Synthesis, Characterization and Antiviral Activity of Novel 3-chlorobenzofuryl Chalcones

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Abstract: *A series of novel 3-chlorobenzofuryl chalcones were synthesized and assayed to determine their in vitro broad-spectrum antiviral activities against Reovirus-1, Parainfluenza-3 virus, Coxsackie virus B4, Sindbis virus, Punta Toro virus in Vero cell cultures. Ribavirin, Dextran sulfate (DS-5000) and (S)-DHPA were used as the reference compounds. The biological results showed that some of the synthesized compounds exhibited potent broad-spectrum antiviral activity. Notably, compound II, VII, VIII, X and XIV showed significant antiviral activity. Structures of the synthesized compounds were supported by means of IR, [1]HNMR and MASS spectral studies.*

Keywords: 3-chlorobenzofuryl, antiviral activity, vero cell cultures. Ribavirin, Dextran sulfate (DS-5000), (S)-DHPA.

1.Introduction

Infectious diseases caused by different microorganisms such as bacteria, fungi and viruses, are still a problem of human civilization. Among all pathogenic microorganisms viruses are notorious, the most active and probably the most dangerous because they penetrate into cells, evolve rapidly and interfere with the genetic material of the host. Viruses with high infection rates and rapid propagation can cause worldwide human and animal pandemics. Antiviral therapy is one of the most exciting aspects of virology, since it has successfully employed basic science to generate very effective treatments for serious viral infections.

Coxsackie B viruses are single-strand RNA viruses; infection with Cox B can cause fever, headache, chest pain and other problems. Cardiac infection with Cox B3 can result in acute myocarditis that is spontaneously resolved or chronic myocarditis with prolonged viral persistence [1]. Currently, there is no specific treatment or vaccine available for Coxsackie virus infections.

A few antiviral agents with broad-spectrum characteristics are currently available. For example, RNA-dependent RNA polymerase inhibitor favipiravir exhibits broad spectrum activity against RNA viruses, including arenavirus, bunyavirus, filovirus [2]. A nucleotide analog cidofovir and its oral bioavailable analog brincidofovir have been reported to demonstrate activity against DNA viruses, including herpes, polyomavirus, adenovirus, and pox viral families [3]. Ribavirin is a purine nucleoside analog with demon strated efficacy against various DNA and RNA viral infections such as RSV (respiratory syncytial virus), hepatitis C, influenza A and B, parainfluenza viruses, and adenoviruses [4]. It is worth noting that the antiviral agents mentioned above have high toxicity and serious side effects. Thus, developing a new effective broad-spectrum antiviral agent is a top priority of medicinal chemistry.

Most current antiviral drugs, including those in development, are direct-acting antiviral (DAA)

molecules that specifically target viral proteins. These drugs are narrow in spectrum and are vulnerable to the rapid emergence of viral resistance [5]. The emergence of drug-resistant viruses, especially multidrug resistant strains, represents a significant problem in current clinical practice that needs to be addressed and should be considered a high priority for new avenues of research [6, 7]. To fulfill all of these requirements, novel classes of antivirals are needed [8]**.** Additionally, due to the high mutation rates that are particularly prevalent in RNA viruses, the lifetime of specific antiviral therapeutics is often severely limited. Broad spectrum antivirals would be one way of circumventing this problem [9]. Despite current achievements in the development of antiviral drugs, there is still a need for new compounds with an unique mechanism of action and limited side-effects.

Heterocyclic chemistry is one of the important and largest classical branches of organic chemistry dealing with the synthesis, properties and applications of heterocyclic compounds. Heterocyclic compounds are very important in drug discovery as emphasized by the fact that 70% of all "drug-like entities" are based around a heterocyclic sub-structure and are often found in biologically important systems. However, synthesizing functionalized heterocycles, especially analogues for drug discovery is imperative to design and implement synthetic strategies to synthesize functionalized heterocycles in a flexible and straightforward manner to provide compounds for lead identification. Heterocycles have been explored for developing pharmaceutically important molecules.

Heterocycles bearing nitrogen atoms constitute the core structure of a number of important physiologically active molecules and play a major role in the metabolism of living cells. Their practical applications range from clinical use to fields as diverse as agriculture, biocide formulation, photography and polymer sciences. Pyrazoline nucleus is one of the bioactive heterocyclic compounds that exhibit a range of biological activity. Pyrazoline derivatives have numerous prominent pharmacological effects, such as antimicrobial (antibacterial, antifungal, antiamoebic, antimycobacterial, antiviral), anti inflammatory, analgesic, antidepressant and anticancer, antidiabetic, antioxidant and anticonvulsant.

The most widely studied application of heterocycles in the preparations of biologically active and medicinally important molecules. Modern drug discovery focuses on the synthesis of specific bimolecular targets, which invariably contain a heterocyclic component. A key challenge in the synthesis of such targets continues to be the development of new pathways and improvement of existing pathways.

