Drugs of the Future 2001, 26(1): 9-14

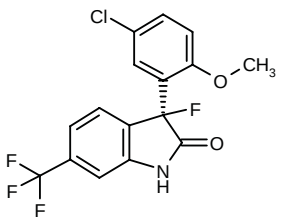
CCC: 0377-8282/2001

BMS-204352

Treatment of Stroke
Potassium (Maxi-K) Channel Opener

MaxiPost™

(+)-3(*S*)-(5-Chloro-2-methoxyphenyl)-3-fluoro-6-(trifluoromethyl)-2,3-dihydro-1*H*-indol-2-one



$C_{16}H_{10}ClF_4NO_2$ Mol wt: 359.7050

CAS: 187523-35-9
CAS: 183720-28-7 (as racemate)

EN: 273916

Synthesis

BMS-204352 can be prepared by two different ways:

1) The reaction of 3-(trifluoromethyl)aniline (I) with $(Boc)_2O$ gives the corresponding carbamate (II), which is cyclized with diethyl oxalate (III) by means of *sec*-butyl lithium (*s*-BuLi) in THF to yield 6-(trifluoromethyl)-2,3-dihydro-1*H*-indole-2,3-dione (IV). The Grignard condensation of (IV) with 5-chloro-2-methoxyphenylmagnesium bromide (V) in THF affords the racemic hydroxyindolone (VI), which is finally treated with diethylaminosulfur trifluoride (DAST) to provide the racemate BMS-194549 (VII) (1). The desired (+)-(*S*)-enantiomer, BMS-204352, can be obtained by HPLC using a Chiracel OD column (2). Scheme 1.

2) Chlorination of 2-(2-methoxyphenyl)acetic acid (VIII) with SO_2Cl_2 in THF gives 2-(5-chloro-2-methoxyphenyl)acetic acid (IX), which is methylated with Me_2SO_4 and K_2CO_3 in acetonitrile to yield the corresponding methyl ester (X). The arylation of (X) with 2-fluoro-5-(trifluoromethyl)nitrobenzene (XI) and LiHMDS in THF, followed by the addition of *N*-fluorobis(phenylsulfonyl)-amine (NFSI), affords 2-(5-chloro-2-methoxyphenyl)-2-fluoro-2-[2-nitro-4-(trifluoromethyl)phenyl]acetic acid methyl ester (XII). Hydrolysis of compound (XII) with NaOH in methanol/water provides the corresponding free acid (XIII), which is optically resolved by enantioselective crystallization with (*S*)-α-methylbenzylamine, followed by acidification to give the (*S*)-enantiomer (XIV). Finally, compound (XIV) is submitted to a reductive cyclization with sodium dithionite followed by exposure to refluxing ethanol (3). Scheme 2.

Description

Crystals, m.p. 202 °C (decomp.); $[\alpha]_D^{25}$ +156° (c 1, MeOH) (3).

Introduction

Stroke is considered the third leading cause of death and is the major cause of disability in the U.S. Approximately 600,000 Americans suffer a stroke each year with about 500,000 of these being first attacks and 100,000 recurrent strokes. In the U.S. and Europe combined, approximately 1.2 million strokes occur every year (4, 5).

A stroke transpires when a blood vessel in or leading to the brain ruptures or is clogged by a thrombus or other particle, thus blocking blood flow to the brain. Stroke is classified into 2 groups: ischemic stroke due to blockage of blood flow and hemorrhagic stroke due to an aneurysm in the brain or head injury. Within these groups, there are 4 subtypes that are most seen. Cerebral thrombosis is a form of ischemic stroke in which a thrombus develops on the wall of a cerebral artery (usually damaged by atherosclerosis) and grows to eventually block the flow of blood. Cerebral embolism is another type of ischemic stroke in which a migratory thrombus or particle forms in a blood vessel located away from the brain (usually in the heart) and is transported toward the brain until it becomes lodged within an artery leading to or in the brain. Subarachnoid hemorrhage is a type of hemorrhagic stroke involving the rupturing of a blood vessel on the surface of the brain. The result is bleeding into the subarachnoid space and contamination of the cerebrospinal fluid (CSF) within. The contaminated CSF causes extensive subsequent damage as it flows through the cranium. Finally, the fourth type of stroke is intracerebral hemorrhage which occurs due to the rupturing of a damaged artery within the brain. The consequence is flooding of

