Bioorganic & Medicinal Chemistry 16 (2008) 8882–8888

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis of new 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines: A search for novel nitric oxide donor anti-inflammatory agents

Morshed Alam Chowdhury, Khaled R. A. Abdellatif, Ying Dong, Edward E. Knaus *

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alta., Canada T6G 2N8

ARTICLE INFO

Article history:
Received 25 July 2008
Revised 22 August 2008
Accepted 26 August 2008
Available online 29 August 2008

Keywords:
Pyrazoles
1,2,3,6-Tetrahydropyridines
Diazen-1-ium-1,2-diolate nitric oxide donors
Anti-inflammatory activity

ABSTRACT

A group of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (**11**–**14**) possessing a variety of substituents (Me, CO_2Et, H, N = O) attached to the 1,2,3,6-tetrahydropyridyl N^1-nitrogen atom were synthesized and evaluated as anti-inflammatory agents. Structure–activity relationship data showed that the *N*-methyl-1,2,3,6-tetrahydropyridyl moiety is a suitable bioisosteric replacement for the tolyl moiety in celecoxib. The most potent compound 4-[5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (**11b**; ED_{50} = 61.2 mg/kg po) exhibited an anti-inflammatory activity between that of the reference drugs celecoxib (ED_{50} = 10.8 mg/kg po) and aspirin (ED_{50} = 128.7 mg/kg po). The synthesis of model hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (**5**) requires further investigation since the reaction of 1,2,3,6-tetrahydropyridines with nitric oxide furnished the undesired *N*-nitroso-1,2,3,6-tetrahydrohydropyridyl product rather than the desired *N*-diazen-1-ium-1,2-diolate-1,2,3,6-tetrahydropyridyl product.

1. Introduction

Drugs that are highly selective inhibitors of the inducible cyclooxygenase-2 (COX-2) isozyme in the periphery are effective anti-inflammatory agents. However, some drugs within this group (see structures in Fig. 1) such as rofecoxib (**1**) and valdecoxib (**3a**) alter the natural balance in the COX pathway wherein the amount of the desirable vasodilatory and anti-aggregatory prostacyclin (PGI_2) produced is decreased in conjunction with a concomitant increase in the level of the undesirable prothrombotic thromboxane A_2 (TxA_2).[1–3] This combination of adverse biochemical changes in the COX pathway are responsible for increased prevalence of high blood pressure and myocardial infarction that subsequently necessitated the withdrawal of rofecoxib (Vioxx®) and valdecoxib (Bextra®).[4,5] Nitric oxide (NO) is an effective vasodilation agent that also inhibits platelet aggregation and adhesion.[6] Hybrid COX-2 inhibitors possessing a NO-donor moiety (NO-coxibs) have been investigated as a method to increase the clinical safety of COX-2 inhibitors. In this regard, NO-coxibs having a nitrate ester NO-donor moiety such as the oxazole (**3b**) exhibit anti-inflammatory activity similar to valdecoxib with antithrombotic action at higher doses,[7] and the pyrazole **4** that exhibits anti-inflammatory activity.[8] We previously reported NONO-coxib ester prodrugs having a NO-donor diazen-1-ium-1,2-diolate moiety that are effectively cleaved by esterases to release the parent anti-inflammatory drug and NO.[9–13] Accordingly, attachment of a NO-donor diazen-1-ium-1,2-diolate moiety to highly selective COX-2 inhibitors offers a potential drug design concept to circumvent the adverse cardiovascular events associated with their chronic clinical use. We now describe an investigation directed toward the design and synthesis of model hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (**5**) that are devoid of adverse cardiovascular effects (see structure **5** in Fig. 1).

2. Chemistry

A group of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (**11**–**14**) possessing a variety of substituents (Me, CO_2Et, H, N = O) attached to the 1,2,3,6-tetrahydropyridyl N^1-nitrogen atom were synthesized using the reaction sequence illustrated in Scheme 1. Accordingly, reaction of a 4-(methylsulfonylphenyl)hydrazine-HCl (**6a**), or 4-(sulfamoylphenyl)hydrazine-HCl (**6b**), with isonicotinoyltrifluoroacetone[14] (**7**) in 95% ethanol at reflux afforded a mixture of the

* Corresponding author. Tel.: +1 780 492 5993; fax: +1 780 492 1217.
E-mail address: eknaus@pharmacy.ualberta.ca (E.E. Knaus).

0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.08.059

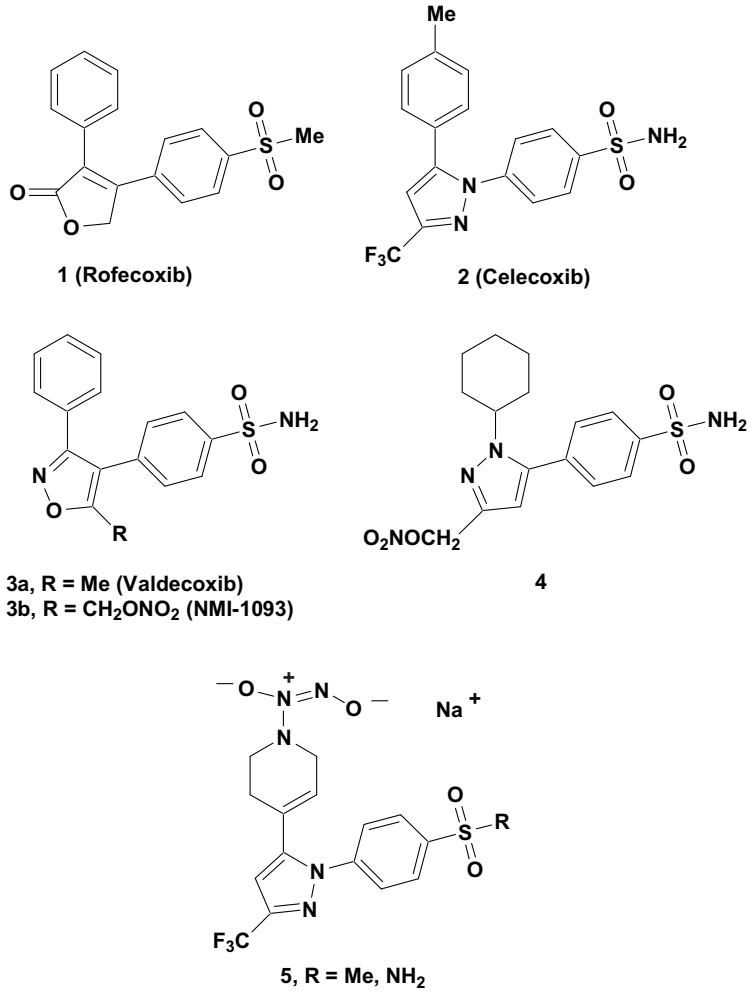
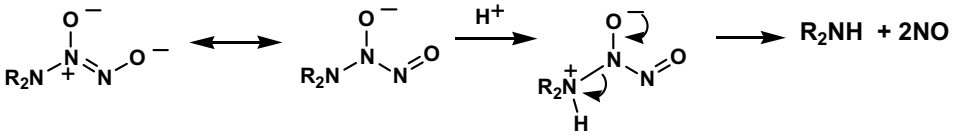


