Rupa Pawar, et. al. International Journal of Engineering Research and Applications
www.ijera.com
ISSN: 2248-9622, Vol. 12, Issue 6, (Series-IV) June 2022, pp. 48-55

RESEARCH ARTICLE OPEN ACCESS

Synthesis, characterization and study of anti-fungal activities of dihydrazide- dihydrazone derivatives of adamantly moiety containing nitro group

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ABSTRACT:
In this study, di methyl 1, 3-adamantane-di-carboxylate was used as the key intermediate. It was initially prepared by esterification of 1, 3-adamantane-di-carboxylic acid (1) and methanol under catalysis of 98% H2SO4 to yield dimethyl ester (2). Then, ester (2) was reacted with hydrazine hydrate to yield corresponding adamantane dihydrazide (3). Subsequently, compound (3) was condensed with aromatic aldehydes or ketones (4) to yield the corresponding dihydrazide-dihydrazones (5) containing nitro group as seen in Figure 1. The structure of dihydrazide-dihydrazones containing nitro group was confirmed by 1H-NMR, FTIR, Mass spectroscopy and elemental analysis.
In present endeavor, I have successfully developed a synthetic route for synthesis of different dihydrazide-dihydrazone derivatives containing nitro group of adamantly moiety.
All synthesized compounds are characterized by FTIR, 1H-NMR, Mass spectroscopy and elemental analysis.
Synthesized compounds are studied for antifungal activities.
Keywords: Dihydrazide, dihydrazone, dihydrazide-dihydrazone, anti-fungal activities, adamantane, adamantly moiety, nitro group.

Date of Submission: 05-06-2022 Date of Acceptance: 20-06-2022

I. INTRODUCTION

Hydrazones possesses an azometine –NHN=CH- proton which is an important constituent for new drug development for the biological activities like anti-microbial [35, 1-3] including anti-bacterial, antifungal, anti-tubercular [6-8], anti-cancer [4, 5], mitigating, anti convulsant, antiprotozoal and antiviral [9] activities.

Literature review reveals the broader significance of the development of a new synthetic material with dihydrazone derivatives. Dihydrazone derivatives exhibit a promising feature towards the development of new therapeutic agents [26-34].

Many adamantane derivatives [9-12] were created due to the biological activities like anti-microbial [15, 18-24], antibacterial, antifungal, anti-inflammatory [25], anti-tubercular, anti-cancer, mitigating, anti convulsant, antiprotozoal and antiviral [13-17] activities.

Heterocyclic compounds have high degree of structural diversity and have proven to be broadly and economically useful therapeutic agents.

Adamantane is the name of tricyclo[3.3.1.13,7]decane. Derivatives of Adamantane compounds exhibits better biological activity than their single counterpart. Because of high lipophilicity of adamantane it can be incorporated into several molecules resulting in compounds with relatively high lipophilicity.

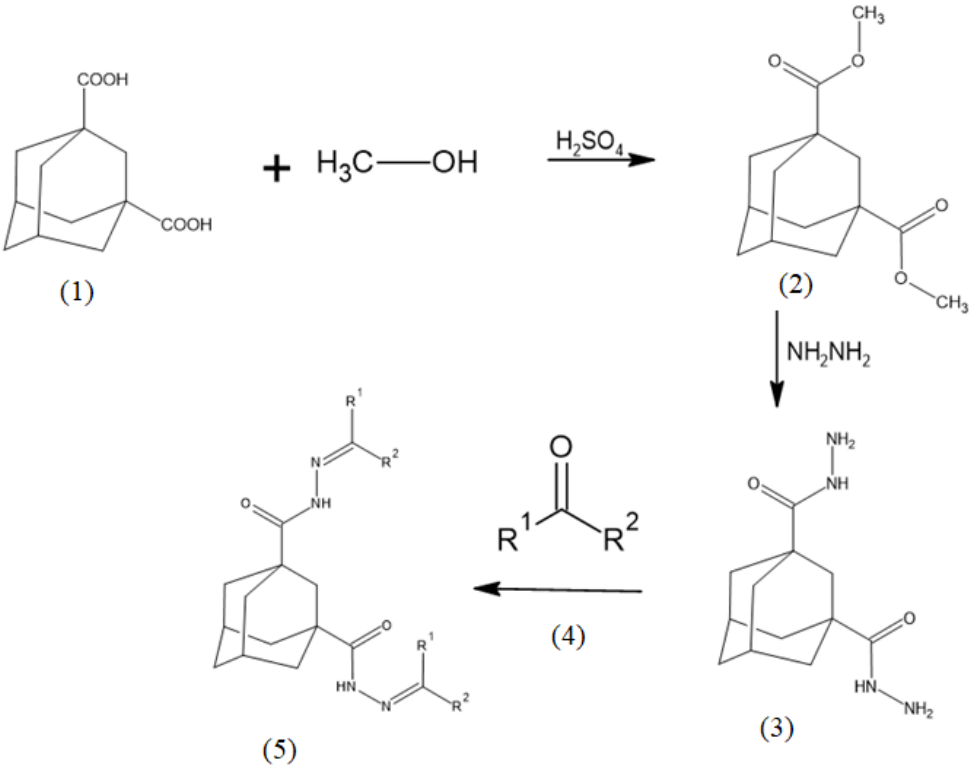
Since both dihydrazones and adamantane derivatives have promising biological activities, the combination of two moieties will be of great value for the development of new therapeutic agents.

