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Synthesis, characterization and antimicrobial screening of some quinoline based dihydropyridine and 2-oxo-azetidine derivatives

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2-Chloro-8-methylquinoline-3-carbaldehyde **1** on treatment with 2-cyanoacetohydrazide and thiosemicarbazide yields schiff bases *N′*-((2-chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide **2** and 2-((2-chloro-8-methylquinolin-3-yl)methylene)hydrazinecarbothioamide **4**, respectively. Compounds **2** and **4** have been used to obtain a series of titled compounds containing azetidinone, thiazole and 2-pyridone scaffolds incorporating quinoline nucleus. The newly synthesized compounds **3a-j** and **6a-g** have been screened for their antibacterial and antifungal activities and their chemical structures have been elucidated by spectral data.

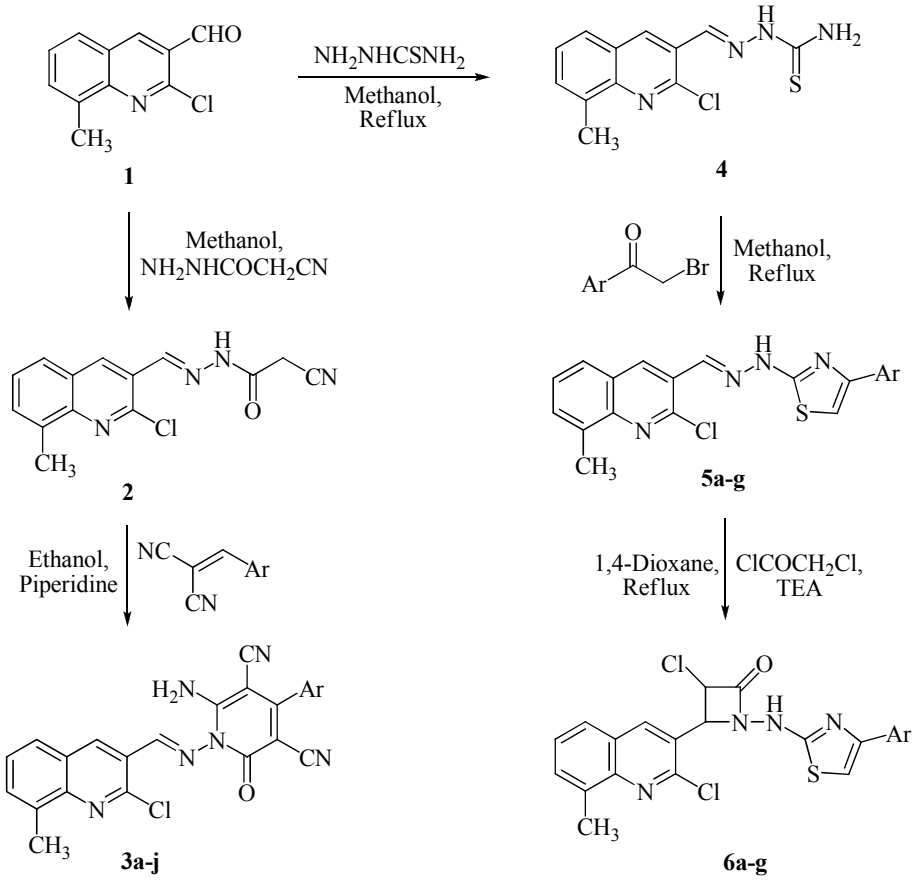
Keywords: Vilsmeier-Haack reaction, quinoline, 2-pyridone, thiazole, azetidinones

One of the most frequently encountered heterocycles in Medicinal Chemistry is quinoline with wide applications including antibacterial[1], antifungal[1,2], antitumor[3,4], antimalarial[5], antiplatelet[6] and anti-depressant[7] activities. Quinoline derivatives are also applied for the preparation of nano- and meso-structures having enhanced electronic and photonic properties[8]. Quinolines and their derivatives are very important compounds because of their wide occurrence in natural products[9] and biologically active compounds[10]. On the other hand, 2-pyridone is a multiple bioactive small molecule and an important pharmacophore that can form hydrogen bonded structures related to the base-pairing mechanism found in DNA and RNA[11,12]. The 2(1*H*)-pyridone ring system and the corresponding dihydro and tetrahydro derivatives are found abundantly in a wide variety of naturally occurring alkaloids and novel synthetic biologically active molecules[13]. Heterocycles incorporating a 2(1*H*)-pyridone framework constitute an extensively studied class of compounds owing to their diverse biological activities ranging from anti-HIV, antibacterial and antifungal to free radical scavengers[14]. Pyridin-2(1*H*)-ones are known to possess a range of biological properties such as analgesic, antimalarial, anti-inflammatory, anti-HIV, phytotoxic, antitumoral and antiviral activities[15-23].

Thiazoles are one of the most intensively investigated classes of aromatic five-membered heterocycles. The thiazole ring has been extensively studied and it forms a part of Thiamin[24] (Vitamin B_1), penicillins and antibacterial thiazoles[25]. Reduced thiazoles serve in the study of polypeptides and proteins and occur as structural units in compounds of biological importance[26]. Thiazole derivatives are found to possess a wide variety of applications ranging from bacteriostatics, antibiotics, CNS regulants to high selling diuretics[27-31]. 2-Azetidinone skeleton is well established as the key pharmacophore of β-lactam antibiotics, the most widely employed class of antibacterial agents[32,33]. Being recognized as a potentially useful structural motif, azetidines have included in many studies for aiming at the development of new drugs, as diverse as antibacterial[34], anti-convulsant[35], antitumor[36], antipsychotic[37], anti-asthmatic[38], antihypertensive agents[39], cocaine antagonists[40] and muscarine agonists[41] in the treatment of Alzheimer's disease. They also function as enzyme inhibitors and are effective on the central nervous system[42-44].

