Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 1711–1717

BIOORGANIC & MEDICINAL CHEMISTRY

Metabolites of Orally Active NO-Independent Pyrazolopyridine Stimulators of Soluble Guanylate Cyclase†

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Received 30 October 2001; accepted 17 January 2002

Abstract—The pyrazolopyridine stimulators of soluble guanylate cyclase BAY 41-2272 and 41-8543 were oxidised in rats and dogs at their 5-pyrimidinyl-cyclopropyl and -morpholino residue. These metabolites activate the soluble guanylate cyclase, induce vasoelaxation and thereby may contribute to the in vivo activity of BAY 41-2272 and BAY 41-8543.

Introduction

Soluble guanylate cyclase (sGC)[2] is a heterodimeric (α/ß) heme-protein that converts GTP to cGMP, which is involved in a wide range of physiological processes in humans and animals. Its natural stimulator is nitric oxide (NO) which acts by coordination to the heme moiety. Organic nitrates like glycerol trinitrate or isosorbide dinitrate have been used for decades as a treatment for angina pectoris. In vivo they generate NO and thus mimic the action of the endogenous mediator. The major drawback of this therapy is the development of tolerance after repeated administrations. Recently, we and others disclosed a novel class of NO-independent sGC-stimulators with vasodilating activities, which on the one hand stimulate sGC directly and on the other hand sensitize the enzyme towards its native activator NO.[3–5] Starting from YC-1[3] as lead structure our research culminated in the pyrazolopyridines BAY 41–2272 (**1**) and BAY 41–8543 (**2**) as the most promising ones out of a series of about two thousand of newly synthesized derivatives.[4]

After oral dosing in animals, **1** and **2** were quickly oxidizes at their 5-pyrimidinyl-cyclopropyl and morpholino residues, respectively (Scheme 1). However, a long lasting blood pressure (bp)-lowering effect was found. As an explanation one might postulate that the metabolites could contribute to this pharmacological effect as well. In order to test this hypothesis we went for their isolation from biological material, proceeded with structural determinations and synthesis and finally studied the pharmacological and pharmacokinetic properties of both main metabolites of **1** and **2**.

Isolation, Purification and Structural Determination

The main metabolites of BAY 41–2272 and BAY 41–8543 were isolated from Wistar rat hepatocyte suspensions. Hepatocytes were isolated as described previously.[6] Incubations were performed at cell densities of 10^7 to 2×10^8 cells per 20 mL for 4 h under a 95% O_2/5% CO_2 atmosphere at 37 °C. Metabolites were isolated from supernatants by solid phase extraction followed by preparative HPLC using RP18 material and trifluoroacetic acid (0.1%)/acetonitrile as eluent system. Structural determinations of the metabolites from biological matrices were performed by 2D-NMR and MS. After synthesis of the proposed structures, they showed to be identical with respect to LC retention times, mass

†Part of this work was presented previously; see ref 1.

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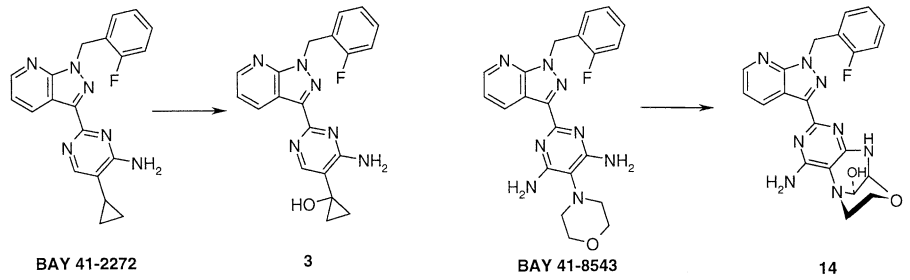
PII: S0968-0896(02)00034-2



Scheme 1. Main metabolites of BAY 41-2272 and BAY 41-8543 in rats and dogs.

