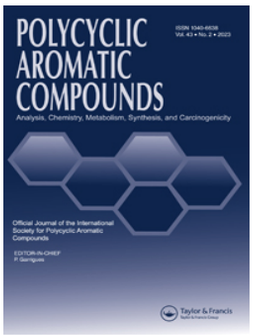

Polycyclic Aromatic Compounds

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Pyridine-1,3,4-Thiadiazole-Schiff Base Derivatives, as Antioxidant and Antimitotic Agent: Synthesis and *in Silico* ADME Studies

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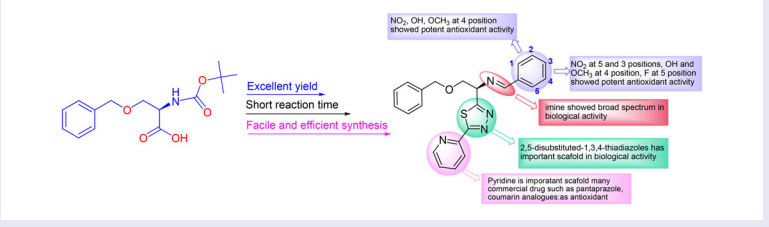
ABSTRACT

An efficient method developed for the synthesis of asymmetric *(S)*-N-benzylidene-2-(benzyloxy)-1-(5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)ethanamine derivatives with excellent yield in short reaction time. The antioxidant and antimitotic activities were estimated and strongly correlated with the potential of Ascorbic acid and Methotrexate respectively. All the synthesized molecules were characterized using various spectral techniques including FTIR, ^{1}H NMR, ^{13}C NMR, and Mass spectrometry. The drug-likeness properties were studied using *in silico* ADME parameters. All the compounds have an acceptable range of values which indicated good drug-like characteristics based on Lipinski's rule of five and to be orally active. The present method is quite easy along with simple operation and offers many benefits including short reaction time, easy work-up, excellent yield, reduced waste production as well as cost effective. In addition structure-activity relationships of **AP-1** to **AP-10** derivatives have been described.



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Antioxidant; antimitotic; asymmetric synthesis; *in silico* ADME parameters; structure-activity relationships

Introduction

The heterocyclic compounds with five-membered heterocylic ring have acquired impressive interest on account of their wide scope of helpful pharmacological properties. Amongst these five membered heterocyclic compounds, 2,5-disubstituted-1,3,4-thiadiazoles are associated with diverse biological activities probably due to the presence of –N = C–S– group. The backbone of these

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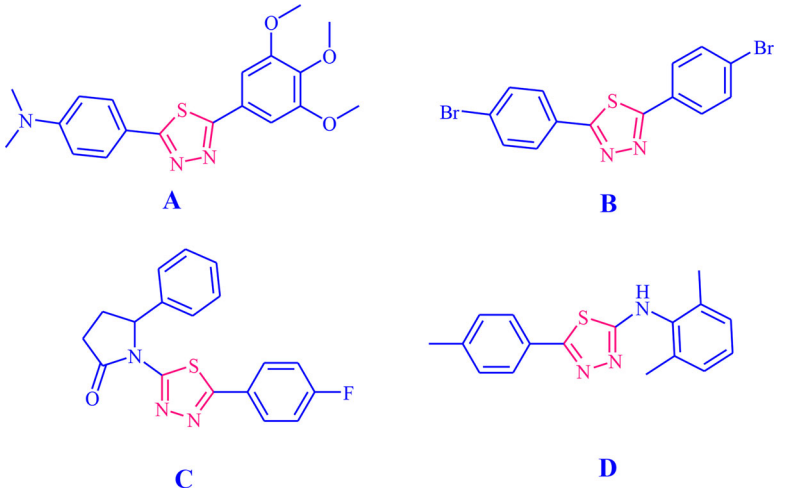


Figure 1. 1,3,4-Thiadiazole heterocycles containing reported molecules.

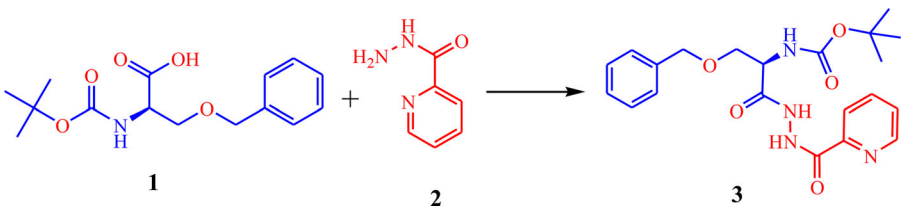
article is the combination of biologically active scaffolds containing pyridine, 1,3,4-thiadiazole and imine moiety. The 1,3,4-thiadiazoles ring system is widely distributed in a broad variety of important compounds with significant pharmacological properties such as antitubercular,[1] antimicrobial,[2] antifungal,[3] antiparasitic,[4] antiviral,[5] anti-inflammatory and analgesic,[6] COX and LOX inhibitory activities,[7] antiproliferative,[8] anticonvulsant,[9] antidepressant,[10] epilepsy,[11] Parkinson's disease.[12] Thiadiazole containing drugs like Acetazolamide, Methazolamide, Cefazolin, Sulfamethizole and Megazol are available in market.[13] Furthermore, an azomethine group exhibited broad spectrum in pharmacological properties, perhaps engaged with the formation of a hydrogen bond with the active canters of cell constituents and interferes in normal cell metabolism.[14a-j]

Moreover, antimitotic agents are classified into three major classes. First one is microtubule-stabilizing agents, these agents prevent the depolymerization of tubulin subunits through binding with fully formed microtubules. The remaining two other classes functioning by binding to tubulin monomers and inhibiting their polymerization into microtubules.[15] Noteworthy, the 2,5-disubstituted-1,3,4-thiadiazole moiety is the backbone in many drugs including antimitotic agents 4-(5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-yl)-N,N-dimethylbenzenamine(**A**),[16] antioxidant agent 2,5-bis(4-bromophenyl)-1,3,4-thiadiazole (**B**),[17] 1-(5-(4-fluorophenyl)-1,3,4-thiadiazol-2-yl)-5-phenylpyrrolidin-2-one (**C**),[18] N-(2,6-dimethylphenyl)-5-p-tolyl-1,3,4-thiadiazol-2-amine (**D**)[19] (Figure 1).

There are numerous reports have been available for the construction of thiadiazole and Schiff's base molecules, the synthesis of 2,5-disubstituted thiadiazole containing imine moiety are rare.

As a part of our ongoing work and in view of above challenges, previously we reported the synthesis of asymmetric *(S)-N*-benzylidene-2-(benzyloxy)-1-(5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)ethanamine derivatives (**AP-1** to **AP-10**) *via* amide coupling using *N,N'*-carbonyldiimidazole (CDI) and evaluated *in vitro* anti-microbial activities.[20] The formation of 2,5-disubstituted-1,3,4-thiadiazole ring could be possible by cyclocondensation of diacyl hydrazine using Lawesson's Reagent (LR) or phosphorus pentasulfide[21] as thionating agent in the presence of tetrahydrofuran (THF) and toluene as solvent. This reaction is always carried out in warm condition and yield of product is moderate and it is very difficult to maintain purity due to harsh reaction conditions such as temperature and workup.

