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RESEARCH ARTICLE OPEN ACCESS

Study of antifungal activities of dihydrazide- dihydrazone derivatives of adamantly moiety containing halo group

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ABSTRACT
In the present work, series of dihydrazone derivatives of adamantly moiety has been prepared by condensation of dihydrazide with different aldehydes and ketones to give the corresponding dihydrazone derivatives. The structure of newly synthesized compound is confirmed by FTIR, 1HNMR and elemental analysis.
The new synthesized compounds were tested for the activities against fungusCandida albicans. The results revealed that the compounds display potential antifungal activity against Candida albicans.
KEYWORDS: Adamantane, Dihydrazide, dihydrazone, antifungal activity, adamantly moiety. (done)

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I. INTRODUCTION

The drugs have been less effective due to frequent and unnecessary use of antibiotics. Theresistance to many antibiotics have led to the study and development of new antibiotics. Thedrugthatinhibitsthegrowthorkillsthemicroorganismsareantimicrobials.Amajorclinicalproblem is the antibiotic resistance which occurs when there is change in a waymicroorganisms reducetheeffectiveness ofdrugs.

Interest in the development of compounds with anti-inflammatory, analgesic, antidepressant,anticonvulsant, antiplatelet, antimalarial, antimicrobial, anti-mycobacterial, antiviral, antitumoral, vasodilator activities have attracted lots of research work in this area. Hydrazonespossesses an azometine –NHN=CH- proton which is an important constituent for new drugdevelopment for above mentioned biological activities. This is the reason hydrazonederivativesaresynthesizedand theirbiologicalactivities arestudied.

Hydrazide- hyrazone derivatives show a wide variety of biological activities likeantimicrobial [10-11, 34], antifungal, anti-tubercular [14-16], anti-cancer, mitigating, anticonvulsant, antiprotozoal and antiviral [17] [12-13] activities.

In the last two decades a carbonyl category of hydrazide-hydrazones with azomethine group (-NH-N=CH-) has become popularasit playsanimportantroleasanintermediate.

Hydrazone basic structure consists of two nitrogen (-NNH_2) atoms and one carbon (C=O)atom with C=N bond by conjugation of a lone pair of electrons of nitrogen. It shows bothelectrophilicas wellas nucleophilic properties.

Nitro furazone [36], nitro furantoin [37] and furazolidone are hydrazide-hydrazone that areusedas medicines.

To develop new potential drugs, adamantane derivatives play an important role inmedicine chemistry [17-20], due to their multiple bioactivities like anti-viral[21-25], antimicrobial[23, 26-32], anti-inflammation[33, 35].

Literature review disclose the great significance of the development of new compounds with dihydrazone derivatives. Dihydrazone derivatives exihibit exceptional feature towards the development of new therapeutic agents [1-9].

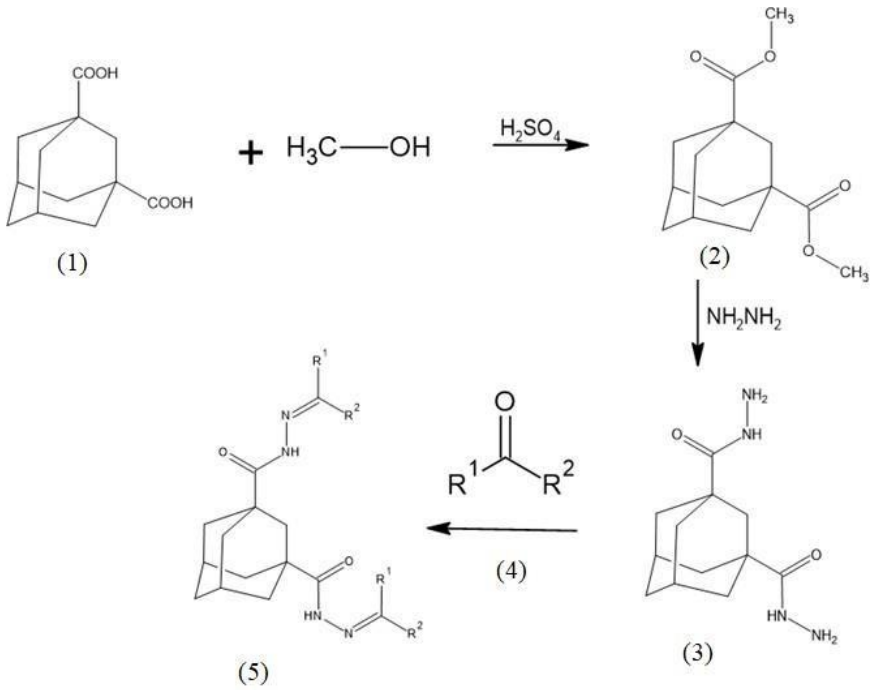
Dihydrazones and adamantane derivatives show promising biological activities which concludes that the combination of two moieties will be of potential value for the development of new therapeutic agents.

