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Synthesis of heterocyclic and non-heterocyclic entities as antibacterial and anti-HIV agents

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3,4-dimethoxy-1-[{(2-aryl/alkyl amino)-2-oxoethyl} amino]-ethylbenzene **4a-o** and 2-[{2-(3,4-dimethoxy phenyl ethyl amino)-2-oxo ethyl}amino]-4,6-diaryl pyrimidines **5a-o** have been synthesized and tested for their antibacterial and anti-HIV activities against different microorganisms. The structures of novel synthesized compounds have been established on the basis of elemental analyses, ^{1}H NMR, IR and mass spectral data.

Keywords: *N*-Chloroacetanilides, heterocyclic amines, non-heterocyclic amines, antibacterial activity, anti-HIV activity

IPC Code: Int.Cl.[8] C07D

Literature survey reveals that phenylethylamine derivatives possess a broad spectrum of biological activity and fulfill an important function in animal metabolism[1]. Synthetic beta-phenylethylamines are the key substances in the synthesis of a number of isoquinoline alkaloids: 1-benzylisoquinolines, *N*-benzylisoquinolines, aporphines, and diisoquinolines[2]. These compounds are used in the synthesis of anti-HIV compounds, pig kidney aldose reductase,[3] schizophrenic[4], also chloro acetyl derivatives posses local anaesthetic[5], herbicides[6], antibiotic[7], anticancer, anti-HIV[8], spasmolytic and anti-epileptic[9], 5-HT_{1A} antagonist[10], antitumor[11], antibacterial[12] and anti-fungal[13] activities. A wide spectrum of biological activities *viz.*, anti-inflammatory[14], antibacterial[15], analgesic, antitubercular, and hypothermic[16], anti-AIDS,[17] antifungal[18] and antituberculosis[19] activities are found to be associated with compounds having pyrimidine moiety.

The required starting compounds 2-amino-4,6-diaryl-pyrimidines were prepared by known method[20], *N*-chloroacetanilide derivatives of amines including 3,4-dimethoxy phenyl ethyl amine were prepared by condensing amine, chloroacetylchloride and triethyl-amine, **Table I**[21]. Various non-heterocyclic entities 3,4-dimethoxy-1-[{(2-aryl/alkyl amino)-2-oxoethyl} amino]-ethylbenzenes[22] **4a-o** (**Scheme I**, **Table II**) were prepared by condensing *N*-chloroacetanilide derivatives of various amine and 3,4-dimethoxy phenyl ethyl amine as well as various heterocyclic entities 2-[{2-(3,4-dimethoxy phenylethylamino)-2-oxoethyl}amino]-4,6-diaryl pyrimidines[22] **5a-o** (**Scheme I**, **Table III**) were prepared by condensing 2-amino-4,6-diaryl-pyrimidines and *N*-chloroacetyl-3,4-dimethoxy phenyl ethyl amine.

The compounds were screened for their HIV-1 and HIV-2 inhibitory activities as per reported method[25], using strains HIV-1 (IIIB) and HIV-2 (ROD). The IC_{50}, CC_{50} values were determined for newly synthesized 23 compounds. During study of both series of compounds **4a-o** and **5a-o**, preliminary findings show that ethyl linker shows increase in the anti-HIV activities.

Experimental Section

Melting points were determined on an electro thermal apparatus (capillary method) and are uncorrected. IR spectra were recorded on a FT "Bommen" spectrometer using potassium bromide. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer using TMS as internal standard (chemical shift δ, ppm). Elemental analyses were done on "Haraeus Rapid Analyser".

Preparation of *N*-chloroacetyl aryl/alkyl amines 3a-o (ref. 21). In benzene (30 mL), chloroacetyl-chloride (0.03 mole , 3.3g, 2.4 mL) was added and the mixture was stirred in water-bath. The solution of aryl amines (0.02 mole) in benzene (30 mL) was added

