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Research Paper

Novel Thiazole Substituted Imidazolin-5-ones: Synthesis, Biological Screening and Molecular Docking Studies

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ABSTRACT

It has been suggested that sphingosine kinase 1 (3VZD) is essential for the advancement of cancer. Increased expression of SK1 mRNA transcript and/or SK1 protein has been seen in cases of non-Hodgkin lymphoma and malignancies of the stomach, lung, brain, colon, kidney, and breast. Patients with oestrogen receptor (ER)-positive breast cancer have also been found to induce tamoxifen resistance, and high tumour expression of SK1 is associated with poor patient survival rates. As a result, medications that block or decrease 3VZD may have antibacterial and anticancer effects. A series of eleven imidazolin-5-ones substituted with thiazoles were synthesised and their antibacterial, antioxidant, and anticancer properties assessed. Moreover, molecular docking experiments on the 3VZD target protein were carried out to confirm our theory. IMD5 and IMD7 were shown to be the most effective drugs against the MDA MB 231 (Triple Negative Breast Cancer) cell line in in vitro anticancer experiments. IMD11 was shown to be active when antioxidant activity was assessed using the DPPH free radical scavenging technique. Using the microorganisms B. subtilis, S. aureus, E. coli, and P. aeruginosa, antibacterial activity was investigated. It was discovered that IMD9, IMD10, and IMD11 were active against Pseudomonas aeruginosa NCIM-5029, whereas IMD4 and IMD5 had action against Candida albicans.

INTRODUCTION

Latest statistical data shows that worldwide cancer has varied in terms of number, rates and types. Cancer treatment generally involves extensive surgery followed by chemotherapy. Generally, after surgery chemotherapy is done to ensure the absence of remnant cells that can regenerate the parent tumour, but while destroying cancerous cells chemotherapeutic agent may also affect normal rapidly growing cells which is one of the major drawback in cancer treatment. Some tumours are poorly irrigated by blood, and this hampers the access of drugs to the cancer cells.

