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Original article

Synthesis and evaluation of some novel isochroman carboxylic acid derivatives as potential anti-diabetic agents

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ABSTRACT

A series of novel isochroman mono-carboxylic acid derivatives were synthesized, characterized and evaluated for their ability to inhibit protein tyrosine phosphatase 1B (PTP1B) *in vitro* in order to use them as potential anti-diabetic agents. Analysis of structure–activity relationships led to the identification of potent compound **4n** which inhibited PTP1B with IC_{50} value of 51.63 ± 0.91 nM. In general, high potency was associated with a dithiolane ring with a spacer of five carbons to the isochroman ring. Compound **4n** has been selected for *in vivo* evaluation as drug candidate for anti-diabetic activity.

1. Introduction

Insulin resistance is associated with a deficit in protein tyrosine phosphorylation in insulin signal transduction cascade. Genetically modified mice that lack protein tyrosine phosphatase 1B (PTP1B) expression and animals treated with a specific PTP1B antisense oligonucleotide have provided crucial "proof-of-concept" data to show that eradicating or reducing PTP1B enhances insulin signaling and glucose tolerance [1]. Zhang and co-workers first identified a second phosphotyrosine (pTyr) binding site (site 2) in the vicinity of PTP1B catalytic site. They also pioneered the notion of achieving selectivity among PTP1B, T-cell protein tyrosine phosphatase (TCPTP) and other phosphatases by targeting the less homologous site 2 [2].

Discovery of small-molecule inhibitors has been pursued extensively in both academia and industry and a number of very potent and selective inhibitors have been identified. These inhibitors typically incorporate a charged pTyr mimetic to achieve strong binding to the highly conserved and polarized active site of PTPases. The commonly used pTyr mimetics include phosphonates, carboxylic acids, sulfamic acids, difluoromethylphosphonates, oxalylaminobenzoic acids, etc. [3]. Given that most of the catalytic site-directed PTP1B inhibitors are highly charged molecules, non-carboxylic acid-containing ligands targeting site 2 are highly desirable for improving the overall druglike properties. Liu et al. reported the discovery of first non-acid-containing, salicylate-based ligands for site 2 of PTP1B, and a structure-based linking approach for identifying a potent PTP1B inhibitor **1** with selectivity over TCPTP (Fig. 1) [4]. Another report by Wan et al. described a series of monocyclic thiophenes with moderate inhibitory potency against PTP1B [5]. In another attempt, Liu et al. identified a selective and cell active PTP1B inhibitor **2** an isoxazole carboxylic acid analog (Fig. 1), from X-ray crystallographic study and NMR-based screening [6]. Larsen et al. prepared compounds based on L-tyrosine with arylalkanoyl groups showing cellular activity [7]. Liu et al. also disclosed an invention based on 3-phenyl propanoic acid derivatives as PTP1B inhibitors [8]. Shim et al. reported the discovery of a formylchromone derivative **3** (Fig. 1) with excellent potency and twelvefold selectivity over TCPTP [9].

From the literature it is evident that a monoacid based fragment binds with the catalytic site of PTP1B and a hydrophobic end of a side chain binds with the secondary site imparting more potency and selectivity towards PTP1B. The objective of our PTP1B inhibitor program was to identify a novel series of selective and reversible inhibitors of PTP, employing a phosphate mimic and a non-peptidyl small molecule. The throughput screening of

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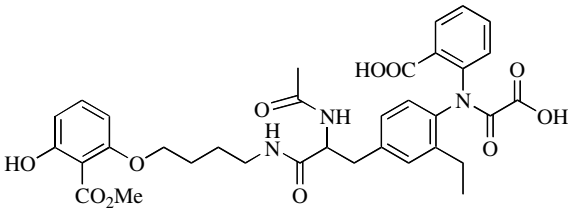
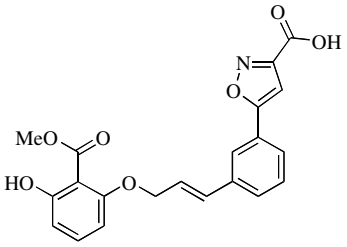
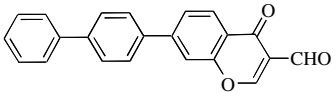


1 K_i: 18 nM (PTP1B)
K_i: 65 nM (TCPTP)



2 K_i: 5.7 uM (PTP1B)
K_i: 202 uM (TCPTP)



3 K_i: 4.3 uM (PTP1B)
K_i: 51 uM (TCPTP)

Fig. 1. Known PTP1B inhibitors with selectivity over TCPTP.

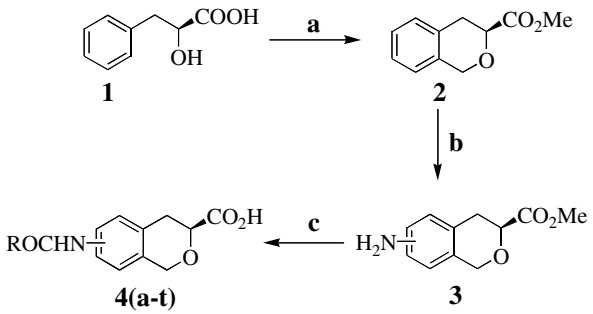
a chemically diverse compound library resulted in the identification of a hit **4a** showing 50% inhibition of PTP1B at 10 μM and had all the requisite functionalities like a carboxylic acid-containing small molecule with a hydrophobic side chain. This prompted us to explore the scaffold of our hit, to optimize the activity by making analogs with sidechains of varying linker lengths and with various substitutions.

At this point we also thought it is worthwhile to study the influence of α-Lipoic acid (LA), a disulfide compound which functions naturally as a co-enzyme and occurs in the R (+) form. LA was demonstrated to stimulate the autophosphorylation of insulin receptor and glucose uptake into 3T3-L1 adipocytes by reducing the thiol reactivity of intracellular proteins. LA also inhibited protein tyrosine phosphatase activity and decreased thiol reactivity of PTP1B. These findings indicate that oxidants produced by LA are involved in activation of insulin receptor and inactivation of protein tyrosine phosphatases, which eventually result in elevated glucose uptake into 3T3-L1 adipocytes [10]. The antioxidant activity of LA is also attributed to its capacity to regenerate intracellular GSH, vitamin C, and vitamin E. Numerous other studies have reported that LA is beneficial in a number of oxidative stress models of cell death pertinent to ischemia–reperfusion injury, neurodegeneration, diabetes, inflammation, and radiation injury. Thus, LA possesses the potential to intervene in various therapeutically interesting pathways. However, it should be noted that LA reportedly exerts most of its effects at high micromolar concentration whereas amides of LA exhibit higher biological activity than the parent compound and that molecular combinations obtained by coupling LA with an amino-substituted bioactive moiety possess multifunctional activity [11].

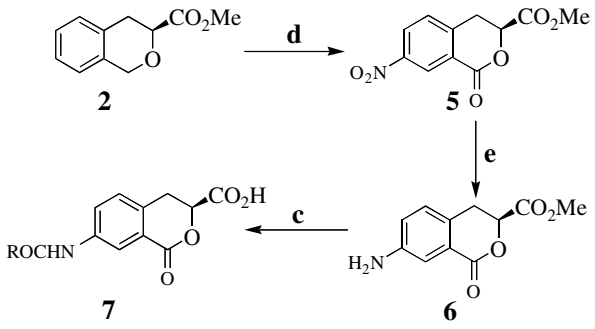
2. Chemistry

L-Phenylalanine was chosen as our chemistry starting point and then functionalized the aromatic ring in order to attach the linker and the hydrophobic group and also modified the amino acid nature before studying the SAR of the analogs. The designed compounds were synthesized as outlined in Schemes 1 and 2, wherein L-phenylalanine was converted to L-(−)-3-phenyl lactic acid through diazotization [12], which was then cyclized using paraformaldehyde, to isochroman-3-(*S*)-carboxylic acid [13] and was esterified in the presence of catalytic amount of conc. sulphuric acid. Nitration of isochroman-3-(*S*)-carboxylic acid methyl ester, when carried out at 0 °C, not only resulted in the introduction of nitro group exclusively at the C7 position but also caused oxidation of the benzylic (C1) carbon to give isochroman-1-one nucleus as seen in compound **7**, whereas nitration at −40 °C, resulted in the formation of both the isomers (6-nitro and 7-nitro isochroman-3-(*S*)-carboxylic acid esters), without oxidation of the C1 carbon. Reduction of the isomeric mixture of nitro compounds and chromatographic separation of the isomers gave appropriately functionalized isochroman-3-(*S*)-carboxylic acid methyl ester.

The corresponding carboxylic acid moieties for preparing various amides were purchased from commercial sources or were prepared as per procedures described in Schemes 4–6. 4-(2-Thienyl)-butanoic acid and 5-(2-thienyl)-pentanoic acid were prepared by Friedel–Craft's reaction of thiophene with succinic anhydride and glutaric anhydride respectively, followed by Clemmensen reduction of the keto-acid, as shown in Scheme 4 [14]. 2,2-Dimethyl or 2,2-diphenyl 1,3-dithiolan-4-yl-3/5-alkanoic acid was prepared in a four step sequence which involved reacting 4-pentenoic acid or 6-heptenoic acid with bromine [15] and esterification, catalysed by few drops of conc. sulphuric acid followed by the reaction of the dibromide with thioacetic acid to give dithioacetyl compound [16]. Deacetylation of the above in refluxing methanolic HCl gave the desired dimercapto ester. Cyclization of the dimercapto ester by reaction with ketone (2,2-dimethoxypropane or benzophenone) in the presence of $BF_3 \cdot Et_2O$ [17], followed by ester hydrolysis gave the desired 2,2,-disubstituted 1,3-dithiolan acids (Scheme 5). 1,3-Dithian-4-yl-5-pentanoic acid or 2,2-diphenyl 1,3-dithian-4-yl-5-pentanoic acid was prepared in a four step sequence which involved esterification of R-Lipoic acid in the presence of EDCI, HOBT, methanol and DMF followed by reduction of the disulfide using $NaBH_4$ in methanol. The obtained dithiol was then reacted with paraformaldehyde or benzophenone in the presence of $BF_3 \cdot Et_2O$ followed by saponification of the ester with NaOH, (Scheme 6) [17]. Compounds without cyclization to the isochroman ring were also prepared. The compounds **13a–d** were synthesized as outlined in Scheme 3 wherein L-phenylalanine was nitrated



Scheme 1. (a) (1) $(HCHO)_n$, TFA, reflux, 72 h. (2) Methanol, Cat. H_2SO_4, reflux, 4 h; (b) (1) fuming HNO_3, −40 °C, 40 min. (2) Pd/C, H_2, EtOAc, 3 h; column purification. (c) (1) RCO_2H, EDCI·HCl, Et_3N, CH_2Cl_2, 3 h. (2) K_2CO_3, aqueous methanol (1:1), 5 h.



Scheme 2. (d) Fuming HNO_3, 0 °C, 40 min; (e) Pd/C, H_2, EtOAc, 3 h; (c) 1). LA, EDCI·HCl, Et_3N, CH_2Cl_2, 3 h. (2) K_2CO_3, aqueous methanol (1:1), 5 h.

