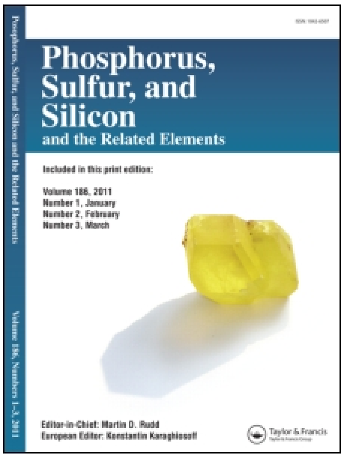

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SYNTHESIS AND ANTI-HIV SCREENING OF SOME HETEROCYCLIC COMPOUNDS

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SYNTHESIS AND ANTI-HIV SCREENING OF SOME HETEROCYCLIC COMPOUNDS

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Pyrimidobenzimidazole derivatives (**I** and **II**), pyrimidoanthraquinonimidazole (**III**), bis-2-amino-2-thiazoline coupled deuteroporphyrine (IX) derivative (**IV**), acridone derivative (**V**) and acridine derivatives (**VI–VIII**) have been synthesized and characterized by using ^{1}H NMR and HRMS spectral data. All these compounds were screened for anti-HIV-1 activity on MT-4 cells *in vitro* and were found to be inactive at a concentration below 100 μM.

Keywords: Heterocyclic; anti-HIV-1 activity; MT-4 cells; NMR; HRMS

INTRODUCTION

Human immunodeficiency virus (HIV) is the cause of a fatal disease known as acquired immune deficiency syndrome. At present there are five drugs i.e. 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxyinosine (ddI), 2′,3′-dideoxy cytidine (ddC), 2′,3′-didehydro-3′-deoxythymidine (d4T), and 3-TC or lamivudine used for the treatment of AIDS.[1] These drugs fail to maintain adequate drug levels at the site of replication over extended periods due to their relatively short half lives[2–5] and thus fail to stop progression of acquired immunodeficiency syndrome (AIDS) which leads to dementia and other neurological manifestations of HIV infection. The large number of research papers published every year[6–8] indicate that the development of an effective drug for the treatment of

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[*] Corresponding author.

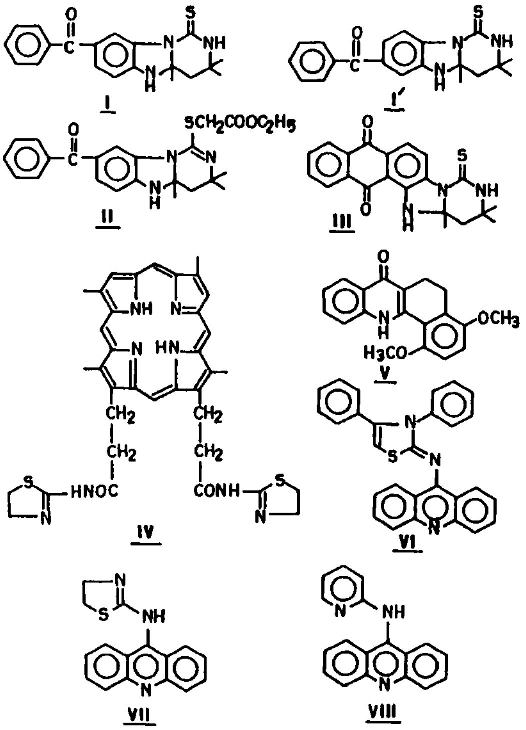
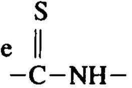


