ISSN: 0976-3031

Available Online at http://www.recentscientific.com

International Journal of Recent Scientific Research
Vol. 6, Issue, 4, pp.3665-3669, April, 2015

International Journal of Recent Scientific Research

RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL SCREENING, AND MOLECULAR DOCKING STUDIES OF SOME NOVEL 2,6-BIS (4-CHLOROBENZOYL)-3,5-BI'S (SUBSTITUTED ARYL) TETRAHYDRO-1,4-THIAZINE 1,1-DIOXIDE DERIVATIVES

Bhavani P and Meena K S*

Department of Chemistry, Queen Mary's College (Autonomous), Chennai- 04, India

ARTICLE INFO

Article History:

Received 14th, March, 2015
Received in revised form 23th, March, 2015
Accepted 13th, April, 2015
Published online 28th, April, 2015

Key words:

1, 4-thiazine 1, 1-dioxide, antibacterial activity, spectral studies, molecular docking, discovery studio 4.0.

ABSTRACT

A series of some new 2,6-bi's (4-Chlorobenzoyl)-3,5-bi's (substituted aryl) tetra hydro 1,4-thiazine -1,1-ioxide has been synthesized by condensing respective aldehydes with 4,4'-dichloro diphenacyl sulphone. They were characterized by 1HNMR, 13CNMR, FT-IR. All the compounds were screened for their in vitro antibacterial activity against Gram positive (Staphylococcus, Bacillus Cereus, B.subtilis) and gram negative organism (Pseudomonas, E.Coli) by disc diffusion method. Among the tested compounds showed the most potent antibacterial activities. The newly synthesized compound were docked with Plasmodium falciparum dihydrofolate reductase-thymidylate synthase (1J3K) using Discovery studio 4.0, the best Lib dock score and Binding energy were obtained for 3,5-Bis(m-nitro phenyl)-2,6-bi's(p-hlorobenzoyl) tetra hydro 1,4-thiazine 1,1-dioxide (A).

INTRODUCTION

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. Heterocycles are important constituents of natural compounds, synthetic medicines and are known to play a vital role in a number of chemical and biochemical processes. We know that Thiazines are six member cyclic compounds containing sulfur and nitrogen atoms at 1, 2; 1, 3 & 1, 4 positions and also posses' two pharmacophores i.e., -NH- and $-SO_2$. A survey about synthesis of thiazines moiety revealed that it had a greater attraction towards medicinal chemists, biochemist, pharmacologist and rendered as one of the leading molecule for designing potential bioactive agents. Thiazine derivative moiety showed more potent pharmacological activities (JS Bojar *et al* 1987; W Foery *et al*, 1986; AW Faull *et al*, 1997; B Narr *et al*, 1975). When substituted diaryl tetra hydro-1,4-thiazine -1,1-dioxide had led to the discovery of wide variety of compounds that show a very high interest in the point of antimicrobial activity(V Sundari and R Valliappan 2002&2004 ; V Sundari, GNagarajan 2007), antimycobacterial (M. Iovu, C *et al*, 2003), antiviral(P.G. Baraldi *et al*,1998), (Silvestri, R., *et al*, 2003), antimalarial(Arthur Barazarate *et al*, 2009), antidiabetic, antidepressant, sedative(O. Bruno *et al*, 1990), tranquilizers, hypoglycemic(B. Cottineau *et al*, 2002), antipileptics, antitubercular, antitumor, bactericidal and parasitical agent(Boult *et al*, 1984). The large numbers of Biologically active (Radadiya *et al*, 2005; Pandeya S, N, *et al*, 1999) molecules that contain heterocyclic rings has played important roles in the drug discovery process and exhibit various biological activities. A literature survey identified several1, 4-thiazine 1, 1-dioxide and its derivatives in the development phase as potential new drugs. The versatility of the 1, 4-thiazine 1, 1-dioxide and in addition to its relative compound a were simplicity and accessibility, makes these chemicals amongst the most promising sources of bioactive compounds. The 4, 4'-dichlorodiphenacyl sulphone was synthesized by the following Baliah and Rangarajan (V Baliah and T Rangarajan, 1954) report, The title of compound A-I was synthesized by the reaction of 4, 4'-dichlorodiphenacyl sulphone, respective aldehyde and ammonium acetate (fig 1).

