Monatsh Chem (2012) 143:497–504
DOI 10.1007/s00706-011-0600-9

ORIGINAL PAPER

Synthesis, characterization, and hypoglycemic activity of 3-(arylsulfonyl)spiroimidazolidine-2,4-diones

Zafar Iqbal · Tashfeen Akhtar · Arthur D. Hendsbee · Jason D. Masuda · Shahid Hameed

Received: 12 May 2010 / Accepted: 15 July 2011 / Published online: 25 August 2011

Abstract Spiroimidazolidine-2,4-diones were prepared from methylcyclohexanones by the Bucherer–Bergs reaction. Synthesis of the target 3-(arylsulfonyl)spiroimidazolidine-2,4-diones was achieved by reaction of arylsulfonyl chlorides with corresponding spiroimidazolidine-2,4-diones. The synthesis was confirmed by spectroanalytical techniques and the crystal structure of 3-(4-methoxyphenylsulfonyl)-6-methyl-1,3-diazaspiro[4.5]decane-2,4-dione, and the purity was checked by GC–MS analysis. The in-vivo hypoglycemic potential of 6-methyl-, 7-methyl-, and 8-methyl-3-(4-methylphenylsulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione was investigated on male albino rats. The screened compounds were found to have excellent hypoglycemic activity. 6-Methyl-3-(4-methylphenylsulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione was found highly active, reducing the blood glucose level by 60.79% compared with 41.60% by the standard (glipizide) at a dose level of 100 mg/kg of the mice body weight. The 8-methyl isomer was also more potent than the standard, with 48.56% reduction in blood glucose level.

Z. Iqbal · S. Hameed (✉)
Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan
e-mail: shameed@qau.edu.pk; shahidhameed@daad-alumni.de

T. Akhtar
Department of Chemistry, Mirpur University of Science and Technology, Mirpur, Azad Kashmir, Pakistan

A. D. Hendsbee · J. D. Masuda
Department of Chemistry, Saint Mary's University, Halifax, NS B3H 3C3, Canada

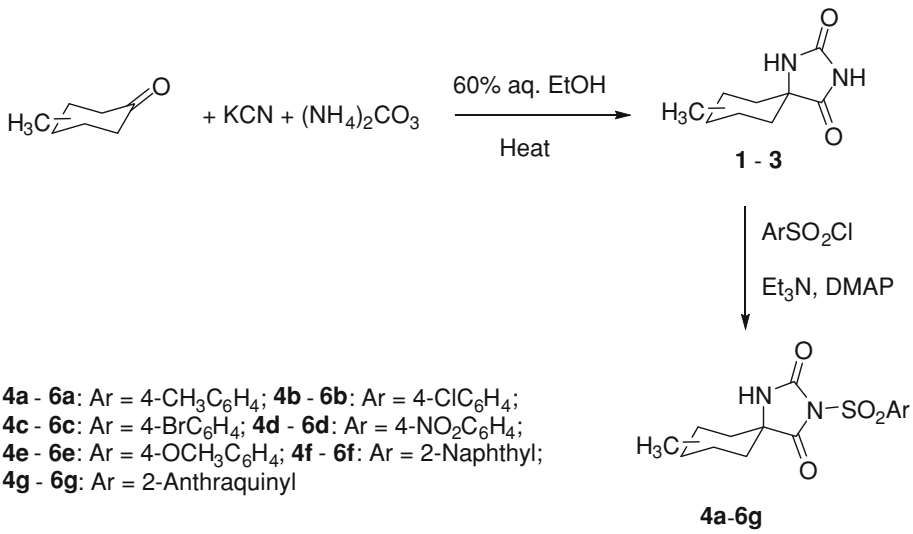
Keywords Antidiabetic · Spiro compounds · Sulfonyl cyclic ureas · Imidazolidine-2,4-diones · Rearrangement · Crystal structure

Introduction

Diabetes is one of the main causes of death at present, and being a chronic disease has played havoc especially with the people of South East Asia [1]. Approximately 5–10% of the world's population has been affected by this disease, 171 million people have been diagnosed to be diabetic [2] and by the end of 2010 this number is expected to approach 230 million [3]. In addition, a huge number of people is still unaware of their fatal disease [4]. Although a number of drugs and many herbal formulations are in use to cure the disease (Refs. [5–7] and references cited therein), there is still a rapid increase in the number of diabetic patients.

Imidazolidine-2,4-diones, which have a cyclic urea core, and spiroimidazolidine-2,4-diones reduce the complications associated with hyperglycemia [8]. The sulfonyl derivatives of cyclic ureas, on the other hand, are known to have enhanced antidiabetic activity [1, 9]. A combined approach of introducing the spiro and sulfonyl moieties into the imidazolidine-2,4-dione nucleus may result in a molecule of choice to treat both diabetes and its associated complications. Hypothesizing this, we planned the synthesis of *N*-(arylsulfonyl)spiroimidazolidine-2,4-diones (Scheme 1). The target molecules have all requirements suggested in pharmacophoric models for enhanced hypoglycemic activity [10] and minimal diabetic complications [11]. This approach is an extension of our previous work on the development of antidiabetic agents [12, 13] including arylsulfonylimidazolidine-2,4-diones and arylsulfonylbenzimidazolone derivatives.

