Design, Synthesis, and Evaluation of the Anticancer Properties of a Novel Series of Imidazolone Fused Pyrazolo[1,5-a]pyrimidine Derivatives

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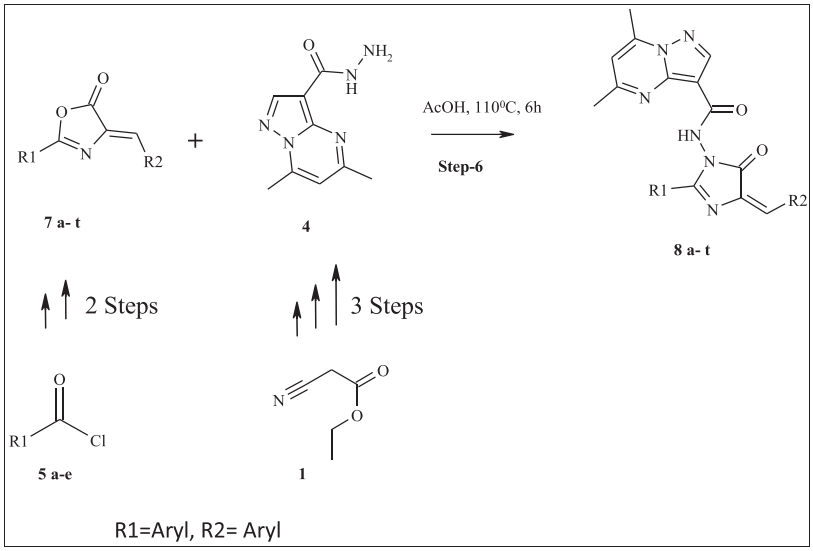

A novel series of imidazolone fused pyrazolo[1,5-a]pyrimidine derivatives has been designed and synthesized using a convergent approach, and the structures of these compounds were confirmed by ^{1}H NMR, ^{13}C NMR, ESI-MS, and IR analyses. These new compounds were tested for their *in vitro* antiproliferative activity using an 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Out of the 20 derivatives prepared in the current study, compounds **8h**, **8n**, and **8r** exhibited good anticancer activities tested against HeLa cells and $HepG_2$ cells. However, the *in vitro* anticancer activity of compound **8r** against HeLa, $HepG_2$, and MCF-7 cell lines is superior to the marketed drugs Paclitaxel and SAHA.

INTRODUCTION

Pyrazolo[1,5-a]pyrimidines and related heterocyclic compounds can be found in a wide range of interesting compounds with applications in numerous fields, including medicine and agriculture [1–3]. Pyrazolo[1,5-a]pyrimidine derivatives have been reported to possess a diverse range of pharmacological activities, as well as being able to mimic the structural characteristic of biogenic purines, making them potential drug candidates [4,5]. Pyrazolo[1,5-a]pyrimidines are also bioisosteres for triazolothie nopyrimidines, imidazoquinazolines, pyrimido quinazolines, and imidazoquinolinones, all of which have shown reported to exhibit good anticancer activity. Furthermore, pyrazolo[1,5-a]pyrimidines have been reported to show tuberculostatic [6], neuroleptic [7], CNS depressant [8], antihypertensive [9], antileishmanial [10], and antimicrobial activities [11].

Substituted imidazolones have been reported to exhibit a wide range of interesting pharmacological activities [12–14], making those excellent substrates for diversity oriented synthesis. Amongst the many substituted imidazolones reported in the literature, several have been used as intermediates for the preparation of polymers and agrochemicals, while others have been used as biotin antagonists in biological systems that are capable of inhibiting the growth of malignant tumors [15,16]. Furthermore, compounds containing imidazolone chromophores have been reported to possess a broad range of biological properties, including anticancer, cardio, anti-inflammatory, and angiotensin II receptor antagonistic activities [17]. Trisubstituted imidazolones induce a high

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level of apoptosis in human leukemia cells, as well as exhibiting pronounced cytotoxicity [18,19]. Furthermore, trisubstituted imidazolones possess antipyretic and analgesic properties [20]. Based on their pharmacological importance, significant research efforts have been directed towards the development of synthetic strategies for the preparation of imidazolones using solution and solid phase techniques.

Imidazolone derivatives are usually prepared from the corresponding oxazolones [21]. Oxazolones themselves have been used as important synthons for the synthesis of several organic molecules, including amino acids, dyes, and drugs [22–24], as well as many biologically active drug compounds, including analgesic, anti-inflammatory, anti-depressant, anticancer, anti-microbial, anti-diabetic, and anti-obesity agents [25–27]. The chemistry of 5-(4)-oxazolones has been reviewed in detail by Carter [28].

Islam *et al.* [21] reported their work towards the synthesis of imidazolones via the reaction of the corresponding oxazolones with an appropriate primary amine under a variety of different experimental conditions. Amongst the many compounds synthesized in this way, imidazolone rings containing a pyrazolo[1,5-a]pyrimidine moiety have been identified as attractive scaffolds for the development of anticancer agents because of their strong hydrogen bond donor and acceptor abilities, which could form strong interactions to the active sites of their target proteins. To the best of our knowledge, there have been no reports in the literature pertaining to the biological activities of imidazolone fused pyrazolo[1,5-a]pyrimidine derivatives.

Inspired by these findings, we report herein our recent work towards the synthesis and evaluation of the anticancer properties of a series of imidazolone fused pyrazolo[1,5-a]pyrimidine derivatives. The design strategy used for the preparation of these compounds is shown in Figure 1 using compound **8r** as a representative example.

RESULTS AND DISCUSSION

Chemistry. The imidazolone fused pyrazolo[1,5-a] pyrimidine derivatives were synthesized over three consecutive sequences via a divergent approach. The first of these three sequences involved the synthesis of a 5,7-Dimethylpyrazolo[1,5-a]pyrimidine-3-carbohydrazide derivative, as shown in **Scheme** 1. Ethyl 5-amino-1H-pyrazole-4-carboxylate (**2**) was previously synthesized via a two-step protocol [29,30]. However, we have developed a one-pot process for the preparation of this material by reacting commercially available ethyl cyanoacetate (**1**) with dimethylformamide dimethyl acetal and hydrazine hydrate in acetic acid under gentle heating with dimethylformamide as a solvent. The subsequent reaction of compound **2** with acetylacetone in acetic acid at 82°C gave ethyl 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3**) in good yield [31]. The treatment of ester **3** with hydrazine hydrate in ethanol at 72°C for 7 h gave the 5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carbohydrazide derivative **4** [32].

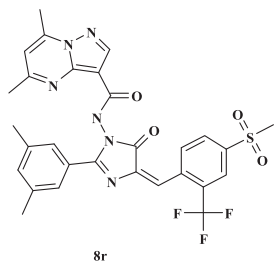


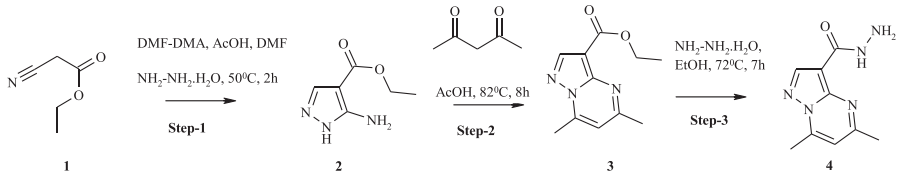
Figure 1. Chemical structure of compound **8r** which showed good anti-proliferative activity.

The second sequence in the synthesis of the imidazolone fused pyrazolo[1,5-a]pyrimidine derivatives involved the synthesis of a series of aryl substituted oxazolones in two steps, as shown in **Scheme** 2. The hippuric acid derivatives **6a–e** was obtained by the treatment of the corresponding acid chlorides **5a–e** with glycine in the presence of an aqueous sodium hydroxide solution at room temperature [33,34]. The hippuric acid derivatives **6a–e** were subsequently treated with a variety of different substituted aldehydes in the presence of acetic anhydride and sodium acetate at 80°C, in accordance with the previously reported Erlenmeyer–Plochl reaction, to give the corresponding oxazolones **7a–t** [27,35].

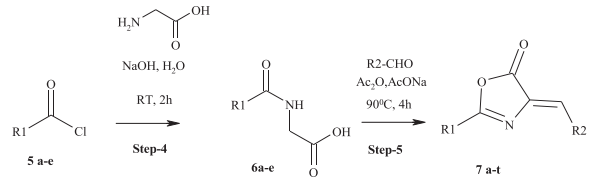
The third sequence in the synthesis of the target compounds involved the synthesis of imidazolones **8a–t**, as shown in **Scheme** 3. Our initial trial reactions were based on reports from the literature and involved (i) the use of a copper catalyst at elevated temperatures [36], (ii) the fusing of both intermediates at elevated temperatures [37], (iii) the heating of the reaction mixture with pyridine at 115°C for 6 h [38], and (iv) the heating of the reaction mixture with DMF at 115°C [39] to allow for the coupling of intermediate **4** with the oxazolones **7**. However, all of these efforts resulted in a low conversion to the required product. Pleasingly, the reaction gave the desired product in a much higher yield when it was conducted in acetic acid at reflux [40]. Thus, the final target compounds **8a–t** were synthesized in good yields by the reaction of intermediates **4** with oxazolones **7a–t** in refluxing acetic acid for a minimum of 6 h.

The structure of ethyl 5-amino-1H-pyrazole-4-carboxylate (**2**) was confirmed by a series of spectral studies. Fourier transform infrared (FTIR) analysis showed a broad peak at 3193.8 cm^{-1}, which was attributed to the stretching of the −NH of the pyrazole ring. Two other peaks were also observed at 1615.9 and 1337.6 cm^{-1}, which were attributed to N–H bending and C–N stretching

Scheme 1. Synthetic route to synthesize compound **4**.



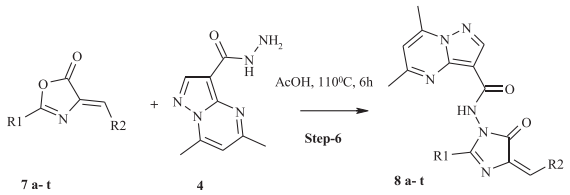
Scheme 2. Synthetic route to synthesize compounds (**7a–t**).



R1 = Aryl

R2 = Aryl

Scheme 3. Synthetic route to synthesize compounds (**8a–t**).



R1 & R2 = Aryl

vibrations, respectively. The ^{1}H NMR spectrum of **2** contained a singlet with a chemical shift of 7.45 ppm, which was consistent with the proton of the pyrazole ring. A broad singlet was also observed with a chemical shift of 11.84 ppm, which was consistent with the −NH proton of the pyrazole ring. The ^{13}C NMR spectrum of **2** contained three signals at 94.00, 139.93, and 151.86 ppm, which were consistent with the aromatic carbons of the pyrazole ring. The structure of compound **2** was further confirmed by mass spectrometry, which gave a molecular ion peak with an *m/z* value of 156.7 for [M + H], which was consistent the molecular formula $C_6H_9N_3O_2$. The structure of compound **3** was confirmed by IR, ^{1}H NMR, ^{13}C NMR, and LC-MS analyses. The FTIR spectrum of **3** contained a broad band at 3193.8 cm^{-1}, which was attributed to the −NH stretching vibration of the pyrazole ring. Two other peaks were observed at 1615.9 and 1337.6 cm^{-1} for the N–H bending and C–N stretching vibrations, respectively. The ^{1}H NMR spectrum of compound **3** contained a singlet with a chemical shift of 7.12 ppm, which was consistent with the proton of the pyrimidine ring, and a singlet with a chemical shift of 8.53 ppm, which was consistent with the proton of the pyrazole ring. The ^{13}C NMR spectrum of **3** contained a signal at 162.13 ppm, which was consistent with the bridging carbon of the pyrazole pyrimidine ring. LC-MS analysis of compound **3** gave a molecular ion peak with an *m/z* value of 220.7 for [M + H], which was consistent with the molecular formula $C_{11}H_{13}N_3O_2$. The structure of compound **4** was determined by IR, ^{1}H NMR, ^{13}C NMR, and LC-MS analyses. The IR spectrum showed peaks at 3054.8 and 2920.8 cm^{-1}, which were attributed to the −NH stretching vibrations of the amine and amide functionalities of the hydrazide group. The ^{1}H NMR spectrum of compound **4** contained a broad singlet with a chemical shift of 8.89 ppm, which was consistent with the amide proton. The ^{1}H NMR spectrum also contained doublet with a chemical shift of 4.50 ppm, which was consistent with the amine group of the carbohydrazide. The structure of compound **4** was further confirmed by mass spectrometry, which gave a molecular ion peak with an *m/z* value of 206.6 for [M + H], which was consistent with the molecular formula $C_9H_{11}N_5O$. The ^{13}C NMR spectrum of compound **4** contained a signal at 162.34 ppm, which was consistent with the carbonyl group of the hydrazide moiety. The ^{13}C NMR spectrum also contained a peak at 161.97 ppm, which was consistent with the

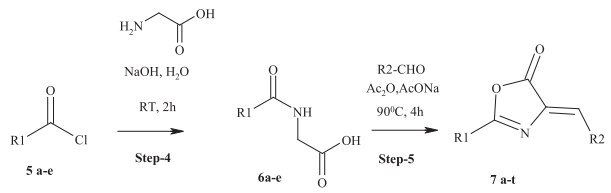
presence of the fused carbon in the pyrazolo[1,5-a] pyrimidine ring.

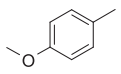
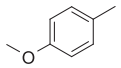
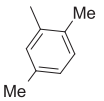
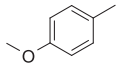
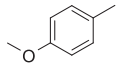
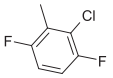
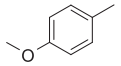
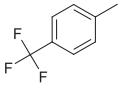
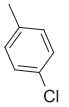
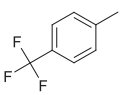
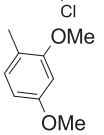
The formation of acid derivatives **6a–e** from the corresponding acid chlorides **5a–e** was confirmed by spectroscopic analysis. The ^{1}H NMR spectra of these compounds all contained a doublet signal in the range of 3.90–3.99 ppm, which suggested that these compounds contained an −NH –CH_2-moiety in their structure. The LC-MS analysis of these compounds gave mass ions that were consistent with their molecular formulae. The IR spectra of compounds **6a–e** revealed the presence of two stretching vibrations for their carbonyl C=O groups. The ^{13}C NMR spectra of all of these compounds contained a signal in the range of 41.6–41.8 ppm, which was consistent with the formation of an −NH–CH_2-moiety in their structure. Furthermore, the ^{13}C NMR spectra of all of these compounds contained two signals in the range of 166–172 ppm, which were consistent with the presence of two carbonyl groups.

The structures of compounds **7a–t** were confirmed by spectroscopic analysis. The IR spectra of compounds **7a–t** contained only one peak for the stretching vibration of a C=O group, while the hippuric acid molecules from which they were prepared contained two carbonyl stretching vibrations. The ^{1}H NMR spectra of compounds **7a–t** all contained a singlet in the range of 7.17–7.6 ppm, which was attributed to the proton on the exocyclic olefin group of their oxazolone ring. The structures of these compounds were further confirmed by LC-MS analysis. The ^{13}C NMR spectra of these compounds showed two signals in the range of 130–135 ppm, which were consistent with the exocyclic carbons of the benzylidine portion of their oxazolone ring. The ^{13}C NMR spectra also contained a signal in the range of 163–165 ppm, which was consistent the bridging carbon between oxygen and the nitrogen atoms (i.e.,−O–C=N) of the oxazolone ring. The physicochemical characteristics of these newly synthesized oxazolone compounds are shown in Table 1.

Table 1

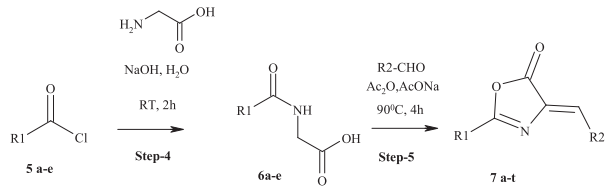
Physicochemical characteristics of compounds (**7a–t**).