The amide coupling of hydrazide and acid moiety to afford diacylhydrazine have been reported using 1-ethyl-3-(3-imethlaminopropyl) carbodiimide hydrochloride (EDC.HCl)[22a-g] which requires column chromatography for purification. Another reagent 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU)[23a-b] has identified to react with acid and



Scheme 1. Synthesis of diacyl hydrazine (**3**)

hydrazide but yield of isolated product is not reasonable. Moreover,*N,N*'-diisopropylcarbodiimide (DIPC)[24a-b] and thionyl chloride[25a-b] were used as coupling reagents for the same reaction of hydrazide and acid but removal of unreacted *N,N*-diisopropyl carbodiimide and thionyl chloride was quite difficult. The CDI[26a-c] was also used for coupling to obtain amide bond and unreacted CDI can be removed with water. By taking the advantage of above reactions we have reported efficient synthesis of the target compounds (**AP-1** to **AP-10**) using condensation of (*S*)-2-(benzyloxy)-1-[5-(pyridin-2-yl)-[1,3,4]-thiadiazol-2yl]ethanamine (**4**) with substituted benzaldehyde in isopropyl alcohol (IPA). The purified product was isolated by simple acidification of 2% aqueous hydrochloric acid with simple workup operation, excellent yield in short reaction time.

Result and discussion

In continuation of our earlier work[20] herein, we focused on facile and efficient synthesis of 1,2,3-thiadiazole-imine hybrids with excellent yield in short reaction time. This is facile, efficient and environmentally benign green protocol which avoids use of strong dehydrating agents, generation of wastes. Moreover, targeted compounds (**AP-1** to **AP-10**) were evaluated for *in vitro* antioxidant and antimitotic activities. In addition to this, we performed *in silico* ADME prediction for the synthesized compounds. The target compounds were prepared in four steps from the commercially available cheap and potentially active starting material *N*-boc-*O*-benzyl-*L*-serine amino acid (**1**).

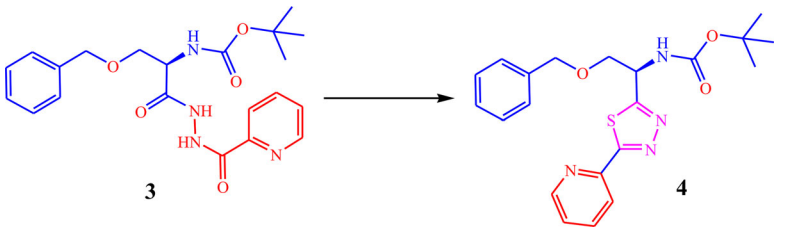
Initially, the coupling of acid (**1**) and hydrazide (**2**) to form diacyl hydrazine (**3**) have been investigated using EDC.HCl, *N*-Methylmorpholine (NMM) and hydroxybenzotriazole (HOBt) in the presence of DMF (Scheme 1). In order to optimize the reaction conditions, initially we carried out the reaction between acid (**1**) and hydrazide (**2**) as a model reaction. Optimum reaction conditions for the synthesis of **3** was designed and developed using various type of coupling reagents, different temperature, time and solvents (Table 1).

The coupling of **1** and **2** to form **3** is possible at 20–30 °C optimum temperature. Initially, Steglich esterification carried out using DCC and reaction was completed in 3 h with 85% yield of product (Table 1, entry 1). During this coupling reaction, dicyclohexylurea (DCU) was formed as a by-product. After completion of the reaction it was very difficult to remove DCU and unreacted DCC from the product. Moreover, we used another amide coupling reagent, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxidehexafluorophosphate (HATU) and required 6 h for the completion of reaction to get 90.2% yield (Table 1, entry 2). Furthermore another coupling reagent CDI was used and the product was formed in 1 h with 96% yield (**Table 1**, **entry 3**). Finally, the amide coupling was carried out by using EDC. HCl. The reaction was completed in 30 min with maximum yield of product (97%), mild reaction conditions and easy work up procedure (Table 1, entry 4). It was simply isolated by filtration and by-product EDC urea and unreacted EDC. HCl washed out in mother liquor.

In next step, cyclization of **3** was carried out in the presence of Lowesson's reagent (LR) and phosphorus pentasulfide to form 2,5-disubstituted-1,3,4-thiadiazole ring (Scheme 2).

Table 1. Screening of different coupling reagent and their effect on reaction time and yield on the synthesis of **3**.

Sr. No.	Coupling agent	Reaction time	% Yield for Compound **3**
1	DCC	3 h	85.3%
2	HATU	6 h	90.2%
3	CDI	1 h	96%
4	EDC.HCl	30 min	97%



Scheme 2. Synthesis of 2,5-disubstituted, 1,3,4-thiadiazole ring

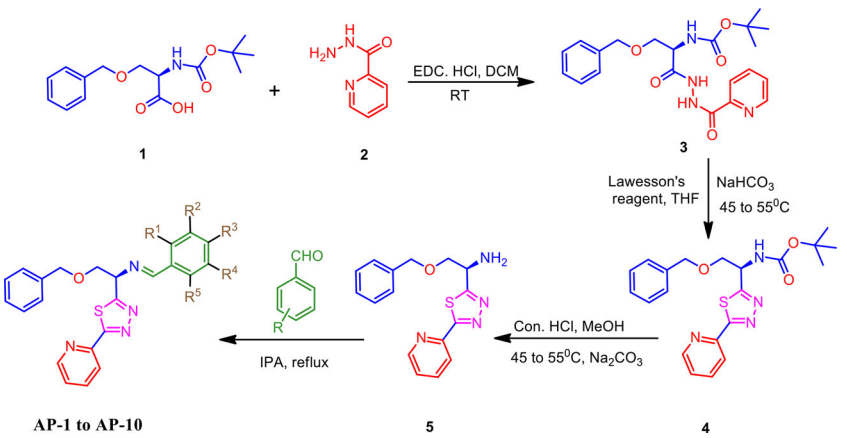
Table 2. Screening of different cyclization reagent and their effect on reaction time for synthesis of **4**.

