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A class of novel conjugates of substituted purine and Gly-AA-OBzl: Synthesis and evaluation of orally analgesic activity

Guifeng Kang [a], Ming Zhao [b,*], Xiaoyi Zhang [b], Li Peng [b], Chunbo Li [c], Wei Mao [c], Weidong Ye [c], Shiqi Peng [a,b,*]

[a] College of Pharmaceutical Sciences, Peking University, Beijing 100083, PR China
[b] College of Pharmaceutical Sciences, Capital Medical University, Beijing 100069, PR China
[c] Zhejiang Medicine Co. Ltd, East Huancheng Rd., Xinchang, Zhejiang 312500, PR China

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ABSTRACT

Aimed at the chemotherapy of chronic pain two kinds of analgesic pharmacophores, substituted purine and Gly-AA-OBzl, were coupled via a five-step-reaction procedure and 19 novel conjugates *N*-[2-chloro-9-(tetrahydropyran-2-yl)-9*H*-purin-6-yl]-*N*-cyclopropylglycylamino acid benzylesters were provided. On mouse-tail flick model their in vivo analgesic activities were assayed. The results indicate that introducing Gly-OC_2H_5 into the 6-position of the substituted purine leads to ambiguous increase of the analgesic activity, while introducing Gly-AA-OBzl into this position leads to significant increase of the analgesic activity.

Clinically, chronic pain from various etiologies, such as inflammation and neural destruction, is generally resistant to the treatments of simple analgesics or traditional agents. Neuropathic pain is accompanied by hypersensitivity to mechanical or thermal stimuli.[1] While inflammatory pain is accompanied by various painful responses of injury of peripheral tissue and/or inflammation produced by trauma, infection, surgery, burns, or diseases with an inflammatory component.[2,3] Chronic pain, due to relative lack of response to current analgesics, represents an unmet medical need. In the development of analgesics for treating chronic pain two receptor families, the adenosine receptors (ARs) and GlyRs, have been concerned.

ARs belong to the superfamily of G-protein-coupled receptors. Among four sub- classes (A_1, A_{2A}, A_{2B}, and A_3) of ARs that have been identified to date A_1 subtype (A_1AR) is the best-characterized member, and has been clearly identified to produce antinociception in the spinal cord by using selective agonists and antagonists.[4–7] With A_1AR as the target numerous adenosine derivatives were reported as selective agonists,[8–13] based on which purine ring was identified as a pharmacophre.[8,14,15]

GlyRs act as pentameric anion channels belonging to the 'cysteine-loop' superfamily of ionotropic neurotransmitter receptors. In the processing of motor and sensory signals, neuronal development, inflammatory pain sensitization, and in inherited neuro-logical disorders such as hyperekplexia GlyRs play predominant roles.[16,17] With GlyRs as the target a lot of glycine derivatives were reported as selective agonists,[18,19] based on which glycine ester was identified as a pharmacophre.[20,21]

In this context the present paper reported the synthesis and in vivo analgesic evaluation of 19 novel conjugates consisted of the mentioned two pharmacophores, substituted purine and Gly-AA-OBzl. Using a five-step-reaction procedure and the corresponding reaction conditions (Scheme 1) *N*-[2-chloro-9-(tetrahydropyran-2-yl)-9*H*-purin-6-yl]-*N*-cyclopropylglycylamino acid benzylesters (**6a–s**) were prepared with **3**, **4** and **5** as the intermediates. The yields of **3**, **4**, **5** and **6a–s** were 78%, 97%, 99% and 30–93%, respectively. The synthetic and chemical physical data of all compounds are given in the file of Supplementary data. The data imply that using this five-step-reaction procedure **6a–s** can be smoothly obtained.

On mouse model the in vivo pain threshold was assayed. The mice were orally administered 0.2 ml of CMC-Na (0.3%, vehicle control), 25 μmol/kg of **3–5** in 0.2 ml of CMC-Na (reference compounds) and 25 μmol/kg of **6a–s** in 0.2 ml of CMC-Na (treating groups). Thirty min later the mice received a180-min tail flick tests at 30-min intervals. The value of the basic pain threshold of each mouse was measured for three times. Analgesic potency was indicated by the pain threshold variation and calculated according to PTV = AAPT ÷ BPT, wherein PTV is the pain threshold variation, BPT is the basic pain threshold and AAPT is the difference of pain

* Corresponding authors. Tel./fax: +86 10 83911535 (M.Z.); tel./fax: +86 10 8391 1528 (S.P.).
E-mail addresses: mzhao@mail.bjum.edu.cn (M. Zhao), sqpeng@mail.bjum.edu.cn (S. Peng).

