Design and Synthesis of New Imidazolinone Derivatives as Potential Antifungal Agents

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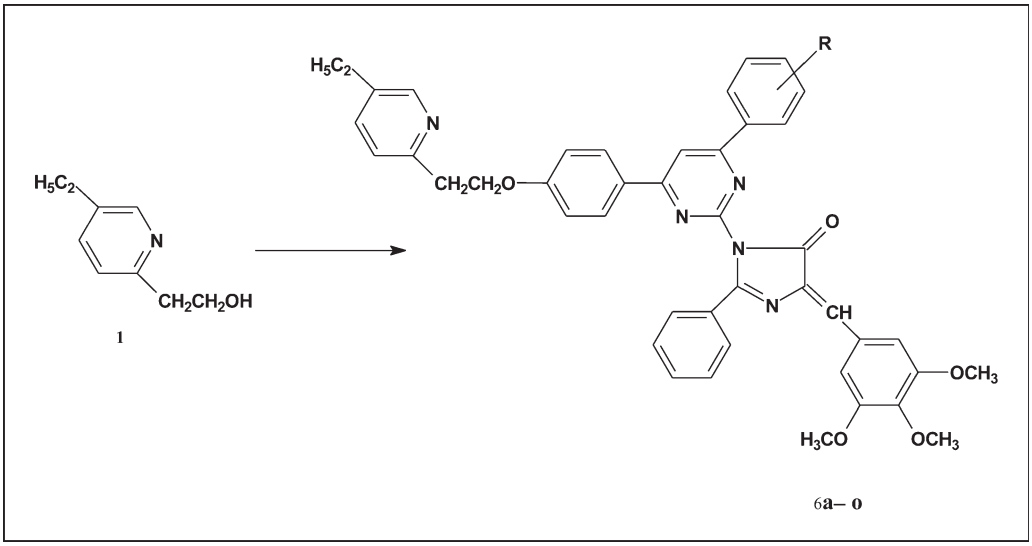

A new series of chalcones, pyrimidines, and imidazolinone is described; chalcones (**4a–o**) were prepared from the lead 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde. Pyrimidines (**5a–o**) were prepared from the reaction of chalcones and guanidine nitrate in alkali media. Imidazolinones (**6a–o**) were synthesized from the reaction of pyrimidine and oxazolone derivatives (prepared by Erlenmeyer azlactone synthesis). The structures of the synthesized compounds were assigned on the basis of elemental analyses, IR, ^{1}H-NMR, and ^{13}C-NMR spectral data. All the products were screened against different strains of bacteria and fungi. Most of these compounds showed better inhibitory activity in comparison with the standard drugs.

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INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years because of their pharmacological activities. Nitrogen and oxygen containing five- and six-membered heterocyclic compounds have occupied enormous significance in the field of medicinal chemistry.

The basic nucleus imidazole emerges from the drug intermediate azlactone. The azlactones possess oxazolone moiety. They are also of great importance to produce penicillin type of drug intermediates and also useful to produce synthetic hormonal compounds. Imidazole is a planer five-membered heterocyclic ring system with three carbon and two nitrogen atoms in 1 and 3 positions; imidazolones are keto dihydro imidazoles and are known as oxoimidazoline; a five-membered heterocyclic ring system having nitrogen atoms in 1 and 3 positions and carbonyl at 5 position. Oxoimidazoline, also known as imidazolinone, is reported to exhibit a wide variety of antibacterial [1,2], antifungal [3], and antimicrobial activities [4–7]. They have also been reported to possess fungicidal activities [8], herbicidal activities [9], vasodilator activities [10], anticonvulsant agents [11], and antitumor agent [12].

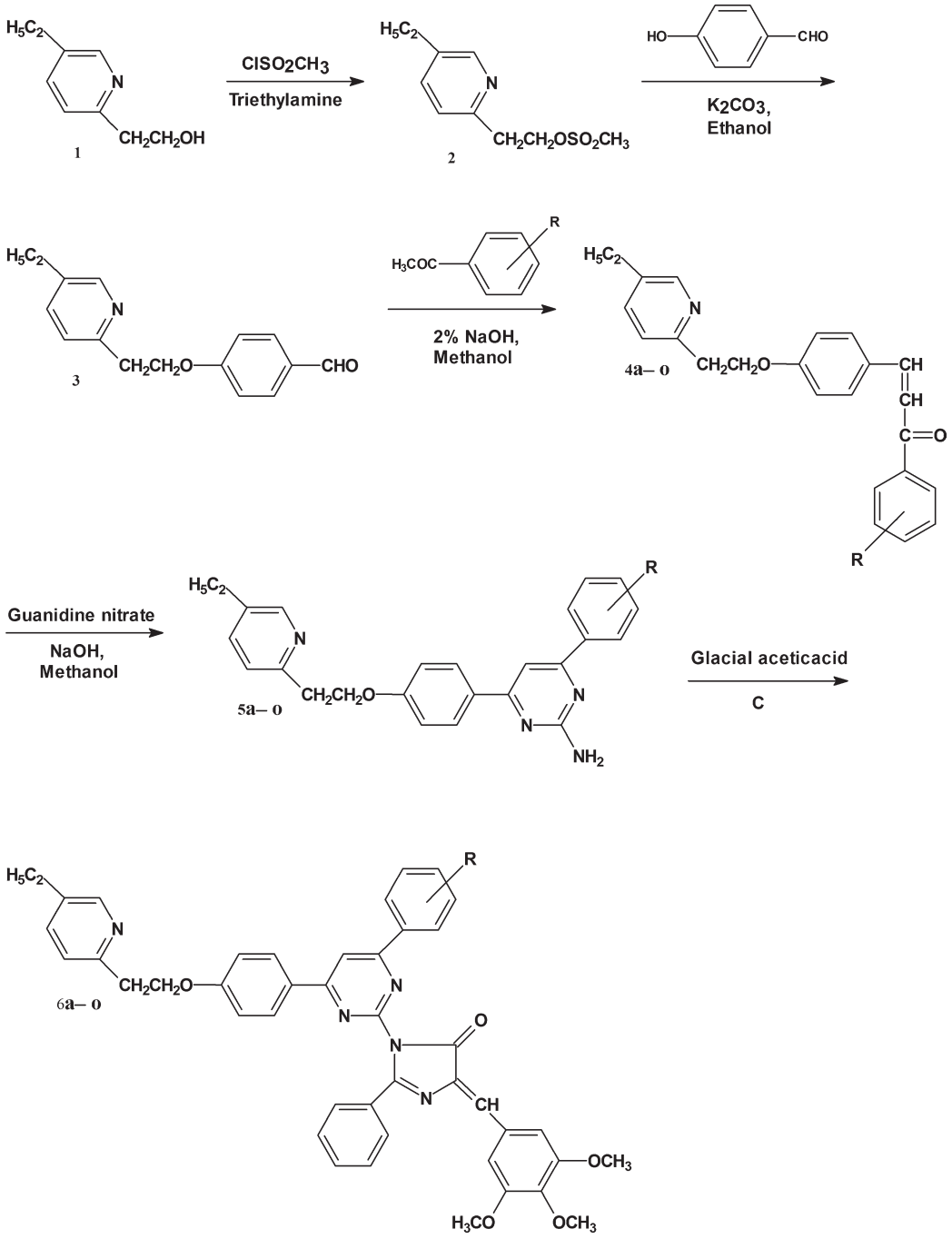
Recently, we have prepared chalcones, pyrimidines, and amide derivatives and studied their antibacterial and antifungal activities [13,14]. In continuation of our work on chalcones and pyrimidines, we planned to attach oxazolones with amino group of pyrimidine and to synthesize imidazolinone derivatives.

