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Note

Synthesis, characterization and biological evaluation of some heterocyclic compounds containing ethoxyphthalimide moiety *via* key intermediate 6-chloro 1,3 benzothiazole 2-amine

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New and simple synthetic methods for the synthesis of ethyl 8-chloro-4(4-substitutedphenyl)-2-[(*N*-ethoxyphthalimido)amino]-4*H*-pyrimido[2,1-*b*][1,3] benzothiazole-3-carboxylate **5a-d** and 6-chloro-*N*-[3-{2-(4-substitutedphenyl)ethenyl}-1-*N*-ethoxyphthalimidoquinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine **10a-d** are described. 4-Chloroaniline **1** is converted to 6-chloro-1,3-benzothiazol-2-amine **2** by reaction with KSCN and Br_2. Compound **2** acts as key intermediate for both the series of final compounds. In one pathway, **2** is converted to corresponding pyrimidothiazoles **4a-d** by treatment with ethyl arylidinecyanoacetate **3a-d**, which on condensation with phthalimidoxyethyl bromide **6** gives **5a-d**. In a parallel route, reaction of **2** with 3-[2-(4-substituted phenyl)ethenyl]quinoxalin-2(1*H*)-one **8a-d** affords 6-chloro-*N*-[3-{2-(4-substituted phenyl)ethenyl}quinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine **9a-d** which on condensation with phthalimidoxyethyl bromide **6**, yields final compound **10a-d**. Structure elucidation is accomplished by elemental analysis and spectral data of the synthesized compounds. Final compounds **5a-d** and **10a-d** have been screened *in vitro* for their antimicrobial activity against different strains of bacteria and fungi.

Keywords: Ethoxyphthlimidoquinoxaline, arylidene, benzothiazol, phthalimidoxyethyl bromide, spectral data, antimicrobial activity

Azoles have played a crucial part in the history of heterocyclic chemistry and also been used extensively as important synthons in organic synthesis. Owing to the versatile chemotherapeutical activities of azoles, a significant amount of research activity has been directed towards this class. The study of benzothiazole derivatives is of considerable current interest as a result of their important biological and biophysical properties such as antitumor[1], antimicrobial[2], antifungal agents[3], as well as imaging agents for β-amyloid[4]. Several substituted benzothiazoles[5-8] have been identified as potent anthelmintic drugs. Aminobenzothiazoles have manifested a large scale of biological activities such as antiparkinsonian, dopamine antagonist[9,10], antibacterial[11] and antiasthamatic drugs[12] .

Similarly the chemistry of quinoxalines have attracted the focus of the scientific community in the past ten years[13,14] due to their potential applications including anti-viral[15], anti-bacterial[16], anti-protozoal, anti-HIV[17], anti-cancer[18] (colon cancer therapies)[19,] anti-depressant[20], and as kinase inhibitors[21,22]. They are also used in the agricultural field as fungicides, herbicides, and insecticides[23]. Also, quinoxaline derivatives were highly potent NMDA receptor antagonist[24-27]. In addition, quinoxaline moieties are present in the structure of various antibiotics such as echinomycin, levomycin and actinoleutin, which are known to inhibit the growth of gram-positive bacteria and they are active against various transplantable tumors[28-30] .

Moreover, compounds containing condensed pyrimidines have been used as effective antitumor agents[31], as herbicide antidotes[32], antibacterials[33], diuretics[34] and antivirals.

Herein we focused on the preparation of novel alkoxyphthalimide substituted quinoxaline and pyrimidine derivatives of aminothiazoles. Several derivatives of alkoxyphthalimide have been synthesized[35,36], and reported to demonstrate a wide range of pharmacological activities i.e. anticancer, antimalarial[37], antiepileptic[38] etc.

In view of above mentioned facts and in connection with our ongoing work on the synthesis of alkoxyphthalimide derivatives of heterocycles, it appeared expedient to synthesize ethyl 8-chloro-4-(4-substituted phenyl)-2-[(*N*-ethoxyphthalimido)amino]-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-3-carboxylate **5a-d** (**Table I**) and 6-chloro-*N*-[3-{2-(4-substitutedphenyl)-ethenyl}-1-*N*-ethoxyphthalimidoquinoxalin-2(1*H*)-ylidene]-1,3-benzothiazo-l-2-amine **10a-d** (**Scheme I**) *via* a series of reactions.

Results and Discussion

The key intermediate used for the synthesis of final compounds of both series was 6-chloro-1,3-benzothiazol-2-amine **2**, which in turn was prepared by