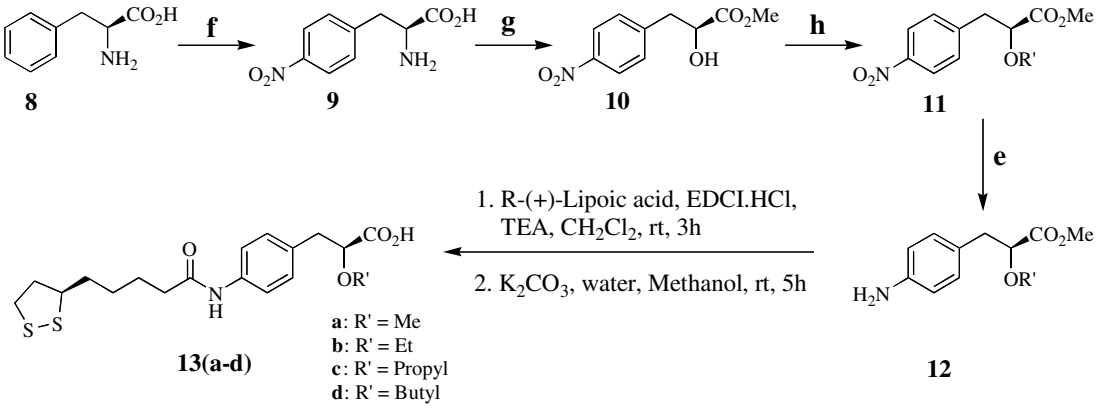
using nitric acid in the presence of conc. sulphuric acid and the obtained 4-nitro-L-phenylalanine was subjected to diazotization in 1 N sulphuric acid followed by esterification to yield 4-nitro-L-phenyl lactic acid ethyl ester. Etherification was done with different alkyliodides in the presence of silver oxide and then the nitro group was converted to amine by catalytic reduction followed by amidation with the carboxylic acid moiety. The physical constants of compounds 4a–4t, and 7 and 13a–13d are as shown in (Tables 1 and 2), respectively. The data from the SAR studies is mentioned in Table 3.

3. Pharmacology

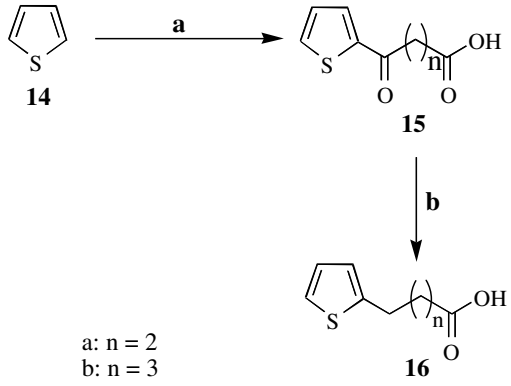
The inhibitory activities of the compounds were determined with minor modifications of the procedure described in the literature using *p*-nitrophenyl phosphate (*p*NPP) as a substrate at 37 °C [9]. IC_{50} values were derived from three independent experiments using the inhibitors at concentrations of 30 nM, 100 nM, 300 nM, 1.0 μM, 3.0 μM and 10.0 μM. For inhibition assay, inhibitor (10 μM in DMSO) was added to a mixture containing enzyme (5 mL), reaction buffer (Hepes 25 mM, 3 mM DTT, 0.15 M NaOH, 1 mM EDTA and Nonidet-P40 (NP-40) 0.01%) and was incubated at 37 °C for 10 min. The reaction was initiated by addition of *para*-nitro phenyl phosphate (*p*NPP, 2.5 mM) and, after 30 min at 37 °C, the reaction was quenched by addition of NaOH solution (2.5 mM). The progress of the reaction was determined for the formation of *p*-nitrophenolate by measuring the absorbance at 405 nm. PTP1B was diluted before use to an appropriate concentration (typically 40 mg/mL) by enzyme dilution buffer: 2 × reaction buffer (NP-40 0.01%, 3 mM DTT, pH 7.5). Healthy male *ob*/*ob* mice (eight animals in each group) were used for the *in vivo* study and were provided with 11% high fat diet. Fasting (18 h) biochemical parameter estimation was done on days 10 and 14. Fed-state WBG was done on day 7. Body weight and feed intake were recorded twice a week.

4. Results and discussion

Compound **4a** showed an IC_{50} of 429 nM, which is our initial hit and its regio isomer **4b** showed 383.7 nM, whereas compounds **4g** and **4h** with saturated alicyclic rings in place of aromatic ring in the side chain, showed improved activity. Reducing the length of the carbon chain, as in compounds **4c** and **4d** resulted in slight loss of activity. Increasing the size of the saturated ring from five membered to six membered as in compounds **4q** and **4r** did not alter the activity much but increasing the bulkiness in the saturated ring by introducing phenyl groups as in compounds **4i**, **4j**, **4s** and **4t** caused loss of activity. Shifting from 1,3-dithiolane to 1,2-dithiolane ring resulted in hugely potent compounds **4k–4n**. The stereochemistry of the LA also seems to be playing a role as is evident with compounds **4m** and **4n** showing greater potency than their racemic compounds. Replacing the LA group with Biotin as in compounds **4o** and **4p** also resulted in loss of activity. Best activity was found to be associated with compounds which have a linker of five carbons. The regioisomers **4m** and **4n** both showed excellent activity, which revealed that there is no specificity associated with the position of the substituent on the isochroman ring, with respect to activity against PTP1B. The activity associated with compounds **4k–4n** may also be attributed to the intrinsic activity of LA against PTP1B. Having studied and optimized the side chain part, it is decided to optimize the isochroman ring, by making the oxidized analog of **4n** and also the uncyclized analogs of it. While compound **7** showed much less potency, the uncyclized ethyl ether **13b** showed reasonable activity. Compounds with lengthier ethers **13c** and **13d** also showed much less potency. Among all the compounds prepared, compound **4n** showed high potency and very good specificity over other PTPases, and hence it was selected for *in vivo* study, using rosiglitazone maleate as the standard. The hyperglycemic condition in *ob*/*ob* mice was normalized when treated with compound **4n.** The treatments showed significant reduction ($p < 0.001$) in fed-state WBG on day 7 of the study. Similar trend was observed in fasting WBG on day 10 of the study with **4n** and rosiglitazone showing a reduction compared with vehicle (93 ± 15, 90 ± 5 and 139 ± 8 mg/dl) respectively (Figs. 2 and 3). Compound **4n** did not show any significant difference in glucose excursion. Rosiglitazone showed significant reduction on fasting plasma glucose and triglyceride levels whereas **4n** showed significant reduction in fasting plasma glucose levels only (Fig. 4).



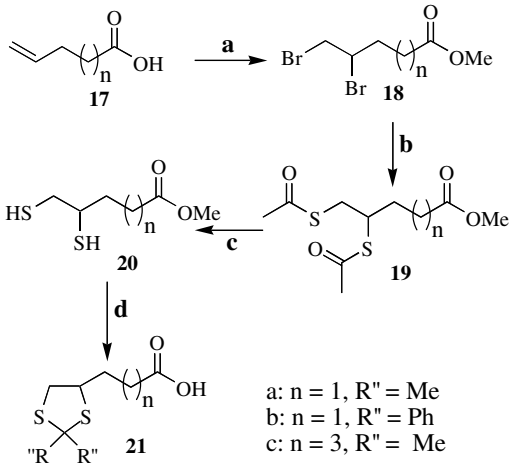
Scheme 3. (f) Conc. HNO_3, conc. H_2SO_4, 0 °C, 1 h; (g) (1) 1 N H_2SO_4, aqueous $NaNO_2$, 0–rt, 6 h, (2) methanol, cat. H_2SO_4, reflux, 4 h; (d) R'I, Ag_2O, toluene, reflux, 5 h; (e) Pd/C, H_2, EtOAc, 3 h.



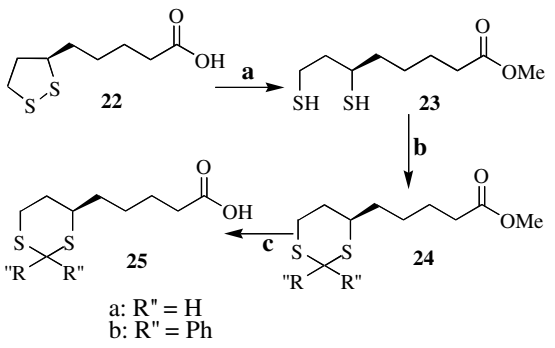
Scheme 4. (a) $AlCl_3$, succinic anhydride or glutaric anhydride, nitrobenzene, 0–5 °C, 4 h; (b) Zn amalgam, 5 N HCl, reflux, 6 h.

5. Conclusion

In summary we have discovered a series of potent, novel, non-phosphonic acid-containing PTP1B inhibitors with good specificity for PTP1B over TCPTP, the most homologous phosphatase to PTP1B. A strategy of occupying both the catalytic site and the nearby, less homologous, non-catalytic phosphotyrosyl binding site is employed in the present study. An examination of the PTP1B inhibitors synthesized revealed the residues important for achieving PTP1B specificity and thus provided an opportunity for designing more potent and selective PTP1B inhibitors. SAR studies revealed the critical role of the dithiolane moiety in the amide chain of the ring which showed promising activity *in vivo*. Although there is much work reported on aryl difluorophosphonate-containing PTP1B inhibitors, the present study was of considerable interest to define a small molecule, nonphosphonate-containing, non-peptide, carboxy-based phenylphosphonate mimetic for use as PTP1B inhibitors. The hitherto unreported mono-carboxy motif and its synergistic activity with LA reported herein provides a new approach, which may be of use in the design of carboxy-based PTP1B inhibitors and could serve as advanced lead for further optimization.



Scheme 5. (a) (1) Br_2, CH_2Cl_2, −40 °C, 1.5 h; (2) MeOH, cat. conc. H_2SO_4, reflux, 4 h. (b) CH_3COSH, alc. KOH, rt, 3 h; (c) methanolic HCl, reflux, 3 h; (d) (1) $BF_3{\cdot}Et_2O$, 2,2-dimethoxypropane or benzophenone, CH_2Cl_2, rt, 6 h; (2) aqueous NaOH, MeOH, rt, 4 h.



Scheme 6. (a) (1) CH_3OH, EDCI·HCl, DMF, HOBT, rt, 5 h; (2) $NaBH_4$, MeOH, rt, 1.5 h; (b) $BF_3{\cdot}Et_2O$, paraformaldehyde or benzophenone, CH_2Cl_2, rt, 6 h; (c) NaOH, MeOH, rt, 4 h.

6. Experimental

Melting points were measured using POLMON MP-96T-X melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury VX 300 spectrometer, using tetramethylsilane as an internal standard and DMSO-d_6 as solvent, unless otherwise specified. IR spectra were acquired on Perkin–Elmer spectrum-one FT-IR spectrometer. Mass spectra were run on Finnigan Navigator spectrometer at 20 eV or 50 eV. Elemental analyses were carried out with a Perkin–Elmer model 2400 series II apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values. Specific optical rotation was recorded on JASCO P-1030 polarimeter.

