European Journal of Medicinal Chemistry 51 (2012) 216–226

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Progresses in the pursuit of aldose reductase inhibitors: The structure-based lead optimization step

Anna Ramunno [b], Sandro Cosconati [d], Stefania Sartini [c], Vita Maglio [b], Sara Angiuoli [b], Valeria La Pietra [a], Salvatore Di Maro [a], Mariateresa Giustiniano [a], Concettina La Motta [c], Federico Da Settimo [c], Luciana Marinelli [a,*], Ettore Novellino [a]

[a] Dipartimento di Chimica Farmaceutica e Tossicologica, Università di Napoli, "Federico II" Via D. Montesano 49, 80131 Napoli, Italy
[b] Dipartimento di Scienze Farmaceutiche, Università di Salerno, Via Ponte Don Melillo 11c, 84084 Fisciano, Italy
[c] Dipartimento di Scienze Farmaceutiche, Università di Pisa, Via Bonanno 6, 56126 Pisa, Italy
[d] Dipartimento di Scienze Ambientali, Seconda Università di Napoli, Via Vivaldi 43, 81100 Caserta, Italy

ARTICLE INFO

Article history:
Received 27 June 2011
Received in revised form
20 February 2012
Accepted 21 February 2012
Available online 5 March 2012

Keywords:
Aldose reductase
Inflammation
Diabetes
Docking
Enzyme

ABSTRACT

Aldose reductase (ALR2) is a crucial enzyme in the development of the major complications of diabetes mellitus. Very recently it has been demonstrated that the ARL2 inhibitor, fidarestat, significantly prevents inflammatory signals (TNF-α, LPS) that cause cancer (colon, breast, prostate and lung), metastasis, asthma, and other inflammatory diseases. Currently, fidarestat is in phase III clinical trial for diabetic neuropathy and was found to be safe. Thus the finding of novel, potent ARL2 inhibitors is today more than in the past in great demand as they can pave the way for a novel therapeutic approach for a number of diseases besides the diabetes. Herein, starting from the virtual screening-derived ALR2 inhibitor S12728 (**1**), a rational receptor-based lead optimization has been undertaken. The design and synthetic efforts here reported led to the discovery of several new compounds endowed with low micromolar/submicromolar activities.

1. Introduction

Diabetes mellitus, alone or in combination with other metabolic disorders as obesity and/or hypercholesterolemia, is recognized as one of the major health problems worldwide in terms of socio-economic impact [1,2]. Despite different therapeutic options to reduce hyperglycemia (eginsulines, oral hypoglycemics) it is often difficult to achieve a normoglycemic status even in patients with a careful control of their glucose levels. As a consequence, both micro- and macrovascular alterations can occur and may increase the risk of diabetes-specific long-term complications as blindness, cardiovascular and chronic renal diseases, peripheral vascular diseases with gangrene of lower limbs, as well as debilitating neuropathies. Of particular interest is neuropathy, the most common complication seen in the ambulatory care setting in patients with type 2 diabetes mellitus [3].

Although the exact mechanisms of these injuries are unknown, several evidences suggest a correlation between diabetes-related complications and downstream effects of osmotic and oxidative stress resulting from polyol pathway hyperactivation inhyperglicemic conditions [4,5].

The first and rate-limiting enzyme of this pathway is aldose reductase (ARL2), a member of the aldo-ketoreductase superfamily [6]. Under normoglycemic conditions this enzyme exerts beneficial effects by acting as an extra hepatic detoxifying enzyme in various tissues. Actually, ALR2 has been shown to be involved in the reduction of a variety of reactive aldhehydes deriving from *in vivo* lipid peroxidation, as well as from some xenobiotics [7]. Nevertheless, in hyperglycemic conditions, ARL2 catalyzes an NADPH-dependent reduction of glucose to sorbitol, which in turn is oxidized to fructose by an NAD^+-dependent sorbitol dehydrogenase. Intracellular accumulation of sorbitol creates a loss of osmotic integrity and cellular damage, while depletion of NADPH and NAD^+ cofactors compromises body's antioxidant defence systems. In addition, high blood levels of fructose may account for increased glycation and accelerating aging [8,9].

Notably, it has been recently found that inhibition of aldose reductase significantly prevented the inflammatory signals induced by cytokines, growth factors, endotoxins, high glucose, allergens and auto-immune reactions in cellular as well as animal models

* Corresponding author. Fax: +39 081 678619.
E-mail address: lmarinel@unina.it (L. Marinelli).

0223-5234/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2012.02.045

[10]. Very recently it has been demonstrated that the ALR2 inhibitor, fidarestat, significantly prevents tumor necrosis factor-alpha (TNF-α), growth factors, lipopolysaccharide (LPS), and environmental allergens-induced inflammatory signals that cause various inflammatory diseases. Indeed, in animal models of asthma, cancer (colon, breast, prostate and lung) and metastasis, inhibition of aldose reductase significantly ameliorated the disease. Particularly, it has been very recently demonstrated that inhibition of ARL2 prevents colon cancer metastasis [10]. Thus, the finding of novel, potent ARL2 inhibitors can pave the way for a novel therapeutic approach for a number of diseases besides long-term diabetic complications.

Today, a variety of structurally different compounds have been identified as potent *in vitro* ALR2 inhibitors (ARIs) and a number of them are in clinical trials to test their efficacy in the prevention and treatment of peripheral neuropathy in diabetes [11]. They can be classified into three general groups based on their structures: acetic acid derivatives (e.g. epalrestat, tolrestat, zenarestat, zopolrestat, NZ-314), cyclic imides (especially spirohydantoins, e.g. sorbinil, fidarestat) and phenolic derivatives (e.g. quercetin) (Fig. 1). Despite being structurally different, all ARIs possess two peculiar pharmacophoric elements: i) an acidic moiety which is able to interact with the "anion-binding site" of the catalytic site (Y48, H110, W111 and the flanking cofactor $NADP^+$), and ii) a lipophilic scaffold which can bind to the highly flexible specificity pocket of the catalytic site lined by L300, W111, T113 residues.

Regardless the numerous efforts made over recent decades, to date epalrestat is the only ARI commercially available and in Japan alone, while fidarestat has already undergone phase III clinical trial for diabetic neuropathy and was found to be safe. In many cases the failure of new candidates can be ascribed to poor pharmacokinetic properties and/or unacceptable side effects [11]. Furthermore, the limited efficacy of many reported ARIs may also be related to reduced binding affinity to ARL2 as a consequence of the oxidation of a critical residue of cysteine (C298) in hyperglycemia-induced oxidative stress [12,13]. For these reasons and for the newly described therapeutic potentials of ARIs, there is still a great interest in the identification of novel ARL2 inhibitors.

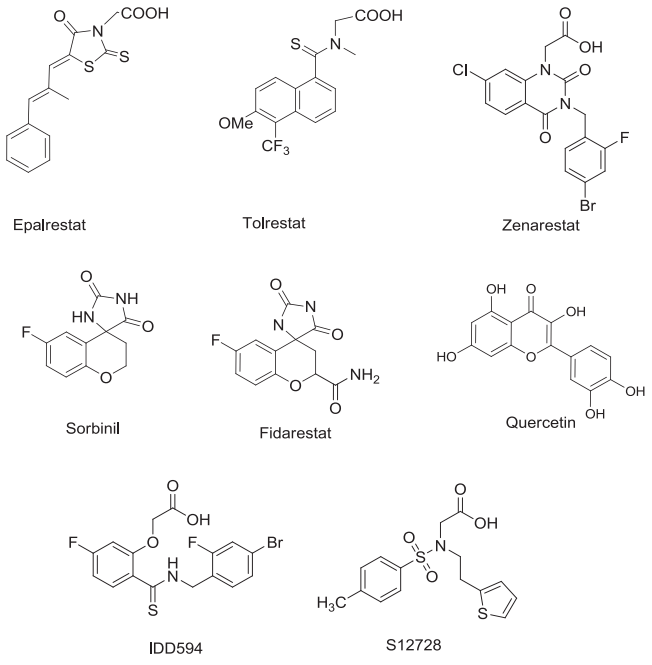


Fig. 1. Chemical structures of known ARL2I together with S12728.

In this respect, our research group has recently undertaken a virtual screening (VS) campaign by integrating a receptor-based approach with a ligand-based one in order to discover new chemotypes able to inhibit ALR2 [14]. Such a strategy revealed to be successful in the identification of twelve new leads with IC50 values ranging from 1.19 μM to 107.30 μM. Herein we report the design and synthetic efforts aimed at optimizing the effectiveness of one of these leads, the carboxylate-type inhibitor S12728 (**1**) (IC50 58.8 μM) (Fig. 1).

2. Results and discussion

2.1. Receptor-based design of S12728 derivatives

The lead optimization campaign presented herein was rationally designed by taking into account the theoretical binding pose of **1** in the ALR2-binding site. Most precisely, in our previous study, this compound was found by the Autodock (AD4) docking program to preferentially bind the ALR2 ultrahigh resolution structure (PBD code 1US0) [15] with respect to other enzyme conformations (PBD codes: 2FZD, 2PDK). As shown in Fig. 2a, the carboxylate of **1** is well inserted in the protein "anion-binding pocket" H-bonding with Y48,

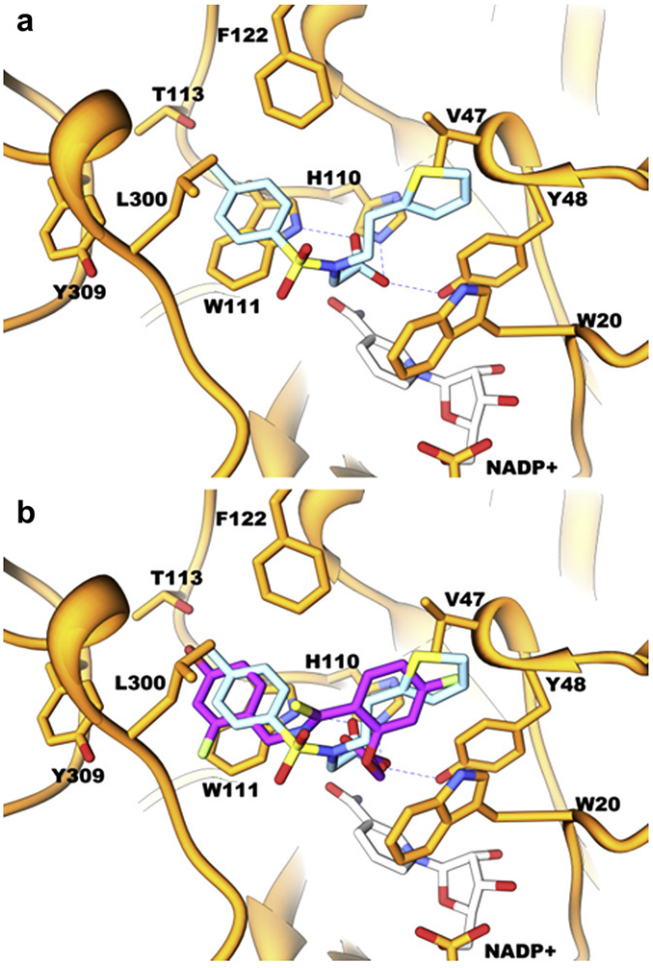


Fig. 2. (a) Theoretical-binding mode of compound S12728 (cyan) into the ALR2 catalytic site represented as orange ribbons. The ligand and the interacting residues are shown in stick representation and colored by atom type. H-bonds are represented with dashed blue lines. All hydrogens were removed for clarity. (b) Superposition of IDD594 experimental-binding mode (violet) with the S12728 (cyan) theoretical binding mode. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

