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Synthesis, Docking studies and In-vitro evaluation of novel chalcones as potent inhibitors of Phosphodiesterase 5 from human platelet and 5 A from bovine recombinant

Manish S. Bhatia[a]. Amol S. Sherikar[b*] and Rakesh P. Dhavale[a]

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[a]Department, of Pharmaceutical Chemistry, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Near Chitranagri, Kolhapur-416 013 (MS) India.;

[b]Department, of Pharmaceutical Chemistry, Tatyasaheb Kore College of Pharmacy, Warananagar, Tal-Panhala, Dist-Kolhapur-416 113 (MS) India.

Email for correnpondence: amol.sherikar@gmail.com

Abstract

A series of new nitric oxide donor chalcone moieties were synthesized and evaluate for Phosphodiesterase 5 (PDE 5) and 5A (PDE 5A) inhibition potential from human plasma and bovine recombinant respectively. Molecular docking showed an excellent binding interaction of the synthesised compounds with the receptors. Synthesis of chalcone intermediate **i** was carried out by reacting substituted aldehydes and acetophenones on the basis of Claisen-Schmidt condensation reaction. The nitration reaction was carried out to obtain substituted cahlcone with phenyl nitrate and nitrate esters as final product. The inhibitory potency of synthesized compounds was evaluated against PDE 5 from human platelet and PDE5A from bovine recombinant and compared with Tadanafil and standard inhibitor. The compounds **AI7, B5, B7, E7** and **E8** containing acetyl, nitro, carboxy methyl, hydroxyl methyl functionality exhibit a marked inhibitory effect against human platelet PDE 5. The compounds **B2, B4, B5, D4, D6** and **E6** containing nitro, fluorine, amino, methyl functionality produces significant inhibition of recombinant bovin PDE5A. Compound **AI7** containing phenyl nitrate moiety and acetyl functionality on chalcone showed 1.197±3.38 μM of inhibitory potency against human platelet PDE5. Compound **B2** containing amide nitrate ester and nitro functionality on chalcone showed 1.241±3.68 μM of inhibitory potency against PDE 5A of recombinant bovine. The biocompatibility of synthesized compounds was checked by in-vitro haemolytic assay. All the tested compounds were observed non-haemolytic. Compound **B2** was tested for in-vitro bacterial reverse mutation test, and found as non-mutagenic.

Key Words Phosphodiesterase, Claisen-Schmidt, Platelet, Bovine, biocompatibility, in-vitro and non-mutagenic.

Introduction

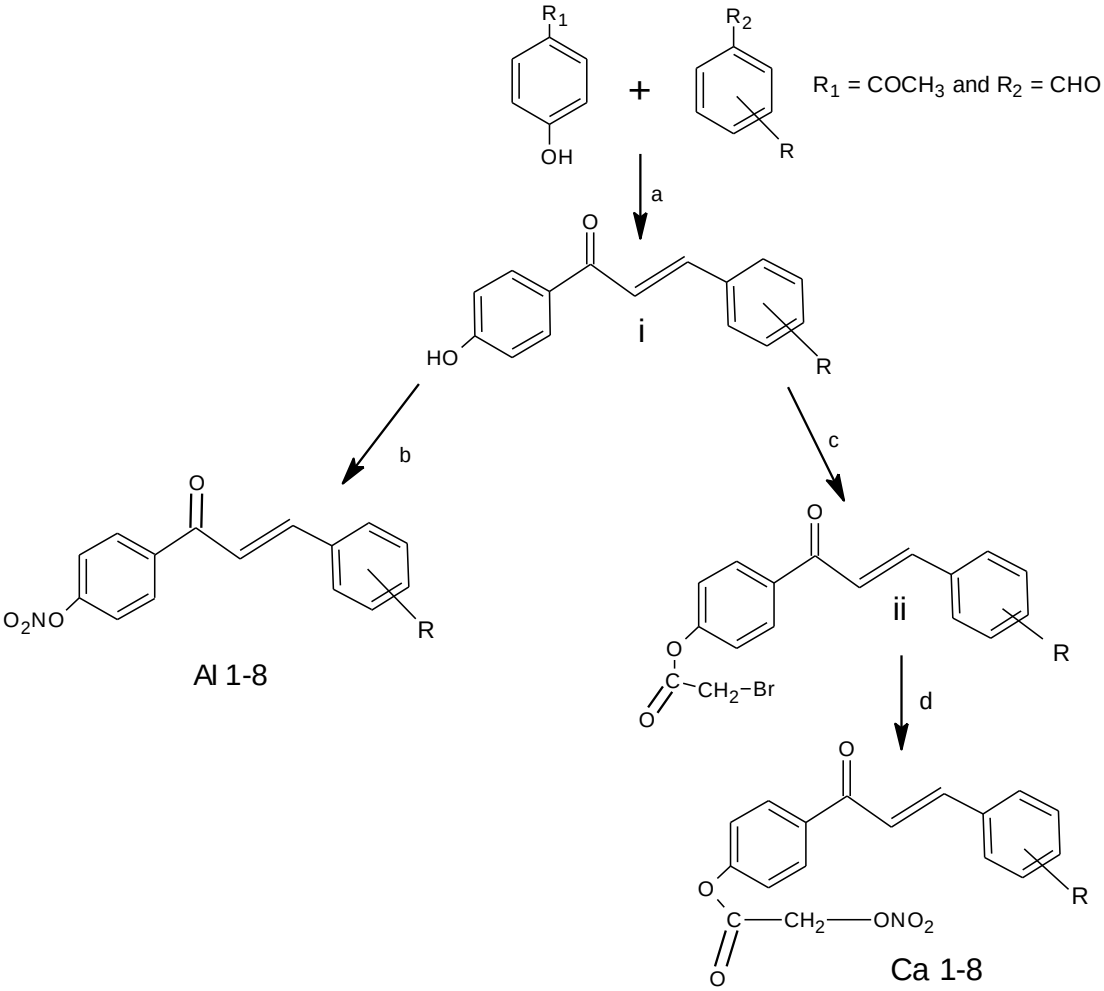
The vascular endothelium plays an important function in the normal regulation of peripheral vasomotor tone in conduit and resistance blood vessels.[1] Vascular endothelial cells releases nitric oxide (NO) in response to hormonal agonists and shear stress. This NO induces vasorelaxation by increasing production of the second messenger cyclic guanosine monophosphate (cGMP) through activation of soluble guanylate cyclase (sGC) in vascular smooth muscle.[2-5] The binding of NO to the heme moiety leads to formation of an inactive but NO-responsive 6-coordinate nitrosyl intermediate. This inactive intermediate in the presence of magnesium, cGMP and pyrophosphate is further converted to a 5-coordinate nitroxyl complex which can be further activated by NO.[6-7] cGMP plays a vital role in various physiologic processes such as ion channel conductance cell growth, cardiovascular homeostasis, inflammation, apoptosis, cellular mobility and contractility.[6-7] Impaired NO mediated vasodilation in heart failure is partly attributable to hyporesponsiveness of vasorelaxation effector mechanisms in vascular smooth muscle.[8-10] The vasodilatory responses to administration of endothelium independent cGMP-mediated vasodilatory agents such as nitroglycerin, nitroprusside (soluble guanylate cyclase activators), atrial and brain natriuretic peptides (particulate guanylate cyclase activators) are decreased in patients with congestive heart failure when compared with normal subjects.[11] The examples of nitric oxide donor compounds reported in literature are nitric oxide-donating pyrazoline derivatives[12], 2-nitrate-1,3-dibuthoxypropan[13] and nitric oxide releasing NSAIDs like nitric oxide-releasing aspirin, nitro-derivatives of flurbiprofen[14-15]. Cyclic nucleotide phosphodiesterases (PDE) are a superfamily of enzymes responsible for the hydrolysis of cyclic adenosine 3',5'-monophosphate (cAMP) and cyclic guanosine 3',5'-monophosphate (cGMP).[16-18] Currently, the PDE system includes 11 families (PDE1-PDE11) comprising 21 different gene products.[19-20] The cGMP specific PDE 5 is abundant in the penile tissue, platelets, vascular and smooth muscle tissues due to which this enzyme is the key target for the development of well-known molecules such as sildenafil (Viagra), vardenafil (Levitra) and tadalafil (Cialis) to treat erectile dysfunction.[21-22] NO activates guanylatecyclase to convert GTP to the second messenger cGMP which, in turn results in smooth muscle relaxation. cGMP is hydrolysed by PDE 5 to inactive cGMP. PDE 5 inhibitors such as sildenafil thus act to inhibit cGMP breakdown. Vascular smooth muscle responses to cGMP-dependent vasodilatory stimuli are regulated by the activity of vascular smooth muscle PDE, which catalyzes hydrolyzation of cGMP to inactive products.[23] Type 5 PDE is the predominant isozyme that contributes to regulation of cGMP content in vascular smooth muscle.[24-25] Chalcones (trans-1,3-diphenyl-2-propen-1-ones) are the biogenetic precursors of all known flavonoids and are abundantly present in edible plants. Chemically, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three carbons and α, β-unsaturated carbonyl system. These moieties report to have a broad spectrum of biological activities. Chalcones were reported to have fungicidal activity when joined with agriculture fungicide Strobilurin.[26] Recently these moieties (chalcones) were reported to have a PDE 5 and 5A1 inhibitory potential.[27-28] Chalcone derivatives of nitric oxide donors were virtually screened and reported as inhibitors of phosphodiesterase 5A.[29]

By keeping in view the above discussion, we have synthesized nitric oxide donating chalcone with phenyl nitrate and nitrate esters moieties. Then the synthesized compounds were screened to evaluate the inhibitory potency against PDE5 isolated from human platelet and PDE5A from recombinant bovine.

Results and discussion

Chemical synthesis

The schemes 1 and 2 illustrate the synthetic routes used to prepare targeted compounds **AI 1-8, Ca 1-8, AII 1-8** and **Cb 1-5.** The chalcones were obtained by condensing substituted acetophenone with substituted aldehydes in presence of 10 % NaOH in ethanol. The obtained chalcones **i** (Scheme 1 and 2) were then treated with acetic anhydrite and nitrating mixture in cold condition to obtain final products **AI 1-8** and **AII 1-8**. The chalcone **i** was treated with bromoacetyl bromide and dichloromethane in ice bath to obtain the intermediate **ii** (Scheme 1 and 2). The resulting intermediate was treated with acetonitrile and silver nitrate to obtain the nitrate esters **Ca 1-8** and **Cb 1-5**. All the resulting compounds were obtained in a good yield and purified by recrystalization.



Where R is

AI1 4- NO_2
AI2 3,4- CH_2OH
AI3 3,4,5- CH_2OH
AI4 4- NCH_3CH_3
AI5 4 - CH_3
AI6 4 - CH_2CH_3
AI7 4-acetyl
AI8 4-t-butyl

Ca1 4-NO_2
Ca2 3,4 - CH_2OH
Ca3 3,4,5- CH_2OH
Ca5 4- Cl
Ca7 4- F
Ca8 3- Cl

Scheme 1 Synthetic route of target compounds **AI 1-8** and **Ca 1-8** (a) 10% NaOH, EtOH; (b) HNO_3, acetic anhydrite, $NaHCO_3$, ethyl acetate; (c) K_2CO_3, $BrCH_2COBr$, CH_2Cl_2; (d) $AgNO_3$; acetonitrile; CH_2Cl_2.

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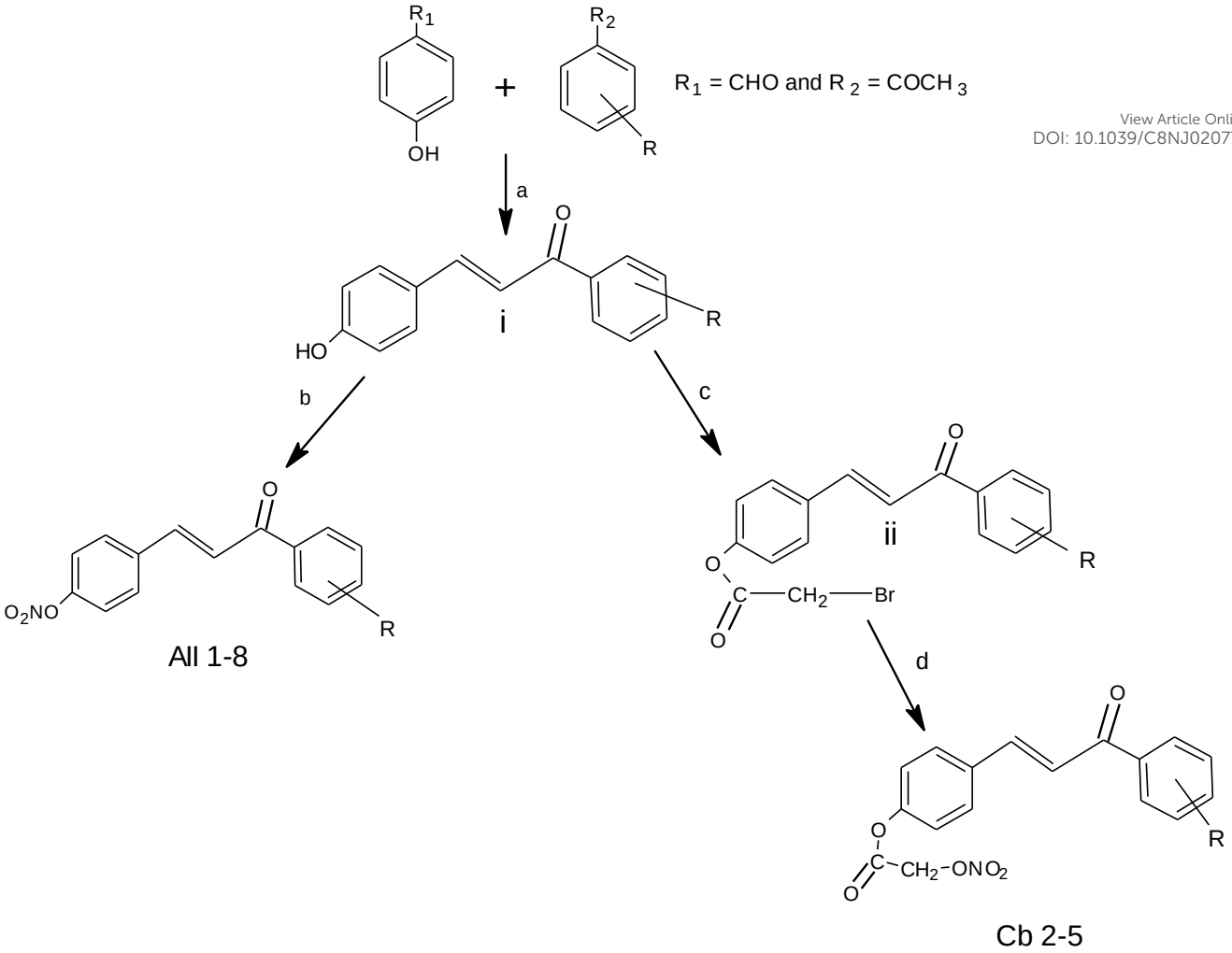

Where R is

AII1	4- Br	**AII8**	4-CH_2CH_3
AII2	3- NO_2	**Cb2**	2,4- CH_2OH
AII3	2,5 - CH_2OH	**Cb3**	4- CH_2OH
AII4	4- NO_2	**Cb4**	3,4- Cl
AII5	4- CH_3	**Cb5**	4- CH_2CH_3
AII7	3,4-CH_2OH		

Scheme 2 Synthetic route of target compounds **AII 1-8** and **Cb 2-5** (a) 10% NaOH, EtOH; (b) HNO_3, acetic anhydrite, $NaHCO_3$, ethyl acetate; (c) K_2CO_3, $BrCH_2COBr$, CH_2Cl_2; (d) $AgNO_3$; acetonitrile; CH_2Cl_2

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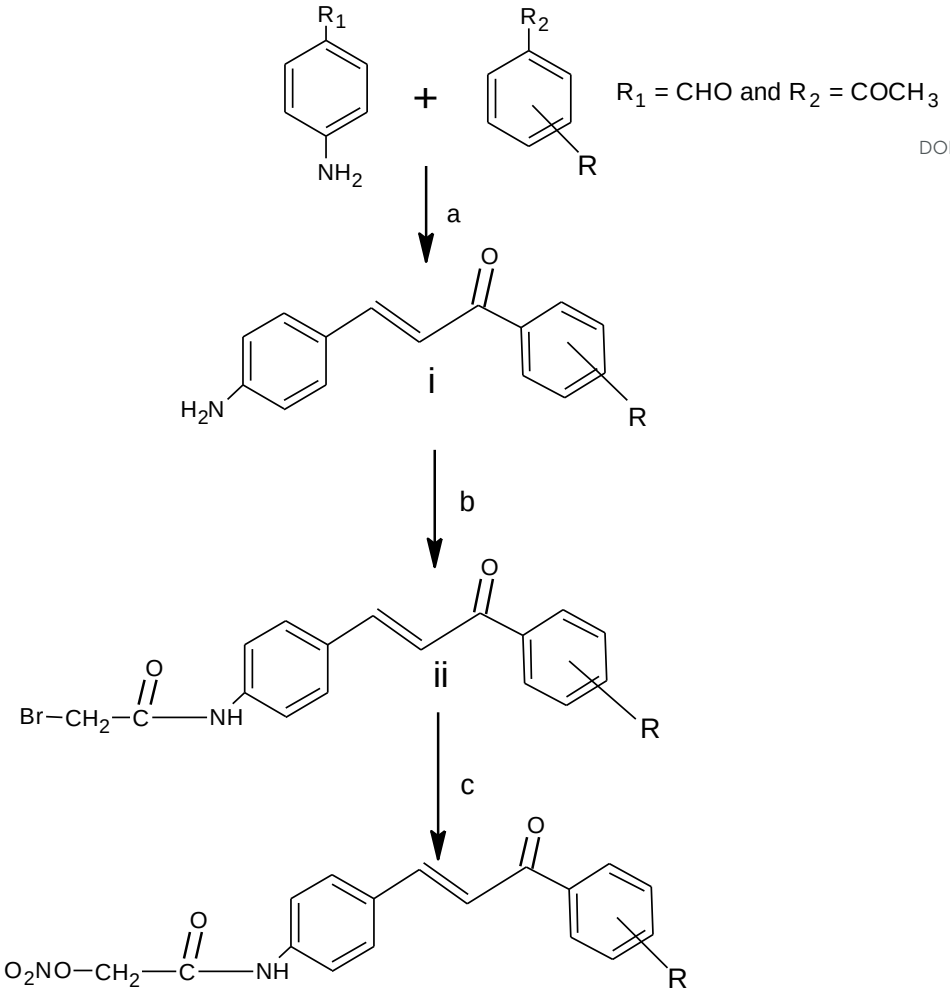

B 2 -11

Where R is

B2	2- NO_2	**B7**	4- $COCH_3$
B3	2- Cl	**B8**	4- ter. butyl
B4	4- F	**B9**	4- CH_3
B5	4- NO_2	**B10**	3,4- CH_2OH
B6	4- Br	**B11**	3,4,5- CH_2OH

Scheme 3 Synthetic route of target compounds **B 2-11** (a) 10% NaOH, EtOH; (b) K_2CO_3, $BrCH_2COBr$, CH_2Cl_2; (c) $AgNO_3$; acetonitrile; CH_2Cl_2.