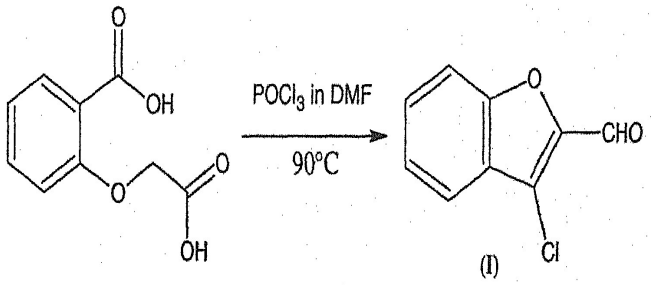
2. Materials and Methods

All the chemical substances used were of laboratory grade & provided by E.Merck (Germany) & S.D. Fine Chemicals (India). Melting points of all the synthesized compounds were determined by Open Tube Capillary Method and were uncorrected. The purity of all the newly synthesized compounds were checked by Thin layer chromatography with silica gel glass plates and the spots were detected by exposure to iodine and viewed under UV light at λ 254nm. The solvent system: toluene: ethyl acetate: formic acid (5:4:1) used to run the Thin layer chromatography. The IR spectra were recorded on a Perkin Elmer 1720 FT-IR spectrophotometer using KBr pellets. ^{1}HNMR spectra were recorded on Bruker AC 400 MHz in general using Tetra Methyl Silane (TMS) as an internal standard in $CDCl_3$ / DMSO-d_6.

2.1 Synthesis and Characterization

Synthesis of 3-chlorobenzofuran-2-carbaldehyde (I)

A freshly prepared solution of 2-(2-carboxyphenoxy)acetic acid (1g) in 5ml dimethyl formamide was added drop wise with constant stirring to 7.8ml of vilsmeier reagent at 0°C. Once the addition was completed, the reaction mixture was allowed to reach the room temperature and then gradually temperature was increased till to 90°C. The reaction was allowed to continue at 90±2°C for further 6hr. Then the mixture was cooled and poured on to 250ml crushed ice. The solid so separated was filtered and washed with water and recrystallized from hydrated ethanol. Percentage yield was 15-20% and melting point recorded 75°C.



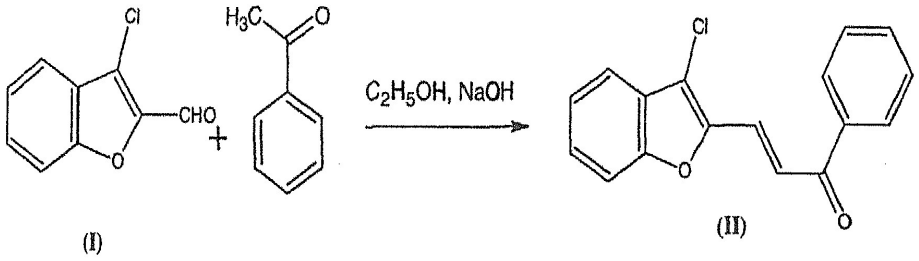
(I)

IR (KBr, cm^{-1}); 2840 (Aldehydic C-H), 1679 (G=0), 758 (C-Cl) ^{1}HNMR ($CDCl_3$, δ, ppm); 7.39-7.43 (1-H, m, Ar-H), 7.58 (2-H, d, J=3.6 Hz, Ar-H), 7.74 (1-H, d, J=8.0 Hz, ArH), 10.03 (1-H, s, -CHO).

General Procedure for Synthesis of Compound (II-XIV)

To 0.01mole ethanolic solution (25ml) of 3-Chlorobenzofuran -2-carbaldehyde (I), an appropriately substituted acetophenone 0.01mole & 5ml of 10% aqueous solution of NaOH was added. The reaction mixture was stirred at 25°C for 2-3hrs. After completion of the reaction, the contents were poured on to the crushed ice and neutralized with dilute HCl. The precipitates so obtained were filtered, washed with water, dried and recrystallized from ethanol to get the compound (II-XIV).

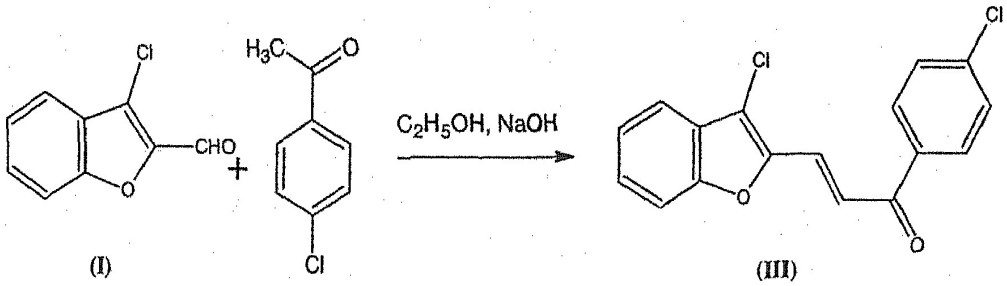
3-(3-chlorobenzofuran-2yl)-1-phenyl -2-propen-1-one (II)



(I) (II)

IR (KBr, cm^{-1}); 1685(C=O), 1606(C=C). ^{1}HNMR (DMSO, d_6, δ, ppm); 6.80(1-H, d, Hα, J=8.4Hz), 7.26-7.65 (9-H, m, Ar-H), 7.69 (1-H,d, Hβ, J=8.8Hz). Anal.Calcd.for $C_{17}H_{11}ClO_2$; C, 72.21; H, 3.91. Found C, 72.05; H,3.92%.

