# Antiviral activity of organic molecules having sulfonamide moiety: An insight of recent research

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*Actividad antiviral de las moléculas orgánicas que tienen una mitad sulfonamida: un conocimiento de reciente investigación*

*Activitat antiviral de les molècules orgàniques que tenen una meitat sulfonamida: un coneixement de recent investigació*

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## SUMMARY

Sulfonamide derivatives are well known for their antibacterial activity as manifested by 'Sulfa Drugs', for example, sulfamethoxazole etc. In addition, they are associated with a large number of pharmacological activities such as anti-microbial, anti-inflammatory, anti-cancer, anti-oxidant, anti-viral etc. This work has emphasized their application as antiviral agents such as HIV (human immunodeficiency virus), HCV (hepatitis C virus) etc. We have presented here a number of sulfonamide derivatives exhibiting remarkable antiviral potential.

**Keywords:** Sulfonamides, antiviral, anti-HIV, anti-HCV.

## RESUMEN

Los derivados de sulfonamida son bien conocidos por su actividad antibacteriana tal como se ha manifestado en los 'Fármacos Sulfa', por ejemplo, el sulfametoxazol, etc... Además, están asociados a un gran número de actividades antifarmacológicas como la antimicrobiana, antinflamatoria, anticancerígena, antioxidante, antiviral, etc. Este estudio ha resaltado su aplicación como agentes antivirales como el HIV (virus de inmunodeficiencia humana), HCV (virus de la hepatitis C) etc. Hemos presentado aquí una serie de derivados de sulfonamida que exhiben un notable potencial antiviral.

**Palabras clave:** Sulfonamidas; antiviral; anti-HIV; anti-HCV.

## RESUM

Els derivats de sulfonamida son ben coneguts per la seva activitat antibacteriana tal como s'ha vist en els 'Fàrmacs Sulfa', per exemple, el sulfametoxazol, etc.. A més a més estan associats a un gran número de activitats antifarmacològiques com la antimicrobiana, antiinflamatòria, anticancerígena, antioxidant, antiviral, etc. Aquest estudi ha ressaltat la seva aplicació com agents antivirals com el HIV (virus de immunodeficiència humana), HCV (virus de la hepatitis C) etc. Hem presentat aquí una sèrie de derivats de sulfonamida que mostren un notable potencial antiviral.

**Paraules clau:** Sulfonamides; antiviral; anti-HIV; anti-HCV.

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## INTRODUCTION

Sulfonamide, a well known functionality, is associated with a wide spectrum of biological activities. A large number of pharmacologically potent sulfonamides having potential as antimicrobial, anti-inflammatory, anti-viral, antioxidant and enzyme inhibitory have also been synthesized[1-8] and well characterized by XRD[9-43]. In order to obtain compounds with enhanced activity against drug-resistant viruses diversified sulfonamide derivatives are being further explored. No effective vaccine to cure HIV-1 is available, so, anti-viral drugs are the only means to cure replication and transmission of this death causing virus. Up till now, many sulfonamide scaffolds with anti-viral potential[44-48] have been presented and some are also available in market (Fig. **1**) which play their inhibitory role during different stages of HIV-1 life cycle.

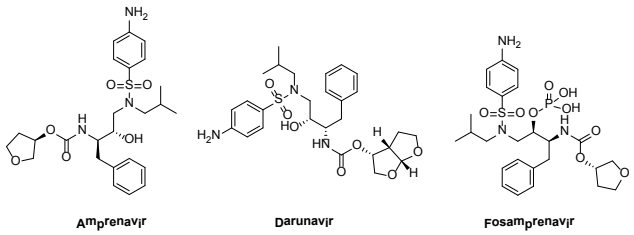


**Fig. 1.** *Some important anti-HIV sulfonamide drugs.*

HCV (Hepatitis C virus) is remarkably associated with chronic liver and acute hepatitis disease which also include liver cancer and fibrosis cirrhosis. It is estimated that HCV has affected 3% people world over while each year 3-4 million people are being infected chronically. Some sulfonamide scaffolds having anti-HCV potential are also available in the market like asunaprevir (Fig. **2**).