Table I — Physical and analytical data of synthesized compounds **2-7**

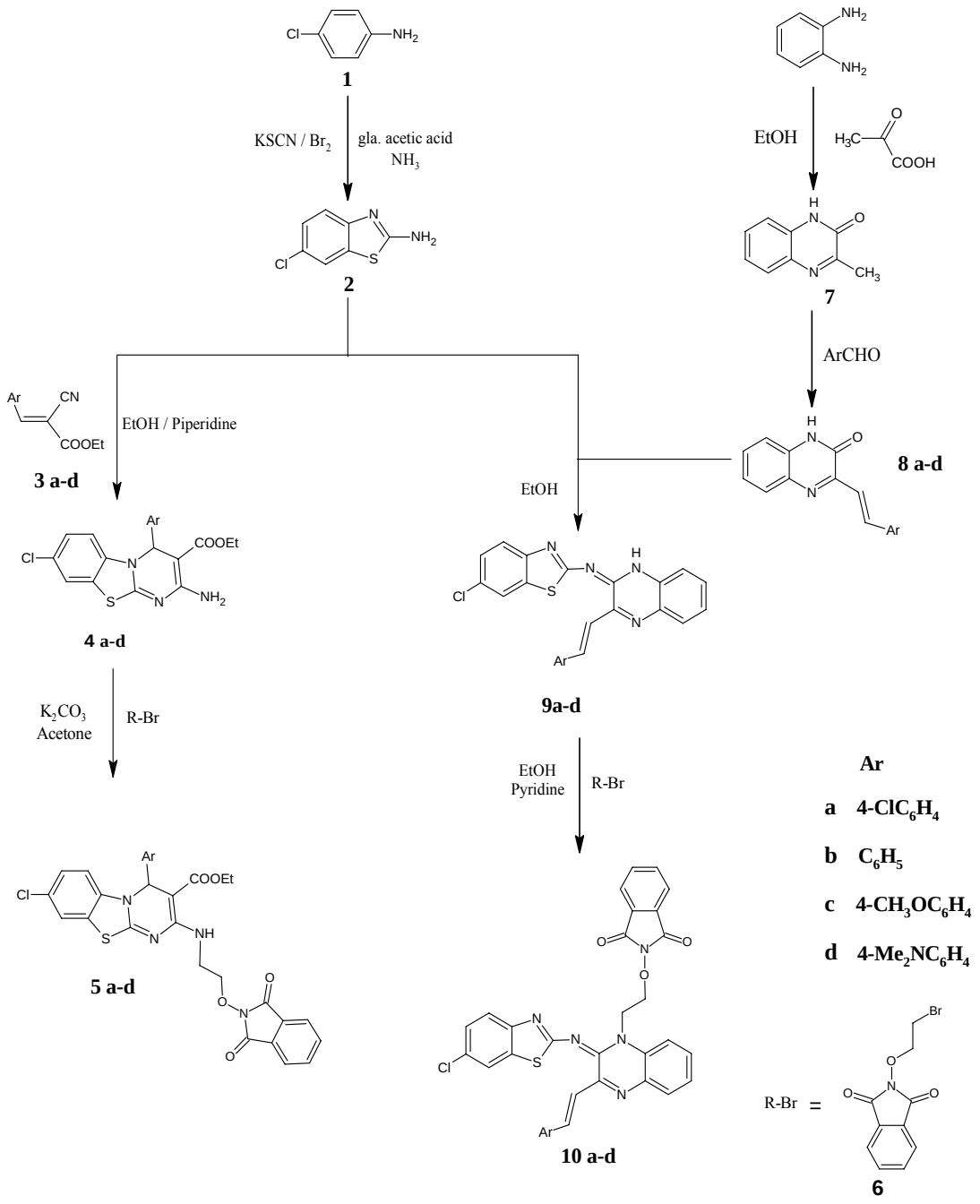
Compd	Mol. formula	Mol. Wt	Ar	m.p. (°C)	Yield (%)	Found (Calcd) %	
						N	S
2	$C_7H_5N_2SCl$	184	-	196	84	15.10 (15.17	17.35 17.37)
4a	$C_{19}H_{15}N_3O_2SCl_2$	420	4-ClC_6H_4	233	78	9.88 (10.00	7.52 7.63)
4b	$C_{19}H_{16}N_3O_2SCl$	385	C_6H_5	230	70	10.85 (10.89	8.30 8.31)
4c	$C_{20}H_{18}N_3O_3SCl$	415	4- $CH_3OC_6H_4$	240	73	10.00 (10.10	7.57 7.71)
4d	$C_{21}H_{21}N_4O_2SCl$	428	4-$(CH_3)_2$ NC_6H_4	235	68	12.95 (13.06	7.50 7.48)
5a	$C_{29}H_{22}N_4O_5SCl_2$	608	4-ClC_6H_4	280	67	9.23 (9.19	5.21 5.26)
5b	$C_{29}H_{23}N_4O_5SCl$	574	C_6H_5	180	61	9.71 (9.74	5.51 5.58)
5c	$C_{30}H_{25}N_4O_6SCl$	604	4- $CH_3OC_6H_4$	258	65	9.13 (9.26	5.28 5.30)
5d	$C_{31}H_{28}N_5O_5SCl$	617	4-$(CH_3)_2$ NC_6H_4	201	59	11.29 (11.33	5.10 5.19)
7	$C_9H_8N_2O$	160	-	205	80	17.48 (17.49	- -)

reaction of 4-chloro aniline **1** with KSCN and Br_2 in glacial acetic acid. Formation of **2** was confirmed by the presence of C=N stretching band at 1630 and C-S-C stretching band at 690 cm^{-1} in IR spectrum. Treatment of **2** with ethyl arylidinecyanoacetate **3a-d** in ethanol and piperidine furnished ethyl 2-amino-8-chloro-4-(4-substituted phenyl)-4*H*-pyrimido[2,1-*b*]benzothiazole-3-carboxylate **4a-d**. Structure of **4a** was elucidated on basis of C-O and C=O stretching band at 1112 and 1715 cm^{-1} respectively. ^1H NMR spectrum showed a triplet and quartet at δ 3.76 and 1.57 for CH_2 and CH_3 respectively. Compound **4a-d** were converted to corresponding ethoxyphthalimide derivatives **5a-d** (**Scheme I**) on reaction with ω-bromoethoxyphthalimide **6**. Confirmation of their structure was obtained through spectral and analytical data. IR and ^1H NMR spectral data revealed carbonyl absorption at 1724 and 1781 cm^{-1}, N–O stretching band at 1381 cm^{-1} and two triplets respectively at δ 3.48 and 4.51 for NCH_2 and OCH_2 of ethoxyphthalimide moiety in **5a**.

