Egypt. J. Chem. **Vol. 65,** No. 2 pp. 449 - 457 (2022)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Preparation, Spectral Characterization, Thermal Study, and Antifungal Assay of (Formazane -Mefenamic acid)– Derivatives

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Abstract

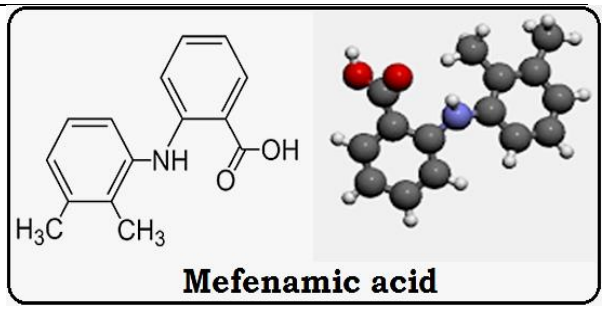
Postane Fortis a well-known pharmaceutical drug that has several medicinal uses and has entered into several chemical reactions in order to increase its biological effectiveness, in this work Postane Fort was linked with formazan to increase its pharmacological effectiveness as an antifungal – microbial via various reactions like condensation of anil compounds ,then coupling steps with imine group in other donating compounds, then linking two active groups to formation new drugs represented by Mefnamic-Formazan or Postan-Formazan. Numerus of Postane Fort (drug) derivatives were prepared as a new organic compounds via several chemical reactions like. All organic reactions and all formatted compounds had been monitored through (FT IR-Spectra , 1H.NMR-Spectra, Mass-Spectra)., Melting points, other studies represented by (Thermal investigation, antifungal Evaluation)., all created ponstan derivatives appeared good antifungi activity because their strctures that involved formazan group (N=N-C=N-) linked with some heterocyclic ring like thiadiazole and other types of cycles.

Keywords: Mefnamic acid, Thiadiazole, Formazane, Imine, Schiff base, Azo, antifungal

1.Introduction

Ponstan drug is Trade name of Mefnamic acid also take orally[1,2] . Ponstan drug reduces patient contractions, with a technique that is important. However, it is via to be associated to prostaglandin reticence [3-7]. Scientific name (2-[(2,6-dichloro-3-methylphenyl) amino]benzoic acid),its formula ($C_{14}H_{11}Cl_2NO_2$)., Mechanism of action[8-12] Hepatic metabolism plays an important role in the elimination of ponstan fort , immunocompromised patients could stand prearranged subordinate measures.

Formazane compounds have a great applications in different fields owed to the presence of hetero atoms in their structures[13-19], azo and imine groups (-N=N-C=N) interconnected with conjugated system, and atoms with high electron convexity, the reason for their gaining importance[21-30] in the chemistry of ligands and complexes in coordination chemistry[31-34], also in the field of biological applications[35-44] as anti-cancer materials, antifungal, malaria and many other applications[45-50].



EXPERIMENTAL PART :

All melting points were uncorrected and measured on an electro-thermal apparatus (Switzerland) in an open capillary tube. FT.IR spectra were recorded on Fourier transform infrared spectrometer (FT-IR) in(FT-IR-3600) infrared spectrometer via employing KBr Pellet technique., 1H.NMR spectra were recorded in DMSO-d6 as solvent using (TMS) as internal standard and chemical shifts are expressed as (δ ppm)., also Mass– Spectra for some of them other studies characterized by (Thermal investigation, antifungal Evaluation).

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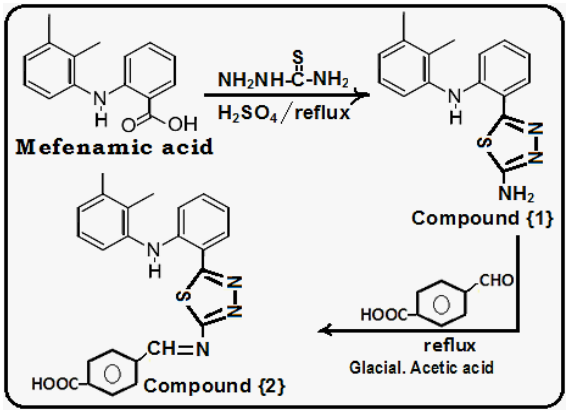
Receive Date: 01 August 2021, Revise Date: 04 August 2021, Accept Date: 08 August 2021

DOI: 10.21608/EJCHEM.2021.88727.4266

Preparation Paths[4-8] :