II. EXPERIMENTALSECTION

All reagents were received from commercial suppliers. Melting points (M.P.) of synthesizedcompoundswereconfirmed

byopencapillarytubemethod.All compoundsweretestedforFTIRspectra and elemental analysis. 1H NMR spectra were recorded using 600.1723046[MHz] NMRspectrophotometer. The chemical shifts were expressed in ppm and constants were given in Hzusing tetramethylsilane as the internal standard. For recording NMR spectra, DMSO-D6 wasusedas asolvent. Reference peak was at 2.5 ppm.

General reaction or preparation of final products is shown below:



General Scheme I

Figure1: Preparation of dihydrazide-dihydrazone derivatives of Adamantane from adamantane-1, 3-dicarboxylic acid

1. General procedure for synthesis of adamantane 1, 3 dicarbohydrazide

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 adamantanedicarboxylate. This di-ester was then reacted with 80% hydrazine hydrate to yield adamantane 1, 3 dicarbohydrazide.

1.1. Synthesis of dimethyl-1, 3 adamantanedicarboxylate 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 reaction mixture was cooled and then it was washed with H_2O. 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.

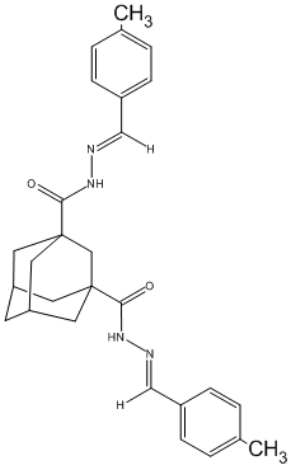
1.2. Synthesis of Adamantane-1, 3-dicarbohydrazide from dimethyl-1, 3 adamantanedicarboxylate:

To the alcoholic solution of (1.00924 g, 0.004 mol) dimethyl 1, 3 adamantane-dicarboxylate, (0.08mol) 80% hydrazine hydrate was added dropwise 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.

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

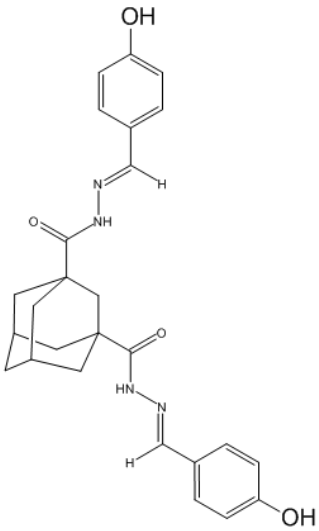
The condensation reaction of adamantane-1, 3-dicarbohydrazide with different aldehydes and ketones give the corresponding dihydrazone derivatives.

1) Bis [N'-(4-methyl)benzylidene]adamantane-1, 3-dicarbohydrazide: M.p.: 53 ◦C, Yield 60 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 9.9-8.65(1H, s, NH-N); 7-8.5 (Ar-H); 3.56 (=CH); 2.7 (-CH3); 1.62-2.00 (Adamantane-H).
Color of the compound is Light yellow
IR (ν cm-1): 1091 (N-N); 1245-1281 (C-N); 1511-1513 (C=C benzene); 1610 (C=N); 1726 (C=O); 2863 (N-H); 2921-2993 (C-H); 3430 (H-C=).
Elemental analysis: for C18H12N6O10 found (calculated): C, 73.63 (73.66); H, 7.06 (7.06); N, 12.25 (12.27) %.