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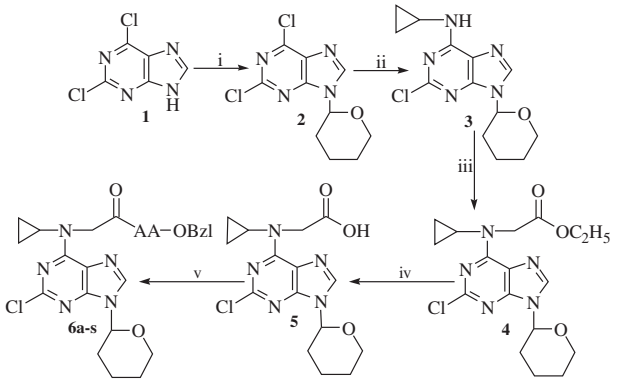

Scheme 1. Synthetic route of amino acid substituted purin derivatives. (i) Pyridine tosylate and 2,3-dihydropyran; (ii) triethylamine and cyclopropylamine; (iii) NaH, $BrCH_2CO_2C_2H_5$; (iv) aqueous solution of NaOH (3 M) and $KHSO_4$ (5%); (v) AA-OBz l/DCC/NMM. In **6a** AA = Ala; **6b** AA = Arg; **6c** AA = Asn; **6d** AA = Asp(OBzl); **6e** AA = Gln; **6f** AA = Glu(OBzl); **6g** AA = Gly; **6h** AA = His; **6i** AA = Ile; **6j** AA = Leu; **6k** AA = Lys(Boc); **6l** AA = Met; **6m** AA = Phe; **6n** AA = Pro; **6o** AA = Ser; **6p** AA = Thr; **6q** AA = Trp; **6r**, AA = Tyr; **6s** AA = Val.

threshold after administration minus the basic pain threshold. All values of pain threshold variation for each mouse were averaged and constituted one sample. The data are listed in Tables 1 and 2, and the statistical analysis is carried out using one way ANOVA test with $p < 0.05$ as significant cut-off.

The data in Table 1 explore that compounds **3–5** are modest analgesics. The duration of the analgesic action for **3** and **5** is 120 min, and for **4** is 150 min. The statistical analyses of the data of **3** and **4** indicate that introducing *N*-cyclopropylglycine ethylester into 6-position of substituted purine **3** does not significantly change the analgesic activity. On the other hand however when the substituted purine **4** was converted to **5** the analgesic activity was significantly decreased. This comparison implies the importance of an ester group for the activity. The data in Table 2 explore that **6a–s** are good analgesics and the activity order is **6a,b,e,g,q** > **6c,d,f,l,m,n** > **6h,I,j,k,o,p,r,s**. The duration of the analgesic action of **6a,d,g,h,j,m,n,p,r** is 120 min, while **6e,f,i,k,l,o,q,s** is 180 min. The statistical analyses of the data of **6a–s** indicate that replacing ethoxy group of **4** with amino acid benzylester results in significant increase of analgesic activity.

Recently, the interaction of GlyRs with substrate was deduced from the interaction of lactose permease or glycerol-3-phosphate transporter with the substrate, and thought to occur in a hydrophilic cavity that extended into the center of the lipid bilayer, as well as the interaction functioned via salt bridges and hydrogen bonds.[22] This knowledge not only explains the importance of the

Table 1
Effect of **3**, **4**, **5** on the pain threshold of the treated mice

Compd[a]	Pain threshold variation ($\bar{x}$ ± SD %)					
	30 min	60 min	90 min	120 min	150 min	180 min
Vehicle	−1.0 ± 2.80	−6.5 ± 1.79	0.20 ± 3.75	0.69 ± 1.38	3.98 ± 4.03	−5.10 ± 2.24
3	10.27 ± 4.80[c]	20.63 ± 4.38[c]	11.93 ± 3.54[b]	12.64 ± 4.56[c]	5.72 ± 3.96	5.92 ± 2.61
4	9.92 ± 4.60[c]	22.64 ± 5.89[c]	13.04 ± 3.01[d]	14.91 ± 4.50[d]	11.85 ± 4.58[e]	5.33 ± 4.09
5	5.21 ± 3.64[b]	15.24 ± 4.22[b]	8.22 ± 3.67[b]	7.68 ± 3.38[b]	3.12 ± 3.22	3.41 ± 3.64

[a] The statistical analyses are carried out for the data of same time point, $n = 10$, vehicle = 0.3% CMC-Na; dose = 25 μmol/kg.
[b] Compare to vehicle $p < 0.01$.
[c] Compare to vehicle $p < 0.01$, and to **5** $p < 0.05$.
[d] Compare to vehicle and **5** $p < 0.01$.
[e] Compare to vehicle, **4** and **5** $p < 0.01$.

