Synthesis of 5-Arylfuran derivatives in search of potential anti-viral agents

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Abstract.

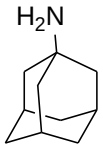
Viral outbreaks are a common cause of morbidity and mortality in livestock and human populations. Lack of good vaccines and poor control measures along with natural viral genetic drifting and shifting are the common causes of new viral strains and outbreaks. The current study reports the synthesis of a series of chalcones derivatives of 5-Arylfuran-2-carbaldehydes. Two important poultry viruses: Avian influenza virus (AIV; A/Chicken/Italy/1994/H9N2) and infectious bronchitis virus (IBV) were selected, grown in 9-11 days old chicken embryonated eggs, and subjected to *in ovo* anti-viral assays. Most of the synthesized compounds were found active against AIV subtype H9N2 and IBV. In the case of AIV, the best results were attained for compound **3,4,6,10,12,13,17** and they retained HA titers at 0 after challenge. The lower titer values of these compounds showed high potency of these compounds, especially in comparison with control groups.The next in order was compound 9 which kept HA titers value at 2. While other compounds were found less effective than above mentioned compounds and they kept the HA titers at 8, 16, 32, 128 and 2048 respectively. While in case of IBV, compound 5,9,13 and 16 found to be more effective and showed titer value zero. While other compounds showed moderate activity against IBV. The standard drugs amantadine and ribavarin were used as positive controls in the case of AIV and IBV, respectively.

Keywords;5-Arylfuran-2-carbaldehyde, Chalcones, Antiviral activity, Antiviral inhibitors etc.

Introduction:

Avian influenza viruses (AIVs) are not only the leading cause of deaths and economic losses in the poultry industry worldwide but also pose great threats to human beings and other species in the ecosystem.[1] Avian influenza viruses constantly fight with the immune system of the host

affecting maturation, cytokine secretion of dendritic cells, and antigenpresenting ability.[2] The H9N2 is a subtype of influenza viruses in chickens and is one of the AIV strains that can also cause human influenza epidemic.[3] Infectious bronchitis virus (IBV) causes respiratory infections in chickens and affects the urogenital and upper respiratory tracts of birds. Nephropathogenic strains cause high death rates in young chickens due to renal pathology compared to other strains.[4]Some anti-virals i.e amantadine **1** and ribavarin **2** are found to be effective against most strains of AIV, but very little experimentally approved data are available.[5]



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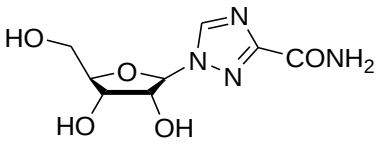

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Chalcone is an α, β-unsaturated carbonyl system and possess varied biological and pharmacological activities, including antimicrobial, anti-inflammatory, analgesic, cytotoxic, antitumor, antimalarial, antitubercular, antiviral, anti-HIV, antiulcerative, antileishmanial, antioxidant, antiprotozoal, antihistaminic, antifedent, immunomodulatory, anticonvulsant, antihyperglycemic, antihyperlipidemic and antiplatelet activities[6-9]. Thus, chalcones continue to attract considerable scientific attention because of their association with a variety of biological activities.We report herein the synthesis of a series of chalcone derivatives, and evaluated for their anti-viral potential against AIV subtype H9N2 and IBV viruses.

Materials and Methods

All reagents and solvents were used as obtained from the supplier or recrystallized or redistilled as necessary. Thin layer chromatography was performed using aluminium sheets (Merck) coated with silica gel 60 F_{254}. IR spectra were recorded using an IR Perkin-Elmer Spectrum 1 FTIR spectrophotometer and peaks were reportedmax(neat)/cm^{-1}which refer to the min wave numbers. Proton magnetic resonance spectra were recorded in $CDCl_3$ with BrukerAM 300 spectrometer (Rheinstetten–Forchheim, Germany) operating at 300 MHz, respectively. The ^{13}C NMR spectra were recorded in $CDCl_3$ with Bruker AM 100spectrometer operating at 100 MHz.Tetramethyl-silanewas used as an internal standard. Elemental analysis for C, H and N were recorded with Perkin-Elmer 2400 Series II CHN Analyzer. Melting points were recorded on a GallenKamp apparatus and are uncorrected

General procedure for the synthesis of Chalcones:

The Chalcones were prepared by method described earlier[10] by the condensation reaction of Aryl aldehydes with various acetophenones in basic media.

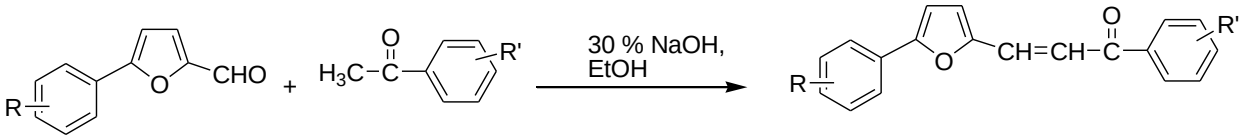
Anti-viral assay.

Antiviral activity was studied by following method described by Mussadiq et al[11] in antiviral studies of thiazolidines derivatives.

Results:

Chemistry

A series of arylfuran-2-carbaldehydes and their chalcone derivatives were synthesized according to Scheme 1. The starting materials were synthesized by catalytic Meerwein arylation of furfural with arenediazonium salts in 40-70% yield, which is fairly good for this reaction. The best yields in the arylation of furfural were obtained with diazonium salts containing a nitro group or two halogen atoms in the aromatic ring, while different chalcones were synthesized by the reaction of arylfurfural and acetophenone derivatives using basic catalyst (NaOH) according to Claisen-Schmidt condensation.



3-17

Scheme 1

Where R and R'= -Cl, -Br, -NO_2, -CH_3, -OCH_3 etc

1-(4'-bromophenyl-3-[5-(2",4"-dichlorophenyl)-2-furyl]-2-propen-1-one (3)

Yield: 2.5 g (80%) **M.P**: 120-22°C **FTIR (KBr) (*v*, cm^{-1}):**2361.49 (Aromatic ring), 1648.62 (C=O conjugated carbonyl group), 1586.20 (C=C conjugated), 1026.06 (C-Br bond), 1463.16 and 1361.92 (Asym and sym -NO_2), **Mass spectra m/z (%):** 422 [M^++2] (100) , 420 [M^+] (63), 341 [M^+-Br] (28), 265 [M^+-PhBr] (28) , 237 [M^+-PhBrCO] (4), 183 [PhBrCO] (91), 157 [PhBr] (57) , 148 [$PhCl_2$] (26),

^{1}H-NMR ($CDCl_3$): δ: 6.9 (2H, d, *J* = 2.7, **furyl proton**), 7.4 (1H, d, *J* = 4.4, **Ar-H**), 7.6 (1H, d, *J* = 15.6, **ethylenic**), 7.7 (2H, d, *J* = 2.7, **Ar-H**), 7.9 (1H, d, *J* = 15.6, **ethylenic**), 8.3 (1H, d, *J* = 4.4, **Ar-H**), 8.4 (1H, d, *J* = 4.4, **Ar-H**), 8.7 (1H, d, *J* = 4.4, **Ar-H**) **^{13}C-NMR ($CDCl_3$): δ:** 187.18 (C=O), 130.24, 127.92 (C=C), 153.58, 148.56, 132.88, 131.03, 130.50, 130.39, 129.97, 129.77, 129.32, 126.71, 123.11, 122.38, 113.60, 112.41 (Ar-C) **Anal.Calcd.for** $C_{19}H_{11}BrCl_2O_2$: C 54.28; H 2.62 % **Found** C 53.9; H 2.15 %.