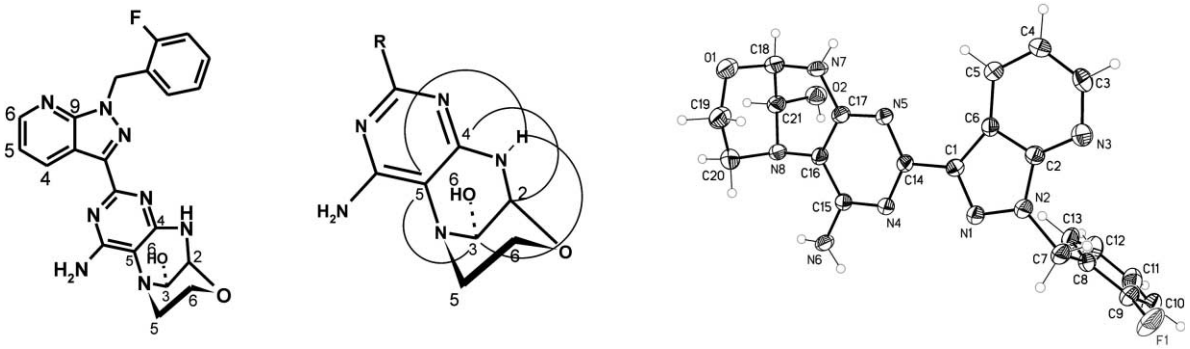


Figure 1. Numbering, HMBC contacts and single crystal X-ray structure of metabolite **14**.

spectra and by NMR spectroscopy. An X-ray analysis of the synthetic material gave the final proof for the structural proposal.[7] Details on the structure of **3** were presented elsewhere,[8] whereas **14** is shown in Figure 1. Carbon chemical shifts were detected by two-dimensional HMQC and HMBC methods. The data are given in Table 1. Three different NH and OH protons could be detected. There were some important HMBC contacts in the HMBC spectrum. The signal of the NH proton at 8.05 ppm showed contacts to C-5 in the pyrimidinyl-moiety and C-3 in the morpholinyl-moiety. In addition, the HMBC contact between H-2 in the morpholinyl part and C-4 of the pyrimidine part also proved the NH bridge. The HMBC contact between H-3 in the morpholinyl moiety and C-5 in the pyrimidine ring served as a further confirmation of the assignment.

Chemistry[9]

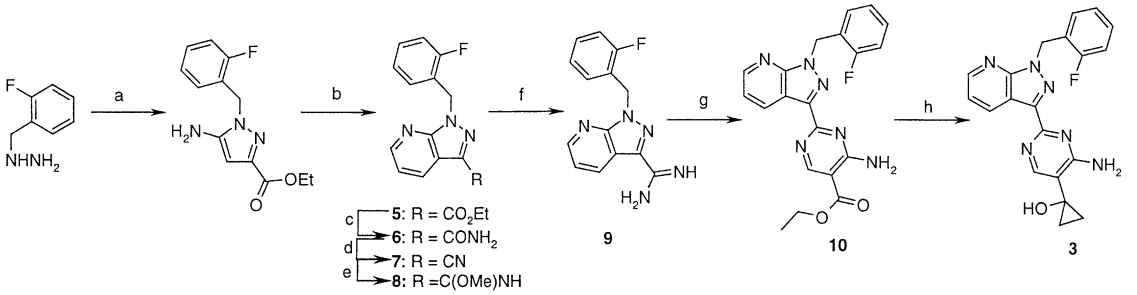
The first synthesis of the hydroxycyclopropyl metabolite **3** proceeded as depicted in Scheme 2.[10] Condensation of 2-fluorophenylhydrazine with the sodium salt of ethyl cyanopyruvate yielded an ethyl 5-aminopyrazole-3-carboxylate which was cyclized with dimethylaminoacrolein to the 1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate **5**. Conversion of the ester into an amidine group yielded **9**, which was condensed with ethyl ethoxymethyleneacetate to the pyrimdine **10**. The ester group was subsequently transformed into the cyclopropanol group (**3**). The construction of the cyclopropyl moiety was adapted from a protocol of Imamoto[11] by using the Kagan reagent SmI_2. The yield was quite low, which could be due to the presence of a free amino group and several heteroatoms in the molecule. A more elaborate synthesis was therefore established recently by the group of DeMeijere et al.[8]