Scheme 1



Results and discussion

Chemistry

Spiroimidazolidine-2,4-diones **1**–**3** were synthesized by the Bucherer–Bergs reaction [14, 15]. The synthesis was confirmed by modern spectroscopic techniques. The IR spectra of compounds **1**–**3** contained two strong absorption bands between 3,415 and 3,388 cm^{-1}, assigned to the N–H of the imide and amide groups. Absorption bands observed between 1,802 and 1,704 cm^{-1} indicated the presence of two carbonyl groups. In the ^1H NMR spectra, the N–H proton at position 3, being more acidic, resonated in the range $\delta = 10.56$–10.58 ppm whereas the second N–H proton appeared in the range 8.26–8.45 ppm. The elemental composition of compounds **1**–**3** was in good agreement to the values calculated for carbon, hydrogen, and nitrogen. It has already been reported from this laboratory that the nitrogen atom (position 1) in spiroimidazolidine-2,4-diones occupies the axial position whereas the carbonyl group is equatorial [16, 17].

The sulfonylation of spiroimidazolidine-2,4-diones **1**–**3** leading to 3-(arylsulfonyl)spiroimidazolidine-2,4-diones **4a**–**6d** was carried out by coupling with arylsulfonyl chlorides in the presence of triethylamine [18]. Formation of the products was indicated in the IR spectra by the disappearance of the NH absorption in the range 3,415–3,410 cm^{-1}. The absorption bands in the ranges 1,392–1,313 cm^{-1} and 1,191–1,155 cm^{-1} were assigned to anti-symmetric and symmetric sulfonamide (O=S=O) stretching, respectively. Synthesis of **4a**–**6g** was confirmed in the ^1H NMR spectra by the appearance of new signals in the aromatic region. The disappearance of the NH signal in the region $\delta = 10.56$–10.58 ppm established the sulfonylation at position 3 of the spiroimidazolidine-2,4-diones. Mass spectral analysis further confirmed the synthesis of compounds **4a**–**6g**. A low-intensity molecular ion peak was observed for all the compounds. The appearance of fragments for [M − SO_2Ar] confirmed the presence of the sulfonamide linkage in the synthesized molecules. The presence of halogens was confirmed by the appearance of corresponding [M + 2] peaks for chloro and bromo substituents. The base peak for all compounds was observed at $m/z = 95$ (except for compounds **4g**, **5g**, and **6g**) corresponding to cleavage of the arylsulfonyl part of the compounds. A common fragment at $m/z = 64$ corresponding to SO_2 was also observed for all the sulfonyl derivatives.

The synthesis of compounds **4a**–**6g** was further confirmed by single-crystal X-ray analysis of the structure of compound **4e**, which was found to crystallize in the monoclinic space group $P2_1/C$. The most significant structural feature is the intermolecular hydrogen bonding between the two imidazolidine-2,4-dione rings. More specifically, the carbonyl and N–H fragments of the rings interact, resulting in the formation of a hydrogen-bonded dimer with an N2–O4 distance of 2.844(2) Å. In addition, one of the S=O groups and the adjacent carbonyl are nearly planar with a torsion angle [O3–C8–S1–O1] of 179.4(2)° (Fig. 1).

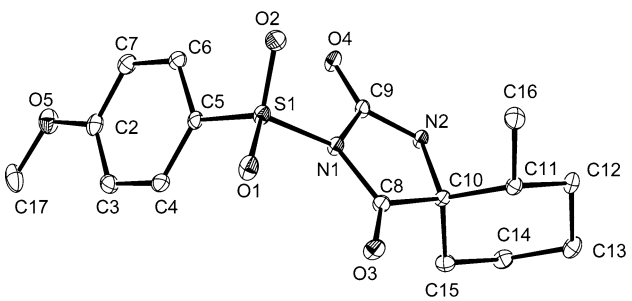


Fig. 1 Ortep diagram of compound **4e**. Hydrogen atoms have been removed for clarity

Table 1 Effect of 3-(arylsulfonyl)spiroimidazolidine-2,4-diones on blood glucose level in normal and alloxanized diabetic rats

Drug injected	Dose/mg kg^{-1}	Blood glucose level[a]/mg/100 cm^3					
		At zero h[b]	After 2 h	Reduction (after 2 h)	After 5 h	Reduction (after 5 h)	Decrease/%[c]
4a	100	329 ± 6	241 ± 9	88 ± 5	110 ± 7	219 ± 8	60.79
	50	330 ± 5	282 ± 7	48 ± 2	261 ± 3	69 ± 9	15.15
5a	100	565 ± 8	473 ± 9	92 ± 7	361 ± 6	203 ± 9	32.56
	50	453 ± 6	402 ± 6	51 ± 3	392 ± 8	61 ± 7	9.27
6a	100	383 ± 8	288 ± 4	95 ± 2	178 ± 2	205 ± 6	48.56
	50	387 ± 9	320 ± 12	67 ± 17	294 ± 14	93 ± 6	19.12
Glipizide	100	560 ± 8	363 ± 6	197 ± 4	308 ± 9	252 ± 6	41.60
Normal		121 ± 9	118 ± 7	3.0 ± 5	114 ± 6	7.0 ± 2	–
Diabetic control		580 ± 16	–	–	562 ± 5	19 ± 7	–

[a] The results are reported as mean ± standard deviation. Statistical evaluation was carried out using one-way analysis of variance (ANOVA), followed by Dunnett's *t* test, *P*-values < 0.05 were considered to be significant

[b] Blood glucose level just before administration of the drug

[c] Relative to alloxan-induced diabetic group

The attempted rearrangement of 3-(arylsulfonyl)spiroimidazolidine-2,4-diones **4a–6g** to the corresponding 1-(arylsulfonyl)spiroimidazolidine-2,4-diones in the presence of sodium hydride [1] met with failure, despite several attempts. The probable reason for this failure seems to be that steric crowding at position 1 prohibits the rearrangement. The N atom at position 1 in compounds **4a–6g** occupies an axial position as indicated by single-crystal X-ray structural analysis. The arylsulfonyl group after rearrangement will be exactly above the cyclohexyl ring, thereby creating steric crowding with the axial protons at position 7 and 9, thus prohibiting the rearrangement.

