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Effect of structurally constrained oxime–ether linker on PPAR subtype selectivity: Discovery of a novel and potent series of PPAR-pan agonists ☆

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ABSTRACT

A novel series of thaizole and oxazole containing phenoxy acetic acid derivatives is reported as PPAR-pan agonists. Incorporation of structurally constrained oxime–ether based linker in the chemotype of a potent PPARδ selective agonist GW-501516 was adapted as designing strategy. In vitro, selected test compounds **12a, 12c, 17a** and **18a** showed PPAR-pan agonists activities and among these four compounds tested, **12a** emerged as highly potent and efficacious compound, while **17a** exhibited moderate and balanced PPAR-pan agonistic activity. In vivo, selected test compounds **12a** and **17a** exhibited significant anti-hyperglycemic and anti-hyperlipidemic activities in relevant animal models. These results support our hypothesis that the introduction of structurally constrained oxime–ether linker between lipophilic tail and acidic head plays an important role in modulating subtype selectivity and subsequently led to the discovery of potent PPAR-pan agonists.

1. Introduction

Metabolic syndrome is a cluster of closely related disorders which include mainly obesity, dislipidemia, hyperglycemia and hypertension that increases the risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases. The prevalence of T2DM is rapidly rising all over the globe at an alarming rate.[1] Clinically T2DM is characterized by increased blood glucose levels, either because of defect in insulin secretion, insulin resistance or both and is usually associated with dyslipidemia, hypertension and obesity. Detailed pathophysiology of this disease is not yet completely understood. Metabolic defects in the liver, pancreatic β-cells, adipose tissues and skeletal muscles could be the probable reasons for the development of this disease.

The peroxisome proliferation activated receptors (PPARs) are ligand-activated transcription factors belonging to nuclear hormone receptor super family.[2–4] In recent years, development of drugs targeting PPARs has attracted the attention of several research groups for the reasons that PPARs modulate the genes which are involved in multiple aspects of lipid and carbohydrate metabolism.[5] Three distinct PPAR subtypes (α, γ and δ) have been identified and their physiological roles in glucose homeostasis, fatty acid metabolism and cellular differentiation have been reviewed extensively.[6–10] PPARα is expressed mostly in tissues involved in lipid oxidation, such as liver, kidney, skeletal and cardiac muscles and adrenal glands. PPARα is known to play an important role in fatty acids oxidation and lipoprotein metabolism.[11] PPARγ is expressed in adipose tissue, macrophages and vascular smooth muscles and is well known for its role in adipogenesis at a cellular level and in insulin sensitization.[12,13] Recent studies suggest that PPARγ is also involved in the expression of many genes that affect energy metabolism, such as the leptin and adiponectin.[14] In contrast to the specific distributions of PPARα and γ, PPARδ is ubiquitously expressed.[6] Though PPARδ was discovered more than 15 years ago, it is the least studied and understood subtype among the PPARs. Recent biological studies have revealed that PPARδ activation significantly increases HDL cholesterol levels and it influences glycemic control in a primate model of metabolic syndrome.[15–17] In addition, various studies have implicated the involvement of PPARδ in adipogenesis, colon cancer, bone metabolism, embryonic implantation, inflammation and skin development.[18,19]

Considering the beneficial effects of selective activation of PPARα, γ and δ in animal models and humans, the concept of simultaneously activating all of the PPAR subtypes with a single compound, termed as PPAR-pan agonist appeared to be an interesting approach for the treatment of different elements of metabolic syndrome. Further simultaneous activation of all the PPARs

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is believed to reduce the occurrence of adverse side effects, such as weight gain, fluid accumulation and pulmonary and macular edemas which are often associated with PPAR selective or α/γ *dual* agonists by their complimentary roles.[20] Bezafibrate (1), a member of fibrate class of drugs and practically considered as a weak PPARα agonist is in fact a PPAR-pan agonist[21] and is the only PPAR-pan agonist available in the market but needs high dose to exert therapeutic effect that to only in the lipid homeostasis. Currently development of potent PPAR-pan agonists has become an area of high thrust among several research groups as there is no potent PPAR-pan agonist in the market (Fig. 1).[15,22–24] Sodelglitazar (2) and Indeglitazar (3)[22] are currently in advanced clinical trials for the treatment of T2DM and the current status of compound **4** is undisclosed.[23]

The gross protein structures of PPARs are similar and possess identical ligand binding pockets with 60–70% identity in amino acid sequence in the ligand binding domain.[24] As PPARδ has a smaller ligand binding pocket, we believed that it would be more feasible approach to enhance PPARα and γ binding potential by incorporating chemical modifications in a PPARδ selective ligand rather than modifying PPARα, γ or dual agonist. To verify our hypothesis, we selected GW-501516,[15] a potent PPARδ agonist with moderate affinity towards PPARα and PPARγ (Fig. 2) as initial chemotype.

In course of our research directed towards the development of novel PPAR agonists, recent efforts have been incurred to modulate the subtype selectivity of ligands, results of which demonstrated that the subtype selectivity of PPAR agonists is sensitive to chemical modifications in the central spacer (tether) region of the molecules.[25–29] Recently it has also been reported that highly potent PPARα/γ dual agonists can be obtained by replacing alkyl ether ring spacer with a rigid spacers such as alkenyl, alkynyl, indol ring, oxime–ether etc.[30–32] Based on the above results and serendipity we hypothesized that incorporation of a structurally constrained oxime–ether linker in place of a flexible thio ether linker of GW-501516 could provide us with new class of pan agonist (Fig. 2). In the present communication we report two different series of oxime–ether based novel compounds (**12a–f**, **17a–f** and **18a–f**) as a new class of PPAR-pan agonists to establish our hypothesis.

2. Results and discussion

2.1. Chemistry

Compounds described in this communication were synthesized according to Schemes 1–3 and the detailed synthetic procedures and characterization data are described in the experimental section. Physical, analytical and spectral data of all the final as well as intermediate compounds are in conformity with the structures assigned. In general, compounds **12a–f**, **17a–f** and **18a–f** were prepared in good yield under mild reaction conditions.

The synthetic route to intermediates **9a–f** is outlined in Scheme 1. Starting materials **6a–f**, prepared by reacting phenol or *o*-cresol with respective acid chloride or anhydride in the presence of triethylamine in dichloromethane, were subjected to $AlCl_3$ mediated Fries rearrangement at 160 °C to obtain the keto compounds **7a–f** in 27–58% yield. Since the *ortho*-position of phenyl ring in **6b** and **6d** is free of any substitution, the Fries migration gave a mixture of two products (*ortho* and *para* substituted products) because of the migration of the acyl group to both *ortho* and *para* positions, which were separated by column chromatography. While **7a**, **7c**, **7e** and **7f** were obtained as exclusively *para* substituted products for an obvious reason that in the precursors of these compounds (**6a**, **6c**, **6e** and **6f**) the *ortho*-position is occupied by methyl group. Nucleophilic substitution reaction of the above obtained intermediates **7a–f** with ethyl chloroacetate in the presence of K_2CO_3 in DMF at 60 °C gave the compounds **8a–f**. Treatment of the keto compounds **8a–f** with hydroxylamine hydrochloride in the presence of sodium acetate for 2 h in refluxing ethanol, gave the corresponding oxime derivatives and the *E*-isomers were formed as major product as they are thermodynamically more stable than *Z*-isomers.[33] Synthesis of compounds **12a–f** was illustrated in Scheme 2. Coupling of **10** with **9a–f** in the presence of cesium carbonate in DMF at 60 °C gave the esters **11a–f**, which were hydrolyzed under aqueous alkaline conditions to yield the carboxylic acids **12a–f**. Further compounds **17a–f** and **18a–f** were synthesized by the reaction of **9a–f** with the intermediates **13** and **14**, respectively, as outlined in Scheme 3, following the same steps as described in Scheme 2. Starting material **10**, **13** and **14** were prepared as described in the literature.[15,34]

2.2. In vitro PPAR transactivation

Thiazole derivatives **12a–f** and oxazole derivatives **17a–f** and **18a–f** were screened for human PPAR (hPPAR) α, γ and δ agonistic activities on full length PPAR receptor transfected in HepG2 cells as described in the experimental section. WY-14643, Rosiglitazone and GW-501516 were used as positive controls for PPARα, γ and δ respectively. The in vitro PPAR subtype agonistic activities are reported as percent maximal activity of each compound compared to reference compound and normalized to 100% as summarized in Table 1. Our aim in the present endeavor was to discover a

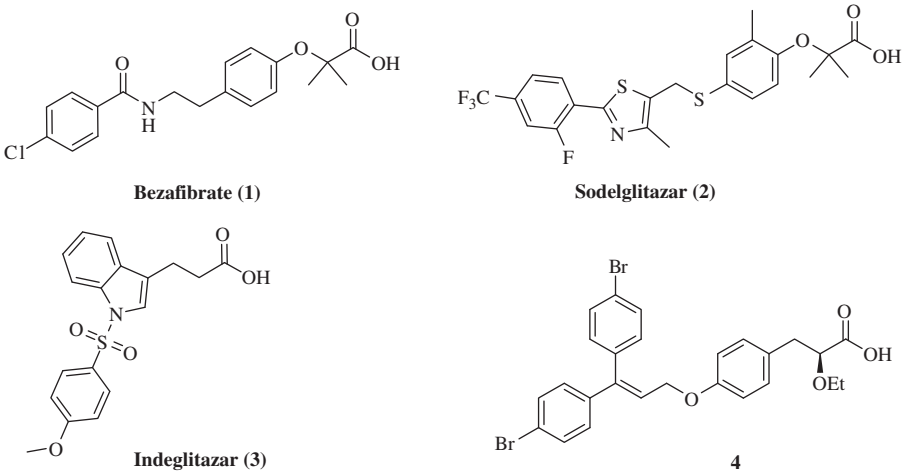


Figure 1. PPAR-pan agonists.