Preparation of Ponstan Derivatives {1 , 2 }:

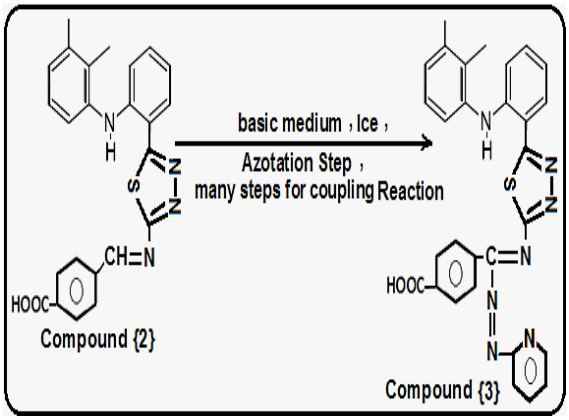
Ponstan Fort(0.01 mole) was reacted with thiosemicarbazide (0.01 mole) with refluxing for (19 hrs) in presence of sulfuric acid to formation amine-thiadiazole Ponstan (Mefnamic –Formazan) which acts compound {1} ,then (0.01 mole) from it reacts with (0.01 mole) from P-carboxybenzaldehyde in presence of drops (glacial acetic acid) in condensation step for (3 hrs) in absolute ethanol to yield Imine-Mefnamic derivative represented by compound {2} according to procedures[4-8], the product filtered ,dried , recrystallized to yield Imine-mefnamic derivative that acts (ponstan derivative).



Scheme 1: Preparation of Ponstane Derivatives {1,2}

Preparation of Ponstan Derivative {3}:

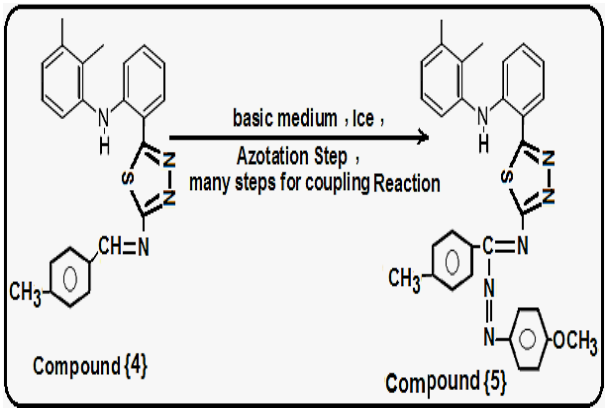
Aminopyridine (0.01 mole) was reacted in many steps represented by azotation, then with (0.01 mole) from compound {2}in cold and basic medium in coupling reaction via three steps , the product filtered ,dried , recrystallized to yield Formazan-Mefnamic derivative represented by compound {3} according to procedures[4-8] .



Scheme.2:Preparation of Ponstan Derivative {3}

Preparation of Ponstan Derivatives {4 , 5 }:

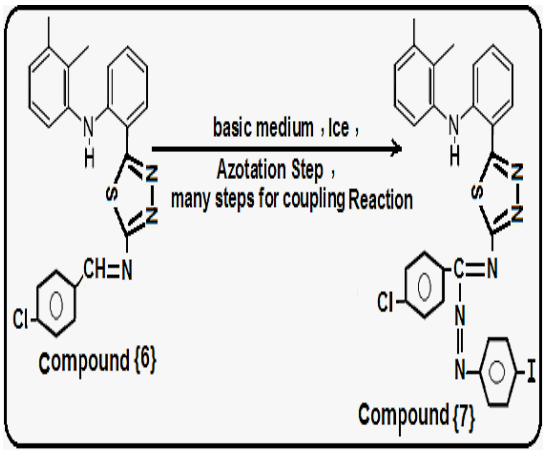
Compound {1} (0.01 mole) was reacted with (0.01 mole) from P-methylbenzaldehyde in presence of drops (glacial acetic acid) in condensation step for (3 hrs) in absolute ethanol to yield Imine-Mefnamic derivative represented by compound {4} according to procedures[4-8], the product filtered ,dried , recrystallized to yield Imine-mefnamic derivative., P-methoxy aniline (0.01 mole) was reacted in many steps represented by azotation, then with (0.01 mole) from compound {4}in cold and basic medium in coupling reaction via three steps, the product filtered ,dried ,recrystallized to yield Formazan-Mefnamic derivative represented by compound {5} according to procedures[4-8] .



