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Synthesis, Antibacterial and Antifungal Activity of N'-(3-Hydroxy-4-Methoxy Benzylidene) Adamantane-1-Carbohydrazide (IVAC) and Its Isomers

D. D. Parab*, H. K. Kohli

Department of Chemistry, G. N. Khalsa College of Arts, Science & Commerce, (Autonomous), Matunga, Mumbai-400019, Mumbai University, Maharashtra, India

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Abstract

Novel 1-adamantyl derivatives were designed, synthesized and evaluated for anti-bacterial activity against Gram-negative bacteria, *Escherichia coli*, Gram-positive bacteria, *Staphylococcus aureus, Bacillus subtilis* and for antifungal activity against pathogen *Candida albicans*. The screening results indicated that the synthesised compounds N'-(3-hydroxy-4-methoxy benzylidene) adamantane-1-carbohydrazide (IVAC) and its isomers exhibited substantial antibacterial and antifungal properties when compared with known drug Ampicillin. The Minimum inhibitory concentration, MIC value obtained was less than 1.95 µg/mL. The structural features of IVAC and its isomers were confirmed by ^{1}H-NMR, FTIR, and elemental analysis.

Keywords: Adamantane-1-carbohydrazide; Hydrazide-hydrazone; Isovanillin; Antibacterial; Antifungal.

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1. Introduction

Adamantane was identified in 1933 in Hodonin, Czechoslovakia, and was obtained from crude oil. The exploration of this ring opened new avenues in chemistry, involving drug development. The adamantane ring was subsequently modified with various substituents, leading to a range of biological activities [1]. Drugs containing adamantane ring display remarkable clinical efficacy. In the 1960s, amantadine, the first adamantane derivative, was discovered to have antiviral activity. Many studies have been done on these derivatives in hope of finding new compounds with biological activities. Few drugs that have adamantane ring are amantadine, rimantadine, memantine, tromantadine and saxagliptin.

Adamantane is a weakly functional hydrocarbon employed in the development of new drug molecules. A key area of research focus is the advancement of novel adamantane based drug molecules with enhanced pharmacokinetic and pharmacodynamic properties [2]. The adamantyl moiety is well established as a crucial pharmacophore in biologically active compounds. Incorporating the adamantyl core into molecules can significantly influence their

* *Corresponding author*: deepa.parab@gnkhalsa.edu.in

lipophilicity, pharmacological, and biological properties [3]. Therefore, adamantane can effectively modify the therapeutic index of parent structures, making it widely utilized for diverse therapeutic applications.

Adamantane derivatives have been shown to interact with various enzymes and exhibit a range of therapeutic activities [4] such as anti-viral e.g. Tromatadine [5,6] and anti-proliferative activities [7]. Adapalene, used in acne vulgaris therapy, which features adamantane in its core structure along with naphthalene derivatives, provides it with relatively high lipophilicity.

To date, many adamantane based compounds with notable biological activities have been synthesized. The review by Lamoureux and Artavia [8] covers a wide range of substances containing an adamantane structure with pronounced biological effects like antiviral [9], antibacterial [10], antimycotic, trypanocidal [11], anti-inflammatory, analgesic, antiulcer, antidepressant, anxiolytic, anticonvulsant, antiparkinsonian, neuroleptic, immuno stimulant, antitumor [12], hypoglycemic, dilating cerebral vessels, antihypertensive, antioxidant [13] etc.

Warda *et al*. provided updated information on the creation and biological effects of novel adamantane containing thiazole compounds [14].

Hydrazones are extensively researched due to their simple synthesis, wide availability and variety. Many hydrazones exhibit inhibitory activities against enzymes [15]. Various hydrazones have demonstrated potent antimicrobial, anti-inflammatory, and antifungal properties [16,17].

Hydrazide hydrazone derivatives have an azomethine linkage bonded to an amide group (-CH=N-NH-CO-), which has a crucial role in pharmacological activities. Hydrazide–hydrazone derivatives have been found to have biological activity, such as antimicrobial [18, 19], antituberculosis [20,21], and anticancer [22] drugs.

The synthesis and carbonic anhydrase activity of adamantane hydrazide-hydrazones were reported by Wassel and his team [23]. Adamantane hydrazone with a pentyl moiety demonstrated good inhibition activity and exhibited favorable pharmacokinetic properties. Pham and his team conducted studies on both the carbonic anhydrase along with antimicrobial activities of adamantane hydrazone derivatives [24].

The recent paper on novel Adamantane derivatives brings light on similar in vitro antimicrobial activity against a number of gram-positive and gram-negative bacterial strains and towards fungi from *Candida spp* [25].

Therefore, combining the hydrazide-hydrazone and adamantane moieties can create novel compounds with excellent biological activities. This research paper is focused on the bactericidal and fungicidal activities of hydrazide-hydrazone derivatives containing adamantane moiety. On the light of foregoing, we have designed and synthesized adamantane hydrazide-hydrazone derivative of isomers of vanillin namely, isovanillin, (IVAC), orthovanillin (OVAC) and 4-methoxy salicyladheyde (4MSAC). The synthesized compounds were assessed for its in vitro antibacterial and antifungal properties. The minimum inhibitory concentration (MIC) was identified as the smallest concentration at which no growth was observed.

