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Design and synthesis of novel bis-oximinoalkanoic acids as potent PPARα agonists ☆

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ABSTRACT

Bis-oximinoalkanoic acid derivatives were designed and synthesized to aid in the characterization of selective PPARα agonists by replacing the oxazole ring with flexible oximino group in the lipophilic tail part of a previously reported compound **3**. Selected compounds **9d** and **9m** showed excellent potency and high selectivity towards PPARα in vitro. These compounds found effective in reducing serum triglycerides (TG) in vivo.

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors in the nuclear hormone receptor superfamily[1] and are activated by endogenous saturated and unsaturated fatty acids and their metabolites, as well as synthetic ligands.[2] Three distinct PPAR subtypes (PPARα, PPARγ and PPARδ) have been identified in most mammalian species. Each PPAR subtype is differentially expressed in a tissue-specific manner. PPARα is mostly expressed in the tissues involved in lipid oxidation, such as liver, kidney, skeletal, cardiac muscle, and adrenal glands.[3] PPARγ is expressed in adipose tissue, macrophages, and vascular smooth muscles.[4] PPARδ is ubiquitously expressed, though it is mainly found in skeletal muscle and adipose tissues.[5] PPARs form heterodimers with another nuclear receptor partner, retinoid X receptor (RXR), and become functional to regulate gene expression by binding to a specific DNA sequence, termed PPRE (peroxisome proliferator responsive element), located in the promoter region of target genes[6] The multiple roles of the PPARs in physiological regulation of glucose homeostasis, fatty acid metabolism, inflammation and cellular differentiation have been reviewed extensively in recent years.[7] PPARγ is known to play a vital role at a cellular level in adipogenesis and identified as the primary receptor modulating insulin sensitization and thereby exerting antidiabetic activity.[8] Two of these PPARγ agonists, namely Rosiglitazone and Pioglitazone are currently available in the market. Unfortunately, they are also known to cause undesirable side effects including weight gain, edema and anemia in both animal models and humans. PPARα is known to play a pivotal role in the uptake and oxidation of fatty acids and also in lipoprotein metabolism.[9] Fibrate compounds such as Fenofibrate and Bezafibrate were originally developed without knowing their molecular target and are in use to treat hyperlipidemia as they are effective in reducing triglycerides, increasing HDL cholesterol and lowering LDL cholesterol. Subsequent research proved these fibrates to be poor activators of PPARα and need high doses to show significant efficacy. In 1990s the hypothesis that PPARα/γ dual agonism provides an additive, and possibly synergistic, pharmacology has resulted in an intensive effort within the pharmaceutical industry to develop and evaluate these agents.[10] but none of these dual agonists including Farglitazar,[11] Ragaglitazar,[12] Tesaglitazar[13] and Muraglitazar,[14] has been marketed. The unsuccessful efforts to develop dual agonist and recent research findings that activation of PPARα lower triglycerides, elevate HDL and exert insulin-sensitizing effects[15] led to the discovery of potent and selective activators of PPARα as remedy for disorders mediated by lipid and carbohydrate metabolism. Disclosure of LY518674[16] and GW590735[17] as potent and selective PPARα agonists hightened the interest among several research groups to develop such agents. Recently a potent and selective PPARα agonist NS-220[18] (Fig. 1) is reported to exert hypoglycemic and lipid modulating effects in animal models but

