Development of an Affinity Ligand for Purification of α_2 -Adrenoceptors from **Human Platelet Membranes**

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Human platelets contain α_2 -adrenoceptors which are negatively coupled to the enzyme adenylate cyclase. In order to better understand the interaction of this subtype of α receptor with this key enzyme, we have initiated a program to isolate and characterize the α_2 -adrenoceptor. This report describes the synthesis and biological characterization of a series of molecules that were prepared as affinity ligands for this purpose. The best of these is 9-(allyloxy)-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SK&F 101253). This compound is an α_2 -adrenoceptor antagonist, which was obtained by synthetic modification of 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SK&F 86466), a novel antagonist with high affinity for the α_2 -receptor.

Over the last decade, a great deal of effort has been expended on the isolation and purification of the adrenergic receptors that mediate the physiological responses of catecholamines. This has resulted in the purification of several subpopulations of receptors and the beginning of a new dimension of understanding about how these macromolecules regulate complex physiological processes. Notable successes have been achieved in the purification of both β^{-1-4} and α_1 -adrenoceptors,^{5,6} while almost no work whatsoever has been done on the α_2 -adrenoceptor. This is an important class of receptors whose role in the regulation of physiological processes is just beginning to be recognized.7

A thorough understanding of the way in which neurotransmitters modulate physiological processes will require the isolation, purification, and chemical characterization of receptor molecules. Little is currently known about how the binding of a catecholamine can evoke a physiological response. As a first effort to understand on a molecular level how α_2 -receptors function, we have undertaken the isolation and purification of the α_2 -adrenoceptor from human platelets.

One of the most difficult problems to deal with in purification of membrane-bound receptors is their extremely small concentration in relation to other membrane and cellular constituents. Additionally, purification of receptor proteins may be hindered by the presence of other proteins that, after solubilization by detergent, have similar physiochemical properties to those of the desired receptor. One of the most powerful techniques for the purification of membrane-bound receptors is affinity chromatography. This methodology exploits the extraordinary and unique specificity of ligand-receptor interactions. When this specificity is utilized it is possible to purify proteins of interest from those that, although similar in physiochemical nature, do not share the same biological specificity.

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An absolute necessity for such affinity chromatography is the identification of a suitable ligand with which to build an affinity column.

This paper describes the synthesis and structure-activity relationships (SAR) of a series of compounds that were specifically designed in a search for a suitable affinity ligand for the isolation and purification of the α_2 -adrenoceptor. This search culminated in the synthesis of such a ligand, 9-(allyloxy)-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SK&F 101253). This compound is an α_2 -antagonist, which was obtained by synthetic modification of 6-chloro-3-methyl-1,3,3,4-tetrahydro-1H-3-benzazepine (SK&F 86466), an α_2 -antagonist, which has high affinity and selectivity for the α_2 -adrenoceptor⁸. The affinity adsorbent prepared from this allyloxy compound demonstrated the proper biospecificity and has been successfully used to substantially purify the α_2 -adrenoceptor.9,10

Discussion

In the technique of affinity chromatography, a ligand with high affinity for the receptor of interest is immobilized via a stable covalent linkage onto an insoluble support matrix, such as agarose. This ligand is usually attached via a linear hydrophilic spacer arm such that the ligand is free to float in the void of the resin where it is accessible to the receptor of interest. A solubilized receptor preparation is placed on the column and allowed to equilibrate with the immobilized ligand. The column is then washed with buffer to remove other nonspecific macromolecules, which are cosolubilized but not specifically adsorbed to the immobilized ligand. Subsequently, elution of bound receptor can be achieved by a variety of agents that can compete with the immobilized ligand for rebinding to the receptor.11

In the design and synthesis of a suitable affinity ligand for the α_2 -adrenoceptor purification, there are three key points that need to be addressed. First, the free ligand must have high affinity for the receptor. This is critical,

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⁽¹¹⁾ For a more detailed discussion of the technique, see: W. H. Scouten "Affinity Chromatography: Bioselective Adsorption on Inert Matrices", Wiley, New York, 1981.

