Synthesis and antimicrobial activity of succinimido(2-aryl-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetates

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Abstract

8-Hydroxyquinoline **1** reacts with ethyl chloroacetate in the presence of anhydrous K_2CO_3 to produce ethyl (quinolin-8-yloxy)acetate **2**. Treatment of **2** with hydrazine hydrate forms 2-(quinolin-8-yloxy)acetohydrazide **3**, which on condensation with various aldehydes **4a-e** gives *N*'-{[(1*Z*)-arylmethylene]-2-(quinolin-8-yloxy)}acetohydrazides **5a-e**. These, on cyclization with mercaptosuccinic acid, yield (2-aryl-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl) acetic acids **6a-e**. Compounds **6a-e** are further converted into acid chloride derivatives **7a-e** by reaction with thionyl chloride. Subsequent treatment of **7a-e** with *N*-hydroxysuccinimide in the presence of TEA furnishes the title compounds **8a-e**. Antibacterial and antifungal activities of the final compounds have been evaluated and all the compounds have shown significant inhibition of bacterial and fungal growth.

Keywords: *N*-Hydroxysuccinimide, quinoline, antimicrobial activity, thiazolidine, ethyl chloroacetate

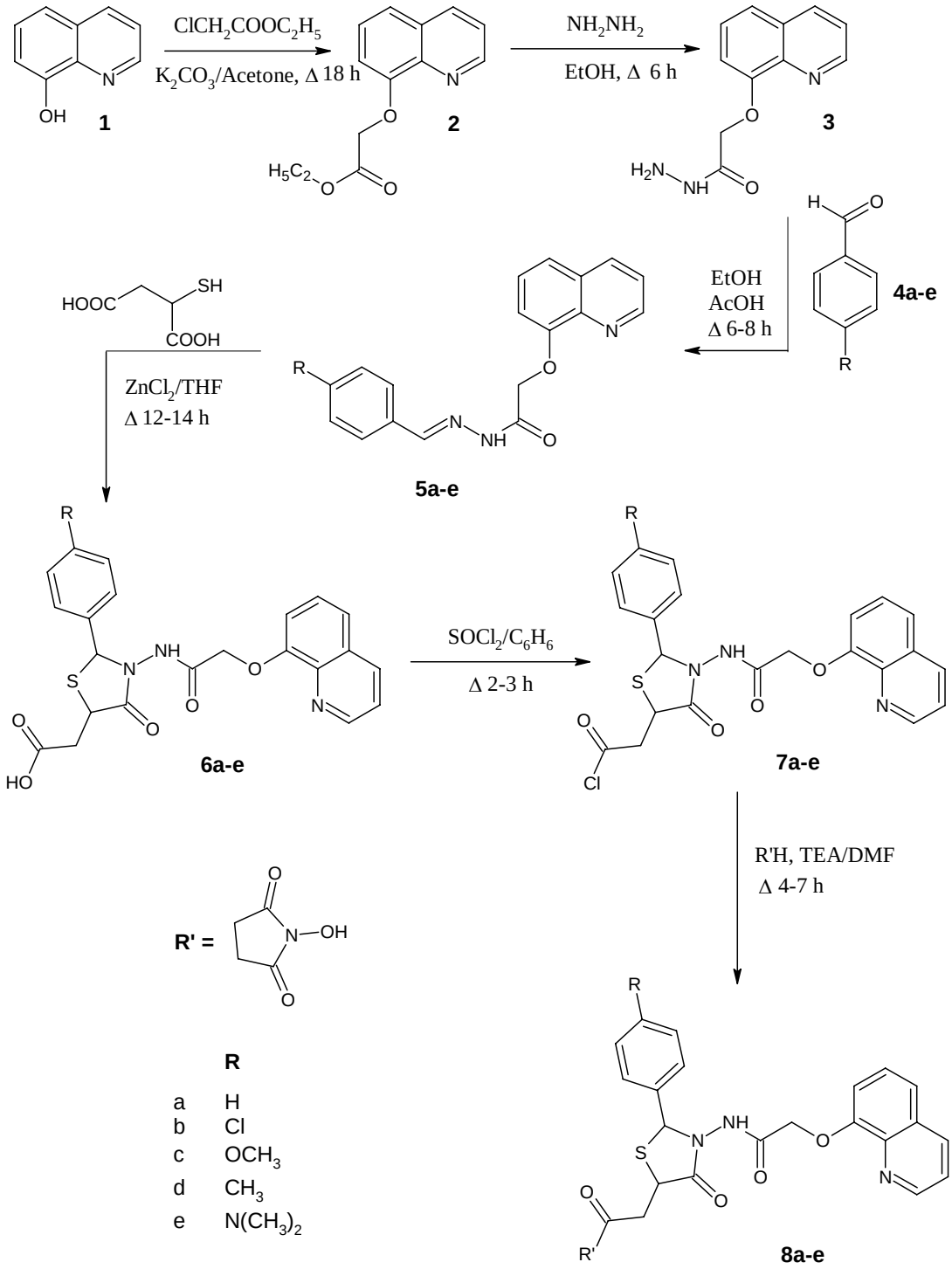
Introduction

The importance of the quinoline nucleus has been well demonstarted as illustrated by the large number of patents employing such species as chemotherapeutic agents. A number of biological activities have been associated with quinoline-containing compounds such as anti-inflammatory, antiallergic[1], antimalarial[2], antibacterial[3], antiproliferative[4], anticancer[5,6] and antiparasitic[6] activities. Similarly, various thiazolidinones[7-9] have attracted considerable attention as they are also endowed with a wide range of pharmaceutical activities including CNS-depressant[10], anaesthetic[11], anticonvulsant[12], antibacterial[13,14], antiviral[15] and antitumor[16]. Furthermore, drug research and development has led to the discovery of new pharmacologically active agents, including imidoxy[17,18] compounds such as phthalimidoxy[19] and succinimidoxy[20]. Succinimidoxy

derivatives were tested against different cancer cells[21] and also have been used in peptide synthesis[22]. They also possess a strong anti-convulsant activity[23]. In the present study, we have synthesized a new class of combinational molecules in which all of these moieties are present. The structures of the compounds synthesized were assigned on the basis of elemental analysis, IR, NMR and Mass spectral data. These compounds were evaluated for their antimicrobial screening.

