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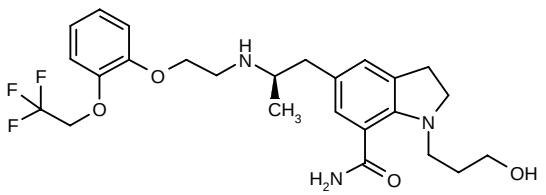
CCC: 0377-8282/2001

KMD-3213

Treatment of BPH
α_1-Adrenoceptor Antagonist

KAD-3213

(–)-1-(3-Hydroxypropyl)-5-[2(*R*)-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethylamino]propyl]indoline-7-carboxamide



$C_{25}H_{32}F_3N_3O_4$ Mol wt: 495.5470

CAS: 160970-64-9
CAS: 169107-04-4 (as dihydrobromide)

EN: 211600

Synthesis

The bromination of 1-acetyl-5-propionylindoline (I) with pyrrolidone hydrotribromide (PTBr) and sulfuric acid in THF gives the α-bromo derivative (II), which is reduced with triethylsilane in TFA yielding the 2-bromopropyl compound (III). Nitration of (III) with HNO_3 in AcOH affords the 7-nitroindoline (IV), which is reduced to the corresponding amine derivative (V) with H_2 over PtO_2 in ethanol. The reaction of amine (V) with $NaNO_2$/HCl, followed by treatment with CuCN, provides 1-acetyl-5-(2-bromopropyl)-indoline-7-carbonitrile (VI), which is treated with NaN_3 in hot ethylene glycol monomethyl ether/water to yield the 2-azidopropyl derivative (VII). Reduction of (VII) with H_2 over Pd/$BaSO_4$ in ethanol affords the expected 2-aminopropyl compound (VIII), which is condensed with 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl bromide (IX) by means of $NaHCO_3$ in ethanol to provide the secondary amine (X). The optical resolution of amine (X), performed by treatment with (+)-mandelic acid in ethanol, followed by crystallization of the resulting salt and then treatment with Na_2CO_3 affords the desired (*R*)-enantiomer (XI). Compound (XI) is protected with Boc_2O to give the corresponding carbamate (XII), which is deacetylated with NaOH in ethanol to yield the intermediate (XIII). Hydrolysis of the cyano group of (XIII) with NaOH and H_2O_2 in DMSO furnishes the corresponding carboxamide (XIV), which is condensed with 3-(*tert*-butyldimethylsilyloxy)propyl 4-nitrobenzenesulfonate (XV) by means of K_2CO_3 and a crown ether in dioxane to provide the indoline adduct (XVI). Finally, desilylation of (XVI) with TBAF in THF yields the 3-hydroxypropyl derivative (XVII), which by removal of the Boc-protecting group by means of TFA in dichloromethane gives KMD-3213 (1, 2). Scheme 1.

The intermediate 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl bromide (IX) has been obtained as follows: Alkylation of 2-methoxyphenol (XVIII) with 2,2,2-trifluoroethyl iodide (XIX) by means of K_2CO_3 in hot DMF gives 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene (XX), which is demethylated by means of BBr_3 in dichloromethane to yield the corresponding phenol (XXI). Finally, this compound is alkylated with 1,2-dibromoethane (XXII) and NaOH in water at 120 °C (1, 2). Scheme 1.

Introduction

Benign prostatic hyperplasia (BPH) is a common condition in aging men that is characterized as the nonmalignant enlargement of the prostate gland. The prostate gland continues to grow approximately 0.4 g every year with two major growth periods occurring at puberty and after age 40. Prostate gland growth is hormone-dependent but the reason for continued enlargement is not known. As the gland enlarges, it exerts pressure on the urethra where it emerges from the bladder resulting in a gradual obstruction of urinary flow. In addition, the bladder neck may become obstructed by the intravesical growth of hypertrophied glandular tissue. Lower urinary tract symptoms (LUTS) associated with BPH include a weak urine stream, urinary hesitancy and/or trouble initiating urination, increased frequency and/or urgency of urination, urinary retention, nocturia, intermittency, persistent pain in the lower back, pelvis or upper thighs, sensations of pain or burning during urination and bloody urine (3).