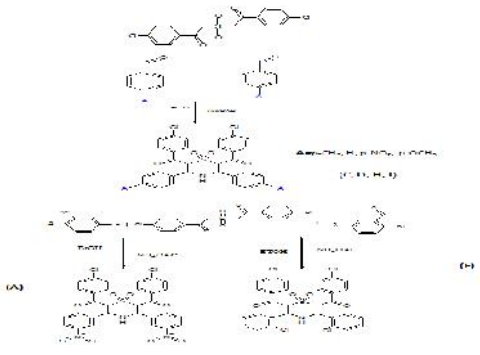

Fig. 1

Corresponding author:* **Meena K S
Department of Chemistry, Queen Mary's College (Autonomous), Chennai- 04, India

The structures of all these new products were elucidated by their IR, ^{1}H NMR and ^{13}C NMR.

Experimental Section

General

The melting point of the synthesized compound was noted in open capillary method. IR absorption spectra were recorded on FT-IR spectrometer using KBr pellet and ^{1}HNMR spectra were recorded (500MHz) spectrometer, using DMSO as internal standard. The purity of the compound was routinely checked using TLC using silica gel G.

General methods of preparation of 2, 6-bi's (4-chlorobenzoyl)-3, 5-bi's (substituted aryl) tetrahydro-1, 4-thiazine-1, 1-dioxide (A-I)

4, 4'-Dichlorodiphenyl sulphone (0.01mole), substituted aromatic aldehydes (0.02mole) and ammonium acetate (0.01 mole) were condensed in the presence of ethanol (10ml) for half an hour. The precipitate was filtered, washed with ethanol and recrystallized from ethanol.

3, 5-Bis (m-nitro phenyl)-2, 6-bis (p-chlorobenzoyl) tetra hydro 1, 4-thiazine1, 1-dioxide (A)

MP 210-212°C **yields** 95%. **^{1}H NMR**: δ6.468-6.489 (d, 2H) (C2, C6); δ5.048-5.077 (q, 2H) (C3, C5); δ7.559-8.438(m, 16H) (aromatic). **^{13}C NMR** 61.18(C3, C5), 69.21(C2, C6), 122.47-147(Aromatic), 188.12(C=O). **IR** 1340-1240cm^{-1} (SO_2,Str.,asym), 1165-1120 cm^{-1} (SO_2,Str., sym),710-700 cm^{-1} (C-S, bond), 1040-101 cm^{-1} (S-O bond), 3400-3000cm^{-1} (N-H Str.,), 3000-3100 cm^{-1} (Ar-C-H Str.,), 2950-2900 cm^{-1} (C-H Str., asym), 1700-1650 cm^{-1} (C=O absorption), 1300-1200 cm^{-1} (C=O bending), 1200-1100cm^{-1} (C=O Str.,), >1000 cm^{-1} (C-Cl bond), 900-450 cm^{-1} (ring deformation vibrations).

3, 5-Bis (p-tolyl) - 2, 6-bis (p-chlorobenzoyl) tetra hydro 1, 4-thiazine 1, 1-dioxide(C))

MP 216-218°C, **yields** 93%. **^{1}H NMR**: δ(6.276-6.297 (d, 2H) (C2, C6); δ4.757 – 4.790 (q, 2H) (C3, C5); δ 2.165(s, 6H)(2CH_3) δ7.058-7.988(m,16H) (aromatic). **^{13}C NMR** 61.93(C3, C5), 69.09(C2, C6), 127.66-139.65(Aromatic), 188.09(CO). **IR** 1340-1240-cm^{-1}(SO_2,Str.,asym), 1165-1120 cm^{-1} (SO_2,Str.,sym), 710-700 cm^{-1} (C-S, bond), 1040-1015 cm^{-1} (S-O bond), 3400-3000 cm^{-1} (N-H Str.,), 3000-3100cm^{-1} (Ar-C-H Str.,), 2950-2900 cm^{-1} (C-H Str., asym), 1700-1650 cm^{-1} (C=O absorption), 1300-1200 cm^{-1}(C=O bending), 1100-1200 cm^{-1} (C=O Str.,) >1000 cm^{-1} ((C-Cl bond), 900-450 cm^{-1} (ring deformation vibrations).

