Synthesis of new 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1H-pyrazoles: A search for novel nitric oxide donor anti-inflammatory agen...

ARTICLE *in* BIOORGANIC & MEDICINAL CHEMISTRY LETTERS · SEPTEMBER 2014

Impact Factor: 2.42 · DOI: 10.1016/j.bmcl.2014.09.024

3 AUTHORS:

Khaled Abdellatif
Beni Suef University
51 PUBLICATIONS **401** CITATIONS
SEE PROFILE

Abeer Moawad
Beni Suef University
8 PUBLICATIONS **19** CITATIONS
SEE PROFILE

Ed Knaus
University of Alberta
187 PUBLICATIONS **1,832** CITATIONS
SEE PROFILE

Bioorganic & Medicinal Chemistry Letters 24 (2014) 5015–5021

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis of new 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles: A search for novel nitric oxide donor anti-inflammatory agents

Khaled R. A. Abdellatif [a,*], Abeer Moawad [b], Edward E. Knaus [c]

[a] Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
[b] Pharmacognosy Department, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
[c] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta T6G 2N8, Canada

ARTICLE INFO

Article history:
Received 5 August 2014
Revised 5 September 2014
Accepted 8 September 2014
Available online 16 September 2014

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

ABSTRACT

A group of 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles (**12a–f**) was synthesized and evaluated as anti-inflammatory agents. While all the compounds (20 mg/kg) showed significant anti-inflammatory activity after 3 h of inflammation induction (69–89%) as compared to celecoxib (80%), 1-(4-methanesulfonylphenyl)-5-(4-methylaminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazole (**12a**) was found to be the most effective one (89%). The synthesis of model hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 1-(4-methanesulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles (**10a–f**) requires further investigation since the reaction of *N*-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)ethanamine (**12b**) or 1-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)piperazine (**12c**) with nitric oxide furnished *N*-nitroso derivatives (**13** and **14**), respectively, rather than the desired *N*-diazen-1-ium-1,2-diolate derivatives (**10b** and **10c**).

The anti-inflammatory activity (AI) of non-steroidal anti-inflammatory drugs (NSAIDs) results from enzymatic inhibition of cyclooxygenase (COX) mediated production of pro-inflammatory prostaglandins (PGs) and thromboxanes (TXs).[1,2] The cyclooxygenase enzyme exists in two distinct isoforms, a constitutive form (COX-1) and an inducible form (COX-2). The constitutive COX-1 plays an important role in the maintenance of physiological functions such as protection of gastric mucosa, vascular homeostasis, and platelet aggregation, whereas the inducible COX-2 is over expressed during acute and chronic inflammation.[3] Traditional NSAIDs interact with both forms (COX-1 and COX-2) and therefore their long term administration often causes gastro intestinal side effects that encompass gastric ulceration and bleeding. For this reason, synthesis of selective COX-2 inhibitor drugs (coxibs) attracted much interest in recent years that achieve the same anti-inflammatory activity as traditional NSAIDs but with minimal risk of undesirable gastrointestinal side effects.[4] Celecoxib (**1**), rofecoxib (**2**), valdecoxib (**3**), and etoricoxib (**4**) were the most common coxibs approved for therapeutic use. Unfortunately, some drugs within this group such as rofecoxib (**1**) and valdecoxib (**3**) 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).[5–7] This combination of adverse biochemical changes in the COX pathway are responsible for increased prevalence of high blood pressure and myocardial infarction that subsequently caused the withdrawal of rofecoxib (Vioxx®) and valdecoxib (Bextra®).[8,9]

Nitric oxide (NO) exhibits a number of useful pharmacological actions that include vascular relaxation (vasodilation), and inhibition of platelet aggregation and adhesion.[10] 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, we previously reported NO-coxib ester prodrugs (**5–9**) 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.[11–15] The spontaneous decomposition reaction of *N*-diazeniumdiolates (**5–9**, Fig. 1) in physiological medium would release (upon esterase-mediated hydrolysis) not only the active components (coxib and NO) but also 1 equiv of the corresponding amine and 1 equiv formaldehyde for **5**, in addition to 1 equiv acetic acid for **6–9**.[11–15] Considering the toxicity of

* Corresponding author. Tel.: +20 1002535444; fax: +20 822317958.
E-mail address: khaled.ahmed@pharm.bsu.edu.eg (K.R.A. Abdellatif).

