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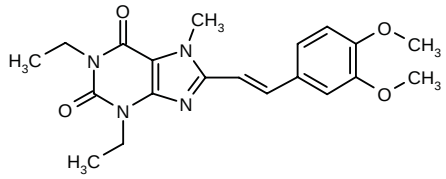
KW-6002

Antiparkinsonian
Antidepressant
Adenosine A_{2A} Antagonist

8-[2(*E*)-(3,4-Dimethoxyphenyl)vinyl]-1,3-diethyl-7-methylxanthine



$C_{20}H_{24}N_4O_4$ Mol wt: 384.4390

CAS: 155270-99-8

EN: 209103

Synthesis

Cyclization of *N*,*N*'-diethylurea (I) with cyanoacetic acid (II) in hot acetic anhydride gives 6-amino-1,3-diethyluracil (III) which is nitrosated with $NaNO_2$/AcOH in water to yield 6-amino-1,3-diethyl-5-nitrosouracil (IV) (1). The reduction of (IV) with $Na_2S_2O_4$ and K_2CO_3 in concentrated aqueous ammonia affords 5,6-diamino-1,3-diethyluracil (V), which is condensed with either 3-(3,4-dimethoxyphenyl)-2(*E*)-propenoyl chloride (VI) in EtOH/water (2) or 3-(3,4-dimethoxyphenyl)-2(*E*)-propenoic acid (VII) and 3-[3-(diethylamino)propyl]-1-ethylcarbodiimide (EDAC) in dioxane/water (3-5) to provide the corresponding amide (VIII). Cyclization of (VIII) by means of NaOH in the same solvent furnishes the xanthine derivative (IX), which is finally methylated with methyl iodide and K_2CO_3 in DMF (2-5). Scheme 1.

Description

Pale yellow powder, m.p. 191 °C (5).

Introduction

Parkinson's disease is a progressive, incurable disorder with no definite preventive treatment although drugs are available to alleviate the symptoms and/or slow down the progress of the disease. Current therapy is based on dopamine replacement therapy, the most common drug treatments being dopaminomimetic agents, including levodopa (a dopamine precursor) as well as direct or indirect dopamine receptor agonists (6). Levodopa is the mainstay in the treatment of Parkinson's disease, but because of tolerance problems and a wide range of adverse reactions, including involuntary movements and vomiting, a strong demand for new therapies exists. A possible alternative strategy would be to reduce the activity of dopaminolytic pathways that modulate the output transmission from the basal ganglia rather than attempt to enhance activity of dopaminomimetic pathways.

Among the various strategies, adenosine A_{2A} receptor blockers are considered a potential approach to the treatment of the disease (6, 7). Nonspecific adenosine receptor antagonists such as caffeine cause locomotor activation in normal and 6-hydroxydopamine-treated animals. Furthermore, adenosine A_{2A} and dopamine D_2 receptors are colocalized on striatopallidal output neurons and A_{2A} receptors are upregulated in the dopamine-depleted striatum. A_{2A} and D_2 receptors are inversely coupled in the second messenger cascade, so that in the absence of the inhibitory action of dopamine via D_2 receptors, there would be overstimulation by adenosine leading to parkinsonian symptomatology. These observations suggest that A_{2A} receptor blockers may be useful as antiparkinsonian drugs. In fact, antagonism of A_{2A} receptors in animal models results in enhanced motor function with no dyskinetic side effects. Treatment also provides neuroprotection (8, 9). Compounds currently under development for Parkinson's disease with therapeutic targets other than the dopaminergic system are shown in Table I. Table II illustrates the receptor binding profile in rat brain of selected adenosine A_{2A} antagonists as compared to the nonselective adenosine antagonists, caffeine and theophylline.

KW-6002 is a selective adenosine A_{2A} receptor blocker under development for the treatment of Parkinson's disease.

