Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 805–809

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Novel 3-(4-Piperidinylthio)-1*H*-Indoles as Potent Nonopioid Orally Active Central Analgesics

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Received 3 December 1999; accepted 10 February 2000

Abstract—A series of 3-(4-piperidinylthio)-1*H*-indoles was synthesized and evaluated in mice in the phenylbenzoquinone(PBQ)-induced writhing and hot plate tests. Most of these compounds are good analgesics with activities comparable to that of morphine. Among them compound **1i** (UP 237-61), which has a strong serotonin binding profile, has an interesting antinociceptive activity which is not reversed by naloxone.

Introduction

Among centrally acting analgesics, opioids are the most commonly used.[1] However these compounds often induce side effects including sedation, constipation, respiratory depression, tolerance and physical dependence.[2] In the search for new central analgesic drugs devoid of side effects, different targets have been identified such as noradrenergic, dopaminergic, cholinergic (muscarinic or nicotinic), adenosinergic and serotoninergic pathways.[3]

We have focused our efforts on this last mechanism of action. Actually, considerable evidence exists for the implication of serotonin (5-HT) in the modulation of nociceptive transmission.[4] Thus, activation of the descending serotoninergic bulbospinal system produces inhibition of the dorsal horn neuronal responses to noxious stimuli. This activation could be obtained either directly by 5-HT receptor agonists or indirectly through an increase in 5-HT concentrations by 5-HT reuptake inhibition.

The minimal structural requirements for mimicking 5-HT are often considered to be one basic nitrogen atom and an aromatic ring.[5] We chose to keep the indole nucleus of 5-HT and use a piperidine ring as a conformationally restricted analogue of its aminoethyl side chain. Compounds bearing these two features have already been found active on 5-HT receptors, for example: RU-24969 [6] a 5-HT_{1A} agonist, RP-68303[7] a 5-HT reuptake inhibitor, naratriptan[8] (GR-85548) a 5-HT_{1D} agonist launched as an antimigraine drug or sertindole[9] (LU-23-174) a dopamine D_2/5-HT antagonist launched as an antipsychotic drug.

We have decided to synthesize 3-(4-piperidinylthio)-1*H*-indole corresponding to the general formula **1** and to evaluate their pharmaceutical potential as antinociceptive agents.

Chemistry

The synthetic approach selected for the preparation of the desired compounds involved the Fischer indole synthesis by condensation of an arylhydrazine with an eventually protected carbonyle compound, bearing a 4-piperidinylthio substituent. The requisite 1-substituted-4-piperidinethiols **4** were prepared by the synthetic sequence outlined in Scheme 1 from commercially available 4-piperidinones or from 1-methoxy-4-piperidinone.[10] Thus treatment of ketones **2** with H_2S in *i*PrOH afforded the corresponding *gem*-dithiols **3**, which were reduced with $NaBH_4$ to give the thiols **4a**–**f**.[11] 1-Methyl-4-piperidinethiol was converted to the *N*-unsubstituted thiol **4g** using a described procedure.[12]

Thiols **4** were converted to their sodium salt with either sodium methylate or ethylate and reacted in THF with a chloroketone (Method A) or 1-bromo-2,2-diethoxyethane (Method B) to afford the ketones **5** and the