Table I—Characterization data of the compounds **3a-o**

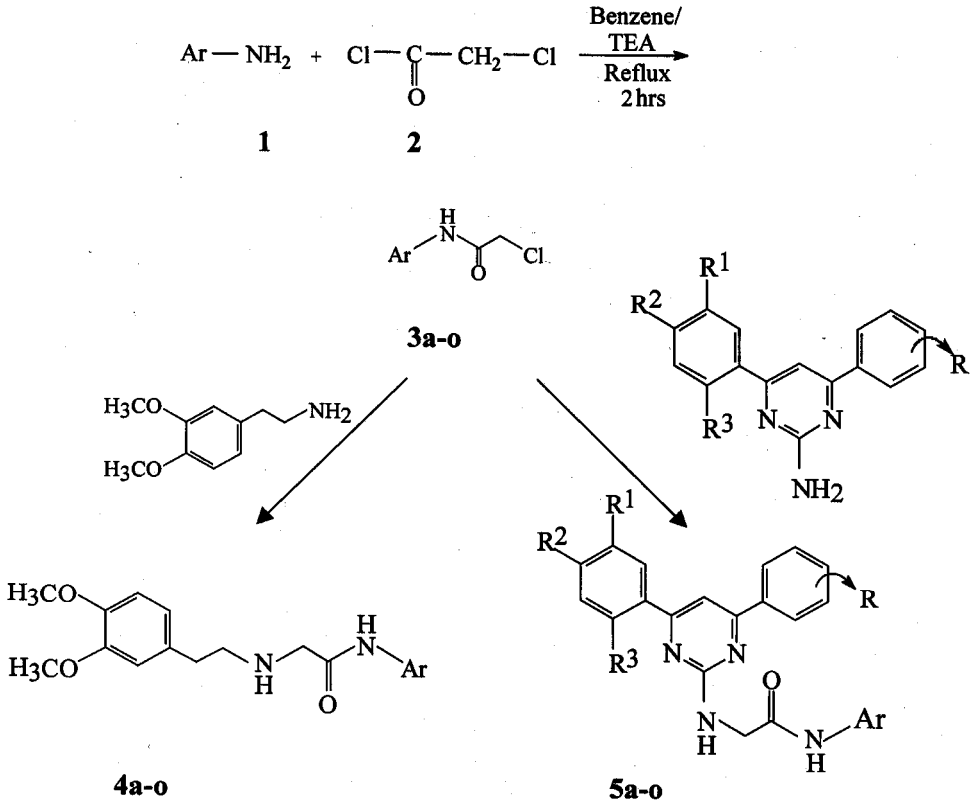
S. No.	Ar	Mol. formula	m.p. ^{0}C	Mol. Weight	Yield (%)
1	C_6H_5	C_8H_8NOCl	87-91	169.5	80
2	$CH_2C_6H_5$	$C_9H_{10}NOCl$	92-95	183.5	90
3	$C_{10}H_7$	$C_{12}H_{10}NOCl$	155-57	219.5	88
4	2-$OCH_3C_6H_4$	$C_9H_{10}NO_2Cl$	Limpid	199.5	85
5	4-$OCH_3C_6H_4$	$C_9H_{10}NO_2Cl$	106-10	199.5	86
6	2-$CH_3C_6H_4$	$C_9H_{10}NOCl$	87-90	183.5	81
7	3-$CH_3C_6H_4$	$C_9H_{10}NOCl$	85-90	183.5	88
8	4-$CH_3C_6H_4$	$C_9H_{10}NOCl$	163-65	183.5	82
9	2-$NO_2C_6H_4$	$C_8H_7N_2O_3Cl$	91-92	214.5	79
10	3-$NO_2C_6H_4$	$C_8H_7N_2O_3Cl$	90-93	214.5	70
11	4-$NO_2C_6H_4$	$C_8H_7N_2O_3Cl$	118-20	214.5	69
12	2-ClC_6H_4	$C_8H_7NOCl_2$	68-70	204	82
13	3-ClC_6H_4	$C_8H_7NOCl_2$	87-92	204	79
14	4-ClC_6H_4	$C_8H_7NOCl_2$	150-55	204	83
15	4-FC_6H_4	C_8H_7NOClF	114-16	187.5	87
16	HVA	$C_{12}H_{15}NO_3Cl$	85-87	257.68	89

dropwise and refluxed for two hr. Then cooled the reaction mixture. The resulting white precipitates were filtered and washed with benzene, purified by recrystallization from alcohol. Physical data of *N*-chloroacetyl aryl amines are given in **Table I**.

Preparation of 3,4-dimethoxy-1-[{(2-aryl/alkyl amino)-2-oxoethyl} amino]-ethylbenzene 4a-o (ref. 22). In pyridine (30 mL), a mixture of *N*-chloroacetyl aryl/alkyl amines (0.02 mole) and 3,4-dimethoxy phenyl ethyl amine (0.02 mole) was refluxed for four hr. Excess of pyridine was distilled off. The resulting residue was poured in ice-cooled water to obtain crude product. It was extracted with CH_2Cl_2 (30× 3 mL). After evaporation of CH_2Cl_2 at room temp., the final product was separated. The progress of reaction was monitored by TLC using acetone-toluene (10:1) as eluent. The physical and analytical data of novel compounds are given in **Table II**.

The spectral data of the novel synthesized compounds **4a-o** are given below.

4a: Mass**,** m/z: 313 (M^+); ^{1}H NMR (DMSO-d_6. δ) 2.80 (t, *J*=12, 14, 2H, -CH_2**),** 3.46(t, *J*=13, 15, 2H,



