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Modulation of PPAR receptor subtype selectivity of the ligands: Aliphatic chain vs aromatic ring as a spacer between pharmacophore and the lipophilic moiety ☆

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ABSTRACT

Oxazole containing glycine and oximinobutyric acid derivatives were synthesized as PPARα agonists by incorporating polymethylene spacer as a replacement of commonly used phenylene group that connects the acidic head with lipophilic tail. Compound **13a** was found to be a selective and potent PPARα agonist. Further 1,3-dioxane-2-carboxylic acid derivative **20** was synthesized by replacing the tetramethylene spacer of NS-220, a selective PPARα agonist with phenylene group and found to exhibit PPARα/γ dual agonism. These results suggest that compounds possessing polymethylene spacer between pharmacophore and lipophilic tail exhibit predominantly PPARα agonism whereas those with an aromatic phenylene spacer shows PPARα/γ dual agonism.

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors in the nuclear hormone receptor superfamily.[1] Three distinct PPAR subtypes (PPARα, PPARγ, and PPARδ) have been identified in most mammalian species. 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.[2] PPARγ is well known at a cellular level for its role in adipogenesis and has been implicated as the primary receptor modulating the antidiabetic activity through insulin sensitization.[3] PPARγ agonists, such as TZDs, have proven to be efficacious as insulin-sensitizing agents in the treatment of type 2 diabetes. Two of these TZDs 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.[4] Fibrate compounds such as Fenofibrate and Bezafibrate used to treat hyperlipidemia are effective in reducing triglycerides, increasing HDL cholesterol and lowering LDL cholesterol are poor activators of PPARα and need high doses to show significant efficacy. 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.[5] The first dual agonist Farglitazar[6] which is a potent PPARγ agonist with a moderate PPARα activation was dropped in an advanced stage due to the emergence of edema. Two more dual agonists with substantial PPARα/γ dual activity Ragaglitazar[7] and Tesaglitazar[8] were also dropped from late clinical development due to carcinogenicity in rodent toxicity models and elevated serum creatinine and associated decrease in glomular filtration rate, respectively. The only dual agonist that has been advanced to NDA filing, Muraglitazar[9] was dropped very recently due to the incidence of edema, heart failure, and cardiovascular complications. Activation of PPARα is known to lower triglycerides, elevate HDL, and exert insulin-sensitizing effects.[10] These findings suggest that even chronic administration of selective PPARα agonist will serve as a better remedy for the treatment of metabolic disorder and led us to develop useful chemical tools to aid discovery of novel PPARα agonists. A typical structural design of a PPAR agonist as shown in Figure 1 comprises of a lipophilic heterocyclic tail and an acidic pharmacophore with a spacer in-between. As a part of our research in the field of PPARs to develop novel therapeutic agents to treat metabolic disorders[11] we have recently reported a series of 1,3-dioxane-2-carboxylic acid derivatives as PPARα/γ dual agonist[12] and the lead compound of this series **20** differs structurally from a recently reported PPARα agonist

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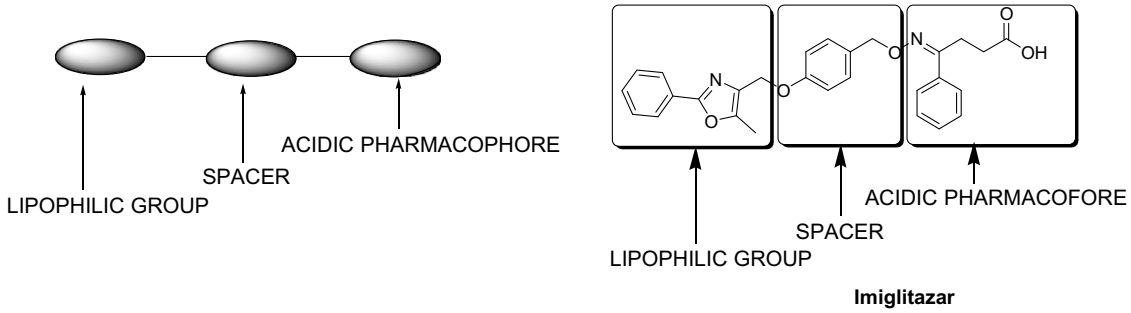


Figure 1. Structural design of PPAR ligand.