BPH is most frequent in men aged 60 years or older with more than 50% of all men in this group showing an enlarged prostate. The incidence of BPH increases with age so that 90% of all men aged 85 years or older suffer from the condition although only half experience troubling

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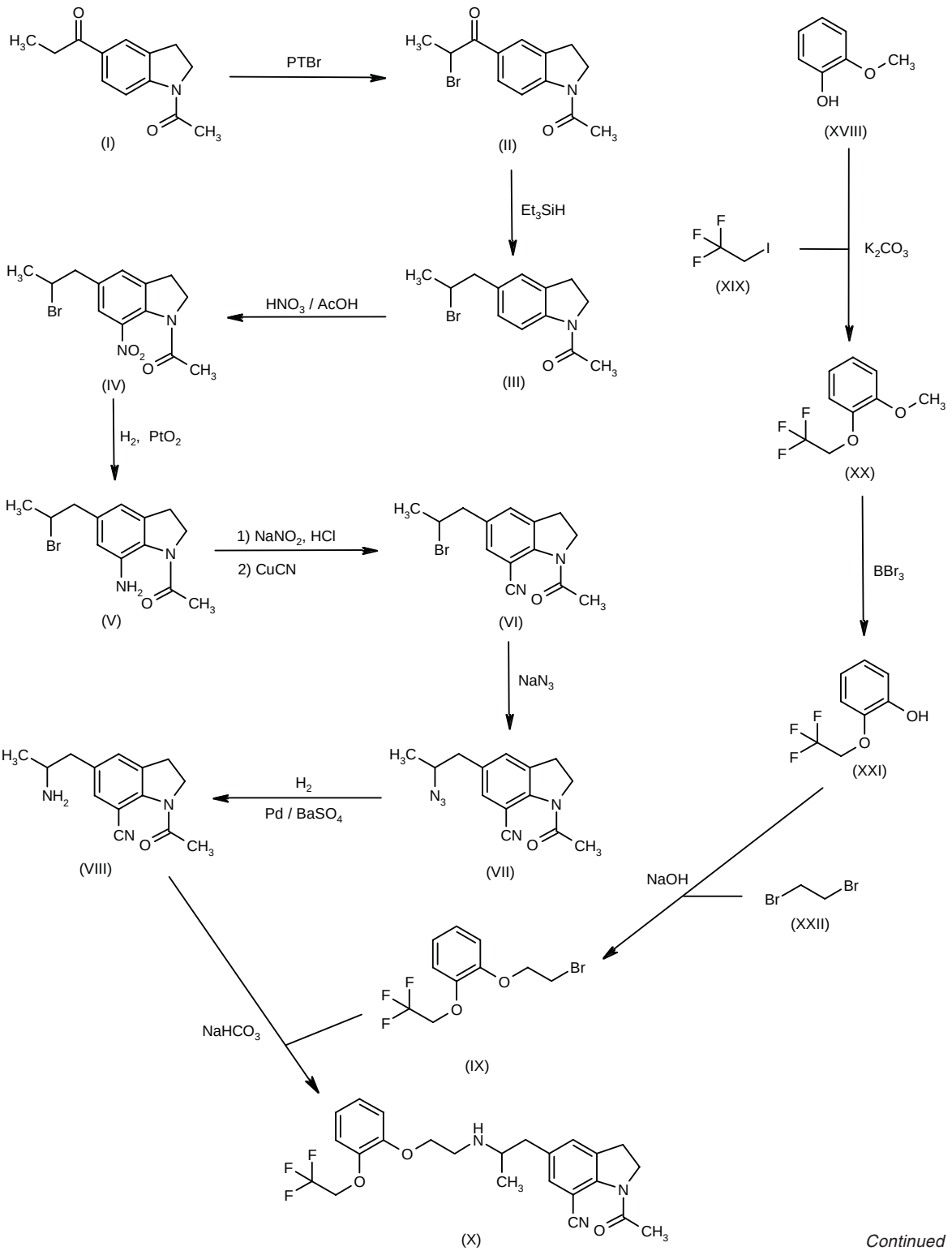
Scheme 1: Synthesis of KMD-3213