Scheme I

Table II—Characterization data of the compounds **4a-o**

S. No.	Ar	Mol. Formula	m. p. °C	Yield (%)	Calcd (Found)% C	H	N
4a	C_6H_5	$C_{18}H_{22}N_2O_3$	Limpid	75	68.74 (68.62	7.00 6.93	8.91 8.84)
4b	$CH_2C_6H_5$	$C_{19}H_{24}N_2O_3$	Limpid	76	69.46 (69.35	7.31 7.22	8.53 8.36)
4c	$C_{10}H_7$	$C_{22}H_{24}N_2O_3$	Limpid	68	72.48 (72.19	6.59 6.39	7.69 7.57)
4d	2-$OCH_3C_6H_4$	$C_{19}H_{24}N_2O_4$	Limpid	70	66.23 (66.13	6.97 6.85	8.13 8.05)
4e	4-$OCH_3C_6H_4$	$C_{19}H_{24}N_2O_4$	Limpid	59	66.23 (66.03	6.97 6.87	8.13 8.00)
4f	2-$CH_3C_6H_4$	$C_{19}H_{24}N_2O_3$	65-70	60	69.46 (69.29	7.31 7.21	8.53 8.41)
4g	3-$CH_3C_6H_4$	$C_{19}H_{24}N_2O_3$	Limpid	67	69.46 (69.25	7.31 7.18	8.53 8.34)
4h	4-$CH_3C_6H_4$	$C_{19}H_{24}N_2O_3$	Limpid	79	69.46 (69.22	7.31 7.13	8.53 8.34)
4i	2-$NO_2C_6H_4$	$C_{18}H_{21}N_3O_5$	110-12	74	60.12 (60.00	5.86 5.69	11.69 11.54)
4j	3-$NO_2C_6H_4$	$C_{18}H_{21}N_3O_5$	165-67	65	60.12 (60.01	5.86 5.67	11.69 11.59)
4k	4-$NO_2C_6H_4$	$C_{18}H_{21}N_3O_5$	180-85	77	60.12 (60.01	5.86 5.77	11.69 11.55)
4l	2-ClC_6H_4	$C_{18}H_{21}N_2O_3Cl$	40-45	62	61.94 (61.54	6.02 5.87	8.03 7.89)
4m	3-ClC_6H_4	$C_{18}H_{21}N_2O_3Cl$	Limpid	62	61.94 (61.59	6.02 5.94	8.03 7.85)
4n	4-ClC_6H_4	$C_{18}H_{21}N_2O_3Cl$	Limpid	56	61.94 (61.87	6.02 5.90	8.03 7.93)
4o	4-FC_6H_4	$C_{18}H_{21}N_2O_3F$	Limpid	73	65.03 (64.92	6.32 6.25	8.43 8.29)

-CH_2) 7.56 (m, 1H, -NH) 2.77 (s, 2H-CH_2**)** 8.21 (s, 1H, -NH) 3.75 (s, 6H, 2 × -OCH_3) 6.60-7.17 (m, 8H, Ar-H) **4b**: 2.69 (t, *J*=12, 14, 2H, -CH_2), 3.23 (t, *J*=12, 14, 2H, -CH_2), 7.49 (m, 1H, -NH), 2.83 (s, 2H, -CH_2), 8.41 (s, 1H, -NH**)**, 3.69 (s, 2H, -CH_2), 3.74 (s, 6H, 2 ×-OCH_3) 6.31 (d, *J*=7, 1H, Ar-H), 6.46 (d, *J*=10, 1H, Ar-H) **4c**: 2.70 (t, *J*=13, 15, 2H, -CH_2), 3.40 (t, *J*=13, 14, 2H, -CH_2), 7.59 (m, 1H, -NH), 2.80 (s, 2H, -CH_2), 8.40 (s, 1H, -NH**)**, 3.74 (s, 6H, 2 × -OCH_3) 6.66 (d, *J*=8, 1H, Ar-H), 6.81 (d, *J*=10, 1H, Ar-H), 8.21 (d, 1H, Ar-H) 7.20-8.0 (m, 7H, Ar-H) **4e**: 2.72 (t, *J*=12, 13, 2H, -CH_2), 3.20 (t, *J*=12, 14, 2H, -CH_2), 7.52 (m,1H, -NH), 2.79 (s, 2H, -CH_2), 8.21 (s, 1H, -NH**)**, 3.82(s,9H, 3 × -OCH_3) 6.90 (d, *J*=8, 1H, Ar-H), 7.10 (d, *J*=9, 1H, Ar-H), 4.41 (s, 1H, Ar-H), 7.90-8.00 (m, 4H, Ar-H) **4f**: 2.82 (t, *J*=13, 15, 2H, -CH_2), 3.68 (t, *J*=12, *J*=14, 2H, -CH_2), 7.66 (m, 1H, -NH), 2.75 (s, 2H, -CH_2), 8.24 (s, 1H, -NH**)**, 2.36 (s, 3H, -CH_3), 3.73 (s, 6H, 2 ×-OCH_3**)** 6.57 (d, *J*=6, 1H, Ar-H), 6.76 (d, *J*=9, 1H, Ar-H), 4.20 (Br.s, 1H, Ar-H), 7.07-7.17 (m, 4H, Ar-H) **4k**: 2.75 (t, *J*=13, 15, 2H, -CH_2**),** 3.25 (t, *J*=14, 15, 2H, -CH_2**)** 7.60 (m, 1H, -NH) 2.80 (s, 2H-CH_2**)** 8.41 (s, 1H, -NH) 3.77 (s, 6H, 2 × -OCH_3) 6.60-7.20 (m, 7H, Ar-H) **4n**: 2.84 (t, *J*=13, 15, 2H, -CH_2**),** 3.25 (t, *J*=12, 14, 2H, -CH_2**)** 7.60 (m, 1H, -NH) 2.78 (s, 2H-CH_2**)** 8.21 (s, 1H, -NH) 3.78 (s, 6H, 2 ×-OCH_3) 6.56 (d, *J*=9, 1H, Ar-H) 6.76 (d, *J*=10, 1H, Ar-H) 4.20(Br.s, 1H, Ar-H) 7.0-7.20 (m, 4H, Ar-H).