1-(4'-bromophenyl-3-[5-(2"-methyl-3"-nitrophenyl)-2-furyl]-2-propen-1-one (4)

Yield: 2.6 g (83%) **M.P**: 162-64°C **FTIR (KBr) (*v*, cm^{-1}):**2363.87(Aromatic ring), 1664.81 (C=O conjugated carbonyl group), 1590.87 (C=C conjugated), 1042.56 (C-Br bond), 1533.70 and 1369.75 (Asym and sym -NO_2), **Mass spectra m/z (%):** 413 [M^++ 2] (67) , 411 [M^+] (65) , 277 [M^++ 2- $PhNO_2CH_3$] (67), 183 [PhBrCO] (67) , 76 [Ph] (39), **^{1}H-NMR ($CDCl_3$): δ:** 8.534-7.604 (8H, m, **Ar-H**,), 7.282 (1H, d, *J* = 15.8, **ethylenic**), 7.259 (1H, d, *J* = 15.8, **ethylenic**), 7.028 (1H, d, *J* = 3.2, **furyl proton**), 6.012 (1H, d, *J* = 3.2, **furyl proton**), 2.005 (3H, s, **CH_3**) **^{13}C-NMR ($CDCl_3$): δ:** 187.66 (C=O), 131.38, 127.23 (C=C), 153.21, 151.97, 151.31, 136.42, 131.86, 131.66, 130.40, 130.35, 128.18, 127.32, 123.56, 119.29, 119.10, 114.38 (Ar-C) 35.60 (CH_3) **Anal.Calcd.for** $C_{20}H_{14}BrNO_4$: C 58.39; H 3.40; N 3.40 %. **Found** C 58.45; H 3.34; N 3.38 %.

1-(4' -bromophenyl)-3-[5-(2"-nitrophenyl)-2-furyl]-2-propen-1-one (5)

Yield: 2.5 g (80%) **M.P**: 126°C **FTIR (KBr) (*v*, cm^{-1}):** 2341.83 (Aromatic ring), 1652.29 (C=O conjugated carbonyl group), 1594.31(C=C conjugated), 1025.87 (C-Br bond), 1518.76 and 1352.76 (Asym and sym -NO_2), **Mass spectra m/z (%):**399 [M^++2] (28) , 397 [M^+] (32) , 352 [M^+-NO_2] (6), 275 [M^+-$PhNO_2$] (4), 209 [PhBrCOCH=CH] (27) , 203 [furyl$PhNO_2CH$]

(8) , 195 [PhBrCOCH] (16) , 183 [PhBrCO] (100) , 157 [PhBr] (60), 76 [Ph] (44), **^{1}H-NMR ($CDCl_3$): δ:** 7.904-7.422 (8H, m, **Ar-H**), 7.383 (1H, d, *J* = 16.6, **ethylenic**), 7.240 (1H, d, *J* = 16.6, **ethylenic**), 6.803 (1H, d, *J* = 2.7, **furyl proton**), 6.782 (1H, d, *J* = 2.7, **furyl proton**) **^{13}C-NMR ($CDCl_3$): δ:** 188.56 (C=O), 131.92, 127.38 (C=C), 156.10, 151.28, 148.90, 140.76, 133.40, 132.46, 130.62, 128.64, 126.12, 121.54, 118.76, 113.44(Ar-C) **Anal.Calcd.for** $C_{19}H_{12}BrNO_4$: C 57.43; H 3.02; N 3.52 %. **Found** C 57.11; H 2.60; N 3.31 %.

1-(4'-chlorophenyl-3-[5-(2"-methyl-3"-nitrophenyl)-2-furyl]-2-propen-1-one (6)

Yield: 2.6 g (82%) **M.P**: 158-60°C **FTIR (KBr) (*v*, cm^{-1}):** 2361.22 (Aromatic ring), 1660.08(C=O conjugated carbonyl group), 1590.20 (C=C conjugated), 1094.09(C-Cl bond), 1519.98 and 1360.14 (Asym and sym -NO_2) **Mass spectra m/z (%):** 369 [M^++2] (12), 367 [M^+] (45), 320 [M^+-NO_2] (9), 139 [PhClCO] (85) , 111 [PhCl] (78) , 75 [Ph] (55) , **^{1}H-NMR ($CDCl_3$): δ:** 8.136(1H, s, **Ar-H**), 8.115(1H, d, *J* = 6, **Ar-H**), 7.870(1H, d, *J* = 6, **Ar-H**), 7.660(1H, d, *J* = 6.6, **Ar-H**), 7.639(1H, d, *J* = 6.6, **Ar-H**), 7.617 (1H, d, *J* = 6, **Ar-H**), 7.574(1H, d, *J* = 6, **Ar-H**), 7.890(1H, d, *J* = 15.5, **ethylenic**), 7.296 (1H, d, *J* = 15.4, **ethylenic**), 7.119(1H, d, *J* = 2.8, **furyl proton**), 7.110 (1H, d, *J* = 2.8, **furyl proton**), 2.521 (3H, s, C**H$_3$**), **^{13}C-NMR ($CDCl_3$): δ:** 187.98 (C=O), 131.60, 127.26 (C=C), 16.42 (CH_3), 155.60, 153.50, 152.08, 151.93, 148.16, 134.50, 132.24, 130.27, 130.22, 123.49, 119.16, 114.29 (Ar-C), **Anal.Calcd.for** $C_{20}H_{14}ClNO_4$: C 65.39; H 3.81; N 3.81 %. **Found** C 64.90; H 3.33; N 3.27 %.