6.1. Synthesis of intermediates

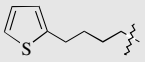
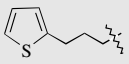
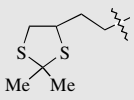
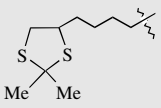
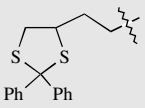
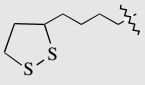
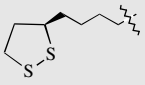
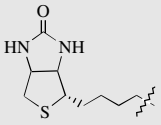
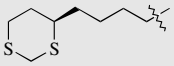
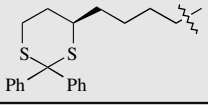
6.1.1. Synthesis of L-(−)-3-phenyl lactic acid (**1**)

To a solution of L-phenylalanine (50 mmol) in 1 N H_2SO_4 (100 mL), while stirring at 0 °C, was added an aqueous solution of sodium nitrite (100 mmol in 20 mL water), dropwise and the reaction mixture was stirred for 6 h while allowing the reaction mixture to warm to room temperature. The reaction mixture was then extracted with ethyl acetate and the organic layer was washed with water and brine and concentrated to give L-(−)-3-phenyl lactic acid. Yield: 82%; ^1H NMR: δ 7.30–7.10 (br s, 5H), 4.20–4.10 (m, 1H), 3.00–2.90 (dd, $J = 3.9$ Hz and 13.5 Hz, 1H), 2.80–2.70 (dd, $J = 8.1$ Hz and 13.5 Hz, 1H); MS (m/z): 167.18 $(M+H)^+$; $[\alpha]^{24}$: −22° (C 2.0, H_2O). Mp: 123–125 °C; [Lit. value: $[\alpha]^{24}$: −20.8° (C 2.0, H_2O). Mp: 122–124 °C].

6.1.2. Synthesis of isochroman-3-(S)-carboxylic acid methyl ester (**2**)

To a solution of L-(−)3-phenyl lactic acid (40 mmol) in trifluoroacetic acid (25 mL), was added paraformaldehyde (13.33 mmol) and the reaction mixture was refluxed for 72 h. Solvent was then distilled off from the reaction mixture, diluted with water and was extracted with ethyl acetate. The organic layer was then washed with brine and concentrated to give isochroman-3-(*S*)-carboxylic acid. The obtained acid was then dissolved in methanol (80 mL) and was added catalytic amount of conc. Sulphuric acid and the reaction mixture was refluxed for 4 h. Solvent was then evaporated from the reaction mixture on rotavapor, diluted the residue with ethyl acetate and was washed with sat. sodium bicarbonate solution followed by water and brine and concentrated to give isochroman-3-(*S*)-carboxylic acid methyl ester. Yield: 74%; Mp: 68 °C; IR (KBr): 3485, 2948, 2843, 1751, 1457, 1441, 1370, 1246, 1220, 1203, 1187, 1116, 1052 and 982 cm^{-1}. ^1H NMR

Table 1
Physical constants of compounds **4a**–**4t**.

Compound no.	R	Isomer	Yield (%)	M.p. (°C)	M. F/M. wt/; C, H, N (% Calc.)	C, H, N (% Found)
4a		6	85	242–245		C, 63.41; H, 5.82; N, 3.93
4b		7	82	211–213	359.43/$C_{19}H_{21}NO_4S$; C, 63.49; H, 5.89; N, 3.90	C, 63.39; H, 5.92; N, 3.85
4c		6	91	203–205		C, 62.49; H, 5.43; N, 4.10
4d		7	93	187–190	345.41/$C_{18}H_{19}NO_4S$; C, 62.59; H, 5.54; N, 4.06	C, 62.65; H, 5.59; N, 4.12
4e		6	85	96–97		C, 56.75; H, 6.01; N, 3.72
4f		7	89	113–118	381.50/$C_{18}H_{23}NO_4S_2$; C, 56.67; H, 6.08; N, 3.67	C, 56.60; H, 6.17; N, 3.61
4g		6	90	97–99		C, 58.73; H, 6.72; N, 3.50
4h		7	87	93–94	409.55/$C_{20}H_{27}NO_4S_2$; C, 58.65; H, 6.64; N, 3.42	C, 58.60; H, 6.78; N, 3.37
4i		6	88	83–86		C, 66.45; H, 5.45; N, 2.70
4j		7	92	96–97	505.66/$C_{28}H_{27}NO_4S_2$; C, 66.51; H, 5.38; N, 2.77	C, 66.41; H, 5.45; N, 2.68
4k		6	91	128–129		C, 56.75; H, 6.15; N, 3.59
4l		7	87	139–142	381.52/$C_{18}H_{23}NO_4S_2$; C, 56.67; H, 6.08; N, 3.67	C, 56.61; H, 6.02; N, 3.75
4m		6	90	133–135		C, 56.59; H, 5.95; N, 3.75
4n		7	88	145–147	381.52/$C_{18}H_{23}NO_4S_2$; C, 56.67; H, 6.08; N, 3.67	C, 56.76; H, 6.15; N, 3.59
4o		6	86	230–232		C, 57.39; H, 6.17; N, 9.91
4p		7	91	211–215	419.50/$C_{20}H_{25}N_3O_5S$; C, 57.26; H, 6.01, N, 10.02	C, 57.33; H, 6.10; N, 10.15
4q		6	84	88–92		C, 57.81; H, 6.32; N, 3.48.
4r		7	89	78–80	395.54/$C_{19}H_{25}NO_4S_2$; C, 57.70; H, 6.37; N, 3.54	C, 57.65; H, 6.29; N, 3.59
4s		6	89	73–76		C, 68.16; H, 6.14; N, 2.65
4t		7	87	73–76	547.74/$C_{31}H_{33}NO_4S_2$; C, 67.98; H, 6.07; N, 2.56	C, 67.89; H, 6.02; N, 2.48

(CDCl$_3$): δ 7.20–7.11 (m, 3H), 7.02–6.98 (m, 1H), 5.03–4.84 (AB q, $J = 15.0$ Hz, 2H), 4.41–4.36 (m, 1H), 3.82 (s, 3H), 3.10–3.06 (m, 2H); MS (m/z): 193.24 $(M + H)^+$; $[\alpha]^{20}$: $-109°$ (C 1.0, MeOH).

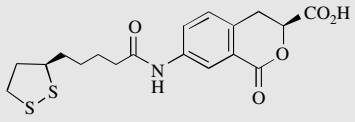
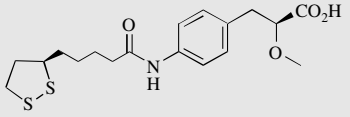
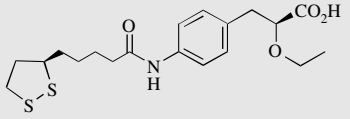
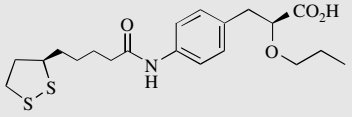
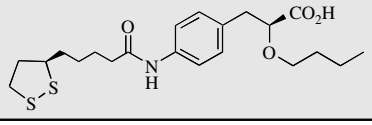
6.1.3. Synthesis of 6 and 7-nitro isochroman-3-(S)-carboxylic acid methyl ester

To fuming nitric acid (15 mL) previously cooled to -40 °C, was added isochroman-3-(*S*)-carboxylic acid methyl ester (25 mmol) in portions over a period of 15 min. The reaction mixture was then maintained at -40 °C while monitoring by TLC. The reaction was complete in 40 min. The reaction mixture was then poured in to ice water and was extracted with chloroform. The organic layer was then washed with sat. sodium bicarbonate solution, followed by water and brine. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated to give a mixture of 6-nitro and 7-nitro isochroman-3-(*S*)-carboxylic acid methyl ester in 77% yield.

6.1.4. Synthesis of 6 and 7-amino isochroman-3-(S)-carboxylic acid methyl ester (**3**)

To a solution of 6/7-nitro isochroman-3-(*S*)-carboxylic acid methyl ester (18 mmol) in ethyl acetate (50 mL) in a hydrogenation flask, 10%pd/C (0.3 g) was added and the reaction mixture was subjected to hydrogenation at 60 psi hydrogen pressure in a Parr apparatus, for 3 h. The reaction mixture was then filtered through celite, the celite bed was washed with ethyl acetate, the filtrate and washings were combined and concentrated to give a mixture of 6 and 7-amino isochroman-3-(*S*)-carboxylic acid methyl ester. The

Table 2
Physical constants of compounds **7** and **13(a–d)**.

Compound no.	Structure	Yield (%)	M.p. (°C)	M. wt./; M. F./; C, H, N (% Calc.)	C, H, N (% Found)
7		76	189–192	395.50; $C_{18}H_{21}NO_5S_2$; C, 54.67; H, 5.35; N, 3.54	C, 54.57; H, 5.41; N, 3.48
13a		89	135–137	383.53; $C_{18}H_{25}NO_4S_2$; C, 56.37; H, 6.57; N, 3.65	C, 56.43; H, 6.60; N, 3.61
13b		93	122–124	397.56; $C_{19}H_{27}NO_4S_2$; C, 57.40; H, 6.85; N, 3.52	C, 57.35; H, 6.81; N, 3.58
13c		86	145–148	411.59; $C_{20}H_{29}NO_4S_2$; C, 58.37; H, 7.10; N, 3.40	C, 58.29; H, 7.05; N, 3.49
13d		88	132–134	425.61; $C_{21}H_{31}NO_4S_2$; C, 59.26; H, 7.34; N, 3.29	C, 59.19; H, 7.40; N, 3.21

isomeric mixture was then purified by column chromatography on a silica gel column using a mixture of ethyl acetate and chloroform as the eluent.

Table 3
$IC_{50} \pm SEM$ (nM)[a] of compounds against various phosphatases.

Compound	PTP1B	TCPTP	LAR
4a	429(7.21)	6471(11.86)	7034(13.89)
4b	383.7(2.03)	5564(7.53)	5912(9.84)
4c	553.3(6.12)	677.7(4.91)	765.3(5.70)
4d	510.3(6.12)	550.3(4.05)	624.7(10.27)
4e	385.7(6.57)	436.7(2.40)	493(12.29)
4f	353.7(7.22)	403.3(3.41)	458.3(6.36)
4g	164.7(4.37)	322.7(11.46)	380(9.24)
4h	135.7(4.63)	321.3(6.74)	382.3(8.45)
4i	668.7(3.76)	4673(9.24)	4982(12.24)
4j	637.7(3.53)	4856(10.74)	5061(16.75)
4k	104.3(2.85)	2309(6.77)	2846(12.22)
4l	95.67(2.40)	2160(10.11)	2375(8.29)
4m	80(0.58)	2546(7.22)	2386(9.53)
4n	51.63(0.91)	1821(10.12)	1941(6.08)
4o	2897(3.51)	6878(11.59)	7045(8.22)
4p	2753(6.38)	6251(7.36)	6469(9.17)
4q	167.3(5.04)	3855(14.73)	4072(9.82)
4r	114.3(5.17)	4112(11.20)	4368(10.79)
4s	566.7(4.10)	7040(10.91)	7303(5.86)
4t	518.7(1.45)	6791(6.49)	7026(12.81)
7	304(2.89)	6207(12.73)	5858(10.60)
13a	148.7(2.60)	3559(10.97)	4658(11.78)
13b	113(2.16)	2674(11.61)	3285(8.08)
13c	373.7(12.55)	5470(10.15)	5982(8.48)
13d	358.3(4.05)	5362(8.57)	5859(6.89)

[a] Values are the mean of three independent experiments with SEM in parentheses.

