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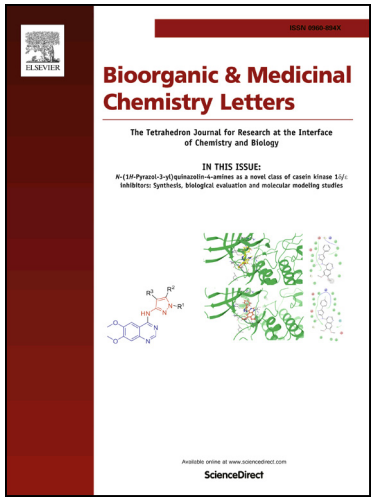

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Graphical Abstract

Synthesis, antioxidant, antifungal, molecular docking and ADMET Studies of Some thiazolyl hydrazones

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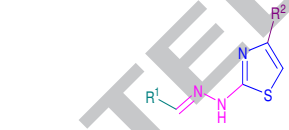
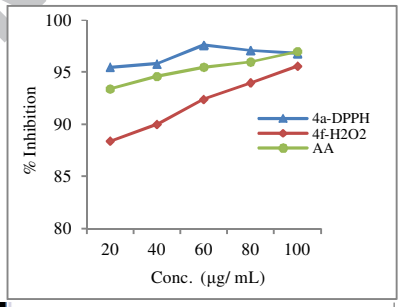
Sushama Kauthale[a], Sunil Tekale[b], Manoj Damale[c], Jaiprakash Sangshetti[d] and Rajendra Pawar[a*]

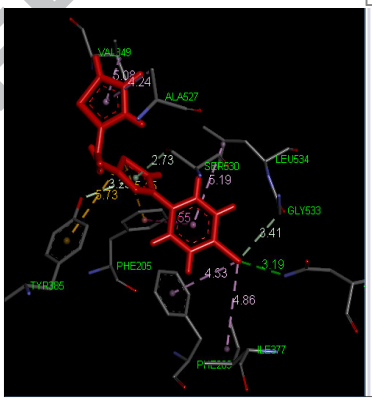
Some thiazolyl hydrazones were synthesized by one pot reaction of thiophene-2-carbaldehyde or 2, 4-dichlorobenzaldehyde, thiosemicarbazide and various phenacyl bromides which were preliminarily screened for *in vitro* antioxidant and antifungal activities. Excellent DPPH and H_2O_2 radical scavenged antioxidant activities were observed with almost all the tested compounds. Compounds **4a**, **4b**, **4c**, **4e**, **4f** and **4i** showed comparable DPPH scavenged antioxidant potential (90.26 to 96.56%) whereas H_2O_2 scavenged antioxidant activity (90.98 to 92.08%) was noticeable in case of **4a** and **4f**; showing significant antioxidant potential comparable with the standard ascorbic acid (95.3%). *In vitro* antifungal activity of synthesized compounds against fungal species *Candida Albicance, Aspergillus Niger* and *Aspergillus Flavus* was found to be moderate to good as compared with the standard fluconazole and MIC values were in the range of 3.12 to 25 µg/mL. Molecular docking studies revealed that the compounds **4a**, **4b** and **4c** have a potential to become lead molecules in drug discovery process. In silico ADMET study was also performed for predicting pharmacokinetic and toxicity profile of the synthesized antioxidants which expressed good oral drug like behaviour and non-toxic nature.

