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Research Article

# SYNTHESIS, DOCKING STUDIES AND BIOLOGICAL EVALUATION OF SOME NEWLY SUBSTITUTED-5-(2 - METHYL IMIDAZO [1,2-a] PYRIDIN-3 -YL) -2,5 - DIHYDRO -1,3,4 - THIADIAZOL-2-AMINES

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**ABSTRACT**

Objective: To synthesize and study the docking pattern and Anti inflammatory activities of some new analogues of Imidazo [1, 2-a] pyridines.

Methods: A scheme involving the synthesis of a modern series of ten substituted 5-(2-Methyl imidazo [1, 2-a] pyridine-3- yl) -2, 5 -dihydro -1, 3, 4-thiadiazol-2-amines **(6a- j)** using 2-amino pyridine **1** as the starting material, through an order of four reactions was proposed. The derivatives were subjected to docking studies using the protein sequences for *prostaglandin reductase*. It was found that all the synthesized derivatives possessed very good binding energy, bringing into consideration that, the compounds are good inhibitors of *prostaglandin reductase* and hence are vested with anti-inflammatory properties. The scheme was then practically preceded and the synthesized compounds were characterized based on spectral data and elemental analysis. The new moieties were then evaluated for *invitro* anti-inflammatory property by Human Red Blood cell (HRBC) membrane stabilization method using Diclofenac as the standard drug.

Results: All the compounds synthesized showed inhibition of inflammation out of which compounds **6a, 6b, 6c & 6f** possessing meta nitro, para nitro, meta hydroxy and trimethoxy substitution respectively were identified as significant inhibitors of inflammation when compared with the activity of standard drug Diclofenac.

Conclusion: On comparing the docking scores of the compounds with their anti-inflammatory activity, it is evident that derivatives **6b, 6d** and **6f** that showed excellent docking scores, possessed maximum anti-inflammatory property.

**Keywords:** Imidazo [1, 2-a] pyridines, Docking studies, *In vitro* anti-inflammatory action, HRBC membrane stabilization method.

Imidazo [1, 2-a] pyridine units are important ł
natural and synthetic bioactive compounds. Because of this, imidazo [1, 2-a] pyridine and their analogues has attracted significant attention in recent years as a class of compounds exhibiting a broad range of pharmacological activity. Substituted imidazo [1, 2-a] pyridine have been recently identified as a new generation of biologically important species due to their multiple pharmacological profile. The various biological activities of imidazo [1, 2-a] pyridine is shown to be critically dependent on the nature of the substituents at $C_2$ and $C_3$ positions [1-2]. Hence, there arises a need to develop a structurally flexible method for the synthesis of this class of compounds. Imidazo [1,2-a] pyridines display an interesting array of biological activities over a broad range of therapeutic classes like anti-inflammatory[3], analgesic[4], antibacterial[5], cytotoxicity[6], anticymegalo-zoster, anti-varicella zoster[7], anxioselective[8] and hypnoselective[9-10] activities. It also acts as selective cyclin-dependant kinase inhibitors [11], GABA and benzodiazepine receptor agonist[12] and cardiotonic agents[13]. Drug formulations containing imidazo [1, 2-a] pyridine nucleus, currently in market includes Alpidem(anxiolytic)[14], Zolimidine(antiulcer)[15]and Olprinone(PDE-3 inhibitor)[16]. Thiadiazole is a versatile moiety and exhibit a wide of biological activities [17]. Many drugs containing thidiazole nucleus are available in market such as Acetazolamide (diuretic), Methazolamide(diuretic), Sulphamethazole (antibacterial), Cefazoline(antibiotic) etc., The review of literature showed that the thiadiazole derivatives possess antimicrobial[18-20], anti-inflammatory[21], anticancer[22-24], antidepressant[25], carbonic anhydrase inhibitor[26] and antioxidant[27] activities.