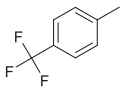
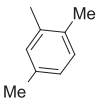
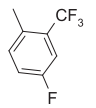
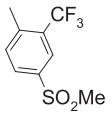
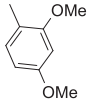
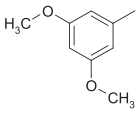
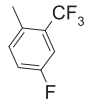
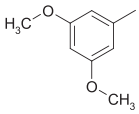
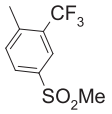
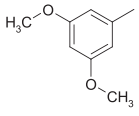
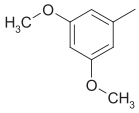
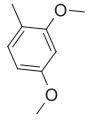


Compound	R1	R2	MF/M. Wt	Yield (%)	MP (°C)[a]
7a			$C_{17}H_{12}FNO_3$/297.28	80	204.2–205.1
7b			C19H17NO3/307.35	76	172.0–173.6
7c			$C_{18}H_{15}NO_4$/309.31	78	200.7–201.8
7d			$C_{17}H_{10}ClF_2NO_3$/349.71	71	174.8–175.4
7e			$C_{17}H_{11}BrFNO_3$/376.17	70	203.8–204.6
7f			$C_{17}H_9ClF_3NO_2$/351.70	81	208.7–210.1
7g			$C_{19}H_{14}F_3NO_4$/377.31	78	212.1–213.0

(*Continued*)

Table 1
(*Continued*)



Compound	R1	R2	MF/M. Wt	Yield (%)	MP (°C)[a]
7h			$C_{17}H_9ClF_3NO_2$/351.70	75	129.3–130.3
7i			$C_{17}H_{12}FNO_2$/281.28	76	166.8–168.1
7j			$C_{17}H_{12}ClNO_2$/297.73	73	151.3–152.3
7k			$C_{19}H_{17}NO_2$/291.34	77	157.1–157.8
7l			$C_{17}H_{11}BrFNO_2$/360.17	72	161.8–163.4
7m			$C_{19}H_{13}F_4NO_2$/363.30	81	156.2–157.6
7n			$C_{20}H_{16}F_3NO_4S$/423.40	83	199.8–201.6
7o			$C_{18}H_{14}ClNO_2$/311.76	80	156.2–157.7
7p			C20H19NO4/337.36	76	209.9–211.6
7q			C19H13F4O4/395.30	80	158.1–159.6
7r			C20H16F3O6S/455.40	79	198.2–199.8
7s			C18H14ClO4/343.76	78	153.4–154.8
7t			C20H19NO6/369.36	81	185.9–187.3

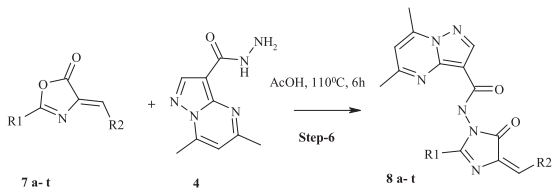
[a]Melting point of compounds at their decomposition.

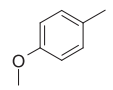
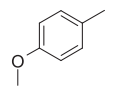
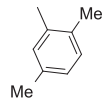
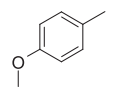
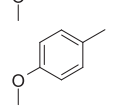
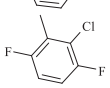
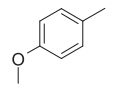
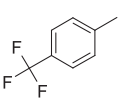
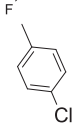
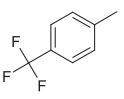
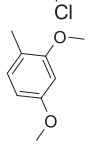
The structures of compounds **8a–t** were confirmed based on their IR, ^{1}H NMR, ^{13}C NMR, and LC-MS analyses. The IR spectrum of **8a** contained two peaks that were consistent with the presence of two carbonyl groups. The first of these bands appeared at 1676 cm^{-1} and was attributed to the carbonyl group of the newly formed imidazolone ring, while the second peak at 1726.7 cm^{-1} was attributed to the C=O group of the carbohydrazide attached to the pyrazolo[1,5-a] pyrimidine. The ^{1}H NMR spectrum of **8a** contained a singlet with a chemical shift of 10.69 ppm, which was attributed to the amide-NH proton. The ^{13}C NMR spectrum of **8a** contained a signal at 163.15 ppm, which was consistent with the presence of a carbonyl functional group in the newly formed imidazolone ring. A signal was also observed at 168.88 ppm, which was attributed to the carbonyl group of the carbohydrazide moiety attached to the pyrazolo[1,5-a]pyrimidine core. The structure of compound **8a** was further confirmed by LC-MS analysis, which gave a molecular ion peak with an *m/z* value of 485.4 [M + H], which was consistent with the molecular formula of compound **8a** (i.e., $C_{26}H_{21}FN_6O_3$). The spectral data generated in the current study were in good agreement with the proposed structures of all of the novel molecules synthesized in this series. The physicochemical characteristics of the newly synthesized imidazolone fused pyrazolo[1,5-a]pyrimidine compounds are shown in Table 2.

Anticancer Evaluation. All of the compounds prepared in the current study were screened for their *in vitro* anticancer activity against HeLa cells, which

Table 2

Physicochemical characteristics of compounds (**8a–t**).

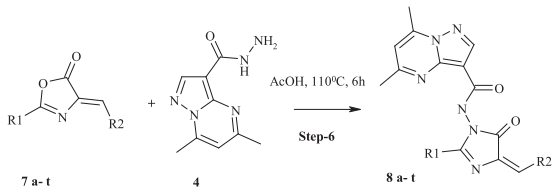


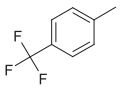
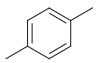
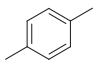
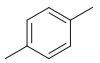
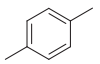
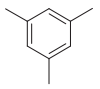
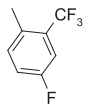
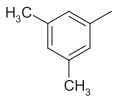
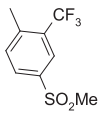
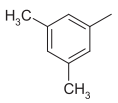
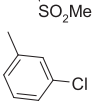
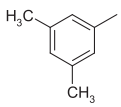
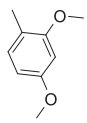
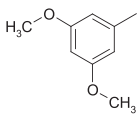
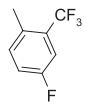
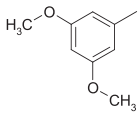
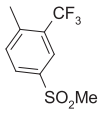
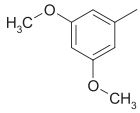
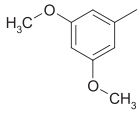
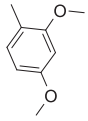
Compound	R1	R2	MF/M. Wt	Yield (%)	MP (°C)[a]
8a			$C_{26}H_{21}FN_6O_3$/484.49	81	146.7–148.1
8b			$C_{28}H_{26}N_6O_3$/494.56	78	138.2–139.4
8c			$C_{27}H_{24}N_6O_4$/496.53	76	138.9–140.2
8d			$C_{26}H_{19}ClF_2N_6O_3$/563.39	83	188.7–190.2
8e			$C_{26}H_{20}BrFN_6O_3$/563.39	79	172.1–173.7
8f			$C_{26}H_{18}ClF_3N_6O_2$/538.92	74	276.8–278.7
8g			$C_{28}H_{23}F_3N_6O_4$/564.53	77	265.9–267.7

(*Continued*)

Table 2

(*Continued*)



Compound	R1	R2	MF/M. Wt	Yield (%)	MP (°C)[a]
8h			$C_{26}H_{18}ClF_3N_6O_2$/538.92	82	203.8–204.6
8i			$C_{26}H_{21}FN_6O_2$/468.49	80	180.3–182.7
8j			$C_{26}H_{21}ClN_6O_2$/484.95	85	211.5–212.9
8k			$C_{28}H_{26}N_6O_2$/478.56	78	195.7–197.2
8l			$C_{26}H_{20}BrFN_6O_2$/547.39	74	254.4–255.5
8m			$C_{28}H_{22}F_4N_6O_2$/550.52	78	221.8–222.8
8n			$C_{29}H_{25}F_3N_6O_4S$/610.62	80	270.1–271.4
8o			$C_{27}H_{23}ClN_6O_2$/498.98	82	188.9–190.6
8p			$C_{29}H_{28}N_6O_4$/524.58	83	196.8–198.1
8q			$C_{28}H_{22}F_4N_6O_4$/582.52	81	198.1–199.8
8r			$C_{29}H_{25}F_3N_6O_6S$/642.62	82	247.2–249.0
8s			$C_{27}H_{23}ClN_6O_4$/530.98	84	201.8–203.5
8t			$C_{29}H_{28}N_6O_6$/556.58	83	216.8–218.0

[a]Melting point of compounds at their decomposition

were used as a representative human cervical cancer cell line, $HepG_2$ cells, which were used as human liver cancer line, and MCF-7 cells, which were used as a representative human breast carcinoma cancer cell line. These cell lines were obtained from American Type Culture Collection. Paclitaxel and SAHA were used as reference standards. The anticancer activities of the compounds are listed in Table 3. These data showed that some of the compounds exhibited good inhibitory activity towards the growth of HeLa, $HePG_2$, and MCF-7 cell lines.

In particular, compounds **8f**, **8g, 8h**, **8m**, **8n**, **8q,** and **8r** showed good anti-proliferative activities against HeLa cells. Furthermore, compounds **8h**, **8m**, **8n**, **8q,** and **8r** exhibited superior anticancer activity than the marketed anticancer drugs Paclitaxel and SAHA. In contrast, all of the other compounds synthesized in this study showed lower levels of anticancer activity than Paclitaxel and SAHA.

In general, compounds **8h**, **8k, 8m**, **8n**, **8p**, **8q, and 8r** showed good anti-proliferative activities against $HePG_2$ cells. Furthermore, compounds **8h**, **8n,** and **8r** exhibited superior anticancer activity than the marketed anticancer drugs Paclitaxel and SAHA. But all of the other compounds synthesized in this study showed lower levels of anticancer activity than Paclitaxel and SAHA in this cell line.

Finally, compounds **8i** and **8r** showed good anti-proliferative activities against MCF-7 cell line. In addition to that, these compounds **8i** and **8r** exhibited superior anticancer activity than the marketed anticancer drugs Paclitaxel and SAHA. In contrast, all of the other compounds synthesized in this study showed lower levels of anticancer activity than Paclitaxel and SAHA in the case of MCF-7 cell line.

Consideration of the structure–activity relationships of these novel compounds (**8a–t**) suggested that the introduction of a bulky trifluoromethyl group (CF_3) at the position *ortho* to the benzylidine ring led to an increase in the anticancer activity compared with a halogen substituent at the same position. A similar trend was also observed for compounds bearing a trifluoromethyl (CF_3) group at the *para* position of the benzene ring compared with a methoxy group (OCH_3) at the same position. Taken together, the results of this study revealed that compounds **8h, 8n,** and **8r** exhibited the greatest anticancer activities of all of the compounds tested against HeLa cells and $HepG_2$ cells. However, the *in vitro* anticancer activity of compound **8r** against HeLa, $HepG_2$, and MCF-7 cell lines is superior to the marketed drugs Paclitaxel and SAHA. It is noteworthy that this compound contained methane sulfonyl group at the *ortho* position and trifluoromethyl group at the *para* position of the benzylidine ring.

Table 3

Anticancer activity of compounds **8a** to **8t**.

		Percentage growth inhibition in different cell lines		
Compound	Concn.(μg)	HeLa	$HepG_2$	MCF-7
8a	10	17.4014	7.7806	4.4554
	20	19.0985	10.8497	12.1099
	30	27.1445	19.6891	18.4576
8b	10	11.6009	3.5714	3.3415
	20	15.3025	7.3202	9.1136
	30	39.1304	22.7979	21.7446
8c	10	5.6844	−2.1683	0.61881
	20	10.3203	−0.5228	6.6167
	30	20.6816	9.4559	13.78
8d	10	9.3967	2.1683	7.797
	20	14.4721	4.0522	10.2372
	30	19.9765	10.2332	14.665
8e	10	6.9605	−2.2959	3.3415
	20	6.287	1.4379	8.3645
	30	7.638	7.5129	11.378
8f	10	52.6682	41.5816	26.7327
	20	53.9739	47.2303	30.7116
	30	59.9295	52.2021	38.5588
8g	10	43.1555	14.1582	22.2772
	20	48.7544	28.7582	30.7116
	30	50.6463	36.2694	43.8685
8h	10	66.2413	61.352	30.9406
	20	66.0735	64.8366	34.9563
	30	74.7356	73.057	37.6738
8i	10	34.8028	37.1173	36.6337
	20	49.2289	40.1307	39.7004
	30	51.1163	45.5959	57.1429
8j	10	39.5592	36.9898	41.3366
	20	49.2289	42.2222	46.1923
	30	51.8214	47.1503	49.4311
8k	10	40.1392	37.3724	38.2426
	20	50.7711	38.9542	45.8177
	30	51.7039	45.7254	47.914
8l	10	19.0985	30.4847	29.8267
	20	19.9536	33.3333	27.3408
	30	24.7944	39.2487	33.8812
8m	10	62.877	43.4949	33.0446
	20	62.5148	45.6209	37.8277
	30	63.3373	47.9275	48.2933
8n	10	67.4014	65.3061	33.4158
	20	68.9205	66.2745	37.9526
	30	75.2056	72.6684	46.2705
8o	10	21.1137	14.9235	16.5842
	20	23.3689	17.3856	23.5955
	30	25.9694	22.2798	25.4109
8p	10	37.355	28.699	17.3267
	20	42.3488	38.4314	19.4757
	30	45.3584	42.0984	23.8938
8q	10	58.0046	50.3827	28.4653
	20	59.6679	52.0261	35.8302
	30	63.4548	57.3834	38.4324
8r	10	72.6218	66.9643	64.2327
	20	73.9027	71.5033	68.04
	30	75.2056	73.7047	71.6814
8s	10	13.9211	2.6785	4.5792
	20	15.777	5.2287	5.8676
	30	27.1445	15.0259	14.0329
8t	10	9.2807	1.403	5.8168
	20	25.7414	20.2614	12.2347

(*Continued*)

Table 3

(*Continued*)

Compound	Concn.(μg)	Percentage growth inhibition in different cell lines HeLa	$HepG_2$	MCF-7
	30	50.1763	37.9534	19.2162
Paclitaxel	10	40.6032	32.6531	34.1584
	20	42.586	37.3856	39.3258
	30	52.879	51.8135	53.3502
SAHA	10	23.6659	21.0459	21.2871
	20	35.2313	29.1503	34.7066
	30	45.5934	40.6736	48.799

HeLa: Cervical carcinoma.
$HepG_2$: Liver carcinoma.
MCF-7: Breast carcinoma.

CONCLUSION

A novel series of imidazolone fused pyrazolo[1,5-a] pyrimidine derivatives has been designed and synthesized using a convergent approach, and the structures of these compounds were confirmed by ^{1}H NMR, ^{13}C NMR, ESI-MS, and IR analyses. These new compounds were tested for their in vitro antiproliferative activity using an MTT assay. Out of the 20 derivatives prepared in the current study, compounds **8h, 8n,** and **8r** exhibited good anticancer activities tested against HeLa cells and $HepG_2$ cells. However, the *in vitro* anticancer activity of compound **8r** against HeLa, $HepG_2$, and MCF-7 cell lines is superior to the marketed drugs Paclitaxel and SAHA.

The results of our *in vitro* anticancer studies revealed that the majority of these derivatives showed high levels of potency against HeLa cells, $HepG_2$, and MCF-7 cell lines. Further structure–activity relationship studies on these compounds are therefore currently in progress in our laboratory.

EXPERIMENTAL

Chemistry chemicals were of analytical grade and obtained from Sigma-Aldrich Co. The purification of all intermediates and final compounds was carried out by column chromatography using Merck silica gel with 230–400 mesh size. The purity of synthesized compounds was determined by thin layer chromatography experiments, performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). Thin-layer chromatography (TLC) observation of these plates were carried out by illuminating under UV (254 nm) lamp and $KMnO_4$ stain solution. Melting points were determined using Buchi B-540 instrument (Buchi India Pvt. Ltd., Mumbai, India) and are uncorrected. All ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and Bruker AM-400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR), Bruker BioSpin Corp., Germany. Molecular weights for all the synthesized compounds were checked by LC-MS 6200 series Agilent Technology (Agilent, Bangalore, India). The chemical shifts are reported in parts per million (δ) with reference to TMS as an internal standard. The signals are designed as follows: s, singlet; d, doublet; t, triplet; m, multiplet; and brs, broad singlet. IR spectra for all the compounds were recorded using a Bruker Alpha FTIR spectrometer using a diamond attenuated total reflection (ATR) single reflectance module (24 scans). Elemental analysis was carried out with a Perkin-Elmer model 240-C apparatus (Perkin-Elmer, Bangalore, India). The results of elemental analysis (C, H, and N) were within ± 0.4% of the calculated amounts.

