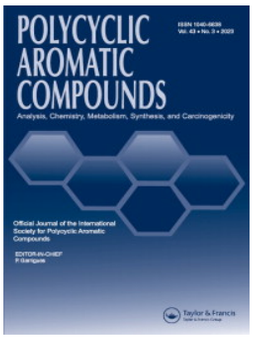


Polycyclic Aromatic Compounds

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpol20

Synthesis and Biological Evaluation of Novel Asymmetric (*E*)-3-(4-(Benzyloxy) Phenyl)-2-((Substituted Benzylidene) Amino)-1-(Thiazolidin-3-yl) Propan-1-One and Computational Validation by Molecular Docking and QSTR Studies

Amit A. Pund, Suresh T. Gaikwad, Mazahar Farooqui, Rajashri A. Pund-Nale, Mubarak H. Shaikh & Baban K. Magare

To cite this article: Amit A. Pund, Suresh T. Gaikwad, Mazahar Farooqui, Rajashri A. Pund-Nale, Mubarak H. Shaikh & Baban K. Magare (2023) Synthesis and Biological Evaluation of Novel Asymmetric (*E*)-3-(4-(Benzyloxy) Phenyl)-2-((Substituted Benzylidene) Amino)-1-(Thiazolidin-3-yl) Propan-1-One and Computational Validation by Molecular Docking and QSTR Studies, Polycyclic Aromatic Compounds, 43:3, 2444-2458, DOI: 10.1080/10406638.2022.2046615

To link to this article: https://doi.org/10.1080/10406638.2022.2046615

POLYCYCLIC AROMATIC COMPOUNDS
2023, VOL. 43, NO. 3, 2444–2458
https://doi.org/10.1080/10406638.2022.2046615

Taylor & Francis
Taylor & Francis Group

Synthesis and Biological Evaluation of Novel Asymmetric (*E*)-3-(4-(Benzyloxy) Phenyl)-2-((Substituted Benzylidene) Amino)-1-(Thiazolidin-3-yl) Propan-1-One and Computational Validation by Molecular Docking and QSTR Studies

Amit A. Pund[a], Suresh T. Gaikwad[b], Mazahar Farooqui[c], Rajashri A. Pund-Nale[d], Mubarak H. Shaikh[e], and Baban K. Magare[a]

[a]UG, PG and Research Centre, Department of Chemistry, Shivaji Arts, Commerce and Science College Kannad, Dist. Aurangabad, Maharashtra, India; [b]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India; [c]Post Graduate and Research Centre, Maulana Azad College of Arts, Science and Commerce, Aurangabad, Maharashtra, India; [d]Department of Zoology, Bhaskar Pandurang Hivale Education Society's Ahmednagar College, Ahmednagar, Maharashtra, India; [e]P.G. and Research, Department of Chemistry, Radhabai Kale Mahila Mahavidyalaya, Ahmednagar, Maharashtra, India

ABSTRACT

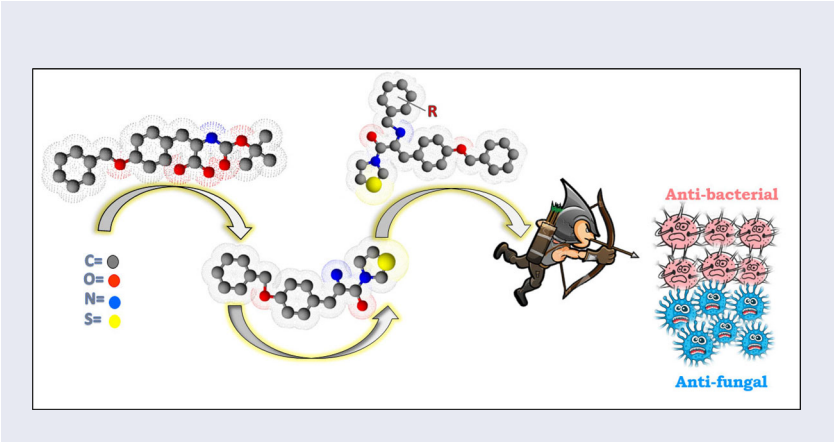
A novel series of asymmetric of (*E*)-3-(4-(benzyloxy) phenyl)-2-((substituted benzylidene) amino)-1-(thiazolidin-3-yl) propan-1-one derivatives (**AAP-1** to **AAP-10**) have been efficiently synthesized from (*S*)-2-amino-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (**4**) and various substituted aldehydes by conventional as well as microwave irradiation method. The structure of newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and Mass spectroscopic methods, further evaluated for their *in vitro* antimicrobial activities. Among these series, the compounds **AAP-2**, **AAP-4**, **AAP-5**, **AAP-7, AAP-8 AAP-9**, and **AAP-10**, showed excellent antibacterial activities against Gram-positive bacteria like *Staphylococcus aureus (SA), Lysinibacillus sphaericus (LS), Bacillus subtilis (BS)* and *Klebsiella aerogenes (KA), Pseudomonas Aeruginosa (PA), Chromobacterium violaceum (CV)* as Gram-negative bacteria as compared to standard Ciprofloxacin. The compounds **AAP-1**, **AAP-4**, **AAP-5**, **AAP-6**, **AAP-7**, and **AAP-8** exhibited good antifungal activities against *Fusarium oxysporum (FO), Rhizoctonia solani (RS), Colletotrichum capsici (CC) strains* as compared to standard Fluconazole. Molecular docking studies of final compounds were performed using Auto Dock Vina software against Lanosterol 14α-demethylase (CYP51A1) enzyme and crystal 4WMZ and showed effective binding affinity of these molecules with enzymes. Quantitative structure toxicity relationship study of target compounds were studied by various computational animal models and defined oral rat LD_{50} values for cytotoxicity. The **AAP-2**, **AAP-4**, **AAP-5**, and **AAP-7** to **AAP-10** showed low toxicity. In addition, the pharmacokinetic of target compounds were studied and revealed acceptable good drug-likeness score properties as well as follow Lipinski's rule of five.

ARTICLE HISTORY
Received 15 March 2021
Accepted 16 February 2022

KEYWORDS
1,3-thiazolidine; antimicrobial; microwave irradiation; oral rat LD_{50}; molecular docking

CONTACT Baban K. Magare magrebk75@gmail.com UG, PG and Research Centre, Department of Chemistry, Shivaji Arts, Commerce and Science College, Kannad. Dist. Aurangabad, Maharashtra 431103, India.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/10406638.2022.2046615



Introduction

The synthesis of novel agents to combat resistant bacteria and fungi has become one of the most important areas of antimicrobial research today.[1] Due to generic mutation, microorganisms become resistant to all standard antibiotic drugs and could only be treated with potentially active drugs. The 1,3-thiazolidine is an important class of heterocyclic compounds and its composites are key components of many drugs and present in natural products. This moiety is core part of magnificent antibiotics drugs like antibiotic penicillin and Teneligliptin (Figure 1).[2]

It is noteworthy that the 1,3-thiazolidine is exhibited potent activity against Gram-positive pathogens like *Staphylococci*, *Enterococci*, and *Streptococci*.[3] The mechanism of action perceived that, thiazolidine bound to the bacterial sub units of 50 S ribosomal and inhibition of the 70 S ribosomal initiation complex formations.[4] Furthermore positive charge on nitrogen atom of 1,3-thiazolidine ring tends to protonate and would be expected to play a significant role on the inhibition of viral or cellular enzymes, which are essential for viral imitation.[5] Recently, the 1,3-thiazolidine ring containing heterocyclic compounds have been reported as antifungal,[6] antimalarial,[7] anti-HIV,[8] anticancer,[9] antiviral,[10] antitubercular,[11] and antimicrobial.[12–15] The diverse pharmaceutical activities of 1,3-thiazolidine have received the attention and incorporated with other functionality. In addition, tyrosine amino acid is a key neurotransmitter like epinephrine, norepinephrine, dopamine, and used as a starting material for many reactions due to easy availability and low cost. The importance of tyrosine compound has been described by James et al. and reported the structure–activity relationships of tyrosine-based inhibitors of autotaxin (ATX).[16] Furthermore, the azomethine group has attracted significant attention due to their wide diversity in medical implications. It has been synthesized via condensation of primary amines with active carbonyl compounds. Many Schiff bases have been reported to possess significant biological properties such as antimicrobial,[17,18] antibacterial,[19] antifungal,[20] antitumor,[21] anti-inflammatory,[22] anti-HIV,[23] anticonvulsant,[24] anticancer,[25] anti-malarial,[26] antiviral,[27] and analgesic.[28]

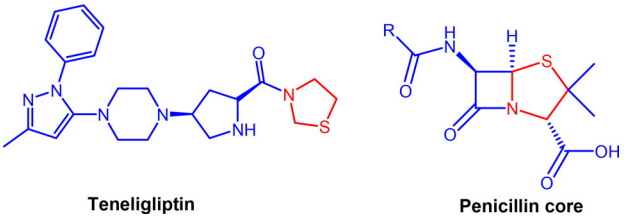
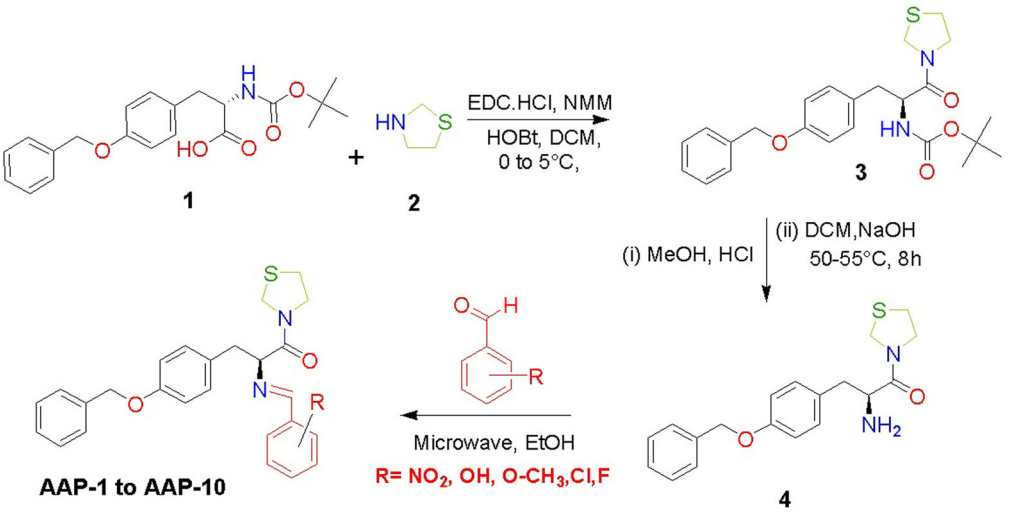


Figure 1. Thiazolidine moiety containing marketed drugs.



