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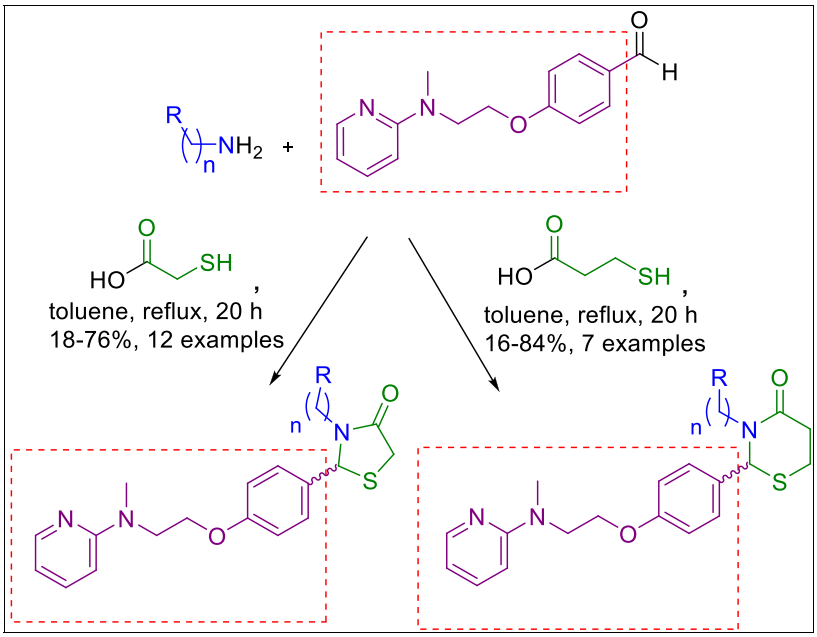

This work reports the synthesis of thiazolidin-4-ones and thiazinan-4-ones analogous to rosiglitazone, a potent antidiabetic drug. The desired compounds were synthesized with moderate to good yields by one-pot reactions between different primary amines, mercaptoacetic or mercaptopropionic acids, and the 4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzaldehyde. The cyclocondensation reactions were carried out for 20 h, and all the products were characterized by ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, mass spectrometry, and one example by X-ray diffraction.

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INTRODUCTION

Diabetes is a major health concern, especially in developing countries. According to the World Health Organization, more than 180 million people have diabetes, and this number is expected to reach 366 million in 2030 [1]. The main characteristic of diabetes is hyperglycemia, and it can be diagnosed as type 1 or type 2. Type-1 diabetes results from chronically low insulin secretion. Type-2 diabetes is a heterogeneous group of disorders that are characterized by varying degrees of insulin resistance, a decrease in insulin secretion, and an increase in glucose production [2].

Thiazolidinedione (TZD) is an important class of heterocycles, because of its unique benefits for the treatment of insulin resistance and type II diabetes. TZDs target the nuclear receptor peroxisome proliferator activated receptor gamma and include rosiglitazone, pioglitazone, and troglitazone drugs (Fig. 1) [3].

It is reported that TZDs have three important interactions for the activation of the receptor peroxisome proliferator activated receptor gamma. Based on the ligand–protein interactions, different features were assigned to the rosiglitazone molecule that include (i) two hydrogen bond acceptor features corresponding to the two carbonyls of TZD ring and one hydrogen bond donor,

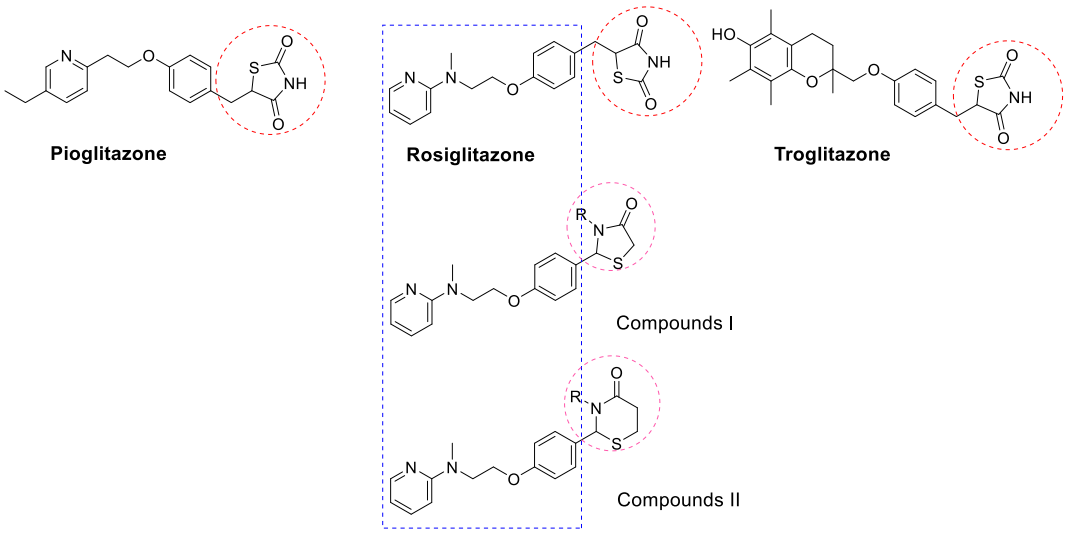


Figure 1. Chemical structures of antidiabetic drugs pioglitazone, rosiglitazone, and troglitazone and similarity of the chemical structures of the compounds synthesized with the drug rosiglitazone. [Color figure can be viewed at wileyonlinelibrary.com]

related to the –NH of the TZD ring, (ii) a hydrophobic aromatic feature was assigned to the central aromatic region, and (iii) a hydrophobic aromatic feature was also assigned to the pyridine ring in the lipophilic side chain [4].

Rosiglitazone (Avandia, GlaxoSmithKline) was initially approved in 1999 to treat hyperglycemia in patients with type-2 diabetes. Original approval was based on the ability of the drug to lower glycemia and glycosylated hemoglobin levels. However, this drug was associated with a significant increase in the risk of myocardial infarction and increased risk of death from cardiovascular causes, and for this reason, the Food and Drug Administration removed rosiglitazone from the market in 2010 [4–6].

Because of this, continuous efforts are needed to design and discover new safe drugs for this therapeutic target. In this context, heterocyclic nucleus have a major role in the field of medicinal chemistry, and they are a key template for the genesis of various therapeutic agents. The majority of drugs in the market have at least one heterocyclic nucleus in their structures [4,7,8].

The TZD heterocycle has a structural similarity to thiazolidin-4-one and thiazinan-4-one because it contains nitrogen, sulfur, and a carbonyl group. These heterocycles differ in number of carbonyl groups and ring size. The thiazolidinone (five-membered heterocycle) is a versatile scaffold that has occupied a prominent position in the medicinal chemistry. Numerous studies describe a wide range of pharmacological properties of thiazolidinones: anti-HCV, anti-HIV, antitumoral, antifungal, tuberculostatic, and antioxidant.[9] Thiazinanones (six-membered heterocycle) are less common in the literature; however, they also show major biological properties as immune potentiating, anti-inflammatory, antimalarial, and antibacterial agents [10–14].