2. Materials and Methods

2.1. *Methodology*

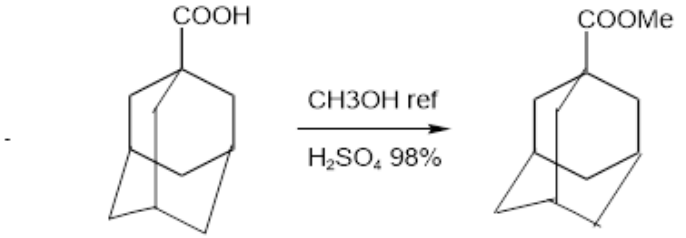
Chemicals were sourced from SBL, Loba Chemie, and Ottokemi. The structural verification of adamantane-based derivative was done using FTIR and NMR spectroscopy. FTIR was obtained using the KBr pellet technique on a Bruker 3000 Hyperion Microscope paired with a Vertex 80 FTIR system (Germany). ^{1}H NMR spectra were acquired in deuterated dimethyl sulfoxide (DMSO-d6) at 600 MHz with a JEOL ECZR Series 600 mega Hertz NMR Spectrometer (Japan), using TMS as an internal standard, and chemical shifts are recorded in δ ppm. Elemental analysis was conducted using Thermo Fisher Scientific Flash Smart V CHNS/O analyzer. Antimicrobial activity was evaluated with INT Microtitre Assay 96 well Plate method using Luria Bertani (LB) broth, Miller.

2.2. *Experimental*

2.2.1. *Synthesis of methyl adamantane-1-carboxylate (2)*

To synthesize methyl adamantane-1-carboxylate (2), 5 g (27 mmol) of adamantane-1-carboxylic acid (1) was mixed with 50 cm^3 of methanol (1235 mmol) and 9.2 g of 98 % sulphuric acid (5.11 cm^3). This mixture was stirred and heated with reflux for 4 h. After this, the mixture was neutralized to pH 7–8 using a 10 % aqueous sodium bicarbonate ($NaHCO_3$) solution. The solution was then cooled to room temperature. Following this, 200 cm^3 of ice and water was added, and then subjected to recrystallization with absolute ethanol yielding 4.92 g of white, needle-shaped crystals of methyl adamantane-1-carboxylate with an 88.2 % yield.

The melting point of the final product was determined to be 37 °C. The compound was identified by comparing its m. p. with the published value [26].



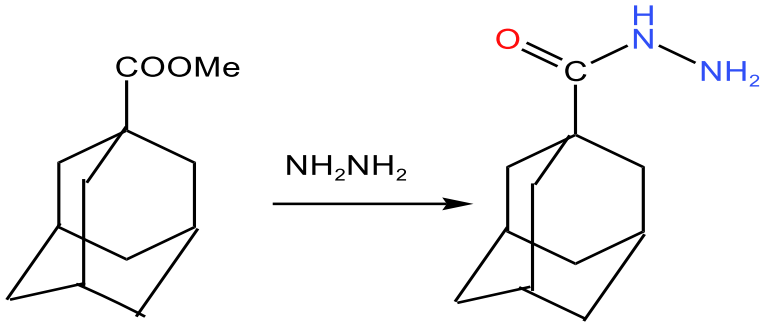
Adamantane-1-carboxylic acid Methyl Adamantane-1-Carboxylate

Scheme 1. Synthesis of methyl adamantane-1-carboxylate.

2.2.2. *Synthesis of adamantane-1-carbohydrazide (3)*

4 g (20 mmol) of compound (2) and 25 cm^3 (412 mmol) of 80 % hydrazine hydrate solution in 18 cm^3 of ethanol was refluxed for 15 h. Upon completion, 200 cm^3 of ice-cold water

was added in the reaction. The formed precipitate was than filtered and given washings with ice water, and dried to yield 3.82 g of an opalescent, scaly solid identified as adamantane-1-carbohydrazide, with an 88.99 % yield. Melting point observed was 148 °C.



Methyl adamantane-1-carboxylate Adamantane-1-carbohydrazide

Scheme 2. Synthesis of adamantane-1-carbohydrazide.

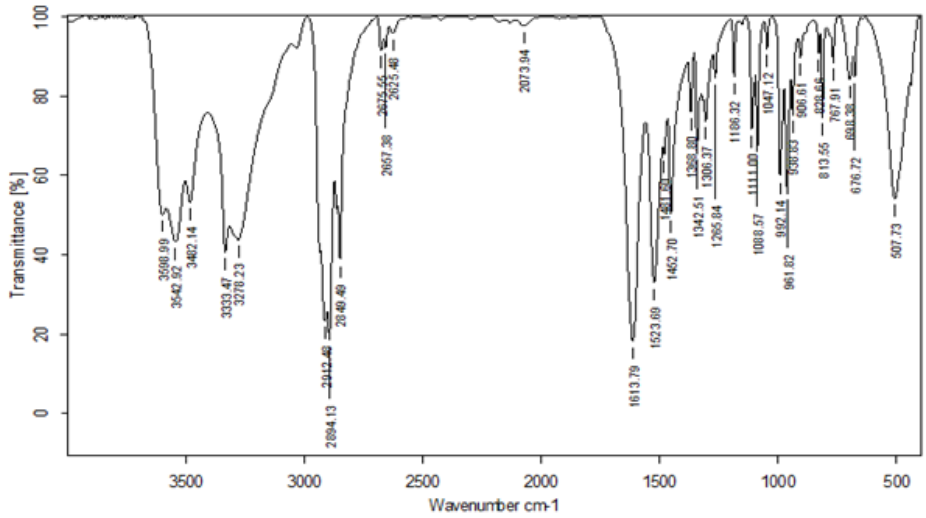


Fig. 1. FTIR spectra of adamantane-1-carbohydrazide

FTIR υ_{max} (cm^{-1}): 3332.47, 3278.23 (N-H), 2912.48, 2894.13, 2849.49 (C-H), 1613.79 (C=O), 1523.69 (N-H), 1452.70, 1368.80 (C-H) [26,27].