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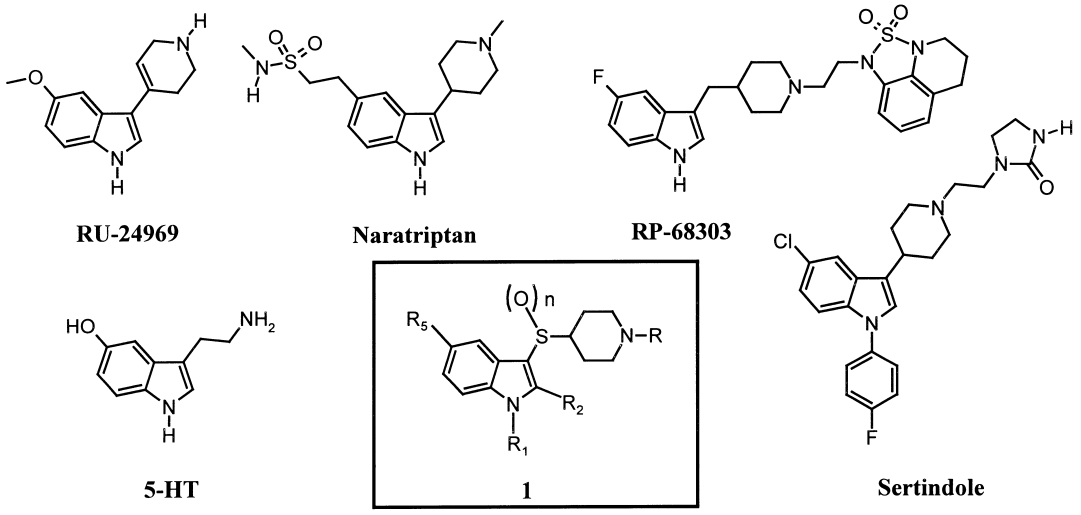
0960-894X/00/$ - see front matter
PII: S0960-894X(00)00102-5



protected aldehydes **6** respectively (Scheme 2). These compounds were then reacted in iPrOH with arylhydrazines in the presence of gaseous hydrochloric acid to yield the desired indoles **1** (Method C).

Alkylation of the indole nitrogen atom with alkyl iodides was performed using sodium amide as a base in a mixture of liquid ammonia and THF (Method D). Compound **1y** was synthesized by metallation with nBuLi followed by quenching with gaseous carbon dioxide (Method E). The 5-hydroxy substituted indole **1k** having a substitution pattern similar to that of serotonin was obtained through demethylation of **1l** with boron tribromide in chloroform (Method F). Acylation of the piperidine nitrogen atom was done under standard conditions (Methods G,H). Finally, oxidation of the sulfur atom was carried out using 1 or 2 equivalents of oxone® to yield either the sulfoxide **1ae** or the sulfones **1af–ag**[13] (Methods I, J).

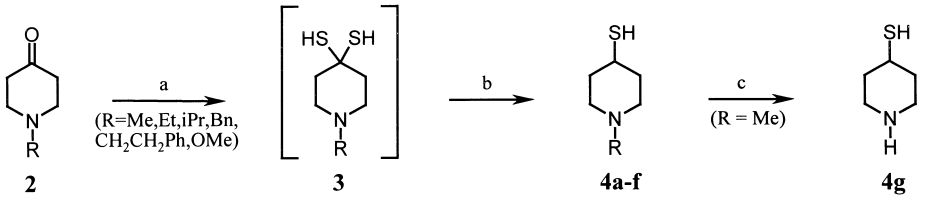
Results

To assess the in vivo analgesic activity of our compounds, they were first evaluated in mice in the phenylbenzoquinone (PBQ)-induced writhing test,[14] which points out analgesic compounds acting either through a peripheral or a central mechanism of action. In this model, compounds were administered orally 1 h prior to the intraperitoneal administration of PBQ. Their potency was then measured as the inhibition of painful reactions (writhings and stretches). Active compounds in the latter test were then subjected to the hot plate test,[15] which in turn is more specific for compounds with a central mechanism of action. Results for both of these tests are shown in Table 1.