Results and Discussion

The starting compound 2-chloro-8-methylquinoline-3-carbaldehyde **1** was prepared by the Vilsmeier-Haack reaction according to literature method[45]. This quinoline derivative **1** was treated with 2-cyano-acetohydrazide in methanol as a solvent which yielded schiff base *N′*-((2-chloroquinolin-3-yl)methyl-



Where Ar = Different aryl groups

Scheme I

ene)-2-cyanoacetohydrazide **2**. Cyclization of compound **2** with benzylidine nitriles in the presence of piperidine as a catalyst and ethanol as a solvent resulted in the formation of 2-pyridone containing series of 6-amino-1-((2-chloroquinolin-3-yl)methyl-eneamino)-4-(aryl)-2-oxo-1,2-dihydropyridine-3,5-di-carbonitriles **3a-j**. Compound **1** on treatment with thiosemicarbazide in the presence of methanol as solvent yielded 2-((2-chloro-8-methylquinolin-3-yl)methylene)hydrazinecarbothioamide **4** in good yield and less reaction time. Compound **4** on reaction with α-halogenoketones afforded 2-(2-((2-chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-arylthiazoles **5a-g**. A novel series of 3-chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-arylthiazol-2-yl-amino)azetidin-2-ones **6a-g** was synthesized by cyclization of **5a-g** with triethylamine and chloroacetyl chloride (**Scheme I**). The purity of the compounds is monitored by TLC technique. The characterization of newly synthesized compounds of the series was carried out by elemental analysis, IR, ^{1}H and ^{13}C NMR and mass spectra. The spectral data are given in experimental section. The physical constants of the compounds **3a-j** and **6a-g** are described in **Table I**.

The structure of the newly synthesized 2-pyridone containing quinoline derivatives were characterised using ^{1}H NMR spectra which revealed the presence of singlet peak at δ 8.80-8.90 (2H, Ar-N*H*$_2$) assignable to amino group at C_6 in 2-pyridone ring system as well as ^{13}C NMR confirmed the proposed structure due to the appearance of characteristic peaks around δ 160.0-160.6 (carbonyl carbon), 115.3-116.0 (cyano carbon at C_3 and C_5 of 2-pyridone). Appearance of two spikes around 3440-3371 cm^{-1} in compounds **3a-j** instead of one spike at 3219 cm^{-1} (secondary amide) observed in compound **2** also confirmed the cyclization of compound **2** resulting in 2-pyridone having free primary amino group at C_6.

Presence of β-lactam ring in compounds **6a-g** was confirmed by ^{1}H and ^{13}C NMR spectra. Which showed doublet in the region δ 5.01-5.13 (1H, N-C*H*) and 4.81-4.87 (1H, COC*H*-Cl) which was not

Table I — Physical characterization data of compounds **3a-j** and **6a-g**

Compd	Ar	Molecular Formula	m.p. (°C)	Elemental Analysis (%)					
				C		H		N	
				Calcd	Found	Calcd	Found	Calcd	Found
3a	$-C_6H_5$	$C_{24}H_{15}ClN_6O$	242	65.68	65.55	3.45	3.00	19.15	19.00
3b	$-4-CH_3-C_6H_4$	$C_{25}H_{17}ClN_6O$	240	66.30	66.22	3.78	3.50	18.56	18.32
3c	$-4-OCH_3-C_6H_4$	$C_{25}H_{17}ClN_6O_2$	246	64.04	63.89	3.65	3.30	17.92	17.66
3d	$-3,4,5-(OCH_3)_3-C_6H_2$	$C_{27}H_{21}ClN_6O_4$	248	61.31	61.28	4.00	3.77	15.89	15.55
3e	$-3-OH-C_6H_4$	$C_{24}H_{15}ClN_6O_2$	255	63.37	63.21	3.32	3.02	18.48	18.15
3f	$-4-OH-C_6H_4$	$C_{24}H_{15}ClN_6O_2$	257	63.37	63.20	3.32	3.24	18.48	18.33
3g	$-3-NO_2-C_6H_4$	$C_{24}H_{14}ClN_7O_3$	250	59.57	59.39	2.92	2.87	20.26	20.03
3h	$-4-NO_2-C_6H_4$	$C_{24}H_{14}ClN_7O_3$	259	59.57	59.35	2.92	2.88	20.26	20.04
3i	$-4-F-C_6H_4$	$C_{24}H_{14}ClFN_6O$	233	63.10	63.00	3.09	2.89	18.40	18.05
3j	$-2-Cl-C_6H_4$	$C_{24}H_{14}Cl_2N_6O$	230	60.90	60.55	2.98	2.67	17.76	17.45
6a	$-C_6H_5$	$C_{22}H_{16}Cl_2N_4OS$	240	58.03	57.89	3.54	3.45	12.30	12.22
6b	$-4-CH_3-C_6H_4$	$C_{23}H_{18}Cl_2N_4OS$	248	58.85	58.70	3.87	3.40	11.94	11.81
6c	$-4-OCH_3-C_6H_4$	$C_{23}H_{18}Cl_2N_4O_2S$	233	56.91	56.60	3.74	3.66	11.54	11.33
6d	$-2-Cl-C_6H_4$	$C_{22}H_{15}Cl_3N_4OS$	219	53.95	53.67	3.09	3.02	11.44	11.32
6e	$-4-Cl-C_6H_4$	$C_{22}H_{15}Cl_3N_4OS$	226	53.95	53.70	3.09	2.99	11.44	11.40
6f	$-4-F-C_6H_4$	$C_{22}H_{15}Cl_2FN_4OS$	239	55.82	55.55	3.19	3.11	11.84	11.77
6g	$-4-NO_2-C_6H_4$	$C_{22}H_{15}Cl_2N_5O_3S$	241	52.81	52.69	3.02	2.87	14.00	13.90

observed in compound **5a-g**. Appearance of a singlet between δ 8.70-8.72 indicates the presence of secondary amine (1H, N-N*H*-Ar) in compounds **6a-g**. The signals obtained from ^{13}C NMR spectra further confirmed the proposed structures; the carbonyl carbon of *β*-lactam resonate at δ 166.4-167.2. Additional proof for the proposed structures **6a-g** were provided by close observation of IR spectra, which showed appearance of stretching frequency 1735-1746 cm^{-1} of carbonyl group present in *β*-lactam ring which was not observed in its precursor.

Biological activity

Antibacterial activity

Antibacterial activity was carried out by broth dilution method[46,47]. The strains used for activity were procured from Institute of Microbial Technology, Chandigarh. The compounds **6a-g** and **3a-j** were screened for their antibacterial activity against *Eschericia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Streptococcus pyogenus* at concentrations of 1000, 500, 200,150, 125, 100, 62.5, 50 µg/mL as shown in **Table II**.