In the above prospective, a scheme involving the synthesis of a series of ten thiadiazole substituted imidazo [1, 2-a] pyridines was drawn and docking studies [28] on *prostaglandin reductase* inhibitory activity was performed. The proposed scheme was then carried out and the synthesized compounds were evaluated for their *in vitro* anti-inflammatory activity. The salient features of this investigation are described here.

Melting points were taken in open capillaries on VEEGO Digital melting point apparatus and are uncorrected. Infrared spectra were recorded on KBr discs on a PERKIN ELMER FTIR Spectrometer. $^1$H NMR spectra were recorded on a BRUKER 500MHZ AVANCE NMR spectrometer using DMSO as solvent. Elemental analysis was performed on a PERKIN ELMER Series II 2400 CHN Elemental Analyzer. Compounds **6a-j** was prepared and the reactions were monitored by thin layer chromatography (TLC) carried out on activated silica gel coated plates with the solvent system benzene: acetone (3: l).

**General Procedure for Synthesis**

**Preparation of Ethyl-2- methyl imidazo [1, 2-a] pyridin-3-carboxylate (3)**

To a solution of ethyl-2-chloroacetoacetate (0.028 mol) (**2**) in dry acetone was added 2-amino pyridine (0.028mol) (**1**). To this mixture anhydrous potassium carbonate (3g) was added and the reaction mixture was refluxed for 6h. Acetone was removed by vaccum distillation and the residue was crystallized from ethanol to give compound (**3**). Yield 80%, m.p.42-44° C, $R_f$: 0.69. IR (KBr) ($cm^{-1}$): 3028 (C-H stretching of aromatic carbon), 2865 (C-H stretching of aliphatic carbon), 1765 (C=O stretching of ester), 1235 (C-O stretching of carboxylic ester).

**Preparation of 1-(2-methylH-imidazo [1, 2-a] pyridine-3-carbonyl) thiosemicarbazide (4)**

A mixture of compound **3** (0.03mol) and thiosemicarbazide (0.03mol) in 1, 4- dioxan (40ml) was refluxed on a water bath for about 5-7 h. The excess solvent was removed under reduced pressure and the product was crystallized from acetone to give compound (**4**). Yield 81%, m.p.195-197° C, $R_f$: 0.55. IR (KBr) ($cm^{-1}$): 3045 (C-H stretching of aromatic carbon), 2852 (C-H stretching of aliphatic carbon), 3420 (N-H stretching of aromatic secondary

amide), 3393 (N-H stretching of primary amine), 1640 (C=O stretching of amide), 1173 (C=S stretching).

**Preparation of 5-(2-methyl imidazo [1, 2–a] pyridin-3-yl)-2,5-dihydro-1,3,4-thiadiazol-2amine (5)**

The compound **4** was treated with concentrated sulphuric acid (15ml) and was kept overnight at room temperature. It was then poured into ice-cold water and neutralized with ammonia. The resulting product was crystallized from methanol which gave compound (**5**). Yield 65%, m.p.182-184° C, $R_f$: 0.68. IR (KBr) ($cm^{-1}$): 3030 (C-H stretching of aromatic carbon), 2923 (C-H stretching of aliphatic carbon), 1438 (C-N stretching of aromatic amine), 717 (C-S stretching vibration).

**General method for the preparation of (substituted)-5-(2-methyl imidazo [ 1, 2-a] pyridin-3-yl)-2,5-dihydro-1,3,4-thiadiazol-2-amine(6a-j)**

The compound **5** (1mmol) and aldehyde (1 mmol) were mixed in 10ml of absolute ethanol and stirred at room temperature in the presence of two drops of concentrated hydrochloric acid as catalyst. The reaction mixture was concentrated under reduced pressure followed by neutralization with 10% aqueous solution of sodium bicarbonate. The resulting precipitate is filtered out followed by washing with 10ml water and then air-dried.

