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Synthesis of alkoxyphthalimide derivatized oxoimidazolidinyl oxazolo/thiazolo dihydropyrimidine and oxoimidazolidinyl tetrahydropyrimidine *via* common Schiff base intermediate and evaluation of their antibacterial activity

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Synthesis of N-(2-(4-substituted phenyl)-3-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-5-oxoimidazolidin-1-yl)-3-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides and N-(2-(4-substituted phenyl)-3-(2-(1,3-dioxo-2,3-dihydro-1*H*-inden-2-yloxy)ethyl)-5-oxoimidazolidin-1-yl)-7-methyl-3-oxo-5-phenyl-3,5-dihydro-2*H*-oxazolo/thiazolo[3,2-a]pyrimidine-6-carboxamides are described in the present investigation by multistep reactions *via* common intermediate. 6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate have been prepared by three component Beginelli reaction between benzaldeyde, urea/thiourea and ethyl acetoacetate which is further converted to carbohydrazide derivatives by treating it with hydrazine hydrate. Condensation of with various araldehydes produces the key intermediate N-(4-substituted benzylidene)-6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazides. Reactions towards route (A) have been carried out by treating it with glycine to afford its imidazolidinone derivatives. Condensation of two replaceable hydrogens with bromoethoxyphthalimide gives the final products. Route (B) have been propagated by reaction of with chloroacetic acid which yields substituted benzylidene)-7-methyl-3-oxo/thioxo-5-phenyl-3,5-dihydro-2*H*-oxazolo/thiozolo [3,2-a]pyrimidine-6-carbohydrazides. Cyclisation of this with glycine produces imidazolidenone ring derivatives N-(2-(4-substituted phenyl)-5-oxoimidazolidin-1-yl)-7-methyl-3-oxo/thioxo-5-phenyl-3,5-dihydro-2*H*-oxazolo[3,2-*a*]pyrimidine-6-carboxamides. Acidic hydrogen of this ring is replaced by ethoxyphthalimide group to give targeted compounds. Structures of synthesized compounds have been confirmed on the basis of chemical tests and spectral studies. Eight compounds have been screened for antibacterial evaluation.

Keywords: Dihydropyrimidine, oxoimidazolidine, bromoethoxyphthalimide, oxazilidinone, thiazolidinone

Dihydropyrimidinones (DHPM)[1] is an important class of compounds due to their therapeutic significance as antimicrobial[2-5], antiviral[6], anti-HIV[7], antineoplastic[8], anticonvulsant[9], anti-inflammatory[10], calcium channel blockers and antihypertensive agents[11,12]. Compounds containing a fused pyrimidine ring have attracted attention due to their wide range of biological activities, particularly in cancer[13]. Thiazolidine scaffold is a powerful biophore fragment used in the rational design of 'drug-like' compounds as innovative drug prototypes[14-16]. Current research in the area of pharmacological potential is centered around 4-thiazolidinone derivatives, a well-known group of biologically active compounds[17,18] which show a broad spectrum of pharmacological properties *viz* antibacterial[19,20], antiinflammatory[21,22], anticonvulsant[23,24], antituberculosis[25,26], anthel-mintics[27], analgesic[28] *etc*. Imidazole derivatives have recently received considerable attention owing to their wide application as antibacterial[29], antifungal[30], antiherbicidal[31], antioxidant[32,33], antiallergic[34], antitumoral[35], antiparasitic[36] and antihelmintic[37] *etc*. 2-(Trifluoromethyl)-1*H* benzimidazole derivatives showed the most desirable *in vitro* antiparasitic profile against *Giardia intestinalis, Entamoeba histolytica, Trichomonas vaginalis and Trichinella spiralis*[38]. The compound methyl 1-(4-methoxyphenethyl)-2-(4-fluoro-3-nitro-phenyl)-1*H*-benzimidazole-5-carboxylate induced maximum cell death in leukemic cells with an IC (50) value of 3 micromole[39]. A series of 1, 2, 5-tri-substituted benzimidazole derivatives has been reported[40] to possess potential anticonvulsant activity. Meena Chandran *et al*[41] reported a series of antimicrobial studies of arylidene acetophenone derivatives from benzimidazoles *via* Claisen-Schimdt condensation with aryl aldehyde to produce corresponding bioactive chalcones. Ajani *et al*[42] have synthesized 2,3-disubstituted benzimidazole derivatives as antiprotozoal[43] agent. In view of these observations and in continuation of the work on different heterocycles assembled to alkoxyphtha-limide functionality[44-46], it was thought worthwhile to

synthesize new chemical entities incorporating these active pharmacophores in a single molecular framework using Schiff bases as basic building blocks, with the hope to achieve enhanced biological activity.

Experimental Section

Melting points of all synthesized compounds were taken in open capillary tubes and are therefore uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 4000 FT IR spectrometer and ^{1}H NMR spectra were determined on a Bruker DRX-300 (300 MHz FT NMR) spectrometer using TMS as internal standard. Mass spectra were recorded on a Jeol AccuTOF JMS-T100LC Mass spectrometer. All compounds gave satisfactory micro analytical results (**Table I**). Homogeneity of the synthesized compounds was checked by TLC using silica gel-G