1-(4'-chlorophenyl)-3-[5-(2",4"-dichloro-5"-nitrophenyl)-2-furyl]-2-propen-1-one (7)

Yield: 1.3 g (60%) **M.P**: 192°C **FTIR (KBr) (*v*, cm^{-1}):**2364.01 (Aromatic ring), 1663.21 (C=O conjugated carbonyl group), 1588.56 (C=C conjugated), 1543.67 and 1345.76 (Asym and sym -NO_2), 1089.00 (C-Cl bond) **Mass spectra m/z (%):** 423 [M^++2] (63), 421 [M^+] (64), 386 [M^+-Cl] (16), 310 [M^+-PhCl] (14), 231 [M^+-PhCl(NO_2)$_2$] (64), 139 [PhClCO] (100) , 111

[PhCl] (88) , 75 [Ph] (36) **^{1}H-NMR ($CDCl_3$): δ:** 7.093 (1H, d, *J* = 3.3, **furyl proton**) , 7.350 (1H, d, *J* = 3.3, **furyl proton)**, 7.598 (1H, d, *J* = 15.7, **ethylenic**), 8.065-7.619 (4H, m, **Ar-H**), 7.611 (1H, d, *J* = 15.9, **ethylenic**), 8.474 (1H, s, **Ar-H**), 8.093(1H, s, **Ar-H**) **^{13}C-NMR ($CDCl_3$): δ:** 187.49 (C=O), 130.24, 128.97, (C=C) 152.34, 147.40138.13, 135.95, 135.85, 130.31, 123.85, 123.77, 123.47, 119.88, 116.03(Ar-C) **Anal.Calcd.for** $C_{19}H_{10}Cl_3NO_4$: C 57.00; H 2.37; N 3.32 %. **Found** C 56.86; H 1.98; N 2.81 %.

1-(4'-chlorophenyl-3-[5-(2"-methyl-5"-nitrophenyl)-2-furyl]-2-propen-1-one (8)

Yield: 2.5 g (80%) **M.P**: 176-78°C **FTIR (KBr) (*v*, cm^{-1}):**2359.32 (Aromatic ring), 1655.89 (C=O conjugated carbonyl group), 1588.76(C=C conjugated), 1529.76 and 1335.56 (Asym and sym -NO_2), 1087.54 (C-Cl bond) **Mass spectra m/z (%):** 369 [M^++2] (45), 367 [M^+] (60), 332 [M^+-Cl] (6), 256 [M^+-PhCl] (6), 191 [PhClCOCHCHCO] (100) , 139 [PhClCO] (82) , 111 [PhCl] (50) , 75 [Ph] (20), **^{1}H-NMR ($CDCl_3$): δ:** 2.70 (3H, s, **CH_3**) 6.88 (2H, d, *J* = 3.1, **furyl proton**), 7.90 (2H, d, *J* = 15.9, **ethylenic**), 8.7 (1H, d, *J* = 3.9, **Ar-H**), 8.2 (1H, d, *J* = 3.9, **Ar-H**), 8.00 (3H, d, *J* = 3.1, **Ar-H**), 7.5 (4H, m, **Ar-H**), **^{13}C-NMR ($CDCl_3$): δ:** 187.66 (C=O), 130.31, 128.98, (C=C) 151.40, 142.72 138.07, 136.16, 133.02, 130.41, 122.69, 121.46, 119.45, 119.32, 114.20 (Ar-C) 21.89 (CH_3) **Anal.Calcd.for** $C_{20}H_{14}ClNO_4$: C 65.39; H 3.81; N 3.81 %. **Found** C 65.19; H 3.18; N 3.19 %.

1-(4"-chlorophenyl)-3-[5-(2"-methyl-4"-nitrophenyl)-2-furyl]-2-propen-1-one (9)

Yield: 2.6 g (90%) **M.P**: 102-04°C **FTIR (KBr) (*v*, cm^{-1}):**2360.51 (Aromatic ring) 1658.77 (C=O conjugated carbonyl group), 1596.33(C=C conjugated), 1092.02 (C-Br bond), 1552.00 and 1334.74 (Asym and sym -NO_2), **Mass spectra m/z (%):** 369 [M^++2] (8), 367 [M^+] (35), 332 [M^+-Cl] (4), 256 [M^+-PhCl] (6), 139 [PhCOCl] (94), 111 [PhCl] (46), **^{1}H-NMR ($CDCl_3$): δ:**

8.619-8.071 (6H, m, **Ar-H**), 7.675 1H, d, *J* = 14.9, **ethylenic**), 7.520 (1H, d, *J* = 14.9, **ethylenic**), 7.353 (1H, d, *J* = 2.7, **Ar-H**), 6.996 (1H, d, *J* = 2.4, **furyl proton**), 6.923 (1H, d, *J* = 2.4, **furyl proton**), 2.150 (3H, s, **Ar-H**), **^{13}C-NMR ($CDCl_3$): δ:** 178.36 (C=O), 131.01, 124.87 (C=C), 155.47, 152.23, 148.57, 130.93, 130.70, 130.42, 129.75, 123.90, 123.06, 122.35, 120.62, 119.21, 118.66, 111.67, 110.83 (Ar-C)**,** 54.78 (CH_3) **Anal.Calcd.for** $C_{20}H_{14}ClNO_4$: C 65.39; H 3.81; N 3.81 %. **Found** C 65.13; H 3.45; N 3.56 %.

1-(4'-nitrophenyl)-3-[5-(2"-chloro-5"-nitrophenyl)-2-furyl]-2-propen-1-one (10)

Yield: 2.5 g (80%)**M.P**: 158-60°C **FTIR (KBr) (*v*, cm^{-1}):** 2360.54 (Aromatic ring), 1662.56 (C=O conjugated carbonyl group), 1587.97(C=C conjugated), 1550.36 and 1345.74 (Asym and sym -NO_2), 1093.21 (C-Cl bond), **Mass spectra m/z (%) :** 400 [M^++2] (18), 398 [M^+] (56), 352 [M^+-NO_2] (45), 276 [M^+-$PhNO_2$] (12) , 242 [M^+-$PhNO_2CO$] (73), 156 [$PhNO_2Cl$] (58), 150 [$PhNO_2CO$] (100) , 122 [$PhNO_2$] (34), 76 [Ph] (10), **^{1}H-NMR ($CDCl_3$): δ:** 6.950 (1H, d, *J* = 2.5, **furyl proton**), 7.350 (1H, d, *J* = 2.5, **furyl proton**), 7.790 (2H, d, *J* = 16.2, **ethylenic**), 7.460 (2H, d, *J* = 16.2, **ethylenic**), 8.845 (1H, s, **Ar-H**), 8.239-7.950 (6H, m, **Ar-H**),**^{13}C-NMR ($CDCl_3$): δ:** 179.55 (C=O), 134.21, 127.60 (C=C), 154.66, 151.92, 137.75, 133.78, 130.90, 128.63, 126.78, 124.61, 122.34, 118.90, 109.70 (Ar-C), **Anal.Calcd.for** $C_{19}H_{11}ClN_2O_6$**:** C 57.28; H 2.76; N 7.03 %. **Found** C 57.03; H 2.44; N 6.65 %.