6.1.4.1. 6-Amino isochroman-3-(S)-carboxylic acid methyl ester. Yield: 40%; Mp: 121 °C; IR (KBr): 3461, 3373, 2960, 1745, 1625, 1509, 1437, 1375, 1312, 1271, 1210, 1112, 1052, and 1031 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.78 (d, $J = 7.8$ Hz, 1H), 6.55–6.51 (dd, $J = 1.8$ Hz and 8.4 Hz, 1H), 6.45 (s, 1H), 4.92–4.75 (AB q, $J = 13.8$ Hz, 2H), 4.36–4.31 (m, 1H), 3.81 (s, 3H), 3.60 (br s, 2H), 3.00–2.95 (m, 2H); MS (*m*/*z*): 208.21 $(M + H)^+$.

6.1.4.2. 7-Amino isochroman-3-(S)-carboxylic acid methyl ester. Yield: 37%; Mp: 115 °C; IR (KBr): 3472, 3365, 2952, 1758, 1496, 1369, 1287, 1252, 1199, 1116, and 1037 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.91 (d, $J = 8.4$ Hz, 1H), 6.55–6.51 (dd, $J = 2.1$ Hz and 8.1 Hz, 1H), 6.32 (s, 1H), 4.92–4.74 (AB q, $J = 15.0$ Hz, 2H), 4.35–4.31 (m, 1H), 3.80 (s, 3H), 3.59 (br s, 2H), 3.00–2.82 (m, 2H); MS (*m*/*z*): 208.21 $(M + H)^+$.

*6.1.5. Synthesis of 7-nitro-1-oxo isochroman-3-(S)-carboxylic acid methyl ester (**5**)*

To fuming nitric acid (15 mL) previously cooled to 0 °C, was added isochroman-3-(*S*)-carboxylic acid methyl ester (25 mmol) in portions over a period of 15 min. The reaction mixture was then maintained at 0 °C while monitoring by TLC. The reaction was complete in 30 min. The reaction mixture was then poured in to ice water and extracted with chloroform. The organic layer was then washed with sat. sodium bicarbonate solution, followed by water and brine. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated to give 7-nitro-1-oxo-isochroman-3-(*S*)-carboxylic acid methyl ester. Yield: 82%; Mp: 163 °C; IR (KBr): 2969, 1757, 1738, 1614, 1532, 1435, 1351, 1236, 1131, 1039 and 998 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.93 (d, $J = 2.1$ Hz, 1H), 8.40–8.37 (dd, $J = 2.4$ Hz and 8.4 Hz, 1H), 7.48 (d, $J = 8.4$ Hz, 1H), 5.26 (t,

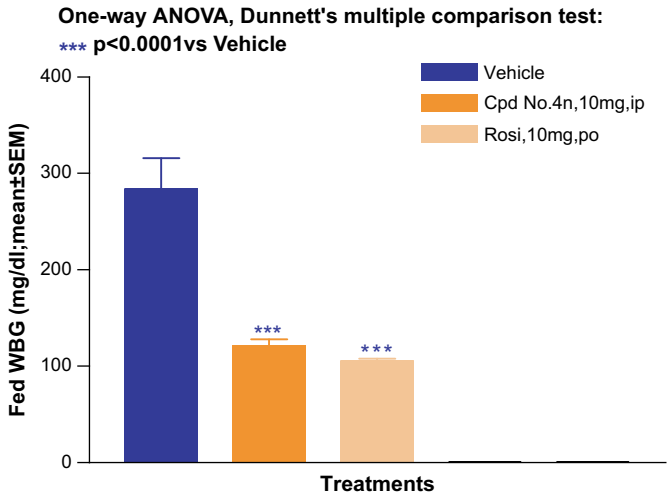


Fig. 2. Effect on fed WBG in *ob*/*ob* mice on day 7.

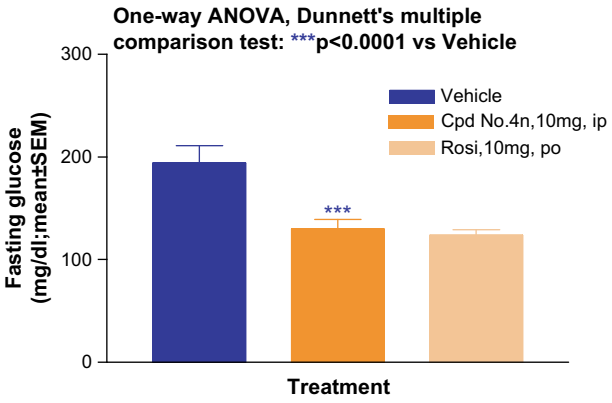


Fig. 4. Effect on plasma glucose in *ob*/*ob* mice on day 14.

$J = 5.4$ Hz, 1H), 3.96 (s, 3H), 3.63–3.56 (dd, $J = 5.7$ Hz and 17.1 Hz, 1H), 3.45–3.38 (dd, $J = 4.8$ Hz and 17.1 Hz, 1H); MS (*m*/*z*): 254.20 $(M + H)^+$.

6.1.6. Synthesis of 7-amino-1-oxo isochroman-3-(S)-carboxylic acid methyl ester (**6**)

To a solution of 7-nitro-1-oxo-isochroman-3-(*S*)-carboxylic acid methyl ester (20 mmol) in ethyl acetate (60 mL) in a hydrogenation flask, 10%Pd/C (0.5 g) was added and the reaction mixture was subjected to hydrogenation at 60 psi hydrogen pressure in a Parr apparatus, for 3 h. The reaction mixture was then filtered through celite, the celite bed was washed with ethyl acetate, combined the filtrate and washings and concentrated to give 7-amino-1-oxo isochroman-3-(*S*)-carboxylic acid methyl ester. Yield: 84%; Mp: 133 °C; IR (KBr): 3442, 2972, 1759, 1736, 1616, 1528, 1435, 1355, 1238, 1134, 1042 and 994 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.95 (d, $J = 2.4$ Hz, 1H), 8.39–8.35 (dd, $J = 2.7$ Hz and 8.1 Hz, 1H), 7.49 (d, $J = 8.7$ Hz, 1H), 5.19 (t, $J = 5.7$ Hz, 1H), 3.89 (s, 3H), 3.71 (br s, 3H), 3.59–3.51 (dd, $J = 5.4$ Hz and 17.1 Hz, 1H), 3.45–3.38 (dd, $J = 5.1$ Hz and 17.4 Hz, 1H); MS (*m*/*z*): 222.19 $(M + H)^+$.

6.1.7. Synthesis of 4-nitro-L-phenylalanine (**9**)

To a mixture of conc. nitric acid (13 mL) and conc. sulphuric acid (18 mL) while stirring at 0 °C, was added L-phenylalanine (60 mmol) in portions over a period of 30 min and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was then poured in to crushed ice and the precipitated solid was then filtered, washed with water and crystallised in hot water to give 4-nitro-L-phenylalanine. Yield: 70%; IR (KBr): 3294, 2895, 1613, 1571, 1419, 1349, 1312, 1106, 1012 and 863 cm^{-1}. ^1H NMR ($D_2O + DCl$): δ 8.24–8.20 (d, $J = 7.2$ Hz, 2H), 7.58–7.54 (d, $J = 6.9$ Hz, 2H), 4.53–4.50 (t, $J = 8.1$ Hz, 1H), 3.54–3.45 (dd, $J = 5.1$ Hz and 12.3 Hz, 1H), 3.46–3.35 (dd, $J = 4.8$ Hz and 12 Hz, 1H); MS (*m*/*z*): 213.23 $(M + H)^+$; $[\alpha]^{25}$: +6.26° (C 1.3, 3 M HCl). Mp: 243–247 °C dec.; [Lit. value: $[\alpha]^{25}$: +6.8° (C 1.3, 3 M HCl). Mp: 245–251 °C (dec.)].

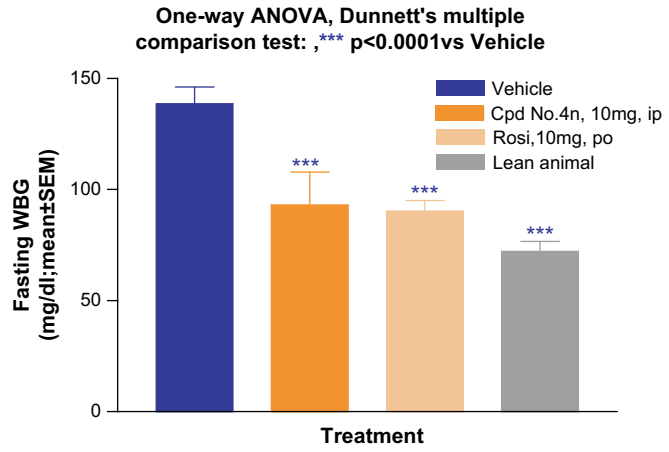


Fig. 3. Effect on fasting WBG in *ob*/*ob* mice on day 10.

6.1.8. Synthesis of L-(−)-3-(4-nitro phenyl) lactic acid

To a solution of 4-nitro-L-phenylalanine (20 mmol) in 1 N H_2SO_4 (120 mL) while stirring at 0 °C, was added an aqueous solution of sodium nitrite (40 mmol), dropwise and the reaction mixture was stirred for 6 h while allowing the reaction mixture to warm to room temperature. The reaction mixture was then extracted with ethyl acetate and the organic layer was washed with water and brine and concentrated to give L-(−)-3-(4-nitro phenyl)-lactic acid. Yield: 77%; Mp: 126 °C; IR (KBr): 3485, 3419, 2930, 1715, 1601, 1539, 1515, 1342, 1279, 1223, 1104, and 932 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 8.14 (d, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 7.8$ Hz, 2H), 4.45 (br s, 1H), 3.32–3.22 (m, 1H), 3.14–3.00 (m, 1H); MS (*m*/*z*): 214.18 $(M + H)^+$.

6.1.9. Synthesis of L-(−)-3-(4-nitro phenyl) lactic acid methyl ester (**10**)

To a solution of L-(−)-3-(4-nitro phenyl)-lactic acid (15 mmol) in methanol (50 mL) was added catalytic amount of conc. sulphuric acid and the reaction mixture was refluxed for 4 h. Solvent was then evaporated from the reaction mixture on rotavapor, diluted the residue with ethyl acetate and was washed with sat. sodium bicarbonate solution followed by water and brine and the organic layer was concentrated to give L-(−)-3-(4-nitro phenyl)-lactic acid methyl ester. Yield: 88%; Mp: 113 °C; ^1H NMR ($CDCl_3$): δ 8.15 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 8.7$ Hz, 2H), 4.50–4.47 (m, 1H), 3.80 (s, 3H), 3.27–3.21 (dd, $J = 4.2$ Hz and 14. 1 Hz, 1H), 3.09–3.02 (dd, $J = 4.2$ Hz and 14.1 Hz, 1H), 2.86 (br s, 1H); MS (*m*/*z*): 228.21 $(M + H)^+$.