In-vivo antidiabetic activity

The hypoglycemic efficacy of compounds **4a**, **5a**, and **6a** was trialed on alloxanized diabetic male albino rats of the Sprague–Dawley strain (180–220 g; six to 8-weeks old) at dose levels of 50 and 100 mg/kg of the mice body weight. The blood glucose levels were measured 2 and 5 h after dose administration. All three screened compounds were highly active (Table 1); however, the activity was more profound at the dose level of 100 mg/kg. Glipizide, a classical drug belonging to the second generation of sulfonylurea compounds, was used as the standard drug under the same conditions and at a dose of 100 mg/kg. Excellent activity was observed for 6-methyl-3-(4-methylphenylsulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione (**4a**). Compound **4a** lowered the blood glucose level by 60.79% which has to be compared with blood glucose lowering of 41.60% by the standard glipizide at the same dose level. The potency of compound **6a** (48.56% reduction in serum glucose) was also higher than that of glipizide whereas compound **5a** was found to be moderately active with blood glucose lowering of 32.56%. However, the blood glucose lowering activity of the tested compounds was not remarkable at a dose of 50 mg/kg. Hypoglycemic activity testing of the other compounds is in progress. The liver function test (LFT) and other data are also being studied to examine the side-effect profile of the drugs; the results will be published elsewhere.

Experimental

Melting points were determined on a Stuart SMP3 melting-point apparatus. IR spectra were recorded on a Shimadzu model 270 Fourier-transform infrared spectrophotometer using an ATR facility. Only strong and the most significant peaks are listed. NMR spectra were acquired on a Bruker Avance 300 MHz NMR spectrometer and the signals calibrated with reference to the residual solvent signal. Mass spectra were recorded on a GC-6890 N; MS-5973 inert MSD; EI-70 eV instrument (Agilent Technologies). Elemental analyses were performed using a Leco CHNS-932 elemental analyzer; results agreed favorably with the calculated values. All the reactions were monitored by thin-layer chromatography on pre-coated silica gel 60 F_{254} plates (Merck, Germany). The compounds 4-methoxyphenylsulfonyl chloride, 4-bromophenylsulfonyl chloride, naphthalene-2-sulfonylchloride, and 4-nitrophenylsulfonyl chloride were purchased from Sigma–Aldrich. 3-Methylcyclohexanone, toluene-4-sulfonyl chloride, 4-chlorophenylsulfonyl chloride, and 4-dimethylaminopyridine were the products of Fluka. 2-Methylcyclohexanone was provided by Merck. Anthraquinone-2-sulfonyl chloride was prepared according to a procedure described in Ref. [19]. All solvents were distilled before use and dried whenever required, in accordance with standard procedures.

General method for synthesis of spiroimidazolidine-2,4-diones ***1–3*** *[20]*

Methylcyclohexanone (5.05 g, 45 mmol), 5.67 g KCN (87 mmol), and 16.77 g $(NH_4)_2CO_3$ (174 mmol) were added to 100 cm^3 50% ethanol in a round-bottomed flask equipped with an air condenser. The reaction mixture was heated with stirring in an oil bath at 55–60 °C for 14–16 h and then cooled to room temperature. The precipitated solid was filtered and washed with water. To obtain the maximum amount of product, the aqueous filtrate was acidified to pH 2–3 by adding 1 M HCl. The crude product was repeatedly recrystallized from 90% ethanol.

6-Methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**1**, $C_9H_{14}N_2O_2$)
Yield 83%; m.p.: 218 °C (Ref. [20]: 215.5–216 °C); $R_f = 0.56$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.65$ (d, 3H, $J = 6.6$ Hz, CH_3), 1.16–1.72 (m, 9H, cyclohex-H), 8.26 (bs, 1H, NH), 10.57 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.8$, 21.1, 25.5, 29.6, 34.7, 36.2, 66.3, 157.5, 178.8 ppm; IR (ATR): $\bar{\nu} = 3{,}415$, 3,388, 1,765, 1,705 cm^{-1}; MS (70 eV): $m/z = 182$ (M^+), 139, 113 (100), 96, 68, 54.

7-Methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**2**, $C_9H_{14}N_2O_2$)
Yield 81%; m.p.: 273 °C (Ref. [20]: 268.5–269 °C); $R_f = 0.52$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.85$ (d, 3H, $J = 6.6$ Hz, CH_3), 1.69–1.95 (m, 9H, cyclohex-H), 8.45 (bs, 1H, NH), 10.58 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.3$, 22.7, 27.5, 33.2, 33.7, 41.7, 63.3, 156.9, 178.9 ppm; IR (ATR): $\bar{\nu} = 3{,}415$, 3,388, 1,768, 1,704 cm^{-1}; MS (70 eV): $m/z = 182$ (M^+), 139, 113 (100), 96, 68, 54.