1-(4'-nitrophenyl)-3-[5-(4''-chloro-2''-nitrophenyl)-2-furyl]-2-propen-1-one (11)

Yield: 1.9 g (78%)**M.P**: 192°C **FTIR (KBr) (*v*, cm^{-1}):**2336.34 (Aromatic ring), 1661.14 (C=O conjugated carbonyl group), 1588.93 (C=C conjugated), 1572.18 and 1344.38 (Asym and sym -NO_2), 1029.51(C-Cl bond), **Mass spectra m/z (%):**400 [M^++2] (18), 398 [M^+] (41), 353 [M^+-NO_2] (5), 248 [M^+-$PhNO_2CO$] (13) , 222 [M^+-176] (54), 150 [$PhNO_2CO$] (100), 104 [PhCO]

(41), 76 [Ph] (28) ,**^{1}H-NMR ($CDCl_3$): δ:** 8.357 (2H, d, *J* = 6.6, **Ar-H**), 8.165 (2H, d, *J* = 6.6, **Ar-H**), 7.722 (1H, d, *J* = 5.7, **Ar-H**), 7.604 (1H, d, *J* = 5.7, **Ar-H**), 7.583 (1H, d, *J* = 5.4, **Ar-H**), 7.422 (1H, d, *J* = 16.4, **ethylenic**), 7.240 (1H, d, *J* = 16.4, **ethylenic**), 6.854 (1H, d, *J* = 2.7, **furyl proton**), 6.807 (1H, d, *J* = 2.7, **furyl proton**) **^{13}C-NMR ($CDCl_3$): δ:** 187.87(C=O), 130.91, 127.95 (C=C), 152.06, 149.80, 149.43, 147.21, 142.28, 134.03, 132.37, 130.40, 130.29, 129.77, 129.55, 124.00, 122.36, 119.75, 113.54 (Ar-C) **Anal.Calcd.for** $C_{19}H_{11}ClN_2O_6$**:** C 57.28; H 2.76; N 7.03 %. **Found** C 57.23; H 2.71; N 6.98 %.

1-(4'-nitrophenyl)-3-[5-(2'', 4''-dichlorophenyl)-2-furyl]-2-propen-1-one (12)

Yield: 2.2 g (72%)**M.P**: > 166°C (decomp.)**FTIR (KBr) (*ν*, cm^{-1}):**1662.66(C=O conjugated carbonyl group), 1588.11(C=C conjugated) 1520.54 and 1344.79 (Asym and sym -NO_2), 1027.90 (C-Cl bond),

Mass spectra m/z (%): 389 [M^++2] (33), 387 [M^+] (100), 352 [M^+-Cl] (17), 341 [M^+-NO_2] (10), 242 [M^+-$PhCl_2$] (37), 150 [$PhCONO_2$] (36), 120 [furanCH=CHCO] (15), 92 [furanCH=CH] (6), 76 [Ph] (9),**^{1}H-NMR ($CDCl_3$): δ:**8.142 (2H, d, *J* = 6, **Ar-H**), 8.166 (2H, d, *J* = 6, **Ar-H**), 7.90 (1H, d, *J* = 2.1, **Ar-H**), 7.855 (1H, d, *J* = 2.1, **Ar-H**), 7.659 (1H, s, **Ar-H**), 7.497 (1H, d, *J* = 4.4, **Ar-H**), 7.408 (1H, d, *J* = 14.9, **ethylenic**), 7.257 (1H, d, *J* = 14.9, **ethylenic**), 7.218 (1H, d, *J* = 3.1, **furyl proton**), 6.914 (1H, d, *J* = 3.1, **furyl proton**) **^{13}C-NMR ($CDCl_3$): δ:** 187.18(C=O), 130.24, 127.92 (C=C), 153.58, 148.56, 132.88, 131.03, 130.50, 130.39, 129.32, 126.71, 123.11, 122.38, 113.60, 112.41 (Ar-C) **Anal.Calcd.for** $C_{19}H_{11}Cl_2NO_4$**:** C 58.91; H 2.84; N 3.61 %. **Found** C 58.90; H 2.81; N 3.56 %.

1-(3'-nitrophenyl)-3-[5-(2"-chloro-5"-nitrophenyl)-2-furyl]-2-propen-1-one (13)

Yield: 2.7 g (88%) **M.P**: 168-70°C **FTIR (KBr) (*v*, cm^{-1}):**2360.57 (Aromatic ring), 1660.44 (C=O conjugated carbonyl group), 1582.08 (C=C conjugated), 1529.33 and 1344.76 (Asym and sym -NO_2), **Mass spectra m/z (%):**400 [M^++2] (21), 398 [M^+] (100), 351 [M^+- NO_2] (10), 276 [M^+- $PhNO_2$] (42), 242 [M^+-$PhClNO_2$] (75), 150 [$PhNO_2CO$] (70), 76 [Ph] (68), **^{1}H-NMR (CDCl$_3$): δ:** 8.540-7.980 (5H, m, Ar-H), 7.765 (1H, d, *J* = 15.6, **ethylenic**), 7.450 (1H, d, *J* = 15.6, **ethylenic**), 7.128 (1H, d, *J* = 2.7, **furyl proton**), 6.650 (1H, d, *J* = 2.7, **furyl proton**), 8.780 (2H, s, **Ar-H**) **^{13}C-NMR (CDCl$_3$): δ:** 186.98 (C=O), 131.98, 127.34 (C=C), 155.45, 151.28, 137.67, 132.18, 130.69, 129.44, 126.48, 122.76, 121.65, 118.78, 109.94 (Ar-C) **Anal.Calcd.for** $C_{19}H_{11}ClN_2O_6$: C 57.28; H 2.76; N 7.03%. **Found** C 57.05; H 2.35; N 6.78%.