Table I — Physical and analytical characterization data of synthesized compounds

Compd	Mol. formula	Mol. Wt.	X	Z	m.p.(°C)	Yield (%)	Found (Calcd) % N
1a	$C_{14}H_{16}N_2O_3$	260.28	-	O	148	92	10.18 (10.76)
1b	$C_{14}H_{16}N_2O_2S$	276.35	-	S	157	90	10.05 (10.74)
2a	$C_{12}H_{14}N_4O_2$	246.26	-	O	178	85	22.10 (22.75)
2b	$C_{12}H_{14}N_4OS$	262.33	-	S	192	83	22.02 (21.36)
4a	$C_{19}H_{18}N_4O_2$	334.37	H	O	222	78	16.28 (16.76)
4b	$C_{19}H_{17}ClN_4O_2$	368.81	Cl	O	246	76	14.80 (15.19)
4c	$C_{20}H_{20}N_4O_3$	364.39	OCH_3	O	238	77	16.42 (15.68)
4d	$C_{19}H_{18}N_4OS$	350.43	H	S	255	73	14. 45 (15.99)
4e	$C_{19}H_{17}ClN_4OS$	384.88	Cl	S	230	71	14.06 (14.56)
4f	$C_{20}H_{20}N_4O_2S$	380.46	OCH_3	S	245	70	14.11 (14.73)
5a	$C_{21}H_{21}N_5O_3$	391.42	H	O	196	69	17.53 (17.89)
5b	$C_{21}H_{20}ClN_5O_3$	425.86	Cl	O	208	68	16.22 (16.44)
5c	$C_{22}H_{23}N_5O_4$	421.44	OCH_3	O	204	62	16.05 (16.62)
5d	$C_{21}H_{21}N_5O_2S$	407.48	H	S	202	60	16.88 (17.19)
5e	$C_{21}H_{20}ClN_5OS$	441.93	Cl	S	212	61	15.13 (15.85)
5f	$C_{22}H_{23}N_5O_3S$	437.51	OCH_3	S	210	60	15.88 (16.01)
7a	$C_{41}H_{35}N_7O_9$	769.75	H	O	170	58	12.12 (12.74)
7b	$C_{41}H_{34}ClN_7O_9$	804.23	Cl	O	186	56	11.24 (12.19)
7c	$C_{42}H_{37}N_7O_{10}$	799.78	OCH_3	O	182	57	11.79 (12.26)
7d	$C_{41}H_{35}N_7O_8S$	785.82	H	S	178	54	11.91 (12.48)
7e	$C_{41}H_{34}ClN_7O_8S$	820.26	Cl	S	192	61	12.19 (11.95)
7f	$C_{42}H_{37}N_7O_9S$	815.84	OCH_3	S	188	58	11.57 (12.02)
8a	$C_{21}H_{18}N_4O_3$	374.39	H	O	242	72	14.33 (14.96)
8b	$C_{21}H_{17}ClN_4O_3$	408.00	Cl	O	250	74	13.12 (13.70)
8c	$C_{22}H_{20}N_4O_4$	404.41	OCH_3	O	249	76	13.37 (13.85)
8d	$C_{21}H_{18}N_4O_2S$	390.45	H	S	254	76	13.90 (14.35)
8e	$C_{21}H_{17}ClN_4O_2S$	424.90	Cl	S	256	78	12.88 (13.19)
8f	$C_{22}H_{20}N_4O_3S$	420.48	OCH_3	S	252	74	12.97 (13.32)
9a	$C_{23}H_{21}N_5O4$	431.44	H	O	265	62	15. 72 (16.23)
9b	$C_{23}H_{20}ClN_5O_4$	465.88	Cl	O	276	60	14.71 (15.03)
9c	$C_{24}H_{23}N_5O_5$	461.46	OCH_3	O	278	57	14.73 (15.18)
9d	$C_{23}H_{21}N_5O_3S$	447.50	H	S	268	64	15.22 (15.65)
9e	$C_{23}H_{20}ClN_5O_3S$	481.95	Cl	S	282	69	14.25 (14.53)
9f	$C_{24}H_{23}N_5O_4S$	477.53	OCH_3	S	280	53	14. 29 (14.67)
10a	$C_{33}H_{28}N_6O_7$	620.62	H	O	205	56	12.97 (13.54)
10b	$C_{33}H_{27}ClN_6O_7$	655.06	Cl	O	210	58	12.35 (12.83)
10c	$C_{34}H_{30}N_6O_8$	650.64	OCH_3	O	206	50	12.32 (12.92)
10d	$C_{33}H_{28}N_6O_6S$	636.68	H	S	208	57	12.69 (13.20)
10e	$C_{33}H_{27}ClN_6O_6S$	671.13	Cl	S	215	63	11.98 (12.52)
10f	$C_{34}H_{30}N_6O_7S$	666.71	OCH_3	S	212	51	12.02 (12.61)

plates, *n*-hexane-ethyl acetate as developing solvent and the spots were visualized in iodine chamber. Bromoethoxyphthalimide **6** was prepared by reported methods[47]. In the text abbreviation hr stands for hours and s, d, t for singlet, doublet and triplet respectively.

Synthesis of ethyl 6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate 1a,b. Benzaldehyde (0.01 mol), urea (0.01 mol)/thiourea (0.01 mol), ethylaceto acetate (0.01 mol) and phosphorus pentaoxide (3.54 mmol) in 250 mL round bottom flask were refluxed on water bath for 3 hr. The reaction mixture was cooled and poured into crushed ice. The separated solid was then filtered, washed with water, dried and purified by recrystallization from ethanol.

Synthesis of 6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide 2a,b. Compounds **1a-b** (0.01 mol) and hydrazine hydrate (0.01 mol) were dissolved in sufficient amount of absolute alcohol in 250 mL round bottom flask. The reaction mixture was refluxed on water bath for 5 hr. The reaction mixture was cooled to RT. Compound was filtered and purified by recrystallization from ethanol.

Synthesis of N'-benzylidene-6-methyl-2-oxo-4-phenyl-1,2, 3, 4-tetrahydropyrimidine-5-carbohydrazide 4a A mixture of compounds **2a** (0.01 mol) and benzaldehyde (1.06 mL, 0.01 mol) was refluxed in methanol (20 mL) containing a trace of acetic acid. The filtrate was concentrated by evaporating the solvent under reduced pressure. Crystals which separated out were filtered and purified by recrystallization from ethanol.

Similarly, other compounds **4b-f** were also synthesized. Their spectral characterization data are presented in **Table II**.

Synthesis of 6-methyl-2-oxo-N-(5-oxo-2-phenyl-imidazolidin-1-yl)-4-phenyl-1, 2, 3, 4-tetrahydro-pyrimidine-5-carboxamide, 5a. To the Schiff base **4a** (0.01 mol) in dry benzene and methanol (1:1, 30 mL), glycine (0.75 g, 0.01 mol) was added with constant stirring. The reaction mixture was kept under reflux for 7 hr. Water formed during the reaction was removed in a Dean-Stark apparatus using azeotropic distillation. Solid separated was filtered from remaining concentrated solution and pressed dry. Some of this was purified by recrystallization from ethanol and the rest was used for the next step.

Compounds **5b-f** were also prepared by similar method with minor change in reaction conditions. Spectral data of these compounds are presented in **Table II**.

Synthesis of 3-(2-(1, 3-dioxoisoindolin-2-yloxy)ethyl)-N-(3-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-5-oxo-2-phenylimidazolidin-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide 7a. A mixture of compound **5a** (0.01 mol) and bromoethoxyphthalimide **6** (5.40 g, 0.02 mol) in acetone using pyridine in catalytic amount was refluxed for 24 hr in a round bottomed flask. It was cooled to RT and the solid which separated out was filtered on a Wattman filter paper. The filtrate was slowly poured on crushed ice while constant stirring. Solid obtained was filtered and washed twice with ice cold water. It was purified by recrystallization from rectified spirit.

Compounds **7b-f** were prepared by similar methods with minor change in reaction conditions. Their spectral data are mentioned in **Table II**.