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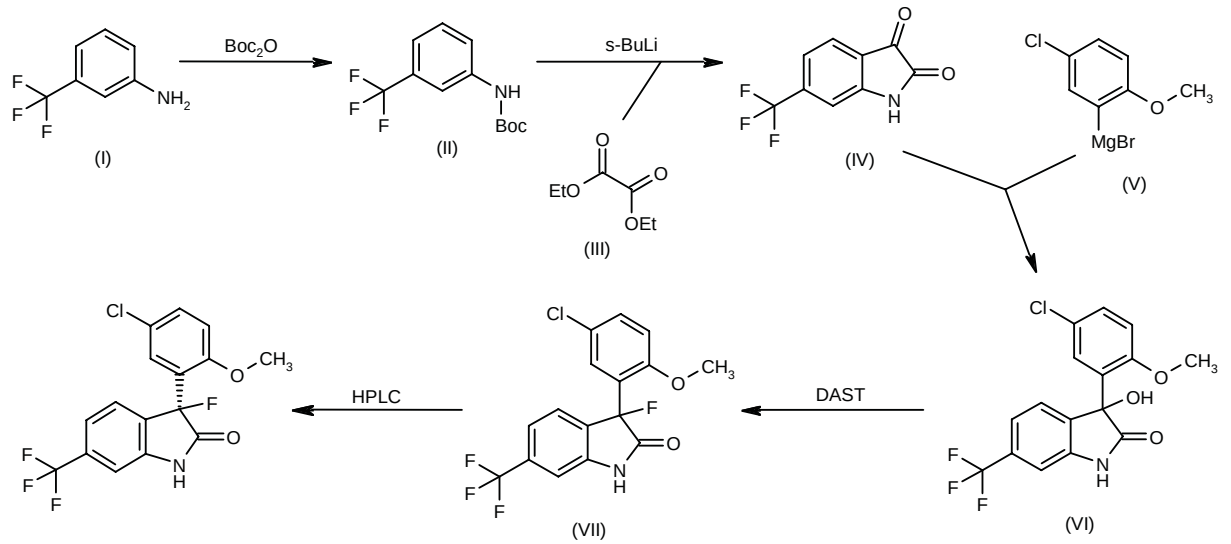
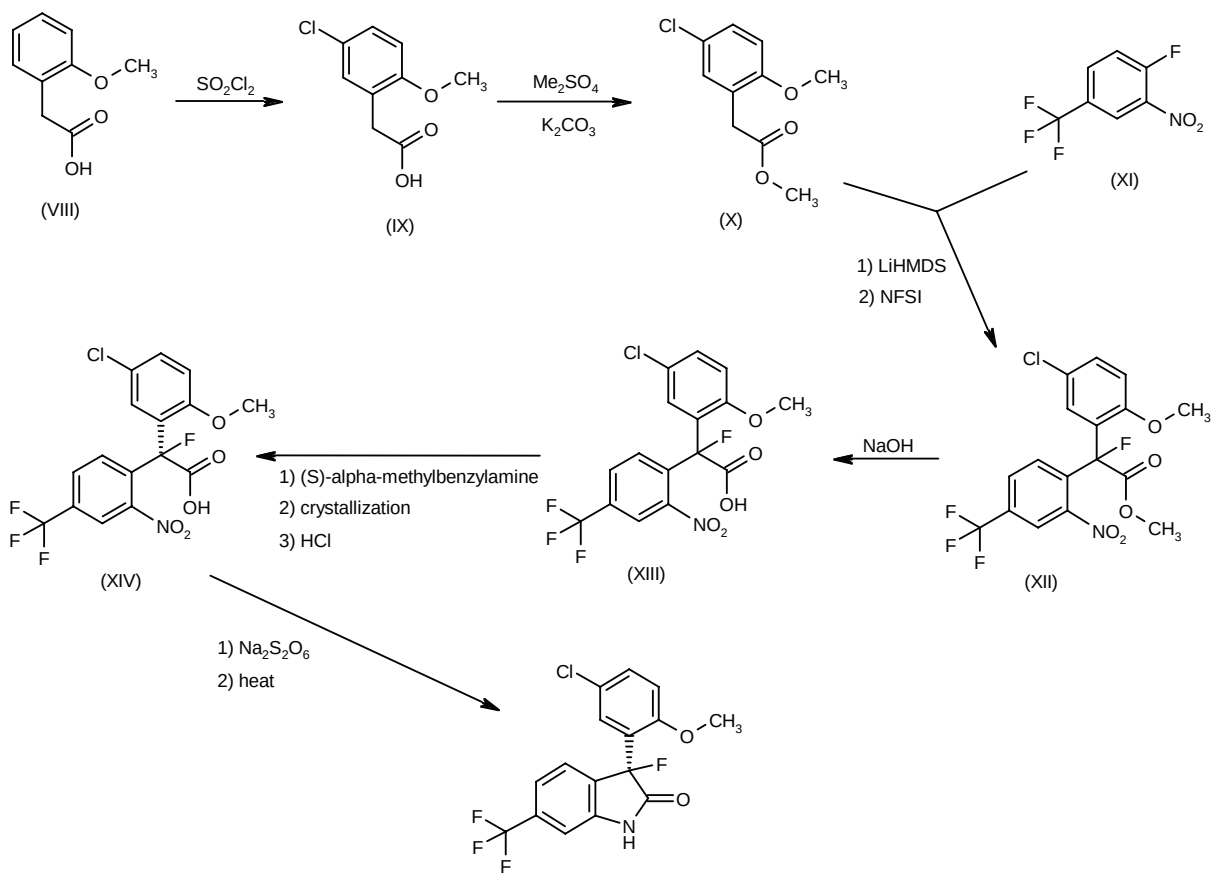
Scheme 1: Synthesis of BMS-204352