NS-220[13] in spacer region as compound **20** and other dual agonists like Imiglitazar[14] and Muraglitazar possess aromatic phenylene spacer whereas NS-220 possesses an alkyl chain as a spacer between acidic head and lipophilic tail (Fig. 2). Based on these observations we envisioned that PPAR subtype selectivity of ligands may be sensitive to chemical variations in the spacer region of the structure and intended to study the effect of changing the phenylene spacer of Imiglitazar and Muraglitazar to a polymethylene spacer in order to develop selective PPARα agonist. In this context we herein report few oxazole containing glycine and oximinobutyric acid derivatives as PPARα agonists designed by incorporating polymethylene spacer as a replacement of phenylene group of Imiglitazar and Muraglitazar. We also report a previously discovered dual agonist **20** synthesized by replacing the polymethylene spacer of NS-220, a selective PPARα agonist with phenylene group in order to show that the replacement of phenylene spacer of dual agonist with a polymethylene spacer makes the compounds PPARα selective agonists.

Synthesis of intermediate hydroxy compound **4a**–**b** and **6a**–**b** was illustrated in Scheme 1. Carboxylic acids **3a**–**b** were synthesized by reacting **1** or **2** with diethylmalonate in presence of sodium hydride followed by hydrolysis of the diester followed by decarboxylation under thermal condition. Esterification of monoacids **3a**–**b** followed by reduction of the resulted esters **3c**–**d** with lithium aluminum hydride yielded the hydroxy compounds **4a**–**b**. The mesylate derivatives **4c**–**d** were subjected to a similar series of reactions described for the synthesis of **4** in order to elongate the methylene chain to yield compounds **6a**–**b**. Compounds **9a**–**c** were synthesized according to Scheme 2. The hydroxy compounds **4b** and **6a**–**b** were oxidized to corresponding aldehydes **7a**–**c** with pyridiniumchlorochromate in dichloromethane which were reacted with glycine ethyl ester under reductive amination conditions followed by acylation of the intermediate with 4-methoxyphenylchloroformate to yield the ester **8a**–**c**. Hydrolysis of **8a**–**c** in aqueous basic medium resulted to yield acid compounds **9a**–**c**. Synthesis of compounds **13a**–**c** were described in Scheme 3. The hydroxy compounds **4b** and **6a**–**b** were converted to their mesylate derivatives **4d** and **10a**–**b**, respectively, and coupled with compound **11** in presence of base and the corresponding esters **12a**–**c** obtained were hydrolyzed with aqueous base to afford acids **13a**–**c**. Compound **20**[12] was synthesized as illustrated in Scheme 4 by coupling the intermediate **18** with **1** and hydrolyzing the ester **19** in presence of aqueous base. Intermediate **18** was prepared by reducing the diester **15** to diol **16** which was then cyclized to 1,3-dioxane by treating with methylpyruvate in the presence of lewis acid to afford compound **17** and debenzylated under hydrogen transfer reaction conditions. Imiglitazar,[14] Muraglitazar,[9] NS-220[13], Intermediates **1**, **2**,[15] and **11**[14] were synthesized following the methods reported in the literature.

Newly synthesized compounds[16] **9a**–**c**, **13a**–**c**, and **20** along with Imiglitazar, Muraglitazar, and NS-220 were screened for hPPARα, γ, and δ agonistic activity on full length PPAR receptor transfected in HepG2 cells following the procedure described in our earlier publication.[12] WY-14643, Rosiglitazone, and GW-