H110 and W111 side chains and engaging an electrostatic interaction with $NADP^+$ nicotinamide moiety. On the other hand, the sulphonamide group well orients the tolyl substituent in the specificity pocket making charge transfer interactions with W111 and hydrophobic contacts with W79, F122 and L300 side-chains. Additionally, the thiophenylethyl group of **1** extends towards a rather hydrophobic cleft made up by W20, V47 and Y48 residues (Fig. 2a). The availability of the ternary complex ARL2–$NADP^+$–IDD594 at subatomic resolution revealed a number of fine details at the active site region of ARL2 that on one hand helped deciphering the reasons for inhibitor potency and selectivity and, on the other, paved the way for a rational optimization of our VS-derived lead compound (**1**). Thus, as first step in our lead optimization process, we compared the above-described theoretical binding mode of **1** with the experimentally determined one of IDD594 [15]. As shown in Fig. 2b, it is clear that the two structurally different inhibitors occupy the same part of the ALR2 active site spanning from the anion-binding site to the specificity pocket. Predictably, in both inhibitors the carboxylate group is firmly anchored in the active site, with hydrogen bonds to H110, Y48, and W111, and with an electrostatic interaction with $NADP^+$. As shown in Fig. 2b, the sulfonamide moiety of **1** allows the tolyl ring to adopt the same orientation of the IDD594 halogenated aromatic ring (2-F-4-Br-phenyl) so that the same stacking interactions with W111 side-chain can be established. However, while IDD594 can establish a favorable interaction with the T113 Oγ due to the high polarization of the bromine atom [16], in our lead the tolyl moiety is unable to engage such an interaction which is critical for enzyme binding and selectivity [16]. Thus, the 4-Br-phenyl (**1c**) and 2-F-4-Br-phenyl (**1e**) analogues were designed and synthesized. Moreover, to investigate the effect of other halogen substituents, a fluorine (**1a**) and a chlorine (**1b**) atom were inserted in position 4 of the phenyl ring of **1** as well as electron withdrawing groups such as trifluoromethyl (**1d**) and a nitro (**1f**) moiety. The nitro moiety was inserted also in position 3 bearing in mind the known activity of several nitro-containing ARL2 inhibitors [16]. Furthermore, with the aim of enhancing the staking interactions between W111 and the phenyl ring of **1** the latter was substituted with a naphthyl, a biphenyl or a dansyl group (compounds **1i**–**l**). As regards the thiophene ring of **1** we attempted a bioisosteric replacement and the resulting phenyl-containing derivative (**2h**) was optimized following the above-illustrated criteria (**2a**–**h**). From the superposition of the binding poses of IDD594 and **1** in ALR2, it also emerges that the pendant thiophene ring of **1** does not overlap with the central fluorophenyl ring of IDD594, thus a third series of compounds was also designed and synthesized where the ethyl linker was shortened and the attached thiophene ring was substituted with a phenyl one resulting in the benzyl derivatives **3a**–**i**.

2.2. Chemistry

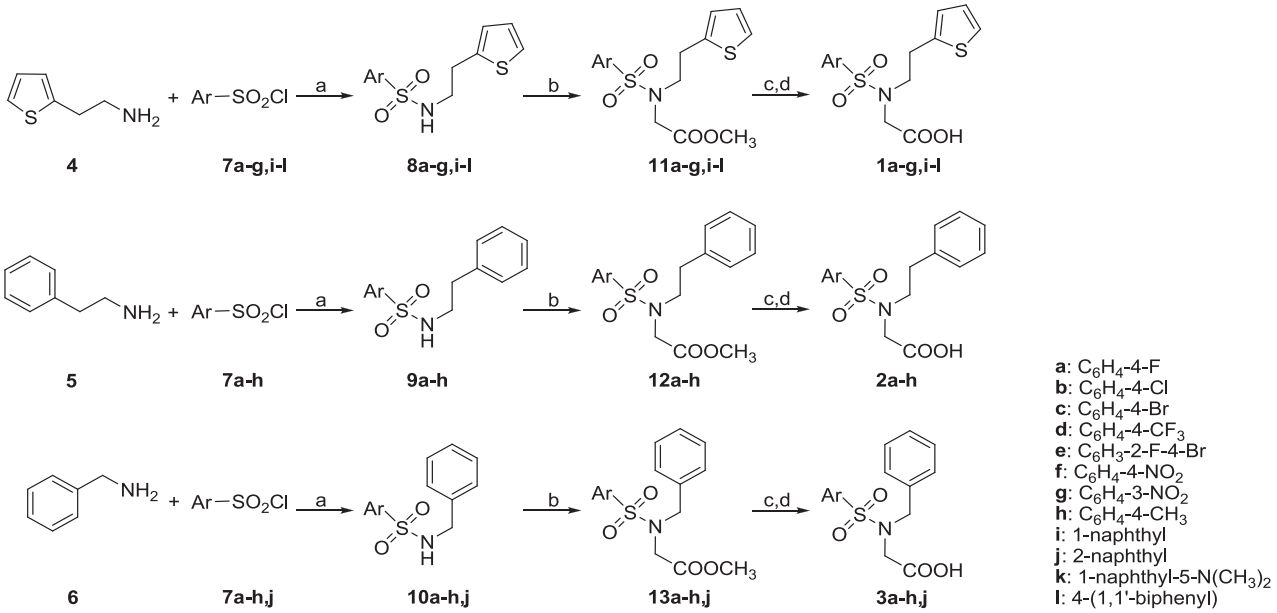
The synthesis of the target compounds **1a**–**g**, **i**–**l**, **2a**–**h** and **3a**–**h**, **j** was accomplished as outlined in Scheme 1. Commercially available 2-(thiophen-2-yl)ethylamine, **4**, 2-phenylethylamine, **5**, and benzylamine, **6**, were converted to the corresponding sulfonamides **8a**–**g**, **i**–**l**, **9a**–**h** and **10a**–**h**, **j** by reaction with the suitably substituted sulfonyl chlorides **7a**–**l** in the presence of triethylamine. Alkylation of sulfonamides with methyl bromoacetate provided the methyl esters **11a**–**g**, **i**–**l**, **12a**–**h** and **13a**–**h**, **j** which were hydrolyzed with sodium hydroxide to obtain, after acidification, the title inhibitors **1a**–**g**, **i**–**l**, **2a**–**h** and **3a**–**h**, **j** in good yields. An alternative procedure for the preparation of **2h**, **3a**–**c**, **3f**–**h**, **j** is reported in literature [17].

2.3. Biology

All the synthesized compounds were tested for efficacy against ALR2 and selectivity for ALR1 through a spectrophotometric assay, performed exploiting D,L-glyceraldehyde as the substrate and epalrestat as the reference standard. The inhibitory activity was assayed at a routine concentration of 100 μM. Those compounds found to be active were tested at additional concentration between 10 and 0.01 μM. Results of the biological evaluation are given in Table 1.

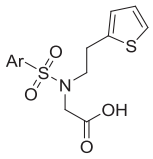
2.4. Structure activity relationships

As shown in Table 1, the optimization process was successful resulting in a set of analogues that generally possess higher inhibitory activities against ALR2 with respect to the lead

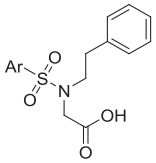


Scheme 1. Synthesis of compounds **1a**–**g**, **i**–**l**, **2a**–**h** and **3a**–**h**, **j**: (a) TEA, DCM, rt, overnight; (b) $BrCH_2COOCH_3$, K_2CO_3, DMF, rt, 24–48 h; (c) NaOH (10 M), reflux, 1 h; (d) HCl (3N), rt.

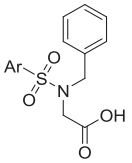
Table 1
Inhibition of ARL2 and ALR1 by the carboxylate-type inhibitor S12728 and its derivatives.



1a-g,i-l



2a-h



3a-h,j

Compound	Ar	ALR2 (IC_{50}, μM)[a]	ALR1 (IC_{50}, μM)[a]
S12728	–	58.8 ± 4.11	n.a.[b]
1a	4-F-phenyl	10.8 ± 0.54	61.2 ± 3.06
1b	4-Cl-phenyl	22.4 ± 1.56	n.a.[b]
1c	4-Br-phenyl	4.55 ± 0.18	57.8 ± 3.45
1d	4-CF_3-phenyl	73.2 ± 5.12	52.5 ± 3.27
1e	2-F-4-Br-phenyl	2.20 ± 0.044	57.6 ± 3.44
1f	4-NO_2-phenyl	11.9 ± 0.71	84.7 ± 4.22
1g	3-NO_2-phenyl	0.431 ± 0.012	7.56 ± 0.30
1i	1-naphthyl	12.4 ± 0.52	14.7 ± 0.88
1j	2-naphthyl	4.27 ± 0.26	5.93 ± 0.25
1k	5-*N*$(CH_3)_2$-1-naphthyl	13.3 ± 0.93	16.0 ± 0.89
1l	4-(1,1′-biphenyl)	26.5 ± 1.85	1.15 ± 0.069
2a	4-F-phenyl	47.1 ± 2.83	74.5 ± 3.79
2b	4-Cl-phenyl	45.4 ± 2.72	n.a.[b]
2c	4-Br-phenyl	3.56 ± 0.11	n.a.[b]
2d	4-CF_3-phenyl	68.3 ± 2.73	n.a.[b]
2e	2-F-4-Br-phenyl	5.48 ± 0.37	65.9 ± 3.22
2f	4-NO_2-phenyl	21.0 ± 1.26	n.a.[b]
2g	3-NO_2-phenyl	1.09 ± 0.043	10.4 ± 0.41
2h	4-CH_3-phenyl	84.7 ± 5.08	n.a.[b]
3a	4-F-phenyl	29.0 ± 2.32	33.9 ± 1.36
3b	4-Cl-phenyl	23.4 ± 1.18	n.a.[b]
3c	4-Br-phenyl	70.4 ± 4.92	n.a.[b]
3d	4-CF_3-phenyl	74.7 ± 5.22	n.a.[b]
3e	2-F-4-Br-phenyl	18.0 ± 1.08	80.4 ± 4.08
3f	4-NO_2-phenyl	17.3 ± 1.38	n.a.[b]
3g	3-NO_2-phenyl	5.51 ± 0.33	88.1 ± 4.48
3h	4-CH_3-phenyl	24.8 ± 1.74	n.a.[b]
3j	2-naphthyl	6.51 ± 0.39	8.32 ± 0.33
Epalrestat		0.17 ± 0.01	0.94 ± 0.04

[a] IC_{50} values, means ± SEM, represent the concentration required to produce 50% enzyme inhibition.
[b] n.a.: not active. Inhibition occurred at a concentration higher than 100 μM.

compound **1**. The structure activity relationships (SARs) data presented here allowed on one hand to identify the nature and the position of the substituents that can, in our lead **1**, produce better inhibitory potencies and on the other hand fully validate its theoretical binding mode. In fact, although only an X-ray analysis could unambiguously determine at an atomic level the enzyme rearrangement upon our inhibitor binding, the binding pose of **1** as identified by AD4 program seems to be strongly supported by all the SARs here presented. Indeed, the interaction between the carboxylate group and enzyme anionic site seems to be highly reasonable. On the other hand, the placement of the tolyl ring in the proximity of T113 is soundly supported by the lower IC50 values of the bromurated analogs **1c** and **2c** with respect to **1**. In fact, in perfect line with the supposed interaction with the T113 Oγ, SARs data clearly indicate that, among the compounds sharing a halogen on the ligand phenyl ring (**1a**–**e**) the ones with a 4-Br substitution (**1c** and **1e**) gave the best IC50 values. Moreover, the ranking in potency observed for derivatives **1a**–**d** and **2a**–**d** is in accordance with *ab-initio* studies performed in our previous work [18] which indicate that the fluorine atom (**1a** and **1d**), due to its small atomic radius, is entirely electronegative and consequently unable to engage the interaction with the oxygen atom lone pair of T113 Oγ, while the larger bromine due to its electropositive crown, can interact with the T113. Also the major inhibitory potencies of **1g** vs **1f** and **2g** vs **2f** would support the binding position of the tolyl ring depicted in Fig. 2. In fact, the 3-NO_2-phenyl moiety (see **1g**) which is common to other ARIs has been shown to positively affect the interactions with the selectivity pocket allowing this group to establish an H-bond with T113 [16,18]. The attempt to increase the charge-transfer interactions with W111 by enlarging the ligand aromatic surface (**1i**, **1j**, **1k**, **1l**) proved to be a less successful strategy. Nevertheless a certain increment in inhibitory potencies with respect to the lead compound has been detected especially in the case of **1j** (4.27 μM).

As detailed above, in the case of compounds **1a**–**g**, **i**–**l** and **2a**–**h** SARs data would support the theoretical-binding mode found for **1**. Conversely, biological data achieved for compounds **3a**–**j**, that feature the substitution of the thiophenetyl group with a benzyl one, would indicate a different binding interaction with the enzyme; even though the 3-NO_2-analogue **3g** is still the most active compound among the benzyl derivatives. Docking studies performed on compounds **3a**–**j** are not helpful in clarifying such a discrepancy and only X-ray studies, which are beyond our possibilities, will unambiguously demonstrate the viability of these predictions.

