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Identification of acidic heterocycle-substituted 1*H*-pyrazolo[3,4-*b*] pyridines as soluble guanylate cyclase stimulators

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ABSTRACT

Novel guanylate cyclase stimulators are disclosed. Design, synthesis, SAR, and pharmacological profile of the compounds are discussed.

Soluble guanylate cyclase (sGC) is the only proven receptor for the ubiquitous biological messenger nitric oxide (NO). Stimulation of the enzyme by NO facilitates the conversion of guanosine-5′-triphosphate (GTP) to the intracellular second messenger cyclic guanosine-3′,5′-monophosphate (cGMP), which regulates various cGMP-specific effector systems such as PDEs, ion channels, and protein kinases.[1] Thus, the NO/cGMP pathway is important in many physiological processes including vasodilatation, neurotransmission, and platelet aggregation.[2] Since the emergence of sGC as a therapeutic target for cardiovascular and pulmonary disease, two classes of molecules have been developed: NO-independent but heme-dependent sGC stimulators and NO- and heme-independent sGC activators.[1,2] The first reported direct stimulator of sGC is YC-1,[3] followed by the discovery of more potent compounds such as BAY 41-8543 and the advanced clinical candidate riociguat (BAY 63-2521) by Bayer[4] (Figure 1).[5] Riociguat is currently in phase III clinical trials for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH).[6] These compounds have a dual mode of action: they sensitize sGC to the body's own NO and can also increase sGC activity in the absence of NO, causing vasorelaxation, anti-proliferation and anti-fibrotic effects. It is postulated that they bind to an allosteric binding site within the catalytic domain and stabilize the nitrosyl-haem complex to keep sGC in its active conformation.[7]

To further improve physicochemical and pharmacokinetic properties, we envisaged to synthesize weakly acidic compounds instead of weakly basic aminopyrimidine congeners. A similar approach was published recently by Roberts et al. (Pfizer, example 25), yielding acidic triazoles.[8] As a starting point we reinvestigated the acidic tetrazole congener **1** (Table 1), which has been reported earlier.[4] Tetrazole **1** was found to have an excellent physicochemical and DMPK profile (Table 2), but its potency was insufficient. Thus, we synthesized a series of other heterocyclic carboxylic acid isosteres,[9] with the aim to improve potency (Table 1), while maintaining the favorable physico chemical and pharmacokinetic profile.

Compounds **2**, **3**, and **4** were synthesized from the intermediate **13**, which was built up in four linear steps (Scheme 1) in analogy to our work on 7-azaindoles.[11] 2-Fluoropyridine (**10**) was converted to the pyrazolopyridine **11** in two steps.[12] Upon lithiation at the 3-position it reacted with ethyl trifluoroacetate to give the corresponding trifluoroketone. Subsequent reaction with hydrazine hydrate provided **11**. The trifluoromethyl group in pyrazolopyridine **11** was anionically activated and underwent aminolysis via a methine intermediate and thus furnished nitrile **12**.[13] Regioselective benzylation in the presence of cesium carbonate gave intermediate **13**. The nitrile **13** was elaborated further to hydroxyamidine **14**. Treating **14** with 1,1′-thiocarbonyldiimidazole (TCDI) under either basic (DBU)[14] or acidic (boron trifluoride etherate)[15]

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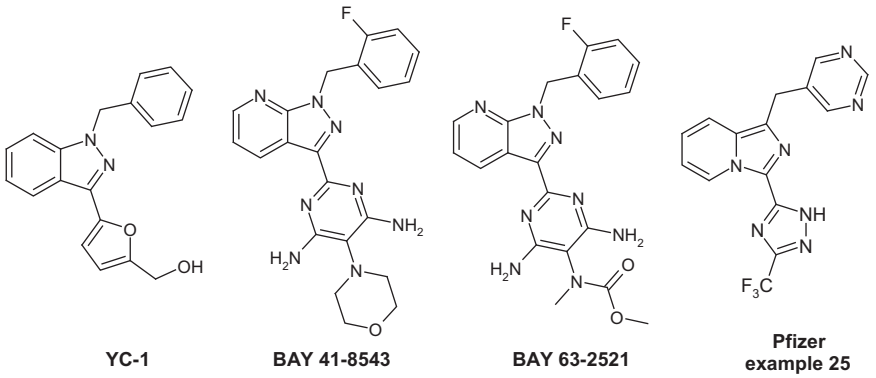
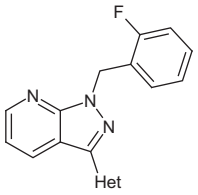


