Drugs of the Future 2003, 28(8): 739-746

CCC: 0377-8282/2003

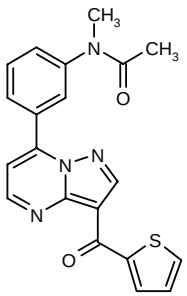
Indiplon

Prop INN; USAN

Treatment of Insomnia
GABA-A Agonist

NBI-34060

N-Methyl-*N*-[3-[3-(2-thienylcarbonyl)pyrazolo[1,5-*a*]pyrimidin-7-yl]phenyl]acetamide



$C_{20}H_{16}N_4O_2S$
Mol wt: 376.4384
CAS: 325715-02-4
EN: 271917

Abstract

Insomnia can result in sleep deprivation which may negatively affect the quality of life and compromise safety. The standard treatment for insomnia has been the sedative hypnotic drugs, benzodiazepines. However, these agents are associated with memory impairment and next-day residual sedation. In contrast, nonbenzodiazepines showed selective binding to the α_1 subunit of the GABA-A receptor and exhibited a reduced adverse event profile. One such agent, the pyrazolopyrimidine indiplon, has shown particular promise as a treatment for insomnia. Indiplon is a GABA-A receptor partial agonist that promotes sleep by enhancing the inhibitory activity of GABA through specific binding to the BZ1 or α_1 subunit of the GABA-A receptor. Indiplon has been shown to be safe and well tolerated and is currently being developed in two formulations to treat all insomnia complaints, including sleep initiation, night awakenings and total sleep maintenance.

Synthesis

Indiplon can de prepared by several related ways:

1) Condensation of 2-acetylthiophene (I) with dimethylformamide dimethylacetal produces enaminone (II), which is then cyclized to the isoxazole (III) by treatment with hydroxylamine. Further condensation of compound (III) with dimethylformamide dimethylacetal, with concomitant isoxazole ring opening, gives the enamino nitrile (IV), which is then cyclized with aminoguanidine nitrate (V) under basic conditions to furnish the aminopyrazole (VI) (1). Alternatively, the enamino nitrile (IV) can be obtained by condensation of 3-oxo-3-(2-thienyl)propionitrile (VII) with dimethylformamide dimethylacetal in chloroform (2). On the other hand, 3-(acetamido)acetophenone (VIII) is condensed with dimethylformamide dimethylacetal to give enaminone (IX), which is then alkylated at the amide nitrogen by means of iodomethane and NaH (1, 3) or, alternatively, under phase-transfer conditions (4) to give compound (X). Finally, this compound is condensed with the aminopyrazole (VI) in refluxing AcOH (1, 4). Scheme 1.

2) Bromination of 5-aminopyrazole (XI) with Br_2 in AcOH gives 4-bromo-5-aminopyrazole (XII), which is cyclized with *N*-[3-[3-(dimethylamino)-2-propenoyl]phenyl]-*N*-methylacetamide (X) in AcOH to yield the 3-bromopyrazolo[1,5-*a*]pyrimidine derivative (XIII). Finally, this compound can be condensed with either 2-thienylcarbonyl chloride (XIV) by means of Zn or Mg or with 2-thienylboronic acid (XV) and CO by means of a Pd(0) catalyst (4). Scheme 2.

3) Cyclization of 2-aminopyrazole (XI) with the acetamide (X) in AcOH gives the pyrazolo[1,5-*a*]pyrimidine derivative (XVI), which is finally acylated with 2-thienylcarbonyl chloride (XIV) by means of $AlCl_3$ (4). Scheme 3.

4) Cyclization of ethoxymethylenemalonodinitrile (XVII) with hydrazine gives 5-aminopyrazole-4-carbonitrile (XVIII), which is further cyclized with acetamide (X) in refluxing AcOH to yield the 3-cyanopyrazolo[1,5-*a*]pyrimidine derivative (XIX). Finally, this compound is condensed with 2-bromothiophene (XX) by means of Mg (4). Scheme 4.