Ethyl 5-amino-1H-pyrazole-4-carboxylate (2). To a solution of ethylcyanoacetate (**1**) (25 g, 221.0 mmol) in dimethylformamide (25 mL) and acetic acid (37.5 mL), dimethylformamide dimethylacetal (47.40 g, 397.8 mmol) was added drop wise at room temperature under nitrogen over a period of 30 min and then stirred at room temperature for 2 h. The reaction mixture was cooled to 0°C and added hydrazine hydrate (25 mL, 80%) drop wise over a period of 45 min and then heated to 50°C for 2 h. Completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ice cold water (1 L) and then extracted to ethyl acetate (2 × 250 mL). The combined ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. Crude material obtained was purified by column chromatography over silica gel, eluted with 2–5% methanol in chloroform to afford ethyl 5-amino-1H-pyrazole-4-carboxylate (**2**) as an off-white solid (24 g, 70%). MP: 106.7–108.9°C; IR (ATR, cm^{-1}) υ: 1125.41 (C–O), 1337.61 (C–N), 1496.40 (C–C), 1615.86 (N–H bend), 1662.37 (ester C = O), 2972.92 (C–H), 3193.79 (N–H stretch); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (t, J = 7.2 Hz, 3H, ester–CH_3), 4.16 (q, J = 6.9 Hz, 2H, ester–CH_2), 5.99 (bs, 2H, pyrazole–NH_2), 7.47 (bs, 1H, pyrazole–CH), 11.84 (bs, 1H, pyrazole–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.92, 59.10, 94.00, 139.93, 151.86, 164.27; LC-MS (ESI, *m/z*): 156.7 (M + H). *Anal.* Calcd. for $C_6H_9N_3O_2$ (155.16): C, 46.45; H, 5.85; N, 27.08. Found: C, 46.39; H, 5.94; N, 27.19.

Ethyl5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxylate (3). Ethyl 5-amino-1*H*-pyrazole-4-carboxylate (**2**) (10 g, 64.4 mmol) was dissolved in acetic acid (20 mL), and acetyl acetone (6.45 g, 64.4 mmol) was added drop wise to it at room temperature, and the resulting solution was heated to 82°C for 8 h under a nitrogen atmosphere. Completion of the reaction was monitored by TLC. Then after, the reaction mixture was concentrated under reduced pressure to remove excess acetic acid, and residue was stirred with

diisopropyl ether at room temperature for 30 min. Precipitated solid was filtered, washed with diisopropyl ether, and dried under high vacuum to afford ethyl 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3**) as a pale yellow solid (12.7 g, 90%). MP: 101.9–103.1°C; IR (ATR, cm^{-1}) υ: 1031.98 (C–N), 1123.05 (C–N), 1181.78 (C–N), 1241.32 (C–O), 1549.20 (C–C), 1683.38 (C=O), 2920.75 (C–H), 3054.82 (C–H), 3099.87 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.31 (t, J = 7.2 Hz, 3H, ester–CH_3), 2.57 (s, 3H, pyrimidine–CH_3), 2.70 (s, 3H, pyrimidine–CH_3), 4.27 (q, J = 7.2 Hz, 2H, ester–CH_2), 7.11 (s, 1H, pyrazole–CH), 8.52 (s, 1H, pyrimidine–CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 14.79, 16.86, 24.85, 59.69, 101.19, 110.93, 146.75, 146.87, 147.34, 162.13, 162.58; LC-MS (ESI, *m/z*): 220.7 (M + H). *Anal.* Calcd. for $C_{11}H_{13}N_3O_2$ (219.25): C, 60.26; H, 5.98; N, 19.17. Found: C, 60.20; H, 6.07; N, 19.26.

5,7-dimethylpyrazolo[1,5-a]pyrimidine-3-carbohydrazide (4). To a suspension of ethyl 5,7-dimethylpyrazolo[1,5-*a*] pyrimidine-3-carboxylate (**3**) (10 g, 45.6 mmol) in ethanol (100 mL) was added 80% hydrazine hydrate (8.55 g, 136.8 mmol) drop wise at 0°C and then heated to 72°C for 7 h under nitrogen atmosphere. Completion of the reaction was monitored by TLC. After completion of the reaction, the reaction medium was concentrated under reduced pressure and residue obtained was stirred with ice cold ethanol for 30 min. Precipitated solid was filtered, washed with cold ethanol, and dried under high vacuum to obtain 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) as an off-white solid (7.86 g, 84%). MP: 158.3–159.8°C; IR (ATR, cm^{-1}) υ: 1035.43 (C–O), 1194.30 (C–N), 1262.26 (C–N), 1559.68 (C–C), 1664.51 (C=O), 2955.95 (C–H), 3038.81 (C–H), 3210.03 (N–H), 3307.80 (N–H), 3348.28 (N–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.60 (s, 3H, pyrimidine–CH_3), 2.72 (s, 3H, pyrimidine–CH_3), 4.50 (bs, 2H, NH_2), 7.10 (s, 1H, pyrimidine–H), 8.50 (s, 1H, pyrazole–H), 8.89 (bs, 1H, amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 16.94, 24.78, 103.54, 110.53, 145.20, 145.51, 147.53, 161.97, 162.34; LC-MS (ESI, *m/z*): 206.6 (M + H). *Anal.* Calcd. for $C_9H_{11}N_5O$ (205.22): C, 52.68; H, 5.40; N, 34.13. Found: C, 52.61; H, 5.51; N, 34.19.

General Procedure for the Synthesis of Hippuric Acid Derivatives (6a–e). Glycine (2 g, 26.64 mmol) was dissolved in sodium hydroxide (10% aqueous solution, 20 mL) at 0°C, and the corresponding acid chlorides **(5a–e)** (26.64 mmol) were added drop wise. After addition was complete, reaction medium was slowly allowed to reach room temperature (25°C) and vigorously stirred for 2–3 h. Completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured to ice cold water and acidified with 4 N aqueous hydrochloric acid under stirring. The reaction medium was stirred for 30 min, and the precipitated solid was filtered, washed with cold water, and dried under vacuum at 55–60°C for 1 h. The crude product was further recrystallized from suitable solvent system to yield the title compounds (**6a–e**).

[(4-Methoxyphenyl) carbonyl] amino} Acetic Acid (6a). This compound was prepared by reacting glycine in aqueous sodium hydroxide solution with 4-methoxybenzoyl chloride **5a**. It was obtained as a pale yellow solid after drying process and on further crystallized from THF: Toluene (1:4, V) at room temperature to obtain [(4-methoxyphenyl) carbonyl] amino} acetic acid (**6a**) as an off-white solid (4.4 g, 79%). MP: 174.2–176.2°C; IR (ATR, cm^{-1}) υ: 1184.11 (ether–C–O), 1221.56 (acid–C–O), 1264.43 (C–N stretch of amide), 1507.19 (C–C of aromatic), 1611.75 (amide C=O), 1742.97 (acid C=O), 3365.89 (N–H amide); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.82 (s, 3H, Ar–OMe), 3.90 (d, J = 6 Hz, 2H, glycine–CH_2), 7.02 (d, J = 8.7 Hz, 2H, Ar–H and Ar–H), 7.86 (d, J = 9 Hz, 2H, Ar–H and Ar–H), 8.71(t, J = 6 Hz, 1H, amide–NH), 12.42 (bs,1H, acid–OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 41.64, 55.80, 114.01, 126.55, 129.57, 162.17, 166.46, 172.00; LC-MS (ESI, *m/z*): 210.4 (M + H). *Anal.* Calcd. for $C_{10}H_{11}NO_4$ (209.20): C, 57.41; H, 5.30; N, 6.70. Found: C, 57.34; H, 5.38; N, 6.81.

({[4-(Trifluoromethyl) phenyl] carbonyl} amino) Acetic Acid (6b). This compound was prepared by treating glycine in aqueous sodium hydroxide with 4-trifluoromethylbenzoyl chloride **5b**. It was obtained as yellow solid after drying process and on further crystallized from THF: n-Heptane (1:4 V) at room temperature to obtain ({[4-(trifluoromethyl) phenyl] carbonyl} amino) acetic acid (**6b**) as an off-white solid (4.9 g, 75%), MP: 157.4–159.2°C; IR (ATR, cm^{-1}) υ: 1016.92 (−C–F), 1046.24 (−C–F), 1331.43 (acid–C–O), 1638.98 (amide–C=O), 1746.81 (acid–C=O), 2986.13 (O–H), 3329.02 (amide–N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.96 (d, J = 5.7Hz, 2H, glycine–CH_2–), 7.89 (d, J = 8.1 Hz, 2H, Ar–H and Ar–H), 8.08 (d, J = 7.8 Hz, 2H, Ar–H and Ar–H), 9.124 (t, J = 5.4 Hz, 1H, amide–NH), 12.70 (bs, 1H, acid–OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 41.76, 120.33, 123.03, 125.74, and 128.45 (q, $^1J_{C-F}$ = 271 Hz, −CF_3), 125.83, 125.87, 125.91, and 125.94 (q, $^3J_{C-F}$ = 4 Hz, ArC and ArC), 128.63 (ArC and ArC), 131.34, 131.65, 131.97, and 132.29 (q, $^2J_{C-F}$ = 32 Hz), 138.04, 165.84, 171.56; LC-MS (ESI, *m/z*): 248.6 (M + H). *Anal.* Calcd. for $C_{10}H_8F_3NO_3$ (247.18): C, 48.59; H, 3.26; N, 5.67. Found: C, 48.52; H, 3.32; N, 5.74.

{[(4-Methylphenyl) carbonyl] amino} Acetic Acid (6c). This compound was prepared by reacting glycine in sodium hydroxide with p-toluoyl chloride **5c**. It was obtained as yellow solid after drying process and was further crystallized from THF: Toluene (1:5, V) at room temperature to afford {[(4-methylphenyl) carbonyl] amino} acetic acid (**6c**) off-white solid (3.96 g, 77%). MP: 163.2–164.9°C; IR (ATR, cm^{-1}) υ: 1304 (−C–O), 1638.40 (amide–C=O), 1739.27 (acid–C=O), 2934.21 (−O–H), 3420.90 (amide–N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.37 (s, 3H, Ar–Me),

3.92 (d, J = 5.7Hz, 2H, glycine–CH_2–), 7.29 (d, J = 6.6 Hz, 2H, Ar–H and Ar–H), 7.78 (d, J = 8.1 Hz, 2H, Ar–H and Ar–H), 8.76 (t, J = 5.6 Hz, 1H, amide–NH), 12.45 (bs, 1H, acid–OH); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 21.36, 41.58, 127.66, 129.27, 131.49, 141.69, 166.76, 171.81; LC-MS (ESI, *m/z*): 194.4 (M + H). *Anal.* Calcd. for $C_{10}H_{11}NO_3$ (193.20): C, 62.17; H, 5.74; N, 7.25. Found: C, 62.11; H, 5.83; N, 7.36.

{[(3,5-Dimethylphenyl) carbonyl] amino} Acetic Acid (6d). This compound was prepared by reacting glycine in aqueous sodium hydroxide with 3,5-dimethylbenzoyl chloride **5d**. It was obtained as a pale green solid after drying process and was further crystallized from THF: n-Heptane (1: 5 V) at room temperature to obtain {[(3,5-dimethylphenyl) carbonyl] amino} acetic acid (**6d**) as an off-white solid (4.19 g, 76%). MP: 167.5–168.9°C; IR (ATR, cm^{-1}) υ: 1309 (−C–O), 1700.61 (amide–C=O), 1743.60 (acid–C=O), 2971.98 (O–H), 3312.21 (amide–N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.38 (s, 6H, Ar-Me), 3.91 (d, J = 5.7Hz, 2H, glycine–CH_2), 7.09 (s, 1H, Ar–H), 7.62 (s, 2H, Ar–H and Ar–H), 8.86 (t, J = 5.4 Hz, 1H, amide–NH), 12.65 (bs, 1H, acid-OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.30, 41.63, 125.89, 132.38, 132.57, 137.54, 167.16, 171.85; LC-MS (ESI, *m/z*): 208.4 (M + H). *Anal.* Calcd. for $C_{11}H_{13}NO_3$ (207.23): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.69; H, 6.39; N, 6.85.

[(3,5-Dimethoxyphenyl) carbonyl] amino} Acetic Acid (6e). This compound was prepared by reacting glycine in aqueous sodium hydroxide with 3,5-dimethoxybenzoyl chloride (**5e**). It was obtained as a pale yellow solid after drying process and was further crystallized from THF: Toluene (1:4, V) at room temperature to obtain [(3,5-dimethoxyphenyl) carbonyl] amino} acetic acid (**6e**) as an off-white solid (4.58 g, 72%). MP: 178.1–179.7°C; IR (ATR, cm^{-1}) υ: 1312 (−C–O), 1690.59 (amide C=O), 1758.97 (acid C=O), 2912.92 (O–H), 3317.27 (amide N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.79 (s, 6H, Ar–OMe and Ar–OMe), 3.91 (d, J = 5.7Hz, 2H, glycine–CH_2–), 6.67 (t, J = 2.1Hz, 1H, Ar–H), 7.03 (d, J = 2.1Hz, 2H, Ar–H and Ar–H), 8.82 (t, J = 5.7 Hz, 1H, amide–NH), 12.63 (bs, 1H, acid–OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 41.72, 55.85, 103.84, 105.63, 136.38, 160.83, 166.53, 171.80; LC-MS (ESI, *m/z*): 240.4 (M + H). *Anal.* Calcd. for $C_{11}H_{13}NO_5$ (239.23): C, 55.23; H, 5.48; N, 5.85. Found: C, 55.16; H, 5.57; N, 5.96.

General Procedure for the Synthesis of Substituted Oxazolones (7a–t). To a suspension of substituted acid **(6a–e)** (500 mg, 2.39 mmol) in acetic anhydride (5 mL), sodium acetate (1.19 mmol) and corresponding aldehyde (2.39 mmol) were taken and heated to 90°C for 4 h under argon atmosphere. Completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was slowly warmed to room temperature (25°C) and poured into ice cold water to precipitate the product. The resulted medium was stirred for further 30 min at room temperature (25°C). The precipitated solid was filtered, washed with cold water, and dried under vacuum at 55–60°C for 3 h. Solid obtained previously was further purified by silica gel column chromatography using 2–5% of methanol in chloroform as the eluent system. The obtained solid was further recrystallized from ethanol to afford the title compounds **(7a–t)**.

(4Z)-4-(2-Fluorobenzylidene)-2-(4-methoxyphenyl)-1,3-oxazol-5(4H)-one (7a). This compound was prepared by reaction of {[(4-methoxyphenyl) carbonyl] amino} acetic acid (**6a**) with 2-fluoro benzaldehyde. It was obtained as a pale yellow solid (710 mg, 80%). MP: 204.2–205.1°C; IR (ATR, cm^{-1}) υ: 841.18 (C–H bend), 1020.42 (C–F), 1095.72 (C–O), 1163.39 (C–O), 1204.61 (C–O), 1265.65 (C–O), 1305.65 (C–N), 1424.97 (C–C), 1500.41 (C–C), 1549.04 (C–C), 1600.54 (C–C), 1644.42 (C=C), 1780.31 (C=O), 3099.31 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.90 (s, 3H, Ar–OMe), 7.17 (s, 1H, benzylidene–H), 7.19 (d, J = 7.3Hz, 2H, Ar–H and Ar–H), 7.20–7.44 (m, 2H, Ar–H), 7.54–7.60 (m, 1H, Ar–H), 8.11 (d, J = 7.2 Hz, 2H, Ar–H and Ar–H), 8.83 (t, J = 5.8 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.63, 114.58, 115.45, and 115.67 (d, $^2J_{C-F}$ = 22 Hz), 117.70, 120.73, and 120.80 (d, $^3J_{C-F}$ = 7 Hz), 122.01 and 122.12 (d, $^3J_{C-F}$ = 11 Hz), 124.58, 130.63, 132.48, and 132.60 (d, $^2J_{C-F}$ = 12 Hz), 134.52, 160.63, and 163.17(d, $^1J_{C-F}$ = 254 Hz), 164.05, 164.12, 167.46; LC-MS (ESI, *m/z*): 298.6 (M + H). *Anal.* Calcd. for $C_{17}H_{12}FNO_3$ (297.29): C, 68.68; H, 4.07; N, 4.71. Found: C, 68.62; H, 4.17; N, 4.78.

(4Z)-4-(2,5-Dimethylbenzylidene)-2-(4-methoxyphenyl)-1,3-oxazol-5(4H)-one (7b). This compound was prepared by reaction of {[(4-methoxyphenyl) carbonyl] amino} acetic acid (**6a**) with 2,5-dimethyl benzaldehyde. It was obtained as a pale yellow solid (558 mg, 76%). MP: 172.0–173.6°C; IR (ATR, cm^{-1})υ: 834.66 (C–H bend), 1018.39 (C–O), 1089.57 (C–O), 1164.99 (C–O), 1255.89 (C–O), 1305.07 (C–N), 1403.39 (C–C), 1500.81 (C–C), 1553.10 (C–C), 1602.22 (C–C), 1642.26 (C=C), 1776.98 (C=O), 3068.69 (C–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.38 (s, 3H, Ar–Me), 2.44 (s, 3H, Ar–Me), 3.89 (s, 3H, Ar–OMe), 7.18–7.22 (m,4H, ArH), 7.30 (s, 1H, benzylidene–H), 8.08 (d, J = 8 Hz, 2H, Ar–H), 8.55 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.62, 21.30, 55.58, 114.50, 117.96), 127.28, 130.40, 130.58, 131.88, 132.04, 132.41, 133.16, 135.92, 136.84, 163.59, 163.85, 168.16; LC-MS (ESI, *m/z*): 308.13 (M + H). *Anal.* Calcd. for $C_{19}H_{17}NO_3$ (307.35): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.19; H, 5.64; N, 4.65.