Hence, with a view to further assess the pharmacological profile of this class of compounds, it was thought worthwhile to synthesize some new congeners of imidazolinone heterocycles by incorporating the chalcone and pyrimidine moieties in a single molecular framework.

RESULTS AND DISCUSSION

Chemistry. The synthesis of chalcones, pyrimidines, and imidazolinone derivatives was performed following the steps shown in Scheme 1. In the initial step,

Scheme 1. Synthesis of compounds **5a–o** and **6a–o**.



chalcones **4a–o** were synthesized by condensing 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde with appropriate aromatic acetophenones in diluted methanolic sodium hydroxide solution at room temperature. The compounds **5a–o** were synthesized by the reaction of an appropriate chalcone with guanidine nitrate and sodium ethoxide solution. Compounds **6a–o** were prepared from the reaction of pyrimidines and oxazolones. The purity of the compounds was determined by thin layer chromatography (TLC) and elemental analyses. Spectral data (IR, ^{1}H-NMR, and ^{13}C-NMR) of all the newly synthesized compounds were in full agreement with the proposed structures.

The synthesis of **4a–o** was confirmed by the IR and NMR spectra. In the IR spectrum, the sharp band of —C=O was observed at 1662 cm^{-1}, —CH=CH— of chalcone was observed at 1599 cm^{-1}, the asymmetric and symmetric band of C—O—C ether linkage in the structure were observed at 1223 and 1036 cm^{-1}. The

^{1}H-NMR spectra exhibited one doublet at δ 7.11 attributed to the =CH—CO— protons and two protons with triplet at δ 4.32 confirmed that —CH_2—O—. In the ^{13}C-NMR spectra of chalcones, the higher field resonances at δ 190.0 ppm were attributed to the carbonyl group present in chalcone. The structures of compounds **5a–o** and **6a–o** were also established by using IR and NMR spectroscopy. The IR spectra of pyrimidine showed disappearance of —C=O band at 1662 cm^{-1} and appearance of asymmetric and symmetric new broad bands at 3355 cm^{-1} and 3220 cm^{-1} for —NH_2, respectively. A signal at δ 5.15 and δ 7.85 for the —NH_2 and —CH of pyrimidine ring, respectively, was observed, and the ^{13}C-NMR spectra of pyrimidine —CH appeared at δ 103.2. The sharp band of —C=O in imidazolinone was observed at 1797 cm^{-1} and another band of —C=N was observed at 1656 cm^{-1}. The ^{1}H-NMR spectra showed a signal at 7.30 with singlet that determined the —CH group of imidazolinone, and the ^{13}C-NMR spectra carbon of —C=O appeared at 170.4.

From the above spectral analysis, we have confirmed the conversion of chalcones to pyrimidines and the conversion of pyrimidines to imidazolinones derivatives.

Antimicrobial activity. ***Methods.*** All microbial type culture collection (MTCC) cultures were collected from the Institute of Microbial Technology, Chandigarh, and tested against the known drugs ampicillin and greseofulvin. Mueller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 10^8 colony-forming unit per milliliter by comparing the turbidity. DMSO was used as diluents to get desired concentration of drugs to test on standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and kept for incubation at 37°C overnight. The tubes were then incubated overnight. The minimum inhibition concentrations (MIC) of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was subcultured and incubated overnight at 37°C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic, a reduced number of colonies indicating a partial or slow bactericidal activity, and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 2000 μg/mL concentration, as a stock solution. In primary screening, 500, 250 and 125 μg/mL concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125, and 1.5625 μg/mL concentrations. The highest dilution showing at least 99% inhibition is taken as MIC.

The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan [15]. Antibacterial activity was screened against two Gram-positive (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenus* MTCC 443) and two Gram-negative (*Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441) bacteria, in which ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *Aspergillus clavatus* MTCC 1323, in which greseofulvin was used as a standard antifungal agent.

