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ISOSTERIC REPLACEMENT OF THE INDOLE NUCLEUS BY BENZOTHIOPHENE IN A SERIES OF PYRIDO[2,3-*b*]INDOLES WITH POTENTIAL ANXIOLYTIC ACTIVITY

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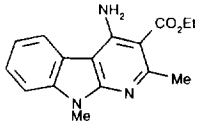
Abstract: Isosteric replacement of the indole nucleus in a series of pyrido[2,3-*b*]indoles *e.g.* **1** and **2** has provided potent $GABA_A$ modulators with potential anxiolytic activity. Both benzothiophene and cycloalkyl fused heterocyclic ring systems are acceptable moieties.

It is well established that modulation of the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and the associated chloride ion channel complex is pivotal to the treatment of anxiety disorders in man.
For a number of years we have been involved with the synthesis of aryl fused pyridines containing a high degree of functionality as targets for the treatment of anxiety disorders.[1,2] In particular, a series of molecules containing the pyrido[2,3-*b*]indole ring system has proved to be of some interest as a novel type of $GABA_A$ modulator.[3,4] Esters of 4-amino-2,9-dimethyl-9H-pyrido[2,3-*b*]indole such as **1** are $GABA_A$ modulators which showed activity in animal models of anxiety but were relatively short acting *in vivo*.[3] However, the incorporation of a cyclic ketone to mimic the intramolecularly hydrogen bonded 4-aminonicotinoate moiety provided the potent quinindoline isostere **2** (BRL 54504AX) which possessed a longer duration of action.[4]



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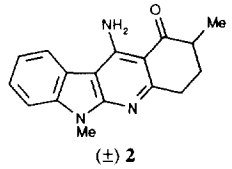
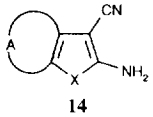
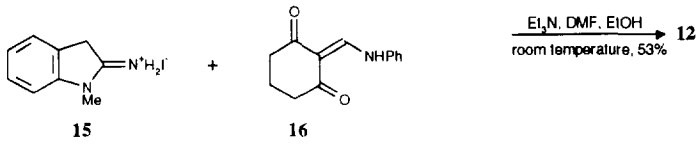


(±) **2**



14

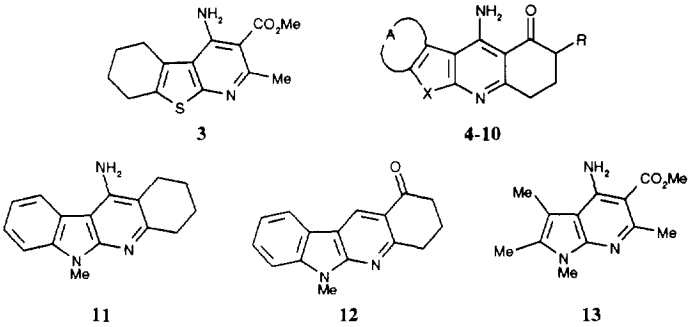
Studies undertaken to determine the metabolic fate of **1** in rodents revealed that the major site of metabolism was the carboxylic ester which was cleaved to the corresponding biologically inactive acid.[5] Some N-9 demethylation was also observed which suggested that replacement of the indole nucleus by a benzothiophene moiety should produce an interesting series of molecular targets. With this in mind, a number of novel thieno [2,3-*b*]pyridines **3** to **8** and quinindolines **9** to **12,** for comparative purposes, as shown in Table 1, were prepared. The chemical strategy and methodology used to assemble these compounds , from **14** , has already been published.[3,4,6] The des amino compound **12** was prepared in 53% yield from 2-amino-1-methyl indole hydriodide[7] **15** and the cyclohexanedione[8] **16** as shown below.



15 16

Biological Results and Discussion.

All the compounds were assessed by measurement of the inhibition of [^{35}S]-t-butyl-bicyclophosphorothionate (TBPS) binding, which has been well established to correlate with GABA/chloride ion channel opening as previously described.[3,9] Benzodiazepine (BDZ) agonists will also displace [^{35}S] TBPS binding by opening the chloride ion channel *via* direct modulation of the BDZ site. The profile of inhibition by $GABA_A$ modulators such as **1** and **2** clearly differs from BDZ's in that representative examples from the chemical series do not significantly displace [^{3}H] flunitrazepam (Flu) binding *in vitro*. For example this can be seen with the indoles (**1**, **2**, **12**) and the thiophene **8** which were inactive (IC_{50}>100μM) and the tetrahydroindole **10** which showed only modest activity (IC_{50} 18μM).



3 4-10

11 12 13

Table 1: Physical and Biological Data for Compounds

Cpd.	m.p. °C[a]	A	X	R	[^{35}S] TBPS[b] IC_{50} μM	[^{3}H] Flu[c] IC_{50} μM
1	80	-	-		2.0	>100
2	156	-	-	-	0.95	>100
3	193	-	-	-	7.5	NT
4	225	benzo	S	Me	0.46	NT
5	222	$(CH_2)_3$	S	Me	1.7	NT
6	227	$(CH_2)_4$	S	Me	1.6	NT
7	228	$(CH_2)_5$	S	Me	0.37	NT
8	257	$(CH_2)_5$	S	H	0.29	>100
9	187	$(CH_2)_4$	NMe	H	6.3	NT
10	200	$(CH_2)_4$	NMe	Me	2.7	18
11	232	-	-	-	>100	NT
12	185	-	-	-	10	>100
13	144	-	-	-	12	>100

[a] Melting points are uncorrected; compounds analysed for C, H, and N within ±0.4% of the theoretical values; satisfactory 250MHz ^{1}H n.m.r data were obtained.

