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**Papers**

# Guanidino substituted isoindolones as novel glycoprotein IIb-IIIa receptor antagonists

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Design and synthesis of a novel potent glycoprotein IIb-IIIa (GP IIb-IIIa) receptor antagonist based on isoindolone skeleton has been described. This scaffold has been derived from earlier reported pseudopeptides. Synthesis by a novel route has been achieved. Few molecules show very potent *in vitro* activity. Further identification of probable additional hydrogen bond donor site has been described.

**Keywords**: Glycoprotein GP IIb-IIIa receptor, guanidine, isoindolone, S-methyl isothiourea, hydrogen bond donor site.

The main physiological role of platelet, present in blood is to interact with fibrinogen leading to platelet aggregation that results in the formation of haemostatic clot. In normal circumstances it is necessary to prevent bleeding at the site of vascular injury.

However under pathological condition such as atherosclerotic plague rupture, the above process leads to arterial thrombosis causing myocardial infarction, ischaemic stroke and peripheral artery disease[1]. The final common step in platelet aggregation is the binding of fibrinogen receptor glycoprotein IIb-IIIa (GP IIb-IIIa) (integrin αIIbβ3) located on the surface of activated platelets. The recognition site for GP IIb-IIIa receptor is believed to be the Arg-Gly-Asp (RGD) sequence occurring in fibrinogen. Therefore any ligand that mimics RGD sequence can stop platelet aggregation[2]. Development of GP IIb-IIIa receptor antagonist remained the focus for medicinal chemist for developing anti thrombotics over last one and half decade[3]. It is generally accepted that the requirement to mimic RGD is to have a basic moiety at N terminus such as guanidine, amidino or amino groups and carboxylic group at C-terminus that should be at a certain distance apart with right orientation on a suitable template. The replacement of Arg by fragments such as piperidine, 4-benzamidine, 4- benzguanidine, replacement of Gly by a suitable template and replacement of Asp with aromatic ring containing carboxylic acid or with other amino acid led to the discovery of several novel GP IIb-IIIa receptor antagonist [4-8].

The designing of novel fibrinogen receptor antagonist on heterocyclic template is also under progress. While going through the literature, the two compounds that attracted attention were open chain pseudopeptides with favorable $IC_{50}$ values [9] (**Figure 1**).

An attempt was made to modify these molecules in such a manner as to restrict the movement of the bond and give the molecule a rigid geometry. It was believed that, this would impart greater stability towards enzymatic cleavage and hence improve its oral bioavailability. If the 2-position of the aromatic ring at the N-terminus is connected with the NMe-carbon in structure **2** and is connected through a methylene bridge in structure **1** it results in the formation of an isoindolone skeleton (**Figure 2**). Therefore, it was decided to synthesize such isoindolone derivatives with the replacement of amidine with guanidine as a starting point as shown below:

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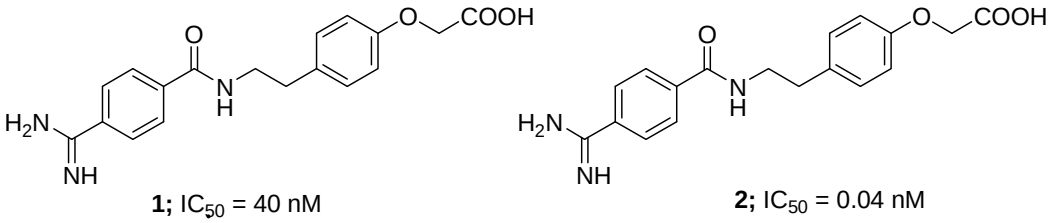



**1;** $IC_{50}$ = 40 nM

**2;** $IC_{50}$ = 0.04 nM

**Fig 1**

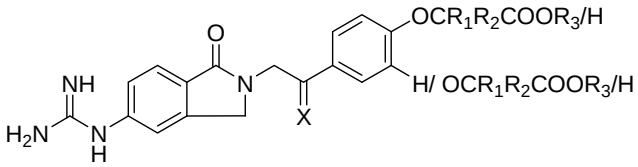



**Fig 2** ( X = O or $H_2$)

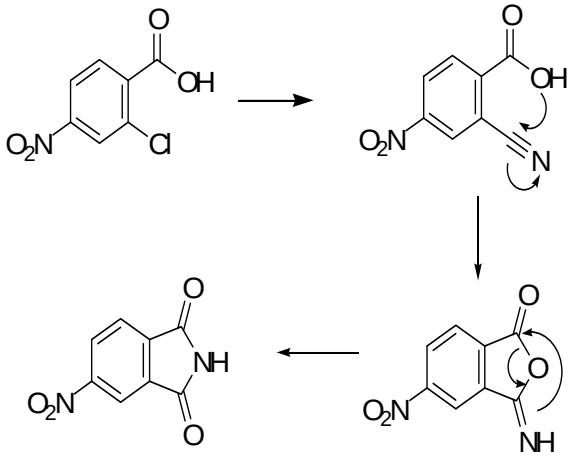
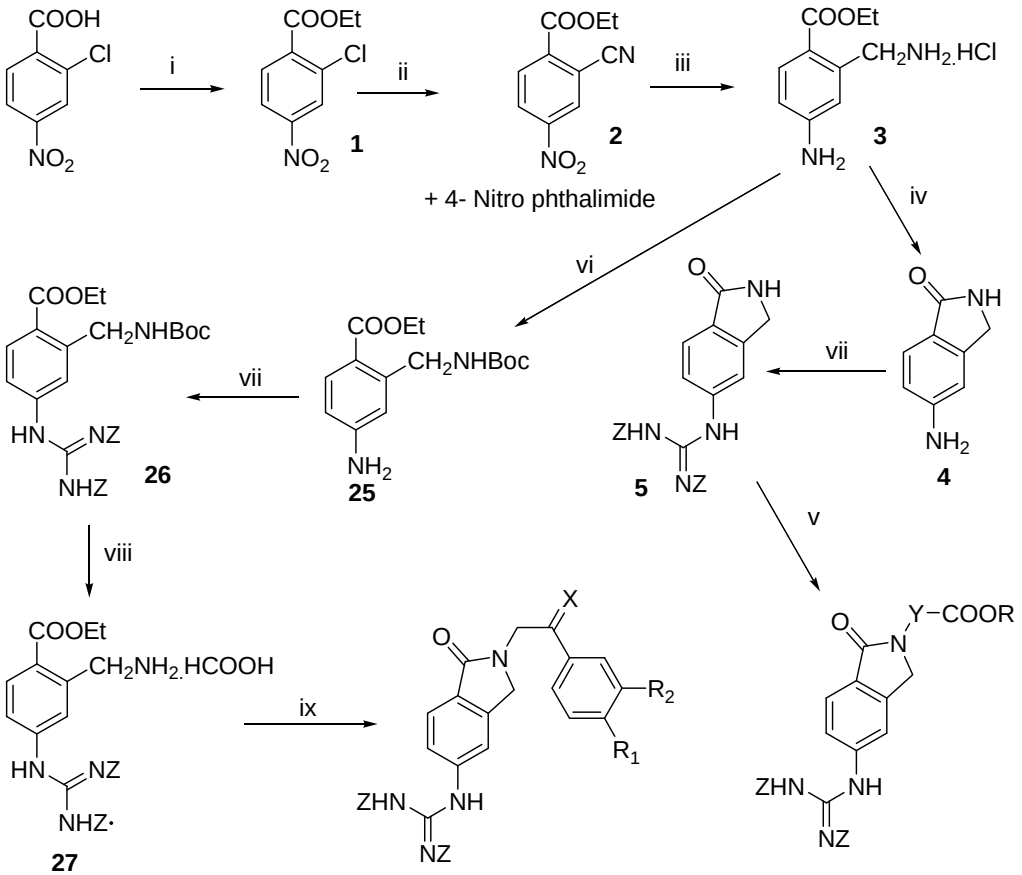



**Figure 3**

## Chemistry

The retro synthetic analysis of the target compounds suggests that 2-cyano-4-nitro-benzoic acid ethyl ester is a suitable template to build isoindolone scaffold. The synthesis of N-substituents on isoindolone could be straight forward from the easily available starting material 4-hydroxy acetophenone and catechol.

Thus 2-chloro-4-nitro-benzoic acid was treated with cuprous cyanide in NMP at 130°C following a reported procedure[10]. The major product was found to be 4-nitro-phthalimide while the required 2-cyano derivative **2** was formed in trace amount (**Scheme I**). The formation of phthalimide can be explained by initial formation of cyanide followed by thermal cyclization as shown in **Figure 3**. Alternatively, 2-chloro-4-nitro-benzoic acid was converted into ethyl ester 1 by standard procedure in near quantitative yield. The ester **1** was heated at 130°C with CuCN in NMP without any reaction. However, when the temperature was raised to 160°C, **2** was obtained in 27% yield and the undesired phthalimide in 23% yield. Subsequently, maintenance of temperature was found to be very critical for the success of this reaction and the best result could be obtained at temperature of 135-140°C. The yield of the required compound was improved to 55% and that of undesired phthalimide as low as 8% with ~15% starting material recovered.



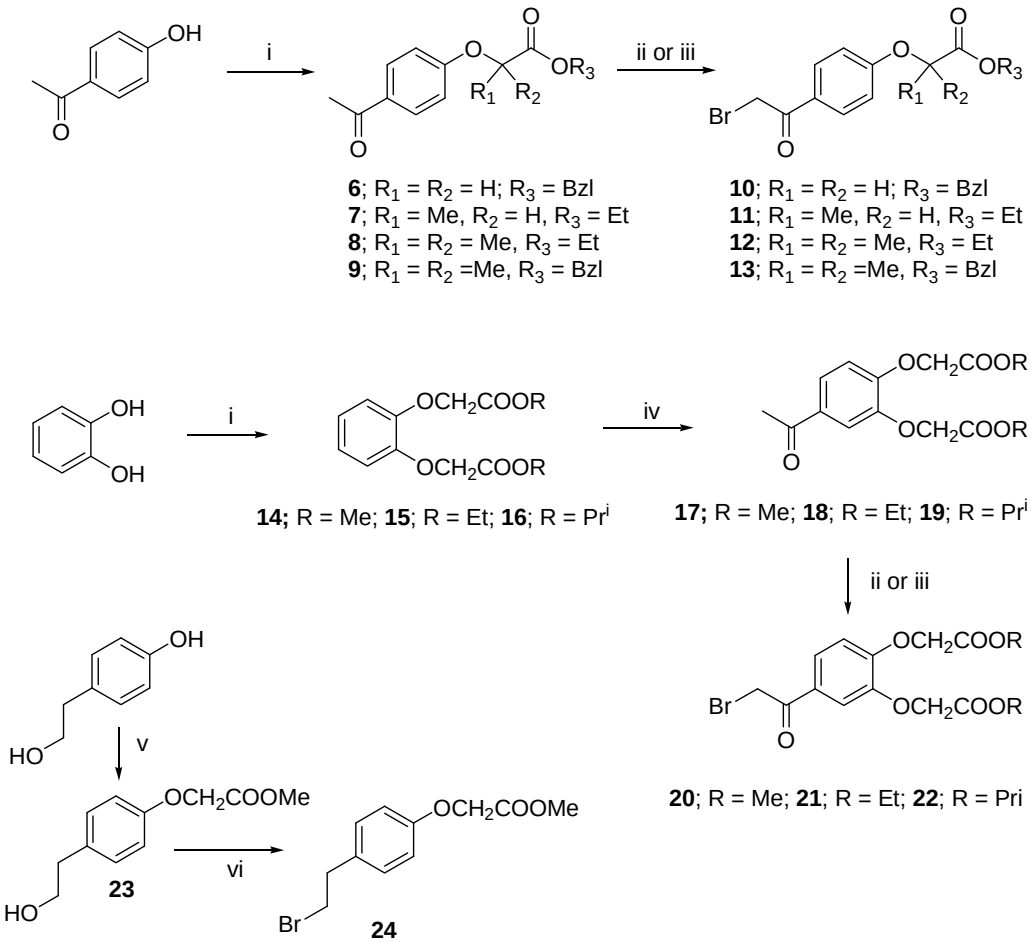

**28**; $R_1$ = $OCH_2COOBzl$; $R_2$ = H; X = O
**29**; $R_1$ = $OCH_2COOMe$; $R_2$ = H; X =O
**30**; $R_1$ = $OCH_2COOEt$; $R_2$ = H; X = O
**31**; $R_1$ = OCHMeCOOEt; $R_2$ = H; X = O
**32**; $R_1$ = $OCMe_2COOEt$; $R_2$ = H; X = O
**33**; $R_1$ = $OCMe_2COOBzl$; $R_2$ = H; X= O
**34**; $R_1$ = $R_2$ = $OCH_2COOMe$; X = O
**35**; $R_1$ = $R_2$ = $OCH_2COOEt$; X = O
**36**; $R_1$ = $R_2$ = $OCH_2COOPr^i$; X= O
**37**; $R_1$ = $OCH_2COOMe$; $R_2$ = H; X = $H_2$

**38**; R = Et; Y = $CH_2$
**39**; R = $Bu^t$; Y = $CH_2$
**40**; R = Et, Y = $(CH_2)_4$
**41**; R = Et; Y = $(CH_2)_5$

**Scheme I:** i. EtOH, $H_2SO_4$ or $SOCl_2$; ii. CuCN, NMP, 135-140°C; iii. $H_2$, $PtO_2$, EtOH, $CHCl_3$, 200 psi; iv. $Et_3N$, DMF, 110°C; v. X-$(CH_2)_n$-COOR, NaH, HMPA; vi. $(Boc)_2O$, $NaHCO_3$, water, Dioxane; vii. MeS-C(=NZ)-NHZ, $CH_3CN$, $Et_3N$, 80°C; viii. HCOOH, anisole; ix. Br-$CH_2$C(=X)-Ar, $NaHCO_3$, $CH_2Cl_2$

When **2** was hydrogenated over 10% Pd-C at 55 psi for 2 hr, only $NO_2$ group was reduced to give **3a**, while the CN remained intact. Subsequently compound **2** was hydrogenated over $PtO_2$ in alcohol and $CHCl_3$ mixture at 200 psi as reported in the literature[11] to give compound **3** in high yield. However during scaling up we encountered difficulty due to poor solubility of the intermediate **3a**, which deactivated the catalyst surface preventing further progress of the reaction. To overcome this difficulty the hydrogenation was carried out at 90°C. Even at this temperature hydrogenation could not be performed beyond 2% solution.