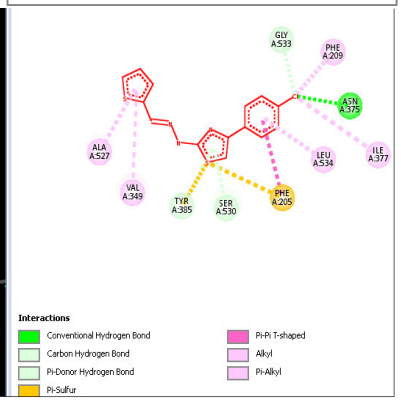


Excellent Antioxidants-IC50

Good antifungal activity - MIC







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ABSTRACT

Some thiazolyl hydrazones were synthesized by one pot reaction of thiophene-2-carbaldehyde or 2, 4-dichlorobenzaldehyde, thiosemicarbazide and various phenacyl bromides which were preliminarily screened for *in vitro* antioxidant and antifungal activities. Excellent DPPH and H_2O_2 radical scavenged antioxidant activities were observed with almost all the tested compounds. Compounds **4a**, **4b**, **4c**, **4e**, **4f** and **4i** showed comparable DPPH scavenged antioxidant potential (90.26 to 96.56%) whereas H_2O_2 scavenged antioxidant activity (90.98 to 92.08%) was noticeable in case of **4a** and **4f**; showing significant antioxidant potential comparable with the standard ascorbic acid (95.3%). *In vitro* antifungal activity of synthesized compounds against fungal species *Candida Albicance, Aspergillus Niger* and *Aspergillus Flavus* was found to be moderate to good as compared with the standard fluconazole and MIC values were found in the range of 3.12 to 25 µg/mL. Molecular docking studies revealed that the compounds **4a**, **4b** and **4c** have a potential to become lead molecules in drug discovery process. In silico ADMET study was also performed for predicting pharmacokinetic and toxicity profile of the synthesized antioxidants which expressed good oral drug like behaviour and non-toxic nature.

Designing and development of heterocyclic compounds with multiple biological activities is a significantly considerable new facet of chemistry. One pot multi-component reactions are highly desirable in modern synthetic organic chemistry and drug discovery due to economic, time saving, cost effective and high atom efficiency benefits. Such reactions assist in creating libraries of drug like molecules and reduce environmental pollution by obeying the principles of sustainable and green chemistry [1].

Thiazole (**a**); a five membered heterocyclic compound bearing sulfur and nitrogen in the ring constitutes a vital role in medicinal and pharmaceutical chemistry due to wide spectrum of biological activities such as antitumor[2], anti-inflammatory[3], enzyme inhibitors[4], antioxidant[5] etc. Besides this, thiazole ring containing heterocyclic compounds are also used as multitasking agents in Alzheimer's disease[6] as well as effective antimicrobial agents[7]. Consequently, thiophene core structured compounds play a crucial role in the context of medicinal and pharmaceutical chemistry[8-9]. During the past decade, more efforts are directed towards the structure-activity modification of thiazole and thiophene based heterocyclic compounds as new potent drug like molecules[10-11]. Dichlorophenyl ring contributes significantly to various biological activities[12-13]. Thus from literature survey and biological screening studies, thiophene and 2, 4-dichlorophenyl ring bearing scaffolds are useful for the creation of diverse chemical libraries of "drug-like" molecules.

Oxidation reactions occurring in various metabolic processes and food products generate free radicals which may damage cell membranes, DNA, cellular proteins and lipids through chain reactions leading to heart, liver, kidney related chronic diseases such as cancer, arthritis and Alzheimer's disease[14]. In various clinical studies it has been seen that inflammatory diseases are caused due to excessive generation of free radicals and thus the search for non-steroidal anti-inflammatory agents becomes essential.

An antioxidant, a molecule inhibiting the oxidation of other molecules; terminates chain reactions thereby preventing oxidation and thus beneficial for body tissues and health effects. Antioxidant potential of a compound is usually determined spectrophotometrically in terms of 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging ability. DPPH radical model is the most widely used method for quick evaluation of free radical scavenging activity of organic compounds. It is an

easy, economic and rapid method to determine the antioxidant potential of non-enzymatic compounds.

Fungi may act as pathogens and parasites. Many fungi existing in nature are parasites and affect human health, plant kingdom as well as the environment. To overcome the resistance shown by fungi through genetic changes to the existing antifungal compounds; the development of novel antifungal agents becomes inevitable[15].

In continuation of our successful attempts in search of biologically active heterocyclic compounds[16]; in present study we report synthesis, characterization, antioxidant and antifungal screening of some thiazole based hydrazones bearing thiophene and 2, 4-dichlorophenyl rings (Scheme 1). Molecular docking study was performed to predict the possible binding modes and to rationalize the observed biological activity. In silico ADMET (Absorption, Distribution, Metabolism, and Excretion - Toxicity) study was also performed to predict the pharmacokinetic and toxicity profile of the synthesized compounds.

