8-8-2007

Synthesis And Evaluation Of Novel Tropane Compounds As Potential Therapeutics For Drug Abuse

Harneet Kaur
University of New Orleans

Synthesis And Evaluation Of Novel Tropane Compounds As Potential Therapeutics For Drug Abuse

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
The Department of Chemistry

by

Harneet Kaur

M.S. (Hons) Panjab University 2001
M.S. University of New Orleans 2004

August 2007

To my family, for their love and support

Father: Dr. Paramjit Singh

Mother: Sukhvinder Kaur

Husband: Rohit Singh

ACKNOWLEDGMENTS

I would like to express sincere gratitude to my research advisor, Professor Mark L. Trudell for his guidance, support and encouragement throughout the period of my study and research. I would also like to thank my committee members, Professor Guijun Wang, Professor Branko Jursic, Professor John B. Wiley and Professor Matthew A. Tarr. In addition, I would like to acknowledge Dr. Edwin D. Stevens for solving X-ray crystal structures for us.

I would also like to thank Dr. Sari Izenwasser of the University of Miami for the biological tests included in this dissertation.

Additionally, I wish to express my gratitude to Dr. Amy Newman of National Institute on Drug Abuse (NIDA), for hosting me while the University of New Orleans was recovering from the hurricanes. Dr. Peter Grundt and Dr. Noel Paul of NIDA are also acknowledged for their help.

I wish to express many thanks and appreciation to my husband, Rohit, for fruitful discussions and overall support.

The National Institute on Drug Abuse and the University of New Orleans are gratefully acknowledged for financial support of this work.

TABLE OF CONTENTS

LIST OF SCHEMES vi

LIST OF FIGURES viii

LIST OF TABLES ix

ABSTRACT x

INTRODUCTION 1

1.1 Structure of Cocaine and Its Abuse Potential 1

1.2 Cocaine and the Dopamine Transporter 4

1.3 The Dopamine Hypothesis 6

1.4 Heterogeneity of Dopamine Transporter Binding 8

1.5 Challenges to the Dopamine Hypothesis 9

1.6 Medication Development for Cocaine Abuse 10

1.7 Binding Affinity and Inhibition Constant 13

1.8 Structure Activity Relationship Studies of 3-Phenyltropanes 14

1.9 Structure Activity Relationship Studies of Meperidine Analogues 22

1.10 Design Strategy for Novel Tropane Analogues 27

RESULTS AND DISCUSSION 34

2.1 Attempted Synthesis of 3-Aryl-3-carbomethoxytropane and its Analogues 34

2.2 Attempted Synthesis of 3-Aryl-3-propyltropane and its Analogues.....38

2.3 Synthesis of 3-Aryl-3-methoxytropanetropane and its Analogues.....40

2.4 Synthesis of 3-Aryl-3-arylmethoxytropanetropane Derivatives.....46

2.5 Novel 3-Aryl-2-nortropene Derivatives as "Triple" Reuptake Inhibitors 55

2.6 Future Directions 62

CONCLUSION.....67

EXPERIMENTAL SECTION.....69

REFERENCES 101

APPENDIX.....116

VITA.....134

LIST OF SCHEMES

Scheme 1 Retrosynthetic analysis for the preparation of target molecules with alkyl and allyl esters.....31

Scheme 2 Retrosynthetic analysis for the preparation of target molecules with benzyl esters and benzyl ethers 32

Scheme 3 Retrosynthetic analysis for the preparation of *N*-H analogues.....33

.....

Scheme 4 Reduction of the unreacted starting material.....35

Scheme 5 Use of freshly prepared phenyllithium reagent for transforming 3-tropinone36

Scheme 6 Attempted functional group interconversion of the hydroxyl group to the nitrile 37

Scheme 7 Formation of the unsaturated compound via β-elimination.....38

Scheme 8 Retrosynthetic analysis for the formation of 3-aryl-3-propyl-tropane analogues.....39

Scheme 9 Attempted functional group interconversion of the hydroxyl group into the oxalate 40

Scheme 10 Retrosynthetic route for the synthesis of 3-phenyl-3-methoxytropane and its analogues.....41

Scheme 11 Quarternerization of the tertiary amine 41

Scheme 12 Synthetic route for the synthesis of 3-aryl-3-methoxytropane derivatives....42

Scheme 13 Retrosynthetic route for the synthesis of 3-aryl-3-arylmethoxytropane and its derivatives 46

Scheme 14 Retrosynthetic route for the synthesis of 3-aryl-2-nortropene derivatives 60

Scheme 15 Attempted synthesis of 3-aryl-2-nortropene derivatives 61

Scheme 16 Synthesis of 3-aryl-2-nortropene derivatives 62

Scheme 17 Retrosynthetic route for the synthesis of analogues of **67** 65

Scheme 18 Synthetic route for the synthesis of analogues of **67** 66

LIST OF FIGURES

Figure 1 Dopamine hypothesis 7

Figure 2 Schematic representation of putative interaction of cocaine with its receptor sites. 11

Figure 3 Target compounds as hybrid structures of 3β-phenyltropanes and meperidine.....30

Figure 4 Structures of some chelating ligands used to enhance reactivity of the alkyllithium reagents.....36

Figure 5 Transformation at the O-H bond of the tropane 40

Figure 6 X-ray structure of 3β-phenyl-3-hydroxytropane **55a** 43

Figure 7 Benzyl ether analogues, **59a-e** and **60a-e** 47

Figure 8 Benzyl ether analogues, **59f-j** and **60f-j** 48

Figure 9 Benzyl ether analogues, **59k-q** and **60k-q** 48

Figure 10 X-ray structure of 3β-phenyl-3α-phenylmethoxytropane **60a** 49

Figure 11 Overlay of geometry optimized structures **64** and **65e** 59

Figure 12 Hybrid structures of benztropine and tropane analogues **60** 64

Figure 13 Overlay of benztropine **67** and benzyl ether **60a** (X=Y=Z=H). 65

LIST OF TABLES

Table 1 DAT binding affinity of 4'-substituted WIN-35,065-2 analogues 16

Table 2 In vitro data for derivatives of 3-aryl-3-methoxytropane and 3-aryl-3-hydroxytropane 44

Table 3 In vitro binding data at the DAT and the SERT for 3β-aryl-3α-arylmethoxy nortropane derivatives.....50

Table 4 In vitro binding data at the DAT and the SERT for 3β-aryl-3α-arylmethoxy -8-methyltropane derivatives 51

ABSTRACT

In an effort to search for potential therapeutic agents for cocaine addiction, a novel class of compounds was synthesized and evaluated for *in vitro* dopamine and serotonin transporter affinities. These unique 3β-aryl-3α-arylmethoxytropane analogues incorporated the structure of dopamine selective 2-substituted-3-phenyltropanes and the design of serotonin selective meperidine derivatives. In general, the 3β-aryl-3α-arylmethoxytropane analogues exhibited greater potency for the serotonin transporter than the dopamine transporter. The most potent compounds of this series were 3β-phenyl-3α–(3″, 4″-dichlorophenyl)methoxy-8–azabicyclo [3.2.1]nortropane (K_i = 0.06 nM) and 3β-(4′-chlorophenyl)-3α–(4″-chlorophenyl)methoxy-8–azabicyclo[3.2.1]nortropane (K_i = 0.09 nM) at the serotonin transporter and their binding affinities were equipotent with paroxetine and fluoxetine (Prozac).

A series of 8-azabicyclo[3.2.1]oct-2-ene derivatives were synthesized from 3-tropinone based on the structure of triple re-uptake inhibitor, DOV 216,303. The compounds were designed as potential triple re-uptake inhibitors which could exhibit equipotent affinities at the monoamine transporters for dopamine, serotonin and norepinephrine.

A short and efficient synthetic methodology was developed for the synthesis of unique compounds which could exhibit potency for both the dopamine and serotonin transporters. The 3β-aryl-3α-(4′, 4″-disubstituteddiphenylmethoxy)tropane analogues were designed as hybrid structures of the dopamine transporter selective benztropines and the serotonin transporter selective meperidine derivatives.

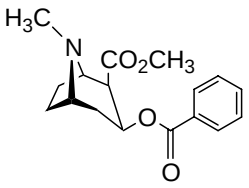
Key Words: tropane, cocaine, dopamine, serotonin, norepinephrine, tropenes.

INTRODUCTION

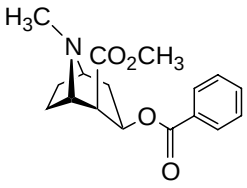
1.1 Structure of Cocaine and Its Abuse Potential

Cocaine is the most powerful central nervous system stimulant found in nature. (-)-Cocaine (**1a**) is a plant alkaloid and is extracted from the leaf of the *Erythroxylon coca* bush which grows primarily in Peru and Bolivia.[1] Albert Niemann, a German chemist, was the first to isolate this alkaloid from the coca plant in 1860.[2] Sigmund Freud was one of the prime investigators who studied the effects of cocaine and proposed its clinical use as a local anesthetic in eye surgery.[3] Its powerful vasoconstrictant properties have been utilized in nose or throat surgery where control of bleeding was desired.[4] However it was soon realized that the toxic effects of this drug were far more severe than its benefit as a medication.[5,6] Instances of addiction, psychotic behavior, convulsions and even death have been reported. Cocaine use is associated with euphoric effects or "high", consisting of hyper stimulation, reduced fatigue and mental alertness for a short period of time. Consequently, it has now become one of the most abused drugs in the country.

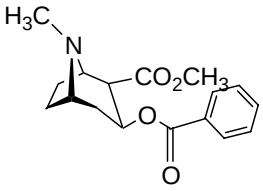
Cocaine is one of the eight possible isomeric forms (**1a-1h**) of the chemical entity methyl 3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octan-2-carboxylate.[7] The potency of R-Cocaine (**1a**) was found to be 60-670 times greater than its isomers.[8] There are two main forms of cocaine-the hydrochloride salt and the freebase ("Crack"). Cocaine sold as the hydrochloride salt is typically snorted, swallowed, or dissolved in water and injected intravenously. The onset of the effects of cocaine relies on the mode of its intake. For example, it takes up to 30 minutes to feel the effects if snorted but only 1-2 minutes if taken by intravenous injection.



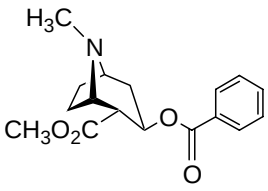
R-Cocaine (**1a**)



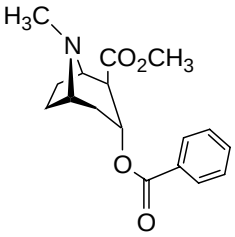
S-Cocaine (**1e**)



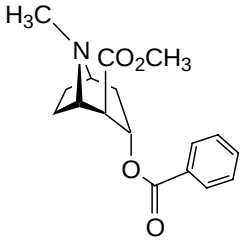
R-Pseudococaine (**1b**)



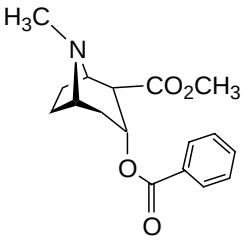
S-Pseudococaine (**1f**)



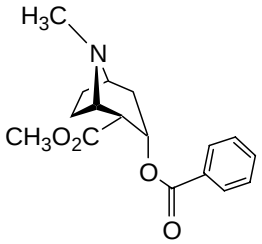
R-Allococaine (**1c**)



S-Allococaine (**1g**)



R-Allopseudococaine (**1d**)



S-Allopseudococaine (**1h**)

The most immediate and intense "high" is produced by smoking the freebase "Crack".[9] Crack is available as a rock crystal and is heated and the vapors inhaled. The term "Crack" refers to the crackling sound heard when it is heated. It is the most dangerous form of the drug as it is cheap,

easy to intake and its effects are rapid and intense.[10, 11] Intake of any form of cocaine will result in constriction of blood vessels, dilation of pupils and increase in body temperature, heart rate and blood pressure. High doses can result in heart attack, strokes, seizures, full blown paranoid psychosis, auditory hallucinations or even sudden death.[12] A recent survey in the United States indicated that 34.2 million Americans aged 12 and over reported lifetime use of cocaine, and 7.8 million reported using crack.[13] There were an estimated 1 million new users of cocaine in 2005, approximating to 2,400 per day. In addition the spread of HIV has been linked to drug abusers who used/shared injections. When cocaine and alcohol are consumed together, human liver manufactures a third substance, cocaethylene, which intensifies cocaine's euphoric effects and increases the risk of sudden death.[14] Cocaine addiction is a chronic relapsing disease and the withdrawal symptoms are associated with serious depression.[15-20]

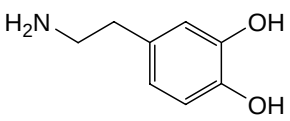
Aside from the physical effects suffered by the individual, our society bears the burden of cocaine abuse because of decreased productivity, increased premature deaths, disruption of families and medical costs associated with emergency room care, as well as treatment and prevention programs.[21] The health, crime, and other problems created by drug abuse cost society nearly half as much money as spent on defense by the Department of Defense.[22, 23] While this underscores the magnitude of the problem, the amount of human suffering is incalculable.

In light of all the detrimental effects associated with cocaine abuse, the need for a therapeutic agent is immediate and necessary. In this regard, a lot of research has focused on the development of a cocaine addiction medication, but at present there are no suitable medications for the complete treatment of cocaine abuse.[24] The aim has been to design a drug that potentially attenuates cocaine intake and yet does not simply substitute one addictive drug for another. This substitution therapy has been widely accepted as a feasible strategy for treatment of other drug

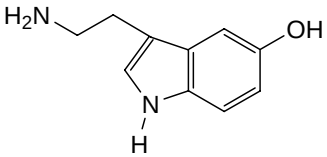
addictions. For example, methadone has been an effective medication in the treatment of heroin abuse[25-27] and nicotine replacement has been useful for smoking cessation.[28]

1.2 Cocaine and the Dopamine Transporter

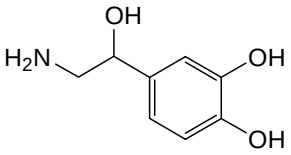
The complex molecular mechanisms associated with the action of cocaine that result in various physiological and behavioral effects are under intensive investigation. Although several binding sites for cocaine have been identified in the brain, the exact mechanisms of interaction with these sites are still not fully understood. Cocaine has affinity for several sites in the central nervous system. It can inhibit the reuptake of dopamine (**2**), serotonin (**3**) and norepinephrine (**4**)[29-31] as well as exert effects on the cholinergic muscarinic[32] and σ receptors and sodium ion channels.[33] Any one or a combination of these could result in effects related to the abuse of cocaine. Although cocaine has a relatively low affinity for most neurotransmitter receptor sites, it has micromolar affinity for σ receptors and the effects of this interaction may be involved in the psychotomimetic effects of the drug.[33] The cardiovascular effects like increased heart rate and blood pressure are believed to be mediated by the inhibition of norepinephrine uptake.[34]



Dopamine (**2**)



Serotonin (**3**)



Norepinephrine (**4**)

The reinforcing properties of cocaine are usually predicted by cocaine self administration in animals and humans as well as by other behavioral techniques.[35] Mechanisms of reinforcement have been explored at the neurochemical and neuroanatomical levels. Numerous studies over the past several years have suggested that the binding site which mediates cocaine self-administration or the reinforcing effects of cocaine is associated with the dopamine transporter (DAT).[36, 37] It has been established that the mesolimbic dopaminergic neurons in the midbrain are mainly responsible for mechanisms associated with reward-related behavior. This midbrain dopaminergic projection originates in the ventral tegmental area and projects to structures associated with the limbic system, most prominently the nucleus accumbens.[38] The dopamine transporter is a protein located on presynaptic nerve terminals that plays a major role in the uptake of synaptic dopamine. The cDNA for dopamine transporter has been cloned from rat,[39-41] mouse,[42, 43] bovine[44] and human brain.[45] Elucidation of the primary structure of the dopamine transporter has revealed that it is a 619-amino acid protein and contains 12 putative transmembrane domains.[40] It is a member of the large family of sodium dependent transporters. Other members of this family include transporters for norepinephrine, serotonin, GABA (γ-aminobutyric acid), proline, glycine, betaine and creatine.[46] Although the dopamine transporter has been cloned and expressed, its 3D structure is still unknown. However, site-directed mutagenesis studies have revealed that aspartate and serine residues lying within the first and seventh hydrophobic putative regions are important for cocaine recognition and dopamine uptake.[47] It has been contemplated that the carboxyl group of the aspartic acid residue 79 engages in an ionic interaction either with the nitrogen of cocaine or with the amino group of dopamine in binding to the transporter.[48]

1.3 The Dopamine Hypothesis

The process of neurotransmission requires synthesis and storage of the neurotransmitter, followed by its release and interaction with specific pre- and post-synaptic receptors. Termination of the signal results in degradation of the neurotransmitter, its diffusion out of the synapse and/or removal from the synapse by one of the sodium-dependent neurotransmitter transporters. The importance of each of these processes for dopamine transmission has been established.[49-51] The predominant theory which tries to explain the reinforcing properties of cocaine is the 'dopamine hypothesis'. It does not associate cocaine addiction with the direct binding of cocaine with the dopamine transporter itself but rather with the accumulation of dopamine in the synapse and its action at one or more of the D_1-D_5 receptors.[52-54] In normal neural stimulation (food, sex, etc.), the presynaptic neuron receives a chemical impulse which travels along the axon promoting the release of dopamine.[55] The dopamine diffuses into the synaptic cleft and interacts with the receptors of the postsynaptic neurons. This interaction results in a biochemical reaction which sends another chemical impulse down the axons of the postsynaptic neuron signaling satisfaction or reward. Dopamine is released from the receptors into the synapse. After its release, the concentration is reduced rapidly due to the presence of uptake sites on the plasma membrane of the presynaptic dopaminergic nerve endings. The dopamine transporter protein controls the extra cellular dopamine levels by transporting it back into the presynaptic neuron where it is recycled for later use. Therefore, the dopamine transporter has a fundamental role in the regulation of pre- and postsynaptic dopaminergic transmission.

Cocaine is considered to be a classic uptake blocker: it inhibits dopamine uptake after normal neuronal activity by binding to the dopamine transporter (Figure 1).[55, 56] This leads to an

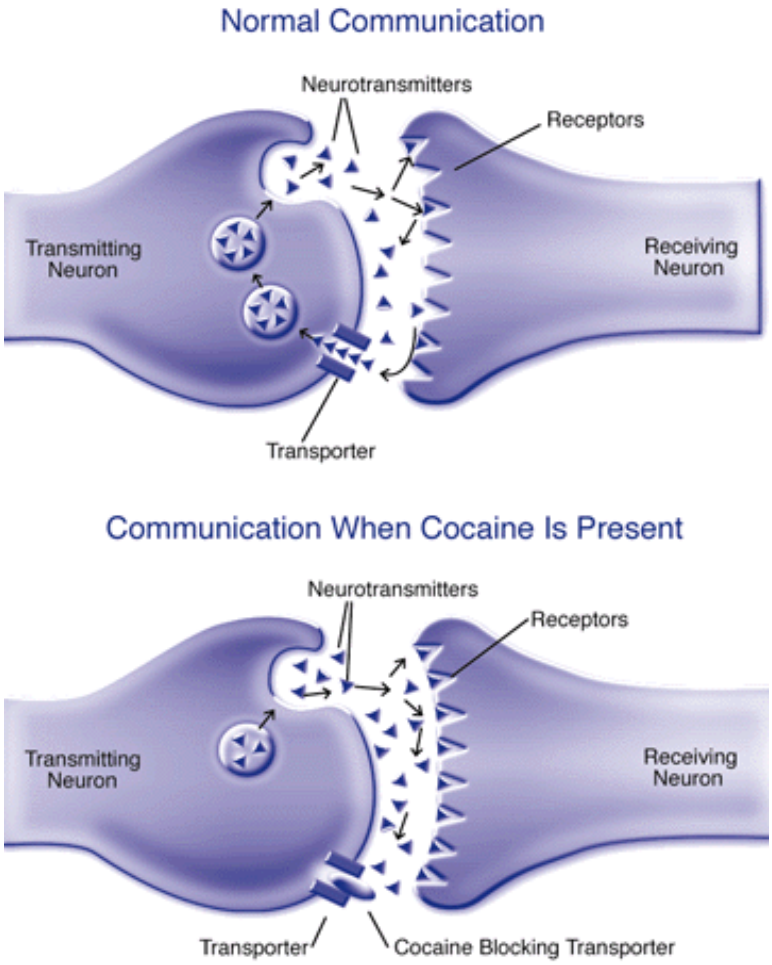


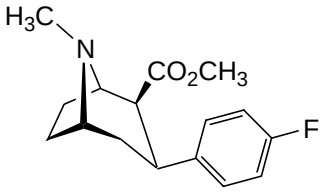
Figure 1. Dopamine Hypothesis. During normal communication between nerve cells, or neurons, the transmitting neuron releases neurotransmitter molecules that stimulate the receiving neuron by binding to receptor molecules on its surface. After this communication has occurred, transporter molecules collect the released neurotransmitters and transport them back into the transmitting neuron for later release. When cocaine is present, the drug blocks the transporter, preventing neurotransmitter reuptake so that the neurotransmitters continue to stimulate the receiving neuron.[55]

increased concentration of dopamine and it enables the postsynaptic neurons to produce an enhanced signal. This enhanced signal results in the euphoric effects of cocaine. But use of cocaine over a period of time causes desensitization of the postsynaptic neurons. In order to maintain equilibrium, the system reduces the number of receptors present and the remaining receptors also become less sensitive to dopamine levels. Meanwhile, the dopamine transporter proteins increase in number. The increased number helps to remove excess dopamine from the

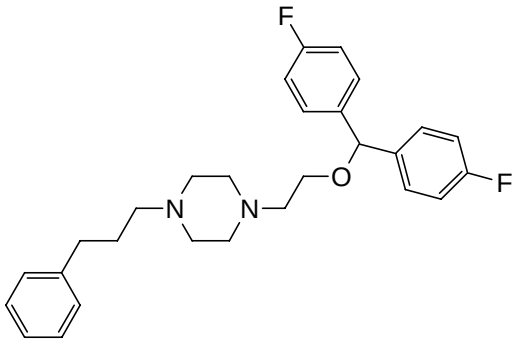
synapse and mitigates over stimulation. Therefore use of cocaine over a period of time will lessen the extent of the initial 'high' felt by the user. This will lead the user to administer higher doses more frequently to achieve the same level of euphoria and stimulation which ultimately leads to a chronic addiction.

1.4 Heterogeneity of Dopamine Transporter Binding

Numerous radio-labeled ligands have been used to identify and study distinct binding sites at the dopamine transporter. The two most extensively characterized molecules are [^{3}H]WIN 35,428 (**5**) and [^{3}H]GBR 12909 (**6**).[57-59]



WIN 35,428 (**5**)



GBR 12909 (**6**)

[^{3}H]Cocaine was initially found to bind saturably to a single site in mouse brain preparations.[60] Later reports showed that [^{3}H]cocaine and other high affinity congeners like [^{3}H]WIN 35,428 saturate the dopamine transporter in a biphasic manner characteristic of binding to high- and low-affinity components or sites.[61-67] The two binding sites might mark discrete

transporter molecules, conformational states, or separate binding sites on the same protein. On the other hand, dopamine transporter inhibitors [^{3}H]mazindol and [^{3}H]GBR 12909 saturate sites on the transporter in a monophasic manner indicative of a single binding site.[68] The significance of this heterogeneity for behavior related to cocaine abuse is still not very clear. However, several studies suggest that the discriminative-stimulus effects of cocaine are mediated mainly by the high-affinity component. The further estimation of the contributions of high- and low-affinity binding components to cocaine related effects will require development of novel selective ligands and advances in their isolation and discriminative study.

1.5 Challenges to the Dopamine Hypothesis

Significant studies supported the idea of the dopamine transporter as a primary mediator of the reinforcing action of cocaine. However, there were numerous reports which noted that under chronic cocaine-taking conditions, the dopaminergic system was not the only system responsible for craving and dependence, but other neural systems were involved as well.[69-72] This was suggested mainly from studies conducted on dopamine transporter knock-out mice. Cloning and expression of rat cDNA was achieved nearly a decade ago and subsequent homologous recombination in which the dopamine transporter gene was disrupted, resulted in the first dopamine transporter knock-out (DAT KO) mice.[46] These genetically altered mice were found to be profoundly hyperactive, conforming with the hypothesis that excessive extracellular dopamine increases locomotor behavior. Nevertheless, tests of locomotor activity cannot predict abuse-related effects of the drug reliably. A more convincing assessment of such effects comes from self-administration procedures, in which the drug serves as a reinforcer of behavioral

activity that trigger rapid intravenous infusions of the drug.[73] Cocaine was self-administered in DAT KO mice despite their already elevated levels of extracellular dopamine. This behavior is in direct contradiction of the dopamine hypothesis and this suggests that increase in dopamine concentrations is not the only mechanism involved in the reinforcing effects of cocaine. Therefore, the role of the serotonin transporter was advocated for mediating these effects.[74] Serotonin knock-out mice were studied and results showed that these mice exhibited the rewarding effects of cocaine too. This depicted that increased levels of extracellular serotonin also play a role in the actions of cocaine. These studies show that although no single monoamine transporter is absolutely necessary for cocaine reward in knock-out mice, several possible roles for these neurotransporters in wild type mice remain. Lifelong deletions of dopamine, serotonin and the norepinephrine transporters or their combinations, each specifically change the rewarding effects of blocking the remaining transporters. It can be concluded from these findings that cocaine works as a "dirty drug" that produces reward through simultaneous action at more than one transporter site.[75] Therefore, strategies for developing drugs acting at both dopamine and serotonin brain systems might provide better insights for treating cocaine abuse and its reward reinforcement rather than focusing on synthesizing dopamine transporter selective ligands exclusively.

1.6 Medication Development for Cocaine Abuse

A large number of compounds have been synthesized and analyzed as potential pharmacotherapeutics for treating cocaine addiction. Most of the compounds are small molecules which should act as cocaine antagonists and inhibit cocaine recognition at transporter sites while

allowing the neurotransporters to maintain all or most of their normal functions. However, despite improved understanding of neural mechanisms underlying the addiction of cocaine, no suitable compound has been discovered that can act as a true cocaine antagonist and therefore be used as a medication for treating cocaine abuse.[76,77] Nevertheless, there are some pharmacotherapeutic agents that have been developed from an immunological standpoint. These drugs can enable the body to produce cocaine antibodies which bind to cocaine and degrade it. The three major classes of pharmacotherapeutics currently available for treating cocaine abuse are: drugs that treat coexisting psychiatric disorders (methylphenidate, desipramine, etc.), drugs that produce an aversion reaction when taken with cocaine (phenelzine) and drugs that treat cocaine craving (L-dopa, tryptophan, carbmazepine, etc.).[78, 79] Other pharmacotherapeutic agents which have been explored also include excitatory amino acid receptor antagonists,[80, 81] 5-HT_3 receptor antagonists,[82, 83] dopamine receptor agonists/antagonists,[84-88] sigma receptor antagonists[89, 90] and kappa,[91] delta opioid receptor ligands.[92, 93]

A pharamacophore model (Fig. 2) for the cocaine binding site was proposed by Carroll et al. This was based on structure-activity relationship (SAR) data of a variety of compounds and preliminary molecular modeling studies.[30]

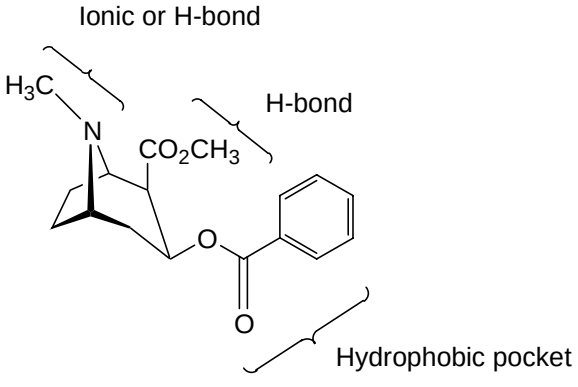


Figure 2. Schematic representation of putative interaction of cocaine with its receptor sites.

The three main sites of interaction envisaged from these studies were: the hydrogen bond or electrostatic site to interact with the nitrogen atom of cocaine, hydrophobic pocket to accommodate the benzoyl group and the hydrogen bond interaction with the ester moiety. However, it was found that the 2β–carbomethoxy ester is not required for potent binding.[94, 95] It was also established that the configuration of cocaine and its analogues is fundamental for binding with high affinity. Moreover, the tropane ring can be replaced by a piperidine ring without significant loss of the binding potency.[96]

A variety of compounds have been evaluated as dopamine uptake inhibitors over the past several years. Five broad categories based on their structure are:

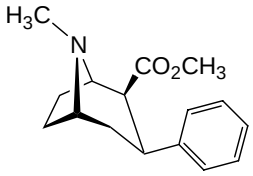
1.) 3-Phenyl tropane analogues (**7**)

2.) GBR related compounds (**6**)

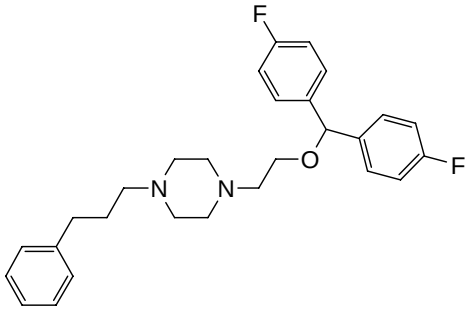
3.) Benztropine analogues (**8**)

4.) Methylphenidates (**9**)

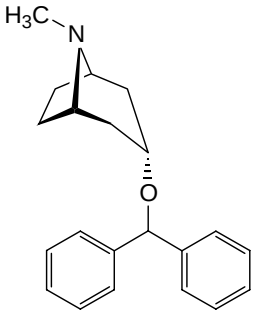
5.) Mazindol analogues (**10**)



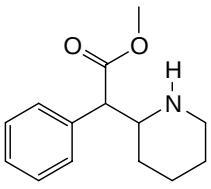
(**7**)



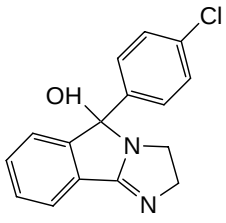
(**6**)



(**8**)



(**9**)

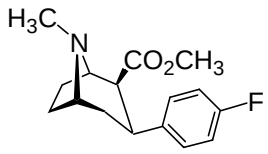


(**10**)

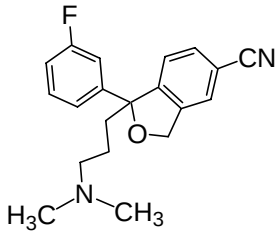
Although almost all of the above analogues have high affinity for the neurotransporters, animal studies have demonstrated that they are not self administered. Many of these compounds have been explored as tools for understanding the underlying neural mechanisms for the reinforcing actions of cocaine. The 3-phenyltropane compounds (**7**) have received paramount attention in this regard and have shown increasing promise as pharmacotherapeutics. They have been the focus of many drug discovery efforts over the past several years. The detailed SAR of this series will be discussed in the following text.

1.7 Binding Affinity and Inhibition Constant

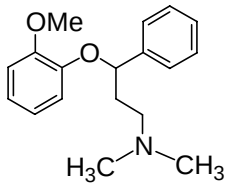
The drugs are evaluated for their potency by the value of their binding affinity to a specific transporter. These values are typically expressed in terms of IC_{50} or K_i. The value IC_{50} is the concentration at which the compound is needed to displace 50% of the bound radio-labeled ligand.[97] The radio-labeled ligands used, usually show high affinity for the targeted transporter. For example, [^{3}H]WIN-35,428, [^{3}H]citalopram and [3H]nisoxetine are used for the dopamine, serotonin and norepinephrine transporters respectively.



WIN 35,428



Citalopram



Nisoxetine

K_i is the inhibition constant and is related to IC_{50} by the following equation-

$$K_i = \frac{IC_{50}}{[^3H]/ K_d+1}$$

$[^3H]$ is the concentration of the radio-labeled ligand used and K_d is the dissociation constant of the radio-labeled ligand previously determined for the specific transporter.[98] Several factors can affect the IC_{50} values according to experimental conditions which include the type and amount of radio-labeled ligand, state of tissue (fresh or frozen), buffer, incubation time, and protein content. Therefore, K_i offers a better comparison of data since it takes into account the concentration and dissociation constant of the radio-labeled ligand and the IC_{50} value for the compound. [99]

1.8 Structure Activity Relationship Studies of 3-Phenyltropanes

Initial studies done for the synthesis of pharmacotherapeutics for cocaine abuse were based on derivatives of cocaine itself. Studies done by the Clark group resulted in the development of WIN-35,065-2 (**7**) where the benzoyl ester was replaced by a phenyl group attached directly to the tropane ring.[100] WIN-35,065-2 (IC_{50} = 23nM) was found to be four times more potent than cocaine (IC_{50} = 89nM) at the dopamine transporter and it provided a new molecular template for investigating the pharamacological properties of compounds related to cocaine.[101]

WIN-35,065-2 has four sites of asymmetry and eight possible isomers. All probable isomers were synthesized and analyzed for dopamine transporter binding, locomotor activity and

drug discrimination properties.[102] It was found that the 1*R* isomer is considerably more potent than the 1*S* isomer. These reports also demonstrated that the relative stereochemistry at the 2- and 3-position and the absolute configuration of the 3-phenyltropanes are important factors to dopamine transporter binding.

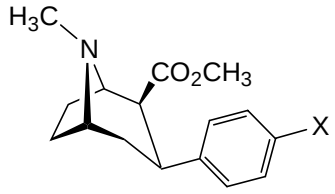
Early structure activity relationship work on 3-phenyltropanes examined substitution at the 4′-position as it plays a critical role in enhancing dopamine transporter affinity. The 4′-fluoro, 4′-chloro, 4′-methyl, 4′-iodo, 4′-ethylene, 4′-acetylene analogues of WIN-35,065-2 (**11a-f**) were found to have high affinities (K_i values less than 2 nM) at the dopamine transporter (Table 1).[103] Derivatives such as 4′-hydroxy (**11i**), 4′-nitro (**11g**), 4′-methoxy (**11j**), and 4′-amino (**11h**) exhibited IC_{50} values between 2 and 12 nM at the dopamine transporter (Table 1). Various heterocycles were also examined at the 4′- position and were found to exhibit moderate affinity for the dopamine transporter.[104] An interesting feature of these analogues was that they were much more selective for the serotonin transporter than the dopamine and norepinephrine transporters.