5) Cyclization of 5-aminopyrazole-4-carboxylic acid ethyl ester (XXI) with either, 3,3-diethoxypropionic acid ethyl ester (XXII) or 3-oxopropionic acid ethyl ester (XXIII)

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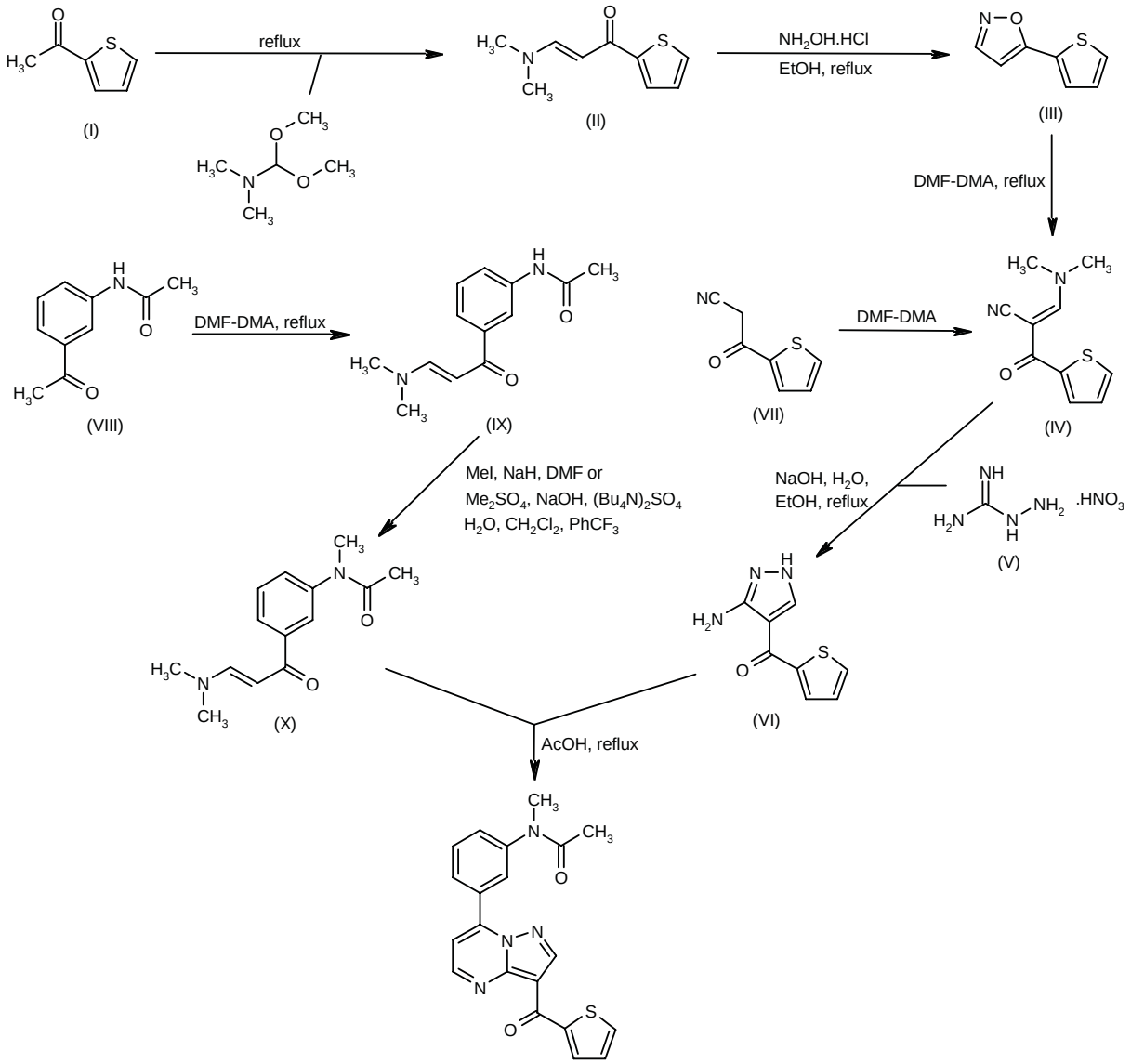
Scheme 1: Synthesis of Indiplon