Results and Discussion

Ethyl (quinolin-8-yloxy)acetate **2** has been synthesized by condensation of 8-hydroxyquinoline **1** with ethyl chloroacetate in dry acetone for 18 h. In the IR spectrum of compound **2**, bands in the range of 1747 cm^{-1} were obtained due to C=O stretching, as expected for the formation of **2**. In the ^1H NMR spectrum, signals were found at δ 4.97 (singlet), 3.22 (quartet) and 2.28 (triplet), which showed the presence of a $OCH_2COOC_2H_5$ group. Compound **2**, on treatment with hydrazine hydrate, yielded 2-(quinolin-8-yloxy)acetohydrazide **3**. In the IR spectrum of **3**, N-H stretching was observed at 3336-3257 cm^{-1}, which was absent in precursor **2**. In the ^1H NMR spectrum, the characteristic proton of the CONH group was observed at δ 8.09 as a singlet. Compound **3**, on reaction with various aldehydes **4a-e**, gave N'-{[(1Z)-arylmethylene]-2-(quinolin-8-yloxy)}acetohydrazides **5a-e**, which in turn afforded (2-aryl-4-oxo-3-{[quinolin-8-yloxy)acetyl]amino}1,3-thiazolidin-5-yl) acetic acids **6a-e** on cyclization with mercaptosuccinic acid. The structures of the products were elucidated further on the basis of the C-S-C linkage in the five membered ring, which caused a weak but sharp absorption band at 760-710 cm^{-1} in all the compounds. A broad band in the range 3223-2891 cm^{-1} was obtained due to the OH stretching vibration and the C=O group was observed as a strong, sharp band at 1733-1674 cm^{-1} in all these compounds. The thiazolidinone CH was observed at δ 3.58-3.29 ppm as a triplet and the CH_2 protons at δ 3.27-3.04 ppm as a doublet, which indicated the formation of **6a-e**. Compounds **6a-e** were further converted into acid chloride derivatives **7a-e** by reaction with $SOCl_2$. Formation of the products was confirmed by disappearance of the IR band at 3223-2891 cm^{-1} due to the OH group and the appearance of a new band at 775-710 cm^{-1} due to the C-Cl bond. Subsequently, the chlorine atom in CH_2CO-Cl was replaced by the succinimidoxy group to give the title compounds **8a-e**. In the MS spectra of the latter, the molecular ion peak indicated the formation of compounds **8a-e**. Attempts to use anhydrous K_2CO_3 and Na_2CO_3 in acetone to condense **7a-e** with N-hydroxysuccinimide gave poor yields and the stronger base, NaH in THF, gave a sticky product that could not be crystallised. Better yields were obtained when TEA in DMF was used.