Sr. No.	Reagent	Reaction temperature (°C)	Reaction time (hr)	Solvent	Remarks
1	Lowessons Reagent	75–80	4.0	Toluene	Reaction done but a yield of **4** is 50% w/w
2	Phosphorus Pentasulfide	75–80	6.0	Toluene	Sticky mass observed and more impurity observed on TLC
3	Lawesson's Reagent	60–70	8.0	Toluene	Reaction done but yield of **4** is 30% w/w
4	Phosphorus Pentasulfide	60–70	8.0	Toluene	Sticky mass observed and more impurity observed on TLC
5	Lawesson's Reagent	45–55	6.0	THF	Reaction done but a yield of compound **4** is 74% w/w
6	Phosphorus Pentasulfide	45–55	8.0	THF	Reaction done and yield of compound 4 is 70% w/w

The experiment was carried out in THF and toluene as solvents at various temperatures. The screening of cyclization reagents and their effect on reaction time and yield for the synthesis of **4** was tabulated in Table 2. It was observed that the best results were accomplished with THF and LR at 45–55 °C temperature. The reaction was completed in 6 h and yield was 74% (Table 2, entry 5). Whereas in case of phosphorus pentasulfide, reaction was completed but low yield was observed as compared to LR. At higher temperature conditions, maximum impurities were observed on TLC (Table 2, entry 1-4) hence optimum temperature was set to 45–55 °C. Moreover, reaction was also carried out using phosphorus pentasulfide in toluene, but reaction mass become sticky and non-stirable (Table 2, entry 2 and 4).Therefore, it was concluded that the cyclization of compound **3** successfully achieved using LR at temperature 45–55 °C in THF to form 2,5-disubstituted-1,3,4-thiadiazole ring compound **4** (Table 2, entry 6).

Finally, the title compounds (**AP-1** to **AP-10**) have been prepared after boc-deprotection of **4** in acidic condition afforded **5**.The synthesis of **AP-1** to **AP-10** was outlined in Scheme 3.

Synthesis of asymmetric *(S)-N*-benzylidene-2-(benzyloxy)-1-(5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)ethanamine derivatives (**AP-1** to **AP-10**) were investigated from (*S*)-2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethylamine (**5**) and substituted aldehydes. The reaction mixture was



Scheme 3. Synthesis of asymmetric *(S)-N*-benzylidene-2-(benzyloxy)-1-(5-(pyridin-2-yl)-1,3,4-thiadiazol-2-yl)ethanamine derivatives (**AP-1** to **AP-10**)

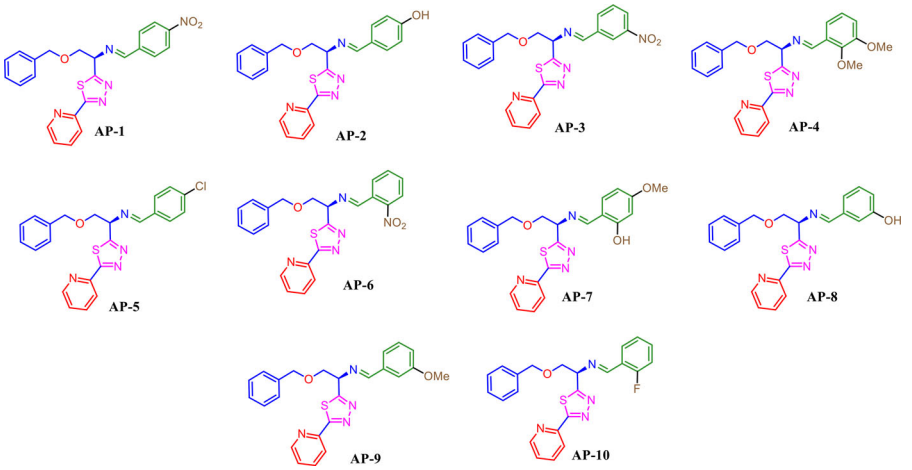


Figure 2. Structures of all the synthesized derivatives **AP-1** to **AP-10**.

refluxed in IPA for 9-12 h. After completion of reaction, pure compounds were obtained using acidic treatment with excellent yield (92-97%) in short reaction time. All synthesized molecules were well identified and characterized using various spectral techniques including FTIR, ^{1}H NMR, ^{13}C NMR, and Mass spectrometry. Structures of all the synthesized compounds were shown in Figure 2.

Biological evaluation

Antioxidant activity

The **AP-1** to **AP-10** were tested for their antioxidant property using free stable radical and commercially available organic nitrogen radical as 2, 2-diphenyl-1-picrylhydrazyl (DPPH). All the synthesized compounds exhibited excellent antioxidant activity. However, the compounds which exhibited relatively good antioxidant activities as compared with standard antioxidant drug Ascorbic acid (80.40 μg/ml).**AP-1**, **AP-6** and **AP-8** to **AP-10** with their % inhibition at 150 µg/ml

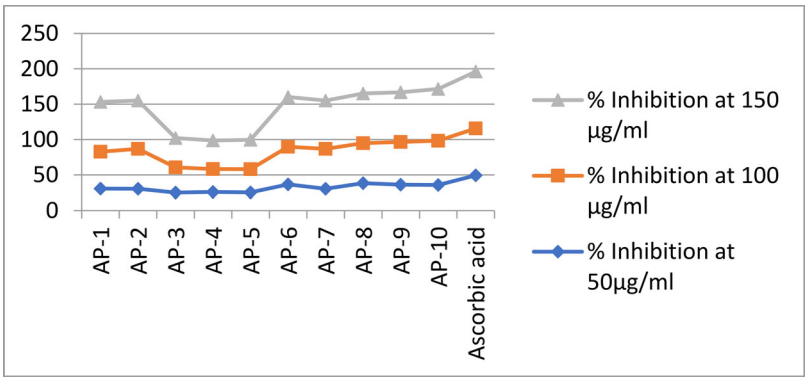
Table 3. DPPH scavenging activity of **AP-1** to **AP-10**.

CONCENTRATION	% Inhibition at 50 μg/ml	% Inhibition at 100 μg/ml	% Inhibition at 150 μg/ml
Control	0	0	0
AP-1	30.6	52.28	70.42
AP-2	30.45	56.48	68.21
AP-3	25.12	35.66	41.32
AP-4	26.10	32.28	40.30
AP-5	25.46	32.68	41.45
AP-6	36.60	53.28	70.42
AP-7	30.45	56.48	68.21
AP-8	38.45	56.48	70.21
AP-9	36.15	60.52	70.21
AP-10	35.90	62.48	73.21
Ascorbic acid	49.40	66.33	80.40

Table 4. Statistical analysis of DPPH scavenging activity.

Goodness of fit	
R square	0.5983
F	16.54
DFn,DFd	1,10
P Value	0.0019
Deviation from horizontal	Significant

was 70.42, 70.42, 70.21, and 73.21, respectively (Table 3). The **AP-1**, **AP-6**, **AP-8** to **AP-10** showed good assay against antioxidant activity, it may be due to nitro group at *ortho-para* position and hydroxy and methoxy at *meta* position as well as fluorine at *ortho* position. Statistical analysis of DPPH scavenging activity is showed in Table 4. The graph of antioxidant activity of **AP-1** to **AP-10** showed in Graph 1.



Graph 1. Antioxidant activity of **AP-1** to **AP-10**.

Antimitotic activity

The results of antimitotic activity have expressed as a reduction in *Allium cepa* root length.[27] In this activity, a mixture of DMSO and water was used as control and Methotrexate as reference standard. At the beginning (zero time), no significant difference ($P > 0.05$) was found in mitotic percent amongst different samples, as showed in Table 5. However, after 48 h of incubation (concentration 500 ppm), the compounds **AP-3**, **AP-8** and **AP-9** showed significant antimitotic activity as compared to a standard drug ($P < 0.05$). This may be attributed due to presence of *meta*

Table 5. Results of the antimitotic assay for **AP-1** to **AP-10**.