In an another pathway, **2** undergo condensation reaction with 3-[2-(4-substituted phenyl)ethenyl]-quinoxalin-2(1*H*)-one **8a-d** (**Table II**) in alcohol to afford 6-chloro-*N*-[3-{2-(4-chlorophenyl)ethenyl}-quinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine **9a-d**. The assigned structure of **9a** was based on appearance of bands at 3443 and 1655 cm^{-1} for N-H and C=N stretching in IR spectrum respectively. Appearance of a singlet at δ 8.88 for NH proton, two doublets at δ 7.67 and 7.27 for ethenyl protons and disappearance of signal for NH_2 protons of **2** in ^1H NMR spectrum further confirmed the structure of **9a.** Subsequently, the NH proton in the quinoxaline ring was replaced by ethoxyphthlimide group to yield 6-chloro-*N*-[3-{2-(4-chlorophenyl)ethenyl}-1-*N*-ethoxy-phthalimidoquinoxalin-2(1*H*)-ylidene]-1,3-benzothia-zol-2-amine **10a**. Structure of the final compound was confirmed by presence of C-O and N-O stretching bands at 1092 and 1427 cm^{-1} respectively in IR spectrum and new signals in ^1H NMR spectrum for side chain protons. The mass spectra also support the proposed structure by viewing molecular ion peak at *m/z* 608 and 637 for final compounds **5a** and **10a** (**Table II**) respectively.

Antimicrobial screening

Antimicrobial activity i.e. antibacterial and anti-fungal was screened by Well or Cup method[39] in nutrient agar and dextrose agar medium. Agar medium was sterilized by autoclaving at 15 psi and 121ºC for twenty minutes. The medium was poured in petri dishes and left to solidify. These petri dishes were inoculated with 0.2 mL suspension of organism



Scheme I

by spread plate method[40]. Wells of 11 mm diameter were made in the medium with the help of a sterile borer and filled with 500 ppm solution of testing compound in DMF. Similarly other wells were made for standard drugs and filled with standard concentration. These petri plates were incubated at 37ºC in an incubator. The petri dishes were examined for zone of inhibition after 24-48 hr. Bacterial strains used for the present investigation are one Gram-positive *P. aureoginosa* and three Gram-negative *P. mirabilis, E. coli* and *K. pneumoniae*. *Candida albicans* (MTCC227) and *Aspergillus fumigatus* (MTCC2550) were used as the testing fungal strains. Ciprofloxacin and Amphotericin B were used as standard drugs for comparative study against bacterial and fungal strains respectively. Zone of inhibition was measured in mm. Activity index of all the synthesized compounds was also calculated against all the standard drugs.

Table II — Physical and analytical data of synthesized compounds **8a-d** to **10a-d**

Compd	Mol. formula	Mol. Wt.	Ar	m.p. (°C)	Yield (%)	Found(Calcd) % N	S
8a	$C_{16}H_{11}N_2Ocl$	282	4-ClC_6H_4	170	78	9.79 (9.91	-)
8b	$C_{16}H_{12}N_2O$	248	C_6H_5	140	73	11.31 (11.28	-)
8c	$C_{17}H_{14}N_2O_2$	278	4- $CH_3OC_6H_4$	165	75	10.01 (10.07	-)
8d	$C_{18}H_{17}N_3O$	291	4-$(CH_3)_2$ NC_6H_4	177	70	14.49 (14.42	-)
9a	$C_{23}H_{14}N_4SCl_2$	449	4-ClC_6H_4	210	82	12.44 (12.47	7.11 7.14)
9b	$C_{23}H_{15}N_4SCl$	414	C_6H_5	178	76	13.36 (13.50	7.59 7.73)
9c	$C_{24}H_{17}N_4SClO$	444	4- $CH_3OC_6H_4$	211	71	12.65 (12.59	7.20 7.21)
9d	$C_{25}H_{20}N_5SCl$	457	4-$(CH_3)_2$ NC_6H_4	223	66	15.25 (15.29	7.05 7.00)
10a	$C_{33}H_{21}N_5SCl_2O_3$	637	4-ClC_6H_4	241	67	10.91 (10.97	4.94 5.02)
10b	$C_{33}H_{22}N_5SClO_3$	603	C_6H_5	200	63	11.48 (11.59	5.19 5.31)
10c	$C_{34}H_{24}N_5SClO_4$	633	4- $CH_3OC_6H_4$	234	60	11.02 (11.04	5.01 5.06)
10d	$C_{35}H_{27}N_6SClO_3$	646	4-$(CH_3)_2$ NC_6H_4	208	58	12.90 (12.99	4.93 4.95)

Table III — Antimicrobial activity of the synthesized compounds **5a-d** and **10a-d**. Zone of inhibition (mm) (activity index)$^{std.}$

