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Synthesis and Vasodilator Effects of 3- and 7-Sulfonylurea-1,2,4-Benzothiadiazin-1,1-Dioxides on Rat Aorta

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Abstract—A series of substituted-1,2,4-benzothiadiazin-1,1-dioxide derivatives was designed and synthesized as potassium channel modulators. Various sulfonylurea moieties were introduced on positions 3 and 7 of the heterocycle without, or by means of, methylene and phenyl spacers. On rat aortic rings, several compounds displayed vasodilating activities, especially compound **24**, which was more active than cromakalim and diazoxide at low doses (0.1 μM) and more active than diazoxide between 1 and 10 μM.

Introduction

The pharmacology of potassium channel openers has made great strides during the last decade. This soaring is due, in part, to the involvement of potassium channels in several diseases affecting many tissues such as smooth muscle, heart and central nervous system, in part, to the preparation of numerous compounds activating or blocking these channels and, finally, to the setting up of electrophysiological methods measuring their activities.[1–4] Potassium channel openers represent a chemically diverse and structurally unrelated group of compounds which include nicorandil, cromakalim, pinacidil, RP49356, diazoxide and minoxidil sulfate (Fig. 1).[5–22]

We have focused our interest firstly on diazoxide, a 1,2,4-benzothiadiazin-1,1-dioxide known as an ATP-dependent potassium channel opener, which is also a vasodilator, an antidiuretic and a hyperglycemic agent,[2–14] and secondly on sulfonylureas, blockers of the same channels with antidiabetic properties.[22,23] Recently and during the course of our research, a pharmacophore model in this class of compounds possessing four distinct areas was described.[24] This model which is mainly based on the skeleton of cromakalim, was subsequently used to design new active molecules. To our knowledge, the introduction of sulfonylurea moieties on the 1,2,4-benzothiadiazin-1,1-dioxide skeleton has never been attempted. So, it seemed interesting to synthesize derivatives of this heterocycle, the positions 3 and 7 of which will be substituted directly or indirectly (through methylene and phenyl spacers) by sulfonylurea moieties, and to study the effects of these compounds on rat aorta. It would be hypothesized that this modification of a non-specific ATP-dependent potassium channel opener (diazoxide) could generate a novel class of compounds exhibiting either agonist or antagonist properties against these channels (Fig. 2). Furthermore, these compounds could be specific for K^+/ATP channels of pancreas versus those of vascular smooth muscles. This paper reports the synthesis and evaluation of relaxing effects of compounds on precontracted rat aorta rings by 1 μM of noradrenaline and

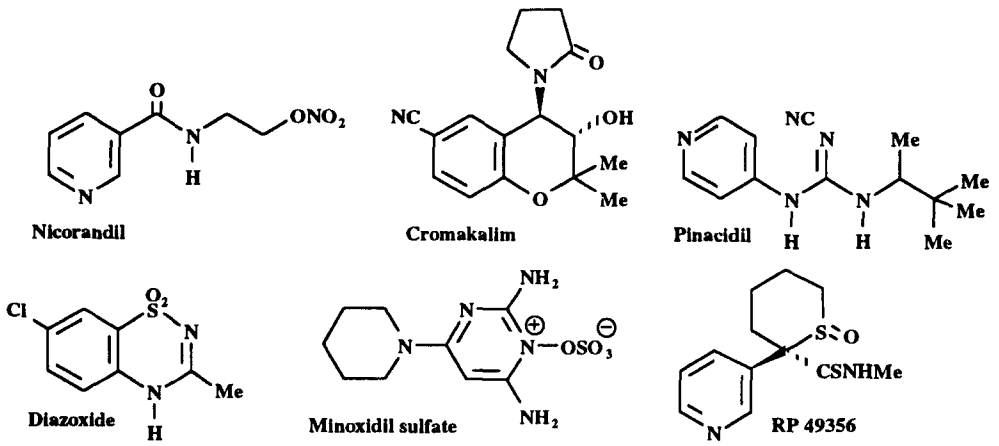


Figure 1. Some representative potassium channel activators.

inhibition of these effects by 1 μM of glibenclamide. We have used as reference for our compounds, cromakalim and diazoxide.

Chemistry

Our strategy for the synthesis of target compounds (Fig. 2) was the construction of the 1,2,4-benzothiadiazin-1,1-dioxide skeleton followed by the attachment of the sulfonylurea moieties in the last stage. Syntheses are summarized in Schemes 1–5. Compound **2** was readily obtained from the commercially available sulfonamide **1**. The former substance was reacted with benzenesulfonyl chloride and pyridine, leading to a zwitterionic compound **3**, which was hydrolyzed by aqueous sodium hydroxide to afford **4** according to a previously described method.[25] Compound **4** was reacted with an arylsulfonyl isocyanate in nitromethane (method A) to give **6a** and **6b**. An alternative method to prepare these later compounds, was the indirect linkage of the sulfonylurea moiety to the amino group of **4** (method B). Indeed, the acylation of **4** by trichloroacetamide in toluene gave the amide **5**, which reacted with an appropriate sulfonamide sodium salt in DMSO, and led to **6a** and **6b** with yields similar to those obtained by method A (Scheme 1).