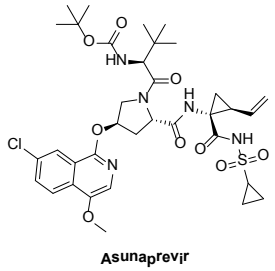


**Fig. 2.** *Commercially available anti-HCV sulfonamide drug, Asunaprevir.*

### Sulfonamides as anti-HCV agents

In 2003, Johansson and co-researchers synthesized novel sulfonamide derivatives which were inhibitors of protease and found active against HCV NS3 (Protease-Helicase/NTPase). Derivatives 1 and 2 exhibited excellent potential with Ki values of 3.8 and 13.6 nM respectively[49]. Similarly, among the synthesized sulfonamide derivatives by Yannopoulos and co-workers, the derivative 3 demonstrated remarkable inhibition against HCV (NS5B polymerase) with an $IC_{50}$ value of 25 μM[50]. Later on, Gopalsamy et al. synthesized a novel series of proline sulfonamides which were found inhibitors of hepatitis C virus NS5b polymerase. The analogues 4 and 5 displayed good activity with $IC_{50}$ values of 0.08 and 0.26 μM respectively[51] (Fig. 3). A series of tetra-and tripeptide based acyl sulfonamides were synthesized and screened against hepatitis C virus (HCV) NS3 protease. Ronn and colleagues observed that the compound 6 and 7 showed good activity with $EC_{50}$ values of 0.040 and 4.6 μM respectively[52]. Several thiazolone-based sulfonamides as inhibitors of NS5B polymerase to target HCV were synthesized by Ding and co-workers. The derivatives 8, 9, 10 and 11 exhibited the most potent antiviral activity with $IC_{50}$ values of 0.6, 1.4, 1.4 and 1.4 uM respectively[53] (Fig. 3).

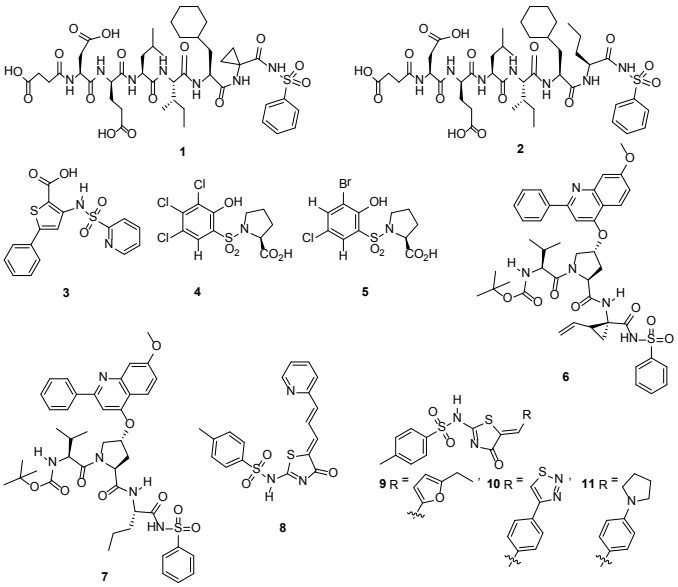


**Fig. 3.** *Potent sulfonamide scaffolds having anti-HCV potential.*

Bogen et al. executed the synthesis of novel sulfonamides which were found inhibitors of HCV NS3 serine protease. The compound **12** and **13** showed highest potential with $EC_{90}$ values of 75 and 55 nM respectively[54]. Synthesis of indole acylsulfonamides was executed by Anilkumar and co-workers and among them the compounds **14-16** displayed significant activity against HCV (NS5B) polymerase with $IC_{50}$ values of 0.018, 0.033 and 0.039 μM respectively[55]. A novel library of *N*-phenylbenzene sulfonamides was prepared and evaluated as inhibitors of polymerase (NS5B) in hepatitis C virus by May and co-researchers. Compounds **17** and **18** demonstrated good activity with $IC_{50}$ values of 0.04 and 0.9 μM respectively[56] (Fig. 4). *N*-(4'-(Indol-2-yl)phenyl) sulfonamides synthesized by Chen et al. were found inhibitors of HCV replication. Compound **19** displayed best activity with $EC_{50}$ value of 0.17 μM[57]. In 2013, Zhang and colleagues prepared a series of 6-(indol-2-yl) pyridine-3-sulfonamides which were found inhibitors of hepatitis C virus (HCV) for the targeting of NS4B. Among these, derivatives **20-22** showed similar potential with $EC_{50}$ value of 2 nM[58] (Fig **4**).

