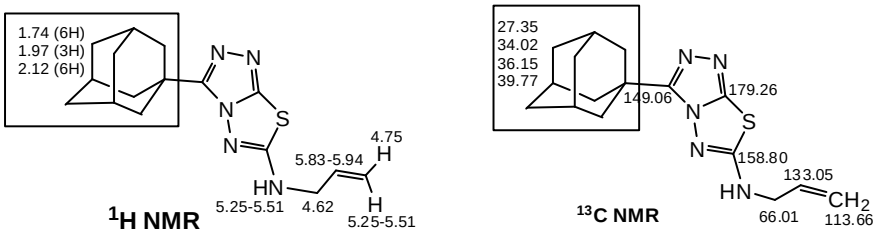
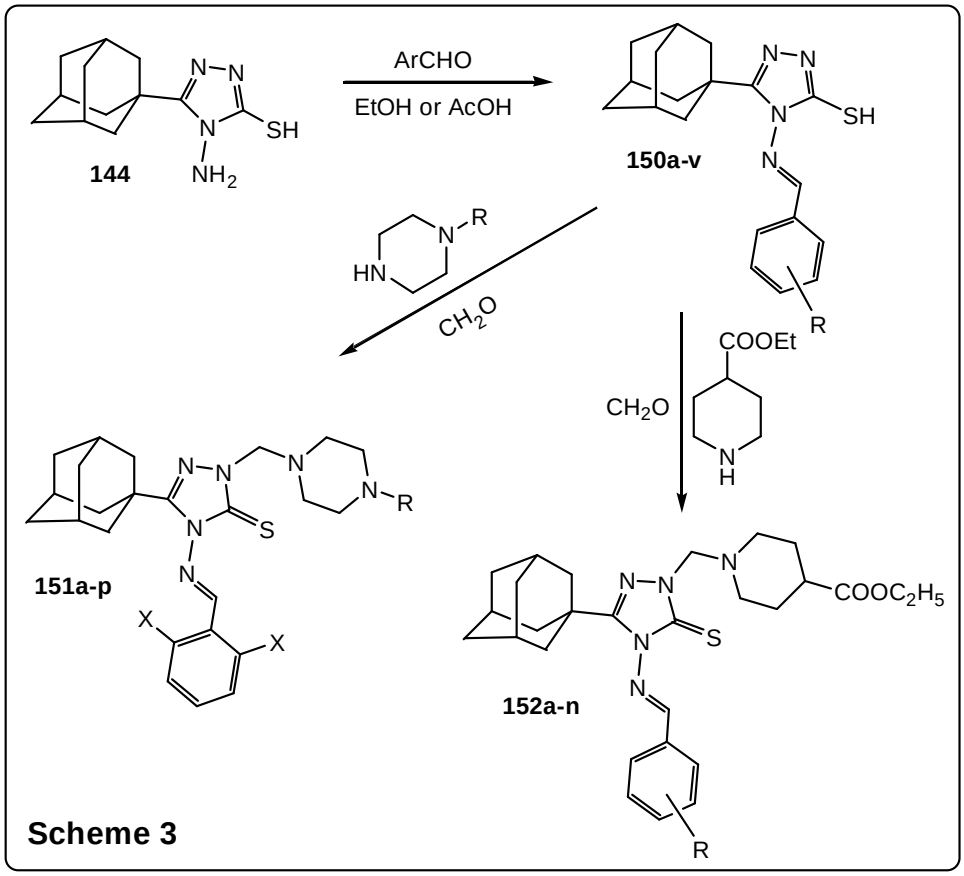


Figure 3: ^{1}H and ^{13}C NMR data of compound **149c**.

The following new 5-(1-adamantyl)-2-amino and substituted amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles **148** and **149a-e** were prepared in this part:

1. 5-(1-Adamantyl)-2-amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **148**.
2. 5-(1-Adamantyl)-2-methylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **149a**.
3. 5-(1-Adamantyl)-2-ethylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **149b**.
4. 5-(1-Adamantyl)-2-allylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **149c**.
5. 5-(1-Adamantyl)-2-(*n*-butylamino)-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **149d**.
6. 5-(1-Adamantyl)-2-benzylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **149e**.

3.3. Synthesis of 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles (150a-v), 5-(1-adamantyl)-4-arylideneamino-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones (151a-p) and 5-(1-adamantyl)-4-arylideneamino-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thiones (152a-n) (Scheme 3)



3.3.1. 5-(1-Adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles (150a-v)

The reaction of 4-amino-5-substituted-3-mercapto-1,2,4-triazoles with aromatic aldehydes have been studied by several authors. On carrying out the reaction under microwave irradiation, intramolecular cyclization took place and the dihydro 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles were obtained as previously described by Shiradkar *et al.* (section *3.1.5*).[131] Meanwhile, Haijian *et al*. reported that the possibility of intramolecular Mannich type cyclization could be minimized

via carrying out the reaction in acidic medium.[132] Several 4-arylideneamino-5-substituted-3-mercapto-1,2,4-triazoles were prepared by heating the corresponding 4-amino-5-substituted-3-mercapto-1,2,4-triazoles with aromatic aldehydes in ethanol, in the presence of catalytic amounts of sulphuric acid.[81,92,94] In addition to the catalytic role of sulphuric acid as acidifying agent, it acts also as dehydrating agent. In the present study, heating 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** with different aromatic aldehydes in ethanol under reflux for five hours was sufficient to yield most of the target arylideneamino derivatives in reasonable yields. The addition of catalytic amount of sulphuric acid to the reaction medium did not affect the rate of the reaction. In case of the reaction with 2-nitrobenzaldehyde, 4-nitrobenzaldehyde, 2,4-dichlorobenzaldehyde, 3,4-dichlorobenzaldehyde, 2,4-dinitrobenzaldehyde or 4,5-dimethoxy-2-nitrobenzaldehyde, the yields were very poor. This may be attributed to the poor solubility of these aldehydes in ethanol. However, carrying out the reaction in acetic acid, in which these aldehydes are freely soluble, greatly increased the yield.

The structures of compounds **150a-v** were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic absorption peaks at 3034 and 3152 cm^{-1} (Ar C-H), 2843-2904 cm^{-1} (Adamantane) and 1390-1687 cm^{-1} (C=N). The ^{1}H NMR spectra are characterized by the presence of the adamantyl protons (15) as a singlet or multiplet around δ 1.70 ppm (6H), a singlet around δ 2.01 ppm (3H) and a singlet around δ 2.07 ppm (6H). The CH=N proton appeared as a singlet at δ 9.21-10.63 ppm, while SH proton appeared around δ 13.46-13.90 ppm. The ^{13}C NMR spectra are characterized by the presence of the adamantyl carbons as four peaks at δ 27.30-27.80, 34.89-35.80, 35.87-36.53 and 37.67-38.76 ppm. The CH=N and C-5 seemed to be overlapping at δ 155.99-162.51 ppm, while the C-3 carbons are shown at δ 162.11-167.73 ppm. The assignment was further supported by two-dimensional (2D) NMR, ^{1}H-^{1}H-Homonuclear COSY NMR, ^{1}H-^{13}C-Heteronuclear COSY NMR, and Distortionless Enhancement by Polarization Transfer (DEPT) spectra of compound **150j**. The detailed NMR and mass spectral data of compounds **150a-v** are given in

the experimental part (section *4.10*). The NMR data of compound **150j** are shown in Figure 4.

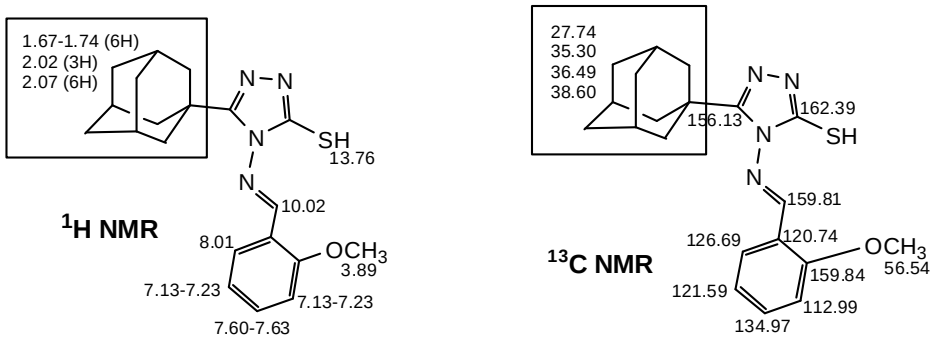


Figure 4: ^{1}H and ^{13}C NMR data of compound **150j**.

The ^{13}C NMR spectrum of compounds **150j** showed the adamantyl carbons at δ 27.74, 35.30, 36.49, 38.60 ppm. According to the DEPT spectrum (Figure 5), the peak at δ 27.74 ppm corresponds to the adamantane CH carbons, the peaks at δ 36.49 and 38.60 ppm (shown as two positive signed signals) corresponds to the two different adamantane CH_2 carbons, while the peak at δ 35.30 ppm which represents the adamantane quaternary carbon did not appear in the DEPT spectrum. The ^{1}H-^{13}C-Heteronuclear COSY NMR spectrum (Figure 6) revealed that the OCH_3 protons at δ 3.89 ppm are coupled with the OCH_3 at δ 56.54 ppm, while the CH=N proton at δ 10.02 ppm is coupled with the CH=N carbon at δ 159.81 ppm.

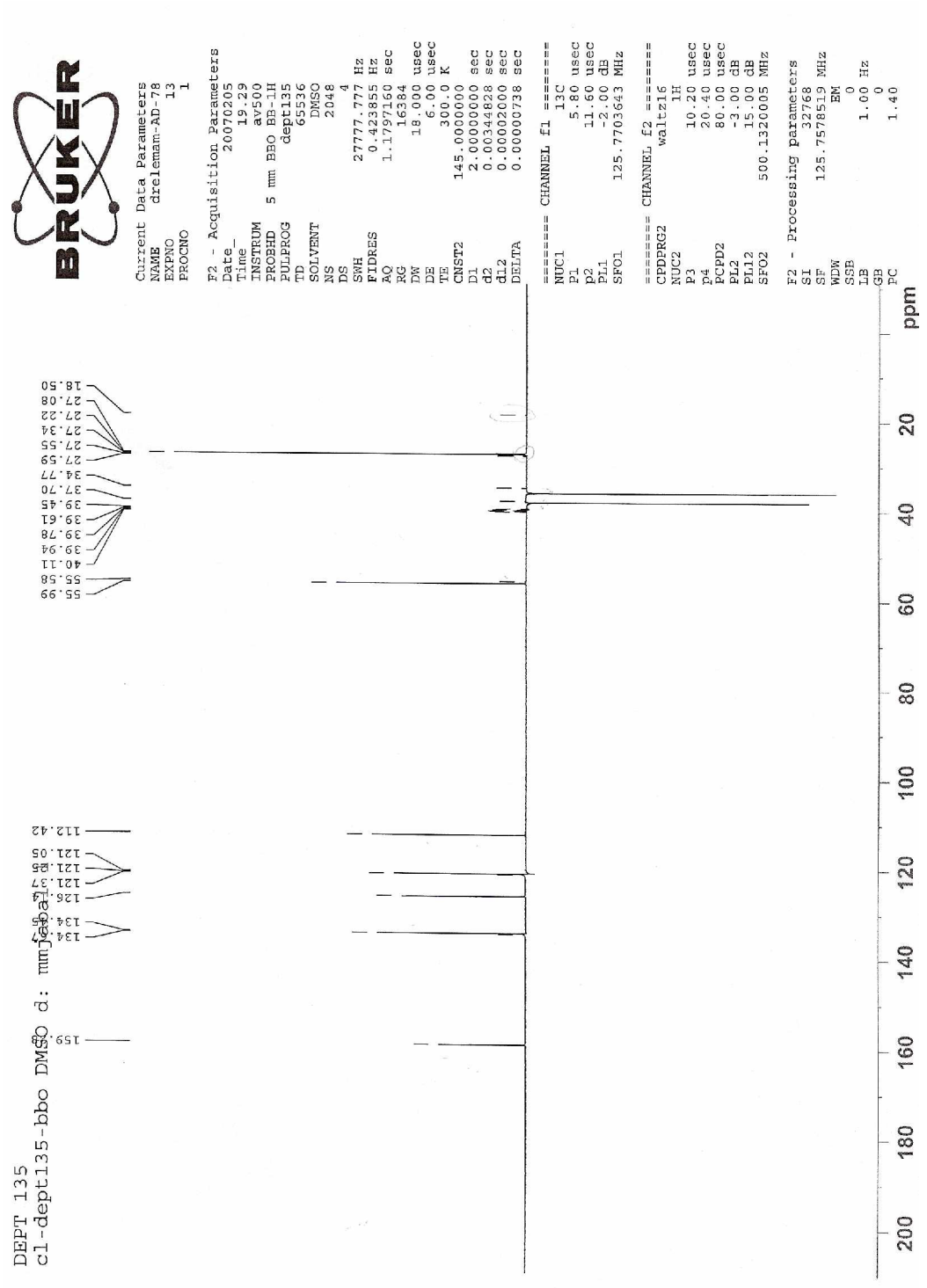


Figure 5: DEPT spectrum of compound **150j**.

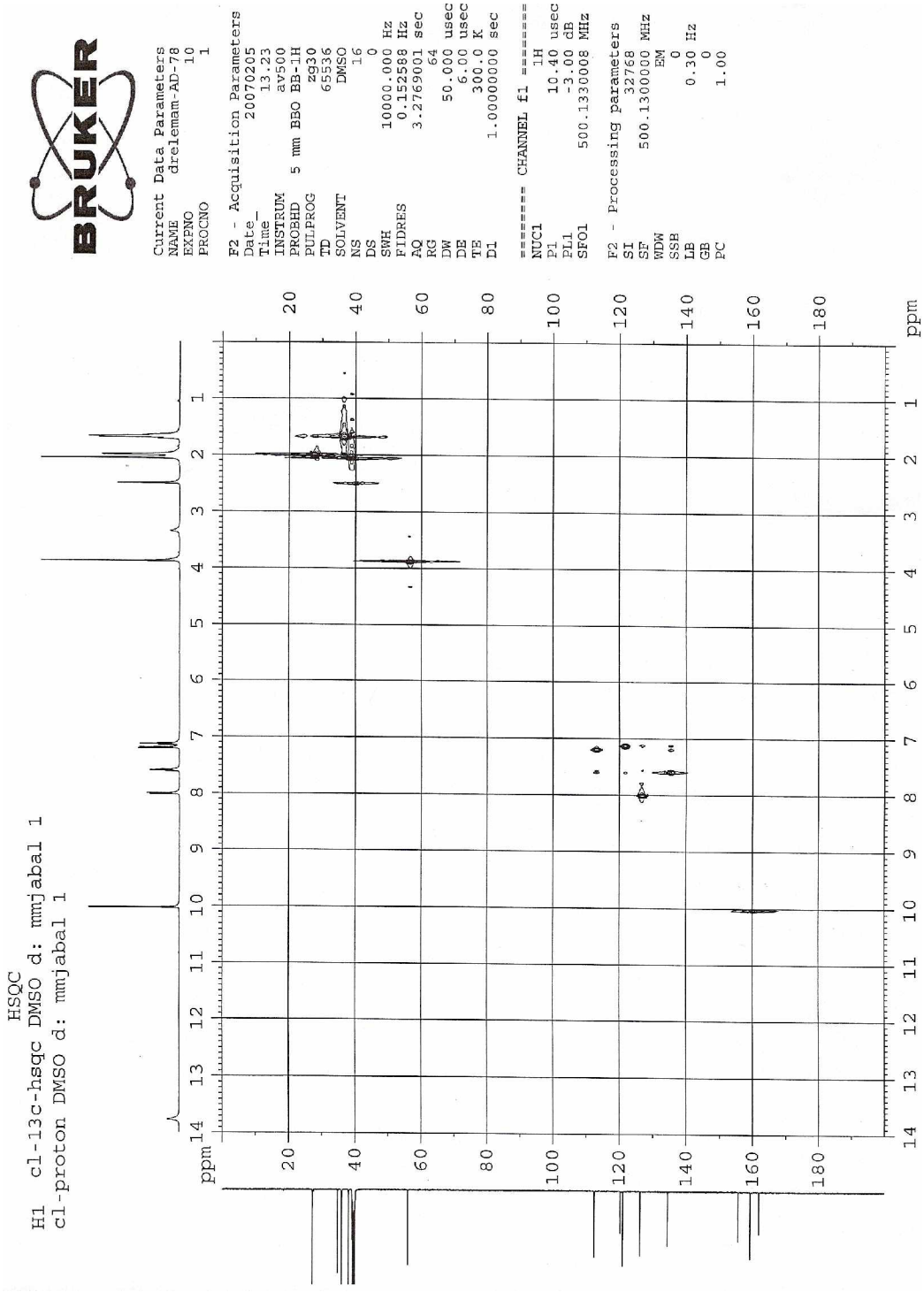


Figure 6: ^{1}H-^{13}C-Heteronuclear COSY NMR spectrum of compound **150j**.

The following new 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles **150a-v** were prepared in this part:

1. 5-(1-Adamantyl)-4-benzylideneamino-3-mercapto-1,2,4-triazole **150a**.
2. 5-(1-Adamantyl)-4-(2-fluorobenzylideneamino)-3-mercapto-1,2,4-triazole **150b**.
3. 5-(1-Adamantyl)-4-(4-fluorobenzylideneamino)-3-mercapto-1,2,4-triazole **150c**.
4. 5-(1-Adamantyl)-4-(2-chlorobenzylideneamino)-3-mercapto-1,2,4-triazole **150d**.
5. 5-(1-Adamantyl)-4-(4-chlorobenzylideneamino)-3-mercapto-1,2,4-triazole **150e**.
6. 5-(1-Adamantyl)-4-(4-bromorobenzylideneamino)-3-mercapto-1,2,4-triazole **150f**.
7. 5-(1-Adamantyl)-4-(2-hydroxybenzylideneamino)-3-mercapto-1,2,4-triazole **150g**.
8. 5-(1-Adamantyl)-4-(4-hydroxybenzylideneamino)-3-mercapto-1,2,4-triazole **150h**.
9. 5-(1-Adamantyl)-4-(4-methylbenzylideneamino)-3-mercapto-1,2,4-triazole **150i**.
10. 5-(1-Adamantyl)-4-(2-methoxybenzylideneamino)-3-mercapto-1,2,4-triazole **150j**.
11. 5-(1-Adamantyl)-4-(4-methoxybenzylideneamino)-3-mercapto-1,2,4-triazole **150k**.
12. 5-(1-Adamantyl)-4-(2-nitrobenzylideneamino)-3-mercapto-1,2,4-triazole **150l**.
13. 5-(1-Adamantyl)-4-(4-nitrobenzylideneamino)-3-mercapto-1,2,4-triazole **150m**.
14. 5-(1-Adamantyl)-4-(4-dimethylaminobenzylideneamino)-3-mercapto-1,2,4-triazole **150n**.
15. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-3-mercapto-1,2,4-triazole **150o**.
16. 5-(1-Adamantyl)-4-(2-chloro-6-fluorobenzylideneamino)-3-mercapto-1,2,4-triazole **150p**.
17. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-3-mercapto-1,2,4-triazole **150q**.
18. 5-(1-Adamantyl)-4-(2,4-dichlorobenzylideneamino)-3-mercapto-1,2,4-triazole **150r**.
19. 5-(1-Adamantyl)-4-(3,4-dichlorobenzylideneamino)-3-mercapto-1,2,4-triazole **150s**.
20. 5-(1-Adamantyl)-4-(3,4-dimethoxybenzylideneamino)-3-mercapto-1,2,4-triazole **150t**.
21. 5-(1-Adamantyl)-4-(2,4-dinitrobenzylideneamino)-3-mercapto-1,2,4-triazole **150u**.

22. 5-(1-Adamantyl)-4-(4,5-dimethoxy-2-nitrobenzylideneamino)-3-mercapto-1,2,4-triazole **150v**.

3.3.2. 5-(1-Adamantyl)-4-arylideneamino-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones (151a-p)

4-Arylideneamino-5-substituted-3-mercapto-1,2,4-triazoles were reported to react with primary or secondary amines and formaldehyde solution to yield the corresponding *N*-aminomethyl derivatives (Mannich bases).[92-94] These Mannich bases were also obtained *via* one-pot reaction of the 4-amino-5-substituted-3-mercapto-1,2,4-triazole with aromatic aldehydes, formaldehyde solution and the secondary amines.[93] The reaction was reported to proceed at room temperature in ethanol or ethanol/dioxan. The 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles **150o** and **150q** were reacted with several monosubstituted piperazines and formaldehyde solution in ethanol to yield the corresponding *N*-Mannich bases **151a-p** in good yields. The reaction was carried out by heating the reactants in ethanol for 15 minutes to enhance the solubility of compounds **150o** and **150q**. On monitoring the reaction with thin layer chromatography (TLC), the starting compounds **150o** and **150q** disappeared completely after 15 minutes and the products either precipitated on standing or after addition of water.

The structures of compounds **151a-p** were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic absorption peaks at 3041 and 3165 cm^{-1} (Ar C-H), 2806-2911 cm^{-1} (Adamantane, NCH_2N and piperazine C-H) and 1388-1674 cm^{-1} (C=N). The ^{1}H NMR spectra are characterized by the presence of the adamantyl protons (15) as singlets at δ 1.75-1.80 ppm (6H), singlets at δ 2.02-2.10 ppm (3H) and singlets or multiplet at δ 2.16-2.20 ppm (6H). The piperazine protons (8H) appeared as two separate singlets or multiplets at δ 2.41-3.51 ppm in all the derivatives except compounds **151g** and **151o** (R = 2-$CH_3OC_6H_4$) whose piperazine protons were magnetically equivalent and were shown as singlets of 8 protons at δ 3.10 and 3.11 ppm, respectively. The NCH_2N proton appeared as singlets at δ 5.16-5.26 ppm, while

the CH=N proton appeared as a singlet at δ 10.46-10.80 ppm. The ^{13}C NMR spectra are characterized by the presence of the adamantyl carbons as four peaks at δ 27.91-28.02, 35.50-35.62, 36.43-36.49 and 38.32-39.55 ppm. The piperazine carbons were shown as two separate peaks at δ 48.87-58.36 ppm, while the NCH_2N carbon appeared at δ 68.68-69.15 ppm. The CH=N and C-5 also seemed overlapping at δ 155.41-161.99 ppm, while the C=S carbons were shown at δ 163.05-163.50 ppm. The detailed NMR and mass spectral data of compounds **151a-p** are given in the experimental part (section *4.11*). The NMR data of compound **151e** are presented in Figure 7.

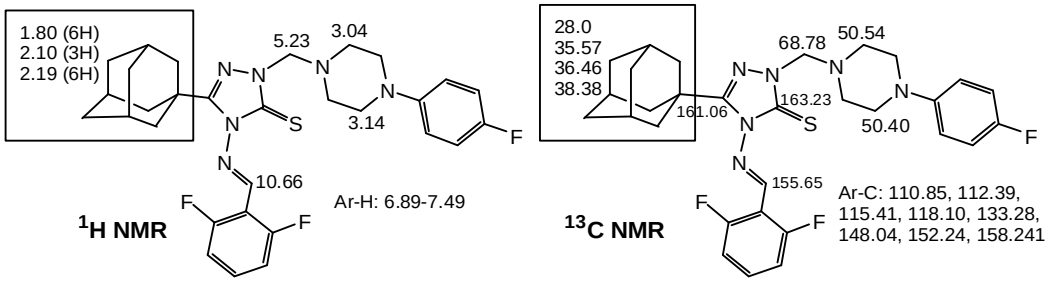


Figure 7: ^{1}H and ^{13}C NMR data of compound **151e**.

The DEPT spectrum of compound **151e** (Figure 8) showed the adamantane CH carbons at δ 28.0 ppm and the two different adamantane CH_2 carbons at δ 36.46 and 38.38 ppm, while the quaternary carbon at δ 35.57 ppm did not appear in the DEPT spectrum. The spectrum also clearly showed the piperazine, NCH_2N and CH=N carbons. The ^{1}H-^{13}C-Heteronuclear COSY NMR spectrum (Figure 9) showed the coupling between the piperazine protons at δ 3.04 (4H) and 3.14 (4H) with the piperazine carbons at δ 50.40 and 50.54 ppm. The NCH_2N protons at δ 5.23 ppm were coupled with the NCH_2N carbon at δ 68.78 ppm. In addition, the CH=N proton at δ 10.66 ppm was coupled with the CH=N carbon at δ 155.65 ppm.

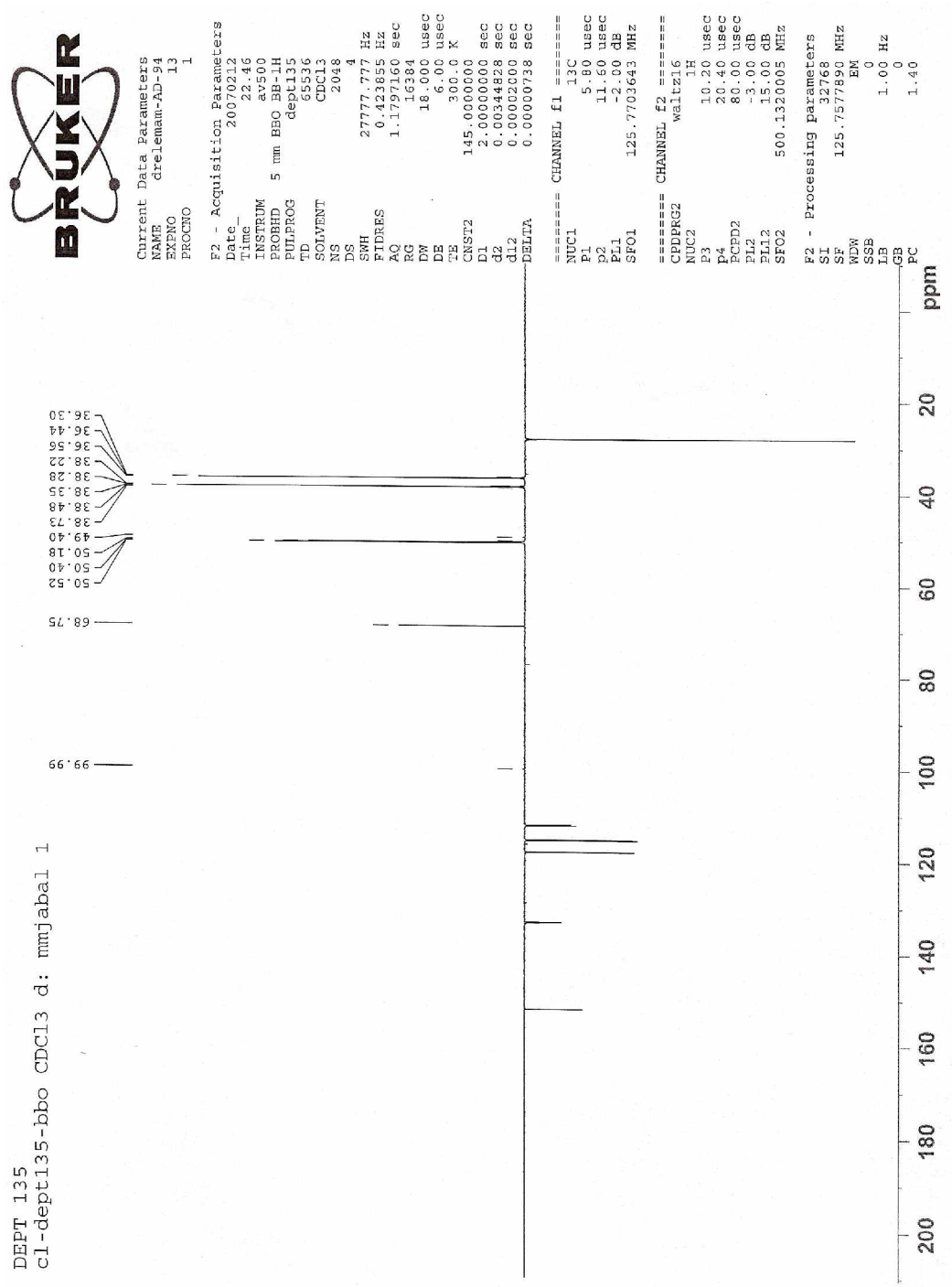


Figure 8: DEPT spectrum of compound **151e**.

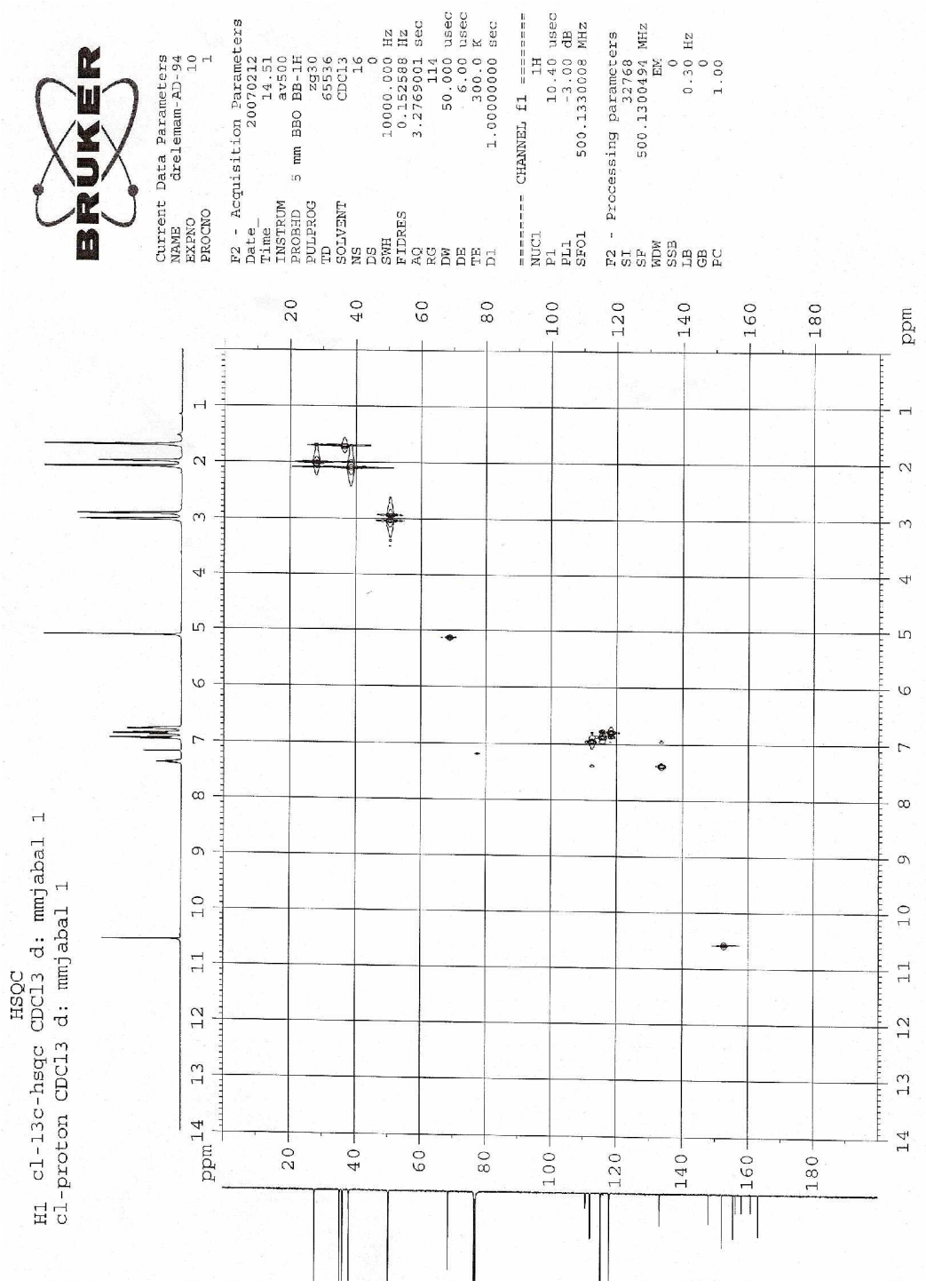


Figure 9: ^{1}H-^{13}C-Heteronuclear COSY NMR spectrum of compound **151e**.

The NMR data of compound **151o** are shown in Figure 10. The DEPT spectrum of compound **151o** (Figure 11) showed the adamantane CH carbons at δ 27.98 ppm and the two different adamantane CH_2 carbons at δ 36.49 and 38.51 ppm, while the quaternary carbon at δ 35.59 ppm did not appear in the DEPT spectrum. The spectrum also clearly showed the piperazine, OCH_3, NCH_2N and CH=N carbons. The ^{1}H-^{13}C-Heteronuclear COSY NMR spectrum (Figure 12) showed the coupling between the piperazine protons at δ 3.11 (8H) with the piperazine carbons at δ 50.76 and 50.84 ppm, the OCH_3 protons at δ 3.87 ppm with the OCH_3 carbon at δ 55.28 ppm, the NCH_2N protons at δ 5.26 ppm were coupled with the NCH_2N carbon at δ 69.22 ppm. In addition, the CH=N proton at δ 10.76 ppm was coupled with the CH=N carbon at δ 157.89 ppm.

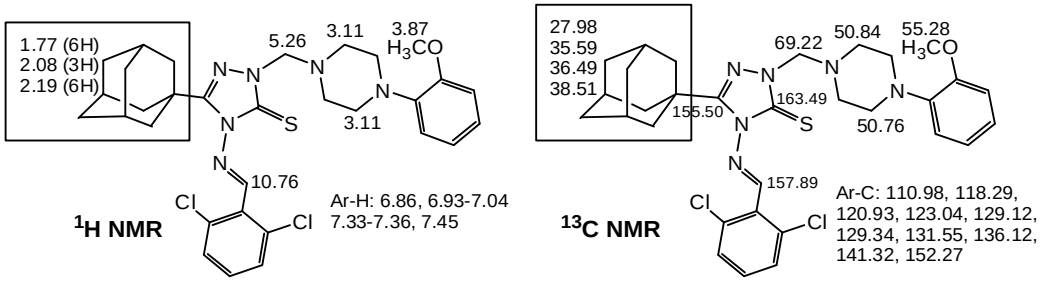


Figure 10: ^{1}H and ^{13}C NMR data of compound **151o**.