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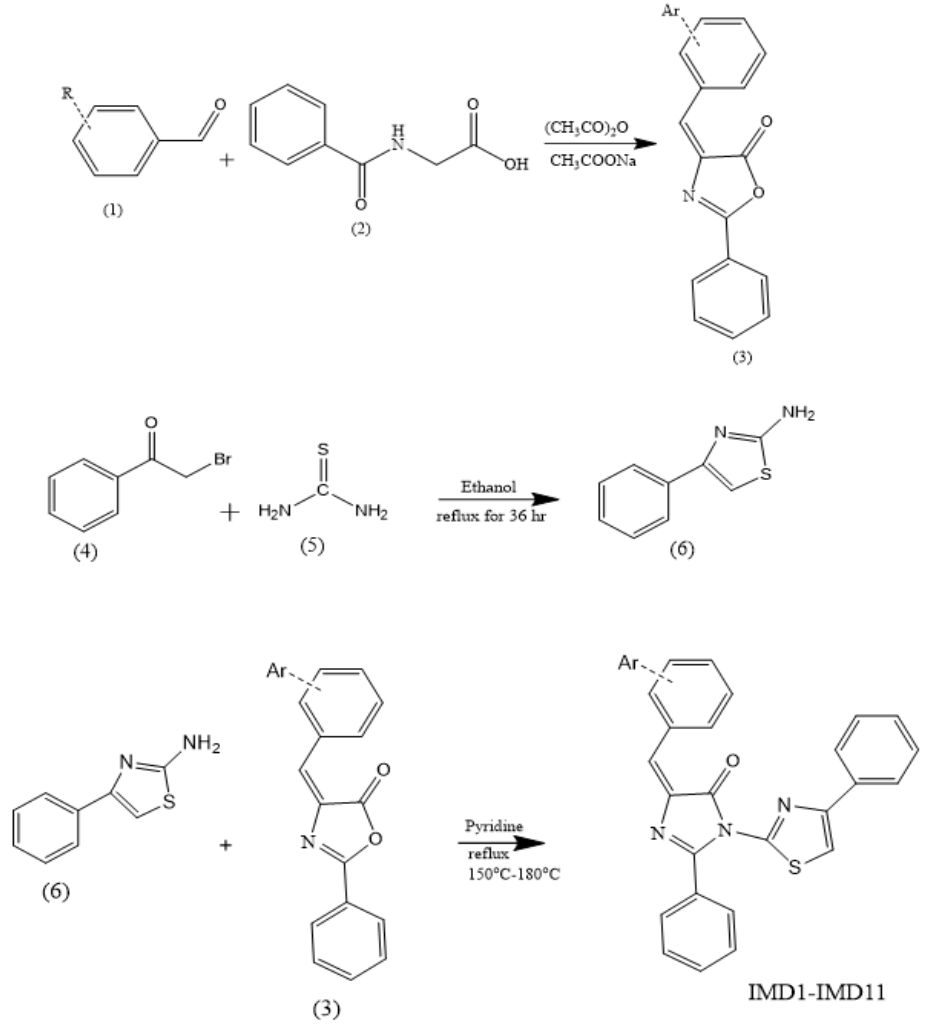
Most of the antineoplastic drugs are toxic to the patients and their toxicity usually cause impairment in rapidly proliferating tissues like bone marrow, intestinal epithelium. On the other hand, re-emergence of infectious diseases is usually observed, and there is a rapid spread of antimicrobial resistance. Even the latest drugs available for the treatment of the cancer and infectious diseases are not free from side effects and toxicity. Hence there is an urgent demand for new, selective, effective and inexpensive drugs in the market that can conquer the world of microbes and cancer. Synthesis (conversion of sphingosine to S1P, catalysed by the two isoforms of sphingosine kinase SK1 and SK2) and removal (by cleavage of S1P catalysed by S1P lyase or dephosphorylation catalysed by S1P phosphatase) regulate the levels of the bioactive sphingolipid sphingosine-1-phosphate (S1P). S1P attaches itself to intracellular protein targets as well as G-protein-coupled receptors that are particular to S1P. There is proof that sphingosine kinase plays a significant part in human malignancies. For example, non-Hodgkin lymphoma and malignancies of the stomach, lung, brain, colon, kidney, and breast have increased expression of the SK1 mRNA transcript and/or SK1 protein. Additionally, reports show a correlation between low patient survival rates and the formation of tamoxifen resistance in patients with oestrogen receptor (ER)-positive breast cancer who had high tumour expression of SK1. Therefore, SK1 appears to play a role in two major hallmarks of cancer, namely, enhanced proliferation and metastasis/invasion. Literature review revealed that substituted imidazolinones have generally shown their activity as anticancer and anti-inflammatory agents and thus it was thought to explore it further. Similarly, thiazoles have established them as biologically important scaffold and have been widely reported for their anticancer, anti-inflammatory and antimicrobial activities. Congiu *et al.*, reported cytotoxic activity of a series of imidazolinone derivatives against leukemic cell lines. N. Xue *et al.*, reported excellent inhibitory activity of imidazolinone derivatives on tumor growth in *in vivo* models. Hassanein *et al.*, reported inhibitory activities of imidazolinone derivatives against COX-2-catalyzed PGE2 production. Therefore, it was thought that further substitution and investigation on these scaffolds may further enhance their activity and this prompted us to undertake this problem. The combination of two pharmacophores on the same molecule is a well-known approach for the designing of more effective drugs with dual activity. Single molecule acting on multiple targets bypasses the need of giving drug combinations and single drug administration becomes effective. Moreover, these drug candidates will have more predictable pharmacokinetic and pharmacodynamic properties with improved patient compliance. Hence, it was thought that the combination of thiazole moiety with imidazolin-5-one will produce more potent and effective derivatives than the existing ones. Therefore, our current work highlights the synthesis and biological evaluation of a series of thiazole substituted imidazolin-5-ones. In order to validate our hypothesis molecular docking studies were done on sphingosine kinase 1 (3VZD) protein target for a series of substituted imidazolinones and their binding affinity towards the target protein was evaluated based on the docking score and glide score.

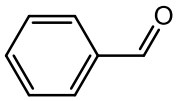
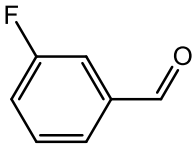
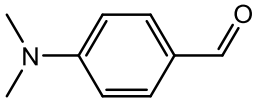
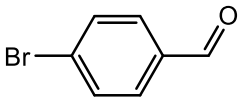
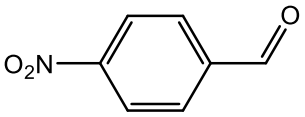
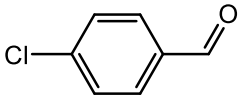
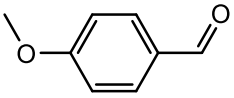
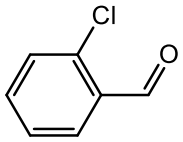
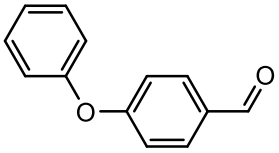
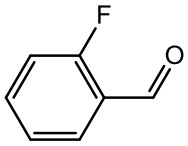
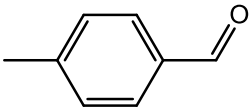
2.0 Results and Discussion

