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A NEW APPROACH TO ANTI-HIV CHEMOTHERAPY DEVISED BY LINKING THE VITAL FRAGMENTS OF ACTIVE RT INHIBITORS SUCH AS ETRAVIRINE TO THE MOLECULAR FRAMEWORK OF ANTI-HIV PRONE PRIVILEGED NUCLEUS OF 1,4-BENZODIAZEPINE AS POSSIBLE SUBSTITUTE TO 'HAART'

NAVJEET KAUR

Department of Chemistry, Banasthali University, Banasthali-304022 (Rajasthan), India

ABSTRACT

In the anticipation of finding potential substitutes of highly active antiretroviral therapy [HAART], several molecular probes (9-12) have been developed by incorporating the vital fragments of RT inhibitor 'etravirine' to the anti-HIV prone privileged template of 1,4-benzodiazepine (2), on the premise that their presence in tandem in the same molecular framework could produce a positive impact in overcoming the problem arising due to the emergence of the multidrug resistant mutants of the virus.

KEYWORDS:AIDS, etravirine, FDA, HAART, privileged heterocyclic scaffolds (1,4-benzodiazepine, pyrimidine), RT inhibitors.

NAVJEET KAUR
Department of Chemistry, Banasthali University,
Banasthali-304022 (Rajasthan), India

Corresponding author

INTRODUCTION

Current therapy[1-6] against AIDS is based on six classes of anti-HIV drugs: the nucleoside and nucleotide reverse transcriptase (RT) inhibitors[7] (NRTIs and NtRTIs), the non-nucleoside reverse transcriptase inhibitors[8] (NNRTIs), the protease inhibitors[9-10] (PIs), the fusion inhibitors[11] (FIs), the entry inhibitors[12] and HIV-1 integrase inhibitors.[13] The treatment for HIV and AIDS target primarily the inhibition of two viral enzymes- the HIV reverse transcriptase[14-15] and HIV protease.[16-17] The highly active anti-retroviral therapy ('the HAART'[18]) comprise of the combination the US-FDA approved drugs for the inhibition of these two enzymes. These combination of regimens have significantly decreased the morbidity and mortality among patients with HIV infections, but long lived nature of the infection, drug toxicity and the emergence of multidrug resistant mutants of the virus underscore its use and warrant the need for other innovative anti-retroviral strategies to be developed to overcome specifically, the problem arising due to the drug resistance.As 'HAART' is associated with several deleterious side effects, it mean that it is not the final answer to the AIDS therapy and needs to be supplanted by other novel alternate ways to combat this disease. Highly encouraged by the treatment option which the HAART had provided, we envisioned that perhaps a still better treatment option could emerge by joining the two or more than two active enzyme inhibitors together in the same molecular framework by resorting to such synthetic endeavours which allowed these to become the part in the same molecule. The genesis of this treatment option derived its inspiration on this premise that their presence in the same molecular framework could contribute significantly to produce an additive effect, not only on the overall potency in the resulting molecule but also to perhaps overcome the problem arising due to the emergence of the drug resistant mutants of the virus. To test this hypothesis we required a 1,4-benzodiazepine molecule which carried a free NH-C=O group on the face 'a' of its nucleus for the incorporation of the active enzyme inhibitors on this face. Herein, in this communication, we report the preliminary results of our studies which aimed to incorporate the vital fragments of etravirine on 2-position at face 'a' of 1,4-benzodiazepine nucleus.