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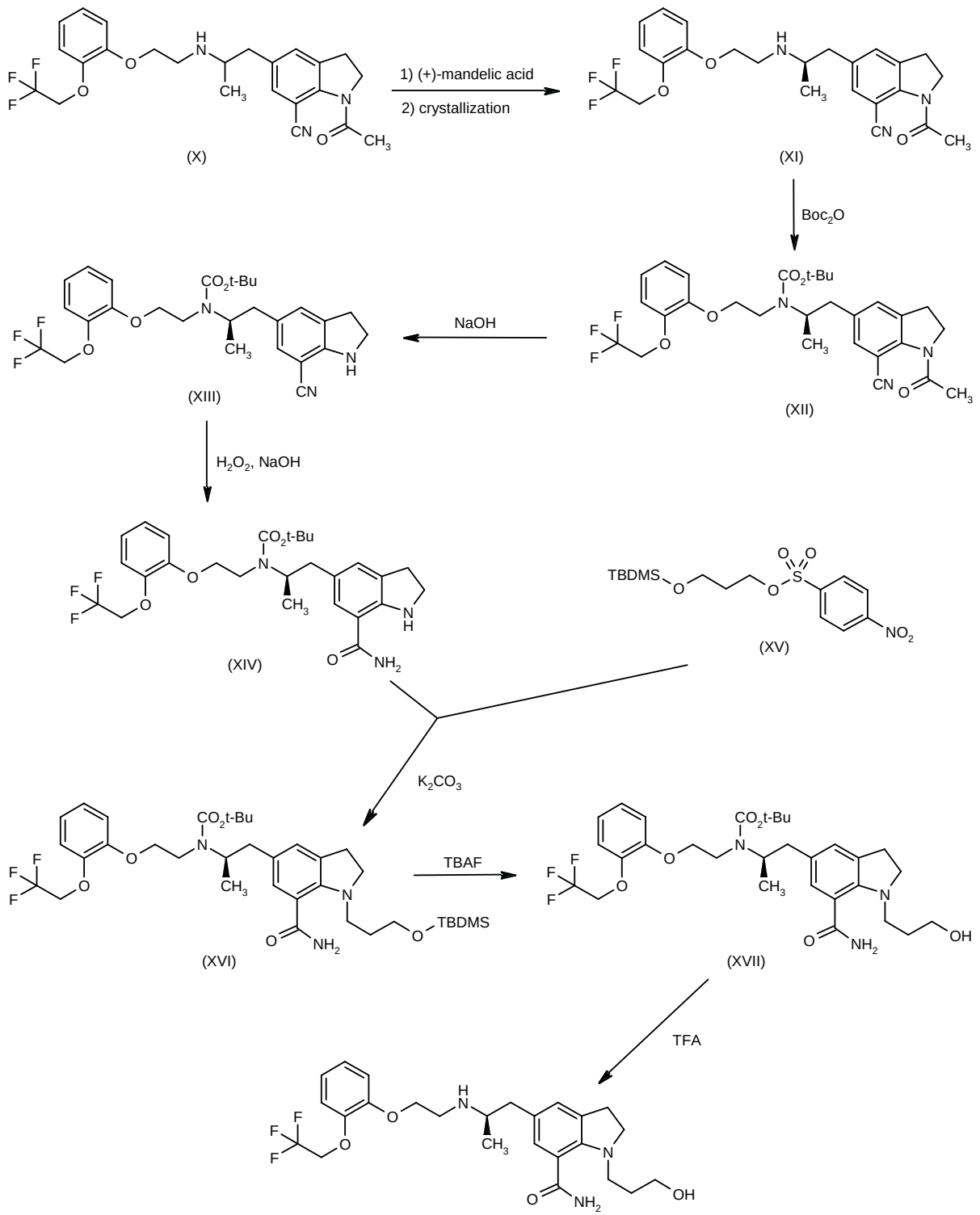
Scheme 1: Synthesis of KMD-3213 (Cont.)



LUTS which can significantly impact the quality of life. In severe cases, some individuals may experience chronic retention where it becomes increasingly more difficult to empty the bladder or acute retention where urination is impossible (3).