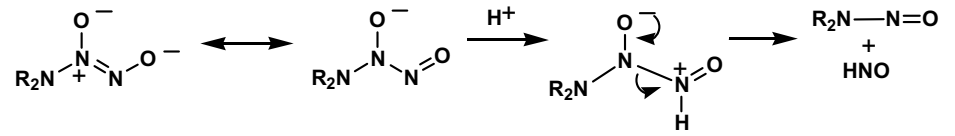
Figure 1. Chemical structures of the selective cyclooxygenase-2 (COX-2) inhibitors rofecoxib (**1**), celecoxib (**2**) and valdecoxib (**3a**), the nitric oxide donor nitrate esters NMI-1093 (**3b**) and **4**, and the putative hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (**5**).

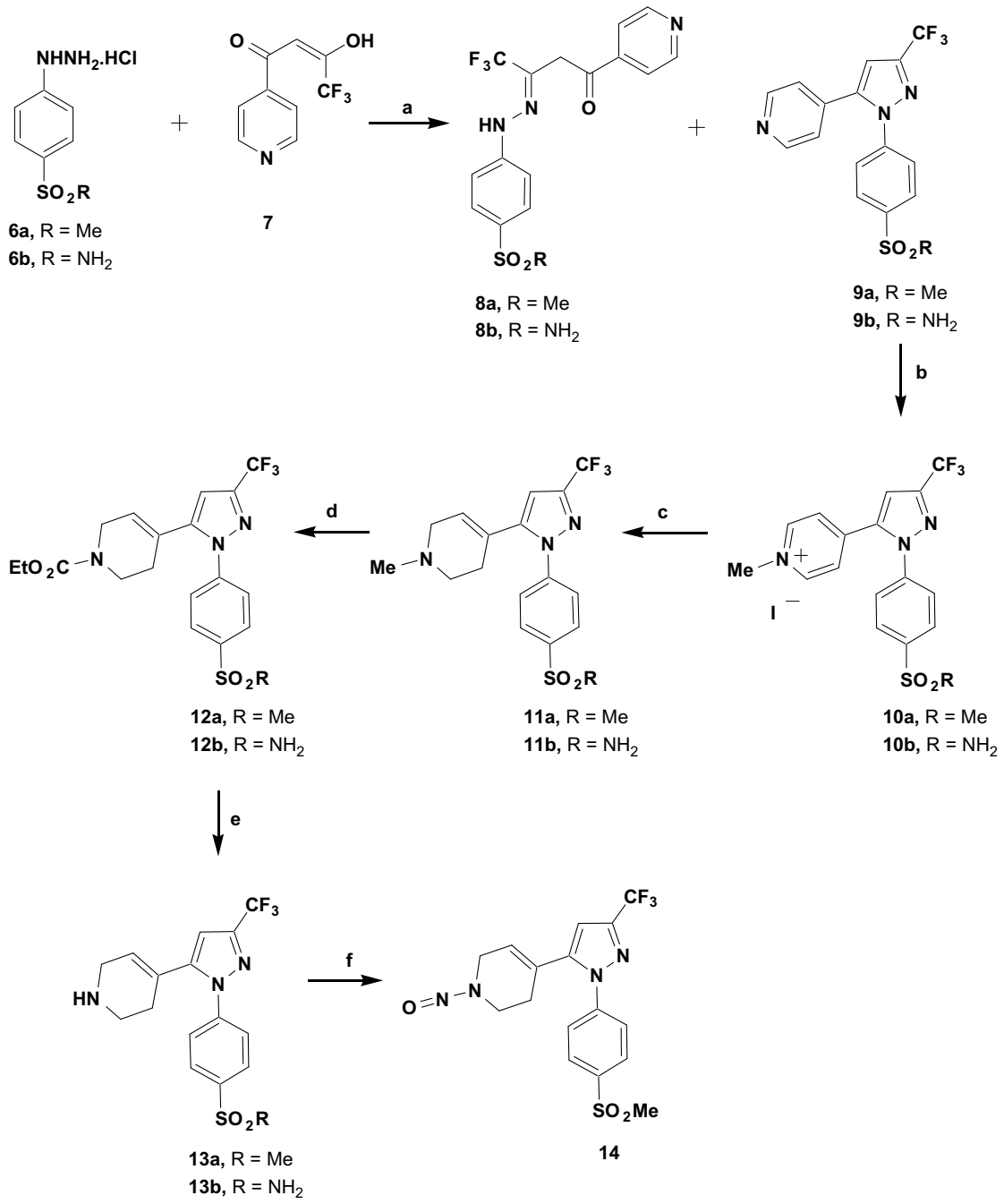
respective acyclic aryl hydrazone[15] (**8a**, 21% or **8b**, 30%) and the 1,5-diaryl-3-trifluoromethylpyrazole regioisomer (**9a**, 37% or **9b**, 41%).[16] Products **8** and **9** were separated by silica gel column chromatography. It is well documented that the cyclization-dehydration reaction proceeds in a regiospecific manner to yield the 1,5-diaryl-3-trifluoromethylpyrazole product (**9**) when a phenylhydrazine hydrochloride is employed and the reaction is carried out in ethanol at reflux temperature.[16] The structural assignment of the 1,5-diaryl-3-trifluoromethyl regioisomer **9a** was confirmed by a nuclear Overhauser enhancement (NOE) experiment. In this regard, irradiation of the resonance at δ 7.69 (phenyl H-2, H-6) showed a very strong NOE enhancement for the resonance at δ 7.35 (25%, pyridyl H-3, H-5) indicating that the pyridyl and phenyl rings must be attached to adjacent positions on the pyrazole ring. This NOE experiment provides unambiguous evidence that compound **9a** is the 1,5-diaryl-3-trifluoromethylpyrazole, rather than the 1,3-diaryl-5-trifluoromethylpyrazole, regioisomer. Reaction of the pyridyl compounds (**9a** and **9b**) with methyl iodide in acetone[17] at 25 °C afforded the corresponding *N*-methylpyridinium salt **10a** (90%) or **10b** (93%). Reduction of the *N*-methylpyridinium salts **10a** and **10b** using sodium borohydride in methanol[18] furnished the respective 4-[2-(4-methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1-methyl-1,2,3,6-tetrahydropyridine (**11a**, 99%) or 4-[5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-trifluoromethylpyrazol-1-yl]-benzenesulfonamide (**11b**, 90%). Subsequent treatment of the *N*-methyl-1,2,3,6-tetrahydropyridine **11a** or **11b** with ethyl chloroformate at reflux in 1,2-dichloroethane[19] afforded the respective *N*-ethoxycarbonyl-1,2,3,6-tetrahydropyridine **12a** (94%) or **12b** (60%). Removal of the *N*-ethoxycarbonyl substituent present in **12a** and **12b** by reaction with 10 N hydrochloric acid at reflux temperature[19] yielded 4-[2-(4-methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridine (**13a**, 55%) and 4-[5-(1,2,3,6-tetrahydropyridin-4-yl)-3-trifluoromethylpyrazol-1-yl]-benzenesulfonamide (**13b**, 33%), respectively. Reaction of the 1,2,3,6-tetrahydropyridine compound **13a** with nitric oxide gas (40 psi) at 25 °C in the presence of NaOMe[20] furnished a product which exhibited a molecular ion in the positive ion electrospray mass spectrum (*m/z* 423.02, M+Na) and microanalytical data that was consistent with the *N*-nitroso product 4-[2-(4-methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1-nitroso-1,2,3,6-tetrahydropyridine (**14**, 53%).