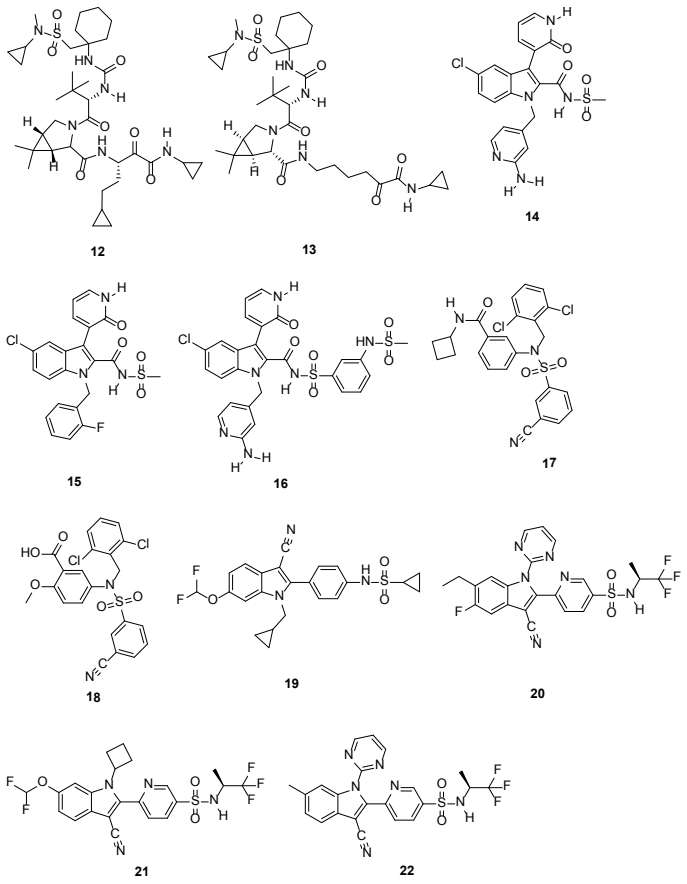

**Fig. 4.** *Structures of important anti-HCV agents.*

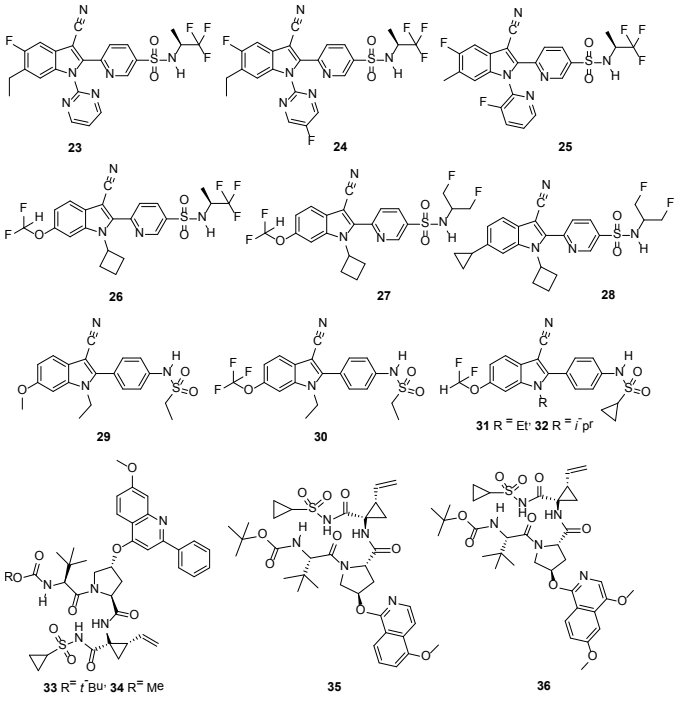

**Fig. 5.** *Sulfonamide derivatives with anti-HCV potential.*

A novel series of 6-(indol-2-yl) pyridine-3-sulfonamides, reported by Zhang et al., was found as anti-HCV (NS4B). Among the reported series, the compounds **23-28** displayed good activity with $IC_{50}$ values of 2, 3, 3, 2, 4 and 4 nM respectively[59] (Fig. 5). Novel 2-phenylindole analogues as HCV replicon inhibitors were synthesized by Chen and co-workers. The compounds **29-32** were found the most potent ones with $IC_{50}$ values of 0.47, 0.17, 0.10 and 0.075 μM respectively[60]. In 2014, acyl sulfonamide derivatives (BMS 605339) were synthesized and screened against NS3 protease inhibitor for the treatment of hepatitis C virus. From the reported series the compounds **33-36** demonstrated good activity with $IC_{50}$ values of 1, 1, 5 and 6 nM respectively[61] (Fig. 5).

A variety of 6-(azaindol-2-yl)pyridine-3-sulfonamides, synthesized by Chen et al., were used as potent and selective inhibitors of hepatitis C virus NS4B. The compound **37, 38** and **39** among the series, displayed best activity with $IC_{50}$ values of 2, 13 and 15 nM respectively[62] (Fig. 6). Acyl sulfonamides were synthesized and screened for their antiviral activity against hepatitis C virus. Rona and colleagues observed that the compound **40** showed good activity with $ED_{50}$ values of 0.040 μM[63]. A novel series of acyclic, acyl and tripeptidic sulfonamides was synthesized by Sun and coworkers in 2016. These compounds were used as protease inhibitors of hepatitis C virus. The compound **41** and **42** showed the best activity with $IC_{50}$ values of 1 and 1.3 nM respectively[64] (Fig. **6**).