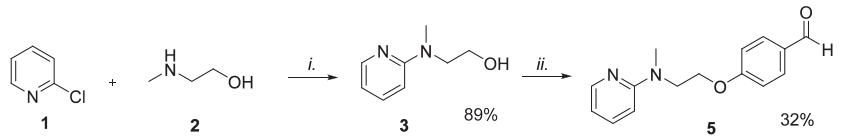
Furthermore, some studies reported the synthesis of analogues of TDZ by performing the changing of TZD by thiazolidinone nucleus, as shown by Patel *et al.* [15] who reported the synthesis of thiazolidinone analogous to pioglitazone and as shown by Raza *et al.* [14] that reported the synthesis of thiazolidinone and thiazinanone analogous to rosiglitazone with significant anti-hyperglycemic activity.

The strategy to synthesize thiazinanones is very similar to the strategy to synthesize thiazolidinones [16]. The main synthetic route reported in literature involves three components: an aldehyde, a primary amine, and mercaptoacetic acid. New derivatives of 4-thiazolidinones have been obtained by modifications of the 2-position, 3-position, and 5-position [9,17–20].

In the present work, our aim is to generate novel thiazolidin-4-ones and novel thiazinan-4-ones analogous to rosiglitazone, from the reaction of aldehyde (containing the rosiglitazone scaffold), primary amines, and mercaptocarboxilic acid. The amines are aromatic or aliphatic and contain heterocyclic rings (five or six membered) in their structures. Because thiazolidin-4-ones and thiazinan-4-ones are similar to TZD, this work targets the contribution to the limited therapeutic arsenal for the treatment of type-2 diabetes, searching for new candidates to drugs (Fig. 1).

The aldehyde precursor was prepared in two steps using the microwave methodology (MO) according to Gaonkar *et al.* [21] as outlined in Scheme 1. In the first step, the aromatic nucleophilic substitution reaction between 2-chloropyridine **1** and 2-(*N*-methylamino)ethanol **2** led to the 2-(methylpyridin-2-yl)aminoethanol **3**. In a second

Scheme 1. Synthesis of 4-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzaldehyde **5**.



i. MO, 160 °C, 1 h;
ii. MO, KOH, H_2O, toluene, TBAHS, 4-fluorobenzaldehyde **4,** 100 °C, 1h 30 min.

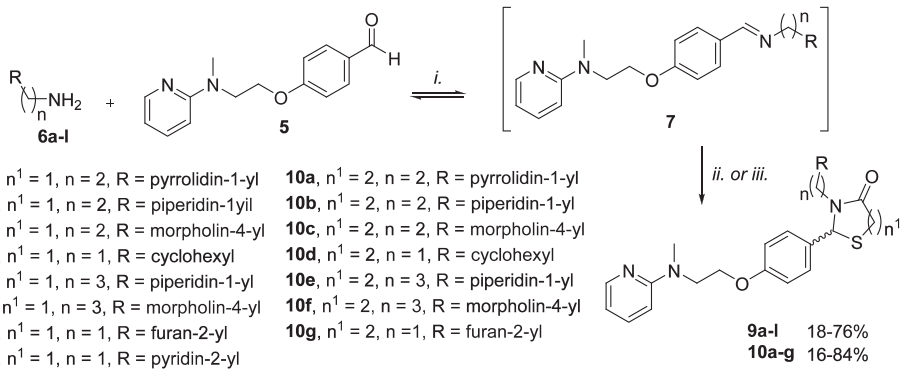
step, compound **3** reacts with 4-fluorobenzaldehyde **4** through the aromatic nucleophilic substitution reaction, using potassium hydroxide and tetrabutylammonium hydrogen sulfate as phase transfer catalyst (Scheme 1). The compound 4-(2-(methyl(pyridin-2-yl)amino)ethoxy) benzaldehyde **5** was obtained after purification by column chromatography using silica gel and solution of hexane/ethyl acetate (7:3) as eluent.

RESULTS AND DISCUSSION

The aldehyde precursor was prepared in two steps using the microwave methodology (MO) according to Gaonkar *et al*. [21] as outlined in Scheme 1. In the first step, the aromatic nucleophilic substitution reaction between 2-chloropyridine **1** and 2-(*N*-methylamino)ethanol **2** produced the 2-(methylpyridin-2-yl)aminoethanol **3**. In a second step, compound **3** reacts with 4-fluorobenzaldehyde **4** through aromatic nucleophilic substitution reaction, using potassium hydroxide and tetrabutylammonium hydrogen sulfate as phase transfer catalyst (Scheme 1). Compound 4-(2-(methyl (pyridin-2-yl)amino)ethoxy)benzaldehyde **5** was obtained after purification by column chromatography using silica gel and solution of hexane/ethyl acetate (7:3) as eluent. Compounds **3** and **5** were characterized and confirmed by mass spectrometry and nuclear magnetic resonance (^{1}H and ^{13}C NMR).

Thus, 4-(2-(methyl(2-pyridinyl)amino)ethoxy) benzaldehyde **5** was used as precursor to synthesize thiazolidin-4-ones **9a–l** and thiazinan-4-ones **10a–g** by standard thermal heating methodology *via* one-pot multicomponent reactions. The syntheses were carried out by the carbonyl addition/elimination reaction between aldehyde **5** and different amines **6** followed by a cyclocondensation reaction with corresponding mercaptocarboxilic acid **8a** or **8b** (Scheme 2). The reactions were monitored by TLC with a solution of hexane/ethyl acetate (7:3), and after formation of imine intermediate **7**, an excess of mercaptocarboxylic acid **8a** or **8b** was added after 2 h to obtain products **9** and **10** through intramolecular cyclization for 18 h. The primary amines used are aliphatic or aromatic and may contain rings with heteroatoms. This factor shows the diversity that the effect of these groups may have on biological activity. The literature reported that different reaction times are needed according to amine [22–25]; however, all compounds were obtained in the same reaction times in this work (18 h). The thiazolidin-4-ones **9a–l** and thiazinan-4-ones **10–g** were purified by column chromatography using as adsorbent, the silica gel (0.2–

Scheme 2. Synthesis of thiazolidin-4-ones **9a–l** and thiazinan-4-ones **10–g**.



9a, n^1 = 1, n = 2, R = pyrrolidin-1-yl
9b, n^1 = 1, n = 2, R = piperidin-1yil
9c, n^1 = 1, n = 2, R = morpholin-4-yl
9d, n^1 = 1, n = 1, R = cyclohexyl
9e, n^1 = 1, n = 3, R = piperidin-1-yl
9f, n^1 = 1, n = 3, R = morpholin-4-yl
9g, n^1 = 1, n = 1, R = furan-2-yl
9h, n^1 = 1, n = 1, R = pyridin-2-yl
9i, n^1 = 1, n = 1, R =pyridin-3-yl
9j, n^1 = 1, n = 0, R = phenylamino
9k, n^1 = 1, n = 0, R = phenyl
9l, n^1 = 1, n = 3, R = diethylamino

10a, n^1 = 2, n = 2, R = pyrrolidin-1-yl
10b, n^1 = 2, n = 2, R = piperidin-1-yl
10c, n^1 = 2, n = 2, R = morpholin-4-yl
10d, n^1 = 2, n = 1, R = cyclohexyl
10e, n^1 = 2, n = 3, R = piperidin-1-yl
10f, n^1 = 2, n = 3, R = morpholin-4-yl
10g, n^1 = 2, n =1, R = furan-2-yl

*i.*Toluene, 110 °C, 2 h;
ii. $HSCH_2COOH$ **8a**, 110 °C, 18 h;
iii. $HSCH_2CH_2COOH$ **8b**, 110 °C, 18 h.