Scheme I



since, in general, when attached to a large insoluble support, many compounds lose some, if not all, of their affinity for the receptor. Second, the molecule must be suitably functionalized such that it can be covalently and irreversibly bound to the column. Finally, the point of attachment of the ligand to the column must be properly oriented so that the critical factors involved in the specific ligand-receptor binding are not substantially disturbed.

The α_2 -antagonist 6-chloro-3-methyl-1,2,3,4-tetrahydro-1H-3-benzazepine (1) was discovered in the course of our α -receptor research. This compound exhibits high affinity ($K_{\rm B}$ = 13 nM) and selectivity for the α_2 -receptor.⁸ Because of its high affinity and relatively uncomplicated structure, it was an ideal candidate for chemical modification. In designing synthetic targets as potential affinity ligands, we decided to couple the ligand to the spacer arm via a free radical process. This approach makes use of an agarose gel spacer, bearing a free thiol, to couple with a terminal allyl group on the ligand. This synthetic technique had been previously employed in the development of an affinity adsorbant for the isolation of the β -receptor.²⁻⁴ We initially hypothesized that the chlorine in position 6 of this molecule is located in a region of significant bulk tolerance on the receptor and, thus, led us to project substitution on the 6- and 7-positions of the parent ring system as our primary focus of chemistry.

Allyloxy compounds 6 and 8 were synthesized as shown in Scheme I. Diacid 2 was reduced with LiAlH_4 to the diol and converted to the dichloride with thionyl chloride. Replacement of both chlorines with potassium cyanide gave dinitrile 4. Reductive cyclization under high-pressure catalytic conditions¹² converted the dinitrile to the seven-membered azepine ring from which the O-methyl was removed to yield 5. The amine of 5 was protected as the carbamate, while the phenol was alkylated and the ethyl carbamate was reduced with lithium aluminum hydride to yield the target 6. (Allyloxy)benzazepine 8 was prepared

Table 1. All milly of Ligands for the α_0 -Autenouce	ceptor
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compd	$K_{ m i}$," nM	guinea pig atrium: K_{β} , nM
1	$16.7 \pm 3.8 \ (3)^b$	13 ± 3 (5)
6	$338 \pm 50 \ (3)^{b}$	$206 \pm 101 (5)$
8	$232 \pm 51 \ (3)^{b}$	NT
9	$6.1 \pm 1.7 \ (3)^b$	$60 \pm 15 (5)$
13	$48 \pm 6 \ (5)^c$	$150 \pm 30 (5)$
phentolamine	$5 \pm 0.7 \ (4)^c$	7 ± 1 (5)

^aDetermined from competition curves by using [³H]yohimbine (10 nM) in preparations of solubilized α_2 -adrenergic receptors from human platelet membranes. Incubations were for 3 h at 4 °C, and bound ligand was separated from free ligand by Sephadex G-50 chromatography.¹⁹ Nonspecific binding was determined in parallel assays in the presence of 10 M phentolamine. The K_d of [³M]yohimbine was 3 nM as determined from saturation isotherms (2–15 nM) in the same preparations.¹⁰ All data were analyzed by computer using nonlinear least-squares curve-fitting techniques.²⁰ ${}^{b}K_i \pm SE$ from three separate experiments using 10 inhibitor concentrations. ${}^{c}K_i \pm SE$ from four to five separate experiments using 12 inhibitor concentrations.





by simple transformation of the known acetamide 7^{13} as shown.

While these compounds were active as α_2 -antagonists (see Table I), neither was of utility as an affinity ligand, since the columns prepared from these agents failed to adsorb receptor. We felt that in these structures the allyl group, instead of being in an area of bulk tolerance, may have been interfering with a critical point of binding between the receptor and the ligand; thus, we chose to vary the point of attachment of the ligand to the spacer arm. Accordingly, we prepared the N-allyl derivative 9 by removal of the methyl and replacing it with allyl (Scheme II). This compound displayed significantly greater affinity than either 6 or 8 for the α_2 -adrenoceptor (Table I), but it also was ineffective as an affinity adsorbent for the receptor, and the column prepared from it also failed to adsorb significant receptor. We now had evidence to suggest that both the chlorine and the nitrogen were critical to ligand-receptor interaction, and we undertook to fix the point of attachment to the column at position 9 of the chloro-substituted molecule.