Antibacterial activity. The minimal bactericidal concentrations (MBCs) of the tested compounds are shown in Table 1. The different compounds **4a–o**, **5a–o**, and **6a–o** were tested in *in vitro* against two Gram-positive (*S. aureus* MTCC 96, *S. pyogenus* MTCC 443) and two Gram-negative (*E. coli* MTCC 442, *P. aeruginosa* MTCC 441) bacteria. From the screening data, chalcones, **4b**, **4f**, and **4h** showed MBC value in the range between 62.5 and 100 μg/mL while ampicillin has standard MBC value of 100 μg/mL against *E. coli* which indicates that these compounds have excellent activity, while other chalcones **4c**, **4d** and **4o** possessed MBC value in the range of 125–150 μg/mL against *E. coli*, and **4h** exhibited very good activity against *P. aeruginosa*. Compounds **4f** and **4h** displayed excellent activity in the range of 100–150 μg/mL while remaining **4b**, **4d** and **4n** were equivalent against *S. aureus* when compared with ampicillin. Compound **4h** have MBC value of 150 μg/mL, which was comparatively good against *S. pyogenus*. The remaining chalcones possessed moderate to poor activity against all four bacterial species. In the pyrimidine derivatives, compound **5b** possessed MBC value of 62.5 μg/mL against *E. coli* and MBC value of 150 μg/mL against *P. aeruginosa*, which was comparable with ampicillin. Compound **5e** exhibited MBC value of 150 μg/mL against *P. aeruginosa*. Compound **5h** showed MBC value of 100 μg/mL against *S. aureus* and MBC value of 100 μg/mL against *S. pyogeneus*. Compound **5i** possessed MBC value of 62.5 μg/mL against *E. coli* and MBC value of 150 μg/mL against *S. aureus*, which showed that this compound is as active as ampicillin. Compound **5l** showed MBC value of 100 μg/mL against *P. aeruginosa* and MBC

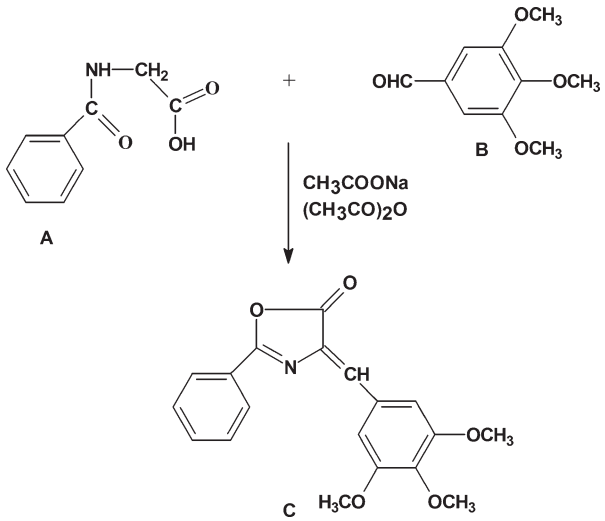
Table 1

Antimicrobial activities of compounds **4a–o**, **5a–o**, and **6a–o**.

		Minimal bactericidal concentration (μg/mL)				Minimal fungicidal concentration (μg/mL)		
		Gram negative		Gram positive				
Compound	R	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
4a	2,4-Cl,5-F	200	250	1000	1000	1000	500	500
4b	4-OCH_3	100	150	250	250	1000	1000	1000
4c	2,4-Cl	150	500	500	500	500	500	1000
4d	4-OH	150	200	250	250	500	500	1000
4e	2,6-Cl,5-F	500	250	500	1000	1000	500	500
4f	4-CH_3	100	150	100	250	1000	1000	1000
4g	-H	500	1000	1000	1000	200	500	500
4h	4-F	62.5	100	150	150	250	>1000	>1000
4i	2,4-F	250	250	500	500	1000	1000	1000
4j	4-Br	500	500	500	250	1000	>1000	>1000
4k	3,4-Cl	500	500	1000	1000	1000	>1000	>1000
4l	4-Cl	500	250	500	250	1000	500	500
4m	3-OCH_3	500	500	1000	1000	500	500	500
4n	3-F	250	500	250	500	500	1000	1000
4o	3,4-F	125	250	500	500	1000	1000	1000
5a	2,4-Cl,5-F	150	250	500	500	500	500	1000
5b	4-OCH_3	62.5	150	250	250	500	>1000	>1000
5c	2,4-Cl	500	500	250	500	500	>1000	>1000
5d	4-OH	250	200	500	500	500	500	1000
5e	2,6-Cl,5-F	250	150	1000	1000	500	500	500
5f	4-CH_3	200	200	250	250	500	500	500
5g	-H	250	250	500	500	500	500	500
5h	4-F	250	250	100	100	500	250	250
5i	2,4-F	62.5	150	150	200	500	1000	1000
5j	4-Br	250	250	200	200	1000	1000	1000
5k	3,4-Cl	250	250	250	250	1000	500	500
5l	4-Cl	250	100	150	250	500	500	500
5m	3-OCH_3	250	250	500	500	1000	500	500
5n	3-F	500	500	250	250	500	1000	1000
5o	3,4-F	250	500	500	250	200	200	200
6a	2,4-Cl,5-F	250	250	500	1000	>1000	>1000	>1000
6b	4-OCH_3	500	250	250	250	500	500	500
6c	2,4-Cl	250	200	250	500	1000	500	500
6d	4-OH	100	100	500	500	500	500	500
6e	2,6-Cl,5-F	250	500	500	500	500	>1000	>1000
6f	4-CH_3	200	250	500	1000	500	1000	1000
6g	-H	200	250	1000	1000	500	>1000	>1000
6h	4-F	100	150	200	200	1000	500	500
6i	2,4-F	100	250	250	500	1000	>1000	>1000
6j	4-Br	200	250	250	250	200	200	200
6k	3,4-Cl	250	200	250	250	500	1000	1000
6l	4-Cl	150	250	1000	150	500	1000	>1000
6m	3-OCH_3	200	250	1000	1000	1000	1000	1000
6n	3-F	1000	500	500	250	1000	500	1000
6o	3,4-F	1000	1000	250	250	1000	1000	1000
Gentamycin		0.05	1	0.25	0.5	–	–	–
Ampicillin		100	100	250	100	–	–	–
Chloramphenicol		50	50	50	50	–	–	–
Ciprofloxacin		25	25	50	50	–	–	–
Norfloxacin		10	10	10	10	–	–	–
Nystatin		–	–	–	–	100	100	100
Greseofulvin		–	–	–	–	500	100	100