The 3′-substituents of WIN 35,065-2 (**7**) were synthesized and analyzed for their binding affinities.[105] It was found that 3′-substitution does not affect the dopamine transporter binding affinity as significantly as substitution at the 4′-position. For example, addition of halogens (F, Cl, Br, I), thiophene, furanyl and phenyl groups at the 3′-position of WIN-35,065-2 yielded analogues which were only four- to nine-fold more potent than cocaine.[106]

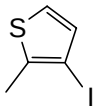
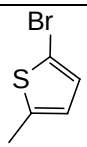
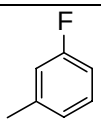
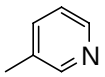
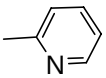
Disubstituion at the 3′, 4′-positions of WIN-35,065-2 was inspected to perceive the effects on the dopamine transporter and this series of compounds has provided some of the most potent 3-phenyltropanes to date.[107] Combinations of 3′- and 4′-chloro, -bromo, -iodo, -fluoro, or

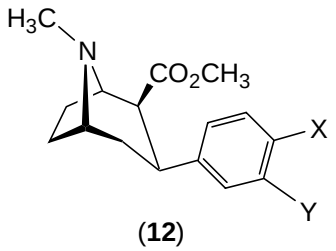
–methyl (**12 a-m**) groups at the 3′, 4′-positions of the phenyl group furnished compounds with subnanomolar affinities at the dopamine transporter (<2nM). [108]

Table 1. DAT Binding affinity of 4′-substituted analogues of WIN 35065-2 in terms of IC_{50} values.



(**11**)

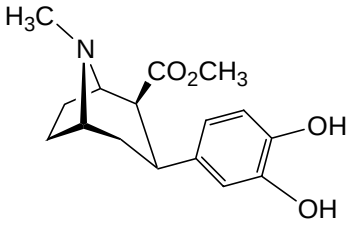
IC_{50} < 2nM		IC_{50}=2-12 nM		IC_{50}=12-30 nM		IC_{50}=30-200 nM	
entry	X	entry	X	entry	X	entry	X
a	CH_3	**g**	NO_2	**m**	CF_3	**s**	$NHCOCH_3$
b	Cl	**h**	NH_2	**n**	c-CH═CHCH$_3$	**t**	$NHCO_2C_2H_5$
c	Br	**i**	OH	**o**		**u**	$CH(CH_3)_2$
d	I	**j**	OCH_3	**p**		**v**	$CH_2CH═CH_2$
e	-CH═CH$_2$	**k**		**q**		**w**	
f	-C≡CH	**l**		**r**		**x**	



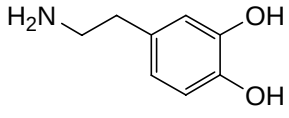
(**12**)

	X, Y		X, Y
a	NH_2, I	**h**	Br, I
b	Cl, Cl	**i**	I, Cl
c	Cl, CH_3	**j**	I, Br
d	Cl, Br	**k**	I, I
e	Cl, I	**l**	CH_3, CH_3
f	Br, Cl	**m**	F, CH_3
g	Br, Br	**n**	NH_2, Br

Although the halogens are well tolerated at the dopamine transporter, there is a limited tolerance for the hydroxyl group. The monosubstituted 3′- and 4′- hydroxyl derivatives exhibited dopamine transporter binding affinities around 12 nM whereas the 3′, 4′-dihydroxy analogue (**13**) was found to be 113-fold less potent at the dopamine transporter.[109] The catechol derivative (**13**) was prepared to determine if the aryl group of phenyltropanes interacted with the dopamine transporter in a similar manner as the 3, 4-dihydroxylphenyl group of dopamine (**2**). The low binding affinity of **13** suggests that dopamine does not occupy the same binding site on the dopamine transporter as the 3-phenyltropanes.

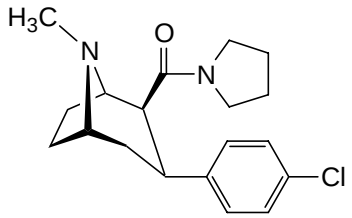


(**13**)

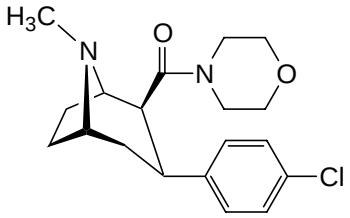


Dopamine (**2**)

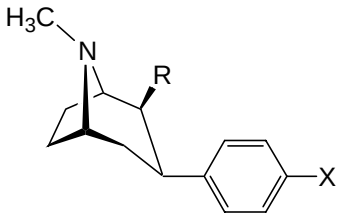
Structural modifications on various 2β-derivatives have received much more attention than the 2α-derivatives since they were found to be significantly more potent at the dopamine transporter.[102] Broad tolerance for a diverse set of amides at the 2β-position of 3β-phenyltropanes is evident through the variety of analogues which are highly potent and selective for the dopamine transporter. The tertiary amides were in general more potent than the 2β-secondary amides.[110, 111] Two noticeable examples are the compounds **14** and **15**. 2β-Alkyl and 2β-alkenyl 3-phenyltropnes were also found to have high affinities at the dopamine transporter (**16a-d**). [112-114]



(**14**)



(**15**)

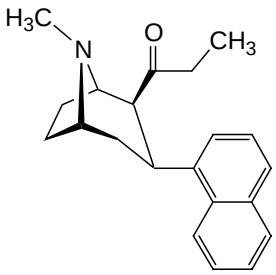


(**16**)

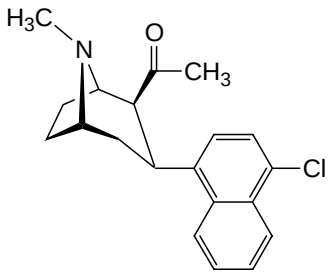
a, R= -$(CH_2)_2CH_3$, X=H
b, R= -CH=CH-Cl, X=Cl
c, R= -CH=CH-C_6H_5, X=Cl
d, R= -CH=CH-CH_2-OH, X=H

Various 2β-ketones were synthesized and evaluated for their potencies at the monoamine transporters.[115-118] The 2β-propanoyltropanes (**17**) and the 3β-4′-(2-naphthylphenyl)-2β-acetyl (**18**) were found to be highly potent with IC_{50} values of 0.15 nM and 0.28 nM, respectively. A

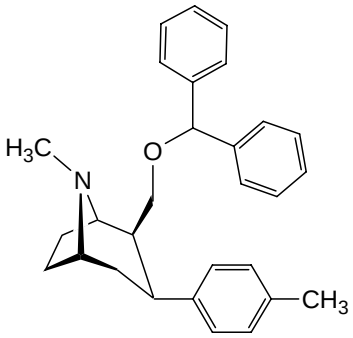
series of 2-diarylmethoxy tropanes also displayed high binding affinities and the unsubstituted analogue **19** had the highest potency for the dopamine transporter.[119]



(**17**)

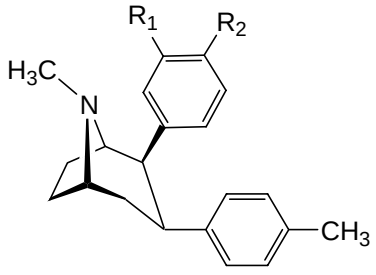


(**18**)



(**19**)

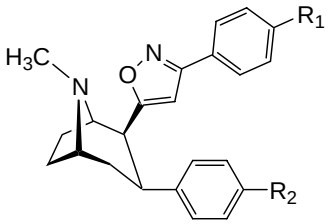
In order to further define the structural requirements at the 2-position in a better way, modifications were done by replacing the carbomethoxy group with substituted aromatic rings. The resulting compounds (**20a-d**) displayed high dopamine transporter affinities and selectivities in general with **20a** having an IC_{50} value of 1.96 nM at the dopamine transporter.[120] However, a compound with a 2-(3, 4-dimethoxyphenyl) group (**20d**) displayed a 10-fold decrease in affinity at the dopamine transporter but improved selectivity over the serotonin and norepinephrine transporters.



(**20**)

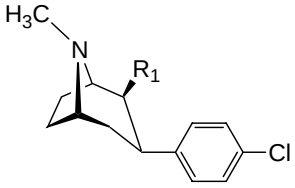
a, R_1=H, R_2=H
b, R_1=H, R_2=CH_3
c, R_1=H, R_2=OCH_3
d, R_1=OCH_3, R_2=OCH_3

The bioisosteric replacement of the 2β-carbomethoxy group with various heterocyclic groups resulted in a class of compounds (**21a-d**, **22a-d**) with DAT affinities ranging from 0.5-26 nM.[121-123] In all cases, compounds with a 3β-(4-methylphenyl) group were less potent at the dopamine transporter than compounds having a 3β-(4-chlorophenyl) group. Although in general, this series of compounds displayed high potencies and selectivities for the dopamine transporter, some compounds appear to have unique pharmacological profiles in vivo. Compounds **21b** and **21c** do not produce locomotor stimulation in mice despite having IC_{50} values of 8.74 nM and 13 nM respectively at the dopamine transporter. This trend has also been observed for other classes of dopamine transporter uptake inhibitors and requires further investigation.[124]

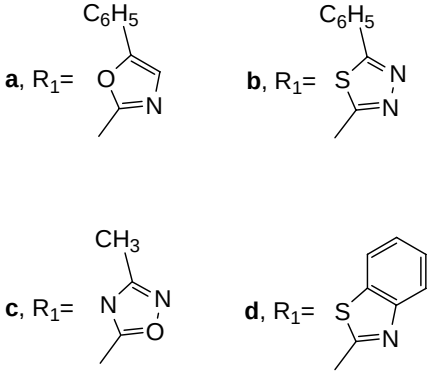


(**21**)

a, R_1=H, R_2=Cl
b, R_1=CH_3, R_2=CH_3
c, R_1=Cl, R_2=CH_3
d, R_1=CH_3, R_2=Cl

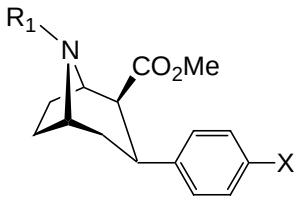


(**22**)



Exchanging the methyl group on the tropane nitrogen with allyl (**23a**), phenylpropyl (**23b**), iodopropenyl (**23c**) showed little effect on dopamine transporter binding affinity.[125-127] *N*-Substituted derivatives **23d** and **23e** retained high affinity at the DAT and even analogues with bulky groups like phthalimido (**23f**, **23g**) were well tolerated.[128, 129] This series of *N*-substituted 3-phenyltropanes was easy to synthesize and has led to the development of a number of tools to

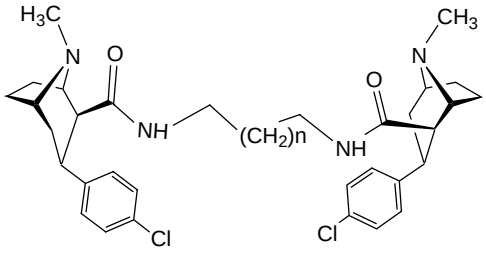
study transporter occupancy and function. Some analogues where R_1 is $^{11}CH_3$ and $CH_2CH_2CH_2{}^{18}F$ have been developed as positron emission tomography (PET) ligands.[129]



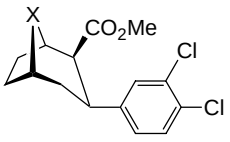
(**23**)

a, R_1=CH_2CH=CH_2, X=F
b, R_1=$CH_2CH_2CH_2$-C_6H_5, X=F
c, R_1=CH_2CH=CH-I, X=F
d, R_1=$CH_2CH_2CH_3$, X=I
e, R_1=CH_2CH_2-F, X=I
f, R_1=$(CH_2)_4$-NPht, X=I
g, R_1=$(CH_2)_8$-NPht, X=I

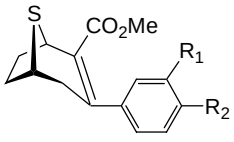
A series of bivalent ligands were synthesized having amide linkers separated by spacers of 3 to 8 methylene units (**24a-d**).[130] The order of potency increased with increasing spacer lengths. The effect of replacement of the 8-aza group on 3-phenyltropanes was investigated and it was discovered that 8-carba (**25a**),[131] 8-oxa (**25b**)[131] and 8-thia (**25c**)[132] groups did not alter the dopamine transporter affinity significantly. Flattening the tropane ring by introduction of a 2, 3-double bond increased dopamine transporter selectivity over the serotonin transporter.[132] The 4′-substituent on the 3-aryl group affects the dopamine transporter affinity. Replacement of 4′-chloro (**26a**) with 4′-bromo (**26b**), 4′-iodo (**26c**), 3′, 4′-dichloro (**26d**) yielded compounds with enhanced affinity at the dopamine transporter.



(**24**)
a, n=1
b, n=2
c, n=4
d, n=6



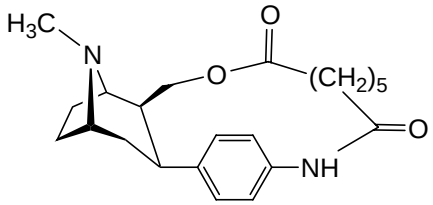
(**25**)
a, X=CH2
b, X=O
c, X=S



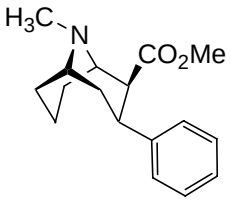
(**26**)
a, R_1=H, R_2=Cl
b, R_1=H, R_2=Br
c, R_1=H, R_2=I
d, R_1=Cl, R_2=Cl

Conformationally constrained analogues can provide better insights regarding the modes of ligand/receptor interactions. A series of tropane macrocyclic derivatives having distinct size, hydrophobicity, and electronic properties were synthesized and analyzed for their transporter binding affinities.[133] One of the most potent ligands at the dopamine transporter was found to be **27** with IC_{50} value of 3.8 nM.[133]

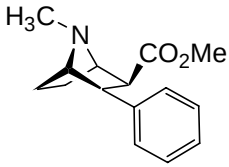
Modifications made to the basic tropane framework resulted in compounds with only moderate or reduced affinity at the DAT. Both expansion (**28**)[134] and reduction (**29**)[135] of the tropane ring by one methylene unit resulted in derivatives with dramatically reduced affinities.



(**27**)



(**28**)

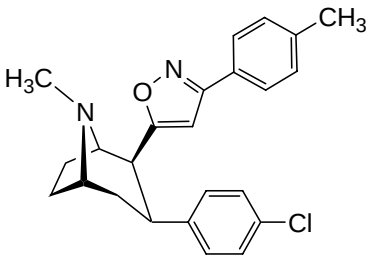


(**29**)

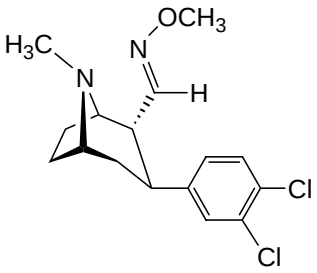
A large number of 3-phenyltropanes have been synthesized and analyzed for the purpose of selectively modulating the dopamine transporter and consequently provide leads for medications for cocaine abuse. Analogues have been developed with high affinity for all three transporters and many of these have been evaluated in locomotor activity and cocaine discrimination studies. Almost all the compounds investigated show reduction of cocaine self-administration in both rat and monkey.[136, 137] Some analogues are in clinical or advanced pre-clinical studies for treating cocaine addiction.[138]

Although no compound has been shown to be a useful pharmacotherapeutic for cocaine abuse, the development of tropane-based compounds has led to some promising leads for

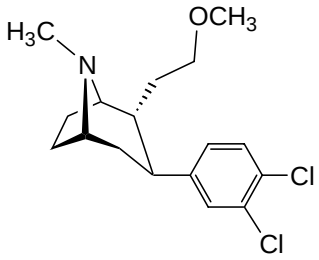
treatment of substance abuse (RTI-336, **30**),[139] Parkinson's disease (Brasofensine, **31**)[140-142] and obesity (Tesofensine, **32**).[143]



(RTI-336, **30**)



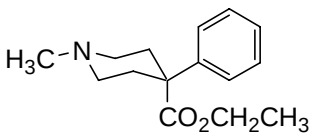
(Brasofensine, **31**)



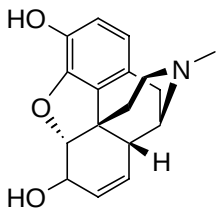
(Tesofensine, **32**)

1.9 Structure Activity Relationship Studies of Meperidine Analogues

Similarities between the symptoms of meperidine (**33**) intoxication and that of cocaine have been well documented.[144,145] Meperidine is an atypical μ-opioid receptor agonist and chronic exposure to it can produce central nervous system stimulant effects, hyperflexia and increased susceptibility to startle.[146] These effects are generally specific to meperidine and usually are not observed with other μ-opioid receptor agonists such as morphine (**34**).[147]

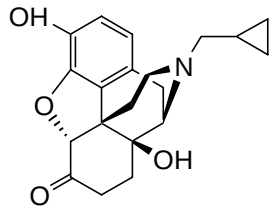


(Meperidine, **33**)



(Morphine, **34**)

Meperidine shares numerous structural features with cocaine and the phenyltropane analogues of cocaine.[148] The piperidine ring is a common ring structure in both meperidine and cocaine congeners. Furthermore, *N*-methyl group occurs in meperidine as well as cocaine and the phenyltropane series of compounds. The phenyl ring attached to the 3-position on the tropane ring of the WIN 35065-2 (**7**) is equivalent to the phenyl substituent on the 4-position of the piperidine ring of meperidine. These common structural features between meperidine and the cocaine congeners combined with the unique pharmacological profile of meperidine suggested that the non-opioid actions of meperidine could be due to a cocaine-like pharmacological action.[148] However, in cocaine discrimination studies, neither meperidine nor morphine alone produced a substitution for cocaine in animals trained to distinguish cocaine from saline.[148] Nevertheless, pretreatment with 0.1 mg/kg naltrexone (**35**) improved the effectiveness of meperidine and produced cocaine-like discriminative stimulus effects in monkeys, whereas morphine was inactive under similar conditions. Naltrexone alone has not been known to substitute for cocaine.[148]

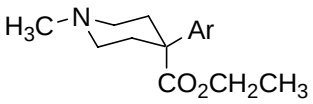


(Naltrexone, **35**)

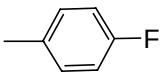
In further studies, both cocaine and meperidine inhibited [^{3}H]dopamine uptake with comparable potencies. Morphine did not inhibit [^{3}H]dopamine uptake, indicating that the effect of meperidine was not via a classic μ-opioid receptor agonist. This data suggests that these actions

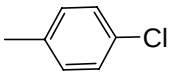
of meperidine which are atypical of opioids are due to activity at the dopamine and serotonin transporters. Moreover, meperidine appears to interact primarily with the high-affinity component of the dopamine transporter. In the absence of other known dopamine uptake inhibitors that can discriminate between high-affinity and low-affinity sites at the dopamine transporter, the data from meperidine binding provides valuable information. The high-affinity component of the response curve of meperidine resembled the high-affinity component of the inhibition of dopamine uptake produced by cocaine and this suggests that this high-affinity component may be the site of importance for the production of cocaine's behavioral effects.[148]

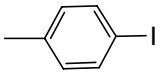
To further explore the selectivity for the high-affinity cocaine binding site, a series of meperidine analogues with variations at the aromatic ring were synthesized and analyzed by Trudell et al (**36a-f**).[149] Compounds that could allow discrimination of high- and low-affinity sites at the dopamine transporter would be useful probes to investigate the subjective effects of cocaine.

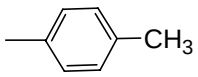


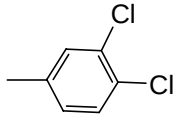
(**36**)

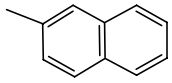
a, Ar= 

b, Ar= 

c, Ar= 

d, Ar= 

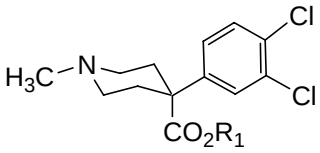
e, Ar= 

f, Ar= 

All the analogues (**36a-f**) exhibited marked increase in dopamine and serotonin transporter selectivity over μ-opioid receptors compared to meperidine ($K_{i,}$ DAT= 18 μM, $K_{i,}$ SERT= 0.41 μM). The 2′-naphthyl derivative (**36f)** was 60-fold more potent at the serotonin transporter than mepridine and exhibited the greatest selectivity for the serotonin transporter over the μ-opioid receptors. The 3, 4-dichloro analogue (**36e**) was found to be the most potent ligand of the series at the dopamine transporter (K_i = 0.125 μM) and displayed the highest selectivity for the dopamine transporter over that of μ-opioid receptors. Both **36e** and **36f** proved to be important ligands for differentiating between the high- and low-affinity components at the dopamine transporter as well. All the compounds in the series exhibited reduced affinity for μ-opioid receptors relative to the parent compound, meperidine. In general, the SAR of these meperidine derivatives at the dopamine transporter exhibited a similar trend to that of the phenyltropanes. The naphthyl and the 3,4-dichloro derivatives were also tested for their locomotor-stimulant activity in mice but they did not produce any locomotor effects or substitute for cocaine in drug discrimination studies. This could be attributed to the fact that both these compounds still exhibited considerable μ-opioid effects (K_i = 2.04 μM for **36e** and K_i = 2.03 μM for **36f**).[149]

As the 3, 4-dichlorophenyl group proved to be an important structural moiety for recognition at the dopamine transporter; further SAR studies were done using **36e** as a molecular scaffold. A series of modified ester and *N*-substituted analogues was synthesized and evaluated for dopamine and serotonin transporter binding affinities.[150] In general the ester analogues (**37a-h**) demonstrated almost equal binding affinities at the serotonin transporter relative to **36e**. The small-branched esters (**37c** and **37e**) exhibited equivalent affinity to the ethyl ester **36e** but long-chain esters (**37d** and **37f**), and sterically demanding esters (**37g** and **37h**), displayed poor

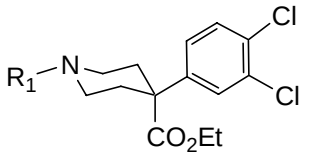
binding affinities at the dopamine transporter. This trend was unlike the 3-phenyltropanes that can tolerate a variety of esters at the 2-position of the tropane system. In the meperidine analogues (**37a-h)**, a slight alteration of the ester group resulted in a noteworthy loss of affinity at the dopamine transporter. Conversely, the increase in the size of the ester chain of **36e** led to an increased affinity at the serotonin transporter. Particularly, the benzyl ester (**37h**) proved to be the most potent and selective meperidine-related ligands at the serotonin transporter.[150]



(**37**)

a, R_1=CH_3
b, R_1=$CH_2CH_2CH_3$
c, R_1=$CH(CH_3)_2$
d, R_1=$CH_2(CH_2)_2CH_3$
e, R_1=$CH(CH_3)CH_2CH_3$
f, R_1=$CH_2(CH_2)_3CH_3$
g, R_1=$CH_2CH_2CH(CH_3)_2$
h, R_1=$CH_2C_6H_5$

Substituting the *N*-methyl group with various *N*-alkyl, *N*-alkyl-aryl, *N*-alkenyl and *N*-alkynyl groups led to decreased affinities at the dopamine transporter. The least potent compounds of the series were the *N*-benzyl **38a** and the *N*-chloro-propenyl **38n** congeners.[150]

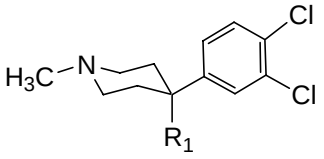


(**38**)

a, R_1=CH_2Ph
b, R_1=$CH_2(CH_2)_2Ph$
c, R_1=CH_2(*E*)-CH=CHPh
d, R_1=CH_2CH_3
e, R_1=$CH_2CH_2CH_3$
f, R_1=$CH_2C{\equiv}CH$
g, R_1=CH_2-*c*-Pr
h, R_1=$CH_2CH_2CH_2Cl$

The SAR of the meperidine derivatives was further surveyed by converting the ester moiety into different functional groups. Conversion into the ketones (**39a** and **39b**) resulted in

analogues with reduced affinity for both the dopamine and the serotonin transporters. The alcohol congeners (**39c** and **39g**) exhibited decreased dopamine transporter binding but displayed equipotent-binding affinity at the serotonin transporter relative to **36e**. The 4-vinyl (**39d**) and 4-ethyl (**39e**) derivatives were the most potent ligands of this series at the serotonin transporter. This study shows that the ester moiety is not a required group for high affinity binding and a variety of functionalities can be tolerated at the 4-position of the meperidine analogues.[150]



(**39**)

a, R_1=C(O)CH_3
b, R_1=C(O)Ph
c, R_1=C(OH)CH_3
d, R_1=CH=CH_2
e, R_1=CH_2CH_3
f, R_1=CH_2OAc
g, R_1=CH_2OH

1.10 Design Strategy for Novel Tropane Analogues

In recent reports it has been demonstrated that meperidine can fully substitute for cocaine in squirrel monkeys under certain specific conditions.[148] SAR studies of various aryl and *N*-substituted meperidine analogues has revealed that these compounds have considerably significant activity at the neural transporters and almost all the congeners displayed an inherent serotonin transporter selectivity over the dopamine transporter. Different esters and various functional groups were also well tolerated and exhibited the same trend of selectivity as other meperidine analogues.

In the last decade, a lot of research was focused on synthesizing only dopamine transporter selective compounds, which ultimately did not provide a viable therapeutic for drug abuse. However, now it is well established that cocaine is a '*dirty*' drug and interacts with all the three transporters (dopamine, serotonin and norepinephrine). The effects of the aryl substitution on the dopamine transporter affinity of the meperidine analogues paralleled the SAR of phenyltropane analogues which typically exhibit high dopamine transporter potency and selectivity. The main goals of this research were to design a series of ligands that could be equipotent for both the dopamine and serotonin transporters and provide leads for developing pharmacotherapeutics to treat cocaine abuse. It was envisioned that target compounds could be synthesized which would incorporate the rigidity of the tropane system with the design of the meperidine analogues in an attempt to increase the dopamine transporter affinity of these novel compounds.

Although SAR studies of the basic meperidine structure are well documented, no work has been carried out to identify the conformation adopted on binding to the dopamine transporter or the serotonin transporter. Meperidine has significant structural flexibility and can exist in both chair and boat conformations. It was of interest to study ring constrained analogues in which the important pharmacophore was held rigid to gain better insights into the conformation adopted while binding to the transporters. Moreover, almost all the meperidine analogues showed μ-opioid receptor activity and since none of the analogues tested, produced locomotor effects or substituted for cocaine completely in drug discrimination studies, it was suggested that the μ-opioid effects may be playing a role in their activity. Incorporating the design of the phenyltropane ring system with the meperidine structure could provide important compounds that would lack activity at the μ-opioid receptors, have a rigid conformation and could

conceivably have affinity for both the dopamine and the serotonin transporters. Affinity for the norepinephrine transporter is not preferred since it can lead to heart disorders and other cardiovascular problems. Based upon this rationale, the target molecules were designed as hybrid structures of 3β-phenyltropanes and meperidine (**Figure 3**).

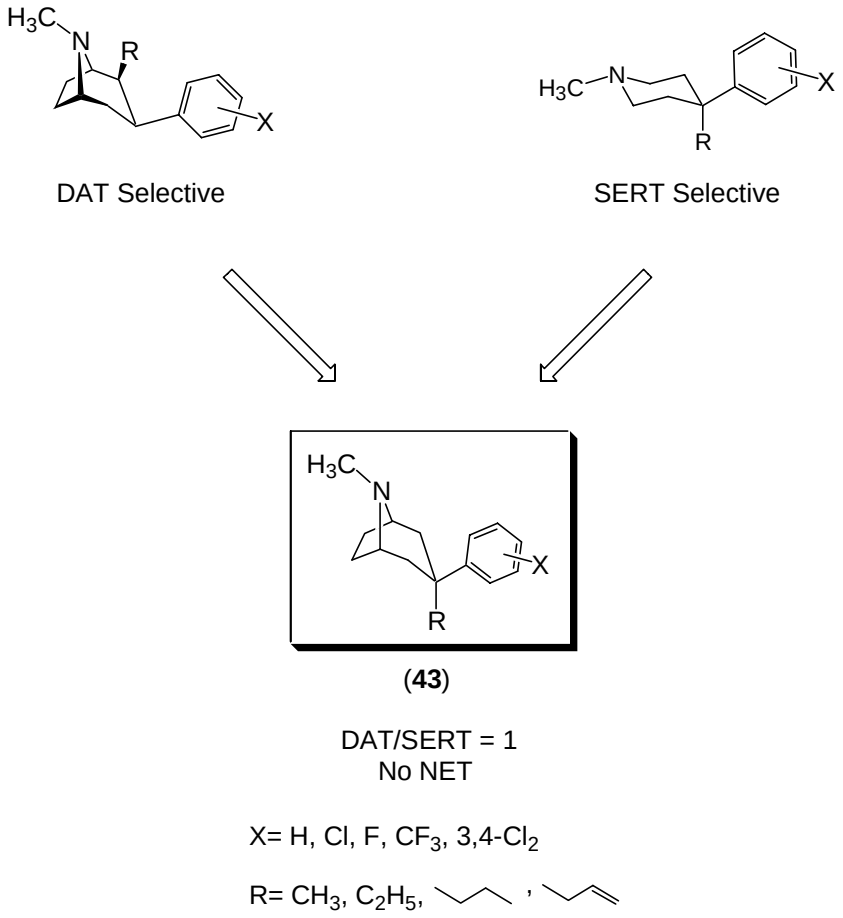
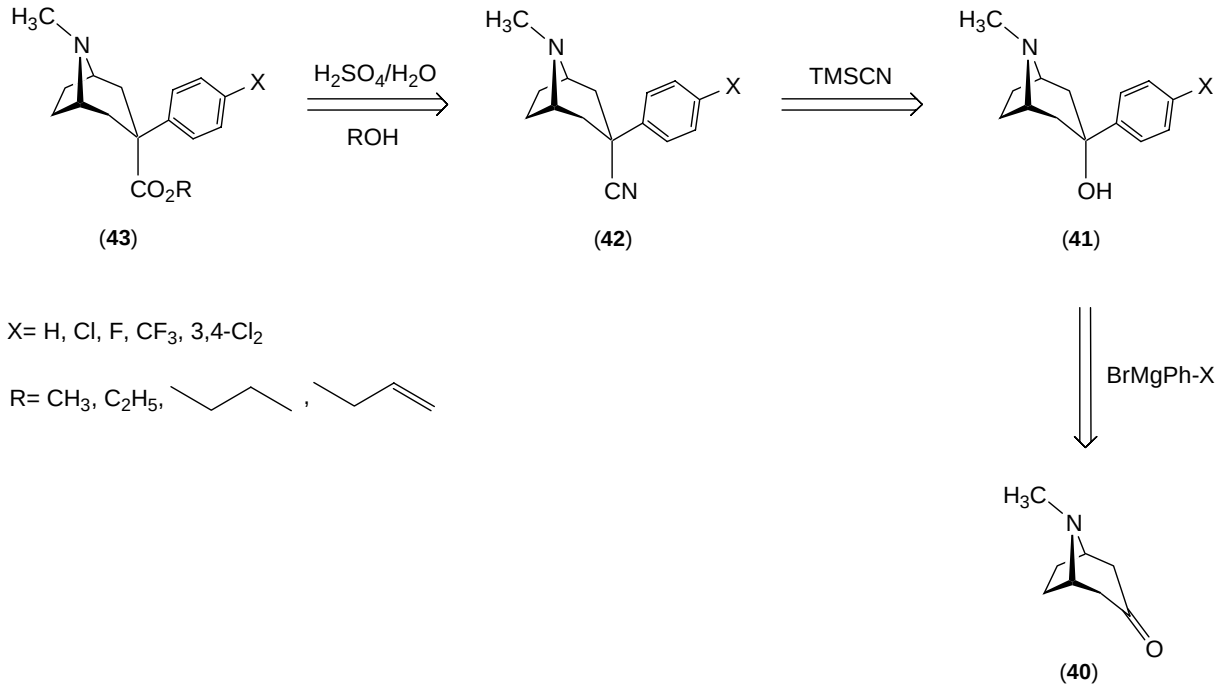


Figure 3. Target compounds as hybrid structures of 3β-phenyltropanes and meperidine.

The retrosynthetic analysis for the synthesis of the target compounds with alkyl and allyl esters is outlined in Scheme 1. The synthesis was envisaged to start from the commercially available 3-tropinone (**40**). The carbonyl group could be used in the Grignard reaction to furnish

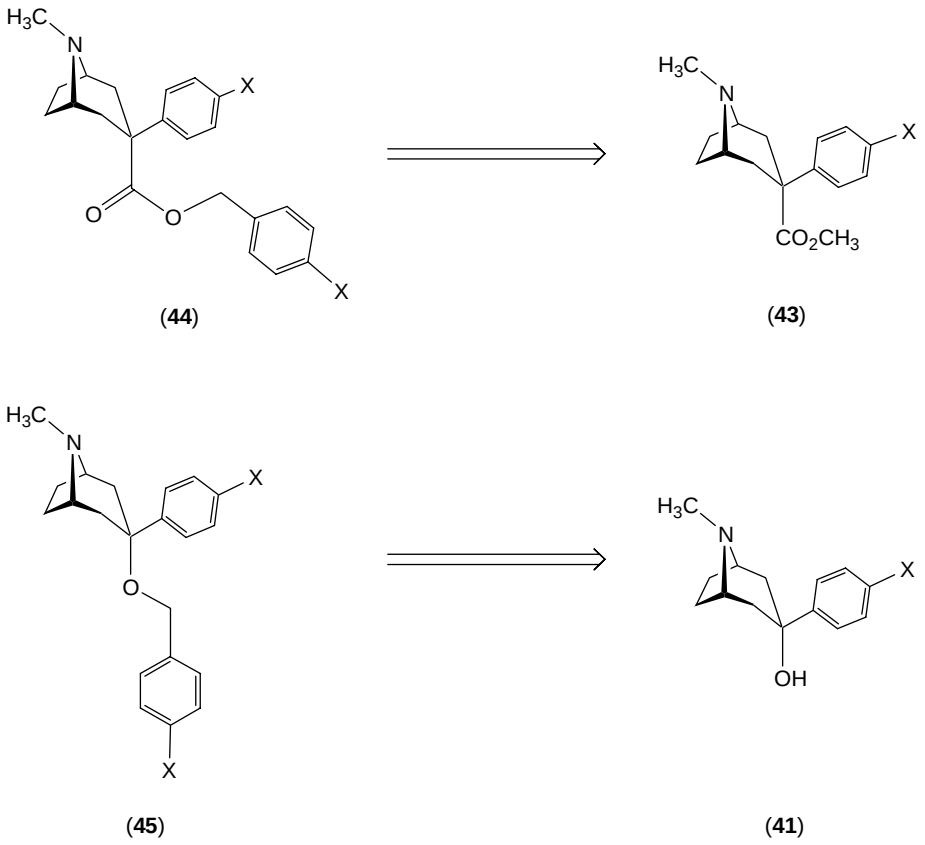
the tertiary alcohol (**41**). Functional group conversion could yield the cyano derivative (**42**). The nitrile could then be converted into the corresponding ester via a two-step reaction sequence to furnish the target products (**43**).



Scheme 1. Retrosynthetic analysis for the preparation of target molecules with alkyl and allyl esters.