http://dx.doi.org/10.1016/j.bmcl.2014.09.024
0960-894X/

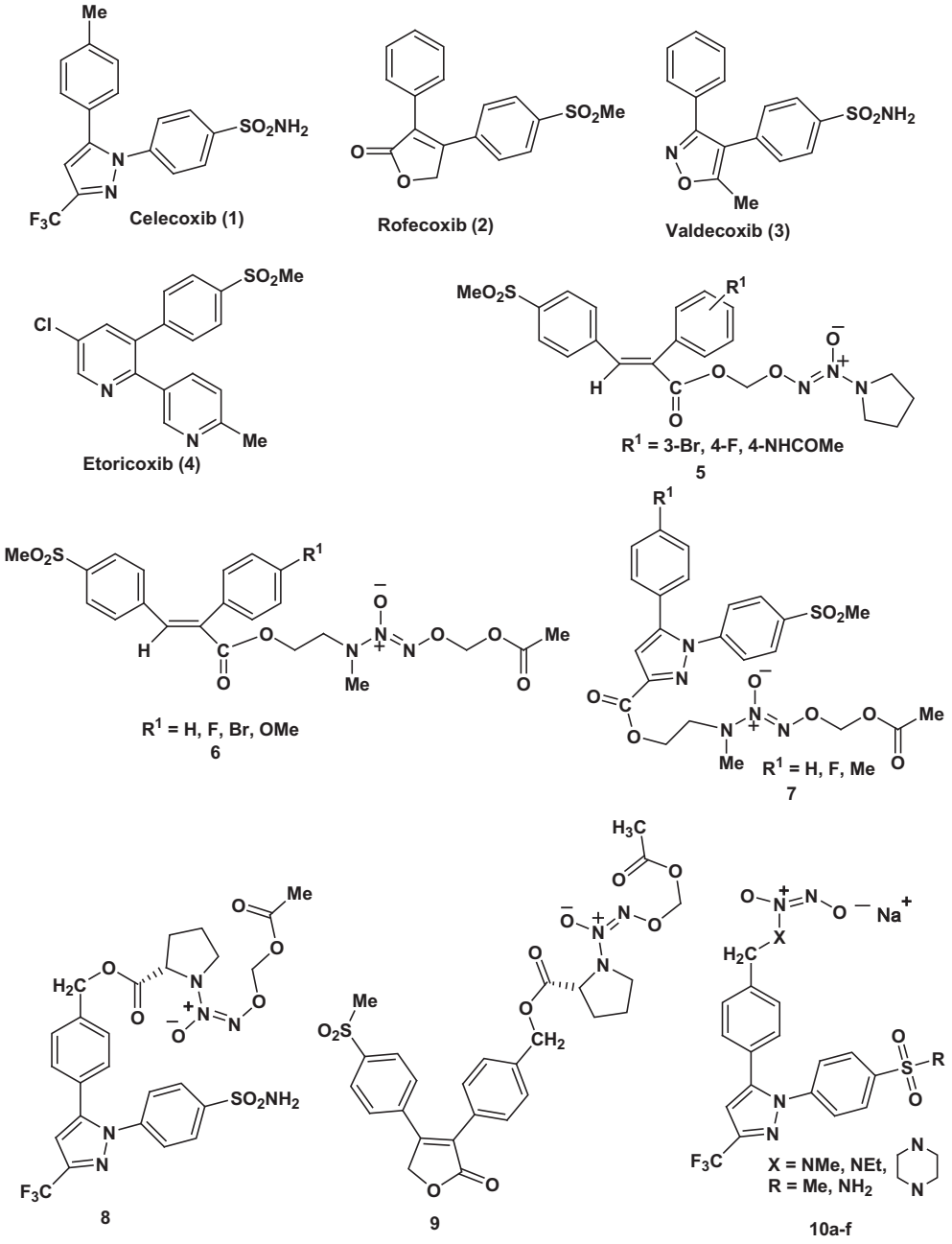
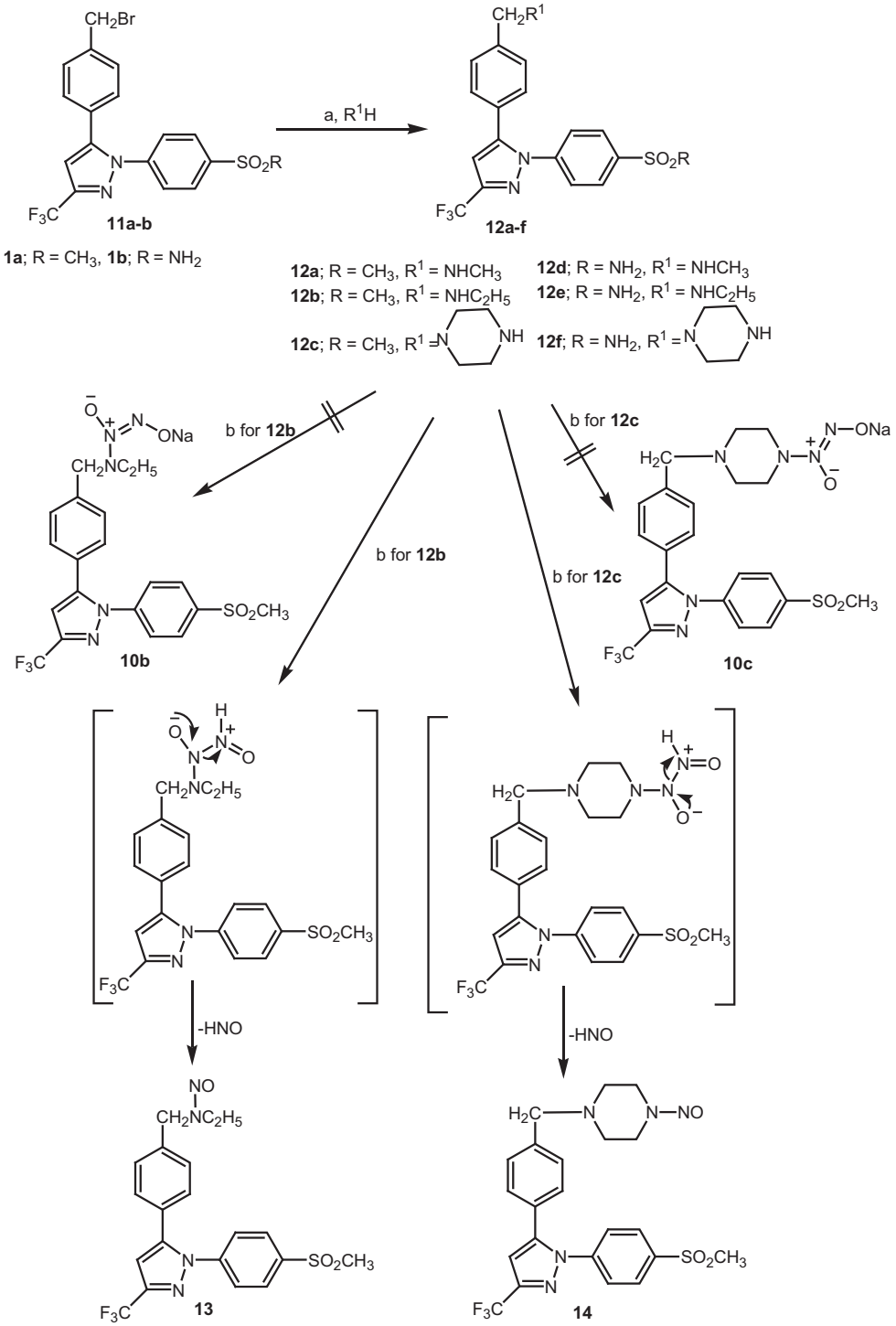


Figure 1. Chemical structures of the selective cyclooxygenase-2 (COX-2) inhibitors rofecoxib (**1**), celecoxib (**2**), valdecoxib (**3**), etoricoxib (**4**), the NO coxibs (**5**–**9**), and the putative hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles (**10a**–**f**).

these byproducts we initiated a study to address this issue by developing strategies to minimize or eliminate the risk of exposure to toxic compounds in patients who may be treated with NO-coxibs. Accordingly, 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 1-(4-methane(amino) sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles (**10a**–**f**) that upon decomposition releases only the active components (coxib and NO) (see structure **10a**–**f** in Fig. 1).