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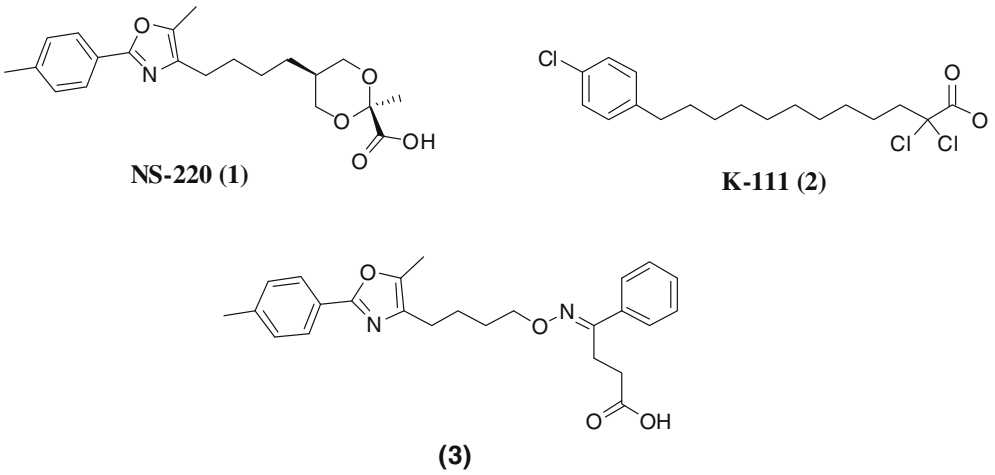


Figure 1. Selective PPARα agonists.

the further development of this compound is discontinued for unknown reasons. Another compound K-111[19] (Fig. 1) a relatively weak PPARα agonist is presently undergoing clinical trails for the treatment of type 2 diabetes. In continuation of our research in the field of PPARs to develop novel therapeutic agents to treat metabolic disorders[20] we have recently reported selective PPARα agonist (**3**)[21] (Fig. 1) derived from the known α/γ dual agonist Imiglitazar employing the chemical modifications in the central spacer region of the typical chemotype of PPAR agonist. Although this compound exhibited high degree of selectivity towards PPARα over γ, its picomolar potency raised concerns of possible toxicity for further development of this compound. Inorder to identify PPARα selective agonists further based on compound **3**, molecular modeling experiments were under taken and based on the results (data not shown) we envisioned that replacement of rigid oxazole heterocycle with a flexible bioisostere would be a good strategy and designed a novel series of bis-oximinoalkanoic acid derivatives centering the modifications in the lipophilic tail as depicted in Figure 2.

Synthesis of intermediate **6** was depicted in Scheme 1. Intermediate **4** was synthesized by Friedel–Crafts acylation of benzene with succinic anhydride. Treatment of **4** with hydroxylamine gave