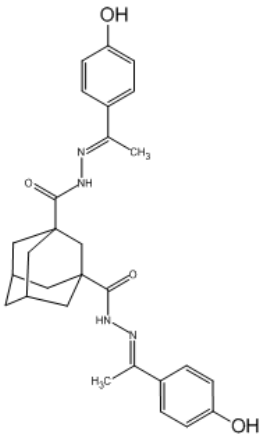
Bis[N'-(4-methyl)benzylidene]adamantane-1,3-dicarbohydrazide

2) Bis [N'-(4-hydroxy)benzylidene]adamantane-1, 3-dicarbohydrazide: M.p.: 160 ◦C, Yield 80.33 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 9.8(1H, s, NH-N); 8.55 (-OH attached to benzene); 3.35-3.6 (=CH); 6.84-7.77 (Ar-H); 1.62-2.08 (Adamantane-H).
Color of the compound is Light brown.
IR (ν cm-1): 1095 (N-N); 1285 (C-N); 1603 (C=N); 1727 (C=O); 2859 (N-H); 2946 (H-C=); 3168 (OH).
Analysis: for C26H28N4O4 found (calculated): C, 67.79 (67.81); H, 6.14 (6.13); N, 12.15 (12.17) %.



Bis[N'-(4-hydroxy)benzylidene]adamantane-1,3-dicarbohydrazide

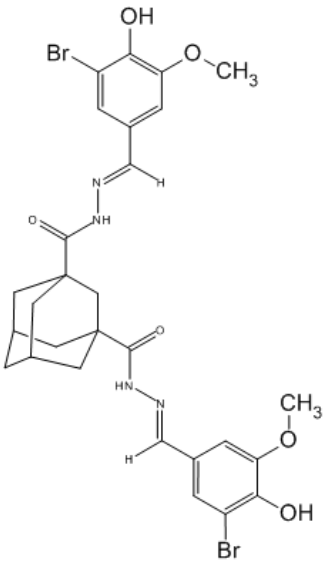
3) Bis [N'-(1-(4-hydroxy phenyl) ethylidene)]adamantane-1, 3-dicarbohydrazide: M.p.: 184 ◦C, Yield 83.96 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 10.34 (1H, s, NH-N); 8.3 (-OH attached to benzene); 3.35-3.6 (-CH3); 6.86-7.82 (Ar-H); 1.62-2.08 (Adamantane-H).
Color of the compound is Light Brown
IR (ν cm-1): 1095.06 (N-N); 1280 (C-N); 1511 (C=C benzene); 1604 (C=N); 1727 (C=O); 2859 (N-H); 2919-2994 (C-H); 3310 (-OH); 3429 (H-C=).
Analysis: for C28H32N4O4 found (calculated): C, 8.80 (68.83); H, 6.64 (6.60); N, 11.45 (11.47) %.



Bis[N'-(1-(4-hydroxyphenyl)ethylidene)]adamantane-1,3-dicarbohydrazide

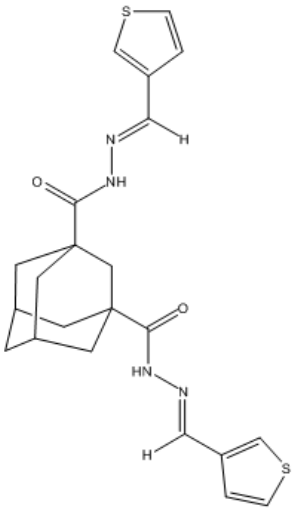
4) Bis [N'-(3-bromo, 4hydroxy, 5-methoxy)benzylidene]adamantane-1, 3-dicarbohydrazide: M.p.: 285 ◦C, Yield

77.47 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.7(1H, s, NH-N); 7.96-7.73 (Ar-H); 4.0 (-OH attached to benzene);); 3.955 (-OCH3); 3.4 (=CH); 1.62-2.08 (Adamantane-H).
Color of the compound is Dark yellow.
IR (ν cm-1): 611-644 (C-Br stretching); 1060 (N-N); 1271 (C-N); 1541 (C=C benzene); 1628 (C=N); 1697 (C=O); 2946 (N-H); 3083 (H-C=); 3209 (-OH).
Analysis: for C28H30N4Br2O6 found (calculated): C, 49.55 (49.57); H, 4.43 (4.46); N, 8.29 (8.26) %.