A group of 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles (**12a**–**f**) were synthesized in good yield (57–71%) via reaction of 1-(4-methane(amino)sulfonylphenyl)-5-(4-bromomethylphenyl)-3-trifluoromethyl-1*H*-pyrazole (**11a**) or (**11b**) with methylamine, ethylamine or piperazine in dry THF at 25 °C. An initial study was directed toward synthesis of the target hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives **10b** and **10c** from *N*-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)ethanamine (**12b**) and 1-(4-(1-(4-(methylsulfonyl) phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)piperazine (**12c**) respectively. However, reaction of the substituted amino derivatives 1**2b** and **12c** with nitric oxide gas (40 psi) under a variety of experimental conditions (aprotic and protic solvent systems, various temperatures) afforded the *N*-nitroso derivatives **13** and **14**, respectively, as the sole isolable products rather than the desired products **10b** and **10c** (see Scheme 1). The formation of the *N*-nitroso products **13** and **14** upon reaction of 1**2b** and **12c**



Scheme 1. Reagents and conditions: (a) THF, 25 °C, 1 h; (b) THF, NaOMe (95%), NO (40 psi), −65 °C, 1 h or MeCN, NaOMe (25% in MeOH), NO (40 psi), 25 °C, 24 h.

with nitric oxide indicates that the initially formed unstable intermediates (*N*-amino-*N*-diazen-1-ium-1,2-diolate products of **12b** and **12c**) must undergo protonation of the diazen-1-ium-1,2-diolate N^2-nitrogen which subsequently eliminates HNO (see mechanism shown in Scheme 1).[16,17]

N-Ethyl-*N*-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1*H*-pyrazol-5-yl)benzyl)nitrous amide (**13**) shows duplicate signals in the ^{1}H NMR and ^{13}C NMR spectra (Figs. 2 and 3) which suggest the presence of a pair of rotamers. Rotamers are conformational isomers where interconversion by rotation around a single bond is restricted. The phenomenon of hindered rotation around C—C bond due to the presence of a bulky group in the vicinity of this bond is well known in many organic compounds. For example, methoxy group can hinder the rotation around the biflavanyl bond in biflavonoids.[18] HPLC analysis for compound **13**, using a variety of solvent systems, showed only one peak. The two rotamers existed in a ratio of 1:0.6 according to the integration for the CH_3 resonance of the ethyl group at δ 0.89 and δ 1.31 in $CDCl_3$ and in a ratio of 1:0.76 in DMSO-d_6. The restricted rotation appears to be around the benzyl (CH_2—N) bond. It can be seen that the signals

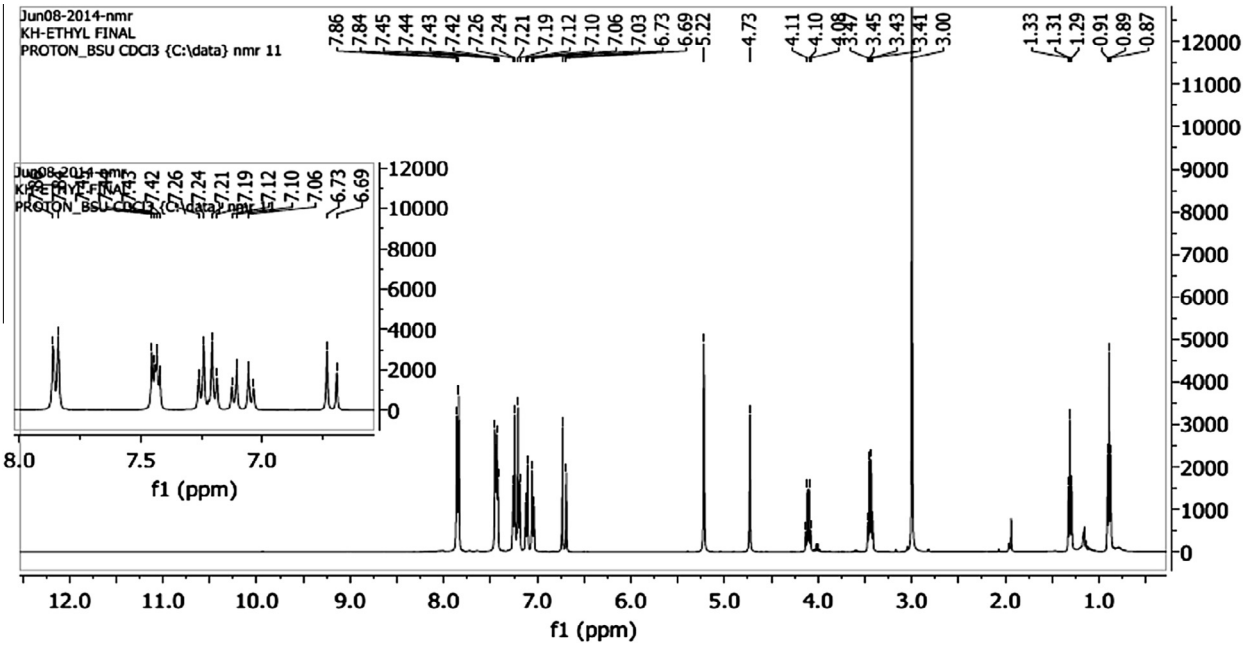


Figure 2. ^{1}H NMR for compound (**13**) (400 MHz, $CDCl_3$).

