Synthesis , identification and evaluation of antibacterial activity for some new heterocyclic derivatives from 4-methoxy-2-nitroaniline

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1.Introduction

Heterocyclic,compounds that,have (N,S) as hetero atoms,are very,important because,of,the applications⁽¹⁾Heterocyclic compounds forms a part of large number,of pharmaceutical relevant molecule andhave major biological significance⁽²⁾Organic heterocyclic compounds currently account for about 70 % of all clinically used drugs⁽³⁾ Azo,compounds,or.dyes are,characterized, by,the,presenc of the,Azo,moiety (–N=N–).)in their,structure,conjugated with two,distinct or,identical,,mono- or,poly-cyclic.aromatic.or heteroaromatic. systems⁽⁴⁾.Thebiological,importance of,Azo,compounds is,well,known due to their use as inflammatory⁽⁵⁾ , antibacterial⁽⁶⁾, anti-diabetic⁽⁷⁾,and antifungal⁽⁸⁾. Schiff bases are condensation products of primary amines and carbonyl compounds and they were discovered by Hugo Schiff in 1864⁽⁹⁾ . A,Schiff base,is the nitrogen,analogue of,aldehyde in,which the

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C=O group, is replaced, by a C=N group⁽¹⁰⁾. There are numbers, of, biologically. important, Schiff, bases have, been noted in, previous, study possessin,, antibacterial, antifungal, antimicrobial,, anticonvulsant,, antitumor,, anti-inflammatory, and, anti, HIV, activities⁽¹¹⁾. Quinazolines, and, thiazine, derivatives, have, six-. membered, containing, (N, and, S), respectively such as antitubercular, anti-inflammatory, antimicrobial , antipyretic. , anti-HIV , analgesic , antitumor , and calcium channel modulatory activities⁽¹²⁾, thiazine derivatives, that exhibit, various, biological, activities, such, as anti-tubercular,, anti-fungal⁽¹³⁾, insecticidal, and, pesticidal⁽¹⁴⁾. Studies, of, heterocycles, containing, hetero, atoms, such as Sulphur and Nitrogen,, are definitel, one of, the supreme, targeted areas, in heterocyclic, chemistry. They, are extensively, used in, several studies, of natural, products, and pharmaceutical, agent's, synthesis Thiazine ring, systems are, considered a, significant, heterosystem in, heterocyclic, chemistry⁽¹⁵⁾, Quinazoline nucleus, is an, interesting molecule, among the, most important, classes of, an aromatic, bicyclic, compounds with two, nitrogen atoms in, their structure, It is, consisting of, aromatic, benzopyrimidine, system, Synthesis⁽¹⁶⁾ made up, of two, fused six member simple, aromatic rings, benzene, and pyrimidine, ring⁽¹⁷⁾. Researchers, have already, determined, many, therapeutic, activities, of, quinazoline, derivatives,, including,, anticancer⁽¹⁸⁾, antiviral⁽¹⁹⁾, antiviral 'antimalarial'⁽²⁰⁾ ,,,

2. Materials

"(FTIR.), Spectra, (400., -4000 .cm-1), in KBr,, disk, were, recorded, on, SHIMADZU.FTIR-, 8400S, Fourier transform. ¹³C-NMR, and ¹H-NMR were recorded on varian agilent USA at (500.MHz) with. (DMSO.-d6) measure. ment were. made at Department of Chemistry, Tehran University,, Iran."

2.1 Preparation of compound A⁽²¹⁾

(0.01) (1.68 g) of 4-methoxy-2-nitro aniline, was dissolved in a solution consisting of (10 ml), hydrochloric acid with the mixture cooled, to. (0,-5) °C and.. then added sodium nitrite (0.8g) NaNO₂ with a brown color drop as a drop to a solution consisting of (1.8g) (0.01mol) of 2,4-dimethoxyacetophenone and (2 g) of NaOH dissolved in (130ml) distilled and cooled water to (20 °C) and (10ml) ethanol was, observed The Azo composite deposit is dark brown color after completing the addition process. This process was carried out in PH = 5 and the solution is left for , (24 hours) after which the precipitate was filtered and then the precipitate was collected after filtering and washed with distilled water, and dried and recrystallized with ethanol.

2.2 Preparation of compound (B1-B2)⁽²²⁾

In a double-beaker flask, (1g) (0.00278mol) of derivative(A) was mixed with (0.303g) (0.00278mol) of p-amino phenol , (0.303g) of, 2-amino phenol, compound with (20ml) of ethyl alcohol added to it (three drops) of, glacial. acetic. acid and the, mixture up .and , left For a period of two hours, at a, temperature , (78 oC) and then cool the mixture and leave it for (24 hours) and then re-crystallize it with absolute ethyl alcohol.