The synthesis of the metabolite **14** is shown in Scheme 3. In the course of our large chemistry program which was aimed to optimize the lead structure, we learned that construction of triaminopyrimidine moieties via a hydroxyethyl-substituted aminomalononitrile C3 building block might offer some obstacles. Furthermore, all attempts to react nitro-, nitroso- or amino-substituted malonic acid diesters or malonodinitriles with the pyrazolopyridinyl amidine failed and did not lead to the desired 5-nitrogen-functionalized pyrimidine. Therefore,

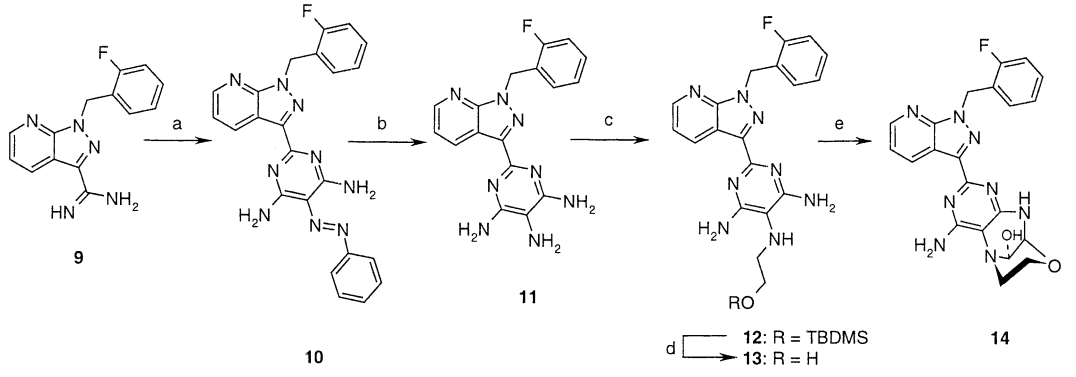
Table 1. 300 MHz $-^1H/^{13}C$ NMR data of **14** in DMSO-d_6[a]

δ (H) ppm	Mult.	Int	δ (C) ppm	Assignment corresponding to Fig. 1
2.98; 3.20	D; M	1; 1	51.1	H-5; C-5 (morpholinyl-ring)
3.28	M	2	53.9	H-6; C-6 (morpholinyl-ring)
4.55	BS	1	75.5	H-3; C-3 (morpholinyl-ring)
4.83	D	1	76.5	H-2; C-2 (morpholinyl-ring)
5.80	S	2	43.8	CH_2 (fluorobenzyl)
5.95	D	1	—	OH (morpholinyl-ring)
6.22	BS	2	—	NH_2 (pyrimidine)
7.13	M	2	124.7; 129.9	(fluorobenzyl)
7.23	M	1	115.4	(fluorobenzyl)
7.35	M	1;1	117.8; 129.9	H-5/C-5 (pyrazolopyridinyl); fluorobenzyl
8.05	D	1	—	NH (morpholinyl-ring)
8.61	D	1	148.9	H-6/C-6 (pyrazolopyridinyl)
9.06	D	1	133.8	H-4/C-4 (pyrazolopyridinyl)
—	—	1	102.9	C-5 (pyrimidine)
—	—	1	151.7	C-9 (pyrazolopyridinyl)
—	—	—	156.9	C-4 (pyrimidine)
—	—	1	160.7	C-F (fluorobenzyl)

[a]Carbon-chemical shifts were determined by HMQC, HMBC.