Scheme 1

The synthesized compounds **8a-e** were screened "*in vitro*" for antimicrobial activity. From the data presented in **Table 1**, it is clear that compound **8b** is highly active against

Staphylococcus aureus, *Staphylococcus albus*, *Streptococcus faecalis*, *Klebsiella pneumoniae* and *Pseudomonas aeuroginosa* as compared to the standard (amicacin), but shows only moderate activity against *Escherichia coli* and *Proteus mirabilis*. Other compounds exhibit moderate to good antibacterial activity against all organisms. Similarly, **8b** and **8e** exhibit good antifungal activity against *Candida albicans* and *Aspergillus fumigatus* as compared to the standard drug used (fluconazole). The remaining compounds are moderately active against these two micro-organisms (*C. albicans* and *A. fumigatus*). It can be concluded that the antimicrobial activity of such compounds may change by introduction or elimination of a specific group.

Table 1. Antimicrobial activity of compounds **8a-e.** Zone of inhibition (mm) (activity index)*

Compd.	Antibacterial activity								Antifungal activity	
	S. aureus	*S. albus*	*S. faecalis*	*K. pneumoniae*	*E. coli*	*P. aeuroginosa*	*P. mirabilis*	*S. typhi*	*C. albicans*	*A. fumigatus*
8a	16	18	23	20	15	15	15	09	20	22
	(0.76)	(0.82)	(0.82)	(0.90)	(0.78)	(0.65)	(0.68)	(0.56)	(0.80)	(0.81)
8b	22	25	29	22	18	24	17	15	24	25
	(1.04)	(1.13)	(1.03)	(1.00)	(0.94)	(1.04)	(0.85)	(0.93)	(0.96)	(0.92)
8c	19	21	24	19	16	20	16	11	22	23
	(0.90)	(0.95)	(0.85)	(0.86)	(0.84)	(0.86)	(0.87)	(0.68)	(0.88)	(0.85)
8d	17	19	26	18	15	17	13	10	21	21
	(0.80)	(0.86)	(0.92)	(0.82)	(0.78)	(0.73)	(0.65)	(0.62)	(0.84)	(0.78)
8e	19	20	23	21	17	21	14	12	23	24
	(0.90)	(0.90)	(0.82)	(0.95)	(0.89)	(0.91)	(0.7)	(0.75)	(0.92)	(0.89)
C_1	21	22	28	22	19	23	20	16	-	-
C_2	-	-	-	-	-	-	-	-	25	27

* Activity index = Inhibition area of the sample/inhibition area of the standard.
C_1 = Amicacin; C_2 = Fluconazole. Diameter of disc is 5 mm

Antimicrobial screening

The disc-diffusion method[24] was used for the screening of anti-microbial activity. The antibacterial activity of the synthesized compounds **8a-e** was tested against gram-positive bacteria *i.e. Staphylococcus aureus*, *Staphylococcus albus*, *Streptococcus faecalis* and gram-negative bacteria *i.e.*, *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeuroginosa*, *Proteus mirabilis*, *Salmonella typhi* using a nutrient agar medium. The antifungal activity of the compounds was screened against *Candia albicans* and *Aspergillus fumigatus* using Sabouraded dextrose agar medium. The sterilized medium (autoclaved at 121°C for 15 min.) was innoculated with the suspension of the micro-organisms and poured into a Petri dish to give a depth of 3-4 mm. The paper impregnated with the synthesized compounds **8a-e** (300 µg/ml in DMF) was placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and

incubated at 37° for 24 h and 48 h for antibacterial and antifungal activity, respectively. Amicacin (300 µg/ml) was used in anti-bacterial activity studies, whereas fluconazole (300 µg/ml) was used in antifungal activity studies, as reference compounds. After incubation, the relative susceptibility of the micro-organisms to the potential antimicrobial agent is demonstrated by a clear zone of growth inhibition around the disc. The inhibition zone caused by the various compounds on the micro-organisms was measured and the activity rated on the basis of the size of the inhibition zone. The observed zone of inhibition is presented in Table 1.