2.3 Preparation of compound (C1-C2):-

(0.00150mol) (0.7 g) of dissolved schiff base B1 and B2 compound was mixed in (1-4-dioxane (20ml) with (0.213g) of (anthranilic acid) or (0.00150mol)(0.7 g) of Schiff base B2 , was mixed in (1-4-dioxane (20ml) with (0.205g) of (anthranilic acid) was mixed in (1-4-dioxane (20ml) with (0.213g) of (anthranilic acid) then add drops of (DMF) and reflux of (36 Hour) and then re-crystallized the product with absolute ethanol .

2.4 Preparation of compound (D1-D2):-

(0.7g) (0.00155mol) of Schiff base B1, B2 compound was mixed in (22ml) of benzene with (0.239g) of 2-mercapto benzoic acid (3ml) of DMF then add drops of triethylamine to the reaction mixture and from Then reflux of (10 hours) , then the product was filtered and re-crystallized with absolute ethanol .

Scheme(1,) prepare of some heterocyclic compounds

3. Results and Discussion

Derivative (A)

(E)-1-(2,6-dimethoxy-3-((E)-(4-methoxy-2-nitrophenyl)diazenyl)phenyl)-N-(4-nitrophenyl)ethan-1-imine C4,C

FT-IR spectrum data for derivative (A) show a peak at 3000 for (Ar-H), 2980 cm⁻¹ for (C-H) in CH₃, 1700 cm⁻¹ for (C=O), 1650 cm⁻¹ for (C=C), (1521-1357) cm⁻¹ for (NO₂). ¹HMR spectrum data for derivative (A) show 2.52 ppm (DMSO), 3.78 ppm (s, 3H, (OCH₃)₁₃), 3.87 ppm (s, 3H, (OCH₃)₁₄), 3.98 ppm (s, 3H, (OCH₃)₁₅), 3.9 ppm (s, 1H, CH₃), 6.3-7.6 ppm (m, 5H, Ar-H), 9.4 ppm. The ¹³C-NMR

spectrum data (DMSO) compound (A) show :197ppm (C_{17}) ,79ppm(C_{16}) 56ppm (C_{15}) , 55ppm (C_{14}) , 31ppm (C_{13}) , 164ppm(C_3) ,161ppm(C_4,C_7), 98-132ppm (CArom)).

Fig(1) FTIR spectrum of compound(A)

Fig(4) FT-IR,spectrum of,compound,(B1)

Fig(5).(¹ H-NMR,)spectrum,of,compound,(B1)

Fig.(6)(^{13}C ,-NMR).spectrum,of compound.(B1)

Compound,(B2) 2-(((Z)-1-(2,4-dimethoxy-5-((E)-(4-methoxy-2-nitrophenyl)diazenylphenyl) ethylidene)amino)phenol

FT-IR,spectrum,data for, derivative ,(B2) show,band,at 3300 cm^{-1} , for (O – H) 3080 cm^{-1} for (Ar – H) , 2985 cm^{-1} for(C- H) in CH_3 , 1600 cm^{-1} or (C=N), 1593 cm^{-1} ,for .(C=C), 1470 cm^{-1} forN=N, ^1H MNR spectrum data of derivative (B2) show 2.52 ppm (DMSO) , 1.9 (S ,3H, (OCH_3)₂₂) , 3.9 (S ,3H, . (CH_3)₂₁), 3.8 (S ,3H, (OCH_3)₂₀), 3.7 (S ,3H, ., (OCH_3)₁₉) , 2.01 (S ,3H, ., (OCH_3)₁₈) , 9.1 (S,1H(OH)), $6.5\text{--}7.6\text{ ppm}$ (m ,9H, , Ar-H). The ^{13}C -NMR spectrum data (,DMSO),compound (B1) show : 79 ppm (C_{21}) , 72 ppm (C_{20}) , 56 ppm (C_{21}) , 161 ppm (C_{22}) , 31 ppm (C_{23}), 164 ppm (C_4, C_7), 196 ppm (C_{17}),

Fig(7) FT-.IR spectrum of.compound (B2) .