Scheme 2. Reagents and conditions: (a) NC–CH=C(ONa)CO_2Et/TFA, dioxane, reflux, 8 h; (b) Me_2NCH=CH–CHO/TFA/dioxane, reflux, 3 days, 50% for steps (a) and (b); (c) NH_3/MeOH, rt, 2 days, quant; (d) TFAA/pyridine, rt, 8 h, quant; (e) MeONa/MeOH, rt, 2 h, quant; (f) NH_4Cl/HAc, MeOH, reflux, 8 h; (2) Na_2CO_3/H_2O, rt, 76%; (g) EtOCH=C(CN)CO_2Et/toluene, 110 °C, 5 h, 21%; (h) (1) CH_2I_2/Sm/THF, 50 °C, 70 min; (2) 1 N HCl, extract; (3) RP18 chromatography, 1%.



Scheme 3. Reagents and conditions: (a) Ph–N=N–CH$(CN)_2$/NaOMe/DMF, 110 °C, 12 h, 73%; (b) (1) Raney–Ni/H_2/DMF, 65 bar, 62 °C, 22 h; (2) 2.5 N HCl, precipitate; (3) $NaHCO_3$, 59%; (c) TBDMS–OCH_2CHO/Molsieve 3A/$NaCNBH_3$/AcOH/MeOH, rt, 5 h, 38%; (d) TBAF/THF, rt, 2 h; (e) OHC–CHO/40% in water, rt, 12 h, 10% (over steps d and e).

we tried a pathway which proceeds in analogy to the route published by Singh and Lesher.[12] Phenylazomalononitrile was prepared according to ref 13 and reacted smoothly with the amidine **9** to give the pyrimidine nucleus. The masked amino group was liberated via catalytic hydrogenation under forced conditions to yield the triaminopyrimidine **11**. This compound is also a valuable synthon since it can serve as starting material for numerous *N*-derivatizations. It was selectively converted to the *N*-5-hydroxyethyl derivative **12** by reductive amination with TBDMS-protected hydroxyacetaldehyde. After deprotection of the TBDMS group with TBAF, the ring-constructing key step of the synthesis is performed in a one-pot procedure by subsequent addition of aqueous glyoxal solution. Whereas several examples of reactions between aminoalcohols and glyoxal equivalents can be traced in the literature,[14] there is no precedent for the current type of bicyclic ring formation. The final material **14** can be isolated after chromatographic purification on reversed-phase silica gel. The use of alcohols as eluents or solvents for this compound is prohibitive since they easily exchange with the semi-aminal part.

Biology[3,4]

Measurement of sGC activity

Rat lung sGC overexpressed in a baculovirus/Sf9 system using a defined mixture of viruses encoding the α1 and β1 subunits was isolated from a batch reactor run via several chromatographic steps yielding 1 mg/2.5 L culture broth. The basal activity of the purified enzyme was 154 nmol min^{-1} mg^{-1} in the presence of Mg^{2+}. Enzyme activity was determined by the formation of [^{32}P]cGMP from α-[^{32}P]GTP.

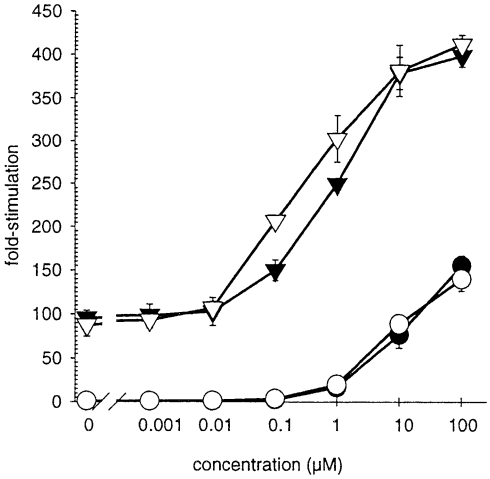


Figure 2. Stimulation of purified sGC by **3** (-○-) and **14** (-●-) in the absence and stimulation of purified sGC by **3** (-▽) and **14** (-▼-) in the presence of 10 μM SIN-1. The specific sGC activity is expressed as *x*-fold stimulation versus specific basal activity (154±11 nmol/mg/min in the presence of Mg^{2+}). The data represent means ±SEM from four determinations. The assay has been performed as previously described by us.[4c]

Tests on aortic rings

Aortic rings (1.5 mm) from Chinchilla rabbits of either sex were suspended under an initial tension of approximately 4 g in 5 mL Krebs–Henseleit solution at 37° C. Contractions to 3×10^{-8} g/mL phenylephrine leading to a submaximum contraction were followed by a series of 16 washing cycles and a resting period of 28 min. The test compounds were added at the beginning of the last resting period.