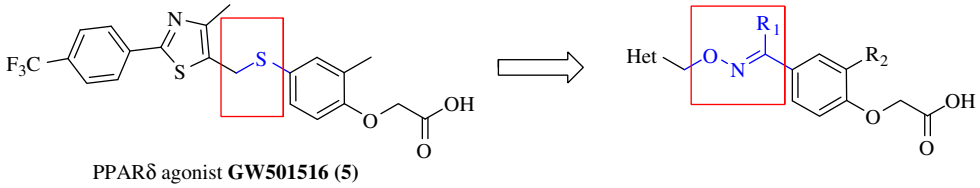
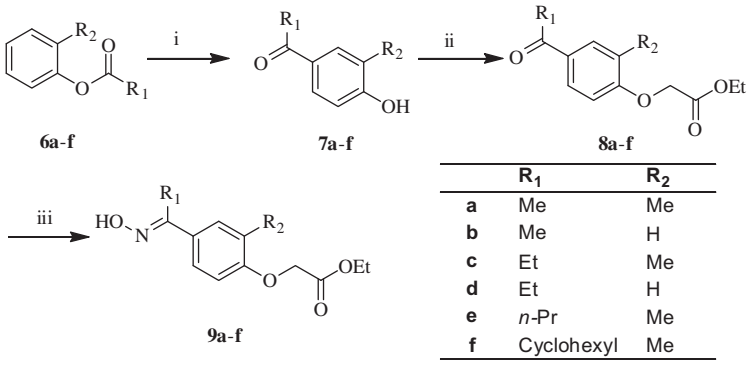
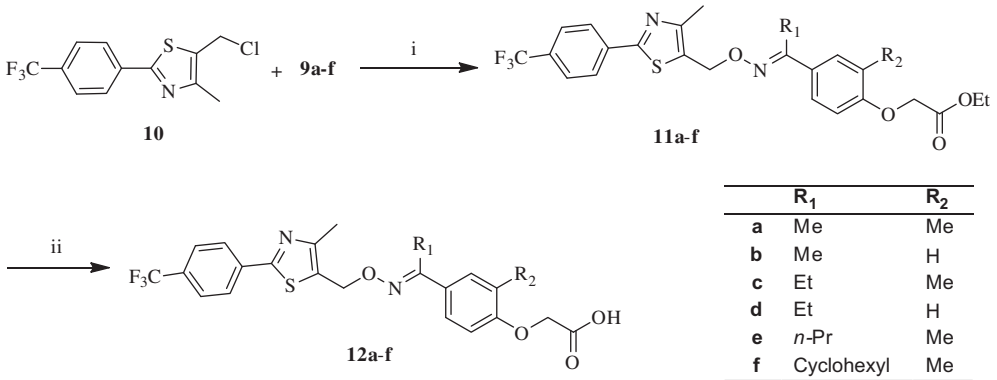


Figure 2. Designing aspect of PPAR-pan agonists.



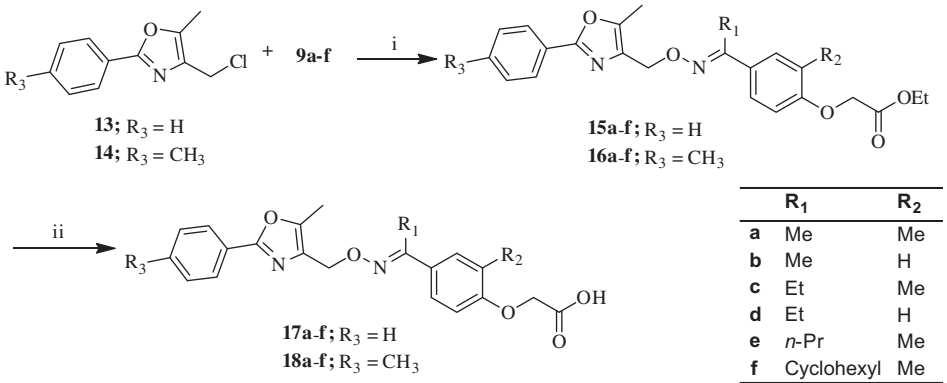
	R_1	R_2
a	Me	Me
b	Me	H
c	Et	Me
d	Et	H
e	*n*-Pr	Me
f	Cyclohexyl	Me

Scheme 1. Reagents and conditions: (i) anhydrous $AlCl_3$, 160 °C, 2 h; (ii) ethyl chloroacetate, K_2CO_3, DMF, 60 °C, 18 h; (iii) $NH_2OH{\cdot}HCl$, CH_3COONa, ethanol, reflux, 1 h.



	R_1	R_2
a	Me	Me
b	Me	H
c	Et	Me
d	Et	H
e	*n*-Pr	Me
f	Cyclohexyl	Me

Scheme 2. Reagents and conditions: (i) Cs_2CO_3, DMF, 60 °C, 18 h; (ii) $LiOH{\cdot}H_2O$, THF, methanol, H_2O, 25 °C, 18 h.

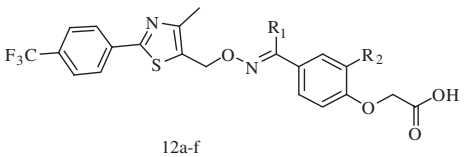


	R_1	R_2
a	Me	Me
b	Me	H
c	Et	Me
d	Et	H
e	*n*-Pr	Me
f	Cyclohexyl	Me

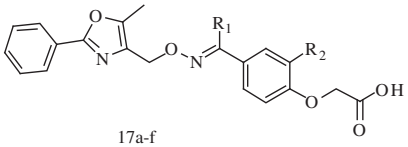
Scheme 3. Reagents and conditions: (i) Cs_2CO_3, DMF, 60 °C, 18 h; (ii) $LiOH{\cdot}H_2O$, THF, methanol, H_2O, 25 °C, 18 h.

PPAR-pan agonist with potent anti-hyperglycemic and anti-hyperlipidemic activities. We started designing compounds taking GW-501516 as initial lead. As GW-501516 is a potent PPARδ agonist and moderately activates PPARα and PPARγ, we felt that chemical modifications in this chemotype in order to improve the activation towards PPARα and PPARγ would be an appropriate strategy. Our initial efforts towards the above said endeavor started with the introduction of structurally constrained oxime–ether as a linker in place of thio ether of GW-501516 as represented in Figure 2. We choose 4-methyl-2-(4-trifluoromethyl)-thi-

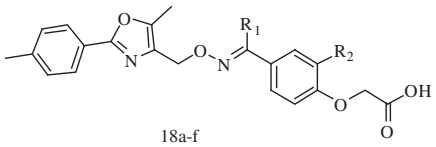
Table 1
In vitro PPAR agonistic activity of test compounds (**12a–f**, **17a–f** and **18a–f**)



12a-f



17a-f



18a-f

Compound	R_1	R_2	hPPAR transactivation E_{max}[a,b] (%)		
			α	γ	δ
12a	Methyl	Methyl	99.8 ± 5.2	85.3 ± 2.1	90.1 ± 3.5
12b	Methyl	H	86.2 ± 4.1	58.4 ± 3.7	60.6 ± 3.0
12c	Ethyl	Methyl	96.4 ± 3.6	64.7 ± 3.2	61.9 ± 6.2
12d	Ethyl	H	97.5 ± 5.4	58.5 ± 3.2	41.4 ± 1.4
12e	*n*-Propyl	Methyl	58.7 ± 2.8	43.4 ± 2.4	48.3 ± 3.5
12f	Cyclohexyl	Methyl	57.9 ± 1.9	52.1 ± 2.2	98.7 ± 7.1
17a	Methyl	Methyl	84.5 ± 5.5	89.5 ± 4.8	74.5 ± 4.4
17b	Methyl	H	58.8 ± 3.8	67.2 ± 4.6	52.1 ± 1.8
17c	Ethyl	Methyl	56.4 ± 4.5	72.8 ± 6.6	72.3 ± 2.5
17d	Ethyl	H	42.5 ± 1.2	44.7 ± 4.1	46.4 ± 3.8
17e	*n*-Propyl	Methyl	14.1 ± 0.9	31.4 ± 1.7	51.7 ± 5.5
17f	Cyclohexyl	Methyl	9.7 ± 1.5	18.1 ± 0.9	58.8 ± 1.9
18a	Methyl	Methyl	45.3 ± 1.8	61.2 ± 4.3	67.6 ± 4.3
18b	Methyl	H	51.1 ± 2.9	45.9 ± 5.5	48.1 ± 1.1
18c	Ethyl	Methyl	72.6 ± 7.3	61.8 ± 6.4	56.3 ± 3.7
18d	Ethyl	H	68.5 ± 6.1	53.3 ± 2.3	49.2 ± 4.5
18e	*n*-Propyl	Methyl	33.3 ± 1.6	32.1 ± 3.1	46.8 ± 2.7
18f	Cyclohexyl	Methyl	14.1 ± 0.8	29.4 ± 1.7	56.6 ± 5.1
GW-501516			76.9 ± 7.1	61.1 ± 2.4	100.4 ± 4.3

[a] HepG2 cells transfected with pSG5 expression vector containing the cDNA of hPPARα or hPPARγ or hPPARδ and cotransfected with PPRE3-TK-luc. The luciferase activity determined using fire-fly luciferase assay and β-galactosidase activity determined in ELISA reader ($n = 3$).
[b] E_{max} of test compounds compared to reference compounds (WY-14643 for α, Rosiglitazone for γ and GW-501516 for δ) normalized to 100%. Fold increase of WY-14643, Rosiglitazone and GW-501516 Vs DMSO is 8.40 ± 0.21 (PPARα), 13.49 ± 0.38 (PPARγ) and 28.54 ± 0.77 (PPARδ) respectively at 10 μM concentration.

azole and 4-methyl-2-phenyloxazole moieties as a lipophilic tail and synthesized compounds **12a–f** and **17a–f** containing oxime–ether with different substitutions at R_1 (Fig. 2). As anticipated, compound **12a** possessing methyl group as R_1 showed significant improvement in affinity towards PPARα and PPARγ as compared to GW-501516. This compound exhibited high and balanced efficacy towards all the three PPAR subtypes with E_{max} of 99.8%, 85.3% and 90.1% towards PPARα, γ and δ respectively. Replacement of methyl group at R_1 in **12a** with ethyl found to be detrimental to PPAR affinity as seen in the compound **12c**. Compounds **12b** and **12d** bearing no substitution at R_2 exhibited poor affinity towards PPARδ compared to their methyl substituted counterpart suggesting the role of methyl group at R_2 for PPARδ activity. We then intended to optimize the substitution at R_1. When the chain length at R_1 was further increased to propyl group, compound **12e** showed unfavorable PPAR affinities. To assess the effect of bulkier group, we synthesized compound **12f** with cyclohexyl group as R_1. Compared to compound **12a**, compound **12f** showed inferior affinity towards PPAR α and γ but interestingly found equipotent towards PPARδ. In another series, the compounds **17a–f** which contains oxazole as a lipophilic tail showed similar tendency as thiazole compounds **12a–f**. Compound **17a** possessing methyl group at R_1 found to be equipotent towards all the three PPAR sub type with E_{max} of 84.5%, 89.5% and 74.5% towards PPARα, γ and δ, respectively, and emerged as a most potent compound in the oxazole series. Whereas compound **17c** having ethyl group at R_1 showed good agonistic activity in all the three PPAR subtypes but was found to be inferior as compared to **17a**. Compounds **17b** and **17d** where methyl group was removed at R_2 showed decrease in PPARδ activity as compared to their respective parent compounds (**17a** and **17c**). Incorporation of *n*-propyl chain at R_1 (compound **17e**) resulted in complete loss of activity towards all three PPAR subtype. Whereas the compound **17f** which possesses cyclohexyl group at R_1, showed equipotent affinity to PPARδ but failed to show good affinity towards PPARα and γ as compared to **17a**.