After neutralizing with $Et_3N$, compound **3** was heated in DMF at 110°C for 2 hr to obtain 5-amino-2, 3-dihydro-1*H*-benzo[*c*]azol-1-one **4** in 65% yield. The




**Scheme II:** i. $BrC(R_1R_2)$-$COOR_3$, $K_2CO_3$, DMF; ii. $CuBr_2$, EtOAc-$CHCl_3$ (for $R_3$ = Et); iii. $CuBr_2$, Benzene-$CHCl_3$ reflux, iv. $Ac_2O$, 70 % $HClO_4$, $CH_2Cl_2$ reflux ; v. NaOH, $BrCH_2COOMe$; vi. $Ph_3P.Br_2$, Pyridine, $CH_3CN$

amino group of **4** was converted into carbobenzoxy protected guanidino function **5** by treatment with Z-protected S-methyl isothiourea[12] in 46% yield. After getting the desired intermediate we focused our attention to synthesize the alkylating chains. Thus 4-hydroxy acetophenone was treated with $BrCR_1R_2COOR_3$ in the presence of $K_2CO_3$ in DMF at room temperature to obtain compounds **6-9** as described in **Scheme II**. When compounds **6-9** were treated with $CuBr_2$ in EtOAc: $CHCl_3$ (1:1) as described in the literature[13] to get the required bromoacyl derivatives **10-13**.

Syntheses of **20-22** were achieved by treating catechol with the corresponding alkyl bromoacetate to obtain di-substituted derivatives **14-16** in good yield. Acetyl group at 4-position was introduced by Friedel-Crafts reaction with $Ac_2O$ and perchloric acid as catalyst to get **17-19** in moderate yield. These intermediates were converted into bromoacyl derivatives **20-22** as described earlier using $CuBr_2$ in $CHCl_3$ and $C_6H_6$ or in dioxane at 80°C. Compound **23** was prepared, according to the reported procedure[14]. Finally it was converted into the required bromo derivative **24** in high yield by treatment of $Ph_3P.Br_2$ and pyridine in acetonitrile[15].

When **5** was treated with **10** in the presence NaH in HMPA required alkylation's product **28** was not formed. On the other hand when the linear ω-halo-alkyl ester was treated with **5** in the presence of NaH in HMPA as shown in **Scheme I**, the corresponding N-alkyl derivatives **38-41** were obtained in reasonably good yields.

At this stage our synthetic strategyn was modified. We conceived the idea of alkylating primary amino group of **3** followed by cyclization. To achieve this target, initially the primary amino group of **3** was selectively protected by Boc group to get **25** in high yield. This was then treated with S-methyl isothiourea at 80°C; the desired product **26** was obtained in high yield. Beyond 85°C the compound was found to decompose rapidly. The Boc group from **26** was removed by using formic acid-anisole[16] at room temperature to obtain **27** in near quantitative yield. When **27** was treated with **10** after neutralizing formate salt with $Et_3N$ in $CH_2Cl_2$ at room temperature the required compound **28** was obtained in poor yield along with the compound **5** and some unidentified products. We also observed complete disappearance of **10** possibly due to the reaction of acyl bromide with triethyl ammonium formate and over alkylation of amino group. The former problem was solved by carrying out the reaction by adding solid $NaHCO_3$ to phase out sodium formate and thus improving the yield of **28** up to 37%. Similar approach was adopted for the synthesis of compounds **29** to **37** using the appropriate bromo compound from [4-(2-bromo-acetyl)-phenoxy]-acetic acid methyl ester, [4-(2-bromo-acetyl)-phenoxy]-acetic acid ethyl ester, **10-13**, **20-22** and **24**.

Compound **28** was hydrogenated over 10% Pd-C in MeOH-$CHCl_3$-AcOH (10:1:1) at 20 psi for 30 min. The final product **42** was obtained as hydrochloride salt in 45% yield. Similarly, compound **43** and **45-52** were prepared from **29-37** in MeOH/EtOH/iPrOH-EtOAc-AcOH (80:20:0.4) at 20 psi for 20 min. Choice of alcohol was made according to the nature of the ester group present in the alkylating agent to avoid transesterification. It was observed that the keto group adjacent to the aromatic ring is reducd to alcohol on prolong hydrogenation in higher acid concentration. Therefore all the hydrogenations were carried out for a short duration (~20 min.).

The observation of keto reduction described above was utilized to prepare compound **44** from **29** by hydrogenation for 5 hr over 10% Pd-C in MeOH-AcOH (6:1) at 50 psi in 95.6% yield.

Several other derivatives were also prepared in which the C-terminus aromatic ring was replaced by linear alkyl chain with $C_5$ or $C_6$ carbon atom or a peptide chain. The compound 60 was prepared by the hydrogenation of **40**. Compounds **57-59** were prepared as shown in the **Scheme III**. Compound **39** was converted into **54** by TFA in $CH_2Cl_2$. The resulting acid was coupled with methyl 6-aminohexanoate and Asp (OBzl)-Phe-OBz[9] separately using mixed anhydride procedure[17] to give 55 and 56 respectively. Hydrogenation of **55** and **56** gave the final compounds **57** and **58** respectively. Compound **58** was further converted into methyl ester **59** by treatment with MeOH and thionyl chloride.

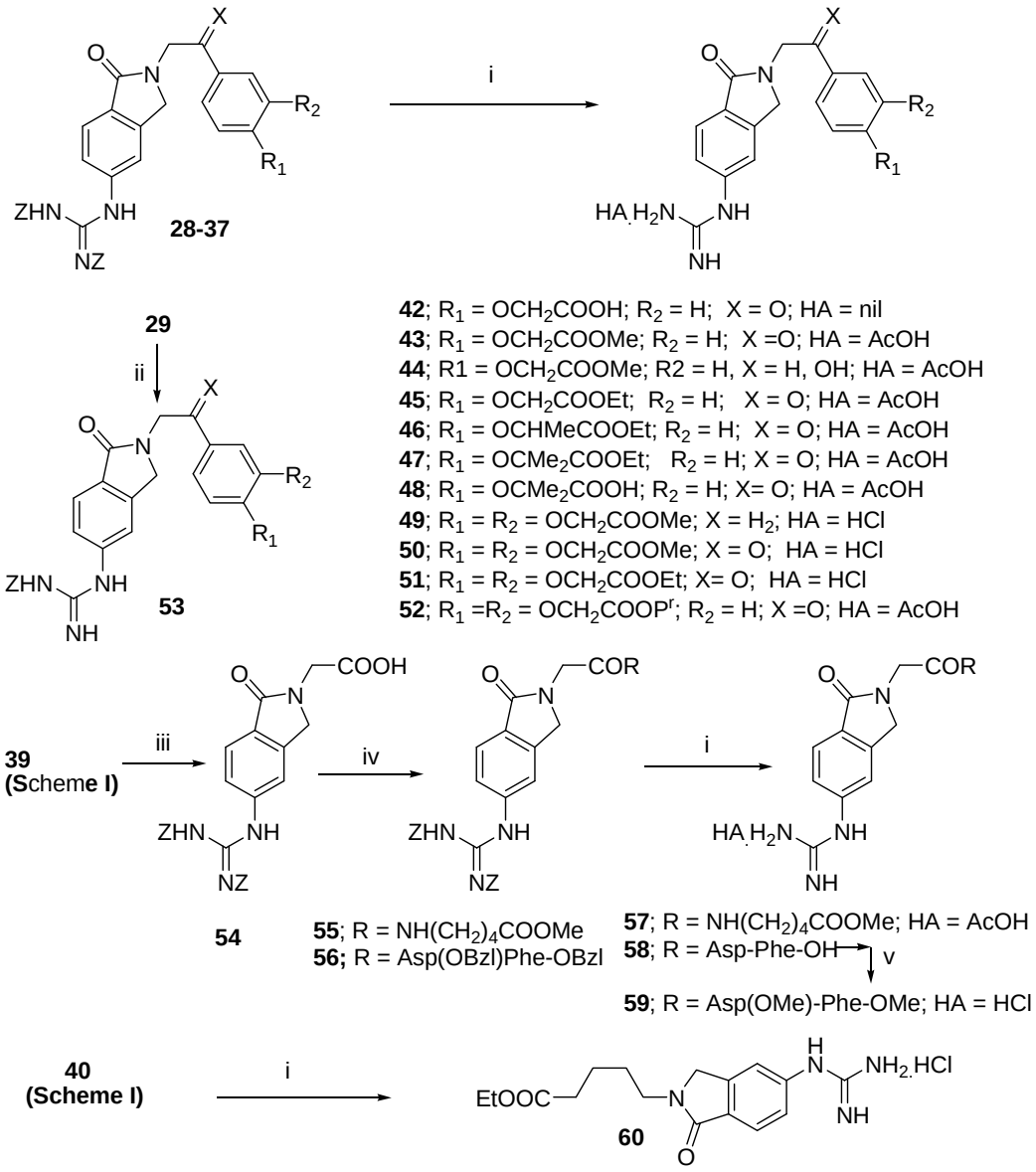
When compound **38**, a proposed synthon for **54** was subjected to hydrolysis, it yielded a mixture, which after partial purification indicated the detachment of one of the Z-group ($^1$H NMR, data not included). When the same reaction was carried out on **29** relatively clean reaction took place and compound **53** was isolated in 56% yield with hydrolysis and simultaneous loss of one carbobenzoxy group. Although it is very unusual for Z-protection to be removed under such mild condition however we found this compound an interesting probe for biological activity in which guanidine group was partially protected.

## Biological activity

### Procedure

Inhibition of platelet aggregation was studied using the method of Born *et al.*[22]. Essentially, the blood from healthy volunteers was collected in acid citrate dextrose (ACD) solution, in the proportion of 9 volumes of blood to 1 volume of ACD. After centrifugation at 200 × g for 15 min, platelet rich plasma (PRP) was collected and the remainder blood fraction was further centrifuged at 3000 × g for 15 min to collect platelet free plasma (PFP). Platelet count of PRP was carried out using Beckman Coulter Cell Counter and then was appropriately diluted with PFP to obtain platelet count of 300, 000 per cubic millimeter. This was used for aggregation studies. Additionally, a part of plasma was also diluted to a platelet count of 50,000 per cubic millimeter (platelet poor plasma, PPP) by appropriate dilution with PFP, and was used for adjustments of the platelet aggregometer.

Platelet aggregation studies were carried out using Daiichi aggrecorder. After adjusting PPP and PRP at 100% and 0% transmittance respectively, aggregation was induced in PRP by addition of adenosine di-phosphate (ADP) solution at a final concentration of 5 μM, either in the absence (control sample tube) or in the presence (test sample tube) of test compounds. Percent inhibition of platelet aggregation




**Scheme III:** i. $H_2$, 10 % Pd-C, $CHCl_3$, EtOAc, ROH, AcOH, 20 psi; ii. 1N NaOH, MeOH; iii. TFA, $CH_2Cl_2$, 4. Isobutyl chloroformate, NMM, R-$NH_2$; v. $SOCl_2$, MeOH;

caused by the test compound was determined by comparison with control aggregation, which was taken as 100%. From the graph of inhibition of platelet aggregation against test compound concentration, $IC_{50}$ value was determined. The $IC_{50}$ values of test compounds were shown in **Table I**.