II. EXPERIMENTAL SECTION

All reagents were provided by commercial suppliers. Open capillary tube method was used to confirm the melting point of all newly synthesized compounds. NMR spectrophotometer

600.1723046[MHz] was used to record NMR spectra. The solvent used was DMSO-D6, for NMR analysis. The constants were given in Hz, using tetra-methyl-silane as the internal standard. The chemical shifts were expressed in ppm. Reference peak was at 2.5 ppm. In addition to NMR spectra, all newly synthesized compounds were tested for elemental and FTIR analysis.

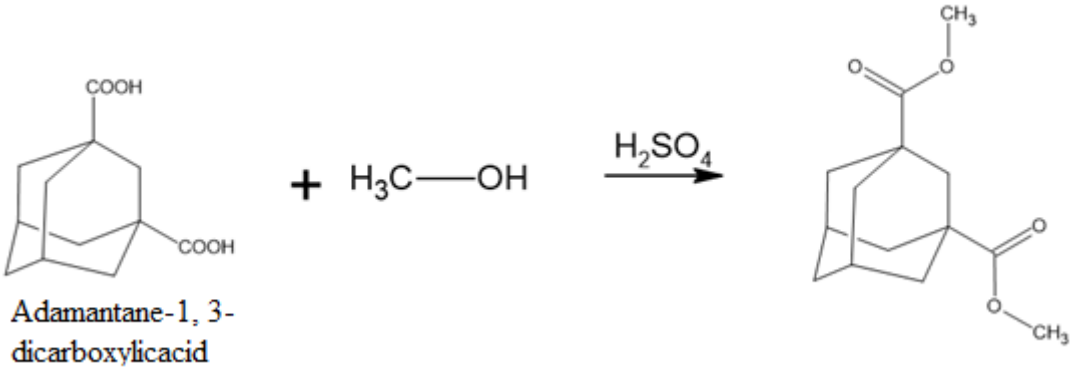
General reaction scheme for preparation of final products.



General Scheme I

Figure1: Preparation of dihydrazide-dihydrazone derivatives containing nitro group from Adamantane-1, 3-dicarbohydrazide

Reaction scheme for preparation of final products: Figure 2, Figure 3



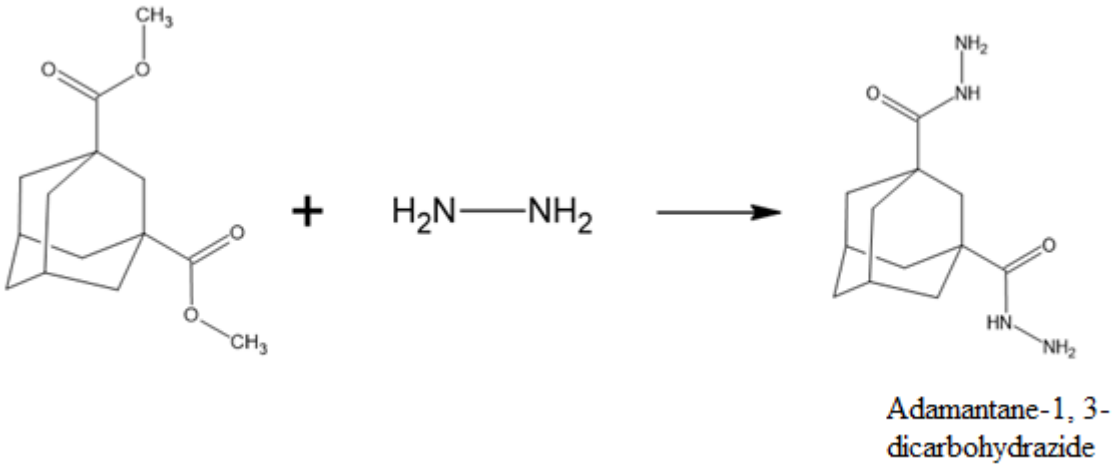


Figure 2: Preparation of Adamantane-1, 3-dicarbohydrazide from of Adamantane-1, 3-dicarboxylicacid