To further support the above findings, we then synthesized compounds **18a–f**, wherein 2-phenyl on the oxazole group was substituted with methyl group at *para* position. We observed the similar trend as shown by compounds **12a–f** and **17a–f**. As expected, compound **18a** which possess methyl group at R_1 is superior to the other compounds of the series. Compound **18c** with ethyl group at R_1 exhibited inferior potency than compound **18a**. Removal of methyl group at R_2 position in **18a** and **18c** is found to be detrimental in terms of PPARδ activity as exhibited by **18b** and **18d**. Linear elongation of the chain length in **18a** to propyl group resulted in decreased activity as evident from **18e**, while the compound **18f** bearing bulkier cyclohexyl group at R_1 showed good PPARδ activity.

Based on the above results compounds **12a**, **12c**, **12f**, **17a** and **18a** were subjected for EC_{50} (half maximal effective concentration) determination and the corresponding EC_{50} values are presented in Table 2. Among the five compounds subjected for EC_{50} determination, compound **12a** emerged as highly potent and efficacious PPAR-pan agonist with balanced EC_{50} of 0.008 ± 0.002, 0.006 ± 0.002 and 0.01 ± 0.003 μM towards PPARα, γ and δ, respectively. The compound **12f** exhibited low in vitro activity, while compounds **12c**, **17a** and **18a** showed moderate and balanced activity (EC_{50}) towards all three PPAR subtype. Although EC_{50} values of **12c** and **18a** was found to be comparable to **17a**, however, compounds **12c** and **18a** showed moderate E_{max} (Table 1) and therefore compounds **12a** and **17a** were selected for subsequent in vivo evaluation. Thus the above results reveal the crucial role of various substitutions at R_1 and R_2, wherein it is evident from the data that the methyl group at R_2 is essential for PPARδ activation. Further the linear elongation of the chain at R_1 found detri-

Table 2
EC_{50} values of selected test compounds

Compound	R_1	R_2	hPPAR Transactivation EC_{50}[a,b] (μM)		
			α	γ	δ
12a	Methyl	Methyl	0.008 ± 0.002	0.006 ± 0.002	0.01 ± 0.003
12c	Ethyl	Methyl	0.12 ± 0.01	0.8 ± 0.02	0.8 ± 0.05
12f	Cyclohexyl	Methyl	1.6 ± 0.21	1.0 ± 0.12	0.7 ± 0.09
17a	Methyl	Methyl	0.5 ± 0.03	0.3 ± 0.05	0.8 ± 0.07
18a	Methyl	Methyl	0.15 ± 0.01	0.4 ± 0.01	0.3 ± 0.009
Bezafibrate			42.5 ± 2.5	57.2 ± 5.4	18.9 ± 0.9
GW-501516			1.1 ± 0.32	0.8 ± 0.008	0.0012 ± 0.0006

[a] HepG2 cells transfected with pSG5 expression vector containing the cDNA of hPPARα or hPPARγ or hPPARδ and cotransfected with PPRE3-TK-luc. The luciferase activity determined using fire-fly luciferase assay and β-galactosidase activity determined in ELISA reader.
[b] EC_{50} is the concentration of the test compound that affords half-maximum transactivation activity.

Table 3
Anti-hyperglycemic activity of the selected compounds (**12a** and **17a**) in *db/db* mice[a]

Compound	Dose (mpk/day/po)	%Change[b]	
		Serum glucose	Serum TG
12a	10	−23.2 ± 3.1	−36.5 ± 2.5
17a	10	−59.9 ± 5.4	−52.4 ± 4.7
Rosiglitazone	30	−41.1 ± 2.5	−53.8 ± 4.2
Tesaglitazar	3	−60.2 ± 6.1	−54.4 ± 5.0

[a] Male *db/db* mice dosed orally (po) with test compounds daily for 14 days and serum glucose, triglycerides (TG) were measured.
[b] Values expressed as % change of compound-treated mice vs vehicle control, indicated as M ± SD ($n = 6$), significant at $p < 0.05$.

mental to PPAR activation while the bulkier substitution at this position is favorable for the PPARδ activation.

2.3. In vivo evaluation

Having encouraged with the in vitro PPAR agonistic activity, compounds **12a** and **17a**, being the most potent compounds in their respective series were selected for in vivo studies in *db/db* mice and HF–HC–fructose fed *hamster* for their anti-hyperglycemic and anti-hyperlipidemic activities. In male *db/db* mice, compounds **12a** and **17a** were dosed orally (po) at 10 mpk/day dose for 14 days. As described in Table 3, both the test compounds **12a** and **17a** showed significant reduction in serum glucose and triglyceride (TG), however serum glucose and TG reduction with compound **17a** were found to be comparable with Rosiglitazone and Tesaglitazar. Furthermore, anti-hyperlipidemic activities of compounds **12a** and **17a** were evaluated in Female *hamsters* at 10 mpk/day/po dose, for 14 days. As demonstrated in Figure 3, compound **12a** showed statistically significant increase in serum HDL-C level whereas compound **17a** showed improvement in serum HDL-C level but found inferior to compound **12a**. Additionally both the compounds **12a** and **17a** showed significant reduction in serum LDL-C level. All together above in vivo results indicate that compound **12a** exhibits good anti-hyperlipidemic activity in *hamster* and compound **17a** showed very good anti-hyperglycemic activity in *db/db* mice.

3. Conclusion

A novel series of thaizole and oxazole containing phenoxy acetic acid derivatives were discovered as PPAR-pan agonists by incorporating oxime–ether linker in a potent PPARδ agonist GW-501516 as exemplified by compounds **12a** and **17a**. These compounds showed potent and balanced PPAR-pan agonistic activity in vitro. Further compounds **12a** and **17a** exhibited potent anti-hyperglycemic and anti-hyperlipidemic effects in rodents. Compound **17a** reduced plasma glucose and triglycerides significantly in *db/db* mice, whereas compound **12a** significantly improved serum HDL-C level along with the reduction in serum LDL-C level in *hamster*. Together, these finding suggest that compounds possessing oxime–ether linker between pharmacophore and lipophilic tail exhibit predominantly PPAR-pan agonism. The above results clearly established that incorporation of structurally constrain oxime–ether linker between the pharmacophore and the lipophilic heterocycle improves affinity towards PPARα and PPARγ in a selective PPARδ agonist. Further research to optimize this series to develop compounds with potent anti-hyperglycemic and anti-hyperlipidemic activity with desired ADME and toxicity profiles is in progress and will be communicated subsequently.

4. Experimental section

4.1. In vitro PPAR agonistic activity (transactivation assay)

4.1.1. Cell culture

HepG2 cells (ATCC, USA) were maintained in growth medium composed of MEM (Sigma) supplemented with 10% FBS (Hyclone),

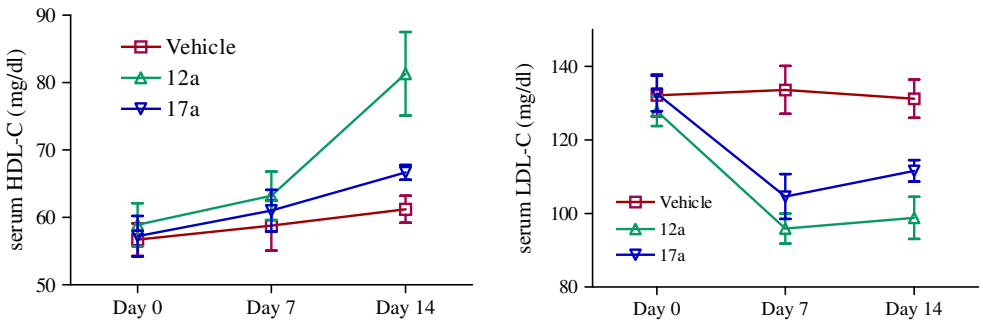


Figure 3. Anti-hyperlipidemic activity of the selected compounds (**12a** and **17a**) in *hamster*.

1 × MEM non essential amino acid (Sigma) and 1 mM sodium pyruvate and 1% penicillin/streptomycin (Sigma).

4.1.2. Transient transfection

HepG2 cells were seeded in 24 well plates at a density of 400,000 cells/well in 1 mL of medium per well. Cells were transfected using the transfection reagent superfect (Qiagen). Cells were transfected with 0.08 μg of the pSG5 expression vector containing the *c*DNA of PPARα or PPARγ or PPARδ and co-transfected with PPRE3-TK-luc. Cells were incubated at 37 °C, 5% CO_2 for 3 h. After this, 1.0 mL of the medium containing the respective ligands to the respective wells were added. The cells were then incubated at 37 °C, 5% CO_2 for 20–22 h. After the incubation period, cells were first washed with PBS, lysed and the supernatant was collected. Supernatant was then assayed for luciferase and β-galactosidase activity. The luciferase activity was determined using commercial fire-fly luciferase assay according to the suppliers's [Promega] instructions in white 96-well plate [Nunc]. β-Galactosidase activity was determined in ELISA reader at 415 nm. The ratio of luciferase versus β-galactosidase was calculated and fold induction was calculated with respect to DMSO. Percent of maximal efficacy (E_{max}) of all compounds was calculated comparing to reference compounds (WY-14643 for α, Rosiglitazone for γ and GW-501516 for δ) normalized to 100%. Fold inductions of the standard compounds were also calculated with respect to DMSO. EC_{50} values for the test compounds were calculated by nonlinear regression analysis using graph pad prism software. Each concentration point represents values in triplicates.

4.2. In vivo anti-hyperglycemic and anti-hyperlipidemic studies (mice and *hamster*)

All animals were used from inbred colony which is maintained on standard laboratory rodent chow ad libitum and the study protocols were approved by institutional animal ethics committee.

4.2.1. *db/db* mice experiments

Male *db/db* mice of 12–14 weeks age and 30–40 g body weight were selected for the study. The animals were weighed, tail-bled prior to the start of study and serum/plasma was analyzed for glucose (PG) and triglyceride (TG) levels. The animals were arranged into an appropriate number of groups with each group having six animals of the same mean PG, TG and TC levels prior to dosing. All the animals were orally dosed once daily either with vehicle (0.5% methylcellulose in water) or test compounds for 14 days and were fed ad libitum throughout the study. Approximately 1 h after the last dose, animals were tail-bled and serum/plasma was analyzed for glucose (PG) and triglyceride (TG) levels to calculate percent change due to drug treatment (this takes into account any changes that may have occurred in the vehicle-treated animals during the study).