Additionally, an array of benzyl esters and benzyl ethers was designed since it was previously discovered from the SAR of meperidine analogues that the benzyl group is an important structural feature for enhancing potency and selectivity at the dopamine and the serotonin transporters. The benzyl esters (**44**) could be prepared from the methyl ester derivative

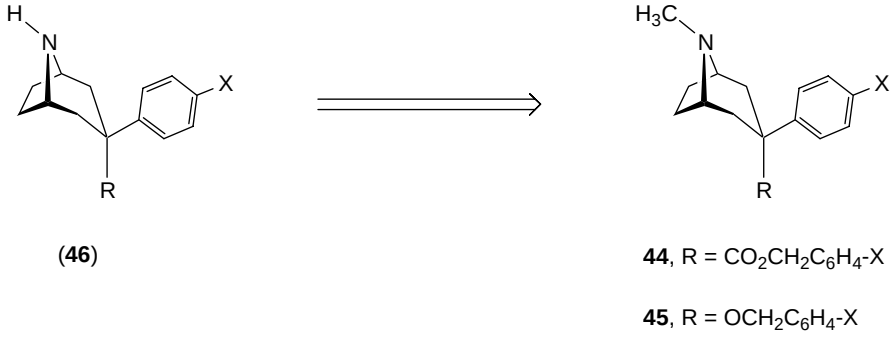
of **43** via *N*-heterocyclic carbene catalyzed transesterification method (Scheme 2). The benzyl ethers **45** could be prepared from direct alkylation of **41** (Scheme 2).



Scheme 2. Retrosynthetic analysis for the preparation of target molecules with benzyl esters and benzyl ethers.

From previous studies of meperidine derivatives it was found that the *N*-H group is a key structural feature for the molecular recognition at the serotonin transporter as well as for differentiating between the serotonin and the dopamine transporters. This suggested that the *N*-H

analogues of the target compounds could exhibit potent and selective serotonin transporter affinity. Analogues with high serotonin transporter affinity and selectivity could then be developed as potential serotonin selective reuptake inhibitors (SSRIs), useful for the treatment of a variety of neurological disorders, which include depression, schizophrenia and post-traumatic stress syndrome. The retrosynthetic strategy for the synthesis of the *N*-H analogues **46** is shown in Scheme 3.



(**46**)

44, R = $CO_2CH_2C_6H_4$-X

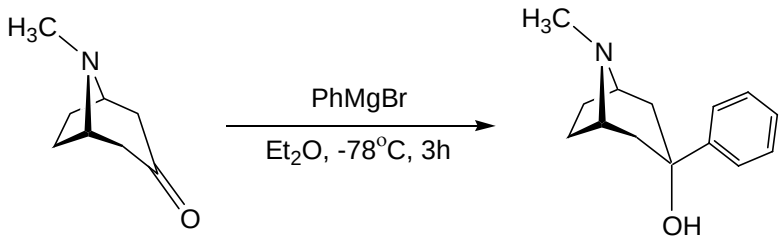
45, R = $OCH_2C_6H_4$-X

Scheme 3. Retrosynthetic analysis for the preparation of *N*-H analogues.

RESULTS AND DISCUSSION

2.1 Attempted Synthesis of 3-Aryl-3-carbomethoxytropane and its Analogues.

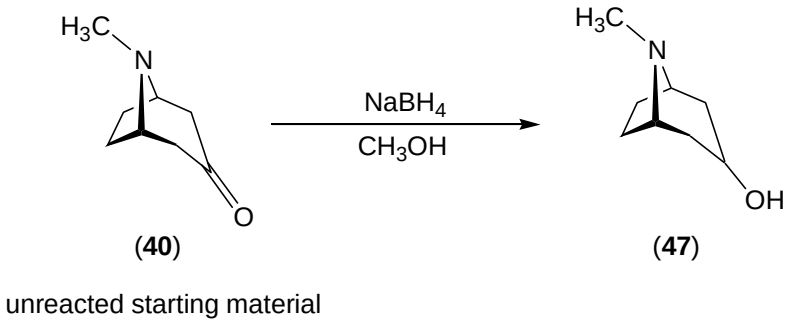
Several synthetic routes were investigated to prepare the target molecules 3-aryl-3-carbomethoxy tropane and its derivatives. The first step of the approach was to transform the commercially available 3-tropinone (**40**) into a 3-phenyl-3-hydroxytropane (**41a**). The reaction was performed by reacting the commercially available Grignard reagent, phenylmagnesium bromide in ether, with the tropinone (**40**) at -78^{o}C.[151]



(**40**) (**41a**)

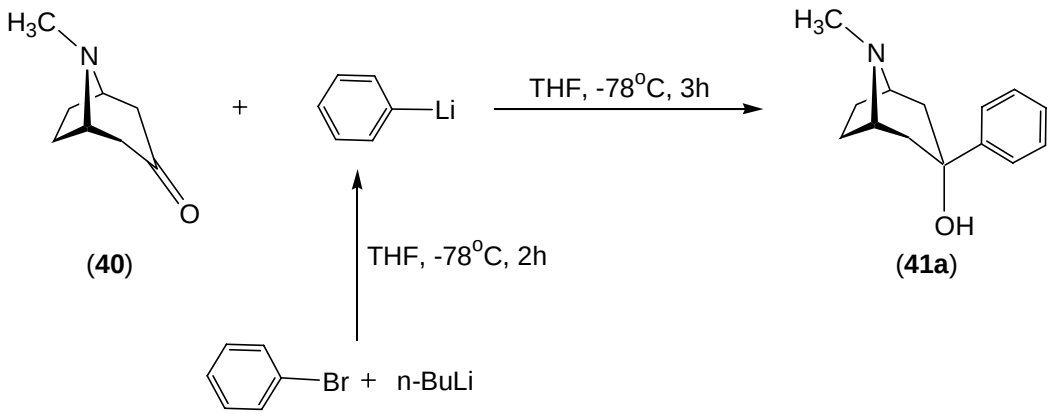
Some problems were encountered regarding the purification of the product because the starting ketone and the resulting product exhibited similar polarity in many solvent systems used for separations column chromatography. A pure product was obtained using Kuglrohr distillation apparatus in 20% yield. The Kuglrohr distillation method of separation allowed for the complete recovery of the unreacted starting material. In an attempt to increase the yield, a different reaction solvent system was utilized. It was discovered that employing tetrahydrofuran instead of diethyl ether as the reaction solvent did not improve the yield significantly. Varying the reaction conditions and temperature led to performing the reaction at reflux in tetrahydrofuran. However, only 4% product was obtained after 24 hours under these modified conditions.

Since separation of the desired product (**41a**) from tropinone (**40**) by the distillation method was efficient on a small scale only (1 gram), the need for large quantities (5-10 grams) led to exploration of a different method of separation. It was envisaged that the reduction of the unreacted tropinone in the reaction mixture to an alcohol would change the relative polarity of compounds to be separated and hence facilitate purification of the product by column chromatography (Scheme 4). This method furnished the desired product (**41a**) in 27% yield by employing mixtures of ethyl acetate, hexanes and chloroform as eluent for purification by column chromatography.



Scheme 4. Reduction of the unreacted starting material.

Since the yield of the resulting 3-phenyl-3-hydroxytropane was not very high, a more reactive aryllithium reagent was used for the transformation. To that end, *n*-BuLi (2.5 M in hexanes) and bromobenzene was used to freshly prepare phenyllithium and then add 3-tropinone to the same flask, making it a one-pot reaction. The change of reagents led to an improvement by affording the product in 38% yield (Scheme 5). Although, the improvement in the yield was modest, on a large scale it translated to a difference of grams. Therefore, freshly prepared lithium reagents were used for this and future transformations.



Scheme 5. Use of freshly prepared phenyllithium reagent for transforming 3-tropinone.

It appears that the use of *n*-BuLi displayed a positive effect on enhancing the yield of the reaction; to this end, reactivity of *n*-BuLi was investigated. *n*-BuLi exists mainly in the hexameric form in hydrocarbon solvents such as hexanes.[152] Chelating ligands such as tetramethylethylenediamine (TMEDA) can reduce the degree of aggregation of *n*-BuLi and favor the formation of monomeric solvated species thus increasing the reactivity.[153] Other reagents which can improve the reactivity of alkyllithium reagents are strong donor molecules for example hexamethylphosphorictriamide (HMPA) and *N*, *N*-dimethylpropyleneurea (DMPU)[154] shown in **Figure 4**.

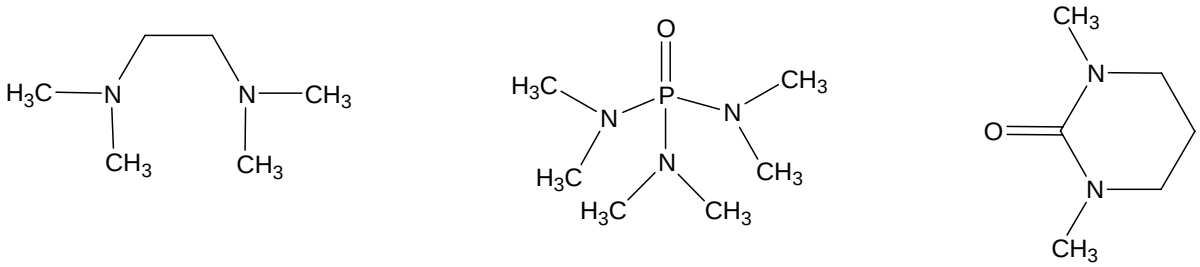
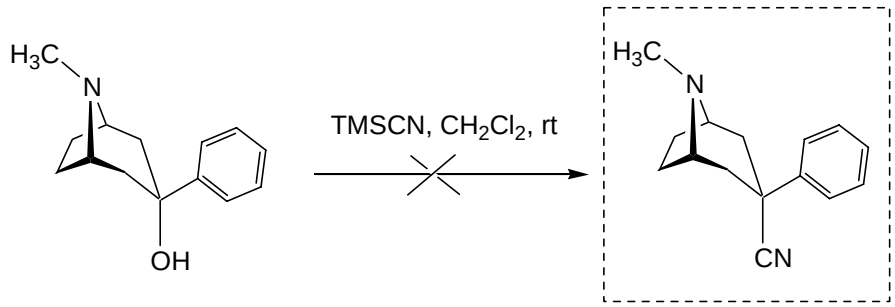


Figure 4. Structures of some chelating ligands used to enhance reactivity of the alkyllithium reagents.

TMEDA was used with *n*-BuLi to convert 3-tropinone into the desired product (**41a**) but it was discovered that it did not enhance the yield considerably.[155] Therefore, further transformations were carried out only in the presence of *n*-BuLi.

With the hydroxyl tropane **41a** in hand, the next step, functional group transformation of the hydroxyl group into the nitrile was investigated (Scheme 6).

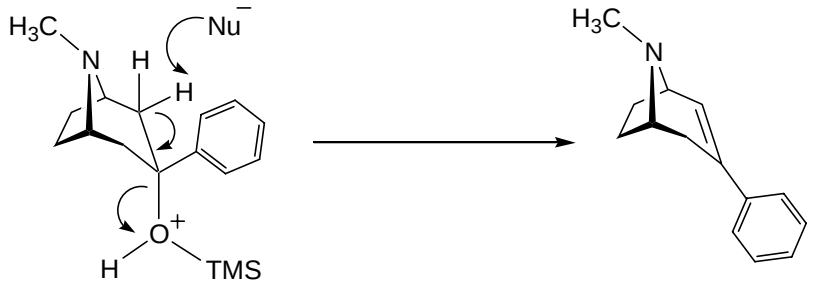


(**41a**) (**42**)

Scheme 6. Attempted functional group interconversion of the hydroxyl group to the nitrile.

Attempts to convert **41a** into **42** did not yield the desired product. A variety of reaction conditions were investigated where the use of a catalyst (zinc iodide) was employed and the temperature was lowered to -78^{o}C.[156] These changes also did not result in the formation of the cyano tropane derivative. *In situ* generation of trimethylsilylcyanide (TMSCN) was attempted by employing a mixture of sodium cyanide, sodium iodide and trimethylsilychloride and using it for the transformation of the hydroxyl group to the cyano group, but it failed to give the desired product.[157] The crude reaction mixtures from all the above attempts indicated the complete consumption of the starting material and generation of another product. An investigation conducted to identify the product revealed that β–elimination was occurring to yield **48** as the

major product (Scheme 7). Several variations of the solvent, temperature profile and reagents also resulted in the formation of the β–elimination product instead of the desired cyano tropane derivative.



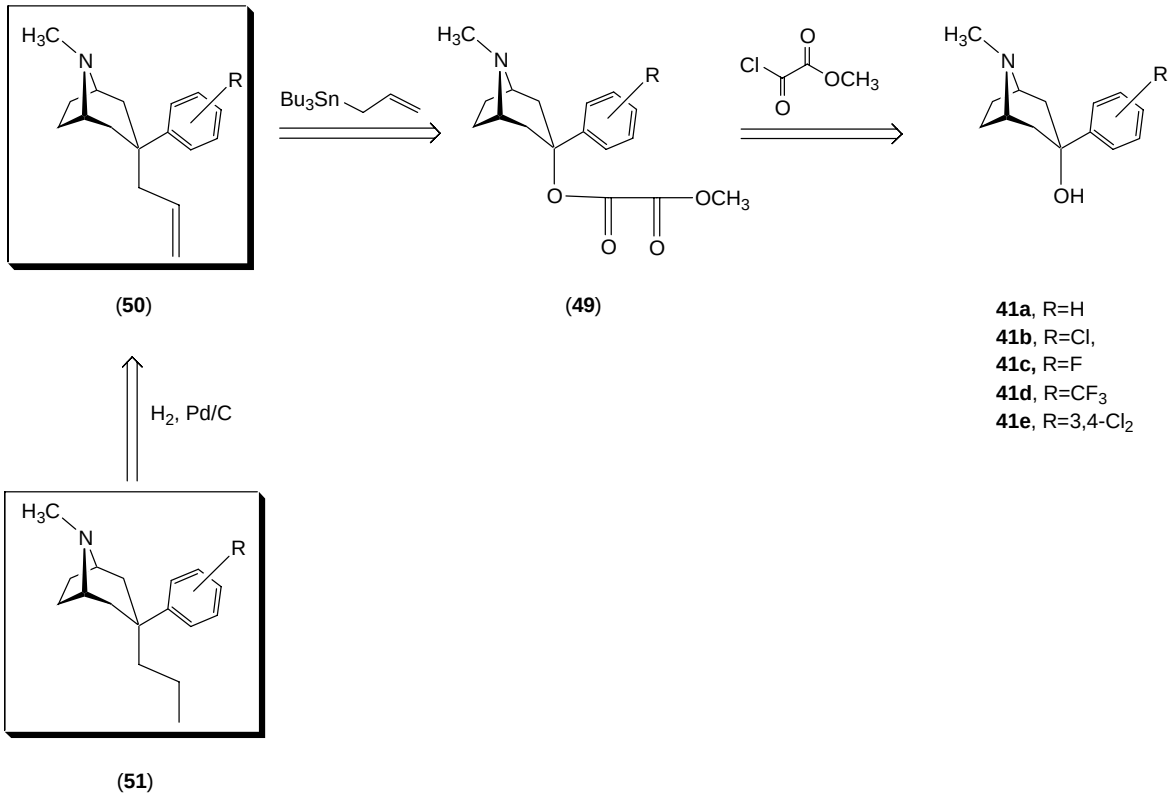
(**41a**) (**48**)

Scheme 7. Formation of the unsaturated compound via β-elimination.

2.2 Attempted Synthesis of 3-Aryl-3-propyltropane and its Analogues.

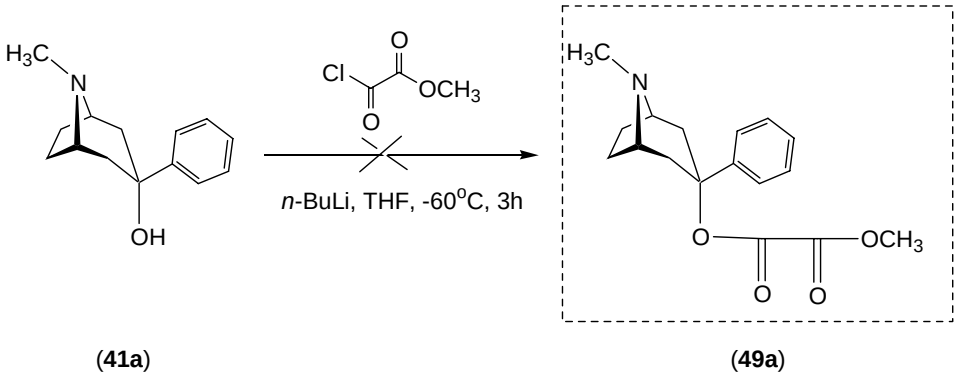
From previous SAR studies, it was known that the ester moiety is not a required structural feature for molecular recognition at the monoamine transporters and a variety of functional groups can be tolerated at the recognition site. Based on this information, another route was devised to obtain products that could be useful as ligands for both the dopamine and the serotonin transporters. Incorporation of an allyl group instead of the ester moiety was envisaged by reacting the hydroxy tropane (**41**) with methylchlorooxoacetate and treating the resulting product with tributylallylstannane (Scheme 8). The 3-aryl-3-allyl tropane derivatives

(**50**) could easily be converted to the propyl analogues (**51**) by hydrogenating the double bond thus providing a series of compounds with variations at the aryl group.



Scheme 8. Retrosynthetic analysis for the formation of 3-aryl-3-propyl-tropane analogues.

Initially, *n*-BuLi was utilized to deprotonate **41a** and then reacting with methyl oxalyl chloride to obtain the oxalate derivative **49a** in a one-pot procedure[158] (Scheme 9). After considerable experimentation with variations in temperature, time and reagent quantities, the desired product was not obtained. Alternatively, either the elimination product (**48**) or the unreacted starting material (**41a**) or a mixture of both was obtained.



(**41a**) (**49a**)

Scheme 9. Attempted functional group interconversion of the hydroxyl group into the oxalate.

2.3 Synthesis of 3-Aryl-3-methoxytropane and its Analogues.

Since any changes requiring the carbon–oxygen bond cleavage resulted in a β-elimination, efforts were redirected toward performing transformations involving the oxygen-hydrogen bond of the hydroxyl tropane (**Figure 5**).

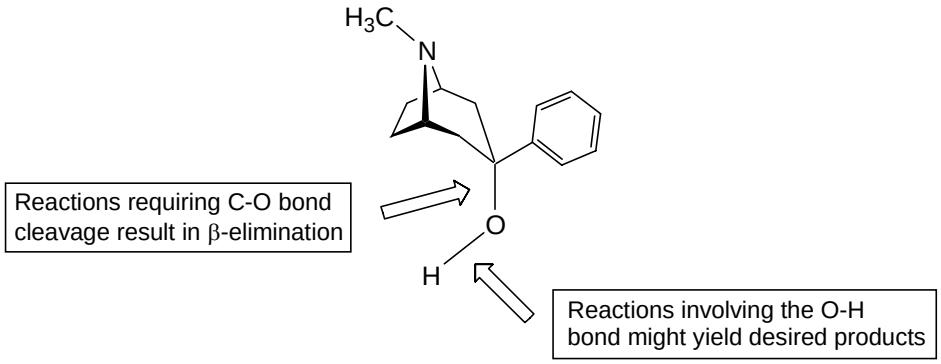
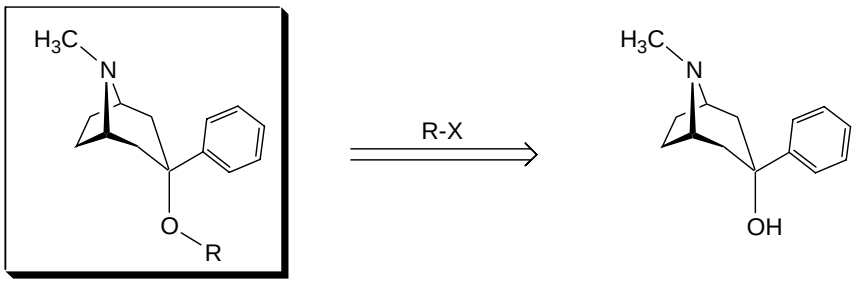


Figure 5

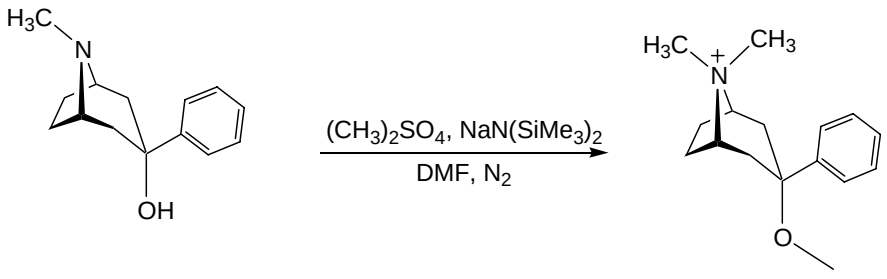
The simplest transformation to functionalize the hydroxyl group is to convert it into an ether moiety. A retrosynthetic strategy was devised to do the same, starting from the hydroxyl tropane **41a** and then synthesizing the analogues with different substituents at the aryl ring.



(**52**) (**41a**)

Scheme 10. Retrosynthetic route for the synthesis of 3-phenyl-3-methoxytropane and its analogues.

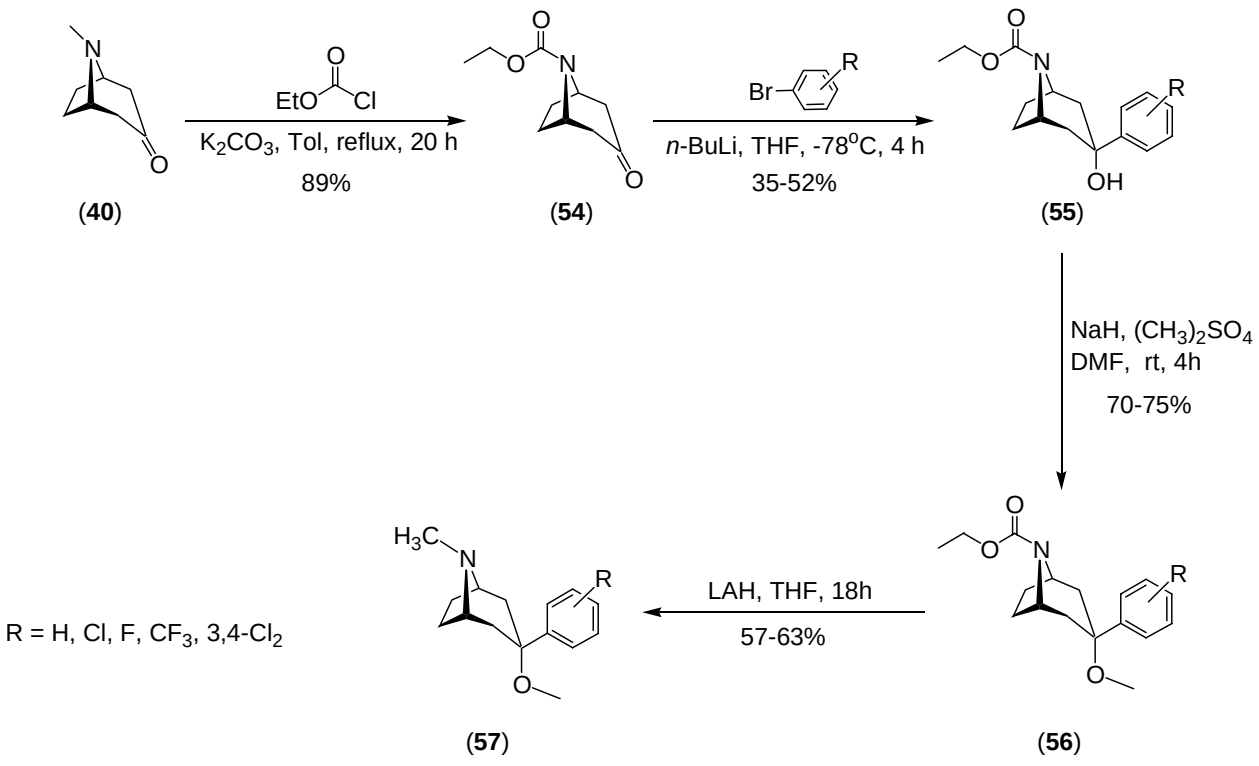
3-Phenyl-3-hydroxy tropane (**41a**) was reacted with dimethylsulphate in the presence of a base under an inert atmosphere. Analysis of the reaction mixture revealed that quarternerization of the tertiary amine had occurred and the desired product was not recovered (Scheme 11).



(**41a**) (**53**)

Scheme 11. Quarternerization of the tertiary amine.

To obtain the 3-aryl-3-methoxytropane analogues, the tertiary amine was required to be protected in order to reduce the basicity of the nitrogen of the tropane. As shown in Scheme 12, the amine of 3-tropinone was protected using ethylchloroformate. The protected tropinone (**54**) was transformed into tertiary alcohols (**55**) using *in situ* generated organolithium reagents. The 3-phenyl-3-hydroxytropane derivatives (**55**) underwent a smooth transformation into the desired methyl ethers (**56**). The protecting group was converted into the *N*-methyl group using lithium aluminium hydride reduction to yield the desired final products (**57**). Following the synthetic route in Scheme 12, the derivatives of **57** were synthesized with different halogen substituents at the 4-position of the aryl ring. Each pure analogue was then converted into the oxalate salt for biological evaluation.



Scheme 12. Synthetic route for the synthesis of 3-aryl-3-methoxytropane derivatives.

Crystallographic data for the tertiary alcohol (**55a**) was obtained to confirm the stereochemistry at the 3-position (**Figure 6**). It was revealed from the X-ray structure that the phenyl ring occupies the β-position at C3 and the hydroxyl group is in the 3α-position of the tropane ring structure. This served to unequivocally establish the relative stereochemistry of the nucleophilic addition of the phenyllithium to 3-tropinones **40** and **54**.

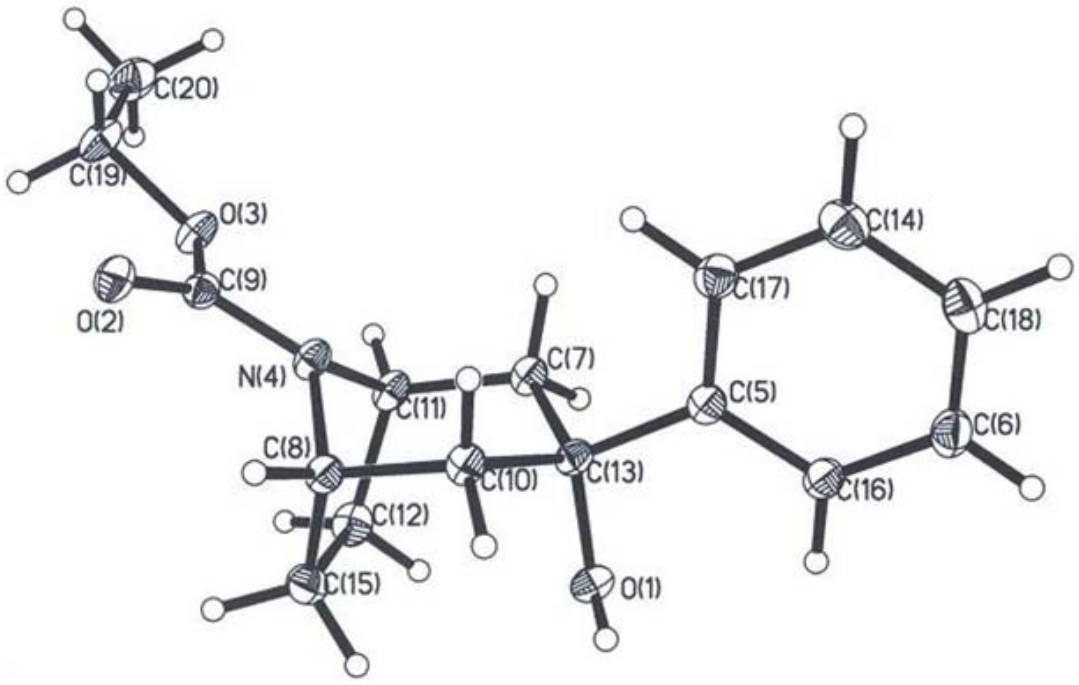
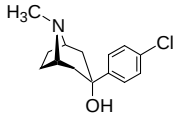
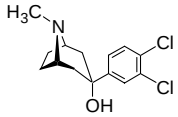
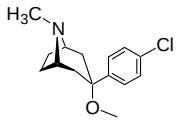
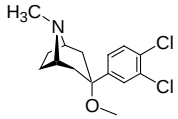


Figure 6. X-ray structure of 3β-phenyl-3-hydroxytropane (**55a**) provided courtesy of Prof. Edwin D. Stevens.

The transporter binding affinities were determined for some of the 3-aryl-3-methoxy tropane analogues (**57**) and for a few of the hydroxyl derivatives (**41**) and are depicted in Table 1. The binding affinity values were obtained by the ability of the compounds to displace bound radiolabeled ligands from rat caudate-putamen tissue. The K_i values reported in Table 1 are the inhibition constants derived from the unlabeled ligands. The binding affinities of the novel tropane analogues were determined at the dopamine transporter (DAT) by inhibition of [^{3}H]WIN- 35,428 and at serotonin transporter (SERT) by inhibition of [^{3}H]citalopram.

Table 2. In vitro data for derivatives of 3-aryl-3-methoxytropane and 3-aryl-3-hydroxytropane.

Compound[a]	[^{3}H]WIN 35428 (DAT) K_i (nM)[b]	[^{3}H]citalopram (SERT) K_i (nM)[b]	DAT/SERT
 **41b**	32,000 ± 2,000	12,000 ± 1500	2.7
 **41e**	4,120 ± 600	1,600 ± 80	2.6
 **57b**	9,600 ± 1,000	1,370 ± 130	7.0
 **57e**	900 ± 100	300 ± 60	3.0

[a] All compounds were tested as oxalate salts. [b] All the values are mean ± SEM of three experiments performed in triplicate.

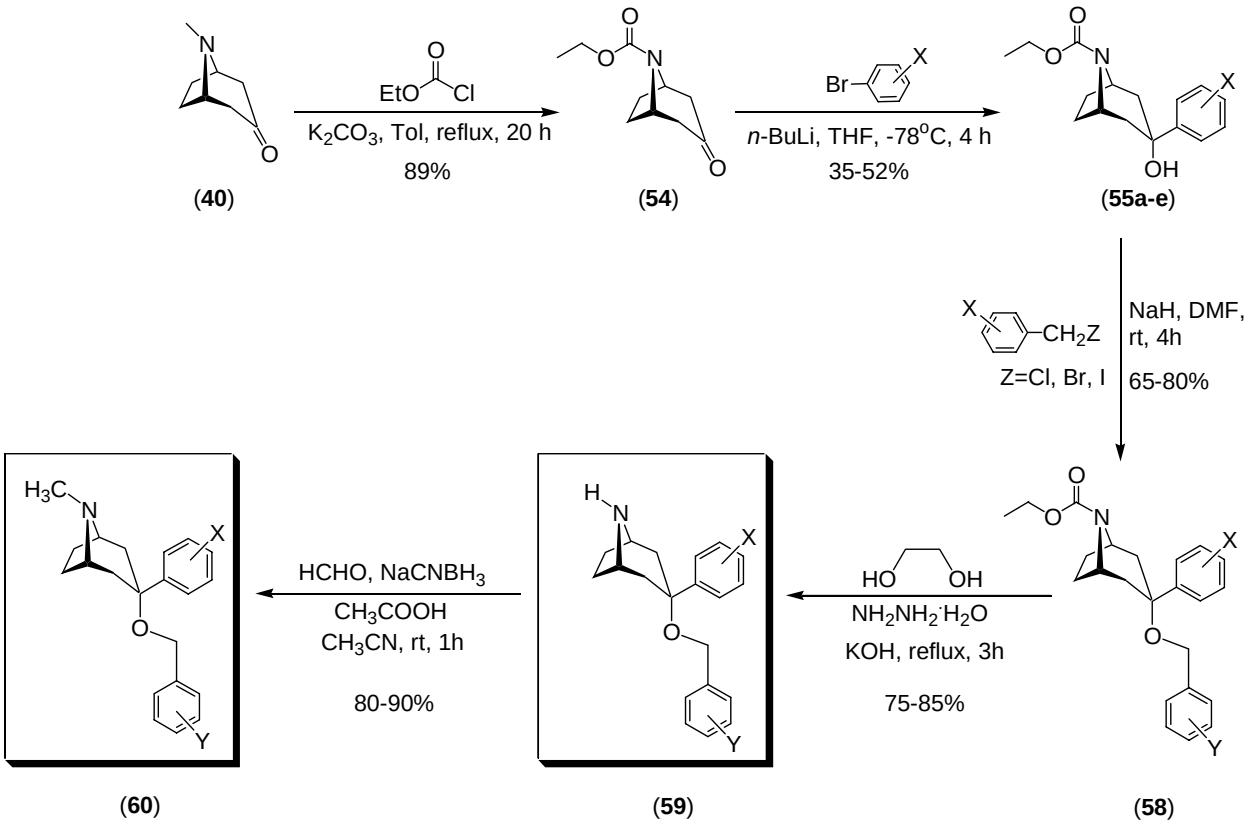
In general, the derivatives evaluated for binding affinity did not prove to be highly potent at either the dopamine or the serotonin transporter. Binding affinity at the norepinephrine transporter was not determined due to the low potency at the other transporters. The 3, 4-Cl_2 substituted alcohol (**41e**) was almost 8-fold more potent than the 4-chloro substituted alcohol (**41b**). Similarly, the 3, 4-Cl_2 substituted methoxy tropane (**57e**) was 10-fold more potent than the 4-chloro substituted methoxy tropane (**57b**). All the analogues in general were more selective for the serotonin transporter than the dopamine transporter.

The 3, 4- Cl_2 aryl substituted methyl ester analogue of meperidine , **37a** (K_i = 383 nM), was only 2.5 times more potent than ring constrained methoxy ether analogue **57e** (K_i = 900 nM) at the dopamine transporter but **37a** was significantly more potent at the serotonin transporter (K_i = 15.4 nM) than **57e**. The binding affinity at the dopamine transporter of the alcohol derivative of the 3, 4- Cl_2 aryl substituted meperidine, **39g** (K_i = 3310 nM), was in the micromolar range along with the tropane derivative **41e** (K_i = 4120 nM).

From the previous SAR of the substituted meperidine analogues, it was discovered that the benzyl ester derivative **37h**, displayed an enhanced potency at the serotonin transporter over other alkyl esters and is the most selective meperidine analogue reported to date (K_i = 3.9 nM, DAT/SERT = 760). Therefore, the benzyl ether analogues of the tropane system were synthesized to determine if the benzyl group can enhance potency of the tropane analogues at the monoamine transporters as well.

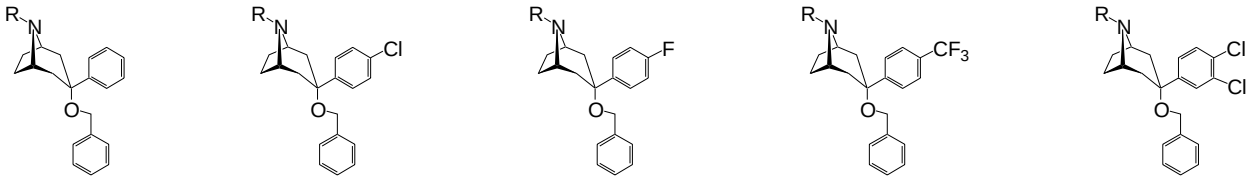
2.4 Synthesis of 3-Aryl-3-arylmethoxytropane Derivatives.