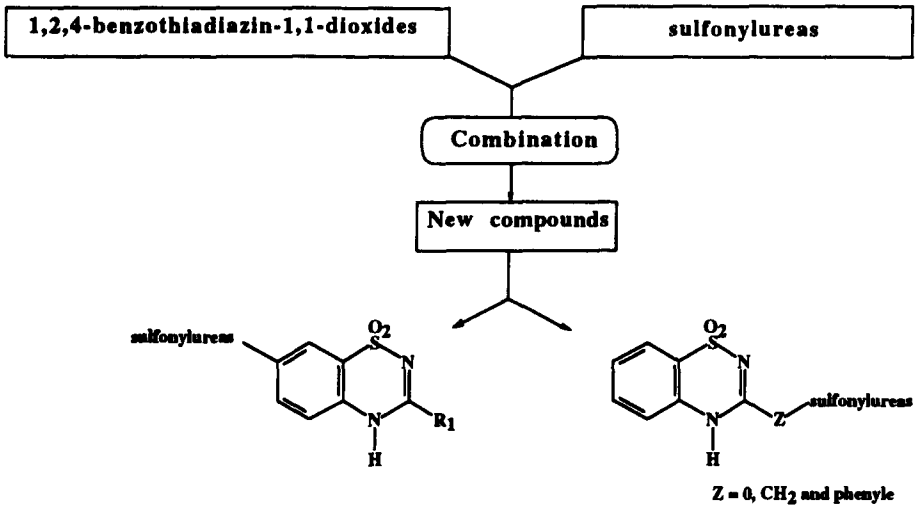
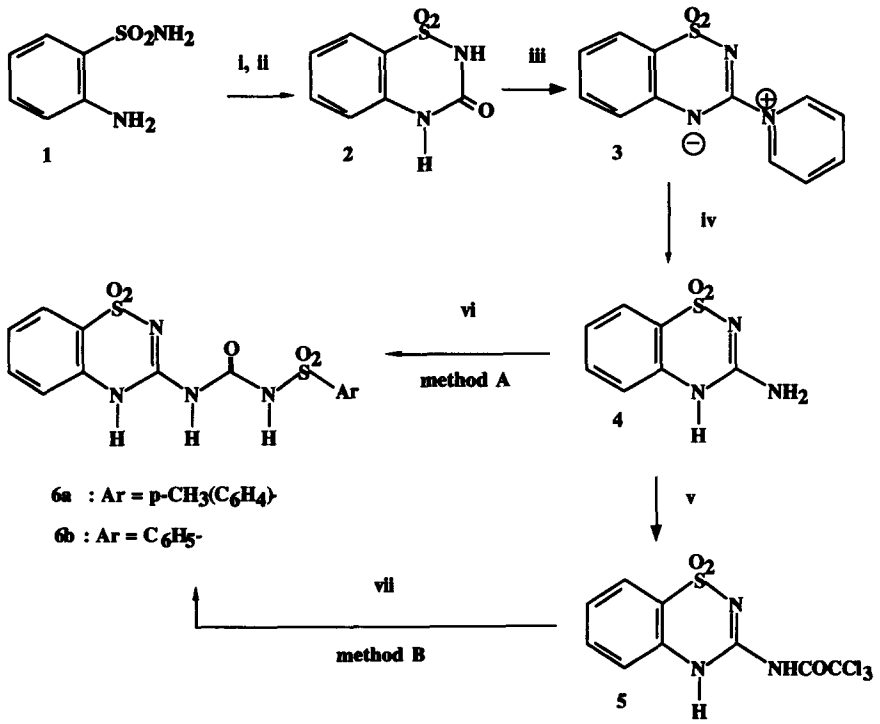


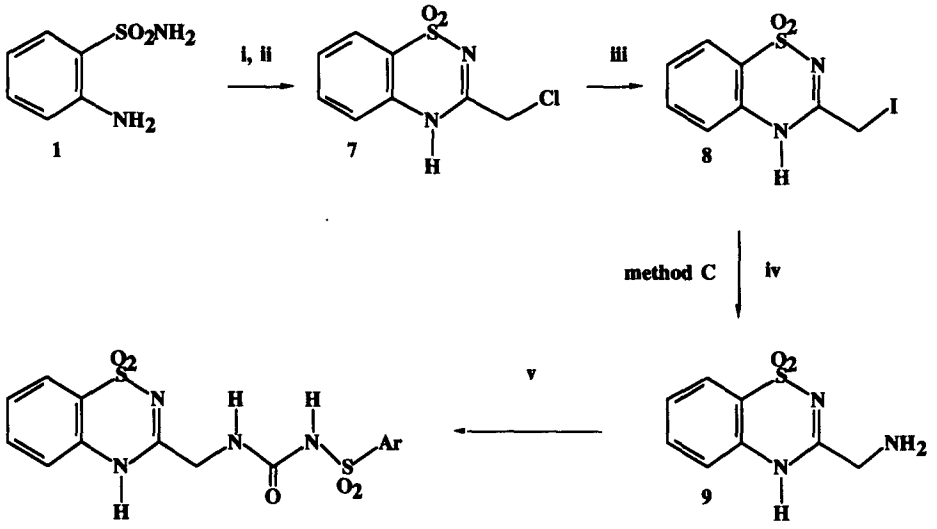
Figure 2. General formulae of target compounds where sulfonylurea moities are directly or indirectly linked to the 1,2,4-benzothiadiazin-1,1-dioxide skeleton.



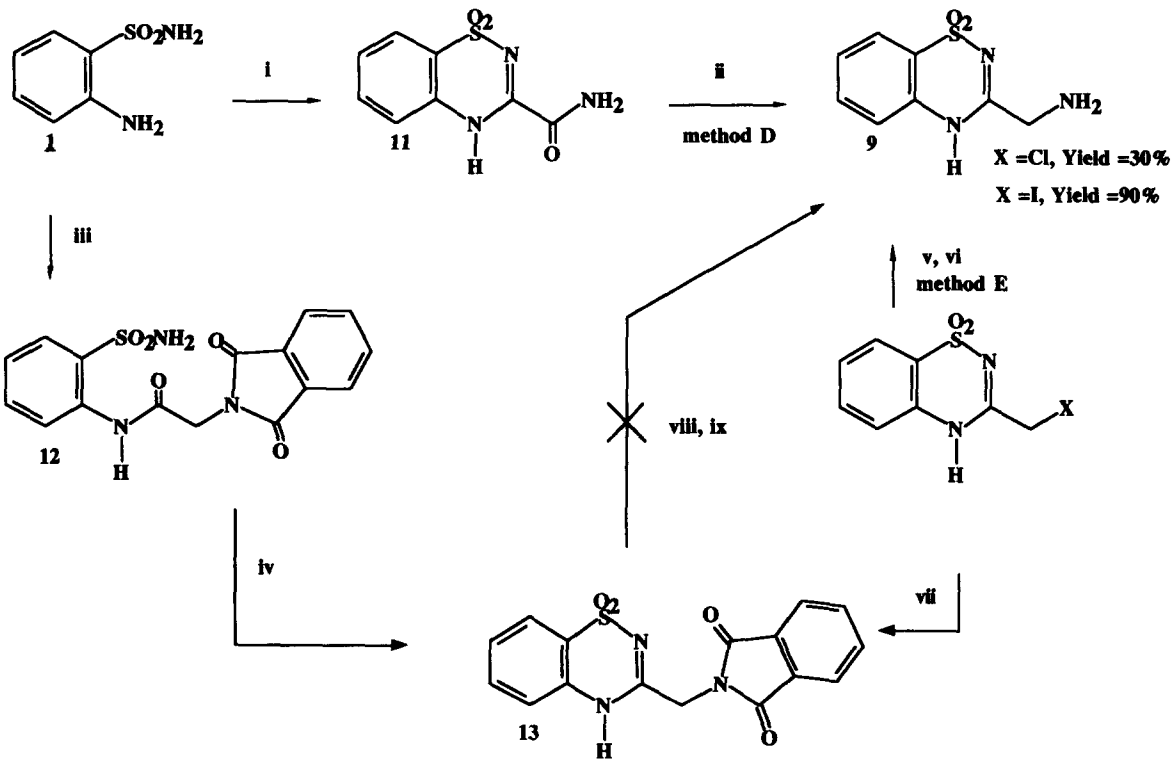
Scheme 1. (i) CCl_3COCl/toluene; (ii) NaOH/H_2O; (iii) pyridine/$C_6H_5SO_2Cl$; (iv) NaOH/H_2O; (v) CCl_3COCl/toluene; (vi) $ArSO_2NCO$/CH_3NO_2; (vii) $ArSO_2NH_2$, NaOH, DMSO.