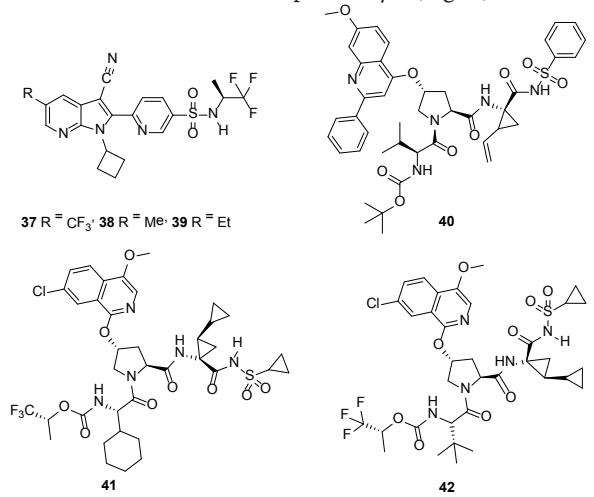

**Fig. 6.** *Some valuable anti-HCV agents with sulfonamide functionality.*

## Sulfonamides as anti-HIV agents

Nagarajan and coworkers synthesized a novel series of benzothiazole sulfonamides as HIV-1 protease inhibitors. It was observed that both the derivatives **43** and **44** exhibited similar activity with $IC_{50}$ value 2 nM[65]. A novel series of benzensulfonamides was prepared and screened against HIV virus by Pomarnacka et al. The compound **45** demonstrated best antiviral activity with $EC_{50}$ value of 28.8 μM[66]. Synthesis of a novel series of Nα-isobutyl-Nα-arylsulfonamido-(Nε-acyl)lysine, lysinol and analogues was executed by Stranix and co-workers. They observed that the compounds **46-48** exhibited good anti-HIV activity with $EC_{50}$ values of 540, 339 and 730 nM respectively[67] (Fig. 7). A novel series of sulfonamides having caffeoyl naphthalene was synthesized by Xu and colleagues. The derivatives **49** and **50** showed good activity against HIV viruses with $IC_{50}$ values of 4.5 and 7.9 μg/ml respectively[68]. Synthe-

sis of lysine sulfonamide derivatives was reported by Stranix et al. From the prepared series the compounds **51** and **52** showed excellent activity with $EC_{50}$ values of 150 and 488 nM respectively against wild type HIV protease[69] (Fig. 7).