0.5 mm) and as eluent, a solution of hexane/ethyl acetate (8:2 to 1:1), and yields ranged from 18% to 76% and 16% to 84%, respectively. A possible explanation for some low yields may be the laborious purification step.

Compounds **3**, **5**, **9a–l**, and **10–g** were characterized, and their chemical structures were confirmed by mass spectrometry and NMR (^{1}H and ^{13}C). The analytical spectral data for all compounds are in full agreement with the proposed structure, and in this work, two-dimensional NMR techniques were used to help assign the signals of the compounds correctly. Compound **9d** was also characterized by single crystal X-ray diffraction, and the ORTEP[26] diagram is depicted in Figure 2.

In the ^{1}H NMR spectrum, the signals that confirm the formation of thiazolidin-4-one and thiazinan-4-one are the asymmetric carbon –CH and the diastereotopic hydrogens of heterocyclic rings. Hydrogen H13 appears with chemical displacement around 5.35–5.85 ppm as singlet or doublet (^4J with H15a). The diastereotopic hydrogens H15a and H15b appear with doublet (^2J), double doublet (^2J and ^4J), or multiplet signals with chemical displacement around 3.59–3.83 ppm. For thiazinan-4-one ring, the diastereotopics H15a, H15b, H16a, and H16b appear more shielded as double doublet or multiplet with chemical displacement around 2.58–3.82 ppm.

In the ^{13}C NMR spectrum, the characteristic signals of thiazolidine-4-one and thiazinan-4-one are C13, C14, C15, plus C16 for thiazin-4-one. The most deshielded carbon in the spectrum is the carbonyl group C14 (169.3–171.6 ppm), and asymmetric C13 appears around 61.7–63.9 ppm for both heterocycles. The thiazolidin-4-one is assigned to C15 in the region of 29.8–33.1 ppm and thiazinan-4-one in the region of 34.4–34.6 ppm. For thiazinan-4-one, the C16 appears in the region of 21.9–21.7 ppm. Other spectral signals of the product belong to the amines and the aldehyde **5** cores.

Two-dimensional NMR experiments help the correct assignment of signals for thiazinan-4-ones. In the HMBC of thiazinan-4-one **10f**, the coupling of H13 can only be verified with C16. In the HSQC, it was possible to verify the coupling of diastereopic hydrogens H15 and H16 with their corresponding C15 and C16 carbons.

The HRMS was performed for six compounds (**9a**, **9b**, **9f**, **10a**, **10b**, and **10f**) and shows interesting results. The molecular ion was identified in all spectra; however, a second peak with *m/z* equal to a half of molecular ion was also observed for all compounds (see Supporting Information).

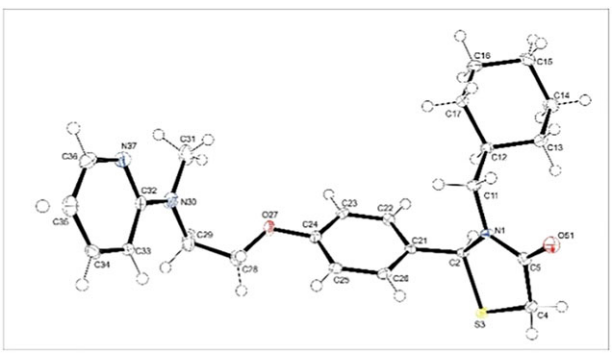


Figure 2. ORTEP diagram of compound **9d** with thermal ellipsoids drawn at 50% probability level. [Color figure can be viewed at wileyonlinelibrary.com]

CONCLUSION

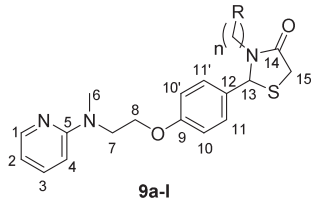
In conclusion, the method was efficient to obtain 12 novel thiazonan-4-one and seven novel thiazinan-4-one analogues to rosiglitazone. No influence of kind of amine (aliphatic or aromatic) or mercaptocarboxilic acid was observed, and the time was the same for all reactions. The synthesis of aldehyde **5** was a critical step necessitating a longer reaction time in microwave (1.5 h), different from that described by Gaonkar *et al*. [21] The yields for the thiazolidi-4-ones and thiazinan-4-ones were moderate to good, because a purification step by chromatographic column was required.

EXPERIMENTAL

The microwave device: CEM Discovery-SP with ActiVent; Model No. 909150; Serial No. DC8141; Volts: 90/140; Vac Max Cur: 7.3 A; Frequency: 50/60 Hz; Max. PWR.: 725 W; MFG. DATA: 32231; MAG. Frequency: 2455 MHz; Max. Microwave Power: 300 W; Prod. Tag.: 2118141. The melting points were determined on a Fisatom machine with three capillary tubes, model 430, 230 V, 60 Hz, 50 W. The thermometer was up to 360°C. The characterization of compounds was performed using NMR techniques and mass spectrometry. ^{1}H and ^{13}C NMR spectra were acquired in an Avance (^{1}H 600 MHz and ^{13}C 150 MHz) equipment. The solvent used was deuterated chloroform ($CDCl_3$) containing tetramethylsilane as an internal standard. Mass spectra were obtained on a Shimadzu CG 2010-Plus equipment, with GCMS-QP2010SE automatic injector. Mass spectra were obtained for all compounds on a LTQ Orbitrap Discovery mass spectrometer (Thermo Fisher Scientific). This hybrid system meets the LTQ XL linear ion trap mass spectrometer and an Orbitrap mass analyzer. The experiments were performed *via* direct infusion of sample (flow: 15 μL/min) in the positive-ion mode using electrospray ionization. Elemental composition calculations for comparison were executed using the specific tool included in the Qual Browser module of

Xcalibur (Thermo Fisher Scientific, release 2.0.7) software. Diffraction measurements of compounds **9d** were performed using a Bruker D8 Venture with a Photon 100 CMOS detector with graphite monochromatized Mo Kα radiation with λ = 0.71073 Å. Absorption corrections were performed using multi-scan methods. Anisotropic displacement parameters for non-hydrogen atoms were applied. The structure was solved and refined using the WinGX[151] software package. The structures were refined based on the full-matrix least-squares method using the SHELXL program [27]. The ORTEP projections of the molecular structures were generated using the ORTEP-3[26] program. Crystallographic information files for the studied compounds have been deposited at the Cambridge Crystallographic Data Centre with the following identification 1841878. X-ray diffraction data for compound **9d** are listed in Table SX.

General procedure for thiazolidin-4-ones 9a–l and 1,3-thiazinan-4-ones 10a–f. The compounds were synthesized using toluene (70 mL), amine **6a–l** (1 mmol), and aldehyde **5** (1 mmol). The system was connected to a *Dean-Stark* for the removal of water *via* azeotropic distillation; the reaction mixture was stirred for 2 h at the reflux temperature of the solvent (110°C). After formation of the imine intermediate **7a–l**, mercaptocarboxylic acid **8a** or **8b** (3 mmol) was added and left to react for 18 h. The mixture was washed with saturated sodium hydrogen carbonate solution (3 × 10 mL); the organic phase was dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The thiazolidin-4-ones **9a–l** and thiazinan-4-ones **10–g** were purified by column chromatography silica gel (0.2–0.5 mm) and as eluents a solution of hexane/ethyl acetate (8:2 to 1:1).