Chart - 1

AIDS continues to be a challenging problem in medicinal research. The above mentioned drugs are nucleoside substrate analogues and often exhibit significant toxic side effects. The discovery of nevirapine (dipyridodiazepinone) which acts by a mechanism distinct from that of nucleoside substrate analogues is expected to avoid clinical toxicities[9]. Besides nevirapine, tetrahydromidazobenzodiazepinone (TIBO)[10], 2-thio-9-acridone derivatives[11] and porphyrin derivatives[12,13] are reported to exhibit anti-HIV activity. Tempted by the anti-HIV activity reported for the above mentioned heterocyclic compounds, we have synthesized various heterocyclic compounds i.e. pyrimidobenzimidazole derivatives **I** and **II**, pyrimidoan-thraquinonimidazole **III**, bis 2-amino-2-thiazoline coupled deuteroporphyrine (IX) derivative **IV**, acridone derivative **V** and acridine derivatives **VI–VIII** and screened them for anti-HIV activity. The synthesis and anti-HIV screening results of the above mentioned compounds (**I–VIII**) are reported in this paper.

RESULTS AND DISCUSSION

When 3,4-diaminobenzophenone was allowed to react with 4-methyl-4-isothiocyanato-2-pentanone and the resulting intermediate was cyclized by refluxing in methanol at pH (3–4), the product obtained was **I** and not the isomeric structure **I′** (Chart-1). The ^{1}H NMR spectra of **I** show a doublet at δ 9.2 showing an aromatic proton at lowest field[14] (9.2 ppm deshielded by near $>C = S$ function) as a doublet having a coupling constant of $J_{(m)} = 2$Hz which is due to meta coupling. This rules out isomeric structure **I′** (which should show ortho coupling with a coupling constant of $J_{(0)} = 6$–10 Hz). Thus 4-methyl-4-isothiocyanato-2-pentanone first react with the more basic amino group of diamino benzophenone (i.e the amino group meta to the benzoyl group) and then the second amino group (i.e. the amino group para to the benzoyl group) undergoes reaction to give cyclized product **I** and not **I′**. The structure of **I** is confirmed by correct ^{1}H NMR and HRMS spectra reported in Table-I. Pyrimidobenzimidazole derivative **II** (Chart-1) was synthesized by the reaction of ethylbromoacetate with compound **I** in the presence of potassium carbonate. The structure of compound **II** was confirmed by correct ^{1}H NMR and HRMS spectra reported in Table-I. The salient feature in the ^{1}H NMR spectra of **II** was the movement of the deshielded aromatic proton of compound **I** (at δ 9.2) from lowest field to high field i.e. at δ 7.85. This movement of the proton from lowest to high field indicate the absence of $C{=}S$ group in compound **II** thus confirming substitution at the more nucleophilic sulphur atom rather than at the less nucleophilic nitrogen atom of the  $\overset{\overset{\displaystyle S}{\|}}{-C}-NH-$ function. Pyrimidoanthraquinonimidazole (**III**) was synthesized according to the method reported earlier[15]. Deuteroporphyrin IX dicarboxylic acid was synthesized from hemin by following the procedure reported in literature[16]. Deuteroporphyrin IX dicarboxylic acid was coupled with 2-amino-2-thiazoline in the presence of 1,1′-carbonyl diimidazole. The structure of bis coupled product **IV** is supported by correct FAB MS and ^{1}H NMR spectra reported in Table-I. Since molecules of this type are fragile[17] and it is difficult to get molecular ion peak using HRMS, FAB MS was used to get the molecular ion peak of **IV**.

Acridone derivative (**V**) was synthesized by the condensation of 5,8-dimethoxy-1-tetralone[18] with anthranilic acid in the presence of anhydrous zinc chloride using n-butanol as solvent. The condensed product **V** was purified by column chromatography and the structure of **V** was confirmed by correct ^{1}H NMR and HRMS spectral data reported in Table-I. Thiazolinoacridines (**VI**) and (**VII**) were synthesized by the condensation of 9-chloroacridine[19] with 2-imino-3,4-diphenyl-4-thiazoline[20] and 2-amino-2-thiazoline respectively. The struc-