## Results and Discussion

The *in vitro* activity of the compounds shown in **Table I** clearly indicate that the modification proposed in **Figure 2** by modifying molecules in Figure 1 has given novel potent GP IIb-IIIa receptor antagonists. Three compounds **42**, **43** and **51** showed $IC_{50}$ values of 0.08 μM, 0.09 μM and 0.025 μM respectively. The in vitro data also clearly demonstrated that the replacement of C-terminal benzene ring (**57**, **59** and **60**) by alkyl chain or amino acid residue drastically reduces the activity. This may be due to free rotation around C-terminus in which most stable conformation led to unwanted orientation. Further we have observed that mono or di-substitution at carbon attached to the phenolic OH group (**46**, **47**

**Table I** — In vitro activity of selected compounds

| Compound No. | Activity/ PRP $IC_{50}$ in μM | Compound No. | Activity/ PRP $IC_{50}$ in μM |
|---|---|---|---|
| **42** | 0.08 | **50** | 0.11 |
| **43** | 0.091 | **51** | 0.025 |
| **44** | 2.1 | **52** | 0.2 |
| **45** | 0.22 | **53** | 2.5 |
| **46** | 3.0 | **57** | 69.0 |
| **47** | 19.0 | **59** | 100.0 |
| **48** | >200 | **60** | 54.0 |
| **49** | 1.55 | | |

and **48**) loses the activity. Another very interesting feature was observed when the carbonyl group attached to the benzene ring was partially and fully reduced (**44**, $IC_{50}$ = 2.1 μM; **49**, $IC_{50}$ = 1.55 μM). It was seen that the activity is reduced which indicates that the presence of hydrogen bond donor is required in that region where it binds with the receptor. The partially Z-protected guanidine at N-terminus (**53**) decreased activity ($IC_{50}$ = 2.5 μM). This may be due to bulky carbobenzoxy group around the N terminal polar interaction site. Although it is well known in the literature that the C-terminus requires the presence of carboxylic group, yet in our examples esters also showed activity. This is due to the hydrolysis of esters by esterase present in PRP. The hydrolysis of esters by incubation of the test compounds with plasma at 37°C at different time point has been confirmed and found complete disappearance of ester within 10 min (data not shown).

While we were at completion stage of our project Egbertson *et.al.*[23-25] published their work wherein the authors hypothesized that the potent inhibitors can be generated from their earlier lead molecule **A-1** and **A-2** by incorporating an element of geometric constrain at the center of the molecule. This should direct the vectors of the N and C terminus in right orientation (**Figure 4**). Based on conformational analysis the authors designed molecules by restricting conformation on both side of the aromatic ring. The result showed that N-terminal constrained compounds gave highly potent GP IIb-IIIa receptor antagonist with $IC_{50}$ value of 0.025 μM (**B-1**) same as our best compound **51** in which the constrain is on the C-terminal side along with an aromatic ring, and **B-2** with $IC_{50}$ values range 4 to 27 nM while the C-terminal constrained analogue gave poor activity ($IC_{50}$ = 10 μM) in their case (**Figure 4**). Both the studies further confirms the belief that two oppositely charged ionic groups should be present at a certain distance apart with right orientation and that the rigidity of the molecule shorten the chain length which gives drug like character to the molecule. Apart from this we have possibly identified another interacting site in the form of CO group that provides additional interaction in the receptor as hydrogen bond donor.

## Conclusion

We have designed and successfully synthesized novel GP IIb-IIIa receptor antagonist. We have adopted a novel synthetic route to build isoindolone skeleton. Few of the molecules showed very potent GP IIb-IIIa receptor antagonist activity. Our study further substantiated the common belief that two oppositely charged polar interactions are required which should be placed at a certain distance from each other with right orientation. Our study further indicated possibility of additional receptor binding site around the central part of the molecule in the form of hydrogen bond donor, which certainly need further confirmation. Compounds **42**, **43** and **51** were found to be good lead compounds and were used to develop new orally active GP IIb-IIIa receptor antagonist[26].

## Experimental Section

### General procedures

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 157 spectrophotometer as KBr film unless otherwise mentioned. $^1H$ NMR spectra were recorded in $CDCl_3$ unless otherwise mentioned on a JEOL FT-90 Spectrometer with TMS as internal standard and coupling constant values are expressed in Hz. Elemental analysis was carried in Carlo Erba EA 1008 and Thermo EA 1112 instruments. Light petroleum refers to the fraction of bp. 60-80°C. For flash column chromatography silica gel (finer than 0.08 mm particle size) was used Pre-coated (silica gel 60 $F_{254}$) TLC plates were used for checking purity of compounds. All compounds were homogeneous on TLC and gave proper spectral characteristics.

**Ethyl 2-cyano-4-nitro-benzoate 2**: To a solution of **1** (130 g; 0.566 mole) in NMP (150 mL) was added cuprous cyanide (108 g; 1.2 mole) and $(Ph_3P)_4Pd$ (0) (0.1 g). The mixture was heated at 135-140°C for 12 hr. The mixture was cooled and poured over

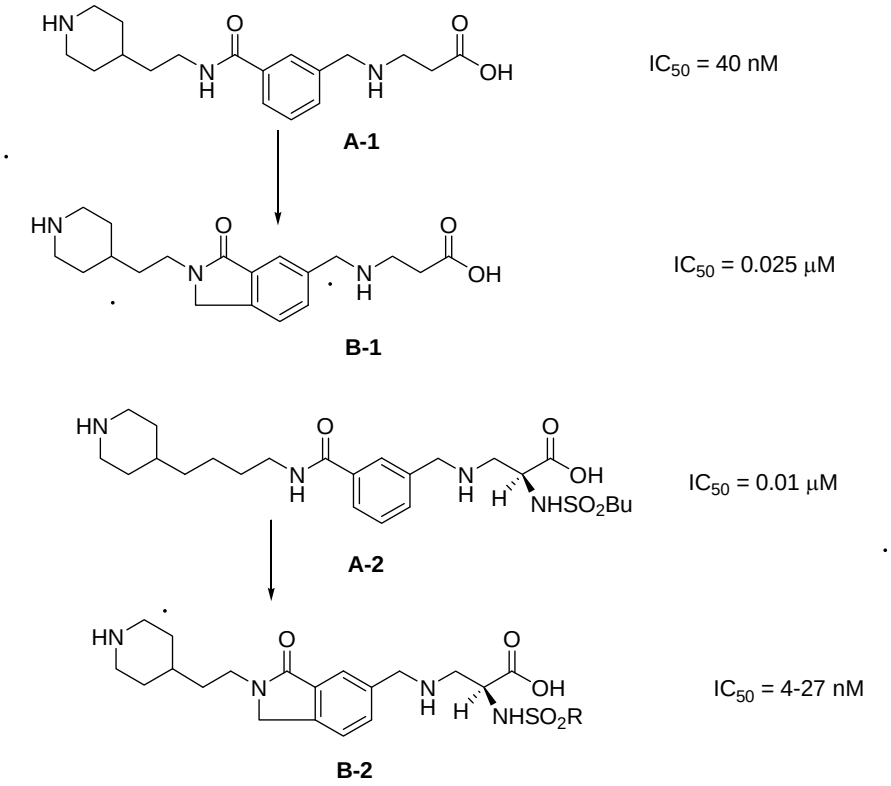



**Figure 4**

crushed ice containing $FeCl_3$ (~100 g) and ethyl acetate (500 mL). The mixture was stirred for 15 minute and filtered through celite. The celite bed was washed with 2 × 200 mL of EtOAc. The combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$.The solvent was removed and the residue was purified by flash chromatography with $CHCl_3$ (20 g starting material), followed by 5% acetonitrile in $CHCl_3$ to give compound **2**; 72g (68%), 10% acetonitrile in $CHCl_3$ (4-nitro-phthalimide, 8.6 g; m.p. 92-94°C (EtOAc-light petroleum). IR: 2330, 1740 (br), 1635, 1605, 1555 $cm^{-1}$; $^1H$ NMR: δ 1.49 (3H, t, $J$ = 7.09, $CH_3$), 4.54 (2H, quartet, $J$ = 7.09, $CH_2$), 8.36 (1H, d, $J$ = 8.6, 6-H), 8.53 (1H, dd, $J$ = 8.6, 2.0, 5-H), 8.66 (1H, d, $J$ = 2.0, 3-H). Anal Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12 73. Found, C, 54.73; H, 3.62; N, 13.10%.

**Ethyl 4- amino-2-aminomethyl benzoate, monohydrochloride 3**: A clear solution of **2** (5 g; 22.7 mmoles) in EtOH (300 mL) and $CHCl_3$ (10 mL) was hydrogenated over $PtO_2$ (0.6 g) at 200 psi for 24 hr. Catalyst was filtered off and the filtrate was concentrated to ~50 mL and cooled in an ice box. The white solid was filtered (3.2 g). The filtrate was concentrated to ~10 mL and cooled in a refrigerator for 1 hr. The second crop of the solid was filtered (0.95 g). The filtrate contained mostly partially hydrogenated product (**3a**). The combined solid was recrystallized from dry alcohol and ether; yield 3.50 g (82%). Attempt was made to use more concentrated solution for hydrogenation viz. 10g/300 mL or 7 g/300 mL, invariably resulted in poor yields; m.p. 200 (s), 220-22°C (d); IR: 3445, 3350, 3265, 2975, 1677, 1645, 1610 $cm^{-1}$; $^1H$ NMR ($CDCl_3$+DMSO-$d_6$): δ 1.37 (3H, t, $J$ = 7.09, $CH_3$), 4.17 (2H, s, $CH_2N$), 4.3 (2H, quart, $J$ = 7.09, $CH_2$), 6.04 (2H, br, $D_2O$ exchangeable, $NH_2$), 6.69 (1H, dd, $J$ = 8.1, 2.0, 5-H), 6.73 (1H, d, $J$ = 2.0, 3-H), 7.84 (1H, d, $J$ = 8.1, 6-H), 8.3 (3H, br, $NH_3^+$, $D_2O$ exchangeable). Anal Calcd for. $C_{10}H_{15}N_2O_2$: C, 52.06; H, 6.55; N, 12.14; Cl, 15.37. Found, C, 52.21; H, 6.51; N, 12.13; Cl, 15.2%.

**Ethyl 4-amino-2-cyano benzoate 3a**: m.p. 222-24°C (hot EtOAc); IR: 3470, 3375, 2235, 1700, 1635 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 1.33 (3H, t, $J$ = 7.09, $CH_3$), 4.29 (2H, quart, $J$ = 7.09, $CH_2$), 6.50 (2H, br, $D_2O$ exchangeable, $NH_2$), 6.88 (1H, dd, $J$ = 8.1, 2.0,

5-H), 7.03 (1H, d, *J* = 2.0, 3-H), 7.83 (1H, d, *J* = 8.1, 6-H). Anal Calcd for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found, C, 63.22; H, 5.34; N, 14.60%.

**5-Amino-2, 3-dihydro-1H-benzo(*c*)-azol-1-one 4**: Compound **3** (1.8g; 7.8 mmoles) was dissolved in DMF (20 mL) and chilled to 0°C. Triethylamine (1.12 mL; 8 mmoles) and DMAP (0.2g; 1.6 mmole) were added successively. The mixture was brought to room temperature and subsequently heated at 110°C for 2hrs. Solvent was removed and the residue was purified by flash chromatography with 10% MeOH in $CHCl_3$ containing 0.1% acetic acid. Yield, 0.75g (64%); m.p. 197-99°C (hot EtOAc); IR: 3440, 3400, 3230, 1685, 1675(br), 1610(br) $cm^{-1}$: $^1H$ NMR ($CDCl_3$ + DMSO-$d_6$): δ 4.09(2H, s, $ArCH_2N$), 5.20 (2H br, $D_2O$ exchangeable, $NH_2$), 6.64-6.74 (2H, m, 4-H and 6-H), 7.46 (1H, d, *J* = 9.1, 7-H), 7.69 (1H, br, $D_2O$ exchangeable, CONH). Anal Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found, C, 64.59; H, 5.36; N, 18.82%.

**5-Di- carbobenzoxy guanidino-2, 3-dihydro-1*H*-benzo(*c*)-azol-1-one 5**: A solution of 4 (4.48 g; 40 mmoles) and dicarbobenzoxy-S-methyl-isothiourea (12 g; 48 mmoles) in dichloromethane (100 mL) and acetonitrile (100 mL) was refluxed for 16 hr. The solid was filtered and was suspended in MeOH (50 mL). The suspension was stirred for 10 min at 50°C. The solid was filtered and washed with MeOH. It was dried for 2 hr. Yield, 8.5g (46%); mp. 247-48°C (d); IR: 3160 (br), 1730, 1685, 1650, 1635 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + TFA-D): δ 4.62 (2H, s, $ArCH_2N$); 5.23 (2H, s, $OCH_2Ph$), 5.42 (2H, s, $OCH_2Ph$), 7.3-7.6 (12H, m, Ph-H, 4-H and 6-H), 8.0 (1H, d, *J* = 8, 7-H). Anal Calcd for $C_{25}H_{22}N_4O_5$: C, 65.49; H, 4.84; N, 12.22. Found, C, 65.40; H, 4.83; N, 12.11%.

**Benzyl 2-(4-acetylphenoxy) acetate 6**: A mixture of 4-hydroxy acetophenone (40.86 g; 300 mmoles), benzyl bromoacetate (47.53 mL; 300 mmoles) and freshly fused $K_2CO_3$ (50 g) in DMF (150 mL) was heated at 75-80°C for 1.5 hr. The reaction mixture was cooled to room temperature and poured over crushed ice (~500 g). The solid separated out was filtered, washed with water thoroughly and dried. It was crystallized from ethyl acetate and light petroleum as colorless needles. Yield 68g (79.8%); m.p. 85-86°C (EtOAC-light petroleum); IR: 1760, 1678, 1615, 1590 $cm^{-1}$; $^1H$ NMR: δ 2.56 (s, 3H, $COCH_3$), 4.74 (s, 2H, $OCH_2CO$), 5.26 (s, 2H, $OCH_2Ph$), 6.95 (d, 2H, *J* = 9.11, 3-H and 5-H), 7.37 (br, 5H, 5 × PhH), 7.95 (d, 2H, *J* = 9.11, 2-H and 6-H). Anal Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.65; H, 5.59%.