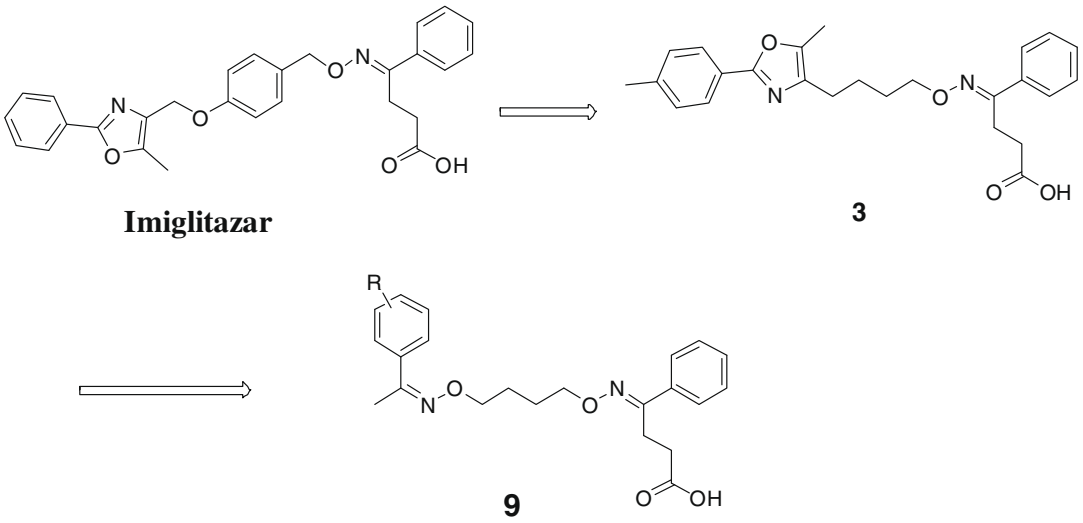
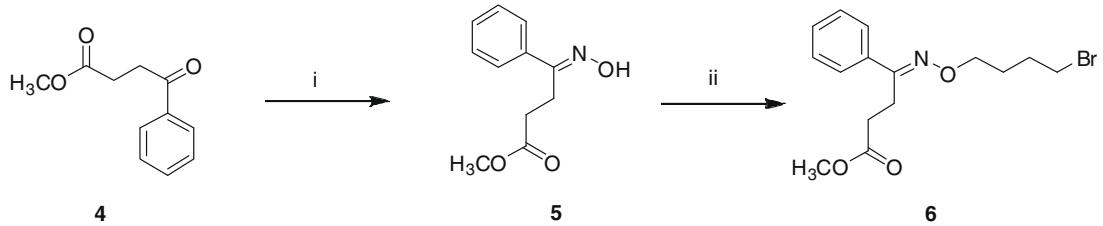
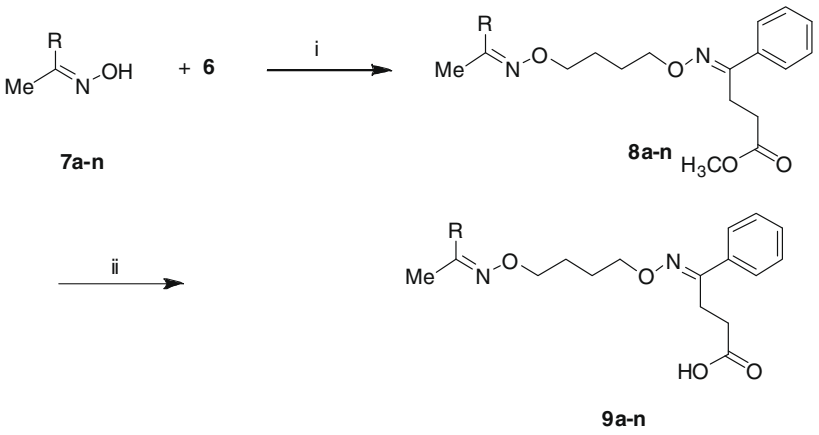


Figure 2. Designing selective PPARα agonist.



Scheme 1. Reagents and conditions: (i) hydroxylammonium chloride, NaOAc, EtOH, reflux, 2 h; (ii) 1,4-dibromobutane, K_2CO_3, DMF, 60 °C, 24 h.

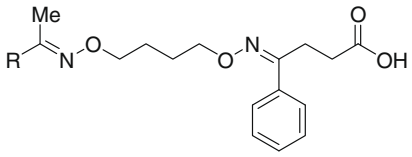


Scheme 2. Reagents and conditions: (i) K_2CO_3, DMF, 60 °C, 8 h; (ii) NaOH, H_2O, MeOH, 25 °C, 18 h.

the oxime derivative as a mixture of *E* and *Z*-isomers and the *E*-isomer **5** was isolated by column chromatography as a major product which showed ^{1}H NMR chemical shifts identical with reported values.[22] Alkylation of **5** with 1,4-dibromobutane gave the intermediate **6** in good yields. Synthesis of compounds **9a**–**n** were described in Scheme 2. Oximes **7a**–**n** were synthesized by reacting the corresponding acetophenone with hydroxylamine and are considered to be *E*-isomers as these are reported to be thermodynamically more stable than *Z*-isomers.[23] Coupling reaction between intermediate **6** and oximes **7a**–**n** under basic conditions gave the ester derivatives **8a**–**n** which upon hydrolysis under aqueous basic conditions gave the acids **9a**–**n**.