Antifungal activity

All the same compounds were tested for antifungal activity against *Candida albicans, Aspergillus niger* and *Aspergillus clavatus* at various concentrations of 1000, 500, 200 and 100 µg/mL as shown in **Table II**. The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted at 1000 µg/mL concentrations, as a stock solution.

The synthesized compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found to be active in primary screening were similarly diluted to obtain 100, 50 µg/mL concentrations. The lowest concentration, which showed no growth after spot subculture was considered as MBC/MFC for each drug. The highest dilution showing at least 99% inhibition was taken as MBC/MFC. The result of this test was affected by the size of the inoculums. The test mixture contained 10^8 organism/mL. The standard drug used in the present study was gentamycin for evaluating antibacterial activity which showed (0.25, 0.05, 0.5 and 1 µg/mL) MBC against *Eschericia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Streptococcus pyogenus* respectively. The test mixture should contain 10^8 organism/mL. Nystatin was used as the standard drug for antifungal activity, which showed 100 µg/mL MFC against all fungi used for the antifungal activity. Compound **6f** was considered to

Table II — Results of antibacterial and antifungal screening of the compounds **3a-j** and **6a-g**

Sr. No.	Ar	Minimal bactericidal concentrations (MBC) in µg / mL				Minimal fungicidal concentrations (MFC) in µg / mL		
		E. coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
3a	$-C_6H_5$	200	150	500	500	1000	500	500
3b	$-4-CH_3-C_6H_4$	62.5	150	250	250	500	>1000	>1000
3c	$-4-OCH_3-C_6H_4$	250	250	500	500	1000	>1000	>1000
3d	$-3,4,5-(OCH_3)_3-C_6H_2$	500	250	250	250	500	500	500
3e	$-3-OH-C_6H_4$	50	200	200	250	500	1000	1000
3f	$-4-OH-C_6H_4$	250	100	150	150	200	500	500
3g	$-3-NO_2-C_6H_4$	250	500	500	500	250	500	1000
3h	$-4-NO_2-C_6H_4$	500	500	250	250	500	1000	1000
3i	$-4-F-C_6H_4$	1000	1000	1000	1000	250	>1000	>1000
3j	$-2-Cl-C_6H_4$	500	500	250	500	500	>1000	>1000
6a	$-C_6H_5$	500	500	250	250	1000	>1000	>1000
6b	$-4-CH_3-C_6H_4$	62.5	100	150	150	1000	>1000	>1000
6c	$-4-OCH_3-C_6H_4$	500	500	500	500	250	>1000	>1000
6d	$-2-Cl-C_6H_4$	100	250	100	100	500	500	500
6e	$-4-Cl-C_6H_4$	500	500	500	250	1000	>1000	>1000
6f	$-4-F-C_6H_4$	100	125	200	200	500	1000	1000
6g	$-4-NO_2-C_6H_4$	250	250	200	200	1000	1000	1000

Protocol for MBC/MFC: For antibacterial activity, in present protocol, 125 µg/mL is considered as moderate active, 100 µg/mL is considered as good active, 62.5 and 50 µg/mL is considered as excellent active as compared to the standard drug gentamycin. In case of antifungal activity, 200 µg/mL is considered as moderate as compared to standard drug nystatin.

be moderately active against *Pseudomonas aeruginosa* and good active against *Eschericia* coli. Compound **6d** was found to be good active against *Eschericia coli, Staphylococcus aureus and Streptococcus pyogenus* where as compounds **3f** and **6b** were found to show good activity against *Pseudomonas aeruginosa*. Compounds **3b**, **3e** and **6b** exhibited excellent activity against *Eschericia coli.* Results of antifungal activity showed that compound **3f** exhibited antifungal activity against *Candida albicans* as compared to standard drug nystatin.

Experimental Section

Elemental analysis data were obtained by using Perkin Elmer 2400 elementary instrument, IR spectra were recorded on IR Thermonicolate 2000 in KBr, ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300 FT-NMR spectrometer by using TMS as an internal standard and $CDCl_3$ as solvent. Mass spectra carried out on Apllied Bio system GC-Mass Spectrometer. Homogeneity of the synthesized compounds were checked by TLC using TLC aluminium sheets silica gel 60, supplied by Merck.

2-Chloro-8-methylquinoline-3-carbaldehyde, 1 is prepared by a reported method[45].

Synthesis of *N′*-((2-chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide, 2

2-Cyanoacetohydrazide was added portion wise to solution of compound, **1** in methanol with constant stirring. The resulting mixture was refluxed for one hr and cooled down to RT. The separated solid was filtered and recrystallized from the mixture of chloroform and methanol. Yield: 90%; m.p. 210°C; IR (KBr): 3219 (N-H, 2° amide), 3150 (C-H, aromatic), 2340, 2331 (-CN), 1711 (C=O, -CONH), 771 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 3.32 (s, 2H, -C*H*$_2$), 2.54 (s, 3H, -C*H*$_3$), 7.62-9.01 (m, 4H, Ar-*H*), 8.21 (s, 1H, -N=C*H*), 8.40 (s, 1H, -N*H*). Anal. Calcd. for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.55; H, 3.76; N, 19.47%.