4.2.2. *Hamster* experiments

Female *hamster* of 8–12 weeks age (80–150 g body weight) were taken for study. Six animals whose average body weight was not significantly different from the rest of the animals were selected for normal NIN diet. Other animals were put on HF–HC–sucrose (High fat, high cholesterol and sucrose) diet for 14 days. On day 14 all the HF–HC–sucrose diet fed animals were selected which had gained their body weight significantly more than the normal diet group animals. The selected animals were divided into different groups in such a way that the average bodyweight of the animals in each group was not significantly different from the other groups. All the animals were orally dosed once daily either with vehicle (0.5% polyethylene glycol in water) or test compounds (10 mpk, dissolved in 0.5% polyethylene glycol in water) for 14 days. Fasted blood samples were collected from each animal on day 7 and 14, after 1 h of dose administration and separated serum samples were subjected for the estimation of high density lipoprotein (HDL) and low density lipoprotein (LDL).

4.3. Synthesis

4.3.1. Synthetic materials and methods

Reagents and solvents were obtained from commercial suppliers and used without further purification. Flash chromatography was performed using commercial silica gel (230–400 mesh). Melting points were determined on a capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT IR 8300 spectrophotometer (ν_{max} in cm^{-1}, using KBr pellets for solid compounds or neat for liquid compounds). The ^1H NMR spectra were recorded on a Bruker Avance-300 spectrometer (300 MHz) and Bruker Avance-400 spectrometer (400 MHz). The chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, either in $CDCl_3$ or DMSO-d_6 solvent. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), br s (broad singlet), and m (multiplet). ^{13}CNMR spectra were recorded on Bruker Avance-400 at 100 MHz either in $CDCl_3$ or DMSO-d_6 solution. Mass spectra (ESI-MS) were obtained on Shimadzu LC-MS 2010-A spectrometer. HPLC analysis were carried out at λ_{max} 220 nm using column ODS C-18, 150 nm × 4.6 nm × 4 μ on AGILENT 1100 series.

4.3.2. 4′-Hydroxy-3′-methylacetophenone (7a)

Anhydrous $AlCl_3$ (22.2 g, 0.166 mol) was added in small portions to *O*-acetyl-2-methylphenol **6a** (25 gm, 0.166 mol) at 25 °C and reaction temperature was slowly raised to 160 °C and stirred at the same temperature for 2 h. The reaction mixture was poured in ice cold 6 N HCl (500 ml) and extracted with ethyl acetate (200 ml × 3). The organic extract was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure to yield 20 g crude product as thick oil. The crude product was purified by column chromatography (10% ethyl acetate in hexane) to give title compound **7a** as yellow solid (7.0 g); yield: 28%; mp: 99–100 °C; purity by HPLC: 99.5%; IR (KBr): 3130, 2925, 1651, 1589, 1514, 1182 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.29 (s, 3H), 2.56 (s, 3H), 5.92 (s, OH), 6.80 (d, J = 8.3 Hz, 1H), 7.74 (dd, J = 8.3 and 1.9 Hz, 1H), 7.79 (s, 1H); ESI/MS m/z: 150.7 $(M+H)^+$.

4.3.3. 4′-Hydroxyacetophenone (7b)

This compound was prepared from **6b** by means of a procedure similar to that reported for **7a**. Off white solid; yield: 40%; mp: 109–110 °C; purity by HPLC: 97.8%; IR (KBr): 3309, 2968, 2424, 1662, 1602, 1577, 1357, 1278, 1219, 1165, 1107, 962, 848, 633, 567 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.57 (s, 3H), 6.89 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H); ESI/MS m/z: 137.2 $(M+H)^+$.

4.3.4. 1-(4-Hydroxy-3-methylphenyl)propan-1-one (7c)

This compound was prepared from **6c** by means of a procedure similar to that reported for **7a**. Off white solid; yield: 58%; mp: 130–131 °C; purity by HPLC: 95.3%; IR (KBr): 3365, 2980, 1664, 1593, 1514, 1465, 1352, 1257, 1170, 1132, 1082, 976, 910, 800, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.20 (t, J = 7.4 Hz, 3H), 2.29 (s, 3H), 2.95 (q, J = 7.2 Hz, 2H), 6.86 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 8.4 and 2.4 Hz, 1H), 7.80 (d, J = 1.2 Hz, 1H); ESI/MS m/z: 165.3 $(M+H)^+$.

4.3.5. 1-(4-Hydroxyphenyl)propan-1-one (7d)

This compound was prepared from **6d** by means of a procedure similar to that reported for **7a**. Off white solid; yield: 52%; mp: 147–148 °C; purity by HPLC: 97.4%; IR (KBr): 3217, 2974, 2939, 2808, 1662, 1606, 1572, 1514, 1450, 1357, 1288, 1172, 1112,

1016, 952, 858, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.22 (t, J = 7.2 Hz, 3H), 2.95 (q, J = 7.2 Hz, 2H), 6.86–6.90 (m, 2H), 7.90–7.93 (m, 2H); ESI/MS m/z: 151.8 $(M+H)^+$.

4.3.6. 1-(4-Hydroxy-3-methylphenyl)butan-1-one (7e)

This compound was prepared from **6e** by means of a procedure similar to that reported for **7a**. Yellow solid; yield: 27%; mp: 129–130 °C; purity by HPLC: 99.6%; IR (KBr): 3269, 3190, 2727, 2414, 1656, 1512, 1407, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.99 (t, J = 7.4 Hz, 3H), 1.66–1.81 (m, 2H), 2.29 (s, 3H), 2.89 (t, J = 7.3 Hz, 2H), 5.78 (s, OH), 6.81 (d, J = 8.3 Hz, 1H), 7.72–7.79 (m, 2H); ESI/MS m/z: 178.7 $(M+H)^+$.

4.3.7. Cyclohexyl(4-hydroxy-3-methylphenyl)methanone (7f)

This compound was prepared from **6f** by means of a procedure similar to that reported for **7a**. Off white solid; yield: 26%; mp: 144–146 °C; purity by HPLC: 98.7%; IR: 3348, 2858, 1899, 1652, 1589, 1512, 1456, 1269, 914, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21–1.63 (m, 5H), 1.72–1.74 (m, 1H), 1.80–1.91 (m, 4H), 2.30 (s, 3H), 3.11–3.31 (m, 1H), 6.82 (d, J = 8.3 Hz, 1H), 7.71–7.80 (m, 2H); ESI/MS m/z: 240.9 $(M+Na)^+$.

4.3.8. Ethyl 2-(4-acetyl-2-methylphenoxy)acetate (8a)

To an ice cold solution of **7a** (20 g, 0.133 mol) in DMF (100 ml), K_2CO_3 (36.8 g, 0.266 mol) and ethyl chloroacetate (15.9 g, 0.150 mol) was added and reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was poured in ice cold water (700 ml) and extracted with ethyl acetate (200 ml × 3). The organic extract was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure to yield 23.8 g product as thick oil. Yield: 98%; purity by HPLC: 95.2%; IR: 3435, 3338, 2983, 2929, 1757, 1676, 1600, 1585, 1502, 1440, 1415, 1382, 1359, 1269, 1205, 1182, 1136, 1091, 1068, 1026, 970, 813 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J = 7.1 Hz, 3H), 2.32 (s, 3H), 2.54 (s, 3H), 4.21 (q, J = 7.1 Hz, 2H), 4.73 (s, 2H), 6.70 (d, J = 8.2 Hz, 1H), 7.70–7.71 (m, 2H); ESI/MS m/z: 236.8 $(M+H)^+$.

4.3.9. Ethyl 2-(4-acetylphenoxy)acetate (8b)

This compound was prepared from **7b** by means of a procedure similar to that reported for **8a**. Thick oil; yield: 95%; purity by HPLC: 92.5%; IR: 3020, 2985, 1755, 1676, 1600, 1508, 1359, 1273, 1172, 1085, 1022, 958, 592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H), 2.56 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 4.69 (s, 2H), 6.92–6.96 (m, 2H), 7.78–7.80 (m, 2H); ESI/MS m/z: 223.3 $(M+H)^+$.

4.3.10. Ethyl 2-(2-methyl-4-propionylphenoxy)acetate (8c)

This compound was prepared from **7c** by means of a procedure similar to that reported for **8a**. Off white solid; yield: 90%; mp 55–57 °C; purity by HPLC: 98.0%; IR: 2976, 1755, 1670, 1600, 1498, 1450, 1381, 1280, 1209, 1145, 1072, 798, 626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J = 7.4 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 2.32 (s, 3H), 2.92 (q, J = 7.2 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.71 (s, 2H), 6.70 (d, J = 8.0 Hz, 1H), 7.78–7.80 (m, 2H); ESI/MS m/z: 251.3 $(M+H)^+$.

4.3.11. Ethyl 2-(4-propionylphenoxy)acetate (8d)

This compound was prepared from **7d** by means of a procedure similar to that reported for **8a**. Thick liquid; yield: 95%; purity by HPLC: 93.3%; IR: 3350, 3020, 2983, 2939, 1757, 1679, 1602, 1508, 1417, 1380, 1353, 1301, 1215, 1172, 1080, 1018, 842, 758, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 2.91 (q, J = 7.2 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.68 (s, 2H), 6.89 (dd, J = 1.9 and 6.9 Hz, 2H), 7.92 (dd, J = 1.9 and 6.9 Hz, 2H).; ESI/MS m/z: 236.9 $(M+H)^+$.

4.3.12. Ethyl 2-(4-butyryl-2-methylphenoxy)acetate (8e)

This compound was prepared from **7e** by means of a procedure similar to that reported for **8a**. Off white solid; yield: 98%; mp 70–71 °C; purity by HPLC: 99.1%; IR (KBr): 3411, 3035, 2873, 1755, 1600, 1500, 1328, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, J = 7.4 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.66–1.78 (m, 2H), 2.32 (s, 3H), 2.88 (t, J = 7.3 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.70 (s, 2H), 6.70 (d, J = 8.3 Hz, 1H), 7.72–7.79 (m, 2H); ESI/MS m/z: 264.9 $(M+H)^+$.