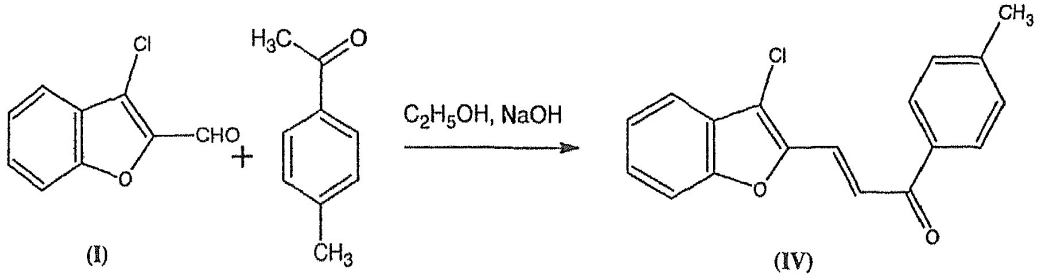
3-(3-chlorobenzofuran-2yl)-1-(4-chlorophenyl)-2-propen-1-one (III)



(I) (III)

IR (KBr, cm^{-1}); 1682(C=0), 1605(C=C), 755(C-Cl). ^{1}HNMR (DMSO, d_6, δ,ppm); 6.86(1-H,d,Hα, J=8 Hz), 6.91 (2-H,d,Ar-H,J=8Hz), 7.25(4H,m,Ar-H), 7.65 (2-H, d, Ar-H, J = 8.8 Hz), 7.96 (1-H, d, Hβ, J = 8.4 Hz). Anal. Calcd. for $C_{17}H_{10}Cl_2O_2$; C,64.39; H,3.19. Found C, 64.15; H, 3.18%.

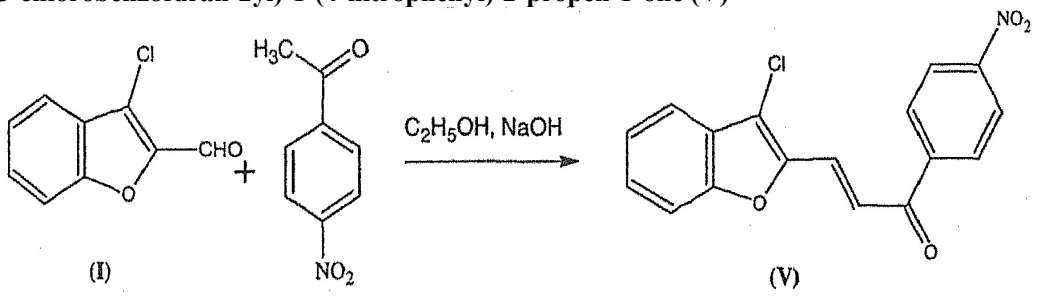
3-(3-chlorobenzofuran-2yl)-1-(4-methylphenyl)-2-propen-1-one (IV)



(I) (IV)

IR (KBr, cm^{-1}); 1690(C=0), 1602(C=Cl). ^{1}HNMR (DMSO,d_6,δ,ppm); 2.45 (3-H,s,-CH_3), 6.73(1-H,d,Hα,J=8Hz), 7.24-7.38(5-H,m,Ar-H), 7.47 (1-H,d,Ar-H,J=6.3Hz), 7.65(2-H,d,Ar-H,J=8.3Hz), 7.85(1-H,d, Hβ, J=8Hz). Anal.Calcd.for $C_{18}H_{13}ClO_2$; C, 72.84; H,4.41. Found: C, 72.95; H, 4.42%.