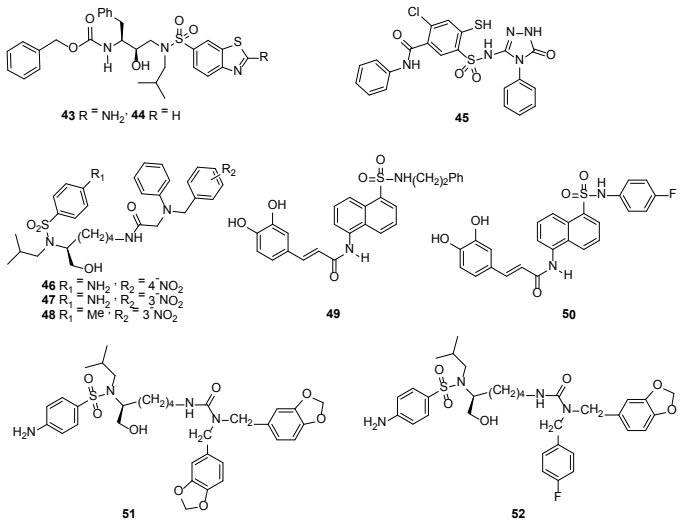


**Fig. 7.** *Potent anti-HIV sulfonamide derivatives.*

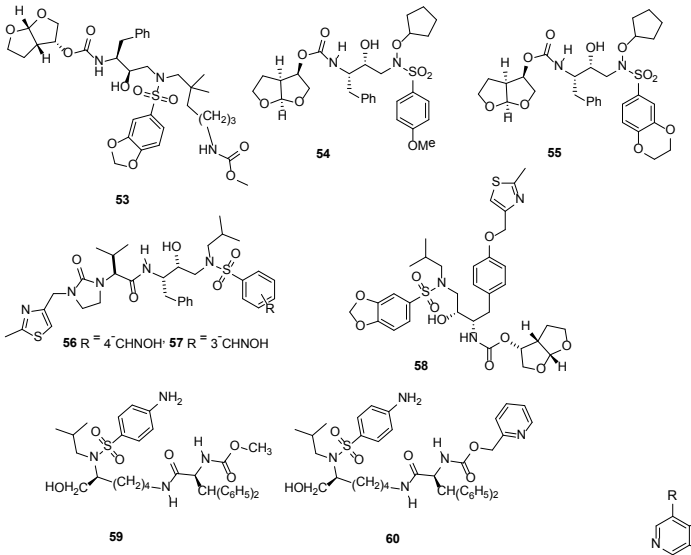


**Fig. 8.** *Structures of important anti-HIV agents.*

In 2004, Miller and colleagues reported the synthesis of anti-HIV aryl sulfonamide and its analogues. Among them the compound **53** demonstrated good activity with $IC_{50}$ value of 1.6 nM, in wild type 9.2 nM and in mutant viruses 15 nM[70]. In the next year, an anti-HIV series of *N*-alkoxy-arylsulfonamide derivatives was synthesized by Sherrill et al. It was observed that compounds **54** and **55** displayed good activity with $IC_{50}$ values of 6 and 3 nM respectively[71]. Oximinoarylsulfonamides were prepared and tested against HIV viral infections by Yeung and colleagues. They identified that the compounds **56** and **57** exhibited potent activity with $IC_{50}$ values of 0.005 and 0.016 μM respectively[72] (Fig. **8**). Later on, aryl sulfonamides were prepared by Miller and co-workers and tested against HIV protease in wild type and protease inhibitor resistant viruses. The compound **58** displayed good activity with $IC_{50}$ value of 0.7 nM for wild type and 0.22 nM[73]. Among the lysine containing antiviral sulfonamides, reported by Stranix and colleagues, the derivatives **59** and **60** demonstrated excellent inhibition against HIV protease cells with $IC_{50}$ values of 0.5 and 0.12 nM respectively[74] (Fig. **8**).