Scheme 1. Synthetic scheme of target compounds (**AAP-1** to **AAP-10**).

This observations enforced us to design and synthesis a small library of the Schiff bases containing thiazolidine ring from Boc-O-benzyl-L-tyrosine (**1**) in three steps. The coupling of 1,3-thiazolidine with substituted carboxylic acid was reported by using bromo tripyrrolidine phosphonium hexafluorophosphate,[29] *N,N*-dicyclohexyl carbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as coupling agents in dimethylformamide solvent[30,31] whereas *N*-(3-Dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC.HCl), *N*-methylmorpholine (NMM), hydroxybenzotriazole (HOBt) in different solvents.[32,33] The boc deprotection of amines were carried out using trifluroacetic acid, hydrogen bromide, tetra-n-butyl ammonium fluoride, boron trifluoride etherate and hydrochloric acid.[34] The formation of Schiff base derivatives were reported by condensation of aldehydes and amines acidic condition by using conventional method in 1948.[35]

In view of continuous efforts on design and synthesis of biologically active molecules, we herein reported the efficient synthesis of novel series of asymmetric of (*E*)-3-(4-(benzyloxy)-phenyl)-2-((substituted-benzylidene)-amino)-1-(thiazolidin-3-yl) propan-1-one derivatives (**AAP-1** to **AAP-10**) by the reaction of novel amine and various substituted aromatic aldehydes by conventional as well as microwave irradiation methods.[36] Further, these compounds have been evaluated for their antimicrobial activities. In addition, the quantitative structure toxicity relationship (QSTR) as well as molecular docking study were carried out for better understanding of effective binding. Furthermore, *in silico* ADME predictions for good drug like properties of newly synthesized compounds were studied.

Results and discussion

Chemistry

Amide coupling of 1,3-thiazolidine and *N*-boc-O-benzyl-*L*-tyrosine (**1**) was carried out using EDC.HCl and HOBt in DCM with NMM as base (Scheme 1). The obtained crude product was crystallized using IPE to afford pure *S*-tert-butyl-3-(4-(benzyloxy) phenyl)-1-oxo-1-(thiazolidin-3-yl) propan-2-ylcarbamate (**3**) with excellent yield (95%). In next stage novel amine **4** was obtained by boc deprotection of **3** using aqueous hydrochloric acid solution. Finally targeted compounds were achieved by condensation of amine **4** with various substituted aromatic aldehydes under microwave irradiation at 560 W for 2–3 min with excellent yield of 92–98%. The purity and

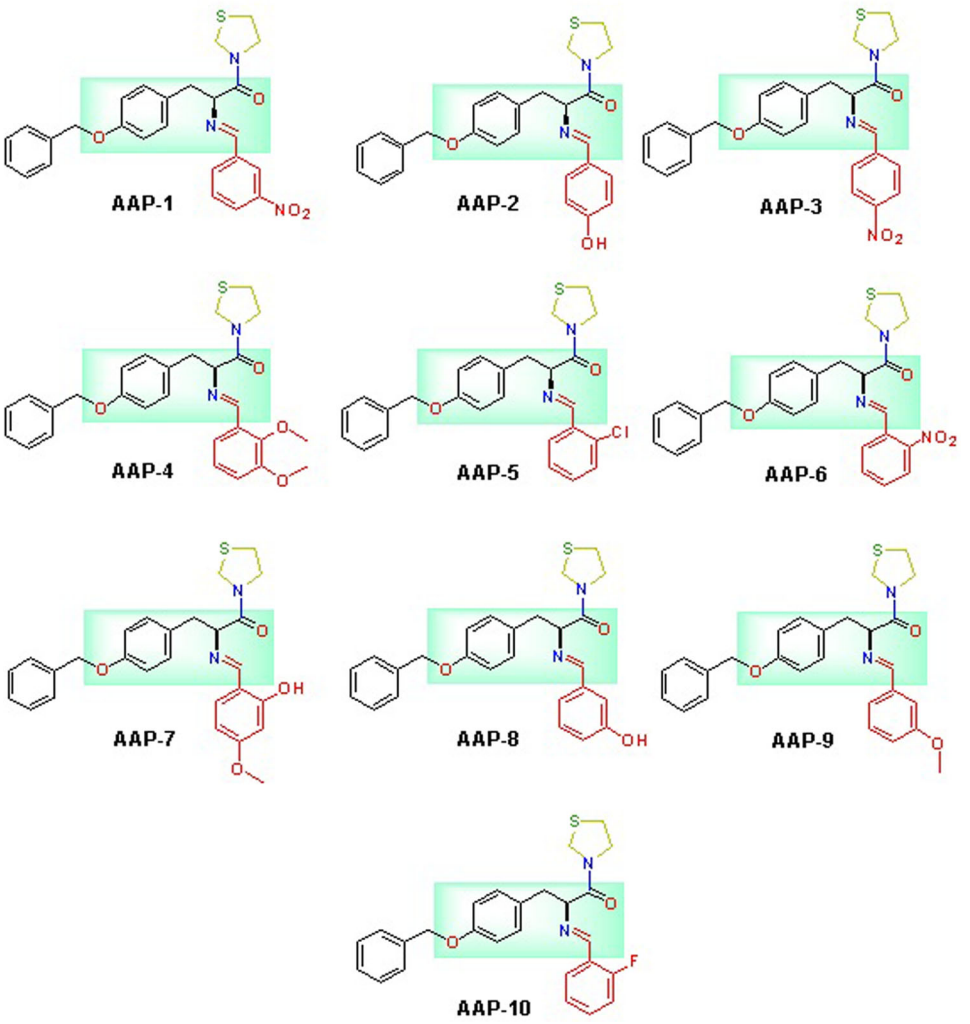


Figure 2. The structural representation of synthesized compounds.

identity were unambiguously established with the help of elemental analysis, ^{1}H NMR, ^{13}C NMR, mass spectroscopy, and FTIR. The structures of the novel derivatives are shown in Figure 2.

Biological evaluation

Antibacterial activity

The ready-made Tryptic soya broth and Malt extract broth medium were used for antibacterial activity.[37] The final compounds were tested against *Staphylococcus aureus (SA), Lysinibacillus sphaericus (LS), Bacillus subtilis (BS)* (Gram-positive bacteria), and *Klebsiella aerogenes (KA), Pseudomonas Aeruginosa (PA), Chromobacterium violaceum (CV)* (Gram-negative bacteria). The results of MIC for antibacterial activity of targeted compounds were showed in Table 1. The **AAP-2**, **AAP-4**, **AAP-5**, **AAP-7**, **AAP-8**, **AAP-9**, and **AAP-10** title compounds which has hydroxyl, methoxy, chloro, fluoro functional groups showed good to excellent MIC activity against Gram-negative bacteria and Gram-positive bacteria, conversely the compounds **AAP-1**,

Table 1. Antibacterial activity of target compounds.

	MIC in μg/mL					
	Gram -ve bacteria			Gram + ve bacteria		
Compounds	*K. A.*	*P. A.*	*C. V.*	*S. A.*	*L. S.*	*B. S.*
AAP-1	38	40	41	35	40	30
AAP-2	20	21	17	27	20	18
AAP-3	35	36	30	39	37	29
AAP-4	19	20	20	28	20	17
AAP-5	19	19	18	27	21	18
AAP-6	35	41	26	31	26	22
AAP-7	18	19	17	29	23	20
AAP-8	19	22	18	28	21	19
AAP-9	20	20	16	26	21	21
AAP-10	21	19	17	28	22	19
Ciprofloxacin	22	23	19	29	23	21

K.A.: Klebsiella aerogenes; P.A.: Pseudomonas Aeruginosa; C.V.: Chromobacterium violaceum; S.A.: Staphylococcus aureus; L.S.: Lysinibacillus sphaericus; B.S.: Bacillus subtilis. Negative control (Dimethyl sulfoxide) – no activity. Values are indicated in μg/mL.

Table 2. Antifungal activity of target compounds.