3, 5-diphenyl 2, 6-bis (p-chlorobenzoyl) tetra hydro 1, 4-thiazine 1, 1-dioxide (D)

MP 188-190°C, **yields** 95%. **^{1}H NMR**: δ6.306-6.327 (d, 2H) (C2, C6); δ4.806-4.840 (q,2H)(C3, C5); δ7.163-7.960(m,18H) (aromatic). **^{13}CNMR** 62.32(C3,C5), 69.15(C2,C6), 127.84-139.66(Aromatic),188.12(CO),**IR**1340-1240-cm^{-1}(SO_2,Str.,asym), 1165-1120 cm^{-1} (SO_2,Str., sym), 710-700 cm^{-1} (C-S, bond), 1040-1015 cm^{-1} (S-O bond), 3400-3000 cm^{-1} (N-cm^{-1}H Str.,), 3000-3100 cm^{-1} (Ar-C-H Str.,), 2950-2900 cm^{-1} (C-H Str., asym),1700-1650 cm^{-1} (C=O absorption), 1300-1200 cm^{-1} (C=O bending), 1200-1100 cm^{-1} (C=O Str.,)>1000 cm^{-1} (C-Cl bond) 900-450cm^{-1} (ring deformation vibrations).

3, 5-Bis (o-chlorophenyl) - 2, 6-bis (p-chlorobenzoyl) tetra hydro 1, 4-thiazine 1, 1-dioxide(F)

MP 195-197°C, **yield** 95%. **^{1}H NMR**: δ6.468-6.489 (d, 2H) (C2, C6); δ5.324-5.363 (t, 2H) (C3, C5); δ7.206-8.050(m, 16H) (aromatic). **^{13}C NMR** 66.32(C3, C5), 68.39(C2, C6), 127.37-139.95(Aromatic), 187.74(CO). **IR 1340**-1240-cm^{-1}(SO_2, Str., asym), 1165-1120 cm^{-1} (SO_2, Str., sym), 710-700 cm^{-1} (C-S, bond), 1040-1015 cm^{-1} (S-O bond), 3400-3000 cm^{-1} (N-H Str.,), 3000-3100 cm^{-1} (Ar-C-H Str.,), 2950-2900 cm^{-1} (C-H Str., asym), 1700-1650 cm^{-1} (C=O absorption), 1300-1200 cm^{-1} (C=O bending), 1200-1100 cm^{-1} (C=O Str.,) >1000 cm^{-1} (C-Cl bond) 900-450 cm^{-1} (ring deformation vibrations).

3, 5-Bis (p-nitro phenyl) - 2, 6-bis (p-chlorobenzoyl) tetra hydro 1,4-thiazine 1,1-dioxide(H)

MP 210-215°C **yields** 97%. **^{1}H NMR**:δ6.410-6.431 (d, 2H) (C2, C6);δ5.009-5.039 (q,2H)(C3, C5); 7.660-8.154(m,16H) (aromatic). **^{13}C NMR** 61.35(C3,C5), 69.25(C2,C6), 123.59-147.22(Aromatic), 187.74(CO). **IR** 1340-1240-cm^{-1}(SO_2, Str.,asym), 1165-1120 cm^{-1} (SO_2,Str., sym), 710-700 cm^{-1} (C-S, bond), 1040-1015 cm^{-1} (S-O bond), 3400-3000 cm^{-1} (N-H Str.,)3000-3100 cm^{-1} (Ar-C-H Str.,), 2950-2900 cm^{-1} (C-H Str., asym),1700-1650 cm^{-1} (C=O absorption), 1300-1200 cm^{-1} (C=O bending), 1200-1100 cm^{-1} (C=O Str.,) >1000 cm^{-1} ((C-C)Cl bond) 900-450 cm^{-1} (ring deformation vibrations).

3,5-Bis(p-methoxyphenyl)- 2,6-bis(p-chlorobenzoyl) tetra hydro 1,4-thiazine 1,1-dioxide(I)

MP 200-204°C **yields** 98%. **^{1}H NMR**:δ(5.261-5.282 (d, 2H) (C2, C6);δ4.978 – 4.999(d,2H)(C3, C5); δ 3.709(s,6H)(2OCH_3), δ6.761-7.809(m,16H) (aromatic). **^{13}C NMR** 55.22(C3,C5), 61.81(C2,C6), 18.29(OCH3), 114.18-140.80(Aromatic),159.80(CO).**IR**1340-1240-cm^{-1}(SO_2,Str.,asym), 1165-1120 cm^{-1} (SO_2,Str., sym),710-700 cm^{-1} (C-S, bond), 1040-1015 cm^{-1} (S-O bond), 3400-3000 cm^{-1} (N-H Str.,), 3000-3100 cm^{-1} (Ar-C-H Str.,), 2950-2900 cm^{-1} (C-H Str., asym),1700-1650 cm^{-1} (C=O absorption), 1300-1200 cm^{-1} (C=O bending), 1200-1100 cm^{-1} (C=O Str.,) >1000 cm^{-1} (C-Cl bond) 900-450 cm^{-1} (ring deformation vibrations).