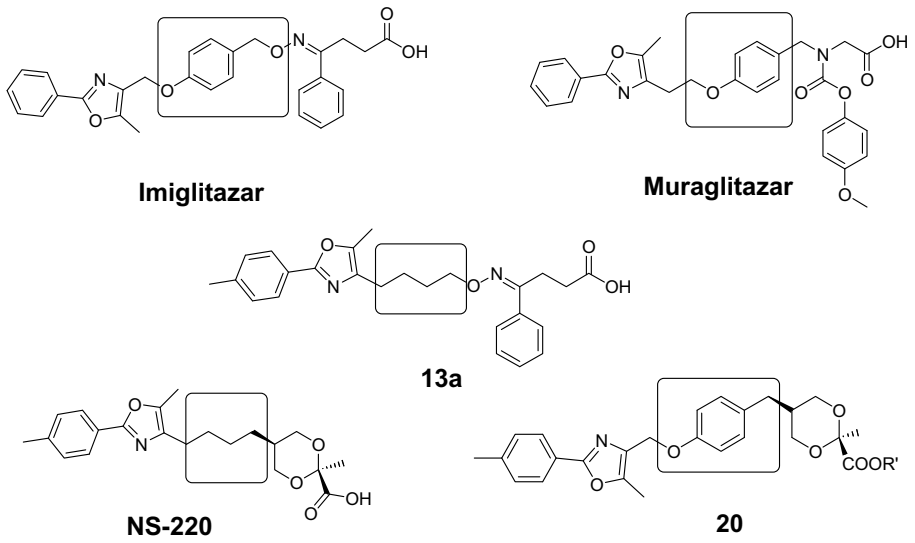
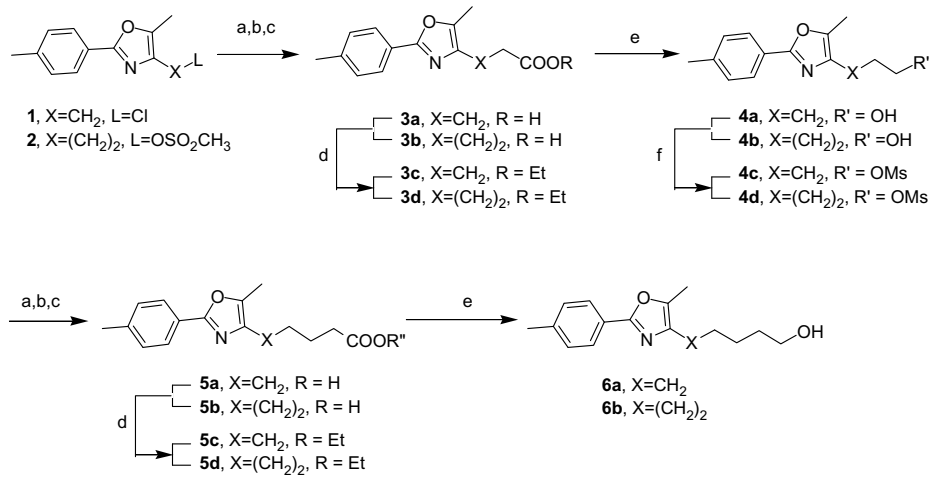
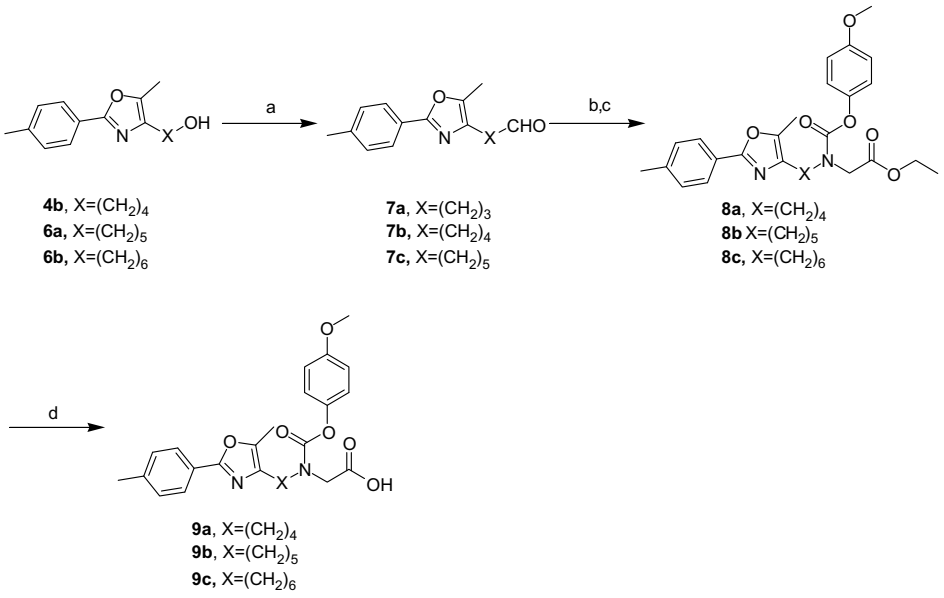


