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Novel phenylamino acetamide derivatives as potent and selective κ opioid receptor agonists

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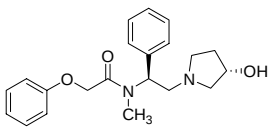
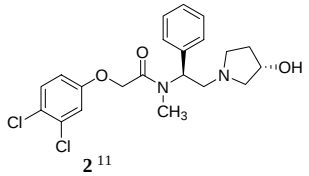
Abstract—A novel series of phenylamino acetamide derivatives was synthesized. These amides were shown to be potent and selective κ opioid receptor agonists.

It is well established that the pharmacological effects of opioid-type drugs are mediated by three opioid receptor types, μ, κ, and δ.[1] The most prominent opiate, morphine, has had a long history of analgesia in clinical practice. Its analgesic potency, mediated through agonism of the μ-opioid receptor, is associated with undesired side effects, such as respiratory depression, constipation, tolerance, and dependence. Receptor selective κ-agonists as potent and efficacious analgesics are of particular interest because they produce analgesia without the undesirable side effects of the μ-opioids.[2–4] However, sedation, dysphoria, and diuresis usually accompany κ-agonist applications, and thus prevented their further development and commercialization as analgesics.[2–4] To avoid the side effects associated with the CNS, in recent years attention has been focused on the development of peripherally acting κ-agonists as potential analgesic therapeutics.[2,5–10]

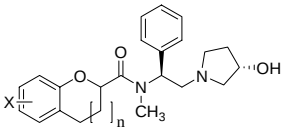
During our screening of a combinatorial library, we identified aryloxyacetamides (e.g., **1** and **2**) as highly potent κ-agonists.[11] Based on these lead compounds, we recently reported the design and synthesis of two novel series of constrained aryloxyacetamides **3**.[12] In this communication, we report a novel series of phenylamino acetamide derivatives with the general structure **I**, which are bioisosteres of aryloxyacetamides with the replacement of oxygen with nitrogen. The replacement of oxygen with nitrogen will increase the polarity and hydrophilicity of the compounds, and may limit the CNS penetration and display peripheral selectivity. This is expected to be beneficial to minimize or eliminate the CNS side effects of the centrally active κ opioid receptor ligands while retaining antihyperalgesic activity.[2] These novel phenylamino acetamides possessed high and selective κ- opioid receptor binding affinity. Compound **4**,



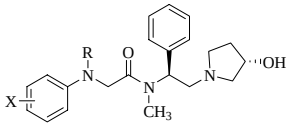
1[11]
K_i (κ) = 2 nM
μ/κ: > 2500; δ/κ: 370



2[11]
K_i (κ) = 0.125 nM
μ/κ: 480; δ/κ: 40



3[12]
n = 0: 2,3-Dihydrobenzofuran class
n = 1: Chromane class



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(this work)

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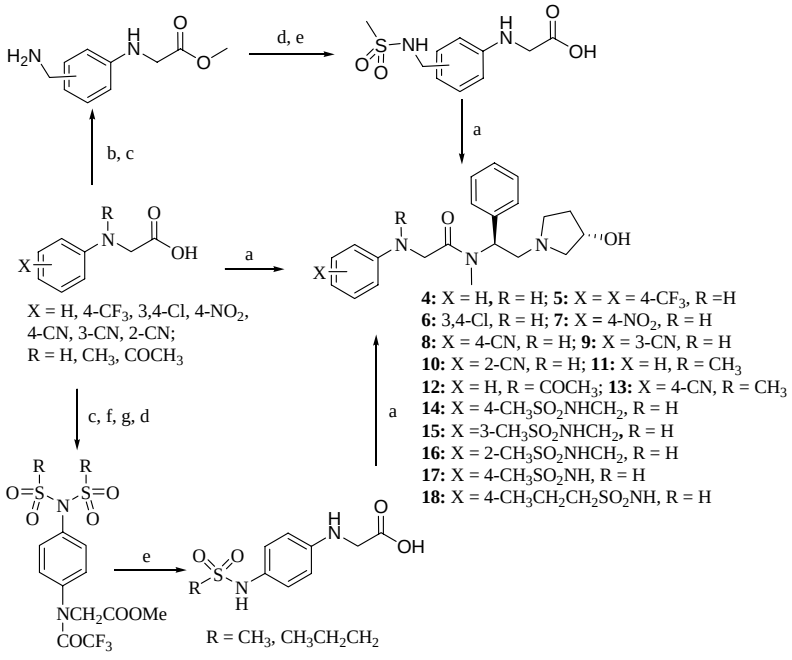
the most potent and selective κ agonist in this novel series of phenylamino acetamides, exhibited potent analgesic effects in the in vivo formalin-induced nociception assay and acetic acid-induced writhing assay.