***Note**: -NH protons not shown in ^{1}HNMR spectrum due to coupling of –NH protons with DMSO (d^6), therefore it converted –N-^{2}D (-N-^{2}D also give the peak but low MHz, but here using 500MHz) therefore not give back. When m-hydroxy benzaldehyde, p-hydroxy benzaldehyde, 2,4- dinitro substituted benzaldehydes, Vanillin, 2-OH-4-NO_2-benzaldehyde no condensation occurred due to stearic interactions, but salicyladehyde and its derivatives give different products. * The remaining band observed in the IR spectra may be due to overtone and combinations of the fundamental modes thereby confirming the present assignment.

Table 1 Antibacterial activities of compound (Diameter of the zone of inhibition in mm)

Compound	Gram positive									Gram negative					
	I			II			III			IV			V		
	10	20	30	10	20	30	10	20	30	10	20	30	10	20	30
A	16	18	22	19	22	26	18	21	28	17	21	25	19	23	26
C	09	10	16	08	12	16	05	13	16	06	10	14	07	12	15
D	18	21	27	26	32	34	19	23	33	22	25	30	27	30	31
F	26	18	25	25	28	30	19	23	25	20	24	26	26	27	30
H	18	19	24	28	30	35	23	25	36	17	20	25	25	26	29
I	22	24	31	29	31	36	24	27	31	21	25	28	28	30	35

Table 2 Score and energy of each compound docked with (PfDHFR-TS) protein.

COMPOUND NAME	-CDOCKER ENERGY	-C DOCKER INTERACTION ENERGY	LIBDOCKSCORE	BINDING ENERGY
Compound- A	18.57	53.49	30.48	-61.31
C	41.22	59.48	58.97	17.94
D	21.60	45.65	80.46	-31.09
F	25.76	55.69	49.96	41.74
H	33.85	68.42	80.18	-31.80
I	39.02	68.28	67.45	244.86

Table 3 Flexible docking results of the (3, 5-Bis (m-nitro phenyl) -2, 6-bis (p-chlorobenzoyl) tetra hydro 1, 4-thiazine 1, 1-dioxide with (PfDHR-TS) protein

Name Of The Compound	-Cocker Energy	- Cdockerinteraction energy	Libdockscore	Binding energy	Hydrogen bond interaction	Distances(å)
					[PHE116]N-H…..O	1.78
					[ARG-59]N-H…..O	1.98
					[LEU-40]N-H…..O	2.06
					[ASN-108]N-H…..O	2.10
					[ASN-108]N-H…..O	2.24
					[ASN-108]N-H…..O	2.66
					C-H…O[ASN108]	2.23
					[ILE112]C-H….O	2.39
					[ILE-112]N-H…..O	2.56
					[PRO-113]C-H…..O	2.36
					[PRO-113]C-H…..O	2.59
					[PRO113]C-H….O	2.62
Compound -A	18.57	53.49	30.48	-61.30	[PRO113]C-H….O	2.67