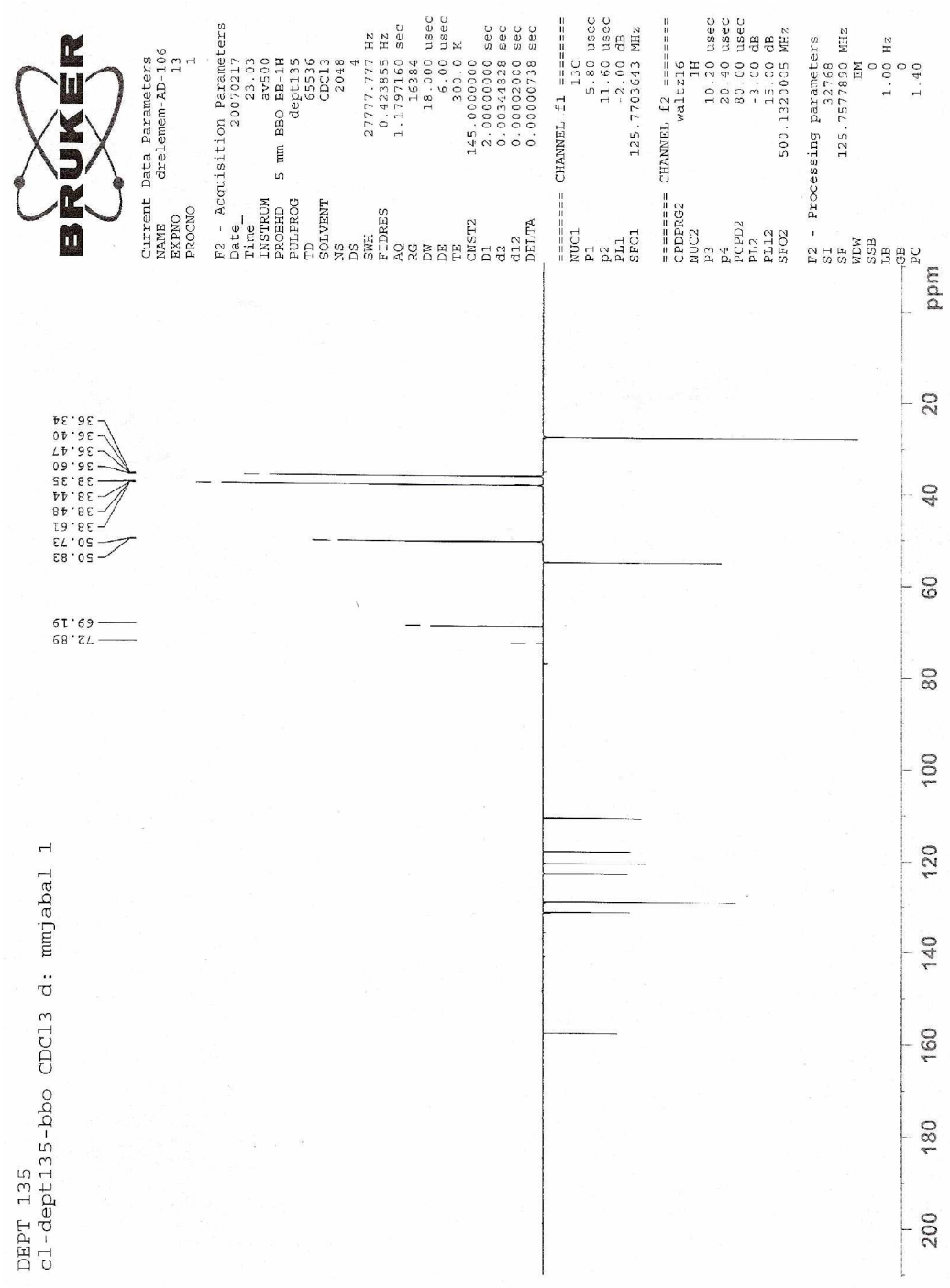


Figure 11: DEPT spectrum of compound **151o**.

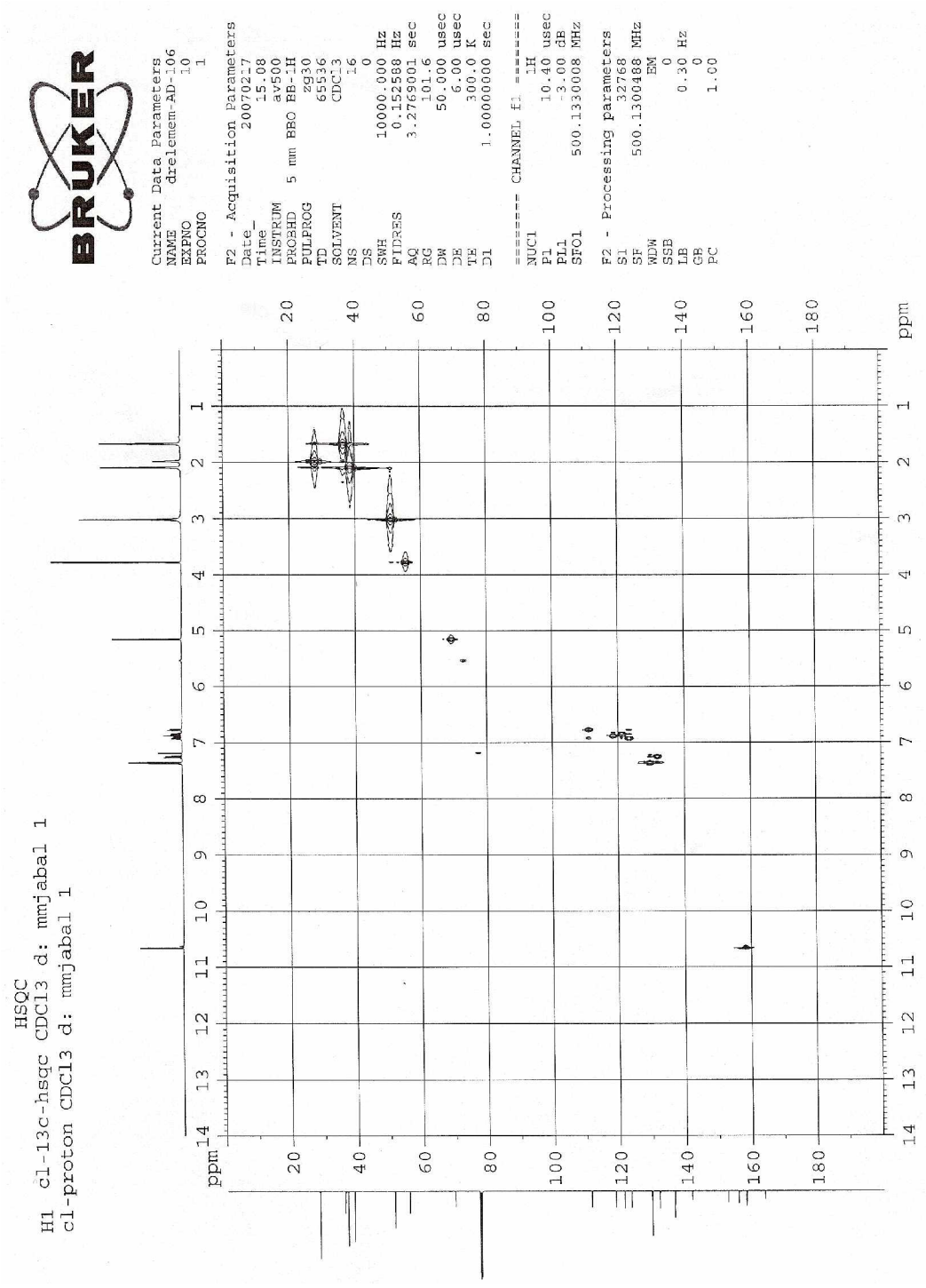


Figure 12: ^{1}H-^{13}C-Heteronuclear COSY NMR spectrum of compound **151o**.

The following new 5-(1-adamantyl)-4-arylideneamino-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones **151a-p** were prepared in this part:

1. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-(4-methyl-1-piperazinylme-thyl)-1,2,4-triazoline-3-thione **151a**.
2. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-(4-ethyl-1-piperazinylmeth-yl)-1,2,4-triazoline-3-thione **151b**.
3. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-(4-ethoxycarbonyl-1-pipera-zinylmethyl)-1,2,4-triazoline-3-thione **151c**.
4. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-(4-phenyl-1-piperazinylme-thyl)-1,2,4-triazoline-3-thione **151d**.
5. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-[4-(4-fluorphenyl)-1-piper- azinylmethyl]-1,2,4-triazoline-3-thione **151e**.
6. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-[4-(3-trifluoromethyl-phenyl)-1-piperazinylmethyl]-1,2,4-triazoline-3-thione **151f**.
7. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-[4-(2-methoxyphenyl)-1-piperazinylmethyl]-1,2,4-triazoline-3-thione **151g**.
8. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-(4-benzyl-1-piperazinylme-thyl)-1,2,4-triazoline-3-thione **151h**.
9. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-(4-methyl-1-piperazinylme-thyl)-1,2,4-triazoline-3-thione **151i**.
10. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-(4-ethyl-1-piperazinylmeth-yl)-1,2,4-triazoline-3-thione **151j**.
11. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-(4-ethoxycarbonyl-1-pipera-zinylmethyl)-1,2,4-triazoline-3-thione **151k**.
12. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-(4-phenyl-1-piperazinylme-thyl)-1,2,4-triazoline-3-thione **151l**.
13. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-[4-(4-fluorphenyl)-1-piper- azinylmethyl]-1,2,4-triazoline-3-thione **151m**.
14. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-[4-(3-trifluoromethyl-phenyl)-1-piperazinylmethyl]-1,2,4-triazoline-3-thione **151n**.

15. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-[4-(2-methoxyphenyl)-1-piperazinylmethyl]-1,2,4-triazoline-3-thione **151o**.
16. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-(4-benzyl-1-piperazinylme-thyl)-1,2,4-triazoline-3-thione **151p**.

3.3.3. 5-(1-Adamantyl)-4-arylideneamino-2-(4-ethoxycarbonyl-1-piperidyl-methyl)-1,2,4-triazoline-3-thiones (152a-n)

The Mannich bases 5-(1-adamantyl)-4-arylideneamino-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thiones **152a-n**, were similarly prepared *via* the reaction of the corresponding 4-arylideneamino-5-substituted-3-mercapto-1,2,4-triazole with ethyl 4-piperidinecarboxylate and formaldehyde solution to yield the corresponding *N*-Mannich bases **152a-n**. The reaction was similarly carried out by heating the reactants in ethanol for 20 minutes to enhance the solubility of compounds **150** and the products either precipitated on standing or after addition of water.

The structures of compounds **152a-n** were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic absorption peaks at 3039 and 3168 cm^{-1} (Ar C-H), 2806-2911 cm^{-1} (Adamantane, NCH_2N, piperidine and ethyl C-H), 1381-1679 cm^{-1} (C=N) and 1733-1776 cm^{-1} (C=O). The ^{1}H NMR spectra are characterized by the presence of the ester ethyl group as triplets (3H) at δ 1.24-1.25 ppm (J = 7.0 Hz) and quartets (2H) at δ 4.11-4.13 ppm (J = 7.0 Hz). The adamantyl protons and two piperidine protons (17H) are shown as singlets or multiplets at δ 1.71-2.18 ppm. The piperidine protons (9H) appeared as five separated multiplets at δ 1.71-1.84 (2H, 3' & 5', overlapped with 6 adamantane H), 1.91-1.96 (2H, 3' & 5'), 2.20-2.26 (1H, 4'), 2.46-2.57 (2H, 2' & 6' H) and 3.18-3.23 ppm (2H, 2' & 6' H). The ^{1}H NMR pattern of the piperidine protons is attributed to the fact that piperidine nucleus is nonplanar, this behaviour was not observed in the semi-planar piperazine nucleus. Similar observation was previously reported for some indane derivatives.[133] The NCH_2N proton appeared as singlets at δ 5.12-5.15 ppm, while the CH=N proton appeared as

singlets at δ 9.55-10.87 ppm. The ^{13}C NMR spectra are characterized by the presence of the ester ethyl group at δ 14.17-14.20 (CH_3) and 58.53-60.29 ppm (CH_2). The adamantyl carbons appeared as four peaks at δ 27.80-28.0, 35.35-35.59, 36.29-36.58 and 38.40-38.97 ppm. The piperidine carbons were shown as three peaks at δ 28.15-28.36 (C 3'&5'), 40.42-40.79 (C 4') and 50.41-50.48 ppm (C 2'&6'). The NCH_2N carbon appeared at δ 69.43-70.22 ppm. The CH=N and the C-5 carbons are shown at δ 154.28-162.69 ppm while the C=S carbons were shown at δ 163.05-164.17 ppm. The ester C=O carbons were shown at δ 174.94-175.32 ppm. The detailed NMR and mass spectral data of compounds **152a-n** are given in the experimental part (section *4.12*). The NMR data of compound **152i** are shown in Figure 13.

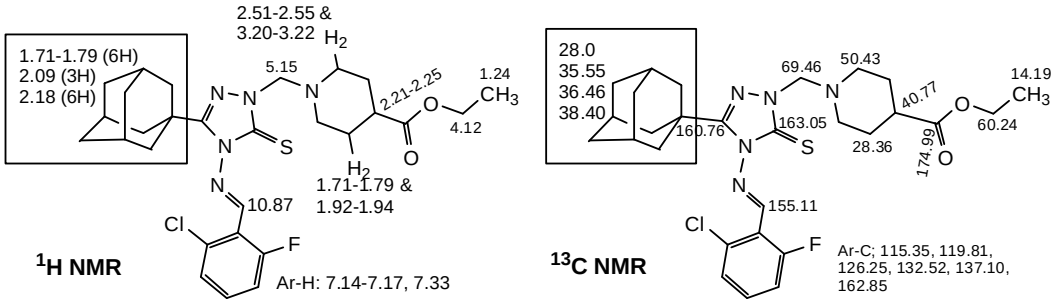


Figure 13: ^{1}H and ^{13}C NMR data of compound **152i**.

The DEPT spectrum of compound **152i** (Figure 14) showed the adamantane CH carbons at δ 28.0 ppm and the two different adamantane CH_2 carbons at δ 36.46 and 38.40 ppm, while the quaternary carbon at δ 35.55 ppm did not appear in the DEPT spectrum. The spectrum also clearly showed the piperidine CH_2 carbons at δ 28.36 and 50.43 ppm, while the secondary piperidine carbon (C-4) was shown at δ 40.77 ppm, the ethyl carbons at δ 14.19 and 60.24 ppm, the NCH_2N carbon at δ 69.46 ppm and the CH=N carbon at δ 155.11 ppm. The ^{1}H-^{13}C-Heteronuclear COSY NMR spectrum (Figure 15) clearly showed the correlation of the ethyl CH_2 protons at δ 4.12 ppm with the CH_2 carbon at δ 60.24 ppm, the NCH_2N protons at δ 5.15 ppm with the NCH_2N carbon at δ 69.46 ppm, the 9 piperidine protons with their

corresponding CH_2 and CH carbons at δ 28.36, 40.77 and 50.43 ppm, the CH=N proton at δ 10.87 ppm with the CH=N carbon at δ 155.11 ppm.

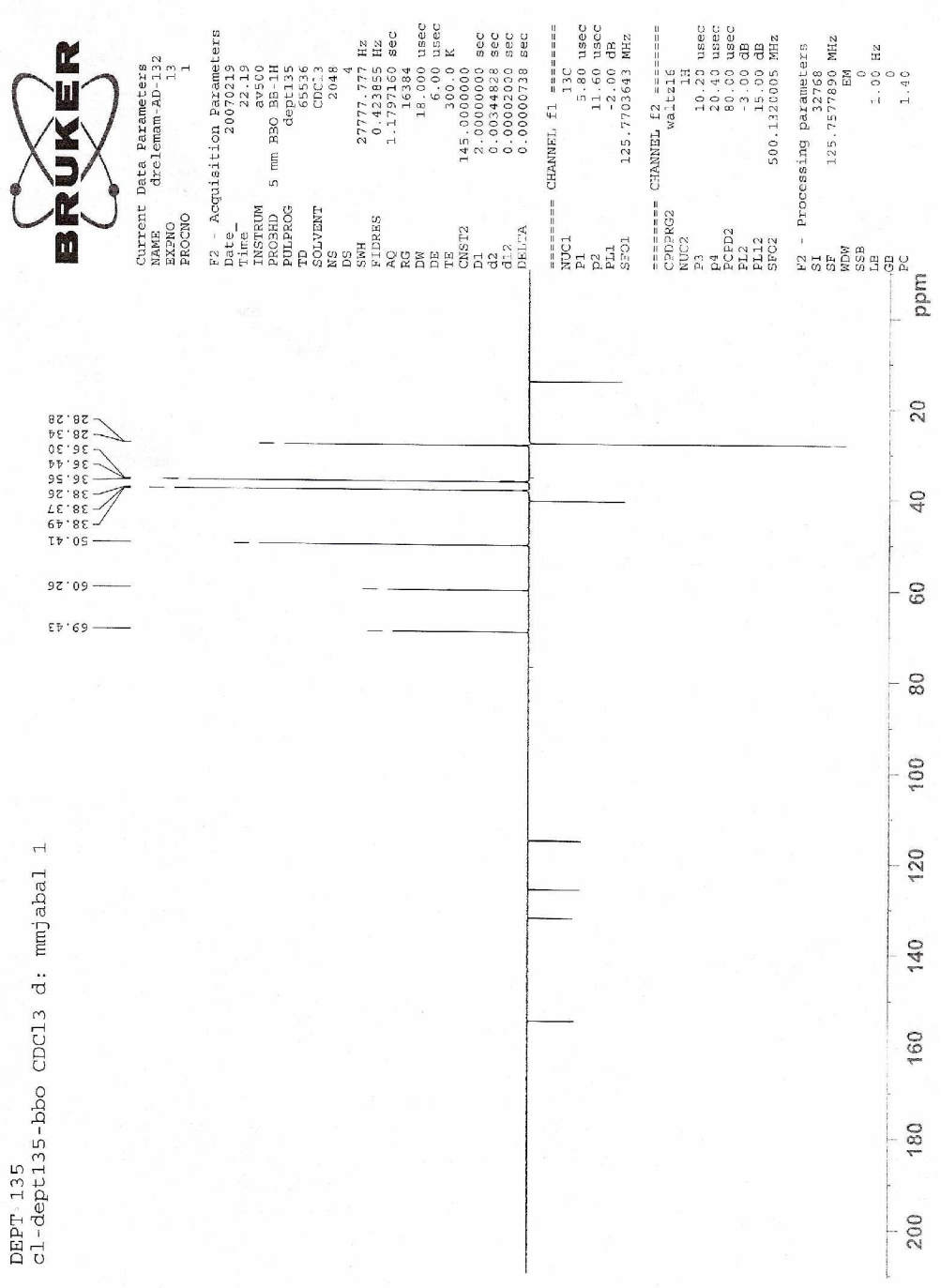


Figure 14: DEPT spectrum of compound **152i**.

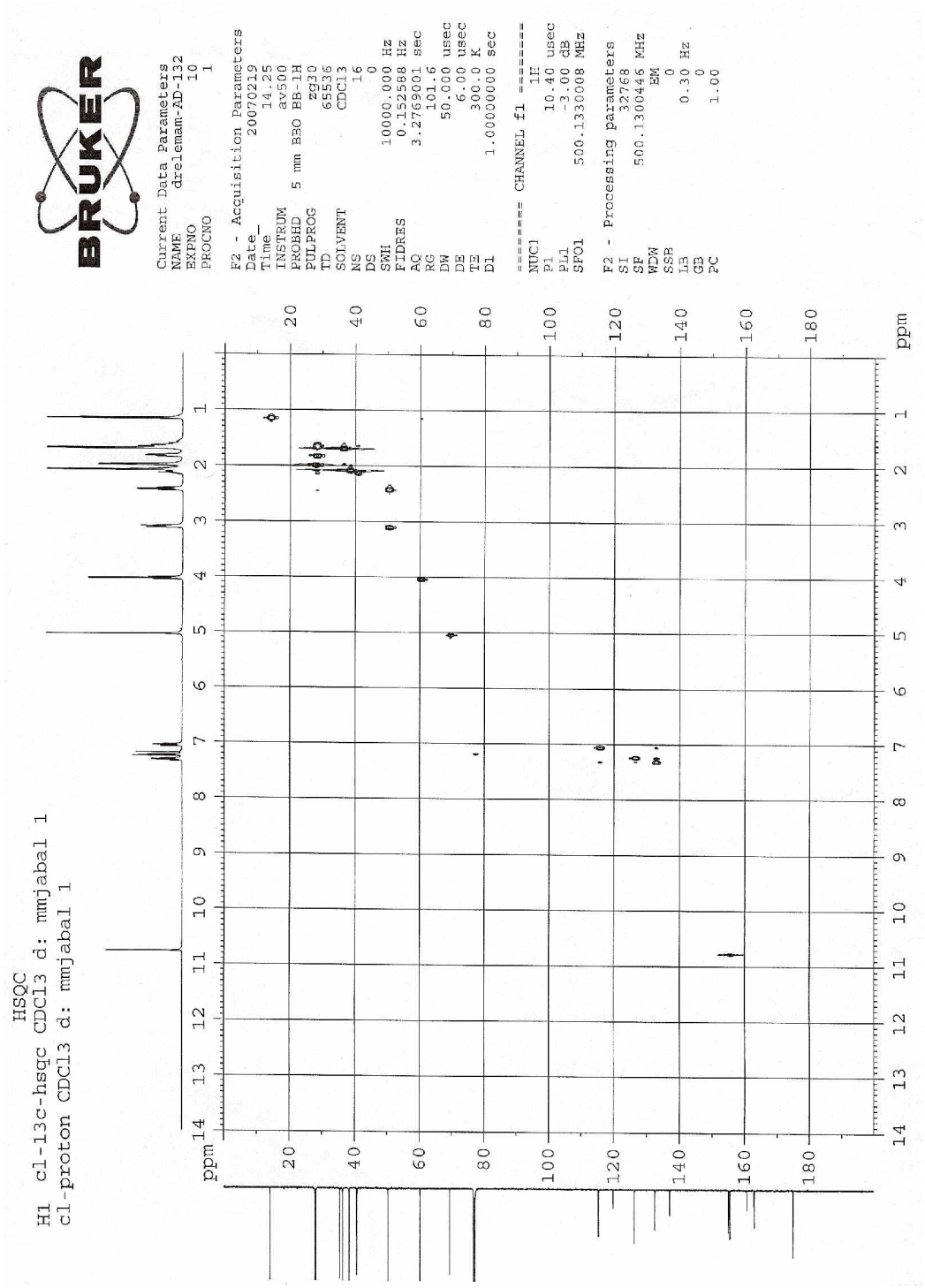
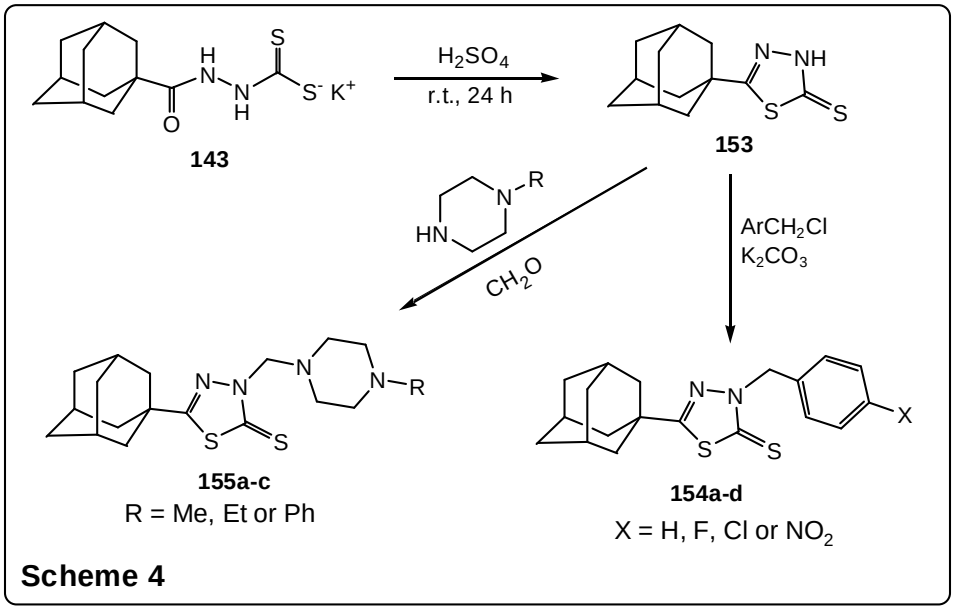


Figure 15: ^{1}H-^{13}C-Heteronuclear COSY NMR spectrum of compound **152i**.

The following new 5-(1-adamantyl)-4-arylideneamino-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thiones **152a-n** were prepared in this part:

1. 5-(1-Adamantyl)-4-benzylideneamino-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thione **152a**.
2. 5-(1-Adamantyl)-4-(2-fluorobenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidyl-methyl)-1,2,4-triazoline-3-thione **152b**.
3. 5-(1-Adamantyl)-4-(2-chlorobenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidyl-methyl)-1,2,4-triazoline-3-thione **152c**.
4. 5-(1-Adamantyl)-4-(4-methylbenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidyl-methyl)-1,2,4-triazoline-3-thione **152d**.
5. 5-(1-Adamantyl)-4-(2-hydroxybenzylideneamino)-2-(4-ethoxycarbonyl-1-piperid-ylmethyl)-1,2,4-triazoline-3-thione **152e**.
6. 5-(1-Adamantyl)-4-(4-hydroxybenzylideneamino)-2-(4-ethoxycarbonyl-1-piperid-ylmethyl)-1,2,4-triazoline-3-thione **152f**.
7. 5-(1-Adamantyl)-4-(4-methoxybenzylideneamino)-2-(4-ethoxycarbonyl-1-piperid-ylmethyl)-1,2,4-triazoline-3-thione **152g**.
8. 5-(1-Adamantyl)-4-(2,6-difluorobenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thione **152h**.
9. 5-(1-Adamantyl)-4-(2-chloro-6-fluorobenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thione **152i**.
10. 5-(1-Adamantyl)-4-(2,6-dichlorobenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thione **152j**.
11. 5-(1-Adamantyl)-4-(2,4-dichlorobenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thione **152k**.
12. 5-(1-Adamantyl)-4-(3,4-dichlorobenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thione **152l**.
13. 5-(1-Adamantyl)-4-(3,4-dimethoxybenzylideneamino)-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thione **152m**.
14. 5-(1-Adamantyl)-4-(4,5-dimethoxy-2-nitrobenzylideneamino)-2-(4-ethoxycarbon-yl-1-piperidylmethyl)-1,2,4-triazoline-3-thione **152n**.

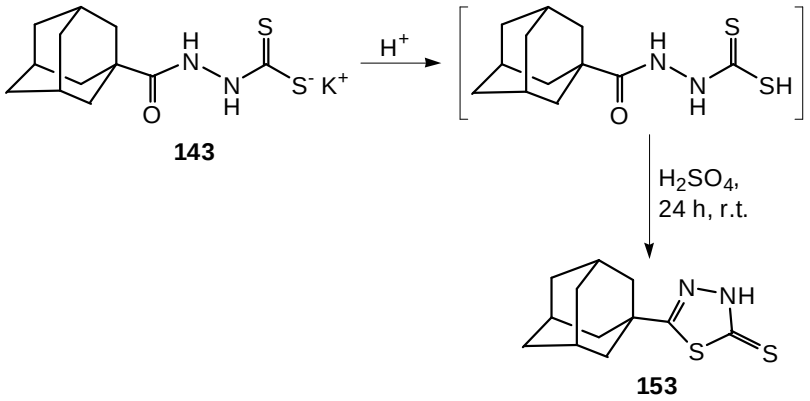
3.4. Synthesis of 5-(1-adamantyl)-1,3,4-thiadiazoline-2-thione (153), 5-(1-adamantyl)-3-(benzyl or 4-substituted benzyl)-1,3,4-thiadiazoline-2-thiones (154a-d) and 5-(1-adamantyl)-3-(4-substituted-1-pipera-zinylmethyl)-1,3,4-thiadiazoline-2-thiones (155a-c) (Scheme 4)



Scheme 4

3.4.1. 5-(1-Adamantyl)-1,3,4-thiadiazoline-2-thione (153)

The adamantyl dithiocarbazic acid of the potassium dithiocarbazate **143** was liberated and simultaneously dehydrated by the action of concentrated sulphuric acid at room temperature to yield the new target 5-(1-adamantyl)-1,3,4-thiadiazoline-2-thione **153** in 62% yield.



The spectral data of compound **153** confirmed its existence in the thione form. The IR spectrum showed characteristic absorption peaks at 3341 cm^{-1} (N-H), 2864 cm^{-1} (Adamantane C-H), 1394 and 1605 cm^{-1} (C=N). The ^{1}H NMR spectrum showed the adamantane protons at δ 1.77-1.84 (6H), 2.10 (6H) and 2.14 (3H), and the NH proton as singlet at δ 6.14 ppm. The ^{13}C NMR spectrum showed the adamantane carbons at δ 28.36, 36.24, 38.86 and 43.39 ppm, the thiadiazole C-5 at 156.09, and the C=S at 184.35 ppm.

3.4.2. 5-(1-adamantyl)-3-(benzyl or 4-substituted benzyl)-1,3,4-thiadiazoline-2-thiones (154a-d)

Compound **153** was aralkylated *via* reaction with benzyl- or 4-substituted benzyl chloride, in ethanol, in the presence of anhydrous potassium carbonate to yield the corresponding *N*-arylmethyl derivatives **154a-d**. Although the alkylation of 1,2,4-triazole-3-thiols were reported to yield a mixture of the *S*- and *N*-alkyl derivatives,[134] the *N*-alkyl derivatives were reported to be the sole product of alkylation of 1,3,4-oxadiazole-2-thiols.[31] The reaction of **153** with benzyl- or 4-substituted benzyl chloride yielded only one product as proved by thin layer chromatography (TLC) which was identified to be the *N*-arylmethyl derivatives **154a-d**. The structure judgments was based on the ^{13}C NMR spectra which showed the presence of the C=S carbon at δ 180.80-180.95 ppm. The structures were also supported by the electron impact mass spectra which all showed significant peaks at (M^{+} -33) indicating the loss of sulphur atom, and another peaks at *m/z* 105, 123, 135 and 150 characteristic for the corresponding NCH_2Ar fragments.

The structures of compounds **154a-d** were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic absorption peaks at 3065 and 3182 cm^{-1} (Ar C-H), 2803-2942 cm^{-1} (Adamantane and CH_2 C-H) and 1413-1656 cm^{-1} (C=N). The ^{1}H NMR spectra are characterized by the presence of the adamantyl protons as multiplets or singlet at δ 1.73-1.83 ppm (6H), singlets at δ 1.96-2.06 ppm (6H) and singlets at δ 1.96-2.06 ppm (3H). The benzylic CH_2 were shown as singlets at δ 4.52-4.60 ppm. The ^{13}C

NMR spectra are characterized by the presence of the adamantyl carbons δ 28.35-28.42, 36.25-36.35, 38.10-38.43 and 43.27-43.40 ppm. The benzylic CH_2 carbons were shown at δ 36.59-38.34 ppm. The C-5 and C=S carbons were shown at δ 162.32-163.99 and 180.80-181.88 ppm, respectively. The detailed NMR and mass spectral data of the compounds are given in the experimental part (section *4.14*). As an example, the NMR data of compound **154c** are shown in Figure 16.

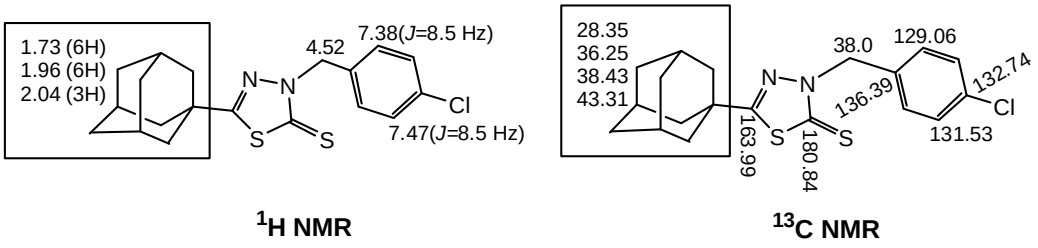


Figure 16: ^{1}H and ^{13}C NMR data of compound **154c**.

The following new 5-(1-adamantyl)-3-(benzyl or 4-substituted benzyl)-1,3,4-thiadiazoline-2-thiones **154a-d** were prepared in this part:

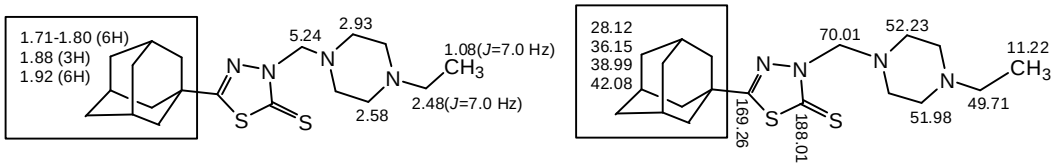
1. 5-(1-Adamantyl)-3-benzyl-1,3,4-thiadiazoline-2-thione **154a**.
2. 5-(1-Adamantyl)-3-(4-fluorobenzyl)-1,3,4-thiadiazoline-2-thione **154b**.
3. 5-(1-Adamantyl)-3-(4-chlorobenzyl)-1,3,4-thiadiazoline-2-thione **154c**.
4. 5-(1-Adamantyl)-3-(4-nitrobenzyl)-1,3,4-thiadiazoline-2-thione **154d**.

3.4.3. 5-(1-Adamantyl)-3-(4-substituted-1-piperazinylmethyl)-1,3,4-thiadiazoline-2-thiones (155a-c)

Compound **153** was reacted with formaldehyde solution and monosubstituted piperazines, in ethanol, by heating for 2 hours then stirring at room temperature for 24 hours to yield relatively low yields (36-52%) of the *N*-Mannich bases **155a-c**. The reaction did not proceed smoothly as in case of the preparation of the *N*-Mannich

bases **151a-p 152a-n**, increasing the reflux time to improve the yields resulted in decomposition of the products and the isolation of unidentified tarry matter.

The structures of compounds **155a-c** were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic absorption peaks at 3152 cm^{-1} of the aromatic C-H (**155c**), 2833-2921 cm^{-1} (Adamantane, NCH_2N, piperazine and alkyl C-H) and 1401-1675 cm^{-1} (C=N). The ^{1}H NMR spectra are characterized by the presence of the adamantyl protons as multiplets at δ 1.71-1.80 ppm (6H), singlets at δ 1.88-2.10 (3H) and singlets at 1.92-2.14 (6H). The piperazine (8H) appeared as singlets or multiplets at δ 2.58-3.03 and 2.93-3.20 ppm. The NCH_2N protons appeared as singlets at δ 5.25-5.31 ppm. The ^{13}C NMR spectra are characterized by the presence of the adamantyl carbons at δ 27.98-28.36, 36.05-36.25, 38.43-38.99 and 42.08-43.39 ppm. The piperazine carbons were shown as two peaks at δ 49.47-51.98 and 50.42-52.23 ppm, while the NCH_2N carbons appeared at δ 70.01-70.33 ppm. The C-5 and C=S carbons were shown at δ 165.85-169.26 and 184.34-188.01 ppm, respectively. The detailed NMR and mass spectral data of the compounds are given in the experimental part (section *4.15*). As an example, the NMR data of compound **155b** are shown in Figure 17.