9a-l

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(2-(pyrrolidin-1-yl)ethyl)thiazolidin-4-one (9a). M.W. 426.58, brown oil (72%), ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 3.7, 1.1 Hz, 1H, H1), 7.44–7.47 (m, 1H, H3), 7.22 (d, *J* = 8.2 Hz, 2H, H11), 6.89 (d, *J* = 8.6 Hz, 2H, H10), 6.56 (dd, *J* = 6.7, 5.3 Hz, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 5.80 (s, 1H, H13), 4.19 (t, *J* = 5.7 Hz, 2H, H8), 3.98 (t, *J* = 5.6 Hz, 2H, H7), 3.74–3.79 (m, 2H, H15a, –C(O)N$\underline{CH_2}CH_2$N–(a)), 3.71 (d, *J* = 15.4 Hz, 1H, H15b), 3.14 (s, 3H, H6), 2.82–2.86 (m, 1H, –C(O)N$\underline{CH_2}CH_2$N–(b)), 2.66 (dd, *J* = 12.7, 6.3 Hz, 1H, –C(O)NCH$_2\underline{CH_2}$N–(a)), 2.52 (sl, 4H, pyrrolidinyl), 2.48 (dd, *J* = 12.4, 6.3 Hz, 1H, –C(O)NCH$_2\underline{CH_2}$N–(b)), 1.76 (sl, 4H, pyrrolidinyl). ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 171.4 (C14), 159.6, 158.3, 147.9, 137.4, 131.2, 128.7, 115.0, 111.8, 105.8, 66.5, 63.8 (C13), 54.1, 53.0, 49.5, 41.3, 37.9, 33.1 (C15), 23.5. MS (70 eV): *m/z* (%) = 292 (1), 253 (1), 207 (2), 151 (1), 133 (2), 120 (1), 84 (100). HRMS: (M + H$^+$): $C_{23}H_{30}N_4O_2S$ calculated 427.2162; found 427.2132; 214.1106.

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(2-(piperidin-1-yl)ethyl)thiazolidin-4-one (9b). M.W. 440.61, brown oil (28%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 4.0 Hz, 1H, H1), 7.45 (t, *J* = 7.3 Hz, 1H, H3), 7.20 (d, *J* = 8.3 Hz, 2H, H11), 6.88 (d, *J* = 8,3 Hz, 2H, H10), 6.55 (t, *J* = 5.9 Hz, 1H, H2), 6.52 (d, *J* = 8.5 Hz, 1H, H4), 5.82 (s, 1H, H13), 4.19 (t, *J* = 5.5 Hz, 2H, H8), 3.98 (t, *J* = 5.5 Hz, 2H, H7), 3.76–3,71 (m, 2H, H15a, –C(O)N$\underline{CH_2}CH_2$N–(a)), 3.68 (d, *J* = 15.4 Hz, 1H, H15b), 3.14 (s, 3H, H6), 2.81–2.77 (m, 1H, –C(O)N$\underline{CH_2}CH_2$N–(b)), 2.51–2.47 (m, 2H, –C(O)NCH$_2\underline{CH_2}$N–), 2.32 (sl, 4H, piperidinyl), 1.59–1.54 (m, 4H, piperidinyl), 1.41 (d, *J* = 4.5 Hz, 2H, piperidinyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171,3 (C14), 159.3, 158.3, 147.8, 137.4, 131.3, 128.9, 114.9, 111.9, 105.8, 66.5, 63.9 (C13), 56.0, 54.5, 49.5, 39.6, 37.9, 33.1 (C15), 25.7, 23.8. MS (70 eV): *m/z* (%) = 306 (1), 281 (2), 207 (4), 151 (1), 133 (3), 113 (4), 98 (100). HRMS: (M + H$^+$): $C_{24}H_{32}N_4O_2S$ calculated 441.2319; found 441.2287; 221.1181.

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(2-morpholinoethyl)thiazolidin-4-one (9c). M.W. 442.58, brown solid (76%), mp = 91–93°C, ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 4.8 Hz, 1H, H1), 7.44–7.47 (m, 1H, H3), 7.20 (d, *J* = 8.5 Hz, 2H, H11), 6.89 (d, *J* = 8.5 Hz, 2H, H10), 6.55–6.57 (m, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 5.79 (s, 1H, H13), 4.19 (t, *J* = 5.5 Hz, 2H, H8), 3.99 (t, *J* = 5.5 Hz, 2H, H7), 3.73–3.78 (m, 2H, H15a, –C(O)N$\underline{CH_2}CH_2$N–(a)), 3.70 (d, *J* = 15.5 Hz, 1H, H15b), 3.66 (t, *J* = 4,1 Hz, 4H, morpholinyl), 3.15 (s, 3H, H6), 2.78 (dt, *J* = 6.7, 13.9 Hz, 1H, –C(O)N$\underline{CH_2}CH_2$N–(b)), 2.45 (dt, *J* = 6.4, 12.8 Hz, 1H, –C(O)NCH$_2\underline{CH_2}$N–(a)), 2.33–2.30 (m, 5H, –C(O)NCH$_2\underline{CH_2}$N–(b), morpholinyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.4 (C14), 159.6, 158.3, 147.9, 137.4, 131.2, 128.8, 115.0, 111.9, 105.8, 67.0, 66.5, 63.8 (C13), 55.9, 53.5, 49.5, 39.4, 38.0, 33.1 (C15). MS (70 eV): *m/z* (%) = 308 (1), 281 (1), 207 (2), 151 (1), 133 (3), 113 (8), 100 (100).

3-(Cyclohexylmethyl)-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one (9d). M.W. 425.59, white crystal (isopropyl alcohol) (23%), mp = 94–96°C, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 4.8, 1.1 Hz, 1H, H1), 7.45 (ddd, *J* = 1.9, 7.1, 8.7 Hz, 1H, H3), 7.17 (d, *J* = 8.6 Hz, 2H, H11), 6.89 (d, *J* = 8.6 Hz, 2H, H10), 6.55 (dd, *J* = 5.1, 6.8 Hz, 1H, H2), 6.51 (d, *J* = 8.6 Hz,

1H, H4), 5.57 (d, *J* = 1.2 Hz, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 3.99 (t, *J* = 5.6 Hz, 2H, H7), 3.78 (dd, *J* = 1.5, 15.4 Hz, 1H, H15a), 3.70 (d, *J* = 15.4 Hz, 1H, H15b), 3.72 (dd, *J* = 8.7, 13.7 Hz, 1H, –C(O)N$\underline{CH_2}$N–(a)), 3.14 (s, 3H, H6), 2.42 (dd, *J* = 5.9, 13.7 Hz, 1H, –C(O)N$\underline{CH_2}$N–(b)), 1.66–1.71 (m, 2H, cyclohexyl), 1.58–1.63 (m, 2H, cyclohexyl), 1.52–1.54 (m, 2H, cyclohexyl), 1.10–1.19 (m, 3H, cyclohexyl), 0.87–0.92 (m, 2H, cyclohexyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.3 (C14), 159.5, 158.3, 147.9, 137.3, 131.4, 128.3, 115.0, 111.8, 105.7, 66.5, 63.7 (C13), 49.4, 48.7, 37.9, 35.4, 32.9 (C15), 31.0, 30.4, 26.3, 25.8, 25.7. MS (70 eV): *m/z* (%) = 291 (34), 258 (50), 216 (16), 195 (41), 148 (100), 122 (50), 107 (78).