2.1 Chemistry

Synthesis of thiazole substituted imidazolin-5-ones, involves 3 steps. First step involves Erlenmeyer azlactone synthesis of substituted oxazolones (3) by reaction of various substituted aryl benzaldehydes (1) and hippuric acid (benzoyl

glycine) (2) in the presence of acetic anhydride and sodium acetate. Step-2 involves synthesis of the heterocyclic amine i.e., 4-phenyl thiazole-2-amine (6) synthesized by refluxing phenacyl bromide (4) and thiourea (5) for 36 hrs in the presence of ethanol. In step-3, 4-phenyl thiazole-2-amine (6) on aminolysis with substituted oxazolones (3) by refluxing in pyridine afforded thiazole substituted imidazolin-5-ones (IMD1-IMD11). Progress of the reaction was monitored by TLC using hexane: ethyl acetate (7:3) as mobile phase. The synthesized compounds were purified by methanol which afforded pale yellow to brown coloured product. Total eleven compounds were synthesized and their yields ranged from 70 to 80%. Structures of the synthesized title compounds were characterized by IR, Mass and NMR techniques. Appearance of characteristic NMR peak between δ= 7.571 to 8.178 (1H, s, Ar-CH= (benzylidene of imidazolinone), confirms the successful synthesis of thiazole substituted imidazolin-5-ones. For eg., 5-(2-fluorobenzylidine-2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one with compound code IMD5 showed ^{1}HNMR peak at δ= 8.178 (1H, s, Ar-CH=(benzylidene of imidazolinone), 7.295-7.736 (15H, m, Ar-H) and ^{13}CNMR characteristic peak for benzylidene group of imidazolinone was seen at δ= 116.38. Characteristic C=O, IR stretching was observed at a frequency ranging between 1635.64 to 1722.43. LC-MS spectra showed characteristic molecular ion (M^{+}) peaks, corresponding to the molecular weight of synthesized compounds.



Ar		Ar			Ar
IMD1		IMD6		IMD11	
IMD2		IMD7			
IMD3		IMD8			
IMD4		IMD9			
IMD5		IMD10			

2 Biological evaluation

2.2 *In vitro* cytotoxic studies (MTT assay)

Synthesised 11 compounds were evaluated using the MTT assay technique primarily for their *in vitro* growth inhibitory properties against the human cultured cell line known as MDA MB 231 (Triple negative breast cancer) cell line by taking the concentration of 62.5µg/ml. Since the proportion of cell mortality for three test compounds—IMD5, IMD6, and IMD7—was greater than 42%, these compounds were moved on to secondary screening. Three doses of secondary screening were carried out: 250 µg/ml, 125 µg/ml, and 62.5 µg/ml. Percent inhibition and IC50 are used to represent the results of secondary screening (Table 1).

Table 1: *In vitro* cytotoxicity of compounds toward MDA MB 231 cell line

Sample code	Concentration (in µg/ml)	Percent inhibition	IC_{50} (in µg/ml)
IMD5	250	69.96%	71.98
	125	59.59%	
	62.5	48.28%	
IMD6	250	75.15%	51.41
	125	67.20%	
	62.5	52.59%	
IMD7	250	69.83%	80.19
	125	57.57%	
	62.5	47.00%	

2.3 Antibacterial activity

All the synthesized thiazole substituted imidazolin-5-ones were screened for antibacterial activity. Two Gram positive (B. subtilis and S. aureus) and two Gram negative (E. coli and P. aeruginosa) microorganisms were used to investigate the antibacterial activity. The method used was agar diffusion (cup plate) method. Screening was done at a concentration of 250 µg/ml. Ciprofloxacin was used as standard at a concentration of 25.98 µM. Three test compounds IMD9, IMD10 and IMD11 was found to be active against *Pseudomonas aeruginosa* NCIM-5029, and the results were expressed in terms of zone of inhibition (Table 2).

Table 2: Effect of test compounds on *Pseudomonas aeruginosa* NCIM-5029

Compound code	Compound Type	Concentration of samples tested (µM)	Zone diameter (mm)	Activity
IMD-9	Synthetic	500	13	Active
IMD-10	Synthetic	590	16	Active
IMD-11	Synthetic	550	17	Active
TZD1	Synthetic	750	14	Active
TZD2	Synthetic	590	14	Active
Ciprofloxacin	Standard	25.98	23	Active

2.2.3 Antifungal activity

All the synthesized thiazole substituted imidazolin-5-ones were screened for antifungal activity. Antifungal activity was studied using *Aspergillus niger* and *Candida albicans* fungi. The method used was agar diffusion (cup plate) method. Screening was done at a concentration of 250 µg/ml. Clotrimazole was used as the standard at a concentration of 25 µg/disc. Test compounds IMD4 and IMD5 showed activity against *Candida albicans*, and the results are expressed in terms of zone of inhibition (Table 3).