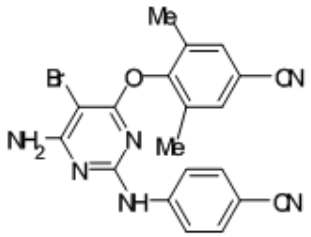


Figure 1
Etravirine

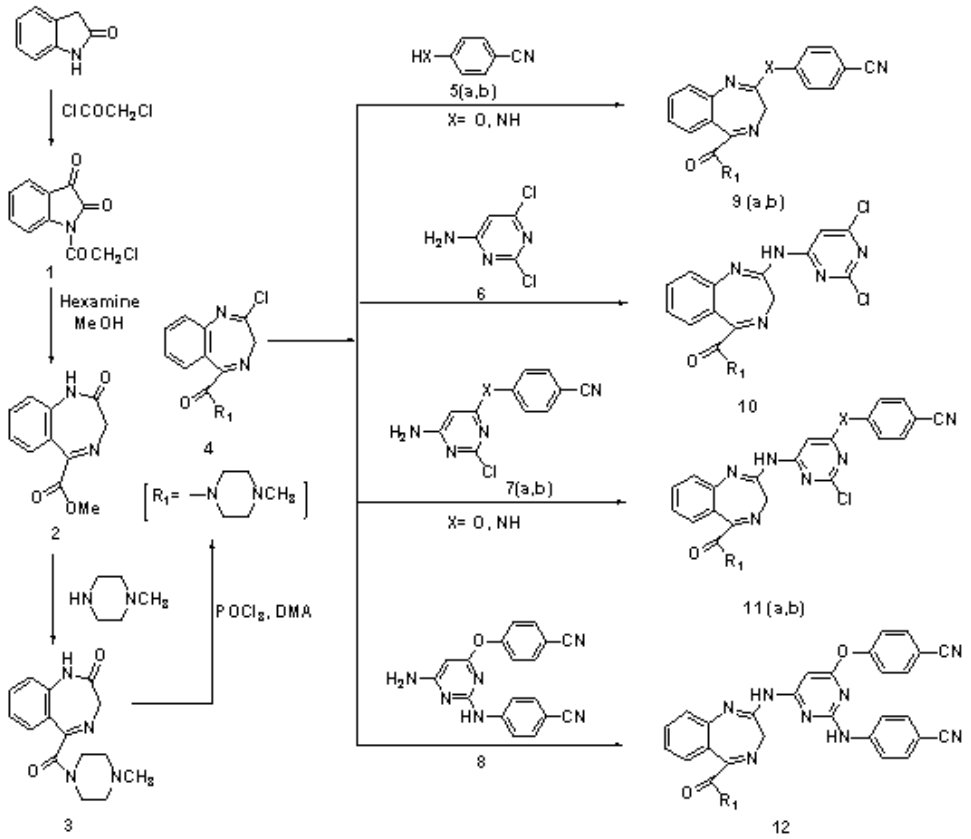
A perusal of the structure of etravirine[19] (Fig. 1) reveals that its molecule essentially consists of three vital fragments viz, (a) 6-aminopyrimidine nucleus (b) p-cyanophenoxyl part and (c) p-cyanophenylamino part.[20] To our knowledge no attempt has been made so far to incorporate these vital fragments on to the anti-HIV prone 1,4-benzodiazepine nucleus. An examination of the structure of 1,4-benzodiazepin-2-one-5-carboxylate revealed that C_2 carbonyl function carrying the NH-C=O group[21] was the only position in the seven membered ring of this nucleus which provided scope for the structural variation and for further functionalization of this molecule to produce structural analogues of medicinal utility. It prompted us to explore the

potential of this position to allow the incorporation of the vital fragments of etravirine on the privileged 1,4-benzodiazepine nucleus. The projected study in its first phase aimed to explore the feasibility of the preparation of three novel series of 2-substituted 1,4-benzodiazepine analogues substituted with the following fragments of etravirine molecule. The first series consisted of compounds which were obtained by loading the 1,4-benzodiazepine nucleus (3) by (i) 4'-cyanophenylhydroxyl (ii) 4'-cyanophenylamino and (iii) 4'6'-dichloropyrimidinylamino fragments to give the compounds 9 (a,b) and 10 respectively. The second series of compounds were realized by loading the 4'-cyanophenylhydroxyl and 4'-cyanophenylamino fragments on 1,4-benzodiazepine nucleus through a chloropyrimidinylamine spacer to give compounds 11a and 11b respectively. The third series was developed by loading the basic backbone of etravirine nucleus on to the 2-position of 1,4-benzodiazepine molecule to give 12 in which one can easily discern the presence of the two anti-HIV prone heterocyclic scaffolds: the 1,4-benzodiazepine and etravirine in the same molecular framework (scheme-1).