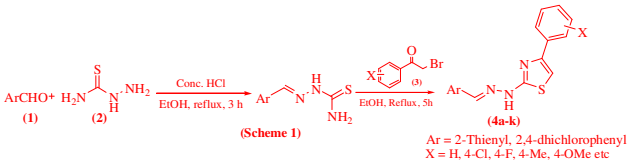

Figure 1: Scheme for the synthesis of thiazolyl hydrazones

The synthesis of thiazolyl hydrazones (**4a-k**) was achieved by one pot approach. Initially, thiophene-2-carbaldehyde or 2, 4-dichlorobenzaldehyde was refluxed at 80°C for 3 h in ethanol in the presence of concentrated HCl. To this mixture, appropriate phenacyl bromide was added and the contents were subsequently refluxed for further 5 hr. After completion of reaction as monitored by TLC, the reaction mass was concentrated under reduced pressure and poured onto ice cold water. The resultant precipitated solid was collected by filtration, washed several times with ice cold water to remove the traces of concentrated HCl and finally purified by recrystallization from ethanol to afford the corresponding thiazolyl hydrazones in highly pure form. The reactions proceeded smoothly in almost all cases. Good yield of thiazolyl hydrazones were obtained in both the cases of thiophene-2-carbaldehyde and 2,4-dichlorobenzaldehyde. However comparatively low yields of the corresponding products (**4c**, **4i** and **4j**) were obtained in case of phenacyl bromides with electron donating groups- 4-Me or 4-OMe (Table 1, Entries 3, 9, 10) whereas good yields were obtained in case of phenacyl bromides with X = H, Cl and F. Structures of the products were confirmed by analysis of spectroscopic data ^{1}H, ^{13}NMR, IR and mass [Supplementary information].

In ^{1}H NMR spectra; the hydrogen of =CH imine C appeared as a singlet in the range of 8.23-8.34 δ ppm, hydrogen of –NH was observed as a broad singlet around 12.5 δ ppm and H of thiazole ring appeared as a singlet from 7.18-7.7 δ ppm value. In ^{13}C NMR the most deshielded C (C between N and S) of thiazole ring appeared around 167 δ ppm. The C of thiazole ring adjacent to S atom was observed to be the most shielded C among the aromatic region between 102.66-104. In IR spectra; the characteristic peak around 3150-3400 cm^{-1} appeared due to the N-H stretch and peaks in the range of 1550-1800 and 1450-1560 cm^{-1} were observed for C=N and C=C stretch respectively. Finally the structures were confirmed from mass analyses by $(M+1)^{+}$ peaks at appropriate values.

Antioxidant activity of the synthesized compounds was evaluated using reported method[17]. Almost all the compounds exhibited promising DPPH and H_2O_2 radical scavenged antioxidant activity (Table 2). Compounds **4a** (95.5%), **4b** (94.4%) and **4e** (94.3%) at the lowest concentration of 20 µg/ mL showed better antioxidant activities as compared to the standard ascorbic acid (93.4%). DPPH scavenged antioxidant activity was more with Ar = 2-thienyl ring as compared to 2, 4-dichlorophenyl moiety. The presence of halogen on either the aldehyde or phenacyl bromide had a remarkable effect on enhancing the antioxidant activity. Compounds **4a**, **4b**, **4c**, **4e**, **4f** and **4i** showed comparable DPPH scavenged antioxidant potential (average % DPPH inhibition from 90.26 to 96.56) whereas H_2O_2 scavenged antioxidant potential was excellently observed in case of **4a** and **4f** (90.98-92.08% inhibition). Thus the compounds **4a** and **4f** showed significant antioxidant potential in both the assays comparable with the standard ascorbic acid (average % inhibition = 95.3). IC_{50} values of the samples were obtained from linear regression analysis of dose-response curve by plotting % inhibition against concentration[18] and summarized in Table 2. The results of antioxidant activities are graphically expressed in Figure 2.

Figure 3 shows the graphical representation of variation of antioxidant activity for the compounds **4a** (% DPPH inhibition) and **4f** (% H_2O_2 inhibition) as a function of concentration and comparison with the standard. Compound **4a** (96.56% DPPH inhibition) was found to be the most prolific and even more potent than the standard ascorbic acid (95.3% inhibition) having highest antioxidant potential in terms of % DPPH inhibition at 60 µg/mL concentration whereas H_2O_2 scavenged antioxidant activity of **4f** was directly proportional to concentration and highest activity was observed at 100 µg/mL as in case of the standard.

Antifungal activity of the synthesized compounds against *Candida Albicance, Aspergillus Niger* and *Aspergillus flavus* fungal strains was studied at different concentrations i. e. 25, 50 and 100 µL using well diffusion method[19-20] and the results were expressed in terms of zones of inhibition and Minimum Inhibitory Concentrations (MICs) as shown in Table 3, 4.