Experimental Section

General Procedures. All melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1800 spectrophotometer. The ^{1}H NMR spectra were scanned on a DRX-300 MHz. Spectrometer (300 MHz) in $CDCl_3$/DMSO d_6 using TMS as the internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on a Jeol SX-102 (FAB). *m*-Nitrobenzyl alcohol (NBA) was used as matrix. Purity of synthesized compounds was checked by TLC using silica gel-G. Spots were exposed in an iodine chamber.

Ethyl (quinolin-8-yloxy)acetate (2). A mixture of 8-hydroxyquinoline **1** (0.01 mole), ethyl chloroacetate (0.01 mole) and anhydrous K_2CO_3 (0.01 mole) in dry acetone was refluxed on a water bath for 18 h. The mixture was then filtered and solvent was removed under reduced pressure. The resulting solid was crystallised from ethanol to afford **2**. Yield 80%, m.p. 60˚C; IR(KBr)cm^{-1}:3052 (C-H, Ar-H), 2990 (C-H, CH_3), 1747 (C=O), 1620-1449 (C=C), 1024 (C-O-C); ^{1}H NMR(DMSO d_6): **7.**41 (m, 6H, Ar-H), 4.97 (s, 2H, OC**H$_2$**COO), 3.22 (q, 2H, C**H$_2$**CH_3), 2.28 (t, 3H, CH_2C**H$_3$**); Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.47; H,5.55; N, 6.01%.

2-(Quinolin-8-yloxy)acetohydrazide (3). A mixture of compound **2** (0.01 mole) and hydrazine hydrate (0.02 mole) in ethanol was refluxed on a water bath for 6 h. After cooling, the solid that separated was washed with water, dried and recrystallized from ethanol. Needle shaped crystals of **3** were obtained**:** Yield 84%, m.p. 140˚C; IR (cm^{-1}): 3326-3257 (N-H, $NHNH_2$), 1062 (C-O-C), 1185 (N-N); ^{1}H NMR(DMSO d_6): 8.09 (s, IH, CONH), 7.72-7.47 (m, 6H, ArH), 4.88 (s, 2H, OCH_2), 4.45 (s, 2H, NH_2); Anal.Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.72; H, 5.00; N, 19.29. Found: C, 60.82 ; H, 5.05; N, 19.35%.

***N*'-[(1*Z*)-Phenylmethylene]-2-(quinolin-8-yloxy)acetohydrazide (5a).** A mixture of compound 3 (0.01 mole) in ethanol (30 mL), benzaldehyde **4a** (0.01 mole) and 1 ml. of glacial acetic acid was refluxed on water bath for 6 h. After cooling, the solvent was removed under reduced pressure and the separated solid was crystallized from methanol to yield **5a**. Yield 70%, m.p. 105˚C; IR(KBr)cm^{-1}: 3470 (N-H, CONH), 1674 (C=N), 1080 (C-O-C), 1181 (N-N), 710 (C-H def., monosub. benzene ring); ^{1}H NMR(DMSO d_6): 8.17 (s, 1H, CONH), 7.61 (m, 11H, ArH),

7.41 (s, 1H, N=CH), 4.98 (s, 2H, OCH_2); Anal.Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.71; H, 4.84; N, 13.72. Found: C, 70.81; H, 4.92; N, 13.77 %.

Compounds **5b-e** were synthesized by a similar method with minor modifications e.g. reflux time, crystallization solvent *etc*. in reaction.

***N'*-[(1*Z*)-4-Chlorophenylmethylene]-2-(quinolin-8-yloxy)acetohydrazide (5b).** Yield 70%, m.p. 132˚C; IR(KBr)cm^{-1}: 3456 (N-H, CONH), 1670 (C=O), 1624 (C=N), 1068 (C-O-C), 1188 (N-N), 831 (C-H def., 1,4-disub. benzene ring), 754 (C-Cl); ^{1}H NMR(DMSO d_6): 8.27 (s, 1H, CONH), 7.41 (d, 2H, Ar-H near Cl), 7.11 (s, 1H, N=CH), 4.71 (s, 2H, OCH_2); Anal.Calcd. for $C_{18}H_{14}N_3O_2Cl$: C, 63.55; H, 4.07, N, 12.34. Found: C, 63.62; H, 4.12; N, 12.37 %.