BPH is only treated when symptoms are severe, kidney function is affected and/or other complications arise (*e.g.*, infection, bleeding). There is both a static and dynamic component to BPH. The static component involves enlargement of the prostate while the dynamic component is related to the tone or degree of contraction of the prostatic smooth muscle responsible for intravesical obstruction. α_1-Adrenergic receptors are G protein-coupled receptors responsible for mediation of contractions of arterial and venous smooth muscle and therefore play an important role in the dynamic component of BPH. The predominant α-adrenergic receptor expressed in the human prostate has been shown to be the α_{1A} subtype and obstruction and LUTS associated with BPH have been shown to be enhanced by noradrenergic activation of stromal α_1-adrenoceptors in the prostate. Therefore, treatment for BPH has focused on α_1-adrenoceptor antagonists which act by blocking sympathetic activity, thus relaxing the smooth muscle component of the prostatic obstruction. The first agents discovered, such as prazosin and terazosin, were nonselective blockers and are associated with undesirable adverse effects such as postural hypotension due to inhibition of α_1-adrenoceptors in vascular tissue. Fortunately, more uroselective blockers are being discovered which could result in significant improvement in the treatment of BPH (3).

Several new α_1-adrenoceptor antagonists have been identified and are in various phases of preclinical and clinical development. These agents are shown in Table I (3). One such novel α_1-adrenoceptor antagonist is KMD-3231. It has shown highly selective inhibitory activity against the α_{1A}-adrenoceptor, which is the predominant receptor in the prostate, and has been chosen for further development.

Pharmacological Actions

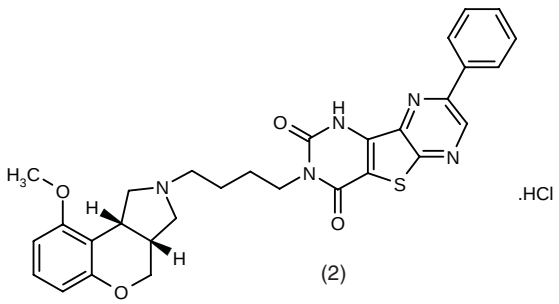
The binding profile of [^{3}H]-labeled KMD-3213 was examined in studies using recombinant α_1-adrenoceptors (human α_{1A}, hamster α_{1B} and rat α_{1D}) expressed in COS-7 cells and native rat α-adrenoceptors from membrane preparations of the submaxillary gland (expressing α_{1A}), liver (expressing α_{1B}), kidney (expressing α_{1A} and α_{1B}) and heart (expressing α_{1A} and α_{1B}). In contrast to [^{3}H]-prazosin and [^{3}H]-tamsulosin which bound with high affinity ($pK_D > 9$) to all receptor subtypes, [^{3}H]-KMD-3213 (10-2000 pM) exhibited a high affinity for α_{1A}-adrenoceptors ($pK_D = 10.5$) with no significant binding to α_{1B}-adrenoceptors and insufficient/unsaturated binding to α_{1D}-adrenoceptors. Competition experiments also demonstrated that [^{3}H]-KMD-3213 had a higher affinity for the α_{1A} subtype ($pK_i = 10.4$) as compared to α_{1B} ($pK_i = 8.1$) and α_{1D} ($pK_i = 8.6$). [^{3}H]-KMD-3213 also displayed high affinity binding to the native rat submaxillary gland α_{1A} subtype but not to the rat liver α_{1B} subtype. In rat kidney, both [^{3}H]-KMD-3213 and [^{3}H]-prazosin bound to a single high affinity site ($pK_D = 10.8$ and 10.1, respectively) with distinct B_{max} values obtained for the two agents ($B_{max} = 159$ and 267 fmol/mg protein, respectively). Other studies examining binding to the native rat tissues revealed that the inhibition curve for KMD-3213 in the liver ($K_i = 16$ nM) and submaxillary gland ($K_i = 0.15$ nM) fit a one-site model while the agent had both low and high affinity sites in heart membrane (4, 5).