The compounds **7-9** and **14-16** were prepared according to the above-mentioned method.

**Ethyl 2-(4-acetylphenoxy) propanoate 7**: Yield 92.2% (liquid); IR: 3500-3400 (br), 1740 (br), 1670, 1600 $cm^{-1}$; $^1H$ NMR: δ 1.26 (t, 3H, *J* = 7.09, $CH_3$), 1.64 (d, 3H, *J* = 6.6, $CHCH_3$), 2.54 (s, 3H, $COCH_3$), 4.22 (quartet, 2H, *J* = 7.09, $OCH_2Me$), 4.86 (quartet, 1H, *J* = 7.09, CHMe), 6.91 (d, 2H, *J* = 9.1, 3-H and 5-H), 7.94 (d, 2H, *J* = 9.1, 2-H and 6-H). Anal Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.87; H, 6.92%.

**Ethyl 2-(4-acetylphenoxy) 2-methylpropanoate 8**: Yield 32.4% (liquid); IR: 3000, 1745, 1690, 1610 $cm^{-1}$; $^1H$ NMR: δ 1.23 (t, 3H, *J* = 7.09, $CH_3$), 1.70 [s, 6H, C $(CH_3)_2$], 2.56 (s, 3H, $COCH_3$), 4.24 (quartet, 2H, *J* = 7.09, $OCH_2Me$), 6.86 (d, 2H, *J* = 9.1, 3-H and 5-H), 7.91 (d, 2H, *J* = 9.1, 2-H and 6-H). Anal Calcd for $C_{14}H_{18}O_4$: C, 69.98; H, 7.55. Found: C, 70.21; H, 7.39%.

**Benzyl 2-(4-acetylphenoxy) 2-methylpropanoate 9**: Yield 32% (liquid); IR (neat): 1725 (br), 1665, 1590 $cm^{-1}$; $^1H$ NMR (300 MHz): δ 1.69 [s, 6H, C $(CH_3)_2$], 2.54 (s, 3H, $COCH_3$), 5.2 (s, 2H, $OCH_2Ph$), 6.76 (d, 2H, *J* = 8.25, 3-H and 5-H), 7.22-7.48 (3m, 5H, 5 × PhH), 7.79 (d, 2H, *J* = 8.25, 2-H and 6-H). Anal Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.25; H, 6.57%.

**Methyl 2-(2-methyloxycarbonylmethoxyphenoxy) acetate 14**: Yield 87%; 61-62°C (EtOAc-light petroleum); IR: 2960, 1750 (br), 1595, 1505 $cm^{-1}$; $^1H$ NMR: δ 3.81 (s, 6H, 2 × $OCH_3$), 4.76 (s, 4H, 2 × $OCH_2CO$), 6.96 (br, 4H, 4ArH). Anal Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 57.07; H, 5.71%.

**Ethyl 2-(2-ethyloxycarbonylmethoxyphenoxy) acetate 15**: Yield 90% (liquid); IR (neat): 3000 (br), 2960, 1780,1770, 1758, 1748 $cm^{-1}$; $^1H$ NMR (T-60): δ 1.28 (t, 6H, *J* = 7.6, 2 × $CH_3$), 4.37 (quartet, 4H, *J* = 7.6, 2 × $OCH_2Me$), 4.83 (s, 4H, 2 × $OCH_2CO$), 7.05 (br, 4H, 4 × ArH). Anal Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.48; H, 6.34%.

**Isopropyl 2-(2-isopropyloxycarbonylmethoxyphenoxy) acetate 16**: Yield 93.2% (liquid); IR: 2980, 1745 (br), 1595, 1500 $cm^{-1}$; $^1H$ NMR: δ 1.24 [d, 12H, *J* = 7.09, 2 $CH(CH_3)_2$], 4.69 (s, 4H, 2 × $OCH_2CO$),

5.14 (heptate, 2H, $J$ = 7.09, 2 × $CHMe_2$), 6.93 (br, 4H, 4 × ArH). Anal Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.48; H, 6.34%.

**Methyl 2-(4-acetyl-2-methyloxycarbonylmethoxyphenoxy) acetate 17**: Perchloric acid (70% aq.; 0.4) was added slowly to freshly distilled $Ac_2O$ (10 mL) maintained at 0°C. Compound 14 (12.7 g; 50 mmoles) in $CH_2Cl_2$ (5 mL) was added drop wise at 10-15°C. When the addition was over (~5 min), the reaction mixture was heated on steam bath for 1 hr. The solvent was removed and the residue poured over crushed ice containing excess of $NaHCO_3$ (~10 g). The residue was extracted with ether. The ethereal layer was washed with brine and dried over anhydrous $Na_2SO_4$. Solvent was removed and the residue was purified by flash chromatography with 5 % $CH_3CN$ in $CHCl_3$. Yield, 9.62 g (65%); m.p, 106-07°C (EtOAc-light petroleum); IR: 1780, 1745, 1740, 1675, 1595 $cm^{-1}$; $^1H$ NMR: δ 2.54 (s, 3H, $COCH_3$), 3.81 (s, 6H, 2 × $COOCH_3$), 4.80, 5.10 (2 × s, 4H, 2 × $OCH_2CO$), 6.88 (d, 1H, $J$ = 8.61, 5-H), 7.54 (d, 1H, $J$ = 2, 2-H), 7.61 (dd, 1H, $J$ = 8.61, 2.0, 6-H). Anal Calcd for $C_{14}H_{16}O_7$: C, 56.76; H, 5.44. Found: C, 57.12; H, 5.58%.

The compounds **18** and **19** were also prepared by the same method:

**Ethyl 2-(4-acetyl-2-ethyloxycarbonylmethoxyphenoxy) acetate 18**: Yield 68% (semisolid): IR: 3010, 2960, 1780 (br), 1770, 1760, 1750 $cm^{-1}$; $^1H$-NMR (T-60): δ 1.30 (t, 6H, $J$ = 7.2, 2 × $OCH_3$), 2.55 (s, 3H, $COCH_3$), 4.28 (quartet, 4H, $J$ = 7.2, $OCH_2Me$), 4.78, (s, 4H, 2 × $OCH_2CO$), 6.87 (d, 1H, $J$ = 8.61, 5-H), 7.53 (d, 1H, $J$ = 2, 2-H), 7.57 (dd, 1H, $J$ = 8.61, 2.0, 6-H). Anal Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.57; H, 6.28%.

**Iopropyl 2-(4-acetyl-2-isopropyloxycarbonylmethoxyphenoxy) acetate 19**: Yield 45.5%; m.p. 73-74°C (EtOAc-light petroleum); IR: 3000, 1760, 1755, 1675, 1600 $cm^{-1}$; $^1H$ NMR: δ 1.29, 1.30 [2 d, 12H, $J$ = 6.7, 2 × $OCH(CH_3)_2$], 2.54 (s, 3H, $COCH_3$), 4.74, 4.77 (2 s, 4H, 2 × $OCH_2CO$), 5.14 (hep, 2H, $J$ = 6.7, 2 × $CHMe_2$), 6.86 (d, 1H, $J$ = 8.1, 5-H), 7.54 (br, 1H, $J$ = 1.8, 2-H), 7.59 (dd, 1H, $J$ = 8.1, 1.8, 6-H). Anal Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 60.96; H, 6.78%.

**Benzyl 2-[4-(2-bromoacetyl) phenoxy] acetate 10**: Cupric bromide (3.72 g; 16.7 mmoles) was suspended in EtOAc (10 mL) and heated to reflux. The compound **6** (2.84 g; 10 mmoles) was dissolved in $CHCl_3$ (10 mL), heated to reflux and was added to $CuBr_2$. The reaction mixture was further refluxed for 25 min. It was brought back to room temperature and the precipitated white solid was filtered. The filtrate was diluted with $CHCl_3$ (50 mL) and quickly washed with water (2 × 15 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and solvent was removed. The residue was purified by flash chromatography with $CHCl_3$ as ululating solvent. Yield 56%; 96-97°C ($CHCl_3$-light petroleum); IR: 1740 (br), 1685, 1600, 1570 $cm^{-1}$; $^1H$ NMR: δ 4.39 (s, 2H, $BrCH_2CO$), 4.74 (s, 2H, $OCH_2CO$), 5.26 (s, 2H, $OCH_2Ph$), 6.94 (d, 2H, $J$ = 9.61, 3-H and 5-H), 7.36 (3 m, 5H, 5 × PhH), 7.96 (d, 2H, $J$ = 9.61, 2-H and 6-H). Anal Calcd for $C_{17}H_{15}O_4Br$: C, 56.22; H, 4.16; Br, 22.0. Found: C, 56.27; H, 4.34; Br, 21.67%.

Compounds **11-13** and **20-22** were prepared by the same method with the use of benzene in place of EtOAc except those cases where ethyl ester was used (viz., **7**, **8**, **9**, and **21**) to avoid transesterification.

Methyl 2-[4-(2-bromoacetyl) phenoxy] acetate[18]:and ethyl 2-[4-(2-bromoacetyl) phenoxy] acetate were prepared by literature method[18,19].

**Ethyl 2-[4-(2-bromoacetyl) phenoxy] propanoate 11**: Yield 64.23% (liquid) (lit. yield, 50.7%[20]); IR: 2980, 1740 (br), 1670 (br), 1595 $cm^{-1}$; $^1H$ NMR: δ 1.29 (t, 3H, $J$ = 7.09, $CH_3$), 1.69 (d, 3H, $J$ = 7.09, $CHCH_3$), 4.29 (quartet, 2H, $J$ = 7.09, $CH_2Me$), 4.43 (s, 2H, $BrCH_2CO$), 4.83 (quartet, 1H, $J$ = 7.09, CHMe), 6.98 (d, 2H, $J$ = 9.11, 3-H and 5-H), 8.03 (d, 2H, $J$ = 9.11, 2-H and 6-H). Anal Calcd for $C_{13}H_{15}O_4Br$: C, 49.55; H, 4.79; Br, 25.35. Found: C, 49.38; H, 4.77; Br, 25.51%.

**Ethyl 2-[4-(2-bromoacetyl) phenoxy] 2-methyl propanoate 12**: Yield 48.6% (liquid) (lit yield, 23%[21]); IR: 3000, 1745, 1735, 1680, 1605 $cm^{-1}$; $^1H$ NMR: δ 1.23 (t, 3H, $J$ = 6.58, $CH_3$), 1.70 [s, 6H, C $(CH_3)_2$], 4.24 (quartet, 2H, $J$ = 6.58, $CH_2Me$), 4.40 (s, 2H, $BrCH_2CO$), 6.86 (d, 2H, $J$ = 9.11, 3-H and 5-H), 7.93 (d, 2H, J= 9.11, 2-H and 6-H). Anal Calcd for $C_{14}H_{17}O_4Br$: C, 51.08; H, 5.21; Br, 24.27. Found: C, 51.21; H, 5.28; Br, 24.39%.

**Benzyl 2-[4-(2-bromoacetyl) phenoxy] 2-methyl propanoate 13**: Yield 45% (liquid); $^1H$-NMR (300 MHz): δ 1.68 [s, 6H, C $(CH_3)_2$], 4.40 (s, 2H, $BrCH_2CO$), 5.21 (s, 2H, $OCH_2Ph$), 6.76 (d, 2H, $J$ = 8.6, 3-H and 5-H), 7.19-7.47 (m, 5H, 5 × PhH), 7.83 (d, 2H, $J$ = 8.6, 2-H and 6-H). Anal Calcd for

$C_{19}H_{19}O_4Br$: C, 58.33; H, 4.89; Br, 20.42. Found: C, 58.25; H, 4.97; Br, 20.38%.

**Methyl 2-[4-(2-bromoacetyl)-2-methyloxycarbonylmethoxyphenoxy) acetate 20**: Yield, 61%; mp. 89-91°C (EtOAc-light petroleum); IR: 2950, 1750, 1735, 1695, 1600 $cm^{-1}$; $^1H$ NMR: δ 3.81 (s, 6H, 2 $COOCH_3$), 4.38 (s, 2H, $BrCH_2CO$), 4.79, 4.81 (2 × s, 4H, 2 × $OCH_2CO$), 6.88 (d, 1H, *J* = 8.1, 5-H), 7.54 (d, 1H, *J* = 2, 2-H), 7.65 (dd, 1H, *J* = 8.1, 2.0, 6-H). Anal Calcd for $C_{14}H_{15}O_7Br$: C, 44.82; H, 4.03; Br, 21.29. Found: C, 45.20; H, 4.02; Br, 21.67%.