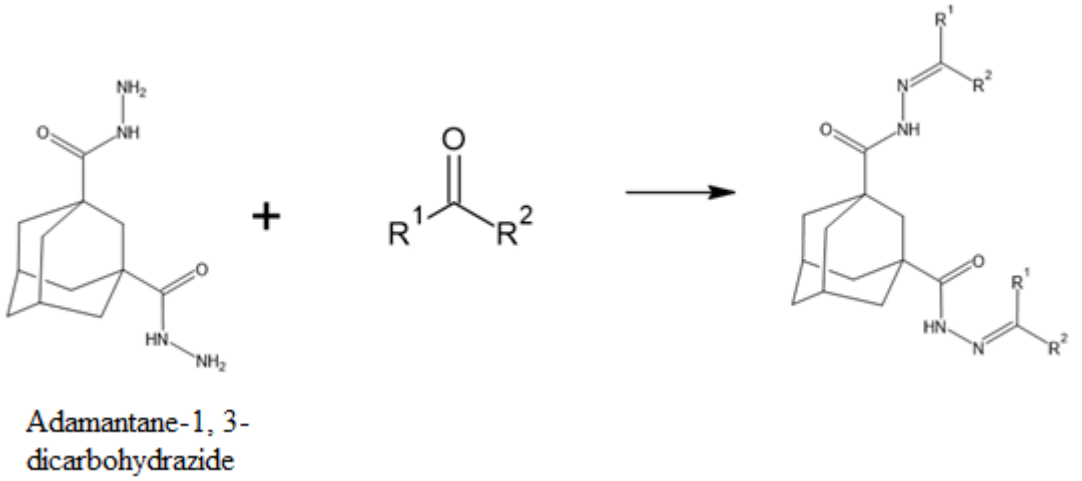


Figure 3: Preparation of dihydrazide-dihydrazone (aldehyde and ketone derivatives) derivatives from Adamantane-1, 3-dicarbohydrazide**.**

Compounds	R1and R2
1	R1 = H, R2 = -C7H4NO2
2	R1 = -CH3, R2= -C7H3ClNO2
3	R1 = -CH3, R2= -C8H7O
4	R1 = -H, R2= -C9H9O2
5	R1 = -CH3, R2= -C9H9O
6	R1 = -H, R2 = -C11H7
7	R1 = H, R2 = -C5H2NO3
8	R1 = -H, R2 = -C8H6NO4
9	R1= -H, R2 = C7H3ClNO2
10	R1 = -H, R2 = -C8H7O2

Table 1: Aldehyde groups are found in compounds 1-3, 5, 8-10 and ketone groups are from 3, 5.

III. RESULTS and DISCUSSIONS

Synthesis for preparation of the final product (dihydrazide-dihydrazone derivatives of adamantly moiety containing nitro group):

Adamantane-1, 3-dicarbohydrazide was used as the key intermediate. It was initially prepared by esterification of adamantane-1, 3-dicarboxylic acid and methanol using 98% H2SO4 as a catalyst to yield corresponding di-ester that is dimethyl-1, 3 adamantane dicarboxylate. This di-ester was then reacted with 80% hydrazine hydrate to yield adamantane 1, 3 dicarbohydrazide. [36].

Synthesis of dimethyl-1, 3 adamantane di-carboxylate from adamantane-1, 3-dicarboxylic acid:

A mixture of 0.02 mol of adamantane-1, 3-dicarboxylic acid, 15 ml of methanol in presence of 98% H2SO4 as catalyst was refluxed. The mixture was cooled and washed with water. Than the mixture was successively washed with Sodium Hydrogen carbonate (15% NaHCO3 aqueous solution) to pH 7 and water again. The organic phase was dried over anhydrous sodium sulfate (Na2SO4), evaporated and crystallized. [36].

Synthesis of Adamantane-1, 3-dicarbohydrazide from dimethyl-1, 3 adamantane di-carboxylate:

To the alcoholic solution of (1.00924 g, 0.004 mol) dimethyl 1, 3 adamantane dicarboxylate, (0.08mol) 80% hydrazine hydrate was added drop wise with constant stirring. The reaction was carried out at 0 degree Celsius. White colored Adamantane-1, 3-dicarbohydrazide obtained was recrystallized in methanol and is confirmed from M.P. [36].