Table 3 : Effect of test compounds on *Candida albicans*

S. No.	Comp. Code	Zone of inhibition (mm) (250 µg /ml)	
		C. albicans	*A. niger*
4	IMD4	15	-
5	IMD5	16	-

2.2.4 Antioxidant activity

The antioxidant activities for all the synthesized 11 test compounds were done by using the DPPH free radical scavenging method. Ascorbic acid was used as standard, its IC_{50} value was found to be 8.71 µg/ml. Preliminary screening was done at a concentration of 125 µg/ml and their percent scavenging was calculated. Results of preliminary screening showed percent scavenging of IMD11 above 50%, thus this compound was taken for further screening. Secondary screening of IMD11 was done at concentrations: 125 µg/ml, 62.5 µg/ml, 31.25 µg/ml and 15.62 µg/ml and the result was expressed in terms of IC_{50} (Table 4).

Table 4: Secondary screening result of test compound IMD11

Sample Code	Sample Concentration (in µg/ml)	OD of sample	OD of control	Percent Scavenging = (control-sample)/control × 100	IC_{50} (in µg/ml)
IMD11	125	0.184	0.469	60.76	97.74
	62.5	0.314		33.05	
	31.25	0.373		20.47	
	15.62	0.403		14.07	

2.3 Molecular docking study

The 3D structures of Sphingosine kinase 1 complex were taken from Protein Data Bank (PDB code: 3VZD). 3VZD consisted of six chains i.e., A, B, C, D, E and F and five unique ligands namely ADP, UUL, POP, CL and MG. Structure of Adenosine-5'-diphosphate (ADP) resembled the structure of the test ligands to be docked on the target protein, therefore it was decided to choose ADP (present in C and E chain) as a binding site on the protein target. Out of C and E chain, E chain was taken into consideration because in this chain ADP was present almost in the centre of the target protein. Structures of the synthesized test compounds were prepared by using ChemBioDraw Ultra 14.0. All non-bonded water molecules were removed and hydrogens were added to protein. Molecular docking was performed by using MAESTRO 10.4 software (a graphical user interface of Schrodinger). Results of screening was expressed in terms of docking score and glide score and additionally RMSD value was also calculated. Docking results of 11 synthesized test compounds on 3VZD are given in Table 5. Among the 11 derivatives of test compounds, IMD8 showed highest docking score and glide score when docked on 3VZD protein target. In the ligand interaction of IMD8, arginine (ARG 57, ARG 185, ARG 191) showed pie stacking interaction with phenyl ring attached to thiazole ring and benzylidene. Glutamic acid (GLH 343) showed hydrogen bonding (2.2 Å) with carbonyl oxygen of imidazolinone ring system (fig., 1 and 2). In addition to this, IMD10 and IMD11 also showed good docking and glide score.

Table 5: Docking results of synthesized test compounds on 3VZD protein target

S.No.	Compound Code	Docking Score	Glide Score
1	IMD1	-2.306	-2.716
2	IMD2	-2.685	-3.096
3	IMD3	-2.9	-3.311
4	IMD4	-1.977	-2.388
5	IMD5	-2.177	-2.588
6	IMD6	-2.643	-3.053
7	IMD7	-2.273	-2.684
8	IMD8	-3.456	-3.866
9	IMD9	-2.488	-2.899
10	IMD10	-3.391	-3.801
11	IMD11	-3.312	-3.733

Root-mean-square deviation (RMSD) value –

In molecular docking RMSD value is used to compare the docked conformation of the reference ligand (ADP) with the original conformation of reference ligand (ADP) which was embedded in the crystal lattice of the target protein 3VZD. ADP which was extracted from the crystal structure was docked on to the original binding site and this docked conformation was then superimposed on the original conformation of reference ligand (ADP). The value of this superimposition should be less than 2 Å (ideally less than 1 Å). In this case superimposition was done on E chain of the 3VZD protein target. RMSD value (less than 2 Å) validates the method of molecular docking studies.

This is done for demonstrating accurateness of the docking procedure adopted. RMSD value obtained was 0.6981Å (fig., 3).