The decomposition pathway of the *N*-amino-*N*-diazen-1-ium-1,2-diolate moiety (see structure **5** in Fig. 1) is dependent upon the site of protonation. In this regard, protonation at the 1,2,3,6-tetrahydropyridine nitrogen and then decomposition would produce the 1,2,3,6-tetrahydropyridine compound **13** and 2 molecules of NO as illustrated below.

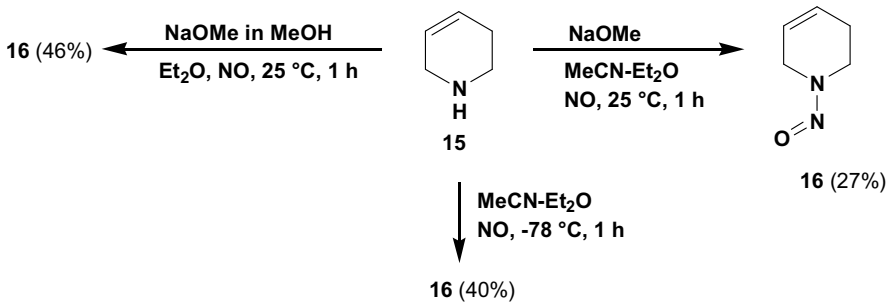


Alternatively, protonation of the diazen-1-ium-1,2-diolate N^2-nitrogen and then decomposition would furnish a nitrosamine (such as product **14** in Scheme 1) and a nitroxyl species (HNO) as indicated below.





Scheme 1. Reagents and conditions: (a) ethanol (95%), reflux, 20 h; (b) MeI, acetone, 25 °C, 12 h; (c) $NaBH_4$, MeOH, 5 °C → 25 °C, 0.5 h; (d) $ClCO_2Et$, 1,2-dichloroethane, reflux, 12 h; (e) i—10 N HCl, reflux, 3 h; ii—Na_2CO_3; (f) compound **13a**, nitric oxide gas, 40 psi, MeCN/diethyl ether (1:1, v/v), NaOMe, 25 °C, 48 h.



Scheme 2. Synthesis of *N*-nitroso-1,2,3,6-tetrahydropyridine (**16**).