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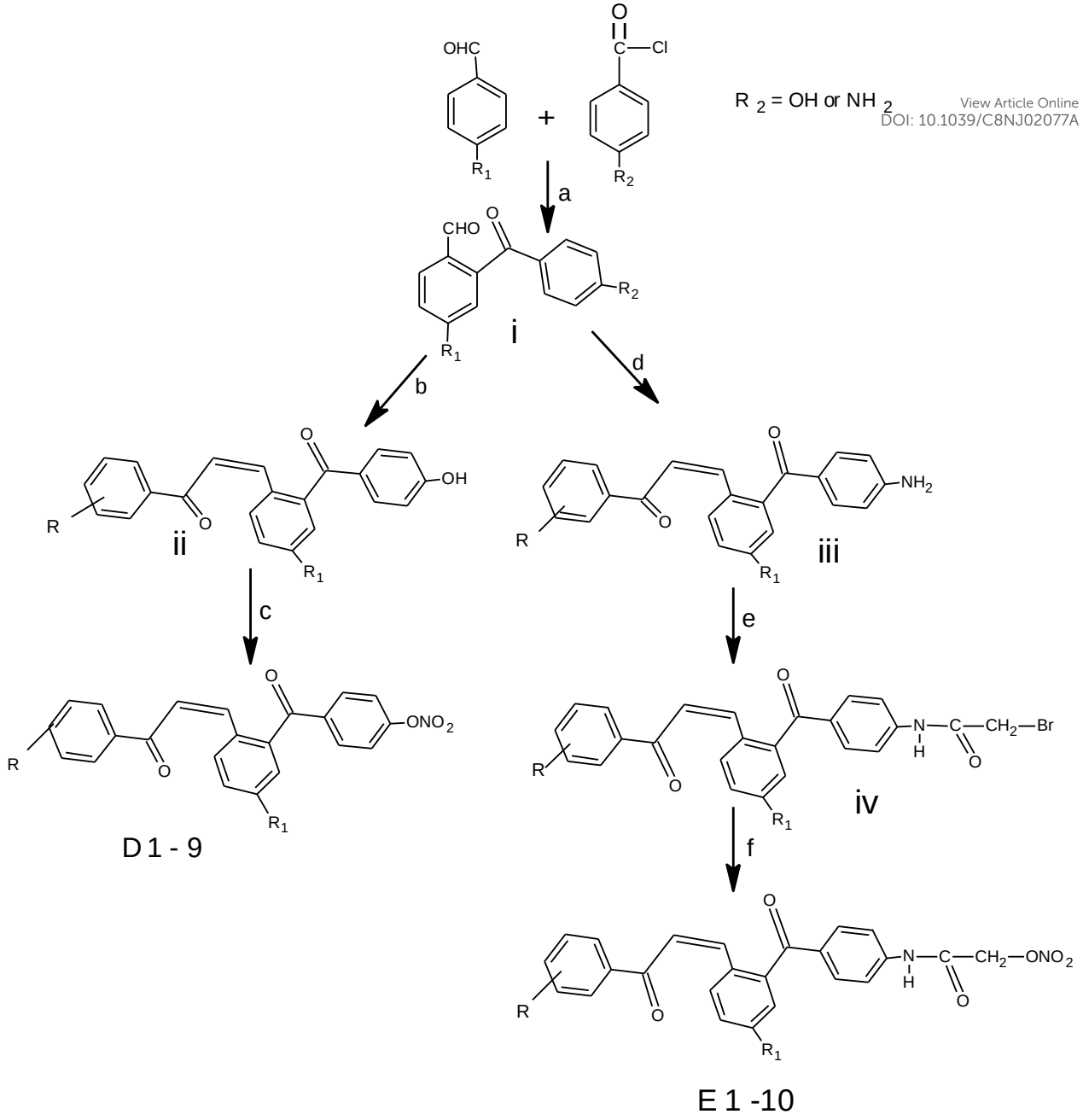

	R1	R2	R		R1	R2	R
D1	F	OH	4- CH_2CH_3	**E2**	NO_2	NH_2	4- CH_2OH
D2	Br	OH	4- CH_2CH_3	**E3**	F	NH_2	4- Br
D3	Cl	OH	4- CH_3	**E4**	F	NH_2	4- Cl
D4	CH_3	OH	4- NO_2	**E5**	Br	NH_2	4- Br
D5	CH_3	OH	4- NH_2	**E6**	Br	NH_2	4-NO_2
D6	CH_3	OH	3- NO_2	**E7**	Br	NH_2	3- Br
D7	CH_3	OH	3,4- CH_2OH	**E8**	Br	NH_2	4- CH_2OH
D8	CH_3	OH	4- Cl	**E9**	Cl	NH_2	3- Br
D9	CH_3	OH	4- CH_2CH_3	**E10**	Cl	NH_2	3,5- CH_2OH
E1	NO_2	NH2	4- CH_2CH_3				

Scheme 4 Synthetic route of target compounds **D 1-9** and **E 1-10** (a) $AlCl_3$, HCl; (b) and (d) Substituted acetophenone, 10% NaOH, EtOH; (c) HNO_3, acetic anhydrite, $NaHCO_3$, ethyl acetate; (e) K_2CO_3, $BrCH_2COBr$, CH_2Cl_2; (f) $AgNO_3$; acetonitrile; CH_2Cl_2.

The scheme 3 explains the synthetic route to prepare targeted compounds **B 2-11**. All the procedures are similar as described in scheme 1 and 2. The scheme 4 explains the synthetic route used for preparing **D 1-9** and **E 1-11**. The intermediate **i** was prepared by Friedel Crafts reaction by reacting acid chloride with substituted aldehydes then treated with substituted ketones to obtain **ii** and **iii** intermediates. The targeted compounds **D 1-9** and **E 1-10** were synthesized by same procedure as described in scheme 1 and 2.

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The IR spectra of prepared chalcones showed (C=O) stretching at 1600 to 1700 cm^{-1} due to formation of carbonyl bond in chalcones. ^{1}H NMR spectra recorded for the prepared compounds in $CDCl_3$ clearly support the proposed structures. The protons of chalcone ring system in all the synthesized compounds were showed prominent peaks from δ 7.00 to 7.90 with singlet, doublet, triplet and multiplets. The aliphatic protons were also confirmed from ^{1}H NMR. From the result of ^{13}C NMR it can be concluded that the synthesis of final targeted compounds was achieved successfully. Mass spectra and elemental analysis are in agreement with proposed structures of the prepared compounds.

Biological evaluation of inhibitory potency

Compounds **AI 1-8, AII 1-8, Ca 1-8, Cb 1-5, B 2-11, D 1-9** and **E 1-11** were evaluated for inhibition of human platelet PDE 5 and recombinant bovin PDE 5A. The synthesized compounds inhibit PDE 5/PDE 5A in a concentration dependent manner. Tested compounds showed statistical significances with $P<0.01$, 0.05 and 0.25 compared with IC_{50} values of standard (inhibitor). As observed in table 1, derivatives **AI7, D5, B5, E6, E7** and **E8** exhibit a marked inhibitory effect on PDE5 obtained from human platelet. Out of these compounds **AI7** and **B5** exhibit maximum inhibitory potency, their IC_{50} were found to be 1.197±3.38 and 1.425±0.09 μM respectively. The standard inhibitor and Tadalafil showed 1.690±3.47 and 1.616±2.37 μM of inhibition of PDE 5 respectively. The study also indicates that the compounds **D5, E6, E7** and **E8** showed 1.625±2.08, 1.817±2.38, 1.663±2.96 and 1.961±3.57 μM IC_{50} values respectively, indicating these compounds are also potent inhibitors of PDE 5.

Table 1 IC_{50} concentrations of synthesized compounds and standards against PDE5 and PDE5A from Human Plasma and Recombinant Bovine respectively.

Comp Code	Human Platelet PDE5 (μM)	Bovine Recombinant PDE5A (μM)	Comp Code	Human Platelet PDE5 (μM)	Bovine Recombinant PDE5A (μM)	Comp Code	Human Platelet PDE5 (μM)	Bovine Recombinant PDE5A (μM)
AI1	5.695±3.10[a]	2.359±4.21[a]	**Ca7**	7.692±2.23	1.993±3.10	**D4**	3.771±8.93[a]	7.066±2.78[b]
AI2	6.812±0.30[a]	5.838±3.35[a]	**Ca8**	2.436±3.45	3.373±2.79	**D5**	1.625±2.08[a]	9.367±2.90[a]
AI3	4.391±3.22[a]	1.910±0.31[a]	**Cb2**	9.761±0.31[ns]	4.347±2.28[a]	**D6**	7.733±3.39[a]	1.745±2.73[a]
AI4	3.692±0.29[a]	5.926±6.45[a]	**Cb3**	5.907±1.34[a]	9.143±2.57[a]	**D7**	8.305±1.77[b]	2.241±3.84[a]
AI5	8.692±2.67[a]	9.158±2.63[a]	**Cb4**	8.174±3.15[c]	2.338±3.28[a]	**D8**	2.764±0.09[a]	9.882±2.67[c]
AI6	9.885±0.32[a]	3.111±2.83[a]	**Cb5**	6.803±3.06[b]	5.353±2.99[a]	**D9**	2.500±3.58[b]	7.350±3.83[c]
AI7	1.197±3.38[a]	2.713±2.44[a]	**B2**	9.913±2.57[a]	1.241±3.68[a]	**E1**	3.705±2.16[a]	1.996±2.65[a]
AI8	3.736±3.79[b]	4.748±2.03[a]	**B3**	6.750±3.08[a]	2.044±0.30[a]	**E2**	4.019±3.18[b]	2.950±2.18[a]
AII1	5.241±3.26[a]	4.751±0.27[a]	**B4**	5.379±2.37[a]	1.322±2.78[a]	**E3**	7.765±2.93[a]	5.593±1.86[a]
AII2	2.886±2.47[a]	5.043±2.60[a]	**B5**	1.425±0.09[a]	7.808±1.94[a]	**E4**	2.620±1.75[a]	6.083±2.64[a]
AII3	2.339±3.21[a]	7.220±0.12[b]	**B6**	9.866±2.48[a]	3.923±2.68[a]	**E5**	3.579±1.99[a]	4.273±2.01

AII4	4.550±0.33[a]	1.339±3.01[a]	**B7**	3.404±3.08[a]	4.057±2.08[a]	**E6**	1.817±2.38[a]	1.356±1.05[a]
AII5	9.791±1.70[c]	1.356±3.02[a]	**B8**	2.782±2.07[a]	5.222±0.06	**E7**	1.663±2.96[a]	6.511±3.12[a]
AII7	9.063±0.32[a]	3.015±0.13[a]	**B9**	4.360±1.87[a]	8.815±3.66[ns]	**E8**	1.961±3.57[b]	6.099±0.34[c]
AII8	9.280±2.12[a]	4.672±2.56[b]	**B10**	8.834±0.19[a]	5.065±1.96[a]	**E9**	7.375±2.78[a]	6.163±0.04[a]
Ca1	4.815±2.98[a]	7.543±0.28[a]	**B11**	5.675±2.07[b]	9.620±2.06[c]	**E10**	2.314±3.07[a]	5.317±0.43[a]
Ca2	2.824±0.18[a]	7.984±3.02[a]	**D1**	4.203±9.84[a]	4.825±0.11[a]	Tadal.	1.616±2.37[a]	1.159±4.98[a]
Ca3	3.865±3.36[b]	6.217±0.31[a]	**D2**	5.447±2.93[a]	5.580±1.36[b]	Inhib.	1.690±3.47	1.195±2.22
Ca5	4.632±0.34[c]	2.144±2.21[a]	**D3**	3.546±2.96[a]	2.655±3.15[a]	Cont.	6.084±2.69a	2.336±4.24[a]

Tadal. = Tadalafil

Inhib. = Standard Inhibitor, was 3- isobutyl-1-methylxanthine (IBMX) given with assay kit.

Cont. = Control

IC_{50} values reported as Conc. ± SEM; SEM of three independent experiments performed in duplicate.

a (95 % confidence interval) $p = < 0.01$, **b** (90 % confidence interval) $p = < 0.05$, **c** (75 % confidence interval) $p = < 0.25$, ns = non significant.All the procedures were performed as per the instructions given in assay manual.

The compounds **AI3, AII4, AII5, Ca7, B2, B4, D6, E1** and **E6** produces significant inhibition of recombinant bovin PDE 5A. The compound **AII5, B2, B4** and **E6** showed IC_{50} values 1.356±3.02, 1.241±3.68, 1.322±2.78 and 1.356±1.05 μM respectively. The standard inhibitor and Tadalafil showed IC_{50} values 1.195±2.22 and 1.159±4.98 μM respectively. The comparison of inhibitory potency of some potent compounds against PDE and PDE5A with standard and Tadalafil is showed in figure 1.

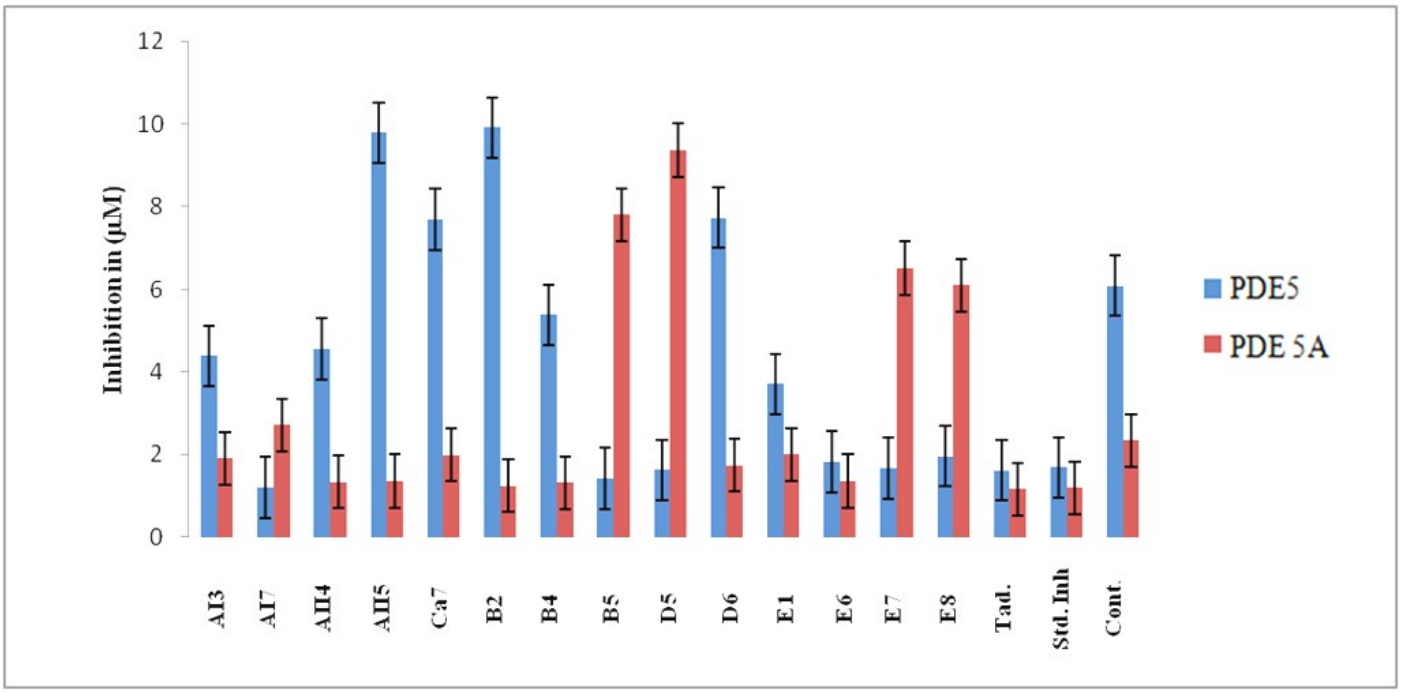

Figure 1 Showing PDE 5 and PDE 5A inhibitory potency of synthesized compounds with Tadalafil and standard inhibitor.

The structure activity relationship data reveals that the inhibitory potency against PDE 5 depends strongly on nature of substitution on **R** in scheme **1, 2** and **3** as well as **R** and **R1** in scheme **4.** In scheme **1**, different substitutions were carried out as shown in series **AI 1-8** and **Ca1-8**. In series **AI 1-8** substitution of acetyl group at para position (**AI7**) produce inhibitory potency of 1.197±3.38 μM IC_{50} against PDE 5 from human platelet, which is more than that of standard inhibitor and Tadalafil. Substitution of methyl, methoxy, ethyl butyl and nitro at **R** decreases inhibitory potency against PDE 5. The same series (**AI 1-8**) was evaluated against PDE 5A

from recombinant bovin which produce interesting and different results. Compound **AI3** with methoxy substitution at **3, 4** and **5** position produce maximum inhibitory potency of about 1.910±0.31 μM IC_{50} against PDE 5A, which is less than that of standard inhibitor and Tadalafil. Compound **AI7** with acetyl substitution at para position was not found to be more potent against PDE 5. All other substitutions in this series (**AI 1-8**) was found to be less potent against PDE 5A than **AI3**. The basic mechanism for this diversity in inhibitory potency may be the difference of gene product present in PDE 5 form human platelet and PDE 5A from recombinant bovin. The second series in scheme **1** includes compounds **Ca 1-8** with variety of substitution on **R**. Compound with chlorine substitution at meta position (**Ca8**) produce inhibitory potency of about 2.436±3.45 μM IC_{50} against PDE 5 from human platelet and it was found to be less potent than **AI7**. This explains the importance of phenyl nitrate and nitrate ester moieties for inhibitory potency against PDE 5. The substitutions like nitro, methoxy, fluorine leads to less potency against PDE 5. Structure **Ca7** with fluorine at para position showed inhibitory potency of 1.993±3.10 μM IC_{50} against PDE 5A which is equal to that of **AI3**. Both structures (**AI3** and **Ca7**) were found to have less potent than standard inhibitor and Tadalafil against PDE 5A. This difference in inhibitory potency towards PDE 5 from human platelet and PDE 5A from recombinant bovin may be the different gene product present in both enzymes.

The scheme **2** includes two series of compounds i.e. **AII 1-8** and **Cb 2-5** with variety of substitutions. In first series (**AII 1-8**) compound with 2, 4 methoxy (**AII3**) substitution produce 2.339±3.21 μM IC_{50} against PDE 5 which was highest amongst same series but lower as compared to **AI7**, standard inhibitor and Tadalafil. The other substitutions like bromine, nitro, methoxy and methyl reduces the inhibition. Molecules with nitro (**AII4**) and methyl (**AII5**) substitution at para position showed inhibitory potency of about 1.339±3.01 and 1.356±3.02 μM IC_{50} respectively against PDE 5A. This inhibitory potency was found to be more than that of **AI3** but less than that of standard inhibitor and Tadalafil. This highlights the importance of carbonyl functionality and position of double bond between two adjacent carbons in chalcones. The other substitutions like bromine, nitro and ethyl were found to produce lesser potency against PDE 5A. In second series (**Cb 2-5**) all the molecules were found to be less active as they showed lower inhibitory potency against PDE 5 and 5A except **Cb4** with **3**, **4** chlorine substitution with IC_{50} 2.338±3.28 μM against PDE 5A. The above results clearly indicate that the phenyl nitrate moiety plays an important role than nitrate ester for inhibition of PDE 5 and 5A. The presence of carbonyl functionality towards phenyl nitrate produces more potent action. The position of double bond between adjacent carbons should be away from phenyl nitrate for maximum potency.

The scheme **3** depicts a series of molecules with amide linkages between benzene ring and nitrate moiety. It includes series of molecules (**B 2-11**) with variety of substitutions. Out of these, the compound containing para nitro substitution (**B5**) showed maximum inhibitory potency against PDE 5 which was found to be 1.425±0.09 μM IC_{50}. This molecule was found to be more potent inhibitor of PDE 5 than standard inhibitor and Tadalafil but it is somewhat less potent than **AI7**. The other substitutions like chlorine, fluorine, bromine, tertiary butyl, methyl, methoxy and carboxymethyl were found to produce lower inhibitory potency against PDE 5. The molecules with nitro substitution at ortho position (**B2**) and fluorine at para position (**B4**) showed inhibitory potency of about 1.241±3.68 and 1.322±2.78 μM IC_{50} respectively against PDE 5A. This inhibitory potency

was observed to be more than that of **AII4** and **AII5** but less than that of standard inhibitor and Tadalafil. The substitutions like bromine, tertiary butyl, methyl, methoxy and carboxymethyl leads to decrease in inhibitory potency. From above results it can be concluded that the amide linkage also leads to a potent PDE 5 and 5A inhibitor.