Compound **7** (Scheme 2) was prepared from **1** according to a described method.[25] Nucleophilic substitution of the chlorine atom of **7** by concentrated methanolic ammonia led to **9** (30%). This yield was improved to 95% by using compound **8** prepared from **7** by reaction with sodium iodide in acetone (method C). Finally, **10a** and **10b** were prepared as **6a** and **6b** in Scheme 1.

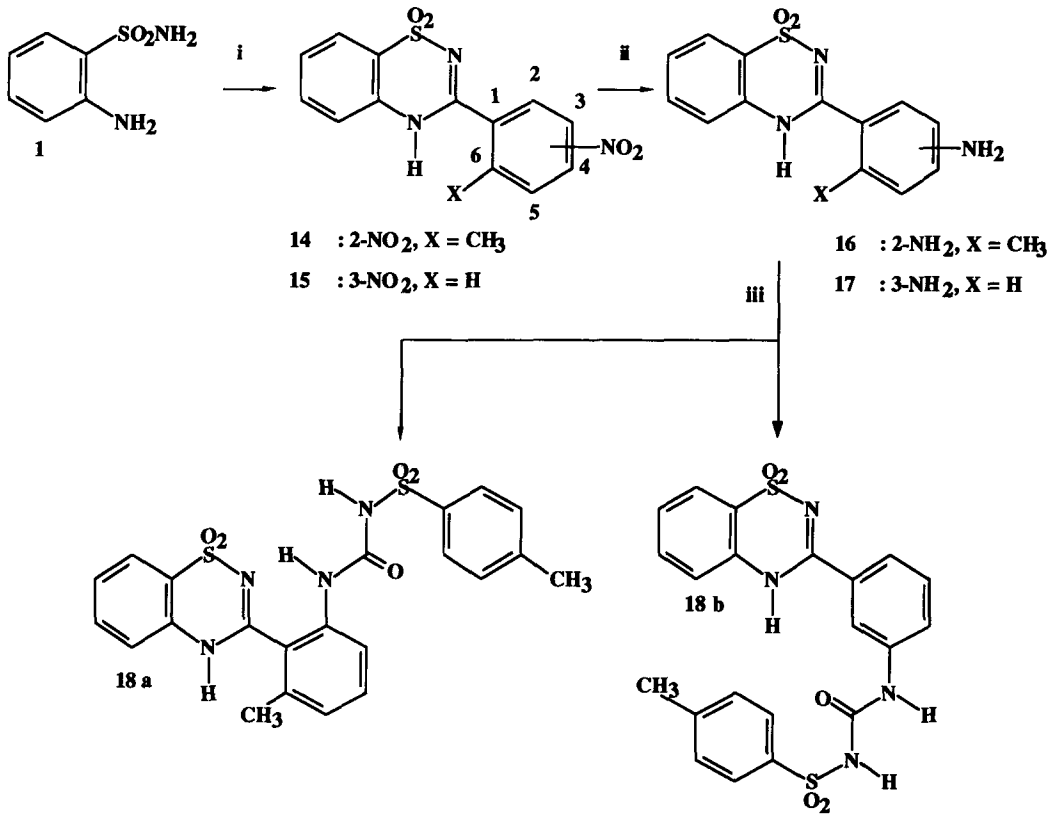
Alternative methods to prepare **9** are presented in Scheme 3. The primary amide function of **11** was selectively reduced by BH_3/THF (method D). Treatment of **7** and **8** with the sodium salt of trichloroacetamide gave **9** with 50% and 95% yields respectively (method E). Compound **13** was prepared from **7** and **8**, but our attempts to prepare **9** using the Gabriel method were unsuccessful. This failure