Synthesis of N-benzylidene-7-methyl-3-oxo-5-phenyl-3, 5-dihydro-2*H*-oxazolo[3, 2-*a*]pyrimidine-6-carbo-hydrazide 8a. A mixture of compound **4a** (0.01 mol), monochloro-acetic acid (0.01 mol), anhydrous sodium acetate (0.02 mol) and acetic acid (10 mL) was heated under reflux for 8 hr. Excess of the solvent was distilled off under reduced pressure and then poured on to crushed ice. The precipitate so obtained was filtered, washed with cold water, dried and purified by recrystallization from glacial acetic acid to furnish **8a**.

Compounds **8b-f** were prepared by similar method with minor change in reaction conditions. Their spectral data are presented in **Table II**.

Synthesis of 7-methyl-3-oxo-N-(5-oxo-2-phenylimi-dazolidin-1-yl)-5-phenyl-3, 5-dihydro-2*H*-oxazolo-[3,2-*a*]pyrimidine-6-carboxamide 9a. To the Schiff base **8a** (0.01 mol) in dry benzene and methanol (1:1, 30 mL), glycine (0.75 g, 0.01 mol) was added with constant stirring. The reaction mixture was kept under reflux for 8-10 hr. Water formed during the reaction was removed in a Dean-Stark apparatus using azeotropic distillation. Solid which separated out was filtered from remaining concentrated solution and pressed dry. Some of this was purified by recrystallization from ethanol and rest was used for the next step.

Compounds **9b-f** were similarly prepared with minor change in reaction conditions, *e.g.*, reflux time, amount of solvent, *etc*. Their spectral data are mentioned in **Table II**.

Table II — IR and ^{1}H NMR and mass spectral data of synthesized compounds

Compd	IR (cm^{-1})	^{1}H NMR (δ)	Mass (*m/z*)
1a	1725 (ester C=O), 3234 (-NH str.), 2910 (-CH str.,CH_2), 1092 (C-O str.)	1.07 (t, 3H, CH_3 ester), 2.25 (s, 3H, dihydropyridyl-CH_3), 3.93 (q, 2H, CH_2-ester), 5.15 (d, 1H, dihydropyridyl-CH), 7.2-7.5 (m, 5H, Ar-H), 7.78 (s, 1H, NH)	260[M] +.
1 b	1225 (dihydropyridyl, C=S), 1714 (ester C=O), 3228 (-NH str.), 2906 (-CH str.,CH_2), 1082 (C-O str.)	1.01 (t, 3H, CH_3-ester), 2.12 (s, 3H, dihydropyridyl-CH_3), 3.73 (q, 2H, CH_2-ester), 5.05 (d, 1H, dihydropyridyl-CH), 6.9-7.2 (m, 5H, Ar-H), 7.56 (s, 1H, NH)	276[M] +.
2a	3064 (C-H str., aromatic), 2874 (C-H str., aliphatic), 1228(C-N str.), 748.6(C-H def, aromatic), 3378 (-$NHNH_2$), 1669 (>C=O amide)	7.22-7.44 (m, 5H,Ar-H), 2.37 (s, 3H, CH_3), 4.18 (s, 2H,-NH_2), 7.67 (s, 1H,-CONH-)	246[M] +.
2b	3055 (C-H str., aromatic), 2867 (C-H str., aliphatic), 1218 (C-N str.), 742.6 (C-H def, aromatic), 3367 (-$NHNH_2$ str.), 1662 (>C=O of amide)	7.18-7.35 (m, 5H, Ar-H), 2.0-2.64 (s, 3H, CH_3), 4.05(s, 2H,-NH_2), 7.57 (s, 1H,-CONH-)	262[M] +.
4a	3340 (-NH str.), 3069 (C-H aromatic str.), 2 871 (C-H aliphatic str.), 1668 (>C=O, amide), 1626 (-N=CH-)	5.38(s,1H,-N=CH-), 8.07 (s, 1H,-CONH-), 6.91-7.68 (m, 10H, Ar-H), 2.2-2.70 (s, 3H, CH_3)	334[M] +.
4b	3336 (-NH str.), 3058 (C-H aromatic str.), 753 (C-Cl str.), 2863 (C-H aliphatic str.), 1665 (>C=O, amide), 1619 (-N=CH-)	5.32 (s,1H,-N=CH-), 7.89 (s, 1H,-CONH-), 6.81-7.68 (m, 9H, Ar-H), 2.09-2.56 (s, 3H, CH_3)	368 [M]+, 370 [M+2]+
4c	3332 (-NH str.), 3049 (C-H str., aromatic), 2830 (Ar-OCH_3), 2859 (C-H str. aliphatic), 1657 (>C=O amide), 1614 (-N=CH-)	5.29 (s, 1H,-N=CH-), 7.76 (s, 1H,-CONH-), 6.74-7.59 (m, 9H, Ar-H), 2.26 (s, 3H,-OCH_3), 2.02 (s, 3H, CH_3)	364[M] +.
4d	1225 (C=S str.), 3332 (-NH str.), 3063 (C-H aromatic str.), 2866 (C-H aliphatic str.), 1659 (>C=O, amide), 1618 (-N=CH-)	5.11 (s, 1H,-N=CH-), 7.01 (s, 1H,-CONH-), 5.98-6.78 (m, 10H, Ar-H), 2.06 (s, 3H, CH_3)	350[M] +.
4e	1217 (C=S str.), 3328 (-NH str.), 3052 (C-H aromatic str.), 749 (C-Cl str.), 2857 (C-H aliphatic str.), 1654 (>C=O, amide), 1615 (-N=CH-)	4.77 (s, 1H,-N=CH-), 6.69 (s, 1H,-CONH-), 5.81-6.69 (m, 9H, Ar-H), 1.89 (s, 3H, CH_3)	384 [M]+, 386 [M+2]+
4f	1207 (C=S str.), 3318 (-NH str.), 3047 (C-H str., aromatic), 2819 (Ar-OCH_3), 2852 (C-H str. aliphatic), 1648 (>C=O amide), 1611 (-N=CH-)	4.63 (s, 1H,-N=CH-), 6.59 (s, 1H,-CONH-), 5.78-6.63 (m, 9H, Ar-H), 1.89 (s, 3H,-OCH_3), 1.76 (s, 3H, CH_3)	380[M] +.
5a	3378 (-NH-), 1722 (-C=O, imidazolidinoine ring), 1672 (>C=O amide)	9.27 (s, 1H, NH of imidazolidinone ring), 4.69 (s, 2H, NCH_2C of imidazolidinone ring), 8.33 (s, 1H,-CONH-), 6.95-7.75 (m, 10H, Ar-H), 2.28 (s, 3H, CH_3)	391[M] +.
5b	760 (C-Cl str.), 3373 (-NH-), 1664 (>C=O amide), 1719 (-C=O, imidazolidinoine ring) 1671 (C=O amide)	9.22 (s, 1H, NH of imidazolidinone ring), 4.52 (s, 2H, NCH_2C of imidazolidinone ring), 8.19 (s, 1H, -CONH-), 6.79-7.65 (m,9H, Ar-H), 2.12 (s, 3H, CH_3)	425 [M]+, 427 [M+2]+
5c	3369 (-NH-), 2818 (Ar-OCH_3), 1712 (-C=O, imidazolidinoine ring), 1668 (>C=O amide)	8.27 (s, 1H, NH of imidazolidinone ring), 4.42 (s, 2H, NCH_2C imidazolidinone ring), 8.12 (s, 1H,-CONH-), 6.65--7.47 (m, 9H, Ar-H), 3.59 (s, 3H,-OCH_3), 2.09 (s, 3H, CH_3)	421[M] +.
5d	1215 (C=S str.), 3375 (-NH-), 1669 (>C=O amide), 1727 (C=O, imidazolidinoine ring),	9.22 (s, 1H, NH imidazolidinone ring), 8.23 (s, 1H, -CONH-), 6.82-7.56 (m, 10H, Ar-H), 4.58 (s, 2H, CH_2 of imidazolidinone ring), 2.17 (s, 3H, CH_3)	407[M] +.
5e	756 (C-Cl str.), 1210 (C=S str.), 3372 (-NH-), 1662 (>C=O amide), 1722 (C=O imidazolidinone ring)	9.18 (s, 1H, NH imidazolidinone ring), 8.17 (s, 1H, -CONH-), 6.57-7.34 (m,9H, Ar-H), 4.46 (s, 2H, CH_2) 2.09 (s, 3H, CH_3)	441 [M]+, 443 [M+2]+
5f	1207 (C=S str.), 3367 (-NH-), 2810 (Ar-OCH_3), 1722 (C=O imidazolidinone ring), 1659 (>C=O amide)	8.47 (s, 1H, NH of imidazolidinone ring), 4.32 (s, 2H, NCH_2C imidazolidinone ring), 8.12 (s, 1H,-CONH-), 6.53-7.22 (m, 9H, Ar-H), 3.59 (s, 3H,-OCH_3), 2.03 (s, 3H, CH_3)	437[M] +.
7a	1065 (C-O str.), 1358 (C-N str.), 1672 (>C=O amide), 3063 (-CH str. aromatic), 1486 (N-O str.)	4.40 (t, 2H, OCH_2), 3.73 (t, 2H, NCH_2), 4.10 (s, 2H, NCH_2C imidazolidinone ring), 6.59-7.79 (m,18H, Ar-H)	769[M] +.