6.1.10. General procedure for etherification of L-(−)-3-(4-nitro phenyl) lactic acid methyl ester (**11**)

To a solution of L-(−)-3-(4-nitro phenyl)-lactic acid methyl ester (2 mmol) in toluene (10 mL) was added the alkyl iodide (6 mmol) followed by silver(I)oxide (2 mmol) and refluxed the reaction mixture for 5 h. The reaction mixture was then filtered through

celite, the celite bed was washed with ethyl acetate, the filtrate and the washings were combined and concentrated to give the corresponding ether. The crude ether was purified by column chromatography on a silica gel column using a mixture of ethyl acetate and chloroform as the eluent.

*6.1.10.1. 2(S)-Methoxy-3-(4-nitro phenyl) propanoic acid methyl ester (**11a**).* Yield: 66%; Mp: 147 °C; ^{1}H NMR ($CDCl_3$): δ 8.14 (d, $J = 8.7$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 2H), 4.02–3.96 (m, 1H), 3.75 (s, 3H), 3.36 (s, 3H), 3.19–3.05 (m, 2H); MS (m/z): 242.24 $(M + H)^+$.

*6.1.10.2. 2(S)-Ethoxy-3-(4-nitro phenyl) propanoic acid methyl ester (**11b**).* Yield: 71%; Mp: 172 °C; ^{1}H NMR ($CDCl_3$): δ 8.15 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.1$ Hz, 2H), 4.00–3.94 (m, 1H), 3.78 (s, 3H), 3.65–3.59 (m, 1H), 3.26–3.19 (m, 1H), 3.19–3.05 (m, 2H), 1.24 (t, $J = 7.8$ Hz, 3H); MS (m/z): 256.18 $(M + H)^+$.

*6.1.10.3. 3-(4-Nitro phenyl)-2(S)-propoxy propanoic acid methyl ester (**11c**).* Yield: 60%; Mp: 168 °C; ^{1}H NMR ($CDCl_3$): δ 8.17 (d, $J = 8.1$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 4.06–3.98 (m, 1H), 3.80 (s, 3H), 3.63–3.60 (m, 1H), 3.25–3.21 (m, 1H), 3.17–3.04 (m, 2H), 1.26 (m, 2H), 0.87 (t, $J = 7.5$ Hz, 3H). MS (m/z): 270.22 $(M + H)^+$.

*6.1.10.4. 2(S)-Butoxy-3-(4-nitro phenyl) propanoic acid methyl ester (**11d**).* Yield: 63%; Mp: 191 °C; ^{1}H NMR ($CDCl_3$): δ 8.14 (d, $J = 8.7$ Hz, 2H), 7.40 (d, $J = 8.7$ Hz, 2H), 4.05–4.00 (m, 1H), 3.74 (s, 3H), 3.62–3.55 (m, 1H), 3.26–3.18 (m, 1H), 3.12–3.08 (m, 2H), 1.55–1.42 (m, 2H), 1.30–1.21 (m, 2H), 0.84 (t, $J = 7.5$ Hz, 3H); MS (m/z): 284.23 $(M + H)^+$.

*6.1.11. General procedure for catalytic hydrogenation of 2(S)-alkoxy-3-(4-nitro phenyl) propanoic acid methyl ester (**12**)*

To a solution of 2(*S*)-alkoxy-3-(4-nitro phenyl) propanoic acid methyl ester (1.2 mmol) in ethyl acetate (10 mL) in a hydrogenation flask, 10%pd/C (20 mg) was added and the reaction mixture was subjected to hydrogenation at 60 psi hydrogen pressure in a Parr apparatus, for 3 h. The reaction mixture was then filtered through celite, the celite bed was washed with ethyl acetate, the filtrate and washings were combined and concentrated to give 2(*S*)-alkoxy-3-(4-amino phenyl) propanoic acid methyl ester in sufficiently pure form to be used in the next step without further purification.

*6.1.11.1. 3-(4-Amino phenyl)-2-methoxy-2(S)-propanoic acid methyl ester (**12a**).* Yield: 89%; Mp: 129 °C; ^{1}H NMR ($CDCl_3$): δ 6.96 (d, $J = 6.9$ Hz, 2H), 6.54 (d, $J = 7.2$ Hz, 2H), 4.00–3.96 (m, 1H), 3.72 (s, 3H), 3.30 (s, 3H), 3.14–3.02 (m, 2H); MS (m/z): 210.18 $(M + H)^+$.

*6.1.11.2. 3-(4-Amino phenyl)-2-ethoxy-2(S)-propanoic acid methyl ester (**12b**).* Yield: 92%; Mp: 158 °C; ^{1}H NMR ($CDCl_3$): δ 7.02 (d, $J = 6.9$ Hz, 2H), 6.73 (d, $J = 7.8$ Hz, 2H), 3.97–3.92 (m, 1H), 3.82 (s, 3H), 3.62–3.58 (m, 1H), 3.24–3.19 (m, 1H), 3.19–3.05 (m, 2H), 1.26 (t, $J = 7.5$ Hz, 3H); MS (m/z): 224.22 $(M + H)^+$.

*6.1.11.3. 3-(4-Amino phenyl)-2-propoxy-2(S)-propanoic acid methyl ester (**12c**).* Yield: 79%; Mp: 147 °C; ^{1}H NMR ($CDCl_3$): δ 7.05 (d, $J = 6.9$ Hz, 2H), 6.71 (d, $J = 7.2$ Hz, 2H), 3.98–3.92 (m, 1H), 3.79 (s, 3H), 3.60–3.58 (m, 1H), 3.23–3.20 (m, 1H), 3.15–3.04 (m, 2H), 1.28 (m, 2H), 0.83 (t, $J = 7.8$ Hz, 3H); MS (m/z): 238.17 $(M + H)^+$.

*6.1.11.4. 3-(4-Amino phenyl)-2-butoxy-2(S)-propanoic acid methyl ester (**12d**).* Yield: 84%; Mp: 162 °C; ^{1}H NMR ($CDCl_3$): δ 7.00 (d, $J = 6.6$ Hz, 2H), 6.60 (d, $J = 7.5$ Hz, 2H), 3.93 (t, $J = 6.9$ Hz, 1H), 3.69 (s, 3H), 3.56–3.48 (m, 1H), 3.28–3.21 (m, 1H), 2.91–2.86 (m, 2H), 1.56–1.46 (m, 2H), 1.36–1.23 (m, 2H), 0.85 (t, $J = 7.2$ Hz, 3H); MS (m/z): 252.24 $(M + H)^+$.

6.2. Spectral data of intermediate acids

*6.2.1. 4-Oxo-4-(2-thienyl)butanoic acid (**15a**)*

IR (KBr): 3101, 1697, 1659, 1514, 1415, 1395, 1361, 1229, 1176, 1067 and 946 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, $J = 3.3$ Hz, 1H), 7.63 (d, $J = 5.1$ Hz, 1H), 7.12 (t, $J = 4.5$ Hz, 1H), 3.25 (t, $J = 6.6$ Hz, 2H), 2.80 (t, $J = 6.6$ Hz, 2H); MS (m/z): 185.20 $(M + H)^+$.

*6.2.2. 4-(2-Thienyl)butanoic acid (**16a**)*

IR (Neat): 3107, 2937, 1707, 1411, 1252, 1230, 1172, 1078, 1022 and 848 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.13–7.11 (dd, $J = 0.9$ Hz and 5.4 Hz, 1H), 6.93–6.90 (dd, $J = 3.6$ Hz and 5.1 Hz, 1H), 6.80 (d, $J = 3.0$ Hz, 1H), 2.91 (t, $J = 7.2$ Hz, 2H), 2.42 (t, $J = 7.2$ Hz, 2H), 2.07–1.97 (p, $J = 7.5$ Hz, 2H); MS (m/z): 171.19 $(M + H)^+$.

*6.2.3. 5-Oxo-5-(2-thienyl)pentanoic acid (**15b**)*

IR (KBr): 2964, 1694, 1655, 1511, 1411, 1289, 1234, 1194, 1060 and 922 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, $J = 3.3$ Hz, 1H), 7.62 (d, $J = 5.1$ Hz, 1H), 7.12 (t, $J = 4.5$ Hz, 1H), 3.02 (t, $J = 6.9$ Hz, 2H), 2.50 (t, $J = 6.9$ Hz, 2H), 2.09 (p, $J = 7.2$ Hz, 2H); MS (m/z): 199.16 $(M + H)^+$.

*6.2.4. 5-(2-Thienyl)pentanoic acid (**16b**)*

IR (Neat): 2931, 1709, 1464, 1409, 1310, 1262, 1203, 1072, 929 and 848 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.10–7.07 (dd, $J = 1.2$ Hz and 5.7 Hz, 1H), 6.96–6.93 (dd, $J = 3.9$ Hz and 5.4 Hz, 1H), 6.83 (d, $J = 3.6$ Hz, 1H), 2.94 (t, $J = 7.5$ Hz, 2H), 2.42 (t, $J = 7.2$ Hz, 2H), 2.07–1.97 (p, $J = 7.5$ Hz, 2H), 1.87–1.83 (m, 2H); MS (m/z): 185.24 $(M + H)^+$.

*6.2.5. 4,5-Dibromo valeric acid methyl ester (**18a**)*

^{1}H NMR ($CDCl_3$): δ 4.27–4.18 (m, 1H), 3.88–3.83 (dd, $J = 4.5$ Hz and 10.2 Hz, 1H), 3.69 (s, 3H), 3.66–3.58 (dd, $J = 6.0$ Hz and 10.5 Hz, 1H), 2.68–2.47 (m, 2H), 2.10–2.00 (m, 1H), 1.92–1.74 (m, 1H); MS (m/z): 275.01 $(M + H)^+$.

*6.2.6. 4,5-Bis (acetyl sulfanyl)valeric acid methyl ester (**19a**)*

^{1}H NMR ($CDCl_3$): δ 3.70–3.60 (m, 1H), 3.66 (s, 3H), 3.26–3.10 (m, 2H), 2.44–2.37 (m, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 2.14–2.02 (m, 1H), 1.89–1.76 (m, 1H); MS (m/z): 265.40 $(M + H)^+$.

*6.2.7. 4,5-Dimercapto valeric acid methyl ester (**20a**)*

^{1}H NMR ($CDCl_3$): δ 3.67 (s, 3H), 2.94–2.84 (m, 1H), 2.79–2.75 (m, 1H), 2.69–2.43 (m, 2H), 2.25–2.05 (m, 1H), 1.80–1.63 (m, 2H); MS (m/z): 167.28 $(M + H)^+$.