Preparation of 3-Nitrobenzyidin-5-(2-methyl imidazo[1,2-a] pyridin-3-yl)-2,5-dihydro-1,3,4-thiadiazol-2-amine (**6a**): Yield 68%, m.p. 180-181° C, $R_f$: 0.55. IR (KBr) ($cm^{-1}$): 3046 (C-H stretching of aromatic carbon), 2967 (C-H stretching of aliphatic carbon), 1611 (C=N stretching vibration), 1520 (asymmetrical C-$NO_2$ stretching), 1350 (symmetrical C-$NO_2$ stretching), 717 (C-S stretching vibration), 726 & 770 (Two medium bands indicating meta disubstituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.6-8.6 (m, 10H, ArH), 2.3 (s, 3H, $CH_3$), 2.8 (s, 1H, CH).Anal. Calcd. for $C_{17}H_{14}N_6O_2S$ (366):C, 55.77; H, 3.85; N, 22.95. Found value: C, 55.79; H, 3.82; N, 22.94.

Preparation of 4-Nitrobenzylidin-5-(2- methyl imidazo [1,2-a] pyridin – 3-yl)- 2,5- dihydro – 3,4– thiadiazol-2-amine (**6b**): Yield 70%, m.p. 185-186° C, $R_f$: 0.57. IR (KBr) ($cm^{-1}$): 3130 (C-H stretching of aromatic carbon), 2923 (C-H stretching of aliphatic carbon), 1609 (C=N stretching vibration), 1507 (asymmetrical stretching of C-$NO_2$), 1325 (symmetrical stretching of C-$NO_2$), 870 (One band indicating para disubstituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.4-8.9 (m, 10H, ArH), 2.2 (s, 3H, $CH_3$), 2.7 (s, 1H, CH).Anal.Calcd. for $C_{17}H_{14}N_6O_2S$ (366):C, 55.77; H, 3.85; N, 22.95. Found value: C, 55.76; H, 3.83; N, 22.97.

Preparation of 3-(5-(2-Methyl imidazo [ 1,2-a] pyridin -3-yl )-2,5-dihydro-1,3,4- thiadiazol – 2- ylimini methyl phenol (**6c**): Yield 81%, m.p. 189-190° C,$R_f$: 0.66. IR (KBr) ($cm^{-1}$): 3344 (O-H stretching of phenol), 3150 (C-H stretching of aromatic carbon), 2865 (C-H stretching of aliphatic carbon), 1609 (C=N stretching vibration), 717 & 770 (Two medium bands indicating meter disubstituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.1-8.3 (m, 10H, ArH), 2.4 (s, 3H, $CH_3$), 2.9 (s, 1H, CH), 5.6 (s, 1H, OH).Anal. Calcd. for $C_{17}H_{15}N_5OS$ (337): C,60.57 ; H,4.48 ; N,20.77 . Found value: C,60.55 ; H,4.46 ; N, 20.79.

Preparation of 4-Chloro benzylidin-5-(2-methyl imidazo [ 1,2-a] pyridine-3-yl)-2,5-dihydro-1,3,4 thiadiazol-2-amine (**6d**) : Yield 74%, m.p. 190-191° C,$R_f$: 0.52. IR (KBr) ($cm^{-1}$): 3135 (C-H stretching of aromatic carbon), 2852 (C-H stretching of aliphatic carbon), 1605 (C=N stretching vibration), 744 (C-Cl stretching vibration), 851 ( one band indicating para disubstituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.3-8.2 (m, 10H, ArH), 2.3 (s, 3H, $CH_3$), 2.6 (s, 1H, CH).Anal. Calcd. for $C_{17}H_{14}ClN_5S$ (355): C,57.50 ; H,3.97 ; N,19.72. Found value: C,57.53 ; H,3.98 ; N,19.70 .