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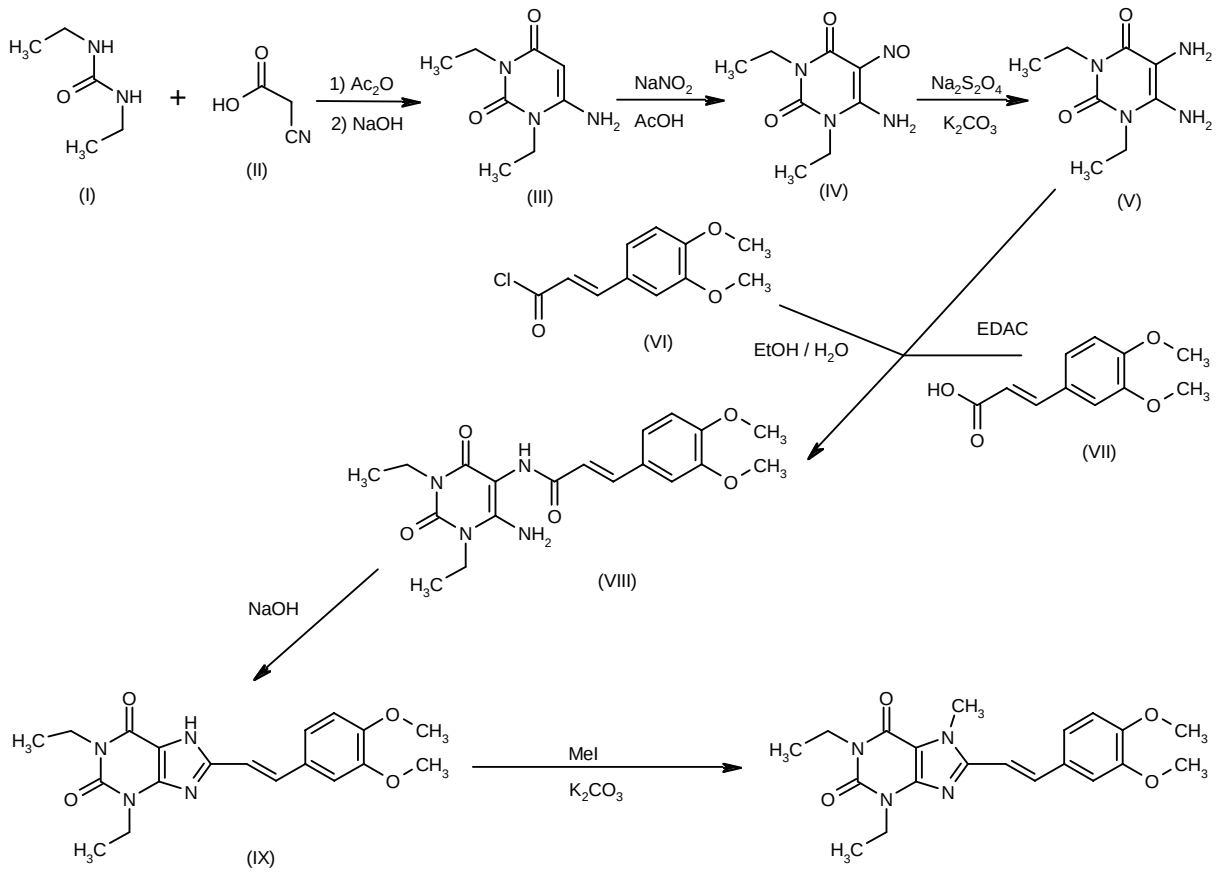
Scheme 1: Synthesis of KW-6002



Pharmacological Actions

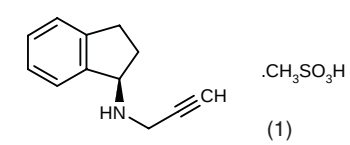
KW-6002 showed high affinity for the rat striatal A_{2A} receptor (K_i = 2.2 nM against [^{3}H]-CGS-21680 binding) with 68-fold less affinity for the rat forebrain A_1 receptor (K_i = 150 nM against [^{3}H]-cyclohexyladenosine binding) (5, 10, 11). Due to its high affinity and selectivity, a radiolabeled derivative, [^{11}C]-KW-6002 labeled at the aromatic *O*-methyl position, was developed to be used in pharmacological testing to trace the adenosine A_{2A} receptors *in vivo* (12).

KW-6002 antagonized cAMP accumulation in PC12 rat pheochromocytoma cells induced by the selective A_{2A} receptor agonist, CGS-21680; no effect of the agent was seen on basal cAMP levels indicating that KW-6002 is a selective A_{2A} receptor antagonist (5, 10). The compound was further shown to antagonize CGS-21680-inhibited GABAergic synaptic transmission on striatal medium spiny projections, demonstrating a direct modulation of striatal GABAergic synaptic transmission by A_{2A} receptors and thus supporting the modulation of striatal inhibitory pathways as a new approach in the therapy of movement disorders (9).