Scheme 2: Synthesis of BMS-204352



blood into the surrounding tissue which becomes compressed from the resulting pressure. Other less common types of stroke include transient ischemic attacks also known an mini-strokes, lacunar infarcts and recurrent stroke (4).

With the extensive research generated in recent years, stroke has become treatable and many new potential therapies have arisen. In general, 2 major therapeutic options are currently available. One method involves targeting the insufficient arterial oxygen and glucose resulting from stroke by enhancing blood flow. This can be achieved by lysing the arterial thrombus within hours of symptom onset or by reducing tissue back-pressure hours to days later. The other method is based on neuroprotection and attempts to decrease the intrinsic vulnerability of brain tissue to ischemia. This latter method is a relatively newer therapeutic approach and it concentrates on reducing neuronal death due to excitotoxicty by suppressing those cerebral mechanisms that are responsible for the heightening vulnerability of the CNS to ischemia. New agents for the treatment of stroke that affect excitotoxicity include glutamate antagonists, GABA agonists, free-radical scavengers, Ca^{2+} channel blocker, Na^{+} channel blocker and K^{+} channel opener. Table I shows agents

Table I: Agents affecting excitotoxicity under development for the treatment of stroke (Prous Science Drug R&D Backgrounders database).

Drug Name	Company	Mechanism of Action	Status
Glutamate Receptor Antagonists			
1. CP-101606	Pfizer	NMDA antagonist	Phase II
2. Dexanabinol	Pharmos	NMDA antagonist, antioxidant, cannabinoid agonist	Phase II
3. Gacyclidine	Ipsen-Beaufour	NMDA antagonist	Phase II
4. Lanicemine HCl	AstraZeneca	NMDA antagonist	Phase II
5. Sipatrigine	GlaxoSmithKline/CeNeS	Glutamate release inhibitor, Na^{+} channel blocker	Phase II
6. YM-872	Yamanouchi	AMPA/kainate antagonist	Phase II
7. Fanapanel	Schering AG/Novo Nordisk	AMPA/kainate antagonist	Phase I
8. NPS-1506	NPS Pharmaceuticals	NMDA antagonist, 5-HT reuptake inhibitor	Phase I
9. SPD-502	NeuroSearch/Shire	AMPA antagonist	Phase I
10. UK-240255	Pfizer	NMDA antagonist	Phase I
11. EAA-090	Wyeth-Ayerst	NMDA antagonist	Phase I