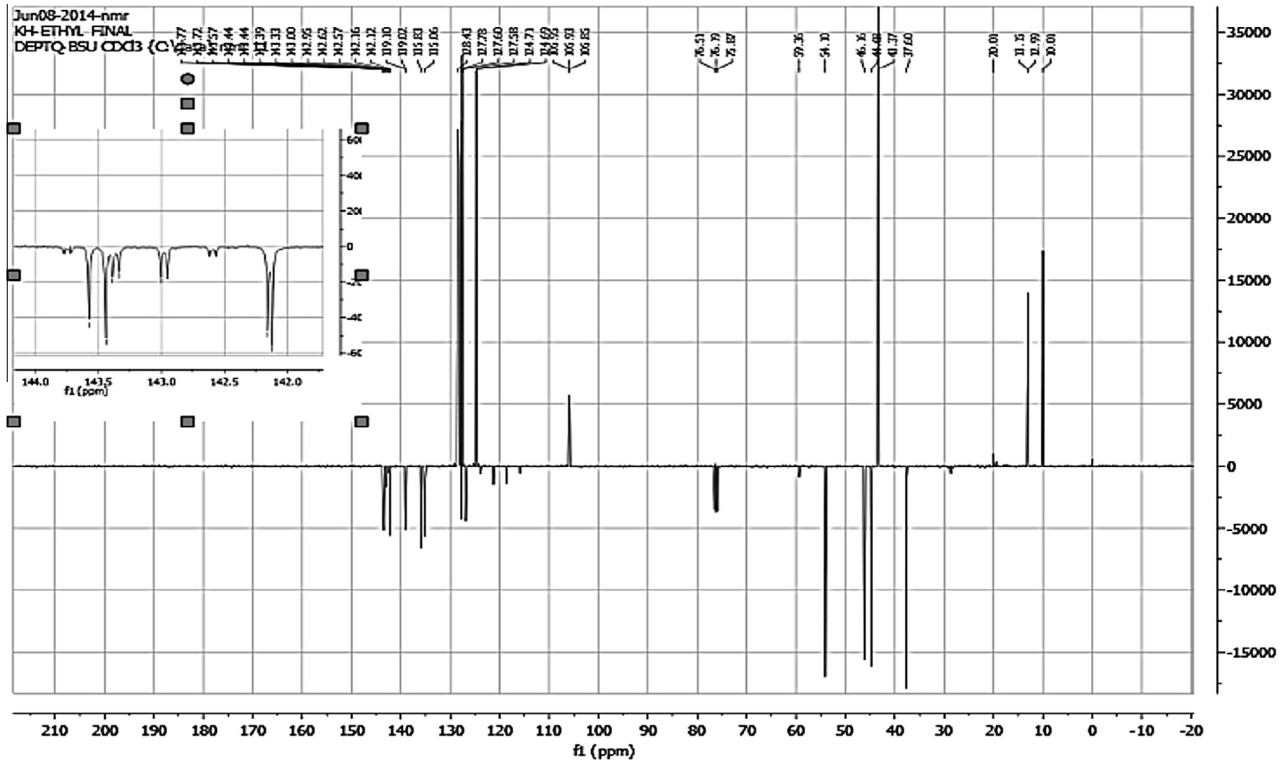


Figure 3. DEPTQ spectrum for compound (**13**) (100 MHz, $CDCl_3$).

for the ethyl and benzyl substituent show some clear differences in the chemical shifts between the two rotamers. Thus, the resonances for the ethyl group of the major rotamer appeared at δ 0.89 (t) and δ 3.44 (q) while those for the minor rotamer were present at δ 1.30 (t) and 4.10 (q). The benzyl group is similarly affected with its CH_2 group showing two singlets near δ 5.22 for the major rotamer and δ 4.74 for the minor rotamer. The aromatic protons showed four doublets at δ 7.20 and 7.25 for the major rotamer and at δ 7.05 and 7.11 for the minor rotamer. A 2D NOESY experiment showed correlations between spatially close protons. Correlations between the ethyl protons and the aromatic proton of the benzyl ring (Fig. 4) supports our assumption that the orientation of the ethyl group is in a position capable of hindering the free rotation of the benzyl group. As the distance from the hindered rotation zone is increased, the signals of the same protons for the two rotamers become closer to each other. In this regard, the

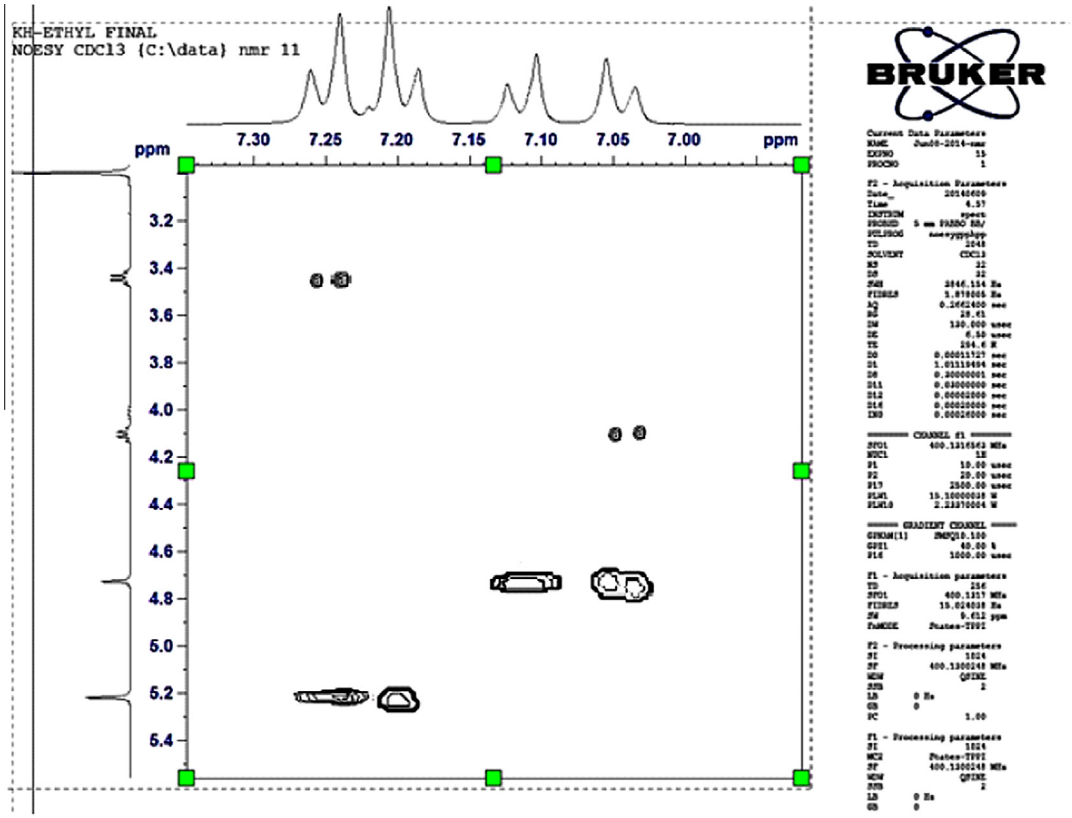


Figure 4. NOESY spectrum for compound (**13**).

