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Pharmacological Studies On Some New 3- Cyclic Oxazepine-2- Aryl Imidazo(1,2-A)Pyridine Derivatives

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Abstract

New series of 3-substituted heterocyclic compounds containing bridge head nitrogen were synthesised through multi--step reactions.In order to prepare the starting 2-substituted heterocyclic compounds of pyridine,a known procedure was used bycondensation of 2-amino pyridine with (4-phenyl phenacyl bromide)or (4-bromo phenyl phenacyl bromide) . Carbaldehyde group was introduced at position-3 of prepared 2-substituted imidazo/ pyridine rings by Vilsmeier-Haack reaction. 3-Carbaldehyde derivatives underwent condensation with different aromatic amines to give Schiff bases of these derivatives, which on condensation with different cyclic anhydrides to give oxazepine afforded 1,3-oxazepine-4,6-dione derivatives of imidazo/ pyridine rings. All prepared compounds were characterised via FT-IR spectroscopy, some of them were characterised by 1H-NMR spectroscopy. These new 3-subistituted derivatives of imidazo/pyridine rings were tested pharmacological activities in mice . Some of tested compounds showed strong activity while the other showed moderate against.

Keywords: Imidazo/pyridine, oxazepine, pharmacological studies

INTRODUCTION

One of the most important imidazole compounds are azaimdolizidine, which are contains a phenyl ring fused toa imidazole ring,which also known as imidazo (1, 2-a) pyridine (1) . Imidazo[1,2-a] pyridine are bridge - head nitrogen heterocyclic , and compounds containing this heterocyclic have been reported for various biological activities (2) and it received considerable interest from the pharmaceutical industry like anti- fungal and anti microbial agents (3) . In order to prepare parent compound of 2-substitiuted imidazo (1, 2-a) pyridine, a known procedure will be used by condensation of suitable 2-amino pyridine with α-halo ketone (4-phenyl phenacyl bromide) , (4-bromo phenacyl bromide) in refluxing ethanol as described by Roe (4) to give 2-(4-bi phenyl) imidazo (1, 2-a) pyridine , 2-(4- bromo phenyl) imidazo (1,2-a) pyridine and introduce it indifferent reactions (3) . The susceptibilityof π-excessive system of these fused rings to electrophilic attack permitted the preparation of a variety of 3-substituted fused rings of pyridines. Therefore the second step will be introduced aldehyde group at position-3 by Vilsmeier-Haack reaction with using mixture of POCl3 and DMF in presence of CHCl3(4). Moreover, the third step will be preparation of Schiff bases derivatives of imidazo pyridine by condensation between aldehyde group and aromatic amine , Schiff bases derivatives of imidazo pyridine ported to have interesting bioactivity such as anti- bacterial and anti fungal (5). In addition , new oxazepine compounds derivatives of imidazo (1,2-a) were synthesized bycondensation cyclization of cyclic anhydride with the imine group(C= N) bydirect addition use reflux or Microwave technique (6). here in this research have designed and synthesized Schiff bases and oxazepine compounds derivatives of imidazo (1,2-a) pyridine . New Schiff bases have been proved to be an important intermediates for the synthesis of many heterocyclic compounds in organic chemistry. These facts encouraged us to synthesis some new oxazepine derivatives imidazo[1,2-a] pyridine nucleus, which were reported to possess various biological activities. Oxazepine compounds have a medical and biological importance and they have medical and pharmaceutical application. Among the wide Chemical derivatives are a heteropolymer which have an activity and effect against cancer (7). They are also effective against fungi (8) and bacteria (9) , hypnotic muscle relaxant (10), antagonistic (11) anti-inflammatory (12), telomerase inhibitors (13) and antiepileptic(14), found that some Oxazepine derivatives are considered a medical drug against the disease (15) and also that oxazepine compounds have an activity against some liver diseases such as hepatic necrosis as in cirrhosis, carcinoma and obstructive jaundice . The effectiveness of treatment has been assessed in albino male mice after inducing hepatic damage with carbon tetrachloride(CCl_4) (16) **.** The aim of the research is synthesis new compound of imidazo (1, 2-a) pyridine and study their bioactive entities, especially with pharmacological activities bearing heterocyclic ring system namely imidazo [1, 2- a] pyridine **.**

MATERIALS AND METHODS

Experimental Instruments

A. Melting point were recorded using electro thermal melting point apparatus.

B. All the (1H and 13C NMR) spectra were recorded on bruker ultra shield 400MHz spectrometer using DMSOd6 as solvent as an internal standard.

C. Chemical shift values are listed in δ scale The IR spectra were recorded on Schimadzu FTIR spectro photometer by using 1% potassium bromide discs.

General procedure for Synthesis of 2-(4-phenyl phenyl) imidazo [1,2-a]pyridine[1a] A mixture of 2-amino pyridine(0.01 mol) 4- phenyl phenacyl bromide (0.01 mol) are dissolved in (20 ml) of ethanol. The mixture was heated under reflux in water bath for 6 hours. Then, the solution was cooled and basified with (5% NaoH) until pH10.The resulting solid washed with water, filtered and recrystallized with ethanol. Orange Solid, Yield 80%, m.p.210, Elemental Analysis calculated for C19H14N2: IR (KBr/Cm-1):: 3035, 3002, 1597,1480 ,1255, 742cm-1; 1H- RMN, 300 MHz(DMSO-d6) δppm: δ 6.83-6.78 (d, 2H, Ar-H),δ 7.22-7.18 (d, 2H, Ar-H) ,δ7.66-7.55 (m, 4H, Ar-H) ,δ 7.56_7.59 (d, H, -CH),δ 8.14-8.11 (d, H, Ar-H).