Synthesis of dihydrazide-dihydrazone derivatives from Adamantane-1, 3-dicarbohydrazide:

The Adamantane-1, 3-dicarbohydrazide on condensation with different aldehydes and ketones containing nitro group give the corresponding dihydrazone derivatives. The reaction was monitored for completion by TLC.

1) Bis [N'-(4-nitro)benzylidene]adamantame-1, 3-dicarbohydrazide: M.p.: 181 ◦C, Yield 77.64 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 10.2-8.8 (1H, s, NH-N); 8.15-8.44 (Ar-H); 3.4-3.6 (=CH); 1.62-2.07 (Adamantane-H).

Color of the compound obtained was: Light yellow.

IR (ν cm-1): 1104 (N-N); 1247 (C-N for NO2); 1286(C-O); 1345 (C-N); 1524 (NO2); 1599 (C=N); 1709 (C=O); 2850 (N-H); 2921-2996 (C-H); 3106 (H-C=).

Analysis: for C26H26N6O6 found (calculated): C, 60.15 (60.22); H, 5.03 (5.05); N, 16.18 (16.21) %.

2) Bis [N'-(1-(3-nitro, 4-chloro) ethylidene)] adamantame-1, 3-dicarbohydrazide: M.p.: 178 ◦C, Yield 66.25 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.54 (1H, s, NH-N); 7.93-8.21 (Ar-H); 3.4 (=CH); 1.62-2.00 (Adamantane-H).

Color of the compound obtained was: Yellow to orange.

IR (ν cm-1): 839 (C-Cl); 1074 (N-N); 1247-1296 (C-N); 1511-1513 (C=C benzene); 1533 (NO2); 1594 (C=N); 1688 (C=O); 2924 (N-H); 3098 (C-H); 3434 (H-C=).

Analysis: for C28H28Cl2N6O6 found (calculated): C, 54.62 (54.64); H, 4.56 (4.59); N, 13.63 (13.65) %. [36].

3) Bis [N'-(1-(2-hydroxy, 5-methyl phenyl) ethylidene)]adamantame-1, 3-dicarbohydrazide: M.p.: 221 ◦C, Yield 72 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 12.75 (-OH attached to benzene ring) 7.58 (1H, s, NH-N); 6.86-7.3 (Ar-H); 3.56 (=CH); 1.62-2.00 (Adamantane-H).

Color of the compound obtained was: Shiny dark yellow.

IR (ν cm-1): 1039 (N-N); 1233 (C-O); 1290 (C-N); 1563-1492 (C=C benzene); 1614 (C=N); 1744 (C=O); 2920 (N-H); 2993 (C-H); 3434 (H-C=); 3752 (-OH).

Analysis: for C28H32N4O4 found (calculated): C, 68.81 (69.74); H, 7.02 (7.02); N, 10.86 (10.84) %.

4) Bis [N'-(3, 4-dimethoxy)benzylidene)]adamantame-1, 3-dicarbohydrazide: M.p.: 215 ◦C, Yield 38.58 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.6 (1H, s, NH-N); 7.06-7.48 (Ar-H); 3.37 (=CH); 1.62-2.00 (Adamantane-H).

Color of the compound obtained was: Light yellow.

IR (ν cm-1): 1016 (N-N); 1157 (C-O); 1259 (C-N); 1508-1464 (C=C benzene); 1623 (C=N); 1729 (C=O); 2839 (N-H); 2929 (C-H); 2961 (H-C=).

Analysis: for C30H36N4O6 found (calculated): C, 65.66 (65.68); H, 6.59 (6.61); N, 10.19 (10.21) %.

5) Bis [N'-(1-(4-ethoxy)ethylidene)] adamantame-1, 3-dicarbohydrazide: M.p.: 185 ◦C, Yield 73.26%. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 7.91-7.93 (1H, s, NH-N); 7.1-7.86 (Ar-H); 4.06-4.13 (-OC2H5); 3.5 (=CH); 1.62-2.00 (Adamantane-H).

Color of the compound obtained was: Yellow.

IR (ν cm-1): 1043 (N-N); 1172 (C-O); 1298 (C-N); 1505 (C=C benzene); 1598 (C=N); 1681 (C=O); 2932 (N-H); 2979 (C-H); 3447 (H-C=).

Analysis: for C32H40N4O4 found (calculated): C, 69.76 (69.74); H, 7.06 (7.02); N, 10.82 (10.84) %.