RESULTS AND DISCUSSION

Ubiquity of 1,4-benzodiazepines in chemical literature is undoubtedly a consequence of multifarious biological response which they elicit in combating a variety of body ailments. Impressive medicinal properties endow with this nucleus has placed them to the class of 'privileged heterocyclic scaffolds'[22] from which useful potential drugs can be expected. The recent demonstration that its dipyridodiazepine analogue- the nevirapine[23] can serve as potential agents for the treatment and control of AIDS has stimulated further interest in 1,4-benzodiazepine nucleus from yet another perspective.An inspection of the literature pertaining to the preparation of 1,4-benzodiazepines revealed that the broad spectrum of biological properties associated with this nucleus has triggered the development of a variety of methods for their synthesis and has led to an impressive armoury of synthetic strategies to be devised in the literature[24-25] for their preparation. In order for our synthetic plan (scheme-1) to succeed, we required a 1,4-benzodiazepine analogue which contained an NH-C=O group on face 'a' of this nucleus. Consideration of factors of reactivity of the starting material, its easy accessibility, synthetic economy and simplicity in the operational procedure led us to favour the use of a reported synthetic procedure for its preparation from 1-chloroacetylisatin (1). The potential of isatin in the synthesis of heterocyclic compounds through the expansion of its ring has been well established in the literature. [26-28] The highly labile nature of the lactam function of the isatin ring allows the cleavage of its ring on reaction with nucleophilic reagents to give the ring opened product which undergoes concurrent cyclocondensation leading to ring enlargement to give the six or seven membered heterocyclic rings. This feature of isatin has been very elegantly exploited by Ogata and Motsumoto [29-31] to develop a highly innovative technique for the synthesis of 5-methylcarboxylate substituted derivatives of 1,4-benzodiazepin-2-one from the reaction of 1-chloroacetylisatin with methanolic solution of hexamine. An attractive feature of this reaction was that it provided a very convenient one pot synthetic entry to the 1,4-benzodiazepine nucleus. This methodology was applied by us to obtain the 5-carbomethoxy substituted analogue of 1,4-benzodiazepin-2-one (2) in an acceptable yield. Treatment of the carbomethoxy function of 2 with N-methylpiperazine[32] formed the corresponding 5-carboxamide derivative (3). The NH-C=O group on face 'a' of the 1,4-benzodiazepine nucleus (3) had the potential to provide an easy access to the corresponding 2-Cl (or 2-SMe group) from its reaction with $POCl_3$[33] (or with 'Lowesson' reagent[33] followed by treatment with MeI). The 2-Cl atom (an iminochloride species) or 2-SMe groups (an iminothiomethylether group) were highly reactive species activated for nucleophilic attack. In order to curtail an extra step which the formation of 2-SMe group required, we preferred to employ the 2-Cl atom

in 4 for its subsequent replacement with the hydroxy and amine bearing pharmacophores indicated in scheme-1, to yield the corresponding 2-substituted analogues 9 (a,b), 10, 11 (a,b), and 12 respectively.



Scheme-1

Experimental

General procedures: All the melting points were determined in open glass capillaries and are uncorrected. The IR spectra were recorded on KBr disc using Perkin Elmer-1800 infrared. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Brucker Advance 400 MHz spectrophotometer with TMS as internal standard (chemical shifts are expressed in δ ppm). The mass spectra were run on a Joel SX-102 (FAB) mass spectrometer at 70 eV. The reactions were monitored by the TLC on silica gel G plates in the solvent system benzene-methanol mixture (9:1). N-chloroacetyl isatin (1) and methyl-1,3- dihydro-2*H*-[1,4]-benzodiazepin-2-one-5-carboxylate (2) were obtained using the procedure reported for their preparation in the literature.[29-31]

Preparation of 1,3-dihydro-[2H]-[1,4]-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide (3).