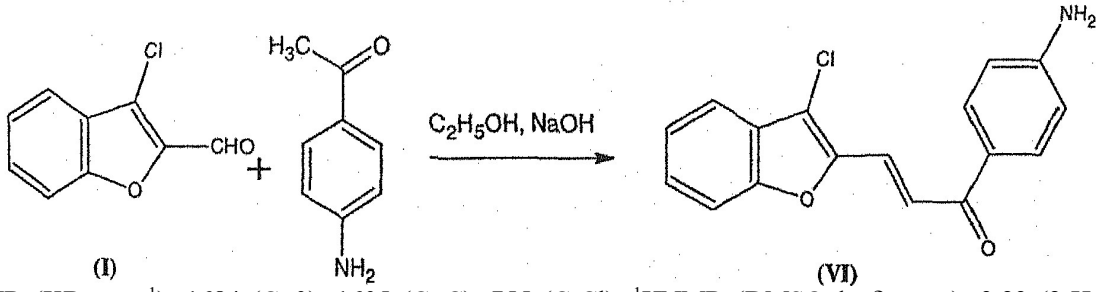
3-(3-chlorobenzofuran-2yl)-1-(4-nitrophenyl)-2-propen-1-one (V)



(I) (V)

IR (KBr, cm^{-1}); 1680(C=O), 1608(C=C), 1523 & 1377(NO_2), 746(C-Cl). ^{1}HNMR(DMSO,d_6,δ,ppm); 6.78(1-H,d,Hα,J=8.7Hz), 6.94(2-H,d,Ar-H,J=8.3Hz), 7.33-7.54(4H,m,Ar-H), 7.6(2-H,d,Ar-H,J=8.3Hz), 7.64(1-H,d,Hβ,J=8.7Hz). Anal.Calcd.for $C_{17}H_{10}ClNO_4$; C,62.30; H,3.08; N,4.27. Found: C, 62.21; H, 3.07; N, 4.27%.

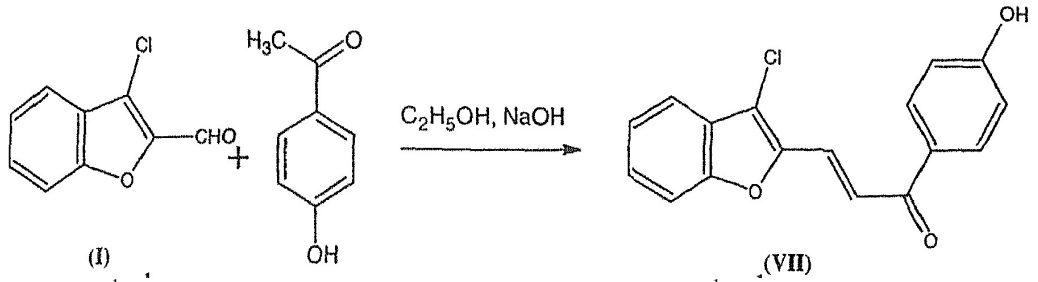
3-(3-chlorobenzofuran-2yl)-1-(4-aminophenyl)-2-propen-1-one (VI)



(I) (VI)

IR (KBr, cm^{-1}): 1684 (C=0), 1605 (C=C), 755 (C-Cl). ^{1}HNMR (DMSO,d_6, δ, ppm): 3.23 (2-H, s, NH2), 6.85 (I-H, d, Hα, J = 8.4 Hz), 7.27-7.46 (4-H, m, Ar-H), 7.48 (1-H, d, Ar-H, J = 6.4 Hz), 7.52 (1-H, d, Ar-H, J = 6.4 Hz), 7.54 (2-H, d, Ar-H, J = 8.4 Hz), 7.86 1-H, d, Hβ, *J* = 8.6 Hz). Anal. Calcd. for $C_{17}H_{12}ClNO_2$; C, 68.58; H, 4.06; N, 4.70. Found: C, 68.45; H, 4.06; N, 4.74%.

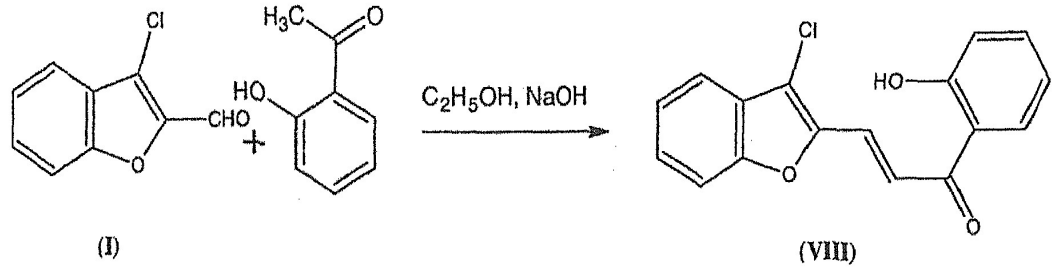
3-(3-chlorobenzofuran-2yl)-1-(4-hydroxyphenyl)-2-propen-l-one (VII)



(I) (VII)

IR(KBr, cm^{-1}): 3322 (OH), 1684 (C=0), 1605 (C=C), 754 (C-Cl). ^{1}HNMR (DMSO, d_6, δ, ppm); 6.82 (1-H, d. Hα, J = 8.4 Hz), 7.22-7.63 (8-H, m, Ar-H), 7.86 (1-H, d, Hβ, J = 8.6 Hz), 9.92 (1-H, s, OH). Mass m/z: 298 (M^{+1}). Anal.Calcd.for $C_{17}H_{11}ClO_3$; C, 68.34; H, 3.72. Found: C, 68.34; H, 3.73%.