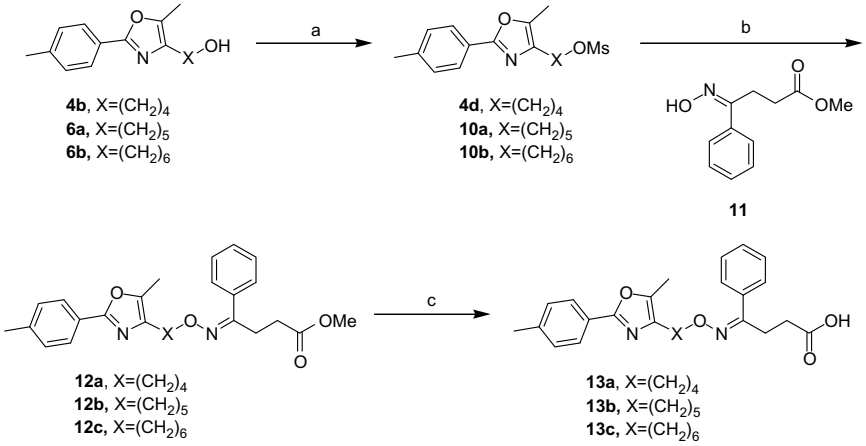
Figure 2. Chemical structures of PPAR ligands. Imiglitazar, Muraglitazar and **20** possess aromatic phenylene spacer between acidic head and lipophilic tail and are PPAR a/g dual agonists whereas NS-220 and **13a** contain polymethylene spacer and are PPARa selective agonists.



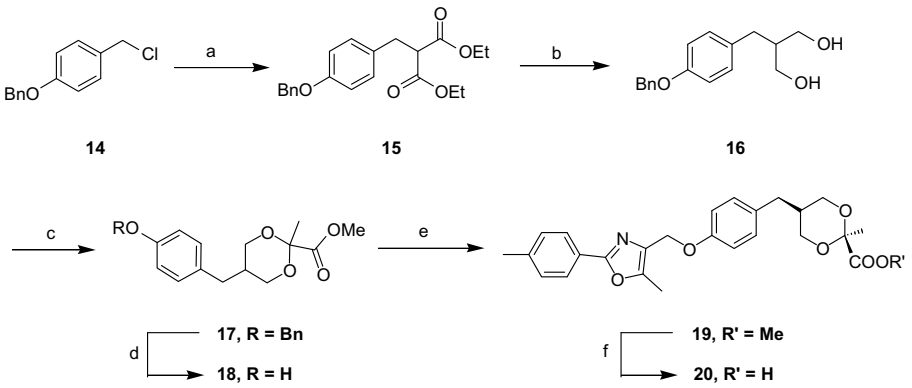
Scheme 1. Reagents and conditions: (a) diethyl malonate, NaH, DMF, 25 °C, 18 h; (b) aq NaOH, MeOH, 25 °C, 0.25 h; (c) xylene, reflux, 5 h; (d) EtOH, H_2SO_4, reflux, 24 h; (e) $LiAlH_4$, THF, 25 °C, 0.5 h; (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 10 °C, 0.25 h.



Scheme 2. Reagents and condition: (a) PCC, celite, CH_2Cl_2, 25 °C, 2 h; (b) glycine ethyl ester hydrochloride, MeOH, $NaBH(OAc)_3$, 25 °C, 1.5 h; (c) 4-methoxyphenylchloroformate, CH_2Cl_2, 25 °C, 2 h; (d) $LiOH{\cdot}H_2O$, THF, H_2O, MeOH, 25 °C, 3 h.



Scheme 3. Reagents and conditions: (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 10 °C, 0.25 h; (b) NaH (50%), DMF, 60 °C, 24 h; (c) $LiOH{\cdot}H_2O$, THF, H_2O, MeOH, 25 °C, 5 h.



Scheme 4. Reagents and conditions: (a) diethyl malonate, NaH (50%), THF, 20 °C, 14 h; (b) $LiAlH_4$, THF, 20 °C, 6 h; (c) methyl pyruvate, BF_3 etherate, CH_3CN, 25 °C, 4 h; (d) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 2 h; (e) **1**, K_2CO_3, DMF, 60 °C, 20 h; (f) NaOH, MeOH, H_2O, 25 °C, 18 h.

Table 1
hPPAR transactivation data.

Compound	hPPAR transactivation[a,b] EC_{50} (μM)			
	α	γ	Ratio γ/α	δ
9a	IA	IA	—	IA
9b	0.044	0.56	12	IA
9c	0.034	0.45	13	IA
13a	0.0000038	0.43	113157	IA
13b	0.002	0.031	15	IA
13c	0.0001	0.1	1000	IA
20	0.072	0.015	0.2	IA
Imiglitazar	0.008	0.004	0.5	IA
Muraglitazar	0.15	0.09	0.6	IA
NS-220	0.052	6.85	131	IA

[a] IA denotes inactive where compounds did not show any fold induction above the basal level (shown by vehicle) up to 1 μM concentration.
[b] EC_{50} is the concentration of the test compound that affords half-maximum transactivation activity.