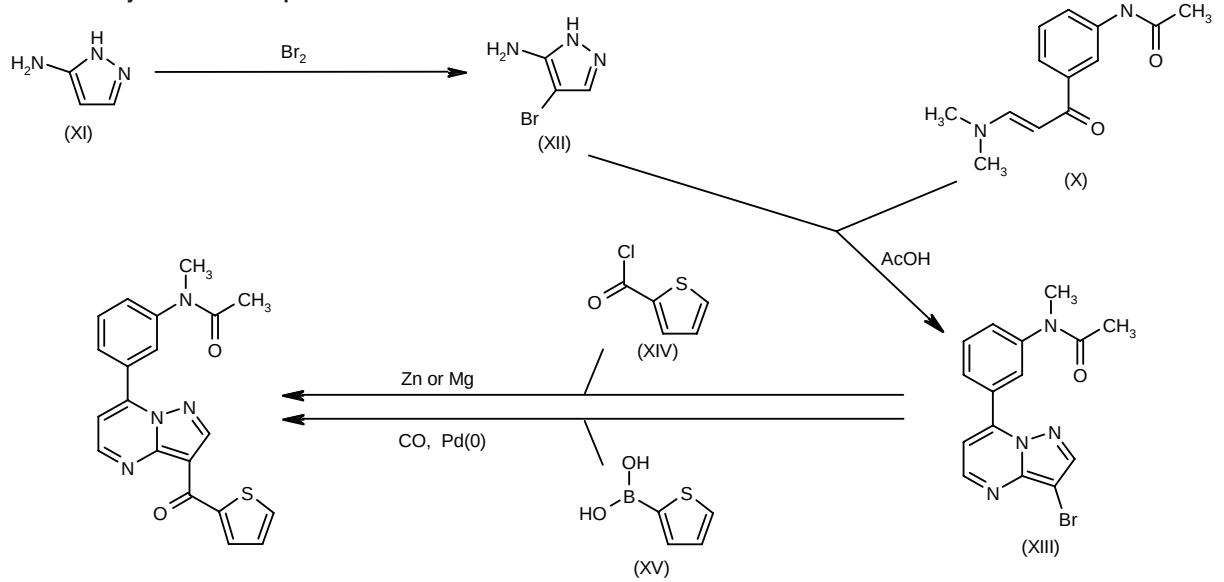
in refluxing AcOH gives 7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester (XXIV), which is treated with $POCl_3$ to yield the corresponding chloro derivative (XXV). Condensation of compound (XXV) with 3-(*N*-methylacetamido)phenylboronic acid (XXVI) by means of $Pd(PPh_3)_4$ and Na_2CO_3 in ethanol affords the pyrazolo-[1,5-*a*]pyrimidine-carboxylic acid ethyl ester (XXVII), which is finally condensed with 2-bromothiophene (XX) and Mg (4). Scheme 5.

6) Reaction of 3-(acetamido)acetophenone (VIII) with iodomethane and NaH gives 3-(*N*-methylacetamido)acetophenone (XXVIII), which is mixed with 3-oxo-3-(2-thienyl)propionitrile (VII) and treated with dimethylformamide dimethylacetal to yield a mixture of the dimethylaminomethylene derivatives (IV) and (X). This mixture, without isolation, is cyclized with aminoguanidine (V) by treatment first with NaOH in ethanol and then with refluxing AcOH (4). Scheme 6.

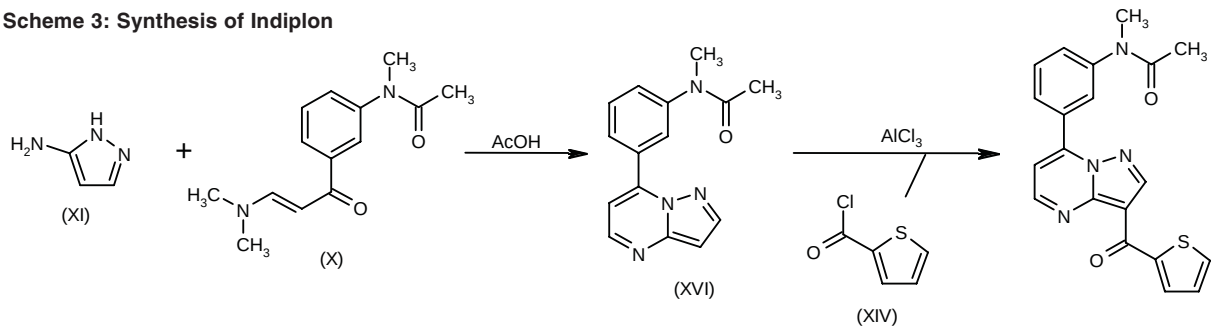
Introduction

Approximately 51% of the U.S. adult population suffers from insomnia according to the National Sleep Foundation, with a higher incidence seen in the elderly. Insomnia can result in sleep deprivation which may