4.3.13. Ethyl 2-(4-(cyclohexanecarbonyl)-2-methylphenoxy)-acetate (8f)

This compound was prepared from **7f** by means of a procedure similar to that reported for **8a**. Thick liquid; yield: 97%; purity by HPLC: 98.9%; IR: 3425, 2935, 1911, 1757, 1658, 1496, 1247, 1004, 916, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21–1.49 (m, 8H), 1.71–1.72 (m, 1H), 1.82–1.84 (m, 4H), 2.33 (s, 3H), 3.11–3.26 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.71 (s, 2H), 6.69 (d, J = 9.1 Hz, 1H), 7.74–7.80 (m, 2H); ESI/MS m/z: 304.9 $(M+H)^+$.

4.3.14. *(E)*-Ethyl 2-(4-(1-(hydroxyimino)ethyl)-2-methylphenoxy)acetate (9a)

To a solution of **8a** (15 g, 0.064 mol) in ethanol (100 mL), a solution of hydroxylammonium chloride (8.82 g, 0.127 mol) and sodium acetate (10.42 g, 0.127 mol) in water (30 ml) was added and the reaction mixture was heated to reflux for a period of about 1 h. Reaction mixture was cooled and diluted with water. Solid separated was filtered and dried under vacuum to yield 22.7 g of product as white solid. Yield: 71%; mp 105–107 °C; purity by HPLC: 98.3%; IR: 3217, 3082, 2981, 2910, 1762, 1604, 1508, 1434, 1415, 1384, 1305, 1278, 1259, 1213, 1168, 1153, 1097, 1074, 945, 889, 813, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J = 7.1 Hz, 3H), 2.25 (s, 3H), 2.31 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.65 (s, 2H), 6.73 (d, J = 8.5 Hz, 1H), 7.37 (dd, J = 8.5 and 2.0 Hz, 1H), 7.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.46, 14.04, 16.14, 60.65, 64.90, 111.13, 124.33, 125.86, 127.85, 129.84, 152.42, 156.23, 168.75; ESI/MS m/z: 251.9 $(M+H)^+$.

4.3.15. (*E*)-Ethyl 2-(4-(1-(hydroxyimino)ethyl)phenoxy)acetate (9b)

This compound was prepared from **8b** by means of a procedure similar to that reported for **9a**. Off white solid; yield: 81%; mp 91–92 °C; purity by HPLC: 98.1%; IR: 3300, 2908, 1761, 1600, 1514, 1483, 1373, 1259, 1209, 1176, 1076, 1006, 927, 829, 765, 601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 4.64 (s, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.47, 14.05, 60.70, 64.65, 114.35, 126.86, 130.18, 152.34, 158.00, 168.65; ESI/MS m/z: 238.3 $(M+H)^+$.

4.3.16. (*E*)-Ethyl 2-(4-(1-(hydroxyimino)propyl)-2-methylphenoxy)acetate (9c)

This compound was prepared from **8c** by means of a procedure similar to that reported for **9a**. Off white solid; yield: 88%; mp 84–86 °C; purity by HPLC: 98.7%; IR (KBr): 3277, 2987, 2928, 1753, 1604, 1508, 1437, 1346, 1284, 1205, 1184, 1139, 1072, 1022, 956, 856, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, J = 7.6 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 2.75 (q, J = 7.6 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.66 (s, 2H), 6.68 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 8.4 and 2.0 Hz, 1H), 7.44 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 8.33, 14.03, 16.02, 30.84, 60.79, 64.90, 110.97, 126.17, 127.80, 129.77, 130.43, 159.51, 168.41, 199.04; ESI/MS m/z: 266.3 $(M+H)^+$.

4.3.17. (*E*)-Ethyl 2-(4-(1-(hydroxyimino)propyl)phenoxy)acetate (9d)

This compound was prepared from **8d** by means of a procedure similar to that reported for **9a**. White solid; yield: 86%; mp 70–

72 °C; purity by HPLC: 84.6%; IR (KBr): 3355, 2981, 2941, 2877, 1705, 1624, 1600, 1514, 1467, 1514, 1448, 1406, 1367, 1313, 1240, 1178, 1116, 1066, 1029, 970, 916, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, J = 7.5 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 2.82 (q, J = 7.6 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.64 (s, 2H), 6.92 (dd, J = 6.9 and 1.9 Hz, 2H), 7.54 (dd, J = 6.9 and 1.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.95, 14.05, 18.28, 60.71, 64.66, 114.47, 127.03, 128.99, 157.18, 157.99, 168.17; ESI/MS m/z: 252.0 $(M+H)^+$.

4.3.18. (*E*)-Ethyl 2-(4-(1-(hydroxyimino)butyl)-2-methylphenoxy)acetate (9e)

This compound was prepared from **8e** by means of a procedure similar to that reported for **9a**. Off white solid; yield: 92%; mp 71–72 °C; purity by HPLC: 97.7%; IR (KBr): 3369, 3033, 2873, 1701, 1606, 1508, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, J = 7.4 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.51–1.64 (m, 2H), 2.30 (s, 3H), 2.74 (t, J = 7.62 Hz, 2H), 4.27 (q, J = 15.5 & 7.14 Hz, 2H), 4.65 (s, 2H), 6.70 (d, J = 8.52 Hz, 1H), 7.37 (dd, J = 8.5 & 2.5 Hz, 1H), 7.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.02, 16.14, 19.51, 26.69, 60.64, 64.88, 111.15, 124.54, 125.93, 128.06, 128.98, 156.16, 168.75; ESI/MS m/z: 279.9 $(M+H)^+$.

4.3.19. (*E*)-Ethyl 2-(4-(cyclohexyl(hydroxyimino)methyl)-2-methylphenoxy)acetate (9f)

This compound was prepared from **8f** by means of a procedure similar to that reported for **9a**. Off white solid; yield: 66%; mp 100–103 °C; purity by HPLC: 85.2%; IR: 3247, 3074, 2929, 1768, 1608, 1506, 1215, 1174, 956, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.12–1.32 (m, 9H), 1.62–1.64 (m, 1H), 1.70–1.83 (m, 4H), 2.31 (s, 3H), 4.2 (q, J = 7.1 Hz, 2H), 4.62 (s, 2H), 6.71 (d, J = 8.1 Hz, 1H), 7.01–7.06 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.03, 16.02, 25.75, 25.84, 30.67, 43.26, 60.63, 64.82, 110.69, 125.26, 126.41, 127.27, 130.15, 155.23, 159.15, 168.82; ESI/MS m/z: 320.0 $(M+H)^+$.

4.3.20. (*E*)-(2-Methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxyimino]-ethyl}-phenoxy)-acetic acid ethyl ester (11a)

To a solution of **10** (1.5 g, 5.14 mmol) and **9a** (1.29 g, 5.14 mmol) in dry DMF (10 mL), Cs_2CO_3 (2.51 g, 7.71 mmol) was added and reaction mixture was stirred at 60 °C for 18 h. Reaction mixture was poured into ice cold water (100 mL) and extracted with ethyl acetate (3 × 40 mL). The organic extract was washed with water and brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (8% ethyl acetate in hexane) to give title compound **11a** as white solid. (1.72 g) yield: 66%; mp 112–114 °C; purity by HPLC: 98.9%; IR: 3433, 2989, 2935, 1764, 1726, 1616, 1500, 1508, 1452, 1325, 1271, 1240, 1172, 1149, 1114, 1068, 1031, 1001, 964, 918, 848, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 2.54 (s, 3H), 4.27 (q, J = 7.1 Hz, 2H), 4.65 (s, 2H), 5.32 (s, 2H), 6.70 (d, J = 8.5 Hz, 1H), 7.41–7.44 (m, 1H), 7.44 (s, 1H), 7.65 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.1 Hz, 2H); ESI/MS m/z: 507.1 $(M+H)^+$.

4.3.21. (*E*)-Ethyl 2-(4-(1-(((4-methyl-2-(4-(trifluoromethyl)-phenyl)thiazol-5-yl)methoxy)imino)ethyl)phenoxy)acetate (11b)

This compound was prepared from **10** and **9b** by means of a procedure similar to that reported for **10a**. Off white solid; yield: 72%; mp 100–102 °C; purity by HPLC: 99.1%; IR (KBr): 3387, 2937, 2854, 1728, 1612, 1514, 1406, 1323, 1236, 1172, 1111, 1068, 1001, 898, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H), 2.21 (s, 3H), 2.55 (s, 3H), 4.25 (q, J = 7.0 Hz, 2H), 4.64 (s, 2H), 5.33 (s, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.60–7.64 (m, 2H), 7.65 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.0 Hz, 2H); ESI/MS m/z: 493.1 $(M+H)^+$.

4.3.22. (*E*)-Ethyl 2-(2-methyl-4-(1-(((4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methoxy)imino)propyl)phenoxy)-acetate (11c)

This compound was prepared from **10** and **9c** by means of a procedure similar to that reported for **10a**. Off white solid; yield: 67%; mp 105–107 °C; purity by HPLC: 98.3%; IR (KBr): 2982, 2935, 1741, 1618, 1508, 1452, 1381, 1321, 1213, 1124, 1066, 1001, 962, 916, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, J = 7.6 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 2.31 (s, 3H), 2.55 (s, 3H), 2.68 (q, J = 7.6 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.66 (s, 2H), 5.32 (s, 2H), 6.68 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 8.4 and 2.0 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.0 Hz, 2H); ESI/MS m/z: 521.1 $(M+H)^+$.

4.3.23. (*E*)-Ethyl 2-(4-(1-(((4-methyl-2-(4-(trifluoromethyl)-phenyl)thiazol-5-yl)methoxy)imino)propyl)phenoxy)acetate (11d)

This compound was prepared from **10** and **9d** by means of a procedure similar to that reported for **10a**. Pale yellow solid; yield: 66%; mp 75–77 °C; purity by HPLC: 98.7%; IR (KBr): 2985, 2966, 2937, 1741, 1612, 1569, 1542, 1512, 1467, 1454, 1406, 1380, 1350, 1321, 1271, 1240, 1211, 1174, 1120, 1066, 1033, 997, 964, 950, 891, 858, 840, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, J = 7.5 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.54 (s, 3H), 2.71 (q, J = 7.6 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.64 (s, 2H), 5.31 (s, 2H), 6.92 (d, J = 8.9 Hz, 2H), 7.59–7.67 (m, 4H), 7.50 (d, J = 8.2 Hz, 2H); ESI/MS m/z: 507.0 $(M+H)^+$.

4.3.24. (*E*)-Ethyl 2-(2-methyl-4-(1-(((4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methoxy)imino)butyl)phenoxy)-acetate (11e)

This compound was prepared from **10** and **9e** by means of a procedure similar to that reported for **10a**. Off white solid; yield: 55%; mp 90–92 °C; purity by HPLC: 95.0%; IR (KBr): 2968, 2872, 1774, 1726, 1616, 1508, 1438, 1327, 1199, 1166, 1122, 1068, 1014, 964, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J = 7.4 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.50–1.52 (m, 2H), 2.31 (s, 3H), 2.54 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.65 (s, 2H), 5.31 (s, 2H), 6.67 (d, J = 8.8 Hz, 1H), 7.34 (dd, J = 8.6 and 2.2 Hz, 1H), 7.48 (d, J = 1.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H); ESI/MS m/z: 535.7 $(M+H)^+$.