General procedure for Synthesis of 2-(4-bromo phenyl)imidazo [1,2-a]pyridine [1b] A mixture of 2-amino pyridine(0.01 mol) 4-bromo phenacyl bromide(0.01 mol) are dissolved in (20 ml) of ethanol. The mixture was heated under reflux in water bath for 6 hours. Then, the solution was cooled and basified with (5% NaoH) until pH 10. The result solid washed with water, filtered and recrystallized with ethanol.yellow Solid, Yield 82 %, m.p.214, Elemental Analysis Calcd for $C_{13}H_9BrN_2$: IR (KBr/ Cm-1) :: 3047, 3002,1 600,1485,1253,742 cm-1; 1H- RMN, 300 MHz(DMSO-d6) δppm: δ 6.83-6.78 (d, 2H, Ar-H),δ 7.22-7.18 (d, 2H, Ar-H) , δ 7.56- 7.59 (d,H,- CH) , δ7.66-7.55 (m,3H, Ar-H) ,δ 7.56_7.59 (d, H, -CH),δ 8.14-8.11 (d, H, Ar-H).

General procedure for Synthesis of 2-(4- phenyl phenyl imidazo [1,2-*a*] pyridine-Carbaldehyde [2a].

To an ice cold solution of DMF (1 ml) in (5 ml $CHCl_3$) was added POCl3 (2 ml) drop-wise and the temperature was maintained below 10^0C since an exothermic reaction takes place . To the reaction mixture, an ice-cold solution of 2-**(**4- biphenyl) imidazo [1,2-a] pyridine (0.0036 mol) in chloroform was added

slowly. After completion of addition, the reaction mixture was refluxed in water bath for about 2 hrs. The reaction mixture was cooled and washed with ice water and filtered. The product solid obtained was purified by recrystallization from mixture of aceton and ethanol. Off brown Solid, Yield 81%, m.p. 195 ,Elemental Analysis Calcd for C20H16N2O: IR (KBr/Cm-1):: 3059, 2956, 2850, 1690 , 1614, 1560, 1551, 759 cm-1; 1H-RMN, 300M Hz(DMSOd6) δppm:δ 7.19-7.15 (d, 2H, Ar-H) δ 7.28 (d, 2H, Ar-H),δ7.85-7.61 (m, 4H, Ar-H),δ 7.56_7.59 (s, 1H, -CHO) ,δ 9.69-9.67 (d, H, Ar-H).

General procedure for Synthesis of 2-(4- bromo phenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde [2b].

To an ice cold solution of DMF (1 ml) in (5ml $CHCl_3$) , was added POCl3 (2 ml) drop-wise and the temperature was maintained below 10^0C since an exothermic reaction takes place. To the reaction mixture, an ice-cold solution of 2-(4-bromo phenyl bromide) imidazo [1,2-a] pyridine (0.0036 mol) in chloroform was added slowly. After completion of addition, the reaction mixture was refluxed in water bath for about 2 hrs.The reaction mixture was cooled

and washed with ice water and filtered. The product solid obtained was purified by recrystallization from mixture of aceton and ethanol. Brown Solid ,Yield 75%, m.p.93, Elemental Analysis for $C_{14}H_{10}BrN_2O$: IR (KBr/Cm-1):: 3059, 2956, 2854, 1695, 1596, 1543,1519,744 cm-1; 1H-RMN, 300 MHz(DMSOd6) δppm:δ 7.19-7.15 (d, 2H, Ar-H) δ 7.28 (d, 2H, Ar- H),δ7.85-7.61 (m,3H, Ar-H) ,δ 9.70-9.76 (d, H, Ar-H) , δ 10.1 (s, 1H, -CHO).

General procedure for Synthesis N{(1E)- [2-(4-substitute phenyl) imidazo [1,2-*a*] pyridine-3-yl] methylene }-N-aryl amine (Schiff base).

3-carbaldehyde imidazo (1,2-a) pyridine (0.004 mol) was dissolved in absolute ethanol then , aromatic amine (0.004 mol) and (2- 3) drops of glacial acetic acid were added and refluxed in water bath for 6 hours , and then cooled until the solid separated, this solid washed with water, filtered and purified by recrystallization from ethanol.

N{(1E)-[2-(4-bi phenyl)imidazo[1,2-*a*] pyridine-3-yl] methylene }-N-(4-methyl phenyl)amine [3a].