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Series **D 1-9** and E **1-10** were reported in scheme **4** with variety of substitutions at **R1** and **R** positions. In series **D 1-9** OH is present at **R2** position which gives phenyl nitrate moiety and in **E 1-10** NH_2 is present at **R2** position which leads to amide linked nitrate moiety. The compound **D5** with methyl at **R1** and amide at para position (**R**) produce maximum inhibitory potency of about 1.625±2.08 μM IC_{50} against PDE 5 from human platelet which is equal to inhibitory potency produced by standard inhibitor and Tadalafil but lesser than that of **AI7** and **B5**. Other substitutions like fluorine, bromine and chlorine on **R1** leads to decrease in inhibitory potency against PDE 5. Substitutions like ethyl, methyl, nitro, methoxy and chlorine at **R** decreases the inhibitory potency against PDE 5. The molecule (**D6**) with methyl at **R1** and nitro at **R** showed 1.745±2.73 μM IC_{50} against PDE 5A from recombinant bovin, which is less than that of **B2**, standard inhibitor and Tadalafil. The other molecules in this series with variety of substitutions like fluorine, bromine, chlorine at **R1** and ethyl, methyl, methoxy and chlorine at **R** in this series leads to decrease in inhibitory potency against PDE 5A. In second series (**E 1-10**), the compound (**E6**) with bromine at both **R1** and **R** showed 1.663±2.96 μM IC_{50} against PDE 5 which is equal to standard inhibitor, Tadalafil and **D5** but less than that of **AI7** and **B5**. The compound (**E7**) with bromine at **R1** and nitro at **R** produce 1.356±1.05 μM IC_{50} against PDE 5A, which is more than **D6** but less than that of **B2**, standard inhibitor and Tadalafil. The different substitutions like nitro, fluorine, chlorine at **R1** and ethyl, methoxy, chlorine at **R** in this series leads to decrease in inhibitory potency. From above observations we can conclude that the phenyl nitrate moiety is crucial for inhibition of PDE 5 and amide linked nitrate on chalcones for inhibition of PDE 5A.

Compound **AI7**, with acetyl substitution at **R** appears to be the most potent PDE5 inhibitor. It is phenyl nitrate containing chalcone molecule. The comparison of PDE 5 inhibitory potency of **AI7** and other active molecules with standard inhibitor and Tadalafil is given in figure 1. It showed that **AI7** is more potent inhibitor of PDE 5 than standard inhibitor and Tadalafil. The side chain length and substitutions also have affect on inhibitory potency. The side chain with carbonyl group and methyl spacer between phenyl ring and organic nitrates was found to be essential requirement for inhibitory potency. The side chain with amide linkage was found to be more potent inhibitor than esters. The basic chalcone backbone was observed to be very important for inhibitory action against PDE 5 and 5A. The substitutions on aromatic ring of chalcone, the position of double bonds in chalcone moiety and the position of C=O seems as a modulator for activity and relative potency against PDE 5 and 5A. The comparison of inhibitory potency of **B2** and other active molecules against PDE 5 and 5A with standard inhibitor (IBMX) and tadalafil is showed in figure 1 which reveals that the **B2** is having inhibitory potency more than 90% against PDE 5A as compared to standard inhibitor (IBMX) and tadalafil. The structure of **B2** reveals the structural requirement for potency against PDE, which includes a chalcone moiety with amide linkage separated from organic nitrate by carbonyl and methyl group, also there is presence of NO group at ortho position on phenyl ring which is electron withdrawing. It also highlights the potential of this approach of evaluating nitric oxide donating molecules with chalcone as a basic skeleton for inhibition of PDE.

The probable mechanism by which these molecules inhibit PDE includes inactivation or degradation of active site of enzyme by binding to catalytic domain. This form of inactive or degraded PDE will not cause hydrolyses of cAMP and/or cGMP, leading to the formation of the active 5′-cAMP and 5′-cGMP, respectively which influences the cellular response of biological system.

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In-vitro toxicity assessment of synthesized compounds

Haemolytic assay

The haemolytic assay is used to test if a chemical (under evaluation) is toxic to circulating RBCs. Peripheral blood is centrifuged to sediment RBCs. The chemical under evaluation is added and incubated to permit reaction between the chemical and RBCs. The optical density readings are taken to measure the amount of haemolysis taken place. The degree of haemolysis is directly proportional to cytotoxicity to the RBCs.

None of concentrations of the tested compounds were haemolytic. Based on these results, the thus synthesized compounds were found to be non-haemolytic. The representative result of compounds having potency against PDE is presented in table 2.

Table 2 Showing result of haemolytic test

Com. Code	**% Haemolysis Observed**			
	0.1 mM	**1 mM**	**5 mM**	**10 mM**
B2	00	00	00	0.01
B4	00	00	00	00
E1	00	00	00	0.74
E6	00	00	00	0.21
E7	00	00	00	0.11

Positive Control = 100, Negative Control = 00, Vehicle Control = 2.1

Triton X-100 was used as positive control and untreated RBC with PBS served as negative control. The percentage of haemolysis under each concentration (0.1 mM, 1 mM, 5 mM and 10 mM) of test compound employed is tabulated.

Bacterial reverse mutation test

AMES (Bacterial reverse mutation test) is used to assess the mutagenicity of any compound or drug using histidine dependent bacterium. If the compound has ability to cause mutation then the bacterium will show reverse reaction in its histidine-based synthesis.

Ames test was done to study the mutagenic potential of compounds (**B2**) in *Salmonella typhimurium* strains TA 98 and TA 100 without metabolic activation system. Four concentrations (0.1 mM, 1 mM, 5 mM and 10 mM) of compounds were incubated with *Salmonella typhimurium* strains did not form any colonies whereas sodium azide treated strains formed revertant colonies. The colonies were counted, the values were also statistically significant between compounds treated and sodium azide treated groups (Table 3).

Table 3 Bacterial reverse mutation test inhibitory effect of **B2** on *Salmonella typhimurium* TA100 without metabolic activation system

Sr. No.	Compound Name and Concentration	*S. typhimurium (TA100)*
1.	Untreated	256
2.	0.1 mM	321
3.	1 mM	342
4.	5 mM	359
5.	10 mM	324
6.	Sodium azide	1,530

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Molecular docking results

The molecular docking has been carried out by two modes, the first one include docking with oxygen in PDB and second is docking without oxygen in PDB. Molecular docking with oxygen showed an excellent binding interaction of the synthesized compounds with the receptor 1XOZ with **B2** showing the docking score –72.50 kcal/mol. The molecular docking for compound **B2** with receptor 1XOZ is shown in figure 2 (a & b) which indicates that amide linked nitrate moiety of compound **B2** bound to aromatic site forms hydrogen bond interactions with ASP 764A. The nitro group of phenyl ring forms hydrogen bond interaction with LEU 725A. The phenyl ring forms hydrophobic interactions with LEU 627A and ILE 778A. The amide linked nitrate produces hydrophobic interactions with SER 766A, ALA 767A and ILE 778A. The oxygen, nitrate and carbon linked with amide linkage and aromatic ring formed Van der Walls interactions with the catalytic PHE 786A, CIA 326A, VAL 782A, TYR 612A, HIS 617A. As supported by the enzymatic activity assays, all these interactions are crucial factors contributing to inhibitory potency. There are 11 amino acid residues (Figure 2 (a & b)) found in the active binding site of 1XOZ complex namely: ASP 764A, LEU627A, ILE 778A, LEU 725A, SER 766A, ALA 767A, PHE 786A, CIA 326A, VAL 782A, TYR 612A, HIS 617A.

The docking of **B2** into 1XOZ without oxygen produces docking score of -67.34 kcal/mol, it shown in figure 3 (a & b). The phenyl nitro group forms hydrogen bonding with LEU 725A. The amide nitrogen forms nitrogen bonding with ASP 764 A. The nitrate molecule forms hydrophobic interactions with SER 766A, ALA 767A, ILE 778A, VAL 782A and LEU 627A. The remaining part of the molecule forms Van der Walls interactions with PHE 786A, LEU 725A, CIA 326A, TYR 612A and HIS 617A. The binding pattern and docking score observed to be differing than that of PDB containing oxygen. The PDB containing oxygen produces more prominent docking interactions and scores than that of PDB without oxygen.

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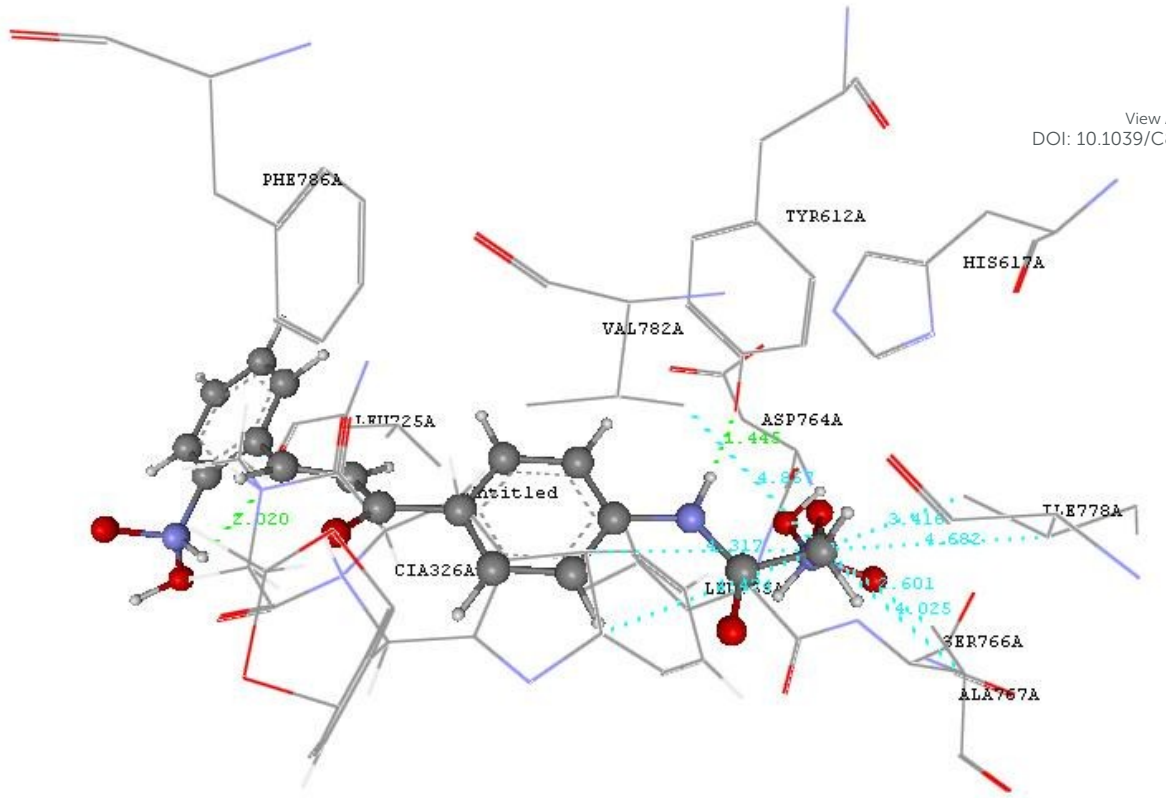
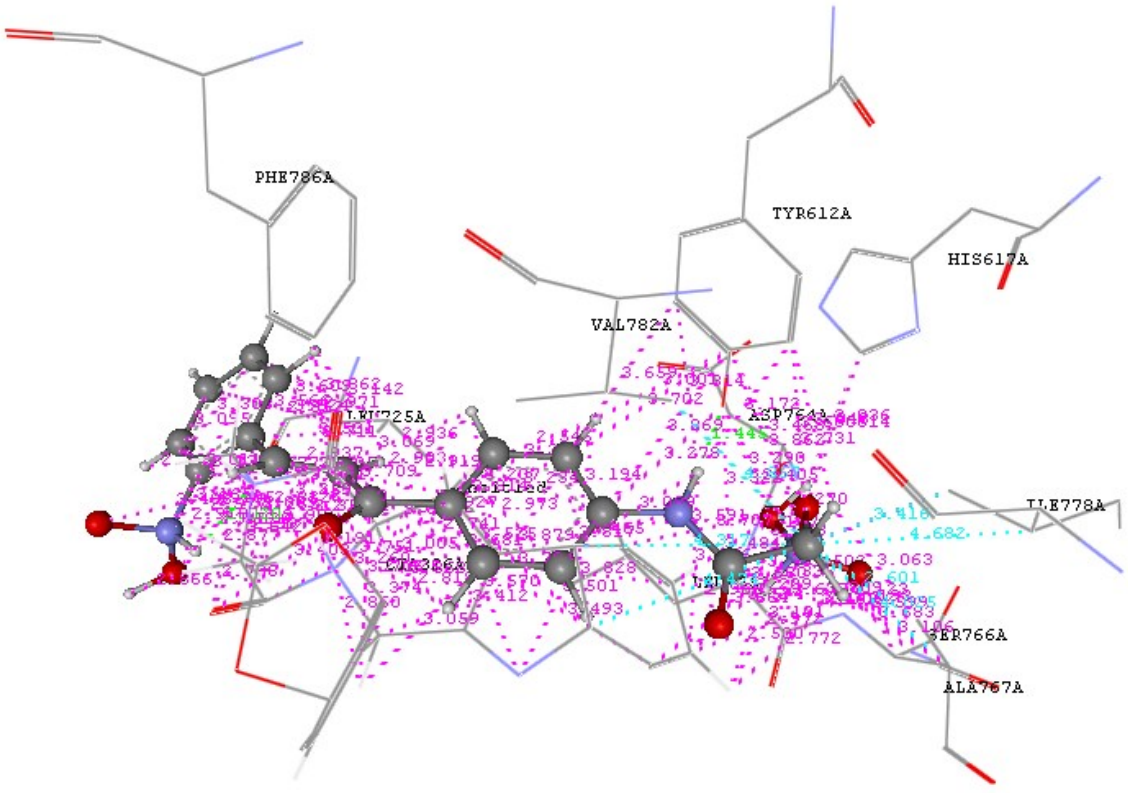


(a)



(b)

Figure 2. a. Binding interactions of the amino acid residues of the protein – 1XOZ containing oxygen complexity, with compound B2 and b showing van der Walls interaction of the protein – 1XOZ containing oxygen complexity, with compound B2.

(Light Blue colour indicates hydrophobic interaction, Green colour indicates hydrogen bonding and pink colour indicates Van der Walls interactions)

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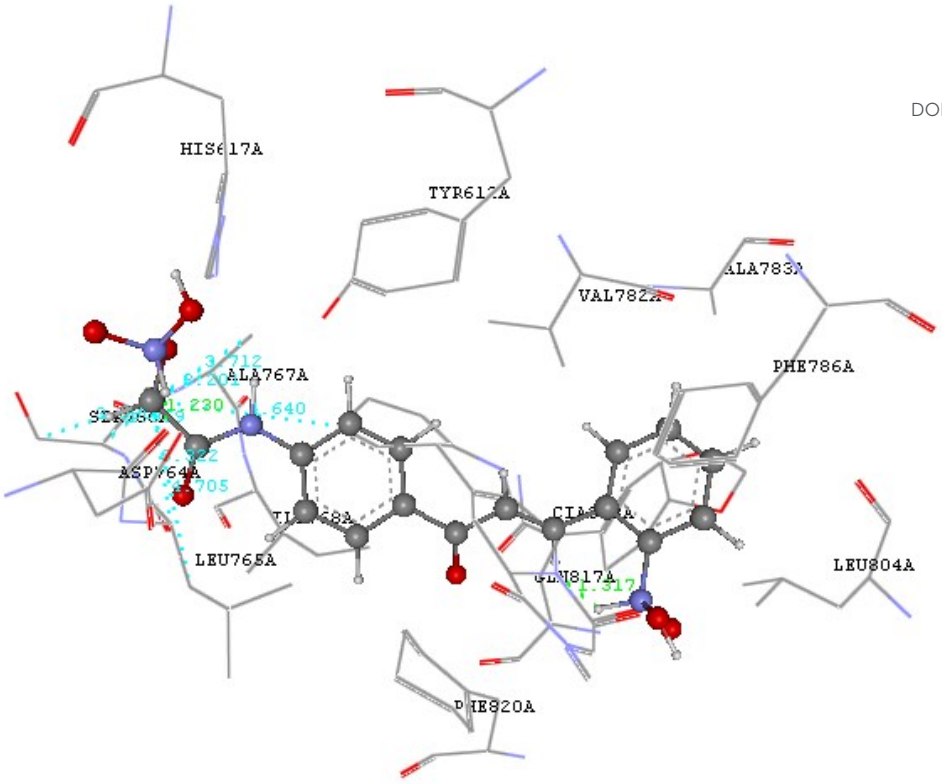
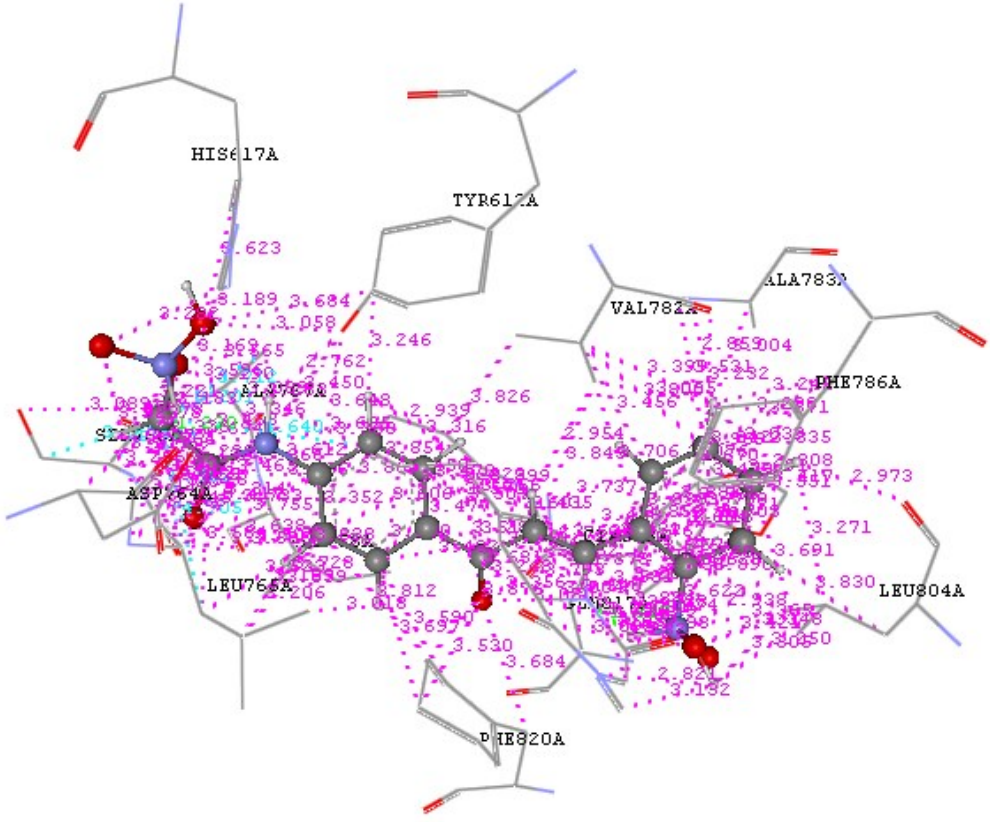


(a)



(b)

Figure 3. a. Binding interactions of the amino acid residues of the protein – 1XOZ without oxygen complexity, with compound B2 and b showing van der Walls interaction of the protein – 1XOZ without oxygen complexity, with compound B2.