4.3.25. (*E*)-ethyl 2-(4-(cyclohexyl(((4-methyl-2-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methoxy)imino)methyl)phenoxy)-acetate (11f)

This compound was prepared from **10** and **9f** by means of a procedure similar to that reported for **10a**. Thick liquid; yield: 31%; purity by HPLC: 95.5%; IR: 3435, 2929, 2854, 1739, 1502, 1450, 1325, 1128, 1066, 904, 675, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.26–1.31 (m, 9H), 1.67–1.79 (m, 4H), 2.28 (s, 3H), 2.46 (s, 4H), 4.26 (q, J = 7.1 Hz, 2H), 4.63 (s, 2H), 5.13 (s, 2H), 6.66 (d, J = 8.1 Hz, 1H), 6.99–7.02 (m, 2H), 7.67 (d, J = 8.2 Hz, 2H), 8.02 (d, J = 8.1 Hz, 2H); ESI/MS m/z: 575.1 $(M+H)^+$.

4.3.26. (*E*)-(2-Methyl-4-{1-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxyimino]-ethyl}-phenoxy)-acetic acid (12a)

To a solution of **11a** (500 mg, 0.99 mmol) in a mixture of tetrahydrofuran (9 mL) and methanol (3 mL) was added another solution of $LiOH{\cdot}H_2O$ (83 mg, 1.97 mmol) in water (3 mL) and the reaction mixture was stirred at ambient temperature for about 18 h. Solvent was evaporated under reduced pressure, water (50 ml) was added to the residue, acidified with 1 N HCl to pH 6 and extracted with ethyl acetate (20 ml × 3). The combined organic extract was washed with water and brine solution, dried over sodium sulfate and evaporated under reduced pressure to yield title

product as off white solid (435 mg). Yield: 92%; mp 158–160 °C; purity by HPLC: 99.8%; IR (KBr): 3435, 2925, 1718, 1618, 1508, 1450, 1406, 1355, 1325, 1274, 1226, 1174, 1114, 1068, 1010, 968, 920, 844, 819, 800 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.89 (s, 3H), 1.96 (s, 3H), 2.46 (s, 3H), 4.66 (s, 2H), 5.33 (s, 2H), 6.80 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.8 (d, J = 8.3 Hz, 2H), 8.0 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.40, 15.14, 16.18, 64.85, 66.49, 111.06, 124.88, 125.92, 126.13, 126.17, 126.55, 127.98, 128.12, 129.87, 136.52, 151.86, 154.94, 157.06, 163.34, 170.20; ESI/MS m/z: 479.0 $(M+H)^+$.

4.3.27. *(E)*-2-(4-(1-(((4-methyl-2-(4-(trifluoromethyl)phenyl)-thiazol-5-yl)methoxy)imino)ethyl)phenoxy)acetic acid (12b)

This compound was prepared from **11b** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 89%; mp 150–152 °C; purity by HPLC: 99.3%; IR (KBr): 2926, 2856, 1701, 1612, 1510, 1437, 1327, 1230, 1111, 1068, 999, 900, 825 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.16 (s, 3H), 2.49 (s, 3H), 4.65 (s, 2H), 5.36 (s, 2H), 6.92 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.38, 15.15, 64.71, 66.49, 114.43, 125.57, 126.17, 127.31, 128.36, 129.85, 136.53, 151.93, 154.82, 158.90, 163.39, 170.09; ESI/MS m/z: 465.5 $(M+H)^+$.

4.3.28. *(E)*-2-(2-methyl-4-(1-(((4-methyl-2-(4-(trifluoromethyl)-phenyl)thiazol-5-yl)methoxy)imino)propyl)phenoxy)acetic acid (12c)

This compound was prepared from **11c** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 80%; mp 174–176 °C; purity by HPLC: 99.3%; IR (KBr): 2982, 2926, 1701, 1616, 1502, 1325, 1228, 1170, 1116, 1068, 1003, 964, 914, 839 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.98 (t, J = 7.6 Hz, 3H), 2.20 (s, 3H), 2.49 (s, 3H), 2.63 (q, J = 7.4 Hz, 2H), 4.67 (s, 2H), 5.35 (s, 2H), 6.81 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 8.4 and 2.0 Hz, 1H), 4.48 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.16, 15.14, 16.22, 19.23, 65.01, 66.51, 111.16, 125.03, 126.07, 126.14, 126.55, 126.66, 128.25, 129.97, 136.52, 151.83, 157.15, 159.83, 163.32, 170.25; ESI/MS m/z: 493.1 $(M+H)^+$.

4.3.29. (*E*)-2-(4-(1-(((4-methyl-2-(4-(trifluoromethyl)phenyl)-thiazol-5-yl)methoxy)imino)propyl)phenoxy)acetic acid (12d)

This compound was prepared from **11d** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 88%; mp 167–169 °C; purity by HPLC: 99.5%; IR (KBr): 3411, 2983, 2935, 2883, 1701, 1610, 1510, 1452, 1352, 1325, 1230, 1184, 1170, 1112, 1068, 999, 966, 893, 846, 829, 675 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.00 (t, J = 7.4 Hz, 3H), 2.41 (s, 3H), 2.66 (q, J = 7.4 Hz, 2H), 4.70 (s, 2H), 5.35 (s, 2H), 6.95 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 8.11 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.10, 15.15, 19.22, 64.47, 66.15, 114.56, 126.14, 126.18, 126.57, 127.21, 127.48, 129.94, 136.51, 151.89, 158.78, 159.65, 163.35, 170.02; ESI/MS m/z: 479.0 $(M+H)^+$.

4.3.30. *(E)*-2-(2-methyl-4-(1-(((4-methyl-2-(4-(trifluoromethyl)-phenyl)thiazol-5-yl)methoxy)imino)butyl)phenoxy)acetic acid (12e)

This compound was prepared from **11e** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 61%; mp 155–157 °C; purity by HPLC: 95.8%; IR (KBr): 3433, 2966, 2872, 1747, 1616, 1506, 1431, 1327, 1242, 1166, 1122, 1068, 1014, 966, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.4 Hz, 3H), 1.45–1.53 (m, 2H), 2.26 (s, 3H), 2.53 (s, 3H), 2.64 (t, J = 7.6 Hz, 2H), 4.60 (s, 2H), 5.29 (s, 2H), 6.67 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 8.4 and 2.0 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.89, 15.12,19.66, 27.48, 65.11, 66.47, 111.10, 125.08, 125.98, 126.13, 126.53, 126.99, 128.26, 129.94, 136.52, 151.78, 157.14, 158.68, 163.28, 170.26; ESI/MS m/z: 507.6 $(M+H)^+$.

4.3.31. (*E*)-2-(4-(Cyclohexyl(((4-methyl-2-(4-(trifluoromethyl)-phenyl)thiazol-5-yl)methoxy)imino)methyl)phenoxy)acetic acid (12f)

This compound was prepared from **11f** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 63%; mp 52–55 °C; purity by HPLC: 97.2%; IR (KBr): 3435, 2929, 2854, 1739, 1502, 1450, 1325, 1128, 1066, 904, 675, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.29 (m, 6H), 1.71–1.73 (m, 4H), 2.22 (s, 3H), 2.47–2.48 (m, 4H), 4.57 (s, 2H), 5.10 (s, 2H), 6.67 (d, J = 8.3 Hz, 1H), 6.97 (s, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.34, 16.40, 26.18, 29.64, 44.48, 65.84, 110.98, 125.98, 126.02, 126.38, 126.68, 126.98, 127.40, 129.94, 130.44, 136.81, 151.95, 155.93, 163.19, 164.76; ESI/MS m/z: 547.1 $(M+H)^+$.

4.3.32. (*E*)-Ethyl 2-(2-methyl-4-(1-(((5-methyl-2-phenyloxazol-4-yl)methoxy)imino)ethyl)phenoxy)acetate (15a)

This compound was prepared from **13** and **9a** by means of a procedure similar to that reported for **11a**. Off white solid; yield: 52%; mp 86–88 °C; purity by HPLC: 94.0%; IR (KBr): 3382, 2981, 2927, 2875, 1759, 1737, 1637, 1606, 1556, 1504, 1448, 1369, 1317, 1278, 1203, 1145, 1068, 1024, 939, 891, 808, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J = 7.1 Hz, 3H), 2.11 (s, 3H), 2.34 (s, 3H), 2.48 (s, 3H), 4.26 (q, J = 7.1 Hz, 2H), 4.64 (s, 2H), 5.12 (s, 2H), 6.68 (d, J = 8.5 Hz, 1H), 7.35–7.49 (m, 5H), 8.01–8.02 (m, 2H); ESI/MS m/z: 423.0 $(M+H)^+$.

4.3.33. *(E)*-Ethyl 2-(4-(1-(((5-methyl-2-phenyloxazol-4-yl)-methoxy)imino)ethyl)phenoxy)acetate (15b)

This compound was prepared from **13** and **9b** by means of a procedure similar to that reported for **11a**. Thick liquid; yield: 59%; purity by HPLC: 98.4%; IR (KBr): 3018, 2983, 2929, 1753, 1604, 1512, 1384, 1319, 1180, 1018, 923, 833, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J = 7.0 Hz, 3H), 2.21 (s, 3H), 2.48 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 4.63 (s, 2H), 5.12 (s, 2H), 6.88 (dd, J = 9.6 and 2.4 Hz, 2H), 7.39–7.45 (m, 3H), 7.58 (dd, J = 9.4 and 2.6 Hz, 2H), 8.00–8.03 (m, 2H); ESI/MS m/z: 409.2 $(M+H)^+$.

4.3.34. *(E)*-Ethyl 2-(2-methyl-4-(1-(((5-methyl-2-phenyloxazol-4-yl)methoxy)imino)propyl)phenoxy)acetate (15c)

This compound was prepared from **13** and **9c** by means of a procedure similar to that reported for **11a**. Off white solid; yield: 55%; mp 95–97 °C; purity by HPLC: 99.2%; IR (KBr): 2974, 2885, 1757, 1639, 1498, 1377, 1203, 1186, 1149, 1105, 1030, 937, 860, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, J = 7.6 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 2.30 (s, 3H), 2.48 (s, 3H), 2.69 (q, J = 7.6 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 4.64 (s, 2H), 5.11 (s, 2H), 6.66 (d, J = 8.4 Hz, 1H), 7.37–7.47 (m, 5H), 8.00–8.03 (m, 2H); ESI/MS m/z: 437.2 $(M+H)^+$.