value of 150 μg/mL against *S. aureus*. The remaining pyrimidines displayed moderate to poor activities against all four bacterial species. For the imidazolinone derivatives, compounds **6h** and **6i** showed MBC value of 100 μg/mL against *E. coli*. Compound **6d** showed MBC value of 100 μg/mL against *E. coli* and *P. aeruginosa*, which was as active as ampicillin; against *S. aureus*, compounds **6b**, **6c**, **6i**, **6j**, **6k**, and **6o** gave MBC value of 250 μg/mL, which

Scheme 2. Synthesis of oxazol-5(4H)-one.



shows that these compounds are as active as ampicillin. Compound **6h** is said to be more active when it was tested against *S. aureus*. Imidazolinones are moderately active against *S. pyogeneus*.

Antifungal activity. Minimal fungicidal concentrations (MFCs) of the synthesized compounds are shown in Table 1. For *in vitro* antifungal activity, three fungal species *C. albicans* MTCC 227, *A. niger* MTCC 282, and *A. clavatus* MTCC 1323 were used and compared with greseofulvin. Most of the compounds possessed very good antifungal activity against *C. albicans* when they were compared greseofulvin; their MFC values were in the range between 100 and 500 μg/mL. For chalcones, compounds **4g** and **4h** showed excellent activities of 200–250 μg/mL; **4c**, **4d**, **4m**, and **4n** possessed very good activity of 500 μg/mL, which is similar to greseofulvin (500 μg/mL) against *C. albicans*, whereas chalcones possessed moderate to poor activity against *A. niger* and *A. clavatus*. For pyrimidines, compound **5o** possessed good activity of 200 μg/mL against *C. albicans*, which showed that this compound is more active when compared with greseofulvin (500 μg/mL); whereas for imidazolinone derivatives, compound **6j** displayed excellent activity of 200 μg/mL against *C. albicans*, *A. niger*, and *A. clavatus*, which indicates that this compound is very active when compared with greseofulvin; while rest of the compounds **6b**, **6d**, **6e**, **6f**, **6g**, **6k**, and **6l** possessed MFC value of 500 μg/mL against *C. albicans*, which have similar values like greseofulvin.

CONCLUSION

Chalcones and pyrimidine derivatives possessed very good activity against all four bacterial species, but the observed results for fungicidal species are satisfactory. In the case of imidazolinone derivatives, compounds **6b**, **6d**, **6e**, **6f**, **6g**, **6k**, and **6l** are said to be as active as greseofulvin when they were tested with *C. albicans*. Compound **6j** displayed excellent activity of 200 μg/mL against *C. albicans*. From these results, it is concluded that the imidazolinone derivatives showed good antifungal activity rather than antibacterial activity.

EXPERIMENTAL

Laboratory chemicals were supplied by Rankem India Ltd., New Delhi, India and Ficher Scientific UK Ltd., Loughborough, Leicestershire. Melting points were determined by the open-tube capillary method and are uncorrected. The purity of the compounds was determined by TLC plates (silica gel G) in the solvent system, *i.e.*, toluene:ethyl acetate (75:25). The spots were observed by exposure to iodine vapors or by UV light. The IR spectra were obtained on a Perkin-Elmer 1720 FTIR spectrometer (KBr pellets). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as the internal standard in $CDCl_3$. Elemental analyses of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer.

Procedure for the synthesis of 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde (3). 4-[2-(5-Ethylpyridin-2-yl)ethoxy]-benzaldehyde (3) was synthesized by the method described in refs. 16 and 17.

General preparation of the compounds 4a–o. Chalcones were synthesized and characterized by the method described in ref. 13.

General preparation of the compounds 5a–o. Pyrimidines were synthesized and characterized by the method described in ref. 13.

General process of oxazol-5(4H)-one (Erlenmeyer azlactone synthesis) (C). A mixture of 3,4,5-trimethoxy benzaldehyde (0.33 mol), hippuric acid (0.33 mol), and potassium acetate (0.33 mol) in acetic anhydride (0.83 mol) was refluxed with stirring for 15 min [reaction progress was monitored by TLC using isohexane:ethyl acetate (3:1) as eluent]. The mixture was then cooled and neutralized by the addition of solid potassium carbonate. The solid product was separated by filtration, dried, and purified from ethanol (as shown in Scheme 2).

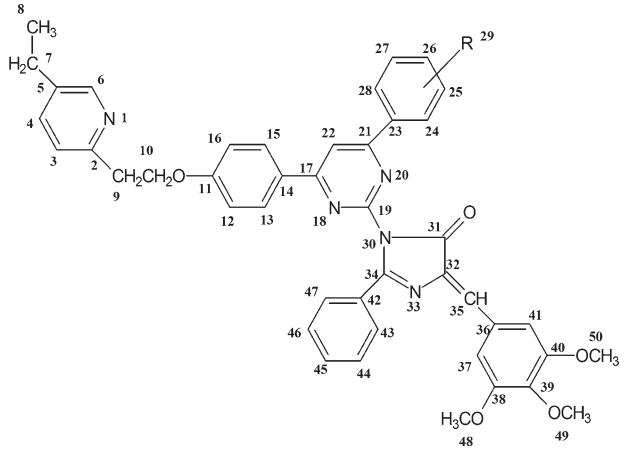


Figure 1. Imidazolinones **6a–o**.