In 2007, potent anti-HIV sulfonamide analogs were synthesized by Lu and co-workers. The compound **61** and **62** displayed best activity with $IC_{50}$ values of 7 and 27 nM respectively[75]. In the same year, Ravichandran et al. reported a novel series of aryl sulfonamides which exhibited anti-HIV activity. The best activity was showed by compound **63** and **64** with $IC_{50}$ values of 2.6 and 2.8 nM respectively[76]. A series of *N*-(3-amino-3,4-dihydro-4-oxopyrimidin-2-yl)-4-chloro-2-mercapto-5-methylbenzenesulfonamide derivatives were synthesized by Brzozowski and colleagues and tested against HIV-1 virus. The compound **65** and **66** exhibited good activity with $EC_{50}$ value of 15 and 29.6 μM respectively[77] (Fig. **9**). Zareef et al. prepared novel oxadiazole based sulfonamides and screened them as anti-HIV-1 (strain IIIB) and HIV-2 (strain ROD) in human T-lymphocyte (MT-4) cells. The compound **67** was found the most potent among all the derivatives against the replication of HIV-1 and HIV-2 in cell culture with an $IC_{50}$ value of 19.5 μg/ml and a $CC_{50}$ value of 55.8 μg/ml against HIV-1[78]. A novel series of isoxazolidine and isoxazole sulfonamides was reported by Low et al. as inhibitors of HIV-1 replication. The compound **68-70** displayed best activity with $IC_{50}$ values of 76, 75 and 93 μM respectively[79]. 6,7-Dihydroxy-1-oxoisoindoline-4-sulfonamides were synthesized by Zhao and colleagues and they observed that derivatives **71** and **72** exhibited good activity with $IC_{50}$ values of 0.047 and 0.054 μM respectively against HIV virus[80]. Kim and co-researchers executed the synthesis of sulfonamides, the derivative **73** showed activity similar to the reference drugs (nevirapine, Azt and saquinavir) with $IC_{50}$ value of 64 nM[81] (Fig. **9**).