	Minimum inhibitory concentration in μg/mL (MIC)		
Compounds	*F.O*	*R. S*	*C. C*
AAP-1	17	14	15
AAP-2	21	18	17
AAP-3	26	23	29
AAP-4	19	14	15
AAP-5	15	13	17
AAP-6	18	15	15
AAP-7	19	15	16
AAP-8	18	14	15
AAP-9	19	15	18
AAP-10	19	16	17
Fluconazole	19	15	17

F.O.: Fusarium oxysporum; R.S.: Rhizoctonia solani; C.C: Colletotrichum capsici.
Negative control (Dimethyl sulfoxide) – no activity. Values are indicated in μg/mL.

AAP-3, and **AAP-6** which has nitro substituent at *meta, para* and *ortho* position, respectively, on the benzene ring showed lower activity as compared to Ciprofloxacin as reference drug (Table 1).

Antifungal activity

The ready-made Muller Hinton agar medium used for evaluation of antifungal activities,[38] *Fusarium oxysporum (FO), Rhizoctonia solani (RS), Colletotrichum capsici (CC)* were used as fungal pathogens. The results of antifungal activities of targeted compounds were showed in Table 2. The compounds **AAP-1**, **AAP-4**, **AAP-5**, **AAP-6**, **AAP-7**, and **AAP-8** showed good antifungal activity as compared to standard Fluconazole drug. The good and enhanced antibacterial and antifungal activities of title compounds may be attributed due to the presence of 1,3-thiazolidine incorporated with imine moiety and different functional groups.

QSTR study

The QSTR study of new compounds were carried out with the help of Toxicity Estimation Software Tool (T.E.S.T). In 2005, according to Hodge and Sterner[39] toxicity scale predicted on

Table 3. Hodge and Sterner scale for LD_{50} (Oral, Rat, mg/kg) toxicity.

Sr. No.	Term for toxicity	LD_{50} (Rat, Oral) Value in mg/kg
1	Extremely toxic	>1
2	Highly toxic	1 to 50
3	Moderately toxic	50 to 500
4	Slightly toxic	500 to 5000
5	Practically nontoxic	5000 to 15,000

Table 4. QSTR derived Oral Rat LD_{50} value for target compounds.

Compound	Predicted LD50 (Oral, Rat, mg/kg) in male rat	Oral rat LD_{50} - Log10 (mol/kg) in male rat	Result
AAP-1	1<	1<	Extremely toxic
AAP-2	1503.16	2.47	Slightly toxic
AAP-3	1<	1<	Extremely toxic
AAP-4	1406.88	2.54	Slightly toxic
AAP-5	1259.89	2.57	Slightly toxic
AAP-6	1<	1<	Extremely toxic
AAP-7	1564.37	2.48	Slightly toxic
AAP-8	1509.77	2.47	Slightly toxic
AAP-9	1454.99	2.50	Slightly toxic
AAP-10	1244.84	2.56	Slightly toxic

the basis of LD_{50} (Oral, Rat, mg/kg) and showed in Table 3. Predicted Oral rat LD_{50} values of final compounds were calculated from consensus method and showed in Table 4.

The LD 50 values calculated by following arithmetic method

n = total number of animal in a group.

a = the difference between two successive doses of administered extract/substance.

b = the average number of dead animals in two successive doses.

LD_{100} = Lethal dose causing the 100% death of all test animals.

The results of oral rat LD_{50} showed that the compounds **AAP-2**, **AAP-4**, **AAP-7**, **AAP-8**, **AAP-9**, and **AAP-10** has slight toxicity. It is revealed that the compounds with nitro group at ortho, meta, and para position on benzene ring (**AAP-1, AAP-3**, and **AAP-6**) possess extreme toxicity.

Computational study

Molecular docking

Molecular docking was performed to evaluate the antifungal activity of target compounds by using Auto Dock Vina (http://vina.scripps.edu) software.[40] Before screening the biologically activity, the molecular docking study was carried out by using a crystal 4WMZ is a chain structure of Baker's yeast and whose ligand is fluconazole and protein Lanosterol 14α-demethylase (CYP51A1) enzyme which is the class of cytochrome P450 superfamily of enzymes. The molecular docking results of target compounds are summarized in Table 5.

Molecular docking study showed that designed compounds fit in the active site cavity of CYP51A1 occupying energetically favorable position to the co-crystallized ligand. The binding affinities were co-related well with the experimentally observed antifungal activity and found that there is good agreement between the values. All the newly synthesized compounds revealed effective interaction between active sites and proteins. The compound **AAP-1** exhibited highest binding affinity (–10.3) whereas **AAP-4** showed lowest binding affinity (–8.1).

The binding affinity indicates that, there is highest binding affinity towards amino acids due to excellent binding at nitrogen and oxygen sites. The representative molecular docking of **AAP-1** and **AAP-4** are showed in Figure 3.

Table 5. Molecular docking results of target compounds.

Compound	Binding affinity	rmsd/ub	rmsd/lb	Binding with amino acids		
				Hydrogen bond	Hydrophobic interaction	π-π cation-π
AAP-1	−10.3	15.038	11.951	HIS 381, ARG 98	ILE 239, LEU 96, ALA 69, PHE 241, SER 508	VAL 242, LEU 95.
AAP-2	−8.8	17.261	14.096	ARG 385	LYS 151, ILE 139, CYS 470, PHE 463, ALA 747, PRO 379	VAL 311, LEU 383
AAP-3	−9.2	17.335	11.608	ARG 98, HIS 381	LEU 95, ALA 69, LEU 380, PRO 238,	MET 509, PHE 241
AAP-4	−8.1	13.166	10.491	ILE 139, PHE 134	PHE 463, ALA 47, CYS 470, PRO 379,	TYR 126, LEU 383
AAP-5	−9.5	14.238	9.478	PRO 238	PH241, TYR 126	MET 509, LEU 95
AAP-6	−9.6	8.188	3.606	LYS 151, HIS 468	HIS 378, LEU 380, LEU 383, LYS 151	TYR 126
AAP-7	−8.5	6.221	3.378	PHE 506	ILE 239, PRO 238, MET 509, TYR 126, PHE 384, ALA 125, PHE 241	PH 241, TYR 7, LEU 95
AAP-8	−10.1	6.381	2.422	GLY 47, PRO 462	CYC 470, ILE 139, LYS 151, VAL311, LEU 158, ALA 47, PRO 37	CYS 470
AAP-9	−8.2	1.933	1.481	ILE 139, PHE 134.	PHE 463, ALA 47, CYS 470, PRO 379,	TYR 126, LEU 383
AAP-10	−9.5	7.626	3.660	HIS 381, TYR 507	TYR 126, PRO 238, PHE 241	MET 590, LEU 95.

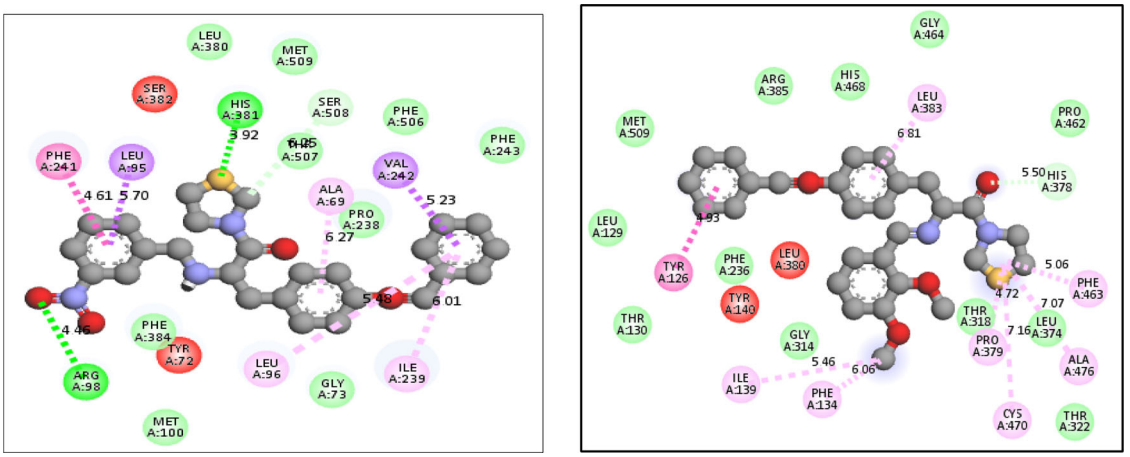


Figure 3. The representative molecular docking of **AAP-1** and **AAP-4**.

The effective interaction between hydrogen bonding, hydrophobic and π–π interaction with amino acid are represented in Figure 3.

In silico ADME prediction

It's very prime task in medicinal chemistry to predict early the drug likeness properties, because it resolves the cost and time of drug development and discovery. Though most of compounds have significant biological activities, have failed in their clinical trials due to the inadequate drug likeness properties. On the basis of Lipinski's rule of five, the drug likeness properties were analyzed by ADME parameters using mol inspiration online property calculation toolkit.[41]

All the newly synthesized compounds exhibited significant values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five and characterized to be likely orally active. None of the synthesized compounds violated the Lipinski's rule of five and results were within the range of accepted values. The parameters like the number of rotatable bonds and total polar surface area are linked with the intestinal absorption, results showed that all synthesized compounds were good absorption. The *in silico* assessment emphasizes to be good pharmacokinetic properties, which is reflected in their physicochemical values, thus, ultimately enhancing pharmacological properties of these molecules.

Table 6. Pharmacokinetic parameters of **AAP-1 to AAP-10** compounds.