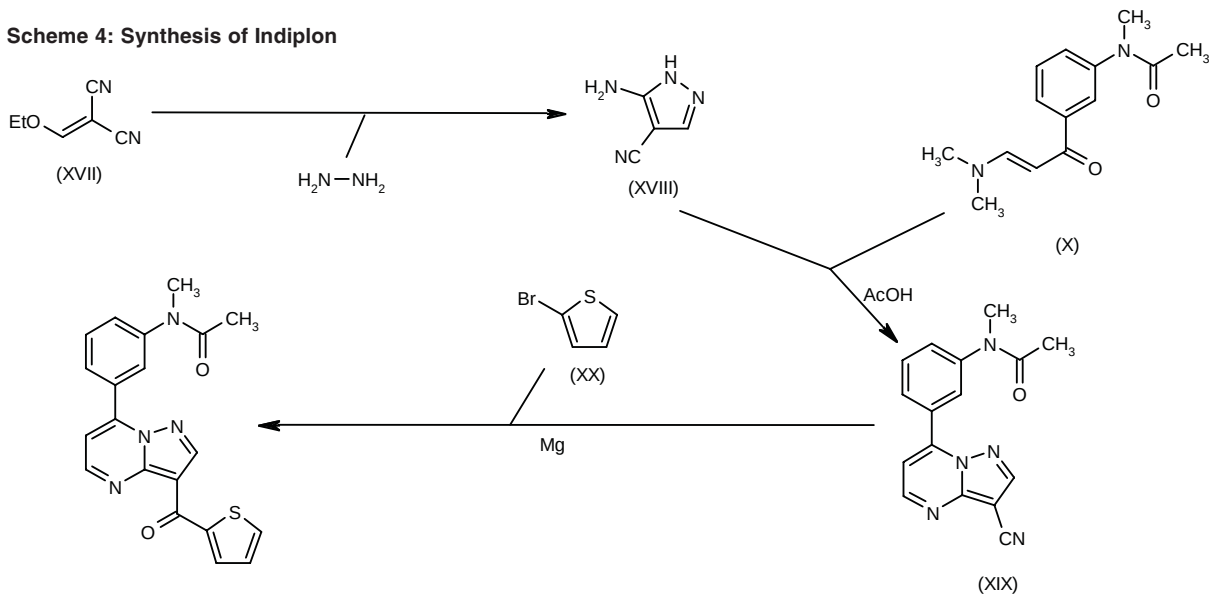
Scheme 2: Synthesis of Indiplon



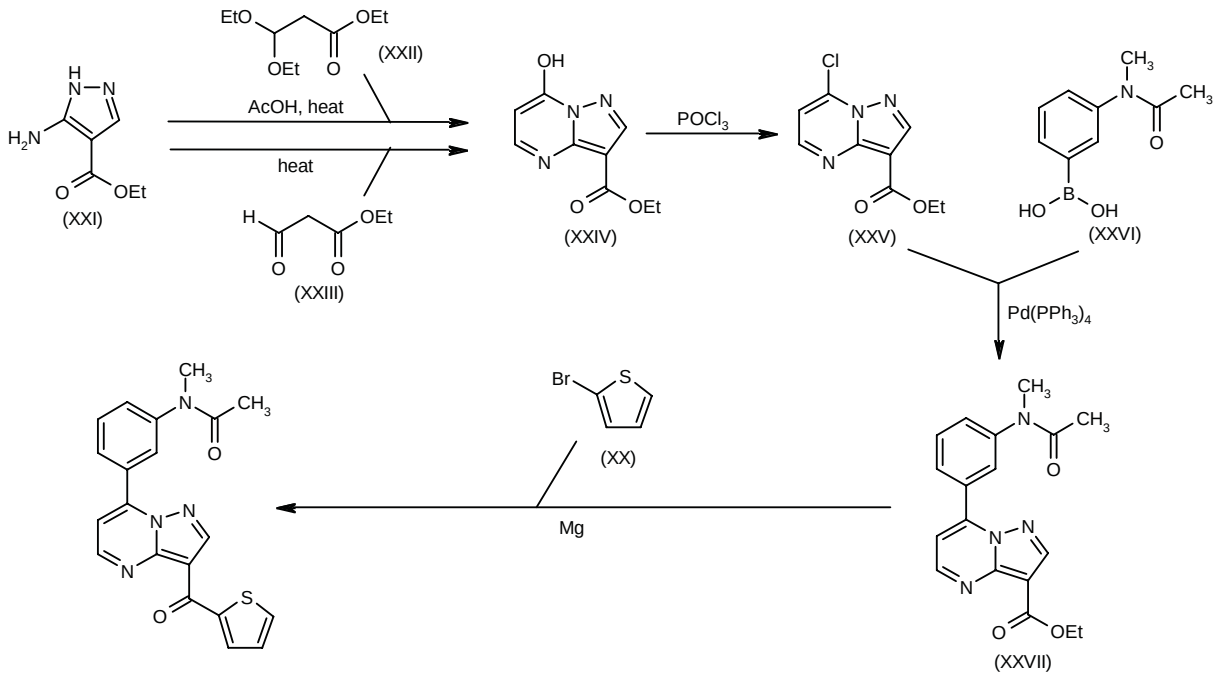
Scheme 3: Synthesis of Indiplon



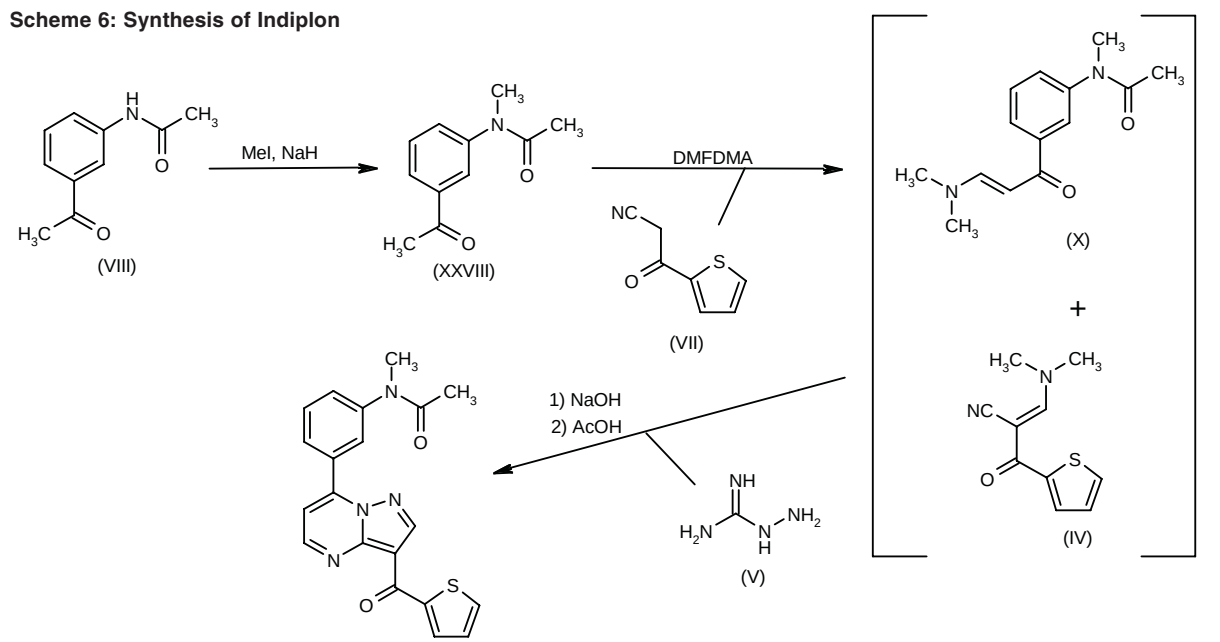
Scheme 4: Synthesis of Indiplon



Scheme 5: Synthesis of Indiplon



Scheme 6: Synthesis of Indiplon

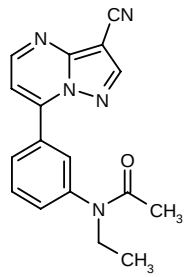


negatively affect the quality of life and even compromise safety in the workplace or while driving. Insomnia has been shown to be associated with other disorders including depression, anxiety, gastrointestinal and cardiovascular problems (5).