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(3-(piperidin-1-yl)propyl)thiazolidin-4-one (9e). M.W. 454.63, light brown oil (54%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 4.8, 1.2 Hz, 1H, H1), 7.45 (ddd, *J* = 1.9, 7.1, 8.8 Hz, 1H, H3), 7.21 (d, *J* = 8.6 Hz, 2H, H11), 6.89 (d, *J* = 8.6 Hz, 2H, H10), 6.55 (dd, *J* = 6.8, 5.1 Hz, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 5.64 (d, *J* = 1.2 Hz, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 3.98 (t, *J* = 5.6 Hz, 2H, H7), 3.77 (dd, *J* = 1.8, 15.4 Hz, 1H, H15a), 3.68 (d, *J* = 15.4 Hz, 1H, H15b), 3.58–3.63 (m, 1H, –C(O)N$\underline{CH_2}$$CH_2CH_2$N–(a)), 3.14 (s, 3H, H6), 2.70 (ddd, *J* = 5.8, 7.9, 13.8 Hz, 1H, –C(O)N$\underline{CH_2}$$CH_2CH_2$N–(b)), 2.25–2.30 (m, 5H, –C(O)N$CH_2CH_2\underline{CH_2}$N–(a), piperidinyl), 2.18–2.22 (m, 1H, –C(O)N$CH_2CH_2\underline{CH_2}$N–(b)), 1.66–1.69 (m,1H, –C(O)N$CH_2\underline{CH_2}CH_2$N–(a)), 1.58–1.62 (m, 1H, –C(O)N$CH_2\underline{CH_2}CH_2$N–(b)), 1.54 (dt, *J* = 5.4, 11.0 Hz, 4H, piperidinyl), 1.40 (sl, 2H, piperidinyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1 (C14), 159.6, 158.3, 147.9, 137.4, 131.2, 128.6, 114.9, 111.8, 105.8, 66.5, 63.4 (C13), 56.2, 54.4, 49.5, 41.2, 37.9, 33.1 (C15), 25.8, 24.3, 24.0. MS (70 eV): *m/z* (%) = 320 (2), 281 (1), 236 (1), 151 (1), 127 (6), 112 (4), 98 (100).

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(3-morpholinopropyl)thiazolidin-4-one (9f). M.W. 456.61, brown solid (38%), mp = 68–70°C, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 4.7 Hz, 1H, H1), 7.46 (dt, *J* = 1.6, 6.9 Hz, 1H, H3), 7.21 (d, *J* = 8.5 Hz, 2H, H11), 6.90 (d, *J* = 8.5 Hz, 2H, H10), 6.56 (dd, *J* = 6.6, 5.3 Hz, 1H, H2), 6.52 (d, *J* = 8.5 Hz, 1H, H4), 5.62 (s, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 3.99 (t, *J* = 5.6 Hz, 2H, H7), 3.78 (dd, *J* = 1.2, 15.5 Hz, 1H, H15a), 3.68 (d, *J* = 15.6 Hz, 1H, H15b), 3.65 (t, *J* = 4.3 Hz, 4H, morpholinyl), 3.58–3.63 (m, 1H, –C(O)N$\underline{CH_2}$$CH_2CH_2$N–(a)), 3.14 (s, 3H, H6), 2.76 (ddd, *J* = 5.8, 8.3, 14.0 Hz, 1H, –C(O)N$\underline{CH_2}$$CH_2CH_2$N–(b)), 2.33 (sl, 4H, morpholinyl), 2.28 (dd, *J* = 6.2, 13.5 Hz, 1H, –C(O)N$CH_2CH_2\underline{CH_2}$N–(a)), 2.20–2.25 (m, 1H, –C(O)N$CH_2CH_2\underline{CH_2}$N–(b)), 1.67 (ddd, *J* = 2.1, 7.8, 13.7 Hz, 1H, –C(O)N$CH_2\underline{CH_2}CH_2$N–(a)), 1.56 (td, *J* = 7.2, 14.3 Hz, 1H, –C(O)N$CH_2\underline{CH_2}CH_2$N–(b)). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1 (C14), 159.6, 158.3, 147.9, 137.4, 131.2, 128.6, 114.9, 111.9, 105.7, 66.9, 66.5, 63.6 (C13), 55.9, 53.4, 49.5, 41.2, 37.9, 33.1 (C15), 23.7. MS (70 eV): *m/z* (%) = 322 (3), 236 (1), 206 (1), 151 (1), 129 (10), 114 (4), 100 (100). HRMS: (M + H^+): $C_{24}H_{32}N_4O_3S$ calculated 457.2268; found 457.2234; 229.1154.

3-(Furan-2-ylmethyl)-2-(4-(2-(methyl (pyridin-2-yl)amino) ethoxy)phenyl)thiazolidin-4-one (9g). M.W. 409.50, light brown oil (18%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 4.8, 1.2 Hz, 1H, H1), 7.46 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H, H3), 7.34 (d, *J* = 1.0 Hz, 1H, furanyl), 7.21 (d, *J* = 8.6 Hz, 2H, H11), 6.90 (d, *J* = 8.6 Hz, 2H, H10), 6.56 (dd, *J* = 6.7, 5.3 Hz, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 6.28 (dd, *J* = 2.9, 1.8 Hz, 1H, furanyl), 6.10 (d, *J* = 3.0 Hz, 1H, furanyl), 5.49 (s, 1H, H13), 4.95 (d, *J* = 15.4 Hz, 1H, –C(O)N$\underline{CH_2}$N–(a)), 4.20 (t, *J* = 5.6 Hz, 2H, H8), 3.99 (t, *J* = 5.6 Hz, 2H, H7), 3.82 (dd, *J* = 15.6, 1.2 Hz, 1H, H15a), 3.71 (d, *J* = 15.6 Hz, 1H, H15b), 3.62 (d, *J* = 15,4 Hz, 1H, –C(O)N$\underline{CH_2}$N–(b)), 3.15 (s, 3H, H6). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0 (C14), 159.6, 158.3, 149.1, 147.9, 142.7, 137.4, 130.6, 128.9, 115.0, 111.9, 110.5, 109.2, 105.8, 66.5, 62.9 (C13), 49.5, 38.9, 38.0, 33.1 (C15). MS (70 eV): *m/z* (%) = 275 (26), 200 (17), 148 (15), 137 (99), 120 (15), 109(27), 81 (100).

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(pyridin-2-ylmethyl)thiazolidin-4-one (9h). M.W. 420.53, brown oil (32%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.51–8.50 (m, 1H, pyridinyl), 8.15 (ddd, *J* = 5.0, 1.9, 0.7 Hz, 1H, H1), 7.61 (td, *J* = 1.8, 7.7 Hz, 1H, pyridinyl), 7.46 (ddd, *J* = 2.0, 7.1, 8.8 Hz, 1H, H3), 7.20–7.16 (m, 3H, H11, pyridinyl), 7.15–7.13 (m, 1H, pyridinyl), 6.85 (d, *J* = 8.7 Hz, 2H, H10), 6.57–6,55 (m, 1H, H2), 6.53 (d, *J* = 8.6 Hz, 1H, H4), 5.68 (d, *J* = 1.2 Hz, 1H, H13), 5.02–4.99 (m, 1H, –C(O)N$\underline{CH_2}$N–(a)), 4.18 (t, *J* = 5.6 Hz, 2H, H8), 3.98 (t, *J* = 5.6 Hz, 2H, H7), 3.90–3,86 (m, 1H, H15a), 3.85–3.84 (m, 1H, –C(O)N$\underline{CH_2}$N–(b)), 3.78 (d, *J* = 15.5 Hz, 1H, H15b), 3.14 (s, 3H, H6). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.5 (C14), 159.6, 158.2, 155.5, 149.5, 147.7, 137.5, 136.8, 130.6, 128.9, 122.6, 122.4, 114.9, 111.9, 105.9, 66.5, 63.4 (C13), 49.5, 47.7, 38.0, 33.0 (C15). MS (70 eV): *m/z* (%) = 193 (2), 179 (5), 151 (1), 136 (2), 119 (5), 105 (7), 93 (100).