The synthesis of the target phenylamino acetamide derivatives **4**–**18** is summarized in Scheme 1. Various known substituted glycines, either commercially available or prepared by literature procedures: *N*-phenylglycine, *N*-4-trifluoromethyl, 3,4-dichloro,[13] 4-nitro,[14] 4-cyano,[14,15] 3-cyano,[16] 2-cyano[17] phenylglycines, and *N*-methyl-*N*-phenylglycine,[18] *N*-acetyl-*N*-phenylglycine,[19] and *N*-methyl-*N*-4-cyanophenylglycine[15] were coupled with the diamine 1-(2-methylamino-(*S*)-2-phenyl-ethyl)-pyrrolidin-(*S*)-3-ol[20] using TBTU [*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate] as the acylating reagent to yield the target compounds **4**–**13**.

In our previous studies of the constrained chroman-2-carboxamides and 2,3-dihydrobenzofuran-2-carboxamides, compounds **3**,[12] as potent κ-agonists, we found that the sulfonylamino groups are the most preferred substituents at the phenyl ring for obtaining both high κ affinity and low inhibitory activity at CYP2D6.[12,21] We incorporated this SAR information into the structure of our new chemical series of phenylamino acetamide derivatives **I**. Thus, compounds **14**–**18**, which contain sulfonylamino groups, were prepared. Hydrogenation of the *N*-*para*-, *meta*-, and *ortho*-cyanophenylglycines gave the amino acids, which were converted to their methyl esters under standard reaction conditions. Reaction of these benzylamines with methanesulfonyl chloride, followed by treatment with LiOH, afforded the corresponding acids, which were converted to the target compounds **14**–**16** using the above-mentioned method.

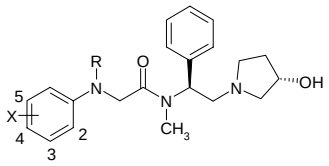
The synthesis of the sulfonamides **17** and **18** was started from *N*-4-nitrophenylglycine. Conversion to its methyl ester under standard condition, protection of the anilinic amino group as trifluoroacetamide, and hydrogenation of the nitro group, followed by reaction of the resulting aniline with methanesulfonyl chloride or propanesulfonyl chloride using triethylamine as a base, afforded the disulfonylated products. These intermediates were then treated with LiOH to simultaneously cleave the trifluoroacetamide, the methyl ester, and one sulfonyl group in the molecules, yielding the desired *N*-4-methanesulfonylamino- and *N*-4-propanesulfonylamino-phenylglycines. The resulting acids were transformed to the target compounds **17** and **18** in the same manner described above.

Phenylamino acetamide derivatives **4**–**18** were evaluated in the in vitro opioid receptor binding assays and the results are shown in Table 1.[22] Compounds **4** and **6**, the bioisosteric analogs of the aryloxyacetamides **1** and **2** with the replacement of oxygen with nitrogen, exhibited sub-nanomolar κ binding affinity and high selectivity over μ and δ receptors. The substituents at the anilinic nitrogen affected κ binding. Compounds **11** and **13** with the replacement of hydrogen with methyl group had a slightly decreased κ affinity and also a 2- to 3-fold decrease in receptor selectivity compared to compounds **4** and **8**, while the acylated analog **12** showed more than a 20-fold loss of κ affinity compared to compound **4**, indicating an unsubstituted amino group (NH) is important for obtaining high κ binding affinity. Substitution



Scheme 1. Synthesis of phenylamino acetamide derivatives **4**–**18**. Reagents: (a) 1-(2-methylamino-(*S*)-2-phenyl-ethyl)-pyrrolidin-(*S*)-3-ol dihydrochloride, TBTU, *i*-Pr_2NEt, MeCN; (b) H_2, Pd/C, MeOH, concd HCl; (c) MeOH, HCl (2.0 M in Et_2O); (d) $MeSO_2Cl$ or *n*-$PrSO_2Cl$, Et_3N, DCM; (e) LiOH, MeOH/THF/H_2O (1:1:1); (f) $(CF_3CO)_2O$, Et_3N, DCM; (g) H_2, Pd/C.