**Ethyl 2-[4-(2-bromoacetyl)-2-ethyloxycarbonylmethoxyphenoxy) acetate 21**: Yield, 66%; mp. 84-85°C (EtOAc-light petroleum); IR: 3010, 1775 (br), 1680, 1605, 1530 $cm^{-1}$; $^1H$ NMR: δ 1.29, 1.30 (2 × t, 6H, *J* = 7.09, 2 × $CH_3$), 4.29 (quartet, 4H, *J* = 7.09, 2 $CH_2Me$), 4.40 (s, 2H, $BrCH_2CO$), 4.79, 4.81 (2 × s, 4H, 2 × $OCH_2CO$), 6.89 (d, 1H, *J* = 8.1, 5-H), 7.59 (d, 1H, *J* = 1.8, 2-H), 7.65 (dd, 1H, *J* = 8.1, 1.8, 6-H). Anal Calcd for $C_{16}H_{19}O_7Br$: C, 47.66; H, 4.75; Br, 19.82. Found: C, 48.08; H, 4.82; Br, 19.40%.

**Iopropyl 2-[4-(2-bromoacetyl)-2-isopropyloxycarbonylmethoxyphenoxy) acetate 22**: Yield 34%; m.p. 94-95°C (EtOAc-light petroleum); IR: 2985, 1750, 1730, 1680, 1600 $cm^{-1}$; $^1H$ NMR: δ 2.59 [d, 12H, *J* = 7.09, 2 × $CH(CH_3)_2$], 4.37 (s, 2H, $COCH_2Br$), 4.73, 4.76 (2 × s, 4H, 2 × $OCH_2CO$), 5.14 (hep, 2H, *J* = 7.09, 2 × *C*H$Me_2$), 6.86 (d, 1H, *J* = 8.1, 5-H), 7.54 (d, 1H, *J* = 1.8, 2-H), 7.61 (dd, 1H, *J* = 8.1, 1.8, 6-H). Anal Calcd for $C_{18}H_{23}O_7Br$: C, 50.13; H, 5.37; Br, 18.55. Found: C, 49.75; H, 5.29; Br, 18.82%.

**Methyl 2-[4-2(hydroxyethyl) phenoxy] acetate 23**: The compound 4-(2-hydroxy-ethyl)-phenol (2.76 g; 20 mmoles) was dissolved in 4 N NaOH (5 mL; 20 mmoles) and then water was removed under reduced pressure. The sodium salt was dried for 6 h under vacuum pump at 40-50°C. The dry sample was taken up in dry DMF and methyl bromoacetate (2.08 mL; 22 mmoles) was added slowly under vigorous stirring. The reaction mixture was kept at room temperature for 4 hr followed by 1 hr at 50°C. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (30 mL) and 1N aq. HCl (10 mL). The organic layer was separated and washed with brine. It was dried over anhydrous $Na_2SO_4$ and solvent was removed. The residue was purified by flash chromatography with 10% $CH_3CN$ in $CHCl_3$. Yield, 3.14 g (75%), oil; IR (neat): 3400 (br), 2960 (br), 1755 (br), 1610 $cm^{-1}$; $^1H$ NMR: δ 2.81 (t, 2H, *J* = 6.58, $ArCH_2$), 3.82 (t, 2H, *J* = 6.58, $CH_2OH$), 3.80 (s, 3H, $COOCH_3$), 4.61 (s, 2H, $OCH_2CO$), 6.87 (d, 2H, J=8.1, 2-H and 6-H), 7.18 (d, 2H, *J* = 8.1, 3-H and 5-H). Anal Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.70; H, 6.66%.

**Methyl 2-[4-(2-bromoethyl) phenoxy] acetate 24**: Yield, 72%, oil; IR (neat): 1745 (br), 1695, 1600, 1500 $cm^{-1}$; $^1H$-NMR: δ 3.07 (t, 2H, *J* = 7.09, $ArCH_2$), 3.51 (t, 2H, *J* = 7.09, $CH_2Br$), 3.79 (s, 3H, $COOCH_3$), 4.61 (s, 2H, $OCH_2CO$), 6.86 (d, 2H, *J* = 8.1, 2-H and 6-H), 7.14 (d, 2H, *J* = 8.1, 3-H and 5-H). Anal Calcd for $C_{11}H_{13}O_3Br$: C, 48.37; H, 4.79; Br, 29.26. Found: C, 48.61; H, 4.83; Br, 29.10%.

**Ethyl 4-amino-2-tertiary butyloxycarbonyl aminomethyl-benzoate 25**: To a vigorously stirred solution of compound **3** (13 g; 56.35 mmoles) and di-tertiarybutyl-di-carbonate (12.3 g; 56.35 mmoles) in dioxane (340 mL), water (340 mL), and $NaHCO_3$ (5.2 g) was added. Stirring was continued for 1 hr at room temperature. Dioxane was removed and the residue was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $Na_2SO_4$. The solvent was removed and the residue was purified by crystallization from hot EtOAc. Yield, 18 g (80.8%); m.p. 168-69°C (EtOAc); IR: 3470 (br), 3390, 1722, 1690, 1655, 1615 $cm^{-1}$; $^1H$ NMR: 1.39 (3H, t, *J* = 7.09, $CH_3$), 1.46 [9H, s, C $(CH_3)_3$], 4.10 (2H, br, $D_2O$ exchangeable $NH_2$), 4.31 (2H, quartet, *J* = 7.09, $CH_2Me$), 4.47 (2H, s, $CH_2NH$), 6.54 (1H, dd, *J* = 8.1, 2.5, 5-H), 6.71 (1H, d, *J* = 2.5, 3-H), 7.87 (1H, d, *J* = 8.1, 6-H). Anal Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found, C, 61.56; H, 7.65; N, 9.59%.

**Ethyl 4-dicarbobenzoxy guanidino-2-(tertiary butyl oxyarbonyl) amino methyl-benzoate 26**: A solution of **25** (9.5 g; 32.27 mmoles) and dicarbobenzoxy-S-methyl isothiourea (15.2 g; 42.46 mmoles) in acetonitrile (190 mL) was heated at 82-85°C (oil bath temperature) for 2 hr. The solvent was removed. The residue was purified by flash chromatography with 5% acetonitrile-chloroform. Yield, 15.5 g (79.44%); m.p. 124-25°C (EtOAc-light petroleum); IR: 3440, 1725 (br), 1645 (br), 1605 $cm^{-1}$; $^1H$ NMR: δ 1.39 (3H, t, *J* = 7.60, $CH_3$), 1.41 [9H, s, C $(CH_3)_3$], 4.35 (2H, quartet, *J* = 7.60, $CH_2Me$), 4.54 (2H, s, $ArCH_2NH$), 5.17, 5.39 (4H, 2 × s, 2 × $OCH_2Ph$), 7.30-7.49 (12H, br, 10 × PhH, 3-H, and 5-H), 7.94 (1H, br, 6-H), 10.42, 11.83 (2H, 2 × br, 2

NH). Anal Calcd for $C_{32}H_{36}N_4O_8$: C, 63.57; H, 6.00; N, 9.27. Found, C, 63,83; H, 6.15; N, 9.31%.

**Ethyl 2-aminomethyl-4-dicarbobenzoxy guanidino-benzoate (formate salt) 27**: Compound **26** (5 g; 8.26 mmoles) and anisole (0.1 mL) were dissolved in 98-100% formic acid (10 mL). The clear solution was kept at room temperature for 6hr. Formic acid was removed and the residue was triturated with dry ether. The solid was filtered and washed with dry ether. Finally the product was crystallized from dry MeOH-ether. Yield, 3.5 g (76.9%); mp. 225-27°C (MeOH-ether); IR: 2990 (br), 1740, 1715 (br), 1645 (br) and 1635 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + DMSO-$d_6$): δ 1.44 (3H, t, $J$ = 7.6, $CH_3$), 4.34 (2H, s, $CH_2NH_3^+$), 4.43 (2H, quartet, $J$ = 7.6, $CH_2Me$), 5.27 (4H, s, 2 × $CH_2Ph$), 6.16 (3H, m, $D_2O$ exchangeable, $CH_2NH_3^+$), 7.30-7.37 (11H, br, 10 × Ph*H* and 5-H), 7.76 (1H, d, $J$ = 1.2, 3-H), 8.07 (1H, d, $J$ = 5.06, 6-H). Anal Calcd for $C_{28}H_{30}N_4O_8$: C, 61.08; H, 5.49; N, 10.18. Found: C, 60.98; H, 5.58; N, 10.46%.

**Benzyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-acetate 28**: The compound **27** (0.7 g; 1.27 mmole) was taken up in dichloromethane (10 mL) and $NaHCO_3$ (1 g) was added followed by benzyl 2-[4-(2-bromo acetyl) phonoxy] acetate (0.8 g; 2.2 mmoles) under vigorous stirring. Stirring was continued overnight. The solid was filtered and the filtrate was diluted with $CHCl_3$ (20 mL). The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$. The solvent was removed and the residue was purified by flash chromatography with 5% acetonitrile in chloroform followed by 10% acetonitrile-chloroform. Yield 0.34 g; (36.15%), m.p. 138-40°C (hot EtOAc); IR: 1742, 1735, 1715, 1685 (br) $cm^{-1}$; $^1H$ NMR: δ 4.53 (2H, s, $ArCH_2N$), 4.74 (2H, s, $OCH_2CO$), 4.98 (2H, s, $NCH_2CO$), 5,27 (6H, s, 3 $OCH_2Ph$), 6.96 (2H, d, $J$ = 9.1, 3′-H and 5′-H), 7.51-7.60 (17H, m, 15 × PhH, 4-H and 6-H), 7.80 (1H, d, $J$ = 7.09, 7-H), 8.02 (2H, d, $J$ = 9.1, 2′-H and 6′-H). Anal Calcd for $C_{42}H_{36}N_4O_9$: C, 68.09; H, 4.89; N, 7.56. Found: C, 68.12; H, 4.80; N, 7.47%.

Compounds **29** to **37** were prepared in a similar manner starting from **27** and corresponding alkylating agent (**10-13**, **20-22**, **24**) respectively.

**Methyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-acetate 29**: Purification of the crude material was achieved by flash chromatography with 7.5% $CH_3CN$ in $CHCl_3$. Yield, 21.44%, m.p. 203-04°C (hot EtOAc); IR: 1780, 1735, 1710, 1650, 1618 $cm^{-1}$; $^1H$ NMR: δ 3.83 (3H, s, $OCH_3$), 4.52 (2H, s, $ArCH_2N$), 4.73 (2H, s, $OCH_2CO$), 4.99 (2H, s, $NCH_2CO$), 5.19, 5.26 (4H, 2 × s, 2 × $OCH_2Ph$), 6.98 (2H, d, $J$ = 8.1, 3′-H and 5′-H), 7.31-7.53 (11H, m, 10 × PhH and 6-H), 7.84 (1H, d, $J$ = 7.09, Ar*H*$^7$), 8.03 (1H, d, $J$ = 1.8, Ar*H*$^4$), 8.04 (2H, d, $J$ = 8.1, Ar*H*$^{2'}$ and Ar*H*$^{6'}$), 10.52, 11.88 (2H, 2 × s, 2 × NH). Anal Calcd for $C_{36}H_{32}N_4O_9$: C, 65.05; H, 4.85; N, 8.43. Found: C, 64.85; H, 4.89; N, 8.34%.

**Ethyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-acetate 30**: The crude product was purified by flash chromatography with 10% $CH_3CN$ in $CHCl_3$. Yield, 26%; m.p. 186-88°C (hot EtOAc); IR: 1747, 1700, 1680, 1650 (br) $cm^{-1}$; $^1H$ NMR: δ 1.30 (3H, t, $J$ = 7.09, $CH_3$), 4.23 (2H, quartet, $J$ = 7.09, $CH_2Me$), 4.51 (2H, s, $ArCH_2N$), 4.70 (2H, s, $OCH_2CO$), 4.99 (2H, s, $NCH_2CO$), 5.17, 5.26 (4H, 2 × s, 2 × $OCH_2Ph$), 6.98 (2H, d, $J$ = 9.1, 3′-H and 5′-H), 7.26-7.54 (11H, m, 10 × PhH and 6-H), 7.84 (1H, d, $J$ = 8.1, 7-H), 8.01 (1H, d, $J$ = 1.8, 4-H), 8.04 (2H, d, $J$ = 9.1, 2′-H and 6′-H). Anal Calcd for $C_{37}H_{34}N_4O_9$: C, 65.48; H, 5.05; N, 8.25. Found: C, 65.23; H, 4.94; N, 7.91%.

**Ethyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1H-benzo[c] azol-2-yl) acetyl]-phenoxy}-propanate 31**: Yield, 14%; m.p. 150-51°C ($CH_2Cl_2$-EtOAc); IR: 1725, 1695, 1680, 1650, 1630, 1600 $cm^{-1}$; $^1H$ NMR: δ 1.25 (3H, t, $J$ = 8.1, $CH_3$), 1.66 [3H, d, $J$ = 8.1, CH ($CH_3$) COOEt], 4.24 (2H, quartet, $J$ = 8.1, $CH_2Me$), 4.50 (2H, s, $ArCH_2N$), 4.85 (1H, quartet, $J$ = 8.1, CHMe), 4.98 (2H, s, $NCH_2CO$), 5.16,5.28 (4H, 2 × s, 2 × $OCH_2Ph$), 6.94 (2H, d, $J$ = 9.1, 3′-H and 5′-H), 7.32-7.42 (10H, br, 10 × ArH), 7.48 (1H, dd, $J$ = 8.2, 1.8, 6-H), 7.83 (1H, d, $J$ = 8.2, 7-H), 7.99 (2H, d, $J$ = 9.1, 2′-H and 6′-H), 8.02 (1H, d, $J$ = 1.8, 4-H). Anal Calcd for $C_{38}H_{36}N_4O_9$: C, 65.89; H, 5.23; N, 8.09. Found: C, 65.64; H, 5.24; N, 7.76%.

Ethyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-2-methyl-propanate 32: Yield, 22%; mp. 152-55°C ($CH_2Cl_2$-EtOAc); IR: 1745, 1685, 1650, 1610 $cm^{-1}$; $^1H$ NMR: δ 1.19 (3H, t, $J$ = 7.2, $CH_3$), 1.63 (6H, s, 2 × $CH_3$), 4.23 (2H, quartet, $J$ = 7.21, $OCH_2Me$), 4.49 (2H, s, $ArCH_2N$), 4.96 (2H, s, $NCH_2CO$), 5.15, 5.26 (4H, 2 × s, 2 × $OCH_2Ph$), 6.84 (2H, d, $J$ = 8.7, 3′-H and 5′-H), 7.30-7.50 (11H, m, 10 × Ph*H* and 6-H), 7.80 (1H, d, $J$ = 8.7, 7-H), 7.94 (2H, d, $J$ = 8.7, 2′-H

and 6′-H), 8.0 (1H, d, *J* = 1.8, 4-H), 10.51, 11.87 (2H, 2 × s, exchangeable, 2 × NH). Anal Calcd for $C_{39}H_{38}N_4O_9$: C, 66.28; H, 5.41; N, 7.93. Found: C, 66.50; H, 5.42; N, 7.66%.

**Benzyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-2-methyl-propanate 33**: Yield, 20%; m.p. 145-46°C ($CH_2Cl_2$-EtOAc); IR: 1730, 1695, 1685, 1645, 1605 $cm^{-1}$; $^1H$ NMR: δ 1.50, 1.58 (6H, 2 × s, 2 × $CH_3$), 4.47 (2H, s, $ArCH_2N$), 4.89 (2H, s, $NCH_2CO$), 5.13, 5.14, 5.19 (6H, 3 × s, 3 × $OCH_2Ph$), 6.72 (2H, d, *J* = 9.01, 3′-H and 5′-H), 7.15-7.35 (15H, m, 15 × Ph*H*), 7.38 (1H, d, *J* = 8.1, 6-H), 7.80 (3H, d, *J* = 8.1, 7-H, 2′-H and 6′-H), 7.94 (1H, s, 4-H), 10.47, 11.85 (2H, 2 × s, 2 × NH). Anal Calcd for $C_{44}H_{40}N_4O_9$: C, 68.74; H, 5.24; N, 7.29. Found: C, 68.43; H, 5.24; N, 7.25%.

**Methyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-2-methyloxycarbonylmethoxyphenoxy} acetate 34**: Yield, 24%; m.p. 150-151°C (EtOAc); IR: 1755, 1730, 1682 (br), 1640, 1455 $cm^{-1}$; $^1H$ NMR: δ 3.80 (6H, s, 2 $OCH_3$), 4.50 (2H, s, $ArCH_2N$), 4.78, 4.80 (4H, 2 × s, 2 × $OCH_2COOMe$), 4.94 (2H, s, $NCH_2$ CO), 5,15, 5.26 (4H, 2 × s, 2 × $OCH_2Ph$), 6.86 (1H, d, *J* = 8.1, 5-H′), 7.30-8.0 (15H, m, 4-H, 6-H, 7-H, 2′-H, 6′-H and 10 × PhH). Anal Calcd for $C_{39}H_{36}N_4O_{12}$: C, 62.23; H, 4.82; N, 7.44. Found: C, 62.18; H, 4.76; N, 7.29%.

**Ethyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-2-ethyloxycarbonylmethoxyphenoxy} acetate 35**: Yield, 25.7%; m.p. 177-78°C (EtOAc); IR: 1740, 1635 (br), 1625, 1445 $cm^{-1}$; $^1H$-NMR: δ 1.30 (6H, t, *J* = 7.09, 2 × $CH_3$), 4.26 (4H, quartet, *J* = 7.09, 2 × $CH_2Me$), 4.49 (2H, s, $ArCH_2N$), 4.76 (4H, 2 × s, 2 × $OCH_2COOEt$), 4.95 (2H, s, $NCH_2CO$), 5.17, 5.26 (4H, 2 × s, 2 × $CH_2Ph$), 6.84-8.03 (16H, m, 10 × PhH, 4-H, 6-H, 7-H, 2′-H, 5′-H and 6′-H), 10.51, 11.87 (2H, 2 × br, 2 × NH). Anal Calcd for $C_{41}H_{40}N_4O_{12}$: C, 63.07; H, 5.16; N, 7.18. Found: C, 63.17; H, 5.21; N, 6.94%.

**Isopropyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-2-isopropyloxycarbonylmethoxyphenoxy} acetate 36**: Yield, 10%; m.p. 167-68°C ($CH_2Cl_2$-EtOAc); IR: 1743, 1690, 1630, 1600 $cm^{-1}$; $^1H$ NMR: δ 1.20 [12H, br, 2 × CH $(CH_3)_2$], 4.51 (2H, s, $ArCH_2N$), 4.71, 4.75 (4H, 2 × s, 2 × $OCH_2CO$), 4.98 (2H, s, $NCH_2CO$), 5.13 (2H, m, 2 × *C*H$Me_2$), 5.13, 5.24 (4H, 2 × s, 2 × $OCH_2Ph$), 6.88 (1H, d, *J* = 9.2, 5′-H), 7.30-7.41 (10H, m, 10 × PhH), 7.48 (1H, d, *J* = 9.1, 6-H), 7.57 (1H, s, 2′-H), 7.69 (1H, d, *J* = 9.1, 7-H), 7.82 (1H, d, *J* = 9.2, 6′-H), 8.02 (1H, s, 4-H), 10.55 (1H, s, N*H*). Anal Calcd for $C_{43}H_{44}N_4O_{12}$: C, 63.85; H, 5.48; N, 6.93. Found: C, 63.24; H, 5.50; N, 6.84%.

**Methyl 2-{4-[2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) ethyl] phenoxy} acetate 37**: The crude product was purified by flash chromatography with 10% $CH_3CN$-$CHCl_3$. Yield 24.7%; m.p. 155-57°C (EtOAc-light petroleum); IR: 1765, 1745, 1730, 1675, 1620 (br) $cm^{-1}$; $^1H$ NMR (300 MHz): δ 2.90 (2H, t, *J* = 8.65, $CH_2$ Ar), 3.82 (5H, br, $NCH_2$ and $OCH_3$), 4.20 (2H, s, $ArCH_2N$), 4.60 (2H, s, $OCH_2$ COOMe), 5.10, 5.25 (4H, 2 × s, 2 × $CH_2Ph$), 6.82 (2H, d, *J* = 8.6, 2′-H and 6′-H), 7.13 (2H, d, *J* = 8.6, 3′-H, 5′-H), 7.35-7.45 (11H, br, 10 × PhH and 6-H), 7.76 (1H, d, *J* = 8.65, 7-H), 7.95 (1H, d, *J* = 1.8, 4-H). Anal Calcd for $C_{36}H_{34}N_4O_8$: C, 66.45; H, 5.27; N, 8.61. Found: C, 66.23; H, 4.94; N, 8.44%.

**Ethyl 2- (5-dicarbobenzoxyguanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetate 38**: Sodium hydride [0.72 g (50%); 15 mmoles) was washed with dry toluene (2 × 5 mL) and suspended in dry HMPA (10 mL). Compound **5** (1.3 g; 3 mmoles) was added slowly under vigorous stirring at room temperature. After the addition was over the mixture was stirred at room temperature for 3 hr. (the mixture turned deep brown in color). Ethyl bromoacetate (0.39 mL; 3.5 mmoles) was added and stirring was continued for 30 minute. The reaction mixture was diluted with EtOAc and poured over dil. aqueous HCl (to *p*H 2). The ethyl acetate layer was washed with brine, dried over anhydrous $Na_2SO_4$. The solvent was removed and the residue was purified by flash chromatography with 10% $CH_3CN$-$CHCl_3$. The homogeneous product was crystallized from EtOAc. Yield, 0.65 g (40%); m.p. 180-82°C; IR: 1755, 1745, 1720, 1670 (br), 1650 $cm^{-1}$; $^1H$ NMR: δ 1.29 (3H, t, *J* = 7.60, $CH_3$), 4.24 (2H, quartet, *J* = 7.60, $CH_2Me$), 4.39 (2H, s, $ArCH_2N$), 4.53 (2H, s, $NCH_2CO$), 5.20, 5.29 (4H, 2 × s, 2 × $OCH_2Ph$), 7.27-7.57; (11H, m, 10 × PhH and 6-H), 7.86 (1H, d, *J* = 8.1, 7-H), 8.09 (1H, d, *J* = 1.8, 4-H). Anal Calcd for $C_{29}H_{28}N_4O_7$: C, 63.96; H, 5.18; N, 10.29. Found: C, 63.91; H, 5.11; N, 9.91%.

Compounds **39** to **41** were also prepared by above method starting from **5** and corresponding bromo ester.

**Tertiarybutyl 2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetate 39**: The crude product was purified by flash chromatography with 8% $CH_3CN$ in $CHCl_3$. Yield, 30%, m.p. 143-45°C; IR: 1745, 1740, 1695, 1640 $cm^{-1}$; $^1H$ NMR: δ 1.49 [9H, s, C $(CH_3)_3$], 4.30 (2H, s, $ArCH_2N$), 4.51 (2H, s, $NCH_2CO$), 5.21, 5.29 (4H, 2 × s, 2 × $CH_2Ph$), 7.20-7.51 (11H, m, 10 × PhH and 6-H), 7.83 (1H, d, *J* = 8.1, 7-H), 8.06 (1H, d, *J* = 1.8, 4-H), 10.52, 11.87 (2H, 2 × s, 2 × NH). Anal Calcd for $C_{31}H_{32}N_4O_7$: C: 65.03; H, 5.63; N, 9.78. Found: C, 65.37; H, 5.63; N, 9.56%.

**Ethyl 5- (5-dicarbobenzoxyguanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl)-pentanoate 40**: The crude product was purified by flash chromatography with 10% $CH_3CN$-$CHCl_3$. Yield, 32.5%; m.p. 99-100°C; IR: 1750 (br), 1705, 1660, and 1345 $cm^{-1}$; $^1H$ NMR: δ 1.25 (3H, t, *J* = 7.09, $CH_3$), 1.69 (4H, m, $CH_2CH_2$), 2.36 (2H, br, $CH_2COOEt$), 3.63 (2H, br, $NCH_2$), 4.14 (2H, quartet, *J* = 7.09, $CH_2Me$), 4.37 (2H, s, $ArCH_2N$), 5.21 (4H, br, 2 × $OCH_2Ph$), 7.29-7.49 (11H, m, 10 × Ph*H* and 6-H), 7.76 (1H, d, *J* = 8.1, 7-H), 8.06 (1H, br, 4-H), 10.49, 11.85 (2H, 2 × br, 2 × NH). Anal Calcd for $C_{32}H_{34}N_4O_7$: C, 65.52; H, 5.84; N, 9.55. Found: C, 65.73; H, 5.95; N, 9.44%.

**Ethyl 6-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) hexa noate 41**: Pure compound was obtained by flash chromatography with 10% $CH_3CN$-$CHCl_3$ followed by 2% MeOH-$CHCl_3$. Yield, 25.4%; m.p. 127-30°C (EtOAc-light petroleum); IR: 1752, 1700, 1655 (br) $cm^{-1}$; $^1H$ NMR (300MHz): δ. 1.37 (2H, m, $NCH_2$), 1.65 (4H, m, $CH_2CH_2$), 2.32 (2H, t, *J* = 8.7, $CH_2COO$ Me), 3.58 (2H, t, *J* = 8.7, $NCH_2$), 3.65 (2H, s, $OCH_3$), 4.36 (2H, s, $ArCH_2N$), 5.15, 5.27 (4H, 2 × s, 2 × $OCH_2Ph$), 7.30-7.42 (11H, br, 10 × Ph*H* and 6-H), 7.76 (1H, d, *J* = 8.5, 7-H), 8.05 (1H, d, *J* = 1.8, 4-H), 10.52 & 11.89 (2H, 2 × s, 2 × NH). Anal Calcd for $C_{32}H_{34}N_4O_7$: C, 65.52; H, 5.84; N, 9.55. Found: C, 65.32; H, 5.77; N, 9.25%.

**2-{4-[2-5-Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl-acetyl]-phenoxy}-acetic acid 42**: Compound **28** (3.9 g; 5.27 mmoles) was dissolved in MeOH (200 mL), chloroform (20 mL), AcOH (20 mL) and hydrogenated over 10% Pd-C (150 mg) at 20 psi for 30 min. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by MPLC over RP-18 column with the use of MeOH: water: AcOH (100:100:0.2). The pure material was further crystallized from hot MeOH-water. Yield, 0.91 g (45.2%); m.p. >250°C; IR: 3380 (br), 3200-3000 (br), 1695, 1680 (br) 1600 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$; 300 MHz): δ 4.49 (2H, s, $ArCH_2N$), 4.67 (2H, s, $OCH_2CO$), 5.08 (2H, s, $NCH_2CO$), 7.03 (2H, d, *J* = 8.5, 3′-H and 5′-H), 7.32 (1H, dd, *J* = 7.86, 2.0, 6-H), 7.43 (1H, d, *J* = 2, 4-H), 7.74 (1H, d, *J* = 7.86, 7-H), 7.88 (4H, br, $NH_2$, 2 NH), 8.01 (2H, d, *J* = 8.5, 2′-H and 6′-H). Anal Calcd for $C_{19}H_{18}N_4O_5$, $H_2O$: C, 56.99; H, 5.03; N, 13.99. Found: C, 56.67; H, 4.95; N, 13.63%.

