Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry 12 (2004) 2059–2077

Baylis–Hillman reaction assisted parallel synthesis of 3,5-disubstituted isoxazoles and their in vivo bioevaluation as antithrombotic agents ☆

S. Batra,[a,*] A. K. Roy,[a] A. Patra,[a] A. P. Bhaduri,[a] W. R. Surin,[b] S. A. V. Raghavan,[b] P. Sharma,[b] K. Kapoor[b] and M. Dikshit[b,*]

[a]*Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226 001, India*
[b]*Division of Pharmacology, Central Drug Research Institute, Lucknow 226 001, India*

Received 3 February 2004; revised 23 February 2004; accepted 24 February 2004

Abstract—The solution-phase parallel synthesis involving reactions of Baylis–Hillman products of 3-substituted-5-isoxazolecarbaldehydes with nucleophiles and their in vivo antithrombotic evaluations are described along with the results of in vitro platelet aggregation inhibition assay of a few compounds. Results of the detailed evaluation of one of the compounds as an inhibitor of platelet aggregation are also presented.

1. Introduction

Thrombotic disorders, resulting from abnormalities in the blood flow, coagulation cascade or fibrinolysis represent the major share of the various cardiovascular diseases encountered both in developed and developing countries.[1,2] The current therapies used for prophylactic and prevention have considerable limitations because they require careful clinical monitoring and are associated with high incidence of cardiovascular events and complications associated with bleeding.[3,4] These therapies include the use of the antiplatelet agents namely aspirin and ticlopidine and anticoagulant agents such as heparin and warfarin.[2,3] The ever-increasing understanding of the pathophysiology and the molecular mechanisms of thrombosis have helped in understanding the role of various biochemical parameters in the coagulation cascade.[2–7] This has provided impetus towards the discovery of newer antithrombotic agents, which target one or more of these novel biochemical parameters and has resulted in identifying a wide range of new chemical compounds including various heterocyclic derivatives.[8] The synthesis of various isoxazole-derivatives and their bioevaluation as antithrombotic has been recently reported.[9,10] We have reported earlier hits in chemical libraries generated from 5-isoxazolecarbaldehydes.[10] In the light of these observations it was desired to build different molecular scaffolds simulating 3,5-disubstituted isoxazoles and this led to solution-phase parallel synthesis of compounds utilizing Baylis–Hillman reaction as the key step.

All the synthesized compounds were evaluated first in high-throughput screen (HTS) mode for thrombin inhibition and later on were subjected to in vivo bioevaluation because earlier experience of this laboratory indicated that many compounds, found inactive in vitro, against protease activity assay of thrombin were however, protective in animal models. This observation can be explained on the basis of various targets for antithrombotic action by the drugs/test agents. During this in vivo screening a number of hits obtained from the chemical library reported here were identified. This prompted us to adopt two different strategies of bioassay. In the first strategy, a few of the active compounds were subjected to in vitro platelet aggregation inhibition assay. In the second strategy, the most active compound

Keywords: Baylis–Hillman reaction; Isoxazolecarbaldehyde; Isoxazole; Nucleophilic substitution; Substituted piperazine; Antithrombotic activity; Platelet aggregation.
☆ CDRI Communication no 6468. In portion presented at BNP-2004 (IUPAC Conference) N. Delhi 26th–31st January, 2004.
* Corresponding authors. Tel.: +91-522-2212411-18x4368; fax: +91-522-2223405/2229338 (S.B.); tel.: +91-522-2212411-18x4254 (M.D.); e-mail addresses: batra_san@yahoo.co.uk; madhudikshit@yahoo.com

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.02.023

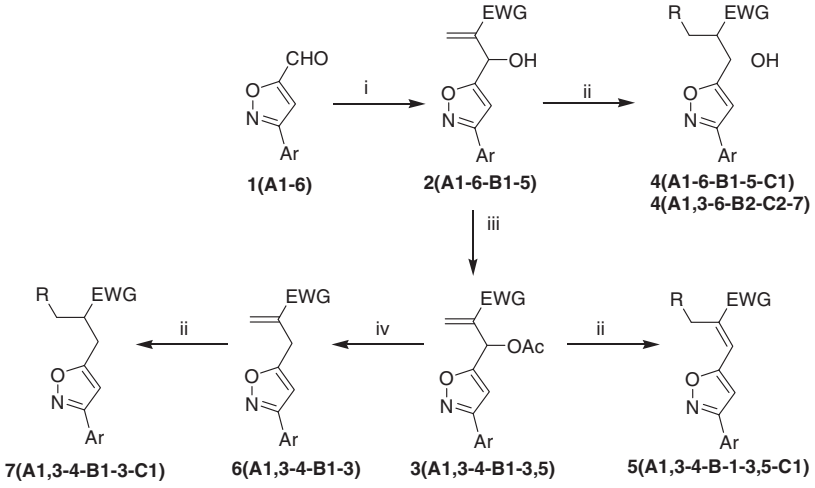
was studied in greater detail for understanding the mechanism of its biological action. The details of our studies are presented here.

2. Chemistry

The various isoxazole derivatives were synthesized by solution-phase parallel synthesis utilizing three different synthetic strategies with Baylis–Hillman reaction[11] as the key step. Since during this exercise our major aim was to discover the antithrombotic activity in synthesized compounds, no attempt was made at any stage to separate the diastereoisomeric mixtures. In the first instance Baylis–Hillman reactions of different 5-isoxazolecarboxaldehydes (**A1-6**) with activated alkenes (**B1-5**) were carried out to obtain adducts **2**(**A1-6-B1-5**). These were then subjected to nucleophilic substitution by *N*-methyl piperazine (**C1**) to obtain diastereoisomeric mixture of amines [**4**(**A1-6-B1-5-C1**)] (Scheme 1). All these reactions were carried out in methanol and the reaction mixtures after the completion of the reaction were directly passed through a small band of basic alumina column to obtain the desired amines. In the next step the nucleophilic substitution in adducts **2**(**A1**,**3-6-B2**), obtained from reactions of aldehydes (**A1**,**3-6**) and ethyl acrylate (**B2**), with substituted piperazines and secondary amines (**C2-7**) afforded compounds **4**(**A1**,**3-6-B2-C2-7**). In another synthetic strategy the acetates **3**(**A1**,**3-4-B1-3**, **5**), derived from acetylation of Baylis–Hillman adducts were subjected to nucleophilic substitution with *N*-methyl piperazine only to obtain compounds **5**(**A1**,**3-4-B1-3**, **5-C1**). On the other hand in a different synthetic sequence the acetates **3**(**A1**,**3-4-B1-3**) were first subjected to S_N2' nucleophilic substitution with hydride utilizing sodium borohydride in the presence of DABCO in aqueous medium, to obtain products **6**(**A1**,**3-4-B1-3**). Further Michael addition of *N*-methyl piperazine on the double bond of these compounds **6**(**A1**,**3-4-B1-3**) led to amines **7**(**A1-3-4-B1-3-C1**).

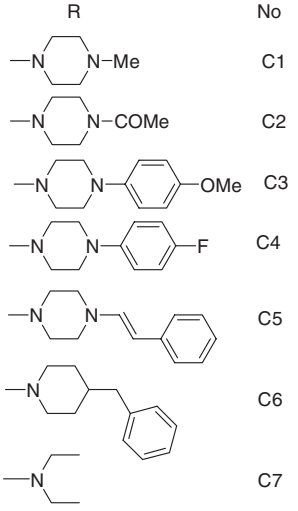
3. Results and discussion

All new compounds belonging to series **4**, **5**, and **7** were first evaluated in the HTS mode against thrombin. None of the compounds showed any promising activity (data



Ar	No
C_6H_5	A1
4-$(CH_3)C_6H_4$	A2
4-(OBn)C_6H_4	A3
2-(Cl)C_6H_4	A4
4-(Cl)C_6H_4	A5
2,4-$(Cl)_2C_6H_3$	A6

EWG	No
CO_2Me	B1
CO_2Et	B2
CO_2Bu-n	B3
CO_2Bu-t	B4
CN	B5



Scheme 1. Reagents: (i) alkene, DABCO; (ii) amine, MeOH; (iii) AcCl, pyridine, CH_2Cl_2; (iv) DABCO, $NaBH_4$, THF/H_2O.

not shown). On the basis of the experience of this laboratory, stated earlier in this communication, in vivo antithrombotic activity including the effect on the bleeding time was evaluated. Initially the bioevaluation of compounds represented by structure **4** (entries 1–30, Table 1) was carried out. These were synthesized using diversity at two points namely the changes in the substituents on the phenyl ring and in the electron-withdrawing group (EWG). The methyl piperazine moiety representing R in all these compounds remained unchanged. The results of the bioevaluation indicated that compounds possessing the ethyl ester group as the EWG with unsubstituted phenyl (entry 7) and *o*-chloro-phenyl (entry 9) as the substituents at position 3 of the isoxazole ring exhibited significant antithrombotic activity. The next set of compounds **4(A1,3-6-B2-C2-7)** (entries 31–60) in which the methyl piperazine moiety was replaced with other substituents did not elicit any antithrombotic activity. This led to the next step in which the need of the secondary hydroxyl group for eliciting antithrombotic activity was evaluated by subjecting compounds representing by series **5** (entries 61–72) and **7** (entries 73–81) for bioevaluation. In both the series, modifications were made in substituents on the phenyl ring and in EWG keeping the *N*-methyl piperazine moiety as the only representative of R.

Results of in vivo evaluation of all the compounds represented by series **4**, **5**, and **7** are presented in Table 1. Out of all the compounds evaluated, seven compounds showed activity more than 50% while 13 compounds exhibited activity between 20–50%. Any activity below 20% was not considered as significant activity. All the seven compounds showing more than 50% activity in the antithrombotic assay belong to series **4**. These compounds also had pronounced effect on the bleeding time. All these compounds had unsubstituted phenyl (entries 1, 7, 13, and 19) or *o*-chloro phenyl (entries 4, 10, and

Table 1. Results of the in vivo antithrombotic activity of compounds belonging to series **4**, **5** and **7**

Entry no	Compound no	Antithrombotic activity (% protection at 30 μM/kg)	Bleeding time (% increase at 30 μM/kg)	Entry no	Compound no	Antithrombotic activity (% protection at 30 μM/kg)	Bleeding time (% increase at 30 μM/kg)
1	**4A1B1C1**	50	80, 150	42	**4A3B2C4**	NA	NA
2	**4A2B1C1**	NA	NA	43	**4A4B2C4**	NA	29
3	**4A3B1C1**	20	37.5	44	**4A5B2C4**	NA	NA
4	**4A4B1C1**	60	38	45	**4A6B2C4**	NA	NA
5	**4A5B1C1**	NA	NA	46	**4A1B2C5**	NA	NA
6	**4A6B1C1**	NA	NA	47	**4A3B2C5**	40	NA
7	**4A1B2C1**	60	50	48	**4A4B2C5**	NA	24
8	**4A2B2C1**	20	NA	49	**4A5B2C5**	NA	NA
9	**4A3B2C1**	NA	ND	50	**4A6B2C5**	NA	NA
10	**4A4B2C1**	80	30	51	**4A1B2C6**	NA	NA
11	**4A5B2C1**	NA	ND	52	**4A3B2C6**	30	12.5
12	**4A6B2C1**	45	NA	53	**4A4B2C6**	NA	ND
13	**4A1B3C1**	70	NA	54	**4A5B2C6**	20	25
14	**4A2B3C1**	40	12.5	55	**4A6B2C6**	NA	NA
15	**4A3B3C1**	30	NA	56	**4A1B2C7**	NA	NA
16	**4A4B3C1**	NA	ND	57	**4A3B2C7**	NA	12.5
17	**4A5B3C1**	NA	37.5	58	**4A4B2C7**	NA	NA
18	**4A6B3C1**	NA	NA	59	**4A5B2C7**	NA	NA
19	**4A1B4C1**	60	112.5, 146	60	**4A6B2C7**	ND	ND
20	**4A2B4C1**	NA	ND	61	**5A1B1C1**	NA	NA
21	**4A3B4C1**	30	ND	62	**5A3B1C1**	NA	NA
22	**4A4B4C1**	80	75	63	**5A4B1C1**	NA	NA
23	**4A5B4C1**	NA	NA	64	**5A1B2C1**	20	18
24	**4A6B4C1**	NA	NA	65	**5A3B2C1**	40	NA
25	**4A1B5C1**	80	62.5	66	**5A4B2C1**	NA	25
26	**4A2B5C1**	20	ND	67	**5A1B3C1**	NA	NA
27	**4A3B5C1**	ND	ND	68	**5A3B3C1**	NA	12.5
28	**4A4B5C1**	30	NA	69	**5A4B3C1**	NA	NA
29	**4A5B5C1**	NA	37.5	70	**5A1B5C1**	NA	NA
30	**4A6B5C1**	NA	NA	71	**5A3B5C1**	NA	NA
31	**4A1B2C2**	20	NA	72	**5A4B5C1**	NA	37.5
32	**4A3B2C2**	NA	NA	73	**7A1B1C1**	NA	NA
33	**4A4B2C2**	NA	NA	74	**7A3B1C1**	NA	NA
34	**4A5B2C2**	NA	NA	75	**7A4B1C1**	NA	NA
35	**4A6B2C2**	NA	NA	76	**7A1B2C1**	NA	NA
36	**4A1B2C3**	NA	NA	77	**7A3B2C1**	NA	NA
37	**4A3B2C3**	NA	12.5	78	**7A4B2C1**	NA	NA
38	**4A4B2C3**	NA	62.5	79	**7A1B3C1**	NA	12.5
39	**4A5B2C3**	30	NA	80	**7A3B3C1**	NA	NA
40	**4A6B2C3**	NA	NA	81	**7A4B3C1**	10	NA

Any in vivo % protection below 20% has been mentioned as NA while any effect that is less than 10% on the bleeding time has been mentioned as NA (not active).

22) group as the substituents at position 3 of the isoxazole ring. It was also observed that the deletion of the secondary hydroxyl group in the analogues of the active compounds led to total loss of biological activity. In order to provide a plausible explanation for this observation, a set of compounds, comprising of active compounds of series **4** and inactive compounds of series **5** and **7**, was subjected to in vitro ADP induced platelet aggregation assay. These compounds were **A1B2C1** (**4**, **5**, and **7**, entries 7, 64 and 77, respectively), **A4B2C1** (**4**, **5**, and **7**, entries 10, 66 and 78, respectively) and **A1B5C1** (**4** and **5**, entries 25 and 70, respectively). It was observed that most of the compounds, found inactive in the in vivo assay, showed significant inhibition against ADP induced aggregation (Table 2). On the basis of these results it was presumed that these compounds possibly had problems with the bioavailability. Finally, only one compound **4A1B2C1** was selected for a detailed study, as this compound was the one that exhibited significant antithrombotic efficacy with minimal effects on the bleeding time. It will be appropriate to mention that for carrying out the detailed study, we proceeded with the diastereoisomeric mixture of compound **4A1B2C1** as all attempts to separate them failed.