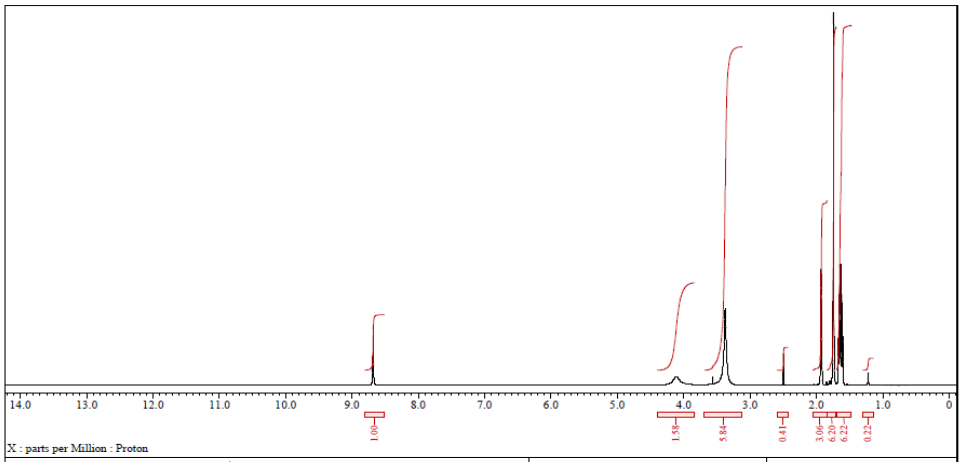
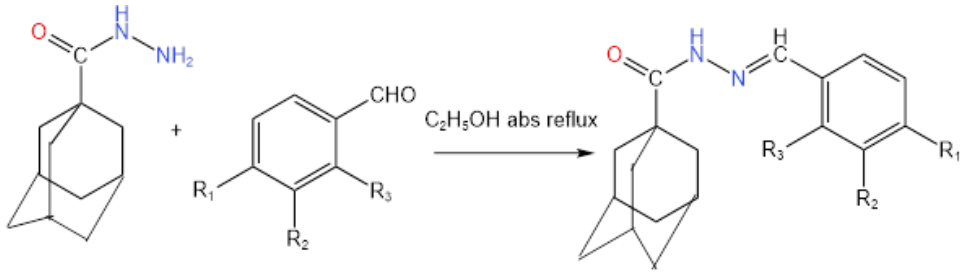


Fig. 2. NMR spectra of adamantane-1-carbohydrazide.

^{1}H NMR (600 MHz, DMSO-d_6, δ ppm): 1.93 (3H, adamantane), 1.74 (6H, adamantane), 1.63 (6H, adamantane), 4.12 (2H, -NH_2), 8.68 (H, NH-C) [26,27].

2.2.3. *Synthesis of* adamantane hydrazide-hydrazones *(a-c)*



Adamantane-1-carbohydrazide aldehyde a-c

(**a**) N'-(3-hydroxy-4-methoxy benzylidene) adamantane-1-carbohydrazide IVAC: R_1=OCH_3, R_2=OH, R_3=H; (**b**) N'-(2-hydroxy-3-methoxy benzylidene) adamantane-1-carbohydrazide OVAC: R_1=H, R_2=OCH_3, R_3=OH; (**c**) N'-(2-hydroxy-4-methoxy benzylidene) adamantane-1-carbohydrazide 4MSAC:R_1=OCH_3, R_2=H, R_3=OH

Scheme 3. Synthesis of hydrazide-hydrazone.

(a) N'-(3-hydroxy-4-methoxy benzylidene) adamantane-1-carbohydrazide (IVAC): A combination of 2 mmol of adamantane-1-carbohydrazide (3) and 2 mmol of isovanillin in 15 cm^3 of ethanol was kept on stirring and refluxing for 4 h. After the reaction was complete, the solvent was evaporated. The mixture was allowed to crystallize at 0–5 °C. The resulting crystals were filtered and given washings with ethanol, and air-dried, yielding IVAC with an 89.94 % yield. The melting point was determined to be 205 °C. Elemental analysis CHN:

Found (Calculated): C, 69.596 (69.51); H, 7.230 (7.32); N, 8.261 (8.54) The Molecular formula was confirmed as $C_{19}H_{24}O_3N_2$, and Molecular wt. as 328 g/mol. FTIR υ_{max} cm^{-1}: 3527.32, 3452.15 (O-H), 3232.23, 3279.52 (N-H), 3060.65 (C-H aromatic), 2902.84, 2848.82 (C-H aliphatic), 1647.01 (C=O), 1607.94 (C=N), 1547.20 (N-H), 1439.94, 1342.24 (C-H). ^{1}H NMR (600 MHz, DMSO-d_6, δ ppm): 1.99 (3H, adamantane), 1.85 (6H, adamantane), 1.69 (6H, adamantane), 3.79 (3H, OCH_3), 7.18, 6.97, 6.94 (3H, Ar-H), 8.22 (H, -N=CH), 9.27 (H, -NH-C), 10.59 (H, -OH).