The synthesis of 3-aryl-3-arylmethoxytropane analogues was achieved by following a synthetic route similar to the one for the methoxy derivatives **57**. As illustrated in Scheme 13, the tertiary alcohols (**55a-e**) were treated with sodium hydride and the desired benzyl halides to afford the benzyl ethers **58**. Compounds **58** were deprotected using hydrazine, potassium hydroxide and ethylene glycol to afford the desired products **59**. These compounds were further modified by replacing the *N*-H group with an *N*-methyl group using formaldehyde and sodium cyanoborohydride to yield compounds **60**.



Scheme 13. Synthetic route for the synthesis of 3-aryl-3-arylmethoxytropane derivatives.

An array of compounds could be synthesized using different combinations of the halide substituents on the aryl rings. Compounds **59a-e** and **60a-e** were obtained by reacting different tertiary alcohols (**55a-e**) with benzyl bromide, and the subsequent removal of the protecting group resulted in a series of compounds with benzyl ether as a substituent in the 3α position of these tropane derivatives (**Figure 7**). Compounds **59a-e**, the *N*-H derivatives, were obtained in 70-92% yields and the corresponding *N*-methyl analogues, **60a-e**, were obtained in 79-87% yields.



59a, R=H
60a, R=CH_3

59b, R=H
60b, R=CH_3

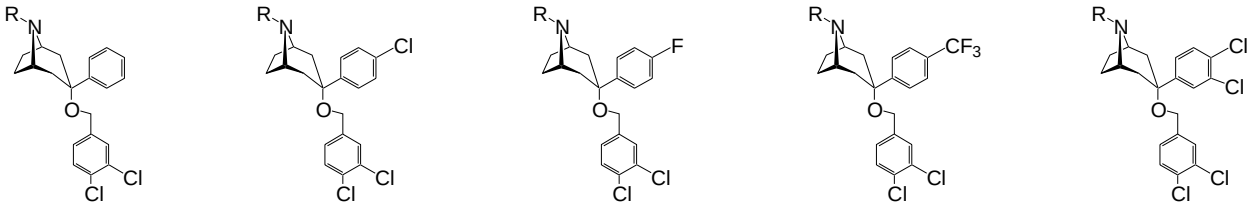
59c, R=H
60c, R=CH_3

59d, R=H
60d, R=CH_3

59e, R=H
60e, R=CH_3

Figure 7. Benzyl ether analogues, **59a-e** and **60a-e**.

Similarly, another series of novel tropane compounds was prepared by using 3, 4-dichlorobenzyl chloride to react with the various tertiary alcohols (**55a-e**). The series of *N*-H analogues, **59f-j**, were obtained in 85-93% yields. Treatment of these compounds with formaldehyde/sodium cyanoborohydride afforded the *N*-methyl derivatives, **60f-j**, in 75-90% yields (**Figure 8**).



59f, R=H
60f, R=CH_3

59g, R=H
60g, R=CH_3

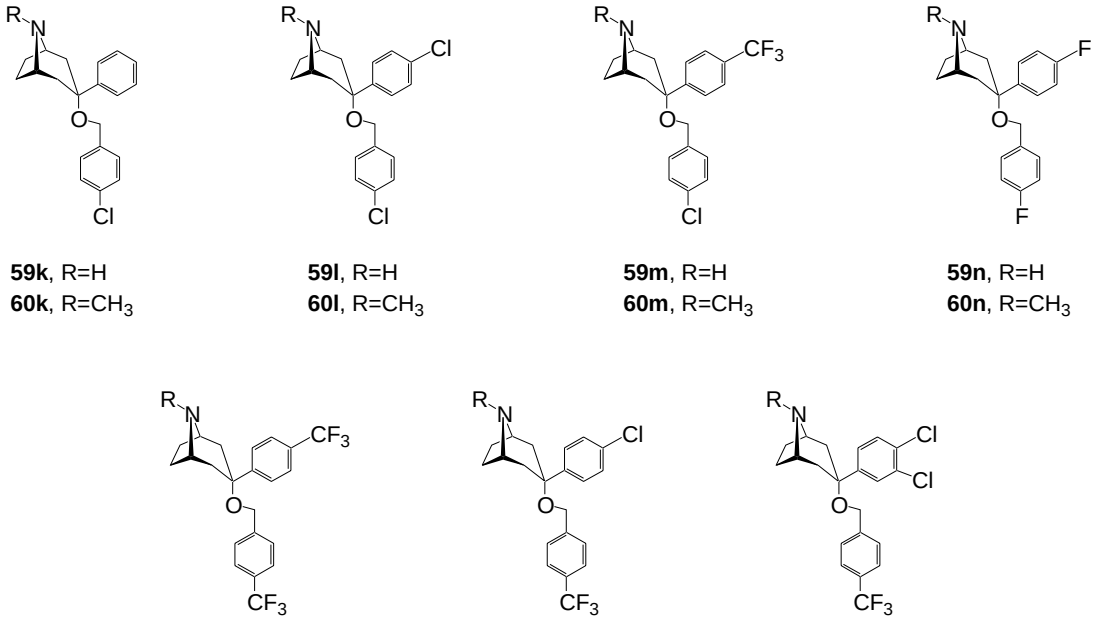
59h, R=H
60h, R=CH_3

59i, R=H
60i, R=CH_3

59j, R=H
60j, R=CH_3

Figure 8. Benzyl ether analogues, **59f-j** and **60f-j**.

A number of other novel tropane derivatives were synthesized in a similar manner. The variations in the tertiary alcohol (**55a-e**) and the desired benzyl halide used, afforded another array of *N*-H compounds, **59k-q** in 72-86% yields. These were also converted into the corresponding *N*-methyl derivatives (**60k-q**) and were obtained in 74-88% yields (**Figure 9**).



59k, R=H
60k, R=CH_3

59l, R=H
60l, R=CH_3

59m, R=H
60m, R=CH_3

59n, R=H
60n, R=CH_3

59o, R=H
60o, R=CH_3

59p, R=H
60p, R=CH_3

59q, R=H
60q, R=CH_3

Figure 9. Benzyl ether analogues, **59k-q** and **60k-q**.

Crystallographic data for the *N*-methyl derivative, **60a** (as an oxalate salt), was obtained to confirm the stereochemistry of the substituents at the 3-position (**Figure 10**). The X-ray structure clearly shows that the phenyl ring occupies the β position at C3 and the phenylmethoxy group is in the α position. The stereochemistry of the groups is retained from the tertiary alcohol **55a** (Figure 5). This data unequivocally establishes the relative stereochemistry of novel 3β-aryl-3α-arylmethoxytropane analogues **60**.

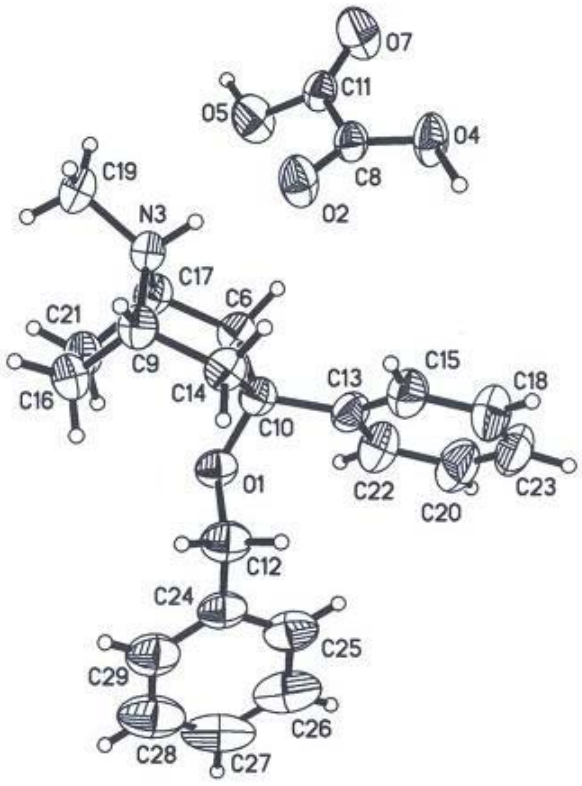
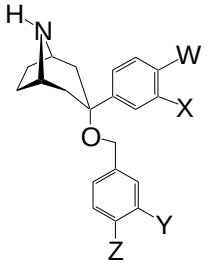


Figure 10. X-ray structure of 3β-phenyl-3α-phenylmethoxytropane (**60a**) provided courtesy of Prof. Edwin D. Stevens.

Transporter binding affinities for several of the novel 3-aryl-3-arylmethoxytropane derivatives were determined by their ability to displace bound radiolabeled ligands from rat caudate-putamen tissue. The K_i values for some of the analogues of **59** are presented in Table 3. The data for derivatives of **60** are summarized in Table 4. They were determined by similar methods as previously reported in Table 1.

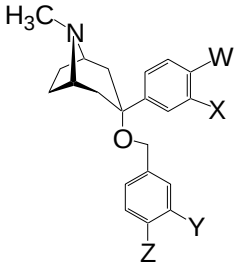
Table 3. In vitro binding data at the DAT and the SERT for 3β-aryl-3α-arylmethoxynortropane derivatives.



Compound[a]	W, X, Y, Z	[^{3}H]WIN 35,428 (DAT) K_i (nM)[b]	[^{3}H]citalopram (SERT) K_i (nM)[b]	DAT/SERT
Cocaine		32 ± 5 388 ± 221		
59a	H, H, H, H	120 ± 20	250 ± 30	0.48
59f	H, H, Cl, Cl	16 ± 1	0.061 ± 0.024	266
59j	Cl, Cl, Cl, Cl	2,800 ± 640	4.7 ± 0.3	600
59l	Cl, H, H, Cl	63 ± 7	0.096 ± 0.022	653
59m	CF_3, H, H, Cl	3,000 ± 730	6 ± 2	500
59n	F, H, H, F	100 ± 10	7.7 ± 3.6	13
59o	CF_3, H, H, CF_3	5,000 ± 900	2.0 ± 1.6	2500

[a] All compounds were tested as oxalate salts. [b] All the values are mean ± SEM of three experiments performed in triplicate.

Table 4. In vitro binding data at the DAT and the SERT for 3β-aryl-3α-arylmethoxy-8-methyltropane derivatives.

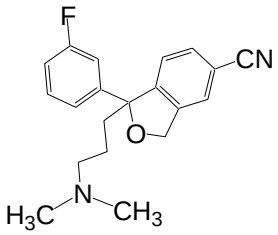


Compound[a]	W, X, Y, Z	[^{3}H]WIN 35428 (DAT) K_i (nM)[b]	[^{3}H]Citalopram (SERT) K_i (nM)[b]	DAT/SERT
60a	H, H, H, H	96 ± 20	140 ± 7	0.68
60j	Cl, Cl, Cl, Cl	2,300 ± 230	9.6 ± 3.6	240
60l	Cl, H, H, Cl	760 ± 70	18.0 ± 0.7	42
60m	CF_3, H, H, Cl	4,800 ± 1,700	100 ± 10	48
60n	F, H, H, F	900 ± 70	4.8 ± 1.3	188
60o	CF_3, H, H, CF_3	3,800 ± 630	7.4 ± 3.2	515

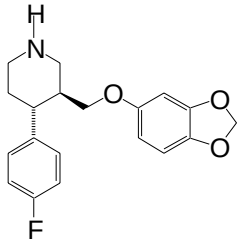
[a] All compounds were tested as oxalate salts. [b] All the values are mean ± SEM of three experiments performed in triplicate.

In general, the *N*-H analogues (Table 3) were found to be more potent and selective for the serotonin transporter than the dopamine transporter with the exception of **59a**, which displayed slight selectivity for the dopamine transporter over the serotonin transporter (DAT/SERT = 0.48). Most notably, compounds **59f** (K_i = 0.061 nM) and **59l** (K_i = 0.096 nM) were the most potent ligands of the series at the serotonin transporter. The binding affinities of **59f** and **59l** are in the subnanomolar range which makes them amongst the most potent ligands for the serotonin transporter reported to date. The binding affinity of **59f** and **59l** exceeded the potency of the radiolabeled ligand citalopram, (K_i = 2 nM)[159] used for obtaining this data.

Moreover, **59f** and **59l** were equipotent with paroxetine (Paxil®, SERT K_i = 0.2 nM),[159] a widely prescribed serotonin selective reuptake inhibitor for the treatment of depression. These two *N*-H analogues also displayed high potency for the dopamine transporter and **59f** (K_i = 16 nM) was four times more potent than **59l** (K_i = 64 nM) and was also the most potent ligand of the series for the dopamine transporter. From this data, it appears that chlorine is an important substituent on the aryl rings of these tropane analogues for molecular recognition at both the monoamine transporters, serotonin and dopamine, as it enhances the potency at these transporters substantially.



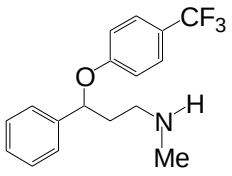
Citalopram



Paroxetine

The *N*-H analogues, **59j**, **59m**, **59n** and **59o** exhibited potent serotonin transporter affinity but displayed poor dopamine transporter affinity. Analogue **59o**, with trifluoromethane group as substituents on both the aryl rings, displayed the highest selectivity for the serotonin transporter in the series (DAT/SERT = 2,515). The binding affinity at the dopamine transporter dropped in the micromolar range for the 3, 4-dichloro substituted derivative, **59j** (K_i = 2,800 nM), the trifluoromethane substituted derivative, **59o** (K_i = 5,000 nM), and the analogue with trifluoromethane and chlorine groups, **59m** (K_i = 3,000 nM). Compound **59n** (K_i = 100 nM),

which has the smallest halide, fluorine, as a substituent on both the aryl rings, is equipotent with the unsubstituted *N*-H analogue, **59a** (K_i = 120 nM), at the dopamine transporter but **59n** (K_i = 7.7 nM) is considerably more potent at the serotonin transporter than **59a** (K_i = 250 nM). From this data it appears that while the serotonin transporter can tolerate a range of functional groups, the dopamine transporter cannot accommodate strong electron withdrawing groups like trifluoromethyl on the aryl rings of the tropane derivatives. However, the high affinity observed for **59o** at the serotonin transporter is consistent with the SAR of potent SSRI fluoxetine (Prozac®).[160]



Fluoxetine

The *N*-methyl analogues (Table 4) were in general less potent at both the dopamine transporter and the serotonin transporter than the corresponding *N*-H derivatives. However, the same trend in selectivity of the serotonin transporter over the dopamine transporter was observed in this series of ligands as well. Compound **60a** which has unsubstituted phenyl rings, was the exception, displaying a slight preference for the dopamine transporter over the serotonin transporter (DAT/SERT = 0.68). The most potent compounds of this series at the serotonin transporter were the fluoro substituted **60n** (K_i = 4.8 nM), the trifluoromethane substituted **60o** (K_i = 7.4 nM) and the 3, 4-dichloro substituted **60j** (K_i = 9.6 nM), whereas the least potent were the unsubstituted *N*-methyl analogue, **60a** (K_i = 140 nM) and the derivative with trifluoromethane and the chlorine groups, **60m** (K_i = 100 nM). The *N*-methyl analogue having a

chloride group on both the aryl rings, **60l**, displayed a reduced affinity for both the dopamine transporter (K_i = 760 nM) and the serotonin transporter (K_i = 18 nM) as compared to its *N*-H counterpart, which was one of the most potent ligands for both the transporters in the series. Replacing one of the chlorine groups of **60l** with a trifluoromethane group resulted in **60m**, which displayed a further drop in the binding affinities at the dopamine transporter (K_i = 4,800 nM) and also at the serotonin transporter (K_i = 100 nM).

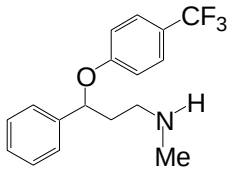
In summary, the results of this study clearly demonstrate that 3β-aryl-3α-arylmethoxytropane derivatives are selective ligands for the serotonin transporter over the dopamine transporter. Moreover, the *N*-H analogues were found to be more selective and potent than the *N*-methyl derivatives for the serotonin transporter and the dopamine transporter. Most notably, the *N*-H derivatives, **59f** and **59l**, exhibited the highest potency for the serotonin transporter reported to date. They are equipotent with paroxetine and fluoxetine, which are widely prescribed serotonin selective reuptake inhibitors for the treatment of depression. This suggests that these analogues could be developed as potential therapeutics for treating depression. Since both **59f** and **59l** also displayed the highest potency for the dopamine transporter in both the series of compounds, it appears that chlorine is an important substituent for molecular recognition at both the dopamine transporter and the serotonin transporter. Also, analogue **59o** was the most selective ligand for the serotonin transporter over the dopamine transporter in the series. In general, the serotonin transporter tolerated a wide range of functional groups but the dopamine transporter affinities were moderate and mainly in the micromolar range. The unsubstituted analogues, **59a** and **60a**, were the only compounds which exhibited a slight selectivity for the dopamine transporter over the serotonin transporter, which suggests that electron withdrawing groups could be necessary for recognition at the serotonin transporter.

Despite some structural similarities to the dopamine transporter selective 2-substituted-3β-phenyltropanes, these novel 3β-aryl-3α-arylmethoxy derivatives retained the inherent serotonin transporter selectivity of meperidine and exhibited more potent affinity for the serotonin transporter and were significantly less potent at the dopamine transporter than the corresponding 2-substituted-3β-aryltropanes. Overall, this investigation suggests that the chloro-substituted aryl rings at the 3-position of tropane is a key structural feature for molecular recognition at the serotonin transporter as well as differentiation between the serotonin transporter and the dopamine transporter. The biology data of more compounds in these series will elucidate further structure-activity relationships and help to optimize the serotonin transporter selectivity. Moreover, the effect of the relationship of various substituents on both the aryl rings of 3β-aryl-3α-arylmethoxytropane analogues will be evaluated more comprehensively. In addition, various serotonin transporter selective ligands will be evaluated to determine if the incorporation of the design of tropane motif to the meperidine structure has led to diminished μ-opioid receptor affinity.

2.5 Synthesis of Novel 3-Aryl-2-nortropene Derivatives as Triple Reuptake Inhibitors.

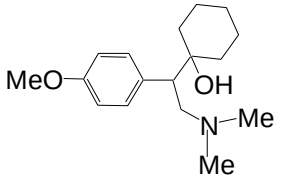
Monoamine re-uptake inhibition has been one of the important neuropharmacological approaches for the treatment of depression. The monoamines, dopamine, serotonin and norepinephrine, are the most intensely studied neurotransmitters in the central nervous system. Many antidepressants employ the use of selective serotonin re-uptake inhibitors (SSRIs) which increase the synaptic availability of serotonin. A well known SSRI is fluoxetine (Prozac®, **61**).[160]

There are various drawbacks with the use of SSRIs, for example, lack of efficacy (30-40% non-responders), requirement of almost three weeks for its full effect and many side effects such as nausea, anxiety, sleep disturbances and reduced appetite.[161]

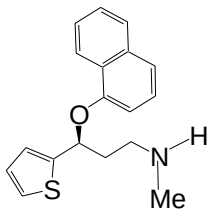


(**61**)

The antidepressants in current use have been developed as dual re-uptake inhibitors, a combination of serotonin and norepinephrine inhibition (SNRIs), for example Efexor® (venlafaxine, **62**) and Cymbalta® (duloxetine, **63**).[162] While these newer medications are safer and easier to use, the previous issues of lack of efficacy and latency of onset, are still not fully resolved.



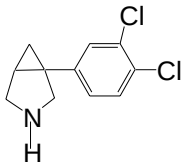
(**62**)



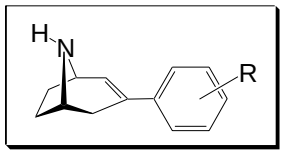
(**63**)

During the past decade, several therapeutic strategies have emerged to increase efficacy and accelerate the onset of antidepressant action compared to compounds in current use. One of the novel biogenic amine-based strategies is the "triple re-uptake" inhibitor which is also called the "broad spectrum" antidepressant as it is capable of simultaneously inhibiting the re-uptake of dopamine, serotonin and norepinephrine.[163] The rationale for the design of the triple re-uptake inhibitor is that superior antidepressant effect can be achieved by the inclusion of a dopaminergic component to the norepinephrine and serotonin inhibitors.[164, 165] There is numerous evidence that supports this hypothesis. Anhedonia, defined as an inability to experience pleasure and diminished interest in most activities, is a common depressive disorder, which has been associated with deficits in dopamine transmission.[166,167] There is clinical evidence to indicate that co-administration of dopaminergic agents with the "standard" antidepressants, improves depressed moods in patients, including those individuals who were either resistant to or partially responsive to SNRIs alone.[168] The improvement observed was in a significant proportion following the addition of these dopamine agonists. The hypothesis for the use of triple re-uptake inhibitors also states that it will act more rapidly than the several weeks of treatment required for conventional antidepressants. This is based on the evidence that chronic use of antidepressants produces a selective sensitization of dopamine receptors.[166, 167] Since, dopaminergic neurons play a pivotal role in the control of motivation and reward-related behavior, the several of weeks of treatment required with conventional SNRIs may be to achieve stimulation of these neurons. Immediate increase in dopamine levels via inhibition of re-uptake of dopamine, may result in a more rapid treatment of symptoms associated with anhedonia than produced by SSRIs or SNRIs alone.

One of the triple re-uptake inhibitors which has been designed and has been studied extensively is DOV 216,303 which is an azabicyclo[3.1.0]hexane (**64**).[169] Based on the structure of this compound, the design of a novel series of analogues was proposed which could also be developed as triple re-uptake inhibitors (**65**).



DOV 216,303 (**64**)



R = H, Cl, F, CF_3, 3,4-Cl_2

(**65**)

Compounds **65** share several structural features with DOV 216,303. **Figure 11** displays the overlay of geometry optimized structures **65e** and **64**. The azabicyclo ring system is a common feature in both the structures. The aryl substituent is attached to the 3-position on the nortropane ring which is analogous to the 3, 4-dichlorophenyl substituent on 1-position of **64**. Further, both **64** and **65** possess the *N*-H group. The similarity of the structures of DOV 216,303 and the target compounds, **65**, suggests that the structure-activity relationships of this series of compounds (**65**) can provide leads with distinct pharmacological profiles for the treatment of depressive disorders.

DOV 216,303 (**64**) Tropene (**65e**)

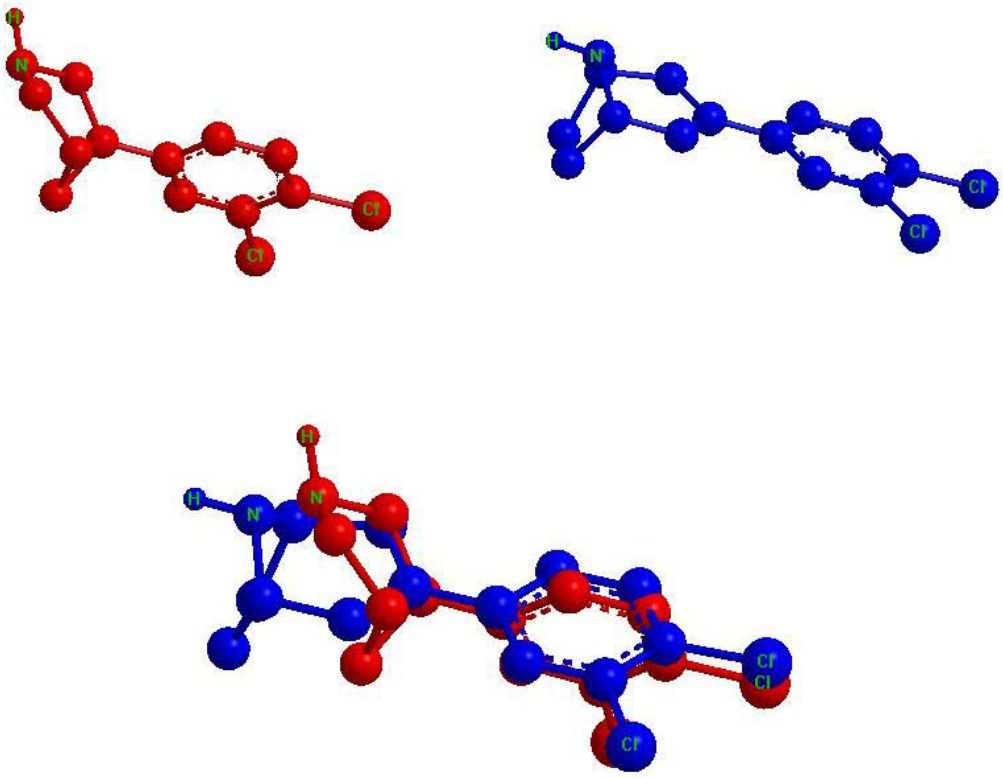
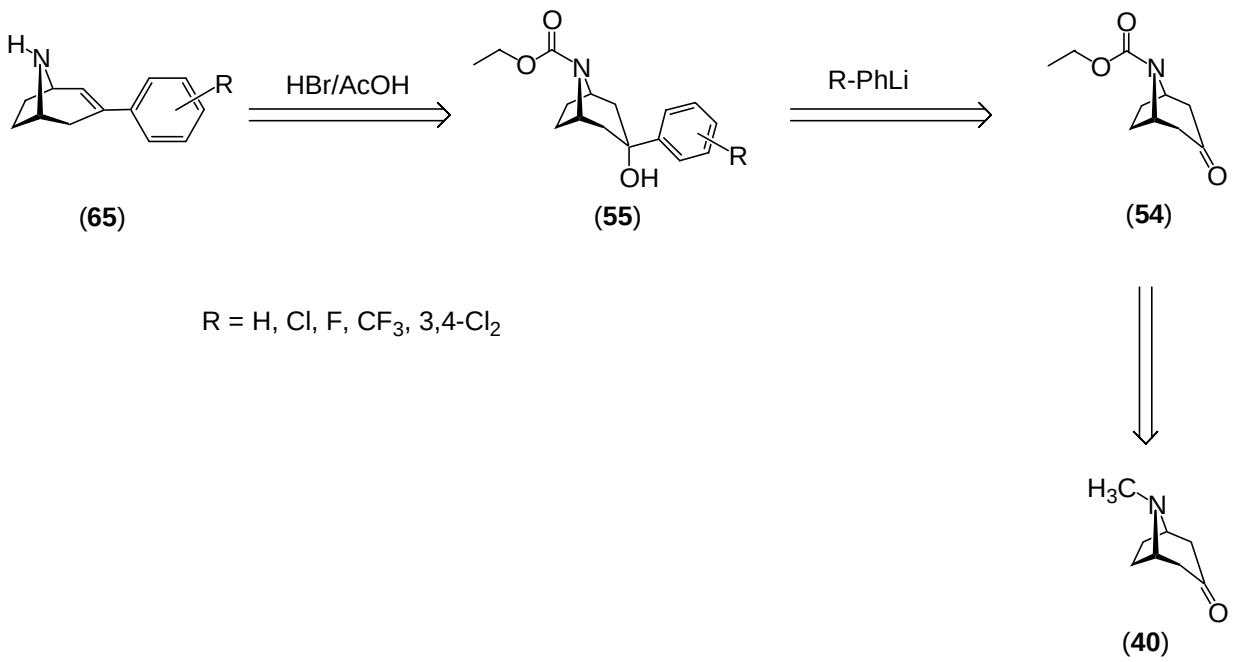


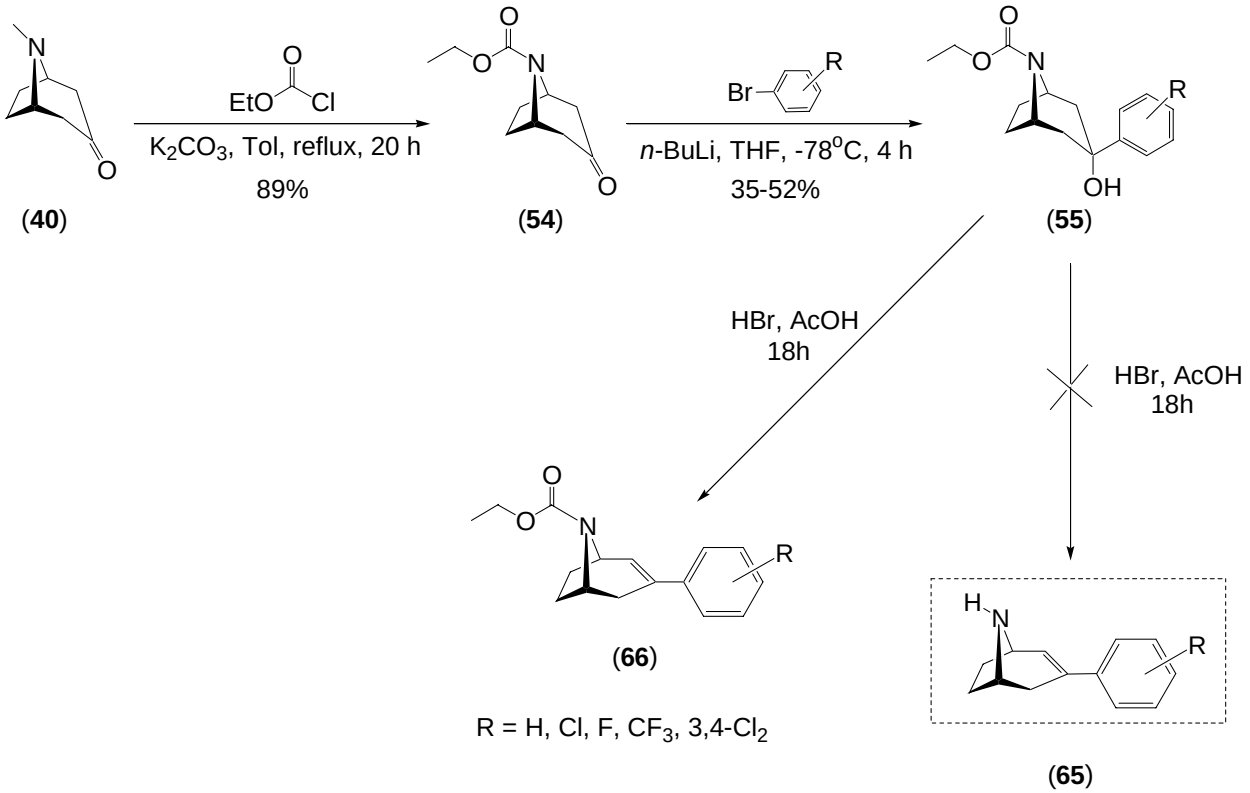
Figure 11. Overlay of geometry optimized structures **64** and **65e**.

The retrosynthetic scheme for the synthesis of analogues of **65** is outlined in Scheme 14. The strategy for the development of these compounds utilizes the β-elimination of the tertiary alcohols (**55**) which were encountered previously while attempting to synthesize 3-aryl-3-carbomethoxytropane analogues (**43**) and 3-aryl-3-propyltropane derivatives (**51**).



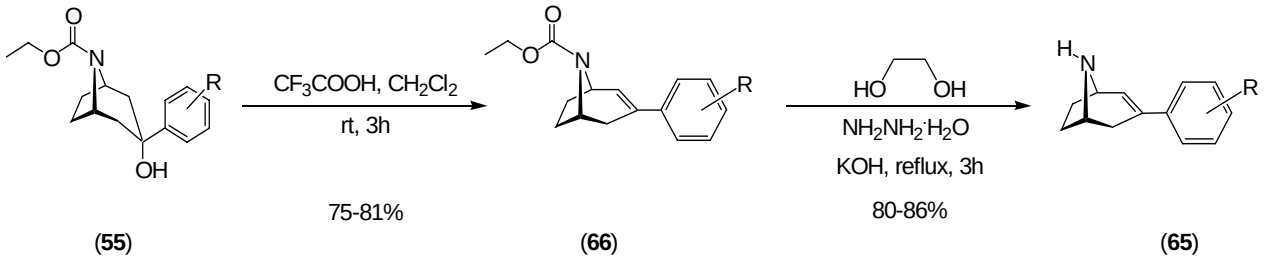
Scheme 14. Retrosynthetic route for the synthesis of 3-aryl-2-nortropene derivatives (**65**).

The first step of the synthetic route for the synthesis of 3-aryl-2-nortropene analogues (**65**) was the protection of the tertiary amine (**40**) as a carbamate by employing ethylchloroformate to obtain the protected amine (**54**) as depicted in Scheme 15. Use of *in situ* generated organolithium reagents furnished the tertiary alcohols (**55**). Initial attempts to achieve the β-elimination and the cleavage of the carbamate in a single step to obtain the desired products (**65**) were unsuccesful. The conditions employed (HBr, AcOH) resulted in the the β-elimination but removal of the carbamate group did not occur to give **66** as the only product.



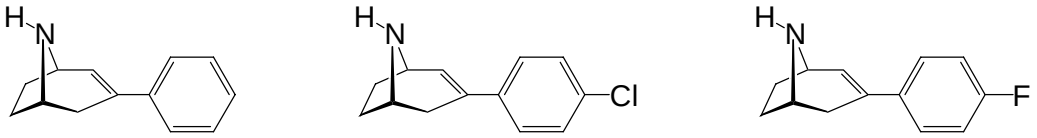
Scheme 15. Attempted synthesis of 3-aryl-2-nortropene derivatives (**65**).

Therefore, the synthetic route was modified (Scheme 16) and milder conditions were employed to obtain the β-elimination products (**66**) which were then deprotected to afford the final products (**65a-e**) in 80-86% yields.

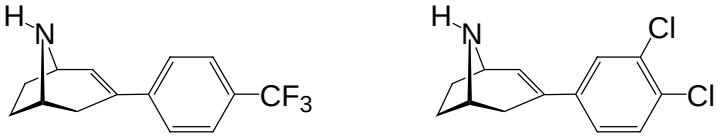


(**55**) (**66**) (**65**)

R = H, Cl, F, CF_3, 3,4-Cl_2



(**65a**) (**65b**) (**65c**)



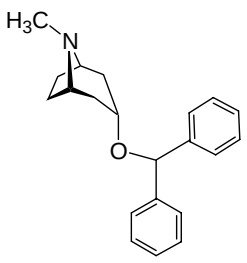
(**65d**) (**65e**)

Scheme 16. Synthetic route for the synthesis of 3-aryl-2-nortropene derivatives (**65**).

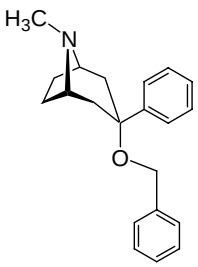
2.6 Synthesis of Novel 3β-Aryl-3α-(4', 4''-disubstituteddiphenylmethoxy)tropane Analogues-Future Directions.

Benztropine (**8**) is the parent compound of a leading class of dopamine uptake inhibitors.[170-172] It is equipotent to cocaine and has displayed central nervous system stimulant activity in animal models.[173-176] Benztropine, like meperidine (**33**), shares some structural features with cocaine and numerous phenyltropane analogues such as WIN 35,428 (**5**). The effects of various *ortho*, *meta* and *para* aromatic substitutions on the structure-activity relationships of benztropine at the dopamine transporter have been widely explored.[177-180] It has been shown that these tropane derivatives bound with high affinity at the dopamine transporter and were selective at this transporter over other monoamine transporters such as serotonin and norepinephrine.