TABLE I Physical constant and spectral data of various heterocyclic compounds

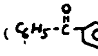
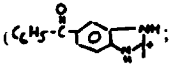
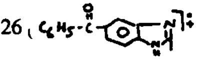
Compound No.	*Solvent of crystallization/ Elution*	*Yield %*	*m.p. °C*	*^1H NMR (300 MHz; DMSO-d_6): δ ppm*	*HRMS (m/z; rel.int.)*
1	2	3	4	5	6
I	THF	68	222	1.20 (s, 3H; -CH_3); 1.30 (s, 3H; -CH_3); 1.5 (s, 3H; -CH_3); 2.1 (d, 1H; 1H of -CH_2-; J_{gem} = 15Hz); 2.4 (d, 1H; 1H of -CH_2; J_{gem} = 15 Hz); 6.55 (d, 1H; Ar); 7.35 (dd, 1H; Ar); 7.45–7.65(m, 5H, Ar); 7.75 (s, 1H; -NH-; exch.); 8.55 (s, 1H; -NH-$\overset{\overset{S}{\|}}{C}$-; -exch.); 9.2 (d, 1H; Ar; $J_{(m)}$ = 2Hz).	351.14056 (M^+; 83.25) Calcd. for $C_{20}H_{21}N_3SO$ 351.14053. 350.13237 (M^+-H; 3.02); 336.11725 (M^+-CH_3; 100); 277.13404 (m/z 336.11725-HSCN; 92.39); 237.10220; ( ; 38.32); 236.09493 (m/z 237.10220-H; 38.56); 159.05613 (m/z 236.09493-C_6H_5; 44.63); 131.06097 (m/z 237.10220 C_7H_5O; 13.47; 105.3400 - (C_6H_5-$\overset{\overset{O}{\|}}{C}^+$; 52.87); 77.03908 ($C_6H_5{}^+$;31.20).
II	THF/MeOH	69	125	1.05 (s, 3H; -CH_3); 1.2 (s + t, 6H; CH_3 + CH_3 of -CH_2-CH_3); 1.40 (s, 3H; -CH_3); 1.90 (d, 1H; one H of -CH_2-; J_{gem} = 14 Hz); 2.15 (d, 1H; one H of -CH_2; J_{gem} = 14 Hz); 3.75 (d, 1H; one H of -S-CH_2-; J_{gem} = 15 Hz); 3.85 (d, 1H; one H of -S-CH_2-; J_{gem} = 15 Hz); 4.1 (q; 2H; CH_2 of -CH_2-CH_3); 6.50 (d, 1H; Ar); 7.2 (d, 1H; Ar); 7.5–7.65 (m, 6H; one H of -NH-, exch. +5H Ar); 7.85 (s; 1H; Ar).	437.17722 (M^+; 19.79) Calcd. for $C_{24}H_{27}$-N_3SO_3 437.17731. 422.15356 (M^+-CH_3; 15.91); 392.14302 (M^+-OC_2H_5; 3.70); 350.13346 (M^+-$CH_2COOC_2H_5$; 10.40); 292.15563 (M^+-$C_2H_5COOCH_2SCN$; 2.34); 237.10106 ( ; 44.20) 236.09526 ( ; 100.00); 235.08711 (m/z 236.09526-H; 10.30); 159.05626 ( ; 97.46); 131.06086 ( ; 17.74); 105.03478 ($\overset{\overset{O}{\|}}{C_6H_5C}{}^+$; 51.28); 77.03928($C_6H_5{}^+$;27.67).