8-Methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**3**, $C_9H_{14}N_2O_2$)
Yield 80%; m.p.: 278 °C (Ref. [20]: 279–280 °C); $R_f = 0.55$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.87$ (d, 3H, $J = 6.3$ Hz, CH_3), 1.13–1.66 (m, 9H, cyclohex-H), 8.44 (bs, 1H, NH), 10.56 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 22.6$, 29.6, 31.2, 33.6, 62.4, 156.8, 179.2 ppm; IR (ATR): $\bar{\nu} = 3{,}415$, 3,388, 1,802, 1,733 cm^{-1}; MS (70 eV): $m/z = 182$ (M^+), 139, 113 (100), 96, 68, 54.

General method for synthesis of 3-(arylsulfonyl) spiroimidazolidine-2,4-diones ***4a–6g***

Arylsulfonyl chloride (5.8 mmol) was added dropwise with stirring to a mixture of spiroimidazolidine-2,4-dione (4.8 mmol), triethylamine (4.8 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in a suitable amount of dichloromethane at room temperature. Completion of the reaction was monitored by TLC. After completion ($\sim$15 h), the reaction mixture was neutralized with 1 M HCl and extracted with dichloromethane (4×25 cm^3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting solid was purified by recrystallization from ethanol–water.

6-Methyl-3-(4-methylphenylsulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione (**4a**, $C_{16}H_{20}N_2O_4S$)
Yield 56%; m.p.: 152 °C; $R_f = 0.78$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.40$ (d, 3H, $J = 6.3$ Hz, CH_3), 1.11–1.76 (m, 9H, cyclohex-H), 2.41 (s, 3H, Ar-CH_3), 7.49 (d, 2H, $J = 8.1$ Hz, Ar–H), 7.87 (d, 2H, $J = 8.4$ Hz, Ar–H), 9.17 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.0$, 21.8, 27.6, 33.5, 33.7, 41.8, 62.6, 128.5, 129.9, 135.0, 146.2, 150.6, 172.6 ppm; IR (ATR): $\bar{\nu} = 3{,}380$, 3,012, 1,821, 1,742, 1,313, 1,189 cm^{-1}; MS (70 eV): $m/z = 334$ (M^+), 179, 155, 91 (100), 65.

3-(4-Chlorophenylsulfonyl)-6-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**4b**, $C_{15}H_{17}ClN_2O_4S$)
Yield 62%; m.p.: 236 °C; $R_f = 0.75$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.43$ (d, 3H, $J = 6.6$ Hz, CH_3), 1.12–1.77 (m, 9H, cyclohex-H), 7.80 (d, 2H, $J = 8.7$ Hz, Ar–H), 8.09 (d, 2H, $J = 8.7$ Hz, Ar–H), 9.27 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.4$, 20.6, 25.0, 29.3, 34.3, 37.2, 65.7, 130.1, 130.4, 136.8, 140.7, 152.5, 172.9 ppm; IR (ATR): $\bar{\nu} = 3{,}382$, 3,009, 1,804, 1,745, 1,390, 1,377, 1,181 cm^{-1}; MS (70 eV): $m/z = 358$ (M + 2), 356 (M^+), 292, 288, 181, 175, 111, 95 (100).

3-(4-Bromophenylsulfonyl)-6-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**4c**, $C_{15}H_{17}BrN_2O_4S$)
Yield 53%; m.p.: 218 °C; $R_f = 0.74$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.44$ (d, 3H, $J = 6.0$ Hz, CH_3), 1.25–1.77 (m, 9H, cyclohex-H), 7.93 (m, 2H, Ar–H), 7.93 (m, 2H, Ar–H), 9.25 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.4$, 20.6, 25.0, 29.3, 34.4, 37.2, 65.7, 129.9, 130.0, 133.3, 137.3, 150.5, 172.8 ppm; IR (ATR): $\bar{\nu} = 3{,}383$, 3,013, 1,810, 1,748, 1,398, 1,376, 1,159 cm^{-1}; MS (70 eV): $m/z = 402$ (M + 2), 400 (M^+), 336, 333, 219, 181, 155, 95 (100).

6-Methyl-3-(4-nitrophenylsulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione (**4d**, $C_{15}H_{17}N_3O_6S$)
Yield 49%; m.p.: 223 °C; $R_f = 0.58$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.46$ (d, 1H, $J = 6.0$ Hz, CH_3), 1.11–1.81 (m, 9H, cyclohex-H), 7.50 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.85 (d, 2H,

$J = 8.7$ Hz, Ar–H), 9.36 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.5$, 20.5, 25.3, 29.3, 34.4, 37.3, 65.8, 129.4, 130.3, 130.9, 137.7, 152.4, 172.7 ppm; IR (ATR): $\bar{\nu} = 3{,}382$, 3,014, 1,776, 1,714, 1,356, 1,158 cm^{-1}; MS (70 eV): $m/z = 367$ (M^+), 351, 337, 303, 181, 95 (100).

3-(4-Methoxyphenylsulfonyl)-6-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**4e**, $C_{16}H_{20}N_2O_5S$)
Yield 43%; m.p.: 234 °C; $R_f = 0.$ 77 (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.40$ (d, 3H, $J = 6.6$ Hz, CH_3), 1.10–1.75 (m, 9H, cyclohex-H), 3.86 (s, 3H, OCH_3), 7.20 (m, 2H, Ar–H), 7.92 (m, 2H, Ar–H), 9.17 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.4$, 20.6, 25.0, 29.3, 34.5, 37.2, 56.5, 65.5, 115.4, 129.3, 130.6, 150.9, 164.7, 173.0 ppm; IR (ATR): $\bar{\nu} = 3{,}381$, 3,023, 1,803, 1,735, 1,379, 1,191 cm^{-1}; MS (70 eV): $m/z = 352$ (M^+), 288, 171, 138, 107 (100), 96, 95.