2-[{2-(3,4-dimethoxy phenyl ethyl amino)-2-oxo ethyl}amino]- 4,6-diarylpyrimidines 5a-o (ref. 23). A solution of 2-amino-4,6-diaryl-pyrimidines (0.005 mole) and *N*-chloroacetyl-3,4-dimethoxy phenyl ethyl amine (0.005 mole) in pyridine (50 mL) was refluxed for 4-7 hr. After completion of reaction, excess of

Table III—Characterization data of the compounds **5a-o**

S. No.	R^1	R^2	R^3	R	Mol. Formula	m.p. °C	Yield (%)	Calcd (Found) % C	H	N
5a	F	Cl	Cl	H	$C_{28}H_{25}N_4O_3Cl_2F$	211-12	73	60.49 (60.20	4.50 4.35	10.08 10.00)
5b	F	Cl	Cl	3-OC_6H_5	$C_{34}H_{29}N_4O_4Cl_2F$	195-200	69	63.00 (62.75	4.47 4.30	8.65 8.49)
5c	F	Cl	Cl	3,4,5-$(OCH_3)_3$	$C_{31}H_{31}N_4O_6Cl_2F$	180-85	77	57.60 (57.30	4.80 4.61	8.67 8.48)
5d	F	Cl	Cl	4-$N(CH_3)_2$	$C_{30}H_{30}N_5O_3Cl_2F$	205(d.)	60	60.15 (60.00	5.01 4.92	11.69 11.59)
5e	F	Cl	Cl	4-OCH_3	$C_{29}H_{27}N_4O_4Cl_2F$	125-30	67	59.45 (59.25	4.61 4.52	9.57 9.42)
5f	F	Cl	Cl	2-Cl	$C_{28}H_{24}N_4O_3Cl_3F$	160-62	66	56.95 (56.65	4.07 3.92	9.49 9.35)
5g	F	Cl	Cl	3-Cl	$C_{28}H_{24}N_4O_3Cl_3F$	145-50	62	56.95 (56.67	4.07 3.95	9.49 9.40)
5h	F	Cl	Cl	3-Br	$C_{28}H_{24}N_4O_3Cl_2BrF$	150-55	72	52.96 (52.69	3.78 3.60	8.83 8.66)
5i	H	Cl	H	H	$C_{28}H_{27}N_4O_3Cl$	140-42	54	66.79 (66.50	5.37 5.20	11.13 11.03)
5j	H	Cl	H	3-OC_6H_5	$C_{34}H_{31}N_4O_4Cl$	155-56	55	68.56 (68.30	5.21 5.10	9.41 9.31)
5k	H	Cl	H	3,4,5-$(OCH_3)_3$	$C_{31}H_{33}N_4O_6Cl$	148-50	79	62.71 (62.53	5.56 5.37	9.44 9.29)
5l	H	Cl	H	4-$N(CH_3)_2$	$C_{30}H_{32}N_5O_3Cl$	145-50	57	65.94 (65.66	5.86 5.69	12.82 12.77)
5m	H	Cl	H	4-OCH_3	$C_{28}H_{29}N_4O_4Cl$	158-59	76	63.01 (62.72	5.44 5.31	10.50 10.37)
5n	H	Cl	H	3-Cl	$C_{28}H_{26}N_4O_3Cl_2$	160-62	70	62.42 (62.17	4.83 4.65	10.40 10.25)
5o	H	Cl	H	3-Br	$C_{28}H_{26}N_4O_3ClBr$	170-72	64	57.73 (57.51	4.47 4.37	9.62 9.45)

pyridine was distilled off and resulting solid was treated with methanol (60 mL) to give the white crystals of the title compounds. The resulting crystals were filtered and washed with methanol and water. The progress of reaction was monitored by TLC using benzene-pyridine (10:1) as eluent. The physical and analytical data of novel title compounds are given in **Table III**.

The spectral data of the novel synthesized compounds **5a-o** are given below.