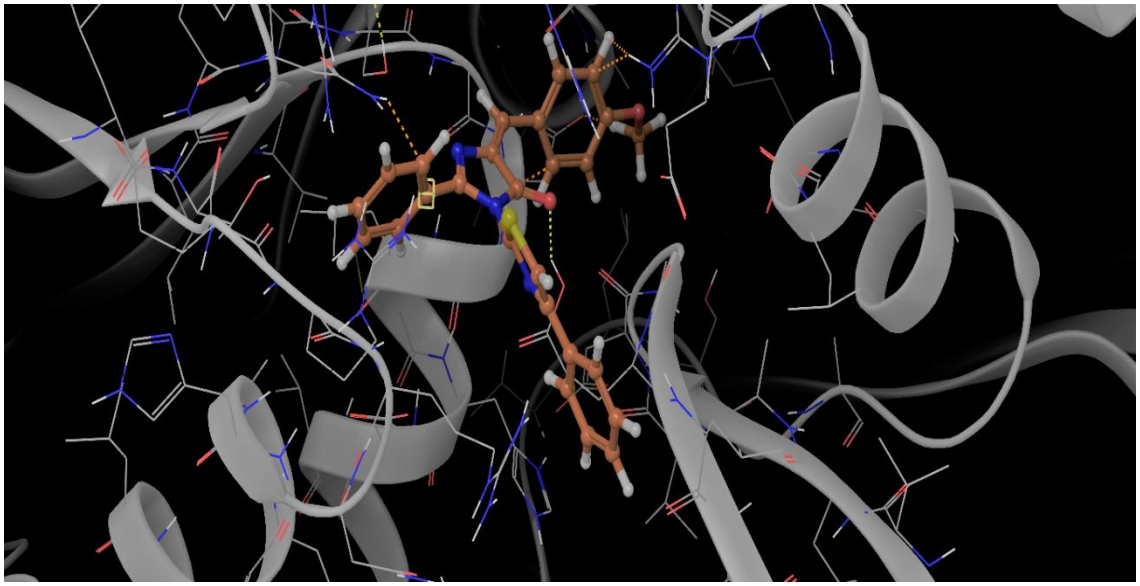


Fig 1: 3D diagram of binding interaction of IMD8 (docking score: -3.456) with target protein 3VZD

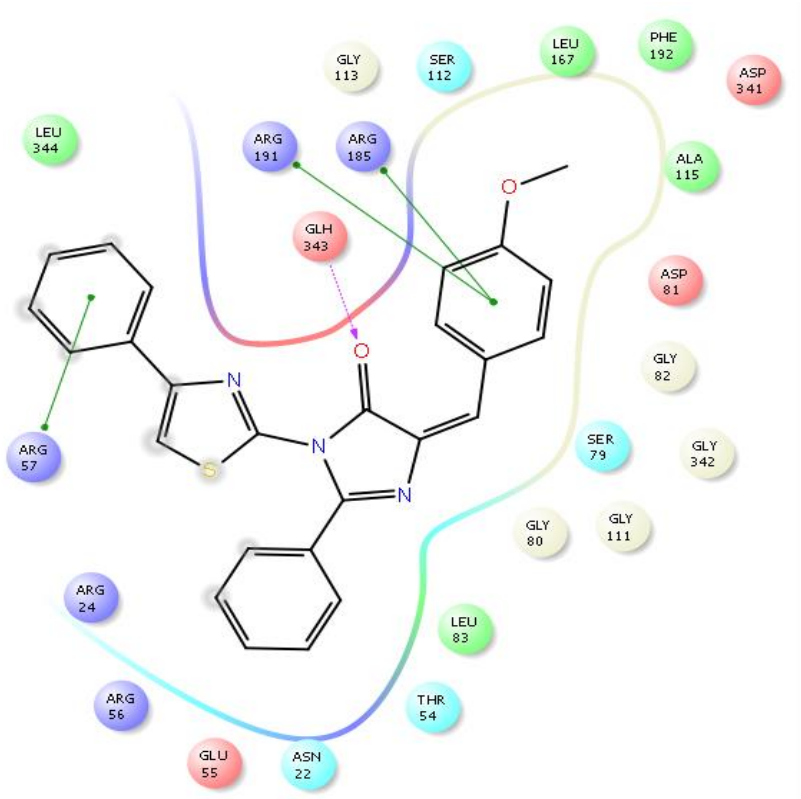


Fig 2: Ligand interaction of IMD8

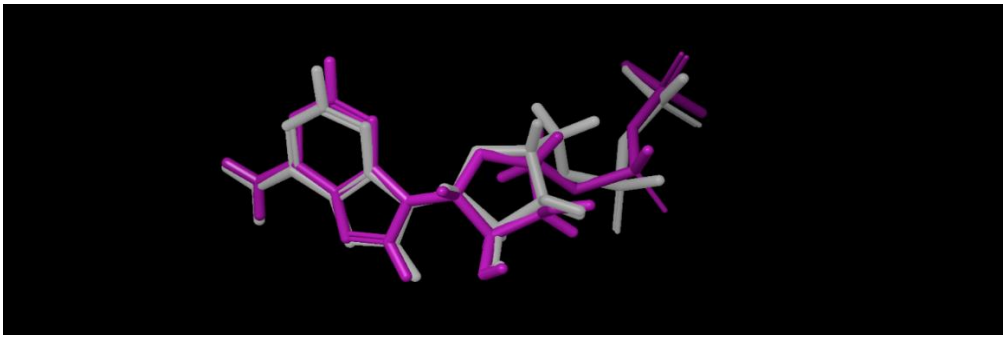


Fig 3: Superimposed conformation of docked conformation and original conformation of reference ligand (ADP)