Compounds **9a**–**n**[24] were screened for hPPARα, γ and δ agonistic activity on full length PPAR receptors transfected in HepG2 cells. WY-14643, Rosiglitazone and GW-501516 were used as controls for PPARα, γ and δ, respectively, and the results are summarized in Table 1 where the activities were reported as EC_{50} values and percent maximal activity of each compound compared to

Table 1
In vitro hPPAR transactivation and TG reducing activity of compounds **9a**–**n**



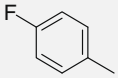
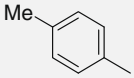
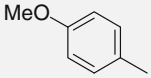
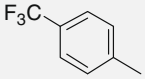
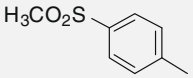
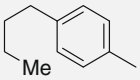
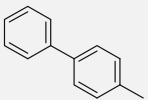
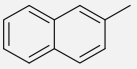
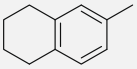
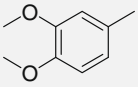
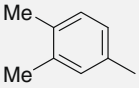
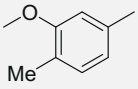
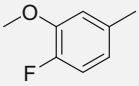
Compd	R	PPAR transactivation[a] EC_{50} (% activation)[b]		% reduction in TG in SAM[c]
		α	γ	
9a		2.3 (46)	IA	ND
9b		0.05 (101)	1.4 (69)	18
9c		0.05 (78)	2.1 (69)	13
9d		0.01 (102)	1.1 (13)	35
9e		0.4 (79)	1.4 (37)	0.6
9f		2.4 (41)	1.9 (49)	14
9g		0.5 (85)	0.2 (64)	31
9h		0.02 (83)	0.1 (52)	23

Table 1 (*continued*)

Compd	R	PPAR transactivation[a] EC_{50} (% activation)[b]		% reduction in TG in SAM[c]
		α	γ	
9i		0.03 (61)	0.2 (50)	25
9j		0.003 (86)	0.2 (61)	36
9k		0.1 (136)	0.8 (45)	30
9l		0.002 (89)	1.0 (48)	12
9m		0.005 (257)	1.6 (60)	36
9n		0.4 (122)	0.7 (76)	19
Imiglitazar		0.005 (116)	0.004 (89)	37

[a] HepG2 cells were transfected with pSG5 expression vector containing the cDNA of hPPARα or hPPARγ or hPPARδ and cotransfected with PPRE3-TK-luc. The Luciferase activity was determined using commercial fire-fly luciferase assay and β-galactosidase activity was determined in ELISA reader.

[b] Percent of maximal activation of all compounds was compared to reference compounds (WY-14643 for α and Rsiglitazone for γ) normalized to 100%. IA denotes inactive.

[c] The test compounds were administered orally at a dose of 10 mg/kg/day to male *swissalbino* mice (SAM) of 6–8 weeks of age for 6 days. Mean values ($n = 6$) are the% change in serum triglyceride (TG) concentration of the compound-treated mice versus vehicle controls. All values are the mean of $n = 6$. ND denotes not determined.