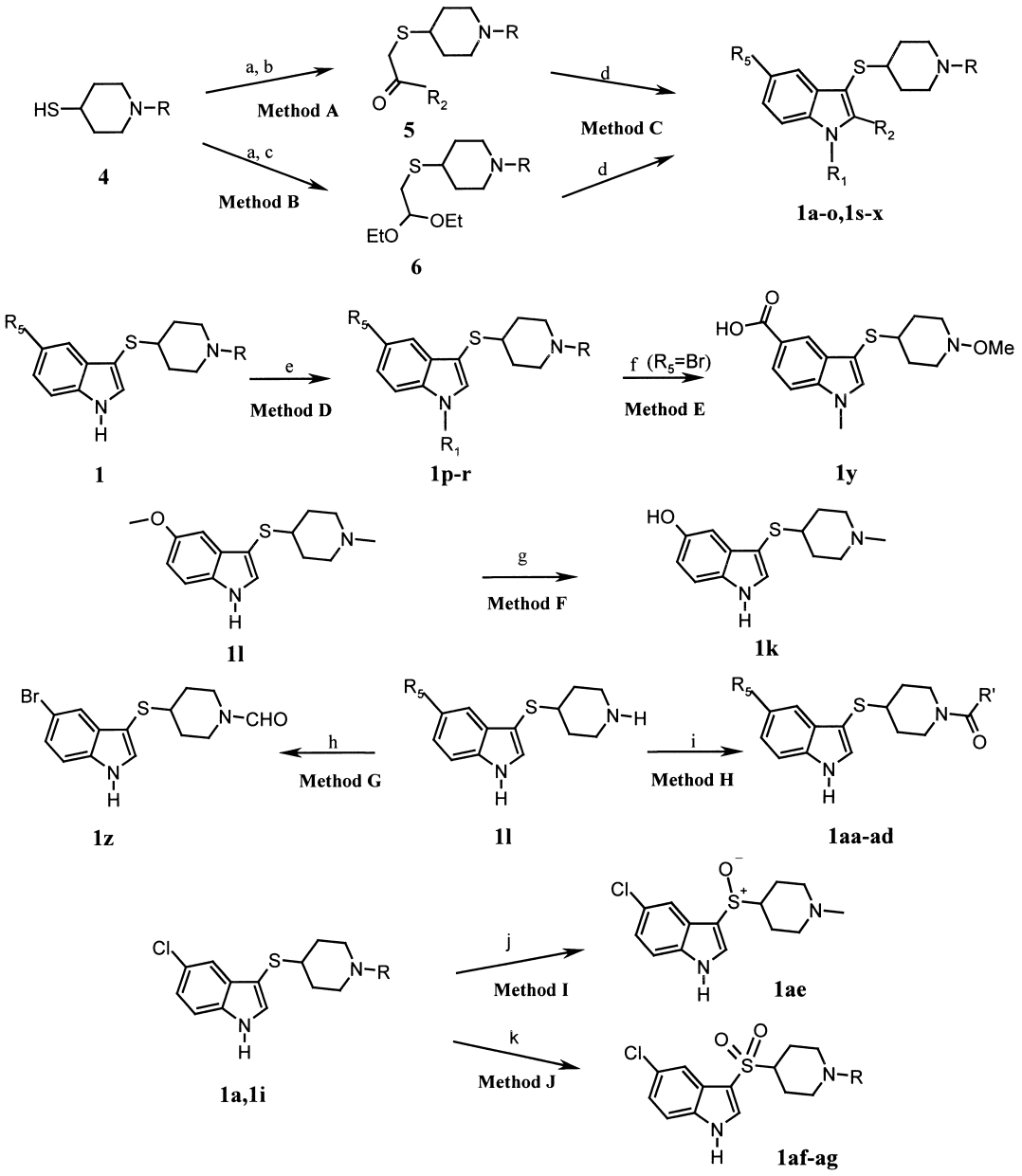
Discussion

It is apparent from the data presented in Table 1 that the studied 3-piperidinylthio-1*H*-indoles are generally interesting analgesics as compared to the activity of morphine. Hydrogen or methyl substituents at indole 1-position give equally potent compounds. When the size of this substituent is increased the activity drops rapidly, as shown by the comparison of **1r** (R_1 = nBu) with **1q** (R_1 = Me), and of **1g** (R_1 = 4-Cl-Bn) with **1b** (R_1 = H). The same trend is observed with the 2-position substitution where activity decreases with the size, hydrogen being more potent than methyle (**1a** and **1b**) and aryle being inactive (**1f**). Halogen atoms at the 5-position were by far the best compounds, with 5-chloro and 5-bromo being more active than 5-fluoro or 5-iodo. 5-CF_3, 5-methyl, 5-methoxy or the unsubstituted indole give less active compounds whereas other substitutions (OH, CO_2H, iPr) give mostly inactive compounds. It should be noticed that the 5-hydroxy compound, having the same indole substitution as 5-HT has no antinociceptive activity.