CONCLUSION

Synthesized compounds were evaluated for anticancer, antioxidant and antimicrobial activity in *in vitro* condition. *In-vitro* cytotoxicity of thiazole substituted imidazolin-5-ones were evaluated by MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] assay in MDA MB 231 breast cancer cell line in which IMD5, IMD6 and IMD7 exhibited maximum cytotoxic effect. Among the synthesized thiazole substituted imidazolin-5-ones IMD9, IMD10 and IMD11 showed moderate activity against *Pseudomonas aeruginosa* NCIM-5029. Antifungal activity of thiazole substituted imidazolin-5-ones identified compound IMD4 and IMD5 showing activity against *Candida albicans*. *In-vitro* antioxidant activities of all the compounds were performed by DPPH free radical scavenging assay in which compound IMD11 showed free radical scavenging activity with IC_{50} 97.74 µg/ml. Molecular docking studies were done for the synthesized compounds in order to validate our hypothesis. Results of biological activities and of molecular docking studies, concluded that the test compounds substituted with electron releasing group like methyl-, methoxy-, phenoxy-, dimethylamino- etc and halogens that release the electron via resonance was found to demonstrate improved biological activities than as compared to the test compounds substituted with other groups. Furthermore, these results confirms our hypothesis that conjugation of two pharmacophores might improve the pharmacological profile of synthesized compounds. Hence the most active compounds found in the preliminary screening and compounds with better binding affinities in docking studies can be taken up for elaborate screening on specific molecular targets and could be considered for further studies on *in vivo* models.

4. Experimental section

4.1 Chemistry

Without additional purification, all of the chemicals and solvents used were of analytical or reagent grades. All of the chemicals were purchased from SD Fine Chemicals Limited, India, Aldrich, Sigma-Aldrich, Spectrochem, and Himedia. A single spot on the pre-coated silica gel plates (TLC silica gel F24, Merck, Germany) was used to determine the purity of each component. Hexane: ethyl acetate was the TLC solvent system that was employed (7:3). The developing reagent was iodine vapour. Using potassium bromide discs, infrared spectra were captured on a Shimadzu FTIR-8310 (Shimadzu, Japan). Using a Bruker 400 MHz spectrophotometer (Bruker, USA), 1H NMR spectra were captured. Parts per million (δ) units are used to indicate chemical shifts in relation to the internal standard of tetramethylsilane. All assignments were in agreement with the relative peak regions, and

coupling constants are expressed in Hz. An LC-MS was used to record the mass spectra (Shimadzu, Japan). Melting points are uncorrected and were measured using a capillary melting point instrument (Shital Scientific Industries, India).

4.2 Synthesis of 4-Phenyl thiazol-2-amine

A mixture of 1 eq. of phenacyl bromide (7 g) and 1 eq. of thiourea (2.67 g) was refluxed for 36 hrs in the presence of ethanol, cooled to room temperature. The progress of reaction was monitored by TLC (petroleum ether: ethyl acetate; 7:3). Reaction mixture turned brown liquid, on completion of reaction. The resultant brown mixture was added into the crushed ice with constant stirring and the yellow coloured precipitate was filtered and washed with cold water. Recrystallization of crude product from methanol afforded yellow crystals (4.3 g, 62%, MP-118 ^{o}C-119 ^{o}C).

4.3 Synthesis of various substituted oxazolones

An electric hot plate with continuous shaking was used to heat a mixture of 27 g (250 mmol) of redistilled substituted aryl benzaldehyde, 45 g (250 mmol) of hippuric acid (benzoyl glycine), 71.5 ml (750 mmol) of acetic anhydride, and 20.5 g (250 mmol) of anhydrous sodium acetate in a 500 ml conical flask. After the reaction mixture had fully liquefied, the conical flask was placed in a water bath and heated for two hours. Following two hours of heating, 100 millilitres of ethanol were gradually added to the flask's contents, and the combination was left to stand for the overnight. Crystalline product was filtered with suction filter, and was washed with two 25 ml portions of ice-cold alcohol and two 25 ml portions of boiling water. The resulting product was then dried at 100°C and recrystallized using benzene.

4.4 Synthesis of thiazole substituted Imidazolinones (IMD1-IMD11)

General method : Substituted oxazolone prepared from various aryl benzaldehyde derivatives (1.12 mmol) and 4-phenyl thiazole-2-amine (1.13 mmol) was taken in a 50 ml round bottomed flask and was dissolved in minimum quantity of pyridine. Reaction mixture was refluxed on a heating mantle on a sand bath for 72 hrs. Throughout the reflux, reaction temperature was maintained between 150 ^{o}C – 180 ^{o}C. The progress of the reaction was monitored by TLC (hexane:ethyl acetate ; 7:3). In a 100 ml beaker, 30 ml of 10% hydrochloric acid was taken, reaction mixture was added dropwise in the beaker with stirring. Precipitate obtained was filtered by suction, washed with water and dried. Recrystallization of the crude product was done using methanol.