Synthesis of 6-amino-1-((2-chloroquinolin-3-yl)methyleneamino)-4-(aryl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles, 3a-j

A mixture containing compound **2** (0.01 mole), benzylidinenitriles (0.01 mole) and 2 drops of piperidine in absolute ethanol (99.9%, 50 mL) was refluxed for 2-3 hr. The mixture was then cooled down to RT and the crystals formed were filtered, air dried and recrystallized from aqueous *N,N*-dimethyl formamide.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile, 3a. Yield: 59%, IR (KBr): 3448 (N-H, 1° amine), 3058 (C-H, Ar-H), 2915, 2822 (C-H, -CH_3), 2220, 2213 (CN), 740 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.80 (s, 2H, Ar-NH_2), 8.21 (s, 1H, Ar-C*H*=N-), 6.71-8.62 (m, 9H, Ar-*H*), 2.50 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): δ 170.0, 160.0, 159.4, 157.7, 152.0, 143.1, 138.1, 136.0, 131.0, 132.5, 128.9, 128.6, 127.9, 126.6, 126.5, 126.3, 123.6, 115.8, 115.3, 76.5, 16.9; MS: *m/z* 438 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-2-oxo-4-p-tolyl-1,2-dihydropyridine-3,5-dicarbonitrile, 3b. Yield: 57%, IR (KBr): 3440 (N-H, 1° amine), 3054 (C-H, Ar-H), 2929, 2820 (C-H, -CH_3), 2219, 2215 (CN), 1690 (C=O, cyclic amide), 741 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.83 (s, 2H, Ar-NH_2), 8.25 (s, 1H, Ar-C*H*=N-), 6.61-8.63 (m, 8H, Ar-*H*), 2.53 (s, 3H, -CH_3, quinoline), 2.10 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): δ 169.4, 160.2, 159.6, 157.9, 152.4, 143.5, 138.2, 137.4, 136.1, 134.6, 131.2, 129.7, 128.8, 126.5, 126.4, 126.2, 123.7, 115.7, 115.5, 76.6, 21.3, 16.8; MS: *m/z* 452 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3c. Yield: 58%, IR (KBr): 3450 (N-H, 1° amine), 3066 (C-H, Ar-H), 2919, 2830 (C-H, -CH_3), 2229, 2210 (CN), 1691 (C=O, cyclic amide), 1116, 1030, (C-O-C, Ar-O-CH_3), 744 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$) δ 8.81 (s, 2H, Ar-NH_2), 8.25 (s, 1H, Ar-C*H*=N-), 6.78-8.67 (m, 8H, Ar-*H*), 3.37 (s, 3H, -OCH_3), 3.22 (s, 6H, -CH_3), 2.50 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): δ 169.5, 160.2, 159.8, 159.6, 157.7, 152.6, 143.4, 138.4, 136.1, 131.0, 130.2, 126.8, 126.7, 126.5, 124.9, 123.4, 115.6, 115.1, 114.2, 76.4, 55.8, 16.9; MS: *m/z* 468 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2-dihydropyridine-3,5-dicarbonitrile, 3d. Yield: 60%, IR (KBr): 3466 (N-H, 1° amine), 3088 (C-H, Ar-H), 2920, 2849 (C-H, -CH_3), 2238, 2215 (CN), 1693 (C=O, cyclic amide), 1120, 1040, (C-O-C, Ar-O-CH_3) 750 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.83 (s, 2H, Ar-NH_2), 8.25 (s, 1H, Ar-C*H*=N-), 6.88-8.71 (m, 6H, Ar-*H*), 3.37 (s, 3H, -CH_3), 3.22 (s, 6H, -(CH_3)$_2$), 2.50 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): δ 169.9, 160.5, 159.6, 157.6, 153.0, 152.4, 143.8, 138.4, 138.1, 136.2, 131.2, 126.6, 126.4, 126.3, 126.1, 115.9, 115.6, 105.1, 76.6, 60.9, 56.4, 16.9; MS: *m/z* 528 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-4-(3-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3e. Yield: 61%; IR (KBr): 3444 (O-H, Ar-OH), 3371 (N-H, 1° amine), 3099 (C-H, Ar-H), 2924, 2855 (C-H, -CH_3), 2242, 2219 (CN), 1690 (C=O, cyclic amide), 760 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.88 (s, 1H, Ar-NH_2), 8.20 (s, 2H, Ar-C*H*=N-), 6.91-8.75 (m, 8H, Ar-*H*), 5.74 (s, 1H, Ar-O*H*), 2.50 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): δ 169.4, 160.6, 159.5, 158.6, 157.9, 152.5, 143.5, 138.2, 136.0, 134.0, 131.2, 130.0, 126.6, 126.5, 126.3, 123.8, 121.6, 115.8, 115.3, 115.1, 112.3, 76.6, 17.0; MS: *m/z* 454 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-4-(4-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3f. Yield: 60% IR (KBr): 3442 (O-H, Ar-OH), 3363 (N-H, 1° amine), 3064 (C-H, Ar-H), 2930, 2840 (C-H, -CH_3), 2233, 2220 (CN), 1691 (C=O, cyclic amide), 755 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.89 (s, 1H, Ar-NH_2), 8.27 (s, 2H, Ar-C*H*=N-), 6.79-8.61 (m, 8H, Ar-*H*), 5.69 (s, 1H, Ar-O*H*), 2.52 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): δ 169.6, 160.0, 159.7, 157.9, 157.8, 152.4, 143.5, 138.1, 136.4, 131.0, 130.7, 126.8, 126.6, 126.3, 125.5, 115.9, 115.6, 76.8, 16.8; MS: *m/z* 454 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-4-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3g. Yield: 55%, IR (KBr): 3461 (N-H, 1° amine), 3059 (C-H, Ar-H), 2922, 2843 (C-H, -CH_3), 2239, 2228 (CN), 1690 (C=O, cyclic amide), 755 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.85 (s, 2H, Ar-NH_2), 8.22 (s, 1H, Ar-C*H*=N-), 6.62-8.67 (m, 8H, Ar-*H*), 2.52 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): δ 169.4, 160.2, 159.7, 157.6, 152,4, 147.8, 143.5, 138.3, 136.0, 135.2, 133.6, 131.2, 129.7, 126.4, 126.3, 126.1, 123.4, 123.1, 120.0, 115.6, 115.3, 76.7, 16.9; MS: *m/z* 483 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3h. Yield: 59%, IR (KBr): 3457 (N-H, 1° amine), 3062 (C-H, Ar-H), 2925, 2844 (C-H, -CH_3), 2233, 2224 (CN), 1691 (C=O, cyclic amide), 763 cm^{-1} (C-Cl); ^{1}H NMR