Adenosine binding to A_{2A} receptors has been suggested to lower the affinity of dopamine for D_2 receptors and in experimental rodent and nonhuman models of Parkinson's disease, A_{2A}-selective blockers have displayed antiparkinsonian activity. In mice and rats, KW-6002, like other adenosine A_{2A} receptor antagonists, dose-dependently prevented reserpine- and haloperidol-induced catalepsy at doses of 0.04-20 mg/kg p.o.; this effect was also observed with the D_2 receptor agonists ropirinole and quinpirole. However, in comparison with reference compounds (*e.g.*, levodopa, bromocriptine or KF-17837, another selective A_{2A} receptor blocker), KW-6002 was the most potent, with ED_{50} values of 0.26 and 0.03 mg/kg p.o. against reserpine- and haloperidol-induced catalepsy, respectively. KW-6002 also prevented catalepsy induced by the adenosine A_{2A} receptor agonist CGS-21680, with an ED_{50} value of 0.05 mg/kg p.o. which was again much lower than values obtained for theophylline, caffeine or KF-17837. KW-2002 was also effective against MPTP-induced hypokinesia, with a MED

Table I: Compounds under development for Parkinson's disease (Prous Science Drug R&D Backgrounders database).

Compound	Company	Mechanism of Action	Status
1. Rasagiline mesilate	Teva; Lundbeck	MAO-B inhibitor	Phase III
2. Riluzole	Aventis	Glutamate release inhibitor	Phase III
3. KW-6002	Kyowa Hakko	Adenosine A_{2A} antagonist	Phase II/III
4. Remacemide HCl	AstraZeneca	NMDA antagonist	Phase II
5. NIL-A*	Guilford/Amgen	Neuroimmunophilin ligand	Phase II
6. CEP-1347/KT-7515	Cephalon; Kyowa Hakko; Lundbeck	SAP kinase inhibitor	Phase I
7. TCH-346*	Novartis	Not available	Phase I
8. CP-101606	Pfizer	NMDA NR_{2B} antagonist	Preclinical
9. JP-1730*	Juvantia	α_2-Adrenoceptor antagonist	Preclinical
10. PAN-483*	Panacea	Inhibitor of Lewy body formation	Preclinical
11. PD-188669	Parke-Davis	NMDA $NR_{1A/2B}$ antagonist	Preclinical
12. PD-196860	Parke Davis	NMDA $NR_{1A/2B}$ antagonist	Preclinical
13. SCH-58261	Schering-Plough	Adenosine A_2 receptor antagonist	Preclinical
14. SR-141716A	Sanofi-Synthélabo	Cannabinoid CB_1 antagonist	Preclinical
15. SNC-80	GlaxoSmithKline	Opioid OP_1 receptor agonist	Preclinical
16. TMN	Virginia Tech. Univ.	MAO inhibitor	Preclinical



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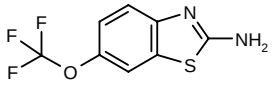

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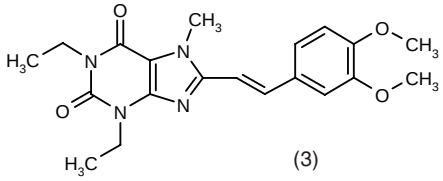

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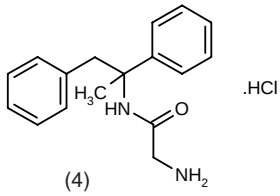

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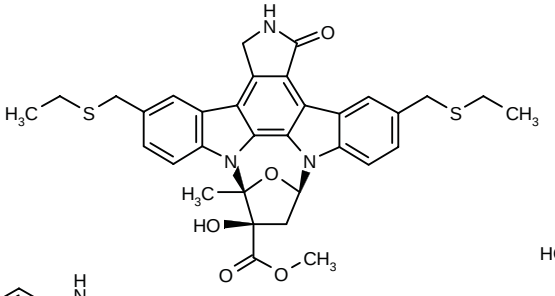

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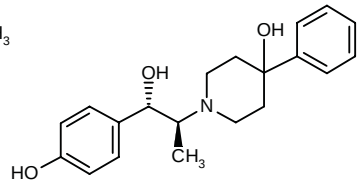

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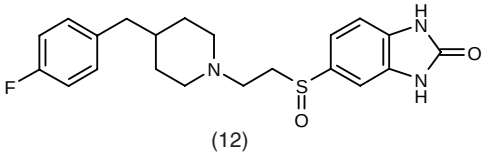

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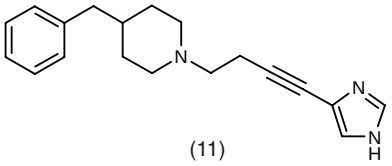

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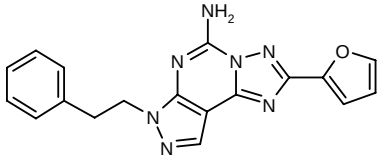

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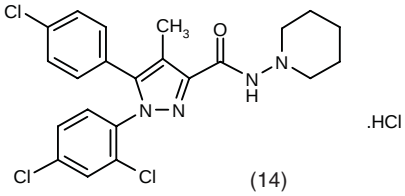

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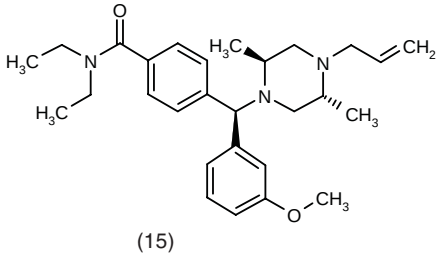

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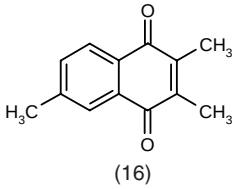

(16)

*Structure not yet detected

Table II: Receptor binding afffinity of selected adenosine A_{2A} receptor antagonists in comparison to caffeine and theophylline (Prous Science MFline database).