Compd	Antibacterial activity				Antifungal activity	
	P. mirabilis	*K. pneumoniae*	*E.coli*	*P. aureoginosa*	*C. albicans*	*A. fumigatus*
5a	15 (0.88) $^{C}_{1}$	18 (1.12) $^{C}_{1}$	17 (1.06) $^{C}_{1}$	21 (1.16) $^{C}_{1}$	17 (1.00) $^{C}_{1}$	19 (1.90) $^{C}_{1}$
5b	13 (0.76)$^{C}_{1}$	15 (0.93) $^{C}_{1}$	7 (0.43) $^{C}_{1}$	16 (0.88) $^{C}_{1}$	26 (1.52) $^{C}_{1}$	24 (2.40) $^{C}_{1}$
5c	16 (0.94) $^{C}_{1}$	11 (0.68) $^{C}_{1}$	18 (1.12) $^{C}_{1}$	19 (1.05) $^{C}_{1}$	18 (1.05) $^{C}_{1}$	27 (2.70) $^{C}_{1}$
5d	14 $(0.82)_1$	8 (0.50) $^{C}_{1}$	NA	9 (0.50) $^{C}_{1}$	36 (2.11) $^{C}_{1}$	18 (1.80)$^{C}_{1}$
10a	13 (0.76) $^{C}_{1}$	17 (1.06) $^{C}_{1}$	19 (1.18) $^{C}_{1}$	17 (0.94) $^{C}_{1}$	27 (1.58) $^{C}_{1}$	28 (2.80) $^{C}_{1}$
10b	15 (0.88) $^{C}_{1}$	19 (1.18) $^{C}_{1}$	13 (0.81) $^{C}_{1}$	20 (1.11) $^{C}_{1}$	34 (2.00) $^{C}_{1}$	20 (2.00) $^{C}_{1}$
10c	14 (0.82) $^{C}_{1}$	9 (0.56)$^{C}_{1}$	10 (0.62) $^{C}_{1}$	13 (0.72) $^{C}_{1}$	28 (1.64) $^{C}_{1}$	23 (2.30)$^{C}_{1}$
10d	18 (1.05)$^{C}_{1}$	13 (0.81) $^{C}_{1}$	19 (1.18)$^{C}_{1}$	18 (1.00) $^{C}_{1}$	25 (1.47) $^{C}_{1}$	17 (1.70) $^{C}_{1}$
C_1	17	16	16	18	17	10

(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug.
For antibacterial activity: C_1 = Ciprofloxacin
For antifungal activity: C_1 = Amphotericin B
NA = Nil Activity

Compounds **5a-d** and **10a-d** were assayed for antimicrobial activity. Screening results (**Table III**) of the compounds **5a-d** established that the **5a** showed comparable activity, while **5c** exhibited good to moderate activity and **5b** and **5d** were either inactive or weakly active against all the four bacterial strains as compared to the standard drug used. Similarly compounds **10a-d** also exhibited good to moderate activity against all bacterial strains. On viewing activity index it was established that most of the compounds are highly active against all fungal strains. Overall activity profile of compounds **5a-d** and **10a-d** were found to be good to moderate.

Experimental Section

General Procedure: Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using *n*-hexane and ethylacetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra of the compounds were recorded in the 4000-450 cm^{-1} ranges using KBr discs on a FTIR IR RX1 Perkin-Elmer spectrometer and ^1H NMR were recorded on a Bruker DRX-300 MHz spectrometer ($CDCl_3$) using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Ethyl arylidene cyanoacetates **3a-d** (ref 41) and phthalimidoxyethyl bromide **6** (ref 42) were prepared by reported methods.

Structure of all the synthesized compounds was assigned on basis of their analytical and spectral data.

Synthesis of 6-chloro-1,3-benzothiazol-2-amine 2: To gl. acetic acid (150 mL) precooled to 5°C, KSCN (0.06 mole) and 4-chloroaniline (0.06 mole) were added. The mixture was placed in freezing mixture and stirred mechanically with addition of Br_2 (0.02 mole in 10 mL gl. acetic acid) from a dropping funnel at such a rate that temperature does not rise above 5°C. Stirring was continued for an additional 3 hr at 0-10°C and the separated hydrochloride salt was filtered, washed with acetic acid and dried. It was dissolved in hot water and neutralized with aqueous ammonia solution (25%), filtered, washed with water and dried, recrystallized with benzene to obtain 6-chloro-1,3-benzothiazol-2-amine.

IR (KBr): 3344, 3420 (N-H str.), 3025 (C-H str., Ar-H), 1630 (C=N str.), 690 (C-S-C str.), 749 (C-Cl str.) cm^{-1}, ^1H NMR ($CDCl_3$): δ 6.97-7.69 (m, 3H, Ar-H), 3.4 (s, 2H, NH_2).

Synthesis of ethyl 2-amino-8-chloro-4-(4-chlorophenyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole 4a: A mixture of compound (**2,** 0.005 mole), ethanol (30 mL), ethyl 4-chlorobenzylidene cyanoacetate (**3a** 0.01 mole) and piperidine (1 mL) was heated under reflux for 7-8 hr. The reaction-mixture was then allowed to cool to RT, poured onto crushed ice and neutralized with conc. HCl. The precipitate was isolated and recrystallized with ethanol.