6-Methyl-3-(2-naphthalenylsulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione (**4f**, $C_{19}H_{20}N_2O_4S$)
Yield 57%; m.p.: 245 °C; $R_f = 0.69$ (petroleum ether–ethyl acetate; 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.81$ (d, 3H, $J = 6.3$ Hz, CH_3), 0.88–1.61 (m, 9H, cyclohex-H), 7.67–8.74 (m, 7H, Ar–H), 9.27 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.5$, 20.6, 25.0, 29.2, 34.5, 37.1, 65.7, 122.1, 128.5, 128.6, 130.2, 130.3, 130.4, 130.6, 131.8, 135.0, 135.6, 150.7, 173.1 ppm; IR (ATR): $\bar{\nu} = 3{,}385$, 3,021, 1,804, 1,731, 1,380, 1,177 cm^{-1}; MS (70 eV): $m/z = 372$ (M^+), 308, 304, 265, 181, 138, 127, 96, 95 (100).

3-[(9,10-Dihydro-9,10-dioxo-2-anthracenyl)sulfonyl]-6-methyl-1,3-diazaspiro[4.5]decane-2,4-dione
(**4g**, $C_{23}H_{22}N_2O_6S$)
Yield 55%; m.p.: 238 °C; $R_f = 0.75$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.83$ (d, 3H, $J = 6.3$ Hz, CH_3), 0.81–1.72 (m, 9H, cyclohex-H), 7.94–8.40 (m, 7H, Ar–H), 9.31 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.1$, 21.2, 25.2, 29.6, 35.0, 37.3, 65.9, 126.4, 127.4, 128.7, 133.1, 133.2, 133.5, 134.0, 135.2, 137.1, 142.2, 151.1, 173.5, 180.3, 181.7 ppm; IR (ATR): $\bar{\nu} = 3{,}384$, 3,012, 1,768, 1,714, 1,378, 1,188 cm^{-1}; MS (70 eV): $m/z = 452$ (M^+), 271, 208, 207 (100), 180, 179, 151.

7-Methyl-3-(4-methylphenylsulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione (**5a**, $C_{16}H_{20}N_2O_4S$)
Yield 54%; m.p.: 251 °C; $R_f = 0.73$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.82$ (d, 3H, $J = 6.3$ Hz, CH_3), 0.83–1.62 (m, 9H, cyclohex-H), 2.42 (s, 3H, Ar-CH_3), 7.49 (d, 2H, $J = 8.1$ Hz, Ar–H), 7.87 (d, 2H, $J = 8.4$ Hz, Ar–H), 9.34 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.9$, 27.2, 33.2, 33.3, 41.4, 62.5, 150.1, 172.7 ppm; IR (ATR): $\bar{\nu} = 3{,}385$, 3,019, 1,805, 1,731, 1,388, 1,186 cm^{-1}; MS (70 eV): $m/z = 334$ (M^+), 179, 155, 95 (100), 65.

3-(4-Chlorophenylsulfonyl)-7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**5b**, $C_{15}H_{17}ClN_2O_4S$)
Yield 54%; m.p.: 251 °C; $R_f = 0.73$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.83$ (d, 3H, $J = 6.0$ Hz, CH_3), 1.24–1.61 (m, 9H, cyclohex-H), 7.78 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.99 (d, 2H, $J = 8.7$ Hz, Ar–H), 9.39 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.9$, 22.4, 27.2, 33.1, 33.3, 41.3, 62.8, 130.3, 136.8, 140.6, 150.0, 172.6 ppm; IR (ATR): $\bar{\nu} = 3{,}384$, 3,023, 1,811, 1,732, 1,385, 1,184 cm^{-1}; MS (70 eV): $m/z = 358$ (M + 2), 356 (M^+), 292, 288, 181, 175, 111, 95 (100).

3-(4-Bromophenylsulfonyl)-7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**5c**, $C_{15}H_{17}BrN_2O_4S$)
Yield 60%; m.p.: 216 °C; $R_f = 0.73$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.83$ (d, 3H, $J = 6.0$ Hz, CH_3), 1.69–1.95 (m, 9H, cyclohex-H), 7.92 (m, 4H, Ar–H), 9.41 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.9$, 22.4, 27.2, 33.1, 33.3, 41.3, 62.8, 129.8, 130.2, 133.3, 137.2, 150.0, 172.6 ppm; IR (ATR): $\bar{\nu} = 3{,}384$, 3,010, 1,811, 1,731, 1,389, 1,178 cm^{-1}; MS (70 eV): $m/z = 402$ (M + 2), 400 (M^+), 336, 331, 219, 155, 181, 95 (100).

7-Methyl-3-(4-nitrophenylsulfonyl)-1,3-diazaspiro[4.5]decane-2,4-dione (**5d**, $C_{15}H_{17}N_3O_6S$)
Yield 56%; m.p.: 168 °C; $R_f = 0.71$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.83$ (d, 3H, $J = 6.0$ Hz, CH_3), 1.25–1.62 (m, 9H, cyclohex-H), 7.50 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.85 (d, 2H, $J = 8.7$ Hz, Ar–H), 9.43 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 15.4$, 20.5, 25.2, 29.4, 34.5, 37.3, 65.8, 129.4, 130.5, 130.8, 137.6, 152.5, 172.5 ppm; IR (ATR): $\bar{\nu} = 3{,}383$, 3,021, 1,811, 1,731, 1,376, 1,188, 1,028 cm^{-1}; MS (70 eV): $m/z = 367$ (M^+), 351, 337, 303, 181, 95 (100).