Table 2
Effect of **6a–s** on the pain threshold of the treated mice

Compd[a]	Pain threshold variation ($\bar{x}$ ± SD %)					
	30 min	60 min	90 min	120 min	150 min	180 min
Vehicle	−1.0 ± 2.80	−6.5 ± 1.79	0.20 ± 3.75	0.69 ± 1.38	3.98 ± 4.03	-5.10 ± 2.24
6a	55.91 ± 19.39[b]	53.00 ± 19.58[b]	32.06 ± 12.53[b]	25.30 ± 8.56[b]	6.01 ± 3.85	5.96 ± 4.72[b]
6b	34.27 ± 12.82[b]	52.35 ± 18.90[b]	61.58 ± 21.80[b]	38.16 ± 16.12[b]	19.60 ± 9.86[c]	7.97 ± 7.10[b]
6c	34.53 ± 12.90[b]	30.54 ± 9.63[c]	34.95 ± 14.14[b]	29.15 ± 10.84[b]	21.71 ± 8.02[b]	15.45 ± 8.05[b]
6d	31.81 ± 10.99[b]	38.15 ± 13.91[b]	25.07 ± 8.83[b]	7.82 ± 8.16[d]	0.06 ± 5.94	0.03 ± 5.24[b]
6e	46.96 ± 17.23[b]	39.40 ± 13.14[b]	37.82 ± 9.61[b]	22.34 ± 8.30[c]	10.72 ± 3.72[d]	7.71 ± 4.02[b]
6f	32.61 ± 10.74[b]	34.74 ± 13.51[c]	25.20 ± 9.78[b]	20.71 ± 7.88[c]	14.14 ± 9.23[d]	10.93 ± 6.73[b]
6g	55.72 ± 20.52[b]	40.44 ± 17.57[b]	25.94 ± 9.30[b]	17.23 ± 9.21[d]	7.26 ± 5.38	−0.06 ± 5.63[b]
6h	24.98 ± 9.29[b]	36.43 ± 13.94[b]	14.45 ± 7.15[d]	10.16 ± 6.67[d]	5.31 ± 4.99	4.38 ± 7.30[b]
6i	25.56 ± 10.06[b]	27.35 ± 10.27[d]	22.57±9.30[b]	20.42 ± 8.34[d]	16.43 ± 9.73[d]	9.15 ± 8.62[b]
6j	26.20 ± 9.25[b]	34.19 ± 9.65[b]	28.22 ± 8.86[b]	12.79 ± 8.08[d]	6.47 ± 3.57	0.04 ± 2.64[b]
6k	18.33 ± 8.89[c]	32.66 ± 10.11[c]	32.85 ± 10.22[b]	28.39 ± 10.32[b]	17.20 ± 9.10[d]	10.06 ± 11.99[b]
6l	30.04 ± 9.31[b]	40.97 ± 15.64[b]	42.70 ± 14.41[b]	28.66 ± 10.61[b]	17.47 ± 9.79[d]	12.89 ± 7.50[b]
6m	39.20 ± 13.70[b]	45.54 ± 17.78[b]	37.73 ± 13.75[b]	26.29 ± 9.89[b]	3.49 ± 9.34	1.79 ± 6.09[b]
6n	32.25 ± 10.69[b]	36.73 ± 13.68[b]	23.31 ± 9.41[b]	17.49 ± 9.85[d]	7.85 ± 4.05	6.63 ± 6.97[b]
6o	27.77 ± 8.14[b]	46.71 ± 17.84[b]	32.17 ± 10.37[b]	29.20±10.13[b]	18.32 ± 9.51[d]	12.85 ± 8.20[b]
6p	23.61 ± 8.76[b]	28.36 ± 10.48[d]	23.38 ± 12.52[c]	10.91 ± 6.25[d]	6.53 ± 5.50	2.34 ± 3.76[b]
6q	43.53 ± 17.13[b]	51.90 ± 12.39[b]	38.93 ± 9.63[b]	22.58 ± 9.81[c]	11.45 ± 5.56[d]	5.15 ± 4.17[b]
6r	20.53 ± 8.58[b]	35.82 ± 10.98[b]	36.45 ± 11.45[b]	17.44 ± 5.49[d]	8.71 ± 6.65	12.02 ± 3.35[b]
6s	21.83 ± 9.18[b]	34.85 ± 11.31[b]	30.14 ± 10.86[b]	25.79 ± 8.54[b]	21.08 ± 9.73[c]	5.65 ± 7.88[b]