Similarly, in experiments using cloned human α_{1A}, α_{1B} and α_{1D} receptor subtypes stably expressed in CHO cells, KMD-3213 had a significantly 583- and 56-fold higher affinity for the alpha1 subtype ($K_i = 0.036 \pm 0.010$ nM) as compared to the α_{1B} ($K_i = 21 \pm 5$ nM) and α_{1D} (Ki = 2 ± 0.4 nM) receptor subtypes, respectively (Table II). Moreover, the affinity of the agent was approximately 10-fold higher for human α_{1A} as compared to the rat α_{1A} adrenoceptor subtypes. KMD-3213 inhibited norepinephrine-induced increases in intracellular Ca^{2+} concentrations more potently in CHO cells expressing the α_{1A} receptor subtype ($IC_{50} = 0.32 \pm 0.05$ nM) as compared to those expressing the α_{1B} and α_{1D} subtypes; even high concentrations of the agent could not completely inhibit this effect in cells expressing the α_{1B} or α_{1D} subtypes. Moreover, experiments using human liver and prostate membrane preparations identified both high and low affinity binding sites with K_i values obtained that corresponded well with those observed using cloned human α_{1A} and α_{1B} subtypes (5). In addition, [^{3}H]-KMD-3213 was found to bind to human prostate membrane preparations which predominantly express the α_{1A} receptor subtype, with a higher affinity than [^{3}H]-prazosin. Furthermore, KMD-3213 bound to human prostate with a 200-fold higher affinity over human aorta preparations which express the α_{1B} subtype (6).

The receptor subtype selectivity of KMD-3213 was further exemplified in *in vivo* experiments in rats. Results demonstrated that the agent binds with higher affinity to α_1-adrenoceptors indicating prostate and submaxillary gland selectivity as compared to the α_{1B} and α_{1D} receptor subtypes which are the predominant subtypes in vascular tissues. Rats were administered [^{3}H]-KMD-3213 (555 kBq; 1.4 nmol/kg i.v. into the femoral vein) or [^{3}H]-prazosin (1.2 nmol/kg) and plasma was taken and the prostate, vas deferens, aorta, cerebral cortex, spleen, liver, submaxillary gland, heart, lung and kidney were removed starting 10 min postinjection. Most tissues examined except the cerebral cortex, spleen and liver showed a significant amount of specific binding of KMD-3213. While specific binding in the lung, kidney and spleen was maximum at 10 min after injection followed by a rapid decrease as KMD-3213 levels disappeared from plasma, KMD-3213 binding in the submaxillary gland, vas deferens and prostate achieved peak levels at 60 min and binding was still present at 240 min postinjection. The $AUC_{0\text{-}120}$ values obtained for KMD-3213 binding were lower than those for prazosin in rat aorta, spleen and liver

Table I: α_1-Adrenoceptor antagonists in development for the treatment of BPH (Prous Science Drug R&D Backgrounders database).

Drug Name	Company	Target Receptor	Status
1. AIO-8507L*	Ono	Uroselective α_1-adrenoceptors	Phase II
2. Fiduxosin hydrochloride	Abbott	α_{1D}- and α_{1A}-Adrenoceptors	Phase II
3. KMD-3213	Kissei	α_{1A}-Adrenoceptors	Phase II
4. L-771688 (SNAP-6383)	Merck & Co./Synaptic	α_{1A}-Adrenoceptors	Phase II
5. RBX-2258*	Ranbaxy	Uroselective α_1-adrenoceptors	Phase II
6. (*S*)-Doxazosin	Sepracor	Nonselective	Phase II
7. GYKI-16084	Inst. Drug Res./Gedeon Richter	α_1 and α_2-Adrenocreptors	Phase II
8. RWJ-38063	R.W. Johnson/Ortho Biotech	α_{1A}-Adrenoceptors	Preclinical
9. RWJ-69736	R.W. Johnson/Ortho Biotech	α_{1A}-Adrenoceptors	Preclinical
10. L-780945 (SNAP-6991)	Merck & Co./Synaptic	α_{1A}-Adrenoceptors	Preclinical
11. Ro-70-0004	Roche Bioscience	α_{1A}-Adrenoceptors	Preclinical
12. RS-100329	Roche Bioscience	α_{1A}-Adrenoceptors	Preclinical
13. SNP-7915	Merck & Co./Synaptic	α_{1A}-Adrenoceptors	Preclinical