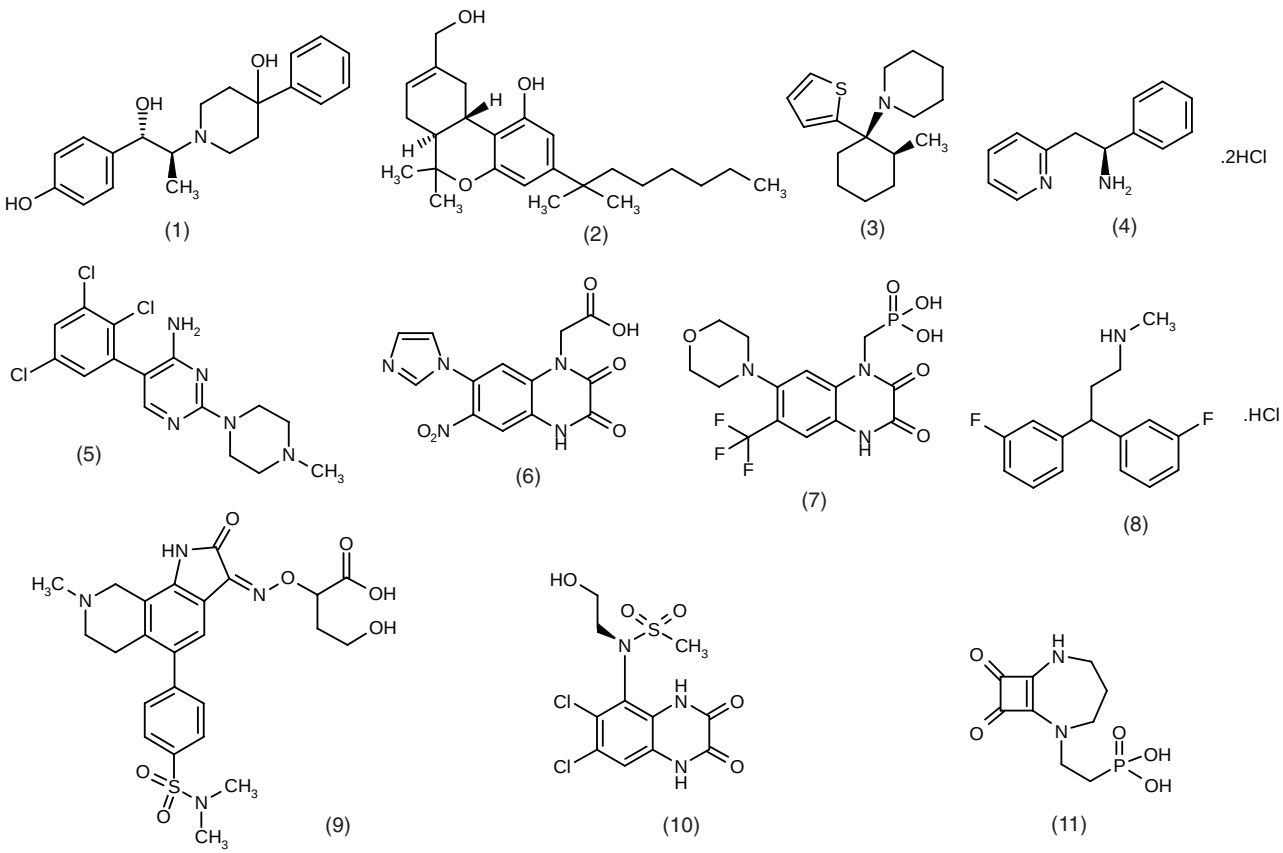


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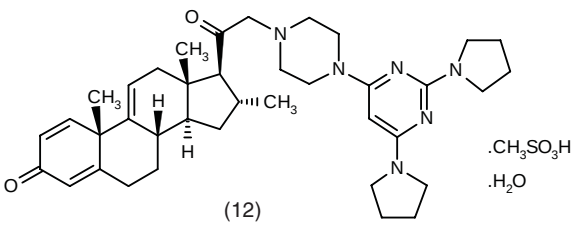
Table I: Continued.