Table 1. Opioid receptor binding results



Compound	X	R	κ K_i (nM)	κ EC_{50} (nM)	μ/κ	δ/κ	CYP2D6 IC_{50} (nM)
4	H	H	0.17	0.05	5882	512	4100
5	4-CF_3	H	0.39	0.8	385	256	190
6	3,4-Cl	H	0.11	0.27	427	91	760
7	4-NO_2	H	0.21	0.23	905	119	3400
8	4-CN	H	0.66	0.49	833	409	2500
9	3-CN	H	0.5	0.58	1140	66	3000
10	2-CN	H	0.39	0.42	667	49	510
11	H	CH_3	0.32	0.23	1656	169	530
12	H	CH_3CO	3.8	7.4	>1315[a]	342	300
13	4-CN	CH_3	1	2.3	250	180	670
14	4-$CH_3SO_2NHCH_2$	H	16	24	81	119	8000
15	3-$CH_3SO_2NHCH_2$	H	3.9	4.8	38	38	8700
16	2-$CH_3SO_2NHCH_2$	H	0.78	0.52	85	10	1500
17	4-CH_3SO_2NH	H	5.7	14	>877[a]	47	<50% inhibition at 10 μM
18	4-$CH_3CH_2CH_2SO_2NH$	H	1.5	8.3	1000	87	9000

[a] μ receptor K_i is estimated to be >5 μM.

groups at the phenyl ring were well tolerated by the κ receptor. Fourteen compounds out of fifteen with various substituents displayed low nM κ binding affinity. The position of the substitution groups on the phenyl ring impacted κ binding affinity and selectivity. The κ affinity increased from *para*-substitution (compounds **8**, **14**) to *meta*-substitution (compounds **9**, **15**), and to *ortho*-substitution (compounds **10**, **16**), the latter being the most preferred pattern for sterically demanding substituents. The trend toward κ selectivity was reversed, with *para*-substitution having highest selectivity and the *ortho*-substitution having lowest selectivity versus the δ receptor. The phenylamino acetamides containing sulfonylamino groups, compounds **14**–**16** and **17**, **18** showed decreased κ binding affinity compared to the non-substituted compound **4**, but most of the compounds still remained low nM κ affinity.

Agonists **4**–**18** were also evaluated against the cytochrome P450 2D6 enzyme using a fluorescent-based assay.[23] The reference compound, ICI 199441, a highly potent and selective arylacetamide κ-agonist, is a potent inhibitor (IC_{50} = 26 nM) of CYP2D6.[23] This is an undesirable property to have in a drug.[21,23] In general, κ agonists **4**–**18** did not significantly inhibit CYP2D6. Unsubstituted **4** displayed an IC_{50} = 4.1 μM. Inhibitory activity tended to correlate with lipophilicity. Agonists **5**, **6**, **11**, and **12** possessing hydrophobic substituents showed the greatest level of enzyme inhibition. Consistent with previous SAR studies,[12,23] sulfonamide-bearing agonists, for example, **14**–**18**, were weak inhibitors of CYP2D6.

Compound **4**, the most potent and selective κ agonist and quite a weak CYP2D6 inhibitor in the new phenylamino acetamide series, was tested in the in vivo nociceptive assays.[24] It displayed potent analgesic effects, producing 96.2% antinociception at 300 μg given intrapaw (sc injection in dorsal surface of paw), in the late phase formalin-induced flinching assay, and inhibited acetic acid-induced writhing when administered subcutaneously with an ED_{50} value of 0.017 mg/kg.

In summary, a novel series of phenylamino acetamide derivatives, bioisosteres of aryloxyacetamides, was synthesized and found to be highly potent κ receptor agonists. This discovery expands the SAR of κ-agonists beyond classic arylacetamides. Most of the compounds displayed low nM κ binding affinity, excellent selectivity against μ and δ, and low CYP2D6 activity. Compound **4** with high κ affinity and potency (K_i = 0.17 nM, EC_{50} = 0.05 nM) and >500-fold selectivity versus both μ and δ receptors demonstrated potent analgesic effects in the in vivo formalin-induced nociception and acetic acid-induced writhing assays.