(b) N'-(2-hydroxy-3-methoxy benzylidene) adamantane-1-carbohydrazide (OVAC): A combination of 2 mmol of adamantane-1-carbohydrazide (3) and 2 mmol of orthovanillin in 15 cm^3 of ethanol was kept on stirring and refluxing for 4 h. After the reaction was complete, the solvent was evaporated. The mixture was allowed to crystallize at 0–5 °C. The resulting crystals were filtered and given washings with ethanol, and air-dried, yielding OVAC with an 88.99 % yield. The melting point was determined to be 155 °C. Elemental analysis CHN: Found (calculated): Found (calculated): C, 69.584 (69.51); H, 7.330 (7.32); N, 8.521 (8.54) The molecular formula was confirmed as $C_{19}H_{24}O_3N_2$, and molecular wt. as 328 g/mol. FTIR υ_{max} cm^{-1}: 3455.68 (O-H), 3316.18 (N-H), 2906.77, 2874 (C-H), 1655.69 (C=O), 1544.25 (C=N), 1519 (N-H), 1452.91, 1408.24, 1382.35 (C-H). ^{1}H NMR (600 MHz, DMSO-d_6, δ ppm): 1.99 (3H, adamantane), 1.85 (6H, adamantane), 1.70 (6H, adamantane), 3.80 (3H, OCH_3), 7.24, 6.99, 6.81 (3H, Ar-H), 8.26 (H, -N=CH), 9.48 (H, -NH-C), 10.59 (H, -OH).

(c) N'-(2-hydroxy-4-methoxy benzylidene) adamantane-1-carbohydrazide (4MSAC): A combination of 2 mmol of adamantane-1-carbohydrazide (3) and 2 mmol of 4-methoxy salicyladehyde in 15 cm^3 of ethanol was kept on stirring and refluxing for 4 h. After the reaction was complete, the solvent was evaporated. The mixture was allowed to crystallize at 0–5 °C. The resulting crystals were filtered and given washings with ethanol, and air-dried, yielding 4MSAC with an 82.02 % yield. The melting point was determined to be 150 °C. Elemental analysis CHN: Found (calculated): C, 69.423 (69.51); H, 7.430 (7.32); N, 8.335 (8.54) The molecular formula was confirmed as $C_{19}H_{24}O_3N_2$, and molecular wt. as 328 g/mol. FTIR υ_{max} cm^{-1}: 3459.94 (O-H), 3320.62 (N-H), 2907.66, 2854 (C-H aliphatic), 1657.63 (C=O), 1622 (C=N), 1545 (N-H), 1451.46, 1387.59 (C-H). ^{1}H NMR (600 MHz, DMSO-d_6, δ ppm): 1.99 (3H, adamantane), 1.85 (6H, adamantane), 1.69 (6H, adamantane), 4.03 (3H, OCH_3), 7.22, 6.99, 6.81 (3H, Ar-H), 8.24 (H, -N=CH), 9.40 (H, -NH-C), 10.59 (H, -OH).

3. Antimicrobial Study

Antimicrobial activity was carried using the INT microtiter assay with flat-bottom 96-well plates. To test for in vitro inhibition of growth against reference strains of Gram-positive bacteria, namely *Bacillus subtilis* NCMI 64, *Staphylococcus aureus* MTCC 741, and one Gram-negative bacteria, *Escherichia coli* MTCC 443 and infectious fungus, *Candida*

albicans MTCC 3017 were used. The screening involved the use of INTMicro titre Assay 96-well plate method, employing LB broth, Miller. The antibiotic Ampicillin served as the positive control.

3.1. *Inoculum preparation*

A small loop of cultures was seeded in suitable broth was cultivated for 24 h. The culture optical density (OD) was adjusted to the 0.5 McFarland standard to achieve a concentration of 1.5 x 10^8 CFU/mL.

3.2. *Minimum inhibitory concentration*

The MIC of the newly synthesized samples against the test organisms was found using resazurin microplate assay. It was determined using 96-well clear microtiter plates with a flat bottom. 10 mg of samples were mixed in10 mL of DMSO making 1000 ppm solution of each sample. Samples were diluted two-fold up to ten times. Samples used were in concentration of 1000, 500, 250, 125, 62.5, 31.25, 15.62, 7.81, 3.91 and 1.95 µg/mL respectively. Final concentrations were ranging from 1:1 to 1:256 dilutions with 1 x 10^6 CFU/mL. All the wells were mixed thoroughly. The microplates were covered with a lid and maintained at 37 °C for 24 h. The MIC of the samples was determined by mixing 20 µL of a 2 mg/mL INT dye to all wells and incubating the plates at 37 °C for half an hour. Microbial growth was assessed by noting the color change of the INT dye in the microplate wells. The *p*-iodonitrotetrazolium chloride dye was employed, with a pinkish-red color indicating growth and a colorless or greenish tinge signifying no growth. The MIC is defined as the lowest concentration of the sample at which no color change was observed, indicating complete inhibition of bacterial growth. No growth was observed for all the four test cultures up to a dilution of less than 1.95 µg/mL, as found by the MIC assay.

4. Results and Discussion

The structure of hydrazones was verified by elemental analysis, FTIR and ^{1}H NMR. The formation of hydrazone structure was proved with IR studies; following the existence of hydrazide C=O and azomethine –CH=N- peak in IR spectra.