Methyl-1,3-dihydro-[*2H*]-[1,4]-benzodiazepin-2-one-5-carboxylate (2) (10.9 g, 0.05 mol) and N-methyl piperazine (5.0 g, 0.05 mol) were taken in ethanol (100 mL). The reaction mixture was refluxed for 12 h on the water bath. The completion of the reaction was checked by TLC. The mixture was cooled and poured on crushed ice, the resulting solid was filtered washed with dilute ethanol dried and recrystallized from ethanol-chloroform mixture (1:9), to give 3 (12.37 g, 75%, m.p. 257-258°C). IR (KBr) cm^{-1}: 3330 (NH str.), 2950 (C-H str. ArH), 1675 (C=O str.), 1660 (C=C str. ArH), 1590 (C=N str.), 1580 (NH bend.), 1430 (C-H bending, CH_3), 1140 (C-N str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.0 (s, 1H), 7.27-7.86 (m, *J*=7.2 Hz, 4H), 3.60 (s, 2H), 3.20 (t, *J*=7.4 Hz, 4H), 2.27 (t, *J*=7.2 Hz,

4H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45.2-45.4, 47.3-47.5, 49.5-49.7, 82.3-82.5, 113.0-113.2, 117.7-117.9, 125.4-125.6, 116.7-116.9, 128.2-128.4, 126.5-126.7, 149.5-149.7, 158.2-158.4, 164.5-164.7; MS: [M^+]: 286, Anal. calcd. for $C_{15}H_{18}N_4O_2$: C, 62.79; H, 6.31; N, 19.54. Found: C, 62.92; H, 6.33; N, 19.48.

Preparation of 2-chloro-[1,4]-benzodiazepin-5-(4'-methylpiperazinyl)-carboxamide (4).

A solution of 3 (10 g, 0.06 mol), $POCl_3$ (5 mL, 0.06 mol), N,N-dimethylaniline (14 mL, 0.1 mol), and benzene (100 mL) were refluxed for 7 h and allowed to cool overnight. The cold reaction mixture was poured in ice water (100 mL) and stirred for 30 min until the reaction mixture reached to room temperature. It was then extracted with ether and the solvent layer was washed with water and brine, dried (over anhydrous. $MgSO_4$), filtered, and evaporated. Trituration with ether gave 5 (8.0 g, 75%, m.p. 120-122°C). IR (KBr) cm^{-1}: 2955 (C-H str. ArH), 1680 (C=O str.), 1590 (C=C str. ArH), 1570 (C=N str.), 1435 (C-H bending, CH_3), 1140 (C-N str.), 710 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33-7.83 (m, *J*=7.2 Hz, 4H), 3.60 (s, 2H), 3.20 (t, *J*=7.4 Hz, 4H), 2.27 (t, *J*=7.5 Hz, 4H), 2.26 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45.2-45.4, 46.0-46.2, 47.8-48.0, 95.3-95.5, 116.6-116.8, 127.8-128.0, 126.5-126.7, 157.2-157.4, 124.6-124.9, 165.2-165.4, 152.5-152.7, 125.3-125.5, 131.1-131.3, 132.7-132.9, 136.6-136.8, 148.6-148.8, 138.5-138.7, 149.4-149.6, 158.3-158.5, 164.6-164.8; MS: [M^+]: 304, Anal. calcd. for $C_{15}H_{17}ClN_4O$: C, 59.24; H, 5.65; N, 18.34. Found: C, 59.11; H, 5.67; N, 18.28.

Preparation of 2-[4'-cyanophenoxyl]-[1,4]-benzodiazepin-5-[4''-methylpiperazinyl)-carboxamide (9a).