IR (KBr): 3310, 3430 (N-H str.), 2933 (C-H str., CH_3), 2893 (C-H str., CH_2) 1654 (C=N str.), 1112 (C-O str.), 1715 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40-7.95 (m, 7H, Ar-H), 3.35 (s, 2H, NH_2), 5.34 (s, 1H, Ar-CH), 1.57 (t, 3H, CH_3), 3.76 (q, 2H, CH_2).

Similarly, compounds **4b-d** were prepared with some change in reflux time and reaction work-up. Their characteristic spectral and analytical data are given below:

2-Amino-8-chloro-4-phenyl-4*H*-pyrimido[2,1-*b*]-[1,3]benzothiazole 4b: IR (KBr) 3331, 3445 (N-H str.), 2900 (C-H str., CH_3), 2810 (C-H str., CH_2) 1620 (C=N str.), 1085 (C-O str.), 1740 (C=O str.), cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.32-8.10 (m, 8H, Ar-H), 3.13 (s, 2H, NH_2), 5.27 (s, 1H, Ar-CH), 1.36 (t, 3H, CH_3), 3.69 (q, 2H, CH_2).

2-Amino-8-chloro-4-(4-methoxyphenyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole 4c: IR (KBr): 3345, 3458 (N-H str.), 2930 (C-H str., CH_3), 2855 (C-H str., CH_2), 1673 (C=N str.), 1058 (C-O str.), 1763 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.98-7.40 (m, 10H, Ar-H), 3.61 (s, 2H, NH_2), 5.31 (s, 1H, Ar-CH), 1.62 (t, 3H, CH_3), 3.87 (q, 2H, CH_2), 3.95 (s, 3H, OCH_3).

2-Amino-8-chloro-4-(4-*N*,*N*-Dimethylphenyl)-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole 4d: IR (KBr): 3337, 3460 (N-H str.), 2912 (C-H str., CH_3), 2841 (C-H str., CH_2), 1640 (C=N str.), 1050 (C-O str.), 1750 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.92-7.38 (m, 10H, Ar-H), 3.50 (s, 2H, NH_2), 5.24 (s, 1H, Ar-CH), 1.49 (t, 3H, CH_3), 3.92 (q, 2H, CH_2), 2.70 (s, 6H, NMe_2).

Synthesis of ethyl 8-chloro-4(4-chlorophenyl)-2-[(*N*-ethoxyphthalimido)amino]-4*H*-pyrimido[2,1-*b*]-[1,3]benzothiazole-3-carboxylate 5a: Compound **4a** (0.01 mole) was refluxed in dry acetone (20 mL) containing K_2CO_3 (0.01 mole) as base and phthalimidoxyethylbromide (**6**, 0.01 mole), for 16-18 hr. Excess of solvent was removed under reduced pressure. The separated solid was filtered, washed and recrystallized from ethanol.

IR (KBr): 3405 (N-H str.), 2929 (C-H str., CH_3), 2840 (C-H str., CH_2), 1642 (C=N str.), 1090 (C-O str.), 1724, 1781 (C=O str.), 1381 (N-O str.), 656 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.12-7.39 (m, 11H, Ar-H), 3.68 (s, 1H, NH), 5.26 (s, 1H, Ar-CH), 3.48 (t, 2H, N-CH_2), 4.51 (t, 2H, O-CH_2); MS: *m/z* 608 $[M]^{+\cdot}$, 610 $[M+2]^{+\cdot}$, 533, 429, 413, 385, 383, 350, 308, 238, 185, 136.

Compounds **5b-d** were also synthesized by a similar method.

Ethyl-8-chloro-4-phenyl-2-[(*N*-ethoxyphthalimido)amino]-4*H*-pyrimido[2,1-*b*][1,3] benzothiazole-3-carboxylate 5b: IR (KBr): 3423 (N-H str.), 2944 (C-H str., CH_3), 2800 (C-H str., CH_2), 1605 (C=N str.), 1115 (C-O str.), 1719, 1777 (C=O str.), 1410 (N-O str.), 683 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.86-7.43 (m, 12H, Ar-H), 3.45 (s, 1H, NH), 5.23 (s, 1H, Ar-CH), 3.39 (t, 2H, N-CH_2), 4.13 (t, 2H, O-CH_2); MS: *m/z* 574 $[M]^{+\cdot}$, 576 $[M+2]^{+\cdot}$, 498, 438, 429, 413, 385, 350, 274, 272, 238, 185, 149.

Ethyl-8-chloro-4(4-methoxyphenyl)-2-[(*N*-ethoxyphthalimido)amino]-4*H*-pyrimido [2,1-*b*][1,3]benzothiazole-3-carboxylate 5c: IR (KBr): 3340 (N-H str.), 2925 (C-H str., CH_3), 2830 (C-H str., CH_2), 1685 (C=N str.), 1044 (C-O str.), 1710, 1793 (C=O str.), 1423 (N-O str.), 620 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.90-7.58 (m, 14H, Ar-H), 3.19 (s, 1H, NH), 5.21 (s, 1H, Ar-CH), 3.74 (t, 2H, N-CH_2), 4.32 (t, 2H, O-CH_2), 3.90 (s, 3H, OCH_3); MS: *m/z* 604 $[M]^{+\cdot}$, 606 $[M+2]^{+\cdot}$, 528, 429, 413, 385, 379, 304, 238, 185, 136.