($CDCl_3$): δ 8.87 (s, 2H, Ar-N*H*$_2$), 8.27 (s, 1H, Ar-C*H*=N-), 6.73-8.77 (m, 8H, Ar-*H*), 2.59 (s, 3H, -C*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 169.8, 160.4, 159.7, 158.0, 152.6, 147.3, 143.7, 138.9, 138.5, 136.4, 131.2, 130.3, 126.8, 126.7, 126.5, 124.0, 123.8, 116.0, 115.5, 76.9, 17.0; MS: *m/z* 483 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3i. Yield: 60%, IR (KBr): 3460 (N-H, 1° amine), 3090 (C-H, Ar-H), 2923, 2844 (C-H, -CH_3), 2230, 2220 (CN), 1695 (C=O, cyclic amide), 760 cm^{-1} (C-Cl), (C-F); ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 2H, Ar-N*H*$_2$), 8.27 (s, 1H, Ar-C*H*=N-), 6.62-8.69 (m, 8H, Ar-*H*), 2.50 (s, 3H, -C*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 169.2, 162.3, 160.2, 159.3, 158.0, 152.0, 143.5, 138.3, 136.4, 131.2, 128.4, 128.0, 126.6, 126.4, 126.1, 123.0, 116.0, 115.6, 115.5, 76.7, 16.9; MS: *m/z* 456 $[M]^+$.

6-Amino-1-((2-chloro-8-methylquinolin-3-yl)methyleneamino)-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3j. Yield: 61%, IR (KBr): 3467 (N-H, 1° amine), 3094 (C-H, Ar-H), 2932, 2846 (C-H, -CH_3), 2234, 2226 (CN), 1692 (C=O, cyclic amide), 757 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.85 (s, 2H, Ar-N*H*$_2$), 8.25 (s, 1H, Ar-C*H*=N-), 6.74-8.66 (m, 8H, Ar-*H*), 2.50 (s, 3H, -C*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 169.4, 160.0, 159.5, 157.9, 152.5, 143.5, 138.4, 136.2, 133.5, 131.4, 130.4, 128.9, 126.8, 126.7, 126.5, 123.6, 115.8, 115.3, 76.5, 16.9; MS: *m/z* 472 $[M]^+$.

2-((2-Chloro-8-methylquinolin-3-yl)methylene)hydrazinecarbothioamide, 4

To a solution of compound **1** (0.01 mole) in methanol was added thiosemicarbazide (0.01 mole) and the mixture was refluxed for 1 hr. The mixture was allowed to attain RT and poured onto crushed ice with stirring. The separated solid was filtered and washed with water. The solid was recrystallized from methanol. Yield: 90%; m.p. 157°C; IR (KBr): 3380 (N-H, 1° amine), 3087 (C-H, aromatic), 2926 (C-H, CH_3 group), 1615 (C=N, hetero ring), 1140 (C=S), 779 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, C*H*$_3$), 7.51-8.92 (m, 4H, Ar-*H*), 8.14 (s, 1H, N=C*H*), 8.93 (s, 1H, -N*H*), 9.52 (s, 2H, -N*H*$_2$); MS: *m/z* 278 $[M]^+$. Anal. Calcd. for $C_{12}H_{11}ClN_4S$: C, 51.70; H, 3.98; N, 20.10. Found: C, 51.31; H, 2.98; N, 19.95%.

General method for the synthesis of 2-(2-((2-chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-arylthiazoles, 5a-g

To a solution of compound **4** (0.01 mole) and corresponding 2-bromo-arylethanones (0.01 mole) in methanol was refluxed for 30 min. The mixture was then cooled down to RT and separated solid was filtered, air dried and recrystallized from chloroform as pale yellow coloured crystals.

2-(2-((2-Chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-phenylthiazole, 5a. Yield: 93%; m.p. 188°C; IR (KBr) 3260 (N-H, 2° amine), 3070 (C-H, aromatic), 2937 (C-H, CH_3 group), 1624 (C=N), 774 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H, N-N*H*), 8.28 (s, 1H, N=C*H*), 7.36-8.33 (m, 10H, Ar-*H*), 2.41 (s, 3H, C*H*$_3$); MS: *m/z* 378 $[M]^+$. Anal. Calcd. for $C_{20}H_{15}ClN_4S$: C, 63.40; H, 3.995; N, 14.79. Found: C, 63.23; H, 3.78; N, 14.59%.

2-(2-((2-Chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-p-tolylthiazole, 5b. Yield: 91%; m.p. 182°C; IR (KBr): 3275 (N-H, 2° amine), 3078 (C-H, aromatic), 2945 (C-H, CH_3 group), 1633 (C=N), 770 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H, N-N*H*), 8.17 (s, 1H, N=C*H*), 7.37-8.36 (m, 9H, Ar-*H*), 2.32 (s, 3H, C*H*$_3$ quinoline), 2.0 (s, 3H, Ar-C*H*$_3$); MS: *m/z* 392 $[M]^+$. Anal. Calcd. for $C_{21}H_{17}ClN_4S$: C, 64.19; H, 4.36; N, 14.26. Found: C, 64.01; H, 4.22; N, 14.15%.

2-(2-((2-Chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-(4-methoxyphenyl)thiazole, 5c. Yield: 92%; m.p. 189°C; IR (KBr): 3280 (N-H, 2° amine), 3081 (C-H, aromatic), 2950 (C-H, CH_3 group), 1641 (C=N), 765 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1H, N-N*H*), 8.35(s, 1H, N=C*H*), 7.33-8.34 (m, 9H, Ar-*H*), 3.32 (s, 3H, OC*H*$_3$), 2.53 (s, 3H, C*H*$_3$); MS: *m/z* 408 $[M]^+$. Anal. Calcd. for $C_{21}H_{17}ClN_4OS$: C, 61.68; H, 4.19; N, 13.70. Found: C, 61.45; H, 4.00; N, 13.47%.

2-(2-((2-Chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-(2-chlorophenyl)thiazole, 5d. Yield: 90%; m.p. 180°C; IR (KBr): 3266 (N-H, 2° amine), 3074 (C-H, aromatic), 2937 (C-H, CH_3 group), 1636 (C=N), 740 cm^{-1} (C-Cl); ^{1}H NMR ($CDCl_3$): δ 8.61 (s, 1H, N-N*H*), 8.26 (s, 1H, N=C*H*), 7.32-8.31 (m, 9H, Ar-*H*), 2.44 (s, 3H, -C*H*$_3$); MS: *m/z* 412 $[M]^+$. Anal. Calcd. for $C_{20}H_{14}Cl_2N_4S$: C, 58.12; H, 3.41; N, 13.56. Found: C, 57.97; H, 3.20; N, 13.44%.