To a solution of compound 4 (1.50 g, 0.01 mol) and 4-hydroxybenzonitrile (5a) (0.60 g, 0.01 mol) in *N*-methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (1.14 g, 0.01 mol) over a period of 6 h. The reaction was allowed to reach to room temperature and then cold water (300 ml) was added. The reaction mixture was filtered; the residue was suspended in water (150 ml) and acidified to pH 6-7 using conc. HCl. The product was filtered and washed with 15 ml of water. It was extracted by ethyl acetate (2 × 50 ml). The product obtained on evaporation of solvent was washed with 5.0 ml of chilled ethyl acetate. It was finally dried at 55-60 °C under vacuum to give 9a (1.26 g, 66% yield); m.p. 297-298.5 °C. IR (KBr) cm^{-1}: 2980 [C-H str. ArH], 2225 [CN str.], 1705 [free C=O str.], 1590 [C=N str.], 1525 [C=C str. ArH], 1470 [C-H bending, CH_3], 1250 [C-N Str.], 1035 [C-O str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33-7.81 [4H, m, ArH], 3.6 [2H, s, CH_2 (azepine ring)], 3.20 [4H, t, CH_2 (piperazine ring)], 2.27 [4H, t, CH_2 (piperazine ring)], 2.26 [3H, s, CH_3]; ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 42 [CH_3], 44 [CH_2, diazepine], 45 and 58 [CH_2, piperazine], 106 [C-CN, cyanophenyloxy], 116 [CH, cyanophenyloxy], 117 and 148 [C, arene], 118 [CN], 127 and 131 [CH, arene], 134 [CH, cyanophenyloxy], 164 [C-O, cyanophenyloxy], 165 [C=N], 200 [C=O]; MS: *m/z*: 387 (22%) [M^+], Analysis: Calcd./found for $C_{23}H_{24}N_5O_2$: C, 68.64/68.43; H, 6.01/5.99; N, 17.40/17.35.

Preparation of 2-[4'-cyanophenylamino)-[1,4]-benzodiazepin-5-[-4''-methylpiperazinyl]-carboxamide (9b).

To a solution of compound 4 (1.50 g, 0.01 mol) and 4-aminobenzonitrile (5b) (0.60 g, 0.01 mol) in *N*-methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (1.14 g, 0.01 mol) over a period of 7 h. The procedure described for the preparation of 9a from 4 was applied in the isolation and purification of 9b, (1.22 g, 64% yield); m.p. 298-299 °C. IR (KBr) cm^{-1}: 3340 [NH str], 2920 [C-H str. ArH], 1715 [free C=O str.], 1645 [C=O str. azepine ring], 1605 [C=C str. ArH], 1560 [NH bend.], 1595 [C=N str.], 1460 [C-H bending, CH_3], 1020 [C-N str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.02 [1H, s, NH], 7.26-7.69 [4H, m, ArH], 3.6 [2H, s, CH_2 (azepine ring)], 3.20 [4H, t, CH_2 (piperazine ring)], 2.28 [4H, t, CH_2 (piperazine ring)], 2.26 [3H, s, CH_3]; ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45 [CH_3], 46 [CH_2, diazepine], 47 and 49 [CH_2, piperazine], 102 [C-CN, aminobenzonitrile], 118 [CN], 120 [CH, aminobenzonitrile], 129 and 130 [CH, arene], 133 [CH, aminobenzonitrile], 136 and 148 [C,

arene], 146 [C-NH], 158 [C=O], 164 [C=N]; MS: *m/z*: 386 (10%) [M^+], Analysis: calcd./found for $C_{22}H_{22}N_6O$: C, 68.38/68.18; H, 5.74/5.72; N, 21.75/21.68.

Preparation of 2-[4'-2',6-dichloropyrimidin-yl-amino]-[1,4]-benzodiazepin-5-[4'-methylpiperazinyl)-carboxamide (10).

To a solution of compound 4 (1.50 g, 0.01 mol) and 2,6-dichloropyrimidin-4-amine (6) (0.60 g, 0.01 mol) in *N*-methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (1.14 g, 0.01 mol) over a period of 6.5 h. The procedure described for the preparation of 9a from 4 applied to give the product 10, (1.31 g, 61% yield); m.p. 290-292 °C. IR (KBr) cm^{-1}: 3280 [NH str], 2960 [C-H str. ArH], 1720 [free C=O str.], 1610 [NH bend.], 1550 [C=N str.], 1540 [C=C str.], 1470 [C-H bending, CH_3], 1120 [C-N str.], 750 [C-Cl str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.3-7.62 [4H, m, ArH], 6.40 [1H, s, CH (pyrimidine ring)], 4.1 [1H, s, NH], 3.6 [2H, s, CH_2 (azepine ring)], 3.21 [4H, t, CH_2 (piperazine ring)], 2.26 [4H, t, CH_2 (piperazine ring)], 2.24 [3H, s, CH_3]; ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 44 [CH_3], 46 [CH_2, diazepine], 47 and 49 [CH_2, piperazine], 102 [CH, pyrimidine], 126 and 133 [CH, arene], 138 and 148 [C, arene], 157 [C=O], 159 and 162 [C-Cl], 164 [C=N], 164.7[C-NH]; MS: *m/z*: 431 (16%) [M^+], 433 (10.6%) [M^++2], 435 (1.6%) [M^++4], Analysis: calcd./found for $C_{19}H_{19}Cl_2N_7O$: C, 52.79/52.64; H, 4.43/4.41; N, 22.68/22.61; Cl, 16.40/16.32.