The formation of the *N*-nitroso product **14** upon reaction of **13a** with nitric oxide indicates that the intermediate *N*-amino-*N*-diazen-1-ium-1,2-diolate product [see structure **5** (R = Me) in Fig. 1] must undergo protonation of the more basic diazen-1-ium-1,2-diolate N^2-nitrogen that is unstable undergoing subsequent elimination of a HNO species.[21]

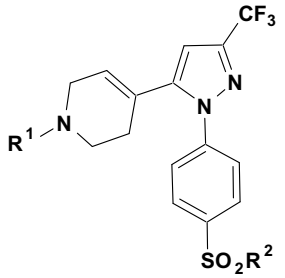
The reaction of 1,2,3,6-tetrahydropyridine (**15**) with nitric oxide under a variety of experimental conditions (aprotic and protic solvent systems, various temperatures) afforded *N*-nitroso-1,2,3,6-tetrahydropyridine (**16**) as the sole isolable product (see Scheme 2). For example, reaction in the aprotic MeCN/Et_2O solvent system in the presence of NaOMe at 25 °C afforded **16** in 27% yield. A 40% yield of **16** was isolated when the same reaction was performed at −78 °C. Alternatively, reaction of **15** in a protic solvent system consisting of NaOMe in MeOH (25% w/v) and Et_2O at 25 °C furnished **16** (46%). These data indicate that 1,2,3,6-tetrahydropyridine (**15**), or a substrate such as the 1,2,3,6-tetrahydropyridyl compound **13a**, are not suitable precursors for the synthesis of isolable nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives.

3. Results and discussion

Hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (see structure **5** in Fig. 1) constitute a potential class of selective COX-2 inhibitor compounds that are devoid of adverse cardiovascular properties. The model structure **5** was designed based on structure–activity data showing that (i) a COX-2 pharmacophore such as $MeSO_2$ or H_2NSO_2 at the *para*-position of a N^1-phenyl ring on a pyrazole ring template confers potent and selective COX-2 inhibitory activity,[16] (ii) attachment of a 1,2,3,6-tetrahydropyridine ring substituent via its C-4 sp^2 hyridized carbon atom is consistent with the observation that two aryl rings on adjacent positions of a 5-membered heterocyclic ring template (scaffold) generally provide optimum COX-2 inhibitory activity,[22] and (iii) the 1,2,3,6-tetrahydropyridyl secondary amino group, such as that present in compounds **13**, provides a logical synthon for elaboration to the corresponding nitric oxide donor *N*-diazen-1-ium-1,2-diolates.[9–13] Unfortunately, reaction of the 1,2,3,6-tetrahydropyridyl compound **13a** with nitric oxide (see Scheme 1) afforded the *N*-nitroso product **14** rather than the desired unisolable intermediate *N*-diazen-1-ium-1,2-diolate product **5** (R = Me).

The anti-inflammatory (AI) activities for this group of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (**11**–**14**) possessing a variety of R^1-substituents (Me, CO_2Et, H, N = O) attached to the 1,2,3,6-tetrahydropyridyl N^1-nitrogen atom were determined using a carrageenan-induced rat foot paw edema model (see data in Table 1). Structure–activity relationships acquired showed that the relative AI potency profile (i) with respect to the COX-2 pharmacophore moiety was $SO_2Me > SO_2NH_2$ when R^1 is CO_2Et or H, but $SO_2NH_2 > SO_2Me$ when R^1 is Me, (ii) within the SO_2Me group of compounds Me > N = O > H > CO_2Et with respect to the R^1 substituent, (iii) within the SO_2NH_2 group of compounds Me > H > CO_2Et (inactive) with respect to the R^1 substituent, and iv) the two most potent compounds **11a** (SO_2Me; ED_{50} = 95.3 mg/kg po) and **11b** (SO_2NH_2; ED_{50} = 61.2 mg/kg po) having a *N*-methyl-1,2,3,6-tetrahydropyridyl moiety exhibited anti-inflammatory activities between that of the reference drugs celecoxib (ED_{50} = 10.8 mg/kg po) and aspirin (ED_{50} = 128.7 mg/kg po).

Table 1
Anti-inflammatory activities for the 4-[2-(4-methane(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1-substituted-1,2,3,6-tetrahydropyridines (**11**–**14**)



Compound	R^1	R^2	AI activity[a]: ED_{50} (mg/kg)
11a	Me	SO_2Me	95.3
11b	Me	SO_2NH_2	61.2
12a	EtO_2C	SO_2Me	Moderate activity[b]
12b	EtO_2C	SO_2NH_2	Inactive[c]
13a	H	SO_2Me	128.7
13b	H	SO_2NH_2	Weak activity[d]
14	O=N	SO_2Me	115.1
Celecoxib	—	—	10.8
Aspirin	—	—	128.7

[a] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as the ED_{50} value (mg/kg) at 3 h after oral administration of the test compound.
[b] A 24.1% inhibition of inflammation was observed at a 100 mg/kg oral dose.
[c] Inactive at a 100 mg/kg oral dose.
[d] A 7.1% inhibition of inflammation was observed at a 100 mg/kg oral dose.

4. Conclusions

A group of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (**11**–**14**) were synthesized in which the tolyl (*para*-methylphenyl) moiety present in celecoxib (**2**) was replaced by 4-(*N*-substituted (Me, CO_2Et, H, N = O)-1,2,3,6-tetrahydropyridyl moiety that were evaluated as anti-inflammatory agents. Anti-inflammatory structure–activity relationships showed that the *N*-methyl-1,2,3,6-tetrahydropyridyl ring (**11b**) is the best bioisosteric replacement for the

tolyl group in celecoxib. The 1,2,3,6-tetrahydropyridyl ring moiety present in compounds **13** is not a suitable precursor to prepare putative hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 4-[2-(4-methyl(amino)sulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridines (**5**) since the unstable *N*-diazen-1-ium-1,2-diolate intermediate product undergoes protonation and elimination of a HNO species to furnish a *N*-nitroso-1,2,3,6-tetrahydropyridyl product (**14**).

5. Experimental

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Unless otherwise noted, infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer in $CDCl_3$, DMSO-d_6, or $CDCl_3$ + DMSO-d_6 with TMS as the internal standard. Microanalyses were performed for C, H, N (MicroAnalytical Service Laboratory, Department of Chemistry, University of Alberta) and were within ±0.4% of theoretical values. Nominal mass, positive polarity, electrospray, spectra were acquired using a Water's Micromass ZQ 4000 mass spectrometer. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70–230 mesh). 4-(Methylsulfonylphenyl)hydrazine-HCl (**6a**) was synthesized in 53% yield starting from 1-chloro-4-methanesulfonylbenzene[23] which was prepared by the Friedel–Crafts reaction of methanesulfonyl chloride with chlorobenzene.[24] 4-(Sulfamoylphenyl)hydrazine-HCl (**6b**) was synthesized in 84% yield starting from sulfanilamide.[25] All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification.