Scheme.3: Preparation of Ponstan Derivatives{4,5}

Preparation of Ponstan Derivatives {6 ,7}:

Compound {1} (0.01 mole) was reacted with (0.01 mole) from P-chlorobenzaldehyde in presence of drops (glacial acetic acid) in condensation step for (3 hrs) in absolute ethanol to yield Imine-Mefnamic derivative represented by compound {6} according to procedures[4-8], the product filtered ,dried , recrystallized to yield Imine-mefnamic derivative., P-iodo aniline (0.01 mole) was reacted in many steps represented by azotation, then with (0.01 mole) from compound {6}in cold and basic medium in coupling reaction via three steps, the product filtered ,dried ,recrystallized to yield Formazan-Mefnamic derivative represented by compound {7} according to procedures[4-8] .



Scheme.4:Preparation of Mefnamic Derivatives{6,7}

RESULTS AND DISCUSSION:

A current study, various of mefnamic derivatives were synthesized ,then studied via spectral identification like: ^{1}H.NMR spectra, FT.IR-Spectra , Mass- Spectra for some of them., other studies represented by (Thermal analysis, Melting points, antifungal Evaluation)., all the results are revealed in Tables and figures:

Spectral Investigation:

FT.IR- Spectral Identification of Mefnamic Derivatives: The identification of prepared derivatives appeared several frequnses in figures according to reference[32], figure (1 ,2):

Mefnamic Derivative {1}: The spectrum appeared numerous frequnses owed to (NH) amine group at (3300) , frequnse at (1642) owed to (C=N) endocycle of thiadiazole., frequnse at (787) owed to (C-S) , frequnse at (2931) owed to (CH) aliphatic ,frequnses at (3350 , 3375) owed to (NH_2) of amine.

Mefnamic Derivative {2}: The spectrum appeared numerous frequnses owed to (NH) amine group at (3320) , frequnse at (1655) owed to (C=N) endocycle of thiadiazole., frequnse at (783) owed to (C-S) , frequnse at (2950) owed to (CH) aliphatic ,frequnses at (1612) owed to (CH=N) of imine , frequnse at (1730) owed to (CO-O)carbonyl of carboxyl group ,broad frequnse at (2700-3150) owed to (OH) hydroxyl of carboxyl group.

Mefnamic Derivative {3}: The spectrum appeared numerous frequnses owed to (NH) amine group at (3340) , frequnse at (1659) owed to (C=N) endocycle of thiadiazole., frequnse at (762) owed to (C-S), frequnse at (2943) owed to (CH) aliphatic ,frequnse at (1635) owed to (N-C=N) of formazan, frequnses at (1430, 1490, 1500) owed to azo group in (-N=N-C-) of formazan , frequnse at (1720) owed to (CO-O)carbonyl of carboxyl group ,broad frequnse at (2800-3180) owed to (OH) hydroxyl of carboxyl group.

Mefnamic Derivative {4}: The spectrum appeared numerous frequnses owed to (NH) amine group at (3319) , frequnse at (1651) owed to (C=N) endocycle of thiadiazole., frequnse at (763) owed to (C-S) , frequnse at (2937) owed to (CH) aliphatic ,frequnses at (1616) owed to (CH=N) of imine.

Mefnamic Derivative {5}: The spectrum appeared numerous frequnses owed to (NH) amine group at (3325) , frequnse at (1653) owed to (C=N) endocycle of thiadiazole., frequnse at (760) owed to (C-S) , frequnse at (2988) owed to (CH) aliphatic , frequnse at (1639) owed to (N-C=N) of formazan, frequnses at (1443, 1478, 1498) owed to azo group in (-N=N-C-) of formazan.

Mefnamic Derivative {6}: The spectrum appeared numerous frequnses owed to (NH) amine group at (3311) , frequnse at (1652) owed to (C=N) endocycle of thiadiazole., frequnse at (759) owed to (C-S) , frequnse at (2946) owed to (CH) aliphatic ,frequnses at (1615) owed to (CH=N) of imine , frequnse at (692) owed to (C-Cl) group.

Mefnamic Derivative {7}: The spectrum appeared numerous frequnses owed to (NH) amine group at (3327) , frequnse at (1657) owed to (C=N) endocycle of thiadiazole., frequnse at (752) owed to (C-S) , frequnse at (2930) owed to (CH) aliphatic , frequnse at (1636) owed to (N-C=N) of formazan, frequnses at (1454, 1468, 1492) owed to azo group in (-N=N-C-) of formazan , frequnse at (694) owed to (C-Cl) group , frequnse at (639) owed to (C-I) group.