***N'*-[(1*Z*)-4-Methoxyphenylmethylene]-2-(quinolin-8-yloxy)acetohydrazide (5c).** Yield 65%, m.p. 118˚C; IR(KBr)cm^{-1}. 3442 (N-H, CONH), 1700 (C=O), 1628 (C=N), 1094 (C-O-C), 1179 (N-N), 820 (CH def., 1,4-disub. benzene ring); ^{1}H NMR(DMSO d_6): 7.96 (s, 1H, CONH), 7.54 (m, 6H, ArH), 6.69 (d, 2H, Ar-H near OCH_3), 7.30 (s, 1H, N=CH), 4.68 (s, 2H, OCH_2), 3.88 (s, 3H, OCH_3); Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.00; H, 5.01; N, 12.49. Found: C, 68.06; H, 5.07; N 12.53%.

***N'*-[(1*Z*)-4-Methylphenylmethylene]-2-(quinolin-8-yloxy)acetohydrazide (5d).** Yield 60%, m.p. 148˚C; IR(KBr)cm^{-1}: 3468 (N-H, CONH), 1682 (C=O), 1620 (C=N), 1602-1435 (C=C), 1099 (C-O-C) 1192(N-N), 884 (CH def., 1,4-disub. benzene ring); ^{1}H NMR(DMSO d_6): 8.24 (s, 1H, CONH), 7.71-7.25, (m, 10H, ArH), 4.71 (s, 2H, OCH_2), 7.27 (s, 1H, N=CH), 2.6 (s, 3H, CH_3); Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.40; H, 5.25; N, 13.11. Found: C, 71.47; H, 5.33; N, 13.16%.

***N'*-[(1*Z*)-4-Dimethylaminophenylmethylene]-2-(quinolin-8-yloxy)acetohydrazide (5e).** Yield 62%, m.p. 166˚C IR(KBr)cm^{-1} 3452 (N-H, CONH), 1690 (C=O), 1620 (C=N), 1291 (C-N), 1070 (C-O-C), 1193 (N-N) 841 (C-H def., 1,4-disubs. benzene ring). ^{1}H NMR(DMSO d6): 7.98 (s, 1H, CONH), 7.61 (m, 10H, ArH), 6.99 (d, 2H, Ar-H near NMe_2), 7.30 (s, 1H, N=CH), 4.59 (s, 2H, OCH_2), 3.12 (s, 6H, $N(CH_3)_2$). Anal.Calcd.for: $C_{20}H_{20}N_4O_2$: C 68.88, H 5.62 N16.03 Found: C 68.96, H 5.75, N 16.09 %.

(2-Phenyl-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetic acid (6a). A mixture of equimolar amounts of **5a** (0.01 mole) and mercaptosuccinic acid (0.01 mole) in THF (30 mL) with a pinch of anhydrous $ZnCl_2$ was refluxed for 12-14 h on a water bath. The reaction mixture was left to cool at room temperature. The solid product so formed was collected and crystallized from methanol to afford **6a.** Yield 54%, m.p. 172˚C; IR(KBr)cm^{-1}: 3406 (NH), 3190-2862 br. (OH of COOH), 1720 (C=O), 1688 (C=O), 1060 (C-O-C), 1182 (N-N), 730 (C-H def., monosub. benzene ring), 710 (C-S-C); ^{1}H NMR(DMSO d_6): 10.48 (s, 1H, COOH), 8.64 (s, 1H, CONH), 7.41-7.06 (m, 11H, ArH), 4.23 (s, 1H, CH-Ar), 3.91 (s, 2H, OCH_2), 3.29 (t, 1H, $CHCH_2$), 3.04 (d, 2H, $CHCH_2$); Anal.Calcd. for $C_{22}H_{19}N_3O_5S$: C, 60.33; H, 4.25; N 9.58. Found: C, 60.41; H, 4.34; N, 9.61%.

(2-{4-Chlorophenyl}-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetic acid (6b). Yield 58%, m.p. 160˚C; IR(KBr)cm^{-1}: 3420 (NH), 3223-2870 br. (OH of COOH), 1722 (C=O), 1674 (C=O), 1071 (C-O-C), 1177 (N-N) 847 (C-H def., 1,4- disub. benzene ring),

728 (C-S-C); ^{1}H NMR(DMSO d_6): 10.22 (s, 1H, COOH), 8.75 (s, 1H, CONH), 7.59 (m, 6H, ArH), 7.44 (d, 2H, Ar-H near cl), 4.37 (s, 1H, CH-Ar) 3.83 (s, 2H, OCH_2), 3.58 (t, 1H, $CHCH_2$), 3.25 (d, 2H, $CHCH_2$); Anal. Calcd. for: $C_{22}H_{18}N_3O_5SCl$: C, 55.88, H, 3.72; N, 8.84. Found: C, 55.99; H, 3.81; N 8.91%.