Table 2. In vitro potency of compounds

Compd	Inhibition of contraction of aortic rings IC_{50}, μM
BAY 41-2272	0.3
3	0.4
BAY 41-8543	0.2
14	1.2
YC-1	10

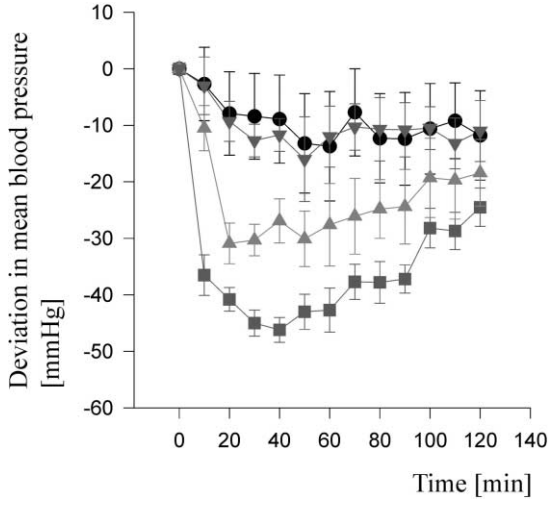


Figure 3. Effect of oral BAY 41-2272 on MAP in anaesthetized Wistar rats: -●- Control ($n=6$), -▼- 0.3 mg/kg ($n=4$), -▲- 1.0 mg/kg ($n=5$), -■- 3.0 mg/kg ($n=4$).

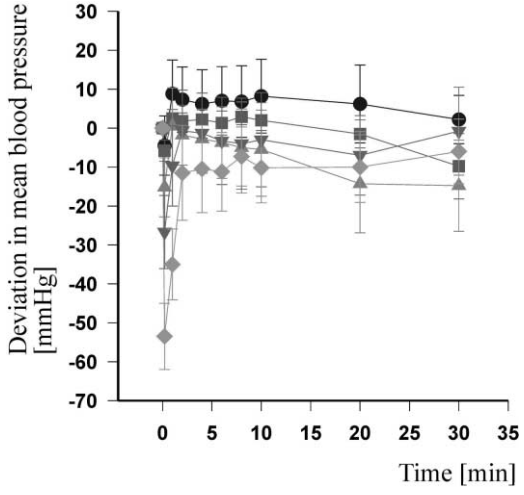


Figure 4. Effect of intravenous BAY 41-2272 on MAP in anaesthetized Wistar rats. -●- Control ($n=4$), -◆- 0.1 mg/kg ($n=4$), -▼- 0.03 mg/kg ($n=4$), -▲- 0.01 mg/kg ($n=5$), -■- 0.003 mg/kg ($n=4$).

Blood pressure measurements

Male Wistar rats weighting 300–250 g were anaesthetized with thiopental Nycomed™ 100 mg/kg ip. A tracheotomy was performed and catheters were inserted into the femoral artery for blood pressure measurement and in the femoral vein for substance administration. The animals were ventilated with room air and their body temperature was controlled. The compounds were administered orally as a solution in Transcutol™/Cremophor™ EL/water (10/20/70 = v/v/v) in a volume of 1 mL/kg by gavage. For iv administration, they were dissolved in a solution of Transcutol™/Cremophor™ EL/0.9% NaCl (10/10/80 = v/v/v), and the administration volume was 1 mL.