General preparation of the compounds 6a–o. A mixture of **5a–o** (0.01 mol) and an appropriate oxazolone (0.01 mol) in 50 mL acetic acid was refluxed for 6–8 h [reaction progress was monitored by TLC using toluene–ethyl acetate (7.5:2.5) as eluent]. After completion of reaction, the resulted mixture was cooled and poured into ice cold water and the formed precipitate was filtered and washed with water till pH neutral. The raw product was crystallized from ethanol (Fig. 1).

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(2,4-dichloro-5-fluoro phenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6a). This compound was obtained as brown solid, yield 54%, m.p. 115–119°C, R_f: 0.62; IR (KBr): Ar-H 3063, CH_2 2952, 2834, C=O of imidazolinone 1797, C=N imidazolinone 1655, C=N of pyrimidine 1613, C—O—C 1223, 1035, C—F 973, C—Cl 744 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.20 (t, 3H, J = 7.63 Hz, —CH_3), 2.51 (q, 2H, J = 7.62 Hz, —CH_2—), 3.26 (t, 2H, J = 6.71 Hz, —CH_2), 3.82 (s, 3H, —OCH_3), 4.35 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.76–8.33 (m, 17H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.2 (C_8), 25.2 (C_7), 37.5 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.3 (C_{22}), 103.8–150.4 (C_{36}–C_{41}), 108.4 (C_{35}), 114.8–157.3 (C_{11}–C_{16}), 122.3–157.3 (C_2–C_6), 126.3–130.0 (C_{42}–C_{47}), 118.7–1161.4 (C_{23}–C_{28}), 130.4 (C_{32}), 160.2 (C_{21}), 163.6 (C_{17}), 164.2 (C_{34}), 169.5 (C_{19}), 170.8 (C_{31}). Anal. Calcd for $C_{44}H_{36}N_5O_5Cl_2F$: C, 65.67; H, 4.51; N, 8.70. Found: C, 65.63; H, 4.50; N, 8.68.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-methoxy phenyl) pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6b). This compound was obtained as brown solid, yield 65%, m.p. 110–112°C, R_f: 0.64; IR (KBr): Ar-H 3064, CH_2 2951, 2833, C=O of imidazolinone 1792, C=N imidazolinone 1655, C=N of pyrimidine 1614, C—O—C 1223, 1032 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.19 (t, 3H, J = 7.62 Hz, —CH_3), 2.53 (q, 2H, J = 7.62 Hz, —CH_2—), 3.23 (t, 2H, J = 6.72 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.34 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.35 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.5 (C_8), 25.3 (C_7), 37.2 (C_9), 55.8 (C_{29}), 56.3 (C_{48}–C_{50}), 67.4 (C_{10}), 103.2 (C_{22}), 103.5–150.7 (C_{36}–C_{41}), 108.2 (C_{35}), 114.5–157.6 (C_{11}–C_{16}), 122.1–157.4 (C_2–C_6), 126.5–130.1 (C_{42}–C_{47}), 114.8–160.6 (C_{23}–C_{28}), 130.2 (C_{32}), 160.6 (C_{21}), 163.3 (C_{17}), 164.3 (C_{34}), 169.1 (C_{19}), 170.3 (C_{31}). Anal. Calcd for $C_{45}H_{41}N_5O_6$: C, 72.27; H, 5.53; N, 9.36. Found: C, 72.25; H, 5.51; N, 9.34.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(2,4-dichloro phenyl) pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6c). This compound was obtained as yellow solid, yield, 58%, m.p. 113–115°C, R_f: 0.59; IR (KBr): Ar-H 3059, CH_2 2950, 2832, C=O of imidazolinone 1791, C=N imidazolinone 1654, C=N of pyrimidine 1615, C—O—C 1225, 1034, C—Cl 743 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.21 (t, 3H, J = 7.64 Hz, —CH_3), 2.55 (q, 2H, J = 7.62 Hz, —CH_2—), 3.25 (t, 2H, J = 6.72 Hz, —CH_2), 3.84 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.32 (m, 18H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.1 (C_8), 25.6 (C_7), 37.6 (C_9), 56.4 (C_{48}–C_{50}), 67.3 (C_{10}), 103.7 (C_{22}), 103.2–150.4 (C_{36}–C_{41}), 108.2 (C_{35}), 115.0–157.2 (C_{11}–C_{16}), 122.1–157.4 (C_2–C_6), 126.6–130.4 (C_{42}–C_{47}), 127.4–135.7 (C_{23}–C_{28}), 130.8 (C_{32}), 160.1 (C_{21}), 163.7 (C_{17}), 164.5 (C_{34}), 169.4 (C_{19}), 170.6 (C_{31}). Anal. Calcd for $C_{44}H_{37}N_5O_5Cl_2$: C, 67.18; H, 4.74; N, 8.90. Found: C, 67.12; H, 4.71; N, 8.91.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-hydroxy phenyl) pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6d). This compound was obtained as yellow solid, yield 57%, m.p. 215–217°C, R_f: 0.61; IR (KBr): Ar-H 3065, OH 3354, CH_2 2953, 2833, C=O of imidazolinone 1795, C=N imidazolinone 1652, C=N of pyrimidine 1612, C—O—C 1224, 1032 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.17 (t, 3H, J = 7.63 Hz, —CH_3), 2.54 (q, 2H, J = 7.63 Hz, —CH_2—), 3.24 (t, 2H, J = 6.72 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.35 (m, 19H, pyridine, pyrimidine, and Ar-H), 9.85 (s, 1H, —OH); ^{13}C-NMR ($CDCl_3$): δ 15.6 (C_8), 25.7 (C_7), 37.5 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.7 (C_{22}), 103.6–150.4 (C_{36}–C_{41}), 108.3 (C_{35}), 114.7–157.6 (C_{11}–C_{16}), 122.3–157.4 (C_2–C_6), 126.5–130.8 (C_{42}–C_{47}), 116.4–158.5 (C_{23}–C_{28}), 130.6 (C_{32}), 160.2 (C_{21}), 163.6 (C_{17}), 164.1 (C_{34}), 169.5 (C_{19}), 170.9 (C_{31}). Anal. Calcd for $C_{44}H_{39}N_5O_6$: C, 72.02; H, 5.36; N, 9.54. Found: C, 72.04; H, 5.35; N, 9.52.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(2,6-dichlouro-5-flouro phenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6e). This compound was obtained as brown solid, yield 56%, m.p. 103–105°C, R_f: 0.60; IR (KBr): Ar-H 3058, CH_2 2958, 2837, C=O of imidazolinone 1789, C=N imidazolinone 1653, C=N of pyrimidine 1617, C—O—C 1223, 1035, C—F 972, C—Cl 745 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.16 (t, 3H, J = 7.63 Hz, —CH_3), 2.50 (q, 2H, J = 7.63 Hz, —CH_2—), 3.25 (t, 2H, J = 6.72 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.34 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.35 (m, 17H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.8 (C_8), 25.8 (C_7), 37.2 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.2 (C_{22}), 103.5–150.4 (C_{36}–C_{41}), 108.7 (C_{35}), 115.1–157.1 (C_{11}–C_{16}), 122.3–157.4 (C_2–C_6), 126.3–130.6 (C_{42}–C_{47}), 118.3–161.4 (C_{23}–C_{28}), 130.1 (C_{32}), 160.7 (C_{21}), 163.4 (C_{17}), 164.5 (C_{34}), 169.0 (C_{19}), 170.6 (C_{31}). Anal. Calcd for $C_{44}H_{36}N_5O_5Cl_2F$: C, 65.67; H, 4.51; N, 8.70. Found: C, 65.61; H, 4.50; N, 8.73.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-methyl phenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6f). This compound was obtained as dark brown solid, yield 61%, m.p. 200–203°C, R_f: 0.65; IR (KBr): Ar-H 3063, CH_2 2953, 2835, C=O of imidazolinone 1797, C=N imidazolinone 1656, C=N of pyrimidine 1614, C—O—C 1222, 1034 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.19 (t, 3H, J = 7.62 Hz, —CH_3), 2.34 (s, 3H, —CH_3), 2.51 (q, 2H, J = 7.62 Hz, —CH_2—), 3.23 (t, 2H, J = 6.70 Hz, —CH_2), 3.80 (s, 3H, —OCH_3), 4.32 (t, 2H, J = 6.70 Hz, —CH_2—O), 6.76–8.32 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.3 (C_8), 25.4 (C_{29}), 25.7 (C_7), 37.3 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.2 (C_{22}), 103.8–149.2 (C_{36}–C_{41}), 108.5 (C_{35}), 114.9–158.9 (C_{11}–C_{16}), 123.3–155.4 (C_2–C_6), 127.0–130.2 (C_{42}–C_{47}), 128.1–137.23 (C_{23}–C_{28}), 130.2 (C_{32}), 158.9 (C_{21}), 160.8 (C_{17}), 163.5 (C_{34}), 165.5 (C_{19}), 170.0 (C_{31}). Anal. Calcd for $C_{45}H_{41}N_5O_5$: C, 73.85; H, 5.65; N, 9.57. Found: C, 73.80; H, 5.62; N, 9.51.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(1-phenyl) pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6g). This compound was obtained as brown solid, yield 55%, m.p. 102–104°C R_f: 0.59; IR (KBr): Ar-H 3064, CH_2 2957, 2836, C=O of imidazolinone 1795, C=N imidazolinone 1655, C=N of pyrimidine 1615, C—O—C 1229, 1033 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.24 (t,