1-(3'-nitrophenyl)-3-[5-(2",4"-dichlorophenyl)-2-furyl]-2-propen-1-one (14)

Yield: 2.2 g (76%) **M.P**: 158-60°C **FTIR (KBr) (*v*, cm^{-1}):** 2359.73 (Aromatic ring), 1652.13 (C=O conjugated carbonyl group), 1588.29(C=C conjugated), 1573.47 and 1345.76 (Asym and sym -NO_2), 1086.19(C-Cl bond), **Mass spectra m/z (%):** 389 [M^++2] (38), 387 [M^+] (100), 352 [M^+- Cl] (15), 265 [M^+- $PhNO_2$] (25), 242 [M^+- $PhCl_2$] (30) , 150 [$PhCONO_2$] (9), 111 [PhCl] (51), 76 [Ph] (19), **^{1}H-NMR (CDCl$_3$): δ:** 8.753 (1H, s, **Ar-H**), 8.593 (1H, d, *J* = 5.7, **Ar-H**), 8.508 (1H, d, *J* = 5.7, **Ar-H**), 8.205 (1H, d, *J* = 6.3, Ar-**H**), 7.907 (1H, d, *J* = 15, **ethylenic**), 7.817 (1H, d, *J* = 15, **ethylenic**), 7.415 (1H, d, *J* = 2.7, **furyl proton**), 7.314 (1H, d, *J* = 2.7, **furyl proton**) 7.714 (1H, s, **Ar-H**), 7.676 (2H, s, Ar-H) **^{13}C-NMR (CDCl$_3$): δ:** 188.17(C=O), 132.09, 129.89, (C=C), 156.93, 152.72, 149.40, 146.86, 140.39, 139.43, 136.29, 135.00, 134.74, 133.91, 129.72, 129.55 124.22, 120.09, 117.90, 112.74 (Ar-C) **Anal.Calcd.for** $C_{19}H_{11}Cl_2NO_4$: C 58.91; H 2.84; N 3.61%. **Found** C 58.68; H 2.61; N 3.48%

1-(3'-nitrophenyl)-3-[5-(2"-methyl-4"-nitrophenyl)-2-furyl]-2-propen-1-one (15)

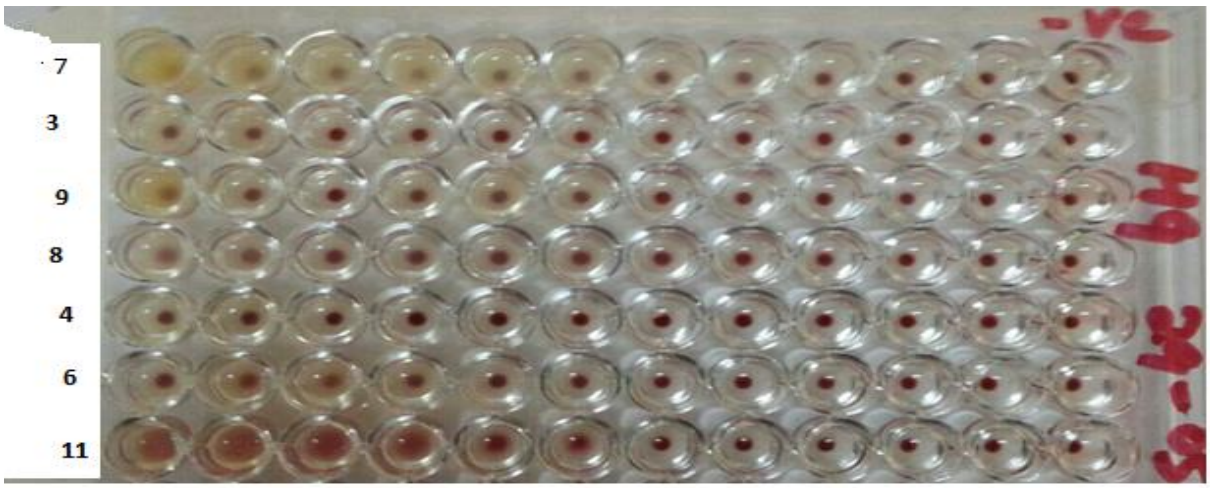
Yield: 2.1 g (75%) **M.P**: 150-52°C **FTIR (KBr) (*v*, cm^{-1}):**2360.57(Aromatic ring), 1660.92 (C=O conjugated carbonyl group), 1591.52(C=C conjugated), 1513.19 and 1338.75 (Asym and sym -NO_2), **Mass spectra m/z (%) :** 378 [M^+] (46), 331 [M^+- NO_2] (8), 242 [M^+-136] (16) , 215 [M^+-163] (16), 202 [M^+-176] (100), 163 [$PhNO_2COCH$] (34) , 76 [C_6H_4] (28), **^{1}H-NMR ($CDCl_3$): δ:** 8.378-7.980 (7H, m, Ar-H) , 7.954 (1H, d, *J* = 15.8, ethylenic), 7.789 (1H, d, *J* = 15.8, ethylenic), 7.287 (1H, d, *J* = 3.1, furyl proton) , 6.950 (1H, d, *J* = 3.1, furyl proton) , 2.957 (3H, s, CH_3), **^{13}C-NMR ($CDCl_3$): δ:** 178.65 (C=O), 133.24, 127.90 (C=C), 154.98, 153.87, 151.65, 151.65, 148.78, 137.65, 131.25, 129.86, 125.46, 123.45, 122.76, 119.78, 109.78 (Ar-C), 22.68 (CH_3), **Anal.Calcd.for** $C_{20}H_{14}N_2O_6$**:** C 63.49; H 3.70; N 7.40%. **Found** C 63.25; H 3.58; N 7.25%.

1-(3',4',5'-trimethoxyphenyl)-3-[5-(2"-chloro-5"-nitrophenyl)-2-furyl]-2-propen-1-one (16)

Yield: 2.6 g (82%) **M.P**: 202-04°C **FTIR (KBr) (*v*, cm^{-1}):**2360.49(Aromatic ring), 1652.43 (C=O conjugated carbonyl group), 1596.36(C=C conjugated), 1555.86 and 1345.80 (Asym and sym -NO_2), **Mass spectra m/z (%):**445 [M^++2] (23), 443 [M^+] (100), 428 [M^+- CH_3] (42), 276 [M^+-Ph $(OCH_3)_3$] (12), 195 [Ph $(OCH_3)_3CO$] (26), **^{1}H-NMR ($CDCl_3$): δ:** 8.290 (2H, s, Ar-H), 8.157-7.985 (3H, m, Ar-H) , 7.590 (1H, d, *J* = 15.3, ethylenic), 7.789 (1H, d, *J* = 15.3, ethylenic), 7.125 (1H, d, *J* = 3.3, furyl proton) , 6.998 (1H, d, *J* = 3.3, furyl proton) , 3.650 (3H, s, OCH_3), 3.735 (6H, s, OCH_3), **^{13}C-NMR ($CDCl_3$): δ:** 177.45 (C=O), 134.12, 128.78 (C=C), 155.78, 154.78, 151.65, 151.29, 150.76, 148.70, 137.65, 126.42, 123.44, 122.89, 121.65, 118.46, 109.75 (Ar-C), 50.98 (OCH_3) **Anal.Calcd.for** $C_{22}H_{18}ClNO_7$**:** C 59.59; H 4.06; N 3.16 %. **Found** C 59.28; H 3.78; N 2.92%.