^{1}H NMR **^{13}C NMR**

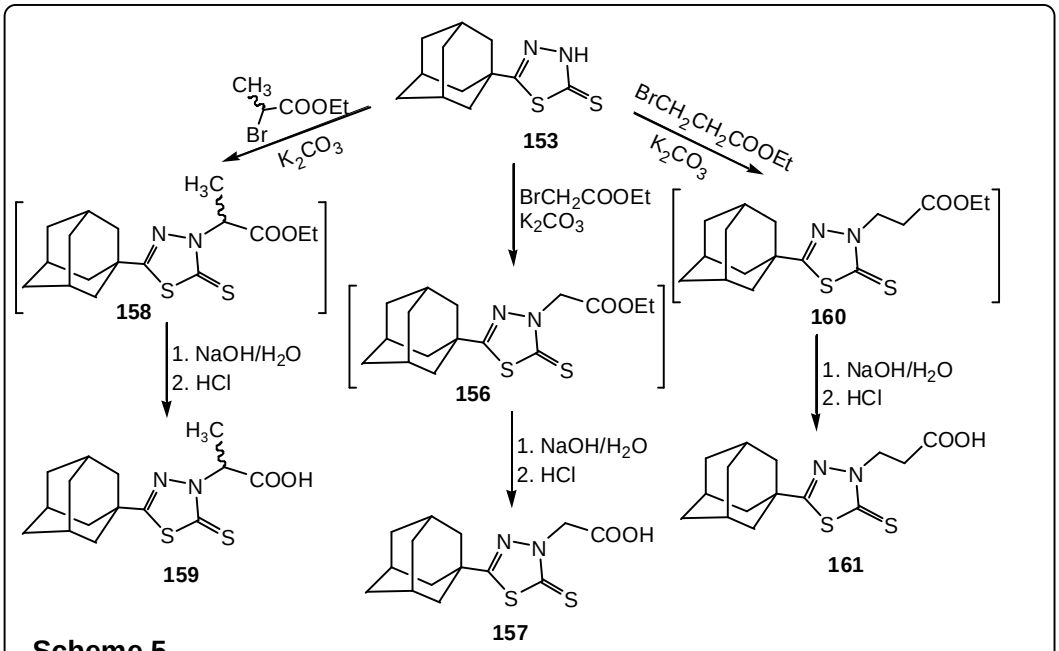
Figure 17: ^{1}H and ^{13}C NMR data of compound **155b**.

The following new 5-(1-adamantyl)-3-(4-substituted-1-piperazinylmethyl)-1,3,4-thiadiazoline-2-thiones **155a-c** were prepared in this part:

1. 5-(1-Adamantyl)-3-(4-methyl-1-piperazinylmethyl)-1,3,4-thiadiazoline-2-thione **155a**.

2. 5-(1-Adamantyl)-3-(4-ethyl-1-piperazinylmethyl)-1,3,4-thiadiazoline-2-thione **155b**.
3. 5-(1-Adamantyl)-3-(4-phenyl-1-piperazinylmethyl)-1,3,4-thiadiazoline-2-thione **155c**.

3.5. Synthesis of 2-[5-(1-adamantyl)-2-thioxo-1,3,4-thiadiazolin-3-yl]acetic acid (157), (±)-2-[5-(1-adamantyl)-2-thioxo-1,3,4-thiadiazolin-3-yl]propionic acid (159*)* and 3-[5-(1-adamantyl)-2-thioxo-1,3,4-thiadiazolin-3-yl]propionic acid (161) (Scheme 5)



Scheme 5

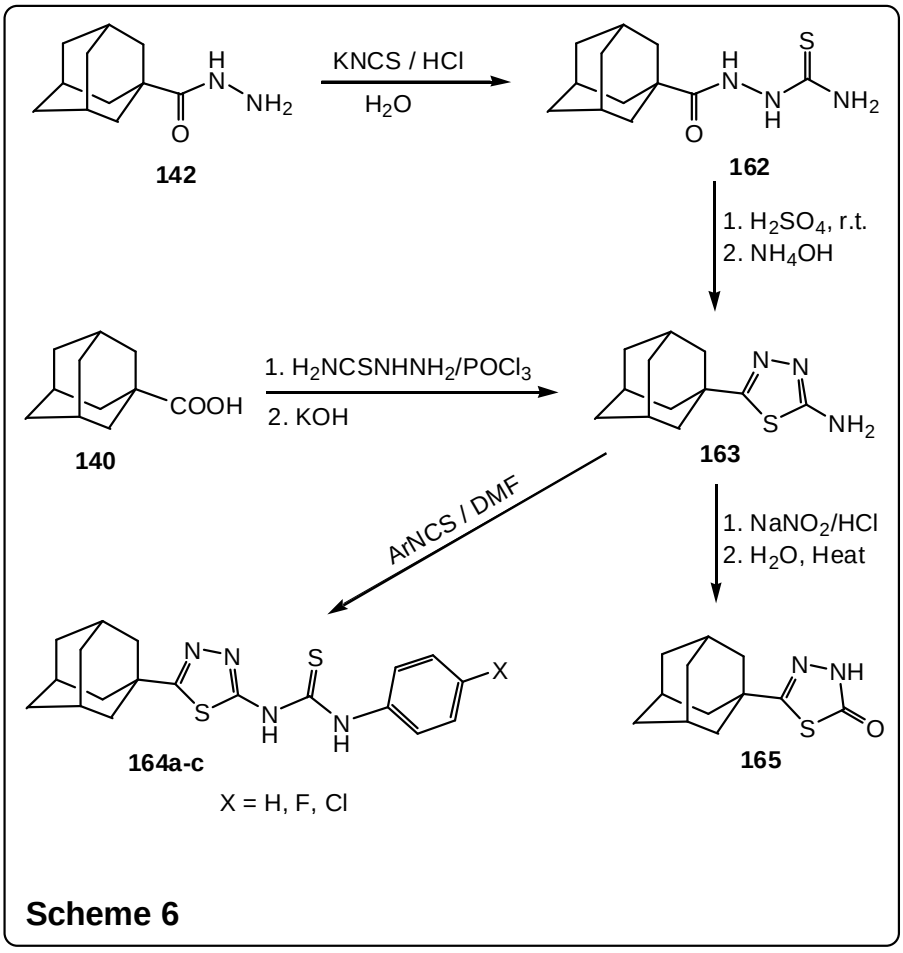
The carboxylic acid derivatives **157**, **159** and **161** were prepared through the reaction of compound **153** with the corresponding ethyl bromoester in ethanol, in the presence of anhydrous potassium carbonate to yield the corresponding ethyl esters **156**, **158** and **160**. These esters were simultaneously hydrolyzed by heating in 10% aqueous sodium hydroxide solution to afford the corresponding carboxylic acids in 55-62% yields.

The structures of compounds **157**, **159** and **161** were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic peaks at 3423-3542 cm^{-1} (OH), 2811-

2913 cm^{-1} (Adamantane, CH, CH_2 and CH_3 C-H), 1742-1751 (C=O) and 1452-1661 cm^{-1} (C=N). The ^1H NMR spectra are characterized by the presence of the adamantyl protons as multiplets or singlets at δ 1.72-1.85 (6H), 1.94-2.04 (6H) and 2.04-2.05 ppm (3H). The aliphatic CH, CH_2 and CH_3 protons were shown as separate peaks or overlapped with the multiplets of the adamantyl protons. The COOH protons appeared as broad singlets at δ 11.78-11.85 ppm. The ^{13}C NMR spectra are characterized by the presence of the adamantyl carbons δ 27.85-28.14, 36.15-36.43, 38.59-38.64 and 42.23-43.38 ppm. The C-5, C=S and C=O carbons were shown at δ 174.27-174.33, 181.13-183.91 and 184.12-188.92 ppm, respectively. The detailed NMR and mass spectral data of the compounds are given in the experimental part (section *4.16*). As an example, the NMR data of compound **157** are shown in Figure 18.

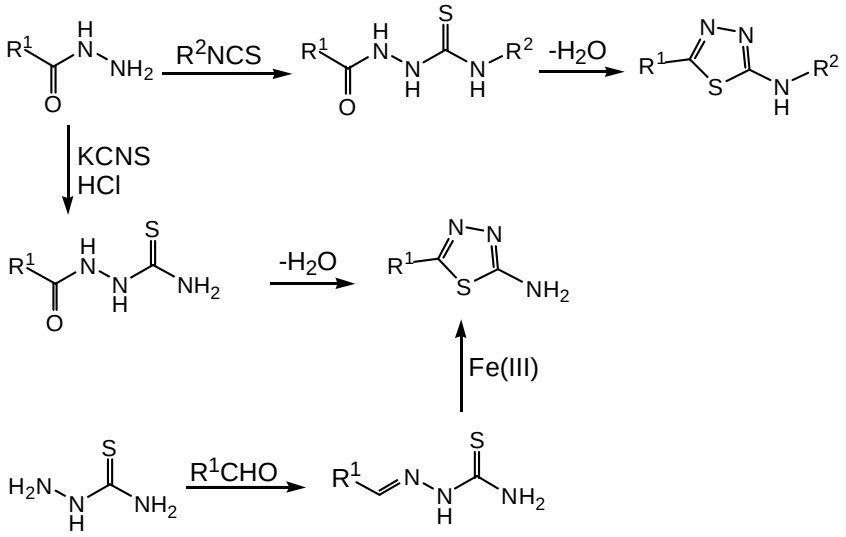
Figure 18: ^1H and ^{13}C NMR data of compound **157**.

3.6. Synthesis of *N*-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-arylthio-ureas (164a-c) and 5-(1-adamantyl)-1,3,4-thiadiazoline-2-one (165) (Scheme 6)



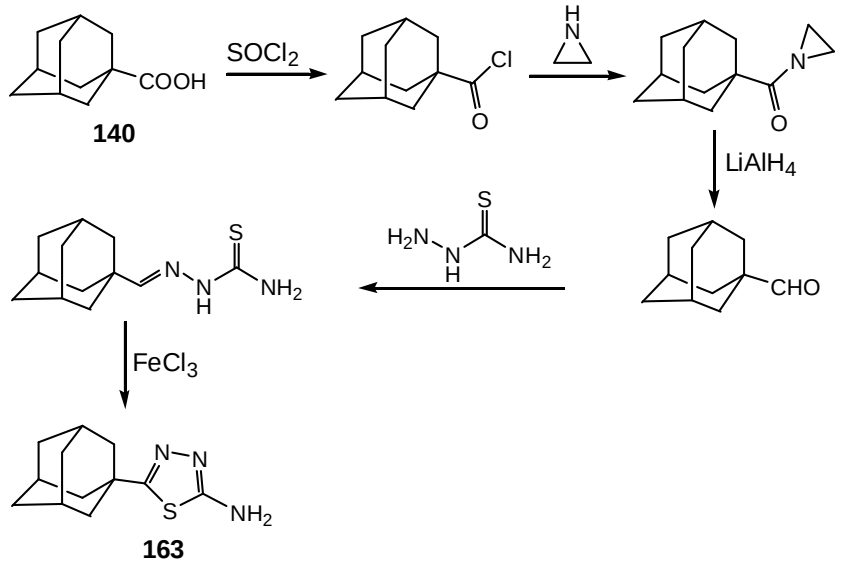
Scheme 6

The most convenient method for the preparation of 2-amino or substituted amino-5-substituted-1,3,4-thiadiazoles is based on dehydrative ring closure of the corresponding 1,4-disubstituted thiosemicarbazides utilizing a variety of dehydrating agents including sulphuric acid,[52,104,135] phosphorus oxychloride,[135] and methanesulphonic acid.[136] 2-Amino-5-substituted-1,3,4-thiadiazole were also prepared *via* oxidative cyclization of the corresponding thiosemicarbazides with ferric chloride or ferric ammonium sulphate.[42,107-111]



3.6.1. 5-(1-Adamantyl)-2-amino-1,3,4-thiadiazole (163)

5-(1-Adamantyl)-2-amino-1,3,4-thiadiazole **163** was previously prepared by Narayanan and Bernstein *via* oxidative cyclization of adamantane-1-carboxaldehyde-thiosemicarzide *via* the following reaction sequences:[42]

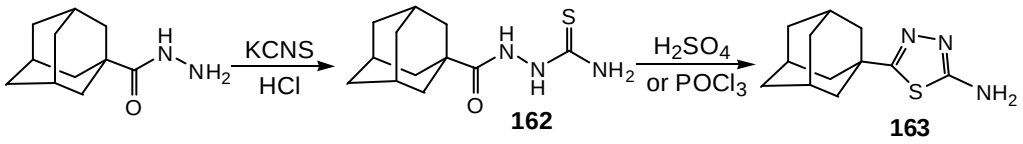


140

163

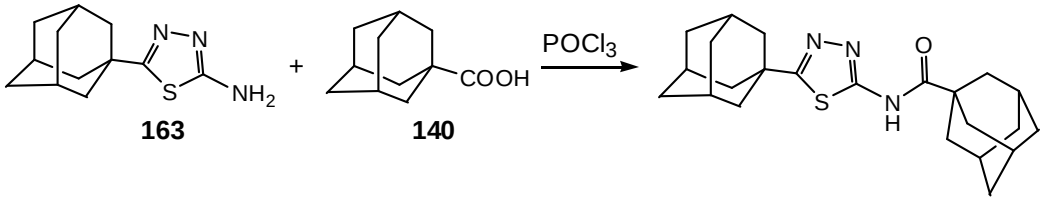
Compound **163** was also isolated as unexpected debenzylated product on dehydrative cyclization of 1-(1-adamantylcarbonyl)-3-benzylthiosemicarbazide with

sulphuric acid.[135] In addition, dehydration of 1-(1-adamantylcarbonyl)-3-thiosemicarbazide with sulphuric acid at room temperature or heating in phosphorus oxychloride yielded compound **163** in 48% and 59% yields, respectively.[135]



162 **163**

The numerous steps and poor overall yields of the previously reported methods for the preparation of compound **163** prompted the trial to prepare it by the one-step three-component 1,3,4thiadiazole synthesis.[107-111] The method depends on the simultaneous condensation of the carboxylic acid and thiosemicarbazide in the presence of phosphorus oxychloride which acts as condensing and dehydrating agent. Thus, adamantane-1-carboxylic acid, thiosemicarbazide and phosphorus oxychloride were heated for one hour to yield compound **163** in 59% yield. It was necessary to heat the reaction mixture for further 4 hours to hydrolyze the amide product with adamantane-1-carboxylic acid which was formed as byproduct. The hydrolysis was catalyzed by the hydrochloric acid being liberated from decomposition of excess phosphorus oxychloride with water.

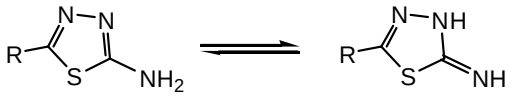


163 **140**

In the present study, compound **163** was prepared by the later two methods. The physical and spectral data of both products were identical. The direct three component method has the advantage of the relatively higher overall yield. The structure of compounds **163** was also supported by IR, NMR, and mass spectral data (section *4.18*), which were consistent with the assigned structure.

3.6.2. N-[5-(1-Adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-arylthioureas (164a-c)

The nucleophilicity of amino group of 2-amino-5-substituted-1,3,4-thiadiazole seems to be dependent on the nature of the 5-substituents. Werber *et al.* reported that amino group is a very weak nucleophile due to the existence of these derivatives mainly in the iminothiadiazoline structure.[137] This assignment was based on the disability of several 2-amino-5-substituted-1,3,4-thiadiazole derivatives to react with alkyl halides and carbonyl compounds to yield the corresponding alkylamino and Schiff's bases, respectively.



On the other hand, several authors reported the reaction of 2-amino-5-substituted-1,3,4-thiadiazoles with aromatic aldehydes to yield the corresponding Schiff's bases.[138-140]

In the present study, trials to react compound **163** with various aromatic aldehydes *via* prolonged heating in ethanol, acetic acid or DMF were not successful, and the reactants were either recovered unchanged in case of ethanol and acetic acid or decomposed in case of DMF. In addition, trials to carry out the reaction under microwave irradiation resulted in decomposition of the reactants. Similarly, compound **163** was also unreactive towards phenacyl or substituted phenacyl halides.

The reaction of 5-(1-adamantyl)-2-amino-1,3,4-thiadiazole **163** with different aliphatic and aromatic isothiocyanate was tried by heating in ethanol or DMF. In case of carrying out the reaction in ethanol, the reactants were recovered unchanged after heating for 6 hours. In case of DMF, the reaction proceeded slowly only in case of the aromatic isothiocyanates (phenyl-, 4-fluorphenyl- or 4-chlorophenylisothiocyanate) to yield the corresponding *N*-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-arylthioureas (**164a-c**) in poor yields (27-34%).

The structures of compounds **164a-c** were confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The IR spectra of these compounds showed common characteristic peaks at 3233-3265 cm^{-1} (NH), 2839-2904 cm^{-1} (Adamantane C-H) and 1431-1631 cm^{-1} (C=N). The ^{1}H NMR spectra are characterized by the

presence of the adamantyl protons as multiplets or singlet at δ 1.72-1.82 (6H), 1.91-2.03 (6H) and 2.02-2.10 ppm (3H). The two NH protons were shown as broad singlets at δ 10.87-11.05 ppm. The ^{13}C NMR spectra of compounds **164a** and **164c** are characterized by the presence of the adamantyl carbons δ 27.03-28.38, 36.44-36.45, 37.72-38.10 and 43.22-43.27 ppm. The C-5, C-2 and C=S carbons were shown at δ 167.48-168.0, 171.99-172.44 and 186.42-188.59 ppm, respectively. The detailed NMR and mass spectral data of the compounds are given in the experimental part (sections *4.19*). As an example, the NMR data of compound **164a** are shown in Figure 19.

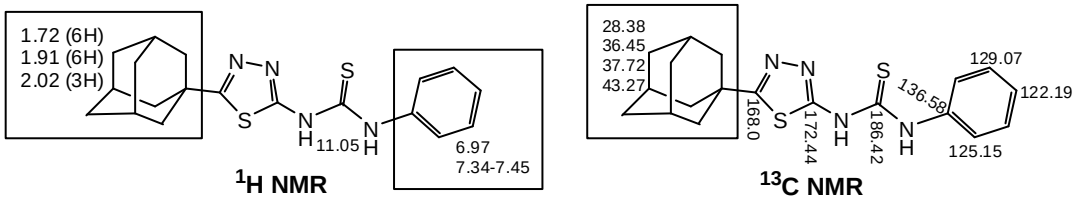


Figure 19: ^{1}H and ^{13}C NMR data of compound **164a**.

The following new *N*-[5-(1-adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-arylthioureas **164a-c** were prepared in this part:

1. *N*-[5-(1-Adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-phenylthiourea **164a**.
2. *N*-[5-(1-Adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-(4-fluorophenyl)thiourea **164b**
3. *N*-[5-(1-Adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-(4-chlorophenyl)thiourea **164c**

3.6.3. 5-(1-Adamantyl)-1,3,4-thiadiazoline-2-one (165)

Compound **163** was successfully converted to its hydroxyl analogue **165** *via* treatment with sodium nitrite in cold aqueous hydrochloric acid solution followed by boiling for 10 minutes. The spectral data of compound **165** revealed that it exists as the lactam structure as proved by IR spectrum which showed sharp peak at 1759 cm^{-1} (C=O) in addition to medium NH peak at 3197 cm^{-1}. The ^{1}H NMR spectrum showed the adamantyl protons as multiplets or singlet at δ 1.74-1.82 (6H), 2.01 (3H) and 2.04

ppm (6H). The ^{13}C NMR spectrum showed the adamantyl carbons δ 28.48, 36.38, 38.82 and 43.69 ppm. The C-5 and C=O carbons were shown at δ 150.75 and 180.26 ppm, respectively.

4. EXPERIMENTAL

4.1. General Considerations

- All reagents and solvents were obtained from commercial suppliers and were used without further purification.

- Melting points (^{o}C) were measured in open glass capillaries using Branstead 9001 electrothermal melting point apparatus and are uncorrected.

- Infrared (IR) spectra were recorded in potassium bromide (KBr) discs using Jasco FT/IR 460 Plus spectrometer (Tokyo, Japan), and expressed in wave number ύ (cm^{-1}).

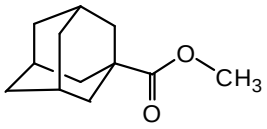
- NMR spectra were obtained on a Bruker AC 500 Ultra Shield NMR spectrometer (Fällanden, Switzerland) at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C, the chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane (TMS) as internal standard; coupling constants (*J*) are expressed in Hz. Deuteriochloroform ($CDCl_3$) and deuteriodimethylsulphoxide (DMSO-d_6) were used as solvents. The splitting patterns were designated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br. s (broad singlet).

- Electron impact mass spectra (EI-MS) were recorded on a Shimadzu GC–MS-QP 5000 instrument (Kyoto, Japan) at 70 eV. Electrospray ionization mass spectra (ESI-MS) were recoded on a Waters QuatroMicro triple quadrupole tandem mass spectrometer at 4.0 and 3.5 kV for positive and negative ions, respectively.

- Microwave irradiation was performed using an Akai MW-GB092MP (800 W) unmodified domestic microwave oven operated at 2450 MHz.

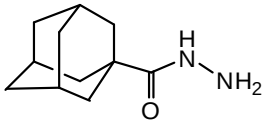
- Monitoring the reactions and checking the purity of the final products were carried out by thin layer chromatography (TLC) using silica gel precoated aluminum sheets (60 F_{254}, Merck) and visualization with Ultraviolet light (UV) at 365 and 254 nm.

4.2. Methyl adamantane-1-carboxylate (141)[54]



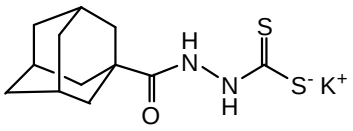
98% Sulphuric acid (8 ml) was added dropwise with continuous stirring to a solution of adamantane-1-carboxylic acid **140** (9 g, 0.05 mole) in methanol (80 ml), and the mixture was heated under reflux for 3 hours. On cooling, the mixture was poured onto crushed ice (250 g) and the precipitated crystalline solid was filtered, washed with water, followed by 10% sodium hydrogen carbonate solution and finally with water and dried to yield 9.5 gm (98%) of methyl adamantane-1-carboxylate (Mp. 65-68 ^{o}C).[54]

4.3. Adamantane-1-carboxylic acid hydrazide (142)[54]



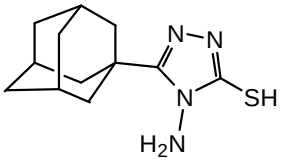
A mixture of methyl adamantane-1-carboxylate **141** (9.7 g, 0.05 mole) and 98% hydrazine hydrate (15 ml) was heated under reflux with stirring for 15 hours. On cooling, cold water (150 ml) was added to the mixture and the separated white crystalline solid was filtered, washed with cold water, dried and crystallized from water to yield 9.5 g (98%) of adamantane-1-carboxylic acid hydrazide (Mp. 148-150 ^{o}C).[45,54]

4.4. Potassium *N*'-(1-adamantylcarbonyl)dithiocarbazate (143)[117]



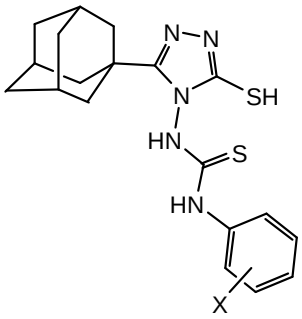
Carbon disulphide (11.4 g, 0.15 mole) was added dropwise to a solution of adamantane-1-carboxylic acid hydrazide **142** (19.4 g, 0.1 mole) and potassium hydroxide (8.4 g, 0.15 mole) in ethanol (250 ml), and the mixture was stirred at room temperature for 3 hours. Dry ether (200 ml) was then added to the mixture and the precipitated solid was filtered, washed with ether and dried at 65 ^{o}C for one hour to yield the title compound **143** in almost quantitative yield (Mp. > 300 ^{o}C).[117]

4.5. 5-(1-Adamantyl)-4-amino-3-mercapto-1,2,4-triazole (144)[117]



A mixture of compound **143** (15.43 g, 0.05 mole) and 98% hydrazine hydrate (10 ml) was heated under reflux till the evolution of hydrogen sulphide completely ceased down (about 1 hour). On cooling, water (200 ml) was added and the mixture was neutralized with 10% hydrochloric acid and allowed to stand for three hours. The separated crude product was filtered, washed with water, dried and crystallized from ethanol to yield 10 g (80%) of the title compound **144** (Mp. 285-7 ^{o}C).[117]

4.6. N-[5-(1-Adamantyl)-3-mercapto-1,2,4-triazol-4-yl]-*N*'-arylthioureas (145a-e)



The appropriate arylisothiocyanate (2.0 mmole) was added to a solution of 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** (0.5 g, 2.0 mmole) in dry DMF (8 ml), and the solution was stirred at room temperature for 24 hours. Water (20 ml) was then added and the mixture was stirred for 20 minutes. The separated precipitate was filtered, washed with water, dried and crystallized from ethanol.

The melting points, yield percentages, molecular formulae and molecular weights of the title compounds **145a-e** are listed in Table **1**.

145a*:* ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, Adamantane-H), 2.07 (s, 9H, Adamantane-H), 7.31-7.52 (m, 5H, Ar-H), 9.85 (s, 1H, NH), 10.02 (s, 1H, NH), 13.48 (s, 1H, SH). ^{13}C NMR: 27.85, 34.82, 36.58, 38.40 (Adamantane-C), 125.41, 126.86, 128.20, 132.55 (Ar-C), 139.53 (Triazole C-5), 157.32 (Triazole C-3), 167.82 (C=S). EI-MS, *m/z* (Rel. Int.): 385 (M^+, 1), 351 (3), 268 (11), 234 (13), 209 (23), 167 (29), 136 (34), 135 (88), 109 (16), 93 (44), 91 (17), 77 (100).

145b: ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 6.81 (s, 1H, Ar-H), 7.35-7.39 (m, 3H, Ar-H), 9.77 (s, 1H, NH), 10.04 (s, 1H, NH), 13.47 (s, 1H, SH). ^{13}C NMR: 27.80, 34.81, 36.52, 38.37 (Adamantane-C), 111.61, 113.10, 118. 65, 130.11, 138.32, 161.09 (Ar-C), 141.50 (Triazole C-5), 163.02 (Triazole C-3), 167.74 (C=S). EI-MS, *m/z* (Rel. Int.): 369 (M^+ -H_2S, 2), 234 (36), 218 (11), 169 (8), 135 (65), 95 (77), 41 (100).

145c: ^{1}H NMR (DMSO-d_6): δ 1.70 (s, 6H, Adamantane-H), 1.96-2.08 (m, 9H, Adamantane-H), 7.16 (d, 2H, Ar-H, *J* = 8.1 Hz), 7.50 (d, 2H, Ar-H, *J* = 8.1 Hz), 9.82 (s, 1H, NH), 10.66 (s, 1H, NH), 13.50 (s, 1H, SH). ^{13}C NMR: 27.88, 34.65, 36.59, 38.44 (Adamantane-C), 114.50, 126.17, 134.52, 157.22 (Ar-C), 136.08 (Triazole C-5), 161.90 (Triazole C-3), 167.90 (C=S). EI-MS, *m/z* (Rel. Int.): 403 (M^+, 1), 369 (3), 234 (42), 135 (81), 95 (75), 41 (100).

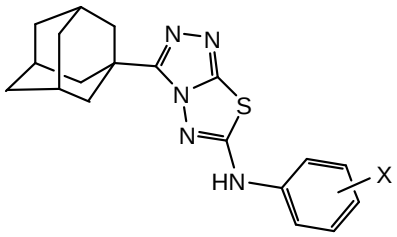
145d: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, Adamantane-H), 2.06 (s, 9H, Adamantane-H), 7.37 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.55 (d, 2H, Ar-H, *J* = 8.0 Hz), 9.98 (s, 1H, NH), 10.72 (s, 1H, NH), 13.49 (s, 1H, SH). ^{13}C NMR: 27.86, 34.85, 36.88, 38.48 (Adamantane-C), 125.52, 128.54, 131.35, 137.98 (Ar-C), 142.60 (Triazole C-5), 157.23 (Triazole C-3), 167.81 (C=S). EI-MS, *m/z* (Rel. Int.): 419 (M^+, 1), 385 (3), 234 (43), 135 (44), 126 (11), 41 (100).

145e: ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.07 (s, 6H, Adamantane-H), 7.40 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.64 (d, 2H, Ar-H, *J* = 8.5 Hz), 9.82 (s, 1H, NH), 10.81 (s, 1H, NH), 13.64 (s, 1H, SH). ^{13}C NMR: 27.81, 34.81, 36.53, 38.38 (Adamantane-C), 121.07, 126.18, 128.43, 133.28 (Ar-C), 139.24 (Triazole C-5), 157.08 (Triazole C-3), 167.73 (C=S). EI-MS, *m/z* (Rel. Int.): 465 (M^+ +2, 1), 463 (M^+, 1), 431 (2), 429 (3), 234 (100), 159 (19), 157 (22), 135 (68), 41 (78).

Table 1: Melting points, yield percentages, molecular formulae and molecular weights of compounds **(145a-e)**

Comp. No.	X	Mp (°C)	Yield (%)	Molecular Formula (Mol. Wt.)
145a	H	231-3	92	$C_{19}H_{23}N_5S_2$ (385.55)
145b	3-F	252-4	89	$C_{19}H_{22}FN_5S_2$ (403.54)
145c	4-F	207-9	95	$C_{19}H_{22}FN_5S_2$ (403.54)
145d	4-Cl	242-4	95	$C_{19}H_{22}ClN_5S_2$ (419.99)
145e	4-Br	246-8	94	$C_{19}H_{22}BrN_5S_2$ (464.45)

4.7. 5-(1-Adamantyl)-2-arylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (146a-e)



Method A:

The appropriate arylisothiocyanate (2.0 mmole) was added to a solution of 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** (0.5 g, 2.0 mmole) in dry DMF (8 ml) and the solution was heated under reflux for 18 hours. On cooling, the mixture was poured onto cold water (20 ml) and the separated precipitate was filtered, washed with water, dried and crystallized to yield compounds **146a-e** in 51-63% yields.

Method B:

The appropriate *N*,*N'*-disubstituted thiourea **145a-e** (2.0 mmole) was placed in 50 ml open round bottom flask and irradiated in the microwave oven for 5 minutes at 454 W (58%). On cooling, chloroform (10 ml) was added and the mixture was stirred for 5 minutes, then filtered and the filtrate was evaporated *in vacuo*. The obtained crude products were crystallized from ethanol to yield compounds **146a-e** in 92-95% yields.

Method C:

Equimolar amounts (2.0 mmole) of compound **144** and the appropriate arylisothiocyanate were thoroughly mixed and placed in 50 ml open round bottom flask, and the mixture was irradiated in the microwave oven for 8 minutes at 454 W (58%). On cooling, chloroform (10 ml) was added and the reaction mixture was treated as mentioned under method B to yield compounds **146a-e** in 82-89% yields.

The melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of the title compounds **146a-e** are listed in Table **2**.

146a: ^{1}H NMR ($CDCl_3$): δ 1.79 (s, 6H, Adamantane-H), 2.10 (s, 3H, Adamantane-H), 2.15 (s, 6H, Adamantane-H), 7.06-7.58 (m, 6H, Ar-H and NH). ^{13}C NMR: 27.85, 34.33, 36.80, 39.15 (Adamantane-C), 118.50, 124.06, 129.82, 139.92 (Ar-C), 149.69 (C-5), 153.14 (C-2), 180.05 (C-8). EI-MS, *m/z* (Rel. Int.): 351 (M^+, 4), 268 (27), 234 (26), 150 (30), 135 (23), 118 (17), 104 (34), 91 (38), 77 (100).

146b: ^{1}H NMR ($CDCl_3$): δ 1.72 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.08 (s, 6H, Adamantane-H), 6.85 (s, 1H, Ar-H), 7.23 (s, 1H, NH), 7.33-7.72 (m, 3H, Ar-H). ^{13}C NMR: 27.80, 34.18, 36.53, 38.38 (Adamantane-C), 106.06, 110.62, 113.29, 130.90, 151.02, 163.25 (Ar-C), 149.90 (C-5), 157.08 (C-2), 179.82 (C-8). EI-MS, *m/z* (Rel. Int.): 369 (M^+, 5), 350 (6), 234 (14), 191 (36), 176 (28), 160 (100) 135 (62), 111 (12), 104 (60).

146c: ^{1}H NMR ($CDCl_3$): δ 1.72 (s, 6H, Adamantane-H), 2.09 (s, 3H, Adamantane-H), 2.14 (s, 6H, Adamantane-H), 7.26-7.30 (m, 2H, Ar-H), 7.56-7.60 (m, 3H, Ar-H and NH). ^{13}C NMR: 27.40, 34.32, 35.99, 39.0 (Adamantane-C), 115.63, 120.28, 136.32, 153.16 (Ar-C), 149.68 (C-5), 159.85 (C-2), 177.86 (C-8). EI-MS, *m/z* (Rel. Int.): 369 (M^+, 8), 350 (3), 234 (11), 191 (47), 176 (15), 135 (68), 109 (100), 104 (33)**.**

146d: ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 6H, Adamantane-H), 1.98 (s, 3H, Adamantane-H), 2.11 (s, 6H, Adamantane-H), 7.27 (d, 2H, Ar-H, *J* = 8.2 Hz), 7.46 (s, 1H, NH), 7.61 (d, 2H, Ar-H, *J* = 8.2 Hz). ^{13}C NMR: 27.86, 35.12, 36.46, 38.31 (Adamantane-C), 117.35, 125.46, 130.02, 138.02 (Ar-C), 149.50 (C-5), 157.98 (C-2), 177.98 (C-8). EI-MS, *m/z* (Rel. Int.): 378 (M^+ +2, 2), 375 (M^+, 5), 349 (4), 220 (28), 161 (49), 135 (68), 118 (17), 126 (100), 111 (44).

146e: ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.08 (s, 6H, Adamantane-H), 7.45 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.51 (s, 1H, NH), 7.52 (d, 2H, Ar-H, *J* = 8.5 Hz). ^{13}C NMR: 27.86, 34.38, 36.45, 38.30 (Adamantane-

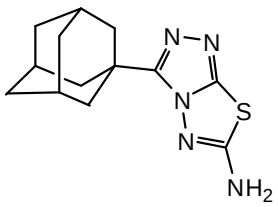
C), 115.01, 117.02, 131.71, 139.24 (Ar-C), 149.86 (C-5), 159.54 (C-2), 176.08 (C-8). EI-MS, *m/z* (Rel. Int.): 431 (M^+ +2, 7), 429 (M^+, 5), 350 (3), 296 (18), 235 (12), 213 (11), 196 (9), 181 (19), 135 (100).