Off White Solid, Yield 80 %, m.p. 220, Elemental Analysis Calcd for $C_{27}H_{21}N$:IR (KBr/Cm-1) : 3060, 2947,1631, 1529,1487,748 cm-1; 1H-RMN,400 MHz (DMSOd-6) δppm: δ 2.33(s, 3H,CH_3) δ 7.23 (m, 2H, Ar- H) ,δ7.25-737- (m,4H,Ar-H) ,δ7.49 (s,1H,CH=N Schiff base) , δ 7.74-7.77 (m,2H,Ar-H) δ7.87-7.93 (m,4H , Ar-H).^{13}CNMR (400MHz, DMSO d-6): δppm : 20, 24 (CH_3), 113.14(Caromatic),115.80(Caromatic) ,117.57(Caromatic),126.19(2Caromatic),126.49(3Carom-atic),127.02(3Caromatic),127.22(Caromatic),127.54(3C-aromatic),128.95(2Caromatic),129.01(Caromatic),131.71(2Carom atic),133.63(2Caromatic),139.66(C=Naromatic),142.69(C=N aromatic), 144.05 (C=N Schiff base) .

N{(1E)-[2-(4-bi phenyl)imidazo[1,2-*a*] pyridine-3-yl]methylene}-N-phenylamine [3b].

Yellow Solid , Yield 78 % , m.p. 218 , Elemental Ana -lysis Calcd for $C_{26}H_{19}N_3$: IR (KBr/Cm-1) : 3082, 2833, 1637, 1566 , 1488 , 756 cm-1. ^{1}H- NMR , 400 MHz(DMSOd-6) δppm: δ 6.84-6.93(2H, m,2CH aroma -tic),7.26-7.37 (2H, m, 2CH aromatic), 7.40 -7.48 2H,m, 2CH aromatic),7.51-7.59 (3H, m,2CH aromatic), 7.6(1H, s, CH=N Schiff base),7.72-7.74(2H, m, 2CH aromatic) 7.77-8.05 (4H, m, 4CH aromatic), 8.08-8.55(4H, m, 4CH aromatic).^{13}CNMR(400MHz, DMSO d-6) : δppm: 109.27(Caromatic),112.37(Caromatic),116.57(Caromatic), 125.05(2Caromatic), 126.07 (3C aromatic), 126.45 (3C aromatic),126.93(Caromatic),127.44(3Caromatic),128.94 (2Caromatic), 132.95(C aromatic), 139.26 (2C aromatic), 139.69(3Caromatic),143.86(C=Naromatic),144.81 (C=N Schiff base).

N{(1E)-[2-(4-biphenyl) imidazo [1,2-*a*] pyridine -3-yl]methylene}-N-(4-nitrophenyl) amine [3c].

Lightyellow Solid, Yield 83 %, m.p. 200, Elemental Analysis Calcd for $C_{26}H_{18}O_2N_4$: IR (KBr/Cm-1) : 3072, 2866 ,1649 ,1568 ,1480 ,754cm-1. ^{1}H- NMR , 400MHz(DMSOd-6)δppm:δ6.58(2H,m,2CH aromatic), 6.61(2H,m,2CHaromatic),7.40-7.49(2H,m,2Caromatic), 7.52-7.54(2H,m,2CHaromatic),7.78(IH,s,CH=NSchiff base),7.80-7.92(5H,m,4CHaromatic), 7.94-8.00(4H,m,4C H aromatic) .

N{(1E)-[2-(4-bromophenyl)imidazo[1,2-*a*] pyridine-3-yl] methylene }-N-(4-methyl phenyl) amine [4a].

Offwhite Solid,Yield75%, m.p.212.Element Aanalysis Calcd for $C_{21}H_{16}N_3Br$: IR (KBr/Cm-1) : 3024,2864 ,1616,1587,1500,742cm-1.^{1}H-NMR,400MHz (DMSO d-6)δppm:δ2.33(3H,s,CH_3),7.23(2H,m,2CH aromatic) ,7.25-7.37-(4H, m, 4CH aromatic), 7.49 (IH, s, CH=N Schiff base), 7.74-7.77(2H, m, 2CH aromatic),7.87-7.93(4H,m,4CH aromatic).^{13}CNMR (400 MHz, DMSO d-6) : δ ppm: 24.00(CH_3) , 116.12(C aromatic),117.22(C aromatic) ,117.66(C aromatic),120.11 (2Caromatic) ,123.44 (2C aromatic) , 126.36 (2Caromatic), 128.2 (C aromatic),131.15(2Caromatic),131.42(Caromtic),131.57 (C aromatic) , 131.82(C aromatic), 132.32(2Caromatic) ,146.96 (C=N aromatic) ,155.18 (C=N Schiff base).

N{ (1E)-[2-(4-bromophenyl)imidazo [1,2-*a*] pyridine-3-yl] methylene}-N-(phenyl) amine [4b].

Brown Solid, Yield 82 %, m.p. 210, Elemental Analysis Calcd for $C_{20}H_{14}N_3Br$: IR (KBr/Cm-1) : 3141, 2943 , 1633 , 1535 , 1475 , 742cm-1 . ^{1}H- NMR 400 MHz(DMSOd-6) δppm: δ 7.20-7.30 (4H, m, 4CH aromatic), 7. 84 (5H, m, 4CH aromatic), 7.85 (IH, s, CH=N Schiff base), 8.13 (2H, m, 2CH aromatic), 8.7 (2H, m,2CH aromatic**) .**^{13}CNMR(400MHz,DMSO d-6) : δppm: 112.87 (C aromatic), 116.68 (C aromatic), 118.54 (C aromatic), 120.48 (2C aromatic), 120.34 (3C aromatic), 125.30 (4C aromatic), 126.87 (C aromatic), 129.79 (3C aromatic) , 131.99 (2C aromatic), 147. 17 (C=N aromatic), 149.23 (C=N Schiff base).