All the above-mentioned compounds were tested for their ability to inhibit aldehyde reductase (EC 1.1.1.2, ALR1), a member of the AKR superfamily possessing the highest structural homology with ALR2. As both ALR1 and ALR2 play a key detoxification role, being involved in the maintenance of specific control over reactive aldehydes, clinically effective and safe ARIs must necessarily combine high levels of ALR2 inhibition with a significant selectivity for ALR1, to keep unaltered its physiological role.

While the lead compound, **1**, showed no appreciable activity, derivatives **1a**, **c**–**l** proved to inhibit ALR1, with IC_{50} values in the micromolar/high micromolar range. Nevertheless, compounds showing the best ALR2 inhibitory activity, like **1e** and **1g**, turned out the most selective ones, inhibiting ALR1 with almost 20-fold less potency. Moreover, in the **2a**–**h** and **3a**–**j** series, most of the synthesized compounds proved to be completely selective inhibitors of ALR2, showing no activity towards ALR1.

2.5. In silico evaluation of the pharmacokinetic properties of the new ARIs

To achieve optimum therapeutic efficacy, ARIs should possess not only a high degree of potency towards the target enzyme, but also the capability to reach a certain concentration in tissues. In our case ARIs could be in principle administered through topical applications to treat diabetic visual impairments or through oral administration for other diabetic complications. Therefore, to provide a qualitative prediction of the pharmacokinetic properties of our ARIs, *in silico* calculations were performed by means of the Qikprop software (Schrödinger, LLC New York). The predicted physicochemical features (MW, SASA, donor HB, log P, Caco-2 permeability reported in Table 1 in SI) are expected to influence bioavailability through dissolution, cell permeation, and metabolism. Interestingly all the most active compounds were predicted to share similar *in silico* physicochemical features with epalrestat which is the only ARI approved so far on the Japanese market (see Table 1 in SI).

3. Conclusion

The recent finding that the ARL2 inhibitor, fidarestat, significantly prevents inflammatory signals (TNF-α, LPS) that cause cancer (colon, breast, prostate and lung) metastasis, asthma, and other inflammatory diseases has been a further prompt for the finding of novel ARL2 inhibitors. Herein, starting from the virtual screening-

derived ALR2 inhibitor S12728 (**1**), a rational receptor-based lead optimization has been undertaken. The optimization process has been successful resulting in a set of analogues that generally possess higher inhibitory activities against ALR2 with respect to the lead compound **1**. Our future research will focus on *in vivo* investigations on the effect of the newly discovered ARIs in inflammatory-related diseases as well as in the diabetes-specific long-term complications.

4. Experimental section

4.1. Materials

Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded with a Varian 400 spectrometer, operating at 400 and 100 MHz respectively. Mass spectra were obtained by electrospray ionization (ESIMS) using a ThermoFinningan LCQ Deca XP Max ion-trap mass spectrometer equipped with Xcalibur software. Chromatographic separations were performed on silica gel (Kieselgel 40, 00.040–0.063 mm, Merck). Reactions and products mixtures were routinely monitored by thin-layer chromatography (TLC) on Merck 0.2 mm precoated silica (60 F254) aluminum sheets, with visualization by irradiation with a UV lamp. Elemental analyses agreed with theoretical values to within ±0.4%. All starting materials, reagents and solvents (reagent grade) were purchased from Sigma–Aldrich and used without further purification.

4.1.1. General procedure for the preparation of sulfonamides *8a–g, i–l, 9a–h* and *10a–h, j*

A solution of appropriate sulfonyl chloride **7a–l** (10 mmol) in dichloromethane (15 mL) was slowly added to a cooled (0 °C) solution of amine **4–6** (15 mmol) in dichloromethane (10 mL) and triethylamine (15 mmol). The resulting mixture was stirred at room temperature overnight. The solvent was removed at reduced pressure, then the resulting residue was taken up in ethyl acetate and washed with a solution of HCl (1 M, 2 × 25 mL) and brine (2 × 25 mL). The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The title compounds were purified by crystallization from ethyl acetate/petroleum ether 40–60 °C. A similar procedure has been employed for the synthesis of **9f–h**, **10f–g**, while a different synthetic approach has been described for **10a–e**, **10h–k**; in all cases our ^{1}H NMR spectral data matched those previously reported for these compounds [19].

*4.1.1.1. N-[2-(2-thienyl)ethyl]-4-fluorobenzenesulfonamide (**8a**).* White solid; yield 73%; mp 85–87 °C; ^{1}H NMR ($CDCl_3$): δ 3.01 (t, J = 6.6 Hz, 2H), 3.27 (t, J = 6.6 Hz, 2H), 4.77 (br s, 1H), 6.78 (s, 1H), 6.94 (t, J = 4.2 Hz, 1H), 7.18–7.23 (m, 3H), 7.84–7.89 (m, 2H).

*4.1.1.2. N-[2-(2-thienyl)ethyl]-4-chlorobenzenesulfonamide (**8b**).* White solid; yield 95%; mp 87–89 °C; ^{1}H NMR ($CDCl_3$): δ 3.02 (t, J = 6.5 Hz, 2H), 3.27 (m, 2H), 4.69 (br s, 1H), 6.79 (s, 1H), 6.94 (t, J = 4.1 Hz, 1H), 7.17 (d, J = 4.9 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H).

*4.1.1.3. N-[2-(2-thienyl)ethyl]-4-bromobenzenesulfonamide (**8c**).* White solid; yield 94%; mp 96–98 °C; ^{1}H NMR ($CDCl_3$): δ 3.01 (t, J = 6.6 Hz, 2H), 3.27 (q, J = 6.5 Hz, 2H), 4.72 (br t, J = 5.7 Hz, 1H), 6.78 (s, 1H), 6.94 (t, J = 4.2 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.64–7.72 (m, 4H).

*4.1.1.4. N-[2-(2-thienyl)ethyl]-4-trifluoromethylbenzenesulfonamide (**8d**).* White solid; yield: 89%; mp 90–92 °C; ^{1}H NMR ($CDCl_3$): δ 3.04 (t, J = 6.5 Hz, 2H), 3.31 (q, J = 6.4 Hz, 2H), 4.65 (br t, J = 5.6 Hz, 1H), 6.79 (s, 1H), 6.94 (t, J = 4.3 Hz, 1H), 7.18 (d, J = 5.1 Hz, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H).

*4.1.1.5. N-[2-(2-thienyl)ethyl]-2-fluoro-4-bromobenzenesulfonamide (**8e**).* White solid; yield 95%; mp 60–62 °C; ^{1}H NMR ($CDCl_3$): δ 3.05 (t, J = 6.6 Hz, 2H), 3.32 (t, J = 6.6 Hz, 2H), 4.84 (br s, 1H), 6.82 (s, 1H), 6.94 (m, 1H), 7.19 (d, J = 5.1 Hz, 1H), 7.37–7.46 (m, 2H), 7.77 (t, J = 8.0 Hz, 1H).

*4.1.1.6. N-[2-(2-thienyl)ethyl]-4-nitrobenzenesulfonamide (**8f**).* Pale yellow solid; yield 68%; mp 82–84 °C; ^{1}H NMR ($CDCl_3$): δ 3.04 (t, J = 6.4 Hz, 2H), 3.33 (q, J = 6.3 Hz, 2H), 4.87 (br s, 1H), 6.80 (s, 1H), 6.94 (t, J = 3.5 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 8.01 (d, J = 8.6 Hz, 2H), 8.35 (d, J = 7.9 Hz, 2H).

*4.1.1.7. N-[2-(2-thienyl)ethyl]-3-nitrobenzenesulfonamide (**8g**).* White solid; yield 92%; mp 84–86 °C; ^{1}H NMR ($CDCl_3$): δ 3.04 (t, J = 6.5 Hz, 2H), 3.34 (q, J = 6.4 Hz, 2H), 4.99 (br s, 1H), 6.79 (s, 1H), 6.90 (t, J = 4.3 Hz, 1H), 7.13 (d, J = 5.1 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.43 (d, J = 8.2 Hz, 1H), 8.64 (s, 1H).

*4.1.1.8. N-[2-(2-thienyl)ethyl]-1-naphthalenesulfonamide (**8i**).* White solid; yield 86%; mp 107–108 °C; ^{1}H NMR ($CDCl_3$): δ 2.90 (t, J = 6.6 Hz, 2H), 3.22 (q, J = 6.5 Hz, 2H), 4.72 (br t, J = 4.5 Hz, 1H), 6.62 (s, 1H), 6.84 (m, 1H), 7.08 (d, J = 5.0 Hz, 1H), 7.57–7.65 (m, 3H), 7.98 (d, J = 6.6 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.29 (d, J = 7.6 Hz, 1H), 8.55 (d, J = 8.2 Hz, 1H).

*4.1.1.9. N-[2-(2-thienyl)ethyl]-2-naphthalenesulfonamide (**8j**).* White solid; yield 83%; mp 102–103 °C; ^{1}H NMR ($CDCl_3$): δ 3.01 (t, J = 6.6 Hz, 2H), 3.31 (q, J = 6.4 Hz, 2H), 4.63 (br t, J = 5.1 Hz, 1H), 6.77 (s, 1H), 6.91 (t, J = 5.1 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 7.66 (m, 2H), 7.80 (m, 1H), 7.97 (m, 3H), 8.44 (s, 1H).

*4.1.1.10. N-[2-(2-thienyl)ethyl]-5-dimethylamino-1-naphthalenesulfonamide (**8k**).* Yellow solid; yield 87%; mp 107–108 °C; ^{1}H NMR ($CDCl_3$): δ 2.93 (m, 8H), 3.20 (m, 2H), 4.73 (br s, 1H), 6.63 (s, 1H), 6.85 (m, 1H), 7.09 (m, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.56 (m, 2H), 8.21 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 7.1 Hz, 1H), 8.59 (d, J = 8.1 Hz, 1H).

*4.1.1.11. N-[2-(2-thienyl)ethyl]-(1,1′-biphenyl)-4-sulfonamide (**8l**).* White solid; yield 77%; mp 102–104 °C; ^{1}H NMR ($CDCl_3$): δ 3.04 (t, J = 6.4 Hz, 2H), 3.31 (m, 2H), 4.53 (br s, 1H), 6.81 (s, 1H), 6.94 (t, J = 4.9 Hz, 1H), 7.17 (d, J = 5.2 Hz, 1H), 7.42–7.53 (m, 3H), 7.63 (d, J = 6.7 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H), 7.91 (d, J = 8.2 Hz, 2H).

*4.1.1.12. N-(2-phenylethyl)-4-fluorobenzenesulfonamide (**9a**).* White solid; yield 97%; mp 81–82 °C; ^{1}H NMR ($CDCl_3$): δ 2.80 (t, J = 6.7 Hz, 2H), 3.26 (m, 2H), 4.37 (br s, 1H), 7.09–7.31 (m, 7H), 7.83 (m, 2H).

*4.1.1.13. N-(2-phenylethyl)-4-chlorobenzenesulfonamide (**9b**).* White solid; yield 93%; mp 89–90 °C; ^{1}H NMR ($CDCl_3$): δ 2.80 (t, J = 6.7 Hz, 2H), 3.26 (m, 2H), 4.44 (br s, 1H), 7.10 (d, J = 7.3 Hz, 2H), 7.30 (m, 3H), 7.48 (d, J = 7.0 Hz, 2H), 7.74 (d, J = 7.0 Hz, 2H).

*4.1.1.14. N-(2-phenylethyl)-4-bromobenzenesulfonamide (**9c**).* White solid; yield 88%; mp 88–90 °C; ^{1}H NMR ($CDCl_3$): δ 2.80 (t, J = 6.9 Hz, 2H), 3.26 (m, 2H), 4.59 (br s, 1H), 7.10 (d, J = 7.6 Hz, 2H), 7.25–7.32 (m, 3H), 7.62–7.69 (m, 4H).

*4.1.1.15. N-(2-phenylethyl)-4-trifluoromethylbenzenesulfonamide (**9d**).* White solid; yield 89%; mp 109–111 °C; ^{1}H NMR ($CDCl_3$): δ 2.81 (t, J = 6.8 Hz, 2H), 3.29 (q, J = 6.7 Hz, 2H), 4.77 (br s, 1H), 7.09

(d, J = 7.7 Hz, 2H), 7.28 (m, 3H), 7.76 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H).