Figure 1. Chemical structure of some sGC stimulators.

Table 1
SAR of several heterocyclic substituents



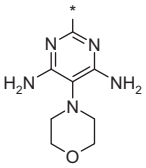
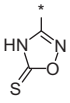
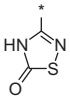
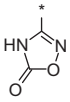
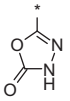
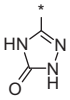
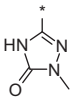
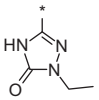
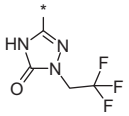
Compd	Het	Rabbit aorta IC_{50}[a] (μM)	Solubility[b] (mg/L)	Fmax[c] (%)	*c*Log*D*[d]
BAY 41-8543		0.10	nd[e]	76	1.78
1		8.60	150	100	0.96
2		1.10	280	69	0.90
3		0.52	11	90	0.95
4		1.26	320	98	0.94
5		0.61	10	59[f]	0.97
6		3.10	16	59	1.77
7		0.87	4	74	1.96
8		0.73	nd[e]	69	2.21

Table 1 (*continued*)

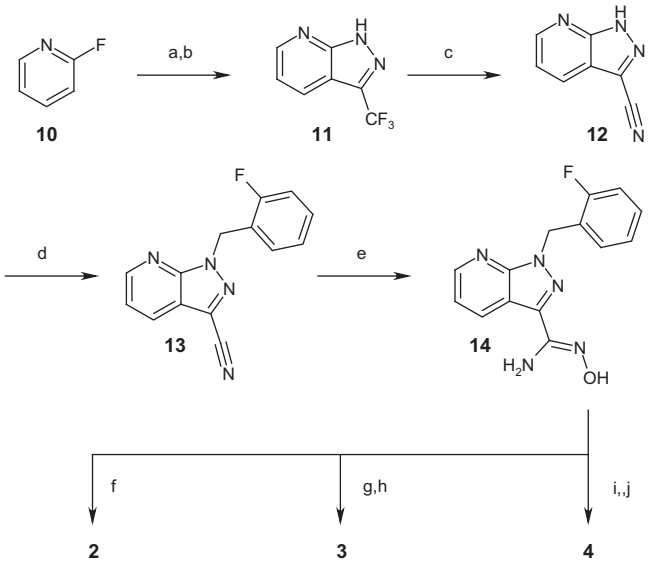
Compd	Het	Rabbit aorta IC_{50}[a] (μM)	Solubility[b] (mg/L)	Fmax[c] (%)	*c*Log*D*[d]
9		0.61	nd[e]	91	2.56

[a] Values are means of three experiments. Relaxing effect on pre-contracted rabbit aortic rings.[10]
[b] Pseudo-thermodynamic solubility assay (at pH 6.5).
[c] Bioavailability determined from incubation in rat liver hepatocytes.
[d] Calculated log*D* (at pH 7.5).
[e] Solubility was not measurable.
[f] Bioavailability determined from incubation in rat liver microsomes.