N{(1E)-[2-(4-bromophenyl) imidazo [1,2-*a*]pyridine-3-yl]methylene}-N-(4-nitro phenyl) amine [4c].

Yellow Solid, Yield 80 %, m.p. 250 , Elemental Analysis Calcd for $C_{20}H_{13}O_2N_4Br$: IR (KBr/Cm-1) : 3072, 2883 ,1631 , 1566 , 1508 , 744 cm-1 . ^{1}H- NMR , 400 MHz(DMSOd-6) δppm: δ 6.61 (2H, m, 2CH aromatic), 7.14 (2H, m, 2CH aromatic), 7.33-7.44 (3H, m, 3CH aromatic), 7.54 (IH, s, CH=N Schiff base), 7.57-7.75 (2H, m, 1CH aromatic), 7.87-8.23 (3H, m, 3CH aromatic).^{13}CNMR (400MHz, DMSO d-6): δppm: 112.32 (C aromatic), 116.13 (C aromatic), 117.21 (C aromatic), 123.44 (2C aromatic), 126.36 (3C aromatic), 128.21 (4C aromatic), 131.16 (C aromatic), 131.58 (3C aromatic),131.82 (2C aromatic), 140. 00 (C=N aromatic), 142.00 (C=N Schiff base).

General procedure for Synthesis of oxazepine

A mixture of Schiff base compound (0.004 mol) and the anhydride, namely maleic anhydride ,succinic anhydride and phthalic anhydride(0.004 mol) in (20 ml) tetrahydrofuran (THF) , was refluxed in water bath for 24hrs. After cooling the formed precipitate was filtered , dried and recrystallized from ethanol .

It is worth to mention that this reaction was carried out also by Microwave-technique and minimizing the reaction time from 24 hrs. to (6-8) minuts .

2-[2-(4-phenyl phenyl) imidazo [1,2-a] pyridine-3-yl]-3-[(4-methylphenyl) amine] 2, 3,5,6-tetra hydro-1,3-oxazepine-4,7-dione [5a] .

New oxazepine derivatives from Schiff base (3a) and succinic anhydride. brown Solid,Yield 83%, m.p.150 , Elemental Analysis Calcd $C_{31}H_{25}O_3N_3$:IR(KBr/Cm-1) : 3041, 2929, 1720 , 1680 ,1540 , 1483 , 752 cm-1 .

2-[2-(4-phenyl phenyl) imidazo [1,2-a] pyridine -3-yl]-3-(phenyl amine) 2,3,5,6-tetrahydro -1,3-oxazepine-4,7-dione [5b] .

New oxazepine derivatives from Schiff base (3b) and succinic anhydride. Yellow pale Solid, Yield 73 %, m.p. 140 , Elemental Analysis Calcd $C_{30}H_{23}O_3N_3$: IR (KBr/Cm-1): 3087,2931,1728, 1675, 1552, 1487,744 cm-1. ^{1}H-NMR,400MHz (DMSO d-6) δ ppm : δ 2.38 (2H,m,CH_2), 2.59(2H,m,CH_2), 4.03(1H,s,CH), 6.88 (2H ,t,ArH), 7.21(2H, t, ArH), 7.33 (2H, t, ArH), 7.45 (2H,t,ArH), 7.57(2H,d, ArH), 7.60 (2H, d, ArH), 7.69 (2H, d, ArH), 7.70(2H, d, ArH), 8.03 (1H, d, ArH), 8.5 (1H, d, ArH). ^{13}CNMR (400 MHz, DMSO d-6) : δppm:29.24(2CH_2), 109.83(CH), 112.87(2C aromatic) , 117.6(C aromatic), 117.17(2C aromatic), 125.56 (2C aromatic),126.65(2C aromatic), 127.02 (2C aromatic), 127.43(2Caromatic), 127.90(2C aromatic),128.01 (2C aromatic),131.93(2C aromatic), 132.14 (2C aromatic), 133.58 (2C aromatic), 139.82 (C=N), 145.42 (C=N), 174.12 (2C=O).

2-[2-(4-phenyl phenyl) imidazo [1,2-a] pyridine-3-yl]-3-[(4-nitrophenyl)amine]2,3,5 ,6-tetrahydro-1,3-oxazepine-4,7-dione [5c] .

New oxazepine derivatives from Schiff base (3c) and Succinic anhydride. yellow Solid, Yield 76%, m.p. 148, Elemental Analysis Calcd $C_{30}H_{22}O_5N_4$:IR (KBr/ Cm-1): 3093,2931,1712,1683,1552,1487,750 cm-1 .

2-[2-(4-bromophenyl) imidazo [1,2-a] pyridine-3-yl]-3-[(4-methylphenyl)amine]2, 3,5,6-tetrahydro-1,3-oxazepine-4,7-dione [6a].

New oxazepine derivatives from Schiff base (4a) and succinic anhydride. dark brown Solid, Yield 80%, m.p.170, Elemental Analysis Calcd $C_{25}H_{20}O_3N_3Br$: IR(KBr/Cm-1): 3043, 2931, 1725 , 1693 ,1543 ,1489 , 745 cm-1 .