[b] The detailed procedure of this test is described in ref. 9 and all determinations were done in the presence of 5μM GABA. Values represent the mean of at least two determinations. [c] Procedure as in ref. 10; NT = not tested.

Compounds **1** to **10** were found to inhibit [^{35}S]TBPS binding in the low micromolar range (see Table 1). From the data it can been seen that replacement of the pyridoindole nucleus of the ester **1** with the 5,6,7,8-tetrahydrobenzo[*b*]thienopyridine **3** gave a compound which was slightly less potent *in vitro*. However, in the cyclic ketone series incorporation of both the aromatised benzothiophene nucleus as in **4** (IC_{50} 0.46μM) and the tetrahydrobenzothiophenes **5** and **6** provided compounds with potencies similar to that of the quinindoline **2**. A comparison of ring sizes showed that cyclopenta-thiophene **5** was of similar potency to **6** whereas the cyclohepta-thiophenes **7** and **8** were some of the most potent compounds tested (IC_{50} 0.37 and 0.29μM respectively). Saturation of the left hand ring of the indole of **2** as in **10** produced a compound of similar potency to the aromatic counterpart **2**. Removal of the left hand ring as in **13** caused a reduction in activity on comparison with **1**. These data suggest that the left hand portion of the molecule provides a lipophilic binding interaction at the receptor site.

Structure activity relationships for the cyclic ketones **4** to **12** reveal similar key features to those reported[3] previously for pyrido[2,3-*b*]indole esters such as **1**. For example, removal of the amino substituent as with structure **12** attenuated activity and removal of the carbonyl group gave the inactive compound **11**. This confirms earlier findings where the 4-aminonicotinoate portion in **1** was crucial for *in vitro* modulation of the $GABA_A$/chloride ion channel.[3]

Table 2: Biological Evaluation in the Geller-Seifter Test[a]

Cpd.	Dose[b] mg/kg p.o.	% changes FR	VI	Nr/N
1	20	+22**	-3	$12/16$
2	20	+52**	0	$5/6$
3	40[c]	+42**	0	$8/8$
4	20	+30***	0	$5/6$
5	20	+26**	0	$5/6$
10	20	+28***	+1	$5/6$
12	20	+4	+2	$3/6$
Diazepam	10	+114**	-10*[d]	$7/8$

[a] * $p<0.05$, ** $p<0.01$, ** $p<0.001$, Two-way ANOVA; FR is the punished responding phase; VI is the variable interval unpunished phase; Nr/N is the number of animals responding out of those tested.

[b] Measurements recorded 1 hour post-dose. [c] i.p. administration. [d] peak effect at up to 2 hours post-dose.

A selection of compounds, representatives of the various structural classes shown in Table 1, was examined in the rat Geller-Seifter test.[11] Pharmacological evaluation in this rodent behavioural model of anxiety revealed that, the thienopyridine ketones **4** and **5** showed robust anxiolytic activity, comparable to that seen with the pyrido-indole ketone **2**, after an oral dose of 20mg/kg (Table 2). However, the ester **3**, unlike the pyrido-indole ester **1**, only showed activity after intraperitoneal administration. The ketone **12**, which possessed only modest *in vitro* potency was inactive. All compounds showed a lower overall effect than diazepam, but importantly, unlike diazepam, no significant decrements were observed in the unpunished phase of responding (VI phase).[12] Such decrements are an indication of a possible propensity to cause unwanted side-effects such as motor incoordination, muscle relaxation and sedation in man. Hence this series of compounds, as typified by the

examples in Table 2, appears to possess an advantage over the classical BDZ's such as diazepam as potential pharmacological tools in the treatment of anxiety disorders.

Acknowledgement

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6. a. The methodology for assembly of quinindolines is detailed in:- Forbes, I.T.; Martin, R.T.; Thompson, M. **1992**, *US Patent* 5079246.
   b. Preparation of the ethyl ester corresponding to **3** is shown in:- Lalezari, I. *J. Het. Chem.*, **1979**, *16*, 603

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12. Compound **2** was examined in rat models for muscle relaxant (rotorod test), sedative (spontaneous locomotor activity test) and ethanol interaction (EtOH-induced sleeptime) properties. **2** was without significant effect at 300mg/kg p.o. In contrast, diazepam produced marked significant effects on all three parameters at doses of 5 to 20mg/kg p.o. (for methods see: *"Animal Models in Psychiatry and Neurology"*. Hannin, I.; Usdin, E. Eds; Pergamon Press, Oxford, **1977**). The minimum effective dose of diazepam in the Geller-Seifter test was 5mg/kg p.o. (FR +57%**; $^{Nr}/_{N}$ $^{6}/_{8}$).

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