5.1. General method for the synthesis of hydrazones (8a–b) and celecoxib analogs (9a–b)

A solution of the hydrazine hydrochloride **6a** or **6b** (36 mmol) and the dione **7** (7.10 g, 32.73 mmol) in 95% ethanol (400 mL) was heated at reflux with stirring for 20 h. After cooling to 25 °C, the reaction mixture was concentrated in vacuo to yield a gummy residue. The two products were separated by silica gel column chromatography using acetone/hexanes (1:1, v/v) as eluent to furnish the respective products **8a** or **8b** and **9a** or **9b**. Some physical and spectroscopic data for **8a**–**b** and **9a**–**b** are listed below.

5.1.1. 4,4,4-Trifluoro-3-[(4-methanesulfonylphenyl)-hydrazono]-1-pyridin-4-ylbutan-1-one (8a)

Yield, 21%; yellow solid; mp 201–204 °C; IR (film) 3510 broad (NH), 1290, 1150 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.18 (s, 3H, SO_2Me), 3.70 (d, 1H, J = 19.5 Hz, =C(CF_3)C*H*H′CO–), 4.07 (d, 1H, J = 19.5 Hz, =C(CF_3)CH*H*′CO–), 7.70–7.80 (m, 4H, pyridyl H-3, H-5, phenyl H-2, H-6), 7.85 (d, J = 9.1 Hz, 2H, phenyl H-3, H-5), 8.70 (d, 2H, J = 6.1 Hz, pyridyl H-2, H-6), 8.84 (s, 1H, N*H* that exchanges with D_2O); MS (M+H)$^+$ 386.05.

5.1.2. 4-[*N*-(3-Oxo-3-pyridin-4-yl-1-trifluoromethyl-propylidene)hydrazino]benzenesulfonamide (8b)

Yield, 30%; yellow solid; mp 170–172 °C; IR (film) 3500–3150 broad (NH_2), 1300, 1120 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 3.65 (d, 1H, J = 18.9 Hz, =C(CF_3)C*H*H′CO–), 3.85 (d, 1H, J = 18.9 Hz, =C(CF_3)CH*H*′CO–), 7.06 (s, 2H, SO_2NH_2), 7.65 (d, 2H, J = 5.5 Hz, pyridyl H-3, H-5), 7.71 (d, J = 9.1 Hz, 2H, phenyl H-3, H-5), 7.82 (d, J = 9.1 Hz, 2H, phenyl H-2, H-6), 8.44 (s, 1H, N*H* that exchanges with D_2O), 8.68 (d, 2H, J = 5.5 Hz, pyridyl H-2, H-6); MS (M+H)$^+$ 386.99.

5.1.3. 4-[2-(4-Methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]pyridine (9a)

Yield, 37%; pale yellow solid; mp 158–160 °C; IR (film) 1325, 1160 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.29 (s, 3H, SO_2Me), 7.35 (d, 2H, J = 6.1 Hz, pyridyl H-3, H-5), 7.50 (s, 1H, pyrazole H-4), 7.69 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 8.06 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 8.65 (d, 2H, J = 6.1 Hz, pyridyl H-2, H-6); MS (M+H)$^+$ 368.05.

5.1.4. 4-(5-Pyridin-4-yl-3-trifluoromethylpyrazol-1-yl)-benzenesulfonamide (9b)

Yield, 41%; pale yellow solid; mp 237–239 °C (lit.[16] mp 236–238 °C); IR (film) 3374, 3281 (NH_2), 1325, 1165 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.34 (d, 2H, J = 6.1 Hz, pyridyl H-3, H-5), 7.48 (s, 1H, pyrazole H-4), 7.56 (s, 2H, SO_2NH_2 that exchanges with D_2O), 7.61 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 7.91 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 8.64 (d, 2H, J = 6.1 Hz, pyridyl H-2, H-6); MS (M+H)$^+$ 369.01.

5.2. General procedure for the synthesis of *N*-methylpyridinium iodides (10a–b)

Methyl iodide (0.66 mL, 10.40 mmol) was added to a stirred solution of either **9a** or **9b** (10 mmol) in acetone (25 mL) and the reaction mixture was stirred at 25 °C for 12 h according to a reported procedure.[17] The solid that precipitated from solution was filtered out to furnish the respective methyl iodide salt **10**. Some physical and spectroscopic data for **10a** and **10b** are listed below.

5.2.1. 1-Methyl-4-[2-(4-methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]pyridinium iodide (10a)

Yield, 90%; yellow solid; mp 255–258 °C; IR (film) 1340, 1125 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 3.16 (s, 3H, SO_2Me), 4.36 (s, 3H, N*Me*), 7.58 (s, 1H, pyrazole H-4), 7.67 (d, 2H, J = 8.5 Hz, phenyl H-2, H-6), 7.95 (d, 2H, J = 6.7 Hz, pyridinium H-3, H-5), 7.69 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 8.04 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 9.02 (d, 2H, J = 6.7 Hz, pyridinium H-2, H-6).

5.2.2. 1-Methyl-4-[2-(4-sulfamoylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]pyridinium iodide (10b)

Yield, 93%; greenish yellow solid; mp 175–177 °C; IR (film) 3325 (broad, NH_2), 1339, 1165 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.97 (s, 3H, N*Me*), 6.87 (s, 2H, SO_2NH_2 that exchanges with D_2O), 7.03 (s, 1H, pyrazole H-4), 7.10 (d, J = 8.6 Hz, 2H, phenyl H-2, H-6), 7.46 (d, 2H, J = 6.8 Hz, pyridinium H-3, H-5), 7.58 (d, J = 8.6 Hz, 2H, phenyl H-3, H-5), 8.62 (d, 2H, J = 6.8 Hz, pyridinium H-2, H-6).