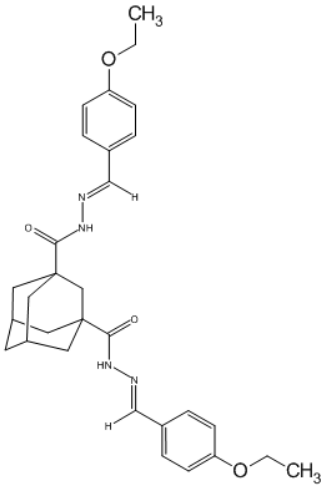
Bis[N'-(3-bromo,4hydroxy,5-methoxy)benzylidene]adamantane-1,3-dicarbohydrazide

5) Bis [N'-thiophene-2-yl)methylene]adamantane-1, 3-dicarbohydrazide: M.p.: 138 ◦C, Yield
55.67 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.9(1H, s, NH-N); 7.78-8.85 (thiophene ring -H); 3.38-3.59 (=CH); 1.62-2.00 (Adamantane-H).
Color of the compound is Dark brown.
IR (ν cm-1): 698 (C-S); 1027 (C=S); 1091 (N-N); 1281 (C-N); 1609 (C=N); 1725 (C=O); 2864 (N-H); 2921 (C-H); 3433 (H-C=).
Analysis: for C22H24N4O2S2 found (calculated): C, 60.01 (59.97); H, 5.52 (5.49); N, 12.70 (12.72) %.



Bis[N'-thiophene-2-yl)methylene]adamantane-1,3-dicarbohydrazide

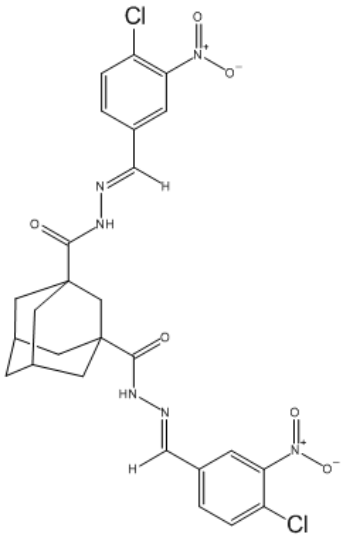
6) Bis [N'-(4-ethoxy)benzylidene]adamantane-1, 3-dicarbohydrazide: M.p.: 58 ◦C, Yield
85.99 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 9.85-8.65(1H, s, NH-N); 7-7.78 (Ar-H); 4.12-4.14 (-O-C2H5); 3.4-3.6 (=CH); 1.6-2.08 (Adamantane-H); 1.33-1.36 (-CH3).
Color of the compound is yellow.
IR (ν cm-1): 1097 (N-N); 1256-1396 (C-N); 1510-1453 (C=C benzene); 1601 (C=N); 1729 (C=O); 2859 (N-H); 2911-3074 (C-H); 3435 (H-C=).
Analysis: for C30H36N4O4 found (calculated): C, 69.76 (69.74); H, 7.01 (7.02); N, 10.82 (10.84) %.



Bis[N'-(4-ethoxy)benzylidene]adamantane-1,3-dicarbohydrazide

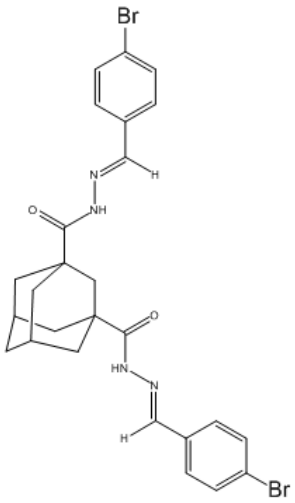
7) Bis [N'-(3-nitro, 4-chloro)benzylidene]adamantane-1, 3-dicarbohydrazide: M.p.: 258 ◦C, Yield

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 is 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) %.