Biological results

We found considerable biological activity for both parent compounds and metabolites. **3** and **14** are potent sGC-stimulators, that at concentrations from 0.01 to 100 μM

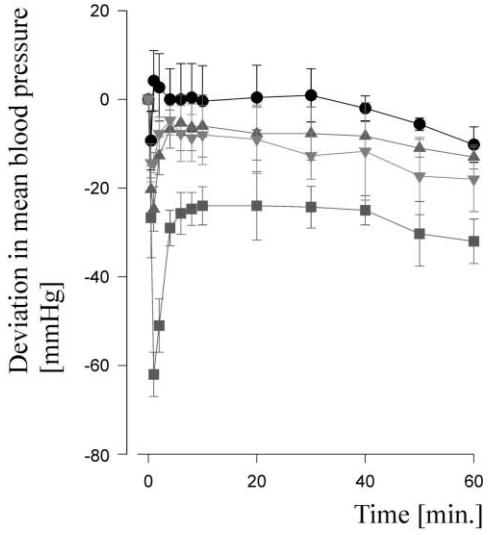


Figure 5. Effect of intravenous **3** on MAP in anaesthetized Wistar rats. -●- Vehicle ($n=4$), -■- **3**: 0.1 mg/kg ($n=2$), -▲- **3**: 0.03 mg/kg ($n=2$), -▼- **3**: 0.01 mg/kg ($n=2$).

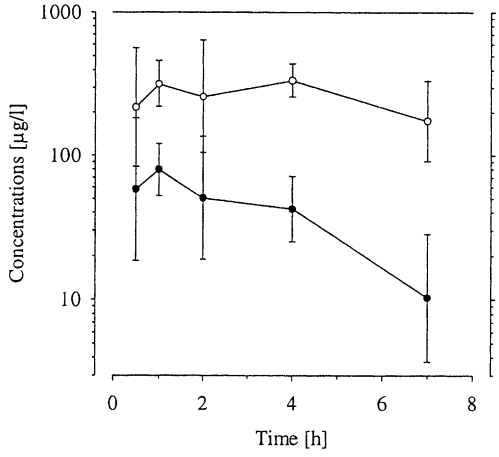


Figure 6. Mean plasma concentrations versus time curves of BAY 41-2272 (-●-) and the metabolite **3** (-○-) in Wistar rats after single oral administration of 5 mg/kg BAY 41-2272.

stimulte recombinant sGC from 1.3- to 155-fold and from 1.4- to 155-fold, respectively (Fig. 2). In combination **3** and **14** and the NO donor SIN-1 potentiate over a wide range of concentrations. Thus, the profile of both metabolites at the isolated enzyme is comparable to that of their parent compounds.[4a,d] Through their interaction with sGC, both metabolites elicited a concentration-dependent vasorelaxation in vitro.[4a] The compounds inhibited the constriction of rabbit aortic rings induced by phenylephrine (3×10^{-8} g/mL) expressed as IC_{50} values (Table 2). For demonstration of the in vivo efficacy the bp-lowering effect of the sGC stimulators was shown in anaesthetized Wistar rats as previously described by us.[4b,c] BAY 41-2272 is a potent bp-lowering substance in these rats after oral administration (Fig. 3). After iv administration BAY 41-2272 and **3** showed comparable in vivo activity (Figs 4 and 5). The plasma concentrations of BAY 41-2272 and its metabolite **3** in rats and dogs are shown in Fig. 6 and 7, respectively. The concentration of **3** is about twice the amount of BAY 41–2272. Dogs behave similarly in this respect, whereas after iv dosing a slower increase in plasma levels of **3** was noticed in this species (Fig. 8). BAY 41-2272 is a high-clearance drug with a short half-life (rat iv 0.5 h; po 1 h; dog iv 1 h; po 2 h).