Preparation of 2,5-Dimethoxy benzylidin-5-(2-methyl imidazo [1,2-a] pyridin-3-yl)-2,5- dihydro-1,3,4-thiadiazol-2-amine (**6e**) : Yield 79%, m.p. 196-197° C,$R_f$: 0.60. IR (KBr) $cm^{-1}$ : 3139 (C-H stretching of aromatic carbon), 2852 (C-H stretching of aliphatic carbon), 1610 (C=N stretching vibration), 1145 (C-O stretching vibration), 746 ( one band indicating ortho disubstituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.5-7.9 (m, 9H, ArH), 2.5 (s, 3H, $CH_3$), 2.8 (s, 1H, CH), 3.5 (s, 6H, $OCH_3$). Anal. Calcd. for $C_{20}H_{19}N_5O_2S$ (393): C,61.10 ; H,4.87 ; N,17.81. Found value: C,61.13 ; H,4.8 6 ; N,17.84 .

Preparation of 3,4,5-Trimethoxy benzylidin-5-(2-methyl imidazo [1,2-a] pyridin-3-yl)- 2,5- dihydro-1,3,4-thiadiazol-2-amine (**6f**) : Yield 83%, m.p. 175-176° C,$R_f$: 0.58. IR (KBr) ($cm^{-1}$) : 3137 (C-H stretching of aromatic carbon), 2852 (C- H stretching of aliphatic carbon), 1605 (C=N stretching vibration), 1235 (C-O stretching vibration).$^1$H NMR (DMSO, 500 MHz) δ 6.1-7.5 (m, 10H, ArH), 2.2 (s, 3H, $CH_3$), 2.6 (s, 1H, CH), 4.1 (s, 9H, $OCH_3$).Anal. Calcd. for $C_{20}H_{21}N_5O_3S$ (411): C,58.43 ; H,5.14 ; N,17.03. Found value: C,58.44 ; H,5.12 ; N,17.04 .

Preparation of 4-Dimethyl amino benzylidin-5-( 2-methyl imidazo [1,2-a] pyridin-3-yl)-2,5 -dihydro-1,3,4 thiadiazol-2-amine (**6g**) : Yield 75%, m.p.193-195 ° C,$R_f$: 0.67. IR ( KBr) ($cm^{-1}$) : 3130 (C-H stretching of aromatic carbon), 2852 (C-H stretching of aliphatic carbon), 1605 (C=N stretching vibration), 2780 (C-N stretching vibration), 870 ( one band indicating para disubtituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.3-7.9 (m, 10H, ArH), 2.4 (s, 3H, $CH_3$), 2.8 (s, 1H, CH), 2.1 (s, 6H, $CH_3$).Anal. Calcd. for $C_{19}H_{20}N_6S$ (364): C, 62.66; H,5.53 ; N,23.07. Found value: C, 62.64; H,5.52 ; N, 23.09 .

Preparation of 4-Methoxy benzylidin-5-(2-methyl imidazo [1,2-a] pyridin-3-yl )-2,5-dihydro- 1,3,4-thiadiazol-2-amine (**6h**) : Yield 71%, m.p. 174-175° C,$R_f$: 0.61. IR ( KBr) ( $cm^{-1}$) : 3140 (C-H stretching of aromatic carbon) 2852 ( C-H stretching of aliphatic carbon), 1605 (C=N stretching vibration), 1090 (C-O stretching vibration), 861 (one band indicating para disubstituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.1-8.3 (m, 10H, ArH), 2.2 (s, 3H, $CH_3$), 2.9 (s, 1H, CH), 3.8 (s, 3H, $OCH_3$).Anal. Calcd. for C18H17N5OS (351): C,61.57 ; H,4.87 ; N,19.94. Found value: C,61.58 ; H, 4.85; N,19.97.