3H, J = 7.61 Hz, —CH_3), 2.53 (q, 2H, J = 7.61 Hz, —CH_2—), 3.26 (t, 2H, J = 6.70 Hz, —CH_2), 3.82 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.70 Hz, —CH_2—O), 6.78–8.37 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.6 (C_8), 25.6 (C_7), 37.4 (C_9), 56.3 (C_{48}–C_{50}), 67.6 (C_{10}), 103.5 (C_{22}), 103.5–150.3 (C_{36}–C_{41}), 108.7 (C_{35}), 114.8–157.6 (C_{11}–C_{16}), 122.4–157.3 (C_2–C_6), 126.4–130.6 (C_{42}–C_{47}), 127.5–133.0 (C_{23}–C_{28}), 130.4 (C_{32}), 160.1 (C_{21}), 163.5 (C_{17}), 164.2 (C_{34}), 169.6 (C_{19}), 170.1 (C_{31}). Anal. Calcd. for $C_{44}H_{39}N_5O_5$: C, 73.62; H, 5.48; N, 9.76. Found: C, 73.65; H, 5.45; N, 9.75.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-fluorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6h). This compound was obtained as brown solid, yield 52%, m.p. 125–128°C, R_f: 0.60; IR (KBr): Ar-H 3068, CH_2 2955, 2832, C=O of imidazolinone 1793, C=N imidazolinone 1653, C=N of pyrimidine 1617, C—O—C 1226, 1038, C—F 974 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.16 (t, 3H, J = 7.63 Hz, —CH_3), 2.56 (q, 2H, J = 7.62 Hz, —CH_2—), 3.23 (t, 2H, J = 6.70 Hz, —CH_2), 3.81 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.70 Hz, —CH_2—O), 6.78–8.32 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.8 (C_8), 25.2 (C_7), 37.5 (C_9), 56.4 (C_{48}–C_{50}), 67.5 (C_{10}), 103.8 (C_{22}), 103.2–150.8 (C_{36}–C_{41}), 108.4 (C_{35}), 114.9–157.5 (C_{11}–C_{16}), 122.4–157.2 (C_2–C_6), 126.1–130.3 (C_{42}–C_{47}), 116.0–162.9 (C_{23}–C_{28}), 130.1 (C_{32}), 160.7 (C_{21}), 163.6 (C_{17}), 164.4 (C_{34}), 169.3 (C_{19}), 170.3 (C_{31}). Anal. Calcd. for $C_{44}H_{38}N_5O_5F$: C, 71.82; H, 5.21; N, 9.52. Found: C, 71.81; H, 5.23; N, 9.51.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(2,4-difluorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6i). This compound was obtained as brown solid, yield 60%, m.p. 95–99°C, R_f: 0.59; IR (KBr): Ar-H 3066, CH_2 2953, 2833, C=O of imidazolinone 1795, C=N imidazolinone 1654, C=N of pyrimidine 1614, C—O—C 1225, 1035, C—F 975 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.20 (t, 3H, J = 7.63 Hz, —CH_3), 2.55 (q, 2H, J = 7.63 Hz, —CH_2—), 3.25 (t, 2H, J = 6.71 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.70 Hz, —CH_2—O), 6.74–8.30 (m, 18H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.2 (C_8), 25.5 (C_7), 37.6 (C_9), 56.3 (C_{48}–C_{50}), 67.6 (C_{10}), 103.2 (C_{22}), 103.6–150.4 (C_{36}–C_{41}), 108.3 (C_{35}), 114.7–157.3 (C_{11}–C_{16}), 122.3–157.4 (C_2–C_6), 126.4–130.6 (C_{42}–C_{47}), 111.6–164.5 (C_{23}–C_{28}), 130.6 (C_{32}), 160.8 (C_{21}), 163.2 (C_{17}), 164.2 (C_{34}), 169.3 (C_{19}), 170.2 (C_{31}). Anal. Calcd. for $C_{44}H_{37}N_5O_5F_2$: C, 70.11; H, 4.95; N, 9.29. Found: C, 70.13; H, 4.92; N, 9.27.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-bromophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6j). This compound was obtained as brown solid, yield 61%, m.p. 130–132°C, R_f: 0.63; IR (KBr): Ar-H 3065, CH_2 2954, 2835, C=O of imidazolinone 1794, C=N imidazolinone 1656, C=N of pyrimidine 1612, C—O—C 1225, 1033, C—Br 864 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.19 (t, 3H, J = 7.63 Hz, —CH_3), 2.55 (q, 2H, J = 7.63 Hz, —CH_2—), 3.24 (t, 2H, J = 6.72 Hz, —CH_2), 3.82 (s, 3H, —OCH_3), 4.34 (t, 2H, J = 6.72 Hz, —CH_2—O), 6.78–8.36 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.5 (C_8), 25.4 (C_7), 37.1 (C_9), 56.4 (C_{48}–C_{50}), 67.4 (C_{10}), 103.3 (C_{22}), 103.7–150.6 (C_{36}–C_{41}), 108.4 (C_{35}), 114.7–157.1 (C_{11}–C_{16}), 122.5–157.8 (C_2–C_6), 126.4–130.6 (C_{42}–C_{47}), 123.1–132.1 (C_{23}–C_{28}), 130.5 (C_{32}), 160.4 (C_{21}), 163.4 (C_{17}), 164.3 (C_{34}), 169.5 (C_{19}), 170.6 (C_{31}). Anal. Calcd. for $C_{44}H_{38}N_5O_5Br$: C, 66.33; H, 4.81; N, 8.79. Found: C, 66.30; H, 4.80; N, 8.77.