(Light Blue colour indicates hydrophobic interaction, Green colour indicates hydrogen bonding and pink colour indicates Van der Walls interactions)

The above docking model was compared with binding model of compounds 8 (A), 9 (B), and 20 (C) with PDE 5 reported by Guang-Fu Yang et al.[30] In this paper the reported compounds 8 (A), 9 (B), and 20 (C) binds with PDE 5 with hydrogen bond interaction between the nitrogen of the amine group of the Glu817 side chain and the carbonyl oxygen of the ligands. This hydrogen bond exists in all of the docked PDE 5-ligand binding structures. In our docking model of B2 with PDE 5 there exist a hydrogen bond interaction between amide linked nitrate moiety of compound **B2** bound to aromatic site with ASP 764A and between nitro group of phenyl ring with LEU 725A. Our binding model of B2 also reveals hydrophobic interaction between phenyl ring with LEU 627A, ILE 778A and amide linked nitrate with SER 766A, ALA 767A and ILE 778A respectively. The Van der Walls interactions was observed between oxygen, nitrate, carbon linked with amide linkage and the catalytic site of 1XOZ containing PHE 786A, CIA 326A, VAL 782A, TYR 612A, HIS 617A.

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Conclusions

The nitric oxide donor compounds with chalcone as a basic skeleton had promising PDE 5 and 5A inhibitory potential. Compounds having substitutions like methoxy, hydroxyl, acetyl, nitro and ethoxy showed better PDE inhibition potential. Compounds having bromo and fluoro substituents have exhibit more PDE 5A inhibition potential. Our results suggest that these structures represent interesting lead compounds for the development of novel molecules for PDE 5 and 5A inhibition. The biocompatibility of these compounds was tested by in-vitro haemolytic and AMES test, All the end points consistently demonstrated the lack of toxicity and mutagenicity in the concentrations tested. These tests are considered gold standards of in-vitro assessment. This outcome may be worth further investigations to understand whether such compounds have real potential to enhance vascular muscle relaxation in clinical trials. A step forward will consist in investigating whether such compounds may prevent some cardiovascular complications and can be used for pain management concurrently with vascular pathophysiologies.

Experimental

Materials

Melting points were determined by open capillary method and values given were uncorrected. IR spectra were recorded on BRUKER ALPHA – 100508. The ^{1}H NMR and ^{13}C spectra were taken on 300 and 125 MHz Varian NMR instrument (Bruker) in $CDCl_3$ with hexamethyldisiloxane (HMDS) as an internal standard. Chemical shifts were reported in δ values (ppm) relative to internal HMDS. The abbreviation s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, ArH = aromatic CH were used throughout. The M/Z was determined on GC-MS (Shimadzu). Gas chromatography interfaced to a Mass spectrometer (GC-MS- 2010) equipped with a Elite-1 fused silica capillary column (RTZ i 5ms 30 mm x 0.25 mm 1D). Helium gas (99.999%) was used as the carrier gas at constant flow rate of 1 ml / min and an injection volume of 2 µl was employed (Split ratio of 50:50); Injector temperature 250° C; ion-source temperature 250° C. Elemental analyses (C, H and N) were realized on a Carlo-Erba EA 1108-elemental analyser and compared with theoretical values. All reactions were routinely checked by TLC on silica gel G.

Chemical synthesis

General Procedure for synthesis of compound i of scheme 1, 2 and 3.

Compound i was obtained by dissolving a specific amount of aromatic aldehyde (0.01 mol) and acetophenone (0.01 mol) in 10 ml of 95% ethanol in a flask with magnetic stirrer. 10% NaOH in ethanol was added in reaction mixture. The whole assembly was kept in ice bath with magnetic stirrer for 10 - 15 min, while the precipitation observed. Reaction mixture was added to 50% dilute acetic acid.[31] Then the respective products were purified by recrystallization. The purity of the compounds was determined by TLC using several solvent systems of different polarity.

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General Procedure for synthesis of compounds AI1-8 of scheme 1.

To acetic anhydride (3 ml) was added gradually, with stirring, 70% nitric acid (0.26 ml), while keeping the temperature between 20-30^0 C by external cooling. With continuous vigorous stirring the mixture was cooled to 5-10^0 C and weighed amount of compound (i) was added. After 10 min the reaction mixture was stirred at 10-15^0 C. The resulting reaction mixture was poured into ice-water, stirred for 1 h. then $NaHCO_3$ was added by portion until CO_2 evolution ceased. The water solution was extracted with 3×20 ml of ethyl acetate. Combined extracts were dried and concentrated and recrystallized from ethanol.

(E)-4-[3-(3-nitrophenyl)prop-2-enoyl]phenyl nitrate (AI1)

By following above methods, the title compound **AI1** was obtained as a pale yellow solid in 68.72 % yields; mp 90–92 ^{0}C; IR (KBr): 760, 1060 (C-N aromatic), 1681 (C-O chalcone), 1714 (aromatic) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.38 (dt, 2H, J = 7.50 Hz), 7.63 (s, 1H), 7.69 (m, 1H), 7.94 (m, 1H), 7.97 (m, 2H, J = 7.50 Hz), 8.39 (dt, 2H) 8.57 (m, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 122.1 (CH, C-16), 123.5 (CH=CH, C-9), 124.7 (CH, C-13), 128.9 (CH, C-2), 128.9 (CH, C-3), 129.6 (CH, C-4), 129.6 (CH, C-5), 129.8 (CH. C-14), 133.8 (C, C-1), 134.2 (CH, C-12), 137.7 (C, C-11), 141.6 (CH=, C-10), 143.3 (C-N, C-6), 147.7 (C-N, C-15), 191.7 (C=O, C-8); MS (m/z) 315.0 [M]$^+$; Anal Calcd for $C_{15}H_{10}N_2O_6$: C, 56.26; H, 3.15; N, 7.29 found C, 56.10; H, 3.10; N, 7.18.

(E)-4-{3-[3,4-bis(hydroxymethyl)phenyl]prop-2-enoyl}phenyl nitrate (AI2)

By following above methods, the title compound **AI2** was obtained as a pale yellow solid in pale yellow solid in 75.09 % yield; mp 110-112 ^{0}C; IR (KBr) 1064 (C-N aromatic), 1681 (C-O chalcone), 1700 (aromatic), 2952 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 4.80 (d, 4H), 7.38 (m, 3H, J = 15.10 Hz), 7.50 (d, 2H), 7.71 (dt, 1H, J = 15.10 Hz), 7.97 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$,) δ: 21.4 (CH_3, C-7), 62.6 (CH_2, C-20), 62.8 (CH_2, C-18), 123.5 (CH, C-9), 127.4 (CH, C-13), 127.9 (CH, C-12), 128.9 (CH, C-2), 128.9 (CH, C-3), 129.3 (CH, C-14), 129.6 (CH, C-4), 129.6 (CH, C-5), 132.9 (C, C-11), 133.8 (C, C-1), 138.5 (C, C-15), 143.3 (C-N, C-6), 144.0 (CH=, C-10), 191.7 (C=O, C-8); MS (m/z) 330.0 [M]$^+$; Anal Calcd for $C_{17}H_{15}NO_6$: C, 62.82; H, 4.74; N, 7.33 found C, 62.76; H, 4.88; N, 7.30.

(E)-4-{3-[3,4,5-tris(hydroxymethyl)phenyl]prop-2-enoyl}phenyl nitrate (AI3)

By following above methods, the title compound **AI3** was obtained as a yellow solid in 74.91 % yield; mp 122-124 ^{0}C; IR (KBr) 842, 1060 (C-N aromatic), 1681 (C-O chalcone), 1702 (aromatic), 3312 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 4.80 (s, 6H, J =4.5 Hz), 7.38(m, 3H, J = 15.10 Hz), 7.53 (s, 2H), 7.72 (dt, 1H, J = 15.10 Hz, =CH), 7.97 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.4 (CH_3, C-7), 59.1 (CH_2, C-20), 63.3 (CH_2, C-18), 122.2 (CH, C-9), 128.3 (CH, C-12), 128.3 (CH, C-13), 128.9 (CH, C-2), 128.9 (CH, C-3), 129.6 (CH, C-4), 129.6 (CH, C-5), 132.3 (C, C-11), 133.8 (C, C-1), 138.4 (C, C-16), 139.8 (C, C-14), 139.8 (C, C-

15), 143.3 (C-N, C-6), 143.7 (CH=, C-10), 185.6 (C=O, C-8); MS (m/z) 360.1 $[M]^+$; Anal Cacld for $C_{18}H_{17}NO_7$: C, 65.39; H, 4.66; N, 3.84 found C, 65.31; H, 4.54; N, 3.80.

(E)-4-{3-[4-(dimethylamino)phenyl]prop-2-enoyl}phenyl nitrate (AI4)

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By following above methods, the title compound **AI4** was obtained as a pale yellow solid in 70.36 % yield; mp 110-112 ^{0}C**;** IR (KBr) 1063 (C-N aromatic), 1681 (C-O chalcone), 1710 (aromatic), 2740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 2.90 (s, 6H), 6.54 (dt, 1H), 6.88 (dd, 1H, J = 7.50 Hz), 7.17 (t, 1H), 7.38 (m, 2H, J = 15.10 Hz), 7.72 (m, 1H, J = 7.50 Hz), 7.97 (m, 2H, J = 7.50 Hz- ArH); ^{13}C NMR ($CDCl_3$) δ: 21.4 (CH_3, C-7), 40.8 (CH_3, C-19), 40.8 (CH_3, C-20), 112.5 (CH, C-13), 115.8 (CH, C-16), 122.0 (CH, C-12), 123.5 (CH, C-9), 128.9 (CH, C-2), 129.2 (CH, C-14), 129.6 (CH, C-4), 129.6 (CH, C-5), 133.8 (C, C-1), 133.8 (C, C-11), 143.3 (C-N, C-6), 144.0 (CH=, C-10), 151.4 (C-N, C-15), 185.4 (C=O. C-8); MS (m/z) 313.1 $[M]^+$; Anal Cacld for $C_{17}H_{17}N_2O_4$: C, 66.83; H, 5.35; N, 3.54 found C, 66.81; H, 5.22; N, 3.57.

(E)-4-[3-(4-methylphenyl)prop-2-enoyl]phenyl nitrate (AI5)

By following above methods, the title compound **AI5** was obtained as a yellowish white solid in 68.71% yield, mp 94-96 ^{0}C; IR (KBr) 1078 (C-N aromatic), 1681 (C-O chalcone), 1710 (aromatic), 2940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 7.20 (t, 1H, J = 7.50 Hz), 7.38 (m, 3H, J = 15.10 Hz), 7.27 (m, 1H, J = 7.50 Hz), 7.33 (tt, 1H), 7.43 (m, 1H, J = 7.50 Hz), 7.73 (m, 1H, J = 15.10 Hz), 7.97 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.3 (CH_3, C-18), 21.4 (CH_3, C-7), 123.5 (CH, C-9), 124.0 (CH, C-12), 128.9 (CH, C-2), 128.9 (CH, C-3), 129.5 (CH, C-14), 129.5 (CH, C-16), 129.6 (CH, C-4), 129.6 (CH, C-5), 129.7 (CH, C-13), 133.8 (C, C-1), 135.9 (C, C-11), 138.9 (C, C-15), 143.3 (C-N, C-6), 144.0 (CH=, C-10), 191.7 (C=O, C-8); MS (m/z) 284.0 $[M]^+$; Anal Calcd for $C_{16}H_{13}NO_4$: C, 63.53; H, 5.45; N, 3.84 found C, 63.71; H, 5.37; N, 3.74.

(E)-4-[3-(4-ethylphenyl)prop-2-enoyl]phenyl nitrate (AI6)

By following above methods, the title compound **AI6** was obtained as a pale yellow solid in 77.00 % yield; mp 108-110 ^{0}C; IR (KBr) 986, 1063 (C-N aromatic), 1671 (C-O chalcone), 1700, 2940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, 3H, J = 12.50 Hz), 2.28 (m, 2H), 7.24 (m, 1H, J = 7.50 Hz) 7.35 (t, 1H, J = 7.50 Hz), 7.37 (m, 1H), 7.38 (m, 3H, J = 7.50 Hz), 7.43(m, 1H, J = 7.50 Hz), 7.73 (dt, 1H, J = 15.10 Hz), 7.97 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.1 (CH_3, C-19), 28.5 (CH_2, C-18), 123.5 (CH. C-9), 124.8 (CH, C-12), 127.4 (CH, C-16), 128.3 (CH, C-14), 128.9 (CH, C-2), 128.9 (CH, C-3), 129.2 (CH, C-13), 129.6 (CH, C-4), 129.6 (CH, C-5), 133.3 (C, C-11), 133.8 (C, C-1), 143.3 (C-N, C-6), 143.5 (C, C-15), 144.0 (CH, C-10), 191.7 (C=O, C-8); MS (m/z) 298.1 $[M]^+$; Anal Calcd for $C_{17}H_{15}NO_4$: C, 64.00; H, 5.15; N, 3.72 found C, 64.11; H, 4.94; N, 3.54.

(E)-4-[3-(4-acetylphenyl)prop-2-enoyl]phenyl nitrate (AI7)

By following above methods, the title compound **AI7** was obtained as a yellowish solid in 73.23 % yield; mp 96-98 ^{0}C; IR (KBr) 1105 (C-N aromatic), 1621 (C-O chalcone), 1790, 2940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.60 (s 3H), 7.38 (m, 3H, J = 15.10 Hz), 7.46 (t, 1H, J = 7.50 Hz), 7.76 (m, 1H), 7.78 (m, 1H, J = 15.10 Hz), 7.97 (m, 2H, J = 7.50), 8.04 (q, 1H), 8.09 (dt, 1H); ^{13}C NMR ($CDCl_3$) δ: 26.8 (CH_3, C-20), 123.5 (CH=, C-9), 127.7 (CH, C-13), 128.2 (CH, C-12), 128.3 (CH, C-14), 128.9 (CH, C-2), 128.9 (CH, C-3), 129.6 (CH, C-4), 129.6 (CH, C-5), 130.0 (CH, C-16), 133.6 (C, C-11), 133.8 (C, C-1), 137.3 (C, C-15), 143.3 (C-N, C-6), 144.0 (CH=,

C-10), 191.7 (C=O, C-8), 197.7 (C=O, C-18); MS (M/Z) 312.0 $[M]^+$; Anal Calcd for $C_{17}H_{13}NO_5$: C, 65.63; H, 5.05; N, 4.72 found C, 65.59; H, 4.94; N, 4.64.

(E)-4-[3-(4-tert-butylphenyl)prop-2-enoyl]phenyl nitrate (AI8)

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By following above methods, the title compound **AI8** was obtained as a yellowish solid in 73.05 % yield; mp 108-110 ^{0}C; IR (KBr) 1056 (C-N aromatic), 1585 (O-NO_2), 1641 (C-O chalcone), 1758 (C=C), 2940 (C-H aromatic) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.29 (s, 9H) 7.20 (t, 1H, J = 7.50 Hz), 7.38 (dd, 3H, J = 7.50 Hz), 7.47 (dt, 2H, J = 15.10 Hz), 7.54 (dt, 1H, J = 7.50 Hz), 7.65 (dt, 1H, J = 15.10 Hz), 7.97 (m, 2H, J = 7.50 Hz); ^{13}C NMR (CDCl) δ: 31.0 (CH_3, C-20), 31.0 (CH_3, C-21), 31.0 (CH_3, C-19), 34.8 (CH_3, C-18),123.5 (CH=, C-9),123.5 (CH, C-16), 124.5 (CH, C-12), 124.8 (CH, C-13), 128.6 (CH, C-14), 128.9 (CH, C-3), 128.9 (CH, C-2), 129.6 (CH, C-4), 129.6 (CH, C-5),133.7 (C, C-11), 133.8 (C, C-1), 143.3 (C-N, C-6),144.0 (C, C-10), 148.3 (C, C-15), 191.7 (C=O, C-8); MS (m/z) 326.1$[M]^+$; Anal Cacld for $C_{19}H_{19}NO_4$: C, 78.63; H, 5.58; N, 3.72 found C, 78.60; H, 5.94; N, 3.64.

General Procedure for synthesis of compound ii of scheme 1 and 2.

To a stirred solution of (i) in dichloromethane in ice-bath, a solution of K_2CO_3 (6.30 mmol) was added. To this solution bromoacetyl bromide (4.60 mmol) in 20 ml of dichloromethane was added in a drop wise manner, while keeping over 30 min. The mixture was left for stirring for further 2 h. at 0^0 C and 24 h. at room temperature. The organic layer was separated and aqueous layer was extracted with (2 x 30 ml) of dichloromethane. The combined organic layer was washed consequently with distilled water. The organic layer dried over anhydrous sodium sulphate, evaporated under reduced pressure and the obtained crude product was recrystallized from ethanol.

General Procedure for synthesis of compounds Ca 1-8 of scheme 1.

To a stirred solution of bromoacetyl derivative (ii and iii) (10.0 mmol) in 20 ml acetonitrile, silver nitrate (40.00 mmol) was added. The mixture was heated for 13-17 h. at 80^0 C. The formed precipitate of silver bromide was filtered off. The filtrate was evaporated till dryness and dissolved in dichloromethane; the organic layer was washed consequently with distilled water (2 x 20 ml) and brine. The organic layer was dried over anhydrous sodium sulphate, evaporated and crude product was recrystallized from methanol.

(E)-4-[3-(3-nitrophenyl)prop-2-enoyl]phenyl (nitrooxy)acetate (Ca1)

By following above methods, the title compound **Ca1** was obtained as a yellow solid in 67.82 % yield; mp 82-84 ^{0}C; IR (KBr) 857, 1073 (C-N aromatic), 1648 (C-O chalcone), 1683 (C-O ester), 1720, 3270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.49 (q, 2H, J = 8.00 Hz), 7.08 (m, 2H, J = 7.50 Hz), 7.67 (m, 1H, J = 15.10 Hz), 7.69 (m, 1H, J = 7.50 Hz), 7.76 (dt, 1H, J = 15.10 Hz), 7.96 (m, 1H, J = 7.50 Hz), 8.05 (m, 2H, J = 7.50 Hz), 8.39 (m, 1H), 8. 60 (q, 1H); ^{13}C NMR ($CDCl_3$) δ: 27.3 (CH_2, C-20), 121.6 (CH, C-4), 121.6 (CH, C-5), 122.1 (CH, C-15), 123.5 (CH=, C-8), 124.7 (CH, C-12), 129.8 (CH, C-13), 130.8 (CH, C-2), 130.8 (CH, C-3), 132.5 (C, C-1), 134.2 (CH, C-11), 137.7 (C, C-10), 141.6 (CH, C-9), 147.7 (C-N, C-14), 154.5 (C-O, C-6), 172.5 (C=O, C-18), 185.5 (C=O, C-7); MS (m/z) 373.0 $[M]^+$; Aanal Calcd for $C_{17}H_{12}N_2O_8$: C, 54.85; H, 3.25; N, 7.52 found C, 54.90; H, 3.55; N,71.29.

(E)-4-{3-[3,4-bis(hydroxymethyl)phenyl]prop-2-enoyl}phenyl (nitrooxy)acetate (Ca2)

By following above methods, the title compound **Ca2** was obtained as a yellow solid in 71.29 % yield; mp 88-90 ^{0}C; IR (KBr) 834, 1102 (C-N aromatic), 1690 (C-O ester), 1765, 3320 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.49 (q, 2H, J = 8.00 Hz), 4. 80 (d, 4H), 7.17 (m, 2H, J = 7.50 Hz), 7.44 (s, 2H, J = 7.50 Hz), 7.50 (m, 2H, J = 7.50 Hz), 7.67 (d, 1H, J = 15.10 Hz), 8.09 (d, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.3 (CH_2, C-20), 62.6 (CH_2, C-23), 62.8 (CH_2, C-22), 121.6 (CH, C-4), 121.6 (CH, C-5), 123.5 (CH=, C-8),127.4 (CH, C-12), 127.7 (CH, C-11) 129.3 (CH, C-13), 130.8 (CH, C-2), 130.8 (CH, C-3), 132.5 (CH, C-1), 132.9 (C, C-10), 136.3 (C, C-15), 138.5 (C, C-14), 144.0 (CH=, C-9),154.5 (CH-, C-6), 172.5 (C=O, C-18), 191.7 (C=O, C-7); MS (m/z) 388.1 [M]$^+$; Anal Calcd for $C_{19}H_{15}NO_8$: C, 58.92; H, 4.42; N, 3.62 found C, 58.78; H, 4.55; N, 3.54.