Table 2
Pharmacokinetics in Wistar rats[a]

Compound	AUC_{norm}[b] (kg h/L)	CL (L/h/kg)	$T_{1/2}$ (h)	MRT[e] (h)	*F*[f] (%)
BAY 41-8543	0.32	4.5[d]	1.2	—	25
1	3.63	0.28[c]	2.4	—	94
4	2.79	0.7[d]	1.4	1.9	75

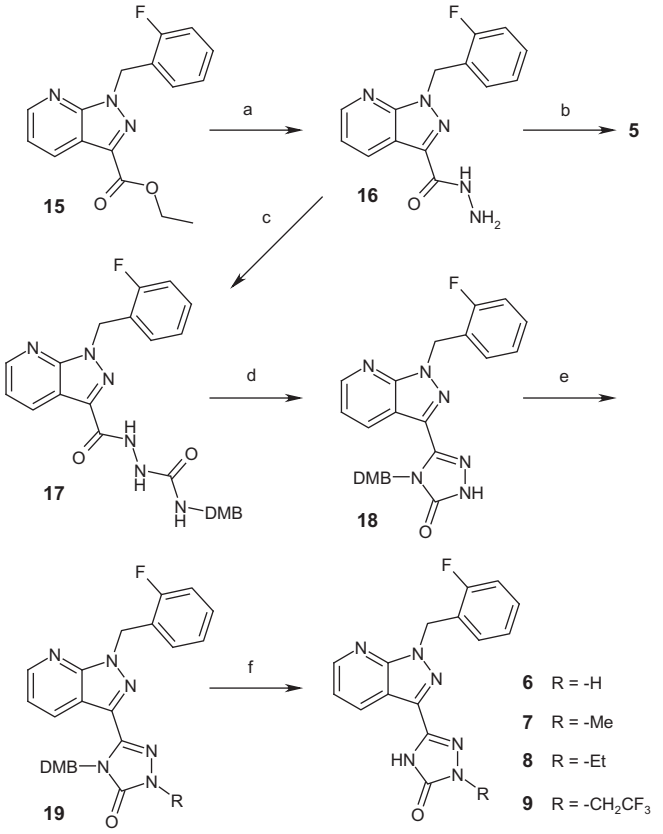
[a] Mean values derived by intravenous (bolus) and oral (gavage) administration of 0.3 mg/kg in EtOH/PEG400/H_2O.
[b] Calculated from concentration/time–curve after intravenous administration.
[c] Total plasma clearance.
[d] Total blood clearance.
[e] Mean residence time.
[f] Oral bioavailability.



Scheme 1. Synthesis of **2**, **3** and **4**. Reagents and conditions: (a) LDA, ethyl trifluoroacetate, THF, −75 °C, 4 h; (b) hydrazine hydrate, 70 °C, 6 h (55% over two steps); (c) aq NH_3, 140 °C μW, 0.2 h (90%); (d) 1-(bromomethyl)-2-fluorobenzene, Cs_2CO_3, DMF, 16 h (81%); (e) hydroxylamine hydrochloride, NEt_3, DMSO, 75 °C, 16 h (quant.); (f) 1,1′-thiocarbonyldiimidazole, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), MeCN, rt, 24 h (64%); (g) 1,1′-thiocarbonyldiimidazole, THF, rt, 2 h; (h) boron trifluoride etherate, THF, rt, 16 h (44% over two steps); (i) 2-ethylhexyl carbonochloridate, pyridine, DMF, 0 °C, 0.5 h; (j) xylenes, rf, 32 h (48% over two steps).

conditions yielded 1,2,4-oxadiazol-5-thione **2** and 1,2,4-thiadiazol-5-one **3**, respectively. Upon treatment with 2-ethylhexyl carbonochloridate followed by cyclization in refluxing xylenes, **14** was converted into the 1,2,4-oxadiazol-5-one **4**.[12]

Starting from key intermediate **15**, which has been described earlier,[4,5] compounds **5**–**9** were synthesized as outlined in Scheme 2.



Scheme 2. Reagents and conditions: (a) Hydrazine hydrate, MeOH, THF, 65 °C, 4 h; (b) 1,1′-carbonyldiimidazole, THF, rf, 1.5 h (49% over two steps); (c) 2,4-dimethoxybenzyl isocyanate (DMB–NCO), DCM, rt, 16 h (84%); (d) 2% aq NaOH, rf, 16 h (36%); (e) MeI or EtI or 2,2,2-trifluoroethyl trichloromethanesulfonate, Cs_2CO_3, DMF, rt or 60 °C, 16 h or 3 h, in case of R=H the step was not performed; (f) TsOH, toluene, rf, 16 h.