reference compound normalized to 100%. None of the compounds show any fold induction above the basal level (shown by vehicle) up to 1 μM concentration towards PPARδ. Triglyceride lowering activity was measured by administering the compounds orally at a dose of 10 mg/kg/day for 6 days to male *swissalbino* mice (SAM) which are moderately hyperlipidemic. Values reported are the % change in plasma triglyceride (TG) concentration of the compound-treated mice relative to vehicle controls and are given in Table 1. Our goal was to develop potent and selective PPARα agonist that did not contain phenyloxazole group starting from compound **3** reported previously by our group. We decided to design the compounds **9** by replacing the oxazole ring with an oximino group expecting it to behave as a bioisostere of oxazole and synthesised the compounds **9a**–**n**. As the initial compound **9a** was found to be inactive, we envisioned based on our experience that substitution at metabolically susceptible *para* position of phenyl ring of tail part may play an important role in the modulation of potency and selectivity of the compounds which became evident from the in vitro activity of **9b**. Compounds **9c** and **9d** with electron-donating methyl and methoxy groups respectively were found to be potent and selective towards PPARα. **9d** exhibited 110-fold selectivity towards PPARα over γ and reduced plasma triglycerides by 35% in the SAM model whereas **9c** though exhibited potency similar to **9d** in vitro did not show significant TG reduction in vivo. Substitution on this position with electron-withdrawing groups exhibited detrimental effects both in vitro and in vivo, which is evident from the activity of **9e** and **9f** possessing trifluoromethyl and methanesulfonyl groups, respectively. We then intended to study the effect of bulky substituents on the phenyl ring. **9g**, with an *n*-butyl group, was found to be a weak activator of PPARα and γ with an EC_{50} of 0.5 and 0.2 μM, respectively. To our surprise this compound reduced TG by 31%. Further increase of the bulk at this position by introducing a phenyl ring made the compound **9h** a potent activator of PPARα but found to be only fivefold selective over PPARγ. Replacing the flexible *n*-butyl chain with a rigid group by fusing the 3- and 4-positions into a naphthyl or tetrahydronaphthyl group gave the respective compounds **9i** and **9j** showed surprising and interesting results. Compounds **9i** and **9j** found to be equipotent towards PPARγ. **9i** exhibited sixfold selectivity towards PPARα over γ and reduced TG by 25% in vivo whereas **9j** is found to be 10-fold more potent than **9i** towards PPARα and showed 36% reduction in TG. These results suggests that increasing the bulk of the lipophilic tail increases the affinity of the compounds towards PPARγ and guided us to study the effect of substituents on both 3- and 4-positions of the phenyl ring. Since electron-donating groups appeared to be favorable, we chose methoxy and methyl as well as electron-withdrawing fluoro groups and synthesised the compounds **9k**, **9l**, **9m** and **9n**. Among these compounds **9k** and **9n** showed weak and equal affinity towards PPARα and γ but **9k** reduced TG by 30% in vivo whereas **9n** did not show significant reduction in TG. Compound **9l** with two methyl groups found to be the most potent and highly selective towards PPARα with an EC_{50} of 0.002 μM and 500-fold selectivity over γ. But this compound is not efficacious in reducing TG in vivo. Compound **9m** with methoxy group at *meta* position and methyl group at *para* position exhibited similar potency and selectivity as **9l** in vitro with an EC_{50} of 0.002 μM towards PPARα and 320-fold selectivity over γ. This compound reduced TG by 36% in vivo. Compounds **9d** and **9m** were identified as lead compounds for further evaluation in lipid lowering animal models and pharmacokinetic parameters.

In summary bis-oximinoalkanoic acids were designed as potent and selective PPARα agonists based on Imiglitazar chemotype and evaluated for their in vitro PPAR agonism and two compounds were found to be potent and selective PPARα agonists. Further evaluation of the lead compounds for their in vivo efficacy in relevant animal models and pharmacokinetic properties is currently being undertaken.