501516 were used as controls for PPARα, γ, and δ, respectively, and the results were summarized in Table 1. As described earlier we intended to replace the central phenylene spacer of Muraglitazar with an alkyl chain and synthesized compounds **9a–c** and evaluated their PPAR transactivation potentials. Among these three compounds, **9a** with tetramethylene spacer was found inactive towards both PPARα and γ whereas **9b** and **9c** were found less potent towards PPARγ compared to PPARα increasing the ratio of EC_{50} γ/α to 12 and 13, respectively, against 0.6 as in case of Muraglitazar. Having felt encouraged with these results and in urge of potent and highly selective PPARα agonist we then synthesized the compounds **13a–c** taking this time Imiglitazar as initial lead. The transactivation results of the compounds **13a–c** were found very interesting and were in line with our hypothesis. Compounds **13a** and **13c** found very potent and selective PPARα agonists with picomolar and nanomolar range EC_{50}, respectively, and multi-fold selectivity towards PPARα over PPARγ whereas Compounds **13b** showed inferior results in terms of selectivity towards PPARα transactivation. To support our hypothesis further and cross validate the same we synthesized the compound **20** by replacing the tetramethylene group of the compound NS-220 with phenylene group. This compound **20** turned out to be a dual PPARα/γ agonist with equipotent activation towards both PPARα and γ whereas its parent compound NS-220 is a selective PPARα agonist.

To better understand the activity of **13a** at molecular level, docking simulations were carried out for this compound and Imiglitrazar using Discovery Studio software version 1.6. The geometry of compounds docked was subsequently optimized using the CHARMM force field. The energy minimization was carried out using smart minimizer option in the software until the gradient value was smaller than 0.001 kcal/mol Å. The complexed X-ray crystal structure of the ligand binding domain (LBD) of PPARα with GW409544[17] (1k7l.pdb) and PPARγ with Rosiglitazone (2PRG.pdb) were obtained from RCSB Protein Data Bank. When docked into PPARα binding pocket the most stable docking models both **13a** and Imiglitazar adopted a confirmation that allows the carboxylic group to form hydrogen bonds with Tyr 314, Tyr 464, and Ser280 (Fig. 3) which are reported to be essential interaction for a PPARα agonist. However, in the docking model of **13a** an additional H-bond between the nitrogen atom of oxazole ring and Cys276 was observed. This additional H-bond may actually be responsible for improved activity of this compound over Imiglitazar. Compound **13a** when docked into PPARγ binding pocket none of the conformations showed H-bond interactions with any of the amino acids though the molecular orientation was similar to that of Imiglitazar which correlates with moderate PPARγ activity of this compound

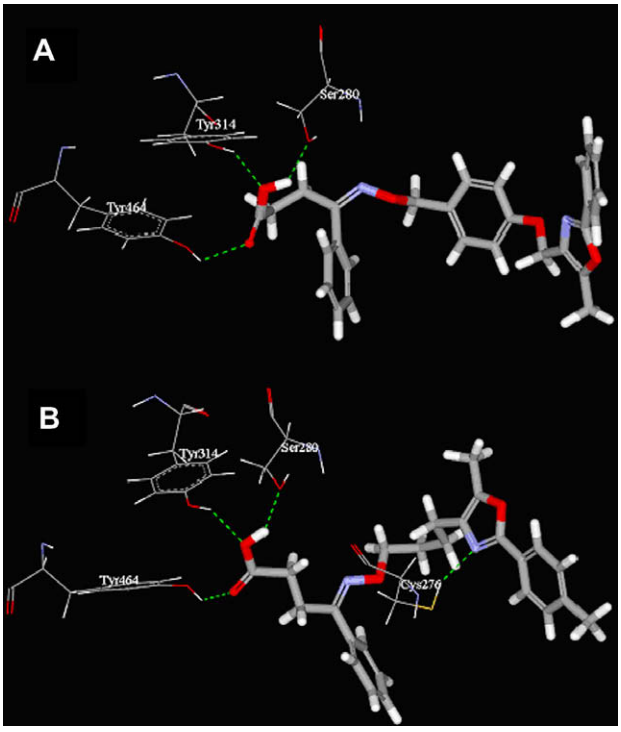


Figure 3. Molecular docking of **13a** (B) and Imiglitazar (A) into PPARα binding site. H-bond interactions with amino acids are shown in dashed lines.

whereas Imiglitazar showed H-bond interactions with Cys295 while Ser289 and Tyr473 are lying in close proximity of the ligand.