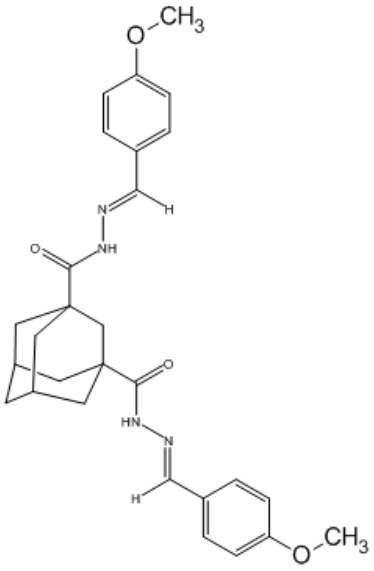
Bis[N'-(3-nitro,4-chloro)benzylidene]adamantane-1,3-dicarbohydrazide

8) Bis [N'-(4-bromo)benzylidene]adamantane-1, 3-dicarbohydrazide: M.p.: 228 ◦C, Yield 41.63 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.71(1H, s, NH-N); 772-7.84 (Ar-H); 3.35 (=CH); 1.62-2.00 (Adamantane-H).
Color of the compound is Light yellow.
IR (ν cm-1): 516-699 (C-Br stretching); 1007 (N-N); 1277 (C-N); 1582-1480 (C=C benzene); 1623 (C=N), 1703 (C=O); 2941 (N-H); 2995-3047 (C-H); 3434 (H-C=).
Analysis: for C26H26Br2N4O2 found (calculated): C, 53.24 (53.26); H, 4.45 (4.47); N, 9.53 (9.56) %.



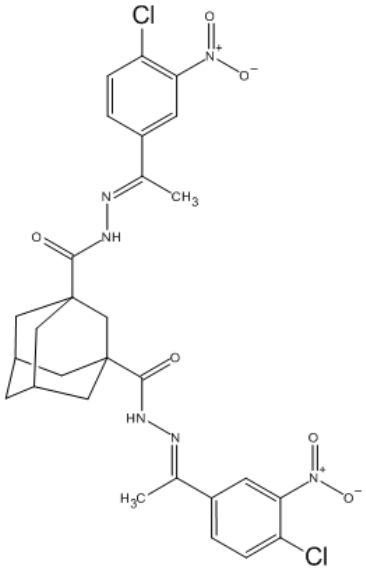
Bis[N'-(4-bromo)benzylidene]adamantane-1,3-dicarbohydrazide

9) Bis [N'-(4-methoxy)benzylidene]adamantane-1, 3-dicarbohydrazide: M.p.: 176 ◦C, Yield 40.95 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.63(1H, s, NH-N); 7.04-7.82 (Ar-H); 3.4 (=CH); 3.8 (-OCH3); 1.62-2.00 (Adamantane-H).
Color of the compound is Light yellow.
IR (ν cm-1): 1024 (N-N); 1166 (C-O); 1250 (C-N); 1507-1461 (C=C benzene); 1621 (C=N); 1658-1777 (C=O); 2986 (N-H); 2838-2967 (C-H); 3434 (H-C=).
Analysis: for C28H32N4O4 found (calculated): C, 8.85 (68.83); H, 6.58 (6.60); N, 11.44 (11.47) %.



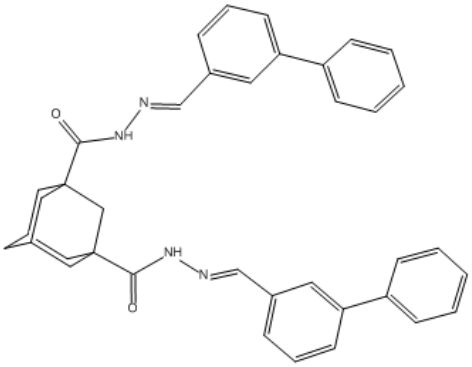
Bis[N'-(4-methoxys)benzylidene]adamantane-1,3-dicarbohydrazide

10) Bis [N'-(1-(3-nitro, 4-chloro)ethylidene)]adamantane-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 is 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) %.