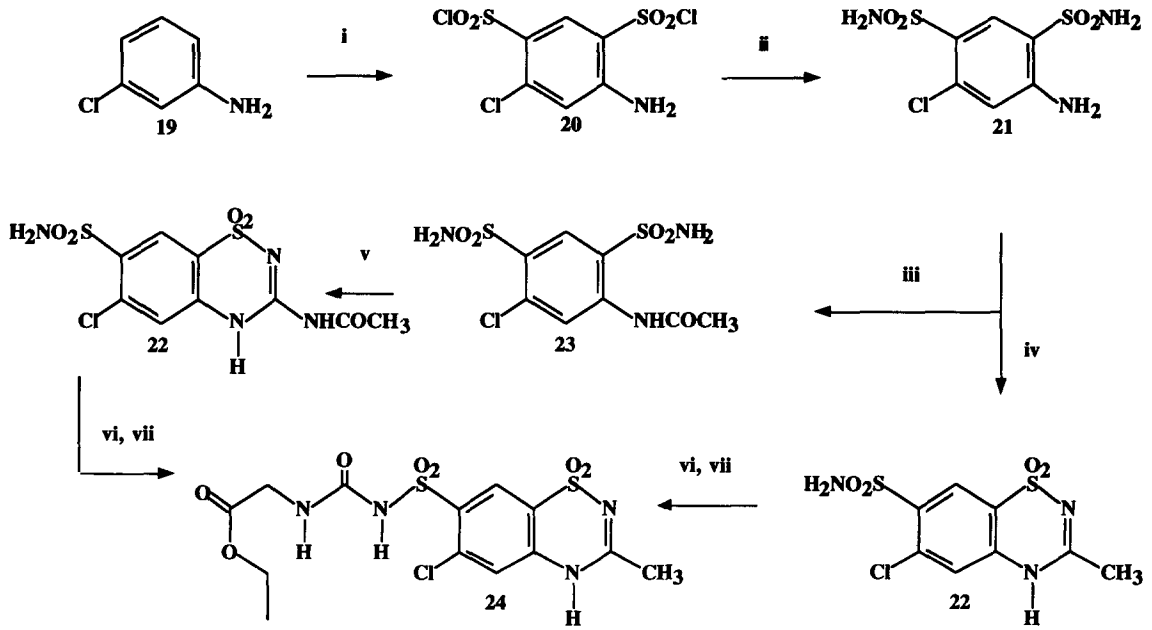
Scheme 2. (i) $ClCH_2COCl$/toluene; (ii) $NaOH/H_2O$; (iii) NaI/acetone; (iv) NH_3/methanol; (v) $ArSO_2NCO/CH_3NO_2$.



Scheme 3. (i) $C_2H_5OCOCONH_2$; MeONa/MeOH; (ii) BH_3/THF; (iii) (*N*-phthaloyl)CH_2COCl/toluene; (iv) $NaOH/H_2O$; (v) CCl_3CONH_2, NaH/DMF; (vi) $NaOH/H_2O$; (vii) potassium phthalimide/DMF; (viii) N_2H_4/C_2H_5OH; (ix) HCl.



Scheme 4. (i) 6-X-2-NO_2- and 4-$NO_2C_6H_3CO_2H$, PPSE/CH_2Cl_2; (ii) H_2, Pd/C; (iii) 4-$CH_3C_6H_4SO_2NCO$/CH_3NO_2.



Scheme 5. (i) $ClSO_3H$; (ii) NH_3/H_2O; (iii) CH3COCl/THF; (iv) CH_3CO_2H/H^+; (v) $^-OH/H_2O$, (vi) NaH/DMF; (vii) $CH_3CH_2OCOCH_2NCO$.

resulted from the cleavage of the 1,2,4-benzothiadiazin-1,1-dioxide skeleton under the drastic conditions used.

Derivatives **14** and **15** (Scheme 4) were prepared by reacting **1** with carboxylic acids (6-methyl-2-nitrobenzoic acid or 3-nitrobenzoic acid) in the presence of polyphosphoric silyl ester (PPSE), a condensing agent prepared from phosphorus pentoxide and hexamethyldisiloxane in an organic solvent such as toluene or chloroform. Condensing **1** with aldehydes (6-methyl-2-nitrobenzaldehyde or 3-nitrobenzaldehyde) in the presence of sodium bisulfite in dimethylacetamide gave yields similar to those obtained with PPSE. Catalytic reduction of **14** and **15** gave amines **16** and **17** in good

yields. These were later reacted with *p*-toluenesulfonyl isocyanate to give **18a** and **18b**.

Compound **24** bearing a sulfonylurea moiety at position 7 of the diazoxide nucleus (Fig. 2) was obtained according to Scheme 5. Starting materials **20** and **21** were prepared following described methods: the former by chlorosulfonation of the 3-chloroaniline **19** using chlorosulfonic acid, the latter by action of aqueous concentrated ammonia. The sulfonamide **22** was then synthesized either by refluxing **21** with acetic acid in the presence of catalytic quantities of sulfuric acid, or via the amide **23** formed by refluxing the disulfonamide **21** with acetyl chloride in THF or dioxane. Treatment of the sodium salt of **22** with an organic isocyanate and stirring at room temperature overnight led to **24**. When this step was performed at reflux of DMF, a mixture of several compounds was obtained, among which a small amount of **24**. This was due to the formation of formamidines resulting from condensation of isocyanates with DMF, for which a mechanism has been described.[25]

Pharmacology

Animals and aortic ring preparation

Six month old normotensive male rats (WAG/Rij) were purchased from IFFA Credo (Arbresle, France). After anaesthesia by intraperitoneal injection of pentobarbital (30 mg kg^{-1}), a segment of 4–5 cm of descending thoracic aorta was rapidly excised and placed in an oxygenated (CO_2 5%; O_2 95%) modified Krebs bicarbonate buffer medium (pH 7.4, 37 °C) of the following composition (mM): NaCl 118, KCl 5.6, $CaCl_2$ 2.4, $MgCl_2$ 1.2, Na_2HPO_4 1.2, $NaHCO_3$ 25, D-glucose 11. The tissue was cleaned of adhering fat and connective tissue and cut into 1 mm long transverse segments. The experiments were performed in an organ bath through which modified Krebs bicarbonate buffer medium flowed at 1.5 mL min^{-1}. A peristaltic pump delivered the different solutions from oxygenated reservoirs to the organ bath in which the aortic ring was placed. A complete change of the bathing solution in the organ bath was effected in less than 1 min. A water jacket, maintained at 37 °C, was provided for the entire system, including reservoirs of Krebs buffer medium, tubes leading from these reservoirs and the organ bath. Aortic rings were placed horizontally between a stationary stainless hook and an isotonic force transducer connected to a microcomputer. An initial passive tension of 1.5 g was applied to the aortic rings. An equilibration period of 60 min was allowed and then a resting stretch optimal tension of 1.5 g was applied to the ring preparation before starting the experiment (after stabilization of stretching out of the rings). The contractile state of each stimulated ring was evaluated as the variation of the tension (mg) per mg of tissue from the resting tone.

Data analysis

All data were expressed as mean ± SEM, and statistical significance was analyzed using the Student *t* test. A $P \leq 0.05$ was considered to be statistically significant. Comparisons were performed for each compound firstly between the contraction induced by 1 μM noradrenaline (NA) which leads to a contraction of 80% of the maximum contraction produced by NA, and secondly between relaxation produced by diazoxide and cromakalim, two known potassium channel openers.