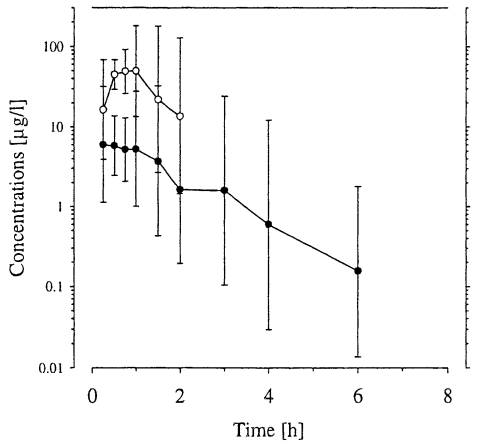


Figure 7. Mean plasma concentrations versus time curves of BAY 41-2272 (-●-) and the metabolite **3** (-○-) in Beagle dogs after oral administration of 2 mg/kg BAY 41-2272.

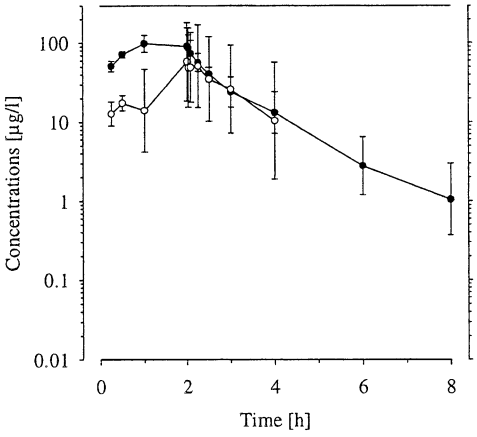


Figure 8. Mean plasma concentrations versus time curves of BAY 41-2272 (-●-) and the metabolite **3** (-○-) in Beagle dogs after intravenous infusion of 1 mg/kg BAY 41-2272.

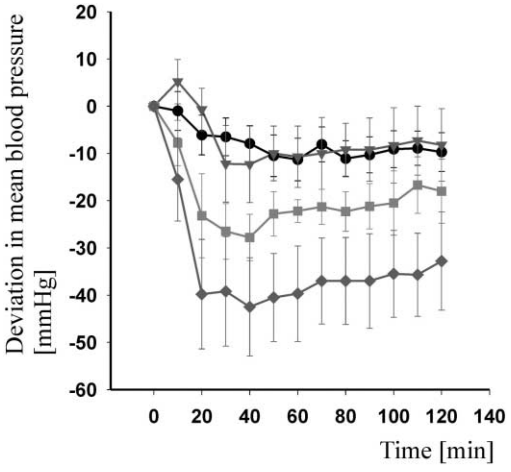


Figure 9. Effect of oral BAY 41-8543 on MAP in anaesthetized Wistar rats. -●- Control ($n=10$), -▼- 0.1 mg/kg ($n=4$), -■- 0.3 mg/kg ($n=4$), -◆- 1 mg/kg ($n=4$).

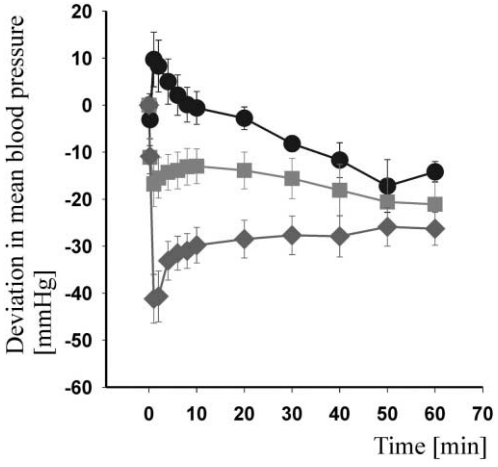


Figure 10. Effect of intravenous **14** on MAP in anaesthetized Wistar rats. -●- Control, -◆- **14**: 0.3 mg/kg ($n=10$), -■- **14**: 0.1 mg/kg ($n=10$).