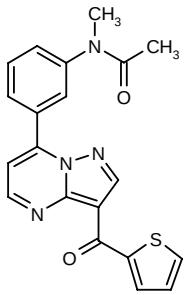
The standard treatment for insomnia has been the sedative hypnotic drugs, benzodiazepines. These agents act by modulating the major inhibitory neurotransmitter GABA. They bind to all 5 subunits of the GABA-A chloride channel, thus increasing GABA release and ultimately

Table I: Nonbenzodiazepines under development for the treatment of insomnia (from Prous Science Integrity®).

Drug	Source	Mechanism of Action	Status
1. Zaleplon	Wyeth/Lundbeck	GABA-A BZ site agonist	Launched 1999
2. Indiplon	Neurocrine Biosciences/Pfizer	GABA-A agonist	Phase III
3. Eszopiclone	Sepracor	GABAergic transmission enhancer	Preregistered
4. Gaboxadol	Lundbeck	GABA-A agonist	Phase III
5. NGD-96-3*	Pfizer	GABA-A receptor modulator	Phase I
6. CP-730330*	Pfizer	GABA-A BZ site partial agonist	Phase I/II



(1)



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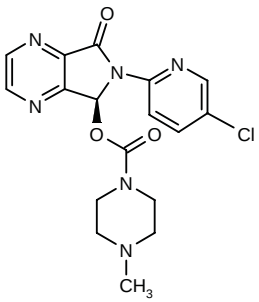

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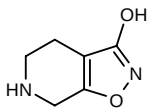

(4)

*Structure not available

dampening neuronal activity. However, it is well established that these agents are associated with unwanted effects such as memory impairment and next-day residual sedation. In the late 1980s, another class of drugs known as nonbenzodiazepines were described that are selective for the BZ1 or α_1 subunit of the GABA-A receptor and exhibit a reduced adverse event profile. However, to date, there are no sedative hypnotics which are effective against the spectrum of different insomnia complaints. Thus, research continues for compounds that can maintain sleep throughout the night and have improved safety profiles and a rapid onset of action (5).

Several nonbenzodiazepines have been described to act via modulation of the GABA-A receptor are shown in Table I. One nonbenzodiazepine that shows promise as a treatment for insomnia is the pyrazolopyrimidine indiplon (NBI-34060), a GABA-A receptor partial agonist that promotes sleep by enhancing the inhibitory activity of GABA. Indiplon has been shown to specifically bind the α_1 subunit of the GABA-A receptor. This specificity may be responsible for reducing the unwanted adverse effect seen with benzodiazepines (6). Indiplon has been shown to be safe and well tolerated and was chosen for further development in two formulations (immediate- and modified-release) to treat all insomnia complaints, including sleep initiation, night awakenings and total sleep maintenance.

Pharmacological Actions

Indiplon was shown to have high affinity for the GABA-A receptor (K_d = 0.6 nM), and autoradiographic examination of treated rat brain sections showed binding of the agent consistent with the distribution of GABA-A receptors rich in the α_1 subunit. *In vitro* experiments using rat cortex, hippocampus and cerebellar membranes demonstrated that the agent could inhibit [^{3}H]-flumazenil binding with an affinity of 1.5 nM and was more potent than zaleplon and zolpidem (K_i = 12 and 50 nM, respectively). In addition, indiplon was more effective than zolpidem and zaleplon in enhancing GABA-induced chloride current in cultured neurons (6-9).

The activities of indiplon, zolpidem and zaleplon (0.03-100 mg/kg p.o. 30 min prior to testing) on locomotor activity were compared *in vivo* in experiments in CD-1 mice. Indiplon was the most potent agent, with a ED_{50} of 2.7 mg/kg as compared to 6 and 25 mg/kg for zaleplon and zolpidem, respectively; the reduction in locomotor activity observed with indiplon was maintained for 70-80 min. The effects of indiplon (1, 3 and 10 mg/kg) on locomotor activity were also examined over 24 h. Results showed that the sedative activity of the agent disappeared at 2 h postdosing, indicating a short half-life; the desmethyl metabolite of indiplon was not effective in the locomotor assay at doses up to 100 mg/kg (7).

Indiplon was also more effective than zaleplon and zolpidem in decreasing passive avoidance retention in CD-1 mice (ED_{50} = 2 *vs.* 6 and 22 mg/kg, respectively). Significant amnesia was noted only in animals administered the agents 30 min (but not 60 or 20 min) prior to training, which is consistent with the clearance rates for the agents. No effects were observed when the agents were administered immediately after training, indicating that the compounds had no effect on memory consolidation (8).