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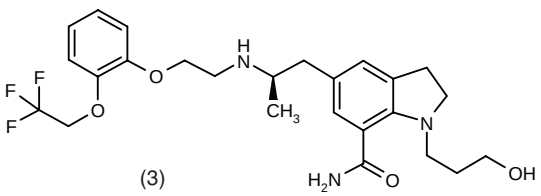

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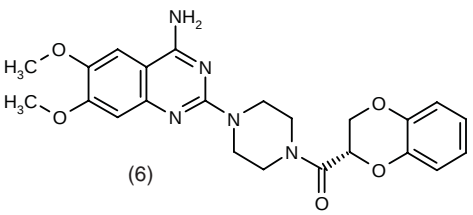

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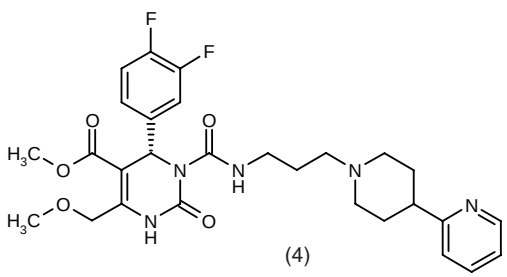

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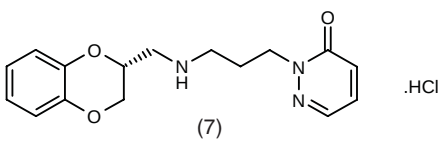

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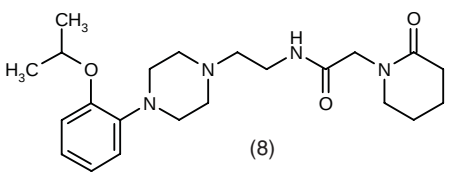

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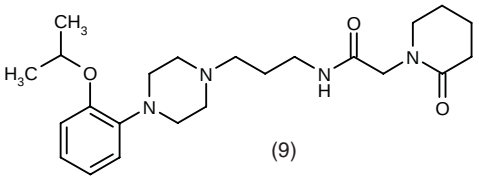

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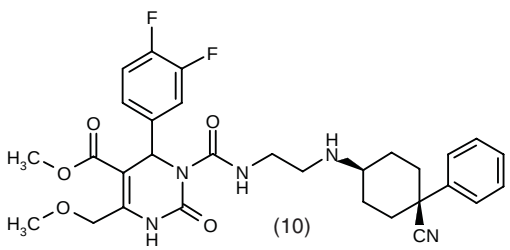

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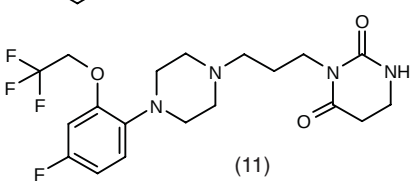

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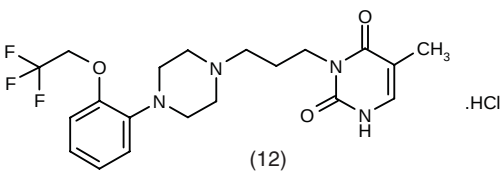

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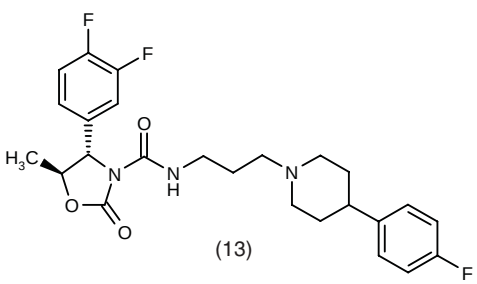

(13)

*Structure not yet detected

Table II: Affinity binding (Ki, nM) to recombinant human α_1-adrenergic receptor subtypes expressed in CHO cells (Prous Science Integrity database).