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24. *Spectroscopic analysis of the compounds* **9a**–**n**: Compound **9a**: *(E,E)-4-Phenyl-4-[4-(1-phenylethylideneaminooxy)-butoxyimino]-butyric acid*; yellow oil. Purity by HPLC: 97.4%; Yield: 60%; IR (neat): 3412, 3020, 1712, 1600, 1444, 1219, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.84–1.88 (m, 4H), 2.23 (s, 3H), 2.58–2.62 (m, 2H), 3.03–3.07 (m, 2H), 4.19–4.26 (m, 4H), 7.32–7.43 (m, 6H), 7.61–7.65 (m, 4H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 12.90, 21.17, 25.98, 30.78, 73.90, 74.23, 125.14, 125.31, 127.89, 128.28, 129.35, 128.82, 135.31, 136.88, 154.65, 156.26, 178.57; ESI/MS *m/z*: 404.9 $(M+Na)^+$; compound **9b**: *(E,E)-4-{4-[1-(4-Fluorophenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid;* white solid; mp: 51 °C; purity by HPLC: 95.4%; yield: 90%; IR (KBr): 3411, 3018, 1712, 1662, 1510, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.83–1.85 (m, 4H), 2.21 (s, 3H), 2.58–2.62 (m, 2H), 3.03–3.07 (m, 2H), 4.22–4.26 (m, 4H), 7.05 (t, *J* = 8.8 Hz, 2H), 7.35–7.37 (m, 3H), 7.59–7.63 (m, 4H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 12.24, 22.06, 25.42, 30.46, 73.23, 73.37, 115.10, 115.32, 126.32, 128.15, 128.43, 128.57, 132.55, 134.94, 152.83, 156.43, 161.41, 163.85, 173.47; ESI/MS *m/z*: 422.9 $(M+Na)^+$; compound **9c**: *(E,E)-4-{4-[1-(4-Methylphenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; purity by HPLC: 95.6%; Yield: 83%; IR (KBr): 3408, 3018, 1710, 1560, 1384, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.83–1.85 (m, 4H), 2.21 (s, 3H), 2.34 (s, 3H), 2.57–2.61 (m, 2H), 3.04–3.08 (m, 2H), 4.19–4.24 (m, 4H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.33–7.43 (m, 3H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.60–7.63 (m, 2H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 12.22, 21.02, 21.92, 25.49, 25.58, 30.19, 72.98, 73.14, 125.72, 126.11, 128.49, 128.96, 129.25, 133.06, 134.69, 138.56, 153.54, 156.30, 173.40; ESI/MS *m/z*: 419.0 $(M+Na)^+$; compound **9d**: *(E,E)-4-{4-[1-(4-Methoxyphenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; White solid; mp: 56 °C; Purity by HPLC: 97.5%; Yield: 81%; IR (KBr): 3008, 2941, 1699, 1608, 1512, 1228, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.81–1.84 (m, 4H), 2.20 (s, 3H), 2.57–2.61 (m, 2H), 3.03–3.07 (m, 2H), 3.81 (s, 3H), 4.22–4.24 (m, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.34–7.36 (m, 3H), 7.56–7.60 (m, 4H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 12.16, 21.91, 25.56, 30.96, 55.12, 73.02, 73.42, 113.73, 126.09, 127.16, 128.46, 129.10, 134.97, 153.22, 156.45, 160.00, 173.34; ESI/MS *m/z*: 435.1 $(M+Na)^+$; compound **9e**: *(E,E)-4-{4-[1-(4-Trifluromethylphenyl)-ethyli deneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; white solid; mp: 52 °C; purity by HPLC: 97.2%; yield: 87%; IR (KBr): 3412, 3018, 1710, 1408, 1327, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.82–1.87 (m, 4H), 2.24 (s, 3H), 2.58–2.62 (m, 2H), 3.03–3.07 (m, 2H), 4.21–4.28 (m, 4H), 7.34–7.38 (m, 3H), 7.58–7.64 (m, 4H), 7.73 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 12.67, 22.20, 25.99, 30.86, 74.28, 125.55, 126.36, 128.71, 129.03, 131.26, 140.23, 153.23, 156.23, 178.80; ESI/MS *m/z*: 472.8 $(M+Na)^+$; compound **9f**: *(E,E)-4-{4-[1-(4-Methanesulfonylphenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; white solid; mp: 88 °C; purity by HPLC: 99.0%; yield: 49%; IR (KBr): 3412, 2929, 1708, 1454, 