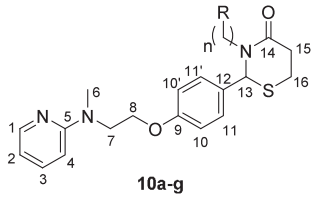
2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(pyridin-3-ylmethyl)thiazolidin-4-one (9i). M.W. 420.53, yellow solid (29%), mp = 99–101°C, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.51–8.52 (m, 1H, pyridinyl), 8.27 (d, *J* = 1.4 Hz, 1H, pyridinyl), 8.15–8.16 (m, 1H, H1), 7.50 (d, *J* = 7.8 Hz, 1H, pyridinyl), 7.47 (ddd, *J* = 1.8, 7.2, 8.7 Hz, 1H, H3), 7.24 (dd, *J* = 4.9, 7.5 Hz, 1H, pyridinyl), 7.12 (d, *J* = 8.6 Hz, 2H, H11), 6.87 (d, *J* = 8.6 Hz, 2H, H10), 6.57 (dd, *J* = 6.7, 5.2 Hz, 1H, H2), 6.53 (d, *J* = 8.6 Hz, 1H, H4), 5.35 (s, 1H, H13), 4.98 (d,

J = 14.7 Hz, 1H, –C(O)N$\underline{CH_2}$N–(a)), 4.20 (t, *J* = 5.3 Hz, 2H, H8), 4.00 (t, *J* = 5.6 Hz, 2H, H7), 3.86 (d, *J* = 15.7 Hz, 1H, –C(O)N$\underline{CH_2}$N–(b)), 3.75 (d, *J* = 15.7 Hz, 1H, H15a), 3.67 (d, *J* = 14.9 Hz, 1H, H15b), 3.16 (s, 3H, H6). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.4 (C14), 159.8, 158.2, 149.6, 149.2, 147.8, 137.4, 136.4, 131.4, 130.0, 128.9, 123.8, 115.1, 111.9, 105.8, 66.5, 62.8 (C13), 49.5, 43.7, 38.0, 33,0 (C15). MS (70 eV): *m/z* (%) = 286 (62), 211 (100), 148 (13), 139 (8), 120 (14), 107 (15), 92 (84).

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(phenylamino)thiazolidin-4-one (9j). M.W. 420.53, reddish brown oil (32%), ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.14 (dd, *J* = 4.9, 1.1 Hz, 1H, H1), 7.45 (ddd, *J* = 8.8, 7.1, 1.9 Hz, 1H, H3), 7.22 (d, *J* = 7.7 Hz, 2H, phenylamine), 7.19 (d, *J* = 8.5 Hz, 2H, H11), 6.92 (dd, *J* = 11.5, 4.1 Hz, 1H, phenylamine), 6.87 (d, *J* = 8.7 Hz, 2H, H10), 6.67 (d, *J* = 7.7 Hz, 2H, phenylamine), 6.56 (dd, *J* = 6.8 Hz, 1H, H2), 6.52 (d, *J* = 8.5 Hz, 1H, H4), 5.68 (s, 1H, H13), 4.18 (t, *J* = 5.6 Hz, 2H, H8), 3.98 (t, *J* = 5.6 Hz, 2H, H7), 3.83 (dd, *J* = 15.9, 1.7 Hz, 1H, H15a), 3.76 (d, *J* = 15.9 Hz, 1H, H15b), 3.15 (s, 3H, H6). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.6 (C14), 159.8, 158.3, 147.8, 144.7, 137.5, 130.0, 129.5, 128.9, 122.0, 115.1, 114.1, 111.9, 105.9, 66.6, 61.7 (C13), 49.5, 38.0, 29,8 (C15). MS (70 eV): *m/z* (%) = 286 (100), 212 (43), 139 (54), 120 (51), 105 (36), 93 (50), 77 (94).

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-phenylthiazolidin-4-one (9k). M.W. 405.52, white solid (44%), mp = 113–115°C, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 4.8 Hz, 1H, H1), 7.43 (t, *J* = 7.8 Hz, 1H, H3), 7.25 (t, *J* = 7.7 Hz, 2H, phenyl), 7.18 (d, *J* = 8.5 Hz, 2H, H11), 7.14 (t, *J* = 7.6 Hz, 1H, phenyl), 7.11 (d, *J* = 8.1 Hz, 2H, phenyl), 6.77 (d, *J* = 8.5 Hz, 2H, H10), 6.54 (m, 1H, H2), 6.48 (d, *J* = 8.6 Hz, 1H, H4), 6.03 (s, 1H, H13), 4.11 (t, *J* = 5.6 Hz, 2H, H8), 3.96–3.91 (m, 3H, H7, H15a), 3.85 (d, *J* = 15.8 Hz, 1H, H15b), 3.09 (s, 3H, H6). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1 (C14), 159.2, 158.3, 147.8, 137.5, 137.4, 131.1, 129.1, 128.5, 127.2, 126.0, 114.7, 111.8, 105.8, 66.3, 65.5 (C13), 49.5, 37.9, 33,6 (C15). MS (70 eV): *m/z* (%) = 271 (37), 196 (66), 148 (67), 151 (64), 124 (60), 107 (29), 77 (100).

3-(3-(Diethylamino)propyl)-2-(4-(2-(methyl (pyridin-2-yl) amino)ethoxy)phenyl)thiazolidin-4-one (9l). M.W. 442.62, brown oil (55%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 3.5, 1.3 Hz, 1H, H1), 7.44–7.47 (m, 1H, H3), 7.21 (d, *J* = 8.6 Hz, 2H, H11), 6.89 (d, *J* = 8.6 Hz, 2H, H10), 6.56 (dd, *J* = 6.9, 5.1 Hz, 1H, H2), 6.52 (d, *J* = 8.5 Hz, 1H, H4), 5.62 (s, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 3.99 (t, *J* = 5.6 Hz, 2H, H7), 3.78 (dd, *J* = 1.7, 15.5 Hz, 1H, H15a), 3.68 (d, *J* = 15.4 Hz, 1H, H15b), 3.59 (ddd, *J* = 6.7, 8.8, 14.0 Hz, 1H, –C(O)N$\underline{CH_2}$$CH_2CH_2$N–(a)), 3.14 (s, 3H, H6), 2.71 (ddd, *J* = 5.4, 8.6, 13.9 Hz, 1H, –C(O)N$\underline{CH_2}$$CH_2CH_2$N–(b)), 2.44 (q, *J* = 7.1 Hz, 5H, diethylamine), 2.29–2.37 (m, 2H, –C(O)N$CH_2CH_2\underline{CH_2}$N–), 1.60–1.66 (m,1H, –C(O)N$CH_2\underline{CH_2}CH_2$N–(a)), 1.50–1.56 (m, 1H, –C(O)N$CH_2\underline{CH_2}CH_2$N–(b)), 0.96 (dd, *J* = 5.5, 8.7 Hz, 6H, diethylamine). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1 (C14), 159.6, 158.3, 147.9, 137.4, 131.2, 128.6, 115.0, 111.9, 105.8, 66.5, 63.5 (C13), 50.1, 49.5, 46.6, 41.4, 37.9, 33.1 (C15), 24.4, 11.4. MS (70 eV): *m/z* (%) = 308 (3), 279 (2), 236 (4), 151 (1), 137 (3), 107 (7), 86 (100).