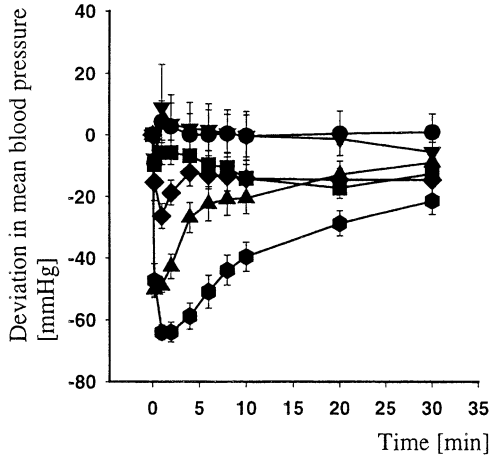


Figure 11. Effect of intravenous BAY 41-8543 on MAP in anaesthetized rats. -●- Control ($n=8$), -▼- 0.03 mg/kg ($n=4$), -■- 0.01 mg/kg ($n=3$), -◆- 0.03 mg/kg ($n=8$), -▲- 0.1 mg/kg ($n=8$), -⬢- 0.3 mg/kg ($n=8$).

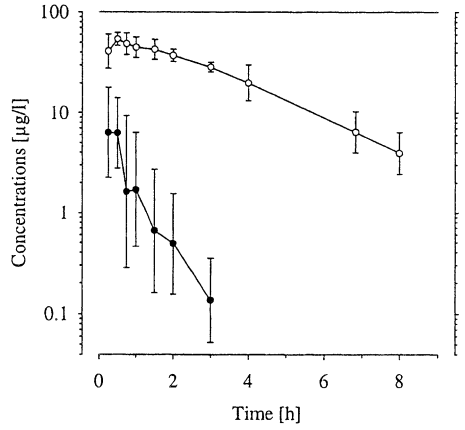


Figure 12. Mean plasma concentrations versus time curves of BAY 41-8543 (-●-) and **14** (-○-) in Beagle dogs after oral administration of 1 mg/kg BAY 41-8543.

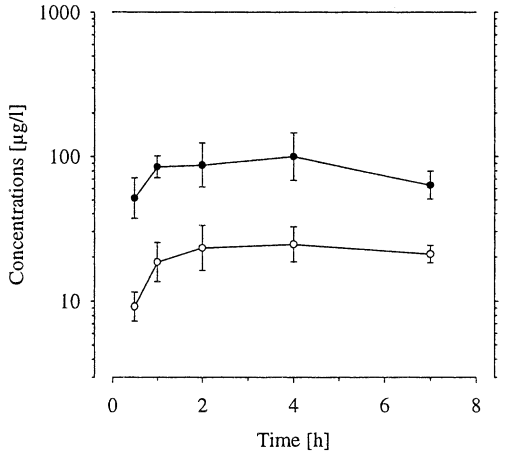


Figure 13. Mean plasma concentrations versus time curves of BAY 41-8543 (-●-) and the metabolite **14** (-○-) in Wistar rats after single oral administration of 5 mg/kg BAY 41-8543.

Figure 9 shows the bp-lowering effect of BAY 41-8543 in rats after oral administration. The compound is about 3-fold more potent than BAY 41-2272 in this model (Fig. 3). **14** is the main metabolite of BAY 41-8543 in different species. For comparision of BAY 41-8543 and **14**, the bp-lowering effect in anaesthetized Wistar rats after iv administration was investigated. Figure 10 shows the effect of **14** on bp after iv application in rats, which is about 3- to 10-fold less potent than BAY 41-8543 but displayed a longer lasting effect compared to BAY 41-8543 (Fig. 11). BAY 41–8543 was investigated in rats and dogs after oral dosing showing that it is metabolized to **14** more intensely in dogs (Fig. 12) as compared to rats, where plasma concentrations of **14** are higher than the levels of BAY 41-8543 (Fig. 13).

Conclusions

After po or iv administration of the guanylate cyclase stimulators BAY 41-2272 and BAY 41-8543 in rats, we have isolated two main metabolites, **3** and **14**, respectively. These metabolites display strong bp-lowering properties. Due to their persistance in plasma, they may contribute to the vasodilation seen in vivo after oral administration of the parent compounds.

References and Notes

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