Results

As shown in Figure 3, only compound **24** at low doses (0.1 μM), induces a vasorelaxation slightly greater than that observed with the two ATP-K^+-channel openers, cromakalim and diazoxide. At higher doses (≥ 0.1 μM) all compounds examined were less active than cromakalim. However, between 0.1 and 10 μM compound **24** was at least as active as diazoxide. The vasodilation induced by each compound was significantly inhibited by glibenclamide (1 μM), a specific ATP-sensitive channel blocker (Fig. 4). Thus, this new class of vasorelaxant agents may act via K^+-induced hyperpolarization of vascular smooth cells. In other words, they may act, at least in part, via activation of ATP-modulated potassium channels.

Conclusion

The combination of diazoxide skeleton-containing molecules bearing a sulfonylurea function led to a new class of vasorelaxant agents. The mechanism of action of these compounds, in particular that of **24**, involves hyperpolarization of vascular smooth muscle cells leading to a vasorelaxation. Since these effects were totally inhibited by glibenclamide, a specific and potent blocker of ATP-sensitive potassium channels, we think that our compounds act, at least in part, via activation of the same channels. Nevertheless, electrophysiological and pharmacological studies performed on other organs (studies under way) are needed to determine their exact molecular mechanism of action. Among the various positions occupied by the sulfonylurea functions on the diazoxide skeleton, position 7 was the most favorable. This observation has led to the preparation of compound **24**.

Experimental

Melting point determinations were made on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infra-red spectra were obtained on a PYE-UNICAM SP3-100 (Philips) spectrometer. Nuclear magnetic resonance spectra were recorded on an AC 200 FT (Bruker) spectrometer (^1H NMR at 200 MHz and ^{13}C NMR at 50 MHz). Chemical shifts are reported in parts per million (δ) downfield relative to tetramethylsilane. Microanalyses were determined by C.N.R.S-Vernaison (France). TLC were performed on silica gel 60F254 MERCK precoated plates (0.063–0.20 nm).

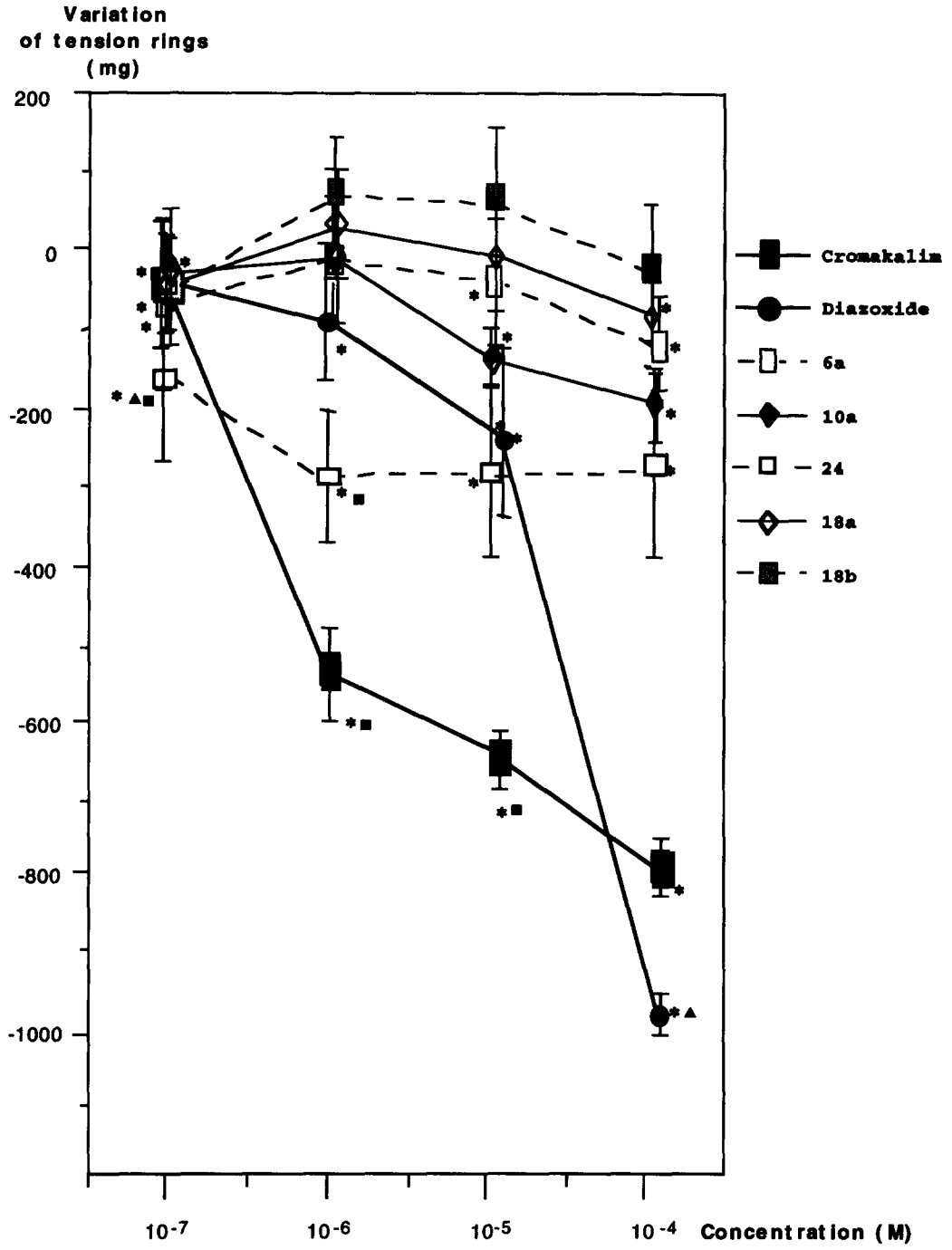


Figure 3. * Indicates a significant relaxation (P = 0.05) compared to that induced by phenylephrine (1 μM) or noradrenaline (1 μM) alone. ■ and ▲ Indicate a relaxation which was more significant than that induced by diazoxide and cromakalim respectively.