*6.2.8. 3-(2,2-Dimethyl-1,3-dithiolan-4-yl)propanoic acid (**21a**)*

^{1}H NMR ($CDCl_3$): δ 3.96–3.86 (m, 1H), 3.46–3.40 (dd, $J = 5.1$ Hz and 12.0 Hz, 1H), 3.15–3.08 (dd, $J = 6.6$ Hz and 12.0 Hz, 1H), 2.58–2.44 (m, 2H), 2.18–2.05 (m, 2H), 1.82 (s, 3H), 1.78 (s, 3H); MS (m/z): 207.35 $(M + H)^+$.

*6.2.9. 3-(2,2-Diphenyl-1,3-dithiolan-4-yl)propanoic acid (**21b**)*

^{1}H NMR ($CDCl_3$): δ 7.62–7.53 (m, 4H), 7.30–7.20 (m, 6H), 4.00–3.92 (p, $J = 6.3$ Hz, 1H), 3.38–3.32 (dd, $J = 5.7$ Hz and 11.7 Hz, 1H), 3.12–3.06 (dd, $J = 6.3$ Hz and 11.7 Hz, 1H), 2.55–2.49 (m, 2H), 2.17–2.10 (m, 2H); MS (m/z): 331.51 $(M + H)^+$.

*6.2.10. 6,7-Dibromoheptanoic acid methyl ester (**18c**)*

^{1}H NMR ($CDCl_3$): δ 4.21–4.11 (m, 1H), 3.68 (s, 3H), 3.62 (t, $J = 9.9$ Hz, 1H), 2.36 (t, $J = 7.5$ Hz, 2H), 2.24–2.12 (m, 1H), 1.88–1.58 (m, 5H), 1.55–1.45 (m, 1H); MS (m/z): 303.05 $(M + H)^+$.

*6.2.11. 6,7-Bis (acetylsulfanyl)heptanoic acid methyl ester (**19c**)*

^{1}H NMR ($CDCl_3$): δ 3.72 (s, 3H), 3.3–3.13 (dd, $J = 6.0$ Hz, 2H), 2.39 (s, 3H), 2.38 (s, 3H), 1.77–1.64 (m, 7H), 1.53–1.43 (m, 2H); MS (m/z): 293.45 $(M + H)^+$.

*6.2.12. 6,7-Dimercapto heptanoic acid methyl ester (**20c**)*

^{1}H NMR ($CDCl_3$): δ 3.72 (s, 3H), 2.91–2.80 (m, 1H), 2.77–2.74 (m, 1H), 2.70–2.49 (m, 2H), 2.23–2.02 (m, 1H), 1.82–1.63 (m, 4H), 1.42–1.29 (m, 2H); MS (*m*/*z*): 195.35 $(M+H)^+$.

*6.2.13. 5-(2,2-Dimethyl-1,3-dithiolan-4-yl)pentanoic acid (**21c**)*

^{1}H NMR ($CDCl_3$): δ 3.94–3.85 (m, 1H), 3.48–3.41 (dd, $J=5.4$ Hz and 11.7 Hz, 1H), 3.17–3.10 (dd, $J=6.9$ Hz and 12.0 Hz, 1H), 2.60–2.48 (m, 2H), 2.21–2.10 (m, 2H), 1.82 (s, 3H), 1.78 (s, 3H), 1.45–1.30 (m, 4H); MS (*m*/*z*): 233.41 $(M-H)^+$.

6.2.14. 5-[(3R)-1,2-Dithiolan-3-yl]pentanoic acid methyl ester (R-lipoic acid methyl ester)

^{1}H NMR ($CDCl_3$): δ 3.67 (s, 3H), 3.62–3.52 (m, 1H), 3.21–3.09 (m, 2H), 2.50–2.40 (m, 1H), 2.38–2.30 (m, 2H), 1.95–1.85 (m, 1H), 1.75–1.60 (m, 4H), 1.55–1.45 (m, 2H); MS (*m*/*z*): 221.38 $(M+H)^+$.

*6.2.15. (6R)-6,8-Dimercapto octanoic acid methyl ester (**23**)*

IR (Neat): 2934, 2861, 1708, 1412, 1282, 1088 and 934 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 3H), 2.97–2.86 (m, 1H), 2.82–2.62 (m, 2H), 2.39 (t, $J=7.5$ Hz, 2H), 1.98–1.87 (m, 1H), 1.82–1.74 (m, 1H), 1.72–1.61 (m, 4H), 1.60–1.45 (m, 2H); MS (*m*/*z*): 223.41 $(M+H)^+$.

*6.2.16. 5-[(4R)-1,3-Dithian-4yl]-pentanoic acid methyl ester (**24a**)*

^{1}H NMR ($CDCl_3$): δ 4.04 (d, $J=14.1$ Hz, 1H), 3.55 (d, $J=14.1$ Hz, 1H), 3.87 (s, 3H), 3.16–3.00 (m, 2H), 2.85–2.80 (m, 1H), 2.36 (t, $J=7.5$ Hz, 2H), 2.19–2.14 (br d, 1H), 1.78–1.68 (m, 3H), 1.60–1.47 (m, 4H); MS (*m*/*z*): 233.34 $(M+H)^+$.

*6.2.17. 5-[(4R)-1,3-Dithian-4yl]-pentanoic acid (**25a**)*

^{1}H NMR ($CDCl_3$): δ 4.05 (d, $J=14.1$ Hz, 1H), 3.57 (d, $J=14.1$ Hz, 1H), 3.15–3.05 (m, 2H), 2.87–2.81 (m, 1H), 2.38 (t, $J=7.5$ Hz, 2H), 2.19–2.14 (br d, 1H), 1.78–1.68 (m, 3H), 1.60–1.47 (m, 4H); MS (*m*/*z*): 221.39 $(M+H)^+$.

*6.2.18. 5-[(4R)-2,2-Diphenyl-1,3-dithian-4yl]-pentanoic acid methyl ester (**24b**)*

^{1}H NMR ($CDCl_3$): δ 7.48–7.42 (m, 2H), 7.36–7.16 (m, 8H), 3.91 (s, 3H), 2.85–2.80 (m, 1H), 2.70–2.62 (m, 2H), 2.64 (t, $J=7.2$ Hz, 2H), 2.06–2.01 (br d, 1H), 1.60–1.48 (m, 4H), 1.47–1.40 (m, 3H); MS (*m*/*z*): 387.52 $(M+H)^+$.

*6.2.19. 5-[(4R)-2,2-Diphenyl-1,3-dithian-4yl]-pentanoic acid (**25b**)*

^{1}H NMR ($CDCl_3$): δ 7.50–7.43 (m, 2H), 7.38–7.12 (m, 8H), 2.91–2.83 (m, 1H), 2.75–2.63 (m, 2H), 2.67 (t, $J=7.2$ Hz, 2H), 2.10–2.03 (br d, 1H), 1.65–1.48 (m, 4H), 1.47–1.40 (m, 3H); MS (*m*/*z*): 373.58 $(M+H)^+$.

6.3. General procedure for amidation and hydrolysis

To a solution of the amine (1 mmol) in CH_2Cl_2 (10 mL) under N_2 atmosphere, was added the carboxylic acid (1 mmol) followed by *N*-ethyl-*N*′-dimethylaminopropyl carbodiimide hydrochloride (EDCI·HCl) (1.2 mmol) and triethylamine (3 mmol) and the reaction mixture was stirred at room temperature for 3–5 h. The reaction mixture was then diluted with chloroform and washed with 1 N HCl. The organic layer was then washed with water, followed by brine, dried over Na_2SO_4 and concentrated. To a solution of the above crude ester in aqueous methanol (1:1, 5 mL), was added potassium carbonate (2 mmol) and the reaction mixture was stirred at room temperature for 5–7 h. Methanol was then evaporated from the reaction mixture on rotavapor, diluted the residue with water, washed with diethyl ether and the aqueous layer was then acidified with 1 N HCl. The precipitated product was then filtered, washed with water and dried under vacuum to give the title compounds as off white to pale yellow solids.

*6.3.1. (3S)-6-[4-(2-Thienyl) butylcarboxamido]-isochroman-3-carboxylic acid (**4a**)*

IR (KBr): 3425, 3298, 2936, 1749, 1723, 1651, 1529, 1415, 1195 and 1104 cm^{-1}. ^{1}H NMR: δ 9.82 (s, 1H), 7.37–7.32 (m, 2H), 7.29–7.26 (dd, $J=1.2$ Hz and 5.1 Hz, 1H), 6.95–6.90 (m, 2H), 6.84–6.82 (m, 1H), 4.80–4.60 (AB q, $J=15$ Hz, 2H), 4.20–4.15 (dd, $J=4.8$ Hz and 9.0 Hz, 1H), 2.88–2.80 (m, 4H), 2.31 (br s, 2H), 1.68–1.58 (m, 4H); MS (*m*/*z*): 360.43 $(M+H)^+$.

*6.3.2. (3S)-7-[4-(2-Thienyl)butylcarboxamido]-isochroman-3-carboxylic acid (**4b**)*

IR (KBr): 3420, 3302, 2936, 1727, 1658, 1524, 1424, 1242, 1198, 1104 and 1031 cm^{-1}. ^{1}H NMR: δ 9.83 (s, 1H), 7.31 (s, 1H), 7.28–7.25 (m, 2H), 7.03 (d, $J=8.4$ Hz, 1H), 6.92–6.90 (m, 1H), 6.83–6.81 (m, 1H), 4.81–4.59 (AB q, $J=15$ Hz, 2H), 4.11–4.06 (dd, $J=5.4$ Hz and 9.3 Hz, 1H), 2.85–2.78 (m, 4H), 2.34–2.28 (m, 2H), 1.68–1.60 (m, 4H); MS (*m*/*z*): 360.43 $(M+H)^+$.

*6.3.3. (3S)-6-[3-(2-Thienyl)propylcarboxamido]-isochroman-3-carboxylic acid (**4c**)*

IR (KBr): 3433, 3289, 2918, 1748, 1724, 1654, 1592, 1529, 1423, 1301, 1228, 1196, 1105 and 1027 cm^{-1}. ^{1}H NMR: δ 9.83 (s, 1H), 7.40 (s, 1H), 7.34 (d, $J=8.4$ Hz, 1H), 7.30 (d, $J=4.8$ Hz, 1H), 6.96–6.91 (m, 2H), 6.85 (s, 1H), 4.81–4.62 (AB q, $J=15$ Hz, 2H), 4.28–4.23 (dd, $J=5.1$ Hz and 8.7 Hz, 1H), 2.88–2.80 (m, 4H), 2.34 (t, $J=7.5$ Hz, 2H), 1.96–1.85 (p, $J=7.2$ Hz, 2H); MS (*m*/*z*): 346.41 $(M+H)^+$.