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug-likeness model score
Rule	–	–	–	–	<500	≤5	<10	<5	≤1	–
AAP-1	78.7	87.7	9	422.3	475.6	4.88	7	0	0	–0.60
AAP-2	87.6	62.1	8	407.0	446.6	4.46	5	1	0	–0.08
AAP-3	78.7	87.7	9	422.3	475.6	4.90	7	0	0	–0.74
AAP-4	88.2	60.4	10	450.1	490.6	4.76	6	0	0	0.24
AAP-5	94.5	41.9	8	412.5	465.0	5.57	4	0	1	–0.18
AAP-6	78.7	87.7	9	422.3	475.6	4.85	7	0	0	–0.88
AAP-7	84.4	71.4	9	432.6	476.6	4.91	6	1	0	–0.06
AAP-8	87.6	62.1	8	407.0	446.6	4.44	5	1	0	0.07
AAP-9	91.3	51.1	9	424.5	460.6	4.97	5	0	0	–0.13
AAP-10	94.5	41.9	8	403.9	448.6	5.06	4	0	1	–0.39

% ABS: Percentage absorption, TPSA: Topological polar surface area, n-ROTB: Number of rotatable bonds, MV: Molecular volume, MW: Molecular weight, milogP: Logarithm of partition coefficient of compound between n-Octanol and water, n-ON Acceptors: Number of hydrogen bond acceptors, n-OHNH donors: Number of hydrogen bonds donors.

In present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB), and Lipinski's rule of five using Molinspiration online property calculation toolkit. Absorption (% ABS) was calculated by: % ABS = 109 – (0.345 × TPSA). Drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by numerical value) was computed by MolSoft software (Table 6).

Conclusion

In summary, we designed and synthesized the new 1, 3-thiazolidine based (*E*)-3-(4-(benzyloxy) phenyl)-2-((substituted benzylidene) amino)-1-(thiazolidin-3-yl) propan-1-one derivatives from novel (*S*)-2-amino-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (**4**) and different substituted aldehydes using microwave irradiation at 560 W. The structures were confirmed by IR, Mass, ^{1}H NMR, and ^{13}C NMR spectroscopic methods. It is seen that **AAP-4**, **AAP-5**, **AAP-7**, and **AAP-8** displayed excellent antibacterial and antifungal activities. Moreover, the molecular docking was carried out with crystal 4WMZ and enzyme CYP51A1 by using Auto Dock software and study revealed that compounds **AAP-1** showed highest binding affinity (–10.3) whereas **AAP-4** showed lowest binding affinity (–8.1). These studies revealed that there is good agreement with experimental antifungal activity results. In addition, the QSTR study showed that **AAP-2**, **AAP-4**, **AAP-5**, and **AAP-7** to **AAP-10** compounds have slight toxicity. Further analysis of the ADME parameters predicted good drug like properties and can be developed as oral drug candidate. All these results suggested that the new compounds have potent antimicrobial activity and can be further optimized as a lead molecule.

Experimental

General

General procedure synthesis of (S)-tert-butyl-3-(4-(benzyloxy) phenyl)-1-oxo-1-(thiazolidin-3-yl) propan-2-ylcarbamate (3)

To a stirred mixture of (*S*)-2-[(2-methylpropan-2-yl)oxycarbonylamino]-3-(4-phenylmethoxyphenyl)propanoic acid **(1)** (50 g, 0.135 mol) and 1,3-thiazolidine (**2**) (13.2 g, 0.148 mol) in DCM (250 mL), HOBt (0.91 g, 0.007 mol) followed by *N*- methylmorphiline (20.4 g, 0.202 mol) were added at 0–5 °C and stirred for 10 min. EDC.HCl (33.6 g, 0.175 mol) was added lot wise and

stirred for 3.0 h at 5–10 °C. Progress of reaction was monitored by TLC (DCM: MeOH:: 9:1). After reaction completion, water (250 mL) was added to quench and extracted with DCM. The organic layer was washed with 10% brine solution (250 mL) and concentrated under vacuum. The residue treated with IPE (200 mL), filtrated and dried to obtain compound **(3)** as white solid. (56.6 g, 95%); M.P.: 184–186 °C. IR (KBr, ν_{max}, cm^{-1}): 695.92 (C-S), 1172.11 (C-O), 1239.73 (C-N), 1444.55 (C = C), 2911.63 and 2883.20 (H-C-C = O), 3382.03 (N-H). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.41–7.31 (m, 5H, Ar-H), 7.10–7.08 (d, 2H, J = 8 Hz, Ar-H), 6.89–6.87 (d, 2H, J = 8 Hz, Ar-H), 5.14 (s, 3H, O-CH_2-Ar and NH-Boc), 4.74–4.72 (t, 1H, J = 4 Hz, N-CH), 4.36 (s, 3H, N-CH_2-S of thiazolidine), 3.63–3.61 (t, 2H, J = 4 Hz, N-CH_2 of thiazolidine), 3.16–3.13 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar), 2.96–2.94 (t, 2H, J = 4 Hz, S-CH_2 of thiazolidine), 2.87–2.84 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar), 1.39 (s, 9H, Boc). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 170.54, 159.23, 157.53, 140.94, 133.55, 129.07, 127.41, 114.87, 77.08, 69.92, 56.12, 55.83, 54.12, 38.71, 28.81. ES-MS m/z 443.3 $(M+H)^+$. Analytical calculated formula for $C_{24}H_{30}N_2O_4S$; C, 65.13; H, 6.83; N, 6.33; O, 14.46; S, 7.25; Found: C, 65.14; H, 6.82; N, 6.34; S, 7.24.

General procedure for synthesis of (S)-2-amino-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (4)

The (*S*)-tert-butyl-3-(4-(benzyloxy)phenyl)-1-oxo-1-(thiazolidin-3-yl)propan-2-ylcarbamate (**3**) (55 g, 0.123 mol) and 15% aqueous hydrochloric acid solution (165 mL) in methanol (165 mL) was stirred at 50–55 °C for 8 h. Progress of reaction was monitored by TLC (DCM: MeOH: : 9:1). After reaction completion, water (550 mL) and DCM (220 mL) were added. The aqueous layer was collected in round bottom flask and product is extracted in DCM (275 mL) after adjusting pH 9–9.5 by using 10% aqueous sodium hydroxide solution. The organic layer was washed with 10% sodium chloride solution (275 mL) and concentrated under vacuum to obtain compound (**4**) as brown color thick sirup. (38 g, 90%); M.P.: 153–156 °C. IR (KBr, ν_{max}, cm^{-1}): 697.35 (C-S), 1177.79 (C-O), 1241.35 (C-N), 1455.76 (C = C), 2924.73 and 3030.45 (H-C-C = O), 3646.81 (N-H). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 7.41–7.32 (m, 5H; Ar-H), 7.11–7.09 (d, 2H, J = 8 Hz, Ar-H), 6.89–6.87 (d, 2H, J = 8 Hz, Ar-H), 5.14 (s, 2H, O-CH_2-Ar-H), 4.74–4.72 (t, 1H, J = 4 Hz, N-CH), 4.37 (s, 2H, N-CH_2-S of thiazolidine), 3.64–3.62 (t, 2H, J = 4 Hz, N-CH_2 of thiazolidine), 3.15–3.12 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar), 2.97–2.95 (t, 2H, J = 4 Hz, S-CH_2 of thiazolidine), 2.88–2.85 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar), 2.19 (s, 2H, NH_2). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 171.94, 159.26, 141.24, 133.57, 129.09, 127.44, 114.78, 78.10, 56.05, 55.13, 54.01, 39.00. ES-MS m/z 343.2 $(M+H)^+$. Analytical calculated formula for $C_{24}H_{30}N_2O_4S$: C, 65.13; H, 6.83; N, 6.33; O, 14.46; S, 7.25; Found: C, 66.66; H, 6.47; N, 8.19; S, 9.37.

General procedure for the synthesis compounds AAP-1 to AAP-10

To a 25 mL single neck round bottom flask, the (*S*)-2-amino-3-(4-(benzyloxy) phenyl)-1-(thiazolidin-3-yl) propan-1-one (**4**) (1.0 eq.) and aromatic aldehyde (0.98 eq.) in ethanol (5.0 times) were put in microwave reaction vessel equipment with magnetic stirrer and irradiated at 560 W for 2–3 min.[36] The reaction was monitored by TLC (DCM: MeOH: : 9:1). After completion of reaction, the cold water was added (20 times) in reaction mixture. The product was then extracted with DCM (5 times). The organic layer washed with 2% aqueous hydrochloric acid solution (3 times) and concentrated under vacuum and residue was allowed to suspend in IPE. It is, then, filtered and purified by column chromatography (mobile phase: Ethyl acetate: hexane: : 1:9) to obtain compounds **AAP-1** to **AAP-10**.