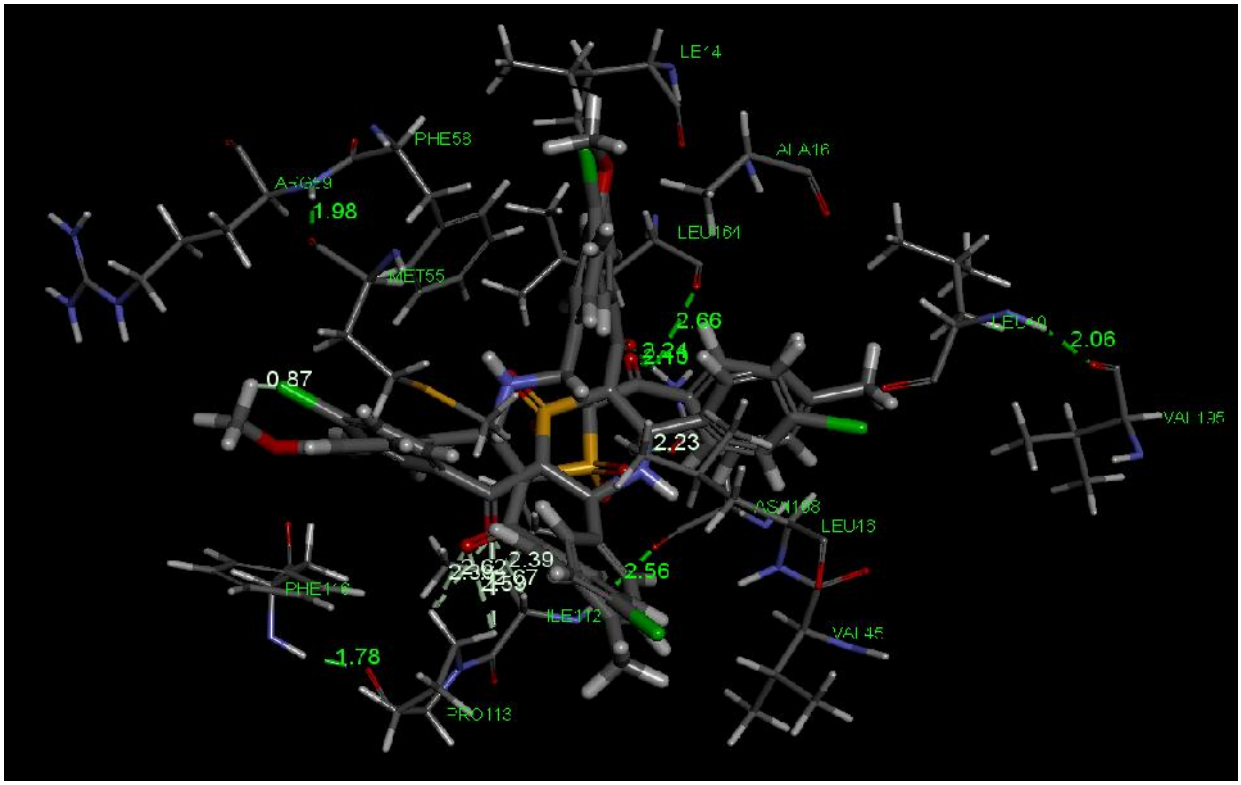

Fig2 Hydrogen Bond Interaction between (PfDHFR-TS) protein with 3,5-Bis(m-nitro phenyl)-2,6-bis(p-chlorobenzoyl) tetra hydro 1,4-thiazine1,1-dioxide.