In summary we discovered novel oxazole containing glycine and oximinobutyric acid derivatives as PPARα agonists by incorporating polymethylene spacer as a replacement of commonly used phenylene group that connects the acidic head with lipophilic tail as exemplified by **13a.** On the other hand we also designed compound **20** as PPARα/γ dual agonist by replacing tetramethylene spacer of a known compound NS-220 with phenylene group. The above results clearly established that the spacer of polymethylene chain of varying length between the pharmacophore and the lipophilic heterocycle improves selectivity of the compound towards PPARα receptor compared to the compounds having phenylene group as a spacer. Further work in the development of SAR of this lead series based on **13a** will be described in a subsequent publication.

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16. *Spectroscopic analysis of the compounds **9a–c**, **13a–c**, and **20**:* **9a**: {(4-methoxyphenoxycarbonyl)-[4-(5-methyl-2-(4-methylphenyl)oxazol-4-yl)-butyl]-amino}acetic acid: thick liquid; yield: 96%; purity by HPLC: 99%; IR (Nujol): 3018, 2939, 1716, 1458, 1180, 761 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.69–1.72 (m, 4H), 2.29 (s, 3H), 2.36 (s, 3H), 2.52–2.57 (m, 2H), 3.52–3.56 (m, 2H), 3.77 (s, 3H), 4.17 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 7.01–7.05 (m, 2H), 7.21 (d, J = 6.4 Hz, 2H), 7.82 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.70, 20.94, 23.68, 24.24, 24.65, 25.80, 26.66, 28.23, 47.80, 53.40, 55.31, 62.96, 113.96, 122.5, 124.69, 125.39, 129.53, 135.52, 139.61, 143.17, 145.14, 155.07, 156.16, 157.76, 158.37. ESI-S m/z: 453.1 $[M+H]^+$; **9b**: {(4-methoxyphenoxycarbonyl)-[5-(5-methyl-2-(4-methylphenyl)oxazol-4-yl)-pentyl]-amino}acetic acid: white solid; mp: 140–141 °C; yield: 32%; purity by HPLC: 96%; IR (KBr): 2925, 1720, 1450, 1182, 827 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40–1.44 (m, 2H), 1.68–1.72 (m, 4H), 2.22 (s, 3H), 2.31 (s, 3H), 2.52 (t, J = 7.4 Hz, 2H), 3.39–3.47 (m, 2H), 3.81 (s, 3H), 4.12 (d, J = 8.0 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.97–7.04 (m, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 9.71, 20.97, 24.90, 25.64, 27.15, 28.23, 48.48, 59.78, 114.16, 122.56, 124.71, 125.39, 129.56, 135.63, 139.64, 143.13, 144.62, 154.57, 156.48, 158.37.; ESI-S m/z: 467.3 $[M+H]^+$; **9c**: {(4-Methoxy-phenoxycarbonyl)-[6-(5-methyl-2-(4-methylphenyl)oxazol-4-yl)-hexyl]amino}acetic acid: thick liquid; yield: 82%; purity by HPLC: 98%; IR (Nujol): 3016, 2935, 1720, 1508, 1199, 1180, 756 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41–1.45 (m, 2H), 1.59–1.63 (m, 6H), 2.32 (s, 3H), 2.36 (s, 3H), 2.52 (t, J = 7.3 Hz, 2H), 3.48–3.52 (m, 2H), 3.72 (s, 3H), 4.12 (d, J = 12.5 Hz, 2H), 6.81 (d, J = 8.1 Hz, 2H), 7.01–7.06 (m, 2H), 7.22 (d, J = 7.9 Hz, 2H), 7.91 (d, J = 8.0 Hz, 2H); ^{13}C NMR: (100 MHz, DMSO-d_6): δ 9.69, 20.93, 24.93, 26.10, 27.25, 27.69, 28.42, 48.16, 50.22, 55.30, 113.90, 114.08, 122.45, 122.84, 124.70, 125.35, 129.49, 135.69, 139.57, 