Theee sedative effects of indiplon were examined *in vivo* in rats. The EC_{50} values obtained ranged between 1 and 3 mg/kg for reduction in locomotor activity, rotarod latency, vigilance and short-term memory. The agent had no effects on vigilance or short-term memory (in DNMTS tasks) at 10 h postdosing (9).

Pharmacokinetics

A randomized, placebo-controlled, double-blind, parallel-group study conducted in 30 young (22-41 years) healthy male subjects demonstrated that repeated dosing with indiplon (10, 30 or 45 mg capsules p.o. in the morning for 14 days) had no effect on the pharmacokinetics or pharmacodynamics of the agent. Treatment was well tolerated with no serious adverse events reported. Indiplon at 45 mg was rapidly absorbed (within 1-2 h) and eliminated (1-2.5 h). The pharmacokinetics on day 1 and 14 were similar for all doses. Analysis of quantitative EEGs from subjects revealed similar dose-related reductions in the amplitude of occipital and cortical alpha 1 waves, a small decrease in amplitude of occipital theta waves and increases in amplitude of frontal cortical beta 1 waves on days 1 and 14. No changes in digit symbol substitution (DSST) or critical flicker fusion (CFF) tests were observed during treatment (10).

A randomized, placebo-controlled, double-blind, 3-way crossover study in 10 healthy males showed that the pharmacokinetics and pharmacodynamics of indiplon (10 mg) were not affected by alcohol (0.7 mg/ml 30 min after indiplon) coadministration. Plasma C_{max} and half-life values for indiplon were 10 ng/ml and 1.3 h, respectively, when the agent was given alone or in combination with alcohol. Similar reductions in DSST and symbol copying test (SCT) scores were observed in subjects treated with indiplon or alcohol alone (DSST –15.2 and –11.5, respectively; SCT = –29.7 and –37.4, respectively) and a slight nonadditive reduction in these scores was observed when alcohol was combined with indiplon (DSST = –20; SCT = –34.7). However, as compared to alcohol alone, indiplon was more effective in increasing subjective sedation (visual analog scale of sleepiness [VAS] = –25.7 *vs.* +11.1) and reaction time (psychomotor vigilance reaction task [PVT] = –53.7 *vs.* –20.9). Sedation and reaction time were unchanged with combination treatment (11, 12).

Clinical Studies

The efficacy and tolerability of indiplon solution (15 or 30 mg p.o. 30 min before lights out) were examined in a model of transient insomnia in a multicenter, randomized, placebo-controlled, parallel-group, 1-night study in 228 young (18-59 years) healthy subjects with no history of insomnia. Transient insomnia was induced in subjects by a combination of first night effect and phase advance of bedtime by 2 h. Treatment was well tolerated with similar adverse events reported for both indiplon and placebo groups. Subjects treated with the two indiplon doses had significantly reduced mean latency to persistent sleep (LPS) as compared to placebo (17.5 and 16.2 min, respectively, *vs.* 34.1 min) and significantly improved mean subjective latency to sleep onset (LSO) as compared to placebo (15.8 and 15.4 min, respectively, *vs.* 31.1 min). The agent had no effects on subjective measures of total sleep time (TST) or on sleep architecture. DSST, SCT and VAS scores were similar in subjects treated with indiplon as compared to baseline and placebo. No residual effects were observed at 9 h postdosing. From these results it was suggested that doses of indiplon of less than 15 mg may be effective since there were no dose-related changes in LPS or LSO (13, 14). The results of these studies and some that follow are summarized in Table II.

A randomized, placebo-controlled, double-blind, parallel-group study involving 36 young (19-42 years) healthy males examined the efficacy of a modified-release formulation of indiplon (40 mg p.o. at 10:00 p.m.) in a transient nighttime venipuncture model of insomnia. A significant improvement in both LSO (30.2 *vs.* 72.2 min), sleep duration (TST = 315.6 *vs.* 246.6 min) and sleep quality were seen in subjects treated with indiplon as compared to placebo. The agent was absorbed rapidly, with plasma levels of 5 ng/ml achieved within 30 min of dosing and sustained for 6-7 h. No changes in next day residual effects tests were observed as compared to baseline and incidence and types of adverse events were similar for subjects treated with indiplon and placebo (15).