In the preliminary in vivo antithrombotic activity evaluation, **4A1B2C1** showed significant protection to collagen and adrenaline induced thrombosis[12] at 30 μM/kg dose, while **4A4B2C1** was not able to significantly reduce stasis induced thrombus formation in rabbits[13,14] (mean wet thrombus weight of 28±7 mg) at a dose, which offered significant protection in mice. Heparin, a potent inhibitor of thrombin action, exhibited a significant inhibition against thrombus formation in the rabbit stasis model (maximum inhibition: 97.5% at 1 mg/kg with a mean wet thrombus weight of 1±0.24 mg) in comparison to the vehicle treated controls (mean wet thrombus weight of 43±13 mg). Results suggest that the compound might be acting predominantly at the platelet targets to prevent thrombosis. Moreover, there was no significant prolongation of bleeding time, indicating that this compound does not interfere with normal haemostasis.[15] Noninterference with the haemostatic machinery was also confirmed by the insignificant alterations in the clotting time parameters, as detailed in Table 3. It, therefore, appeared that the compound **4A1B2C1** elicited its antithrombotic activity by inhibiting platelet aggregation. Hence the need arose to evaluate compound **4A1B2C1** as an antagonist for platelet aggregation. Platelet aggregation inducers such as ADP, collagen, and thrombin act at the receptor level to bring about the activation of platelets and subsequent exposure of GPIIb–IIIa.[5–7,16–18] GPIIb–IIIa is fibrinogen receptor, which interlinks with the same receptor of the adjacent platelets through fibrinogen, leading to aggregation of platelets.[19] While other inducers such as PMA, AA, or A23187[20–22] induces aggregation by acting at the intermediate mediator level, PMA is also an activator of protein kinase C (PKC), which in turn brings about the phosphorylation of various proteins involved in the activation pathway. Calcium ionophore A23187 increases the influx of calcium ions into the platelets and causes GPIIb–IIIa exposure and platelet aggregation. Arachidonic acid is metabolized by the enzyme cyclooxygenase in the platelets to form thromboxane A_2 that binds to the Tp-receptor and thus activates the platelets in positive feed back mechanism leading to platelet aggregation.[19]

Table 2. Effect of compounds on ADP (5 μM)-induced aggregation in rats

Compounds	IC_{50} (μM) (95% lower limit–95% upper limit)	In vivo % protection from Table 1
4A1B2C1	20.0 (16.6–25.9)	60
5A1B2C1	8.0 (6.2–10.3)	20
7A1B2C1	78.8 (51.9–119.8)	NA
4A4B2C1	95.8 (75.8–121.2)	80
5A4B2C1	28.1 (23.8–33.1)	NA
7A4B2C1	82.3 (66.7–101.7)	NA
4A1B5C1	216.4 (183.4–255.4)	80
5A1B5C1	124.7 (98.3–158.1)	NA

Data represents the mean IC_{50} of at least three independent experiments.

Table 3. Effect of **4A4B2C1** on coagulation parameters

Clotting time parameters (in seconds)	Vehicle treated	**4A4B2C1**
Thrombin time (TT)	18.6 ± 0.2	18.3 ± 0.2
Prothrombin time (PT)	16.6 ± 0.1	16.3 ± 0.2
Activated partial thromboplastin time (APTT)	23.7 ± 1.4	20.7 ± 0.5

Table 4. Effect of **4A4B2C1** on platelet aggregation

Agonist	IC_{50} (μM) (95% lower limit–95% upper limit)
Collagen	73.1 (59–90)
ADP	95.8 (75.8–121.2)
Thrombin	96.4 (71.6–129.6)
PMA	255.1 (198–328.6)
A23187	303.9 (258.3–357.7)
Arachidonic acid	1214.2 (833–1770)

Compound **4A1B2C1** inhibited platelet aggregation irrespective of the agonists used (Table 4). Though it was more selective to collagen, ADP and thrombin, suggesting that it interfered at the receptor surface to subsequently inhibit the events involved in the aggregation, it seemed likely that this compound interfered at the common receptor in the platelet aggregation cascade. As all the cascades eventually terminate at the expression of GPIIb–IIIa receptor and fibrinogen binding, it thus seems likely that compound **4A1B2C1** interfered with the fibrinogen binding to the GPIIb–IIIa receptor to display the antithrombotic activity. Thus, compound **4A1B2C1** is a significant lead molecule that can be tailored further to derive a new class of antithrombotic agents.

4. Conclusion

In conclusion, we have described facile parallel synthesis and in vivo antithrombotic evaluation of various 3,5-

disubstituted isoxazole derivatives obtained from 3-substituted-5-isoxazolecarbaldehyde utilizing Baylis–Hillman chemistry. The present study has also provided an insight into the plausible mode of action of these derivatives.

5. Experimental section

5.1. General methods

Reactions were run in oven-dried glassware. Dried solvents were prepared by standard procedures. The column chromatography for all compounds other than amines was carried on silica gel (60–1200 mesh) using distilled solvents. The final amines were passed through basic alumina column using distilled solvents. Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using an FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were run in $CDCl_3$ and recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, J in Hz). The EIMS and FABMS were recorded on appropriate spectrometers and ESMS were recorded through direct injections in an LCMS system. Elemental analyses were performed on a microanalyzer. The diastereoisomeric ratios are based on ^{1}H NMR. Due to the complex nature of ^{1}H NMR spectra for compounds having **C6** (4-benzylamino piperidine) as substitution, they are not being provided. The spectroscopic data corresponding to Baylis–Hillman adducts and their corresponding acetates have been published earlier.[23]

5.2. Baylis–Hillman reaction—general procedure

To a mixture of DABCO (0.12 g, 1.06 mmol) and appropriate alkene (5.3 mmol) that has been stirred at rt for 20 min. was added appropriate aldehyde from **1**(**A1-6**) (5.3 mmol) under stirring and the reaction was allowed to proceed for a period 30 min. Thereafter 5% aq HCl soln (50 mL) was added to the reaction mixture to neutralize the base and extracted with ethyl acetate (2×50 mL). The organic layers were combined, washed with brine (75 mL), dried over anhyd Na_2SO_4 and evaporated under vacuum to yield an oily residue. The residue was purified by column chromatography over silica gel (60–120 mesh) using hexane/ethyl acetate as eluent. A mixture of hexane/ethyl acetate (65:35, v/v) yielded the desired products **2**(**A1-6-B1-5**) as solids or oils.

5.3. Reaction with amines—general procedure

To the appropriate derivative from **2**, **3** and **6** (5.0 mmol) in methanol (4 mL) was added amine (6.0 mmol) and the mixture was stirred at rt from 14–20 h (preferentially overnight). On completion, the excess solvent was evaporated and the residue was filtered from a small band of basic alumina using chloroform (0.5 mL of methanol in 200 mL of chloroform was added in few cases). The eluent was evaporated to obtain the required products as pale yellow oils or solid. Most of the amines were immediately converted to their corresponding oxalate salts. To the solution of amine in dry methanol (ca. 2–4 mL) was added a solution of oxalic acid dihydrate (1.0 equiv) in dry methanol (ca. 2–4 mL). The mixture was hand shaked for 10–15 min. and then dry ether was added freely to precipitate the salt. In few cases the salts were recrystallized from methanol.

5.4. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-propionic acid methyl ester (4A1B1C1) (6:1)

The product was obtained as colourless oil (59%); IR (neat) 1735 (CO_2Me), 3319 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 2.29$ (s, 6H, $2 \times NCH_3$), 2.48–2.88 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.06–3.22 (m, 4H, $2 \times NCH_2$), 3.66 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 5.33, 5.37 (d, 1H, $J = 7.2$ Hz, CH), 5.46, 5.48 (d, 1H, $J = 7.2$ Hz, CH), 6.56 (s, 1H, =CH), 6,59 (s, 1H, =CH), 7.43–7.46 (m, 6H, Ar–H), 7.78–7.82 (m, 4H, Ar–H); Mass (EI) m/z 359 (M^+). Oxalate salt: mp 206–208 °C; Anal. [$C_{19}H_{23}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.5. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-*p*-tolyl-isoxazol-5-yl)-propionic acid methyl ester (4A2B1C1) (5:1)

The product was obtained as colourless oil (61%); IR (neat, cm^{-1}) 1732 (CO_2Me), 3385 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 2.28$ (s, 6H, $2 \times NCH_3$), 2.39 (s, 6H, $2 \times CH_3$), 2.47–2.86 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.10–3.16 (m, 4H, $2 \times NCH_2$), 3.65 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 5.31, 5.35 (d, 1H, $J = 7.8$ Hz, CH), 5.46, 5.50 (d, 1H, $J = 7.8$ Hz, CH), 6.52 (s, 1H, =CH), 6.55 (s, 1H, =CH), 7.23, 7.27 (d, 4H, $J = 8.0$ Hz, Ar–H), 7.66, 7.70 (d, 4H, $J = 8.0$ Hz, Ar–H); Mass (ES+) m/z 374.67 (M^+), 396.53 (M^++Na). Oxalate salt: mp 198–199 °C; Anal. [$C_{20}H_{27}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.6. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid methyl ester (4A3B1C1) (9:1)

The product was obtained as light brown solid (58%), mp 63–64 °C; IR (neat) 1732 (CO_2Me), 3424 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 2.28$ (s, 3H, NCH_3), 2.46 (s, 3H, NCH_3), 2.43–2.93 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.10–3.16 (m, 4H, $2 \times NCH_2$), 3.70 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 5.11 (s, 4H, $2 \times OCH_2O$), 5.30, 5.34 (d, 1H, $J = 7.8$ Hz, CH), 5.41, 5.45 (d, 1H, $J = 7.8$ Hz, CH), 6.49 (s, 1H, =CH), 6.52 (s, 1H, =CH), 7.01, 7.05 (d, 4H, $J = 8.6$ Hz, Ar–H), 7.30–7.46 (m, 10H, Ar–H), 7.71, 7. 75 (d, 4H, $J = 8.6$ Hz, Ar–H); Mass (ES+) m/z 466.93 (M^++1), 488.60 (M^++Na). Oxalate salt: mp 197–198 °C (dec); Anal. [$C_{26}H_{31}N_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.7. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid methyl ester (4A4B1C1) (5:1)

The product was obtained as colourless oil (61%); IR (neat) 1733 (CO_2Me), 3331 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.29$ (s, 6H, $2 \times NCH_3$), 2.39–2.86 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.09–3.14 (m, 4H, $2 \times NCH_2$), 3.66 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 5.31, 5.35 (d, 1H, $J = 7.8$ Hz, CH), 5.40, 5.44 (d, 1H, $J = 7.2$ Hz, CH), 6.55 (s, 1H, =CH), 6.58 (s, 1H, =CH), 7.32–7.49 (m, 6H, Ar–H), 7.69–7.74 (m, 2H, Ar–H); Mass (EI) m/z 393 (M^+). Oxalate salt: mp 198–199 °C; Anal. [$C_{19}H_{24}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.8. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid methyl ester (4A5B1C1) (5:1)

The product was obtained as colourless oil (65%); IR (neat) 1730 (CO_2Me), 3362 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.29$ (s, 6H, $2 \times NCH_3$), 2.39–2.89 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.09–3.17 (m, 4H, $2 \times NCH_2$), 3.66 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 5.31, 5.35 (d, 1H, $J = 7.8$ Hz, CH), 5.42, 5.46 (d, 1H, $J = 7.4$ Hz, CH), 6.52 (s, 1H, =CH), 6.56 (s, 1H, =CH), 7.40, 7.44 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.71, 7.75 (d, 4H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 416.00 (M^++Na). Oxalate salt: mp 198–200 °C; Anal. [$C_{19}H_{24}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.9. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid methyl ester (4A6B1C1) (5:1)

The product was obtained as colourless oil (56%); IR (neat, cm^{-1}) 1736 (CO_2Me), 3447 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.29$ (s, 6H, $2 \times NCH_3$), 2.34–2.87 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.10–3.18 (m, 4H, $2 \times NCH_2$), 3.66 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 5.33, 5.37 (d, 1H, $J = 7.6$ Hz, CH), 5.41, 5.45 (d, 1H, $J = 7.4$ Hz, CH), 6.70 (s, 1H, =CH), 6.71 (s, 1H, =CH), 7.33, 7.35 (dd, 2H, $J_1 = 2.0$ Hz, $J_2 = 8.2$ Hz, Ar–H), 7.50, 7.51 (d, 2H, $J = 2.0$ Hz, Ar–H), 7.66, 7.70 (d, 2H, $J = 8.4$ Hz, Ar–H); Mass (FAB+) m/z 428 (M^++1). Oxalate salt: mp 171–172 °C; Anal. [$C_{19}H_{23}Cl_2N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.10. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-propionic acid ethyl ester (4A1B2C1) (6:1)

The product was obtained as white solid (69%), mp 110–111 °C; IR (KBr, cm^{-1}) 1728 (CO_2Et), 3220 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.14$–1.27 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.29 (s, 3H, NCH_3), 2.31 (s, 3H, NCH_3), 2.45–2.87 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.10–3.16 (m, 4H, $2 \times NCH_2$), 4.05–4.16 (m, 2q merged, 4H, $J = 7.2$ Hz, $2 \times CH_2$), 5.32, 5.35 (d, 1H, $J = 5.4$ Hz, CH), 5.39, 5.42 (d, 1H, $J = 5.4$ Hz, CH), 6.58 (s, 1H, =CH), 6.60 (s, 1H, =CH), 7.42–7.45 (m, 6H, Ar–H), 7.77–7.84 (m, 4H, Ar–H); Mass (EI) m/z 373 (M^+). Oxalate salt: mp 196–198 °C; Anal. [$C_{20}H_{27}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.11. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-*p*-tolyl-isoxazol-5-yl)-propionic acid ethyl ester (4A2B2C1) (single)

The product was obtained as white solid (54%), mp 139–140 °C; IR (KBr, cm^{-1}) 1730 (CO_2Et), 3437 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.17$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.28 (s, 3H, NCH_3), 2.39 (s, 3H, CH_3), 2.47–2.87 (m, 9H, $4 \times NCH_2$ and CH), 3.04–3.14 (m, 2H, NCH_2), 4.10 (q, 2H, $J = 7.1$ Hz, OCH_2), 5.29, 5.33 (d, 1H, $J = 7.8$ Hz, CH), 6.65 (s, 1H, =CH), 7.22, 7.26 (d, 4H, $J = 8.0$ Hz, Ar–H), 7.66, 7.70 (d, 4H, $J = 8.0$ Hz, Ar–H); Mass (EI) m/z 387 (M^+). Oxalate salt: mp 143–144 °C; Anal. [$C_{21}H_{29}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.12. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid ethyl ester (4A3B2C1) (4:1)

The product was obtained as white solid (50%), mp 69–70 °C; IR (KBr) 1730 (CO_2Et), 3437 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.14$–1.29 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.29 (s, 6H, $2 \times NCH_3$), 2.44–2.86 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 4.05–4.14 (m, 2q merged, 4H, $J = 7.2$ Hz, $2 \times OCH_2$), 5.11 (s, 4H, $2 \times OCH_2O$), 5.29, 5.31 (d, 1H, $J = 7.8$ Hz, CH), 5.35, 5.38 (d, 1H, $J = 7.8$ Hz, CH), 6.49 (s, 1H, =CH), 6.51 (s, 1H, =CH), 7.01, 7.05 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.32–7.46 (m, 5H, Ar–H), 7.70, 7.74 (d, 2H, $J = 8.8$ Hz, Ar–H); Mass (ES+) m/z 481.00 (M^++1), 502.67 (M^++Na). Oxalate salt: mp 217–219 °C; Anal. [$C_{27}H_{33}N_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.13. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid ethyl ester (4A4B2C1) (9:1)