4.3.35. *(E)*-Ethyl 2-(4-(1-(((5-methyl-2-phenyloxazol-4-yl)methoxy)imino)propyl)phenoxy)acetate (15d)

This compound was prepared from **13** and **9d** by means of a procedure similar to that reported for **11a**. Off white solid; yield: 59%; mp 84–86 °C; purity by HPLC: 92.9%; IR (KBr): 2976, 2923, 1759, 1604, 1558, 1512, 1485, 1454, 1379, 1338, 1315, 1303, 1234, 1195, 1186, 1105, 1082, 1068, 1035, 1024, 954, 910, 833, 794, 781, 715, 700, 599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (t, J = 7.6 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.47 (s, 3H), 2.79 (q, J = 7.6 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.68 (s, 2H), 5.29 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.41–7.44 (m, 3H), 7.60 (d, J = 8.7 Hz, 2H), 8.01–8.03 (m, 2H); ESI/MS m/z: 423.1 $(M+H)^+$.

4.3.36. *(E)*-Ethyl 2-(2-methyl-4-(1-(((5-methyl-2-phenyloxazol-4-yl)methoxy)imino)butyl)phenoxy)acetate (15e)

This compound was prepared from **13** and **9e** by means of a procedure similar to that reported for **11a**. Thick liquid; yield: 51%; purity by HPLC: 97.4%; IR: 3018, 2968, 1753, 1508, 1384, 1145, 1026, 929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.47–1.57 (m, 2H), 2.30 (s, 3H), 2.48 (s, 3H), 2.67 (t, J = 7.4 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.64 (s, 2H), 5.11 (s, 2H), 6.65 (d, J = 8.4 Hz, 1H), 7.35–7.47 (m, 5H), 8.00–8.03 (m, 2H); ESI/MS m/z: 451.2 $(M+H)^+$.

4.3.37. *(E)*-Ethyl 2-(4-(cyclohexyl(((5-methyl-2-phenyloxazol-4-yl)methoxy)imino)methyl)-2-methylphenoxy)acetate (15f)

This compound was prepared from **13** and **9f** by means of a procedure similar to that reported for **11a**. Thick liquid; yield: 55%; purity by HPLC: 94.1%; IR: 3018, 2931, 2854, 1757, 1500, 1448, 1384, 1149, 1035, 934 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.19–1.33 (m, 9H), 1.74–1.81 (m, 4H), 2.26 (s, 3H), 2.29 (s, 3H), 2.40–2.45 (m, 1H), 4.23 (q, J = 7.0 Hz, 2H), 4.62 (s, 2H), 4.95 (s, 2H), 6.64 (d, J = 8.4 Hz, 1H), 7.01–7.04 (m, 2H), 7.39–7.45 (m, 3H), 7.98–8.02 (m, 2H); ESI/MS m/z: 513.2 $(M+Na)^+$.

4.3.38. *(E)*-Ethyl 2-(2-methyl-4-(1-(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)methoxy)imino)ethyl)phenoxy)acetate (16a)

This compound was prepared from **14** and **9a** by means of a procedure similar to that reported for **11a**. Off white solid; yield: 61%; mp 114–116 °C; purity by HPLC: 98.2%; IR (KBr): 3429, 2981, 2918, 2850, 1724, 1618, 1500, 1433, 1375, 1365, 1313, 1294, 1269, 1240, 1145, 1002, 981, 918, 858, 817, 794, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 3H), 2.23 (s, 3H), 2.30 (s, 3H), 2.41 (s, 3H), 2.47 (s, 3H) 4.27 (q, J = 7.1 Hz, 2H), 4.64 (s, 2H), 5.11 (s, 2H), 6.68 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.41 (dd, J = 8.5 and 2.0 Hz, 1H), 7.49 (d, J = 1.4 Hz, 1H), 7.92 (d, J = 8.1 Hz, 2H); ESI/MS m/z: 437.2 $(M+H)^+$.

4.3.39. *(E)*-Ethyl 2-(4-(1-(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)methoxy)imino)ethyl)phenoxy)acetate (16b)

This compound was prepared from **14** and **9b** by means of a procedure similar to that reported for **11a**. Off white solid; yield: 68%; mp 112–113 °C; purity by HPLC: 97.8%; IR (KBr): 2987, 2918, 1757, 1599, 1512, 1500, 1435, 1373, 1273, 1201, 1074, 1026, 927, 727, 599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H), 2.21 (s, 3H), 2.39 (s, 3H), 2.47 (s, 3H), 4.24 (q, J = 7.0 Hz, 2H), 4.63 (s, 2H), 5.11 (s, 2H), 6.87 (dd, J = 11.6 and 2.8 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.58–7.61 (m, 2H), 7.89 (d, J = 8.0 Hz, 2H); ESI/MS m/z: 423.2 $(M+H)^+$.

4.3.40. *(E)*-Ethyl 2-(2-methyl-4-(1-(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)methoxy)imino)propyl)phenoxy)acetate (16c)

This compound was prepared from **14** and **9c** by means of a procedure similar to that reported for **11a**. Off white solid; yield: 68%; mp 116–118 °C; purity by HPLC: 99.8%; IR (KBr): 2966, 2872, 1743, 1612, 1500, 1448, 1377, 1213, 1149, 1103, 1074, 993, 846, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, J = 7.6 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 2.30 (s, 3H), 2.38 (s, 3H), 2.47 (s, 3H), 2.69 (q, J = 7.6 Hz, 2H), 4.23 (q, J = 7.0 Hz, 2H), 4.64 (s, 2H), 5.10 (s, 2H), 6.65 (d, J = 8.4 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.37 (dd, J = 8.6 & 2.2 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H); ESI/MS m/z: 451.2 $(M+H)^+$.

4.3.41. *(E)*-Ethyl 2-(4-(1-(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)methoxy)imino)propyl)phenoxy)acetate (16d)

This compound was prepared from **14** and **9d** by means of a procedure similar to that reported for **11a**. Thick liquid; yield: 45%; purity by HPLC: 96.9%; IR: 3018, 2981, 2937, 1757, 1610, 1512, 1500, 1442, 1299, 1215, 1180, 1078, 1018, 968, 827, 759, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, J = 7.5 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 2.38 (s, 3H), 2.46 (s, 3H), 2.74 (q, J = 7.5 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.62 (s, 2H), 5.29 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.1 Hz, 2H); ESI/MS m/z: 437.1 $(M+H)^+$.

4.3.42. *(E)*-Ethyl 2-(2-methyl-4-(1-(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)methoxy)imino)butyl)phenoxy)acetate (16e)

This compound was prepared from **14** and **9e** by means of a procedure similar to that reported for **11a**. White solid; yield: 45%; mp 110–111 °C; purity by HPLC: 99.1%; IR: 3060, 2958, 2871, 1743, 1614, 1502, 1190 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.48–1.62 (m, 2H), 2.71 (s, 3H), 2.30 (s, 3H), 2.46 (s, 3H), 2.67 (t, J = 6.6 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 4.64 (s, 2H), 5.30 (s, 2H), 6.65 (d, J = 8.5 Hz, 1H), 7.21–7.23 (m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 7.90 (d, J = 8.1 Hz, 2H); ESI/MS m/z: 465.0 $(M+H)^+$.

4.3.43. *(E)*-Ethyl 2-(4-(cyclohexyl(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)methoxy)imino)methyl)-2-methylphenoxy)acetate (16f)

This compound was prepared from **14** and **9f** by means of a procedure similar to that reported for **11a**. Thick liquid; yield: 22%; purity by HPLC: 94.2%; IR: 3130, 3020, 2029, 1732, 1633, 1502, 1215, 1145, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21–1.35 (m, 9H), 1.69–1.72 (m, 5H), 2.24 (s, 3H), 2.30 (s, 3H), 2.32 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 4.61 (s, 2H), 4.90 (s, 2H), 6.64 (d, J = 8.1 Hz, 1H), 7.01–7.02 (m, 2H), 7.21 (s, 2H), 7.85 (d, J = 8.0 Hz, 2H); ESI/MS m/z: 527.1 $(M+Na)^+$.

4.3.44. *(E)*-2-(2-Methyl-4-(1-(((5-methyl-2-phenyloxazol-4-yl)methoxy)imino)ethyl)phenoxy)acetic acid (17a)

This compound was prepared from **15a** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 94%; mp 184–186 °C; purity by HPLC: 99.7%; IR (KBr): 3429, 3049, 3049, 2949, 2916, 2852, 1724, 1632, 1618, 1556, 1508, 1488, 1448, 1436, 1315, 1265, 1242, 1195, 1159, 1145, 1062, 1020, 970, 870, 871, 800., 702 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.14 (s, 3H), 2.21 (s, 3H), 2.47 (s, 3H), 4.73 (s, 2H), 5.05 (s, 2H), 6.85 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.50–7.52 (m, 4H), 7.95 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.17, 12.35, 16.16, 64.74, 66.90, 111.01, 124.78, 125.57, 125.91, 126.96, 128.04, 128.30, 129.10, 130.28, 132.83, 147.77, 154.04, 156.87, 158.60, 170.16; ESI/MS m/z: 395.0 $(M+H)^+$.

4.3.45. (*E*)-2-(4-(1-(((5-Methyl-2-phenyloxazol-4-yl)methoxy)imino)ethyl)phenoxy)acetic acid (17b)

This compound was prepared from **15b** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 92%; mp 186–188 °C; purity by HPLC: 98.9%; IR (KBr): 3072, 2920, 1718, 1612, 1149, 1103, 1072, 1004, 970, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 3H), 2.46 (s, 3H), 4.68 (s, 2H), 5.05 (s, 2H), 6.91 (d, J = 8.8 Hz, 2H), 7.46–7.53 (m, 3H), 7.58 (d, J = 8.8 Hz, 2H), 7.91–7.94 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.17, 12.34, 64.57, 66.98, 114.37, 125.57, 126.95, 127.20, 128.67, 129.09, 130.27, 132.82, 147.80, 153.93, 158.59, 158.67, 170.07; ESI/MS m/z: 381.1 $(M+H)^+$.