		Root Length in (cm)		
Compound	Concentration μg/ml	0 h	48 h	96 h
AP-1	10	3.1	3.4	3.8
AP-2	10	3.1	3.3	3.8
AP-3	10	3.2	4.2	4.5
AP-4	10	3.2	3.8	4.0
AP-5	10	3.2	3.6	4.0
AP-6	10	3.1	3.8	3.9
AP-7	10	3.1	4.0	4.2
AP-8	10	3.2	4.1	4.2
AP-9	10	3.2	3.8	4.2
AP-10	10	3.1	3.4	3.9
Methotrexate	10	3.2	3.9	4.0

substitution of nitro, hydroxy and methoxy on benzene ring. The result of the antimitotic assay for **AP-1** to **AP-10** has mentioned in Table 5.

Structure-activity relationship (SAR)

Ten new Schiff base derivatives, bearing hetero aromatic ring pyridine, 1,3,4-thiadiazole and substituted aromatic ring were synthesized and evaluated *in vitro* for antioxidant and antimitotic activities. In order to enhance the potency of Schiff base derivatives, we elucidated the structure-activity relationship (SAR) based on the mode of action. We used electron donating and electron withdrawing substituted aromatic aldehydes to study, its effect on the biological activity. The nitro substitution at *ortho* and *para* position, hydroxy and methoxy moiety at *meta* position and fluorine substitution at *ortho* position in Schiff base derivatives showed potent antioxidant activity. The compound **AP-4** in which methoxy group present at *meta* and *ortho* position exhibited two-fold more antioxidant activity as compared to standard drug. Similarly, compound **AP-3** (nitro group at *meta* position) and compound **AP-5** (chloro group at *para* position) exhibited near about two-fold more antioxidant activity as compared to the standard drug. In compound **AP-1**, **AP-3**, and **AP-6** nitro group present *para, meta*, and *ortho* position respectively; though all these three compounds having nitro group at different position, compound **AP-3** exhibited excellent antioxidant activity due to presence of nitro functional group at *meta* position. These results confirm that the activity varies depending on the various substituents present on the phenyl rings. Diverse substituted forms of hetero aromatic ring are tolerated on the Schiff base derivative and the presence or orientation of –OH at *ortho* and *para* position, –Cl at *para* position, $-NO_2$ at *meta* position, $-OCH_3$ at *ortho*, *para*, *and meta* position in the hetero aromatic ring affected the antioxidant activity.

Moreover, the compounds **AP-1**, **AP-2**, **AP-6** and **AP-10** showed significant antimitotic activity as compared to a standard drug ($P < 0.05$). This may be attributed due to presence of substitution of $-NO_2$, –OH, and –F on benzene ring. In compound **AP-1**, **AP-3** and **AP-6**, NO_2 group present *para*, *meta* and *ortho* position respectively though all these three compounds having $-NO_2$ at different position, compound **AP-1** and **AP-6** exhibited excellent antimitotic activity. These results confirm that the activity varies depending on the various substituents present on the phenyl rings.

Diverse substituted forms of hetero aromatic ring are tolerated on the Schiff base derivative and the presence or orientation of $-NO_2$ and –OH functional group at *ortho* and *para* position, –Cl at *para* position, $-OCH_3$ substitution at *ortho*, *meta*, and *para* position as well as -F substitution at *ortho* position in the hetero aromatic ring affected the antimitotic activity.

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

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHN H	Lipinski violation	Drug-likeness model score
Rule	–	–	–	–	< 500	≤ 5	< 10	< 5	≤ 1	–
AP-1	72.39	106.10	9	382.52	445.5	3.99	8	0	0	−0.73
AP-2	81.22	80.50	8	367.21	416.5	3.55	6	1	0	−0.19
AP-3	72.39	106.10	10	399.32	459.5	3.56	8	0	0	−0.54
AP-4	81.83	78.74	10	410.28	460.5	3.85	7	0	0	0.09
AP-5	88.21	60.27	8	372.72	434.9	4.71	5	0	0	0.06
AP-6	72.39	106.10	9	382.52	445.8	3.94	8	0	0	−0.96
AP-7	78.04	89.74	9	392.75	446.5	4.00	9	1	0	0.16
AP-8	81.22	80.50	8	367.21	416.5	3.53	8	1	0	−0.01
AP-9	85.02	69.51	9	384.73	430.5	4.07	6	0	0	0.06
AP-10	88.20	60.27	8	364.12	418.5	4.15	5	0	0	−0.56

Note: % 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 a compound between n-octanol and water, n-ON Acceptors: Number of hydrogen bond acceptors, n-OHNH donors: Number of hydrogen bonds donors.

In silico ADME Prediction

Based on Lipinski's rule of five, the drug-likeness properties were analyzed by ADME parameters using Molinspiration online property calculation toolkit[28] and data are summarized in Table 6.

All the compounds exhibited values and showed good drug-like characteristics based on Lipinski's rule of five and to be likely orally active. The data obtained for all the synthesized compounds were within the range of accepted values. None of the synthesized compounds violated Lipinski's rule of five. The parameters like the number of rotatable bonds and total polar surface area were linked with the intestinal absorption and results showed all synthesized compounds had good absorption ranging from 72.39% to 88.20%. The *in-silico* assessment of all the synthesized compounds showed very good pharmacokinetic properties, which is reflected in their physicochemical values, thus ultimately enhancing the pharmacological properties of these molecules. The molecule likely to be developed as an orally active drug candidate and should not show more than one violation of the following four criteria: miLog P (octanol-water partition coefficient) ≤5, molecular weight ≤500, number of hydrogen bond acceptors ≤10, and number of hydrogen bond donors ≤5.[29] The larger value of the drug-likeness model score reflects the higher probability of molecule to be active. All the tested compounds **AP-1** to **AP-10** were followed the criteria of an orally active drug, and therefore, these compounds may have a good potential for eventual development as oral agents.

Experimental

Material and methods

The starting material (2*S*)-3-(benzyloxy)-2-[(tert-butoxycarbonyl) amino] propanoic acid or *N*-boc-*O*-benzyl-*L*-serine obtained from Alichem and 2-hydrazinopyridine and phosphorus pentasulfide from Sigma Aldrich. Anhydrous sodium carbonate and other chemicals were obtained from SDFCL. The anhydrous solvents were obtained from Rankem. The reactions were monitored by TLC (Silica gel60, GF254, Merck) and visualized under UV light chamber. The melting points of synthesized compounds were recorded on melting point apparatus (Veego,Model-VMP-AD). The IR spectra were recorded on Shimadzu FTIR-8400S spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were run on a Bruker spectrophotometer at 500 MHz and 125 MHz, respectively. The elemental (C, H, and N) analyses were measured on Perkin-Elmer 2400.