Compound	1A	1B	1D	Ref.
KMD-3213	0.036	21	2.0	5
Prazosin HCl	0.17	0.25	0.066	5, 19
Tamsulosin HCl	0.019	0.29	0.063	5, 19

Table III: Inhibition of noradrenaline-induced arterial vasoconsctriction (pA_2) (Prous Science Integrity database).

Compound	Aorta	Carotid	Mesenteric	Ref.
KMD-3213	8.3	7.7	9.9	4
Prazosin HCl	8.9-9.7	9.5	8.1	4, 20-22
Tamsulosin HCl	9.7-9.9	9.2	9.8	4, 20-22

and higher in the prostate, submaxillary gland and lung. Dose-dependent increases in specific KMD-3213 (1.4-13.6 nmol/kg) binding were observed in the prostate and submaxillary gland but not in the spleen in contrast to prazosin (1.2-10.6 nol/kg) which showed dose-dependent increases in specific binding in all tissues (7, 8).

KMD-3213 was also shown to bind with high affinity (pK_d = 10.3) to rabbit iris membrane preparations which contain a significant amount of α_{1A}-adrenoceptor binding sites responsible for the adrenergic contraction of the iris dilator muscle (9).

Experiments using wild-type and constructed constitutively active mutant (replacement of Ala271 with Thr in the third intracellular loop) α_{1A}-adrenoceptors expressed in CHO cells revealed that KMD-3213 was a neutral antagonist. In contrast, prazosin was an inverse agonist since it upregulated receptor density, decreased basal GTPγS binding and decreased basal inositol-1,4,5-triphosphate (IP_3) levels. Exposure of prazosin-treated cells expressing the mutant receptor with KMD-3213 resulted in reversal of prazosin agonism causing rapid increases in cellular IP_3 levels, intracellular [Ca^{2+}] and rate of extracellular acidification. Thus, from these results it appears that the neutral antagonist KMD-3213 reversed the action of the inverse agonist, prazosin. These results indicate that caution should be used when antagonists are used in combination or when one antagonist is switched for another. This may result in undesirable and unexpected adverse events (10).

Further comparison of KMD-3213 action with that of prazosin showed that chronic administration of prazosin (2 mg/kg/day i.p. for 2 weeks) to rats upregulated α_{1B}-adrenoceptors density in the liver by about 52%. Although chronic prazosin administration did not alter α_{1A} receptor density in the prostate and submaxillary gland, it upregulated α_{1A} and α_{1B} subtypes in heart tissue by 86% and 108%, respectively. In contrast, chronic treatment with KMD-3213 (2 mg/kg/day i.p. for 2 weeks) had no effect on receptor density in any of the tissues examined (liver, submaxillary gland, prostate, kidney, spleen and heart) (11).

Several functional experiments have characterized the inhibitory effects of KMD-3213 and confirmed the tissue selectivity of the agent. Studies using isolated arteries showed that the agent antagonized NS-49- and norepinephrine-induced contractile responses with higher affinity in tissues expressing the α_{1A} adrenoceptors (rat caudal artery; pA_2 = 10 for NS-49-induced contractions) and α_{1L}-adrenoceptors (dog carotid mesenteric artery; pA_2 = 9.9 for norepinephrine-induced contractions) as compared to dog carotid artery expressing the α_{1B} subtype (pA_2 = 737 against norepinephrine-induced contractions) and rat thoracic aorta (pA_2 = 8.3 against norepinephrine-induced contractions) (4) (Table III).

Similar results were obtained in a study examining the effects of KMD-3213 on phenylephrine-induced contraction of isolated rabbit prostate, rabbit thoracic aorta and rat thoracic aorta. Mean pA_2 value obtained for KMD-3213-induced inhibition of rabbit prostate contraction was 10.05 as compared to values of 9.36 and 8.13 observed for rabbit and rat aorta, respectively. KMD-3213 was more potent or as effective as tamsulosin but markedly more effective than prazosin (*i.e.*, KMD-3213 > tamsulosin > prazosin) in inhibiting rabbit prostatic contraction. However, the rank order of potency for rabbit and rat aortic contracture was tamsulosin > KMD-3213 > prazosin and tamsulosin > prazosin > KMD-3213, respectively. KMD-3213 had no effect on isoproterenol-induced chronotropic activity in guinea pig atria or on 5-hydroxytryptamine-, histamine- or acetylcholine-stimulated contractions in rabbit aorta. Thus, KMD-3213 action was shown to be dependent on tissue type reflecting tissue receptor subtype expression with preferential antagonism seen against prostatic contraction (12).