5a: Mass, m/z: 554 (M^+); ^{1}H NMR (DMSO- d_6, δ) 2.65 (t, *J*=13, 15, 2H, -CH_2), 3.26 (m, 2H, -CH_2) 9.45 (m, 1H, -NH) 2.84 (s, 2H-CH_2) 6.70 (Br. s, 1H, -NH) 3.80 (s, 6H, 2 × -OCH_3) 6.91 (d, *J*=8, 1H, Ar-H) 7.12 (d, *J*=10, 1H, Ar-H) 4.41 (s, 1H, Ar-H) 7.80-8.10 (m, 8H, Ar-H); **5b**: 2.68 (t, *J*=13, 15, 2H, -CH_2), 3.27 (q, *J*=12, 14, 15, 2H,-CH_2), 9.40 (s,1H, -NH), 2.85 (s, 2H, -CH_2) 6.72 (s, 1H, -NH) 3.82 (s, 9H, 3 ×-OCH_3) 6.80 (d, *J*=6, 1H, Ar-H) 7.10 (d, *J*=8, 1H, Ar-H) 4.42 (s, 1H, Ar-H) 7.90-8.20 (m, 12H, Ar-H)**;** **5c**: 2.73 (t, *J*=12, 14, 2H, -CH_2), 3.25 (m, 2H,-CH_2), 9.44 (s,1H, -NH), 2.84 (s, 2H, -CH_2) 6.76 (s, 1H, -NH) 3.60 (s, 6H, 2 ×-OCH_3) 3.80 (s, 6H, 2 ×-OCH_3) 3.90 (s, 3H, Ar- OCH_3) 7.10-8.00 (m, 8H, Ar-H)**;** **5d**: 2.72 (t, *J*=12, 15, 2H, -CH_2), 3.28 (q, *J*=13, 14, 15, 2H,-CH_2), 9.43 (s,1H, -NH), 2.87 (s, 2H, -CH_2) 6.74 (s, 1H, -NH) 3.84(s, 6H, 2 ×-OCH_3) 2.84 (s, 6H, -$N(CH_3)_2$) 7.10 (d, *J*=8, 1H, Ar-H) 4.41 (s, 1H, Ar-H) 7.49 (d, *J*=7, 2H, Ar-H) 7.65 (d, *J*=9, 2H, Ar-H) 7.90-8.20 (m, 5H, Ar-H)**;** **5m**: 2.70 (t, *J*=12, 15, 2H, -CH_2), 3.25 (m, 2H,-CH_2), 9.45 (s,1H, -NH), 2.85 (s, 2H, -CH_2) 6.71 (Br.S., 1H, -NH) 3.82 (s, 9H, 3 ×-OCH_3) 6.90 (d, *J*=6, 1H, Ar-H) 7.10 (d, *J*=10, 1H, Ar-H) 4.41 (s, 1H, Ar-H) 7.49 (d, *J*=8, 2H, Ar-H) 7.65 (d, *J*=9, 2H, Ar-H) 7.90-8.20 (m, 5H, Ar-H); **5n**: 2.64 (t, *J*=12, 15, 2H, -CH_2), 3.33 (m, 2H, -CH_2), 9.40 (s, 1H, -NH), 2.80 (s, 2H, -CH_2) 6.85 (Br. s,1H, -NH), 3.82 (s, 6H, 2 × -OCH_3), 6.87 (d, *J*=6, 1H, Ar-H), 7.00 (d, *J*=9, 1H, Ar-H) 4.50 (s, 1H, Ar-H), 7.47 (d, *J*=8, 2H, Ar-H) 7.85 (d, *J*=10, 2H, Ar-H) 8.18-8.40 (m, 5H, Ar-H).

Antimicrobial activity. The compounds synthesized are screened for various biological-screening programmes. The various screening programmes carried out include the *in vitro* study against Gram-positive and Gram-negative bacteria *viz. E.coli*, *S.aureus*, *S.typhi*, *B.subtilis* and also *in vitro* anti-HIV study against human immunodeficiency virus (HIV) using different cell lines like IIIB=HIV-1 and ROD-HIV-2.

The antibacterial activity was determined using cup-plate agar diffusion method[23, 24] by measuring the inhibition zones in mm. The compounds were screened for their HIV-1 and HIV-2 inhibitory activities as per reported method[25]. All the compounds were subjected to the various screening programmes. This series contain amino-amide linkage with homoveratrylamine through different types of *N*-chloroacetanilides.

In antibacterial activity, media control, organism control and solvent control have been used. For anti-HIV activity MTT assay[25] control has been used. DMF was taken as a solvent for solubilization.

Conclusion

SAR studies

Antibacterial activity. Parent compound showed moderate activity against *E.coli*, *S.aureus*, *S.typhi* and *B.subtilis,* but in case of amino-amide linkage with parent compound through nitrogen much deviation of activity from the parent molecule has been observed.

Amino-amide linkage showed so much increase in the biological activity. Some of the compounds showed comparable activity against standard drug but others found moderate or inactive. Compounds **4e** for *E.coli*, **4o** for *S.aureus*, **4g** for *S.typhi* and *B.subtilis* exhibited maximum zone of inhibition 13 mm, 15 mm, 14 mm and 20 mm respectively (**Table IV**). Compound no. **4g** with 3-tolyl group showed maximum zone of inhibition (20 mm) too near from standard drugs (tetracycline 21 mm and chloramphenicol 20 mm).

As shown above, this series also contain amino-amide linkage connected to the 2-amino-4,6-diaryl pyrimidine derivatives. All the novel compounds were subjected to the various screening programmes.

The novel heterocyclic amino-amide linkage with ethyl spacer showed excellent increase in activity from the parent compound.

Results of the antibacterial screening showed that the all compounds exhibited comparable activity (**Table V**). Compounds **5c**, **5l** showed maximum zone of inhibition (17 mm) against *E.coli*, compounds **5a**, **5b** and **5l** showed maximum zone of inhibition (10 mm) against *S.aureus*, compound **5i** showed maximum zone of inhibition (11 mm) against *S.typhi* whereas compound **5b** showed maximum zone of inhibition (14 mm) against *B.subtilis*.

Anti-HIV activity. We have described a series of compounds, which belongs to NNRTIs. All the compounds were tested in HIV-1 (IIIB) and HIV-2 (ROD) RT enzyme assays. All the present compounds in this series can be divided into four groups: (i) phenyl ethyl derivatives, (ii) amino-amide linkage and (iii) substituted phenyl ring/pyrimidine ring.