Ethyl-8-chloro-4(4-*N*,*N*-dimethylphenyl)-2-[(*N*-ethoxyphthalimido)amino]-4*H*-pyrimido[2,1-*b*]-[1,3]benzothiazole-3-carboxylate 5d: IR (KBr): 3387 (N-H str.), 2955 (C-H str., CH_3), 2841 (C-H str., CH_2), 1650 (C=N str.), 728 (C-Cl str.), 1050 (C-O str.), 1734, 1780 (C=O str.), 1420 (N-O str.), 677 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.10-7.82 (m, 14H, Ar-H), 3.70 (s, 1H, NH), 5.28 (s, 1H, Ar-CH), 3.89 (t, 2H, N-CH_2), 4.21 (t, 2H, O-CH_2), 2.83 (s, 6H, NMe_2); MS: *m/z* 617 $[M]^{+\cdot}$, 619 $[M+2]^{+\cdot}$, 541, 497, 429, 413, 385, 392, 350, 317, 238, 185.

Synthesis of 3-methylquinoxalin-2(1*H*)-one 7: Equimolar quantities of pyruvic acid and *o*-phenylene diamine were refluxed in alcohol for 3 hr. The contents were cooled down to separate out the solid. The compound was filtered out and recrystallized with ethanol.

IR (KBr): 3322 (N-H str.), 3051 (C-H str., Ar-H), 2955 (C-H str., CH_3), 1694 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 6.70-7.81 (m, 4H, Ar-H), 8.39 (s, 1H, NH).

Synthesis of 3-[2-(4-chlorophenyl)ethenyl]quinoxalin-2(1*H*)-one 8a: A mixture of compound **7** (0.01 mole), 4-chlorobenzaldehyde (0.01 mole) and piperidine (0.5 mL) was fused at 165°C for 3 hr. The obtained product was crystallized from ethanol to afford compounds **8a**.

IR (KBr): 3340 (N-H str.), 1680 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.66 (d, 1H, =CH-Ar), 7.25 (d, =CH-C=), 7.86-8.22 (8H, m, Ar-H), 8.70 (s, 1H, NH).

Using similar way with minor changes in reflux time, compounds **8b-d** were also prepared.

Synthesis of 3-[2-phenylethenyl]quinoxalin-2(1*H*)-one 8b: IR (KBr): 3300 (N-H str.), 1670 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.62 (d, 1H, =CH-Ar), 7.21 (d, =CH-C=), 7.90-8.40 (9H, m, Ar-H), 8.60 (1H, s, NH).

Synthesis of 3-[2-(4-methoxyphenyl)ethenyl]-quinoxalin-2(1*H*)-one 8c: IR (KBr): 3320 (N-H str.), 1677 (C=O str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.98 (3H, s, OCH_3), 7.64 (d, 1H, =CH-Ar), 7.26 (d, =CH-C=), 7.81-8.30 (8H, m, Ar-H), 8.9 (1H, s, NH).

Synthesis of 3-[2-(4-*N*,*N*-Dimethylphenyl)ethenyl]quinoxalin-2(1*H*)-one 8d: IR (KBr): 3285 (N-H str.), 1665 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 3.19 (s, 6H, NMe_2), 7.58 (d, 1H, =CH-Ar), 7.29 (d, =CH-C=), 7.79-8.33 (8H, m, Ar-H), 8.2 (1H, s, NH).

Synthesis of 6-chloro-*N*-[3-{2-(4-chlorophenyl)-ethenyl}quinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine 9a: Compound **2** and 3-[2-(4-chlorophenyl)ethenyl]quinoxalin-2(1*H*)-one **8a-d** were refluxed in an equimolar ratio in alcohol for 16 hr. The reaction-mixture was concentrated and allowed to cool. The resultant product was filtered out and recrystallized from ethanol.

IR (KBr): 3443 (N-H str.), 3054 (C-H str., Ar-H), 1655 (C=N str.), 748 (C-Cl str.), 630 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.13-8.42 (m, 11H, Ar-H), 8.88 (s, 1H, NH), 7.67 (d, 1H, =CH-Ar), 7.27 (d, =CH-C=).

Compounds **9b-d** were prepared in similar way with the change in reflux time. Their spectral data are given below:

6-Chloro-*N*-[3-{2-(phenyl)ethenyl}quinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine 9b: IR (KBr): 3381 (N-H str.), 3025 (C-H str., Ar-H), 1633 (C=N str.), 767 (C-Cl str.), 694 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.29-8.13 (m, 12H, Ar-H), 8.77 (s, 1H, NH), 7.32 (d, 1H, =CH-Ar), 6.84 (d, =CH-C=).

6-Chloro-*N*-[3-{2-(4-methoxyphenyl)ethenyl}quinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine 9c: IR (KBr): 3424 (N-H str.), 3037 (C-H str., Ar-H), 1620 (C=N str.), 1123 (C-O str.), 782 (C-Cl str.), 663 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.22-8.10 (m, 14H, Ar-H), 8.64 (s, 1H, NH), 7.49 (d, 1H, =CH-Ar), 6.71 (d, =CH-C=), 3.85 (s, 3H, OCH_3).

6-Chloro-*N*-[3-{2-(4-*N*,*N*-Dimethylphenyl)ethenyl}quinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine 9d: IR (KBr): 3390 (N-H str.), 3020 (C-H str., Ar-H), 1613 (C=N str.), 769 (C-Cl str.), 675 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.10-8.33 (m, 14H, Ar-H), 8.60 (s, 1H, NH), 7.45 (d, 1H, =CH-Ar), 6.80 (d, =CH-C=), 3.10 (s, 6H, NMe_2).