3-(4-Methoxyphenylsulfonyl)-7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**5e**, $C_{16}H_{20}N_2O_5S$)
Yield 53%; m.p.: 198 °C; $R_f = 0.72$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.83$ (d, 3H, $J = 6.3$ Hz, CH_3), 1.02–1.61 (m, 9H, cyclohex-H), 3.24 (s, 3H, OCH_3), 7.20 (m, 2H, Ar–H), 7.92 (m, 2H, Ar–H), 9.31 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 3.2$, 20.0, 27.8, 33.3, 42.2, 56.4, 62.5, 115.3, 129.4, 130.7, 150.3, 164.6, 172.7 ppm; IR (ATR): $\bar{\nu} = 3{,}386$, 3,023, 1,803, 1,731, 1,388, 1,180 cm^{-1}; MS (70 eV): $m/z = 352$ (M^+), 288, 171, 107 (100), 138, 96, 95 (100).

7-Methyl-3-(2-naphthalenylsulfonyl)-1,3-diazaspiro-[4.5]decane-2,4-dione (**5f**, $C_{19}H_{20}N_2O_4S$)
Yield 67%; m.p.: 166 °C; $R_f = 0.68$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.43$ (d, 3H, $J = 6.6$ Hz, CH_3), 1.12–1.77 (m, 9H, cyclohex-H), 7.67–8.74 (m, 7H, Ar–H), 9.36 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.9$, 22.4, 27.2, 33.3, 33.7, 41.4, 62.7, 126.2, 122.3, 128.5, 129.5, 130.3, 130.4, 130.5, 131.8, 135.1, 135.7, 150.1, 170.8 ppm; IR (ATR): $\bar{\nu} = 3{,}382$, 3,035, 1,808, 1,731, 1,362, 1,155 cm^{-1}; MS (70 eV): $m/z = 372$ (M^+), 308, 304, 265, 181, 138, 127, 96 (100).

3-[(9,10-Dihydro-9,10-dioxo-2-anthracenyl)sulfonyl]-7-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**5g**, $C_{23}H_{22}N_2O_6S$)
Yield 55%; m.p.: 238 °C; $R_f = 0.75$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.81$–1.72 (m, 9H, cyclohex-H), 0.83 (d, 3H, $J = 6.3$ Hz, CH_3), 7.97–8.56 (m, 7H, Ar–H), 9.31 (bs,1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.2$, 22.6, 27.7, 33.5, 34.0, 41.6, 62.9, 126.6, 127.5, 128.9, 133.2, 133.3, 133.4, 133.9, 134.2, 135.4, 137.4, 142.6, 150.4, 171.3, 181.3, 181.6 ppm; IR (ATR): $\bar{\nu} = 3{,}383$, 3,012, 1,768, 1,714, 1,378, 1,188 cm^{-1}; MS (70 eV): $m/z = 452$ (M^+), 271, 208, 207 (100), 180, 179, 151.

8-Methyl-3-(4-methylphenylsulfonyl)-1,3-diazaspiro-[4.5]decane-2,4-dione (**6a**, $C_{16}H_{20}N_2O_4S$)
Yield 64%; m.p.: 175 °C; $R_f = 0.67$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.82$ (d, 3H, $J = 6.3$ Hz, CH_3), 1.05–1.63 (m, 9H, cyclohex-H), 2.54 (s, 3H, Ar-CH_3), 7.49 (d, 2H, $J = 8.1$ Hz, Ar–H), 7.87 (d, 2H, $J = 8.4$ Hz, Ar–H), 9.34 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.8$, 22.4, 23.7, 27.6, 41.4, 66.5, 128.5, 129.9, 135.0, 146.2, 151.6, 172.7 ppm; IR (ATR): $\bar{\nu} = 3{,}381$, 3,085, 1,795, 1,731, 1,374, 1,175, 1,070 cm^{-1}; MS (70 eV): $m/z = 334$ (M^+), 179, 155, 95 (100), 65.

3-(4-Chlorophenylsulfonyl)-8-methyl-1,3-diazaspiro-[4.5]decane-2,4-dione (**6b**, $C_{15}H_{17}ClN_2O_4S$) [18]
Yield 54%; m.p.: 197 °C; $R_f = 0.66$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.83$ (d, 3H, $J = 6.0$ Hz, CH_3), 1.13–1.62 (m, 9H, cyclohex-H), 7.78 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.99 (d, 2H, $J = 8.7$ Hz, Ar–H), 9.39 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 22.4$, 23.7, 27.6, 41.3, 62.8, 128.5, 129.9, 135.0, 146.2, 150.0, 172.6 ppm; IR (ATR): $\bar{\nu} = 3{,}385$, 3,100, 1,805, 1,739, 1,392, 1,173, 1,030 cm^{-1}; MS (70 eV): $m/z = 358$ (M + 2), 356 (M^+), 292, 288, 181, 175, 111, 95 (100).

3-(4-Bromophenylsulfonyl)-8-methyl-1,3-diazaspiro-[4.5]decane-2,4-dione (**6c**, $C_{15}H_{17}BrN_2O_4S$) [21]
Yield 50%; m.p.: 178 °C; $R_f = 0.69$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.10$ (d, 3H, $J = 6.0$ Hz, CH_3), 1.12–1.63 (m, 9H, cyclohex-H), 7.91 (m, 4H, Ar–H), 9.41 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 22.4$, 29.0, 30.9, 33.5, 62.0, 129.8, 130.2, 133.3, 137.2, 149.9, 172.9 ppm; IR (ATR): $\bar{\nu} = 3{,}384$, 3,080, 1,798, 1,737, 1,342, 1,179, 1,030 cm^{-1}; MS (70 eV): $m/z = 402$ (M + 2), 400 (M^+), 336, 333, 219, 181, 155, 95 (100).