Table 2: Melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of compounds **(146a-e)**

Comp. No.	X	Cryst. Solvent	Mp (^oC)	Yield (%)	Molecular Formula (Mol. Wt.)
146a	H	EtOH/H_2O	> 300	56 (82)*	$C_{19}H_{21}N_5S$ (351.47)
146b	3-F	EtOH/H_2O	> 300	55 (86)*	$C_{19}H_{20}FN_5S$ (369.46)
146c	4-F	EtOH/H_2O	> 300	51 (88)*	$C_{19}H_{20}FN_5S$ (369.46)
146d	4-Cl	MeOH	> 300	56 (89)*	$C_{19}H_{20}ClN_5S$ (385.91)
146e	4-Br	EtOH/H_2O	> 300	63 (85)*	$C_{19}H_{20}BrN_5S$ (430.36)

* The figures shown in parentheses represent the yields obtained *via* microwave irradiation (Method C).

4.8. 5-(1-Adamantyl)-2-amino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole (148)

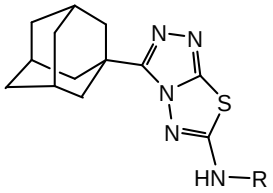


A mixture of cyanogen bromide (1.17 g, 11.0 mmole) and 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** (2.5 g, 10.0 mmole) in ethanol (30 ml) was heated under reflux for 4 hours and the solvent was then evaporated *in vacuo*. The residue was washed with saturated sodium hydrogen carbonate solution (10 ml), then

with water, dried and crystallized from aqueous ethanol to yield 2.1 g (76%) of the title compound **148** (Mp. 187-9 ^{o}C).

^{1}H NMR ($CDCl_3$): δ 1.74 (s, 6H, Adamantane-H), 2.03 (s, 3H, Adamantane-H), 2.13 (s, 6H, Adamantane-H), 6.14 (s, 2H, NH_2). ^{13}C NMR: 27.95, 35.14, 36.52, 39.02 (Adamantane-C), 143.57 (C-5), 162.49 (C-2), 164.91 (C-8). EI-MS, *m/z* (Rel. Int.): 275 (M^+, 100), 259 (61), 429 (3), 234 (23), 218 (28), 135 (86), 41 (96).

4.9. 5-(1-Adamantyl)-2-alkylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles (149a-e)



Method A:

The appropriate alkylisothiocyanate (2.0 mmole) was added to a solution of 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** (0.5 g, 2.0 mmole) in dry DMF (8 ml) and the mixture was heated under reflux for 24 hours. On cooling, the mixture was poured onto cold water (30 ml) and the separated precipitate was filtered, washed with water, dried and crystallized to yield compounds **149a-e** in 34-42% yields.

Method B:

A mixture of the appropriate halides namely; methyl iodide, ethyl iodide, allyl bromide, *n*-butyl bromide or benzyl chloride (2.0 mmole), compound **148** (0.55 g, 2.0 mmole) and anhydrous potassium carbonate (0.28 g, 2.0 mmole), in ethanol (10 ml) was heated under reflux for 2 hours and the solvent was then distilled off under reduced pressure. The obtained residue was washed with water, dried and crystallized.

The melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of the title compounds **149a-e** are listed in Table **3**.

149a: ^{1}H NMR ($CDCl_3$): δ 1.71 (s, 6H, Adamantane-H), 1.98 (s, 3H, Adamantane-H), 2.10 (s, 6H, Adamantane-H), 3.59 (s, 3H, CH_3), 5.27 (s, 1H, NH). ^{13}C NMR: 27.83, 34.72, 35.99, 38.37 (Adamantane-C), 39.05 (CH_3), 150.03 (C-5), 158.18 (C-2), 175.05 (C-8). EI-MS, *m/z* (Rel. Int.): 289 (M^+, 26), 234 (87), 154 (11), 135 (100), 55 (92).

149b: ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 3H, CH_3, *J* = 7.3 Hz), 1.75 (s, 6H, Adamantane-H), 1.93 (s, 3H, Adamantane-H), 2.08 (s, 6H, Adamantane-H), 3.32 (q, 2H, $CH_3C\boldsymbol{H}_2$, *J* = 7.3 Hz), 5.52 (s, 1H, NH). ^{13}C NMR: 14.25 (CH_3), 27.40, 34.21, 36.28, 39.32 (Adamantane-C), 42.56 (CH_2NH), 150.11 (C-5), 157.12 (C-2), 176.73 (C-8). EI-MS, *m/z* (Rel. Int.): 303 (M^+, 17), 234 (100), 135 (53), 104 (40), 90 (51), 60 (88).

149c: ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 6H, Adamantane-H), 1.97 (s, 3H, Adamantane-H), 2.12 (s, 6H, Adamantane-H), 4.62 (s, 2H, CH_2), 4.75 (d, 1H, $=CH^a$, *J* = 17.6 Hz), 5.25-5.51 (m, 2H, $=CH^b$ & NH), 5.83-5.94 (m, 1H, -CH=). ^{13}C NMR: 27.53, 34.02, 36.15, 39.77 (Adamantane-C), 66.01 (CH_2NH), 113.66 ($\boldsymbol{C}H_2$=CH), 133.05 (CH_2=$\boldsymbol{C}$H), 149.06 (C-5), 158.80 (C-2), 179.26 (C-8). EI-MS, *m/z* (Rel. Int.): 315 (M^+, 2), 234 (21), 227 (24), 185 (31), 153 (88), 135 (61), 95 (72), 57 (100)**.**

149d: ^{1}H NMR ($CDCl_3$): δ 1.01 (t, 3H, CH_3, *J* = 7.5 Hz), 1.36-1.68 (m, 4H, CH_2CH_2), 1.73 (s, 6H, Adamantane-H), 1.98-2.16 (m, 9H, Adamantane-H), 3.18 (q, 2H, $C\boldsymbol{H}_2NH$, *J* = 7.5 Hz), 5.72 (s, 1H, NH). ^{13}C NMR: 14.72 (CH_3), 19.50 ($CH_3\boldsymbol{C}H_2$), 27.35, 32.85, 34.28, 35.88, 39.03 (Adamantane-C & $\boldsymbol{C}H_2CH_2NH$), 58.52 (CH_2NH), 149.03 (C-5), 158.80 (C-2), 175.62 (C-8). EI-MS, *m/z* (Rel. Int.): 331 (M^+, 3), 288 (5), 234 (100), 135 (52), 43 (48).

149e: ^{1}H NMR ($CDCl_3$): δ 1.76 (s, 6H, Adamantane-H), 1.99 (s, 3H, Adamantane-H), 2.12 (s, 6H, Adamantane-H), 4.98 (s, 2H, $C_6H_5C\boldsymbol{H}_2$), 5.49 (s, 1H, NH), 7.15-7.32 (m, 5H, Ar-H). ^{13}C NMR: 27.42, 34.09, 36.15, 39.01 (Adamantane-C), 65.50 ($C_6H_5\boldsymbol{C}H_2$), 124.57, 126.55, 130.02, 137.50 (Ar-C), 148.80 (C-5), 156.65 (C-2),

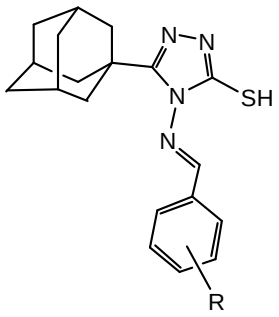
177.05 (C-8). EI-MS, *m/z* (Rel. Int.): 365 (M^+, 3), 273 (8), 234 (100), 135 (82), 91 (94).

Table 3: Melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of compounds **(149a-e)**

Comp. No.	R	Cryst. Solvent	Mp (°C)	Yield (%)	Molecular Formula (Mol. Wt.)
149a	CH_3	MeOH	245-7	34 (88)*	$C_{14}H_{19}N_5S$ (289.40)
149b	C_2H_5	MeOH	252-4	37 (89)*	$C_{15}H_{21}N_5S$ (303.43)
149c	CH_2=$CHCH_2$	EtOH/H_2O	280-2	39 (82)*	$C_{16}H_{21}N_5S$ (315.44)
149d	C_4H_9(*n*)	MeOH	269-71	42 (85)*	$C_{17}H_{25}N_5S$ (331.48)
149e	$C_6H_5CH_2$	MeOH	271-3	41 (92)*	$C_{20}H_{23}N_5S$ (365.50)

* The figures shown in parentheses represent the yields obtained *via* the reaction of compound **148** with the aliphatic halides (Method B).

4.10. 5-(1-Adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles (150a-v)



Method A:

A mixture of the appropriate aromatic aldehyde (2.0 mmole) and 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** (0.5 g, 2.0 mmole) in absolute

ethanol (10 ml) was heated under reflux for 5 hours. On cooling, the separated solid was filtered, washed with cold ethanol (5 ml), dried and crystallized.

Method B: **(Compounds 150l, 150m, 150r, 150s, 150u and 150v)**

A mixture of the appropriate aromatic aldehyde (2.0 mmole) and 5-(1-adamantyl)-4-amino-3-mercapto-1,2,4-triazole **144** (0.5 g, 2 mmole) in acetic acid (8 ml) was heated under reflux for 4 hours. On cooling, the separated solid was filtered, washed with cold ethanol (5 ml), dried and crystallized.

The melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of the title compounds **150a-v** are listed in Table **4**.

150a: ^{1}H NMR (DMSO-d_6): δ 1.69-1.73 (m, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.07 (s, 6H, Adamantane-H), 7.58-7.65 (m, 3H, Ar-H), 7.92 (d, 2H, Ar-H, *J* = 7.0 Hz), 9.71 (s, 1H, CH=N), 13.82 (s, 1H, SH). ^{13}C NMR: 27.72, 35.28, 36.47, 38.61 (Adamantane-C), 128.94, 129.78, 132.67, 133.17 (Ar-C), 156.04, 162.50 (Triazole C-5 & CH=N), 165.02 (Triazole C-3). EI-MS, *m/z* (Rel. Int.): 338 (M^+, 51), 261 (12), 236 (26), 235 (100), 221 (14), 202 (17), 135 (15), 104 (12), 90 (11), 77 (6).

150b: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.08 (s, 6H, Adamantane-H), 7.40-7.45 (m, 2H, Ar-H), 7.67-7.71 (m, 1H, Ar-H), 8.04 (t, 1H, Ar-H, *J* = 7.0 Hz), 10.18 (s, 1H, CH=N), 13.85 (s, 1H, SH). ^{13}C NMR: 27.77, 35.36, 36.49, 38.37 (Adamantane-C), 117.0, 120.45, 125.92, 127.86, 135.25, 156.88 (Ar-C), 156.20, 162.44 (Triazole C-5 & CH=N), 163.18 (Triazole C-3). EI-MS, *m/z* (Rel. Int.): 356 (M^+, 44), 339 (25), 297 (17), 266(24), 260 (20), 235 (100), 234 (60), 220 (31), 135 (25), 122 (26), 108 (29), 96 (10).

150c: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.07 (s, 6H, Adamantane-H), 7.34 (d, 2H, Ar-H, *J* = 6.5 Hz), 7.94 (d, 2H, Ar-H, *J* = 6.5 Hz), 9.71 (s, 1H, CH=N), 13.81 (s, 1H, SH). ^{13}C NMR: 27.73, 35.28, 36.47, 38.63 (Adamantane-C), 116.40, 129.28, 131.09, 163.95 (Ar-C), 156.02, 162.54 (Triazole C-5 & CH=N), 165.37 (Triazole C-3). EI-MS, *m/z* (Rel. Int.): 356

(M^+, 17), 235 (100), 234 (58), 220 (14), 135 (34), 122 (22), 121 (62), 107 (18), 95 (44).

150d: ^{1}H NMR (DMSO-d_6): δ 1.73 (s, 6H, Adamantane-H), 2.03 (s, 3H, Adamantane-H), 2.09 (s, 6H, Adamantane-H), 7.58-7.70 (m, 3H, Ar-H), 8.15 (d, 1H, Ar-H, *J* = 7.5 Hz), 10.48 (s, 1H, CH=N), 13.89 (s, 1H, SH). ^{13}C NMR: 27.76, 35.41, 36.51, 38.70 (Adamantane-C), 127.77, 128.64, 130.40, 130.96, 134.46, 135.69 (Ar-C), 156.27, 158.73 (Triazole C-5 & CH=N), 162.44 (Triazole C-3). EI-MS, *m/z* (Rel. Int.): 374 (M^+ +2, 25), 372 (M^+, 100), 337 (34), 261 (25), 249 (26), 235 (58), 234 (48), 221 (20), 140 (32), 135 (21), 125 (26), 110 (12).

150e: ^{1}H NMR (DMSO-d_6): δ 1.70 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 7.66 (d, 2H, Ar-H, *J* = 6.5 Hz), 7.93 (d, 2H, Ar-H, *J* = 6.5 Hz), 9.76 (s, 1H, CH=N), 13.81 (s, 1H, SH). ^{13}C NMR: 27.73, 35.29, 36.46, 38.63 (Adamantane-C), 129.98, 130.56, 131.56, 137.89 (Ar-C), 156.04, 162.53 (Triazole C-5 & CH=N), 163.66 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 374 (M^+ +2, 10), 373 (M^+ +1, 40), 372 (M^+, 23), 371 (100).

150f: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.09 (s, 6H, Adamantane-H), 7.99 (d, 2H, Ar-H, *J* = 8.5), 7.86 (d, 2H, Ar-H, *J* = 8.5 Hz), 9.75 (s, 1H, CH=N), 13.82 (s, 1H, SH). ^{13}C NMR: 27.80, 35.30, 36.53, 38.64 (Adamantane-C), 126.89, 130.71, 131.89, 132.93 (Ar-C), 156.04, 162.51 (Triazole C-5 & CH=N), 162.73 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 418 (M^+ +2, 20), 417 (M^+ +1, 100), 416 (M^+, 20), 415 (100).

150g: ^{1}H NMR (DMSO-d_6): δ 1.69-1.73 (m, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.07 (s, 6H, Adamantane-H), 6.97-7.02 (m, 2H, Ar-H), 7.42-7.46 (m, 1H, Ar-H), 7.90-7.92 (m, 1H, Ar-H), 9.91 (s, 1H, CH=N), 10.55 (s, 1H, OH), 13.46 (s, 1H, SH). ^{13}C NMR: 27.74, 35.29, 36.47, 38.61 (Adamantane-C), 117.26, 118.95, 120.26, 127.24, 134.72, 158.97 (Ar-C), 156.01, 161.63 (Triazole C-5 & CH=N), 162.49 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 355 (M^+ +1, 7), 354 (M^+, 28), 353 (100).

150h: ^{1}H NMR (DMSO-d_6): δ 1.67-1.71 (m, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 6.94 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.76 (d, 2H, Ar-H, *J* = 8.5 Hz), 9.36 (s, 1H, CH=N), 10.38 (s, 1H, OH), 13.70 (s, 1H, SH). ^{13}C NMR: 27.73, 35.21, 36.48, 38.57 (Adamantane-C), 116.65, 123.51, 131.18, 162.51 (Ar-C), 155.91, 162.32 (Triazole C-5 & CH=N), 165.79 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 355 (M^+ +1, 6), 354 (M^+, 26), 353 (100).

150i: ^{1}H NMR (DMSO-d_6): δ 1.69-1.73 (m, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 2.40 (s, 3H, CH_3), 7.39 (d, 2H, Ar-H, *J* = 7.5 Hz), 7.81 (d, 2H, Ar-H, *J* = 7.5 Hz), 9.61 (s, 1H, CH=N), 13.77 (s, 1H, SH). ^{13}C NMR: 21.72 (CH_3), 27.73, 35.26, 36.47, 38.60 (Adamantane-C), 128.96, 129.99, 130.37, 143.57 (Ar-C), 156.0, 162.51 (Triazole C-5 & CH=N), 165.19 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 351 (M^+ -1, 14), 234 (100), 233 (32).

150j: ^{1}H NMR (DMSO-d_6): δ 1.67-1.74 (m, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.07 (s, 6H, Adamantane-H), 3.89 (s, 3H, OCH_3), 7.13-7.23 (m, 2H, Ar-H), 7.60-7.63 (m, 1H, Ar-H), 8.01 (d, 1H, Ar-H, *J* = 8.0 Hz), 10.02 (s, 1H, CH=N), 13.76 (s, 1H, SH). ^{13}C NMR: 27.74, 35.30, 36.49, 38.60 (Adamantane-C), 56.54 (OCH_3), 112.99, 120.74, 121.59, 126.69, 134.97, 159.84 (Ar-C), 156.13 (Triazole C-5), 159.81 (CH=N), 162.39 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 369 (M^+ +1, 7), 368 (M^+, 23), 367 (100).

150k: ^{1}H NMR (DMSO-d_6): δ 1.67-1.73 (m, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 3.86 (s, 3H, OCH_3), 7.13 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.87 (d, 2H, Ar-H, *J* = 8.5 Hz), 9.50 (s, 1H, CH=N), 13.79 (s, 1H, SH). ^{13}C NMR: 27.73, 35.24, 36.48, 38.59 (Adamantane-C), 56.04 (OCH_3), 115.32, 125.11, 130.91, 163.43 (Ar-C), 155.95, 162.50 (Triazole C-5 & CH=N), 165.12 (Triazole C-3). EI-MS, *m/z* (Rel. Int.): 369 (M^+ +1, 29), 368 (M^+, 76), 353 (33), 259 (33), 249 (37), 236 (51), 235 (49), 234 (29), 135 (54), 133 (100), 108 (112).

150l: ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.07 (s, 6H, Adamantane-H), 7.85 (t, 1H, Ar-H, *J* = 7.5 Hz), 7.94 (t, 1H, Ar-H, *J* = 7.5 Hz), 8.17 (d, 2H, Ar-H, *J* = 8.0 Hz), 10.43 (s, 1H, CH=N), 13.90

(s, 1H, SH). ^{13}C NMR: 27.76, 35.39, 36.42, 38.63 (Adamantane-C), 125.40, 126.87, 129.43, 133.54, 134.53, 149.29 (Ar-C), 156.26, 159.20 (Triazole C-5 & CH=N), 162.65 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 384 (M^+ +1, 7), 383 (M^+, 24), 382 (100).

150m: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 7.89 (d, 2H, Ar-H, *J* = 8.4 Hz), 8.32(d, 2H, Ar-H, *J* = 8.4 Hz), 10.21 (s, 1H, CH=N), 13.88 (s, 1H, SH). ^{13}C NMR: 27.73, 35.21, 36.40, 38.61 (Adamantane-C), 124.12, 128.83, 136.55, 150.22 (Ar-C), 155.66, 161.26 (Triazole C-5 & CH=N), 162.85 (Triazole C-3).

150n: ^{1}H NMR (DMSO-d_6): δ 1.66-1.71 (m, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 3.04 (s, 6H, CH_3), 6.83 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.71 (d, 2H, Ar-H, *J* = 9.0 Hz), 9.21 (s, 1H, CH=N), 13.74 (s, 1H, SH). ^{13}C NMR: 27.74, 35.18, 36.50, 38.55 (Adamantane-C), 39.89 (CH_3), 112.20, 119.31, 130.66, 153.72 (Ar-C), 155.88, 162.51 (Triazole C-5 & CH=N), 165.99 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 382 (M^+ +1, 8), 381 (M^+, 36), 379 (100).

150o: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.09 (s, 6H, Adamantane-H), 7.30-7.34 (m, 2H, Ar-H), 7.67-7.72 (m, 1H, Ar-H), 10.37 (s, 1H, CH=N), 13.87 (s, 1H, SH). ^{13}C NMR: 27.30, 34.89, 35.87, 37.67 (Adamantane-C), 109.74, 112.67, 134.86, 160.06 (Ar-C), 155.87, 160.06 (Triazole C-5 & CH=N), 162.11 (Triazole C-3). EI-MS, *m/z* (Rel. Int.): 375 (M^+ +1, 10), 374 (M^+, 33), 343 (14), 236 (37), 235 (100), 234 (43), 220 (17), 139 (40), 135 (18), 126 (18), 113 (13).

150p: ^{1}H NMR (DMSO-d_6): δ 1.71 (s, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.09 (s, 6H, Adamantane-H), 7.44-7.48 (m, 1H, Ar-H), 7.52 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.63-7.67 (m, 1H, Ar-H), 10.54 (s, 1H, CH=N), 13.89 (s, 1H, SH). ^{13}C NMR: 27.79, 35.41, 36.36, 38.23 (Adamantane-C), 116.52, 119.14, 127.17, 134.57, 135.99, 162.59 (Ar-C), 156.41, 160.51 (Triazole C-5 & CH=N), 162.21 (Triazole C-3). EI-MS, *m/z* (Rel. Int.): 392 (M^+ +2, 8), 390 (M^+, 20), 371 (12), 355

(22), 336 (9), 236 (56), 235 (100), 234 (18), 220 (26), 156 (33), 135 (14), 129 (7), 127 (22).

150q: ^{1}H NMR (DMSO-d_6): δ 1.68 (s, 6H, Adamantane-H), 1.99 (s, 3H, Adamantane-H), 2.09 (s, 6H, Adamantane-H), 7.53-7.68 (m, 3H, Ar-H), 10.63 (s, 1H, CH=N), 13.93 (s, 1H, SH). ^{13}C NMR: 27.77, 35.48, 36.38, 38.38 (Adamantane-C), 128.33, 130.42, 133.60, 135.32 (Ar-C), 156.43, 158.38 (Triazole C-5 & CH=N), 162.46 (Triazole C-3). MS *m/z* (Rel. Int.): ESI-MS, *m/z* (Rel. Int.): 410 (M^+ +4, 4), 409 (M^+ +3, 16), 408 (M^+ +2, 18), 407 (M^+ +1, 74), 406 (M^+, 22), 405 (100).

150r: ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6H, Adamantane-H), 2.03 (s, 3H, Adamantane-H), 2.08 (s, 6H, Adamantane-H), 7.67-7.69 (m, 1H, Ar-H), 7.84 (s, 1H, Ar-H), 8.12 (d, 1H, Ar-H, *J* = 8.0 Hz), 10.50 (s, 1H, CH=N), 13.89 (s, 1H, SH). ^{13}C NMR: 27.76, 35.41, 36.49, 38.71 (Adamantane-C), 128.91, 129.12, 129.49, 130.48, 136.44, 138.29 (Ar-C), 156.26, 157.41 (Triazole C-5 & CH=N), 162.44 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 410 (M^+ +4, 3), 409 (M^+ +3, 15), 408 (M^+ +2, 17), 407 (M^+ +1, 69), 406 (M^+, 22), 405 (100).

150s: ^{1}H NMR (DMSO-d_6): δ 1.70-1.72 (m, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 7.85-7.93 (m, 2H, Ar-H), 8.13 (s, 1H, Ar-H), 9.88 (s, 1H, CH=N), 13.86 (s, 1H, SH). ^{13}C NMR: 27.74, 35.33, 36.47, 38.67 (Adamantane-C), 128.34, 130.61, 132.19, 132.74, 133.40, 135.64 (Ar-C), 156.09, 161.65 (Triazole C-5 & CH=N), 162.56 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 410 (M^+ +4, 3), 409 (M^+ +3, 15), 408 (M^+ +2, 17), 407 (M^+ +1, 73), 406 (M^+, 23), 405 (100).

150t: ^{1}H NMR (DMSO-d_6): δ 1.67-1.74 (m, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.08 (s, 6H, Adamantane-H), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 7.15 (d, 1H, Ar-H, *J* = 8.5 Hz), 7.47 (d, 1H, Ar-H, *J* = 8.5 Hz), 7.50 (s, 1H, Ar-H), 9.56 (s, 1H, CH=N), 13.74 (s, 1H, SH). ^{13}C NMR: 27.76, 35.28, 36.52, 38.64 (Adamantane-C), 56.0 (OCH_3), 56.28 (OCH_3), 110.09, 112.34, 124.20, 125.25, 149.74, 153.35 (Ar-C), 156.01, 162.46 (Triazole C-5 & CH=N), 164.54 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 399 (M^+ +1, 7), 398 (M^+, 24), 397 (100).

150u: ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.08 (s, 6H, Adamantane-H), 8.41 (d, 1H, Ar-H, *J* = 8.5 Hz), 8.65 (d, 1H, Ar-H, *J* = 8.5 Hz), 9.03 (s, 1H, Ar-H), 11.51 (s, 1H, CH=N), 13.46 (s, 1H, SH). ^{13}C NMR: 27.80, 34.80, 36.52, 38.36 (Adamantane-C), 120.79, 128.01, 129.52, 131.72, 135.05, 147.74 (Ar-C), 157.09, 157.86 (Triazole C-5 & CH=N), 167.73 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 451 (M^+ +Na, 4), 450 (11), 451 (48), 436 (100), 428 (M^+, 3), 427 (10).

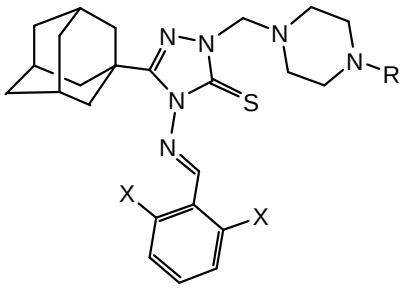
150v: ^{1}H NMR (DMSO-d_6): δ 1.70-1.74 (m, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 2.10 (s, 6H, Adamantane-H), 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.64 (s, 1H, Ar-H), 7.75 (s, 1H, Ar-H), 10.56 (s, 1H, CH=N), 13.86 (s, 1H, SH). ^{13}C NMR: 27.77, 35.44, 36.49, 38.76 (Adamantane-C), 56.67 (OCH_3), 57.05 (OCH_3), 108.73, 109.16, 120.95, 143.12, 151.89, 153.10 (Ar-C), 156.28, 157.92 (Triazole C-5 & CH=N), 162.56 (Triazole C-3). ESI-MS, *m/z* (Rel. Int.): 444 (M^+ +1, 7), 443 (M^+, 24), 442 (100).

Table 4: Melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of compounds **(150a-v)**

Comp. No.	R	Mp (^oC)	Cryst. Solv.	Yield (%)	Molecular Formula (Mol. Wt.)
150a	H	222-4	EtOH/H_2O	81	$C_{19}H_{22}N_4S$ (338.47)
150b	2-F	226-8	EtOH	74	$C_{19}H_{21}FN_4S$ (356.46)
150c	4-F	255-7	EtOH	71	$C_{19}H_{21}FN_4S$ (356.46)
150d	2-Cl	223-5	EtOH	75	$C_{19}H_{21}ClN_4S$ (372.91)
150e	4-Cl	207-9	AcOH	68	$C_{19}H_{21}ClN_4S$ (372.91)
150f	4-Br	228-30	EtOH/H_2O	59	$C_{19}H_{21}BrN_4S$ (417.37)
150g	2-OH	238-40	EtOH	79	$C_{19}H_{22}N_4OS$ (354.47)
150h	4-OH	264-6	EtOH	82	$C_{19}H_{22}N_4OS$ (354.47)
150i	4-CH_3	208-10	EtOH/H_2O	80	$C_{20}H_{24}N_4S$ (352.50)
150j	2-OCH_3	226-8	EtOH	77	$C_{20}H_{24}N_4OS$ (368.50)
150k	4-OCH_3	214-6	EtOH	81	$C_{20}H_{24}N_4OS$ (368.50)
150l*	2-NO_2	226-8	EtOH	52	$C_{19}H_{21}N_5O_2S$ (383.47)
150m*	4-NO_2	242-4	AcOH	50	$C_{19}H_{21}N_5O_2S$ (383.47)
150n	4-$(CH_3)_2N$	223-5	EtOH	66	$C_{21}H_{27}N_5S$ (381.54)
150o	2,6-F_2	241-3	EtOH	68	$C_{19}H_{20}F_2N_4S$ (374.45)
150p	2-Cl,6-F	219-21	EtOH	62	$C_{19}H_{20}ClFN_4S$ (390.91)
150q	2,6-Cl_2	207-9	DMF	49	$C_{19}H_{20}Cl_2N_4S$ (407.36)
150r*	2,4-Cl_2	233-5	AcOH	62	$C_{19}H_{20}Cl_2N_4S$ (407.36)
150s*	3,4-Cl_2	237-9	AcOH	69	$C_{19}H_{20}Cl_2N_4S$ (407.36)
150t	3,4-$(CH_3O)_2$	191-3	EtOH	86	$C_{21}H_{26}N_4O_2S$ (398.52)
150u*	2,4-$(NO_2)_2$	245-7	AcOH	49	$C_{19}H_{20}N_6O_4S$ (428.46)
150v*	2-NO_2,4,5-$(CH_3O)_2$	145-7	AcOH	68	$C_{21}H_{25}N_5O_4S$ (443.52)

* Prepared by method B.

4.11. 5-(1-Adamantyl)-4-arylideneamino-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones (151a-p)



A mixture of the 5-(1-adamantyl)-4-(2,6-dihalobenzylideneamino)-3-mercapto-1,2,4-triazoles **150o** or **150q** (1.0 mmole), the appropriate *N*-substituted piperazine (1.0 mmole) and 37% formaldehyde solution (1 ml), in ethanol (8 ml), was heated under reflux for 15 minutes when a clear solution was obtained. Stirring was continued for 12 hours at room temperature and the mixture was allowed to stand overnight. Cold water (5 ml) was added and the reaction mixture was stirred for 20 minutes. The precipitated crude products were filtered, washed with water, dried, and crystallized.

The melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of the title compounds **151a-p** are listed in Table **5**.

151a: ^{1}H NMR ($CDCl_3$): 1.78 (s, 6H, Adamantane-H), 2.08 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 2.30 (s, 3H, CH_3), 2.47 (s, 4H, Piperazine-H), 2.92 (s, 4H, Piperazine-H), 5.18 (s, 2H, CH_2), 7.02-7.07 (m, 2H, Ar-H), 7.46-7.48 (m. 1H, Ar-H), 10.64 (s, 1H, CH=N). ^{13}C NMR: 27.95, 35.51, 36.45, 38.32 (Adamantane-C), 46.05 (CH_3), 55.05, 58.36 (Piperazine-C), 68.68 (CH_2), 110.87, 112.16, 133.21, 152.24 (Ar-C), 155.52, 160.99 (Triazole C-5 & CH=N), 163.05 (C=S). ESI-MS, *m/z* (Rel. Int.): 509 (M^+ +Na, 48), 488 (M^+ +2, 30), 487 (M^+ +1, 100).

151b: ^{1}H NMR ($CDCl_3$): δ 1.07 (t, 3H, CH_3, J = 7.0 Hz), 1.78 (s, 6H, Adamantane-H), 2.08 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 2.40 (q, 2H, C***H***$_2$CH$_3$, J = 7.0 Hz), 2.48-2.49 (m, 4H, Piperazine-H), 2.92 (s, 4H, Piperazine-H), 5.18 (s,

2H, CH_2), 7.02 (t, 2H, Ar-H, *J* = 8.5 Hz), 7.44-7.48 (m. 1H, Ar-H), 10.62 (s, 1H, CH=N). ^{13}C NMR: 11.91 (CH_3), 28.0, 35.50, 36.46, 38.33 (Adamantane-C), 52.32 (***C***H_2CH_3), 50.42, 52.80 (Piperazine-C), 68.79 (CH_2), 110.89, 112.16, 133.20, 152.22 (Ar-C), 155.45, 161.0 (Triazole C-5 & CH=N), 163.14 (C=S). ESI-MS, *m/z* (Rel. Int.): 523 (M^+ +Na, 19), 502 (M^+ +2, 32), 501 (M^+ +1, 100).

151c: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, CH_3, *J* = 7.0 Hz), 1.79 (s, 6H, Adamantane-H), 2.09 (s, 3H, Adamantane-H), 2.17 (s, 6H, Adamantane-H), 2.81 (s, 4H, Piperazine-H), 3.50 (s, 4H, Piperazine-H), 4.10 (q, 2H, C***H***$_2CH_3$, *J* = 7.0 Hz), 5.16 (s, 2H, CH_2), 7.02 (t, 2H, Ar-H, *J* = 7.0 Hz), 7.46-7.50 (m. 1H, Ar-H), 10.64 (s, 1H, CH=N). ^{13}C NMR: 14.62 (CH_3), 27.98, 35.55, 36.43, 38.35 (Adamantane-C), 50.37, 52.39 (Piperazine-C), 61.32 (***C***H_2CH_3), 68.97 (CH_2), 110.81, 112.22, 133.29, 152.23 (Ar-C), 155.46, 155.70, 161.04 (C=O, Triazole C-5 & CH=N), 163.20 (C=S). ESI-MS, *m/z* (Rel. Int.): 567 (M^+ +Na, 100), 546 (M^+ +2, 6), 445 (M^+ +1, 20).

151d: ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 6H, Adamantane-H), 2.10 (s, 3H, Adamantane-H), 2.19 (s, 6H, Adamantane-H), 3.04 (s, 4H, Piperazine-H), 3.23 (s, 4H, Piperazine-H), 5.24 (s, 2H, CH_2), 6.89 (t, 1H, Ar-H, *J* = 7.0 Hz), 6.94 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.03 (t. 2H, Ar-H, *J* = 8.5 Hz), 7.26-7.28 (m, 2H, Ar-H), 7.47-7.50 (m. 1H, Ar-H), 10.67 (s, 1H, CH=N). ^{13}C NMR: 28.0, 35.56, 36.46, 38.37 (Adamantane-C), 49.41, 50.55 (Piperazine-C), 68.82 (CH_2), 110.76, 112.19, 116.31, 119.88, 129.10, 133.27, 151.38, 152.24 (Ar-C), 155.64, 161.06 (Triazole C-5 & CH=N), 163.22 (C=S). ESI-MS, *m/z* (Rel. Int.): 571 (M^+ +Na, 58), 550 (M^+ +2, 36), 549 (M^+ +1, 100).

151e: ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 6H, Adamantane-H), 2.10 (s, 3H, Adamantane-H), 2.19 (s, 6H, Adamantane-H), 3.04 (s, 4H, Piperazine-H), 3.14 (s, 4H, Piperazine-H), 5.23 (s, 2H, CH_2), 6.89-6.99 (m, 4H, Ar-H), 7.03 (t. 2H, Ar-H, *J* = 8.5 Hz), 7.48-7.49 (m, 1H, Ar-H), 10.66 (s, 1H, CH=N). ^{13}C NMR: 28.0, 35.57, 36.46, 38.38 (Adamantane-C), 50.40, 50.54 (Piperazine-C), 68.78 (CH_2), 110.85, 112.39, 115.41, 118.10, 133.28, 148.04, 152.24, 158.24 (Ar-C), 155.65 (CH=N), 161.06 (Triazole C-5), 163.23 (C=S). MS *m/z* (Rel. Int.): ESI-MS, *m/z* (Rel. Int.): 589 (M^+ +Na, 14), 568 (M^+ +2, 33), 567 (M^+ +1, 100).

151f: ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 6H, Adamantane-H), 2.10 (s, 3H, Adamantane-H), 2.19 (s, 6H, Adamantane-H), 3.03-3.04 (m, 4H, Piperazine-H), 3.21-3.27 (m, 4H, Piperazine-H), 5.24 (s, 2H, CH_2), 7.04-7.13 (m, 5H, Ar-H), 7.34 (t. 1H, Ar-H, *J* = 8.0 Hz), 7.46-7.50 (m, 1H, Ar-H), 10.67 (s, 1H, CH=N). ^{13}C NMR: 27.99, 35.57, 36.44, 38.38 (Adamantane-C), 48.87, 50.36 (Piperazine-C), 68.73 (CH_2), 118.86 (CF_3), 110.83, 112.36, 115.09, 123.22, 125.39, 129.53, 131.58, 133.31, 151.44, 152.27 (Ar-C), 155.71, 161.01 (Triazole C-5 & CH=N), 163.25 (C=S). ESI-MS, *m/z* (Rel. Int.): 639 (M^+ +Na, 13), 618 (M^+ +2, 35), 617 (M^+ +1, 100).