Characterization of synthesized compounds (AAP-1 to AAP-10)

(E)-2-(3-nitrobenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-1): White solid; (1.32 g, 95%); M.P.: 100–104 °C. IR (KBr, ν_{max}, cm^{-1}): 696.89 (C-S), 1174.17 (C-O), 1243.92 (C-N), 1366.41 & 1509.48 (NO_2), 1417.72 (C = C), 1638.52 (C = N), 2931.43 and 2766.70 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 8.55 (s, 1H, Ar-H of 3-nitrobenzene), 8.26–8.25 (d, 1H, J = 4 Hz, Ar-H of 3-nitrobenzene), 8.04 (s, 1H, N = CH), 8.02–8.01 (d, 1H, J = 4 Hz, Ar-H of 3-nitrobenzene), 7.56–7.54 (t, 1H, J = 4 Hz, Ar-H of 3-nitrobenzene), 7.42–7.31 (m, 5H, Ar-H), 7.11–7.09 (d, 2H, J = 8 Hz, Ar-H), 6.88–6.86 (d, 2H, J = 8 Hz, Ar-H), 5.04 (s, 2H; O-CH_2-Ar), 4.64–4.62 (t, 1H, J = 4 Hz, N-CH), 4.46 (s, 2H, N-CH_2-S of thiazolidine), 3.63–3.61 (t, 2H, J = 4 Hz, N-CH_2 of thiazolidine), 3.16–3.13 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar), 2.96–2.94 (t, 2H, J = 4 Hz, S-CH_2 of thiazolidine), 2.87–2.84 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.45, 160.41, 157.23, 148.58, 140.94, 139.58, 137.28, 135.02, 130.85, 129.07, 128.59, 128.00, 127.41, 123.99, 114.87, 73.87, 69.93, 49.12, 48.05, 38.71, 31.31. ES-MS m/z 477.3 $(M+H)^+$. Analytical calculated formula for $C_{26}H_{25}N_3O_4S$: C, 65.67; H, 5.30; N, 8.84; O, 13.46; S, 6.74; Found: C, 65.68; H, 5.30; N, 8.83; S, 6.73.

(E)-2-(4-hydroxybenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(hiazolidine-3-yl)propan-1-one (AAP-2): White solid; (1.24 g, 95%); M.P.:151–156 °C. IR (KBr, ν_{max}, cm^{-1}): 695.84 (C-S), 1175.59 (C-O), 1250.32 (C-N), 1382.03 (OH), 1454.29 (C = C), 1625.61 (C = N), 2956.99 and 2843.15 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 9.96 (s, 1H, OH), 8.02 (s, 1H, N = CH), 7.51–7.49 (d, 1H, J = 8 Hz, Ar-H of 4-hydroxybenzene), 7.42–7.31 (m, 5H, Ar-H), 7.10–7.08 (d, 2H, J = 8 Hz, Ar-H), 6.89–6.87 (d, 2H, J = 8 Hz, Ar-H), 6.80–6.78 (d, 1H, J = 8 Hz, Ar-H of 4-hydroxybenzene), 5.03 (s, 2H, O-CH_2-Ar), 4.65–4.63 (t, 1H, J = 4 Hz, N-CH), 4.45 (s, 2H, N-CH_2-S of thiazolidine), 3.63–3.61 (t, 2H, J = 4 Hz, N-CH_2 of thiazolidine), 3.14–3.11 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar), 2.94–2.92 (t, 2H, J = 4 Hz, S-CH_2 of thiazolidine), 2.84–2.81 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.44, 162.64, 160.55, 157.21, 137.23, 130.87, 130.15, 128.56, 127.94, 127.64, 127.23, 115.69, 114.66, 73.87, 69.93, 49.08, 48.09, 38.80, 31.28. ES-MS m/z 447.3 $(M+H)^+$. Analytical calculated formula for $C_{26}H_{26}N_2O_3S$: C, 69.93; H, 5.87; N, 6.27; O, 10.75; S, 7.18; Found: C, 69.94; H, 5.86; N, 6.26; S, 7.19.

(E)-2-(4-nitrobenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-3): White solid; (1.34 g, 97%); M.P.: 89–93 °C. IR (KBr, ν_{max}, cm^{-1}): 697.09 (C-S), 1174.77 (C-O), 1243.72 (C-N), 1369.47 & 1499.96 (NO_2), 1419.72 (C = C), 1688.02 (C = N), 2832.93 and 2726.72 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 8.29–8.28 (d, 2H, J = 4 Hz, Ar-H of 4-nitrobenzene), 8.04 (s, 1H, N = CH), 7.94–7.92 (d, 2H, J = 8 Hz, Ar-H of 4-nitrobenzene at position 2), 7.40–7.31 (m, 5H, Ar-H), 7.12–7.10 (d, 2H, J = 8 Hz, Ar-H), 6.88–6.86 (d, 2H, J = 8 Hz, Ar-H), 5.04 (s, 2H, CH_2-Ar), 4.63–4.61 (t, 1H, J = 4 Hz, N-CH), 4.46 (s, 2H, N-CH_2-S of thiazolidine), 3.67–3.64 (t, 2H, J = 6 Hz, N-CH_2 of thiazolidine), 3.20–3.17 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar), 2.94–2.92 (t, 2H, J = 4 Hz, S-CH_2 of thiazolidine), 2.85–2.82 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.41, 160.59, 157.23, 149.28, 140.94, 137.28, 130.85, 129.07, 128.59, 128.00, 127.41, 123.91, 114.88, 73.87, 69.93, 49.12, 48.05, 38.71, 31.31. ES-MS m/z 476.3 $(M+H)^+$. Analytical calculated formula for $C_{26}H_{25}N_3O_4S$: C, 65.67; H, 5.30; N, 8.84; O, 13.46; S, 6.74; Found: C, 65.66; H, 5.31; N, 8.85; S, 6.75.

(E)-2-(2,3-dimethoxybenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-4): White solid; (1.34 g, 94%); M.P.:199–203 °C; IR (KBr, ν_{max}, cm^{-1}): 696.87 (C-S), 1190.18 (C-O), 1258.35 (C-N), 1426.35 (C = C), 1648.35 (C = N), 2926.76 and 2832.40 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 8.06 (s, 1H, N = CH), 7.42–7.31 (m, 5H, Ar-H), 7.12–7.10 (d, 3H, J = 8 Hz, Ar-H (2H) and Ar-H (1H) of 2,3-dimethoxybenzene), 6.99–6.97 (d, 1H, J = 8 Hz, Ar-H of 2,3-dimethoxybenzene), 6.89–6.87 (d, 2H, J = 8 Hz, Ar-H), 6.68–6.66 (m, 1H, Ar-H of 2,3-dimethoxybenzene), 5.03 (s, 2H; O-CH_2-Ar), 4.64–4.62 (t, 1H, J = 4 Hz, N-CH), 4.47 (s, 2H, N-CH_2-S of thiazolidine), 3.78 (s, 6H, O-CH_3), 3.66–3.63 (t, 2H, J = 4 Hz, N-CH_2 of thiazolidine), 3.16–3.12 (dd, 1H, J = 4 Hz, 8 Hz, CH_2-Ar), 2.94–2.92 (t, 2H, J = 4 Hz, S-CH_2 of

thiazolidine), 2.87–2.84 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.40, 162.66, 157.45, 150.03, 137.02, 130.88, 129.95, 128.59, 127.47, 124.15, 123.01, 117.03, 114.75, 73.89, 69.62, 55.40, 49.18, 48.15, 38.90, 31.34. ES-MS *m/z* 491.3 $(M + H)^+$. Analytical calculated formula for $C_{28}H_{30}N_2O_4S$: C, 68.55; H, 6.16; N, 5.71; O, 13.04; S, 6.54; Found: C, 68.53; H, 6.15; N, 5.72; S, 6.54.

***(E)-2-(2-chlorobenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-5)*:** White solid; (1.30 g, 96%); M.P.:146–151 °C. IR (KBr, ν_{max}, cm^{-1}): 695.64 (C-S), 826.65 (Cl), 1177.61 (C-O), 1245.97 (C-N), 1427.73 (C = C), 1638.17 (C = N), 2933.37 and 2876.10 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 8.02 (s, 1H, N = CH), 7.63–7.60 (t, 2H, $J = 4$ Hz, Ar-H of 2-chlorobenzene), 7.40–7.32 (m, 7H, Ar-H (5H) and Ar-H (2H) of 2-chlorobenzene), 7.10–7.08 (d, 2H, $J = 8$ Hz, Ar), 6.87–6.85 (d, 2H, $J = 8$ Hz, Ar), 5.04 (s, 2H, CH_2-Ar), 4.65–4.63 (t, 1H, $J = 4$ Hz, N-CH), 4.45 (s, 2H, N-CH_2-S of thiazolidine), 3.63–3.61 (t, 2H, $J = 4$ Hz, N-CH_2 of thiazolidine), 3.14–3.11 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar), 2.94–2.92 (t, 2H, $J = 4$ Hz, S-CH_2 of thiazolidine), 2.84–2.81 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.51, 160.58, 157.51, 137.20, 136.96, 134.07, 130.83, 129.18, 128.93, 128.58, 127.96, 127.44, 114.79, 73.86, 69.93, 49.19, 48.12, 38.76, 31.32. ES-MS *m/z* 465.3 $(M + H)^+$. Analytical calculated formula for $C_{26}H_{25}ClN_2O_2S$: C, 67.16; H, 5.42; Cl, 7.62; N, 6.02; O, 6.88; S, 6.90; Found: C, 67.17; H, 5.43; N, 6.01; S, 6.91.