^{1}H NMR spectra also proved the formation of hydrazide. ^{1}H NMR signals from the adamantane moiety appeared in the range of δ 1.69–1.99 ppm. The aromatic protons appeared as expected in the range of δ 6.81–7.24 ppm. The signal from the methyne proton (CH=N) as a singlet was observed around δ 8.22-8.26 ppm, whereas that of the amide proton resonated as a singlet around δ 9.27-9.48 ppm. The –OH proton appeared at δ 10.59 ppm, whereas the –OCH_3 protons appeared at around δ 3.79-4.03 ppm. All spectra were in full agreement with the proposed structure.

The dilutions inhibit the growth of test strains. No growth was detected in any test

cultures up to a dilution of 1.95 µg/mL, as established by the MIC assay. Concerning the structure-antimicrobial activity relationship of the synthesized compounds, inhibition enhanced because of presence of -OH group. The inhibition demonstrated positive outcomes while possessing substituent of $-OCH_3$ on the benzyl ring. The antimicrobial profile of IVAC and its isomer reveal that the compounds exhibited excellent bactericidal and fungicidal property.

5. Conclusion

The synthesis and characterization of new hydrazone of isomers of vanillin with Adamantane -1-carbohydrazide was achieved. The chemical structure which includes the adamantane group discussed here, demonstrated strong bactericidal and fungicidal activity. The lipophilic and rigid nature of adamantane facilitates the creation of molecules that can disrupt microbial membranes or inhibit crucial enzymes. According to the latest research, derivatives of adamantane are reported to influence the biofilm formation of methicillin-resistant *S. aureus*, and their antimicrobial activity may be attributed to membranotropic activity. Although, these compounds are strong candidates for the formation of new antimicrobial agents, further studies such as mechanism determination, should be undertaken.

Acknowledgment

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Supplementary File

IR and NMR SPECTRA

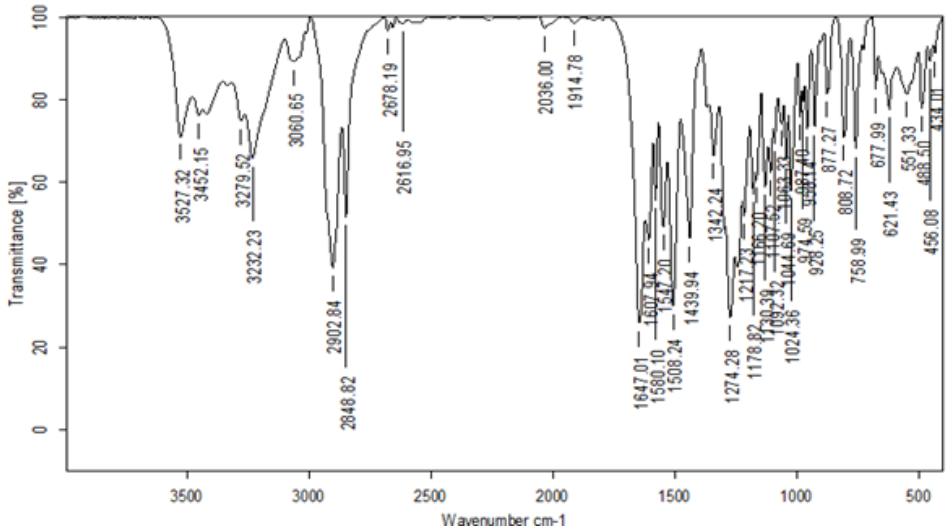

Fig. S1. FTIR spectrum of (a) N'-(3-hydroxy-4-methoxy benzylidene) adamantane-1-carbohydrazide (IVAC).

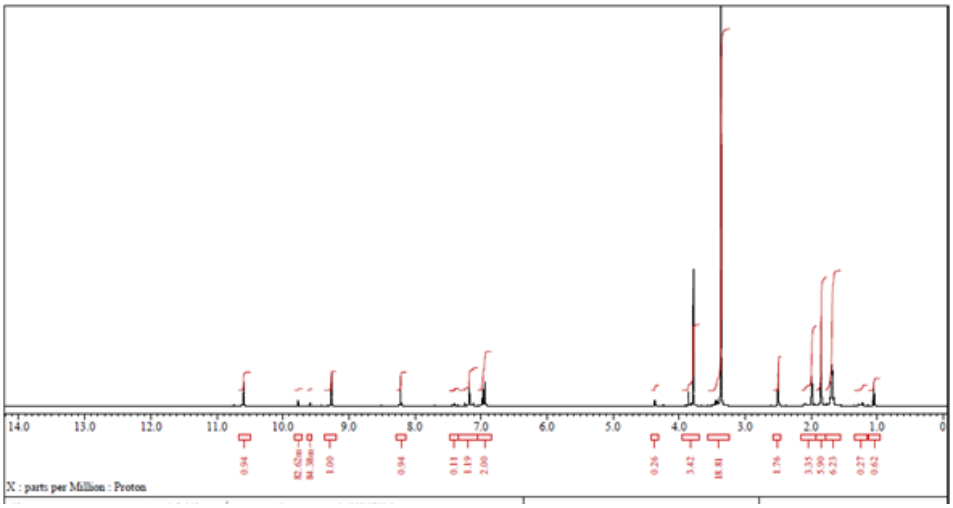

Fig. S2. ^{1}H NMR spectrum (a) N'-(3-hydroxy-4-methoxy benzylidene) adamantane-1-carbohydrazide (IVAC).