General procedure for the synthesis of compound 3

In three neck 250 ml round bottom flask, 2-hydrazinopyridine (**2**) (20 gm, 1.0 mol) and (2S)-3-(benzyloxy)-2-[(*tert*-butoxycarbonyl) amino] propanoic acid (**1**) (45.3 gm, 1.1 mol) was stirred in water (100 ml). In this stirred solution added HOBt (1.97 gm, 0.1 mol) followed by addition of NMM (22.45 gm, 1.52 mol). Then EDC.HCl (41.98 gm, 1.5 mol) was added lot wise and whole reaction was stirred for30minutes at 20–30 °C. The reaction was monitored by TLC (DCM:MeOH: 9:1), after reaction completion, the reaction mixture was filtrated and dried to get white compound **(3)** as white solid, yield 58.65 gm(97%), mp 187 °C. IR spectrum, ν, cm^{-1}:1242.16 (C–N),1421.54 (C = C), 699.91(C–S), 2980.02 (C–H), 1695.43 (C = O), 1070.49 (C–O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 10.12 s (1H, NH), 9.16 s (1H, NH), 8.59–8.58 d (J = 5 Hz,1H, H-2 pyridine), 8.16–8.15 d (J = 5 Hz,1H, H-5 pyridine) , 7.88–7.85 t (1H, H-4 pyridine) , 7.48–7.46 t (1H, H-3 pyridine), 7.35–7.29 m (5H,Ar-H), 5.43 s (1H, NH-Boc), 4.60 s (2H, CH_2-Ph), 4.51-4.49 t (1H, CH-N-Boc), 3.97–3.96 d (J = 5 Hz,1H, CH = N), 3.67–3.66 d (J = 5 Hz,1H, CH), 1.47 s (9H, Boc) and NH proton confirmed by D_2O exchange.^{13}C-NMR spectrum δ, ppm: 167.3, 160.6, 148.5, 148.1, 137.4, 137.2, 128.5, 128.0, 127.9, 126.8, 122.5, 73.6, 69.3, 28.2.Anal. calcd for $C_{21}H_{26}N_4O_5$: C 60.86, H 6.32, N 13.52, O 19.30, found: C 60.85, H 6.33, N 13.52.

General procedure for the synthesis of Compound5

In a three neck 250 ml round bottom flask diacylhydrazine derivative (**3**) (50 gm 1.0 mol), sodium carbonate (12.8 gm 1.0 mol) and Lowessons reagent (29.31 gm, 0.6 mol), in THF (150 mL) were stirred at 45–55 °C for 6 hours. The reaction was monitored by TLC (DCM:MeOH, 9:1) after completion of reaction, quenched with 5% sodium bicarbonate solution (500 mL) and product so obtained was extracted in ethylacetate (250 mL). After layer separation, the ethylacetate layer was distilled out undervacuum. The obtained residue dissolved in methanol (50 mL) and added 35% aqueous hydrochloric acid solution (100 mL,warmed 50–75 °C temperature for 8 hours. After reaction completion by TLC (DCM:MeOH, 9:1) and it was cooled to room temperature and added water (500 mL). The two layers were separated, aqueous layer was collected in two neck 1000 ml round bottom flask and pH 8.5 to 9.5 adjust by using 10% aqueous sodium hydroxide solution. The product thus obtained and was extracted in DCM and the DCM layer washed with water and concentrated and obtained residue was purified by silica gel chromatography to get compound (**5**) as dark brown color solid,yield 27.88 gm(68%), mp: 160 °C. IR spectrum, ν, cm^{-1}: 1245.53 (C–N), 1431.14 (C = C), 700.98 (C–S), 3061.86 (C–H), 3376.11 (N–H). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.64–8.63 d (J = 5 Hz, 1H,H-2 pyridine), 8.33–8.31 d (J = 10 Hz, 1H,H-5pyridine), 7.84–7.81 t (1H,H-4 pyridine), 7.37–7.28 m (6H, Ar-H and H-3 pyridine), 4.67–4.66 t (1H, CH–N), 4.60 s (2H, CH_2-Ph), 3.92–3.90 d (J = 10Hz,1H, CH = N), 3.76–3.73 d (J = 15 Hz,1H, CH), 2.23 s (2H, NH_2) and NH proton confirmed by D_2O exchange.^{13}C-NMR spectrum δ, ppm: 175.7, 170.7, 149.7, 149.3, 137.5, 137.0, 128.4, 127.8, 127.7, 125.1, 120.7, 73.8, 73.4, 52.2. ESMS (M + 1): 313.Anal. calcd for $C_{16}H_{16}N_4OS$: C 61.52, H 5.16, N 17.93, S 10.26, found: C 61.53, H 5.16, N 17.92, S 10.27.

General procedure for synthesis of compounds AP-1 to AP-10

To a solution of corresponding 1.0 mol of (*S*)-2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4] thiadiazol-2-yl)-ethylamine (**5**) in 5 ml IPA, 0.98 mol substituted benzaldehyde was added and refluxed for 8-12 hours. The progress of reaction was monitored by TLC (DCM:MeOH, 9.5:0.5). Reaction quenched using 25 ml water (confirmed qty) and product was extracted in DCM and organic layer washed with 3 ml 2% aqueous hydrochloric acid solution. The obtained residue was suspended in MTBE to get **AP-1** to **AP-10** compounds.

(S)-[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethyl]-(4-nitro-benzylidene)-amine (AP-1)

Brown color solid; Yield: 96%; M.p.: 196–198 °C; IR (KBr ν, cm^{-1}): 1201 (C–N), 1521.84 & 1342.46 (NO_2), 1400.32 (C = C), 165:1.07 (C = N), 698.23 (C–S), 1107.14 (C–O), 3172.90 (C–H).^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.64 d (J = 5 Hz, 1H, pyridine H-2), 8.36 s (1H, N = CH), 8.34–832 m (3H, pyridine H-5, 4-nitrobenzene H-3 & 5), 7.89–7.83 t (3H, pyridine H-4, 4-nitrobenzene H-2 & 6), 7.40–7.37 t (1H, pyridine H-3), 7.29–7.26 m (5H, Ar-H), 5.13–5.11 t (1H, CH–N = C), 4.61 s (2H, CH_2-ph), 4.16–4.13 d (J = 15 Hz, 1H, CH), 3.90–3.89 t (1H, CH).^{13}C-NMR spectrum δ, ppm: 171.9, 171.1, 162.1, 152.7, 149.8, 149.5, 149.1, 140.7, 137.5, 137.3, 129.6, 129.4, 128.5, 127.9, 127.7, 125.4, 124.3, 123.9, 120.8, 73.5, 72.8, 69.4. ES-MS, m/z = 447.1 [M + 1].Anal. calcd for $C_{23}H_{19}N_5O_3S$: C, 62.01; H, 4.30; N, 15.72; S, 7.20; Found: C, 62.00; H, 4.31; N, 15.73; S, 7.21.