*4.1.1.16. N-(2-phenylethyl)-2-fluoro-4-bromobenzenesulfonamide (**9e**).* White solid; yield: 79%; mp 82–84 °C; ^{1}H NMR ($CDCl_3$): δ 2.83 (t, J = 6.8 Hz, 2H), 3.31 (q, J = 6.7 Hz, 2H), 4.68 (br t, J = 5.7 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.26–7.45 (m, 5H), 7.76 (t, J = 8.0 Hz, 1H).

*4.1.1.17. N-(2-phenylethyl)-4-nitrobenzenesulfonamide (**9f**).* White solid; yield 87%; mp 89–91 °C [Lit. 92.5–93.5 °C] [20]; ^{1}H NMR ($CDCl_3$): δ 2.84 (t, J = 6.7 Hz, 2H), 3.32 (m, 2H), 4.79 (br s, 1H), 7.10 (d, J = 7.2 Hz, 2H), 7.28 (m, 3H), 7.97 (d, J = 8.9 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H).

*4.1.1.18. N-(2-phenylethyl)-3-nitrobenzenesulfonamide (**9g**).* Pale yellow solid; yield 97%; mp 90–92 °C; ^{1}H NMR ($CDCl_3$): δ 2.83 (t, J = 6.8 Hz, 2H), 3.34 (q, J = 6.7 Hz, 2H), 4.75 (br t, J = 5.5 Hz, 1H), 7.09 (d, J = 6.5 Hz, 2H), 7.28 (m, 3H), 7.71 (t, J = 8.0 Hz, 1H), 8.12 (d, J = 7.3 Hz, 1H), 8.42 (d, J = 8.2 Hz, 1H), 8.61 (s, 1H).

*4.1.1.19. N-(2-phenylethyl)-4-methylbenzenesulfonamide (**9h**).* White solid; yield 96%; mp 62–64 °C [Lit. 51–53 °C] [21]; ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 2.78 (t, J = 7.0 Hz, 2H), 3.22 (m, 2H), 4.74 (br s, 1H), 7.10 (d, J = 7.7 Hz, 2H), 7.23–7.32 (m, 5H), 7.72 (d, J = 8.2 Hz, 2H).

*4.1.1.20. N-benzyl-4-fluorobenzenesulfonamide (**10a**).* White solid; yield 97%; mp 96–98 °C [Lit. 99.4 °C] [19e]; ^{1}H NMR ($CDCl_3$): δ 4.18 (d, J = 6.0 Hz, 2H), 4.83 (br s, 1H), 7.16–7.31 (m, 7H), 7.89 (m, 2H).

*4.1.1.21. N-benzyl-4-chlorobenzenesulfonamide (**10b**).* White solid; yield 95%; mp 104–106 °C; ^{1}H NMR ($CDCl_3$): δ 4.18 (d, J = 5.9 Hz, 2H), 4.78 (br s, 1H), 7.21 (m, 2H), 7.30 (m, 3H), 7.49 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H).

*4.1.1.22. N-benzyl-4-bromobenzenesulfonamide (**10c**).* White solid; yield 91%; mp 118–120 °C [Lit. 101 °C] [19f]; ^{1}H NMR ($CDCl_3$): δ 4.18 (d, J = 6.1 Hz, 2H), 4.79 (br t, J = 5.7 Hz, 1H), 7.21 (m, 2H), 7.30 (m, 3H), 7.65 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H).

*4.1.1.23. N-benzyl-4-trifluoromethylbenzenesulfonamide (**10d**).* White solid; yield 79%; mp 121–122 °C [Lit 113–114 °C] [19g]; ^{1}H NMR ($CDCl_3$): δ 4.22 (d, J = 6.0 Hz, 2H), 4.87 (br t, J = 5.6 Hz, 1H), 7.20 (m, 2H), 7.29 (m, 3H), 7.77 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H).

*4.1.1.24. N-benzyl-2-fluoro-4-bromobenzenesulfonamide (**10e**).* White solid; yield 91%; mp 103–105 °C; ^{1}H NMR ($CDCl_3$): δ 4.23 (d, J = 6.1 Hz, 2H), 5.00 (br t, J = 6.1 Hz, 1H), 7.20–7.37 (m, 6H), 7.42 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 8.3 Hz, 1H).

*4.1.1.25. N-benzyl-4-nitrobenzenesulfonamide (**10f**).* Pale yellow solid; yield 87%; mp 126–128 °C [Lit. 126.6–127 °C] [22]; ^{1}H NMR ($CDCl_3$): δ 4.25 (d, J = 6.0 Hz, 2H), 5.07 (br t, J = 5.7 Hz, 1H), 7.19 (m, 2H), 7.28 (m, 3H), 8.00 (d, J = 8.9 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H).

*4.1.1.26. N-benzyl-3-nitrobenzenesulfonamide (**10g**).* White solid; yield 93%; mp 95–97 °C; ^{1}H NMR ($CDCl_3$): δ 4.28 (d, J = 6.0 Hz, 2H), 4.99 (br t, J = 5.2 Hz, 1H), 7.19 (m, 2H), 7.28 (m, 3H), 7.70 (t, J = 8.0 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.40 (d, J = 8.1 Hz, 1H), 8.62 (s, 1H).

*4.1.1.27. N-benzyl-4-methylbenzenesulfonamide (**10h**).* White solid; yield 88%; mp 112–114 °C [Lit. 117 °C] [19f]; ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H), 4.14 (d, J = 5.9 Hz, 2H), 4.76 (br s, 1H), 7.20–7.34 (m, 7H), 7.78 (d, J = 8.2 Hz, 2H).

*4.1.1.28. N-benzyl-2-napthalenesulfonamide (**10j**).* White solid; yield 80%; mp 94–96 °C [Lit 133 °C] [19f]; ^{1}H NMR ($CDCl_3$): δ 4.20 (d, J = 6.0 Hz, 2H), 4.72 (br s, 1H), 7.22 (m, 5H), 7.68 (m, 2H), 7.88–8.01 (m, 4H), 8.47 (s, 1H).

*4.1.2. General procedure for the preparation of compounds **11a–g**, **i–l**, **12a–h**, **13a–h**, **j***

Methyl bromoacetate (15 mmol) and anhydrous K_2CO_3 (25 mmol) were added to a solution of sulfonamides **8a–g**, **i–l**, **9a–h**, **10a–h**, **j** (5 mmol) in *N,N*-dimethylformamide (5 mL), and the resulting mixture was stirred at room temperature until starting material was not detected by TLC. The solvent was removed under reduced pressure and the resulting residue was taken up in ethyl acetate, and washed with HCl (1 M, 2 × 25 mL) and brine (2 × 25 mL). The title compounds were obtained after purification by flash chromatography.

*4.1.2.1. N-[2-(2-thienyl)ethyl]-N-[(4-fluorophenyl)sulfonyl]glycine methyl ester (**11a**).* White solid; yield 77%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 43–45 °C; ^{1}H NMR ($CDCl_3$): δ 3.12 (t, J = 7.4 Hz, 2H), 3.53 (t, J = 7.4 Hz, 2H), 3.63 (s, 3H), 4.04 (s, 2H), 6.82 (s, 1H), 6.92 (t, J = 4.0 Hz, 1H), 7.15 (m, 3H), 7.86 (m, 2H).

*4.1.2.2. N-[2-(2-thienyl)ethyl]-N-[(4-chlorophenyl)sulfonyl]glycine methyl ester (**11b**).* White solid; yield 96%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 80–82 °C; ^{1}H NMR ($CDCl_3$): δ 3.14 (t, J = 7.4 Hz, 2H), 3.54 (t, J = 7.4 Hz, 2H), 3.65 (s, 3H), 4.04 (s, 2H), 6.84 (s, 1H), 6.94 (t, J = 4.2 Hz, 1H), 7.17 (t, J = 5.1 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H).

*4.1.2.3. N-[2-(2-thienyl)ethyl]-N-[(4-bromophenyl)sulfonyl]glycine methyl ester (**11c**).* White solid; yield 86%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 75–77 °C; ^{1}H NMR ($CDCl_3$): δ 3.14 (t, J = 7.4 Hz, 2H), 3.52 (t, J = 7.4 Hz, 2H), 3.65 (s, 3H), 4.04 (s, 2H), 6.83 (s, 1H), 6.93 (t, J = 4.3 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.63–7.73 (m, 4H).

*4.1.2.4. N-[2-(2-thienyl)ethyl]-N-[(4-trifluoromethylphenyl)sulfonyl]glycine methyl ester (**11d**).* White solid; yield 93%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 58–60 °C; ^{1}H NMR ($CDCl_3$): δ 3.15 (t, J = 7.3 Hz, 2H), 3.56 (t, J = 7.3 Hz, 2H), 3.64 (s, 3H), 4.07 (s, 2H), 6.83 (s, 1H), 6.94 (t, J = 4.0 Hz, 1H), 7.16 (d, J = 4.2 Hz, 1H), 7.77 (d, J = 7.9 Hz, 2H), 7.97 (d, J = 7.8 Hz, 2H).

*4.1.2.5. N-[2-(2-thienyl)ethyl]-N-[(2-fluoro-4-bromophenyl)sulfonyl]glycine methyl ester (**11e**).* White solid; yield 98%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 7:3 v/v); mp 68–70 °C; ^{1}H NMR ($CDCl_3$): δ 3.14 (t, J = 7.3 Hz, 2H), 3.64 (t, J = 7.7 Hz, 2H), 3.67 (s, 3H), 4.11 (s, 2H), 6.82 (s, 1H), 6.93 (t, J = 4.2 Hz, 1H), 7.15 (d, J = 4.9 Hz, 1H), 7.39 (m, 2H), 7.76 (t, J = 7.9 Hz, 1H).

*4.1.2.6. N-[2-(2-thienyl)ethyl]-N-[(4-nitrophenyl)sulfonyl]glycine methyl ester (**11f**).* Pale yellow oil; yield 87%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); ^{1}H NMR ($CDCl_3$): δ 3.17 (t, J = 7.1 Hz, 2H), 3.59 (t, J = 7.1 Hz, 2H), 3.65 (s, 3H), 4.11 (s, 2H), 6.86 (s, 1H); 6.96 (t, J = 4.7 Hz, 1H), 7.19 (d, J = 4.8 1H), 8.03 (d, J = 8.4 Hz, 2H), 8.36 (d, J = 8.4 Hz, 2H).

*4.1.2.7. N-[2-(2-thienyl)ethyl]-N-[(3-nitrophenyl)sulfonyl]glycine methyl ester (**11g**).* White solid; yield 76%; SiO_2 (dichloromethane); mp 65–67 °C; ^{1}H NMR ($CDCl_3$): δ 3.13 (t, J = 7.2 Hz, 2H), 3.56 (t, J = 7.2 Hz, 2H), 3.63 (s, 3H), 4.11 (s, 2H), 6.82 (s, 1H), 6.89 (t, J = 4.3 Hz, 1H), 7.12 (d, J = 5.1 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.41 (d, J = 8.2 Hz, 1H), 8.62 (s, 1H).

*4.1.2.8. N-[2-(2-thienyl)ethyl]-N-[(1-naphthalenyl)sulfonyl]glycine methyl ester (**11i**).* White solid; yield 92%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 7:3 v/v); mp 69–71 °C; ^1H NMR ($CDCl_3$): δ 3.04 (t, J = 7.5 Hz, 2H), 3.51 (s, 3H), 3.66 (t, J = 7.5 Hz, 2H), 4.15 (s, 2H), 6.71 (s, 1H), 6.85 (t, J = 5.1 Hz, 1H), 7.08 (d, J = 5.1 Hz, 1H), 7.53–7.60 (m, 3H), 7.93 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 7.4 Hz, 1H), 8.65 (d, J = 8.6 Hz, 1H).

*4.1.2.9. N-[2-(2-thienyl)ethyl]-N-[(2-naphthalenyl)sulfonyl]glycine methyl ester (**11j**).* White solid; yield 77%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 63–65 °C; ^1H NMR ($CDCl_3$): δ 3.16 (t, J = 7.5 Hz, 2H), 3.57–3.63 (m, 5H), 4.09 (s, 2H), 6.82 (s, 1H), 6.91 (t, J = 5.1 Hz, 1H), 7.14 (d, J = 5.1 Hz, 1H), 7.68 (m, 2H), 7.82 (m, 1H), 7.98 (m, 3H), 8.44 (s, 1H).