MIC value of an antimicrobial compound is its lowest concentration that prevents visible growth of the microorganism. It is a measure of effective ability of the antimicrobial against the concerned microbe. MIC values of compounds (**4a-4k**) as determined by serial dilution technique are expressed in Table 4. Compounds with thiophene ring were found to be effective antifungal agents against *C. Albicance.* Compounds **4a**, **4b** and **4k** showed good antifungal activity against *Candida albicance* and *Aspergillus Niger* whereas the compounds **4g** and **4h** were effective against all the three fungal strains. Compound **4d** showed good antifungal results against *C. Albicance* and *A. Niger.* In general, almost all the synthesized compounds exhibited excellent antioxidant activities and moderate to good antifungal activity but less potent than the standard fluconazole.

In order to explore binding affinity, binding mode and molecular interactions of synthesized compounds; molecular docking study was carried out against COX-2; an isoform of cycloxygenase or prostaglandin endoperoxidase synthease (PGHS). COX-1 is the first isoform of PGHS mostly responsible for maintaining gastric functions. It provides integrity and vascular homeostasis in case of gastric protective layer i.e. gastric mucosa. COX-2 expresses inflammatory response so it acts as strong target for non- steroidal anti-inflammatory and antioxidant agents[21-23]. The reference standard NSAIDs like Diclofenac and DPPH standard ascorbic acid which have strong radical scavengers were used to compare antioxidant activity of the synthesized 1, 3-thiazole derivatives.

Table 1: Yield and melting points of thiazolyl hydrazones **4a-k**

Entry	Ar	X	Product	Yield (%)[@]	Melting point (°C)
1	2-Thienyl	H	4a	84	160-162
2	2-Thienyl	4-Cl	4b	90	228-230
3	2-Thienyl	4-Me	4c	76	192-194
4	2-Thienyl	4-F	4d	89	156-158
5	2-Thienyl	3-COOMe, 4-OCH_2Ph	4e	91	164-166
6	2,4-Dichlorophenyl	4-F	4f	88	208-210
7	2,4-Dichlorophenyl	H	4g	87	193-195
8	2,4-Dichlorophenyl	4-Cl	4h	90	201-203
9	2,4-Dichlorophenyl	4-Me	4i	80	190-192
10	2,4-Dichlorophenyl	4-OMe	4j	85	225-227
11	2,4-Dichlorophenyl	3-$COOCH_2Ph$, 4-OH	4k	83	196-198

[@] Isolated yields on the reaction of aldehyde (3 mmol), thiosemicarbazide (3 mmol) and phenacyl bromide (3 mmol).

Table 2: Antioxidant activities of **4a-4k**

Compound / Conc. µg/ mL	DPPH % Inhibition					A*	IC_{50} (µg/mL)	H_2O_2 % Inhibition					A*	IC_{50} (µg/mL)
	20	40	60	80	100			20	40	60	80	100		
4a	95.5	95.8	97.6	97.1	96.8	**96.56**	**26.008**	87.5	90.0	91.0	92.4	94.0	**90.98**	**31.03**
4b	94.4	96.0	96.1	96.6	97.0	**96.02**	**26.335**	82.8	83.2	85.2	86.0	87.1	84.86	39.58
4c	90.9	97.0	97.6	97.8	98.1	**96.28**	**29.837**	79.6	82.8	84.4	88.4	91.0	85.24	35.933
4d	92.4	93.3	94.6	66.3	97.0	88.72	44.12	84.2	87.5	90.3	91.9	92.4	89.26	35.206
4e	94.3	94.9	95.5	96.0	96.3	**95.4**	**28.131**	79.6	82.8	84.4	87.6	92.4	85.36	29.212
4f	90.7	93.3	94.6	95.5	96.0	**94.02**	**27.139**	88.4	90.0	92.4	94.0	95.6	**92.08**	**35.539**
4g	76.6	90.2	92.8	92.6	95.8	89.6	29.307	78.1	78.9	80.4	83.1	87.4	81.58	43.712
4h	73.9	85.9	88.9	92.3	92.4	86.68	32.224	76.0	76.2	80.4	83.1	84.4	80.02	43.537
4i	86.0	86.2	93.3	90.7	95.1	**90.26**	**30.791**	76.2	80.4	83.2	84.2	85.3	81.86	40.004
4j	65.5	69.5	86.9	90.6	93.3	81.16	34.966	78.1	79.7	82.8	84.2	87.5	82.46	40.405
4k	19.2	37.2	41.9	45.5	56.1	39.98	88.844	58.9	63.5	66.3	71.8	75.0	67.1	57.873
Ascorbic acid	93.4	94.6	95.5	96.0	97.0	**95.3**	**26.771**	93.4	94.6	95.5	96.0	97.0	**95.3**	**26.771**