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(3,4-dichlorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6k). This compound was obtained as brown solid, yield 65%, m.p. 83–85°C, R_f: 0.66; IR (KBr): Ar-H 3060, CH_2 2952, 2834, C=O of imidazolinone 1798, C=N imidazolinone 1658, C=N of pyrimidine 1610, C—O—C 1220, 1035, C—Cl 749 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.22 (t, 3H, J = 7.63 Hz, —CH_3), 2.50 (q, 2H, J = 7.63 Hz, —CH_2—), 3.20 (t, 2H, J = 6.72 Hz, —CH_2), 3.83 (s, 3H, —OCH_3), 4.30 (t, 2H, J = 6.72 Hz, —CH_2—O), 6.78–8.32 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.6 (C_8), 25.1 (C_7), 37.6 (C_9), 56.4 (C_{48}–C_{50}), 67.8 (C_{10}), 103.0 (C_{22}), 103.1–150.2 (C_{36}–C_{41}), 108.2 (C_{35}), 114.9–157.2 (C_{11}–C_{16}), 122.7–157.3 (C_2–C_6), 126.5–130.5 (C_{42}–C_{47}), 127.0–133.8 (C_{23}–C_{28}), 130.5 (C_{32}), 160.2 (C_{21}), 163.4 (C_{17}), 164.2 (C_{34}), 169.4 (C_{19}), 170.7 (C_{31}). Anal. Calcd. for $C_{44}H_{37}N_5O_5Cl_2$: C, 67.18; H, 4.74; N, 8.90. Found: C, 67.12; H, 4.72; N, 8.88.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(4-chlorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6l). This compound was obtained as dark yellow solid, yield 67%, m.p. 115–118°C, R_f: 0.54; IR (KBr): Ar-H 3063, CH_2 2951, 2834, C=O of imidazolinone 1794, C=N imidazolinone 1653, C=N of pyrimidine 1615, C—O—C 1227, 1035, C—Cl 743 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.23 (t, 3H, J = 7.64 Hz, —CH_3), 2.56 (q, 2H, J = 7.64 Hz, —CH_2—), 3.26 (t, 2H, J = 6.72 Hz, —CH_2), 3.84 (s, 3H, —OCH_3), 4.33 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.78–8.31 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.4 (C_8), 25.7 (C_7), 37.7 (C_9), 56.3 (C_{48}–C_{50}), 67.4 (C_{10}), 103.4 (C_{22}), 103.4–150.6 (C_{36}–C_{41}), 108.4 (C_{35}), 114.8–157.6 (C_{11}–C_{16}), 122.7–157.4 (C_2–C_6), 126.4–130.0 (C_{42}–C_{47}), 128.9–134.3 (C_{23}–C_{28}), 130.6 (C_{32}), 160.2 (C_{21}), 163.4 (C_{17}), 164.2 (C_{34}), 169.5 (C_{19}), 170.6 (C_{31}). Anal. Calcd. for $C_{44}H_{38}N_5O_5Cl$: C, 70.25; H, 5.09; N, 9.31. Found: C, 70.24; H, 5.02; N, 9.32.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(3-methoxyphenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6m). This compound was obtained as yellow solid, yield 52%, m.p. 114–116°C, R_f: 0.61; IR (KBr): Ar-H 3062, CH_2 2952, 2831, C=O of imidazolinone 1796, C=N imidazolinone 1658, C=N of pyrimidine 1617, C—O—C 1221, 1036 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.17 (t, 3H, J = 7.64 Hz, —CH_3), 2.53 (q, 2H, J = 7.64 Hz, —CH_2—), 3.26 (t, 2H, J = 6.72 Hz, —CH_2), 3.81 (s, 3H, —OCH_3), 4.33 (t, 2H, J = 6.71 Hz, —CH_2—O), 6.73–8.36 (m, 19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.6 (C_8), 25.3 (C_7), 37.2 (C_9), 55.8 (C_{29}), 56.4 (C_{48}–C_{50}), 67.2 (C_{10}), 103.2 (C_{22}), 103.3–150.6 (C_{36}–C_{41}), 108.7 (C_{35}), 114.2–157.5 (C_{11}–C_{16}), 122.5–157.3 (C_2–C_6), 126.1–130.3 (C_{42}–C_{47}), 112.2–161.1 (C_{23}–C_{28}), 130.4 (C_{32}), 160.3 (C_{21}), 163.2 (C_{17}), 164.1 (C_{34}), 169.4 (C_{19}), 170.2 (C_{31}). Anal. Calcd. for $C_{45}H_{41}N_5O_6$: C, 72.27; H, 5.53; N, 9.36. Found: C, 72.25; H, 5.55; N, 9.34.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(3-fluorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6n). This compound was obtained as brown solid, yield 51%, m.p. 100–103°C, R_f: 0.62; IR (KBr): Ar-H 3067, CH_2 2955, 2835, C=O of imidazolinone 1795, C=N imidazolinone 1654, C=N of pyrimidine 1613, C—O—C 1224, 1032, C—F 974 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.19 (t, 3H, J = 7.62 Hz, —CH_3), 2.51 (q, 2H, J = 7.61 Hz, —CH_2—), 3.25 (t, 2H, J = 6.72 Hz, —CH_2), 3.82 (s, 3H, —OCH_3), 4.35 (t, 2H, J = 6.72 Hz, —CH_2—O), 6.78–8.34 (m,