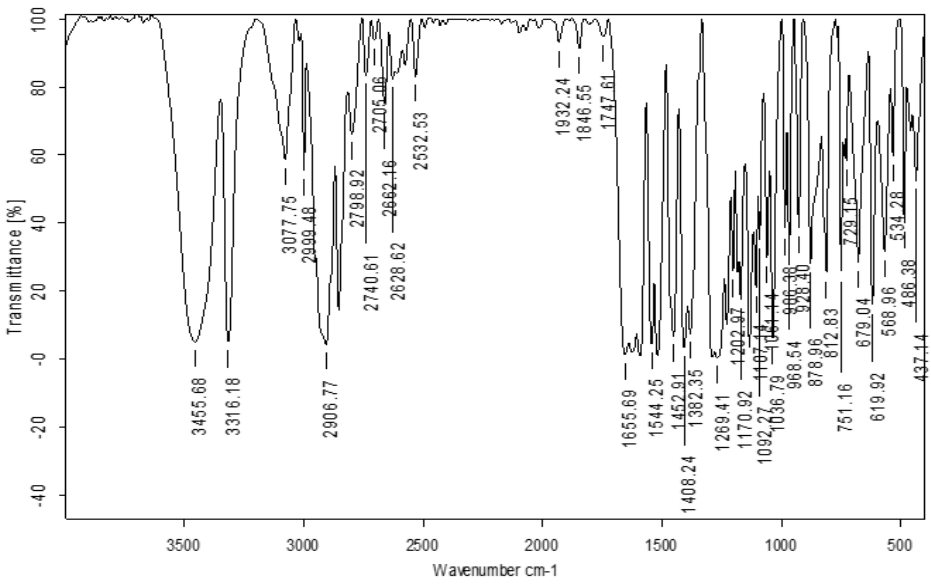

Fig. S3. FTIR spectrum of (b) N'-(2-hydroxy-3-methoxy benzylidene) adamantane-1-carbohydrazide (OVAC).

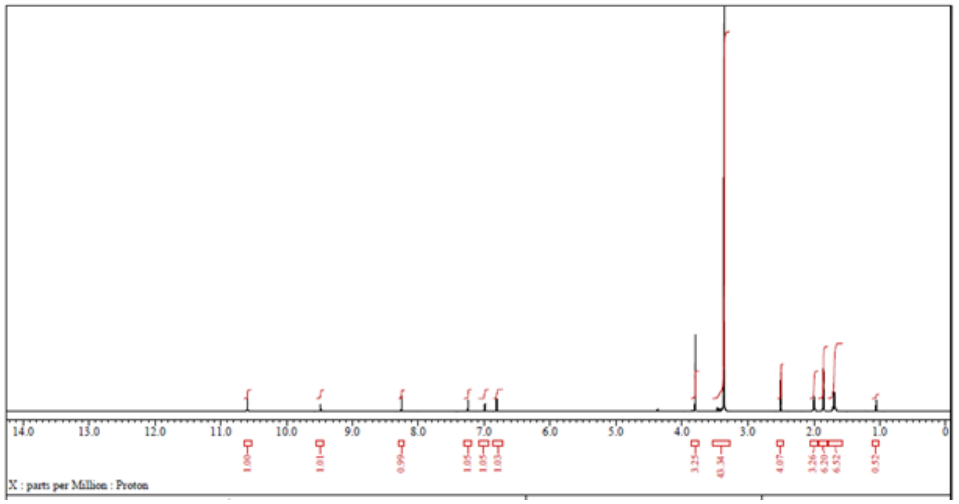

Fig. S4. ^{1}H NMR spectrum of (b) N'-(2-hydroxy-3-methoxy benzylidene) adamantane-1-carbohydrazide (OVAC).

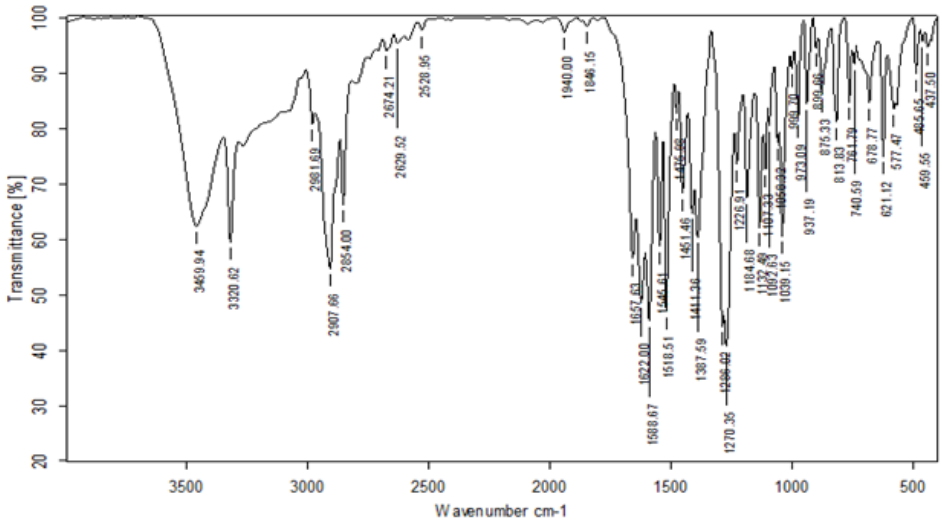

Fig. S5. FTIR spectrum of (c) N'-(2-hydroxy-4-methoxy benzylidene) adamantane-1-carbohydrazide (4MSAC).