2-(2-((2-Chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-(4-chlorophenyl)thiazole, 5e. Yield: 92%; m.p. 191°C; IR (KBr): 3260 (N-H, 2° amine), 3076 (C-H, aromatic), 2930 (C-H, CH_3 group), 1632 (C=N), 733 cm^{-1} (C-Cl); ^1H NMR ($CDCl_3$): δ 8.62 (s, 1H, N-N*H*), 8.29 (s, 1H, N=C*H*), 7.31-8.30 (m, 9H, Ar-*H*), 2.35 (s, 3H, CH_3); MS: *m/z* 412 $[M]^+$. Anal. Calcd. for $C_{20}H_{14}Cl_2N_4S$: C, 58.12; H, 3.41; N, 13.56. Found: C, 57.98; H, 3.19; N, 13.43%.

2-(2-((2-Chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-(4-fluorophenyl)thiazole, 5f. Yield: 91%; m.p.: 193°C; IR (KBr): 3254 (N-H, 2° amine), 3071 (C-H, aromatic), 2924 (C-H, CH_3 group), 1629 (C=N), 730 cm^{-1} (C-Cl); ^1H NMR ($CDCl_3$): δ 8.63 (s, 1H, N-N*H*), 8.33 (s, 1H, N=C*H*), 7.28-8.31 (m, 9H, Ar-*H*), 2.51 (s, 3H, CH_3); MS: *m/z* 396 $[M]^+$. Anal. Calcd. for $C_{20}H_{14}ClFN_4S$: C, 60.53; H, 3.56; N, 14.12. Found: C, 60.44; H, 3.30; N, 13.98%.

2-(2-((2-Chloro-8-methylquinolin-3-yl)methylene)hydrazinyl)-4-(4-nitrophenyl)thiazole, 5g. Yield: 90%; m.p.: 190°C; IR (KBr): 3230 (N-H, 2° amine), 3055 (C-H, aromatic), 2920 (C-H, CH_3 group), 1629 (C=N), 719 cm^{-1} (C-Cl); ^1H NMR ($CDCl_3$): δ 8.62 (s, 1H, N-N*H*), 8.17 (s, 1H, N=C*H*), 7.23-8.52 (m, 9H, Ar-*H*), 2.22 (s, 3H, CH_3); MS: *m/z* 423 $[M]^+$. Anal. Calcd. for $C_{20}H_{14}ClN_5O_2S$: C, 56.67; H, 3.33; N, 16.52. Found: C, 56.43; H, 3.13; N, 16.39%.

General method for the synthesis of 3-chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-arylthiazol-2-ylamino)azetidin-2-ones, 6a-g.

To a stirred solution of the corresponding compounds **5a-g** (0.01 mol), triethylamine (0.01 mol) in 1,4-dioxane and $ClCOCH_2Cl$ (0.01 mol) was added drop wise at 0-5°C. The mixture was heated and refluxed for about 12 hr. After the reaction was completed, reaction mixture was filtered. The solid was obtained on removal of solvent from filtrate. The solid was recrystallized from methanol as light yellow coloured crystals.

3-Chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-phenylthiazol-2-ylamino)azetidin-2-one, 6a. Yield: 72%; IR (KBr): 3430 (NH), 1739 (CONH), 669 cm^{-1} (C-Cl); ^1H NMR ($CDCl_3$): δ 8.70 (s, 1H, N*H*), 5.01 (d, 1H, N-C*H*), 4.84 (d, 1H, COC*H*-Cl), 7.26-8.53 (m, 10H, Ar-*H*), 2.93 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.5, 166.5, 153.6, 152.3, 150.2, 135.7, 134.3, 132.2, 130.2, 129.9, 129.2, 128.4, 127.5, 126.4, 126.2, 125.7, 106.0, 63.4, 61.8, 16.4; MS: *m/z* 455 $[M]^+$.

3-Chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-p-tolylthiazol-2-ylamino)azetidin-2-one, 6b. Yield: 70%; IR (KBr): 3435 (NH), 1743 (CONH), 675 cm^{-1} (C-Cl); ^1H NMR ($CDCl_3$): δ 8.72 (s, 1H, N*H*), 7.26-8.54 (m, 9H, Ar-*H*), 5.13 (d, 1H, N-C*H*), 4.81 (d, 1H, COC*H*-Cl), 2.93 (s, 3H, CH_3, quinoline), 2.73 (s, 3H, Ar-CH_3); ^{13}C NMR ($CDCl_3$): δ 175.2, 165.5, 153.4, 151.8, 149.8, 135.1, 133.6, 132.4, 131.3, 130.6, 130.4, 129.5, 129.2, 126.2, 126.3, 125.5, 106.2, 63.6, 62.0, 16.5, 21.2; MS: *m/z* 469 $[M]^+$.

3-Chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-(4-methoxyphenyl)thiazol-2-ylamino)azetidin-2-one, 6c. Yield: 70%; IR (KBr): 3440 (NH), 1746 (CONH), 671 cm^{-1} (C-Cl), ^1H NMR ($CDCl_3$): δ 8.72 (s, 1H, N*H*), 7.25-8.51 (m, 9H, Ar-*H*), 5.03 (d, 1H, N-C*H*), 4.81 (d, 1H, COC*H*-Cl), 3.62 (s, 3H, OCH_3), 2.91 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.7, 167.2, 160.2, 153.3, 152.8, 151.0, 135.2, 134.6, 130.4, 130.6, 129.8, 128.2, 126.3, 126.4, 125.8, 125.3, 114.6, 106.3, 63.9, 62.2, 56.2, 16.7; MS: *m/z* 485 $[M]^+$.

3-Chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-(2-chlorophenyl)thiazol-2-ylamino)azetidin-2-one, 6d. Yield: 75%; IR (KBr): 3438 (NH), 1741 (CONH), 678 cm^{-1} (C-Cl), ^1H NMR ($CDCl_3$): δ 8.71 (s, 1H, N*H*), 7.22-8.52 (m, 9H, Ar-*H*), 5.02 (d, 1H, N-C*H*), 4.85 (d, 1H, COC*H*-Cl), 2.92 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 174.3, 166.4, 153.7, 152.6, 148.2, 135.6, 134.5, 130.1, 130.8, 130.4, 132.6, 132.7, 129.9, 129.8, 128.9, 126.6, 126.7, 125.7, 106.5, 63.7, 62.4, 16.7; MS: *m/z* 489 $[M]^+$.