151g: ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 6H, Adamantane-H), 2.10 (s, 3H, Adamantane-H), 2.20 (s, 6H, Adamantane-H), 3.10 (s, 8H, Piperazine-H), 3.87 (s, 3H, OCH_3), 5.25 (s, 2H, CH_2), 6.86 (d, 1H, Ar-H, *J* = 7.5 Hz), 6-92-6.98 (m, 2H, Ar-H), 7.0-7.07 (m, 3H, Ar-H), 7.47-7.49 (m, 1H, Ar-H), 10.63 (s, 1H, CH=N). ^{13}C NMR: 28.02, 35.55, 36.48, 38.34 (Adamantane-C), 50.72, 50.83 (Piperazine-C), 55.27 (OCH_3), 69.04 (CH_2), 110.03, 112.18, 112.38, 118.28, 120.94, 123.02, 133.23, 141.34, 152.26, 152.33 (Ar-C), 155.55, 161.02 (Triazole C-5 & CH=N), 163.21 (C=S). ESI-MS, *m/z* (Rel. Int.): 601 (M^+ +Na, 100), 580 (M^+ +2, 33), 579 (M^+ +1, 92).

151h: ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 6H, Adamantane-H), 2.09 (s, 3H, Adamantane-H), 2.18 (s, 6H, Adamantane-H), 2.41-2.52 (m, 4H, Piperazine-H), 2.95 (s, 4H, Piperazine-H), 3.52 (s, 2H, PhC***H***$_2$), 5.17 (s, 2H, CH_2), 7.03 (t, 2H, Ar-H, *J* = 8.5 Hz), 7.25-7.32 (m, 5H, Ar-H), 7.45-7.49 (m, 1H, Ar-H), 10.65 (s, 1H, CH=N). ^{13}C NMR: 28.0, 35.52, 36.47, 38.36 (Adamantane-C), 50.51, 53.12 (Piperazine-C), 63.18 (Ph***C***H_2), 68.96 (CH_2), 110.89, 112.17, 127.04, 128.18, 129.29, 133.11, 137.96, 152.11 (Ar-C), 155.47, 161.05 (Triazole C-5 & CH=N), 163.19 (C=S). ESI-MS, *m/z* (Rel. Int.): 585 (M^+ +Na, 7), 564 (M^+ +2, 34), 563 (M^+ +1, 100).

151i: ^{1}H NMR ($CDCl_3$): δ 1.76 (s, 6H, Adamantane-H), 2.07 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 2.33 (s, 3H, CH_3), 2.50-2.54 (m, 4H, Piperazine-H), 2.92-2.96 (m, 4H, Piperazine-H), 5.17 (s, 2H, CH_2), 7.22-7.48 (m, 3H, Ar-H), 10.80 (s, 1H, CH=N). ^{13}C NMR: 27.91, 35.54, 36.43, 38.44 (Adamantane-C), 43.85 (CH_3), 54.36, 56.42 (Piperazine-C), 68.71 (CH_2), 128.62, 129.43, 131.75, 136.18 (Ar-C),

155.42, 158.18 (Triazole C-5 & CH=N), 163.44 (C=S). ESI-MS, *m/z* (Rel. Int.): 522 (M^+ +4, 6), 520 (M^+ +2, 55), 518 (M^+, 100).

151j: ^{1}H NMR ($CDCl_3$): δ 1.08 (t, 3H, CH_3, *J* = 7.0 Hz), 1.75 (s, 6H, Adamantane-H), 2.06 (s, 3H, Adamantane-H), 2.16-2.17 (m, 6H, Adamantane-H), 2.42 (q, 2H, C***H***$_2$$CH_3$, *J* = 7.0 Hz), 2.52-2.53 (m, 4H, Piperazine-H), 2.95 (s, 4H, Piperazine-H), 5.19 (s, 2H, CH_2), 7.32-7.37 (m, 1H, Ar-H), 7.42-7.47 (m. 2H, Ar-H), 10.74 (s, 1H, CH=N). ^{13}C NMR: 11.87 (CH_3), 27.96, 35.55, 36.47, 38.51 (Adamantane-C), 50.41 (***C***H_2CH_3), 52.31, 52.76 (Piperazine-C), 68.93 (CH_2), 129.32, 129.40, 131.53, 136.10 (Ar-C), 155.41, 157.82 (Triazole C-5 & CH=N), 163.42 (C=S). ESI-MS, *m/z* (Rel. Int.): 536 (M^+ +4, 5), 534 (M^+ +2, 43), 532 (M^+, 100).

151k: ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3, *J* = 7.0 Hz), 1.76 (s, 6H, Adamantane-H), 2.07 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 2.83 (s, 4H, Piperazine-H), 3.51 (s, 4H, Piperazine-H), 4.11 (q, 2H, C***H***$_2$$CH_3$, *J* = 7.0 Hz), 5.17 (s, 2H, CH_2), 7.30-7.36 (m, 1H, Ar-H), 7.41-7.46 (m. 2H, Ar-H), 10.79 (s, 1H, CH=N). ^{13}C NMR: 14.64 (CH_3), 27.94, 35.61, 36.44, 38.52 (Adamantane-C), 50.30, 52.50 (Piperazine-C), 61.33 (***C***H_2CH_3), 69.15 (CH_2), 128.94, 129.37, 131.61, 136.09 (Ar-C), 155.30, 155.46, 157.76 (C=O, Triazole C-5 & CH=N), 163.46 (C=S). ESI-MS, *m/z* (Rel. Int.): 603 (M^+ +4+Na, 13), 602 (M^+ +3+Na, 15), 601 (M^+ +2+Na, 76), 599 (M^+ +Na, 100), 577 (M^+ +1, 7).

151l: ^{1}H NMR ($CDCl_3$): δ 1.77 (s, 6H, Adamantane-H), 2.08 (s, 3H, Adamantane-H), 2.18 (s, 6H, Adamantane-H), 3.06 (s, 4H, Piperazine-H), 3.23 (s, 4H, Piperazine-H), 5.25 (s, 2H, CH_2), 6.87 (t, 1H, Ar-H, *J* = 7.5 Hz), 6.95 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.27-7.37 (m, 4H, Ar-H), 7.46-7.47 (m, 1H, Ar-H), 10.80 (s, 1H, CH=N). ^{13}C NMR: 27.96, 35.61, 36.46, 38.54 (Adamantane-C), 49.45, 50.60 (Piperazine-C), 69.0 (CH_2), 116.35, 119.92, 129.06, 129.11, 129.37, 131.60, 136.12, 151.39 (Ar-C), 155.61, 156.09, 157.83 (Triazole C-5 & CH=N), 163.48 (C=S). ESI-MS, *m/z* (Rel. Int.): 608 (M^+ +4+Na, 4), 606 (M^+ +2+Na, 15), 605 (M^+ +1+Na, 47), 604 (M^+ +Na, 21), 585 (M^+ +4, 16), 583 (M^+ +2, 77), 581 (M^+, 100).

151m: ^{1}H NMR ($CDCl_3$): δ 1.76 (s, 6H, Adamantane-H), 2.08 (s, 3H, Adamantane-H), 2.18 (s, 6H, Adamantane-H), 3.05-3.06 (m, 4H, Piperazine-H), 3.15 (s, 4H, Piperazine-H), 5.24 (s, 2H, CH_2), 6.88-6.91 (m, 2H, Ar-H), 6.96-6.99 (m, 2H, Ar-H), 7.33-7.36 (m, 1H, Ar-H), 7.45 (d, 2H, Ar-H, *J* = 7.0 Hz), 10.79 (s, 1H, CH=N). ^{13}C NMR: 27.96, 35.61, 36.46, 38.55 (Adamantane-C), 50.44, 50.59 (Piperazine-C), 68.95 (CH_2), 115.43, 115.60, 118.08, 118.14, 129.37, 131.60, 136.11, 148.06 (Ar-C), 155.62, 157.83 (Triazole C-5 & CH=N), 163.49 (C=S). ESI-MS, *m/z* (Rel. Int.): 623 (M^+ +2+Na, 9), 621 (M^+ +Na, 12), 602 (M^+ +4, 23), 601 (M^+ +3, 78), 600 (M^+ +2, 32), 599 (M^+ +1, 100).

151n: ^{1}H NMR ($CDCl_3$): δ 1.77 (s, 6H, Adamantane-H), 2.08 (s, 3H, Adamantane-H), 2.18 (s, 6H, Adamantane-H), 3.05-3.06 (m, 4H, Piperazine-H), 3.27-3.28 (m, 4H, Piperazine-H), 5.24 (s, 2H, CH_2), 7.07 (t, 2H, Ar-H, *J* = 8.5 Hz), 7.14 (s, 1H, Ar-H), 7.34-7.37 (m, 2H, Ar-H), 7.46 (d, 2H, Ar-H , *J* = 8.0 Hz), 10.80 (s, 1H, CH=N). ^{13}C NMR: 27.94, 35.62, 36.44, 38.55 (Adamantane-C), 48.89, 50.40 (Piperazine-C), 68.91 (CH_2), 118.89 (CF_3), 112.43, 115.98, 123.22, 125.39, 129.02, 129.39, 129.55, 131.78, 136.12, 151.44 (Ar-C), 155.68, 157.86 (Triazole C-5 & CH=N), 163.50 (C=S). ESI-MS, *m/z* (Rel. Int.): 673 (M^+ +2+Na, 8), 671 (M^+ +Na, 14), 652 (M^+ +4, 16), 651 (M^+ +3, 76), 650 (M^+ +2, 32), 649 (M^+ +1, 100).

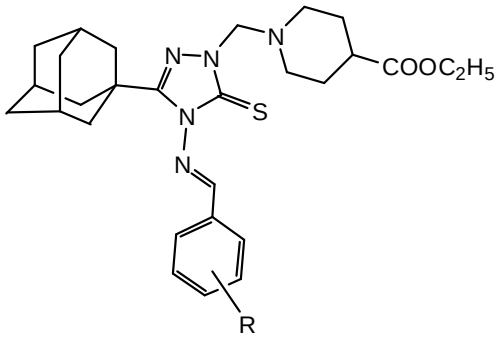
151o: ^{1}H NMR ($CDCl_3$): δ 1.77 (s, 6H, Adamantane-H), 2.08 (s, 3H, Adamantane-H), 2.19 (s, 6H, Adamantane-H), 3.11 (s, 8H, Piperazine-H), 3.87 (s, 3H, OCH_3), 5.26 (s, 2H, CH_2), 6.86 (d, 1H, Ar-H, *J* = 7.5 Hz), 6.93-7.04 (m, 3H, Ar-H), 7.33-7.36 (m, 1H, Ar-H) 7.45 (d, 2H, Ar-H, *J* = 8.0 Hz), 10.76 (s, 1H, CH=N). ^{13}C NMR: 27.98, 35.59, 36.49, 38.51 (Adamantane-C), 50.76, 50.84 (Piperazine-C), 55.28 (OCH_3), 69.22 (CH_2), 110.98, 118.29, 120.93, 123.04, 129.12, 129.34, 131.55, 136.12, 141.32, 152.27 (Ar-C), 155.50 (Triazole C-5), 157.89 (CH=N), 163.49 (C=S). ESI-MS, *m/z* (Rel. Int.): 637 (M^+ +4+Na, 8), 636 (M^+ +3+Na, 13), 635 (M^+ +2+Na, 74), 633 (M^+ +Na, 100), 614 (M^+ +4, 9), 613 (M^+ +3, 35), 612 (M^+ +2, 14), 611 (M^+ +1, 46).

151p: ^{1}H NMR ($CDCl_3$): δ 1.76 (s, 6H, Adamantane-H), 2.07 (s, 3H, Adamantane-H), 2.17 (s, 6H, Adamantane-H), 2.51 (s, 4H, Piperazine-H), 2.92 (s, 4H, Piperazine-H), 3.52 (s, 2H, PhC***H***$_2$), 5.17 (s, 2H, CH_2), 7.26-7.36 (m, 6H, Ar-H), 7.45 (d, 2H, Ar-H , *J* = 8.0 Hz), 10.78 (s, 1H, CH=N). ^{13}C NMR: 27.96, 35.56, 36.47, 38.53 (Adamantane-C), 50.53, 53.14 (Piperazine-C), 63.24 (Ph***C***H_2), 69.11 (CH_2), 127.07, 128.20, 129.12, 129.33, 129.42, 131.54, 136.10, 137.90 (Ar-C), 155.45, 157.68 (Triazole C-5 & CH=N), 163.45 (C=S). ESI-MS, *m/z* (Rel. Int.): 621 (M^+ +4+Na, 3), 619 (M^+ +2+Na, 8), 617 (M^+ +Na, 11), 598 (M^+ +4, 13), 597 (M^+ +3, 76), 596 (M^+ +2, 35), 595 (M^+ +1, 100).

Table 5: Melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of compounds **(151a-p)**

Comp. No.	X	R	Mp (°C)	Cryst. Solv.	Yield (%)	Molecular Formula (Mol. Wt.)
151a	F	CH_3	102-4	EtOH/H_2O	54	$C_{25}H_{32}F_2N_6S$ (486.62)
151b	F	C_2H_5	169-71	EtOH/H_2O	89	$C_{26}H_{34}F_2N_6S$ (500.65)
151c	F	$COOC_2H_5$	156-8	EtOH/H_2O	82	$C_{27}H_{34}F_2N_6O_2S$ (544.66)
151d	F	C_6H_5	151-3	EtOH	79	$C_{30}H_{34}F_2N_6S$ (548.69)
151e	F	4-FC_6H_4	140-2	EtOH/H_2O	80	$C_{30}H_{33}F_3N_6S$ (566.68)
151f	F	3-$CF_3C_6H_4$	132-4	EtOH/H_2O	88	$C_{31}H_{33}F_5N_6S$ (616.69)
151g	F	2-$CH_3OC_6H_4$	184-6	EtOH/$CHCl_3$	85	$C_{31}H_{36}F_2N_6OS$ (578.72)
151h	F	$C_6H_5CH_2$	148-50	EtOH	80	$C_{31}H_{36}F_2N_6S$ (562.72)
151i	Cl	CH_3	109-11	EtOH/H_2O	68	$C_{25}H_{32}Cl_2N_6S$ (519.53)
151j	Cl	C_2H_5	117-9	EtOH/H_2O	75	$C_{26}H_{34}Cl_2N_6S$ (533.56)
151k	Cl	$COOC_2H_5$	136-8	EtOH/H_2O	72	$C_{27}H_{34}Cl_2N_6O_2S$ (577.57)
151l	Cl	C_6H_5	170-2	EtOH	83	$C_{30}H_{34}Cl_2N_6S$ (581.60)
151m	Cl	4-FC_6H_4	184-6	EtOH	85	$C_{30}H_{33}Cl_2FN_6S$ (599.59)
151n	Cl	3-$CF_3C_6H_4$	159-61	EtOH	86	$C_{31}H_{33}Cl_2F_3N_6S$ (649.60)
151o	Cl	2-$CH_3OC_6H_4$	139-41	EtOH	67	$C_{31}H_{36}Cl_2N_6OS$ (611.63)
151p	Cl	$C_6H_5CH_2$	178-80	EtOH	80	$C_{31}H_{36}Cl_2N_6S$ (595.63)

4.12. 5-(1-Adamantyl)-4-arylideneamino-2-(4-ethoxycarbonyl-1-piperidylmethyl)-1,2,4-triazoline-3-thiones (152a-n)



A mixture of the 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazole **150** (1.0 mmole), ethyl 4-piperidinecarboxylate (0.16 g, 1.0 mmole) and 37% formaldehyde solution (1 ml), in ethanol (8 ml), was heated under reflux for 20 minutes when a clear solution was obtained. Stirring was continued for 12 hours at room temperature and the mixture was allowed to stand overnight. Cold water (5 ml) was added and the reaction mixture was stirred for 20 minutes. The precipitated crude products were filtered, washed with water, dried, and crystallized.

The melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of the title compounds **152a-n** are listed in Table **6**.

152a: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, CH_3, *J* = 7.0 Hz), 1.72-1.83 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.92-1.94 (m, 2H, Piperidine-H), 2.10 (s, 3H, Adamantane-H), 2.17 (s, 6H, Adamantane-H), 2.20-2.25 (m, 1H, Piperidine-4 H), 2.46-2.50 (m, 2H, Piperidine-H), 3.20-3.22 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2$$CH_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH_2), 7.51-7.58 (m, 3H, Ar-H), 7.91 (d, 2H, Ar-H, *J* = 7.0 Hz), 10.08 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH_3), 27.93, 35.44, 36.58, 38.77 (Adamantane-C), 28.35 (Piperidine C-3), 40.42 (Piperidine C-4), 50.42 (Piperidine C-2), 60.25 (***C***H_2CH_3), 69.63 (CH_2), 128.72, 129.02, 132.28, 132.84 (Ar-C), 155.28, 162.26 (Triazole C-5 & CH=N), 163.21 (C=S), 174.99 (C=O). ESI-MS, *m/z* (Rel. Int.): 530 (M^+ +Na, 100), 509 (M^+ +2, 21), 508 (M^+ +1, 72).

152b: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.72-1.82 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.92-1.94 (m, 2H, Piperidine-H), 2.10 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 2.20-2.25 (m, 1H, Piperidine-4 H), 2.50-2.54 (m, 2H, Piperidine-H), 3.19-3.22 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH_2), 7.18 (t, 1H, Ar-H, *J* = 8.0 Hz), 7.30 (d, 1H, Ar-H, *J* = 7.5 Hz), 7.53-7.56 (m, 1H, Ar-H), 8.08-8.11 (m, 1H, Ar-H), 10.42 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH_3), 27.93, 35.46, 36.56, 38.76 (Adamantane-C), 28.35 (Piperidine C-3), 40.77 (Piperidine C-4), 50.42 (Piperidine C-2), 60.25 (***C***H$_2$CH$_3$), 69.64 (CH_2), 116.31, 120.89, 124.66, 127.57, 133.90, 155.82 (Ar-C), 155.28, 161.54 (Triazole C-5 & CH=N), 163.31 (C=S), 174.99 (C=O). ESI-MS, *m/z* (Rel. Int.): 548 (M^+ +Na, 93), 527 (M^+ +2, 33), 526 (M^+ +1, 100).

152c: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.72-1.79 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.92-1.94 (m, 2H, Piperidine-H), 2.11 (s, 3H, Adamantane-H), 2.17 (s, 6H, Adamantane-H), 2.21-2.25 (m, 1H, Piperidine-4 H), 2.51-2.55 (m, 2H, Piperidine-H), 3.20-3.22 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH_2), 7.40 (t, 1H, Ar-H, *J* = 7.5 Hz), 7.46-7.51 (m, 2H, Ar-H), 8.19 (d, 1H, Ar-H, *J* = 7.5 Hz), 10.69 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH_3), 27.93, 35.49, 36.58, 38.83 (Adamantane-C), 28.35 (Piperidine C-3), 40.78 (Piperidine C-4), 50.43 (Piperidine C-2), 60.25 (***C***H$_2$CH$_3$), 69.65 (CH_2), 127.20, 127.60, 130.34, 130.85, 132.97, 136.68 (Ar-C), 155.28, 158.27 (Triazole C-5 & CH=N), 163.37 (C=S), 174.99 (C=O). ESI-MS, *m/z* (Rel. Int.): 566 (M^+ +2+Na, 44), 564 (M^+ +Na, 100), 544 (23), 542 (54).

152d: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.72-1.78 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.91-1.94 (m, 2H, Piperidine-H), 2.09 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 2.20-2.25 (m, 1H, Piperidine-4 H), 2.45 (s, 3H, PhC***H***$_3$), 2.50-2.54 (m, 2H, Piperidine-H), 3.19-3.22 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH_2), 7.31 (d, 2H, Ar-H, *J* = 8.0 Hz), 7.80 (d, 2H, Ar-H, *J* = 8.0 Hz), 9.94 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH_3), 21.71 (Ph***C***H$_3$), 27.93, 35.40, 36.58, 38.75 (Adamantane-C), 28.35 (Piperidine C-3), 40.78 (Piperidine C-4), 50.41 (Piperidine C-2), 60.24 (***C***H$_2$CH$_3$), 69.62 (CH_2),

128.75, 129.76, 130.10, 143.05 (Ar-C), 155.24, 162.69 (Triazole C-5 & CH=N), 163.21 (C=S), 174.99 (C=O). ESI-MS, *m/z* (Rel. Int.): 544 (M^+ +Na, 100), 523 (M^+ +2, 43), 522 (M^+ +1, 76).

152e: ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.73-1.79 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.92-1.95 (m, 2H, Piperidine-H), 2.10 (s, 9H, Adamantane-H), 2.22-2.24 (m, 1H, Piperidine-4 H), 2.51-2.55 (m, 2H, Piperidine-H), 3.19-3.21 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH_2), 7.03-7.06 (m, 1H, Ar-H), 7.08 (d, 1H, Ar-H, *J* = 8.5 Hz), 7.44-7.51 (m, 2H, Ar-H), 9.69 (s, 1H, CH=N), 10.45 (s, 1H, OH). ^{13}C NMR: 14.20 (CH_3), 27.80, 35.35, 36.29, 38.97 (Adamantane-C), 28.32 (Piperidine C-3), 40.73 (Piperidine C-4), 50.42 (Piperidine C-2), 60.28 (***C***H$_2$CH$_3$), 70.22 (CH_2), 116.09, 117.56, 120.09, 133.60, 134.69, 169.08 (Ar-C), 154.28, 160.08 (Triazole C-5 & CH=N), 164.01 (C=S), 174.94 (C=O). ESI-MS, *m/z* (Rel. Int.): 546 (M^+ +Na, 100), 525 (M^+ +2, 26), 524 (M^+ +1, 84).

152f: ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.75-1.78 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.94-1.96 (m, 2H, Piperidine-H), 2.07 (s, 3H, Adamantane-H), 2.12 (s, 6H, Adamantane-H), 2.24-2.28 (m, 1H, Piperidine-4 H), 2.52-2.56 (m, 2H, Piperidine-H), 3.21-3.23 (m, 2H, Piperidine-H), 4.13 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.14 (s, 2H, CH_2), 6.92 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.72 (d, 2H, Ar-H, *J* = 8.5 Hz), 9.55 (s, 1H, CH=N). ^{13}C NMR: 14.17 (CH_3), 27.88, 35.37, 36.52, 38.66 (Adamantane-C), 28.15 (Piperidine C-3), 40.72 (Piperidine C-4), 50.43 (Piperidine C-2), 58.53 (***C***H$_2$CH$_3$), 69.64 (CH_2), 116.24, 124.64, 130.91, 163.01 (Ar-C), 155.38, 160.42 (Triazole C-5 & CH=N), 164.17 (C=S), 175.32 (C=O). ESI-MS, *m/z* (Rel. Int.): 546 (M^+ +Na, 98), 525 (M^+ +2, 33), 524 (M^+ +1, 100).

152g: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.72-1.79 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.91-1.93 (m, 2H, Piperidine-H), 2.09 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 2.20-2.24 (m, 1H, Piperidine-4 H), 2.50-2.53 (m, 2H, Piperidine-H), 3.19-3.21 (m, 2H, Piperidine-H), 3.90 (s, 3H, OCH_3), 4.12 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH_2), 7.02 (d, 2H, Ar-H, *J* =

8.5 Hz), 7.86 (d, 2H, Ar-H , *J* = 8.5 Hz), 9.81 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH_3), 27.93, 35.37, 36.58, 38.74 (Adamantane-C), 28.35 (Piperidine C-3), 40.79 (Piperidine C-4), 55.48 (Piperidine C-2), 60.23 (***C***H_2CH_3), 69.64 (CH_2), 114.54, 125.35, 130.59, 162.76 (Ar-C), 155.18, 162.69 (Triazole C-5 & CH=N), 163.21 (C=S), 174.99 (C=O). ESI-MS, *m/z* (Rel. Int.): 560 (M^+ +Na, 100), 539 (M^+ +2, 38), 538 (M^+ +1, 86).

152h: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3CH_2$, *J* = 7.0 Hz), 1.71-1.80 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.92-1.94 (m, 2H, Piperidine-H), 2.09 (s, 3H, Adamantane-H), 2.18 (s, 6H, Adamantane-H), 2.21-2.25 (m, 1H, Piperidine-4 H), 2.50-2.54 (m, 2H, Piperidine-H), 3.19-3.21 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2CH_3$, *J* = 7.0 Hz), 5.14 (s, 2H, CH_2), 7.03 (t, 2H, Ar-H, *J* = 8.5 Hz), 7.45-7.49 (m, 1H, Ar-H), 10.70 (s, 1H, CH=N). ^{13}C NMR: 14.19 (CH_3), 28.0, 35.53, 36.46, 38.41 (Adamantane-C), 28.35 (Piperidine C-3), 40.77 (Piperidine C-4), 50.42 (Piperidine C-2), 60.25 (***C***H_2CH_3), 69.43 (CH_2), 110.89, 112.37, 133.21, 161.04 (Ar-C), 155.53, 160.99 (Triazole C-5 & CH=N), 163.21 (C=S), 174.98 (C=O). ESI-MS, *m/z* (Rel. Int.): 566 (M^+ +Na, 100), 545 (M^+ +2, 18), 544 (M^+ +1, 61).

152i: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3CH_2$, *J* = 7.0 Hz), 1.71-1.79 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.92-1.94 (m, 2H, Piperidine-H), 2.09 (s, 3H, Adamantane-H), 2.18 (s, 6H, Adamantane-H), 2.21-2.25 (m, 1H, Piperidine-4 H), 2.51-2.55 (m, 2H, Piperidine-H), 3.20-3.22 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2CH_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH_2), 7.14-7.17 (m, 2H, Ar-H), 7.33 (d, 1H, Ar-H, *J* = 7.5 Hz), 10.87 (s, 1H, CH=N). ^{13}C NMR: 14.19 (CH_3), 28.0, 35.55, 36.46, 38.40 (Adamantane-C), 28.36 (Piperidine C-3), 40.77 (Piperidine C-4), 50.43 (Piperidine C-2), 60.24 (***C***H_2CH_3), 69.46 (CH_2), 115.35, 119.81, 126.25, 132.52, 137.10, 162.85 (Ar-C), 155.11 (CH=N), 160.76 (Triazole C-5), 163.05 (C=S), 174.99 (C=O). ESI-MS, *m/z* (Rel. Int.): 584 (M^+ +2+Na, 41), 582 (M^+ +Na, 100), 562 (29), 561 (M^+ +2, 21), 560 (M^+ +1, 63).

152j: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3CH_2$, *J* = 7.0 Hz), 1.72-1.81 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.92-1.95 (m, 2H, Piperidine-H), 2.07 (s, 3H,

Adamantane-H), 2.17 (s, 6H, Adamantane-H), 2.21-2.26 (m, 1H, Piperidine-4 H), 2.53-2.57 (m, 2H, Piperidine-H), 3.20-3.22 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH$_2$), 7.33-7.36 (m, 1H, Ar-H), 7.45 (d, 2H, Ar-H, *J* = 8.0 Hz), 10.84 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH$_3$), 27.96, 35.59, 36.46, 38.58 (Adamantane-C), 28.36 (Piperidine C-3), 40.77 (Piperidine C-4), 50.44 (Piperidine C-2), 60.24 (***C***H$_2$CH$_3$), 69.62 (CH$_2$), 128.77, 129.36, 131.54, 136.08 (Ar-C), 155.52, 157.56 (Triazole C-5 & CH=N), 163.22 (C=S), 174.99 (C=O). ESI-MS, *m/z* (Rel. Int.): 602 (M^+ +4+Na, 14), 600 (M^+ +2+Na, 74), 598 (M^+ +Na, 100), 578 (52), 577 (M^+ +2, 23), 576 (M^+ +1, 73).

152k: ^{1}H NMR (CDCl$_3$): δ 1.24 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.72-1.83 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.91-1.94 (m, 2H, Piperidine-H), 2.11 (s, 3H, Adamantane-H), 2.16 (s, 6H, Adamantane-H), 2.20-2.25 (m, 1H, Piperidine-4 H), 2.50-2.54 (m, 2H, Piperidine-H), 3.19-3.21 (m, 2H, Piperidine-H), 4.12 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.14 (s, 2H, CH$_2$), 7.40 (d, 1H, Ar-H, *J* = 8.5 Hz), 7.53 (s, 1H, Ar-H), 8.11 (d, 1H, Ar-H, *J* = 8.5 Hz), 10.73 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH$_3$), 27.91, 35.50, 36.57, 38.86 (Adamantane-C), 28.34 (Piperidine C-3), 40.76 (Piperidine C-4), 50.42 (Piperidine C-2), 60.26 (***C***H$_2$CH$_3$), 69.62 (CH$_2$), 127.88, 128.28, 129.55, 130.16, 137.15, 138.58 (Ar-C), 155.23, 156.68 (Triazole C-5 & CH=N), 163.33 (C=S), 174.96 (C=O). ESI-MS, *m/z* (Rel. Int.): 602 (M^+ +4+Na, 17), 600 (M^+ +2+Na, 79), 598 (M^+ +Na, 100), 578 (56), 577 (M^+ +2, 24), 576 (M^+ +1, 78).

152l: ^{1}H NMR (CDCl$_3$): δ 1.24 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.71-1.84 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.91-1.93 (m, 2H, Piperidine-H), 2.12 (s, 3H, Adamantane-H), 2.15 (s, 6H, Adamantane-H), 2.20-2.24 (m, 1H, Piperidine-4 H), 2.49-2.53 (m, 2H, Piperidine-H), 3.18-3.20 (m, 2H, Piperidine-H), 4.11 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.13 (s, 2H, CH$_2$), 7.59 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.72 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.98 (s, 1H, Ar-H), 10.29 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH$_3$), 27.90, 35.50, 36.57, 38.86 (Adamantane-C), 28.33 (Piperidine C-3), 40.74 (Piperidine C-4), 50.41 (Piperidine C-2), 60.27 (***C***H$_2$CH$_3$), 69.63 (CH$_2$), 127.44, 130.03, 131.16, 133.01, 133.67, 136.40 (Ar-C), 155.25, 158.17 (Triazole C-5 &

CH=N), 163.20 (C=S), 174.94 (C=O). ESI-MS, *m/z* (Rel. Int.): 602 (M^+ +4+Na, 16), 600 (M^+ +2+Na, 72), 598 (M^+ +Na, 100), 578 (49), 577 (M^+ +2, 20), 576 (M^+ +1, 67).

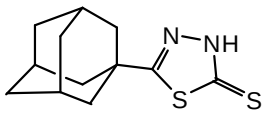
152m: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.76-1.82 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.91-1.93 (m, 2H, Piperidine-H), 2.09 (s, 3H, Adamantane-H), 2.17 (s, 6H, Adamantane-H), 2.20-2.24 (m, 1H, Piperidine-4 H), 2.49-2.54 (m, 2H, Piperidine-H), 3.19-3.21 (m, 2H, Piperidine-H), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.11 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.15 (s, 2H, CH_2), 6.79 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.40 (d, 1H, Ar-H, *J* = 8.0 Hz), 7.54 (s, 1H, Ar-H), 9.85 (s, 1H, CH=N). ^{13}C NMR: 14.19 (CH_3), 27.94, 35.39, 36.61, 38.80 (Adamantane-C), 28.35 (Piperidine C-3), 40.78 (Piperidine C-4), 50.41 (Piperidine C-2), 55.92 (OCH_3), 56.08 (OCH_3), 60.24 (***C***H$_2$CH$_3$), 69.63 (CH_2), 109.19, 110.96, 124.42, 125.61, 149.60, 152.98 (Ar-C), 155.13, 162.48 (Triazole C-5 & CH=N), 163.18 (C=S), 174.98 (C=O). ESI-MS, *m/z* (Rel. Int.): 590 (M^+ +Na, 100), 569 (M^+ +2, 26), 568 (M^+ +1, 84).

152n: ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.73-1.80 (m, 8H, 6 Adamantane-H & 2 Piperidine-H), 1.92-1.94 (m, 2H, Piperidine-H), 2.08 (s, 3H, Adamantane-H), 2.15 (s, 6H, Adamantane-H), 2.21-2.23 (m, 1H, Piperidine-4 H), 2.51-2.55 (m, 2H, Piperidine-H), 3.18-3.21 (m, 2H, Piperidine-H), 4.04 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.11 (q, 2H, C***H***$_2$CH$_3$, *J* = 7.0 Hz), 5.14 (s, 2H, CH_2), 7.65 (s, 1H, Ar-H), 7.63 (s, 1H, Ar-H), 10.54 (s, 1H, CH=N). ^{13}C NMR: 14.20 (CH_3), 27.89, 35.42, 36.51, 38.81 (Adamantane-C), 28.34 (Piperidine C-3), 40.75 (Piperidine C-4), 50.41 (Piperidine C-2), 56.60 (OCH_3), 56.68 (OCH_3), 60.25 (***C***H$_2$CH$_3$), 69.85 (CH_2), 107.82, 110.0, 122.50, 142.33, 151.45, 153.30 (Ar-C), 155.03, 160.57 (Triazole C-5 & CH=N), 163.57 (C=S), 174.99 (C=O). ESI-MS, *m/z* (Rel. Int.): 635 (M^+ +Na, 100), 614 (M^+ +2, 23), 613 (M^+ +1, 68).

Table 6: Melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of compounds **(152a-n)**

Comp. No.	R	Mp (°C)	Cryst. Solv.	Yield (%)	Molecular Formula (Mol. Wt.)
152a	H	125-7	EtOH/H_2O	82	$C_{28}H_{37}N_5O_2S$ (507.69)
152b	2-F	134-6	EtOH/H_2O	72	$C_{28}H_{36}FN_5O_2S$ (525.68)
152c	2-Cl	158-60	EtOH	75	$C_{28}H_{36}ClN_5O_2S$ (542.14)
152d	4-CH_3	135-7	EtOH/H_2O	92	$C_{29}H_{39}N_5O_2S$ (521.72)
152e	2-OH	127-9	EtOH/H_2O	79	$C_{28}H_{37}N_5O_3S$ (523.69)
152f	4-OH	195-7	EtOH/H_2O	84	$C_{28}H_{37}N_5O_3S$ (523.69)
152g	4-OCH_3	124-6	EtOH/H_2O	88	$C_{29}H_{39}N_5O_3S$ (537.72)
152h	2,6-F_2	148-50	EtOH/H_2O	69	$C_{28}H_{35}F_2N_5O_2S$ (543.67)
152i	2-Cl,6-F	148-50	EtOH	74	$C_{28}H_{35}ClFN_5O_2S$ (560.13)
152j	2,6-Cl_2	151-3	EtOH	75	$C_{28}H_{35}Cl_2N_5O_2S$ (576.58)
152k	2,4-Cl_2	129-31	EtOH	68	$C_{28}H_{35}Cl_2N_5O_2S$ (576.58)
152l	3,4-Cl_2	186-8	EtOH	71	$C_{28}H_{35}Cl_2N_5O_2S$ (576.58)
152m	3,4-$(CH_3O)_2$	113-5	EtOH/H_2O	76	$C_{30}H_{41}N_5O_4S$ (567.74)
152n	2-NO_2,4,5-$(CH_3O)_2$	182-4	EtOH/$CHCl_3$	80	$C_{30}H_{40}N_6O_6S$ (612.74)

4.13. 5-(1-Adamantyl)-1,3,4-thiadiazoline-2-thione (153)

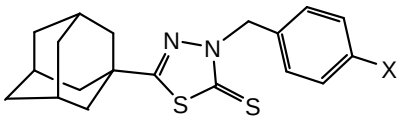


Potassium *N*'-(1-adamantylcarbonyl)dithiocarbazate **143** (15.43 g, 0.05 mole) was added portionwise to 98% sulphuric acid (15 ml) and the resulted clear solution was stirred at room temperature for 24 hours. The mixture was cautiously added to crushed ice (about 200 gm), stirred for one hour, refrigerated for two hours, and the

separated white precipitate was filtered, washed with water, dried and crystallized from ethanol to yield 7.8 g (62%) of the title compound **153** (Mp. 155-6 ^{o}C).