(4Z)-4-(2-Methoxybenzylidene)-2-(4-methoxyphenyl)-1,3-oxazol-5(4H)-one (7c). This compound was prepared by reaction of {[(4-methoxyphenyl) carbonyl] amino} acetic acid (**6a**) with 2-methoxybenzaldehyde. It was obtained as a pale yellow solid (577 mg, 78%). MP: 200.7–201.8°C; IR (ATR, cm^{-1}) υ: 836.60 (C–H bend), 1024.38 (C–O), 1097.39 (C–O), 1172.90 (C–O), 1219.90 (−C–O), 1256.44 (C–O), 1307.67 (C–O), 1307.67 −(C–N), 1423.58 (C–C), 1500.65 (C–C),

1553.47 (−C–C), 1599.59 (C–C), 1644.14 (−C=C), 1780.84 (C=O), 3017.06 (C–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.89 (s, 3H, Ar–OMe), 3.92 (s, 3H, Ar–OMe), 7.12–7.19 (m, 4H, ArH), 7.48–7.51 (m, 2H, ArH and benzylidene–H), 8.08 (d, J = 8 Hz, 2H, Ar–H), 8.77 (d, J = 4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.59, 55.68, 110.74, 114.47, 118.14, 120.98, 122.87, 124.43, 130.34), 132.62, 132.77, 132.78, 159.15, 162.92, 163.73, 168.18; LC-MS (ESI, *m/z*): 310.7 (M + H). *Anal.* Calcd. for $C_{18}H_{15}NO_4$ (309.32): C, 69.89; H, 4.89; N, 4.53. Found: C, 69.82; H, 4.96; N, 4.64.

(4Z)-4-(2-Chloro-3,6-difluorobenzylidene)-2-(4-methoxyphenyl)-1,3-oxazol-5(4H)-one (7d). This compound was prepared by reaction of {[(4-methoxyphenyl) carbonyl] amino} acetic acid (**6a**) with 2-chloro-3,6-difluoro benzaldehyde. It was obtained as an off-white solid (592 mg, 71%). MP: 174.8–175.4°C; IR (ATR, cm^{-1}) υ: 782.11 (C–Cl), 839.30 (C–H bend), 975.95 (C–F), 1021.12 (C–F), 1098.88 (C–O), 1171.38 (C–O), 1236.38 (C–O), 1309.47 (C–N), 1417.36 (C–C), 1471.19 (C–C), 1504.75 (C–C), 1557.95 (C–C), 1601.39 (C–C), 1660.96 (C=C), 1791.97 (C=O), 3035.48 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.87 (s, 3H, Ar–OMe), 7.14–7.19 (m, 3H, ArC and benzylidene–H), 7.44–7.50 (tt, J_1 = 4.4 Hz, J_2 = 8.8 Hz, 1H, Ar–H), 7.60–7.66 (tt, J_1 = 4.8 Hz, J_2 = 8.8 Hz, 1H, Ar–H), 8.04 (d, J = 8.8 Hz, 2H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.64, 114.57, 114.62–115.29, 117.19–117.71, 119.61, 121.89–122.71, 130.60, 130.95, 138.61, 139.06, 153.51–157.57, 163.35, 164. 27, 166.77, and 164.79, 164.32, 164.43, 166.18; LC-MS (ESI, *m/z*): 350.4 (M + H). *Anal.* Calcd. for $C_{17}H_{10}ClF_2NO_3$ (349.72): C, 58.39; H, 2.88; N, 4.01. Found: C, 58.30; H, 2.97; N, 4.10.

(4Z)-4-(2-Bromo-5-fluoro benzylidene)-2-(4-methoxyphenyl)-1,3-oxazol-5(4H)-one (7e). This compound was pre pared by reaction of {[(4-methoxy phenyl) carbonyl] amino} acetic acid (**6a**) with 2-bromo-5-fluorobenzaldehyde. It was obtained as a pale yellow solid (625 mg, 70%). MP: 203.8–204.6°C; IR (ATR, cm^{-1}) υ: 690.23 (C–Br), 836.61 (C–H bend), 1025.55 (C–F), 1102.15 (C–O), 1165.23 (C–O), 1240.23 (C–O), 1268.85 (C–O), 1314.45 (C–N), 1457.94 (C–C), 1505.50 (C–C), 1555.47 (C–C), 1603.84 (C–C), 1653.40 (C=C), 1785.19 (C=O), 2975.12 (C–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.90 (s, 3H, Ar–OMe), 7.20 (d, J = 6.8 Hz, 2H, Ar–H), 7.27 (s, 1H, benzylidene–H), 7.32–7.37 (dt, J_1 = 3.9 Hz, J_2 = 8.1 Hz, 1H, Ar–H), 7.83 (t, J = 9.2 Hz, 1H, Ar–H), 8.12 (d, J = 6.8 Hz, 2H, Ar–H), 8.62 (dd, J_1 = 5.68 Hz, J_2 = 7.8 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.68, 114.70, 117.30, 118.76, and 118.99 (d, $^2J_{C–F}$ = 24 Hz), 119.65 and 119.90 (d, $^2J_{C–F}$ = 25 Hz), 121.34, 125.94, 130.94, 134.32, and 134.35 (d, $^3J_{C–F}$ = 8 Hz), 134.75 and 134.84 (d, $^3J_{C–F}$ = 9 Hz), 135.85, 160.52, and 162.98 (d, $^1J_{C–F}$ = 245 Hz), 164.48, 164.96, 167.10; LC-MS (ESI, *m/z*): 376.6 (M + H). *Anal.* Calcd. for $C_{17}H_{11}BrFNO_3$ (376.18): C, 54.28; H, 2.95; N, 3.72. Found: C, 54.19; H, 3.04; N, 3.81.

(4Z)-4-(4-Chlorobenzylidene)-2-[4-(trifluoromethyl) phenyl]-1,3-oxazol-5(4H)-one (7f). This compound was prepared by reaction of ({[4-(trifluoromethyl) phenyl] carbonyl} amino) acetic acid (**6b**) with 4-chlorobenzaldehyde. It was obtained as an off-white solid (576 mg, 81%). MP: 208.7–210.1°C; IR (ATR, cm^{-1}) υ: 725.07 (C–Cl), 821.38 (C–H bend), 956.15 (C–F), 994.14 (C–F), 1027.66 (C–F), 1102.55 (C–O), 1268.63 (C–O), 1318.99 (C–N), 1407.78 (C–C), 1452.15 (C–C), 1499.82 (C–C), 1551.82 (C–C), 1647.10 (C=C), 1788.68 (C=O), 3060.35 (C–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.47 (s, 1H, benzylidene–H), 7.63 (d, J = 12 Hz, 2H, Ar–H), 8.01 (d, J = 8 Hz, 2H, Ar–H), 8.33 (t, J = 8 Hz, 4H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 119.46, 122.16, 124.87, and 127.57 (q, $^1J_{C–F}$ = 271Hz), 125.96, 126.00, 126.04, and 126.07 (q, $^3J_{C–F}$ = 3.6 Hz), 128.71, 129.41, 131.73, 131.80, 133.13, 133.76, 134.26, 134.58, 134. 91, and 135.24 (q, $^2J_{C–F}$ = 32.7 Hz), 137.91, 162.56, 166.82; LC-MS (ESI, *m/z*): 352.7 (M + H). *Anal.* Calcd. for $C_{17}H_9ClF_3NO_2$ (351.71): C, 58.06; H, 2.58; N, 3.98. Found: C, 58.01; H, 2.67; N, 4.07.

(4Z)-4-(2,4-Dimethoxybenzylidene)-2-[4-(trifluoromethyl) phenyl]-1, 3-oxazol-5(4H)-one (7g). This compound was prepared by reaction of ({[4-(trifluoromethyl) phenyl] carbonyl} amino) acetic acid (**6b**) with 2,4-dimethoxy benzaldehyde. It was obtained as a pale yellow solid (603 mg, 78%). MP: 212.1–213.0°C; IR (ATR, cm^{-1}) υ: 851.11 (C–H bend), 891.55 (C–F), 978.43 (C–F), 1012.75 (C–F), 1063.49 (C–O), 1092.84 (C–O), 1128.50 (C–O), 1165.25 (C–O), 1321.73 (C–N), 1409.48 (C–C), 1486.52 (C–C), 1559.16 (C–C), 1585.37 (C–C), 1657.54 (C=C), 1793.14 (C=O), 3061.21 (C–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 3.89 (s, 3H, Ar–OMe), 3.94 (s, 3H, Ar–OMe), 6.69 (d, J = 2.4 Hz, 1H, Ar–H), 6.78 (dd, J_1 = 6.8 Hz, J_2 = 8.8 Hz, 1H, Ar–H), 7.59 (s, 1H, benzylidene–H), 7.98 (d, J = 8 Hz, 2H, Ar–H), 8.27 (d, J = 8 Hz, 2H, Ar–H), 8.78 (d, J = 9.2 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 55.65, 55.75, 97.70, 106.56, 115.98, 119.60, 122.30, 125.01, and 129.72 (q, $^1J_{C–F}$ = 270.7 Hz), 125.83, 125.86, and 125.90 (t, $^3J_{C–F}$ = 3.6 Hz), 127.94, 128.22, 129.46, 129.57, 133.41, 133.74, 134.07, and 134.39 (q, $^2J_{C–F}$ = 33 Hz), 134.79, 160.41, 161.47, 164.65, 167.76; LC-MS (ESI, *m/z*): 378.8 (M + H). *Anal.* Calcd. for $C_{19}H_{14}F_3NO_4$ (377.32): C, 60.48; H, 3.74; N, 3.71. Found: C, 60.41; H, 3.82; N, 3.83.

(4Z)-4-(3-Chlorobenzylidene)-2-[4-(trifluoromethyl) phenyl]-1,3-oxazol-5(4H)-one (7h). This compound was prepared by reaction of ({[4-(trifluoromethyl) phenyl] carbonyl} amino) acetic acid (**6b**) with 3-chlorobenzaldehyde. It was obtained as an off-white solid (532 mg, 75%). MP: 129.3–130.3°C; IR (ATR, cm^{-1}) υ: 822. 44 (C–Cl), 852.39 (C–H bend), 888.71 (C–F), 978.32 (C–F), 1025.02 (C–F), 1166.10 (C–O), 1275.00 (C–O), 1323.62 (C–N), 1413.96 (C–C),

1463.64 (C–C), 1503.16 (C–C), 1605.68 (C–C), 1647.10 (C=C), 1794.12 (C=O), 3074.76 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 7.46 (s, 1H, benzylidene–H), 7.58–7.60 (m, 2H, Ar–H), 8.02 (d, J = 8.4 Hz, 2H, Ar–H), 8.32 (d, J = 8.3 Hz, 2H, Ar–H), 8.31–8.36 (m, 1H, Ar–H), 8.37 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 119.43, 122.14, 124.85, 127.57 (q, $^1J_{C-F}$ = 271.3 Hz), 125.96, 126.00, 126.04, 126.07 (q, $^3J_{C-F}$ = 4 Hz), 128.64, 128.79, 130.17, 130.71, 131.33, 131.42, 131.99, 133.79, 134.36, 134.69, 135.02, 135.34 (q, $^2J_{C-F}$ = 33 Hz), 134.84), 135.01, 162.96, 166.57; LC MS (ESI, *m/z*): 352.6 (M + H). *Anal.* Calcd. for $C_{17}H_9ClF_3NO_2$ (351.71): C, 58.06; H, 2.58; N, 3.98. Found: C, 58.02; H, 2.65; N, 4.09.

(4Z)-4-(2-Fluorobenzylidene)-2-(4-methylphenyl)-1,3-oxazol-5 (4H)-one (7i). This compound was prepared by reaction of {[(4-methylphenyl) carbonyl] amino} acetic acid (**6c**) with 2-fluoro benzaldehyde. It was obtained as an off-white solid (553 mg, 76%). MP: 166.8–168.1°C; IR (ATR, cm^{-1}) υ: 871.89 (C–H bend), 981.53 (C–F), 1097.13 (C–O), 1199.84 (C–O), 1291.88 (C–N), 1415.88 (C–C), 1487.25 (C–C), 1546.61 (C–C), 1606.95 (C–C), 1649.54 (C=C), 1799.72 (C=O), 3060.59 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.42 (s, 3H, Ar–Me), 7.23 (s, 1H, benzylidene–H), 7.32–7.41 (m, 2H, Ar–H), 7.44 (d, J = 8.1Hz, 2H, Ar–H), 7.53–7.60 (m, 1H, Ar–H), 8.02 (d, J = 8.1Hz, 2H, Ar–H), 8.81 (t, J = 7.5 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 21.83, 115.32, and 115.61 (d, $^2J_{C-F}$ = 21.6 Hz, 121.43 and 121.52 (d, $^3J_{C-F}$ = 7.42 Hz), 121.78 and 121.92 (d, $^2J_{C-F}$ = 10.65 Hz), 122.55, 124.51, and 124.56 (d, $^3J_{C-F}$ = 3.52 Hz), 128.44, 129.69, 132.60, 132.68, 134.29, 144.61, 160.17, and 163.56 (d, $^1J_{C-F}$ = 254.7 Hz), 164.25, 167.19; LC MS (ESI, *m/z*): 282.7 (M + H). *Anal.* Calcd. for $C_{17}H_{12}FNO_2$ (281.29): C, 72.59; H, 4.30; N, 4.98. Found: C, 72.52; H, 4.38; N, 5.09.

(4Z)-4-(3-Chlorobenzylidene)-2-(4-methylphenyl)-1,3-oxazol-5 (4H)-one (7j). This compound was prepared by reaction of {[(4-methylphenyl) carbonyl] amino} acetic acid (**6c**) with 3-chloro benzaldehyde. It was obtained as an off-white solid (562 mg, 73%). MP: 151.3–152.3°C; IR (ATR, cm^{-1}) υ: 825.04 (C–Cl), 879.20 (C–H bend), 1161.64 (C–O), 1278. 90 (C–O), 1362.45 (C–N), 1422.00 (C–C), 1457.73 (C–C), 1507.13 (C–C), 1564.39 (C–C), 1652.91 (C=C), 1788.20 (C=O), 3009.98 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.44 (s, 1H, Ar–Me), 7.32 (s, 1H, benzylidene–H), 7.47 (d, J = 8.1 Hz, 2H, Ar–H), 7.56 (dd, J_1 = 3.6 Hz, J_2 = 6.4 Hz, 2H, Ar–H), 8.03 (d, J = 8.1 Hz,2H, Ar–H), 8.28 (t, J = 6.3 Hz, 2H, Ar–H), 8.35 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 17.19, 117.74, 123.84, 124.09, 125.05, 125.26, 125.62, 125.99, 126.97, 129.73, 130.06, 130.53, 140.06, 159.64, 162.58; LC MS (ESI, *m/z*): 298.6 (M + H). *Anal.* Calcd. for $C_{17}H_{12}ClNO_2$ (297.74): C, 68.58; H, 4.06; N, 4.70. Found: C, 68.51; H, 4.12; N, 4.79.

(4Z)-4-(2,5-Dimethylbenzylidene)-2-(4-methylphenyl)-1,3-oxazol-5(4H)-one (7k). This compound was prepared by reaction of {[(4-methylphenyl) carbonyl] amino} acetic acid (**6c**) with 2,5-dimethyl benzaldehyde. It was obtained as a pale yellow solid (580 mg, 77%). MP: 157.1–157.8°C; IR (ATR, cm^{-1}) υ: 866.58 (C–H bend), 1095.61 (C–O), 1170.76 (C–O), 1290.13 (C–N), 1322.29 (C–N), 1411.48 (C–C), 1497.60 (C–C), 1552.05 (C–C), 1607.66 (C–C), 1645.02 (C=C), 1788.40 (C=O), 3024.82 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.37 (s, 3H, Ar–Me), 2.43 (s, 6H, Ar–Me and Ar–Me), 7.21 (s, 2H, Ar–H), 7.33 (s, 1H, benzylidene–H), 7.44 (d, J = 8.1Hz, 2H, Ar–H), 7.99 (d, J = 7.8 Hz, 2H, Ar–H), 8.52 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 19.49, 21.18, 21.81, 122.81, 128.04, 128.27), 129.62, 130.50, 131.85, 131.95, 132.43, 132.94, 135.86, 136.87, 144.18, 163.58, 167.91; LC-MS (ESI, *m/z*): 292.7 (M + H).*Anal.* Calcd. for $C_{19}H_{17}NO_2$ (291.35): C, 78.33; H, 5.88; N, 4.81. Found: C, 78.28; H, 5.96; N, 4.89.