The product was obtained as colourless oil (65%); IR (neat) 1728 (CO_2Et), 3329 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.06$–1.17 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.26 (s, 3H, NCH_3), 2.28 (s, 3H, NCH_3), 2.48–2.87 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 4.105–4.16 (m, 2q merged, 4H, $J = 7.2$ Hz, $2 \times OCH_2$), 5.32. 5.36 (d, 1H, $J = 7.8$ Hz, CH), 5.38. 5.42 (d, 1H, $J = 7.8$ Hz, CH), 6.72 (s, 1H, =CH), 6.78 (s, 1H, =CH), 7.33–7.50 (m, 6H, Ar–H), 7.69–7.74 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 14.39$, 45.45, 46.23, 46.87, 53.68, 55.27, 56.55, 59.65, 61.65, 69.62, 70.39, 77.67, 103.47, 104.15, 127.48, 128.75, 130.78, 131.34, 133.27, 161.14, 170.88, 171.13, 172.72, 173.43; Mass (FAB+) m/z 408 (M^++1). Oxalate salt: mp 205–206 °C; Anal. [$C_{20}H_{26}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.14. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid ethyl ester (4A5B2C1) (6:1)

The product was obtained as colourless oil (64%); IR (neat) 1730 (CO_2Et), 3374 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.13$–126 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.28 (s, 6H, $2 \times NCH_3$), 2.33–2.92 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.09–3.15 (m, 4H, $2 \times NCH_2$), 3.09–3.15 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 5.29, 5.33 (d, 1H, $J = 7.6$ Hz, CH), 5.36, 5.40 (d, 1H, $J = 7.6$ Hz, CH), 6.53 (s, 1H, =CH), 6.56 (s, 1H, =CH), 7.40, 7.44 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.71, 7.75 (d, 4H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 408.67 (M^++1), 430.40 (M^++Na). Oxalate salt: mp 202–205 °C; Anal. [$C_{20}H_{26}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.15. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid ethyl ester (4A6B2C1) (3:1)

The product was obtained as colourless oil (61%); IR (neat, cm^{-1}) 1730 (CO_2Et), 3404 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.14$–1.33 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.29 (s, 6H, $2 \times NCH_3$), 2.47–2.86 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.10–3.15 (m, 2H, NCH_2), 4.10 (q, 4H, $J = 7.2$ Hz, OCH_2), 5.32, 5.36 (d, 1H, $J = 7.8$ Hz, CH), 5.41, 5.44 (d, 1H, $J = 7.6$ Hz, CH), 6.70 (s, 1H, =CH), 6.71 (s, 1H, =CH), 7.32, 7.36 (dd, 1H, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, Ar–H), 7.51, 7.52 (d, 1H, $J = 2.0$ Hz, Ar–H), 7.66, 7.70 (d, 1H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 444.07 (M^++1), 464.00 (M^++Na). Oxalate salt: mp 180–182 °C (dec); Anal. [$C_{20}H_{25}Cl_2N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.16. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)- propionic acid butyl ester (4A1B3C1) (5:1)

The product was obtained as colourless oil (57%); IR (neat, cm^{-1}) 1708 (CO_2Bu-*n*), 3377 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.81$–0.94 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 1.23–1.31 (m, 4H, $2 \times CH_2$), 1.47–1.56 (m, 4H, $2 \times CH_2$), 2.29 (s, 6H, $2 \times NCH_3$), 2.35–2.86 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.07–3.17 (m, 4H, $2 \times NCH_2$), 4.06 (t, 2H, $J = 6.6$ Hz, OCH_2), 4.13 (t, 2H, $J = 6.6$ Hz, OCH_2), 5.32, 5.34 (d, 1H, $J = 7.8$ Hz, CH), 5.36, 5.38 (d, 1H, $J = 7.8$ Hz, CH), 6.55 (s, 1H, =CH), 6.58 (s, 1H, =CH), 7.43–7.45 (m, 6H, Ar–H), 7.77–7.84 (m, 4H, Ar–H); Mass (EI) m/z 401 (M^+). Oxalate salt: mp 195–197 °C; Anal. [$C_{22}H_{31}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.17. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-*p*-tolyl-isoxazol-5-yl)-propionic acid butyl ester (4A2B3C1) (3:1)

The product was obtained as pale yellow oil (61%); IR (neat, cm^{-1}) 1709 (CO_2Bu-*n*), 3380 (OH); ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 0.82$–0.93 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 1.21–1.29 (m, 4H, $2 \times CH_2$), 1.49–1.63 (m, 4H, $2 \times CH_2$), 2.27 (s, 6H, $2 \times CH_3$), 2.39 (s, 6H, $2 \times NCH_3$), 2.42–2.86 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.10–3.14 (m, 4H, $2 \times NCH_2$), 4.04 (t, 2H, $J = 6.6$ Hz, OCH_2), 4.13 (t, 2H, $J = 6.6$ Hz, OCH_2), 5.31, 5.33 (d, 1H, $J = 5.4$ Hz, CH), 5.38 (br s, 1H, CH), 6.52 (s, 1H, =CH), 6.55 (s, 1H, =CH), 7.23, 7.26 (d, 4H, $J = 8.0$ Hz, Ar–H), 7.67, 7.69 (d, 4H, $J = 8.0$ Hz, Ar–H); Mass (ES+) m/z 416.27 (M^++1). Oxalate salt: mp 220–221 °C; Anal. [$C_{23}H_{33}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.18. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid butyl ester (4A3B3C1) (5:1)

The product was obtained as colourless oil (57%); IR (neat, cm^{-1}) 1729 (CO_2Bu-*n*), 3400 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.84$ (t, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 1.21–1.32 (m, 4H, $2 \times CH_2$), 1.45–1.55 (m, 4H, $2 \times CH_2$) 2.28 (s, 6H, $2 \times NCH_3$), 2.38–2.82 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.09–3.15 (m, 4H, $2 \times NCH_2$), 4.02–4.12 (m, 2t merged, 4H, $J = 6.6$ Hz, $2 \times OCH_2$), 5.11 (s, 4H, $2 \times OCH_2O$), 5.29, 5.33 (d, 1H, $J = 7.8$ Hz, CH), 5.46, 5.50 (d, 1H, $J = 7.8$ Hz, CH), 6.47 (s, 1H, =CH), 6.51 (s, 1H, =CH), 7.01, 7.05 (d, 4H, $J = 8.8$ Hz, Ar–H), 7.32–7.45 (m, 10H, Ar–H), 7.70, 7.74 (d, 4H, $J = 8.8$ Hz, Ar–H); Mass (FAB+) m/z 508 (M^++1). Oxalate salt: mp 196–197 °C; Anal. [$C_{29}H_{37}N_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.19. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid butyl ester (4A4B3C1) (9:1)

The product was obtained as colourless oil (50%); IR (neat) 1730 (CO_2Bu-*n*), 3329 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.87$ (t, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 1.23–1.34 (m, 4H, $2 \times CH_2$), 1.50–1.57 (m, 4H, $2 \times CH_2$) 2.28 (s, 3H, NCH_3), 2.31 (s, 3H, NCH_3), 2.48–2.83 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.11–3.18 (m, 4H, $2 \times NCH_2$), 4.05 (t, 4H, $J = 6.6$ Hz, $2 \times OCH_2$), 5.33, 5.37 (d, 1H, $J = 8.0$ Hz, CH), 5.45, 4.49 (d, 1H, $J = 7.8$ Hz, CH), 6.72 (s, 2H, $2 \times$=CH), 7.32–7.50 (m, 6H, Ar–H), 7.69-7.74 (m, 2H, Ar–H); Mass (EI) m/z 435 (M^+). Oxalate salt: mp 208–210 °C; Anal. [$C_{22}H_{30}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.20. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid butyl ester (4A5B3C1) (5:1)

The product was obtained as colourless oil (50%); IR (neat) 1730 (CO_2Bu-*n*), 3330 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.84$ (t, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 1.21–1.32 (m, 4H, $2 \times CH_2$), 1.48–1.55 (m, 4H, $2 \times CH_2$) 2.29 (s, 6H, $2 \times NCH_3$), 2.48–2.83 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.10–3.16 (m, 4H, $2 \times NCH_2$), 4.07 (m, 4H, $2 \times OCH_2$), 5.30, 5.32 (d, 1H, $J = 4.2$ Hz, CH), 5.45, 5.47 (d, 1H, $J = 4.2$ Hz, CH), 6.52 (s, 1H, =CH), 6.55 (s, 1H, =CH), 7.40, 7.44 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.71,

7.75 (d, 4H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 436.73 (M^++1), 458.67 (M^++Na). Oxalate salt: mp >225 °C; Anal. [$C_{22}H_{30}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.21. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid butyl ester (4A6B3C1) (5:1)

The product was obtained as pale yellow oil (52%); IR (neat, cm^{-1}) 1729 (CO_2Bu-*n*), 3329 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 0.86$ (t, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 1.23–1.34 (m, 4H, $2 \times CH_2$), 1.50–1.57 (m, 4H, $2 \times CH_2$), 2.28 (s, 3H, NCH_3), 2.31 (s, 3H, NCH_3), 2.48–2.83 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.11–3.18 (m, 4H, $2 \times NCH_2$), 4.04 (t, 4H, $J = 6.6$ Hz, $2 \times OCH_2$), 5.32, 5.36 (d, 1H, $J = 8.0$ Hz, CH), 5.45, 5.49 (d, 1H, $J = 7.8$ Hz, CH), 6.70 (s, 1H, CH), 6.72 (s, 1H, CH), 7.31, 7.36 (dd, 2H, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, Ar–H), 7.50, 7.51 (d, 2H, $J = 1.8$ Hz, Ar–H), 7.66, 7.70 (m, 2H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 470.80 (M^++1), 492.73 (M^++Na). Oxalate salt: mp 208–210 °C; Anal. [$C_{22}H_{29}Cl_2N_3O_4 \cdot 2(CO_2H)_2H_2O$] C, H, N.

5.22. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-propionic acid *tert*-butyl ester (4A1B4C1) (5:1)

The product was obtained as colourless oil (61%); IR (neat, cm^{-1}) 1726 (CO_2Bu-*t*), 3398 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 1.36$ (s, 9H, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 2.23 (s, 3H, NCH_3), 2.25 (s, 3H, NCH_3), 2.45–2.80 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.01–3.07 (m, 4H, $2 \times NCH_2$), 5.24, 5.27 (d, 1H, $J = 7.8$ Hz, CH), 5.31, 5.34 (d, 1H, $J = 7.8$ Hz, CH), 6.55 (s, 1H, =CH), 6.58 (s, 1H, =CH), 7.42–7.44 (m, 6H, Ar–H), 7.75–7.81 (m, 4H, Ar–H); Mass (EI) m/z 401 (M^+). Oxalate salt: mp 190–192 °C; Anal. [$C_{22}H_{31}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.23. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-*p*-tolyl-isoxazol-5-yl)-propionic acid-*tert*-butyl ester (4A2B4C1) (5:1)

The product was obtained as white solid (54%), mp 100–102 °C; IR (KBr, cm^{-1}) 1722 (CO_2Bu-*t*), 3394 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 1.36$ (s, 9H, $C(CH_3)_3$), 1.42 (s, 9H, $C(CH_3)_3$), 2.28 (s, 3H, $2 \times NCH_3$), 2.39 (s, 6H, $2 \times CH_3$), 2.49–2.85 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 2.98–3.28 (m, 4H, $2 \times NCH_2$), 5.24, 5.27 (d, 1H, $J = 7.8$ Hz, CH), 5.38, 5.40 (d, 1H, $J = 7.8$ Hz, CH), 6.52 (s, 1H, =CH), 6.54 (s, 1H, =CH), 7.21, 7.25 (d, 4H, $J = 8.0$ Hz, Ar–H), 7.66, 7.70 (d, 4H, $J = 8.0$ Hz, Ar–H); Mass (EI) m/z 415 (M^+). Oxalate salt: mp. 176–178 °C; Anal. [$C_{23}H_{33}N_3O_4 \cdot 2(CO_2H)_2 \cdot H_2O$] C, H, N.

5.24. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid-*tert*-butyl ester (4A3B4C1) (5:1)

The product was obtained as white solid (58%), mp 135–137 °C; IR (KBr, cm^{-1}) 1728 (CO_2Bu-*t*), 3398 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 1.28$ (s, 9H, $C(CH_3)_3$), 1.38 (s, 9H, $C(CH_3)_3$), 2.22 (s, 3H, NCH_3), 2.26 (s, 3H, NCH_3), 2.32–2.80 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 2.96–2.99 (m, 4H, $2 \times NCH_2$), 5.04 (s, 4H, $2 \times OCH_2O$), 5.16, 5.19 (d, 1H, $J = 7.4$ Hz, CH), 5.29, 5.31 (d, 1H, $J = 7.4$ Hz, CH), 6.41 (s, 1H, =CH), 6.44 (s, 1H, =CH), 6.94, 6.98 (d, 4H, $J = 8.8$ Hz, Ar–H), 7.25–7.39 (m, 10H, Ar–H), 7.63, 7.67 (d, 4H, $J = 8.8$ Hz, Ar–H); Mass (EI) m/z 507 (M^+). Oxalate salt: mp 189–191 °C; Anal. [$C_{29}H_{37}N_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.25. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid *tert*-butyl ester (4A4B4C1)

The product was obtained as white solid (65%), mp 105–107 °C; IR (KBr, cm^{-1}) 1724 (CO_2Bu-*t*), 3434 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 1.37$ (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 2.29 (s, 6H, $2 \times NCH_3$), 2.48–2.83 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.06–3.10 (m, 4H, $2 \times NCH_2$), 5.26, 5.30 (d, 1H, $J = 7.6$ Hz, CH), 5.40, 5.44 (d, 1H, $J = 7.8$ Hz, CH), 6.72 (s, 1H, =CH), 6.73 (s, 1H, =CH), 7.30–7.51 (m, 6H, Ar–H), 7.69–7.73 (m, 2H, Ar–H); Mass (EI) m/z 435 (M^+). Oxalate salt: mp 174–176 °C; Anal. [$C_{22}H_{30}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.26. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid *tert*-butyl ester (4A5B4C1) (5:1)

The product was obtained as white solid (59%), mp 105–107 °C; IR (KBr, cm^{-1}) 1723 (CO_2Bu-*t*), 3485 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 1.36$ (s, 9H, $C(CH_3)_3$), 1.45 (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 2.27 (s, 6H, $2 \times NCH_3$), 2.47–2.81 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.03–3.07 (m, 4H, $2 \times NCH_2$), 5.31, 5.33 (d, 1H, $J = 4.2$ Hz, CH), 5.40, 5.42 (d, 1H, $J = 4.2$ Hz, CH), 6.50 (s, 1H, =CH), 6.55 (s, 1H, =CH), 7.39, 7.43 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.71, 7.75 (d, 4H, $J = 8.4$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 28.19$, 28.34, 46.22, 47.76, 53.65, 55.26, 55.41, 56.69, 60.03, 69.49, 70.40, 82.37, 100.03, 100.58, 127.90, 128.03, 128.44, 129.54, 136.30, 161.53, 170.24, 174.06, 174.88; Mass (FAB+) m/z 436 (M^++1). Oxalate salt: mp 184–185 °C; Anal. [$C_{22}H_{30}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.27. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid *tert*-butyl ester (4A6B4C1) (3:1)

The product was obtained as white solid (61%), mp 105–107 °C; IR (KBr, cm^{-1}) 1721 (CO_2Bu-*t*), 3402 (OH); ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 1.37$ (s, 9H, $C(CH_3)_3$), 1.46 (s, 9H, $C(CH_3)_3$), 2.29 (s, 6H, $2 \times NCH_3$), 2.39–2.81 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.05–3.09 (m, 4H, $2 \times NCH_2$), 5.26, 5.29 (d, 1H, $J = 7.2$ Hz, CH), 5.40, 5.42 (d, 1H, $J = 7.2$ Hz, CH), 6.70 (s, 1H, =CH), 6.72 (s, 1H, =CH), 7.35, 7.39 (dd, 4H, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, Ar–H), 7.50–7.51 (d, 2H, $J = 1.6$ Hz, Ar–H), 7.65, 7.69 (d, 2H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 480.80

(M^++1). Oxalate salt: mp 191–192 °C; Anal. [$C_{22}H_{29}Cl_2N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.28. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-propionitrile (4A1B5C1) (3:1)

The product was obtained as yellow oil (51%); IR (neat, cm^{-1}) 2256 (CN), 3390 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.28$ (s, 3H, NCH_3), 2.29 (s, 3H, NCH_3), 2.39–2.98 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.29–3.34 (m, 4H, $2 \times NCH_2$), 5.27, 5.30 (m, 2H, $2 \times CH$), 6.70 (s, 1H, =CH), 6.75 (s, 1H, =CH), 7.44–7.47 (m, 6H, Ar–H), 7.78–7.82 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 35.12$, 35.92, 46.13, 53.52, 53.93, 55.22, 56.75, 57.14, 66.55, 67.66, 100.96, 118.51, 119.13, 127.24, 128.90, 129.41, 130.70, 162.90, 172.24, 172.47; Mass (EI) m/z 326 (M^+). Oxalate salt: mp 169–170 °C; Anal. [$C_{18}H_{24}N_4O_2 \cdot 2(CO_2H)_2$] C, H, N.