2-[2-(4-bromo phenyl) imidazo [1,2-a] pyridine -3-yl]-3-(phenyl amine)-2,3,5,6-tetrahydro -1,3-oxazepine-4,7-dione [6b] .

New oxazepine derivatives from Schiff base (4b) and succinic anhydride. offwhite Solid, Yield 77%, m.p. 180,Elemental Analysis Calcd $C_{24}H_{18}O_3N_3Br$: IR(KBr /Cm-1):3087,2885,1730,1690,1539,1488,750 cm-1. ^{1}H-NMR, 400 MHz(DMSOd-6) δppm: δ 2.44 (2H, m, CH_2),2.49(2H,m,CH_2),4.0(1H,s,CH),6.76(2H,d, ArH), 6.79(2H,d,ArH), 6.81(2H, d, ArH), 6.91(2H, d, ArH), 7.28(2H,m,ArH), 7.72(1H, d, ArH), 7.86(1H, d, ArH). ^{13}CNMR (400MHz, DMSO d-6): δppm: 110.03 (CH), 113.34(2Caromatic), 116.74(2Caromatic), 126.36(2C aromatic),126.71(2C aromatic), 127.96 (2C aromatic), 128.07(2Caromatic),128.08(2C aromatic),129.07(2C aromatic),129.08(2C aromatic), 129.25 (2C aromatic), 131.27(2C aromatic),132.86(2Caromatic), 133.47 (3C aromatic),140.07(2C aromatic), 140.19 (C=N), 144.99 (C=N), 169.17 (2C=O).

2-[2-(4-bromo phenyl) imidazo [1,2-a] pyridine-3-yl]-3-[(4-nitrophenyl)amine]-2,3, 5,6-tetrahydro-1,3-oxazepine-4,7-dione [6c].

New oxazepine derivatives from Schiff base (4c) and succinic anhydride. Dark yellow Solid, Yield 74 %, m.p. 140 , Elemental Analysis Calcd $C_{24}H_{15}O_5N_4Br$: IR (KBr/Cm-1): 3053, 2887, 1715 ,1695 ,1540 ,1483 , 752 cm-1 .

2-[2-(4-phenyl phenyl) imidazo [1,2-a] pyridine-3-yl]-3-[(4-methylphenyl) amine] -2, 3-dihydro-1,3-oxazepine-4,7-dione [7a] .

New oxazepine derivatives from Schiff base (3a) and maleic anhydride. Dark brown Solid, Yield 80 %, m.p. 135 , Elemental Analysis Calcd $C_{31}H_{23}O_3N_3$: IR (KBr/Cm-1): 3056 , 2898 , 1712 , 1690 ,1517 ,1488 , 765 cm-1 .

2-[2-(4-phenyl phenyl) imidazo [1,2-a] pyridine-3-yl]-3-(phenyl amine)2,3,-dihydro -1,3-oxazepine-4,7-dione [7b] .

New oxazepine derivatives from Schiff base (3b) and maleic anhydride . yellow Solid, Yield 79 %, m.p. 160 Elemental Analysis Calcd $C_3H_{21}O_3N_3$:IR (KBr/Cm-1): 3082, 2873, 1730 , 1693 ,1530 ,1492 , 738 cm-1 .

2-[2-(4-phenyl phenyl) imidazo [1,2-a] pyridine -3-yl]-3-[(4-nitrophenyl)amine]-2,3 -dihydro-1,3-oxazepine-4,7-dione [7c] .

New oxazepine derivatives from Schiff base (3c) and maleic anhydride. yellow Solid, Yield 70 %, m.p. 180 Elemental Analysis Calcd $C_{30}H_{20}O_5N_4$:IR (KBr/Cm-1) : 3085, 2856, 1722 , 1697 ,1541 ,1487 , 759 cm-1 .

2-[2-(4-bromo phenyl) imidazo [1,2-a] pyridine-3-yl]-3-[(4-methyl phenyl) amine] -2, 3-dihydro-1,3-oxazepine-4,7-dione [8a].

New oxazepine derivatives from Schiff base (4a) and maleic anhydride. brown Solid, Yield 75 %, m.p. 120 Elemental Analysis Calcd $C_{25}H_{18}O_3N_3Br$: IR (KBr/ Cm-1) : 3089,2914,1724 ,1690 ,1547,1461 ,746 cm-1

2-[2-(4-bromo phenyl) imidazo [1,2-a] pyridine-3-yl]-3-(phenylamine)2,3,-dihydro -1,3-oxazepine-4,7-dione [8b] .

New oxazepine derivatives from Schiff base (4b) and maleic anhydride. Dark yellow Solid, Yield 69 %, m.p 130,Elemental Analysis Calcd $C_{24}H_{16}O_3N_3Br$:IR(KBr / Cm-1):3056,2803,1706 ,1685 ,1549,1478 ,748 cm-1.

2-[2-(4-bromo phenyl) imidazo [1,2-a] pyridine-3-yl]-3-[(4-nitrophenyl)amine]-2,3-dihydro-1,3-oxazepine-4,7-dione [8c] .