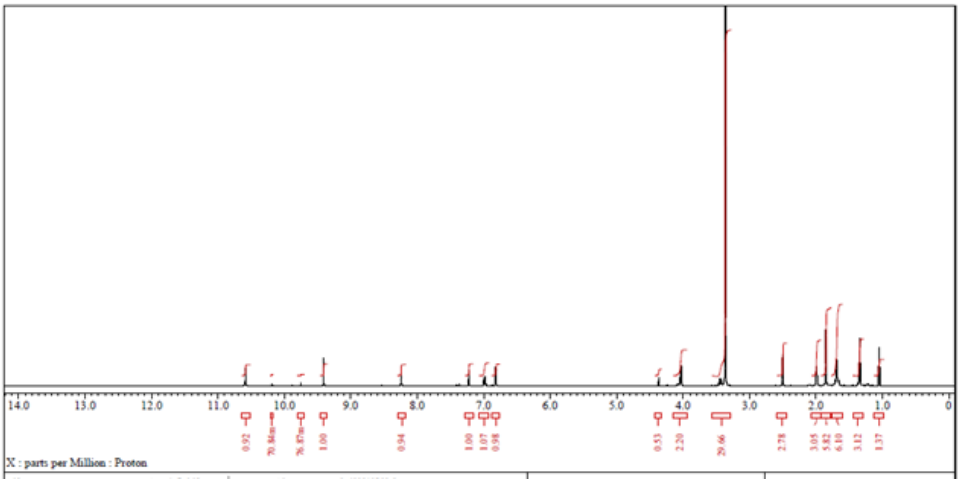

Fig. S6. [1]H NMR spectrum of (c)N'-(2-hydroxy-4-methoxy benzylidene)adamantane-1-carbohydrazide (4MSAC).

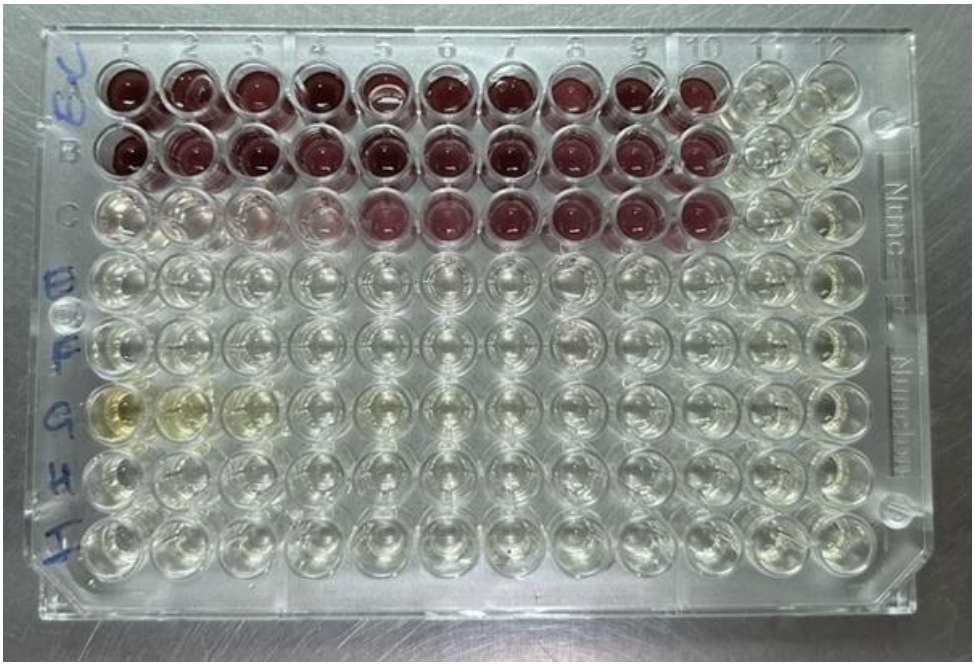

Fig. S7. MIC of samples IVAC (a), OVAC (b), 4MSAC (c) with *Escherichia coli* culture.