(4Z)-4-(2-Bromo-5-fluorobenzylidene)-2-(4-methylphenyl)-1,3-oxazol-5(4H)-one (7l). This compound was prepared by reaction of {[(4-methylphenyl) carbonyl] amino} acetic acid (**6c**) with 2-bromo-5-fluorobenzaldehyde. It was obtained as a pale yellow solid (670 mg, 72%). MP: 161.8–163.4°C; IR (ATR, cm^{-1}) υ: 678.94 (C–Br), 852.06 (C–H bend), 988.94 (C–F), 1107.67 (C–O), 1173.46 (C–O), 1324.80 (C–N), 1414.41 (C–C), 1474.31 (C–C), 1511.12 (C–C), 1560.25 (C–C), 1656.01 (C=C), 1804.03 (C=O), 3082.46 (C–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.43 (s, 3H, Ar–Me), 7.29 (s, 1H, benzylidene-H), 7.30–7.35 (dt, J_1 = 3.2 Hz, J_2 = 8 Hz, 1H, Ar–H), 7.46 (d, J = 8 Hz, 2H, Ar–H), 7.84 (t, J = 8.8 Hz, 1H, Ar–H), 8.03 (d, J = 8 Hz, 2H, Ar–H), 8.61 (dd, J_1 = 7.2 Hz, J_2 = 10.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 21.94, 118.96, and 119.19 (d, $^2J_{C-F}$ = 23.3 Hz), 119.76 and 120.01 (d, $^2J_{C-F}$ = 24.9 Hz), 121.49 and 121.53 (d, $^3J_{C-F}$ = 3.3 Hz), 122.29, 126.83, and 126.86 (d, $^3J_{C-F}$ = 2.6 Hz), 128.79, 129.90, 134.30, and 134.38 (d, $^2J_{C-F}$ = 8.1 Hz), 134.59 and 134.68 (d, $^2J_{C-F}$ = 8.8 Hz), 135.25, 135.67, 145.27, 160.51, and 162.96 (d, $^1J_{C-F}$ = 245 Hz), 165.29, 166.94; LC MS (ESI, *m/z*): 362.9 (M + 2H). *Anal.* Calcd. for $C_{17}H_{11}BrFNO_2$ (360.19): C, 56.69; H, 3.08; N, 3.89. Found: C, 56.62; H, 3.17; N, 3.98.

(4Z)-2-(3,5-Dimethylphenyl)-4-[4-fluoro-2-(trifluoromethyl) benzy lidene]-1,3-oxazol-5(4H)-one (7m). This compound was prepared by reaction of {[(3,5-dimethylphenyl) carbonyl] amino} acetic acid (**6d**) with 4-fluoro-2-trifluoro methyl benzaldehyde. It was obtained as an off-white solid (700 mg, 81%). MP: 156.2–157.6°C; IR (ATR, cm^{-1}) υ: 808.09 (C–H bend), 837.05 (C–F), 905.10 (C–F), 983.26 (C–F), 1046.97 (C–F), 1107.47 (C–O), 1157.08 (C–O), 1289.56 (C–N), 1318.97 (C–N), 1433.33 (C–C), 1492.90 (C–C), 1560.39 (C–C), 1604.66 (C–C), 1655.35 (C=C), 1807.65 (C=O), 3081.77 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.40 (s, 6 H, Ar–Me), 7.20 (s, 1H, Ar–H),

7.25 (s, 1H, Ar–H), 7.47 (s, 1H, Ar–H), 7.77 (s,1H, Ar–H), 7.85 (dt, J_1 = 8.9 Hz, J_2 = 5.2 Hz, 1H, Ar–H), 9.03 (dt, J_1 = 8.6 Hz, J_2 = 5.6 Hz, 1H, Ar–H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 21.18, 113.99–114.42 (m, $^2J_{C-F}$ = 25 Hz), 119.07 and 119.27 (d, $^2J_{C-F}$ = 21 Hz), 118.95, 121.65, 124.38, and 127.11 (q, $^1J_{C-F}$ = 271 Hz), 123.36, 123.38, and 123.40 (t, $^3J_{C-F}$ = 3Hz), 124.86, 126.37, 127.66, and 127.694 (d, $^3J_{C-F}$ = 2.5 Hz), 131.80–132.49 (dq, $^2J_{1C-F}$ = 24 Hz, $^2J_{2C-F}$ = 7 Hz), 135.22, 135.24, 136.03, 136.12, 138.91, 161.54, and 164.08 ($^1J_{C-F}$ = 253.7 Hz), 165.65, 166.85; LC MS (ESI, *m/z*): 364.4 (M + H). *Anal.* Calcd. for $C_{19}H_{13}F_4NO_2$ (363.31): C, 62.81; H, 3.61; N, 3.86. Found: C, 62.76; H, 3.69; N, 3.95.

(4Z)-2-(3,5-Dimethylphenyl)-4-[4-(methylsulfonyl)-2-(trifluoromethyl)benzylidene]-1,3-oxazol-5(4H)-one (7n). This compound was prepared by reaction of {[(3,5-dimethylphenyl) carbonyl] amino} acetic acid (**6d**) with 4-methyl sulf-onyl-2-trifluoro methyl benzaldehyde. It was obtained as an off-white solid (846 mg, 83%). MP: 199.8–201.6°C; IR (ATR, cm^{-1}) υ: 848.88 (=C–H bend), 1012.53 (C–F), 1059.35 (C–F), 1158.09 (C–F), 1206.06 (C–O), 1255.44 (C–O), 1313.02 (C–N), 1354.73 (C–N), 1425.59 (C–C), 1464.99 (C–C), 1561.78 (C–C), 1602.92 (C–C), 1656.13 (C=C), 1798.20 (C=O), 3014.21 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.39 (s, 6H, Ar–Me), 3.33 (s, 3H, Ar–SO_2Me), 7.22 (s, 1H, Ar–H), 7.41(s, 1H, Ar–H), 7.78 (s, 2H, Ar–H), 8.31(s, 1H, Ar–H), 8.43 (d, J = 8.7 Hz, 1H, Ar–H), 9.09 (d, J = 8.4 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 21.17, 55.78, 106.56, 107.14, 118.88, 121.62, 124.36, and 127.10 (q, $^1J_{C-F}$ = 274 Hz), 122.56 and 122.58 (d, $^3J_{C-F}$ = 2.2 Hz), 125.42, and 125.48 (d, $^3J_{C-F}$ = 5.9 Hz), 126.28, 130.72, 130.57, 130.88, 131.20, and 131.51 (q, $^2J_{C-F}$ = 31 Hz), 134.52, 135.28, 136.17, 136.56, 137.89, 140.89, 166.06, 166.88; LC-MS (ESI, *m/z*): 424.6 (M + H). *Anal.* Calcd. for $C_{20}H_{16}F_3NO_4S$ (423.41): C, 56.73; H, 3.81; N, 3.31. Found: C, 56.66; H, 3.89; N, 3.39.

(4Z)-4-(3-Chlorobenzylidene)-2-(3,5-dimethylphenyl)-1,3-oxazol-5(4H)-one (7o). This compound was prepared by reaction of {[(3,5-dimethylphenyl) carbonyl] amino} acetic acid (**6d**) with 3-chloro benzaldehyde. It was obtained as a pale yellow solid (600 mg, 80%). MP: 156.2–157.7°C; IR (ATR, cm^{-1}) υ: 788. 65 (C–Cl), 888.09 (C–H bend), 1166.29 (C–O), 1221.37 (C–O), 1275.06 (C–N), 1327.63 (C–N), 1431.79 (C–C), 1462.45 (C–C), 1563.40 (C–C), 1599.23 (C–C), 1653.60 (C=C), 1789.10 (C=O), 3070.49 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.40 (s, 6H, Ar–Me), 7.37 (d, J = 8.1 Hz, 2H, Ar–H), 7.57 (d, J = 8.1 Hz, 2H, Ar–H), 7.75 (s, 2H, Ar–H), 8.32 (s, 2H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 21.25, 125.07, 126.29, 129.07, 130.06, 130.38, 130.81, 131.7, 134.45, 134.82, 135.25, 135.63, 138.79, 164.59, 167.29; LC-MS (ESI, *m/z*): 312.8 (M + H). *Anal.* Calcd. for $C_{18}H_{14}ClNO_2$ (311.77): C, 69.35; H, 4.53; N, 4.49. Found: C, 69.28; H, 4.59; N, 4.54.

(4Z)-4-(2,4-Dimethoxybenzylidene)-2-(3,5-dimethylphenyl)-1,3-oxazol-5(4H)-one (7p). This compound was prepared by reaction of {[(3,5-dimethylphenyl) carbonyl] amino} acetic acid (**6d**) with 2, 4-dimethoxybenzaldehyde. It was obtained as an off-white solid (619 mg, 76%). MP: 209.9–211.6°C; IR (ATR, cm^{-1}) υ: 898.72 (=C–H bend), 1032.17 (C–O), 1111.31 (C–O), 1168.28 (C–O), 1224.17 (C–O), 1284.19 (C–N), 1461.01 (C–C), 1499.76 (C–C), 1559.28 (C–C), 1601.21 (C–C), 1644.53 (C=C), 1774.14 (C=O), 3010.95 (C–H), 3053.23 (C–H), 3090.52 (C–H). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.41 (s, 6H, Ar–Me), 3.90 (s, 6H, Ar–OMe), 6.45 (d, J = 2.4 Hz, 1H, Ar–H), 6.68 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, Ar–H), 7.21 (s, 1H, Ar–H), 7.78 (d, J = 3.2 Hz, 3H, Ar–H), 8.90 (d, J = 8.8 Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.13, 55.47, 55.59, 97.65, 106.21, 116.18, 125.67, 125.78, 130.25, 134.10, 134.51, 138.47, 160.98, 162.14, 163.95, 168.22; LC-MS (ESI, *m/z*): 338.5 (M + H). *Anal.* Calcd. for $C_{20}H_{19}NO_4$ (337.38): C, 71.20; H, 5.68; N, 4.15. Found: C, 71.11; H, 5.77; N, 4.26.

(4Z)-2-(3,5-Dimethoxyphenyl)-4-[4-fluoro-2-(trifluoromethyl) benzylidene]-1,3-oxazol-5(4H)-one (7q). This compound was prepared by reaction of [(3,5-dimethoxyphenyl) carbonyl] amino} acetic acid (**6e**) with 4-fluoro-2-trifluoro methyl benzaldehyde. It was obtained as an off-white solid (660 mg, 80%). MP: 158.1–159.6°C; IR (ATR, cm^{-1}) υ: 837.08 (=C–H bend), 1044. 78 (C–F), 1106.69 (C–F), 1156.24 (C–F), 1208.26 (C–O), 1257.44 (C–O), 1288.66 (C–N), 1319.77 (C–N), 1432.43 (C–C), 1491.80 (C–C), 1561.23 (C–C), 1602.76 (C–C), 1653.35 (−C=C), 1799.65 (C=O), 3078.76 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.84 (s, 6H, Ar–OMe and Ar–OMe), 6.89 (s, 1H, Ar–H), 7.22 (s, 3H, Hz, Ar–H), 7.83 (dt, J_1 = 9 Hz, J_2 = 5.16 Hz, 2H, Ar–H), 9.03 (dt, J_1 = 8.7 Hz, J_2 = 5.7 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 44.46, 113.69–114.48 (m, $^2J_{C-F}$ = 25 Hz), 119.06 and 119.26 (d, $^2J_{C-F}$ = 21 Hz), 118.97, 121.67, 124.40, and 127.13 (q, $^1J_{C-F}$ = 271 Hz), 123.37, 123.39, and 123.41 (t, $^3J_{C-F}$ = 3Hz), 124.82, 126.33, 127.63, and 127.66 (d, $^3J_{C-F}$ = 2.5 Hz), 131.80–132.49 (dq, $^2J_{1C-F}$ = 24 Hz, $^2J_{2C-F}$ = 7 Hz), 135.29, 136.06, 138.98, 161.27, 161.54, and 164.08 ($^1J_{C-F}$ = 253.7 Hz), 165.67, 166.88; LC-MS (ESI, *m/z*): 396.0 (M + H). *Anal.* Calcd. for $C_{19}H_{13}F_4NO_4$ (395.31): C, 57.73; H, 3.31; N, 3.54. Found: C, 57.66; H, 3.40; N, 3.64.

(4Z)-2-(3,5-Dimethoxyphenyl)-4-[4-(methylsulfonyl)-2-(trifluoromethyl) benzylidene]-1,3-oxazol-5(4H)-one (7r). This compound was prepared by reaction of [(3,5-dimethoxyphenyl) carbonyl] amino} acetic acid (**6e**) with 4-methane sulfonyl-2-trifluoro methyl benzaldehyde. It was obtained as an off-white solid (750 mg, 79%). MP: 198.2–199.8°C; IR (ATR, cm^{-1}) υ: 847.98 (C–H bend), 913.10 (C–F), 966.79 (C–F), 1011.73 (C–F), 1058.15 (C–O), 1157.07 (C–O), 1205.96 (C–O), 1256.34 (C–O), 1312.02 (C–N), 1354.33 (C–N), 1424.39 (C–C), 1464.79 (C–C), 1560.78 (C–C), 1602.72 (C–C), 1655.13 (C=C), 1799.20 (C=O), 3013.21 (C–H); ^{1}H

NMR (300 MHz, DMSO-d_6) δ (ppm): 3.39 (s, 3H, Ar–SO_2Me), 3.87 (s, 6H, Ar–OMe), 6.93 (s, 1H, Ar–H), 7.25 (s, 1H, Ar–H), 7.27 (s, 2H, Ar–H), 8.32 (s, 1H, Ar–H), 8.44 (d, J = 8.1 Hz, 1H, Ar–H), 9.13 (d, J = 8.1 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 44.45, 55.79, 106.59, 107.34, 118.85, 121.59, 124.33, and 127.07 (q, $^1J_{C-F}$ = 274 Hz), 122.53 and 122.55 (d, $^3J_{C-F}$ = 2.2 Hz), 125.39 and 125.45 (d, $^3J_{C-F}$ = 5.9 Hz), 126.29, 130.76, 130.58, 130.89, 131.21, and 131.52 (q, $^2J_{C-F}$ = 31 Hz), 134.54, 136.51, 137.91, 141.36, 161.22, 166.04, 166.85; LC-MS (ESI, *m/z*): 456.5 (M + H). *Anal.* Calcd. for $C_{20}H_{16}F_3NO_6S$ (455.41): C, 52.75; H, 3.54; N, 3.08. Found: C, 52.68; H, 3.62; N, 3.14.

(4Z)-4-(3-Chlorobenzylidene)-2-(3,5-dimethoxyphenyl)-1,3-oxazol-5(4H)-one (7s). This compound was prepared by reaction with [(3,5-dimethoxyphenyl) carbonyl] amino} acetic acid (**6e**) with 3-chloro benzaldehyde. It was obtained as an off-white solid (557 mg, 78%). MP: 153.4–154.8°C; IR (ATR, cm^{-1}) υ: 781.46 (C–Cl), 886.57 (=C–H bend), 1007.52 (C–O), 1061.55 (C–O), 1101.47 (C–O), 1202.32 (C–O), 1317.87 (C–N), 1359.96 (C–N), 1429.01 (C–C), 1471.40 (C–C), 1563.86 (C–C), 1602.33 (C–C), 1649.70 (C=C), 1808.81 (C=O), 3095.64 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.87 (s, 3H, Ar–OMe), 6.88 (s, 1H, Ar–H), 7.21(d, J = 8.2 Hz, 2H, Ar–H), 7.37 (d, J = 3.9 Hz, 1H, Ar–H), 7.57 (d, J = 8.2 Hz, 2H, Ar–H), 8.28 (t, J = 6.4 Hz, 1H, Ar–H), 8.35 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 55.72, 106.15, 106.53, 126.96, 129.87, 130.11, 130.50, 131.02, 131.90, 134.29, 134.90, 135.11, 161.09, 164.20, 167.20; LC-MS (ESI, *m/z*): 344.9 (M + H). *Anal.* Calcd. for $C_{18}H_{14}ClNO_4$ (343.77): C, 62.89; H, 4.10; N, 4.07. Found: C, 62.80; H, 4.19; N, 4.18.