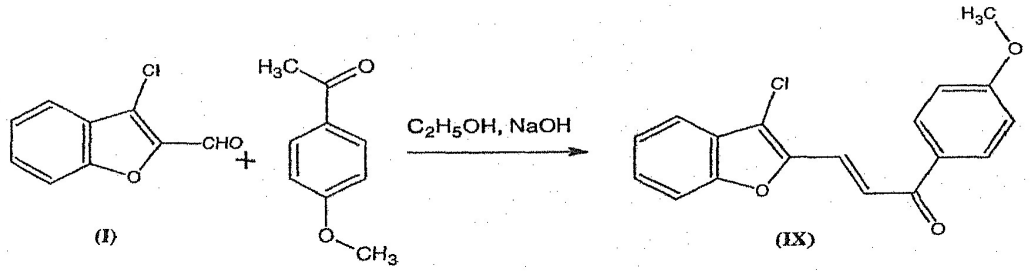
3-(3-chlorobenzofuran-2yl)-1-(2-hydroxyphenyl)-2-propen-l-one (VIII)



(I) (VIII)

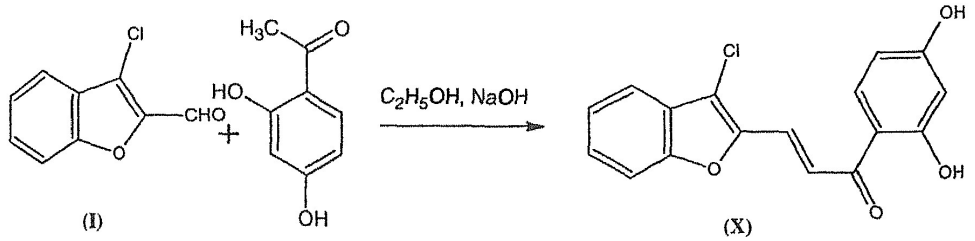
IR(KBr, cm^{-1}): 3526 (OH), 1684 (C=0), 1613 (C=C), 743 (C-Cl). ^{1}HNMR (DMSO, d_6, δ, ppm): 6.93 (1-H, d, Hα, J= 8.0 Hz), 7.23-7.80 (8-H, m, Ar-H), 7.91 (1-H, d, Hβ, J = 8.0 Hz), 10 .12 (1-H, s, OH). Anal.Calcd.for $C_{17}H_{11}ClO_3$; C, 68.34; H, 3.72. Found: C, 68.26; H, 3.71%.

3-(3-chlorobenzofuran-2yl)-1-(4-methoxyphenyl)-2-propen-1-one (IX)



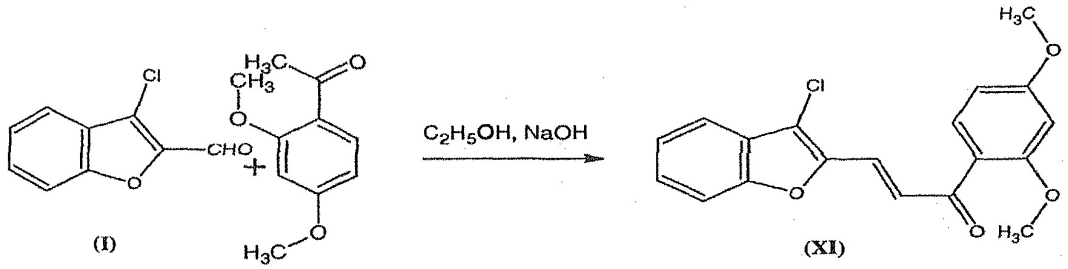
IR(KBr, cm^{-1}): 1684 (C=0), 1643 (C=C), 750 (C-Cl); ^{1}HNMR (DMSO, d_6, δ, ppm): 3.51 (3-H, s, -OCH_3), 6.81 (1-H, d, Hα, J = 8.4 Hz), 6.90 (2-H, d, Ar-H, J= 8.0 Hz), 6.98-7.66 (5-H, m, Ar-H), 7.68 (1-H, d, Ar-H, J = 6.8 Hz), 7.76 (1-H, d, Hβ, J = 8.8 Hz), Anal.Calcd. for $C_{18}H_{13}ClO_3$; C, 69.14; H, 4.18. Found: C, 69.25; H, 4.21%.