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(E)-4-{3-[3,4,5-tris(hydroxymethyl)phenyl]prop-2-enoyl}phenyl (nitrooxy)acetate (Ca3)

By following above methods, the title compound **Ca3** was obtained as a yellow solid in 60.21 % yield; mp 104-106 ^{0}C; IR (KBr) 748, 1100 (C-N aromatic), 1689 (C-O ester), 1720, 3270 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.17 (t, 3H), 2.49 (q, 2H, J = 8.00 Hz), 4.80 (s, 6H), 7.17 (m, 2H, J = 7.50 Hz), 7.50 (m, 1H, J = 7.50 Hz), 7.52 (m, 2H) 7.67 (m, 2H), 8.07 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 59.1 (CH_2, C-23), 63.3 (CH_2, C-22), 63.3 (CH_2, C-26), 120.2 (CH, C-4), 120.2 (CH, C-5), 122.2 (CH=, C-8), 128.3 (CH, C-11), 128.3 (CH, C-12), 131.0 (CH, C-2), 131.0 (CH, C-3), 132.3 (C, C-10), 133.2 (C, C-1), 138.4 (C, C-15), 139.8 (C, C-13), 139.8 (C, C-14), 140.1 (C-O, C-6), 143.7 (CH=, C-9), 172.5 (C=O, C-18), 185.6 (C=O, C-7); MS (m/z) 418.1 [M]$^+$; Anal Calcd for $C_{20}H_{19}N_2O_8$: C, 57.55; H, 4.59; N, 3.36 found C, 57.60; H, 4.75; N, 3.41.

(E)-4-[3-(4-chlorophenyl)prop-2-enoyl]phenyl (nitrooxy)acetate (Ca5)

By following above methods, the title compound **Ca5** was obtained as a yellow solid in 71.28 % yield; mp 110-112 ^{0}C; IR (KBr) 810, 1079 (C-N aromatic), 1695 (C-O ester), 1728, 2952 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.49 (q, 2H, J = 8.00 Hz), 7.18 (m, 2H, J = 7.50 Hz), 7.69 (d, 1H, J = 15.10 Hz), 7.73 (m, 2H, J = 7.50 Hz), 7.78 (m, 1H, J = 7.50 Hz), 8.10 (m, 2H, J = 7.50 Hz), 8.34 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 9.1 (CH, C-21), 27.6 (CH_2, C-20), 120.4 (CH, C-4), 120.4 (CH, C-5), 120.4 (CH=, C-8), 121.8 (C-Cl, C-15), 130.5 (CH, C-11) 130.8 (CH, C-12), 131.0 (CH, C-2), 131.0 (CH, C-3), 13.5 (CH, C-13), 131.5 (CH, C-14), 133.2 (C, C-1), 140.1 (C-O, C-6), 142.6 (CH=, C-9), 173.3 (C=O, C-18), 186.5 (C=O, C-7); MS (m/z) 362.0 [M]$^+$; Anal Calcd for $C_{17}H_{12}ClNO_6$: C, 56.45; H, 3.34; N, 3.87 found C, 56.66; H, 3.51; N, 3.71.

(E)-4-[3-(4-fluorophenyl)prop-2-enoyl]phenyl (nitrooxy)acetate (Ca7)

By following above methods, the title compound **Ca7** was obtained as a white solid in 71.08 % yield; mp 142-144 ^{0}C; IR (KBr) 710, 1610 (C-O chalcone), 1690 (C-O ester), 1748, 2990 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.49 (q 2H, J = 8.00 Hz), 7.17 (m, 2H, J = 7.50 Hz), 7.45 (d, 1H, J = 15.10 Hz), 7.50 (m, 2H, J = 7.50), 7.57 (m, 2H, J = 15.10 Hz), 7.66 (m, 1H, J = 7.50 Hz), 8.08 (dt, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.3 (CH_2, C-20), 120.4 (CH=, C-8), 121.6 (CH, C-4), 121.6 (CH, C-5), 129.2 (CH, C-13), 129.2 (CH, C-14), 129.7 (CH, C-11), 129.7 (CH, C-13), 130.8 (C, C-2), !30.8 (CH, C-3), 132.5 (CH, C-1), 133.4 (CH, C-10), 133.4 (C-F, C-15), 143.1 (C=C, C-9), 154.5 (C-O, C-6), 172.5 (C=O, C-8), 188.8 (C=O, C-7); MS (m/z) 362.0 [M]$^+$; Anal for $C_{17}H_{12}FNO_6$: C, 59.14; H, 3.50; N, 4.06 found C, 59.24; H, 3.38; N, 4.10.

(E)-4-[3-(3-chlorophenyl)prop-2-enoyl]phenyl (nitrooxy)acetate (Ca8)

By following above methods, the title compound **Ca8** was obtained as a brown solid in 68.03 % yield; mp 108-110 ^{0}C; IR (KBr) 723, 1005 (C-N aromatic), 1670 (C-O chalcone), 1750 (aromatic), 3200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.49 (q, 2H, J = 8.00 Hz), 7.09 (m, 2H, J = 7.50 Hz), 7.46 (m, 1H, J = 15.10 Hz), 7.48 (m, 1H, J = 7.50 Hz), 7.49 (m, 1H), 7.64 (m, 1H), 7.65 (m, 1H), 7.67 (m, 1H), 8.04 (dt, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.3 (CH_2, C-20), 121.6 (CH, C-4), 121.6 (CH, C-5), 123.5 (CH=, C-8), 126.7 (CH, C-11), 127.4 (CH, C-15), 127.8 (CH, C-12), 130.2 (CH, C-13), 130.8 (CH, C-2), 130.8 (CH, C-3), 132.5 (CH, C-1), 135.3 (C-Cl, C-14), 136.8 (C, C-10), 142.8 (CH=, C-9), 154.5 (C-O, C-6), 172.5 (C-O, C-18), 185.5 (C-O, C-7); MS (m/z) 362.0 $[M]^+$; Anal for $C_{17}H_{12}ClNO_6$: C, 56.45; H, 3.34; N, 3.83 found C, 56.47; H, 3.38; N, 3.80.

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General procedure of synthesis of compounds AII1-8 of scheme 2.

The procedure is similar as that of synthesis of compound AI1-8 of scheme 1.

(E)-4-[3-(4-bromophenyl)-3-oxoprop-1-en-1-yl]phenyl nitrate (AII1)

By following above methods, the title compound **AII1** was obtained as a whitish brown solid in 73.54 % yield: mp 110-112 ^{0}C; IR (KBr) 745, 1075 (C-N aromatic), 1630 (C-O chalcone), 1720 (aromatic), 2972 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.21 (m, 2H, J = 7.50 Hz), 7.36 (m, 2H, J = 7.50 Hz), 7.48 (d, 1H, J = 15.10 Hz), 7.69 (m, 1H, J = 15.10 Hz), 7.75 (m, 2H, J = 7.50 Hz), 8.00 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 120.4 (CH=, C-9), 127.2 (C-Br, C-16), 129.4 (CH, C-2), 129.4 (CH, C-3), 129.7 (CH, C-4), 129.7 (CH, C-5), 130.1 (CH, C-12), 130.1 (CH, C-13), 131.4 (CH, C-14), 131.4 (CH, C-15), 132.1 (C, C-1), 136.8 (C, C-11), 138.7 (C-N, C-6), 143.6 (CH=, C-8) 188.9 (C=O, C-10); MS (m/z) 347.9 $[M]^+$; Anal Calcd for $C_{15}H_{10}BrNO_4$: C, 56.26; H, 3.15; N, 7.29 found C, 56.08; H, 3.11; N, 7.24.

(E)-4-[3-(3-nitrophenyl)-3-oxoprop-1-en-1-yl]phenyl nitrate (AII2)

By following above methods, the title compound **AII2** was obtained as a yellow solid in 69.03 % yield; mp 122-124 ^{0}C; IR (KBr) 857, 1093 (C-N aromatic), 1670 (C-O chalcone), 2972, 3350 (N-O, nitrite) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.21 (m, 2H, J = 7.50 Hz) 7.38 (m, 2H, J = 7.50 Hz), 7.45 (d, 1H, J = 15.10 Hz), 7.64 (m, 1H. J = 15.10 Hz), 7.66 (m, 1H), 8.47 (m, 1H, J = 7.50 Hz), 8.48 (m, 1H, J = 7.50 Hz), 8.69 (t, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 121.9 (CH=, C-9), 123.2 (CH, C-13), 127.2 (CH, C-16), 129.4 (CH, C-2), 129.4 (CH, C-3), 129.7 (CH, C-4), 129.7 (CH, C-5), 130.6 (CH, C-14), 132.1 (C, C-1), 134.1(CH, C-12), 138.7 (C-N, C-6), 139.6 (C, C-11), 143.9 (CH=, C-8), 148.5 (C-N, C-15), 187.8 (C=O, C-10); MS (m/z) 315.0 $[M]^+$; Anal Calcd for $C_{15}H_{10}N_2O_6$: C, 61.79; H, 4.09; N, 3.79 found C, 61.52; H, 4.06; N, 3.70.

(E)-4-{3-[2,5-bis(hydroxymethyl)phenyl]-3-oxoprop-1-en-1-yl}phenyl nitrate (AII3)

By following above methods, the title compound **AII3** was obtained as a yellow solid in 64.17 % yield; mp 120-122 ^{0}C; IR (KBr) 1100 (C-N aromatic), 1670 (C-O chalcone), 1705, 2953 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 2H), 4.41 (d, 2H), 4.80 (d, 2H), 7.21 (m, 2H, J = 7.50 Hz), 7.38 (m, 2H, J = 7.50 Hz), 7.41 (d, 1H, J = 15.10 Hz), 7.58 (dt, 1H), 7.65 (dd, 1H, J = 15.10 Hz), 7.71 (ddt, 1H, J = 7.50 Hz), 7.92 (t, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ: 62.0 (CH_2, C-18), 64.5 (CH_2, C-19), 120.7 (CH=, C-9), 125.0 (CH, C-16), 128.8 (CH, C-15), 129.4 (CH, C-2), 129.4 (CH, C-3), 129.7 (CH, C-4), 129.7 (CH, C-5), 130.5 (C, C-1), 131.4 (CH, C-12), 137.4 (C, C-14), 138.7 (C-N, C-6), 139.6 (C, C-13), 143.8 (C, C-11), 144.0 (CH=, C-8), 193.9 (C=O, C-10); MS (m/z)

330.0 $[M]^+$; Anal Calcd for $C_{17}H_{15}NO_6$: C, 60.15; H, 4.29; N, 3.51. found C, 60.13; H, 4.25; N, 3.50. **4-[(1E)-(E)-4-[3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]phenyl nitrate (AII4)**

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By following above methods, the title compound **AII4** was obtained as a yellow solid in 67.81% yield; mp 102-104 ^{0}C; IR (KBr) 1075 (C-N aromatic), 1670 (C-O chalcone), 1702, 2900, 2972 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.21 (m, 2H, J = 7.50 Hz), 7.36 (m, 2H, J = 7.50 Hz), 7.45 (d, 1H, J = 15.10 Hz), 7.65 (m, 1H, J = 15.10 Hz), 8.12 (m, 2H, J = 7.50 Hz), 8.26 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 120.4 (CH=, C-9), 125.2 (CH, C-14), 125.2 (CH, C-15), 129.4 (CH, C-2), 129.4 (CH, C-3), 129.7 (CH, C-4), 129.7 (CH, C-5), 130.1 (CH, C-12), 130.1 (CH, C-13), 132.1 (C, C-1), 138.7 (C-N, C-6), 143.0 (C, C-11), 143.6 (CH=, C-8), 150.0 (C-N, C-16), 188.9(C=O, C-10); MS (m/z) 315.0 $[M]^+$; Anal Calcd for $C_{15}H_{10}N_2O_6$: C, 65.39; H, 4.66; N, 3.81 found C, 65.34; H, 4.61; N, 3.87.

(E)-4-[3-(4-methylphenyl)-3-oxoprop-1-en-1-yl]phenyl nitrate (AII5)

By following above methods, the title compound **AII5** was obtained as a yellow solid in 67.12 % yield; mp 96-98 ^{0}C; IR (KBr) 1075 (C-N aromatic), 1690 (C-O chalcone), 1770, 2980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.21 (m, 2H, J = 7.50 Hz), 7.37 (ddt, 2H, J = 7.50 Hz), 7.38 (d, 2H, J = 7.50 Hz), 7.45 (dt, 1H, J = 15.10 Hz), 7.65 (m, H, J = 15.10 Hz), 7.97 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.4 (CH_3, C-18), 120.4 (CH=, C-9), 128.9 (CH, C-12), 128.9 (CH, C-13), 129.4 (CH, C-2), 129.4 (CH, C-3), 129.7 (CH, C-14), 129.7 (CH, C-15), 129.7 (CH, C-4), 129.7 (CH, C-5), 132.1 (C, C-1), 133.8 (C, C-11), 138.7 (C-N, C-6), 143.3 (C, C-16), 143.6 (CH=, C-8), 188.2 (C=O, C-10); MS (m/z); 284.0 $[M]^+$; Anal Calcd for $C_{16}H_{13}NO_4$: C, 65.18; H, 4.88; N, 3.51 found C, 65.24; H, 4.81; N, 3.78.

(E)-4-{3-[3,4-bis(hydroxymethyl)phenyl]-3-oxoprop-1-en-1-yl}phenyl nitrate (AII7)

By following above methods, the title compound **AII7** was obtained as a yellow solid in 68.83 % yield; mp 120-122 ^{0}C; IR (KBr) 1089 (C-N aromatic), 1600 (C-O chalcone), 1740, 2900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (m, 2H), 4.53 (d, 4H), 7.21 (m, 2H, J = 7.50 Hz), 7.38 (m, 2H, J = 7.50 Hz), 7.45 (m, 2H, J = 15.10), 7.65 (dt 1H, J = 15.10 Hz), 7. 86 (dt, 1H), 8.08 (dd, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 62.7 (CH, C-18), 62. 7 (CH, C-20), 121.9 (CH=, C-9), 128.1 (CH, C-15), 128.2 (CH, C-13), 128.3 (CH, C-12), 129.4 (CH, C-2), 129.4 (CH, C-3), 129.7 (CH, C-4), 129.7 (CH, C-5), 132.1 (C, C-1), 136.3 (C-C, C-16), 138.0 (C, C-11), 138.5 (C-C, C-14), 138.7 (C-N, C-6), 143.9 (CH=, C-8), 190.7 (C=O, C-10); MS (m/z) 330.0 $[M]^+$; Anal Calcd for $C_{17}H_{15}NO_6$: C, 65.00; H, 4.45; N, 3.91 found C, 65.04; H, 4.81, N, 3.78.

(E)-4-[3-(4-ethylphenyl)-3-oxoprop-1-en-1-yl]phenyl nitrate (AII8)

By following above methods, the title compound **AII8** was obtained as a yellow solid in 68.23 % yield; mp 130-132 ^{0}C; IR (KBr) 1090 (C-N aromatic), 1648 (C-O chalcone), 1710, 2900, 2992 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, 3H, J = 8.00 Hz), 2.67 (tdd, 2H, J = 8.00 Hz), 7.21 (m, 2H, J = 7.50 Hz), 7.35 (m, 2H, J = 7.50 Hz) 7.37 (m, 2H, J = 7.50 Hz), 7.45 (m, 1H, J = 15.10), 7.65 (dt, 1H, J = 15.10 Hz), 7.90 (dt, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.5 (CH_3, C-19), 28.6 (CH_2, C-18), 120.4 (CH=, C-9), 127.6 (CH, C-12), 127.60 (CH, C-13), 128.6 (CH, C-14), 128.6 (CH, C-15), 129.4 (CH, C-2), 129.4 (CH, C-3), 129.7 (CH, C-4), 129.7 (CH, C-5), 132.1 (C, C-1), 136.7 (C, C-11), 138.7 (C, C-6), 143.6 (CH=, C-8), 146.4 (C, C-16), 185.4 (C=O, C-10); MS (m/z) 298.1$[M]^+$; Anal Calcd for $C_{17}H_{15}NO_4$: C, 64.80; H, 4.40; N, 3.80 found C, 64.01; H, 4.85; N, 3.76.

General Procedure for synthesis of compounds Cb2-5 of scheme 2.

The procedure is similar as that of synthesis of compounds Ca1-7 of scheme 1.

(E)-4-{3-[2,4-bis(hydroxymethyl)phenyl]-3-oxoprop-1-en-1-yl}phenyl (nitrooxy)acetate (Cb2)

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By following above methods, the title compound **Cb2** was obtained as a yellow solid in 72.72 % yield; mp 102-104 ^{0}C; IR (KBr) 830, 1600 (C-O ester), 1690 (C-O chalcone), 1700, 3220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.21 (dt, 2H), 2.49 (q, 2H, J = 8.00 Hz), 4.80 (m, 2H), 4.81 (m, 2H), 7.08 (m, 2H, J = 7.50 Hz), 7.41 (d, 1H, J = 15.10 Hz), 7.53 (dt, 1H), 7.57 (m, 1H, J = 7.50 Hz), 7.61 (m, 2H, J = 7.50 Hz), 7.66 (dt, 1H, J = 15.10 Hz), 7.89 (d, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.3 (CH_2, C-20), 62.8 (CH_2, C-22), 64.2 (CH_2, C-23), 120.7 (CH=, C-8), 122.0 (CH, C-4), 122.0 (CH, C-5), 124.6 (CH, C-13), 129.1 (CH, C-14), 129.2 (C, C-1), 129.5 (CH, C-2), 129.5 (CH, C-3), 130.1 (CH, C-11), 136.9 (C, C-15), 138.5 (C, C-10), 142.0 (C, C-12), 144.0 (CH=, C-7), 152.0 (C-O, C-6), 172.5 (C=O, C-18), 193.9 (C=O, C-9); MS (m/z) 388.1 [M]$^+$; Anal Calcd for $C_{19}H_{17}NO_8$: C, 58.92; H, 4.42; N, 3.62 found C, 58.90; H, 4.40; N, 3.51.

(E)-4-{3-[4-(hydroxymethyl)phenyl]-3-oxoprop-1-en-1-yl}phenyl (nitrooxy)acetate (Cb3)

By following above methods, the title compound **Cb3** was obtained as a yellow solid in 57.21 % yield; mp 98-100 ^{0}C; IR (KBr) 780, 1600 (C-O ester), 1680 (C-O chalcone), 1710, 3280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (m. 1H), 2.49 (q, 2H, J = 8.00 Hz), 4.53 (d, 2H), 7.15 (m, 2H, J = 7.50 Hz), 7.48 (d, 1H, J = 8.00 Hz), 7.58 (dt, 2H, J = 7.50 Hz), 7.64 (m, 2H, J = 15.10 Hz), 7.67 (m,1H), 7.95 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.3 (CH_2, C-20), 64.7 (CH_2, C-22), 120.4 (CH=, C-8), 122.0 (CH, C-4), 122.0 (CH, C-5), 127.3 (CH, C-11), 127.3 (CH, C-12), 128.2 (CH, C-13), 128.2 (CH, C-14), 128.7 (C, C-1), 129.5 (CH, C-2), 129.5 (CH, C-3), 137.9 (C, C-10), 144.9 (CH=, C-7), 145.3 (C, C-15), 152.0 (C-O, C-6), 172.5 (C=O, C-18), 185.4 (C=O, C-9); MS (m/z) 358.0[M]$^+$; Anal Calcd for $C_{18}H_{15}NO_7$: C, 60.50; H, 4.23; N, 3.92 found C, 60.61; H, 4.11; N, 3.78.