Drug Name	Company	Mechanism of Action	Status
Antioxidants and Free Radical Scavengers			
12. Tirilazad mesilate (*Freedox*)[1]	Pharmacia	Lipid peroxidation inhibitor, NO synthase inhibitor	Launched 1995
13. Ebselen	Daiichi Pharm.	Antioxidant, antiinflammatory, glutathione peroxidase mimic	Preregistered
14. Edaravone (*Radicut*)	Mitsubishi Chem.	Antioxidant, free radical scavenger	Preregistered
15. Nicaraven (*Antevas*)	Chugai	Free radical scavanger	Preregistered
16. EPC-K1	Senju/Toyama	Antioxidant, AGE inhibitor	Phase II
17. NXY-059	Centaur/AstraZeneca	Free radical scavanger	Phase II
18. NS-7	Nippon Shinyaku/ Schering AG	NO synthase inhibitor, voltage-gated Na^+ and Ca^{2+} channel blocker	Phase I
Ion Channel Modulators			
19. Nimodipine (*Nimotop*)	Bayer	Ca^{2+} channel blocker	Launched 1985
20. Fasudil HCl (*Eril*)[2]	Asahi Chem.	Ca^{2+} channel blocker	Phase III
21. BMS-204352 (*MaxiPost*)	Bristol-Myers Squibb	K^+ (maxi-K) channel opener	Pahse III
22. Magnesium sulfate	Univ. California	Nonselective Ca^{2+} channel blocker	Phase III
23. Crobenetine HCl	Boehringer Igelheim	Na^+ channel blocker	Phase I



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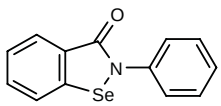

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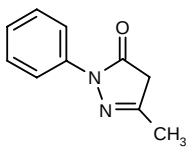

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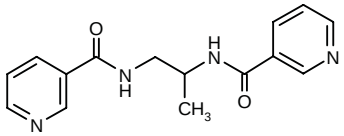

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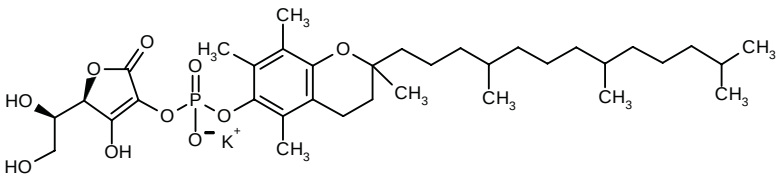

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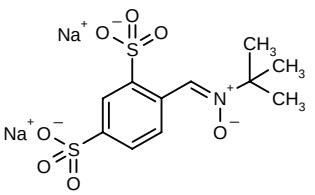

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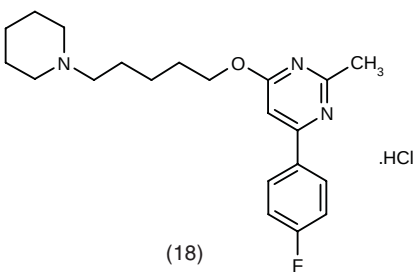

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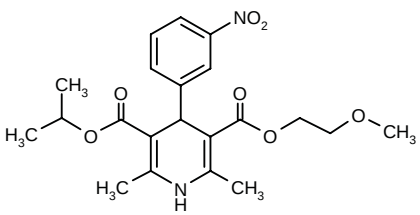

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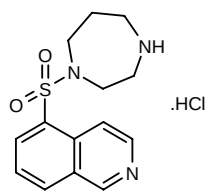

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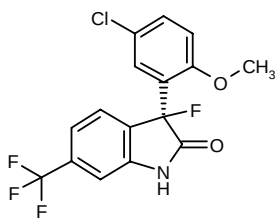

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MgSO4

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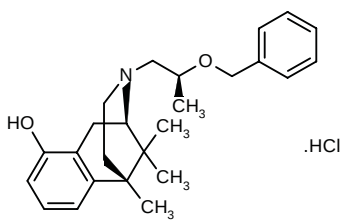

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[1]Indicated for the treatment of subarachnoid hemorrhage; [2]Launched in 1995 for the treatment of vasospasm following surgery for subarachnoid hemorrhage.

which target excitotoxicty as a treatment for acute stroke (4, 6).

One such agent that offers new hope for neuroprotection during stroke is BMS-204352, the (*S*)-enantiomer of BMS-194549. It is known that large conductance Ca^{2+}-activated K^+ channels (maxi-K) can serve as an endogenous protection mechanism to limit Ca^{2+} entry into cells, thus modulating neurotransmitter release and cell excitability. These channels are widely distributed throughout the brain, including such areas as the cortex, hippocampus and thalamic nuclei. BMS-204352 has been shown to be a voltage-dependent K^+ channel opener and has been selected for further development as a potential treatment for stroke (2, 7).