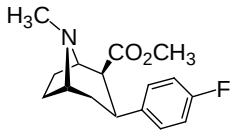
As discussed earlier, meperidine analogues **60** can act as inhibitors for the reuptake of serotonin and to some extent for the dopamine. A hybrid structure can be designed which incorporates the structural features of both the benztropine analogues as well as the meperidine derivatives to achieve a series of compounds that could exhibit affinity for both the dopamine and the serotonin transporters (**Figure 12**). Since cocaine has been found to display its reinforcing effects by binding to all three monoamine transporters, this series of ligands can provide leads for the development of novel medications for cocaine abuse.



Benztropine (**8**)



3β-aryl-3α-arylmethoxytropane (**60**)



WIN 35,428 (**5**)

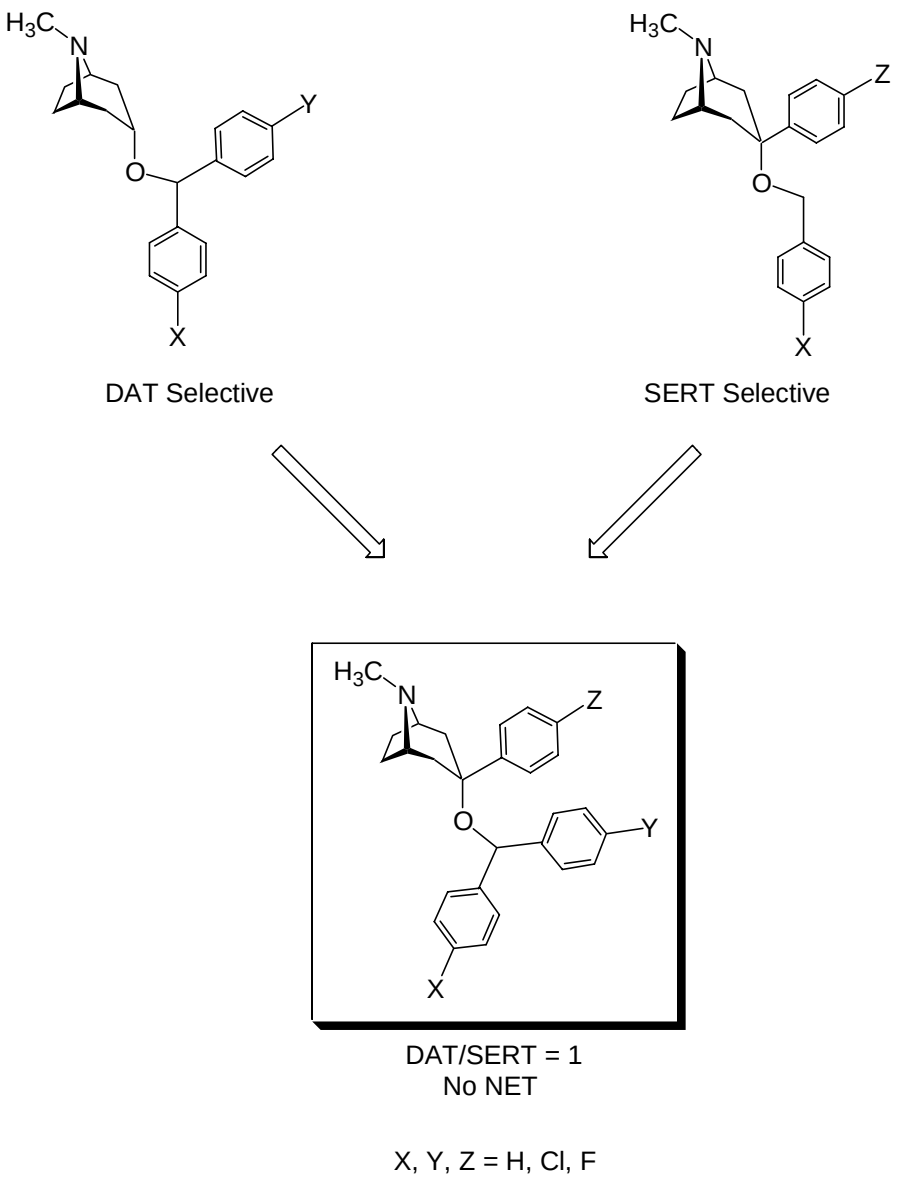


Figure 12. Hybrid structures of benztropine and tropane analogues **60**.

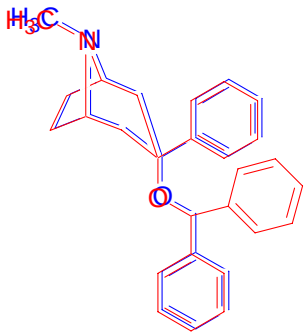
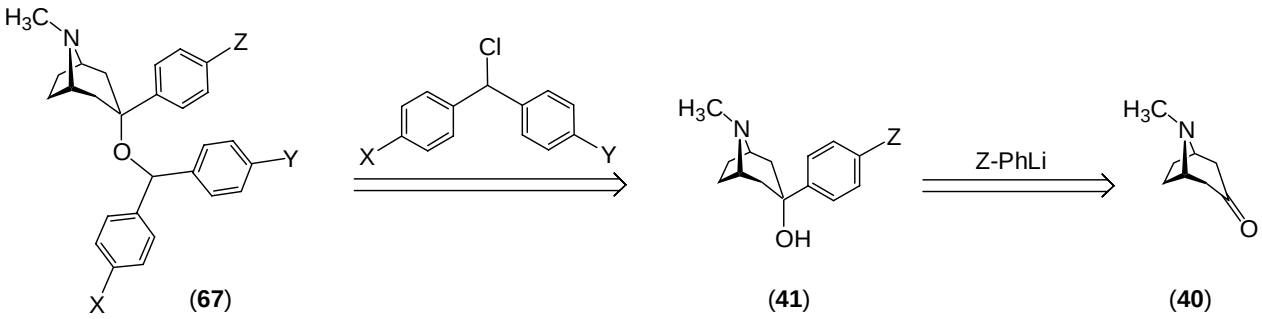


Figure 13. Overlay of benztropine **67** and benzyl ether **60a**.

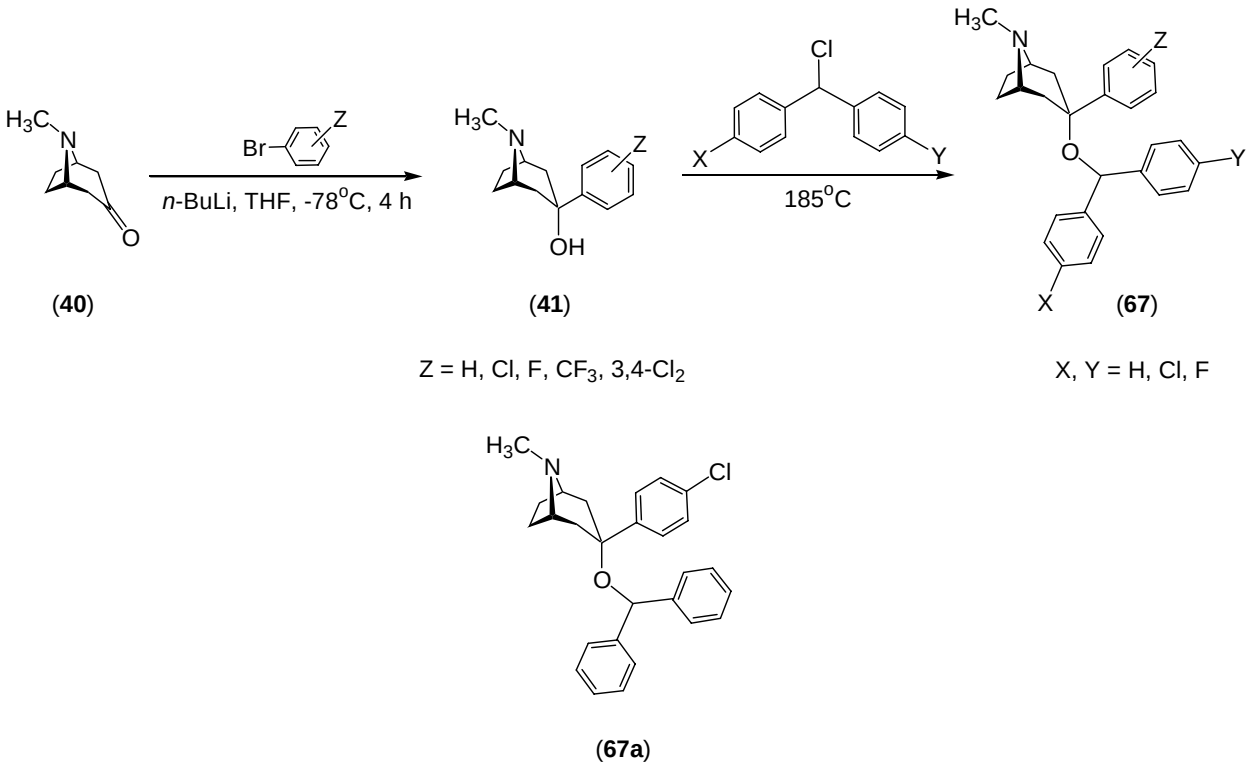
A simple and efficient synthetic route was designed for the synthesis of these unique tropane derivatives (**67**) which is presented in Scheme 17. The target compounds could be achieved from the reaction of benzhydryl chlorides with the tertiary alcohols (**41**). It has been previously demonstrated that these alcohols can be directly obtained from the commercially available 3-tropinone (**40**).



Scheme 17. Retrosynthetic route for the synthesis of analogues of **67**.

The synthesis of the desired compounds, **67**, is presented in Scheme 18. The 3β-aryl-3α-hydroxytropanes (**41**) can be obtained from the commercially available 3-tropinone (**40**) by the action of *in situ* generated organolithium reagents. The reaction of chlorodiphenylmethane with the hydroxytropanes (**41**) was performed at 185°C in the absence of any solvent to yield the desired ligands. The analogue **67a** was obtained in 35% yield by utilizing this synthetic strategy.

A series of novel compounds can be synthesized by following the synthetic route presented in Scheme 18 with variations in the substituents on the aromatic rings. Since these hybrid compounds contain the structural features of both the benztropines (DAT selective) and meperidine analogues (SERT selective), they could display equipotent binding affinities for both the dopamine and the serotonin transporters. Future investigations of these unique ligands can provide leads for the identification of novel medications for the treatment of cocaine addiction.



Scheme 18. Synthetic route for the synthesis of analogues of **67**.

CONCLUSION

A series of *N*-H and *N*-methyl 3β-aryl-3α-arylmethoxytropane analogues were synthesized and evaluated as dopamine and serotonin transporter ligands. The *in vitro* affinity (K_i) for the dopamine transporter and the serotonin transporter of this series was determined by inhibition of [^{3}WIN]-35,428 and [^{3}H]citalopram, respectively, in rat caudate putamen tissue. The results of this study clearly demonstrate that 3β-aryl-3α-arylmethoxytropane derivatives are selective ligands for the serotonin transporter over the dopamine transporter. The *N*-H analogues (**59**) were found to be more selective and potent than the *N*-methyl derivatives (**60**) for the serotonin transporter and the dopamine transporter. Most notably, the *N*-H derivatives, 3β-phenyl-3α-(3", 4"-dichlorophenyl)methoxy-8-azabicyclo[3.2.1]octane **59f** and 3β-(4'-chlorophenyl)-3α-(4"-chlorophenyl)methoxy-8-azabicyclo[3.2.1]octane **59l**, exhibited the highest potency for the serotonin transporter reported to date for this class of compounds. They were found to be equipotent with paroxetine and fluoxetine, which are widely prescribed serotonin selective reuptake inhibitors for the treatment of depression. Also, 3β-(4'-trifluoromethanephenyl)-3α-(4"-trifluoromethanephenyl)methoxy-8-azabicyclo[3.2.1]octane **59o** was the found to be the most selective ligand for the serotonin transporter over the dopamine transporter in the series. Despite some structural similarities to the dopamine transporter selective 2-substituted-3β-phenyltropanes, these novel 3β-aryl-3α-arylmethoxy derivatives retained the inherent serotonin transporter selectivity of meperidine and exhibited more potent affinity for the serotonin transporter and were significantly less potent at the dopamine transporter than the corresponding 2-substituted-3β-aryltropanes. Overall, this investigation suggested that the chloro-substituted aryl rings at the 3-position of tropane is a key structural

feature for molecular recognition at the serotonin transporter as well as differentiation between the serotonin transporter and the dopamine transporter.

A new class of 8-azabicyclo[3.2.1]oct-2-ene derivatives (**65a-e**) has been synthesized based on the structure of triple reuptake inhibitor, DOV 216,303 which was developed for the treatment of depression. A short and efficient synthetic route has been developed for synthesizing the novel compounds **65**. The final products were obtained from the tertiary alcohols (**55a-e**) in 64-72% overall yields.

A general method was designed for the preparation of a novel class of compounds as hybrids of benztropines and the benzyl ethers. These unique 3β-aryl-3α-(4', 4"-disubstituteddiphenylmethoxy)tropane analogues (**67**) could potentially exhibit affinity for both the dopamine and the serotonin transporters since they are hybrid structures of the dopamine transporter selective benztropines and the serotonin transporter selective meperidine derivatives **60**.

All the compounds synthesized in this study are in various stages of biological evaluation. The potency and efficacy that is determined for these compounds will provide the direction for further studies with these novel tropane derivatives. All the biological studies will be reported in due course.

EXPERIMENTAL SECTION

All the chemicals were purchased form Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Anhydrous THF was purchased from Mallindkrodt Baker. Anhydrous solvents toluene, dimethylformamide and acetonitrile were purchased from VWR International Co. and were used under argon without any further purification. Chromatography refers to column chromatography on silica gel (Silica Gel 60, 230-400 mesh). Reported melting points are uncorrected. NMR spectra were recorded on a Varian-Gemini 400 MHz spectrometer. Chemical shifts are reported in δ values with teteramethylsilane (TMS), employed as the internal standard. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.

General procedure A. Preparation of oxalate salts.

All the compounds were converted into the oxalate salts for biological testing, as well as for storage and handling purposes. The base (50-100mg) was dissolved in a minimum amount of THF (2-3 mL) and a saturated solution of oxalic acid (1.0 equiv.) in THF (5-7 mL) was added. The oxalate salts crystallized and were washed with THF (3 × 2mL) and purified by trituration with diethyl ether. Fractional moles of water could not be prevented, despite vigorous drying under vacuum (0.01 mmHg, overnight). All compounds were homogenous by thin-layer chromatography ($CHCl_3/CH_3OH/NH_4OH$, 95:4.5:0.5).

General procedure B. Preparation of tertiary alcohols.

A solution of the appropriate arylbromide (2 eqiv.) in anhydrous THF (80 mL) was cooled to -78^{o}C under an atmosphere of nitrogen. *n*-BuLi (2.5 M in hexanes, 2 eqiuv.) was added via syringe to the reaction flask and the mixture was stirred at -78^{o}C for 2 h. Tropinone (**40** or **54**) was dissolved in THF (20 mL) and added to the flask and the reaction mixture was stirred for another 2 h at -78^{o}C. The reaction mixture was allowed to warm to room temperature and washed with 10% NH_4Cl solution (50 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the solvent was removed under reduced pressure.

Reduction of the unreacted tropinone.

The residue was dissolved in CH_3OH (100 mL). $NaBH_4$ (1 equiv.) was added to the flask and the reaction mixture stirred at room temperature for 1 h. The reaction was quenched with 10% NH_4Cl solution (50 mL) and concentrated under reduced pressure. The residue was partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude mixture obtained was purified by flash chromatography (Hexanes/EtOAc/$CHCl_3$, 80:10:10) to afford the tertiary alcohols **41** and **55**.

*General procedure C. Preparation of methyl ethers (***O***-Alkylation).*

A suspension of NaH (1.1 equiv.) in anhydrous DMF (10 mL) was prepared in a flask under the atmosphere of argon. Tertiary alcohol (**55**) was dissolved in DMF (10 mL) and added to the reaction flask at room temperature and the reaction mixture was stirred for 3 h (or till the evolution of hydrogen gas ceased). Dimethylsulphate (1.5 equiv.) was added via syringe to the

reaction flask and the mixture was stirred for another 2 h. Upon completion of the reaction, the reaction mixture was partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (Hexanes/EtOAc, 85:15) to afford the methoxy derivatives **56**.

General procedure D. Decarbonylation via LAH reduction.

A suspension of lithium aluminium hydride (5equiv.) was prepared in anhydrous THF (10 mL) and cooled to -78^{o}C. The methoxytropane derivative (**56**) was dissolved in THF (10 mL) and added to the reaction flask and the reaction mixture stirred at -78^{o}C for 10-15 minutes and then allowed to stir at room temperature for 18 h. The reaction mixture was again cooled to -78^{o}C and quenched with $Na_2SO_4 \cdot H_2O$. The mixture was then stirred at room temperature for 1 h. After LAH was completely quenched, the solids were filtered and washed with THF (5 × 30 mL). The solvent was removed under reduced pressure. The residue was purified by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1) to afford the *N*-Methyl derivatives **57**.

8-Ethoxycarbonyl-8-azabicyclo[3.2.1]-3-tropinone (54).

3-Tropinone (**40,** 20.0 g, 144 mmol) was dissolved in anhydrous toluene (150 mL). Potassium carbonate (993 mg, 7.18 mmol) and ethylchloroformate (68 mL, 718 mmol) were added to the solution and the reaction mixture was heated to reflux for 24 h. Upon completion of the reaction, solvent was removed from the reaction mixture under reduced pressure. The residue

was partitioned between water and CH_2Cl_2. Aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (Hexanes/Ethylacetate, 85:15) to afford the product, **54**, as a colorless oil (22.4 g, 80%). ^{1}H-NMR ($CDCl_3$): δ 4.56 (s, 2H), 4.20 (q, *J* = 7.4 Hz, 2H), 2.66 (s, 2H), 2.36 (d, *J* = 15.6 Hz, 2H), 2.12-1.69 (m, 6H), 1.30 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 206.2, 152.8, 60.1, 52.2, 47.7, 28.3, 13.6.

8-Ethoxycarbonyl-3β-phenyl-3α-hydroxy-8-azabicyclo[3.2.1]octane (55a).

General procedure B. This compound was obtained as a white solid (2.8 g, 40% yield). ^{1}H-NMR ($CDCl_3$): δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 9.6 Hz, 1H), 4.41 (s, 2H), 4.17 (q, *J* = 2.4 Hz, 2H), 2.45-1.69 (m, 8H), 1.27 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 149.8, 127.9, 126.4, 124.4, 73.0, 60.8, 53.3, 44.6, 28.0, 14.6. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79, H, 7.69, N, 5.09. Found: C,

8-Ethoxycarbonyl-3β-(4′-chlorophenyl)-3α-hydroxy-8-azabicyclo[3.2.1]octane (55b).

General procedure B. This compound was obtained as a white solid (2.5 g, 32% yield). ^{1}H-NMR ($CDCl_3$): δ 7.33-7.26 (m, 4H), 4.38 (s, 2H), 4.17 (q, *J* = 6.8 Hz, 2H), 2.30-1.73 (m, 8H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.2, 148.3, 132.8, 128.5, 126.1, 73.4, 61.2, 53.4, 45.0, 28.3, 14.9. Anal. Calcd for $C_{16}H_{20}ClNO_3$: C, 62.03, H, 6.51, N, 4.52. Found: C, 62.03, H, 6.50, N, 4.43.

8-Ethoxycarbonyl-3β-(4′-fluorophenyl)-3α-hydroxy-8-azabicyclo[3.2.1]octane (55c).

General procedure B. This compound was obtained as a white solid (4.7 g, 36% yield). ^{1}H-NMR ($CDCl_3$): δ 7.37-7.33 (m, 2H), 7.02-6.97 (m, 2H), 4.39 (s, 2H), 4.17 (q, *J* = 6.8 Hz, 2H), 2.30-1.82 (m, 8H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 163.0, 154.2, 145.6, 126.4, 115.2, 73.3, 61.2, 53.4, 44.6, 27.9, 14.9. Anal. Calcd for $C_{16}H_{20}FNO_3$: C, 65.51, H, 6.87, N, 4.78. Found: C, 65.44, H, 6.95, N, 4.71.

8-Ethoxycarbonyl-3β-(4′-trifluoromethanephenyl)-3α-hydroxy-8-azabicyclo[3.2.1]octane (55d).

General procedure B. This compound was obtained as a white solid (2.6 g, 50% yield). ^{1}H-NMR ($CDCl_3$): δ 7.58 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 4.43 (s, 2H), 4.19 (q, *J* = 4.8 Hz, 2H), 2.45-1.82 (m, 8H), 1.29 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.2, 153.6, 125.4, 122.9, 119.2, 115.8, 73.7, 53.4, 45.1, 28.4, 14.9. Anal. Calcd for $C_{17}H_{20}F_3NO_3$: C, 59.47, H, 5.87, N, 4.08. Found: C, 59.24, H, 5.86, N, 4.06.

8-Ethoxycarbonyl-3β-(3′, 4′-dichlorophenyl)-3α-hydroxy-8-azabicyclo[3.2.1]octane (55e).

General procedure B. This compound was obtained as a colorless oil (3.0 g, 18% yield). ^{1}H-NMR ($CDCl_3$): δ 7.51 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 4.39 (s, 2H), 4.19 (q, *J* = 6.4 Hz, 2H), 2.28-1.80 (m, 8H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.2, 150.3, 132.4, 130.8, 130.2, 127.1, 124.4, 73.1, 61.3, 53.4, 44.8, 28.3, 14.9. Anal. Calcd for $C_{16}H_{19}Cl_2NO_3$: C, 55.83, H, 5.56, N, 4.07. Found: C, 55.75, H, 5.59, N, 3.98.

3β-(4′-chlorophenyl)-3α-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (41b).

General procedure B. This compound was purified by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1). The compound was obtained as a white solid (2.3 g, 62% yield). ^{1}H-NMR (DMSO): δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 4.82 (s, 2H), 3.33 (s, 3H), 2.26-1.69 (m, 8H). ^{13}C-NMR (DMSO): δ 150.9, 130.4, 127.5, 126.8, 71.1, 60.3, 44.9, 40.1, 25.2.

3β-(3′, 4′-dichlorophenyl)-3α-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane (41e).

General procedure B. This compound was purified by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1). The compound was obtained as a white solid (2.2 g, 35% yield). ^{1}H-NMR (DMSO): δ 7.63 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 4.99 (s, 2H), 3.36 (s, 3H), 2.25-1.70 (m, 8H). ^{13}C-NMR (DMSO): δ 154.0, 131.3, 130.9, 129.3, 128.0, 126.4, 71.9, 61.2, 45.7, 41.0, 26.1.

8-Ethoxycarbonyl-3β-(4′-chlorophenyl)-3α-methoxy-8-azabicyclo[3.2.1]octane (56b).

General procedure C. This compound was obtained as orange oil. (0.8 g, 75% yield). ^{1}H-NMR ($CDCl_3$): δ 7.32-7.23 (m, 4H), 4.38 (s, 2H), 4.12 (q, *J* = 6.0 Hz, 2H), 2.9 (s, 3H), 2.16-1.92 (m, 8H), 1.23 (t, *J* = 8.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.8, 143.8, 132.9, 128.5, 127.2, 77.5, 60.9, 52.9, 50.9, 401, 36.7, 28.3, 27.4, 14.8.

3β-(4′-chlorophenyl)-3α-methoxy-8-methyl-8-azabicyclo[3.2.1]octane (57b).

General procedure D. This compound was obtained as colorless oil. (250 mg, 46% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, CD_3OD): δ 7.37-7.30 (m, 4H), 3.30 (s, 2H), 2.90 (s, 3H), 2.29 (s, 3H), 2.14-2.00 (m, 8H). ^{13}C-NMR (free base, $CDCl_3$): δ 144.5, 132.7, 128.2, 127.4, 76.4, 60.8, 50.0, 38.9, 24.9. Anal. Calcd for $C_{15}H_{20}ClNO{\cdot}HCl{\cdot}H_2O$: C, 56.26, H, 7.24, N, 4.37. Found: C, 56.67, H, 7.21, N, 4.35.

3β-(3′, 4′-dichlorophenyl)-3α-methoxy-8-methyl-8-azabicyclo[3.2.1]octane (57e).

General procedure D. This compound was obtained as colorless oil. (380 mg, 70% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.46 (s, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 3.19 (s, 2H), 2.92 (s, 3H), 2.30 (s, 3H), 2.08-1.96 (m, 8H). Anal. Calcd for $C_{15}H_{19}Cl_2NO{\cdot}HCl$: C, 53.51, H, 5.99, N, 4.16. Found: C, 53.60, H, 6.03, N, 4.09.

*General procedure E. Preparation of benzyl ethers (***O***-Alkylation).*

A suspension of NaH (1.1 equiv.) in anhydrous DMF (10 mL) was prepared in a flask under the atmosphere of argon. Tertiary alcohol (**55a-e**) was dissolved in DMF (10 mL) and added to the reaction flask at room temperature and the reaction mixture was stirred for 3 h (or till the evolution of hydrogen gas ceased). The appropriate benzyl halide (1 equiv.) was added

via syringe or dissolved in DMF (7-10 mL) and added to the reaction flask and the mixture was stirred for another 2 h. Upon completion of the reaction, the reaction mixture was partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (Hexanes/EtOAc, 85:15) to afford the benzyl ether derivatives **58a-q**.

8-Ethoxycarbonyl-3β-phenyl-3α-phenylmethoxy-8-azabicyclo[3.2.1]octane (58a).

General procedure E. This compound was obtained as a light yellow oil (1.7 g, 90% yield). ^{1}H-NMR ($CDCl_3$): δ 7.40-7.23 (m, 10H), 4.43 (s, 2H), 4.14-4.08 (m, 4H), 2.35-1.93 (m, 8H), 1.24 (t, *J* = 8.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 145.4, 139.0, 128.6, 128.5, 127.5, 127.4, 127.2, 125.8, 78.1, 65.4, 61.0, 53.5, 40.7, 37.3, 28.6, 14.9.

8-Ethoxycarbonyl-3β-(4′-chlorophenyl)-3α-phenylmethoxy-8-azabicyclo[3.2.1]octane (58b).

General procedure E. This compound was obtained as a light yellow oil (296 mg, 30% yield). ^{1}H-NMR ($CDCl_3$): δ 7.34-7.22 (m, 9H), 4.39 (s, 2H), 4.16-4.10 (m, 4H), 2.32-1.59 (m, 8H), 1.24 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.0, 144.0, 138.7, 133.4, 128.8, 128.6, 127.5, 127.3, 127.2, 77.8, 65.5, 61.1, 53.3, 28.1, 14.9.

8-Ethoxycarbonyl-3β-(4′-fluorophenyl)-3α-phenylmethoxy-8-azabicyclo[3.2.1]octane (58c).

General procedure E. This compound was obtained as a light yellow oil (390 mg, 40% yield). ^{1}H-NMR ($CDCl_3$): δ 7.37-6.98 (m, 9H), 4.39 (s, 2H), 4.13-4.10 (m, 4H), 2.34-1.93 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 163.3, 160.9, 153.9, 141.3, 138.8, 128.5, 127.6, 127.5, 127.5, 115.5, 77.7, 65.4, 61.1, 53.3, 40.8, 37.4, 27.8, 14.9.

8-Ethoxycarbonyl-3β-(4′-trifluoromethanephenyl)-3α-phenylmethoxy-8-azabicyclo [3.2.1]octane (58d).

General procedure E. This compound was obtained as a light yellow oil (780 mg, 82.3% yield). ^{1}H-NMR ($CDCl_3$): δ 7.60-7.23 (m, 9H), 4.41 (s, 2H), 4.16-4.11 (m, 4H), 2.34-1.97 (m, 8H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 149.5, 138.5, 129.9, 128.6, 127.2, 126.2, 125.7, 78.1, 65.7, 61.1, 53.3, 40.7, 37.1, 28.6, 14.9.

8-Ethoxycarbonyl-3β-(3′,4′-dichlorophenyl)-3α-phenylmethoxy-8-azabicyclo[3.2.1]octane (58e).

General procedure E. This compound was obtained as a light yellow oil (815 mg, 72% yield). ^{1}H-NMR ($CDCl_3$): δ 7.47-7.22 (m, 8H), 4.40 (s, 2H), 4.16-4.11 (m, 4H), 2.31-1.94 (m, 8H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 145.9, 138.3, 132.8, 131.6, 130.6, 128.6, 128.1, 127.6, 127.3, 125.4, 77.6, 65.7, 61.1, 53.0, 40.6, 37.1, 28.5, 14.9.

8-Ethoxycarbonyl-3β-phenyl-3α-(3″, 4″-dichlorophenyl)methoxy-8-azabicyclo[3.2.1]octane (58f).

General procedure E. This compound was obtained as a light yellow oil (380 mg, 24% yield). ^{1}H-NMR ($CDCl_3$): δ 7.37-7.03 (m, 8H), 4.43 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.02 (s, 2H), 2.34-1.97 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 144.8, 139.3, 132.6, 130.4, 128.7, 127.8, 126.4, 125.7, 78.4, 64.1, 61.1, 53.3, 37.4, 28.2, 14.9.

8-Ethoxycarbonyl-3β -(4′-chlorophenyl)-3α -(3″,4″-dichlorophenyl)methoxy-8-azabicyclo [3.2.1] octane (58g).

General procedure E. This compound was obtained as a light yellow oil (796 mg, 62% yield). ^{1}H-NMR ($CDCl_3$): δ 7.38-7.02 (m, 7H), 4.40 (s, 2H), 4.13 (q, *J* = 6.8 Hz, 2H), 4.04 (s, 2H), 2.30-1.97 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 143.8, 138.9, 133.6, 132.5, 131.3, 130.5, 128.9, 128.8, 127.1, 126.3, 78.0, 64.1, 61.1, 53.0, 40.5, 37.0, 28.5, 14.9.

8-Ethoxycarbonyl-3β -(4′-fluorophenyl)-3α -(3″,4″-dichlorophenyl)methoxy-8-azabicyclo [3.2.1]octane (58h).

General procedure E. This compound was obtained as a light yellow oil (230 mg, 20% yield). ^{1}H-NMR ($CDCl_3$): δ 7.38-6.99 (m, 7H), 4.39 (s, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 2.32-1.96 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 163.4, 153.9, 140.7, 139.0, 130.5, 128.9, 127.4, 126.3, 115.6, 77.9, 64.1, 61.2, 53.2, 40.7, 37.4, 28.6, 14.9.

8–Ethoxycarbonyl-3β-(4′-trifluoromethane phenyl)-3α -(3″, 4″-dichlorophenyl) methoxy – 8 – azabicyclo [3.2.1] octane (58i).

General procedure E. This compound was obtained as a light yellow oil (687 mg, 55% yield). ^{1}H-NMR ($CDCl_3$): δ 7.61-7.03 (m, 7H), 4.42 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 2H), 2.33-1.97 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 148.8, 138.7, 130.5, 128.9, 126.3, 126.1, 125.8, 78.3, 64.4, 61.2, 52.9, 40.6, 37.0, 28.6, 27.6, 14.9.

8–Ethoxycarbonyl- 3β-(3′, 4′-dichlorophenyl)-3α -(3″, 4″- dichlorophenyl) methoxy–8– aza bicyclo[3.2.1] octane (58j).

General procedure E. This compound was obtained as a light yellow oil (850 mg, 57% yield). ^{1}H-NMR ($CDCl_3$): δ 7.41-7.02 (m, 6H), 4.43 (s, 2H), 4.12 (q, *J* = 6.8 Hz, 2H), 4.02 (s, 2H), 2.28-1.98 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 145.3, 138.6, 133.0, 132.7, 131.9, 131.6, 130.8, 130.6, 129.1, 128.0, 126.4, 125.2, 77.9, 64.5, 61.2, 53.1, 40.6, 37.1, 28.6, 27.7, 14.9.

8–Ethoxycarbonyl-3β-phenyl-3α -(4″-chlorophenyl)methoxy–8–azabicyclo[3.2.1]octane (58k).

General procedure E. This compound was obtained as a light yellow oil (300 mg, 40% yield). ^{1}H-NMR ($CDCl_3$): δ 7.38-7.15 (m, 9H), 4.39 (s, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.06 (s, 2H), 2.33-1.95 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 144.0, 133.0, 131.2, 129.7, 128.7, 128.6, 128.6, 127.7, 127.2, 125.8, 124.5, 77.43, 64.7, 61.1, 53.5, 27.9, 14.9.

8–Ethoxycarbonyl-3β -(4′-chlorophenyl)-3α -(4″-chlorophenyl)methoxy–8–azabicyclo [3.2.1] octane (58l).

General procedure E. This compound was obtained as a light yellow oil (616 mg, 40% yield). ^{1}H-NMR ($CDCl_3$): δ 7.32-7.15 (m, 8H), 4.42 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.02 (s, 2H), 2.29-1.93 (m, 8H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.0, 143.8, 137.2, 135.5, 133.6, 133.3, 128.8, 128.7, 128.6, 128.5, 127.3, 126.1, 77.9, 64.8, 61.2, 53.3, 40.7, 37.2, 28.6, 27.7, 14.9.

8–Ethoxycarbonyl-3β -(4′-trifluoromethanephenyl)-3α -(4″-chlorophenyl)methoxy–8–aza bicyclo[3.2.1] octane (58m).

General procedure E. This compound was obtained as a light yellow oil (1.0 g, 56% yield). ^{1}H-NMR ($CDCl_3$): δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.45 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.04 (s, 2H), 2.32-1.95 (m, 8H), 1.25 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 149.1, 136.8, 133.3, 130.0, 129.7, 128.7, 126.1, 125.7, 78.2, 64.9, 61.1, 53.2, 40.7, 37.0, 28.6, 14.8.

8–Ethoxycarbonyl-3β -(4′-fluorophenyl)-3α -(4″-fluorophenyl)methoxy–8–azabicyclo [3.2.1] octane (58n).

General procedure E. This compound was obtained as a light yellow oil (493 mg, 30% yield). ^{1}H-NMR ($CDCl_3$): δ 7.36-6.97 (m, 8H), 4.38 (s, 2H), 4.11 (q, *J* = 6.8 Hz, 2H), 4.04 (s,

2H), 2.32-1.94 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 163.5, 161.1, 153.9, 141,1, 134.5, 128.9, 127.6, 115,5, 77.7, 64.7, 61.1, 53.2, 40.7, 37.3, 28.5, 14.9.

8–Ethoxycarbonyl-3β -(4′-trifluoromethanephenyl)-3α -(4″-trifluoromethanephenyl) methoxy –8–azabicyclo[3.2.1]octane (58o).

General procedure E. This compound was obtained as a light yellow oil (955 mg, 60% yield). ^{1}H-NMR ($CDCl_3$): δ 7.58 (t, *J* = 5.2 Hz, 4H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 4.46 (s, 2H), 4.21 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.35-1.97 (m, 8H), 1.25 (t, *J* = 6.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 148.9, 142.5, 129.8, 127.2, 125.7, 125.5, 122.9, 78.3, 65.0, 61.2, 53.2, 40.7, 37.2, 28.6, 14.9.