(E)-4-[3-(3,4-dichlorophenyl)-3-oxoprop-1-en-1-yl]phenyl (nitrooxy)acetate (Cb4)

By following above methods, the title compound **Cb4** was obtained as a yellow solid in 70.23 % yield; mp 110-112 ^{0}C; IR (KBr) 790, 1620 (C-O ester), 1690 (C-O chalcone), 1760, 2900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.49 (q, 2H, J = 8.00 Hz), 7.15 (m, 2H, J = 7.50 Hz), 7.47 (d, 1H, J = 7.50 Hz), 7.49 (m, 2H, J = 8.00 Hz), 7.65 (m, 1H), 7.67 (dt, 2H, J = 15.10 Hz), 8.14 (d, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.3 (CH_2, C-20), 121.9 (CH=, C-8), 122.0 (CH, C-4), 122.0 (CH, C-5), 127.6 (CH, C-11), 128.7 (C, C-1), 128.7 (CH, C-12), 129.5 (CH, C-2), 129.5 (CH, C-3), 129.9 (CH, C-13), 132.8 (C-Cl, C-14), 134.3 (C-Cl, C-15), 136.3 (C, C-10), 144.0 (CH=, C-7), 152.0 (C-O, C-6), 172.5 (C=O, C-18), 190.7 (C=O, C-9); MS (m/z) 396.0 [M]$^+$; Anal Calcd for $C_{17}H_{11}Cl_2NO_6$: C, 51.54; H, 2.80; N, 3.54 found C, 51.46; H, 2.65; N, 3.37.

(E)-4-[3-(4-ethylphenyl)-3-oxoprop-1-en-1-yl]phenyl (nitrooxy)acetate (Cb5)

By following above methods, the title compound **Cb5** was obtained as a yellow solid in 63.82 % yield; mp 92-94 ^{0}C; IR (KBr) 800, 1610 (C-O ester), 1680 (C-O chalcone), 1738, 3012 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.19 (dt, 3H, J = 8.00 Hz), 2.49 (q, 2H, J = 8.00 Hz), 2.67 (tdd, 2H, J = 8.00 Hz), 7.15 (m, 2H, J = 7.50 Hz), 7.35 (dt, 2H, J = 7.50 Hz), 7.47 (d, 1H, J = 15.10 Hz), 7.63 (m, 2H, J = 15.10 Hz), 7.67 (m, 1H), 7.90 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.5 (CH_3, C-23), 27.3 (CH_2, C-20), 28.6 (CH_2, C-22), 120.4 (CH=, C-8), 122.0 (CH, C-4), 122.0 (CH, C-5), 127.6 (CH, C-11), 127.6 (CH, C-12), 128.6 (CH, C-13), 128.6 (CH, C-14), 128.7 (C, C-1),

129.5 (CH, C-2), 129.5 (CH, C-3), 136.7 (C, C-10), 144.9 (CH=, C-7), 146.4 (C, C-15), 152.0 (C-O, C-6), 172.5 (C-O, C-18), 185.4 (C-O, C-9); MS (m/z) 356.1 $[M]^+$; Anal Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94 found C, 64.33; H, 4.70; N, 3.87.

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General Procedure for synthesis of compound ii of scheme 3

The procedure is similar to that of synthesis of compound ii of scheme 1 and 2.

General Procedure for synthesis of compound B2 – B11 of scheme 2

The procedure is similar to that of synthesis of compounds Ca1-7 and Cb1-5 of scheme 1 and 2.

(E)-2-({4-[3-(2-nitrophenyl)prop-2-enoyl]phenyl}amino)-2-oxoethyl nitrate (B2)

By following above methods, the title compound **B2** was obtained as a yellow solid in 67.34 % yield; mp 122-124 ^{0}C; IR (KBr) 864, 1602 (C-O amino ester), 1690 (C-O chalcone), 3320 (N-H amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 7.24 (m, 2H, J = 7.50 Hz), 7.57 (m, 1H, J = 7.50 Hz), 7.60 (dt, 1H). 7.70 (m, 1H, J = 7.50 Hz), 7.80 (ddd, 1H, J = 7.50 Hz), 7.96 (m, 2H, J = 7.50 Hz), 8.06 (dd, 1H, J = 15.10 Hz), 8.25 (dd, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 120.2 (CH, C-4), 120.2 (CH, C 5), 124.8 (CH=, C-8), 128.8 (CH, C-15), 129.6 (CH, C-14), 131.0 (CH, C-2), 131.0 (CH, C-3), 132.3 (CH, C-11), 132.7 (C, C-10), 132.8 (CH, C-13), 133.5 (C, C-1), 140.1 (C-N, C-6), 141.7 (CH=, C-9), 149.4 (C-N, C-12), 173.3 (C-O, C-18), 190.2 (C-O, C-7); MS (m/z) 372.0$[M]^+$; Anal Calcd for $C_{17}H_{13}N_3O_7$: C, 55.99; H, 3.53; N, 11.32 found C, 56.06; H, 3.50; N, 11.34.

(E)-2-({4-[3-(2-chlorophenyl)prop-2-enoyl]phenyl}amino)-2-oxoethyl nitrate (B3)

By following above methods, the title compound **B3** was obtained as a yellow solid in 69.03 % yield; mp 122-124 ^{0}C; IR (KBr) 760, 1100, 1640 (C-O amino ester), 1700, 3270 (N-H amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 7.22 (m, 2H, J = 7.50 Hz), 7.27 (m, 1H, J = 7.50 Hz), 7.31 (m, 1H, J = 15.10 Hz), 7.36 (m, 1H, J = 7.50 Hz), 7.38 (m, 1H, J = 7.50 Hz), 7.46 (dd, 1H, , J = 7.50 Hz), 7.85 (dd, 1H, J = 15.10 Hz), 7.91 (dd, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 120.2 (CH, C-4), 120.2 (CH, C-5), 123.8 (CH=, C-8), 127.5 (CH, C-13), 128.5 (CH, C-11), 129.5 (CH, C-14), 130.6 (CH, C-15), 131.0 (CH, C-2), 131.0 (CH, C-3), 132.5 (C, C-10), 133.1 (C-Cl, C-12), 133.5 (C, C-1), 138.8 (CH=, C-9), 140.1 (C-N, C-6), 173.3 (C-O, C-18), 190.2 (C-O, C-7); MS (m/z) 361.0 $[M]^+$; Anal Calcd for $C_{17}H_{13}ClN_2O_5$: C, 56.60; H, 3.63; N, 7.77 found C, 56.58; H, 3.55; N, 7.71.

(E)-2-({4-[3-(4-fluorophenyl)prop-2-enoyl]phenyl}amino)-2-oxoethyl nitrate (B4)

By following above methods, the title compound **B4** was obtained as a yellow solid in 67.03 % yield; mp 128-130 ^{0}C; IR (KBr) 750, 1670 (C-O amino ester), 1705, 1751, 3200 (N-H amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 7.23 (m, 2H, J = 7.50 Hz), 7.32 (m, 2H, J = 7.50 Hz), 7.40 (d, 1H, J = 15.10), 7.52 (d, 2H, J = 7.50 Hz), 7.65 (dt, 1H, J = 15.10 Hz), 7.92 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 114.7 (CH, C-13), 114.7 (CH, C-14), 120.2 (CH, C-4), 120.2 (CH, C-5), 120.4 (CH=, C-8), 130.2 (CH, C-11), 130.2 (CH, C-12), 131.0 (CH, C-2), 131.0 (CH, C-3), 131.1 (C, C-10), 133.2 (C, C-1), 140.1 (C-N, C-6), 143.3 (CH, C-9), 163.2 (C-F, C-15), 173.3 (C-O, C-18), 186.5 (C-O, C-7); MS (m/z) 345.0 $[M]^+$; Anal Calcd for $C_{17}H_{13}FN_2O_5$: C, 59.30; H, 3.81; N, 8.14 found C, 59.43; H, 3.68, N, 8.17.

(E)-2-({4-[3-(4-nitrophenyl)prop-2-enoyl]phenyl}amino)-2-oxoethyl nitrate (B5)

By following above methods, the title compound **B5** was obtained as a yellow solid in 68.23 % yield; mp 188-120 ^{0}C; IR (KBr) 815, 1640 (C-O amino ester), 1690 (C-O chalcone), 1738, 3352 (N-H, amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 7.25 (m, 2H, J = 7.50 Hz), 7.71 (m, 1H), 7.75 (m, 2H, J = 7.50 Hz), 7.78 (m,1H), 7.95 (m, 2H, J = 7.50 Hz), 8.35 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 120.2 (CH, C-4), 120.2 (CH, C-5), 120.4 (CH=, C-8), 124.6 (CH, C-13), 124.6 (CH, C-14), 129.0 (CH, C-11), 129.0 (CH, C-12), 131.0 (CH, C-2), 131.0 (CH, C-3), 133.2 (C, C-1), 140.1 (C-N, C-6), 141.1 (C, C-10), 141.9 (CH=, C-9), 147.1 (C-N, C-15), 173.3 (C-O, C-18), 186.5(C-O, C-7); MS (m/z) 372.0 [M]$^+$; Anal Calcd for $C_{17}H_{13}N_3O_7$: C, 54.99; H, 3.53; N, 11.32. found C, 55.08; H, 3.57; N, 11.20.

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(E)-2-({4-[3-(4-bromophenyl)prop-2-enoyl]phenyl}amino)-2-oxoethyl nitrate (B6)

By following above methods, the title compound **B6** was obtained as a yellow solid in 56.72 % yield; mp 134-136 ^{0}C; IR (KBr) 810, 1641 (C-O amino ester), 1680 (C-O chalcone), 1782, 3260 (N-H, amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 7.23 (m, 2H, J = 7.50 Hz), 7.41 (m, 2H, J = 7.50 Hz), 7.44 (m,1H), 7.65 (m, 1H, J = 15.10 Hz), 7. 69 (m, 2H, J = 7.50 Hz), 7.91 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 120.2 (CH, C-4), 120.2 (CH, C-5), 120.4 (CH=, C-8), 121.8 (C-Br, C-15), 130.5 (CH, C-11), 130.5 (CH, C-12), 131.0 (CH, C-2), 131.0 (CH, C-3), 131.5 (CH, C-13), 131.5 (CH, C-14), 133.2 (C, C-1), 133.8 (C, C-10), 140.1 (C-N, C-6), 142.6 (CH=, C-9), 173.3 (C-O, C-18), 186.5 (C-O, C-7); MS (m/z) 405.0 [M]$^+$; Anal Calcd for $C_{17}H_{13}BrN_2O_5$: C, 50.39; H, 3.23; N, 6.91 found C, 50.48; H, 3.14; N, 6.85.

(E)-2-({4-[3-(4-acetylphenyl)prop-2-enoyl]phenyl}amino)-2-oxoethyl nitrate (B7)

By following above methods, the title compound **B7** was obtained as a yellow solid in 66.12 % yield; mp 110-112 ^{0}C; IR (KBr) 700, 1614 (C-O amino ester), 1662 (C-O chalone), 1780, 3260 (N-H amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 2.51 (dt, 3H, J = 8.00 Hz), 7.23 (m, 2H, J = 7.50 Hz), 7.49 (d, 1H, J = 15.10 Hz), 7.56 (m, 2H), 7.69 (dt, 1H, J = 15.10 Hz), 7.92 (m, 2H, J = 7.50 Hz), 7.96 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 26.8 (CH_3, C-24), 27.6 (CH_2, C-20), 120.2 (CH, C-4), 120.2 (CH, C-5), 120.4 (CH=, C-8), 128.3 (CH, C-11), 128.3 (CH, C-12), 128.4 (CH, C-13), 128.4 (CH, C-14), 131.0 (CH, C-2), 131.0 (CH, C-3), 133.2 (C, C-1), 134.1 (C, C-10), 138.5 (C, C-15), 140.1 (C-N, C-6), 143.9 (CH=, C-9), 173.3 (C-O, C-18), 186.5 (C-O, C-7), 197.6 (C-O, C-22); MS (m/z) 369.1 [M]$^+$; Anal Calcd for $C_{19}H_{16}N_2O_6$: C, 61.95; H, 4.38; N, 7.61 found C, 61.90; H, 4.28; N, 7.56.

(E)-2-({4-[3-(4-tert-butylphenyl)prop-2-enoyl]phenyl}amino)-2-oxoethyl nitrate (B8)

By following above methods, the title compound **B8** was obtained as a yellow solid in 70.23 % yield; mp 132-134 ^{0}C; IR (KBr) 800, 1078, 1610 (C-O, amino ester), 1650 (C-O chalcone), 1720, 3220 (C-N amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (m, 1H), 1.28 (s, 9H), 2.35 (q, 2H, J = 8.00 Hz) 7.23 (m, 2H, J = 7.50 Hz), 7.38 (m, 2H, J = 7.50 Hz), 7.44 (d, 1H, J = 15.10 Hz), 7.48 (m, 2H, J = 7.50 Hz), 7.65 (dt, 1H, J = 15.10 Hz), 7.92 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 31.1 (CH_3, C-23), 31.1 (CH_3, C-24), 31.1 (CH_3, C-25), 34.1 (C, C-22), 120.2 (CH, C-4), 120.2 (CH, C-5), 120.4 (CH=, C-8), 126.0 (CH, C-13), 126.0 (CH, C-14), 126.4 (CH, C-11), 126.4 (CH, C-12), 131.0 (CH, C-2), 131.0 (CH, C-3), 132.6 (C, C-10), 133.2 (C, C-1), 137.6 (C, C-15), 140.1 (C-N, C-6), 143.9 (CH=, C-9), 173.3 (C-O, C-18), 186.5 (C-O, C-7); MS (m/z) 341.1 [M]$^+$. Anal Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33 found C, 65.85; H, 5.78; N, 7.22.

(E)-2-({4-[3-(4-methylphenyl)prop-2-enoyl]phenyl}amino)-2-oxoethyl nitrate (B9)

By following above methods, the title compound **B9** was obtained as a yellow solid in 74.91 % yield; mp 130-132 ^{0}C; IR (KBr) 830, 1078, 1600 (C-O amino ester), 1690 (C-O chalcone), 1700, 3220 (C-N amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (q, 3H), 2.35 (m, 2H, J = 8.00 Hz), 7.21 (m, 2H, , J = 7.50 Hz), 7.24 (m, 2H, J = 7.50 Hz), 7.38 (m, 2H, J = 7.50 Hz), 7.48 (m, 1H, J = 15.10 Hz), 7.64 (dt, 2H, J = 15.10 Hz), 7.95 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.7 (CH_3, C-22), 27.6 (CH_2, C-20), 120.2 (CH, C-4), 120.2 (CH, C-5), 120.4 (CH=, C-8), 129.4 (CH, C-11), 129.4 (CH, C-12), 129.7 (CH, C-13), 129.7 (CH, C-14), 131.0 (CH, C-2), 131.0 (CH, C-3), 132.1 (C, C-10), 133.2 (C, C-1), 138.7 (C, C-15), 140.1 (C-N, C-6), 143.6 (=CH, C-9), 173.3 (C-O, C-18), 186.5 (C-O, C-7); MS (m/z) 341.1 [M]$^+$; Anal Calcd Anal for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23 found C, 63.50; H, 4.64; N, 8.21.

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(E)-2-[(4-{3-[3,4-bis(hydroxymethyl)phenyl]prop-2-enoyl}phenyl)amino]-2-oxoethyl nitrate (B10)

By following above methods, the title compound **B10** was obtained as a yellow solid in 72.01 % yield; mp 140-142 ^{0}C; IR (KBr) 780, 1100, 1680 (C-O, chalcone), 1740, 3260 (C-N amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (m, 3H), 2.35 (q, 2H, J = 8.00 Hz, -CH_2), 4.80 (m, 4H, J = 8.00 Hz), 7.24 (d, 2H, J = 7.50 Hz), 4.43 (m, 1H, J = 7.50 Hz), 7.45 (d, 1H, J = 7.50 Hz), 7.50 (m, 1H, J = 15.10 Hz), 7.52 (m, 1H, J = 15.10 Hz), 7.66 (dd, 1H, J = 15.10), 7.94 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 62.6 (CH_2, C-23), 62.8 (CH_2, C-22), 120.2 (CH, C-4), 120.2 (CH, C-5), 123.5 (CH=, C-8), 127.4 (CH, C-12), 127.9(CH, C-11), 129.3 (CH, C-13), 131.0 (CH, C-2), 131.0 (CH, C-3), 133.2 (C, C-1), 132.9 (C, C-10), 136.3 (C, C-15), 138.5 (C, C-18), 140.1 (C-N, C-6), 144.0 (=CH, C-9), 173.3 (C-O, C-18), 187.9 (C-O, C-7); MS (m/z) 387.1 [M]$^+$; Anal Calcd for $C_{19}H_{18}N_2O_7$: C, 59.07; H, 4.70; N, 7.25. found C, 59.12; H, 4.71; N, 7.28.

(E)-2-oxo-2-[(4-{(3-[3,4,5-tris(hydroxymethyl)phenyl]prop-2-enoyl}phenyl)amino]ethyl nitrate (B11)

By following above methods, the title compound **B11** was obtained as a yellow solid in 68.90 % yield; mp 156-158 ^{0}C; IR (KBr) 784, 1154, 1680 (C-O chalone), 1750, 3260 (C-N amide) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (m. 4H), 2.35 (q, 2H, J = 8.00 Hz), 4.80 (s, 6H), 7.23 (m, 2H, J = 7.50 Hz), 7.48 (m, 1H), 7.52 (m, 2H, J = 15.10 Hz), 7.68 (dd, 1H, J = 15.10 Hz), 7.91 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-20), 59.1 (CH_2, C-23), 63.3 (CH_2, C-22), 63.3 (CH_2, C-26), 120.2 (CH, C-4), 120.2 (CH, C-5), 122.2 (CH=, C-8), 128.3 (CH, C-11), 128.3 (CH, C-12), 131.0 (CH, C-2), 131.0 (CH, C-3), 132.3 (C, C-10), 133.2 (C, C-1), 138.4 (C, C-15), 139.8 (C, C-13), 139.8 (C, C-14), 140.1 (C-N, C-6), 143.7 (=CH, C-9), 173.3 (C-O, C-18), 185.5 (C-O, C-5); MS (m/z) 417.1 [M]$^+$; Anal Calcd for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73 found C, 57.64; H, 4.75; N, 6.72.

General Procedure for synthesis of compound i of scheme 4.

Into a round bottom flask 1.35 mol of compound (substituted aldehyde) was placed and 0.25 mol of acid chloride was taken. Weighed out 0.275 mol of powdered, anhydrous aluminium chloride into a dry stoppered conical flask, and added the solid, with frequent shaking, during 10 min to the contents of the flask, and treated in microwave. After complete evolution of hydrogen chloride poured the content of the flask while still warm into a mixture of 200 gm of crushed ice and 100 ml of conc. hydrochloric acid. Filter it and washed with 50 ml of 5% sodium hydroxide solution, then with water, and dried with calcium chloride.

General Procedure for synthesis of compounds ii and iii of scheme 3.

The procedure is similar to that of synthesis of compound i of scheme 1 and 2.

General Procedure for synthesis of compound iv of scheme 3.

The procedure is similar to that of synthesis of compound ii of scheme 1 and 2.

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General Procedure for synthesis of compounds D 1- 9 of scheme 4.

The procedure is similar to that of synthesis of compounds AI1-8 and AII1-8 of scheme 1 and 2.

General Procedure for synthesis of compounds E 1-10 of scheme 4.

The procedure is similar to that of synthesis of compounds Ca 1-8 and Cb 2-5 of scheme 1 and 2.