1-(3',4',5'-trimethoxyphenyl)-3-[5-(4"-carboxyphenyl)-2-furyl]-2-propen-1-one (17)

Yield: 2.5 g (80%) **M.P**: 208-210°C **FTIR (KBr) (*v*, cm^{-1}):** 2365.25 (Aromatic ring), 1690.79 (C=O acid), 1610.98 (C=O conjugated carbonyl group), 1610.65 (C=C conjugated), 3240.76 (-OH) **Mass spectra m/z (%):** 408 [M^+] (100), 395 [M^+- CH_3] (34), 241 [M^+-Ph $(OCH_3)_3$] (10), 213 [M^+-Ph $(OCH_3)_3CO$] (76), 195 [Ph $(OCH_3)_3CO$] (50), 167 [Ph $(OCH_3)_3$] (18), **^{1}H-NMR ($CDCl_3$): δ:** 8.367 (2H, s, Ar-H), 8.234-7.992 (4H, m, Ar-H) , 7.885 (1H, d, *J* = 15.8, ethylenic), 7.653 (1H, d, *J* = 15.8, ethylenic), 7.543 (1H, d, *J* = 2.7, furyl proton) , 7.021 (1H, d, *J* = 2.7, furyl proton) , 3.554 (3H, s, OCH_3), 3.760 (6H, s, OCH_3) 10.520 (1H, s, COO**H**) **^{13}C-NMR ($CDCl_3$): δ:** 179.80 (C=O), 134.56, 127.89 (C=C), 167.80 (C=O of acid), 155.45, 155.20, 154.30, 151.67, 151.19, 137.65, 132.56, 130.80, 129.87, 126.56, 122.65, 118.45, and 108.97 (Ar-C), 56.92 (OCH_3) **Anal.Calcd.for** $C_{23}H_{20}O_7$: C 67.64; H 4.90%.; **Found** C 67.25; H 4.59%.;



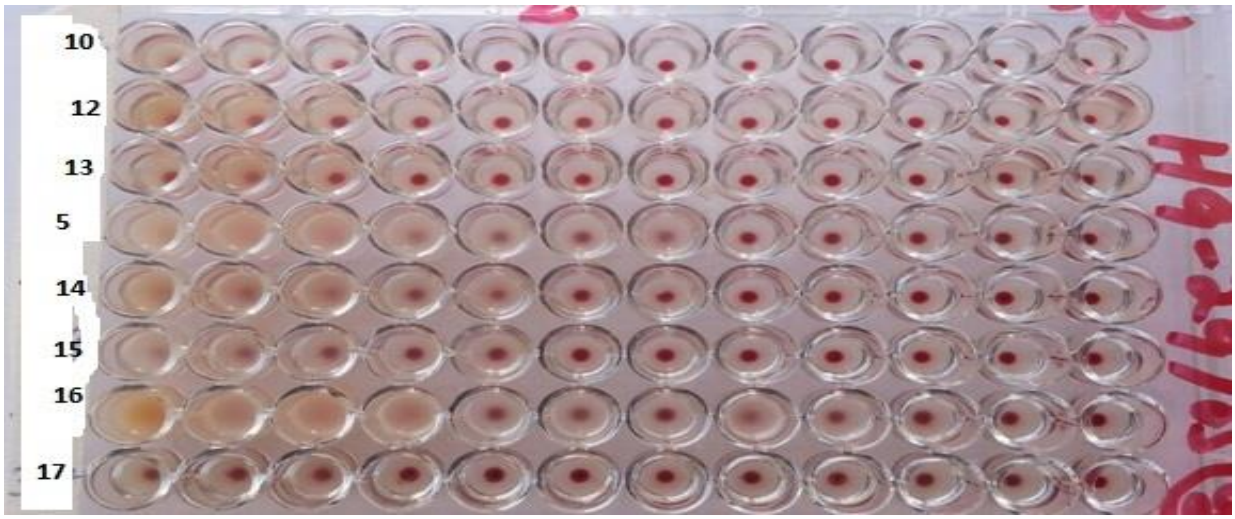
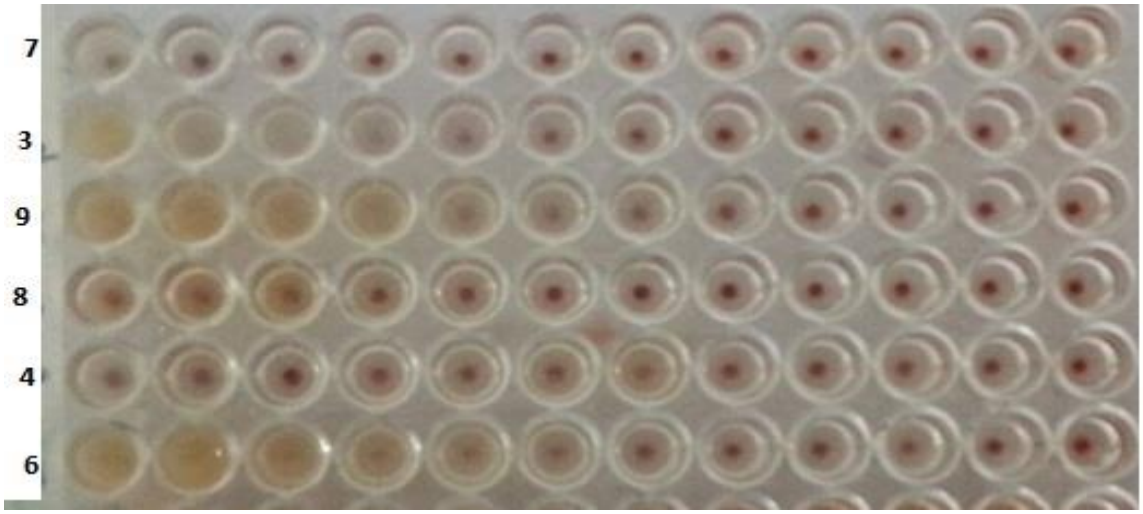
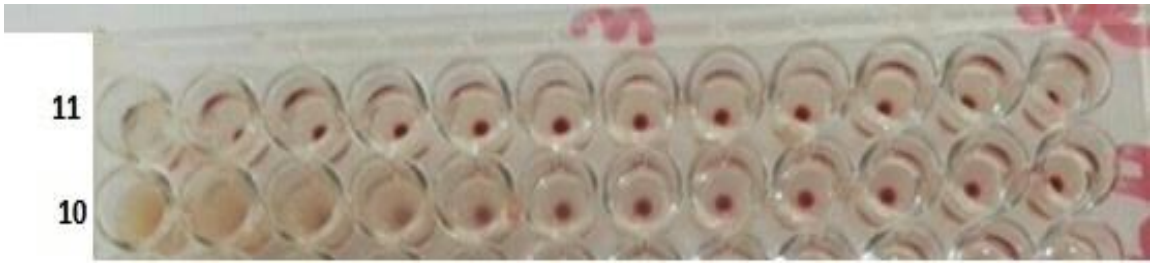