Contd —

Table II — IR and ^{1}H NMR and mass spectral data of synthesized compounds — *Contd*

Compd	IR (cm^{-1})	^{1}H NMR (δ)	Mass (*m/z*)
7b	1059 (C-O str.), 765 (C-Cl str.), 1346 (C-N str.), 1470 (N-O str.), 1666 (>C=O amide), 3058 (-CH str. aromatic)	4.37 (s, 2H, NCH_2C imidazolidinone ring), 6.51-7.62 (m,17H, Ar-H), 4.78 (t, 2H, OCH_2), 3.16 (t, 2H, NCH_2)	803 [M]+, 805 [M+2]+
7c	2826 (Ar-OCH_3), 1053 (C-O str.), 1339(C-N str.), 1468 (N-O str.), 1663 (>C=O amide)	4.32 (s, 2H, NCH_2C imidazolidinone ring), 6.44-7.56 (m, 17H, Ar-H), 3.65 (s, 3H,-OCH_3), 4.63 (t, 2H, OCH_2), 3.08 (t, 2H, NCH_2)	799[M] +.
7d	1670 (>C=O amide), 1255 (C=S str.), 1059 (C-O str.), 1353 (C-N str.), 1482 (N-O str.)	4.36 (s, 2H, NCH_2C imidazolidinone ring), 6.53-7.66 (m, 18H, Ar-H), 4.54 (t, 2H, OCH_2), 3.69 (t, 2H, NCH_2)	785[M] +.
7e	1247(C=S str.), 758 (C-Cl str.), 1054 (C-O str.), 1348 (C-N str.), 1476 (N-O str.)	4.29 (s, 2H, NCH_2C imidazolidinone ring), 6.43-7.56 (m, 17H, Ar-H), 4.49 (t, 2H, OCH_2), 3.56 (t, 2H, NCH_2)	819 [M]+, 821 [M+2]+
7f	2819 (Ar-OCH_3), 1247 (C=S str.), 1034 (C-O str.), 1337 (C-N str.), 1472 (N-O str.)	4.22 (s, 2H, NCH_2C imidazolidinone ring), 6.39-7.42 (m, 17H, Ar-H), 3.48 (s, 3H,-OCH_3), 4.41 (t, 2H, OCH_2), 3.43 (t, 2H, NCH_2)	815 [M]+
8a	3065 (C-H aromatic str.), 1625 (-N=CH str.), 1724 (C=O str. Oxazolidinone ring), 2870 (C-H aliphatic str.)	6.90-7.67 (m,10H, Ar-H), 5.65 (s, 2H, CH_2 oxazolidinone ring), 5.36 (s, 1H, –N=CH str.)	374 [M]+
8b	762 (C-Cl str.), 3061 (C-H aromatic str.), 1620 (-N=CH str.), 1718 (C=O str. Oxazolidinone ring), 2862 (C-H aliphatic str.)	6.77-7.56 (m, 9H, Ar-H), 5.35 (s, 2H, CH_2 oxazolidinone ring), 5.28 (s, 1H,–N=CH str.)	408 [M]+, 410 [M+2]+
8c	2823 (Ar-OCH_3 str.), 3055 (C-H aromatic str.), 1612 (-N=CH str.), 1711 (C=O str. Oxazolidinone ring), 2857 (C-H aliphatic str.)	6.56-7.45 (m, 9H, Ar-H), 5.15 (s, 2H, CH_2 oxazolidinone ring), 5.16 (s, 1H, –N=CH str.), 3.45 (s, 3H,-OCH_3)	404 [M]+
8d	1221 (C=S str.), 3062 (C-H aromatic str.), 1619 (-N=CH str.), 1717 (C=O str. thiazolidinone ring), 2861 (C-H aliphatic str.)	6.88-7.62 (m, 10H, Ar-H), 4.52 (s, 2H, CH_2 thiazolidinone ring), 5.27(s, 1H, –N=CH str.)	390 [M]+
8e	757 (C-Cl str.), 1219 (C=S str.), 3057 (C-H aromatic str.), 1616 (-N=CH str.), 1712 (C=O str. thiazolidinone ring), 2858 (C-H aliphatic str.)	6.72-7.46 (m, 9H, Ar-H), 4.35 (s, 2H, CH_2 thiazolidinone ring), 5.18 (s, 1H,–N=CH str.)	424 [M]+, 426 [M+2]+
8f	2816 (Ar-OCH_3 str.), 1214 (C=S str.), 1610 (-N=CH str.), 1707 (C=O str. thiazolidinone ring), 2846 (C-H aliphatic str.)	6.52-7.43 (m, 9H, Ar-H), 4.26 (s, 2H, CH_2 thiazolidinone ring), 5.06 (s, 1H,–N=CH str.), 3.12 (s, 3H,-OCH_3)	420 [M]+
9a	3362 (C-H aromatic str.), 1721 (-C=O, oxazolidinoine ring), 2860 (C-H aliphatic str.)	9.27 (s, 1H, NH imidazolidinone ring), 4.68 (s, 2H, NCH_2C of imidazolidinone ring), 6.95-7.75 (m, 10H, Ar-H), 2.27 (s, 3H, CH_3)	431 [M]+
9b	752 (C-Cl str,), 3358 (C-H aromatic str.), 1717 (-C=O, oxazolidinoine ring), 2855 (C-H aliphatic str.)	9.22(s, 1H, NH imidazolidinone ring), 4.56 (s, 2H, NCH_2C imidazolidinone ring), 6.73-7.62 (m,9H, Ar-H), 2.13 (s, 3H, CH_3)	465 [M]+, 467 [M+2]+
9c	2814 (Ar-OCH_3 str.), 3352 (C-H aromatic str.), 1712 (-C=O, oxazolidinoine ring), 2846 (C-H aliphatic str.)	9.12 (s, 1H, NH imidazolidinone ring), 4.34 (s, 2H, NCH_2C imidazolidinone ring), 6.65-7.34 (m, 9H, Ar-H), 2.03 (s, 3H, CH_3), 3.67 (s, 3H,-OCH_3)	461 [M]+
9d	1216 (C=S str.), 3356 (C-H aromatic str.), 1718 (-C=O, thiazolidinoine ring), 2848 (C-H aliphatic str.)	9.17 (s, 1H, NH imidazolidinone ring), 4.34 (s, 2H, NCH_2C imidazolidinone ring), 6.97-7.32 (m,10H, Ar-H), 2.17 (s, 3H, CH_3)	447 [M]+
9e	747 (C-Cl str,) 1207 (C=S str.), 3351 (C-H aromatic str.), 1711 (-C=O, thiazolidinoine ring), 2844 (C-H aliphatic str.)	9.16 (s, 1H, NH imidazolidinone ring), 4.23 (s, 2H, NCH_2C imidazolidinone ring), 6.63-7.56 (m, 9H, Ar-H), 2.02 (s, 3H, CH_3)	481 [M]+, 483 [M+2]+
9f	2807 (Ar-OCH_3 str.), 1201 (C=S str.), 3346 (C-H aromatic str.), 1705 (-C=O, thiazolidinoine ring), 2835 (C-H aliphatic str.)	9.02 (s, 1H, NH imidazolidinone ring), 4.23 (s, 2H, NCH_2C imidazolidinone ring), 6.34-7.25 (m, 9H, Ar-H), 1.94 (s, 3H, CH_3), 3.47 (s, 3H,-OCH_3)	477 [M]+
10a	1063 (C-O str.), 1355 (C-N str.), 1671 (>C=O amide), 3062 (-CH str. aromatic), 1476 (N-O str.)	4.68 (t, 2H, OCH_2), 3.71 (t, 2H, NCH_2), 4.0 (s, 2H, NCH_2C imidazolidinone ring), 6.87-7.59 (m,14H, Ar-H)	619 [M]+
10b	767 (C-Cl str.) 1053 (C-O str.), 1347 (C-N str.), 1663 (>C=O amide), 3054 (-CH str. aromatic), 1471 (N-O str.)	4.60 (t, 2H, OCH_2), 3.21 (t, 2H, NCH_2), 4.32 (s, 2H, NCH_2C imidazolidinone ring), 6.57-7.79 (m, 13H, Ar-H)	653 [M]+, 655 [M+2]+