(Z)-4-{2-[3-(4-ethylphenyl)-3-oxoprop-1-en-1-yl]-5-fluorobenzoyl}phenyl nitrate (D1)

By following above methods, the title compound **D1** was obtained as a yellow solid in 64.23 % yield; mp 168-170 ^{0}C; IR (KBr) 782 (C-H aromatic bending), 1119 (C-F stretching), 1584 (O-NO_2), 1630 (C=C alkene), 1680 (C-O chalcone), 1738 (C-O ketone), 3060 (C-H aromatic streching) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, 3H, J = 8.00 Hz), 2.67 (tdd, 2H, J = 8.00 Hz), 7.00 (m, 1H), 7.28 (m, 2H, J = 7.50 Hz), 7.30 (m, 1H, J = 7.50), 7.34 (m, 2H), 7.44 (m, 2H, J = 7.50 Hz), 7.50 (m, 1H), 7.83 (m, 2H, J = 7.50 Hz) 7.85 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.4 (CH_3, C-28), 28.5 (CH_2, C-27), 119.7 (C, C-4), 125.1 (CH=, C-16), 127.6 (CH, C-19), 127.6 (CH, C-20), 128.6 (CH, C-21), 128.6 (CH, C-22), 129.1 (CH, C-11), 129.1 (CH, C-12), 129.7 (CH, C-5), 129.7 (CH, C-9), 129.7 (CH, C-10), 131.3 (C-C. C-1), 131.7 (CH, C-6), 132.3 (CH, C-2), 133.7 (C, C-3), 134.5 (C-C, C-8), 136.9 (C, C-18), 137.7 (CH=, C-15), 142.5 (C-N, C-13), 146.4 (C, C-23), 191.9 (C-O, C-17), 195.1 (C-O, C-7); MS (m/z) 420.1 [M]$^+$; Anal Calcd for $C_{24}H_{18}FNO_5$: C, 68.73; H, 4.33; N, 3.34 found C, 68.75; H, 4.31; N, 3.30.

(Z)-4-{5-bromo-2-[3-(4-ethylphenyl)-3-oxoprop-1-en-1-yl]benzoyl}phenyl nitrate (D2)

By following above methods, the title compound **D2** was obtained as a yellow solid in 66.01 % yield; mp 156-158 ^{0}C; IR (KBr) 1320, 1640 (C-O chalcone), 1689, 1760, 3180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, 3H, J = 8.00 Hz), 2.67 (tdd, 2H), 7.01 (d, 1H, J = 10.90), 7.26 (m, 1H, J = 7.50), 7.28 (m, 2H, J = 7.50 Hz), 7.35 (dd, 1H, J = 10.90 Hz), 7.43 (dt, 2H, J = 7.50 Hz), 7.82 (dt, 2H, J = 7.50 Hz), 7.85 (m, 2H, J = 7.50 Hz), 7.86 (dt, 1H), 7.97 (d, 1H); ^{13}C NMR ($CDCl_3$) δ: 15.5 (CH_3, C-28), 28.6 (CH_2, C-27), 119.7 (C-Br, C-4), 125.1 (CH, C-16), 127.6 (CH, C-19), 127.6 (CH, C-20), 128.6 (CH, C-21), 128.6 (CH, C-22), 129.1 (CH, C-11), 129.1 (CH, C-12), 129.7 (CH, C-5), 129.7 (CH, C-9), 129.7 (CH, C-10), 131.3 (C, C-1), 131.7 (CH, C-6), 132.3 (CH, C-2), 133.7 (C, C-3), 134.5 (C, C-8), 136.9 (C, C-18), 137.7 (CH=, C-15), 142.5 (C-N, C-13), 146.4 (C, C-23), 191.9 (C-O, C-17), 195.1 (C-O, C-7); MS (m/z) 480.3 [M]$^+$. Anal Calcd for $C_{24}H_{18}BrNO_5$: C, 60.02; H, 3.78; N, 2.92 found C, 60.01; H, 3.73; N, 2.90.

(Z)-4-{5-chloro-2-[3-(4-methylphenyl)-3-oxoprop-1-en-1-yl]benzoyl}phenyl nitrate (D3)

By following above methods, the title compound **D3** was obtained as a yellow solid in 69.01 % yield; mp 138-140 ^{0}C; IR (KBr) 1074, 1686 (C-O chalcone), 1705, 1764, 2850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 7.00 (d, 1H, J = 10.90 Hz), 7.28 (m, 2H, J = 7.50 Hz), 7.29 (dt, 1H, J = 10.90), 7.37 (m, 1H, J = 7.50 Hz), 7.38 (ddd, 2H, J = 7.50 Hz), 7.74 (m, 2H), 7.77 (m, 3H, J = 7.50 Hz), 7.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.4 (CH, C-26), 125.1 (CH, C-16), 128.9 (CH, C-5), 128.9 (CH, C-19), 128.9 (CH, C-20), 129.1 (CH, C-11), 129.1 (CH, C-12), 129.3 (CH, C-2), 129.6 (CH, C-21), 129.6 (CH, C-22), 129.7 (CH, C-9), 129.7 (CH, C-10), 131.2 (C, C-1),

132.3 (C-Cl, C-4), 132.5 (CH, C-6), 134.1 (C, C-3), 134.4 (C, C-8), 135.0 (C, C-18), 139.1 (CH=, C-15), 142.5 (C-N, C-13), 143.3 (C, C-23), 192.2 (C-O, C-17), 194.7 (C-O, C-7); MS (m/z) 422.0 $[M]^+$; Anal Calcd for $C_{23}H_{16}ClNO_5$: C, 65.49; H, 3.82; N, 3.32 found C, 65.46; H, 3.83; N, 3.30.

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(Z)-4-{5-methyl-2-[3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl]benzoyl}phenyl nitrate (D4)

By following above methods, the title compound **D4** was obtained as a yellow solid in 59.18 % yield; mp 156-158 ^{0}C; IR (KBr) 740, 1550, 1670 (C-O, chalcone), 1680, 1760, 3320 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 7.03 (d, 1H, J = 10.90 Hz), 7.27 (m, 1H, J = 7.50 Hz), 7.28 (m, 2H, J = 7.50 Hz), 7.38 (m, 1H, J = 10.90 Hz), 7.40 (m, 1H), 7.52 (dd, 1H), 7.88 (d, 2H, J = 7.50 Hz), 8.03 (m, 2H, J = 7.50 Hz), 8.34 (m, 2H, J = 7.50); ^{13}C NMR ($CDCl_3$) δ: 21.1 (CH_3, C-25), 125.1 (CH, C-16), 125.2 (CH, C-21), 125.2 (CH, C-22), 128.7 (CH, C-5), 128.7 (CH, C-6), 129.1 (CH, C-11), 129.1 (CH, C-12), 129.4 (CH, C-2), 129.7 (CH, C-9), 129.7 (CH, C-10), 130.1 (CH, C-19), 130.1 (CH, C-20), 130.2 (C, C-1), 133.0 (C, C-3), 134.2 (C, C-8), 136.2 (C, C-4), 140.3 (CH=, C-15), 142.5 (C-N, C-13), 143.1 (C, C-18), 150.0 (C-N, C-23), 192.3 (C-O, C-17), 194.5 (C-O, C-7); MS (m/z) 433.1 $[M]^+$. Anal Calcd for $C_{23}H_{16}N_2O_7$: C, 63.89; H, 3.73; N, 6.48 found C, 63.90; H, 3.70; N, 6.50.

(Z)-4-{2-[3-(4-aminophenyl)-3-oxoprop-1-en-1-yl]-5-methylbenzoyl}phenyl nitrate (D5)

By following above methods, the title compound **D5** was obtained as a yellow solid in 61.43 % yield; mp 162-164 ^{0}C; IR (KBr) 850, 1020, 1610 (C-O chalcone), 1758, 3140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 5H), 6.73 (m, 2H, J = 7.50 Hz), 7.03 (d, 1H, J = 10.90 Hz), 7.27 (m, 1H, J = 7.50 Hz), 7.28 (m, 2H, J = 7.50 Hz), 7.38 (m, 1H, J = 10.90 Hz), 7.40 (m, 1H), 7.44 (m, 2H, J = 7.50 Hz), 7.52 (dd, 1H, J = 7.50 Hz), 7.88 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.1 (CH_3, C-25), 114.2 (CH, C-21), 114.2 (CH, C-22), 125.1 (CH, C-16), 128.7 (CH, C-5), 128.7 (CH, C-6), 129.1 (CH, C-11), 129.1 (CH, C-12), 129.4 (CH, C-2), 129.7 (CH, C-9), 129.7 (CH, C-10), 131.2 (C, C-18), 132.0 (CH, C-19), 132.0 (CH, C-20), 133.0 (C, C-3), 134.2 (C, C-8), 136.2 (C, C-4), 139.4 (C, C-1), 140.3 (CH, C-15), 142.5 (C-N, C-13), 155.0 (C-N, C-23), 192.4 (C-O, C-17), 194.5 (C-O, C-7); MS (m/z) 403.1 $[M]^+$. Anal Calcd for $C_{23}H_{18}N_2O_5$: C, 68.65; H, 4.51; N, 6.96 found C, 68.61; H, 4.50; N, 6.92.

(Z)-4-{5-methyl-2-[3-(3-nitrophenyl)-3-oxoprop-1-en-1-yl]benzoyl}phenyl nitrate (D6)

By following above methods, the title compound **D6** was obtained as a yellow solid in 61.03 % yield; mp 162-164 ^{0}C; IR (KBr) 820, 1120, 1630 (C-O chalcone), 1680 (C-O ketone), 1780, 3180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 7.01 (d, 1H, J = 10.90 Hz), 7.26 (m, 1H, J = 10.90 Hz), 7.28 (m, 2H, J = 7.50 Hz), 7.43 (m, 2H, J = 7.50 Hz), 7.53 (q, 1H), 7.68 (m, 1H), 7.72 (m, 2H, J = 7.50 Hz), 8.40 (ddt, 2H, J = 7.50 Hz), 8.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.1 (CH_3, C-25), 123.2 (CH, C-20), 125.1 (=CH, C-16), 127.2 (CH, C-23), 128.7 (CH. C-5), 128.7 (CH, C-6), 129.1 (CH, C-11), 129.1 (CH, C-12), 129.4 (CH, C-2), 129.7 (CH, C-9), 129.7 (CH, C-10), 130.6 (CH, C-21), 133.0 (C, C-3), 134.1 (CH, C-19), 134.2 (C, C-8), 136.2 (C, C-4), 139.4 (C, C-1), 139.8 (C, C-18), 141.2 (CH=, C-15), 142.5 (C-N, C-13), 148.5 (C-N, C-22), 191.7 (C-O, C-17), 194.5 (C-O, C-7); MS (m/z) 433.1 $[M]^+$; Anal Calcd for $C_{23}H_{16}N_2O_7$: C, 63.89; H, 3.73; N, 6.48. found C, 63.90; H, 3.71; N, 6.42.

(Z)-4-(2-{3-[3,4-(dihydroxymethyl)phenyl]-3-oxoprop-1-en-1-yl}-5-methylbenzoyl)phenyl nitrate (D7)

By following above methods, the title compound **D7** was obtained as a yellow solid in 64.91 % yield; mp 170-172 ^{0}C; IR (KBr) 780, 1024, 1675 (C-O chalcone), 1725, 1774, 2950 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 5H), 4.80 (d, 4H), 6.98 (d, 1H, J = 10.90 Hz), 7.26 (m, 1H), 7.28 (m, 2H, J = 10.90 Hz), 7.43 (s, 2H, J = 7.50 Hz),

7.48 (dd, 1H, J = 7.50 Hz), 7.53 (q, 1H), 7.72 (m, 2H, J = 7.50 Hz), 7.74 (m, 1H), 7.85 (dd, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.6 (CH, C-25), 62.61 (CH_2, C-28), 62.79 (CH_2, C-27), 123.2 (CH_2, C-12), 125.1 (CH, C-16), 128.2 (CH, C-11), 128.7 (CH, C-19), 128.7 (CH, C-20), 129.1 (CH, C-5), 129.1 (CH, C-6), 129.4 (CH, C-21), 129.7 (CH, C-9), 129.7 (CH, C-10), 133.0 (C, C-3), 134.1 (CH, C-2), 134.2 (C, C-8), 136.1 (C, C-4), 138.0 (CH, C-23), 138.5 (CH, C-22), 139.5 (C, C-1), 139.8 (C, C-18), 141.3 (CH=, C-15), 142.5 (C-N, C-13), 192.1 (C-O, C-17), 194.4 (C-O, C-7); MS (m/z) 448.1 $[M]^+$; Anal Calcd for $C_{25}H_{21}NO_7$: C, 67.11; H, 4.73; N, 3.13 found C, 67.14; H, 4.70; N, 3.14.

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(Z)-4-{2-[3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl]-5-methylbenzoyl}phenyl nitrate (D8)

By following above methods, the title compound **D8** was obtained as a yellow solid in 56.05 % yield; mp 150-152 ^{0}C; IR (KBr) 765, 1050, 1630 (C-O chalcone), 1680 (C-O ketone), 1760, 3210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.30 (s, 3H), 6.98 (d, 1H, J = 10.90 Hz), 7.28 (m, 3H, J = 7.50, 10.90 Hz), 7.41 (m, 1H, J = 7.50 Hz), 7.43 (m, 1H), 7.51 (m, 2H, J = 7.50 Hz), 7.53 (m, 1H), 7.74 (m, 2H, J = 7.50 Hz), 7.80 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.1 (CH_3, C-25), 125.1 (=CH-, C-16), 128.7 (CH, C-5), 128.7 (CH, C-6), 129.1 (CH, C-11), 129.1 (CH, C-12), 129.4 (CH, C-2), 129.5 (CH, C-19), 129.5 (CH, C-20), 129.7 (CH, C-9), 129.7 (CH, C-10), 129.7 (CH, C-21), 129.7 (CH, C-22), 133.0 (C, C-3), 134.2 (C, C-8), 136.2 (C, C-4), 139.1 (C-Cl, C-23), 139.4 (C, C-1), 140.5 (C, C-18), 142.0 (CH=, C-15), 142.5 (C-N, C-13), 192.0 (C-O, C-17), 194.5 (C-O, C-7); MS (m/z) 422.0 $[M]^+$; Anal Calcd for $C_{23}H_{16}ClNO_5$: C, 65.49; H, 3.82; N, 3.12 found C, 65.45; H, 3.80; N, 3.14.

(Z)-4-{5-methyl-2-[3-(4-ethylphenyl)--3-oxo-3-phenylprop-1-en-1-yl]benzoyl}phenyl nitrate (D9)

By following above methods, the title compound **D9** was obtained as a yellow solid in 67.05 % yield; mp 146-148 ^{0}C; IR (KBr) 762, 1070, 1644 (C-O chalcone), 1690 (C-O ketone), 1760, 3200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.19 (t, 3H, J = 8.00 Hz), 2.30 (s, 5H), 2.67 (dt, 2H, J = 8.00 Hz), 6.98 (d, 1H, J = 10.90 Hz), 7.26 (m, 1H, J = 7.50 Hz), 7.28 (m, 2H, J = 7.50 Hz), 7.31 (d, 1H, J = 10.90 Hz), 7.38 (ddd, 1H, J = 7.50 Hz), 7.44 (m, 2H, J = 7.50 Hz), 7.49 (dd, 1H), 7.83 (m, 2H, J = 7.50 Hz), 7.86 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.5 (CH_3, C-28), 21.1 (CH_3, C-25), 28.6 (CH_2, C-27), 125.1 (=CH-, C-16), 127.6 (CH, C-19), 127.6 (CH, C-20), 128.6 (CH, C-21), 128.6 (CH, C-22), 128.7 (CH, C-5), 128.7 (CH, C-6), 129.1 (CH, C-11), 129.1 (CH, C-12), 129.4 (CH, C-2), 129.7 (CH, C-9), 129.7 (CH, C-10), 133.0 (C, C-3), 134.2 (C, C-8), 136.2 (C, C-4), 136.8 (C, C-18), 139.4 (C, C-1), 142.0 (-CH=, C-15), 142.5 (C-N, C-13), 146.4 (C, C-23), 192.2 (C-O, C-17), 194.5 (C-O, C-7); MS (m/z) 416.1 $[M]^+$; Anal Calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37 found C, 72.24; H, 5.12; N, 3.34.

(Z)-2-oxo-2-[(4-{2-[3-(2-benzoyl-4-nitrophenyl)-1-(4-ethylphenyl)prop-1-enyl]benzoyl}phenyl)amino] ethyl nitrate (E1)

By following above methods, the title compound **E1** was obtained as a yellow solid in 67.09 % yield; mp 134-136 ^{0}C; IR (KBr) 1075, 1360, 1678 (C-O chalcone), 1701, 1730, 2972 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 1.19 (t, 3H, J = 8.00 Hz), 2.35 (q, 2H, J = 8.00 Hz), 2.67 (tdd, 2H, J = 8.00 Hz), 7.04 (d, 1H, J = 10.90 Hz), 7.23 (m, 2H, J = 10.90 Hz), 7.27 (m, 1H), 7.46 (dt, 2H, J = 7.50 Hz), 7.56 (dd, 1H, J = 7.50 Hz), 7.86 (dd, 2H, J = 7.50 Hz), 7.90 (m, 2H, J = 7.50 Hz), 8.46 (dd, 1H, J = 7.50 Hz), 8.75 (d, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 15.5 (CH_3, C-34), 27.6 (CH_2, C-27), 28.6 (CH_2, C-32), 119.4 (CH, C-11), 119.4 (CH, C-12), 125.1 (=CH-, C-

16), 126.5 (CH, C-2), 127.3 (CH, C-6), 127.6 (CH, C-19), 127.6 (CH, C-20), 128.3 (CH, C-5), 128.6 (CH, C-21), 128.6 (CH, C-22), 131.1 (CH, C-9), 131.1 (CH, C-10), 132.3 (C, C-8), 134.4 (C, C-1), 136.8 (C, C-18), 137.8 (C, C-3), 139.7 (C-N, C-13), 142.6 (CH=, C-15), 144.9 (C-N, C-4), 146.4 (C, C-23), 173.3 (C-O, C-26), 192.2 (C-O, C-17), 194.4 (C-O, C-7); MS (m/z) 504.1 $[M]^+$; Anal Calcd for $C_{26}H_{21}N_3O_8$: C, 62.03; H, 4.20; N, 8.35 found C, 62.08; H, 4.22; N, 8.32.

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(Z)-2-oxo-2-[(4-{2-[3-(2-benzoyl-4-nitrophenyl)-1-[4-(hydroxymethyl)prop-1-en-1-yl]benzoyl}phenyl) amino]ethyl nitrate (E2)

By following above methods, the title compound **E2** was obtained as a yellow solid in 67.82 % yield; mp 168-170 ^{0}C; IR (KBr) 1020, 1500, 1620 (C-O chalcone), 1705, 1754, 2980 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 3H), 2.35 (q, 2H, J = 8.00 Hz), 4.53 (d, 2H), 6.95 (m, 2H, J = 7.50 Hz), 7.08 (d, 1H, J = 10.90 Hz), 7.26 (m, 1H, J = 10.90 Hz), 7.59 (m, 1H, J = 7.50 Hz), 7.61 (m, 1H, J = 7.50 Hz), 7.82 (m, 2H, J = 7.50 Hz), 7.84 (d, 2H, J = 7.50 Hz), 8.47 (dd, 1H), 8.74 (d, 1H); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 64.7 (CH_2, C-30), 119.4 (CH, C-11), 119.4 (CH, C-12), 125.1 (=CH-, C-16), 126.5 (CH, C-2), 127.2 (CH, C-19), 127.2 (CH, C-20), 127.3 (CH, C-6), 128.2 (CH, C-21), 128.2 (CH, C-22), 128.3 (CH, C-5), 131.1 (CH, C-9), 131.1 (CH, C-10), 132.3 (C, C-8), 137.4 (C, C-18), 137.9 (C, C-3), 139.7 (C-N, C-13), 142.6 (CH=, C-15), 143.6 (C, C-1), 144.9 (C-N, C-4), 145.3 (C, C-23), 173.3 (C-O, C-26), 192.2 (C-O, C-17), 194.4 (C-O, C-7); MS (m/z) 506.1 $[M]^+$; Anal Calcd for $C_{25}H_{19}N_3O_9$: C, 59.41; H, 3.79; N, 8.31 found C, 59.44; H, 3.80; N, 8.29.