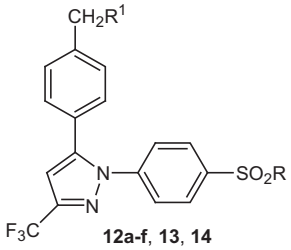
aromatic protons of the methanesulfonylphenyl ring showed two overlapped doublets, and the SO_2–CH_3 protons appeared as one singlet that integrated as 5.6 protons at δ 3.00. Complete assignment of the two rotamers was performed using 1D and 2D NMR techniques (COSY, NOESY, HSQC, and HMBC). Careful examination of HMBC spectrum showed no long range coupling between the protons of one rotamer and the carbons of the other indicating that compound **13** is not a dimer. The possibility of having a dimer is also unlikely due to the presence of the two identical compounds in different ratios, and the fact that their ratio is altered depending upon the NMR solvent used. The NMR solvent is a determinant of hydrogen bonding capability which in turn affects the stability (ratio) of the rotamers.[19]

Hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles (see structure **10a–f** in Fig. 1) constitute a potential class of selective COX-2 inhibitor compounds that are devoid of adverse cardiovascular properties. The design of **10a–f** was 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, (ii) attachment of a substituted-aminomethylphenyl ring substituent via its C-4 sp^2 hybridized carbon atom is consistent with the observation that two aryl rings on adjacent positions of a five-membered heterocyclic ring template (scaffold) generally provide optimum COX-2 inhibitory activity, and (iii) the *N*,*N*-di substituted-aminomethylphenyl secondary amino group that is present in compounds **12a–f**, provides a logical synthon for elaboration to the corresponding nitric oxide donor *N*-diazen-1-ium-1,2-diolates.[20] Unfortunately, reaction of **12b** and **12c** with nitric oxide afforded the corresponding *N*-nitroso products **13** and **14** rather than the desired unisolable intermediate *N*-diazen-1-ium-1,2-diolate product **10b** and **10c**, respectively (see Scheme 1).

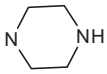
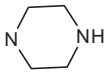
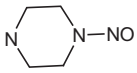
The anti-inflammatory (AI) activities for a group of 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles (**12a–f**) and *N*-nitroso derivatives (**13** and **14**) were determined using a carrageenan-induced rat foot paw edema model (see data in Table 1). Structure–activity relationships acquired for **12a–f** showed that the relative AI potency profile (i) with respect to the COX-2 pharmacophore moiety was $SO_2Me > SO_2NH_2$ in all derivatives (R^1 = NHMe, NHEt, piperazino) and at all time intervals (1, 3 and 5 h), (ii) within the SO_2Me group of compounds, the relative potency profile was NHMe > piperazino > NHEt with respect to the R^1 substituent, (iii) within the SO_2NH_2 group of compounds, the three derivatives showed similar AI activity (54%, 53%, 58% at the 1 h interval) and (69%, 71%, 70% at the 3 h interval). In comparison at the 5 h time interval, the relative potency order was NHMe (57%) > NHEt (39%) > piperazino (35%) with respect to the R^1 substituent, and (iv) the most potent compound **12a** (R = Me, R^1 = NHMe, % AI inhibition = 72%, 89%, 67% at 1, 3, 5 h intervals, respectively) exhibited anti-inflammatory activities higher than that of the reference drug celecoxib (% AI inhibition = 40%, 80%, 48% at 1, 3, 5 h intervals, respectively). In contrast, the *N*-nitroso derivatives **13** and **14** showed poor activity at all time intervals.

In conclusion, a group of 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethyl-phenyl)-3-trifluoromethyl-1*H*-pyrazoles (**12a–f**) were synthesized[21] and evaluated as anti-inflammatory agents[22]. All compounds showed significant anti-inflammatory activity after 3 h of inflammation induction (69–89%) as compared to celecoxib (80%). The *N*,*N*-disubstituted amino moiety present in compounds **12a–f** is not a suitable precursor to prepare putative hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles **10a–f** since the reaction of **12b** or **12c** with NO afforded the unstable *N*-diazen-1-ium-1,2-diolate products that undergo protonation

Table 1
Anti-inflammatory activities for the 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1*H*-pyrazoles (**12a–f**), nitroso derivatives (**13** and **14**) and reference drug (celecoxib)



12a-f, **13**, **14**

Compound	R	R^1	% of anti-inflammatory activity (AI)		
			1 h	3 h	5 h
12a	Me	$NHCH_3$	72	89	67
12b	Me	NHC_2H_5	66	72	66
12c	Me		67	73	66
12d	NH_2	$NHCH_3$	54	69	57
12e	NH_2	NHC_2H_5	53	71	39
12f	NH_2		58	70	35
13	Me	$NNOC_2H_5$	24	39	25
14	Me		19	43	29
Celecoxib	—	—	40	80	48

All test compounds (**12a–f**, celecoxib) were administrated (20 mg/kg) 30 min prior to testing. The anti-inflammatory activity % is expressed according to the following equation:
AI (%) = $(V_c - V_t/V_c) \times 100$ where V_c represents the paw volume of control group of animals and V_t represents the paw volume in drug treated animals.

and elimination of HNO to furnish the *N*-nitroso derivatives (**13** and **14**), respectively.