Compounds **43** to **52** were obtained by the hydrogenation of the corresponding Z-protected guanidino compounds over 10% Pd-C in MeOH/EtOH: EtOAc: AcOH (40:10:0.2, for each 100 mg compound) at 20 psi for 20 min. unless otherwise stated. Most of the final compounds were isolated as acetate salt. Those that were not easily crystallized were converted into hydrochloride salt by adding dry HCl-ether in $CHCl_3$ solution.

**Methyl 2-{4-[2-(5-Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-acetate 43**: The crude product was purified by MPLC over RP-18 with MeOH-water (40:60) containing 1 mL of AcOH per liter of solvent. Yield, 74 %; m.p. 176-79°C (MeOH-ether); IR: 3490-3000 (br), 1705 (br), 1680, 1605 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): δ 1.92 (3H, s, $CH_3COO^-$), 3.81 (3H, s, $COOCH_3$), 4.64 (2H, s, $ArCH_2N$), 4.89 (2H, s, $OCH_2COOMe$), 5.19 (2H, s, $NCH_2CO$), 7.10 (2H, d, *J* = 8.35, 3′-H and 5′-H), 7.42 (1H, dd, *J* = 7.95, 1.8, 6-H), 7.51 (1H, d, *J* = 1.8, 4-H), 7.91 (1H, d, *J* = 7.95, 7-H), 8.11 (2H, d, *J* = 8.35, 2′-H and 6′-H). Anal Calcd for $C_{22}H_{24}N_4O_7$, 0.5 $H_2O$: C, 56.76; H, 5.41; N, 12.04. Found: C, 56.96; H, 5.37; N, 11.91%.

**Methyl 2-{4-[2-(5- Amino (imino) methylamino-1-oxo-2, 3-dihydro-1H-benzo[c] azol-2-yl) -1-hydroxyethyl]-phenoxy}-acetate 44**: The compound **29** (0.7 g; 1.05 mmoles) was dissolved in MeOH (150 mL) and AcOH (25 mL). It was hydrogenated over 10% Pd-C at 50 psi for longer duration (5 hh). The catalyst was filtered off. The filtrate was concentrated. The crude product was purified over RP-18 MPLC column with MeOH: water (40:60, containing 1 mL AcOH/lit of solvent system). The pure product was

crystallized from dry MeOH-ether. Yield, 0.459 g (95.6%); m.p. 164-66°C; IR: 3400-3300 (br), 1740, 1655 (br), 1645 (br) $cm^{-1}$; $^1H$ NMR ($D_2O$): δ 1.89 (3H, s, $CH_3COO$-), 3.77 (3H, s, $OCH_3$), 3.72, 3.92 [2H, 2 dd, $J_{gem}$ = 14.31, *J* =5.76, $NCH_2$ C (OH)], 4.39, 4.52 (2H, 2Xdd, $J_{gem}$ = 18.36, $ArCH_2N$), 4.74 (2 H, s, $OCH_2COOMe$), 5.03 [1H, t, *J* = 5.76, C*C*H (OH)], 6.92 (2H, d, *J* = 8.85, 2′-H and 6′-H), 7.34 (2H, d, *J* = 8.85, 3′-H and 5′-H), 7.38 (1H, d, *J* = 8.37, 7-H). Anal Calcd for $C_{22}H_{26}N_4O_7$, $H_2O$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.21; H, 5.75; N, 11.54%.

**Ethyl 2-{4-[2-(5-amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-acetate 45**: This compound was prepared from 30 by a method similar to compound **43**.Yield, 70%; m.p. 179-81°C; IR: 2980 (br), 1780, 1768, 1700, 1685 $cm^{-1}$; 1H NMR ($CD_3OD$): δ 1.30 (3H, t, *J* = 7.05, $CH_3$), 1.90 (3H, s, $CH_3COO^-$), 4.29 (2H, quartet, *J* = 7.05, $CH_2Me$), 4.59 (2H, s, $ArCH_2N$), 4.81 (2H, s, $OCH_2COOEt$), 5.10 (2H, s, $NCH_2CO$), 7.09 (2H, d, *J* = 8.34, 3′-H and 5′-H), 7.41 (1H, dd, *J* = 7.95 and 1.8, 6-H), 7.52 (1H, d, *J* = 1.8, 4-H), 7.87 (1H, d, *J* = 7.95, 7-H), 8.09 (2H, d, *J* = 8.34, 2′-H and 6′-H). Anal Calcd for $C_{23}H_{26}N_4O_7$: C: 58.71; H, 5.57; N, 11.91. Found: C, 58.36; H, 5.37; N, 12.19%.

**Ethyl 2-{4-[2-(5- Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-propanoate 46**: Yield, 40%; m.p. 163-64°C (EtOH-ether); IR: 3300 (br), 1760 (br), 1675, 1605 $cm^{-1}$; $^1H$ NMR ($D_2O$): δ 1.27 (3H, t, *J* = 8.1, $OCH_3$), 1.66 [3H, d, *J* = 8.1, $OC(CH_3)COO$], 1.93 (3H, $CH_3COO$-), 4.28 (2H, quartet, *J* =8.1, $OCH_2Me$), 4.64 (2H, s, $ArCH_2N$), 5.16 [1H, quartet, *J* = 8.1, OCHCOO], 5.21 (2H, s, $NCH_2CO$), 7.19 (2H, d, *J* = 8.1, 3′-H and 5′-H), 7.48 (1H, br d, *J* = 8.1, 6-H), 7.57 (1H, br, 4-H), 7.88 (1H, d, *J* = 8.1, 7-H), 8.08 (2H, d, *J* = 8.1, 2′-H and 6′H). Anal Calcd for $C_{24}H_{28}N_4O_7$, 2.5 $H_2O$: C, 54.45; H, 6.28; N, 10.58. Found: C, 54.88; H, 5.58; N, 10.71%.

**Ethyl 2-{4-[2-(5- Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-2-methyl-propanoate 47**: Yield, 56%; m.p. 166-67°C (EtOH-ether); IR: 3300 (br), 1760 (br), 1680, 1605 $cm^{-1}$; $^1H$ NMR ($D_2O$): δ 1.24 (3H, t, *J* = 8.05, $CH_3$), 1.64 [6H, s, $OC(CH_3)_2$], 1.89 (3H, s, $CH_3COO^-$), 4.28 (2H, quartet, *J* = 8.05, $OCH_2Me$), 4.61 (2H, s, $ArCH_2N$), 5.18 (2H, s, $NCH_2CO$), 6.99 (2H, d, *J* = 8.05, 3′-H and 5′-H), 7.45 (1H, dd, *J* = 8.05, 1.8, 6-H), 7.56 (1H, d, *J* = 1.8, 4-H), 7.86 (1H, d, *J* = 8.05, 7-H), 8.03 (2H, d, *J* = 8.05, 2′-H and 6′-H). Anal Calcd for $C_{25}H_{30}N_4O_7$: C: 60.24; H, 6.06; N, 11.24. Found: C, 59.75; H, 6.10; N, 11.25%.

**2-{4-[2-(5- Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-2-methyl-propanoic acid 48**: Yield, 49%; m.p. 210°C (d) (AcOH- EtOAc); IR: 3400 (br), 1670, 1660, 1585 $cm^{-1}$; $^1H$ NMR ($D_2O$): δ 1.53 [6H, s, $OC(CH_3)_2COO$], 1.89 (3H, s, $CH_3COO$), 4.38 (2H, s, $ArCH_2N$), 4.95 (2H, s, $NCH_2CO$), 6.88 (2H, d, *J* = 9.31, 3′-H and 5′-H), 7.17 (2H, m, 6-H and 4-H), 7.63 (1H, d, *J* = 8.3, 7-H), 7.79 (2H, d, *J* = 9.31, 2′-H and 6′-H). Anal Calcd for $C_{23}H_{26}N_4O_7$, 1 $H_2O$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.25; H, 5.79; N, 11.38%.

**Methyl 2-{4-[2-(5- Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) ethyl]-phenoxy}-acetate 49**: This compound was obtained from 37 by hydrogenaration as described above to yield, 95%; m.p. 192-95°C (MeOH-ether); IR: 3400-3000 (br), 1745, 1680 (br), 1590 $cm^{-1}$; $^1H$ NMR ($D_2O$): δ 2.89 (2H, t, *J* = 8.65, $ArCH_2$), 3.75 (3H, s, $COOCH_3$), 3.78 (2H, t, *J* = 8.65, $CH_2N$), 4.31 (2H, s, $ArCH_2N$), 4.68 (2H, s, $OCH_2COO$ Me), 6.79 (2H, d, *J* = 8.6, 2′-H and 6′-H), 7.10 (2H, d, *J* = 8.6, 3′-H and 5′-H), 7.36 (2H, m, 4-H and 6-H), 7.7 (1H, d, *J* = 8.6, 7-H). Anal Calcd for $C_{20}H_{24}N_4O_4Cl$: C, 57.21; H, 5.76; N, 13.34; Cl, 8.44. Found: C, 57.04; H, 5.90; N, 12.97; Cl, 8.40%.

**Methyl 2-{4-[2-(5- Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-2-methyloxycarbonylmethoxyphenoxy}-acetate (HCl) 50**: This compound was obtained by the hydrogenation of **34** to yield, 91%; m.p. 148-50°C (MeOH-EtOAc); IR: 3400-3000 (br), 1745, 1660 (br), 1580 $cm^{-1}$; $^1H$ NMR ($D_2O$, 300 MHz): δ 3.77, 3.83 (6H, 2 × s, 2 × $COOCH_3$), 4.55 (2H, s, $ArCH_2N$), 4.85, 4.92 (4H, 2 × s, 2 × $OCH_2COO$), 5.11 (2H, s, $NCH_2CO$), 7.05 (1H, d, *J* = 8.65, 5′-H), 7.41-7.50 (3H, m, 4-H, 6-H and 2′-H), 7.74 (1H, dd, *J* = 8.65,1.8, 6-H′), 7.80 (1H, d, *J* = 8.65, 7-H). Anal Calcd for $C_{23}H_{25}ClN_4O_8$, $3H_2O$: C, 48.05; H, 5.43; N, 9.74; Cl, 6.17. Found: C, 48.17; H, 4.80; N, 9.31; Cl, 5.83%.

**Ethyl 2-{4-[2-(5- Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-2-ethyloxycarbonylmethoxyphenoxy}-acetate (HCl) 51**: Hydrogenation of **35** gave **51** in 95.4% yield; m.p.

186-88°C; IR: 3400-2900 (br), 1750 (br), 1700, 1675 $cm^{-1}$: $^1H$ NMR ($D_2O$): δ 1.29, 1.31 (6H, 2 t, *J* = 7.09, 2 × $CH_3$), 4.15-4.28 (4H, m, 2 × $CH_2Me$), 4.48 (2H, s, $ArCH_2N$), 4.90, 4.96 (4H, 2 × s, 2 × $OCH_2COO$), 5.19 (2H, s, $NCH_2CO$), 7.13 (1H, d, *J* = 8.1, 5-H′), 7.5 (1H, dd, *J* = 8.1 and 1.8, 6-H), 7.55 (2H, br, 2′-H and 4-H), 7.82, 7.86 (2H, 2 × m, 6′-H and 7-H). Anal Calcd for $C_{25}H_{29}N_4O_8Cl$, 1.5 $H_2O$: C, 52.13; H, 5.59; N, 9.73; Cl, 6.16. Found: C, 52.09; H, 5.04; N, 9.58; Cl, 6.15%.

**Isopropyl 2-{4-[2-(5- Amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-2-isopropyloxycarbonylmethoxyphenoxy}-acetate (AcOH) 52**: It was prepared by the hydrogenation of **36** in 97% yield; m.p. 192-93°C (MeOH ether); IR: 3400 (br), 1755 (br), 1680, 1595 $cm^{-1}$; $^1H$ NMR ($D_2O$): δ 1.22 (12H, br, 4 × $CH_3$), 1.88 (3H, s, $CH_3COO^-$), 4.58 (2H, s, $ArCH_2N$), 4.84, 4.90 (4H, 2 × s, 2 × $OCH_2COO$), 5.09 (2H, m, 2 × *C*H$Me_2$), 5.14 (2H, s, $NCH_2CO$), 7.08 (1H, d, *J* = 8.05, 5′-H), 7.44 (1H, d, *J* = 8.05, 6-H), 7.51 (2H, s, 4-H and 2′-H), 7.78, 7.83 (2H, 2 d, *J* = 8.05, 7-H and 6-H′). Anal Calcd for $C_{29}H_{36}N_4O_{10}$ , 1.5 $H_2O$: C, 54.09; H, 5.88; N, 9.34. Found: C, 53.97; H, 5.79; N, 8.66%.

