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# DESIGN, SYNTHESIS AND MOLECULAR DOCKING STUDIES OF SOME NOVEL SPIRO DERIVATIVES BY 1,3-CYCLOADDITION REACTION

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**ABSTRACT:**Synthesis of polycyclic compounds having spiro nucleus has attracted the attention of synthetic organic chemists because of their highly pronounced biological activities such as antiviral, antimicrobial etc. Therefore, the development of new, rapid, and clean synthetic routes of such compounds is of great importance to both medicinal and synthetic chemists. The 1,3-dipolar-cycloaddition reactions are proved to be an efficient method for regio and stereo selective synthesis of structurally complex spiro heterocycles from relatively simple precursors. Molecular docking provides a consistent and more precise picture of the interaction of biologically active molecules at the receptor level thereby facilitating the designing of novel therapeutic agents. Therefore, potency of the spiro compounds (4i) was evaluated preliminary through the molecular docking studies. Later substitutions were made in the reference molecule to get the potent compounds.

*Keywords: Spiro derivatives, Indanone, Molecular docking.*

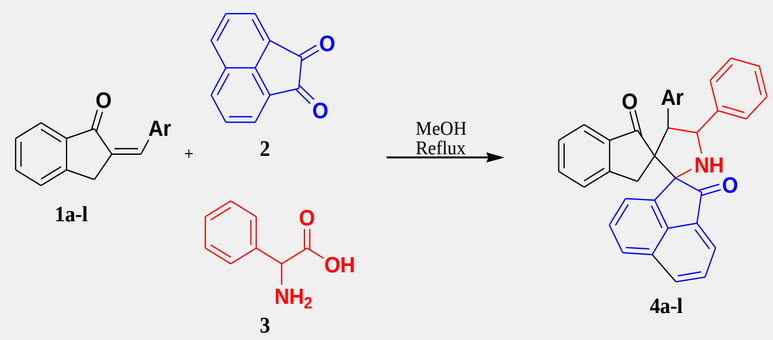
## INTRODUCTION

Dengue virus (DENV) belongs to the Flavivirus genus of the Flaviviridae family and exists as four serotypes: DENV-1, DENV-2, DENV-3, and DENV-4[1]. Then latest existing of dengue viruses is DENV-5 which has been discovered by Normile D. in October 2013. DENV may cause an acute illness ranging to mild dengue fever (DF), to more severe known as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[2]. DENV is transmitted by Aedes mosquitoes, mainly Aedes aegypti and to a lesser extent, Aedes albopictus[3-4]. Natural products have been a major source for development of new drugs and spiro structure is present in many natural products[5] . In the past decade, most heterocyclic systems have been used as a sources because of nitrogen containing heterocyclic systems like novel pyrolidine moieties and highly pronounced biological activities such as antiviral, antimicrobial potentials[6]. Here in we report the synthesis of indanone substituted through cycloaddition reaction that generated from acenaphthenequinone and 2-aminophenylglycine, evaluated their activities and predicted the binding mode of the spiro compounds to the protein target using molecular docking.

## OBJECTIVE

To design novel spiro compounds as potential antiviral agents and study their interaction at the active site of target protein through molecular docking.

## EXPERIMENTAL




## RESULTS

**Table 1.** Physical characteristic of spiro derivatives 4(a-l).

| Comp | Ar | M.P.°C | $R_f$ Value | Yield (%) |
|---|---|---|---|---|
| **4a** | 3-Nitrophenyl- | 144 | 0.8 | 61 |
| **4b** | 4-Dimhetylamino phenyl- | 154 | 0.5 | 74 |
| **4c** | 2-Hydrophenyl- | 130 | 0.84 | 19 |
| **4d** | 4-(1-Piperidinyl)phenyl- | 140 | 0.76 | 62 |
| **4e** | 3-Bromophenyl- | 146 | 0.8 | 88 |
| **4f** | 2,4-Dichlorophenyl- | 132 | 0.88 | 75 |
| **4g** | 4-Dichlorophenyl- | 140 | 0.8 | 72 |
| **4h** | 2-Dichlorophenyl- | 180 | 0.63 | 87 |
| **4i** | 4-methoxyphenyl- | 170 | 0.76 | 59 |
| **4j** | Phenyl- | 160 | 0.8 | 77 |
| **4k** | 4-(4-Morpholinyl)phenyl- | 180 | 0.8 | 75 |
| **4l** | 4-trifluoromethoxyphenyl- | 180 | 0.72 | 55 |