*4.1.2.10. N-[2-(2-thienyl)ethyl]-N-[(5-dimethylamino-1-naphthalenyl) sulfonyl]glycine methyl ester (**11k**).* Yellow oil; yield 94%; SiO_2 (dichloromethane); ^1H NMR ($CDCl_3$): δ 2.91 (s, 6H), 3.03 (t, J = 7.3 Hz, 2H), 3.55 (s, 2H), 3.66 (t, J = 7.3 Hz, 2H), 4.14 (s, 2H), 6.70 (s, 1H), 6.85 (m, 1H), 7.08 (m, 1H), 7.24 (m, 1H), 7.51–7.59 (m, 3H), 8.30 (d, J = 7.5 Hz, 2H), 8.55 (d, J = 8.0 Hz, 1H).

*4.1.2.11. N-[2-(2-thienyl)ethyl]-N-[(1,1′-biphenyl)-4-sulfonyl]glycine methyl ester (**11l**).* Colorless oil; yield 93%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); ^1H NMR ($CDCl_3$): δ 3.16 (t, J = 7.4 Hz, 2H), 3.58 (t, J = 7.4 Hz, 2H), 3.64 (s, 3H), 4.06 (s, 2H), 6.84 (s, 1H), 6.93 (m, 1H), 7.16 (d, J = 4.03 Hz, 1H), 7.43–7.52 (m, 3H), 7.62 (d, J = 7.0 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.2 Hz, 2H).

*4.1.2.12. N-(2-phenylethyl)-N-[(4-fluorophenyl)sulfonyl]glycine methyl ester (**12a**).* Pale yellow oil; yield 93%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); ^1H NMR ($CDCl_3$): δ 2.90 (t, J = 7.7 Hz, 2H), 3.50 (t, J = 7.7 Hz, 2H), 3.64 (s, 3H), 4.03 (s, 2H), 7.15–7.32 (m, 7H), 7.86 (m, 2H).

*4.1.2.13. N-(2-phenylethyl)-N-[(4-chlorophenyl)sulfonyl]glycine methyl ester (**12b**).* White solid; yield 96%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 72–73 °C; ^1H NMR ($CDCl_3$): δ 2.90 (t, J = 7.6 Hz, 2H), 3.50 (t, J = 7.7 Hz, 2H), 3.65 (s, 3H), 4.03 (s, 2H), 7.16 (d, J = 7.3 Hz, 2H), 7.24–7.32 (m, 3H), 7.47 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H).

*4.1.2.14. N-(2-phenylethyl)-N-[(4-bromophenyl)sulfonyl]glycine methyl ester (**12c**).* White solid; yield 93%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 65–67 °C; ^1H NMR ($CDCl_3$): δ 2.90 (t, J = 7.6 Hz, 2H), 3.50 (t, J = 7.6 Hz, 2H), 3.79 (s, 3H), 4.02 (s, 2H), 7.16 (d, J = 7.4 Hz, 2H), 7.21–7.32 (m, 3H), 7.62 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H).

*4.1.2.15. N-(2-phenylethyl)-N-[(4-trifluoromethylphenyl)sulfonyl] glycine methyl ester (**12d**).* White solid; yield 97%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 61–63 °C; ^1H NMR ($CDCl_3$): δ 2.92 (t, J = 7.5 Hz, 2H), 3.54 (t, J = 7.5 Hz, 2H), 3.63 (s, 3H), 4.06 (s, 2H), 7.16 (d, J = 6.9 Hz, 2H), 7.24–7.30 (m, 3H), 7.75 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H).

*4.1.2.16. N-(2-phenylethyl)-N-[(2-fluoro-4-bromophenyl)sulfonyl] glycine methyl ester (**12e**).* White solid; yield 81%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 72–74 °C; ^1H NMR ($CDCl_3$): δ 2.89 (t, J = 7.5 Hz, 2H), 3.61 (t, J = 7.5 Hz, 2H), 3.67 (s, 3H), 4.10 (s, 2H), 7.15 (d, J = 7.8 Hz, 2H), 7.23–7.41 (m, 5H), 7.75 (t, J = 8.0 Hz, 1H).

*4.1.2.17. N-(2-phenylethyl)-N-[(4-nitrophenyl)sulfonyl]glycine methyl ester (**12f**).* White solid; yield 98%; SiO_2 (dichloromethane); mp 97–99 °C; ^1H NMR ($CDCl_3$): δ 2.92 (t, J = 7.4 Hz, 2H), 3.54 (t, J = 7.4 Hz, 2H), 3.65 (s, 3H), 4.08 (s, 2H), 7.17 (d, J = 7.8 Hz, 2H), 7.21–7.43 (m, 3H), 7.99 (d, J = 8.7 Hz, 2H), 8.32 (d, J = 8.8 Hz, 2H).

*4.1.2.18. N-(2-phenylethyl)-N-[(3-nitrophenyl)sulfonyl]glycine methyl ester (**12g**).* Pale yellow oil; yield 95%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 7:3 v/v); ^1H NMR ($CDCl_3$): δ 2.92 (t, J = 7.5 Hz, 2H), 3.54 (t, J = 7.5 Hz, 2H), 3.65 (s, 3H), 4.10 (s, 2H), 7.15–7.31 (m, 5H), 7.69 (t, J = 8.0 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.64 (s, 1H).

*4.1.2.19. N-(2-phenylethyl)-N-[(4-methylphenyl)sulfonyl]glycine methyl ester (**12h**).* Colorless oil; yield 92%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 7:3 v/v); ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H), 2.89 (t, J = 7.8 Hz, 2H), 3.63 (s, 3H), 4.01 (s, 2H), 7.17–7.31 (m, 7H), 7.73 (d, J = 8.3 Hz, 2H).

*4.1.2.20. N-benzyl-N-[(4-fluorophenyl)sulfonyl]glycine methyl ester (**13a**).* White solid; yield 91%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 49–51 °C; ^1H NMR ($CDCl_3$): δ 3.59 (s, 3H), 3.96 (s, 2H), 4.51 (s, 2H), 7.20–7.38 (m, 7H), 7.94 (m, 2H).

*4.1.2.21. N-benzyl-N-[(4-chlorophenyl)sulfonyl]glycine methyl ester (**13b**).* White solid; yield 96%; SiO_2 (dichloromethane); mp 44–46 °C; ^1H NMR ($CDCl_3$): δ 3.59 (s, 3H), 3.96 (s, 2H), 4.51 (s, 2H), 7.26–7.35 (m, 5H), 7.52 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H).

*4.1.2.22. N-benzyl-N-[(4-bromophenyl)sulfonyl]glycine methyl ester (**13c**).* White solid; yield 88%; SiO_2 (dichloromethane); mp 71–73 °C; ^1H NMR ($CDCl_3$): δ 3.59 (s, 3H), 3.96 (s, 2H), 4.51 (s, 2H), 7.26–7.36 (m, 5H), 7.69 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 8.6 Hz, 2H).

*4.1.2.23. N-benzyl-N-[(4-trifluoromethylphenyl)sulfonyl]glycine methyl ester (**13d**).* White solid; yield 81%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 73–75 °C; ^1H NMR ($CDCl_3$): δ 3.57 (s, 3H), 3.99 (s, 2H), 4.53 (s, 2H), 7.26–7.34 (m, 5H), 7.81 (d, J = 8.3 Hz, 2H), 8.04 (d, J = 8.2 Hz, 2H).

*4.1.2.24. N-benzyl-N-[(2-fluoro-4-bromophenyl)sulfonyl]glycine methyl ester (**13e**).* White solid; yield 96%; SiO_2 (dichloromethane); mp 52–54 °C; ^1H NMR ($CDCl_3$): δ 3.60 (s, 3H), 4.02 (s, 2H), 4.62 (s, 2H), 7.26–7.44 (m, 7H), 7.78 (t, J = 8.0 Hz, 1H).

*4.1.2.25. N-benzyl-N-[(4-nitrophenyl)sulfonyl]glycine methyl ester (**13f**).* Pale yellow solid; yield 82%; SiO_2 (ethyl ether/petroleum ether 40–60 °C, 1:1 v/v); mp 88–90 °C; ^1H NMR ($CDCl_3$): δ 3.60 (s, 3H), 4.02 (s, 2H), 4.54 (s, 2H), 7.27–7.37 (m, 5H), 8.08 (d, J = 8.6 Hz, 2H), 8.39 (d, J = 8.6 Hz, 2H).

*4.1.2.26. N-benzyl-N-[(3-nitrophenyl)sulfonyl]glycine methyl ester (**13g**).* White solid; yield 87%; SiO_2 (ethyl acetate/dichloromethane 0.5:9.5 v/v); mp 67–69 °C; ^1H NMR ($CDCl_3$): δ 3.61 (s, 3H), 4.04 (s, 2H), 4.54 (s, 2H), 7.28–7.39 (m, 5H), 7.77 (t, J = 8.0 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 8.2 Hz, 1H), 8.73 (s, 1H).

*4.1.2.27. N-benzyl-N-[(4-methylphenyl)sulfonyl]glycine methyl ester (**13h**).* White solid; yield 90%; SiO_2 (dichloromethane); mp 45–48 °C; ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H), 3.56 (s, 3H), 3.94 (s, 2H), 4.50 (s, 2H), 7.25–7.36 (m, 7H), 7.80 (d, J = 8.1 Hz, 2H).

*4.1.2.28. N-benzyl-N-[(2-napthalenyl)sulfonyl]glycine methyl ester (**13j**).* White solid; yield 66%; mp 82–84 °C; ^1H NMR ($CDCl_3$): δ 3.49 (s, 3H), 4.00 (s, 2H), 4.59 (s, 2H), 7.30 (m, 5H), 7.65 (m, 2H), 7.87–8.03 (m, 4H), 8.49 (s, 1H).

4.1.3. General procedure for the preparation of acids ***1a–g, i–l, 2a–h, 3a–h, j***

To a solution of methyl esters **11a–g**, **i–l**, **12a–h**, **13a–h**, **j** (5 mmol) in methanol (10 mL) was added NaOH (10 M, 25 mmol) and the resulting mixture was refluxing for 1 h. After cooling at room temperature, the mixture was concentrated under reduced pressure and then HCl (3N) was added (pH ~ 2). After extraction with ethyl acetate, the organic solvent was dried over anhydrous Na_2SO_4 and removed under reduced pressure. The resulting residue was purified by flash chromatography (methanol/ethyl acetate, 2:8 v/v as eluent) and recrystallized from ethyl acetate/petroleum ether 40–60 °C to give the title compounds in good yields.

*4.1.3.1. N-[2-(2-thienyl)ethyl]-N-[(4-fluorophenyl)sulfonyl]glycine (**1a**).* White solid; yield 80%; mp 164–166 °C; ^{1}H NMR ($CDCl_3$): δ 3.14 (t, J = 7.3 Hz, 2H), 3.55 (t, J = 7.4 Hz, 2H), 4.06 (s, 2H), 6.81 (d, J = 3.2 Hz, 1H), 6.95 (t, J = 4.2 Hz, 1H), 7.19 (m, 3H), 7.86 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 29.17, 48.99, 50.52, 117.05 (d, $J_{C\text{-}F}$ = 22.5 Hz), 125.02, 126.28, 127.76, 130.70 (d, $J_{C\text{-}F}$ = 9.5 Hz), 136.59 (d, $J_{C\text{-}F}$ = 3.0 Hz), 140.90, 165.05 (d, $J_{C\text{-}F}$ = 249.6 Hz), 170.93. ESIMS m/z: 342.0 [M − H]$^-$. Anal. calcd. for $C_{14}H_{14}FNO_4S_2$: C, 48.97; H, 4.11; N, 4.08. Found: C, 48.74; H, 3.97; N, 4.31.

*4.1.3.2. N-[2-(2-thienyl)ethyl]-N-[(4-chlorophenyl)sulfonyl]glycine (**1b**).* White solid; yield 71%; mp 196–198 °C; ^{1}H NMR (DMSO-d_6): δ 3.05 (t, J = 7.7 Hz, 2H), 3.44 (t, J = 7.7 Hz, 2H), 4.01 (s, 2H), 6.87 (s, 1H), 6.94 (t, J = 4.2 Hz, 1H), 7.33 (d, J = 5.0 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 23.60, 49.15, 50.47, 125.03, 126.28, 127.76, 129.57, 130.00, 138.32, 139.13, 140.92, 170.92. ESIMS m/z: 358.0 [M − H]$^-$, 360.0 [M − H]$^-$. Anal. calcd. for $C_{14}H_{14}ClNO_4S_2$: C, 46.73; H, 3.92; N, 3.89. Found: C, 46.54; H, 3.78; N, 3.65.