The ester **15** was converted to hydrazide **16** upon treatment with hydrazine hydrate. Cyclization with 1,1′-carbonyldiimidazole provided 1,3,4-oxadiazol-2-one **5**. Further elaboration of hydrazide **16** to the DMB-protected 1,2,4-triazole-3-one **18** was performed via reaction with 2,4-dimethoxybenzyl isocyanate[16] followed by alkaline cyclization. N-Alkylation and acidic deprotection yielded the target 1,2,4-triazole-3-ones **7**, **8**, and **9**.[17] In case of compound **6** the alkylation step was omitted.

Compared with the tetrazole derivative **1**, the potency of analogs **2**–**9** was 3- to 17-fold improved. Of the range of heterocycles prepared, 1,2,4-thiadiazol-5(4*H*)-one **3** and 1,3,4-oxadiazol-2(3*H*)-one **5** showed the best potencies of 0.52 μM and 0.61 μM, respectively. Introduction of a second hydrogen bond donor, such as in heterocycle **6** caused a significant loss of potency. Substitution of

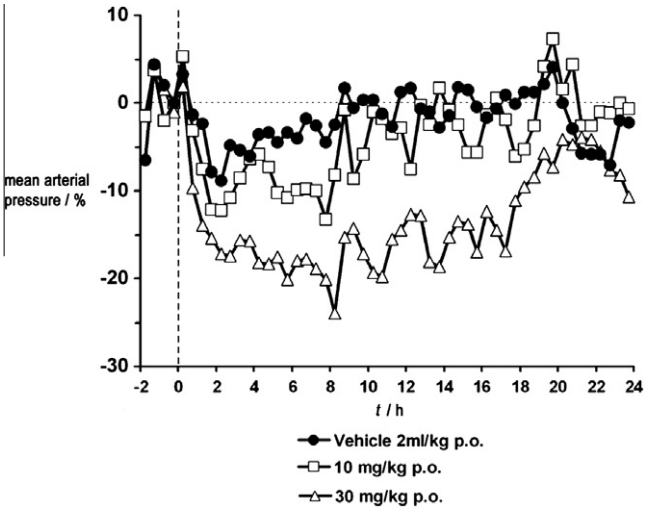


Figure 2. 24-h profile of mean arterial blood pressure in conscious spontaneously hypertensive rats (SHR) after a single oral dose of **4**. Controls were treated with vehicle. The substance was administered orally by gavage at 0 h. Shown are mean values of 6–12 animals as a percentage of initial values (131–142 mmHg).[5,12]

the nitrogen of **6** at the 2-position resulted in improved potency, increasing with steric bulk and lipophilicity of the substituent (see **7**–**9**).

However, only 1,2,4-oxadiazol-5(2*H*)-thione **2** and the corresponding 1,2,4-oxadiazol-5(2*H*)-one **4** were characterized by aqueous solubilities of ca. 300 mg/L. The oxadiazol-one **4** showed a higher stability in rat liver hepatocytes than oxadiazolthione **2** (98% vs 69%). Thus, compound **4** was progressed further to pharmacokinetic and pharmacological in vivo investigations. Compared to BAY 41-8543 improved pharmacokinetics in rats were observed regarding exposure, clearance, and oral bioavailability (Table 2).

In conscious spontaneously hypertensive rats, oral administration of **4** resulted in a long-lasting and dose-dependent blood pressure decrease (Fig. 2).

In conclusion, we have synthesized a novel series of acidic heterocycle-substituted 1*H*-pyrazolo[3,4-*b*]pyridines. Lead optimization resulted in the identification of oxadiazol-one **4**, which showed the expected profile of an sGC stimulator combined with a favorable pharmacokinetic and physicochemical profile and improved solubility. Further in vivo characterization of **4** will be reported in due course.

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