Compound **4a** with a phenyl ring was most active on HIV-1 (IIIB) and compound **4m** with a 3-chloro phenyl ring was most active on HIV-2 (ROD) as its selectivity index (SI) is 9 and 4 respectively while other compounds of the series showed poor activity as its selectivity index is less than one (**Table VI**).

It was found in primary findings that the central ethyl linkage showed some effect on the anti-HIV activity. However, some of the compounds do not seem to improve the potency. This may suggest that though such compounds are identified as NNRTIs show poor HIV-1 and HIV-2 activity as the selectivity index is less than one. As shown in **Table VI**, some of the compounds like **5a**, **5k**, **5m** and **5o** showed moderate to very good HIV-2 activity against ROD cell culture as their selectivity index (SI) is >15, >2, >17 and >16 respectively while poor active against HIV-1 as their SI is less than one.

The antimicrobial screening of the novel synthesized compounds revealed that the introduction of methoxy group and fluoro group at *p*-position while methyl group at *m*-position on phenyl ring of 3,4-dimethoxy-1-[{(2-arylamino)-2-oxoethyl}amino]-ethyl benzene gave compounds with increase in antibacterial activity. The above results suggest that *p*-substitution correlates with better antibacterial activity. Among them *p*-methoxy is the substituent conferring the highest activity at the strain studied.

The SAR studies were extended to assess the effect of a variety of substituents bound to the *ortho*, *meta* and *para* position of phenyl ring for anti-HIV activities. The encouraging results obtained with unsubstituted and *o*-chloro monosubstituted derivatives, and the high anti-HIV (IIIB) and HIV-2 (ROD) activity shown by some of the NNRT's. Phenyl ring without substituent showed good activity on HIV-1 (IIIB) while *o*-chloro phenyl ring showed high

Table IV—Antibacterial activity of compounds **4a-o**

S. No.	Ar	Antibacterial activity Zone of inhibition in mm (50μg/mL)			
		E. coli	*S. aureus*	*S. typhi*	*B. subtilis*
4a	C_6H_5	---	11	09	---
4b	$CH_2C_6H_5$	---	09	---	---
4c	$C_{10}H_7$	---	---	08	---
4d	2-$OCH_3C_6H_4$	---	09	12	10
4e	4-$OCH_3C_6H_4$	13	11	10	10
4f	2-$CH_3C_6H_4$	---	---	09	---
4g	3-$CH_3C_6H_4$	---	12	14	20
4h	4-$CH_3C_6H_4$	10	10	09	---
4i	2-$NO_2C_6H_4$	09	09	08	09
4j	3-$NO_2C_6H_4$	10	11	10	10
4k	4-$NO_2C_6H_4$	10	09	---	---
4l	2-ClC_6H_4	12	12	09	09
4m	3-ClC_6H_4	12	09	09	13
4n	4-ClC_6H_4	12	14	11	10
4o	4-FC_6H_4	---	15	12	---
Standard drugs	tetracycline	15	19	24	21
	chloramphenicol	18	25	24	20

Table V—Antibacterial activity of compounds **5a-o**

S. No.	R^1	R^2	R^3	R	Antibacterial activity Zone of inhibition in mm (50μg/mL)			
					E. coli	*S. aureus*	*S. typhi*	*B. subtilis*
5a	F	Cl	Cl	H	09	10	---	---
5b	F	Cl	Cl	3-OC_6H_5	15	10	10	14
5c	F	Cl	Cl	3,4,5-$(OCH_3)_3$	17	---	---	---
5d	F	Cl	Cl	4-N-$(CH_3)_2$	12	09	---	---
5e	F	Cl	Cl	4-OCH_3	11	08	---	---
5f	F	Cl	Cl	2-Cl	13	09	10	---
5g	F	Cl	Cl	3-Cl	12	10	09	---
5h	F	Cl	Cl	3-Br	11	---	---	---
5i	H	Cl	H	H	12	---	11	---
5j	H	Cl	H	3-OC_6H_5	---	---	09	---
5k	H	Cl	H	3,4,5-$(OCH_3)_3$	---	08	---	09
5l	H	Cl	H	4-N-$(CH_3)_2$	17	10	09	10
5m	H	Cl	H	4-OCH_3	11	09	10	---
5n	H	Cl	H	3-Cl	14	09	09	---
5o	H	Cl	H	3-Br	13	08	---	08
Standard drugs				tetracycline	15	19	24	21
				chloramphenicol	18	25	24	20