Preparation of 2-[4'-[2'-chloro-6'-(4''-cyanophenoxyl)-amino-1,4]-benzodiazepin-5-[4''-methyl-piperazinyl-carboxamide (11a).

To a solution of compound 4 (1.50 g, 0.01 mol) and 4-(6-amino-2-chloropyrimidin-4-yloxy)benzonitrile (7a) (0.60 g, 0.01 mol) in *N*-methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (1.14 g, 0.01 mol) over a period of 6 h. The procedure described for the preparation of 9a from 4 was applied to give the product 11a (1.64 g, 59% yield); m.p. 286-287 °C. IR (KBr) cm^{-1}: 3285 [NH str], 3000 [C-H str. ArH], 2210 [CN str.], 1710 [free C=O str.], 1630 [NH bend.], 1570 [C=Cstr. ArH], 1560 [C=N str.], 1450 [C-H bending, CH_3], 1125 [C-N str.], 1110 [C-O str.], 760 [C-Cl str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.39-7.76 [4H, m, ArH], 6.62-7.12 [4H, m, ArH (benzonitrile ring)], 5.54 [1H, s, ArH (pyrimidine ring)], 4.1 [1H, s, NH], 3.4 [2H, s, CH_2 (azepine ring)], 3.21 [4H, t, CH_2 (piperazine ring)], 2.26 [4H, t, CH_2 (piperazine ring)], 2.24 [3H, s, CH_3]; ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45 [CH_3], 46 [CH_2, diazepine], 47 and 57 [CH_2, piperazine], 90 [CH, pyrimidine], 108 [C-CN, cyanophenyloxy], 118 [CN], 122 and 133 [CH, cyanophenyloxy], 126, 127 and 130 [CH, arene], 132 and 148 [C, arene], 157 [C-Cl], 159 [C-O], 164 [C=N], 165 [C-NH], 173 [C-O], 200 [C=O]; MS: *m/z*: 546 (11%) [M^+], 548 (3.9%) [M^++2], Analysis: Calcd./found for $C_{28}H_{30}ClN_8O_2$: C, 61.59/61.47; H, 5.54/5.52; N, 20.52/20.44; Cl, 6.49/6.45.

Preparation of 2-[4'-[2'-chloro-6'-(4''-cyanophenylamino)-amino-pyrimidinyl-4''-amino-1,4]-benzodiazepin-5-[4''-methyl-piperazinyl-carboxamide (11b).

To a solution of compound 4 (1.50 g, 0.01 mol) and 4-(6-amino-2-chloropyrimidin-4-ylamino)benzonitrile (7b) (0.60 g, 0.01 mol) in *N*-methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (1.14 g, 0.01 mol) over a period of 5.5 h. The procedure described for the preparation of 9a from 4 was applied to give 11b (1.58 g, 62% yield); m.p. 285-287 °C. IR (KBr) cm^{-1}: 3350 [NH str], 2930 [C-H str. ArH], 2205 [CN str.], 1710 [free C=O str.], 1640 [C=C str.], 1620 [C=N str.], 1590 [NH bend.], 1535 [C=Cstr. ArH], 1440 [C-H bending, CH_3], 1160 [C-N str.], 790 [C-Cl str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.30 [1H, s, NH], 7.39-7.71 [4H, m, ArH], 6.62-7.17 [4H, m, ArH (benzonitrile ring)], 5.13 [1H, s, ArH (pyrimidine ring)], 4.0 [1H, s, NH], 3.6 [2H, s, CH_2 (azepine ring)], 3.21 [4H, t, CH_2 (piperazine ring)], 2.26 [4H, t, CH_2 (piperazine ring)], 2.24 [3H, s, CH_3]; ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 45 [CH_3], 46 [CH_2, diazepine], 47 and 48 [CH_2, piperazine], 81 [CH, pyrimidine], 104 [C-CN, aminobenzonitrile], 118 [CN], 128 and 130 [CH, arene], 118.7 and 135 [CH, aminobenzonitrile], 137 and 148 [C, arene], 150 [C-NH, aminobenzonitrile], 158 [C=O], 161 [C-Cl], 163 and 170 [C-NH, pyrimidine], 166 [C=N]; MS:

m/z: 513 (25%) [M^+], 515 (8.3%) [M^++2], Analysis: calcd./found for $C_{26}H_{24}ClN_9O$: C, 60.76/60.54; H, 4.71/4.70; N, 24.53/24.42; Cl, 6.90/6.87.

Preparation of 2-[4'-(2'-(4''-cyanoaminophenyl-6''-(4'''-cyanophenylamino)-4'-pyrimidinyl-4''yl-amino-1,4]-benzodiazepin-5-[4''-methyl-piperazinyl-carboxamide (12).

To a solution of compound 4 (1.50 g, 0.01 mol) and 4-(6-amino-2-(4-cyanophenylamino)pyrimidin-4-yloxy)benzonitrile (8) (0.60 g, 0.01 mol) in *N*-methylpyrrolidone (7.5 ml) at 0-5 °C was added potassium *tert*-butoxide (1.14 g, 0.01 mol) over a period of 5 h. The procedure described for the preparation of 9a from 4 was applied in the preparation of 12, (1.70 g, 58 % yield); m.p. 278-280 °C. IR (KBr) cm^{-1}: 3275-3290 [NH str], 3010 [C-H str. ArH], 2210-2220 [CN str.], 1710 [free C=O str.], 1630 [C=N str.], 1610 [NH bend.], 1580 [C=C str. ArH], 1440 [C-H bending, CH_3], 1210 [C-N str.], 1110 [C-O str.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.12 [1H, s, NH], 7.40-7.73 [4H, m, ArH], 6.81-7.90 [4H, m, ArH (oxyphenyl ring)], 6.92-7.39 [4H, m, ArH (benzonitrile ring)], 5.14 [1H, s, ArH (pyrimidine ring)], 3.98 [1H, s, NH], 3.6 [2H, s, CH_2 (azepine ring)], 3.24 [4H, t, CH_2 (piperazine ring)], 2.28 [4H, t, CH_2 (piperazine ring)], 2.23 [3H, s, CH_3]; ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 43 [CH_3], 44 and 45 [CH_2, piperazine], 46 [CH_2, diazepine], 83 [CH, pyrimidine], 103 [C-CN, aminobenzonitrile], 108 [C-CN, cyanophenyloxy], 118 [CH, aminobenzonitrile], 118.6 [CN], 123 [CH cyanophenyloxy], 124 and 126 [CH, arene], 133 [CH, aminobenzonitrile and cyanophenyloxy], 137 and 147 [C, arene], 138 [C-NH aminobenzonitrile], 158 [C=O], 159 [C-O, cyanophenyloxy], 163 and 166 [C-NH, pyrimidine], 163.8 [C=N], 170 [C-O, pyrimidine]; MS: *m/z*: 596 (10%) [M^+], Analysis: calcd./found for $C_{33}H_{28}N_{10}O_2$: C, 66.43/66.64; H, 4.73/4.74; N, 23.48/23.55.

CONCLUSION

While exploring the possibility of developing materials which could find application as substitute of HAART, we devised an efficient one step synthetic protocol to the formation of corresponding 2- (oxy and amino) substituted analogues, of the privileged nucleus of 1,4-benzodiazepine. The formulated plan provided an easy incorporation of the vital fragments of the FDA approved anti-HIV agent etravirine and the anti-HIV prone 1,4-benzodiazepine nuclei together, in the same molecular framework in acceptable yield and purity, for the evaluation of their bioefficiency over the existing potential anti-HIV agents. The assessment of biological activity of compounds is in progress.

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