6) Bis [N'-(2-napthyl)methylene)] adamantame-1, 3-dicarbohydrazide: M.p.: 241 ◦C, Yield

18.91 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.92 (1H, s, NH-N); 7.6-8.38 (napthalene-H); 3.4 (=CH); 1.62-2.00 (Adamantane-H).
Color of the compound obtained was: Light yellow.
IR (ν cm-1): 1016 (N-N); 1172 (C-N); 1502 (C=C benzene); 1616 (C=N);1692 (C=O); 2800 (N-H); 3054 (C-H); 3434 (H-C=).
Analysis: for C34H32N4O2 found (calculated): C, 77.28 (77.25); H, 6.09 (6.10); N, 10.58 (10.60) %.

7) Bis [N'-(5-nitro, furan-2-yl)methylene)] adamantame-1, 3-dicarbohydrazide: M.p.: 186 ◦C, Yield
84.41 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 6.9-7.6 (1H, s, NH-N); 3.5-3.6 (=CH broad peak); 1.62-2.00 (Adamantane-H).
Color of the compound obtained was: Dark brown.
IR (ν cm-1): 1026 (N-N); 1220-1280 (C-N); 1405 (NO2); 1610 (C=N); 1728 (C=O); 2863 (N-H); 2920 (C-H); 3430 (H-C=).
Analysis: for C22H22N6O8 found (calculated): C, 53.04 (53.01); H, 4.48 (4.45); N, 16.88 (16.86) %.

8) Bis [N'-(3-nitro, 4-hydroxy, 5-methoxy) benzylidene] adamantame-1, 3-dicarbohydrazide: M.p.: 180 ◦C, Yield
72.03 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 9.9 (-OH attached to benzene); 9.8 (1H, s, NH-N); 7.62-8.1 (Ar-H); 3.4 (=CH); 1.62-2.00 (Adamantane-H).
Color of the compound obtained was: Brown.
IR (ν cm-1): 1049 (N-N); 1111 (C-O); 1235-1273 (C-N); 1406 (NO2); 1577 (N-O); 1614 (C=N); 1689 (C=O); 2871 (N-H); 2992 (C-H); 3216 (H-C=).
Analysis: for C28H30N6O10 found (calculated): C, 55.07 (55.08); H, 4.93 (4.95); N, 13.73 (13.76) %.
9) Bis [N'-(3-nitro, 4-chloro)benzylidene]adamantame-1, 3-dicarbohydrazide: M.p.: 258 ◦C, Yield
75.84 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.82 (1H, s, NH-N); 7.93-8.5 (Ar-H); 3.37 (=CH); 1.62-2.00 (Adamantane-H).
Color of the compound obtained was: Light yellow.
IR (ν cm-1): 838 (C-Cl); 1049 (N-N); 1212-1132 (C-N); 1476 (C=C benzene); 1351 (N-O); 1530 (C-NO2); 1602 (C=N); 1626 (C=O); 3069 (H-C=).
Analysis: for C26H24Cl2N6O6 found (calculated): C, 53.19 (53.16); H, 4.10 (4.12); N, 12.09 (12.07) %.

10) Bis [N'-(3-methoxy, 4-hydroxy)benzylidene] adamantame-1, 3-dicarbohydrazide: M.p.: 158 ◦C, Yield
84.43 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 9.7 (1H, s, NH-N); 8.56 (-OH attached to benzene); 3.4-3.6 (=CH); 3.85 (-OCH3); 6.86-7.39 (Ar-H); 1.62-2.07 (Adamantane-H).
Color of the compound obtained was: Light yellow to light brown.
IR (ν cm-1): 1097 (N-N); 1214-1273 (C-N); 1513 (C=C benzene); 1598 (C=N); 1727 (C=O); 2857 (N-H); 2920-3069 (C-H); 3190 (-OH); 3410 (H-C=). [36].

Serial no	yield (%)	M.P	color	R1,R2,R3 or R	Molecular Wt	Molecular Formula
1.	77.64	181	Light Yellow	R1 = H, R2 = 4-NO2, R3 = H	518.52124	C26H26N6O6
2.	66.25	178	Yellow to Orange	R1 = 3-NO2, R2= 4-Cl, R3 = H	615.46452	C28H28Cl2N6O6
3.	72	221	Shiny Dark Yellow	R1 = 2-OH, R2= 5-CH3, R3 = H	516.63124	C28H32N4O4
4.	38.58	215	Light Yellow	R1 = 3-OCH3, R2= 4-OCH3, R3 = H	548.63004	C30H36N4O6
5.	73.26	285	Yellow	R1 = H, R2= 4-OC2H5, R3 = H	516.63124	C32H40N4O4
6.	18.91	241	Light Yellow	Napthyl (R)	528.64348	C34H32N4O2
7.	84.41	186	Dark Brown	5-Nitro Furan (R)	498.44548	C22H22N6O8
8.	72.03	180	Brown	R1 = 3-NO2, R2 = 4-OH, R3 = 5-OCH3	609.798	C28H30N6O10
9.	75.84	258	Light Yellow	Biphenyl (R)	587.41136	C26H24Cl2N6O6
10.	84.43	158	Light Yellow to Light Brown	R1 = 3-OCH3, R2 = 4-OH, R3 = H	520.57688	C28H32N4O6