A* = Average percentage inhibition for concentrations 20, 40, 60, 80 and 100 µg/mL recorded after 15 minutes of incubation.

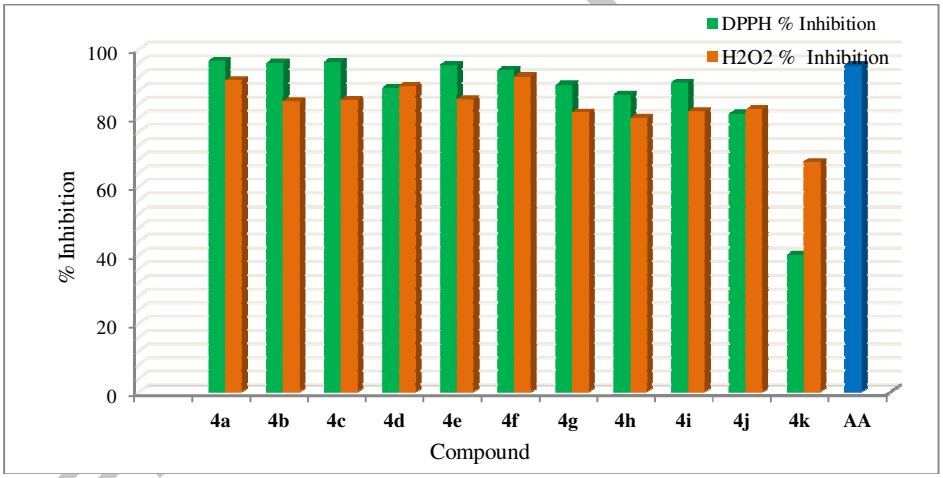

Figure 2: Graphical representation of antioxidant activity of **4a-4k**

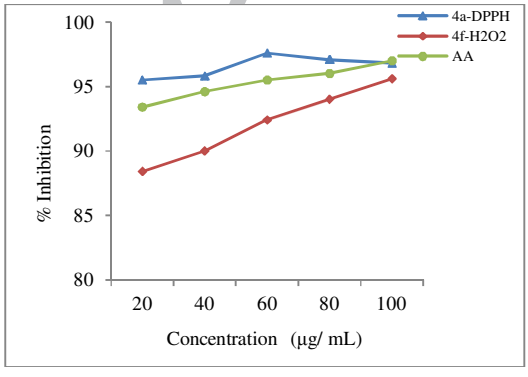

Figure 3: Concentration dependent antioxidant activity of **4a**, **4f** and ascorbic acid.

Table 3: Antifungal activity of **4a-4k** against different fungi

	Zone of Inhibition (mm)								
	Candida Albicance			***Aspergillus Niger***			***Aspergillus Flavus***		
Comp/ Conc (µg/ mL)	**100**	**50**	**25**	**100**	**50**	**25**	**100**	**50**	**25**
4a	12	10	06	10	8	6	15	12	8
4b	18	14	11	8	6	6	20	17	8
4c	15	14	13	6	6	6	6	6	6
4d	15	14	12	13	10	6	6	6	6
4e	10	8	6	6	6	6	6	6	6
4f	13	11	10	6	6	6	12	10	8
4g	15	14	12	11	10	8	25	15	12
4h	18	15	10	17	13	12	16	15	12
4i	8	6	6	6	6	6	16	10	6
4j	7	6	6	6	6	6	6	6	6
4k	13	10	12	6	6	6	14	6	6
Fluconazole	28	22	15	25	20	14	20	18	15

Table 4: MIC values of thiazolyl hydrazones (**4a-4k**)

