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Design, Synthesis, and Docking Studies of Some New 5-(([1,1'-Biphenyl]-4-yloxy) methyl)-2-(*N*-methylene) amino-1,3,4-thiadiazoles as Anti-inflammatory Agents

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ABSTARCT A series of new 5-(([1,1'-biphenyl]-4-yloxy)methyl)-2-(*N*-methylene)amino-1,3,4-thiadiazoles was prepared by a two steps route starting from 2-(4-phenylphenoxy)acetyl chloride and thiosemicarbazide. Using molecular docking techniques, the newly synthesized derivatives were investigated for their inhibition potentialities toward COX-2 protein. The docking results established that the derivatives **M8** and **M12** with 4-methylphenyl and 4-N-dimethylphenyl substituents have higher affinity than that of standard toward the COX-2 protein (PDB Code: 3LN1). Other compounds also displayed good to moderate binding affinity values.

KEYWORDS Thiadiazole derivatives, Molecular docking, COX-2 inhibition, Anti-inflammatory activity.

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INTRODUCTION

Heterocyclic compounds bearing a symmetrical 1,3,4–thiadiazole moieties[1] are associated with an extensive spectrum of pharmacological activities. Due to –N=C-S group presence in the structure of 1,3,4-thiadiazoles, they exhibit various biological activities. Inflammation is a complex process depicted by COX-2[2,3] (cyclooxygenase) enzyme which is associated with the transformation of the arachidonic acid to prostaglandin, that responsible to get inflammation reactions. Nonsteroidal anti-inflammatory drugs (NSAIDs)[4] help in the treatment of chronic and acute inflammation, fever, and pain. In view of our interest in heterocyclic synthesis and based on the reported studies[5,6,7], we planned to synthesize 1,3,4 -thiadiazole analogues of biphenyl-4-yloxy acetate. At present accessible NSAIDs like fenbufen, ibuprofen, naproxen and flurbifrofen are drugs of choice for the treatment of inflammation for the last few decades. Moreover, review of literature disclosed that the structural changes in carboxyl group of NSAID show reduced gastro intestinal side effects and increased anti-inflammatory activity[8]. It is also well reported that the enzyme COX-2 is over communicated in various human disease cells like colorectal, gastric and breast malignant growth. Thiadiazole moiety associated with various biological activities such as leishmanicidal activity[9], antimicrobial[10], analgesic[11], anticancer[12], antidepressant[13], diuretic[14,15], antidiabetic[16] and antioxidant activities.

In the middle of 1998 and 2002, many compounds have been designed, synthesized and many of them proved as selective COX-2 inhibitors like celecoxib, roficoxib, etoricoxib, and these molecules are termed as coxibs. When compared with traditional NSAIDs these coxibs display improved gastrointestinal safety profile. Among the selective inhibitors, other than the celecoxib they are either

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(d, 1H, Ar-H), 7.17 (d,2H,Ar-H), 7.39 (t,1H,Ar-H), 7.433 (d,1H,Ar-H),7.45 (d,2H,Ar-H), 7.56 (d,2H,Ar-H), 7.59 (d,2H,Ar-H), 7.61 (d,2H,Ar-H), 9.4 (s,1H,NCH); Mass (m/z): 399[M^+].

5-(([1,1'-Biphenyl]-4-yloxy)methyl)-2-(N-(3,4-dichloro-benzylidene))amino-1,3,4-thiadiazole [M14]

Chemical formula: $C_{22}H_{15}Cl_2N_3O_2S$; Molecular weight: 439 g/mol; Yield: 68%; Melting point: 458 K or 185 °C; IR (υmax, cm^{-1}): 3109(C-H),2950 (Ar-C-H), 1669 (C=C),1613 (C=N), 1253 (C-O-C), 1220 (C-N), 660(C-Cl);H NMR (400 MHz, DMSO-d6); δ 5.0 (s,2H,OCH_2),7.17 (d,2H,Ar-H), 7.34 (d,2H,Ar-H),7.40 (t,1H,Ar-H), 7.45 (d,*2H,Ar-H*), 7.56 (d,2H,Ar-H), 7.59 (d,2H,Ar-H), 7.69 (d,2H, Ar-H), 7.92 (d,2H, Ar-H),9.41 (s,1H,NCH); Mass (m/z): 439[M^+], 441[M+2].

5-(([1,1'-Biphenyl]-4-yloxy)methyl)-2-(N-(furan-3-yl) methyl)amino-1,3,4-thiadiazole [M15]

Chemical formula: $C_{20}H_{15}N_3O_2S$; Molecular weight: 361 g/mol; Yield: 73%; Melting point: 381 K or 108 °C; IR (υmax, cm^{-1}):3385 (N-H), 3109(C-H),2950 (Ar-C-H), 1669 (C=C),1613 (C=N), 1253 (C-O-C), 1220 (C-N); ^{1}H NMR (400 MHz, DMSO-d6); δ 5.2 (s,2H,OCH_2), 6.57 (d,1H,Ar-H), 7.17 (d,2H,Ar-H), 7.27 (d,1H,Ar-H),7.40 (t,1H,Ar-H), 7.45 (d,2H,Ar-H), 7.56 (d,2H,Ar-H), 7.59 (d,2H,Ar-H), 7.92 (d,1H, Ar-H), 8.82 (s,1H,NCH); Mass (m/z): 361[M^+].

In silico studies

Pre-ADMET (http://preadmet.bmdrc.org/) and Molinspiration (https://www.molinspiration.com) tools were used for *in silico* studies. By the help of Molinspiration software predicted molecular properties, bioactivity scores of the compounds toward human therapeutic targets. ADME properties of the molecules were predicted using PreADME server. This software determines the *in vitro* skin penetration, binding affinity toward plasma proteins (<90–weakly bound >90–strongly bound), gastrointestinal absorption, and BBB (>1–CNS active compounds (+), <1–CNS inactive compounds).

In the present scenario of drug discovery process, the molecular docking studies[21] are one of the promising approaches for establishing the molecular interactions[22] of the ligand molecules. The current research work involved in usage of AutoDock software for docking novel compounds on COX-2 receptor and calculated binding affinity values were compared with the standard drug (Diclofenac) to estimate the anti-inflammatory activity of newly designed compounds.

CONCLUSION

In the present study, new 5-(([1,1'-biphenyl]-4-yloxy) methyl)-2-(N-methylene)amino-1,3,4-thiadiazol derivatives were designed, synthesized and scrutinized for anti-inflammatory activity by taking Diclofenac as standard drug. Among the series, subordinates **M8** with 4-methyl group and **M12** with 4-N-dimethyl group showed high anti-inflammatory activity. Compounds **M4 (**4-amino), **M5 (**4-flouro), **M7 (**4-bromo), and **M13 (**3,4-dimethyl) compounds showed considerable activity comparable to that of standard. Among all, **M6** and **M9** derivatives exhibited good bioactivity with substituent's 3-hydroxy and 4-hydroxy groups, respectively. Most of the compounds fall within the Lipinski rule of five that enhances oral bioavailability. The study demonstrates that 5-(([1,1'-biphenyl]-4-yloxy) methyl)-2-(N-methylene)amino-1,3,4-thiadiazol scaffold can be utilized as a lead for the advancement of novel anti-inflammatory agents.

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