(S)-4-{[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethylimino]-methyl}-phenol (AP-2)

Off white color solid; Yield: 93%; M.p.: 158–160 °C; IR (KBr ν, cm^{-1}): 1224.80 (C–N), 1276.88 (OH), 1444.68 (C = C), 1639.49 (C = N), 683.81 (C–S), 1064.71 (C–O), 3066.82 (C–H). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.64 d (J = 5 Hz, 1H, pyridine H-2), 8.36–8.34 m (2H, N = CH and pyridine H-5), 7.87–7.83 t (1H, pyridine H-4), 7.69–7.68 d (J = 5 Hz, 2H, 4-hydroxybenzene H-2 & 6), 7.40–7.37 t (1H, pyridine H-3), 7.29–7.26 m (4H, Ar-H), 6.89–6.88 d (J = 5 Hz, 2H, 4-hydroxybenzene H-3 & 5), 6.33 bs (1H, OH), 5.13–5.11 t (1H, CH–N = C), 4.61 s (2H, CH_2-Ph), 4.16–4.13 d (J = 15 Hz, 1H, CH), 3.90–3.89 t (1H, CH).^{13}C-NMR spectrum δ, ppm: 173.6, 170.8, 163.9, 152.2, 149.7, 149.2, 137.6, 137.4, 130.6, 128.4, 128.0, 127.8, 125.4, 120.9, 115.7, 73.5, 73.3, 69.2. ES-MS, m/z: 417.1 [M + 1]; Anal. calcd for $C_{23}H_{20}N_4O_2S$: C, 66.33; H, 4.84; N, 13.45; S, 7.70; Found: C, 66.33; H, 4.83; N, 13.44; S, 7.70.

(S)-[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethyl]-(3-nitro-benzylidene)-amine (AP-3)

Light brown color solid; Yield: 94%; M.p.: 200–203 °C; IR (KBr ν, cm^{-1}):1205.51 (C–N), 1527.62 & 1350.17 (–NO_2), 1436.97 (C = C), 1645.28 (C = N), 686.66 (C–S), 1091.71(C–O), 3086.11 (C–H).^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.63 d (J = 10 Hz, 1H, pyridine H-2), 8.51 s (1H, 3-Nitrobenzene H-2), 8.36 s (1H, N = CH), 8.35–8.34 d (J = 5Hz, 1H, pyridine H-5), 8.21–8.20 d (J = 5 Hz, 1H, 3-Nitrobenzene H-4), 7.86–7.85 d (J = 5 Hz, 1H, 3-Nitrobenzene H-6), 7.84–7.82 t (1H, pyridine H-4), 7.53–7.51 d.d (J = 10 Hz, 1H, 3-Nitrobenzene H-5), 7.38–7.36 t (1H, pyridine H-3), 7.29–7.27 m (5H, Ar-H), 5.13–5.11 t (1H, CH-N = C), 4.61 s (2H, CH_2-Ph), 4.16–4.13 d (J = 15 Hz, 1H, CH), 3.90-3.89 t (1H, CH).^{13}C-NMR spectrum δ, ppm: 173.6, 170.8, 163.9, 152.2, 149.7, 149.2, 137.6, 137.4, 130.6, 128.4, 128.0, 127.8, 125.4, 120.9, 115.7, 73.5, 73.3, 69.2. ES-MS, m/z: 447.2 [M + 1]; Anal. calcd for $C_{23}H_{19}N_5O_3S$: C, 62.01; H, 4.30; N, 15.72; S, 7.20; Found: C, 62.02; H, 4.31; N, 15.72; S, 7.19.

(S)-[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethyl]-(2,3-dimethoxy-benzylidene)-amine (AP-4)

Dark brown color Solid; Yield: 93%; M.p.: 191–194 °C; IR (KBr ν, cm^{-1}):1234.07 (C–N), 1454.80 (C = C), 1645.82 (C = N), 699.91 (C–S), 1030.08 (C–O), 2936.26 (C–H). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.64–8.63 d (J = 10 Hz, 1H, pyridine H-2), 8.37 s (1H, N = CH), 8.35–8.34 d (J = 5 Hz, 1H, pyridine H-5), 7.86–7.82 d (J = 5 Hz, 1H, 3-Nitrobenzene H-6), 7.53–7.52 d

($J = 5$ Hz, 1H, 2,3-dimethoxy benzene H-6), 7.38–7.36 t (1H, pyridine H-3), 7.29–7.24 m (5H, Ar-H), 6.99–6.98 d ($J = 5$ Hz, 1H, 2,3-dimethoxy benzene H-4), 6.91–6.90 d ($J = 5$ Hz, 1H, 2,3-dimethoxy benzene H- 4), 5.15–5.14 t (1H, CH–N), 4.61 s (2H, CH_2-Ph), 4.17–4.14 d ($J = 15$ Hz, 1H, CH), 3.98 s (3H, O–CH_3), 3.94 s (3H, O–CH_3), 3.90–3.88 t (t, 1H, CH). ^{13}C-NMR spectrum δ, ppm: 173.3, 170.9, 163.9, 152.1, 149.8, 149.8, 137.2, 137.2, 128.6, 128.4, 127.9, 127.9, 127.7, 125.3, 124.0, 120.9, 73.5, 69.4, 56.2; ES-MS, *m/z*: 461.1 [M + 1]; Anal. calcd for $C_{25}H_{24}N_4O_3S$: C, 65.20; H, 5.25; N, 12.17; S, 6.96; Found: C, 65.21; H, 5.26; N, 12.17; S, 6.96.

(S)-[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethyl]-(2-chloro-benzylidene)-amine (AP-5)

Light yellow color solid; Yield: 95%; M.p. = 95–98 °C; IR (KBr ν, cm^{-1}):1203.58 (C–N), 827.46 (Cl), 1431.18 (C = C), 1651.07 (C = N), 698.23 (C–S), 1111.00 (C–O), 3059.10 (C–H). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.64 d ($J = 5$ Hz, 1H, pyridine H-2), 8.37 s (1H, N = CH), 8.35-8.33 dd ($J = 10$ Hz, 1H, pyridine H-5), 7.86–7.83 t (1H, pyridine H-4), 7.78–7.76 d ($J = 10$ Hz, 2H, 4-chlorbenzene H-2 & 6), 7.43–7.39 d ($J = 20$ Hz, 2H, 4-chlorbenzene H-3 & 5), 7.39–7.37 t (1H, pyridine H-3), 7.28–7.26 m (5H, Ar-H), 5.17–5.16 t (1H, CH–N = C), 4.60 s (2H, CH_2-Ph), 4.17–4.14 d ($J = 15$ Hz, 1H, CH), 3.88–3.84 t (1H, CH).^{13}C-NMR spectrum δ, ppm: 172.7, 170.9, 163.0, 152.1, 149.8, 149.3, 137.7, 137.5, 137.2, 133.9, 130.9, 129.9, 129.5, 129.0, 128.5, 128.4, 127.8, 127.8, 127.7, 125.3, 120.8, 73.4, 69.3. ES-MS, m/z: 435.1 [M + 1].Anal. calcd for $C_{23}H_{19}ClN_4OS$: C, 63.51; H, 4.40; N, 12.88; S, 7.37; Found: C, 63.50; H, 4.40; N, 12.87; S, 7.37.