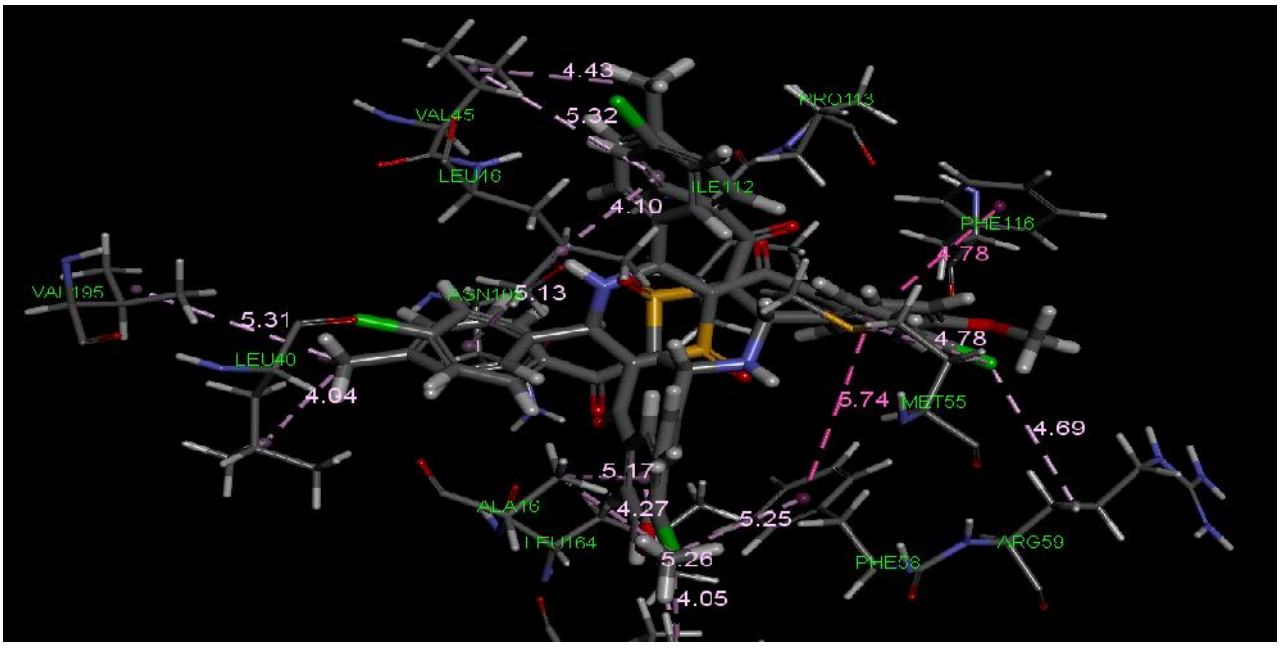

Fig 3 Hydrophobic Interaction between (PfDHFR-TS)protein with 3,5-Bis(m-nitro phenyl)-2,6-bi's(p-chlorobenzoyl) tetra hydro 1,4-thiazine1,1-dioxide.

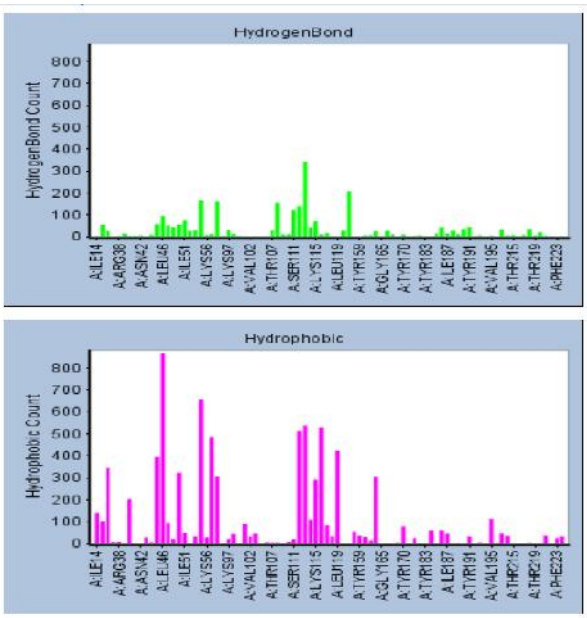

Fig 4 Residue Interaction Histogram

RESULTS AND DISCUSSION

Antimicrobial Activity

The compound **A, C, D, F, H, I** was evaluated in vitro for antibacterial activity against Escherichia coli, Staphylococcus, Bacillus B.subtilis, Pseudomonas and Bacillus Cereus for in acetone of 10-30 μg concentrations by cup-plate method. After 24h of incubation at 37°C the zone of inhibition was measured in mm. The result is given in table 1.

I-Staphylococcus; II-Bacillus cereus; III-B.subtiles; IV-E.Coli; V-Pseudomonas; 10, 20, 30-concen.,

All the compound tested, compound A, D, F, H, I inhibit the growth of testing bacteria at a minimum concentration of 10 µg/ml showed higher activity. Compound C showed moderate activity at C it showed higher activity at 30µg/ml concentrations. It is evident from our result that all six compounds possess high antibacterial activity.

Molecular Docking

Molecular docking has become an important process in the course of drug discovery and the aim of docking is to predict the binding mode and binding affinity of the protein-ligand complex. The molecular docking approach can be used for the study of interaction (hydrogen bond, hydrophobic) between a protein and a small molecule at the atomic level. The docking process involves three basic steps: protein flexibility, ligand sampling, and scoring function. Synthetic organic chemistry plays an important role in anti-malarial drug development.

In the present study, all the six organic compounds were docked with malarial protein [Plasmodium falciparum dihydrofolate reductase-thymidylate synthase (PfDHFR TS)] PDBID (1j3k).pfDHFR-TS which are an important target of anti malarial drugs. The ligand-protein docking techniques were performed by using Discovery Studio- 4.0 software. All the compound were given a good docking score, though Compound (3,5-Bis(m-nitro phenyl)-2,6-bi's(p-chlorobenzoyl) tetra hydro 1,4-thiazine1,1-dioxide) were found to be the best out of these, which might due the interaction with the protein which posses a maximum number of hydrogen bond at their active site of Plasmodium falciparum dihydrofolate reductase-thymidylate synthase protein(PfDHFR-TS).