1408, 1315, 1151, 1051, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.77–1.87 (m, 4H), 2.25 (s, 3H), 2.59–2.63 (m, 2H), 3.03–3.07 (m, 5H), 4.22–4.30 (m, 4H), 7.34–7.39 (m, 3H), 7.59–7.63 (m, 2H), 7.82 (dd, *J* = 6.8 and 1.8 Hz, 2H), 7.91 (dd, *J* = 6.8 and 1.6 Hz, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 12.61, 22.16, 25.94, 30.60, 44.58, 74.10, 74.45, 126.24, 126.86, 127.53, 128.68, 129.37, 133.71, 140.38, 142.05, 152.75, 156.21, 178.28; ESI/MS *m/z*: 460.9 $(M+H)^+$; compound **9g**: *(E,E)-4-{4-[1-(4-Butylphenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; oil; purity by HPLC: 98.1%; yield: 71%; IR (neat): 3398, 3018, 2931, 1712, 1614, 1500, 1382, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.29–1.38 (m, 2H), 1.56–1.62 (m, 2H), 1.83–1.85 (m, 4H), 2.21 (s, 3H), 2.58–2.66 (m, 4H), 3.03–3.07 (m, 2H), 4.21–4.25 (m, 4H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.32–7.36 (m, 3H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.60–7.63 (m, 2H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 12.59, 14.28, 21.95, 22.13, 25.73, 25.89, 29.44, 33.18, 34.98, 73.53, 125.80, 126.12, 128.19, 128.41, 129.30, 132.55, 133.99, 139.06, 143.79, 153.94, 153.98, 173.73; ESI/MS *m/z*: 461.0 $(M+Na)^+$; compound **9h**: *(E,E)-4-[4-(1-Biphenyl-4-yl-ethylideneaminooxy)-butoxyimino]-4-phenyl-butyric acid*; white solid; mp: 79 °C; purity by HPLC: 95.2%; yield: 64%; IR (KBr): 3411, 3018, 1710, 1691, 1564, 1384, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.86–1.87 (m, 4H), 2.26 (s, 3H), 2.58–2.62 (m, 2H), 3.04–3.08 (m, 2H), 4.24–4.27 (m, 4H), 7.35–7.37 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.57–7.63 (m, 6H), 7.71 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 12.38, 21.93, 25.50, 31.53, 73.31, 73.44, 126.00, 126.37, 126.61, 127.70, 128.50, 129.09, 129.15, 134.97, 135.09, 138.71, 140.66, 153.36, 156.30, 173.41; ESI/MS *m/z*: 481.0 $(M+Na)^+$; compound **9i**: *(E,E)-4-[4-(1-Naphthalen-2-yl-ethylideneaminooxy)-butoxyimino]-4-phenyl-butyric acid*; white solid; mp: 72 °C; purity by HPLC: 97.8%; yield: 71%; IR (KBr): 3409, 2929, 1733, 1629, 1498, 1438, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.86–1.90 (m, 4H), 2.34 (s, 3H), 2.58–2.62 (m, 2H), 3.02–3.06 (m, 2H), 4.24–4.31 (m, 4H), 7.34–7.36 (m, 3H), 7.46–7.49 (m, 2H), 7.61–7.64 (m, 2H), 7.78–7.86 (m, 3H), 7.90–7.93 (dd, *J* = 8.7 and 1.8 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.97, 21.94, 25.43, 30.55, 73.33, 123.07, 125.53, 126.03, 126.33, 126.56, 127.39, 127.67, 128.33, 128.37, 129.01, 132.72, 133.08, 133.42, 134.94, 153.53, 156.47, 173.35; ESI/MS *m/z*: 455.0 $(M+Na)^+$; compound **9j**: *(E,E)-4-Phenyl-4-{4-[1-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylideneaminooxy]-butoxyimino}-butyric acid*; oil; purity by HPLC: 95.4%; yield: 90%; IR (KBr): 3411, 3018, 1710, 15001384, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.76–1.80 (m, 4H), 1.86–1.89 (m, 4H), 2.20 (s, 3H), 2.58–2.62 (m, 2H), 2.75–2.77 (m, 4H), 3.04–3.08 (m, 2H), 4.21–4.25 (m, 4H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.32–7.43 (m, 5H), 7.61–7.63 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.19, 21.08, 22.64, 25.52, 28.56, 28.77, 30.44, 72.91, 73.02, 122.89, 126.04, 126.23, 128.41, 128.83, 129.00, 129.06, 133.83, 134.92, 136.08, 136.48, 153.64, 156.40, 173.42; ESI/MS *m/z*: 459.1 $(M+Na)^+$; compound **9k**: *(E,E)-4-{4-[1-(3,4-Dimethoxyphenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; oil;