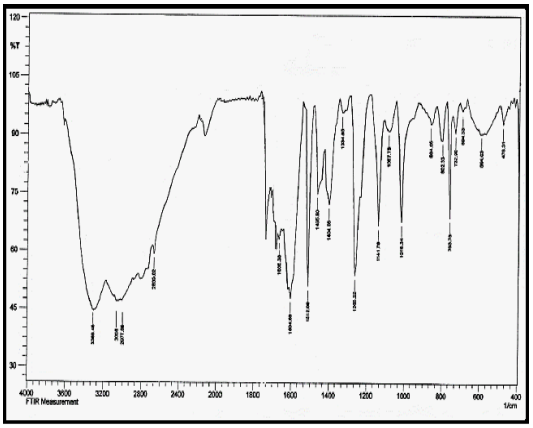


Fig.(1):FT.IR-Spectrum of Mefnamic Derivative{2}

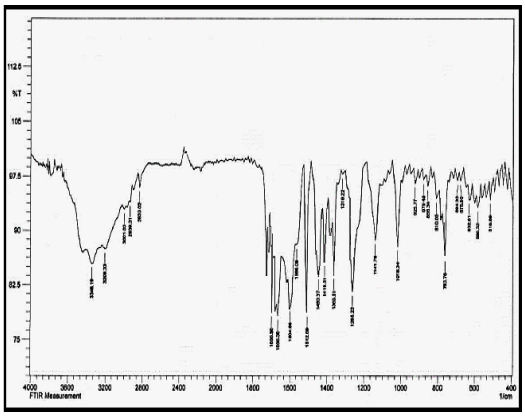


Fig.(1):FT.IR-Spectrum of Mefnamic Derivative or Ponstan-Derivative{3}

^{1}H.NMR- Spectral Identification of Mefnamic Derivative: The identification of spectra appeared numerous peaks in figures (3, 4) according to reference[32] :

Mefnamic Derivative {1}: Several peaks appeared in this compound represented by peaks at ƃ (0. 87 , 1.02) owed to protons of methyl groups (CH_3)., peak at (5. 42) owed to proton of (NH) amine group., peaks at (6. 97-7. 65) owed to protons of phenyl ring. ,peak at (5. 78) owed to protons for amine group (NH_2).

Mefnamic Derivative {2}: Several peaks appeared in this compound represented by peaks at ƃ (0. 99 , 1.05) owed to protons of methyl groups (CH_3)., peak at (5. 35) owed to proton of (NH) amine group., peaks at (7. 39-7. 99) owed to protons of phenyl ring. ,peak at (8. 59) owed to proton for imine group (CH=N) ,peak at (11. 89) owed to proton for hydroxyl group of carboxyl (OH).

Mefnamic Derivative {3}: Several peaks appeared in this compound represented by peaks at ƃ (1. 00 , 1.03) owed to protons of methyl groups (CH_3)., peak at (5. 33) owed to proton of (NH) amine group., peaks at (7. 04-7. 89) owed to protons of phenyl ring ,peak at (11. 53) owed to proton for hydroxyl group of carboxyl (OH).

Mefnamic Derivative {4}: Several peaks appeared in this compound represented by peaks at ƃ (0. 92 , 1.07 , 1. 14) owed to protons of methyl groups (CH_3)., peak at (5. 54) owed to proton of (NH) amine group., peaks at (7. 11 -7. 85) owed to protons of phenyl ring., peak at (8. 32) owed to proton for imine group (CH=N).

Mefnamic Derivative {5}: Several peaks appeared in this compound represented by peaks at ƃ (0. 86 , 0.91 , 1. 09) owed to protons of methyl groups (CH_3)., peak at (5. 23) owed to proton of (NH) amine group., peaks at (7. 00 -7. 73) owed to protons of phenyl ring., peak at (3. 14) owed to protons for methoxy group (-OCH_3).

Mefnamic Derivative {6}: Several peaks appeared in this compound represented by peaks at ƃ (0. 95 , 1.00) owed to protons of methyl groups (CH_3)., peak at (5. 22) owed to proton of (NH) amine group., peaks at (7. 19-7. 81) owed to protons of phenyl ring. ,peak at (8. 64) owed to proton for imine group (CH=N) .

Mefnamic Derivative {7}: Several peaks appeared in this compound represented by peaks at ƃ (0. 94 , 1.12) owed to protons of methyl groups (CH_3)., peak at (5. 20) owed to proton of (NH) amine group., peaks at (7. 08-7. 77) owed to protons of phenyl ring.