*3-Amino-4*H*-1,2,4-benzothiadiazin-1,1-dioxide (4)*

Compound **2** (1 g, 5.05 mmol), benzenesulfonyl chloride (0.8 mL, 6.57 mmol) and pyridine (1.6 mL, 20.2 mmol) were stirred together at room temperature. The yellow product which precipitated rapidly was washed with water and then dried. This compound (1 g) was refluxed in 40 mL of 20% sodium hydroxide at 90 °C for 35 min. The hot mixture was filtered, the filtrate was saturated with CO_2 and extracted with methanol. After evaporation of methanol, compound **4** was washed with water and then dried. Recrystallization from methanol/water gave 75% of **4**; mp 334–336 °C (lit.[26] 335–337 °C). IR (KBr): 3250, 3375, 1620, 1630, 1160, 1250 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.15 (*d*, *J* = 8 Hz, 1H), 7.24 (1 *td*, *J* = 8 and 3 Hz, 1H), 7.52 (*m*, *J* = 8 Hz, 1H), 7.64 (*dd*, *J* = 8 and 3 Hz, 1H), 6.98 (*s*, 2H), 10.74 (*s*, 1H).

*3-Trichloroacetylamino-4*H*-1,2,4-benzothiadiazin-1,1-dioxide (5)*

Compound **4** (1 g, 5.08 mmol) and trichloroacetylchloride (0.57 mL, 5.08 mmol) were refluxed in toluene (20 mL) for 4 h. After cooling, the precipitate was filtered, washed

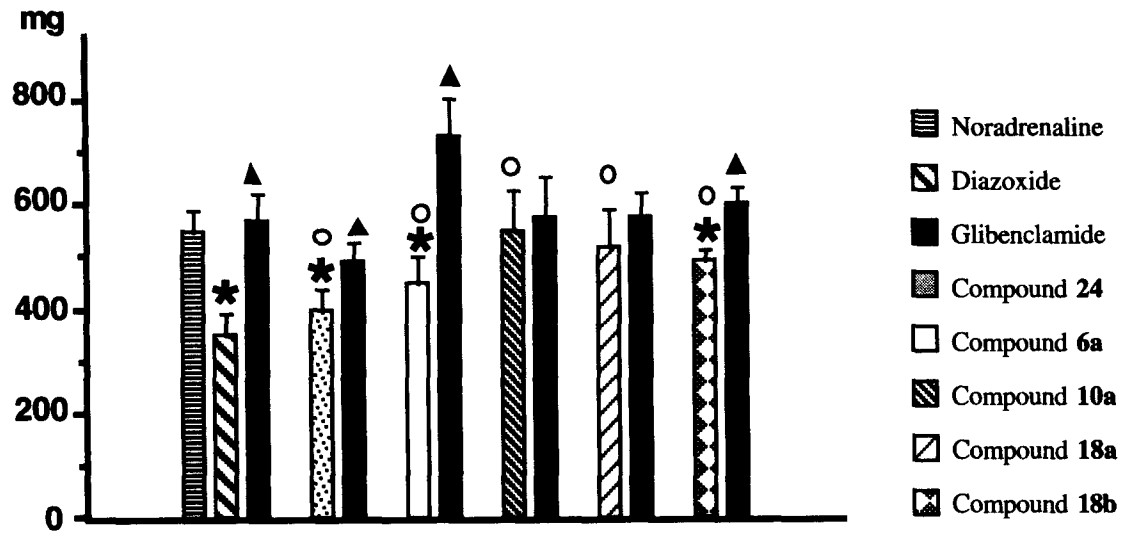


Figure 4. Tonus of aortic rings after the action of noradrenaline, diazoxide, compounds **6a**, **10a**, **18a**, **18b**, **24** and glibenclamide. Each substance has been perfused for 20 min. Each point represents the mean ± SEM of 5 to 7 experiments. ✱ Indicates a significant difference with the tonus of aortic rings induced by noradrenaline (1 μM). O Indicates a significant difference with tonus of aortic rings measured after the action of diazoxide (1 μM). ▲ Indicates a significant inhibition of effects of diazoxide and compounds (1 μM) with glibenclamide (1 μM).

with cold toluene and then dried. Recrystallization from methanol/water gave 95% of **5**; mp 260–262 °C. IR (KBr): 3250, 1640, 1740, 1160, 1180, 1260, 1310 cm^{-1}.

3-(p-Tolylsulfonylaminocarbonylamino)-4H-1,2,4-benzothiadiazin-1,1-dioxide (6a)

Method A. Compound **3** (1 g, 5 mmol) and *p*-toluenesulfonyl isocyanate (0.5 mL, 5 mmol) were refluxed in nitromethane (20 mL) for 5 h. After cooling, the formed precipitate was filtered, washed with ether and then dried. Recrystallization from water/DMF gave 85% of **6a**. *Method B.* Compound **5** (1.71 g, 5 mmol) was added to a stirred suspension of *p*-toluenesulfonamide (0.86 g, 5 mmol) and sodium hydroxide powder (0.5 g, 12.5 mmol) in DMSO (15 mL). The mixture was stirred at 80 °C for 30 min, and after cooling, it was poured into water (50 mL). The precipitate was washed with water and then dried. Recrystallization from water/DMF gave 90% of **6a**; mp 258–260 °C. TLC R_f 0.31 (EtOAc:EtOH = 90:10). IR (KBr): 3250, 1610, 1640, 1700, 1150, 1200, 1250 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.38 (*m*, *J* = 8 Hz, 4H), 7.58 (*m*, *J* = 7 Hz, 1H), 7.70 (*t*, *J* = 7 Hz, 1H), 7.79 (*d*, *J* = 8 Hz, 2H), 10.04 (*s*, 1H), 12.05 (*s*, 1H), 2.37 (*s*, 3H); ^{13}C NMR (DMSO-d_6) δ 21.03, 118.61, 122.56, 122.86, 126.00, 127.51, 129.56, 132.83, 133.76, 136.71, 144.10, 147.03, 150.93. Anal. $C_{15}H_{14}N_4S_2$, C, H, N, S.