Compound	A_1	A_{2A}	Ref.
KW-6002	0.58[a]	0.013[b]	5
Sch-58261	0.121[a]	0.0023[c]	30
ZM-241385	0.257[d]	0.0018[c]	31
Caffeine	55[e]	48[b]	32, 33
Caffeine	29[a]		33
Theophylline	14[e]	25[b]	32, 33
Theophylline	8.5[a]	27[c]	33, 34

Adenosine receptor affinities (K_i, μM) evaluated by displacement of: [a][^{3}H]-CHA, [b][^{3}H]-NECA, [c][^{3}H]-CGS-21680, [d][^{3}H]-DPCPX, [e][^{3}H]-*R*-PIA.

of 0.16 mg/kg p.o. The agent also potentiated the anticataleptic effects of levodopa/benserazide and potentiated levodopa- and apomorphine-induced contralateral turning in rats with unilateral 6-hydroxydopamine lesion of the dopaminergic nigrostriatal pathway, while lacking any turning effect per se. However, KW-6002 (1 mg/kg and higher p.o.) potentiated levodopa- and apomorphine-induced rotational behavior. These results suggest that KW-6002 modulates dopaminergic neurotransmission in mice and rats and, thus, is a potential candidate for the treatment of Parkinson's disease (5, 11, 13-16).

On the other hand, a study using dopamine D_2 receptor knockout mice, which are a model of motor impairment that resembles Parkinson's disease, showed that blockade of adenosine A_{2A} receptors with KW-6002 rescued the behavioral parameters and reestablished altered enkephalin and substance P expression. These findings suggest a nondopaminergic mechanism for the antiparkinsonian activity of KW-6002 (17).

KW-6002 improved motor disability in experimental nonhuman primate parkinsonian models. In MPTP-treated marmosets, orally administered KW-6002 dose-dependently reversed motor disability with only a modest increase in overall locomotor activity and no abnormal movements. No development of tolerance was observed after 21 days of repeated administration (15, 18-20). In the same parkinsonian model, the agent when combined with levodopa or selective D_1 or D_2 agonists (*e.g.*, quinpirole, SKF-80723) enhanced the antiparkinsonian activity of the dopaminomimetic agents, especially in the case of levodopa and quinpirole. However, no increased dyskinesia was observed in MPTP-treated marmosets previously primed with levodopa to induce dyskinesia (21-23).

Similar results were obtained in studies using MPTP-treated, levodopa-primed cynomolgus monkeys, where KW-6002 (60-180 mg/kg p.o.) alone resulted in dose-dependent antiparkinsonian effects that were equipotent to levodopa/benserazide (50/12.5 mg) although without the risk of dyskinesia. Coadministration of KW-6002 and levodopa/benserazide potentiated the motor effects of levodopa (30%) without increasing the dyskinetic response (24, 25).

The results from studies using parkinsonian models suggest that use of KW-6002 would allow a reduction in levodopa dose, thus preventing or delaying dyskinesia. Moreover, the agent could be useful as monotherapy in early stages of the disease.

Pharmacokinetics

A study using rats administered oral doses of KW-6002 (0.3-100 mg/kg) reported linear pharmacokinetics for the agent up to 30 mg/kg and nonlinear pharmacokinetics at the higher doses due to saturation of absorption. Results following administration of [^{14}C]-labeled KW-6002 (3 mg/kg p.o.) showed that the agent was predominanty eliminated in bile; elimination was nearly complete within 48 h of dosing. 4'-*O*-Demethylation and 3', 4'-*O*-demethylation were the major metabolic pathways with glucuronide and sulfate conjugates the metabolites detected. Unchanged KW-6002 was the major substance detected in both plasma and brain. Further studies in rats showed that the compound accumulated in the striate body of the brain where it selectively binds A_{2A} receptors (26, 27).

Clinical Studies

KW-6002 is currently undergoing phase II clinical testing for Parkinson's disease and depression in the U.S. and Japan (28, 29).

Manufacturer

Kyowa Hakko Kogyo Co., Ltd. (JP).

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