^{1}H NMR ($CDCl_3$): δ 1.77-1.84 (m, 6H, Adamantane-H), 2.10 (s, 6H, Adamantane-H), 2.14 (s, 3H, Adamantane-H), 6.14 (s, 1H, NH). ^{13}C NMR: 28.36, 36.24, 38.86, 43.39 (Adamantane-C), 156.09 (C-5), 184.35 (C=S). EI-MS, *m/z* (Rel. Int.): 252 (M^+, 100), 209 (12), 195 (17), 135 (87), 119 (18), 59 (79).

4.14. 5-(1-Adamantyl)-3-(benzyl or 4-substituted benzyl)-1,3,4-thiadiazoline-2-thiones (154a-d)



A mixture of 5-(1-adamantyl)-1,3,4-thiadiazoline-2-thione **153** (0.5 g, 2.0 mmole), the appropriate benzyl- or 4-substituted benzyl chloride (2.0 mmole) and anhydrous potassium carbonate (0.28 g, 2.0 mmole), in ethanol (15 ml) was heated under reflux for 2 hours, and the solvent was distilled off under reduced pressure. Water (15 ml) was added to the residue and the separated crude product was filtered, washed with water, dried and crystallized.

The melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of the title compounds **154a-d** are listed in Table **7**.

154a: ^{1}H NMR ($CDCl_3$): δ 1.77-1.83 (m, 6H, Adamantane-H), 2.07 (s, 6H, Adamantane-H), 2.13 (s, 3H, Adamantane-H), 4.55 (s, 2H, ArC***H***$_2$), 7.29-7.34 (m, 3H, Ar-H), 7.44 (s, 2H, Ar-H). ^{13}C NMR: 28.42, 36.35, 38.10, 43.40 (Adamantane-C), 38.34 (Ar***C***H$_2$), 127.78, 128.69, 129.27, 136.21 (Ar-C), 163.68 (C-5), 180.80 (C=S). EI-MS, *m/z* (Rel. Int.): 343 (M^+ +1, 14), 342 (M^+, 66), 309 (12), 148 (85), 135 (19), 105 (14), 91 (100), 77 (18).

154b: ^{1}H NMR ($CDCl_3$): δ 1.77-1.81 (m, 6H, Adamantane-H), 2.07 (s, 6H, Adamantane-H), 2.12 (s, 3H, Adamantane-H), 4.52 (s, 2H, ArC***H***$_2$), 7.0 (t, 2H, Ar-H, *J* = 8.5 Hz), 7.41-7.43 (m, 2H, Ar-H). ^{13}C NMR: 28.41, 36.27, 38.36, 43.27 (Adamantane-C), 37.17 (Ar***C***H_2), 115.48, 130.94, 132.16, 161.30 (Ar-C), 163.33 (C-5), 180.95 (C=S). EI-MS, *m/z* (Rel. Int.): 361 (M^+ +1, 19), 360 (M^+, 79), 345 (35), 327 (11), 166 (94), 135 (25), 123 (13), 109 (100).

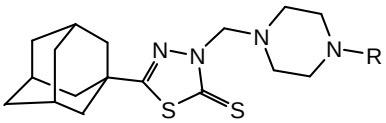
154c: ^{1}H NMR ($CDCl_3$): δ 1.73 (s, 6H, Adamantane-H), 1.96 (s, 6H, Adamantane-H), 2.04 (s, 3H, Adamantane-H), 4.52 (s, 2H, ArC***H***$_2$), 7.38 (d, 2H, Ar-H, *J* = 8.5 Hz), 7.45 (d, 2H, Ar-H, *J* = 8.5 Hz), ^{13}C NMR: 28.35, 36.25, 38.43, 43.31 (Adamantane-C), 38.0 (Ar***C***H_2), 129.06, 131.53, 132.74, 136.39 (Ar-C), 163.99 (C-5), 180.84 (C=S). EI-MS, *m/z* (Rel. Int.): 378 (M^+ +2, 14), 376 (M^+, 33), 343 (5), 184 (29), 182 (80), 141 (4), 139 (11), 135 (18), 127 (39), 125 (100).

154d: ^{1}H NMR ($CDCl_3$): δ 1.76-1.83 (m, 6H, Adamantane-H), 2.06 (s, 6H, Adamantane-H), 2.12 (s, 3H, Adamantane-H), 4.60 (s, 2H, ArC***H***$_2$), 7.64 (d, 2H, Ar-H, *J* = 8.5 Hz), 8.17 (d, 2H, Ar-H, *J* = 8.5 Hz), ^{13}C NMR: 28.37, 36.29, 38.42, 43.40 (Adamantane-C), 36.59 (Ar***C***H_2), 123.83, 130.47, 144.44, 148.33 (Ar-C), 162.32 (C-5), 181.88 (C=S). EI-MS, *m/z* (Rel. Int.): 388 (M^+ +1, 23), 387 (M^+, 100), 354 (6), 265 (4), 193 (34), 182 (80), 150 (7), 136 (38), 135 (47), 121 (15).

Table 7: Melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of compounds **(154a-d)**

Comp. No.	R	Mp (^{o}C)	Cryst. Solv.	Yield (%)	Molecular Formula (Mol. Wt.)
154a	H	139-41	$EtOH/H_2O$	75	$C_{19}H_{22}N_2S_2$ (342.52)
154b	F	133-5	$EtOH/H_2O$	77	$C_{19}H_{21}FN_2S_2$ (360.51)
154c	Cl	148-50	EtOH	86	$C_{19}H_{21}ClN_2S_2$ (376.97)
154d	NO_2	196-8	EtOH	90	$C_{19}H_{21}N_3O_2S_2$ (387.52)

4.15. 5-(1-Adamantyl)-3-(4-substituted-1-piperazinylmethyl)-1,3,4-thiadiazoline-2-thiones (155a-c)



A mixture of 5-(1-adamantyl)-1,3,4-thiadiazoline-2-thione **153** (0.5 g, 2.0 mmole), the *N*-substituted piperazine (2.0 mmole) and 37% formaldehyde solution (1 ml), in ethanol (8 ml), was heated under reflux for 2 hours and stirred at room temperature for 24 hours. The crude product was separated in case of compound **155c**, while in case of compounds **155a** and **155b** it was necessary to add water (5 ml) to precipitate the products. The crude products were filtered, washed with water, dried and crystallized.

The melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of the title compounds **155a-c** are listed in Table **8**.

155a: ^{1}H NMR ($CDCl_3$): δ 1.73-1.80 (m, 6H, Adamantane-H), 1.94 (s, 3H, Adamantane-H), 2.05 (s, 6H, Adamantane-H), 2.34 (s, 3H, CH_3), 2.61-2.78 (m, 4H, Piperazine-H), 2.99 (s, 4H, Piperazine-H), 5.25 (s, 2H, CH_2). ^{13}C NMR: 27.98, 36.05, 38.43, 42.11 (Adamantane-C), 46.52 (CH_3), 50.12, 52.68 (Piperazine-C), 70.13 (CH_2), 168.33 (C-5), 186.75 (C=S). EI-MS, *m/z* (Rel. Int.): 364 (M^+, 1), 252 (9), 135 (46), 113 (100), 98 (7).

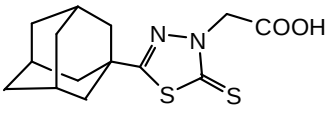
155b: ^{1}H NMR ($CDCl_3$): δ 1.08 (t, 3H, C***H***$_3$CH$_2$, *J* = 7.0 Hz), 1.71-1.80 (m, 6H, Adamantane-H), 1.88 (s, 3H, Adamantane-H), 1.92 (s, 6H, Adamantane-H), 2.48 (q, 2H, CH$_3$C***H***$_2$, *J* = 7.0 Hz), 2.58 (br. s, 4H, Piperazine-H), 2.93 (s, 4H, Piperazine-H), 5.24 (s, 2H, CH_2). ^{13}C NMR: 11.22 (***C***H$_3$CH$_2$), 28.12, 36.15, 38.99, 42.08 (Adamantane-C), 49.71 (CH$_3$***C***H$_2$), 51.98, 52.23 (Piperazine-C), 70.01 (CH_2), 169.26 (C-5), 188.01 (C=S). EI-MS, *m/z* (Rel. Int.): 378 (M^+, 1), 266 (3), 252 (30), 135 (100), 127 (56).

155c: ^{1}H NMR ($CDCl_3$): δ 1.73-1.80 (m, 6H, Adamantane-H), 2.10 (s, 6H, Adamantane-H), 2.14 (s, 3H, Adamantane-H), 3.03 (s, 4H, Piperazine-H), 3.20 (s, 4H, Piperazine-H), 5.31 (s, 2H, CH_2), 6.93-7.28 (m, 5H, Ar-H). ^{13}C NMR: 28.36, 36.25, 38.86, 43.39 (Adamantane-C), 49.47, 50.42 (Piperazine-C), 70.33 (CH_2), 116.35, 120.04, 129.14, 151.27 (Ar-C), 165.85 (C-5), 184.34 (C=S). EI-MS, *m/z* (Rel. Int.): 426 (M^+, 1), 263 (2), 265 (1), 252 (100), 195 (7), 175 (66), 135 (65).

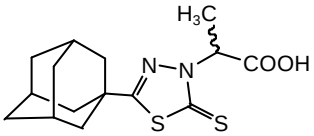
Table 8: Melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of compounds **(155a-c)**

Comp. No.	R	Mp (°C)	Cryst. Solv.	Yield (%)	Molecular Formula (Mol. Wt.)
155a	CH_3	93-5	EtOH/H_2O	36	$C_{18}H_{28}N_4S_2$ (364.57)
155b	C_2H_5	112-4	EtOH/H_2O	45	$C_{19}H_{30}N_4S_2$ (378.60)
155c	C_6H_5	149-51	EtOH	52	$C_{23}H_{30}N_4S_2$ (426.64)

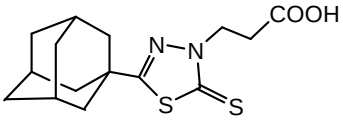
4.16. 2-[5-(1-Adamantyl)-2-thioxo-1,3,4-thiadiazolin-3-yl]acetic acid (157), (±)-2-[5-(1-adamantyl)-2-thioxo-1,3,4-thiadiazolin-3-yl]-propionic acid (159*)* and 3-[5-(1-adamantyl)-2-thioxo-1,3,4-thiadiazolin-3-yl]propionic acid (161)



157



159



161

A mixture of 5-(1-adamantyl)-1,3,4-thiadiazoline-2-thione **153** (0.5 g, 2.0 mmole), the appropriate ethyl bromoester (2.0 mmole) and anhydrous potassium

carbonate (0.28 g, 2.0 mmole), in ethanol (15 ml), was heated under reflux for 2 hours, and the solvent was distilled off under reduced pressure. 10% Aqueous sodium hydroxide (15 ml) was added to the residue and the mixture was heated under reflux for 1 hour and filtered hot. The cold filtrate was acidified with hydrochloric acid to *p*H 2-3 and allowed to stand for 3 hours. The separated crude product was filtered, washed with water, dried and crystallized from aqueous ethanol.

The melting points, yield percentages, molecular formulae and molecular weights of the title compounds **157**, **159** and **161** are listed in Table **9**.

157: ^{1}H NMR ($CDCl_3$): δ 1.71-1.82 (m, 6H, Adamantane-H), 1.94-1.96 (m, 6H, Adamantane-H), 2.05 (s, 3H, Adamantane-H), 2.12 (s, 2H, NCH_2), 11.80 (br. s, 1H, COOH). ^{13}C NMR: 28.14, 36.15, 38.64, 42.24 (Adamantane-C), 40.49 (NCH_2), 174.33 (C-5), 183.13 (C=S), 188.85 (C=O). ESI-MS, *m/z* (Rel. Int.): 311 (M^+ +1, 11), 310 (M^+, 18), 319 (100).

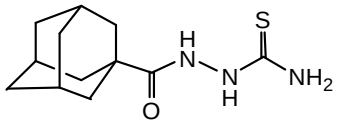
159: ^{1}H NMR ($CDCl_3$): δ 1.69-1.85 (m, 9H, Adamantane-H, CH_3), 1.93 (s, 6H, Adamantane-H), 2.04 (s, 3H, Adamantane-H), 2.14-2.16 (m, 1H, NCH), 11.78 (br. s, 1H, COOH). ^{13}C NMR: 17.11 (CH_3), 27.85, 36.43, 38.59, 43.38 (Adamantane-C), 40.50 (NCH), 174.27 (C-5), 181.71 (C=S), 184.12 (C=O). ESI-MS, *m/z* (Rel. Int.): 325 (M^+ +1, 13), 324 (M^+, 18), 323 (100).

161: ^{1}H NMR ($CDCl_3$): δ 1.73-1.83 (m, 8H, Adamantane-H, NCH_2), 1.94-1.96 (m, 8H, Adamantane-H, CH_2CO), 2.05 (s, 3H, Adamantane-H), 11.85 (br. s, 1H, COOH). ^{13}C NMR: 27.85, 36.15, 38.60, 42.23 (Adamantane-C), 28.14 (NCH_2), 40.49 (CH_2CO), 174.29 (C-5), 183.91 (C=S), 188.92 (C=O). ESI-MS, *m/z* (Rel. Int.): 325 (M^+ +1, 20), 324 (M^+, 23), 323 (100).

Table 9: Melting points, yield percentages, molecular formulae and molecular weights of compounds **(157**, **159** and **161)**

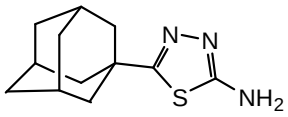
Comp. No.	Mp (^oC)	Yield (%)	Molecular Formula (Mol. Wt.)
157	208-10	59	$C_{14}H_{18}N_2O_2S_2$ (310.43)
159	150-2	62	$C_{15}H_{20}N_2O_2S_2$ (324.46)
161	149-51	55	$C_{15}H_{20}N_2O_2S_2$ (324.46)

4.17. 1-(1-Adamantylcarbonyl)-3-thiosemicarbazide (162)[54]



A suspension of adamantane-1-carboxylic acid hydrazide **142** (9.71 g, 0.05 mole), potassium thiocyanate (9.72 g, 0.1 mole) and concentrated hydrochloric acid (50 ml), in water (250 ml), was heated under reflux for 2 hours. On cooling, the separated solid was filtered, washed with cold water, dried and crystallized from ethanol to yield 9.5 g (75%) of the title compound **162** (Mp. 172-4 ^oC).[54]

4.18. 5-(1-Adamantyl)-2-amino-1,3,4-thiadiazole (163)



Method A:[135]

98% Sulphuric acid (20 ml) was added to 1-(1-adamantylcarbonyl)-3-thiosemicarbazide **162** (12.67 g, 0.05 mole), and the mixture was stirred for 24 hours at room temperature. The mixture was then poured onto crushed ice (200 g), neutralized with concentrated ammonium hydroxide solution and stirred for 20

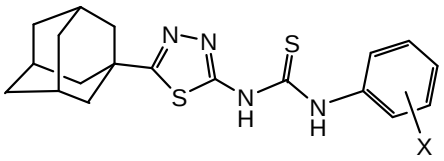
minutes. The separated crude product was filtered, washed with water, dried and crystallized from aqueous ethanol to yield 5.65 g (48%) of the title compound **163** (Mp. 201-3 ^{o}C).[135]

Method B:

Phosphorus oxychloride (20 ml) was added to adamantane-1-carboxylic acid **140** (9 gm, 0.05 mole) and the mixture was stirred for 20 minutes at room temperature. Thiosemicarbazide (4.56 g, 0.05 mole) was added and the mixture was heated under reflux for 1 hour. On cooling, water (50 ml) was added dropwise and cautiously with continuous stirring to decompose the excess phosphorus oxychloride. The mixture was then heated under reflux for 4 hours. On cooling, the mixture was neutralized by addition of potassium hydroxide pellets and refrigerated overnight. The precipitated crude product was filtered, washed with water, dried and crystallized from aqueous ethanol to yield 6.94 g (59%) of the title compound **163** (Mp. 201-3 ^{o}C).

^{1}H NMR ($CDCl_3$): δ 1.79 (s, 6H, Adamantane-H), 2.04 (s, 6H, Adamantane-H), 2.11 (s, 3H, Adamantane-H), 5.25 (s, 2H, NH_2). ^{13}C NMR: 28.46, 36.45, 38.11, 43.24 (Adamantane-C), 166.82 (C-5), 171.34 (C-2). EI-MS, *m/z* (Rel. Int.): 235 (M^+, 92), 202 (9), 178 (32), 135 (100).

4.19. N-[5-(1-Adamantyl)-1,3,4-thiadiazol-2-yl]-*N*'-arylthioureas (164a-c)



The appropriate arylisothiocyanate (2.0 mmole) was added to a solution of 5-(1-adamantyl)-2-amino-1,3,4-thiadiazole **163** (0.47 g, 2.0 mmole) in dry DMF (10 ml) and the mixture was heated under reflux for 6 hours. On cooling, the mixture was

poured onto cold water (15 ml) and the separated precipitate was filtered, washed with water and crystallized to yield compounds **164a-c**.

The melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of the title compounds **164a-c** are listed in Table **10**.

164a: ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6H, Adamantane-H), 1.91 (s, 6H, Adamantane-H), 2.02 (s, 3H, Adamantane-H), 6.97 (s, 3H, Ar-H), 7.34-7.45 (m, 2H, Ar-H), 11.05 (br. s, 2H, NH). ^{13}C NMR: 28.38, 36.45, 37.72, 43.27 (Adamantane-C), 122.19, 125.15, 129.07, 136.58 (Ar-C), 168.0 (C-5), 172.44 (C-2), 186.42 (C=S). EI-MS, *m/z* (Rel. Int.): 370 (M^+, 3), 235 (94), 220 (4), 135 (59), 91 (100)**.**

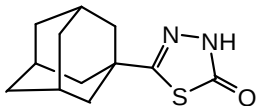
164b: ^{1}H NMR (DMSO-d_6): δ 1.75 (s, 6H, Adamantane-H), 1.99 (s, 6H, Adamantane-H), 2.06 (s, 3H, Adamantane-H), 6.82-6.86 (m, 2H, Ar-H), 7.22-7.36 (m, 2H, Ar-H), 11.0 (br. s, 2H, NH).

164c: ^{1}H NMR (DMSO-d_6): δ 1.74-1.82 (m, 6H, Adamantane-H), 2.03 (s, 6H, Adamantane-H), 2.10 (s, 3H, Adamantane-H), 7.02 (d, 2H, Ar-H, *J* = 7.5 Hz), 7.31 (d, 2H, Ar-H, *J* = 7.5 Hz), 10.87 (br. s, 2H, NH). ^{13}C NMR: 28.03, 36.44, 38.10, 43.22 (Adamantane-C), 122.96, 128.85, 129.05, 138.55 (Ar-C), 167.48 (C-5), 171.99 (C-2), 188.59 (C=S).

Table 10: Melting points, crystallization solvents, yield percentages, molecular formulae and molecular weights of compounds **(164a-c)**

Comp. No.	Ar	Mp (°C)	Cryst. Solv.	Yield (%)	Molecular Formula (Mol. Wt.)
164a	H	295-7	EtOH/H_2O	33	$C_{19}H_{22}N_4S_2$ (370.53)
164b	4-F	> 300	EtOH	27	$C_{19}H_{21}FN_4S_2$ (388.53)
164c	4-Cl	291-3	EtOH	34	$C_{19}H_{21}ClN_4S_2$ (404.98)

4.20. 5-(1-Adamantyl)-1,3,4-thiadiazoline-2-one (165)



10% Aqueous sodium nitrite solution (10 ml) was added dropwise to an ice-cooled suspension of 5-(1-adamantyl)-2-amino-1,3,4-thiadiazole **163** (2.35 g, 0.01 mole) and hydrochloric acid (5 ml) in cold water (20 ml), with continuous stirring over a period of 20 minutes. The temperature was then allowed to rise to room temperature and the mixture was heated to boiling for 10 minutes, cooled and allowed to stand overnight. The separated crude product was filtered, washed with water, dried and crystallized from aqueous ethanol to yield 1.44 g (61%) of the title compound **165** (Mp. 165-7 ^{o}C).

^{1}H NMR ($CDCl_3$): δ 1.74-1.82 (m, 6H, Adamantane-H), 2.01 (s, 3H, Adamantane-H), 2.14 (s, 6H, Adamantane-H), ^{13}C NMR: 28.48, 36.38, 38.82, 43.69 (Adamantane-C), 150.75 (C-5), 180.26 (C=O). EI-MS, *m/z* (Rel. Int.): 236 (M^+, 17), 235 (M^+ -1, 43), 220 (100), 163 (25), 135 (83), 100 (8).

5. BIOLOGICAL TESTING

All the newly synthesized compounds were tested for their *in vitro* growth inhibitory activity against a panel of standard strains of pathogenic microorganism including Gram-positive bacteria, Gram-negative bacteria and the yeast-like pathogenic fungus *Candida albicans*. In addition, the acute anti-inflammatory activity of 26 representative compounds was determined *in vivo* following the carrageenan-induced paw oedema method in rats. The oral acute toxicity of compounds **151l** and **159**, which possessed the best anti-inflammatory activity, was determined *via* determination of their lethal doses LD_{16}, LD_{50} and LD_{84} in mice. The antiviral activities of the new derivatives are planned to be evaluated later in an international laboratory after setting suitable screening agreement.

5.1. Antimicrobial Testing

The newly synthesized compounds **145a-e**, **146a-e**, **148**, **149a-e**, **150a-v**, **151a-p**, **152a-n**, **153**, **154a-d**, **155a-c**, **157**, **159**, **161**, **164a-c** and **165** were tested for their *in vitro* growth inhibitory activity against the standard strains of the Institute of fermentation of Osaka (IFO) namely; *Staphylococcus aureus* IFO 3060, *Bacillus subtilis* IFO 3007, *Micrococcus luteus* IFO 3232 (Gram-positive bacteria), *Escherichia coli* IFO 3301, *Pseudomonas aeuroginosa* IFO 3448 (Gram-negative bacteria), and the yeast-like pathogenic fungus *Candida albicans* IFO 0583. The primary screening was carried out using the agar disc-diffusion method using Müller-Hinton agar medium.[141] The minimal inhibitory concentration (MIC) for the most active compounds **145a**, **145b**, **145e**, **150h**, **150o**, **151n**, **152a**, **152e**, **152f**, **152m**, **153**, **157**, **159**, **164b** and **164c** against the same microorganism used in the primary screening was carried out using the microdilution susceptibility method in Müller-Hinton Broth and Sabouraud Liquid Medium.[142]

5.1.1. Methods

5.1.1.1. Agar disc-diffusion method[141]

Sterile filter paper discs (8 mm diameter) were moistened with the compound solution in dimethylsulphoxide of specific concentration (200 μg/disc), the antibacterial antibiotics Gentamicin and Ampicillin trihydrate (100 μg/disc) and the antifungal drug Clotrimazole (100 μg/disc) were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37 ^{o}C, and the diameter of the growth inhibition zones were measured after 24 hours in case of bacteria and 48 hours in case of *Candida albicans*.

5.1.1.2. Determination of Minimal inhibitory concentration (MIC)[142]

Compounds **145a**, **145b**, **145e**, **150h**, **150o**, **151n**, **152a**, **152e**, **152f**, **152m**, **153**, **157**, **159**, **164b**, **164c**, Gentamicin, Ampicillin trihydrate and Clotrimazole were dissolved in dimethylsulphoxide at concentration of 128 μg/ml. The twofold dilutions of the solution were prepared (128, 64, 32, …, 0.5 μg/ml). The microorganism suspensions at 10^6 CFU/ml (colony forming unit/ml) concentrations were inoculated to the corresponding wells. The plates were incubated at 36 ^{o}C for 24 and 48 hours for the bacteria and *Candida albicans*, respectively. The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganism as detected by unaided eye.

5.1.2. Results

The results of the preliminary antimicrobial testing of the 83 new compounds (200 μg/disc), the antibacterial antibiotics Ampicillin trihydrate, Gentamicin (100 μg/disc) and the antifungal drug Clotrimazole (100 μg/disc) are shown in Tables 11-16. The results revealed that they showed varying degrees of inhibition against the tested microorganisms. In general, strong activity was displayed by the compounds **145a**, **145b**, **145e**, **150h**, **150o**, **151n**, **152a**, **152e**, **152f**, **152m**, **153**, **157**, **159**, **164b** and **164c**, which produced growth inhibition zones ≥ 19 mm against one or more of the tested microorganisms. Meanwhile, 31 compounds showed moderate

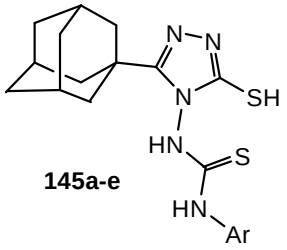
activity (growth inhibition zones 14-18 mm), 15 compounds exhibited weak activity (growth inhibition zones 10-13 mm) and 22 compounds were practically inactive (growth inhibition zones < 10 mm) against the tested microorganisms. The Gram-positive bacteria *Bacillus subtilis* and to a lesser extent *Staphylococcus aureus* and *Micrococcus luteus* are considered the most sensitive among the tested microorganisms. The activity against the tested Gram-negative bacteria was generally lower than that of the Gram-positive bacteria, compounds **150h**, **151n**, **152m** and **153** were strongly active against *Escherichia coli*, while only compound **153** was strongly active against *Pseudomonas aeuroginosa*. The inhibitory activity of the compounds against *Candida albicans* was rather lower than their antibacterial activity, only compound **152f** showed strong activity comparable to Clotrimazole, while compounds **150c**, **150f**, **151h**, **152h**, **154b** and **157** were moderately active. The minimal inhibitory concentrations (MIC) for the most active compounds **145a**, **145b**, **145e**, **150h**, **150o**, **151n**, **152a**, **152e**, **152f**, **152m**, **153**, **157**, **159**, **164b** and **164c** which are shown in Table 17, were in accordance with the results obtained in the primary screening.

In general, the antibacterial activity seemed to be dependent on the nature of substituents rather than basic skeleton of the molecules. Within the adamantyl triazoles derivatives **145a-e** and their 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole analogues **146a-e**, **148** and **149a-e**, it could be concluded that the antibacterial activity is limited to the tested Gram-positive bacteria. The antibacterial activity was greatly diminished on cyclization of the *N*-arylthiourea derivatives **145a-e** to their 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole analogues **146a-e** which showed marginal activity mainly against *Bacillus subtilis*. In addition, the 2-amino, 2-alkyl-, allyl- or benzylamino-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **148** and **149a-e** were weakly active or almost inactive (Table 11).

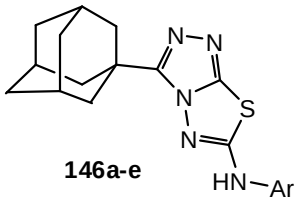
Regarding the 4-arylideneaminotriazoles **150a-v** (Table 12), it was observed that the aryl substituents greatly influenced the antimicrobial activity. The halo and hydroxyl derivatives were highly active, while the nitro and methoxy derivatives were generally inactive. In addition, the hydroxy derivatives **150g** and **150h** showed

marked activity against the tested Gram-negative bacteria, while the 4-fluoro **150c** and 4-bromo **150f** derivatives were significantly active against *Candida albicans*. Based on the antibacterial activity of the arylideneamino derivatives **150a-v**, and the previously reported high chemotherapeutic activity of several 2,6-dihalophenyl derivatives,[143-147] the 2,6-difluoro and dichlorobenzylidene derivatives **150o** and **150q** were selected to prepare their 4-substituted-1-piperazinyl Mannich bases **151a-p**. The results of the antimicrobial activity of the 4-substituted-1-piperazinyl Mannich bases **151a-p** (Table 13) were generally lower than those of the arylideneamino derivatives **150a-v** but the specificity was almost similar. On the other hand, the antimicrobial activity of the 4-ethoxycarbonyl-1-piperidyl Mannich bases **152a-n** (Table 14) was higher than the 4-substituted-1-piperazinyl Mannich bases **151a-p**. The most potent member of these derivatives were the 4-hydroxybenzylidene **152f** and the 3,4-dimethoxybenzylidene **152m** derivatives which displayed strong broad spectrum activity. Regarding the antimicrobial activity of the adamantylthiadiazole derivatives **153**, **154a-d**, **155a-c**, **157**, **159**, **161** (Table 15), the unsubstituted adamantylthiadiazole derivatives **153** was found to be highly active against the tested Gram-negative bacteria. It would be concluded that the activity greatly diminished on introduction of the benzyl or 4-substituted benzyl moieties (compounds **154a-d**). Meanwhile, the introduction of the 4-substituted-1-piperazinylmethyl moieties (compounds **155a-c**) led to the lack of the Gram-negative activity, while the moderate Gram-positive activity was retained. The acetic and propionic acid derivatives **157**, **159** and **161** were characterized by good activity against the Gram-positive bacteria but totally inactive against the Gram-negative bacteria. In addition, compound **159** showed moderate activity against *Candida albicans*. The thiourea derivatives **164a-c** were generally active against the Gram-positive bacteria and totally inactive against the tested Gram-negative bacteria and *Candida albicans*. The thiadiazoline-2-one **165** was completely inactive against the tested microorganisms (Table 16)**.**

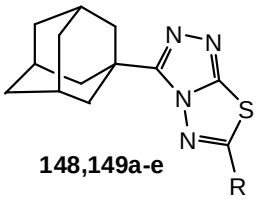
Table 11: Antimicrobial activity of compounds **145a-e**, **146a-e**, **148** and **149a-e** (200 µg/8 mm disc), the broad spectrum antibacterial drugs Gentamicin (100 µg/8 mm disc), Ampicillin (100 µg/8 mm disc) and the antifungal drug Clotrimazole (100 µg/8 mm disc) against *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Micrococcus luteus* IFO 3232 (*ML*), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*)



145a-e



146a-e

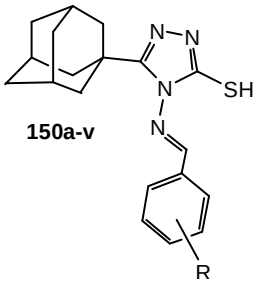


148,149a-e

Comp. No.	Ar/R	Diameter of Growth Inhibition Zone (mm)*					
		SA	***BS***	***ML***	***EC***	***PA***	***C A***
145a	C_6H_5	16	22	20	-	-	-
145b	3-FC_6H_4	15	20	18	-	-	-
145c	4-FC_6H_4	13	18	16	-	-	-
145d	4-ClC_6H_4	15	18	13	-	-	-
145e	4-BrC_6H_4	22	27	11	-	-	-
146a	C_6H_5	-	10	-	-	-	-
146b	3-FC_6H_4	-	12	-	-	-	-
146c	4-FC_6H_4	-	12	-	-	-	-
146d	4-ClC_6H_4	-	11	-	-	-	-
146e	4-BrC_6H_4	-	12	10	-	-	-
148	NH_2	-	13	12	-	-	-
149a	CH_3NH	-	11	-	-	-	-
149b	CH_3CH_2NH	-	-	-	-	-	-
149c	$CH_3(CH_2)_3NH$	-	-	-	-	-	-
149d	CH_2=CH-CH_2NH	-	-	-	-	-	-
149e	$C_6H_5CH_2NH$	-	-	-	-	-	-
Gentamicin		26	25	18	20	19	NT
Ampicillin		23	21	19	17	16	NT
Clotrimazole		NT	NT	NT	NT	NT	21

* (-): Inactive (inhibition zone < 10 mm). (NT): Not tested

Table 12: Antimicrobial activity of compounds **150a-v** (200 μg/8 mm disc), the broad spectrum antibacterial drugs Gentamicin (100 μg/8 mm disc), Ampicillin (100 μg/8 mm disc) and the antifungal drug Clotrimazole (100 μg/8 mm disc) against *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Micrococcus luteus* IFO 3232 (*ML*), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*)

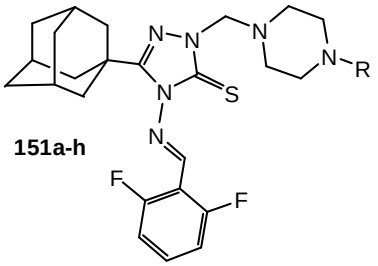


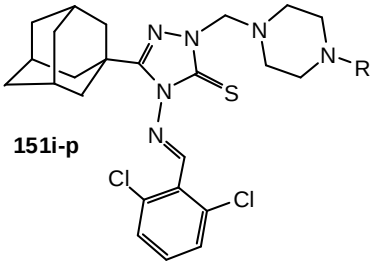
150a-v

Comp. No.	R	Diameter of Growth Inhibition Zone (mm)*					
		SA	***BS***	***ML***	***EC***	***PA***	***C A***
150a	H	10	13	-	-	-	-
150b	2-F	14	14	-	-	-	-
150c	4-F	16	17	-	-	-	17
150d	2-Cl	11	14	-	-	-	-
150e	4-Cl	14	16	-	-	-	-
150f	4-Br	13	14	14	-	-	16
150g	2-OH	14	16	12	15	13	-
150h	4-OH	19	25	13	19	14	-
150i	4-CH_3	15	18	15	-	-	-
150j	2-OCH_3	-	-	-	-	-	-
150k	4-OCH_3	-	-	-	-	-	-
150l	2-NO_2	14	14	-	-	-	-
150m	4-NO_2	-	-	-	-	-	-
150n	4-$(CH_3)_2N$	-	-	-	-	-	
150o	2,6-F_2	18	19	-	-	-	-
150p	2-Cl,6-F	-	-	-	-	-	-
150q	2,6-Cl_2	14	16	-	-	-	-
150r	2,4-Cl_2	16	17	-	-	-	-
150s	3,4-Cl_2	17	17	-	-	-	12
150t	3,4-$(CH_3O)_2$	-	-	-	-	-	-
150u	2,4-$(NO_2)_2$	-	-	-	-	-	-
150v	2-NO_2,4,5-$(CH_3O)_2$	-	-	-	-	-	-
Gentamicin		26	25	18	20	19	NT
Ampicillin		23	21	19	17	16	NT
Clotrimazole		NT	NT	NT	NT	NT	21