(S)-[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethyl]-(2-nitro-benzylidene)-amine (AP-6)

Reddish brown color solid; Yield: 95%; M.p.: 128–130 °C; IR (KBr ν, cm^{-1}): 1210.47 (C–N), 1281.35 (OH), 1455.59 (C = C), 1644.10 (C = N), 699.05 (C–S), 1045.98 (C–O), 3064.83 (C–H). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.63 d ($J = 10$ Hz, 1H, pyridine H-2), 8.37 s (1H, N = CH), 8.35–8.34 d ($J = 5$ Hz, 1H, pyridine H-5), 8.23–8.22 d ($J = 5$ Hz,1H, 2-Nitrobenzene H-3), 7.86-7.85 d ($J = 5$ Hz, 1H, 2-Nitrobenzene H-6), 7.84–7.82 t (1H, pyridine H-4), 7.53–7.51 d.d ($J = 10$ Hz, 2-Nitrobenzene H-4 & 5), 7.38–7.36 t (1H, pyridine H-3), 7.29–7.27 m (5H, Ar-H), 5.15–5.14t (1H, CH–N = C), 4.61 s (2H, CH_2-Ph), 4.17–4.14 d ($J = 15$ Hz, 1H, CH), 3.91–3.88 t (1H, CH). ^{13}C-NMR spectrum δ, ppm: 171.9, 171.1, 162.1, 152.0, 149.3, 149.3, 137.5, 137.2, 131.1, 129.6, 129.4, 128.5, 127.9, 127.7, 125.4, 124.3, 123.9, 121.8, 73.5, 72.8, 69.4.ES-MS, *m/z*: 447.1 [M + 1]. Anal. calcd for $C_{23}H_{19}N_5O_3S$: C, 62.01; H, 4.30; N, 15.72; S, 7.20; Found: C, 62.00; H, 4.31; N, 15.72; S, 7.19.

(S)-2-{[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethylimino]-methyl}-5-methoxy-phenol (AP-7)

Off white solid; Yield: 92%; M.p.: 273–274 °C; IR (KBr ν, cm^{-1}):1210.20 (C–N), 1455.59 (C = C), 1695.80 (C = N), 699.76 (C–S), 1098.20 (C–O), 2983.64 (C–H). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.64 d ($J = 5$ Hz, pyridine H-2), 8.36–8.34 m (2H, N = CH and pyridine H-5), 7.87–7.83 t (1H, pyridine H-4), 7.40–7.38 t (1H, pyridine H-3), 7.38–7.36 d ($J = 10$ Hz, 1H, 2-hydroxy-4-methoxybenzne H-6), 7.29–7.26 m (5H, Ar-H), 6.42–6.40 d (J = 10 Hz, 1H, 2-hydroxy-4-methoxybenzene H-5), 6.28 s (1H, 2-hydroxy-4-methoxybenzene H-3), 6.03 bs (1H, OH), 5.13–5.10 t (1H, CH–N = C), 4.61 s (2H, CH_2-Ph), 4.16–4.13 d ($J = 15$ Hz, 1H, CH), 4.01 s (3H, O–CH_3), 3.90–3.86 t (1H, CH).^{13}C-NMR spectrum δ, ppm: 173.3, 170.9, 163.9, 154.6, 152.1, 149.9, 149.5, 137.3, 137.2, 130.2, 128.6, 128.4, 127.9, 127.9, 127.8, 125.3, 124.0, 120.9, 110.5, 109.3,

74.0, 69.5, 56.3. ES-MS, *m/z:* 445.1 [M + 1]. Anal. calcd for $C_{24}H_{22}N_4O_3S$: C, 64.56; H, 4.97; N, 12.55; S, 7.18; Found: C, 64.55; H, 4.98; N,12.55; S, 7.17.

(S)-3-{[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethylimino]-methyl}-phenol (AP-8)

Brown color solid; Yield: 93%; M.p.: 183–185 °C; IR (KBr ν, cm^{-1}):1210.47 (C–N), 1281.35 (OH), 1455.59 (C = C), 1644.10 (C = N), 699.05 (C–S), 1045.98 (C–O), 3064.83 (C–H).^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.64 d (J = 5 Hz, 1H, pyridine H-2), 8.36–8.34 m (2H, N = CH and pyridine H-5), 7.87–7.83 t (1H, pyridine H-4), 7.40–7.37 t (1H, pyridine H-3), 7.29–7.26 m (5H, Ar-H), 7.19–7.18 d (J = 5 Hz, 1H, 3-hydroxybenzene H-6), 7.16–7.14 t (1H, 3-hydroxybenzene H-5), 7.13-7.12 d (J = 5 Hz, 1H, 3-hydroxybenzene H-4), 6.89–688 d (J = 5 Hz, 1H, 3-hydroxybenzene H-3), 6.33 bs (1H, OH), 5.13–5.11 t (1H, CH-N = C), 4.61 s (2H, CH_2-Ph), 4.16–4.13 d (J = 15 Hz, 1H, CH), 3.90–3.86 t (1H, CH).^{13}C-NMR spectrum δ, ppm: 173.7, 170.8, 163.9, 153.2, 149.7, 149.2, 137.6, 137.4, 130.0, 128.4, 128.0, 127.8, 121.6, 118.2, 116.2, 73.5, 973.4, 69.2. ES-MS, *m/z*: 417.1 [M + 1].Anal. calcd for $C_{23}H_{20}N_4O_2S$: C, 66.33; H, 4.84; N, 13.45; S, 7.70; Found: C, 66.34; H, 4.84; N, 13.45; S, 7.71.

(S)-[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethyl]-(3-methoxy-benzylidene)-amine (AP-9)

Brown color solid; Yield: 92%; M.p.: 146–149 °C; IR (KBr ν, cm^{-1}):1247.75 (C–N), 1432.48 (C = C), 1645.93 (C = N), 699.69 (C–S), 1178.81 (C–O), 3063.39 (C–H). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.63 d (J = 10 Hz, 1H, pyridine H-2), 8.37 s (1H, N = CH), 8.35–8.34 d.d (J = 5 Hz, 1H, pyridine H-5), 7.86–7.82 t (1H, pyridine H-4), 7.51–7.50 d (J = 5 Hz, 1H, 3-dimethoxy benzene H-6), 7.37–7.36 t (1H, pyridine H-3), 7.29–7.25 m (5H, Ar-H), 7.14 s (1H, 3-dimethoxy benzene H-2), 7.00–6.99 d (J = 5 Hz, 1H, 3-dimethoxy benzene H-4), 6.92–6.90 d (J = 10 Hz, 1H, 3-dimethoxy benzene H-3), 5.15–5.14 t (1H, CH-N), 4.61 s (2H, CH_2-Ph), 4.16–4.13 d (J = 15 Hz, 1H, CH), 3.99 s (3H, O–CH_3), 3.91–3.88 t (1H, CH).^{13}C-NMR spectrum δ, ppm: 172.8, 170.2, 163.9, 161.0, 152.1, 149.9, 149.9, 141.0, 137.3, 137.2, 130.0, 128.6, 128.4, 127.9, 127.9, 127.8, 125.3, 124.0, 120.9, 117.0, 113.4, 74.0, 73.5, 69.5, 55.0. ES-MS, *m/z*: 431.1 [M + 1]. Anal. calcd for $C_{24}H_{22}N_4O_2S$: C, 66.96; H, 5.15; N, 13.01; S, 7.45; Found: C, 66.97; H, 5.15; N, 13.00; S, 7.45.