References and notes

1. Zarghi, A.; Najafnia, L.; Daraee, B.; Dadrass, O. G.; Hedayati, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5634.
2. Zebardast, T.; Zarghi, A.; Daraie, B.; Hedayati, M.; Dadrass, O. G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3162.
3. Al-Hourani, B. J.; Sharma, S. K.; Mane, J. Y.; Tuszynski, J.; Baracos, V.; Kniess, T.; Suresh, M.; Pietzsch, J.; Wuest, F. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1823.
4. Rathish, I. G.; Javed, K.; Ahmad, S.; Bano, S.; Alam, M. S.; Pillai, K. K.; Singh, S.; Bagchi, V. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 255.
5. Hinz, B.; Brune, K. *J. Pharmacol. Exp. Ther.* **2002**, *300*, 367.
6. Patel, H. H.; Gross, G. J. *J. Mol. Cell Cardiol.* **2002**, *34*, 1.
7. Mukherjee, D. *Biochem. Pharmacol.* **2002**, *63*, 817.
8. Scheen, A. J. *Rev. Med. Liege* **2004**, *59*, 565.
9. Dogné, J.-M.; Supuran, C. T.; Pratico, D. *J. Med. Chem.* **2005**, *48*, 2251.
10. Butler, A. R.; Williams, D. L. H. *Chem. Soc. Rev.* **1993**, *22*, 233.
11. Abdellatif, K. R. A.; Dong, Y.; Chen, Q.-H.; Chowdhury, M. A.; Knaus, E. E. *Bioorg. Med. Chem.* **2007**, *15*, 6796.
12. Abdellatif, K. R. A.; Chowdhury, M. A.; Dong, Y.; Chen, Q.-H.; Knaus, E. E. *Bioorg. Med. Chem.* **2008**, *16*, 3302.
13. Abdellatif, K. R. A.; Chowdhury, M. A.; Dong, Y.; Knaus, E. E. *Bioorg. Med. Chem.* **2008**, *16*, 6528.
14. Abdellatif, K. R. A.; Chowdhury, M. A.; Dong, Y.; Das, D.; Yu, G.; Knaus, E. E. *Bioorg. Med. Chem.* **2009**, *17*, 5182.
15. Abdellatif, K. R. A.; Huang, Z.; Chowdhury, M. A.; Kaufman, S.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3951.
16. Toscano, J. P.; Pavlos, C. M.; Boppana, K. Int. PCT Patent WO 2005/074598 A2, Issued August 18, 2005.
17. Abdellatif, K. R. A.; Chowdhury, M. A.; Knaus, E. E. *J. Heterocycl. Chem.* **2008**, *45*, 1707.
18. Moawad, A.; Hetta, M.; Zjawiony, J. K.; Jacob, M. R.; Hifnawy, M.; Ferreira, D. *Planta Med.* **2010**, *76*, 796.
19. Deet, M. J.; Fahey, J. E.; Smith, B. D. *J. Phys. Org. Chem.* **2001**, *14*, 463.
20. Abdellatif, K. R. A.; Chowdhury, M. A.; Dong, Y.; Das, D.; Yu, G.; Velázquez, C.; Suresh, M. R.; Knaus, E. E. *Bioorg. Med. Chem.* **2008**, *16*, 8882.
21. Experimental procedures and spectral data for compounds **12a–f**, **13** and **14**. *General*. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avence III 400 MHz Spectrophotometer, Faculty of Pharmacy, Beni-Suef University, Egypt in $CDCl_3$ or DMSO-d_6, where *J* (coupling constant) values are estimated in Hertz (Hz). Microanalyses were performed for C, H and N were carried out on Perkin–Elmer 2400 analyzer (Perkin–Elmer, Norwalk, CT, USA) at the Micro analytical unit of Cairo University, Egypt. All compounds were within ±0.4% of the theoretical values. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70–230 mesh). 1-(4-Methane(amino)sulfonylphenyl)-5-(4-bromomethylphenyl)-3-trifluoromethyl-1*H*-pyrazole (**11a** and **11b**) were prepared according to our previously reported procedure (Abdellatif, K. R. A.; Chowdhury, M. A.; Dong, Y.; Velázquez, C.; Das, D.; Suresh, M. R.; Knaus, E. E. *Bioorg. Med. Chem.* **2008**, *16*, 9694). All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification.
*General procedure for the synthesis of 1-(4-methane(amino)sulfonylphenyl)-5-(4-substituted-aminomethylphenyl)-3-trifluoromethyl-1H-pyrazoles (**12a–f**):* The corresponding amine (2.2 mmol) was added drop wise with stirring to a solution of 1-(4-methane(amino)sulfonylphenyl)-5-(4-bromomethylphenyl)-3-trifluoromethyl-1*H*-pyrazole (**11a**) or (**11b**) (1.0 mmol) in dry THF (10 mL). The reaction mixture was stirred at 25 °C for 1 h, and the solvent was removed in vacuo. Potassium carbonate (0.138 g, 1.0 mmol) in water (5 ml) was added to the residue prior to extraction with EtOAc (3 × 15 mL). The combined organic fractions were washed successively with water and brine, and the organic fraction was dried ($MgSO_4$). Filtration and removal of the solvent from the organic fraction in vacuo afforded the crude product which was purified by silica gel column chromatography using EtOAc/MeOH (3:2, v/v) as eluent to furnish the respective title compounds **12a–f**. Physical and spectroscopic data for **12a–f** are listed below.
*N-Methyl-1-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl) phenyl)methan-amine (**12a**):* The product was obtained as a pale yellow powder in 68% yield; mp 112–114 °C; IR (film) 3340 (broad NH), 2975 (C–H aromatic), 2932 (C–H aliphatic), 1319, 1155 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 1H, N*H*, D_2O exchangeable), 2.49 (s, 3H, NCH_3), 3.08 (s, 3H, SO_2CH_3), 3.80 (s, 2H, CH_2), 6.78 (s, 1H, pyrazole H-4), 7.21 (d, *J* = 8.0 Hz, 2H, methylaminomethanephenyl H-3, H-5), 7.36 (d, *J* = 8.0 Hz, 2H, methylaminomethanephenyl H-2, H-6), 7.55 (d, *J* = 8.8 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.94 (d, *J* = 8.8 Hz, 2H, methanesulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 36.17, 44.50, 55.49, 106.69, 120.98 (q, *J* = 268 Hz, CF_3), 125.69, 127.17, 128.57, 128.83, 128.90, 139.86, 142.03, 143.41, 144.35 (q, *J* = 38 Hz, *C*-CF_3), 145.11; MS 410.1 (M+1). Anal. Calcd for $C_{19}H_{18}F_3N_3O_2S{\cdot}1/5H_2O$: C, 55.25; H, 4.49; N, 10.17. Found: C, 55.59; H, 4.79; N, 9.79.