3-(3-chlorobenzofuran-2yl)-1-(2,4-dihydroxyphenyl)-2-propen-1-one (X)



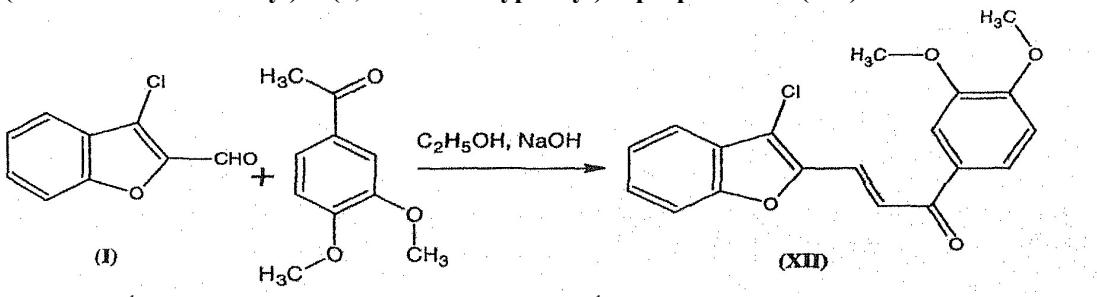
IR(KBr, cm^{-1}) 3532 (OH), 1681 (C=0), 1604 (C=C), 753 (C-Cl). ^{1}HNMR (DMSO, d_6, δ, ppm): 6.84 (1-H, d, Hα, J= 8.6 Hz), 7.25-7.66 (7-H, m, Ar-H), 7.71 (1-H, d, Hβ, J= 8.7 Hz), 10.24 (2-H, s, 2-OH). Anal Calcd. for $C_{17}H_{11}ClO_4$; C, 64.86; H, 3.51. Found: C, 64.88; H, 3.52%.

3-(3-chlorobenzofuran-2yl)-1-(2, 4-dimethoxyphenyl)-2-propen-1-one (XI)



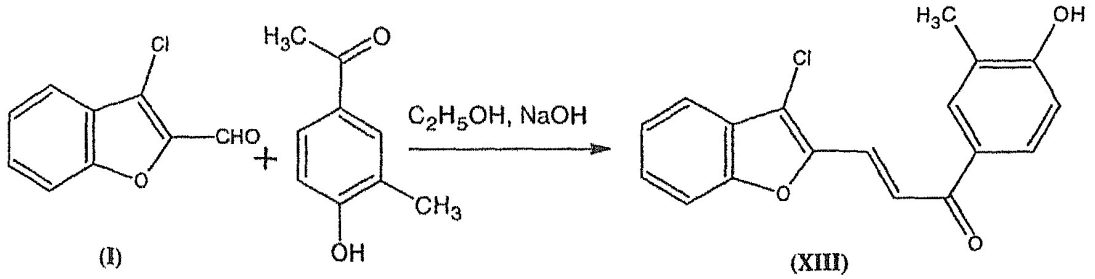
IR(KBr, cm^{-1}): 1684 (C=0), 1655 (C=C), 734 (C-Cl). ^{1}HNMR (DMSO, d_6, δ, ppm): 3.65 (6-H, s, 2-OCH_3), 6.91 (1-H, d. Hα, J= 8Hz), 7.23-7.85 (7-H, m, Ar-H), 7.87 (1-H, d, Hβ, J = 8.3 Hz). Anal. Calcd. for $C_{19}H_{15}ClO_4$; C, 66.57; H, 4.42. Found: C, 66.60; H, 4.41%.

3-(3-chlorobenzofuran-2yl)-1-(3, 4-dimethoxyphenyl)-2-propen-1-one (XII)



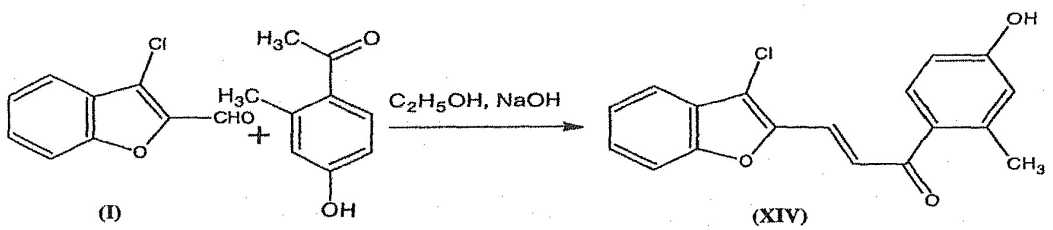
IR (KBr, cm^{-1}): 1684 (C=0). 1601 (C=C), 764 (C-Cl). ^{1}HNMR (DMSO, d_6, δ, ppm): 3.66 (6-H, s, 2-OCH_3), 6.81 (1-H, d, Hα, J = 8.3 Hz), 6.88-7.69 (7-H, m, Ar-H), 7.29 (1-H, d, Hβ, J = 8Hz). Anal. Calcd. for $C_{19}H_{15}Cl0_4$; C, 66.56; H, 4.40. Found: C, 66.52; H, 4.41%.