19H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.3 (C_8), 25.6 (C_7), 37.4 (C_9), 56.4 (C_{48}–C_{50}), 67.3 (C_{10}), 103.7 (C_{22}), 103.3–150.6 (C_{36}–C_{41}), 108.3 (C_{35}), 114.4–157.4 (C_{11}–C_{16}), 128.5–157.2 (C_2–C_6), 126.3–130.2 (C_{42}–C_{47}), 115.5–163.4 (C_{23}–C_{28}), 130.5 (C_{32}), 160.2 (C_{21}), 163.5 (C_{17}), 164.5 (C_{34}), 169.3 (C_{19}), 170.2 (C_{31}). Anal. Calcd. for $C_{44}H_{38}N_5O_5F$: C, 71.82; H, 5.21; N, 9.52. Found: C, 71.84; H, 5.22; N, 9.51.

1-(4-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]phenyl}-6-(3,4-difluorophenyl)pyrimidin-2-yl)-2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-imidazol-5(4H)-one (6o). This compound was obtained as brown solid, yield 62%, m.p. 180–182°C, R_f: 0.60; IR (KBr): Ar-H 3063, CH_2 2957, 2836, C=O of imidazolinone 1796, C=N imidazolinone 1652, C=N of pyrimidine 1612, C—O—C 1224, 1037, C—F 972 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.21 (t, 3H, J = 7.63 Hz, —CH_3), 2.54 (q, 2H, J = 7.62 Hz, —CH_2—), 3.21 (t, 2H, J = 6.72 Hz, —CH_2), 3.81 (s, 3H, —OCH_3), 4.36 (t, 2H, J = 6.72 Hz, —CH_2—O), 6.78–8.40 (m, 18H, pyridine, pyrimidine, and Ar-H); ^{13}C-NMR ($CDCl_3$): δ 15.5 (C_8), 25.8 (C_7), 37.8 (C_9), 56.3 (C_{48}–C_{50}), 67.4 (C_{10}), 103.8 (C_{22}), 103.4–150.6 (C_{36}–C_{41}), 108.3 (C_{35}), 114.7–157.4 (C_{11}–C_{16}), 122.3–157.3 (C_2–C_6), 126.3–130.2 (C_{42}–C_{47}), 117.5–149.5 (C_{23}–C_{28}), 130.4 (C_{32}), 160.7 (C_{21}), 163.6 (C_{17}), 164.3 (C_{34}), 169.4 (C_{19}), 170.6 (C_{31}). Anal. Calcd. for $C_{44}H_{37}N_5O_5F_2$: C, 70.11; H, 4.95; N, 9.29. Found: C, 70.09; H, 4.94; N, 9.27.

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