Table 2: Physical parameters of all the compounds

IV. ANTI-MICROBIAL TEST RESULTS

	C albicans		
Sample Name	Inoculum Count	Final Count	% killing
1	6400000	0	100.00
2	6400000	0	100.00
3	7000000	10	100.00
4	6800000	0	100.00
5	5900000	0	100.00
6	6600000	0	100.00
7	6700000	0	100.00
8	6100000	0	100.00
9	6000000	0	100.00
10	6400000	0	100.00

ANTI-MICROBIAL TEST

Anti-microbial test for anti-fungal activity (tube dilution method):

1. Description: powder substance in closed glass vials were used.
2. Organism named Candida Albicans (ATCC 10231) (Fungi) was used.
3. Additional information is as follows:

1	Method used for the test	Tube dilution method In-house (Rei : USP)
2	Method of sterilization used	Steam Sterilization using Autoclave
3	Contact Time (Sample Culture)	3 Minutes
4	Control sample	Initial Inoculum Count (Positive Control)
5	CFU	Colony Forming Units
6	Media used	Sabouraud's Dextrose Ajar (Fungi)
7	Sample Concentration (Dilution)	50 mg sample in 1 ml of DMSO
8	Incubation Temperature & Time	INCUBATION A4 20"C TO 25 C FOR FUNGI FOR 3-5 DAYS.

Opinion: All the samples were found to be very effective against Candida albicans and had minimum killing percentage of 100.

V. CONCLUSIONS:

The synthesis and characterization of dihydrazide-dihydrazones derivatives of adamantly moiety with nitro group were achieved. The synthesis was conducted by condensation of dihydrazide with different aldehydes and ketones to give the corresponding dihydrazone derivatives containing nitro group.

The characterization of newly synthesized dihydrazide-dihydrazones derivatives of adamantly moiety containing nitro group were achieved by FTIR, NMR and elemental analysis. Melting points of synthesized compounds were confirmed by open capillary tube method.

The anti-fungal activity of the synthesized compounds were determined. Synthesized compounds possesses excellent anti-fungal activity. Method used for the synthesis is simple, easy and cost effective.

It can be concluded that dihydrazide-dihydrazone derivatives of Adamantyl moiety containing nitro group holds promising future with excellent pharmacological properties.

REFERENCES:

[1]. Popiołek, Ł.; Biernasiuk, A. Synthesis and investigation of antimicrobial activities of nitrofurazone analoguescontaining hydrazide-hydrazone moiety. Saudi Pharm. J. 2017,25, 1097–1102.

[2]. He, H.; Wang, X.; Shi, L.; Yin, W.; Yang, Z.; He, H.; Liang, Y. Synthesis, antitumor activity and mechanism ofaction of novel 1,3-thiazole derivatives containing hydrazide–hydrazone and carboxamide moiety.

Bioorg.Med. Chem. Lett. 2016,26, 3263–3270.

[3]. Nasr, T.; Bondock, S.; Rashed, H.M.; Fayad, W.; Youns, M.; Sakr, T.M. Novel hydrazide-hydrazone and amidesubstituted coumarin derivatives: Synthesis, cytotoxicity screening, microarray, radiolabeling andin vivopharmacokinetic studies. Eur. J. Med. Chem. 2018,151, 723–739.

[4]. Velezheva, V.; Brennan, P.; Ivanov, P.; Kornienko, A.; Lyubimov, S.; Kazarian, K.; Nikonenko, B.; Majorov, K.;Apt, A. Synthesis and antituberculosis activity of indole–pyridine derived hydrazides, hydrazide–hydrazones,and thiosemicarbazones. Bioorg. Med. Chem. Lett. 2016,26, 978–985.

[5]. Pavan, F.R.; Maia, P.I.S.; Leite, S.R.A.; Deflon, V.M.; Batista, A.A.; Sato, D.N.; Franzblau, S.G.; Leite, C.Q.F.Thiosemicarbazones, semicarbazones, dithiocarbazates and hydrazide/hydrazones: Anti–Mycobacteriumtuberculosis activity and cytotoxicity. Eur. J. Med. Chem. 2010,45, 1898–1905.