(Z)-2-[(4-{2-[3-(4-bromophenyl)-3-oxoprop-1-en-1-yl]-5fluorobenzoyl}phenyl)amino]-2-oxoethyl nitrate (E3)

By following above methods, the title compound **E3** was obtained as a yellow solid in 67.92 % yield; mp 162-164 ^{0}C; IR (KBr) 730, 1610 (C-O chalcone), 1660, 1720, 2960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 6.92 (t, 1H, J = 10.90 Hz), 7.27 (m, 1H, J = 10.90 Hz), 7.29 (m, 2H, J = 7.50 Hz), 7.39 (m, 1H), 7.43 (m, 1H, J = 8.90 Hz), 7.47 (m, 1H), 7.75 (m, 2H, J = 7.50 Hz), 7.84 (m, 2H, J = 7.50 Hz), 7.90 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 115.8 (CH, C-2), 116.5 (CH, C-6), 119.4 (CH, C-11), 119.4 (CH, C-12), 125.1 (CH-, C-16), 127.2 (C, C-23), 129.4 (CH, C-5), 130.1 (CH, C-19), 130.1 (CH, C-20), 131.1 (CH, C-9), 131.1 (CH, C-10), 131.4 (CH, C-21), 131.4 (CH, C-22), 131.6 (C, C-8), 134.8 (C, C-1), 135.2 (C, C-3), 138.6 (C, C-18), 139.7 (C-N, C-13), 143.1 (CH=, C-15), 161.6 (C-F, C-4), 173.3 (C-O, C-26), 192.3 (C-O, C-17), 194.3 (C-O, C-7); MS (m/z) 527.0. Anal Calcd for $C_{24}H_{16}BrFN_2O_6$: C, 54.67; H, 3.06; N, 5.31 found C, 54.65; H, 3.07; N, 5.28.

(Z)-2-[(4-{2-[3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl]-5-fluorobenzoyl}phenyl)amino]-2-oxoethyl nitrate (E4)

By following above methods, the title compound **E4** was obtained as a yellow solid in 68.82 % yield; mp 168-170 ^{0}C; IR (KBr) 820, 1008, 1650 (C-O chalcone), 1720, 3120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 6.94 (d, 1H, J = 10.90 Hz), 7.15 (m, 2H, J = 7.50 Hz), 7.28 (d, 1H, J = 10.90 Hz), 7.39 (dd, 2H, J = 8.90 Hz), 7.47 (m, 1H, J = 7.50 Hz), 7.51 (m, 2H), 7.76 (m, 2H, J = 7.50 Hz), 7.81 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 115.8 (CH, C-2), 116.5 (CH, C-6), 119.4 (CH, C-11), 119.4 (CH, C-12), 125.1 (CH-, C-16), 127.2 (C, C-23), 129.4 (CH, C-5), 130.1 (CH, C-19), 130.1 (CH, C-20), 131.1 (CH, C-9), 131.1

(CH, C-10), 131.4 (CH, C-21), 131.4 (CH, C-22), 131.6 (C, C-8), 134.8 (C, C-1), 135.2 (C, C-3), 138.6 (C, C-18), 139.1 (C-Cl, C-23), 139.7 (C-N, C-13), 143.1 (CH=, C-15), 173.3 (C-O, C-26), 192.3 (C-O, C-17), 194.3 (C-O, C-7); MS (m/z) 483.0 $[M]^+$; Anal Calcd for $C_{24}H_{16}ClFN_2O_6$: C, 59.70; H, 3.34; N, 5.80 found C, 59.71; H, 3.29; N, 5.82.

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(Z)-2-[(4-{5-bromo-2-[3-(4-bromophenyl)-3-oxoprop-1-en-1-yl]benzoyl}phenyl)amino]-2-oxoethyl nitrate (E5)

By following above methods, the title compound **E5** was obtained as a yellow solid in 63.02 % yield; mp 140-142 ^{0}C; IR (KBr) 80, 1078, 1610 (C-O chalcone), 1680, 1700, 3120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H, J = 8.00 Hz), 2.35 (q, 2H, J = 8.00 Hz), 6.92 (d, 1H, J = 10.90 Hz), 7.22 (m, 2H, J = 7.50 Hz), 7.28 (m, 1H, J = 10.90 Hz), 7.32 (m, 1H, J = 7.50 Hz), 7.75 (m, 2H, J = 7.50 Hz), 7.84 (m, 2H, J = 7.50 Hz), 7.90 (m, 1H, J = 7.50 Hz), 7.96 (d, 1H), 8.02 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 119.4 (CH, C-11), 119.4 (CH, C-12), 119.7 (C-Br, C-4), 125.1 (=CH-, C-16), 127.2 (C-Br, C-23), 129.7 (CH, C-5), 130.1 (CH, C-19), 130.1 (CH, C-20), 131.1 (C, C-8), 131.1 (CH, C-9), 131.1 (CH, C-10), 131.4 (CH, C-21), 131.4 (CH, C-22), 131.7 (CH, C-6), 132.3 (CH, C-2), 134.5 (C, C-3), 135.2 (C, C-1), 138.6 (C, C-18), 139.7 (C-N, C-13), 143.4 (CH=, C-15), 173.3 (C-O, C-26), 192.6 (C-O, C-17), 194.3 (C-O, C-7); MS (m/z) 586.9 $[M]^+$; Anal Calcd for $C_{24}H_{16}Br_2N_2O_6$: C, 49.01; H, 2.74; N, 4.76 found C, 49.00; H, 2.74; N, 4.71.

(Z)-2-oxo-2-[(4-{2-[3-(2-benzoyl-4-bromophenyl)-1-(4-nitrophenyl)prop-2-en-1-one}phenyl)amino]ethyl nitrate (E6)

By following above methods, the title compound **E6** was obtained as a yellow solid in 67.02 % yield; mp 164-166 ^{0}C; IR (KBr) 710, 1120, 1610 (C-O chalcone), 1742, 3230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H, J = 8.00 Hz), 2.35 (q, 2H, J = 8.00 Hz), 6.99 (d, 1H, J = 10.90 Hz), 7.17 (m, 2H, J = 7.50 Hz), 7.29 (m, 1H, J = 10.90 Hz), 7.39 (dd, 1H, J = 7.50 Hz), 7.87 (m, 2H, J = 7.50 Hz), 7.91 (m, 1H, J = 7.50 Hz), 7.93 (d, 2H, J = 7.50 Hz), 7.98 (m, 1H), 8.22 (m, 2H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 119.4 (CH, C-11), 119.4 (CH, C-12), 119.7 (C-Br, C-4), 125.1 (=CH-, C-16), 125.2 (CH, C-21), 125.2 (CH, C-22), 129.7 (CH, C-5), 130.1 (CH, C-19), 130.1 (CH, C-20), 131.1 (C, C-8), 131.1 (CH, C-9), 131.1 (CH, C-10), 131.7 (CH, C-6), 132.3 (CH, C-2), 134.5 (C, C-3), 139.7 (C-N, C-13), 143.1 (C, C-18), 143.4 (CH=, C-15), 143.7 (C, C-1), 150.0 (C-N, C-23), 173.3 (C-O, C-26), 192.7 (C-O, C-17), 194.3 (C-O, C-7); MS (m/z) 554.0 $[M]^+$; Anal Calcd for $C_{24}H_{16}BrN_3O_8$: C 52.00; H, 2.91; N, 7.58 found C, 52.04; H, 2.90; N, 7.56.

(Z)-2-[(4-{5-bromo-2-[3-(3-bromophenyl)-3-oxoprop-1-en-1yl]benzoyl}phenyl)amino]-2-oxoethyl nitrate (E7)

By following above methods, the title compound **E7** was obtained as a yellow solid in 62.92 % yield; mp 160-162 ^{0}C; IR (KBr) 714, 1124, 1620 (C-O chalcone), 1750, 3240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q. 2H, J = 8.00 Hz), 6.99 (d, 1H, J = 10.90 Hz), 7.15 (m, 2H, J = 7.50 Hz), 7.27 (m, 1H, J = 10.90 Hz), 7.38 (m, 2H, J = 7.50 Hz), 7.73 (dt, 1H, J = 7.50 Hz), 7.82 (m, 1H), 7.84 (m, 2H, J = 7.50 Hz), 7.88 (m, 1H), 7.91 (m, 1H), 7.94 (d, 1H); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 119.4 (CH, C-11), 119.4 (CH, C-12), 119.7 (C-Br, C-4), 123.0 (C-Br, C-22), 125.1 (=CH-, C-16), 126.9 (CH, C-19), 129.7 (CH, C-5), 130.8 (CH, C-21), 131.1 (C, C-8), 131.1 (CH, C-9), 131.1 (CH, C-10), 131.5 (CH, C-20), 131.7 (CH, C-6), 132.3 (CH, C-2), 134.5 (C, C-3),

135.5 (CH, C-23), 139.7 (C-N, C-13), 140.0 (C, C-18), 143.7 (C, C-1), 143.7 (-CH=, C-15), 173.3 (C-O, C-26), 191.7 (C-O, C-17), 194.3 (C-O, C-7); MS (m/z) 586.9 $[M]^+$; Anal Calcd for $C_{24}H_{16}Br_2N_2O_6$: C, 49.01; H, 2.74; N, 4.76 found C, 49.04; H, 2.75; N, 4.72.

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(Z)-2-[(4-{5-bromo-2-[3-(2-benzoylphenyl)-1-[4-(hydroxymethyl)phenyl]prop-2-en-1-oneamino]-2-oxoethyl nitrate (E8)

By following above methods, the title compound **E8** was obtained as a yellow solid in 59.81 % yield; mp 172-174 ^{0}C; IR (KBr) 720, 1630 (C-O chalcone), 1664, 1722, 3260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 2H), 2.35 (q, 2H, J = 8.00 Hz), 4. 53 (d, 2H), 6.99 (d, 1H, J = 10.90 Hz), 7.07 (m, 2H, J = 7.50 Hz), 7.27 (dd, 1H, J = 10.90 Hz), 7.36 (dd, 1H, J = 7.50 Hz), 7.59 (m, 2H, J = 7.50 Hz), 7.72 (m, 2H, J = 7.50 Hz), 7.79 (m, 2H, J = 7.50 Hz), 7.90 (m, 1H), 7.93 (m, 1H, J = 7.50 Hz); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 64.7 (CH_2, C-31), 119.4 (CH, C-11), 119.4 (CH, C-12), 119.7 (C-Br, C-4), 125.1 (=CH-, C-16), 127.3 (CH, C-19), 127.3 (CH, C-20), 128.2 (CH, C-21), 128.2 (CH, C-22), 129.7 (CH, C-5), 131.1 (C, C-8), 131.1 (CH, C-9), 131.1 (CH, C-10), 131.7 (CH, C-6), 132.3 (CH, C-2), 134.5 (C, C-8), 139.7 (C-N, C-13), 137.9 (C, C-18), 143.7 (C, C-1), 144.0 (-CH=, C-15), 145.3 (C, C-23), 192.0 (C-O, C-17), 194.3 (C-O, C-7); MS (m/z) 539.0 $[M]^+$; Anal Calcd for $C_{25}H_{19}BrN_2O_7$: C, 55.67; H, 3.55; N, 5.19 found C, 55.70; H, 3.52; N, 5.20.

(Z)-2-[(4-{2-[3-(3-bromophenyl)-3-oxoprop-1-en-1-yl]-5-chlorobenzoyl}phenyl)amino]-2-oxoethyl nitrate (E9)

By following above methods, the title compound **E9** was obtained as a yellow solid in 67.02 % yield; mp 170-172 ^{0}C; IR (KBr) 800, 1008, 1610 (C-O chalcone), 1650, 1700, 3100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 1H), 2.35 (q, 2H, J = 8.00 Hz), 6.99 (dd, 1H, J = 10.90 Hz), 7.15 (m, 2H, J = 7.50 Hz), 7.26 (dd, 1H, J = 10.90 Hz), 7.37 (m, 2H, J = 7.50 Hz), 7.74 (m, 1H, J = 7.50 Hz) 7.77 (m, 1H, J = 7.50 Hz), 7.80 (m, 1H), 7.82 (m, 1H), 7.84 (m, 2H, J = 7.50 Hz), 7.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 119.4 (CH, C-11), 119.4 (CH, C-12), 123.0 (C-Br, C-22), 125.1 (=CH-, C-16), 126.9 (CH, C-19), 128.9 (CH, C-5), 129.3 (CH, C-2), 130.6 (C, C-8), 130.8 (CH, C-21), 131.1 (CH, C-9), 131.1 (CH, C-10), 131.5 (CH, C-20), 132.3 (C-Cl, C-4), 132.5 (CH, C-6), 134.3 (C, C-1), 134.5 (C, C-3), 135.5 (CH, C-23), 139.7 (C-N, C-13), 140.0 (C, C-18), 144.2 (-CH=, C-15), 173.3 (C-O, C-26), 191.6 (C-O, C-17), 194.3 (C-O, C-7); MS (m/z) 542.9 $[M]^+$; Anal Calcd for $C_{24}H_{16}BrClN_2O_6$: C, 53.01; H, 2.97; N, 5.15. found C, 53.00; H, 2.98; N, 5.18.

(Z)-2-[(4-{5-chloro-2-[3-(2-benzoylphenyl)-1-[3,5-bis(hydroxymethyl)phenyl]prop-2-en-1-one amino]-2-oxoethylnitrate (E10)

By following above methods, the title compound **E10** was obtained as a yellow solid in 61.03 % yield; mp 156-158 ^{0}C; IR (KBr) 805, 1008, 1600 (C-O chalcone), 1680, 1710, 3120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.12 (t, 3H), 2.35 (q, 2H, J = 8.00 Hz), 4.81 (s, 4H,), 7.03 (d, 1H, J = 10.90), 7.08 (m, 2H, , 7.50 Hz), 7.25 (dd, 1H, J = 10.90 Hz), 7.36 (dd, 1H, J = 7.50 Hz), 7.50 (dt, 1H), 7.77-7.78 (m, 3H, J = 7.50 Hz), 7. 79 (m, 1H, J = 7.50 Hz), 7.88 (d, 2H); ^{13}C NMR ($CDCl_3$) δ: 27.6 (CH_2, C-27), 64.2 (CH_2, C-31), 64.2 (CH_2, C-32), 119.4 (CH, C-11), 119.4 (CH, C-12), 125.1 (=CH-, C-16), 128.9 (CH, C-5), 129.1 (CH, C-23), 129.3 (CH, C-2), 130.0 (CH, C-19), 130.0 (CH, C-20), 130.6 (C, C-8), 131.1 (CH, C-9), 131.1 (CH, C-10), 132.3 (C-Cl, C-4), 132.5 (CH, C-6), 134.5 (C, C-3), 138.0 (C, C-18), 139.7 (C-N, C-13), 141.2 (C, C-1), 143.6 (C, C-21), 143.6 (C, C-22), 144.3 (-

CH=, C-15), 173.3 (C-O, C-26), 191.3 (C-O, C-17), 194.3 (C-O, C-7); MS (m/z) 525.1 $[M]^+$; Anal Calcd for $C_{26}H_{21}ClN_2O_8$: C, 59.49; H, 4.03; N, 5.34 found C, 59.50; H 4.01; N, 5.31.

Enzyme Preparation

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Isolation of PDE5 from human platelet by using method described by Zhongcheng XIN et al[32] with minor modification, centrifuging fresh human blood at 360 g for 10 min, enriched the platelet-rich plasma (PRP). The PRP was then centrifuged for 10 min to sediment the platelets. Platelets were resuspended in 1 mL ice-cold homogenization buffer (20 mmol/L HEPES containing 0.25 mol/L sucrose, 1 mmol EDTA, 1 mmol/L phenylmethylsulfonyl fluoride [PMSF], pH 7.2) for every 10 mL of blood and disrupted by sonication. The homogenate of platelets was centrifuged for 60 min at 4 g and the supernatants were recovered and filtered through a 0.2 μm filter. Soluble fractions of platelets were prepared by using a column which was pre-equilibrated with 20 mmol/L HEPES buffer (pH 7.2) containing 1 mmol/L EDTA and 0.5 mmol/L PMSF and then, loaded with platelets soluble fraction, followed by washing with 5 mL of buffer. The PDE isozyme was eluted and stored at - 80°C until use in inhibition experiments. The bovine recombinant PDE 5A was procured from Enzo life sciences (ALX-201-257-1). All the procedures and dilutions were performed as per the instruction given in manual of assay kit.

Inhibitory potency assay

The PDE 5 and 5A inhibitory activity was performed by the instruction given in the manual of the Cyclic Nucleotide Phosphodiesterase Assay Kit by Enzo Life Sciences. The compounds were prepared and diluted for optimum activity. The optical density was measured at 620 nm on microplate reader (BIORAD).

In-vitro toxicity assessment of synthesized compounds

Haemolytic assay

Haemolytic assay [33] was performed using the heparinized whole human blood and the RBC pellet was obtained by centrifuging at 3,000 rpm for 5 min. Supernatant was discarded and the RBC pellet was washed with Phosphate-buffered saline (PBS). 1% RBC suspension was prepared and 100 μl of RBC suspension was incubated with test compounds (0.1 mM, 1 mM, 5 mM and 10 mM). After the incubation, the samples were centrifuged at 3,000 rpm for 5 min. Supernatant was collected and O.D was measured at 545 nm to determine the RBC lysis. Triton X-100 was used as positive control and untreated RBC with PBS served as negative control. Percentage of lysis was calculated using the formula mentioned below.

% of haemolysis = O.D of test O.D of negative control / O.D of positive control -

O.D of negative control 100

Bacterial reverse mutation test

To determine the mutagenic property of synthesized compounds (**B2**), the AMES test was performed using *Salmonella typhimurium* strains TA98 and TA100 (His–) without metabolic activation system.[34] For pre incubation method, overnight culture of strains were inoculated into nutrient broth and sub cultured to obtain 1 × 109 cells/ml. 100 μl of culture and test compounds (0.1 mM, 1 mM, 5 mM and10 mM) were added in a tube containing 0.5 ml of phosphate buffer (pH 7.4) and incubated at 37°C for 20 min. After incubation, 2 ml of soft agar which contains 0.5 mM of histidine/biotin was added. The tubes were mixed and poured onto minimal glucose agar plates, the plates were incubated for 48 h and the revertant colonies were counted manually. 0.1%

DMSO was used as vehicle control; Sodium azide (2 μg) were used as positive controls. The experiments were done in triplicates.[35]

Molecular docking studies

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Docking studies were carried out on Vlife molecular docking suite 3.5 by using Biopredicta. All the molecular modelling studies were performed on Pentium Core2Duo workstation using Sybyl. Molecules were optimized using MMFF method till gradient convergence 0.01 kcal/mol. The protein databases of PDE 5A (PDBID: 1XOZ) were downloaded from RCSB. The protein structures were optimized using MMFF forcefield till gradient convergence 0.01 Kcal/mol. The synthesized molecules were docked into active site using the default GRID parameter setting. Docking score was analyzed; different Vander Waals, hydrophobic, hydrogen bond and pi stacking interaction were calculated. The docking is carried out into the active site of PDB containing oxygen and without oxygen and the results are compared.

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Chalcones with nitric oxide (NO) donating scaffold and variety of substitutions were synthesized. Docking study was performed and molecules were evaluated for in-vitro Phosphodiesterase 5 and 5A inhibitory potency.

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