TABLE I Continued

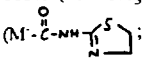
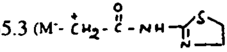
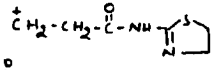
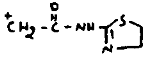
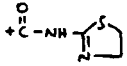
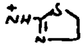
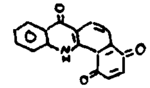
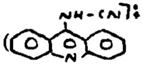
Compound No.	*Solvent of crystallization/ Elution*	*Yield %*	*m.p. °C*	*^{1}H NMR (300 MHz; DMSO-d_6): δ ppm*	*HRMS (m/z; rel.int.)*
1	2	3	4	5	6
IV	DMF/H_2O	60	220(d)	(DMSO-d_6+D_2O): 3.05 (m, 4H); 3.3 (t, 4H); 3.5–3.7 (m, 14H); 4.3 (s, 6H); 9.3 (s, 2H); 10.2 (3s, look like a triplet; 3H); 10.5 (s, 1H)	FABMS (Cleland): 678.1 (M^+: 0.53); 677.3 (M^+-H; 1.06): 663.0 (M^+-CH_3: 2.55); 549.1  ; 1.39); 535.3  ; 1.13); 156.9 ( ; 4.74); 143.0 ( ; 1.36); 129.2 ( ; 1.63); 101.0 ( ; 26.72).
V	$CHCl_3$:EtOAc (8:2)	30	205	2.7 (m, 4H; -CH_2-CH_2-); 3.85 (s, 3H; -OCH_3), 3.95 (s, 3H; -OCH_3); 7.1 (q, 2H; Ar); 7.3 (q, 1H; Ar); 7.6 (d, 1H; Ar); 7.8 (d; 1H; Ar); 8.1 (d, 1H; Ar); 11.2 (s, 1H; -NH-; exch.).	307.11950 (M^+; 80.06) Calcd. for $C_{19}H_{17}$-$NO_3$307.12085; 306.11270 (M^+-H; 100.00); 305.10580 (M^+-2H; 5.61); 292.09760 (M^+-CH_3; 13.34); 277.07388 (M^+-2CH_3; 17.29); 276.10292 (M^+-OCH_3; 3.20); 276.06632 (m/z 306.11270-2CH_3; 61.58); 275.05883 ( 5.76).
VI	$CHCl_3$	40	185–90	6.5 (s, 1H; >C=CH-); 7.25 (s, 5H; Ar); 7.50 (m, 5H; Ar); 7.75 (m, 4H; Ar); 8.10 (d, 4H; Ar).	429.12841 (M^+; 21.37) Calcd. for $C_{28}H_{19}N_3S$ 429.12997

TABLE I Continued

Compound No.	*Solvent of crystallization/ Elution*	*Yield %*	*m.p. °C*	*^{1}H NMR (300 MHz; DMSO-d_6): δ ppm*	*HRMS (m/z; rel.int.)*
1	2	3	4	5	6
VII	Hexane:$CHCl_3$ (2:8)	30	192–95	3.3 (t, 2H, $-CH_2-$); 3.65 (t; 2H; $-CH_2-$); 7.5 (m, 2H; Ar); 7.75 (m; 2H; Ar); 8.0 (d, 4H, Ar); 8.2 (s, 1H; -NH-, exch.)	279.08292 (M^+; 100.00); Calcd. for $C_{16}H_{13}N_3S$ 279.08301; 278.07528 (M^+-H; 34.74); 251.05145 (M^+-C_2H_4-; 4.15); 219.07983 ( ; 34.98).
VIII	$CHCl_3$	30	180	7.0 (t, 2H; Ar); 7.3 (m, 2H; Ar); 8.0 (m, 7H; Ar); 8.2 (m, 1H; Ar); 13.2 (s, 1H; -NH-, exch.).	271.10915 (M^+; 100.00) Calcd. for $C_{18}H_{13}N_3$271.11096; 270.10216 (M^+-H; 98.83); 178.06433 (M^+-$C_5H_5N_2$; 3.51); 78.03472 ($C_5H_4N^+$; 3.99).

tures of **VI** and **VII** are supported by ^{1}H NMR and HRMS reported in Table-I. The known pyridinoacridine[21] (**VIII**) was synthesized by the condensation of 9-chloroacridine with 2-aminopyridine. The structure of pyridinoacridine **VIII** is confirmed by ^{1}H NMR and HRMS reported in Table-I.