Table VI—Anti-HIV activity of compounds **4a-o** and **5a-o**

S. No.	Strain	Exp_No	IC_{50} (µg/mL)	CC_{50} (µg/mL)	*SI	Max Prot	Appr.	av.IC_{50} (µg/mL)	SD	av.CC_{50} (µg/mL)	SD	*SI
4a	IIIB	P3.3722	=10.2	=64.8	=6	78	1					
		P3.3725	=2.45	=35.5	=14	56	1	6.33	5.48	59.67	22.05	9
	ROD	P3.3726	>78.7	=78.7	<1	38	1	>59.67		59.67	22.05	<1
4b	IIIB	P3.3722	>82.2	=82.2	<1	15	1					
		P3.3725	>89.7	=89.7	<1	14	1	>88.87		88.87	6.29	<1
	ROD	P3.3726	>94.7	=94.7	<1	36	1	>88.87		88.87	6.29	<1
4c	IIIB	P3.3722	>89.8	=89.8	<1	20	1					
		P3.3725	>85.4	=85.4	<1	18	1	>86.70		86.70	2.70	<1
	ROD	P3.3726	>84.9	=84.9	<1	47	1	>86.70		86.70	2.70	<1
4d	IIIB	P3.3722	>17.1	=17.1	<1	18	1					
		P3.3725	>15.4	=15.4	<1	2	1	>16.23		16.23	0.85	<1
	ROD	P3.3726	>16.2	=16.2	<1	1	1	>16.23		16.23	0.85	<1
4e	IIIB	P3.3722	>18.3	=18.3	<1	24	1					
		P3.3725	>9.73	=9.73	<1	4	1	>15.51		15.51	5.01	<1
	ROD	P3.3726	>18.5	=18.5	<1	2	1	>15.51		15.51	5.01	<1
4f	IIIB	P3.3722	>50.8	=50.8	<1	27	1					
		P3.3725	>22.7	=22.7	<1	4	1	>36.75		36.75	19.87	<1
	ROD	P3.3726	>25	>25	X 1	0	2	>36.75		36.75	19.87	<1
4g	IIIB	P3.3722	>11.2	=11.2	<1	13	1					
		P3.3725	>5.66	=5.66	<1	2	1	>10.75		10.75	4.89	<1
	ROD	P3.3726	>15.4	=15.4	<1	2	1	>10.75		10.75	4.89	<1
4h	IIIB	P3.3722	>14.3	=14.3	<1	20	1					
		P3.3725	>13.8	=13.8	<1	13	1	>15.13		15.13	1.89	<1
	ROD	P3.3726	>17.3	=17.3	<1	0	1	>15.13		15.13	1.89	<1
4i	IIIB	P3.3722	>125	>125	X 1	16	1					
		P3.3725	>113	=113	<1	16	1	>113		> or = 113		
	ROD	P3.3726	>125	>125	X 1	10	1					
4j	IIIB	P3.3722	>96.3	=96.3	<1	10	1					
		P3.3725	>96.2	=96.2	<1	8	1	>95.30		95.30	1.65	<1
	ROD	P3.3726	>93.4	=93.4	<1	4	1	>95.30		95.30	1.65	<1
4k	IIIB	P3.3722	>16.3	=16.3	<1	12	1					
		P3.3725	>19.1	=19.1	<1	13	1	>18.40		18.40	1.85	<1
	ROD	P3.3726	>19.8	=19.8	<1	11	1	>18.40		18.40	1.85	<1
4l	IIIB	P3.3722	>79	=79	<1	19	1					
		P3.3725	>96	=96	<1	30	1	>91.13		91.13	10.58	<1
	ROD	P3.3726	=24.8	=98.4	=4	50	1	24.8		91.13	10.58	4
4m	IIIB	P3.3722	>16.9	=16.9	<1	24	1					
		P3.3725	>18.4	=18.4	<1	38	1	>17.57		17.57	0.76	<1
	ROD	P3.3726	>17.4	=17.4	<1	33	1	>17.57		17.57	0.76	<1
4n	IIIB	P3.3722	>11	=11	<1	10	1					
		P3.3725	>4.06	=4.06	<1	18	1	>10.02		10.02	5.54	<1
	ROD	P3.3726	>15	=15	<1	11	2	>10.02		10.02	5.54	<1

Contd

Table VI—Anti-HIV activity of compounds **4a-o** and **5a-o**—(*Contd*)