[6]. Bedia, K.K.; Elçin, O.; Seda, U.; Fatma, K.; Nathaly, S.; Sevim, R.; Dimoglo, A. Synthesis and characterizationof novel hydrazide–hydrazones and the study of their structure–antituberculosis activity. Eur. J. Med. Chem.2006,41, 1253–1261.

[7]. Senkarde¸s, S.; Kaushik-Basu, N.; Durmaz, ˙I.; Manvar, D.; Basu, A.; Atalay, R.; Küçükgüzel, ¸S.G. Synthesisof novel diflunisal hydrazide–hydrazones as anti-hepatitis C virus agents and hepatocellular carcinomainhibitors. Eur. J. Med. Chem. 2016,108, 301–308.

[8]. Davies, W.L.; Grunert, R.R.; Haff , R.F.; McGahen, J.W.; Neumayer, E.M.; Paulshock, M.; Watts, J.C.; Wood, T.R.;Hermann, E.C.; Hoff mann, C.E. Antiviral activity of 1-adamantanamine (amantadine). Science1964,144,862–863.

[9]. Wendel, H.A.; Snyder, M.T.; Pell, S. Trial of amantadine in epidemic influenza. Clin. Pharmacol. Ther.1966,7,38–43.

[10]. Vernier, V.G.; Harmon, J.B.; Stump, J.M.; Lynes, T.E.; Marvel, J.P.; Smith, D.H. The toxicologic andpharmacologic properties of amantadine hydrochloride. Toxicol. Appl. Pharmacol.1969,15, 642–665.

[11]. Tilley, J.W.; Levitan, P.; Kramer, M.J. Adamantylthiourea derivatives as antiviral agents. J. Med. Chem.1979,22, 1009–1010.

[12]. Aigami, K.; Inamoto, Y.; Takaishi, N.; Hattori, K.; Takatsuki, A.; Tamura, G. Biologically activepolycycloalkanes. 1. Antiviral adamantane derivatives. J. Med. Chem. 1975,18, 713–721.

[13]. Basari´c, N.; Sohora, M.; Cindro, N.; Mlinari´c-Majerski, K.; De Clercq, E.; Balzarini, J. Antiproliferative andantiviral activity of three libraries of adamantane derivatives. Archiv Pharm.2014,347, 334–340.

[14]. Hassan, G.S.; El-Emam, A.A.; Gad, L.M.; Barghash, A.E.M. Synthesis, antimicrobial and antiviral testing ofsome new 1-adamantyl analogues. Saudi Pharm. J. 2010,18, 123–128.

[15]. Gökta¸s, F.; Vanderlinden, E.; Naesens, L.; Cesur, N.; Cesur, Z. Microwave assisted synthesis and anti-influenza virus activity of 1-adamantyl substituted N-(1-thia-4-azaspiro[4.5]decan-4-yl)carboxamide derivatives. Bioorg.Med. Chem. 2012,20, 7155–7159.

[16]. Al-Wahaibi, L.; Hassan, H.; Abo-Kamar, A.; Ghabbour, H.; El-Emam, A. Adamantane-Isothiourea HybridDerivatives: Synthesis, Characterization, In Vitro Antimicrobial, and In Vivo Hypoglycemic Activities.Molecules 2017,22, 710.

[17]. Al-Abdullah, E.; Al-Tuwaijri, H.; Hassan, H.; Al-Alshaikh, M.; Habib, E.; El-Emam, A. Synthesis, antimicrobial and hypoglycemic activities of novel N-(1-adamantyl) carbothioamide derivatives. Molecules2015,20,8125–8143.

[18]. Tabbi, A.; Tebbani, D.; Caporale, A.; Saturnino, C.; Nabavi, S.F.; Giuseppe, P.; Arra, C.; Canturk, Z.;Turan-Zitouni, G.; Merazig, H. New Adamantyl Chalcones: Synthesis, Antimicrobial and AnticancerActivities. Curr. Top. Med. Chem. 2017,17, 498–506.

[19]. Fesatidou, M.; Zagaliotis, P.; Camoutsis, C.; Petrou, A.; Eleftheriou, P.; Tratrat, C.; Haroun, M.; Geronikaki, A.;Ciric, A.; Sokovic, M. 5-Adamantan thiadiazole-based thiazolidinones as antimicrobial agents. Design,synthesis, molecular docking and evaluation. Bioorg. Med. Chem. 2018,26, 4664–4676.

[20]. El-Emam, A.A.; Al-Tamimi, A.M.S.; Al-Omar, M.A.; Alrashood, K.A.; Habib, E.E. Synthesis and antimicrobialactivity of novel 5-(1-adamantyl)-2-aminomethyl-4-substituted-1,2,4-triazoline-3-thiones. Eur. J. Med. Chem.2013,68, 96–102.