*6.3.4. (3S)-7-[3-(2-Thienyl)propylcarboxamido]-isochroman-3-carboxylic acid (**4d**)*

IR (KBr): 3292, 2920, 2851, 1729, 1654, 1597, 1533, 1419, 1361, 1239, 1190, 1104 and 1030 cm^{-1}. ^{1}H NMR: δ 9.83 (s, 1H), 7.36 (s, 1H), 7.30–7.26 (m, 2H), 7.07 (d, $J=8.4$ Hz, 1H), 6.94–6.91 (m, 1H), 6.85–6.84 (m, 1H), 4.83–4.67 (AB q, $J=15$ Hz, 2H), 4.33–4.28 (dd, $J=4.8$ Hz and 9.3 Hz, 1H), 2.95–2.80 (m, 4H), 2.34 (t, $J=7.2$ Hz, 2H), 1.95–1.80 (p, $J=7.2$ Hz, 2H); MS (*m*/*z*): 346.41 $(M+H)^+$.

*6.3.5. (3S)-6-[2-(2,2-Dimethyl-1,3-dithiolan-4-yl)ethylcarboxamido]-isochroman-3-carboxylic acid (**4e**)*

IR (KBr): 3289, 2915, 1726, 1652, 1530, 1426, 1363, 1242, 1193, 1105 and 1037 cm^{-1}. ^{1}H NMR: δ 7.37 (s, 1H), 7.31 (d, $J=8.4$ Hz, 1H), 7.16 (s, 1H), 6.97 (d, $J=8.1$ Hz, 1H), 5.01–4.85 (AB q, $J=15$ Hz, 2H), 4.38–4.33 (dd, $J=4.5$ Hz and 10.5 Hz, 1H), 3.98–3.90 (m, 1H), 3.47–3.40 (dd, $J=5.1$ Hz and 12 Hz, 1H), 3.17–3.04 (m, 3H), 2.52–2.41 (m, 2H), 2.32–2.22 (m, 1H), 2.16–2.08 (m, 1H), 1.82 (s, 3H), 1.79 (s, 3H); MS (*m*/*z*): 382.50 $(M+H)^+$.

*6.3.6. (3S)-7-[2-(2,2-Dimethyl-1,3-dithiolan-4-yl)ethylcarboxamido]-isochroman-3-carboxylic acid (**4f**)*

IR (KBr): 3291, 2917, 1729, 1655, 1533, 1429, 1367, 1246, 1197, 1103 and 1039 cm^{-1}. ^{1}H NMR: δ 7.46 (s, 1H), 7.23 (s, 1H), 7.10 (s, 2H), 5.02–4.87 (AB q, $J=15$ Hz, 2H), 4.37–4.32 (dd, $J=3.9$ Hz and 10.5 Hz, 1H), 3.96–3.91 (m, 1H), 3.46–3.41 (dd, $J=5.4$ Hz and 12 Hz, 1H), 3.17–2.96 (m, 3H), 2.51–2.36 (m, 2H), 2.31–2.23 (m, 1H), 2.14–2.05 (m, 1H), 1.81 (s, 3H), 1.79 (s, 3H); MS (*m*/*z*): 382.50 $(M+H)^+$.

*6.3.7. (3S)-6-[4-(2,2-Dimethyl-1,3-dithiolan-4-yl)butylcarboxamido]-isochroman-3-carboxylic acid (**4g**)*

IR (KBr): 3292, 2916, 1729, 1656, 1537, 1429, 1365, 1246, 1197, 1107 and 1035 cm^{-1}. ^{1}H NMR: δ 7.38 (s, 1H), 7.32 (d, $J=8.1$ Hz, 1H), 7.15 (s, 1H), 7.02 (d, $J=8.1$ Hz, 1H), 4.96–4.79 (AB q, $J=15$ Hz, 2H), 4.30–4.40 (m, 1H), 3.90–3.79 (m, 1H), 3.39–3.33 (dd, $J=4.5$ Hz, 1H), 3.12–3.04 (m, 3H), 2.38–2.34 (t, $J=6.9$ Hz, 2H), 1.82–1.69 (m, 10H), 1.51–1.43 (m, 2H); MS (*m*/*z*): 410.55 $(M+H)^+$.

*6.3.8. (3S)-7-[4-(2,2-Dimethyl-1,3-dithiolan-4-yl)butylcarboxamido]-isochroman-3-carboxylic acid (**4h**)*

IR (KBr): 3292, 2917, 1725, 1651, 1535, 1422, 1369, 1254, 1201, 1111 and 1042 cm^{-1}. ^1H NMR: δ 7.4 (s, 1H), 7.35 (br s, 1H), 7.13 (d, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 8.1$ Hz, 1H), 4.98–4.79 (AB q, $J = 15$ Hz, 2H), 4.31–4.41 (m, 1H), 3.91–3.80 (m, 1H), 3.40–3.34 (dd, $J = 4.5$ Hz, 1H), 3.11–3.05 (m, 3H), 2.39–2.35 (t, $J = 7.2$ Hz, 2H), 1.82–1.69 (m, 10H), 1.51–1.43 (m, 2H); MS (m/z): 410.55 $(M + H)^+$.

*6.3.9. (3S)-6-[2-(2,2-Diphenyl-1,3-dithiolan-4-yl)ethylcarboxamido]-isochroman-3-carboxylic acid (**4i**)*

IR (KBr): 3290, 2919, 1729, 1647, 1538, 1427, 1372, 1257, 1204, 1108 and 1047 cm^{-1}. ^1H NMR: δ 7.60–7.53 (m, 3H), 7.32–7.21 (m, 10H), 6.96 (d, $J = 8.1$ Hz, 1H), 5.00–4.84 (AB q, $J = 15$ Hz, 2H), 4.37–4.32 (dd, $J = 4.2$ Hz and 10.8 Hz, 1H), 4.02–3.97 (m, 1H), 3.39–3.33 (m, 1H), 3.15–3.02 (m, 3H), 2.54–2.42 (m, 2H), 2.33–2.26 (m, 1H), 2.22–2.14 (m, 1H); MS (m/z): 506.66 $(M + H)^+$.

*6.3.10. (3S)-7-[2-(2,2-Diphenyl-1,3-dithiolan-4-yl)ethylcarboxamido]-isochroman-3-carboxylic acid (**4j**)*

IR (KBr): 3287, 2921, 1731, 1649, 1528, 1423, 1370, 1252, 1207, 1102 and 1049 cm^{-1}. ^1H NMR: δ 7.60–7.53 (m, 3H), 7.43 (br s, 1H), 7.30–7.21 (m, 8H), 7.09 (br s, 2H), 5.02–4.88 (AB q, $J = 15$ Hz, 2H), 4.38–4.33 (dd, $J = 3.9$ Hz and 10.5 Hz, 1H), 4.05–3.95 (m, 1H), 3.39–3.34 (dd, $J = 6.0$ Hz and 12 Hz, 1H), 3.17–3.00 (m, 3H), 2.54–2.41 (m, 2H), 2.33–2.26 (m, 1H), 2.22–2.14 (m, 1H); MS (m/z): 506.66 $(M + H)^+$.

*6.3.11. (3S)-6-[4-(1,2-Dithiolan-3-yl)butylcarboxamido]-isochroman-3-carboxylic acid (**4k**)*

IR (KBr): 3515, 3294, 2929, 1653, 1592, 1528, 1425, 1331, 1257, 1093 and 1052 cm^{-1}. ^1H NMR: δ 9.80 (s, 1H), 7.40–7.30 (m, 2H), 6.90 (d, $J = 8.2$ Hz, 1H), 4.80–4.49 (AB q, $J = 14.6$ Hz, 2H), 3.76–3.42 (m, 2H), 3.22–3.06 (m, 3H), 2.90–2.70 (m, 2H), 2.45–2.30 (m, 1H), 2.27 (t, $J = 7.0$ Hz, 2H), 1.92–1.81 (m, 1H), 1.76–1.30 (m, 5H); ^{13}C (75 MHz, DMSO-d_6, δ): 173.92, 171.01, 137.53, 134.24, 129.47, 119.12, 117.04, 75.63, 66.87, 56.33, 38.86, 38.35, 36.42, 34.44, 31.94, 28.65, 25.21. MS (m/z): 382.53 $(M + H)^+$.

*6.3.12. (3S)-7-[4-(1,2-Dithiolan-3-yl)butylcarboxamido]-isochroman-3-carboxylic acid (**4l**)*

IR (KBr): 3512, 3297, 2931, 1650, 1589, 1526, 1423, 1328, 1259, 1096 and 1049 cm^{-1}. ^1H NMR: δ 9.81 (s, 1H), 7.42–7.31 (m, 2H), 6.92 (d, $J = 8.1$ Hz, 1H), 4.82–4.51 (AB q, $J = 14.6$ Hz, 2H), 3.78–3.43 (m, 2H), 3.21–3.07 (m, 3H), 2.92–2.73 (m, 2H), 2.47–2.32 (m, 1H), 2.27 (t, $J = 7.0$ Hz, 2H), 1.92–1.83 (m, 1H), 1.76–1.32 (m, 5H); MS (m/z): 382.53 $(M + H)^+$.

*6.3.13. (3S)-6-{4-[(3R)-1,2-Dithiolan-3-yl]butylcarboxamido}-isochroman-3-carboxylic acid (**4m**)*

IR (KBr): 3535, 3303, 2930, 1718, 1652, 1591, 1526, 1414, 1248, 1195, 1118 and 1060 cm^{-1}. ^1H NMR: δ 9.80 (s, 1H), 7.41 (s, 1H), 7.35 (d, $J = 8.4$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 4.82–4.65 (AB q, $J = 15$ Hz, 2H), 4.34–4.29 (dd, $J = 4.8$ Hz and 8.7 Hz, 1H), 3.68–3.58 (m, 2H), 3.23–3.07 (m, 3H), 2.95–2.87 (m, 2H), 2.48–2.36 (m, 1H), 2.28 (t, $J = 6.9$ Hz, 2H), 1.93–1.82 (m, 1H), 1.71–1.56 (m, 2H), 1.44–1.37 (m, 2H); ^{13}C (75 MHz, DMSO-d_6, δ): 172.15, 170.98, 137.67, 132.18, 128.71, 124.52, 119.02, 117.45, 72.39, 66.41, 56.29, 38.88, 38.32, 36.41, 34.39, 30.55, 28.57, 25.15. MS (m/z): 382.53 $(M + H)^+$.

*6.3.14. (3S)-7-{4-[(3R)-1,2-Dithiolan-3-yl]butylcarboxamido}-isochroman-3-carboxylic acid (**4n**)*

IR (KBr): 3483, 3290, 2935, 1729, 1655, 1599, 1534, 1505, 1423, 1238, 1195 and 1105 cm^{-1}. ^1H NMR: δ 9.81 (br s, 1H), 7.35 (s, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 4.90–4.71 (AB q, $J = 15$ Hz, 2H), 4.24–4.19 (dd, $J = 6.0$ Hz and 9.0 Hz, 1H), 3.54–3.45 (m, 1H), 3.14–3.00 (m, 2H), 2.96–2.90 (m, 2H), 2.43–2.32 (m, 1H), 2.27 (t, $J = 7.5$ Hz, 2H), 1.89–1.80 (m, 1H), 1.68–1.58 (m, 4H), 1.47–1.39 (m, 2H); ^{13}C (75 MHz, DMSO-d_6, δ): 172.20, 171.02, 137.48, 134.27, 128.98, 126.42, 117.67, 114.57, 72.55, 66.77, 56.33, 38.86, 38.35, 36.43, 34.43, 29.93, 28.61, 25.20. MS (m/z): 382.53 $(M + H)^+$.