Nitration of 1 under standard conditions in sulfuric acid gave a mixture of o- and p-nitro isomers 10 and 11, which were separated by preparative chromatography. Reduction of the nitro group of 10 followed by diazotization and displacement, produced phenol 12, which was alkylated with allyl bromide to yield the target structure 13 (Scheme III).

Biology. All of the target ligands were evaluated for their affinity at the α_2 -adrenoceptor. This was determined physiologically by measuring the inhibition of clonidineinduced depression of neurotransmission in the guinea pig atrium.¹⁴ Additional evidence for the α_2 affinity of these agents was obtained by measuring the inhibition of specific

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Scheme III



[³H]yohimbine binding in a digitonin-solubilized preparation of human platelet membranes.¹⁵ As the data in Table I show, all the compounds have reasonably high affinity for α_2 -receptor with K_i 's less than 1 μ M, as determined in both physiological and biochemical assays. The data for phentolamine, a standard α antagonist, has been included as a reference standard. These four allylsubstituted benzazepines were covalently attached to activated Sepharose C1-4B via the free radical process de-scribed previously.¹⁶ The concentration of ligand coupled to the Sepharose C1-4B was measured both by differential analysis of recovered starting material, as well as by direct ultraviolet spectroscopy of the coupled gel in ethylene glycol.¹⁷ These analyses indicated that the amount of ligand coupled to the gel is in the range of 1–3 μ mol of ligand per gram of moist gel. At this concentration, sufficient ligand is present to allow adsorption of receptor proten. Activated Sepharose C1-4B served as a negative control and did not adsorb receptor in the absence of ligand. Affinity of columns were prepared from all of these agents (6, 8, 9, and 13) by the methods described earlier.^{10,16} Even though all of the uncoupled molecules had good affinity for the α_2 -receptor, only the column prepared from 13 was able to adsorb receptor. In the other cases, solubilized receptor was not bound to the column in any appreciable amount but passed through without adequate retention to allow sufficient purification. Having shown that in all cases enough ligand is coupled to the gel to allow binding of receptor, we conclude that leakage of the receptor must be due in these cases to an insufficiently active affinity adsorbant. Since unbound ligands show good affinity, it is possible that in doing the coupling to the gel a key factor necessary for tight binding has been disturbed by the spacer arm. Thus, substitution of the benzazepine ring at positions other than 9 or removal of the chlorine from the molecule gave ligands that lost their affinity for α_2 -receptors when they were coupled to the column. The

SAR that emerges from the four affinity adsorbants prepared indicates that in this structure chlorine must provide an important lipophilic interaction, and the area around nitrogen must be relatively unhindered.

We have previously reported that compound 13 has been coupled to Sepharose C1-4B for the preparation of an affinity adsorbent. This gel adsorbed solubilized α_2 -receptors from human platelet membranes, and the receptor protein could be biospecifically eluted with a series of agonists and antagonists with the correct rank order of potency.^{9,10} Compound 13 promises to be useful for further work directed to the isolation and purification of the α_2 -adrenoceptor from human platelets and should be applicable to other tissues as well.

Experimental Section

Melting points were determined in open capillary tubes on a Thomas-Hoover Uni-melt apparatus and are uncorrected. Elemental analyses and mass spectra were determined by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by symbols of the elements, results were within 0.4% of calculated values. Satisfactory IR, NMR, and mass spectral data were obtained for all new compounds.