Contd —

Table II — IR and ^{1}H NMR and mass spectral data of synthesized compounds — *Contd*

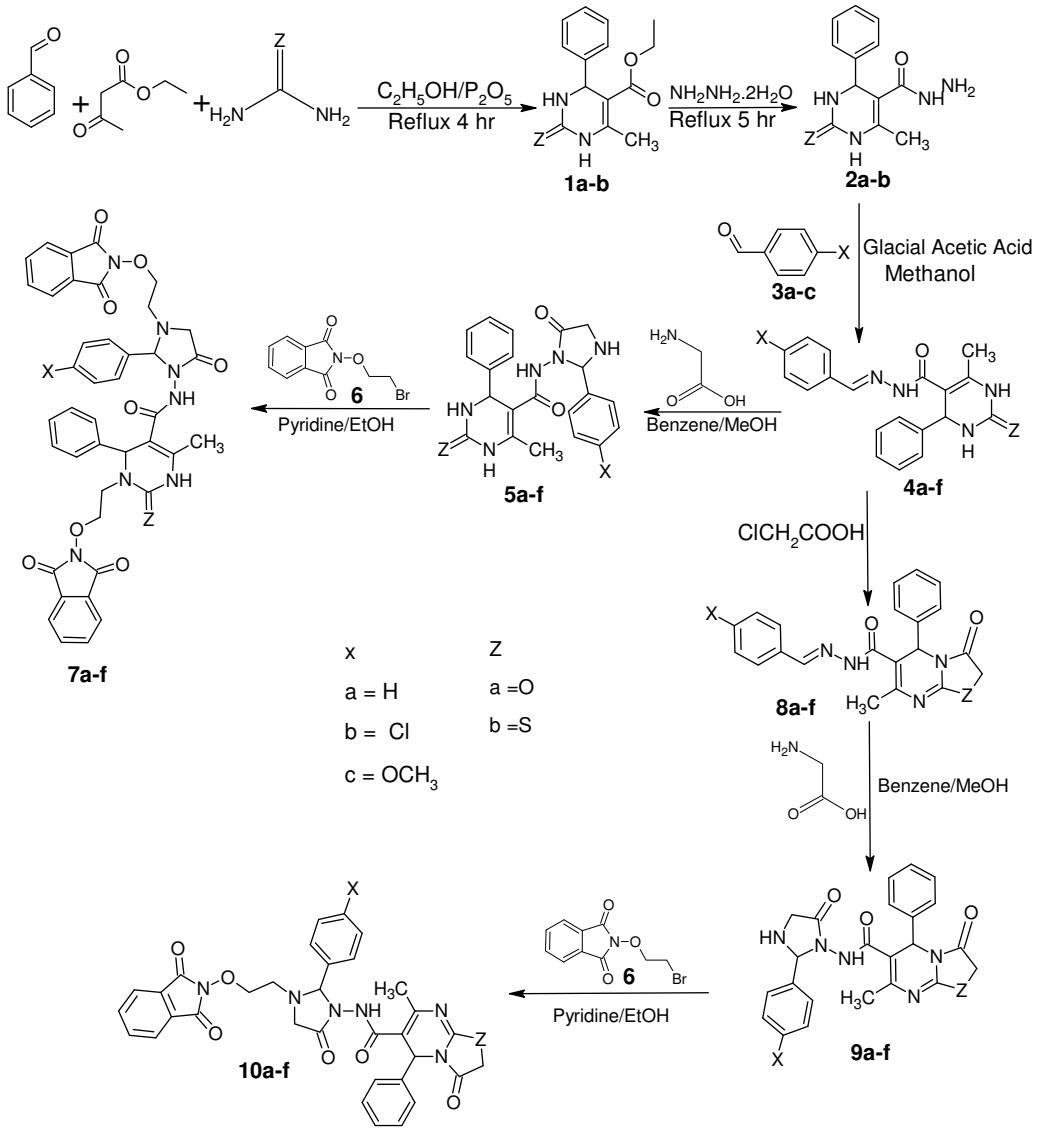
Compd	IR (cm^{-1})	^{1}H NMR (δ)	Mass (*m/z*)
10c	2818 (Ar-OCH_3 str.), 1034 (C-O str.), 1332 (C-N str.), 1661 (>C=O amide), 3043 (-CH str. aromatic), 1465 (N-O str.)	4.49 (t, 2H, OCH_2), 3.17 (t, 2H, NCH_2), 4.25 (s, 2H, NCH_2C imidazolidinone ring), 6.37-7.54 (m,13H, Ar-H), 3.45 (s, 3H,-OCH_3)	649 [M]+
10d	1217 (C=S str.), 1053 (C-O str.), 1345 (C-N str.), 1663 (>C=O amide), 3059 (-CH str. aromatic), 1462 (N-O str.)	4.52 (t, 2H, OCH_2), 3.44 (t, 2H, NCH_2), 4.22 (s, 2H, NCH_2C imidazolidinone ring), 6.65-7.38(m, 14H, Ar-H)	635 [M]+
10e	1209 (C=S str.), 761(C-Cl str.), 1039 (C-O str.), 1332 (C-N str.), 1654 (>C=O amide), 3038 (-CH str. aromatic), 1454 (N-O str.)	4.48 (t, 2H, OCH_2), 3.11 (t, 2H, NCH_2), 4.25 (s,2H, NCH_2C imidazolidinone ring), 6.37-7.71 (m, 13H, Ar-H)	669 [M]+, 671 [M+2]+
10f	1202(C=S str.), 2808 (Ar-OCH_3 str.), 1028 (C-O str.), 1326(C-N str.), 1645 (>C=O amide), 3027 (-CH str. aromatic), 1434 (N-O str.)	4.45 (t, 2H, OCH_2), 3.07 (t, 2H, NCH_2), 4.15 (s, 2H, NCH_2C imidazolidinone ring), 6.27-7.35 (m,13H, Ar-H), 3.35 (s, 3H,-OCH_3)	665 [M]+

Synthesis of N-(3-(2-(1, 3-dioxo-2,3-dihydro-1*H*-inden-2-yloxy) ethyl)-5-oxo-2-phenylimidazolidin-1-yl)-7-methyl-3-oxo-5-phenyl-3, 5-dihydro-2*H*-oxazolo-[3,2-*a*]pyrimidine-6-carboxamide 10a A mixture of compound **9a** (0.01 mol) and bromoethoxy-phthalimide **6** (5.40 g, 0.01 mol) in acetone using pyridine in catalytic amount was refluxed for 18-20 hr in a round bottomed flask. It was cooled to RT and the solid separated was filtered on a Wattman filter paper. The filtrate was slowly poured on crushed ice with constant stirring. Solid obtained was filtered and washed twice with ice cold water. The desired compound was purified by recrystallization from rectified spirit.

Compounds **10b-f** were synthesized by similar methods with minor modifications, *e.g.*, reflux time, recrystallization solvent, *etc*. Their characteristic spectral data are presented in **Table II**.

Results and Discussion

The synthetic route for obtaining final product is presented in **Scheme I**. The initial compound ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate/ ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1a,b** have been prepared by using Biginelli reaction between three components *viz*: Benzaldehyde, urea/thiourea and ethyl acetoacetate in ethanolic media in presence of catalytic amount of P_2O_5 under reflux for 3-5 hr. Absorbtion band at 3234 (-NH str.) and 1725 cm^{-1}(C=O ester) in IR spectrum and δ 7.78 singlet for-NH and triplet at δ 2.25 for CH_3 group in ^{1}H NMR spectrum confirmed the structure of **1a**. Additional peak for C=S at 1225 cm^{-1} in IR confirms its Beginelli reaction with thiourea and formation of **1b**. Compounds **1a-b** on treatment with hydrazine hydrate yielded compounds 6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide / 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazides **2a,b**. In the IR spectrum of **2** –NH str. of-NH-NH_2 group was observed at 3378 cm^{-1} which was absent in its precursor **1**. Characteristic proton of –CONH group was observed at δ 7.67 as singlet. This compound on reaction with various araldehyde in glacial acetic acid gave N-(4-substituted benzylidene)-6-methyl-2-oxo/thioxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carbohydrazide **4a-f**. Appearance of C=N IR peak at 1626 cm^{-1} confirms the formation of compounds **4a-f** which acted as key intermediate for two routes to obtained final compounds **7a-f** and **10a-f**. In route A **4a-f** were treated with equimolar quantity of glycine in reflux condition with methanol and benzene to yield N-(2-(4-substituted phenyl)-5-oxoimidazolidin-1-yl)-6-methyl-2-oxo/thioxo-4-phenyl-1, 2, 3, 4-tetra-hydropyrimidine-5-carboxamide **5a-f**. Formation of **5a-f** was confirmed by ^{1}H NMR spectra for –NH proton of oxoimidazolidine ring at δ 9.27 and also disappearance of C=N str. in IR at 1626 cm^{-1}. Compounds **5a-f** were then condensed with bromoethoxyphthalimide **6** in presence of catalytic amount of pyridine under reflux for 18-22 hr in absolute alcohol to furnish N-(2-(4-substituted phenyl)-3-(2-(1, 3-dioxoisoindolin-2-yloxy)ethyl)-5-oxoimidazolidin-1-yl)-3-(2-(1, 3-dioxoisoindolin-2-yloxy)ethyl)-6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides **7a-f**. Structures of these compounds have been confirmed by disappearance of NMR signal for –NH functionality at δ 9.27 for oxoimidazolidine ring and also at δ 7.78 for –NH of dihydropyrimidinone ring, appearance of C-O and N-O str. at 1065, 1486 respectively and two triplets at δ 3.73 and 4.40 for N-CH_2 and O-CH_2 of ethoxyphthalimide moiety in ^{1}H NMR spectra. Additional confirmation of phthalimidoxyl group