**2-{4-[2-(5-Benzyloxycarbonylamino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetyl]-phenoxy}-acetic acid 53**: The compound **29** (0.332 g; 0.5 mmole) was dissolved in MeOH (5 mL). To this solution 1*N* NaOH (1.2 mL; 1.2 mmole) was added under stirring. It was further stirred at room temperature for 30 min. The reaction mixture was acidified to pH 2 with dil. HCl. Methanol was removed and the residue was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$. The solvent was removed. The residue was purified by flash chromatography with 20% MeOH-$CHCl_3$ containing0.01% AcOH. The pure material was taken up in MeOH and HCl-ether was added. The solid separated was filtered and recrystallized from dry MeOH-EtOAc. Yield, 0.145 g (56.2%); m.p. 192-95°C; IR: 3340 (br), 1750 (br), 1690, 1670 (br) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 4.56 (2H, s, $ArCH_2N$), 4.86 (2H, s, $OCH_2CO$), 5.14 (2H, s, $NCH_2CO$), 5.31 (2H, s, $OCH_2Ph$), 7.12 (2H, d, *J* = 9.1, 3′-H and 5′-H), 7.31 (5H, br, 5 × $CH_2PhH$), 7.38 (1H, dd, *J* = 8.1 and 1.8, 6-H), 7.69 (d, 1H, *J* = 1.8, 4-H), 7.86 (1H, d, *J* = 8.1, 7-H), 8.07 (2H, d, *J* = 9.1, 2′-H and 6′-H). Anal Calcd for $C_{27}H_{25}N_4O_7Cl$: C, 58.65; H, 4.56; N, 10.13; Cl, 6.41. Found: C, 58.44; H, 4.52; N, 10.34; Cl, 6.89 %.

**2-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl) acetic acid 54**: Compound **39** (0.85 g; 1.4 mmole) was dissolved in dichloromethane (15 mL) and TFA (3 mL) was added. The clear solution was kept at room temperature for 4 hr. The solvent was removed and ether was added. The solid was filtered and crystallized from dichloromethane-ether. Yield, 0.63 g (87%); m.p. 168-70°C; IR: 3500-3400 (br), 1710 (br), 1685, 1630 (br) $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + DMSO-$d_6$): δ 4.24 (2H, s, Ar $CH_2N$), 4.30 (2H, s, $NCH_2CO$), 5.09 (4H, br, 2 × $OCH_2Ph$), 7.20-7.33 (10H, br, 10 × PhH), 7.38 (1H, dd, *J* = 8.1 and 1.7, 6-H), 7.68 (1H, d, *J* = 8.1, 7-H), 7.88 (1H, d, *J* = 1.7, 4-H). Anal Calcd for $C_{27}H_{24}N_4O_7$: C, 62.79; H, 4.68; N, 10.86. Found: C, 62.04; H, 4.61; N, 10.67%.

**Methyl 5-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-ylmethylcarboxamido) pentanoate 55**: Compound **35** (0.08 g; 0.2 mmole), $Et_3N$ (0.027 mL; 0.2 mmole) were dissolved in $CH_2Cl_2$ (2 mL) and chilled at -15°C. Isobutyl chloroformate (0.026 mL; 0.2 mmole) was added. After 5 min. a chilled solution of methyl-5-amino pentanoate hydrochloride (0.05 g; 0.3 mmole) and $Et_3N$ (0.039 mL; 0.3 mmole) was added under vigorous stirring. After 30 min 5% aqueous $NaHCO_3$ was added and stirred for 5 min. The reaction mixture was diluted with $CH_2Cl_2$ (15 mL). The $CH_2Cl_2$ layer was washed with water, aqueous 1N HCl followed by brine. The organic layer was dried over anhydrous $Na_2SO_4$, The solvent was removed and the residue was purified by flash chromatography with 5% MeOH-$CH_2Cl_2$. Yield 0.102 g (81.1%); m.p. 124-25°C; IR: 3330, 1735 (br), 1700, 1650, 1620 $cm^{-1}$; $^1H$ NMR (300MHz): δ 1.40-1.62 (4H, m, $CH_2$ $CH_2$-), 2.26 (2H, t, *J* = 7.6, $CH_2COOMe$), 3.20 (2H, m, $NHCH_2$), 3.59 (3H, s, $COOCH_3$), 4.21(2H, s, $ArCH_2N$), 4.49 (2H, s, $NCH_2CO$), 5.13, 5.24 (4H, 2 × s, 2 × $OCH_2Ph$), 6.33 (1H, m, $NHCH_2$-), 7.27-7.45 (11H, m, 10 × PhH and 6-H), 7.74 (1H, d, *J* = 8.5, 7-H), 7.99 (1H, s, 4-H), 10.5, 11.85 (2H, 2Xs, 2XNH). Anal Calcd for $C_{33}H_{35}N_5O_8$: C, 62.96; H, 5.60; N, 11.12. Found: C, 60.92; H, 5.42; N, 10.59%.

**Benzyl 2-S- [1-(5-dicarbobenzoxy guanidino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-ylmethyl carboxamido)-2-S-benzyloxycarbonylethylcarbo xamido]-3-phenylpropanate 56**: This compound was prepared by the same method as described for the

synthesis of **55**. The crude material was purified by flash chromatography with 5% MeOH-$CHCl_3$. Yield 84.2%; m.p. 143-44°C; IR: 3270 (br), 1735, 1725, 1645 (br) $cm^{-1}$; $^1H$ NMR (300 MHz): δ 2.58 [1H, dd, $J_{gem}$ = 17.26, $J_{trans}$ = 6.47, CH ($CH^{\beta}COO$-)CO-], 2.81 [1H, dd, $J_{gem}$ = 17.26, $J_{cis}$ = 4.5, CH ($CH^{\alpha}COO$], 2.95 [1H, dd, $J_{gem}$ = 16.40, $J_{trans}$ = 6.47, CH ($CH^{\beta}Ph$)COO], 3.08 [1H, dd, $J_{gem}$ = 16.40, $J_{cis}$ = 5.61, -CH ($CH^{\alpha}Ph$)COO], 4.04(2H, s, Ar $CH_2N$), 4.25 (2H, s, $NCH_2CO$), 4.73, 4.89-5.23(10H, 2 m, 4 × $OCH_2Ph$, CH of Asp and CH of Phe), 6.99-7.32 (20H, m, 20 × Ph*H*), 7.38 (1H, d, *J* = 9.09, 6-H), 7.73 (1H, d, *J* = 9.09, 7-H), 8.0 (1H, s, 5-H), 10.52, 11.88 (2H, 2 × s, 2 × NH). Anal Calcd for $C_{54}H_{50}N_6O_{11}$: C, 67.64; H, 5.25; N, 8.76. Found: C, 67.12; H, 5.35; N, 8.55%.

**Methyl 5-(5- Amino (imino) methylamino -1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl methylcarboxamido) pentanoate (AcOH) 57**: Compound **55** was hydrogenated as described for the synthesis of **42** to generate **57**. The crude product was purified by MPLC on RP-18 with 5% MeOH-water (containing 0.1% AcOH) to yield 55%; m.p. 165-66°C; IR: 3300 (br), 1748, 1672 (br), 1655 $cm^{-1}$; $^1H$ NMR ($D_2O$, 300 MHz): δ 1.44-1.62 (4H, m, $-CH_2CH_2$-), 1.89 (3H, s, $CH_3COO$-), 2.37 (2H, t, *J* = 7.6, $CH_2COOMe$), 3.22 (2H, t, *J* = 7.0, $NHCH_2$-), 3.65 (3H, s, $COOCH_3$), 4.34 (2H, s, $ArCH_2N$), 4.59 (2H, s, $NCH_2CO$), 7.44 (1H, dd, *J* = 8.8, 1.8, 6-H), 7.52 (1H, d, *J* = 1.8, 4-H), 7.82 (1H, d, *J* = 8.8, 7-H). Anal Calcd for $C_{19}H_{27}N_5O_6$: C, 54.15; H, 6.46; N, 16.62. Found: C, 53.98; H, 6.49; N, 16.32%.

**2-S- [1-(5- Amino (imino) methylamino -1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-ylmethylcarboxamido)-2-S-carboxyethylcarboxamido]-3-phenylpropanoic acid 58**: The compound **58** was prepared by hydrogenation of **56** as described for 42.Yield 45.4%; m.p. >220°C; IR: 3400 (br), 1720, 1660 (br) $cm^{-1}$; $^1H$ NMR ($D_2O$, 300 MHz): δ 2.65(1H, dd, $J_{gem}$ = 17.5, $J_{trans}$ = 7.3, -$CH^{\beta}COOH$), 2.78 (1H, dd, $J_{gem}$ = 17.50, $J_{cis}$ = 4.65, $CH^{\alpha}$ COOH), 2.94 (1H, dd, $J_{gem}$ = 15.12, $J_{trans}$ = 7.30, $CH^{\beta}Ph$), 3.19 (1H, dd, $J_{gem}$ = 15.12, $J_{cis}$ = 7.0, *C*$H^{\alpha}Ph$), 4.23, 4.37 (2H, 2 × dd $J_{gem}$ = 18.3, $ArCH_2N$), 4.48 (2H, s, $NCH_2CO$), 4.58, 4.68 (2H, 2× m, 2 × $C^{\alpha}H$), 7.15-7.28 (5H, m, ×$CH_2PhH$), 7.42 (1H, d, *J* = 9.15, 7-H), 7.51 (1H, s, 4-H), 7.85 (1H, d, *J* = 9.15, 6-H). Anal Calcd for $C_{24}H_{26}N_6O_7$, $H_2O$: C, 54.54; H, 5.34; N, 15.91. Found: C, 54.29; H, 5.39; N, 15.68%.

**Methyl 2-S- [1-(5- amino (imino) methylamino -1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-ylmethyl-carboxamido)-2-s-methyloxycarbonylethylcarbo-xamido]-3-phenyl propanate; hydrochloride 59**: The compound **58** (0.055 g; 0.1 mmole), was taken in MeOH (5 mL) and chilled to 0°C. Freshly distilled $SOCl_2$ (0.1 mL; 1.5 mmole) was added under vigorous stirring. After 1hr ice bath was removed and stirring continued for another 30 min. Solvent was removed and the residue was purified by MPLC over RP-18 with 5% MeOH in water containing 0.1% AcOH. Yield 0.04g (69.6%); m.p. 121-22°C; IR: 3380 (br), 3370 (br), 1745, 1730, 1710, 1670 (br) $cm^{-1}$; $^1H$ NMR ($D_2O$+DMSO-$d_6$): δ 2.75 (1H, dd, $J_{gem}$ = 18.75, $J_{trans}$ = 9.12, $CH^{\beta}COOMe$), 2.88 (1H, dd, $J_{gem}$ = 18.75, $J_{cis}$ = 7.02, $CH^{\alpha}COOMe$), 3.07 (1H, dd, $J_{gem}$ = 16.3, $J_{trans}$ = 9.01, $CH^{\beta}Ph$), 3.25 (1H, dd, $J_{gem}$ = 16.30, $J_{cis}$ = 7.02, *C*$H^{\alpha}Ph$), 3.73, 3.75 (6H, 2 × s, 2 × $OCH_3$), 4.38 (2H, s, $ArCH_2N$), 4.60 (2H, s, $NCH_2CO$), 4.70, 4.95 (2H, 2 × m, 2 × $C^{\alpha}H$), 7.25-7.43 (5H, m, 5 PhH), 7.52 (1H, dd, *J* = 8.5 and 2.0, 6-H), 7.63 (1H, d, *J* = 2.0, 4-H), 7.95 (1H, d, *J* = 8.5, 7-H). Anal Calcd for $C_{26}H_{31}N_6O_7Cl$: C, 54.31; H, 5.43; N, 14.62; Cl, 6.17. Found: C, 53.98; H, 5.40; N, 11.43; Cl, 6.18%.

**Ethyl 5-[5-amino (imino) methylamino-1-oxo-2, 3-dihydro-1*H*-benzo[*c*] azol-2-yl] pentanoate; hydrochloride 60**: The compound **40** (0.48 g; 0.81 mmole), was dissolved in EtOH (40 mL), EtOAc (20 mL) and AcOH (0.5 mL) and hydrogenated over 10 % Pd-C for 10 min. The catalyst was filtered off and the solvent was removed. The residue was purified by MPLC over RP-18 with 50% MeOH in water containing 0.1% AcOH. Yield 0.2 g (69.6%); m.p. 177-79°C; IR: 3345 (br), 2950 (br), 1720, 1690 $cm^{-1}$; $^1H$ NMR ($D_2O$; 300 MHz): δ 1.19 (3H, t, *J* = 7.09, $CH_3$), 1.61, 1.69 (4H, 2 × m, $-CH_2CH_2$-), 2.39 (2H, t, *J* = 7.09, $CH_2COOEt$), 3.59 (2H, t, *J* = 7.09, $NCH_2CH_2$-), 4.10 (2H, quartet, *J* = 7.09, $COOCH_2Me$), 4.53 (2H, s, 7-H Ar*H*[7]). Anal Calcd for $C_{16}H_{23}N_4O_3Cl$: C, 54.31; H, 6.55; N, 15.84; Cl, 9.74. Found: C, 54.29; H, 6.57; N, 15.77; Cl, 9.82%.

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