*6.3.15. (3S)-6-{4-[(4S)-2-Oxoperhydrothieno-[3,4-d]imidazol-4-yl]butylcarboxamido}-isochroman-3-carboxylic acid (**4o**)*

IR (KBr): 3284, 2933, 1701, 1674, 1651, 1532, 1426, 1313, 1195 and 1031 cm^{-1}. ^1H NMR: δ 9.80 (s, 1H), 7.40 (s, 1H), 7.34 (d, $J = 9.0$ Hz, 1H), 6.95 (d, $J = 8.1$ Hz, 1H), 6.42 (s, 1H), 6.35 (s, 1H), 4.81–4.64 (AB q, $J = 15$ Hz, 2H), 4.33–4.26 (m, 2H), 4.14–4.10 (m, 1H), 3.15–3.07 (m, 1H), 2.90–2.77 (m, 2H), 2.56 (d, $J = 12.6$ Hz, 1H), 2.27 (t, $J = 7.2$ Hz, 2H), 1.65–1.55 (m, 3H), 1.40–1.30 (m, 2H); MS (m/z): 418.51 $(M - H)^-$.

*6.3.16. (3S)-7-{4-[(4S)-2-Oxoperhydrothieno-[3,4-d]imidazol-4-yl]butylcarboxamido}-isochroman-3-carboxylic acid (**4p**)*

IR (KBr): 3286, 2937, 1697, 1678, 1654, 1536, 1429, 1317, 1201 and 1028 cm^{-1}. ^1H NMR: δ 9.79 (s, 1H), 7.42 (s, 1H), 7.36 (d, $J = 8.7$ Hz, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 6.41 (s, 1H), 6.36 (s, 1H), 4.81–4.66 (AB q, $J = 15$ Hz, 2H), 4.34–4.27 (m, 2H), 4.12–4.10 (m, 1H), 3.15–3.09 (m, 1H), 2.90–2.78 (m, 2H), 2.56 (d, $J = 12.3$ Hz, 1H), 2.28 (t, $J = 7.2$ Hz, 2H), 1.65–1.57 (m, 3H), 1.40–1.32 (m, 2H); MS (m/z): 418.51 $(M - H)^-$.

*6.3.17. (3S)-6-{4-[(4R)-1,3-Dithian-4-yl]butylcarboxamido}-isochroman-3-carboxylic acid (**4q**)*

IR (KBr): 3285, 2939, 1701, 1673, 1657, 1539, 1432, 1315, 1198 and 1031 cm^{-1}. ^1H NMR: δ 7.39 (s, 1H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.18 (s, 1H), 6.97 (d, $J = 8.1$ Hz, 1H), 5.01–4.85 (AB q, $J = 15$ Hz, 2H), 4.40–4.35 (dd, $J = 4.5$ Hz and 10.2 Hz, 1H), 4.04 (d, $J = 13.8$ Hz, 1H), 3.55 (d, $J = 14.1$ Hz, 1H), 3.16–3.00 (m, 2H), 2.86–2.79 (m, 3H), 2.37 (t, $J = 6.9$ Hz, 2H), 2.19–2.14 (br d, 1H), 1.78–1.68 (m, 3H), 1.60–1.47 (m, 4H); MS (m/z): 396.54 $(M + H)^+$.

*6.3.18. (3S)-7-{4-[(4R)-1,3-Dithian-4-yl]butylcarboxamido}-isochroman-3-carboxylic acid (**4r**)*

IR (KBr): 3288, 2941, 1693, 1678, 1655, 1541, 1434, 1319, 1204 and 1034 cm^{-1}. ^1H NMR: δ 7.47 (br s, 1H), 7.11 (br s, 3H), 5.02–4.86 (AB q, $J = 15$ Hz, 2H), 4.39–4.34 (dd, $J = 4.2$ Hz and 10.2 Hz, 1H), 4.04 (d, $J = 14.1$ Hz, 1H), 3.55 (d, $J = 14.1$ Hz, 1H), 3.17–2.95 (m, 2H), 2.88–2.80 (m, 3H), 2.36 (t, $J = 7.5$ Hz, 2H), 2.19–2.14 (br d, 1H), 1.82–1.67 (m, 3H), 1.60–1.50 (m, 4H); MS (m/z): 396.54 $(M + H)^+$.

*6.3.19. (3S)-6-{4-[(4R)-2,2-Diphenyl-1,3-dithian-4-yl]butylcarboxamido}-isochroman-3-carboxylic acid (**4s**)*

IR (KBr): 3283, 2942, 1697, 1671, 1659, 1541, 1434, 1317, 1201 and 1029 cm^{-1}. ^1H NMR: δ 9.83 (s, 1H), 7.91 (d, $J = 8.4$ Hz, 2H), 7.46 (t, $J = 7.8$ Hz, 2H), 7.40 (s, 1H), 7.36–7.32 (m, 2H), 7.30–7.16 (m, 5H), 6.95 (d, $J = 8.4$ Hz, 1H), 4.82–4.63 (AB q, $J = 15$ Hz, 2H), 4.31–4.26 (dd, $J = 5.1$ Hz and 8.7 Hz, 1H), 2.95–2.82 (m, 3H), 2.70–2.60 (m, 2H), 2.27 (t, $J = 7.5$ Hz, 2H), 2.03 (d, $J = 12.9$ Hz, 1H), 1.60–1.40 (m, 7H); MS (m/z): 548.74 $(M + H)^+$.

*6.3.20. (3S)-7-{4-[(4R)-2,2-Diphenyl-1,3-dithian-4-yl]butylcarboxamido}-isochroman-3-carboxylic acid (**4t**)*

IR (KBr): 3289, 2950, 1692, 1676, 1653, 1545, 1437, 1319, 1205 and 1032 cm^{-1}. ^1H NMR: δ 9.85 (s, 1H), 7.91 (d, $J = 7.5$ Hz, 2H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.34–7.16 (m, 8H), 7.04 (d, $J = 8.1$ Hz, 1H), 4.81–4.62 (AB q, $J = 15$ Hz, 2H), 4.21–4.16 (dd, $J = 4.2$ Hz and 9.3 Hz, 1H), 2.92–2.80 (m, 3H), 2.70–2.60 (m, 2H), 2.27 (t, $J = 7.5$ Hz, 2H), 2.03 (d, $J = 12.9$ Hz, 1H), 1.60–1.40 (m, 7H); MS (m/z): 548.74 $(M + H)^+$.

*6.3.21. (3S)-7-{4-[(3R)-1,2-Dithiolan-3-yl]butylcarboxamido}-1-oxo-isochroman-3-carboxylic acid (**7**)*

IR (KBr): 3486, 3287, 2937, 1731, 1674, 1658, 1601, 1532, 1507, 1428, 1235, 1199 and 1107 cm^{-1}. ^1H NMR: δ 10.08 (s, 1H), 8.17 (d, $J = 2.4$ Hz, 1H), 7.76–7.72 (dd, $J = 2.1$ Hz and 8.4 Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 5.28–5.24 (m, 1H), 3.67–3.55 (m, 2H), 3.22–3.06 (m, 4H), 2.48–2.35 (m, 1H), 2.31 (t, $J = 7.2$ Hz, 2H), 1.92–1.81 (m, 1H), 1.76–1.35 (m, 5H); MS (*m*/*z*): 396.51 $(M + H)^+$.

*6.3.22. (2S)-3-(4-{4-[(3R)-1,2-Dithiolan-3-yl]butylcarboxamido}phenyl)-2-methoxypropanoic acid (**13a**)*

IR (KBr): 3486, 3287, 2938, 1732, 1658, 1601, 1530, 1508, 1428, 1242, 1193 and 1097 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.59 (s, 1H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 8.1$ Hz, 2H), 4.04–3.96 (m, 1H), 3.62–3.52 (m, 1H), 3.39 (s, 3H), 3.21–2.96 (m, 4H), 2.50–2.40 (m, 1H), 2.40–2.30 (m, 2H), 1.96–1.84 (m, 1H), 1.80–1.65 (m, 4H), 1.55–1.44 (m, 2H); MS (*m*/*z*): 384.54 $(M + H)^+$.

*6.3.23. (2S)-3-(4-{4-[(3R)-1,2-Dithiolan-3-yl]butylcarboxamido}phenyl)-2-ethoxypropanoic acid (**13b**)*

IR (KBr): 3493, 3284, 2933, 1736, 1654, 1604, 1527, 1505, 1431, 1246, 1198 and 1094 cm^{-1}. ^1H NMR: δ 9.80 (s, 1H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 3.96–3.91 (m, 1H), 3.67–3.58 (m, 1H), 3.52–3.44 (m, 2H), 3.25–3.10 (m, 3H), 2.90–2.70 (m, 3H), 2.50–2.35 (m, 1H), 2.31–2.26 (t, $J = 7.8$ Hz, 2H), 1.92–1.80 (m, 1H), 1.70–1.50 (m, 3H), 1.45–1.30 (m, 2H), 1.05–1.01 (t, $J = 6.9$ Hz, 3H); MS (*m*/*z*): 398.56 $(M + H)^+$.

*6.3.24. (2S)-3-(4-{4-[(3R)-1,2-Dithiolan-3-yl]butylcarboxamido}phenyl)-2-propoxypropanoic acid (**13c**)*

IR (KBr): 3489, 3288, 2937, 1738, 1658, 1607, 1531, 1508, 1436, 1248, 1203 and 1097 cm^{-1}. ^1H NMR: δ 9.81 (s, 1H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 3.92–3.86 (m, 1H), 3.67–3.55 (m, 1H), 3.52–3.44 (m, 2H), 3.27–3.09 (m, 4H), 2.89–2.73 (m, 2H), 2.43–2.34 (m, 1H), 2.30–2.27 (m, 2H), 1.94–1.85 (m, 1H), 1.70–1.49 (m, 2H), 1.26–1.17 (m, 4H), 0.85–0.79 (t, $J = 7.2$ Hz, 3H); MS (*m*/*z*): 412.60 $(M + H)^+$.

*6.3.25. (2S)-2-Butoxy-3-(4-{4-[(3R)-1,2-dithiolan-3-yl]butylcarboxamido}phenyl)propanoic acid (**13d**)*

IR (KBr): 3484, 3289, 2934, 1735, 1656, 1606, 1533, 1511, 1431, 1245, 1197 and 1095 cm^{-1}. ^1H NMR: δ 9.78 (s, 1H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.11 (d, $J = 8.7$ Hz, 2H), 3.94–3.88 (m, 1H), 3.66–3.58 (m, 1H), 3.50–3.42 (m, 2H), 3.25–3.06 (m, 4H), 2.92–2.74 (m, 2H), 2.46–2.36 (m, 1H), 2.32–2.25 (m, 2H), 1.92–1.82 (m, 1H), 1.72–1.50 (m, 2H), 1.45–1.35 (m, 2H), 1.28–1.16 (m, 4H), 0.82–0.77 (t, $J = 7.2$ Hz, 3H); MS (*m*/*z*): 426.60 $(M + H)^+$.

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