Entry	Compound	MIC (µg/mL)		
		CA	*A N*	*AF*
1	4a	12.5	25	NT
2	4b	6.25	NT	12.5
3	4c	6.25	NT	NT
4	4d	6.25	25	NT
5	4e	25	NT	NT
6	4f	6.25	NT	12.5
7	4g	3.12	12.5	< 3.12
8	4h	3.12	6.12	6.25
9	4i	25	NT	25
10	4j	25	NT	NT
11	4k	6.25	NT	NT
12	Fluconazole	< 3.12	< 3.12	< 3.12

MIC = Minimum Inhibitory Concentration, NT = Not tested
CA- Candida Albicance, AN - Aspergillus Niger, AF- Aspergillus flavus

Molecular docking has given brief insight about strength of molecular complexes, suggesting that the synthesized derivatives have a strong potential to inhibit the prostaglandin precursor COX-2. Physicochemical properties prediction (ADMET) has highlighted that these compounds have potential of acting as orally active anti-inflammatory agents. In silico study was performed to evaluate pharmacokinetic and safety potential of synthesized 1,3-thiazole derivatives **4a-k**, standard Diclofenac and Ascorbic acid using ADMET predictor FAF Drugs2 which runs on Linux OS[24-25]. In particular, we calculated the compliance of synthesized compounds to the Lipinski's rule of five[26-27].

To identify the possible identical poses of synthesized 1, 3-thiazole derivatives they were docked into active site of protein and further ranked based on total docking score and interactions. To perform molecular docking three dimensional X-ray crystal structure of COX-2 (PDB ID: 1PXX Resolution 2.90 Å) complex with Diclofenac was used[28]. The complex 1PXX is advantageous over other COX-2 complexes as COX-2 protein present in complex Diclofenac and Diclofenac which have a number of activities including antimicrobial, ulcerogenic, analgesic, anti-inflammatory, lipid peroxidation, antitumor and inhibitor formation of transthyretin amyloid so it will provide important clue in understanding of details inhibition at molecular level[29]. Docking study was carried out using Surflex-Dock module of Sybyl 2.1.1 package following standard procedure[30]. To represent the details of docking score, the following terms were used: a) Total score as total docking score b) Crash score as degree of inappropriate penetration by the ligand into the protein and interpenetration between ligand atoms that are separated by rotatable bonds of compounds. c) Polar score giving an idea about the contribution of polar non-hydrogen bonding interactions to the total score are shown in Table 5.

Table 5: % Inhibition (DPPH Assay) and Molecular Docking details.

Compound	% DPPH Inhibition[@]	Molecular Docking Score		
		Total Score (-log Ki)	Crash Score	Polar Score
4a	95.5	4.15	-1.3255	0.7188
4b	94.4	4.3072	-0.9746	0.8591
4c	90.9	3.9574	-0.4864	0
4e	94.3	3.327	-0.6737	0.5479
4f	90.7	3.0994	-0.8576	0.0028
4i	86	3.2562	-0.7686	1.0846
Diclofenac	97.14	3.4402	-1.8105	1.4606
AA	93.4	3.5259	-0.7739	0.0009

[@] % Inhibition at 20 µg/mL concentration.

The analysis of binding affinity (-logki) values and molecular interactions of thiazolyl hydrazone derivatives such as **4b** (4.3072), **4a** (4.1500) and **4c** (3.9574) suggested that they are the most active among all the synthesized derivatives. When the most active derivative **4b** was compared with reference co-crystallised ligand Diclofenac and Ascorbic acid; it has a strong potential to inhibit COX-2 and produces both radical scavenging and anti-inflammatory activity. Compounds **4e**, **4f** and **4i** had potential to act as anti-inflammatory and antioxidant agents which is indicated by intermediate total docking score (3.3 to 3.0) given in Table 5. The thiazolyl hydrazones **4b** (4.3072), **4a** (4.1500) and **4c** (3.9574) showed efficient binding mode and penetrating active site cavity by forming hydrogen bond interactions (conventional/pi donor) and π interactions with active site residues. The most active **4b** (4.3072) derivative interacts with active site of amino acid residue ASN375 and GLY533 forms by conventional hydrogen bond and Carbon-Hydrogen bond interactions with phenyl ring para substituted (-Cl) of distance 3.19 and 4.41 Å respectively. The amino acid TYR385 and SER530 showed pi-donor hydrogen bond interactions with distance of 2.23 and 2.73 Å respectively with thiazole ring. The amino acid ALA527, TYR385, VAL349, PHE205, LEU534, PHE209 and ILE377 various pi interactions with thiophene, thiazole, phenyl ring and chlorine atom which includes pi-sigma, alkyl, pi-pi T shaped and pi-sulfur shown in Figure 4. The second most active thiazolyl derivative **4a** (4.1500) forming hydrogen bond interactions (Conventional/Pi-Donor) with amino acids VAL523 and TYR355 with hydrogen atom of nitrogen and phenyl ring of thiazole of distance 2.801 and 3.88 Å respectively. The amino acid PHE381, PHE518, GLY526, ALA527, VAL349 and LEU359 forms pi-sulfur, pi-pi T shaped and amide- pi-stacked and pi-alkyl interactions with thiophene, thiazole, phenyl ring (Figure 5).