5.3. General procedure for the synthesis of *N*-methyl-1,2,3,6-tetrahydropyridines (11a–b)

A solution of the *N*-methylpyridinium iodide **10a** or **10b** (8.84 mmol) in methanol (250 mL) was cooled to 5 °C[18] and sodium borohydride (1.50 g, 39.65 mmol) was added in small aliquots with stirring during a period of a few minutes. The reaction mixture was allowed to warm to 25 °C and the reaction mixture was stirred for an additional 30 min at 25 °C. The contents of the reaction mixture were concentrated in vacuo to dryness and a solution of saturated Na_2CO_3 (150 mL) was added. This mixture was extracted with EtOAc (3× 100 mL), the organic phase was washed successively with water and brine, and the EtOAc fraction was dried ($MgSO_4$). Filtration and then removal of the solvent in vacuo from the organic fraction gave the respective *N*-methyl-1,2,3,6-tetrahydropyridine **11a** or **11b**. Some physical and spectroscopic data for **11a** and **11b** are listed below.

5.3.1. 4-[2-(4-Methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1-methyl-1,2,3,6-tetrahydropyridine (11a)

Yield, 99%; white solid; mp 153–155 °C; IR (film) 1317, 1165 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.25–2.29 (m, 2H, tetrahydropyridyl H-3), 2.37 (s, 3H, N*Me*), 2.56 (t, 2H, *J* = 5.5 Hz, tetrahydropyridyl H-2), 3.02–3.06 (m, 2H, tetrahydropyridyl H-6), 3.09 (s, 3H, SO_2*Me*), 5.82–5.86 (m, 1H, tetrahydropyridyl H-5) 6.59 (s, 1H, pyrazole H-4), 7.76 (d, 2H, *J* = 8.5 Hz, phenyl H-2, H-6), 8.05 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5); MS $(M+H)^+$ 386.09. Anal. Calcd for $C_{17}H_{18}F_3N_3O_2S$: C, 52.98; H, 4.71; N, 10.90. Found: C, 52.94; H, 4.93; N, 11.09.

5.3.2. 4-[5-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (11b)

Yield, 90%; white solid; mp 243–245 °C; IR (film) 3322 (broad NH_2), 1325, 1145 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.13–2.19 (m, 2H, tetrahydropyridyl H-3), 2.26 (s, 3H, N*Me*), 2.47 (t, 2H, *J* = 5.5 Hz, tetrahydropyridyl H-2), 2.93–2.96 (m, 2H, tetrahydropyridyl H-6), 5.78–5.79 (m, 1H, tetrahydropyridyl H-5), 6.58 (s, 1H, pyrazole H-4), 7.28 (s, 2H, SO_2NH_2 that exchanges with D_2O), 7.58 (d, 2H, *J* = 8.5 Hz, phenyl H-3, H-5), 7.95 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6); MS $(M+H)^+$ 387.12. Anal. Calcd for $C_{16}H_{17}F_3N_4O_2S$: C, 49.73; H, 4.43; N, 14.50. Found: C, 49.55; H, 4.75; N, 14.40.

5.4. General procedure for the synthesis of *N*-ethoxycarbonyl-1,2,3,6-tetrahydropyridines (12a–b)

Ethyl chloroformate (2.23 mL, 23.37 mmol) was added drop wise to a stirred solution of a *N*-methyl-1,2,3,6-tetrahydropyridine **11a** or **11b** (7.79 mmol) in 1,2-dichloroethane (30 mL) at 25 °C following a procedure analogous to a literature method.[19] The reaction was allowed to proceed at reflux with stirring for 12 h, and the solvent was removed in vacuo to afford the crude product. Purification by silica gel column chromatography using EtOAc/hexanes (2:1, v/v) as eluent furnished the respective *N*-ethoxycarbonyl-1,2,3,6-tetrahydropyridine **12a** or **12b**. Some physical and spectroscopic data for **12a** and **12b** are listed below.

5.4.1. 4-[2-(4-Methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1-ethoxycarbonyl-1,2,3,6-tetrahydropyridine (12a)

Yield, 95%; viscous oil; IR (film) 1693 (CO), 1325, 1153 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 2.11–2.29 (m, 2H, tetrahydropyridyl H-3), 3.12 (s, 3H, SO_2*Me*), 3.51–3.65 (m, 2H, tetrahydropyridyl H-2), 4.02–4.12 (m, 2H, tetrahydropyridyl H-6), 4.17 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 5.82–6.02 (m, 1H, tetrahydropyridyl H-5) 6.62 (s, 1H, pyrazole H-4), 7.74 (d, 2H, *J* = 8.5 Hz, phenyl H-2, H-6), 8.07 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5); MS $(M+Na)^+$ 466.09.

5.4.2. 4-[2-(4-Sulfamoylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1-ethoxycarbonyl-1,2,3,6-tetrahydropyridine (12b)

Yield, 60%; viscous oil; IR (film) 3310 (broad NH_2), 1708 (CO), 1377, 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, *J* = 7.3 Hz, CH_2CH_3), 2.13–2.21 (m, 2H, tetrahydropyridyl H-3), 3.54 (t, 2H, *J* = 5.5 Hz, tetrahydropyridyl H-2), 4.04–4.10 (m, 2H, tetrahydropyridyl H-6), 4.13 (q, 2H, *J* = 7.3 Hz, CH_2CH_3), 5.49 (s, 2H, SO_2NH_2 that exchanges with D_2O), 5.85–5.94 (m, 1H, tetrahydropyridyl H-5), 6.59 (s, 1H, pyrazole H-4), 7.63 (d, 2H, *J* = 8.5 Hz, phenyl H-2, H-6), 8.01 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5); MS $(M+Na)^+$ 467.05.