(S)-[2-Benzyloxy-1-(5-pyridin-2-yl-[1,3,4]-thiadiazol-2-yl)-ethyl]-(2-fluoro-benzylidene)-amine (AP-10)

Pale yellow color solid; Yield: 94%; M.p.: 129–131 °C. IR (KBr ν, cm^{-1}):1203.77(C–N), 1010.31 (Ph–F), 1431.74 (C = C), 1651.00 (C = N), 698.23 (C–S), 1112.00 (C–O), 3060.00 (C–H). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.65–8.64 d (1H, J = 10 Hz, pyridine H-2), 8.36 s (1H, N = CH), 8.35–8.34 d (J = 5 Hz, 1H, pyridine H-5), 7.87–7.83 t (1H, pyridine H-4), 7.58–7.56 d (J = 10 Hz, 1H, 2-flurobenzene H-6), 7.38–7.36 t (1H, pyridine H-3), 7.29–7.26 m (6H, 2-flurobenzene H-4 and Ar), 7.04–7.02 t (1H, 2-flurobenzene H-5), 6.94–6.92 t (1H, 2-flurobenzene H-3), 5.13–5.10 t (1H, CH–N), 4.61 s (2H, CH_2–Ph), 4.16-4.13 d (J = 15 Hz, 1H, CH), 3.90–3.86 t (1H, CH).^{13}C-NMR spectrum δ, ppm: 173.3, 170.9, 163.9, 162.0, 152.1, 149.7, 149.8, 137.3, 137.2, 132.8, 130.2, 128.6, 128.4, 127.7, 127.7, 127.8, 125.3, 124.0, 120.9, 115.0, 74.0, 73.4, 69.4, 56.3. ES-MS, *m/z*: 419.1 [M + 1]. Anal. calcd for $C_{23}H_{19}FN_4OS$: C, 66.01; H, 4.58; N, 13.39; S, 7.66; Found: C, 66.00; H, 4.58; N, 13.39; S, 7.66.

Biological

Antioxidant activity

In this method, 0.1 mM solution of 2, 2-diphenyl-1-picrylhydrazyl (DPPH) in methanol was prepared. The 1.0 ml of this solution was added into 3 ml solution of hybrid compounds (**AP-1** to **AP-10**) in dimethyl sulfoxide (DMSO) at different concentrations (50,100 &150 μg/ml) mentioned in Table 3. The mixtures were shaken vigorously and allowed to stand at 25-30 °C for 30 minutes. The absorbance was dignified at 517 nm by using a UV-VIS spectrophotometer. The Ascorbic acid used as a reference standard and DMSO as a control. The lower absorbance values of the compounds indicate higher free radical scavenging activity. The capability of scavenging DPPH radical was calculated by using the following formula:

$$\text{DPPH scavenging effect } (\%\text{ inhibition}) = (A_0 - A_1)/A_0) \times 100$$

where A_0 is the absorbance of the control reaction and A_1 is the absorbance in the presence of selected sample of compounds. All the tests were performed in triplicates and the data are expressed as mean ± standard deviation (SD). The results of the scavenging activity were statistically evaluated by one-way analysis of variance (ANOVA) which is designed to compare the means of independent samples, simultaneously the DPPH assay[30] is a simple and sensitive method to study antioxidant activity. This assay is based on the theory, that a hydrogen donor is an antioxidant and it measures compounds that are radical scavengers. The assay shows the mechanism by which DPPH radical accepts hydrogen from an antioxidant. The antioxidant effect is proportional to the disappearance of DPPH radicals in test samples. Monitoring DPPH with a UV spectrometer has become the most commonly used method because of its simplicity and accuracy. DPPH radical shows a strong absorption maximum at 517 nm (purple). The color turns from purple to yellow followed by the formation of DPPH upon absorption of hydrogen from an antioxidant. This reaction is stoichiometric concerning the number of hydrogen atoms absorbed. Hence, the antioxidant effect can be easily calculated by following the decrease of UV absorption at 517 nm.

Antimitotic activity

The model used for this activity was *Allium cepa* root tip meristem mode in which onion bulbs were cleaned and kept with root tips in the beaker containing distilled water till the tips grew up to 2–3 cm. Then these bulbs were expelled from the water and put on a layer of tissue paper to remove an excess of water. The solutions were divided into groups, the first group served as control (DMSO) 0.6 ml and distilled water volume adjusted to 600 ml, the second group target compounds dissolved in DMSO of concentration 10 μg/ml. The third group methotrexate also dissolved in DMSO of concentration 10 μg/ml was used as a standard drug. The grown root tips were dipped into solutions mentioned above and these were stored at temperature 25 ± 2 °C for 96 h of direct daylight. The test sample was changed day by day with new ones. The length of roots developed during incubation (recently showing up roots excluded), root number, and the mitotic index was recorded after 96 h. The percent of root growth inhibition was calculated by

$$\text{Percent of root growth inhibition} = \text{Control} - \text{Test} \times 100.$$

The EC_{50} value was calculated by plotting treatment concentration versus mean of root length as a percentage of the water control group.

In silico ADME prediction

An important task in drug design and discovery is to early prediction of drug-likeness properties, as it resolves the cost and time in drug development and discovery. Due to the inadequate drug-

likeness properties of many active agents with a significant biological activity have failed in clinical trials.

In silico ADME is significant tool to predict properties regarding drug development. Absorption (% ABS) was calculated by:

$$\%\ \mathrm{ABS} = 109 - (0.345 \times \mathrm{TPSA})$$

Conclusion

Facile, efficient synthetic route has been developed for the synthesis of compounds **3**, **4** and **AP-1** to **AP-10**. This practical protocol is easy, simple, eco-friendly and required less time for reaction completion with higher yield. The antimitotic properties of final compounds were evaluated and results showed that, **AP-3**, **AP-8**and **AP-9** showed significant antimitotic activity as compared with standard drug which is attributed the presence of *meta* substitution of nitro, hydroxy and methoxy on benzene ring. The **AP-1**, **AP-6**, **AP-8** to **AP-10** showed good assay against antioxidant activity, it might be due to nitro group at *ortho* and *para* position and hydroxy and methoxy at *meta* position as well as fluorine at *ortho* position. Finally, *insilico* ADME prediction, the **AP-1** to **AP-10** showed a good drug linkage score.

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Disclosure statement

The authors declare no conflict of interest.

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