[21]. El-Emam, A.A.; Alrashood, K.A.; Al-Omar, M.A.; Al-Tamimi, A.M.S. Synthesis and antimicrobial activityof N'-heteroarylidene-1-

adamantylcarbohydrazides and (+/-)-2-(1-adamantyl)-4-acetyl-5-[5-(4-substitutedphenyl-3-isoxazolyl)]-1,3,4-oxadiazolines. Molecules 2012,17, 3475–3483.

[22]. Kadi, A.A.; Al-Abdullah, E.S.; Shehata, I.A.; Habib, E.E.; Ibrahim, T.M.; El-Emam, A.A. Synthesis,antimicrobial and anti-inflammatory activities of novel 5-(1-adamantyl)-1,3,4-thiadiazole derivatives. Eur. J.Med. Chem. 2010,45, 5006–5011.

[23]. H. Mohammad , A. S. Mayhoub , M. Cushman and M. N. Seleem , *J. Antibiot.*, 2015, **68** , 259 —266.

[24]. A. P. Magiorakos , A. Srinivasan , R. B. Carey , Y. Carmeli , M. E. Falagas , C. G. Giske and D. L. Paterson , *Clin. Microbiol. Infect.*, 2012, **18** , 268 —281.

[25]. K. P. Rakesh , C. S. Shantharam and H. M. Manukumar , *Bioorg. Chem.*, 2016, **68** , 1 — 8.

[26]. K. P. Rakesh , N. Darshini , S. L. Vidhya , Rajesha and N. Mallesha , *Med. Chem. Res.*, 2017, **26** , 1675 —1681.

[27]. S.-M. Wang , G.-F. Zha , K. P. Rakesh , N. Darshini , T. Shubhavathi , H. K. Vivek , N. Mallesha and H.-L. Qin , *MedChemComm*, 2017, **8** , 1173 —1189.

[28]. X. Chen , J. Leng , K. P. Rakesh , N. Darshini , T. Shubhavathi , H. K. Vivek , N. Mallesha and H.-L. Qin , *MedChemComm*, 2017, **8** , 1706 —1719.

[29]. K. P. Rakesh , R. Suhas , H. M. Manukumar , S. Chandan and D. C. Gowda , *Eurasian J. Anal. Chem*, 2015, **6** , 254 —260.

[30]. Yuvraj S. Malghe*1 , Varsha V. Thorat1 , Abhay S. Chowdhary2 and Anil S. Bobade2, Synthesis, characterization and biological activities of new bis-1,3,4-oxadiazoles. *Journal of Chemical and Pharmaceutical Research*, 2015, 7(6):392-398

[31]. Varsha V.Thorat, Chloramine T Mediated Synthesis Of 2-Substituted-5-(2'- Thiophene) -1, 3, 4-Oxadiazole Using Microwave Irradiation, IOSR Journal of Applied Chemistry (IOSR-JAC) e-ISSN: 2278-5736.Volume 7, Issue 11 Ver. I. (Nov. 2014), PP 46-48

[32]. IK Jassim; W Jassim; S Alsatar; A Mohammed, Karbala J. of Pharmaceutical Sciences, 2012, 3, 213-222

[33]. Pham, V. H., Phan, T. P. D., Phan, D. C., & Vu, B. D. (2019). Synthesis and Bioactivity of Hydrazide-Hydrazones with the 1-Adamantyl-Carbonyl Moiety. *Molecules*, *24*(21). https://doi.org/10.3390/molecules24214000

[34]. Malghe, Y.S.; Thorat, V.V.; Chowdhary, A.S.; Bobade, A.S, Patil, V.N, Tandem synthesis of thia-oxadiazolophanes. *Journal of Chemical and Pharmaceutical Research*, 2015, 7(5), 729-734.

[35]. Backes, G.L.; Neumann, D.M.; Jursic, B.S. Synthesis and antifungal activity of substituted salicylaldehydehydrazones, hydrazides and sulfohydrazides. Bioorg. Med. Chem.2014,22, 4629–4636.

[36]. Rupa Pawar., Dr. Jayshree Parikh, Synthesis, characterization and study of antibacterial activities of di-hydrazide- di-hydrazone derivatives of adamantly moiety containing halo group. International Journal of Science & Engineering Development Research (www.ijsdr.org), 2022, 7(4), 101 – 106.

Rupa Pawar, et. al. "Synthesis, characterization and study of anti-fungal activities of dihydrazide-dihydrazone derivatives of adamantly moiety containing nitro group." *International Journal of Engineering Research and Applications (IJERA)*, vol.12 (06), 2022, pp 48-55.