* (-): Inactive (inhibition zone < 10 mm). (NT): Not tested

Table 13: Antimicrobial activity of compounds **151a-p** (200 µg/8 mm disc), the broad spectrum antibacterial drugs Gentamicin (100 µg/8 mm disc), Ampicillin (100 µg/8 mm disc) and the antifungal drug Clotrimazole (100 µg/8 mm disc) against *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Micrococcus luteus* IFO 3232 (*ML*), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*)

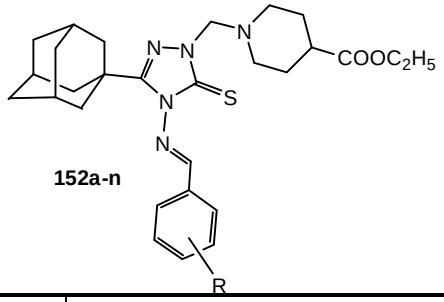




Comp. No.	R	Diameter of Growth Inhibition Zone (mm)*					
		SA	***BS***	***ML***	***EC***	***PA***	***C A***
151a	CH_3	13	15	-	-	-	-
151b	C_2H_5	15	14	-	15	-	-
151c	$COOC_2H_5$	11	15		-	-	-
151d	C_6H_5	-	-	14	-	-	-
151e	4-FC_6H_4	-	-	-	-	12	-
151f	3-$CF_3C_6H_4$	12	11	-	18	11	-
151g	2-$CH_3OC_6H_4$	-	-	-	-	-	-
151h	$C_6H_5CH_2$	-	-	-	-	-	17
151i	CH_3	12	11	-	-	-	-
151j	C_2H_5	14	12	-	-	-	-
151k	$COOC_2H_5$	-	11	-	-	-	-
151l	C_6H_5	-	-	-	-	-	-
151m	4-FC_6H_4	13	12	-	-	-	-
151n	3-$CF_3C_6H_4$	-	-	-	19	14	-
151o	2-$CH_3OC_6H_4$	-	-	-	-	-	-
151p	$C_6H_5CH_2$	-	-	-	-	-	-
Gentamicin		26	25	18	20	19	NT
Ampicillin		23	21	19	17	16	NT
Clotrimazole		NT	NT	NT	NT	NT	21

* (-): Inactive (inhibition zone < 10 mm). (NT): Not tested

Table 14: Antimicrobial activity of compounds **152a-n** (200 µg/8 mm disc), the broad spectrum antibacterial drugs Gentamicin (100 µg/8 mm disc), Ampicillin (100 µg/8 mm disc) and the antifungal drug Clotrimazole (100 µg/8 mm disc) against *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Micrococcus luteus* IFO 3232 (*ML*), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*)

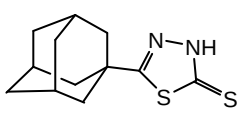


152a-n

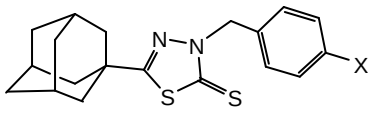
Comp. No.	R	Diameter of Growth Inhibition Zone (mm)*					
		SA	***BS***	***ML***	***EC***	***PA***	***C A***
152a	H	12	19	16	-	-	-
152b	2-F	-	-	-	-	-	-
152c	2-Cl	-	-	-	15	-	-
152d	4-CH_3	11	15	-	-	-	-
152e	2-OH	17	22	-	-	-	13
152f	4-OH	22	26	-	-	-	19
152g	4-OCH_3	15	11	-	-	-	-
152h	2,6-F_2	-	-	-	-	-	14
152i	2-Cl,6-F	14	15	-	-	-	-
152j	2,6-Cl_2	12	16	16	-	-	-
152k	2,4-Cl_2	15	17	-	-	-	-
152l	3,4-Cl_2	11	13	-	-	-	-
152m	3,4-$(CH_3O)_2$	20	24	17	19	16	-
152n	2-NO_2,4,5-$(CH_3O)_2$	-	-	-	-	-	-
Gentamicin		26	25	18	20	19	NT
Ampicillin		23	21	19	17	16	NT
Clotrimazole		NT	NT	NT	NT	NT	21

* (-): Inactive (inhibition zone < 10 mm). (NT): Not tested

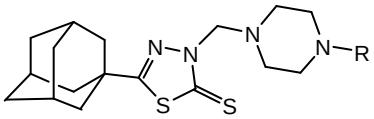
Table 15: Antimicrobial activity of compounds **153**, **154a-d**, **155a-c**, **157**, **159**, **161** (200 µg/8 mm disc), the broad spectrum antibacterial drugs Gentamicin (100 µg/8 mm disc), Ampicillin (100 µg/8 mm disc) and the antifungal drug Clotrimazole (100 µg/8 mm disc) against *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Micrococcus luteus* IFO 3232 (*ML*), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*)



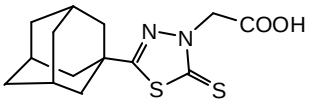
153



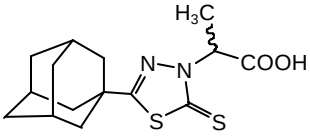
154a-d



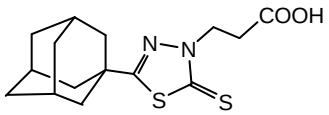
155a-c



157



159

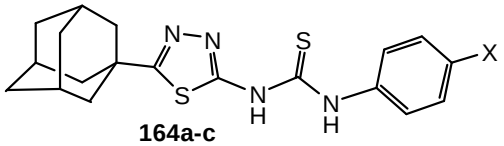


161

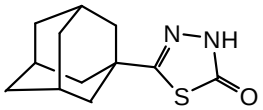
Comp. No.	R/X	Diameter of Growth Inhibition Zone (mm)*					
		SA	***BS***	***ML***	***EC***	***PA***	***C A***
153	-	13	13	-	27	20	-
154a	H	-	-	-	-	-	-
154b	F	-	-	-	-	-	14
154c	Cl	-	-	-	-	-	-
154d	NO_2	-	-	-	-	-	-
155a	CH_3	13	14	14	-	-	-
155b	CH_3CH_2	12	13	-	-	-	-
155c	C_6H_5	-	14	-	-	-	-
157	-	18	22	16	-	-	17
159	-	18	20	13	-	-	-
161	-	11	13	-	-	-	11
Gentamicin		26	25	18	20	19	NT
Ampicillin		23	21	19	17	16	NT
Clotrimazole		NT	NT	NT	NT	NT	21

* (-): Inactive (inhibition zone < 10 mm). (NT): Not tested

Table 16: Antimicrobial activity of compounds **164a-c**, **165** (200 µg/8 mm disc), the broad spectrum antibacterial drugs Gentamicin (100 µg/8 mm disc), Ampicillin (100 µg/8 mm disc) and the antifungal drug Clotrimazole (100 µg/8 mm disc) against *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Micrococcus luteus* IFO 3232 (*ML*), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*)



164a-c



165

Comp. No.	X	Diameter of Growth Inhibition Zone (mm)*					
		SA	***BS***	***ML***	***EC***	***PA***	***C A***
164a	H	13	14	15	-	-	-
164b	F	14	19	11	-	-	-
164c	Cl	15	20	12	-	-	-
165	-	-	-	-	-	-	-
Gentamicin		26	25	18	20	19	NT
Ampicillin		23	21	19	17	16	NT
Clotrimazole		NT	NT	NT	NT	NT	21

* (-): Inactive (inhibition zone < 10 mm). (NT): Not tested

Table 17: The minimal inhibitory concentrations (MIC, μg/ml) of compounds **145a**, **145b**, **145e**, **150h**, **150o**, **151n**, **152a**, **152e**, **152f**, **152m**, **153**, **157**, **159**, **164b** and **164c**, the broad spectrum antibacterial drugs Gentamicin, Ampicillin and the antifungal drug Clotrimazole against *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Micrococcus luteus* IFO 3232 (*ML*), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*)

Comp. No.	Minimal Inhibitory Concentration (MIC, μg/ml)*					
	SA	***BS***	***ML***	***EC***	***PA***	***C A***
145a	ND	2	2	ND	ND	ND
145b	ND	4	ND	ND	ND	ND
145e	2	1	ND	ND	ND	ND
150h	2	1	ND	2	ND	ND
150o	ND	4	ND	ND	ND	ND
151n	ND	ND	ND	2	ND	ND
152a	ND	4	ND	ND	ND	ND
152e	ND	2	ND	ND	ND	ND
152f	2	1	ND	ND	ND	8
152m	2	1	ND	2	ND	ND
153	ND	ND	ND	0.5	2	ND
157	ND	2	ND	ND	ND	ND
159	ND	4	ND	ND	ND	ND
164b	ND	4	ND	ND	ND	ND
164c	ND	2	ND	ND	ND	ND
Gentamicin	2	2	2	0.5	1	ND
Ampicillin	2	0.5	2	2	2	ND
Clotrimazole	ND	ND	ND	ND	ND	2

* ND: Not determined.

5.2. Anti-inflammatory Testing

The acute anti-inflammatory activity of 26 representative compounds (**150b**, **150e**, **150h**, **150j**, **150r**, **150t**, **151b**, **151d**, **151g**, **151j**, **151l**, **151m**, **151p**, **152a**, **152c**, **152e**, **152f**, **152h**, **152k**, **152l**, **152n**, **154a**, **155b**, **157**, **159** and **161**) was determined *in vivo* following the carrageenan-induced paw oedema method in rats.[149] The selection of the representative compounds and dose levels were made after carrying out pilot experiments which showed the absence of anti-inflammatory activity in compounds **146a-e**, **148** and **149a-e**. The compounds were tested at 20 and 40 mg/kg dose levels.

5.2.1. Method[148]

Male Sprague-Dawley rats weighing 140-190 g were maintained at room temperature (20-23 ^{o}C). The animals were randomly divided into 52 groups each of 5 animals. The animals were housed with food and water *ad libitum* and allowed to be accustomed to their environment for two days before testing. Each group was injected with the specific dose of the test compound (20 and 40 mg/kg), or Indomethacin (5 mg/kg) intraperitoneally as a uniform suspension in 1 ml of 0.5% (w/v) aqueous carboxymethyl cellulose solution, one hour before injection of 0.1 ml of carrageenan (1% solution in normal saline) into the plantar tissue of the right hind paw. The left hind paw was injected with 0.1 ml of normal saline solution. Four hours after carrageenan injection, the volume of paw oedema (ml) was determined using water plethysmometer. The percentage protection against inflammation was calculated as follows:

$$\frac{V_c - V_d}{V_c} \times 100$$

Where V_c is the mean percentage increase in paw volume in the absence of the test compound (control) and V_d is the mean percentage increase in paw volume after injection of the test compound. The values are expressed as the mean percentage reduction ± S.E.M. Statistical significance between the control and treated groups was performed using the Student "*t*" test.

5.2.2. Results

The results of the anti-inflammatory activity of the tested compounds (20 & 40 mg/kg) and the potent anti-inflammatory drug Indomethacin (5 mg/kg) are listed in Table 18. The majority of the tested compounds showed varying degrees of activity. The highest activity was shown by compounds **151l** and **159**, which produced strong dose-dependent inhibition of carrageenan-induced paw oedema (> 50%), while compounds **151d** and **152c** were moderately active (30-50%) at 20 & 40 mg/kg dose level. Compounds **151g**, **151j**, **152e**, **152l**, **157** and **161** were moderately active at 40 mg/kg dose level and weakly active at 20 mg/kg level. The structure-anti-inflammatory activity of the tested adamantyltriazole derivatives revealed that the triazoles N-2 and N-4 substituents greatly influence the anti-inflammatory activity. The N-2 unsubstituted adamantyltriazole **150b**, **150e**, **150h**, **150j**, **150r** and **150t** were weakly active or completely inactive, while the N-2 piperazinomethyl derivatives (**151b**, **151d**, **151g**, **151j**, **151l**, **151m** and **151p**) were generally active. The activity was found to be dependent on the nature of the 4-arylideneamino and the 4-piperazinyl substituents. The activity of the 2,6-dichlorobenzylidene derivatives were slightly higher than their 2,6-difluorobenzylidene analogues. It could be also concluded that the phenyl substituents are optimistic compared with the ethyl, 4-fluorophenyl, 2-methoxyphenyl and benzyl substituents. The replacement of the 4-substituted-1-piperazinyl moiety with a 4-carbethoxy-1-piperidyl moiety resulted in marked decrease in activity, only the chloro derivatives **152c** and **151l** and the 2-hydroxy derivative **152e** exhibited moderate activity. Isosteric replacement of the 1,2,4-triazole nucleus with 1,3,4-thiadiazole nucleus in compounds **154a** and **155b** greatly decreased the anti-inflammatory activity. On the other hand, the introduction of acetic or propionic function at thiadiazole N-3 (compounds **157**, **159** and **161**) greatly enhanced the anti-inflammatory activity. The activity of the 2-propionic acid derivative **159** was superior to the acetic and 3-propionic acid derivatives **157** and **161** which were moderately active.

Table 18: Anti-inflammatory effect of intraperitoneal injection of (20 & 40 mg/kg) of compounds **150b**, **150e**, **150h**, **150j**, **150r**, **150t**, **151b**, **151d**, **151g**, **151j**, **151l**, **151m**, **151p**, **152a**, **152c**, **152e**, **152f**, **152h**, **152k**, **152l**, **152n**, **154a**, **155b**, **157**, **159**, **161** and Indomethacin (5 mg/kg) against carrageenan-induced paw oedema in rats

Comp. No.	R/X	Mean % Reduction of paw oedema from control[a]	
		20 mg/kg	**40 mg/kg**
Control[b]		0 (± 0.036)	
150b	2-F	-5.50 (± 0.132)*	-2.71 (± 0.117)*
150e	4-Cl	3.16 (± 0.112)*	-8.56 (± 0.071)*
150h	4-OH	13.28 (± 0.147)**	11.29 (± 0.136)**
150j	2-OCH_3	11.06 (± 0.129)**	13.91 (± 0.108)**
150r	2,4-Cl_2	10.32 (± 0.092)**	10.54 (± 0.113)**
150t	3,4-$(CH_3O)_2$	21.92 (± 0.083)**	19.37 (± 0.069)**
151b	C_2H_5	17.88 (± 0.108)**	20.01 (± 0.090)**
151d	C_6H_5	39.16 (± 0.093)**	39.88 (± 0.892)**
151g	2-$CH_3OC_6H_4$	25.88 (± 0.066)**	38.37 (± 0.074)**
151j	C_2H_5	27.95 (± 0.122)**	34.76 (± 0.098)**
151l	C_6H_5	28.86 (± 0.076)**	50.44 (± 0.063)**
151m	4-FC_6H_4	13.06 (± 0.082)**	22.90 (± 0.075)**
151p	$C_6H_5CH_2$	2.05 (± 0.062)*	4.99 (± 0.078)*
152a	H	23.23 (± 0.016)**	15.27 (± 0.051)**
152c	2-Cl	33.02 (± 0.107)**	37.66 (± 0.141)**
152e	2-OH	20.41 (± 0.065)**	31.20 (± 0.092)**
152f	4-OH	-18.25 (± 0.126)	1.36 (± 0.044)
152h	2,6-F_2	-20.21 (± 0.112)	-9.80 (± 0.071)
152k	2,6-Cl_2	9.91 (± 0.133)*	6.81 (± 0.092)*
152l	3,4-Cl_2	10.45 (± 0.097)**	35.01 (± 0.117)**
152n	2-(NO_2),4,5-$CH_3O)_2$	-13.75 (± 0.181)*	-11.61 (± 0.095)*
154a	H	1.12 (± 0.099)*	0.92 (± 0.082)*
155b	C_2H_5	11.32 (± 0.131)**	10.62 (± 0.140)**
157	-	29.54 (± 0.097)**	32.70 (± 0.129)**
159	-	50.60 (± 0.132)**	65.19 (± 0.144)***
161	-	7.47 (± 0.060)**	36.83 (± 0.171)**
Indomethacin (5 mg/kg)		52.79 (± 0.044)	

[a] Results are expressed as mean % inhibition ± S.E.M. (n = 5) and compared with student "*t*" test.

[b] The group was injected with 1 ml of 0.5% aqueous carboxymethyl cellulose solution.

* Inactive: Significantly different from Indomethacin at $p < 0.05$.

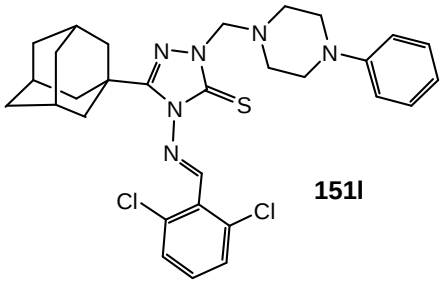
** Activity comparable to Indomethacin (significantly different from Indomethacin at

$p < 0.05$.

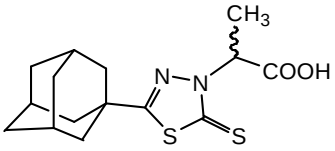
*** Significantly different (higher than) Indomethacin at $p < 0.05$.

5.3. Oral Acute Toxicity Testing

The method of Litchfield and Wilcoxon was adopted for measuring the acute oral toxicity of compounds **151l** and **159**, which possessed the highest anti-inflammatory activity.[149]



151l



159

5.3.1. Method[149]

Freshly prepared suspensions of compounds **151l** and **159** in concentrations of 1, 3, 4, 6, 8 and 12% in 0.5% aqueous carboxymethyl cellulose solution were prepared. Each compound was given to six groups each of 6 normal albino mice of both sexes by oral intubation in doses of 0.5, 1.5, 2.0, 3.0, 4.0 and 6 g/kg. The percentage mortality was recorded 24 hours after compound administration and the oral lethal doses LD_{16}, LD_{50} and LD_{84} were calculated.

5.3.2. Results

The acute toxicity results of compounds **151l** and **159** are listed in Table 19. The oral LD_{50} of Indomethacin was reported to be 50 mg/kg in mice.[150] The results show that the toxicities of compounds **151l** and **159** are 3.05 and 1.98% of the toxicity of Indomethacin, respectively. Taking into consideration the potency ratio of compounds **151l** and **159** which is about 1/10, it could be suggested that compounds **151l** and **159** have wider therapeutic indices than that of Indomethacin.

Table 19: Results of acute toxicity (g/kg) of compounds **151l** and **159** in mice

Comp. No.	LD_{16}	LD_{50}	LD_{84}	LD_{50} (95% Confidence limit)
151l	0.82	1.64	2.88	1.64 (1.23-1.89)
159	1.77	2.52	4.43	2.52 (1.97-3.10)

6. REFERENCES

1. V. Prelog, R. Seiwerth. Synthesis of adamantane. *Ber*. **1941**, *74B*, 1644-1648.

2. V. Prelog, R. Seiwerth. New method for the preparation of adamantane. *Ber*. **1941**, *74B*, 1769-1772.

3. W. L. Davies, R. R. Grunnert, R. F. Haff, J. W. McGahen, E. M. Neumeyer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, C. E. Hoffmann. Antiviral activity of 1-adamantamine (amantadine). *Science* **1964**, *144*, 862-863.

4. Y. Togo, R. B. Hornick, A. T. Dawkins. Studies on induced influenza in man. I. Double blind studies designed to assess prophylactic efficacy of amantadine hydrochloride against A_2/Rockville/1/65 strain. *J. Am. Med. Assoc.* **1968**, *203*, 1089-1094.

5. H. A. Wendel, M. T. Snyder, S. Pell. Trial of amantadine in epidemic influenza. *Clin. Pharmacol. Therap.* **1966**, *7*, 38-43.

6. V. G. Vernier, J. B. Harmon, J. M. Stump, T. L. Lynes, M. P. Marvel, D. H. Smith. The toxicologic and pharmacologic properties of amantadine hydrochloride. *Toxicol. Appl. Pharmacol.* **1969**, *15*, 642-665.

7. S. Rabinovich, J. T. Baldini, R. Bannister. Treatment of influenza. The therapeutic efficacy of rimantadine HCl in a naturally occurring influenza A_2 outbreak. *Am. J. Med. Sci.* **1969**, *257*, 328-335.

8. F. G. Hayden, J. M. I. Gwaltney, C. R. L. Van, K. F. Adam, B. Giordani. Comparative toxicity of amantadine hydrochloride and rimantadine hydrochloride in healthy adaults. *Antimicrob. Agents Chemother.* **1981**, *19*, 226-233.

9. A. J. Hay, A. J. Wolstenholm, J. J. Skehel, M. H. Smith. The molecular basis of the specific anti-influenza action of amantadine. *EMBO J.* **1985**, *4*, 3021-3024.

10. L. H. Pinto, L. J. Holsinger, L. A. Lamb. Influenza virus M2 protein has ion channel activity. *Cell* **1992**, *69*, 517-528.

11. P. S. Manchand, R. L. Cerruti, J. A. Martin, C. H. Hill, J. H. Merrett. Synthesis and antiviral activity of metabolites of rimantadine. *J. Med. Chem.* **1990**, *33*, 1992-1995.

12. K. W. Kochran, H. F. Maassab, A. Tsunoda, B. S. Berlin. Studies on the antiviral activity of amantadine hydrochloride. *Ann. N. Y. Accad. Sci.* **1965**, *130*, 432-439.

13. J. S. Oxford, I. S. Logan. *In vivo* selection of an influenza A2 strain resistant to amantadine. *Nature* **1970**, *226*, 82-83.

14. F. G. Hayden. Antivirals for influenza: Historical perspectives and lessons learned. *Antiviral Res.* **2006**, *71*, 372-378.

15. E. C. Class, A. D. M. E. Osterhaus, R. Van Beek, J. C. De Long, G. F. Rimmelzwaam, D. A. Senne, S. Krauss, K. F. Shortridge, R. G. Webster. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. *Lancet* **1998**, *351*, 472-477.

16. C. J. Dunn, K. L. Dora. Zanamivir: a review of its use in influenza. *Drugs* **1999**, *58*, 761-784.

17. W. Lew, X. Chen, C. U. Kim. Discovery and development of GS 4104 (oseltamivir): an orally active influenza neuramidase inhibitor. *Curr. Med. Chem.* **2000**, *7*, 663-672.

18. N. A. Ilyushina, N. V. Bovin, R. G. Webster, E. A. Govorkova. Combination chemotherapy, a potential strategy for reducing the emergence of drug-resistant influenza A variants. *Antiviral Res.* **2006**, *70*, 121-131.

19. A. Scherm, D. Peteri. Antiviral 1-(aminoethoxyacetylamino)adamantanes. *Ger. Pat.* 1,941,218 (**1971**); *Chem. Abstr.* **1971**, *74*, 99516.

20. A. Kreutzberger, H. H. Schroeders. Synthesis and antiviral activity of adamantly-1-thioureas. *Tetrahedron Lett.* **1969**, *58*, 5101-5104.

21. J. W. Tilley, P. Levitan, M. J. Kramer. Adamantylthiourea derivatives as antiviral agents. *J. Med. Chem.* **1979**, *22*, 1009-1010.

22. J. Mills, E. Krumkalns. Adamantyl secondary amines. *US Patent* 3,391,142 (**1968**); *Chem. Abstr.* **1968**, *69*, 59281.

23. G. I. Danilenko, V. I. Votyakov, O. T. Andreeva, M. N. Shashikhina, M. M. Timofeeva, L. V. Denisova, E. I. Boreko, M. I. Novikova. Synthesis and biological activity of adamantane derivatives. V. Virus-inhibiting effect of arylamides of adamantanecarboxylic acids. *Khim. –Farm. Zh.* **1976**, *10*, 60-62; *Chem. Abstr.* **1977**, *86*, 120855.

24. S. Sallay, S. J. Childress. Antiviral adamantly thiosemicarbazone. *US Patent* 3,406,180 (**1968**); *Chem. Abstr.* **1969**, *70*, 11223.

25. K. Lundahl, J. Schut, J. L. M. A. Schlatmann, G. G. Paerels, A. Peters. Synthesis and antiviral activity of adamantane spiro compounds. 1. Adamantane and analogous spiro-3'-pyrrolidines. *J. Med. Chem.* **1972**, *15*, 129-132.

26. M. –J. Pérez-Pérez, J. Balzarini, M. Hosoya, E. De Clercq, M. –J. Camarasa. Synthesis of adamantane-spiro sultones as potential antiviral agents. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 647-648.

27. I. Stylianakis, A. Kolocouris, N. Kolocouris, G. Fytas, G. B. Foscolos, E. Padalko, J. Neyts, E. De Clercq. Spiro[pyrrolidine-2,2'-adamantanes]: Synthesis, anti-influenza virus activity and conformational properties. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1699-1703.

28. G. Zoidis, C. Fytas, I. Papanastasiou, G. B. Foscolos, G. Fytas, E. Padalko, E. De Clercq. L. Naesens, J. Neyts, N. Kolocouris. Heterocyclic rimantadine analogues with antiviral activity. *Bioorg. Med. Chem.* **2006**, *14*, 3341-3348.

29. K. Van Derpoorten, J. Balzarini, E. De Clercq, J. H. Poupaert. Anti-HIV activity of *N*-1-adamantyl-4-aminophthalimide. *Biomed. Pharmacother.* **1997**, *51*, 464-468.

30. M. E. Burstein, A. V. Serbin, T. V. Khakhulina, I. V. Alymova, L. L. Stotskaya, O. P. Bogdan, E. E. Manukchina, V. V. Jdanov, N. K. Sharova. Inhibition of HIV-1 replication by newly developed adamantane-containing polyanionic agents. *Antiviral Res.* **1999**, *41*, 135-144.

31. A. A. El-Emam, O. A. Al-Deeb, M. Al-Omar, J. Lehmann. Synthesis, antimicrobial, and anti-HIV-1 activity of certain 5-(1-adamantyl)-2-substituted thio-1,3,4-oxadiazoles and 5-(1-adamantyl)-3-substituted aminomethyl-1,3,4-oxadiazoline-2-thiones. *Bioorg. Med. Chem.* **2004**, *12*, 5107-5113.

32. J. Balzarini, B. Orzeszko, J. K. Mauri, A. Orzeszko. Synthesis and anti-HIV studies of 2-adamantyl-substituted thiazolidin-4-ones. *Eur. J. Med. Chem.* **2007**, *42* (In Press, Available online January 2007).

33. O. E. Pedersen, E. B. Pedersen. Non-nucleoside reverse transcriptase inhibitors: the NNRTI boom. *Antiviral Chem. Chemother.* **1999**, *10*, 285-314.

34. M. Maynard, P. Pradat, F. Bailly, F. Rozier, C. Nemoz, S. N. Ahmed, P. Adeliene, C. Trépo. Amantadine triple therapy for non-responder hepatitis C patients. Clues for controversies (ANRS HC 03 BITRI). *J. Hepatol.* **2006**, *44*, 484-490.

35. S. D. Griffin, L. P. Paeles, D. S. Clarke, O. Worsfold, S. D. Evans, J. Jaeger. M. P. Harris, D. J. Rowlands. The p7 protein of hepatitis C virus forms an ion channel that is blocked by the antiviral drug, amantadine. *FEBS Lett.* **2003**, *535*, 34-38.

36. S. D. Griffin, R. Harvey, D. S. Clarke, W. S. Barclay, M. P. Harris, D. J. Rowlands. A conversed basic loop in hepatitis C virus p7 protein is required for amantadine-senstive ion channel activity in mammalian cells but is dispensable for localization to mitochondria. *J. Gen. Virol.* **2004**, *85*, 451-461.

37. C. P. Krimmel. *N*-(Dialkylaminoalkyl)adamantanecarboxamides. *U.S. Patent* 3,374,244 (**1968**); *Chem. Abstr.* **1968**, *69*, 35575t.

38. C. P. Krimmel. Dialkylaminoaminoalkyl esters of adamantanecarboxylic acids. *U.S. Patent* 3,565,942 (**1971**).

39. V. L. Narayanan. Adamantyl sulfonamide compounds. *U.S. Patent* 3,501,511 (**1970**).

40. V. S. Georgiev, G. B. Mullen. Adamantyl containing 1,4-oxazinone derivatives. *U.S. Patent* 4,549,014 (**1985**); *Chem. Abstr.* **1986**, *104*, 129916y.

41. V. L. Narayanan. Adamantyl-*s*-triazines. *U.S. Patent* 3,471,491 (**1969**).

42. V. L. Narayanan, J. Bernstein. Antifungal adamantyl thiadiazoles. *U.S. Patent* 3,483,204 (**1969**); *Chem. Abstr.* **1970**, *72*, 55462.

43. V. S. Georgiev, G. A. Bennett, L. A. Radov, D. K. Kamp, L. A. Trusso. Synthesis and biological activity of 2-adamantanone oxime carbamate derivatives. *Arch. Pharm.* **1987**, *320*, 465-470.

44. A. Papadaki-Valiraki, S. Papakonstantinou-Garoufalias, P. Makaros, A. Chytyroglou-Lada, M. Hosoya, J. Balzarini, E. De Clercq. Synthesis, antifungal and antiviral effects of some adamantaneketoxime ethers. *Il Farmaco* **1993**, *48*, 1091-1102.

45. R. Ficarra, P. Ficarra, A. Tommasini, G. Fenech, F. C. Pizzimenti, G. Bisignano. 1-Adamantanecarboxylic acid hydrazides with presumed antimicrobial activity. *Boll. Chim. Farmaceutico* **1984**, *123*, 317-321.

46. A. A. El-Emam. Synthesis and biological activity of certain 1-adamantyl Derivatives. *Chin. Pharm. J.* **1990**, *42*, 309-315.

47. J. J. Wang, S. S. Wang, C. F. Lee, M. A. Chung, Y. T. Chern. *In vitro* antitumor and antimicrobial activity of *N*-substituents of maliemide by adamantane and diamantane. *Chemotherapy* **1997**, *43*, 182-189.

48. E. Antoniadou-Vyza, P. Tsitsa, E. Hytiroglou, A. Tsantili-Kakoulidou. New adamantan-2-ol and adamantan-1-methanol derivatives as potent antibacterials, synthesis, antibacterial activity and lipophilicity studies. *Eur. J. Med. Chem.* **1996**, *31*, 105-110.

49. A. Orzeszko, B. Kamińska, G. Orzeszko. Synthesis and antimicrobial activity of new adamantane derivatives II. *Il Farmaco* **2000**, *55*, 619-623.

50. A. Orzeszko, B. Kamińska, B. J. Starościak. Synthesis and antimicrobial activity of new adamantane derivatives III. *Il Farmaco* **2002**, *57*, 619-624.

51. O. A. Al-Deeb, M. A. Al-Omar, N. R. El-Brollosy, E. E. Habib, T. M. Ibrahim, A. A. El-Emam. Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]acetic acids,

2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]propionic acids and related derivatives. *Arzneim.-Forsch./Drug Res.* **2006**, *56*, 40-47.

52. A. A. Kadi, N. R. El-Brollosy, O. A. Al-Deeb, E. E. Habib, T. M. Ibrahim, A. A. El-Emam. Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-Adamantylamino)-5-substituted-1,3,4-thiadiazoles. *Eur. J. Med. Chem.* **2007**, *42*, 235-242.

53. V. S. Georgiev, G. B. Mullen, C. G. Acker. Synthesis of spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane]. *Heterocycles* **1986**, *24*, 751-753.

54. A. A. El-Emam, T. M. Ibrahim. Synthesis, anti-inflammatory and analgesic activity of certain 3-(1-adamantyl)-4-substituted-5-mercapto-1,2,4-triazole derivatives. *Arzneim.-Forsch./Drug Res.* **1991**, *41*, 1260-1264.

55. E. Antoniadou-Vyza, N. Avramidis, A. Kourounakis, L. Hadjipetrou. Anti-inflammatory properties of new adamantane derivatives. Design, synthesis, and biological evaluation. *Arch. Pharm.* **1999**, *331*, 72-78.

56. A. Baxter, J. Bent, K. Bowers, M. Braddock, S. Brough, M. Fagura, M. Lawson, T. McInally, M. Mortimore, M. Robertson, R. Weaver, P. Webborn. Hit-to-lead studies: The discovery of potent adamantane amide $P2X_7$ receptor antagonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4047-4050.

57. V. M. Millet, M. Dreisbach, Y. J. Bryson. Double-blind controlled study of central nervous system side effects of amantadine, rimantadine, and chlorpheniramine. *Antimicrob. Agents Chemother.* **1982**, *21*, 1-4.

58. R. S. Schwab, A. C. England, Jr., D. C. Poskanzer, R. R. Young. Amantadine in the treatment of Parkinson's disease. *J. Am. Med. Assoc.* **1969**, *208*, 1168-1170.

59. J. C. E. Owen, P. S. Whitton. Effect of amantadine and budipune on antidepressant drug-evoked changes in extracellular dopamine in the frontal cortex of freely moving rats. *Brain Res.* **2006**, *1117*, 206-212.

60. G. Page, M. Peeters, J. M. Maloteaux, E. Hermans. Increased dopamine uptake in striatal synaptosomes after treatment of rats with amantadine. *Eur. J. Pharmacol.* **2000**, *403*, 75-80.

61. P. S. Whitton, S. Maione, C. S. Biggs, L. J. Flower. *N*-methyl-D-aspartate receptors modulate extracellular dopamine concentration and metabolism in rat hippocampus and striatum. *Brain Res.* **1994**, *635*, 312-316.

62. N. V. Klimova, N. L. Lavrov, N. M. Zaitseva, B. M. Pyatin, I. S. Morozov, N. P. Bykov, A. A. Khranilov. Hydroxyaminoadamantanes and their biological activity. *Khim.-Farm. Zh.* **1986**, *20*, 810-815; *Chem. Abstr.* **1986**, *105*, 190525.

63. J. Skolimowski, A. Kochman, L. Gębicka, D. Metodiewa. Synthesis and antioxidant activity evaluation of novel antiparkinsonian agents, adamantane derivatives of nitroxyl free radical. *Bioorg. Med. Chem.* **2003**, *11*, 3529-3539.

64. V. L. Narayanan. Adamantyl analogs of the antidepressive, 5-(2-dimethylaminoethyl)-2,3-dihydro-2-phenylbenzothiazepin-4(5*H*)-one. *J. Med. Chem.* **1972**, *15*, 682-684.

65. M. A. Abou-Gharbia, W. E. Childers, Jr., H. Fletcher, G. McGaughey, U. Patel, M. B. Webb, J. Yardley, T. Andree, C. Boast, R. J. Kucharik, Jr., K. Marquis, H. Morris, R. Scerni, J. A. Moyer. Synthesis and SAR of adatanserin: novel adamantly aryl- and heteroarylpiperazines with dual serotonin 5-HT_{1A} and 5-HT_2 activity as potential anxiolytic and antidepressant agents. *J. Med. Chem.* **1999**, *42*, 5077-5094.