3-(3-chlorobenzofuran-2yl)-1-(4-hydroxy-3-methylphenyl)-2-propen-1-one (XIII)



IR (KBr, cm^{-1}): 3532 (OH), 1684 (C=0), 1605 (C=C), 756 (C-Cl). ^{1}HNMR (DMSO, d_6, δ, ppm): 2.25 (3-H, s, CH_3), 6.78 (1-H, d, Hα, J = 8.6 Hz), 6.94-7.61 (7-H, m, Ar-H), 7.66 (1-H, d, Hβ, J = 8.7 Hz) 8.82 (I-H, s, OH). Anal. Calcd. for $C_{18}H_{13}ClO_4$; C, 69.14; H, 4.18. Found: C, 69.22; H, 4.21%.

3-(3-chlorobenzofuran-2yl)-1-(4-hydroxy-2-methylphenyl)-2-propen-1-one (XIV)



IR(KBr, cm^{-1}): 3532 (OH), 1685 (C=0), 1604 (C=C), 753 (C-Cl). ^{1}HNMR (DMSO, d_6, δ, ppm): 2.41 (3-H, s, -CH_3), 6.82 (1-H, d, Hα, J = 8.0 Hz), 7.26-7.66 (7-H, m, Ar-H), 7.66 (1-H, d, Hβ, J = 8.3 Hz), 8.92 (1-H, s, OH). Anal. Calcd. for $C_{18}H_{13}ClO_3$; C, 69.14; H, 4.20. Found: C, 69.13; H, 4.21%.

2.2 In Vitro Antiviral Studies

Confluent cell culture microtiter 96-well trays were inoculated with 100$CCID_{50}$ [10]. $CCID_{50}$ corresponding to the virus stock dilution that proved infective for 50% of the cell cultures. After 1 hr of virus adsorption to the cells, residual virus was removed and replaced by cell culture medium (Eagle's minimal essential medium) containing 3% fetal calf serum. Cytopathogenicity was recorded as soon as it reached completion in the untreated virus infected cell cultures. The antiviral activity of the compound is expressed as the concentration required inhibiting viral cytopathogenicity by 50%. The activity was performed in vero cell cultures against parainfluenza-3 virus, reovirus-1, sindbis virus, coxsackie virus B4, punta toro phlebovirus.

For each compound both EC_{50} & CC_{50} were determined. The EC_{50} value (50% antivirally effective concentration) corresponds to the concentration of the compound that inhibits viral cytopathogenicity by 50% and CC_{50} value (minimum cytotoxic concentration) corresponds to the concentration that cause microscopically detectable alteration in normal cell morphologies. Ribavirin, Dextran sulfate

(DS-5000) and (S)-DHPA (Dihydroxy propyl adenine) were used as the reference compounds.

2.3 Cytotoxicity Assay

Cytotoxicity assay was monitored by direct microscopical inspection of the cell monolayers which had not been infected but were treated by the compounds at the same concentration as used in the antiviral activity assays.

3. Results and Discussion

3.1 Synthesis of 3-chlorobenzofuran-2-carboxaldehyde (I)

The starting material was synthesized by cyclisation of appropriate aromatic dicarboxylic acid i.e. 2-(2-carboxyphenoxy) acetic acid by the use of Vilsmeier Haack reagent. The reaction was critical in terms of maintenance of temperature (90±2°C) although cyclisation, formylation and chlorination all occurs *in situ.* The yield of the product was not very good but purity was appreciable. In IR spectra (KBr) a band at 2840cm^{-1} for aldehydic C-H stretching was very clear. The proton NMR spectra left no doubt with peaks in aromatic zone (7.39-7.74ppm) equivalent to four protons with respect to one aldehydic proton (10.03ppm). The usual splitting for *ortho* and *meta* couplings was very much clear with *J* values 3.6 & 8.0Hz respectively.

3.2 Synthesis of 3-chlorobenzofuryl chalcones (II-XIV)

The Claisen-Schmidt condensation of (I) was performed with appropriately substituted acetophenone to obtain desired chalcones (II-XIV). The overall reaction time recorded for condensation was considerably less. It may be due to presence of oxygen as hetero at position one and chloro substitution at position three (both electro negative) in 3-chloro benzofuran-2-carboxaldehyde. The reaction time of (I) with anisaldehyde was found to be least (2h) with maximum yield of 98%. TLC pure compounds were analyzed for elemental analysis and were found in theoretical agreement. In general, the IR spectra of chalcones revealed C=0, C=C and C-Cl stretching at 1685, 1605 and 750cm^{-1}. ^{1}HNMR spectrum further confirmed the structure due to disappearance of aldehydic proton and appearance of 2 characteristic doublets one each for vinylic protons. The physical data are presented in Table 1.