*N-(4-(1-(4-(Methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)benzyl) ethanamine (**12b**):* The product was obtained as a pale yellow powder in 62% yield; mp 83–85 °C; IR (film) 3335 (broad NH), 2966 (C–H aromatic), 2932 (C–H aliphatic), 1323, 1157 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.96 (s, 1H, N*H*, D_2O exchangeable), 2.71 (q, J = 7.1 Hz, 2H, CH_2CH_3), 3.06 (s, 3H, SO_2CH_3), 3.83 (s, 2H, CH_2), 6.77 (s, 1H, pyrazole H-4), 7.19 (d, J = 8.1 Hz, 2H, ethylaminomethanephenyl H-3, H-5), 7.36 (d, J = 8.1 Hz, 2H, ethylaminomethanephenyl H-2, H-6), 7.53 (d, J = 8.7 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.93 (d, J = 8.7 Hz, 2H, methanesulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 15.27, 43.91, 44.50, 53.39, 106.69, 120.98 (q, J = 268 Hz, CF_3), 125.70, 127.06, 128.72, 128.77, 128.88, 139.84, 142.36, 143.41, 144.33 (q, J = 38 Hz, C-CF_3), 145.13; MS 424.1 (M+1). Anal. Calcd for $C_{20}H_{20}F_3N_3O_2S{\cdot}1/3H_2O$: C, 55.94; H, 4.85; N, 9.78. Found: C, 55.95; H, 4.82; N, 9.41.

*1-(4-(1-(4-(Methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)benzyl) piperazine (**12c**):* The product was obtained as a yellow powder in 71% yield; mp 102–104 °C; IR (film) 3323 (broad NH), 2969 (C–H aromatic), 2937 (C–H aliphatic), 1321, 1156 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 1H, N*H*, D_2O exchangeable), 2.50 (t, J = 5.0 Hz, 4H, piperazinyl H-3, H-5), 2.97 (t, J = 5.0 Hz, 4H, piperazinyl H-2, H-6), 3.07 (s, 3H, SO_2CH_3), 3.49 (s, 2H, CH_2), 6.70 (s, 1H, pyrazole H-4), 7.10 (d, J = 8.0 Hz, 2H, piperazinylmethanephenyl H-3, H-5), 7.28 (d, J = 8.0 Hz, 2H, piperazinylmethanephenyl H-2, H-6), 7.47 (d, J = 8.7 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.86 (d, J = 8.7 Hz, 2H, methanesulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 44.50, 45.96, 54.35, 63.00, 106.69, 120.96 (q, J = 268 Hz, CF_3), 125.70, 127.18, 128.56, 128.71, 129.66, 139.86, 140.26, 143.44, 144.34 (q, J = 38 Hz, C-CF_3), 145.13; MS 465.2 (M+1). Anal. Calcd for $C_{22}H_{23}F_3N_4O_2S$: C, 56.89; H, 4.99; F, 12.27; N, 12.06. Found: C, 56.62; H, 4.87; N, 12.31.

*4-(5-(4-((Methylamino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl) benzenesulfonamide (**12d**):* The product was obtained as a pale yellow powder in 57% yield; mp 121–123 °C; IR (film) 3247 (broad NH), 2968 (C–H aromatic), 2923 (C–H aliphatic), 1338, 1165 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$+DMSO-d_6) δ 2.36 (s, 3H, NCH_3), 3.01 (s, 2H, SO_2NH_2, D_2O exchangeable), 3.68 (s, 2H, CH_2), 6.69 (s, 1H, pyrazole H-4), 7.11 (d, J = 8.0 Hz, 2H, methylaminomethanephenyl H-3, H-5), 7.25 (d, J = 8.0 Hz, 2H, methylaminomethanephenyl H-2, H-6), 7.34 (d, J = 8.5 Hz, 2H, sulfamoylphenyl H-2, H-6), 7.83 (d, J = 8.5 Hz, 2H, sulfamoylphenyl H-3, H-5); ^{13}C NMR (DMSO-d_6) δ 37.23, 54.13, 106.47, 121.01 (q, J = 268 Hz, CF_3), 125.53, 127.36, 127.45, 129.01, 129.53, 140.31, 141.74, 142.28, 144.13 (q, J = 38 Hz, C-CF_3), 145.07; MS 411.1 (M+1). Anal. Calcd for $C_{18}H_{17}F_3N_4O_2S$: C, 52.68; H, 4.18; N, 13.65. Found: C, 52.45; H, 4.22; N, 13.68.

*4-(5-(4-((Ethylamino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzene-sulfonamide (**12e**):* The product was obtained as a pale yellow powder in 59% yield; mp 170–172 °C; IR (film) 3341 (broad NH), 2962 (C–H aromatic), 2924 (C–H aliphatic), 1338, 1163 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.73 (q, J = 7.1 Hz, 2H, CH_2CH_3), 2.92 (s, 2H, SO_2NH_2, D_2O exchangeable), 3.83 (s, 2H, CH_2), 6.77 (s, 1H, pyrazole H-4), 7.19 (d, J = 8.1 Hz, 2H, ethylaminomethanephenyl H-3, H-5), 7.35 (d, J = 8.1 Hz, 2H, ethylaminomethanephenyl H-2, H-6), 7.47 (d, J = 8.7 Hz, 2H, sulfamoylphenyl H-2, H-6), 7.91 (d, J = 8.7 Hz, 2H, sulfamoylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 13.75, 41.93, 55.03, 106.47, 121.00 (q, J = 268 Hz, CF_3), 125.50, 127.46, 127.57, 129.01, 129.11, 140.61, 141.75, 142.25, 144.11 (q, J = 38 Hz, C-CF_3), 144.88; MS 425.1 (M+1). Anal. Calcd for $C_{19}H_{19}F_3N_4O_2S$: C, 53.77; H, 4.51; N, 13.20. Found: C, 53.94; H, 4.43; N, 13.18.