Scheme I

attachment was acheived by usual chemical test including florocence formation. In other route B compounds **4a-f** were refluxed with chloroacetic acid/ sodiumacetate for 8-10 hr which afforded further cyclized products N-(4-substituted benzylidene)-7-methyl-3-oxo/thioxo-5-phenyl-3, 5-dihydro-2*H*-oxazolo-[3,2-*a*]pyrimidine-6-carbohydrazides **8a-f**. Disappearance of ^{1}H NMR signal at δ 7.78 for –NH of pyrimidine and also IR peak at 3234 cm^{-1} and appearance of new signals at δ 4.52 singlet for S-CH_2 and δ 5.65 singlet for O-CH_2 confirms the formation of thiazolidinone and oxazolidinone rings respectively. A new oxoimidazolidine ring is created in compounds **8a-f** on Schiff base site in the next step by treating these with the amino acid glycine again in mixed reflux media (methanol and benzene) to get the penultimate compounds N-(2-(4-substituted phenyl)-5-oxoimidazolidin-1-yl) - 7 - methyl - 3-oxo/thioxo-5-phenyl-3, 5-dihydro-2*H*-oxazolo[3,2-*a*]pyrimidine-6-carboxamides **9a-f**. Confirmation for formation of these compound is again obtained on the same pattern as those of **4a-f** to **5a-f** from the –NH signal at δ 9.27 singlet. Target compounds N-(2-(4-substituted phenyl)-3-(2-(1, 3-dioxo-2, 3-dihydro-1*H*-inden-2-yloxy) ethyl)-5-oxoimidazolidin-1-yl)-7-methyl-3-oxo-5-phenyl-3, 5-dihydro-2*H*-oxazolo/thiazolo[3, 2-*a*]pyrimidine-6-carboxamides **10a-f** in this route were also achieved by base catalyzed (pyridine) condensation of