3-(Phenylsulfonylaminocarbonylamino)-4H-1,2,4-benzothiadiazin-1,1-dioxide (6b)

Method A. Yield 70%. *Method B.* yield 90%. Recrystallization from water/DMF, TLC R_f 0.29 (EtOAc:EtOH = 90:10). IR (KBr): 3250, 1610, 1640, 1700, 1150, 1200, 1250 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.38 (1 *td*, *J* = 7 and 3 Hz, 1H), 7.45 (*t*, *J* = 7.5 Hz, 1H), 7.61 (*td*, *J* = 6.5 and 3 Hz, 4H), 7.72 (*dd*, *J* = 8 and 3 Hz, 1H), 7.93 (*dt*, *J* = 8 and 3 Hz, 2H), 10.04 (*s*, 1H), 12.05 (*s*, 1H), 2.37 (*s*, 3H). Anal. $C_{14}H_{12}N_4S_2O_5$, C, H, N.

3-Iodomethyl-4H-1,2,4-benzothiadiazin-1,1-dioxide (8)

Compound **7** (1 g, 4.34 mmol) and sodium iodide (0.75 g, 5 mmol) were refluxed for 15 h in acetone (20 mL). After evaporation of acetone, **6** was washed with hot water and then dried. Recrystallization from methanol/water gave 95% of **6**; mp 248–254 °C. TLC R_f 0.25 (chloroform). IR (KBr): 3175, 3250, 1140, 1160, 1280 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.32 (*dd*, *J* = 8 and 3 Hz, 1H), 7.45 (*m*, *J* = 7 Hz, 1H), 7.69 (*m*, *J* = 6 Hz, 1H), 7.9 (*dd*, *J* = 8 and 3 Hz, 1H), 8.71 (*s*, 1H), 4.08 (*s*, 2H).

3-Aminomethyl-1,2,4-benzothiadiazin-1,1-dioxide (9)

Method C. Compound **8** (0.3 g, 1.42 mmol) was dissolved in 20 mL of concentrated methanolic ammonia at 0 °C. This solution was stirred for 12 h at room temperature. After evaporation under vacuum, the crude product (**7**) was washed with water and then dried. Recrystallization from methanol/water gave 95% of **9**. *Method D.* To a cooled solution of **11** (1 g) at –20 °C in anhydrous THF (20 mL) was added the BH_3/THF complex (8.9 mL, 1 M, d = 0.898). The mixture was stirred and the temperature allowed to rise slowly. After stirring at room temperature for 5 h, methanol (10 mL) was added. After evaporation of methanol and THF, the residue was dissolved in water (20 mL), then the solution was acidified with 1 N HCl. The precipitate was collected by filtration and dried. Recrystallization from methanol/water gave 75% of **9**. *Method E.* NaH (0.3 g, 6.15 mmol) was added at 0 °C to a stirred solution of trichloroacetamide (1 g, 6.15 mmol) dissolved in a minimum of anhydrous DMF. The mixture was heated at 80 °C for 1 h, then, **8** (2 g, 6.15 mmol) was added. The resulting mixture was refluxed for 1 h. After cooling, water (30 mL) was added, the precipitate filtered and then heated in 1 N aqueous sodium hydroxide (20 mL) for 30 min. After cooling again, the solution obtained was acidified with 1 N HCl, the precipitate collected by filtration and dried. Recrystallization from methanol/water

gave 90% of **9**; mp 320–322 °C (lit.[27] 320–321 °C). TLC R_f 0.25 (chloroform). IR (KBr): 3425, 3325, 3225, 1640, 1150, 1170, 1190, 1240, 1270 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.32 (*dd*, *J* = 8 and 3 Hz, 1H), 7.41 (*t*, *J* = 8 Hz, 1H), 7.65 (*t*, *J* = 7 Hz, 1H), 7.78 (*d*, *J* = 7 Hz, 1H), 8.5 (broad signal, 1H), 3.92 (*s*, 2H).

*3-(p-Tolylsulfonylaminocarbonylaminomethylen)-4H-1,2,4-benzothiadiazin-1,1-dioxide (**10a**)*

Method A. Recrystallization from methanol/water gave 70% of **10a**; mp 248–250 °C. TLC R_f 0.56 (EtOAc:EtOH = 90:10). IR (KBr): 3200, 3250, 3400, 1700, 1160, 1180, 1265, 1300 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.31–7.47 (*m*, *J* = 8 Hz, 4H), 7.67 (*m*, *J* = 8 Hz, 1H), 7.78 (*d*, *J* = 6.5 Hz, 1H), 7.80 (*d*, *J* = 8 Hz, 2H), 7.01 (*t*, *J* = 5 Hz, 1H), 10.98 (*s*, 1H), 11.01 (*s*, 1H), 4.11 (*d*, *J* = 5 Hz, 2H), 2.37 (*s*, 3H); ^{13}C NMR (DMSO-d_6) δ 21.00, 42.14, 117.37, 121.45, 123.47, 126.34, 127.13, 129.47, 133.10, 134.83, 137.22, 143.67, 151.51, 157.07, ^{13}C DEPT δ 21.01, 42.14, 117.37, 123.48, 126.34, 127.13, 129.48, 133.11. Anal. $C_{16}H_{16}N_4O_5S_2$ C, H, N.

*3-(Phenylsulfonylaminocarbonylaminomethylen)-4H-1,2,4-benzothiadiazin-1,1-dioxide (**10b**)*

Method A. Recrystallization from methanol/water gave 70% of **10b**; mp 246–248 °C, TLC R_f 0.25 (EtOAc:EtOH = 90:10). IR (KBr): 3350, 1630, 1660, 1160, 1180, 1250, 1310 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.30 (*d*, *J* = 8 Hz, 1H), 7.43 (*t*, *J* = 8 Hz, 1H), 7.61 (*m*, *J* = 7.5 Hz, 4H), 7.78 (*d*, *J* = 8 Hz, 1H), 7.92 (*d*, *J* = 8 Hz, 2H), 7.04 (*t*, *J* = 3 Hz, 1H), 11.03 (*s*, 1H), 4.12 (*d*, *J* = 3 Hz, 2H). Anal. $C_{15}H_{14}N_4O_5S_2$ C, H, N.