(4Z)-4-(2, 4-Dimethoxybenzylidene)-2-(3,5-dimethoxyphenyl)-1,3-oxazol-5(4H)-one (7t). This compound was prepared by reaction with [(3,5-dimethoxyphenyl) carbonyl] amino} acetic acid (**6e**) with 2,4-dimethoxy benzaldehyde. It was obtained as an off-white solid (623 mg, 81%). MP: 185.9–187.3°C; IR (ATR, cm^{-1}) υ: 827.10 (=C–H bend), 1012.52 (C–O), 1033.68 (C–O), 1058.80 (C–O), 1112.45 (C–O), 1163.95 (C–O), 1209.32 (C–O), 1279.67 (C–N), 1308.14 (C–N), 1423.67 (C–C), 1463.78 (C–C), 1502.18 (C–C), 1564.87 (C–C), 1601.69 (C–C), 1649.29 (−C=C), 1775.22 (C=O), 3097.29 (C–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.85 (s, 6H, Ar–OMe), 3.88 (s, 3H, Ar–OMe), 3.93 (s, 3H, Ar–OMe), 6.68 (d, J = 2.3 Hz, 1H, Ar–H), 6.77–6.87 (m, 2H, Ar–H), 7.17 (d, J = 2.1 Hz, 2H, Ar–H), 7.53 (s, 1H, Ar–H), 8.77 (d, J = 9.0 Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 55.60, 55.70, 97.72, 105.63, 105.66, 106.35, 116.14, 126.50, 127.78, 130.07, 134.65, 161.00, 161.21, 161.71, 164.24, 168.24; LC-MS (ESI, *m/z*): 370.6 (M + H). *Anal.* Calcd. for $C_{20}H_{19}NO_6$ (369.38): C, 65.03; H, 5.18; N, 3.79. Found: C, 65.09; H, 5.22; N, 3.86.

General Procedure for the Synthesis of (8a–t). 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg, 0.974 mmol) and the corresponding oxazolone derivatives (**7a–t)** (0.974 mmol) were suspended in acetic acid (2 mL) and heated to 110°C for 6 h under argon atmosphere. Completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured to ice cold water, stirred for 30 min. The precipitated solid was filtered, washed with cold water, and dried under vacuum at 55–60°C for 1–2 h. The solid obtained was further purified by silica gel column chromatography using 2–5% of methanol in chloroform as the eluent system and was further recrystallized from ethanol to yield the title compounds **(8a–t)**.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(2-fluoro-phenyl)-meth-(Z)-ylidene]-2-(4-methoxy phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8a). This compound was prepared by reaction of 5,7-dimethyl pyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2-fluorobenzylidene)-2-(4-methoxy phenyl)-1,3-oxazol-5(4*H*)-one (**7a**). It was obtained as a pale yellow solid (382 mg, 81%). MP: 146.7–148.1°C; IR (ATR, cm^{-1}) υ: 756.22 (C–H bend), 1026.48 (C–N), 1175.38 (C–O), 1198.66 (C–O), 1257.63 (C–N), 1299.19 (C–N), 1501.61 (C–C), 1556.58 (C–C), 1632.67 (C=C),1676.49 (C=O),1726.68 (C=O), 2936.24 (C–H), 3331.17 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.68 (s, 3H, pyrimidine–Me), 2.77 (s, 3H, pyrimidine–Me), 3.80 (s, 3H, Ar–OMe), 7.08 (d, J = 8.7 Hz, 2H, Ar–H), 7.21 (s, 1H, benzylidene–H), 7.23 (s, 1H, pyrazole–CH), 7.33–7.46 (m, 2H, Ar–H), 7.56–7.68 (m, 1H, Ar–H), 8.13 (d, J = 8.7 Hz, 2H, Ar–H), 8.62 (s, 1H, pyrimidine–H), 8.98 (t, J = 6.3 Hz, 1H, Ar–H), 10.69 (s, 1H, Amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.96, 24.70, 55.97, 101.77, 114.81, 115.96, and 116.17 (d, $^2J_{C-F}$ = 21 Hz), 116.37 and 116.44 (d, $^2J_{C-F}$ = 7 Hz), 119.92, 122. 17, 122.28 (d, $^3J_{C-F}$ = 11 Hz), 125.54, 131.03, 132.95, and 133.03 (d, $^3J_{C-F}$ = 8 Hz), 138.06, 145.93, 146.48, 147.80, 161.07, 160.46, and 162.97 (d, $^1J_{C-F}$ = 251 Hz), 161.82, 163.13, 163.15, 168.88; LC-MS (ESI, *m/z*): 485.4 (M + H). *Anal.* Calcd. for $C_{26}H_{21}FN_6O_3$ (484.49): C, 64.46; H, 4.37; N, 17.35. Found: C, 64.39; H, 4.45; N, 17.46.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid 4-[1-(2,5-dimethyl-phenyl)-meth-(Z)-ylidene]-2-(4-methoxy-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8b). This compound was prepared by reaction with 5,7-Dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2,5-dimethylbenzylidene)-2-(4-methoxyphenyl)-1,3-oxazol-5 (4*H*)-one (**7b**). It was obtained as a pale yellow solid (388 mg, 78%). MP: 138.2–139.4°C; IR (ATR, cm^{-1}) υ: 839.67 (C–H bend), 1028.29 (C–N), 1112.49 (C–O), 1181.20 (C–O), 1256.94 (C–N), 1301.72 (C–N), 1500.66 (C–C), 1556.38 (C–C), 1631.52 (C=C), 1684.29 (C=O), 1729.62 (C=O), 2922.28 (C–H), 3245.30 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.35 (s, 3H, Ar–Me), 2.44 (s, 3H, Ar–Me), 2.67 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 3.78 (s, 3H, Ar–OMe), 7.06 (d, J = 9.2 Hz, 2H, Ar–H),

7.18–7.22 (m, 3H, Ar–H), 7.29 (s, 1H, benzylidene–H), 8.09 (d, J = 9.2 Hz, 2H, Ar–H), 8.61 (s, 1H, pyrazole–CH), 8.66 (s, 1H, pyrimidine–CH), 10.66 (s, 1H, amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.96, 21.63, 24.85, 55.93, 101.71, 111.29, 114.78, 125.38, 126.83, 129.91, 130.89, 131.03, 132.45, 133.27, 135.68, 136.09, 146.31, 146.56 147.27, 160.14, 161.44, 162.47, 163.06, 168.93; LC-MS (ESI, *m/z*): 495.3 (M + H). *Anal.* Calcd. for $C_{28}H_{26}N_6O_3$ (494.56): C, 68.00; H, 5.30; N, 16.99. Found: C, 67.93; H, 5.38; N, 17.08.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid {2-(4-methoxy-phenyl)-4-[1-(2-methoxy-phenyl)-meth-(Z)-ylidene]-5-oxo-4,5-dihydro-imidazol-1-yl}-amide (8c). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2-methoxybenzylidene)-2-(4-meth oxyphenyl)-1,3-oxazol-5(4*H*)-one (**7c**). It was obtained as a pale yellow solid (379 mg, 76%). MP: 138.9–140.2°C; IR (ATR, cm^{-1}) υ: 757.16 (C–H bend), 1027.70 (C–N), 1112.18 (C–O), 1181.88 (C–O), 1253.70 (C–N), 1302.14 (C–N), 1499.77 (C–C), 1555.95 (C–C), 1630.71 (C=C), 1684.79 (C=O), 1728.81 (C=O), 2939.39 (C–H), 3253.74 (N–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.66 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 3.78 (s, 3H, Ar–OMe), 3.92 (s, 3H, Ar–OMe), 7.05 (d, J = 8.8 Hz, 2H, Ar–H), 7.10–7.14 (m, 2H, Ar–H), 7.20 (s, 1H, benzylidene–H), 7.45–7.49 (m, 1H, Ar–H), 7.52 (s, 1H, pyrazole–CH), 8.09 (d, J = 8.8 Hz, 2H, Ar–H), 8.61 (s, 1H, pyrimidine–CH), 8.92 (d, J = 6.4 Hz, 1H, Ar–H), 10.65 (s, 1H, amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.96, 19.73, 21.62, 24.83, 55.92, 101.76, 111.32, 114.83, 121.13, 125.46, 126.93, 128.29, 129.94, 130.88, 131.09, 132.47, 136.83, 146.41, 146.59, 147.33, 160.18, 16 1.42, 162.54, 162.85, 163.18, 168.76; LC-MS (ESI, *m/z*): 497.3 (M + H). *Anal.* Calcd. for $C_{27}H_{24}N_6O_4$ (496.53): C, 65.31; H, 4.87; N, 16.93. Found: C, 65.23; H, 4.98; N, 17.02.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(2-chloro-3,6-difluoro-phenyl)-meth-(Z)-ylidene]-2-(4-methoxy-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8d). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4)** (200 mg) with (4*Z*)-4-(2-chloro-3,6-difluoro benzylidene)-2-(4-methoxyphenyl)-1,3-oxazol-5(4*H*)-one (**7d**). It was obtained as an off-white solid (433 mg, 83%). MP: 188.7–190.2°C; IR (ATR, cm^{-1}) υ: 839.73(C-H bend), 1026.33 (C–N), 1118.84 (C–O), 1181.32 (C–O), 1260.71 (C–N), 1296.93 (C–N), 1476.00 (C–C), 1502.89 (C–C), 1555.80 (C–C), 1605.01 (C=C), 1685.14 (C=O),1742.75 (C=O), 3071.05 (C–H), 3239.96 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.68 (s, 3H, pyrimidine–Me), 2.77 (s, 3H, pyrimidine–Me), 3.77 (s, 3H, Ar–OMe), 7.03 (d, J = 9 Hz, 2H, Ar–H), 7.19 (s, 1H, benzylidene–H), 7.23 (s, 1H, pyrazole–CH), 7.46–7.50 (m, 1H, Ar–H), 7.58–7.62 (m, 1H, Ar–H), 7.97 (d, J = 9 Hz, 2H, Ar–H), 8.63 (s, 1H, pyrimidine–CH), 10.67 (s, 1H, Amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.96, 24.70, 55.95, 101.69, 111.28, 114.76, 119.26, and 119. 51 (d, $^2J_{1C-F}$ = 18.75 Hz), 119.58, 119.61, and 119.84 (d, $^2J_{1C-F}$ = 17.25 Hz), 121.3 6 and 121. 40 (d, $^3J_{C-F}$ = 4 Hz), 121.85, 131.17, 135.00, and 135.13 (d, $^3J_{C-F}$ = 9.75 Hz), 135.25, 139.11, 145.93, 146.48, 147.81, 159.93, and 163.08 (d, $^1J_{1C-F}$ = 236.25 Hz), 161.03, 162.92, 163.16, 163.42, 168.87; LC-MS (ESI, *m/z*): 537.4 (M + H). *Anal.* Calcd. for $C_{26}H_{19}ClF_2N_6O_3$ (536.93): C, 58.16; H, 3.57; N, 15.65. Found: C, 58.08; H, 3.68; N, 15.76.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(2-bromo-5-fluoro-phenyl)-meth-(Z)-ylidene]-2-(4-methoxy-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8e). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2-bromo-5-fluorobenzylidene)-2-(4-methoxyphenyl)-1,3-oxazol-5(4*H*)-one (**7e**). It was obtained as a pale yellow solid (432 mg, 79%). MP: 172.1–173.7°C; IR (ATR, cm^{-1}) υ: 906.54 (=C–H bend), 1027.16 (C–N), 1104.62 (C–O), 1118.13 (C–O), 1172.08 (C–O), 1261.25 (C–N), 1236.46 (C–N), 1299.54 (C–N), 1423.56 (C–C), 1458.06 (C–C), 1500.62 (C–C), 1559.11 (C–C), 1627.10 (C=C),1674.78 (C=O), 1734.83 (C=O), 3068.53 (C–H), 3213.39 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.68 (s, 3H, pyrimidine–Me), 2.73 (s, 3H, pyrimidine–Me), 3.80 (s, 3H, Ar-OMe), 7.09 (d, J = 9 Hz, 2H, Ar–H), 7.21 (s, 1H, benzylidene–H), 7.29 (s, 1H, pyrazole–CH), 7.31–7.36 (m, 1H, Ar–H), 7.82–7.87 (m, 1H, Ar–H), 8.13 (d, J = 9 Hz, 2H, Ar–H), 8.63 (s, 1H, pyrimidine–CH), 8.83 (dd, J_1 = 3 Hz, J_2 = 10.5 Hz, 1H, Ar–H), 10.71 (s, 1H, Amide–NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.94, 24.69, 56.00, 101.69, 111.28, 114.95, 119.26, and 119. 51 (d, $^2J_{1C-F}$ = 18.75 Hz), 119.58, 119.61–119.84 (d, $^2J_{1C-F}$ = 17.25 Hz), 121.3 6 and 121.40 (d, $^3J_{C-F}$ = 4 Hz), 121.85, 131.17, 135.00, and 135.13 (d, $^3J_{C-F}$ = 9.75 Hz), 135.25, 139.11, 145.93, 146.48, 147.81, 159.93, and 163.08 (d, $^1J_{C-F}$ = 236.25 Hz), 161.03, 162.92, 163.16, 163.42, 168.87; LC-MS (ESI, *m/z*): LC-MS (ESI, *m/z*): 565.4 (M + 2H). *Anal.* Calcd. for $C_{26}H_{20}BrFN_6O_3$ (563.39): C, 55.43; H, 3.58; N, 14.92. Found: C, 55.36; H, 3.67; N, 15.04.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-1-(4-chloro-phenyl)-meth-(Z)-ylidene]-5-oxo-2-(4-trifluoromethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-amide (8f). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(4-chlorobenzylidene)-2-[4-(trifluoro methyl) phenyl]-1,3-oxazol-5(4*H*)-one (**7f**). It was obtained as a pale yellow solid (400 mg, 74%). MP: 276.8–278.7°C; IR (ATR, cm^{-1}) υ: 757.15 (C–H bend), 1017.44 (C–F), 1065.78 (C–N), 1123.24 (C–O), 1176.81 (C–O), 1233.00 (C–N), 1300.93 (C–N), 1321.35 (C–N), 1418.54 (C–C), 1495.28 (C–C), 1556.45 (C–C), 1588.22 (C–C), 1625. 91 (–C=C), 1687.02 (C=O), 1741.20 (C=O), 3040.33 (C–H), 3192.63 (N–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.67 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 7.21 (s, 1H, benzylidene–H), 7.43 (s, 1H, pyrazole–CH), 7.61 (d, J = 8 Hz, 2H, Ar–H), 7.92