[a] The statistical analyses are carried out for the data of same time point, $n = 10$, vehicle = 0.3% CMC-Na; dose = 25 μmol/kg.
[b] Compare to vehicle and **4** $p < 0.01$.
[c] Compare to vehicle $p < 0.01$, and to **4** $p < 0.05$.
[d] Compare to vehicle $p < 0.01$.

hydrophobicity and the hydrogen bond for the interaction of GlyRs with the substrate but also helps us to understand the distinct activity. As depicted in Figure 1 the hydrophobicity of the compounds is in the order of Bzl of **6** > C_2H_5 of **4** > H of **5**, and the nucleophilicity of the compounds is in the order of two carbonyls of **6** > ester carbonyl of **4** > acid carbonyl of **5**. Therefore the interactions of GlyRs with the compounds are in the order of **6** > **4** > **5**.

To know the effect of the dose on the activity the most active compounds (**6a,b,g**) were observed for dose-dependently analgesic response. The mice were orally administered 30.0, 3.0 and 0.3 μmol/kg of **6a,b,g** and the data are listed in Table 3. It is clear that with the increase of the dose the pain threshold of the mice significantly increases. This dose-based difference may last 120 min.

To gain insight into the effect of metabolism on analgesic activity **6a** was selected as model compound at random and its possible metabolites, **1**, **2**, **3**, Gly and Gly-Ala-OBzl were used as reference compound. The mice were orally administered 30.0 μmol/kg of them and the data are listed in Table 4. It is clear that the pain threshold of the mice receiving reference compound and their mixture is significantly lower than that of the mice receiving **6a**. Thus, we hypothesize **6a–s** exert their in vivo analgesic activities not through metabolism conversion.

In conclusion, though no any datum of synergistic or additive analgesic action of AR and GlyR agonists is available in the literature, the observation that *N*-[2-chloro-9-(tetra-hydropyran-2-yl)-9*H*-purin-6-yl]-*N*-cyclopropylglycylamino acid benzylesters exhibit higher activities than substituted purine and glycine explores that the conjugation of AR agonist with GlyR agonist may result in synergistic or additive analgesic action. In the literature[1,3] adenosine receptor agonist 2-amino-3-(4-chlorobenzoyl)-5,6,7,8-tetrahydro-benzothiophene (T62)[1] and glycine receptor agonist H-

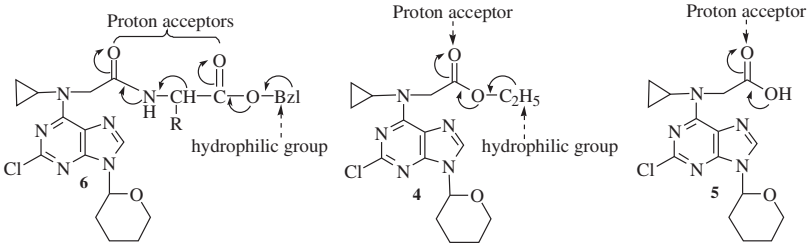

Figure 1. Comparison of hydrophobicity and the ability of forming hydrogen bonds of **4**, **5** and **6** in their interactions with receptor.

Table 3
Dose-dependent effect of **6a,b,g** on the pain threshold of the treated mice

Compd[a]		Pain threshold variation ($\bar{x}$ ± SD %)					
		30 min	60 min	90 min	120 min	150 min	180 min
Vehicle		0.13 ± 0.14	0.15 ± 0.16	0.17 ± 0.14	0.18 ± 0.15	0.16 ± 0.13	0.15 ± 0.12
6a	H	60.11 ± 12.19[b]	58.18 ± 11.52[b]	37.16 ± 10.03[b]	30.44 ± 9.12[b]	11.20 ± 4.35	11.00 ± 5.00
	M	43.25 ± 11.07[c]	39.81 ± 10.11[c]	25.34 ± 9.17[c]	18.03 ± 8.66[d]	12.00 ± 4.50	10.00 ± 4.98
	L	25.60 ± 9.04	21.56 ± 8.11	11.43 ± 6.10	11.03 ± 6.62	10.00 ± 4.45	8.09 ± 4.70
6b	H	39.41 ± 10.24[b]	57.51 ± 11.73[b]	66.71 ± 12.81[b]	43.30 ± 11.21[b]	24.69 ± 9.00	14.01 ± 6.17
	M	20.55 ± 8.32[d]	41.07 ± 10.29[c]	50.14 ± 11.08[c]	29.09 ± 9.18[c]	15.00 ± 6.06	10.34 ± 5.10
	L	12.15 ± 5.28	25.11 ± 9.33	32.88 ± 9.20	12.14 ± 6.22	10.03 ± 5.01	7.56 ± 3.19
6g	H	60.84 ± 12.50[b]	45.52 ± 11.60[b]	31.04 ± 9.22[b]	22.31 ± 8.15[b]	12.33 ± 6.15	10.16 ± 5.02
	M	45.27 ± 11.07[c]	29.07 ± 9.62[c]	20.25 ± 6.20[d]	14.53 ± 5.10[d]	10.04 ± 5.16	9.20 ± 4.33
	L	18.00 ± 7.70	16.24 ± 6.59	11.20 ± 5.22	10.02 ± 4.21	9.45 ± 4.55	9.00 ± 4.20