6-(Allyloxy)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine Hydrochloride (6). A solution of 3-methoxyphthalic acid¹⁸ (19.6 g, 0.1 mol) in 100 mL of THF was added to 10 g (0.263 mol) of LiAlH₄ in 500 mL of Et_2O at a rate sufficient to maintain a constant reflux. The mixture was refluxed for 2 h after the addition was completed. It was cooled and decomposed by the addition of 10 mL of H₂O, 20 mL of 10% NaOH, and 40 mL of H_2O . The resulting solid was separated by filtration and washed with THF. The combined filtrates were concentrated to give 12 g (71%) of 3-methoxy-o-xylene- α, α' -diol, mp 95 °C. To a solution of 16.8 g (0.1 mol) of the diol in 47 mL (0.6 mol) of pyridine and 100 mL of toluene was added dropwise 44 mL (0.6 mol) of thionyl chloride. The mixture was stirred at room temperature for 2 h. Water (500 mL) was added, and the organic layer was separated, washed with 3 N HCl, 10% NaOH, and water. The organic layer was dried and filtered, and the filtrate was evaporated to give 18 g (88%) of an oil, 3-methoxy-1,2-bis(chloromethyl)benzene (3). A solution of 60 g (0.292 mol) of the dichloro compound in 600 mL of Me₂SO was stirred while finely powdered sodium cyanide (57.36 g, 1.19 mol) was added. The mixture was stirred at 40-45 °C for 4 h, cooled, and diluted with 2 L of ice-water to give a white solid. It was separated, washed with water, and dried to give 42 g (77%) of white solid; 3-methoxy-o-phenylenediacetonitrile (4); mp 103 °C. Twenty grams (0.107 mol) of dinitrile was cyclized by the procedure of Ruggli et al.¹² to obtain 15 g (79%) of 6methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine as an oil. The 6-methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (1.00 g, 0.0056 mol) was heated at reflux in 15 mL of 48% HBr overnight, under argon. It was concentrated to obtain a brown solid, which was dispersed in acetonitrile. The mixture was filtered, and the solid was dried to give 0.94 g (69%) of 6-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (5), mp 220-224 °C. To a solution of 0.9 g (3.6 mmol) of the 6-hydroxy compound in 3 mL of pyridine was added 5 mL of ethyl chloroformate. It was allowed to stir at room temperature for 1 h, poured over 20 mL of 3 NHCl in ice, and extracted with CH_2Cl_2 . The organic layer was washed with 10% NaOH, 3 N HCl, and water, dried, and evaporated to give 0.7 g of the bis(carboethoxy) compound. This was dissolved in 10 mL of ethanol, and 10 mL of 10% NaOH was added. The mixture was heated to 50 °C for 30 min, cooled, diluted with water, made acidic, and extracted with CH₂Cl₂. The extracts were dried and evaporated to give 0.4 g of 6-hydroxy-3-carboethoxy-2,3,4,5,-tetrahydro-1H-3-benzazepine. A mixture of 0.4 g (1.7 mmol) of this phenol, 0.242 g (2 mmol) of allyl bromide, and 0.276 g (2 mmol) of anhydrous potassium carbonate in 20 mL of dry acetone was heated at reflux for 8 h. It was diluted with water, extracted with CH2Cl2, washed twice with 10% NaOH and dried. After filtration, removal of the solvent gave 0.4 g of

⁽¹⁵⁾ For a description of the methodology used, see ref 10.

⁽¹⁶⁾ For a description of the methodology used, see ref 2-4 for the synthesis of Sepharose 4B-alprenolol.

⁽¹⁷⁾ C. R. Lowe, "Laboratory Techniques in Biochemistry and Molecular Biology", Vol. 7, T. S. Work and E. Work, Eds., Elsevier/North Holland, New York, 1979 p 274.

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6-(allyloxy)-3-carbethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine. A solution of 0.4 g (1.5 mol) of this carbamate and 0.735 g (19 mmol) of lithium aluminum hydride in 50 mL of Et₂O was refluxed for 5 h, cooled, and decomposed with water–alkali. The solid was removed by filtration, and the filtrate was concentrated. Addition of ethereal HCl gave a solid, which was recrystallized from acetone/ether to give 0.158 g of 6-(allyloxy)-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (6), mp 160 °C. Anal. (C₁₄H₁₉NO·HCl·¹/₄H₂O) C, H, N.