New oxazepine derivatives from Schiff base (4c) and maleic anhydride. yellow Solid, Yield 71 %, m.p. 148 Elemental Analysis Calcd $C_{24}H_{15}O_5N_4Br$: IR (KBr/ Cm-1) : 3065,2910,1718 ,1680,1538 ,1495 ,748 cm-1.

2-[2-(4-phenyl phenyl) imidazo[1,2-a] pyridine-3-yl]-3-[(4-methylphenyl)amine]-2, 3-dihydro(5,6,e)benzo-1,3-oxazepine-4,7-dione [9a] .

New oxazepine derivatives from Schiff base (3a) and phthalic anhydride . Off white Solid, Yield 80 % , m.p 185 , Elemental Analysis Calcd $C_{35}H_{25}O_3N_3$: IR (KBr/ Cm-1) : 3081,2893,1717 ,1690 ,1553 ,1491,740 cm-1.

2-[2-(4-phenyl phenyl) imidazo[1,2-a] pyridine-3-yl]-3-(phenylamine)-2,3-dihydro (5,6,e)benzo-1,3-oxazepine-4,7-dione [9b] .

New oxazepine derivatives from Schiff base (3b) and phthalic anhydride. Yellow pale Solid, Yield 69 %, mp.170,Elemental Analysis Calcd $C_{34}H_{23}O_3N_3$:R(KBr /Cm-1):3082 , 2873,1722 ,1693,1547,1492,742 cm-1 . ^{1}H-NMR400MHz(DMSOd-6)δppm:δ 4.2 (1H, s, CH), 6.93(2H,t,ArH), 7.27(2H,t, ArH), 7.33(2H, t, ArH), 7.45(2H,t,ArH), 7.57(2H, d, ArH), 7.60(2H, d, ArH), 7.65(2H,d,ArH),7.69(2H, d, ArH), 7.70(2H, d, ArH), 7.80(1H,d,ArH), 7.83(1H,d,ArH), 8.03(1H, d, ArH), 8.5(1H,d,ArH).^{13}CNMR(400MHz,DMSO d-6): δppm: 110.03(CH), 113.34(2Caromatic),116.74 2Caromatic), 126.36(2Caromatic), 126.71(2Caromatic), 127.96(2C aromatic), 128.07(2C aromatic), 128.08(2Caromatic), 129.07(2C aromatic), 129.08(2Caromatic), 129.25(2C aromatic), 131.27(2C aromatic), 132.86 (2Caromatic), 133.47(3C aromatic), 140.07(2C aromatic), 140.19 (C=N), 144.99(C=N), 169.17(2C=O) .

2-[2-(4-phenyl phenyl) imidazo[1,2-a] pyridine-3-yl]-3-[(4-nitrophenyl)amine]-2,3- dihydro(5,6,e)benzo-1,3-oxazepine-4,7-dione [9c] .

New oxazepine derivatives from Schiff base (3c) and phthalic anhydride.Darkyellow Solid,Yield 78 % ,m.p. 180, Elemental Analysis Calcd $C_{34}H_{22}O_5N_4$: IR (KBr/ Cm-1): 3080, 2885,1720 ,1691,1543,1498,738 cm-1 .

2-[2-(4-bromophenyl) imidazo[1,2-a] pyridine-3-yl]-3-[(4-methylphenyl)amine]-2, 3-dihydro (5,6,e)benzo-1,3-oxazepine-4,7-dione [10a].

New oxazepine derivatives from Schiff base (4a) and phthalic anhydride.brown Solid,Yield 76 %, m.p. 120 Elemental Analysis Calcd $C_{29}H_{20}O_3N_3Br$: IR (KBr/ Cm-1): 3089, 2914,1724 ,1689,1540,1461, 746 cm-1**.**

2-[2-(4-bromo phenyl) imidazo[1,2-a] pyridine-3-yl]-3-(phenyl amine)-2,3-dihydro (5,6,e)benzo-1,3-oxazepine-4,7-dione [10 b].

New oxazepine derivatives from Schiff base (4b) and phthalic anhydride. yellow Solid, Yield 80 %, m.p. 156, Elemental Analysis Calcd $C_{28}H_{18}O_3N_3Br$:IR(KBr /Cm-1): 3056,2804 ,1706,1689,1538,1490,742 cm-1**.**

2-[2-(4-bromo phenyl) imidazo[1,2-a] pyridine-3-yl]-3-[(4-nitrophenyl)amine]-2,3- dihydro(5,6,e)benzo-1,3-oxazepine-4,7-dione