3-Chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-(4-chlorophenyl)thiazol-2-ylamino)azetidin-2-one, 6e. Yield: 62%; IR (KBr): 3445 (NH), 1745 (CONH), 680 cm^{-1} (C-Cl), ^1H NMR ($CDCl_3$): δ 8.71 (s, 1H, N*H*), 7.27-8.50 (m, 9H, Ar-*H*), 5.06 (d, 1H, N-C*H*), 4.81 (d, 1H, COC*H*-Cl), 2.93 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.3, 166.5, 153.8, 152.5, 150.4, 136.8, 134.8, 134.2, 131.4, 130.2, 129.7, 129.5, 128.7, 126.6, 126.5, 125.9, 106.0, 63.5, 62.6, 16.7; MS: *m/z* 489 $[M]^+$.

3-Chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-(4-fluorophenyl)thiazol-2-ylamino)azetidin-2-one, 6f. Yield: 70%; IR (KBr): 3436 (NH), 1742 (CONH), 674 cm^{-1} (C-Cl), ^1H NMR ($CDCl_3$): δ 8.71 (s, 1H, N*H*), 7.22-8.50 (m, 9H, Ar-*H*), 5.04 (d, 1H, N-C*H*), 4.84 (d, 1H, COC*H*-Cl), 2.92 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.8, 166.7, 162.9, 153.7, 152.4, 150.3, 135.6, 134.4, 130.8, 130.6, 129.7, 128.3, 126.5,

126.4, 125.5, 116.0, 106.6, 63.9, 62.4, 16.8; MS: *m/z* 473 $[M]^+$.

3-Chloro-4-(2-chloro-8-methylquinolin-3-yl)-1-(4-(4-nitrophenyl)thiazol-2-ylamino)azetidin-2-one, 6g. Yield: 68%; IR (KBr): 3431 (NH), 1735 (CONH), 1345,1521 (NO_2), 670 cm^{-1} (C-Cl); ^1H NMR ($CDCl_3$): δ 8.72 (s, 1H, N*H*), 7.28-8.53 (m, 9H, Ar-*H*), 5.10 (d, 1H, N-C*H*), 4.87 (d, 1H, COC*H*-Cl), 2.91 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.7, 166.5, 153.5, 152.6, 150.6, 147.7, 139.4, 135.7, 134.3, 130.6, 129.5, 126.4, 126.5, 126.6, 125.7, 124.6, 106.0, 63.7, 62.9, 16.6; MS: *m/z* 500 $[M]^+$.