*4.1.3.3. N-[2-(2-thienyl)ethyl]-N-[(4-bromophenyl)sulfonyl]glycine (**1c**).* White solid; yield 74%; mp 189–190 °C; ^{1}H NMR (DMSO-d_6): δ 3.05 (t, J = 7.3 Hz, 2H), 3.45 (t, J = 7.3 Hz, 2H), 4.04 (s, 2H), 6.87 (s, 1H), 6.93 (m, 1H), 7.32 (d, J = 4.3 Hz, 1H), 7.76 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 29.18, 48.96, 50.25, 125.02, 126.29, 127.38, 127.72, 129.61, 132.96, 139.44, 140.85, 170.84. ESIMS m/z: 401.9 [M − H]$^-$, 403.9 [M − H]$^-$. Anal. calcd. for $C_{14}H_{14}BrNO_4S_2$: C, 41.59; H, 3.49; N, 3.46. Found: C, 41.75; H, 3.22; N, 3.67.

*4.1.3.4. N-[2-(2-thienyl)ethyl]-N-[(4-trifluoromethylphenyl)sulfonyl] glycine (**1d**).* White solid; yield 93%; mp 132–134 °C; ^{1}H NMR ($CDCl_3$): δ 3.14 (t, J = 7.3 Hz, 2H), 3.57 (t, J = 7.3 Hz, 2H), 4.08 (s, 2H), 6.82 (s, 1H), 6.93 (t, J = 4.2 Hz, 1H), 7.16 (d, J = 5.0 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 29.47, 48.61, 50.55, 124.56, 126.01, 126.39 (q, $J_{C\text{-}F}$ = 7.2 Hz), 127.41, 128.01, 134.49, 134.82, 139.90, 143.21, 173.80. ESIMS m/z: 392.0 [M − H]$^-$. Anal. calcd. for $C_{15}H_{14}F_3NO_4S_2$: C, 45.80; H, 3.59; N, 3.56. Found: C, 45.59; H, 3.21; N, 3.28.

*4.1.3.5. N-[2-(2-thienyl)ethyl]-N-[(2-fluoro-4-bromophenyl)sulfonyl] glycine (**1e**).* White solid; yield 79%; mp 170–171 °C; ^{1}H NMR ($CDCl_3$): δ 3.13 (t, = 7.1 Hz, 2H), 3.63 (t, J = 7.1 Hz, 2H), 4.16 (s, 3H), 6.81 (s, 1H), 6.92 (t, J = 4.2 Hz, 1H), 7.16 (d, J = 5.1 Hz, 1H), 7.34–7.43 (m, 2H), 7.77 (t, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 29.21, 48.84, 50.28, 121.02 (d, $J_{C\text{-}F}$ = 24.4 Hz), 124.39, 125.88, 127.30, 127.44, 127.91 (d, $J_{C\text{-}F}$ = 3.6 Hz), 128.61 (d, $J_{C\text{-}F}$ = 9.4 Hz), 131.72, 140.13, 158.74 (d, $J_{C\text{-}F}$ = 258.2 Hz), 174.36. ESIMS m/z: 419.9 [M − H]$^-$, 421.9 [M − H]$^-$. Anal. calcd. for $C_{14}H_{13}BrFNO_4S_2$: C, 39.82; H, 3.10; N, 3.32. Found: C, 39.98; H, 2.86; N, 3.67.

*4.1.3.6. N-[2-(2-thienyl)ethyl]-N-[(4-nitrophenyl)sulfonyl]glycine (**1f**).* White solid; yield 91%; mp 168–170 °C; ^{1}H NMR ($CDCl_3$): δ 3.15 (t, J = 7.2 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 4.11 (s, 2H), 6.82 (s, 1H), 6.93 (t, J = 4.8 Hz, 1H), 7.16 (d, J = 5.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 8.33 (d, J = 8.6 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 29.08, 49.08, 50.53, 125.09, 125.10, 126.38, 127.74, 129.21, 140.75, 145.72, 150.30, 170.70. ESIMS m/z: 369.1 [M − H]$^-$. Anal. calcd. for $C_{14}H_{14}N_2O_6S_2$: C, 45.40; H, 3.81; N, 7.56. Found: C, 45.62; H, 3.49; N, 7.38.

*4.1.3.7. N-[2-(2-thienyl)ethyl]-N-[(3-nitrophenyl)sulfonyl]glycine (**1g**).* White solid; yield 88%; mp 134–137 °C; ^{1}H NMR ($CDCl_3$): δ 3.16 (t, J = 7.1 Hz, 2H), 3.57 (t, J = 7.1 Hz, 2H), 4.15 (s, 2H), 6.84 (s, 1H), 6.92 (t, J = 4.2 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 7.73 (t, J = 4.0 Hz, 1H), 8.16 (d, J = 7.7 Hz, 1H), 8.42 (d, J = 8.0 Hz, 1H), 8.65 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 28.95, 48.91, 50.48, 122.37, 125.06, 126.39, 127.70, 128.02, 131.93, 133.72, 140.76, 141.84, 148.46, 170.87. ESIMS m/z: 369.1 [M − H]$^-$. Anal. calcd. for $C_{14}H_{14}N_2O_6S_2$: C, 45.40; H, 3.81; N, 7.56. Found: C, 45.63; H, 3.53; N, 7.27.

*4.1.3.8. N-[2-(2-thienyl)ethyl]-N-[(1-naphthalenyl)sulfonyl]glycine (**1i**).* White solid; yield 84%; mp 120–122 °C; ^{1}H NMR ($CDCl_3$): δ 3.01 (t, J = 7.0 Hz, 2H), 3.67 (t, J = 6.9 Hz, 2H), 4.16 (s, 2H), 6.68 (s, 1H), 6.85 (m, 1H), 7.09 (d, J = 4.9 Hz, 1H), 7.53–7.70 (m, 3H), 7.95 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 8.30 (d, J = 7.0 Hz, 1H), 8.60 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 29.10, 48.37, 50.15, 124.27, 124.36, 124.96, 125.74, 127.16, 127.20, 128.53, 128.76, 129.26, 130.17, 134.63, 134.67, 134.85, 140.10, 174.13. ESIMS m/z: 374.0 [M − H]$^-$. Anal. calcd. for $C_{18}H_{17}NO_4S_2$: C, 57.58; H, 4.56; N, 3.73. Found: C, 57.75; H, 4.21; N, 3.96.

*4.1.3.9. N-[2-(2-thienyl)ethyl]-N-[(2-naphthalenyl)sulfonyl]glycine (**1j**).* White solid; yield 74%; mp 121–123 °C; ^{1}H NMR ($CDCl_3$): δ 3.14 (t, J = 7.6 Hz, 2H), 3.60 (t, J = 7.2 Hz, 2H), 4.07 (s, 2H), 6.82 (s, 1H), 6.91 (m, 1H), 7.14 (m, 1H), 7.62 (m, 2H), 7.68 (m, 1H), 7.96 (m, 3H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 29.61, 48.96, 50.68, 122.71, 124.37, 125.89, 127.32, 127.80, 128.13, 128.97, 129.13, 129.52, 129.66, 132.29, 135.13, 136.40, 140.26, 173.84. ESIMS m/z: 374.1 [M − H]$^-$. Anal. calcd. for $C_{18}H_{17}NO_4S_2$: C, 57.58; H, 4.56; N, 3.73. Found: C, 57.84; H, 4.17; N, 3.49.

*4.1.3.10. N-[2-(2-thienyl)ethyl]-N-[(5-dimethylamino-1 naphthalenyl) sulfonyl]glycine (**1k**).* Yellow solid; yield 64%; mp 113–115 °C; ^{1}H NMR ($CDCl_3$): δ 2.98–3.04 (m, 8H), 3.66 (t, J = 7.4 Hz, 2H), 4.16 (s, 2H), 4.89 (br s, 1H), 6.69 (s, 1H), 6.86 (t, J = 4.9 Hz, 1H), 7.10 (d, J = 4.3 Hz, 1H), 7.28 (m, 1H), 7.59 (m, 2H), 8.33 (m, 2H), 8.64 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 29.07, 45.69, 48.50, 50.19, 115.61, 119.74, 123.50, 124.21, 125.73, 127.19, 128.50, 130.14, 130.17, 130.21, 130.83, 134.87, 140.20, 151.64, 174.02. ESIMS m/z: 417.1 [M − H]$^-$. Anal. calcd. for $C_{20}H_{22}N_2O_4S_2$: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.52; H, 4.98; N, 6.43.

*4.1.3.11. N-[2-(2-thienyl)ethyl]-N-[(1,1′-biphenyl)-4-sulfonyl]glycine (**1l**).* White solid; yield 70%; mp 137–139 °C; ^{1}H NMR ($CDCl_3$): δ 3.15 (t, J = 7.4 Hz, 2H), 3.58 (t, J = 7.4 Hz, 2H), 4.05 (s, 2H), 6.83 (s, 1H), 6.93 (m, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.14–7.52 (m, 3H), 7.62 (d, J = 6.9 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 29.60, 48.96, 50.72, 124.40, 125.91, 127.35, 127.57, 127.91, 128.07, 128.78, 129.31, 138.04, 138.45, 140.29, 146.07, 174.48. ESIMS m/z: 400.0 [M − H]$^-$. Anal. calcd. for $C_{20}H_{19}NO_4S_2$: C, 59.83; H, 4.77; N, 3.49. Found: C, 58.85; H, 4.81; N, 3.66.

*4.1.3.12. N-(2-phenylethyl)-N-[(4-fluorophenyl)sulfonyl]glycine (**2a**).* White solid; yield 67%; mp 173–175 °C; ^{1}H NMR ($CDCl_3$): δ 2.89 (t, J = 7.6 Hz, 2H), 3.51 (t, J = 7.6 Hz, 2H), 4.04 (s, 2H), 7.16 (m, 4H), 7.28 (m, 3H), 7.84 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 34.83, 48.84, 50.47, 116.90 (d, $J_{C\text{-}F}$ = 22.5 Hz), 127.00, 129.10, 129.34, 130.67 (d, $J_{C\text{-}F}$ = 9.5 Hz), 136.68 (d, $J_{C\text{-}F}$ = 3.0 Hz), 139.05, 165.02 (d, $J_{C\text{-}F}$ = 250.3 Hz), 170.99. ESIMS m/z: 336.1 [M − H]. Anal. calcd. for

$C_{16}H_{16}FNO_4S$: C, 56.96; H, 4.78; N, 4.15. Found: C, 56.58; H, 4.39, N, 4.23.

*4.1.3.13. N-(2-phenylethyl)-N-[(4-chlorophenyl)sulfonyl]glycine (**2b**).* White solid; yield 90%; mp 196–199 °C; ^{1}H NMR (DMSO-d_6): δ 2.80 (t, J = 7.8 Hz, 2H), 3.41 (t, J = 7.8 Hz, 2H), 4.03 (s, 2H), 7.17–7.27 (m, 5H), 7.62 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 8.5 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 34.61, 50.00, 55.55, 126.94, 129.09, 129.28, 129.57, 129.78, 137.90, 139.30, 139.63, 171.79. ESIMS m/z: 352.0 [M − H]$^-$, 354.1 [M − H]$^-$. Anal. calcd. for $C_{16}H_{16}ClNO_4S$: C, 54.31; H, 4.56; N, 3.96. Found: C, 54.25; H, 4.62; N, 4.18.

*4.1.3.14. N-(2-phenylethyl)-N-[(4-bromophenyl)sulfonyl]glycine (**2c**).* White solid; yield 70%; mp 186–187 °C; ^{1}H NMR ($CDCl_3$): δ 2.92 (t, J = 7.4 Hz, 2H), 3.53 (t, J = 7.5 Hz, 2H), 4.06 (s, 2H), 7.17 (m, 2H), 7.30 (m, 3H), 7.62–7.71 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 34.85, 48.81, 50.49, 127.00, 127.31, 129.09, 129.36, 129.61, 132.92, 139.01, 139.53, 170.88. ESIMS m/z: 395.9 [M − H]$^-$, 397.9 [M − H]$^-$. Anal. calcd. for $C_{16}H_{16}BrNO_4S$: C, 48.25; H, 4.05; N, 3.52. Found: C, 48.53; H, 3.86; N, 3.84.