7-(Allyloxy)-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (8). A mixture of 0.95 g (4.6 mmol) of 3-acetyl-7hydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine,¹³ 0.75 g (5.5 mmol) of anhydrous potassium carbonate, and 0.66 g (5.4 mmol) of allyl bromide in 50 mL of dry acetone was stirred and heated at reflux for 7 h. The acetone was removed under vacuum, and the residue was partitioned between water and CH₂Cl₂. The organic phase was washed with water, dried, and evaporated to give a solid, which was dissolved in 14 mL of 10% NaOH. The solution was heated at reflux for 15 h, poured into ice-water, and extracted with CH₂Cl₂. The organic layer washed with water, dried, and evaporated. This residual base was taken up in a small amount of 2-propanol and precipitated with ethereal HCl. The resulting solid was crystallized from acetone to give 550 mg (50%) of white solid, mp 153-154 °C. Anal. (C₁₃H₁₇NO-HCl⁻¹/4H₂O) C, H, N.

3-Allyl-6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine Hydrochloride (9). A solution of 12 g of 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine⁸ in 30 mL of toluene was stirred at 50 °C under N2 while a solution of 0.7 of cyanogen bromide in 25 mL of toluene was added dropwise. After the addition was completed, the mixture was stirred for 1 h. It was cooled and filtered, and the filtrate was evaporated to yield 0.82 g (63%) of 6-chloro-3-cyano-2,3,4,5-tetrahydro-1H-3-benzazepine, mp 81–82 °C (hexane– Et_2O). This was refluxed for 19 h in a mixture of 30 mL of HOAc and 30 mL of 6 N HCl. The mixture was evaporated, and the residue was crystallized from EtOH to give 6-chloro-2.3.4.5-tetrahydro-1H-3-benzazepine hydrochloride. mp 214-215 °C (0.52 g, 70%). A mixture of 0.52 g of the free base of this compound, 0.34 g of allyl bromide, and 0.6 g of potassium carbonate in 20 mL of 90% EtOH was stirred at room temperature for 17 h. The mixture was filtered, and the filtrate was evaporated. The resulting residue was dissolved in 35 mL of Et₂O and treated with excess etherial HCl. A precipitate formed, which was re-moved by filtration and crystallized from EtOH to give 0.35 g (50%) of 9 as white crystals, mp 248-249 °C. Anal. ($C_{13}H_{16}$ -CIN·HCl) C, H, N.

9-(Allyloxy)-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3benzazepine Hydrochloride (13). To a cold solution of 62.7 g (0.34 mol) of 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine⁸ in 100 mL of concentrated H_2SO_4 was added, dropwise over 2 h, 40 mL of concentrated nitric acid. The mixture was stirred at room temperature overnight and quenched in ice. It was made basic with 10% NaOH and extracted with CH₂Cl₂. The organic phase was washed, dried, and evaporated to leave an oily residue. This was chromatographed over silica gel with a "Waters prep 500" high-pressure liquid chromatograph, eluting with 2propanol-hexane-diethylamine (75:25:1) to give pure 6-chloro-3-methyl-9-nitro-2,3,4,5-tetrahydro-1H-3-benzazepine (10; 35.9 g, 44%). A solution of 10 g (0.04 mol) of this nitro compound and 6.0 mL of hydrazine hydrate in 400 mL of ethanol was warmed to 45 °C while activated Raney nickel was added in small portions until the evolution of gas ceased. The mixture was cooled, filtered through filter aid, and concentrated to give 8 g (95%) 9-amino-6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine. This compound was dissolved in 85 mL of 3 N H_2SO_4 and cooled in an ice bath while a solution of 3.72 g (54 mmol) of sodium nitrite in 18.5 mL of H_2O was added dropwise. The solution was stirred for an additional hour after completion of addition. It was cooled in the freezer at -20 °C for 2 days. Crystals formed, which were removed by filtration. These were dissolved in water, neutralized