4.3.46. *(E)*-2-(2-Methyl-4-(1-(((5-methyl-2-phenyloxazol-4-yl)methoxy)imino)propyl)phenoxy)acetic acid (17c)

This compound was prepared from **15c** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 85%; mp 144–145 °C; purity by HPLC: 99.3%; IR (KBr): 3387, 2968, 2875, 1726, 1647, 1597, 1550, 1504, 1446, 1344, 1215, 1149, 1103, 1072, 1004, 970, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, J = 7.6 Hz, 3H), 2.19 (s, 3H), 2.45 (s, 3H), 2.62 (q, J = 7.2 Hz, 2H), 4.71 (s, 2H), 5.04 (s, 2H), 6.81 (d, J = 8.4 Hz, 1H), 7.39 (d,

J = 8.8 Hz, 1H), 7.46–7.52 (m, 4H), 7.91–7.93 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.13, 11.10, 16.15, 19.10, 64.75, 66.84, 111.07, 124.90, 125.54, 126.03, 126.97, 127.01, 128.20, 129.07, 130.23, 132.89, 147.67, 156.87, 158.57, 159.03, 170.18; ESI/MS m/z: 409.2 (M+H)$^+$.

4.3.47. *(E)*-2-(4-(1-(((5-Methyl-2-phenyloxazol-4-yl)methoxy)-imino)propyl)phenoxy)acetic acid (17d)

This compound was prepared from **15d** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 80%; mp 131–133 °C; purity by HPLC: 98.0%; IR (KBr): 3070, 2956, 2875, 1741, 1651, 1606, 1587, 1558, 1512, 1487, 1467, 1415, 1350, 1321, 1296, 1249, 1215, 1182, 1120, 1105, 1080, 1026, 975, 956, 904, 835, 717, 700 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.05 (t, J = 7.4 Hz, 3H), 2.45 (s, 3H), 2.67 (q, J = 7.4 Hz, 2H), 4.69 (s, 2H), 5.04 (s, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.50–7.52 (m, 3H), 7.59 (d, J = 8.8 Hz, 2H), 7.91–7.93 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.15, 11.05, 19.11, 64.48, 66.86, 114.49, 125.55, 126.97, 127.37, 127.45, 129.09, 130.26, 132.89, 147.72, 158.58, 158.63, 158.90, 170.04; ESI/MS m/z: 395.0 (M+H)$^+$.

4.3.48. *(E)*-2-(2-Methyl-4-(1-(((5-methyl-2-phenyloxazol-4-yl)methoxy)imino)butyl)phenoxy)acetic acid (17e)

This compound was prepared from **15e** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 91%; mp 141–142 °C; purity by HPLC: 99.9%; IR (KBr): 3389, 2935, 2812, 1728, 1728, 1647, 1597, 1504, 1448, 1419, 1342, 1269, 1207, 1149, 1070, 1001, 968, 864, 702 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.82 (t, J = 7.2 Hz, 3H), 1.38–1.44 (m, 2H), 2.18 (s, 3H), 2.45 (s, 3H), 2.62 (t, J = 7.6 Hz, 2H), 4.62 (s, 2H), 5.03 (s, 2H), 6.77 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.45 (s, 1H), 7.49–7.51 (m, 3H), 7.91–7.93 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.16, 13.89, 16.20, 19.59, 27.38, 65.20, 66.81, 111.03, 124.95, 125.54, 125.90, 126.98, 127.19, 128.17, 129.09, 130.25, 132.54, 147.65, 157.03, 157.91, 158.53, 170.33; ESI/MS m/z: 423.2 (M+H)$^+$.

4.3.49. *(E)*-2-(4-(Cyclohexyl(((5-methyl-2-phenyloxazol-4-yl)-methoxy)imino)methyl)-2-methylphenoxy)acetic acid (17f)

This compound was prepared from **15f** by means of a procedure similar to that reported for **12a**. White solid; yield: 88%; mp 84–86 °C; purity by HPLC: 95.7%; IR (KBr): 3412, 2926, 2852, 1608, 1500, 1429, 1338, 1300, 1230, 1143, 989, 895, 798, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92–0.94 (m, 6H), 1.56–1.59 (m, 1H), 1.65–1.67 (m, 4H), 2.11 (s, 3H), 2.35 (s, 3H), 4.22 (s, 2H), 4.84 (s, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.99 (s, 1H), 7.47–7.49 (m, 3H), 7.88–7.90 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.17, 16.24, 25.55, 25.73, 30.38, 43.21, 66.47, 99.54, 110.78, 124.92, 125.13, 125.47, 126.03, 126.97, 129.06, 129.57, 130.19, 132.93, 147.45, 158.38, 161.34; ESI/MS m/z: 463.2 (M+H)$^+$.

4.3.50. *(E)*-2-(2-Methyl-4-(1-(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)-methoxy)imino)ethyl)phenoxy)acetic acid (18a)

This compound was prepared from **16a** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 92%; mp 194–196 °C; purity by HPLC: 99.5%; IR (KBr): 3030, 2947, 2914, 2848, 1722, 1618, 1556, 1500, 1436, 1371, 1321, 1265, 1240, 1195, 1145, 1083, 1066, 1014, 970, 916, 873, 800, 729, 661 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.13 (s, 3H), 2.20 (s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 4.73 (s, 2H), 5.0 (s, 2H), 6.85 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.6 Hz, 1H), 7.49 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.13, 12.33, 16.14, 20.99, 64.71, 66.93, 110.99, 124.34, 124.76, 125.55, 125.89, 128.02, 128.30, 129.64, 132.63, 140.09, 147.36, 153.98, 156.84, 158.75, 170.13; ESI/MS m/z: 409.0 (M+H)$^+$.

4.3.51. *(E)*-2-(4-(1-(((5-Methyl-2-(*p*-tolyl)oxazol-4-yl)methoxy)-imino)ethyl)phenoxy)acetic acid (18b)

This compound was prepared from **16b** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 90%; mp 185–186 °C; purity by HPLC: 99.5%; IR (KBr): 2920, 1720, 1612, 1514, 1500, 1371, 1240, 1182, 1066, 1010, 885, 825, 731 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.13 (s, 3H), 2.35 (s, 3H), 2.44 (s, 3H), 4.63 (s, 2H), 5.03 (s, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.15, 12.34, 20.99, 64.86, 66.93, 114.39, 124.34, 125.55, 127.16, 128.56, 129.65, 132.63, 140.08, 147.40, 153.90, 158.75, 158.80, 170.25; ESI/MS m/z: 395.2 (M+H)$^+$.

4.3.52. *(E)*-2-(2-Methyl-4-(1-(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)-methoxy)imino)propyl)phenoxy)acetic acid (18c)

This compound was prepared from **16c** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 92%; mp 190–191 °C; purity by HPLC: 99.3%; IR (KBr): 3387, 2972, 2875, 1726, 1504, 1446, 1332, 1215, 1151, 1103, 1004, 970, 821, 732 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.96 (t, J = 7.6 Hz, 3H), 2.20 (s, 3H), 2.34 (s, 3H), 2.44 (s, 3H), 2.60 (q, J = 7.4 Hz, 2H), 4.72 (s, 2H), 5.02 (s, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.46 (s, 1H), 7.80 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.12, 11.11, 16.15, 19.10, 20.99, 20.99, 64.68, 66.89, 111.09, 124.36, 124.92, 125.54, 126.05, 127.07, 128.22, 129.64, 132.71, 140.07, 147.29, 156.84, 158.75, 158.99, 170.13; ESI/MS m/z: 423.2 (M+H)$^+$

4.3.53. *(E)*-2-(4-(1-(((5-Methyl-2-(*p*-tolyl)oxazol-4-yl)methoxy)-imino)propyl)phenoxy)acetic acid (18d)

This compound was prepared from **16d** by means of a procedure similar to that reported for **12a**. Off white solid; yield: 91%; mp 155–157 °C; purity by HPLC: 97.5%; IR (KBr): 3433, 2916, 2941, 2875, 2503, 1726, 1643, 1610, 1556, 1512, 1498, 1446, 1434, 1336, 1269, 1244, 1211, 1190, 1074, 987, 970, 871, 827, 731, 688 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (t, J = 7.4 Hz, 3H), 2.34 (s, 3H), 2.43 (s, 3H), 2.67 (q, J = 7.4 Hz, 2H), 4.69 (s, 2H), 5.35 (s, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.12, 11.06, 19.11, 20.99, 64.48, 66.91, 114.49, 124.36, 125.55, 127.37, 127.47, 129.64, 132.70, 140.72, 147.32, 158.63, 158.75, 158.85, 170.04; ESI/MS m/z: 409.0 (M+H)$^+$

4.3.54. *(E)*-2-(2-Methyl-4-(1-(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)-methoxy)imino)butyl)phenoxy)acetic acid (18e)

This compound was prepared from **16e** by means of a procedure similar to that reported for **12a**. White solid; yield: 68%; mp 151–152 °C; purity by HPLC: 99.4%; IR (KBr): 2964, 2873, 1728, 1645, 1558, 1338, 1001 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, J = 7.3 Hz, 3H), 1.49–1.51 (m, 2H), 2.30 (s, 3H), 2.39 (s, 3H), 2.46 (s, 3H), 2.68 (t, J = 7.5 Hz, 2H), 4.66 (s, 2H), 5.11 (s, 2H), 6.67 (d, J = 8.5 Hz, 1H), 7.22 (s, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.64, 14.35, 16.50, 20.15, 21.63, 28.61, 65.38, 67.19, 110.96, 124.58, 125.22, 126.34, 127.28, 129.07, 129.15, 129.60, 132.60, 140.66, 147.28, 156.87, 160.19, 172.22; ESI/MS m/z: 437.0 (M+H)$^+$.

4.3.55. *(E)*-2-(4-(Cyclohexyl(((5-methyl-2-(*p*-tolyl)oxazol-4-yl)-methoxy)imino)methyl)-2-methylphenoxy)acetic acid (18f)

This compound was prepared from **16f** by means of a procedure similar to that reported for **12a**. White solid; yield: 80%; mp 58–60 °C; purity by HPLC: 97.2%; IR (KBr): 3431, 2927, 2852, 1618, 1560, 1500, 1431, 1332, 1226, 1072, 985, 823, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20–1.23 (m, 8H), 2.16–2.17 (m, 3H), 2.32 (s, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 4.88 (s, 2H), 5.01 (s, 2H),

6.66–6.67 (m, 1H), 6.89–6.91 (m, 1H), 7.04–7.09 (m, 1H), 7.11–7.14 (m, 2H), 7.78–7.80 (m, 1H), 7.88 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.18, 16.25, 21.01, 22.82, 25.21, 25.57, 25.76, 25.89, 28.77, 29.30, 30.41, 43.22, 66.53, 66.66, 66.83, 99.57, 110.67, 124.38, 124.98, 125.20, 125.31, 125.49, 126.14, 127.19, 129.66, 132.75, 140.06, 147.08, 156.56, 156.99, 158.57, 161.34, 163.02, 171.24; ESI/MS m/z: 499.1 $(M+Na)^+$.

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