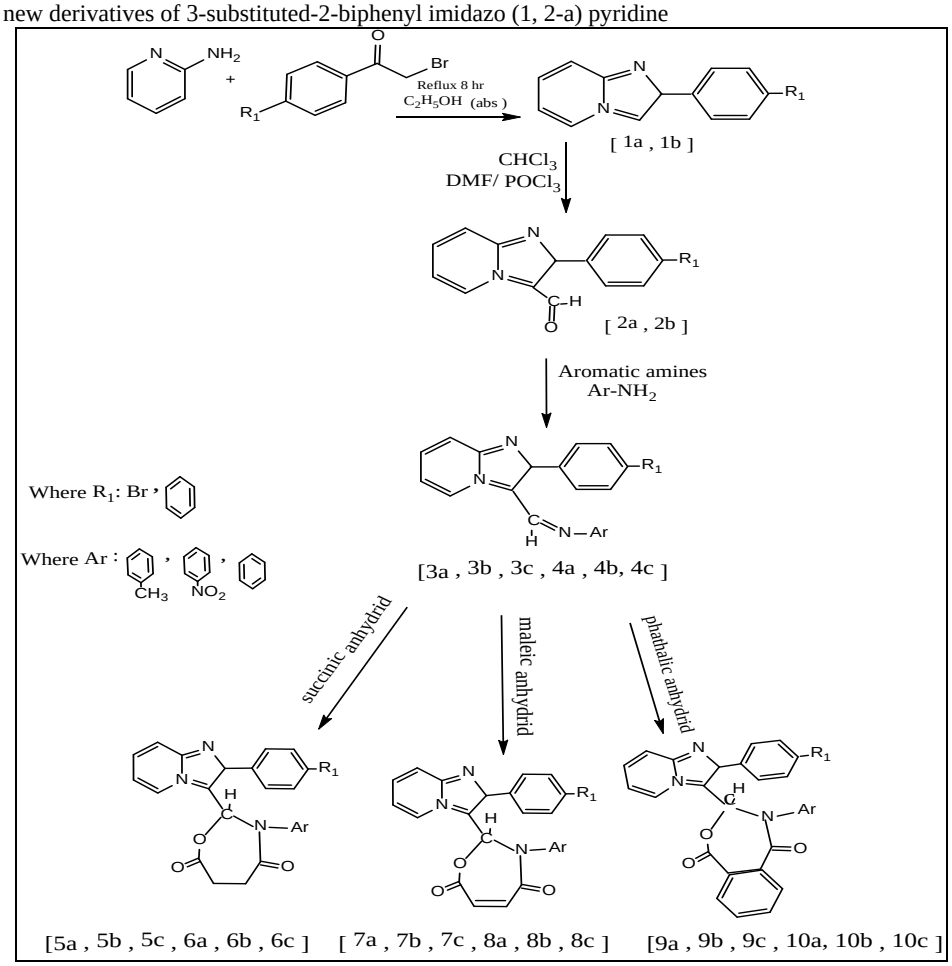
[10 c] .

New oxazepine derivatives from Schiff base (4c) and phthalic anhydride. Yellow Solid,Yield 83% , m.p.150 , Elemental Analysis Calcd $C_{28}H_{17}O_5N_4Br$: IR (KBr / Cm-1): 3065, 2910,1718 ,1680,1540,1490, 748 cm-1**.**

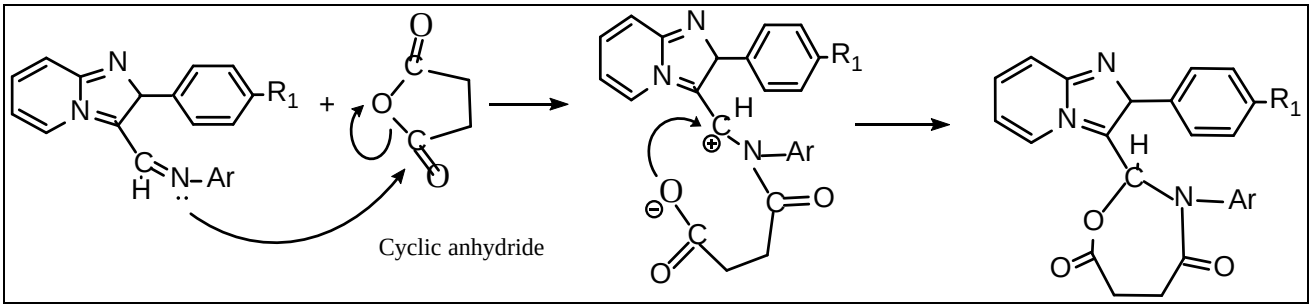
RESULTS AND DISCUSSION

The route for the synthesis of compounds is shown under Scheme 1. The starting materials 2-amino pyridine were reacted with (4-phenyl phenacyl bromide), (4- bromo phenacyl bromide) in Ethanol to give 2-(4- phenyl phenyl) imidazo [1, 2-a] pyridine derivatives [1a] , (4-bromo phenyl) imidazo [1,2-a] pyridine [1 b] . The FT-IR spectra of these derivatives indicated that the peak of amino group was disappeared and appeared new absorption peak at (1590 - 1620 cm-1) owing to (C=N) cyclic imidazo . The second step was Vilsmeier-Haack reaction of compounds (1a , 1b) to give different 2–aryl imidazo (1,2-a) pyridine-3-carbaldehydes (2a , 2b) in good yields. Structures of imidazo pyridine carbaldehydes were confirmed by FTIR spectral data .The compound showed absorption peak (1690 – 1700 cm-1) due to carbonyl absorption of aldehyde group CHO. Carbaldehydes derivatives [2a , 2b] were introduced in multi reactions such as condensation reactions using aromatic amines, 4-methyl aniline , aniline , 4- nitro aniline to afford Schiff bases **[**3a , 3b, 3c] which it derivatives from 2-(4- phenyl phenyl imidazo [1,2-*a*] pyridine-3-carbaldehyde [2a] and [4a ,4b,4c] derivatives from 2-(4- bromo phenyl imidazo [1,2-*a*] pyridine-3-carbaldehyde [2b] **.** The FT-IR spectra of all (3 , 4) compounds showed absorption peaks around (1600 - 1640 cm-1) due to stretching of Schiff base C=N and the peak of carbonyl group CHO was disappeared.While the FT-IRspectra of all compounds (5, 6, 7, 8, 9, 10) showed absorption peaks around (1700-1730cm-1) owing to carbonyl of oxazepine ring and peak of carbonylamide group at (1660–1695cm-1) . The mechanism synthesis of oxazepine shown under Scheme2. In same manner, the formation of other compounds was confirmed.Compounds (2),(3),(4) ,(6a) ,(6b) and (6c) have been screened for their biological assay like antimicrobial activity invitro towards *Staphylococcus aureus* Gram positive and *Pseudomonas aeruginosa* Gram negative bacterial strain and antifungal activity towards *Aspergillus flavus* at a concentration of 40 µg/ml. Most of these compounds showed strong activity and others moderate activity.