Table 1. Physical Properties of the Synthesized Compounds

Compound	IUPAC Name	Mol. Formula	Mol. Weight	% Yield	M.P (°)
II	3-(3-chlorobenzofuran-2yl)-1-phenyl -2-propen-1-one	$C_{17}H_{11}ClO_2$	282	77	142-144
III	3-(3-chlorobenzofuran-2yl)-1-(4-chlorophenyl)-2-propen-1-one	$C_{17}H_{10}Cl_2O_2$	317	86	148-150
IV	3-(3-chlorobenzofuran-2yl)-1-(4-methylphenyl)-2-propen-1-one	$C_{18}H_{13}ClO_2$	296	75	124-126
V	3-(3-chlorobenzofuran-2yl)-1-(4-nitrophenyl)-2-propen-1-one	$C_{17}H_{10}ClNO_4$	327	71	182-184
VI	3-(3-chlorobenzofuran-2yl)-1-(4-aminophenyl)-2-propen-1-one	$C_{17}H_{12}ClNO_2$	297	85	186-188
VII	3-(3-chlorobenzofuran-2yl)-1-(4-hydroxyphenyl)-2-propen-l-one	$C_{17}H_{11}ClO_3$	298	75	210-212
VIII	3-(3-chlorobenzofuran-2yl)-1-(2-hydroxyphenyl)-2-propen-l-one	$C_{17}H_{11}ClO_3$	298	75	110-112
IX	3-(3-chlorobenzofuran-2yl)-1-(4-methoxyphenyl)-2-propen-1-one	$C_{18}H_{13}ClO_3$	312	97	106-108
X	3-(3-chlorobenzofuran-2yl)-1-(2,4-	$C_{17}H_{11}ClO_4$	314	81	96-100

	dihydroxyphenyl)-2-propen-1-one				
XI	3-(3-chlorobenzofuran-2yl)-1-(2,4-dimethoxyphenyl)-2-propen-1-one	$C_{19}H_{15}ClO_4$	342	85	136-138
XII	3-(3-chlorobenzofuran-2yl)-1-(3,4-dimethoxyphenyl)-2-propen-1-one	$C_{19}H_{15}ClO_4$	342	88	172-174
XIII	3-(3-chlorobenzofuran-2yl)-1-(4-hydroxy-3-methylphenyl)-2-propen-1-one	$C_{18}H_{13}ClO_3$	312	77	202-204
XIV	3-(3-chlorobenzofuran-2yl)-1-(4-hydroxy-2-methylphenyl)-2-propen-1-one	$C_{18}H_{13}ClO_3$	312	77	162-164

3.3 Antiviral Activity

The newly synthesized compounds were evaluated for their *in vitro* antiviral activity against Reovirus-1, Parainfluenza-3 virus, Coxsackie virus B4, Sindbis virus, Punta Toro virus (in vero cell cultures); For each compound, the minimum cytotoxic concentration (MCC) [or 50% cytotoxic concentration (CC_{50}) was determined.

The results of antiviral assays for newly synthesized compounds are shown in Table 2. Both antiproliferative and cytotoxic concentrations in µg/ml were determined and recorded. Cytotoxicity towards uninfected host cells was estimated microscopically under same conditions as the antiviral activity. The criterion for specific antiviral activity was taken as the inhibition of virus induced cytopathogenicity at a concentration that was at least 5 fold lower than the cytotoxic concentration required altering the morphology of the uninfected host cells. As per this criterion, none of the compounds tested showed any specific antiviral activity. [$EC_{50} \geq CC_{50}$]. Several compounds i.e II, VII, VIII, X and XIV proved quite cytotoxic to the host cells (Minimum Cytotoxic Concentration: 1-10µg/ml).

Table 2. Cytotoxicity and anti-viral activity of compounds in vero cell cultures

Compound	Minimum cytotoxic concentration[a] (µg/ml)	EC_{50}[b] (µg/ml)				
		Para-influenza-3-virus	Reo virus-1	Sindbis virus	Coxsackie virus B4	Punta Toro virus
II	20	> 4	>4	>4	>4	>4
III	100	>20	>20	>20	>20	>20
IV	>20	> 20	>20	>20	>20	>20
V	100	>20	>20	>20	>20	>20
VI	100	>20	>20	>20	>20	>20
VII	>4	>4	>4	>4	>4	>4
VIII	20	>4	>4	>4	>4	>4
IX	100	>20	>20	>20	>20	>20
X	>4	>4	>4	>4	>4	>4
XI	100	>20	>20	>20	>20	>20
XII	100	>20	>20	>20	>20	>20
XIII	>20	>20	>20	>20	>20	>20
XIV	20	>4	>4	>4	>4	>4
(S)-DHPA	>250	250	>250	>250	>250	>250
DS-5000	>100	>100	>100	>100	>100	100
Ribavirin	>250	45	145	145	>250	146

[a]Required to cause a microscopically detectable alteration of normal cell morphology
[b]Required to reduce virus induced cytopathogenicity by 50%.

4. Conclusion

Total fifteen compounds were screened for antiviral activity, out of which 5 compounds were

considered as active with CC_{50} value. The CC_{50} values were determined for all the active compounds and used to calculate the EC_{50}. The newly synthesized derivatives II, VII, VIII, X and XIV do possess significant cytotoxic to the host cells. Further lead optimization can be considered for obtaining compounds with better anti-viral activity.

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6. References

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