Fig1: Representative antiviral activity of compound 3-17 of AIV





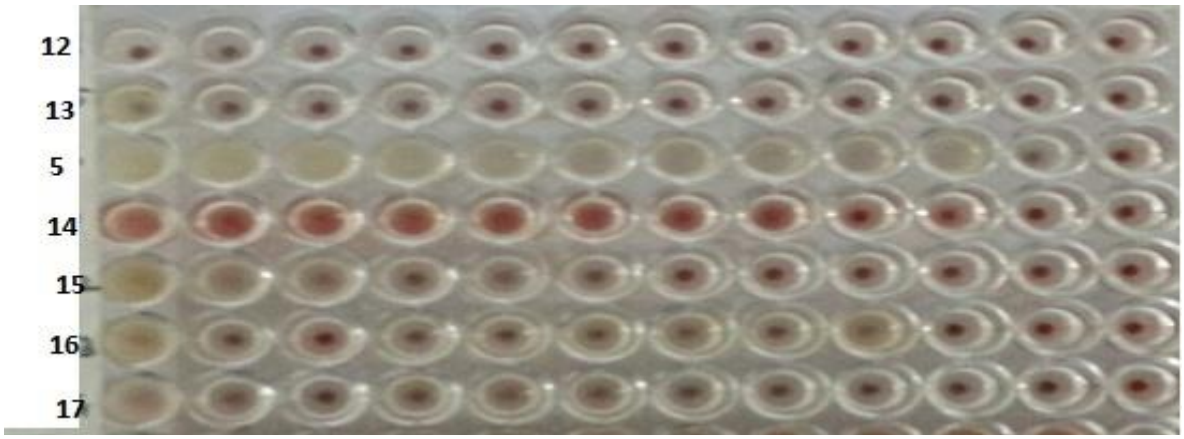


Fig2: Representative antiviral activity of compound 3-17 of IBV

Discussion:

Viral diseases are a major threat to living organisms ranging from humans to plants and large mammals to poultry. Several preventive measures have been made to control viral infections including the development of a vaccine, synthesis of new potent anti-viral drugs, and using plant extracts as anti-viral drugs.[12-21] As we know, viruses can mutate and develop resistance against available drugs. Some viruses like IBV do not have proper medicine in the field. So, there is an urgent need to develop new and more potent anti-viral drugs. Advance studies in the molecular biology of viruses have highlighted many potential targets for anti-viral drugs. Amino acid derivatives of different been known for their anti-viral ability against different poultry, animal, plant, and human viruses.16 Amino acid derivatives of 4-chloro-3,5-dinitrobenzotrifluoride are found potential plant activator against tomato yellow leaf virus. These compounds have substantially reduced the viral DNA level in plants.[22] The β-amino acid ester derivatives containing quinazoline and benzothiazole moieties have been evaluated for their anti-viral potential against the tobacco mosaic virus and showed variable inhibitory effects.[23]

Pure chalcones and their synthetic analogs have not been intensively studied for their potency as antivirals inhibitors. According to the published scientific literature, the antiviral properties of a

number of chalcones have been studied on some plant and human viruses. However, experimental data show that the various antiviral activities of the studied chalcones depend on their specific substitution patterns.[24]

Chalcones derivatives having thiophene sulphonate group showed antiviral efficiency against tobacco masaic virus TMV, while chalcones derivatives having pyrazole moiety showed activity against herpes virus. A set of naphthalene-benzofuran chalcones was synthesized and evaluated for antiviral activity against hepatitis A virus (HAV). [25]

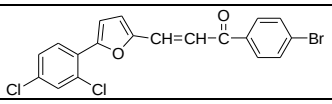
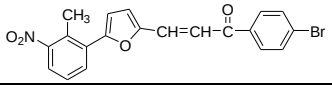
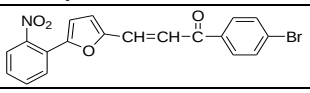
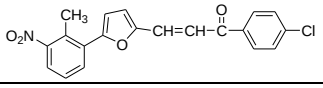
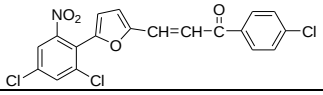
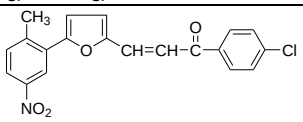
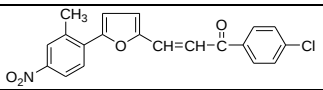
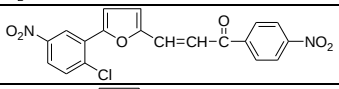
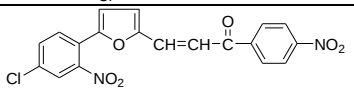
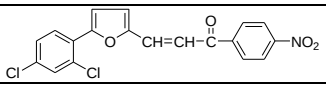
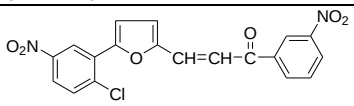
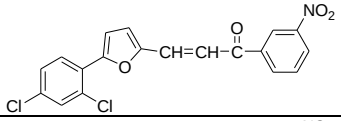
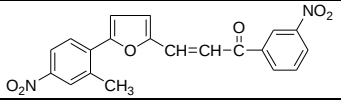
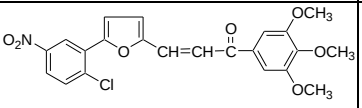
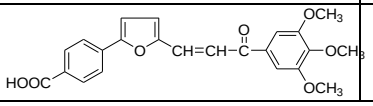
In the current study, 5-Arylfuran-2-carbaldehydes has been utilized for the synthesis of chalcones. Starting from 5-Arylfuran-2-carbaldehydes, a series of chalcones were prepared from their reaction with various acetophenone derivatives i.e 4-chloro actophenone, 4-bromo acetophenone, 4-bromo acetophenone, 3-nitro acetophenone and 3,4,5-trimethoxy acetophenone.

In our laboratory, a series of chalcones were previously were prepared and reported showd excellent potential as antioxidant and antibacterial agents.[26] To the best of our knowledge, no studies have been previously reported for chalcone derivatives against IBV and AIV strain H9N2. During performing anti-viral evaluations against selected viruses, compounds **3-17** were found anti-AIV and anti-IBV positive, the best antiviral activity was shown by **3, 4, 6, 10, 12, 13** and **17** in the case of AIV H9N2 (0 HA Titer). While in the case of IBV, compounds **5, 9, 13** and **16** showed excellent antiviral activity having Zero HA Titer value. All other compounds also showed good anti-viral activity except **16** which showed least activity i.e. 2048 for AIV H9N2.