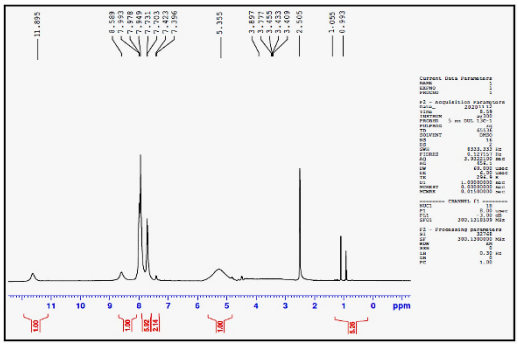


Fig.(3):H.NMR-Spectrum of Mefnamic Derivative{2}

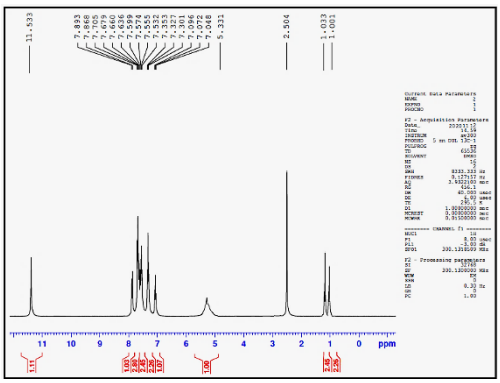


Fig.(4):H.NMR-Spectrum of Mefnamic Derivative{3}

Mass–Spectra of New Compounds:

Mass- spectrum scanned for some compounds that indicated to formatted Mefnamic derivatives (Ponstan-Derivatives) through fragments which appeared in spectra in figures (5 ,6). All spectra of Mass acted fragments for all parts of ponstan derivatives that indicate to molecular wight of parts and fragments which gave othe r evidence of formation our created ponstan derivatives.

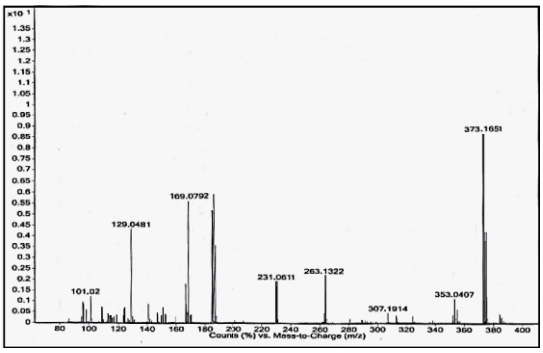


Fig.(5):Mass–Spectrum Compound{2}

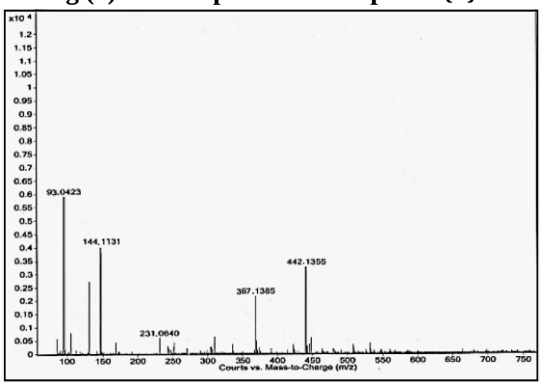


Fig.(6):Mass-Spectrum Compound{3}

Thermal Analysis of Derivatives:

The curves presented that the produced mefnamic derivatives (Ponstan Derivatives) in this paper, they were stable in high temperatures, which showed in figures (7 , 8):

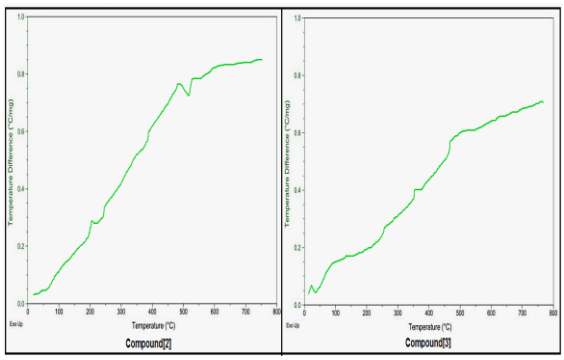
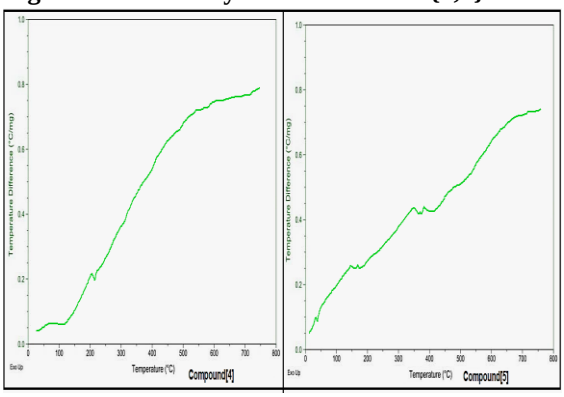