## MOLECULAR DOCKING

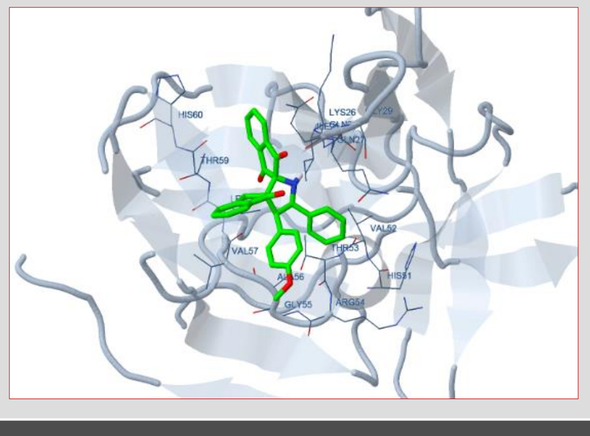



**Figure 1:** NS2B-NS3 is a serine protease of the Dengue virus considered a key target in the search for new antiviral drugs. (PDB CODE: 3U1I)[9]




**Figure 2**: Binding modes of 4i at the active site of 3U1I. Binding energy was found to be -7.79 kcal/mol and inhibition constant *ki* was found to be 1.95 μM.

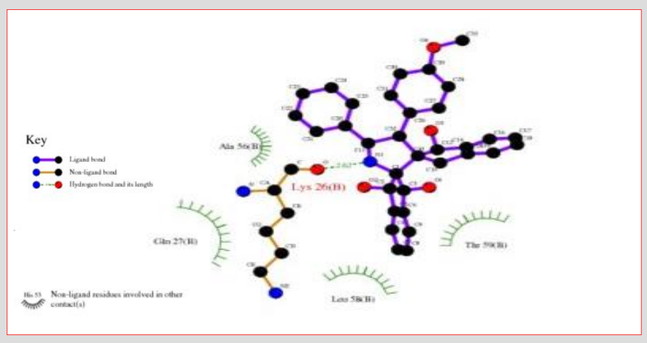
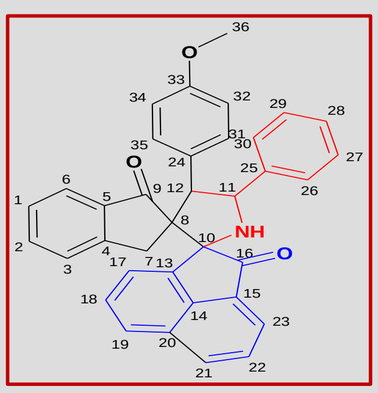



**Figure 3**: 2D binding interactions of compound **4i** at active site showing one H-bonding with Lys 26 (2.26)




**$^1$H NMR (500 MHz, $CDCl_3$):** 2.04 (s, 1H, NH), 2.60 (s, 2H, $CH_2$), 3.77 (d, 1H, CH), 3.80 (s, 3H, $OCH_3$), 4.41 (d, 1H, CH), 6.70-7.92 (m, 19H, ArH).

## CONCLUSION

In this study spiro derivatives were found to be inhibitors of NS2B-NS3 proteases of the Dengue virus with *ki* value of 1.95 μM. Analysis of molecular docking studies help to understand the mechanism of inhibition of the Dengue virus serine protease by spiro compounds, which is essential for the development of improved inhibitors.

## ACKNOWLEDGEMENTS

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