Various substitutions of the piperidine nitrogen have been studied. The most favorable groups are hydrogen, methoxy or acetyl. Less active compounds are obtained



Scheme 1. (a) H_2S, iPrOH, 10 °C; (b) $NaBH_4$, *i*PrOH, reflux; (c) (i) $ClCO_2Et$, acetone, 15–20 °C, (ii) $ClCO_2Et$, toluene, 80–110 °C, (iii) concd HCl, AcOH, reflux.



Scheme 2. (a) NaOMe or NaOEt, THF, 20 °C; (b) $ClCH_2COCH_2R_2$, 20 °C; (c) $BrCH_2CH(OEt)_2$, 20 °C; (d) R_5-$PhNR_1NH_2$, HCl gas, iPrOH, 0 to 20 °C; (e) (1) $NaNH_2$, NH_3 liq, THF, −40 °C, (2) R_1I, −40 to 20 °C; (f) (1) nBuLi, THF, −78 °C, (2) CO_2 gas, −78 to 0 °C; (g) BBr_3, $CHCl_3$, 0 °C; (h) HCO_2H, DCC, DMAP cat, CH_2Cl_2, 20 °C; (i) $ClCO_2Et$ or ClCOR′, Et_3N, CH_2Cl_2, 0 to 20 °C; (j) $KHSO_5$ (1 eq), H_2O, MeOH, 0 to 20 °C; (k) $KHSO_5$ (2 eq), H_2O, MeOH, 0 to 20 °C.

with either methyl, benzyl, phenethyl or butyryl substituents. Finally, poorly active molecules are found among those *N*-substituted by ethyl, isopropyl or formyl groups. The oxidation state of the sulfur atom also plays an important role. The sulfoxide **1ae** is considerably less active than the corresponding thioether **1i**, whereas sulfone **1af** is equivalent in potency to **1i** and sulfone **1ag** is slightly less active than **1a**.

Extremely active compounds such as **1a–c**, **1i**, **1p–q**, **1w–x, 1aa–ab** and **1af** were discovered. Due to its good activity:tolerance ratio,[16] **1i** (UP 237-61) was further evaluated. In addition to its good activity in our two screening assays (ED_{50} values (po) of 4 mg/kg (PBQ) and 16.9 mg/kg (hot plate)), it is highly potent in the kaolin-induced arthritis model[17] (ED_{50} = 4.9 mg/kg, rats, po; morphine: 4.4 mg/kg) and in the tail pinch test[18] (ED_{50} = 25.3 mg/kg, mice, ip; morphine: 15 mg/kg), but poorly active in the Freund's adjuvant-induced polyarthritis model[19] (62% inhibition at 60 mg/kg, rats, po; morphine: 5.2 mg/kg). Its activity was not blocked in the hot plate test after the administration of the opioid antagonist naloxone (3 mg/kg, sc), demonstrating its nonopioid mechanism of action. In fact its strong serotonin binding profile[20] (Fig. 1), especially with a K_i value of 3.01 nM on 5-HT uptake sites, might suggest a serotoninergic antinociceptive mechanism of action.

Further mechanistic and pharmacokitenic studies of **1i** are under way and will be reported in due time.

Table 1.