*4-(5-(4-(Piperazin-1-ylmethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzene-sulfonamide (**12f**):* The product was obtained as a yellow powder in 64% yield; mp 106–108 °C; IR (film) 3331 (broad NH), 2965 (C–H aromatic), 2935 (C–H aliphatic), 1329, 1161 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (t, J = 5.0 Hz, 4H, piperazinyl H-3, H-5), 2.82 (t, J = 5.0 Hz, 4H, piperazinyl H-2, H-6), 2.99 (s, 2H, SO_2NH_2, D_2O exchangeable), 3.44 (s, 2H, CH_2), 6.69 (s, 1H, pyrazole H-4), 7.10 (d, J = 8.0 Hz, 2H, piperazinylmethanephenyl H-3, H-5), 7.26 (d, J = 8.0 Hz, 2H, piperazinylmethanephenyl H-2, H-6), 7.39 (d, J = 8.7 Hz, 2H, sulfamoylphenyl H-2, H-6), 7.83 (d, J = 8.7 Hz, 2H, sulfamoylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 45.78, 54.15, 62.94, 106.48, 121.08 (q, J = 268 Hz, CF_3), 125.51, 127.34, 127.45, 128.75, 129.69, 139.82, 141.74, 142.37, 144.11 (q, J = 38 Hz, C-CF_3), 145.04; MS 466.1 (M+1). Anal. Calcd for $C_{21}H_{22}F_3N_5O_2S$: C, 54.18; H, 4.76; N, 15.05. Found: C, 54.09; H, 4.82; N, 15.27.

*N-Ethyl-N-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl) benzyl)nitrous amide (**13**):* The ethanamine compound **12b** (724 mg, 1.7 mmol) was added to a solution of NaOMe (210 mg of 95% purity, 1.7 mmol) in THF (30 mL) with stirring at −65 °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 −65 °C for 1 h. The reaction mixture was allowed to warm to 25 °C, and the solvent was removed from the filtrate to furnish product **13** as a pale yellow powder in 55% yield. In a second reaction, nitric oxide gas was bubbled into a solution of **12b** using a protic solvent system consisting of NaOMe in MeOH (25% w/v) and MeCN at 25 °C for 24 h which afforded **13** in 90% yield as a pale yellow powder; mp 117–119 °C; IR (film) 2977 (C–H aromatic), 2926 (C–H aliphatic), 1317, 1157 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) of the major rotamer δ 0.89 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.00 (s, 3H, SO_2CH_3), 3.44 (q, J = 7.2 Hz, 2H, CH_2CH_3), 5.22 (s, 2H, CH_2), 6.73 (s, 1H, pyrazole H-4), 7.20 (d, J = 8.1 Hz, 2H, substituted-aminomethanephenyl H-3, H-5), 7.25 (d, J = 8.1 Hz, 2H, substituted-aminomethanephenyl H-2, H-6), 7.44 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.84 (d, J = 8.7 Hz, 2H, methanesulfonylphenyl H-3, H-5); ^1H NMR ($CDCl_3$) of the minor rotamer δ 1.31 (t, J = 7.3 Hz, 3H, CH_2CH_3), 3.00 (s, 3H, SO_2CH_3), 4.11 (q, J = 7.3 Hz, 2H, CH_2CH_3), 4.74 (s, 2H, CH_2), 6.69 (s, 1H, pyrazole H-4), 7.05 (d, J = 8.1 Hz, 2H, substituted-aminomethanephenyl H-3, H-5), 7.11 (d, J = 8.1 Hz, 2H, substituted-aminomethanephenyl H-2, H-6), 7.43 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.85 (d, J = 8.7 Hz, 2H, methanesulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) of the major rotamer δ 10.01, 37.60, 43.37, 54.10, 105.95, 119.90 (q, J = 268 Hz, CF_3), 124.71, 127.60, 127.69, 127.78, 128.43, 135.83, 139.10, 142.12, 143.20 (q, J = 38 Hz, C-CF_3), 143.44; ^{13}C NMR ($CDCl_3$) of the minor rotamer δ 12.99, 43.37, 44.60, 46.16, 105.85, 119.90 (q, J = 268 Hz, CF_3), 126.89, 127.48, 127.58, 128.21, 128.47, 135.06, 139.02, 142.16, 143.18 (q, J = 38 Hz, C-CF_3), 143.57; MS 453.1 (M+1). Anal. Calcd for $C_{20}H_{19}F_3N_4O_3S$: C, 53.09; H, 4.23; N, 12.38. Found: C, 53.43; H, 4.48; N, 12.73.

*1-(4-(1-(4-(Methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)benzyl)-4-nitrosopiperazine (**14**):* The title compound **14** was prepared, using a similar procedure to that described for the preparation of **13**, by using **12c** in place of **12b**, in 60% and 93% yields, respectively, using the two solvent systems described previously as a yellow powder; mp 130–132 °C; IR (film) 2968 (C–H aromatic), 2935 (C–H aliphatic), 1321, 1159 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (t, J = 5.0 Hz, 2H, piperazinyl H-2, H-6), 2.68 (t, J = 5.0 Hz, 2H, piperazinyl H-2, H-6), 3.03 (s, 3H, SO_2CH_3), 3.59 (s, 2H, CH_2), 3.75 (t, J = 5.0 Hz, 2H, piperazinyl H-3, H-5), 4.21 (t, J = 5.0 Hz, 2H, piperazinyl H-3, H-5), 6.72 (s, 1H, pyrazole H-4), 7.16 (d, J = 8.0 Hz, 2H, piperazinylmethanephenyl H-3, H-5), 7.33 (d, J = 8.0 Hz, 2H, piperazinylmethanephenyl H-2, H-6), 7.47 (d, J = 8.7 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.85 (d, J = 8.7 Hz, 2H, methanesulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$) δ 36.17, 44.40, 48.34, 51.57, 53.00, 61.6, 106.77, 120.98 (q, J = 268 Hz, CF_3), 125.73, 127.80, 128.57, 128.99, 129.62, 139.97, 140.42, 143.31, 144.23 (q, J = 38 Hz, C-CF_3), 144.88; MS 494.2 (M+1). Anal. Calcd for $C_{22}H_{22}F_3N_5O_3S$: C, 53.54; H, 4.49; N, 14.19. Found: C, 53.69; H, 4.46; N, 14.47.

22. *In vivo anti-inflammatory assay:* The test compounds **12a–f**, **13**, **14** and the reference drugs celecoxib were evaluated using the in vivo carrageenan-induced rat foot paw edema model reported previously (Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544).