All the compounds synthesized were screened for *in vitro* inhibition of HIV-1 replication in MT-4 blood lymphocytes. They were found to be inactive at concentrations below 100μM as compared to the standard drug AZT which has an IC_{50} value for anti-HIV activity around 0.1μM. These compounds were also toxic at 100μM concentrations against uninfected MT-4 cells.

EXPERIMENTAL

The melting points, determined on a JSGW apparatus are uncorrected. ^{1}H NMR spectra were recorded on approximately 5–15%(w/v) solution in appropriate deuterated solvents with tetramethylsilane as internal standard. Line positions are recorded in ppm from the reference. The MS spectrometer peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000. TLC was performed by using silica gel G (Merck) and spots were visualized by iodine vapour or by irradiation with U.V. light 254 nm. Silica gel (60–120 mesh) was used for column chromatography.

Synthesis of Pyrimidobenzimidazole Derivative (I)

3,4-Diaminobenzophenone (2.1 gm., 10.0 m mol) was dissolved in methanol (50 ml) and to it was added 4-methyl-4-isothiocyanato-2-pentanone (2 ml; 0.013 mol). The reaction contents were allowed to stand at R.T. for 48 h. White coloured solid separated out which was filtered and crystallized from methanol. Yield 2.9 gm; m.p. 208°C. The solid compound obtained above was dissolved in MeOH (250 ml) and to it was added conc. sulphuric acid and the pH was about 3–4. The reaction mixture was heated under reflux for 6 h. Solvent was removed under reduced pressure and to the residue left behind was added sodium carbonate solution. The solid so obtained was filtered washed with water and air dried. The crude product was crystallized from THF to give pyrimidobenzimidazole derivative (**I**). Yield 2.4gm (68%) m.p. 222°C. ^{1}H NMR and HRMS is reported in Table-I.

Synthesis of Pyrimidobenzimidazole Derivative (II)

Pyrimidobenzimidazole derivative (**I**) (351 mg; 1.0 m mol) was taken in THF (30 ml) and to it was added anhydrous potassium carbonate (210 mg) and ethylbromoacetate (0.2 ml; 1.2 m mol). The reaction contents were heated under reflux for 10 h. The reaction contents were then cooled, filtered and solid residue left behind was washed with THF. The solvent from the filtrate was removed under reduced pressure. To the residue left behind was added methanol (5 ml), the solid crystalline product separated out. It was filtered and washed with methanol. The solid compound was recrystallized from THF/MeOH to give pure compound **II**. Yield 300 mg (69%) m.p. 125°C, ^{1}H NMR and HRMS of compound **II** is reported in Table-I.

Synthesis of Pyrimidoanthraquinonimidazole (III)

Compound **III** was synthesized according to the method reported earlier[15].

Synthesis of Bis Coupled 2-Amino-2-thiazoline Deuteroporphyrin (IX) Derivative (IV)

Deuteroporphyrine (IX) dicarboxylic acid (102 mg; 0.2 m mol), 1,1′-carbonyldiimidazole (98 mg; 0.6 m mol) were dissolved in dry DMF (15 ml) and stirred at R.T. for 4 h. 2-Amino-2-thiazoline (61 mg; 0.6 m mol) was added to the reaction mixture and stirring was further continued for 60 h. The reaction mixture was filtered and solid residue left behind on the filter paper was washed with THF. Solvent from the filtrate was removed under reduced pressure and the residue left behind was diluted with water. The insoluble compound was filtered and washed with methanol to give bis coupled product **IV**. Compound **IV** was crystallized from DMF/water and washed with methanol. Yield 81 mg (60%) m.p. 220°(d). ^{1}H NMR and FAB MS of compound **IV** is reported in Table-I.