142.95, 145.03, 154.44, 154.82, 156.23, 158.32.; ESI-S m/z: 481.3 $[M+H]^+$; **13a**: 4-[4-(5-methyl-2-(4-methylphenyl)oxazol-4-yl)-butoxyimino]-4-phenylbutyric acid: white solid; mp: 102–104 °C; yield: 85%; purity by HPLC: 99%; IR (KBr): 3429, 2922, 1649, 1596, 1577, 1307, 1265, 1147 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.76–1.82 (bm, 4H), 2.31 (s, 3H), 2.36 (s, 3H), 2.47–2.54 (m, 4H), 3.17 (t, J = 6.8 Hz,2H), 4.26 (bt, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.32–7.38 (m, 3H), 7.60–7.66 (m, 2H), 7.84 (d, J = 8.0 Hz, 2H).; ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.94, 20.93, 21.93, 24.76, 24.97, 28.49, 30.46, 73.41, 124.75, 125.39, 126.08, 128.44, 129.08, 129.46, 135.00, 135.57, 139.81, 143.09, 154.93, 158.40, 173.51; ESI-MS m/z: 421.2 $[M+H]^+$; **13b**: 4-[5-(5-methyl-2-(4-methylphenyl)oxazol-4-yl)-pentyloxyimino]-4-phenylbutyric acid: off white solid; mp: 91–93 °C; yield: 86%; purity by HPLC: 97%; IR (KBr): 3413, 2931, 1718, 1500, 1269, 1163, 732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.47–1.54 (m, 2H), 1.64–1.69 (m, 2H), 1.72–1.79 (m, 2H), 2.30 (s, 3H), 2.36 (s, 3H), 2.52 (t, J = 7.5 Hz, 2H), 2.58 (t, J = 7.5 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 4.20 (t, J = 6.0 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 7.34–7.36 (m, 3H), 7.60–7.63 (m, 2H), 7.85 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.67, 20.92, 21.90, 24.90, 28.25, 28.56, 30.40, 73.55, 124.72, 125.36, 126.05, 128.40, 129.08, 129.47, 133.88, 134.97, 135.61, 139.54, 143.02, 156.33, 158.36, 173.33; ESI-MS m/z: 435.1 $[M+H]^+$; **13c**: 4-[6-(5-methyl-2-(4-methylphenyl)oxazol-4-yl)-hexyloxyimino]-4-phenyl-butyric acid: white solid; mp: 79–81 °C; yield: 63%; purity by HPLC: 99%; IR (KBr): 3020, 1714, 1625, 1402, 1217, 771 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43–1.45 (m, 2H), 1.59–1.64 (m, 4H), 1.71–1.74 (m, 2H), 2.31 (s, 3H), 2.38 (s, 3H), 2.53 (t, J = 7.5 Hz, 2H), 2.64 (t, J = 7.5 Hz, 2H), 3.09 (t, J = 7.4 Hz, 2H), 4.22 (t, J = 5.7 Hz, 2H), 7.21–7.25 (m, 2H), 7.35–7.37 (m, 3H), 7.61–7.63 (m, 2H), 7.85 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.65, 20.89, 21.86, 24.84, 25.18, 28.26, 28.65, 73.56, 124.70, 125.32, 126.02, 128.40, 129.04, 129.44, 134.95, 135.67, 139.51, 142.94, 156.29, 158.29, 173.27; ESI-MS m/z: 449.1 $[M+H]^+$; **20**: 2-methyl-c-5-[4-(5-methyl-2-(4-methylphenyl)oxazol-4-ylmethoxy)benzyl]-1,3 dioxane-r-2-carboxylic acid: white solid; mp: 197–198 °C; yield: 95%; purity by HPLC: 99%; IR (KBr): 2929, 1759, 1610, 1502,1286, 1226, 1182, 827 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.32 (s, 3H), 2.09–2.13 (m, 1H), 2.27 (d, J = 6.9 Hz, 2H), 2.36 (s, 3H), 2.42 (s, 3H), 3.42 (t, J = 11.4 Hz, 2H), 3.69–3.74 (dd, J = 11.6 and 4.1 Hz, 2H), 4.94 (s, 2H), 6.94 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 9.93, 20.96, 25.52, 32.87, 34.86, 61.38, 67.07, 97.56, 114.64, 124.24, 125.57, 129.62, 130.58, 131.85, 140.15, 146.95, 156.65, 158.98, 171.31; ESI-MS m/z: 438.4 $[M+H]^+$.
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