***(E)-2-(2-nitrobenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-6)*:** White solid; (1.36 g, 98%); M.P.: 165–169 °C. IR (KBr, ν_{max}, cm^{-1}): 697.00 (C-S), 1204.67 (C-O), 1242.99 (C-N), 1319.31 & 1514.17 (NO_2), 1419.72 (C = C), 1640.15 (C = N), 2946.03 and 2769.38 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 8.23–8.22 (d, 1H, $J = 4$ Hz, Ar-H of 2-nitrobenzene), 8.03 (s, 1H, N = CH), 7.90–7.88 (d, 1H, $J = 8$ Hz, Ar-H of 2-nitrobenzene), 7.80–7.72 (m, 2H, Ar-H, 2-nitrobenzene), 7.40–7.27 (m, 5H, Ar-H) 7.14–7.11 (d, 2H, $J = 12$ Hz, Ar-H), 6.89–6.87 (d, 2H, $J = 8$ Hz, Ar-H), 5.03 (s, 2H, CH_2-Ar), 4.66–4.64 (t, 1H, $J = 4$ Hz, N-CH), 4.46 (s, 2H, N-CH_2-S of thiazolidine), 3.67–3.65 (t, 2H, $J = 4$ Hz, N-CH_2 of thiazolidine), 3.19–3.15 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar), 3.01–2.98 (t, 2H, $J = 4$ Hz, S-CH_2 of thiazolidine), 2.92–2.89 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.59, 160.45, 157.28, 148.68, 137.30, 135.01, 132.07, 130.85, 129.07, 128.59, 127.41, 121.31, 114.87, 73.89, 69.98, 49.14, 48.05, 38.74, 31.28. ES-MS *m/z* 476.3 $(M + H)^+$. Analytical calculated formula for $C_{26}H_{25}N_3O_4S$: C, 65.67; H, 5.30; N, 8.84; O, 13.46; S, 6.74; Found: C, 65.65; H, 5.31; N, 8.83; S, 6.75.

***(E)-2-(2-hydroxy-4-methoxybenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-7)*:** White solid; (1.30 g, 93%); M.P. 134–138 °C. IR (KBr, ν_{max}, cm^{-1}): 696.24 (C-S), 1172.19 (C-O), 1237.91 (C-N), 1375.61 (OH), 1444.35 (C = C), 1641.95 (C = N), 2933.67 and 2880.30 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 10.04 (s, 1H, OH), 8.07 (s, 1H, N = CH), 7.42–7.30 (m, 6H Ar-H (5H) and Ar-H (1H) of 2-hydroxy-4-methoxybenzene), 7.10–7.06 (d, 2H, $J = 8$ Hz, Ar), 6.90–6.88 (d, 2H, $J = 8$ Hz, Ar), 6.42–6.41 (d, 1H, $J = 4$ Hz, Ar-H of 2-hydroxy-4-methoxybenzene), 6.28 (s, 1H, Ar-H of 2-hydroxy-4-methoxybenzene), 5.04 (s, 2H, CH_2-Ar), 4.64–4.62 (t, 1H, $J = 4$ Hz, N-CH), 4.46 (s, 2H, N-CH_2-S of thiazolidine), 3.76 (s, 3H, O-CH_3), 3.64–3.62 (t, 2H, $J = 4$ Hz, N-CH_2 of thiazolidine), 3.15–3.12 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar), 2.96–2.93 (t, 2H, $J = 4$ Hz, S-CH_2 of thiazolidine), 2.86–2.83 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.54, 165.56, 163.75, 160.70, 157.64, 136.92, 133.13, 130.64, 128.58, 127.97, 127.45, 116.89, 114.94, 106.77, 101.11, 74.02, 69.95, 55.43, 49.13, 48.12, 38.74, 31.34. ES-MS *m/z* 477.1 $(M + H)^+$. Analytical calculated formula for $C_{27}H_{28}N_2O_4S$: C, 68.04; H, 5.92; N, 5.88; O, 13.43; S, 6.73; Found: C, 68.05; H, 5.92; N, 5.87; S, 6.74.

***(E)-2-(3-hydroxybenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-8)*:** White solid; (1.26 g, 96%); M.P.: 106–108 °C. IR (KBr, ν_{max}, cm^{-1}): 695.34 (C-S), 1175.59 (C-O), 1257.32 (C-N), 1382.23 (OH), 1454.22 (C = C), 1636.61 (C = N), 2959.29 and 2893.95 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 9.59 (s, 1H, OH), 8.06 (s, 1H,

N = CH), 7.42–7.31 (m, 5H, Ar-H), 7.24–7.21 (m, 1H, Ar-H of 3-hydroxybenzene), 7.12–7.09 (m, 3H, Ar-H (2H) and Ar-H (1H) of 3-hydroxybenzene), 7.05–7.03 (d, 1H, $J = 8$ Hz, Ar-H of 3-hydroxybenzene), 6.88–6.86 (d, 3H, $J = 8$ Hz, Ar-H (2H) and Ar-H (1H) and Ar-H (1H) of 3-hydroxybenzene), 5.04 (s, 2H, CH_2-Ar), 4.64–4.62 (t, 1H, $J = 4$ Hz, N-CH), 4.46 (s, 2H, N-CH_2-S of thiazolidine), 3.64–3.62 (t, 2H, $J = 4$ Hz, N-CH_2 of thiazolidine)), 3.16–3.13 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar), 2.95–2.93 (t, 2H, $J = 4$ Hz, S-CH_2 of thiazolidine), 2.87–2.84 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.38, 161.94, 160.37, 157.23, 137.29, 130.77, 130.19, 128.60, 127.97, 127.64, 127.27, 120.27, 115.99, 114.69, 73.87, 69.63, 49.08, 48.09, 38.80, 31.28. ES-MS *m/z* 447.5 $(M + H)^+$. Analytical calculated formula for $C_{26}H_{26}N_2O_3S$: C, 69.93; H, 5.87; N, 6.27; O, 10.75; S, 7.18; Found: C, 69.93; H, 5.86; N, 6.28; S, 7.19.

***(E)-2-(3-methoxybenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-9)*:** White solid; (1.28 g, 95%); M.P.: 176–180 °C. IR (KBr, ν_{max}, cm^{-1}): 696.74 (C-S), 1170.35 (C-O), 1248.72 (C-N), 1426.81 (C = C), 1639.34 (C = N), 2932.67 and 2876.41 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 8.07 (s, 1H, N = CH), 7.62–7.61 (d, 2H, $J = 4$ Hz, Ar-H of 3-methoxybenzene), 7.42–7.31 (m, 5H, Ar-H), 7.10–7.07 (d, 3H, $J = 12$ Hz, Ar-H (2) and Ar-H (1H) of 3-methoxybenzene), 6.99–6.97 (d, 2H, $J = 8$ Hz, Ar-H of 3-methoxybenzene), 6.90–6.88 (d, 2H, $J = 8$ Hz, Ar-H), 5.03 (s, 2H, CH_2-Ar), 4.64–4.62 (t, 1H, $J = 4$ Hz, N-CH), 4.45 (s, 2H, N-CH_2-S of thiazolidine), 3.77 (s, 3H, O-CH_3), 3.65–3.63 (t, 2H, $J = 4$ Hz, N-CH_2 of thiazolidine), 3.16–3.12 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar), 2.95–2.92 (t, 2H, $J = 4$ Hz, S-CH_2 of thiazolidine), 2.86–2.84 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.48, 162.60, 157.44, 137.03, 130.82, 130.05, 128.56, 127.93, 127.45, 124.15, 114.72, 113.99, 73.81, 69.64, 55.39, 49.17, 48.25, 38.88, 31.33. ES-MS *m/z* 461.3 $(M + H)^+$. Analytical calculated formula for $C_{27}H_{28}N_2O_3S$: C, 70.41; H, 6.13; N, 6.08; O, 10.42; S, 6.96; Found: C, 70.42; H, 6.12; N, 6.06; S, 6.97.

***(E)-2-(2-fluorobenzylideneamino)-3-(4-(benzyloxy)phenyl)-1-(thiazolidin-3-yl)propan-1-one (AAP-10)*:** Dark brown solid (1.21 g, 92%); M.P.: 99–102 °C. IR (KBr, ν_{max}, cm^{-1}): 695.89 (C-S), 1197.70 (Ar-F), 1227.79 (C-O), 1252.08 (C-N), 1427.93 (C = C), 1628.99 (C = N), 2999.13 and 2973.18 (H-C-C = O). ^{1}H NMR (400 MHz, DMSO-d6, δ ppm): 8.11 (s, 1H, N = CH), 7.82–7.81 (d, 1H, $J = 4$ Hz, Ar-H of 2-fluorobenzene), 7.44–7.30 (m, 5H, Ar-H), 7.22–7.17 (m, 1H, Ar-H of 2-fluorobenzene), 7.10–7.05 (m, 3H, Ar-H (2H) and Ar-H (1H) of 2-fluorobenzene), 6.88–6.86 (d, 3H, $J = 8$ Hz, Ar-H (2H) and Ar-H (1H) of 2-fluorobenzen), 5.00 (s, 2H, CH_2-Ar), 4.63–4.61 (t, 1H, $J = 4$ Hz, N-CH), 4.46 (s, 2H, N-CH_2-S of thiazolidine), 3.65–3.63 (t, 2H, $J = 4$ Hz, N-CH_2 of thiazolidine), 3.16–3.13 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar), 2.95–2.93 (t, 2H, $J = 4$ Hz, S-CH_2 of thiazolidine), 2.87–2.84 (dd, 1H, $J = 4$ Hz, 8 Hz, CH_2-Ar). ^{13}C-NMR (125 MHz, DMSO-d6, δ ppm): 169.43, 160.39, 157.23, 137.27, 131.28, 130.79, 128.67, 127.96, 127.64, 127.29, 124.08, 120.27, 116.20, 73.88, 69.79, 49.10, 48.11, 38.81, 32.08. ES-MS *m/z* 449.2 $(M + H)^+$. Analytical calculated formula for $C_{26}H_{25}FN_2O_2S$: C, 69.62; H, 5.62; F, 4.24; N, 6.25; O, 7.13; S, 7.15; Found: C, 69.63; H, 5.63; N, 6.25; S, 7.15.