*4.1.3.15. N-(2-phenylethyl)-N-[(4-trifluoromethylphenyl)sulfonyl] glycine (**2d**).* White solid; yield 86%; mp 148–149 °C; ^{1}H NMR ($CDCl_3$): δ 2.91 (t, J = 7.5 Hz, 2H), 3.55 (t, J = 7.5 Hz, 2H), 4.07 (s, 2H), 7.15 (d, J = 7.3 Hz, 2H) 7.28 (m, 3H), 7.74 (d, J = 8.3 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 35.17, 48.29, 50.35, 122.07, 124.78, 126.34 (q, $J_{C\text{-}F}$ = 7.1 Hz), 127.11, 127.98, 128.93 (d, $J_{C\text{-}F}$ = 9.5 Hz), 134.58 (d, $J_{C\text{-}F}$ = 33 Hz), 137.81, 143.25, 173.90. ESIMS m/z: 386.0 [M − H]$^-$. Anal. calcd. for $C_{17}H_{16}F_3NO_4S$: C, 52.71; H, 4.16; N, 3.62. Found: C, 52.96; H, 4.28; N, 3.49.

*4.1.3.16. N-(2-phenylethyl)-N-[(2-fluoro-4-bromophenyl)sulfonyl] glycine (**2e**).* White solid; yield 75%; mp 175–177 °C; ^{1}H NMR ($CDCl_3$): δ 2.89 (t, J = 7.4 Hz, 2H), 3.61 (t, J = 7.3 Hz, 2H), 4.16 (s, 3H), 7.13 (d, J = 7.3 Hz, 2H), 7.23–7.41 (m 4H), 7.75 (t, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 35.10, 48.27, 50.06, 120.99 (d, $J_{C\text{-}F}$ = 24.7 Hz), 126.99, 127.48 (d, $J_{C\text{-}F}$ = 14.5 Hz), 127.88 (d, $J_{C\text{-}F}$ = 3.7 Hz), 128.60 (d, $J_{C\text{-}F}$ = 9.1 Hz), 128.86, 128.93, 131.64, 137.84, 158.72 (d, $J_{C\text{-}F}$ = 257.5 Hz), 174.05. ESIMS m/z: 413.9 [M − H]$^-$, 415.9 [M − H]$^-$. Anal. calcd. for $C_{16}H_{15}BrFNO_4S$: C, 46.17; H, 3.63; N, 3.36. Found: C, 46.26; H, 3.39; N, 3.65.

*4.1.3.17. N-(2-phenylethyl)-N-[(4-nitrophenyl)sulfonyl]glycine (**2f**).* White solid; yield 60%; mp 168–170 °C; ^{1}H NMR ($CDCl_3$): δ 2.92 (t, J = 7.5 Hz, 2H), 3.56 (t, J = 7.5 Hz, 2H), 4.08 (s, 2H), 7.15 (d, J = 7.4 Hz, 2H), 7.28 (m, 3H), 7.96 (d, J = 8.7 Hz, 2H), 8.30 (d, J = 8.7 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 34.75, 48.80, 50.53, 125.10, 127.02, 129.07, 129.18, 129.40, 138.89, 145.75, 150.28, 170.75. ESIMS m/z: 363.0 [M − H]$^-$. Anal. calcd. for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.48; H, 4.13, N, 7.47.

*4.1.3.18. N-(2-phenylethyl)-N-[(3-nitrophenyl)sulfonyl]glycine (**2g**).* White solid; yield 63%; mp 157–158 °C; ^{1}H NMR ($CDCl_3$): δ 2.94 (t, J = 7.4 Hz, 2H), 3.56 (t, J = 7.4 Hz, 2H), 4.15 (s, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.26 (m, 3H), 7.72 (t, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.65 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 34.63, 48.77, 50.41, 122.34, 126.97, 127.97, 129.02, 129.38, 131.87, 133.72, 138.92, 141.95, 148.44, 170.92. ESIMS m/z: 362.9 [M − H]$^-$. Anal. calcd. for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.99; H, 4.72; N, 7.55.

*4.1.3.19. N-(2-phenylethyl)-N-[(4-methylphenyl)sulfonyl]glycine (**2h**).* White solid; yield: 69%; mp 141–143 °C; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H), 2.90 (t, J = 7.8 Hz, 2H), 3.51 (t, J = 7.8 Hz, 2H), 4.03 (s, 2H), 7.16 (d, J = 7.1 Hz, 2H), 7.25–7.32 (m, 5H), 7.74 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.77, 35.27, 48.73, 50.51, 126.92, 127.57, 128.91, 128.95, 129.91, 136.56, 138.18, 143.97, 174.28. ESIMS m/z: 332.0 [M − H]$^-$. Anal. calcd. for $C_{17}H_{19}NO_4S_2$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.59; H, 5.96; N, 4.54.

*4.1.3.20. N-benzyl-N-[(4-fluorophenyl)sulfonyl]glycine (**3a**).* White solid; yield 65%; mp 137–139 °C; ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 2H), 4.52 (s, 2H), 7.25–7.54 (m, 7H), 7.85 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 48.04, 51.76, 116.95 (d, $J_{C\text{-}F}$ = 22.6 Hz), 128.42, 128.89, 129.16, 130.85 (d, $J_{C\text{-}F}$ = 9.5 Hz), 136.28, 136.82 (d, $J_{C\text{-}F}$ = 249.4 Hz), 170.32. ESIMS m/z: 321.9 [M − H]$^-$. Anal. calcd. for $C_{15}H_{14}FNO_4S$: C, 55.72; H, 4.36; N, 4.33. Found: C, 55.93; H, 4.41; N, 4.27.

*4.1.3.21. N-benzyl-N-[(4-chlorophenyl)sulfonyl]glycine (**3b**).* White solid; yield 52%; mp 148 °C; ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 2H), 4.52 (s, 2H), 7.27 (m, 2H), 7.30 (m, 3H), 7.53 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 48.04, 51.79, 128.44, 128.90, 129.18, 129.72, 129.93, 136.24, 138.39, 139.24, 170.25. ESIMS m/z: 337.9 [M − H]$^-$, 339.9 [M − H]$^-$. Anal. calcd. for $C_{15}H_{14}ClNO_4S$: C, 53.02; H, 4.15; N, 4.12. Found: C, 52.76; H, 3.85; N, 4.33.

*4.1.3.22. N-benzyl-N-[(4-bromophenyl)sulfonyl]-glycine (**3c**).* White solid; yield 93%; mp 156–158 °C; ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 2H), 4.52 (s, 2H), 7.27 (m, 2H), 7.36 (m, 3H), 7.69 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 48.03, 51.78, 127.41, 128.44, 128.90, 129.18, 129.78, 132.87, 136.23, 139.63, 170.24. ESIMS m/z: 382.2 [M − H]$^-$, 384.2 [M − H]$^-$. Anal. calcd. for $C_{15}H_{14}BrNO_4S$: C, 46.89; H, 3.67; N, 3.65. Found: C, 46.53; H, 3.41; N, 3.89.

*4.1.3.23. N-benzyl-N-[(4-trifluoromethylphenyl)sulfonyl]glycine (**3d**).* White solid; yield 70%; mp 136 °C; ^{1}H NMR ($CDCl_3$): δ 4.02 (s, 2H), 4.54 (s, 2H), 7.26 (m, 2H), 7.37 (m, 3H), 7.81 (d, J = 8.2 Hz, 2H), 8.03 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 46.54, 51.72, 126.36 (q, $J_{C\text{-}F}$ = 7.2 Hz), 128.10, 128.78, 128.82, 129.20, 134.28, 134.69 (d, $J_{C\text{-}F}$ = 32.8 Hz), 173.98. ESIMS m/z: 372.0 [M − H]$^-$. Anal. calcd. for $C_{16}H_{14}F_3NO_4S$: C, 51.47; H, 3.78; N, 3.75. Found: C, 51.64; H, 3.39; N, 3.64.

*4.1.3.24. N-benzyl-N-[(2-fluoro-4-bromophenyl)sulfonyl]-glycine (**3e**).* White solid; yield 57%; mp 147–148 °C; ^{1}H NMR ($CDCl_3$): δ 4.09 (s, 2H), 4.63 (s, 2H), 7.28 (m, 2H), 7.36–7.46 (m, 5H), 7.81 (t, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 46.57, 51.71, 120.89 (d, $J_{C\text{-}F}$ = 24.6 Hz), 127.73 (d, $J_{C\text{-}F}$ = 14.4 Hz), 127.95 (d, $J_{C\text{-}F}$ = 3.6 Hz), 128.67, 128.73, 128.82, 129.17, 131.62, 134.57, 158.96 (d, $J_{C\text{-}F}$ = 257.7 Hz), 174.05. ESIMS m/z: 399.9 [M − H]$^-$, 401.0 [M − H]$^-$. Anal. calcd. for $C_{15}H_{13}BrFNO_4S$: C, 44.79; H, 3.26; N, 3.48. Found: C, 44.85; H, 3.08; N, 3.59.

*4.1.3.25. N-benzyl-N-[(4-nitrophenyl)sulfonyl]glycine (**3f**).* White solid; yield 76%; mp 157–159 °C; ^{1}H NMR ($CDCl_3$): δ 4.05 (s, 2H), 4.56 (s, 2H), 7.30–7.37 (m, 5H), 8.08 (d, J = 8.6 Hz, 2H), 8.40 (d, J = 8.3 Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 48.20, 51.94, 125.04, 128.55, 128.95, 129.24, 129.42, 135.97, 145.86, 150.35, 170.12. ESIMS m/z: 349.0 [M − H]$^-$. Anal. calcd. for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00. Found: C, 51.76; H, 3.93; N, 8.31.

*4.1.3.26. N-benzyl-N-[(3-nitrophenyl)sulfonyl]glycine (**3g**).* White solid; yield 60%; mp 125–127 °C; ^{1}H NMR ($CDCl_3$): δ 4.09 (s, 2H), 4.53 (s, 2H), 7.29 (m, 2H), 7.37 (m, 3H), 7.77 (t, J = 8.0 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.45 (d, J = 8.3 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 48.52, 51.99, 122.60, 128.02, 128.48, 128.97, 129.18, 131.86, 133.93, 135.97, 142.08, 148.35, 170.37. ESIMS m/z: 348.9 [M − H]$^-$. Anal. calcd. for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00. Found: C, 51.30; H, 3.78; N, 8.23.

*4.1.3.27. N-benzyl-N-[(4-methylphenyl)sulfonyl]glycine (**3h**).* White solid; yield 80%; mp 120–122 °C [Lit 192–194 °C] [17b]; ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H), 3.95 (s, 2H), 4.49 (s, 2H), 7.23–7.35 (m, 7H), 7.79 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.82, 46.57, 51.59, 127.68, 128.53, 128.87, 129.07, 129.91, 134.87, 136.74, 144.07, 174.70. ESIMS m/z: 318.0 $[M - H]^-$. Anal. calcd. for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 59.86; H, 5.11; N, 4.23.

*4.1.3.28. N-benzyl-N-[(2-napthalenyl)sulfonyl]glycine (**3j**).* White solid; yield 75%; mp 149–150 °C; ^{1}H NMR ($CDCl_3$): δ 3.97 (s, 2H), 4.55 (s, 2H), 7.21 (m, 5H), 7.60–7.65 (m, 2H), 7.84–7.96 (m, 4H), 8.47 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 46.81, 51.63, 122.90, 127.76, 128.14, 128.47, 128.87, 129.03, 129.10, 129.52, 129.56, 129.60, 132.28, 134.91, 135.12, 136.66, 173.91. ESIMS m/z: 354.0 $[M - H]^-$. Anal. calcd. for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.35; H, 4.93; N, 3.76.

4.2. Biology

4.2.1. Materials and methods

Aldose reductase (ALR2) and aldehyde reductase (ALR1) were obtained from Sprague Dawley albino rats, 120–140 g b.w., supplied by Harlan Nossan, Italy. Enzymes preparation was carried out as previously reported [18].

NADPH and D,L-glyceraldehyde were from Sigma–Aldrich. Epalrestat was from Haorui Pharma-Chem Inc. All other chemicals were of reagent grade.

4.2.2. Enzymatic assays

The activity of the two test enzymes was determined spectrophotometrically by monitoring the change in absorbance at 340 nm, which is due to the oxidation of NADPH catalyzed by ALR2 and ALR1. The change in pyridine coenzyme concentration/min was determined using a Beckman DU-64 kinetics software program (Solf Pack TM Module).