Synthesis of 6-chloro-*N*-[3-{2-(4-chlorophenyl)-ethenyl}-1-*N*-ethoxyphthalimido quinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine 10a: An equimolar mixture of compound (**9a,** 0.01 mole) and phthalimidoxyethyl bromide (0.01 mole) in absolute ethanol was refluxed for 16 hr using pyridine (0.02 mole) as base. Excess of solvent was removed *in vacuo* and the resultant product left was poured on crushed ice to obtain the product, which was filtered, dried and recrystallized from alcohol. IR (KBr): 3087 (C-H str., Ar-H), 1092 (C-O str.), 1663 (C=N str.), 1427 (N-O str.), 1749 (C=O str.), 674 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43-7.79 (m, 15H, Ar-H), 3.44 (t, 2H, N-CH_2), 7.35 (d, 1H, =CH-Ar), 4.32 (t, 2H, O-CH_2), 6.98 (d, =CH-C=); MS: *m/z* 637 $[M]^{+\cdot}$, 639 $[M+2]^{+\cdot}$, 501, 492, 417, 391, 338, 356, 289, 241, 226, 154, 121.

Likewise, compounds **10b-d** were prepared with some change in reaction conditions. Their characteristic spectral and analytical data are given below:

6-Chloro-*N*-[3-{2-(phenyl)ethenyl}-1-*N*-ethoxyphthalimidoquinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine 10b: IR (KBr): 3055 (C-H str., Ar-H), 1047 (C-O str.), 1610 (C=N str.), 1410 (N-O str.), 763 (C-Cl str.), 1733 (C=O str.), 650 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.12-7.72 (m, 16H, Ar-H), 3.31 (t, 2H, N-CH_2), 7.44 (d, 1H, =CH-Ar), 4.67 (t, 2H, O-CH_2), 6.79 (d, =CH-C=); MS: *m/z* 603 $[M]^{+\cdot}$, 605 $[M+2]^{+\cdot}$, 501, 458, 391, 303, 356, 290, 241, 226, 154.

6-Chloro-*N*-[3-{2-(4-methoxyphenyl)ethenyl}-1-*N*-ethoxyphthalimidoquinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine 10c: IR (KBr): 3042 (C-H str., Ar-H), 1063 (C-O str.), 1635 (C=N str.), 1434 (N-O str.), 730 (C-Cl str.), 1720 (C=O str.), 683 (C-S-C str.) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.21-7.82 (m, 18H, Ar-H), 3.63 (t, 2H, N-CH_2), 7.20 (d, 1H, =CH-Ar), 4.59 (t, 2H, O-CH_2), 6.60 (d, =CH-C=), 3.88(s, 3H, OCH_3); MS: *m/z* 633 $[M]^{+\cdot}$, 635 $[M+2]^{+\cdot}$, 501, 471, 417, 391, 333, 289, 241, 226, 154, 121.

6-Chloro-*N*-[3-{2-(4-*N*,*N*-dimethylphenyl)ethenyl}-1-*N*-ethoxyphthalimido quinoxalin-2(1*H*)-ylidene]-1,3-benzothiazol-2-amine 10d: IR (KBr): 3050 (C-H str., Ar-H), 1040 (C-O str.), 1620 (C=N str.), 1444 (N-O str.), 773 (C-Cl str.), 1739 (C=O str.), 683 (C-S-C str.) $cm^{-1;}$ ^1H NMR ($CDCl_3$): δ 7.23-7.98 (m, 18H, Ar-H), 3.60 (t, 2H, N-CH_2), 7.31 (d, 1H, =CH-Ar), 4.52 (t, 2H, O-CH_2), 6.80 (d, =CH-C=), 2.90 (s, 6H, NMe_2); MS: *m/z* 646 $[M]^{+\cdot}$, 648 $[M+2]^{+\cdot}$, 500, 417, 391, 346, 356, 289, 226, 154, 121.

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References

1 O'Brien S E, Browne H L, Bradshaw T D, Westwell A D, Stevens M F G & Laughton C A, *Org Biomol Chem*, I, **2003**, 493.
2 Yildiz-Oren I, Yalcin I, Aki-Sener E & Ucarturk N, *Eur J Med Chem*, 39, **2004**, 291.
3 Ra C S, Jung B Y & Park G, *Heterocycl*, 62, **2004**, 793.
4 Khurana R, Coelmen C, Ionescu-Zanetti C, Carter S A, Krishna V, Grover R K, Roy R & Singh S, *J Struct Biol*, 151, **2005**, 229.
5 McCracken R O & Lipkowitz K B, *J Parasitol*, 76, **1990**, 180.
6 McCracken R O & Lipkowitz K B, *J Parasitol*, 76, **1990**, 853.
7 Yousef M Y, Eisa A M, Nasra M N & El-Bialy S A, *J Pharm Sci*, 13, **1997**, 79.
8 Delmas F, Avellaneda A, DiGiorgio C, Robin M, De Clerq F, Timon-Devid P & Galy J P, *Eur J Med Chem*, 39, **2004**, 685.
9 Pifl C, Pichler L, Kobinger W & Hornykiewicz O, *Eur J Pharmacol*, 153, **1988**, 33.
10 Schneider C S & Mierau J, *J Med Chem*, 30, **1987**, 494.
11 Clark J M, Olsen S J, Weinberg D S, Dalvi M, Whiteny R R, Bonner D P & Sykes R B, *Antimicrob Agents Chemother*, 31, **1987**, 226.
12 Eriks J C, Vandergoot H, Sterk G J & Timmerman H, *J Med Chem*, 35, **1992**, 3239.
13 Katritzky A R & Rees C W, *Comprehensive Heterocyclic Chemistry*, Part 2B, 3, **1984**, 157.
14 Sherman D, Kawakami J, He H Y, Dhun F, Rios R, Liu H, Pan W, Xu Y J, Hong S P, Arbour M, Labelle M & Duncton M A J, *Tetrahedron Lett*, 48, **2007**, 8943.
15 Loriga M, Piras S, Sanna P & Paglietti G, *Il Farmaco*, 52, **1997**, 157.