3-(4-Nitrophenylsulfonyl)-8-methyl-1,3-diazaspiro-[4.5]decane-2,4-dione (**6d**, $C_{15}H_{17}N_3O_6S$)
Yield 48%; m.p.: 191 °C; $R_f = 0.74$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.84$ (d, 3H, $J = 6.0$ Hz, CH_3), 1.11–1.69 (m, 9H, cyclohex-H), 7.51 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.85 (d, 2H, $J = 8.7$ Hz, Ar–H), 9.42 (bs, 1H, NH) ppm; ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 22.4$, 25.3, 29.3, 37.3, 65.8, 129.4, 130.3, 130.9, 137.7, 152.4, 172.7 ppm; IR (ATR): $\bar{\nu} = 3{,}385$, 3,031, 1,776, 1,714, 1,358, 1,145, 1,028 cm^{-1}; MS (70 eV): $m/z = 367$ (M^+), 351, 337, 303, 181, 95 (100).

3-(4-Methoxyphenylsulfonyl)-8-methyl-1,3-diazaspiro-[4.5]decane-2,4-dione (**6e**, $C_{16}H_{20}N_2O_5S$)
Yield 59%; m.p.: 208 °C; $R_f = 0.71$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.83$ (d, 3H, $J = 6.3$ Hz, CH_3), 1.02–1.62 (m, 9H, cyclohex-H), 3.24 (s, 3H, OCH_3), 7.20 (m, 2H, Ar–H), 7.92 (m, 2H, Ar–H), 9.31 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 22.4$, 28.8, 30.8, 33.2, 56.4, 62.4, 115.3, 129.7, 130.7, 150.3, 164.7, 172.7 ppm; IR (ATR): $\bar{\nu} = 3{,}383$, 3,053, 1,801, 1,728 cm^{-1}; MS (70 eV): $m/z = 352$ (M^+), 288, 171, 107 138, 96, 95 (100).

8-Methyl-3-(2-naphthalenylsulfonyl)-1,3-diazaspiro-[4.5]decane-2,4-dione (**6f**, $C_{19}H_{20}N_2O_4S$)
Yield 65%; m.p.: 203 °C; $R_f = 0.63$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.81$ (d, 3H, $J = 6.3$ Hz, CH_3), 0.87–1.68 (m, 9H, cyclohex-H), 7.70–8.73 (m, 7H, Ar–H), 9.34 (bs,1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 22.4$, 29.0, 30.9, 33.6, 61.9, 122.3, 128.4, 128.5, 130.3, 130.4, 130.5, 131.8, 135.1, 135.6, 150.1, 173.1 ppm; IR (ATR): $\bar{\nu} = 3{,}384$, 3,105, 1,802, 1,729 cm^{-1}; MS (70 eV): $m/z = 372$ (M^+), 308, 304, 265, 181, 138, 127, 95 (100).

3-[(9,10-Dihydro-9,10-dioxo-2-anthracenyl)sulfonyl]-8-methyl-1,3-diazaspiro[4.5]decane-2,4-dione (**6g**, $C_{23}H_{22}N_2O_6S$)
Yield 68%; m.p.: 219 °C; $R_f = 0.71$ (petroleum ether–ethyl acetate 6:4); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.81$–1.72 (m, 9H, cyclohex-H), 0.83 (d, 3H,

$J = 6.3$ Hz, CH_3), 7.84–8.36 (m, 7H, Ar–H), 9.31 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 22.6$, 29.2, 31.2, 33.8, 62.1, 126.6, 127.5, 128.9, 133.2, 133.3, 133.4, 133.6, 134.2, 135.4, 137.5, 142.7, 150.2 173.3, 181.4, 181.7 ppm; IR (ATR): $\bar{\nu} = 3{,}383$, 3,105, 1,802, 1,729 cm^{-1}; MS (70 eV): $m/z = 452$ (M^+), 271, 208, 207 (100), 180, 179, 151.

X-ray crystallography

Crystals of **4e** were grown by the vapor diffusion method. The compound was dissolved in a small volume of ethanol in a 50 cm^3 beaker. This beaker was half dipped in petroleum ether contained in a 500 cm^3 beaker. Finally, the 500 cm^3 beaker was covered with aluminium foil. The crystals so formed were filtered. Single crystals were mounted in thin-walled capillaries. Data were collected using the Bruker APEX2 software package [22] on a Siemens diffractometer equipped with an APEXII CCD detector, a graphite monochromator, and Mo-Kα radiation ($\lambda = 0.71073$ Å) source. A hemisphere of data was collected in 1,664 frames with 40 s exposure times. Data processing and absorption correction were performed by use of the APEX2 software package [22, 23]. The structure was solved by use of direct methods and all non-H atoms were refined anisotropically. Hydrogen atoms were placed in the calculated positions by use of an appropriate riding model and coupled isotropic temperature factors. The thermal ellipsoid diagram (30% probability level) was produced using Ortep-3 for Windows [24] (Table 2).

CCDC 776494 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Biological assay

The in-vivo hypoglycemic activity of the synthesized 3-(arylsulfonyl)spiroimidazolidine-2,4-diones was determined by use of a standard procedure [25].