Pharmacological Actions

BMS-204352 was shown to significantly open a maxi-K channel α-subunit clone (hSlo) expressed in human embryonic kidney (HEK 293) cells. The agent increased whole-cell hSlo-mediated outward currents in a concentration-dependent and reversible manner (EC_{50} < 500 nM). No apparent desensitization was detected with prolonged exposure of maxi-K channels to BMS-204352 and its action was also found to be calcium-dependent, with minimal effects observed when intracellular calcium levels were < 1 nM. In contrast, both BMS-204352 and BMS-194549 produced only slight changes in native voltage-dependent I_{Ca} in GH3 cells and I_{Cl} recorded from CFTR channels expressed in oocytes and had no effects on native I_{Cl} or cloned voltage-dependent K^+ channel current in oocytes (8, 9).

In stringent rodent models of acute focal stroke, following administration of BMS-204352 (1 ng/kg to 3 mg/kg i.v.) to spontaneously hypertensive rats (SHR) 2 h after the onset of permanent occlusion of the middle cerebral artery (MCA) and to normotensive Wistar rats 2 h after the onset of MCA occlusion with concomitant reversible occlusion (60 min) of the common carotid artery, a significant reduction in the infarct volume (measured 24 h postocclusion) was observed. Moreover, in the normotensive animals, BMS-204352 was effective over a dose range of 10 ng/kg to 1 mg/kg, displaying an inverted-U dose-response relationship (*i.e.*, decreased activity was observed with doses > 1 mg/kg) (10, 11).

The toxicity of BMS-204352 was evaluated in *in vitro* and *in vivo* assays. Results showed that the compound was not genotoxic nor teratogenic in rats and rabbits and no antigenic responses were observed in guinea pigs. Furthermore, the safety of BMS-204352 was shown in a repeated-dose (i.v.) toxicity study conducted in rats (up to 10 mg/kg/day for 1 month) and dogs (up to 20 mg/kg/day for 10 days). Although a transient decrease in blood pressure in dogs was detected with the 20 mg/kg/day dose, it was not observed with the lower dose of 10 mg/kg/day. As compared to the AUC and C_{max} values obtained in humans at a proposed dose of < 1 mg, plasma levels in rats were 133-146 times and 42-54 times higher, respectively, and plasma levels in dogs were 263-267 times and 70-110 times higher, respectively. Results indicate that a good safety margin was established (12).

Clinical Studies

The safety, tolerability and pharmacokinetics of BMS-204352 were evaluated in healthy subjects and patients with suspected acute stroke. Healthy subjects participated in 3 randomized, double-blind, placebo-controlled, escalating dose trials receiving single (0.001-0.4 mg/kg; n = 48) or multiple (0.001-0.2 mg/kg/day for 7 days; n = 36) i.v. doses. Patients (n = 36) received i.v. doses (0.1, 1 or 2 mg for up to 4 doses over 72 h at 24-h intervals) or vehicle within 48 h of stroke symptom onset. Although i.v. doses of BMS-204352 (0.3 and 0.4 mg/kg) were associated with self-limited postural hypotension in healthy subjects, all other single and multiple i.v. doses (0.001-0.2 mg/kg) were safe and well tolerated with no effects observed on psychomotor performance or cardiovascular function. In patients with suspected acute stroke, i.v. dosing with BMS-204352 was safe and well tolerated and there was no evidence that the agent or its discontinuation were associated with any clinically significant adverse events. Healthy subjects given BMS-204352 displayed high clearance (0.92-1.26 l/min), extensive distribution (521-604 l) and a $t_{1/2}$ of 16-20 h; a similar pharmacokinetic profile was obtained in stroke patients (13, 14).

BMS-204352 (Maxipost™) is currently in phase III trials as a treatment for acute ischemic stroke (15). Unfortunately, the results from one such trial reported no significant differences in the efficacy, safety and tolerability of BMS-204352 as compared to placebo. A second phase III study is ongoing (16).

Manufacturer

Bristol-Meyers Squibb Co. (US).

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