5.29. 3-Hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-3-(3-*p*-tolyl-isoxazol-5-yl)-propionitrile (4A2B5C1) (3:1)

The product was obtained as yellow oil (50%); IR (neat, cm^{-1}) 2248 (CN), 3354 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.28$ (s, 3H, NCH_3), 2.29 (s, 3H, NCH_3), 2.40 (s, 6H, $2 \times CH_3$), 2.50–3.04 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.29–3.34 (m, 4H, $2 \times NCH_2$), 5.25–5.28 (m, 2H, $2 \times CH$), 6.67 (s, 1H, =CH), 6.72 (s, 1H, =CH), 7.25. 7.29 (d, 4H, $J = 8.0$ Hz, Ar–H), 7.68, 7.72 (m, 4H, $J = 8.0$ Hz, Ar–H); Mass (EI) m/z 340 (M^+). Oxalate salt: mp 180–182 °C; Anal. [$C_{19}H_{24}N_4O_2 \cdot 2(CO_2H)_2 \cdot H_2O$] C, H, N.

5.30. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionitrile (4A3B5C1) (3:1)

The product was obtained as yellow oil (65%); IR (neat, cm^{-1}) 2247 (CN), 3354 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.28$ (s, 3H, NCH_3), 2.29 (s, 3H, NCH_3), 2.43–2.99 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.29–3.36 (m, 4H, $2 \times NCH_2$), 5.11 (s, 4H, $2 \times OCH_2O$), 5.39–5.45 (m, 2H, $2 \times CH$), 6.64 (s, 1H, =CH), 6.67 (s, 1H, =CH), 7.25. 7.29 (d, 4H, $J = 8.0$ Hz, Ar–H), 7.31–7.45 (m, 10H, Ar–H), 7.68, 7.72 (m, 4H, $J = 8.0$ Hz, Ar–H); Mass (ES+) m/z 433.80 (M^++1), 455.53 (M^++Na). Oxalate salt: mp 119–121 °C; Anal. [$C_{25}H_{28}N_4O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.31. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionitrile (4A4B5C1) (3:1)

The product was obtained as yellow oil (47%); IR (neat, cm^{-1}) 2257 (CN), 3390 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.29$, 2.31 (2s, 6H, $2 \times NCH_3$), 2.45–2.85 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.08–3.15 (m, 4H, $2 \times NCH_2$), 5.28–5.31 (m, 2H, $2 \times CH$), 6.86 (s, 1H, =CH), 6.90 (s, 1H, =CH), 7.35–7.52 (m, 6H, Ar–H), 7.72–7.76 (m, 2H, Ar–H); Mass (FAB+) m/z 361 (M^++1). Oxalate salt: mp 156–158 °C; Anal. [$C_{18}H_{21}ClN_4O_2 \cdot 2(CO_2H)_2$] C, H, N.

5.32. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionitrile (4A5B5C1) (3:1)

The product was obtained as yellow oil (49%); IR (neat, cm^{-1}) 2257 (CN), 3439 (OH); ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 2.29$ (s, 3H, NCH_3), 2.31 (s, 3H, NCH_3), 2.50–2.86 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.04–3.16 (m, 4H, $2 \times NCH_2$), 5.28, 5.29 (d, 1H, $J = 3.6$ Hz, CH), 5.43, 5.44 (d, 1H, $J = 3.6$ Hz, CH), 6.86 (s, 1H, =CH), 6.90 (s, 1H, =CH), 7.48–7.51 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.81-7.84 (d, 4H, $J = 8.4$ Hz, Ar–H); Mass (FAB+) m/z 361 (M^++1). Oxalate salt: mp 180–181 °C; Anal. [$C_{18}H_{21}ClN_4O_2 \cdot 2(CO_2H)_2$] C, H, N.

5.33. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-(4-methyl-piperazin-1-ylmethyl)-propionitrile (4A6B5C1) (3:1)

The product was obtained as yellow oil (47%); IR (neat, cm^{-1}) 2251 (CN), 3390 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.29$ (s, 6H, $2 \times NCH_3$), 2.44–2.96 (m, 18H, $8 \times NCH_2$ and $2 \times CH$), 3.31–3.36 (m, 4H, $2 \times NCH_2$), 5.29–5.31 (m, 2H, $2 \times CH$), 6.86 (s, 1H, =CH), 6.90 (s, 1H, =CH), 7.33, 7.37 (dd, 4H, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, Ar–H), 7.52, 7.53 (d, 2H, $J = 1.6$ Hz, Ar–H), 7.68, 7.72 (d, 2H, $J = 8.4$ Hz, Ar–H); Mass (FAB+) m/z 395 (M^++1). Oxalate salt: mp 163–164 °C; Anal. [$C_{18}H_{20}Cl_2N_4O_2 \cdot 2(CO_2H)_2$] C, H, N.

5.34. 2-(4-Acetyl-piperazin-1-ylmethyl)-3-hydroxy-3-(3-phenyl-isoxazol-5-yl)-propionic acid ethyl ester (4A1B2C2) (5:1)

The product was obtained as pale yellow oil (59%): IR (neat, cm^{-1}) 1731 (CO_2Et and COMe), 3320 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.16$–1.29 (m, 2t merged, 6H, $J = 7.0$ Hz, $2 \times CH_3$), 2.04 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.52–2.65 (m, 8H, $4 \times NCH_2$), 2.80–3.26 (m, 4H, NCH_2 and $2 \times CH$), 3.47 (t, 4H, $J = 4.6$ Hz, $2 \times NCH_2$), 3.63 (t, 4H, $J = 4.6$ Hz, $2 \times NCH_2$), 4.05–4.16 (m, 2q merged, 4H, $2 \times OCH_2$), 5.30–5.36 (m, 2H, $2 \times CH$), 6.58 (s, 1H, =CH), 7.43–7.46 (m, 6H, Ar–H), 7.77–7.81 (m, 4H, Ar–H); Mass (ES+) m/z 402.47 (M^++1), 423.80 (M^++Na). Oxalate salt: mp 90–92 °C; Anal. [$C_{21}H_{27}N_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.35. 2-(4-Acetyl-piperazin-1-ylmethyl)-3-[3-(4-benzyloxy-phenyl)-isoxazol-5-yl]-3-hydroxy-propionic acid ethyl ester (4A3B2C2) (6:1)

The product was obtained as pale yellow oil (53%): IR (neat, cm^{-1}) 1728 (CO_2Et and COMe), 3401 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.19$–1.29 (m, 2t merged, 6H, $J = 7.0$ Hz, $2 \times CH_3$), 2.05 (s, 3H, $COCH_3$), 2.08 (s,

3H, $COCH_3$), 2.52–2.66 (m, 8H, $4 \times NCH_2$), 2.71–2.85 (m, 4H, $2 \times NCH_2$), 2.97–3.14 (m, 2H, $2 \times CH$), 3.48 (t, 4H, $J = 4.8$ Hz, $2 \times NCH_2$), 3.62 (t, 4H, $J = 4.8$ Hz, $2 \times NCH_2$), 4.02–4.15 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 5.12 (s, 4H, $2 \times OCH_2O$), 5.32, 5.35 (d, 2H, $J = 7.2$ Hz, CH), 6.53 (s, 1H, =CH), 7.02, 7.06 (d, 4H, $J = 8.6$ Hz, Ar–H), 7.33–7.46 (m, 10H, Ar–H), 7.70, 7.74 (d, 4H, $J = 8.6$ Hz, Ar–H); Mass (FAB+) m/z 508 (M^++1). Oxalate salt: mp 168–170 °C; Anal. [$C_{28}H_{33}N_3O_6 \cdot 2(CO_2H)_2$] C, H, N.

5.36. 2-(4-Acetyl-piperazin-1-ylmethyl)-3-[3-(2-chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-propionic acid ethyl ester (4A4B2C2) (6:1)

The product was obtained as pale yellow oil (57%): IR (neat, cm^{-1}) 1731 (CO_2Et and COMe), 3443 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.19$–1.30 (m, 2t merged, 6H, $J = 7.0$ Hz, $2 \times CH_3$), 1.96 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 2.38–2.67 (m, 8H, $4 \times NCH_2$), 2.74–2.90 (m, 4H, $2 \times NCH_2$), 2.92–3.19 (m, 2H, $2 \times CH$), 3.46 (t, 4H, $J = 4.6$ Hz, $2 \times NCH_2$), 3.63 (t, 4H, $J = 4.6$ Hz, $2 \times NCH_2$), 4.02–4.15 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 5.31–5.38 (m, 2H, CH), 6.53 (s, 1H, =CH), 6.56 (s, 1H, =CH), 7.34–7.51 (m, 6H, Ar–H), 7.72–7.76 (m, 2H, Ar–H); Mass (ES+) m/z 436.67 (M^++1), 458.67 (M^++Na). Oxalate salt: mp 126–128 °C; Anal. [$C_{21}H_{26}ClN_3O_6 \cdot 2(CO_2H)_2$] C, H, N.

5.37. 2-(4-Acetyl-piperazin-1-ylmethyl)-3-[3-(4-chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-propionic acid ethyl ester (4A5B2C2) (6:1)

The product was obtained as pale yellow oil (55%): IR (neat, cm^{-1}) 1731 (CO_2Et and COMe), 3444 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.16$–1.29 (m, 2t merged, 6H, $J = 7.0$ Hz, CH_3), 2.04 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.52–2.67 (m, 8H, $4 \times NCH_2$), 2.74–2.90 (m, 4H, $2 \times NCH_2$), 2.99–3.26 (m, 2H, $2 \times CH$), 3.46 (t, 4H, $J = 4.8$ Hz, $2 \times NCH_2$), 3.63 (t, 4H, $J = 4.8$ Hz, $2 \times NCH_2$), 4.08–4.18 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 5.33, 5.36 (d, 2H, $J = 7.2$ Hz, $2 \times CH$), 6.53 (s, 1H, =CH), 6.56 (s, 1H, =CH), 7.41, 7.45 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.71, 7.75 (d, 2H, $J = 8.6$ Hz, Ar–H); Mass (ES+) m/z 458.00 (M^++Na). Oxalate salt: mp 78–81 °C; Anal. [$C_{21}H_{26}ClN_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.38. 2-(4-Acetyl-piperazin-1-ylmethyl)-3-[3-(2,4-dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-propionic acid ethyl ester (4A6B2C2) (3:1)

The product was obtained as pale yellow oil (52%): IR (neat, cm^{-1}) 1728 (CO_2Et and COMe), 3394 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.16$–130 (m, 6H, $2 \times CH_3$), 2.09 (s, 3H, $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.50–2.58 (m, 8H, $4 \times NCH_2$), 2.63–2.68 (m, 4H, $2 \times NCH_2$), 3.09–3.15 (m, 2H, $2 \times CH$), 3.48 (t, 4H, $J = 4.8$ Hz, $2 \times NCH_2$), 3.64 (t, 4H, $J = 4.8$ Hz, $2 \times NCH_2$), 4.12–4.21 (m, 4H, $2 \times OCH_2$), 5.35, 5.38 (d, 2H, $J = 7.4$ Hz, CH), 5.42, 5.45 (d, 2H, $J = 7.4$ Hz, CH), 6.70 (s, 1H, =CH), 6.73 (s, 1H, =CH), 7.32, 7.36 (dd, 2H, $J = 1.8$ Hz, $J = 8.4$ Hz, Ar–H), 7.51, 7.52 (d, 2H, $J = 1.6$ Hz, Ar–H), 7.66, 7.70 (d, 2H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 470.40 (M^++1), 492.00 (M^++Na). Oxalate salt: mp 85–88 °C; Anal. [$C_{21}H_{25}Cl_2N_3O_6 \cdot 2(CO_2H)_2$] C, H, N.

5.39. 3-Hydroxy-2-[4-(4-methoxy-phenyl)-piperazin-1-ylmethyl]-3-(3-phenyl-isoxazol-5-yl)-propionic acid ethyl ester (4A1B2C3) (5:1)

The product was obtained as pale yellow oil (59%): IR (neat, cm^{-1}) 1729 (CO_2Et), 3320 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.15$–1.27 (m, 2t merged, 6H, $J = 7.0$ Hz, $2 \times CH_3$), 2.52–2.65 (m, 8H, $4 \times NCH_2$), 2.67–2.93 (m, 12H, $6 \times NCH_2$), 3.09–3.21 (m, $4 \times NCH_2$ and $2 \times CH$), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.13 (m, 2q merged, 4H, $2 \times OCH_2$), 5.34, 5.38 (d, 1H, $J = 7.4$ Hz, CH), 5.41, 5.45 (d, 1H, $J = 7.4$ Hz, CH), 6.56 (s, 1H, =CH), 6.59 (s, 1H, =CH), 6.81–6.91 (m, 8H, Ar–H), 7.43–7.46 (m, 6H, Ar–H), 7.77–7.81 (m, 4H, Ar–H); Mass (FAB+) m/z 466 (M^++1). Oxalate salt: mp 143–145 °C; Anal. [$C_{26}H_{31}N_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.40. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-3-hydroxy-2-[4-(4-methoxy-phenyl)-piperazin-1-ylmethyl]-propionic acid ethyl ester (4A3B2C3) (5:1)

The product was obtained as pale yellow oil (61%): IR (neat, cm^{-1}) 1724 (CO_2Et), 3419 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.15$–1.30 (m, 2t merged, 6H, $J = 7.0$ Hz, $2 \times CH_3$), 2.70–2.92 (m, 12H, $6 \times NCH_2$), 3.09–3.20 (m, $4 \times NCH_2$ and $2 \times CH$), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.14 (m, 2q merged, 4H, $2 \times OCH_2$), 5.11 (s, 4H, $2 \times OCH_2O$), 5.34, 5.38 (d, 1H, $J = 7.4$ Hz, CH), 5.41, 5.45 (d, 1H, $J = 7.4$ Hz, CH), 6.52 (s, 1H, =CH), 6.53 (s, 1H, =CH), 6.85–6.87 (m, 8H, Ar–H), 7.01, 7.05 (d, 4H, $J = 8.8$ Hz, Ar–H), 7.32–7.45 (m, 10H, Ar–H), 7.71-7.75 (d, 4H, $J = 8.8$ Hz, Ar–H); Mass (FAB+) m/z 572 (M^++1). Oxalate salt: mp 176–178 °C; Anal. [$C_{33}H_{37}N_3O_6 \cdot 2(CO_2H)_2$] C, H, N.