(2-{4-Methoxyphenyl}-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetic acid (6c). Yield 61%, m.p. 144˚C; IR(KBr)cm^{-1}: 3404 (N-H), 3200-2891 br. (OH of COOH), 1733 (C=O), 1681 (C=O), 1208 (C-N), 1090 (C-O-C), 1120 (N-N), 854 (C-H def., 1,4-disub. benzene ring), 744 (C-S-C); ^{1}H NMR(DMSO d_6): 10.45 (s, 1H, COOH), 8.62 (s, 1H, CONH), 7.41 (m, 6H, ArH), 6.72 (d, 2H, Ar-H near OCH_3), 4.85 (s,1H, CH-Ar) 3.62 (s, 2H, OCH_2), 3.43 (t, 1H, $CHCH_2$), 3.27 (d, 2H, $CHCH_2$); Anal. Calcd. for $C_{23}H_{21}N_3O_6S$: C, 59.02; H, 4.38; N, 8.90. Found: C, 59.10; H, 4.49; N, 8.99%.

(2-{4-Methylphenyl}-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetic acid (6d). Yield 63%, m.p. 191˚C; IR(KBr)cm^{-1}: 3412 (NH), 3210-2880 br. (OH of COOH), 1714 (C=O), 1669 (C=O), 1600 – 1489 (C=C), 1099 (C-O-C), 1168 (N-N), 866 (C-H def., 1,4-disub. benzene ring), 718 (C-S-C); ^{1}H NMR(DMSO d_6): 10.35 (s, 1H, COOH), 8.52 (s, 1H, CONH), 7.42-7.11 (m, 10H, ArH), 4.66 (s,1H, CH-Ar) 3.71 (s, 2H, OCH_2), 3.39 (t, 1H, $CHCH_2$), 3.11 (d, 2H, $CHCH_2$); Anal. Calcd for $C_{23}H_{21}N_3O_5S$: C, 61.09; H. 4.59; N, 9.25. Found: C, 61.19; H, 4.65; N 9.31%.

(2-{4-Dimethylaminophenyl}-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetic acid (6e). Yield 59%, m.p. 183˚C; IR(KBr)cm^{-1}: 3412 (NH), 3210-2880 br. (OH of COOH), 1714 (C=O), 1669 (C=O) 1600 – 1489 (C=C), 1099 (C-O-C), 1168 (N-N), 866 (C-H def., 1,4-disub. benzene ring), 718 (C-S-C); ^{1}H NMR(DMSO d_6): 10.35 (s, 1H, COOH), 8.52 (s, 1H, CONH), 7.42-7.11 (m, 10H, ArH), 4.66 (s,1H, CH-Ar) 3.71 (s, 2H, OCH_2), 3.39 (t, 1H, $CHCH_2$), 3.11 (d, 2H, $CHCH_2$); Anal. Calcd for $C_{24}H_{24}N_4O_5S$: C, 59.95; H, 4.89; N, 11.60. Found: C, 60.00; H, 5.00; N, 11.66%.

(2-Aryl-4-oxo-3-{[quinolin-8-yloxy)acetyl]amine}-1,3-thiazolidin-5-yl)acid chlorides 7a-e. A mixture of **6a-e** (0.01 mole) and thionyl chloride (0.02 mole) in benzene (30 mL) was refluxed on a water bath for 2-3 h. Excess of solvent and thionyl chloride was removed under reduced pressure. On cooling, the solid obtained was crystallized from absolute alcohol to afford **7a** Yield 62%, m.p. 104˚C; IR(KBr)cm^{-1} 3465 - 3360 (NH), 3069 (CH, ArH), 2862 (C-H, CH_2), 1710 (C=O), 1669 (C=O), 1550-1409 (C^{----}C), 1294 (C-N), 1169 (N-N), 1057 (C-O-C), 747 (C-Cl), 697 (C-S-C) ^{1}H NMR(DMSO d_6): 8.55 (s, 1H, CONH), 7.43-7.10 (m, 11H, ArH), 3.99 (s, 1H, CH-Ar), 3.59 (s, 2H, OCH_2), 3.31 (t, 1H, $CHCH_2$), 3.11 (d, 2H, $CHCH_2$). Anal.Calcdfor: $C_{22}H_{18}N_3O_4SCl$: C, 56.07; H, 3.53; N, 8.87. Found: C, 56.23; H, 3.83; N, 8.94%.