*3-(6-Methyl-2-nitrophenyl)-4H-1,2,4-benzothiadiazin-1,1-dioxide (**14**)*

Preparation of polyphosphoric silyl ester (PPSE). P_2O_5 (6.6 g, 46.48 mmol) and hexamethyldisiloxane $[(CH_3)_3SiO]_2$ (9.9 mL, 46.48 mmol) were refluxed for 30 min in anhydrous chloroform (20 mL). A clear solution was obtained.

Coupling reaction. Compound **1** (1 g, 5.8 mmol) and 6-methyl-2-nitrobenzoic acid (1 g, 5.8 mmol) were refluxed for 2 h in the previous solution. After partial evaporation of chloroform under vacuum, the mixture was poured into cold water. The precipitate was filtered, washed with water and then dried. Recrystallization from water/DMF gave 95% of **14**; mp 190–192 °C. IR (KBr): 3275, 1620, 1170, 1180, 1300, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.41 (*d*, *J* = 8 Hz, 1H), 7.53 (*td*, *J* = 7 and 3 Hz, 1H), 7.71 (*m*, *J* = 7 Hz, 2H),7.92 (*td*, *J* = 8 and 3 Hz, 2H), 8.13 (*dd*, *J* = 8 and 3 Hz, 1H) , 12.64 (*s*, 1H), 2.44 (*s*, 3H). ^{13}C NMR (DMSO-d_6) δ 15.25, 118.10, 121.33, 123.47, 126.14, 127.10, 130.07, 132.76, 133.35, 135.15, 135.61, 150.49, 154.73.

*3-(3-Nitrophenyl)-4H-1,2,4-benzothiadiazin-1,1-dioxide (**15**)*

This was obtained by the same method as **14**. Recrystallization from methanol/water gave 95% of **15**; mp 344–346 °C (lit.[28] 345–346 °C). IR (KBr): 3310, 1140, 1160, 1260, 1290, 1530 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.53 (1 *td*, *J* = 7 and 3 Hz, 1H), 7.72 (*m*, *J* = 7 Hz, 2H), 7.91 (*t*, *J* = 8 Hz, 2H), 8.51 (*m*, *J* = 6 Hz, 2H), 8.88 (*t*, *J* = 6 Hz, 1H), 12.58 (*s*, 1H); ^{13}C NMR (DMSO-d_6) δ 118.60, 121.46, 123.10, 123.37, 127.07, 127.18, 130.59, 133.27, 134.64, 135.29, 147.00, 152.71.

*9-(6-Methyl-2-[[4-methylphenylsulfonylaminocarbonylamino]phenyl]-4H-1,2,4-benzothiadiazin-1,1-dioxide (**18a**)*

Method A. Recrystallization from acetone/water gave 90% of **18a**; mp 216–218 °C, TLC R_f 0.66 (EtOAc:MeOH = 90:10). IR (KBr): 3200, 3250, 1710, 1140, 1165, 1270, 1290 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.42 (*m*, *J* = 8 Hz, 6H), 7.71 (*m*, *J* = 8 Hz, 2H), 7.86 (*d*, *J* = 8 Hz, 3H), 8.34 (*s*, 1H), 11.1 (broad signal, 1H), 12.43 (*s*, 1H), 2.15 (*s*, 3H), 2.38 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 14.00, 21.00, 117.96, 121.21, 123.34, 124.41, 124.95, 126.16, 126.78, 127.38, 128.01, 129.47, 133.14, 134.06, 135.24, 136.51, 136.94, 143.89, 149.56, 156.25; ^{13}C DEPT δ 14.03, 21.02, 117.97, 123.34, 124.41, 124.96, 126.17, 126.78, 127.39, 129.48, 133.15. Anal. $C_{22}H_2ON_4O_5S_2$ C, H, N.

*10-(3-[[4-Methylphenylsulfonylaminocarbonylamino]-phenyl]-4H-1,2,4-benzothiadiazin-1,1-dioxide (**18b**)*

Method A. Recrystallization from acetone/water gave 90% of **18b**; mp 208–212 °C. TLC R_f 0.54 (EtOAc:MeOH = 90:10). IR (KBr): 3300, 3325, 3250, 1700, 1170, 1290, 1320 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.9–7.8 (*m*, *J* = 6 Hz, 8H), 8.04 (*t*, *J* = 6 Hz, 1H), 9.17 (*s*, 1H), 12.21 (*s*, 1H), 2.37 (*s*, 3H); ^{13}C NMR (DMSO-d_6) δ 21.10, 18.49, 121.46, 122.79, 123.19, 123.37, 126.85, 127.56, 129.39, 129.54, 132.56, 133.33, 135.43, 137.24, 138.88, 143.86, 149.86, 154.71. Anal. $C_{21}H_{18}N_4S_2O_5 \cdot H_2O$, C, H, N.

*6-Chloro-7-((ethoxycarbonylmethylene)aminocarbonyl-aminosulfonyl)-4H-1,2,4-benzothiadiazin-1,1-dioxide (**24**)*

To a cooled (at 0 °C) solution of **22**[29] (0.5 g) in DMF was added sodium hydride (0.1 g). The mixture was stirred for 15 min, then ethyl isocyanatoacetate (0.19 mL) was added. Stirring was continued for 15 h at room temperature. The solution obtained was then poured into cold water and acidified with 1 N HCl. The precipitate was collected by filtration, washed with water and dried. Recrystallization from acetone/water gave 90% of **6a**; mp (decomposes before melting). IR (KBr 2%) ν 3300, 3350, 1620, 1700, 1160, 1170, 1190, 1280, 1330, 1640. ^1H NMR (DMSO-d_6) δ 7.54 (*s*, 1H,), 8.30 (*s*, 1H), 6.78 (*t*, 1H, *J* = 5.56, 1H), 11.82 (*s*, 1H), 12.48 (*s*, 1H), 8.12 (*s*, 1H), 3.74 (*t*, *J* = 5.68), 4.04 (*q*, *J* = 7.13, 2H), 1.12 (*t*, *J* = 7.13); ^{13}C NMR (DMSO-d_6): δ 13.95, 41.25, 60.53, 120.32, 120.42, 128.58, 134.44, 138.96, 148.80, 151.14, 169.49; ^{13}C DEPT (DMSO-d_6) δ 13.95, 41.25, 60.53, 120.42, 128.58, 148.80.

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