Fig(8) (¹ H-NMR).spectrum,of.:compound (B2)

Fig,(9) (^{13}C -NMR,) spectrum,of,compound (B2)

Compound,(C1) و ((E)-2-(2,6-dimethoxy-3-((4-methoxy-2-nitrophenyl)diazenyl)phenyl)-3-(4-hydroxyphenyl)-2-methyl-2,3-dihydroquinazolin-4(1H)-one

FT-IR:,spectrum,data:,for derivative ,(C1) show,peak at ,1420 for (N=N), 3078 for (Ar – H) , 2947cm⁻¹ for (C– H) in CH₃ ,1670cm⁻¹ for(C=O) , 1620.cm⁻¹ for(C=C),3425cm⁻¹for(N–H).¹HMR.spectrum;,data,of derivative (C1) show 4.0ppm (s, 1H , NH) , 2.6.ppm (S ,3H, OCH₃)30 , 3.8.ppm (S ,3H, OCH₃)28 , 2.8.ppm (S,,3H,OCH₃)29,1.2.ppm (S ,3H, OCH₃)27, (s, 1H, CH) , 1.8ppm (s, 2H, CH₂) , 6.5-7.8ppm 13H , (Ar-H) ,8.4 ppm.(s,1H,OH),4.1ppm 9s,1H NH). C₁₃_NMR spectrum data (DMSO) compound (C1) show :79ppm (C27) ,56ppm(C28), 56.2ppm (C29) , 32ppm (C30) , 31ppm (C19) ,164ppm(C3) , 63ppm (C13) 196ppm(C14), 164-,98ppm (CArom) .

Fig.(10)
 :- (FT-IR) spectrum of compound (C1)

Fig(11),
 (^1H NMR) spectrum of compound (C1)

Fig(12):-(^{13}C NMR),spectrum,.of.compound(C1)

Compound (C2) (E)-2-(2,6-dimethoxy-3-((4-methoxy-2-nitrophenyl)diazenyl)phenyl)-3-(2-hydroxyphenyl)-2-methyl-2,3-dihydroquinazolin-4(1H)-one

FT-,IR spectrum,:data for,derivative,(C2) show,peak at 3325 cm^{-1} for,(O – H) , , 3060 for (Ar – H) , 2920 cm^{-1} for (C- H) in CH_3 , 1680, cm^{-1} ,for,(C=O) , 1600 cm^{-1} ,for (C=C),1550 cm^{-1} , (C=N),(1500-1360) cm^{-1} NO₂ . 1HMN, spectrum,data of,:compound (C2) show,,2.8ppm(S ,3H, OCH₃)27) 2ppm (S ,3H, OCH₃)26) ,3.9ppm (S ,3H, OCH₃)25),0.8ppm (s, 3H, CH₃)29) , 1.2ppm (s,3H, CH₃)28), 6.3 -8.4ppm (m , 13H , Ar-H) ,4ppm (s,1H,N-H). The C13_NMR spectrum, data (DMSO). compound (C2) show :31ppm (C29), , 32ppm (C28) , 56.05ppm (C27),36ppm (C26) ,56.28ppm(C25) 167ppm(C23),162,ppm(C21),164ppm,(C5-C7)),164-96 ppm(CArom),196(C=O).

Fig(13):- (FT-IR)spectrum of:compound. (C2)

Fig(.14):- ($^1\text{H-NMR}$),spectrum,,:of:compound (C2)

Fig:(15):- (^{13}C -NMR) spectrum: of: compound (C2)

Compound (D1):- ((E)-2-(2,6-dimethoxy-3-((4-methoxy-2-nitrophenyl)diazenyl)phenyl)-3-(4-hydroxyphenyl)-2-methyl-2,3-dihydro-4H-benzo[e][1,3]thiazin-4-one

FT-IR spectrum: data for derivative (D1) show: peak at, 3090 for (Ar – H) , 2910 cm^{-1} for (C- H) in CH_3 , 1680 cm^{-1} for (C=O) , 1412 cm^{-1} for (N=N) , 1600 cm^{-1} for (C=C) , (1550-1396) cm^{-1} for (NO₂). ^1H NMR spectrum: data of: compound (D1) show, 1.2 ppm (s, 3H, OCH_3)₂₈ , 0.8 ppm (s, 3H, CH_3)₂₉ , 1.2 ppm (s, 3H, OCH_3)₂₈ , 3.8 ppm (s, 3H, OCH_3)₂₉ , 2.4 ppm (s, 3H, OCH_3)₃₀ , (6.5-7.9) ppm (s, 13H, Ar-H). The ^{13}C -NMR spectrum data (DMSO) compound (D1) show : 16.6 ppm (C_{28} , 56 ppm (C_{30}) , 153 ppm ($\text{C}_4, \text{C}_{14}, \text{C}_{17}$) 191 ppm (C_{31}) , 111-134 ppm (C_{Arom}).