S. No.	Strain	Exp_No	IC_{50} (µg/mL)	CC_{50} (µg/mL)	*SI	Max Prot	Appr.	av.IC_{50} (µg/mL)	SD	av.CC_{50} (µg/mL)	SD	*SI
4o	IIIB	P3.3722	>18	=18	<1	10	1					
		P3.3725	>16.3	=16.3	<1	24	1	>17.15		17.15	1.20	<1
	ROD	P3.3726	>25	>25	X 1	13	1	>17.15		17.15	1.20	<1
5a	IIIB	P3.3722	>125	>125	X 1	22	1					
		P3.3725	>125	>125	X 1	30	1	>125		>125		
	ROD	P3.3726	=8.22	>125	>15	71	2	8.22		>125		>15
5b	IIIB	P3.3722	>48.6	=48.6	<1	6	1					
		P3.3725	>61.4	=61.4	<1	3	1	>62.00		62.00	13.71	<1
	ROD	P3.3726	>76	=76	<1	4	1	>62.00		62.00	13.71	<1
5c	IIIB	P3.3722	>11.9	=11.9	<1	11	1					
		P3.3725	>14.5	=14.5	<1	15	1	>14.33		14.33	2.35	<1
	ROD	P3.3726	>16.6	=16.6	<1	2	1	>14.33		14.33	2.35	<1
5d	IIIB	P3.3722	>0.0955	=0.0955	<1	5	3					
		P3.3725	>0.0744	=0.0744	<1	1	1	>0.84		0.084	0.011	<1
	ROD	P3.3726	>0.083	=0.083	<1	0	1	>0.83		0.084	0.011	<1
5e	IIIB	P3.3722	>0.137	=0.137	<1	6	1					
		P3.3725	>0.0852	=0.0852	<1	0	1	>0.11		0.11	0.03	<1
	ROD	P3.3726	>0.0996	=0.0996	<1	9	1	>0.10		0.11	0.03	<1
5f	IIIB	P3.3722	>125	>125	X 1	14	1					
		P3.3725	>90.2	=90.2	<1	11	1	>90.2		> or = 90.2		
	ROD	P3.3726	>125	>125	X 1	25	1	>125		> or = 90.2		
5g	IIIB	P3.3722	>125	>125	X 1	16	1					
		P3.3725	>125	>125	X 1	15	1	>125		>125		
	ROD	P3.3726	>125	>125	X 1	27	2	>125		>125		
5h	IIIB	P3.3722	>125	>125	X 1	26	1					
		P3.3725	>125	>125	X 1	8	1	>125		>125		
	ROD	P3.3726	>125	>125	X 1	20	1	>125		>125		
5i	IIIB	P3.3722	>8.03	=8.03	<1	8	1					
		P3.3725	>13.9	=13.9	<1	9	1	>11.51		11.51	3.08	<1
	ROD	P3.3726	>12.6	=12.6	<1	0	1	>12.6		11.51	3.08	<1
5j	IIIB	P3.3722	>77	=77	<1	26	1					
		P3.3725	>83.2	=83.2	<1	5	1	>82.57		82.57	5.28	<1
	ROD	P3.3726	>87.5	=87.5	<1	2	1	>87.5		82.57	5.28	<1
5k	IIIB	P3.3722	>125	>125	X 1	20	1					
		P3.3725	>125	>125	X 1	7	1	>125		>125		
	ROD	P3.3726	=70.4	>125	>2	56	1	70.4		>125		>1
5l	IIIB	P3.3722	>15.2	=15.2	<1	6	1					
		P3.3725	>16.9	=16.9	<1	3	1	>16.80		16.80	1.55	<1
	ROD	P3.3726	>18.3	=18.3	<1	8	1	>18.3		16.80	1.55	<1
5m	IIIB	P3.3722	>125	>125	X 1	46	1					
		P3.3725	>117	=117	<1	27	1	>117		> or = 117		
	ROD	P3.3726	=7.54	>125	>17	154	1	7.54		> or = 117		

Contd

Table VI—Anti-HIV activity of compounds **4a-o** and **5a-o**—(*Contd*)

S. No.	Strain	Exp_No	IC_{50} (µg/mL)	CC_{50} (µg/mL)	*SI	Max Prot	Appr.	av.IC_{50} (µg/mL)	SD	av.CC_{50} (µg/mL)	SD	*SI
5n	IIIB	P3.3722	>17.7	=17.7	<1	38	1					
		P3.3725	>16.4	=16.4	<1	15	1	>18.10		18.10	1.93	<1
	ROD	P3.3726	>20.2	=20.2	<1	16	1	>20.2		18.10	1.93	<1
5o	IIIB	P3.3722	>125	>125	X 1	41	1					
		P3.3725	>125	>125	X 1	29	1	>125		>125		
	ROD	P3.3726	=7.9	>125	>16	151	1	7.9		>125		>16

EC_{50}= Effective concentration at 50 µg/mL; CC_{50}= Cytotoxic concentration at 50 µg/mL; IIIB=HIV-1 strain, ROD=HIV-2 strain; *SI=Selectivity Index; Max Prot= Maximum protection

activity on HIV-2 (ROD). In general, *meta* and *para* substitution gave derivatives with cytotoxicities and anti-HIV activities comparable to those of *ortho* and unsubstituted counterpart. Unsubstituted phenyl derivative (SI=9) was significantly more potent than *ortho*- (SI=4) counterpart.

From the biological results and discussion, it is revealed that electron-donating groups like 3,4,5-trimethoxy and *para*-*N*,*N*-dimethylamino attached to the phenyl ring at 6-position of pyrimidine nucleus showed maximum zone of inhibition in amino-amide linkage connected to homoveratryl amine. Some *meta*-substituted compounds like *meta*-phenoxy on phenyl ring at position-6 of pyrimidine nucleus also exhibit very good antibacterial activity. Results also indicate that 2,4-dichloro-5-fluoro substituents on phenyl ring of pyrimidine nucleus at position-4 correlate with the antibacterial activity better than the 4-chloro substituent on phenyl ring of pyrimidine nucleus at position-4.

In the case of anti-HIV activity, electron donating 3,4,5-trimethoxy group on phenyl ring of pyrimidine nucleus at position-6 increases its potency to that of parent compound. Results also revealed that compounds of this series showed HIV-2 (ROD) activity rather than HIV-1 (IIIB). In comparison with above series, presence of heterocyclic nucleus to amino-amide linkage exhibited high selectivity (SI=15, 16, 17) than the selectivity (SI=9,4, above series) of simple non-heterocyclic nucleus. It is concluded that the presence of heterocyclic ring to amino-amide linkage is beneficial for its selectivity for antiviral activity.

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