8–Ethoxycarbonyl-3β-(4′-chlorophenyl)-3α -(4″-trifluoromethanephenyl)methoxy–8–aza bicyclo[3.2.1] octane (58p).

General procedure E. This compound was obtained as a light yellow oil (683 mg, 57% yield). ^{1}H-NMR ($CDCl_3$): δ 7.58-7.25 (m, 8H), 4.44 (s, 2H), 4.18 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.32-1.95 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 143.5, 142.7, 133.6, 128.8, 127.1, 125.5, 125.4, 78.0, 64.7, 61.1, 53.2, 40.6, 37.2, 28.6, 14.8.

8–Ethoxycarbonyl-3β-(3′, 4′-dichlorophenyl)-3α -(4″-trifluoromethane phenyl)methoxy– 8 –azabicyclo[3.2.1]octane (58q).

General procedure E. This compound was obtained as a light yellow oil (690 mg, 47% yield). ^{1}H-NMR ($CDCl_3$): δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.44-7.34 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.41 (s, 2H), 4.16-4.11 (m, 4H), 2.32-1.96 (m, 8H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 153.9, 145.3, 142.4, 132.9, 130.7, 128.0, 125.6, 125,5, 125.2, 77.8, 64.9, 61.2, 53.0, 40.5, 37.0, 28.5, 14.8.

General procedure F. Decarbonylation via hydrazine hydrate/KOH.

The benzylether derivative (**58a-q**) or the 8-azabicyclo[3.2.1]oct-2-ene derivative (**66a-e**) was dissolved in ethyleneglycol (20-30 mL). Potassium hydroxide (26 equiv.) and hydrazine hydrate (5 equiv.) were added to the flask and the mixture was heated at reflux for 3 h. Upon cooling to room temperature, the reaction mixture was partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1) to afford the *N*-H benzylether derivatives **59a-q** or *N*-H 3-aryl-2-nortropene derivatives **65a-e**.

3β-Phenyl-3α–phenylmethoxy-8–azabicyclo[3.2.1]nortropane (59a).

General procedure F. This compound was obtained as a light yellow oil (660 mg, 55% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.40-7.17 (m, 10H), 4.06 (s, 2H), 3.70 (s, 2H), 2.36-1.80 (m, 8H). Anal. Calcd for $C_{20}H_{23}NO•HCl•0.25H_2O$: C, 71.84; H, 7.39; N, 4.19. Found: C, 71.58; H, 7.37; N, 4.18.

3β-(4′-Chlorophenyl)-3α–phenylmethoxy-8–azabicyclo[3.2.1]nortropane (59b).

General procedure F. This compound was obtained as a light yellow oil (226 mg, 90% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.36-7.21 (m, 9H), 4.09 (s, 2H), 3.73 (s, 2H), 2.34-1.79 (m, 8H). Anal. Calcd for $C_{20}H_{22}ClNO•C_2H_2O_4$: C, 63.23; H, 5.79; N, 3.35. Found: C, 63.08; H, 5.67; N, 3.32.

3β-(4′-Fluorophenyl)-3α–phenylmethoxy-8–azabicyclo[3.2.1]nortropane (59c).

General procedure F. This compound was obtained as a light yellow oil (261 mg, 87% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.40-6.97 (m, 9H), 4.07 (s, 2H), 3.66 (s, 2H), 2.35-1.77 (m, 8H). Anal. Calcd for $C_{20}H_{22}FNO•C_2H_2O_4•0.5H_2O$: C, 64.38; H, 6.14; N, 3.41. Found: C, 64.09; H, 6.13; N, 3.49.

3β-(4′-Trifluoromethanephenyl)-3α–phenylmethoxy-8–azabicyclo[3.2.1]nortropane (59d).

General procedure F. This compound was obtained as a light yellow oil (418 mg, 69% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.55 (q, J = 8.4 Hz, 4H), 7.35-7.25 (m, 5H), 4.10 (s, 2H), 3.67 (s, 2H), 2.35-1.78 (m, 8H). Anal. Calcd for $C_{21}H_{22}F_3NO•C_2H_2O_4$: C, 61.19; H, 5.36; N, 3.10. Found: C, 61.32; H, 5.55; N, 3.15.

3β-(3′, 4′-Dichlorophenyl)-3α–phenylmethoxy-8–azabicyclo[3.2.1]nortropane (59e).

General procedure F. This compound was obtained as a light yellow oil (590 mg, 92% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.51-7.24 (m, 8H), 4.09 (s, 2H), 3.67 (s, 2H), 2.31-1.77 (m, 8H). Anal. Calcd for $C_{20}H_{21}Cl_2NO•C_2H_2O_4$: C, 58.42; H, 5.13; N, 3.10. Found: C, 58.16; H, 5.21; N, 3.05.

3β-Phenyl-3α–(3″, 4″-dichlorophenyl)methoxy-8–azabicyclo[3.2.1]nortropane (59f).

General procedure F. This compound was obtained as a light yellow oil (212 mg, 85% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.39-7.05 (m, 8H), 4.04 (s, 2H), 3.73 (s, 2H), 2.42-1.86 (m, 8H). Anal. Calcd for $C_{20}H_{21}Cl_2NO•C_2H_2O_4•0.5H_2O$: C, 57.28; H, 5.24; N, 3.04. Found: C, 57.32; H, 5.13; N, 3.07.

3β-(4′-Chlorophenyl)-3α–(3″, 4″-dichlorophenyl)methoxy-8–aza[3.2.1]nortropane (59g).

General procedure F. This compound was obtained as a light yellow oil (591 mg, 93% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.38-7.04 (m, 7H), 4.02 (s, 2H), 3.68 (s, 2H), 2.31-1.78 (m, 8H). Anal. Calcd for $C_{20}H_{20}Cl_3NO\bullet C_2H_2O_4$: C, 54.28; H, 4.56; N, 2.88. Found: C, 54.26; H, 4.63; N, 2.81.

3β-(4′-Fluorophenyl)-3α–(3″, 4″-dichlorophenyl)methoxy-8–aza[3.2.1]-nortropane (59h).

General procedure F. This compound was obtained as a light yellow oil (162 mg, 90% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.38-7.32 (m, 4H), 7.06-6.98 (m, 3H), 4.02 (s, 2H), 3.70 (s, 2H), 2.34-1.81 (m, 8H). Anal. Calcd for $C_{20}H_{20}Cl_2FNO\bullet C_2H_2O_4\cdot H_2O$: C, 54.11; H, 4.95; N, 2.87. Found: C, 53.92; H, 4.77; N, 2.71.

3β-(4′-Trifluoromethanephenyl)-3α– (3″, 4″-dichlorophenyl)methoxy-8–azabicyclo[3.2.1] nortropane (59i).

General procedure F. This compound was obtained as a light yellow oil (498 mg, 92.5% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.59 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 4.04 (s, 2H), 3.72 (s, 2H), 2.34-1.81 (m, 8H). Anal.

Calcd for $C_{21}H_{20}Cl_2F_3NO•C_2H_2O_4•0.5H_2O$: C, 52.19; H, 4.38; N, 2.65. Found: C, 52.50; H, 4.37; N, 2.73.

3β-(3′,4′-Dichlorophenyl)-3α–(3″,4″-dichlorophenyl)methoxy-8–azabicyclo[3.2.1] nortropane (59j).

General procedure F. This compound was obtained as a light yellow oil (620 mg, 88% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.46-7.34 (m, 4H), 7.22 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 4.04 (s, 2H), 3.70 (s, 2H), 2.30-1.79 (m, 8H). Anal. Calcd for $C_{20}H_{19}Cl_4NO•C_2H_2O_4$: C, 50.70; H, 4.06; N, 2.69. Found: C, 50.71; H, 4.12; N, 2.76.

3β-Phenyl-3α–(4″-chlorophenyl)methoxy-8–azabicyclo[3.2.1]nortropane (59k).

General procedure F. This compound was obtained as a light yellow oil (209 mg, 85% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.40-7.17 (m, 9H), 4.06 (s, 2H), 3.70 (s, 2H), 2.36-1.80 (m, 8H). Anal. Calcd for $C_{20}H_{22}ClNO•C_2H_2O_4$: C, 63.23; H, 5.79; N, 3.35. Found: C, 62.95; H, 5.81; N, 3.32.

3β-(4′-Chlorophenyl)-3α–(4″-chlorophenyl)methoxy-8–azabicyclo[3.2.1]nortropane (59l).

General procedure F. This compound was obtained as a light yellow oil (143 mg, 70% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.32-7.16 (m, 8H), 4.04 (s, 2H), 3.69 (s, 2H), 2.28-1.79 (m, 8H). Anal. Calcd for $C_{20}H_{21}Cl_2NO•C_2H_2O_4$: C, 58.42; H, 5.13; N, 3.10. Found: C, 58.33; H, 5.12; N, 3.12.

3β-(4′-Trifluoromethanephenyl)-3α– (4″-chlorophenyl)methoxy-8–azabicyclo[3.2.1] nortropane (59m).

General procedure F. This compound was obtained as a light yellow oil (390 mg, 46% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.59 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 4.06 (s, 2H), 3.70 (s, 2H), 2.34-1.79 (m, 8H). Anal. Calcd for $C_{21}H_{21}ClF_3NO•HCl•0.75H_2O$: C, 53.86; H, 5.60; N, 2.99. Found: C, 54.06; H, 5.53; N, 2.97.

3β- (4′-Fluorophenyl)- 3α– (4″-fluorophenyl) methoxy-8–azabicyclo[3.2.1]nortropane (59n).

General procedure F. This compound was obtained as a light yellow oil (366 mg, 97% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.38-7.35 (m, 2H), 7.20-7.17 (m, 2H), 7.02-6.97 (m, 4H),

4.02 (s, 2H), 3.67 (s, 2H), 2.34-1.78 (m, 8H). Anal. Calcd for $C_{20}H_{21}F_2NO•C_2H_2O_4•0.25H_2O$: C, 62.33; H, 5.59; N, 3.39. Found: C, 62.34; H, 5.75; N, 3.35.

3β-(4′-Trifluoromethanephenyl)-3α– (4″-trifluoromethanephenyl)methoxy-8–azabicyclo [3.2.1]nortropane (59o).

General procedure F. This compound was obtained as a light yellow oil (610 mg, 85% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.59-7.51 (m, 6H), 7.39 (d, J = 8.0 Hz, 2H), 4.16 (s, 2H), 3.75 (s, 2H), 2.37-1.84 (m, 8H). Anal. Calcd for $C_{22}H_{21}F_6NO•C_2H_2O_4•H_2O$: C, 53.63; H, 4.69; N, 2.61. Found: C, 53.46; H, 4.77; N, 2.78.

3β-(4′-Chlorophenyl)-3α–(4″-trifluoromethanephenyl)methoxy-8–azabicyclo [3.2.1]nortropane (59p).

General procedure F. This compound was obtained as a light yellow oil (436 mg, 81% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.58-7.26 (m, 8H), 4.13 (s, 2H), 3.68 (s, 2H), 2.34-1.78 (m, 8H).

3β -(3′, 4′-Dichlorophenyl)-3α–(4″-trifluoromethanephenyl)methoxy-8–azabicyclo[3.2.1] nortropane (59q).

General procedure F. This compound was obtained as a light yellow oil (472 mg, 85% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.60 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 2.4 Hz, 2H), 7.37 (t, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 1H), 4.14 (s, 2H), 3.68 (s, 2H), 2.32-1.78 (m, 8H). Anal. Calcd for $C_{21}H_{20}Cl_2F_3NO\bullet C_2H_2O_4$: C, 53.09; H, 4.26; N, 2.69. Found: C, 53.09; H, 4.42; N, 2.80.

General procedure G. N-*Methylation of secondary amines.*

The secondary amine (**59a-q**) was dissolved in CH_3CN (7-10 mL) and 37% aqueous formaldehyde solution (5 equiv.) was added to it followed by sodium cyanoborohydride (1.5 equiv.). The reaction mixture was stirred for 10 minutes, and then glacial acetic acid was added dropwise until the solution became neutral. The reaction mixture was stirred at room temperature for another 1 h. A saturated solution of $NaHCO_3$ was added to basify the mixture and the solvent was removed under reduced pressure. The residue was partitioned between water and Et_2O. Aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$, 96:3.5:0.5) to afford the *N*-methyl benzylether derivatives **60a-q.**

3β-Phenyl-3α–phenylmethoxy-8-methyl-8–azabicyclo[3.2.1]octane (60a).

General procedure G. This compound was obtained as a light yellow oil (515 mg, 82% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.44-7.22 (m, 10H), 4.10 (s, 2H), 3.25 (s, 2H), 2.35 (s, 3H), 2.32-1.98 (m, 8H). Anal. Calcd for $C_{22}H_{21}F_6NO•C_2H_2O_4•H_2O$: C, 53.63; H, 4.69; N, 2.61. Found: C, 53.46; H, 4.77; N, 2.78.

3β-(4′-Chlorophenyl)-3α–phenylmethoxy-8-methyl -8–azabicyclo[3.2.1]octane (60b).

General procedure G. This compound was obtained as a light yellow oil (159 mg, 79% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.39-7.24 (m, 9H), 4.10 (s, 2H), 3.32 (s, 2H), 2.39 (s, 3H), 2.34-2.02 (m, 8H). Anal. Calcd for $C_{21}H_{24}ClNO•C_2H_2O_4•0.25H_2O$: C, 63.30; H, 6.12; N, 3.21. Found: C, 63.02; H, 6.20; N, 3.25.

3β-(4′-Fluorophenyl)-3α–phenylmethoxy-8-methyl-8–azabicyclo[3.2.1]octane (60c).

General procedure G. This compound was obtained as a light yellow oil (80 mg, 50% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.45-6.98 (m, 9H), 4.11 (s, 2H), 3.44 (s, 2H), 2.48 (s, 3H), 2.33-2.08 (m, 8H). Anal. Calcd for $C_{21}H_{24}FNO•C_2H_2O_4$: C, 66.49; H, 6.31; N, 3.37. Found: C, 66.19; H, 6.39; N, 3.38.

3β-(4′-Trifluoromethanephenyl)-3α–phenylmethoxy-8-methy-8–azabicyclo[3.2.1]octane (60d).

General procedure G. This compound was obtained as a light yellow oil (214 mg, 84% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.56-7.26 (m, 9H), 4.11 (s, 2H), 3.29 (s, 2H), 2.36 (s, 3H), 2.28-2.02 (m, 8H). Anal. Calcd for $C_{22}H_{24}F_3NO•C_2H_2O_4$: C, 61.93; H, 5.63; N, 3.01. Found: C, 62.04; H, 5.67; N, 2.98.

3β-(3′, 4′-Dichlorophenyl)-3α–phenylmethoxy-8-methyl-8–azabicyclo[3.2.1]octane (60e).

General procedure G. This compound was obtained as a light yellow oil (340 mg, 87% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.53-7.24 (m, 8H), 4.10 (s, 2H), 3.30 (s, 2H), 2.36 (s, 3H), 2.31-2.01 (m, 8H). Anal. Calcd for $C_{21}H_{23}Cl_2NO•C_2H_2O_4$: C, 59.24; H, 5.40; N, 3.00. Found: C, 59.00; H, 5.47; N, 2.97.

3β-Phenyl-3α–(3″, 4″-dichlorophenyl)methoxy-8-methyl-8–azabicyclo[3.2.1]octane (60f).

General procedure G. This compound was obtained as a light yellow oil (149 mg, 82% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.42-7.08 (m, 8H), 4.06 (s, 2H), 3.39 (s, 2H), 2.44 (s, 3H), 2.29-2.04 (m, 8H). Anal. Calcd for $C_{21}H_{23}Cl_2NO•C_2H_2O_4$: C, 59.24; H, 5.40; N, 3.00. Found: C, 59.05; H, 5.60; N, 2.98.

3β- (4′-Chlorophenyl)-3α– (3″, 4″-dichlorophenyl)methoxy-8-methyl-8–azabicyclo [3.2.1] octane (60g).

General procedure G. This compound was obtained as a light yellow oil (360 mg, 90% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.38-7.04 (m, 7H), 4.02 (s, 2H), 3.30 (s, 2H), 2.35 (s, 3H), 2.27-2.02 (m, 8H). Anal. Calcd for $C_{21}H_{22}Cl_3NO•C_2H_2O_4$: C, 55.16; H, 4.83; N, 2.80. Found: C, 55.31; H, 4.85; N, 2.80.

3β-(4′-Fluorophenyl)-3α–(3″, 4″-dichlorophenyl)methoxy-8-methyl-8–azabicyclo [3.2.1] octane (60h).

General procedure G. This compound was obtained as a light yellow oil (74 mg, 79% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.43-7.35 (m, 4H), 7.06-7.00 (m, 3H), 4.08 (s, 2H), 3.56 (s, 2H), 2.57 (s, 3H), 2.34-2.14 (m, 8H). Anal. Calcd for $C_{21}H_{22}Cl_2FNO•C_2H_2O_4$: C, 57.04; H, 4.99; N, 2.89. Found: C, 56.81; H, 5.15; N, 2.78.

3β -(4′-Trifluoromethanephenyl)-3α – (3″,4″-dichlorophenyl)methoxy-8-methyl-8-azabicyclo[3.2.1]octane (60i).

General procedure G. This compound was obtained as a light yellow oil (316 mg, 84% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.59 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.38 (t, J

= 8.0 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.06 (s, 2H), 3.38 (s, 2H), 2.38 (s, 3H), 2.33-2.04 (m, 8H). Anal. Calcd for $C_{22}H_{22}Cl_2F_3NO \bullet C_2H_2O_4$: C, 53.95; H, 4.53; N, 2.62. Found: C, 53.77; H, 4.54; N, 2.66.

3β-(3′, 4′-Dichlorophenyl) -3α– (3″, 4″-dichlorophenyl)methoxy-8- methyl-8–azabicyclo [3.2.1]octane (60j).

General procedure G. This compound was obtained as a light yellow oil (366 mg, 67% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.48 (d, *J* = 2.4 Hz, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 7.35 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 2H), 3.35 (s, 2H), 2.39 (s, 3H), 2.36-2.01 (m, 8H). Anal. Calcd for $C_{21}H_{21}Cl_4NO \bullet C_2H_2O_4 \bullet 0.75H_2O$: C, 50.34; H, 4.50; N, 2.55. Found: C, 50.43; H, 4.57; N, 2.57.

3β-Phenyl-3α–(4″-chlorophenyl)methoxy-8-methyl-8–azabicyclo[3.2.1]octane (60k).

General procedure G. This compound was obtained as a light yellow oil (144 mg, 84% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.44-7.18 (m, 9H), 4.08 (s, 2H), 3.41 (s, 2H), 2.46 (s, 3H), 2.31-2.05 (m, 8H). Anal. Calcd for $C_{21}H_{24}ClNO \bullet C_2H_2O_4$: C, 63.96; H, 6.07; N, 3.24. Found: C, 64.21; H, 5.98; N, 3.20.

3β-(4′-Chlorophenyl)-3α–(4″-chlorophenyl)methoxy-8-methyl-8–azabicyclo[3.2.1]octane (60l).

General procedure G. This compound was obtained as a light yellow oil (129 mg, 79% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.34-7.16 (m, 8H), 4.03 (s, 2H), 3.26 (s, 2H), 2.34 (s, 3H), 2.25-2.02 (m, 8H). Anal. Calcd for $C_{21}H_{23}Cl_2NO•HCl•H_2O$: C, 58.55; H, 6.08; N, 3.25. Found: C, 58.53; H, 6.19; N, 3.28.

3β-(4′-Trifluoromethanephenyl)-3α–(4″-chlorophenyl)methoxy-8-methyl-8–azabicyclo[3.2.1]octane (60m).

General procedure G. This compound was obtained as a light yellow oil (117 mg, 60% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.56 (q, J = 8.8 Hz, 4H), 7.31 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 4.07 (s, 2H), 3.33 (s, 2H), 2.39 (s, 3H), 2.27-2.03 (m, 8H). Anal. Calcd for $C_{22}H_{23}ClNO•HCl•0.75H_2O$: C, 57.46; H, 5.59; N, 3.05. Found: C, 57.22; H, 5.54; N, 3.09.

3β-(4′-Fluorophenyl)-3α–(4″-fluorophenyl)methoxy-8-methyl-8–azabicyclo[3.2.1]octane (60n).

General procedure G. This compound was obtained as a light yellow oil (152 mg, 68% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.42-7.38 (m, 2H), 7.21-7.02 (m, 2H), 7.00 (t, J = 8.4 Hz,

4H), 4.05 (s, 2H), 3.38 (s, 2H), 2.43 (s, 3H), 2.29-2.04 (m, 8H). Anal. Calcd for $C_{21}H_{23}F_2NO \bullet C_2H_2O_4$: C, 63.73; H, 5.81; N, 3.27. Found: C, 63.52; H, 5.82; N, 3.27.

3β-(4′-Trifluoromethanephenyl)-3α–(4″-trifluoromethanephenyl)methoxy-8-methyl-8–azabicyclo[3.2.1]octane (60o).

General procedure G. This compound was obtained as a light yellow oil (340 mg, 70% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.60-7.51 (m, 6H), 7.39 (d, *J* = 7.6 Hz, 2H), 4.16 (s, 2H), 3.30 (s, 2H), 2.36 (s, 3H), 2.31-2.03 (m, 8H). Anal. Calcd for $C_{23}H_{23}F_6NO \bullet C_2H_2O_4 \bullet 0.5H_2O$: C, 55.35; H, 4.83; N, 2.58. Found: C, 55.36; H, 4.93; N, 2.66.

3β -(4′-Chlorophenyl)-3α – (4″-trifluoromethanephenyl)methoxy-8-methyl-8–azabicyclo [3.2.1]octane (60p).

General procedure G. This compound was obtained as a light yellow oil (307 mg, 95% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.37-7.26 (m, 6H), 4.14 (s, 2H), 3.29 (s, 2H), 2.35 (s, 3H), 2.26-2.04 (m, 8H).

3β-(3′,4′-Dichlorophenyl)-3α–(4″-trifluoromethanephenyl)methoxy-8-methyl-8–azabicyclo [3.2.1]octane (60q).

General procedure G. This compound was obtained as a light yellow oil (300 mg, 89% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.37 (q, *J* = 4.0 Hz, 3H), 7.25 (d, *J* = 8.8 Hz, 1H), 4.15 (s, 2H), 3.29 (s, 2H), 2.35 (s, 3H), 2.30-2.02 (m, 8H). Anal. Calcd for $C_{22}H_{22}Cl_2F_3NO•C_2H_2O_4$: C, 53.95; H, 4.53; N, 2.62. Found: C, 54.18; H, 4.55; N, 2.60.

General procedure H. β-elimination.

The tertiary alcohol (**55a-e**) was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (1 equiv.) was added to the solution. The reaction mixture was stirred at room temperature for 2 h. After the completion of the reaction, water was added to it. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford the product (**66a-e**).

8–Ethoxycarbonyl-3-phenyl-8-azabicyclo[3.2.1]oct-2-ene (66a).

General procedure H. This compound was obtained as a colorless oil (189 mg, 68% yield). ^{1}H-NMR ($CDCl_3$): δ 7.37-7.24 (m, 5H), 6.43 (s, 1H), 4.56 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.14 (s, 1H), 2.26-1.68 (m, 5H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.5, 139.9, 135.3, 128.5, 127.5, 124.9, 61.0, 53.3, 52.1, 36.34, 34.9, 30.2, 14.8.

8–Ethoxycarbonyl-3-(4′-chlorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (66b).

General procedure H. This compound was obtained as a colorless oil (592 mg, 90% yield). ^{1}H-NMR ($CDCl_3$): δ 7.33-7.21 (m, 4H), 6.41 (s, 1H), 4.55 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.05 (s, 1H), 2.20-1.70 (m, 5H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.5, 138.3, 133.3, 129.2, 128.6, 126.5, 126.3, 61.2, 53.3, 52.0, 36.4, 34.9, 29.8, 14.8.

8–Ethoxycarbonyl-3-(4′-fluorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (66c).

General procedure H. This compound was obtained as a colorless oil (434 mg, 92.5% yield). ^{1}H-NMR ($CDCl_3$): δ 7.26-7.19 (m, 2H), 6.94-6.89 (m, 2H), 6.29 (s, 1H), 4.48 (s, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.04 (s, 1H), 2.15-1.89 (m, 5H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 163.5, 161.1, 154.4, 136.0, 128.4, 126.6, 115.3, 61.1, 53.3, 52.0, 36.5, 34.2, 29.4, 14.7.

8–Ethoxycarbonyl-3-(4′-trifluoromethanephenyl)-8-azabicyclo[3.2.1]oct-2-ene (66d).

General procedure H. This compound was obtained as a colorless oil (230 mg, 92% yield). ^{1}H-NMR ($CDCl_3$): δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 6.51 (s, 1H), 4.57 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.14 (s, 1H), 2.25-1.70 (m, 5H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.6, 143.5, 130.8, 130.4, 129.4, 125.5, 125.3, 123.0, 61.3, 53.4, 52.1, 35.9, 34.3, 29.5, 14.9.

8–Ethoxycarbonyl-3-(3′, 4′-dichlorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (66e).

General procedure H. This compound was obtained as a colorless oil (415 mg, 90% yield). ^{1}H-NMR ($CDCl_3$): δ 7.40-7.34 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 6.43 (s, 1H), 4.55 (s, 2H), 4.11 (q, J = 6.8 Hz, 2H), 3.06 (s, 1H), 2.06-1.93 (m, 5H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C-NMR ($CDCl_3$): δ 154.5, 140.0, 132.6, 131.3, 130.3, 127.0, 124.3, 61.2, 53.3, 52.0, 35.8, 34.8, 29.5, 14.8.

3-Phenyl-2-nortropene (65a).

General procedure F. This compound was obtained as colorless oil (38 mg, 29% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.37-7.20 (m, 5H), 6.44 (d, J = 5.6 Hz, 1H), 3.82 (dt, J_A = 5.6 Hz, J_{AB} = 24.4 Hz, 2H), 2.85 (dd, J_A = 4.0 Hz, J_{AB} = 16.8 Hz, 1H), 2.26-1.61 (m, 5H).

3-(4′-Chlorophenyl)-2-nortropene (65b).

General procedure F. This compound was obtained as colorless oil (399 mg, 92% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.28-7.18 (m, 4H), 6.42 (d, J = 3.6 Hz, 1H), 3.81 (dt, J_A = 5.6 Hz, J_{AB} = 22.8 Hz, 2H), 2.80 (dd, J_A = 4.4 Hz, J_{AB} = 16.8 Hz, 1H), 2.27-1.18 (m, 5H).

3-(4′-Fluorophenyl)-2-nortropene (65c).

General procedure F. This compound was obtained as colorless oil (160 mg, 60% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.32-7.28 (m, 2H), 7.00-76.83 (m, 2H), 6.36 (d, J = 5.6 Hz, 1H), 4.06 (t, J = 4.4 Hz, 1H), 3.93 (t, J = 4.8 Hz, 1H), 2.80 (d, J = 4.4 Hz, 1H), 2.21-1.16 (m, 5H).

3-(4′-trifluoromethanephenyl)-2-nortropene (65d).

General procedure F. This compound was obtained as colorless oil (150 mg, 88% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.55 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 5.6 Hz, 1H), 3.88 (t, J = 6.0 Hz, 1H), 3.83 (t, J = 5.6 Hz, 1H), 2.89 (dd, J_A = 4.0 Hz, J_{AB} = 16.8 Hz, 1H), 2.25-1.64 (m, 5H).

3-(3′, 4′-dichlorophenyl)-2-nortropene (65e).

General procedure F. This compound was obtained as colorless oil (277 mg, 95% yield) and converted into an oxalate salt (General Procedure A) which was obtained as a white solid. ^{1}H-NMR (free base, $CDCl_3$): δ 7.40-7.33 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 5.6 Hz, 1H), 3.86 (t, J = 5.2 Hz, 1H), 3.81 (t, J = 5.6 Hz, 1H), 2.82 (dd, J_A = 4.4 Hz, J_{AB} = 17.2 Hz, 1H), 2.17-1.86 (m, 5H).

3β-(4′-Chlorophenyl)-3α-diphenylmethoxytropane (67a).

Tertiary alcohol **41b** was heated to 185°C and chlorodiphenylmethane (0.84 mL, 2.4 equiv.) was added dropwise to the flask over 5 minutes. Evolution of HCl gas over 30 minutes resulted in a bronze oil which solidified to a glass upon cooling. The solid was dissolved in chloroform and purification was done by column chromatography ($CHCl_3/CH_3OH/NH_4OH$, 97:2.5:0.5) to yield **67a** in 35% yield as a yellow oil. It was converted into an oxalate salt (General Procedure A). ^{1}H-NMR (free base, $CDCl_3$): δ 7.20-6.97 (m, 14H), 4.99 (s, 1H), 3.32 (s, 2H), 2.52-2.49 (m, 4H), 2.38 (s, 3H), 2.09-1.88 (m, 4H). ^{13}C-NMR (free base, $CDCl_3$): δ 144.3, 143.0, 133.1, 128.2, 128.1, 127.7, 126.9, 126.6, 78.7, 76.9, 60.7, 40.4, 39.6, 25.1.

REFERENCES

1. Ruetsch, Y. A.; Boni, T.; Borgeat A. From Cocaine to Ropivocaine: The History of Local Anesthetic Drug. *Curr. Trends. Med. Chem.* **2001**, *1*, 175-182.

2. Niemann, N. Uber eine Neue Organische Base in den Cocabiattern [thesis], Gottingen, **1860**.

3. Ben-Zur, E. Die Geschichte der Lokalanashesie unter besonderer Berucksichtigung der Entdeckung des Kokains [thesis]; Zurich, **1960**.

4. Manheim, P. U. Z. Klin. Med., **1891**, *18*, 380.

5. Koller, C. Wien. Med. Wochenschr., **1884**, *34*, 1276.

6. Armstrong Davison, M. H. In The Evolution of Anaesthesia: Sherrat, J., ed.; Altrincham, **1965**, pp. 171-177.

7. Cahn, R. S.; Ingold, C. K.; Prelog, V. Specification of Molecular Chirality. *Angew. Chem., Intl. Ed. Engl.* **1966**, *5*, 385-415.

8. Carroll, F. I.; Lewin, A. H.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. Synthesis and Ligand Binding of Cocaine Isomers at the Cocaine Receptor. *J. Med. Chem.* **1991**, *34*, 883-886.

9. Commissaris, R. In Cocaine, Marijuana and Designer Drugs, Redda, K. K.; Walker, C.; Barnett, G. CRC Press: Boca Raton, Florida, **1989**, 71-81.

10. U. S. Drug Enforcement Administration, Drug of Abuse. http://www.usdoj.gov/dea (accessed April 2007).

11. Flynn, J. C. Cocaine: An In-depth Look at the Facts, Science, History, and Future of the World's Most Addictive Drug. Carol Publishing Group: New York, NY, 1991, pp. 42-46.

12. American Council for Drug Elucidation's Basic Facts about Drug Abuse: Cocaine. http://www.acde.org (accessed April 2007).

13. U. S. Department of Health and Human Service, office of applied Studies/National Survey on Drug Abuse and Health. http://www.oas.samhsa.gov/oasftp.cfm (accessed April 2007).

14. Perezreyes, M.; Jeffcoat, A. R. Comparison in Humans of the Potency and Pharmacokinetics of Intravenously Injected Cocaethylene and Cocaine. *Psychopharmacology* **1994**, *116*, 428-432.

15. Jaffe, J. H. Drug Addiction and Drug Abuse. In The Pharmacological Basis of Therapeutics: Gilman, A. G.; Rall, T. W.; Nies, A. S.; Taylor, P., eds., Pergamon Press: Elmsford, NY, 1990, pp 522-573.

16. Wise, R. A.; Bozarth, M. A. A Psychomotor Stimulant Theory of Addiction. *Psychosol. Rev.* **1987**, *94*, 469-492.

17. Johanson, C. E.; Fischman, M. W.; The Pharmacology of Cocaine Related to its Abuse. *Pharmacol. Rev.* **1989**, *41*, 3-52.

18. Schuster, C. R.; Kuhar, M. J. Pharmacological Aspects of Drug Dependence: Toward an Integrated Neurobehavioral Approach; Springer-Verlag: New York, **1996**; Vol. 118.

19. Woolverton, W. L.; Johnson, K. M. Neurobiology of Cocaine Abuse. *Trends Pharmacol. Sci.* **1992**, *13*, 193-200.

20. Hyman, S. E. Addiction to Cocaine and Amphetamine. *Neuron* **1996**, *16*, 901-904.

21. Cartwright, W. S. Cocaine Medications, Cocaine Consumption and Societal Costs. *Pharmacoeconomics* **2000**, 405-413.

22. Swan, N. Drug Abuse Cost to Society Set at $97.7 Billion, Continuing Steady Increase since 1975. *NIDA Notes* **1998**, 13.

23. The Economic Cost of Alcohol and Drug Abuse in the United States: National Clearinghouse for Alcohol and Drug Use. **1992**, BKD265.

24. Carroll, F. I.; Howell, L. L.; Kuhar, M. J. Pharmacotherapies for the Treatment of Cocaine Abuse. *J. Med. Chem.* **1999**, *42*, 2721-2736.

25. Dole, V. P.; Nyswander, M. E. A Medical Treatment for Diacetylmorphine (heroin) Addiction. *J. Am. Med. Assoc.* **1965**, *193*, 646-650.

26. Dole, V. P. Research on Addictive Behavior. *Clin. Invest. Med.* **1986**, *9*, 290-292.

27. Kreek, M. J. Rationale for Maintainenace Pharmacotherapy of Opiate Dependence. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* **1992**, *70*, 205-230.

28. Rose, J. E.; Behm, F. M.; Westman, E. C. Nicotine-mecamylamine Treatment for Smoking Cessation: The Role of Pre-cessation Therapy. *Exp. Clin. Psychopharmacol.* **1998**, *6*, 331-343.

29. Calligaro, D. O.; Eldefrawi, M. E. Central and Peripheral Cocaine Receptor. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 61-68.

30. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine Receptor: Biochemical Characterization and Structure-Activity Relationships for the Dopamine Transporter. *J. Med. Chem.* **1992**, *35*, 969-981.

31. Kuhar, M. J. Ritz, M. C.; Boja, J. W. The Dopamine Hypothesis of the Reinforcing Properties of Cocaine. *Trends Neurosci.* **1991**, *14*, 299-302.

32. Sharkey, J.; Ritz, M. C.; Schenden, J. A.; Hanson, R. C.; Kuhar, M. J. Cocaine Inhibits Muscarinic Cholinergic Receptor in Heart and Brain. *J. Pharmacol. Exp. Ther.* **1988**, *246*, 1048-1052.

33. Sharkey, J.; Glen, K. A.; Wolfe, S.; Kuhar, M. J. Cocaine Binding at σ Receptors. *Eur. J. Pharmacol.* **1988**, *149*, 171-174.

34. Cregler, L. L.; Mark, H.Cardiovascular Dangers of Cocaine Abuse. *Am. J. Cardiol.* **1985**, *57*, 1185-1186.

35. Griffiths, R. R. ; Bigelow, G. E.; Henningfield, J. E. Similarities in Animal and Human Drug-taking Behavior. In *Advances in Substances Abuse*; Mello, N. K., ed.; JAI Press Inc.: Greenwich, CT, **1980**; vol. 1, pp. 1-90.

36. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine Receptors on Dopamine Transporters are Related to Self-administration of Cocaine. *Science* **1987**, *237*, 1219-1223.

37. Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D. Effects of Cocaine and Related Drug in Nonhuman Primates. III. Self-administration by Squirrel Monkeys. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 150-155.

38. Wise, R. A.; Rompre, P. P. *Annu. Rev. Psychol.* **1985**, *40*, 191-225.

39. Giros, B.; Mestikawy, S. E.; Bertrand, L.; Caron, M. G. Cloning and Functional Characterization of a Cocaine-sensitive Dopamine Transporter. *FEBS Lett.* **1991**, *295*, 149-154.

40. Kilty, J. E.; Lorang, D. B.; Amara, S. G. Cloning and Expression of a Cocaine-sensitive Dopamine Transporter. *Science* **1991**, *254*, 578-579.

41. Shimada, S.; Kitayama, S.; Lin, C.-L.; Patel, A.; Nanthakumar, E.; Gregor, P.; Kuhar, M.; Uhl, G. Cloning and Expression of a Cocaine-sensitive Dopamine Transporter Complimentary DNA. *Science* **1991**, *254*, 576-578.

42. Bruss, M.; Wieland, A.; Bonisch, H. Molecular Cloning and Functional Expression of the Mouse Dopamine Transporter. *J. Neural Transm.* **1999**, *106*, 657-662.

43. Wu, X.; Gu, H. H. Molecular Cloning of the Mouse Dopamine Transporter and Pharmacological Comparison with the Human Homologue. *Gene* **1999**, *233*, 163-170.

44. Usdin, T. B.; Mezey, E.; Chen, C.; Brownstein, M. J.; Hoffman, B. J. Cloning of the Cocaine-sensitive Bovine Dopamine Transporter. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 11168-11171.

45. Vandenbergh, D. J.; Persico, A. M.; Hawkins, A. L.; Griffin, C. A.; Li, X.; Jabs, E. W. Uhl, G. R. Human Dopamine Transporter Gene (DAT1) Maps to Chromosome 5p15.3 and Displays a VNTR. *Geonomics* **1992**, *14*, 1104-1106.

46. Giros, B.; Jaber, M.; Jones, S. R.; Wightman, R. M.; Caron, M. G. Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature* **1996**, *379*, 606-612.

47. Chen, N.; Reith, M. E. A. Structure and Function of the Dopamine Transporter. *Eur. J. Pharmacol.* **2000**, *405*, 329-339.

48. Kitayama, S.; Shimada, S.; Xu, H.; Markham, L.; Donovan, D. M.; Uhl, G. R. Dopamine Transporter Site-Directed Mutations Differentially Alter Substrate Transport and Cocaine Binding. *Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7782-7785.

49. Drago, J.; Gerfen, C. R.; Lachowicz, J. E.; Steiner, H.; Hollon, T. R.; Love, P. E.; Ooi, G. T.; Grinberg, A.; Lee, E. J.; Huang, S. P. Altered Striatal Function in a Mutant Mouse Lacking D1A Dopamine Receptors. *Proc. Natn. Acad. Sci. U.S.A.* **1994**, *91*, 12564-12568.

50. Xu, M.; Moratalla, R.; Gold, L. H.; Hiroi, N.; Koob, G. F.; Graybiel, A. M.; Tonegawa, S. Dopamine D1 Receptor Mutant Mice are Deficient in Striatal Expression of Dynorphin and in Dopamine-Mediated Behavioral Responses. *Cell* **1994**, *79*, 729-742.

51. Balk, J.-H.; Picetti, R.; Saiardi, A.; Thirlet, G.; Dierich, A.; Depaulls, A.; Le Meur, M.; Borrelli, E. Parkinsonian-Like Locomotor Impairment in Mice Lacking Dopamine D2 Receptors. *Nature* **1995**, *377*, 424-428.

52. Spiz, M. L.; Rosecan, J. S.; Cocaine Abuse: New Directions in Treatment and Research. Brunner/Mazel: New York, NY, **1987**, 58-79.

53. Houston-Lyons, D.; Kornetsky, C. In *Cocaine: Pharmacology, Physiology and Clinical Strategies* Lakoski, J. M.; Galloway, M. P.; White, F. J., eds.; CRC Press: Boca Raton, Florida, **1992**, 47-71.

54. Kuhar, M. J.; Ritz, M. C.; Boja, J. W. The Dopamine Hypothesis of the Reinforcing Properties of Cocaine. *Trends in Neuroscience.* **1991**, *14*, 299-302.

55. Stocker, S. Cocaine's Pleasurable Effects May Involve Multiple Chemical Sites in the Brain. *NIDA Notes* **1999**, *14*, 5-7.

56. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, 1219-1223.

57. Horn, A. S. Dopamine Uptaker: A Review of Progress in the Last Decade. *Progr. Neurobiol.* **1990**, *34*, 387-400.

58. Reith, M. E. A.; Selmeci, G. Radiolabeling of Dopamine Uptake Sites in Mouse Striatum: Comparison of Binding Sites for Cocaine, Mazindol and GBR12935. *Naunyn-Schmeideberg's Arch. Pharmacol.* **1992**, *345*, 309-318.

59. Boja, J. W.; Vaughan, R. A.; Patel, A.; Shaya, E.; Kuhar, M. J. The Dopamine Transporter, in *Dopamine Receptors and Transporters: Pharmacology, Structure and Function* Niznik, H. B., ed.; Marcel Dekker, Inc., New York, **1994**, 611-644.

60. Reith, M. E. A.; Sersen, H.; Lajtha, A. Satiable [3H] Cocaine Binding in Central Nervous System of Mouse. *Life Sci.* **1980**, *27*, 1055-1062.

61. Madras, B. K.; Spealman, R. D.; Fahey, M. A.; Neumeyer, J. L.; Saha, J. K.; Milius, R. A. Cocaine Receptors labeled by [^{3}H]2β-carbomethoxy-3β-(4-fluorophenyl)tropane. *Mol. Pharmacol.* **1989**, *36*, 518-524.

62. Fahey, M. A.; Canfield, D. R.; Spealman, R. D.; Madras, B. K. Comparison of [^{3}H]GBR12935 and [3H]Cocaine Binding Sites in Monkey Brain. *Soc. Neurosci. Abstr.* **1989**, *15*, 1090.

63. Kennedy, L. T.; Hanbauer, I. Sodium-Sensitive Cocaine Binding to Rat Striatal Membrane: Possible Relation to Dopamine Uptake Sites. *J. Neurochem.* **1983**, *41*, 172-78.

64. Berger, P.; Elsworth, J. D.; Reith, M. E. A.; Tanen, D.; Roth, R. H. Complex Interaction of Cocaine with the Dopamine Uptake Carrier. *Eur. J. Pharmacol.* **1990**, *176*, 251-252.

65. Maurice, T.; Barbanel, G.; Kamenka, J.-M.; Vignon, J. Modulation of Dopamine of [^{3}H]N-[1-(2-benzo(b)thiophenyl)cyclohexyl]piperidine ([^{3}H] BTCP, a Phencyclidine Derivative) Binding to the Dopamine Uptake Complex. *Neuropharmacol.* **1991**, *30*, 591-598.

66. Maurice, T.; Barbanel, G.; Vignon, J. Endogeneous Dopamine Differently Affects N-[1-(2-benzo(b)thiophenyl)cyclohexyl]piperidine and Cocaine Binding to the Dopamine Uptake Complex. *Gen. Pharmacol.* **1993**, *24*, 191-194.

67. Wilson, J. M.; Nobrega, J. N.; Carroll, M. E.; Niznik, H. B.; Shannak, K.; Lac, S. T.; Pristupa, Z. B.; Dixon, L. M.; Kish, S. J. Heterogeneous Subregional Binding Patterns of [^{3}H]WIN 35,428 and [^{3}H]GBR 12,935 are Differentially Regulated by Chronic Cocaine Self-Administration. *J. Neurosci*. **1994**, *14*, 2966-79.

68. Izenwasser, S.; Terry, P.; Heller, B.; Witkin, J. M.; Katz, J. L. Differential Relationships Among Dopamine Transporter Affinities and Stimulant Potencies of Various Uptake Inhibitors. *Eur. J. Pharmacol.* **1994**, *263*, 277-283.

69. Kuhar, M. J.; Ritz, M. C.; Noja, J. W. The Dopamine Hypothesis of the Re-inforcing Properites of Cocaine. *Trends Neurosci.* **1991**, *14*, 299-301.

70. Madras, B. K.; Miller, G. M.; Meltzer, P. C.; Brownell, A.-L. Fischman, A. J. Molecular and Regional Targets of Cocaine in Primate Brain: Liberation from Prosaic Views. *Addiction Biol.* **2000**, *5*, 351-359.

71. Spanagal, R.; Weiss, F. The Dopamine Hypothesis of Reward: past and Current Status. *Trends Neurosci.* **1999**, *22*, 521-527.

72. Carboni, E.; Speilewoy, C.; Vacca, C.; Nosten-Bertrand, M.; Giros, B.; DiChiara, G. Cocaine and Amphetamine Increase Extracellular Dopamine in the Nucleus Accumbens of Mice Lacking the Dopamine Transporter Gene. *J. Neurosci.* **2000**, *21 (RC141)*, 1-4.

73. Rocha, B. A.; Fumagalli, F.; Gainetdinov, R. R.; Jones, S. R.; Ator, R.; Giros, B.; Miller, G. W.; Caron, M. G. Cocaine Self-Administration in Dopamine-Transporter Knockout Mice. *Nat. Neurosci.* **1998**, *1*, 132-137.

74. Sora, I.; Wichems C.; Takahashi, N.; Li, X.-F.; Zeng, Z.; Revay, R.; Lesch, K.-P.; Murphy, D. L.; Uhl. G. R. Cocaine Reward Models: Conditioned Place Preference can be Established in Dopamine- and in Serotonin- Transporter knockout Mice. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 7699-7704.

75. Uhl, G. R.; Hall, F. S.; Sora, I. Cocaine, Reward, Movement and Monoamine Transporters. *Molecular Psychiatry* **2002**, *7*, 21-25.

76. Witkin, J. M. Pharmacotherapy of Cocaine Abuse: Preclinical Development. *Neurosci. Behav. Rev.* **1994**, *18*, 121-142.

77. Carroll, F. I.; Lewin, A. H. (Substituted Phenyl) Tropan-2-Carboxylic Acid Ester Analogues of Cocaine. In *Drug Design for Neuroscience. J. Pharmaceut. News* **1994**, *1*, 11-16.

78. Tutton, C. S,; Crayton, J. W. Current Pharmacotherapies for Cocaine Abuse: A Review. *J. Addict. Dis.* **1993**, *12*, 109-127.

79. Withers, N. W.; Pulvirenti, L.; Koob, G. G.; Gillian, J. C. Cocaine Abuse and Dependence. *J. Clin. Psychopharmacol.* **1995**, *15*, 63-78.

80. Rockhold, R. W.; Oden, G.; Ho, I. K.; Andrew, M.; Farley, J. M. Glutamate Receptor Antagonists Block Cocaine-Induced Convulsions and Death. *Brain Res. Bull.* **1991**, *27*, 21-723.

81. Karler, R.; Calder, L. D. Excitatory Amino Acids and the Actions of Cocaine. *Brain Res.* **1992**, *582*, 143-146.

82. Svingos, A. L.; Hitzemann, R. 5-HT3 Receptor Antagonists Block Cocaine-Induced Locomotion via a PCPA-Sensitive Mechanism. *Pharmacol. Biochem. Behav.* **1992**, *43*, 871-879.

83. Suzuki, T.; Shiozaki, Y.; Masukawa, Y.; Misawa, M. 5-HT3 Antagonists Block Cocaine- and Methamphetamine-Induced Place-Preference. *J. Psychopharmacol.* **1992**, *12*, 33-38.

84. Koob, J. F.; Intravenous Drug Self-Administration Techniques in Animals. Behavioral Neuroscience: A Practcal Approach. *Science* **1993**, *18*, 1814.

85. Piercey, M. F.; Lum, J. T.; Hoffman, W. E.; Carlsson, A.; Ljung, E.; Svensson, K. Antagonism of Cocaine's Pharmacological Effects by the Stimulant Dopaminergic Antagonists, (+)-AJ76 and (+)-UH232. *Brain Res.* **1992**, *588*, 217-222.

86. Witkin, J. M.; Newman, A. H.; Nowak, G.; Katz, J. L. Role of Dopamine D1 Receptors in the Lethal Effects of Cocaine and a Quaternary Methiodide Analog. *J. Pharmacol. Exp. Ther.* **1993**, *267*, 266-274.

87. Pulvirenti, L.; Koob, G. F. Dopamine Receptor Agonists, Partial Agonists and Psychostimulant Addiction. *Trends Pharmacol. Sci.* **1994**, *15*, 374-379.

88. Self, D. W.; Barnhart, W. J.; Lehman, D. A.; Nestler, E. J. Opposite Modulation of Cocaine Seeking Behavior by D1- and D2-like Dopamine Receptor Agonists. *Science* **1996**, *271*, 1586-1589.

89. Ujike, H.; Kuroda, S.; Otsuki, S. Sigma Receptor Antagonists Block the Development of Sensitization to Cocaine. *Eur. J. Pharmacol.* **1996**, *296*, 123-128.

90. Menkel, M.; Terry, P.; Pontecorvo, M.; Katz, J. L.; Witkin, J. M. Selective σ Ligands Block Stimulant Effects of Cocaine. *Eur. J. Pharmacol.* **1991**, *201*, 251-252.

91. Heidbreder, C. A.; Goldberg, S. R.; Shippenberg, T. S. The Kappa-Opioid Receptor Agonists U-69593 Attenuates Cocaine-Induced Behavioral Sensitization in the Rat. *Brain. Res.* **1993**, *616*, 335-338.

92. Jones, D. N.; Bowen, W. D.; Portoghese, P. S.; Holtzman, S. G. Delta-Opioid Receptor Antagonists Attenuate Motor Activity Induced by Amphetamine but not Cocaine. *Eur. J. Pharmacol.* **1993**, *249*, 167-177.

93. Reid, L. D.; Hubbell, C. L.; Glaccum, M. B.; Bilsky, E. J.; Portoghese, P. S.' Porreca, F. Naltrindole, an Opioid Delta Receptor Antagonist, Blocks Cocaine-Induced Facilitation of Responding for Rewarding Brain Stimulation. *Life Sci.* **1993**, *52*, 67-71.

94. Kozikowski, A. P.; Roberti, M.; Xiang, L.; Bergman, J. S.; Callahan, P. M.; Patrick, M.; Cunningham, K. A.; Johnson, K. M.; Structure-Activity Relationship Studies of Cocaine:

Replacement of the C-2 Ester Group by Vinyl Argues Against H-Bonding and Provides an Esterase-Resistant, High-Affinity Cocaine Analogue. *J. Med. Chem.* **1992**, *35*, 4764-4766.

95. Kozikowski, A. P.; Xiang, L.; Tanaka, J. Bergamn, J. S.; Johnson, K. M. Use of Nitrile Oxide Cycloaddition (NOC) Chemistry in the Synthesis of Cocaine Analogues: Mazindol Binding and Dopamine Uptake Studies. *Med. Chem. Res.* **1991**, *1*, 312-330.

96. Kozikowski, A. P.; Araldi, G. L.; Boja, J.; Meil, W. M.; Johnson, K. M.; Flippen-Anderson, J. L.; George, C.; Saiah, E.; Chemistry and Pharmacology of Piperidine Based Analogs of Cocaine-Identification of Potent DAT Inhibitors Lacking the Tropane Skeleton. *J. Med. Chem.* **1998**, *41*, 1962-1969.

97. Thomas, G. Medicinal Chemistry: An Introduction, John Wiley & Sons, Ltd: New York, NY, 2000, pp. 306-321.

98. Cheng, Y. C.; Prusoff, W. H. Relationship Between the Inhibition Constant (K_i) and the Concentration of Inhibitor Which Causes 50 Percent Inhibition (IC_{50}) of an Enzymatic Reaction. *Biochemical Pharmacology* **1973**, *22*, 3099-3108.

99. Kozikowski, A. P.; Araldi, G. L.; Prakash, K. R. C.; Zhang, M.; Johnson, K. M. Synthesis and Biological Properties of New 2β-Alkyl- and 2β-Aryl-3-(Substituted Phenyl)tropane Derivatives: Stereochemical Effect of C-3 on Affinity and Selectivity for Neuronal Dopamine and Serotonin Transporters. *J. Med. Chem.* **1998**, *41*, 4973-4982.

100. Clarke, R. L.; The Tropane Alkaloids in Manske RHF, ed., *The Alkaloids*, Academic Press. New York, **1977**, *16*, Ch-2.

101. Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis, Ligand Binding and QSAR (CoMFA and Classical) Study of 3β-(3'-Substituted phenyl)-, 3β-(4'-Substituted phenyl) and 3β-(3',4'-Disubstituted Phenyl)tropane-2β-carboxylic acid Methyl Esters. **1994**, *J. Med. Chem. 37*, 2865-2873.

102. Carroll, F. I.; Runyon, S. P.; Abraham, P.; Navarro, H. A.; Kuhar, M. J.; Pollard, G. T.; Howard, J. L. Monoamine Transporter Binding, Locomotor Activity and Drug Discrimination Properties of 3-(4-Substituted phenyl)tropane-2-carboxylic acid Methyl Ester Isomers. *J. Med. Chem.* 2004, *47*, 6401-6409.

103. Carroll, F. I.; Lewin, A. H.; Mascarella, S. W. Dopamine Transporter Uptake Blockers: Structure-Activity Relationships. In Reith M. E. A., ed., *Neurotransmitter Transporters: Structure, Functioning and Regulation (2nd edition)*, Humana Press, Totowa, NJ, **2001**, 381-432 and references cited therein.

104. Tamagnan, G.; Alagille, D.; Fu, X.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B.; Baldwin, R. M. Synthesis and Monoamine Transporter Affinity of New 2β-Carbomethoxy-3β-[4-(substituted thiophenyl)]phenyltropanes: Discovery of a Selective SERT Antagonist with Picomolar Potency. **2005**, *15*, 1131-1133.

105. Meltzer, P. C.; Liang, A. Y.; Brownell, A.-L.; Elmaleh, D. R.; Madras, B. K. Substituted 3-Phenyltropane Analogues of Cocaine: Synthesis, Inhibition of Binding at Cocaine Recognition Sites and Positron Emission Tomography Imaging. *J. Med. Chem.* **1993**, *36*, 855-862.

106. Bois, F.; Baldwin, R. M.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B.; Tamagnan, G. Synthesis and Monoamine Transporter Affinity of 3'-Analogues of 2-β-Carbomethoxy-3-β-(4'-iodophenyl)tropane (β-CIT). *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2117-2120.

107. Carroll, F. I.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Synthesis and Ligand Binding of 3b-(3-Substituted phenyl)- and 3b-(3,4-Disubstituted phenyltropane-2β-carboxylic acid Methyl Esters. *Med. Chem. Res.* **1992**, *1*, 382-387.

108. Carroll, F. I.; Blough, B. E.; Nie, Z.; Kuhar, M. J.; Howell, L. L.; Navarro, H. A. Synthesis and Monoamine Transporter Binding Properties of 3β-(3',4'-Disusbtituted phenyl)tropane-2-carboxylic acid Methyl Esters. *J. Med. Chem.* **2005**, *48*, 2767-2771.

109. Meltzer, P. C.; McPhee, M.; Madras, B. K.; Synthesis and Biological Activity of 2-Carbomethoxy-3-catechol-8-azabicyclo[3.2.1]octanes. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4133-4137.

110. Carroll, F. I.; Kotian, P.; Dehgani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. Cocaine and 3β-(4'-Substituted phenyl)tropane-2β-carboxylic acid Ester and Amide Analogues. New High-Affinity and Selective Compounds for the Dopamine Transporter. *J. Med. Chem.* **1995**, *38*, 379-388.

111. Carroll. F. I.; Kotian, P.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. 3β-(4'-Chlorophenyl)tropan-2β-carboxamides and Cocaine Amide Analogues: New High Affinity and Selective Compounds for the Dopamine Transporter. *Med. Chem. Res.* **1993**, *3*, 468-472.

112. Kozikowski, A. P.; Roberti, M.; Xiang, L.; Bergman, J. S.; Callahan, P. M.; Cunningham, K. A.; Johnson, K. M. Structure-Activity Relationship Studies of Cocaine: Replacement of the C-2 Ester group by Vinyl Argues Against H-bonding and Provides an Esterase-Resisitant High-Affinity Cocaine Analogue. *J. Med. Chem.* **1992**, *35*, 4764-4766.

113. Kozikowski, A. P.; Saiah, M. K. E.; Johnson, K. M.; Bergman, J. S. Chemistry and Biology of the 2b-Alkyl-3b-phenyl Analogues of Cocaine: Subnanomolar Affinity Ligands that Suggest a New Pharmacophore Model at the C-2 Position. *J. Med. Chem.* **1995**, *38*, 3086-3093.

114. Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. Synthesis, Cocaine Receptor Affinity and Dopamine Uptake Inhibition of Several New 2β-Substituted 3β-Phenyltropanes. *J. Med. Chem.* **1994**, *37*, 3875-3877.

115. Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliat, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. Synthesis of 2b-Acyl-3b-aryl-8-azabicyclo[3.2.1]octanes and their Binding Affinities at Dopamine and Serotonin Transport Sites in rat Striatum and Frontal Cortex. *J. Med. Chem.* **1994**, *37*, 1262-1268.

116. Davies, H. M. L.; Saikali, E.; Sexton, T.; Childers, S. R. Novel 2-substituted Cocaine Analogues: Binding Properties at Dopamine transport Sites in rat Striatum. *Eur. J. Pharmacol.-Mol. Pharmacol. Sec.* **1993**, *244*, 93-97.

117. Davies, H. M. L.; Kuhn, L. A.; Thornley, C.; Matasi, J. J.; Sexton, T.; Childers S. R. C. Synthesis of 3b-Aryl-8-azabicyclo[3.2.1]octanes with High Binding Affinities and Selectivities for the Serotonin Transporter Site. *J. Med. Chem.* **1996**, *39*, 2554-2558.

118. Bennett, B. A.; Wichems, C. H.; Hollingsworth, C. K.; Davies, H. M. L.; Thornley, C.; Sexton, T.; Childers, S. R. Novel 2-Substituted Cocaine Analogues: Uptake and Ligand Binding Studies at Dopamine, Serotonin and Norepinephrine Transport Sites in the Rat Brain. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 1176-1186.

119. Xu, L.; Kulkarni, S. S.; Izenswasser, S.; Katz, J. L.; Kopajtic, T.; Lomenzo, S. A.; Newman, A. H.; Trudell, M. L. Synthesis and Monoamine TransportrBinding of 2-(Diarylmethoxymethyl)-3b-aryltropane Derivatives. *J. Med. Chem.* **2004**, *47*, 1676-1682.

120. Kotturi, S. V.; Jiang, S,; Chang, A. C.; Abraham, P. Navarro, H. A.; Kuhar, M. J.; Carroll, F. I. Synthesis and Monoamine Transporter Binding Properties of 2,3-Diaryltropanes. *J. Med. Chem.* **2005**, *48*, 7437-7444.

121. Kottian, P.; Mascarella, S. W.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J.; Carroll. F. I. Synthesis, Ligand Binding and Quantitative Structure-Activity Relationship Study of 3b-(4'-Substituted phenyl)-2b-(heterocyclic)tropanes: Evidence for an Electrostatic Interaction at the 2b-Position. *J. Med. Chem.* **1996**, *39*, 2753-2763.

122. Carroll, F. I.; Pawlush, N.; Kuhar, M. J.; Pollard, G. T.; Howard, J. L. Synthesis, Monoamine Transporter Binding Properties and Behavioral Pharmacology of a Series of 3b-(Substituted phenyl)-2b-(3'-Substituted isoxazol-5-yl)tropanes. *J. Med. Chem.* **2004**, *47*, 296-302.

123. Kotian, P.; Abraham, P.; Lewin, A. H.; Mascarella, S. W.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. Synthesis and Ligand Binding Study of 3b-(4'-Substituted phenyl)-2b-(heterocyclic)tropanes. *J. Med. Chem.* **1995**, *38*, 3451-3453.

124. Newman, A. H.; Allen, A. C.; Izenwasser, S.; Katz, J. L. Novel 3α-(diphenylmethoxy)tropane analogs: Potent Dopamine Uptake Inhibitors Without Cocaine-like Beahvioral Profiles. *J. Med. Chem.* **1994**, *37*, 2258-2261.

125. Milius, R. A.; Saha, J. K.; Madras, B. K.; Neumeyer, J. L. Synthesis and Receptor binding of N-Substituted Tropane Derivatives. High Affinity Ligands for the Cocaine Receptor. *J. Med. Chem.* **1991**, *34*, 1728-1731.

126. Madras, B. K.; Kamien, J. B.; Fahey, M. A.; Canfield, D. R.; Milius R. A.; Saha, J. K.; Neumeyer, J. L.; Spealman, R. D. N-Modified Fluorophenyltropane Analogues of Cocaine with High Affinity for Cocaine Receptors. *Pharmacol. Biochem. Behav.* **1990**, *35*, 949-953.

127. Boja, J. W.; Kuhar, M. J.; Kopatjic, T.; Yang, E.; Abraham, P.; Lewin, A. H.; Carroll. F. I. Secondary Amine Analogues of 3β-(4'-Substituted phenyl)tropane-2β-carboxylic acid Esters and N-Norcocaine Exhibit Enhanced Affinity for Serotonin and Norepinephrine Transporters. J. Med. Chem. 1994, 37, 1220-1223.

128. Neumeyer, J. L.; Tamagnan, G.; Wang, S.; Gao, Y.; Milius, R. A.; Kula, N. S.; Baldessarini, R. J. N-Substituted Analogs of 2β-Carbomethoxy-3β-(4'-iodophenyl)tropane)β-CIT) with Selective Affinity to Dopamine or Serotonin Transporters in Rat Forebrain. *J. Med. Chem.***1996**, *39*, 543-548.

129. Elmaleh, D. R.; Fischman, A. J.; Shoup, T. M.; Byon, C.; hanson, R. N.; Liang, A. Y.; Meltzer, P. C.; Madras, B. K. Preparation and Biological Evaluation of Iodine-125-IACFT: A Selective SPECT Agent for Imaging Dopamine Transporter Sites. *J. Nucl. Med.* **1996**, *37*, 1197-1202.

130. Fandrick, K.; Feng, X.; Janowsky, A.; Johnson, R.; Cashman, J. R. Bivalent Biogenic Amine Reuptake Inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2151-2154.

131. Meltzer, P. C.; Blundell, P.; Yong, Y. F.; Chen, Z. George, C.; Gonzalez, M. D.; madras, B. K. 2-Carbomethoxy-3-aryl-8-bicyclo[3.2.1]octanes: Potent Non-Nitrogen Inhibitors of Monoamine Transporters. *J. Med. Chem.* **2000**, *43*, 2982-2991.

132. Meltzer, P. C.; Pham-Huu, D. P.; Madras, B. K. Synthesis of 8-Thiabicyclo[3.2.1]oct-2-enes and their Binding Affinity for the Dopamine and Serotonin Transporters. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6007-6010.

133. Carroll, F. I.; Blough, B. E.; Huang, X.; Nie, Z.; Mascarella, S. W.; Deschamps, J.; Navarro, A. H. Synthesis and Monoamine Transporter Binding Properties of 2,3-Cyclo Analogues of 3β-(4'-Aminophenyl)-2β-tropanemethanol. *J. Med. Chem.* **2006**, *49*, 4589-4594.

134. Chen, Z.; Izenwasswer, S.; Katz, J. L.; Zhu, N.; Klein, C. L.; Trudell, M. L. Synthesis and Dopamine Transporter Affinity of 2-(Methoxycarbonyl)-9-methyl-3-phenyl-9-azabicyclo[3.3.1]nonane Derivatives. *J. Med. Chem.* **1996**, *39*, 4744-4749.

135. Zhang, C.; Izenwasser, S.; Katz, J. L.; Teryy, P. D.; Trudell, M. L. Synthesis and Dopamine Transporter Affinity of the Four Stereoisomers of (+/-)-2-(Methoxycarbonyl)-7-methyl-3-phenyl-7-azabicyclo[2.2.1]heptane. *J. Med. Chem.* **1998**, *41*, 2430-2435.

136. Howell, L. L.; Wilcox, K. M. The Dopamine Transporter and Cocaine Medication Development: Drug Self-Administration in Non-human Primates. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 1-6.

137. Mello, N. K.; Negus, S. S. Preclinical Evaluation of Pharmacotherapies for Treatment of Cocaine and Opioid Abuse Using Self-Administration Procedures. *Neuropsychopharmacology* **1996**, *14*, 375-424.

138. Nader, M. A.; Grant, K.A.; Davies, H. M.; Mach, R. H.; Childers, S. R. The Re-inforcing and Discriminative Stimulus Effects of the Novel Cocaine Analogue 2β-Propanoyl-3β-(4-tolyl)tropane in Rhesus Monkeys. *J. Pharmacol. Exp. Ther.* **1997**, *280*, 541-550.

139. Carroll, F. I.; Howard, J. L.; Howell, L. L.; Fox, B. S.; Kuhar, M. J. Development of the Dopamine Transporter Selective RTI-336 as a Pharmacotherapy for Cocaine Abuse. *AAPS Journal* **2006**, *8*, Article 24, E196-203.

140. Moldt, P.; Watjen, F.; Scheel-Kruger, J. Tropane-2-aldoxine Derivatives as Neurotransmitter Reuptake Inhibitors. In Denmark, Neurosearch A/S **1995**.

141. Frackiewicz, E. J.; Jhee, S. S.; Shiovitz, T. M.; Webster, J.; Topham, C.; Dockens, R. C.; Whigan, D.; Salazar, D. E.; Cullen, N. R. Brasofensine Treatment for Parkinson's Disease in Combination with Levodopa/Carbidopa. *Ann. Pharmacother.* **2002**, *36*, 225-230.

142. Yu, P. Brasofensine Neurosearch. *Curr. Opin. Investig. Drugs* **2000**, *1*, 504-507.

143. Solid pharmaceutical preparation form of 2, 3-disubstituted tropanes for use as central nervous system agents. PCT Int. Appl. (**2005**).

144. Himmelsbach, C. K. Studies of the addiction liability of 'demerol.' *J. Pharmacol. Exp. Ther.* **1942**, *75*, 64.

145. Polonio, P.; Lisbon, M. B. Pethidine Addiction. *Lancet* **1947**, 592.

146. Andrews, H. L. Cortical Effects of Demerol. *J. Pharmacol. Exp. Ther.* **1942**, *76*, 89.

147. Martin, W. R.; Sloan, J. W. Neuropharmacology and Neuro-chemistry of Subjective Effects, Analgesia, Tolerance and Dependance Produced by Narcotic Analgesics, in: Drug Addiction I, Springer-Verlag, Berlin, p-43.

148. Izenwasser, S.; Newman, A. H.; Cox, B. M.; Katz, J. L. The Cocaine-like Behavioral Effects of Meperidine are Mediated by Activity at the Dopamine Transporter. *Eur. J. Pharmacol.* **1996**, *297*, 9-17.

149. Lomenzo, S. A.; Rhoden, J. B.; Izenwasser, S.; Wade, D.; Kopajtic, T.; Katz, J. L.; Trudell, M. L. Synthesis and Biological Evaluation of Meperidine Analogues at Monoamine Transporters. *J. Med. Chem.* **2005**, *48*, 1336-1343.

150. Rhoden, J. B.; Bouvet, M.; Izenwasser, S.; Wade, D.; Lomenzo, S. A.; Trudell, M. L. Structure-Activity Studies of 3'-4'-Dichloro-meperidine Analogues at Dopamine and Serotonin Transporters. *Bioorg. Med. Chem.* **2005**, *13*, 5623-5634.

151. Toda, N.; Ori, M.; Takami, K.; Tago, K.; Kogen, H. Total Synthesis of (+)-Benzastatin E via Diastereoselective Grignard Addition to 2-Acylindone. *Org. Lett.* **2003**, *5*, 269-271.

152. Fraenkel, G.; Beckenbaugh, W. E.; Yang, P. P. *J. Am. Chem. Soc.* **1976**, *98*, 6878.

153. Bauer, W.; Griesinger, C. *J. Am. Chem. Soc.* **1993**, *115*, 10871.

154. Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. O.; Dykstra, R. R.; Philips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201.

155. Moreau, A.; Lorion, M.; Couture, A.; Deniau, E.; Grandclaudon, P. A New Total Syntheis of Porritoxin. *J. Org. Chem.* **2006**, *71*, 3303-3305.

156. Kitano, Y.; Chiba, K.; Tada, M. A Direct Conversion of Alcohols to Isocyanides. *Tet. Lett.* **1998**, *39*, 1911-1912.

157. Davis, R.; Untch, K. G. Direct One-Step Conversion of Alcohols into Nitriles. *J. Org. Chem.* **1981**, *46*, 2987-2988.

158. Lecomte, V.; Stephan, E.; Rager, M.; Jaouen, G. Versatile use of hindered oxalates for the stereoselective preparation of novel 11-modified androst-5-ene derivatives. *J. Org. Chem.* **2004**, *69*, 3216-19.

159. Goodnick, P. J.; Goldstein, B. J. Selective Reuptake Inhibitors in Affective Disorders-Basic Pharmacology. *J. Psychopharmacology* **1998**, *12*, S55-S87.

160. Wong, D. T.; Bymaster, F. P.; Engelman, E. A. Prozac (Fluoxetine, Lilly 110140), The First Selective Serotonin Uptake Inhibitor and Antidepressant Drug: Twenty Years Sine its First Publication. *Life Sci.* **1995**, *57*, 411-441.

161. Paul, I. A. Excitatory Amino Acid Signalling, Major Depression and the Actions of Antidepressants. *Pharmaceut News* **2001**, *8*, 33-44.

162. Question Mark Axford, L.; Boot, J. R.; Hotten, T. M.; Keenan, M.; martin, F. M.; Milutinovic, S.; Moore, N. A.; O'Neill, M. F.; Pullar, I. A.; Tupper, D. E.; Van Belle, K. R.; Vivien, V. Bicyclo[2.2.1]heptanes as Novel Triple Re-uptake Inhibitors for the Treatment of Depression. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3277-3280.

163. Skolnick, P.; Popik, P.; Janowsky, A.; Beer, B.; Lippa, A. S. Antidepressant-like Actions of DOV 21,947: a "Triple" Reuptake Inhibitor. *Eur. J. Pharmacol.* **2003**, *461*, 99-104.

164. Kelley, A. E. Neural Integrative Activities of Nucleus Accumbens Subregions in Relation to Learning and Motivation. *Psychobiology* **1999**, *27*, 198-213.

165. Wise, R. A.; Brain Reward Circuitry: Insights from Unsensed Incentives. *Neuron* **2002**, *36*, 229-40.

166. D'Aquila, P. S.; Collu, M.; Gessa, G. L. Et al. The Role of Dopamine in the Mechanism of Action of Antidepressant Drugs. *Eur. J. Pharmacol.* **2000**, *405*, 365-373.