Fig(16):- (FT:-IR): spectrum of compound (D1)

Fig(17):-¹H NMR, spectrum, of,compound (D1)

Fig(18):-(^{13}C -NMR), spectrum, of compound (D1)

Compound (D2) (E)-,2-(2,6-dimethoxy-3,-((4-methoxy,-2-nitrophenyl)diazenyl)phenyl)-3-(5-hydroxy-4-methylpyrimidin-2-yl)-2-methyl-:2,3-dihydro:-4H-benzo[:e][1,3]thiazin-4-:one

FT-IR:spectrum data for,derivative (D2),show:,band at 3332 cm^{-1} , for (O – H) ,,, 3080 cm^{-1} for ,(Ar – H) , 2931 cm^{-1} for(C– H) in CH_3 , 1700 cm^{-1} for (C=O), ,, 1458 cm^{-1} for (N=N) , 1600 cm^{-1} for(C=C) , 1650 cm^{-1} for(C=N),(1535-1357) cm^{-1} for(NO_2). ^1H MNR spectrum,data,of:compound (D2) show 0.8 ppm (s, 3H , CH_3)₂₈ , 1.2 ppm (S, 3H, OCH_3)₂₆ , 2.4 ppm (s, 3H, OCH_3)₂₇ , 3.8 ppm (s, 3H, OCH_3)₂₅) 8.4 ppm (s,1H,OH), $6.5\text{--}7.6\text{ ppm}$ (m , 10H , Ar-H) The ^{13}C -NMR spectrum data (DMSO) compound (D2) show : 196 ppm (C_{14}) , 36 ppm (C_{29}) , 32 ppm (C_{28}) , 32 ppm (C_{26}) 38 ppm (C_{27}), 56 ppm (C_{25}), 67 ppm (C_{13}) 30 ppm (C_{30}), 164 ppm (C_4,C_7).

Fig(19):- (FT-IR) spectrum of: compound (D2)

Fig(20):- (¹H-NMR) spectrum ,of,compound (D2)

Fig(21):-(^{13}C -NMR:)spectrum:,of::compound (D2)

4. Biological activity

4.1 antibacterial

The results, show that, derivatives, reduce significant, antibacterial, effectiveness against bacteria "staphylococcus aureus: and Escherichia: coli" . the compounds that show good: activity, are (A, B1, C1, C2, , D1) against (staphylococcus aureus) , and compound that show very good activity are (A-D1), against. (Escherichia coli:), the results, of the antibacterial, activity are, shown: in, the fig (6). The results show that derivatives reduce significant antibacterial effectiveness against bacteria "staphylococcus aureus and Escherichia, coli", the compounds that show good activity are (A, B1, B2, C1, C2, D1, D1) against (staphylococcus aureus) , and compound that show very good activity are (A-D1) against, (Escherichia coli) , the results of the antibacterial activity are shown in the fig (6).

Fig, (30) effect: compounds : (Staph Aureus) against and (E.Coli) against

Table (1) the results of the antibacterial activity for (A-D3) derivatives

Comp No	Staph aureus	Mm	E.Coli	Mm
A	+++	37	+++	40
B1	+++	45	+++	30
B2	-	0	-	Zero
C1	-	Zero	+++	45
C2	-	Zero	-	Zero
D1	++	22.3	+++	30
D2	+++	30.5	-	Zero

(-) No discouragement

"+= (5-10)mm ,=slightly, :active, +=, (11-20)mm moderately +++= More, than ,20: good, active"

Table:(2) Proaratese of derivtive (A-D3)derivatives

Comp	M.F M.wat	m.p	R _f	Colour	%
A	C ₁₇ H ₁₇ N ₄ O ₆ 359.11	45	0.5	Brown	72
B1	C ₂₃ H ₂₂ N ₄ O ₆ 450.5	120	0.47	Black	90
B2	C ₂₃ H ₂₂ N ₄ O ₆ 450.5	115	0.5	Brown	93
C1	C ₃₀ H ₂₇ N ₅ O ₇ 569.6	180	0.4	Black	90
C2	C ₃₀ H ₂₇ N ₅ O ₇ 569.6	134	0.3	Brown	87
D1	C ₃₀ H ₂₅ N ₅ O ₈ S 615.6	160	0.2	Black	79
D2	C ₂₉ H ₂₆ N ₆ O ₇ S 602.6	182	0.29	Black	85

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