References and notes

1. Dhawan, B. N.; Cesselin, F.; Raghubir, R.; Reisine, T.; Bradely, P. B.; Portoghese, P. S.; Hamon, M. *Pharmacol. Rev.* **1996**, *48*, 567.
2. DeHaven-Hudkins, D. L.; Dolle, R. E. *Curr. Pharm. Des.* **2004**, *10*, 743.
3. Holzgrabe, U.; Brand, W. *J. Med. Chem.* **2003**, *46*, 1383.
4. Soukara, S.; Maier, C. A.; Predoiu, U.; Ehret, A.; Jackisch, R.; Wünsch, B. *J. Med. Chem.* **2001**, *44*, 2814.
5. Kumar, V.; Guo, D.; Cassel, J. A.; Daubert, J. D.; DeHaven, R. N.; DeHaven-Hudkins, D. L.; Gauntner, E. K.; Gottshall, S. L.; Greiner, S. L.; Koblish, M.; Little, P. J.; Mansson, E.; Maycock, A. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1091.
6. Tuthill, P. A.; Seida, P. R.; Barker, W.; Cassel, J. A.; Belanger, S.; DeHaven, R. N.; Koblish, M.; Gottshall, S.

L.; Little, P. J.; DeHaven-Hudkins, D. L.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5693.
7. Giardina, G.; Clarke, G. D.; Grugni, M.; Sbacchi, M.; Vecchietti, V. *Farmaco* **1995**, *50*, 405.
8. Barber, A.; Gottschlich, R. *Expert Opin. Investig. Drugs* **1997**, *6*, 1351.
9. Stein, C.; Machelska, H.; Binder, W.; Schafer, M. *Curr. Opin. Pharmacol.* **2001**, *1*, 62.
10. Rivière, P. J.-M. *Br. J. Pharmacol.* **2004**, *141*, 1331.
11. Unpublished data.
12. Chu, G.-H.; Gu, M. H.; Cassel, J. A.; Belanger, S.; Graczyk, T. M.; DeHaven, R. N.; Conway-James, N.; Koblish, M.; Little, P. J.; DeHaven-Hudkins, D. L.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5114.
13. Anderson, W. K.; Jones, A. N. *J. Med. Chem.* **1984**, *27*, 1559.
14. Dyer, E.; McCarthy, F. L.; Johnson, R. L.; Nagle, E. V. *J. Org. Chem.* **1957**, *22*, 78.
15. Kaji, M.; Kojima, Y.; Katogi, S.; Nunomura, M. Eur. Pat. Appl. EP 636939, 1995.
16. Bryson, A.; Davies, N. R.; Serjeant, E. P. *J. Am. Chem. Soc.* **1963**, *85*, 1933.
17. Peet, N. P.; Sunder, S. *J. Heterocycl. Chem.* **1977**, *14*, 561.
18. Brady, W. T.; Gu, Y. Q. *J. Org. Chem.* **1989**, *54*, 2834.
19. DeRuiter, J.; Swearingen, B. E.; Wandrekar, V.; Mayfield, C. A. *J. Med. Chem.* **1989**, *32*, 1033.
20. Zhang, W. Y.; Maycock, A. L.; Kumar, V.; Gaul, F.; Chang, A.-C.; Guo, D. WO00014065, 2000.
21. Nelson, D. R.; Koymans, L.; Kamataki, T.; Stegeman, J. J.; Feyereisen, R.; Waxman, D. J.; Waterman, M. R.; Gotoh, O.; Coon, M. J.; Estabrook, R. W.; Gunsalus, I. C.; Nebert, D. W. *Pharmacogenetics* **1996**, *6*, 1.
22. Opioid receptor binding assay: (a) DeHaven, R. N.; DeHaven-Hudkins, D. L. In *Current Protocols in Pharmacology*; Enna, S. J., Williams, M., Ferkany, J. W., Kenakin, T., Porsolt, R. D., Sullivan, J. P., Eds.; John Wiley & Sons Inc.: New York, 1998; pp 1.4.1–1.4.12; (b) Raynor, K.; Kong, H.; Chen, Y.; Yasuda, K.; Yu, L.; Bell, G. I.; Reisine, T. *Mol. Pharmacol.* **1994**, *45*, 330; (c) All the compounds listed in Table1 were full agonists as determined in a [^{35}S]GTPγS functional binding assay.
23. Le Bourdonnec, B.; Ajello, C. W.; Seida, P. R.; Susnow, R. G.; Cassel, J. A.; Belanger, S.; Stabley, G. J.; DeHaven, R. N.; DeHaven-Hudkins, D. L.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2647.
24. For a description of the in vivo assays, see Ref. 5.