Synthesis of some new derivatives of 3-substituted-2-biphenyl imidazo (1, 2-a) pyridine



Scheme 1. Synthetic route of compounds [1- 10]



Scheme 2. Mechanism synthesis of oxazepine

Table 1: Biological activities of several prepared compounds

Comp. NO.	*Staphylococcus aureus(+ve)*	*pseudomonas aerogenosa(-ve)*	*Aspergillus flavus*
3b	**18**	**21**	**12**
4a	**9**	**8**	**10**
5b	**15**	**10**	**---**
6a	**22**	**18**	**15**
7b	**14**	**24**	**18**
8a	**21**	**13**	**12**
9b	**19**	**16**	**---**
10a	**18**	**19**	**11**

Table 2: Effect of of several prepared compounds on liver function enzymes (GOT, GPT and ALP)

Groups		Dose(mg/kg)	GOT Mean ± SD (Unit/L)	GPT Mean ± SD (Unit/L)	ALP Mean ± SD (Unit/L)
Control I: (DMSO)		0.2	32.35 ± 2.02^{BC}	44.81 ± 5.13^{BC}	67.83 ± 2.027^{B}
Control II: CCL_4		0.2	54.06 ± 1.73^{A}	62.03 ± 6.33^{A}	101.57 ± 10.92^{A}
Group III: comp.5c		0.3	14.63 ± 1.73^{E}	23.53 ± 2.40^{D}	39.46 ± 2.96^{D}
Group IV: comp.8b		0.3	21.02 ± 1.73^{E}	27.21 ± 5.69^{D}	41.53 ± 4.37^{D}
Group V: comp.9a		0.3	19.13 ± 3.05^{D}	30.03 ± 2.40^{D}	36.03 ± 2.84^{D}
interactions	**CCL_4+ comp.5c**	0.3	32.76 ± 2.90^{C}	41.26 ± 2.18^{C}	58.93 ± 2.30^{C}
	CCL_4+ comp.8b	0.3	38.17 ± 1.20^{BC}	44.07 ± 2.08^{BC}	64.00 ± 2.08^{BC}
	CCL_4+ comp.9a	0.3	40.01 ± 3.71^{B}	49.65 ± 1.45^{AB}	60.78 ± 2.40^{BC}

Anti-bacterial Activity :

The inhibition of growth of microorganisms against *Staphylococcus aureus* (Gram +ve) and *Pseudomonas aeruginosa* (Gram –ve) at concentration (0.04 g/ml) of compounds with 24 hr, was measured as the Zone of inhibition produced by test and as well as standard drugs using Cup-Plate method. The zone of inhibition of test solution is recorded in Table (1) **.**

Antifungal activity :

Aspergillus flavus was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on Potato dextrose agar extract medium was inoculated with 72 hr. old 0.5ml suspension of fungal spores in a separate flask. The zones of inhibition of test solution are recorded in Table (1) **.**

Histpathological Evaluation of Liver:

Hepatoprotective effects were assessed in albino male mice after inducing hepatic damage with carbon tetrachloride (CCl_4). The parameters of assessment in determined after treatment of mice with three chemical compound one determination liver function enzymes in serum, and histopatholo- -gycal evaluation of liver tissue. The serum was used for the assessment of liver function enzymes (aspartate amino transferase ; AST and alanine amino transferase ; ALT) , in addition to alkaline phosphatase (ALP) . The effect of compounds on liver function enzymes in sera of carbon tetra chloride treated albino male mice recorded in Table (2).

CONCLUSION

Designed and synthesized 28 new analogs substituted imidazo [1, 2-a] pyridine derivatives with different substitution at position 3 and characterized by physical and spectral analysis. These derivatives were evaluated for antimicrobial, antifungal and pharmacological activity. It can be concluded from antimicrobial and antifungal activity screening (Table-1) that compound 3b,6a,7b,8a and 10a were found to be active against *Pseudomonas auroginosa*, *Staphylococcus aureus* and *Aspergillus***.** Further these compounds have a therapeutically properties in the treatment of liver tumors, the parameters of assessment therapeutic effectiveness for compounds 5c,8b and 9a liver function enzymes in serum. The results of interactions indicated tha tall compounds had ability to repair damage produced by CCl_4 for all enzymes as the results show in (Table-2) .

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