Therefore, compound 'A' gives a good Libdock score, Binding energy and hydrogen bond interaction. Thus ,molecular docking studies showed Compound 3,5-Bis(m-nitro phenyl)-2,6-bis(p-chlorobenzoyl) tetrahydro 1,4-thiazine1,1-dioxide may consider to be a better inhibitor with stronger activities

Plasmodium falciparum dihydrofolate reductase-thymidylate synthase protein(PfDHFR-TS).

CONCLUSION

In summary, the present method is very simple, mild and efficient for the synthesis of 2, 6-bi's (4-chlorobenzoyl) -3,5-bi's (substituted aryl) tetra hydro-1,4-thiazine -1,1-dioxide. In addition, this protocol has advantages in terms of short reaction time, solvent-free reaction, high yield, easy work-up and eco-friendly. We believe that this method is a useful addition to that 4, 4'-Dichlorodiphenyl sulphone, with substituted aromatic aldehydes shows excellent biological activities and also it give good Lib docking score binding energy and with antimalarial proteins.

Acknowledgement

The authors are thankful to the Department of Biotechnology Queen Mary's college for providing Discovery studio 4.0.

References

Arthur Barazarate, Gricela lobe, Naira Gamboa, *et al*, European *Journals of Medicinal Chemistry* (2009) 1303-1310.

Aryl sulfones active against HIV-1 carrying NNRTI resistance mutations

AW Faull, *Appl. W.,* 1996 29104; *Chem. Abstr.,* 1997 127 234328.

B Narr, J Roch, E Mueller and W Haarmann, *Ger. Offen.*,1975 2 341 925; *Chem. Abstr.,* 1975 83 43369.

B. Cottineau, P. Toto, C. Marot, A. Pipaud, *J. Chenault, Bioorg. Med. Chem. Lett*.12 (2002) 2105–2108.

Boult A J and McKillop A Comprehensive Heterocyclic Chemistry,Ist Ed, Pergamon Press,London,1984,1038.

E. Marmo, Farmaco 45 (1990) 147–166.

JS Bojar, MG Bock, R Freidinger, DF Veber, AA Patchett, WJ Greenlee and WH Parsons, *Appl. Ep.*1987209 897; *Chem. Abstr.,* 1988108 6427

L., Mura, M., Loi, A.G., Marceddu, T., La Colla, P., 2003. Novel indolyl

M. Iovu, C. Zalaru, F. Dumitrascu, C. Draghici, M. Moraru, E. Criste, Farmaco 58(2003) 301–3

Nucleos. Nucleot. Nucleic Acids 17 (1998) 2165–2171.

O. Bruno, F. Bondavalli, A. Ranise, P. Schenone, C. Losasso, L. Cilenti, C. Matera,

P.G. Baraldi, S. Manfredini, R. Romagnoli, L. Stevanato, A.N. Zaid, R. Manservigi,

Pandeya S N, Sriram D, Nath G and De Clercq E, *IL Farmaco.,* 1999, 54, 624-628.

Radadiya V R, Purohit D M and Patolia V N, *Indian J Chem.,* 2005, 44B, 1112-1114.

Silvestri, R., De Martino, G., La Regina, G., Artico, M., Massa, S., Vargiu,

V Baliah and T Rangarajan *J. Am. Chem. Soc.,(1954) 3068.*

V Sundari and R Valliappan, *Indian J. Heterocyclic Chemistry* 2004 1447-50 and 71.

V Sundari and R Valliappan, *Indian J. Heterocyclic Chemistry,* 2002 11 187

V Sundari, GNagarajan and R Valliappan*Med. Chem. Res.,* 2007 16402-407.

W Foery, A Nyffeler, HR Gerber , and H Martin, *Appl. Ep.* 1986,190 205; *Chem. Abstr.,* 1986205 166904

How to cite this article:

Bhavani P and Meena K S., Synthesis, Characterization, Antimicrobial Screening, And Molecular Docking Studies Of Some Novel 2, 6-Bis (4-Chlorobenzoyl)-3, 5-Bi's (Substituted Aryl) Tetrahydro-1, 4-Thiazine 1, 1-Dioxide Derivatives. *International Journal of Recent Scientific Research Vol. 6, Issue, 4, pp.3665-3669, April, 2015*

****