Preparation of 4-Methoxy -4-(5-( 2-methyl imidazo [1,2-a] pyridin-3-yl)-2,5-dihydro-1,3,4 thiadiazol-2-ylimino)methyl phenol (**6i**) : Yield 69%, m.p. 183-184° C,$R_f$: 0.69. IR (KBr) ($cm^{-1}$) : 3135 (C-H stretching of aromatic carbon), 2852 (C-H stretching of aliphatic carbon), 1605 (C=N stretching vibration), 1100 ( C-O stretching vibration), 861 (one band indicating para disubstituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.7-8.5 (m, 10H, ArH), 2.3 (s, 3H, $CH_3$), 2.7 (s, 1H, CH), 3.9 (s, 3H, $OCH_3$), 5.9 (s, 1H, OH).Anal. Calcd. for C18H17N5O2S (367): C, 58.84; H,3.85 ; N,22.94. Found value: C,58.82 ; H,3.82 ; N,22.96 .

Preparation of 4-(5-(2-methyl imidazo [1,2-a] pyridin-3-yl)-2,5-dihydro-1,3, 4-thiadiazol-2-yl imino)methyl phenol (**6j**) : Yield 77%, m.p.187-188 ° C,$R_f$: 0.53. IR ( KBr) ( $cm^{-1}$) : 3735 (O-H stretching of aromatic carbon), 2860 (C-H stretching of aliphatic carbon), 1605 (C=N stretching vibration), 849 ( one band indicating para disubstituted aromatic ring).$^1$H NMR (DMSO, 500 MHz) δ 6.3-8.1 (m, 10H, ArH), 2.1 (s, 3H, $CH_3$), 3.0 (s, 1H, CH), 5.1 (s, 1H, OH).Anal. Calcd. for $C_{17}H_{15}N_5OS$ (337): C,60.57 ; H,4.48 ; N,20.77. Found value: C,60.54 ; H,4.47 ; N,20.79 .

**Molecular Docking Studies**

The protein sequences for *prostaglandin reductase*, was taken from NCBI. The sequences were converted into FASTA format. The FASTA format sequences were allowed into BLAST database. The protein structure file (PDB code: 2ZB4) was taken from protein Data Bank 2. CASTP server was used to cross check the active pockets on target protein molecules. The ligand molecules were designed and the structure was analyzed using Chemsketch ACD labs. Argus Lab was used to perform molecular docking. PyMol 3 software was used to view the structure and calculate the length of the hydrogen bond. The docking scores presented in **Table 1.**

**Biological screening**

All the synthesized compounds were evaluated for their *in vitro* anti inflammatory activity by HRBC membrane stabilization method [15]. This method involves the stabilization of human red blood cell membrane by hypotonicity induced membrane lysis. Blood collected from a healthy volunteer was mixed with equal volume of sterilized Alsievier's solution and centrifuged at 3000 rpm. The packed cells were washed with isotonic saline and a 10% v /v HRBC suspension

of packed cells was made with isotonic saline. The assay mixture contained the drug (100 µg/ml), 1 ml of phosphate buffer, 2 ml of hypotonic saline and 0.5ml of HRBC suspension. Distilled water was used as control and Diclofenac (50 µg/ml) was used as reference drug. All the assay mixtures were included at 37°C for 30 minutes and centrifuged at 3000 rpm. The absorbance of the supernatants was estimated using UV spectrophotometer at 560 mm & the results presented in **Table 1.**