Fig7:Thermal Analysis of Derivatives{2,3}



Fig(8):Thermal Analysis of Derivatives{4,5}

Other Characterization:

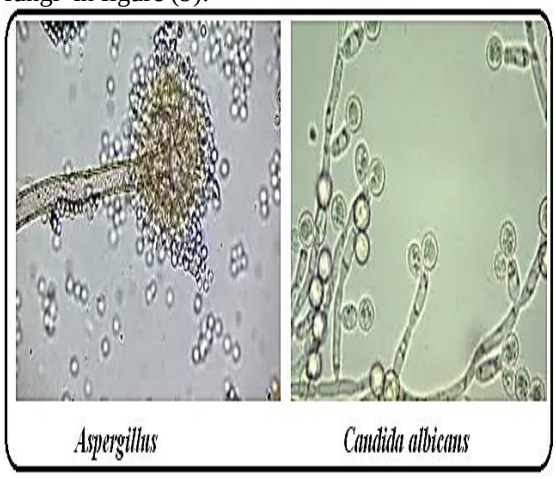
The chemical characterization appeared in table(1), all chemical-physical properties with information about (TLC) ,melting points (m.p), Rf ,colors, products %, solvents in Table(1)

Table(1):Other characterization and all chemical-physical properties

Derivatives	*P %*	*Color*	*M .P C °*	*Rf*	*Solvents (TLC)*
Derivative{1}	70	Deep Yellow	168	0.68	Ethanol : Benzene
Derivative{2}	76	Yellowish Orange	188	0.60	Ethanol : Benzene
Derivative{3}	78	Reddish Orang	214	0.64	Ethanol : Benzene
Derivative{4}	80	Orange	196	0.60	Ethanol : Benzene
Derivative{5}	84	Reddish Yellow	222	0.64	Ethanol : Benzene
Derivative{6}	72	Yellowish Orange	194	0. 60	Ethanol : Benzene
Derivative{7}	82	Orange	224	0.64	Ethanol : Benzene

Selected Fungi in Evaluation-Study[15-22] :

Species of *Aspergillus* are important medically and commercially. Some species can cause infection in humans and other animals. *Candida albicans* is an opportunistic pathogenic yeast that is a common member of the human gut flora. It can also survive outside the human body. The prepared Mefnamic-formazan derivatives were scanned via conducting a live fungal study toward types of fungi to evaluation[15-22] of efficiency of the synthesized derivatives on growth of the selected fungi in the study., the selected fungi in figure (9):



Fig(9):*Types of Fungi in This Study*

Antifungal Evaluation [15] of Mefnamic Derivatives :

The evaluation of mefnamic derivatives studied against two types of fungi represented by (*Aspergillus*) with (*Candida albicans*) for all the derivatives at

three concentrations were taken range of three readings that taken for every concentration (15, 25, 50 µgm) according to the method[15] , Table (2) :

Table2:Antifungal Assay of Mefnamic Derivatives in Concentration(25 µ .gm)

Products	*Aspergillus*	*Candida albicans*
Product {1}	+	+
Product {2}	++	++
Product {3}	+++	+++
Product {4}	++	+
Product {5}	+++	++
Product {6}	++	++
Product {7}	+++	+++

(+) : inhibition (4-8) mm
(++) : inhibition (9-12) mm
(+++) : inhibition (13-16) mm

The results appeared good evidence for efficiency of mefnamic -formazane derivatives(Ponstan-derivatives) that compounds [3 , 5 , 7] gave high inhibition in fungi more than other compounds via formation of interaction with (-N=C-N=N-) in formazane compounds more than starting materials from imine compounds that caused inhibit activity of fungi. The prepared ponstan derivatives performed good antifungi commotion for their strctures that involved formazan group (N=N-C=N-) linked with some heterocyclic ring like thiadiazole and other types of cycles.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding source : None

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