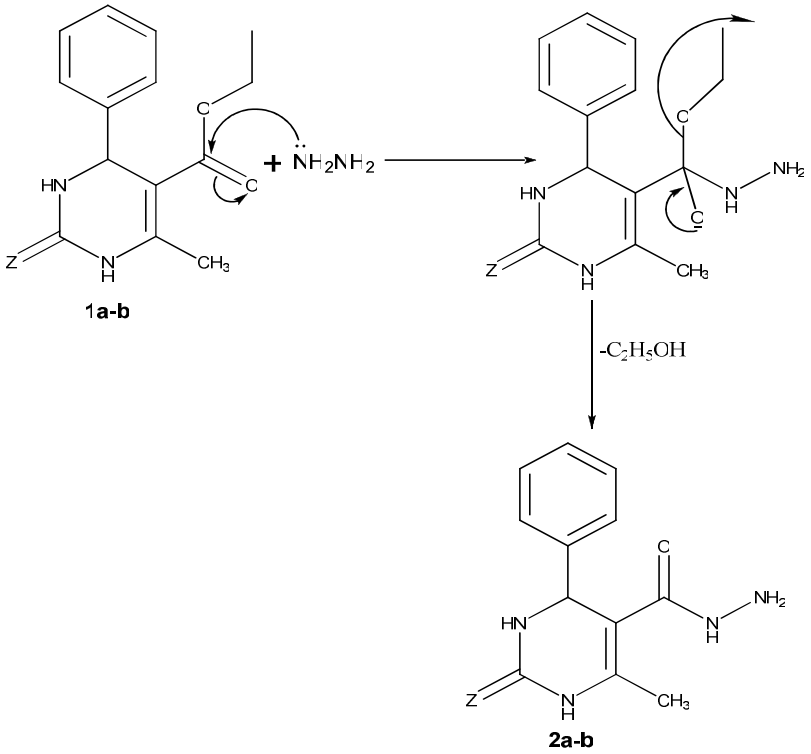


Figure 1

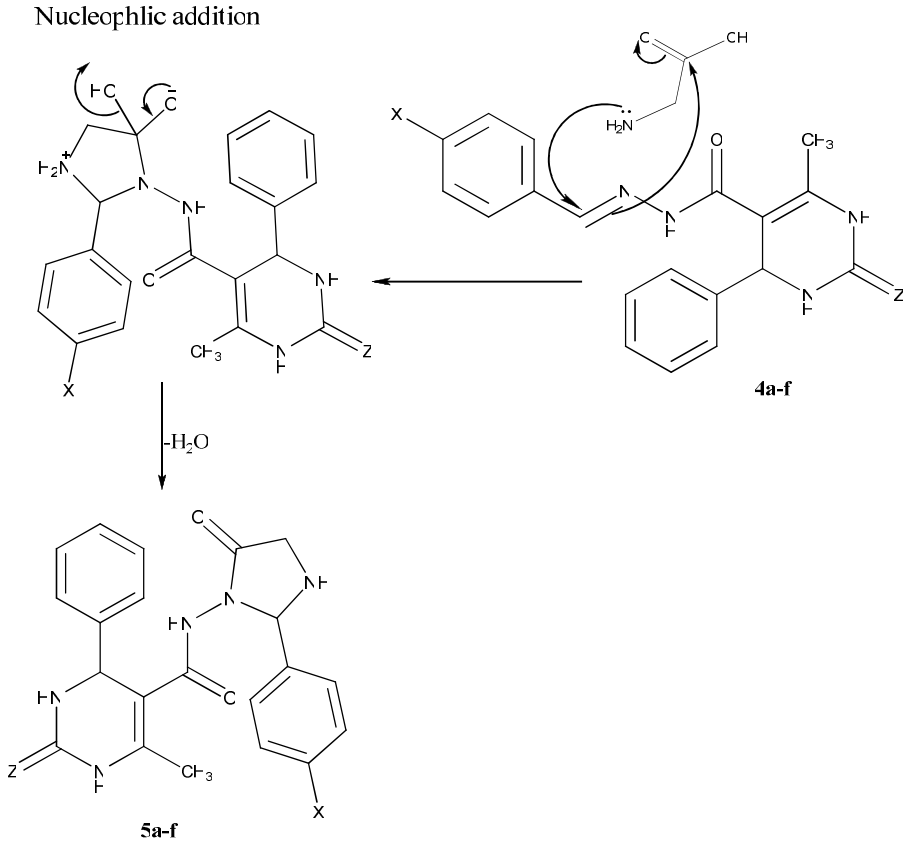


Figure 2

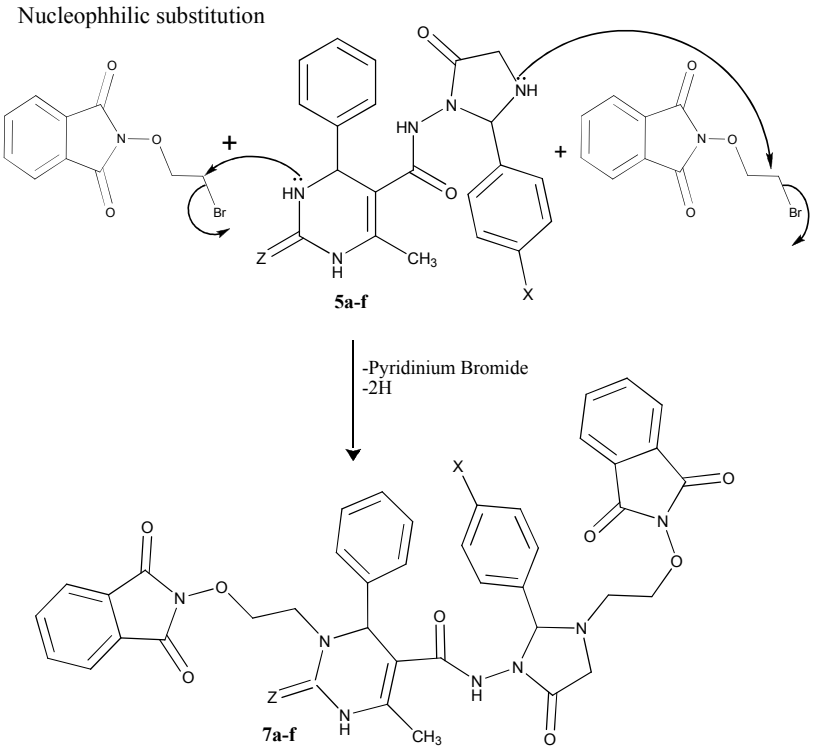


Figure 3

9a-f (Scheme I) with bromoethoxyphthalimide and their formation were also confirmed on the same grounds as given above (*vide-supra*).

Plausible Mechanism

The initial substrates **1a,b** is formed by the three components well known Beginelli reaction. Conversion of **1a,b** to **2a,b (Figure 1)** is a nucleophilic addition of hydrazine hydrate at carbonyl carbon of ester moiety. This is followed by formation of carbonyl group and elimination of ethoxy group. Formation of **2a,b** to **4a-f** is Schiff base formation reaction in which nucleophilic addition cum elimination takes place. Conversion of **4a-f** to **5a-f (Figure 2)** is a cyclisation process of Schiff base with glycine followed by elimination of H_2O to yield **5a-f**. Replacement of active hydrogen **(Figure 3)** from imidazole and pyrimidine derivatives takes place by nucleophilic substitution of alkoxyphthalimide moiety in **5a-f** and results in the formation of bisphtha-limidoxy derivatised compounds **7a-f**. Conversion of **4a-f** to **8a-f (Figure 4)** is a cyclisation reaction of chloroacetic acid on dihydropyrimidinone ring followed by nucleophilic substitution and π-electron of oxygen or sulphur with that of chloroacetic acid.

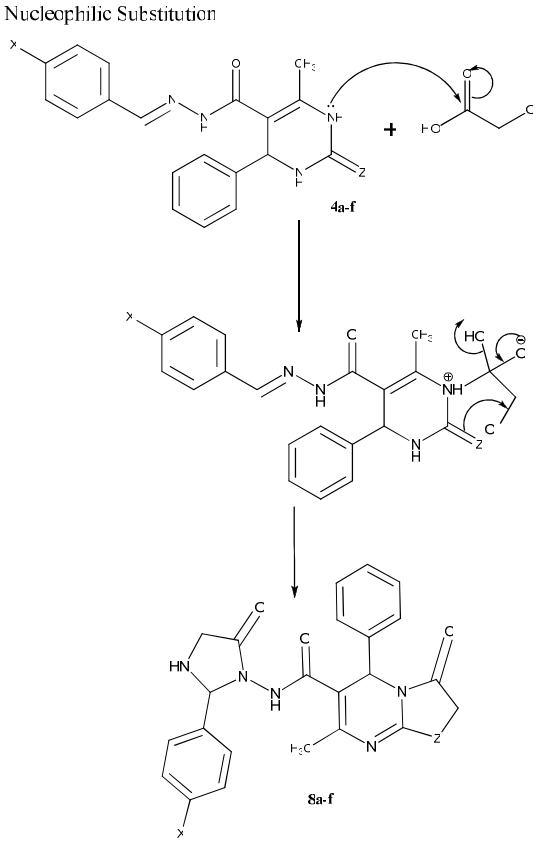


Figure 4

Table III — Results of antibacterial activity of synthesized compounds

Compd	Zone of inhibition of growth in mm (activity index)			
	B. subtilis	*E. coli*	*K. pneumoniae*	*P. aeruginosa*
7a	5(0.33)	6(0.37)	9(0.50)	8(0.47)
7b	8(0.53)	8(0.50)	11(0.61)	9(0.52)
7d	7(0.46)	7(0.43)	14(0.77)	11(0.64)