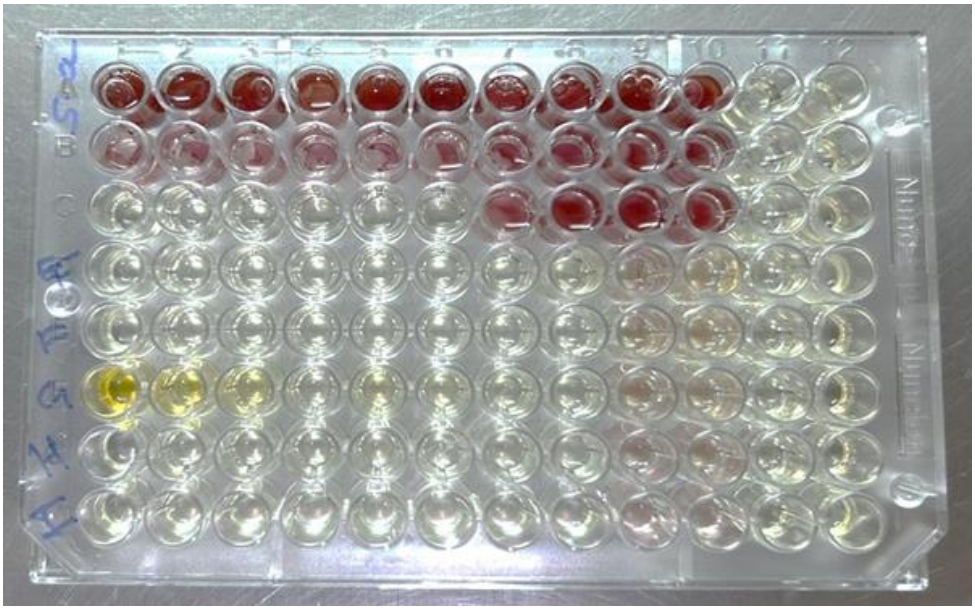

Fig. S8. MIC of samples IVAC (a), OVAC (b), 4MSAC (c) with *Staphylococcus aureus* culture.

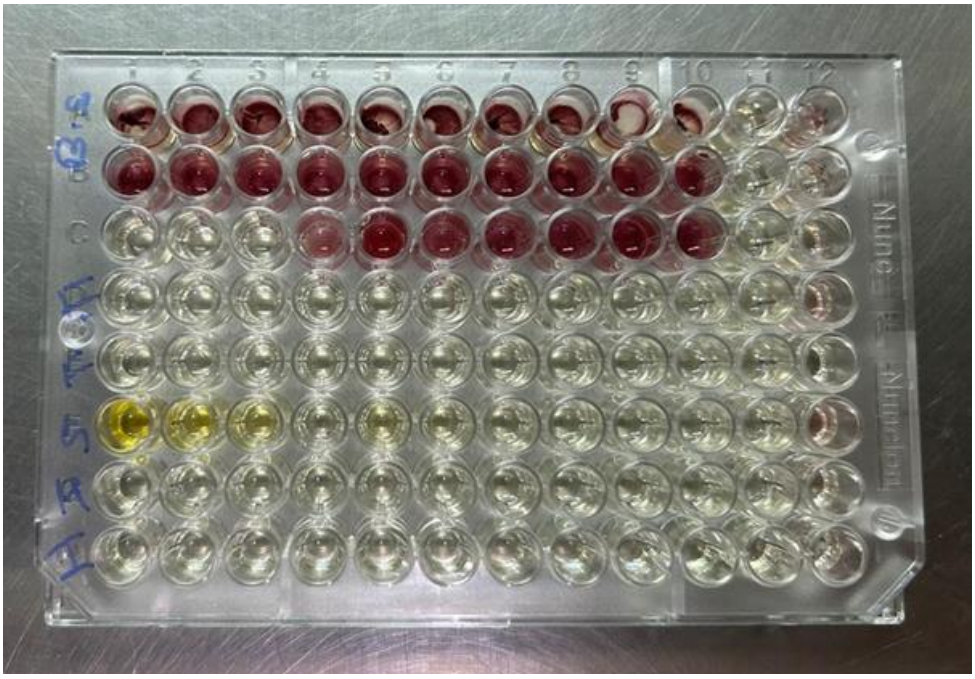

Fig. S9. MIC of samples I VAC(a), OVAC(b), 4 MSAC (c) with *Bacillus subtilis* culture.

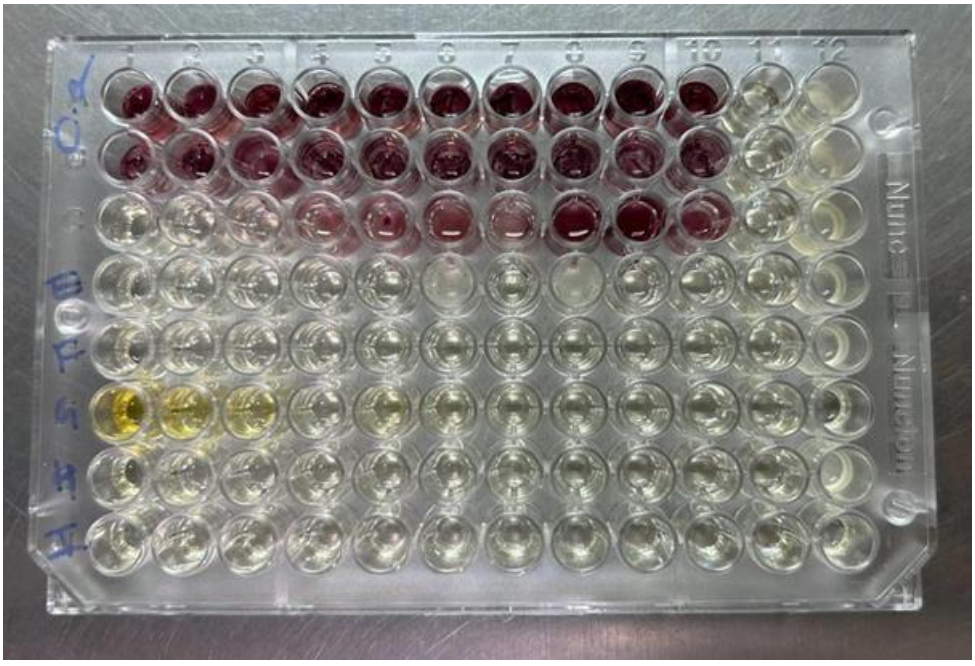

Fig. S10. MIC of samples I VAC(a), OVAC(b), 4 MSAC (c) with *Candida albicans culture.*