5.5. General Procedure for the synthesis of 1,2,3,6-tetrahydropyridines (13a–b)

A solution of a *N*-ethoxycarbonyl-1,2,3,6-tetrahydropyridine **12a** or **12b** (6 mmol) in hydrochloric acid (10 N, 10 mL) was refluxed for 3 h using a modified literature method.[19] The reaction mixture was cooled to 25 °C prior to evaporated to dryness in vacuo. A solution of saturated $NaCO_3$ (20 mL) was added and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed successively with water and then brine, and the EtOAc fraction was dried ($MgSO_4$). Filtration and removal of the solvent from the organic fraction in vacuo afforded the impure product which was purified by silica gel column chromatography. Elution with EtOAc/methanol (1:1, v/v) furnished the respective 1,2,3,6-tetrahydropyridine product **13a** or **13b**. Some physical and spectroscopic data for **13a** and **13b** are listed below.

5.5.1. 4-[2-(4-Methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridine (13a)

Yield, 55%; brown solid; mp 88–91 °C; IR (film) 3337 (NH), 1320, 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11–2.23 (m, 2H, tetrahydropyridyl H-3), 2.65 (br s, 1H, tetrahydropyridyl N*H* that exchanges with D_2O), 2.98 (t, 2H, *J* = 5.5 Hz, tetrahydropyridyl H-2), 3.08 (s, 3H, SO_2*Me*), 3.42–3.51 (m, 2H, tetrahydropyridyl H-6), 5.90–5.98 (m, 1H, tetrahydropyridyl H-5) 6.58 (s, 1H, pyrazole H-4), 7.77 (d, 2H, *J* = 8.5 Hz, phenyl H-2, H-6), 8.04 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5); MS $(M+H)^+$ 372.08. Anal. Calcd for $C_{16}H_{16}F_3N3O_2S{\cdot}1/3H_2O$: C, 50.92; H, 4.45; N, 11.13. Found: C, 51.26; H, 4.72; N, 10.85.

5.5.2. 4-[5-(1,2,3,6-Tetrahydropyridin-4-yl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (13b)

Yield, 33%; brown solid; IR (film) 3320 (broad NH), 1350, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 1.71–1.82 (m, 2H, tetrahydropyridyl H-3), 2.06 (t, 2H, *J* = 5.5 Hz, tetrahydropyridyl H-2), 2.50–2.61 (m, 2H, tetrahydropyridyl H-6), 5.35–5.45 (m, 1H, tetrahydropyridyl H-5), 6.15 (s, 1H, pyrazole H-4), 6.80 (s, 2H, SO_2NH_2 that exchanges with D_2O), 7.18 (d, 2H, *J* = 8.5 Hz, phenyl H-3, H-5), 7.56 ppm (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6); ^{13}C NMR (DMSO-d_6) δ 27.9 (tetrahydropyridyl C-3), 42.0 (tetrahydropyridyl C-2 or C-6), 44.6 (tetrahydropyridyl C-6 or C-2), 104.9 (pyrazole C-4), 123.0 (pyrazole C-5), 124.8 (CF_3), 125.3 (phenyl C-3, C-5), 126.9 (phenyl C-2, C-6), 132.2 (tetrahydropyridyl C-5), 141.5 (phenyl C-4), 142.1 (tetrahydropyridyl C-4), 143.9 (phenyl C-1), 146.5 (pyrazole C-3); MS $(M+H)^+$ 373.08.

5.6. 4-[2-(4-Methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1-nitroso-1,2,3,6-tetrahydropyridine (14)

4-[2-(4-Methanesulfonylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-1,2,3,6-tetrahydropyridine (**13a**, 0.83 g, 2.24 mmol) was added to a solution of NaOMe (2.24 mmol, 0.5 mL of a 25% w/v solution in MeOH) and diethyl ether (10 mL) with stirring at 25 °C. Acetonitrile (10 mL) was then added to the reaction mixture to increase the solubility of **13a**. This mixture was purged with dry nitrogen gas for 5 min, and then the reaction was allowed to proceed under an atmosphere of nitric oxide (40 psi internal pressure) with stirring at 25 °C for 48 h. Removal of the solvents in vacuo gave a the dark brown residue that was purified by silica gel column chromatography using a EtOAc/hexane (1:1, v/v) as eluent to yield the *N*-nitroso product (**14**) in 53% yield, mp 190–192 °C; IR (film) 1320, 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45–2.55 (m, 2H, tetrahydropyridyl H-3), 3.12 (s, 3H, SO_2*Me*), 4.30–4.38 (m, 2H, tetrahydropyridyl H-6), 4.43 (t, 2H, *J* = 5.5 Hz, tetrahydropyridyl H-2), 5.95–6.0 (m, 1H, tetrahydropyridyl H-5) 6.66 (s, 1H, pyrazole H-4), 7.73 (d, 2H, *J* = 8.5 Hz, phenyl H-2, H-6), 8.09 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5); MS $(M+Na)^+$ 423.02. Anal. Calcd for $C_{16}H_{15}F_3N_4O_3S$: C, 48.00; H, 3.78; N, 13.99. Found: C, 48.07; H, 4.03; N, 13.81.