5.41. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-[4-(4-methoxy-phenyl)-piperazin-1-ylmethyl]-propionic acid ethyl ester (4A4B2C3) (5:1)

The product was obtained as pale yellow oil (58%): IR (neat, cm^{-1}) 1722 (CO_2Et), 3401 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.15$–1.29 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.70–2.93 (m, 12H, $6 \times NCH_2$), 3.09–3.20 (m, $4 \times NCH_2$ and $2 \times CH$), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.08–4.19 (m, 2q merged, 4H, $2 \times OCH_2$), 5.34, 5.38 (d, 1H, $J = 7.4$ Hz, CH), 5.41, 5.45 (d, 1H, $J = 7.4$ Hz, CH), 6.56 (s, 1H, =CH), 6.57 (s, 1H, =CH), 6.56 (s, 1H, =CH), 6.82–6.88 (m, 8H, Ar–H), 7.44–7.68 (m, 8H, Ar–H); Mass (ES+) m/z 500.38 (M^++1), 522.67 (M^++Na). Oxalate salt: mp 120–121 °C; Anal. [$C_{26}H_{30}ClN_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.42. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-[4-(4-methoxy-phenyl)-piperazin-1-ylmethyl]-propionic acid ethyl ester (4A5B2C3) (5:1)

The product was obtained as pale yellow oil (59%): IR (neat, cm^{-1}) 1731 (CO_2Et), 3373 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.15$–1.29 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.70–2.93 (m, 12H, $6 \times NCH_2$), 3.09–3.20 (m, $4 \times NCH_2$ and $2 \times CH$), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.06–4.17 (m, 2q merged, 4H, $2 \times OCH_2$), 5.34, 5.38 (d, 1H, $J = 7.4$ Hz, CH), 5.41, 5.45 (d, 1H, $J = 7.4$ Hz, CH), 6.56 (s, 1H, =CH), 6.57 (s, 1H, =CH), 6.85–6.91 (m, 8H, Ar–H), 7.40, 7.44 (d, 4H, $J = 8.6$ Hz, Ar–H), 7.71–7.75 (d, 4H, $J = 8.6$ Hz, Ar–H); Mass (ES+) m/z 500.67 (M^++1), 522.67 (M^++Na). Oxalate salt: mp 163–164 °C; Anal. [$C_{26}H_{30}ClN_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.43. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-[4-(4-methoxy-phenyl)-piperazin-1-ylmethyl]-propionic acid ethyl ester (4A6B2C3) (5:1)

The product was obtained as pale yellow oil (59%): IR (neat, cm^{-1}) 1730 (CO_2Et), 3389 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.16$–1.28 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.68–2.94 (m, 12H, $6 \times NCH_2$), 3.09–3.22 (m, $4 \times NCH_2$ and $2 \times CH$), 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.10–4.19 (m, 2q merged, 4H, $2 \times OCH_2$), 5.35, 5.39 (d, 1H, $J = 7.4$ Hz, CH), 5.42, 5.46 (d, 1H, $J = 7.4$ Hz, CH), 6.73 (s, 1H, =CH), 6.74 (s, 1H, =CH), 6.85–6.87 (m, 8H, Ar–H), 7.31, 7.34 (dd, 4H, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, Ar–H), 7.50, 7.51 (d, 2H, $J = 1.8$ Hz, Ar–H), 7.66, 7.70 (d, 2H, $J = 8.4$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 14.43$, 45.54, 46.94, 51.04, 53.96, 56.62, 59.62, 59.61, 61.76, 70.34, 103.34, 114.94, 118.91, 127.30, 127.95, 130.68, 132.13, 134.03, 136.69, 145.55, 153.64, 160.35, 171.14, 173.04; Mass (ES+) m/z 534.53 (M^++1), 556.80 (M^++Na). Oxalate salt: mp 95–98 °C; Anal. [$C_{26}H_{29}Cl_2N_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.44. 2-[4-(4-Fluoro-phenyl)-piperazin-1-ylmethyl]-3-hydroxy-3-(3-phenyl-isoxazol-5-yl)-propionic acid ethyl ester (4A1B2C4) (3:1)

The product was obtained as pale yellow oil (58%): IR (neat, cm^{-1}) 1730 (CO_2Et), 3401 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.16$–1.27 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.67–2.93 (m, 12H, $6 \times NCH_2$), 3.12–3.21 (m, 10H, $4 \times NCH_2$ and $2 \times CH$), 4.09–4.16 (m, 2q merged, 4H, $2 \times OCH_2$), 5.35, 5.38 (d, 1H, $J = 7.6$ Hz, CH), 5.42, 5.45 (d, 1H, $J = 7.6$ Hz, CH), 6.57 (s, 1H, =CH), 6.59 (s, 1H, =CH), 6.82–7.01 (m, 8H, Ar–H), 7.43–7.46 (m, 6H, Ar–H), 7.77–7.82 (m, 4H, Ar–H); Mass (ES+) m/z 476.07 (M^++Na). Oxalate salt: mp 146–148 °C; Anal. $C_{25}H_{28}FN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.45. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-[4-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-3-hydroxy-propionic acid ethyl ester (4A3B2C4) (5:1)

The product was obtained as pale yellow oil (51%): IR (neat, cm^{-1}) 1729 (CO_2Et), 3422 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.16$–1.27 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.67–2.93 (m, 6H, $3 \times NCH_2$), 3.11–3.21 (m, 5H, $2 \times NCH_2$ and CH), 4.08–4.16 (m, 2q merged, 4H, $2 \times OCH_2$), 5.12 (s, 2H, OCH_2), 5.34, 5.38 (d, 1H, $J = 7.6$ Hz, CH), 6.54 (s, 1H, =CH), 6.82–7.06 (m, 7H, Ar–H), 7.33–7.46 (m, 4H, Ar–H), 7.71, 7.75 (d, 2H, $J = 8.6$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 14.54$, 46.89, 50.59, 52.69, 53.82, 59.32, 70.26, 70.48, 100.04, 115.69, 116.25, 114.47, 118.61, 122.18, 127.88, 128.53, 128.68, 129.06, 137.02, 155.45, 160.22, 160.64, 162.20, 171.81, 173.27; Mass (ESMS) m/z 559.67 (M^++1), 582.73 (M^++Na). Oxalate salt: mp 126–128 °C; Anal. [$C_{32}H_{34}FN_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.46. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-[4-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-3-hydroxy-propionic acid ethyl ester (4A4B2C4) (6:1)

The product was obtained as pale yellow oil (59%): IR (neat, cm^{-1}) 1736 (CO_2Et), 3435 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.15$–1.28 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.66–2.93 (m, 12H, $6 \times NCH_2$), 3.13–3.21 (m, 10H, $4 \times NCH_2$ and $2 \times CH$), 4.08–4.17 (m, 2q merged, 4H, $2 \times OCH_2$), 5.33, 5.36 (d, 1H, $J = 7.6$ Hz, CH), 5.41, 5.44 (d, 1H, $J = 7.6$ Hz, CH), 6.52 (s, 1H, =CH), 6.56 (s, 1H, =CH), 6.81–7.02 (m, 8H, Ar–H), 7.43–7.67 (m, 8H, Ar–H); Mass (ES+) m/z 488.87 (M^++1). Oxalate salt: mp 149–150 °C; Anal. [$C_{25}H_{27}ClFN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.47. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-2-[4-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-3-hydroxy-propionic acid ethyl ester (4A5B2C4) (6:1)

The product was obtained as pale yellow oil (61%): IR (neat, cm^{-1}) 1739 (CO_2Et), 3445 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.16$–1.27 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.67–2.93 (m, 12H, $6 \times NCH_2$), 3.12–3.20 (m, 10H, $4 \times NCH_2$ and $2 \times CH$), 4.13 (m, 2q merged, 4H, $2 \times OCH_2$), 5.34, 5.37 (d, 1H, $J = 7.6$ Hz, CH), 5.41, 5.44 (d, 1H, $J = 7.6$ Hz, CH), 6.53 (s, 1H, =CH), 6.56 (s, 1H, =CH), 6.84–7.01 (m, 8H, Ar–H), 7.40, 7.44 (d, 4H, $J = 8.6$ Hz, Ar–H), 7.71, 7.75 (d, 4H, $J = 8.6$ Hz, Ar–H); Mass (ES+) m/z 488.00 (M^++1), 509.93 (M^++Na). Oxalate salt: mp 180–182 °C; Anal. [$C_{25}H_{27}ClFN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.48. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-2-[4-(4-fluoro-phenyl)-piperazin-1-ylmethyl]-3-hydroxy-propionic acid ethyl ester (4A6B2C4) (6:1)

The product was obtained as pale yellow oil (59%): IR (neat, cm^{-1}) 1729 (CO_2Et), 3383 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.16$–1.28 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.68–2.94 (m, 12H, $6 \times NCH_2$), 3.12–3.22 (m, 10H, $4 \times NCH_2$ and $2 \times CH$), 4.13 (m, 2q merged, 4H, $2 \times OCH_2$), 5.36, 5.39 (d, 1H, $J = 7.6$ Hz, CH), 5.42, 5.45 (d, 1H, $J = 7.6$ Hz, CH), 6.71 (s, 1H, =CH), 6.73 (s, 1H, =CH), 6.83–7.01 (m, 8H, Ar–H),

7.31, 7.36 (dd, 4H, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, Ar–H), 7.50, 7.51 (d, 2H, $J = 1.8$ Hz, Ar–H), 7.66–7.70 (d, 2H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 522.07 (M^++1), 544.33 (M^++Na). Oxalate salt: mp 167–168 °C; Anal. [$C_{25}H_{26}Cl_2FN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.49. 3-Hydroxy-2-[4-(3-phenyl-allyl)-piperazin-1-yl-methyl]-3-(3-phenyl-isoxazol-5-yl)-propionic acid ethyl ester (4A1B2C5) (6:1)

The product was obtained as pale yellow oil (58%): IR (neat, cm^{-1}) 1731 (CO_2Et), 3381 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.14$–1.27 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.44–2.88 (m, 22H, $10 \times NCH_2$ and $2 \times CH$), 3.15–3.19 (m, 4H, $2 \times NCH_2$), 4.10 (m, 2q merged, 4H, $2 \times OCH_2$), 5.31, 5.35 (d, 1H, $J = 7.0$ Hz, CH), 5.38, 5.41 (d, 1H, $J = 7.0$ Hz, CH), 6.19–6.48 (m, 2t merged, 2H, $J = 8.4$ Hz, $2 \times$=CH), 6.48 (s, 2H, $2 \times$=CH), 6.57 (s, 1H, =CH), 6.58 (s, 1H, =CH), 7.22–7.45 (m, 16H, Ar–H), 7.77–7.81 (m, 4H, Ar–H); Mass (ES+) m/z 476.47 (M^++1), 498.07 (M^++Na). Oxalate salt: mp 192–194 °C (dec); Anal. [$C_{28}H_{33}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.50. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-3-hydroxy-2-[4-(3-phenyl-allyl)-piperazin-1-ylmethyl]-propionic acid ethyl ester (4A3B2C5) (6:1)

The product was obtained as pale yellow oil (58%): IR (neat, cm^{-1}) 1731 (CO_2Et), 3381 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.14$–1.30 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.57–2.88 (m, 22H, $10 \times NCH_2$ and $2 \times CH$), 3.11–3.17 (m, 4H, $2 \times NCH_2$), 4.05–4.17 (m, 2q merged, 4H, $2 \times OCH_2$), 5.11 (s, 4H, $2 \times OCH_2O$), 5.30, 5.33 (d, 1H, $J = 7.6$ Hz, CH), 5.35, 5.38 (d, 1H, $J = 7.6$ Hz, CH), 6.19–6.30 (m, 2t merged, 2H, $J = 6.6$ Hz, $2 \times$=CH), 6.48 (s, 2H, $2 \times$=CH), 6.52 (s, 1H, =CH), 6.57 (s, 1H, =CH), 7.01, 7.05 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.22–7.45 (m, 20H, Ar–H), 7.70–7.74 (d, 4H, $J = 8.4$ Hz, Ar–H); Mass (FAB+) m/z 582 (M^++1). Oxalate salt: mp 205–206 °C; Anal. [$C_{35}H_{39}N_3O_5 \cdot 2(CO_2H)_2$] C, H, N.

5.51. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-[4-(3-phenyl-allyl)-piperazin-1-ylmethyl]-propionic acid ethyl ester (4A4B2C5) (6:1)

The product was obtained as pale yellow oil (62%): IR (neat, cm^{-1}) 1735 (CO_2Et), 3445 (OH); ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 1.16$–1.27 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.50–2.91 (m, 22H, $10 \times NCH_2$ and $2 \times CH$), 3.13–3.17 (m, 4H, $2 \times NCH_2$), 4.07–4.14 (m, 2q merged, 4H, $2 \times OCH_2$), 5.31, 5.34 (d, 1H, $J = 7.6$ Hz, CH), 5.28–5.38 (m, 2H, $2 \times CH$), 6.12–6.30 (m, 2t merged, 2H, $2 \times$=CH), 6.48 (s, 2H, $2 \times$=CH), 6.55 (s, 1H, =CH), 6.60 (s, 1H, =CH), 6.75–6.85 (m, 8H, Ar–H), 7.30–7.67 (m, 18H, Ar–H); Mass (ES+) m/z 511.00 (M^++1). Oxalate salt: mp 197–199 °C; Anal. [$C_{28}H_{32}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.52. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-[4-(3-phenyl-allyl)-piperazin-1-ylmethyl]-propionic acid ethyl ester (4A5B2C5) (6:1)

The product was obtained as pale yellow oil (58%): IR (neat, cm^{-1}) 1730 (CO_2Et), 3328 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.13$–1.28 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.57–2.82 (m, 22H, $10 \times NCH_2$ and $2 \times CH$), 3.14–3.17 (m, 4H, $2 \times NCH_2$), 4.07–4.14 (m, 2q merged, 4H, $2 \times OCH_2$), 5.30, 5.33 (d, 1H, $J = 7.6$ Hz, CH), 5.28–5.38 (m, 2H, $2 \times CH$), 6.12–6.29 (m, 2t merged, 2H, $2 \times$=CH), 6.48 (s, 2H, $2 \times$=CH), 6.54 (s, 1H, =CH), 6.55 (s, 1H, =CH), 7.22–7.43 (m, 14H, Ar–H), 7.70–7.74 (d, 4H, $J = 8.4$ Hz, Ar–H); Mass (FAB+) m/z 510 (M^++1). Oxalate salt: mp 207–209 °C; Anal. [$C_{28}H_{32}ClN_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.53. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-[4-(3-phenyl-allyl)-piperazin-1-ylmethyl]-propionic acid ethyl ester (4A6B2C5) (6:1)

The product was obtained as pale yellow oil (58%): IR (neat, cm^{-1}) 1730 (CO_2Et), 3358 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.14$–1.28 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.57–2.87 (m, 22H, $10 \times NCH_2$ and $2 \times CH$), 3.14–3.17 (m, 4H, $2 \times NCH_2$), 4.05–4.21 (m, 2q merged, 4H, $2 \times OCH_2$), 5.32, 5.36 (d, 1H, $J = 7.6$ Hz, CH), 5.40, 5.44 (d, 1H, $J = 7.6$ Hz, CH), 5.28–5.38 (m, 2H, $2 \times CH$), 6.19–6.30 (m, 2t merged, 2H, $2 \times$=CH), 6.48 (s, 2H, $2 \times$=CH), 6.69 (s, 1H, =CH), 6.71 (s, 1H, =CH), 7.22–7.39 (m, 12H, Ar–H), 7.50, 7.51 (d, 2H, $J = 1.8$ Hz, Ar–H), 7.66-7.70 (d, 2H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 544.60 (M^++1), 566.93 (M^++Na). Oxalate salt: mp 207–209 °C; Anal. [$C_{28}H_{31}Cl_2N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.54. 2-(4-Benzyl-piperidin-1-ylmethyl)-3-hydroxy-3-(3-phenyl-isoxazol-5-yl)-propionic acid ethyl ester (4A1B2C6)

The product was obtained as pale yellow oil (51%): IR (neat, cm^{-1}) 1732 (CO_2Et), 3384 (OH); Mass (ES+) m/z 449.80 (M^++1), 471.47 (M^++Na). Oxalate salt: mp 103–104 °C. Anal. [$C_{27}H_{32}N_2O_4 \cdot (CO_2H)_2$] C, H, N.