(d, J = 8 Hz, 2H, Ar–H), 8.28 (d, J = 8 Hz, 2H, Ar–H), 8.41 (d, J = 8 Hz, 2H, Ar–H), 8.61 (s, 1H, pyrimidine–CH), 10.68 (s, 1H, amide–NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.93, 24.71, 101.58, 111.26, 120.1, 122.81, 125.52, and 128.23 (q, $^{1}J_{C-F}$ = 271 Hz), 126.18 and 126.22 (d, $^{3}J_{C-F}$ = 4 Hz), 128.60, 129.49, 129.74, 131.84, 131.72, 132.04, 132.36, and 132.68 (q, $^{2}J_{C-F}$ = 32 Hz), 133.05, 134.69, 136.21, 136.87, 145.95, 146.50, 147.81, 160.73, 161.21, 163.20, 168.58; LC-MS (ESI, *m/z*): 539.4 (M + H). *Anal.* Calcd. for $C_{26}H_{18}ClF_3N_6O_2$ (538.92): C, 57.95; H, 3.37; N, 15.59. Found: C, 57.88; H, 3.46; N, 15.71.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(2,4-dimethoxy-phenyl)-meth-(Z)-ylidene]-5-oxo-2-(4-trifluoromethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-amide (8g). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2,4-dimethoxy benzylidene)-2-[4-(trifluoromethyl) phenyl]-1,3-oxazol-5(4*H*)-one (**7g**). It was obtained as a pale yellow solid (435 mg, 77%). MP: 265.9–267.7°C; IR (ATR, cm^{-1}) υ: 756.80 (=C–H bend), 1026.17 (C–F), 1068.52 (C–N), 1107.59 (C–O), 1166.52 (C–O), 1232.39 (C–N), 1282.96 (C–N), 1321.29 (C–N), 1421.90 (C–C), 1465.22 (C–C), 1506.10 (C–C), 1558.86 (C–C), 1603.90 (C=C), 1683.26 (C=O), 1719.93 (C=O), 2963.09 (C–H), 3366.08 (N–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.67 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 3.89 (s, 3H, Ar–OMe), 3.95 (s, 3H, Ar–OMe), 6.69 (s, 1H, Ar–H), 6.77 (d, J = 8 Hz, 1H, Ar–H), 7.20 (s, 1H, benzylidene–H), 7.61 (s, 1H, pyrazole–CH), 7.89 (d, J = 8 Hz, 2H, Ar–H), 8.25 (d, J = 8 Hz, 2H, Ar–H), 8.60 (s, 1H, pyrimidine–CH), 8.92 (d, J = 12 Hz, 1H, Ar–H), 10.65 (s, 1H, amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.96, 24.72, 56.16, 56.55, 98.37, 101.70, 101.80, 111.26, 120.14, 122.85, 125.56, and 128.27 (q, $^{1}J_{C-F}$ = 271 Hz), 126.19 and 126.23 (d, $^{3}J_{C-F}$ = 4 Hz), 128.42, 129.18, 131.70, 132.02, 132.34, and 132.66 (q, $^{2}J_{C-F}$ = 32 Hz), 132.24, 133.72, 134.72, 145.94, 146.50, 147.81, 158.17, 161.23, 161.57, 163.17, 164.41, 168.56; LC-MS (ESI, *m/z*): 565.5 (M + H). *Anal.* Calcd. for $C_{28}H_{23}F_3N_6O_4$ (564.53): C, 59.57; H, 4.11; N, 14.89. Found: C, 59.49; H, 4.20; N, 14.98.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(3-chloro-phenyl)-meth-(Z)-ylidene]-5-oxo-2-(4-trifluoromethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-amide (8h). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(3-chlorobenzylidene)-2-[4-(trifluoromethyl) phenyl]-1,3-oxazol-5 (4*H*)-one (**7h**). It was obtained as an off-white solid (429 mg, 82%). MP: 203.8–204.6°C; IR (ATR, cm^{-1}) υ: 680.43 (=C–H bend), 850.26 (C–Cl), 1017.04 (C–F),1066.94 (C–N), 1130.09 (C–O), 1167.69 (C–O), 1234.15 (C–N), 1271.13 (C–N), 1324.64 (C–N), 1419.52 (C–C), 1444.23 (C–C), 1495.80 (C–C), 1559.20 (C–C), 1646.02 (−C=C), 1683.87 (C=O), 1738.30 (C=O), 2956.07 (C–H), 3316.04 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.68 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 7.22 (s, 1H, benzylidene–H), 7.42 (s, 1H, pyrazole–CH), 7.57 (d, J = 5.1 Hz, 2H, Ar–H), 7.94 (d, J = 8.1 Hz, 2H, Ar–H), 8.29 (d, J = 8.2 Hz, 2H, Ar–H), 8.35 (t, J = 6.1 Hz, 1H, Ar–H), 8.47 (s, 1H, Ar–H), 8.61 (s, 1H, pyrimidine–CH), 10.69 (s, 1H, Amide–NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.92, 24.72, 101.57, 111.23, 120.08, 122.79, 125.50, and 128.21 (q, $^{1}J_{C-F}$ = 271 Hz), 125.78, 126.20, and 126.24 (q, $^{3}J_{C-F}$ = 4 Hz), 128.12), 128.36, 128.92, 129.09, 129.74, 131.64, 131.96, 132.28, and 132.60 (q, $^{2}J_{C-F}$ = 32 Hz), 133.34, 135.98, 136.76, 136.84, 145.93, 146.58, 147.78, 158.19, 161.51, 164.41, 168.56; LC-MS (ESI, *m/z*): 539.4 (M + H). *Anal.* Calcd. for $C_{26}H_{18}ClF_3N_6O_2$ (538.92): C, 57.95; H, 3.37; N, 15.59. Found: C, 57.88; H, 3.48; N, 15.70.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid {4-[1-(2-fluoro-phenyl)-meth-(Z)-ylidene]-5-oxo-2-p-tolyl-4,5-dihydro-imidazol-1-yl]-amide (8i). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2-fluorobenzylidene)-2-(4-methylphen yl)-1,3-oxazol-5(4*H*)-one (**7i**). It was obtained as a pale yellow solid (377 mg, 80%). MP: 180.3–182.7°C; IR (ATR, cm^{-1}) υ: 758.48 (=C–H bend), 1032.28 (C–F), 1121.69 (C–N), 1158.72 (C–O), 1190.93 (C–O), 1235.21 (C–N), 1295.47 (C–N), 1374.43 (C–N), 1446.62 (C–C), 1499.98 (C–C), 1554.78 (C–C), 1633.85 (−C=C), 1680.70 (C=O), 1730.84 (C=O), 3172.81 (C–H), 3353.08 (N–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.34 (s, 3H, Ar–Me), 2.68 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 7.20 (s, 1H, benzylidene–H), 7.28 (s, 1H, pyrazole–CH),7.33 (d, J = 8 Hz, 2H, Ar–H), 7.34–7.43 (m, 2H, Ar–H), 7.53–7.58 (m, 1H, Ar–H), 8.03 (d, J = 8 Hz, 2H, Ar–H), 8.61 (s, 1H, pyrimidine–CH), 8.96 (t, J = 8 Hz, 1H, Ar–H), 10.68 (s, 1H, amide–NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.97, 21.61, 24.71, 101.71, 111.24, 116.02, and 116.23 (d, $^{2}J_{C-F}$ = 21 Hz), 117.28 and 117.35 (d, $^{3}J_{C-F}$ = 7 Hz), 122.03 and 122.14 (d, $^{2}J_{C-F}$ = 11 Hz), 125.01, 125.57, 129.02, 129.83, 133.10, 133.19, 133.28 (d, $^{3}J_{C-F}$ = 9 Hz), 137.99, 143.34), 145.91, 146.46, 147.81, 161.01, 160.53, and 163.04 (d, $^{1}J_{C-F}$ = 251 Hz), 162.45, 163.14, 168.79; LC-MS (ESI, *m/z*): 469.4 (M + H). *Anal.* Calcd. for $C_{26}H_{21}FN_6O_2$ (468.49): C, 66.66; H, 4.52; N, 17.94. Found: C, 66.59; H, 4.59; N, 18.06.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(3-chloro-phenyl)-meth-(Z)-ylidene]-5-oxo-2-p-tolyl-4,5-dihydro-imidazol-1-yl]-amide (8j). This compound was prepared by reaction of 5,7-dimethyl pyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(3-chlorobenzylidene)-2-(4-methylpheny l)-1,3-oxazol-5 (4H)-one (**7j**). It was obtained as an off-white solid (401 mg, 85%). MP: 211.5–212.9°C; IR (ATR, cm^{-1}) υ: 682.29 (C–Cl), 777.23 (=C–H bend), 1119.70 (C–N), 1146.46 (C–O), 1187.32 (C–O), 1233.97 (C–N), 1295.59 (C–N), 1368.77 (C–N), 1422.56 (C–C), 1500.42 (C–C), 1556.96 (C–C), 1635.22 (−C=C), 1684.99 (C=O), 1733.72 (C=O), 3003.87 (C–H), 3212.42 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.34 (s, 3H, Ar–Me), 2.68 (s, 3H,

pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 7.21 (s, 1H, benzylidene–H), 7.29 (s, 1H, pyrazole–CH), 7.33 (d, J = 8.1 Hz, 2H, Ar–H), 7.55 (d, J = 6.0 Hz, 2H, Ar–H), 8.01 (d, J = 8.1 Hz, 2H, Ar–H), 8.33 (d, J = 5.4 Hz, 1H, Ar–H), 8.47 (s, 1H, Ar–H), 8.61 (s, 1H, pyrimidine–CH), 10.66 (s, 1H, Amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.98, 21.60, 24.72, 101.72, 111.26, 125.94, 126.10, 128.95, 129.56, 130.52, 131.12, 131.40, 131.93, 133.93, 136.52, 137.84, 143.25, 145.91, 146.46, 147.82, 161.01, 162.23, 163.14, 168.85; LC-MS (ESI, *m/z*): 485.4 (M + H). *Anal.* Calcd. for $C_{26}H_{21}ClN_6O_2$ (484.95): C, 64.40; H, 4.36; N, 17.33. Found: C, 64.31; H, 4.45; N, 17.43.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid {4-[1-(2,5-dimethyl-phenyl)-meth-(Z)-ylidene]-5-oxo-2-p-tolyl-4,5-dihydro-imidazol-1-yl]-amide (8k). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-a] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4Z)-4-(2,5-dimethylbenzylidene)-2-(4-methylphenyl)-1,3-oxazol-5(4H)-one (**7k**). It was obtained as a pale yellow solid (376 mg, 78%). MP: 195.7–197.2°C; IR (ATR, cm^{-1}) υ: 818.46 (=C–H bend), 1037.41 (C–N), 1120.50 (C–O), 1185.51 (C–O), 1235.89 (C–N), 1298.10 (C–N), 1379.99 (C–N), 1443.01 (C–C), 1501.55 (C–C), 1557.31 (C–C), 1633.55 (−C=C), 1684.33 (C=O), 1725.80 (C=O), 3028.47 (C–H), 3250.45 (N–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.33 (s, 3H, Ar–Me), 2.35 (s, 3H, Ar–Me), 2.45 (s, 3H, Ar–Me), 2.68 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 7.20 (s, 1H, Ar–H), 7.17–7.23 (m, 2H, Ar–H), 7.32 (d, J = 8 Hz, 2H, Ar–H), 7.35 (s, 1H, benzylidene–H), 7.99 (d, J = 8 Hz, 2H, Ar–H), 8.60 (s, 1H, pyrazole–CH), 8.64 (s, 1H, pyrimidine–CH), 10.65 (s,1H, amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 17.10, 19.75, 21.30, 21.67, 24.86, 101.38, 110.37, 125.35, 128.63, 129.36, 129.87, 130.38, 131.43, 132.54, 133.19, 135.75, 136.15, 136.99, 142.35, 146.40, 146.59, 14 7.44, 160.06, 161.56, 162.35, 169.45; LC-MS (ESI, m/z): 479.5 (M + H). *Anal.* Calcd. for $C_{28}H_{26}N_6O_2$ (478.56): C, 70.28; H, 5.48; N, 17.56. Found: C, 70.21; H, 5.57; N, 17.65.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid {4-[1-(2-bromo-5-fluoro-phenyl)-meth-(Z)-ylidene]-5-oxo-2-p-tolyl-4,5-dihydro-imidazol-1-yl]-amide (8l). This compound was prepared by reaction with 5,7-Dimethyl pyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2-bromo-5-fluorobenzylidene)-2-(4-methylphenyl)-1,3-oxazol-5(4*H*)-one (**7l**). It was obtained as a pale yellow solid (406 mg, 74%). MP: 254.4–255.5°C. IR (ATR, cm^{-1}) υ: 595.82 (C–Br), 754.20 (=C–H bend), 903.53 (C–F), 1029.77 (C–N), 1114.55 (C–O), 1187.83 (C–O), 1235.31 (C–N), 1298.39 (C–N), 1369.62 (C–N), 1417.85 (C–C), 1452.51 (C–C), 1500.22 (C–C), 1557.37 (C–C), 1630.76 (−C=C), 1687.64 (C=O), 1737.65 (C=O), 3068.88 (C–H), 3268.16 (N–H); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.33 (s, 3H, Ar–Me), 2.68 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 7.21(s, 1H, benzylidene–H), 7.31–7.35 (m, 1H, Ar–H), 7.34 (d, J = 8.4 Hz, 2H, Ar–H), 7.37 (s, 1H, Ar–H), 7.83–7.87 (m, 1H, Ar–H), 8.02 (d, J = 8.4 Hz, 2H, Ar–H), 8.32 (s, 1H, pyrazole–CH), 8.61 (s, 1H, pyrimidine–CH), 8.80 (d, J = 7.2 Hz, 1H, Ar–H), 10.69 (s, 1H, amide–NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.91, 21.58, 24.67, 101.57, 111.23, 119. 46, and 119.76 (d, $^2J_{C-F}$ = 22.65 Hz, 119. 58 and 119.91 (d, $^2J_{C-F}$ = 24.9 Hz), 121.47, 122.74, 124.69, 129.07, 129.88, 134.83, and 134.94 (d, $^3J_{C-F}$ = 8.6 Hz), 135.19 and 135.03 (d, $^3J_{C-F}$ = 8.6 Hz), 139.03, 143.68, 145.86, 146.45, 147.81, 159.89, and 163.67 78 (d, $^1J_{C-F}$ = 283.8 Hz), 160.97, 163.12, 163.67, 168.71; LC-MS (ESI, *m/z*): 548.3 (M + H). *Anal.* Calcd. for $C_{26}H_{20}BrFN_6O_2$ (547.39): C, 57.05; H, 3.68; N, 15.35. Found: C, 56.98; H, 3.76; N, 15.46.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [2-(3,5-dimethyl-phenyl)-4-[1-(4-fluoro-2-trifluoromethyl-phenyl)-meth-(Z)-ylidene]-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8m). This compound was prepared by reaction with 5,7-Dimet hylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-2-(3,5-dimethyl phenyl)-4-[4-fluoro-2-(trifluorome thyl)benzylidene]-1,3-oxazol-5(4*H*)-one (**7m**). It was obtained as an off-white solid (418 mg, 78%). MP: 221.8–222.8°C. IR (ATR, cm^{-1}) υ: 776.78 (=C–H bend), 859.77 (C–F), 896.27 (C–F), 911.36 (C–F), 951.15 (C–F), 1054.05 (C–N), 1126.03 (C–O), 1157.68 (C–O), 1230.14 (C–N), 1286.34 (C–N), 1319.97 (C–N), 1432.58 (C–C), 1495.29 (C–C), 1560.08 (C–C), 1598.26 (C–C), 1627.71 (−C=C), 1685.71 (C=O), 1726.11 (C=O), 3042.56 (C–H), 3242.38 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.32 (s, 6H, Ar–Me and Ar–Me), 2.69 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 7.21 (d, J = 3.9 Hz, 2H, Ar–H), 7.26 (s, 1H, benzylidene–H), 7.73 (s, 1H, pyrazole–CH), 7.80–7.84 (m, 3H, Ar–H), 8.60 (s, 1H, pyrimidine-CH), 9.10 (dd, J_1 = 2.7 Hz, J_2 = 8.7 Hz, 1H, Ar–H), 10.70 (s, 1H, Amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.97, 21.12, 22.61, 24.72, 101.59, 111.38, 114.81, and 115.01 (d, $^2J_{1C-F}$ = 21 Hz), 120.13, 120.48, and 120.70 (d, $^2J_{C-F}$ = 22 Hz), 119.61, 122.33, 125.05, and 127.77 (q, $^1J_{C-F}$ = 272 Hz), 128.02 and 128.09 (d, $^3J_{C-F}$ = 7Hz), 129.17, 130.81, 130.89, 131.11, and 131.19 (dq, $^2J_{1C-F}$ = 22 Hz, $^2J_{2C-F}$ = 8 Hz), 136.14, 137. 68, 139.78, 145.62, 146.81, 148.13, 161.54, 162.57 (d, $^1J_{C-F}$ = 253 Hz), 163.34, 163.67, 168.89; LC-MS (ESI, *m/z*): 551.5 (M + H). *Anal.* Calcd. for $C_{28}H_{22}F_4N_6O_2$ (550.52): C, 61.09; H, 4.03; N, 15.27. Found: C, 61.02; H, 4.09; N, 15.38.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [2-(3,5-dimethyl-phenyl)-4-[1-(4-methanesulfonyl-2-trifluoromethyl-phenyl)-meth-(Z)-ylidene]-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8n). This compound was prepared by reaction of 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-2-(3,5-dimethylphenyl)-4-[4-(methane sulfonyl)-2-(trifluoromethyl) benzylidene]-1,3-oxazol-5(4*H*)-one (**7n**). It was obtained as a pale yellow solid (476 mg, 80%). MP: 270.1–271.4°C; IR (ATR, cm^{-1}) υ: 761.59 (=C–H bend), 856.89 (C–F), 910.46 (C–F), 959. 96 (C–F),