7e	10(0.66)	9(0.56)	16(0.88)	15(0.88)
10a	10(0.66)	11(0.68)	12(0.66)	13(0.76)
10b	13(0.86)	13(0.81)	14(0.77)	15(0.88)
10d	11(0.73)	12(0.75)	12(0.66)	14(0.77)
10e	12(0.80)	15(0.93)	15(0.83)	16(0.94)
Standard	15	16	18	17

Standard = Ciprofloxocin

Biological activity

In the present investigation all the synthesized compounds were screened at 500 ppm level against various pathogenic strains *viz. P. aeruginosa*, *K. pneumoniae*, *E. coli*, *B. subtilis* for antibacterial activity. Preliminary antibacterial susceptibility tests for all the synthesized compounds were performed by using cup and well method[48]. Standard used for antibacterial activity, Ciprofloxacin were also screened under similar conditions for comparison. The screening results have been summarized in **Table III**.

Conclusion

Tested compounds show moderate to strong activity ranging from 0.33-0.94 for compounds **7a**, **7b**, **7d** show moderate activity against all the four strains whereas compound **7e** shows moderate activity against *B. subtilis and E. coli* but strong activity against *K. pneumoniae* and *P. aeruginosa*. Compound **10a** showed moderate activity where as **10b**, **10d**, **10e** showed strong activity, **10e** showed the activity comparable to the standred index (0.8-0.94). Overall, it can be concluded that these compounds showed strong activity against *K. pneumoniae* and *P. aeruginosa* as compared to *B. subtilis and E. coli.* Introduction of thiazolidinone and oxazolidinone fused ring along with ethoxyphthalimide moiety enhanced the activity. Substitution of *p*-chloro moiety generally increases the activity of the compound.

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