5.55. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-(4-benzyl-piperidin-1-ylmethyl)-3-hydroxy-propionic acid ethyl ester (4A3B2C6)

The product was obtained as pale yellow oil (56%): IR (neat, cm^{-1}) 1730 (CO_2Et), 3418 (OH); Mass (ES+) m/z 449.80 (M^++1), 471.47 (M^++Na). Oxalate salt: mp 103–104 °C. Anal. [$C_{27}H_{32}N_2O_4 \cdot (CO_2H)_2$] C, H, N.

5.56. 2-(4-Benzyl-piperidin-1-ylmethyl)-3-[3-(2-chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-propionic acid ethyl ester (4A4B2C6)

The product was obtained as pale yellow oil (54%): IR (neat, cm^{-1}) 1729 (CO_2Et), 3358 (OH); Mass (FAB+)

m/z 483 (M^++1). Oxalate salt: mp 97–98 °C. Anal. [$C_{27}H_{31}ClN_2O_4 \cdot (CO_2H)_2$] C, H, N.

5.57. 2-(4-Benzyl-piperidin-1-ylmethyl)-3-[3-(4-chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-propionic acid ethyl ester (4A5B2C6)

The product was obtained as pale yellow oil (55%): IR (neat, cm^{-1}) 1729 (CO_2Et), 3380 (OH); Mass (ES+) m/z 471.73 ($M^+ + 1$). Oxalate salt: mp 150–153 °C. Anal. [$C_{27}H_{31}ClN_2O_4 \cdot (CO_2H)_2$] C, H, N.

5.58. 2-(4-Benzyl-piperidin-1-ylmethyl)-3-[3-(2,4-dichloro-phenyl)-isoxazol-5-yl]-3-hydroxy-propionic acid ethyl ester (4A6B2C6)

The product was obtained as pale yellow oil (54%): IR (neat, cm^{-1}) 1725 (CO_2Et), 3420 (OH); Mass (FAB+) m/z 505 ($M^+ + 1$). Oxalate salt: mp 95–98 °C. Anal. [$C_{27}H_{30}Cl_2N_2O_4 \cdot (CO_2H)_2$] C, H, N.

5.59. 2-Diethylaminomethyl-3-hydroxy-3-(3-phenyl-isoxazol-5-yl)-propionic acid ethyl ester (4A1B2C7) (2:1)

The product was obtained as pale yellow oil (52%): IR (neat, cm^{-1}) 1732 (CO_2Et), 3381 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.04$–1.19 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.46–2.87 (m, 10H, $4 \times NCH_2$ and $2 \times CH$), 2.73–2.87 (m, 4H, $2 \times NCH_2$), 4.04–4.12 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 5.27, 5.31 (d, 1H, $J = 7.0$ Hz, CH), 5.38, 5.41 (d, 1H, $J = 7.0$ Hz, CH), 6.46 (s, 1H, =CH), 6.58 (s, 1H, =CH), 7.42–7.45 (m, 6H, Ar–H), 7.77–7.81 (m, 4H, Ar–H); Mass (FAB+) m/z 347 (M^++1). Oxalate salt: mp 122–123 °C (dec); Anal. [$C_{19}H_{26}N_2O_4 \cdot (CO_2H)_2$] C, H, N.

5.60. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-diethyl-aminomethyl-3-hydroxy-propionic acid ethyl ester (4A3B2C7) (2:1)

The product was obtained as pale yellow oil (50%): IR (neat, cm^{-1}) 1725 (CO_2Et), 3354 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.99$–1.19 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.52–3.18 (m, 14H, $6 \times NCH_2$ and $2 \times CH$), 3.72–3.79 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 5.11 (s, 4H, $2 \times OCH_2O$), 5.28, 5.32 (d, 1H, $J = 7.0$ Hz, CH), 5.36, 5.39 (d, 1H, $J = 7.0$ Hz, CH), 6.45 (s, 1H, =CH), 6.52 (s, 1H, =CH), 7.01, 7.05 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.32–7.42 (m, 10H, Ar–H), 7.70–7.74 (d, 4H, $J = 8.4$ Hz, Ar–H); Mass (ES+) m/z 452.73 (M^++1), 474.60 (M^++Na). Oxalate salt: mp 150–152 °C (dec); Anal. [$C_{26}H_{32}N_2O_5 \cdot (CO_2H)_2$] C, H, N.

5.61. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-diethyl-aminomethyl-3-hydroxy-propionic acid ethyl ester (4A4B2C7) (2:1)

The product was obtained as pale yellow oil (55%): IR (neat, cm^{-1}) 1730 (CO_2Et), 3421 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.00$–1.19 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.51–3.15 (m, 14H, $6 \times NCH_2$ and $2 \times CH$), 3.72–3.80 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 5.30, 5.34 (d, 1H, $J = 7.0$ Hz, CH), 5.38, 5.42 (d, 1H, $J = 7.0$ Hz, CH), 6.47 (s, 1H, =CH), 6.55 (s, 1H, =CH), 7.46–7.68 (m, 8H, Ar–H); Mass (ES+) m/z 381.80 (M^++1). Oxalate salt: mp 101–102 °C (dec); Anal. [$C_{19}H_{25}ClN_2O_4 \cdot (CO_2H)_2$] C, H, N.

5.62. 3-[3-(4-Chloro-phenyl)-isoxazol-5-yl]-2-diethyl-aminomethyl-3-hydroxy-propionic acid ethyl ester (4A5B2C7) (2:1)

The product was obtained as pale yellow oil (50%): IR (neat, cm^{-1}) 1728 (CO_2Et), 3368 (OH); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.00$–1.15 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.46–2.56 (m, 4H, $2 \times NCH_2$), 2.69–2.87 (m, 6H, $2 \times NCH_2$ and $2 \times CH$), 3.09–3.19 (m, 4H, $2 \times NCH_2$), 3.72–3.79 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 5.27, 5.31 (d, 1H, $J = 7.8$ Hz, CH), 5.41, 5.45 (d, 1H, $J = 7.8$ Hz, CH), 6.46 (s, 1H, =CH), 6.55 (s, 1H, =CH), 7.39, 7.43 (d, 4H, $J = 8.4$ Hz, Ar–H), 7.71, 7.75 (d, 4H, $J = 8.4$ Hz, Ar–H); Mass (FAB+) m/z 381 (M^++1). Oxalate salt: mp 150–152 °C (dec); Anal. [$C_{19}H_{25}ClN_2O_4 \cdot (CO_2H)_2$] C, H, N.

5.63. 3-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-2-diethyl-aminomethyl-3-hydroxy-propionic acid ethyl ester (4A6B2C7)

ND.

5.64. 2-(4-Methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-acrylic acid methyl ester [*E*+*Z*(15%)] (5A1B1C1)

The product was obtained as pale yellow oil (58%); IR (neat, cm^{-1}) 1718 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.27$ (s, 3H, NCH_3), 2.29 (s, 3H, NCH_3), 2.44 (br s, 8H, $4 \times NCH_2$), 2.58 (br s, 8H, $4 \times NCH_2$), 3.36 (s, 2H, NCH_2), 3.63 (s, 2H, NCH_2), 3.86 (s, 6H, $2 \times CO_2\ CH_3$), 6.82 (s, 1H, =CH), 6.86 (s, 1H, =CH), 7.01 (s, 1H, =CH), 7.47–7.49 (m, 6H, Ar–H), 7.62 (s, 1H, =CH), 7.80–7.84 (m, 4H, Ar–H); Mass (FAB+) m/z 342 (M^++1). Oxalate salt: mp 202–203 °C; Anal. [$C_{19}H_{23}N_3O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.65. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-acrylic acid methyl ester (*E*) (5A3B1C1)

The product was obtained as pale yellow oil (55%); IR (neat, cm^{-1}) 1707 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.28 (s, 3H, NCH_3), 2.32–2.66 (m, 8H, $4 \times NCH_2$), 3.63 (s, 2H, NCH_2), 3.85 (s, 3H, CO_2CH_3), 5.13 (s, 2H, OCH_2O), 6.94 (s, 1H, =CH), 7.05, 7.09 (d, 2H, $J = 8.6$ Hz, Ar–H), 7.36–7.43 (m, 5H, Ar–H), 7.60 (s, 1H, =CH), 7.73, 7.77 (d, 2H, $J = 8.6$ Hz, Ar–H); Mass (ES+) m/z 447.93 (M^++1), 469.60 (M^++Na).

Oxalate salt: mp 180–182 °C; Anal. [$C_{26}H_{29}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.66. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-acrylic acid methyl ester (5A4B1C1) [*E*+*Z*(25%)]

The product was obtained as pale yellow oil (57%); IR (neat, cm^{-1}) 1720 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.26$ (s, 3H, NCH_3), 2.30 (s, 3H, NCH_3), 2.43 (br s, 8H, $4 \times NCH_2$), 2.58 (br s, 8H, $4 \times NCH_2$), 3.36 (s, 2H, NCH_2), 3.59 (s, 2H, NCH_2), 3.86 (s, 6H, $2 \times CO_2$ CH_3), 6.78 (s, 1H, =CH), 6.96 (s, 1H, =CH), 7.29 (s, 1H, =CH), 7.35–7.42 (m, 2H, Ar–H), 7.45–7.52 (m, 1H, Ar–H), 7.67 (s, 1H, =CH), 7.78–7.83 (m, 1H, Ar–H); Mass (ES+) m/z 375.80 (M^++1), 397.80 (M^++Na). Oxalate salt: mp 188–190 °C; Anal. [$C_{19}H_{22}ClN_3O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.67. 2-(4-Methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-acrylic acid ethyl ester (5A1B2C1) [*E*+*Z*(15%)]

The product was obtained as pale yellow oil (57%); IR (neat, cm^{-1}) 1714 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.25$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.36 (t, 3H, $J = 7.2$ Hz, CH_3), 2.33 (s, 3H, NCH_3), 2.35 (s, 3H, NCH_3), 2.43–2.66 (m, 16H, $8 \times NCH_2$), 3.37 (s, 2H, NCH_2), 3.66 (s, 2H, NCH_2), 4.12 (q, 2H, $J = 7.0$ Hz, OCH_2), 4.30 (q, 2H, $J = 7.0$ Hz, OCH_2), 6.79 (s, 1H, =CH), 6.86 (s, 1H, =CH), 6.97 (s, 1H, =CH), 7.43–7.50 (m, 6H, Ar–H), 7.60 (s, 1H, =CH), 7.78–7.84 (m, 4H, Ar–H). Mass (FAB+) m/z 356 (M^++1). Oxalate salt: mp 177–179 °C; Anal. [$C_{20}H_{25}N_3O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.68. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-acrylic acid ethyl ester (5A3B2C1) (*E*)

The product was obtained as pale yellow oil (56%); IR (neat, cm^{-1}) 1703 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.36$ (t, 3H, $J = 7.1$ Hz, CH_3), 2.28 (s, 3H, NCH_3), 2.40–2.60 (m, 8H, $4 \times NCH_2$), 3.63 (s, 2H, NCH_2), 4.30 (q, 2H, $J = 7.2$ Hz, OCH_2), 5.13 (s, 2H, OCH_2 O), 6.94 (s, 1H, =CH), 7.05, 7.09 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.33–7.45 (m, 5H, Ar–H), 7.60 (s, 1H, =CH), 7.73, 7.77 (d, 2H, $J = 8.8$ Hz, Ar–H); Mass (ES+) m/z 462.07 (M^++1), 484.20 (M^++Na). Oxalate salt: mp 188–190 °C; Anal. [$C_{27}H_{31}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.69. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-acrylic acid ethyl ester (5A4B2C1) [*E*+*Z*(20%)]

The product was obtained as pale yellow oil (61%); IR (neat, cm^{-1}) 1718 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.25$–1.39 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 2.26 (s, 3H, NCH_3), 2.29 (s, 3H, NCH_3), 2.43 (br s, 8H, $4 \times NCH_2$), 2.58 (br s, 8H, $4 \times NCH_2$), 3.36 (s, 2H, NCH_2), 3.58 (s, 2H, NCH_2), 4.25–4.35 (m, 2q merged, 4H, $J = 7.0$ Hz, $2 \times OCH_2$), 6.74 (s, 1H, =CH), 6.95 (s, 1H, =CH), 7.29 (s, 1H, =CH), 7.34–7.52 (m, 6H, Ar–H), 7.67 (s, 1H, =CH), 7.79–7.83 (m, 2H, Ar–H). Mass (ES+) m/z 390.20 (M^++1), 411.87 (M^++Na). Oxalate salt: mp 177–179 °C; Anal. [$C_{20}H_{24}ClN_3O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.70. 2-(4-Methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-acrylic acid butyl ester (5A1B3C1) [*E*+*Z*(15%)]

The product was obtained as pale yellow oil (61%); IR (neat, cm^{-1}) 1715 (CO_2Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.89$–1.01 (m, 2t merged, 6H, $J = 7.2$ Hz, $2 \times CH_3$), 1.40–1.55 (m, 4H, $2 \times CH_2$), 1.68–1.78 (m, 4H, $2 \times CH_2$), 2.27 (s, 3H, NCH_3), 2.29 (s, 3H, NCH_3), 2.44 (br s, 8H, $4 \times NCH_2$), 2.59 (br s, 8H, $4 \times NCH_2$), 3.35 (s, 2H, CH_2), 3.62 (s, 2H, CH_2), 4.22–4.31 (m, 2t merged, 4H, $J = 6.4$ Hz, OCH_2), 6.74 (s, 1H, =CH), 6.86 (s, 1H, =CH), 7.01 (s, 1H, =CH), 7.43–7.50 (m, 6H, Ar–H), 7.61 (s, 1H, =CH), 7.80-7.85 (m, 4H, A–Hr); Mass (FAB+) m/z 384 (M^++1). Oxalate salt: mp 192–194 °C; Anal. [$C_{22}H_{29}N_3O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.71. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-acrylic acid butyl ester (5A3B3C1) [*E*+*Z*(15%)]