Pharmacological methods

To examine the efficacy of the synthesized arylsulfonylspiroimidazolidine-2,4-diones as hypoglycemic agents, six to eight-week-old albino rats were purchased from National Institute of Health (NIH), Islamabad, Pakistan. The animals were housed in cages with 12-h light/dark cycles. Adult fasted male rats of the Sprague–Dawley strain (180–220 g) were made diabetic by intra-abdominal injection of 225 mg/kg alloxan monohydrate [26] freshly dissolved in distilled water. Three days later, by use of an Accu-check blood glucose analyzer, the blood glucose level of each rat was tested. Rats having blood glucose levels above 300 mg/100 cm^3 were selected for further experiments. The diabetic rats were segregated into groups of six rats each. Control blood samples were collected from the tail vein by making snip with a scalpel or sharp scissors. In order to compare glucose-lowering potential, the synthesized compounds were administered orally at doses of 50 mg/kg and 100 mg/kg of the mice body weight and the standard drug was administered at a dose of 100 mg/kg.

Blood samples were obtained for glucose assay 2 h and 5 h after compound administration. An appropriate vehicle control (DMSO) was also run. One group of diabetic rats was left intact (untreated diabetic) for comparison. After six days of treatment the mice were subjected to anesthesia with diethyl ether and blood samples were collected by cardiac puncture to conduct the liver function test (LFT) and to obtain other data to examine the side-effect profile of the drugs. The results are reported as mean ± standard deviation, $n = 6$ in each group.

Table 2 Crystal and structure refinement data for compound **4e**

Formula	$C_{16}H_{20}N_2O_5S$
Formula weight	352.40
Crystal size/mm^3	0.450 × 0.398 × 0.383
Space group	$P2(1)/c$
a/Å	7.5928(6)
b/Å	12.4801(10)
c/Å	17.7627(15)
β/°	99.3390(10)
V/$Å^3$	1660.9(2)
Z	4
D_{calc}/g cm^{-3}	1.409
M/mm^{-1}	0.224
$F(000)$	744
θ for data collection	2.32–24.99°
Total number of reflections	10,661
No. of unique reflections	2,918
R_1 ($I > 2\sigma(I)$)[a]	0.0414
R_w (all data)[b]	0.0630

[a] $R = \sum(|F_o| - |F_c|)|/\sum|F_o|$

[b] $R_w = \left[\sum w(F_o^2 - F_c^2)^2/\sum(F_o)^4\right]^{1/2}$ where $w = 1/[\sigma^2(F_o^2) + (0.0324 \times P)^2 + 0.6970 \times P]$ where $P = (F_o^2 + 2F_c^2)/3$

References

1. Kashif MK, Ahmad I, Hameed S (2008) Arkivoc xvi:311
2. Wild S, Roglic G, Green A, Sicree R, King H (2004) Diabetes Care 27:1047
3. Hamdan II, Afifi FU (2004) J Ethnopharmacol 93:117
4. Zhang Q, Tang N, Schepmoes AA, Phillips LS, Smith RD, Metz TO (2008) J Proteome Res 7:2025

5. Phung OJ, Scholle JM, Talwar M, Coleman CI (2010) J Am Med Assoc 303:1410
6. Waqar MA, Aijaz S, Shaukat S, Waqar A (2009) J Chem Soc Pak 31:677
7. Shaukat S, Waqar A, Waqar MA (2009) J Chem Soc Pak 31:480 and references cited therein
8. Ono H, Nozawa Y, Hayano S (1982) Nippon Ganka Gakkai Zasshi 86:1343
9. Varma SD, Kinoshita JH (1976) Biochem Pharmacol 25:2505
10. Murcia-Soler M, Pérez-Giménez F, Nalda-Molina R, Salabert-Salvador MT, García-March FJ, Cercós-del-Pozo RA, Garrigues TM (2001) J Chem Inf Comput Sci 41:1345
11. Pandeya SN, Raja AS, Stables JP (2002) J Pharm Pharmaceut Sci 5:266
12. Kashif MK, Hussain A, Rauf MK, Ebihara M, Hameed S (2008) Acta Cryst E64:o444
13. Ahmad I, Hameed S, Duddeck H, Lenzen S, Rustenbeck I, Ahmad R (2002) Z Naturforsch 57B:349
14. Mahmoodi NO, Khodaee Z (2007) Arkivoc iii:29
15. Brimelow HC, Carrington HC, Vasey CH, Waring WS (1962) J Chem Soc 2789
16. Gauthier TJ, Yokum TS, Morales GA, McLaughlin ML, Liu YH (1997) Acta Cryst C53:1659
17. Kashif MK, Rauf MK, Bolte M, Hameed S (2009) Acta Cryst E65:o1893
18. Meanwell NA, Sing YS, Gao J, Wong HS, Gao Q, Denis R, Laurent S, Balasubramanian N (1995) J Org Chem 60:1565
19. Feng F, Uno B, Goto M, Zhang Z, An D (2002) Talanta 57:481
20. Henze HR, Speer RJ (1942) J Am Chem Soc 64:522
21. Kashif MK, Rauf MK, Bolte M, Hameed S (2009) Acta Cryst E65:o1892
22. APEX2 Ver. 2008.5 (2008) Bruker AXS, Inc, Madison, Wisconsin, USA
23. Sheldrick GM (2008) Acta Cryst A64:112
24. Farrugia LJ (1997) J Appl Cryst 30:565
25. Brown GR, Foubister AJ (1984) J Med Chem 27:79
26. Shukla R, Barve V, Padhye S, Bhonde R (2004) Bioorg Med Chem Lett 14:4961