Compd.	R	R_1	R_2	R_5	*n*	Mp (°C)	Synthetic methods	PBQ writhing[a]	Hot plate[a]
Morphine								1.5	28.9
1a	H	H	H	Cl	0	251–252[b]	B, C	0.3	1.2
1b	H	H	Me	Cl	0	198–199	A, C	0.8	9.9
1c	H	H	Me	Br	0	207–208	A, C	0.7	3.1
1d	H	H	Me	F	0	201	A, C	5.9	12.7
1e	H	H	Me	CF_3	0	298–301[b]	A, C	19.4	41%
1f	H	H	4-Cl-Ph	Cl	0	230–231	A, C	26%	
1g	H	4-Cl-Bn	Me	Cl	0	121–122	A, C	27%	
1h	Me	H	H	H	0	143–144	B, C	26%	
1i	Me	H	H	Cl	0	136–137	B, C	4	16.9
1j	Me	H	H	I	0	136–137	B, C	54.2	
1k	Me	H	H	OH	0	183–184	B, C, F	9%	
1l	Me	H	H	OMe	0	153	B, C	24.9	
1m	Me	H	H	Me	0	134	B, C	25%	
1n	Me	H	H	iPr	0	110	B, C	48%	
1o	Me	H	Me	F	0	158–159	A, C	35.6	
1p	Me	Me	H	Cl	0	78–79	B, C, D	3.9	9.3
1q	Me	Me	H	Br	0	83–84	B, C, D	5.4	8.6
1r	Me	nBu	H	Br	0	65–66	B, C, D	21%	
1s	Et	H	H	Cl	0	75–77[c]	B, C	42%	33.3
1t	iPr	H	H	Cl	0	123	B, C	38%	
1u	Bn	H	H	Cl	0	158–160[c]	B, C	9.7	32%
1v	CH_2CH_2Ph	H	H	Cl	0	137–140	B, C	8.9	14%
1w	OMe	H	H	Cl	0	132	B, C	1.4	2.3
1x	OMe	H	H	Br	0	134–135	B, C	1.6	3.2
1y	OMe	Me	H	COOH	0	170–172	B, C, D, E	25%	
1z	CHO	H	H	Br	0	204–207	B, C, G	31%	
1aa	Ac	H	H	Cl	0	160–161	B, C, H	2.9	3.8
1ab	Ac	H	H	Br	0	155–156	B, C, H	2.9	2.8
1ac	COC_3H_7	H	H	Cl	0	129–130	B, C, H	8.9	22.7
1ad	CO_2Et	H	H	Br	0	147–149	B, C, H	6.3	27.3
1ae	Me	H	H	Cl	1	221–222	B, C, I	44%	
1af	Me	H	H	Cl	2	220–225	B, C, J	5.4	16
1ag	H	H	H	Cl	2	225–227	B, C, J	12.5	8.4

[a]ED_{50} (mg/kg) or inh% at 30 mg/kg.
[b]HCl salt.
[c]HCl salt, 0.5 H_2O.