The product was obtained as pale yellow oil (62%); IR (neat, cm^{-1}) 1715 (CO_2Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.93$ (t, 3H, $J = 7.2$ Hz, $2 \times CH_3$), 1.40–1.51 (m, 2H, $2 \times CH_2$), 1.64–1.74 (m, 2H, $2 \times CH_2$), 2.28 (s, 3H, NCH_3), 2.30 (s, 3H, NCH_3), 2.31–2.62 (m, 2×4H, NCH_2), 3.62 (s, 2H, CH_2), 3.85 (s, 2H, CH_2), 4.25 (t, 2×2H, OCH_2, $J = 6.5$ Hz), 5.12 (s, 2H, OCH_2 O), 5.13 (s, 2H, CH_2Ph), 6.80 (s, 1H, CH), 6.93 (s, 1H, =CH), 7.05, 7.09 (d, 2×2H, $J = 8.8$ Hz, Ar–H), 7.34–7.43 (m, 10H, Ar–H), 7.72, 7.76 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.73, 7.77 (d, 2H, $J = 8.8$ Hz, Ar–H). Mass (ES+) m/z 490.07 (M^++1), 511.93 (M^++Na). Oxalate salt: mp 153–155 °C; Anal. [$C_{29}H_{35}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.72. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-acrylic acid butyl ester (5A4B3C1) [*E*+*Z*(15%)]

The product was obtained as pale yellow oil (60%); IR (neat, cm^{-1}) 1716 (CO_2 Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.98$ (t, 6H, J = 7.2 Hz, $2 \times CH_3$), 1.40–1.47 (m, 4H, $2 \times CH_2$), 1.64–1.75 (m, 4H, $2 \times CH_2$), 2.26 (s,3H, NCH_3), 2.29 (s, 3H, NCH_3), 2.43 (br s, 8H, $2 \times 4NCH_2$), 2.57 (br s, 8H, $2 \times NCH_2$), 3.35 (s, 2H, NCH_2), 3.58 (s, 2H, NCH_2), 4.26 (q, 4H, $J = 6.6$ Hz, $2 \times OCH_2$), 6.73 (s, 1H, CH), 6.95 (s, 1H, =CH), 7.28 (s, 1H, =CH), 7.34–7.51(m, 6H, Ar–H), 7.65 (s, 1H, =CH), 7.79–7.83 (m, 2H, Ar–H). Mass (ES+) m/z 439.87 (M^++Na). Oxalate salt: mp 193–195 °C; Anal. [$C_{22}H_{28}ClN_3O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.73. 2-(4-Methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-acrylonitrile (5A1B5C1) (*Z*)

The product was obtained as pale yellow oil (59%); IR (neat, cm^{-1}) 2220 (CN); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.32$ (s, 3H, NCH_3), 2.40–2.70 (m, 8H, $4 \times NCH_2$), 3.34 (s, 2H, NCH_2), 7.25 (s, 1H, =CH), 7.37 (s, 1H, =CH), 7.46–7.49 (m, 3H, Ar–H), 7.83–7.88 (m, 2H, Ar–H); Mass (FAB+) m/z 309 (M^++1). Oxalate salt: mp 205–207 °C; Anal. [$C_{18}H_{20}N_4O{\cdot}2(CO_2H)_2$] C, H, N.

5.74. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-acrylonitrile (5A3B5C1) (*Z*)

The product was obtained as pale yellow oil (59%); IR (neat, cm^{-1}) 2218 (CN); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.31$ (s, 3H, NCH_3), 2.42–2.64 (m, 8H, $4 \times NCH_2$), 3.32 (s, 2H, CH_2), 5.13 (s, 2H, OCH_2O), 7.04, 7.08 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.22–7.43 (m, 6H, 5Ar–H and =CH), 7.77, 7.81 (d, 2H, $J = 8.8$ Hz, Ar); Mass (ES+) m/z 436.60 (M^++Na). Oxalate salt: mp 207–208 °C; Anal. [$C_{25}H_{26}N_4O_2{\cdot}2(CO_2H)_2$] C, H, N.

5.75. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl) acrylonitrile (5A4B5C1) (*Z*)

The product was obtained as pale yellow oil (61%); IR (neat, cm^{-1}) 2218 (CN); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.23$ (s, 3H, NCH_3), 2.40–2.61 (m, 8H,, NCH_3), 3.34 (s, 2H, NCH_2), 7.36–7.54 (m, 4H, 2Ar–H merged with $2 \times$ =CH), 7.71–7.76 (m, 2H, Ar–H). Mass (ES+) m/z 447.93 (M^++1), 469.60 (M^++Na). Oxalate salt: mp 190–192 °C; Anal. [$C_{18}H_{19}ClN_4O{\cdot}2(CO_2H)_2$] C, H, N.

5.76. 2-(4-Methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-propionic acid methyl ester (7A1B1C1)

The product was obtained as pale yellow oil (71%); IR (neat, cm^{-1}) 1734 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.28$ (s, 3H, NCH_3), 2.43–2.68 (m, 10H, $5 \times NCH_2$), 3.08 (br s, 3H, CH and CH_2), 3.68 (s, 3H, CO_2CH_3), 6.33 (s, 1H, =CH), 7.42–7.45 (m, 3H, Ar–H), 7.75–7.80 (m, 2H, Ar); Mass (FAB+) m/z 344 (M^++1). Oxalate salt: mp194–195 °C; Anal. [$C_{19}H_{25}N_3O_3{\cdot}2(CO_2H)_2$] C, H, N.

5.77. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid methyl ester (7A3B1C1)

The product was obtained as pale yellow oil (68%); IR (neat, cm^{-1}) 1732 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.28$ (s, 3H, NCH_3), 2.36–2.66 (m, 10H, $5 \times NCH_2$), 3.09 (br s, 3H, CH and CH_2), 3.68 (s, 3H, CO_2 CH_3), 5.11 (s, 2H, OCH_2 O), 6.26 (s, 1H, =CH), 7.01, 7.05 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.32–7.51 (m, 5H, Ar–H), 7.69, 7.73 (d, 2H, $J = 8.7$ Hz, Ar–H); Mass (ES+) m/z 472.87 (M^++Na). Oxalate salt: mp 197–198 °C; Anal. [$C_{26}H_{31}N_3O_4{\cdot}2(CO_2H)_2$] C, H, N.

5.78. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid methyl ester (7A4B1C1)

The product was obtained as pale yellow oil (72%); IR (neat, cm^{-1}) 1736 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 2.29$ (s, 3H, NCH_3), 2.46–2.70 (m, 10H, $5 \times NCH_2$), 3.13 (br s, 3H, CH and CH_2), 3.69 (s, 3H, OCH_3), 6.49 (s, 1H, =CH), 7.34–7.41 (m, 2H, Ar–H), 7.46–7.50 (m, 1H, Ar–H), 7.69–7.74 (m, 1H, Ar–H); Mass (ES+) m/z 379.20 (M^++1), 401.00 (M^++Na). Oxalate salt: mp 190–191 °C; Anal. [$C_{19}H_{30}ClN_3O_3{\cdot}2(CO_2H)_2$] C, H, N.

5.79. 2-(4-Methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-propionic acid ethyl ester (7A1B2C1)

The product was obtained as colourless oil (63%); IR (neat, cm^{-1}) 1731 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.23$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.27 (s, 3H, NCH_3), 2.32–2.75 (m, 10H, $5 \times$ N CH_2), 3.07 (br s, 3H, CH and CH_2), 4.14 (q, 2H, $J = 7.1$ Hz, OCH_2), 6.33 (s, 1H, =CH), 7.42–7.45 (m, 3H, Ar–H), 7.75–7.80 (m, 2H, Ar–H); Mass (FAB+) m/z 358 (M^++1). Oxalate salt: mp 201–202 °C; Anal. [$C_{20}H_{27}N_3O_3{\cdot}2(CO_2H)_2$] C, H, N.

5.80. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid ethyl ester (7A3B2C1)

The product was obtained as pale yellow oil (68%); IR (neat, cm^{-1}) 1732 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.23$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.29 (s, 3H, NCH_3), 2.30–2.78 (m, 10H, $5 \times$ N CH_2 and CH), 3.07 (br s, 3H, CH and CH_2), 4.14 (q, 2H, $J = 7.1$ Hz, OCH_2), 5.11 (s, 2H, OCH_2 O), 6.27 (s, 1H, =CH), 7.01, 7.05 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.32–7.65 (m, 5H, Ar), 7.68, 7.72 (d, 2H, $J = 8.8$ Hz, Ar–H); Mass (ES+) m/z 464.13 (M^++1), 485.8 (M^++Na). Oxalate salt: mp 203–204 °C; Anal. [$C_{27}H_{33}N_3O_4{\cdot}2(CO_2H)_2$] C, H, N.

5.81. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid ethyl ester (7A4B2C1)

The product was obtained as yellow oil (65%); IR (neat, cm^{-1}) 1732 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.24$ (t, 3H, $J = 7.2$ Hz, CH_3), 2.27 (s, 3H, NCH_3), 2.42–2.57 (m, 10H, $5 \times NCH_2$), 3.16 (m, 3H, CH_2), 4.15 (q, 2H, $J = 7.1$ Hz, OCH_2), 6.49 (s, 1H, =CH), 7.34–7.38 (m, 2H, Ar–H), 7.46–7.50 (m, 1H, Ar–H,), 7.69–7.74 (m, 1H, Ar–H); Mass (FAB+) m/z 392 (M^++1). Oxalate salt: mp 202–203 °C; Anal. [$C_{20}H_{26}ClN_3O_3{\cdot}2$ $(CO_2H)_2$] C, H, N.

5.82. 2-(4-Methyl-piperazin-1-ylmethyl)-3-(3-phenyl-isoxazol-5-yl)-propionic acid butyl ester (7A1B3C1)

The product was obtained as light brown oil (67%); IR (neat, cm^{-1}) 1728 (CO_2 Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.88$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.28–1.39 (m, 4H, CH_2), 1.51–1.61 (m, 2H, CH_2), 2.27 (s, 3H, NCH_3), 2.43–2.69 (m, 10H, $5 \times NCH_2$), 3.07–3.16 (m, 3H, CH and CH_2), 4.09 (t, 2H, $J = 6.5$ Hz, OCH_2), 6.33 (s, 1H, =CH), 7.42–7.45 (m, 3H, Ar–H), 7.75–7.79 (m, 2H, Ar–H); Mass (FAB+) *m/z* 386 (M^++1). Oxalate salt: mp 190–191 °C; Anal. [$C_{22}H_{31}N_3O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.83. 3-[3-(4-Benzyloxy-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid butyl ester (7A3B3C1)

The product was obtained as light brown oil (67%); IR (neat, cm^{-1}) 1731 (CO_2 Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.88$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.25–1.39 (m, 2H, CH_2), 1.50–1.66 (m, 2H, CH_2), 2.28 (s, 3H, NCH_3), 2.31–2.69 (m, 10H, $5 \times NCH_2$), 3.07 (br s, 3H, CH and CH_2), 4.09 (t, 2H, $J = 6.4$ Hz, OCH_2), 5.11 (s, 2H, OCH_2 O), 6.26 (s,1H, =CH) 7.01, 7.05 (d, 2H, Ar, $J = 8.8$ Hz), 7.33–7.42 (m, 5H, Ar–H), 7.68, 7.72 (d, 2H, $J = 8.8$ Hz, Ar–H); Mass (FAB+) *m/z* 492 (M^++1). Oxalate salt: mp 193–194 °C; Anal. [$C_{29}H_{37}N_3O_4 \cdot 2(CO_2H)_2$] C, H, N.

5.84. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-2-(4-methyl-piperazin-1-ylmethyl)-propionic acid butyl ester (7A4B3C1)

The product was obtained as brown oil (69%); IR (neat, cm^{-1}) 1733 (CO_2 Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.89$ (m, 3H, CH_3), 1.25–1.40 (m, 4H, CH_2), 2.28 (s, 3H, NCH_3), 2.43–2.70 (m, 10H, $5 \times NCH_2$), 3.09 (br s, 3H, CH and CH_2), 4.09 (t, 2H, $J = 6.6$ Hz, OCH_2), 6.49 (s, 1H, =CH), 7.33–7.41 (m, 2H, Ar–H), 7.46–7.50 (m, 1H, Ar–H), 7.69-7.74 (m, 1H, Ar–H); Mass (FAB+) *m/z* 420 (M^++1). Oxalate salt: mp 195–196 °C; Anal. [$C_{22}H_{30}ClN_3O_3 \cdot 2(CO_2H)_2$] C, H, N.

5.85. Acetylation—general procedure

To a stirred solution of appropriate compound from **2** (3.25 mmol) in dry dichloromethane (5 mL) was added pyridine (0.48 mL, 6.0 mmol) followed by a dropwise addition of solution of acetyl chloride (0.46 mL, 6.5 mmol) in dry dichloromethane (3 mL) at 0 °C. After the addition was complete, the reaction was continued at rt for 1 h. The reaction mixture was extracted with dichloromethane (2×30 mL) and water (50 mL). The organic layers were combined, washed with brine, dried over anhyd Na_2SO_4 and evaporated to obtain an oily residue. The residue was purified on a small band of silica gel using hexane/ethyl acetate (85:15, v/v) as eluent to obtain pure acetates **3**.

5.86. DABCO-mediated reaction of $NaBH_4$ with acetate of Baylis–Hillman adducts—general procedure

To the solution of appropriate acetate **3** (2 mmol) in THF/water (3 mL, 1:1, v/v) was added DABCO (0.22 g, 2 mmol) and the reaction was allowed to proceed at rt. As soon as the solution becomes clear (ca 15 min), $NaBH_4$ (0.08 g, 2 mmol) was added with stirring. The reaction was complete in 15 min, after which the reaction mixture was extracted with ethyl acetate (2×30 mL). The organic layers were combined, dried over anhyd Na_2 SO_4 and evaporated to obtain compounds **6** in sufficiently pure form. In few cases the analytical sample was prepared by column chromatography over silica gel using hexane/ethyl acetate (85:15, v/v) as eluent.

5.87. 2-(3-Phenyl-isoxazol-5-ylmethyl)-acrylic acid methyl ester (6A1B1)

The product was obtained as colourless oil (81%); IR (neat, cm^{-1}) 1721 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 3.79$ (s, 3H, CO_2 CH_3), 3.84 (s, 2H, CH_2), 5.77 (s, 1H, $=CH_2$), 6.36 (s, 1H, $=CH_2$), 6.39 (s, 1H, =CH), 7.42–7.45 (m, 3H, Ar–H), 7.76–7.81 (m, 3H, Ar–H); Mass (FAB+) *m/z* 244 (M^++1); Anal. [$C_{14}H_{13}NO_3$] C, H, N.

5.88. 2-[3-(4-Benzyloxy-phenyl)-isoxazol-5-ylmethyl]-acrylic acid methyl ester (6A3B1)

The product was obtained as a white solid (89%); mp 90–92 °C; IR (KBr, cm^{-1}) 1718 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 3.78$ (s, 3H, CO_2CH_3), 3.82 (s, 2H, CH_2), 5.11 (s, 2H, OCH_2O), 5.76 (s, 1H, $=CH_2$), 6.30 (s, 1H, $=CH_2$), 6.38 (s, 1H, =CH), 7.01, 7.05 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.33–7.42 (m, 5H, Ar–H), 7.70, 7.74 (d, 2H, $J = 8.8$ Hz Ar–H); Mass (FAB+) *m/z* 350 (M^++1); Anal. [$C_{21}H_{19}NO_4$] C, H, N.

5.89. 2-[3-(2-Chloro-phenyl)-isoxazol-5-ylmethyl]-acrylic acid methyl ester (6A4B1)

The product was obtained as colourless oil (99%); IR (neat, cm^{-1}) 1722 (CO_2Me); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 3.79$ (s, 3H, CO_2 CH_3), 3.86 (s, 2H, CH_2), 5.77 (s, 1H, $=CH_2$), 6.39 (s, 1H $=CH_2$), 6.52 (s, 1H, =CH), 7.34–7.38 (m, 2H, Ar–H), 7.46–7.51 (m, 1H, Ar–H), 7.70–7.74 (m, 1H, Ar–H); Mass (FAB+) *m/z* 278 (M^++1); Anal. [$C_{14}H_{12}ClNO_3$] C, H, N.