FAF Drug2 tool was used for in silico ADMET predictions. In particular, we calculated the compliance of synthesized compounds to the Lipinski's rule of five which is widely used as a filter for lead molecules that would likely be further developed for drug design programs. We have assessed parameters like %ABS, MW, logP, N-ROTB and H/C. The values obtained are summarized in Table 6. Topological polar surface area (TPSA) i.e. surface belonging to polar atoms and molecular weight are the descriptors which correlate with passive molecular transport through membranes that allows prediction of route of transport of drugs through the barrier membranes the intestine and blood-brain barrier (BBB). The percentage of absorption (% ABS) was calculated using TPSA by using formula %ABS=109-(0.345xTPSA)[31].The values of partition coefficient, number of rotatable bonds, number of rigid bonds and ratio of H/C determine the absorption performance through the lipophilic phospholipid membranes and toxicity. Moreover, none of the synthesized compounds violated Lipinski's rule of five and it's varients. Thus all the thiazolyl hydrazones have the potential to be developed as an orally active drug like candidates and may be potentially active anti-inflammatory and antioxidants drug candidates against COX-2.

In summary, different thiazolyl hydrazones were synthesized by one pot reaction of thiophene-2-carbaldehyde or 2, 4-dichlorobenzaldehyde, thiosemicarbazide and various phenacyl bromides. The synthesis is simple, facile and high yielding to afford the corresponding products in high yields. *In vitro* antioxidant and antifungal activities revealed that compounds **4a**, **4b**, **4c**, **4e**, **4f** and **4i** exhibited excellent DPPH scavenged antioxidant potential which was comparable at 20 µg/mL as the lowest concentration. H_2O_2 scavenged antioxidant activities of **4a** and **4f** were comparable with the standard ascorbic acid at 40 µg/mL concentration.

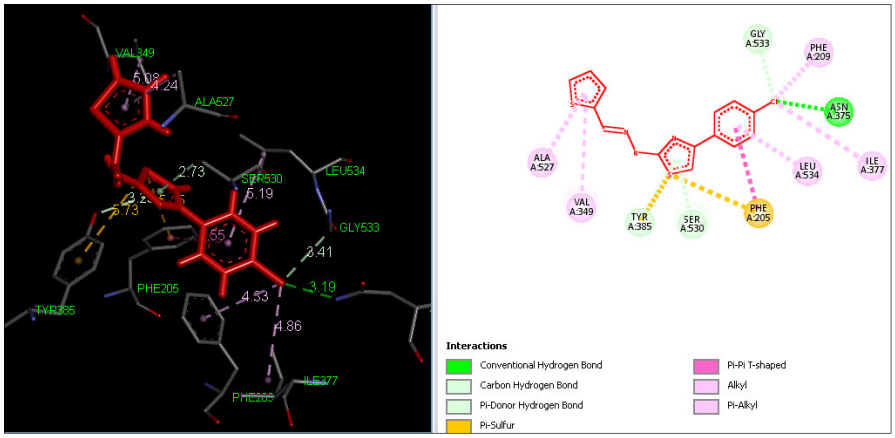

Figure 4. Binding pose and molecular interactions of **4b** into the active site of COX-2