4.4.1 5-Benzylidine-2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD1)

Crystallized from methanol to give pale yellow to brown coloured product, yield 71%, mp 166-170 ^{o}C. Anal. calcd. for $C_{25}H_{17}N_3OS$ (407.49). IR (KBr), (ν cm^{-1}): 3057.17 (C-H, str, ArC-H), 1718.58 (C=O, str, carbonyl group of imidazolinone ring), 1643.35 (C=N, str), 1544.98 (C=C, str), 694.37 (C-S, str). LC-MS (APCI) m/z: 405.67 (M-1).

4.4.2 5-(4-bromobenzylidene)- 2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD2)

Crystallized from methanol to give pale yellow to brown coloured product, yield 72.45%, mp 172-176 ^{o}C. Anal. calcd. for $C_{25}H_{16}BrN_3OS$ (486.39). IR (KBr), (ν cm^{-1}): 3059.10, 3030.17 (C-H, str, ArC-H), 1668.43 (C=O, str, carbonyl group of imidazolinone ring), 1560.41 (C=C, str), 715.59 (C-S, str). ^{1}H NMR (DMSO-d_6, δ in ppm): 7.571

(1H, s, Ar-CH=(benzylidine) of imidazolinone), 7.321-8.059 (15H, m, Ar-H). LC-MS (APCI) m/z: 485.47 (M-1).

4.4.3 5-(4-chlorobenzylidine-2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD3)

Crystallized from methanol to give pale yellow to brown coloured product, yield 75.21%, mp 148-150 ^{o}C. Anal. calcd. for $C_{25}H_{16}ClN_3OS$ (441.93). IR (KBr), (ν cm^{-1}): 3057.17 (C-H, str, ArC-H), 1635.64 (C=O, str, carbonyl group of imidazolinone ring), 1546.91 (C=C, str), 696.30 (C-S, str). ^{1}H NMR (DMSO-d_6, δ in ppm): 8.160 (1H, s, Ar-CH=(benzylidine) of imidazolinone), 7.348-8.412 (15H, m, Ar-H). LC-MS (APCI) m/z: 440.15 (M-1).

4.4.4 5-(2-chlorobenzylidene)- 2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD4)

Crystallized from methanol to give pale yellow to brown coloured product, yield 78.15%, mp 152-154 ^{o}C. Anal. calcd. for $C_{25}H_{16}ClN_3OS$ (441.93). IR (KBr), (ν cm^{-1}): 3062.96 (C-H, str, ArC-H), 2970.38 (C-H, str, AlpC-H), 1637.56 (C=O, str, carbonyl group of imidazolinone ring), 1541.12 (C=C, str), 698.23 (C-S, str). LC-MS (APCI) m/z: 440.76 (M-1).

4.4.5 5-(2-fluorobenzylidine-2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD5)

Crystallized from methanol to give pale yellow to brown coloured product, yield 73.12%, mp 174-180 ^{o}C. Anal. calcd. for $C_{25}H_{16}FN_3OS$ (425.48). IR (KBr), (ν cm^{-1}): 3061.03 (C-H, str, ArC-H), 1732.08 (C=O, str, carbonyl group of imidazolinone ring), 1649.14 (C=N, str), 1543.05 (C=C, str), 692.44 (C-S, str). ^{1}H NMR (DMSO-d_6, δ in ppm): 8.178 (1H, s, Ar-CH=(benzylidene) of imidazolinone), 7.295-7.736 (15H, m, Ar-H). ^{13}CNMR (DMSO.d6, δ in ppm): 168.55 (C-5, carbonyl group of imidazolinone ring), 163 (C-2'), 160.64 (C-2**), 153.84 (C-2), 151.06 (C-4'), 138.72 (C-1*), 133.86 (C-1"), 133.79 (C-4*), 133.10 (C-4**), 129.54 (C-5"), 129.29 (C-6**), 129.24 (C-5*), 128.72 (C-2*, C-6*), 126.2 (C-6", C-2"), 125.72 (C-4), 121.87 (C-5**), 119.32 (C-1**), 116.38 (C-6 of benzylidene), 116.17 (C-3**), 115.3 (C-5'). LC-MS (APCI) m/z: 424.62 (M-1).

4.4.6 5-(3-fluorobenzylidene)- 2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD6)

Crystallized from methanol to give pale yellow to brown coloured product, yield 77.05%, mp 174-176 ^{o}C. Anal. calcd. for $C_{25}H_{16}FN_3OS$ (425.48). IR (KBr), (ν cm^{-1}): 3062.96 (C-H, str, ArC-H), 1720.50 (C=O, str, carbonyl group of imidazolinone ring), 1647.21 (C=N, str), 1577.77 (C=C, str), 690.52 (C-S, str). ^{1}H NMR (DMSO-d_6, δ in ppm): 8.165 (1H, s, Ar-CH=(benzylidene) of imidazolinone), 7.293-8.165 (15H, m, Ar-H). LC-MS (APCI) m/z: 424.47 (M-1).