[a] The statistical analyses are carried out for the data of same time point, n = 10, vehicle = 0.3% CMC-Na; dose of **6a,b,g**: H = 30 μmol/kg, M = 3 μmol/kg and L = 0.3 μmol/kg.
[b] Compare to 3 μmol/kg $p < 0.01$.
[c] Compare to 0.3 μmol/kg $p < 0.01$.
[d] Compare to 0.3 μmol/kg $p < 0.05$.

Table 4
Effect of building block of **6a** on the pain threshold of the treated mice

Compd[a]	Pain threshold variation ($\bar{x}$ ± SD%)					
	30 min	60 min	90 min	120 min	150 min	180 min
Vehicle	0.13 ± 0.14	0.15 ± 0.16	0.17 ± 0.14	0.18 ± 0.15	0.16 ± 0.13	0.15 ± 0.12
1	12.22 ± 3.89[c]	21.62 ± 4.86[c]	14.02 ± 3.61[c]	12.97 ± 3.46[c]	8.77 ± 3.21[c]	7.99 ± 2.57[c]
2	14.30 ± 4.37[c]	23.99 ± 4.81[c]	15.01 ± 3.81[c]	14.13 ± 4.00[c]	9.89 ± 3.50[c]	8.03 ± 2.71[c]
3	15.20 ± 4.42[c]	25.61 ± 4.77[c]	16.96 ± 3.99[c]	15.66 ± 4.11[c]	10.78 ± 3.88[c]	9.95 ± 2.98[c]
Gly	10.13 ± 2.95[c]	11.21 ± 3.72[c]	11.31 ± 3.88[c]	12.03 ± 3.39[c]	11.54 ± 3.37[c]	10.96 ± 2.62[c]
Gly-Ala-OBzl	12.25 ± 2.99[c]	13.32 ± 3.69[c]	13.45 ± 3.57[c]	13.57 ± 3.42[c]	13.00 ± 3.42[c]	12.99 ± 2.71[c]
3 + Gly	15.39 ± 4.51[c]	26.08 ± 4.85[c]	18.11 ± 4.26[c]	16.04 ± 4.13[c]	11.12 ± 3.79[c]	10.21 ± 2.96[c]
3 + Gly-Ala-OBzl	15.53 ± 4.48[c]	25.30 ± 4.69[c]	17.05 ± 3.89[c]	15.49 ± 4.23[c]	13.29 ± 3.90[c]	11.01 ± 2.89[c]
6a	60.11 ± 12.19[b]	58.18 ± 11.52[b]	37.16 ± 10.03[b]	30.44 ± 9.12[b]	11.20 ± 3.35[c]	11.00 ± 3.00[c]

[a] The statistical analyses are carried out for the data of same time point, n = 10, vehicle = 0.3% CMC-Na; dose of **1**, **2**, **3**, Gly, Gly-Ala-OBzl and **6a**: 30 μmol/kg.
[b] Compare to the others $p < 0.01$.
[c] Compare to vehicle $p < 0.01$.

Arg-15-15C[3] were assayed for in vivo analgesic activity. On rat model T62 was orally administered at a dose of 0.34 mmol/kg while H-Arg-15-15C was intraperitoneally administered at a dose of 15.8 μmol/kg. In respect of oral administration the dose of 25 μmol/kg of *N*-[2-chloro-9-(tetrahydropyran-2-yl)-9*H*-purin-6-yl]-*N*-cyclopropylglycyl amino acid benzylesters is 13.6-fold lower than that of T62 and closes with the intraperitoneal dose of H-Arg-15-15C. Therefore the conjugation of AR agonist with GlyR agonist benefits oral administration and could be a promising approach of developing lead compound with orally analgesic activity.

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Supplementary data

Experimental procedures, biological evaluation methods, synthetic data, analytical data, physical chemical constants and spectral data associated with this article are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.05.077.

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