to pH 8.0 with ammonium hydroxide, and extracted with CH₂Cl₂. The organic phase was dried and evaporated to give 4.9 g (62%)of 6-chloro-9-hvdroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, as a crystalline solid, mp 178–180 °C. A solution of 2.12 g (10 mmol) of this compound in 25 mL of dry DMF was cooled in an ice bath while 0.48 g (10 mmol) of 50% NaH was added. This was stirred until complete solution was effected, and the solution was treated with 1.01 g (10 mmol) of allyl bromide in 10 mL of dry DMF. It was stirred at room temperature for 20 h, quenched in water, and extracted with CH_2Cl_2 . The organic extracts were washed with water, dried, and evaporated to a solid residue. This was taken up in ether and precipitated with ethereal HCl. The precipitated solid was collected and recrystallized from MeOH-Et₂O to give white crystals of 9-(allyloxy)-6-chloro-3methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, mp 190-192 °C. Anal. (C14H18CINO·HCl) C, H, N

Determination of K_D in [³H]Yohimbine Binding. The total binding of [³H]yohimbine to solubilized α_2 -adrenoceptors was determined in 0.5-mL assay mixtures containing 10 nM [³H]yohimbine; nonspecific binding was determined in parallel assays in the presence of 10 μ M phentolamine. Incubations were 3 h at 4 °C, and bound ligand was separated from free ligand by Sephadex G-50 chromatography.¹⁹ Saturation experiments were conducted similarly with seven concentrations of [³H]yohimbine, ranging from 2 to 15 nM. Radioactivity was measured by liquid scintillation spectrometry (45% counting efficiency). Binding data from competition and saturation experiments were analyzed by computer and nonlinear least-squares curve-fitting techniques.²⁰

Determination of $K_{\rm B}$ by Blockade of Clonidine-Induced Inhibition of Neurotransmission in the Guinea Pig Atrium. The heart is removed from a pentobarbital-anesthetized male guinea pig. The left atrium is removed, dissected free of extraneous tissue, and mounted in a 2-mL superfusion chamber. The tissue is paced at 30 pulses/min with low-voltage (5–10 V) 5-ms square wave pulses, and the sympathetic nerves are excited at 6-min intervals by field stimulation with a 500-ms train of high-voltage (80 V) 0.7-ms pulses at 10-15 Hz. The response to nerve stimulation is measured as the difference in contractile force between the basal contraction and peak contraction following a nerve stimulation. A concentration-response curve for clonidine $(\alpha_2$ -agonist) is prepared by administering an increase concentration of clonidine following each successive stimulation. The tissue is then superfused with the α_2 -antagonist to be tested for 30 min, and the clonidine concentration-effect curve is repeated in the presence of antagonist. The receptor dissociation constant of the antagonist $(K_{\rm B})$ is defined as the antagonist concentration required to shift the log concentration-response curve of clonidine to the right by a factor of 2.

Registry No. 1, 73943-10-9; 2, 14963-97-4; 3, 90047-44-2; 4, 90047-45-3; 5, 90047-46-4; 6, 90047-57-7; 6·HCl, 90047-47-5; 7, 90047-48-6; 8, 90047-58-8; 8·HCl, 90047-49-7; 9, 90047-59-9; 9·HCl, 87349-81-3; 10, 78495-50-8; 11, 73943-11-0; 12, 90047-50-0; 13, 86120-57-2; 13·HCl, 90047-51-1; 3·methoxy-o-xylene- α, α' -diol, 90047-52-2; 6-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-53-3; ethyl chloroformate, 541-41-3; 3,6-bis(carboeth-oxy)-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-55-5; 6-(allyloxy)-3.carboethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-55-5; 6-(allyloxy)-3.carboethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-55-5; 6-(allyloxy)-3.carboethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-56-6; 6-chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-1*H*-3-benzazepine, 90047-1*H*-3-benzazepine, 90047-1*H*-3-benzazepine, 90047-1*H*-3-benzazepine, 90047-56-6; 6-chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-56-6; 6-chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-1*H*-3-benzazepine, 90047-56-6; 6-chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 90047-56

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