Other acid chlorides **7b-e** were prepared in a similar manner and were characterized by their physical and analytical data.

Succinimido(2-phenyl-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetates (8a). N-Hydroxysuccinimide was added to a well-stirred solution of **7a** (0.01 mole) in dry DMF (30 mL) containing TEA (0.01 mole) as a base. The reaction mixture was refluxed for 4-7 h, filtered and the filtrate was poured on crushed ice. The precipitated solid was collected

and crystallized from ethanol to afford **8a.** Yield 66%, m.p. 222˚C; IR(KBr)cm^{-1}: 3350 (NH), 3044 (C-H, ArH), 2821 (CH, CH_2), 1712 (C=O), 1672 (C=O), 1543–1504 (C=C), 1280 (C-N), 1163 (N-N), 1040 (C-O-C), 680 (C-S-C); ^{1}H NMR(DMSO d_6): 8.53 (s, 1H, CONH), 7.39-7.19 (m, 11H, ArH), 4.18 (s, 1H, CH-Ar) 3.65 (s, 2H, OCH_2), 3.43 (t, 1H, C**H**CH_2), 3.30 (d, 2H, CHC**H$_2$**); ^{13}C NMR (DMSO-d_6): 190.1 (CO, cyclic), 180 (O**C**OCH_2), 168.9 ($NHCOCH_2$), 130-142.8 (C of Quinoline ring), 110-125.9 (C-of phenyl ring), 49 ($COCH_2O$), 36.9 (SCHN), 33.7 ($OCOCH_2C$), 40.9 (CH of thiazolidinone ring), 24.2 (CO**C**H_2CH_2CO); MS: m/z : 534 $[M]^{+\bullet}$, 457, 392, 378, 333, 201, 186, 158, 156, 142, 114, 98, 84; Anal. Calcd. for $C_{26}H_{22}N_4O_7S$: C, 58.37; H, 4.07; N, 10.43. Found: C 58.42; H, 4.11; N, 10.48%.

Succinimido(2-{4-chlorophenyl}-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetate (8b). Yield 50%, m.p. 214˚C; IR(KBr)cm^{-1}: 3370 (N-H), 3062 (C-H, ArH), 1718 (C=O), 1681 (C=O), 1561 (C=C), 1296 (C-N), 1167 (N-N), 1031 (C-O-C), 814 (C-H def., 1,4-disub. benzene ring), 729 (C-Cl), 701 (C-S-C); ^{1}H NMR(DMSO d_6): 8.48 (s, 1H, CONH), 7.51 (m, 6H, Ar-H), 7.22 (d, 2H, Ar-H near Cl) 4.11 (s, 1H, CH-Ar) 3.61 (s, 2H, OCH_2), 3.33 (t, 1H, C**H**CH_2), 3.08 (d, 2H, CHC**H$_2$**), 2.78 (s, 4H, CH_2); ^{13}C NMR (DMSO-d_6): 193.1 (CO, cyclic), 184 (O**C**OCH_2), 169.9 ($NHCOCH_2$), 134-142.8 (C of Quinoline ring), 116-129.9 (C-of phenyl ring), 49.5 ($COCH_2O$), 37.7 (SCHN),33.7($OCOCH_2C$), 41.4 (CH of thiazolidinone ring), 24.3 (CO**C**H_2CH_2CO); MS: m/z : 570 $[M+2]^{+\bullet}$, 568 $[M]^{+\bullet}$, 457, 426, 382, 201, 186, 142, 114, 98, 84, 56; Anal. Calcd. for $C_{26}H_{21}N_4O_7SCl$: C, 54.80; H, 3.58; N, 9.83. Found: C, 54.88; H, 3.69; N, 9.85%.