5.7. *N*-Nitroso-1,2,3,6-tetrahydropyridne (16)

1,2,3,6-Tetrahydropyridine (**15**, 100 mg, 1.2 mmol) was added to a solution of NaOMe (65 mg of 95% purity, 1.2 mmol) in Et_2O (5 mL) and acetonitrile (2 mL) with stirring at 25 °C. This mixture was purged with argon for 5 min, and the reaction was allowed to proceed under an atmosphere of nitric oxide gas (40 psi internal pressure) with stirring at 25 °C for 1 h. The reaction mixture was filtered to remove some solid material which ^{1}H NMR indicated did not contain any of the sodium diazeniumdiolate product. The solvent was removed from the filtrate to furnish *N*-nitroso-1,2,3,6-tetrahydropyridine (**16**) in 27% yield. A similar reaction performed using NaOMe (25% in MeOH) in Et_2O afforded **16** in 46% yield. In a third reaction, nitric oxide gas was bubbled into a solution of **15** using an aprotic solvent system[26] comprised of acetonitrile and diethyl ether (1:0.5, v/v) at -78 °C to also give *N*-nitroso-1,2,3,6-tetrahydropyridine (**16**) as a dark brown liquid in 40% yield. ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 0.4H, H-3), 2.48 (m, 1.6H, H-3), 3.96 (t, J = 6.0 Hz, 0.4H, H-2), 4.37 (t, J = 6.0 Hz, 1.6H, H-2), 4.20 (m, 1.6H, H-6), 4.77 (m, 0.4H, H-6), 5.65–6.00 (m, 2H, H-4, H-5); MS $(M+H)^+$ 113.02. This ^{1}H NMR spectral data is in agreement with previously reported data for *N*-nitroso-1,2,3,6-tetrahydropyridine (**16**).[27]

5.8. In vivo anti-inflammatory assay

The test compounds **11**–**14**, and the reference drugs celecoxib and aspirin, were evaluated using the in vivo carrageenan-induced foot paw edema model reported previously.[28]

Acknowledgment

The authors are grateful to the Canadian Institutes of Health Research (CIHR) (MOP-14712) for financial support of this research.

References and notes

1. Hinz, B.; Brune, K. *Pharmacol. Exp. Ther.* **2002**, *300*, 367.
2. Patel, H. H.; Gross, G. J. *J. Mol. Cell. Cardiol.* **2002**, *34*, 1.
3. Mukherjee, D. *Biochem. Pharmacol.* **2002**, *63*, 817.
4. Scheen, A. J. *Rev. Med. Liege* **2004**, *59*, 565.
5. Dogné, J.-M.; Supuran, C. T.; Pratico, D. *J. Med. Chem.* **2005**, *48*, 2251.
6. Butler, A. R.; Williams, D. L. H. *Chem. Soc. Rev.* **1993**, *22*, 233.
7. Dhawan, V.; Schwalb, D. J.; Shumway, M. J.; Warren, M. C.; Wexler, R. S.; Zemtseva, I. S.; Zifcak, B. M.; Janero, D. R. *Free Radical Biol. Med.* **2005**, *39*, 1191.
8. Ranatunge, R. R.; Augustyniak, M.; Bandarage, U. K.; Earl, R. A.; Ellis, J. L.; Garvey, D. S.; Janero, D. R.; Letts, L. G.; Martino, A. M.; Murty, M. G.; Richardson, S. K.; Schroeder, J. D.; Shumway, M. J.; Tam, S. W.; Trocha, M.; Young, D. V. *J. Med. Chem.* **2004**, *47*, 2180.
9. Abdellatif, K. R. A.; Dong, Y.; Chen, Q.-H.; Chowdhury, M. A.; Knaus, E. E. *Bioorg. Med. Chem.* **2007**, *15*, 6796.
10. Abdellatif, K. R. A.; Chowdhury, M. A.; Dong, Y.; Chen, Q.-H.; Knaus E, E. *Bioorg. Med. Chem.* **2008**, *16*, 3302.
11. Velázquez, C. A.; Praveen Rao, P. N.; Citro, M. L.; Keefer, L. K.; Knaus, E. E. *Bioorg. Med. Chem.* **2007**, *15*, 4767.
12. Velázquez, C. A.; Chen, Q.-H.; Citro, M. L.; Keefer, L. K.; Knaus, E. E. *J. Med. Chem.* **2008**, *51*, 1954.
13. Abdellatif, K. R. A.; Chowdhury, M. A.; Dong, Y.; Knaus, E. E. *Bioorg. Med. Chem.* **2008**, *16*, 6528.
14. Levine, R.; Sneed, J. K. *J. Am. Chem. Soc.* **1951**, *73*, 4478.
15. Thomas, J.; Berkoff, C. E.; Flagg, W. B.; Gallo, J. J.; Haff, R. F.; Pinto, C. A. *J. Med. Chem.* **1975**, *18*, 245.
16. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.
17. Nielsen, A. T.; Moore, D. W.; Mazur, J. H.; Berry, K. H. *J. Org. Chem.* **1964**, *29*, 2898.
18. Waters, J. A.; Spivak, C. E.; Hermsmeier, M.; Yadav, J. S.; Liang, R. F.; Gund, T. M. *J. Med. Chem.* **1988**, *31*, 545.
19. Labouta, I. M.; Falch, E.; Hjeds, H.; Krogsaard-Larsen, P. *Eur. J. Med. Chem.* **1982**, *17*, 531.
20. Tang, X.; Xian, M.; Trikha, M.; Honn, K. V.; Wang, P. G. *Tetrahedron Lett.* **2001**, *42*, 2625.
21. Toscano, J. P.; Pavlos, C. M.; Boppana, K. International PCT Patent, WO 2005/074598 A2, Issued August 18, 2005.
22. Rao, P. N. P.; Amini, M.; Li, H.; Habeeb, A. G.; Knaus, E. E. *J. Med. Chem.* **2003**, *46*, 4872. and references cited therein.
23. Pommery, N.; Taverne, T.; Telliez, A.; Goossens, L.; Charlier, C.; Pommery, J.; Goossens, J.-F.; Houssin, R.; Durant, F.; Henichart, J.-P. *J. Med. Chem.* **2004**, *47*, 6195.
24. Truce, W. E.; Vriesen, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 5032.
25. Soliman, R. *J. Med. Chem.* **1979**, *22*, 321.
26. Cai, T. B.; Tang, X.; Nagorski, J.; Brauschweigerb, P. G.; Wanga, P. G. *Bioorg. Med. Chem.* **2003**, *11*, 4971.
27. Saavedra, J. E. *J. Org. Chem.* **1979**, *44*, 4511.
28. Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.