16 Seitz L E, Suling W J & Reynolds R C, *J Med Chem*, 45, **2002**, 5604.
17 Hui X, Desrivot J, Bories C, Loiseau P M, Franck X, Hocquemiller R & Figadere B, *Bioorg Med Chem Lett*, 16, **2006**, 815.
18 Lindsley C W, Zhao Z, Leister W H, Robinson R G, Barnett S F, Defeo-Jones D, Jones R E, Hartman G D, Huff J R, Huber H E & Duggan M E, *Bioorg Med Chem Lett*, 15, **2005**, 761.
19 Labarbera D V & Skibo E B, *Bioorg Med Chem*, 13, **2005**, 387.
20 Sarges R, Howard H R, Browne R G, Lebel L A, Seymour P A & Koe B K, *J Med Chem*, 33, **1990**, 2240.
21 Srinivas C, Kumar C N S S P, Rao V J & Palaniappan S, *J Mol Catal A: Chem*, 265, **2007**, 227.
22 Ghomsi N T, Ahabchane N E H, Es-Safi N E, Garrigues B & Essassi E M, *Spectroscopy Lett*, 40, **2007**, 741.
23 Sakata G, Makino K & Karasawa Y, *Heterocycl,* 27, **1988**, 2481.
24 Ohmori J, Sakamoto S, Kubota H, Shimizu-Sasamata M, Okada M, Kawasaki S, Hidaka K, Togami J, Furuya T & Murase K, *J Med Chem*, 34, **1994**, 467.
25 Epperson J R, Hewawasam P, Meanwell N A, Boissard C G, Gribkoff V K & Post-Munson D, *Bioorg Med Chem Lett*, 3, **1993**, 2801.
26 Nagata R, Tanno N, Kodo T, Ae N, Ogita K, Nishimura T, Tatsuno T, Nakamura M, Ogita K & Yoneda Y, The 207th American Chemical Society National Meeting, San Diego, California, March 13-17, **1994**, Poster, MEDI 181, 16 March **1994**.
27 Kulagowaski J J, Baker R, Curtis N R, Lesson P D, Mawer IM, Moseley M, Ridgill M P, Rowley M, Stansfield I, Foster A C, Grimwood S, Hill R G, Kemp J A, Marshall G R, Saywell K L & Tricklebank M D, *J Med Chem*, 37, **1994**, 1402.
28 Dell A, William D H, Morris H R, Smith G A, Feeney J & Roberts G C K, *J Am Chem Soc*, 97, **1975**, 2497.
29 Heravi M M, Bakhtiari K, Tehrani M H, Javadi N M & Oskooie H A, *ARKIVOC* (xvi), **2006**, 16.
30 Raw S A, Wilfred C D & Taylor R J K, *Chem Commun*, 18, **2003**, 2286.
31 Akimoto H, Miwa T & Otsu K, *JP* 04, 1992, 235, 986; *Chem Abstr*, 118, **1993**, 213101a.
32 Bratz M, Kober R, Seele R, Saupe T, Meyer N, Walker N, Landes A & Walter H, *Canadian Pat Appl* 2, **1993**, 078, 4767; *Chem Abstr*, 120, **1994**, 77293b.
33 Hurlbert B S & Valenti B F, *J Med Chem*, 11, **1968**, 708.
34 Parish H A, Gilliom R D, Purcell W P, Browne R K, Spirk R F & White H D, *J Med Chem*, 25, **1982**, 98.
35 Sharma R, Nagda D P & Talesara G L, *ARKIVOC*, (i), **2006**, 1.
36 Banu T, Rajora S, Khatri D & Talesara G L, *J Indian Chem Soc*, 77, **2000**, 300.
37 Ure J A & Perassalo M, *J Neuro Sc*, 1, **2000**, 177.
38 Singh B, Mehta D, Baregama L K & Talesara G L, *Indian J Chem*, 43B, **2004**, 1306.
39 Simmons A, *Practical Medical Microbiology*, 14th Edn, (Churchill Livingston, Edinberg), 11, **1996**, 163.
40 Bisen P S & Verma K, *Hand Book of Microbiology*, 1st Edn (CBS Publishers and Distributors, New Delhi), **1996**.
41 Heravi M M, Bakhtiari K, Taheri S & Oskooie H A, *J Chin Chem Soc*, 54, **2007**, 1557.
42 Orndroff W R & Pratt D S, *Am Chem J*, 47, **1917**, 89.