The safety and efficacy of modified-release indiplon (10, 20, 30 and 35 mg) were shown in a multicenter, randomized, double-blind, placebo-controlled trial in 79 elderly (mean age = 39.1 ± 32.1 years) patients with DSM-IV primary insomnia for at least 3 months. Sixty patients completed all conditions, with 8 patients discontinuing for nonserious adverse events, protocol violations or scheduling problems and 10 patients were excluded due to deviations from entry criteria. Significant improvements in mean sleep efficiency were observed with indiplon doses of 20, 30 and 35 mg as compared to placebo (80-81% *vs.* 74%). All doses of indiplon significantly reduced LSO and the 3 higher doses significantly reduced wake after sleep onset (102.1, 87.3 and 81.9 min *vs.* 103.2 min) as compared to placebo. Significant differences between indiplon and placebo groups were noted for the number of polysomnography (PSG) awakenings during the night and for all subjective sleep measures. No next day residual effects were observed in VAS and SCT as compared to placebo. It was concluded that modified-release indiplon at doses of 20-35 mg significantly improved sleep maintenance and sleep onset PSG measures in this patient population (16).

A multicenter, randomized, placebo-controlled, double-blind, 4-period crossover study involving 42 elderly (mean age = 70 years) patients with DSM-IV primary insomnia examined the safety and efficacy of immediate-release indiplon (5, 10 and 20 mg). All doses of indiplon were well tolerated with no serious adverse events report-

Table II: Clinical studies of indiplon (from Prous Science Integrity (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Insomnia	Randomized, double-blind, multicenter	Indiplon, 15 mg sd Indiplon, 30 mg sd Placebo	228	Indiplon significantly improved the latency to persistent sleep and the subjective latency to sleep onset in a model of transient insomnia, but had no effects on total sleep time or on sleep architecture. The drug was well tolerated and no residual effects were found 9 h after dosing	13, 14
Insomnia	Randomized, double-blind	Indiplon, 40 mg po sd Placebo	36	Indiplon was significantly more effective than placebo in improving both sleep initiation and sleep duration in healthy subjects suffering from insomnia caused by venipuncture	15
Insomnia	Randomized, double-blind, multicenter	Indiplon, 10 mg od x 2 d Indiplon, 20 mg od x 2 d Indiplon, 30 mg od x 2 d Indiplon, 35 mg od x 2 d Placebo	79	Indiplon administered once daily for 2 consecutive nights improved sleep maintenance and dose-dependently reduced the time to latency sleep and the wake after sleep onset in patients with chronic sleep maintenance insomnia	16
Insomnia	Randomized, double-blind, crossover, multicenter	Indiplon, 5 mg po Indiplon, 10 mg po Indiplon, 20 mg po Placebo	42	Indiplon dose-dependently improved the mean latency to persistent sleep, the mean total sleep time and the latency to sleep onset of elderly patients with insomnia. The drug was well tolerated, and no serious adverse events were reported	17

ed. Significant improvements in mean LPS (13.8, 10.4 and 9.8 min *vs.* 25.2 min on placebo) and mean LSO (28.8, 24.7 and 20.2 min *vs.* 41.8 min) were observed for the three indiplon doses (respectively). Both the 10 and 20 mg indiplon doses also significantly improved mean TST (372.1 and 385.36 min, respectively, *vs.* 354.4 min) as compared to placebo. No differences were observed between indiplon groups and placebo in next day residual effects according to DSST, SCT and VAS scores (17).

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III trial involving 200 patients with chronic primary insomnia examining the efficacy of 10 and 20 mg doses of immediate-release indiplon reported that there was no rebound insomnia or withdrawal effects after discontinuation following 35 consecutive nights of treatment. Results from this study also showed that both doses were well tolerated, with no serious adverse events reported. Significant improvements in both primary (*e.g.*, LPS) and secondary endpoints of sleep initiation were observed with treatment. No significant differences in next day residual sedation were observed in VAS, SCT and DSST tests as compared to placebo (18, 19).

Indiplon continues to undergo phase III testing in over 6,000 adult subjects. NDA registration is expected in early 2004 for multiple indications associated with insomnia (19).

Source

Discovered by DOV Pharmaceutical, Inc. (US); licensed to Neurocrine Biosciences Inc. (US) who subsequently entered into a development agreement with Pfizer Inc. (US). (20, 21).

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