4.4.7 5-(4-nitrobenzylidine-2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD7)

Crystallized from methanol to give pale yellow to brown coloured product, yield 72.52%, mp 156-160 ^{o}C. Anal. calcd. for $C_{25}H_{16}N_4O_3S$ (452.49). IR (KBr), (ν cm^{-1}): 3072.60 (C-H, str, Ar-H), 2983.88 (C-H, str, AlpC-H), 1645.28 (C=O, str, carbonyl group of imidazolinone ring), 1589.34 (C=N, str), 1546.91 (C=C, str), 1514.12 (Asymmetric N-O, str), 1340.53 (Symmetric N-O, str), 717.52 (C-S, str). ^{1}H NMR (DMSO-d_6, δ in ppm): 7.693 (1H, s, Ar-CH=(benzylidene) of imidazolinone), 7.327-8.267 (15H, m, Ar-H). LC-MS (APCI) m/z: 451.42 (M-1).

4.4.8 5-(4-methoxybenzylidene)- 2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD8)

Crystallized from methanol to give pale yellow to brown coloured product, yield 74.44%, mp 144-148 ºC. Anal. calcd. for $C_{26}H_{19}N_3O_2S$ (437.52). IR (KBr), (ν cm^{-1}): 3062.96 (C-H, str, Ar-H), 2960.73 (C-H, str, AlpC-H), 1716.65 (C=O, str, carbonyl group of imidazolinone ring), 1645.28 (C=N, str), 1597.06 (C=C, str), 1028.06 (C-O, str), 696.30 (C-S, str). LC-MS (APCI) m/z: 435.76 (M-1).

4.4.9 5-(4-phenoxybenzylidine-2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD9)

Crystallized from methanol to give pale yellow to brown coloured product, yield 72.50%, mp 140-142 ºC. Anal. calcd. for $C_{31}H_{21}N_3O_2S$ (499.59). IR (KBr), (ν cm^{-1}): 3062.96 (C-H, str, ArC-H), 1647.21 (C=O, str, carbonyl group of imidazolinone ring), 1568.13 (C=C, str), 694.37 (C-S, str). LC-MS (APCI) m/z: 497.61 (M-1).

4.4.10 5-(4-methylbenzylidene)- 2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD10)

Crystallized from methanol to give pale yellow to brown coloured product, yield 79.22%, mp 156-158 ºC. Anal. calcd. for $C_{26}H_{19}N_3OS$ (421.52). IR (KBr), (ν cm^{-1}): 3059.10, 3030.17 (C-H, str, ArC-H), 2918.30 (C-H, str, Alp-H), 1722.43 (C=O, str, carbonyl group of imidazolinone ring), 1645.28 (C=N, str), 1602.85 (C=C, str), 698.23 (C-S, str). ^{1}H NMR (DMSO-d_6, δ in ppm): 8.158 (1H, s, Ar-CH=(benzylidene) of imidazolinone), 7.319-8.295 (15H, m, Ar-H), 2.515 (3H, s, -C$\underline{H}_3$). LC-MS (APCI) m/z: 420.40 (M-1).

4.4.11 5-(4-(dimethylamino)-benzylidine-2-phenyl-3-(4-phenylthiazol-2-yl-)-3,5-dihydro-4H-imidazol-5-one (IMD11)

Crystallized from methanol to give pale yellow to brown coloured product, yield 77.41%, mp 168-170 ºC. Anal. calcd. for $C_{27}H_{22}N_4OS$ (450.56). IR (KBr), (ν cm^{-1}): 3062.96 (C-H, str, ArC-H), 2906.73 (C-H, str, AlpC-H), 1705.07 (C=O, str, carbonyl group of imidazolinone ring), 1639.49 (C=N, str), 1585.49 (C=C, str), 698.23 (C-S, str). ^{1}H NMR (DMSO-d_6, δ in ppm): 8.125 (1H, s, Ar-CH=(benzylidene) of imidazolinone), 7.257-8.271 (15H, m, Ar-H), 3.090 (6H, s, -N(C$\underline{H}_3$)$_2$). ^{13}CNMR (DMSO.d6, δ in ppm): 167.83 (C-5, carbonyl group of imidazolinone ring), 160.15 (C-2'), 152.80 (C-2), 135.58 (C-4**), 135.27 (C-1*), 133.41 (C-4*), 133.16 (C-2"), 132.29 (C-4"), 131.17 (C-1**), 129.74 (C-3", C-5"), 129.25 (C-4), 129.19 (C-1"), 128.52 (C-2**, C-6**), 127.73 (C-3*, C-5*), 127.48 (C-2*, C-6*), 126.19 (C-5'), 121.30 (C-6 of benzylidene), 112.33 (c-3**, c-5**), 40.08 (C of -N(C$\underline{H}_3$)$_2$). LC-MS (APCI) m/z: 448.75 (M-1).

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