Synthesis of Acridone Derivative (V)

5,8-Dimethoxy-1-tetralone (206 mg; 1.0 m mole) and anthranilic acid (274 mg; 2.0 m mol) were taken in n-butanol (7 ml) and to it was added anhydrous zinc chloride (400 mg). The reaction contents were heated under reflux for 3 days and then filtered to remove zinc chloride and washed with methanol. The filtrate was concentrated under reduced pressure. The residue left behind was dissolved in ethyl acetate and treated with 5% hydrochloric acid and filtered. The organic layer was washed with water, sodium bicarbonate and then with water, dried over sodium sulphate and the solvent removed on a water bath. The solid residue left behind was subjected to column chromatography over silica gel. Elution with chloroform: ethylacetate (8:2) gave acridone derivative **V**. Yield 92 mg (30%), m.p. 205°C. ^{1}H NMR and HRMS of **V** is reported in Table-I.

Synthesis of Thiazolinoacridine Derivative (VI)

9-Chloroacridine (426 mg, 2.0 m mol) was dissolved in methanol (50 ml) and to it was added 2-imino-3,4-diphenyl-4-thiazoline (504 mg; 2.0 m mol). The reaction contents were heated under reflux for 10 h. and then solvent was removed under reduced pressure. The solid residue left behind was dissolved in benzene (50 ml) and the insoluble material was filtered, washed with benzene and air dried. This solid was found to be 2-imino-3,4-diphenyl-4-thiazoline hydrochloride (250 mg). The benzene solution was concentrated and subjected to column chromatography over silica gel. Elution with chloroform gave yellow coloured solid compound **VI**. Yield 180 mg (40%); m.p. 185–90°C. ^{1}H NMR and HRMS of compound **VI** is reported in Table-I.

Condensation of 2-Amino-2-Thiazoline with 9-Chloroacridine (VII)

9-Chloroacridine (426 mg; 2.0 m mol) was dissolved in methanol (50 ml) and to it was added 2-amino-2-thiazoline (306 mg; 3.0 m mol). The reaction mixture was heated under reflux for 16 h. The crystalline solid that separated out was filtered. The filtrate was evaporated and the residue left behind was subjected to column chromatography over silica gel. Elution with hexane: chloroform (2:8) gave orange coloured compound **VII**, which was crystallized from methanol yield 165 mg (30%), m.p. 192–5°C. ^{1}H NMR and HRMS of **VII** is reported in Table-I.

Condensation of 2-Aminopyridine with 9-Chloroacridine (VIII)

9-Chloroacridine (426 mg; 2.0 m. mol) was dissolved in methanol (30 ml) and to it was added 2-aminopyridine (190 mg; 2.0 m mol). The reaction contents were heated under reflux for 8 h. and then solvent was removed under reduced pressure. The solid residue left behind was stirred with sodium carbonate (10%; 10 ml) for 30 minutes and then filtered, washed with water and air dried. The crude product so obtained was crystallized from $CHCl_3$ to give orange yellow solid compound **VIII**. Yield 130 mg (30%), m.p 180°C. ^{1}H NMR and HRMS of **VIII** is reported in Table-I.

In Vitro Inhibition of HIV-1 Replication in MT-4 Blood Lymphocytes

All the compounds synthesized (Chart-1) were tested for their ability to inhibit HIV-1 infected cell culture in comparison with the drug reference AZT. The fusogenic effect of HIV in the MT-4 cell line[21] was determined as described by Desolms et al.[22] and Rey et al.[23] A total of 3×10^5 MT-4 cells was infected with 100 µL of diluted virus for 1h at 37°C. After three washes, the infected cells were cultured in 24-well cell culture plates in the presence of the inhibitor. The appearance of syncitia was measured with an inverted optical microscope five days after infection. The inhibitory concentration was expressed as concentration of tested compound which causes 50% inhibition of syncitia formation (IC_{50}) but was not toxic for the cells. For toxicity testing three replication cultures of each uninfected MT-4 cells (2×10^5 cells) were incubated with various concentrations of the drugs. Cell viability was determined 6 days from drug addition by Trypan blue exclusion.

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