purity by HPLC: 95.3%; yield: 72%; IR (KBr): 3411, 3020, 1712, 1579, 1512, 1384, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.84–1.87 (m, 4H), 2.21 (s, 3H), 2.57–2.61 (m, 2H), 3.03–3.07 (m, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 4.22–4.26 (m, 4H), 6.82 (d, J = 8.4 Hz, 1H), 7.11–7.14 (dd, J = 8.4 and 2.0 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 7.34–7.36 (m, 3H), 7.60–7.63 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.27, 21.95, 25.51, 25.62, 30.21, 55.41, 72.99, 73.09, 108.80, 111.49, 118.98, 126.01, 128.51, 128.73, 133.92, 147.83, 148.81, 153.41, 156.50, 173.45; ESI/MS m/z: 465.1 $(M+Na)^+$; compound **9l**: *(E,E)-4-{4-[1-(3,4-Dimethylphenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; oil; purity by HPLC: 95.5%; yield: 76%; IR (Nujol): 3124, 3018, 1735, 1610, 1498, 1404, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.83–1.85 (m, 4H), 2.21 (s, 3H), 2.25 (s, 3H), 2.26 (s, 3H), 2.57–2.62 (m, 2H), 3.03–3.07 (m, 2H), 4.20–4.23 (m, 4H), 7.09 (d, J = 7.7 Hz, 1H), 7.33–7.35 (m, 4H), 7.42 (s, 1H), 7.60–7.63 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.24, 19.18, 19.41, 21.93, 25.36, 30.45, 73.11, 73.46, 123.33, 126.10, 126.75, 128.48, 129.12, 129.44, 133.70, 134.99, 136.11, 137.30, 153.63, 156.43, 173.41; ESI/MS m/z: 411.1 $(M+H)^+$; compound **9m**: *(E,E)-4-{4-[1-(3-Methoxy-4-methylphenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; oil; purity by HPLC: 96.5%; yield: 50%; IR (neat): 3411, 3018, 1710, 1610, 1508, 1384, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.83–1.86 (m, 4H), 2.20 (s, 3H), 2.21 (s, 3H), 2.58–2.62 (m, 2H), 3.04–3.08 (m, 2H), 3.83 (s, 3H), 4.21–4.26 (m, 4H), 6.77 (d, J = 8.4 Hz, 1H), 7.34–7.36 (m, 3H), 7.39–7.42 (dd, J = 8.4 and 2.0 Hz, 1H), 7.44 (s, 1H), 7.61–7.63 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.18, 16.06, 21.90, 25.32, 25.45, 30.47, 55.28, 72.96, 73.41, 109.87, 124.90, 125.77, 126.09, 127.63, 128.04, 128.48, 129.13, 134.95, 153.31, 156.29, 158.14, 173.37; ESI/MS m/z: 449.1 $(M+Na)^+$; compound **9n**: *(E,E)-4-{4-[1-(4-Fluoro-3-methoxyphenyl)-ethylideneaminooxy]-butoxyimino}-4-phenyl-butyric acid*; oil; purity by HPLC: 95.5%; yield: 82%; IR (neat): 3411, 3018, 1710, 1562, 1502, 1384, 1215, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.83–1.86 (m, 4H), 2.18 (s, 3H), 2.58–2.62 (m, 2H), 3.04–3.08 (m, 2H), 3.89 (s, 3H), 4.21–4.26 (m, 4H), 6.91 (t, J = 8.8 Hz, 1H), 7.32–7.37 (m, 4H), 7.42–7.46 (dd, J = 12.8 and 2.0 Hz, 1H), 7.60–7.63 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.46, 21.26, 25.83, 25.93, 30.90, 56.45, 73.63, 73.78, 113.48, 113.86, 113.87, 122.85, 126.39, 128.45, 129.54, 134.29, 148.25, 150.46, 152.90, 156.93, 173.85; ESI/MS m/z: 453.0 $(M+Na)^+$.