66. R. Spano, G. Linari, R. Marri. 1-Adamantanecarboxylic acid amide of 4-aminoantipyrine. *J. Med. Chem.* **1970**, *13*, 554.

67. Delmar Chemicals Limited. Novel adamantane derivatives, processes for making them and pharmaceutical compositions containing them. *Brit. Pat.* 1,347,871 (**1971**).

68. G. Zoidis, I. Papanastasiou, I. Dotsikas, A. Sandoval, R. G. Dos Santos, Z. Papdopoolou-Daifoti, A. Vamvakides, N. Kolocouris, R. Felix. The novel GABA adamantane derivative (AdGABA): Design, synthesis and activity relationship with gabapentin. *Bioorg. Med. Chem.* **2005**, *13*, 2791-2798.

69. J. M. Balkovec, R. Thieringer, S. S. Mundt, A. Hermanowski-Vosatka, D. W. Graham, W. Donald, G. F. Patel, S. D. Susan, S. T. Waddell, T. Sherman, S. H. Olson, M. Maletic, *PCT Int. Appl.* WO 20030814 (**2003**); *Chem. Abstr.* **2003**, *139*, 180065.

70. M. B. Feinstein, R. P. Schleimer. in: *Glucocorticoids* (N. J. Goulding, P. J. Flower, Eds.), Birkhäuser, Switzerland, **2001**, pp. 147-158.

71. S. Olson, S. D. Aster, K. Brown, L. Carbin, D. W. Graham, A. Hermanowski-Vosatka, C. B. LeGrand, S. S. Mundt, M. A. Robbins, J. M. Schaeffer, L. H. Slossberg, M. J. Szymonifka, R. Thieringer, S. D. Wright, J. M. Balkovec. Adamantyl triazoles as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4359-4362.

72. J. R. Patel, Q. Shuai, J. T. Link, J. J. Rohde, J. Dinges, B. K. Sorensen, M. Winn, H. Yong, J. S. Yeh. *World Pat.* 074244 (Patent in registration).

73. V. S. C. Yeh, J. R. Patel, H. Yong, R. Kurukulasuriya, S. Fung, K. Monzon, W. Chiou, J. Wang, D. Stolarik, H. Imade, D. Bino, M. Brune, P. Jacobson, H. Sham, J. T. Link. Synthesis and biological evaluation of heterocycle containing

adamantane 11β-HSD1 inhibitors. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5414-5419.

74. B. Sorensen, J. Rohde, J. Wang, S. Fung, K. Monzon, W. Chiou, L. Pan, X. Deng, D. Stolarik, E. U. Frevert, P. Jacobson, J. T. Link. Adamantane 11β-HSD-1 inhibitors: Application of an isocyanide multicomponent reaction. *Bioorg. Med. Chem Lett.* **2006**, *16*, 5958-5962.

75. J. R. Patel, Q. Shuai, J. Dinges, M. Winn, M. Pliushchev, S. Fung, K. Monzon, W. Chiou, J. Wang, L. Pan, S. Wagaw, K. Engstrom, F. A. Kerdesky, K. Longenecker, R. Judge, W. Qin, H. M. Imade, D. Stolarik, D. W. A. Beno, M. Brune, L. E. Chovan, H. L. Sham, P. Jacobson, J. T. Link. Discovery of adamantane ethers as inhibitors of 11β-HSD-1: Synthesis and biological evaluation. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 750-755.

76. J. J. Rohde, M. A. Pliushchev, B. K. Sorensen, D. Wodka, Q. Shuai, J. Wang, S. Wang, K. Monzon, J. R. Patel, Q. Shuai, J. Dinges, M. Winn, M. Pliushchev, S. Fung, W. J. Chiou, L. Pan, X. Deng, L. E. Chovan, A. Ramaiya, R. F. Henry, D. F. Stolarik, H. M. Imade, K. C. Marsh, D. W. A. Beno, T. A. Fey, B. A. Droz, M. E. Brune, H. S. Camp, H. L. Sham, E. U. Frevert, P. B. Jacobson, J. T. Link. Discovery and metabolic stabilization of potent and selective 2-amino-*N*-(adamant-2-yl) acetamide 11β-hydroxysteroid dehydrogenase type 1 inhibitors. *J. Med. Chem.* **2007**, *50*, 149-164.

77. K. Gerzon, E. V. Krumkalns, R. L. Brindle, F. J. Marshall. The adamantyl group in medicinal agents. 1. Hypoglycemic *N*-Arylsulfonyl-*N*'adamanylureas. *J. Med. Chem.* **1963**, *6*, 760-763.

78. F. C. Y. Chan, G. A. Potter, S. E. Barrie, B. P. Haynes, M. G. Rowland, J. Houghton, M. Jarman. 3- and 4-Pyridylalkyl adamantanecarboxylates: Inhibition of human Cytochrome $P450_{17\alpha}$ (17_{α}-hydroxylase/$C_{17,20}$-lyase) Potential nonsteroid agent for the treatment of prostatic cancer. *J. Med. Chem.* **1996**, *39*, 3319-3323.

79. M. A. El-Sherbeny. Synthesis, antitumor activity, and anti-HIV-1 testing of certain heterocyclic systems containing an adamantyl nucleus. *Arch. Pharm.* **2000**, *333*, 323-328.

80. Z. Kazimierczuk, A. Górska, T. Świtaj, W. Lasek. Adamantylaminopyrimidines and –pyridines are potent inducers of tumor necrosis factor-α. *Bioorg. Med. Chem Lett.* **2001**, *11*, 1197-1200.

81. T. George, D. V. Mehta, R. Tahilramani, J. David, P. K. Talwalker. Synthesis of some *s*-triazoles with potential analgetic and anti-inflammatory activity. *J. Med. Chem.* **1971**, *14*, 335-338.

82. P. C. Wade, B. R. Vogt, T. S. Kissick, L. M. Simpkins, D. M. Palmer. 1-Acyltriazoles as anti-inflammatory agents. *J. Med. Chem.* **1982**, *25*, 331-333.

83. J. R. Maxwell, D. A. Wasdahl, A. C. Wolfson, V. I. Stenberg. Synthesis of 5-aryl-2*H*-tetrazoles, 5-aryl-2*H*-tetrazole-2-acetic acids, and [(4-phenyl-5-aryl-4*H*-1,2,4-triazol-3-yl)thio]acetic acids as possible superoxide scavengers and anti-inflammatory agents. *J. Med. Chem.* **1984**, *27*, 1565-1570.

84. E. Palask, G. Sahin, P. Kelicen, N. T. Durlu, G. Altinok. Synthesis and anti-inflammatory activity of 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones. *Il Farmaco* **2002**, *57*, 101-107.

85. L. Labanauskas, E. Udrenaite, P. Gaidelis, A. Brukštus. Synthesis of 5-(2,3,4-methoxyphenyl)-4*H*-1,2,4-triazole-3-thiol derivatives exhibiting anti-inflammatory activity. *Il Farmaco* **2004**, *59*, 255-259.

86. M. Amir, K. Shikla. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of some new 2-[(2,6-dichloroanilino)phenyl]acetic acid derivatives. *Eur. J. Med. Chem.* **2004**, *39*, 535-545.

87. L. Navidpour, H. Shafaroodi, K. Abdi, M. Amini, M. H. Ghahremani, A. R. Dehpour, A. Shafiee. Design, synthesis, and biological evaluation of substituted 3-alkylthio-4,5-diaryl-4*H*-1,2,4-triazoles as selective COX-2 inhibitors. *Bioorg. Med. Chem.* **2006**, *14*, 2507-2517.

88. B. N. Gosowami, J. C. S. Kataky, J. N. Baruah. Synthesis and antibacterial activity of 1-(2,4-dichlorophenyl)-4-substituted thiosemicarbazides, 1,2,4-triazoles and their methyl derivatives. *J. Heterocycl. Chem.* **1984**, *21*, 1225-1229.

89. P. –F. Xu, Z. –H. Zhang, X. –P. Hui, Z. –Y. Zhang, R. -L. Zheng. Synthesis of triazoles, oxadiazoles and condensed heterocyclic compounds containing cinchophenyl and studies on biological activity of representative compounds. *J. Chin. Chem. Soc.* **2004**, *51*, 315-319.

90. G. Turan-Zitouni, Z. A. Kaplancikli, M. T. Yildiz, P. Chevallet, D. Kaya. Synthesis and antimicrobial activity of 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[*N*-(2-thiazolyl)acetamido]thio-4-*H*-1,2,4-triazole derivatives. *Eur. J. Med. Chem.* **2005**, *40*, 607-613.

91. S. Tehranchian, T. Akbarzadeh, M. R. Fazeli, H. Jamalfar, A. Shafiee. Synthesis and antibacterial activity of 1-[1,2,4-Triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydrobenzo[*c*]thiophen-4(5*H*)ones. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1023-1025.

92. M. S. Karthikeyan, D. J. Prasad, B. Boojary, K. S. Bhat, B. S. Holla, N. S. Kumari. Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorphenyl moiety. *Bioorg. Med. Chem.* **2006**, *14*, 7482-7489.

93. M. Ashok, B. S. Holla, B. Boojary. Convenient one-pot synthesis and antimicrobial evaluation of some new Mannich bases carrying 4-methylthiobenzyl moiety. *Eur. J. Med. Chem.* **2007**, *42* (In Press, Available online February 2007).

94. B. S. Holla, B. Veerendra, M. K. Shivananda, B. Boojary. Synthesis, characterization and anticancer studies on some Mannich bases derived from 1,2,4-triazoles. *Eur. J. Med. Chem.* **2003**, *39*, 759-767.

95. I. Kucukguzel, S. G. Kucukguzel, S. Rollas, G. Otuk-Sanis, O. Ozdemir, I. Bayrak, J. P. Stables. Synthesis of some 3-(aralkylthio)-4-alkyl/aryl-5-(4-aminophenyl)-4*H*-1,2,4-triazole detivatives and their anticonvulsant activity. *Il Farmaco* **2004**, *59*, 893-901.

96. N. F. Eweiss, A. A. Bahajaj. Synthesis of heterocycles. Part VII. Synthesis and antimicrobial activity of some 7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazine and *s*-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives. *J. Heterocycl. Chem.* **1987**, *24*, 1173-1181.

97. B. Chaturvedi, N. Tiwari, N. Nirupama. A convenient synthesis of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles as potential pesticides. *Agri. Biol. Chem.* **1988**, *52*, 1229-1232; *Chem. Abstr.* **1988**, *109*, 128918.

98. S. N. Swamy, Basappa, B. S. Priya, B. Prabhuswamy, B. H. Doreswamy, J. S. Shahidhara, K. S. Rangappa. Synthesis of pharmaceutically important condensed heterocyclic 4,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives as antimicrobials. *Eur. J. Med. Chem.* **2006**, *41*, 531-538.

99. V. Mathew, J. Keshavayya, V. P. Vaidya. Heterocyclic system containing bridged nitrogen atom: Synthesis and pharmacological activities of some substituted 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles. *Eur. J. Med. Chem.* **2006**, *41*, 1048-1058.

100. C. T. Supuran, A. Scozzafava. Carbonic anhydrase inhibitors. *Curr. Med. Chem. Immunol. Endocrinol. Agents* **2001**, *1*, 61-97.

101. R. W. Young, K. H. Wood, J. A. Eichler, J. R. Vaughan, Jr., G. W. Anderson. 1,3,4-Thiadiazole- and thiadiazolinesulfonamides as carbonic anhydrase inhibitors. *J. Am. Chem. Soc.* **1956**, *78*, 4649-4654.

102. E. E. Chufán, J. C. Pedregosa, O. N. Baldini, L. Bruno-Blanch. Anticonvulsant activity of analogues of acetazolamide. *Il Farmaco* **1999**, *54*, 838-841.

103. A. Casini, A. Scozzafava, F. Mincione, L. Menabuoni, M. Stranotti, C. T. Supura. Carbonic anhydrase inhibitors: Topically acting antiglucoma sulfonamides incorporating esters and amides of 3- and 4-carboxybenzolamide. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2867-2873.

104. H. N. Dogan, A. Duran, S. Rollas, G. Sener, M. K. Uysal, D. Gülen. Synthesis of new 2,5-disubstituted-1,3,4-thiadiazoles and preliminary evaluation of anticonvulsant and antimicrobial activities. *Bioorg. Med. Chem.* **2002**, *10*, 2893-2898.

105. L. M. Thomasco, R. C. Gadwood, E. A. Weaver, J. M. Ochoada, C. W. Ford, G. E. Zurenko, J. C. Hamel, D. Stapert. The synthesis and antibacterial activity of 1,3,4-thiadiazole phenyl oxazolidinone analogues. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4193-4196.

106. A. K. Padhy, V. L. Nag, C. S. Panda. Studies on the synthesis and bioactivity of some thiadiazole derivatives. *Indian J. Chem.* **1999**, *38B*, 998-1001.

107. A. Foroumadi, M. Daneshtalab, A. Shafiee. Synthesis and *in vitro* antifungal activity of 2-aryl-5-phenylsulfonyl-1,3,4-thiadiazole derivatives. *Arzneim.–Forsch./Drug Res.* **1999**, *49*, 1035-1038.

108. A. Foroumadi, M. Mirzaei, A. Shafiee. Antituberculosis agents, I: Synthesis and antituberculosis activity of 2-aryl-1,3,4-thiadiazole derivatives. *Pharmazie.* **2001**, *56*, 610-612.

109. A. Foroumadi, A. Asadipour, M. Mirzaei, J. Karimi, S. Emami. Antituberculosis agents, V. Synthesis, evaluation of *in vitro* antituberculosis and cytotoxic activity of some 2-(5-nitro-2-furyl)-1,3,4-thiadiazole drivatives. *Il Farmaco*. **2002**, *57*, 765-769.

110. A. Foroumadi, F. Soltani, H. Moallemzadeh, A. Shafiee. Synthesis, *in vitro* antimycobacterium activity and cytotoxicity of some alkyl alpha-(5-aryl-1,3,4-thiadiazol-2-ylthio)acetate. *Arch. Pharm.* **2005**, *338*, 112-116.

111. A. Foroumadi, Z. Kiani, F. Soltani. Antituberculosis agents, VIII: Synthesis and *in vitro* antimycobacterium activity of alkyl α-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazol-2-ylthio]acetate. *Il Farmaco.* **2003**, *58*, 1073-1076.

112. L. S. Varandas, C. A. M. Fraga, A. L. P. Miranda, E. J. Barreiro. Design, synthesis and pharmacological evaluation of new nonsteroidal anti-inflammatory 1,3,4-thiadiazole derivatives. *Letters in Drug Design & Discovery* **2005**, *2*, 62-67.

113. T. Y. Shen, C. A. Winter, in: Advances in drug research (A. B. Simmons, ed.), Academic Press, New York, Vol. 12 (**1977**).

114. M. Nomura, M. Kyouda, T. Hirokawa, Y. Fujihara, M. Sugiura. Adamantane carboxylic acids through cyanation of bromoadamantanes. *Nippon Nogei Kagaku Kaishi* **1994**, *68*, 973-976; *Chem. Abstr.* **1994**, *121*, 57030.

115. B. Zacharie, T. P. Connolly, C. L. Penny. A simple one-pot conversion of carboxylic acids to esters using EEDQ. *J. Org. Chem.* **1995**, *60*, 7072-7074.

116. J. R. Reid, N. D. Heindel. Improved synthesis of 5-substituted-4-amino-5-mercapto(4*H*)-1,2,4-triazoles. *J. Heterocycl. Chem.* **1976**, *13*, 925-926.

117. A. A. El-Emam, M. A. Moustafa, A. M. Abdelal, M. B. El-Ashmawy. Triazoles and Fused Triazoles IV: Synthesis of 3-(1-adamantyl)-6-substituted-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles and 3-(1-adamantyl)-6-aryl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thia-diazines as potential chemotherapeutic Agents. *Chin. Pharm. J.* **1993**, *45*, 101-107.

118. P. Molina, A. Tàrraga. A novel preparation of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives. *Synthesis* **1983**, 411-413.

119. H. Golgolab, I. Lalesari, L. Hosseini-Gohari. 1,3,4-Thiadiazolo[2,3-*c*]-*as*-triazines and *s*-triazolo[3,4-b]-1,3,4-thiadiazoles. *J. Heterocycl. Chem.* **1973**, *10*, 387-390.

120. M. K. Mody, A. R. Prasad, T. Ramalingam, P. B. Sattur. Synthesis and Pharmacology of 2-aryl-5-aryloxyalkyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles. *J. Indian. Chem. Soc.* **1982**, *LIX*, 769-770.

121. F. Malbec, R. Milcent, G. Barbier. Dérivés de la dihydro-2,4 triazole-1,2,4 thione-3 et de l'amino-2 thiadiazole-1,3,4 à partir de nouvelles thiosemicarbazone d' esters. *J. Heterocycl. Chem.* **1984**, *21*, 387-390.

122. A. A. El-Emam, M. A. Moustafa, S. M. Bayomi, M. B. El-Ashmawy. Triazoles and fused triazoles II: Synthesis of certain substituted *s*-triazoles, *s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles and *s*-triazolo[3,4-*b*]-1,3,4-thiadiazines. *J. Chin. Chem. Soc.* **1989**, *36*, 353-356.

123. T. George, R. Tahilramani, D. A. Dabholkar. Synthesis of condensed *s*-triazole heterocycles. *Indian J. Chem.* **1969**, *7*, 959-963.

124. A. A. El-Emam, M. A. Moustafa, H. I. El-Subbagh, M. B. El-Ashmawy. Triazoles and fused triazoles III: facile and efficient synthesis of 2,4-disubstituted-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles. *Monatsh. Chem.* **1990**, *121*, 221-225.

125. K. T. Potts, R. M. Husbey. 1,2,4-Triazoles. XVI. Derivatives of *s*-triazolo[3,4-*b*][1,3,4]thiadiazole ring system. *J. Org. Chem.* **1966**, *31*, 3528-3531.

126. T. Sasaki, E. Ito. Synthesis of bridged nitrogen systems. *s*-triazolo[3,4-*b*]-*as*-triazine, *s*-triazolo[3,4-*d*]-*as*-triazine and *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole ring systems. *J. Heterocycl. Chem.* **1981**, *18*, 1353-1356.

127. N. J. Lawrence, E. S. M. Armitage, B. Greedy, D. Cook, S. Ducki, A. T. McGown. The synthesis of indanones related to combretastatin A-4 *via* microwave-assisted Nazarov cyclization of chalcones. *Tetrahedron Lett.* **2006**, *47*, 1637-1640.

128. A. A. dos Santos, E. P. Wendler, F. A. Marques, F. Simonelli. Microwave-accelerated epoxidation of α,β-unsaturated ketones with urea-hydrogen peroxide. *Lett. Org. Chem.* **2004**, *1*, 47-49.

129. J. Lu, Y. Li, Y. Bai, M. Tian. Green chemistry approaches to the synthesis of 5-arylidenthiobarbituric acids by a condensation reactions between aromatic aldehydes and thiobarbituric acid. Comparison of water, microwave irradiation, and grinding. *Heterocycles* **2004**, *63*, 583-589.

130. H. M. Hirpara, V. A. Sodha, A. M. Trivedi, B. L. Khatri, A. R. Parikh. Microwave-assisted synthesis and biological activities of some bridge-head nitrogen heterocycles. *Indian J. Chem.* **2003**, *42B*, 1756-1759.

131. M. Shiradkar, H. N. Shivaprasad. Microwave-assisted synthesis and bioactivity of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles and *s*-triazolo[3',4':2,3]-thiadiazino[5,6-*b*]Quinoxaline. *Asian J. Chem.* **2005**, *18*, 319-324.

132. S. Haijian, W. Zhongyi, S. Haoxin. Study of the intramolcular Mannich reaction of 4-amino-3-aryl-2,3-dihydro-5-mercapto-1,2,4-triazoles. *Synth*. *Commun*. **1998**, *28*, 3973-3982.

133. N. R. El-Brollosy, C. Nielsen, E. B. Pedersen. Synthesis of *N*-1-(indanyloxymethyl) and *N*-(4-hydroxybut-2-enyloxymethyl) analogues of the HIV- drugs emivirine and GCA-186. *Monatsh*. *Chem.* **2005**, *136*, 1247-1254.

134. A. A. El-Emam, J. Lehmann. *N*- And *S*-alkylation of 3-(1-adamantyl)-4-methyl-1,2,4-triazole-5-thiol and 2-(1-adamantyl)-1,3,4-oxadiazole-5-thiol. *Phosphorus, Sulfur Silicon Rel. Elem.* **1997,** *121*, 473-474.

135. A. A. El-Emam, J. Lehmann. Adamantane Derivatives IV: unexpected debenzylation on ring closure of 1-(1-adamantycarbonyl)-4-benzylthiosemicarbazide with sulphuric acid. *Monatsh*. *Chem.* **1994**, *125*, 587-591.

136. T. J. Kress, S. M. Costantino. A convenient and general synthesis of 2-amino-1,3,4-thiadiazoles. Dehydration of acylthiosemicarbazides with methanesulfonic acid. *J. Heterocycl. Chem.* **1980**, *17*, 607-608.

137. G. Werber, F. Buccheri, M. Gentile. Reactivity of 2-amino-1,3,4-thiadiazoles. Nucleophilic behaviour of some 2-amino-1,3,4-thiadiazoles: Model compounds. *J. Heterocycl. Chem.* **1977**, *14*, 1263-1265.

138. S. Giri, H. Singh. Synthesis of certain Schiff bases derived from 2-amino5-aryl-1,3,4-thiadiazoles. *J. Indian Chem.Soc.* **1966**, *43*, 281-282.

139. D. N. Tai, N. D. Trieu, T. T. Tu. Azomethine bases and their transformation products. I. Synthesis of some azomethine bases of 1,3,4-thiadiazole series. *Tap Chi Hoa Hoc* **1981**, *19*, 13-15; *Chem. Abstr.* **1981**, *95*, 132771.

140. V. K. Pandey, Z. Tusi, M. Tandon, M. N. Joshi, S. K. Bajpai. Synthesis of thiadiazole-*s*-triazines for their antiviral activity bases on QSAR studies. *Indian J. Chem.* **2003**, *42B*, 2583-2588.

141. P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover, R. H. Yolken, in: Manual of Clinical Microbiology (G. L. Wood, J. A. Washington, eds.), Am. Soc. Microbiol., Washington D.C. (**1995**).

142. National Committee for Clinical Laboratory Standards (NCCLS) Approved standard document M-7A, Villanova, PA (**1985**).

143. A. Mai, M. Artico, G. Sbardella, A. Massa, E. Novellino, G. Greco, A. G. Loi, E. Tramontano, M. E. Marongiu, P. La Colla. 5-Alkyl-2-(alkylthio)-6-(2,6-dihalophenylmethyl)-3,4-dihydropyrimidin-4(*H*)-ones: novel potent and selective dihydro-alkoxy-benzyl-oxopyrimidine derivatives. *J. Med. Chem.* **1999**, *42*, 619-627.

144. E. A. Sudbeck, S. Massa, R. Vig, T. K. Venkatachalam, L. Tuel-Ahlgren, F. M. Uckun. Structure-based design of novel dihydroalkoxy-benzyloxypyrimidine derivatives as potent nonnucleoside inhibitors of the human immunodeficiency virus reverse transcriptase. *Antimicrob. Agents Chemother.* **1998**, *42*, 3225-3233.

145. C. Sahlberg, R. Noreen, P. Engelhardt, M. Högberg, J. Kangasmetsä, L. Vrang, H. Zhang. Synthesis and anti-HIV activities of urea-PETT analogs belonging to a new class of potent non-nucleoside HIV-1 reverse transcriptase inhibitors. *Bioorg. Med. Chem.Lett.* **1998**, *8*, 1511-1516.

146. K. Ijichi, M. Fujiwara, H. Nagano, Y. Matsumoto, Y. Hanasaki, T. Ide, K. Katsuura, H. Takayama, S. Shirakawa, N. Aimi, S. Shigeta, K. Konno, M. Matsushima, T. Yokota, M. Baba. Anti-HIV-1 activity of thiazole derivatives: Structure-activity relationship, reverse transcriptase inhibition, and lipophilicity. *Antiviral Res.* **1996**, *31*, 87-94.

147. Y. Hanasaki, H. Watanabe, K. Katsuura, H. Takayama, S. Shirakawa, K. Yamaguchi, S. I. Sakai, K. Ijichi, M. Fujiwara, K. Konno, T. Yokota, S. Shigeta, M. Baba. Thiadiazole derivatives: Highly potent and specific HIV-1 reverse transcriptase inhibitors. *J. Med. Chem* **1995**, *38*, 2038-2040.

148. C. A. Winter, E. A. Risely, G. W. Nuss. Carrageenin-induced paw oedema in hind paw of the rat as an assay for anti-inflammatory drugs. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544-547.

149. J. T. Litchfield, T. Wilcoxon. A simplified method of evaluating dose-effect experiments. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99-104.

150. M. Hichens, in: Anti-inflammatory agents (R. A. Scherrier, M. W. Whitehouse, eds.), Academic Press, New York, London, Vol. II, pp. 293 (**1974**).

بسم الله الرحمن الرحيم

الملخص العربي

لقد عرفت المركبات التي تحتوي على حلقات الأدمانتان بفاعليتها الكبيرة في مجالات مختلفة بناءً على ما ذكر في الدوريات العلمية في هذا المجال. وقد تم في هذه الأطروحة تشييد عدة سلاسل من مشتقات الأدمانتان المتصلة بحلقات ٤،٢،١، ترايازول و ٤،٣،١-ثياديازول إضافة إلى مشتقاتها ثنائية الحلقات المدمجة ذات الصلة بالمركبات المعروفة كمضادات للميكروبات ومضادات للإلتهابات وذلك بهدف الوصول إلى مركبات جديدة أكثر فاعلية وذات أعراض جانبية أقل وللحصول على هذه المركبات الجديدة المستهدفة فقد تم إجراء عدة تفاعلات كيميائية تتلخص فيما يلي:

١. تحضير مشتقات ٥-(١-أدمانتايل)-٢-أريل امينو – ٤،٢،١– ترايازولو[٤،٢،١][٤،٣-ب] ثياديازول وتم ذلك بالطرق التالية:

أ) تفاعل المركب ٥-(١-أدمانتايل)-٤-أمينو-٣-مركابتو-٤،٢،١-ترايازول مع مستبدلات الأيزوثيوسيانات العطرية عند درجة حرارة الغرفة لمدة ٢٤ ساعة في ثنائي ميثيل الفورماميد كمذيب للحصول على مركبات ن -[٥-(١-أدمانتايل)-٣-مركابتو-٤،٢،١– ترايازول-٤-آيل] –نَ-أريل ثيويورايثم حلقنتها بـ تعريضها للأشعة الميكرونية (الميكروويف) لمدة ٥ دقائق عند ٤٥٤ وات.

ب) تفاعل المركب ٥-(١-أدمانتايل)-٤-أمينو-٣-مركابتو-٤،٢،١-ترايازول مع مستبدلات الأيزوثيوسيانات العطرية باستخدام ثنائي ميثيل الفورماميد كمذيب لمدة ١٨ ساعة عند درجة غليانه لمدة ١٨ ساعة.

جـ) تعريض خليط من المركب ٥-(١-ادمانتايل)-٤-أمينو-٣- مركابتو-٤،٢،١-ترايازول ومستبدلات الأيزوثيوسيانات العطرية للأشعة الميكرونية لمدة ٨ دقائق عند ٤٥٤ وات.

٢. تفاعل المركب ٥-(١-أدمانتايل)-٢-أمينو-٣-مركابتو-١،٢،٤- ترايازول مع بروميد السيانوجين في الكحول الايثيلي أعطى مركب ٥-(١-أدمانتايل)-٢-أمينو-١،٢،٤-ترايازولو[١،٢،٤][٣،٤-ب] ثياديازول الذي تم ألكنته باستخدام بعض المستبدلات الهالوجينية في وجود كربونات البوتاسيوم اللامائية . ونتج عن ذلك سلسلة من مركبات ٥-(١-أدمانتايل)-٢-مستبدلات الأمينو-١،٢،٤- تريازولو[١،٣،٤][٣،٤-ب] ثياديازول.

٣. تم الحصول على مشتقات الترايازول و[١،٢،٤][٣،٤-ب] ثياديازول أيضاً بطريقة أخرى عن طريق تسخين المركب ٥-(١-أدمانتايل)-٤-أمينو-٣-مركابتو-١،٢،٤-ترايازول مع مستبدلات الأيزوثيوسيانات الغير عطرية باستخدام ثنائي ميثيل الفورماميد كمذيب لمدة ١٨ ساعة عند درجة غليانه.

٤. تفاعل مركب ٥-(١-أدمانتايل)-٤-أمينو-٣-مركابتو-١،٢،٤-ترايازول مع العديد من الألدهيدات العطرية باستخدام الكحول الإيثيلي أو حمض الخليك ونتج عن ذلك سلسلة من مركبات ٥-(١- أدمانتايل)-٤-أريليدين أمينو-٣-مركابتو-١،٢،٤- ترايازول.

٥. تم تحضير سلسلة من مشتقات ٥-(١-أدمانتايل)-٤-أرايليدين أمينو-٢-(٤- مستبدل -١-ببرازينيل ميثيل)- ١،٢،٤-ترايازولين-٣ثيون وذلك بتفاعل المشتقات ٥-(١-أدمانتايل)-٤-(٦،٢ثنائي كلورو أو فلورو بنزيليدين أمينو)- ٣-مركابتو-١،٢،٤- ترايازول مع مستبدلات الببرازين الأحادية المقابلة والفورمالين باستخدام الكحول الإيثيلي كمذيب.

٦. تفاعل مشتقات ٥-(١-أدمانتايل)-٤-أريليدين أمينو-٣- مركابتو-١،٢،٤- ترايازول مع إيثيل ٤ببريدين كربوكسيلات والفورمالين بالتسخين في الكحول الإيثيلي ونتج عن ذلك سلسلة من مركبات ٥-(١-أدمانتايل)-٤-أريليدين أمينو-٢-(٤-إيثوكسي كربونيل)-١-ببريديل ميثيل)- ١،٢،٤-ترايازولين-٣-ثيون.

٧. تفاعل ٥-(١-أدمانتايل)-١،٣،٤-ثياديازولين-٢ثيون مع كلوريد البنزيل أو مستبدلاته في الموضع ٤ في وجود كربونات البوتاسيوم اللامائية باستخدام الكحول الإيثيلي كمذيب ونتج عن ذلك مركبات ٥-(١-أدمانتايل)-٣-(بنزايل أو ٤ مستبدلات البنزايل)-١،٣،٤-ثياديازولين-٢-ثيون.

٨. تسخين مركب ٥-(١-أدمانتايل)-٤،٣،١-ثياديازولين-٢-ثيون مع مستبدلات البرازين والفورمالين باستخدام الكحول الإيثيلي كمذيب للحصول علي مشتقات ٥-(١-أدمانتايل)-٣-(٤-مستبدلات ببرازينيل ميثيل)-٤،٣،١- ثياديازولين-٢-ثيون.

٩. تم الحصول على مركبات ٢-[٥-(١-أدمانتايل)-٢-ثيوكسو-٤،٣،١-ثياديازولين-٣-آيل] حمض الخليك و (±) -٢-[٥-(١-أدمانتايل)-٢-ثيوكسو-٤،٣،١-ثياديازولين-٣-آيل] حمض البروبيونيك وكذلك ٣-[٥-(١-أدمانتايل)-٢-ثيوكسو-٤،٣،١-ثياديازولين-٣-آيل] حمض البروبيونيك بتفاعل استرات البروموايثيل مع ٥-(١-أدمانتايل)-٤،٣،١-ثياديازولين -٢-ثيون في وجود كربونات البوتاسيوم اللامائيةباستخدام الكحول الإ يثيلي كمذيب ثم متبوعاً بالتحلل المائي للإسترات المتكونة باستخدام محلول هيدروكسيد الصوديوم.

١٠. تفاعل مركب ٥-(١-أدمانتايل)-٢-أمينو-٤،٣،١-ثياديازول مع مستبدلات الايزوثيوسيانات العطرية بالتسخين في ثنائي ميثيل الفورماميد لمدة ٦ ساعات للحصول مشتقات ن-[٥-(١-أدمانتايل)-٤،٣،١-ثياديازول-٢-آيل] -ن′-أريل ثيويوريا.

١١. تفاعل ٥-(١-أدمانتايل)-٢-أمينو-٤،٣،١-ثياديازول معمحلول نيتريت الصوديوم المائي وحمض الهيدروكلوريك للحصول علي ٥-(١-أدمانتايل)-٤،٣،١-ثياديازولين-٢-أون.

وقد تم في هذه الأطروحة تحضير ٨٣ مركباً نهائياً جديداً وقد استلزم ذلك تحضير العديد من المركبات الوسيطة الغير متاحة تجارياً وهي:

١) ميثيل أدمانتان-١-كربوكسيلات.
٢) أدمانتان-١-هيدرازيد حمض الكربوكسيليك.
٣) بوتاسيوم نَ-(١-أدمانتايل كربونيل) ثنائي ثيوكربازات.
٤) ٥- (١-أدمانتايل)-٤-أمينو-٣-مركابتو-٤،٢،١-ترايازول.
٥) ١-(١-أدمانتايل كربونيل)-٣-ثيوسيميكاربازايد.
٦) ٥-(١-أدمانتايل)-٢-أمينو-٤،٣،١-ثياديازول.

وقد تم فصل جميع المركبات في صورة نقية وتم التأكد من تراكيبها الجزيئية عن طريق التحاليل الطيفية بالأشعة تحت الحمراء والرنين النووي المغناطيسي لنظيري الهيدروجين والكربون وطيف الكتلة.

وقد اشتملت الرسالة أيضاً على دراسة تأثير جميع المركبات الجديدة كمثبطات لنمو عدة عترات من البكتيريا الموجبة والسالبة الجرام وكذلك فطر الكانديدا البيكانس المسببة للأمراض وقد دلت النتائج علي وجود فاعلية قوية لعدد ١٥ مركباً جديداً مقارنة بنتائج المضادات الحيوية المعروفة. هذا بالإضافة إلى النتائج الإيجابية الملحوظة لعدد ٤٦ مركباً وافتقار ٢٢ مركباً للفاعلية.

كذلك تم اختيار فعالية ٢٦ مركباً جديداً كمضادات للالتهابات في جرذان التجارب وقد دلت النتائج علي وجود فعالية عالية لمركبين جديدين مقارنة بعقار الإندوميثاسين المعروف كمضاد للالتهابات بالإضافة إلى النتائج الإيجابية الملحوظة للعديد من المركبات الأخرى . وقد تم دراسة السمية الحادة للمركبين ذات الفعالية العالية وذلك بقياس الجرعات القاتلة للفئران، وقد أثبتت الدراسة تميز المركبين الجديدين بمعاملات أمان واسعة مقارنة بعقار الإندوميثاسين.