1057.05 (C–N), 1152.68 (C–O), 1188.32 (C–O), 1239.61 (C–N), 1311.18 (C–N), 1381.77 (C–C), 1440.82 (C–C), 1491.39 (C–C), 1558.77 (C–C), 1627.80 (−C=C), 1686.71 (C=O), 1746.83 (C=O), 3011.01 (C–H), 3276.28 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.25 (s, 6H, Ar–Me), 2.69 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 3.40 (s, 3H, Ar–SO_2Me), 7.22 (s, 1H, benzylidene–H), 7.25 (s, 1H, Ar–H), 7.30 (s, 1H, Ar–H), 7.76 (s, 2H, Ar–H), 8.31 (s, 1H, pyrazole–CH), 8.43 (d, J = 8.7 Hz, 1H, Ar–H), 8.61(s, 1H, pyrimidine–CH), 9.18 (d, J = 8.4 Hz, 1H, Ar–H), 10.73 (s, 1H, Amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.97, 21.75, 22.24, 24.55, 43.60, 101.46, 111.39, 119.74, 122.47, 125.20, 127.93 (q, $^1J_{C–F}$ = 273 Hz), 125.32, 125.44, and 125.50 (d, $^3J_{C–F}$ = 6 Hz), 128.17, 128. 78, 129.08, 129.39, 129.69 (q, $^2J_{C–F}$ = 31 Hz), 128.96, 131.86, 135.33, 135.70, 136.08, 136.30, 140.51, 141.89, 145.96, 146.43, 147.94, 160.82, 163.22, 165.41, 168.77; LC-MS (ESI, *m/z*): 611.4 (M + H). *Anal.* Calcd. for $C_{29}H_{25}F_3N_6O_4S$ (610.62): C, 57.04; H, 4.13; N, 13.76. Found: C, 56.97; H, 4.22; N, 13.87.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(3-chloro-phenyl)-meth-(Z)-ylidene]-2-(3,5-dimethyl-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8o). This compound was prepared by reaction with 5,7-Dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(3-chlorobenzylidene)-2-(3,5-di methyl phenyl)-1,3-oxazol-5 (4*H*)-one (**7o**). It was obtained as a pale yellow solid (398 mg, 82%). MP: 188.9–190.6°C. IR (ATR, cm^{-1}) υ: 682.23 (C–Cl), 755.75 (=C–H bend), 1034.16 (C–N), 1160.90 (C–O), 1192.74 (C–O), 1238.72 (C–N), 1274.84 (C–N), 1311.39 (C–N), 1385.87 (C–C), 1434.50 (C–C), 1500.40 (C–C), 1556.60 (C–C), 1656.03 (C=O), 1727.00 (C=O), 3062.96 (C–H), 3193.21 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.25 (s, 6H, Ar–Me and Ar–Me), 2.69 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 7.20 (s, 1H, benzylidene–H), 7.30 (s, 2H, Ar–H and Ar–H), 7.55 (s, 2H, Ar–H), 7.71 (s, 2H, Ar–H), 8.34 (d, J = 5.7 Hz, 1H, Ar–H), 8.42 (s, 1H, pyrazole–CH), 8.59 (s, 1H, pyrimidine–CH), 10.66 (s, 1H, Amide–NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.92, 24.54, 55.86, 101.63, 104.65, 106.92, 111.28, 126.97, 129.58, 130.69, 131.23, 131.58, 132.25, 133.87, 136.29, 137.60, 145.86, 146.45, 147.88, 160.81, 162.31, 163.18, 168.72; LC-MS (ESI, *m/z*): 499.5 (M + H). *Anal.* Calcd. for $C_{27}H_{23}ClN_6O_2$ (498.98): C, 64.99; H, 4.65; N, 16.84. Found: C, 64.91; H, 4.72; N, 16.93.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(2,4-dimethoxy-phenyl)-meth-(Z)-ylidene]-2-(3,5-dimethyl-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8p). This compound was prepared by reaction with 5,7-dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2,4-dimethoxybenzylidene)-2-(3,5-dimethylphenyl)-1,3-oxazol-5 (4*H*)-one (**7p**). It was obtained as a pale yellow solid (425 mg, 83%). MP: 196.8–198.1°C. IR (ATR, cm^{-1}) υ: 752.57 (=C–H bend), 1030.29 (C–N), 1108.46 (C–O), 1161.01 (C–O), 1188.57 (C–O), 1206.25 (C–O), 1238.14 (C–N), 1275.50 (C–N), 1430.26 (C–C), 1463.27 (C–C), 1501.01 (C–C), 1558.22 (C–C), 1599.70 (C–C), 1631.98 (−C=C–), 1675.73 (C=O), 1711.46 (C=O), 3186.05 (C–H), 3211.12 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.24 (s, 6H, Ar–Me and Ar–Me), 2.69 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 3.88 (s, 3H, Ar–OMe), 3.94 (s, 3H, Ar–OMe), 6.68 (s, 1H, Ar–H), 6.77 (d, J = 8.7 Hz, 1H, Ar–H), 7.18 (s, 1H, Ar–H), 7.20 (s, 1H, benzylidene–H), 7.52 (s, 1H, pyrazole–CH), 7.68 (s, 2H, Ar–H), 8.58 (s, 1H, pyrimidine–CH), 8.91 (d, J = 8.7 Hz, 1H, Ar–H), 10.63 (s, 1H, Amide–NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.98, 21.28, 24.69, 56.10, 56.49, 98.40, 101.91, 107.55, 111.19, 115.80, 121.73, 126.51, 128.20, 133.53, 134.16, 134.56, 138.15, 145.80, 146.42, 147.80, 159.79, 160.84, 161.20, 162.98, 163.93, 168.85; LC-MS (ESI, *m/z*): 525.4 (M + H). *Anal.* Calcd. for $C_{29}H_{28}N_6O_4$ (524.58): C, 66.40; H, 5.38; N, 16.02. Found: C, 66.32; H, 5.47; N, 16.13.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [2-(3,5-dimethoxy-phenyl)-4-[1-(4-fluoro-2-trifluoromethyl-phenyl)-meth-(Z)-ylidene]-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8q). This compound was prepared by reaction with 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-2-(3,5-dimethoxyphenyl)-4-[4-fluoro-2-(trifluoromethyl) benzylidene]-1,3-oxazol-5(4*H*)-one (**7q**). It was obtained as an off-white solid (460 mg, 81%). MP: 198.1–199.8°C; IR (ATR, cm^{-1}) υ: 730.31 (=C–H bend), 838.88 (C–F), 876.43 (C–F), 900.95(C–F), 962.14(C–F), 1055.69 (C–N), 1121.18 (C–O), 1199.74 (C–O), 1229.74 (C–N), 1311.59 (C–N), 1348.34 (C–N), 1424.96 (C–C), 1492.57 (C–C), 1551.56 (C–C), 1592.26 (C–C), 1628.49 (−C=C), 1685.85 (C=O), 1726.14 (C=O), 3116.34 (C–H), 3375.13 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.66 (s, 3H, pyrimidine–Me), 2.75 (s, 3H, pyrimidine–Me), 3.71 (s, 6H, Ar–OMe and Ar–OMe), 6.72 (s, 1H, Ar–H), 7.20 (s, 1H, Ar–H), 7.25 (s, 1H, benzylidene H), 7.29 (s, 1H, pyrazole–CH), 7.77–7.84 (m, 2H, Ar–H), 8.60 (s, 1H, pyrimidine–CH), 9.12 (t, J = 6.3 Hz, 1H, Ar–H), 10.71(s, 1H, Amide–NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 17.82, 22.91, 57.43, 101.55, 104.93, 107.09, 111.30, 114.82, and 115.02 (d, $^2J_{C–F}$ = 20 Hz), 120.05 and 120.13 (d, $^3J_{C–F}$ = 8 Hz), 120.47 and 120.69 (d, $^2J_{C–F}$ = 22 Hz), 119.60, 122.32, 125.04, and 127.76 (q, $^1J_{C–F}$ = 272 Hz), 128.03 and 128.09 (d, $^3J_{C–F}$ = 6 Hz), 129.19, 130.81, 130.89, 131.11,131.19 (dq, $^2J_{1C–F}$ = 22 Hz, $^2J_{2C–F}$ = 8 Hz), 137.04, 137.12, 138.46, 145.90, 146.42, 147.93, 160.83, 161.32, and 163.83 (d, $^1J_{C–F}$ = 251 Hz), 163.19, 164.01, 168.86; LC-MS (ESI, *m/z*): 583.6 (M + H). *Anal.* Calcd. for $C_{28}H_{22}F_4N_6O_4$ (582.52): C, 57.73; H, 3.81; N, 14.43. Found: C, 57.66; H, 3.89; N, 14.55.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [2-(3,5-dimethoxy-phenyl)-4-[1-(4-methanesulfonyl-2-trifluoromethyl-phenyl)-meth-(Z)-ylidene]-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8r). This compound was prepared by reaction with 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-2-(3,5-dimethoxyphenyl)-4-[4-(methanes ulfonyl)-2-(trifluoromethyl)benzylidene]-1,3-oxazol-5(4*H*)-one

(**7r**). It was obtained as a pale yellow solid (513 mg, 82%). MP: 247.2–249.0°C. IR (ATR, cm^{-1}) υ: 766.95 (=C–H bend), 906.29 (C–F), 932.38 (C–F), 964.94 (C–F), 1063.33 (C–N), 1153.49 (C–O), 1193.51 (C–O), 1230.47 (C–N), 1273.44 (C–N), 1308.74 (C–N), 1375.57 (C–N), 1451.77(C–C), 1494.82 (C–C), 1558.69 (C–C), 1599.02 (C–C), 1615.49 (−C=C), 1689.43 (C=O), 1746.50 (C=O), 3003.72 (C–H), 3288.64 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.66 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 3.40 (s, 3H, Ar–SO_2Me), 3.72 (s, 6H, Ar–OMe and Ar–OMe), 6.74 (s, 1H, Ar–H), 7.21 (s, 1H, benzylidene–H), 7.27 (s, 2H, Ar–H), 7.33 (s, 1H, pyrazole–CH), 8.32 (s, 1H, Ar–H), 8.43 (d, J = 8.4 Hz, 1H, Ar–H), 8.62 (s, 1H, pyrimidine–CH), 9.19 (d, J = 8.4 Hz, 1H, Ar–H), 10.74 (s, 1H, Amide–NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 16.98, 24.56, 43.61, 55.94, 101.47, 105.39, 107.20, 111.36, 119.14, 119.73, 122.46, 125.19, 127.92 (q, $^1J_{C-F}$ = 273 Hz), 125.43 and 125.49 (d, $^3J_{C-F}$ = 6 Hz), 128. 77, 129.07, 129.38, 129.68 (q, $^2J_{C-F}$ = 31 Hz), 128.94, 131.88, 135.32, 136.31, 140.54, 141.84, 145.93, 146.47, 147.99, 160.85, 163.25, 165.40, 168.76; LC-MS (ESI, *m/z*): 643.4 (M + H). *Anal.* Calcd. for $C_{29}H_{25}F_3N_6O_6S$ (642.62): C, 54.20; H, 3.92; N, 13.08. Found: C, 54.11; H, 3.99; N, 13.17.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [4-[1-(3-chloro-phenyl)-meth-(Z)-ylidene]-2-(3,5-dimethoxy-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8s). This compound was prepared by reaction with 5,7-dimethylpyrazolo[1,5-*a*] pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(3-chlorobenzylidene)-2-(3,5-dimethoxyphenyl)-1,3-oxazol-5 (4*H*)-one (**7s**)**.** It was obtained as an off-white solid (433 mg, 84%). MP: 201.8–203.5°C. IR (ATR, cm^{-1}) υ: 755.66 (=C–H bend), 850.06 (C–Cl), 1060.23 (C–N), 1115.28 (C–O), 1155.18 (C–O), 1197.37 (C–O), 1234.78 (C–O), 1259.22 (C–N), 1307.24 (C–N), 1331.30 (C–N), 1428.38 (C–C), 1498.78 (C–C), 1596.49 (C–C), 1651.31(−C=C–), 1681.68 (C=O), 1729.03 (C=O), 2935.04 (C–H), 3197.00 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.66 (s, 3H, pyrimidine–Me), 2.76 (s, 3H, pyrimidine–Me), 3.72 (s, 6H, Ar–OMe and Ar–OMe), 6.71(s, 1H, Ar–H), 7.19 (s, 1H, benzylidene–H), 7.25 (s, 2H, Ar–H), 7.33 (s, 1H, pyrazole–CH), 7.55 (s, 2H, Ar–H), 8.30 (d, J = 3.9 Hz, 1H, Ar–H), 8.48 (s, 1H, Ar–H), 8.60 (s, 1H, pyrimidine–CH), 10.68 (s, 1H, Amide–NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.94, 24.52, 55.85, 101.65, 104.67, 106.93, 111.25, 126.93, 129.50, 130.66, 131.14), 131.51, 132.04, 133.94, 136.35, 137.63, 145.88, 146.41, 147.87, 160.82, 162.23, 163.14, 168.77; LC-MS (ESI, *m/z*): 531.5 (M + H). *Anal.* Calcd. for $C_{27}H_{23}ClN_6O_4$ (530.98): C, 61.08; H, 4.37; N, 15.83. Found: C, 61.01; H, 4.46; N, 15.95.

5,7-Dimethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid [2-(2,4-dimethoxy-phenyl)-4-[1-(3,5-dimethoxy-phenyl)-meth-(Z)-ylidene]-5-oxo-4,5-dihydro-imidazol-1-yl]-amide (8t). This compound was prepared by reaction with 5,7-dime thylpyrazolo[1,5-*a*]pyrimidine-3-carbohydrazide (**4**) (200 mg) with (4*Z*)-4-(2,4-dimethoxy benzylidene)-2-(3,5-dimethoxyphenyl)-1,3-oxazol-5(4*H*)-one (**7t**). It was obtained as a pale yellow solid (424 mg, 83%). MP: 216.8–218.0°C; IR (ATR, cm^{-1}) υ: 756.63 (=C–H bend), 1031.09 (C–N), 1054.25 (C–O), 1114.92 (C–O), 1158.76 (C–O), 1187.80 (C–O), 1204.79 (C–O), 1232.29 (C–O), 1276.28 (C–N), 1294.06 (C–N), 1311.61 (C–N), 1425.22 (C–C), 1457.34 (C–C), 1502.42 (C–C), 1558.42 (C–C), 1592.13 (C–C), 1629.57 (−C=C–), 1678.76 (C=O), 1714.35 (C=O), 2985.04 (C–H), 3182.32 (N–H); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 2.66 (s, 3H, pyrimidine–Me), 2.75 (s, 3H, pyrimidine–Me), 3.71 (s, 6H, Ar–OMe and Ar–OMe), 3.88 (s, 3H, Ar–OMe), 3.94 (s, 3H, Ar–OMe), 6.67 (d, J = 4.8 Hz, 2H, Ar–H), 6.77 (d, J = 8.7 Hz, 1H, Ar–H), 7.19 (s, 2H, Ar–H), 7.21 (s, 1H, benzylidene–H), 7.54 (s, 1H, pyrazole–CH), 8.59 (s, 1H, pyrimidine–CH), 8.92 (d, J = 8.7 Hz, 2H, Ar–H), 10.64 (s, 1H, Amide–NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 16.96, 24.52, 55.79, 55.83, 56.11, 56.50, 98.41, 101.80, 104.08, 106.72, 107.64, 111.22, 115.74, 122.23, 130.02, 133.90, 134.67, 134.76, 145.85, 146.38, 14 7.84, 159.37, 160.76, 160.82, 160. 97, 161.31, 163.08, 164.07, 168.81; LC-MS (ESI, *m/z*): 557.5 (M + H). *Anal.* Calcd. for $C_{29}H_{28}N_6O_6$ (556.58): C, 62.58; H, 5.07; N, 15.10. Found: C, 62.51; H, 5.15; N, 15.21.

ANTICANCER ACTIVITY

All compounds were screened for their *in vitro* anticancer activity against representative human cancer cell line (HeLa cell line) by MTT assay. This is a colorimetric assay that measures the reduction of yellow 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The MTT enters the cells and passes into the mitochondria where it is reduced to an insoluble, colored (dark purple) formazan product. The cells are then solubilized with an organic solvent (e.g., dimethyl sulfoxide and isopropanol) and then released solubilized formazan reagent is measured spectrophotometrically. Because reduction of MTT can only occur in metabolically active cells, the level of activity is a measure of the viability of these cells.

The 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) was made a solution in such a way that 10 mg was dissolved in 10 mL of Hank's balanced solution. The cell lines were maintained in 96 wells micro titer plate containing MEM media supplemented with 10% heat inactivated fetal calf serum, containing 5% of mixture of Gentamycin, Penicillin (100 Units/mL) and Streptomycin (100 µg/mL) in presence of 5% CO_2 at 37°C for 3–4 days. Then after, remove the supernatant and replace MEM media with Hank's balanced solution, and the cells were incubated overnight. The *in vitro* growth inhibitions of test compounds were assessed by calorimetric or spectrophotometric method. This helps to determine the conversion of MTT into

formazan blue by living cells. Remove the supernatant from the plate, add fresh Hank's balanced salt solution, and treated with different concentration of compound (approx diluted with DMSO). The marketed anticancer drug Paclitaxel was tested as a reference compound in the assay. The control group contains only DMSO. After 24 h of incubation at 37°C in a humidified atmosphere of 5% CO_2, the medium was replaced with MTT solution (100 µL, 5 mg/mL in MEM medium) for further 4 h. The supernatant was carefully aspirated and the precipitated crystals of Formazan blue were solubilized by adding DMSO (200 µL), and optical density was measured at wavelength of 570 nm using LISA micro plate reader. The results were represented out in triplicates for each concentration. Concentration at which the optical density of treated cells was reduced by 50% with respect to the untreated control. Calculation of the percentage of lyses of cells was carried out by comparing the optical density of sample to that of the control and also by microscopic analysis.

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