Succinimido(2-{4-methoxyphenyl}-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetate (8c). Yield 50%, m.p. 214˚C; IR(KBr)cm^{-1}: 3366 (NH), 1710 (C=O), 1688 (C=O), 1611-1510 (C=C), 1303 (C-N), 1157 (N-N), 1061 (C-O-C), 712 (C-S-C); ^{1}H NMR(DMSO d_6): 8.55 (s, 1H, CONH), 7.41 (m, 6H, ArH), 6.89 (d, 2H, Ar-H near OCH_3), 4.33 (s, 1H, CH-Ar), 3.51 (s, 2H, OCH_2), 3.31 (s, 3H, OCH_3), 3.29 (t, 1H, $CHCH_2$), 3.04 (d, 2H,$CHCH_2$),2.65(s,4H,CH_2); ^{13}C NMR (DMSO-d_6): 191.1 (CO, cyclic), 183 (O**C**OCH_2), 169.3 ($NHCOCH_2$) 133-141.8 (C of Quinoline ring), 112-128.9 (C-of phenyl ring), 49.2 ($COCH_2O$), 36.7 (SCHN), 33.4($OCOCH_2C$), 41.1 (CH of thiazolidinone ring), 26.7 (OCH_3), 24.1 (CO**C**H_2CH_2CO); MS: m/z: 564 $[M]^{+\bullet}$, 457, 422, 408, 378, 363, 201, 186, 158, 142, 114; Anal. Calcd. for $C_{27}H_{24}N_4O_8S$: C, 57.33; H, 4.20; N, 9.89. Found: C, 57.44; H, 4.25; N, 9.92%.

Succinimido(2-{4-methylphenyl}-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetate (8d). Yield 60%, m.p. 234˚C; IR(KBr)cm^{-1}: 3356 (N-H), 3060 (C-H, ArH), 1727 (C=O), 1701 (C=O), 1296 (C-N), 1175 (N-N), 1033 (C-O-C), 837 (C-H def., 1,4-disub. benzene ring), 719 (C-S-C); ^{1}H NMR(DMSO d_6): 8.33 (s, 1H, CONH), 7.31-7.11 (m, 10H, ArH), 4.12 (s, 1H, CHAr), 3.62 (s, 2H, OCH_2), 3.31 (t, 1H, $CHCH_2$), 3.12 (d, 2H, $CHCH_2$), 2.85 (s, 3H, CH_3), 2.79 (s, 4H, CH_2); ^{13}C NMR (DMSO-d_6): 190.4 (CO, cyclic), 181 (O**C**OCH_2), 168.8 ($NHCOCH_2$) 133-140.4 (C of Quinoline ring), 110-125.7 (C-of phenyl ring), 49.3 ($COCH_2O$), 36.2 (SCHN), 33.1($OCOCH_2C$), 40.4 (CH of thiazolidinone ring), 24.1 (CO**C**H_2CH_2CO), 22.4 (CH_3); MS: m/z: 548 $[M]^{+\bullet}$, 457, 434, 406, 390, 362, 347, 201, 142, 114, 98; Anal. Calcd for $C_{27}H_{24}N_4O_7S$: C, 59.02; H, 4.29; N, 10.17. Found: C, 59.02; H, 4.37; N 10.21%.

Succinimido(2-{4-dimethylaminophenyl}-4-oxo-3-{[(quinolin-8-yloxy)acetyl]amino}-1,3-thiazolidin-5-yl)acetate (8e). Yield 63%, m.p. 246˚C; IR(KBr)cm^{-1}: 3377 (NH), 1721 (C=O), 1695 (C=O), 1314 (C-N), 1160 (N-N), 1061 (C-O-C), 833 (C-H def. 1,4-disub. benzene ring), 711 (C-S-C); ^{1}H NMR(DMSO d_6): 8.55 (s, 1H, CONH), 7.44 (m, 6H, ArH), 6.94 (d, 2H, Ar-H near NMe_2), 4.21 (s, 1H, CH-Ar), 3.56 (s, 2H, OCH_2), 3.41 (t, 1H, $CHCH_2$), 3.19 (d, 2H, $CHCH_2$), 2.35 (s, 6H, N $(CH_3)_2$); ^{13}C NMR (DMSO-d_6): 191.6 (CO, cyclic), 181.8 (O**C**OCH_2), 169.2 ($NHCOCH_2$) 131-140.9 (C of Quinoline ring), 112-124.7 (C-of phenyl ring), 49.8 ($COCH_2O$), 36.8 (SCHN), 33.4($OCOCH_2C$), 40.9 (CH of thiazolidinone ring), 24.4 (CO**C**H_2CH_2CO), 23.8 ($N(CH_3)_2$); MS: m/z: 577 $[M]^{+\bullet}$, 457, 421, 419, 391, 376, 142, 114, 98, 84, 56; Anal. Calcd. for $C_{28}H_{27}N_5O_7S$: C, 58.11; H, 4.59; N, 12.10. Found: C, 58.23; H, 4.68; N, 12.13%.

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