The HA Titer values of cahcones derivatives of 5-Arylfuran-2-carbaldehydes are several times lower than positive controls, amantadine, and ribavarin, which indicates the potency of these compounds. All compounds showed better results against AIV H9N2 and IBV and shown in Fig **1 and 2 and** in **Table 1.** A graphical representation of antiviral activities of synthesized compounds against AIV H9N2 and IBV is given in Figure **3 and 4**.

The study concludes that chalcone derivatives **3-17** having –Cl, -Br, -NO_2, -CH_3 and –OCH_3 groups were better anti-viral drugs and support the idea that these synthesized compounds are good anti-viral drugs and hold the promise to be used as anti-viral agents against AIV H9N2 and IBV infections in near future.

Table 1.: Anti-avian influenza virus (AIV) H9N2 and anti-infectious bronchitis virus (IBV) activities of Chalcones derivatives.

S.no	Structure of Product	AIV		IBV	
		*HA Titer	Virus Control	*HA Titer	Virus Control
3		0	2048	16	2048
4		0	2048	4	2048
5		16	2048	0	2048
6		0	2048	16	2048
7		8	2048	2	2048
8		8	2048	32	2048
9		2	2048	0	2048
10		0	2048	256	2048
11		32	2048	8	2048
12		0	2048	2	2048
13		0	2048	0	2048
14		32	2048	32	2048
15		32	2048	32	2048
16		2048	2048	0	2048
17		0	2048	8	2048

*Hemagglutination (HA) titer 0-8: Strongly effective drug (no growth or very limited growth of virus); 16-32: Effective drug (limited growth of the virus, the drug has controlled viral growth effectively); 64-128: Moderately effective drug (the drug is not able to control the growth of virus very efficiently, but it is still able to control growth to some extent); 256-2048: Ineffective drug (unable to control the growth of virus).

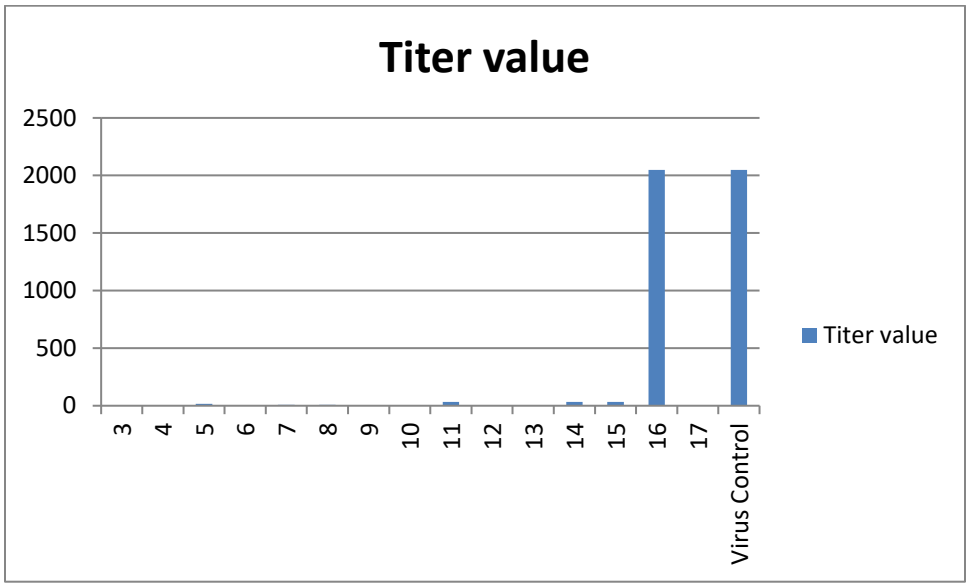


Fig3: Antiviral activity of synthesized compound 3-17 against AIV

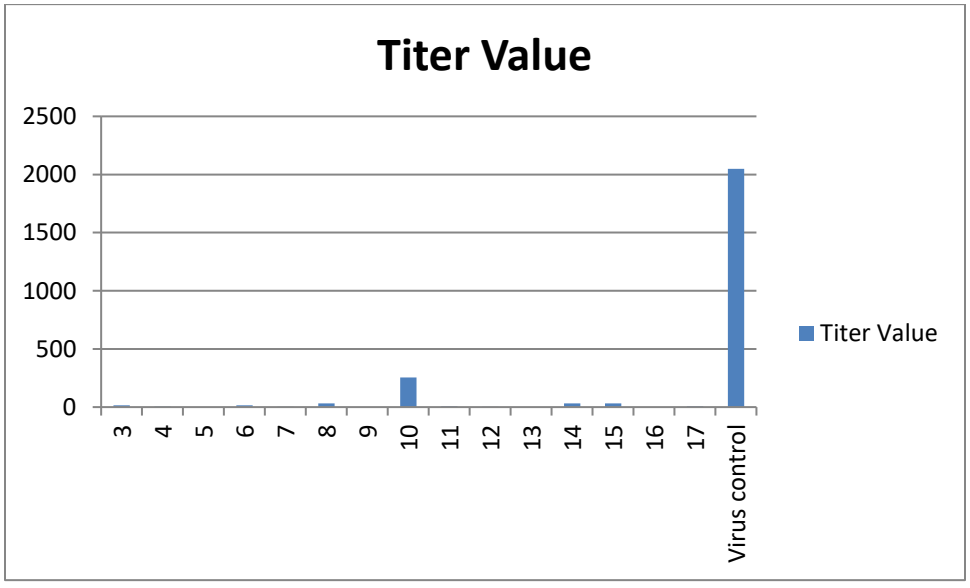


Fig3: Antiviral activity of synthesized compound 3-17 against IBV

Conclusion:

During this work we synthesized series of chalcones derivatives of 5-Arylfuran-2-carbaldehydes and checked for their antiviral activity against two poultry viruses: Avian influenza virus (AIV; A/Chicken/Italy/1994/H9N2) and infectious bronchitis virus (IBV).Most of the synthesized compounds were found active against AIV subtype H9N2 and IBV. In the case of AIV, the best results were attained for compound **3,4,6,10,12,13,17** and they retained HA titers at 0 after challenge. The lower titer values of these compounds showed high potency of these compounds, especially in comparison with control groups. The next in order was compound 9 which kept HA titers value at **2**. While other compounds were found less effective than above mentioned compounds and they kept the HA titers at **8, 16, 32, 128 and 2048** respectively. While in case of IBV, compound **5,9,13 and 16** found to be more effective and showed titer value zero. While other compounds showed moderate activity against IBV. The standard drugs amantadine and ribavarin were used as positive controls in the case of AIV and IBV, respectively.

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Conflict of Interest:

There is no conflict of interest.

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