167. Skolnick, P.; Dopamine and Glutamate in Psychiatric Disorders in: Dopamine and Depression. Schmidt, W. ed.; Totown, Humana Press, **2005**, *9*, 199-214.

168. Fava, M. Augmentation and Combination Strategies in Treatment-Resistant Depression. *J. Clin. Psychiatry* **2001**, *62*(Suppl 18), 4-11.

169. Skolnick, P.; Krieter, P.; Tizzano, J.; Basile, A.; Popik, P.; Czobor, P.; Lippa, A. Preclinical and Clinical Pharmacology of DOV 216, 303, a "Triple" Reuptake Inhibitor. *CNS Drug Reviews* **2006**, *12*, 123-134.

170. Coyle, J. T.; Snyder, S. H. Antiparkinsonian Drugs: Inhibition of Dopamine Uptake in the Corpus Striatum as a Possible Mechanism of Action. *Science* **1969**, *166*, 899-901.

171. van der Zee, P.; Hespe, W. A. Comparison of the Inhibitory Effects of Aromatic Substituted Benzhydryl Esters on the Uptake of Catecholamines and Serotonin into Synaptosomal Preparations of the Rat Brain. *Neuropharmacology* **1978**, *17*, 483-490.

172. van der Zee, P.; Koger, H. S.; Gootjes, J.; Hespe, W. Aryl 1,4-Dialk(en)ylpiperazines as Selective and Very Potent Inhibitors of Dopamine Uptake. *Eur. J. Med. Chem.* **1980**, *15*, 363-370.

173. Scheel-Kruger, J. Behavioral and Biochemical Comparison of Amphetamine Derivatives, Cocaine, Benztropine and Tricyclic Anti-Depressant Drugs. *Eur. J. Pharmacol.* **1972**, *18*, 63-73.

174. Koe, B. K. Molecular Geometry of Inhibitors of the Uptake of Catecholamines and Serotonin in Synaptosomal Preparations of Rat Brain. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 649-661.

175. McKearney, J. W. Effects of Dopamine Uptake Inhibitors on Schedule-Controlled Behavior in the Squirrel Monkey. *Psychopharmacology* **1982**, *78*, 377-379.

176. Acri, J. B.; Seidleck, B.; Witkin, J. M. Effects of Dopamine Uptake Inhibitors on Behavioral and Toxic Effects of Cocaine in: Problems of Drug Dependence 1993, Harris, L. S. ed.; NIDA Monograph 141; NIDA: Washington, DC, 1994; p 441.

177. Newman, A. H.; Allen, A. C.; Izenwasser, S.; Katz, J. L. Novel 3α-(Diphenylmethoxy)tropane Analogs: Potent Dopamine Uptake Inhibitors without Cocaine-like Behavioral Profiles. *J. Med. Chem.* **1994**, *37*, 2258-2261.

178. Newman, A. H.; Kline, R. H.; Allen, A. C.; Izenwasser, S.; George, C.; Katz, J. L. Novel 4'-Substituted and 4,4'-Disubstituted 3a-(Diphenylmethoxy)tropane Analogs as Potent and Selective Dopamine Uptake Inhibitors. J. Med. Chem. 1995, 38, 3933-3940.

179. Kline, R. H.; Izenwasser, S.; Katz, J. L.; Joseph, D. B.; Bowen, W. D.; Newman, A. H. 3'-Chloro-3a-(diphenylmethoxy)tropane But Not 4'-Chloro-3a-(diphenylmethoxy)tropane produces a Cocaine-like Behavioral Profile. *J. Med. Chem.* **1997**, *40*, 851-857.

180. Newman, A. H.; Kulkarni, S. Probes for the Dopamine Transporter: New Leads Toward a Cocaine-Abuse Therapeutic – A Focus on Analogues of Benztropine and Rimcazole. *Medicinal Research Reviews* **2002**, *22*, 429-464.

APPENDIX

1. Crystal data and structure refinement for 55a.

Table 1.1

Identification code	mlt42m	
Empirical formula	$C_{16}H_{21}NO_3$	
Formula weight	275.34	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/n$	
Unit cell dimensions	a = 7.0649(5) Å	α = 90 deg.
	b = 16.7415(13) Å	β = 98.951(2) deg.
	c = 11.8086(9) Å	γ = 90 deg.
Volume	1379.68(18) $Å^3$	
Z, Calculated density	4, 1.326 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	592	
Crystal size	0.60 x 0.40 x 0.10 mm	
Theta range for data collection	2.13 to 30.60 deg.	
Limiting indices	$-10 \le h \le 10, -23 \le k \le 23, -16 \le l \le 16$	
Reflections collected / unique	22821 / 4208 [R(int) = 0.0253]	
Completeness to theta = 30.60	99.4 %	

Absorption correction	Empirical
Max. and min. transmission	1.000000 and 0.951697
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4208 / 0 / 265
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0335, wR2 = 0.0877
R indices (all data)	R1 = 0.0416, wR2 = 0.0934
Largest diff. peak and hole	0.373 and -0.217 e.A^-3

Table 1.2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for MLT42M. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
C(1)	-1225(1)	880(1)	5004(1)	16(1)
C(2)	613(1)	1381(1)	5254(1)	16(1)
C(3)	371(1)	2163(1)	5908(1)	15(1)
C(4)	-1603(1)	2548(1)	5491(1)	16(1)
C(5)	-3238(1)	1943(1)	5246(1)	16(1)
C(6)	-3442(1)	1366(1)	6240(1)	20(1)
C(7)	-2095(1)	657(1)	6082(1)	21(1)
N(8)	-2721(1)	1391(1)	4372(1)	16(1)
C(9)	-4020(1)	1153(1)	3475(1)	15(1)
O(10)	-5456(1)	1532(1)	3079(1)	20(1)
O(11)	-3511(1)	458(1)	3029(1)	19(1)

C(12)	-4592(2)	235(1)	1931(1)	23(1)
C(13)	-3535(2)	-449(1)	1490(1)	27(1)
O(14)	483(1)	1943(1)	7089(1)	18(1)
C(15)	1976(1)	2754(1)	5767(1)	15(1)
C(16)	2114(1)	3094(1)	4700(1)	19(1)
C(17)	3517(1)	3660(1)	4585(1)	23(1)
C(18)	4808(1)	3896(1)	5534(1)	23(1)
C(19)	4722(1)	3550(1)	6591(1)	22(1)
C(20)	3327(1)	2979(1)	6705(1)	18(1)

Table 1.3. Bond lengths [Å] and angles [deg] for MLT42M.

C(1)-N(8)	1.4695(10)
C(1)-C(2)	1.5346(12)
C(1)-C(7)	1.5429(13)
C(2)-C(3)	1.5440(12)
C(3)-O(14)	1.4331(10)
C(3)-C(15)	1.5328(12)
C(3)-C(4)	1.5457(11)
C(4)-C(5)	1.5293(12)
C(5)-N(8)	1.4723(11)
C(5)-C(6)	1.5441(12)
C(6)-C(7)	1.5513(13)
N(8)-C(9)	1.3497(10)
C(9)-O(10)	1.2257(10)
C(9)-O(11)	1.3486(10)
O(11)-C(12)	1.4473(10)
C(12)-C(13)	1.5031(14)

C(15)-C(20)	1.3972(12)
C(15)-C(16)	1.3991(12)
C(16)-C(17)	1.3926(13)
C(17)-C(18)	1.3884(14)
C(18)-C(19)	1.3859(14)
C(19)-C(20)	1.3934(13)

N(8)-C(1)-C(2)	107.47(7)
N(8)-C(1)-C(7)	102.28(7)
C(2)-C(1)-C(7)	114.08(7)
C(1)-C(2)-C(3)	113.76(7)
O(14)-C(3)-C(15)	110.03(7)
O(14)-C(3)-C(2)	105.94(7)
C(15)-C(3)-C(2)	110.60(7)
O(14)-C(3)-C(4)	109.13(7)
C(15)-C(3)-C(4)	110.04(7)
C(2)-C(3)-C(4)	111.01(7)
C(5)-C(4)-C(3)	113.73(7)
N(8)-C(5)-C(4)	106.57(7)
N(8)-C(5)-C(6)	101.73(7)
C(4)-C(5)-C(6)	115.27(7)
C(5)-C(6)-C(7)	104.80(7)
C(1)-C(7)-C(6)	104.13(7)
C(9)-N(8)-C(1)	125.05(7)
C(9)-N(8)-C(5)	121.51(7)
C(1)-N(8)-C(5)	104.28(6)
O(10)-C(9)-O(11)	123.54(8)
O(10)-C(9)-N(8)	124.61(8)
O(11)-C(9)-N(8)	111.80(7)
C(9)-O(11)-C(12)	115.91(7)
O(11)-C(12)-C(13)	106.61(8)

C(20)-C(15)-C(16)	117.98(8)
C(20)-C(15)-C(3)	120.89(8)
C(16)-C(15)-C(3)	121.12(7)
C(17)-C(16)-C(15)	120.98(8)
C(18)-C(17)-C(16)	120.24(9)
C(19)-C(18)-C(17)	119.46(9)
C(18)-C(19)-C(20)	120.31(9)
C(19)-C(20)-C(15)	120.98(8)

Symmetry transformations used to generate equivalent atoms:

Table 1.4. Anisotropic displacement parameters ($Å^2$ x10^3) for MLT42M.
The anisotropic displacement factor exponent takes the form:
$-2\ pi^2[\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U12\ ]$

	U11	U22	U33	U23	U13	U12
C(1)	17(1)	14(1)	17(1)	-1(1)	-2(1)	4(1)
C(2)	15(1)	16(1)	17(1)	-2(1)	0(1)	4(1)
C(3)	15(1)	15(1)	13(1)	0(1)	0(1)	2(1)
C(4)	15(1)	14(1)	17(1)	-2(1)	1(1)	3(1)
C(5)	14(1)	16(1)	16(1)	-2(1)	1(1)	3(1)
C(6)	19(1)	23(1)	19(1)	2(1)	4(1)	0(1)
C(7)	22(1)	18(1)	21(1)	4(1)	0(1)	0(1)
N(8)	16(1)	15(1)	16(1)	-2(1)	-2(1)	4(1)
C(9)	16(1)	15(1)	14(1)	2(1)	1(1)	-1(1)

O(10)	18(1)	22(1)	19(1)	2(1)	-2(1)	2(1)
O(11)	23(1)	17(1)	16(1)	-3(1)	-3(1)	1(1)
C(12)	27(1)	22(1)	16(1)	-3(1)	-5(1)	-2(1)
C(13)	35(1)	24(1)	22(1)	-7(1)	2(1)	-3(1)
O(14)	22(1)	19(1)	13(1)	0(1)	1(1)	1(1)
C(15)	14(1)	15(1)	17(1)	-1(1)	2(1)	3(1)
C(16)	18(1)	21(1)	18(1)	1(1)	1(1)	2(1)
C(17)	22(1)	22(1)	25(1)	5(1)	5(1)	2(1)
C(18)	18(1)	19(1)	32(1)	-1(1)	6(1)	-1(1)
C(19)	16(1)	24(1)	24(1)	-6(1)	2(1)	-1(1)
C(20)	16(1)	21(1)	17(1)	-3(1)	2(1)	2(1)

Table 1.5. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2$ $x10^3$) for MLT42M.

	x	y	z	U(eq)
H(1)	-1009(17)	429(7)	4527(10)	18(3)
H(2A)	1038(18)	1511(7)	4510(11)	19(3)
H(2B)	1647(18)	1070(8)	5710(11)	21(3)
H(4A)	-1578(17)	2850(7)	4766(11)	20(3)
H(4B)	-1873(18)	2927(7)	6079(11)	21(3)
H(5)	-4409(17)	2219(7)	4947(10)	19(3)
H(6A)	-3104(19)	1625(8)	7008(11)	25(3)
H(6B)	-4810(20)	1189(8)	6164(12)	27(3)
H(7A)	-1107(19)	569(8)	6768(11)	26(3)
H(7B)	-2847(19)	164(8)	5930(11)	27(3)

H(12A)	-5890(20)	78(8)	2045(12)	30(3)
H(12B)	-4690(20)	694(9)	1422(12)	32(3)
H(13A)	-3430(20)	-916(10)	2014(14)	41(4)
H(13B)	-4180(20)	-616(9)	751(13)	37(4)
H(12C)	-2200(20)	-284(9)	1386(14)	43(4)
H(14)	160(20)	2348(10)	7447(13)	38(4)
H(16)	1203(19)	2923(8)	4020(11)	26(3)
H(17)	3610(20)	3893(8)	3821(12)	32(3)
H(18)	5790(20)	4291(9)	5436(12)	34(4)
H(19)	5637(19)	3689(8)	7255(12)	27(3)
H(20)	3246(17)	2741(7)	7439(11)	21(3)

Table 1.6. Torsion angles [deg] for MLT42M.

N(8)-C(1)-C(2)-C(3)	56.05(9)
C(7)-C(1)-C(2)-C(3)	-56.58(9)
C(1)-C(2)-C(3)-O(14)	80.36(8)
C(1)-C(2)-C(3)-C(15)	-160.44(7)
C(1)-C(2)-C(3)-C(4)	-37.99(9)
O(14)-C(3)-C(4)-C(5)	-77.14(8)
C(15)-C(3)-C(4)-C(5)	162.03(7)
C(2)-C(3)-C(4)-C(5)	39.26(9)
C(3)-C(4)-C(5)-N(8)	-58.16(9)
C(3)-C(4)-C(5)-C(6)	53.87(9)
N(8)-C(5)-C(6)-C(7)	27.37(8)
C(4)-C(5)-C(6)-C(7)	-87.48(9)
N(8)-C(1)-C(7)-C(6)	-27.27(8)
C(2)-C(1)-C(7)-C(6)	88.43(8)
C(5)-C(6)-C(7)-C(1)	-0.13(9)

C(2)-C(1)-N(8)-C(9)	139.22(8)
C(7)-C(1)-N(8)-C(9)	-100.37(9)
C(2)-C(1)-N(8)-C(5)	-73.93(8)
C(7)-C(1)-N(8)-C(5)	46.48(8)
C(4)-C(5)-N(8)-C(9)	-136.87(8)
C(6)-C(5)-N(8)-C(9)	102.02(9)
C(4)-C(5)-N(8)-C(1)	74.80(8)
C(6)-C(5)-N(8)-C(1)	-46.31(8)
C(1)-N(8)-C(9)-O(10)	166.71(8)
C(5)-N(8)-C(9)-O(10)	25.15(13)
C(1)-N(8)-C(9)-O(11)	-15.86(12)
C(5)-N(8)-C(9)-O(11)	-157.42(7)
O(10)-C(9)-O(11)-C(12)	9.53(12)
N(8)-C(9)-O(11)-C(12)	-167.93(8)
C(9)-O(11)-C(12)-C(13)	168.36(8)
O(14)-C(3)-C(15)-C(20)	2.42(11)
C(2)-C(3)-C(15)-C(20)	-114.28(8)
C(4)-C(3)-C(15)-C(20)	122.71(8)
O(14)-C(3)-C(15)-C(16)	-176.51(7)
C(2)-C(3)-C(15)-C(16)	66.79(10)
C(4)-C(3)-C(15)-C(16)	-56.22(10)
C(20)-C(15)-C(16)-C(17)	-2.12(13)
C(3)-C(15)-C(16)-C(17)	176.85(8)
C(15)-C(16)-C(17)-C(18)	0.01(14)
C(16)-C(17)-C(18)-C(19)	1.71(14)
C(17)-C(18)-C(19)-C(20)	-1.27(14)
C(18)-C(19)-C(20)-C(15)	-0.89(14)
C(16)-C(15)-C(20)-C(19)	2.56(13)
C(3)-C(15)-C(20)-C(19)	-176.41(8)

Symmetry transformations used to generate equivalent atoms:

Table 1.7. Hydrogen bonds for MLT42M [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(14)-H(14)...O(10)#1	0.849(16)	2.089(17)	2.9272(10)	169.1(15)

Symmetry transformations used to generate equivalent atoms:
#1 x+1/2,-y+1/2,z+1/2

2. Crystal data and structure refinement for 60a.

Table 2.1

Identification code	mlt45
Empirical formula	$C_{21}H_{26}NO^+ . C_2O_4H^-$
Formula weight	397.46
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 13.742(2) Å α = 90 deg. b = 11.131(2) Å β = 113.726(3) deg. c = 14.837(2) Å γ = 90 deg.
Volume	2077.6(5) $Å^3$
Z, Calculated density	4, 1.271 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	848
Crystal size	0.50 x 0.40 x 0.20 mm
Theta range for data collection	2.37 to 22.49 deg.
Limiting indices	$-14 \le h \le 14, -11 \le k \le 11, -15 \le l \le 15$
Reflections collected / unique	17041 / 2695 [R(int) = 0.0236]
Completeness to theta = 22.49	99.9 %
Absorption correction	Empirical
Max. and min. transmission	0.952135 and 0.840080
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2695 / 489 / 393

Goodness-of-fit on F^2 1.071

Final R indices [$I>2\sigma(I)$] R1 = 0.0302, wR2 = 0.0797

R indices (all data) R1 = 0.0348, wR2 = 0.0825

Extinction coefficient 0.0178(13)

Largest diff. peak and hole 0.171 and -0.123 e.$Å^{-3}$

Table 2.2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ $x10^3$) for Mlt45.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	8499(1)	2279(1)	1623(1)	42(1)
C(2)	7975(1)	3313(1)	1936(1)	42(1)
C(3)	7049(1)	2932(1)	2211(1)	39(1)
C(4)	7326(1)	1741(1)	2789(1)	40(1)
C(5)	7904(1)	823(1)	2413(1)	43(1)
C(6)	7351(1)	528(2)	1315(1)	50(1)
C(7)	7753(1)	1483(2)	796(1)	50(1)
N(8)	8923(1)	1411(1)	2477(1)	41(1)
C(9)	9719(1)	535(2)	2413(1)	56(1)
C(10)	6761(1)	3883(1)	2816(1)	44(1)
C(11)	7356(2)	4895(2)	3215(1)	58(1)
C(12)	7017(2)	5733(2)	3721(2)	75(1)
C(13)	6090(2)	5576(2)	3835(2)	75(1)
C(14)	5499(2)	4563(2)	3460(2)	74(1)
C(15)	5831(2)	3719(2)	2958(1)	62(1)
O(16)	6100(1)	2661(1)	1341(1)	42(1)
C(17)	5685(1)	3644(2)	666(1)	53(1)
C(18)	4540(5)	3512(16)	163(7)	50(1)
C(18B)	4510(7)	3400(20)	-35(10)	48(2)
C(19)	3898(4)	3930(5)	616(4)	64(1)

C(19B)	3646(5)	3603(8)	201(6)	66(2)
C(20)	2808(3)	3814(5)	146(4)	86(2)
C(20B)	2611(6)	3357(13)	-445(8)	85(2)
C(21)	2352(4)	3287(9)	-777(5)	88(2)
C(21B)	2450(5)	2854(8)	-1339(7)	91(2)
C(22)	2974(4)	2904(6)	-1243(5)	85(2)
C(22B)	3291(6)	2629(7)	-1601(6)	89(2)
C(23)	4069(4)	3025(8)	-764(5)	63(1)
C(23B)	4315(6)	2910(13)	-949(7)	65(2)
C(24)	10126(1)	3122(1)	4821(1)	36(1)
C(25)	10280(1)	1864(1)	5294(1)	38(1)
O(26)	10153(1)	3988(1)	5389(1)	52(1)
O(27)	9992(1)	3208(1)	3954(1)	53(1)
O(28)	9857(1)	1031(1)	4662(1)	59(1)
O(29)	10764(1)	1733(1)	6168(1)	67(1)

Table 2.3. Bond lengths [Å] and angles [deg] for Mlt45.

C(1)-N(8)	1.5116(18)
C(1)-C(2)	1.526(2)
C(1)-C(7)	1.527(2)
C(2)-C(3)	1.544(2)
C(3)-O(16)	1.4507(16)
C(3)-C(10)	1.538(2)
C(3)-C(4)	1.5411(19)
C(4)-C(5)	1.529(2)
C(5)-N(8)	1.5134(19)
C(5)-C(6)	1.531(2)
C(6)-C(7)	1.540(2)
N(8)-C(9)	1.4973(18)
C(10)-C(11)	1.378(2)
C(10)-C(15)	1.388(2)
C(11)-C(12)	1.389(2)
C(12)-C(13)	1.361(3)
C(13)-C(14)	1.370(3)
C(14)-C(15)	1.385(3)
O(16)-C(17)	1.4369(17)
C(17)-C(18)	1.453(6)
C(17)-C(18B)	1.553(9)
C(18)-C(23)	1.374(5)
C(18)-C(19)	1.387(5)
C(18B)-C(23B)	1.384(6)

C(18B)-C(19B)	1.386(6)
C(19)-C(20)	1.381(5)
C(19B)-C(20B)	1.385(6)
C(20)-C(21)	1.386(5)
C(20B)-C(21B)	1.374(6)
C(21)-C(22)	1.365(5)
C(21B)-C(22B)	1.382(6)
C(22)-C(23)	1.389(5)
C(22B)-C(23B)	1.385(6)
C(24)-O(27)	1.2266(16)
C(24)-O(26)	1.2713(16)
C(24)-C(25)	1.5422(19)
C(25)-O(29)	1.2054(16)
C(25)-O(28)	1.2796(16)

N(8)-C(1)-C(2)	107.26(11)
N(8)-C(1)-C(7)	102.17(12)
C(2)-C(1)-C(7)	115.81(13)
C(1)-C(2)-C(3)	114.44(12)
O(16)-C(3)-C(10)	108.20(11)
O(16)-C(3)-C(4)	104.37(11)
C(10)-C(3)-C(4)	109.38(11)
O(16)-C(3)-C(2)	111.28(11)
C(10)-C(3)-C(2)	113.45(11)
C(4)-C(3)-C(2)	109.75(11)
C(5)-C(4)-C(3)	114.87(11)
N(8)-C(5)-C(4)	106.95(11)
N(8)-C(5)-C(6)	102.11(12)
C(4)-C(5)-C(6)	115.04(13)
C(5)-C(6)-C(7)	105.06(12)
C(1)-C(7)-C(6)	104.98(12)
C(9)-N(8)-C(1)	114.04(11)
C(9)-N(8)-C(5)	113.37(12)
C(1)-N(8)-C(5)	100.91(11)
C(11)-C(10)-C(15)	117.66(15)
C(11)-C(10)-C(3)	124.50(14)
C(15)-C(10)-C(3)	117.83(14)
C(10)-C(11)-C(12)	120.75(19)
C(13)-C(12)-C(11)	121.0(2)
C(12)-C(13)-C(14)	119.13(18)
C(13)-C(14)-C(15)	120.4(2)
C(14)-C(15)-C(10)	121.05(19)
C(17)-O(16)-C(3)	115.10(11)
O(16)-C(17)-C(18)	108.9(8)
O(16)-C(17)-C(18B)	110.3(10)
C(18)-C(17)-C(18B)	11.1(5)

C(23)-C(18)-C(19)	118.8(5)
C(23)-C(18)-C(17)	122.0(5)
C(19)-C(18)-C(17)	119.1(5)
C(23B)-C(18B)-C(19B)	117.7(7)
C(23B)-C(18B)-C(17)	117.7(6)
C(19B)-C(18B)-C(17)	124.6(6)
C(20)-C(19)-C(18)	119.8(5)
C(20B)-C(19B)-C(18B)	122.6(7)
C(19)-C(20)-C(21)	120.4(5)
C(21B)-C(20B)-C(19B)	118.0(7)
C(22)-C(21)-C(20)	120.4(5)
C(20B)-C(21B)-C(22B)	121.2(7)
C(21)-C(22)-C(23)	118.8(5)
C(21B)-C(22B)-C(23B)	119.5(6)
C(18)-C(23)-C(22)	121.8(5)
C(18B)-C(23B)-C(22B)	121.0(7)
O(27)-C(24)-O(26)	126.02(12)
O(27)-C(24)-C(25)	118.86(11)
O(26)-C(24)-C(25)	115.12(11)
O(29)-C(25)-O(28)	126.25(13)
O(29)-C(25)-C(24)	121.03(12)
O(28)-C(25)-C(24)	112.72(11)

Table 2.4. Anisotropic displacement parameters ($Å^2 x10^3$) for Mlt45.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2[h^2a^{*2}U11 + ... + 2hka^*b^*U12]$

	U11	U22	U33	U23	U13	U12
C(1)	45(1)	43(1)	46(1)	0(1)	25(1)	-4(1)
C(2)	45(1)	34(1)	50(1)	2(1)	21(1)	-5(1)
C(3)	42(1)	32(1)	43(1)	1(1)	18(1)	-1(1)
C(4)	45(1)	36(1)	45(1)	5(1)	23(1)	2(1)
C(5)	51(1)	32(1)	49(1)	4(1)	24(1)	1(1)
C(6)	57(1)	39(1)	55(1)	-8(1)	23(1)	-6(1)
C(7)	57(1)	54(1)	44(1)	-6(1)	24(1)	-2(1)
N(8)	45(1)	39(1)	41(1)	-6(1)	19(1)	3(1)

C(9)	57(1)	55(1)	60(1)	-8(1)	29(1)	13(1)
C(10)	52(1)	36(1)	47(1)	5(1)	22(1)	9(1)
C(11)	65(1)	43(1)	65(1)	-8(1)	25(1)	2(1)
C(12)	93(1)	52(1)	79(1)	-18(1)	34(1)	8(1)
C(13)	101(2)	58(1)	71(1)	-4(1)	41(1)	30(1)
C(14)	81(1)	73(1)	86(1)	-2(1)	52(1)	18(1)
C(15)	68(1)	55(1)	76(1)	-5(1)	42(1)	4(1)
O(16)	45(1)	31(1)	48(1)	8(1)	17(1)	0(1)
C(17)	55(1)	42(1)	57(1)	16(1)	19(1)	-1(1)
C(18)	53(2)	38(4)	56(3)	21(3)	18(2)	5(2)
C(18B)	49(3)	38(4)	58(4)	18(4)	21(3)	5(3)
C(19)	55(2)	67(3)	69(3)	23(2)	24(2)	9(2)
C(19B)	58(3)	66(4)	81(4)	21(3)	35(3)	7(3)
C(20)	56(2)	101(3)	100(3)	48(3)	32(2)	14(2)
C(20B)	51(3)	87(5)	108(6)	37(5)	24(4)	3(4)
C(21)	49(3)	91(4)	99(4)	51(4)	5(2)	-7(3)
C(21B)	67(4)	63(4)	110(5)	30(3)	2(4)	7(4)
C(22)	67(3)	71(3)	91(3)	28(2)	6(3)	-12(3)
C(22B)	96(4)	62(3)	80(4)	7(3)	5(3)	6(3)
C(23)	61(2)	50(3)	70(3)	15(2)	18(2)	-1(2)
C(23B)	69(4)	54(3)	64(4)	9(3)	18(3)	13(4)
C(24)	43(1)	26(1)	39(1)	-3(1)	17(1)	-2(1)
C(25)	46(1)	28(1)	42(1)	0(1)	21(1)	2(1)
O(26)	86(1)	25(1)	51(1)	-5(1)	34(1)	0(1)
O(27)	85(1)	33(1)	42(1)	0(1)	27(1)	-1(1)
O(28)	86(1)	23(1)	53(1)	-1(1)	14(1)	-4(1)
O(29)	106(1)	40(1)	44(1)	4(1)	17(1)	2(1)

Table 2.5. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2 x10^3$) for Mlt45.

	x	y	z	U(eq)
H(1)	9101(12)	2575(13)	1508(10)	44(4)
H(2A)	8524(12)	3678(13)	2500(11)	44(4)
H(2B)	7717(11)	3919(14)	1403(11)	45(4)
H(4A)	7780(11)	1925(13)	3487(11)	47(4)

H(4B)	6672(12)	1397(12)	2770(10)	40(4)
H(5)	8110(11)	120(14)	2844(10)	47(4)
H(6A)	7567(12)	-293(16)	1186(11)	57(4)
H(6B)	6544(13)	575(14)	1093(11)	52(4)
H(7A)	8130(12)	1114(14)	446(12)	56(4)
H(7B)	7185(13)	1938(14)	335(12)	54(4)
H(8)	9264(12)	1806(15)	3068(12)	56(5)
H(9A)	9386	30	1847	83
H(9B)	9986	48	2996	83
H(9C)	10297	965	2355	83
H(11)	8036(15)	5039(17)	3152(12)	77(6)
H(12)	7444(18)	6450(20)	3971(16)	106(8)
H(13)	5834(17)	6150(20)	4163(15)	94(6)
H(14)	4870(16)	4417(18)	3543(14)	86(6)
H(15)	5382(14)	3027(18)	2651(13)	75(6)
H(17A)	5825(13)	4403(18)	1030(13)	69(5)
H(17B)	6061(13)	3670(15)	206(13)	65(5)
H(19)	4200	4287	1234	77
H(19B)	3765	3918	817	79
H(20)	2377	4091	450	103
H(20B)	2042	3527	-277	102
H(21)	1618	3193	-1081	105
H(21B)	1764	2662	-1777	109
H(22)	2669	2569	-1869	102
H(22B)	3170	2290	-2210	107
H(23)	4496	2769	-1080	76
H(23B)	4880	2767	-1129	78
H(26)	10000	5000	5000	130(11)
H(28)	10000	0	5000	112(10)

Table 2.6. Torsion angles [deg] for Mlt45.

N(8)-C(1)-C(2)-C(3)	-59.60(16)
C(7)-C(1)-C(2)-C(3)	53.70(18)
C(1)-C(2)-C(3)-O(16)	-75.50(15)
C(1)-C(2)-C(3)-C(10)	162.19(12)
C(1)-C(2)-C(3)-C(4)	39.51(17)
O(16)-C(3)-C(4)-C(5)	79.85(15)
C(10)-C(3)-C(4)-C(5)	-164.56(12)
C(2)-C(3)-C(4)-C(5)	-39.49(17)
C(3)-C(4)-C(5)-N(8)	59.21(16)
C(3)-C(4)-C(5)-C(6)	-53.39(18)
N(8)-C(5)-C(6)-C(7)	-28.43(15)

C(4)-C(5)-C(6)-C(7)	87.00(16)
N(8)-C(1)-C(7)-C(6)	29.62(15)
C(2)-C(1)-C(7)-C(6)	-86.58(16)
C(5)-C(6)-C(7)-C(1)	-0.70(17)
C(2)-C(1)-N(8)-C(9)	-163.54(12)
C(7)-C(1)-N(8)-C(9)	74.22(15)
C(2)-C(1)-N(8)-C(5)	74.57(13)
C(7)-C(1)-N(8)-C(5)	-47.67(13)
C(4)-C(5)-N(8)-C(9)	163.58(12)
C(6)-C(5)-N(8)-C(9)	-75.23(15)
C(4)-C(5)-N(8)-C(1)	-74.06(13)
C(6)-C(5)-N(8)-C(1)	47.12(13)
O(16)-C(3)-C(10)-C(11)	-133.73(14)
C(4)-C(3)-C(10)-C(11)	113.15(16)
C(2)-C(3)-C(10)-C(11)	-9.7(2)
O(16)-C(3)-C(10)-C(15)	45.34(17)
C(4)-C(3)-C(10)-C(15)	-67.78(17)
C(2)-C(3)-C(10)-C(15)	169.34(14)
C(15)-C(10)-C(11)-C(12)	-1.5(2)
C(3)-C(10)-C(11)-C(12)	177.53(16)
C(10)-C(11)-C(12)-C(13)	0.0(3)
C(11)-C(12)-C(13)-C(14)	1.4(3)
C(12)-C(13)-C(14)-C(15)	-1.1(3)
C(13)-C(14)-C(15)-C(10)	-0.5(3)
C(11)-C(10)-C(15)-C(14)	1.8(3)
C(3)-C(10)-C(15)-C(14)	-177.33(16)
C(10)-C(3)-O(16)-C(17)	64.31(14)
C(4)-C(3)-O(16)-C(17)	-179.27(12)
C(2)-C(3)-O(16)-C(17)	-60.97(15)
C(3)-O(16)-C(17)-C(18)	-149.9(3)
C(3)-O(16)-C(17)-C(18B)	-161.6(4)
O(16)-C(17)-C(18)-C(23)	-98.6(14)
C(18B)-C(17)-C(18)-C(23)	0(8)
O(16)-C(17)-C(18)-C(19)	83.8(13)
C(18B)-C(17)-C(18)-C(19)	-177(10)
O(16)-C(17)-C(18B)-C(23B)	-96.1(18)
C(18)-C(17)-C(18B)-C(23B)	179(11)
O(16)-C(17)-C(18B)-C(19B)	82(2)
C(18)-C(17)-C(18B)-C(19B)	-3(7)
C(23)-C(18)-C(19)-C(20)	2.2(18)
C(17)-C(18)-C(19)-C(20)	179.8(10)
C(23B)-C(18B)-C(19B)-C(20B)	-1(3)
C(17)-C(18B)-C(19B)-C(20B)	-179.2(16)
C(18)-C(19)-C(20)-C(21)	-0.3(11)
C(18B)-C(19B)-C(20B)-C(21B)	2(2)
C(19)-C(20)-C(21)-C(22)	-1.7(11)

C(19B)-C(20B)-C(21B)-C(22B)	-1.7(18)
C(20)-C(21)-C(22)-C(23)	1.6(12)
C(20B)-C(21B)-C(22B)-C(23B)	0.2(16)
C(19)-C(18)-C(23)-C(22)	-2(2)
C(17)-C(18)-C(23)-C(22)	-179.8(11)
C(21)-C(22)-C(23)-C(18)	0.3(15)
C(19B)-C(18B)-C(23B)-C(22B)	0(3)
C(17)-C(18B)-C(23B)-C(22B)	177.8(14)
C(21B)-C(22B)-C(23B)-C(18B)	1(2)
O(27)-C(24)-C(25)-O(29)	153.84(14)
O(26)-C(24)-C(25)-O(29)	-26.0(2)
O(27)-C(24)-C(25)-O(28)	-25.46(18)
O(26)-C(24)-C(25)-O(28)	154.67(12)

Table 2.7. Hydrogen bonds for Mlt45 [Å and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N8-H8...O27	0.923	2.026	2.894	155.98
N8-H8...O28	0.923	2.335	2.998	128.54
O26-H26...O26[-x+2,-y+1,-z+1]	1.244	1.244	2.488	180.00
O28-H28...O28[-x+2,-y,-z+1]	1.236	1.236	2.471	179.97

VITA

The author was born in Patiala, Punjab, India on October 03, 1977. She graduated from Sacred Heart Convent School, Chandigarh, India in June 1995. She received her B.Sc. (Hons. School) degree at Panjab University, Chandigarh, India in 1999. She graduated from Panjab University in 2001 with M.Sc. (Hons. School) degree in Chemistry. In the Spring of 2002, she came to the University of New Orleans and obtained a M.S. degree in Chemistry in June 2004. She completed the requirements for the degree of Doctor of Philosophy in Organic Chemistry in August 2007 under the supervision of Professor Mark L. Trudell.