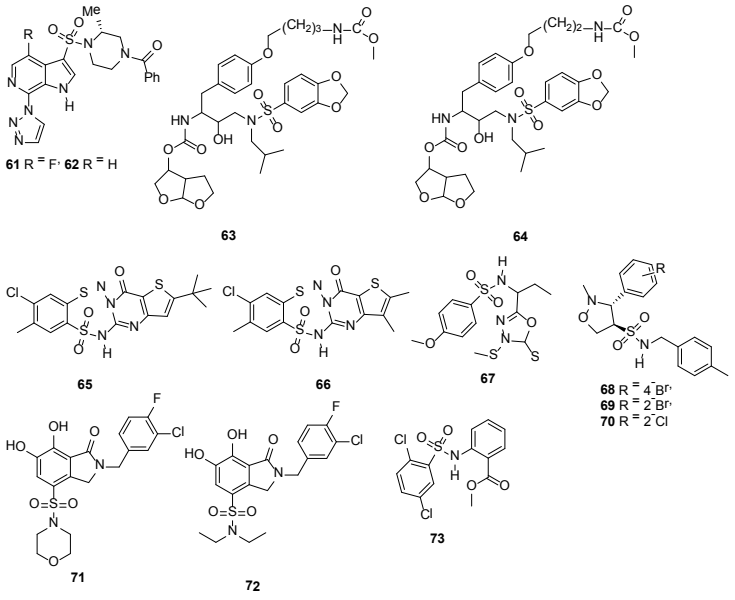


**Fig. 9.** *Sulfonamide derivatives with anti-HIV potential.*

### Sulfonamides as anti-Influenza, anti-dengue and anti-Coxacki agents

A series of benzenesulfonamide derivatives were reported by Tang and co-researchers which prohibited cytopathic effects (CPE) caused by infection of influenza (A/Weiss/43 strain (H1N1)). The derivatives **74** and **75** showed good activity with $EC_{50}$ values of 86 and 86 nM respectively[82]. Recently, chiral sulfonamides and derivatives (anti-influenza agents) were synthesized by Basaran and colleagues. From the prepared series compound **76** and **77** exhibited good antiviral activity with $EC_{50}$ values of 1.6 and 1.7 μM respectively[83] (Fig. **10**).

### Sulfonamides as anti-dengue and anti-Coxacki agents

Synthesis of 4-(1,3-dioxo-2,3-dihydro-1*H*-isoindol-2-yl)benzene-1-sulfonamide and derivatives were reported by Timiri et al. These sulfonamide derivatives were found to be active against dengue virus. The compound **78** and **79** showed good activity with $IC_{50}$ values of 48.2 and 121.9 μM[84]. Synthesis of novel 4-(1-aryl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-*N*-substituted benzene sulfonamide derivatives was executed by Kumar and coworkers. These derivatives were evaluated for their *in vitro* anti-microbial, antiviral and cytotoxic activities. The derivative **80** and **81** showed moderate activity against Coxacki virus at 45 ug/ml in both (vero and helta) cell cultures[85] (Fig. **10**).

### Sulfonamides as anti-HBV and anti-TMV agents

Synthesis of di-substituted sulfonamides was reported by Cai and colleagues which were screened against hepatitis B virus infection. The compound **82** displayed excellent activity with $EC_{50}$ value of 4.55 μM[86]. Synthesis of 1,3,4-thiadiazole sulfonamides was reported by Chen and colleagues in 2010. Screening against TMV showed that the compound **83** and **84** demonstrated good anti-tobacco mosaic virus (TMV) activity with the inhibition of 42.0% and 42.49% respectively at the concentration of 0.5 mg/ml[87] (Fig **10**).

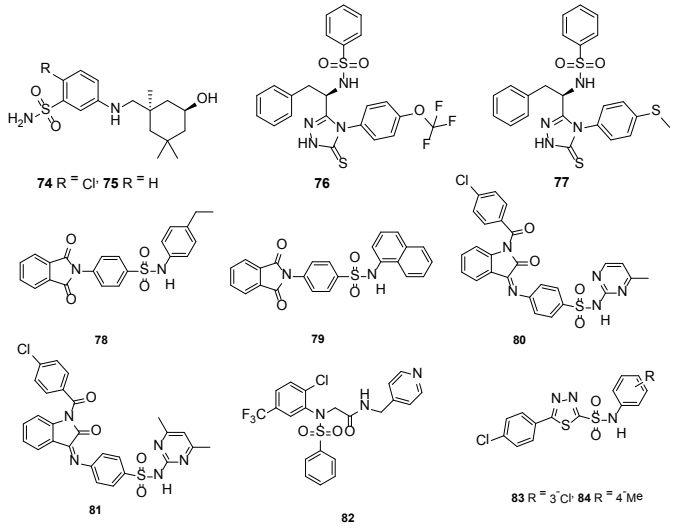


**Fig. 10.** *Structures of some antiviral sulfonamide molecules.*

## CONCLUSION

Viral infections have been an extreme threat to human and animal life on this globe. Currently, a significant portion of human population is suffering from varius viruses like HCV, HBV, HIV etc and are passing their lives in miserable conditions. The development of drug resistance strains is an alarming situation which requires a continued need for the development of new drugs with promising activities. In this work, we have focused on antiviral ability of various sulfonamide derivatives based on heterocyclic templates especially. We have shown that the modification in the structure of anti-viral sulfonamide drugs have also resulted in their increased activity. We hope that this elegant presentation will lead the researchers to develop more effective antiviral agents in future.

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