5.90. 2-(3-Phenyl-isoxazol-5-ylmethyl)-acrylic acid ethyl ester (6A1B2)

The product was obtained as colourless oil (82%); IR (neat, cm^{-1}) 1716 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.30$ (t, 3H, J= 7.2 Hz, CH_3), 3.83 (s, 2H, CH_2), 4.23 (q, 2H, $J = 7.2$ Hz, OCH_2); 5.75 (s, 1H, $=CH_2$), 6.36 (s, 1H, $=CH_2$), 6.38 (s, 1H, =CH), 7.42–7.45 (m,

3H, Ar–H), 7.76–7.80 (m, 2H, Ar–H); Mass (ES+) m/z 258.27 (M^++1), 280.40 (M^++Na); Anal. [$C_{15}H_{15}NO_3$] C, H, N.

5.91. 2-[3-(4-Benzyloxy-phenyl)-isoxazol-5-ylmethyl]-acrylic acid ethyl ester (6A3B2)

The product was obtained as colourless oil (99%); IR (neat, cm^{-1}) 1705 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.29$ (t, 3H, $J = 7.2$ Hz, CH_3), 4.22 (q, 2H, $J = 7.1$ Hz, OCH_2), 5.11 (s, 2H, OCH_2O), 5.74 (s, 1H, $=CH_2$), 6.30 (s, 1H, =CH), 6.37 (s, 1H, =CH), 7.01, 7.05 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.30-7.52 (m, 5H, Ar–H), 7.70, 7.74 (d, 2H, $J = 8.8$ Hz Ar–H); Mass (ES+) m/z 386.33 (M^++Na); Anal. [$C_{22}H_{21}NO_4$] C, H, N.

5.92. 2-[3-(2-Chloro-phenyl)-isoxazol-5-ylmethyl]-acrylic acid ethyl ester (6A4B2)

The product was obtained as colourless oil (88%); IR (neat, cm^{-1}) 1718 (CO_2Et); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.29$ (t, 3H, $J = 7.2$ Hz, CH_3), 3.86 (s, 2H, CH_2), 4.23(q, 2H, $J = 7.2$ Hz, OCH_2), 5.75 (s, 1H $=CH_2$), 6.39 (s, 1H, $=CH_2$), 6.52 (s, 1H, =CH), 7.33–7.41 (m, 2H, Ar–H), 7.45–7.50 (m, 1H, Ar–H), 7.70–7.75 (m, 1H, Ar–H); Mass (ES+) m/z 314.00 (M^++Na); Anal. [$C_{15}H_{14}ClNO_3$] C, H, N.

5.93. 2-(3-Phenyl-isoxazol-5-ylmethyl)-acrylic acid butyl ester (6A1B3)

The product was obtained as colourless oil (89%); IR (neat, cm^{-1}) 1715 (CO_2Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.92$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.29–1.47 (m, 2H, CH_2), 1.59–1.72 (m, 2H, CH_2), 3.84 (s, 2H, CH), 4.18 (t, 2H, $J = 6.5$ Hz, OCH_2), 5.75 (s, 1H, $=CH_2$), 6.36 (s, 1H, $=CH_2$), 6.38 (s, 1H, =CH), 7.42–7.47 (m, 3H, Ar–H), 7.76–7.81 (m, 2H, Ar–H); Mass (ES+) m/z 286.60 (M^++1), 308.40 (M^+Na); Anal. [$C_{17}H_{19}NO_3$] C, H, N.

5.94. 2-[3-(4-Benzyloxy-phenyl)-isoxazol-5-ylmethyl]-acrylic acid butyl ester (6A3B3)

The product was obtained as a white solid (69%); mp 66–68 °C; IR (KBr, cm^{-1}) 1716 (CO_2Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.92$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.26–1.47 (m, 2H, CH_2), 1.57–1.72 (m, 2H, CH_2), 3.81 (s, 2H, CH_2), 4.17 (t, 2H, $J = 6.4$ Hz, OCH_2), 5.11 (s, 2H, OCH_2O), 5.74 (s, 1H, $=CH_2$), 6.29 (s, 1H, $=CH_2$), 6.37 (s, 1H, =CH), 7.01, 7.05 (d, 2H, $J = 8.8$ Hz, Ar–H), 7.33–7.46 (m, 5H, Ar–H), 7.70, 7.74 (d, 2H, $J = 8.8$ Hz Ar–H); Mass (FAB+) m/z 392 (M^++1); Anal. [$C_{24}H_{25}NO_4$] C, H, N.

5.95. 2-[3-(2-Chloro-phenyl)-isoxazol-5-ylmethyl]-acrylic acid butyl ester (6A4B3)

The product was obtained as colourless oil (90%); IR (neat, cm^{-1}) 1719 (CO_2 Bu-*n*); ^1H NMR ($CDCl_3$, 200 MHz) $\delta = 0.93$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.26–1.47 (m, 2H, CH_2), 1.57–1.72 (m, 2H, CH_2), 3.86 (s, 2H, CH_2), 4.18 (t, 2H, $J = 6.5$ Hz, OCH_2), 5.75 (s, 1H, $=CH_2$), 6.39 (s, 1H, $=CH_2$), 6.52 (s, 1H, =CH), 7.30–7.42 (m, 2H, Ar–H), 7.46–7.50 (m, 1H, Ar–H), 7.70–7.75 (m, 1H, Ar–H); Mass (FAB+) m/z 320 (M^++1); Anal. [$C_{17}H_{18}ClNO_3$] C, H, N.

6. Biological assays

6.1. Animals

Experiments on pulmonary thromboembolism and bleeding time were performed on male Swiss mice (average wt 23 g). New Zealand white strain rabbits of either sex were also used to evaluate antithrombotic effect of the test compound. While, male Sprague Dawley rats (250–300 g) were used for the aggregation experiments. All the animals were kept in polypropylene cages and maintained at 24 ± 0.5 °C, 12 h day/night cycle in the Animal House of the Central Drug Research Institute, and were provided with chow pellets and water ad libitum. All the experiments were performed in accordance with the ethical and animal care guidelines of the Institute.

6.2. Chemicals

Adenosine 5′-diphosphate (ADP), arachidonic acid (AA), calcium ionophore (A23187), collagen, phorbol myristate acetate (PMA) and thrombin were dissolved in either saline or DMSO and stored at −20 °C. Fresh dilutions were prepared at the time of experiment. All the reagents were obtained from Sigma Chemical Co. (St. Louis, USA).

6.3. Thrombin assay

The compound and its analogues (100 μg/mL) were assayed for their thrombin inhibitory activity (in vitro) by the amidolytic assay.[22] Enzyme inhibition in presence of compound was measured in a total volume of 250 L containing Tris buffer 100 M (0.75 M NaCl, 10 mM $CaCl_2$, 0.1% BSA, pH 7.5), thrombin substrate (0.2 mM) and thrombin (3 nM). Stock solutions of the compounds were prepared in triple distilled water and diluted in the assay buffer prior to the experiment.

6.4. Evaluation of coagulation parameters

Blood was collected by cardiac puncture of the ether-anaesthetized rat into a syringe containing 3.8% tri-sodium citrate (9:1, v/v). It was centrifuged at 2500 g for 15 min at 20 °C. Test compounds were prepared in physiological saline (0.9% NaCl). Coagulation parameters, that is, thrombin time (TT), prothrombin time (PT) and activated partial thromboplastin time (APTT) were evaluated according to the manufacturer's instructions and measured in a coagulometer (Stago, France).

6.5. Evaluation of compounds on platelet aggregation

Sprague Dawley rats (wt 250–300 gm) were anaesthetized with ether and blood (9 mL) was drawn from the heart into a plastic syringe containing 1 mL of 1.9% trisodium citrate. It was centrifuged at $275 \times g$ for 20 min, at 20 °C and the platelet rich plasma (PRP) was separated. The remaining blood was further centrifuged at $1500 \times g$ for 15 min at 20 °C to obtain platelet poor plasma (PPP). The platelet count in the PRP was adjusted to 2×10^8 cells/mL by using PPP. Aggregation was induced by adenosine-5′-diphosphate (ADP), thrombin, collagen, or calcium ionophore A23187 and was monitored on a dual channel aggregometer (Chronolog, USA).[16] The test compound was incubated with PRP for 5 min before the addition of aggregation inducing agent. Percent inhibition of the test compounds at various concentrations was calculated as follows:

$$\%\text{Inhibition} = [1 - \text{Aggregation}_{\text{test}}/\text{Aggregation}_{\text{vehicle}}] \times 100$$

IC_{50} for the test compounds was determined by a nonlinear plot between % inhibition and concentration of the test substance.

6.6. Effect on mouse thrombosis

Pulmonary thromboembolism was induced by a method described earlier.[16] The compounds to be tested or the vehicle were administered orally 60 min prior to the thrombotic challenge. Thrombosis was induced by a mixture of collagen (150 μg/mL) and adrenaline (50 μg/mL) by the rapid intravenous injection into the tail vein to induce hind limb paralysis or death. In each group 10 animals were used for evaluating the test compound, aspirin or vehicle.

Protection against collagen plus epinephrine was expressed as

$$(1 - P_{\text{test}}/P_{\text{control}}) \times 100$$

where P_{test} is the number of animals paralyzed/dead in test compound-treated group, and P_{control} is the number of animals paralyzed/dead in vehicle treated group.

6.7. Rabbit venous thrombosis model

Experiments were performed on New Zealand white strain rabbits (2–3 kg) either sex. *Escherichia coli* LPS strain 1055:B5 (Sigma Chemicals, USA) was injected intravenously via ear vein (1 μg/kg).[13,14] Jugular veins on the both sides were exposed and dissected free from surrounding tissue. Two loose sutures were placed 1.5 cm apart and all collateral veins were ligated. Four hours after *E. coli* endotoxin injection (animal is watched for any signs of hypersensitivity reaction during this period), stasis was established and maintained for 45 min by tightening the two sutures. Ligated segments were removed and opened longitudinally and the thrombus was carefully removed and weighed. Heparin sodium (Beparine from beef intestinal mucosa $\geqslant 140$ USP units/mg; Biological E. Limited, India) was given in the doses of (0.5, 0.25, 0.1 mg/kg iv, via ear vein; $n = 6$ observations for each dose in nine animals) 5 min before stasis and test compound (99/353; $n = 12$ observations in 3 animals at 30 μM kg^{-1}, po) or its saline vehicle ($n = 10$ observations in five animals) were administered per orally 2 h prior to stasis.

Acknowledgements

The financial support in the form of fellowships to four of the authors AP, PS, SAVR and WRS from CSIR and AKR from ICMR, India is gratefully acknowledged. This work was supported partially through financial grant under DST Project no **SR/SI/OC-04/2003**. The technical assistance by Mrs. K. Bhutani and Mr. M. S. Ansari towards biological evaluation of compounds is also gratefully acknowledged.

References and notes

1. *Thrombosis in Cardiovascular Disorders*; Fuster, V., Verstraete, M., Eds.; W.B. Saunders: Philadelphia, 1992.
2. (a) Gresele, P.; Agnelli, G. *TIPS* **2002**, *23*, 25–32; (b) Collins, B.; Hollidge, C. *Nature Rev. Drug Discovery* **2003**, *2*, 11–12.
3. Raghavan, S. A. V.; Dikshit, M. *Drugs Future* **2002**, *27*, 669–683, and references cited therein.
4. Gachet, C.; Cattaneo, M.; Ohlmann, P.; Hechler, B.; Lecchi, A.; Chevalier, J.; Cassel, D.; Mannucci, P. M.; Cazenave, J. P. *Br. J. Haematol* **1995**, *91*, 434–444.
5. Gachet, C.; Hechler, B.; Leon, C.; Vial, C.; Leray, C.; Ohlmann, P.; Cazenave, J. P. *Thromb. Haemost.* **1997**, *78*, 306–309.
6. Tandon, N. N.; Kralisz, U.; Jamieson, G. A. *J. Biol. Chem.* **1989**, *264*, 7576–7583.
7. Kainoh, M.; Ikeda, Y.; Nishio, S.; Nakadate, T. *Thromb. Res.* **1992**, *65*, 165–176.
8. (a) Hanessian, S.; Therrien, E.; Granberg, K.; Nilsson, I. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2907–2911; (b) Sielecki, T. M.; Liu, J.; Mousa, S. A.; Racanelli, A. L.; Hausner, E. A.; Wexler, R. R.; Olson, R. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2201–2204; (c) Ballabeni, V.; Tognolini, M.; Calcina, F.; Impicciatore, M.; Vicini, P.; Barocelli, E. *Pharmacol. Res.* **2002**, *46*, 389–393.
9. (a) Pruitt, J. R.; Pinto, D. J.; Estrella, M. J.; Bostrom, L. L.; Knabb, R. M.; Wong, P. C.; Wright, M. R.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 685–689; (b) Nantermet, P. G.; Barow, J. C.; Lundell, G. F.; Pellicore, J. M.; Rittle, K. E.; Young, M. B.; Friedanger, R. M.; Connoly, T. M.; Condra, C.; Karczewski, J.; Bednar, R. M.; Gaul, S. L.; Gould, R. J.; Prendergast, K.; Selnick, H. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 319–323.
10. Batra, S.; Srinivasan, T.; Rastogi, S. K.; Kundu, B.; Patra, A.; Bhaduri, A. P.; Dikshit, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1905–1908.
11. Original papers on Baylis–Hillman reaction (a) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815; (b) Baylis, A.B.; Hillman, M.E.D. German Patent 2155113, **1972**; *Chem Abstr*. **1972**, *77*, 34174q; (c) Reviews

Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670; (d) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062; (e) Ciganek, E. *Org. React.* **1997**, *51*, 201–350; (f) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (g) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–890.
12. Diminno, G.; Silver, M. J. *J. Pharmacol. Exp. Ther.* **1983**, *225*, 57–60.
13. Berry, C. N.; Girard, D.; Girardot, C.; Lochot, S.; Lunven, C.; Visconte, C. *Semin. Thromb. Haemost.* **1996**, *22*, 233–241.
14. Herbert, J. M.; Bernat, A.; Dol, F.; Herault, J. P.; Crepon, B.; Lormeau, J. M. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 1030–1038.
15. Dejna, E.; Collioni, A.; Quntana, A. *Thromb. Res.* **1979**, *15*, 191–197.
16. Dikshit, M.; Kumari, R.; Srimal, R. C. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 1369–1373.
17. Tolentino, A. R.; Bahou, W. F. In *Platelets*; Michelson, A. D., Ed.; Academic, 2002; pp 117–129.
18. Heyu, N.; Freedman, J. *Science* **2003**, *28*, 264–275.
19. Hato, T.; Ginsberg, M. H.; Shattil, S. J. In *Platelets*; Michelson, A. D., Ed.; Academic, 2002; pp 105–110.
20. Siess, W.; Lapetina, E. G. *Biochem. J.* **1988**, *255*, 309–318.
21. Vuori, K.; Ruoslahti, E. *J. Biol. Chem.* **1993**, *268*, 21459–21462.
22. Moon, J. C.; Junling, L.; Tamara, I. P.; Shirley, S.; Dennis, W. T.; Thomas, M. C.; Demin, W.; Carl, W. J.; Gartner, T. K. *Blood* **2003**, *101*, 2646–2651.
23. Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Bhaduri, A. P. *Synthesis* **2001**, 276–280.