10a-g

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(2-(pyrrolidin-1-yl)ethyl)-1,3-thiazinan-4-one (10a). M.W. 440.61, light brown oil (48%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14–8.15 (m, 1H, H1), 7.45 (ddd, *J* = 8.8, 7.1, 1.9 Hz, 1H, H3), 7.12 (d, *J* = 8.5 Hz, 2H, H11), 6.88 (d, *J* = 8.7 Hz, 2H, H10), 6.64–6.56 (m, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 5.71 (s, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 4.14–4.17 (m, 1H, –C(O)N$\underline{CH_2}$$CH_2$N–(a)), 3.98 (t, *J* = 5.6 Hz, 2H, H7), 3.15 (s, 3H, H6), 2.74–2.77 (m, 1H, –C(O)N$\underline{CH_2}$$CH_2$N–(b)), 2.79–2.81 (m, 4H, H16a, H16b, H15a, H15b), 2.60–2.64 (m, 1H, –C(O)N$CH_2\underline{CH_2}$N–(a)), 2.55–2.59 (m, 1H, –C(O)N$CH_2\underline{CH_2}$N–(b)), 2.47–2.50 (sl, 4H, pyrrolidinyl), 1.73 (t, *J* = 6.1 Hz, 4H, pyrrolidinyl). ^{13}C NMR (150 MHz, $CDCl^3$): δ = 169.4 (C14), 158.7, 158.3, 147.9, 137.4, 131.4, 128.8, 114.5, 111.8, 105.8, 66.7, 62.3 (C13), 54.3, 53.8, 49.6, 46.6, 37.9, 35.6 (C15), 23.6, 21.9 (C16). MS (70 eV): *m/z* (%) = 306 (2), 273 (1), 133 (1), 120 (1), 98 (6), 84 (100), 70 (7). HRMS: (M + H^+): $C_{24}H_{32}N_4O_2S$ calculated 441.2319; found 441.2286; 221.1181.

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(2-(piperidin-1-yl)ethyl)-1,3-thiazinan-4-one (10b). M.W. 454.63, light brown solid (84%), mp = 75–77°C, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.14–8.15 (m, 1H, H1); 7.45 (ddd, *J* = 1.9, 7.1, 8.7 Hz, 1H, H3), 7.13 (d, *J* = 8.6 Hz, 2H, H11), 6.88 (d, *J* = 8.7 Hz, 2H, H10), 6.54–6.56 (m, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 5.83 (s, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 4.14 (ddd, *J* = 4.9, 7.1, 13.4 Hz, 1H, –C(O)N$\underline{CH_2}$$CH_2$N–(a)), 3.98 (t, *J* = 5.6, 2H, H7), 3.15 (s, 3H, H6), 2.79–2.81 (m, 2H, H16a, H15a), 2.74–2.77 (m, 2H, –C(O)N$\underline{CH_2}$$CH_2$N–(b), H16b), 2.61–2.63 (m, 1H, H15b). 2.56–2.59 (m, 1H, –C(O)N$CH_2\underline{CH_2}$N–(a)), 2.43–2.47 (m, 1H, –C(O)N$CH_2\underline{CH_2}$N–(b)), 2.34–2.39 (m, 4H, piperidinyl), 1.51–1.58 (m, 4H, piperidinyl), 1.39–1.41 (m, 2H, piperidinyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4 (C14), 158.7, 158.3, 147.9, 137.4, 131.5, 127.8, 114.5, 111.8, 105.8,

66.5, 62.3 (C13), 56.8, 54.8, 49.5, 44.8, 37.9, 34.6 (C15), 26.1, 24.3, 21.8 (C16). MS (70 eV): *m/z* (%) = 320 (2), 287 (1), 133 (2), 113 (4), 98 (100), 84 (9), 70 (4). HRMS: (M + H^+): $C_{25}H_{34}N_4O_2S$ calculated 455.2475; found 455.2441; 228.1257.

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(2-morpholinoethyl)-1,3-thiazinan-4-one (10c). M.W. 456.61, yellow solid (50%), mp = 89–91°C, ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 4.8, 1.1 Hz, 1H, H1), 7.45 (ddd, *J* = 8.8, 7.2, 1.9 Hz, 1H, H3), 7.14 (d, *J* = 8.6 Hz, 2H, H11), 6.89 (d, *J* = 8.6 Hz, 2H, H10), 6.56 (dd, *J* = 6.7, 5.2 Hz, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 5.77 (s, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 4.11 (ddd, *J* = 13.6, 6.5, 5.3 Hz, 1H, –C(O)N$\underline{CH_2}CH_2N$–(a)), 3.99 (t, *J* = 5.6 Hz, 2H, H7), 3.66 (dd, *J* = 8.8, 4.5 Hz, 4H, morpholinyl), 3.15 (s, 3H, H6), 2.82–2.85 (m, 1H, H16a), 2.80–2.81 (m, 2H, H16b, –C(O)N$\underline{CH_2}CH_2N$–(b)), 2.76 (dd, *J* = 9.9, 4.8 Hz 1H, H15a), 2.63–2.65 (m, 1H, H15b), 2.59 (dd, *J* = 13.3, 6.4 Hz, 1H, –C(O)$NCH_2\underline{CH_2}N$–(a)), 2.48–2.50 (m, 1H, –C(O)$NCH_2\underline{CH_2}N$–(b)), 2.41–2.44 (m, 4H, morpholinyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.5 (C14), 158.8, 158.3, 147.9, 137.4, 131.3, 127.8, 114.6, 111.9, 105.8, 67.1, 66.5, 62.5 (C13), 56.5, 53.8, 49.5, 44.4, 37.9, 34.6 (C15), 21.9 (C16). MS (70 eV): *m/z* (%) = 322 (2), 289 (1), 208 (3), 148 (1), 137 (2), 113 (30), 100 (100).