**RESULTS AND DISCUSSION**

**Synthesis**

Synthesis of the title compounds as per the scheme depicted in **Figure-1** is effected by reacting the starting compound 2-aminopyridine with ethyl-2- chloroacetate in the presence of acetone and potassium carbonate by refluxing for 6 hrs to form an intermediate compound (**3**) which on reaction with thiosemicarbazide gives compound (**4**). Compound (**4**) on reaction with sulphuric acid gives compound (**5**) which gives compounds (**6a-j**) on treatment with various substituted aldehydes. The FTIR spectra and $^1$H NMR spectra of all the synthesized compounds were in agreement with the assigned structure. In case of IR spectral analysis, a sharp band in the region between 1620-1600 cm$^{-1}$ confirms the presence of C=N stretching in all the title compounds in addition to the stretching vibration for aromatic C-H stretching between 3150-3050 cm$^{-1}$ and aliphatic C-H stretching between 2960-2850 cm$^{-1}$.Compounds **6a** and **6b** shows two strong bands in the region between 1520- 1507 cm$^{-1}$ and 1350-1325cm$^{-1}$ respectively, indicating the presence of aromatic $NO_2$ group. The phenolic OH appeared as a sharp band in the region between 3700-3300 cm$^{-1}$ in addition to a strong, band near 1200 cm$^{-1}$ and another between 1410-1380 cm$^{-1}$ indicating C-O stretching in **6c, 6i** & **6j.** Another band around 744 cm$^{-1}$ appeared in the IR spectra of the compound **6d** indicating the presence of C-Cl group. The Compounds **6c, 6f** & **6h** showed absorbance around 1240-1095 cm$^{-1}$ indicating the presence of C-O-C stretching. A strong band around 2780cm$^{-1}$ in compound **6g** indicates presence of N-$CH_2$-stretching vibration. $^1$H NMR spectral analysis of compounds **6a-6j** exhibited a multiplet between 6.5-8.9 ppm indicating presence of aromatic protons and a singlet between 2.1-2.5 ppm indicating $CH_3$ group. Compounds **6c, 6i,** & **6j** showed a singlet at 5.6 ppm, 5.9ppm & 5.1ppm respectively confirming the presence of OH group. A singlet in the range between 3.5 – 4 .0 ppm for compounds **6e, 6f, 6h,** & **6i** indicates the presence of -$OCH_3$ group. The mass spectra of the compounds **6b** & **6i** showed a molecular ion peak at m/z 365 and 366 respectively confirming the molecular weight of the appropriate title compounds. The elemental analysis data of all the synthesized compounds were within ± 0.4% of the theoretical values.