KMD-3213 was shown to markedly inhibit noradrenaline-induced human prostate contracture (pK_B = 9.45 ± 0.039) as potently as tamsulosin but more effectively than prazosin. KMD-3213 exhibited 100-fold higher affinity for the human prostate as compared to the human mesenteric artery (6, 13).

Results from *in vivo* experiments in rats have demonstrated the potent selective effects of KMD-3213. Results from a study using rats showed that KMD-3213 was 20-fold less effective than tamsulosin and prazosin in inhibiting blood pressure responses to tilting. While tamsulosin and prazosin at doses of 10 μg/kg i.v. completely inhibited blood pressure responses to tilting, 7.5 μg/kg KMD-3213 had no effect and only a dose of 230 μg/kg could inhibit the response (14).

On the other hand, KMD-3213 administered i.v. to rats dose-dependently and markedly inhibited the intraurethral pressure (IUP) response to phenylephrine (30 μg/kg) with an ID_{50} of 1.4 μg/kg i.v. obtained; in contrast, the ED_{15} value for KMD-3213 for decreasing mean blood pressure was 12 μg/kg i.v. as compared to 0.70 and 1.4 μg/kg i.v. obtained for tamsulosin and prazosin, respectively. The agent exhibited a higher degree of uroselectivity (uroselective index = ED_{15}/ID_{50} = 8.6) than tamsulosin

(1.0), prazosin (0.29) or terazosin (0.15) following both i.v. and i.d. administration. Oral administration of KMD-3213 also resulted in dose-dependent inhibition of IUP which was maintained at 12, 18 and 24 h postdosing; the effects of tamsulosin disappeared at 18 h postdosing. Thus, KMD-3213 exhibited higher uroselectivity and a longer duration of action (15).

Intravenous administration of KMD-3213 to intercollicular decerebrated dogs was shown to dose-dependently inhibit IUP responses induced by electrical stimulation of the hypogastric nerve. The ID_{50} values obtained for KMD-3213, tamsulosin and prazosin were 3.15, 1.73 and 11.8 μg/kg i.v., respectively, as compared to the ED_{20} values obtained for reductions in mean blood pressure of 8.03, 0.59 and 2.46 μg/kg i.v., respectively. Thus, once again KMD-3213 was 7.5- and 12-fold more uroselective (uroselective index = ED_{20}/ID_{50}) than tamsulosin and prazosin, respectively. Results also showed that KMD-3213 was at least 3.8-fold more uroselective than tamsulosin after oral administration, indicating good absorption of the agent (16).

A study conducted in healthy volunteers has predicted the prostatic α_1-adrenoceptor occupancy following oral administration of KMD-3213, tamsulosin or terazosin in order to estimate the optimal dosage regimens for these agents as treatments of urinary obstruction in BPH. Receptor occupancy was predicted following oral administration using α_1-adrenoceptor binding parameters of subjects estimated from in vitro experiments using rat or human prostate glands. Although plasma-free concentrations of the agent varied considerably with dose, the extent of prostatic α_1-adrenoceptor occupancy was comparable. Following oral dosing, occupancy ranged from 60-90% at 0.5-6 h postdosing and subsequently decreased to 40% 24 h later. The sustained occupancy observed was found to correlate with the relatively long duration of effects seen in clinical trials conducted in patients with BPH (17).

Clinical Studies

Kissei has entered into an agreement with Daiichi Pharmaceutical under which they will codevelop KMD-3213 for urinary disturbances associated with benign prostatic hypertrophy, starting in phase III trials. They will comarket the product in Japan under different brand names, while Kissei retains development and marketing rights overseas. The compound has completed phase II studies in Japan and is currently in U.S. phase II trials (18).

Manufacturer

Kissei Pharmaceutical Co., Ltd. (JP) licensed to Daiichi Pharmaceutical Co., Ltd. (JP).

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