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References

1 Desai N C, Maheta A S, Rajpara K M, Joshi V V, Vaghani H V & Satodiya H M, *J Saudi Chem Soc*, **2011** doi: 10.1016/j.jscs.2011.11.021
2 Musiol R, Jampilek J, Buchta V, Silva L, Niedbala H, Podeszwa B, Palka A, Majerz-Maniecka K, Oleksyn B & Polanski, *J Bioorg Med Chem,* 14, **2006**, 3592.
3 Kuo S C, Lee H Z, Juang J P, Lin Y T, Wu T S, Chang J J, Lednicer D, Paull K D, Lin C M & Hamel E, *J Med Chem,* 36, **1993**, 1146.
4 Xia Y, Yang Z Y, Xia P, Bastow K F, Tachibana Y, Kuo S C, Hamel E, Hackl T & Lee K H, *J Med Chem,* 41, **1998**, 1155.
5 Xiao Z, Waters N C, Woodard C L, Li P K & Li Z, *Bioorg Med Chem Lett*, 11, **2001,** 2875.
6 Nishi T, Kimura Y & Nakagawa K, *Yaku-gaku Zasshi*, 120, **2000,** 1247.
7 Oshiro Y, Sakurai Y, Sato S, Kurahashi N, Tanaka T, Kikuchi T, Tottori K, Uwahodo Y, Miwa T & Nishi T, *J Med Chem,* 43, **2000,** 177.
8 (a) Zhang X, Shetty A S & Jenekhe S A, *Macromolecules*, 32, **1999,** 7422; (b) Jenekhe S A, Lu L & Alam M M, *Macromolecules,* 34, **2001**, 7315.
9 (a) Morimoto Y, Matsuda F & Shirahama H, *Synlett,* 1991, **1991**, 202; (b) Balasubramanian M & Keay J G, in *Comprehensive Heterocyclic Chemistry II*; edited by A R Katritzky, C W Rees & E F V Scriven (Pergamon Oxford, New York), Vol. 5, **1996**, p 245; (c) Michael J P, *Nat Prod Rep,* 14, **1997**, 605.
10 (a) Markees D G, Dewey V C & Kidder G W, *J Med Chem,* 13, **1970**, 324; (b) Campbell S F, Hardstone J D & Palmer M J, *J Med Chem,* 31, **1988**, 1031; (c) Maguire M P, Sheets K R, McVety K, Spada A P & Zilberstein A, *J Med Chem*, 37, **1994,** 2129; (d) Kalluraya B & Sreenivasa S, *Il Farmaco,* 53, **1998**, 399; (e) Roma G, Braccio M D, Grossi G, Mattioli F & Ghia M, *Eur J Med Chem,* 35, **2000**, 1021; (f) Chen Y L, Fang K C, Sheu J Y, Hsu S L & Tzeng C C, *J Med Chem,* 44, **2001**, 2374.
11 Tipparaju S K & Joyasawal S, *Bioorg Med Chem Lett*, 18, **2008,** 3565.
12 Hanessian S, Simard D & Bayrakdarian M, *Bioorg Med Chem*, 18, **2008,** 1972.
13 (a) Desai N C, Pandya M R, Rajpara K M, Joshi V V, Vaghani H V, Satodiya H M, *Med Chem Res*, **2012** doi: 10.1007/s00044-012-9988-y; (b) Paulvanan K & Chen T, *J Org Chem*, 65, **2000,** 6160; (c) Arrayas R G, Alcudia A L & Liebeskind L S, *Org Lett*, 3, **2001,** 3381.
14 Upadhyay P K, Prasad R, Pandey M & Kumar P, *Tetrahedron Letters*, 50, **2009**, 2440.
15 Ozturk G, Erol D D, Uzbay T & Aytemir M D, *Il Farmaco*, 56, **2001,** 251.
16 Findlay J A, Tam W H J & Krepinsky J, *Can J Chem*, 56, **1978,** 613.
17 Abadi A, Al-Deeb O, Al-Afify A & El-Kashef H, *Il Farmaco*, 54, **1999,** 195.
18 Storck P, Aubertin A & Grierson D S, *Tetrahedron Lett,* 46, **2005,** 2919.
19 Macdonald G E, Puri A & Shillinget D G, *Weed Sci*, 56, **2008,** 189.
20 Wakabayashi K & Boger P, *Weed Biol Manag,* 4, **2004,** 59.
21 Evidente A, Fiore M, Bruno G, Sparapano L & Motta A, *Phytochemistry*, 67, **2006,** 1019.
22 Cocco M T, Congiu C & Onnis V, *Eur J Med Chem*, 35, **2000,** 545.
23 Cocco M T, Congiu C & Onnis V, *Eur J Med Chem*, 38, **2003,** 37.
24 Williams R R, Waterman R E, Keresztesy J C & Buchman E R, *J Am Chem Soc*, 57, **1935,** 536.
25 Fosbinder R J & Walter L A, *J Am Chem Soc,* 61, **1939,** 2032; The committee on medical research, O.S.R.D, Washington and medical research council, London, *Science*, 102, **1945**, 627; Clark, T Hans, J R Johnson & R Robinson *The Chemistry of Penicillins*, (Princeton University Press) **1949**.
26 (a) Alamino R J, *US Patent,* 4 012 409, **1977**; (b) Bhargava P N, Lakhan R & Tripathi K, *J Indian Chem Soc,* 59, **1982,** 773; (c) Maulard T, Lagorce J F, Thomos J C & Raby C, *J Pharm Pharmacol,* 45, **1993,** 731; (d) Tsuruoka A, Kaku Y Y, Kakinumato H, Tsukada I & Yanagishawa M, *Naito J Chem Pharm Bull*, 45, **1997,** 1169.
27 Beyer H, Hohn H & Lassing W, *Chem Abstr,* 47, **1954,** 11183.
28 Mazzone G, Aignatello R, Panico A, Mazzone S, Puglisi G, Pennisi G, Raciti G, Mazzone P & Matera M, *Pharmazie*, 47**, 1992**, 902.
29 Mahajan M P, Sondhi S M & Ralhan N K, *Bull Chem Soc Jpn,* 49, **1976,** 2651.
30 Metzer V, *Chem Heterocycl Compd*, 34, **1976,** 1.
31 Beyer H, Lassing W & Ruhlig G, *Chem Ber,* 86**, 1953**, 764.
32 Desai N C, Rajpara K M, Joshi V V, Vaghani H V, Satodiya H M, *Anti-Infective Agents*, 10, **2012**, 75.
33 (a) Neuhaus F C & Georgeopapadakou N H, in *Emerging Targets in Antibacterial and Antifungal Chemotherapy*, edited by J Sutcliffe & N H Georgeopapadakou, Urbino J A, 'Lipid biosynthesis pathways as chemotherapeutic targets in kinetoplastid parasites (Chapman and Hall, New York) **1992,** pp. 410; (b) Waley S G, in *The Chemistry of β-Lactams*, edited by M I Page, (Chapman and Hall, London) **1992,** pp 229.
34 (a) Egawa H, *J Med Chem*, 27, **1984,** 1543; (b) Frigola J, *ibid*, 37, **1994,** 4195; (c) Frigola J, *ibid,* 8, **1995,** 1203; (d) Remuzon P, *ibid*, 34, **1991,** 29; (e) Cechetti V, *ibid*, 39, **1996**, 436; (f) Abe T, Hayashi K, Mihari A, Satoh C, Tamai S, Yamamoto S, Hikida M, Kumagai T & Kitamura M, *The 38th interscience conference on antimicrobial agents and*

chemotherapy, San Diego, Abstract No: F-64, **1998**; (g) Jacquet J P, Bouzard D, Kiechel J R & Remuzon P, *Tetrahedron Lett*, 32, **1991,** 1565; (h) Li Q, *J Med Chem*, 39, **1996,** 3070.
35 Kelley J L & Krochmal M P, *J Med Chem*, 31, **1988,** 1005.
36 (a) Schnur R C, *ibid*, 38, **1995,** 3806; (b) Meyalarp S P, *ibid*, 39, **1996,** 531.
37 Kelley J L, *ibid*, 40, **1997,** 3207.
38 Billotte S, *Synlett*, **1998,** 379.
39 Masuda K, Okutani T, Morimoto A, Kaneka T, Kikuchi K, Hirata M, Tazima Y, Jimpu T & Nagaoko A, *Takeda Kenkyusho*, 31, **1972,** 453; *Chem Abstr,* 78, 135969d.
40 Ivy Carroll F, *ibid*, 38, **1995,** 379.
41 Ward J S, *ibid*, 41, **1998,** 379.
42 Ameya A C & Nandini R P, *Molecules,* 12, **2007,** 2467.
43 Freddy H H & Sushil Kumar J M, *Indian J Heterocycl Chem,* 13, **2004,** 197.
44 Patel K H & Mehta A G, *Eur J Chem,* 3, **2006,** 267.
45 Meth-Cohn O, Narine B & Tarnowski B, *J Chem Soc Perkin Trans 1*, **1981,** 1520.
46 (a) Robert C, *Medical Microbiology*, 11 Edn.; (ELBS and E & S, Livingstone, Brighton), **1970**, pp 895. (b) Desai N C, Pandya D D, Joshi V V, Rajpara K M, Vaghani H V, Satodiya H M, *Med Chem Res*, **2012** doi: 10.1007/s00044-012-9990-4
47 National committee for clinical laboratory standard. Reference method for broth dilution antifungal susceptibility testing of yeasts approved standard M27A, **1997**, NCCL, Wayne PA.