Biological activity procedure

Minimum inhibitory concentration

The ready-made Tryptic Soya broth and Malt extract broth medium (30 g) was suspended in distilled water (100 mL) and warmed until it dissolved completely. The test tube as well as medium tubes were autoclaved at a pressure of 1.0 bar for 30 min. A set of sterilized test tubes with Tryptic Soya broth and Malt extract broth medium was capped with cotton plugs. The newly synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) and in first test tube added 100 µg/mL concentration of the newly synthesized compounds and which was serially diluted. A fixed volume of 0.5 mL of overnight culture was added in all the test tubes which were incubated at 37 °C for 24 h. After 24 h these tubes were measured for turbidity. For the antifungal assay, the ready-made Muller Hinton agar medium (30 g) was suspended in distilled water (100 mL) and

warmed until it dissolved completely. The medium and glass petri dishes were autoclaved at a pressure of 1.0 bar for 30 min. under sterilized conditions in a Laminar flow chamber; the medium was poured into sterile petri dishes. The 0.5 mL of the culture of fungal spore suspension was injected and uniformly spread over the agar surface with a sterile glass rod. The newly synthesized compounds solution were prepared in DMSO. After inoculation, cups were lifted out with 6-mm sterile cork borer and the lids of the dishes were replaced. To each cup, different concentrations of test solution of each synthesized compounds were added. Controls were maintained with DMSO and fluconazole. The treated and the controls were kept at 27–28 °C for 60–84 h. The minimum inhibitory concentration (MIC) was recorded in μg/mL. Three to four replicates were maintained for each treatment.

Molecular docking

Molecular docking of the protein–ligand complexes was executed with the help of AutoDock Vina (http://vina.scripps.edu) software. PDB sum and CASTp servers used for identification of ligand-binding site of each complex. This process was used to make binding of its crystal with ligand in a similar region to avoid the binding with other areas. With the help of AutoDock tools the ligand coordinates and protein were separated from each complex, the ligand structures and protein were processed to a format as pdbqt files (Recognized by ADT), by adding Gasteiger charges, all hydrogen atoms and merging the non-polar hydrogen atoms. By using babel in AutoDock the hydrogens are added to the receptor and ligand structures. The AutoDock, an inbuilt tool in the ADT were used for determined by the number of torsions for the ligand. The torsional root for the ligand molecule is usually branches with rotatable bonds surface of rigid part of the ligand molecule. The AutoDock frequently tries to detect the root for the molecule unless the user specifies it. In this process, AutoDock was automatically selected its root. As per the information from the PDB sum and CastP servers the grid box was sited. Auto grid were computed the atom specific affinity maps for all ligand atom types, electrostatic and desolvation potentials. The docking simulation consisted of 100 iterations by Genetic Algorithm methods for every protein ligand pair. Lamarckian Genetic Algorithm, local search method in AutoDock was used to set population size 150 with 25 million energy evaluations. All the other factors like the number of generations, the maximum number of top individuals to persist to the next generation, the crossover rate and mutation rate were set to their default value. The binding energy was analysis after total minimum energy resulting from the 100 docking runs.

Acknowledgements

This research work is dedicated to my dear father late Mr. Ashok Trambak Pund and friends late Mr. Somanath Darkunde and late Dr. Nilesh Patil. Authors are thankful to Principal, Shivaji Arts, Commerce and Science College Kannad, District Aurangabad (M.S.) for availing research laboratory and FTIR facilities. Authors also thankful to Mr. Prathmesh Pramod Deshpande for support and Mr. Vijay Maskar, Sprint testing solution, Mumbai for characterization of samples.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Amit A. Pund http://orcid.org/0000-0002-3406-6783
Suresh T. Gaikwad http://orcid.org/0000-0002-3212-4185
Mazahar Farooqui http://orcid.org/0000-0003-2236-6639
Rajashri A. Pund-Nale http://orcid.org/0000-0002-0967-7777

Mubarak H. Shaikh http://orcid.org/0000-0002-1190-2371
Baban K. Magare http://orcid.org/0000-0001-6719-0441

References

1. Y. Hu, Z. Xu, S. Zhang, Wu Xiang, D. Jun-Wei, Lv Zao-Sheng, and F. Lian-Shun, "Recent Developments of Coumarin-Containing Derivatives and Their Anti-Tubercular Activity," *European Journal of Medicinal Chemistry* 136 (2017): 122–30. doi:10.1016/j.ejmech.2017.05.004.
2. S. Musrat, S. Ayushi, S. Jay, A. Dinesh, and A. Shikha, "Saturated Five-Membered Thiazolidines and Their Derivatives: From Synthesis to Biological Applications," *Topics in Current Chemistry* 378, no. 2 (2020): 1–90.
3. M. Nasr, M. Gineinah, and E. El-Bendary, "Synthesis and In Vitro Antibacterial Evaluation of Novel Imidazo[2',1':5,1]-1,2,4-Triazolo[4,3-c]-Quinazoline Derivatives Of 5-Thioxo-1, 2, 4-Triazole, 4-Oxothiazolidine, and Their Open-Chain Counterparts," *Archiv Der Pharmazie* 336, no. 12 (2003): 560–6. doi:10.1002/ardp.200300809.
4. B. Belleau, L. Brasili, L. Chan, M. DiMarco, B. Zacharie, N. Nguyen-Ba, H. Jenkinson, J. Coates, and J. Cameron, "A Novel Class of 1, 3-Oxathiolane Nucleoside Analogues Having Potent Anti-HIV Activity," *Bioorganic & Medicinal Chemistry Letters* 3, no. 8 (1993): 1723–8. doi:10.1016/S0960-894X(00)80050-5.
5. M. Peterson and R. Vince, "Synthesis and Biological Evaluation of 4-Purinylpyrrolidine Nucleosides," *Journal of Medicinal Chemistry* 34, no. 9 (1991): 2787–97. doi:10.1021/jm00113a017.
6. K. Obydennov, A. Khamidullina, A. Galushchinskiy, A. Shatunova, M. Kosterina, T. Kalinina, Z. Fan, T. Glukhareva, and Y. Morzherin, "Discovery of Methyl (5 Z)-[2-(2,4,5-Trioxopyrrolidin-3-ylidene)-4-Oxo-1,3-Thiazolidin-5-Ylidene]Acetates as Antifungal Agents against Potato Diseases," *Journal of Agricultural and Food Chemistry* 66, no. 24 (2018): 6239–45. doi:10.1021/acs.jafc.8b02151.
7. V. Solomon, W. Haq, K. Srivastava, S. Puri, and B. Katti, "Synthesis and Antimalarial Activity of Side Chain Modified 4-Aminoquinoline Derivatives," *Journal of Medicinal Chemistry* 50, no. 2 (2007): 394–8. doi:10.1021/jm061002i.
8. M. Barreca, A. Chimirri, L. Luca, A. Monforte, P. Monforte, A. Rao, M. Zappala, J. Balzarini, E. Clercq, C. Pannecouque, et al. "Discovery of 2,3-Diaryl-1,3-Thiazolidin-4-Ones as Potent Anti-HIV-1 Agents," *Bioorganic & Medicinal Chemistry Letters* 11, no. 13 (2001): 1793–6. doi:10.1016/S0960-894X(01)00304-3.
9. N. Fuloria, V. Singh, M. Shaharyar, and M. Ali, "Synthesis, Characterization and Biological Studies of New Schiff Bases and Azetidinone Derived from Propionic Acid Derivatives," *Asian Journal of Chemistry*. 20, no. 8 (2008): 6457–62.
10. G. Kucukguzel, A. Kocatepe, E. Clercq, F. Sahin, and M. Gulluce, "Synthesis and Biological Activity of 4-Thiazolidinones, Thiosemicarbazides Derived from Diflunisal Hydrazide," *European Journal of Medicinal Chemistry* 41, no. 3 (2006): 353–9. doi:10.1016/j.ejmech.2005.11.005.
11. Ş. G. Küçükgüzel, E. E. Oruç, S. Rollas, F. Şahin, and A. Özbek, "Synthesis, Characterization and Biological Activity of Novel 4-Thiazolidinones, 1,3,4-Oxadiazoles and Some Related Compounds," *European Journal of Medicinal Chemistry* 37, no. 3 (2002): 197–206. doi:10.1016/S0223-5234(01)01326-5.
12. P. Vicini, A. Geronikaki, K. Anastasia, M. Incerti, and F. Zani, "Cyclobutane Derivatives as Potent NK1 Selective Antagonists," *Bioorganic & Medicinal Chemistry Letters* 16, no. 14 (2006): 3859–64.
13. K. V. G. C. Sekhar, V. S. Rao, A. S. Reddy, R. Sunandini, and V. S. A. Kumar Satuluri, "Solvent Free Microwave Accelerated Synthesis of Heterocyclic Thiazolidin-4-Ones as Anti-Microbial and Anti-Fungal Agents," *Bulletin of the Korean Chemical Society* 31, no. 5 (2010): 1219–22. doi:10.5012/bkcs.2010.31.5.1219.
14. B. M. Gurupadayya, M. Gopal, B. Padmashali, and Y. N. Manohara, "Synthesis and Pharmacological Evaluation of Azetidin-2-Ones and Thiazolidin-4-Ones Encompassing Benzothiazole," *Indian Journal of Pharmaceutical Sciences* 70, no. 5 (2008): 572–7. doi:10.4103/0250-474X.45393.
15. D. Visagaperumal, K. Jaya, R. Vijayaraj, and N. Anbalgan, "Microwave Induced Synthesis of Some New 3-Substituted-1,3-Thiazolidin-4-Ones for Their Potent Anti-Microbial and Antitubercular Activities," *International Journal of ChemTech Research* 1, no. 4 (2009): 1048–51.
16. J. East, A. Kennedy, J. Tomsig, A. De Leon, K. Lynch, and T. Macdonald, "Synthesis and Structure-Activity Relationships of Tyrosine-Based Inhibitors of Autotaxin (ATX)," *Bioorganic & Medicinal Chemistry Letters* 20, no. 23 (2010): 7132–6. doi:10.1016/j.bmcl.2010.09.030.
17. J. Cobb, S. Blanchard, E. Boswell, K. Brown, P. Charifson, J. Cooper, J. Collins, M. Dezube, B. Henke, E. Hull-Ryde, et al. " N-(2-Benzoylphenyl)-L-Tyrosine PPARgamma Agonists. 3. Structure-Activity Relationship and Optimization of the N-Aryl Substituent," *Journal of Medicinal Chemistry* 41, no. 25 (1998): 5055–69. doi:10.1021/jm980414r.
18. A. Pund, S. Saboo, G. Sonawane, A. Dukale, and B. Magare, "Synthesis of 2,5-Disubstituted-1,3,4-Thiadiazole Derivatives from (2S)-3-(Benzyloxy)-2-[(Tert-Butoxycarbonyl)Amino] Propanoic Acid and Evaluation of Anti-Microbial Activity," *Synthetic Communications* 50, no. 24 (2020): 3854–64. doi:10.1080/00397911.2020.1817488.