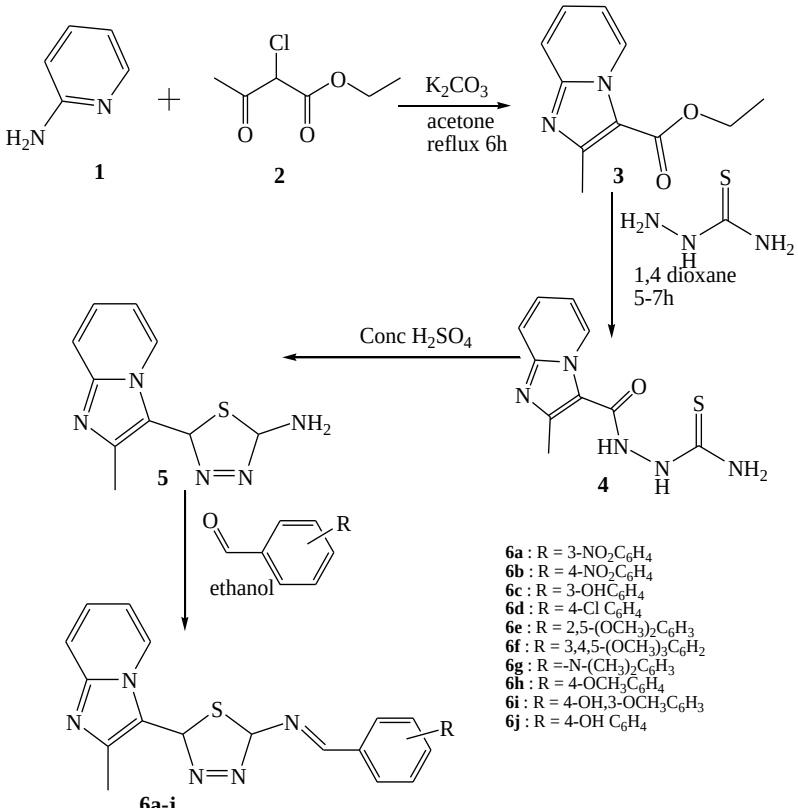


**Fig.1: Scheme of Synthesis of compounds 6a-j**

**Fig. 1: Scheme of Synthesis of compounds 6a-j**

**Docking studies**

Docking studies of the synthesized Imidazo [1, 2 -a] pyridine derivatives on *Prostaglandin reductase* was performed. All the compounds **6a-6j** showed hydrogen bonding within the limit of 3.2 indicating very good binding energy. Among the 10 moieties synthesized, compounds **6a, 6b, 6c, 6d, 6f, 6g,** & **6i** showed the best ligand pose between – 11.542 to -14.432 kcal / mol. The estimated high binding energy of Imidazo [1, 2-a] pyridines confirms better anti-inflammatory character of the suggested compounds, which were further confirmed by *in vitro* studies.

**Anti-inflammatory activity**

All the synthesized compounds were evaluated for *in vitro* anti-inflammatory properties by HRBC membrane stabilization method. Diclofenac was used as standard. Compounds **6a, 6b, 6c, 6d, 6f, 6g** and **6i** showed good percentage inhibition of inflammatory response. Especially compounds **6b, 6d** and **6f** possessing nitro, choro and trimethoxy substituents respectively were significantly active against inflammation with a percentage inhibition score of 61%, 65% and 63% respectively as given in **Table 1.**

**Table 1: Molecular docking score and *in vitro* anti inflammatory activity**

| Compound code | Docking scores (kcal/mol) of *prostaglandin reductase* | | | Percentage of inhibition by HRB Membrane stabilization method |
|---|---|---|---|---|
| | Energy level(kcal/mol) | Binding site | Hydrogen bonding | |
| 6a | -11.5673 | Ser 217, Glm222 | 2.7, 2.3, 3.3, 3.3 | 58.60±0.12 |
| 6b | -12.443 | Ser 217 | 3.5, 2.5 | 61.32±0.31 |
| 6c | -13.3423 | Glm 222, Ser 217 | 3.4, 2.1, 2.4 | 59.71±0.16 |
| 6d | -11.9736 | Tyr 218 | 2.3,3.1 | 64.67±0.48 |
| 6e | -8.325 | Ser 217 | 2.4,`2.7 | 32.28±0.55 |
| 6f | -11.542 | Ser 229, Glm 118 | 3.2, 2.5, 2.6 | 62.93±0.49 |
| 6g | -12.4256 | Ser 217, Glm22 | 2.1, 3.2, 2.6 | 58.61±0.22 |
| 6h | -8.1678 | Ser 217 | 2.4, 2.7 | 51.71±0.48 |
| 6i | -14.4321 | Tyr 319, Tyr 216 | 2.8, 3.0, 3.3, 3.2 | 56.67±0.19 |
| 6j | -9.5563 | Leu19, Pro 117 | 3.6, 2.8 | 31.01±0.73 |
| Standard | - | - | - | 66.78±0.43 |

SD mean of three values

## CONCLUSION

In this study, about 10 new analogs of 5- (2-methyl imidazo [1, 2-a] pyridin-3-yl)-2, 5 dihydro-1, 3, 4 –thiadiazol-2-yl)-1-phenyl substituted methamine were synthesized and confirmed by spectral analysis. Docking studies on the analogs with *prostaglandin reductase* revealed good binding scores of the synthesized compounds. Further *in vitro* anti-inflammatory study on the analogues indicated moderate anti-inflammatory potency in them. On comparing the docking scores of the compounds with their anti-inflammatory activity, it is evident that derivatives **6b, 6d** and **6f** that showed excellent docking scores, possessed maximum anti-inflammatory property. This revelation paved the way for further *in vivo* studies on these analogs which is under progress.

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