ALR2 activity was assayed at 30 °C in a reaction mixture containing 0.25 mL of 10 mM D,L-glyceraldehyde, 0.25 mL of 0.104 mM NADPH, 0.25 mL of 0.1 M sodium phosphate buffer (pH 6.2), 0.1 mL of enzyme extract and 0.15 mL of deionized water in a total volume of 1 mL. All the above reagents, except D,L-glyceraldehyde, were incubated at 30 °C for 10 min; the substrate was then added to start the reaction, which was monitored for 5 min. Enzyme activity was calibrated by diluting the enzymatic solution in order to obtain an average reaction rate of 0.011 ± 0.0010 absorbance units/min for the sample.

ALR1 activity was determined at 37 °C in a reaction mixture containing 0.25 mL of 20 mM sodium D-glucuronate, 0.25 mL of 0.12 mM NADPH, 0.25 mL of dialyzed enzymatic solution and 0.25 mL of 0.1 M sodium phosphate buffer (pH 7.2) in a total volume of 1 mL. The enzyme activity was calibrated by diluting the dialyzed enzymatic solution in order to obtain an average reaction rate of 0.015 ± 0.0010 absorbance/min for the sample.

4.2.3. Enzymatic inhibition

The inhibitory activity of the newly synthesized compounds against ALR2 and ALR1 was assayed by adding 0.1 mL of the inhibitor solution to the reaction mixture described above. All the inhibitors were solubilized in water and the solubility was facilitated by adjustment to a favorable pH. After complete solution, the pH was readjusted to 7. To correct for the non-enzymatic oxidation of NADPH and for absorption by the compounds tested, a reference blank containing all the above assay components except the substrate was prepared. The inhibitory effect of the new derivatives was routinely estimated at a concentration of 100 μM. Those compounds found to be active were tested at additional concentrations between 10 μM and 10 nM. Epalrestat (100 μM–1 nM) was used as the reference standard. The determination of the IC_{50} values was performed by linear regression analysis of the log dose–response curve, which was generated using at least five concentrations of the inhibitor causing an inhibition between 20% and 80%. Results are expressed as means ± SEM of percentage inhibition values, obtained through two determinations carried out in triplicate.

4.2.4. Modeling studies

4.2.4.1. AD4 docking calculations. The new version of the docking program AutoDock (version 4, AD4) [23] as implemented through the graphical user interface called AutoDockTools (ADT), was used to dock **1f**, **1g**, **1j**, **3g** and **3h**. Such a program has been successfully used in studying the ligand–protein as well as the ligand–DNA interactions [24]. Ligand structures were built using the builder in the Maestro package of Schroedinger Suite 2007 and optimized using a version of MacroModel also included. The constructed compounds and the receptor structure were converted to AD4 format files using ADT generating automatically all other atom values. The docking area was centered around the enzyme active site. A set of grids of 60 Å × 60 Å × 60 Å with 0.375 Å spacing was calculated around the docking area for the ligand atom types using AutoGrid4. For each ligand, 100 separate docking calculations were performed. Each docking calculation consisted of 10 million energy evaluations using the Lamarckian genetic algorithm local search (GALS) method. The GALS method evaluates a population of possible docking solutions and propagates the most successful individuals from each generation into the subsequent generation of possible solutions. A low-frequency local search according to the method of Solis and Wets is applied to docking trials to ensure that the final solution represents a local minimum. All dockings described in this paper were performed with a population size of 250, and 300 rounds of Solis and Wets local search were applied with a probability of 0.06. A mutation rate of 0.02 and a crossover rate of 0.8 were used to generate new docking trials for subsequent generations, and the best individual from each generation was propagated over the next generation. The docking results from each of the 100 calculations were clustered on the basis of root-mean square deviation (rmsd) (solutions differing by less than 2.0 Å) between the Cartesian coordinates of the atoms and were ranked on the basis of free energy of binding (ΔGAD4). The top-ranked compounds were visually inspected for good chemical geometry. Since AD4 does not perform any structural optimization and energy minimization of the complexes found, a molecular mechanics/energy minimization (MM/EM) approach was applied to refine the AD4 output. The computational protocol applied consisted of the application of 100,000 steps of the Polak–Ribiére conjugate gradients (PRCG) or until the derivative convergence was 0.05 kJ/mol. All complexes pictures were rendered employing the UCSF Chimera software [25].

Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2012.02.045.

References

[1] (a) A.F. Amos, D.J. McCarty, P. Zimmet, Diabet. Med. 14 (1997) S7–S85; (b) P. Zimmet, K.G.M.M. Alberti, J. Shaw, Nature 4 (2001) 782–787.
[2] H. King, R.E. Aubert, W.H. Herman, Diabetes Care 21 (1998) 1414–1431.
[3] C.L. Triplitt, C.A. Reasner, W.L. Isley, in: R. Di Pirio, L. Talbert, G.C. Yee (Eds.), Pharmacotherapy: A Pathophysiologic Approach, McGrawHill, New York, 2005, p. 1361.
[4] J.A. Scott, G.L. King, Ann. N. Y. Acad. Sci. 1031 (2004) 204–213.
[5] M. Brownlee, Nature 414 (2001) 813–820.

[6] J.M. Jez, M.J. Bennett, B.P. Schlegel, M. Lewis, T.M. Penning, Biochem. J. 326 (1997) 625–636.
[7] D.L. Vander Jagt, N.S. Kolb, T.J. Vander Jagt, J. Chino, F.J. Marlinez, L.A. Hunsaker, R.E. Royer, Biochim. Biophys. Acta 1249 (1995) 117–126.
[8] A.M. Vincent, J.W. Russell, P. Low, E.L. Feldman, Endocr. Rev. 25 (2004) 612–628.
[9] (a) S.K. Srivastava, K.V. Ramana, A. Bhatnagar, Endocr. Rev. 26 (2005) 380–392;
(b) T.P. Degenhardt, S.R. Thorpe, J.W. Baynes, Cell. Mol. Biol. 44 (1998) 1139–1145.
[10] (a) S.K. Srivastava, U.C. Yadav, A.B. Reddy, A. Saxena, R. Tammali, M. Shoeb, N.H. Ansari, A. Bhatnagar, M.J. Petrash, S. Srivastava, K.V. Ramana, Chem. Biol. Interact. 191 (2011) 330–338;
(b) R.Tammali, A.B.Reddy, A.Saxena, P.G.Rychahou, M.B.Evers, S.Qiu, S.Awasthi, K.V.Ramana, S.K. Srivastava Carcinogenesis, (in press).
[11] (a) F. Da Settimo, G. Primofiore, C. La Motta, S. Sartini, S. Taliani, F. Simorini, A.M. Marini, A. Lavecchia, E. Novellino, E. Boldrini, J. Med. Chem. 48 (2005) 6897–6907;
(b) F. Da Settimo, G. Primofiore, A. Da Settimo, C. La Motta, F. Simorini, E. Novellino, G. Greco, A. Lavecchia, F. Boldrini, J. Med. Chem. 46 (2003) 1419–1428;
(c) P. Alexiou, K. Pegklidou, M. Chatzopoulou, I. Nicolaou, V.J. Demopoulos, Curr. Med. Chem. 16 (2009) 734–752;
(d) O. El-Kabbani, V. Carbone, C. Darmanin, M. Oka, A. Mitschler, A. Podjarny, C. Schulze-Briese, R.P.-T. Chung, J. Med. Chem. 48 (2005) 5536–5542;
(e) K.E. Schemmel, R.S. Padiyara, J.J. D'Souza, J. Diabet. Complications 24 (2010) 354–360.
[12] M. Cappiello, M. Voltarelli, I. Cecconi, P.G. Vilardo, M. Dal Monte, A. Del Corso, D.K. Wilson, F.A. Quiocho, J.M. Petrash, U. Mura, J. Biol. Chem. 271 (1996) 33539–33544.
[13] C.E. Grimshaw, C.J. Lai, Arch. Biochem. Biophys. 327 (1996) 89–97.
[14] S. Cosconati, L. Marinelli, C. La Motta, S. Sartini, F. Da Settimo, A.J. Olson, E. Novellino, J. Med. Chem. 52 (2009) 5578–5581.
[15] E.I. Howard, R. Sanishvili, R.E. Cachau, A. Mitschler, B. Chevrier, P. Barth, V. Lamour, M. Van Zandt, E. Sibley, C. Bon, D. Moras, T.R. Schneider, A. Joachimiak, A. Podjarny, Proteins 55 (2004) 792–804.
[16] H. Steuber, P. Czodrowski, C.A. Sotriffer, G. Klebe, J. Mol. Biol. 373 (2007) 1305–1320.
[17] (a) S.M. Dankwardt, D.B. Smith Jr., J.A. Porco, C.H. Nguyen, Synlett 7 (1997) 854–856;
(b) A. Scozzafava, C.T. Supuran, Eur. J. Med. Chem. 35 (2000) 299–307.
[18] C. La Motta, S. Sartini, S. Salerno, F. Simorini, S. Taliani, A.M. Marini, F. Da Settimo, L. Marinelli, V. Limongelli, E. Novellino, J. Med. Chem. 51 (2008) 3182–3193.
[19] (a) M. Schlitzer, M. Bohm, I. Sattler, H.-M. Dahse, Bioorg. Med. Chem. 8 (2000) 1991–2006;
(b) K. Kettler, J. Sakowski, J. Wiesner, R. Ortmann, H. Jomaa, M. Schlitzer, Pharmazie 60 (2005) 323–327;
(c) S.S. Kinderman, M.T. Wekking, Jan H. van Maarseveen, H.E. Schoemaker, H. Hiemstra, F.P.J.T. Rutjes, J. Org. Chem. 70 (2005) 5519–5527;
(d) T. Inoue, M. Ohmi, K. Kawamura, K. Ando, Y.Shishido PCT Int. Appl. WO 2010-JP3121. (e) F. Shi, M.K. Tse, S. Zhou, M.-M. Pohl, J. Radnik, S. Huebner, K. Jaehnisch, A. Brueckner, M. Beller, J. Am. Chem. Soc. 131 (2009) 1775–1779;
(f) M. Zhu, K. Fujita, R. Yamaguchi, Org. Lett. 12 (2010) 1336–1339;
(g) F. Shi, M.-K. Tse, X. Cui, D. Goerdes, D. Michalik, K. Thurow, Y. Deng, M. Beller, Ang. Chem. Int. Ed. 48 (2009) 5912–5915;
(h) M. Harmata, P. Zheng, C. Huang, M.G. Gomes, W. Ying, K.-O. Ranyanil, G. Balan, N.L. Calkins, J. Org. Chem. 72 (2007) 683–685;
(i) T. Kataoka, T. Iwama, T. Setta, A. Takagi, Synthesis 4 (1998) 423–426.
[20] P.J. DeChristopher, J.P. Adamek, G.D. Lyon, S.A. Klein, R.J. Baumgarten, J. Org. Chem. 39 (1974) 3525–3532.
[21] M.K. Ghorai, A. Kumar, D.P. Tiwari, J. Org. Chem. 75 (2010) 137–151.
[22] B. Nyasse, L. Grehn, U. Ragnarsson, H.L.S. Maia, L.S. Monteiro, L. Leito, J. Koppel, J. Chem. Soc. Perkin Trans. 1 (1995) 2025–2031.
[23] R. Huey, G.M. Morris, A.J. Olson, D.S. Goodsell, J. Comput. Chem. 28 (2007) 1145–1152.
[24] (a) D. Simoni, N. Gebbia, F.P. Invidiata, M. Eleopra, P. Marchetti, R. Rondanin, R. Baruchello, S. Provera, C. Marchioro, M. Tolomeo, L. Marinelli, V. Limongelli, E. Novellino, A. Kwaasi, J. Dunford, S. Buccheri, N. Caccamo, F. Dieli, J. Med. Chem. 51 (2008) 6800–6807;
(b) S. Cosconati, L. Marinelli, R. Trotta, A. Virno, L. Mayol, E. Novellino, A.J. Olson, A. Randazzo, J. Am. Chem. Soc. 45 (2009) 16336–16337.
[25] E.F. Pettersen, T.D. Goddard, C.C. Huang, G.S. Couch, D.M. Greenblatt, E.C. Meng, T.E. Ferrin, J. Comput. Chem. 25 (2004) 1605–1612.