3-(Cyclohexylmethyl)-2-(4-(2-(methyl (pyridin-2-yl)amino) ethoxy)phenyl)-1,3-thiazinan-4-one (10d). M.W. 439.62, brown oil (16%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 4.8, 1.1 Hz, 1H, H1), 7.45 (ddd, *J* = 8.7, 7.1, 1.9 Hz, 1H, H3), 7.10 (d, *J* = 8.6 Hz, 2H, H11), 6.88 (d, *J* = 8.6 Hz, 2H, H10), 6.55 (dd, *J* = 6.8, 5.2 Hz, 1H, H2), 6.52 (d, *J* = 8.5 Hz, 1H, H4), 5.45 (s, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H7), 4.12 (dd, *J* = 13.6, 7.1 Hz, 1H, –C(O)N$\underline{CH_2}$N–(a)), 3.98 (t, *J* = 5.6 Hz, 2H, H7), 3.15 (s, 3H, H6), 2.79–2.83 (m, 1H, H16a), 2.73–2.77 (m, 2H, H15a, H15b), 2.58–2,61 (m, 1H, H16b), 2.25 (dd, *J* = 13.6, 7.3 Hz, 1H, –C(O)N$\underline{CH_2}$N–(b)), 1.64–1.75 (m, 4H, cyclohexyl), 1.18–1.26 (m, 4H, cyclohexyl), 1.12–1.16 (m, 1H, cyclohexyl), 0.87–0.97 (m, 2H, cyclohexyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.6 (C14), 158.7, 158.3, 147.9, 137.4, 131.4, 127.8, 114.5, 111.8, 105.8, 66.5, 62.5 (C13), 54.2, 49.5, 37.9, 36.4, 34.4 (C15), 31.2, 30.7, 26.4, 25.9, 25.8, 21.7 (C16). MS (70 eV): *m/z* (%) = 406 (1), 305 (41), 216 (42), 176 (17), 134 (61), 122 (56), 107 (100).

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(3-(piperidin-1-yl)propyl)-1,3-thiazinan-4-one (10e). M.W. 468.66, reddish brown oil (27%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (ddd, *J* = 4.8 Hz, 1H, H1), 7.45 (ddd, *J* = 8.8, 7.2, 1.9, Hz, 1H, H3), 7.11 (d, *J* = 8.6 Hz, 2H, H11), 6.88 (d, *J* = 8.6 Hz, 2H, H10), 6.55 (dd, *J* = 6.7, 5.2 Hz, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 5.77 (s, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 4.07 (ddd, *J* = 13.2, 7.6, 5.3 Hz, 1H, –C(O)N$\underline{CH_2}CH_2CH_2N$–(a)), 3.98 (t, *J* = 5.6 Hz, 2H, H7), 3.15 (s, 3H, H6), 2.74–2.80 (m, 3H, H16a, H15a, –C(O)N$\underline{CH_2}CH_2CH_2N$–(b)), 2.65 (dd, *J* = 13.0, 7.0 Hz, 1H, H16b), 2.59–2.61 (m, 1H, H15b), 2.36–2.40 (m, 1H, –C(O)$NCH_2CH_2\underline{CH_2}N$–(a)), 2.34 (sl, 4H, piperidinyl), 2.21–2.24 (m, 1H, –C(O)$NCH_2CH_2\underline{CH_2}N$–(b)), 1.75–1.84 (m, 2H, –C(O)$NCH_2\underline{CH_2}CH_2N$-), 1.54 (dt, *J* = 10.9, 5.5 Hz, 4H, piperidinyl), 1.41 (sl, 2H, piperidinyl). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.3 (C14), 158.7, 158.3, 147.9, 137.3, 131.6, 127.8, 114.5, 111.8, 105.8, 61.8 (C13), 55.8, 54.4, 49.5, 46.2, 37.9, 34.5 (C15), 26.1, 24.8, 24.5, 21.8 (C16). MS (70 eV): *m/z* (%) = 399 (1), 301 (4), 250(1), 153 (1), 134 (6), 112 (7), 98 (100).

2-(4-(2-(Methyl(pyridin-2-yl)amino)ethoxy)phenyl)-3-(3-morpholinopropyl)-1,3-thiazinan-4-one (10f). M.W. 470.63, light brown oil (35%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 4.9, 1.1 Hz, 1H, H1), 7.45 (ddd, *J* = 8.8, 7.1, 1.9 Hz, 1H, H3), 7.12 (d, *J* = 8.6 Hz, 2H, H11), 6.89 (d, *J* = 8.7 Hz, 2H, H10), 6.56 (dd, *J* = 6.6, 5.1 Hz, 1H, H2), 6.52 (d, *J* = 8.6 Hz, 1H, H4), 5.70 (s, 1H, H13), 4.19 (t, *J* = 5.6 Hz, 2H, H8), 4.07 (ddd, *J* = 13.4, 7.9, 5.2 Hz, 1H, –C(O)N$\underline{CH_2}CH_2CH_2N$–(a)), 3.99 (t, *J* = 5.6 Hz, 2H, H7), 3.68 (t, *J* = 4.4 Hz, 4H, morpholinyl), 3.15 (s, 3H, H6), 2.75–2.81 (m, 3H, H16a, H15a, –C(O)N$\underline{CH_2}CH_2CH_2N$–(b)), 2.66–2.70 (m, 1H, H16b), 2.60–2.63 (m, 1H, H15b), 2.60–2.63 (m, 1H, H16b), 2.39–2.44 (m, 3H, –C(O)$NCH_2CH_2\underline{CH_2}N$–(a), morpholinyl), 2.38 (sl, 2H, morpholinyl), 2.28 (ddd, *J* = 12.3, 7.3, 4.9 Hz, 2H, –C(O)$NCH_2CH_2\underline{CH_2}N$–(b)), 1.73–1.85 (m, 2H, –C(O)$NCH_2\underline{CH_2}CH_2N$–). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4 (C14), 158.7, 158.3, 147.9, 137.4, 131.5, 127.8, 114.6, 111.9, 105.8, 67.1, 66.6, 62.0 (C13), 55.9, 53.5, 49.7, 46.3, 37.9, 34.5 (C15), 24.3, 21.8 (C16). MS (70 eV): *m/z* (%) = 336 (4), 303 (4), 208 (3), 134 (12), 114 (7), 107 (14), 100 (100). HRMS: (M + H^+): $C_{25}H_{34}N_4O_3S$ calculated 471.2424; found 471.2387; 236.1231.

3-(Furan-2-ylmethyl)-2-(4-(2-(methyl (pyridin-2-yl)amino) ethoxy)phenyl)-1,3-thiazinan-4-one (10g). M.W. 423.53, light brown oil (16%), ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 4.2 Hz, 1H, H1), 7.45 (t, *J* = 7.2 Hz, 1H, H3), 7.32 (s, 1H, furanyl), 7.12 (d, *J* = 8.3 Hz, 2H, H11), 6.89 (d, *J* = 8.3 Hz, 2H, H10), 6.57–6.55 (m, 1H, H2), 6.52 (d, *J* = 8.3 Hz, 1H, H4), 6.28 (s, 1H, furanyl), 6.19 (d, *J* = 2.0 Hz, 1H, furanyl), 5.54 (s, 1H, H13), 5.40 (d, *J* = 15.5 Hz, 1H, –C(O)N$\underline{CH_2}$N–(a)), 4.19 (t, *J* = 5.5 Hz, 2H, H8), 3.99 (t, *J* = 5.4 Hz, 2H, H7), 3.74 (d, *J* = 15.5 Hz, 1H, –C(O)N$\underline{CH_2}$N–(b)), 3.15 (s, 3H, H6), 2.86 (d, *J* = 5.2 Hz, 2H, H16a, H16b), 2.81–2.77 (m, 1H, H15a), 2.65–2.63 (m, 1H, H15b). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4 (C14), 158.8, 158.3, 150.1, 147.9, 142.5, 137.4, 130.8, 127.8, 114.6, 111.8, 110.4, 109.0, 105.8, 66.5, 61.2 (C13), 49.5, 42.3, 37.9, 34.7 (C15),

22.0 (C16). MS (70 eV): *m/z* (%) = 289 (11), 182 (42), 137 (11), 122 (17), 107 (11), 96(29), 81 (100).

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