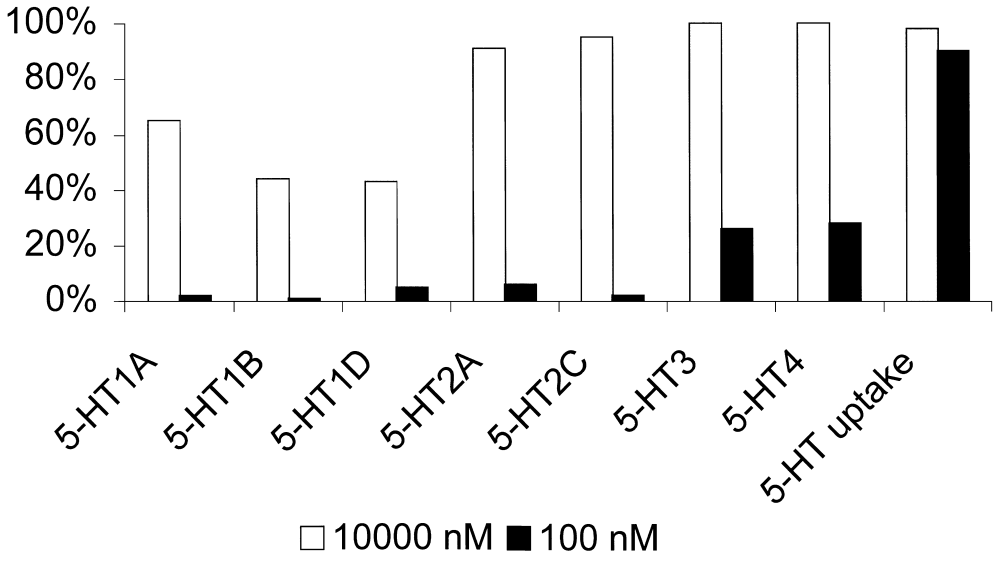


Figure 1. Serotonin binding profile of **1i**.

References and Notes

1. Hayes, S. R.; Vogelsang, J. *J. Post. Anesth. Nurs.* **1991**, *6*, 125.

2. (a) Vanegas, G.; Ripamonti, C.; Sbanotto, A.; De Conno, F. *Cancer Nurs.* **1998**, *21*, 289. (b) Ecoffey, C. *Cah. Anesthesiol.* **1991**, *39*, 115. Walsh, T. D. *J. Pain Symptom. Manage.* **1990**, *5*, 362.

3. For a recent review of approaches to pain therapy: Williams, M.; Kowaluk, E. A.; Arneric, S. P. *J. Med. Chem.* **1999**, *42*, 1481.
4. *Serotonin and Pain: Proceedings of the International Symposium on Serotonin and Pain*, La Roque-Gageac, 17–21 September 1989; Besson, J.-M., Ed.; Excerpta Medica: Amsterdam, New York, Oxford, 1990; pp 1–339.
5. Hibert, M. F.; Gittos, M. W.; Middlemiss, D. N.; Mir, A. K.; Fozard, J. R. *J. Med. Chem.* **1988**, *31*, 1087.
6. Guillaume, J.; Dumont, C.; Laurent, J.; Nédélec, L. *Eur. J. Med. Chem.* **1987**, *22*, 33.
7. Mignani, S.; Damour, D.; Doble, A.; Labaudinière, R.; Malleron, J. L.; Piot, O.; Gueremy, C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1913.
8. Bomhof, M.; Enahoro, H.; Winter, P.; Hassani, H. *Cephalalgia* **1997**, *17*, 424.
9. Perregaard, J.; Arnt, J.; Bøgesø, K. P.; Hyttel, J.; Sánchez, C. *J. Med. Chem.* **1992**, *35*, 1092.
10. Major, R. T.; Dürsch, F. *J. Org. Chem.* **1961**, *26*, 1867.
11. Barrera, H.; Lyle, R. E. *J. Org. Chem.* **1962**, *27*, 641.
12. Engel, J.; Bork, A.; Nubert, I.; Schönenberger, H. *Arch. Pharm. (Weinheim)* **1988**, *321*, 821.
13. It is not necessary to protect the piperidine nitrogen atom from oxydation since this amine is protonated under the reaction conditions (pH around 4–5).
14. Siegmund, E.; Cadmus, R.; Lu, G. A. *Proc. Soc. Exp. Biol. Med.* **1957**, *95*, 729.
15. Eddy, N. B.; Toucheberry, C. F.; Lieberman, J. E. *J. Pharmacol. Exp. Ther.* **1950**, *98*, 121.
16. In tolerance studies **1i** exhibited serotonin-related side effects (flat body posture, tremors, forepaw treadings) at doses approximately 25 times the active dose in both mice and rats.
17. Hertz, F.; Ranson, M.; Lwoff, J. M. *Arzneim. Forsch.* **1980**, *30*, 1549.
18. Haffner, F. *Dtsch. Med. Wochenschr.* **1929**, *55*, 731.
19. Pearson, C. M.; Wood, F. D. *Arthritis Rheum.* **1959**, *2*, 440.
20. Receptor binding profile performed at Cerep [5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT uptake (rat); 5-HT_{1D} (bovine); 5-HT_{2C} (pig); 5-HT_3 (mouse); 5-HT_4 (guinea pig)].