19. B. Kahveci, O. Bekircan, and S. Karaoglu, "Synthesis and Anti-Microbial Activity of Some 3-Alkyl-4-(Arylmethyleneamino)-4,5-Dihydro-1*H*-1,2,4-Triazol-5-Ones," *Indian Journal of Chemistry* 40, no. B (2005): 2614–7.
20. O. Bekircan, B. Kahveci, and M. Kucuk, "Synthesis and Anticancer Evaluation of Some New Unsymmetrical 3,5-Diaryl-4*H*-1,2,4-Triazole Derivatives," *Turkish Journal of Chemistry* 30 (2006): 29–40.
21. M. Singh, and C. Dash, "Synthesis of Some New Schiff Bases Containing Thiazole and Oxazole Nuclei and Their Fungicidal Activity," *Pesticides* 22, no. 11 (1988): 33–7.
22. S. Holla, K. Shivananda, S. Shenoy, and G. Antony, "Studies on Aryl Furan Derivatives: Part VII. Synthesis and Characterization of Some Mannich Bases Carrying Halophenylfuryl Moieties as Promising Antibacterial Agents," *Farmaco* 53 (1998): 531–5.
23. S. Holla, B. Veerendra, K. Shivananda, and B. Poojary, "Synthesis Characterization and Anticancer Activity Studies on Some Mannich Bases Derived from 1,2,4-Triazoles," *European Journal of Medicinal Chemistry* 38, no. 7–8 (2003): 759–67. doi:10.1016/S0223-5234(03)00128-4.
24. E. Gokce, G. Bakir, F. Sahin, E. Kupeli, and E. Yesilada, "Synthesis of New Mannich Bases of Arylpyridazinones as Analgesic and Anti-Inflammatory Agents," *Arzneimittel Forschung* 55 (2005): 318–25.
25. R. Dimmock, S. Jonnalagadda, A. Phillips, E. Erciyas, K. Shyam, and A. Semple, "Anticonvulsant Properties of Some Mannich Bases of Conjugated Arylidene Ketones," *Journal of Pharmaceutical Sciences* 81, no. 5 (1992): 436–40. doi:10.1002/jps.2600810509.
26. F. Lopes, R. Capela, J. O. Gonçaves, P. N. Horton, M. B. Hursthouse, J. Iley, C. M. Casimiro, J. Bom, and R. Moreira, "Amidomethylation of Amodiaquine: Antimalarial N-Mannich Base Derivatives," *Tetrahedron Letters* 45, no. 41 (2004): 7663–6. doi:10.1016/j.tetlet.2004.08.093.
27. J. Knabe, P. Buch, and W. Schmit, "Derivatives of Barbituric Acid Cytostatic and CNS Activities of Chiral Barbiturate Mannich-Bases," *Archiv Der Pharmazie* 316, no. 12 (1983): 1051–3. doi:10.1002/ardp.19833161216.
28. R. Islam, J. Abedin, M. Hossain, and H. Duddeck, "Synthesis of 1-Methyl Bis-Dioxopyrolino [2,3:2,3:2,3:6,5] Benzene and Its Heterocycles via Thiocarbohydrazone, Thiosemicarbazone," *Journal of the Bangladesh Chemical Society* 11 (1998): 71–8.
29. E. Michel, H. John, and T. Elizabeth, "FAP Inhibitors," (WO2007085895A2, filed August 31, 2006, and issued August 02, 2007).
30. N. Andersen, J. Cadahia, V. Previtali, J. Bondebjerg, C. Hansen, A. Hansen, T. Andresen, and M. Clausen, "Methotrexate Prodrugs Sensitive to Reactive Oxygen Species for the Improved Treatment of Rheumatoid Arthritis," *European Journal of Medicinal Chemistry* 156 (2018): 738–46. doi:10.1016/j.ejmech.2018.07.045.
31. C. Decicco and P. Grover, "Total Asymmetric Synthesis of the Potent Immunosuppressive Marine Natural Product Microcolin A," *The Journal of Organic Chemistry* 61, no. 10 (1996): 3534–41. doi:10.1021/jo952123l.
32. N. Kumar, S. Devineni, K. Aggile, P. Gajjala, P. Kumar, and S. Dubey, "Facile New Industrial Process for Synthesis of Teneligliptin through New Intermediates and Its Optimization with Control of Impurities," *Research on Chemical Intermediates* 44, no. 1 (2018): 567–84. doi:10.1007/s11164-017-3120-3.
33. T. Yoshida, F. Akahoshi, H. Sakashita, H. Kitajima, M. Nakamura, S. Sonda, M. Takeuchi, Y. Tanaka, N. Ueda, S. Sekiguchi, et al. "Discovery and Preclinical Profile of Teneligliptin (3-[(2S,4S)-4-[4-(3-Methyl-1-Phenyl-1H-Pyrazol-5-yl)Piperazin-1-yl]Pyrrolidin-2-Ylcarbonyl]Thiazolidine): A Highly Potent, Selective, Long-Lasting and Orally Active Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type 2 Diabetes," *Bioorganic & Medicinal Chemistry* 20, no. 19 (2012): 5705–19. doi:10.1016/j.bmc.2012.08.012.
34. A. Karmakar, M. Basha, G. Babu, M. Botlagunta, N. Malik, R. Rampulla, A. Mathur, and A. Gupta, "Tertiary-Butoxycarbonyl (Boc)-A Strategic Group for *N*-Protection/Deprotection in the Synthesis of Various Natural/Unnatural *N*-Unprotected Aminoacid Cyanomethyl Esters," *Tetrahedron Letters* 59, no. 48 (2018): 4267–71. doi:10.1016/j.tetlet.2018.10.041.
35. O. Bekircan and H. Bektas, "Synthesis of Schiff and Mannich Bases of Isatin Derivatives with 4-Amino-4,5-Dihydro-1*H*-1,2,4-Triazole-5-Ones," *Molecules (Basel, Switzerland)* 13, no. 9 (2008): 2126–35. doi:10.3390/molecules13092126.
36. H. Jiyaul, S. Vandana, C. Dheeraj, L. Hassane, and Q. Mumtaz, "Microwave-Induced Synthesis of Chitosan Schiff Bases and Their Application as Novel and Green Corrosion Inhibitors, Experimental and Theoretical Approach," *ACS Omega* 3 (2018): 5654–68.
37. K. Campbell, C. Helbing, M. Florkowsk, and B. Campbell, "The Reaction of Grignard Reagents with Schiff Bases," *Journal of the American Chemical Society* 70, no. 11 (1948): 3868–70. doi:10.1021/ja01191a099.
38. S. Magaldi, C. Mata-Essayag, C. Capriles, C. Perez, M. Colella, C. Olaizola, and Y. Ontiveros, "Well Diffusion for Antifungal Susceptibility Testing," *International Journal of Infectious Diseases* 8, no. 1 (2004): 39–45. doi:10.1016/j.ijid.2003.03.002.
39. M. Ahmed, "Acute Toxicity (Lethal Dose 50 Calculation) of Herbal Drug Somina in Rats and Mice," *Pharmacology & Pharmacy* 06, no. 03 (2015): 185–9. doi:10.4236/pp.2015.63019.
40. S. Zhang, Y. Luo, L. He, Z. Liu, A. Jiang, Y. Yang, and H. Zhu, "Synthesis, Biological Evaluation, and Molecular Docking Studies of Novel 1,3,4-Oxadiazole Derivatives Possessing Benzotriazole Moiety as FAK