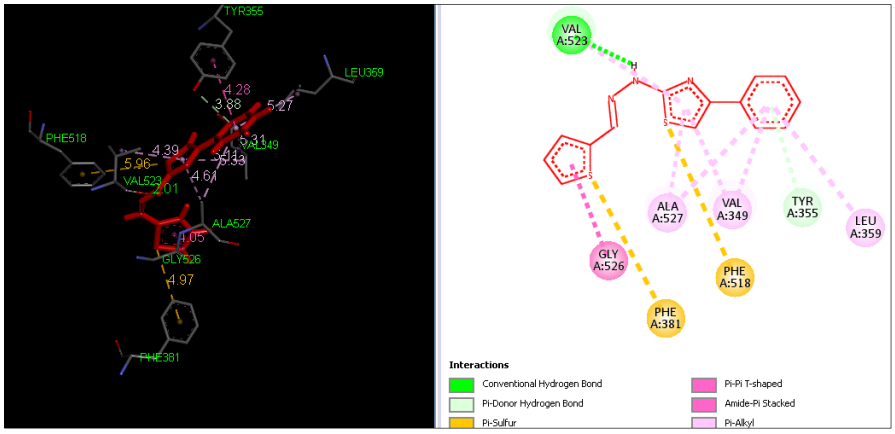

Figure 5. Binding pose and molecular interactions of **4a** into the active site of COX-2

Table 6: In silico drug like (physicochemical) properties of **4a-k**, diclofenac and ascorbic acid

Comp.	**MW** (<500Da)	**%ABS** (100%)	**LogP** (<5.6)	**PSA** (<140Å)	**RotatableB** (<10)	**HBD** (<5)	**HBA** (<10)	**Rings** (3-5)	**Ratio H/C** (<1)	**Toxicity**
4a	285.3872	76.6528	4.3906	93.76	4	1	4	3	0.357	NT
4b	319.8323	76.6528	5.044	93.76	4	1	4	3	0.428	NT
4c	299.41	73.46845	4.3992	102.99	5	1	5	3	0.4	NT
4d	303.3777	76.6528	4.5297	93.76	4	1	4	3	0.428	NT
4e	449.55	60.59995	3.8828	140.29	6	2	7	3	0.5	NT
4f	366.2401	86.3956	5.775	65.52	4	1	3	3	0.437	NT
4g	348.2496	86.3956	5.6359	65.52	4	1	3	3	0.375	NT
4h	382.6947	86.3956	6.2893	65.52	4	1	3	3	0.437	NT
4i	362.2762	86.3956	5.9443	65.52	4	1	3	3	0.352	NT
4j	378.2756	83.21125	5.6445	74.75	5	1	4	3	0.411	NT
4k	512.41	70.34275	5.1281	112.05	6	2	6	3	0.5	NT
Diclofenac	295.1407	92.095	3.1024	49	4	1	2	2	0.357	NT
AA	176.12	72.0091	NA	107.22	2	4	6	1	0.32	NT

(Percent absorption, MW: molecular weight, LogP: logarithm of partition coefficient of compound between n-octanol and water, PSA: Polar surface area, n-RotBond: number of rotatable bonds, n-RigBond: number of rigid bonds, HBA: hydrogen bond acceptors and HBD: hydrogen bond donor); NT = Non Toxic.

Thus the compounds **4a** and **4f** were found as the most promising antioxidants exhibiting potential comparable with the standard ascorbic acid. *Invitro* antifungal activity of the synthesized compounds revealed that most of them exhibited good antifungal activity against *C. Albicans* with MIC values in the concentration range of range of 3.12 to 25 µg/mL.

Compounds **4a**, **4b, 4d** and **4k** showed good antifungal activity against *Candida albicance* and *Aspergillus Niger* whereas, compounds **4g** and **4h** were found as broad spectrum antifungal agents effective against all the three fungal strains. In general, all the synthesized compounds exhibited excellent antioxidant activities; percentage radical scavenging activity of **4a** and **4f** being comparable with the standard even at 20 and 40 µg/mL concentrations respectively. Some of the compounds showed

moderate to good antifungal activity but less potent than the standard fluconazole. Computational molecular docking study highlights and supports the experimental results for the observed antioxidant activity and demonstrated that **4a, 4b** and **4c** are the most active forms having potential to act as strong antioxidant and anti-inflammatory agents. Prediction of pharmacokinetics parameter suggests that the synthesized compounds have potential of high oral drug bio-availability. Thus, thiazolyl hydrazone skeleton has broad spectrum activities as potential antioxidants, anti-inflammatory and good antifungal agents and there exist new opportunities for the possible modification as per pharmaceutical requirement in future.

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Supplementary data Spectroscopic data and full experimental details associated this article are available in the supplementary information.

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