Bis[N'-(1-(3-nitro,4-chloro)ethylidene)]adamantane-1,3-dicarbohydrazide

11) Bis [N'-(4-phenyl)benzylidene]adamantane-1, 3-dicarbohydrazide: M.p.: 151 ◦C, Yield 5.70 %. 1H-NMR (600 MHz, DMSO-d6, δ ppm): 8.8 (1H, s, NH-N); 7.42-8.3 (Ar-H); 3.4 (=CH); 1.62-2.00 (Adamantane-H).
Color of the compound is shiny yellow.
IR (ν cm-1): 1074 (N-N); 1179 (C=C benzene); 1223 (C-N); 1620 (C=N); 1726 (C=O); 2929 (N-H); 2993 (C-H); 3448 (H-C=).
Analysis: for C38H36N4O2 found (calculated): C, 78.61 (78.59); H, 6.2 (6.25); N, 9.63 (9.65) %.



Bis [N'-(4-phenyl)benzylidene]adamantane-1, 3-dicarbohydrazide

III. PHYSICAL PROPERTIES OF ALL THE COMPOUNDS

Serial no	Yield (%)	M.P	color	Molecular Wt	Molecular Formula
1	60	53	Light Yellow	456.57928	$C_{28}H_{32}N_4O_2$
2	80.33	160	Light Brown	460.52492	$C_{26}H_{28}N_4O_4$
3	83.96	184	Light Brown	488.57808	$C_{28}H_{32}N_4O_4$
4	77.47	285	Dark Yellow	678.369	$C_{28}H_{30}N_4Br_2O_6$
5	55.67	138	Dark Brown	440.58156	$C_{22}H_{24}N_4O_2S_2$
6	85.99	58	Yellow	516.63124	$C_{30}H_{36}N_4O_4$
7	75.84	258	Light Yellow	587.41136	$C_{26}H_{24}Cl_2N_6O_6$
8	41.63	228	Light Yellow	586.31824	$C_{26}H_{26}Br_2N_4O_2$
9	40.95	176	Light Yellow	488.57808	$C_{28}H_{32}N_4O_4$
10	66.25	178	Yellow to Orange	615.46452	$C_{28}H_{28}Cl_2N_6O_6$
11	5.70	151	ShinyYellow	580.71804	$C_{38}H_{36}N_4O_2$

Table2: Physical properties of all the compounds.

IV. ANTI-MICROBIALTEST

	Calbicans		
Sample Name	Inoculum Count	Final Count	%killing
1	6800000	0	100.00
2	6600000	0	100.00
3	6100000	0	100.00
4	6900000	0	100.00
5	7100000	0	100.00
6	5800000	0	100.00
7	6000000	0	100.00
8	6100000	0	100.00
9	6500000	0	100.00
10	6400000	0	100.00
11	6600000	0	100.00

Table3:Anti-microbialtest results of all the compounds(1-11).

All thesamples were found to be very effective against Candida albicans and had minimum killingpercentage of 100.

Anti-microbialtest(tube dilutionmethod):

1. Discription: powderysubstanceinclosedglass vials.
2. Organismused:

CandidaAlbicans(ATCC 10231)(Fungi)

3. Additional information

1	Methodfollowed	In-house tubedilutionmethod(USP)
2	Methodofsterilization	SteamSterilizationusingAutoclave
3	Contacttimefor sampleculture	3minutes
4	Controlsample	Initialinoculumcount(positivecontrol)
5	CFU	ColonyFormingUnits
6	Mediaused	Sabouraud'sDextroseAjar(Fungi)
7	SampleConcentration(Dilution)	50mgsamplein1mlofDMSO
8	IncubationTemperature&Time	INCUBATIONA420"CTO25CFORFUNGIFOR3-5DAYS.

V. CONCLUSIONS

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

The synthesized compounds were established for their antifungal activities.Synthesized compounds possesses excellent antifungal activity. The screening results revealed that all compounds exhibit hundred percent antifungal activity.

It can be concluded that dihydrazidedihydrazone derivatives of Adamantyl moiety holds promising future with excellent pharmacological properties.

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